Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL)

Carmine Ungaro and Teresa Sprovieri

Abstract

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is an inherited cerebrovascular disease whose key features are recurrent transient ischemic attacks (TIA), strokes, migraine with aura, vascular dementia, and diffuse white matter abnormalities detectable through neuroimaging. The disease results from mutations in the NOTCH3 gene, encoding a transmembrane receptor involved in cellular signaling and fate during embryonic development. Genetic testing is the gold standard for diagnosing this condition, but the syndrome can be suspected clinically based on family history and characteristic findings of white matter changes. Nevertheless, different individual symptom types, onset, and disease severity, even among individuals in the same family, have been increasingly recognized. The molecular mechanisms by which NOTCH3 mutations lead to vascular degeneration remain unclear. Most CADASIL-associated mutations result in either a gain or loss of cysteine residue in one of the 34 EGF-like repeats in the extracellular domain of the Notch3 protein, thus sparing the number of cysteine residues. More than 200 different mutations in the NOTCH3 gene have been reported in CADASIL patients, of which 95% are missense point mutations. Although it has been suggested that some mutations may be associated with a milder or more severe phenotype, so far no clear genotype-phenotype correlation has been found. To date, no disease-modifying treatment is available for this condition.

Keywords: arteriopathy, leukoencephalopathy, cerebrovascular disease, NOTCH3 gene, Notch3 protein

1. Introduction

CADASIL (MIM 125310) is the acronym for cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, coined in 1993 to define a hereditary small vessel disease of the brain affecting middle-aged adults and leading to disability and dementia [1, 2]. The disease was first described in 1955 by Van Bogaert as “Binswanger’s disease with a rapid course in two sisters” [3]. Before 1993, a number of families with an apparently hereditary vascular dementia accompanied by a Binswanger-like arteriopathy were described [3–5], but only in 1991, Tournier-Lasserve et al. [6] described nine patients of a single family, with
recurrent cerebrovascular ischemic events and dementia, variably associated with migraine headaches and epilepsy, suggesting the term “autosomal dominant syndrome with stroke-like episodes and leukoencephalopathy.” In 1993, a linkage analysis of two unrelated European families led to the mapping of the defective gene to chromosome 19q12, and the syndrome was renamed CADASIL [1]. Compared with other inherited brain disorders such as Huntington’s disease or inherited early-onset Alzheimer’s dementia, CADASIL is still relatively unknown in the medical community. This is not so much due to the fact that it is a rare disease but more to the fact that there is only a short history of recognition of the disease [7].

2. Clinical picture

CADASIL is an inherited cerebrovascular disorder, whose main clinical features are migraine with aura, recurrent subcortical ischemic attacks, strokes, vascular dementia, cognitive impairment, psychiatric disturbances, and apathy [8–16]. Due to the rarity of the disease, CADASIL is often overlooked and misdiagnosed; nevertheless, the combined symptomatic and asymptomatic prevalence of CADASIL is estimated at least 10.7 per 100,000 adults [11, 12, 17–20]. Migraine with aura is an early sign, with average onset in the third decade of life, and it is typically reported to occur in 20–40% of patients [9, 21]. Transient ischemic attacks (TIA) or lacunar ischemic strokes are the most common signs, occurring in up to 85% of individuals with a mean onset in the fifth or sixth decade; usually they take the form of clinical lacunar syndromes [21, 22]. The second most frequent clinical manifestation is cognitive impairment, often leading to dementia, which occurs in a very high proportion of patients by the age of 50 years. Mood disturbances are reported in 20% of CADASIL patients, presenting as severe depressive episodes [21]. Moreover, researchers recognize apathy, which is independent from depression, as a major clinical manifestation, affecting about 40% of patients [23]. Patients with CADASIL exhibit, even more rarely, other clinical manifestations such as seizures in 5–10% of cases [22]; intracerebral hemorrhages [24], mostly in hypertensive patients, in 16–25% of cases [25, 26]; and, in a few cases, territorial infarcts [27], deafness [6], and parkinsonism [28]. All symptomatic patients present typical magnetic resonance imaging (MRI) findings, including noticeable signal abnormalities with hyperintense lesions on the T2-weighted images in the subcortical white matter, basal ganglia, and thalamus (a crucial difference from multiple sclerosis, a frequent mimic of CADASIL) [1, 6, 29–33]. Anterior temporal lobe hyperintensities may be more specific than external capsule changes and appear in young presymptomatic subjects [34]. In the vast majority of patients, brain MRI abnormalities precede the onset of symptoms by 10–15 years; thus, brain MRI is crucial for the diagnosis of CADASIL. Although marked population differences in the clinical and radiological manifestation of CADASIL have been recognized, potentially due to differences in underlying genetic mutations [21, 35–37], in the proper clinical evaluation based on symptoms suggestive of CADASIL, confluent anterior temporal pole white matter changes show sensitivity and specificity of 89 and 86%, respectively, based on case series. From a pathological point of view, CADASIL patients have a systemic non-amyloid, non-atherosclerotic angiopathy affecting the walls of small blood vessels [38, 39]. The accumulation of granular osmiophilic material (GOM) within the smooth muscle cell basement membrane and the surrounding extracellular matrix is pathognomonic [40–42]. Because the arteriopathy in CADASIL is systemic, GOM deposits, which contain Notch3 proteins, among other poorly defined components [40, 43, 44], can be detected in arteries of many different organs, including dermal arterioles. In fact, actually GOMs are detected in skin biopsies, but the reported
sensitivity is variable [45, 46]. CADASIL is inherited dominantly, with over 500 families detected worldwide and de novo cases observed sporadically [47].

