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EMX2-Independent Familial Schizencephaly: Clinical and Genetic Analyses

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Schizencephaly is a human brain malformation distinguished by full-thickness unilateral or bilateral clefts through the neocortex. Heterozygous mutations in the *EMX2* locus are reported to give rise to schizencephaly. However, the comprehensive identification of causative genetic loci is precluded by a lack of large pedigrees and genome-wide linkage analyses. We present here a large Turkish pedigree with three individuals with schizencephaly. The similarity of clinical signs in affected individuals strongly suggests an underlying genetic cause; however, genome-wide linkage analysis rules out *EMX2* linkage and instead suggests additional candidate loci. These results indicate that genetic forms of schizencephaly are likely to be heterogeneous.

KEY WORDS: familial schizencephaly; brain malformation; epilepsy; polymicrogyria; *EMX2*

INTRODUCTION

Schizencephaly is a human congenital brain malformation characterized by a full-thickness cleft in one or both cerebral hemispheres [reviewed in Barkovich, 2000; Guerrini and Carrozo, 2001; Battaglia and Granata, 2003]. Cleft lips were first described as fused in a pial-ependymal seam (closed-lip) or separated with the resulting gap filled with cerebrospinal fluid (open-lip) [Yakovlev and Wadsworth, 1946a,b]. Schizencephalic clefts are often found in the perisylvian region and lined with poorly laminated gray matter, polymicrogyria, and heterotopia. Schizencephaly is also associated in some cases with microcephaly, hydrocephalus, or other malformations such as septo-optic dysplasia [Barkovich and Kjos, 1992; Packard et al., 1997; Denis et al., 2000]. The advent of magnetic resonance imaging (MRI) techniques has afforded more descriptive diagnoses of cortical malformations, even at prenatal ages [Denis et al., 2001], and shown that cortical malformations such as schizencephaly are a frequent cause of mental retardation, epilepsy, and motor deficits [Barkovich and Kjos, 1992; Packard et al., 1997; Barkovich, 2000; Denis et al., 2000; Hayashi et al., 2002]. Individuals with schizencephaly can display a variety of clinical signs including developmental delay of cognitive and language functions, motor deficits such as hemiparesis or quadriparesis, hypotonicity, and epileptic seizures [Barkovich and Kjos, 1992; Barkovich, 2000; Battaglia and Granata, 2003]. The severity of clinical features can vary widely among individuals, but bilateral and/or open-lip lesions tend to result in more pronounced symptoms [Barkovich and Kjos, 1992; Packard et al., 1997; Denis et al., 2000].

Although vascular disruptions, cytomegalovirus (CMV) infection, and other environmental insults during early gestation are postulated as causes of schizencephaly [Yakovlev and Wadsworth, 1946a,b; Barkovich and Kjos, 1992; Iannetti et al., 1998; Sener, 1998; Barkovich, 2000], reported cases of familial schizencephaly suggest that genetic components are also involved [Hosley et al., 1992; Hilburger et al., 1993; Haverkamp et al., 1995]. Mutations in the *EMX2* transcription factor locus, for example, are associated with schizencephaly in several sporadic and familial cases [Brunelli et al., 1996; Faiella et al., 1997; Granata et al., 1997]. Genetic analysis of additional families with schizencephaly should allow for the identification of additional causative genes, which in turn may provide insights into *EMX2* function and/or other aspects of neocortex development. However, additional genetic loci responsible for schizencephaly remain unknown, in part because large pedigrees of affected individuals have yet to be described and severely-affected individuals rarely have children, thus precluding informative genome-wide linkage analysis screens.

Here we identify a large family with three individuals affected by schizencephaly in a stereotyped radiographic pattern. The clinical features of affected individuals are comparatively mild, as all three have relatively preserved intelligence and two have completed primary schooling and started families. Microsatellite marker analysis for this pedigree rules out linkage to *EMX2* and suggests linkage to other chromosomal locations. These observations suggest that familial schizencephaly is likely to have multiple genetic causes.

MATERIALS AND METHODS

Subjects

Analyses were performed on three affected individuals, two children, six unaffected siblings, and their parents. Informed consent was obtained from all patients and/or their parents in accordance with protocols approved by the institutional review

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Ian Tietjen, Füsun Erdogan, and Sophie Currier contributed equally to this work.

