Genetic background of ataxia in children younger than 5 years in Finland

Erika Ignatius, MD, Pirjo Isohanni, MD, PhD, Max Pohjanpelto, Päivi Lahermo, PhD, Simo Ojanen, MSc, Virginia Brilhante, PhD, Eino Palin, MD, PhD, Anu Suomalainen, MD, PhD, Tuula Lönqvist, MD, PhD, and Christopher J. Carroll, PhD

Neurol Genet 2020;6:e444. doi:10.1212/NXG.0000000000000444

Abstract

Objective
To characterize the genetic background of molecularly undefined childhood-onset ataxias in Finland.

Methods
This study examined a cohort of patients from 50 families with onset of an ataxia syndrome before the age of 5 years collected from a single tertiary center, drawing on the advantages offered by next generation sequencing. A genome-wide genotyping array (Illumina Infinium Global Screening Array MD-24 v.2.0) was used to search for copy number variation undetectable by exome sequencing.

Results
Exome sequencing led to a molecular diagnosis for 20 probands (40%). In the 23 patients examined with a genome-wide genotyping array, 2 additional diagnoses were made. A considerable proportion of probands with a molecular diagnosis had de novo pathogenic variants (45%). In addition, the study identified a de novo variant in a gene not previously linked to ataxia: MED23. Patients in the cohort had medically actionable findings.

Conclusions
There is a high heterogeneity of causative mutations in this cohort despite the defined age at onset, phenotypical overlap between patients, the founder effect, and genetic isolation in the Finnish population. The findings reflect the heterogeneous genetic background of ataxia seen worldwide and the substantial contribution of de novo variants underlying childhood ataxia.
The most common etiology of ataxia in the pediatric population is genetic, with the prevalence of genetic childhood ataxia in Europe estimated at 14.6 per 100,000 population.1 Determining the etiology of childhood-onset ataxia has important clinical relevance, including ending the stressful and costly diagnostic odyssey, guiding genetic counseling, and facilitating precise follow-up and treatment.

The most common causes of hereditary ataxia vary regionally in populations of different genetic backgrounds.1 Owing to the founder effect and genetic isolation, Finland has a unique disease heritage.2 Accordingly, the most common ataxias seen elsewhere in the world, such as Friedreich ataxia, are rare in Finland.

As next generation sequencing (NGS) technologies have evolved, there have been many reports of exome sequencing in single families or single cases with childhood-onset cerebellar ataxia. Many previously reported ataxia cohorts analyze patients with adult or varied age-of-onset3 or are defined by having structural cerebellar abnormalities4 instead of the symptom of ataxia. There are a few smaller studies that analyze cohorts of pediatric patients with the symptom of ataxia.7,8

This study applied exome sequencing and a genome-wide genotyping array to examine a cohort of patients with childhood-onset ataxia collected from a single tertiary center, allowing better characterization of the genetic background of molecularly undefined childhood-onset ataxias in Finland. An age limit of 5 years at onset was applied to demarcate a clinical entity within the heterogeneous group of hereditary ataxias and is based on the Human Phenotype Ontology (HPO)9 defining childhood-onset as onset before the fifth birthday.

Standard protocol approvals, registrations, and patient consents
The study was approved by the Helsinki University Hospital ethics review board. All patients and/or their legal guardians gave informed consent in accordance with the Declaration of Helsinki.

Phenotyping
A child neurologist with expertise in childhood-onset ataxia examined all patients, whereas all available clinical, laboratory, and imaging data were reviewed by several clinicians undertaking the study. Primary phenotypes were mapped to HPO terms9 and included in the in-house semiautomated variant prioritization pipeline.

Sequencing and bioinformatics analysis
We performed exome sequencing on genomic DNA for 50 probands, 2 affected parents, and an affected sibling in 2 families.
The variant calling pipeline of the Finnish Institute of Molecular Medicine was used for the reference genome alignment and variant calling.\(^\text{10}\) We prioritized recessive-type non-synonymous variants with a minor allele frequency of less than 0.1% on the Exome Aggregation Consortium (ExAC)\(^\text{11}\) server. For potential de novo or dominantly inherited variants, heterozygous variants that were not found at all on the ExAC server were prioritized for consideration. We further prioritized variants by their predicted deleterious effect using amino acid conservation and, in the case of potential de novo variants, by gene constraint to mutation according to the framework previously described.\(^\text{11}\) The prediction tools SIFT\(^\text{12}\) and Polyphen\(^\text{13}\) as well as Combined Annotation Dependent Depletion (CADD) C-score\(^\text{14}\) were used in variant evaluation. Variants with a CADD C-score\(^\text{14}\) of less than 10 were excluded. Variants were also compared with our in-house database containing 520 exomes.