3. Genetics

NOTCH3 gene mutations are causative of the disease. This gene, consisting of 33 exons spanning roughly 7 kb and located on chromosome 19p13 [48], encodes a single-pass transmembrane heterodimer receptor Notch3 of 2321 amino acids involved in cellular signaling and fate during embryonic development [49, 50]. Notch3 protein comprising an N-terminal extracellular domain (NECD) involved in ligand binding, a transmembrane domain (NTMD), and an intracellular domain (NICD), which contains seven ankyrin repeats is required for downstream signal transduction (Figure 1) [51, 52]. More specifically, the NECD is non-covalently associated with the membrane-tethered intracellular domain, and it is composed of 34 epidermal growth factor (EGF)-like repeats, followed by 3 Notch/lin12 repeats [53]. Each EGF-like repeat encompasses six cysteine residues, forming three pairs of disulfide bonds [54, 55]. The receptor is synthesized as single precursor protein which is cleaved during transport to the cell surface (S1 cleavage), where it is expressed as heterodimer. Upon binding of its ligand (a protein of the delta/jagged family) [56] at EGF repeats 10–11, Notch3 receptor undergoes two other proteolytic cleavages: at first, N3 is cleaved (S2 cleavage) in its extracellular domain by a TNF-α-converting enzyme (TACE), subsequently in its transmembrane domain (S3 cleavage) in a presenilin-dependent manner. These proteolytic events, mutually dependent, generate the NICD fragment, which released from the NTMD enters the nucleus for activating the transcription of its target genes [53, 57–59]. Although the mutations are highly stereotyped, atypical phenotypes have been recognized, and the disease is probably underdiagnosed in most of the stroke population. Most CADASIL-associated mutations result in a gain or loss of cysteine residue in one of the 34 EGF-like repeats in the extracellular domain of the Notch3 protein, thus sparing the number of cysteine residues within the domain [60–62]. The alteration of the 3-D structure of the Notch3 protein, which is due to an aberrant dimerization of Notch3 through an abnormal disulfide bridging with another Notch3 molecule or with another protein, may play a central role in the pathogenesis of CADASIL [63–65]. A founder effect has been documented for the Finnish population but

![Figure 1](image_url)

Schematic structure of Notch3 protein: Notch3 domains are differently colored.
not for other countries [66]. To date, more than 200 different mutations in the NOTCH3 gene have been reported in CADASIL patients, of which 95% are heterozygous missense point mutations [67]. The remaining consist of small deletions, duplications, in frame [68–71] and frame shift mutations, splice site mutations [36], and a small deletion not directly involving a cysteine residue [72]. Moreover, a three-nucleotide insertion has been described as the first pathogenic insertion [73]. Recent studies have found that mutations that do not affect the number of cysteines (unlike the typical mutations) seem to be associated with clinical CADASIL syndrome. However, the pathogenic role of these mutations is uncertain. Although it has been suggested that some mutations may be associated with a milder or more severe phenotype, so far no clear genotype-phenotype correlation has been found [7]. Moreover, only a few cases in the literature reported homozygous mutations of NOTCH3 [74–78]. Many polymorphisms have also been identified in the NOTCH3 coding sequence [67], some of them leading to amino acid substitutions [79]. However, it is unknown whether these polymorphisms affect Notch signaling or whether they are involved in cerebrovascular disease.

