SYSTEMATIC REVIEW AND META-ANALYSIS

Systematic Review of Cerebral Phenotypes Associated With Monogenic Cerebral Small-Vessel Disease

Ed Whittaker MBChB*; Sophie Thrippleton, MBChB*; Liza Y. W. Chong, BMedSci; Victoria G. Collins MBChB; Amy C. Ferguson, PhD; David E. Henshall MBChB; Emily Lancastle, BMedSci; Tim Wilkinson, PhD; Blair Wilson, MBChB; Kirsty Wilson, MBChB; Cathie Sudlow FRSE; Joanna Wardlaw MD, FRCR; Kristiina Rannikmäe MD, PhD

BACKGROUND: Cerebral small-vessel disease (cSVD) is an important cause of stroke and vascular dementia. Most cases are multifactorial, but an emerging minority have a monogenic cause. While NOTCH3 is the best-known gene, several others have been reported. We aimed to summarize the cerebral phenotypes associated with these more recent cSVD genes.

METHODS AND RESULTS: We performed a systematic review (PROSPERO [International Prospective Register of Systematic Reviews]: CRD42020196720), searching Medline/Embase (conception to July 2020) for any language publications describing COL4A1/2, TREX1, HTRA1, ADA2, or CTSA pathogenic variant carriers. We extracted data about individuals’ characteristics and clinical and vascular radiological cerebral phenotypes. We summarized phenotype frequencies per gene, comparing patterns across genes. We screened 6485 publications including 402, and extracted data on 390 individuals with COL4A1, 123 with TREX1, 44 with HTRA1 homozygous, 41 with COL4A2, 346 with ADA2, 82 with HTRA1 heterozygous, and 14 with CTSA. Mean age ranged from 15 (ADA2) to 59 (HTRA1 heterozygotes). Clinical phenotype frequencies varied widely: stroke, 9% (TREX1) to 52% (HTRA1 heterozygotes); cognitive features, 0% (ADA2) to 64% (HTRA1 homozygotes); and psychiatric features, 0% (COL4A2; ADA2) to 57% (CTSA). Among individuals with neuroimaging, vascular radiological phenotypes appeared common, ranging from 62% (ADA2) to 100% (HTRA1 homozygotes; CTSA). White matter lesions were the most common pathology, except in ADA2 and COL4A2 cases, where ischemic and hemorrhagic lesions dominated, respectively.

CONCLUSIONS: There appear to be differences in cerebral manifestations across cSVD genes. Vascular radiological changes were more common than clinical neurological phenotypes, and present in the majority of individuals with reported neuroimaging. However, these results may be affected by age and biases inherent to case reports. In the future, better characterization of associated phenotypes, as well as insights from population-based studies, should improve our understanding of monogenic cSVD to inform genetic testing, guide clinical management, and help unravel underlying disease mechanisms.

Key Words: Mendelian ▪ radiological features ▪ small-vessel disease ▪ stroke ▪ systematic review

Cerebral small-vessel disease (cSVD) is recognized as an important cause of stroke and vascular cognitive impairment worldwide. The term cSVD describes a group of pathological processes that affect the small arteries, arterioles, venules, and capillaries within the brain. Features of cSVD on neuroimaging include subcortical infarcts, white matter lesions (WMLs), deep intracerebral hemorrhage (ICH), enlarged perivascular spaces (PVSs), cerebral microbleeds, and brain atrophy. Despite the increase in...
cSVD burden among an aging population, the underlying disease mechanisms are incompletely understood, and therapeutic options limited, with vascular risk factor management remaining the mainstay of cSVD prevention and treatment.\(^3\)

While the majority of cSVD cases are thought to result from the interaction of multiple genetic variants and environmental factors, an important minority of cases are monogenic, that is, caused by a pathogenic rare variant in a single gene. \(\text{NOTCH3}\) (Notch Receptor 3) is the best known of these genes and is implicated in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy.\(^4\) However, since \(\text{NOTCH3}\) was first described in 1996, several additional cSVD genes have been identified, including \(\text{COL4A1}\) (Collagen, Type Iv, Alpha-1), \(\text{TREX1}\) (3-Prime Repair Exonuclease 1), \(\text{HTRA1}\) (HTRA Serine Peptidase 1), \(\text{COL4A2}\) (Collagen, Type Iv, Alpha-2), \(\text{ADA2}\) (Adenosine Deaminase 2) and, most recently, \(\text{CTSA}\) (Cathepsin A). Pathogenic rare variants in these genes have been associated with various clinical phenotypes alongside cSVD, including extracerebral manifestations (Table 1), as well as certain radiological features seen on neuroimaging.\(^5\)

Better characterization of these rare disorders, including which radiological and clinical phenotypes are associated with specific genes, can inform genetic testing and counseling, including the appropriate selection of patients and screening of family members. This knowledge can also aid in the management of affected individuals, for example, by guiding appropriate screening for certain associated phenotypes. Furthermore, an improved understanding of monogenic cSVD may offer insights into the disease mechanisms underlying sporadic cSVD, as there is increasing evidence to suggest an overlap of disease pathways involved in both sporadic and monogenic disease.\(^6\)–\(^8\) Observations from large-scale genetic association studies have also shown common variation in monogenic cSVD genes to be associated with sporadic cSVD. Examples include \(\text{COL4A2}\) single-nucleotide polymorphisms’ association with lacunar ischemic stroke and deep ICH, \(\text{HTRA1}\) single-nucleotide polymorphism association with ischemic stroke, and possibly association of \(\text{NOTCH3}\) single-nucleotide polymorphisms with WMLs.\(^9\)–\(^12\)

We undertook a systematic literature review with the aim of identifying all reported individuals with putative pathogenic rare variants in any of the following monogenic cSVD genes: \(\text{COL4A1}\), \(\text{TREX1}\), \(\text{HTRA1}\), \(\text{COL4A2}\), \(\text{ADA2}\) and \(\text{CTSA}\). We aimed to summarize and compare both clinical and vascular radiological cerebral phenotypes associated with each monogenic cSVD gene.

## METHODS

As a systematic review based on data from published studies, this work does not require approval from an ethical standards committee.
Transparency and Openness Promotion Statement
The authors declare that all supporting data are available within the article (and its supplemental material).

Registration
We have registered a PROSPERO (International Prospective Register of Systematic Reviews) protocol (ID: CRD42020196720) at https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020196720. We followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines.14

Search Strategy
We searched the MEDLINE and EMBASE databases using OvidSP (from conception to July 2020) for publications about individuals with pathogenic rare variants in any of our genes of interest: COL4A1, TREX1, HTRA1, COL4A2, ADA2, or CTSA. We did not restrict the search by language or publication date; we limited it to human studies; and we included conference abstracts. We used a previously published search strategy (Data S1).5 In summary, the search included:

1. Text words, phrases, and Medical Subject Headings for relevant monogenic syndromes/diseases associated with our genes of interest, and
2. Text words, phrases, and Medical Subject Headings terms associated with cSVD combined with those for our genes of interest and their proteins.

Screening
We carried out the screening using Covidence (www.covidence.org). At least two reviewers (E. W., S. T., L. Y. W. C., D. E. H., K. R.) independently screened titles and abstracts of all publications identified in our search, blinded to each other’s decisions. Full texts of studies included at this stage were then retrieved and screened by 2 reviewers for eligibility, recording any reasons for exclusion. We resolved disagreements through discussion and mutual consensus with a third reviewer. The included publications were combined with those identified via a previous systematic review.5

Inclusion/Exclusion Criteria
We included studies that met the following conditions:

1. A case report, case series, or other study design (except review papers) describing the clinical or cerebral radiological phenotype of ≥1 individual. Such description could be anything between stating that the individual was healthy to an in-depth case report.
2. Genetically confirmed rare variant (in a heterozygous [HetZ] or homozygous or compound heterozygous state [HomZ]) in any of our genes of interest.
3. Study authors considered the rare variant to be probably or definitely pathogenic.

We excluded studies describing individuals with rare variants in CTSA and TREX1 associated with galactosialidosis, Aicardi-Goutieres syndrome, and chilblain or systemic lupus. We excluded individuals with a presumed pathogenic variant in >1 gene.

Data Extraction
From each included publication, we (one of E. W., S. T., L. Y. W. C., V. C., E. L., D. E. H., K. R.) extracted data on the first author, publication year, journal, and number of eligible individuals and pedigrees. For foreign language articles, we sought a full translation where an English language abstract did not provide sufficient information or was not available. For each eligible individual, we extracted data using a standardized form, including:

1. The individual’s characteristics (region of origin, sex, age at time of assessment); genetic variant, and resulting protein change;
2. Clinical cerebral phenotype (presence, type and age at diagnosis of clinical stroke[s], cognitive features, psychiatric features, and headache);

| Table 1. Modes of Inheritance and Extracerebral Features for Each Gene |
|-------------------------|------------------|---------------------|
| Gene        | Mode of inheritance | Extracerebral features                                      |
| COL4A1/COL4A2 | AD               | Retinal artery tortuosity∗; cataract; kidney cysts; hematuria; muscle cramps and raised creatinine kinase; anterior segment defects; arrhythmia; Raynaud phenomenon; hemolytic anemia |
| TREX1       | AD               | Retinal vasculopathy; nephropathy; liver disease; Raynaud phenomenon; skin lesions |
| HTRA1       | AR/AD            | Hair loss; degenerative spine disease; back pain            |
| ADA2        | AR               | Inflammation; skin involvement; liver disease; nephropathy; splenomegaly; myalgia; hematological features |
| CTSA        | AR               | Hypertension; dry mouth/eyes; muscle cramps                  |

AD indicates autosomal dominant; and AR, autosomal recessive.

∗The relationship between this phenotype and the gene is classed as provisional in the Online Mendelian Inheritance in Man (OMIM) database. Otherwise, all phenotype-genotype relationships are classed as established in OMIM or were taken from the first reporting where not included in the OMIM database (CTSA).
3. Vascular radiological cerebral phenotype (presence, location, burden, scan type used, age at diagnosis of ischemia, ICH, WMLs, microbleeds, atrophy, enlarged PVSs, calcification, and cerebral aneurysms); and
4. Vascular risk factors (presence of ≥1 of hypertension, smoking, diabetes, excess alcohol consumption, or hypercholesterolemia).

We selected the list of clinical cerebral phenotypes to extract to represent known manifestations of cSVD, including stroke, and the broad categories of cognitive and psychiatric features. We additionally included headache as phenotype of interest because of its association with several monogenic cSVD genes in the Online Mendelian Inheritance in Man (OMIM) database (ADA2, COL4A1, TREX1, and HTRA1). Finally, we also noted any other cerebral clinical phenotypes on our data extraction form.

We selected the list of vascular radiological cerebral phenotypes to extract to represent known manifestations of cSVD and again noted any other features on our data extraction form. Finally, we noted any specific radiological patterns to lesion location or severity that might help identify cases in everyday clinical practice.

To assess agreement in data extraction, at least 2 members of the team extracted data from 10% of publications, working independently and blinded to each other’s decisions.

Where radiological imaging findings were described, the terminology used across publications varied widely, as has been noted previously in the literature. We made an effort to sort the imaging descriptions into our prespecified categories to deal with the variable terminology (see Data S1 for a list of decisions and assumptions), discussing uncertainties with an expert neuroradiologist (J.W.).

Data Synthesis
For each gene, we summarized the total number of relevant publications, pedigrees, individuals and rare variants, and the individuals’ characteristics. We summarized data on the presence or absence of each cerebral phenotype (clinical and vascular radiological) as well as cumulative evidence of any vascular radiological feature, to assess their apparent frequency. We compared findings between genes, highlighting shared patterns and differences in the frequencies of associated phenotypes.

We stratified the presence of clinical stroke and any vascular feature(s) on neuroimaging by presence of ≥1 vascular risk factors. We used the chi-squared test (significance threshold of 0.05) to assess differences in phenotype frequency in patients with and without vascular risk factors.

Variant Pathogenicity Assessment
We used the Ensembl Variant Effect Predictor (VEP) to assess the consequences of the genetic variants included in our systematic review. We extracted information on the variants on the basis of the following VEP subcomponents: (1) SnpEff variant annotation and effect prediction tool to assess variant impact; (2) ClinVar to assess variant’s clinical significance; (3) SIFT to predict whether an amino acid substitution is likely to affect protein function; and (4) Polymorphism Phenotyping v2 to predict the effect of an amino acid substitution on the structure and function of a protein. Where conflicting evidence was provided for the same variant (usually because an allele may have a different effect in different transcripts), we selected the category with a more significant/negative effect. We calculated the results (expressed as percentages) among variants per each individual VEP subcomponent.

RESULTS
We included 402 publications from 6485 identified for screening (Figure 1, Supplemental References). As in our previous systematic review, despite only being first reported in 2013, ADA2 had the largest number of eligible publications (n=149), while the number of publications for other genes appears to be related to their order of discovery (COL4A1, n=137; TREX1, n=38; HTRA1HOMZ, n=32; COL4A2, n=20; HTRA1HETZ, n=32; CTSA, n=5) (Figure 2). A likely explanation is the combination of existing treatment options and the severe early-onset systemic phenotype of ADA2, prompting more widespread genetic testing. We extracted data on 1040 individuals, with the number of individuals per gene ranging from 14 (CTSA) to 390 (COL4A1), and the number of pedigrees ranging from 3 (CTSA) to 266 (ADA2). The percentage of pedigrees carrying a private variant ranged from 0% (CTSA) to 76% (COL4A2). As expected, the proportion carrying a private variant has decreased since our previous systematic review, presumably because of new reported individuals now becoming increasingly likely to have had their rare variant identified previously (Figure 2).

The subset of included studies with data independently extracted for comparison showed 96.3% agreement.

Summary of Individuals’ Characteristics
The most common region of origin was Europe for individuals with COL4A1, TREX1, COL4A2, and CTSA (67% [263/390], 57% [70/123], 49% [20/41], and 100% [14/14], respectively); Asia for individuals with HTRA1HOMZ and HTRA1HETZ (75% [33/44] and 56% [46/82]); and Turkey for individuals with ADA2 (28% [98/346]). The region of origin was unknown in 0% to 16% of individuals per gene.
Sex distribution was generally approximated equal (45%–52% female sex) where the number of individuals per gene was considered sufficient to allow meaningful comparison (>100 individuals per gene).

Data about the age of individuals at the time of assessment were not available for >20% of COL4A1/2 individuals. Mean (median) age ranged from 15 (13) years for individuals with ADA2 to 59 (60) years for individuals with HTRA1HetZ. For COL4A1/2 and ADA2, the median age of individuals was <18 years, while the age ranges were broad (ranging from <1 to 77, 72, and 76, respectively) (Table 2).

**Frequency of Clinical Cerebral Phenotypes**

Cognitive features were the most common clinical cerebral phenotype for 4 of 7 genes (HTRA1HomZ,
Whittaker et al Cerebral Phenotypes in Monogenic cSVD

COL4A2, HTRA1HetZ, and CTSA); stroke was the most common among individuals with COL4A1 and ADA2, and headache was most common among individuals with TREX1 (Figure 3, Table S1).

Stroke

The frequency of clinical stroke ranged from 22% to 52% for 6 of 7 genes (COL4A2, 22% [9/41]; HTRA1homZ, 30% [13/44]; ADA2, 33% [115/346]; COL4A1, 41% [161/390]; CTSA, 50% [7/14]; HTRA1HetZ, 52% [43/82]), while only 9% (11/123) of TREX1 individuals were reported to have suffered a clinical stroke. Hemorrhagic events (ICH, porencephaly, and intraventricular hemorrhage) were the most commonly reported stroke type among COL4A1/2 individuals, affecting 73% (118/161) and 100% (9/9) of stroke cases, respectively. Ischemic events (including arterial and venous ischemic stroke, transient ischemic attacks, and ocular
vascular occlusions) were most common for all other genes and were reported in 54% to 100% of stroke cases (HTRAL{HomoZ}, 54% [7/13]; ADA2, 61% [70/115]; HTRAL{HetZ}, 62% [27/43]; TREX1, 82% [9/11]; CTSA, 100% [7/7]), although hemorrhagic events also occurred in a substantial minority.

### Cognitive Features

The frequency of cognitive features ranged from 27% to 64% for 6 of 7 genes (COL4A2, 27% [11/41]; TREX1, 29% [36/123]; COL4A1, 33% [128/390]; HTRAL{HetZ}, 56% [46/82]; HTRAL{HomZ}, 64% [28/44]; and CTSA, 64% [9/14]), while only 2% [7/346] of individuals with ADA2 were reported to have cognitive features. Developmental delay was present in over 80% of individuals with COL4A1/2 with cognitive features; however, no cases of developmental delay were reported for other genes. For other genes, publications were generally lacking in detail, so we could not draw conclusions about the nature and severity of cognitive decline (ie, cognitive impairment versus dementia).

### Psychiatric Features

The frequency of psychiatric features ranged from 22% to 57% for 4 of 7 genes (HTRAL{HetZ}, 22% [18/82]; TREX1, 29% [36/124], HTRAL{HomZ}, 32% [14/44], and CTSA, 57% [8/14], in ascending order of frequency). The most commonly reported psychiatric features were depression, followed by irritability or agitation. In contrast, only 2% (8/390) of individuals with COL4A1 reported psychiatric features, and no psychiatric features were reported among individuals with COL4A2 and ADA2 (Table S1).

### Headache

Headache was reported in 31% (38/123) of TREX1 individuals and 43% (6/14) of CTSA individuals, with >80% of headache cases being specified as migraine. For all other genes, the frequency of headache ranged from 2% to 10%.

### Other Clinical Cerebral Phenotypes

Thirty-two percent of individuals with COL4A1/2 (123/390 and 13/41, respectively) were reported to
have suffered a seizure or have epilepsy. Forty-three percent of individuals with (6/14) CTSA were reported to suffer from vertigo or balance problems of unclear etiology but suggested to signify brain stem and lower cranial nerve involvement.

**Frequency of Radiological Cerebral Phenotypes**

The proportion of individuals with neuroimaging (magnetic resonance imaging [MRI], computed tomography, magnetic resonance angiography, or computed tomography angiography) was 74% (290/390) for COL4A1, 59% (73/123) for TREX1, 100% (44/44) for HTRA1<sup>HomZ</sup>, 76% (31/41) for COL4A2, 34% (119/346) for ADA2, 85% (70/82) for HTRA1<sup>HetZ</sup>, and 100% (14/14) for CTSA. Where neuroimaging was done, it included an MRI scan in 71% to 100% of cases. The rest of this section applies to those with neuroimaging only.

The majority of individuals showed vascular feature(s) on neuroimaging: ≥86% for all genes except ADA2 (62%). Figure 4 shows the proportion of individuals with specific features suggestive of vascular brain disease, and Table S2 shows the breakdown of these features by location and severity.

**Ischemia**

Presence ranged from 0% (COL4A2) to 66% (HTRA1<sup>HetZ</sup>). Ischemia was the most common radiological manifestation for individuals with ADA2 (45%). Location was reported for most individuals (80%), and as expected, where reported, was mainly in deep/lacunar areas. Most individuals (70%) had multiple lesions.

**Intracerebral Hemorrhage**

Presence ranged from 0% (TREX1) to 68% (COL4A2). It was predominantly present in individuals with COL4A1/2. However, ICH was also present in a small minority (7%–10%) of individuals with HTRA1, ADA2, and CTSA. Porencephaly was present in individuals with COL4A1/2 only (61% and 76%, respectively) and intraventricular hemorrhage was present in individuals with COL4A1 only (7%). Location, where reported, was mostly deep. The burden is less clear: Single lesions were common, though a minority of individuals did have multiple lesions.

**White Matter Lesions**

Presence ranged from 3% (ADA2) to 100% (CTSA). WMLs were the most common radiological manifestation for 5 of 7 genes (not COL4A2 and ADA2). Location was poorly reported, though, where reported, was common in the temporal regions in several genes. Individuals with CTSA appear to have lesions mainly in the frontal and parietal regions (though numbers are low). The burden of WMLs, where reported, was mostly severe, though the burden was not reported well (data missing for 51% individuals). The exception to this was individuals with HTRA1<sup>HetZ</sup>, who appear to have less severe WMLs. All individuals with CTSA with WMLs with known location had temporal lobe sparing.

**Microbleeds**

Presence ranged from 1% (TREX1 and ADA2) to 30% (HTRA1<sup>HomZ</sup>). Microbleeds were also common in
individuals with \( \text{HTRA1}^{\text{HetZ}} \) (27%). Location, where reported, was mostly deep. All individuals had multiple lesions where burden was reported.

**Atrophy**
Presence ranged from 0% (\( \text{COL4A2} \)) to 71% (\( \text{CTSA} \)). Location and burden were poorly described overall, and the low numbers make it difficult to make any conclusions.

**Enlarged PVSs**
Presence was infrequent: Enlarged PVSs were present in \( \text{COL4A1} \) (3%), \( \text{HTRA1}^{\text{HetZ}} \) (16%), and \( \text{CTSA} \) (64%) individuals only.

**Calcification**
Presence was infrequent: Calcification was present in individuals with \( \text{COL4A1/2} \) only (12% and 32%, respectively).

**Cerebral Aneurysm**
Present in 36% (13/36) of individuals with \( \text{COL4A1} \), 60% (3/5) with \( \text{COL4A2} \) and 6% (1/17) with \( \text{ADA2} \) (of those with computed tomography angiograms or magnetic resonance angiograms reported).

**Other Radiological Cerebral Phenotypes**
Individuals with \( \text{COL4A1/2} \) were also reported to manifest with schizencephaly (8% [24/290] of individuals with \( \text{COL4A1} \) and 13% [4/31] with \( \text{COL4A2} \)) and cerebellar atrophy (5% [14/290]) of individuals with \( \text{COL4A1} \) and 3% [1/31] with \( \text{COL4A2} \)). Fifteen percent of individuals with \( \text{TREX1} \) (11/73) had pseudotumoral lesions.

**Particular Patterns to Lesion Location or Severity to Help Identify Cases in Practice**
A unique feature of individuals with \( \text{HTRA1}^{\text{HomZ}} \) was the presence of arc-shaped hyperintense lesions from the...
pons to the middle cerebellar peduncles referred to as the “arc sign” (9% [4/44] of individuals) (Figure 5). A unique feature of individuals with HTRAI HetZ was the presence of dilated PVSs in the basal ganglia referred to as “status cribrosum” or “état crible” (13% [9/70] individuals) (Figure 6). Overall, the descriptions provided were not detailed enough to identify further patterns for other genes.

**Vascular Risk Factor Stratification**

Fourteen percent (134/928) of individuals across all genes were reported to have ≥1 vascular risk factors. Of these individuals, 62% (88/134) reported clinical stroke, compared with 34% (272/794) of individuals with no reported risk factors ($P<0.01$), while 78% (104/134) reported vascular features on neuroimaging, compared with 51% (401/794) of individuals with no reported risk factors ($P<0.01$) (Figure 7). The mean (median) age was 43 (48) years for those with ≥1 risk factor, and 22 (17) years for those with no reported risk factors. This analysis excludes individuals for whom data on risk factors or phenotypes were not available on an individual basis.

**Variant Pathogenicity Assessment**

VEP produced results from ≥1 of its subcomponents for 15% to 66% of variants overall (SnpEff, 66%; ClinVar, 15%; SIFT, 60%; and Polymorphism Phenotyping v2, 62%), although there was substantial variability for these estimates across different genes. The percentage of variants with supporting evidence of pathogenicity was high (81%–99%) when studying only the group of variants with data available, this appeared much lower when including all variants regardless of whether VEP was able to process them (12%–65%). Again, there was substantial variability across individual genes (Tables S3 and S4).

**DISCUSSION**

Vascular changes are commonly seen on neuroimaging in individuals with rare variant(s) in cSVD genes. Where data are available, the most frequent radiological manifestations are WMLs and ischemic changes and, as expected, most lesions are deep. Common clinical phenotypes include clinical stroke, psychiatric symptoms, and, most frequently reported, cognitive decline. Overall, radiological vascular phenotypes were more common than clinical neurological phenotypes. However, when interpreting these results, it is important to bear in mind that variation in the mean age of affected individuals may explain some of the differences in phenotypes between genes (eg, increased age is a risk factor for both clinical stroke and vascular cerebral phenotypes on neuroimaging).

Both ICH and ischemic stroke were described for all cSVD genes, although the most common stroke subtype was hemorrhagic for COL4A1/2 and ischemic for the remaining genes. Enlarged perivascular spaces were infrequently reported, which may reflect this feature being less apparent with older imaging modalities, difficult to differentiate from other lesions such as lacunes, or less commonly reported on neuroimaging.

The frequency of both clinical stroke and vascular radiological features on neuroimaging was higher for those with at least 1 vascular risk factor, compared with those with no reported risk factors. However, vascular risk factors were generally poorly reported (therefore, their presence cannot be excluded in most cases), age is highly likely to be a confounding factor, and individuals presenting with stroke/vascular radiological features are more likely to be investigated for vascular risk factors. More research is needed to understand the role for a focused effort on addressing modifiable vascular risk factors in the management of monogenic cSVDs.

We identified only 14 individuals with a putative pathogenic variant in CTSA. This is likely (at least partly) explained by the relatively recent description of its association with cSVD, but the small overall number of affected individuals limit the conclusions that can be drawn about its phenotype associations.

The strengths of our study are (1) a comprehensive search strategy, including foreign-language papers and abstracts; (2) systematic data extraction following a preset spreadsheet with a comprehensive list of
variables to be collected, while also allowing for novel phenotypes to be recorded; and (3) inclusion of several cSVD genes, allowing comparisons to be made across these.

This research also has some limitations. First, reporting for some variables was poor. For example, region of origin as a marker of ethnicity was frequently poorly reported and therefore often had to be assumed on the basis of information such as the location of the authors' institute. It is possible that some true differences between ethnicities may not have been revealed because of incorrect categorization. Furthermore, individuals from African and South American regions were reported rarely (none reported in 5/7 genes; ≤2% of individuals in 2/7 genes). The understudy of these populations, which comprise over a fifth of the world population, may limit our appreciation of the breadth and frequency of phenotypes that exist. The frequency of neuroimaging reporting was also low for some genes, and it is unknown if neuroimaging was not reported because of lack of positive findings or whether it was not done at all. Second, case reports and case series have many inherent biases that are difficult to control for (eg, testing bias, publication bias, and reporting bias). In addition, the case reports included in this research appeared to lack use of a reporting structure. Current guidelines such as CARE (CAse REports)24,25 do not work so well in the field of rare genetic diseases, so new, tailored guidelines could help improve the consistency of reporting.

Figure 6. Example of “état crible” on MRI imaging. Reprinted with permission from Pati et al [23] Copyright 2018, Springer.

The frequency profile of clinical cerebral phenotypes associated with monogenic cSVDs suggests that it is important to consider a broader spectrum of manifestations when identifying potential patients for genetic testing. Specifically, cognitive involvement appeared even more frequently than clinical stroke for several genes. Our results also show that in monogenic cSVD a radiological vascular phenotype is described more frequently than clinical cerebral phenotypes, suggesting a potential benefit of radiological screening, both for patients and for at-risk family members.

Mancuso et al26,27 and Guéy et al26,27 provide expert recommendations regarding indications for monogenic cSVD testing in a clinical context. Our work broadly supports these existing recommendations, including “red flag” suggestive clinical and radiological features and age of onset for each gene.

It is also notable that across several monogenic cSVDs, WMLs were commonly identified in the temporal region, a feature that has previously been associated with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (caused by NOTCH3 mutations). 28 It is therefore important to also consider other cSVD genes in the presence of this feature.

Finally, according to OMIM (https://www.omim.org), headache is a known phenotype associated with TREX1 rare variants, thus its high frequency in individuals with TREX1 was expected. However, other genes associated in OMIM with headache (COL4A1, ADA2, and HTRA1) were not found to have a clear association with this phenotype in our review. Forty-three percent of individuals with CTSA (albeit among a total of only 14 individuals) also reported headache, which is more than the expected population prevalence of 15%,29 suggesting a potentially novel associated phenotype. Epilepsy was another common phenotype in COL4A1/2, as suggested by OMIM and previous literature.30
VEP predicted 81% to 99% of the processed variants to have a high likelihood of being pathogenic. However, since these percentages are calculated only among variants with data available, this introduces a bias, as some variants without data (e.g., synonymous single-nucleotide polymorphisms) have a lower prior likelihood of being pathogenic. Adjusting these calculations to include all variants resulted in only 12% to 65% of variants having supporting evidence of pathogenicity, with substantial variability for results across individual genes. Also, it is possible that some variants have been submitted to ClinVar on the basis of the same case report/case series included in our review. This makes it difficult to draw robust conclusions about included variants’ pathogenicity.

The findings summarized here have potential clinical implications for the diagnosis and follow-up of monogenic cSVDs, especially in conjection with previous data of associated extracerebral phenotypes. Having said this, to get a more comprehensive and less biased overview of the clinical and radiological consequences of monogenic cSVDs, further work should address these same questions using a genotype-first approach (i.e., studying this in a population-based setting and among individuals selected on the basis of carrying the variant of interest, regardless of their phenotype). The emergence of prospective population-based studies with biosamples yielding genetic data at scale, such as the UK Biobank (https://www.ukbiobank.ac.uk), will make this possible and complement our study findings.

In summary, we found that individuals with rare variant(s) in our genes of interest appear to develop vascular features on neuroimaging. Clinical stroke and cognitive and psychiatric features are also common. The phenotype profiles appear to differ across monogenic cSVD genes; however, these results may be affected by age and other biases inherent to case reports. In the future, better characterization of associated phenotypes, as well as insights from population-based studies, should improve our understanding of monogenic cSVD to inform genetic testing, guide clinical management, and help unravel underlying disease mechanisms.

ARTICLE INFORMATION
Received February 1, 2022; accepted April 19, 2022.

Affiliations
Medical School (E.W., S.T., L.Y.C., V.G.C., E.L.); Centre for Medical Informatics, Usher Institute (A.C.F., D.E.H., T.W., C.S., K.R.); and Centre for Clinical Brain Sciences (T.W., J.W.), University of Edinburgh, Edinburgh, United Kingdom; NHS Greater Glasgow and Clyde, Glasgow, United Kingdom (B.W.); NHS Lothian, Edinburgh, United Kingdom (K.W.); BHF Data Science Centre, London, United Kingdom (C.S.); and UK Dementia Research Institute Centre, University of Edinburgh, Edinburgh, United Kingdom (J.W.).

Acknowledgments
Mr Aidan Hutchison developed a database for data storage; Dr Michael Poon translated full texts.

Sources of Funding
Dr Wardlaw: UK Dementia Research Institute Centre with funding received from Dementia Research Institute Ltd, UK Medical Research Council, Alzheimer’s Society, Alzheimer’s Research UK. Dr Rannikmäe: Rutherford fellowship MR/S004130/1. Dr Ferguson: British Heart Foundation award RE/18/S/34216, MR/S004130/1.

Disclosures
None.

Supplemental Material
Data S1 Tables S1–S4

REFERENCES
1. Pantoni L. Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges. Lancet Neurol. 2010;9:689–701. doi: 10.1016/S1474-4422(10)70104-8
2. Wardlaw JM, Smith EE, Biessels GJ, Cordonnier C, Fazekas F, Frayne R, Lindley RI, O’Brien JT, Barkhof F, Benavente OR, et al. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. Lancet Neurol. 2013;12:822–838. doi: 10.1016/S1474-4422(13)70124-8
3. Shi Y, Wardlaw JM. Update on cerebral small vessel disease: a dynamic whole-brain disease. Stroke Vasc Neurol. 2016;1:83–92. doi: 10.1136/svn-2016-000335
4. Joutel A, Corpechot C, Ducros A, Vahedi K, Chabriat H, Mouton P, Alamowitch S, Domenga V, Cécillon M, Marechall E, et al. Notch3 mutations in CADASIL, a hereditary adult-onset condition causing stroke and dementia. Nature. 1996;383:707–710. doi: 10.1038/383707a0
5. Rannikmäe K, Henshall DE, Thriviprol S, Giri Kong Q, Chong M, Grami N, Kuan I, Wilkinson T, Wilson B, Wilson K, et al. Beyond the brain: systematic review of extracerebral phenotypes associated with monogenic cerebral small vessel disease. Stroke. 2020;51:3007–3017. doi: 10.1161/STROKEAHA.120.029517
6. Giau VV, Bagijnisky E, Youn YC, An SSA, Kim SY. Genetic factors of cerebral small vessel disease and their potential clinical outcome. Int J Mol Sci. 2019;20:4298. doi: 10.3390/jms20172498
7. Dicghans M, Pult SL, Rosand J. Stroke genetics: discovery, biology, and clinical applications. Lancet Neurol. 2019;18:587–599. doi: 10.1016/S1474-4422(19)30043-2
8. Joutel A, Faraci FM. Cerebral small vessel disease: insights and opportunities from mouse models of collagen IV-related small vessel disease and cerebral autosomal dominant arteriopathy with subcortical infarcts and leuocencephalopathy. Stroke. 2014;45:1215–1221. doi: 10.1161/STROKEAHA.113.002878
9. Rannikmäe K, Sivakumaran V, Millar H, Malik R, Anderson CD, Chong M, Dave T, Falcone GJ, Fernandez-Cadenas I, Jimenez-Conde J, et al. COL4A2 is associated with lacunar ischemic stroke and deep ICH: meta-analyses among 21,500 cases and 40,600 controls. Neurology. 2017;89:1830–1839.
10. Mishra A, Chauhan G, Violeteau M-H, Vojnovic D, Jian X, Bis JC, Li S, Saba Y, Grenier-Boles B, Yang Q, et al. Association of variants in HTRA1 and NOTCH3 with MRI-defined extremes of cerebral small vessel disease in older subjects. Brain. 2019;142:1009–1023. doi: 10.1093/brain/awx024
11. Schmidt H, Zegning M, Wittgen M, Freudenberg P, Petrovic K, Cavalieri M, Gider P, Enzinger C, Fornage M, Debette S, et al. Genetic variants of the NOTCH3 gene in the elderly and magnetic resonance imaging correlates of age-related cerebral small vessel disease. Brain. 2011;134(Pt 11):3384–3397. doi: 10.1093/brain/awr252
12. Rutten-Jacobs LCA, Traylor M, Adib-Samii P, Thvls V, Sudlow C, Rothwell PM, Boncoragilo G, Dichgans M, Bevan S, Meschia J, et al. Common NOTCH3 variants and cerebral small-vessel disease. Stroke. 2015;46:1482–1487. doi: 10.1161/STROKEAHA.114.008540
13. Rannikmäe K, Whittaker E, Henshall D, Thriviprol S, Chong L, Wardlaw J, Sudlow C. A systematic review of cerebral phenotypes associated with mutations in Mendelian cerebral small vessel disease genes. PROSPERO 2020 CRD42020196720. Available at: https://www.crd.york.ac.uk/prosporo/display_record.php?ID=CRD42020196720. Accessed May 21, 2022.
14. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Muirrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71. doi: 10.1136/bmj.n71

15. McLaren W, Gil L, Hunt SE, Riat HS, Ritchie GR, Thomann A, Flicek P, Cunningham F. The ensembl variant effect predictor. Genome Biol. 2016;17:122. doi: 10.1186/s13059-016-0074-4

16. Cingolani P, Platts A, Le Wang L, Coon M, Nguyen T, Wang L, Land SJ, Lu X, Ruden DM. A program for annotating and predicting the effects of single nucleotide polymorphisms, SnpEff: SNPs in the genome of Drosophila melanogaster strain w1118; iso-2; iso-3. Fly (Austin). 2012;6:80–92. doi: 10.4161/fly.19496

17. Landrum MJ, Lee JM, Benson M, Brown GR, Chao C, Chitipiralla S, Gu B, Hart J, Hoffman D, Jiang W, et al. ClinVar: improving access to variant interpretations and supporting evidence. Nucleic Acids Res. 2018;46:D1062–D1067. doi: 10.1093/nar/gky1153

18. Sim NL, Kumar P, Hu J, Henikoff S, Schneider G, Ng PC. SIFT web server: predicting effects of amino acid substitutions on proteins. Nucleic Acids Res. 2012;40:W452–W457. doi: 10.1093/nar/gks539

19. Adzhubei IA, Schmidt S, Peshkin L, Ramensky VE, Gerasimova A, Bork P, Kondrashov AS, Sunyaev SR. A method and server for predicting damaging missense mutations. Nat Methods. 2010;7:248–249. doi: 10.1038/nmeth0410-248

20. Nozaki H, Sekine Y, Fukutake T, Nishimoto Y, Shimoe Y, Shirata A, Yanagawa S, Hirayama M, Tamura M, Nishizawa M, et al. Characteristic features and progression of abnormalities on MRI for CARASIL. Neurology. 2015;85:459–463. doi: 10.1212/WNL.0000000000001803

21. Groeschel S, Chong WK, Surtees R, Hanefeld F. Vruchtw-Robin spaces on magnetic resonance images: normative data, their dilatation, and a review of the literature. Neuroradiology. 2006;48:745–754. doi: 10.1007/s00234-006-0112-1

22. Yu Z, Cao S, Wu A, Yue H, Zhang C, Wang J, Xia M, Wu J. Genetically confirmed CARASIL: case report with novel HTRA1 mutation and literature review. World Neurosurg. 2020;143:121–128. doi: 10.1016/j.wneu.2020.05.128

23. Patti AR, Battisti C, Taglia I, Galluzzi P, Bianchi M, Federico A. A new case of autosomal dominant small vessel disease carrying a novel heterozygous mutation in HTRA1 gene: 2-year follow-up. Neurol Sci. 2018;39:1479–1481. doi: 10.1007/s10072-018-3294-5

24. Gagnier JJ, Kienle G, Atmam DG, Moher D, Sox H, Riley D; CARE Group. The CARE guidelines: consensus-based clinical case reporting guideline development. Glob Adv Health Med. 2013;2:38–43. doi: 10.7453/gahmj.2013.008

25. Riley DS, Barber MS, Kienle GS, Aronson JK, von Schoen-Angerer T, Tugwell P, Kiene H, Heifand M, Atmam DG, Sox H, et al. CARE guidelines for case reports: explanation and elaboration document. J Clin Epidemiol. 2017;89:218–235. doi: 10.1016/j.jclinepi.2017.04.026

26. Mancuso M, Arnold M, Bersano A, Burlina A, Chabriat H, Debette S, Enzinger C, Federico A, Filla A, Finsterer J, et al. Monogenic cerebrovascular small-vessel diseases: diagnosis and therapy. Consensus recommendations of the European Academy of Neurology. Eur J Neurol. 2020;27:909–927. doi: 10.1111/ene.14183

27. Guey S, Lesnik Oberstein SAJ, Tournier-Lasserve E, Chabriat H. Hereditary cerebral small vessel diseases and stroke: a guide for diagnosis and management. Stroke. 2021;52:3025–3032. doi: 10.1161/STROKEAHA.121.032620

28. Mizuta I, Watanabe-Hosomi A, Koizumi T, Mukai M, Hamano A, Tomii Y, Kondo M, Nakagawa M, Tomimoto H, Hirano T, et al. New diagnostic criteria for cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy in Japan. J Neurol Sci. 2017;381:62–67. doi: 10.1016/j.jns.2017.08.009

29. GBD 2016 Headache Collaborators. Global, regional, and national burden of migraine and tension-type headache, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol. 2018;17:954–976. doi: 10.1016/S1474-4422(18)30322-3

30. Zagaglia S, Selch C, Nisevic JR, Mei D, Michalak Z, Hernandez-Hernandez L, Kirthika S, Vezygroulou K, Varadkar SM, Pepler A, et al. Neurologic phenotypes associated with COL4A1/2 mutations: expanding the spectrum of disease. Neurology. 2018;91:e2078–e2088. doi: 10.1212/WNL.0000000000006567
SUPPLEMENTAL MATERIAL
Supplemental Methods: Decisions and Assumptions made when extracting data

Demographic data

- Age: sometimes specific ages weren’t reported but rather an approximate age or greater/less than a particular age was provided. In these cases we took a best estimation, erring towards overestimating age in some cases so as to minimise overestimation of the burden of the disease in younger brains. For example: <1 = 0, <2 = 1, <27 = 26, ≤26 = 26, early 50s = 52, mid-40s = 45.

Clinical data

- Clinical stroke classification required reporting of symptoms, i.e. not just radiological description
- Intellectual disability was classified under developmental delay

Radiology data

- When scan findings only described ‘hemosiderin deposits’ we did not take it to mean a confirmed bleed or microbleed
- Cerebral matter loss in <18 year old was recorded as ‘other’ rather than ‘atrophy’
- If a scan was described as showing ‘stable findings’/‘no changes’ or equivalent, we marked the scan as showing the same pathology as the previous scan of the same patient
- In general, author interpretations which used words such as ‘probable’ or ‘suggests’ were taken to mean the feature was present, while author interpretations which used words such as ‘possible’ or ‘might be’ were not sufficient to consider the feature present
- We took ‘periventricular gliosis’ to mean white matter lesions
- We classified haemorrhage at the splenium of corpus callosum as ‘deep’
- We took ‘Hyperintense signal adjacent to the horn of the lateral ventricle’ to mean periventricular white matter lesions
- External capsule, internal capsule, centrum semiovale and corona radiata locations qualified as deep
- Punctate hemorrhages were taken to mean brain microbleeds
- Regarding severity of white matter lesions, we assumed the following:
  - ‘Severe’ when described as: extensive, diffuse, severe, widespread, confluent, Fazekas score 3, disseminated
  - ‘Not severe’ when described as subtle, early/beginning confluent, limited, moderate, mild, weak, Fazekas score 1 or 2, punctiform
- If a scan was implied but not explicitly stated, we decided whether it was more likely a scan was done than not and assumed based on that – e.g. “haemorrhage in the right frontal area” was taken to mean a scan had been done
- We took a ‘petechial spot’ to mean a microbleed
- We took porencephalic cysts to be a subcategory of intracerebral haemorrhage
Search Strategy

1. CADASIL/

2. (CADASIL or "Cerebral autosomal dominant arterio$ with subcortical infarct$ and leukoencephalopathy" or (Dementia and hereditary and multi?infarct) or "Familial vascular leukoencephalopathy" or CASIL or "Cerebral arterio$ with subcortical infarct$ and leukoencephalopathy" or "Chronic familial vascular encephalopathy" or "Familial disorder with subcortical ischemic stroke$" or "Agnogenic medial arteriopathy" or "FamilialBinswanger$ disease" or (cerebral and autosomal dominant and arterio$ and infarct$ and leukoencephalopathy)).af.

3. (CARASIL or "Maeda$ syndrome" or "Cerebral autosomal recessive arterio$ with subcortical infarct$ and leukoencephalopathy" or ("Subcortical Vascular Encephalopathy" and Progressive) or "Cerebrovascular Disease With Thin Skin Alopecia And Disc Disease" or "Nemoto disease" or (cerebral and autosomal recessive and arterio$ and infarct$ and leukoencephalopathy) or "Familial young adult onset arterio$ leukoencephalopathy with alopecia and lumbago").af.

4. ((COL4A1$ and (leukoencephalopathy or small vessel disease or autosomal dominant or infantile hemiparesis or retinal arter$ tortuosity or RATOR or PADMAL or "pontine autosomal dominant microangiopathy and leukoencephalopathy" or Walker Warburg or porencephaly 1 or "small vessel disease of the brain with or without ocular abnormalities" or BSVD)) or HANAC or (hereditary angio$ and nephropath$ and aneurysm$ and cramp$) or (autosomal dominant or familial or hereditary) and (h?ematuria and Retinal Arter$ Tortuosity)) or ("Autosomal dominant familial porencephaly" or "Hereditary multi infarct dementia" or HEMID or hMID) or (multi-infarct dementia and Swedish) or "Nonsyndromic autosomal dominant congenital cataract").af.

5. Muscle Cramp/ and Raynaud Disease/

6. (COL4A2 and (Porencephaly or stroke or Microbleed$ or h?emorrhage or leukoencephalopathy or small vessel disease or autosomal recessive or infantile hemiparesis or retinal arter$ tortuosity)).af.

7. (RVCL or "Retinal vasculopathy with cerebral leukodystrophy" or (Retinal vascul$ and (hereditary or familial)) or ((Cerebroretinal Vasculopathy and Hereditary) or "hereditary vascular retinopathy") or "Grand-Kaine-Fulling syndrome" or HERNS or Hereditary Systemic Angiopathy or (hereditary and endotheliopathy and retin$ and nephro$ and stroke$) or (hereditary and retin$ and (raynaud$ or migraine)) or ADRVCL or (Autosomal Dominant and Retin$ and (leukodystrophy or leukoenchalopathy))).af.

