American Journal of Medical Genetics Part B (Neuropsychiatric Genetics) 144B:58–63 (2007)

The Role of *RELN* in Lissencephaly and Neuropsychiatric Disease

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Reelin is an extracellular matrix-associated protein important in the regulation of neuronal migration during cerebral cortical development. Point mutations in the *RELN* gene have been shown to cause an autosomal recessive human brain malformation termed lissencephaly with cerebellar hypoplasia (LCH). Recent work has raised the possibility that reelin may also play a pathogenic role in other neuropsychiatric disorders. We sought, therefore, to define more precisely the phenotype of *RELN* gene disruption. To do this, we performed a clinical, radiological, and molecular study of a family in whom multiple individuals carry a chromosomal inversion that disrupts the *RELN* locus. A 6-year-old girl homozygous for the pericentric inversion 46,XX,inv7(p11.2q22) demonstrated the same clinical features that have been previously described in association with *RELN* point mutations. The girl's brain magnetic resonance imaging (MRI) findings, including pachygyria and severe cerebellar hypoplasia, were identical to those seen with *RELN* point mutations. Fluorescence in situ hybridization confirmed that one of the breakpoints of this inversion mapped to within the *RELN* gene, and Western blotting revealed an absence of detectable serum reelin protein. Several relatives who were heterozygous for this inversion were neurologically normal and had no signs of psychotic illness. Our findings demonstrate the distinctive phenotype of LCH, which is easily distinguishable from other forms of lissencephaly. Although *RELN* appears to be critical for normal cerebral and cerebellar development, its role, if any, in the pathogenesis of psychiatric disorders remains unclear.

KEY WORDS: pachygyria; cerebellar hypoplasia; malformation of cortical development

Please cite this article as follows: Chang BS, Duzcan F, Kim S, Cinbis M, Aggarwal A, Apse KA, Ozdel O, Atmaca M, Zencir S, Bagci H, Walsh CA. 2007. The role of *RELN* in lissencephaly and neuropsychiatric disease. Am J Med Genet Part B 144B:58–63.

INTRODUCTION

Lissencephaly with cerebellar hypoplasia (LCH) is a brain malformation caused by abnormal development of both the cerebral cortex and the cerebellum. Although several clinical syndromes have been described in which lissencephaly and cerebellar abnormalities coexist [Ross et al., 2001], the autosomal recessive form of LCH associated with mutations in the *RELN* gene [Hong et al., 2000] appears highly distinctive. Clinically, patients have developmental delay, hypotonia, severe ataxia, and seizures, while brain magnetic resonance imaging (MRI) demonstrates diffuse pachygyria, hippocampal dysplasia, and a profoundly hypoplastic cerebellum and brainstem, with a nearly complete absence of cerebellar folia [Hourihane et al., 1993; Hong et al., 2000].

RELN encodes an extracellular matrix-associated glycoprotein (reelin) that is secreted by Cajal–Retzius cells in the developing cerebral cortex and appears critical for the regulation of neuronal migration during cortical development, although its exact mechanisms of action remain unknown [Tissir and Goffinet, 2003]. The binding of reelin to its cell-surface receptors very-low-density lipoprotein receptor (VLDLR) and apolipoprotein E receptor type 2 (ApoER2) leads to phosphorylation of the intracellular protein disabled-1 (Dab1) and activation of a downstream signaling cascade that is thought to influence cell migration [Howell et al., 1997; Hiesberger et al., 1999; Trommsdorff et al., 1999]. In the spontaneous mouse mutant *reeler*, the usual lamination pattern of the cerebral cortex is essentially inverted, and the cerebellum is hypoplastic with decreased Purkinje cell number [Falconer, 1951; Lambert de Rouvroit and Goffinet, 1998].

In addition to LCH, reelin has been hypothesized to play a pathogenic role in other, more common neuropsychiatric illnesses [Fatemi, 2005]. Reelin expression is decreased in postmortem frontal cortex of patients with schizophrenia,

Bernard S. Chang and Fusun Duzcan contributed equally to this work.

Grant sponsor: National Institute of Neurological Disorders and Stroke; Grant numbers: K23 NS049159, R37 NS35129.