4. Diagnosis

The pathology should be suspected in all cases with unexplained white matter hyperintensities and a family history of stroke and/or vascular dementia, consistent with an autosomal dominant inheritance. However, because affected family members may have been misdiagnosed [80] and de novo cases have been described [69, 81], the lack of an apparent family history of CADASIL does not preclude the diagnosis. Several groups of clinicians [13, 14, 82] proposed suitable diagnostic strategies to be used in the clinical setting for the selection of patients to be subjected to NOTCH3 gene analysis. In fact, in order to establish a correct diagnosis, clinical signs, neuroimaging findings, and family history need to be evaluated. Molecular screening is the gold standard for the diagnosis and is based on the identification in a proband of a pathogenic variation in the NOTCH3 coding sequence [36, 83]. With a suggestive diagnosis of CADASIL, a single-gene testing or a multigene panel could be applied; if NOTCH3 screening is unavailable or gives a negative result in a patient with convincing clinical and MRI findings highly suggestive of CADASIL, a skin biopsy analysis using both Notch3 immunostaining and electron microscopy should be recommended to confirm or reject the diagnosis [21, 84]. If CADASIL phenotype overlaps with other inherited cerebrovascular diseases, a comprehensive genomic testing, such as exome sequencing, should be recommended in evaluating different genes involved.

5. Therapeutic approach and outlooks

CADASIL is one of the most monogenic causes of stroke. No disease-modifying treatment is available. Being a genetic disease, two possible gene therapeutic approaches have been highlighted [85, 86], but, to date, only a symptomatic therapy focused on mitigating symptoms and management of the patient’s vascular risk factor can be applied [87, 88], beginning as immediate action to promote healthy individual behaviors, i.e., to refrain from smoking. Anyway, it is important that patients be referred to multidisciplinary and specialized centers, not only providing genetic counseling but also integrating the clinical and neuroimaging follow-up with neuropsychiatric, psychologic, and physical rehabilitation consultations.
Acknowledgements

Authors gratefully acknowledge Ariangela Belvedere, Walter Carpino, Patrizia Rizzuto, Tiziana Martire, Benedetto Bruno, and Angelo Bagalà for their administrative and technical support.

Conflict of interest

The authors declare no conflict of interest.

Author details

Carmine Ungaro* and Teresa Sprovieri
Institute for Research and Biomedical Innovation, National Research Council, Mangone (CS), Italy

*Address all correspondence to: carmine.ungaro@cnr.it

IntechOpen

© 2019 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/3.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.
References

[1] Tournier-Lasserve E, Joutel A, Melki J, Weissenbach J, Lathrop GM, Chabriat H, et al. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy maps on chromosome 19q12. Nature Genetics. 1993;3:256-259. DOI: 10.1038/ng0393-256

[2] Bousser MG, Tournier-Lasserve E. Summary of the proceedings of the first international workshop on CADASIL. Stroke. 1994;25:704-707

[3] Van Bogaert L. Encéphalopathie sous-corticale progressive (Binswanger) à évolution rapide chez deux soeurs. Médecine Hellénique. 1955;24:961-972

[4] Stevens DL, Hewlett RH, Brownell B. Chronic familial vascular encephalopathy. The Lancet. 1977;1(8026):1364-1365

[5] Sourander P, Wålinder J. Hereditary multi-infarct dementia. Morphological and clinical studies of a new disease. Acta Neuropathologica. 1977;39(3):247-254

[6] Tournier-Lasserve E, Iba-Zizen MT, Romero N, Bousser MG. Autosomal dominant syndrome with strokelike episodes and leukoencephalopathy. Stroke. 1991;22(10):1297-1302

[7] Rutten JW, Haan J, Terwindt GM, van Duinen SG, Boon EM, Lesnik Oberstein SA. Interpretation of NOTCH3 mutations in the diagnosis of CADASIL. Expert Review of Molecular Diagnostics. 2014;14(5):593-603. DOI: 10.1586/14737159.2014.922880

[8] Majersik JJ. Single gene causes of stroke. Seminars in Neurology. 2017;37(3):351-365. DOI: 10.1055/s-0037-1603952

[9] Majersik JJ. Inherited and uncommon causes of stroke. Continuum (Minneap Minn). 2017;23(1, Cerebrovascular Disease):211-237. DOI: 10.1212/CON.0000000000000432