8. ("Early-onset stroke and vasculopathy associated with mutations in ADA2" or (Stroke and vasc$ and ADA2) or ((deficien$ and (ADA 2 or ADA2 or adenosine deaminase-2)) or DADA2 or DADA 2 or (Vasculitis and ADA2 deficien$)) or Sneddon Syndrome or (Polyarteritis nodosa and Childhood onset)).af.
9. (CARASAL or (Cathepsin A related arteriopathy with stroke? and leukoencephalopathy)).af.
10. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11. (NOTCH?3 or Notch 3 or "Neurogenic locus notch homolog protein 3").af.
12. (TREX?1 or TEx 1 or "Three prime repair exonuclease 1").af.
13. (COL4A1 or COL4A2 or COL4 A1 or COL4 A2 or "COL4 A 1" or "COL4 A 2" or "COL 4 A1" or "COL 4 A2").af.
14. (Collagen and ("type IV" or "type 4") and (alpha?1 or alpha?2 or alpha 1 or alpha 2)).af.
15. Collagen Type IV/
16. (alpha?1 or alpha?2 or alpha 1 or alpha 2).af.
17. 15 and 16
18. (HTRA?1 or HTRA 1 or "HtrA serine peptidase 1" or "HtrA serine protease 1").af.
19. (CECR?1 or CECR 1 or "Cat eye syndrome critical region protein 1" or "adenosine deaminase 2" or ADA2 or ADA 2).af.
20. (FOXC?1 or FOX C1 or FOXC 1 or "FOX C 1" or "forkhead box C?1" or "Forkhead box C 1").af.
21. (PITX?2 or PITX 2 or "paired-like homeodomain 2" or "pituitary homeobox 2" or "Paired-like homeodomain transcription factor 2").af.
22. (Cathepsin?A or Cathepsin A or CathA or Cath A or CTSA).af.
23. 11 or 12 or 13 or 14 or 17 or 18 or 19 or 20 or 21 or 22
24. exp Cerebral Small Vessel Diseases/
25. exp Cerebrovascular Disorders/
26. exp stroke/
27. exp dementia, vascular/
28. Brain Diseases/
29. exp basal ganglia cerebrovascular disease/
30. exp brain ischemia/
31. exp intracranial arterial diseases/
32. exp Cerebral Hemorrhage/
33. exp intracranial hemorrhages/
34. leukomalacia, periventricular/
35. stroke, lacunar/
36. Leukoaraiosis/
37. Leukoencephalopathies/
38. White Matter/
39. Infarction/
40. ("Cerebral Small Vessel Disease?" or cerebrovascular).af.
41. (White matter hyperintensit$ or WMH$ or White matter MR hyperintensit$ or White matter magnetic resonance hyperintensit$ or Subcortical hyperintensit$ or White matter
lesion? or WML or Hyper intensiti$ or Leukodystroph$ or Leukoaraiosis or Leukomalacia or
White Matter Change? or WMC? or White Matter Disease or WMD or White matter damage
or Grey matter hyperintensiti$ or Brainstem hyperintensiti$ or Subcortical hyperintensiti$ or
White matter hypoa$u$uation? or White matter hypodensi$ or Leukoencephalopath$).af.
42. (Subcortical infarct? or Cerebral infarct$ or Brain infarct$ or Silent brain infarct$ or
Striatocapsular infarct$ or Lacunar infarct$ or Lacune? or Lacunar stroke? or Lacunar
syndrome or Stroke? or Vascular lesion?).af.
43. (Microbleed? or Cerebral Microbleed or CMB? or Hypointense lesion? or Subcortical
H?emorrhage or Intracerebral h?emorrhage or Cortical siderosis or Superficial siderosis).af.
44. (Perivascular space? or Virchow Robin space? or Type 3 lacune? or Etat crible).af.
45. (Brain atrophy or Cerebral atrophy or Global atrophy or Corpus callosum atrophy or
Central atrophy or Mesencephalic atrophy or Hippocampal atrophy or Cortical thinning).af.
46. 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or
39 or 40 or 41 or 42 or 43 or 44 or 45
47. 23 and 46
48. 10 or 47
49. limit 48 to humans
50. remove duplicates from 49
## PRISMA 2020 Checklist

| Section and Topic | Item # | Checklist Item | Location where Item is reported |
|-------------------|--------|----------------|----------------------------------|
| TITLE             | 1      | Identify the report as a systematic review. | p.0 |
| ABSTRACT          | 2      | See the PRISMA 2020 for Abstracts checklist. | p.1-2 |
| INTRODUCTION      | 3      | Describe the rationale for the review in the context of existing knowledge. | p.3-4 |
|                   | 4      | Provide an explicit statement of the objective(s) or question(s) the review addresses. | p.4 |
| METHODS           | 5      | Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses. | p.5-6 |
|                   | 6      | Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted. | p.4 |
|                   | 7      | Present the full search strategies for all databases, registers and websites, including any filters and limits used. | Suppl. |
|                   | 8      | Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each record retrieved, whether they worked independently, and if applicable, details of automation tools used in the process. | p.5 |
|                   | 9      | Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process. | p.6-7 |
|                   | 10a    | List and define all outcomes for which data were sought. Specify whether all outcomes that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect. | p.8-7, Suppl. |
|                   | 10b    | List and define all additional variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or uncertain information. | p.8-7, Suppl. |
|                   | 11     | Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process. | p.15 para2 |
|                   | 12     | Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results. | N/A |
| Synthesis methods | 13a    | Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item 4)). | p.7 |
|                   | 13b    | Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions. | p.7 |
|                   | 13c    | Describe any methods used to tabulate or visually display results of individual studies and syntheses. | p.7 |
|                   | 13d    | Describe any methods used to synthesise results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software packages used. | p.7 |
|                   | 14     | Describe any assumptions made about any missing or uncertain information. | N/A |
|                   | 15     | Describe any methods used to assess certainty (or confidence) in the body of evidence for each outcome. | N/A |
|                   | 16     | Describe any methods used to assess certainty (or confidence) in the body of evidence for each outcome. | N/A |
|                   | 17     | Cite these studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded. | Suppl. |
| RESULTS           | 18     | Cite each included study and present its characteristics. | Fig. 1, Suppl. |
| Study selection   | 19     | Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram. | p.8, Fig. 1 |
| Study characteristics | 20   | Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded. | p.8, Fig. 1 |
| Risk of bias in studies | 21 | Present assessments of risk of bias for each included study. | N/A |
| Results of individual studies | 22 | For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots. | Suppl. |
| Results of syntheses | 23 | For each study, briefly summarise the characteristics and risk of bias among contributing studies. | Table 1, Fig. 2, 3 |
|                   | 24a    | For each study, briefly summarise the characteristics and risk of bias among contributing studies. | Table 1, Fig. 2, 3 |
|                   | 24b    | Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect. | N/A |
|                   | 24c    | Present results of all sensitivity analyses conducted to assess robustness of the synthesised results. | N/A |
|                   | 25     | Describe any assumptions made about any missing or uncertain information. | N/A |
|                   | 26     | Describe any assumptions made about any missing or uncertain information. | N/A |
|                   | 27     | Present assessments of risk of bias due to missing results in a synthesis (arising from reporting biases). | p.15 para 2 |
| DISCUSSION        | 28     | Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed. | N/A |
|                   | 29     | Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed. | N/A |
| OTHER INFORMATION | 30     | Provide a general interpretation of the results in the context of other evidence. | p.14-17 |
| Registration and protocol | 31 | Discuss any limitations of the evidence included in the review. | p.15-16 |
|                   | 32     | Discuss any limitations of the review process used. | p.16-17 |
|                   | 33     | Discuss implications of the results for practice, policy, and future research. | N/A |
| Availability of data, code and other materials | 34 | Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review. | Suppl. |

*For more information, visit [http://www.prisma-statement.org/]*
Table S1. Frequency and Subtypes of Cerebral Clinical Features

|                  | COL4A1 (N=390) | TREX1 (N=123) | HTRA1<sup>HomZ</sup> (N=44) | COL4A2 (N=41) | ADA2 (N=346) | HTRA1<sup>HetZ</sup> (N=82) | CTSA (N=14) |
|------------------|----------------|---------------|-------------------------------|---------------|---------------|-------------------------------|-------------|
| **Unknown/ absent** | 59 (229/390) | 91 (112/123) | 70 (31/44) | 78 (32/41) | 67 (231/346) | 48 (39/82) | 50 (7/14) |
| Present          | 41 (161/390) | 9 (11/123) | 30 (13/44) | 22 (9/41) | 33 (115/346) | 52 (43/82) | 50 (7/14) |
| **Ischaemic**    | 15 (24/161) | 82 (9/11) | 54 (7/13) | 0 (0/9) | 53 (61/115) | 53 (23/43) | 71 (5/7) |
| **Ischaemic**    | 15 (24/161) | 73 (8/11) | 46 (6/13) | 11 (1/9) | 55 (63/115) | 44 (19/43) | 43 (3/7) |
| **TIA**          | 2 (3/161) | 0 (0/11) | 8 (1/13) | 0 (0/9) | 5 (6/115) | 14 (6/43) | 43 (3/7) |
| **Eye infarction** | 0 (0/161) | 9 (1/11) | 0 (0/13) | 0 (0/9) | 3 (4/115) | 0 (0/43) | 14 (1/7) |
| **Venous**       | 0 (0/161) | 0 (0/11) | 0 (0/13) | 0 (0/9) | 0 (0/115) | 0 (0/43) | 14 (1/7) |
| **Haemorrhagic** | 72 (116/161) | 0 (0/11) | 8 (1/13) | 89 (8/9) | 12 (14/115) | 5 (2/43) | 0 (0/7) |
| **ICH**          | 32 (51/161) | 0 (0/11) | 8 (1/13) | 22 (2/9) | 20 (23/115) | 14 (6/43) | 29 (2/7) |
| **IVH**          | 4 (7/161) | 0 (0/11) | 0 (0/13) | 0 (0/9) | 0 (0/115) | 0 (0/43) | 0 (0/7) |
| **Porencephalic cyst** | 47 (76/161) | 0 (0/11) | 0 (0/13) | 78 (7/9) | 0 (0/115) | 0 (0/43) | 0 (0/7) |
| **Ischaemic and haemorrhagic** | 1 (2/161) | 0 (0/11) | 0 (0/13) | 11 (1/9) | 8 (9/115) | 9 (4/43) | 29 (2/7) |
| **Unspecified/ no detail** | 12 (19/161) | 18 (2/11) | 38 (5/13) | 0 (0/9) | 27 (31/115) | 33 (14/43) | 0 (0/7) |
| **Unknown/ absent** | 67 (262/390) | 71 (87/123) | 36 (16/44) | 73 (30/41) | 100 (346/346) | 44 (36/82) | 36 (5/14) |
| Present          | 33 (128/390) | 29 (36/123) | 64 (28/44)* | 27 (11/41) | 0 (0/346) | 56 (46/82) | 64 (9/14) |
| Present (≥18 y)  | 23 (30/131) | 34 (36/106) | 65 (20/31) | 0 (0/13) | 0 (0/85) | 62 (46/74) | 64 (9/14) |
| Dementia*        | 3 (4/128) | 0 (0/36) | 32 (9/28) | 0 (0/11) | 0 (0/0) | 13 (6/46) | 0 (0/9) | 13 (6/46) | 0 (0/9) |
| Cognitive impairment- no ADL impact* | 2 (2/128) | 0 (0/36) | 0 (0/28) | 0 (0/11) | 0 (0/0) | 15 (7/46) | 0 (0/9) |
|-------------------------------------|-----------|---------|---------|---------|-------|---------|------|
| 7 (2/30) | 0 (0/36) | 0 (0/20) | 0 (0/0) | 0 (0/0) | 0 (0/28) | 0 (0/0) | 0 (0/9) |
| Cognitive impairment- no ADL detail* | 12 (15/128) | 97 (35/36) | 68 (19/28) | 0 (0/11) | 0 (0/0) | 65 (30/46) | 100 (9/9) |
| (22/30) | 100 (35/36) | 55 (11/20) | 0 (0/0) | 0 (0/0) | 0 (0/0) | 65 (30/46) | 100 (9/9) |
| Subjective cognitive decline* | 0 (0/128) | 0 (0/36) | 0 (0/28) | 0 (0/11) | 0 (0/0) | 7 (3/46) | 0 (0/9) |
| 73 (0/30) | 0 (0/36) | 0 (0/20) | 0 (0/0) | 0 (0/0) | 0 (0/0) | 7 (3/46) | 0 (0/9) |
| Developmental delay | 83 (106/128) | 0 (0/36) | 0 (0/28) | 100 (11/11) | 0 (0/0) | 0 (0/46) | 0 (0/9) |

**PSYCHIATRIC FEATURES**

| Unknown/ absent | 98 (382/390) | 71 (87/123) | 68 (30/44) | 100 (41/41) | 100(346/346) | 78 (64/82) | 43 (6/14) |
| Present | 2 (8/390) | 29 (36/123) | 32 (14/44) | 0 (0/41) | 0 (0/346) | 22 (18/82) | 57 (8/14) |
| Psychosis | 0 (0/8) | 6 (2/36) | 7 (1/14) | 0 (0/0) | 0 (0/0) | 6 (1/18) | 0 (0/8) |
| Depression symptoms | 25 (2/8) | 17 (6/36) | 64 (9/14) | 0 (0/0) | 0 (0/0) | 67 (12/18) | 88 (7/8) |
| Anxiety | 0 (0/8) | 3 (1/36) | 14 (2/14) | 0 (0/0) | 0 (0/0) | 0 (0/18) | 0 (0/8) |
| Irritability/ agitation | 25 (2/8) | 8 (3/36) | 64 (9/14) | 0 (0/0) | 0 (0/0) | 0 (0/18) | 13 (1/8) |
| Emotional lability | 13 (1/8) | 0 (0/36) | 21 (3/14) | 0 (0/0) | 0 (0/0) | 28 (5/18) | 13 (1/8) |
| OCD | 0 (0/8) | 0 (0/36) | 0 (0/14) | 0 (0/0) | 0 (0/0) | 6 (1/18) | 0 (0/8) |
| Unspecified/ no detail | 0 (0/8) | 78 (28/36) | 0 (0/14) | 0 (0/0) | 0 (0/0) | 0 (0/18) | 0 (0/8) |

**HEADACHE**

| Unknown/ absent | 93 (362/390) | 69 (85/123) | 95 (42/44) | 98 (40/41) | 95 (329/346) | 91 (75/82) | 57 (8/14) |
| Present | 7 (28/390) | 31 (38/123) | 5 (2/44) | 2 (1/41) | 5 (17/346) | 9 (7/82) | 43 (6/14) |
| Migraine | 68 (19/28) | 84 (32/38) | 50 (1/2) | 100 (1/1) | 24 (4/17) | 43 (3/7) | 83 (5/6) |
| Unspecified | 32 (9/28) | 16 (6/38) | 50 (1/2) | 0 (0/1) | 76 (13/17) | 57 (4/7) | 17 (1/6) |

HetZ=heterozygous; HomZ=homozygous/compound heterozygous; N=overall number of individuals; n=number of affected individuals; ADL=activities of daily living; #8 cases with unknown age; * second row: only individuals ≥18 years; assumed Stam et al cohort were all ≥18 y.
|                   | COL4A1 (N=290) | TREX1 (N=73) | HTRA1^{HetZ} (N=44) | COL4A2 (N=31) | ADA2 (N=119) | HTRA1^{HomZ} (N=70) | CTSA (N=14) |
|-------------------|----------------|--------------|----------------------|---------------|--------------|---------------------|-------------|
| **% (n/N)**       |                |              |                      |               |              |                     |             |
| ISCHAEMIA         |                |              |                      |               |              |                     |             |
| Total             |                |              |                      |               |              |                     |             |
| Present           | 16 (47/290)    | 8 (6/73)     | 34 (15/44)           | 0 (0/31)      | 44 (52/119)  | 66 (46/70)          | 57 (8/14)   |
| Unknown/Absent    | 84 (243/290)   | 92 (67/73)   | 66 (29/44)           | 100 (31/31)   | 56 (67/119)  | 34 (24/70)          | 43 (6/14)   |
| **Location**      |                |              |                      |               |              |                     |             |
| Supratentorial     |                |              |                      |               |              |                     |             |
| Deep/lacunar      | 43 (20/47)     | 100 (6/6)    | 53 (8/15)            | 0 (0/0)       | 42 (22/52)   | 46 (21/46)          | 75 (6/8)    |
| Cortical          | 2 (1/47)       | 0 (0/6)      | 0 (0/15)             | 0 (0/0)       | 2 (1/52)     | 2 (1/46)            | 25 (2/8)    |
| Unknown           | 4 (2/47)       | 0 (0/6)      | 20 (3/15)            | 0 (0/0)       | 10 (5/52)    | 15 (7/46)           | 0 (0/8)     |
| Brainstem         | 51 (24/47)     | 0 (0/6)      | 53 (8/15)            | 0 (0/0)       | 44 (23/52)   | 26 (12/46)          | 0 (0/8)     |
| Cerebellum        | 2 (1/47)       | 0 (0/6)      | 0 (0/15)             | 0 (0/0)       | 2 (1/52)     | 0 (0/46)            | 25 (2/8)    |
| Unknown           | 0 (0/47)       | 0 (0/6)      | 0 (0/15)             | 0 (0/0)       | 0 (0/52)     | 0 (0/46)            | 0 (0/8)     |
| Infraentorial      |                |              |                      |               |              |                     |             |
| Any deep          | 83 (39/47)     | 100 (6/6)    | 67 (10/15)           | 0 (0/0)       | 77 (40/52)   | 78 (36/46)          | 100 (8/8)   |
| No deep           | 2 (1/47)       | 0 (0/6)      | 0 (0/15)             | 0 (0/0)       | 0 (0/52)     | 0 (0/46)            | 0 (0/8)     |
| Unknown           | 15 (7/47)      | 0 (0/6)      | 33 (5/15)            | 0 (0/0)       | 23 (12/52)   | 22 (10/46)          | 0 (0/8)     |
| Overall           |                |              |                      |               |              |                     |             |
| Single lesion     | 2 (1/47)       | 33 (2/6)     | 0 (0/15)             | 0 (0/0)       | 37 (19/52)   | 0 (0/46)            | 50 (4/8)    |
| Multiple lesions  | 57 (27/47)     | 50 (3/6)     | 87 (13/15)           | 0 (0/0)       | 56 (29/52)   | 100 (46/46)         | 38 (3/8)    |
| HAEMORRHAGE | Location | Total | Present | Unknown/Absent | Any deep | No deep | Unknown |
|-------------|----------|-------|---------|----------------|----------|---------|---------|
| | | Unknown | 40 (19/47) | 17 (1/6) | 13 (2/15) | 0 (0/0) | 8 (4/52) | 0 (0/46) | 13 (1/8) |
| | | Present | 41 (118/290) | 0 (0/73) | 2 (1/44) | 68 (21/31) | 10 (12/119) | 7 (5/70) | 7 (1/14) |
| | | Unknown/Absent | 59 (172/290) | 100 (73/73) | 98 (43/44) | 32 (10/31) | 90 (107/119) | 93 (65/70) | 93 (13/14) |
| | | Porencephaly | 61 (72/118) | 0 (0/0) | 0 (0/1) | 76 (16/21) | 0 (0/12) | 0 (0/5) | 0 (0/1) |
| | | IVH | 7 (8/118) | 0 (0/0) | 0 (0/1) | 0 (0/21) | 0 (0/12) | 0 (0/5) | 0 (0/1) |
| | | Deep/ lacunar | 25 (29/118) | 0 (0/0) | 0 (0/1) | 14 (3/21) | 50 (6/12) | 40 (2/5) | 100 (1/1) |
| | | Cortical | 2 (2/118) | 0 (0/0) | 0 (0/1) | 0 (0/21) | 8 (1/12) | 0 (0/5) | 0 (0/1) |
| | | Unknown | 13 (15/118) | 0 (0/0) | 0 (0/1) | 10 (2/21) | 42 (5/12) | 0 (0/5) | 0 (0/1) |
| | | Brainstem | 2 (2/118) | 0 (0/0) | 0 (0/1) | 0 (0/21) | 0 (0/12) | 20 (1/5) | 0 (0/1) |
| | | Cerebellum | 6 (7/118) | 0 (0/0) | 100 (1/1) | 0 (0/21) | 0 (0/12) | 0 (0/5) | 0 (0/1) |
| | | Unknown | 0 (0/118) | 0 (0/0) | 0 (0/1) | 0 (0/21) | 0 (0/12) | 0 (0/5) | 0 (0/1) |
| | | Any deep | 56 (36/64) | 0 (0/0) | 100 (1/1) | 60 (3/5) | 50 (6/12) | 60 (3/5) | 100 (1/1) |
| | | No deep | 3 (2/64) | 0 (0/0) | 0 (0/1) | 0 (0/5) | 8 (1/12) | 0 (0/5) | 0 (0/1) |
| | | Unknown | 41 (26/64) | 0 (0/0) | 0 (0/1) | 40 (2/5) | 42 (5/12) | 40 (2/5) | 0 (0/1) |
| Burden     | Single lesion | Multiple lesions | Unknown |
|------------|---------------|------------------|---------|
| Present    | 45 (53/118)   | 39 (46/118)      | 16 (19/118) |
| Unknown/Absent | 0 (0/0)       | 0 (0/1)         | 0 (0/0)            |
| Totals     | 58 (167/290)  | 89 (65/73)       | 96 (67/70)        |

| Location   | Periventricular only | Deep only | Both | Unknown |
|------------|----------------------|-----------|------|---------|
| Present    | 26 (43/167)          | 5 (9/167) | 14 (24/167) | 54 (91/167) |
| Unknown/Absent | 9 (6/65)        | 2 (1/65)   | 2 (1/65)   | 88 (57/65) |
| Totals     | 35 (116/167)         | 7 (11/167) | 21 (9/63)  | 100 (149/167) |

| Region     | Temporal | Frontal | Parietal | Brainstem |
|------------|----------|---------|----------|-----------|
| Present    | 30 (13/43) | 5 (2/43) | 0 (0/5)  | 0 (0/3)   |
| Unknown/Absent | 0 (0/65)  | 5 (2/43) | 0 (0/5)  | 0 (0/3)   |
| Totals     | 49 (33/67) | 35 (13/43) | 12 (8/67) | 93 (13/44) |

| Burden     | Severe | Not severe |
|------------|--------|------------|
| Present    | 35 (59/167) | 12 (20/167) |
| Unknown/Absent | 5 (3/65)      | 3 (2/65)    |
| Totals     | 40 (64/167)  | 15 (22/167) |
| Location      | Total                      | Present                  | Unknown/Absent | Overall                   | Burden   |
|---------------|----------------------------|--------------------------|----------------|---------------------------|----------|
|               | Unknown                    | 53 (88/167)              | 92 (60/65)     | 5 (2/43)                  | 78 (7/9) |
|               | Present                    | 10 (29/290)              | 1 (1/73)       | 30 (13/44)                | 6 (2/31) |
|               | Unknown/Absent             | 90 (261/290)             | 99 (72/73)     | 70 (31/44)                | 94 (29/31)|
| Microbleeds   | Deep/lacunar               | 52 (15/29)               | 0 (0/1)        | 31 (4/13)                 | 50 (1/2) |
|               | Cortical                   | 3 (1/29)                 | 0 (0/1)        | 8 (1/13)                  | 0 (0/2)  |
|               | Unknown                    | 14 (4/29)                | 0 (0/1)        | 46 (6/13)                 | 0 (0/2)  |
|               | Brainstem                  | 21 (6/29)                | 0 (0/1)        | 31 (4/13)                 | 0 (0/2)  |
|               | Cerebellum                 | 10 (3/29)                | 0 (0/1)        | 0 (0/13)                  | 0 (0/2)  |
|               | Unknown                    | 3 (1/29)                 | 0 (0/1)        | 23 (3/13)                 | 0 (0/2)  |
|               | Any deep                   | 69 (20/29)               | 0 (0/1)        | 62 (8/13)                 | 50 (1/2) |
|               | No deep                    | 0 (0/29)                 | 0 (0/1)        | 0 (0/13)                  | 0 (0/2)  |
|               | Unknown                    | 31 (9/29)                | 100 (1/1)      | 38 (5/13)                 | 50 (1/2) |
|               | Single lesion              | 14 (4/29)                | 0 (0/1)        | 0 (0/13)                  | 0 (0/2)  |
|               | Multiple lesions           | 76 (22/29)               | 100 (1/1)      | 85 (11/13)                | 100 (2/2) |
|               | Unknown                    | 10 (3/29)                | 0 (0/1)        | 15 (2/13)                 | 0 (0/2)  |
|                               | Present |           |           |           |           |           |           |
|-------------------------------|---------|-----------|-----------|-----------|-----------|-----------|-----------|
| Total                         | 4 (12/290) | 1 (1/73) | 20 (9/44) | 0 (0/31) | 3 (4/119) | 11 (8/70) | 71 (10/14) |
| Unknown/Absent                | 96 (278/290) | 99 (72/73) | 80 (35/44) | 100 (31/31) | 97 (115/119) | 89 (62/70) | 29 (4/14) |

| Location          | Present |           |           |           |           |           |           |
|-------------------|---------|-----------|-----------|-----------|-----------|-----------|-----------|
| Global            | 25 (3/12) | 0 (0/1) | 0 (0/9) | 0 (0/0) | 25 (1/4) | 25 (2/8) | 0 (0/10) |
| Focal             | 42 (5/12) | 0 (0/1) | 11 (1/9) | 0 (0/0) | 25 (1/4) | 50 (4/8) | 10 (1/10) |
| Unknown           | 33 (4/12) | 100 (1/1) | 89 (8/9) | 0 (0/0) | 50 (2/4) | 25 (2/8) | 90 (9/10) |

| Burden            | Present |           |           |           |           |           |           |
|-------------------|---------|-----------|-----------|-----------|-----------|-----------|-----------|
| Severe            | 42 (5/12) | 0 (0/1) | 0 (0/9) | 0 (0/0) | 0 (0/4) | 0 (0/8) | 0 (0/10) |
| Not severe        | 0 (0/12) | 100 (1/1) | 11 (1/9) | 0 (0/0) | 25 (1/4) | 50 (4/8) | 90 (9/10) |
| Unknown           | 58 (7/12) | 0 (0/1) | 89 (8/9) | 0 (0/0) | 75 (3/4) | 50 (4/8) | 10 (1/10) |

| Total                         | 12 (34/290) | 32 (23/73) | 0 (0/44) | 0 (0/31) | 0 (0/119) | 0 (0/70) | 0 (0/14) |
| Unknown/Absent                | 88 (256/290) | 68 (50/73) | 100 (44/44) | 100 (31/31) | 100 (119/119) | 100 (70/70) | 100 (14/14) |

| Total                         | 3 (8/290) | 0 (0/73) | 0 (0/44) | 0 (0/31) | 0 (0/119) | 16 (1170) | 64 (9/14) |
| Unknown/Absent                | 97 (282/290) | 100 (73/73) | 100 (44/44) | 100 (31/31) | 100 (119/119) | 84 (59/70) | 36 (5/14) |

| Total                         | 36 (13/36) | 0 (0/1) | 0 (0/9) | 60 (3/5) | 6 (1/17) | 0 (0/2) | 0 (0/1) |
| Unknown/Absent                | 64 (23/36) | 100 (1/1) | 100 (9/9) | 40 (2/5) | 94 (16/17) | 100 (2/2) | 100 (1/1) |

HetZ=heterozygous; HomZ=homozygous/compound heterozygous; N=overall number of individuals with neuroimaging; n=number of affected individuals; WML=white matter lesions(s); PVS=perivascular space(s);
Table S3. Variant Effect Predictor Output Summary

| Variant | Number of variants | % variants with info | % pathogenic* among variants with data | % pathogenic* among all variants |
|---------|-------------------|----------------------|--------------------------------------|---------------------------------|
|         | no info | low | moderate* | high* |           |                             |                                         |                                         |
| HTRA1   | 7       | 0   | 35        | 11    | 87%      | 100%                         | 87%                                   |
| ADA2    | 43      | 3   | 24        | 18    | 51%      | 93%                          | 48%                                   |
| COL4A1  | 43      | 0   | 88        | 23    | 72%      | 100%                         | 72%                                   |
| COL4A2  | 1       | 0   | 14        | 1     | 94%      | 100%                         | 94%                                   |
| TREX1   | 21      | 0   | 2         | 8     | 32%      | 100%                         | 32%                                   |
| CTSA    | 1       | 0   | 0         | 0     | 0%       | 0%                           | 0%                                    |
| Total   | 116     | 3   | 163       | 61    | 66%      | 99%                          | 65%                                   |

VARIANT IMPACT/CLASSIFICATION OF SEVERITY (SNPEff)

| Variant | no info | low | moderate* | high* | % variants with info | % pathogenic* among variants with data | % pathogenic* among all variants |
|---------|---------|-----|-----------|-------|----------------------|--------------------------------------|---------------------------------|
| HTRA1   | 30      | 3   | 0         | 0     | 43%                  | 87%                                  | 38%                             |
| ADA2    | 76      | 2   | 1         | 0     | 14%                  | 75%                                  | 10%                             |
| COL4A1  | 150     | 1   | 0         | 0     | 3%                   | 75%                                  | 2%                              |
| COL4A2  | 5       | 0   | 3         | 3     | 69%                  | 73%                                  | 50%                             |
| TREX1   | 29      | 0   | 0         | 1     | 6%                   | 100%                                 | 6%                              |
| CTSA    | 1       | 0   | 0         | 0     | 0%                   | 0%                                   | 0%                              |
| Total   | 291     | 6   | 1         | 3     | 15%                  | 27%                                  | 12%                             |

CLINICAL SIGNIFICANCE (ClinVar)

| Variant | no info | uncertain clinical significance | benign | likely benign | likely pathogenic* | pathogenic* |
|---------|---------|---------------------------------|--------|--------------|-------------------|-------------|
| HTRA1   | 30      | 3                               | 0      | 0            | 5                 | 15          | 43%         | 87%         | 38%         |
| ADA2    | 76      | 2                               | 1      | 0            | 6                 | 3           | 14%         | 75%         | 10%         |
| COL4A1  | 150     | 1                               | 0      | 0            | 0                 | 3           | 3%          | 75%         | 2%          |
| COL4A2  | 5       | 0                               | 0      | 3            | 3                 | 5           | 69%         | 73%         | 50%         |
| TREX1   | 29      | 0                               | 0      | 0            | 1                 | 1           | 6%          | 100%        | 6%          |
| CTSA    | 1       | 0                               | 0      | 0            | 0                 | 0           | 0%          | 0%          | 0%          |
| Total   | 291     | 6                               | 1      | 3            | 15                | 27          | 15%         | 81%         | 12%         |

IMPACT ON PROTEIN FUNCTION (SIFT)

| Variant | no info | tolerated | deleterious* |
|---------|---------|-----------|--------------|
| HTRA1   | 18      | 1         | 34           | 66%         | 97%         | 64%         |
### Impact on Protein Structure and Function (PolyPhen-2)

| Gene   | No Info | Benign | Possibly Damaging* | Probably Damaging* | HTRA1 | ADA2 | COL4A1 | COL4A2 | TREX1 | CTS | Total |
|--------|---------|--------|--------------------|--------------------|-------|------|--------|--------|-------|-----|-------|
|        | no info | benign | possibly          | probably           |       |      |        |        |       |     |       |
|        |         |        | damaging*          | damaging*           | 66%   | 100% | 66%    | 74%    | 94%   | 6%  | 62%   |
| HTRA1  | 18      | 0      | 4                  | 31                 |       |      |        |        |       |     |       |
| ADA2   | 43      | 5      | 1                  | 39                 | 51%   | 89%  | 45%    | 73%    | 94%   | 6%  | 96%   |
| COL4A1 | 40      | 2      | 15                 | 97                 | 66%   | 100% | 66%    | 74%    | 98%   | 0%  | 96%   |
| COL4A2 | 1       | 0      | 4                  | 11                 | 94%   | 100% | 94%    |        |       |     |       |
| TREX1  | 29      | 2      | 0                  | 0                  | 6%    | 0%   | 0%     |        |       |     |       |
| CTS    | 1       | 0      | 0                  | 0                  | 0%    | 0%   | 0%     |        |       |     |       |
| Total  | 132     | 9      | 24                 | 178                | 62%   | 96%  | 59%    |        |       |     |       |

*Category considered to provide supporting evidence for pathogenicity; SnpEff classifies each variant in one of the following output categories: high impact (variant is assumed to have a disruptive impact in the protein, probably causing protein truncation, loss of function or triggering nonsense mediated decay), moderate impact (non-disruptive variant that might change protein effectiveness), and low impact (variant assumed to be mostly harmless or unlikely to change protein behaviour). The ‘modifier’ category is taken to represent no information about these categories; ClinVar assigns each variant as pathogenic, likely pathogenic, likely benign, benign, or of uncertain clinical significance; SIFT predicts whether an amino acid substitution is likely to affect protein function based on sequence homology and the physico-chemical similarity between the alternate amino acids, concluding with a qualitative prediction if a variant is deleterious or tolerated; PolyPhen-2 predicts the effect of an amino acid substitution on the structure and function of a protein using sequence homology, 3D structures where available, and a number of other databases and tools. It classifies each variant as probably damaging, possibly damaging or benign.
| Genetic mutation | Protein change | Variant information |
|------------------|----------------|---------------------|
| c.589C>T        | p.R197X        | Stop gained, likely deleterious, high impact. Pathogenic |
| c.865C>T        | p.Q289X        | Stop gained, likely deleterious, high impact. Pathogenic |
| c.1108C>T       | p.R370X        | Stop gained, high impact variant. Pathogenic/likely pathogenic |
| c.904C>T        | p.R302X        | Stop gained, high impact variant. Likely pathogenic |
| c.502A>T        | p.K168ter      | Stop gained, high impact variant |
| c.847G>T        | p.G283Ter      | Stop gained, high impact variant |
| c.983C>A        | p.S328*        | Stop gained, high impact variant |
| c.1005+1G>T     |                | Splice donor variant, high impact |
| c.971A>C        | p.N324T        | Missense variant, possible splice region variant with moderate impact. Possibly damaging to protein structure and conflicting evidence of tolerated/deleterious to protein function. Likely pathogenic |
| c.754G>A        | p.A252T        | Missense variant, non-coding exon variant with moderate impact. Possibly damaging to protein structure and deleterious to protein function. Pathogenic |
| c.956C>T        | p.T319I        | Missense variant, moderate impact. Probably damaging to protein structure and likely to have deleterious effect on protein function |
| c.451C>A        | p.Q151K        | Missense variant, moderate impact and potential modifier of both upstream and downstream gene regulation (ARMS2), and lncRNA. Possibly damaging to protein structure and likely to have deleterious effect on protein function. Uncertain clinical significance |
| c.359G>A        | p.G120D        | Missense variant, moderate impact and potential modifier of both upstream and downstream gene regulation (ARMS2), and lncRNA. Probably damaging to protein structure and likely to have deleterious effect on protein function. Likely pathogenic |
| c.361A>C        | p.S121R        | Missense variant, moderate impact and potential modifier of both upstream and downstream gene regulation (ARMS2), and lncRNA. Probably damaging to protein structure and likely to have deleterious effect on protein function |
| Variant | Protein | Description |
|---------|---------|-------------|
| c.397C>G | p.R133G | Missense variant, moderate impact and potential modifier of both upstream and downstream gene regulation (ARMS2), and IncRNA. Possibly damaging to protein structure but tolerated by protein function |
| c.367G>T | p.A123S | Missense variant, moderate impact and potential modifier of both upstream and downstream gene regulation (ARMS2), and IncRNA. Only possibly damaging to protein structure and likely to have deleterious effect on protein function |
| c.821G>A | p.R274Q | Missense variant with moderate impact. Probably/possibly damaging to protein structure and deleterious/some reports of tolerated to protein function. Pathogenic |
| c.496C>T | p.R166C | Missense variant with moderate impact. Probably/possibly damaging to protein structure and deleterious to protein function |
| c.517G>A | p.A173T | Missense variant with moderate impact. Probably/possibly damaging to protein structure and deleterious to protein function |
| c.517G>C | p.A173P | Missense variant with moderate impact. Probably/possibly damaging to protein structure and deleterious to protein function |
| c.856T>G | p.F286V | Missense variant with moderate impact. Probably/possibly damaging to protein structure and deleterious to protein function |
| c.854C>A | p.P285Q | Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function. Uncertain clinical significance/pathogenic |
| c.854C>T | p.P285L | Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function. Uncertain clinical significance/pathogenic |
| c.616G>A | p.G206R | Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function. Uncertain clinical significance |
| c.961G>A | p.A321T | Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function. Uncertain clinical significance |
| c.1091T>C | p.L364P | Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function. Pathogenic |
| c.497G>T | p.R166L | Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function. Pathogenic |
| c.614C>G | p.S205C | Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function. Pathogenic |
| Variant | Genotype | Description | Pathogenicity |
|---------|----------|-------------|---------------|
| c.852C>A | p.S284R | Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function. | Pathogenic |
| c.883G>A | p.G295R | Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function. | Pathogenic |
| c.889G>A | p.V297M | Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function. | Pathogenic |
| c.536T>A | p.I179N | Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function. | Likely pathogenic |
| c.827G>C | p.G276A | Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function. | Likely pathogenic |
| c.1021G>A | p.G341J | Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function. | |
| c.524T>A | p.V175E | Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function | |
| c.527T>C | p.V176A | Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function | |
| c.646 G>A | p.V216 M | Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function | |
| c.847G>A | p.G283R | Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function | |
| c.848G>A | p.G283E | Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function | |
| c.850A>G | p.S284G | Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function | |
| c.905G>A | p.R302Q | Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function | |
| c.1348G>C | p.D450H | Missense variant with moderate impact. Only possibly damaging to protein structure and deleterious to protein function | |
| Genetic mutation | Protein change | Variant information                                                                                                                                 |
|------------------|----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------|
| c.184-185del     |                | Intronic variant, with possible impact on both upstream and downstream gene regulation, ARMS2. Possible influence on lncRNA.                         |
| c.830_831delAG   | p.E277Vfs      | Intronic variant with possible influence on upstream gene                                                                                              |
| c.126delG        | p.E42fs        | Frameshift variant with high impact. Pathogenic                                                                                                       |
| c.543delT        | p.A182Pfs*33   | Frameshift mutation with high impact. Potentially leading to premature stop. Pathogenic                                                              |
| c.739delG        | p.E247Rfs      | Frameshift mutation with high impact. Potentially leading to premature stop                                                                           |
| c.958G>A         | p.D320N        | Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function.                                        |

B. ADA2

| Genetic mutation | Protein change | Variant information                                                                                                                                 |
|------------------|----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------|
| c.982G>A         | p.E328K        | Missense variant with potential impact on upstream and downstream gene regulation, possible 3'UTR variant involved in nonsense-mediated decay. Possible impact on processing of pseudogene, and CTCF binding site. Probably damaging/benign to protein structure and likely deleterious to protein function/potentially tolerated. |
| c.138/144delG    |                | 5'UTR variant, intronic variant with possible impact on regulation of upstream gene through processing of pseudogene/nonsense mediated decay          |
| c.37_39del       | p.K13del       | 5'UTR variant, intronic variant with possible impact on regulation of upstream gene through processing of pseudogene/nonsense mediated decay          |
| c.143_144insG    | p.R49Afs*13    | Frameshift variant with high impact, possible impact on both upstream and downstream gene regulation. Likely pathogenic                               |
| c.144 dup        | p.R49Afs*13    | Frameshift variant with high impact, possible impact on both upstream and downstream gene regulation. Likely pathogenic                               |
| c.144_145ins     |                | Frameshift variant with high impact, possible impact on both upstream and downstream gene regulation. Likely pathogenic                               |
| c.144del         | p.R49Gfs*4     | Frameshift variant with high impact, possible impact on both upstream and downstream gene regulation. Likely pathogenic                               |
| Variant     | Effect | Description                                                                 |
|------------|--------|-----------------------------------------------------------------------------|
| c.144delG  | p.R49fs| Frameshift variant with high impact, possible impact on both upstream and downstream gene regulation. Likely pathogenic |
| c.144dupG  | p.R49fs| Frameshift variant with high impact, possible impact on both upstream and downstream gene regulation. Likely pathogenic |
| c.629delT  |        | Frameshift variant, high impact with potential impact on both upstream and downstream genes. |
| c.427del   | p.I143Sfs*41| Frameshift variant, high impact. Impact on nonsense mediated decay transcript processing. Possible impact on downstream genes |
| c.1447_1451del| p.S483Pfs*5| Intron variant, possible impact on transcript processing |
| c.680-681delAT|        | Intron variant, possible impact on transcript processing |
| c.973-?_1081+?del| p.V325Tfs*7| Intron variant, possible retained intron. Could have impact on both upstream, downstream genes and nonsense mediated decay transcript processing. |
| c.972+3A>G |        | Intron, splice region variant with low impact. Possible retained intron and impact on nonsense mediated decay transcript processing |
| c.326C>A   | p.A109D| Missense variant with moderate impact, possible 5'UTR variant. Probably damaging to protein structure and deleterious to protein function. |
| c.336C>A   | p.H112Q| Missense variant with moderate impact, possible 5'UTR variant. Probably damaging to protein structure and deleterious to protein function. |
| c.336C>G   | p.H112Q| Missense variant with moderate impact, possible 5'UTR variant. Probably damaging to protein structure and deleterious to protein function. |
| c.336G>C   | p.H112Q| Missense variant with moderate impact, possible 5'UTR variant. Probably damaging to protein structure and deleterious to protein function. |
| c.962G>A   | p.G321E| Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function. |
| c.133C>T   | p.A45T | Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function. |
| c.1358A>G  | p.Y453C| Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function. |
| c.385A>C   | p.T129P| Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function. |
| Chromosome | Base Change |氨基酸位置 |Impact| Pathogenicity |
|------------|-------------|---------------------------------------------|------|--------------|
| c.932T>G   | p.L311R     | Missense variant with moderate impact. Possibly damaging to protein structure and deleterious to protein function. Pathogenic. |
| c.1352T>G  | p.L451W     | Missense variant with potential impact on downstream gene regulation, possible 3'UTR variant involved in nonsense-mediated decay. Possibly damaging to protein structure and likely deleterious to protein function. |
| c.1353G>T  | p.L451F     | Missense variant with potential impact on downstream gene regulation, possible 3'UTR variant involved in nonsense-mediated decay. Possibly damaging to protein structure and likely deleterious to protein function. |
| c.1360G>C  |             | Missense variant with potential impact on downstream gene regulation, possible 3'UTR variant involved in nonsense-mediated decay. Possibly damaging to protein structure and likely deleterious to protein function. |
| c.1373T>A  | p.V458D     | Missense variant with potential impact on downstream gene regulation, possible 3'UTR variant involved in nonsense-mediated decay. Possibly damaging to protein structure and likely deleterious to protein function. |
| c.1223G>A  | p.C408Y     | Missense variant with potential impact on downstream gene regulation, possible 3'UTR variant involved in nonsense-mediated decay. Possibly damaging to protein structure and likely deleterious to protein function. |
| c.1348G>T  | p.G450C     | Missense variant with potential impact on downstream gene regulation, possible 3'UTR variant involved in nonsense-mediated decay. Possibly damaging to protein structure and likely deleterious to protein function. |
| c.1367A>G  | p.Y456C     | Missense variant with potential impact on downstream gene regulation, possible 3'UTR variant involved in nonsense-mediated decay. Possibly damaging to protein structure and likely deleterious to protein function. Pathogenic |
| c.1065C>A  | p.F355L     | Missense variant with potential impact on upstream and downstream gene regulation, possible 3'UTR variant involved in nonsense-mediated decay. Possible impact on processing of pseudogene. Benign protein structure and tolerated by protein function. |
| c.1052T>A  | p.L351Q     | Missense variant with potential impact on upstream and downstream gene regulation, possible 3'UTR variant involved in nonsense-mediated decay. Possible impact on processing of pseudogene. Possibly damaging to protein structure and likely deleterious to protein function. |
| Variant | Protein Change | Description |
|---------|----------------|-------------|
| c.1057T>C | p.Y353H | Missense variant with potential impact on upstream and downstream gene regulation, possible 3’UTR variant involved in nonsense-mediated decay. Possible impact on processing of pseudogene. Probably damaging to protein structure and likely deleterious to protein function. |
| c.1069G>A | p.A357T | Missense variant with potential impact on upstream and downstream gene regulation, possible 3’UTR variant involved in nonsense-mediated decay. Possible impact on processing of pseudogene. Probably damaging to protein structure and likely deleterious to protein function. |
| c.1072G>A | p.G358R | Missense variant with potential impact on upstream and downstream gene regulation, possible 3’UTR variant involved in nonsense-mediated decay. Possible impact on processing of pseudogene. Probably damaging to protein structure and likely deleterious to protein function. |
| c.1078A>G | p.T360A | Missense variant with potential impact on upstream and downstream gene regulation, possible 3’UTR variant involved in nonsense-mediated decay. Possible impact on processing of pseudogene. Probably damaging to protein structure and likely deleterious to protein function. |
| c.140G>C | p.G47A | Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function. |
| c.278T>C | p.I93T | Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function. |
| c.506C>T | p.R169Q | Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function. |
| c.506G>A | R169Q | Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function. |
| c.533T>C | p.F178S | Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function. Possible retained intron. |
| c.139G>T | p.G47W | Missense variant, moderate impact and potential modifier of upstream and downstream gene regulation, possible impact on processing of pseudogene (FAM32BP). Probably damaging to protein structure and likely to have deleterious effect on protein function. Pathogenic |
| c.563T>C | p.L188P | Missense variant, moderate impact and potential modifier of upstream and downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function. |
| SNP     | Protein  | Description                                                                 |
|---------|----------|-----------------------------------------------------------------------------|
| c.578C>T| p.P193L  | Missense variant, moderate impact and potential modifier of upstream and downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function. |
| c.139G>A| p.G47R   | Missense variant, moderate impact and potential modifier of upstream and downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function. Conflicting evidence on clinical significance |
| c.650T>A| p.V217D  | Missense variant, moderate impact and potential modifier of upstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function. |
| c.712G>A| p.D238N  | Missense variant, moderate impact and potential modifier of upstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function. |
| c.872C>T| p.S291L  | Missense variant, moderate impact and potential modifier of upstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function. |
| c.620T>C|          | Missense variant, moderate impact and potential modifier of upstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function. Uncertain clinical significance |
| c.791G>C| p.W264S  | Missense variant, moderate impact and potential modifier of upstream gene regulation. Probably damaging/benign to protein structure and could have deleterious/tolerated impact on protein function. May cause retained intron. |
| c.1110C>A| p.N370K | Missense variant, moderate impact, possible 3'UTR variant involved in nonsense mediated decay. Probably damaging to protein structure and likely to have deleterious effect on protein function. |
| c.1445A>G|         | Missense variant, splice variant with potential impact on downstream gene regulation, possible 3'UTR variant involved in nonsense-mediated decay. Probably damaging to protein structure and likely deleterious to protein function. |
| c.1226C>A|          | Missense variant, splice variant with potential impact on downstream gene regulation, possible 3'UTR variant involved in nonsense-mediated decay. Probably damaging to protein structure and likely deleterious to protein function. |
| c.752C>T| p.P251L  | Missense variant, splice region variant with moderate impact. Possibly damaging to protein structure and tolerated by protein function. |
| c.424G>A| p.G142S  | Missense variant. Change tolerated by protein function, benign impact on protein structure |
| Genetic mutation | Protein change | Variant information |
|-----------------|----------------|-------------------|
| c.25C>T         | p.R9W          | Missense variant. Deleterious (but some evidence of low confidence in finding) to protein function, benign impact on protein structure |
| c.2T>C          | p.M1T          | Missense variant. Deleterious (but some evidence of low confidence in finding) to protein function, benign impact on protein structure |
| c.73G>T         | p.G25C         | Missense, splice region variant. Change tolerated by protein function and has benign impact on protein structure |
| c.882 -2A>G     |                | Splice acceptor variant, high impact. Also potential impact on upstream gene regulation |
| c.973 -1G>A     |                | Splice acceptor variant, high impact. Also potential regulatory region variant altering TF binding site. Could impact upstream gene regulation (RPL32P5) |
| c.973 -2A>G     |                | Splice acceptor variant, high impact, may result in retained intron, could impact nonsense mediated decay. Also potential regulatory region variant altering TF binding site. Could impact upstream and downstream gene regulation (RPL32P5). |
| c.973-2A>G      |                | Splice acceptor variant, high impact, may result in retained intron, could impact nonsense mediated decay. Also potential regulatory region variant altering TF binding site. Could impact upstream and downstream gene regulation (RPL32P5). |
| c.542+1G>A      |                | Splice donor variant with high impact. Possible impact on nonsense mediated decay |
| c.753+2T>A      |                | Splice donor variant with high impact. Possible retained intron |
| c.753G>A        |                | Splice region variant with low impact. May influence downstream and upstream gene regulation. |
| c.781delinsCCATA| p.D261Pfs*2    | Stop gained, frameshift variant with high impact |
| c.1196G>A       | p.W399*        | Stop gained, high impact |
| c.794C>G        | p.Q265X        | Stop gained, high impact variant. Possible impact on upstream gene regulation |
| c.916C>T        | p.R306*        | Stop gained, high impact variant. Possible impact on upstream gene regulation. |
| c.660C>A        | p.Y220X        | Stop gained, high impact variant. Possible impact on upstream gene regulation. Benign. |
| c.47+2T>C       |                | Synonymous, intron variant with low impact. Potential retained intron |

**C. COL4A1**

| Genetic mutation | Protein change | Variant information |
|-----------------|----------------|-------------------|
| c.*35C>A        |                | 3' UTR variant, regulatory region variant |
| c.*31G>T        |                | 3'UTR variant, regulatory region variant |
| Variant | Description |
|---------|-------------|
| c.*32G>A | 3'UTR variant, regulatory region variant |
| c.*32G>T | 3'UTR variant, regulatory region variant |
| c.*33T>A | 3'UTR variant, regulatory region variant |
| c.-2C>T | 5'UTR variant, with possible impact on upstream gene regulation |
| c.2545G>T | p.G808V Evidence of stop gained, high impact |
| c.2424delT | p.P810fs Frameshift mutation with high impact. Potentially leading to premature stop |
| c.2931dupT | p.G978WfsX15 Frameshift mutation with high impact. Potentially leading to premature stop |
| c.3702delC | p.G1236* Frameshift mutation with high impact. Potentially leading to premature stop |
| c.2085del | p.G696fs Frameshift mutation with high impact. Potentially leading to premature stop. Pathogenic. |
| c.1121-18G>A | Intronic variant possibly leading to retained intron |
| c.2645_2646delinsAA | p.G882E Intronic variant potentially leading to retained intron |
| c.3877-30C>A | Intronic variant with possible impact on upstream gene regulation. Intron retained |
| c.4582 -4586 dupCCCATG ins. | Intronic variant, retained intron. Likely deleterious and probably damaging. Possible impact on upstream gene regulation |
| c.4642T>G | p.C1548G Missense & splice region variant with low to moderate effect. Likely to impact protein function and probably damaging |
| c.2969G>A | p.G990E Missense variant and splice region variant. May result in retained intron. Possible modifier of downstream gene regulation. Likely deleterious and probably damaging. |
| c.2969G>T | p.G990V Missense variant and splice region variant. May result in retained intron. Possible modifier of downstream gene regulation. Likely deleterious and probably damaging. |
| c.3200G>A | p.G1067E Missense variant and splice region variant. May result in retained intron. Possible modifier of downstream gene regulation. Likely deleterious and probably damaging. |
| c.3200G>C | p.G1067A Missense variant and splice region variant. May result in retained intron. Possible modifier of downstream gene regulation. Likely deleterious and probably damaging. |
| c.3770G>C | p.G1257E Missense variant in possible regulatory region. Likely deleterious and probably damaging |
| c.3796G>C | p.G1266R Missense variant in possible regulatory region. Likely deleterious and probably damaging |
| c.3832G>T | p.G1278S Missense variant in possible regulatory region. Likely deleterious and probably damaging. Uncertain clinical significance |
| Variant   | Amino Acid Change | Description                                                                 |
|-----------|-------------------|-----------------------------------------------------------------------------|
| c.3245G>A | p.G1082E          | Missense variant with moderate impact and possible modifier of downstream gene regulation. Likely deleterious and possibly damaging |
| c.3280G>C | p.G1094R          | Missense variant with moderate impact and possible modifier of downstream gene regulation. Likely deleterious and possibly damaging |
| c.1249G>C | p.G417R           | Missense variant with moderate impact. Benign impact on protein structure and deleterious to protein function |
| c.3997G>A | p.D1333N          | Missense variant with moderate impact. Conflicting evidence of effect on protein function, potentially tolerated/potentially deleterious |
| c.3592G>A | p.G1198R          | Missense variant with moderate impact. Likely deleterious and probably damaging |
| c.3620G>T | p.G1207V          | Missense variant with moderate impact. Likely deleterious and probably damaging |
| c.3656G>A | p.G1219E          | Missense variant with moderate impact. Likely deleterious and probably damaging |
| c.3671C>T | p.P1224L          | Missense variant with moderate impact. Likely deleterious and probably damaging |
| c.3704A>G | p.K1235R          | Missense variant with moderate impact. Likely deleterious and probably damaging |
| c.3706G>A | p.G1236R          | Missense variant with moderate impact. Likely deleterious and probably damaging |
| c.3707G>A | p.G1237E          | Missense variant with moderate impact. Likely deleterious and probably damaging |
| c.3712C>T | p.R1238C          | Missense variant with moderate impact. Likely deleterious and probably damaging |
| c.3505G>A | p.G1169S          | Missense variant with moderate impact. Possible splice region variant, with potential impact on downstream gene regulation. Likely deleterious and probably damaging |
| c.2512A>G | p.M838V           | Missense variant with moderate impact. Possibly damaging to protein structure and deleterious to protein function |
| c.3389G>A | p.G1130D          | Missense variant with moderate impact. Potentially modifies upstream and downstream gene regulation. Likely deleterious and probably damaging |
| c.4088 G > A | p.G1363D | Missense variant with moderate impact. Probably damaging and deleterious to protein function |
| c.1502G>A | p.G510R           | Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function |
| c.1528G>A | p.G528E           | Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function |
| Variant   | Effect   | Description                                                                 |
|-----------|----------|-----------------------------------------------------------------------------|
| c.1619A>G | p.K540R  | Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function |
| c.2008G>A | p.G670R  | Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function |
| c.2045G>T | p.G682V  | Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function |
| c.2063G>A | p.G688D  | Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function |
| c.2078G>A | p.G693E  | Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function |
| c.2086G>A | p.G696S  | Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function |
| c.2086G>T | p.G696C  | Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function |
| c.2132G>A | p.G711E  | Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function |
| c.2159G>A | p.G720D  | Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function |
| c.2168G>A | p.G723E  | Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function |
| c.2504G>A | p.G835E  | Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function |
| c.625G>A  | p.G209S  | Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function |
| c.634G>A  | p.G212S  | Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function |
| c.1493G>A | p.G498D  | Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function. Pathogenic. |
| SNP       | Effect | Description                                                                                   |
|-----------|--------|-----------------------------------------------------------------------------------------------|
| c.1493G>T | p.G498V| Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function. Pathogenic. |
| c.3383T>A | p.I1128N| Missense variant with moderate impact. Substitution seems to be tolerated by protein function but probably damaging to protein structure |
| c.3715G>A | p.G1239R| Missense variant with possible impact on upstream gene regulation. Probably damaging variant |
| c.3941G>T | p.G1314V| Missense variant with possible impact on upstream gene regulation. Probably damaging variant |
| c.3976G>A | p.G1326R| Missense variant with possible impact on upstream gene regulation. Probably damaging variant |
| c.3995G>A | p.G1332D| Missense variant with possible impact on upstream gene regulation. Probably damaging variant |
| c.4031G>C | p.G1344A| Missense variant with possible impact on upstream gene regulation. Probably damaging variant |
| c.4105G>C | p.G1369R| Missense variant with possible impact on upstream gene regulation. Probably damaging variant |
| c.4213G>A | p.G1405S| Missense variant with possible impact on upstream gene regulation. Probably damaging variant |
| c.1801G>A | p.G601S| Missense variant, moderate impact and potential modifier of downstream gene regulation. Only possibly damaging to protein structure and likely to have deleterious effect on protein function |
| c.1807C>T | p.P603S| Missense variant, moderate impact and potential modifier of downstream gene regulation. Only possibly damaging to protein structure and likely to have deleterious effect on protein function |
| c.1555G>A | p.G519R| Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function |
| c.1835G>A | p.G612D| Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function |
| c.1853G>A | p.G618E| Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function |
| c.2494G>A | p.G832R| Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function |
| c.2563G>C | p.G855R| Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function |
| c.2581G>A | p.G861S| Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function |
| c.2599G>A | p.G867R| Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function |
| Chromosome | SNP | Protein | Description |
|------------|-----|---------|-------------|
| c.2608G>A  | p.G870R | Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function |
| c.2636G>A  | p.G879E | Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function |
| c.2645G>A  | p.G882D | Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function |
| c.2662G>A  | p.G888R | Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function |
| c.2689G>A  | p.G897S | Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function |
| c.2699G>A  | p.G900E | Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function |
| c.2744G>A  | p.G915E | Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function |
| c.2782G>C  | p.D928H | Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function |
| c.2842G>A  | p.G948S | Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function |
| c.2987G>A  | p.G996D | Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function |
| c.3022G>A  | p.G1008R | Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function |
| c.3040G>C  | p.G1014R | Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function |
| c.3104G>T  | p.G1035V | Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function |
| c.3122G>A  | p.G1041E | Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function |
| Variant   | Mutation  | Description                                                                                     |
|-----------|-----------|-------------------------------------------------------------------------------------------------|
| c.3130G>C | p.G1044E  | Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function |
| c.3190G>A | p.G1064S  | Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function |
| c.191G>T  | p.G64V    | Missense variant, moderate impact and potential modifier of upstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function. Possible 3'UTR variant. |
| c.4739G>C | p.G1580A  | Missense variant, moderate impact, deleterious and likely to impact protein function, probably damaging |
| c.4881C>G | p.N1627K  | Missense variant, moderate impact, deleterious and likely to impact protein function, probably damaging |
| c.4843G>A | p.E1615K  | Missense variant, Moderate impact, possibly retained intron, probably damaging                   |
| c.4232G>C | p.G1411A  | Missense variant, moderate impact. Probably damaging and likely to have deleterious effect on protein function |
| c.4380T>G | p.C1460W  | Missense variant, moderate impact. Probably damaging and likely to have deleterious effect on protein function |
| c.4652G>A | p.C1551Y  | Missense variant, moderate impact. Probably damaging and likely to have deleterious effect on protein function |
| c.4717G>A | p.G1573R  | Missense variant, moderate impact. Probably damaging and likely to have deleterious effect on protein function |
| c.4738G>A | p.G1580S  | Missense variant, moderate impact. Probably damaging and likely to have deleterious effect on protein function |
| c.1955G>A | p.G652E   | Missense variant, moderate impact. Probably damaging to protein structure and likely to have deleterious effect on protein function |
| c.1963G>A | p.G655R   | Missense variant, moderate impact. Probably damaging to protein structure and likely to have deleterious effect on protein function |
| Variant  | Effect                        | Description                                                                 |
|----------|------------------------------|-----------------------------------------------------------------------------|
| c.1964G>A | p.G655E                      | Missense variant, moderate impact. Probably damaging to protein structure and likely to have deleterious effect on protein function |
| c.1973C>A | p.G658V                      | Missense variant, moderate impact. Probably damaging to protein structure and likely to have deleterious effect on protein function |
| c.1973G>A | p.G658D                      | Missense variant, moderate impact. Probably damaging to protein structure and likely to have deleterious effect on protein function |
| c.2441 G>T | p.G814V                      | Missense variant, non-coding exon variant with moderate impact. Possibly damaging to protein structure and deleterious to protein function |
| c.2413G>A | p.G805R                      | Missense variant, non-coding exon variant with moderate impact. Possibly damaging to protein structure and deleterious to protein function |
| c.2413G>C | p.G805R                      | Missense variant, non-coding exon variant with moderate impact. Possibly damaging to protein structure and deleterious to protein function |
| c.2317G>A | p.G773R                      | Missense variant, non-coding exon variant with moderate impact. Probably damaging to protein structure and deleterious to protein function |
| c.2317G>C | p.G773R                      | Missense variant, non-coding exon variant with moderate impact. Probably damaging to protein structure and deleterious to protein function |
| c.2228G>T | p.G743V                      | Missense variant, non-coding exon variant with moderate impact. Regulatory region variant, leading to open chromatin structure. Probably damaging to protein structure and deleterious to protein function |
| c.2245G>A | p.G749S                      | Missense variant, non-coding exon variant with moderate impact. Regulatory region variant, leading to open chromatin structure. Probably damaging to protein structure and deleterious to protein function |
| c.2263G>A | p.G755R                      | Missense variant, non-coding exon variant with moderate impact. Regulatory region variant, leading to open chromatin structure. Probably damaging to protein structure and deleterious to protein function |
| c.4267G>C | p.G1423R                     | Missense variant, possibly resulting in retained intron. Possibly damaging and likely deleterious to protein function |
| c.4133G>A | p.G1378D                     | Missense variant, potentially impacting upstream gene regulation. Likely deleterious and probably damaging |
| Variant       | Description                                                                 |
|--------------|-----------------------------------------------------------------------------|
| c.4150+1(IVS46) G>T | Missense variant, splice donor variant with potential impact on upstream gene regulation. High impact. Probably damaging and likely deleterious. |
| c.4150+1G>A    | Missense variant, splice donor variant with potential impact on upstream gene regulation. High impact. Probably damaging and likely deleterious. |
| c.4150G>A      | Missense variant, splice donor variant with potential impact on upstream gene regulation. High impact. Probably damaging and likely deleterious. |
| c.2345G>C      | Missense variant, splice region variant with low-moderate impact. Likely deleterious and probably damaging |
| c.2096G>A      | Missense variant, splice region variant with low-moderate impact. Likely deleterious to protein function and probably damaging to protein structure |
| c.236G>T       | Missense variant, splice region variant with low-moderate impact. Likely deleterious to protein function and probably damaging to protein structure |
| c.443G>A       | Missense variant, splice region variant with low-moderate impact. Likely deleterious to protein function and probably damaging to protein structure |
| c.196C>A       | Missense variant. Change tolerated by protein function but possibly damaging to protein structure |
| c.2641A>G      | Missense variant. Change tolerated by protein function but possibly damaging to protein structure |
| c.3046A>G      | Missense variant. Change tolerated by protein function but possibly damaging to protein structure |
| c.31C>A        | Missense variant. Change tolerated by protein function but possibly damaging to protein structure |
| c.1612C>G      | Missense variant. Change tolerated by protein function with benign impact on protein structure |
| c.1769G>A      | Missense variant. Change tolerated by protein function with benign impact on protein structure |
| c.3946C>G      | Missense variant. Change tolerated by protein function, likely benign some evidence of possibly damaging protein structure |
| c.1537-2A>G    | Potential frameshift variant and splice acceptor variant with high impact |
| c.1537–2delA   | Potential frameshift variant and splice acceptor variant with high impact |
| c.1121-2dupA   | Splice acceptor variant, intronic variant leading to retained intron. High impact variant. |
| c.1382-1G>C    | Splice acceptor variant, intronic variant leading to retained intron. High impact variant. |
| c.2194-1G.A    | Splice acceptor variant, intronic variant leading to retained intron. High impact variant. Also potential regulatory region variant leading to open chromatin structure |
### c.553-2A>G
- **Splice acceptor variant, intronic variant leading to retained intron. High impact variant. Also potential regulatory region variant leading to open chromatin structure and altered downstream gene regulation. Potential 3' UTR variant**

