

Tyrosine Hydroxylase Deficiency-Related Disorders via *TH* Gene Sequencing--Test #159

Brief Description of Clinical Features: Tyrosine hydroxylase deficiency (THD, OMIM 605407) is an autosomal recessive disorder that results from cerebral catecholamine deficiency. THD is heterogeneous in regard to the clinical features and response to Levodopa therapy. At least three different forms of the disease are distinguished: **1. Dopa-responsive dystonia (DRD)** is characterized by onset in early childhood and progressive dystonia with diurnal fluctuation. Symptoms are mild in the mornings and exacerbate during the day. Patients with DRD are treated with low-doses of Levodopa in combination with a decarboxylase inhibitor. **2. Severe progressive encephalopathy** appears during the first months of life and is characterized by truncal hypotonia, rigidity, tremor, and myoclonic jerks and ocular symptoms. Levodopa therapy is usually not effective. **3. Infantile parkinsonism** is characterized by onset before one year of age and mild symptoms. Levodopa therapy is more effective (Doummar et al. *Mov Disord* 24:943-945, 2009). In addition to these three forms, various intermediary phenotypes have been reported. See also Swoboda and Furukawa (GeneReviews, 2008, www.genetests.org).

Genetics: THD is caused by mutations in the *TH* gene (Lüdecke et al. *Hum Genet* 95:123-125, 1995). To date, ~30 different mutations have been described in patients from various populations. Most mutations were missense, however splice site mutations and small deletions were also reported. In addition, homozygous and compound heterozygous mutations in the promoter region were reported in patients with dopa-responsive encephalopathy and dopa-responsive dystonia (Ribasés et al. *Mol Genet Metab* 92:274-277, 2007; Verbeek et al. *Ann Neurol* 62:422-426, 2007). Although heterozygous carriers are usually asymptomatic, exercise-induced stiffness was reported in heterozygous family members (Furukawa et al. *Neurology* 56:260-263, 2001).

Description of This Particular Test: The *TH* gene encodes the tyrosine hydroxylase enzyme, which catalyzes the rate-limiting step in catecholamine biosynthesis. It is expressed mainly in brain and adrenal medulla. This test involves bidirectional DNA sequencing of all 14 coding exons and splice sites of the *TH* gene, and the region of the promoter that harbors the three known regulatory mutations. The full coding sequence of each exon plus ~ 50 bp of flanking DNA on either side are sequenced. As indicated, we will also sequence one (Test #100) or two (Test #200) exons in family members of patients with known mutations or to confirm research results (\$190-340).

Reference Sequences: Genomic: **NC_000011.8** mRNA: **NM_199292.2** protein: **NP_954986.2 (CCDS 7731.1)**

Indications for Test: All patients with symptoms compatible with TH deficiency and autosomal recessive inheritance; and potential heterozygous carriers.

Sensitivity of Test: Unknown

Turn Around Time: Maximum of 40 calendar days, although many tests are completed in 2-3 weeks.

Specimen Requirements: See page 4 of the Requisition Form.

Price: **Sequencing of all coding exons of the *TH* Gene:** **\$ 840**

CPT Codes:

Sample Ascertainment x1	83890 \$ 30	DNA Isolation x1	83891 \$ 40
Amplification x 14	83898 \$ 240	Sequencing x14	83904 \$ 360
Separation x1	83894 \$ 80	Interpretation/Report x1	83912 \$ 90

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

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