We classified novel sequence variants using the guidelines provided by the American College of Medical Genetics and Genomics (ACMG).\(^\text{15}\)

Sanger sequencing was used to validate the variants identified by exome sequencing and for segregation analysis. In the case of P12, samples from the child’s biological parents were unavailable, and as confirmation, western blot was used to confirm the deleterious effect of the variant identified.

Technical information on exome sequencing, a list of the primers used in Sanger sequencing and details of experimental validation of variants identified for P3 and P12, is provided in appendix e-1 (links.lww.com/NXG/A269).

**Global screening array analysis**

We screened for copy number variation and uniparental disomy after exome analysis was negative in 23 probands, for whom there was available DNA, using the 759993 single nucleotide polymorphism (SNP) markers of Illumina Infinium Global Screening Array MD-24 v.2.0 (GSAMD; Illumina, San Diego, CA). Log R ratio and B allele frequency values were generated with GenomeStudio 2.0 software (Illumina), and copy number variation regions were detected with PennCNV software using standard quality control checks.\(^\text{16}\) Standard quality control of genome-wide genotyping data was performed with PLINK 1.9 software.\(^\text{17}\)

**Data availability**

The data that support the findings of this study are available on request. The data are not publicly available because of the information that could compromise the privacy of research participants.
Diagnostic yield of exome sequencing
We obtained a molecular diagnosis for 20 probands (40%) using exome sequencing. We identified 26 diagnostic variants in 16 genes, 13 of which were novel and include a variant in the gene GPAA1 that was published from this cohort. A recessive form of inheritance was found in 9 probands, with 3 of the diagnosed probands having homozygous variants and 6 having compound heterozygous variants. We identified dominant variants in 11 probands, including de novo variants in 8 probands, 2 familial autosomal dominant variants, and a suspicion of parental somatic mosaicism in 1 parent of 1 proband. In all familial cases, there were no pedigrees involving 3 or more generations. After multidisciplinary evaluation, a novel variant in COQ8A and STUB1 was considered diagnostic for the probands’ ataxia although they remained as variants of uncertain significance as per strict application of the ACMG guidelines.

After multidisciplinary evaluation, a novel variant in COQ8A and STUB1 was considered diagnostic for the probands’ ataxia although they remained as variants of uncertain significance as per strict application of the ACMG guidelines.

The diagnostic variants we found are listed in table 2. We annotated variants to the Ensembl canonical transcript for each gene. Allele frequencies are reported as found in the Genome Aggregation Database.

Diagnostic yield of genome-wide genotyping array
We uncovered 2 copy number variants (CNVs) that we considered pathogenic using the GSAMD genome-wide genotyping array. For P21, we identified a heterozygous 570 kb deletion in the 10q26.3 region (chr10:131538728-132108832), encompassing the genes EBF3, GLRX, LINCO00939, and part of MGMT. The same deletion had already been identified in the patient’s clinical molecular karyotype when analyzed in 2015 but was, at that time, considered to be of uncertain significance. The parents of the patient were screened for the mutation, and it was found to be de novo. The GSAMD finding prompted re-evaluation of the deletion. Since 2017, haploinsufficiency of EBF3 has been reported to cause hypotonia, ataxia, and delayed development syndrome (MIM #617330).

