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 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. Individuals with SD have been reported to have a shortened life expectancy.[10] 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] Death usually occurs in early childhood. ISSD can also present prenatally or in the neonatal period with non-immune hydrops fetalis and/or isolated ascites.[6,7] Cases of free sialic acid storage disease have been reported with symptoms that are intermediate between SD and ISSD.[2] SD has mostly been reported in individuals from Finland, where the p.Arg39Cys (R39C) founder mutation in the *SLC17A5* gene was identified in approximately 1 in 200 individuals.[3] In the northeastern region of Finland, 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
Using genomic DNA extracted from the submitted specimen, the complete coding regions and splice site junctions of the *SLC17A5* 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.

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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 R39C variant is a founder mutation in Finnish individuals with SD having been identified on 95% of *SLC17A5* alleles in this population.[3] Individuals who are homozygous for R39C have SD, while individuals who are compound heterozygotes for R39C 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 nonScandinavian individuals with SASD and in approximately 1% of alleles from Finnish patients with SD.[3] In another study of 12 French individuals with severe prenatal or perinatal ISSD, large deletions were identified on 16% of SLC17A5 alleles.[4]

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