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Received 15 February 2006; Accepted 7 June 2006

DOI 10.1002/ajmg.b.30392

bipolar disorder, and autism [Impagnatiello et al., 1998; Guidotti et al., 2000; Fatemi et al., 2005]. In addition, heterozygous mouse mutants who have a ~50% decrease in reelin expression demonstrate both behavioral abnormalities (such as decreased prepulse inhibition) and anatomical abnormalities (such as decreased frontal dendritic spine density) that are consistent with schizophrenia and autism [Tueting et al., 1999; Carboni et al., 2004].

Here we describe the clinical, radiological, and molecular study of a large family in which one individual is homozygous for a chromosomal inversion that interrupts the *RELN* gene and multiple others are heterozygous for this inversion. Our findings expand our current understanding of the *RELN* phenotype and the role of *RELN* in cortical development and neuropsychiatric disorders.

MATERIALS AND METHODS

Clinical and Radiological Analysis

This study was performed in compliance with the Code of Ethics of the World Medical Association (Declaration of Helsinki); informed consent was obtained according to a protocol approved by the institutional review board of Children's Hospital, Boston. Detailed medical history, family history, and general physical and neurological examinations of the proband were performed by a pediatric neurologist. Family members affected by the chromosomal inversion were examined by both a neurologist and a psychiatrist, who classified diagnoses according to criteria of the Diagnostic and Statistical Manual version IV (DSM-IV). Electroencephalography (EEG) was performed using standard clinical protocols and the International 10–20 System of Electrode Placement. Brain MRI of the proband was performed on an Intera 1.5-Tesla scanner (Philips Medical Systems, Best, Netherlands) with the acquisition of T1-weighted, T2-weighted, FLAIR, and inversion-recovery spin-echo images in the axial, coronal, and sagittal planes.

Cytogenetic Analysis

Standard karyotype analysis was initially performed for the proband and multiple family members at the Cytogenetics Laboratory, Centre for Genetic Diagnosis of Pamukkale University, Turkey. Subsequently, bacterial artificial chromosome (BAC) clones covering the *RELN* locus at 7q22 were obtained from the Children's Hospital of Oklahoma Research Institute and grown using LB media containing 12.5 μg/ml chloramphenicol. BAC DNA was isolated with the NucleoBond BAC/PAC purification kit (Clontech Laboratories, Inc., Mountain View, CA). BAC probes were then directly labeled by incubation with fluorescently labeled nucleotide precursors (Vysis, Inc., Downers Grove, IL), followed by precipitation with human Cot-1 DNA. Fluorescence in situ hybridization (FISH) was performed using labeled probes on metaphase chromosomes from the proband and results were directly visualized by fluorescence microscopy. Labeled probes were validated by hybridization to normal human metaphase chromosomes, with only one fluorescent signal seen on each long arm of chromosome 7 per normal metaphase spread.

Serum Reelin Protein Analysis

Serum samples from the proband, a patient with a known *RELN* point mutation, and a normal control were diluted 1:20 into PBS. Denaturing sample buffer was added and the samples were run on 4–15% gradient gels (Bio-Rad Laboratories, Hercules, CA). Gels were transferred overnight onto Immobilon-P membranes (Millipore, Billerica, MA). Blots were stained with Ponceau to normalize loading, then blocked in 5% nonfat dry milk for an hour, and finally incubated overnight in anti-reelin (142) antiserum at 1:200 dilution. Blots were then washed with TBST and incubated in horseradish peroxidase-conjugated goat anti-mouse IgG secondary antibody at 1:2,000 dilution for 2 hr. They were rinsed again, incubated in LumiGLO chemiluminescent substrate (KPL, Inc., Gaithersburg, MD) for 5 min, and exposed to film for 2–45 min.

RESULTS

Clinical Features of Proband

The proband was a 6-year-old girl from a village in the Denizli region of Turkey who was evaluated for growth and motor retardation. Her parents were first cousins once removed (Fig. 1). She was born to a 20-year-old woman by spontaneous vaginal delivery at term following an uncomplicated pregnancy without associated prenatal care. Birth weight was 3 kg. She began having convulsive seizures at 3 months of age. By 6 years of age, she had tonic convulsions lasting for 60 sec each that were occurring three to four times a day, typically upon awakening. Myoclonic seizures were also seen.

