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High Intellectual Function in Individuals with Mutation-Positive Microform Holoprosencephaly

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FGF8 · *GLI2* · Holoprosencephaly · HPE · Microform · *SHH* · *SIX3* · Sonic Hedgehog

Abstract
Holoprosencephaly is the most common malformation of the forebrain and typically results in severe neurocognitive impairment with accompanying midline facial anomalies. Holoprosencephaly is heterogeneous and may be caused by chromosome aberrations or environmental factors, occur in the context of a syndrome or be due to heterozygous mutations in over 10 identified genes. The presence of these mutations may result in an extremely wide spectrum of severity, ranging from brain malformations incompatible with life to individuals with normal brain findings and subtle midline facial differences. Typically, clinicians regard intellectual disability as a sign that a parent or relative of a severely affected patient may be a mildly affected mutation 'carrier' with what is termed microform holoprosencephaly. Here we present 5 patients with clear phenotypic signs of microform holoprosencephaly, all of whom have evidence of above-average intellectual function. In 4 of these 5 individuals, the molecular cause of holoprosencephaly has been identified and includes mutations affecting *SHH*, *SIX3*, *GLI2*, and *FGF8*. This report expands the phenotypic spectrum of holoprosencephaly and is important in the counseling of patient and affected families.

Holoprosencephaly (HPE), the most common malformation of the human forebrain, results from failed forebrain separation in early gestation. HPE is etiologically heterogeneous, and causes include environmental factors, syndromes that include HPE as one of a combination of features, chromosome aberrations, and heterozygous mutations in over 10 identified genes. In this latter circumstance, mutations may arise de novo or be inherited. Inherited forms are classically autosomal dominant with a wide range of phenotypic expression. At the more severe end of the spectrum, patients may have frank HPE, with incomplete cerebral hemispheric separation and accompanying midline craniofacial anomalies related to abnormal signaling from the region of the developing forebrain [Cohen, 2006; Hahn and Barnes, 2010; Roessler and Muenke, 2010; Solomon et al., 2010; Mercier et al., 2011]. At the mildest end of the spectrum, often termed 'microform' HPE, patients may have normal brains by conventional neuroimaging, but display subtle craniofacial anomalies consistent with a midline defect, including hypotelorism (closely spaced eyes), a flat or sharp nasal bridge, choanal stenosis, or a single maxillary central incisor (SMCI) [Cohen, 2006; Lacbawan et al., 2009; Solomon et al., 2009, 2010; Mercier et al., 2011]. Traditionally, mild neurocognitive impairment has been thought to correlate with the presence of a mutation in microform individuals [Solomon et al., 2010]. However, we present a series of 5 patients with micro-

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Table 1. Summary information of patients described here

Patient	Features consistent with microform HPE	Genetic etiology	Neuroimaging findings (MRI)	Evidence of intellectual function
1	hypotelorism, sharp nasal bridge, choanal stenosis, SMCI	*FGF8*: c.686C>T, p.Thr229Met	Chiari I malformation, otherwise normal brain	skipped a grade in school, high scores on school achievement testing; FS-IQ: 141
2	microcephaly, hypotelorism, SMCI	*SHH*: c.584_598del, p.196_200del	normal	honors student
3	microcephaly, midface hypoplasia, flat nasal bridge, severe hypotelorism	unknown	normal	advanced early milestones and school placement
4	midface hypoplasia	*GLI2*: deletion (ascertained by microarray): arr 2q14.2(121,412,559–121,530,829) × 1 mat (NCBI36/hg18)	Chiari I malformation, small, ectopic pituitary, otherwise normal brain	advanced early milestones; FS-IQ: 118
5	unknown	*SIX3*: c.100G>C, p.Gly34Arg	normal	advanced early milestones and school placement

FS-IQ = Full-scale intelligence quotient; MRI = magnetic resonance imaging; SMCI = single maxillary central incisor.

form HPE, 4 of whom had identified mutations in HPE-associated genes, who all had evidence for above-normal intelligence.

Subjects and Methods

Patients are referred to our National Human Genome Research Institute IRB-approved research protocols on HPE for molecular genetic studies involving known and candidate HPE-associated genes; a selected subset of individuals are invited to the National Institutes of Health (NIH) Clinical Center for evaluation. Informed consent is obtained from all participants.

