Published in final edited form as:

Ann Neurol. 2018 June ; 83(6): 1072–1074. doi:10.1002/ana.25262.

Collaborative Science Unites Researchers and a Novel Spastic Ataxia Gene

Brent L. Fogel, MD, PhD

Departments of Neurology and Human Genetics, David Geffen School of Medicine, University of California Los Angeles, California, 90095, USA

The hereditary ataxias are diverse and varied, comprising roughly 90 genes constituting the primary ataxias^{1, 2} and nearly 600 additional genes that can present with symptoms that include cerebellar ataxia.³ Despite this, at least one-third of patients remain undiagnosed by current technologies, including whole exome sequencing,^{4–7} suggesting that additional genes await discovery.

In this issue, Seong et al. describe a collaborative international effort identifying 12 patients from 7 families with a novel autosomal recessive cerebellar ataxia caused by mutation in *VPS13D*.⁸ Their largest family, with 5 affected individuals, had been previously reported and designated phenotypically as SCAR4 (spinocerebellar ataxia recessive type 4) characterized by adult onset cerebellar ataxia, macrosaccadic intrusions, pyramidal signs, and neuropathy, and thus resolves the precise molecular basis of that disorder. Another two families presented somewhat similarly with adult onset spasticity or spastic ataxia. The other four families had onset ranging from birth to age 5. Three of these had varying degrees of developmental delay with the most severe having intellectual disability, seizures, and white matter changes on brain MRI.⁸ The collaborative effort uniting these cases was brought about in part through the use of GeneMatcher,⁹ one of a growing numbers of tools and initiatives that unite researchers interested in specific genes based on genomic and phenotypic data with the goal of facilitating resolution of complex diagnostic dilemmas, identifying the molecular basis of unsolved rare diseases, and discovering new disease genes.^{10, 11}

Separately, in this same issue, Gauthier et. al. report a family with 2 patients with spastic ataxia, chorea, and dystonia also harboring variants in *VPS13D*. Another 5 cases from 4 additional families were located at collaborative sites, also utilizing contributions from GeneMatcher.¹² In this cohort, all patients showed early onset before age 12, developmental delay, intellectual disability, axial hypotonia, and chorea, eventually progressing to spastic ataxia and dystonia in adulthood.¹² Two patients from different families also had microcephaly and seizures. Further complicating the phenotypic spectrum, one family presented with early tremor progressing to dystonia, spasticity and mild ataxia as adults.

Corresponding Author: Brent L. Fogel, MD, PhD, University of California at Los Angeles, 695 Charles E. Young Drive South, Gonda Room 1206, Los Angeles, CA 90095, bfogel@ucla.edu.

Potential Conflicts of Interest:

The author reports no potential conflicts of interest.

MRI of the brains of the cohort showed T2/FLAIR hyperintensities either in a pattern restricted to the putamen and caudate, or more diffusely involving the white matter, reminiscent of patterns described in Leigh syndrome.¹²

The *VPS13* family consists of four genes, *VPS13A*, *VPS13B*, *VPS13C*, and *VPS13D*,^{3, 13} all of which have now been shown to cause recessive neurological disease. *VPS13A* causes a progressive neurodegenerative disorder, chorea-acanthocytosis, primarily characterized by progressive chorea but can include other movement problems such as parkinsonism or dystonia, frontal cognitive impairment, and, in some patients, seizures and/or myopathy.¹⁴ *VPS13B* is associated with a clinically variable syndromic neurodevelopmental disorder, termed Cohen syndrome, generally associated with features of microcephaly, intellectual disability, motor delay, joint hypermobility, neutropenia, and progressive retinopathy, among other findings.¹⁵ Mutations in *VPS13C* lead to an early-onset rapidly progressive form of parkinsonism with pyramidal signs and early cognitive impairment.¹⁶ *VPS13D* is now the final member of the *VPS13* family to be associated with human neurological disease. The gene is highly intolerant to missense variation and even more so to loss of function variants.^{8, 12, 17} *VPS13D* has recently been shown to be essential for mitochondrial metabolism in *Drosophila*, including viability, autophagy, and clearance.¹⁸ The gene is also essential in human cell lines and its deletion leads to abnormal mitochondrial morphology.^{18, 19} While the precise cellular functions of the other family members are not yet fully established, mutation of *VPS13C* also appears to lead to mitochondrial dysfunction.¹⁶