[10] Bersano A, Bedini G, Oskam J, Mariotti C, Taroni F, Baratta S, et al. CADASIL: Treatment and management options. Current Treatment Options in Neurology. 2017;19(9):31. DOI: 10.1007/s11940-017-0468-z

[11] Chabriat H, Vahedi K, Iba-Zizen MT, Joutel A, Nibbio A, Nagy TG, et al. Clinical spectrum of CADASIL: A study of 7 families. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. The Lancet. 1995;346:934-939

[12] Opherk C, Peters N, Herzog J, Luedtke R, Dichtgans M. Long-term prognosis and causes of death in CADASIL: A retrospective study in 411 patients. Brain. 2004;127:2533-2539. DOI: 10.1093/brain/awh282

[13] Mizuta I, Watanabe-Hosomi A, Koizumi T, Mukai M, Hamano A, Tomii Y, et al. New diagnostic criteria for cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy in Japan. Journal of the Neurological Sciences. 2017;381:62-67. DOI: 10.1016/j.jns.2017.08.009

[14] Bersano A, Bedini G, Markus HS, Vitali P, Colli-Tibaldi E, Taroni F, et al. Lombardia GENS-group. The role of clinical and neuroimaging features in the diagnosis of CADASIL. Journal of Neurology. 2018;265(12):2934-2943. DOI: 10.1007/s00415-018-9072-8

[15] Vahedi K, Chabriat H, Levy C, Joutel A, Tournier-Lasserve E, Bousser MG. Migraine with aura and brain magnetic resonance imaging abnormalities in patients with CADASIL. Archives of Neurology. 2004;61:1237-1240. DOI: 10.1001/archneur.61.8.1237
[16] Rhea YYT, Markus HS. CADASIL: Migraine, encephalopathy, stroke and their inter-relationships. PLoS One. 2016;11(6):e0157613. DOI: 10.1371/journal.pone.0157613

[17] Moreton FC, Razvi SS, Davidson R, Muir KW. Changing clinical patterns and increasing prevalence in CADASIL. Acta Neurologica Scandinavica. 2014;130(3):197-203. DOI: 10.1111/anee.12266

[18] Portegies MLP, Koudstaal PJ, Ikram MA. Cerebrovascular Disease. In: Rosano C, Ikram MA, Ganguli M, editors. Handbook of Clinical Neurology. 3rd Series: Neuroepidemiology. Amsterdam: Elsevier BV; 2016. Vol. 138. p. 239-261. Available from: http://dx.doi.org/10.1016/B978-0-12-802973-2.00014-8

[19] Narayan SK, Gorman G, Kalaria RN, Ford GA, Chinnery PF. The minimum prevalence of CADASIL in Northeast England. Neurology. 2012;78(13):1025-1027. DOI: 10.1212/WNL.0b013e31824d586c

[20] Adib-Samii P, Brice G, Martin RJ, Markus HS. Clinical spectrum of CADASIL and the effect of cardiovascular risk factors on phenotype: Study in 200 consecutively recruited individuals. Stroke. 2010;41:630-634. DOI: 10.1161/STROKEAHA.109.568402

[21] Chabriat H, Joutel A, Dichgans M, Tournier-Lasserve E, Bousser MG. Casadir. Lancet Neurology. 2009;8(7):643-653. DOI: 10.1016/S1474-4422(09)70127-9

[22] Dichgans M, Mayer M, Uttner I, Brüning R, Müller-Höcker J, Rungger G, et al. The phenotypic spectrum of CADASIL: Clinical findings in 102 cases. Annals of Neurology. 1998;44(5):731-739. DOI: 10.1002/ana.410440506

[23] Reyes S, Viswanathan A, Godin O, Dufouil C, Benisty S, Hernandez K, et al. Apathy: A major symptom in CADASIL. Neurology. 2009;72(10):905-910. DOI: 10.1212/01.wnl.0000344166.03470.f8

[24] Ragoschke-Schumm A, Axer H, Witte O, Isenmann S, Fitzek C, Dichgans M, et al. Intracerebral haemorrhage in CADASIL. Journal of Neurology, Neurosurgery, and Psychiatry. 2005;76(11):1606-1607. DOI: 10.1136/jnnp.2004.059212. Correction in: Journal of Neurology, Neurosurgery, and Psychiatry. 2006; 77(1):125

[25] Choi JC, Kang SY, Kang JH, Park JK. Intracerebral hemorrhages in CADASIL. Neurology. 2006;67(11):2042-2044. DOI: 10.1212/01.wnl.0000246601.70918.06

