

GCH1 Gene Analysis in Dopa-Responsive Dystonia and GTP Cyclohydrolase I Deficiency

Disorder also known as: Hereditary Progressive Dystonia with Marked Diurnal Fluctuation; Dystonia 5 (DYT5); Segawa Syndrome, Dystonia-Parkinsonism with Diurnal Fluctuation

Clinical Features:

Dopa-Responsive Dystonia (DRD) is a treatable neurological condition which can present with a variety of symptoms ranging from dystonia, spastic paraparesis, and proximal weakness to Parkinsonism. A family history of dystonia or Parkinson disease is common. At least 50% of patients have diurnal fluctuation with marked progression of their symptoms toward the end of the day and relief after sleep. The clinical features in patients with mutations in the *GCH1* gene are characterized by pure dystonia with onset in the lower limbs and dramatic improvement with small doses of L-Dopa. Dystonia generally starts in the first decade, but later onset is also observed. In contrast to patients with Juvenile Parkinson's disease, these patients do not usually develop levodopa-induced fluctuations or dyskinesia. There are at least three causative genes for DRD including genes that encode GTP cyclohydrolase 1 (*GCH1*), tyrosine hydroxylase (TH), and sepiapterin reductase (SPR). Females predominate among clinically affected individuals.¹¹ Genetic testing should be guided by the analysis of cerebrospinal fluid levels of biopterin and neopterin, which are low in GTPCH1- deficient DRD.¹¹ Prevalence of DRD in Japan and England is estimated at 1 in 2 million. No increased prevalence has been reported in any ethnic group¹²

GTP Cyclohydrolase I (GTPCH1) deficiency is a disorder of the BH4 biosynthesis pathway, presenting with hyperphenylalaninemia (HPA) associated with monoamine neurotransmitter deficiency. Symptoms of this disorder include intellectual disability, convulsions, tone and posture disturbances, drowsiness, irritability, abnormal movements, recurrent hyperthermia without infections, hypersalivation, and swallowing difficulties. The high levels of phenylalanine are often detected on newborn screening.

Inheritance Pattern/Genetics:

- *GCH1*- related Dopa-Responsive Dystonia – Autosomal Dominant with reduced penetrance
- GTP Cyclohydrolase I deficiency – Autosomal Recessive

Test Methods:

Using genomic DNA obtained from the submitted biological material, bi-directional sequence of the coding region and splice junctions of the *GCH1* gene (exons 1-6) is analyzed. Concurrently, targeted array CGH analysis with exon-level resolution (ExonArrayDx) is performed to evaluate for a deletion or duplication of one or more exons of this gene. repeat analysis using sequencing, restriction fragment analysis, or another appropriate method. 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:

Approximately 80-90% of families with autosomal dominant DRD show pathogenic variants in *GCH1*. Approximately 10% of these variants are large deletions of one or more exons, not detectable by sequencing.^{7,8,10} Penetrance in individuals with GTPCH1-deficient DRD is lower in males (38%) than in females (87%).⁵

References:

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