

Holoprosencephaly-3 (Autosomal Dominant Nonsyndromic) via *SHH* Gene Sequencing (Test #581)

Brief Description of Clinical Features: Holoprosencephaly (HPE; OMIM #236100) is a common developmental anomaly of the human forebrain and midface affecting 1 in 16,000 live births (Muenke and Gropman; *GeneReviews*, 2008) and approximately 1 in 200 spontaneous abortions (Orioli et al., *Hum Genet* 109:1-6, 2001). HPE results from failure of the developing forebrain to divide into two hemispheres and ventricles causing a continuum of structural brain malformations ranging from alobar HPE to semilobar HPE to lobar HPE. In addition to the structural brain abnormality, patients with HPE may exhibit variable craniofacial anomalies including cyclopia, ocular hypotelorism, structurally and positionally abnormal proboscis, bilateral cleft lip, anophthalmia or microphthalmia, absent nasal septum, flat nose, or single central incisor. Because incomplete penetrance is a feature of dominantly inherited HPE, relatively normal facial appearance can be seen in individuals who have causative gene mutations and affected first degree relatives. Developmental delay is a nearly constant clinical manifestation of HPE. Other findings include short stature, failure to thrive, seizures, feeding problems, and hypothalamic and brain stem dysfunction. Severely affected newborns with alobar HPE and cyclopia and ethmocephaly usually do not live beyond the first week of life (Croen et al., *Am J Med Genet.* 64:465-472, 1996), but survival is greater in those cases with less severe craniofacial anomalies (Barr and Cohen, *Am J Med Genet.* 89:116-120, 1999). Greater than half of all infants with semilobar or lobar HPE and no other major organ system involvement survive the first year of life (Olsen et al., *Am J Med Genet.* 73:217-226, 1997; Barr and Cohen, 1999).

Genetics: Holoprosencephaly has both genetic and non genetic causes. The most common non genetic cause is maternal diabetes, which confers a risk of 1% to infants of diabetic mothers (Barr et al., *J Pediatr.* 102:565-568, 1983). Chromosome aneuploidy and structural abnormality is the overall single most common cause accounting for 25%-50% of all cases; while another 18%-25% of all cases occur as part of syndromes resulting from single gene mutations (Muenke and Gropman; *GeneReviews*, 2008). Both autosomal recessive and dominant syndromes with HPE as a feature are known. Nonsyndromic HPE is inherited as an autosomal dominant disorder with incomplete penetrance and intrafamilial variable expression. It is estimated that approximately one-third of obligate carriers of autosomal dominant forms of HPE are asymptomatic with normal cognitive function (Cohen, *Teratology* 40:211-35, 1989). Seven causative loci, including five proven genes and one candidate gene (*TMEM1*), have been identified as causes of autosomal dominant nonsyndromic HPE. The five HPE genes are *SHH*, *ZIC2*, *SIX3*, *TGIF*, and *PTCH1*. Another gene, *GLI2*, is associated with facial features typical of HPE, but not typical CNS findings. Over 50 *SHH* mutations, mostly missense, have been documented as causative for HPE3 (OMIM #142945).

Description of This Particular Test: The sonic hedgehog protein is coded by the *SHH* gene located on chr 7q36. Testing is accomplished by amplifying the 3 coding exons and ~50 bp of adjacent noncoding sequence, then determining the nucleotide sequence using standard dideoxy sequencing methods and a capillary electrophoresis instrument.

Reference Sequences: Genomic: NC_000007.12 mRNA and Protein: CCDS 5942.1

Indication for Testing: Individuals with clinical presentations in the HPE spectrum.

Sensitivity of test: *SHH* mutations have been reported to account for 30%-40% of autosomal dominant nonsyndromic HPE and <5% of simplex cases (Nanni et al., *Hum Mol Genet* 8:2479-2488, 1999; Muenke and Gropman; *GeneReviews*, 2008).

Turn Around Time: Maximum of 40 days.

Specimen Requirements: See page 4 of the Requisition Form.

Price: Sequencing of *SHH* \$ 590

CPT Codes:

Sample Ascertainment	83890	\$ 30	DNA Isolation	83891	\$ 40
Amplification x 4	83898	\$ 160	Sequencing x4	83904	\$ 240
Separation	83894	\$ 40	Interpretation/Report	83912	\$ 80

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

Contact: Thomas L. Winder, PhD, FACMG, tom.winder@preventiongenetics.com, www.preventiongenetics.com