For P22, we identified a heterozygous 1.2 kb deletion in SLC2A1 (chr1:43392250-43393465), encompassing most of

Table 1 Demographic and clinical background of the cohort (continued)

| Demyelinating peripheral neuropathy | 2 (11.8) |
|-------------------------------------|---------|
| Intellectual developmental disability | n (%) ; n = 50 |
| Presence of intellectual developmental disability | 22 (44.0) |

* Findings additional to cerebellar atrophy: brainstem atrophy (2); basal ganglia abnormality (1).
* Other abnormality: hypoplasia of the cerebellum, pons, brainstem and corpus callosum (1); pontocerebellar hypoplasia (1); small volume of the thalamus (1); mild cerebral cortical atrophy (1).
Results of an ENMG study were available for 17 patients.
## Table 2 Diagnostic variants underlying the patients’ ataxia

| Chr | Pos. Start | Gene   | CDS position | Functional change | gnomAD AF Finnish | gnomAD AF All | CADD C-score | Inheritance | Reference/ClinVar ID if reported previously (annotation in report) | ACMG classification |
|-----|------------|--------|--------------|------------------|-------------------|---------------|--------------|-------------|---------------------------------------------------------------|---------------------|
| P1  | 1          | SLC2A1 | c.971C>A     | p.(Ser324Ter)    | 0                 | 0             | 44           | De novo     | Novel variant                                                | Pathogenic          |
| P2  | 1          | COQ8A  | c.811C>T     | p.(Arg271Cys)    | 0.0007748         | 0.0001061     | 33           | AR          | Reported\(^{29}\)                                            | Established variant |
| P2  | 1          | COQ8A  | c.1677C>G    | p.(His559Gln)    | 0.002802          | 0.0004296     | 26.4         | AR          | ClinVar ID 423260                                            | VUS                 |
| P3  | 2          | HIBCH  | c.559C>T     | p.(Leu187Phe)    | 0                 | 0.00003185    | 29           | AR          | Novel variant                                                | Likely pathogenic\(^{4}\) |
| P3  | 2          | HIBCH  | c.220-2A>T   | r.spl            | 0                 | 0.00001769    | 24.3         | AR          | Novel variant                                                | Pathogenic          |
| P4  | 2          | BC51L  | c.232A>G     | p.(Ser78Gly)     | 0.004062          | 0.0004737     | 23           | AR          | Reported\(^{30}\)                                            | Established variant |
| P4  | 2          | BC51L  | c.464G>A     | p.(Arg155Gln)    | 0.000008838       | 0.00003994    | 25.8         | AR          | Novel variant                                                | Likely pathogenic   |
| P5  | 3          | ITPR1  | c.1736C>T    | p.(Thr579Ile)    | 0                 | 0             | 29.5         | AD          | Reported\(^{31}\) (Thr594Ile)                                | Established variant |
| P6  | 3          | ITPR1  | c.7786_7788delAAG | p.(Lys2596del) | 0 | 0 | 22.8 | De novo | Reported\(^{32}\)                                             | Established variant |
| P7  | 8          | GPA4A  | c.160_161delinsAA | p.(Ala54Asn) | 0 | 0 | 29.9 | AR | Reported from this cohort\(^{18}\)                           | Established variant |
| P8  | 10         | EBF3   | c.1183C>T    | p.(Arg395Ter)    | 0                 | 0             | 42           | AD\(^{p}\)    | ClinVar ID 620273                                            | Pathogenic          |
| P9  | 10         | EBF3   | c.625C>T     | p.(Arg209Trp)    | 0                 | 0             | 35           | De novo      | Reported\(^{33}\)                                            | Established variant |
| P10 | 10         | EBF3   | c.622dupA    | p.(Met208AsnfsTer56) | 0 | 0 | 35 | AD | Novel variant                                                 | Pathogenic          |
| P11 | 11         | TPP1   | c.1259C>A    | p.(Ser420Ter)    | 0                 | 0             | 40           | AR          | Novel variant                                                | Likely pathogenic   |
| P12 | 12         | TCTN1  | c.221-2A>G   | r.spl            | 0                 | 0             | 24.9         | AR          | reported\(^{34}\) (IVS1–2A>G)                                | Established variant |
| P12 | 12         | TCTN1  | c.1635+1G>A  | r.spl            | 0.000008845       | 0.000008022   | 24.8         | AR          | Novel variant                                                | Pathogenic\(^{4}\) |
| P13 | 13         | CLNS5  | c.1175_1176delAT | p.(Tyr392Ter) | 0.0008137       | 0.0009384    | 35           | AR          | Reported\(^{35}\)                                            | Established variant |
| P14 | 14         | NXX2-1 | c.596C>A     | p.(Ser199Ter)    | 0                 | 0             | 39           | De novo      | Reported\(^{36}\) (C2519A)                                   | Established variant |
| P15 | 16         | STUB1  | c.689_692delACCT | p.(Tyr230CysfsTer9) | 0.000008841 | 0.000007985 | 35 | AR | Novel variant                                                 | Likely pathogenic   |
| P15 | 16         | STUB1  | c.865G>A     | p.(Val289Ile)    | 0                 | 0.00007998    | 23           | AR          | Novel variant                                                | VUS                 |
| P16 | 17         | PTRH2  | c.127_128insA | p.(Ser43LysfsTer11) | 0 | 0 | 24.3 | AR | Novel variant                                                 | Likely pathogenic   |
| P17 | 19         | CACNA1A| c.4988G>A    | p.(Arg1663Gln)   | 0                 | 0             | 25.4         | De novo      | Reported\(^{37}\) (Arg1664Gln)                                | Established variant |

