

Cohen Syndrome via *VPS13B (COH1)* Gene Sequencing (Test #134)

Brief Description of Clinical Features: Cohen syndrome (COH1; OMIM #216550) is characterized clinically by developmental delay, early onset myopia, joint laxity, and a characteristic facies (Hennies et al., *Am J Hum Genet* 75:138-145, 2004). In the Finnish population, where Cohen syndrome is relatively more common, patients uniformly exhibit microcephaly, developmental delay, retinal dystrophy, neutropenia, joint laxity, and characteristic facies (Kolehmainen et al., *Am J Hum Genet* 72:1359-1369, 2003). In patients from a more diverse geographic region, however, microcephaly, neutropenia, retinopathy in school-aged children and the typical facies are not constant findings (Hennies et al., 2004; Seifert et al., *J Med Genet* 43:e22, 2006). Developmental delay varies in severity from profound to mild mental retardation (Kivitie-Kallio and Norio *Am J Med Genet* 102:125-135, 2001), and most patients have a cheerful disposition. Patients also have motor clumsiness, muscle weakness and hypotonia beyond infancy. Microcephaly, when present is of postnatal onset. Facial dysmorphism includes high arched eyelids, mildly downslanting palpebral fissures, a short philtrum, open mouth with prominent upper incisors, high arched narrow palate, and large ears. Other features sometimes occurring in Cohen syndrome include slender fingers, thick hair with low hairline, delayed puberty, and a high pitched voice. Obesity in Cohen syndrome patients has been found to be unremarkable (Kolehmainen et al., 2003).

Genetics: Cohen syndrome is inherited as an autosomal recessive disorder, most often involving private mutations. Allelic heterogeneity underlies the variability in observed clinical phenotypes. Truncating *VPS13B (COH1)* mutations are the most abundant class of mutation and they are distributed throughout the gene.

Description of This Particular Test: The Vacuolar Protein Sorting 13B protein is coded by exons 2-62 of the *VPS13B* gene on chromosome 8q22. Testing is accomplished by amplifying each coding exon and ~50 bp of adjacent noncoding sequence, then determining the nucleotide sequence using standard dideoxy sequencing methods and a capillary electrophoresis instrument.

Reference Sequences: Genomic: NC_000008.9 mRNA and Protein: CCDS 6281.1 and 6280.1

Indication for Testing: Individuals with clinical features resembling Cohen syndrome. Because of the broad clinical spectrum documented for this disorder, not all mutation proven cases will have a classic presentation.

Sensitivity of test: Clinical sensitivity of the *VPS13B (COH1)* sequencing test has been shown to be high in patients from wide geographic origins with highly variable clinical phenotypes. For example, Hennies et al. (2004) found two mutations in probands from all twelve families originating from countries in Eastern and Southern Europe, South America and the Middle East. Similarly, Seifert et al. (2006) found two mutations in all but one proband from sixteen families with diverse ethnic origins. A single mutant *VPS13B* allele was found in the other proband.

Turn Around Time: Maximum of 40 days.

Specimen Requirements: See page 4 of the Requisition Form.

Price: Sequencing of *VPS13B* Gene Exons 2-62 \$ 2,990

CPT Codes:

Sample Ascertainment	83890	\$ 30	DNA Isolation	83891	\$ 40
Amplification x63	83898	\$1030	Sequencing x63	83904	\$1540
Separation	83894	\$ 190	Interpretation/Report	83912	\$ 160

Accreditation: CLIA ID #: 52D1027685 (expires 1/18/13) (CAP#: 7185561, AU ID: 1407125 expires 12/20/12)

Contact: Thomas L. Winder, PhD, FACMG, tom.winder@preventiongenetics.com, www.preventiongenetics.com