

Holoprosencephaly-7 (Autosomal Dominant, Nonsyndromic) via *PTCH1* Sequencing (Test #585)

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 loci, including five documented genes and one candidate gene (*TMEM1*), have been identified as causes of autosomal dominant nonsyndromic HPE. The five HPE genes are *SHH*, *ZIC2*, *SIX3*, *TGIF1*, and *PTCH1*. Another gene, *GLI2*, is associated with facial features typical of HPE, but not typical CNS findings. In addition to HPE, *PTCH1* mutations cause Gorlin syndrome as well as sporadic basal cell carcinoma (Bale and Yu *Hum Mol Genet* 10:757-762, 2001). All HPE7 cases have been found to harbor *PTCH1* missense mutations.

Description of This Particular Test: The protein, homolog of *Drosophila* patched is encoded by the *PTCH1* gene on chr 9q22. In addition to HPE, *PTCH1* mutations also cause Gorlin syndrome as well as sporadic basal cell carcinoma (Bale and Yu, *Hum Mol Genet* 10:757-762, 2001). Testing is accomplished by amplifying the 23 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_000009.10** **mRNA and Protein: CCDS6714.1**

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

Sensitivity of test: *PTCH1* mutations are a rare cause of HPE. Thus far five unrelated individuals with HPE have been found to have *PTCH1* mutations (Ming et al. *Hum Genet* 110:297-301, 2002).

Turn Around Time: Maximum of 40 days.

Specimen Requirements: See page 4 of the Requisition Form.

