TH Gene Analysis in Tyrosine Hydroxylase Deficiency, Dopa-Responsive Dystonia, and Autosomal Recessive Infantile Parkinsonism

DISORDER ALSO KNOWN AS
Autosomal Recessive Segawa Syndrome

CLINICAL FEATURES
Tyrosine hydroxylase (TH) deficiency is a rare autosomal recessive movement disorder with onset typically within the first years of life. It is associated with phenotypic variability that ranges from dopa-responsive dystonia (DRD) to dopa-responsive infantile parkinsonism to infantile progressive encephalopathy that is not dopa-responsive. Additional features may include hypotonia, hypokinesia, oculogyric crises and ptosis, and autonomic signs (temperature instability, hypoglycemia). A diurnal fluctuation of symptoms may be evident. Carriers are usually asymptomatic but some have been reported with restless leg symptoms and exercise-induced stiffness. TH deficiency is typically characterized by decreased levels of homovanillic acid (HVA) and 3-methoxy-4-hydroxyphenylglycol (MHPG) with normal levels of 5-hydroxyindoleacetic acid (5-HIAA) and a decreased HVA/5-HIAA ratio in cerebrospinal fluid. There is no specific biochemical test for this disorder. The phenotype associated with TH deficient dopa-responsive dystonia may significantly overlap with DRD caused by pathogenic variants in the GCH1 gene, but may also be more complex (DRD-plus syndrome).

INHERITANCE PATTERN/GENETICS
Autosomal Recessive

TEST SENSITIVITY
In several small studies of patients with TH deficiency diagnosed by CSF testing, analysis of the TH gene identified pathogenic variants in all patients (16 patients or 32/32 TH alleles characterized).[2,3,5,6,7,9] In one study, pathogenic variants in the TH gene were identified in 3/17 patients without variants in the GCH1 gene, and in 3/7 patients with DRD-plus syndrome.[8]

TEST METHODS
Using genomic DNA from the submitted specimen, the coding regions, splice junctions, and the cAMP response element (located at -74 to -67 bp) of the TH 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.

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