On physical examination at 6 years of age, her weight was 14.5 kg (<3rd percentile), height 100 cm (<3rd percentile), and head circumference 49 cm (11th percentile). She had a wide nasal bridge and upslanting palpebral fissures. Fundoscopy was normal. Unlike some of the *RELN* mutation patients

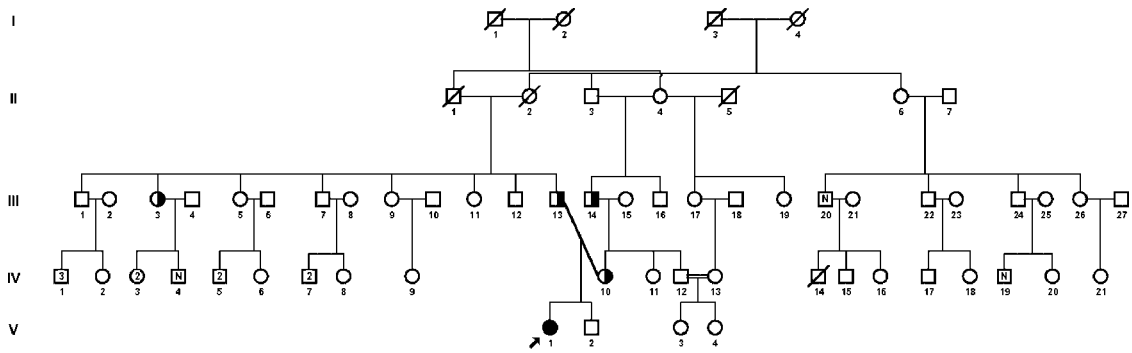

Fig. 1. Pedigree of family with chromosome 7 inversion with breakpoint within the *RELN* locus. The proband (V:1; arrow) is indicated by a solid symbol and is homozygous for the chromosome 7 inversion. Individuals denoted by a half-solid symbol are heterozygous for the inversion. Symbols labeled "N" denote individuals with normal karyotype.

previously described [Hourihane et al., 1993], she did not have lymphedema. Neurological examination demonstrated that she could occasionally say "papa" and "mama" nonspecifically, but did not speak any other words or definitively recognize those around her. She could not follow instructions but at times smiled when her mother spoke to her, although this was not consistent. There were no signs of autistic behavior. She could track objects with conjugate eye movements. Motor exam revealed the presence of severe hypotonia; she was unable to control her head movements, sit without support, or stand. She was able to move her extremities against gravity but not against any resistance. The deep tendon reflexes were hyperactive and Babinski signs were present bilaterally. There was no obvious ataxia, although motor testing was limited.

Her EEG demonstrated alpha–theta background activity and multifocal spike and spike-and-slow-wave activity.

Radiological Analysis of Proband

Brain MRI of the proband (Fig. 2A) demonstrated broad gyri that were too few in number with shallow sulcation, worse anteriorly than posteriorly. The cortical thickness appeared normal to mildly increased, ranging from 3 to 6 mm throughout. White matter volume was reduced and the ventricles were moderately enlarged bilaterally. The hippocampi appeared small, simplified, and partially unfolded on coronal sections. The cerebellum was profoundly hypoplastic, with only a small superior portion of vermis and adjacent hemispheres visible. These radiological findings were indistinguishable from those seen in patients with *RELN* point mutations (Fig. 2B) [Hong et al., 2000], but were quite distinct from those seen in more common forms of lissencephaly including those associated with mutations in the *DCX* or *LIS1* genes (Fig. 2C,D). Although cerebellar hypoplasia of a mild degree can be seen in patients with *DCX*- or *LIS1*-associated lissencephaly, pachygyria or agyria is typically the most striking finding and is generally present in a widespread distribution, often with an anterior > posterior gradient in *DCX*-associated cases and a posterior > anterior gradient in *LIS1*-associated cases [Pilz et al., 1998; Dobyns et al., 1999].

Cytogenetic Analysis of Proband

Routine karyotype demonstrated a pericentric inversion of chromosome 7 in the homozygous state, 46,XX,inv (7)(p11.2q22) (Fig. 3A,B). FISH analysis using BAC probe RP11-975H14 on metaphase chromosomes prepared from the proband revealed hybridization signals at both p11.2 and q22, indicating that the inversion occurred within the DNA contained in this BAC clone (Fig. 3C). This clone is contained entirely within the boundaries of the *RELN* gene (Fig. 3D) [Kent et al., 2002]. FISH analysis of BAC RP11-975H14 was validated on normal human metaphase chromosomes and mapped exclusively to the long arm of chromosome 7 in band 22.

