

**Holoprosencephaly (Autosomal Dominant, Nonsyndromic)  
 via SHH, ZIC2, SIX3, TGIF1, PTCH1, GLI2 Sequencing (Test #580)**

**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. Mutations of the *SHH* gene are the most common cause of HPE (Roessler et al. *Hum Mutat* 30:E921-930, 2009). 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. 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. Chromosome aneuploidy and structural abnormality are the overall most common cause accounting for 25%-50% of all cases; 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 exist. 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.

**Description of This Particular Test:** Testing is accomplished by sequentially amplifying the coding exons and ~50 bp of adjacent noncoding sequence of each gene, then determining the nucleotide sequence using standard dideoxy sequencing methods and a capillary electrophoresis instrument. The genes will be sequenced in the order specified by the client. The gene tests may also be ordered separately.

**Reference Sequences:**

Gene:	Genomic: NC	mRNA: NM	Protein: NP	mRNA and Protein: CCDS
<i>SHH</i>	000007.12	000193.2	000184.1	5942.1
<i>SIX3</i>	000002.10	005413.2	005404.1	1821.1
<i>PTCH1</i>	000009.10	000264.3	000255.2	6714.1
<i>TGIF1</i>	000018.8	003244.2	003235.1	11834.1
<i>ZIC2</i>	000013.9	007129.2	009060.2	9495.1
<i>GLI2</i>	000002.10	005270.3	005261.2	33283.1

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

**Sensitivity of test:** Mutations in these genes cumulatively account for perhaps 5-10% of HPE (Nanni et al. *Hum Molec Genet* 8:2479-2488, 1999), and approximately 40-50% of cases demonstrating autosomal dominant inheritance (Muenke and Gropman, 2008). One study of 111 patients found 19 to have *de novo* chromosomal anomalies detectable by array-CGH (Bendavid et al. *Hum Mutat* 30:1175-1182, 2009).

**Turn Around Time:** Maximum of 60 days.

**Specimen Requirements:** See page 4 of the Requisition Form.

**Price: Sequential Sequencing of: SHH, ZIC2, SIX3, TGIF1, PTCH1, GLI2**

CPT Codes	SHH	ZIC2	SIX3	TGIF1	PTCH1	GLI2	Entire Panel
83890	\$ 30 (x1)	\$ 30 (x1)	\$ 30 (x1)	\$ 30 (x1)	\$ 30 (x1)	\$ 30 (x1)	\$ 30 (x1)
83891	\$ 40 (x1)	\$ 40 (x1)	\$ 40 (x1)	\$ 40 (x1)	\$ 40 (x1)	\$ 40 (x1)	\$ 40 (x1)
83898	\$ 160 (x4)	\$ 180 (x5)	\$140(x4)	\$ 90 (x3)	\$400(x23)	\$330 (x17)	\$ 1370 (x56)
83904	\$ 240 (x4)	\$ 280 (x5)	\$210(x4)	\$140(x3)	\$600(x23)	\$510 (x17)	\$ 2060 (x56)
83894	\$ 40 (x1)	\$ 40 (x1)	\$ 40 (x1)	\$ 30 (x1)	\$ 90 (x1)	\$ 60 (x1)	\$ 190 (x1)
83912	\$ 80 (x1)	\$ 80 (x1)	\$ 80 (x1)	\$ 60 (x1)	\$130 (x1)	\$120 (x1)	\$ 180 (x1)
<b>Totals:</b>	<b>\$590</b>	<b>\$650</b>	<b>\$540</b>	<b>\$390</b>	<b>\$1290</b>	<b>\$1090</b>	<b>\$3870*</b>

\*When three or more of the genes on this panel are sequentially tested, a 15% discount will apply to the total cost.

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

**Contact:** Thomas L. Winder, PhD, FACMG, [tom.winder@preventiongenetics.com](mailto:tom.winder@preventiongenetics.com), [www.preventiongenetics.com](http://www.preventiongenetics.com)