Continued
Mutations in SLC2A1 are known to cause GLUT1 deficiency syndrome 1 (MIM #606777) and GLUT1 deficiency syndrome 2 (MIM #612126). Multiexon deletions in SLC2A1 are known to cause disease. The GSAMD finding was confirmed with multiplex ligation-dependent probe amplification in a clinical laboratory and confirmed to be de novo.

**Patient phenotypes and effect on clinical management**

The findings of the study affected the clinical management of multiple patients. Table e-1 (links.lww.com/NXG/A268) describes the patient phenotypes and possible effects on clinical treatment and management.

**Variants of uncertain significance in ataxia genes**

Four probands had a variant of uncertain significance in a gene previously implicated in ataxia, listed in table 3.

**Gene of uncertain significance**

We found a heterozygous de novo missense variant for P27 in a gene not previously linked to ataxia, MED23 (figure 2A). The patient has hypotonia, tremor, and ataxia that developed at the age of 1.5 years. A detailed phenotypic description for P27 is in appendix e-1 (links.lww.com/NXG/A269). MED23 encodes a transcription factor in which recessive mutations are known to cause autosomal recessive nonsyndromic mental retardation-18 (MIM #614249). De novo status was confirmed by DNA fingerprinting of the patient and parents using 7 microsatellite markers. MED23 has a high constraint for missense mutations (missense Z: 4.53556). The variant, chr6g.131919485A>G, c.2549T>C, p.(Leu850Pro) has a high CADD C-score (28.6) and causes the change of a conserved amino acid (figure 2B).

**Discussion**

Exome sequencing is a robust diagnostic method for childhood-onset ataxias manifesting before the age of 5. We found disease-causing mutations in many different genes in this cohort despite the defined age at onset, phenotypical overlap between patients, the founder effect, and genetic isolation in the Finnish population. This is surprising because Finland has a unique disease heritage; however, our findings reflect the heterogeneous genetic background of ataxia seen worldwide and the substantial contribution of de novo variants underlying childhood ataxia.

The patients who were investigated with exome sequencing formed a "hard-to-diagnose" cohort, which did not include patients from the same clinic whose genetic diagnosis had previously been made by single gene or panel testing. In this study, the combination of exome sequencing and GSAMD provided a diagnosis for 44% of the investigated families. This is slightly higher than in ataxia cohorts comprising patients with varying ages of disease onset, where an estimated diagnostic rate for exome sequencing is 36%. Our diagnostic yield was at

| Chr | Post Start | Gene | CDS position | Functional change | CADD | gnomAD AF Fin | Inheritance | ACMG classification | Reference/ClinVar ID if reported previously (annotation in report) |
|-----|------------|------|--------------|------------------|------|---------------|-------------|---------------------|---------------------------------------------------------------|
| P18 | 19 | ATP1A3 | c.2305C>T p.(Arg769Cys) | 34 | 0 | 0 | 0 | De novo | Reported (Arg756Cys) |
| P19 | 19 | ATP1A3 | c.2306G>A p.(Arg769His) | 34 | 0 | 0 | 0 | De novo | Reported (Arg756His) |
| P20 | X | CASK | c.879_880dupC p.(Gln294ArgfsTer3) | 35 | 0 | 0 | 0 | Novel variant | |
| P21 | 19 | ATP1A3 | c.2305C>T p.(Arg769Cys) | 34 | 0 | 0 | 0 | De novo | Reported (Arg756Cys) |
| P22 | 19 | ATP1A3 | c.2306G>A p.(Arg769His) | 34 | 0 | 0 | 0 | De novo | Reported (Arg756His) |