### c.1990+1G>A
- **Splice donor variant with high impact. Possible retained intron**

### c.3406+1G>T
- **Splice donor variant with high impact. Potential impact on both upstream and downstream gene regulation**

### c.2716+1G>A
- **Splice donor variant with high impact. Potential impact on downstream gene regulation**

### c.2716+G>T
- **Splice donor variant with high impact. Potential impact on downstream gene regulation**

### c.2716+2T>C
- **Splice donor variant with high impact. Potential impact on downstream gene regulation modification**

### c.1A>T
- **Start lost, but seems to be tolerated by protein function but possibly damaging to protein structure. Possible impact on upstream gene regulation**

### c.739C>T
- **p.Q247* Stop gained, high impact. Possible modifier of downstream gene regulation**

### c.607G>T
- **p. G203R Stop gained, high impact. Potential 3'UTR regulatory variant**

### c.4875C>A
- **p.Y1625* Stop gained, likely deleterious, high impact**

### c.4887C>A
- **p.Y1629X Stop gained, likely deleterious, high impact**

### c.1870G>T
- **p.G624* Stop gained, likely deleterious, high impact. Possible modifier of downstream gene regulation modification**

### D. COL4A2

| Genetic mutation | Protein change | Variant information |
|------------------|----------------|---------------------|
| c.1396G>A        | p.G466S        | Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function. Possible intron variant causing alteration to IncRNA influencing gene AS2 |
| c.1776+1G>A      |                | Splice donor variant with high impact. Possible retained intron and impact to IncRNA influencing gene AS2. Pathogenic but also reported to have uncertain clinical significance |
| c.1810G>C        | p.G604R        | Missense variant, moderate impact and potential modifier of upstream and downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function. Potential influence on promoter regulation and IncRNA influencing AS2 |
| Mutation       | Protein Effect                        | Potential Impact                                           |
|---------------|--------------------------------------|-----------------------------------------------------------|
| c.1856G>A     | p.G619D Missense variant, moderate   | Probably damaging to protein structure and likely to have   |
|               | impact and potential modifier of     | deleterious effect on protein function. Potential influence|
|               | upstream and downstream gene         | on promoter regulation and lncRNA influencing AS2. Likely  |
|               | regulation.                         | pathogenic                                                |
| c.2105G>A     | p.G702D Missense variant with        | Probably damaging to protein structure and deleterious to  |
|               | moderate impact.                    | protein function                                           |
| c.2399G>A     | p.G800E Missense variant with        | Probably damaging to protein structure and deleterious to  |
|               | moderate impact.                    | protein function. With possible impact on upstream gene   |
|               |                                     | regulation and promoter regions                           |
| c.2821G>A     | p.G941R Missense variant with        | Possibly damaging to protein structure and deleterious to  |
|               | moderate impact.                    | protein function. Possible retained intron.               |
| c.3110G>A     | p.G1037E Missense variant, moderate  | Probably damaging to protein structure and likely to have  |
|               | impact and potential modifier of     | deleterious effect on protein function.                    |
|               | downstream gene regulation.         |                                                           |
| c.3368A>G     | p.E1123G Missense variant, non-coding| Possibly damaging to protein structure and deleterious to  |
|               | exon variant with moderate impact.   | protein function. Likely benign clinical significance but |
|               |                                     | possible risk factor                                       |
| c.3448C>A     | p.Q1150K Missense variant, non-coding| Possibly damaging to protein structure and tolerated to  |
|               | exon variant with moderate impact.   | protein function. Likely benign clinical significance but |
|               |                                     | possible risk factor                                       |
| c.3455G>A     | p.G1152D Missense variant, splice    | Probably damaging to protein structure and deleterious to  |
|               | region variant.                     | protein function. Pathogenic                               |
| c.3490G>A     | p.R1164G Missense variant with       | Probably damaging to protein structure and deleterious to  |
|               | moderate impact.                    | protein function. Pathogenic                               |
| c.4129G > A   | p.G1377R Missense variant, moderate  | Possibly damaging to protein structure and deleterious to  |
|               | impact and potential modifier of     | protein function. Possible impact on lncRNA influencing    |
|               | upstream gene regulation, possible   | AS2. Probably damaging to protein structure and likely to   |
|               | impact on lncRNA influencing AS2.   | have deleterious effect on protein function. Pathogenic    |
| c.4147G>A     | p.G1383R Missense variant, moderate  | Probably damaging to protein structure and likely to have   |
|               | impact and potential modifier of     | deleterious effect on protein function.                    |
|               | upstream gene regulation, possible   | likely pathogenic                                          |
|               | impact on lncRNA influencing AS2.   |                                                           |
| c.4987G>A     | p.G1663S Missense variant, moderate  | Possibly damaging to protein structure and likely to have   |
|               | impact and potential modifier of both| deleterious effect on protein function. Conflicting clinical|
|               | upstream and downstream gene         | clinical significance, reported both likely benign and      |
|               | regulation, possible impact on       | likely pathogenic                                          |
|               | lncRNA influencing AS2.             |                                                           |
| c.5068G>A     | p.A1690T Missense variant, non-coding| Possibly damaging to protein structure and tolerated to   |
|               | exon variant with moderate impact.   | protein function. Likely benign clinical significance but   |
|               |                                     | possible risk factor                                       |
### E. Trehalose-6-phosphate synthase 1 (TREX1)

| Genetic mutation | Protein change | Variant information |
|------------------|----------------|---------------------|
| c.703dup         | p.V235GfsX6    | Frameshift mutation with high impact. Potentially leading to premature stop. Possible impact on downstream gene regulation of ATRIP and SHISA5 (non-mediated decay) |
| c.822delT        | p.P275Qfsx2    | Frameshift mutation with high impact. Potentially leading to premature stop. Possible impact on downstream gene regulation of ATRIP and SHISA5 (non-mediated decay) |
| c.830-833dupAGGA | p.D278fs       | Intronic variant. Potential 3'UTR variant with downstream gene variation. Possible influence on ATRIP and nonsense mediated decay of SHISA5 |
| c.829A>T         | p.K277*        | Stop gained, high impact. Possible modifier of downstream gene regulation. Likely pathogenic. |
| c.828_831dupGA   | p.D278EfsTer48 | Frameshift mutation with high impact. Potentially leading to premature stop. Possible impact on downstream gene regulation of ATRIP and SHISA5 (non-mediated decay) |
| c.829A>T         | p.K277*        | Stop gained, high impact. Possible modifier of downstream gene regulation. Likely pathogenic. |
| c.830-833dupAGGA | p.D278fs       | Frameshift mutation with high impact. Potentially leading to premature stop. Possible impact on downstream gene regulation of ATRIP and SHISA5 (non-mediated decay) |
| c.685A>G         | p.Arg229Gly    | Missense variant, moderate impact and potential modifier of downstream gene regulation. Benign impact on protein structure and tolerated by protein function |
| c.690G>T         | p.Lys230Asn    | Missense variant, moderate impact and potential modifier of downstream gene regulation. Benign impact on protein structure and could have deleterious effect on protein function, but tolerated also reported |
| c.581delC        | p.Ala194fs     | Frameshift variant with high impact, possible downstream gene regulation of ATRIP and SHISA5. Pathogenic |
| c.742_745dupGTC  | p.T249fs       | Intrinsic variant. Potential 3'UTR variant with downstream gene variation. Possible influence on ATRIP and nonsense mediated decay of SHISA5 |
| c.734dupC        | ?              | Frameshift mutation with high impact. Potentially leading to premature stop. Possible impact on downstream gene regulation of ATRIP and SHISA5 (non-mediated decay) |
| c.911_912delCA   | p.T304Nfs*12   | Intronic variant. Potential 3'UTR variant with downstream gene variation. Possible influence on ATRIP and nonsense mediated decay of SHISA5 |
| c.703_704insG    | p.V235GfsX6    | Frameshift mutation with high impact. Potentially leading to premature stop. Possible impact on downstream gene regulation of ATRIP and SHISA5 (non-mediated decay) |
Supplemental References:

1. Abe Y, Matsuduka A, Okanari K, Miyahara H, Kato M, Miyatake S, Saitsu H, Matsumoto N, Tomoki M, Ihara K. A severe pulmonary complication in a patient with COL4A1-related disorder: A case report. Eur J Med Genet. 2017;60:169-171.

2. Adams KL, Riparini G, Banerjee P, Breur M, Bugiani M, Gallo V. Endothelin-1 signaling maintains glial progenitor proliferation in the postnatal subventricular zone. Nat. Commun. 2020;11:2138.

3. Agharahimi A, Bergerson J, Sun A, Similuk M, Oler A, Mace E, Stone D, Ombrello A, Freeman A. Warts as a predominant manifestation of ADA2 deficiency. J Clin Immunol. 2018;38:417. (Abstract)

4. Akgun-Dogan O, Simsek-Kiper PO, Taskiran E, Lissewski C, Brinkmann J, Schanze D, Gocmen R, Cagdas D, Bilginer Y, Uetine GE, et al. ADA2 deficiency in a patient with Noonan syndrome-like disorder with loose anagen hair: The co-occurrence of two rare syndromes. Am. J. Med. Genet. A. 2019;179:2474–2480.

5. Al Mosawi Z, Abduljawad H, Busehail M, Al Moosawi B. Adenosine deaminase 2 deficiency with a novel variant of CECR1 gene mutation: Responding to tumor necrosis factor antagonist therapy. Indian J. Rheumatol. 2019;14:236–240.

6. Alababbas F, El Yamany G, Alsharif O, Hershfield M, Meyts I. Childhood Hodgkin Lymphoma: Think DADA2. J Clin Immunol. 2019;39:26-29.

7. Alamowitch S, Plaisier E, Favrole P, Prost C, Chen Z, Van Agtmael T, Marro B, Ronco P. Cerebrovascular disease related to COL4A1 mutations in HANAC syndrome. Neurology. 2009;73:1873-1882.

8. Alao H, Kleiner D, Han MAT, Takyar V, Stone D, Hoffmann P, Ombrello A, Jones A, Kastner D, Heller T. Deficiency of adenosine deaminase 2 (DADA2); a rare cause of hepatoporal sclerosis and non-cirrhotic portal hypertension. Gastroenterology. 2016;150:S1172-1173. (Abstract)

9. Alaygut D, Alparslan C, Perihan Oncel E, Mutlubas F, Ozdemir T, Yavascan O, Kasap Demir B. A child diagnosed with treatment-resistant polyarthritis nodosa: Can the clinical diagnosis be different? Arch. Rheumatol. 2019;34:338–342.

10. Alsultan A, Basher E, Alqanatish J, Mohammed R, Alfadhel M. Deficiency of ADA2 mimicking autoimmune lymphoproliferative syndrome in the absence of livedo reticularis and vasculitis. Pediatr Blood Cancer. 2018;65.

11. Araujo JM, Alves JN, Taipa R, Alonso I, Ferreira C, Pinho J. Small vessel disease and intracerebral hemorrhages associated with novel pathogenic variants of col4a1. Europ Stroke J. 2018;3:582-583.

12. Arts K, Bergerson JRE, Ombrello AK, Similuk M, Oler AJ, Agharahimi A, Mace EM, Hershfield M, Wouters C, De Somer L et al. Warts and DADA2: a Mere Coincidence? J Clin Immunol. 2018;38:836-843.

13. Ayrignac X, Carra-Dalliere C, Menjot de Champfleur N, Denier C, Aubourg P, Bellesme C, Castelnovo G, Pelletier J, Audoin B, Kaphan E et al. Adult-onset genetic leukoencephalopathies: a MRI pattern-based approach in a comprehensive study of 154 patients. Brain. 2015;138:284-292.

14. Bademkiran F, Nalcaci S, Eraslan C, Durmaz A. The first Turkish family with the diagnosis of retinal vasculopathy with cerebral leukodystrophy (RVCL) where a new mutation was found. J Neurol Sci. 2017;381:378-379.
15. Balakrishna JP, Hsu A, Ombrello A, Wang W, Holland SM, Hickstein DD, Kastner DL, Aksentijevich I, Calvo KR. Spectrum of bone marrow pathology in patients with germline mutations in CECR1. Lab Invest. 2017;97:338A. (Abstract)

16. Barron K, Ombrello A, Stone D, Hoffmann P, Aksentijevich I, Zhou Q, Jones A, Kastner D. Clinical follow-up on a cohort of patients with deficiency of adenosine deaminase 2 (DADA2). Pediatric Rheumatology. 2015;13:19. (Abstract)

17. Barron K, Ombrello A, Stone D, Hoffmann P, Aksentijevich I, Zhou Q, Jones A, Kastner D. Deficiency of adenosine deaminase type ii-expanding the clinical spectrum. Arthritis Rheumatol. 2015;67. (Abstract)

18. Barron K, Ombrello A, Stone D, Hoffmann P, Romeo T, Jones A, Moura NS, Schnappauf O, Aksentijevich I, Bergerson J et al. The clinical spectrum of the deficiency of adenosine deaminase 2 (DADA2) continues to expand. Pediatr Rheumatol. 2019;17:1. (Abstract)

19. Barzaghi F, Minniti F, Mauro M, Bortoli M, Balter R, Bonetti E, Zaccaron A, Vitale V, Omrani M, Zoccolillo M et al. ALPS-Like Phenotype Caused by ADA2 Deficiency Rescued by Allogeneic Hematopoietic Stem Cell Transplantation. Front Immunol. 2018;9:2767.

20. Batu ED, Karadag O, Taskiran EZ, Kalyoncu U, Aksentijevich I, Alikasifoglu M, Ozen S. A case series of adenosine deaminase 2 deficient patients emphasizing treatment and genotype-phenotype correlations. Pediatr Rheumatol. 2015;13:P62. (Abstract)

21. Batu ED, Karadag O, Taskiran EZ, Kalyoncu U, Aksentijevich I, Alikasifoglu M, Ozen S. A Case Series of Adenosine Deaminase 2-deficient Patients Emphasizing Treatment and Genotype-phenotype Correlations. J Rheumatol. 2015;42:1532-1534.

22. Batu ED, Karadag O, Taskiran EZ, Kalyoncu U, Aksentijevich I, Ozen S. A case series of adenosine deaminase 2 deficient patients emphasizing genotype-phenotype correlations. Ann Rheum Dis. 2015;74:518. (Abstract)

23. Batu ED, Sonmez HE, Erden A, Taskiran EZ, Karadag O, Kalyoncu U, Oncel I, Kaplan B, Arici ZS, Temucin CM et al. The characteristic features of the patients with deficiency of adenosine deaminase 2 (DADA2). Pediatr Rheumatol. 2017;15:P403. (Abstract)

24. Batu ED, Taskiran EZ, Ozkara HA, Unal S, Guleray N, Erden A, Karadag O, Gumruk F, Cetin M, Bilginer Y, et al. A monogenic disease with wide range of symptoms: Deficiency of adenosine deaminase 2. Ann. Rheum. Dis. 2019;78:1748. (Abstract)

25. Bayrakli F, Balaban H, Gurelik M, Hizmetli M, Topaktas S. Mutation in the HTRA1 gene in a patient with degenerated spine as a component of CARASIL syndrome. Turk Neurosurg. 2014;24:67-69.

26. Baytaroglu A, Kadayifcilar S, Agin A, Delktas O, Demr S, Bigner Y, Karakaya J, Ozen S, Eldem B. Choroidal vascular density as a biomarker of systemic inflammation in childhood Polyarteritis Nodosa and adenosine deaminase-2 deficiency. Pediatr Rheumatol. 2020;18:29.

27. Beaufort N, Scharrer E, Kremmer E, Lux V, Ehrmann M, Huber R, Houlden H, Werring D, Haffner C, Dichgans M. Cerebral small vessel disease-related protease HtrA1 processes latent TGF-beta binding protein 1 and facilitates TGF-beta signaling. Proc Natl Acad Sci USA. 2014;111:16496-16501.

28. Belot A, Wassmer E, Twilt M, Lega JC, Zeef LA, Oojageer A, Kasher PR, Mathieu AL, Malcus C, Demaret J et al. Mutations in CECR1 associated with a neutrophil signature in peripheral blood. Pediatr Rheumatol Online J. 2014;12:44.
29. Ben-Ami T, Revel-Vilk S, Brooks R, Shaag A, Hershfield MS, Kelly SJ, Ganson NJ, Kfir-Erenfeld S, Weintraub M, Elpeleg O et al. Extending the Clinical Phenotype of Adenosine Deaminase 2 Deficiency. J Pediatr. 2016;177:316-320.

30. Bertamino M, Grossi A, Severino M, Tortora D, Signa S, Amico G, Di Rocco M, Ceccherini I. Next generation sequencing based gene panel for enhanced rapid diagnosis of monogenic pediatric stroke. Eur. Stroke J. 2019;4:355. (Abstract)

31. Bianchi S, Di Palma C, Gallus GN, Gallus GF, Taglia I, Poggiani A, Rosini F, Rufa A, Muresanu DF, Cerase A et al. Two novel HTRA1 mutations in a European CARASIL patient et al. Neurology 2014, 82 (10), 898-900.

32. Bianchi S, Di Palma C, Gallus GN, Taglia I, Poggiani A, Rosini F, Cerase A, Rufa A, Muresanu D, Dotti MT et al. Journal of the Neurological Sciences. 2013;333:e660. (Abstract)

33. Bick D, Fraser PC, Gutzeit MF, Harris JM, Hambuch TM, Helbling DC, Jacob HJ, Kersten JN, Leuthner SR, May T et al. Successful Application of Whole Genome Sequencing in a Medical Genetics Clinic. J Pediatr Genet. 2017;6:61-76.

34. "Bilguvar K, DiLuna ML, Bizzarro MJ, Bayri Y, Schneider KC, Lifton RP, Gunel M, Ment LR. COL4A1 mutation in preterm intraventricular hemorrhage. J Pediatr. 2009;155:743-745."

35. Bougea A, Velonakis G, Spantideas N, Anagnostou E, Paraskevas G Kapaki E, Kararizou E. The first Greek case of heterozygous cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy: An atypical clinicoradiological presentation. Neuroradiol J. 2017;30:583-585.

36. Breedveld G, de Coo IF, Lequin MH, Arts WF, Heutink P, Gould DB, John SW, Oostra B, Mancini GM. Novel mutations in three families confirm a major role of COL4A1 in hereditary porencephaly. J Med Genet. 2006;43:490-495.

37. Bucciol G, Delafontaine S, Segers H, Bossuyt X, Hershfield MS, Moens L, Meyts I. Hematopoietic Stem Cell Transplantation in ADA2 Deficiency: Early Restoration of ADA2 Enzyme Activity and Disease Relapse upon Drop of Donor Chimerism. J Clin Immunol. 2017;37:746-750.

38. Bugiani M, Bakels HS, Waisfisz Q, Ceuterick-de Groote C, Niessen HW, Abbink TE, Lesnik Oberstein SA, van der Knaap MS. Cathepsin A-related arteriopathy with strokes and leukoencephalopathy (CARASAL). Neurology. 2016;87:1777-1786.

39. Bulut E, Erden A, Karadag O, Oguz KK, Ozen S. Deficiency of adenosine deaminase 2; special focus on central nervous system imaging. J Neuroradiol. 2019;46:193-198.

40. Caetano A, Barbosa R, Costa J, Viana-Baptista M. Sindrome HANAC (Hereditary angiopathy, nephropathy, aneurysms, and muscle cramps) incompleto e 1a mutacao descrita do gene COL4A1 em Portugal (G236T). Sinapse. 2015;15:23-26.

41. Cai B, Zeng J, Lin Y, Lin W, Li Z, Wang N. A frameshift mutation in HTRA1 expands CARASIL syndrome and peripheral small arterial disease to the Chinese population. Neurrol Sci. 2015;36:1387-1391.

42. Cakan M, Aktay-Ayaz N, Karadag SG, Tahir-Turanli E, Stafstrom K, Bainter W, Geha RS, Chou J. Atypical phenotype of an old disease or typical phenotype of a new disease: Deficiency of adenosine deaminase 2. Turk. J. Pediatr. 2019;61:413–417.

43. Campo-Caballero D, Rodriguez-Antiguedad J, Ekiza-Bazan J, Iruzubieta-Agudo P, Fernandez-Eulate G., Munoz-Lopetegui A, Martinez-Zaabaleta M, de la Riva P, Urtasun-Ocariz M, de Munain AL, et al. COL4A1 Mutation as a Cause of Familial Recurrent Intracerebral Hemorrhage. J. Stroke Cerebrovasc. Dis. 2020;29:104652.
44. Caorsi R, Grossi A, Cusano R, Rusmini M, Penco F, Schena F, Anna Podda R, Uva P, Gattorno M, Ceccherini I. ADA2 deficiency without ADA2 mutations explained by a structural homozygous variation in 22q11.1. Pediatr Rheumatol. 2018;16. (Abstract)

45. Caorsi R, Grossi A, Insalaco A, Alessio M, Martino S, Cortis E, Morreale A, Caroli F, Martini A, Ceccherini I et al. Prevalence of cecr1 mutations in pediatric patients with polyarteritis nodosa, livedo reticularis and/or stroke. Ann Rheumat Dis. 2015;74:835. (Abstract)

46. Caorsi R, Grossi A, Insalaco A, Alessio M, Martino S, Cortis E, Morreale A, Caroli F, Martini A, Ceccherini I et al. Prevalence of CECR1 mutations in pediatric patients with polyarteritis nodosa, livedo reticularis and/or stroke. Pediatr Rheumatol. 2015;13:O87. (Abstract)

47. Caorsi R, Omenetti A, Morreale A, Insalaco A, Buoncompagni A, Picco P, Malattia C, Gandolfo C, Aksentijevich I, Martini A et al. Rapid and sustained effect of anti-TNF treatment in patients with ADA2 deficiency. Pediatr Rheumatol. 2016;13:74. (Abstract)

48. Caorsi R, Omenetti A, Picco P, Buoncompagni A, Minoa F, Federici S, Finetti M, Martini A, Aksentijevich I, Gattorno M. Long-term efficacy of etanercept in ADA2 deficiency. Pediatr Rheumatol. 2014;12. (Abstract)

49. Caorsi R, Severino MS, Gandolfo C, Ravelli A, Rossi A, Gattorno M. Distinct cerebrovascular features in patients with ADA2 deficiency. Pediatr Rheumatol. 2018;16. (Abstract)

50. Carneiro D, Fernandes C, Santo GC. Familial sneddon’s syndrome revisited: The natural history of deficiency of adenosine deaminase 2. Eur. Stroke J. 2019;4:355–356. (Abstract)

51. Carra-Dalliere C, Ayriagnac X, Prieto-Morin C, Girard P, Tournier-Lasserve E, Labauge P. TREX1 Mutation in Leukodystrophy with Calcifications and Persistent Gadolinium-Enhancement. Eur Neurol. 2017;77:113-114.

52. Cavallin M, Mine M, Philbert M, Boddaert N, Lepage JM, Coste T, Lopez-Gonzalez V, Sanchez-Soler MJ, Ballesta-Martinez MJ, Remerand G et al. Further refinement of COL4A1 and COL4A2 related cortical malformations. Eur J Med Genet. 2018;61:765-772.

53. Chang Y, Derfalvi B, Issekutz A, Shi J, Alonzo P, Pascual CJ, Issekutz T, Walter JE. ADA2 deficiency: Case report of a rare phenotype with alps and CVID-like presentation. J Clin Immunol. 2018;38:341-342.

54. Chen Y, He Z, Meng S, Li L, Yang H, Zhang X. A novel mutation of the high-temperature requirement A serine peptidase 1 (HTRA1) gene in a Chinese family with cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL). J Int Med Res. 2013;41:1445-1455.

55. Chong-Neto HJ, Segundo GRS, Bandeira M, Riedi CA, Hershfield M, Torgerson TR, Rosario N. Novel CECR1 gene mutation causing ADA-2 deficiency. J Clin Immunol. 2018;38:387. (Abstract)

56. Christ S, Haber B, Grulich-Henn J, Helling-Bakke A, Hoffmann GF, Lutz T, Tonshoff B, Syrbe S, Haas D, Youssef H et al. Unclear strokes in pediatrics-adenosine deaminase 2
(ADA2) deficiency as a therapeutic relevant differential diagnosis to acquired inflammatory CNS diseases. Neuropediatrics. 2018;49. (Abstract)

58. Cimino M, Soo S, Morrow M. Ring-enhancing lesions, stroke and vascular retinopathy associated with a novel TREX1 mutation. Neurology. 2018;90:15. (Abstract)

59. Cipe FE, Aydogmus C, Serwas NK, Keskindemirci G, Boztuğ K. Novel Mutation in CECR1 Leads to Deficiency of ADA2 with Associated Neutropenia. J Clin Immunol. 2018;38:273-277.

60. Clarke K, Campbell C, Omoyinmi E, Hong Y, Obaidi MAL, Sebire N, Brogan P. Testicular ischemia in deficiency of adenosine deaminase 2 (DADA2). Pediatr Rheumatol. 2019;17. (Abstract)

61. Cohn AC, Kotschet K, Veitch A, Delatycki MB, McCombe MF. Novel ophthalmological features in hereditary endotheliopathy with retinopathy, nephropathy and stroke syndrome. Clin Exp Ophthalmol. 2005;33:181-183.

62. Colin E, Sentilhes L, Sarfati A, Mine M, Guichet A, Ploton C, Bousson F, Delorme B, Tournier-Lasserve E, Bonnaud D. Fetal intracerebral hemorrhage and cataract: think COL4A1. J Perinatol. 2014;34:75-77.

63. Corlobe A, Tournier-Lasserve E, Mine M, Menjot de Champfleur N, Carra Dalliere C, Ayrganax C, Labauge P, Arquigan C. COL4A1 mutation revealed by an isolated brain hemorrhage. Cerebrovasc Dis. 2013;35:593-594.

64. Cornec-Le Gall E, Chebib FT, Madsen SR, Heyer CM, Lanphier BC, Patterson MC, Albright RC, Yu AS, Torres VE et al. The Value of Genetic Testing in Polycystic Kidney Diseases Illustrated by a Family With PKD2 and COL4A1 Mutations. Am J Kidney Dis. 2018;72:302-308.

65. Coupry I, Sibon I, Mortemousque B, Rouanet F, Mine M, Goizet C. Ophthalmological features associated with COL4A1 mutations. Arch Ophthalmol. 2010;128:483-489.

66. Coufts SB, Matysiak-Scholze U, Kohlhase J, Innes AM. Intracerebral hemorrhage in a young man. CMAJ. 2011;183:E61-E64.

67. Craggs LJ, Haged C, Kuhlenbaeumer G, Borjesson-Hanson A, Andersen O, Viitanen M, Kalimo H, McLean CA, Slade JY, Hall RA et al. Quantitative vascular pathology and phenotyping familial and sporadic cerebral small vessel diseases. Brain Pathol. 2013;23:547-557.

68. Dahl S, Pettersson M, Eisfeldt J, Schroder AK, Wickstrom R, Tear Fahnehjelm K, Anderlid BM, Lindstrand A. Whole genome sequencing unveils genetic heterogeneity in optic nerve hypoplasia. PLoS One. 2020;15:e0228622.

69. De Vries LS, Koopman C, Groenendaal F, Van Schooneveld M, Verheijen FW, Verbeek E, Witkamp TD, van der Worp HB, Mancini G. COL4A1 mutation in two preterm siblings with antenatal onset of parenchymal hemorrhage. Ann Neurol. 2009;65:12-18.

70. Decio A, Tonduti D, Pichiecchio A, Vetro A, Ciccone R, Limongelli I, Giorda R, Caffi L, Balottin U, Zuffardi O et al. A novel mutation in COL4A1 gene: a possible cause of early postnatal cerebrovascular events. Am J Med Genet. 2015;167A:810-815.
72. Değerliyurt A, Ceylaner G, Koçak H, Bilginer Gürbüz B, Cihan BS, Rizzu P, Ceylaner S. A new family with autosomal dominant porencephaly with a novel Col4A1 mutation. Are arachnoid cysts related to Col4A1 mutations? Genet Couns. 2012;23:185–193.
73. Deml B, Reis LM, Maheshwari M, Griffis C, Bick D, Semina EV. Whole exome analysis identifies dominant COL4A1 mutations in patients with complex ocular phenotypes involving microphthalmia. Clin Genet. 2014;86:475-481.
74. Dhamija R, Schiff D, Lopes MB, Jen JC, Lin DD, Worrall BB. Evolution of brain lesions in a patient with TREX1 cerebroretinal vasculopathy. Neurology. 2015;85:1633-1634.
75. Di Donato I, Bianchi S, Gallus GN, Cerase A, Federico A, Dotti MT. Heterozygous mutation of HTRA1 gene in an Italian family with cerebral ischemic small vessel disease. Eur J Neurol. 2016;23:559. (Abstract)
76. Di Donato I, Bianchi S, Gallus GN, Cerase A, Taglia I, Pescini F, Nannucci S, Battisti C, Inzitari D et al. Heterozygous mutations of HTRA1 gene in patients with familial cerebral small vessel disease. CNS Neurosci Ther. 2017;23:759-765.
77. DiFrancesco JC, Novara F, Zuffardi O, Forlino A, Gioia R, Cossu F, Bolognesi M, Andreoni S, Saracchi E, Frigeni B et al. TREX1 C-terminal frameshift mutations in the systemic variant of retinal vasculopathy with cerebral leukodystrophy. Neurousci. 2015;36:323-330.
78. Durrani-Kolarik S, Manickam K, Chen B. COL4A1 Mutation in a Neonate With Intrauterine Stroke and Anterior Segment Dysgenesis. Pediatr Neurol. 2017;66:100-103.
79. Ekinci RMK, Balci S, Bisgin A, Sasmaz I, Leblebisatan G, Inceck F, Yilmaz M. A homozygote novel L451W mutation in CECR1 gene causes deficiency of adenosine deaminase 2 in a pediatric patient representing with chronic lymphoproliferation and cytopenia. Pediatr. Hematol. Oncol. 2019;36:376–381.
80. Ekinci RMK, Balci S, Hershfield M, Bisgin A, Dogruel D, Altintas DU, Yilmaz M. Deficiency of adenosine deaminase 2: A case series revealing clinical manifestations, genotypes and treatment outcomes from Turkey. Rheumatol. U. K. 2020;59:254–256.
81. El Hasbani G, Balaghi A, Assaker R, Rojas A, Troya M, Kofahi A, Assaker JP, Diab C, Al Husayni H. Intraparenchymal hemorrhage and cerebral venous thrombosis in an adult with congenital porencephalic cyst presenting for generalized tonic-clonic seizures. Radiol. Case Rep. 2020;15:95–99.
82. Elbracht M, Mull M, Wagner N, Kuhl C, Abicht A, Kurth I, Tenbrock K, Häusler M. Stroke as Initial Manifestation of Adenosine Deaminase 2 Deficiency. Neuropediatrics. 2017;48:111-114.
83. Erden A, Batu ED, Taskiran EZ, Sonmez HE, Sari A, Armagan B, Kilic L, Arici ZS, Bilginer Y, Akdogan A et al. The characteristic features of the patients with deficiency of adenosine deaminase 2 (DADA2). Arthritis Rheumatol. 2016;68:4112-4114. (Abstract)
84. F. Variable clinical phenotypes and relation of interferon signature with disease activity in ADA 2 deficiency. Pediatr Rheumatol. 2017;15. (Abstract)
87. Fasano A, Formichi P, Taglia I, Bianchi S, Di Donato I, Battisti C, Federico A, Dotti MT. HTRA1 expression profile and activity on TGF-β signaling in HTRA1 mutation carriers. J. Cell. Physiol. 2020;235:7120–7127.

88. Favaretto S, Margoni M, Salviati L, Pianese L, Manara R, Baracchini C. A new Italian family with HTRA1 mutation associated with autosomal-dominant variant of CARASIL: Are we pointing towards a disease spectrum? J Neurol Sci. 2019;396:108-111.

89. Fujita M, Shimoyama K, Otsuka N, Maeda Y, Hayashi K, Saitsu H, Matsumoto N, Takanashi J-I. Familial patients with congenital hemiplegia due to a COL4A1 mutation. No To Hattatsu. 2018;50:424-426.

90. Gale D, Oygar DD, Lin F, Oygar DP, Connor TMF, Khan N, Lapsley M, Maxwell PH, Neild GH. A novel COL4A1 frameshift mutation and kidney disease without extra-renal involvement in a large Turkish cypriot family. Nephrol Dial Transplant. 2015;30:iii385. (Abstract)

91. Gale D, Oygar DD, Lin F, Oygar DP, Khan N, Connor TM, Lapsley M, Maxwell PH, Neild GH. A novel COL4A1 frameshift mutation in familial kidney disease: the importance of the C-terminal NC1 domain of type IV collagen. Nephrol Dial Transplant. 2016;31:1908–1914.

92. Garbarino F, Caorsi R, Volpi S, Grossi A, Ceccherini I, Gattorno M. A case of adenosine deaminase 2 deficiency (DADA2) with an uncommon clinical presentation and response to IVIG. Pediatr Rheumatol. 2019;17. (Abstract)

93. Garel C, Rosenblatt J, Moutard ML, Heron D, Gelot A, Gonzales M, Miné E, Jouannic JM. Fetal intracerebral hemorrhage and COL4A1 mutation: promise and uncertainty. Ultrasound Obstet Gynecol. 2013;41:228-230.

94. Garg N, Kasapcopur O, Foster J, Barut K, Tekin A, Kızılkılıç O, Tekin M. Novel adenosine deaminase 2 mutations in a child with a fatal vasculopathy. Eur J Pediatr. 2014;173:827-830.

95. Gasparini S, Qualtieri A, Ferlazzo E, Cianci V, Patitucci A, Spadafora P, Aguglia U. Normal immunofluorescence pattern of skin basement membranes in a family with porencephaly due to COL4A1 G749S mutation. Neurol Sci. 2016;37:459-463.

96. Geis T, Schirmer S, Walter M, Rodl T, Albrecht B, Schara U, Hehr U, Kolbel H. Massive parallel sequencing with a multigene panel (MGPS): Experiences with alpha-dystroglycanopathies. Neuropediatrics. 2016;47. (Abstract)

97. Gerasimenko A, Heron D, Billette De Villemeur T, Rodriguez D, Garel C, Tournier-Lasserve E, Chalard F, Mine M, Coste T, Mignot C. TORCH-like encephalopathy due to de novo COL4A1 mutation. Eur. J. Hum. Genet. 2019;27:1428–1429. (Abstract)

98. Ghurye RR, Sundaram K, Smith F, Clark B, Simpson MA, Fairbanks L, Adhya Z, Mufti GJ, Marsh JCW, Ibrahim MAA. Novel ADA2 mutation presenting with neutropenia, lymphopenia and bone marrow failure in patients with deficiency in adenosine deaminase 2 (DADA2). Br J Haematol. 2019;186:e60-64.

99. Gibson K, Cabral D, Drogemoller B, Xhan X, Miao F, Morishita K, Gill E, Hancock REW, Ross C, Brown K. Characterization of adenosine deaminase 2 variants identified in an international pediatric vasculitis cohort. Arthritis Rheumatol. 2017;69:Supplement 10. (Abstract)

100. Gibson KM, Morishita KA, Dancey P, Moorhead P, Drögelmöller B, Han X, Graham J, Hancock REW, Foell D, Benseler S et al. Identification of Novel Adenosine Deaminase
2 Gene Variants and Varied Clinical Phenotype in Pediatric Vasculitis. Arthritis Rheumatol. 2019;71:1747-1755.

101. Giorgio E, Vaula G, Bosco G, Giacone S, Mancini C, Calcia A, Cavalieri S, Di Gregorio E, Rigault De Longrais R, Lembruni S et al. Two families with novel missense mutations in COL4A1: When diagnosis can be missed. Neurol Sci. 2015;352:99-104.

102. Gomes I, Galego O, Santo GAPRC, Nunes C. CARASIL: An underdiagnosed disease. Eur. J. Neurol. 2019;26:381. (Abstract)

103. Goncalves T da S, Alves CAPF, da Paz JA, Lucato LT. Teaching NeuImages: Lacunar stroke and polyarteritis nodosa: Consider ADA2 deficiency (DADA2). Neurology. 2019;92:e1801–e1802.

104. Gonzalez Santiago TM, Zavialov A, Saarela J, Seppanen M, Reed AM, Abraham RS, Gibson LE. Dermatologic Features of ADA2 Deficiency in Cutaneous Polyarteritis Nodosa. JAMA Dermatol. 2015;151:1230-1234.

105. Goschl L, Winkler S, Dmytrus J, Heredia RJ, Lagler H, Ramharter M, Scheinecker C, Bonelli M, Schmetterer K, Pickl WF, et al. Unreported Missense Mutation in the Dimerization Domain of ADA2 Leads to ADA2 Deficiency Associated with Severe Oral Ulcers and Neutropenia in a Female Somali Patient-Addendum to the Genotype-Phenotype Puzzle. J. Clin. Immunol. 2020;40:223–226.

106. Gould DB, Phalan FC, Breedveld GJ, van Mil SE, Smith RS, Schimenti JC, Aguglia U, van der Knaap MS, Heutink P, John SW. Mutations in Col4a1 cause perinatal cerebral hemorrhage and porencephaly. Science. 2005;308:1167-1171.

107. Gould DB, Phalan FC, van Mil SE, Sundberg JP, Vahedi K, Massin P, Bousser MG, Heutink P, Miner JH, Tournier-Lasserve E et al. NEJM. 2006;354:1489-1496.

108. Green LMC, Berry I, McCullagh HG. Cecr1 mutation is an important cause of brainstem stroke. Dev Med Child Neurol. 2017;59:82-83.

109. Grego L, Pignatto S, Rassu N, Passone E, Cogo P, Lanzetta P. Optic Nerve Hypoplasia, Corpus Callosum Agenesis, Cataract, and Lissencephaly in a Neonate with a Novel COL4A1 Mutation. Case Rep. Ophthalmol. 2019;10:424–430.

110. Grond-Ginsbach C, Brandt T, Kloss M, Aksay SS, Lyrer P, Traenka C, Erhart P, Martin JJ, Altintas A, Siva A et al. Next generation sequencing analysis of patients with familial cerebral artery dissection. Eur Stroke J. 2017;2:137-143.

111. Grossi A, Cusano R, Rusmini M, Penco F, Schena F, Podda RA, Caorsi R, Gattorno M, Uva P, Ceccherini I. ADA2 deficiency due to a novel structural variation in 22q11.1. Clinical Genetics. 2019;95:732-733.

112. Grossi A, Garbarino F, Caorsi R, Cusano R, Rusmini M, Penco F, Schena F, Podda RA, Uva P, Ceccherini I et al. ADA2 deficiency without ADA2 mutations explained by a structural homozygous variation in 22Q11.1. Pediatr Rheumatol. 2019;17. (Abstract)

113. Gruber AM, Schoenfield L, Coleman JF, Hajji-Ali R, Rodriguez ER, Tan CD. Novel ophthalmic pathology in an autopsy case of autosomal dominant retinal vasculopathy with cerebral leukodystrophy. J Neuroophthalmol. 2011;31:20-24.

114. Gu J, Bennetts B, Holman K, Wong K, Parratt J, Krishnan A, Tchan M. Cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL): The first Australian cases. Twin Research and Human Genetics. 2016;19:567. (Abstract)

115. Gulati A, Bale AE, Dykas DJ, Bia MJ, Danovitch GM, Moeckel GW, Somlo S, Dahl NK. TREX1 Mutation Causing Autosomal Dominant Thrombotic Microangiopathy and CKD-A Novel Presentation. Am J Kidney Dis. 2018;72:895-899.
116. Gümrük F, Soltanova G, Akarsu N, Cetin M, Unal S. Immunological status of patients with diamond blackfan anemia. Am J Hum Genet. 2018;2:832-833. (Abstract)

117. Gunda B, Kovács T, Hornyák C, Bereczki D, Várallyay G, Rudas G, Mine M, Tournier-Lasserve E. Recurrent intracerebral hemorrhage in a young adult caused by COL4A2 mutation. Int J Stroke. 2015;10:369. (Abstract)

118. Gunda B, Mine M, Kovács T, Hornyák C, Bereczki D, Várallyay G, Rudas G, Audrezet MP, Tournier-Lasserve E. COL4A2 mutation causing adult onset recurrent intracerebral hemorrhage and leukoencephalopathy. J Neurol. 2014;261:500-503.

119. Gunda B, Mine M, Kovács T, Hornyák C, Bereczki D, Várallyay G, Rudas G, Tournier-Lasserve E. Col4a2 mutation causing recurrent intracerebral hemorrhage - Importance of screening both Col4a1 and Col4a2 in ICH of unknown origin. J Neurol Sci 2013;333:e174-175. (Abstract)

120. Gunduz T, Demirkol Y, Dogan O, Demir S, Akcakaya NH. A Case of Leukoencephalopathy and Small Vessels Disease Caused by a Novel HTRA1 Homozygous Mutation. J. Stroke. 2019;28:104354.

121. Ha TT, Sadleir LG, Mandelstam SA, Paterson SJ, Scheffer IE, Gecz J, Corbett MA. A mutation in COL4A2 causes autosomal dominant porencephaly with cataracts. Am J Med Genet. 2016;170A:1059-1063.

122. Ha TT, Sadleir LG, Mandelstam SA, Paterson SJ, Scheffer IE, Gecz J, Corbett MA. A mutation in COL4A2 causes autosomal dominant porencephaly with cataracts. Am J Med Genet. 2016;170A:1059-1063.

123. Hanson-Kahn A, Vlessis K, Smith EJ, Manning M. Defining the clinical features associated with variants in COL4A2: Case report and review of the literature. Eur. J. Hum. Genet. 2019;27:1274.

124. Hara K, Shiga A, Fukutake T, Nozaki H, Miyashita A, Yokoseki A, Kawata H, Koyama A, Arima K, Takahashi T et al. Association of HTRA1 mutations and familial ischemic cerebral small-vessel disease. N Engl J Med. 2009;360:1729-1739.

125. Harada T, Uegaki T, Arata K, Tsunetou T, Taniguchi F. Schizencephaly and Porencephaly Due to Fetal Intracranial Hemorrhage: A Report of Two Cases. Yonago Acta Med. 2017;60:241-245.

126. Hardy TA, Young S, Sy JS, Colley AF, Terwindt GM, Ferrari MD, Hayes MW, Hodkinson S. Tumefactive lesions in retinal vasculopathy with cerebral leucoencephalopathy and systemic manifestations (RVCL-S): a role for neuroinflammation? J Neurol Neurosurg Psychiatry. 2017:316142

127. Harel A, Raynowska J, Miskin D, Pramanik B, Asiry S, Anderson T, Boockvar J, Najjar S. Retinal vasculopathy with cerebral leucoencephalopathy (RVCL): A rare familial mimic of tumefactive multiple sclerosis (MS). Neurology. 2018;90:15. (Abstract)

128. Harteman JC, Groenendaal F, van Haastert IC, Liem KD, Stroink H, Bierings MB, Huisman A, de Vries LS. Atypical timing and presentation of periventricular haemorrhagic infarction in preterm infants: the role of thrombophilia. Dev Med Child Neurol. 2012;54:140-147.

129. Hashem H, Egler R, Dalal J. Refractory Pure Red Cell Aplasia Manifesting as Deficiency of Adenosine Deaminase 2. J Pediatr Hematol Oncol. 2017;39:e293-6.

130. Hashem H, Kumar AR, Müller I, Babor F, Bredius R, Dalal J, Hsu AP, Holland SM, Hickstein DD, Jalles S et al. Hematopoietic stem cell transplantation rescues the hematological, immunological, and vascular phenotype in DADA2. Blood. 2017;130:2682-2688.
131. Hashem H, Vatsayan A, Gupta A, Nagle K, Hershfield M, Dalal J. Successful reduced intensity hematopoietic cell transplant in a patient with deficiency of adenosine deaminase 2. Bone Marrow Transplant. 2017;52:1575-1576.

132. Hatano T, Daida K, Hoshino Y, Li Y, Saitsu H, Matsumoto N, Hatter N. Dystonia due to bilateral caudate hemorrhage associated with a COL4A1 mutation. Movement Disorders. 2017;32:823-824. (Abstract)

133. Hatano T, Daida K, Hoshino Y, Li Y, Saitsu H, Matsumoto N, Hattori N. Dystonia due to bilateral caudate hemorrhage associated with a COL4A1 mutation. Parkinsonism Relat Disord. 2017;40:80-82.

134. Hedderich DM, Lummel N, Deschauer M, Kumpfel T, Schuh E, Patzig M, Zimmer C, Huber T. Magnetic Resonance Imaging Characteristics of Retinal Vasculopathy with Cerebral Leukoencephalopathy and Systemic Manifestations. Clin Neuroradiol. 2019;1-8.

135. Heinrich T, Dufke A, Waldmuller S, Schoning M. Identification of a COL4A1 mutation in a boy with developmental delay, brain malformations, and bilateral cataract allows for prenatal testing in a subsequent pregnancy. Medizinische Genetik. 2016;28:153. (Abstract)

136. Hinman JD, Lee MD, Tung S, Vinters HV, Carmichael ST. Molecular disorganization of axons adjacent to human lacunar infarcts. Brain. 2015;138:736-745.

137. Hoffmann P, Ombrello AK, Stone DL, Barron K, Pinto-Patarroyo G, Jones A, Romeo T, Follmann D, Toro C, Soldatos A et al. Analysis of the use of anticoagulants and antiplatelet agents in strokes caused by the deficiency of adenosine deaminase 2. Arthritis Rheumatol. 2016;68:3110-3111. (Abstract)

138. Hoffmann PM, Ombrello A, Stone DL, Follmann D, Barron K, Jones A, Romeo T, Toro C, Soldatos A, Hay A et al. Risk of hemorrhagic strokes in patients with adenosine deaminase 2 deficiency. Arthritis Rheumatol. 2018;70:2517. (Abstract)

139. Hsu AP, West RR, Calvo KR, Cuellar-Rodriguez J, Parta M, Kelly SJ, Ganson NJ, Hershfield MS, Holland SM, Hickstein DD. Adenosine deaminase type 2 deficiency masquerading as GATA2 deficiency: Successful hematopoietic stem cell transplantation. Ann Rheum Dis. 2017;76:1648-1656.

