HESX1 Gene Analysis in Septo-Optic Dysplasia

Disorder also known as: Pituitary hormone deficiency-5 (CPHD5); Growth hormone deficiency with pituitary anomalies

Clinical Features:
Septo-optic dysplasia (SOD) is a disorder of early brain development with a variable phenotype. The diagnosis of this disorder is established by the presence of any combination of optic nerve hypoplasia, pituitary gland hypoplasia, and midline brain abnormalities. The brain abnormalities include absence of the corpus callosum and septum pellucidum.[1] About one-third of people diagnosed with septo-optic dysplasia have all three major features; most affected individuals have two of the major features. Mutations in the HESX1 gene have also been identified in patients with combined pituitary hormone deficiency without other abnormalities being present.[3]

Inheritance Pattern/Genetics:
Autosomal recessive and autosomal dominant with incomplete penetrance.

Test Methods:
Using genomic DNA obtained from the submitted biological material, bi-directional sequencing of all four exons and their respective splice sites of the HESX1 gene is performed. 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:
McNay et al., identified a pathogenic variant in the HESX1 gene in less than 1% of a cohort of 861 patients (724 sporadic, 126 familial, and 11 consanguineous) presenting phenotypes ranging from the complete SOD triad to any one part of the triad.[2] In another study the HESX1 gene was sequenced in 105 patients with the complete SOD triad, 85 patients with isolated pituitary hypoplasia, and 38 patients with holoprosencephaly or a related disorder. This study reported 1 pathogenic variant in the SOD cohort (~1%) and 3 in the cohort with isolated pituitary hypoplasia (~3.5%).[5]

Missense, frameshift, and splice site variants have been reported, as well as an insertion of a 300bp Alu repeat segment.

References:

1. Dattani et al., (1998) Nat Genet 19:125-133
2. McNay et al., (2007) J Clin Endocr Metab 92:691-697
3. Sobrier et al., (2006) J Clin Endocr Metab 91:4528-4536
4. Tajima et al., (2003) J Clin Endocr Metab 88: 45-50
5. Thomas et al., (2001) Hum Molec Genet 10: 39-45
6. Genetic Home Reference: (http://ghr.nlm.nih.gov/condition/septo-optic-dysplasia)