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Holoprosencephaly Panel

Holoprosencephaly (HPE) is a brain malformation resulting from incomplete separation of the forebrain at 3-5 weeks postconception. Diagnosis is confirmed by brain magnetic resonance imaging (MRI) or computed tomography (CT) imaging. Genetic testing helps families understand the cause of HPE and the risk for recurrence.

DISEASE OVERVIEW

Associated Findings

- Microcephaly (or macrocephaly due to hydrocephalus)
- Central nervous system (CNS) malformations
- Seizures
- Pituitary dysfunction
- Craniofacial abnormalities
- Intellectual disabilities ranging from mild to severe

Types of HPE

Based on degree of brain separation:

- Alobar
- Semilobar
- Lobar
- Middle interhemispheric fusion variant
- Microform HPE

Etiology

Multifactorial, with both genetic and environmental contributions:

- Maternal diabetes mellitus is known environmental risk factor
- Numerical or structural chromosome abnormalities ~25-50%
- Pathogenic single-gene variants

Prevalence

1/250 embryos and 1/10,000-16,000 live births (Edison, 2003; Leoncini, 2008; Matsunaga, 1977)

Inheritance

Dependent on etiology

- Autosomal dominant for all genes tested on HPE panel

Genotype-Phenotype Correlation

- Reduced penetrance
- Variable expressivity depending on gene and variant

TEST DESCRIPTION

See Genes Tested table for genes included in the panel.

TESTS TO CONSIDER

Holoprosencephaly Panel, Sequencing and Deletion/Duplication 2008848
Method: Massively Parallel Sequencing/Exonic Oligonucleotide-based CGH Microarray

Indications for ordering:

To determine etiology of holoprosencephaly (HPE) or determine if parents of an affected individual are carriers (the affected individual should be tested first, if possible).

Holoprosencephaly Panel, Sequencing and Deletion/Duplication, Fetal 2008863
Method: Massively Parallel Sequencing/Exonic Oligonucleotide-based CGH Microarray

Testing strategy:

Because clinical sensitivity of chromosome analysis may approach 50% for HPE, chromosome analysis should be performed before the HPE panel.

Familial Mutation, Targeted Sequencing 2001961
Method: Polymerase Chain Reaction/Sequencing

- Recommended test for a known familial sequence variant previously identified in a family member.
- A copy of the family member's test result documenting the known familial variant is required.

For chromosome analysis testing, see Related Tests

Clinical Sensitivity

- 35-45% for familial holoprosencephaly (Odent, 1999; Orioli, 2001; Nanni, 1999; Roessler, 1996; Roessler, 1997; Brown, 2001; Brown 1998)
- Unknown for sporadic cases

Limitations

- A negative result does not exclude a heritable form of holoprosencephaly.
- Diagnostic errors can occur due to rare sequence variations.
- Interpretation of this test result may be affected if the individual has had an allogeneic stem cell transplantation.
- The following will not be evaluated:
  - Variants outside the coding regions and intron-exon boundaries of the targeted genes
  - Regulatory region variants and deep intronic variants
  - Breakpoints of large deletions/duplications
  - Deletions/duplications in *CDON, FGFR1,* and *GLI3*
  - Noncoding transcripts
- The following exons are not sequenced due to technical limitations of the assay: *ZIC2* (NM_007129) 3
- The following may not be detected:
  - Deletions/duplications/insertions of any size by massively parallel sequencing
  - Deletions/duplications less than 1kb in the targeted genes by array
  - Some variants due to technical limitations in the presence of pseudogenes, repetitive, or homologous regions
  - Low-level somatic variants
  - Single exon deletions/duplications in the following exons:
    - *FGF8* (NM_033163) 1; *PTCH1* (NM_001083602) 1; *SHH* (NM_001310462) 2

Analytical Sensitivity

For massively parallel sequencing:

Variant Class	Analytical Sensitivity (PPA) Estimate[a] (%)	Analytical Sensitivity (PPA) 95% Credibility Region[a] (%)
SNVs	99.2	96.9-99.4
Deletions 1-10 bp	93.8	84.3-98.2
Deletions 11-44 bp	100	87.8-100
Insertions 1-10 bp	94.8	86.8-98.5
Insertions 11-23 bp	100	62.1-100

[a]Genes included on this test are a subset of a larger methods-based validation from which the PPA values are derived.

bp, base pairs; PPA, positive percent agreement; SNVs, single nucleotide variants