[26] Liao YC, Hsiao CT, Fuh JL, Chern CM, Lee WJ, Guo YC, et al. Characterization of CADASIL among the Han Chinese in Taiwan: Distinct genotypic and phenotypic profiles. PLoS One. 2015;10(8):e0136501. DOI: 10.1371/journal.pone.0136501

[27] Choi EJ, Choi CG, Kim JS. Large cerebral artery involvement in CADASIL. Neurology. 2005;65(8):1322-1324. DOI: 10.1212/01.wnl.0000180965.79209.50

[28] Van Gerpen JA, Ahlskog JE, Petty GW. Progressive supranuclear palsy phenotype secondary to CADASIL. Parkinsonism & Related Disorders. 2003;9(6):367-369

[29] Chabriat H, Mrissa R, Levy C, Vahedi K, Taillia H, Iba-Zizen MT, et al. Brain stem MRI signal abnormalities in CADASIL. Stroke. 1999;30(2):457-459

[30] Chabriat H, Pappata S, Poupon C, Clark CA, Vahedi K, Poupon F, et al. Clinical severity in CADASIL related to ultrastructural damage in white matter: in vivo study with diffusion tensor MRI. Stroke. 1999;30(12):2637-2643
[31] Chabriat H, Levy C, Taillia H, Iba-Zizen MT, Va��edi K, Joutel A, et al. Patterns of MRI lesions in CADASIL. Neurology. 1998;51(2):452-457. DOI: 10.1212/wnl.51.2.452

[32] Dichgans M, Holtmannspötter M, Herzog J, Peters N, Bergmann M, Yoursy TA. Cerebral microbleeds in CADASIL: A gradient-echo magnetic resonance imaging and autopsy study. Stroke. 2002;33(1):67-71

[33] van Den Boom R, Lesnik Oberstein SA, van Duinen SG, Bornebroek M, Ferrari MD, Haan J, et al. Subcortical lacunar lesions: An MR imaging finding in patients with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. Radiology. 2002;224(3):791-796. DOI: 10.1148/radiol.2243011123

[34] Wang MM. CADASIL. Handbook of Clinical Neurology. 2018;148:733-743. DOI: 10.1016/B978-0-444-64076-5.00047-8

[35] Zhu S, Nahas SJ. CADASIL: Imaging characteristics and clinical correlation. Current Pain and Headache Reports. 2016;20(10):57. DOI: 10.1007/s11916-016-0584-6

[36] Markus HS, Martin RJ, Simpson MA, Dong YB, Ali N, Crosby AH, et al. Diagnostic strategies in CADASIL. Neurology. 2002;59(8):1134-1138. DOI: 10.1212/wnl.59.8.1134

[37] Singhal S, Rich P, Markus HS. The spatial distribution of MR imaging abnormalities in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy and their relationship to age and clinical features. American Journal of Neuroradiology. 2005;26(10):2481-2487

[38] Ruchoux MM, Guerouaou D, Vandenhaute B, Pruvo JP, Vermeersch P, Leys D. Systemic vascular smooth muscle cell impairment in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. Acta Neuropathologica. 1995;89(6):500-512

[39] Schröder JM, Züchner S, Dichgans M, Nagy Z, Molnar MJ. Peripheral nerve and skeletal muscle involvement in CADASIL. Acta Neuropathologica. 2005;110(6):587-599. DOI: 10.1007/s00401-005-1082-9

[40] Lorenzi T, Ragno M, Paolinelli F, Castellucci C, Scarpelli M, Morroni M. CADASIL: Ultrastructural insights into the morphology of granular osmiophilic material. Brain and Behavior: A Cognitive Neuroscience Perspective. 2017;7(3):e00624. DOI: 10.1002/brb3.624

[41] Lewandowska E, Dziewulska D, Parys M, Pasennik E. Ultrastructure of granular osmiophilic material deposits (GOM) in arterioles of CADASIL patients. Folia Neuropathologica. 2011;49(3):174-180

[42] Gridley T. Notch signaling in the vasculature. Current Topics in Developmental Biology. 2010;92:277-309. DOI: 10.1016/S0070-2153(10)92009-7

[43] Ishiko A, Shimizu A, Nagata E, Takahashi K, Tabira T, Suzuki N. Notch3 ectodomain is a major component of granular osmiophilic material (GOM) in CADASIL. Acta Neuropathologica. 2006;112(3):333-339. DOI: 10.1007/s00401-006-0116-2

