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

Test Methods:

Using genomic DNA obtained from the submitted biological material, bi-directional sequence of the entire coding region and splice junctions of the *SMPD1* gene (exons 1-6) is obtained and analyzed. If sequencing identifies a variant on only one allele of the *SMPD1* gene, and if clinically indicated, reflex deletion/duplication testing (ExonArrayDx) will be performed at no additional charge to evaluate for a deletion/duplication of one or more exons of this gene. Variants found in the first person of a family to be tested are confirmed by repeat analysis using sequencing, restriction fragment analysis, or another appropriate method.

Test Sensitivity:

Sequence analysis of the *SMPD1* gene is expected to identify pathogenic variants in approximately 99% of affected individuals with enzymatically confirmed ASM deficiency. The methods used by GeneDx are expected to be greater than 99% sensitive at detecting variants identifiable by sequencing.

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.

References:

1. Simonaro CM, Park J-H, Eliyahu E, Shtraizent N, McGovern MM, Schuchman EH (2006). Am J Hum Genet 78:865-70;
2. Sikora J, Pavlu-Pereira H, Elleder M, Roelofs H, Wevers RA (2003). Annals of Human Genetics 67:63-70;
3. Simonaro CM, Desnick RJ, McGovern MM, Wasserstein MP, Schuchman EH (2002). Am J Hum Genet 71:1413-9.
4. Fernandez-Burriel M, Pena L, Ramos JC, Cabrera JC, Marti M, Rodriguez-Quinones F, Chabas A (2003). Clin Genet 63(3):235-6;
5. Wasserstein MP, Schuchman EH (Updated 06-08-2015) Acid sphingomyelinase deficiency, In: GeneReviews at GeneTests: Medical Genetics Information Resource (database online). Copyright, University of Washington, Seattle. 1993-2007. Available at http://www.genetests.org. Accessed 04/2017.