Serum Reelin Protein Analysis of Proband

Serum expression of reelin protein in the proband was determined by Western blot analysis (Fig. 4). Reelin has been shown to be present in serum as three bands of approximately 420, 310, and 160 kDa molecular weight, which may represent proteins with post-translational modifications [Smalheiser et al., 2000]. In the proband, reelin immunoreactive bands were undetectable whereas control serum showed three appropriate distinct bands. The proband's findings were comparable to those from a patient with a known *RELN* point mutation, in whom Western blotting also demonstrated an absence of detectable protein.

Heterozygote Carriers of Chromosomal Inversion

The proband's father (III:13), mother (IV:10), paternal aunt (III:3), and maternal grandfather (III:14) were found to be heterozygous for the chromosomal inversion by karyotype analysis (Fig. 3B). None of these individuals showed signs of schizophrenia, bipolar disorder, or autism. The father (III:13) had developed post-traumatic stress disorder after the death of a friend in a terrorist attack; he had recurrent distressing dreams about the event as well as illusions, hallucinations, and dissociative flashblack episodes. Hypervigilance and disturbances of sleep and concentration were also seen. The proband's mother (IV:10) developed adjustment disorder in

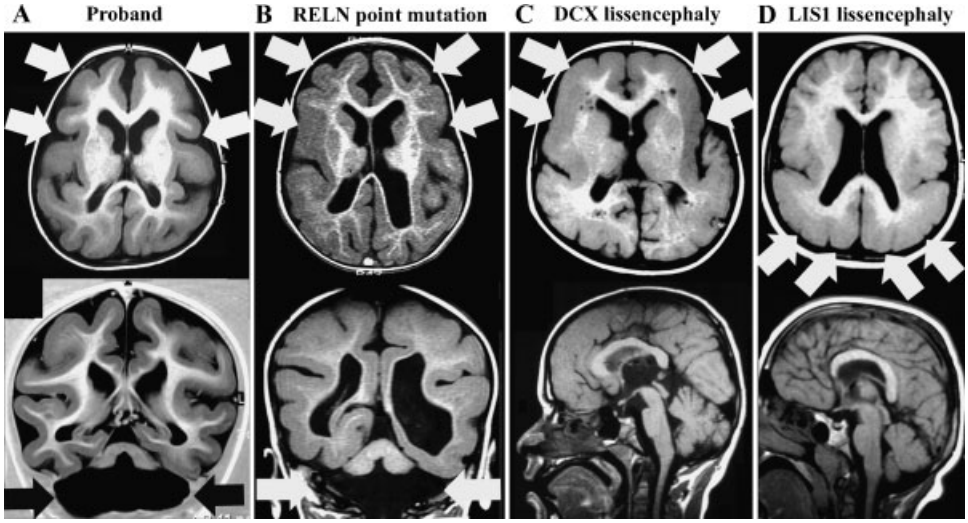

Fig. 2. Brain magnetic resonance imaging of *RELN*-associated lissencephaly with cerebellar hypoplasia compared to classical lissencephaly. T1-weighted axial (top row) and coronal (bottom row) brain magnetic resonance images from the proband with homozygous chromosome 7 inversion (**A**) and an individual with a known *RELN* point mutation (**B**) demonstrate the typical features of LCH, including bilateral pachygyria (white arrows) and profound hypoplasia of the cerebellar vermis and hemispheres (black arrows in A and white arrows in B). Comparison T1-weighted axial (top row) and sagittal (bottom row) images from patients with classical lissencephaly due to *DCX* mutation (**C**) and *LIS1* mutation (**D**) demonstrate the differing anterior–posterior gradients of pachygyria in these malformations (white arrows), as well as the relative preservation of cerebellar size compared to LCH. (LIS1 images courtesy of A. James Barkovich, M.D.)