[44] Yamamoto Y, Craggs LJ, Watanabe A, Booth T, Attems J, Low RW, et al. Brain microvascular accumulation and distribution of the NOTCH3 ectodomain and granular osmiophilic material in CADASIL. Journal of Neuropathology and Experimental Neuropathy. 2013;72(5):416-431. DOI: 10.1097/NEN.0b013e31829020b5
[45] Tikka S, Mykkänen K, Ruchoux MM, Bergholm R, Junna M, Pöyhönen M, et al. Congruence between NOTCH3 mutations and GOM in 131 CADASIL patients. Brain. 2009;132(Pt 4):933-939. DOI: 10.1093/brain/awn364

[46] Morroni M, Marzioni D, Ragno M, Di Bella P, Cartechini E, Pianese L, et al. Role of electron microscopy in the diagnosis of cadasil syndrome: A study of 32 patients. PLoS One. 2013;8(6):e65482. DOI: 10.1371/journal.pone.0065482

[47] Pippucci T, Maresca A, Magini P, Cenacchi G, Donadio V, Palombo F, et al. Homozygous NOTCH3 null mutation and impaired NOTCH3 signaling in recessive early-onset arteriopathy and cavitating leukoencephalopathy. EMBO Molecular Medicine. 2015;7(6):848-858. DOI: 10.15252/emmm.201404399

[48] Joutel A, Corpechot C, Ducros A, Vahedi K, Chabriat H, Mouton P, et al. Notch3 mutations in CADASIL, a hereditary adult-onset condition causing stroke and dementia. Nature. 1996;383(6602):707-710. DOI: 10.1038/383707a0

[49] Xu X, Choi SH, Hu T, Tiyanont K, Habets R, Groot AJ, et al. Insights into autoregulation of Notch3 from structural and functional studies of its negative regulatory region. Structure. 2015;23(7):1227-1235. DOI: 10.1016/j.str.2015.05.001

[50] Domenga V, Fardoux P, Lacombe P, Monet M, Maciazeck J, Krebs LT, et al. Notch3 is required for arterial identity and maturation of vascular smooth muscle cells. Genes & Development. 2004;18:2730-2735. DOI: 10.1101/gad.308904

[51] Weinmaster G. The ins and outs of notch signaling. Molecular and Cellular Neurosciences. 1997;9(2):91-102. DOI: 10.1006/mcne.1997.0612

[52] Monet M, Domenga V, Lemaire B, Souilhol C, Langa F, Babinet C, et al. The archetypal R90C CADASIL-NOTCH3 mutation retains NOTCH3 function in vivo. Human Molecular Genetics. 2007;16(8):982-992. DOI: 10.1093/hmg/ddm042

[53] Tikka S, Baumann M, Siitonen M, Pasanen P, Pöyhönen M, Myllykangas L, et al. CADASIL and CARASIL. Brain Pathology. 2014;24(5):525-544. DOI: 10.1111/bpa.12181

[54] Hiruma-Shimizu K, Hosoguchi K, Liu Y, Fujitani N, Ohta T, Hinou H, et al. Chemical synthesis, folding, and structural insights into O-fucosylated epidermal growth factor-like repeat 12 of mouse Notch-1 receptor. Journal of The American Chemical Society. 2010;132(42):14857-14865. DOI: 10.1021/ja105216u

[55] Hambleton S, Valeyev NV, Muranyi A, Knott V, Werner JM, McMichael AJ, et al. Structural and functional properties of the human notch-1 ligand binding region. Structure. 2004;12(12):2173-2183. DOI: 10.1016/j.str.2004.09.012

[56] Artavanis-Tsakonas S, Muskavitch MA. Notch: The past, the present, and the future. Current Topics in Developmental Biology. 2010;92:1-29. DOI: 10.1016/S0070-2153(10)92001-2

[57] Belin de Chantemèle EJ, Retailleau K, Pinaud F, Vessières E, Bocquet A, Guihot AL, et al. Notch3 is a major regulator of vascular tone in cerebral and tail resistance arteries. Arteriosclerosis, Thrombosis, and Vascular Biology. 2008;28:2216-2224. DOI: 10.1161/ATVBAHA.108.171751

[58] Guruharsha KG, Kankel MW, Artavanis-Tsakonas S. The notch signalling system: Recent insights into the complexity of a conserved pathway. Nature Reviews. Genetics. 2012;13(9):654-666. DOI: 10.1038/nrg3272
[59] Boucher J, Gridley T, Liaw L. Molecular pathways of notch signaling in vascular smooth muscle cells. Frontiers in Physiology. 2012;3:81. DOI: 10.3389/fphys.2012.00081