140. Hsu AP, West RR, Calvo KR, Cuellar-Rodriguez J, Parta M, Kelly SJ, Ganson NJ, Hershfield MS, Holland SM, Hickstein DD. Adenosine deaminase type 2 deficiency masquerading as GATA2 deficiency: Successful hematopoietic stem cell transplantation. J. Allergy Clin. Immunol. 2016;138:628-630.e2.

141. Hwang YT, Lakshmanan R, Davagnanam I, Thompson AGB, Lynch DS, Houlden H, Bajaj N, Eriksson SH, Bamiou DE, Warren JD. Brainstem phenotype of cathepsin A-related arteriopathy with strokes and leukoencephalopathy. Neurol Genet. 2017;3:e165.

142. Ibrahim M, Nozaki H, Lee A, Onodera O, Reichwein R, Wicklund M, El-Ghanem M. A CARASIL Patient from Americas with Novel Mutation and Atypical Features: Case Presentation and Literature Review. Cerebrovasc Dis. 2017;44:135-140.

143. "Insalaco A, Moneta G, Pardeo M, Passarelli C, Celani C, Messia V, De Benedetti F. Variable clinical phenotypes and relation of interferon signature with disease activity in ADA 2 deficiency. Pediatr Rheumatol. 2017;15. (Abstract)"
145. Insalaco A, Moneta G, Pardeo M, Passarelli C, Celani C, Messia V, De Benedetti F. Variable clinical phenotypes and relation of interferon signature with disease activity in ADA 2 deficiency. Arthritis Rheumatol. 2016;68:3111-3112. (Abstract)

146. Insalaco A, Moneta GM, Pardeo M, Caiello I, Messia V, Bracaglia C, Passarelli C, De Benedetti F. Variable Clinical Phenotypes and Relation of Interferon Signature with Disease Activity in ADA2 Deficiency. J Rheumatol. 2019;46:523-526.

147. Ito J, Nozaki H, Toyoshima Y, Abe T, Sato A, Hashidate H, Igarashi S, Onodera O, Takahashi H, Kakita A. Histopathologic features of an autopsied patient with cerebral small vessel disease and a heterozygous HTRA1 mutation. Neuropathology. 2018;38:428-432.

148. Ito S, Takao M, Fukutake T, Hatsuta H, Funabe S, Ito N, Shimoe Y, Niki T, Nakano I, Fukayama M et al. Histopathologic Analysis of Cerebral Autosomal Recessive Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CARASIL): A Report of a New Genetically Confirmed Case and Comparison to 2 Previous Cases. J Neuropathol Exp Neurol. 2016;75:1020-1030.

149. Ito S, Takao M, Nogami A, Funabe S, Hatsuta H, Niki T, Ito N, Fukutake T, Shimoe Y, Fukayama M, et al. Cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL): neuropathological examinations of three genetically confirmed autopsied cases. Neuropathology. 2012;32:363. (Abstract)

150. Jeanne M, Labelle-Dumais C, Jorgensen J, Kauffman WB, Mancini GM, Favor J, Valant V, Greenberg SM, Rosand J, Gould DB. COL4A2 mutations impair COL4A1 and COL4A2 secretion and cause hemorrhagic stroke. Am J Hum Genet. 2012;90:91-101.

151. John S, Jehi L, Manno EM, Conway DS, Uchino K. COL4A1 gene mutation—beyond a vascular syndrome. Seizure. 2015;31:19-21.

152. Jordan MA, Pierpont ME, Johnston RH, Lee MS, Mcclelland CM. Hereditary angiopathy with nephropathy, aneurysm, and muscle cramps (hanac) syndrome presenting to neuro-ophthalmology with metamorphopsia. J. Neuroophthalmol. 2019;39:506–510.

153. Kaljas Y, Liu C, Skaldin M, Wu C, Zhou Q, Lu Y, Aksentijevich I, Zavialov AV. Human adenosine deaminases ADA1 and ADA2 bind to different subsets of immune cells. Cell. Mol. Life Sci. 2017;74:555–570.

154. Kamo H, Conedera SA, Ogaki K, Daida K, Li Y, Funabashi M, Yoshino H, Funayama M, Nishioka K, Hattori N. Genetic analyses of HTRA1 and CTSA in Japanese patients with cerebral small vessel disease. Clin. Neurol. 2019;59:S409. (Abstract)

155. Karacan İ, Balamir A, Uğurlu S, Aydin AK, Everest E, Zor S, Önen M, Daşdemir S, Özkaya O, Sözeri B et al. Diagnostic utility of a targeted next-generation sequencing gene panel in the clinical suspicion of systemic autoinflammatory diseases: a multicenter study. Rheumatol Int. 2019;39:911-919.

156. Keer N, Hershfield M, Caskey T, Unizony S. Novel compound heterozygous variants in CECR1 gene associated with childhood onset polyarteritis nodosa and deficiency of ADA2. Rheumatology. 2016;55:1145-1147.

157. Kellett S, Lemaire M, Miller SP, Licht C, Yoon G, Dlamini N, Noone D. Neonatal stroke and haematuria: Answers. Pediatr Nephrol. 2018;33:807-811.
159. Kellett S, Lemaire M, Miller SP, Licht C, Yoon G, Dlamini N, Noone D. Neonatal stroke and haematuria: Questions. Pediatr Nephrol. 2018;33:805-806.

160. Khaleeli Z, Jaunmuktane Z, Beaufort N, Houlden H, Haffner C, Brandner S, Dichgans M, Werring D. A novel HTRA1 exon 2 mutation causes loss of protease activity in a Pakistani CARASIL patient. J Neurol. 2015;262:1369-1372.

161. Khalid R, Krishnan P, Andres K, Blaser S, Miller S, Mohair M, Dlamini N. COL4A1 and fetal vascular origins of schizencephaly. Neurology. 2018;90:232-234.

162. Khalid R, Krishnan P, Blaser S, Andres K, Miller S, Mohair M, Dlamini N. Fetal vascular origins of schizencephaly. Ann Neurol. 2016;80:S341-S343. (Abstract)

163. Kilic SS, Cekic S, Karali Y. Cerebral ischemic attacks in ADA2 deficiency treated with adalimumab. Allergy Eur. J. Allergy Clin. Immunol. 2019;74:828. (Abstract) (a)

164. Kilic SS, Cekic S, Karali Y. Severe neutropenia in ADA2 deficiency. Arch. Dis. Child. 2019;104:A304. (Abstract) (b)

165. Kinoshita K, Ishizaki Y, Yamamoto H, Sonoda M, Yonemoto K, Kira R, Sanefuji M, Ueda A, Matsui H, Ando Y, et al. De novo p.G696S mutation in COL4A1 causes intracranial calcification and late-onset cerebral hemorrhage: A case report and review of the literature COL4A1-associated vasculopathy. Eur. J. Med. Genet. 2020;63:103825.

166. Kitzler TM, Schneider R, Kohl S, Kolvenbach CM, Connaughton DM, Dai R, Mann N, Nakayama M, Majmundar AJ, Wu CW et al. COL4A1 mutations as a potential novel cause of autosomal dominant CAKUT in humans. Hum Genet. 2019;138:1105-1115.

167. Klemans RJB, Leavis HL, van Montfrans JM, van Dijk MR, Sanders CJG. Recurrent painful ulcers. Ned. Tijdschr. Voor Dermatol. En Venereol. 2019;29:46-48.

168. Koerber I, Kudernatsch M, Hartlieb T, Selch C, Sisodiya S, Coras R, Blumcke I, Winkler P, Berweck S, Kluger G. Histopathology and MRI findings in two children with COL4A1/-2 mutation related epilepsy. Epilepsia. 2018;59:S188. (Abstract)

169. Kollmann P, Peeters A, Vanacker O, Sznajer Y. 'De novo' Col4A2 mutation in a patient with migraine, leukoencephalopathy, and small carotid aneurysms. J Neurol. 2016;263:2327-2329.

170. Komaki R, Ueda T, Tsuji Y, Miyawaki T, Kusuhara S, Hara S, Toda T. Retinal vasculopathy with cerebral leukoencephalopathy carrying TREX1 mutation diagnosed by the intracranial calcification: a case report. Rinsho Shinkeigaku. 2018;58:111-117.

171. Kono Y, Nishioka K, Komatsu Y, Ito Y, Yoshino H, Tanaka R, Hattori N, Iguchi Y. CADASIL type 2 in two families presenting mimic symptoms of CARASIL. J Neurol Sci. 2017;381. (Abstract)

172. Kono Y, Nishioka K, Li Y, Komatsu Y, Ito Y, Yoshino H, Tanaka R, Iguchi Y, Hattori N. Heterozygous HTRA1 mutations with mimicking symptoms of CARASIL in two families. Clin Neurol Neurosurg. 2018;172:174-176.

173. Konstantoulaki E, Siddiqui A, Amaya L, Gowda V. Case presentation: Developmental delay, cataracts and seizures with white matter infarctions explained by a novel COL4A1 mutation on a young child. Dev Med Child Neurol. 2017;59:93.(Abstract) (a)

174. Konstantoulaki E, Siddiqui A, Livingston J, Gowda V. Novel mutation in COL4A1 in a boy with cataracts, gross motor and speech delay, seizures, stroke and deep white matter changes on neuroimaging. Dev Med Child Neurol. 2017;59:99. (Abstract) (b)

175. Krutzke S, Horneff G. Treatment of Two Male Children Suffering From Deficiency of Adenosine Deaminase Type 2 (DADA2) With TNF-Inhibitor Etanercept. J. Clin. Rheumatol. Pract. Rep. Rheum. Musculoskelet. Dis. 2019;Publish Ahead of Print.
176. Kumar AR, Hickstein DD, Ghadir SS, Bertuch AA, Krance RA, Hsu AP, Hashem H, Babor F, Meisel R, Koskenvuo M et al. Hematopoietic stem cell transplantation rescues the vascular, haematological and immunological phenotype in adenosine deaminase 2 deficiency. J Clin Immunol. 2017;37:247-248.

177. Kunii M, Doi H, Kubota S, Hashiguchi S, Hirama N, Ogawa Y, Takahashi K, Tanaka K, Tada M et al. Genetic analysis of adult leukoencephalopathy patients using whole exon sequencing. J Neurol Sci. 2017;381:455. (Abstract)

178. Labauge P, Carra-Dalliere C, Ayrignac X, De Champfleur NM, Aubourg P, Bellesme C, Pelletier J, Audoin B, De Seze J, Collongues N, et al. Diagnosis of adult onset leukodystrophy in a consecutive study of 156 patients. Neurology. 2013;80:1 MeetingAbstracts. (Abstract)

179. Labelle-Dumais C, Dilworth DJ, Harrington EP, de Leau M, Lyons D, Kabaeva Z, Manzini MC, Dobyns WB, Walsh CA, Michele DE et al. COL4A1 mutations cause ocular dysgenesis, neuronal localization defects, and myopathy in mice and Walker-Warburg syndrome in humans. PLoS Genet. 2011;7:e1002062.

180. Labelle-Dumais C, Schuitema V, Hayashi G, Hoff K, Gong W, Dao DQ, Ullian EM, Oishi P, Margeta M, Gould DB. COL4A1 Mutations Cause Neuromuscular Disease with Tissue-Specific Mechanistic Heterogeneity. Am J Hum Genet. 2019;104:847-860.

181. Lamprecht P, Humrich JY, Diebold I, Riemekasten G. Diagnosis of deficiency of adenosine deaminase 2 with early onset polyarteritis nodosa in an adult patient with a novel compound heterozygous CECR1 mutation. Clin Exp Rheumatol. 2018;36:177.

182. Lee PY, Kellner ES, Huang Y, Furutani E, Huang Z, Bainter W, Alosaimi MF, Stafstrom K, Platt CD, Stauber T, et al. Genotype and functional correlates of disease phenotype in deficiency of adenosine deaminase 2 (DADA2). J. Allergy Clin Immunol. 2020;145:1664–1672.

183. Lee YC, Chung CP, Chao NC, Fuh JL, Chang FC, Soong BW, Liao YC. Characterization of Heterozygous HTRA1 Mutations in Taiwanese Patients with Cerebral Small Vessel Disease. Stroke. 2018;49:1593-1601.

184. Lee YC, Huang Y, Zhou Q, Schnappauf O, Hershfield MS, Li Y, Ganson NJ, Sampaio Moura N, Delmonte OM, Stone SS et al. Disrupted N-linked glycosylation as a disease mechanism in deficiency of ADA2. J Allerg Clin Immunol. 2018;142:1363-1365.

185. Lemmens R, Maugeri A, Niessen HW, Goris A, Tousseyn T, Damaerel P, Corveleyn A, Robberecht W, van der Knaap MS, Thijs VN et al. Novel COL4A1 mutations cause cerebral small vessel disease by haploinsufficiency. Hum Mol Genet. 2013;22:391-397.

186. Leung M, Lewis EC, Humphreys P, Miller E, Geraghty M, Lines M, Sell E. COL4A1 mutation in a pediatric patient presenting with post-ictal hemiparesis. Can J Neurol Sci. 2012;39:654-657.

187. Leung M, Lewis EC, Humphreys P, Miller E, Lines M, Sell E. COL4A1 mutation in a pediatric patient presenting with a Todd's paresis. Can J Neurol Sci. 2011;38:568-569. (Abstract)

188. Li WR, Zhao DH, Wang ZX, Hong DJ, Zhang W, Yuan Y. Novel mutation of HTRA1 gene causes cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy: one case. Chinese Journal of Neurology. 2012;45:566-569.

189. Liao YC, Chao NC, Lee YC. Heterozygous HTRA1 mutation in Taiwanese patients with cerebral small vessel disease. Neurology. 2017;88(16). (Abstract) (a)
190. Liao YC, Chao NC, Tsai PC, Soong BW, Lee YC. Heterozygous HTRA1 mutation in Taiwanese patients with cerebral small vessel disease. J Neurol Sci. 2017;381:456. (Abstract) (b)

191. Lichtenbelt KD, Pistorius LR, De Tollenaer SM, Mancini GM, De Vries LS. Prenatal genetic confirmation of a COL4A1 mutation presenting with sonographic fetal intracranial hemorrhage. Ultrasound Obstet Gynecol. 2012;39:726-727.

192. Liebowitz J, Hellmann DB, Schnappauf O. Thirty Years of Follow up in 3 Patients with Familial Polyarteritis Nodosa due to Adenosine Deaminase 2 Deficiency. J Rheumatol. 2019;46:1059-1060.

193. Liu L, Wang W, Wang Y, Hou J, Ying W, Hui X, Zhou Q, Liu D, Yao H, Sun J et al. A Chinese DADA2 patient: report of two novel mutations and successful HSCT. Immunogenetics. 2019;71:299-305.

194. Livingston J, Doherty D, Orcesi S, Tonduti D, Piechciechio A, La Piana R, Tourner-Lasserve E, Majumdar A, Tomkins S, Rice G et al. COL4A1 mutations associated with a characteristic pattern of intracranial calcification. Neuropediatrics. 2011;42:227-233.

195. Livingston JH, Stivaros S, van der Knaap MS, Crow YJ. Recognizable phenotypes associated with intracranial calcification. Dev Med Child Neurol. 2013;55:46-57.

196. Loureiro G, Oliveira D, Ganhaos S, Aguiar F, Rodrigues M, Brito I. ADA2 deficiency presenting as infantile polyarteritis nodosa. Ann. Rheum. Dis. 2019;78:1985.

197. Low WC, Junna M, Börjesson-Hanson A, Morris CM, Moss TH, Stevens DL, St Clair D, Mizuno T, Zhang WW, Mykkänen K et al. Hereditary multi-infarct dementia of the Swedish type is a novel disorder different from NOTCH3 causing CADASIL. Brain. 2007;130:357-367.

198. Low WC, Junna M, Börjesson-Hanson A, Morris CM, Moss TH, Stevens DL, St Clair D, Mizuno T, Zhang WW, Mykkänen K et al. Hereditary multi-infarct dementia of the Swedish type is a novel disorder different from NOTCH3 causing CADASIL. Brain. 2007;130:357-367.

199. Lynch D, De Paiva ARB, Zhang WJ, Lakshmanan R, Davagnanam I, Fox N, Murphy E, Kok F, Chataway J, Houlden H. Clinical and genetic characterisation of adult onset leukoencephalopathy. Neurology. 2017;88:16 Supplement 1. (Abstract)

200. Lynch DS, Rodrigues Brandão de Paiva A, Zhang WJ, Bugiardini E, Freua F, Tavares Lucato L, Macedo-Souza LI, Lakshmanan R, Kinsella JA, Merwick A et al. Clinical and genetic characterization of leukoencephalopathies in adults. Brain. 2017;140:1204-1211.

201. Maccora I, Frongia I, Azzari C, Ricci S, Cimaz R, Simonini G. A misleading case of deficiency of adenosine deaminase 2 (DADA2): the magnifying glass of the scientific knowledge drives the tailored medicine in real life. Clin Exp Rheumatol. 2018;36:146.

202. Magnin E, Ayrignac X, Berger E, Mine M, Tournier-Lasserve E, Labauge P. Late diagnosis of COL4A1 mutation and problematic vascular risk factor management. Eur Neurol. 2014;72:150-152.

203. Maisonneuve E, M’Barek IB, Leblanc T, Da Costa L, Friszer S, Pernot F, Thomas P, Castaigne V, N’Dour CT, Mailloux A et al. Managing the Unusual Causes of Fetal Anemia. Fetal Diagn. Ther. 2020;47:156–164.

204. Mancini GM, de Coo IF, Lequin MH, Arts WF. Hereditary porencephaly: clinical and MRI findings in two Dutch families. Eur J Paediatr Neurol. 2004;8:45-54.
205. Martin H, Bursztejn AC, Cuny JF, Sarrabay G, Schmutz JL, Touitou I, Wahl D,
    Bonhomme A. Chronic leg ulcer revealing adenosine deaminase 2 deficiency: an
    atypical presentation. Eur J Dermatol. 2018;28:847-848.

206. Mateen FJ, Krecke K, Younge BR, Ford AL, Shaikh A, Kothari PH, Atkinson JP.
    Evolution of a tumor-like lesion in cerebroretinal vasculopathy and TREX1 mutation.
    Neurology. 2010;75:1211-1213.

207. Matias-Perez D, Garcia-Montano LA, Cruz-Aguilar M, Garcia-Montalvo IA, Nava-
    Valdez J, Barragan-Arevalo T, Villanueva-Mendoza C, Villarroel CE, Guadarrama-
    Vallejo C, la Cruz RV-D et al. Identification of novel pathogenic variants and novel
    gene-phenotype correlations in Mexican subjects with microphthalmia and/or
    anophthalmia by next-generation sequencing. J Hum Genet. 2018;63:1169-1180.

208. Matsumoto T, Miyakoshi K, Fukutake M, Ochiai D, Minegishi K, Tanaka M.
    Intracranial sonographic features demonstrating in utero development of
    hemorrhagic brain damage leading to schizencephaly-associated COL4A1 mutation. J
    Med Ultrason. 2015;42:445-446.

209. Matthew S, Graf W, Szekely A. An autosomal dominant arteriopathy of the brain due
    to a novel mutation in collagen 4A1 gene in a family with early-onset stroke and
    leukoencephalopathy. Neurology. 2014;82:10 Suppl 1. (Abstract)

210. McGovern M, Flanagan O, Lynch B, Lynch SA, Allen NM. Novel COL4A2 variant in a
    large pedigree: Consequences and dilemmas. Clin Genet. 2017;92:447-448.

211. Mendioroz M, Fernandez-Cadenas I, del Rio-Espinola A, Rovira A, Sole E, Fernandez-
    Figueras MT, Garcia-Patos V, Sastre-Garriga J, Domingues-Montanari S, Alvarez-Sabin
    J, et al. A missense HTRA1 mutation expands CARASIL syndrome to the Caucasian
    population. Neurology. 2010;75:2033–2035.

212. Menezes Cordeiro I, Nzwalo H, Sá F, Ferreira RB, Alonso I, Afonso L, Basílio C. Shifting
    the CARASIL paradigm: report of a non-Asian family and literature review. Stroke.
    2015;46:1110-1112.

213. Menter T, Winkler D, Isimbaldi G, Hopfer H, Mihatsch M. TREX1 mutations - one of
    the genetic causes for renal vascular diseases in younger patients. Swiss Medical
    Weekly. 2013;143:23S. (Abstract) (a)

214. Menter T, Winkler D, Isimbaldi G, Hopfer H, Mihatsch M. TREX1 mutations - one of
    the genetic causes for renal vascular diseases in younger patients. Virchows Archiv.
    2013;463:298. (Abstract) (b)

215. Meuwissen ME, de Vries LS, Verbeek HA, Lequin MH, Govaert PP, Schot R, Cowan
    FM, Hennekam R, Rizzu P, Verheijen FW et al. Sporadic COL4A1 mutations with
    extensive prenatal porencephaly resembling hydranencephaly. Neurology.
    2011;76:844- 846.

216. Meuwissen ME, Halley DJ, Smit LS, Lequin MH, Cobben JM, de Coo R, van Harssel J,
    Sallevelt S, Woldringh G, van der Knaap MS, de Vries LS, Mancini GM. The expanding
    phenotype of COL4A1 and COL4A2 mutations: clinical data on 13 newly identified
    families and a review of the literature. Genet Med. 2015;17:843-853.

217. Michniacki TF, Hannibal M, Ross CW, Frame DG, DuVall AS, Khoriaty R, Vander Lugt
    MT, Walkovich KJ. Hematologic Manifestations of Deficiency of Adenosine
    Deaminase 2 (DADA2) and Response to Tumor Necrosis Factor Inhibition in DADA2-
    Associated Bone Marrow Failure. J Clin Immunol. 2018;38:166-173.
218. Michniacki TF, Hannibal M, Walkovich KJ, VanderLugt MT, Hershfield M, Frame DG, DuVall AS. Bone marrow failure secondary to ADA2 deficiency in adult siblings. J Clin Immunol. 2017;37:246. (Abstract)

219. Mishra A, Chauhan G, Violleau M-H, Vojinovic D, Jian X, Bis JC, Li S, Saba Y, Grenier-Boley B, Yang Q, et al. Association of variants in HTRA1 and NOTCH3 with MRI-defined extremes of cerebral small vessel disease in older subjects. Brain. 2019;142:1009–1023.

220. Mishra A, Violleau MH, Chauhan G, Mazoyer B, Tzourio C, Debette S. Exome sequence study on extreme MRI markers of cerebral small vessel disease. Stroke. 2018;49. (Abstract)

221. Monroy-Jaramillo N, Cerón A, León E, Rivas V, Ochoa-Morales A, Arteaga-Alcaraz MG, Nocedal-Rustrian FC, Gallegos C, Alonso-Vilatela ME, Corona T. Phenotypic Variability in a Mexican Mestizo Family with Retinal Vasculopathy with Cerebral Vasculopathy with Cerebral Leukodystrophy and TREX1 Mutation p.V235Gfs*6. Rev Invest Clin. 2018;70:68-75.

222. Morsi A, Maldonado A, Lal D, Moosa ANV, Pestana-Knight E, Bingaman W. Vasospasm Following Hemispherectomy: A Case Report of a Novel Complication. World Neurosurg. 2020;137:357–361.

223. Muinjonov B, Giyazitdinova E. Myelin repair correlates with CARASIL-associated neurological deficits. Eur J Neurol. 2016;23:500. (Abstract)

224. Munshi S, Eason J, Shetty AK, Sunman W, Evans A, Gruener A, Ho E, Lakhani B. COL4A1 variant presenting as recurrent stroke and cerebral small vessel disease. Int J Stroke. 2018;13:65. (Abstract)

225. Murray LS, Lu Y, Taggart A, Van Regemorter N, Vilain C, Abramowicz M, Kadler KE, Van Agtmael T. Chemical chaperone treatment reduces intracellular accumulation of mutant collagen IV and ameliorates the cellular phenotype of a COL4A2 mutation that causes haemorrhagic stroke. Hum Mol Genet. 2014;23:283-292.

226. Nagiel A, Lalane RA, Jen JC, Kreiger AE. Superficial and deep capillary ischemia as a presenting sign of retinal vasculopathy with cerebral leukoencephalopathy and systemic manifestations. Retin Cases Brief Rep. 2018;12 Suppl 1:S87-S91.

227. Naidu G, Acharya N, Jha S, Chattopadhyay A, Dhir V, Goyal M, Modi M, Nada R, Minz RW, Jain S et al. Deficiency of adenosine deaminase 2: Report of three cases from single center in North India. Indian J Rheum. 2018;13:S211–212. (Abstract)

228. Nandeesh BN, Bindu PS, Narayanappa G, Chickabasaviah Yasha T, Mahadevan A, Kulanthaivelu K, Santosh V. Cerebral small vessel disease with hemorrhagic stroke related to COL4A1 mutation: A case report. Neuropathology. 2020;40:93–98.

229. Nanthapisal S, Murphy C, Omoyinmi E, Hong Y, Standing A, Berg S, Ekelund M, Jolles S, Harper L, Youngstein T et al. Deficiency of Adenosine Deaminase Type 2: A Description of Phenotype and Genotype in Fifteen Cases. Arthritis Rheumatol. 2016;68:2314-2322.

230. Nanthapisal S, Murphy C, Omoyinmi E, Standing A, Hong Y, Gomes SM, Klein N, Eleftheriou D, Brogan PA. Monogenic polycystic kidney disease caused by ADA2 deficiency: The GOSH experience. Pediatr Rheumatol. 2015;13:89. (Abstract)

231. Nau S, McCourt EA, Maloney JA, Van Hove JL, Saenz M, Jung JL. COL4A1 mutations in two infants with congenital cataracts and porencephaly: an ophthalmologic perspective. J. AAPOS. 2019;23:246–248.
232. Navon Elkan P, Pierce SB, Segel R, Walsh T, Barash J, Padeh S, Zlotogorski A, Berkun Y, Press JJ, Mukamel M et al. Mutant adenosine deaminase 2 in a polyarteritis nodosa vasculopathy. N Engl J Med. 2014;370:921-931.

233. Navon Elkan P, Pierce SB, Segel R, Walsh T, Barash J, Padeh S, Zlotogorski A, Berkun Y, Press JJ, Mukamel M et al. Mutant adenosine deaminase 2 in a polyarteritis nodosa vasculopathy. N Engl J Med. 2014;370:921-931.

234. Neishabury M, Mehri M, Fattahi Z, Najmabadi H, Azarkeivan A. Novel variants in Iranian individuals suspected to have inherited red blood cell disorders, including bone marrow failure syndromes. Haematologica. 2020;105:E1–E4.

235. Ng J, Gunny R, Prabhakar PS, Carr LJ, Saunders DE. The expanding neuroradiological phenotype of COL4A1 gene mutations. Dev Med Child Neurol. 2013;55:23. (Abstract)

236. Nishimoto Y, Shibata M, Nihonmatsu M, Nozaki H, Shiga A, Shirata A, Yamane K, Kosakai A, Takahashi K, Nishizawa M et al. Neurology. 2011;76:1353-1355. (a)

237. Nishimoto Y, Shibata M, Onodera O, Suzuki N. Neurological picture. Neuroaxonal integrity evaluated by MR spectroscopy in a case of CARASIL. J Neurol Neurosurg Psychiatry. 2011;82:860-861. (b)

238. Niwa T, Aida N, Osaka H, Wada T, Saitsu H, Imai Y. Intracranial Hemorrhage and Tortuosity of Veins Detected on Susceptibility-weighted Imaging of a Child with a Type IV Collagen α1 Mutation and Schizencephaly. Magn Reson Med Sci. 2015;14:223-226.

239. Nozaki H, Kato T, Nihonmatsu M, Saito Y, Mizuta I, Noda T, Koike R, Miyazaki K, Kaito M, Ito S et al. Distinct molecular mechanisms of HTRA1 mutants in manifesting heterozygotes with CARASIL. Clin Neurol. 2016;56:S325. (Abstract)

240. Nozaki H, Kato T, Nihonmatsu M, Saito Y, Mizuta I, Noda T, Koike R, Miyazaki K, Kaito M, Ito S et al. Distinct molecular mechanisms of HTRA1 mutants in manifesting heterozygotes with CARASIL. Neurology. 2016;86:1964-1974.

241. Nozaki H, Nishizawa M, Onodera O. Features of cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy. Stroke. 2014;45:3447-3453.

242. Nozaki H, Sekine Y, Fukutake T, Nishimoto Y, Shibata M, Yutaka S, Shirata A, Yanagawa S, Hirayama M, Yamane K, et al. MRI features of cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy. Neurology. 2013;80:1 MeetingAbstracts. (Abstract)

243. Nozaki H, Sekine Y, Fukutake T, Nishimoto Y, Shimoe Y, Shirata A, Yanagawa S, Hirayama M, Tamura M, Nishizawa M et al. Characteristic features and progression of abnormalities on MRI for CARASIL. Neurology. 2015;85:459-463.

244. O’Neill R, O’Mahony O, McSweeney N. COL4A1 mutation inherited from maternal mosaicism in an infant presenting with microcephaly, haemolytic anaemia and cataracts. Arch. Dis. Child. 2019;104:A126–A127.

245. Ohta K, Ozawa T, Fujinaka H, Goto K, Nakajima T. Cerebral Small Vessel Disease Related to a Heterozygous Nonsense Mutation in HTRA1. Intern. Med. 2020;59:1309–1313.

246. Okano S, Shimada S, Tanaka R, Okayama A, Kajihama A, Suzuki N, Nakau K, Takahashi S, Matsumoto N, Saitsu H, et al. Life-threatening muscle complications of COL4A1-related disorder. Brain Dev. 2020;42:93–97.
247. Oluwole OJ, Ibrahim H, Garozzo D, Ben Hamouda K, Ismail Mostafa Hassan S, Hegazy AM, Msaddi AK. Cerebral small vessel disease due to a unique heterozygous HTRA1 mutation in an African man. Neurol. Genet. 2020;6:e382.

248. Ombrello A, Stone D, Hoffmann P, Jones A, Barham B, Barron K, Flegel W, Sheldon S, Zhou Q, Hershfield M et al. The deficiency of adenosine deaminase type 2-results of therapeutic intervention. Pediatr Rheumatol. 2015;13:37. (Abstract)

249. Ombrello AK, Barron K, Hoffmann P, Toro C, Stone DL, Pinto-Patarroyo G, Jones A, Romeo T, Soldatos A, Zhou Q et al. The deficiency of adenosine deaminase type 2 (DADA2)-results of anti-TNF treatment in a cohort of patients with a history of stroke. Arthritis Rheumatol. 2016;68:4288-4289. (Abstract)

250. Ombrello AK, Stone DL, Barron K, Hoffmann PM, Cudrici C, Jones A, Romeo T, Dimitrova D, Dotan A, Wall D et al. Analysis of the efficacy of treatment on 45 patients with deficiency of adenosine deaminase 2. Pediatr Rheumatol. 2019;17. (Abstract)

251. Ouail DE, Tebbani M, Si Ahmed D, Bouali F. Youth hypertension associated with ADA2 deficiency. About three cases. J. Hypertens. 2019;37:e215. (Abstract)

252. Ozen S, Batu ED, Taskiran EZ, Ozkara HA, Unal S., Guleray N, Erden A, Karadag O, Gumruk F, Cetin M, et al. A monogenic disease with a variety of phenotypes: Deficiency of adenosine deaminase 2. J. Rheumatol. 2020;47:117–125.

253. Paisal V, Al-Abadi E, Southwood T, Wassmer E. Childhood onset stroke and vasculitis associated with deficiency of adenosine deaminase 2 (dada2). Ann Rheum Dis. 2017;76:1395. (Abstract)

254. Paola K, Gomes FHR, Benevides LC, Leite MF, Medeiros P, Santos AC, De Carvalho LM, Ferriani V. CECR1/ADA2 mutation in a Brazilian family. Ann. Rheum. Dis. 2019;78:2009. (Abstract)

255. Papandreou A, Tisdall MM, Chong WK, Cross JH, Harkness WF, Varadkar SM. COL4A1 mutations should not be a contraindication for epilepsy surgery. Childs Nerv Syst. 2014;30:1467-1469.

256. Papandreou A, Tisdall MM, Harkness WF, Cross JH, Varadkar SM. COL4A1 mutations should not be a contraindication for epilepsy surgery. Epilepsia. 2014;55:245. (Abstract)

257. Pati AR, Battisti C, Taglia I, Galluzzi P, Bianchi M, Federico A. A new case of autosomal dominant small vessel disease carrying a novel heterozygous mutation in HTRA1 gene: 2-year follow-up. Neurol Sci. 2018;39:1479-1481.

258. Pelzer N, Bijkerk R, Reinders MEJ, van Zonneveld AJ, Ferrari MD, van den Maagdenberg AMJM, Eikenboom J, Terwindt GM. Circulating Endothelial Markers in Retinal Vasculopathy With Cerebral Leukoencephalopathy and Systemic Manifestations. Stroke. 2017;48:3301-3307.

259. Pelzer N, Hoogeveen ES, Haan J, Bunnik R, Poot CC, van Zwet EW, Inderson A, Fogteloo AJ, Reinders MEJ, Middelkoop HAM et al. Systemic features of retinal vasculopathy with cerebral leukoencephalopathy and systemic manifestations: a monogenic small vessel disease. J Intern Med. 2019;285:317-332.

260. Pescini F, Donni I, Asaro A, Rinnoci V, Squitieri M, Nannucci S, Poggesi A, Di Donato I, Bianchi S, Cereda C, et al. Screening for COL4A1 and COL4A2 mutations in patients with familiar microangiopathy. Eur. Stroke J. 2019;4:699–700.
261. Pichard DC, Ombrello AK, Hoffmann P, Stone DL, Cowen EW. Early-onset stroke, polyarteritis nodosa (PAN), and livedo racemosa. J Am Acad Dermatol. 2016;75:449-453.

262. Plaisier E, Chen Z, Gekeler F, Benhassine S, Dahan K, Marro B, Alamowitch S, Paques M, Ronco P. Novel COL4A1 mutations associated with HANAC syndrome: a role for the triple helical CB3[IV] domain. Am J Med Genet. 2010;152A:2550-2555.

263. Plaisier E, Gribouval O, Alamowitch S, Mougenot B, Prost C, Verpont MC, Marro B, Desmettre T, Cohen SY, Roulet E. et al. COL4A1 mutations and hereditary angiopathy, nephropathy, aneurysms, and muscle cramps. N Engl J Med. 2007;357:2687-2695.

264. Plancher JM, Hufnagel RB, Vagal A, Pearlso K, Saal HM, Broderick JP. Case of Small Vessel Disease Associated with COL4A1 Mutations following Trauma. Case Rep Neurol. 2015;7:142-147.

265. Plancher JM, Hufnagel RB, Vagal A, Pearlso K, Saal HM, Broderick JP. Case of Small Vessel Disease Associated with COL4A1 Mutations following Trauma. Case Rep Neurol. 2015;7:142-147.

266. Pode-Shakked B, Marek-Yagel D, Navon-Elkan P, Pierce SB, Segel R, Walsh T, Padeh S, Fairbanks L, Pras E, Winkelmann J et al. Adenosine deaminase 2 (ADA2) deficiency: A novel inborn error of purine metabolism. Mol Genet Metab. 2014;111:232-233.

267. Poswar F, Da Fonseca RM, de Albuquerque LC, Zhou Q, Jardim LB, Monte TL, Aksentijevich I, Saute JA. Adenosine deaminase 2 deficiency presenting as spastic paraplegia and systemic vasculitis. J Neurol. 2016;263:818-820.

268. Preethish-Kumar V, Nozaki H, Tiwari S, Vengalil S, Bhat M, Prasad C, Onodera O, Uemura M, Doniparthi S, Saini J et al. CARASIL families from India with 3 novel null mutations in the HTRA1 gene. Neurology. 2017;89:2392-2394.

269. Rama M, Duflos C, Melki I, Bessis D, Bonhomme A, Martin H, Doummar D, Valence S, Rodriguez D, Carme E et al. A decision tree for the genetic diagnosis of deficiency of adenosine deaminase 2 (DADA2): a French reference centres experience. Eur J Hum Genet. 2018;26:960-971.

270. Rasmussen M, Hareide LL, Skogen AR, Nedregaard B, Antal E-A, Plaisier E. Work-up of an increased level of CK leading to the diagnosis of HANAC. Eur J Paed Neurol. 2017;21:e226. (Abstract)

271. Raynowska J, Miskin DP, Pramanik B, Asiry S, Anderson T, Boockvar J, Najjar S, Harel A. Retinal vasculopathy with cerebral leukoencephalopathy (RVCL): A rare mimic of tumefactive MS. Neurology. 2018;91:e1423-e1428.

272. Richards A, van den Maagdenberg AM, Jen JC, Kavanagh D, Bertram P, Spitzer D, Liszewski M, Barilla-Labarca ML, Terwindt GM, Kasai Y et al. C-terminal truncations in human 3'-5' DNA exonuclease TREX1 cause autosomal dominant retinal vasculopathy with cerebral leukodystrophy. Nat Genet. 2007;39:1068-1670.

273. Riley CS, Roth LA, Sampson JB, Radhakrishnan J, Herlitz LC, Blitz AM, Moazami G. A 31-Year-Old Man With a Ring-Enhancing Brain Lesion. J Neuroophthalmol. 2017;37:172-175.

274. Rødahl E, Knappskog PM, Majewski J, Johansson S, Telstad W, Kråkenes J, Boman H. Variants of anterior segment dysgenesis and cerebral involvement in a large family with a novel COL4A1 mutation. Am J Ophthalmol. 2013;155:946-953.

275. Roeben B, Uhrig S, Bender B, Synofzik M. Teaching NeuroImages: When alopecia and disk herniations meet vascular leukoencephalopathy. Neurology. 2016;86:e166.
276. Rouaud T, Labauge P, Tournier Lasserve E, Mine M, Coustans M, Deburghgraeve V, Edan G. Acute urinary retention due to a novel collagen COL4A1 mutation. Neurology. 2010;75:747-749.

277. Ruiz-Escribano Menchen L, Flores Barragan JM, Camacho Nieto A, Franco Salinas AR, Villanueva Ruiz FJ, Hernandez Gonzalez A, Vaamonde Gamo J. COL4A1 novel missense mutation causing recurrent spontaneous intracerebral haemorrhage and encephalopathy. Eur. Stroke J. 2019;4:364. (Abstract)

278. Russo A, Pinto AM, Lopergolo D, Renieri A, Battisti C. An Italian family carrying a new mutation in the COL4A1 gene. J. Neurol. Sci. 2020;414:116815.

279. Saffari A, Kolker S, Merkenschlager A, Hoffmann GF, Ziegler A, Syrbe S. Axenfeld-Rieger anomaly and neuropsychiatric symptoms. Neuropediatrics. 2018;49:2. (Abstract)

280. Saffari A, Ziegler A, Merkenschlager A, Kruger S, Kolker S, Hoffmann GF, Syrbe S. Axenfeld-Rieger Anomaly and Neuropsychiatric Problems—More than Meets the Eye. Neuropediatrics. 2020;51:192–197.

281. Sahin S, Adrovic A, Barut K, Baran S, Tahir Turanli E, Canpolat N, Kizilkilic O, Ozkaya O, Kasapcopur O. A 9.5-year-old boy with recurrent neurological manifestations and severe hypertension, treated initially for polyarteritis nodosa, was subsequently diagnosed with adenosine deaminase type 2 deficiency (DADA2) which responded to anti-TNF-α. Paediatr Int Child Health. 2019;1-4.

282. Sahin S, Adrovic A, Barut K, Baran S, Tahir Turanli E, Canpolat N, Kizilkilic O, Ozkaya O, Kasapcopur O. A 9.5-year-old boy with recurrent neurological manifestations and severe hypertension, treated initially for polyarteritis nodosa, was subsequently diagnosed with adenosine deaminase type 2 deficiency (DADA2) which responded to anti-TNF-alpha. Paediatr. Int. Child Health. 2020;40:65–68.

283. Sahin S, Adrovic A, Barut K, Ugurlu S, Turanli ET, Ozdogan H, Kasapcopur O. Anti TNF-alpha therapy would be lifesaving in deficiency of adenosine deaminase-2. Ann Rheumat Dis. 2017; 76:1402-1403. (Abstract)

284. Sahin S, Adrovic A, Barut K, Ugurlu S, Turanli ET, Ozdogan H, Kasapcopur O. Clinical, imaging and genotypical features of three deceased and five surviving cases with ADA2 deficiency. Rheumatol Int. 2018;38:129-136.

285. Saito R, Nozaki H, Kato T, Toyoshima Y, Tanaka H, Tsubata Y, Morioka T, Horikawa Y, Oyanagi K, Morita T et al. Retinal Vasculopathy With Cerebral Leukodystrophy: Clinicopathologic Features of an Autopsied Patient With a Heterozygous TREX 1 Mutation. J Neuropathol Exp Neurol. 2019;78:181-186.

286. Saitsu H, Yoneda Y, Haginoya K, Arai H, Yamaoka S, Matsumoto N. De novo and inherited mutations in COL4A2, encoding the type IV collagen alpha2 chain, cause porencephaly. Congenital Anomalies. 2012;52:A8-A9. (Abstract)

287. Sakai N, Uemura M, Kato T, Nozaki H, Koyama A, Ando S, Kamei H, Kato M, Onodera O. Hemorrhagic cerebral small vessel disease caused by a novel mutation in 3’ UTR of collagen type IV alpha 1. Neuro. Genet. 2020;6:e383.

288. Santo GC, Baldeiras I, Guerreiro R, Ribeiro JA, Cunha R, Youngstein T, Nanthapisal S, Leitão J, Fernandes C, Caramelo F et al. Adenosine Deaminase Two and Immunoglobulin M Accurately Differentiate Adult Sneddon’s Syndrome of Unknown Cause. Cerebrovasc Dis. 2018;46:257-264.
289. Sarkar K, Way C, Verro P. A case of retinal vasculopathy and cerebral leukodystrophy with predominantly central nervous system manifestations. Neurology. 2012;78. (Abstract)

290. Sarrabay G, Insalaco A, Uettwiller F, Tieulie N, Quartier-Dit-Maire P, Melki J, Toutou I. Identification of three ADA2 deficiency families with novel CECR1 mutations. Ped Rheumatol. 2015;13:229. (Abstract)

291. Sasa GS, Elghetany MT, Bergstrom K, Nicholas S, Himes R, Krance RA, Hershfield M, Van Montfrans J, Bertuch A. Adenosine deaminase 2 deficiency as a cause of pure red cell aplasia mimicking diamond blackfan anemia. Blood. 2015;126:3615. (Abstract)

292. Sasaki S, Nozaki F, Saitsu H, Miyatake S, Matsumoto N, Kumada T, Shibata M, Fujii T. A case of COL4A1-related disorder with a variety of brain imaging findings. No To Hattatsu. 2017;49:405-407.

293. Sasaki S, Nozaki F, Saitsu H, Miyatake S, Matsumoto N, Kumada T, Shibata M, Fujii T. A case of COL4A1-related disorder with a variety of brain imaging findings. No To Hattatsu. 2017;49:405-407.

294. Sato Y, Shibasaki J, Aida N, Hiiragi K, Kimura Y, Akahira-Azuma M, Enomo Y, Tsurusaki Y, Kurosawa K. Novel COL4A1 mutation in a fetus with early prenatal onset of schizencephaly. Hum Genome Var. 2018;5:4.

295. Scalais E, Ceuterick-De Groot C, Martin JJ, Maugeri A, Varlet P, Devaux B, De Meirleir L. Cortical dysplasia, antenatal porencephaly, recurrent retinal hemorrhages: Different insults at different times-COL4A1 deficiency and environmental factors. Ann Neurol. 2015;78:S198. (Abstract)

296. Schena F, Pastorino C, Penco F, Volpi S, Caorsi R, Kalli F, Fenoglio D, Salis A, Prigione I, Bocca P et al. Dysregulation of B and Tfh cells functions in DADA2 patients Pediatr Rheumatol. 2018;16:2. (Abstract)

297. Schena F, Penco F, Volpi S, Pastorino C, Caorsi R, Bertoni A, Kalli F, Fenoglio D, Salis A, Prigione I et al. B cell defect in ADA2 deficiency patients. Pediatr Rheumatol. 2019;17. (Abstract)

298. Schena F, Volpi S, Caorsi R, Penco F, Pastorino C, Kalli F, Omenetti A, Chiesa S, Bertoni A, Picco P et al. Defect of adaptive immunity in ADA2 deficiency patients. Pediatr Rheumatol. 2017;15(Suppl 1). (Abstract)

299. Schepp J, Bulashevska A, Mannhardt-Laakmann W, Cao H, Yang F, Seidl M, Kelly S, Hershfield M, Grimbacher B. Deficiency of Adenosine Deaminase 2 Causes Antibody Deficiency. J Clin Immunol. 2016;36:179-186.

300. Schepp J, Proietti M, Frede N, Buchta M, Hübscher K, Rojas Restrepo J, Goldacker S, Warnatz K, Pachlponik Schmid J, Duppenthaler A et al. Screening of 181 Patients With Antibody Deficiency for Deficiency of Adenosine Deaminase 2 Sheds New Light on the Disease in Adulthood. Arthritis Rheumatol. 2017;69:1689-1700.

301. Schnappauf O, Stoffels M, Aksentijevich I, Kastner DL, Grayson PC, Cuthbertson D, Carette S, Chung SA, Forbess LJ, Khalidi NA et al. Screening of patients with adult-onset idiopathic polyarteritis nodosa for deficiency of adenosine deaminase 2. Arthritis Rheumatol. 2018;70(suppl10). (Abstract)

302. Schnappauf O, Stoffels M, Aksentijevich I, Ombrello A, Moura NS, Barron K, Kastner D, Grayson P, Merkel P. Screening of patients with idiopathic polyarteritis nodosa, granulomatosis with polyangiitis, and microscopic polyangiitis for deficiency of adenosine deaminase 2. Pediatr Rheumatol. 2019;17. (Abstract)
303. Schnider C, Theodoropoulou K, Candotti F, Angelini F, Perreau M, Hershfield M, Hofer M. A family case of ADA 2 deficiency with CECR1 mutation. Swiss Medical Weekly. 2018;148:115-12S. (Abstract)

304. Schnider C, Theodoropoulou K, Candotti F, Angelini F, Perreau M, Riccio O, Hershfield M, Hofer M. A family case of ADA2 deficiency with cecr1 mutation. Pediatr Rheumatol. 2018;16:P233. (Abstract)

305. Schuh E, Ertl-Wagner B, Lohse P, Wolf W, Mann JF, Lee-Kirsch MA, Hohlfeld R, Kumpfel T. Multiple sclerosis-like lesions and type I interferon signature in a patient with RVCL. Neurol Neuroimmunol Neuroinflamm. 2015;2:e55.

306. Schuh E, Lohse P, Kumpfel T. A rare case of cerebroretinal vasculopathy caused by a novel Trex 1 mutation. Journal of Neurology. 2013;260:S137. (Abstract)

307. Scoppettuolo P, Ligot N, Naeije G, Wermenbol V, Van Bogaert P. A novel mutation of COL4A1 responsible of familial porencephaly and severe hypermetropia. Eur Stroke J. 2018;3:486.

308. Segel R, Padeh S, Goldzweig O, Gerstein M, Barash J, Zlotogorski A, Pres J, Hashkes P, Horev L, Harel L, et al. Natural history and treatment outcome of patients with adenosine deaminase (ADA) 2 deficiency: Twenty years of the Israeli experience. Eur. J. Hum. Genet. 2019;26:314. (Abstract)

309. Selch C, Winkler P, Pringsheim M, Hasse A, Baumeister F, Staudt M, Kluger G. Epilepsy, clinical presentation and MRI features in patients with COL4A1 mutations. Eur J Paed Neurol. 2015;19:S6. (Abstract)

310. Severino MS, Caorsi R, Gandolfo C, Martinetti C, Martini A, Gattorno M. Distinct cerebrovascular features in patients with ADA2 deficiency. Pediatr Rheumatol. 2015;13:233. (Abstract)

311. Shah S, Ellard S, Kneen R, Lim M, Osborne N, Rankin J, Stoodley N, van der Knaap M, Whitney A, Jardine P. Childhood presentation of COL4A1 mutations. Dev Med Child Neurol. 2012;54:569-574.

312. Shah S, Kumar Y, McLean B, Churchill A, Stoodley N, Rankin J, Rizzo P, van der Knaap M, Jardine P. A dominantly inherited mutation in collagen IV A1 (COL4A1) causing childhood onset stroke without porencephaly. Eur J Paediatr Neurol. 2010;14:182-187.

313. Shan LD, Peng J, Xiao H, Wu LW, Duan HL, Pang N, Miriam K, Yin F. Clinical features and COL4A1 genotype of a toddler with hereditary angiopathy with nephropathy, aneurysms and muscle cramps syndrome. Chin. J. Contemp. Pediatr. 2019;21:754-760.

314. Sharma A, Naidu GSRSNK, Chattopadhyay A, Acharya N, Jha S, Jain S. Novel CECR1 gene mutations causing deficiency of adenosine deaminase 2, mimicking antiphospholipid syndrome. Rheumatology. 2019;58:181–182.

315. Shibata M. Clinical manifestations and neuroradiological findings of CARASIL with a novel mutation. Clinical Neurology. 2012;52:1363-1364.

316. Shwin KW, Carmona-Rivera C, Tsai W, Richard Lee CC, Novakovich E, Stone DL, Ombrello AK, Goldbach-Mansky R, Gadina M, Kastner D et al. Role of adenosine and neutrophils in inflammation associated with mutations in CECR1 gene. Arthritis Rheumatol. 2015;67. (Abstract)

317. Sibon I, Coupry I, Menegon P, Bouchet JP, Gorry P, Burgelin I, Calvas P, Orignac I, Dousset V, Lacombe D, et al. COL4A1 mutation in Axenfeld-Rieger anomaly with leukoencephalopathy and stroke. Ann Neurol. 2007;62:177-184.
318. Siitonen M, Hanson AB, Pasanen P, Bras JT, Kern S, Kern J, Andersen O, Stanescu H, Kleta R, Baumann M et al. Multi-infarct dementia of Swedish type is caused by 3'utr COL4A1 mutation. Brain. 2017;40:e29.

319. Siri A, Tournier-Lasserve E, Mine M, Magnin E, Berger E, Arquizan C, Ayrignac X, Carrar-Dalliere C, Castelnovo G, De Champfleur N et al. COL4A1 mutations: Clinical and radiological phenotypes in a french adult cohort. Neurology 2014;82:10 Supplement. (Abstract)

320. Skrabl-Baumgartner A, Plecko B, Schmidt WM, König N, Hershfield M, Gruber-Sedlmayr U, Lee-Kirsch MA. Autoimmune phenotype with type I interferon signature in two brothers with ADA2 deficiency carrying a novel CECR1 mutation. Pediatr Rheumatol Online J. 2017;15:67.

321. Slavotinek AM, Garcia ST, Chandratillake G, Bardakjian T, Ullah E, Wu D, Umeda K, Lao R, Tang PL, Wan E et al. Exome sequencing in 32 patients with anophthalmia/microphthalmia and developmental eye defects. Clin Genet. 2015;88:468-473.

322. Soldatos A, Toro C, Ombrello A, Stone D, Hoffman P, Romeo T, Jones A, Pinto-Patarroyo G, Aksentijevich I, Grayson P et al. Expanding the neurological phenotype of adenosine deaminase 2 deficiency (DADA2 syndrome) due to biallelic mutations in the CECR1 gene: A treatable pediatric lacunar stroke syndrome. Annals of Neurol. 2016;80:S338-340. (Abstract)

323. Sonmez HE, Karaaslan C, de Jesus AA, Batu ED, Anlar B, Sozeri B, Bilginer Y, Karaguzel D, Cagdas Ayvaz D, Tezcan I, et al. A clinical score to guide in decision making for monogenic type I IFNopathies. Pediatr. Res. 2020;87:745–752.