Consistent with the proposed role of *VPS13D* in mitochondrial function,¹⁸ Seong et al. also noted that disruption of the *Drosophila* homologue was lethal and caused severely altered mitochondrial morphology.⁸ Large spherical mitochondria and impaired trafficking were seen when loss was restricted to motor neurons.⁸ Similar structural defects were observed in patient fibroblasts.⁸ In patients, muscle biopsy within one affected family showed subsarcolemmal mitochondrial aggregates and mild lipidosis supporting mitochondrial dysfunction, although enzymatic studies in patient fibroblast cell lines were normal.¹² Not surprisingly, disruption of mitochondrial function is not an uncommon theme in cerebellar ataxia.²²⁰

These reports illustrate the clinical challenge of achieving a molecular diagnosis among disorders that lie on the phenotypic spectrum bridging disorders of ataxia and spasticity.^{4, 21} The genetics of this new disorder appear complex and both studies acknowledged difficulty in establishing clear correlations between genotype and phenotype. Seong et al. noted that patients with both a nonsense and a missense variant tended to have adult onset disease (8 of 9 patients) and earlier and more severe phenotypes were seen in patients with suspected splicing mutations.⁸ Gauthier et al. saw early onset in all cases, although with a variable range from birth to age 12. The majority of cases (3 of 5 families) had a missense variant coupled with a variable deletion or duplication disrupting the protein reading frame.¹² Interestingly, the remaining two families possessed only missense variants (one family homozygous and the other compound heterozygous), one of which had the most severe phenotype of the entire cohort.¹² Considering the lethality of *VPS13D* knockout in flies,^{8, 18} it is reasonable to hypothesize that the presence of a hypomorphic allele in a haploinsufficient background is the minimum requirement for disease, but given the varying

types of mutations, their location within the protein, and the diverse genetic backgrounds between the patients in these studies, more work is needed to ascertain the nature of the differences leading to more severe presentations.

The decreasing cost and widespread utilization of genomic sequencing technology has considerably broadened the search space for novel genetic disorders to span the entire human genome. This has enabled the creation of large and rapidly searchable research datasets for gene discovery. These studies clearly illustrate the power of linking such efforts as several of the cases were brought together using a combination of one such tool, GeneMatcher, in conjunction with the authors extensive networks of clinical collaborators.^{8, 12} As precision medicine health care models²² become more commonplace, a critical effort should be made to broadly unite the comprehensive patient genomic datasets being created with precise clinical and phenotypic information and subsequently create mechanisms to effectively link these data to further accelerate discovery and translate research back to patients more rapidly. The ongoing development of methods to efficiently clinically annotate these various datasets from the electronic health record while insuring privacy of the genetic and health information will be crucial. In the modern genomic era, as the low-hanging fruit rapidly disappears, leaving newly discovered genes that show ever-decreasing prevalence, the availability of centralized resources comprising unified well-phenotyped genomic datasets from patients with complex neurological disorders, such as cerebellar ataxia and/or spasticity, will greatly facilitate the identification of families who share mutations in suspected novel disease genes.

Acknowledgments

This work was supported in part by the National Institute for Neurological Disorders and Stroke (R01NS082094).

References

1. Mundwiler A, Shakkottai VG. Autosomal-dominant cerebellar ataxias. *Handb Clin Neurol*. 2018; 147:173–85. [PubMed: 29325610]
2. Fogel BL. Autosomal-recessive cerebellar ataxias. *Handb Clin Neurol*. 2018; 147:187–209. [PubMed: 29325611]
3. Online Mendelian Inheritance in Man, OMIM. [Internet] McKusick-Nathans Institute of Genetic Medicine. Johns Hopkins University; Baltimore, MD: [accessed April 2018]. Available from: World Wide Web URL: <http://omim.org/>
4. Fogel BL, Lee H, Deignan JL, Strom SP, Kantarci S, Wang X, Quintero-Rivera F, Vilain E, Grody WW, Perlman S, Geschwind DH, Nelson SF. Exome sequencing in the clinical diagnosis of sporadic or familial cerebellar ataxia. *JAMA Neurol*. 2014; 71(10):1237–46. [PubMed: 25133958]
5. Pyle A, Smertenko T, Bargiela D, Griffin H, Duff J, Appleton M, Douroudis K, Pfeffer G, Santibanez-Koref M, Eglon G, Yu-Wai-Man P, Ramesh V, Horvath R, Chinnery PF. Exome sequencing in undiagnosed inherited and sporadic ataxias. *Brain*. 2015; 138(Pt 2):276–83. [PubMed: 25497598]
6. Farwell KD, Shahmirzadi L, El-Khechen D, Powis Z, Chao EC, Tippin Davis B, Baxter RM, Zeng W, Mroske C, Parra MC, Gandomi SK, Lu I, Li X, Lu H, Lu HM, Salvador D, Ruble D, Lao M, Fischbach S, Wen J, Lee S, Elliott A, Dunlop CL, Tang S. Enhanced utility of family-centered diagnostic exome sequencing with inheritance model-based analysis: results from 500 unselected families with undiagnosed genetic conditions. *Genet Med*. 2015; 17(7):578–86. [PubMed: 25356970]