[60] Dichgans M, Herzog J, Gasser T. NOTCH3 mutation involving three cysteine residues in a family with typical CADASIL. Neurology. 2001;57(9):1714-1717. DOI: 10.1212/wnl.57.9.1714

[61] Rutten JV, Dauwerse HG, Gravesteijn G, van Belzen MJ, van der Grond J, Polke JM, et al. Archetypal NOTCH3 mutations frequent in public exome: Implications for CADASIL. Annals of Clinical Translational Neurology. 2016;3(11):844-853. DOI: 10.1002/acn3.344

[62] Muiño E, Gallego-Fabrega C, Cullell N, Carrera C, Torres N, Krupinski J, et al. Systematic review of cysteine-sparing NOTCH3 missense mutations in patients with clinical suspicion of CADASIL. International Journal of Molecular Sciences. 2017;18(9):1964. DOI: 10.3390/ijms18091964

[63] Duering M, Karpinska A, Rosner S, Hopfner F, Zechmeister M, Peters N, et al. Co-aggregate formation of CADASIL-mutant NOTCH3: A single-particle analysis. Human Molecular Genetics. 2011;20(16):3256-3265. DOI: 10.1093/hmg/ddr237

[64] Meng H, Zhang X, Yu G, Lee SJ, Chen YE, Prudovsky I, et al. Biochemical characterization and cellular effects of CADASIL mutants of NOTCH3. PLoS One. 2012;7(9):e44964. DOI: 10.1371/journal.pone.0044964

[65] Opherk C, Duering M, Peters N, Karpinska A, Rosner S, Schneider E, et al. CADASIL mutations enhance spontaneous multimerization of NOTCH3. Human Molecular Genetics. 2009;18(15):2761-2767. DOI: 10.1093/hmg/ddp211

[66] Mykkänen K, Savontaus ML, Juvonen V, Sistonen P, Tuisku S, Tuominen S, et al. Detection of the founder effect in Finnish CADASIL families. European Journal of Human Genetics. 2004;12(10):813-819. DOI: 10.1038/sj.ejhg.5201221

[67] Federico A, Bianchi S, Dotti MT. The spectrum of mutations for CADASIL diagnosis. Neurological Sciences. 2005;26(2):117-124. DOI: 10.1007/s10072-005-0444-3

[68] Dichgans M, Ludwig H, Müller-Höcker J, Messerschmidt A, Gasser T. Small in-frame deletions and missense mutations in CADASIL: 3D models predict misfolding of Notch3 EGF-like repeat domains. European Journal of Human Genetics. 2000;8(4):280-285. DOI: 10.1038/sj.ejhg.5200460

[69] Joutel A, Chabriat H, Vahey K, Domenga V, Vayssière C, Ruchoux MM, et al. Splice site mutation causing a seven amino acid Notch3 in-frame deletion in CADASIL. Neurology. 2000;54(9):1874-1875. DOI: 10.1212/wnl.54.9.1874

[70] Joutel A, Dodick DD, Parisi JE, Cecillon M, Tournier-Lasserve E, Bousser MG. De novo mutation in the Notch3 gene causing CADASIL. Annals of Neurology. 2000;47(3):388-391

[71] Dotti MT, De Stefano N, Bianchi S, Malandrini A, Battisti C, Cardaioli E, et al. A novel NOTCH3 frameshift deletion and mitochondrial abnormalities in a patient with CADASIL. Archives of Neurology. 2004;61(6):942-945. DOI: 10.1001/archneur.61.6.942

[72] Mazzei R, Conforti FL, Lanza PL, Sprovieri T, Lupo MR, Gallo O, et al. A novel Notch3 gene mutation not involving a cysteine residue in an Italian family with CADASIL. Neurology. 2004;63(3):561-564. DOI: 10.1212/01.wnl.0000133399.37716.84
[73] Mazzei R, Guidetti D, Ungaro C, Conforti FL, Muglia M, Cenacchi G, et al. First evidence of a pathogenic insertion in the NOTCH3 gene causing CADASIL. Journal of Neurology, Neurosurgery, and Psychiatry. 2008;79(1):108-110. DOI: 10.1136/jnnp.2007.128009

