SLC17A5 Gene Analysis in Free Sialic Acid Storage Disorders

Disorder also known as: Salla disease (SD); infantile free sialic acid storage disease (ISSD)

Clinical Features:
The lysosomal free sialic acid storage diseases (SASDs) include the allelic disorders Salla disease (SD), common in the Finnish population, and infantile free sialic acid storage disease (ISSD). Patients with SD usually have a normal appearance and neurological findings at birth followed by slowly progressive neurologic deterioration resulting in moderate to severe psychomotor retardation, spasticity, ataxia and seizures. The life expectancy appears to be shortened; however, some affected patients have been reported to live into their early seventies.[1] ISSD has a much more severe phenotype characterized by severe developmental delay, coarse facial features, hepatosplenomegaly, and failure to thrive. Cardiomegaly, renal involvement and dysostosis multiplex may also be present.[2] ISSD can present prenatally or in the neonatal period with non-immune hydrops fetalis and/or isolated ascites. Death usually occurs in early childhood. Cases of SASD have been reported with symptoms that are intermediate between SD and ISSD.[2] SD has mostly been reported in individuals from Finland, where a p.Arg39Cys (R39C) founder mutation in the *SLC17A5* gene was identified in approximately 1 in 200 individuals.[3] In the northeastern region of Finland where SD is more common, the carrier frequency of R39C is approximately 1 in 100.[3]

Genetics:
The SASDs are caused by pathogenic variants in the *SLC17A5* gene that encodes the sialin protein; a lysosomal membrane protein that is responsible for exporting free sialic acid from lysosomes. Variants in the *SLC17A5* gene cause defective sialin and elevated lysosomal storage of free sialic acid. Patients with SASD excrete large amounts of free sialic acid in their urine and accumulate it in several types of tissues including fibroblasts. The *SLC17A5* gene is located on chromosome 6q14-q15 and has 11 exons.

Inheritance Pattern:
Autosomal Recessive

Test Methods:
Variant analysis of the *SLC17A5* gene is performed on genomic DNA from the submitted specimen using bi-directional sequence analysis of coding exons and corresponding intron/exon boundaries. In addition, targeted array CGH analysis with exon-level resolution (ExonArrayDx) is performed concurrently to evaluate for a deletion or duplication of one or more exons of this gene. A variant/deletion is confirmed by repeat analysis using sequencing,

restriction fragment analysis, quantitative PCR or oligo-array comparative genome hybridization (ExonArrayDx), as appropriate.

Test Sensitivity:
In 80 Finnish patients with SD, 95% of *SLC17A5* alleles harbored the R39C variant and 91% of patients were homozygous for R39C.[3] In 26 patients from varying ethnicities with SD and ISSD, including Finnish patients in whom only a single R39C variant was identified, analysis of the *SLC17A5* gene identified variants on 86% of alleles (45/52).[3] In 12 French patients with ISSD, including 8 fetuses diagnosed in utero, analysis of the *SLC17A5* gene identified variants on all alleles (24/24).[4] The methods used by GeneDx are expected to be greater than 99% sensitive at detecting variants identifiable by sequencing.

Variant Spectrum:
More than 50 variants have been identified in the *SLC17A5* gene that include missense, nonsense, splicing, small deletions, and large deletions and insertions.[5] The R93C variant is a founder mutation in Finnish patients with SD having been identified on 95% of *SLC17A5* alleles in this population.[3] Patients who are homozygous for R93C have SD, while individuals who are compound heterozygotes for R93C and another *SLC17A5* variant have an intermediate phenotype.[1] Compound heterozygotes for variants other than R39C have the severe ISSD phenotype.[1] However, the severity of SASDs can vary even among members of the same family.[2] Large deletions appear to be relatively common in the *SLC17A5* gene having been identified on approximately 6% of alleles in non-Scandinavian patients with SASD and in approximately 1% of alleles from Finnish patients with SD.[3] In another study of 12 French patients with ISSD, large deletions were identified on approximately 16% of *SLC17A5* alleles.[4]

References:

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