Genes Tested

Gene	Alias Symbol(s)	MIM Number	Disorder
CDON	ORCAM, CDO, CDON1	608707	Holoprosencephaly 11
DISP1	DISPA, MGC13130, DKFZP434I0428, MGC16796	607502	Holoprosencephaly 10, microform
FGF8	AIGF	600483	Hypogonadotropic hypogonadism 6 with or without anosmia
FGFR1	FLT2, KAL2, H2, H3, H4, H5, CEK, FLG, BFGFR, N-SAM, CD331	136350	Hypogonadotropic hypogonadism 2 with or without anosmia Hartsfield syndrome
FOXH1	FAST1	603621	
GLI2	THP2, HPE9, THP1	165230	Holoprosencephaly 9 Culler-Jones syndrome
GLI3	GCPS, PHS, PAP-A, PAPA, PAPA1, PAPB, ACLS, PPDIV	165240	Pallister-Hall syndrome

Gene	Alias Symbol(s)	MIM Number	Disorder
NODAL		601265	Nodal-related holoprosencephaly
PTCH1	NBCCS, PTCH, BCNS	601309	Holoprosencephaly 7
SHH	HPE3, HLP3, HHG1, SMMCI, TPT, TPTPS, MCOPCB5	600725	Holoprosencephaly 3 solitary median maxillary central incisor
SIX3	HPE2	603714	Holoprosencephaly 2
TGIF1	HPE4, TGIF	602630	Holoprosencephaly 4
ZIC2	HPE5	603073	Holoprosencephaly 5

REFERENCES

Brown LY, Odent S, David V, Blayau M, Dubourg C, Apacik C, Delgado MA, Hall BD, Reynolds JF, Sommer A, Wieczorek D, Brown SA, Muenke M. Holoprosencephaly due to mutations in ZIC2: alanine tract expansion mutations may be caused by parental somatic recombination. Hum Mol Genet. 2001; 10(8): 791-6. PubMed

Brown SA, Warburton D, Brown LY, Yu CY, Roeder ER, Stengel-Rutkowski S, Hennekam RC, Muenke M. Holoprosencephaly due to mutations in ZIC2, a homologue of Drosophila odd-paired. Nat Genet. 1998; 20(2): 180-3. PubMed

Edison R, Muenke M. The interplay of genetic and environmental factors in craniofacial morphogenesis: holoprosencephaly and the role of cholesterol. Congenit Anom (Kyoto). 2003; 43(1): 1-21. PubMed

Leoncini E, Baranello G, Orioli IM, Annerén G, Bakker M, Bianchi F, Bower C, Canfield MA, Castilla EE, Cocchi G, Correa A, De Vigan C, Doray B, Feldkamp ML, Gatt M, Irgens LM, Lowry B, Maraschini A, Donnell RM, Morgan M, Mutchinick O, Poetzsch S, Riley M, Ritvanen A, Gnansia ER, Scarano G, Sipek A, Tenconi R, Mastroiacovo P. Frequency of holoprosencephaly in the International Clearinghouse Birth Defects Surveillance Systems: searching for population variations. Birth Defects Res A Clin Mol Teratol. 2008; 82(8): 585-91. PubMed

Matsunaga E, Shiota K. Holoprosencephaly in human embryos: epidemiologic studies of 150 cases. Teratology. 1977; 16(3): 261-72. PubMed

Nanni L, Ming JE, Bocian M, Steinhaus K, Bianchi DW, Die-Smulders C, Giannotti A, Imaizumi K, Jones KL, Campo MD, Martin RA, Meinecke P, Pierpont ME, Robin NH, Young ID, Roessler E, Muenke M. The mutational spectrum of the sonic hedgehog gene in holoprosencephaly: SHH mutations cause a significant proportion of autosomal dominant holoprosencephaly. Hum Mol Genet. 1999; 8(13): 2479-88. PubMed

Orioli IM, Vieira AR, Castilla EE, Ming JE, Muenke M. Mutational analysis of the Sonic Hedgehog gene in 220 newborns with oral clefts in a South American (ECLAMC) population. Am J Med Genet. 2002; 108(1): 12-5. PubMed

Roessler E, Belloni E, Gaudenz K, Jay P, Berta P, Scherer SW, Tsui LC, Muenke M. Mutations in the human Sonic Hedgehog gene cause holoprosencephaly. Nat Genet. 1996; 14(3): 357-60. PubMed

Roessler E, Belloni E, Gaudenz K, Vargas F, Scherer SW, Tsui LC, Muenke M. Mutations in the C-terminal domain of Sonic Hedgehog cause holoprosencephaly. Hum Mol Genet. 1997; 6(11): 1847-53. PubMed

RELATED TESTS

Chromosome Analysis, Peripheral Blood 2002289
Method: Giemsa Band

Chromosome Analysis, Amniotic Fluid 2002293
Method: Giemsa Band

Chromosome Analysis, Products of Conception 2002288
Method: Giemsa Band