**Abbreviations:** AD = autosomal dominant; AF = allele frequency; AR = autosomal recessive; CADD = Combined Annotation Dependent Depletion; CDS = coding sequence; gnomAD = Genome Aggregation Database; VUS = variant of uncertain significance.
The percentage of genetically diagnosed patients that were found to have a de novo variant underlying their disease in previous studies varied. In the first such published study,\textsuperscript{7} in a cohort of 28 families (6 consanguineous), 9% had a pathogenic de novo variant. Our study revealed a remarkably higher de novo rate of 45% in patients with previously molecularly undiagnosed childhood-onset ataxia. Other reports include a 25% de novo rate in a study that investigated congenital ataxia in consanguineous families\textsuperscript{8} and another study\textsuperscript{23} that found a 42% de novo rate in a pediatric movement disorder cohort including patients with ataxia.

One of the limitations in our study was that in most cases only the proband, and not parents, was sequenced. Trio exome analysis is associated with a higher diagnostic yield compared with single exome analysis in rare Mendelian disorders,\textsuperscript{24} and trio analysis is especially useful in an early onset, mainly sporadic ataxia cohort.\textsuperscript{3} However, a large number of de novo mutations were still identified by prioritizing deleterious heterozygous variants using CADD C-scores and gene constraint scores.\textsuperscript{11,14} Nevertheless, the high burden of de novo variants in this cohort adds to the recommendation of a triosequencing approach. Furthermore, our exome sequencing analysis may have underestimated the number of CNVs and may have overlooked uniparental disomy because their analysis is not straightforward from exome sequencing data. Software that infer copy number variation from exome sequencing data, such as ExomeDepth,\textsuperscript{25} can have suboptimal specificity and sensitivity, especially in the case of small CNVs spanning one exon.\textsuperscript{26} In children with developmental delay, a first-tier diagnostic test revealing CNVs has been chromosomal microarray, either with array-based CGH or SNP array.\textsuperscript{27} Not all copy number variation is revealed even with the combination of microarray CGH and exome sequencing because CNVs at the intragene level will usually be too small to be identified using the microarrays in clinical use. High-resolution microarray or genome sequencing can still better identify CNVs, especially the long indels and small CNVs that are otherwise not found. We found GSAMD to be a cost-effective method to screen for copy number variation and uniparental disomy and to confirm maternity and paternity in suspected de novo cases in a research setting. In the patients examined with GSAMD, 4 had previous findings reported in clinical molecular karyotypes. These previously identified variations had been inherited from an unaffected parent or had otherwise been interpreted to be of uncertain significance. The GSAMD detected all 4 of these CNVs, adding to our confidence in the method.

We did not find any pathologic repeat expansions, such as those underlying Friedreich ataxia or many of the dominant spinocerebellar ataxias, which are poorly detected using NGS technologies. Many of the common spinocerebellar ataxias caused by trinucleotide repeats are rare in Finland, with the exception of spinocerebellar ataxia type 7,\textsuperscript{28} and are unlikely to be represented in an early-childhood-onset cohort. However, repeat expansions
Most Finnish patients with childhood-onset ataxia are candidates for exome or genome sequencing when the phenotype and background do not clearly point to a specific disease entity. Patients in the cohort had medically actionable findings, underscoring the importance of exome, or genome sequencing as a first-line diagnostic method. Concurrently, it is crucial for the clinician to understand the inherent weaknesses of exome sequencing, especially the inefficiency concerning current analysis tools to detect copy number variation and triplet repeats.

**Acknowledgment**

The authors thank all the patients and relatives that participated in this study as well as Milla Kuronen, Lilli Hinds, Tuula Manninen, Markus Innilä, and Anu Harju for technical assistance.

**Study funding**

This work was funded by the University of Helsinki, Helsinki University Hospital, Arvo and Lea Ylppö Foundation, Foundation for Pediatric Research, Päivikki and Sakari Sohlberg Foundation, Biomedicum Helsinki Foundation and Maire Taponen Foundation.

**Disclosure**

The authors report no disclosures relevant to the manuscript. Go to Neurology.org/NG for full disclosures.