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board of Boston Children's Hospital. Consent for the use of identifiable photographs was obtained from the family. All affected individuals were examined by a clinical neurologist. Neuroimaging was performed on affected individuals with a Philips 1.5T MRI scanner (Best, the Netherlands) using conventional multiplanar T1- and T2-weighted sequences.

Linkage Analysis

Genomic DNA was extracted from peripheral whole blood lymphocytes using previously described protocols (Qiagen, Valencia, CA). A 10 cM average genomewide screen was performed using ~400 fluorophore-labeled PCR primer pairs (ABI Prism Linkage Mapping Set v. 2.5) spanning highly polymorphic microsatellite regions. Additional microsatellite markers as annotated in the human genome (July 2003 version, UCSC genome bioinformatics, http://genome.ucsc.edu) were then analyzed in chromosomal regions of interest using individually designed PCR primers (Sigma-Genosys, The Woodlands, TX) or commercially available microsatellite primer pairs (Invitrogen, Carlsbad, CA). PCR products of patient samples were run on an ABI Prism 3100 genetic analyzer. Alleles were determined using standard software (Genotyper Analysis). Two-point and multipoint logarithm of the odds (LOD) scores were determined using the GeneHunter and Allegro statistical software programs [Kruglyak et al., 1996; Gudbjartsson et al., 2000].

For analysis of linkage to *EMX2* and additional candidate loci, data were analyzed for recessive, paternal dominant, and maternal dominant modes of inheritance. For dominant modes of inheritance, a susceptibility allele with frequency 0.001 and penetrance 0.9 was assumed. For recessive modes of inheritance, a susceptibility allele with frequency 0.001 and penetrance 0.99 was assumed. For each marker, four alleles at equal frequencies were assumed.

Sequencing

To sequence *EMX2* in affected and unaffected individuals, PCR primers were designed to flank the exons and adjacent intron boundaries of *EMX2* using standard software (Primer 3). *EMX2* sequencing coverage was performed to the same extent as described previously [Brunelli et al., 1996]. *EMX2* exons and adjacent intron boundaries were PCR amplified from genomic DNA of affected and unaffected individuals, and PCR products were purified (Qiagen) and sequenced at the Dana-Farber/Harvard Cancer Center High-Throughput DNA Sequencing Facility. Sequence information was compared against annotated *EMX2* genomic sequence (July 2003 version, UCSC genome bioinformatics, http://genome.ucsc.edu).

RESULTS

Clinical and Radiological Features

The pedigree described in this report is illustrated in Figure 1A. The parents deny any relation to one another but grew up in neighboring villages. Although MRI could not be performed on the parents, the clinical examination and mental status of both parents are normal. The parents have six unaffected (II:1–II:3, II:5–II:7) and three affected (II:8, II:9, II:11) living offspring. The parents also had three children that died in the newborn period reportedly from febrile disease and lower respiratory tract infections (II:4, II:13, II:14). The mother also had three additional miscarriages whose timings are not known. No obvious changes in environmental or maternal habits were reported from the family during each of the pregnancies. All six unaffected offspring are married and have had offspring of their own, all of whom are unaffected