324. Sourander P, Wålinder J. Hereditary multi-infarct dementia. Morphological and clinical studies of a new disease. Acta Neuropathol. 1977;39:247-54.

325. Sozeri B, Ercan G, Dogan OA, Yildiz J, Demir F, Doganay L. Deficiency of ADA2 from childhood to adult; the same mutation in a family. Ped Rheumatol. 2019;41:227–233.

326. Staples E, Simeoni I, Stephens JC, Allen HL, Wright P, Davies EG, Javid B, Gkrania-Klotsas E, Gattens M, Firth H, et al. ADA2 deficiency complicated by EBV-driven lymphoproliferative disease. Clin. Immunol. 2020;215:108443.

327. Stutterd C, Delatycki M, Lockhart P, Taft R, Vanderver A, Simons C, Leventer R. Whole-genome sequencing for patients with unclassified leukodystrophies. Twin Res. Hum. Genet. 2019;21:410–411.
332. Sundin M, Marits P, Nierkens S, Kolios AGA, Nilsson J. "Immune" Thrombocytopenia as Key Feature of a Novel ADA2 Deficiency Variant: Implication on Differential Diagnostics of ITP in Children. J Pediatr Hematol Oncol. 2019;41:155-157.

333. Takenouchi T, Ohyagi M, Torii C, Kosaki R, Takahashi T, Kosaki K. Porencephaly in a fetus and HANAC in her father: variable expression of COL4A1 mutation. Am J Med Genet A. 2015;167A:156-158.

334. Tan RY, Traylor M, Megy K, Duarte D, Deevi SVV, Shamardina O, Mapeta RP, Consortium NBRD, Ouwehand WH, Graf S, et al. How common are single gene mutations as a cause for lacunar stroke? A targeted gene panel study. Neurology. 2019;93:e2007–e2020.

335. Tanatar A, Karadag SG, Sozeri B, Sonmez HE, Cakan M, Kendir Demirkol Y, Aktay Ayaz N. ADA2 Deficiency: Case Series of Five Patients with Varying Phenotypes. J. Clin. Immunol. 2020;40:253–258.

336. Taskinen MH, Mustjoki S, Jahnukainen K, Trotta L, Siitonen T, Hautala T, Zavalov A, Heiskanen K, Haapaniemi EM, Saarela J et al. Large granular lymphocyte infiltration in the bone marrow in children and young adults may suggest primary immune deficiency. Blood. 2015;126:1024. (Abstract)

337. Tateoka T, Onda H, Hirota K, Kasuya H, Shinohara T, Kinouchi H, Akagawa H. Unusual case of cerebral small vessel disease with a heterozygous nonsense mutation in HTRA1. J Neurol Sci. 2016;362:144-146.

338. Teixeira VA, Ramos FO, Costa M. Severe and refractory childhood-onset polyarteritis nodosa associated with CECR1 mutation. Pediatr Rheumatol. 2017;15. (Abstract)

339. Thaler FS, Catac C, Einhäupl M, Müller S, Seelos K, Wollenweber FA, Kümpfel T. Cerebral small vessel disease caused by a novel heterozygous mutation in HTRA1. J Neurol Sci. 2018;388:19-21.

340. Thomas AS, Lin P. A Case of TREX1-Associated Retinal Vasculopathy with Cerebral Leukodystrophy. Ophthalmol. Retina. 2020;4:115–117.

341. Tonduti D, Pichiecchio A, La Piana R, Livingston JH, Doherty DA, Majumdar A, Tomkins S, Mine M, Ceroni M, Ricca I et al. COL4A1-related disease: raised creatine kinase and cerebral calcification as useful pointers. Neuropediatrics. 2012;43:283-288.

342. Topkarci Z, Ayaz NA, Karadag SG, Tanatar A, Sonmez HE. Deficiency of adenosine deaminase 2 presenting as livedo racemosa. Pediatr Dermatol. 2019;36:S22. (Abstract)

343. Topkarci Z, Ayaz NA, Karadag SG, Tanatar A, Sonmez HE. Deficiency of adenosine deaminase 2 presenting as livedo racemosa. Gazi Med. J. 2020;31:P32. (Abstract)

344. Tournier-Lasserve E, Verdura E, Herve D, Bergametti F, Jacquet C, Morvan T, Prieto-Morin C, Mackowiak A, Manchon E, Hosseini H, et al. Up-regulation of COL4A1 and COL4A2 genes through various mechanisms leads to severe early onset ischaemic small vessel disease, including padmal. Eur. Stroke J. 2017;2:25.

345. Toz B, Erer B, Kamali S, Ocal L, Gul A. Differential response to anakinra and adalimumab in a patient with DADA2 syndrome. Pediatr Rheumatol. 2015;13:P201. (Abstract)

346. Traenka C, Kloss M, Strom T, Lyrer P, Brandt T, Bonati LH, Grond-Ginsbach C, Engelter S. Rare genetic variants in patients with cervical artery dissection. Eur. Stroke J. 2019;4:355–362.
347. Trotta L, Martelius T, Siitonen T, Hautala T, Hämäläinen S, Juntti H, Taskinen M, Ilander M, Andersson EI, Zavialov A et al. ADA2 deficiency: Clonal lymphoproliferation in a subset of patients. J Allergy Clin Immunol. 2018;141:1534-1537.e8.

348. Tsubata Y, Morita T, Morioka T, Sasagawa T, Ikarashi K, Saito N, Shimada H, Miyazaki S, Sakai S, Tanaka H et al. Renal histopathological findings of retinal vasculopathy with cerebral leukodystrophy. CEN Case Rep. 2018;7:83-89.

349. Uemura M, Nozaki H, Koyama A, Sakai N, Ando S, Kanazawa M, Kato T, Onodera O. HTRA1 Mutations Identified in Symptomatic Carriers Have the Property of Interfering the Trimer-Dependent Activation Cascade. Front. Neurol. 2019;10:693.

350. Uettwiller F, Sarrabay G, Rodero MP, Rice GI, Lagrue E, Marot Y, Deiva K, Touitou I, Crow YJ, Quartier P. ADA2 deficiency: case report of a new phenotype and novel mutation in two sisters. RMD Open. 2016;2:1-5.

351. Vahedi K, Boukobza M, Massin P, Gould DB, Tournier-Lasserve E, Bousser MG. Clinical and brain MRI follow-up study of a family with COL4A1 mutation. Neurology. 2007;69:1564-1568. (a)

352. Vahedi K, Kubis N, Boukobza M, Arnoult M, Massin P, Tournier-Lasserve E, Bousser MG. COL4A1 mutation in a patient with sporadic, recurrent intracerebral hemorrhage. Stroke. 2007;38:1461-1464. (b)

353. Van Agtmael T, Murray L, Vilain C, Abramowicz M, Kadler K. Chemical chaperone treatment influences the cellular phenotype of a COL4A2 mutation that causes haemorrhagic stroke. Cerebrovasc Dis. 2014;37:535. (Abstract)

354. Van der Knaap MS, Smit LM, Barkhof F, Pijnenburg YA, Zweegman S, Niessen HW, Imhof S, Heutink P. Ann Neurol. 2006;59:504-511.

355. Van Eyck L, Hershfield MS, Pombal D, Kelly SJ, Ganson NJ, Moens L, Frans G, Schaballie H, De Hertogh G, Dooley J et al. Hematopoietic stem cell transplantation rescues the immunologic phenotype and prevents vasculopathy in patients with adenosine deaminase 2 deficiency. J Allergy Clin Immunol. 2015;135:283-287.e5.

356. Van Eyck L, Hershfield MS, Pombal D, Kelly SJ, Ganson NJ, Moens L, Frans G, Schaballie H, DeHertogh G, Dooley J et al. HSCT rescues the immunological and vascular phenotype of ADA2-deficiency. J Clin Immunol. 2014;34:S196-197. (Abstract)

357. Van Eyck L, Liston A, Meyts I. Mutant ADA2 in vasculopathies. NEJM. 2014;371:478-479.

358. Van Eyck L, Liston A, Wouters C. Mutant ADA2 in vasculopathies (NEJM letter 2). NEJM. 2014;371:480.

359. Van Montfrans J, Hartman E, Braun K, Hennekam F, Hak A, Nederkoorn P, Westendorp W, Bredius R, Kollen W, Scholvinck E et al. Phenotypic variability in patients with ADA2 deficiency due to identical homozygous R169Q mutations. Pediatr Rheumatol. 2015;13:1. (Abstract)

360. Van Montfrans J, Van Royen-Kerkhof A, Bierings M, Aksentijevich I, Zavialov A, Zhou Q. Hematological stem cell transplantation in ADA2 deficiency. J Clin Immunol. 2014;34:S230-231. (Abstract)

361. Van Montfrans JM, Hartman EA, Braun KP, Hennekam EA, Hak EA, Nederkoorn PJ, Westendorp WF, Bredius RG, Kollen WJ, Schölvink EH et al. Phenotypic variability in patients with ADA2 deficiency due to identical homozygous R169Q mutations. Rheumatology. 2016;55:902-910.
362. Van Nieuwenhove E, Humblet-Baron S, Van Eyck L, De Somer L, Dooley J, Tousseyn T, Hershfield M, Liston A, Wouters C. ADA2 Deficiency Mimicking Idiopathic Multicentric Castleman Disease. Pediatrics. 2018;142:e20172266

363. van Well GTJ, Kant B, van Nistelrooij A, Sirma Ekmekci S, Henriet SV, Hoppenreijs E, van Deuren M, van Montfrans J, Nierkens S, Gul A, et al. Phenotypic variability including Behcet’s disease-like manifestations in DADA2 patients due to a homozygous c.973-2A>G splice site mutation. Clin. Exp. Rheumatol. 2019;121:142–146.

364. Verbeek E, Meuwissen ME, Verheijen FW, Govaert PP, Licht DJ, Kuo DS, Poulton CJ, Schot R, Lequin MH, Dudink J et al. COL4A2 mutation associated with familial porencephaly and small-vessel disease. Eur J Hum Genet. 2012;20:844-851.

365. Verdura E, Hervé D, Bergametti F, Jacquet C, Morvan T, Prieto-Morin C, Mackowiak A, Manchon E, Hosseini H, Cordonnier C et al. Disruption of a miR-29 binding site leading to COL4A1 upregulation causes pontine autosomal dominant microangiopathy with leukoencephalopathy. Ann Neurol. 2016;80:741-753.

366. Verdura E, Hervé D, Scharrer E, Amador M, Guyant-Maréchal L, Philipp A, Corlobé A, Bergametti F, Gazal S, Prieto-Morin C et al. Heterozygous HTRA1 mutations are associated with autosomal dominant cerebral small vessel disease. Brain. 2015;138:2347-2358.

367. Vermeulen RJ, Peeters-Scholte C, Van Vugt J, Barkhof F, Rizzu P, Van Der Schoor SR, Van Der Knaap MS. Fetal origin of brain damage in two infants with a COL4A1 mutation: Fetal and neonatal neuroimaging. Dev Med Child Neurol. 2012;54:197. (Abstract)

368. Vermeulen RJ, Peeters-Scholte C, Van Vugt JJ, Van Vught JJ, Barkhof F, Rizzu P, van der Schoor SR, van der Knaap MS. Fetal origin of brain damage in 2 infants with a COL4A1 mutation: fetal and neonatal MRI. Neuropediatrics. 2011;42:1-3.

369. Viana-Baptista M, Cruz-E-Silva V, Caetano A, Marto JP, Azevedo E., Ferreira C, Pinho-E-Melo T, Silva F, Ros Forteza FJ, Inacio N, et al. Vascular White Matter Lesions in Young Adults: A Neurology Outpatient Clinic Registry. Eur. Neurol. 2019;82:23–31.

370. Viana-Baptista M, De Silva VC, Caetano A, Azevedo E, Ferreira C, De Melo TP, Silva F, Ros J, Inacio NMO, Veiga A, et al. PORTYWHITE-Portuguese registry on incidental white matter lesions of presumed vascular etiology in young adults: Preliminary results. Eur. J. Neurol. 2017;24:89. (Abstract)

371. Vilain C, Van Regemorter N, Verloes A, David P, Van Bogaert P. Neuroimaging fails to identify asymptomatic carriers of familial porencephaly. Am J Med Genet. 2002;112:198-202.

372. Vitale G, Pichiecchio A, Ormitti F, Tonduti D, Asaro A, Farina L, Piccolo B, Percesepe A, Bastianello S, Orcesi S. Cortical malformations and COL4A1 mutation: Three new cases. Eur J Ped Neurol. 2019;23:410-417.

373. Vodopivec I, Oakley DH, Perugino CA, Venna N, Hedley-Whyte ET, Stone JH. A 44-year-old man with eye, kidney, and brain dysfunction. Ann Neurol. 2016;79:507-519.

374. Wang QH, Zou LP, Zhang MN, Wang YY, Lu Q, Shen YW, He W, Chen HM, Luo XM, Wang J, et al. Phenotypic characterization of COL4A1-related West syndrome. Epilepsy Res. 2020;164:106349.

375. Wang XL, Li CF, Guo HW, Cao BZ. A novel mutation in the HTRA1 gene identified in Chinese CARASIL pedigree. CNS Neuroscience and Therapeutics. 2012;18:867-869.
376. Watanabe J, Okamoto K, Ohashi T, Natsumeda M, Hasegawa H, Oishi M, Miyatake S, Matsumoto N, Fujii Y. Malignant Hyperthermia and Cerebral Venous Sinus Thrombosis After Ventriculoperitoneal Shunt in Infant with Schizencephaly and COL4A1 Mutation. World Neurosurg. 2019;1:446–450.

377. Weng YC, Sonni A, Labelle-Dumais C, de Leau M, Kauffman WB, Jeanne M, Biffi A, Greenberg SM, Rosand J, Gould DB. COL4A1 mutations in patients with sporadic late-onset intracerebral hemorrhage. Ann Neurol. 2012;71:470-477.

378. Wikan TO, Tzoulis C, Hogenesch RJ. A mother and her daughter with small vessel disease associated with COL4A1 mutations. Eur. J. Neurol. 2019;26:889.

379. Winkler DT, Lyrer P, Probst A, Devys D, Haufschild T, Haller S, Willi N, Mihatsch MJ, Steck AJ, Tolnay M. Hereditary systemic angiopathy (HSA) with cerebral calcifications, retinopathy, progressive nephropathy, and hepatopathy. J Neurol. 2008;255:77-88.

380. Wu X, Li C, Mao J, Li L, Liu Y, Hou Y. Heterozygous HTRA1 missense mutation in CADASIL-like family disease. Braz J Med Biol Res. 2018;51:e6632.

381. Xia XY, Li N, Cao X, Wu QY, Li TF, Zhang C, Li WW, Cui YX, Li XJ, Xue CY. A novel COL4A1 gene mutation results in autosomal dominant non-syndromic congenital cataract in a Chinese family. BMC Med Genet. 2014;15:97.

382. Xie F, Zhang LS. A Chinese CARASIL Patient Caused by Novel Compound Heterozygous Mutations in HTRA1. J Stroke Cerebrovasc Dis. 2018;27:2840-2842.

383. Yamashita T, Nozaki H, Wakutani Y, Tadokoro K, Nomura E, Takahashi Y, Sato K, Hishikawa N, Takemoto M, Shang J, et al. A Japanese family of autosomal dominant cerebral small vessel disease with heterozygous HTRA1 mutation showing dementia, gait disturbance and subarachnoid hemorrhage. Japenese Soc. Vasc. Cogn. Impair. 2019;5:20–26.

384. Yanagawa S, Ito N, Arima K, Ikeda S. Cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy. Neurology. 2002;58:817-820.

385. Yang M, Li S, Liu J, Qin W, Li G, Shi Y, Zang W, Zhang J. Pedigree study of hereditary small cerebral vascular disease caused by c.821G>A heterozygous mutation of HtrA serine protease-1 gene. Chin. J. Neurol. 2019;52:478–486.

386. Yaramis A, Lochmüller H, Töpf A, Sonmezler E, Yilmaz E, Hiz S, Yis U, Gungor S, Ipek Polat A, Edem P, et al. COL4A1-related autosomal recessive encephalopathy in 2 Turkish children. Neurol. Genet. 2020;6:e392.

387. Yoneda Y, Haginoya K, Arai H, Yamaoka S, Tsursuki Y, Doi H, Miyake N, Yokochi K, Osaka H, Kato M et al. De novo and inherited mutations in COL4A2, encoding the type IV collagen α2 chain cause porencephaly. Am J Hum Genet. 2012;90:86-90.

388. Yoneda Y, Haginoya K, Kato M, Osaka H, Yokochi K, Arai H, Kakita A, Yamamoto T, Otsuki Y, Shimizu S et al. Phenotypic spectrum of COL4A1 mutations: porencephaly to schizencephaly. Ann Neurol. 2013;73:48-57.

389. Yu Y, Qi X. Uncommon stroke disorders / difficult cases a complicated case of herns. Int J Stroke. 2018;13:28. (Abstract) (a)

390. Yu Y. A Complicated Case of HERNS. Alzheimer’s and Dementia. 2018;14:P1295. (Abstract) (b)

391. Yu Z, Cao S, Wu A, Yue H, Zhang C, Wang J, Xia M, Wu J. Genetically Confirmed CARASIL: Case Report with Novel HTRA1 Mutation and Literature Review. World Neurosurg. 2020;143:121–128.
392. Zagaglia S, Selch C, Nisevic JR, Mei D, Michalak Z, Hernandez-Hernandez L, Krithika S, Vezyroglou K, Varadar SM, Pepler A. Neurologic phenotypes associated with COL4A1/2 mutations: Expanding the spectrum of disease. Neurology. 2018;91:e2078-2088.
393. Zenteno JC, Crespí J, Buentello-Volante B, Buil JA, Bassaganyas F, Vela-Segarra JJ, Diaz-Cascajosa J, Marieges MT. Next generation sequencing uncovers a missense mutation in COL4A1 as the cause of familial retinal arteriolar tortuosity. Graefes Arch Clin Exp Ophthalmol. 2014;252:1789-1794.
394. Zhang WY, Xie F, Lu PL. Two novel heterozygous HTRA1 mutations in two pedigrees with cerebral small vessel disease families. Neurol Sci. 2018;39:497-501.
395. Zhao YY, Duan RN, Ji L, Liu QJ, Yan CZ. Cervical Spinal Involvement in a Chinese Pedigree With Pontine Autosomal Dominant Microangiopathy and Leukoencephalopathy Caused by a 3' Untranslated Region Mutation of COL4A1 Gene. Stroke. 2019;50:2307-2313.
396. Zhou Q, Chae J, Hershfield M, Sood R, Burgess S, Zavialov A, Chin D, Gadina M, Goldbach-Mansky R, Ombrello A et al. OR13-001 loss-of-function mutations in CECR1, encoding adenosine deaminase 2 (ADA2), cause recurrent fevers and early onset strokes. Pediatr Rheumatol. 2013;11. (Abstract)
397. Zhou Q, Yand D, Ombrello A, Kuehn H, Chae JJ, Zavialov A, Chin D, Stone D, Toro C, Milner J et al. Intermittent fever, immune dysregulation, and systemic vasculopathy due to loss-of-function mutations in adenosine deaminase 2. Arthritis and Rheumatism. 2013;65:S383-384. (Abstract)
398. Zhou Q, Yang D, Ombrello AK, Zavialov AV, Toro C, Stone DL, Chae JJ, Rosenzweig SD, Bishop K, Barron KS et al. Early-onset stroke and vasculopathy associated with mutations in ADA2. N Engl J Med. 2014;370:911-920.
399. Zhuo Z, Cong L, Zhang J, Zhao X. A novel heterozygous HTRA1 mutation is associated with autosomal dominant hereditary cerebral small vessel disease. Mol. Genet. Genomic Med. 2020;8:e1111.
400. Ziaei A, Xu X, Dehghani L, Bonnard C, Reversade B, Shaygannejad V, Pouladi MA. Novel mutation in HTRA1 identified in a family with diffuse demyelination lesions. J Neurochem. 2017;142:94. (Abstract)
401. Ziaei A, Xu X, Dehghani L, Bonnard C, Zellner A, Jin Ng AY, Tohari S, Venkatesh B, Haffner C, Reversade B, et al. Novel mutation in HTRA1 in a family with diffuse white matter lesions and inflammatory features. Neurol. Genet. 2019;5:e345.
402. Zlamy M, Heugenhauser K, Scholl-Buergi S, Zoegeler T, Sailer-Hoeck M, Brunner J, Karall D. Myalgia and dystrophic gait results in a diagnosis of deaminase 2 deficiency. J. Inherit. Metab. Dis. 2019;42:296–297. (Abstract)
SUPPLEMENTAL MATERIAL
Supplemental Methods: Decisions and Assumptions made when extracting data

Demographic data
- Age: sometimes specific ages weren’t reported but rather an approximate age or greater/less than a particular age was provided. In these cases we took a best estimation, erring towards overestimating age in some cases so as to minimise overestimation of the burden of the disease in younger brains. For example: <1 = 0, <2 = 1, <27 = 26, ≤26 = 26, early 50s = 52, mid-40s = 45.

Clinical data
- Clinical stroke classification required reporting of symptoms, i.e. not just radiological description
- Intellectual disability was classified under developmental delay

Radiology data
- When scan findings only described ‘hemosiderin deposits’ we did not take it to mean a confirmed bleed or microbleed
- Cerebral matter loss in <18 year old was recorded as ‘other’ rather than ‘atrophy’
- If a scan was described as showing ‘stable findings’/’no changes’ or equivalent, we marked the scan as showing the same pathology as the previous scan of the same patient
- In general, author interpretations which used words such as ‘probable’ or ‘suggests’ were taken to mean the feature was present, while author interpretations which used words such as ‘possible’ or ‘might be’ were not sufficient to consider the feature present
- We took ‘periventricular gliosis’ to mean white matter lesions
- We classified haemorrhage at the splenium of corpus callosum as ‘deep’
- We took ‘Hyperintense signal adjacent to the horn of the lateral ventricle’ to mean periventricular white matter lesions
- External capsule, internal capsule, centrum semiovale and corona radiata locations qualified as deep
- Punctate hemorrhages were taken to mean brain microbleeds
- Regarding severity of white matter lesions, we assumed the following:
  - ‘Severe’ when described as: extensive, diffuse, severe, widespread, confluent, Fazekas score 3, disseminated
  - ‘Not severe’ when described as subtle, early/beginning confluent, limited, moderate, mild, weak, Fazekas score 1 or 2, punctiform
- If a scan was implied but not explicitly stated, we decided whether it was more likely a scan was done than not and assumed based on that – e.g. “haemorrhage in the right frontal area” was taken to mean a scan had been done
- We took a ‘petechial spot’ to mean a microbleed
- We took porencephalic cysts to be a subcategory of intracerebral haemorrhage
Search Strategy
1. CADASIL/
2. (CADASIL or "Cerebral autosomal dominant arterio$ with subcortical infarct$ and leukoencephalopathy" or (Dementia and hereditary and multi?infarct) or "Familial vascular leukoencephalopathy" or CASIL or "Cerebral arterio$ with subcortical infarct$ and leukoencephalopathy" or "Chronic familial vascular encephalopathy" or "Familial disorder with subcortical ischemic stroke$" or "Agnogenic medial arteriopathy" or "Familial Binswanger$ disease" or (cerebral and autosomal dominant and arterio$ and infarct$ and leukoencephalophy)).af.
3. (CARASIL or "Maeda$ syndrome" or "Cerebral autosomal recessive arterio$ with subcortical infarct$ and leukoencephalopathy" or ("Subcortical Vascular Encephalopathy" and Progressive) or "Cerebrovascular Disease With Thin Skin Alopecia And Disc Disease" or "Nemoto disease" or (cerebral and autosomal recessive and arterio$ and infarct$ and leukoencephalophy) or "Familial young adult onset arterio$ leukoencephalopathy with alopecia and lumbago").af.
4. ((COL4A1$ and (leukoencephalopathy or small vessel disease or autosomal dominant or infantile hemiparesis or retinal arter$ tortuosity or RATOR or PADMAL or "pontine autosomal dominant microangiopathy and leukoencephalopathy" or Walker Warburg or porencephaly 1 or "small vessel disease of the brain with or without ocular abnormalities" or BSVD)) or HANAC or (hereditary angio$ and nephropath$ and aneurysm$ and cramp$) or ((autosomal dominant or familial or hereditary) and (h?ematuria and Retinal Arter$ Tortuosity)) or ("Autosomal dominant familial porencephaly" or "Hereditary multi infarct dementia" or HEMID or hMID) or (multi-infarct dementia and Swedish) or "Nonsyndromic autosomal dominant congenital cataract").af.
5. Muscle Cramp/ and Raynaud Disease/
6. (COL4A2 and (Porencephaly or stroke or Microbleed$ or h?emorrhage or leukoencephalopathy or small vessel disease or autosomal recessive or infantile hemiparesis or retinal arter$ tortuosity)).af.
7. (RVCL or "Retinal vasculopathy with cerebral leukodystrophy" or (Retinal vasculopathy and (hereditary or familial)) or ((Cerebroretinal Vasculopathy and Hereditary) or "hereditary vascular retinopathy") or "Grand-Kaine-Fulling syndrome" or HERNS or Hereditary Systemic Angiopathy or (hereditary and endotheliopathy and retin$s and nephro$s and stroke$) or (hereditary and retin$s and (raynaud$ or migraine)) or ADRVCL or (Autosomal Dominant and Retin$s and (leukodystrophy or leukoenchalopathy))).af.
8. ("Early-onset stroke and vasculopathy associated with mutations in ADA2" or (Stroke and vasc$ and ADA2) or ((deficien$s and (ADA 2 or ADA2 or adenosine deaminase-2)) or DADA2 or DADA 2 or (Vasculitis and ADA2 deficien$s)) or Sneddon Syndrome or (Polyarteritis nodosa and Childhood onset)).af.
9. (CARASAL or (Cathepsin A related arteriopathy with stroke? and leukoencephalopathy)).af.
10. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11. (NOTCH?3 or Notch 3 or "Neurogenic locus notch homolog protein 3").af.
12. (TREX?1 or TREX 1 or "Three prime repair exonuclease 1").af.
13. (COL4A1 or COL4A2 or COL4 A1 or COL4 A2 or "COL4 A 1" or "COL4 A 2" or "COL 4 A1" or "COL 4 A2").af.
14. (Collagen and ("type IV" or "type 4") and (alpha?1 or alpha?2 or alpha 1 or alpha 2)).af.
15. Collagen Type IV/
16. (alpha?1 or alpha?2 or alpha 1 or alpha 2).af.
17. 15 and 16
18. (HTRA?1 or HTRA 1 or "HtrA serine peptidase 1" or "HtrA serine protease 1").af.
19. (CECR?1 or CECR 1 or "Cat eye syndrome critical region protein 1" or "adenosine deaminase 2" or ADA2 or ADA 2).af.
20. (FOXC?1 or FOX C1 or FOXC 1 or "FOX C 1" or "forkhead box C?1" or "Forkhead box C 1").af.
21. (PITX?2 or PITX 2 or "paired-like homeodomain 2" or "pituitary homeobox 2" or "Paired-like homeodomain transcription factor 2").af.
22. (Cathepsin?A or Cathepsin A or CathA or Cath A or CTSA).af.
23. 11 or 12 or 13 or 14 or 17 or 18 or 19 or 20 or 21 or 22
24. exp Cerebral Small Vessel Diseases/
25. exp Cerebrovascular Disorders/
26. exp stroke/
27. exp dementia, vascular/
28. Brain Diseases/
29. exp basal ganglia cerebrovascular disease/
30. exp brain ischemia/
31. exp intracranial arterial diseases/
32. exp Cerebral Hemorrhage/
33. exp intracranial hemorrhages/
34. leukomalacia, periventricular/
35. stroke, lacunar/
36. Leukoaraiosis/
37. Leukoencephalopathies/
38. White Matter/
39. Infarction/
40. ("Cerebral Small Vessel Disease?" or cerebrovascular).af.
41. (White matter hyperintensit$ or WMH$ or White matter MR hyperintensit$ or White matter magnetic resonance hyperintensit$ or Subcortical hyperintensit$ or White matter
lesion? or WML$ or Hyper intensit$ or Leukodystroph$ or Leukoaraiosis or Leukomalacia or White Matter Change? or WMC? or White Matter Disease or WMD or White matter damage or Grey matter hyperintensit$ or Brainstem hyperintensit$ or Subcortical hyperintensit$ or White matter hypoattenuation? or White matter hypodensit$ or Leukoencephalopath$).af.
42. (Subcortical infarct? or Cerebral infarct$ or Brain infarct$ or Silent brain infarct$ or Striatocapsular infarct$ or Lacunar infarct$ or Lacune? or Lacunar stroke? or Lacunar syndrome or Stroke? or Vascular lesion?).af.
43. (Microbleed? or Cerebral Microbleed or CMB? or Hypointense lesion? or Subcortical H$emorrhage or Intracerebral h$emorrhage or Cortical siderosis or Superficial siderosis).af.
44. (Perivascular space? or Virchow Robin space? or Type 3 lacune? or Etat crible).af.
45. (Brain atrophy or Cerebral atrophy or Global atrophy or Corpus callosum atrophy or Central atrophy or Mesencephalic atrophy or Hippocampal atrophy or Cortical thinning).af.
46. 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45
47. 23 and 46
48. 10 or 47
49. limit 48 to humans
50. remove duplicates from 49
PRISMA 2020 Checklist

| Section and Topic | Item # | Checklist Item | Location where item is reported |
|-------------------|--------|----------------|---------------------------------|
| TITLE             | 1      | Identify the report as a systematic review. | p.0 |
| ABSTRACT          | 2      | See the PRISMA 2020 for Abstracts checklist. | p.1-2 |
| INTRODUCTION      | 3      | Describe the rationale for the review in the context of existing knowledge. | p.3-4 |
|                   | 4      | Provide an explicit statement of the objective(s) or question(s) the review addresses. | p.4 |
| METHODS           | 5      | Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses. | p.5-6 |
|                   | 6      | Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted. | p.4 |
|                   | 7      | Present the full search strategies for all databases, registers and websites, including any filters and limits used. | Suppl. |
|                   | 8      | Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process. | p.5 |
|                   | 9      | Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process. | p.6-7 |
|                   | 10     | List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses) and if not, the methods used to decide which results to collect. | p.8-7; Suppl. |
|                   | 11     | List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information. | p.8-7; Suppl. |
|                   | 12     | Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results. | N/A |
| Synthesis methods | 13a    | Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)). | p.7 |
|                   | 13b    | Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions. | p.7 |
|                   | 13c    | Describe any methods used to tabulate or visually display results of individual studies and syntheses. | p.7 |
|                   | 13d    | Describe any methods used to synthesize results and provide a rationale for the choice(s); if meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software packages used. | p.7 |
|                   | 14a    | Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression). | N/A |
|                   | 14b    | Describe any sensitivity analyses conducted to assess robustness of the synthesized results. | N/A |
|                   | 14c    | Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases). | N/A |
|                   | 14d    | Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome. | N/A |

PRISMA 2020 Checklist

| Section and Topic | Item # | Checklist Item | Location where item is reported |
|-------------------|--------|----------------|---------------------------------|
| RESULTS           | 16a    | Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram. | p.8, Fig. 1 |
|                   | 16b    | Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded. | Suppl. |
| Study characteristics | 17    | Cite each included study and present its characteristics. | Suppl. |
| Risk of bias in studies | 18    | Present assessments of risk of bias for each included study. | N/A |
| Results of individual studies | 19    | For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots. | Suppl. |
| Results of syntheses | 20a    | For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies. | Table 1, Fig. 2.3 |
|                   | 20b    | Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect. | N/A |
|                   | 20c    | Present results of all sensitivity analyses conducted to assess robustness of the synthesized results. | N/A |
| Reporting biases | 21    | Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed. | p.15 para 2 |
| Certainty of evidence | 22    | Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed. | N/A |

DISCUSSION

| Discussion | 23a    | Provide a general interpretation of the results in the context of other evidence. | p.14-17 |
|           | 23b    | Discuss any limitations of the evidence included in the review. | p.15 |
|           | 23c    | Discuss any limitations of the review processes used. | p.16-17 |
|           | 23d    | Discuss implications of the results for practice, policy, and future research. | p.17 |

OTHER INFORMATION

| Registration and protocol | 24a    | Provide registration information for the review, including register name and registration number, or state that the review was not registered. | p.4 |
|                         | 24b    | Indicate where the review protocol can be accessed, or state that a protocol was not prepared. | p.4 |
|                         | 24c    | Describe and explain any amendments to information provided at registration or in the protocol. | N/A |
| Support | 25    | Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review. | N/A |
| Competing interests | 26    | Describe any competing interests of review authors. | p.17 |
| Availability of data, code and other materials | 27    | Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review. | Suppl. |

For more information, visit: http://www.prisma-statement.org/
|                  | COL4A1 (N=390) | TREX1 (N=123) | HTRA1\textsuperscript{HomZ} (N=44) | COL4A2 (N=41) | ADA2 (N=346) | HTRA1\textsuperscript{HetZ} (N=82) | CTSA (N=14) |
|------------------|----------------|---------------|-----------------------------------|---------------|--------------|------------------------------------|-------------|
| **CLINICAL STROKE** |                |               |                                   |               |              |                                    |             |
| Unknown/ absent   | 59 (229/390)   | 91 (112/123)  | 70 (31/44)                        | 78 (32/41)    | 67 (231/346) | 48 (39/82)                        | 50 (7/14)   |
| Present           | 41 (161/390)   | 9 (11/123)    | 30 (13/44)                        | 22 (9/41)     | 33 (115/346) | 52 (43/82)                        | 50 (7/14)   |
| Ischaemic         | 15 (24/161)    | 82 (9/11)     | 54 (7/13)                         | 0 (0/9)       | 53 (61/115)  | 53 (23/43)                        | 71 (5/7)    |
| Ischaemic         | 15 (24/161)    | 73 (8/11)     | 46 (6/13)                         | 11 (1/9)      | 55 (63/115)  | 44 (19/43)                        | 43 (3/7)    |
| TIA               | 2 (3/161)      | 0 (0/11)      | 8 (1/13)                          | 0 (0/9)       | 5 (6/115)    | 14 (6/43)                         | 43 (3/7)    |
| Eye infarction    | 0 (0/161)      | 9 (1/11)      | 0 (0/13)                          | 0 (0/9)       | 3 (4/115)    | 0 (0/43)                          | 14 (1/7)    |
| Venous thrombosis/infarct | 0 (0/161) | 0 (0/11) | 0 (0/13) | 0 (0/9) | 0 (0/115) | 0 (0/43) | 14 (1/7) |
| Haemorrhagic      | 72 (116/161)   | 0 (0/11)      | 8 (1/13)                          | 89 (8/9)      | 12 (14/115)  | 5 (2/43)                          | 0 (0/7)     |
| ICH               | 32 (51/161)    | 0 (0/11)      | 8 (1/13)                          | 22 (2/9)      | 20 (23/115)  | 14 (6/43)                         | 29 (2/7)    |
| IVH               | 4 (7/161)      | 0 (0/11)      | 0 (0/13)                          | 0 (0/9)       | 0 (0/115)    | 0 (0/43)                          | 0 (0/7)     |
| Porencephalic cyst | 47 (76/161)    | 0 (0/11)      | 0 (0/13)                          | 78 (7/9)      | 0 (0/115)    | 0 (0/43)                          | 0 (0/7)     |
| Ischaemic and haemorrhagic | 1 (2/161) | 0 (0/11) | 0 (0/13) | 11 (1/9) | 8 (9/115) | 9 (4/43) | 29 (2/7) |
| Unspecified/ no detail | 12 (19/161) | 18 (2/11) | 38 (5/13) | 0 (0/9) | 27 (31/115) | 33 (14/43) | 0 (0/7) |
| **COGNITIVE FEATURES** |                |               |                                   |               |              |                                    |             |
| Unknown/ absent   | 67 (262/390)   | 71 (87/123)   | 36 (16/44)                        | 73 (30/41)    | 100 (346/346) | 44 (36/82)                        | 36 (5/14)   |
| Present           | 33 (128/390)   | 29 (36/123)   | 64 (28/44)\textsuperscript{a}    | 27 (11/41)    | 0 (0/346)    | 56 (46/82)                        | 64 (9/14)   |
| Present (≥18 y)   | 23 (30/131)    | 34 (36/106)   | 65 (20/31)                        | 0 (0/13)      | 0 (0/85)     | 62 (46/74)                        | 64 (9/14)   |
| Dementia*         | 3 (4/128)      | 0 (0/36)      | 32 (9/28)                         | 0 (0/11)      | 0 (0/0)      | 13 (6/46)                         | 0 (0/9)     |

\*Note: \textsuperscript{a} Denotes significant difference.
| Cognitive impairment - no ADL impact* | Cognitive impairment - no ADL detail* | Subjective cognitive decline* | Developmental delay |
|-------------------------------------|-------------------------------------|-------------------------------|--------------------|
| 2 (2/128)                          | 12 (15/128)                        | 0 (0/128)                    | 83 (106/128)       |
| 7 (2/30)                            | (22/30)                            | 73 (0/30)                    | 0 (0/36)           |
| 0 (0/36)                            | 97 (35/36)                         | 0 (0/36)                     | 0 (0/36)           |
| 0 (0/28)                            | 100 (35/36)                        | 0 (0/36)                     | 0 (0/36)           |
| 0 (0/11)                            | 68 (19/28)                         | 0 (0/28)                     | 0 (0/28)           |
| 0 (0/0)                             | 55 (11/20)                         | 0 (0/20)                     | 0 (0/20)           |
| 0 (0/0)                             | 0 (0/0)                            | 0 (0/0)                      | 0 (0/0)            |
| 0 (0/11)                            | 0 (0/0)                            | 0 (0/0)                      | 0 (0/0)            |
| 15 (7/46)                           | 65 (30/46)                         | 7 (3/46)                     | 65 (30/46)         |
| 100 (9/9)                           | 100 (9/9)                          | 0 (0/0)                      | 100 (9/9)          |

| PSYCHIATRIC FEATURES |
|-----------------------|
| Unknown/ absent       | Present                           |
| 98 (382/390)          | 2 (8/390)                         |
| 71 (87/123)           | 29 (36/123)                       |
| 68 (30/44)            | 32 (14/44)                        |
| 100 (41/41)           | 0 (0/41)                          |
| 100(346/346)          | 0 (0/346)                         |
| 78 (64/82)            | 22 (18/82)                        |
| 43 (6/14)             | 57 (8/14)                         |
| Psychosis             | Depression symptoms               |
| 0 (0/8)               | 25 (2/8)                          |
| 6 (2/36)              | 17 (6/36)                         |
| 7 (1/14)              | 64 (9/14)                         |
| 0 (0/0)               | 0 (0/0)                            |
| 0 (0/0)               | 67 (12/18)                        |
| 88 (7/8)              |                                     |
| Anxiety               | Irritability/ agitation           |
| 0 (0/8)               | 25 (2/8)                          |
| 3 (1/36)              | 8 (3/36)                          |
| 14 (2/14)             | 64 (9/14)                         |
| 0 (0/0)               | 0 (0/0)                            |
| 0 (0/0)               | 0 (0/18)                          |
| 0 (0/0)               | 0 (0/18)                          |
| 0 (0/8)               | 13 (1/8)                          |
| OCD                   | Emotional lability                |
| 0 (0/8)               | 13 (1/8)                          |
| 0 (0/0)               | 0 (0/36)                          |
| 0 (0/0)               | 21 (3/14)                         |
| 0 (0/0)               | 0 (0/0)                            |
| 28 (5/18)             | 13 (1/8)                          |
| 0 (0/0)               | 0 (0/18)                          |
| 0 (0/8)               | 0 (0/18)                          |
| Unspecified/ no detail |                                   |
| 0 (0/0)               | 78 (28/36)                        |
| 0 (0/0)               | 0 (0/14)                          |
| 0 (0/0)               | 0 (0/0)                            |
| 0 (0/0)               | 0 (0/0)                            |
| 0 (0/8)               |                                     |

| HEADACHE |
|----------|
| Unknown/ absent | Present | Migraine | Unspecified |
| 93 (362/390)   | 7 (28/390) | 68 (19/28) | 32 (9/28) |
| 69 (85/123)    | 31 (38/123) | 84 (32/38) | 16 (6/38) |
| 95 (42/44)     | 5 (2/44)   | 50 (1/2)   | 50 (1/2)  |
| 98 (40/41)     | 2 (1/41)   | 100 (1/1)  | 0 (0/1)   |
| 95 (329/346)   | 5 (17/346) | 24 (4/17)  | 76 (13/17) |
| 91 (75/82)     | 9 (7/82)   | 43 (3/7)   | 57 (4/7)  |
| 57 (8/14)      | 43 (6/14)  | 83 (5/6)   | 17 (1/6)  |

HetZ=heterozygous; HomZ=homozygous/compound heterozygous; N=overall number of individuals; n=number of affected individuals; ADL=activities of daily living; #8 cases with unknown age; * second row: only individuals ≥18 years; assumed Stam et al cohort were all ≥18 y.
### Table S2. Frequency of Vascular Radiological Cerebral Phenotypes by Location and Severity

| Location         | COL4A1 (N=290) | TREX1 (N=73) | HTRA1\(^{HetZ}\) (N=44) | COL4A2 (N=31) | ADA2 (N=119) | HTRA1\(^{HetZ}\) (N=70) | CTSA (N=14) |
|------------------|-----------------|--------------|--------------------------|---------------|--------------|--------------------------|--------------|
| **ISCHAEMIA**    | % (n/N)         | % (n/N)      | % (n/N)                  | % (n/N)       | % (n/N)      | % (n/N)                  | % (n/N)      |
| **Total**        | % (n/N)         | % (n/N)      | % (n/N)                  | % (n/N)       | % (n/N)      | % (n/N)                  | % (n/N)      |
| Present          | 16 (47/290)     | 8 (6/73)     | 34 (15/44)               | 0 (0/31)      | 44 (52/119)  | 66 (46/70)               | 57 (8/14)    |
| Unknown/Absent   | 84 (243/290)    | 92 (67/73)   | 66 (29/44)               | 100 (31/31)   | 56 (67/119)  | 34 (24/70)               | 43 (6/14)    |
| **Supratentorial** |                 |              |                          |               |              |                          |              |
| Deep/ Lacunar    | 43 (20/47)      | 100 (6/6)    | 53 (8/15)                | 0 (0/0)       | 42 (22/52)   | 46 (21/46)               | 75 (6/8)     |
| Cortical         | 2 (1/47)        | 0 (0/6)      | 0 (0/15)                 | 0 (0/0)       | 2 (1/52)     | 2 (1/46)                 | 25 (2/8)     |
| Unknown          | 4 (2/47)        | 0 (0/6)      | 20 (3/15)                | 0 (0/0)       | 10 (5/52)    | 15 (7/46)                | 0 (0/8)      |
| **Brainstem**    |                 |              |                          |               |              |                          |              |
| Deep/ Lacunar    | 51 (24/47)      | 0 (0/6)      | 53 (8/15)                | 0 (0/0)       | 44 (23/52)   | 26 (12/46)               | 0 (0/8)      |
| Cortical         | 2 (1/47)        | 0 (0/6)      | 0 (0/15)                 | 0 (0/0)       | 2 (1/52)     | 0 (0/46)                 | 25 (2/8)     |
| Unknown          | 0 (0/47)        | 0 (0/6)      | 0 (0/15)                 | 0 (0/0)       | 0 (0/52)     | 0 (0/46)                 | 0 (0/8)      |
| **Overall**      | 83 (39/47)      | 100 (6/6)    | 67 (10/15)               | 0 (0/0)       | 77 (40/52)   | 78 (36/46)               | 100 (8/8)    |
| **Infratentorial** |                |              |                          |               |              |                          |              |
| Deep/ Lacunar    | 2 (1/47)        | 0 (0/6)      | 0 (0/15)                 | 0 (0/0)       | 0 (0/52)     | 0 (0/46)                 | 0 (0/8)      |
| Cortical         | 15 (7/47)       | 0 (0/6)      | 33 (5/15)                | 0 (0/0)       | 23 (12/52)   | 22 (10/46)               | 0 (0/8)      |
| Unknown          | 15 (7/47)       | 0 (0/6)      | 33 (5/15)                | 0 (0/0)       | 23 (12/52)   | 22 (10/46)               | 0 (0/8)      |
| **Overall**      | 57 (27/47)      | 50 (3/6)     | 87 (13/15)               | 0 (0/0)       | 56 (29/52)   | 100 (46/46)              | 38 (3/8)     |
| **Burden**       |                 |              |                          |               |              |                          |              |
| Single lesion    | 2 (1/47)        | 33 (2/6)     | 0 (0/15)                 | 0 (0/0)       | 37 (19/52)   | 0 (0/46)                 | 50 (4/8)     |
| Multiple lesions | 57 (27/47)      | 50 (3/6)     | 87 (13/15)               | 0 (0/0)       | 56 (29/52)   | 100 (46/46)              | 38 (3/8)     |
| HAEMORRHAGE                  | Unknown     | 40 (19/47) | 17 (1/6) | 13 (2/15) | 0 (0/0) | 8 (4/52) | 0 (0/46) | 13 (1/8) |
|-----------------------------|-------------|------------|----------|-----------|---------|----------|---------|----------|
| Total                       | Present     | 41 (118/290) | 0 (0/73) | 2 (1/44) | 68 (21/31) | 10 (12/119) | 7 (5/70) | 7 (1/14) |
|                            | Unknown/Absent | 59 (172/290) | 100 (73/73) | 98 (43/44) | 32 (10/31) | 90 (107/119) | 93 (65/70) | 93 (13/14) |
| Porencephaly                |             | 61 (72/118) | 0 (0/0) | 0 (0/1) | 76 (16/21) | 0 (0/12) | 0 (0/5) | 0 (0/1) |
| IVH                         |             | 7 (8/118) | 0 (0/0) | 0 (0/1) | 0 (0/21) | 0 (0/12) | 0 (0/5) | 0 (0/1) |
| Location                    | Deep/ lacunar | 25 (29/118) | 0 (0/0) | 0 (0/1) | 14 (3/21) | 50 (6/12) | 40 (2/5) | 100 (1/1) |
|                            | Cortical    | 2 (2/118) | 0 (0/0) | 0 (0/1) | 0 (0/21) | 8 (1/12) | 0 (0/5) | 0 (0/1) |
|                            | Unknown     | 13 (15/118) | 0 (0/0) | 0 (0/1) | 10 (2/21) | 42 (5/12) | 0 (0/5) | 0 (0/1) |
|                            | Brainstem   | 2 (2/118) | 0 (0/0) | 0 (0/1) | 0 (0/21) | 0 (0/12) | 20 (1/5) | 0 (0/1) |
|                            | Cerebellum  | 6 (7/118) | 0 (0/0) | 100 (1/1) | 0 (0/21) | 0 (0/12) | 0 (0/5) | 0 (0/1) |
|                            | Unknown     | 0 (0/118) | 0 (0/0) | 0 (0/1) | 0 (0/21) | 0 (0/12) | 0 (0/5) | 0 (0/1) |
|                            | Any deep    | 56 (36/64) | 0 (0/0) | 100 (1/1) | 60 (3/5) | 50 (6/12) | 60 (3/5) | 100 (1/1) |
|                            | No deep     | 3 (2/64) | 0 (0/0) | 0 (0/1) | 0 (0/5) | 8 (1/12) | 0 (0/5) | 0 (0/1) |
|                            | Unknown     | 41 (26/64) | 0 (0/0) | 0 (0/1) | 40 (2/5) | 42 (5/12) | 40 (2/5) | 0 (0/1) |
|                  | Burden | Single lesion | Multiple lesions | Unknown | Totals | Present | Unknown/Absent | Totals | Present | Unknown/Absent |
|------------------|--------|---------------|------------------|---------|--------|---------|----------------|--------|---------|----------------|
| Burden           |        |               |                  |         |        |         |                |        |         |                |
| Single lesion    | 45 (53/118) | 0 (0/0)      | 100 (1/1)        | 76 (16/21) | 25 (3/12) | 100 (5/5) | 100 (1/1)      |        |         |                |
| Multiple lesions | 39 (46/118) | 0 (0/0)      | 0 (0/1)          | 19 (4/21) | 8 (1/12)  | 0 (0/5)   | 0 (0/1)        |        |         |                |
| Unknown          | 16 (19/118) | 0 (0/0)      | 0 (0/1)          | 5 (1/21)  | 67 (8/12) | 0 (0/5)   | 0 (0/1)        |        |         |                |
| **Totals**       |         |               |                  |         |        |         |                |        |         |                |
| **Present**      | 58 (167/290) | 89 (65/73) | 98 (43/44)       | 29 (9/31) | 3 (3/119) | 96 (67/70) | 100 (14/14)   |        |         |                |
| **Unknown/Absent** | 42 (123/290) | 11 (8/73) | 2 (1/44)         | 71 (22/31) | 97 116/119 | 4 (3/70)  | 0 (0/14)       |        |         |                |
| **Location**     |         |               |                  |         |        |         |                |        |         |                |
| Periventricular only | 26 (43/167) | 9 (6/65)   | 0 (0/43)         | 78 (7/9)  | 33 (1/3)  | 7 (5/67)  | 0 (0/14)       |        |         |                |
| Deep only        | 5 (9/167)   | 2 (1/65)    | 14 (6/43)        | 0 (0/9)   | 33 (1/3)  | 24 (16/67) | 0 (0/14)       |        |         |                |
| Both             | 14 (24/167) | 2 (1/65)    | 21 (9/43)        | 0 (0/9)   | 0 (0/3)   | 25 (17/67) | 93 (13/14)     |        |         |                |
| Unknown          | 54 (91/167) | 88 (57/65) | 65 (28/43)       | 22 (2/9)  | 33 (1/3)  | 43 (29/67) | 7 (1/14)       |        |         |                |
| Temporal         | 7 (11/167)  | 0 (0/65)    | 30 (13/43)       | 11 (1/9)  | 0 (0/3)   | 7 (5/67)  | 0 (0/14)       |        |         |                |
| Frontal          | 3 (5/167)   | 0 (0/65)    | 5 (2/43)         | 11 (1/9)  | 0 (0/3)   | 0 (0/67)  | 86 (12/14)     |        |         |                |
| Parietal         | 2 (3/167)   | 0 (0/65)    | 2 (1/43)         | 0 (0/9)   | 0 (0/3)   | 0 (0/67)  | 86 (12/14)     |        |         |                |
| Brainstem        | 2 (3/167)   | 0 (0/65)    | 21 (9/43)        | 0 (0/9)   | 0 (0/3)   | 9 (6/67)  | 7 (1/14)       |        |         |                |
| Unknown          | 89 (149/167)| 100 (65/65) | 63 (27/43)       | 89 (8/9)  | 100 (3/3) | 85 (57/67) | 7 (1/14)       |        |         |                |
| **Burden**       |         |               |                  |         |        |         |                |        |         |                |
| Severe           | 35 (59/167) | 5 (3/65)    | 95 (41/43)       | 22 (2/9)  | 0 (0/3)   | 12 (8/67) | 93 (13/14)     |        |         |                |
| Not severe       | 12 (20/167) | 3 (2/65)    | 0 (0/43)         | 0 (0/9)   | 0 (0/3)   | 49 (33/67) | 0 (0/14)       |        |         |                |
| Location         | Unknown | Single lesion | Multiple lesions | Burden |
|------------------|---------|---------------|------------------|--------|
| Unknown/Absent   | 90 (261/290) | 31 (9/29) | 100 (119/119) | 0 (0/3) |
| Total            | 10 (29/290) | 14 (4/29) | 76 (22/29) | 10 (3/29) |
| Supratentorial   | Deep/ lacunar | 52 (15/29) | 69 (20/29) | 14 (4/29) |
|                 | Cortical | 3 (1/29) | 0 (0/29) | 0 (0/29) |
|                 | Unknown | 14 (4/29) | 31 (9/29) | 3 (1/29) |
| Infratentorial   | Brainstem | 21 (6/29) | 62 (8/13) | 0 (0/1) |
|                 | Cerebellum | 10 (3/29) | 0 (0/1) | 0 (0/1) |
|                 | Unknown | 3 (1/29) | 23 (3/13) | 0 (0/1) |
| Overall          | Any deep | 69 (20/29) | 50 (1/2) | 14 (4/29) |
|                 | No deep | 0 (0/29) | 0 (0/2) | 0 (0/2) |
|                 | Unknown | 31 (9/29) | 38 (5/13) | 0 (0/0) |
| MICROBLEEDS      | Total   | Present | Unknown | Present |
| Location     | Total         | Present | 1 (1/73) | 20 (9/44) | 0 (0/31) | 3 (4/119) | 11 (8/70) | 71 (10/14) |
|--------------|---------------|---------|----------|-----------|----------|-----------|-----------|------------|
| Global       |               | 25 (3/12)| 0 (0/1)  | 0 (0/9)   | 0 (0/0)  | 25 (1/4)  | 25 (2/8)  | 0 (0/10)   |
| Focal        |               | 42 (5/12)| 0 (0/1)  | 11 (1/9)  | 0 (0/0)  | 25 (1/4)  | 50 (4/8)  | 10 (1/10)  |
| Unknown      |               | 33 (4/12)| 100 (1/1)| 89 (8/9)  | 0 (0/0)  | 50 (2/4)  | 25 (2/8)  | 90 (9/10)  |
| Severe       |               | 42 (5/12)| 0 (0/1)  | 0 (0/9)   | 0 (0/0)  | 0 (0/4)   | 0 (0/8)   | 0 (0/10)   |
| Not severe   |               | 0 (0/12)| 100 (1/1)| 11 (1/9)  | 0 (0/0)  | 25 (1/4)  | 50 (4/8)  | 90 (9/10)  |
| Unknown      |               | 58 (7/12)| 0 (0/1)  | 89 (8/9)  | 0 (0/0)  | 75 (3/4)  | 50 (4/8)  | 10 (1/10)  |
| Present      | 4 (12/290)    | 1 (1/73) | 20 (9/44) | 0 (0/31) | 3 (4/119) | 11 (8/70) | 71 (10/14) |
| Unknown/Absent| 96 (278/290)  | 99 (72/73)| 80 (35/44)| 100 (31/31)| 97 (115/119)| 89 (62/70)| 29 (4/14) |
| Present      | 12 (34/290)   | 32 (23/73)| 0 (0/44) | 0 (0/31) | 0 (0/119) | 0 (0/70)  | 0 (0/14)  |
| Unknown/Absent| 88 (256/290)  | 68 (50/73)| 100 (44/44)| 100 (31/31)| 100 (119/119)| 100 (70/70)| 100 (14/14)|
| Present      | 3 (8/290)     | 0 (0/73) | 0 (0/44) | 0 (0/31) | 0 (0/119) | 16 (11/70) | 64 (9/14) |
| Unknown/Absent| 97 (282/290)  | 100 (73/73)| 100 (44/44)| 100 (31/31)| 100 (119/119)| 84 (59/70)| 36 (5/14) |
| Present      | 36 (13/36)    | 0 (0/1)  | 0 (0/9)  | 60 (3/5)  | 6 (1/17)  | 0 (0/2)   | 0 (0/1)   |
| Unknown/Absent| 64 (23/36)    | 100 (1/1)| 100 (9/9) | 40 (2/5)  | 94 (16/17) | 100 (2/2) | 100 (1/1) |