**Publication history**

Received by Neurology: Genetics January 3, 2020. Accepted in final form April 27, 2020.

**Appendix Authors**

| Name                     | Location                                                                 | Contribution                                                                 |
|--------------------------|--------------------------------------------------------------------------|------------------------------------------------------------------------------|
| Erika Ignatius, MD       | Children’s Hospital, University of Helsinki and Helsinki University Hospital; and Research Programs Unit, University of Helsinki, Finland | Research project conception, organization, and execution; acquisition, analysis, and interpretation of data; and manuscript: writing of the first draft and review and critique |
| Pirjo Isohanni; MD, PhD   | Children’s Hospital, University of Helsinki and Helsinki University Hospital; and Research Programs Unit, University of Helsinki, Finland | Research project conception, organization, and execution; acquisition, analysis, and interpretation of data; and manuscript: review and critique |
| Max Pohjanpelto          | Research Programs Unit, University of Helsinki, Finland                  | Research project execution; acquisition, analysis, and interpretation of data; and manuscript: review and critique |
| Paivi Lahermo, PhD       | Institute for Molecular Medicine Finland, University of Helsinki, Finland | Research project execution; acquisition, analysis, and interpretation of data; and manuscript: writing of the first draft and review and critique |

in novel ataxia disease genes are possibly yet to be discovered, and identification of such mutations is likely to be enabled by application of long-read genome sequencing technologies.

NGS techniques have become ubiquitous diagnostic methods in centers studying neurodevelopmental and neurodegenerative disorders. Developing effective diagnostic algorithms requires experience of the utility of these methods as first- or second-line studies. As new genes and broader phenotypes in ataxia continue to be identified, targeted gene panels may overlook recently identified disease genes. In the case of our cohort, many findings would not have been made using the panels available at the time of sequencing. In the case of a negative exome or genome, systematic re-evaluation at a later time point may reveal a diagnosis. Publications of candidate genes potentially causing diseases in humans, as well as internet resources listing rare variants, aid researchers in finding other families with the same disease.

**Figure 2 MED23 variant**

The P27 heterozygous variant, chr6:131919485A>G, c.2549T>C, p.(Leu850-Pro) in MED23 (A) causes the change of a conserved amino acid (B).
Appendix (continued)

| Name                  | Location                                                                 | Contribution                                                                 |
|-----------------------|---------------------------------------------------------------------------|------------------------------------------------------------------------------|
| Simo Ojansen, MSc      | Research Programs Unit, University of Helsinki, Finland                    | Research project organization; analysis and interpretation of data; and manuscript: review and critique |
| Virginia Brilhante, PhD| Research Programs Unit, University of Helsinki, Finland                    | Research project organization; analysis and interpretation of data; and manuscript: review and critique |
| Eino Palin, MD, PhD    | Research Programs Unit, University of Helsinki, Finland                    | Research project organization; analysis and interpretation of data; and manuscript: review and critique |
| Anu Suomalainen, MD, PhD| Research Programs Unit, University of Helsinki, Finland                    | Research project conception and organization; and manuscript: review and critique |
| Tuula Lonqvist, MD, PhD | Children’s Hospital, University of Helsinki and Helsinki University Hospital, Finland | Research project conception, organization, and execution; acquisition, analysis, and interpretation of data; and manuscript: review and critique |
| Christopher J. Carroll, PhD | St. George’s, University of London, United Kingdom                        | Research project conception, organization, and execution; acquisition, analysis, and interpretation of data; and manuscript: review and critique |