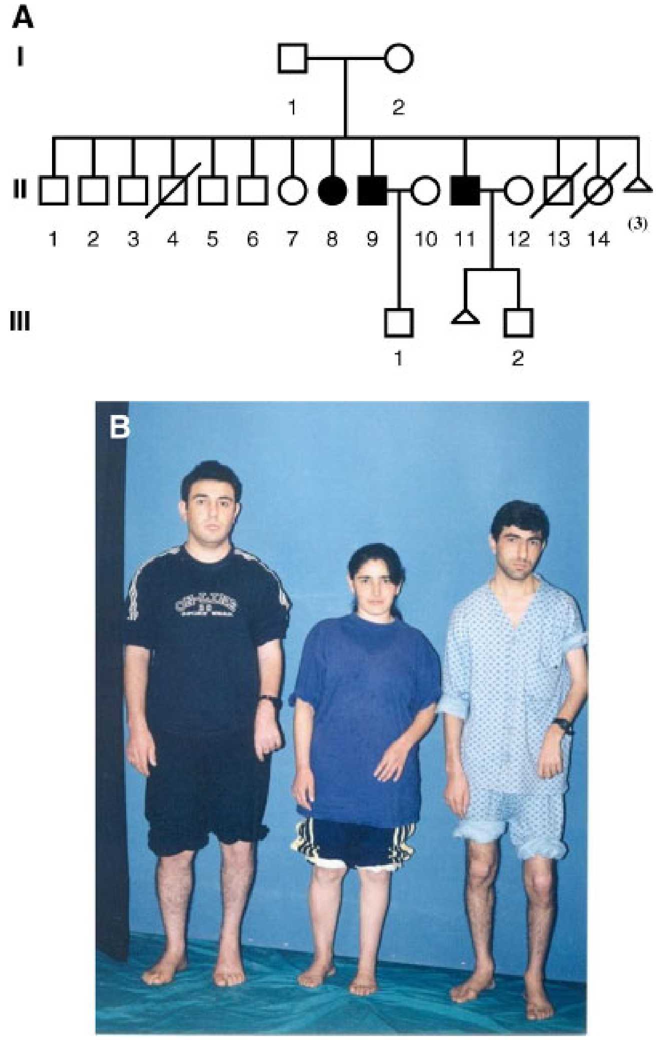

Fig. 1. **A**: Pedigree. Black symbols, affected individuals; slashes, neonatal deaths; triangles, miscarriages. Individuals are ordered according to age. The timing of miscarriages of individual I:2 is not known. Children of individuals II:1–II:7 are not shown. **B**: Individuals II:9, II:8, and II:11 (left to right), with apparent left-sided hemiplegia and hemiatrophy. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

(data not shown). Of the three affected living offspring, two are married with one unaffected child each (III:1–III:2). No additional pregnancy losses were reported except for one miscarriage by unaffected individual II:12 coinciding with trauma resulting from a fall.

The three affected individuals display highly similar clinical signs including left spastic hemiparesis and hemiatrophy (Fig. 1B) and seizures characterized by head turning to the left side and left-sided clonic movements with subsequent secondary generalization. Seizures were reported to begin from age 15 (Individual II:9, II:11) to age 20 (Individual II:8). Additional signs include dysarthric speech and choreoathetosis in the left hand. Individuals II:9 and II:11 finished primary school, but individual II:8 did not complete primary school and is illiterate. Verbal IQs for individuals II:9, II:11, and II:8, respectively, were 86, 79, and 64, while performance IQs were 54, 82, and 50. Neuropsychological testing of individuals II:9 and II:11 revealed dyslexia, constructional apraxia, impairment of verbal fluency, dysgraphia, and difficulties in recognizing and comparing figures.

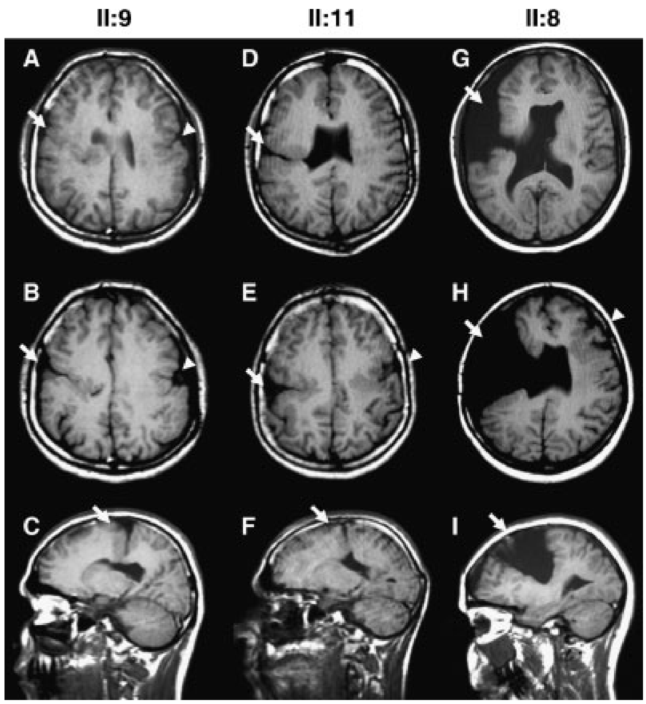

Fig. 2. Representative T1-weighted axial (**A**, **B**, **D**, **E**, **G**, **H**) and sagittal (**C**, **F**, **I**) magnetic resonance imagings (MRIs) of individuals affected with schizencephaly. A, D, and G, respectively, show sections inferior to B, E, and H. A–C: MRI of patient II:9 showing a right-sided, closed-lip cleft (arrows) and contralateral polymicrogyria (arrowheads). D–F: MRI of patient II:11 showing a small, right-sided open-lip cleft (arrows) and left-side dysplastic cortex (arrowhead). G–I: MRI of patient II:8 showing right-sided open-lip schizencephaly (arrows) and contralateral dysplastic infolding (arrowhead).