7. Nibbeling EAR, Duarri A, Verschuuren-Bemelmans CC, Fokkens MR, Karjalainen JM, Smeets C, de Boer-Bergsma JJ, van der Vries G, Dooijes D, Bampi GB, van Diemen C, Brunt E, Ippel E, Kremer B, Vlak M, Adir N, Wijmenga C, van de Warrenburg BPC, Franke L, Sinke RJ, Verbeek DS. Exome sequencing and network analysis identifies shared mechanisms underlying spinocerebellar ataxia. *Brain*. 2017; 140(11):2860–78. [PubMed: 29053796]
8. Seong E, Insolera R, Dulovic M, Kamsteeg E-J, Trinh J, Brüggemann N, Sandford E, Li S, Ozel AB, Li JZ, Jewett T, Kievit AJA, Münchau A, Shakkottai V, Klein C, Collins C, Lohmann K, Warrenburg BPvd, Burmeister M. Mutations in VPS13D lead to a new recessive ataxia with spasticity and mitochondrial defects. *Annals of Neurology*. 2018
9. Sobreira N, Schiettecatte F, Valle D, Hamosh A. GeneMatcher: a matching tool for connecting investigators with an interest in the same gene. *Hum Mutat*. 2015; 36(10):928–30. [PubMed: 26220891]
10. Philippakis AA, Azzariti DR, Beltran S, Brookes AJ, Brownstein CA, Brudno M, Brunner HG, Buske OJ, Carey K, Doll C, Dumitriu S, Dyke SO, den Dunnen JT, Firth HV, Gibbs RA, Girdea M, Gonzalez M, Haendel MA, Hamosh A, Holm IA, Huang L, Hurles ME, Hutton B, Krier JB, Misyura A, Mungall CJ, Paschall J, Paten B, Robinson PN, Schiettecatte F, Sobreira NL, Swaminathan GJ, Taschner PE, Terry SF, Washington NL, Zuchner S, Boycott KM, Rehm HL. The Matchmaker Exchange: a platform for rare disease gene discovery. *Hum Mutat*. 2015; 36(10): 915–21. [PubMed: 26295439]
11. Gahl WA, Mulvihill JJ, Toro C, Markello TC, Wise AL, Ramoni RB, Adams DR, Tifft CJ, Udn. The NIH Undiagnosed Diseases Program and Network: Applications to modern medicine. *Mol Genet Metab*. 2016; 117(4):393–400. [PubMed: 26846157]
12. Gauthier J, Meijer IA, Lessel D, Mencacci NE, Krainc D, Hempel M, Tsiakas K, Prokisch H, Rossignol E, Helm MH, Rodan LH, Karamchandani J, Carecchio M, Lubbe SJ, Telegrafi A, Henderson LB, Lorenzo K, Wallace SE, Glass IA, Hamdan FF, Michaud JL, Rouleau GA, Campeau PM. Recessive mutations in VPS13D cause childhood-onset movement disorders. *Annals of Neurology*. 2018
13. Velayos-Baeza A, Vettori A, Copley RR, Dobson-Stone C, Monaco AP. Analysis of the human VPS13 gene family. *Genomics*. 2004; 84(3):536–49. [PubMed: 15498460]
14. Velayos Baeza A, Dobson-Stone C, Rampoldi L, Bader B, Walker RH, Danek A, Monaco AP. Chorea-Acanthocytosis. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Stephens K, Amemiya A, editors *GeneReviews*(R)). Seattle (WA): 1993.
15. Douzgou S, Petersen MB. Clinical variability of genetic isolates of Cohen syndrome. *Clin Genet*. 2011; 79(6):501–6. [PubMed: 21418059]
