VPS13B (COH1) Gene Analysis in Cohen Syndrome

Clinical Features:
Cohen syndrome (CS) represents a complex developmental disorder. Commonly observed features include: microcephaly, mental retardation, childhood hypotonia, motor clumsiness and non-progressive psychomotor retardation, joint hyperextensibility, ophthalmologic findings such as progressive myopia, retinochoroidal dystrophy, and pigmentary retinopathy, truncal obesity with slender hands and feet, and intermittent neutropenia. The facial gestalt, which becomes more distinct with age, is characterized by a low anterior hairline, thick hair, eyebrows, and eyelashes, high-arched or wave-shaped eyelids, prominent, beak-shaped nose, low nasal bridge, short, upturned philtrum, and open-mouthed appearance. Cohen syndrome is especially common in the Finnish population due to a founder mutation. While the phenotype is relatively homogenous in Finnish patients, the clinical spectrum is much wider in non-Finnish patients.

Inheritance Pattern/Genetics:
Autosomal recessive

CS is rare, and affected individuals in consanguineous and as well as non-consanguineous families have been reported. CS is caused by variants in the VPS13B (COH1) gene located on chromosome 8q22-q23. The VPS13B gene is composed of 62 exons and spans a genomic region of 864 kb. It encodes a protein of 4,022 amino acids. Evidence suggests alternative splicing of exons 8, 17, 22, and 31, predicted to result in either truncated forms of VPS13B or in-frame, alternatively spliced forms. The VPS13B protein is predicted to have ten transmembrane domains and a complex pattern of functional motifs. The N- and C-terminal domains share homology with vacuolar protein sorting-associated protein 13 (Vps13) in yeast, suggesting a role in vesicle-mediated sorting and intracellular protein transport.

Test Sensitivity:
Published studies have indicated that the vast majority of patients who fit the clinical diagnosis of Cohen syndrome have variants in the VPS13B (COH1) gene. One study in which variant screening was performed on 37 patients with classical Cohen syndrome of Finnish and other ancestry revealed a test sensitivity of 76%.[1] Interestingly, between 17% and 40% of the variant-positive patients had only one detectable pathogenic variant by sequencing. Large intragenic deletions and duplications of one or more exons in the VPS13B (COH1) gene are identified in about 30% of affected families.[5,6,7] One individual with Cohen syndrome has been reported to be compound heterozygous for two deletions.[6]

Test Methods:

Using genomic DNA from the submitted specimen, the coding regions and splice junctions of the requested gene are PCR amplified and capillary sequencing is performed. Bi-directional sequence is assembled, aligned to reference gene sequences based on NCBI RefSeq transcript and human genome build GRCh37/UCSC hg19, and analyzed for sequence variants. Concurrent deletion/duplication testing is performed for most, if not all, of the coding exons using exon-level oligo array CGH (ExonArrayDx), and data analysis is performed using gene-specific filtering. Probe sequences and locations are based on human genome build GRCh37/UCSC hg19. Reported clinically significant variants are confirmed by an appropriate method. Sequence and copy number variants are reported according to the Human Genome Variation Society (HGVS) or International System for Human Cytogenetic Nomenclature (ISCN) guidelines, respectively. 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.

References:

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