Brain MRIs of affected individuals were remarkably consistent (Fig. 2). Individual II:9 displayed a closed-lip cleft in the right posterior frontal and suprasylvian cortex (Fig. 2A–C, arrows), while focal polymicrogyria was seen in the left hemisphere at comparable rostral–caudal levels (Fig. 2A,B, arrowheads). Individual II:11 showed a small, open-lip cleft lined by polymicrogyric gray matter from the posterior end of the right Sylvian fissure to the mid-right lateral ventricle (Fig. 2D–F, arrows), while deep infolding of dysplasic cortex to the ventricular surface was observed on the left (Fig. 2E, arrowhead). Individual II:8 showed a large, open-lip cleft from the superior portion of the right Sylvian fissure to the mid-body of the right lateral ventricle with polymicrogyria (Fig. 2G–I, arrows), in addition to deep dysplastic infolding of the cortex of the left frontal lobe that approached the frontal horn and was associated with polymicrogyria (Fig. 2H, arrowhead). For each affected individual, MRI examinations also revealed an enlarged right trigone of the right lateral ventricle, a thin posterior body of the corpus callosum, and absence of a septum pellucidum. White matter volume was slightly reduced, most notably in the right hemisphere of individual II:8. Intracranial calcifications, an indication of congenital CMV infection [Iannetti et al., 1998; Sener, 1998], were not detected. All other aspects of the brain appeared normal.

Analysis of EMX2 Linkage

The similarity of clinical and radiological findings in affected individuals strongly suggested a genetic influence. We, therefore, obtained genomic DNA from peripheral-blood lymphocytes from the parents, the six unaffected and three affected offspring, and the two children of affected individuals. A 10 cM genome-wide linkage screen was performed for each individual using microsatellite markers, and data were analyzed assuming recessive, paternal dominant, and maternal dominant modes of inheritance.

Heterozygous *EMX2* mutations are implicated in schizencephaly [Brunelli et al., 1996; Faiella et al., 1997; Granata et al., 1997]. We, therefore, investigated the probability of *EMX2* linkage in this family. Microsatellite markers flanking the *EMX2* locus generated maximal multipoint LOD scores <-5.00 for recessive and paternal dominant modes of inheritance, thereby excluding linkage under these models, and <0 for maternal dominant inheritance (Fig. 3A–C). Thus no significant evidence for linkage to the *EMX2* locus was identified, although dominant linkage from the mother, albeit very unlikely, could not be completely excluded.