Results

Summary Data

Sixty-one patients were seen at the NIH Clinical Center in a 4-year period (2007–2011). Of these, 46/61 (75%) had severe HPE, while the remaining 15/61 (25%) had microform HPE. We present 5 individuals with microform HPE (4 of whom were found to have an HPE-associated mutation) who had evidence of above-average intelligence. Magnetic resonance imaging of these 5 individuals, which were reviewed by clinicians and neuroradiologists highly familiar with HPE, did not show any signs of HPE or any other midline anomalies, though patients 1 and 4 had Chiari I malformations, and patient 4 had a small, ectopic pituitary. Patients 1–4 (below) were examined in person at the NIH Clinical Center; patient 5 provided medical details via phone and e-mail.

Patient Descriptions

Patient 1

This 8-year-old female patient (for all patient descriptions see table 1) carries a maternally-inherited mutation in *FGF8*: c.686C>T, p.Thr229Met [Arauz et al., 2010]. Her dizygotic twin, who also had this mutation, passed away secondary to sequelae of severe HPE. Patient 1 had facial features of microform HPE, including marked hypotelorism, a sharp nasal bridge, choanal stenosis, and SMCI. Due to high intellectual ability, patient 1 'skipped a grade' during early education and standardized school-based achievement tests results were reported to be at the upper limits of the achievement percentiles for her age. Full-scale IQ was measured at 141.

Patient 2

This 2-year-old male patient carries a maternally-inherited mutation in *SHH*: c.584_598del, p.196_200del [Roessler et al., 2009]. This mutation was also found in the patient's deceased brother, who had severe HPE. Patient 2 had clear features of microform HPE, including microcephaly (head circumference 2 SD below the mean), hypotelorism and a SMCI. He has ADHD, but excels at school, is an honors student and plans to pursue a career in genetics.

Patient 3

This 3-year-old female patient presents with classic facial findings of microform HPE, including microcephaly (head circumference 1 SD below the mean), midface hypoplasia with a flat na-

sal bridge, and severe hypotelorism. She had no mutations in the genes commonly associated with HPE, but had a paternally-inherited *GLI2* variant not thought to be clinically significant (family history is noncontributory). Early milestones were advanced; for example, she combined words at 15 months of age, was toilet-trained at 22 months of age, could recognize all letters at 36 months of age, and started school early because of precocity.

Patient 4

This 3-year-old female patient carries a maternally-inherited pure deletion of almost the entire *GLI2* gene initially detected by microarray comparative genomic hybridization (arr 2q14.2(121,412,559–121,530,829)×1 mat (NCBI36/hg18), SignatureChipOS oligoarray 105K, Signature Genomics, Wash., USA) and confirmed by FISH. She was nondysmorphic except for very mild midface hypoplasia, and she did not have microcephaly. Medical issues related to *GLI2* deletion included isolated growth hormone deficiency (detailed endocrinological testing did not reveal any other abnormalities), failure to thrive and a history of right postaxial polydactyly. Early milestones were advanced; full-scale IQ was measured at 118.

Patient 5

This patient is a 5-year-old female with a maternally-inherited mutation in *SIX3*: c.100G>C, p.Gly34Arg, which was also present in her maternal half-brother, who had severe HPE. She was able to speak in full sentences by the age of 12–15 months, was toilet-trained at 16 months, and in early childhood, was placed in a class for gifted children.

Discussion

When encountering families affected by HPE, clinicians often inquire about the presence of cognitive impairment in an effort to identify mildly affected mutation carriers. However, the patients described here function at the high end of the cognitive spectrum despite the presence of a pathogenic HPE-associated mutation and/or clear features of microform HPE. As these facial anomalies result from abnormal forebrain signaling, their intellectual functioning is especially remarkable.

Admittedly, a significant limitation in our data is the lack of standardized neurocognitive testing confirming these patients' intellectual capabilities. However, the aims of this report are to raise awareness of average or possibly above-average cognitive skills within the phenotypic spectrum of HPE and in mutation-positive individuals, and to facilitate the identification of previously unrecognized mutation carriers. Hopefully, this information will aid patient and family education, counseling, and reproductive decision-making.

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