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

*Also known as:* Autosomal Recessive Segawa Syndrome, Tyrosine Hydroxylase Deficiency, Dopa-Responsive Infantile Parkinsonism, Dopa-Responsive Spastic Paraplegia, Progressive Infantile Encephalopathy, Dopa-Non-Responsive Dystonia

*Mendelian Inheritance in Man Number:* 605407- Autosomal Recessive Dopa-Responsive Dystonia; 191290- *TH* gene

**Clinical features, Biochemistry and Genetics:**
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. TH deficiency is caused by mutations in the *TH* gene on chromosome 11p15.5. Definitive diagnosis requires the identification of mutations in the *TH* gene. The phenotype associated with TH deficient dopa-responsive dystonia may significantly overlap with DRD caused by *GCH1* gene mutations, but may also be more complex (DRD-plus syndrome). Molecular testing of the *TH* gene should be undertaken in patients with a complex DRD presentation, and in patients negative for a *GCH1* gene mutation with simple DRD. Mutation analysis of the *GCH1* gene is available at GeneDx.

**Inheritance pattern:** Autosomal recessive

**Reasons for referral:**
1. Confirmation of a clinical diagnosis
2. Identification of at-risk family members
3. Genetic counseling
4. Prenatal diagnosis

**Test method:**
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 mutation 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. Mutations 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 mutations in all patients (16 patients or 32/32 *TH* alleles characterized).\(^2\) In one study, mutations in the *TH* gene were identified in 3/17 patients without mutations in the *GCH1* gene, and in 3/7 patients with DRD-plus syndrome.\(^9\)

**Mutation spectrum:**

Less than 50 mutations\(^13\) in the *TH* gene have been reported, the majority of which are missense mutations. Splice-site mutations, small deletions and several mutations involving the cyclic adenosine monophosphate (cAMP) response element within the promoter region have also been identified.\(^6\) Most mutations are private, except for the Dutch founder mutation c.698G>A, the Greek founder mutation L236P\(^11\), and the c.-70G>A and c.707T>C mutations. The presence of at least one promoter mutation appears to predict a simple form of DRD most likely responsive to L-Dopa.\(^12\)

**Specimen Requirements and Shipping/Handling:**

- **Blood:** A single tube with 1-5 mL whole blood in EDTA. Ship overnight at ambient temperature, using a cool pack in hot weather. Specimens may be refrigerated for 7 days prior to shipping.
- **Buccal Brushes:** Can be used as an alternative to blood for *TH* sequencing only. Gene deletion/duplication testing requires submission of a blood sample. When sending a buccal sample, use a GeneDx buccal kit (others not accepted). Submit by mail. Buccal brushes are not accepted on children under 6 months of age.
- **Prenatal Diagnosis:** For prenatal testing for a known mutation in the *TH* gene, please refer to the specimen requirements table on our website at: [http://www.genedx.com/test-catalog/prenatal/](http://www.genedx.com/test-catalog/prenatal/). Ship specimen overnight at ambient temperature, using a cool pack in hot weather.

**Required Forms:**

- Sample Submission (Requisition) Form – complete all pages
- Payment Options Form or Institutional Billing Instructions

For test codes, prices, CPT codes, and turn-around-times, please refer to the “*Tyrosine Hydroxylase Deficiency,*” “*Dopa-Responsive Dystonia*” or “*Autosomal Recessive Infantile Parkinsonism*” page on our website: [www.genedx.com](http://www.genedx.com)

**References:**