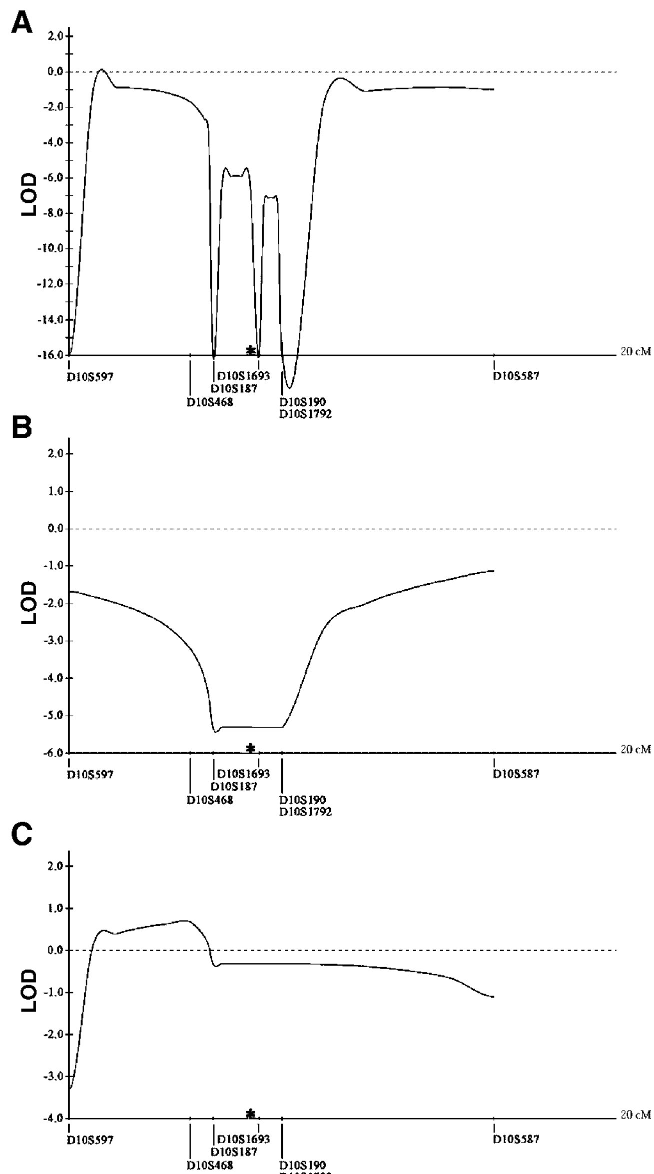

Fig. 3. No significant linkage to *EMX2* is detected, as assessed by analysis of microsatellite markers flanking the *EMX2* locus. Multipoint LOD scores (*y*-axis) are shown assuming (**A**) recessive, (**B**) paternal dominant, and (**C**) maternal dominant modes of inheritance. The approximate location of the *EMX2* locus (*) and relative genetic map distances for each marker (*x*-axis) are shown.

It remained possible, although improbable, that the family harbored an *EMX2* mutation with low penetrance that might not be detected by standard linkage analyses. For example, although both parents (I:1, I:2) showed no clinical signs of schizencephaly, one or both parents could be genetic mosaics in which an *EMX2* mutation is carried in a fraction of the germline. Moreover, a specific point mutation in the *EMX2* homeodomain has been reported where the mother has no clinical signs but can pass the mutated allele and schizencephaly onto her children [Brunelli et al., 1996; Faiella et al., 1997]. We, therefore, sequenced the *EMX2* gene of affected individuals. No mutations were identified in the *EMX2* coding sequence and $\geq$100 bp of flanking intron sequence, including all regions where *EMX2* mutations have been described previously [data not shown; Brunelli et al., 1996; Faiella et al., 1997; Granata et al., 1997]. Thus, although it remains possible that one or more unreported, noncoding *EMX2* mutations with low penetrance are present in this family, the simpler interpretation of these observations is a lack of significant linkage to the *EMX2* locus.

Potential Linkage to Other Genomic Regions

We then searched additional genomic regions for linkage to schizencephaly. Assuming a recessive mode of inheritance, microsatellite markers at Chromosome 8q24.22-24.3 generated a maximal multipoint LOD score of 1.95 and, therefore, could not be ruled out (D8S256-D8S1836; data not shown). No significant LOD scores were detected assuming dominant inheritance from the father. However, by assuming a dominant maternal mode of inheritance, microsatellite markers at Chromosome 5q21.3-23.2 suggested linkage with a maximal two-point LOD score of 2.68 (D5S433-D5S2059; data not shown). Chromosome 8q24.22-24.3 and Chromosome 5q21.3-23.2 thus represent promising regions in which to search for causative loci of schizencephaly.

DISCUSSION

We have described a large pedigree with a familial form of schizencephaly. Radiological features in affected individuals correspond well to previously described findings [Barkovich and Kjos, 1992; Packard et al., 1997; Denis et al., 2000]. However, the clinical features in this family are relatively mild, as two of three affected individuals successfully completed primary school and have started families. The observation that the three youngest surviving children are affected is striking and, at first glance, could implicate environmental causes leading to prenatal injury. However, CMV infection is unlikely as intracranial calcifications were not detected by MRI [Fig. 2; Iannetti et al., 1998; Sener, 1998]. In addition, an environmental predisposition for prenatal injuries resulting from vasculopathy, autoimmune thrombocytopenia, vascular occlusions, or other insults is also unlikely as they would be expected to cause variable clinical and radiological findings [Norman, 1980; Barkovich and Kjos, 1992; Kuijpers et al., 1994; Landrieu and Lacroix, 1994; Suchet, 1994; Hahn and Lewis, 2003]. Instead, the consistency of clinical and radiological findings in affected individuals described here, combined with the identification of candidate genomic loci, raise the strong possibility of an underlying genetic cause.