HetZ=heterozygous; HomZ=homozygous/compound heterozygous; N=overall number of individuals with neuroimaging; n=number of affected individuals; WML=white matter lesions(s); PVS=perivascular space(s);
## Table S3. Variant Effect Predictor Output Summary

| Gene   | Number of variants | % variants with info | % pathogenic* among variants with data | % pathogenic* among all variants |
|--------|--------------------|----------------------|----------------------------------------|---------------------------------|
|        | no info | low | moderate* | high* |                        |                        |                        |
| HTRA1  | 7       | 0   | 35       | 11    | 87%                     | 100%                   | 87%                     |
| ADA2   | 43      | 3   | 24       | 18    | 51%                     | 93%                    | 48%                     |
| COL4A1 | 43      | 0   | 88       | 23    | 72%                     | 100%                   | 72%                     |
| COL4A2 | 1       | 0   | 14       | 1     | 94%                     | 100%                   | 94%                     |
| TREX1  | 21      | 0   | 2        | 8     | 32%                     | 100%                   | 32%                     |
| CTSA   | 1       | 0   | 0        | 0     | 0%                      | 0%                     | 0%                      |
| Total  | 116     | 3   | 163      | 61    | 66%                     | 99%                    | 65%                     |

### VARIANT IMPACT/CLASSIFICATION OF SEVERITY (SNPEff)

| Gene   | no info | uncertain clinical significance | benign | likely benign | likely pathogenic* | pathogenic* |
|--------|---------|----------------------------------|--------|---------------|--------------------|-------------|
| HTRA1  | 30      | 3                                | 0      | 0             | 5                  | 15          |
| ADA2   | 76      | 2                                | 1      | 0             | 6                  | 3           |
| COL4A1 | 150     | 1                                | 0      | 0             | 3                  | 3           |
| COL4A2 | 5       | 0                                | 0      | 3             | 3                  | 5           |
| TREX1  | 29      | 0                                | 0      | 1             | 1                  | 1           |
| CTSA   | 1       | 0                                | 0      | 0             | 0                  | 0           |
| Total  | 291     | 6                                | 1      | 3             | 15                 | 27          |

### CLINICAL SIGNIFICANCE (ClinVar)

| Gene   | no info | uncertain clinical significance | benign | likely benign | likely pathogenic* | pathogenic* |
|--------|---------|----------------------------------|--------|---------------|--------------------|-------------|
| HTRA1  | 30      | 3                                | 0      | 0             | 5                  | 15          |
| ADA2   | 76      | 2                                | 1      | 0             | 6                  | 3           |
| COL4A1 | 150     | 1                                | 0      | 0             | 3                  | 3           |
| COL4A2 | 5       | 0                                | 0      | 3             | 3                  | 5           |
| TREX1  | 29      | 0                                | 0      | 1             | 1                  | 1           |
| CTSA   | 1       | 0                                | 0      | 0             | 0                  | 0           |
| Total  | 291     | 6                                | 1      | 3             | 15                 | 27          |

### IMPACT ON PROTEIN FUNCTION (SIFT)

| Gene   | no info | tolerated | deleterious* |
|--------|---------|-----------|--------------|
| HTRA1  | 18      | 1         | 34           |

Impact on protein function (SIFT): 66%, 97%, 64%
| Gene   | No Info | Benign | Possibly Damaging* | Probably Damaging* |
|--------|---------|--------|--------------------|--------------------|
| ADA2   | 43      | 4      | 41                 | 51%                |
| COL4A1 | 46      | 9      | 99                 | 70%                |
| COL4A2 | 1       | 2      | 13                 | 94%                |
| TREX1  | 29      | 1      | 1                  | 0%                 |
| CTSA   | 1       | 0      | 0                  | 0%                 |
| Total  | 138     | 17     | 188                | 60%                |

**IMPACT ON PROTEIN STRUCTURE AND FUNCTION (PolyPhen-2)**

*Category considered to provide supporting evidence for pathogenicity; SnpEff classifies each variant in one of the following output categories: high impact (variant is assumed to have a disruptive impact in the protein, probably causing protein truncation, loss of function or triggering nonsense mediated decay), moderate impact (non-disruptive variant that might change protein effectiveness), and low impact (variant assumed to be mostly harmless or unlikely to change protein behaviour). The ‘modifier’ category is taken to represent no information about these categories; ClinVar assigns each variant as pathogenic, likely pathogenic, likely benign, benign, or of uncertain clinical significance; SIFT predicts whether an amino acid substitution is likely to affect protein function based on sequence homology and the physico-chemical similarity between the alternate amino acids, concluding with a qualitative prediction if a variant is deleterious or tolerated; PolyPhen-2 predicts the effect of an amino acid substitution on the structure and function of a protein using sequence homology, 3D structures where available, and a number of other databases and tools. It classifies each variant as probably damaging, possibly damaging or benign.*
## TABLE S4. Variant Effect Predictor outputs per gene A. HTRA1

| Genetic mutation | Protein change | Variant information |
|------------------|----------------|---------------------|
| c.589C>T         | p.R197X        | Stop gained, likely deleterious, high impact. Pathogenic |
| c.865C>T         | p.Q289X        | Stop gained, likely deleterious, high impact. Pathogenic |
| c.1108C>T        | p.R370X        | Stop gained, high impact variant. Pathogenic/likely pathogenic |
| c.904C>T         | p.R302X        | Stop gained, high impact variant. Likely pathogenic |
| c.502A.T         | p.K168ter      | Stop gained, high impact variant |
| c.847G>T         | p.G283Ter      | Stop gained, high impact variant |
| c.983C>A         | p.S328*        | Stop gained, high impact variant |
| c.1005+1G>T      |                | Splice donor variant, high impact |
| c.971A>C         | p.N324T        | Missense variant, possible splice region variant with moderate impact. Probably damaging to protein structure and conflicting evidence of tolerated/deleterious to protein function. Likely pathogenic |
| c.754G>A         | p.A252T        | Missense variant, non-coding exon variant with moderate impact. Possibly damaging to protein structure and deleterious to protein function. Pathogenic |
| c.956C>T         | p.T319I        | Missense variant, moderate impact. Probably damaging to protein structure and likely to have deleterious effect on protein function |
| c.451C>A         | p.Q151K        | Missense variant, moderate impact and potential modifier of both upstream and downstream gene regulation (ARMS2), and lncRNA. Probably damaging to protein structure and likely to have deleterious effect on protein function. Uncertain clinical significance |
| c.359G>A         | p.G120D        | Missense variant, moderate impact and potential modifier of both upstream and downstream gene regulation (ARMS2), and lncRNA. Probably damaging to protein structure and likely to have deleterious effect on protein function. Likely pathogenic |
| c.361A>C         | p.S121R        | Missense variant, moderate impact and potential modifier of both upstream and downstream gene regulation (ARMS2), and lncRNA. Probably damaging to protein structure and likely to have deleterious effect on protein function |
| SNP      | Ref_Alt | p.| Description                                                                                                                                 |
|----------|---------|---|--------------------------------------------------------------------------------------------------------------------------------------------|
| c.397C>G | p.R133G |   | Missense variant, moderate impact and potential modifier of both upstream and downstream gene regulation (ARMS2), and lncRNA. Possibly damaging to protein structure but tolerated by protein function |
| c.367G>T | p.A123S |   | Missense variant, moderate impact and potential modifier of both upstream and downstream gene regulation (ARMS2), and lncRNA. Only possibly damaging to protein structure and likely to have deleterious effect on protein function |
| c.821G>A | p.R274Q |   | Missense variant with moderate impact. Probably/possibly damaging to protein structure and deleterious/some reports of tolerated to protein function. Pathogenic |
| c.496C>T | p.R166C |   | Missense variant with moderate impact. Probably/possibly damaging to protein structure and deleterious to protein function |
| c.517G>A | p.A173T |   | Missense variant with moderate impact. Probably/possibly damaging to protein structure and deleterious to protein function |
| c.517G>C | p.A173P |   | Missense variant with moderate impact. Probably/possibly damaging to protein structure and deleterious to protein function |
| c.856T>G | p.F286V |   | Missense variant with moderate impact. Probably/possibly damaging to protein structure and deleterious to protein function |
| c.854C>A | p.P285Q |   | Missense variant with moderate impact. Probably/possibly damaging to protein structure and deleterious to protein function. Uncertain clinical significance/pathogenic |
| c.854C>T | p.P285L |   | Missense variant with moderate impact. Probably/possibly damaging to protein structure and deleterious to protein function. Uncertain clinical significance/pathogenic |
| c.616G>A | p.G206R |   | Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function. Uncertain clinical significance |
| c.961G>A | p.A321T |   | Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function. Uncertain clinical significance |
| c.1091T>C | p.L364P |   | Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function. Pathogenic |
| c.497G>T | p.R166L |   | Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function. Pathogenic |
| c.614C>G | p.S205C |   | Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function. Pathogenic |
| Variant | Protein | Description |
|---------|---------|-------------|
| c.852C>A | p.S284R | Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function. Pathogenic |
| c.883G>A | p.G295R | Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function. Pathogenic |
| c.889G>A | p.V297M | Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function. Pathogenic |
| c.536T>A | p.I179N | Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function. Likely pathogenic |
| c.827G>C | p.G276A | Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function. Likely pathogenic |
| c.1021G>A | p.G341J | Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function. |
| c.524T>A | p.V175E | Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function. |
| c.527T>C | p.V176A | Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function. |
| c.646G>A | p.V216M | Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function. |
| c.847G>A | p.G283R | Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function. |
| c.848G>A | p.G283E | Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function. |
| c.850A>G | p.S284G | Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function. |
| c.905G>A | p.R302Q | Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function. |
| c.1348G>C | p.D450H | Missense variant with moderate impact. Only possibly damaging to protein structure and deleterious to protein function. |
| Genetic mutation     | Protein change | Variant information                                                                                                                                 |
|---------------------|----------------|------------------------------------------------------------------------------------------------------------------------------------------------------|
| c.184-185del        |                | Intronic variant, with possible impact on both upstream and downstream gene regulation, ARMS2. Possible influence on IncRNA.                          |
| c.830_831delAG      | p.E277Vfs      | Intronic variant with possible influence on upstream gene                                                                                            |
| c.126delG           | p.E42fs        | Frameshift variant with high impact. Pathogenic                                                                                                       |
| c.543delT           | p.A182Pfs*33   | Frameshift mutation with high impact. Potentially leading to premature stop. Pathogenic                                                               |
| c.739delG           | p.E247Rfs      | Frameshift mutation with high impact. Potentially leading to premature stop                                                                          |
| c.958G>A            | p.D320N        | Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function.                                   |

B. ADA2

| Genetic mutation     | Protein change | Variant information                                                                                                                                 |
|---------------------|----------------|------------------------------------------------------------------------------------------------------------------------------------------------------|
| c.982G>A            | p.E328K        | Missense variant with potential impact on upstream and downstream gene regulation, possible 3'UTR variant involved in nonsense-mediated decay. Possible impact on processing of pseudogene, and CTCF binding site. Probably damaging/benign to protein structure and likely deleterious to protein function/potentially tolerated. |
| c.138/144delG       |                | 5'UTR variant, intronic variant with possible impact on regulation of upstream gene through processing of pseudogene/nonsense mediated decay              |
| c.37_39del          | p.K13del       | 5'UTR variant, intronic variant with possible impact on regulation of upstream gene through processing of pseudogene/nonsense mediated decay              |
| c.143_144insG       | p.R49Afs*13    | Frameshift variant with high impact, possible impact on both upstream and downstream gene regulation. Likely pathogenic                               |
| c.144 dup           | p.R49Afs*13    | Frameshift variant with high impact, possible impact on both upstream and downstream gene regulation. Likely pathogenic                               |
| c.144_145ins        |                | Frameshift variant with high impact, possible impact on both upstream and downstream gene regulation. Likely pathogenic                               |
| c.144del            | p.R49Gfs*4     | Frameshift variant with high impact, possible impact on both upstream and downstream gene regulation. Likely pathogenic                               |
| Variant | Effect | Description |
|---------|--------|-------------|
| c.144delG | p.R49fs | Frameshift variant with high impact, possible impact on both upstream and downstream gene regulation. Likely pathogenic. |
| c.144dupG | p.R49fs | Frameshift variant with high impact, possible impact on both upstream and downstream gene regulation. Likely pathogenic. |
| c.629delT |  | Frameshift variant, high impact with potential impact on both upstream and downstream genes. |
| c.427del | p.I143Sfs*41 | Frameshift variant, high impact. Impact on nonsense mediated decay transcript processing. Possible impact on downstream genes. |
| c.1447-1451del | p.S483Pfs*5 | Intronic variant, possible impact on transcript processing. |
| c.680-681delAT |  | Intronic variant, possible impact on transcript processing. |
| c.973-?_1081+?del | p.V325Tfs*7 | Intronic variant, possible retained intron. Could have impact on both upstream, downstream genes and nonsense mediated decay transcript processing. |
| c.972+3A>G |  | Intron, splice region variant with low impact. Possible retained intron and impact on nonsense mediated decay transcript processing. |
| c.326C>A | p.A109D | Missense variant with moderate impact, possible 5'UTR variant. Probably damaging to protein structure and deleterious to protein function. |
| c.336G>A | p.Y453C | Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function. |
| c.336C>G | p.H112Q | Missense variant with moderate impact, possible 5'UTR variant. Probably damaging to protein structure and deleterious to protein function. |
| c.962G>A | p.G321E | Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function. |
| c.133C>T | p.A45T | Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function. |
| c.1358A>G | p.Y453C | Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function. |
| c.385A>C | p.T129P | Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function. |
| Variant       | Protein  | Description                                                                 |
|--------------|----------|------------------------------------------------------------------------------|
| c.932T>G     | p.L311R  | Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function. Pathogenic. |
| c.1352T>G    | p.L451W  | Missense variant with potential impact on downstream gene regulation, possible 3'UTR variant involved in nonsense-mediated decay. Probably damaging to protein structure and likely deleterious to protein function. |
| c.1353G>T    | p.L451F  | Missense variant with potential impact on downstream gene regulation, possible 3'UTR variant involved in nonsense-mediated decay. Probably damaging to protein structure and likely deleterious to protein function. |
| c.1360G>C    |          | Missense variant with potential impact on downstream gene regulation, possible 3'UTR variant involved in nonsense-mediated decay. Probably damaging to protein structure and likely deleterious to protein function. |
| c.1373T>A    | p.V458D  | Missense variant with potential impact on downstream gene regulation, possible 3'UTR variant involved in nonsense-mediated decay. Probably damaging to protein structure and likely deleterious to protein function. |
| c.1223G>A    | p.C408Y  | Missense variant with potential impact on downstream gene regulation, possible 3'UTR variant involved in nonsense-mediated decay. Probably damaging to protein structure and likely deleterious to protein function. |
| c.1348G>T    | p.G450C  | Missense variant with potential impact on downstream gene regulation, possible 3'UTR variant involved in nonsense-mediated decay. Probably damaging to protein structure and likely deleterious to protein function. |
| c.1367A>G    | p.Y456C  | Missense variant with potential impact on downstream gene regulation, possible 3'UTR variant involved in nonsense-mediated decay. Probably damaging to protein structure and likely deleterious to protein function. Pathogenic |
| c.1065C>A    | p.F355L  | Missense variant with potential impact on upstream and downstream gene regulation, possible 3'UTR variant involved in nonsense-mediated decay. Possible impact on processing of pseudogene. Benign protein structure and tolerated by protein function. |
| c.1052T>A    | p.L351Q  | Missense variant with potential impact on upstream and downstream gene regulation, possible 3'UTR variant involved in nonsense-mediated decay. Possible impact on processing of pseudogene. Probably damaging to protein structure and likely deleterious to protein function. |
| Variant | Effect | Description |
|---------|--------|-------------|
| c.1057T>C | p.Y353H | Missense variant with potential impact on upstream and downstream gene regulation, possible 3'UTR variant involved in nonsense-mediated decay. Possible impact on processing of pseudogene. Probably damaging to protein structure and likely deleterious to protein function. |
| c.1069G>A | p.A357T | Missense variant with potential impact on upstream and downstream gene regulation, possible 3'UTR variant involved in nonsense-mediated decay. Possible impact on processing of pseudogene. Probably damaging to protein structure and likely deleterious to protein function. |
| c.1072G>A | p.G358R | Missense variant with potential impact on upstream and downstream gene regulation, possible 3'UTR variant involved in nonsense-mediated decay. Possible impact on processing of pseudogene. Probably damaging to protein structure and likely deleterious to protein function. |
| c.1078A>G | p.T360A | Missense variant with potential impact on upstream and downstream gene regulation, possible 3'UTR variant involved in nonsense-mediated decay. Possible impact on processing of pseudogene. Probably damaging to protein structure and likely deleterious to protein function. |
| c.140G>C | p.G47A | Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function. |
| c.278T>C | p.I93T | Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function. |
| c.506C>T | p.R169Q | Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function. |
| c.506G>A | R169Q | Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function. |
| c.533T>C | p.F178S | Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function. Possible retained intron. |
| c.139G>T | p.G47W | Missense variant, moderate impact and potential modifier of upstream and downstream gene regulation, possible impact on processing of pseudogene (FAM32BP). Probably damaging to protein structure and likely to have deleterious effect on protein function. Pathogenic |
| c.563T>C | p.L188P | Missense variant, moderate impact and potential modifier of upstream and downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function. |
| Variant | Codon | Gene Effect | Clinical Significance |
|---------|-------|-------------|-----------------------|
| c.578C>T | p.P193L | Missense variant, moderate impact and potential modifier of upstream and downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function. |
| c.139G>A | p.G47R | Missense variant, moderate impact and potential modifier of upstream and downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function. Conflicting evidence on clinical significance. |
| c.650T>A | p.V217D | Missense variant, moderate impact and potential modifier of upstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function. |
| c.712G>A | p.D238N | Missense variant, moderate impact and potential modifier of upstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function. |
| c.872C>T | p.S291L | Missense variant, moderate impact and potential modifier of upstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function. |
| c.620T>C | Missense variant, moderate impact and potential modifier of upstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function. Uncertain clinical significance. |
| c.791G>C | p.W264S | Missense variant, moderate impact and potential modifier of upstream gene regulation. Probably damaging/benign to protein structure and could have deleterious/tolerated impact on protein function. May cause retained intron. |
| c.1110C>A | p.N370K | Missense variant, moderate impact, possible 3'UTR variant involved in nonsense mediated decay. Probably damaging to protein structure and likely to have deleterious effect on protein function. |
| c.1445A>G | Missense variant, splice variant with potential impact on downstream gene regulation, possible 3'UTR variant involved in nonsense-mediated decay. Probably damaging to protein structure and likely deleterious to protein function. |
| c.1226C>A | Missense variant, splice variant with potential impact on downstream gene regulation, possible 3'UTR variant involved in nonsense-mediated decay. Probably damaging to protein structure and likely deleterious to protein function. |
| c.752C>T | p.P251L | Missense variant, splice region variant with moderate impact. Possibly damaging to protein structure and tolerated by protein function. |
| c.424G>A | p.G142S | Missense variant. Change tolerated by protein function, benign impact on protein structure |
| Genetic mutation | Protein change | Variant information |
|------------------|---------------|---------------------|
| c.25C>T        | p.R9W         | Missense variant. Deleterious (but some evidnce of low confidence in finding) to protein function, benign impact on protein structure |
| c.2T>C         | p.M1T         | Missense variant. Deleterious (but some evidnce of low confidence in finding) to protein function, benign impact on protein structure |
| c.73G>T        | p.G25C        | Missense, splice region variant. Change tolerated by protein function and has benign impact on protein structure |
| c.882 -2A>G    |               | Splice acceptor variant, high impact. Also potential impact on upstream gene regulation |
| c.973 -1G>A    |               | Splice acceptor variant, high impact. Also potential regulatory region variant altering TF binding site. Could impact upstream and downstream gene regulation (RPL32P5) |
| c.973 -2A>G    |               | Splice acceptor variant, high impact, may result in retained intron, could impact nonsense mediated decay. Also potential regulatory region variant altering TF binding site. Could impact upstream and downstream gene regulation (RPL32P5). |
| c.542+1G>A     |               | Splice donor variant with high impact. Possible impact on nonsense mediated decay |
| c.753+2T>A     |               | Splice donor variant with high impact. Possible retained intron |
| c.753G>A       |               | Splice region variant with low impact. May influence downstream and upstream gene regulation. |
| c.781delinsCCATA | p.D261Pfs*2  | Stop gained, frameshift variant with high impact |
| c.1196G>A      | p.W399*       | Stop gained, high impact |
| c.794C>G       | p.Q265X       | Stop gained, high impact variant. Possible impact on upstream gene regulation |
| c.916C>T       | p.R306*       | Stop gained, high impact variant. Possible impact on upstream gene regulation. |
| c.660C>A       | p.Y220X       | Stop gained, high impact variant. Possible impact on upstream gene regulation. Benign. |
| c.47+2T>C      |               | Synonymous, intron variant with low impact. Potential retained intron |

**C. COL4A1**

| Genetic mutation | Protein change | Variant information |
|------------------|---------------|---------------------|
| c.*35C>A        |               | 3' UTR variant, regulatory region variant |
| c.*31G>T        |               | 3'UTR variant, regulatory region variant |
| Variant | Description |
|---------|-------------|
| c.*32G>A | 3'UTR variant, regulatory region variant |
| c.*32G>T | 3'UTR variant, regulatory region variant |
| c.*33T>A | 3'UTR variant, regulatory region variant |
| c.-2C>T | 5'UTR variant, with possible impact on upstream gene regulation |
| c.2545G>T | p.G808V | Evidence of stop gained, high impact |
| c.2424delT | p.P810fs | Frameshift mutation with high impact. Potentially leading to premature stop |
| c.2931dupT | p.G978WfsX15 | Frameshift mutation with high impact. Potentially leading to premature stop |
| c.3702delC | p.G1236* | Frameshift mutation with high impact. Potentially leading to premature stop |
| c.2085del | p.G696fs | Frameshift mutation with high impact. Potentially leading to premature stop. Pathogenic. |
| c.1121-18G>A | Intron variant possibly leading to retained intron |
| c.2645_2646delinsAA | p.G882E | Intron variant potentially leading to retained intron |
| c.3877-30C>A | Intron variant with possible impact on upstream gene regulation. Intron retained |
| c.4582-4586dupCCCATG ins. | Intron variant, retained intron. Likely deleterious and probably damaging. Possible impact on upstream gene regulation |
| c.4642T>G | p.C1548G | Missense & splice region variant with low to moderate effect. Likely to impact protein function and probably damaging |
| c.2969G>A | p.G990E | Missense variant and splice region variant. May result in retained intron. Possible modifier of downstream gene regulation. Likely deleterious and probably damaging. |
| c.2969G>T | p.G990V | Missense variant and splice region variant. May result in retained intron. Possible modifier of downstream gene regulation. Likely deleterious and probably damaging. |
| c.3200G>A | p.G1067E | Missense variant and splice region variant. May result in retained intron. Possible modifier of downstream gene regulation. Likely deleterious and probably damaging. |
| c.3200G>C | p.G1067A | Missense variant and splice region variant. May result in retained intron. Possible modifier of downstream gene regulation. Likely deleterious and probably damaging. |
| c.3770G>C | p.G1257E | Missense variant in possible regulatory region. Likely deleterious and probably damaging |
| c.3796G>C | p.G1266R | Missense variant in possible regulatory region. Likely deleterious and probably damaging |
| c.3832G>T | p.G1278S | Missense variant in possible regulatory region. Likely deleterious and probably damaging. Uncertain clinical significance |
| Reference | Protein Position | Description                                                                 |
|-----------|------------------|-----------------------------------------------------------------------------|
| c.3245G>A | p.G1082E         | Missense variant with moderate impact and possible modifier of downstream gene regulation. Likely deleterious and possibly damaging |
| c.3280G>C | p.G1094R         | Missense variant with moderate impact and possible modifier of downstream gene regulation. Likely deleterious and possibly damaging |
| c.1249G>C | p.G417R          | Missense variant with moderate impact. Benign impact on protein structure and deleterious to protein function |
| c.3997G>A | p.D1333N         | Missense variant with moderate impact. Conflicting evidence of effect on protein function, potentially tolerated/potentially deleterious |
| c.3592G>A | p.G1198R         | Missense variant with moderate impact. Likely deleterious and probably damaging |
| c.3620G>T | p.G1207V         | Missense variant with moderate impact. Likely deleterious and probably damaging |
| c.3656G>A | p.G1219E         | Missense variant with moderate impact. Likely deleterious and probably damaging |
| c.3671C>T | p.P1224L         | Missense variant with moderate impact. Likely deleterious and probably damaging |
| c.3704A>G | p.K1235R         | Missense variant with moderate impact. Likely deleterious and probably damaging |
| c.3706G>A | p.G1236R         | Missense variant with moderate impact. Likely deleterious and probably damaging |
| c.3707G>A | p.G1237E         | Missense variant with moderate impact. Likely deleterious and probably damaging |
| c.3712C>T | p.R1238C         | Missense variant with moderate impact. Likely deleterious and probably damaging |
| c.3505G>A | p.G1169S         | Missense variant with moderate impact. Possible splice region variant, with potential impact on downstream gene regulation. Likely deleterious and probably damaging |
| c.2512A>G | p.M838V          | Missense variant with moderate impact. Possibly damaging to protein structure and deleterious to protein function |
| c.3389G>A | p.G1130D         | Missense variant with moderate impact. Potentially modifies upstream and downstream gene regulation. Likely deleterious and probably damaging |
| c.4088 G > A | p.G1363D       | Missense variant with moderate impact. Probably damaging and deleterious to protein function |
| c.1502G>A |                 | Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function |
| c.1528G>A | p.G510R          | Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function |
| c.1583G>A | p.G528E          | Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function |
| Variant       | Amino Acid Change | Description                                                                 |
|--------------|------------------|-----------------------------------------------------------------------------|
| c.1619A>G    | p.K540R          | Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function |
| c.2008G>A    | p.G670R          | Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function |
| c.2045G>T    | p.G682V          | Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function |
| c.2063G>A    | p.G688D          | Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function |
| c.2078G>A    | p.G693E          | Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function |
| c.2086G>A    | p.G696S          | Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function |
| c.2086G>T    | p.G696C          | Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function |
| c.2132G>A    | p.G711E          | Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function |
| c.2159G>A    | p.G720D          | Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function |
| c.2168G>A    | p.G723E          | Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function |
| c.2504G>A    | p.G835E          | Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function |
| c.625G>A     | p.G209S          | Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function |
| c.634G>A     | p.G212S          | Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function |
| c.1493G>A    | p.G498D          | Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function. Pathogenic. |
| Variant | Allele | Description |
|---------|--------|-------------|
| c.1493G>T | p.G498V | Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function. Pathogenic. |
| c.3383T>A | p.I1128N | Missense variant with moderate impact. Substitution seems to be tolerated by protein function but probably damaging to protein structure |
| c.3715G>A | p.G1239R | Missense variant with possible impact on upstream gene regulation. Probably damaging variant |
| c.3941G>T | p.G1314V | Missense variant with possible impact on upstream gene regulation. Probably damaging variant |
| c.3715G>A | p.G1239R | Missense variant with possible impact on upstream gene regulation. Probably damaging variant |
| c.4031G>C | p.G1344A | Missense variant with possible impact on upstream gene regulation. Probably damaging variant |
| c.1801G>A | p.G601S | Missense variant, moderate impact and potential modifier of downstream gene regulation. Only possibly damaging to protein structure and likely to have deleterious effect on protein function |
| c.1807C>T | p.P603S | Missense variant, moderate impact and potential modifier of downstream gene regulation. Only possibly damaging to protein structure and likely to have deleterious effect on protein function |
| c.1555G>A | p.G519R | Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function |
| c.1835G>A | p.G612D | Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function |
| c.1853G>A | p.G618E | Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function |
| c.2494G>A | p.G832R | Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function |
| c.2563G>C | p.G855R | Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function |
| c.2581G>A | p.G861S | Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function |
| c.2599G>A | p.G867R | Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function |
|  |  |  |
|---|---|---|
| c.2608G>A | p.G870R | Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function |
| c.2636G>A | p.G879E | Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function |
| c.2645G>A | p.G882D | Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function |
| c.2662G>A | p.G888R | Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function |
| c.2689G>A | p.G897S | Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function |
| c.2699G>A | p.G900E | Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function |
| c.2744G>A | p.G915E | Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function |
| c.2782G>C | p.D928H | Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function |
| c.2842G>A | p.G948S | Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function |
| c.2987G>A | p.G996D | Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function |
| c.3022G>A | p.G1008R | Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function |
| c.3040G>C | p.G1014R | Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function |
| c.3104G>T | p.G1035V | Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function |
| c.3122G>A | p.G1041E | Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function |
| Variant | Allele | Description |
|---------|--------|-------------|
| c.3130G>C | p.G1044E | Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function |
| c.3190G>A | p.G1064S | Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function |
| c.191G>T | p.G64V | Missense variant, moderate impact and potential modifier of upstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function. Possible 3'UTR variant. |
| c.4739G>C | p.G1580A | Missense variant, moderate impact, deleterious and likely to impact protein function, probably damaging |
| c.4881C>G | p.N1627K | Missense variant, moderate impact, deleterious and likely to impact protein function, probably damaging |
| c.4843G>A | p.E1615K | Missense variant, Moderate impact, possibly retained intron, probably damaging |
| c.4232G>C | p.G1411A | Missense variant, moderate impact. Probably damaging and likely to have deleterious effect on protein function |
| c.4380T>G | p.C1460W | Missense variant, moderate impact. Probably damaging and likely to have deleterious effect on protein function |
| c.4652G>A | p.C1551Y | Missense variant, moderate impact. Probably damaging and likely to have deleterious effect on protein function |
| c.4717G>A | p.G1573R | Missense variant, moderate impact. Probably damaging and likely to have deleterious effect on protein function |
| c.4738G>A | p.G1580S | Missense variant, moderate impact. Probably damaging and likely to have deleterious effect on protein function |
| c.1955G>A | p.G652E | Missense variant, moderate impact. Probably damaging to protein structure and likely to have deleterious effect on protein function |
| c.1963G>A | p.G655R | Missense variant, moderate impact. Probably damaging to protein structure and likely to have deleterious effect on protein function |
| rsID    | Gene   | cDNA alteration | Protein alteration | Impact on Protein Structure and Function |
|---------|--------|----------------|-------------------|-----------------------------------------|
| c.1964G>A | p.G655E | Missense variant, moderate impact. Probably damaging to protein structure and likely to have deleterious effect on protein function |
| c.1973C>A | p.G658V | Missense variant, moderate impact. Probably damaging to protein structure and likely to have deleterious effect on protein function |
| c.1973G>A | p.G658D | Missense variant, moderate impact. Probably damaging to protein structure and likely to have deleterious effect on protein function |
| c.2441 G > T | p.G814V | Missense variant, non-coding exon variant with moderate impact. Possibly damaging to protein structure and deleterious to protein function |
| c.2413G>A | p.G805R | Missense variant, non-coding exon variant with moderate impact. Possibly damaging to protein structure and deleterious to protein function |
| c.2413G>C | p.G805R | Missense variant, non-coding exon variant with moderate impact. Possibly damaging to protein structure and deleterious to protein function |
| c.2317G>A | p.G773R | Missense variant, non-coding exon variant with moderate impact. Probably damaging to protein structure and deleterious to protein function |
| c.2317G>C | p.G773R | Missense variant, non-coding exon variant with moderate impact. Probably damaging to protein structure and deleterious to protein function |
| c.2228G>T | p.G743V | Missense variant, non-coding exon variant with moderate impact. Regulatory region variant, leading to open chromatin structure. Probably damaging to protein structure and deleterious to protein function |
| c.2245G>A | p.G749S | Missense variant, non-coding exon variant with moderate impact. Regulatory region variant, leading to open chromatin structure. Probably damaging to protein structure and deleterious to protein function |
| c.2263G>A | p.G755R | Missense variant, non-coding exon variant with moderate impact. Regulatory region variant, leading to open chromatin structure. Probably damaging to protein structure and deleterious to protein function |
| c.4267G>C | p.G1423R | Missense variant, possibly resulting in retained intron. Possibly damaging and likely deleterious to protein function |
| c.4133G>A | p.G1378D | Missense variant, potentially impacting upstream gene regulation. Likely deleterious and probably damaging |
| Variation                  | Description                                                                 | Impact                                      |
|---------------------------|----------------------------------------------------------------------------|---------------------------------------------|
| c.4150+1(IVS46) G>T       | Missense variant, splice donor variant with potential impact on upstream gene regulation. High impact. Probably damaging and likely deleterious. |
| c.4150+1G>A               | Missense variant, splice donor variant with potential impact on upstream gene regulation. High impact. Probably damaging and likely deleterious. |
| c.4150G>A                 | p.G1384S                                                                   | Missense variant, splice region variant with low-moderate impact. Likely deleterious and probably damaging |
| c.2345G>C                 | p.G782A                                                                   | Missense variant, splice region variant with low-moderate impact. Likely deleterious to protein function and probably damaging to protein structure |
| c.2096G>A                 | p.G699D                                                                   | Missense variant, splice region variant with low-moderate impact. Likely deleterious to protein function and probably damaging to protein structure |
| c.2366G>T                 | p.G79V                                                                    | Missense variant, splice region variant with low-moderate impact. Likely deleterious to protein function and probably damaging to protein structure |
| c.443G>A                  | p.G148E                                                                   | Missense variant, splice region variant with low-moderate impact. Likely deleterious to protein function and probably damaging to protein structure |
| c.196C>A                  | p.Q66K                                                                    | Missense variant. Change tolerated by protein function but possibly damaging to protein structure |
| c.2641A>G                 | p.M881V                                                                   | Missense variant. Change tolerated by protein function but possibly damaging to protein structure |
| c.3046A>G                 | p.M1016V                                                                  | Missense variant. Change tolerated by protein function but possibly damaging to protein structure |
| c.31C>A                   | p.L11M                                                                    | Missense variant. Change tolerated by protein function but possibly damaging to protein structure |
| c.1612C>G                 | p.R538G                                                                   | Missense variant. Change tolerated by protein function with benign impact on protein structure |
| c.1769G>A                 | p.G562E                                                                   | Missense variant. Change tolerated by protein function with benign impact on protein structure |
| c.3946C>G                 | p.Q1316E                                                                  | Missense variant. Change tolerated by protein function, likely benign some evidence of possibly damaging protein structure |
| c.1537-2A>G               |                                                                           | Potential frameshift variant and splice acceptor variant with high impact |
| c.1537–2delA              |                                                                           | Potential frameshift variant and splice acceptor variant with high impact |
| c.1121-2dupA              | p.G374_N429 delinsD                                                      | Splice acceptor variant, intronic variant leading to retained intron. High impact variant. |
| c.1382-1G>C               |                                                                           | Splice acceptor variant, intronic variant leading to retained intron. High impact variant. |
| c.2194-1G.A               |                                                                           | Splice acceptor variant, intronic variant leading to retained intron. High impact variant. Also potential regulatory region variant leading to open chromatin structure |
| Genetic mutation | Protein change | Variant information |
|------------------|----------------|---------------------|
| c.553-2A>G       | Splice acceptor variant, intronic variant leading to retained intron. High impact variant. Also potential regulatory region variant leading to open chromatin structure and altered downstream gene regulation. Potential 3' UTR variant |
| c.1990+1G>A      | Splice donor variant with high impact. Possible retained intron |
| c.3406+1G>T      | Splice donor variant with high impact. Potential impact on both upstream and downstream gene regulation |
| c.2716+1G>A      | Splice donor variant with high impact. Potential impact on downstream gene regulation |
| c.2716+ G>T      | Splice donor variant with high impact. Potential impact on downstream gene regulation |
| c.2716+2T>C      | Splice donor variant with high impact. Potential impact on downstream gene regulation |
| c.2458+1G>A      | Splice donor variant, high impact. Possibly retained intron and downstream gene regulation modification |
| c.1A>T           | Start lost, but seems to be tolerated by protein function but possibly damaging to protein structure. Possible impact on upstream gene regulation |
| c.739C>T         | p.Q247* Stop gained, high impact. Possible modifier of downstream gene regulation |
| c.607G>T         | p. G203R Stop gained, high impact. Potential 3' UTR regulatory variant |
| c.4875C>A        | p.Y1625* Stop gained, likely deleterious, high impact |
| c.4887C>A        | p.Y1629X Stop gained, likely deleterious, high impact |
| c.1870G>T        | p.G624* Stop gained, likely deleterious, high impact. Possible modifier of downstream gene regulation |

**D. COL4A2**

| Genetic mutation | Protein change | Variant information |
|------------------|----------------|---------------------|
| c.1396G>A       | p.G466S Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function. Possible intron variant causing alteration to IncRNA influencing gene AS2 |
| c.1776+1G>A     | Splice donor variant with high impact. Possible retained intron and impact to IncRNA influencing gene AS2. Pathogenic but also reported to have uncertain clinical significance |
| c.1810G>C       | p.G604R Missense variant, moderate impact and potential modifier of upstream and downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function. Potential influence on promoter regulation and IncRNA influencing AS2 |
| rsID     | variants   | Description                                                                 |
|----------|------------|------------------------------------------------------------------------------|
| c.1856G>A| p.G619D    | Missense variant, moderate impact and potential modifier of upstream and downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function. Potential influence on promoter regulation and IncRNA influencing AS2. Likely pathogenic. |
| c.2105G>A| p.G702D    | Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function. |
| c.2399G>A| p.G800E    | Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function. With possible impact on upstream gene regulation and promoter regions. |
| c.2821G>A| p.G941R    | Missense variant, non-coding exon variant with moderate impact. Possibly damaging to protein structure and deleterious to protein function. Possible retained intron. |
| c.3110G>A| p.G1037E   | Missense variant, moderate impact and potential modifier of downstream gene regulation. Probably damaging to protein structure and likely to have deleterious effect on protein function. |
| c.3368A>G| p.E1123G   | Missense variant, non-coding exon variant with moderate impact. Possibly damaging to protein structure and deleterious to protein function. Likely benign clinical significance but possible risk factor. |
| c.3448C>A| p.Q1150K   | Missense variant, non-coding exon variant with moderate impact. Possibly damaging to protein structure and tolerated to protein function. Likely benign clinical significance but possible risk factor. |
| c.3490G>A| p.R1164G   | Missense variant with moderate impact. Probably damaging to protein structure and deleterious to protein function. Pathogenic. |
| c.4129G > A | p.G1377R  | Missense variant, moderate impact and potential modifier of upstream gene regulation, possible impact on IncRNA influencing AS2. Probably damaging to protein structure and likely to have deleterious effect on protein function. Pathogenic. |
| c.4147G>A| p.G1383R   | Missense variant, moderate impact and potential modifier of upstream gene regulation, possible impact on IncRNA influencing AS2. Probably damaging to protein structure and likely to have deleterious effect on protein function. Likely pathogenic. |
| c.4987G>A| p.G1663S   | Missense variant, moderate impact and potential modifier of both upstream and downstream gene regulation, possible impact on IncRNA influencing AS2. Probably damaging to protein structure and likely to have deleterious effect on protein function. Conflicting clinical significance, reported both likely benign and likely pathogenic. |
| c.5068G>A| p.A1690T   | Missense variant, non-coding exon variant with moderate impact. Possibly damaging to protein structure and tolerated to protein function. Likely benign clinical significance but possible risk factor. |
## E. TREC1

| Genetic mutation | Protein change | Variant information |
|------------------|----------------|---------------------|
| c.703dup         | p.V235GfsX6    | Frameshift mutation with high impact. Potentially leading to premature stop. Possible impact on downstream gene regulation of ATRIP and SHISA5 (non-mediated decay) |
| c.822delT        | p.P275Qfsx2    | Frameshift mutation with high impact. Potentially leading to premature stop. Possible impact on downstream gene regulation of ATRIP and SHISA5 (non-mediated decay) |
| c.830-833dupAGGA | p.D278fs       | Intronic variant. Potential 3'UTR variant with downstream gene variation. Possible influence on ATRIP and nonsense mediated decay of SHISA5 |
| c.829A>T         | p.K277*        | Stop gained, high impact. Possible modifier of downstream gene regulation. Likely pathogenic. |
| c.828_831dupGA   | p.D278EfsTer48 | Frameshift mutation with high impact. Potentially leading to premature stop. Possible impact on downstream gene regulation of ATRIP and SHISA5 (non-mediated decay) |
| c.703dupG        | p.V235Gfs      | Frameshift mutation with high impact. Potentially leading to premature stop. Possible impact on downstream gene regulation of ATRIP and SHISA5 (non-mediated decay) |
| c.685A>G         | p.Arg229Gly    | Missense variant, moderate impact and potential modifier of downstream gene regulation. Benign impact on protein structure and tolerated by protein function |
| c.690G>T         | p.Lys230Asn    | Missense variant, moderate impact and potential modifier of downstream gene regulation. Benign impact on protein structure and could have deleterious effect on protein function, but tolerated also reported |
| c.581delC        | p.Ala194fs     | Frameshift variant with high impact, possible downstream gene regulation of ATRIP and SHISA5. Pathogenic |
| c.742_745dupGTC   | p.T249fs      | Intrinsic variant. Potential 3'UTR variant with downstream gene variation. Possible influence on ATRIP and nonsense mediated decay of SHISA5 |
| c.734dupC        | ?              | Frameshift mutation with high impact. Potentially leading to premature stop. Possible impact on downstream gene regulation of ATRIP and SHISA5 (non-mediated decay) |
| c.911_912delCA   | p.T304Nfs*12  | Intronic variant. Potential 3'UTR variant with downstream gene variation. Possible influence on ATRIP and nonsense mediated decay of SHISA5 |
| c.703_704insG    | p.V235GfsX6    | Frameshift mutation with high impact. Potentially leading to premature stop. Possible impact on downstream gene regulation of ATRIP and SHISA5 (non-mediated decay) |
Supplemental References:

1. Abe Y, Matsuduka A, Okanari K, Miyahara H, Kato M, Miyatake S, Saitsu H, Matsumoto N, Tomoki M, Ibara K. A severe pulmonary complication in a patient with COL4A1-related disorder: A case report. Eur J Med Genet. 2017;60:169-171.
2. Adams KL, Riparini G, Banerjee P, Breur M, Bugiani M, Gallo V. Endothelin-1 signaling maintains glial progenitor proliferation in the postnatal subventricular zone. Nat. Commun. 2020;11:2138.
3. Agharahimi A, Bergerson J, Sun A, Similuk M, Oler A, Mace E, Stone D, Ombrello A, Freeman A. Warts as a predominant manifestation of ADA2 deficiency. J Clin Immunol. 2018;38:417. (Abstract)
4. Akgun-Dogan O, Simsek-Kiper PO, Taskiran E, Lissewski C, Brinkmann J, Schanze D, Gocmen R, Cagdas D, Bilginer Y, Utine GE, et al. ADA2 deficiency in a patient with Noonan syndrome-like disorder with loose anagen hair: The co-occurrence of two rare syndromes. Am. J. Med. Genet. A. 2019;179:2474–2480.
5. Al Mosawi Z, Abduljawad H, Busehail M, Al Moosawi B. Adenosine deaminase 2 deficiency with a novel variant of CECR1 gene mutation: Responding to tumor necrosis factor antagonist therapy. Indian J. Rheumatol. 2019;14:236–240.
6. Alabbas F, Elyamany G, Alsharif O, Hershfield M, Meyts I. Childhood Hodgkin Lymphoma: Think DADA2. J Clin Immunol. 2019;39:26-29.
7. Alamowitch S, Plaisier E, Favrole P, Prost C, Chen Z, Van Agtmael T, Marro B, Ronco P. Cerebrovascular disease related to COL4A1 mutations in HANAC syndrome. Neurology. 2009;73:1873-1882.
8. Alao H, Kleiner D, Han MAT, Takyar V, Stone D, Hoffmann P, Ombrello A, Jones A, Kastner D, Heller T. Deficiency of adenosine deaminase 2 (DADA2); a rare cause of hepatoportal sclerosis and non-cirrhotic portal hypertension. Gastroenterology. 2016;150:S1172-1173. (Abstract)
9. Alaygut D, Alparslan C, Perihan Oncel E, Mutlubas F, Ozdemir T, Yavaskan O, Kasap Demir B. A child diagnosed with treatment-resistant polyarteritis nodosa: Can the clinical diagnosis be different? Arch. Rheumatol. 2019;34:338–342.
10. Alsultan A, Basher E, Alqanatish J, Mohammed R, Alfadhel M. Deficiency of ADA2 mimicking autoimmune lymphoproliferative syndrome in the absence of livedo reticularis and vasculitis. Pediatr Blood Cancer. 2018;65.
11. Araujo JM, Alves JN, Taipa R, Alonso I, Ferreira C, Pinho J. Small vessel disease and intracerebral hemorrhages associated with novel pathogenic variants of col4a1. Europ Stroke J. 2018;3:582-583.
12. Arts K, Bergerson JRE, Ombrello AK, Similuk M, Oler AJ, Agharahimi A, Mace EM, Hershfield M, Wouters C, De Somer L et al. Warts and DADA2: a Mere Coincidence? J Clin Immunol. 2018;38:836-843.
13. Ayriñac X, Carra-Dalliere C, Menjot de Champfleur N, Denier C, Aubourg P, Bellesme C, Castelnovo G, Pelletier J, Audoin B, Kaphan E et al. Adult-onset genetic leukoencephalopathies: a MRI pattern-based approach in a comprehensive study of 154 patients. Brain. 2015;138:284-292.
14. Bademkiran F, Nalcaci S, Eraslan C, Durmaz A. The first Turkish family with the diagnosis of retinal vasculopathy with cerebral leukodystrophy (RVCL) where a new mutation was found. J Neurol Sci. 2017;381:378-379.
15. Balakrishna JP, Hsu A, Ombrello A, Wang W, Holland SM, Hickstein DD, Kastner DL, Aksentijevich I, Calvo KR. Spectrum of bone marrow pathology in patients with germline mutations in CECR1. Lab Inv. 2017;97:338A. (Abstract)

16. Barron K, Ombrello A, Stone D, Hoffmann P, Aksentijevich I, Zhou Q, Jones A, Kastner D. Clinical follow-up on a cohort of patients with deficiency of adenosine deaminase 2 (DADA2). Pediatric Rheumatology. 2015;13:19. (Abstract)

17. Barron K, Ombrello A, Stone D, Hoffmann P, Aksentijevich I, Zhou Q, Jones A, Kastner D. Deficiency of adenosine deaminase type ii-expanding the clinical spectrum. Arthritis Rheumatol. 2015;67. (Abstract)

18. Barron K, Ombrello A, Stone D, Hoffmann P, Romeo T, Jones A, Moura NS, Schnappauf O, Aksentijevich I, Bergerson J et al. The clinical spectrum of the deficiency of adenosine deaminase 2 (DADA2) continues to expand. Pediatr Rheumatol. 2019;17:1. (Abstract)

19. Barzaghi F, Minniti F, Mauro M, Bortoli M, Balter R, Bonetti E, Zaccaron A, Vitale V, Omrani M, Zoccolillo M et al. ALPS-Like Phenotype Caused by ADA2 Deficiency Rescued by Allogeneic Hematopoietic Stem Cell Transplantation. Front Immunol. 2018;9:2767.

20. Batu ED, Karadag O, Taskiran EZ, Kalyoncu U, Aksentijevich I, Alikasifoglu M, Ozen S. A case series of adenosine deaminase 2 deficient patients emphasizing treatment and genotype-phenotype correlations. Pediatr Rheumatol. 2015;13:P62. (Abstract)

21. Batu ED, Karadag O, Taskiran EZ, Kalyoncu U, Aksentijevich I, Alikasifoglu M, Özen S. A Case Series of Adenosine Deaminase 2-deficient Patients Emphasizing Treatment and Genotype-phenotype Correlations. J Rheumatol. 2015;42:1532-1534.

