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 Methods:
Using genomic DNA obtained from the submitted biological material, bi-directional sequence of the coding region, splice junctions and the cAMP response element (located at -74 to -67 bp) of the *TH* gene is analyzed. If clinically indicated, if sequencing identifies a pathogenic variant on only one allele of the *TH* gene, reflex deletion/duplication testing (ExonArrayDx) may be performed at no additional charge to evaluate for a deletion/duplication of one or more exons of this gene. Pathogenic variants found in the first person of a family to be tested are confirmed by repeat analysis using sequencing, restriction fragment analysis, or another appropriate method.

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]

References:

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