Multiple spontaneous and familial cases of schizencephaly have been linked to heterozygous mutations in *EMX2*, which were identified by direct sequencing of the *EMX2* gene in affected individuals [Brunelli et al., 1996; Faiella et al., 1997; Granata et al., 1997]. *EMX2* encodes a homeodomain transcription factor implicated in neural precursor proliferation, cortical plate lamination, and proper positioning of area-specific domains of the developing mammalian neocortex [Bishop et al., 2000; Mallamaci et al., 2000a,b; Heins et al., 2001; Galli et al., 2002; Fukuchi-Shimogori and Grove, 2003; Hamasaki et al., 2004]. In humans, specific *EMX2* mutations identified in individuals with schizencephaly are predicted to cause frameshift mutations or interfere with mRNA splicing, while the effects of other identified mutations are less clear. However, "severe" *EMX2* mutations tend to correspond to bilateral, open-lip schizencephaly cases, while missense mutations tend to correlate with less severe phenotypes. One form of *EMX2* missense mutation was also detected reproducibly in the mothers of affected children, although the mothers showed no overt signs of schizencephaly. In these reports, a large percentage of affected children harbored *EMX2* mutations, raising the possibility that *EMX2* is the primary, if not sole, genetic locus for schizencephaly [Brunelli et al., 1996; Faiella et al., 1997; Granata et al., 1997].

However, despite several subsequent analyses of individuals with schizencephaly, no additional individuals with *EMX2* mutations have been reported, thereby raising the possibility of the existence of other causative loci. Using linkage analysis and sequencing data, we have provided strong evidence against linkage to *EMX2* in the pedigree described in this report. Assuming standard modes of inheritance, these results suggest that *EMX2* is not the sole genetic cause of familial schizencephaly and that familial schizencephaly is likely to be genetically heterogeneous.

What, then, are the additional genetic loci that can give rise to schizencephaly? The size of the pedigree described here precludes definitively identifying an exact location for a causative gene. However, linkage analysis has indicated two strong candidate regions including Chromosome 8q24.22-24.3 (assuming a recessive mode of inheritance) and Chromosome 5q21.3-23.2 (assuming a dominant mode of inheritance and germinal mosaicism). To pinpoint conclusive locations of additional causative loci of schizencephaly, analysis of additional pedigrees with familial schizencephaly that do not map to *EMX2* is required. Ultimately, the identification of additional loci will help to increase our understanding of the molecular mechanisms that underlie embryonic neocortex patterning and development, in addition to further elucidating the etiology of schizencephaly and other cortical malformation disorders.

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REFERENCES

Barkovich AJ. 2000. Congenital malformations of the brain and skull. In: Barkovich AJ, editor. Pediatric neuroimaging, 3rd ed.Philadelphia: Lippincott, Williams and Wilkins, pp 289–292.

Barkovich AJ, Kjos BO. 1992. Schizencephaly: Correlation of clinical findings with MR characteristics. AJNR 13:85–94.

Battaglia G, Granata T. 2003. Schizencephaly. In: Barth PG, editor. Disorders of neuronal migration. London: MacKeith Press, pp 127–134.

Bishop KM, Goudreau G, O'Leary DD. 2000. Regulation of area identity in the mammalian neocortex by *Emx2* and *Pax6*. Science 288:344–349.

Brunelli S, Faiella A, Capra V, Nigro V, Simeone A, Cama A, Boncinelli E. 1996. Germline mutations in the homeobox gene *EMX2* in patients with severe schizencephaly. Nat Genet 12:94–96.

Denis D, Chateil JF, Brun M, Brissaud O, Lacombe D, Fontan D, Flurin V, Pedespan JM. 2000. Schizencephaly: Clinical and imaging features in 30 infantile cases. Brain Dev 22:475–483.

Denis D, Maugey-Laulom B, Carles D, Pedespan JM, Brun M, Chateil JF. 2001. Prenatal diagnosis of schizencephaly by fetal magnetic resonance imaging. Fetal Diagn Ther 16:354–359.

Faiella A, Brunelli S, Granata T, D'Incerti L, Cardini R, Lenti C, Battaglia G, Boncinelli E. 1997. A number of schizencephaly patients including two brothers are heterozygous for germline mutations in the homeobox gene *EMX2*. Eur J Hum Genet 5:186–190.

Fukuchi-Shimogori T, Grove EA. 2003. *Emx2* patterns the neocortex by regulating *FGF* positional signaling. Nat Neurosci 6:825–831.

Galli R, Fiocco R, De Filippis L, Muzio L, Gritti A, Mercurio S, Broccoli V, Pellegrini M, Mallamaci A, Vescovi AL. 2002. *Emx2* regulates the proliferation of stem cells of the adult mammalian central nervous system. Development 129:1633–1644.