References

1. Muselman KE, Stoyanov CT, Maraganar R, et al. Prevalence of ataxia in children: a systematic review. Neurology 2014;82:80–89.
2. Norio R. The Finnish Disease Heritage III: the individual diseases. Hum Genet 2003; 112:470–526.
3. Galtolò D, Tessa A, Filli A, Santorelli FM. Clinical application of next generation sequencing in hereditary spinocerebellar ataxia: increasing the diagnostic yield and broadening the ataxia-spasticity spectrum. A retrospective analysis. Neurogenetics 2018;19:1–8.
4. Chemin J, Siquier-Pernet K, Nicouleau M, et al. De novo mutation screening in childhood-onset cerebellar atrophy identifies gain-of-function mutations in the CACNA1G calcium channel gene. Brain 2018;141:1998–2013.
5. Megahed H, Nicouleau M, Barcia G, et al. Utility of whole exome sequencing for the diagnosis of pediatric-onset cerebellar atrophy associated with developmental delay in an inbred population. Orphanet J Rare Dis 2016;11:57.
6. Obha C, Osaka H, Iai M, et al. Diagnostic utility of whole exome sequencing in patients showing cerebellar and/or vermis atrophy in childhood. Neurogenetics 2013;14:225–232.
7. Sawyer SL, Schwartzentuber J, Beauchesne CL, et al. Exome sequencing as a diagnostic tool for pediatric-onset ataxia. Hum Mutat 2014;35:45–49.
8. Valence S, Cochet E, Rouget C, et al. Exome sequencing in congenital ataxia identifies two new candidate genes and highlights a pathophysiological link between some congenital ataxias and early infantile epileptic encephalopathies. Genet Med 2019;21:553–563.
9. Kedher S, Vasilevska NA, Engelstad M, et al. The Human Phenotype Ontology in 2017. Nucleic Acids Res 2017;45:D865–D876.
10. Sulonen AM, Ellonen P, Almusa H, et al. Comparison of solution-based exome capture methods for next generation sequencing. Genome Biol 2011;12:B94.
11. Lek M, Karczewski KJ, Minkiel EV, et al. Analysis of protein-coding genetic variation in 60,706 humans. Nature 2016;536:285–291.
12. 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.
13. Adzhubei IA, Schmidt S, Peshkin L, et al. A method and server for predicting damaging missense mutations. Nat Methods 2010;7:248–249.
14. Kircher M, Witten DM, Jain P, O’Roak BJ, Cooper GM, Shendure J. A general framework for estimating the relative pathogenicity of human genetic variants. Nat Genet 2014;46:310–315.
15. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med 2015;17:405–424.
16. Wang K, Li M, Hadley D, et al. PennCNV: an integrated hidden Markov model designed for high-resolution copy number variation detection in whole-genome SNP genotyping data. Genome Res 2007;17:1665–1674.
17. Purcell S, Neale B, Todd-Brown K, et al. PLINK: a tool set for whole-genome association and population-based linkage analyses. Am J Hum Genet 2007;81:559–575.
18. Nguyen TTM, Murakami Y, Sheridan E, et al. Mutations in GIPA1, encoding a GPI transamidase complex protein, cause developmental delay, epilepsy, cerebellar atrophy, and osteopenia. Am J Hum Genet 2017;101:856–865.
19. Zerbino DR, Achuthan P, Akanni W, et al. Ensembl 2018. Nucleic Acids Res 2018;46:D754–D761.
20. Karczewski KJ, Francioli LC, Tao G, et al. Variation across 141,456 human exomes and genomes reveals the spectrum of loss-of-function intolerance across human protein-coding genes. bioRxiv 2019;513221.
21. Leen WG, Klapper J, Verbeek MM, et al. Glucose transporter-1 deficiency syndrome: the expanding clinical and genetic spectrum of a treatable disorder. Brain 2010;133:655–670.
22. Hashimoto S, Boissel S, Zarhant M, et al. MED23 mutation links intellectual disability to dysregulation of immediate early gene expression. Science 2011;333:1161–1163.
23. Cordeiro D, Bullivant G, Sirtwadena K, et al. Genetic landscape of pediatric movement disorders and management implications. Neurol Genet 2018;4:e265.
24. Lee H, Deignan JL, Dorrani N, et al. Clinical exome sequencing for genetic identification of rare Mendelian disorders. JAMA 2014;312:1880–1887.
25. Plagnol V, Curtis J, Epstein M, et al. A robust model for read count data in exome sequencing experiments and implications for copy number variant calling. Bioinformatics 2012;28:2747–2754.
26. Samarakoon PS, Sorte HS, Kristiansen BE, et al. Identification of copy number variants from exome sequence data. BMC Genomics 2014;15:661.
27. Miller DT, Adam MP, Aradhya S, et al. Consensus statement: chromosomal microarray is a first-tier clinical diagnostic test for individuals with developmental disabilities or congenital anomalies. Am J Hum Genet 2010;86:749–764.
28. Jonason J, Juronen V, Sirtonen P, et al. Evidence for a common Spino cerebellar ataxia type 7 (SCA7) founder mutation in Scandinavia. Eur J Hum Genet 2000;8:918–922.
29. Horvath R, Czermuz B, Gulati S, et al. Adult-onset cerebellar ataxia due to mutations in CABC1/ADCK3. J Neurol Neurosurg Psychiatry 2012;83:174–178.
30. Vapila I, Fullman V, Vesa J, et al. GRACILE syndrome, a lethal metabolic disorder with iron overload, is caused by a point mutation in BCS1L. Am J Hum Genet 2002;71:863–876.
31. Sasaki M, Obha C, Iai M, et al. Sporadic infantile-onset spinocerebellar ataxia caused by missense mutations in the inositol 1,4,5-triphosphate receptor type 1 gene. J Neurovirol 2015;21:1278–1284.
32. McIntartg M, Williamson KA, Rainier JK, et al. A restricted repertoire of the novel mutations in ITPR1 cause Gillespie syndrome with evidence for dominant-negative effect. Am J Hum Genet 2016;98:981–992.
33. Harms FL, Girisha KM, Hardigan AA, et al. Mutations in EBFB1 disturb transcriptional profiles and cause intellectual disability, ataxia, and faciodynamic amyotrophy. Am J Hum Genet 2017;100:117–127.
34. Garcia-Gonzalo FR, Corbet KC, Sierol-Piquer MS, et al. A transition zone complex regulates mammalian ciliogenesis and ciliary membrane composition. Nat Genet 2011;43:776–778.
35. Savukoski M, Klockars T, Holmberg V, Santavuori P, Lander ES, Peltonen L. CLNS, a novel gene encoding a putative transmembrane protein mutated in Finnish variant late infantile neuronal ceroid lipofuscinosis. Nat Genet 1998;19:286–288.
36. Knude H, Schult B, Biebelmann H, et al. Choreoathetosis, hypothyroidism, and pulmonary alterations due to human NX2K-1 haplosufficiency. J Clin Invest 2002;109:475–480.
37. Tonelli A, D’Angelo MG, Salat R, et al. Early onset, non fluctuating spinocerebellar ataxia and a novel missense mutation in CACNA1A gene. J Neurol Sci 2006;241:13–17.
38. Brashar A, Mink JW, Hill DF, et al. ATPIA3 mutations in infants: a new rapid-onset dystonia-Parkinsonism phenotype characterized by motor delay and ataxia. Dev Med Child Neurol 2012;54:1065–1067.
39. Dard R, Mignon C, Durr A, et al. Relapsing encephalopathy with cerebellar ataxia related to an ATPIA3 mutation. Dev Med Child Neurol 2015;57:1185–1186.
40. Data available from Dryad (Additional References, References e1 to e5): links.bwh.

