SMPD1 Gene Analysis in Acid Sphingomyelinase Deficiency

Clinical Features

Acid sphingomyelinase (ASM) deficiency is a rare lipid storage disorder due to variants in the *SMPD1* gene and is characterized by accumulation of sphingomyelin in reticulo-endothelial and other cell types in the body. Historically, ASM deficiency has been classified as either the neurodegenerative form (Niemann-Pick Disease, Type A [NPD-A]), with death in early childhood, or the non-neurodegenerative, visceral form (Niemann-Pick Disease, Type B [NPD-B]). NPD-A is panethnic but especially common in the Ashkenazi Jewish population. It is more severe and progressive than NPD-B because the *SMPD1* gene product, acid sphingomyelinase, has activity of < 5%. The disorder usually presents early with abdominal enlargement due to hepatosplenomegaly. Starting at around 6 months of age, other symptoms follow, including persistent jaundice, cherry red spots of the retina, hypotonia, progressive growth, motor and developmental delay with failure to achieve developmental milestones such as independent sitting, crawling, or walking. The disorder then results in rapid neurological degeneration, hypotonia, rigidity, and mental retardation, with fatal outcome within approximately 3 years after onset. NPD-B is panethnic, although increased frequency in Turkish, Arabic and North African populations due to founder variants has been noted. The clinical phenotype of NPD-B is less homogeneous than NPD-A, and symptoms may involve the spleen, liver, and lungs. NPD-B patients remain mostly free of neurological manifestations and typically live into adulthood. In NPD-B, the defective enzyme retains residual catalytic activity, thus resulting in the milder phenotype. Intermediate Type A/B falls clinically on a continuum, with symptoms ranging from slightly less severe than NPD-A to slightly more severe than classic NPD-B.

Inheritance Pattern

ASM deficiency has an autosomal recessive pattern of inheritance; imprinting of the paternal allele, i.e. only expression of the maternal allele, has been reported in one family.[1]

Test Methods

Using genomic DNA extracted from the submitted specimen, the complete coding regions and splice site junctions of the *SMPD1* gene are enriched using a proprietary targeted capture system developed by GeneDx for next-generation sequencing with CNV calling (NGS-CNV). The enriched targets are simultaneously sequenced with paired-end reads on an Illumina platform. Bi-directional sequence reads are assembled and aligned to the reference sequence based on NCBI RefSeq transcripts and human genome build GRCh37/UCSC hg19. After gene specific filtering, data are analyzed to identify sequence variants and most deletions and duplications involving coding exons; however, technical limitations and inherent sequence properties effectively reduce this resolution for some genes. Alternative sequencing or copy number detection methods are used to analyze or confirm regions with inadequate sequence or copy number data by NGS. Reportable variants include pathogenic variants, likely pathogenic variants and variants of uncertain significance. Likely benign and benign variants, if present, are not routinely reported but are available upon request.

The technical sensitivity of sequencing is estimated to be >99% at detecting single nucleotide events. It will not reliably detect deletions greater than 20 base pairs, insertions or rearrangements greater than 10 base pairs, or low-level mosaicism. The copy number assessment methods used with this test cannot reliably detect copy number variants of less than 500 base pairs or mosaicism and cannot identify balanced chromosome aberrations. Assessment of exon-level copy number events is dependent on the inherent sequence properties of the targeted regions, including shared homology and exon size.

Variant Spectrum

Over 200 distinct variants have been reported in the *SMPD1* gene. In Ashkenazi-Jewish patients with NPD-A, three common variants account for about 90% of mutant alleles, including the missense variants R498L (aka

R496L) and L304P (aka L302P), and c.990delC.[1,2] Variants in NPD-B are usually missense variants or in-frame deletions that reduce but do not eliminate enzyme activity.[3]
Although most variants are private, a few are more prevalent in certain ethnic groups, such as the 3-bp deletion (p.Arg608del, aka ΔR608) that has been found on almost 90% of disease alleles in individuals from North Africa (Maghreb region: Tunisia, Algeria, and Morocco), in almost all patients from the Grand Canaria Island,[4] and also on approximately 20%-30% of disease alleles in individuals from the United States.

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