22. Batu ED, Karadag O, Taskiran EZ, Kalyoncu U, Aksentijevich I, Ozen S. A case series of adenosine deaminase 2 deficient patients emphasizing genotype-phenotype correlations. Ann Rheumat Dis. 2015;74:518. (Abstract)

23. Batu ED, Sonmez HE, Erden A, Taskiran EZ, Karadag O, Kalyoncu U, Oncel I, Kaplan B, Arici ZS, Temucin CM et al. The characteristic features of the patients with deficiency of adenosine deaminase 2 (DADA2). Pediatr Rheumatol. 2017;15:P403. (Abstract)

24. Batu ED, Taskiran EZ, Ozkara HA, Unal S, Guleray N, Erden A, Karadag O, Gumruk F, Cetin M, Bilginer Y, et al. A monogenic disease with wide range of symptoms: Deficiency of adenosine deaminase 2. Ann. Rheum. Dis. 2019;78:1748. (Abstract)

25. Bayrakli F, Balaban H, Gurelik M, Hizmetli M, Topaktas S. Mutation in the HTRA1 gene in a patient with degenerated spine as a component of CARASIL syndrome. Turk Neurosurg. 2014;24:67-69.

26. Baytaroglu A, Kadayiftcil S, Agin A, Delktas O, Demr S, Bigner Y, Karakaya J, Ozen S, Eldem B. Choroidal vascularity index as a biomarker of systemic inflammation in childhood Polyarteritis Nodosa and adenosine deaminase-2 deficiency. Pediatr. Rheumatol. 2020;18:29.

27. Beaufort N, Scharrer E, Kremmer E, Lux V, Ehrmann M, Huber R, Houlden H, Werring D, Haffner C, Dichtgans M. Cerebral small vessel disease-related protease HtrA1 processes latent TGF-beta binding protein 1 and facilitates TGF-beta signaling. Proc Natl Acad Sci USA. 2014;111:16496-16501.

28. Belot A, Wassmer E, Twilt M, Lega JC, Zeef LA, Oojageer A, Kasher PR, Mathieu AL, Malcus C, Demaret J et al. Mutations in CECR1 associated with a neutrophil signature in peripheral blood. Pediatr Rheumatol Online J. 2014;12:44.
29. Ben-Ami T, Revel-Vilk S, Brooks R, Shaag A, Hershfield MS, Kelly SJ, Ganson NJ, Kfir-Erenfeld S, Weintraub M, Elpeleg O et al. Extending the Clinical Phenotype of Adenosine Deaminase 2 Deficiency. J Pediatr. 2016;177:316-320.

30. Bertamino M, Grossi A, Severino M, Tortora D, Signa S, Amico G, Di Rocco M, Ceccherini I. Next generation sequencing based gene panel for enhanced rapid diagnosis of monogenic pediatric stroke. Eur. Stroke J. 2019;4:355. (Abstract)

31. Bianchi S, Di Palma C, Gallus GN, Gallus GF, Taglia I, Poggiani A, Rosini F, Rufa A, Muresanu DF, Cerase A et al. Two novel HTRA1 mutations in a European CARASIL patient et al. Neurology 2014, 82 (10), 898-900.

32. Bianchi S, Di Palma C, Gallus GN, Taglia I, Poggiani A, Rosini F, Cerase A, Rufa A, Muresanu D, Dotti MT et al. Journal of the Neurological Sciences. 2013;333:e660. (Abstract)

33. Bick D, Fraser PC, Gutzeit MF, Harris JM, Hambuch TM, Helbling DC, Jacob HJ, Kersten JN, Leuthner SR, May T et al. Successful Application of Whole Genome Sequencing in a Medical Genetics Clinic. J Pediatr Genet. 2017;6:61-76.

34. "Bilguvar K, DiLuna ML, Bizzarro MJ, Bayri Y, Schneider KC, Lifton RP, Gunel M, Ment LR. COL4A1 mutation in preterm intraventricular hemorrhage. J Pediatr. 2009;155:743-745." 

35. Bougea A, Velonakis G, Spantideas N, Anagnostou E, Paraskevas G Kapaki E, Kararizou E. The first Greek case of heterozygous cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy: An atypical clinicoradiological presentation. Neuroradiol J. 2017;30:583-585.

36. Breedveld G, de Coo IF, Lequin MH, Arts WF, Heutink P, Gould DB, John SW, Oostra B, Mancini GM. Novel mutations in three families confirm a major role of COL4A1 in hereditary porencephaly. J Med Genet. 2006;43:490-495.

37. Bucciol G, DelaFontaine S, Segers H, Bossuyt X, Hershfield MS, Moens L, Meyts I. Hematopoietic Stem Cell Transplantation in ADA2 Deficiency: Early Restoration of ADA2 Enzyme Activity and Disease Relapse upon Drop of Donor Chimerism. J Clin Immunol. 2017;37:746-750.

38. Bugiani M, Bakels HS, Waisfisz Q, Ceuterick-de Groote C, Niessen HW, Abbink TE, Lesnik Oberstein SA, van der Knaap MS. Cathepsin A-related arteriopathy with strokes and leukoencephalopathy (CARASAL). Neurology. 2016;87:1777-1786.

39. Bulut E, Erden A, Karadag O, Oguz KK, Ozen S. Deficiency of adenosine deaminase 2; special focus on central nervous system imaging. J Neurol Radiol. 2019;46:193-198.

40. Caetano A, Barbosa R, Costa J, Viana-Baptista M. Sindrome HANAC (Hereditary angiopathy, nephropathy, aneurysms, and muscle cramps) incompleto e 1a mutacao descrita do gene COL4A1 em Portugal (G236T). Sinapse. 2015;15:23-26.

41. Cai B, Zeng J, Lin Y, Lin W, Li Z, Wang N. A frameshift mutation in HTRA1 expands CARASIL syndrome and peripheral small arterial disease to the Chinese population. Neurol Sci. 2015;36:1387-1391.

42. Cakan M, Aktay-Ayaz N, Karadag SG, Tahir-Turanli E, Stafstrom K, Bainter W, Geha RS, Chou J. Atypical phenotype of an old disease or typical phenotype of a new disease: Deficiency of adenosine deaminase 2. Turk. J. Pediatr. 2019;61:413–417.

43. Campo-Caballero D, Rodriguez-Antiguedad J, Ekiza-Bazan J, Iruzubieta-Agudo P, Fernandez-Eulate G., Munoz-Lopetegui A, Martinez-Zabaleta M, de la Riva P, Urtasun-Ocariz M, de Munain AL, et al. COL4A1 Mutation as a Cause of Familial Recurrent Intracerebral Hemorrhage. J. Stroke Cerebrovasc. Dis. 2020;29:104652.
44. Caorsi R, Grossi A, Cusano R, Rusmini M, Penco F, Schena F, Anna Podda R, Uva P, Gattorno M, Ceccherini I. ADA2 deficiency without ADA2 mutations explained by a structural homozygous variation in 22q11.1. Pediatr Rheumatol. 2018;16. (Abstract)
45. Caorsi R, Grossi A, Insalaco A, Alessio M, Martino S, Cortis E, Morreale A, Caroli F, Martini A, Ceccherini I et al. Prevalence of cecr1 mutations in pediatric patients with polyarteritis nodosa, livedo reticularis and/or stroke. Ann Rheumat Dis. 2015;74:835. (Abstract)
46. Caorsi R, Grossi A, Insalaco A, Alessio M, Martino S, Cortis E, Morreale A, Caroli F, Martini A, Ceccherini I et al. Prevalence of CECR1 mutations in pediatric patients with polyarteritis nodosa, livedo reticularis and/or stroke. Pediatr Rheumatol. 2015;13:O87. (Abstract)
47. Caorsi R, Omenetti A, Morreale A, Insalaco A, Buoncompagni A, Picco P, Malattia C, Gandolfo C, Aksentijevich I, Martini A et al. Rapid and sustained effect of anti-TNF treatment in patients with ADA2 deficiency. Pediatr Rheumatol. 2016;13:74. (Abstract)
48. Caorsi R, Omenetti A, Picco P, Buoncompagni A, Minoia F, Federici S, Finetti M, Martini A, Aksentijevich I, Gattorno M. Long-term efficacy of etanercept in ADA2 deficiency. Pediatr Rheumatol. 2014;12. (Abstract)
49. Caorsi R, Severino MS, Gandolfo C, Ravelli A, Rossi A, Gattorno M. Distinct cerebrovascular features in patients with ADA2 deficiency. Pediatr Rheumatol. 2018;16. (Abstract)
50. Carneiro D, Fernandes C, Santo GC. Familial sneddon’s syndrome revisited: The natural history of deficiency of adenosine deaminase 2. Eur. Stroke J. 2019;4:355–356. (Abstract)
51. Carra-Dalliere C, Ayrignac X, Prieto-Morin C, Girard P, Tournier-Lasserve E, Labauge P. TREX1 Mutation in Leukodystrophy with Calcifications and Persistent Gadolinium-Enhancement. Eur Neurol. 2017;77:113-114.
52. Cavallin M, Mine M, Philbert M, Bodaert N, Lepage JM, Coste T, Lopez-Gonzalez V, Sanchez-Soler MJ, Ballesta-Martinez MJ, Remerand G et al. Further refinement of COL4A1 and COL4A2 related cortical malformations. Eur J Med Genet. 2018;61:765-772.
53. Chang Y, Derfalvi B, Issekutz A, Shi J, Alonzo P, Pascual CJ, Issekutz T, Walter JE. ADA2 deficiency: Case report of a rare phenotype with alps and CVID-like presentation. J Clin Immunol. 2018;38:341-342.
54. Chen Y, He Z, Meng S, Li L, Yang H, Zhang X. A novel mutation of the high-temperature requirement A serine peptidase 1 (HTRA1) gene in a Chinese family with cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL). J Int Med Res. 2013;41:1445-1455.
55. Chong-Neto HJ, Segundo GRS, Bandeira M, Riedi CA, Hershfield M, Torgerson TR, Rosario N. Novel CECR1 gene mutation causing ADA-2 deficiency. J Clin Immunol. 2018;38:387. (Abstract)
56. Christ S, Haber B, Grulich-Henn J, Helling-Bakki A, Hoffmann GF, Lutz T, Tonshoff B, Syrbe S, Haas D, Youssef H et al. Unclear strokes in pediatrics-adenosine deaminase 2
(ADA2) deficiency as a therapeutic relevant differential diagnosis to acquired inflammatory CNS diseases. Neuropediatrics. 2018;49. (Abstract)

58. Cimino M, Soo S, Morrow M. Ring-enhancing lesions, stroke and vascular retinopathy associated with a novel TREX1 mutation. Neurology. 2018;90:15. (Abstract)

59. Cipe FE, Aydogmus C, Serwas NK, Keskindemirci G, Boztuğ K. Novel Mutation in CECR1 Leads to Deficiency of ADA2 with Associated Neutropenia. J Clin Immunol. 2018;38:273-277.

60. Clarke K, Campbell C, Omoyinmi E, Hong Y, Obaidi MAL, Sebire N, Brogan P. Testicular ischemia in deficiency of adenosine deaminase 2 (DADA2). Pediatr Rheumatol. 2019;17. (Abstract)

61. Cohn AC, Kotschet K, Veitch A, Delatycki MB, McCombe MF. Novel ophthalmological features in hereditary endotheliopathy with retinopathy, nephropathy and stroke syndrome. Clin Exp Ophthalmol. 2005;33:181-183.

62. Colin E, Sentilhes L, Sarfati A, Mine M, Guichet A, Ploton C, Bousson F, Delorme B, Tournier-Lasserre E, Bonneau D. Fetal intracerebral hemorrhage and cataract: think COL4A1. J Perinatol. 2014;34:75-77.

63. Corlobe A, Tournier-Lasserre E, Mine M, Menjot de Champfleur N, Carra Dalliere C, Ayriignac X, Labauge P, Arquizan C. COL4A1 mutation revealed by an isolated brain hemorrhage. Cerebrovasc Dis. 2013;35:593-594.

64. Cornece-Le Gall E, Chebib FT, Madsen CD, Senum SR, Heyer CM, Lanpher BC, Patterson MC, Albright RC, Yu AS, Torres VE et al. The Value of Genetic Testing in Polycystic Kidney Diseases Illustrated by a Family With PKD2 and COL4A1 Mutations. Am J Kidney Dis. 2018;72:302-308.

65. Dahl S, Pettersson M, Eisfeldt J, Schroder AK, Wickstrom R, Tear Fahnehjelm K, Anderlid BM, Lindstrand A. Whole genome sequencing unveils genetic heterogeneity in optic nerve hypoplasia. PloS One. 2020;15:e0228622.

66. Decio A, Tonduti D, Picchiecchi A, Vetro A, Ciccone R, Limongelli I, Giorda R, Caffi L, Balottin U, Zuffardi O et al. A novel mutation in COL4A1 gene: a possible cause of early postnatal cerebrovascular events. Am J Med Genet. 2015;167A:810-815.
72. Değerliyurt A, Ceylaner G, Koçak H, Bilginer Gürbüz B, Cihan BS, Rizzu P, Ceylaner S. A new family with autosomal dominant porencephaly with a novel Col4A1 mutation. Are arachnoid cysts related to Col4A1 mutations? Genet Couns. 2012;23:185-193.
73. Deml B, Reis LM, Maheshwari M, Griffis C, Bick D, Semina EV. Whole exome analysis identifies dominant COL4A1 mutations in patients with complex ocular phenotypes involving microphthalmia. Clin Genet. 2014;86:475-481.
74. Dhamija R, Schiff D, Lopes MB, Jen JC, Lin DD, Worrall BB. Evolution of brain lesions in a patient with TREX1 cerebroretinal vasculopathy. Neurology. 2015;85:1633-1634.
75. Di Donato I, Bianchi S, Gallus GN, Cerase A, Federico A, Dotti MT. Heterozygous mutation of HTRA1 gene in an Italian family with cerebral ischemic small vessel disease. Eur J Neurol. 2016;23:559. (Abstract)
76. Di Donato I, Bianchi S, Gallus GN, Cerase A, Taglia I, Pescini F, Nannucci S, Battisti C, Inzitari D et al. Heterozygous mutations of HTRA1 gene in patients with familial cerebral small vessel disease. CNS Neurosci Ther. 2017;23:759-765.
77. DiFrancesco JC, Novara F, Zuffardi O, Forlino A, Gioia R, Cozz F, Bolognesi M, Andreoni S, Saracchi E, Frigeni B et al. TREX1 C-terminal frameshift mutations in the systemic variant of retinal vasculopathy with cerebral leukodystrophy. Neurou Sci. 2015;36:323-330.
78. Dimachkie MD, Fraga GR, Moura NS, Springer JM. A Rare Case of Adenosine Deaminase 2 Deficiency Presenting With Temporal Arteritis. J. Clin. Rheumatol. Pract. Rep. Rheum. Musculoskelet. Dis. 2020;00:Publish Ahead of Print.
79. Durrani-Kolarik S, Manickam K, Chen B. COL4A1 Mutation in a Neonate With Intrauterine Stroke and Anterior Segment Dysgenesis. Pediatr Neurol. 2017;66:100-103.
80. Ekinci RMK, Balci S, Bisgin A, Sasmaz I, Leblebisatan G, Incecik F, Yilmaz M. A homozygote novel L451W mutation in CECR1 gene causes deficiency of adenosine deaminase 2 in a pediatric patient representing with chronic lymphoproliferation and cytopenia. Pediatr. Hematol. Oncol. 2019;36:376-381.
81. Ekinci RMK, Balci S, Hershfield M, Bisgin A, Dogruel D, Altintas DU, Yilmaz M. Deficiency of adenosine deaminase 2: A case series revealing clinical manifestations, genotypes and treatment outcomes from Turkey. Rheumatol. U. K. 2020;59:254-256.
82. El Hasbani G, Balaghi A, Assaker R, Rojas A, Troyo M, Kofahi A, Assaker JP, Diab C, Al Husayni H. Intraparenchymal hemorrhage and cerebral venous thrombosis in an adult with congenital porencephalic cyst presenting for generalized tonic-clonic seizures. Radiol. Case Rep. 2020;15:95-99.
83. Elbracht M, Mull M, Wagner N, Kuhl C, Abicht A, Kurth I, Tenbrock K, Häusler M. Stroke as Initial Manifestation of Adenosine Deaminase 2 Deficiency. Neuropediatrics. 2017;48:111-114.
84. Erden A, Batu ED, Taskiran EZ, Sonmez HE, Sari A, Armagan B, Kilic L, Arici ZS, Bilginer Y, Akdogan A et al. The characteristic features of the patients with deficiency of adenosine deaminase 2 (DADA2). Arthritis Rheumatol. 2016;68:4112-4114. (Abstract)
85. Ersoy G, Bayram C, Gokce M, Unal S, Ozdemir NN. Ada 2 enzyme deficiency manifesting as pure red cell aplasia. HemaSphere. 2018;2:835. (Abstract)
86. F. Variable clinical phenotypes and relation of interferon signature with disease activity in ADA 2 deficiency. Pediatr Rheumatol. 2017;15. (Abstract)
87. Fasano A, Formichi P, Taglia I, Bianchi S, Di Donato I, Battisti C, Federico A, Dotti MT. HTRA1 expression profile and activity on TGF-β signaling in HTRA1 mutation carriers. J. Cell. Physiol. 2020;235:7120–7127.
88. Favaretto S, Margoni M, Salviati L, Pianese L, Manara R, Baracchini C. A new Italian family with HTRA1 mutation associated with autosomal-dominant variant of CARASIL: Are we pointing towards a disease spectrum? J Neurol Sci. 2019;396:108-111.
89. Fujita M, Shimoyama K, Otsuka N, Maeda Y, Hayashi K, Saitsu H, Matsumoto N, Takanashi J-I. Familial patients with congenital hemiplegia due to a COL4A1 mutation. No To Hattatsu. 2018;50:424-426.
90. Gale D, Oygar DD, Lin F, Oygar DP, Connor TMF, Khan N, Lapsley M, Maxwell PH, Neild GH. A novel COL4A1 frameshift mutation and kidney disease without extra-renal involvement in a large Turkish cypriot family. Nephrol Dial Transplant. 2016;31:1908–1914.
91. Garbarino F, Caorsi R, Volpi S, Grossi A, Ceccherini I, Gattorno M. A case of adenosine deaminase 2 deficiency (DADA2) with an uncommon clinical presentation and response to IVIG. Pediatr Rheumatol. 2019;17. (Abstract)
92. Garel C, Rosenblatt J, Moutard ML, Heron D, Gelot A, Gonzales M, Miné E, Jouannic JM. Fetal intracerebral hemorrhage and COL4A1 mutation: promise and uncertainty. Ultrasound Obstet Gynecol. 2013;41:228-230.
93. Garg N, Kasapcopur O, Foster J, Barut K, Tekin A, Kızılkılıç O, Tekin M. Novel adenosine deaminase 2 mutations in a child with a fatal vasculopathy. Eur J Pediatr. 2014;173:827-830.
94. Gasparini S, Qualtieri A, Ferlazzo E, Cianci V, Patitucci A, Spadafora P, Aguglia U. Normal immunofluorescence pattern of skin basement membranes in a family with porencephaly due to COL4A1 G749S mutation. Neurol Sci. 2016;37:459-463.
95. Geis T, Schirmer S, Walter M, Rodl T, Albrecht B, Schara U, Hehr U, Kolbel H. Massive parallel sequencing with a multigene panel (MGPS): Experiences with alpha-dystroglycanopathies. Neuropediatrics. 2016;47. (Abstract)
96. Gerasimenko A, Heron D, Billette De Villemeur T, Rodriguez D, Garel C, Tournier-Lasserve E, Chalard F, Mine M, Coste T, Mignot C. TORCH-like encephalopathy due to de novo COL4A1 mutation. Eur. J. Hum. Genet. 2019;27:1428–1429. (Abstract)
97. Ghurye RR, Sundaram K, Smith F, Clark B, Simpson MA, Fairbanks L, Adhya Z, Mufti GJ, Marsh JCW, Ibrahim MAA. Novel ADA2 mutation presenting with neutropenia, lymphopenia and bone marrow failure in patients with deficiency in adenosine deaminase 2 (DADA2). Br J Haematol. 2019;186:e60-64.
98. Gibson K, Cabral D, Drogemoller B, Xhan X, Miao F, Morishita K, Gill E, Hancock REW, Ross C, Brown K. Characterization of adenosine deaminase 2 variants identified in an international pediatric vasculitis cohort. Arthritis Rheumatol. 2017;69:Supplement 10. (Abstract)
99. Gibson KM, Morishita KA, Dancey P, Moorehead P, Drögemöller B, Han X, Graham J, Hancock REW, Foell D, Benseler S et al. Identification of Novel Adenosine Deaminase
2 Gene Variants and Varied Clinical Phenotype in Pediatric Vasculitis. Arthritis Rheumatol. 2019;71:1747-1755.

101. Giorgio E, Vaula G, Bosco G, Giacone S, Mancini C, Calcia A, Cavalieri S, Di Gregorio E, Rigault De Longrais R, Leombruni S et al. Two families with novel missense mutations in COL4A1: When diagnosis can be missed. Neurol Sci. 2015;352:99-104.

102. Gomes I, Galego O, Santo GAPRC, Nunes C. CARASIL: An underdiagnosed disease. Eur. J. Neurol. 2019;26:381. (Abstract)

103. Goncalves T da S, Alves CAPF, da Paz JA, Lucato LT. Teaching NeuImages: Lacunar stroke and polyarteritis nodosa: Consider ADA2 deficiency (DADA2). Neurology. 2019;92:e1801–e1802.

104. Gonzalez Santiago TM, Zavialov A, Saarela J, Seppanen M, Reed AM, Abraham RS, Gibson LE. Dermatologic Features of ADA2 Deficiency in Cutaneous Polyarteritis Nodosa. JAMA Dermatol. 2015;151:1230-1234.

105. Goschl L, Winkler S, Dmytrus J, Heredia RJ, Lagler H, Ramharter M, Scheinecker C, Bonelli M, Schmetterer K, Pickl WF, et al. Unreported Missense Mutation in the Dimerization Domain of ADA2 Leads to ADA2 Deficiency Associated with Severe Oral Ulcers and Neutropenia in a Female Somali Patient-Addendum to the Genotype-Phenotype Puzzle. J. Clin. Immunol. 2020;40:223–226.

106. Gould DB, Phalan FC, Breedveld GJ, van Mil SE, Smith RS, Schimenti JC, Aguglia U, van der Knaap MS, Heutink P, John SW. Mutations in Col4a1 cause perinatal cerebral hemorrhage and porencephaly. Science. 2005;308:1167-1171.

107. Gould DB, Phalan FC, van Mil SE, Sundberg JP, Vahedi K, Massin P, Bousser MG, Heutink P, Miner JH, Tournier-Lasserve E et al. NEJM. 2006;354:1489-1496.

108. Green LMC, Berry I, McCullagh HG. Cecr1 mutation is an important cause of brainstem stroke. Dev Med Child Neurol. 2017;59:82-83.

109. Grego L, Pignatto S, Rassu N, Passone E, Cogo P, Lanzetta P. Optic Nerve Hypoplasia, Corpus Callosum Agenesis, Cataract, and Lissencephaly in a Neonate with a Novel COL4A1 Mutation. Case Rep. Ophthalmol. 2019;10:424–430.

110. Grond-Ginsbach C, Brandt T, Kloss M, Aksay SS, Lyrer P, Traenka C, Erhart P, Martin JJ, Altintas A, Siva A et al. Next generation sequencing analysis of patients with familial cerebral artery dissection. Eur Stroke J. 2017;2:137-143.

111. Grossi A, Cusano R, Rusmini M, Penco F, Schena F, Podda RA, Caorsì R, Gattorno M, Uva P, Ceccherini I. ADA2 deficiency due to a novel structural variation in 22q11.1. Clinical Genetics. 2019;95:732-733.

112. Grossi A, Garbarino F, Caorsì R, Cusano R, Rusmini M, Penco F, Schena F, Podda RA, Uva P, Ceccherini I et al. ADA2 deficiency without ADA2 mutations explained by a structural homozygous variation in 22Q11.1. Pediatr Rheumatol. 2019;17. (Abstract)

113. Gruver AM, Schoenfield L, Coleman JF, Hajj-Ali R, Rodriguez ER, Tan CD. Novel ophthalmic pathology in an autopsy case of autosomal dominant retinal vasculopathy with cerebral leukodystrophy. J Neuroophthalmol. 2011;31:20-24.

114. Gu J, Bennetts B, Holman K, Wong K, Parratt J, Krishnan A, Tchan M. Cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL): The first Australian cases. Twin Research and Human Genetics. 2016;19:567. (Abstract)

115. Gulati A, Bale AE, Dykas DJ, Bia MJ, Danovitch GM, Moeckel GW, Somlo S, Dahl NK. TREX1 Mutation Causing Autosomal Dominant Thrombotic Microangiopathy and CKD-A Novel Presentation. Am J Kidney Dis. 2018;72:895-899.
116. Gümrük F, Soltanova G, Akarsu N, Cetin M, Unal S. Immunological status of patients with diamond blackfan anemia. Am J Hum Genet. 2018;2:832-833. (Abstract)

117. Gunda B, Kovács T, Hornyák C, Bereczki D, Várallyay G, Rudas G, Mine M, Tournier-Lasserve E. Recurrent intracerebral hemorrhage in a young adult caused by COL4A2 mutation. Int J Stroke. 2015;10:369. (Abstract)

118. Gunda B, Mine M, Kovács T, Hornyák C, Bereczki D, Várallyay G, Rudas G, Audrezet MP, Tournier-Lasserve E. COL4A2 mutation causing adult onset recurrent intracerebral hemorrhage and leukoencephalopathy. J Neurol. 2014;261:500-503.

119. Gunda B, Mine M, Kovács T, Hornyák C, Bereczki D, Várallyay G, Rudas G, Tournier-Lasserve E. Col4a2 mutation causing recurrent intracerebral hemorrhage - Importance of screening both Col4a1 and Col4a2 in ICH of unknown origin. J Neurol Sci 2013;333:e174-175. (Abstract)

120. Gunduz T, Demirkol Y, Dogan O, Demir S, Akcakaya NH. A Case of Leukoencephalopathy and Small Vessels Disease Caused by a Novel HTRA1 Homozygous Mutation. J. Stroke. 2019;28:104354.

121. Ha TT, Sadleir LG, Mandelstam SA, Paterson SJ, Scheffer IE, Gecz J, Corbett MA. A mutation in COL4A2 causes autosomal dominant porencephaly with cataracts. Am J Med Genet. 2016;170A:1059-1063.

122. Ha TT, Sadleir LG, Mandelstam SA, Paterson SJ, Scheffer IE, Gecz J, Corbett MA. A mutation in COL4A2 causes autosomal dominant porencephaly with cataracts. Am J Med Genet. 2016;170A:1059-1063.

123. Hanson-Kahn A, Vlessis K, Smith EJ, Manning M. Defining the clinical features associated with variants in COL4A2: Case report and review of the literature. Eur. J. Hum. Genet. 2019;27:1274.

124. Hara K, Shiga A, Fukutake T, Nozaki H, Miyashita A, Yokoseki A, Kawata H, Koyama A, Arima K, Takahashi T et al. Association of HTRA1 mutations and familial ischemic cerebral small-vessel disease. N Engl J Med. 2009;360:1729-1739.

125. Harada T, Uegaki T, Arata K, Tsunetou T, Taniguchi F. Schizencephaly and Porencephaly Due to Fetal Intracranial Hemorrhage: A Report of Two Cases. Yonago Acta Med. 2017;60:241-245.

126. Hardy TA, Young S, Sy JS, Colley AF, Terwindt GM, Ferrari MD, Hayes MW, Hodkinson S. Tumefactive lesions in retinal vasculopathy with cerebral leukoencephalopathy and systemic manifestations (RVCL-S): a role for neuroinflammation? J Neurol Neurosurg Psychiatry. 2017:316142

127. Harel A, Raynowska J, Miskin D, Pramanik B, Asiry S, Anderson T, Boockvar J, Najjar S. Retinal vasculopathy with cerebral leukoencephalopathy (RVCL): A rare familial mimic of tumefactive multiple sclerosis (MS). Neurology. 2018;90:15. (Abstract)

128. Harteman JC, Groenendaal F, van Haastert IC, Liem KD, Stroink H, Bierings MB, Huisman A, de Vries LS. Atypical timing and presentation of periventricular haemorrhagic infarction in preterm infants: the role of thrombophilia. Dev Med Child Neurol. 2012;54:140-147.

129. Hashem H, Egler R, Dalal J. Refractory Pure Red Cell Aplasia Manifesting as Deficiency of Adenosine Deaminase 2. J Pediatr Hematol Oncol. 2017;39:e293-6.

130. Hashem H, Kumar AR, Müller I, Babor F, Bredius R, Dalal J, Hsu AP, Holland SM, Hickstein DD, Jolles S et al. Hematopoietic stem cell transplantation rescues the hematological, immunological, and vascular phenotype in DADA2. Blood. 2017;130:2682-2688.
131. Hashem H, Vatsayan A, Gupta A, Nagle K, Hershfield M, Dalal J. Successful reduced intensity hematopoietic cell transplant in a patient with deficiency of adenosine deaminase 2. Bone Marrow Transplant. 2017;52:1575-1576.

132. Hatano T, Daida K, Hoshino Y, Li Y, Saitsu H, Matsumoto N, Hatter N. Dystonia due to bilateral caudate hemorrhage associated with a COL4A1 mutation. Movement Disorders. 2017;32:823-824.(Abstract)

133. Hatano T, Daida K, Hoshino Y, Li Y, Saitsu H, Matsumoto N, Hattori N. Dystonia due to bilateral caudate hemorrhage associated with a COL4A1 mutation. Parkinsonism Relat Disord. 2017;40:80-82.

134. Hedderich DM, Lummel N, Deschauer M, Kumpfel T, Schuh E, Patzig M, Zimmer C, Huber T. Magnetic Resonance Imaging Characteristics of Retinal Vasculopathy with Cerebral Leukoencephalopathy and Systemic Manifestations. Clin Neuroradiol. 2019;1-8.

135. Heinrich T, Dufke A, Waldmuller S, Schoning M. Identification of a COL4A1 mutation in a boy with developmental delay, brain malformations, and bilateral cataract allows for prenatal testing in a subsequent pregnancy. Medizinische Genetik. 2016;28:153. (Abstract)

136. Hinman JD, Lee MD, Tung S, Vinters HV, Carmichael ST. Molecular disorganization of axons adjacent to human lacunar infarcts. Brain. 2015;138:736-745.

137. Hoffmann P, Ombrello AK, Stone DL, Barron K, Pinto-Patarroyo G, Jones A, Romeo T, Follmann D, Toro C, Soldatos A et al. Analysis of the use of anticoagulants and antiplatelet agents in strokes caused by the deficiency of adenosine deaminase 2. Arthritis Rheumatol. 2016;68:3110-3111. (Abstract)

138. Hoffmann PM, Ombrello A, Stone DL, Follmann D, Barron K, Jones A, Romeo T, Toro C, Soldatos A, Hay A et al. Risk of hemorrhagic strokes in patients with adenosine deaminase 2 deficiency. Arthritis Rheumatol. 2018;70:2517. (Abstract)

139. Hsu AP, West RR, Calvo KR, Cuellar-Rodriguez J, Parta M, Kelly SJ, Ganson NJ, Hershfield MS, Holland SM, Hickstein DD. Adenosine deaminase type 2 deficiency masquerading as GATA2 deficiency: Successful hematopoietic stem cell transplantation. Ann Rheum Dis. 2017;76:1648-1656.

140. Hsu AP, West RR, Calvo KR, Cuellar-Rodriguez J, Parta M, Kelly SJ, Ganson NJ, Hershfield MS, Holland SM, Hickstein DD. Adenosine deaminase type 2 deficiency masquerading as GATA2 deficiency: Successful hematopoietic stem cell transplantation. J. Allergy Clin. Immunol. 2016;138:628-630.e2.

141. Hwang YT, Lakshmanan R, Davagnanam I, Thompson AGB, Lynch DS, Houlden H, Bajaj N, Eriksson SH, Bamiou DE, Warren JD. Brainstem phenotype of cathepsin A-related arteriopathy with strokes and leukoencephalopathy. Neurol Genet. 2017;3:e165.

142. Ibrahim M, Nozaki H, Lee A, Onodera O, Reichwein R, Wicklund M, El-Ghanem M. A CARASIL Patient from Americas with Novel Mutation and Atypical Features: Case Presentation and Literature Review. Cerebrovasc Dis. 2017;44:135-140.

143. "Insalaco A, Moneta G, Pardeo M, Passarelli C, Celani C, Messia V, De Benedetti F. Variable clinical phenotypes and relation of interferon signature with disease activity in ADA 2 deficiency. Pediatr Rheumatol. 2017;15. (Abstract)"
145. Insalaco A, Moneta G, Pardeo M, Passarelli C, Celani C, Messia V, De Benedetti F. Variable clinical phenotypes and relation of interferon signature with disease activity in ADA 2 deficiency. Arthritis Rheumatol. 2016;68:3111-3112. (Abstract)

146. Insalaco A, Moneta GM, Pardeo M, Caiello I, Messia V, Bracaglia C, Passarelli C, De Benedetti F. Variable Clinical Phenotypes and Relation of Interferon Signature with Disease Activity in ADA2 Deficiency. J Rheumatol. 2019;46:523-526.

147. Ito J, Nozaki H, Toyoshima Y, Abe T, Sato A, Hashidate H, Igarashi S, Onodera O, Takahashi H, Kakita A. Histopathologic features of an autopsied patient with cerebral small vessel disease and a heterozygous HTRA1 mutation. Neuropathology. 2018;38:428-432.

148. Ito S, Takao M, Fukutake T, Hatsuta H, Funabe S, Ito N, Shimoe Y, Niki T, Nakano I, Fukayama M et al. Histopathologic Analysis of Cerebral Autosomal Recessive Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CARASIL): A Report of a New Genetically Confirmed Case and Comparison to 2 Previous Cases. J Neuropathol Exp Neurol. 2016;75:1020-1030.

149. Ito S, Takao M, Nogami A, Funabe S, Hatsuta H, Niki T, Ito N, Fukutake T, Shimoe Y, Fukayama M, et al. Cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL): neuropathological examinations of three genetically confirmed autopsied cases. Neuropathology. 2012;32:363. (Abstract)

150. Jeanne M, Labelle-Dumas C, Jorgensen J, Kauffman WB, Mancini GM, Favor J, Valant V, Greenberg SM, Rosand J, Gould DB. COL4A2 mutations impair COL4A1 and COL4A2 secretion and cause hemorrhagic stroke. Am J Hum Genet. 2012;90:91-101.

151. John S, Jehi L, Manno EM, Conway DS, Uchino K. COL4A1 gene mutation—beyond a vascular syndrome. Seizure. 2015;31:19-21.

152. John S, Jehi L, Manno EM, Conway DS, Uchino K. COL4A1 gene mutation—beyond a vascular syndrome. Seizure. 2015;31:19-21.

153. Jordan MA, Pierpont ME, Johnston RH, Lee MS, Mccllelland CM. Hereditary angiopathy with nephropathy, aneurysm, and muscle cramps (hanac) syndrome presenting to neuro-ophthalmology with metamorphopsia. J. Neuroophthalmol. 2019;39:506–510.

154. Kaljas Y, Liu C, Skaldin M, Wu C, Zhou Q, Lu Y, Aksentijевич I, Zavialov AV. Human adenosine deaminases ADA1 and ADA2 bind to different subsets of immune cells. Cell. Mol. Life Sci. 2017;74:555–570.

155. Kamo H, Conedera SA, Ogaki K, Daida K, Li Y, Funabashi M, Yoshino H, Funayama M, Nishioka K, Hattori N. Genetic analyses of HTRA1 and CTSA in Japanese patients with cerebral small vessel disease. Clin. Neurol. 2019;59:S409. (Abstract)

156. Karacan İ, Balamir A, Uğurlu S, Aydın AK, Everest E, Zor S, Önen M, Daşdemir S, Özkaya O, Sözeri B et al. Diagnostic utility of a targeted next-generation sequencing gene panel in the clinical suspicion of systemic autoinflammatory diseases: a multicenter study. Rheumatol Int. 2019;39:911-919.

157. Keer N, Hershfield M, Caskey T, Unizony S. Novel compound heterozygous variants in CECR1 gene associated with childhood onset polyarteritis nodosa and deficiency of ADA2. Rheumatology. 2016;55:1145-1147.

158. Kellett S, Lemaire M, Miller SP, Licht C, Yoon G, Dlamini N, Noone D. Neonatal stroke and haematuria: Answers. Pediatr Nephrol. 2018;33:807-811.
159. Kellett S, Lemaire M, Miller SP, Licht C, Yoon G, Dlamini N, Noone D. Neonatal stroke and haematuria: Questions. Pediatr Nephrol. 2018;33:805-806.

160. Khaleeli Z, Jaunmuktane Z, Beaufort N, Houlden H, Haffner C, Brandner S, Dichgans M, Werring D. A novel HTRA1 exon 2 mutation causes loss of protease activity in a Pakistani CARASIL patient. J Neurol. 2015;262:1369-1372.

161. Khalid R, Krishnan P, Andres K, Blaser S, Miller S, Moharir M, Dlamini N. COL4A1 and fetal vascular origins of schizencephaly. Neurology. 2018;90:232-234.

162. Khalid R, Krishnan P, Blaser S, Andres K, Miller S, Moharir M, Dlamini N. Fetal vascular origins of schizencephaly. Ann Neurol. 2016;80:S341-S343. (Abstract)

163. Kilic SS, Cekic S, Karali Y. Cerebral ischemic attacks in ADA2 deficiency treated with adalimumab. Allergy Eur. J. Allergy Clin. Immunol. 2019;74:828. (Abstract) (a)

164. Kilic SS, Cekic S, Karali Y. Severe neutropenia in ADA2 deficiency. Arch. Dis. Child. 2019;104:A304. (Abstract) (b)

165. Komaki R, Ueda T, Tsuji Y, Miyawaki T, Kusuhara S, Hara S, Toda T. Retinal vasculopathy with cerebral leukoencephalopathy carrying TREX1 mutation diagnosed by the intracranial calcification: a case report. Rinsho Shinkeigaku. 2018;58:111-117.

166. Kono Y, Nishioka K, Komatuzaki Y, Ito Y, Yoshino H, Tanaka R, Hattori N, Iguchi Y. CADASIL type 2 in two families presenting mimic symptoms of CARASIL. J Neurol Sci. 2017;381. (Abstract)

167. Kono Y, Nishioka K, Li Y, Komatuzaki Y, Ito Y, Yoshino H, Tanaka R, Hattori N, Iguchi Y. Heterozygous HTRA1 mutations with mimicking symptoms of CARASIL in two families. Clin Neurol Neurosurg. 2018;172:174-176.

168. Konstantoulaki E, Siddiqui A, Amaya L, Gowda V. Case presentation: Developmental delay, cataracts and seizures with white matter infarctions explained by a novel COL4A1 mutation on a young child. Dev Med Child Neurol. 2017;59:93. (Abstract) (a)

169. Konstantoulaki E, Siddiqui A, Livingston J, Gowda V. Novel mutation in COL4A1 in a boy with cataracts, gross motor and speech delay, seizures, stroke and deep white matter changes on neuroimaging. Dev Med Child Neurol. 2017;59:99. (Abstract) (b)

170. Krutzke S, Hornreff G. Treatment of Two Male Children Suffering From Deficiency of Adenosine Deaminase Type 2 (DADA2) With TNF-Inhibitor Etanercept. J. Clin. Rheumatol. Pract. Rep. Rheum. Musculoskelet. Dis. 2019;Publish Ahead of Print.
Kumar AR, Hickstein DD, Ghadir SS, Bertuch AA, Krance RA, Hsu AP, Hashem H, Babor F, Meisel R, Koskenvuo M et al. Hematopoietic stem cell transplantation rescues the vascular, haematological and immunological phenotype in adenosine deaminase 2 deficiency. J Clin Immunol. 2017;37:247-248.

Kunii M, Doi H, Kubota S, Hashiguchi S, Hirama N, Ogawa Y, Takahashi K, Tanaka K, Tada M et al. Genetic analysis of adult leukoencephalopathy patients using whole exon sequencing. J Neurol Sci. 2017;381:455. (Abstract)

Labauge P, Carra-Dalliere C, Ayrignac X, De Champfleur NM, Aubourg P, Bellesme C, Pelletier J, Audoin B, De Seze J, Collongues N, et al. Diagnosis of adult onset leukodystrophy in a consecutive study of 156 patients. Neurology. 2013;80:1 MeetingAbstracts. (Abstract)

Labelle-Dumais C, Dilworth DJ, Harrington EP, de Leau M, Lyons D, Kabaeva Z, Manzini MC, Dobyns WB, Walsh CA, Michele DE et al. COL4A1 mutations cause ocular dysgenesis, neuronal localization defects, and myopathy in mice and Walker-Warburg syndrome in humans. PLoS Genet. 2011;7:e1002062.

Labelle-Dumais C, Schuitema V, Hayashi G, Hoff K, Gong W, Dao DQ, Ullian EM, Oishi P, Margeta M, Gould DB. COL4A1 Mutations Cause Neuromuscular Disease with Tissue-Specific Mechanistic Heterogeneity. Am J Hum Genet. 2019;104:847-860.

Lamprecht P, Humrich JY, Diebold I, Riemekasten G. Diagnosis of deficiency of adenosine deaminase 2 with early onset polyarteritis nodosa in an adult patient with a novel compound heterozygous CECR1 mutation. Clin Exp Rheumatol. 2018;36:177.

Lee PY, Kellner ES, Huang Y, Furutani E, Huang Z, Bainter W, Alosaimi MF, Stafstrom K, Platt CD, Stauber T, et al. Genotype and functional correlates of disease phenotype in deficiency of adenosine deaminase 2 (DADA2). J. Allergy Clin. Immunol. 2020;145:1664–1672.

Lee YC, Chung CP, Chao NC, Fuh JL, Chang FC, Soong BW, Liao YC. Characterization of Heterozygous HTRA1 Mutations in Taiwanese Patients with Cerebral Small Vessel Disease. Stroke. 2018;49:1593-1601.

Lee YC, Huang Y, Zhou Q, Schnappauf O, Hershfield MS, Li Y, Ganson NJ, Sampaio Moura N, Delmonte OM, Stone SS et al. Disrupted N-linked glycosylation as a disease mechanism in deficiency of ADA2. J Allerg Clin Immunol. 2018;142:1363-1365.

Lemmens R, Maugeri A, Niessen HW, Goris A, Tousseyn T, Damaereel P, Corveleyn A, Robberecht W, van der Knaap MS, Thijs VN et al. Novel COL4A1 mutations cause cerebral small vessel disease by haploinsufficiency. Hum Mol Genet. 2013;22:391-397.

Leung M, Lewis EC, Humphreys P, Miller E, Geraghty M, Lines M, Sell E. COL4A1 mutation in a pediatric patient presenting with post-ictal hemiparesis. Can J Neurol Sci. 2012;39:654-657.

Leung M, Lewis EC, Humphreys P, Miller E, Lines M, Sell E. COL4A1 mutation in a pediatric patient presenting with a Todd's paresis. Can J Neurol Sci. 2011;38:568-569. (Abstract)

Li WR, Zhao DH, Wang ZX, Hong DJ, Zhang W, Yuan Y. Novel mutation of HTRA1 gene causes cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy: one case. Chinese Journal of Neurology. 2012;45:566-569.

Liao YC, Chao NC, Lee YC. Heterozygous HTRA1 mutation in Taiwanese patients with cerebral small vessel disease. Neurology. 2017;88(16). (Abstract) (a)
190. Liao YC, Chao NC, Tsai PC, Soong BW, Lee YC. Heterozygous HTRA1 mutation in Taiwanese patients with cerebral small vessel disease. J Neurol Sci. 2017;381:456. (Abstract) (b)
191. Lichtenbelt KD, Pistorius LR, De Tollenaer SM, Mancini GM, De Vries LS. Prenatal genetic confirmation of a COL4A1 mutation presenting with sonographic fetal intracranial hemorrhage. Ultrasound Obstet Gynecol. 2012;39:726-727.
192. Liebowitz J, Hellmann DB, Schnappauf O. Thirty Years of Follow up in 3 Patients with Familial Polyarteritis Nodosa due to Adenosine Deaminase 2 Deficiency. J Rheumatol. 2019;46:1059-1060.
193. Liu L, Wang W, Wang Y, Hou J, Ying W, Hui X, Zhou Q, Liu D, Yao H, Sun J et al. A Chinese DADA2 patient: report of two novel mutations and successful HSCT. Immunogenetics. 2019;71:299-305.
194. Livingston J, Doherty D, Orcesi S, Tonduti D, Piechiecchio A, La Piana R, Tournier-Lasserve E, Majumdar A, Tomkins S, Rice G et al. COL4A1 mutations associated with a characteristic pattern of intracranial calcification. Neuropediatrics. 2011;42:227-233.
195. Livingston JH, Stivaros S, van der Knaap MS, Crow YJ. Recognizable phenotypes associated with intracranial calcification. Dev Med Child Neurol. 2013;55:46-57.
196. Loureiro G, Oliveira D, Ganhao S, Aguiar F, Rodrigues M, Brito I. ADA2 deficiency presenting as infantile polyarteritis nodosa. Ann. Rheum. Dis. 2019;78:1985.
197. Low WC, Junna M, Börjesson-Hanson A, Morris CM, Moss TH, Stevens DL, St Clair D, Mizuno T, Zhang WW, Mykkänen K et al. Hereditary multi-infarct dementia of the Swedish type is a novel disorder different from NOTCH3 causing CADASIL. Brain. 2007;130:357-367.
198. Low WC, Junna M, Börjesson-Hanson A, Morris CM, Moss TH, Stevens DL, St Clair D, Mizuno T, Zhang WW, Mykkänen K et al. Hereditary multi-infarct dementia of the Swedish type is a novel disorder different from NOTCH3 causing CADASIL. Brain. 2007;130:357-367.
199. Lynch D, De Paiva ARB, Zhang WJ, Lakshmanan R, Davagnanam I, Fox N, Murphy E, Kok F, Chataway J, Houlden H. Clinical and genetic characterisation of adult onset leukoencephalopathy. Neurology. 2017;88:16 Supplement 1. (Abstract)
200. Lynch DS, Rodrigues Brandão de Paiva A, Zhang WJ, Bugiardini E, Freua F, Tavares Lucato L, Macedo-Souza Li, Lakshmanan R, Kinsella JA, Merwick A et al. Clinical and genetic characterization of leukoencephalopathies in adults. Brain. 2017;140:1204-1211.
201. Maccora I, Frongia I, Azzari C, Ricci S, Cimaz R, Simonini G. A misleading case of deficiency of adenosine deaminase 2 (DADA2): the magnifying glass of the scientific knowledge drives the tailored medicine in real life. Clin Exp Rheumatol. 2018;36:146.
202. Magnin E, Ayrignac X, Berger E, Mine M, Tournier-Lasserve E, Labauge P. Late diagnosis of COL4A1 mutation and problematic vascular risk factor management. Eur Neurol. 2014;72:150-152.
203. Maisonneuve E, M’Barek IB, Leblanc T, Da Costa L, Friszer S, Pernot F, Thomas P, Castaigne V, N’Dour CT, Mailloux A, et al. Managing the Unusual Causes of Fetal Anemia. Fetal Diagn. Ther. 2020;47:156–164.
204. Mancini GM, de Coo IF, Lequien MH, Arts WF. Hereditary porencephaly: clinical and MRI findings in two Dutch families. Eur J Paediatr Neurol. 2004;8:45-54.
205. Martin H, Bursztejn AC, Cuny JF, Sarrabay G, Schmutz JL, Touitou I, Wahl D, Bonhomme A. Chronic leg ulcer revealing adenosine deaminase 2 deficiency: an atypical presentation. Eur J Dermatol. 2018;28:847-848.

206. Mateen FJ, Krecke K, Younge BR, Ford AL, Shaikh A, Kothari PH, Atkinson JP. Evolution of a tumor-like lesion in cerebroretinal vasculopathy and TREX1 mutation. Neurology. 2010;75:1211-1213.

207. Matias-Perez D, Garcia-Montano LA, Cruz-Aguilar M, Garcia-Montalvo IA, Nava-Valdez J, Barragan-Arevalo T, Villanueva-Mendoza C, Villarroel CE, Guadarrama-Vallejo C, la Cruz RV-D et al. Identification of novel pathogenic variants and novel gene-phenotype correlations in Mexican subjects with microphthalmia and/or anophthalmia by next-generation sequencing. J Hum Genet. 2018;63:1169-1180.

208. Matsumoto T, Miyakoshi K, Fukutake M, Ochial D, Minegishi K, Tanaka M. Intracranial sonographic features demonstrating in utero development of hemorrhagic brain damage leading to schizencephaly-associated COL4A1 mutation. J Med Ultrason. 2015;42:445-446.

209. Matthew S, Graf W, Szekely A. An autosomal dominant arteriopathy of the brain due to a novel mutation in collagen 4A1 gene in a family with early-onset stroke and leukoencephalopathy. Neurology. 2014;82:10 Suppl 1. (Abstract)

210. McGovern M, Flanagan O, Lynch B, Lynch SA, Allen NM. Novel COL4A2 variant in a large pedigree: Consequences and dilemmas. Clin Genet. 2017;92:447-448.

211. Mendioroz M, Fernandez-Cadenas I, del Rio-Espinola A, Rovira A, Sole E, Fernandez-Figueras MT, Garcia-Patos V, Sastre-Garriga J, Dominguez-Montanari S, Alvarez-Sabin J, et al. A missense HTRA1 mutation expands CARASIL syndrome to the Caucasian population. Neurology. 2010;75:2033–2035.

212. Menezes Cordeiro I, Nzwalo H, Sá F, Ferreira RB, Alonso I, Afonso L, Basílio C. Shifting the CARASIL paradigm: report of a non-Asian family and literature review. Stroke. 2015;46:1110-1112.

213. Menter T, Winkler D, Isimbaldi G, Hopfer H, Mihatsch M. TREX1 mutations - one of the genetic causes for renal vascular diseases in younger patients. Swiss Medical Weekly. 2013;143:23S. (Abstract) (a)

214. Menter T, Winkler D, Isimbaldi G, Hopfer H, Mihatsch M. TREX1 mutations - one of the genetic causes for renal vascular diseases in younger patients. Virchows Archiv. 2013;463:298. (Abstract) (b)

215. Meuwissen ME, de Vries LS, Verbeek HA, Lequin MH, Govaert PP, Schot R, Cowan FM, Hennekam R, Rizzu P, Verheijen FW et al. Sporadic COL4A1 mutations with extensive prenatal porencephaly resembling hydranencephaly. Neurology. 2011;76:844-846.

216. Meuwissen ME, Halley DJ, Smit LS, Lequin MH, Cobben JM, de Coo R, van Harssel J, Salleveldt S, Woldringh G, van der Knaap MS, de Vries LS, Mancini GM. The expanding phenotype of COL4A1 and COL4A2 mutations: clinical data on 13 newly identified families and a review of the literature. Genet Med. 2015;17:843-853.