[74] Tuominen S, Juvonen V, Amberla K, Jolma T, Rinne JO, Tuisku S, et al. Phenotype of a homozygous CADASIL patient in comparison to 9 age-matched heterozygous patients with the same R133C Notch3 mutation. Stroke. 2001;32(8):1767-1774

[75] Liem MK, Lesnik Oberstein SA, Vollebregt MJ, Middelkoop HA, van der Grond J, Helderman-van den Enden AT. Journal of Neurology. 2008;255(12):1978-1980. DOI: 10.1007/s00415-008-0036-x

[76] Soong BW, Liao YC, Tu PH, Tsai PC, Lee IH, Chung CP, et al. A homozygous NOTCH3 mutation p.R544C and a heterozygous TREX1 variant p.C99MfsX3 in a family with hereditary small vessel disease of the brain. Journal of the Chinese Medical Association. 2013;76(6):319-324. DOI: 10.1016/j.jcma.2013.03.002

[77] Ragno M, Pianese L, Morrone M, Cacchiò G, Manca A, Di Marzio F, et al. “CADASIL coma” in an Italian homozygous CADASIL patient: Comparison with clinical and MRI findings in age-matched heterozygous patients with the same G528C NOTCH3 mutation. Neurological Sciences. 2013;34(11):1947-1953. DOI: 10.1007/s10072-013-1418-5

[78] Vinciguerra C, Rufa A, Bianchi S, Sperduto A, De Santis M, Malandrini A, et al. Homozygosity and severity of phenotypic presentation in a CADASIL family. Neurological Sciences. 2014;35(1):91-93. DOI: 10.1007/s10072-013-1580-9

[79] Joutel A, Vahedi K, Corpechot C, Troesch A, Chabriat H, Vayssière C, et al. Strong clustering and stereotyped nature of Notch3 mutations in CADASIL patients. The Lancet. 1997;350(9090):1511-1515. DOI: 10.1016/S0140-6736(97)08083-5

[80] Razvi SS, Davidson R, Bone I, Muir KW. Is inadequate family history a barrier to diagnosis in CADASIL? Acta Neurologica Scandinavica. 2005;112(5):323-326. DOI: 10.1111/j.1600-0404.2005.00495.x

[81] Coto E, Menéndez M, Navarro R, García-Castro M, Alvarez V. A new de novo Notch3 mutation causing CADASIL. European Journal of Neurology. 2006;13(6):628-631. DOI: 10.1111/j.1468-1313.2006.01337.x

[82] Pescini F, Nannucci S, Bertaccini B, Salvadori E, Bianchi S, Ragno M, et al. The cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) scale: A screening tool to select patients for NOTCH3 gene analysis. Stroke. 2012;43(11):2871-2876. DOI: 10.1161/STROKEAHA.112.665927

[83] Peters N, Opherk C, Bergmann T, Castro M, Herzog J, Dichgans M. Spectrum of mutations in biopsy-proven CADASIL: Implications for diagnostic strategies. Archives of Neurology. 2005;62(7):1091-1094. DOI: 10.1001/archneur.62.7.1091

[84] Hack R, Rutten J, Lesnik Oberstein SAJ. CADASIL. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, LJH B, Stephens K, Amemiya A, editors. Source GeneReviews®. 1993-2019. Seattle, WA: University of Washington; 2000 [Updated March 14, 2019]

[85] Koutsilieri E, Rethwilm A, Scheller C. The therapeutic potential of siRNA in gene therapy of neurodegenerative disorders. Journal of
Neural Transmission. Supplementum. 2007;72:43-49

[86] Scholefield J, Watson L, Smith D, Greenberg J, Wood MJ. Allele-specific silencing of mutant Ataxin-7 in SCA7 patient-derived fibroblasts. European Journal of Human Genetics. 2014;22(12):1369-1375. DOI: 10.1038/ejhg.2014.39

[87] Di Donato I, Bianchi S, De Stefano N, Dichgans M, Dotti MT, Duering M, et al. Cerebral autosomal dominant Arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) as a model of small vessel disease: Update on clinical, diagnostic, and management aspects. BMC Medicine. 2017;15(1):41. DOI: 10.1186/s12916-017-0778-8

[88] del Río-Espínola A, Mendióroz M, Domingues-Montanari S, Pozo-Rosich P, Solé E, Fernández-Morales J, et al. CADASIL management or what to do when there is little one can do. Expert Review of Neurotherapeutics. 2009;9(2):197-210. DOI: 10.1586/14737175.9.2.197