Granata T, Farina L, Faiella A, Cardini R, D'Incerti L, Boncinelli E, Battaglia G. 1997. Familial schizencephaly associated with *EMX2* mutation. Neurology 48:1403–1406.

Gudbjartsson DF, Jonasson K, Frigge M, Kong A. 2000. Allegro, a new computer program for multipoint linkage analysis. Nat Genet 25:12–13.

Guerrini R, Carrozo R. 2001. Epilepsy and genetic malformations of the cerebral cortex. Am J Med Genet 106:160–173.

Hahn JS, Lewis AJ. 2003. Unilateral schizencephaly and contralateral polymicrogyria associated with umbilical cord mass. J Child Neurol 18:232–234.

Hamasaki T, Leingartner A, Ringstedt T, O'Leary DD. 2004. *EMX2* regulates sizes and positioning of the primary sensory and motor areas in neocortex by direct specification of cortical progenitors. Neuron 43:359–372.

Haverkamp F, Zerres K, Ostertun B, Emons D, Lentze MJ. 1995. Familial schizencephaly: Further delineation of a rare disorder. J Med Genet 32:242–244.

Hayashi N, Tsutsumi Y, Barkovich AJ. 2002. Morphological features and associated anomalies of schizencephaly in the clinical population: Detailed analysis of MR images. Neuroradiology 44:418–427.

Heins N, Cremisi F, Malatesta P, Gangemi RMR, Corte G, Price J, Goudreau G, Gruss P, Götz M. 2001. *Emx2* promotes symmetric cell divisions and a multipotential fate in precursors from the cerebral cortex. Mol Cell Neurosci 18:485–502.

Hilburger AC, Willis JK, Bouldin E, Henderson-Tilton A. 1993. Familial schizencephaly. Brain Dev 15:234–236.

Hosley MA, Abroms IF, Ragland RL. 1992. Schizencephaly: Case report of familial incidence. Pediatr Neurol 8:148–150.

Iannetti P, Nigro G, Spalice A, Faiella A, Boncinelli E. 1998. Cytomegalovirus infection and schizencephaly: Case reports. Ann Neurol 43:123–127.

Kruglyak L, Daly MJ, Reeve-Daly MP, Lander ES. 1996. Parametric and nonparametric linkage analysis: A unified multipoint approach. Am J Hum Genet 58:1347–1363.

Kuijpers RWAM, van den Anker JN, Baerts W, von dem Borne AEGK. 1994. A case of severe neonatal thrombocytopenia with schizencephaly associated with anti-HPA-1b and anti-HPA-2a. Br J Haematol 87:576–579.

Landrieu P, Lacroix C. 1994. Schizencephaly, consequence of a developmental vasculopathy? Clin Neuropathol 13:192–196.

Mallamaci A, Muzio L, Chan CH, Parnavelas J, Boncinelli E. 2000a. Area identity shifts in the early cerebral cortex of *Emx2*-/- mutant mice. Nat Neurosci 3:679–686.

Mallamaci A, Mercurio S, Muzio L, Cecchi C, Pardini CL, Gruss P, Boncinelli E. 2000b. The lack of *Emx2* causes impairment of Reelin signaling and defects of neuronal migration in the developing cerebral cortex. J Neurosci 20:1109–1118.

Norman MG. 1980. Bilateral encephaloclastic lesions in a 26 week gestation fetus: Effect on neuroblast migration. Can J Neurol Sci 7:191–194.

Packard AM, Miller VS, Delgado MR. 1997. Schizencephaly: Correlations of clinical and radiologic features. Neurology 48:1427–1434.

Sener RN. 1998. Schizencephaly and congenital cytomegalovirus infection. J Neuroradiol 25:151–152.

Suchet IB. 1994. Schizencephaly: Antenatal and postnatal assessment with colour-flow Doppler imaging. Can Assoc Radiol J 45:193–200.

Yakovlev PL, Wadsworth RC. 1946a. Schizencephalies: A study of the congenital clefts in the cerebral mantle. I. Clefts with fused lips. J Neuropathol Exp Neurol 5:116–130.

Yakovlev PL, Wadsworth RC. 1946b. Schizencephalies: A study of congenital clefts in the cerebral mantle. II. Clefts with hydrocephalus and lips separated. J Neuropathol Exp Neurol 5:169–206.