Published in final edited form as:

Am J Med Genet A. 2009 July ; 149A(7): 1592–1594. doi:10.1002/ajmg.a.32940.

Maternally Inherited Heterozygous Sequence Change in the Sonic Hedgehog Gene in a Male Patient with Bilateral Closed-Lip Schizencephaly and Partial Absence of the Corpus Callosum

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TO THE EDITOR

Mutations in the human Sonic Hedgehog (*SHH*; OMIM *600725) gene can result in severe brain malformations. Haploinsufficiency of *SHH* has been shown to cause not only midline structure defects such as holoprosencephaly (HPE, OMIM #142945) and corpus callosum agenesis but also developmental delays [Muenke and Cohen, 2000; Roessler et al., 1996] and/or craniofacial dysmorphic features including microcephaly, hypotelorism, isolated microphthalmia with coloboma [OMIM #611638; Schimmenti et al., 2003], preaxial polydactyly type II [OMIM #174500; Lettice et al., 2003], or a solitary median maxillary central incisor [Nanni et al., 1999, 2001]. *SHH* mutations have also been identified in asymptomatic parents that have affected children. It has been shown that the clinical variability can be striking within a single pedigree from individuals with the full range of holoprosencephaly, microforms, and even clinically normal individuals carrying a *SHH* mutation [Roessler et al., 1996, 1997; Nanni et al., 1999; Hehr et al., 2004].

We describe a boy who is the first child of unrelated healthy parents. He was delivered after an uneventful pregnancy at 39 weeks gestation. His birth length (50 cm), birth weight (3,240 g), and head circumference at birth (34 cm) were all within the normal range (>50th centile). While the neonatal period was described as normal, he had muscular hypotonia and was visually inattentive when he was first presented at the age of 5 months.

Magnetic resonance imaging of the brain revealed a complex brain malformation with partial absence of the corpus callosum, bilateral parietotemporal closed-lip schizencephaly, polymicrogyria and optic atrophy (Figs. 1–3).

At the age of 10 months (Fig. 4) he presented with developmental delay and distinct dysmorphic features. He was able to sit unassisted at the age of 8 months but was not able to crawl at the age of 10 months. The dysmorphic features included microbrachycephaly, hypotelorism, broad

nasal root, short philtrum, and a thin upper lip. His height (75 cm; >50th centile) and weight (8.5 kg; 25th centile) were within the normal range, while his head circumference (41.5 cm) was below the normal range (<3rd centile).

Chromosomal analysis was normal (GTG-banding; 450–500 band level). Mutation analysis of the *EMX2* gene was performed as mutations in this gene have been previously reported in bilateral schizencephaly [Brunelli et al., 1996; Faiella et al., 1997; Tietjen et al., 2007]. All three exons were sequenced including the exon–intron boundaries. No mutations were identified.

Mutation analysis of the *SHH* was also performed. Fragments of the *SHH* gene (exons 1–3) were amplified by PCR and sequenced as described previously [Hehr et al., 2004]. *SHH* analysis revealed a DNA sequence change predicting Gly290Asp in exon 3 in one copy of the gene. This alteration was first published by Nanni et al. [1999] in the case of a 20-year-old woman with holoprosencephaly. The Gly290Asp alteration was not detected by these authors in > 200 Caucasian and >200 Hispanic controls.

Analyses of the child's parents showed that the phenotypically normal mother carries the same heterozygous alteration in the *SHH* gene. No other family members were available for testing. Magnetic resonance imaging of the brain of the mother was unremarkable.

SHH mutations have been shown to be causative in midline structure defects, such as holoprosencephaly (HPE), corpus callosum agenesis and/or craniofacial dysmorphic features. They have, however, not yet been reported to be involved in the occurrence of bilateral parietotemporal closed-lip schizencephaly. To the best of our knowledge, this is the first report of a patient with schizencephaly who has a missense alteration in the *SHH* gene. In addition to a bilateral parietotemporal schizencephaly, the patient also had partial absence of the corpus callosum, polymicrogyria and optic atrophy. Further studies including animal models will be needed to further elucidate the role of *SHH* in brain development and the spectrum of different brain and craniofacial phenotypes resulting from *SHH* mutations.

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FIG. 1.

The axial T1-weighted MR image demonstrates a bilateral closed-lip schizencephaly lined with dysplastic gray matter (arrows). In addition, polymicrogyria is present in the area of the clefts as well as in the frontal lobes bilaterally.

FIG. 2.
The sagittal T2-weighted image shows a partial absence of the posterior part of the corpus callosum (arrow).

FIG. 3.
The coronal STIR-image demonstrates bilateral optic atrophy (arrows).

FIG. 4. Patient at the age of 10 months. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]