Neurology.org/NG | Volume 6, Number 4 | August 2020
Genetic background of ataxia in children younger than 5 years in Finland
Erika Ignatius, Pirjo Isohanni, Max Pohjanpelto, et al.
Neurol Genet 2020;6; DOI 10.1212/NXG.0000000000000444

This information is current as of June 5, 2020

Updated Information & Services
including high resolution figures, can be found at:
http://ng.neurology.org/content/6/4/e444.full.html

References
This article cites 38 articles, 4 of which you can access for free at:
http://ng.neurology.org/content/6/4/e444.full.html##ref-list-1

Subspecialty Collections
This article, along with others on similar topics, appears in the following collection(s):
All Genetics
http://ng.neurology.org/cgi/collection/all_genetics
All Pediatric
http://ng.neurology.org/cgi/collection/all_pediatric
Cerebellum
http://ng.neurology.org/cgi/collection/cerebellum
Gait disorders/ataxia
http://ng.neurology.org/cgi/collection/gait_disorders_ataxia

Permissions & Licensing
Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
http://ng.neurology.org/misc/about.xhtml#permissions

Reprints
Information about ordering reprints can be found online:
http://ng.neurology.org/misc/addir.xhtml#reprintsus

Neurol Genet is an official journal of the American Academy of Neurology. Published since April 2015, it is an open-access, online-only, continuous publication journal. Copyright © 2020 The Author(s). Published by Wolters Kluwer Health, Inc. on behalf of the American Academy of Neurology. All rights reserved. Online ISSN: 2376-7839.