Clinical Application of Whole-Exome Sequencing

A Novel Autosomal Recessive Spastic Ataxia of Charlevoix-Saguenay Sequence Variation in a Child With Ataxia

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Importance: Ataxia in children is a diagnostic challenge. Besides the more common acquired causes of ataxia, there are more than 50 inherited disorders associated with ataxia. Our objective was to highlight whole-exome sequencing as a rapidly evolving clinical tool for diagnosis of mendelian disorders, and we illustrate this in the report of a single case of a novel sequence variation in the SACS gene.

Observations: A 4-year-old girl presented with delayed gross motor development, ataxia, and polyneuropathy. Results of initial testing for the common causes of inherited and acquired ataxia were unrevealing. Whole-exome sequencing showed a novel frame-shift homozygous sequence variation in the SACS gene, consistent with the diagnosis of autosomal recessive spastic ataxia of Charlevoix-Saguenay.

Conclusions: Whole-exome sequencing is a powerful clinical tool that has been increasingly used to assist in the diagnosis of mendelian disorders. It provides a cost-effective, efficient, and expedited approach to making a clinical diagnosis and, in some cases, may be the only way to make a diagnosis.


Whole-exome sequencing (WES) has been used successfully in research to identify novel genes for numerous mendelian disorders. Although still improving, WES provides a powerful clinical tool to assist in the diagnosis of mendelian disorders. We report the use of WES to diagnose the condition of a 4-year-old girl who presented for evaluation of ataxia.

REPORT OF A CASE

A 4-year-old girl presented with ataxia and delayed gross motor development. She sat at 12 months and walked unassisted by 20 months. She had an unsteady gait with frequent falls. Her fine motor, language, and social skills were within normal limits, and there was no neurological regression. Her family history was remarkable for extensive consanguinity and 3 cousins who died as infants; subsequently, these cousins were diagnosed as having severe neonatal aspartylglucosaminuria (Figure 1).

On physical examination, she was on the 1st centile for weight, 7th centile for height, and 50th centile for head circumference. She was nondysmorphic with no neurocutaneous stigmata or telangiectasias. Cognition was intact. She had decreased axial tone with mild distal appendicular spasticity. Strength was preserved. Tendon reflexes were present with flexor plantar responses. Sensation was normal. She had mild terminal intentional tremor on finger-nose testing. She had a broad-based ataxic gait and climbed the stairs with assistance.

Her initial workup included measurement of plasma amino acids, urine organic acids, transferrin isoelectric focusing, lysosomal enzyme activity, and levels of immunoglobulins, triglycerides, vitamin E, and very long-chain fatty acids. Lysosomal enzyme activity in leukocytes showed decreased galactocerebrosidase enzyme activity, but test results in skin fibroblasts were normal. Magnetic reso-
Nance imaging of the brain demonstrated findings illustrated in Figure 2 and Figure 3. A muscle biopsy specimen was normal. Test results for common autosomal recessive forms of ataxia, including aprataxin, senataxin, frataxin, and α-tocopherol transfer protein genes, were normal. Electromyography and nerve conduction studies demonstrated generalized sensorimotor demyelinating polyneuropathy. Chromosomal microarray showed multiple copy-neutral areas of long stretches of homozygosity on 12 chromosomes, consistent with the family history of consanguinity.

Clinical WES showed a previously unreported homozygous sequence variation, c.11637_11638delAG (p.Arg3879fs), in the SACS gene (OMIM 604490) (Figure 4). The girl’s parents were heterozygous for the same sequence variation (Figure 4). The sequence variation was predicted to cause a frameshift and downstream premature termination and was interpreted as pathogenic. A heterozygous c.1715C>G (p.Ala572Gly) variant of unknown significance in the GAN gene (OMIM 605379) and a heterozygous c.7132T>C (p.Phe2378Leu) variant of unknown significance in the SPG11 gene (OMIM 610844) were also detected in the proband.

**DISCUSSION**

Sequence variations in the SACS gene are known to cause autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS) (OMIM 270550). Sequence variations in the GAN and SPG11 genes are associated with giant axonal neuropathy (OMIM 256850) and spastic paraplegia autosomal recessive type 11 (OMIM 604360), respectively. Both conditions are inherited in an autosomal recessive manner and, given that the second variant alleles were not detected, were thus not considered to be the primary cause of the patient’s ataxia.

ARSACS is a progressive neurological disorder and presents in childhood or adulthood with gait unsteadiness. Common clinical features include dysarthria, nys-
tagmus, spasticity, and sensorimotor polyneuropathy. Characteristic magnetic resonance imaging findings of cerebellar atrophy and pontine abnormalities were seen in our patient. Hypermyelinated retinal fibers may be observed but were not present in our patient. Most patients become wheelchair dependent by the fifth decade of life. Cognition is typically not affected. Management in ARSACS is supportive. Our patient was homozygous for a novel pathogenic frameshift sequence variation in the SACS gene and had a clinical presentation consistent with the ARSACS phenotype.

Ataxia in a child is a diagnostic challenge. There are more than 50 inherited causes of ataxia. Clinical testing for individual genes is available for more than 40 of these disorders and is expensive, costing more than $500 for each gene when tested individually ($1900 for SACS gene testing) and more than $15000 when tested as a panel of 20 genes (SACS gene not included). However, the diagnosis often remains elusive despite extensive testing. Not only is this process costly, it also prolongs the diagnostic odyssey. Whole-exome sequencing provides a cost-effective, efficient, and expedited approach to making a clinical diagnosis; in some cases, WES may be the only way to make a diagnosis.

Whole-exome sequencing is a rapidly evolving tool for the diagnosis of mendelian disorders and is an especially powerful method in consanguineous families. With decreasing sequencing costs and improving analysis pipelines, we expect this technology to be in widespread clinical use in the near future. It will provide a cost-effective means of making genetic diagnoses in rare and/or genetically heterogeneous disorders and will simplify diagnostic strategies to decrease the time and cost to diagnosis, allowing us to focus on appropriate treatment and supportive care.

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