217. Michniacki TF, Hannibal M, Ross CW, Frame DG, DuVall AS, Khoriaty R, Vander Lugt MT, Walkovich KJ. Hematologic Manifestations of Deficiency of Adenosine Deaminase 2 (DADA2) and Response to Tumor Necrosis Factor Inhibition in DADA2-Associated Bone Marrow Failure. J Clin Immunol. 2018;38:166-173.
218. Michniacki TF, Hannibal M, Walkovich KJ, VanderLugt MT, Hershfield M, Frame DG, DuVall AS. Bone marrow failure secondary to ADA2 deficiency in adult siblings. J Clin Immunol. 2017;37:246. (Abstract)

219. Mishra A, Chauhan G, Violleau M-H, Vojinovic D, Jian X, Bis JC, Li S, Saba Y, Grenier-Boley B, Yang Q, et al. Association of variants in HTRA1 and NOTCH3 with MRI-defined extremes of cerebral small vessel disease in older subjects. Brain. 2019;142:1009–1023.

220. Mishra A, Violleau MH, Chauhan G, Mazoyer B, Tzourio C, Debette S. Exome sequence study on extreme MRI markers of cerebral small vessel disease. Stroke. 2018;49. (Abstract)

221. Monroy-Jaramillo N, Cerón A, León E, Rivas V, Ochoa-Morales A, Arteaga-Alcaraz MG, Nocedal-Rustrian FC, Gallegos C, Alonso-Vilatela ME, Corona T. Phenotypic Variability in a Mexican Mestizo Family with Retinal Vasculopathy with Cerebral Leukodystrophy and TREX1 Mutation p.V235Gfs*6. Rev Invest Clin. 2018;70:68-75.

222. Morsi A, Maldonado A, Lal D, Moosa ANV, Pestana-Knight E, Bingaman W. Vasospasm Following Hemispherectomy: A Case Report of a Novel Complication. World Neurosurg. 2020;137:357–361.

223. Muinjonov B, Giyazitdinova E. Myelin repair correlates with CARASIL-associated neurological deficits. Eur J Neurol. 2016;23:500. (Abstract)

224. Munshi S, Eason J, Shetty AK, Sunman W, Evans A, Gruener A, Ho E, Lakhani B. COL4A1 variant presenting as recurrent stroke and cerebral small vessel disease. Int J Stroke. 2018;13:65. (Abstract)

225. Murray LS, Lu Y, Taggart A, Van Regemorter N, Vilain C, Abramowicz M, Kadler KE, Van Agtmael T. Chemical chaperone treatment reduces intracellular accumulation of mutant collagen IV and ameliorates the cellular phenotype of a COL4A2 mutation that causes haemorrhagic stroke. Hum Mol Genet. 2014;23:283-292.

226. Nagiel A, Lalane RA, Jen JC, Kreiger AE. Superficial and deep capillary ischemia as a presenting sign of retinal vasculopathy with cerebral leukencephalopathy and systemic manifestations. Retin Cases Brief Rep. 2018;12 Suppl 1:S87-S91.

227. Naidu G, Acharya N, Jha S, Chattopadhyay A, Dhir V, Goyal M, Modi M, Nada R, Minz RW, Jain S et al. Deficiency of adenosine deaminase 2: A description of phenotype and genotype in fifteen cases. Arthritis Rheumatol. 2016;68:2314-2322.

228. Nandeesh BN, Bindu PS, Narayanappa G, Chickabasaviah Yasha T, Mahadevan A, Kulanthaivelu K, Santosh V. Cerebral small vessel disease with hemorrhagic stroke related to COL4A1 mutation: A case report. Neuropathology. 2020;40:93–98.

229. Nanthapisal S, Murphy C, Omojimi E, Hong Y, Standing A, Berg S, Ekelund M, Jolles S, Harper L, Youngstein T et al. Deficiency of Adenosine Deaminase Type 2: A Description of Phenotype and Genotype in Fifteen Cases. Arthritis Rheumatol. 2016;68:2314-2322.

230. Nanthapisal S, Murphy C, Omojimi E, Standing A, Hong Y, Gomes SM, Klein N, Eleftheriou D, Brogan PA. Monogenic polyarteritis nodosa caused by ADA2 deficiency: The GOSH experience. Pediatr Rheumatol. 2015;13:89. (Abstract)

231. Nau S, McCourt EA, Maloney JA, Van Hove JL, Saenz M, Jung JL. COL4A1 mutations in two infants with congenital cataracts and porencephaly: an ophthalmologic perspective. J. AAPOS. 2019;23:246–248.
232. Navon Elkan P, Pierce SB, Segel R, Walsh T, Barash J, Padeh S, Zlotogorski A, Berkun Y, Press JJ, Mukamel M et al. Mutant adenosine deaminase 2 in a polyarteritis nodosa vasculopathy. N Engl J Med. 2014;370:921-931.

233. Navon Elkan P, Pierce SB, Segel R, Walsh T, Barash J, Padeh S, Zlotogorski A, Berkun Y, Press JJ, Mukamel M et al. Mutant adenosine deaminase 2 in a polyarteritis nodosa vasculopathy. N Engl J Med. 2014;370:921-931.

234. Neishabury M, Mehri M, Fattahi Z, Najmabadi H, Azarkeivan A. Novel variants in Iranian individuals suspected to have inherited red blood cell disorders, including bone marrow failure syndromes. Haematologica. 2020;105:E1–E4.

235. Ng J, Gunny R, Prabhakar PS, Carr LJ, Saunders DE. The expanding neuroradiological phenotype of COL4A1 gene mutations. Dev Med Child Neurol. 2013;55:23. (Abstract)

236. Nishimoto Y, Shibata M, Nihonmatsu M, Nozaki H, Shiga A, Shirata A, Yamane K, Kosakai A, Takahashi K, Nishizawa M et al. Neurology. 2011;76:1353-1355. (a)

237. Nishimoto Y, Shibata M, Onodera O, Suzuki N. Neurological picture. Neuroaxonal integrity evaluated by MR spectroscopy in a case of CARASIL. J Neurol Neurosurg Psychiatry. 2011;82:860-861. (b)

238. Niwa T, Aida N, Osaka H, Wada T, Saitsu H, Imai Y. Intracranial Hemorrhage and Tortuosity of Veins Detected on Susceptibility-weighted Imaging of a Child with a Type IV Collagen α1 Mutation and Schizencephaly. Magn Reson Med Sci. 2015;14:223-226.

239. Nozaki H, Kato T, Nihonmatsu M, Saito Y, Mizuta I, Noda T, Koike R, Miyazaki K, Kaito M, Ito S et al. Distinct molecular mechanisms of HTRA1 mutants in manifesting heterozygotes with CARASIL. Clin Neurol. 2016;56:S325. (Abstract)

240. Nozaki H, Kato T, Nihonmatsu M, Saito Y, Mizuta I, Noda T, Koike R, Miyazaki K, Kaito M, Ito S et al. Distinct molecular mechanisms of HTRA1 mutants in manifesting heterozygotes with CARASIL. Neurology. 2016;86:1964-1974.

241. Nozaki H, Nishizawa M, Onodera O. Features of cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy. Stroke. 2014;45:3447-3453.

242. Nozaki H, Sekine Y, Fukutake T, Nishimoto Y, Shibata M, Yutaka S, Shirata A, Yanagawa S, Hirayama M, Yamane K, et al. MRI features of cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy. Neurology. 2013;80:1 MeetingAbstracts. (Abstract)

243. Nozaki H, Sekine Y, Fukutake T, Nishimoto Y, Shimoe Y, Shirata A, Yanagawa S, Hirayama M, Tamura M, Nishizawa M et al. Characteristic features and progression of abnormalities on MRI for CARASIL. Neurology. 2015;85:459-463.

244. O’Neill R, O’Mahony O, McSweeney N. COL4A1 mutation inherited from maternal mosaicism in an infant presenting with microcephaly, haemolytic anaemia and cataracts. Arch. Dis. Child. 2019;104:A126–A127.

245. Ohta K, Ozawa T, Fujinaka H, Goto K, Nakajima T. Cerebral Small Vessel Disease Related to a Heterozygous Nonsense Mutation in HTRA1. Intern. Med. 2020;59:1309–1313.

246. Okano S, Shimada S, Tanaka R, Okayama A, Kajihama A, Suzuki N, Nakau K, Takahashi S, Matsumoto N, Saitsu H, et al. Life-threatening muscle complications of COL4A1-related disorder. Brain Dev. 2020;42:93-97.
247. Oluwole OJ, Ibrahim H, Garozzo D, Ben Hamouda K, Ismail Mostafa Hassan S, Hegazy AM, Msaddi AK. Cerebral small vessel disease due to a unique heterozygous HTRA1 mutation in an African man. Neurol. Genet. 2020;6:e382.

248. Ombrello A, Stone D, Hoffmann P, Jones A, Barham B, Barron K, Flegel W, Sheldon S, Zhou Q, Hershfield M et al. The deficiency of adenosine deaminase type 2-results of therapeutic intervention. Pediatr Rheumatol. 2015;13:37. (Abstract)

249. Ombrello AK, Barron K, Hoffmann P, Toro C, Stone DL, Pinto-Patarroyo G, Jones A, Romeo T, Soldatos A, Zhou Q et al. The deficiency of adenosine deaminase type 2 (DADA2)-results of anti-TNF treatment in a cohort of patients with a history of stroke. Arthritis Rheumatol. 2016;68:4288-4289. (Abstract)

250. Ombrello AK, Stone DL, Barron K, Hoffmann PM, Cudrici C, Jones A, Romeo T, Dimitrova D, Dotan A, Wall D et al. Analysis of the efficacy of treatment on 45 patients with deficiency of adenosine deaminase 2. Pediatr Rheumatol. 2019;17. (Abstract)

251. Ouail DE, Tebbani M, Si Ahmed D, Bouali F. Youth hypertension associated with ADA2 deficiency. About three cases. J. Hypertens. 2019;37:e215. (Abstract)

252. Ozen S, Batu ED, Taskiran EZ, Ozkara HA, Unal S., Guleray N, Erden A, Karadag O, Gumruk F, Cetin M, et al. A monogenic disease with a variety of phenotypes: Deficiency of adenosine deaminase 2. J. Rheumatol. 2020;47:117–125.

253. Paisal V, Al-Abadi E, Southwood T, Wassmer E. Childhood onset stroke and vasculitis associated with deficiency of adenosine deaminase 2 (dada2). Ann Rheum Dis. 2017;76:1395. (Abstract)

254. Paola K, Gomes FHR, Benevides LC, Leite MF, Medeiros P, Santos AC, De Carvalho LM, Ferriani V. CECR1/ADA2 mutation in a Brazilian family. Ann. Rheum. Dis. 2019;78:2009. (Abstract)

255. Papandreou A, Tisdall MM, Chong WK, Cross JH, Harkness WF, Varadkar SM. COL4A1 mutations should not be a contraindication for epilepsy surgery. Childs Nerv Syst. 2014;30:1467-1469.

256. Papandreou A, Tisdall MM, Harkness WF, Cross JH, Varadkar SM. COL4A1 mutations should not be a contraindication for epilepsy surgery. Epilepsia. 2014;55:245. (Abstract)

257. Pati AR, Battisti C, Taglia I, Galluzzi P, Bianchi M, Federico A. A new case of autosomal dominant small vessel disease carrying a novel heterozygous mutation in HTRA1 gene: 2-year follow-up. Neurol Sci. 2018;39:1479-1481.

258. Pelzer N, Bijkerk R, Reinders MEJ, van Zonneveld AJ, Ferrari MD, van den Maagdenberg AMJM, Eienboom J, Terwindt GM. Circulating Endothelial Markers in Retinal Vasculopathy With Cerebral Leukoencephalopathy and Systemic Manifestations. Stroke. 2017;48:3301-3307.

259. Pelzer N, Hoogeveen ES, Haan J, Bunnik R, Poot CC, van Zwet EW, Inderson A, Fogteloo AJ, Reinders MEJ, Middelkoop HAM et al. Systemic features of retinal vasculopathy with cerebral leukoencephalopathy and systemic manifestations: a monogenic small vessel disease. J Intern Med. 2019;285:317-332.

260. Pescini F, Donni I, Asaro A, Rinnoci V, Squitieri M, Nannucci S, Poggesi A, Di Donato I, Bianchi S, Cereda C, et al. Screening for COL4A1 and COL4A2 mutations in patients with familiar microangiopathy. Eur. Stroke J. 2019;4:699–700.
261. Pichard DC, Ombrello AK, Hoffmann P, Stone DL, Cowen EW. Early-onset stroke, polyarteritis nodosa (PAN), and livedo racemosa. J Am Acad Dermatol. 2016;75:449-453.

262. Plaisier E, Chen Z, Gekeler F, Benhassine S, Dahan K, Marbo B, Alamowitch S, Paques M, Ronco P. Novel COL4A1 mutations associated with HANAC syndrome: a role for the triple helical CB3[IV] domain. Am J Med Genet. 2010;152A:2550-2555.

263. Plaisier E, Griboval O, Alamowitch S, Mougenot B, Prost C, Verpont MC, Marbo B, Desmettre T, Cohen SY, Roulet E. et al. COL4A1 mutations and hereditary angiopathy, nephropathy, aneurysms, and muscle cramps. N Engl J Med. 2007;357:2687-2695.

264. Plancher JM, Hufnagel RB, Vagal A, Peariso K, Saal HM, Broderick JP. Case of Small Vessel Disease Associated with COL4A1 Mutations following Trauma. Case Rep Neurol. 2015;7:142-147.

265. Plancher JM, Hufnagel RB, Vagal A, Peariso K, Saal HM, Broderick JP. Case of Small Vessel Disease Associated with COL4A1 Mutations following Trauma. Case Rep Neurol. 2015;7:142-147.

266. Pode-Shakked B, Marek-Yagel D, Navon-Elkan P, Pierce SB, Segel R, Walsh T, Padeh S, Fairbanks L, Pras E, Winkelmann J et al. Adenosine deaminase 2 (ADA2) deficiency: A novel inborn error of purine metabolism. Mol Genet Metab. 2014;111:232-233.

267. Poswar F, Da Fonseca RM, De Albuquerque LC, Zhou Q, Jardim LB, Monte TL, Aksentijevich I, Saute JA. Adenosine deaminase 2 deficiency presenting as spastic paraplegia and systemic vasculitis. J Neurol. 2016;263:818-820.

268. Preethish-Kumar V, Nozaki H, Tiwari S, Vengalil S, Bhat M, Prasad C, Onodera O, Uemura M, Doniparthi S, Saini J et al. CARASIL families from India with 3 novel null mutations in the HTRA1 gene. Neurology. 2017;89:2392-2394.

269. Rama M, Duflos C, Melki I, Bessis D, Bonhomme A, Martin H, Doummer D, Valence S, Rodriguez D, Carme E et al. A decision tree for the genetic diagnosis of deficiency of adenosine deaminase 2 (DADA2): a French reference centres experience. Eur J Hum Genet. 2018;26:960-971.

270. Rasmussen M, Hareide LL, Skogen AR, Nedregaard B, Antal E-A, Plaisier E. Work-up of an increased level of CK leading to the diagnosis of HANAC. Eur J Paed Neurol. 2017;21:e226. (Abstract)

271. Raynowska J, Miskin DP, Pramanik B, Asiry S, Anderson T, Boockvar J, Najjar S, Harel A. Retinal vasculopathy with cerebral leukoencephalopathy (RVCL): A rare mimic of tumefactive MS. Neurology. 2018;91:e1423-1428.

272. Richards A, van den Maagdenberg AM, Jen JC, Kavanagh D, Bertram P, Spitzer D, Liszewski M, Barilla-Labarca ML, Terwindt GM, Kasai Y et al. C-terminal truncations in human 3'-5' DNA exonuclease TREX1 cause autosomal dominant retinal vasculopathy with cerebral leukodystrophy. Nat Genet. 2007;39:1068-1670.

273. Riley CS, Roth LA, Sampson JB, Radhakrishnan J, Herlitz LC, Blitz AM, Moazami G. A 31-Year-Old Man With a Ring-Enhancing Brain Lesion. J Neuroophthalmol. 2017;37:172-175.

274. Rødahl E, Knappskog PM, Majewski J, Johansson S, Telstad W, Kråkenes J, Boman H. Variants of anterior segment dysgenesis and cerebral involvement in a large family with a novel COL4A1 mutation. Am J Ophthalmol. 2013;155:946-953.

275. Roeben B, Uhrig S, Bender B, Synozrik M. Teaching NeuroImages: When alopecia and disk herniations meet vascular leukoencephalopathy Neurology. 2016;86:e166.
276. Rouaud T, Labauge P, Tournier Lasserve E, Mine M, Coustans M, Deburghgraeve V, Edan G. Acute urinary retention due to a novel collagen COL4A1 mutation. Neurology. 2010;75:747-749.

277. Ruiz-Escribano Menchen L, Flores Barragan JM, Camacho Nieto A, Franco Salinas AR, Villanueva Ruiz FJ, Hernandez Gonzalez A, Vaamonde Gamo J. COL4A1 novel missense mutation causing recurrent spontaneous intracerebral haemorrhage and encephalopathy. Eur. Stroke J. 2019;4:364. (Abstract)

278. Russo A, Pinto AM, Lopergolo D, Renieri A, Battisti C. An Italian family carrying a new mutation in the COL4A1 gene. J. Neurol. Sci. 2020;414:16815.

279. Saffari A, Kolker S, Merkenschlager A, Hoffmann GF, Ziegler A, Syrbe S. Axenfeld-rieger anomaly and neuropsychiatric symptoms. Neuropediatrics. 2018;49:2. (Abstract)

280. Saffari A, Ziegler A, Merkenschlager A, Kruger S, Kolker S, Hoffmann GF, Syrbe S. Axenfeld-Rieger Anomaly and Neuropsychiatric Problems—More than Meets the Eye. Neuropediatrics. 2020;51:192–197.

281. Sahin S, Adrovic A, Barut K, Baran S, Tahir Turanli E, Canpolat N, Kizilkilic O, Ozkaya O, Kasapcopur O. A 9.5-year-old boy with recurrent neurological manifestations and severe hypertension, treated initially for polyarteritis nodosa, was subsequently diagnosed with adenosine deaminase type 2 deficiency (DADA2) which responded to anti-TNF-α. Paediatr Int Child Health. 2019;1-4.

282. Sahin S, Adrovic A, Barut K, Baran S, Tahir Turanli E, Canpolat N, Kizilkilic O, Ozkaya O, Kasapcopur O. A 9.5-year-old boy with recurrent neurological manifestations and severe hypertension, treated initially for polyarteritis nodosa, was subsequently diagnosed with adenosine deaminase type 2 deficiency (DADA2) which responded to anti-TNF-alpha. Paediatr. Int. Child Health. 2020;40:65–68.

283. Sahin S, Adrovic A, Barut K, Ugurlu S, Turanli ET, Ozdogan H, Kasapcopur O. Anti TNF-alpha therapy would be lifesaving in deficiency of adenosine deaminase-2. Ann Rheumat Dis. 2017; 76:1402-1403. (Abstract)

284. Sahin S, Adrovic A, Barut K, Ugurlu S, Turanli ET, Ozdogan H, Kasapcopur O. Clinical, imaging and genotypical features of three deceased and five surviving cases with ADA2 deficiency. Rheumatol Int. 2018;38:129-136.

285. Saito R, Nozaki H, Kato T, Toyoshima Y, Tanaka H, Tsubata Y, Morioka T, Horikawa Y, Oyanagi K, Morita T et al. Retinal Vasculopathy With Cerebral Leukodystrophy: Clinicopathologic Features of an Autopsied Patient With a Heterozygous TREX 1 Mutation. J Neuropathol Exp Neurol. 2019;78:181-186.

286. Saitsu H, Yoneda Y, Haginoaya K, Arai H, Yamaoka S, Matsumoto N. De novo and inherited mutations in COL4A2, encoding the type IV collagen alpha2 chain, cause porencephaly. Congenital Anomalies. 2012;52:A8-A9. (Abstract)

287. Sakai N, Uemura M, Kato T, Nozaki H, Koyama A, Ando S, Kamei H, Kato M, Onodera O. Hemorrhagic cerebral small vessel disease caused by a novel mutation in 3’UTR of collagen type IV alpha 1. Neuro. Genet. 2020;6:e383.

288. Santo GC, Baldeiras I, Guerreiro R, Ribeiro JA, Cunha R, Youngstein T, Nanthapisal S, Leitão J, Fernandes C, Caramelo F et al. Adenosine Deaminase Two and Immunoglobulin M Accurately Differentiate Adult Sneddon’s Syndrome of Unknown Cause. Cerebrovasc Dis. 2018;46:257-264.
289. Sarkar K, Way C, Verro P. A case of retinal vasculopathy and cerebral leukodystrophy with predominantly central nervous system manifestations. Neurology. 2012;78. (Abstract)

290. Sarrabay G, Insalaco A, Uettwiller F, Tieulie N, Quartier-Dit-Maire P, Melki J, Touitou I. Identification of three ADA2 deficiency families with novel CECR1 mutations. Ped Rheumatol. 2015;13:229. (Abstract)

291. Sasa GS, Elghetany MT, Bergstrom K, Nicholas S, Himes R, Krance RA, Hershfield M, Van Montfrans J, Bertuch A. Adenosine deaminase deficiency as a cause of pure red cell aplasia mimicking diamond blackfan anemia. Blood. 2015;126:3615. (Abstract)

292. Sasaki S, Nozaki F, Saitsu H, Miyatake S, Matsumoto N, Kumada T, Shibata M, Fujii T. A case of COL4A1-related disorder with a variety of brain imaging findings. No To Hattatsu. 2017;49:405-407.

293. Sato Y, Shibasaki J, Aida N, Hiiragi K, Kimura Y, Akahira-Azuma M, Enomoto Y, Tsurusaki Y, Kurosawa K. Novel COL4A1 mutation in a fetus with early prenatal onset of schizencephaly. Hum Genome Var. 2018;5:4.

294. Scalais E, Ceuterick-De Groot C, Martin JJ, Maugeri A, Varlet P, De Meirleir L. Cortical dysplasia, antenatal porencephaly, recurrent retinal hemorrhages: Different insults at different times-COL4A1 deficiency and environmental factors. Ann Neurol. 2015;78:S198. (Abstract)

295. Schena F, Pastorino C, Penco F, Volpi S, Caorsi R, Kalii F, Fenoglio D, Salis A, Prigione I, Bocca P et al. Dysregulation of B and Tfh cells functions in DADA2 patients Pediatr Rheumatol. 2018;16:2. (Abstract)

296. Schena F, Penco F, Volpi S, Pastorino C, Caorsi R, Bertoni A, Kalli F, Salis A, Prigione I et al. B cell defect in ADA2 deficiency patients. Pediatr Rheumatol. 2019;17. (Abstract)

297. Schena F, Volpi S, Caorsi R, Penco F, Pastorino C, Kalli F, Omenetti A, Chiesa S, Bertoni A, Picco P et al. Defect of adaptive immunity in ADA2 deficiency patients. Pediatr Rheumatol. 2017;15(Suppl 1). (Abstract)

298. Scheppe J, Bulashevska A, Mannhardt-Laakmann W, Cao H, Yang F, Seidl M, Kelly S, Hershfield M, Grimbacher B. Deficiency of Adenosine Deaminase 2 Causes Antibody Deficiency. J Clin Immunol. 2016;36:179-186.

299. Scheppe J, Proietti M, Frede N, Buchta M, Hübscher K, Rojas Restrepo J, Goldacker S, Warnatz K, Pacholpik Schmid J, Duppenthaler A et al. Screening of 181 Patients With Antibody Deficiency for Deficiency of Adenosine Deaminase 2 Sheds New Light on the Disease in Adulthood. Arthritis Rheumatol. 2017;69:1689-1700.

300. Schnappauf O, Stoffels M, Aksentijevich I, Kastner DL, Grayson PC, Cuthbertson D, Carette S, Chung SA, Forbess LJ, Khalidi NA et al. Screening of patients with adult-onset idiopathic polyarteritis nodosa for deficiency of adenosine deaminase 2. Arthritis Rheumatol. 2018;70(suppl10). (Abstract)

301. Schnappauf O, Stoffels M, Aksentijevich I, Ombrello A, Moura NS, Barron K, Kastner D, Grayson P, Merkel P. Screening of patients with idiopathic polyarteritis nodosa, granulomatosis with polyangiitis, and microscopic polyangiitis for deficiency of adenosine deaminase 2. Pediatr Rheumatol. 2019;17. (Abstract)
303. Schnider C, Theodoropoulou K, Candotti F, Angelini F, Perreau M, Hershfield M, Hofer M. A family case of ADA 2 deficiency with CECR1 mutation. Swiss Medical Weekly. 2018;148:115-12S. (Abstract)

304. Schnider C, Theodoropoulou K, Candotti F, Angelini F, Perreau M, Riccio O, Hershfield M, Hofer M. A family case of ADA2 deficiency with cecr1 mutation. Pediatr Rheumatol. 2018;16:P233. (Abstract)

305. Schuh E, Ertl-Wagner B, Lohse P, Wolf W, Mann JF, Lee-Kirsch MA, Hohlfeld R, Kämpfel T. Multiple sclerosis-like lesions and type I interferon signature in a patient with RVCL. Neurol Neuroimmunol Neuroinflamm. 2015;2:e55.

306. Schuh E, Lohse P, Kumpfel T. A rare case of cerebroretinal vasculopathy caused by a novel Trex 1 mutation. Journal of Neurology. 2015;260:S137. (Abstract)

307. Scoppettuolo P, Ligot N, Naeije G, Wermenbol V, Van Bogaert P. A novel mutation of COL4A1 responsible of familial porencephaly and severe hypermetropia. Eur Stroke J. 2013;2:486.

308. Segel R, Padeh S, Goldzweig O, Gerstein M, Barash J, Zlotogorski A, Pres J, Hashkes P, Horev L, Harel L, et al. Natural history and treatment outcome of patients with adenosine deaminase (ADA) 2 deficiency: Twenty years of the Israeli experience. Eur J Hum Genet. 2019;26:314. (Abstract)

309. Selch C, Winkler P, Pringsheim M, Hasse A, Baumeister F, Staudt M, Kluger G. Epilepsy, clinical presentation and MRI features in patients with COL4A1 mutations. Eur J Paediatr Neurol. 2015;19:S6. (Abstract)

310. Severino MS, Caorsi R, Gandolfo C, Martinetti C, Martini A, Gattorno M. Distinct cerebrovascular features in patients with ADA2 deficiency. Pediatr Rheumatol. 2015;13:233. (Abstract)

311. Shah S, Ellard S, Kneen R, Lim M, Osborne N, Rankin J, Stoodley N, van der Knaap M, Whitney A, Jardine P. Childhood presentation of COL4A1 mutations. Dev Med Child Neurol. 2012;54:569-574.

312. Shah S, Kumar Y, McLean B, Churchill A, Stoodley N, Rankin J, Rizzu P, van der Knaap M, Jardine P. A dominantly inherited mutation in collagen IV A1 (COL4A1) causing childhood onset stroke without porencephaly. Eur J Paediatr Neurol. 2010;14:182-187.

313. Shan LD, Peng J, Xiao H, Wu LW, Duan HL, Pang N, Miriam K, Yin F. Clinical features and COL4A1 genotype of a toddler with hereditary angioopathy with nephropathy, aneurysms and muscle cramps syndrome. Chin J Contemp Pediatr. 2019;21:754–760.

314. Sharma A, Naidu GSRSNK, Chattopadhyay A, Acharya N, Jha S, Jain S. Novel CECR1 gene mutations causing deficiency of adenosine deaminase 2, mimicking antiphospholipid syndrome. Rheumatology. 2019;58:181–182.

315. Shibata M. Clinical manifestations and neuroradiological findings of CARASIL with a novel mutation. Clinical Neurology. 2012;52:1363-1364.

316. Shwin KW, Carmona-Rivera C, Tsai W, Richard Lee CC, Novakovich E, Stone DL, Ombrello AK, Goldbach-Mansky R, Gadina M, Kastner D et al. Role of adenosine and neutrophils in inflammation associated with mutations in CECR1 gene. Arthritis Rheumatol. 2015;67. (Abstract)

317. Sibon I, Coupri I, Menegon P, Bouchet JP, Gorry P, Burgelin I, Calvas P, Orignaec I, Doussset V, Lacombe D, et al. COL4A1 mutation in Axenfeld-Rieger anomaly with leukoencephalopathy and stroke. Ann Neurol. 2007;62:177-184.
318. Siitonen M, Hanson AB, Pasanen P, Bras JT, Kern S, Kern J, Andersen O, Stanescu H, Kleta R, Baumann M et al. Multi-infarct dementia of Swedish type is caused by 3'utr COL4A1 mutation. Brain. 2017;40:e29.

319. Siri A, Tournier-Lasserve E, Mine M, Magnin E, Berger E, Arquizan C, Ayrignac X, Carra-Dalliere C, Castelnovo G, De Champfleur N et al. COL4A1 mutations: Clinical and radiological phenotypes in a french adult cohort. Neurology 2014;82:10 Supplement. (Abstract)

320. Skrabl-Baumgartner A, Plecko B, Schmidt WM, König N, Hershfield M, Gruber-Sedlmayr U, Lee-Kirsch MA. Autoimmune phenotype with type I interferon signature in two brothers with ADA2 deficiency carrying a novel CECR1 mutation. Pediatr Rheumatol Online J. 2017;15:67.

321. Slavotinek AM, Garcia ST, Chandratillake G, Bardakjian T, Ullah E, Wu D, Umeda K, Lao R, Tang PL, Wan E et al. Exome sequencing in 32 patients with anophthalmia/microphthalmia and developmental eye defects. Clin Genet. 2015;88:468-473.

322. Soldatos A, Toro C, Ombrello A, Stone D, Hoffman P, Romeo T, Jones A, Pinto-Patarroyo G, Aksentijevich I, Grayson P et al. Expanding the neurological phenotype of adenosine deaminase 2 deficiency (DADA2 syndrome) due to biallelic mutations in the CECR1 gene: A treatable pediatric lacunar stroke syndrome. Annals of Neurol. 2016;80:S338-340. (Abstract)

323. Sonmez HE, Karaaslan C, de Jesus AA, Batu ED, Anlar B, Sozeri B, Bilginer Y, Karaguzel D, Cagdas Ayvaz D, Tezcan I, et al. A clinical score to guide in decision making for monogenic type I IFNopathies. Pediatr. Res. 2020;87:745–752.

324. Sourander P, Wålinder J. Hereditary multi-infarct dementia. Morphological and clinical studies of a new disease. Acta Neuropathol. 1977;39:247-54.

325. Sozeri B, Ercan G, Dogan OA, Yildiz J, Demir F, Doganay L. Deficiency of ADA2 from childhood to adult; the same mutation in a family. Ped Rheumatol. 2019;17. (Abstract)

326. Sozeri B, Ercan G, Dogan OA, Yildiz J, Demir F, Doganay L. The same mutation in a family with adenosine deaminase 2 deficiency. Rheumatol. Int. 2019;41:227–233.

327. Springer JM, Gierer SA, Jiang H, Kleiner D, Deuitch N, Ombrello AK, Grayson PC, Aksentijevich I. Deficiency of Adenosine Deaminase 2 in Adult Siblings: Many Years of a Misdiagnosed Disease With Severe Consequences. Front Immunol. 2018;9:1361.

328. Stam AH, Kothari PH, Shaikh A, Gschwendtner A, Jen JC, Hodgkinson S, Hardy TA, Hayes M, Kempster PA, Kotschet KE et al. Retinal vasculopathy with cerebral leukoencephalopathy and systemic manifestations. Brain. 2016;139:2909-2922.

329. Staples E, Simeoni I, Stephens JC, Allen HL, Wright P, Davies EG, Javid B, Gkrania-Klotsas E, Gattens M, Firth H, et al. ADA2 deficiency complicated by EBV-driven lymphoproliferative disease. Clin. Immunol. 2020;215:108443.

330. Stutterd C, Delatycki M, Lockhart P, Taft R, Vanderver A, Simons C, Leventer R. Whole-genome sequencing for patients with unclassified leukodystrophies. Twin Res. Hum. Genet. 2019;21:410–411.
332. Sundin M, Marits P, Nierkens S, Kolios AGA, Nilsson J. "Immune" Thrombocytopenia as Key Feature of a Novel ADA2 Deficiency Variant: Implication on Differential Diagnostics of ITP in Children. J Pediatr Hematol Oncol. 2019;41:155-157.

333. Takenouchi T, Ohyagi M, Torii C, Kosaki R, Takahashi T, Kosaki K. Porencephaly in a fetus and HANAC in her father: variable expression of COL4A1 mutation. Am J Med Genet A. 2015;167A:156-158.

334. Tan RY, Traylor M, Megy K, Duarte D, Deevi SVV, Shamardina O, Mapeta RP, Consortium NBRD, Ouwehand WH, Graf S, et al. How common are single gene mutations as a cause for lacunar stroke? A targeted gene panel study. Neurology. 2019;93:e2007–e2020.

335. Tanatar A, Karadag SG, Sozeri B, Sonmez HE, Cakan M, Kendir Demirkol Y, Aktay Ayaz N. ADA2 Deficiency: Case Series of Five Patients with Varying Phenotypes. J. Clin. Immunol. 2020;40:253–258.

336. Taskinen MH, Mustjoki S, Jahnukainen K, Trotta L, Siitonen T, Hautala T, Zavalov A, Heiskanen K, Haapaniemi EM, Saarela J et al. Large granular lymphocyte infiltration in the bone marrow in children and young adults may suggest primary immune deficiency. Blood. 2015;126:1024. (Abstract)

337. Tateoka T, Onda H, Hirota K, Kasuya H, Shinohara T, Kinouchi H, Akagawa H. Unusual case of cerebral small vessel disease with a heterozygous nonsense mutation in HTRA1. J Neurol Sci. 2016;362:144-146.

338. Teixeira VA, Ramos FO, Costa M. Severe and refractory childhood-onset polyarteritis nodosa associated with CECR1 mutation. Pediatr Rheumatol. 2017;15. (Abstract)

339. Thaler FS, Catac C, Einhäupl M, Müller S, Seelos K, Wollenweber FA, Kümpfel T. Cerebral small vessel disease caused by a novel heterozygous mutation in HTRA1. J Neurol Sci. 2018;388:19-21.

340. Thomas AS, Lin P. A Case of TREX1-Associated Retinal Vasculopathy with Cerebral Leukodystrophy. Ophthalmol. Retina. 2020;4:115–117.

341. Tonduti D, Picchiecchio A, La Piana R, Livingston JH, Doherty DA, Majumdar A, Tomkins S, Mine M, Ceroni M, Ricca I et al. COL4A1-related disease: raised creatine kinase and cerebral calcification as useful pointers. Neuropediatrics. 2012;43:283-288.

342. Topkarci Z, Ayaz NA, Karadag SG, Tanatar A, Sonmez HE. Deficiency of adenosine deaminase 2 presenting as livedo racemosa. Pediatr Dermatol. 2019;36:S22. (Abstract)

343. Topkarci Z, Ayaz NA, Karadag SG, Tanatar A, Sonmez HE. Deficiency of adenosine deaminase 2 presenting as livedo racemosa. Gazi Med. J. 2020;31:P32. (Abstract)

344. Tournier-Lasserve E, Vertuda E, Herve D, Bergametti F, Jacquet C, Morvan T, Prieto-Morin C, Mackowiak A, Manchon E, Hosseini H, et al. Up-regulation of COL4A1 and COL4A2 genes through various mechanisms leads to severe early onset ischaemic small vessel disease, including padmal. Eur. Stroke J. 2017;2:25.

345. Toz B, Erer B, Kamali S, Ocal L, Gul A. Differential response to anakinra and adalimumab in a patient with DADA2 syndrome. Pediatr Rheumatol. 2015;13:P201. (Abstract)

346. Traenka C, Kloss M, Strom T, Lyrer P, Brandt T, Bonati LH, Grond-Ginsbach C, Engelter S. Rare genetic variants in patients with cervical artery dissection. Eur. Stroke J. 2019;4:355–362.
347. Trotta L, Martelius T, Siitonen T, Hämäläinen S, Juntti H, Taskinen M, Ilander M, Andersson EI, Zavialov A et al. ADA2 deficiency: Clonal lymphoproliferation in a subset of patients. J Allergy Clin Immunol. 2018;141:1534-1537.e8.

348. Tsubata Y, Morita T, Morioka T, Sasagawa T, Ikarashi K, Saito N, Shimada H, Miyazaki S, Sakai S, Tanaka H et al. Renal histopathological findings of retinal vasculopathy with cerebral leukodystrophy. CEN Case Rep. 2018;7:83-89.

349. Uemura M, Nozaki H, Koyama A, Sakai N, Ando S, Kanazawa M, Kato T, Onodera O. HTRA1 Mutations Identified in Symptomatic Carriers Have the Property of Interfering the Trimer-Dependent Activation Cascade. Front. Neurol. 2019;10:693.

350. Uettwiller F, Sarraabay G, Rodero MP, Rice GI, Lagrue E, Marot Y, Deiva K, Touitou I, Crow YJ, Quartier P. ADA2 deficiency: case report of a new phenotype and novel mutation in two sisters. RMD Open. 2016;2:1-5.

351. Vahedi K, Boukobza M, Massin P, Gould DB, Tournier-Lasserve E, Bousser MG. Clinical and brain MRI follow-up study of a family with COL4A1 mutation. Neurology. 2007;69:1564-1568. (a)

352. Vahedi K, Kubis N, Boukobza M, Arnoult M, Massin P, Tournier-Lasserve E, Bousser MG. COL4A1 mutation in a patient with sporadic, recurrent intracerebral hemorrhage. Stroke. 2007;38:1461-1464. (b)

353. Van Agtmael T, Murray L, Vilain C, Abramowicz M, Kadler K. Chemical chaperone treatment influences the cellular phenotype of a COL4A2 mutation that causes haemorrhagic stroke. Cerebrovasc Dis. 2014;37:535. (Abstract)

354. Van der Knaap MS, Smit LM, Barkhof F, Pijnenburg YA, Zweegman S, Niessen HW, Imhof S, Heutink P. Ann Neurol. 2006;59:504-511.

355. Van Eyck L, Hershfield MS, Pombal D, Kelly SJ, Ganson NJ, Frans G, Schaballie H, De Hertogh G, Dooley J et al. Hematopoietic stem cell transplantation rescues the immunologic phenotype and prevents vasculopathy in patients with adenosine deaminase 2 deficiency. J Allergy Clin Immunol. 2015;135:283-287.e5.

356. Van Eyck L, Hershfield MS, Pombal D, Kelly SJ, Ganson NJ, Moens L, Frans G, Schaballie H, DeHertogh G, Dooley J et al. HSCT rescues the immunological and vascular phenotype of ADA2-deficiency. J Clin Immunol. 2014;34:S196-197. (Abstract)

357. Van Eyck L, Liston A, Meyts I. Mutant ADA2 in vasculopathies. NEJM. 2014;371:478-479.

358. Van Eyck L, Liston A, Wouters C. Mutant ADA2 in vasculopathies (NEJM letter 2). NEJM. 2014;371:480.

359. Van Montfrans J, Hartman E, Braun K, Hennekam F, Hak A, Nederkoorn P, Westendorp W, Bredius R, Kollen W, Scholvink E et al. Phenotypic variability in patients with ADA2 deficiency due to identical homozygous R169Q mutations. Pediatr Rheumatol. 2015;13:1. (Abstract)

360. Van Montfrans J, Van Royen-Kerkhof A, Bierings M, Akstentijevich I, Zavialov A, Zhou Q. Hematological stem cell transplantation in ADA2 deficiency. J Clin Immunol. 2014;34:S230-231. (Abstract)

361. Van Montfrans JM, Hartman EA, Braun KP, Hennekam EA, Hak EA, Nederkoorn PJ, Westendorp WF, Bredius RG, Kollen WJ, Scholvinck EH et al. Phenotypic variability in patients with ADA2 deficiency due to identical homozygous R169Q mutations. Rheumatology. 2016;55:902-910.
362. Van Nieuwenhove E, Humblet-Baron S, Van Eyck L, De Somer L, Dooley J, Tousseyn T, Hershfield M, Liston A, Wouters C. ADA2 Deficiency Mimicking Idiopathic Multicentric Castleman Disease. Pediatrics. 2018;142:e20172266

363. van Well GTJ, Kant B, van Nistelrooij A, Sirma Ekmekci S, Henriet SV, Hoppenreijis E, van Deuren M, van Montfrans J, Nierkens S, Gul A, et al. Phenotypic variability including Behcet’s disease-like manifestations in DADA2 patients due to a homozygous c.973-2A>G splice site mutation. Clin. Exp. Rheumatol. 2019;121:142–146.

364. Verbeek E, Meuwissen ME, Verheijen FW, Govaert PP, Licht DJ, Kuo DS, Poulton CJ, Schot R, Lequin MH, Dudink J et al. COL4A2 mutation associated with familial porencephaly and small-vessel disease. Eur J Hum Genet. 2012;20:844-851.

365. Verdura E, Hervé D, Bergametti F, Jacquet C, Morvan T, Prieto-Morin C, Mackowiak A, Manchon E, Hosseini H, Cordonnier C et al. Disruption of a miR-29 binding site leading to COL4A1 upregulation causes pontine autosomal dominant microangiopathy with leukoencephalopathy. ANN Neurol. 2016;80:741-753.

366. Verdura E, Hervé D, Scharrer E, Amador M, Guyant-Maréchal L, Philipp A, Corlobé A, Bergametti F, Gazal S, Prieto-Morin C et al. Heterozygous HTRA1 mutations are associated with autosomal dominant cerebral small vessel disease. Brain. 2015;138:2347-2358.

367. Vermeulen RJ, Peeters-Scholte C, Van Vught J, Barkhof F, Rizzu P, Van Der Schoor SR, Van Der Knaap MS. Fetal origin of brain damage in two infants with a COL4A1 mutation: Fetal and neonatal neuroimaging. Dev Med Child Neurol. 2012;54:197. (Abstract)

368. Vermeulen RJ, Peeters-Scholte C, Van Vught JJ, Van Vught JJ, Barkhof F, Rizzu P, van der Schoor SR, van der Knaap MS. Fetal origin of brain damage in 2 infants with a COL4A1 mutation: fetal and neonatal MRI. Neuropediatrics. 2011;42:1-3.

369. Viana-Baptista M, Cruz-E-Silva V, Caetano A, Marto JP, Azevedo E., Ferreira C, Pinho-E-Melo T, Silva F, Ros Forteza FJ, Inacio N, et al. Vascular White Matter Lesions in Young Adults: A Neurology Outpatient Clinic Registry. Eur. Neurol. 2019;82:23–31.

370. Viana-Baptista M, De Silva VC, Caetano A, Azevedo E, Ferreira C, De Melo TP, Silva F, Ros J, Inacio NMO, Veiga A, et al. PORTYWHITE-Portuguese registry on incidental white matter lesions of presumed vascular etiology in young adults: Preliminary results. Eur. J. Neurol. 2017;24:89. (Abstract)

371. Vilain C, Van Regemorter N, Verloes A, David P, Van Bogaert P. Neuroimaging fails to identify asymptomatic carriers of familial porencephaly. Am J Med Genet. 2002;112:198–202.

372. Vitale G, Pichiecchio A, Ormitti F, Tonduti D, Asaro A, Farina L, Piccolo B, Percesepe A, Bastianello S, Orcesi S. Cortical malformations and COL4A1 mutation: Three new cases. Eur J Ped Neurol. 2019;23:410-417.

373. Vodopivec I, Oakley DH, Perugino CA, Venna N, Hedley-Whyte ET, Stone JH. A 44-year-old man with eye, kidney, and brain dysfunction. Ann Neurol. 2016;79:507-519.

374. Wang QH, Zou LP, Zhang MN, Wang YY, Lu Q, Shen YW, He W, Chen HM, Luo XM, Wang J, et al. Phenotypic characterization of COL4A1-related West syndrome. Epilepsy Res. 2020;164:106349.

375. Wang XL, Li CF, Guo HW, Cao BZ. A novel mutation in the HTRA1 gene identified in Chinese CARASIL pedigree. CNS Neuroscience and Therapeutics. 2012;18:867-869.
376. Watanabe J, Okamoto K, Ohashi T, Natsumeda M, Hasegawa H, Oishi M, Miyatake S, Matsumoto N, Fujii Y. Malignant Hyperthermia and Cerebral Venous Sinus Thrombosis After Ventriculoperitoneal Shunt in Infant with Schizencephaly and COL4A1 Mutation. World Neurosurg. 2019;1:446–450.

377. Weng YC, Sonni A, Labelle-Dumais C, de Leau M, Kauffman WB, Jeanne M, Biffi A, Greenberg SM, Rosand J, Gould DB. COL4A1 mutations in patients with sporadic late-onset intracerebral hemorrhage. Ann Neurol. 2012;71:470-477.

378. Wikan TO, Tzoulis C, Hogenesch RJ. A mother and her daughter with small vessel disease associated with COL4A1 mutations. Eur. J. Neurol. 2019;26:889.

379. Winkler DT, Lyrer P, Probst A, Devys D, Haufschild T, Haller S, Willi N, Mihatsch MJ, Steck AJ, Tolnay M. Hereditary systemic angiopathy (HSA) with cerebral calcifications, retinopathy, progressive nephropathy, and hepatopathy. J Neurol. 2008;255:77-88.

380. Wu X, Li C, Mao J, Li L, Liu Y, Hou Y. Heterozygous HTRA1 missense mutation in CADASIL-like family disease. Braz J Med Biol Res. 2018;51:e6632.

381. Xia XY, Li N, Cao X, Wu QY, Li TF, Zhuang C, Li WW, Cui YX, Li XJ, Xue CY. A novel COL4A1 gene mutation results in autosomal dominant non-syndromic congenital cataract in a Chinese family. BMC Med Genet. 2014;15:97.

382. Xie F, Zhang LS. A Chinese CARASIL Patient Caused by Novel Compound Heterozygous Mutations in HTRA1. J Stroke Cerebrovasc Dis. 2018;27:2840-2842.

383. Yamashita T, Nozaki H, Wakutani Y, Tadokoro K, Nomura E, Takahashi Y, Sato K, Hishikawa N, Takemoto M, Shang J, et al. A Japanese family of autosomal dominant cerebral small vessel disease with heterozygous HTRA1 mutation showing dementia, gait disturbance and subarachnoid hemorrhage. Japenese Soc. Vasc. Cogn. Impair. 2019;5:20–26.

384. Yanagawa S, Ito N, Arima K, Ikeda S. Cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy. Neurology. 2002;58:817-820.

385. Yang M, Li S, Liu J, Qin W, Li G, Shi Y, Zang W, Zhang J. Pedigree study of hereditary small cerebral vascular disease caused by c.821G>A heterozygous mutation of HtrA serine protease-1 gene. Chin. J. Neurol. 2019;52:478–486.

386. Yaramis A, Lochmüller H, Töpf A, Sonmezler E, Yilmaz E, Hiz S, Yis U, Gungor S, İpek Polat A, Edem P, et al. COL4A1-related autosomal recessive encephalopathy in 2 Turkish children. Neurol. Genet. 2020;6:e392.

387. Yoneda Y, Haginoaka Y, Arai H, Tsurusaki Y, Doi H, Miyake N, Yokochi K, Osaka H, Kato M et al. De novo and inherited mutations in COL4A2, encoding the type IV collagen α2 chain cause porencephaly. Am J Hum Genet. 2012;90:86-90.

388. Yoneda Y, Haginoaka K, Kato M, Osaka H, Yokochi K, Arai H, Kakita A, Yamanoto T, Otsuki Y, Shimizu S et al. Phenotypic spectrum of COL4A1 mutations: porencephaly to schizencephaly. Ann Neurol. 2013;73:48-57.

389. Yu Y, Qi X. Uncommon stroke disorders / difficult cases a complicated case of herns. Int J Stroke. 2018;13:28. (Abstract) (a)

390. Yu Y. A Complicated Case of HERNS. Alzheimer's and Dementia. 2018;14:P1295. (Abstract) (b)

391. Yu Z, Cao S, Wu A, Yue H, Zhang C, Wang J, Xia M, Wu J. Genetically Confirmed CARASIL: Case Report with Novel HTRA1 Mutation and Literature Review. World Neurosurg. 2020;143:121–128.
392. Zagaglia S, Selch C, Nisevic JR, Mei D, Michalak Z, Hernandez-Hernandez L, Krithika S, Vezyroglou K, Varadkar SM, Pepler A. Neurologic phenotypes associated with COL4A1/2 mutations: Expanding the spectrum of disease. Neurology. 2018;91:e2078-2088.

393. Zenteno JC, Crespi J, Buentello-Volante B, Buil JA, Bassaganyas F, Vela-Segarra JJ, Diaz-Cascajosa J, Marieges MT. Next generation sequencing uncovers a missense mutation in COL4A1 as the cause of familial retinal arteriolar tortuosity. Graefes Arch Clin Exp Ophthalmol. 2014;252:1789-1794.

394. Zhang WY, Xie F, Lu PL. Two novel heterozygous HTRA1 mutations in two pedigrees with cerebral small vessel disease families. Neurol Sci. 2018;39:497-501.

395. Zhao YY, Duan RN, Ji L, Liu QJ, Yan CZ. Cervical Spinal Involvement in a Chinese Pedigree With Pontine Autosomal Dominant Microangiopathy and Leukoencephalopathy Caused by a 3' Untranslated Region Mutation of COL4A1 Gene. Stroke. 2019;50:2307–2313.

396. Zhou Q, Chae J, Hershfield M, Sood R, Burgess S, Zavialov A, Chin D, Gadina M, Goldbach-Mansky R, Ombrello A et al. OR13-001 loss-of-function mutations in CECP1, encoding adenosine deaminase 2 (ADA2), cause recurrent fevers and early onset strokes. Pediatr Rheumatol. 2013;11. (Abstract)

397. Zhou Q, Yand D, Ombrello AK, Zavialov A, Chae JJ, Zavialov A, Chin D, Stone D, Toro C, Milner J et al. Intermittent fever, immune dysregulation, and systemic vasculopathy due to loss-of-function mutations in adenosine deaminase 2. Arthritis and Rheumatism. 2013;65:S383-384. (Abstract)

398. Zhou Q, Yang D, Ombrello AK, Zavialov AV, Toro C, Stone DL, Chae JJ, Rosenzweig SD, Bishop K, Barron KS et al. Early-onset stroke and vasculopathy associated with mutations in ADA2. N Engl J Med. 2014;370:911-920.

399. Zhuo Z, Cong L, Zhang J, Zhao X. A novel heterozygous HTRA1 mutation is associated with autosomal dominant hereditary cerebral small vessel disease. Mol. Genet. Genomic Med. 2020;8:e1111.

400. Ziaei A, Xu X, Dehghani L, Bonnard C, Reversade B, Shaygannejad V, Pouladi MA. Novel mutation in HTRA1 identified in a family with diffuse demyelination lesions. J Neurochem. 2017;142:94. (Abstract)

401. Ziaei A, Xu X, Dehghani L, Bonnard C, Zellner A, Jin Ng AY, Tohari S, Venkatesh B, Haffner C, Reversade B, et al. Novel mutation in HTRA1 in a family with diffuse white matter lesions and inflammatory features. Neurol. Genet. 2019;5:e345.

402. Zlamy M, Heugenhauser K, Scholl-Buergi S, Zoeggeler T, Sailer-Hoeck M, Brunner J, Karall D. Myalgia and dystrophic gait results in a diagnosis of deaminase 2 deficiency. J. Inherit. Metab. Dis. 2019;42:296–297. (Abstract)