16. Lesage S, Drouet V, Majounie E, Deramecourt V, Jacoupy M, Nicolas A, Cormier-Dequaire F, Hassoun SM, Pujol C, Ciura S, Erpapazoglou Z, Usenko T, Maurage CA, Sahbatou M, Liebau S, Ding J, Bilgic B, Emre M, Erginel-Unaltuna N, Guven G, Tison F, Tranchant C, Vidailhet M, Corvol JC, Krack P, Leutenegger AL, Nalls MA, Hernandez DG, Heutink P, Gibbs JR, Hardy J, Wood NW, Gasser T, Durr A, Deleuze JF, Tazir M, Destee A, Lohmann E, Kabashi E, Singleton A, Corti O, Brice A, French Parkinson's Disease Genetics S, International Parkinson's Disease Genomics, C. Loss of VPS13C Function in Autosomal-Recessive Parkinsonism Causes Mitochondrial Dysfunction and Increases PINK1/Parkin-Dependent Mitophagy. *Am J Hum Genet*. 2016; 98(3):500–13. [PubMed: 26942284]
17. Lek M, Karczewski KJ, Minikel EV, Samocha KE, Banks E, Fennell T, O'Donnell-Luria AH, Ware JS, Hill AJ, Cummings BB, Tukiainen T, Birnbaum DP, Kosmicki JA, Duncan LE, Estrada K, Zhao F, Zou J, Pierce-Hoffman E, Berghout J, Cooper DN, Deflaux N, DePristo M, Do R, Flannick J, Fromer M, Gauthier L, Goldstein J, Gupta N, Howrigan D, Kiezun A, Kurki MI, Moonshine AL, Natarajan P, Orozco L, Peloso GM, Poplin R, Rivas MA, Ruano-Rubio V, Rose SA, Ruderfer DM, Shakir K, Stenson PD, Stevens C, Thomas BP, Tiao G, Tusie-Luna MT, Weisburd B, Won HH, Yu D, Altshuler DM, Ardissino D, Boehnke M, Danesh J, Donnelly S, Elosua R, Florez JC, Gabriel SB, Getz G, Glatt SJ, Hultman CM, Kathiresan S, Laakso M, McCarroll S, McCarthy MI, McGovern D, McPherson R, Neale BM, Palotie A, Purcell SM, Saleheen D, Scharf JM, Sklar P, Sullivan PF, Tuomilehto J, Tsuang MT, Watkins HC, Wilson JG, Daly MJ, MacArthur DG, Exome Aggregation C. Analysis of protein-coding genetic variation in 60,706 humans. *Nature*. 2016; 536(7616):285–91. [PubMed: 27535533]

18. Anding AL, Wang C, Chang TK, Sliter DA, Powers CM, Hofmann K, Youle RJ, Baehrecke EH. Vps13D Encodes a Ubiquitin-Binding Protein that Is Required for the Regulation of Mitochondrial Size and Clearance. *Curr Biol*. 2018; 28(2):287–95 e6. [PubMed: 29307555]
19. Wang T, Birsoy K, Hughes NW, Krupczak KM, Post Y, Wei JJ, Lander ES, Sabatini DM. Identification and characterization of essential genes in the human genome. *Science*. 2015; 350(6264):1096–101. [PubMed: 26472758]
20. Bargiela D, Shanmugarajah P, Lo C, Blakely EL, Taylor RW, Horvath R, Wharton S, Chinnery PF, Hadjivassiliou M. Mitochondrial pathology in progressive cerebellar ataxia. *Cerebellum Ataxias*. 2015; 2:16. [PubMed: 26640698]
21. Galatolo D, Tessa A, Filla 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):1–8. [PubMed: 29209898]
22. Wolf SM, Thyagarajan B, Fogel BL. The need to develop a patient-centered precision medicine model for adults with chronic disability. *Expert Rev Mol Diagn*. 2017; 17(5):415–8. [PubMed: 28325089]