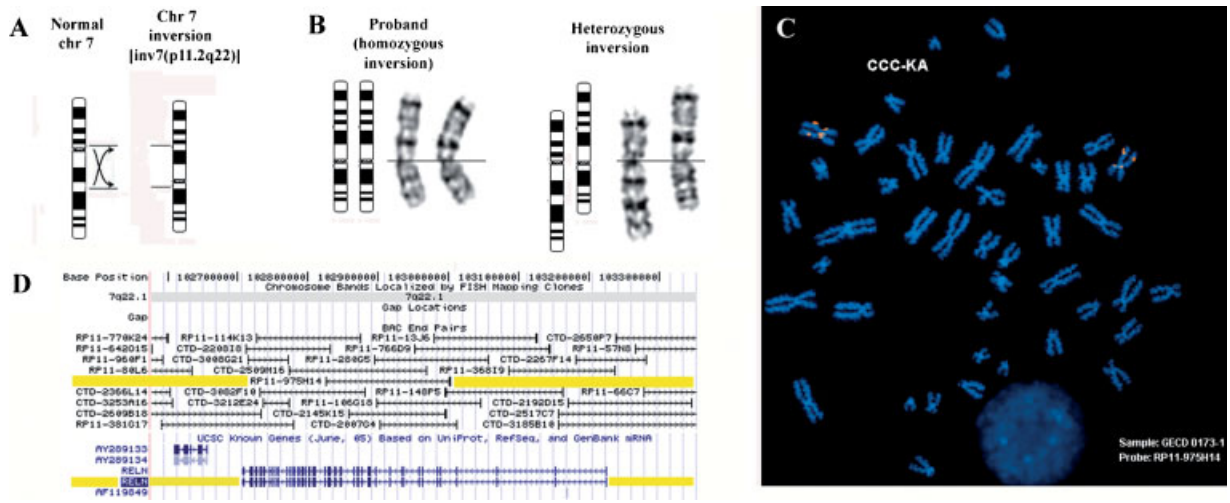

Fig. 3. Cytogenetic analysis of proband and parents with chromosome 7 inversion. The banding pattern of normal chromosome 7 and the chromosome that results from the pericentric inversion 46,XX,inv(7)(p11.2q22) are shown (**A**). The appearance of both copies of chromosome 7 in a metaphase spread from the homozygous proband and a heterozygous parent are shown (**B**). Fluorescence in situ hybridization (FISH) performed using the labeled bacterial artificial chromosome (BAC) probe RP11-975H14 on a metaphase spread from the proband demonstrates hybridization signals at both p11.2 and q22, indicating that the inversion breakpoint occurs within the DNA contained in this clone (**C**). The RP11-975H14 BAC clone maps entirely within the boundaries of the *RELN* gene (rows with BAC clone and gene highlighted in yellow), according to the UCSC genome browser, human May 2004 assembly [**D**; Kent et al., 2002].

response to the onset of the proband's illness, exhibiting difficulties with concentration, hypervigilance, hopelessness, fatigue, irritability, and sleep problems. Finally, the paternal aunt (III:3) was diagnosed with panic disorder based on recurrent attacks characterized by palpitations, shortness of breath, chest pain, derealization, and depersonalization, as well as the presence of agoraphobia.

Other Family Members

A history of epilepsy was described in a maternal great-grandfather (II:3) and a maternal great-aunt (III:17). A second cousin once removed (IV:19) also had epilepsy and a paternal first cousin (IV:4) had nonspecific mental retardation; both of these individuals had normal karyotype analysis. Another second cousin once removed (IV:14) died at age 24 and had a history of severe cognitive and motor delay, being unable to walk or speak. Chromosome analysis was not performed on this individual but his father (III:20) had a normal karyotype.

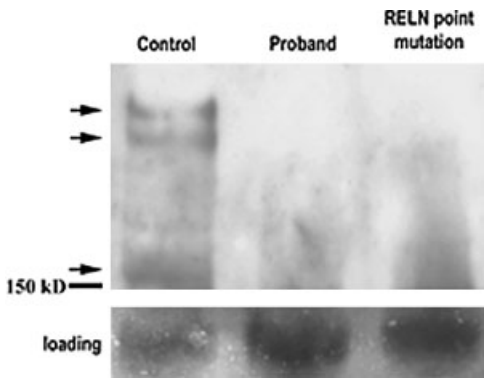

Fig. 4. Serum Western blot analysis of reelin protein. Western blot analysis of serum from a control subject demonstrates that reelin is present as three bands of approximately 420, 310, and 160 kDa molecular weight (arrows). No detectable reelin protein is seen in serum from the proband (with homozygous chromosome 7 inversion) or from a patient with a known *RELN* point mutation, despite overloading these lanes. The location of a 150 kDa size standard is indicated.

DISCUSSION

Here we describe in detail the neuropsychiatric phenotype of *RELN* gene disruption based on the study of an extensive pedigree that includes multiple individuals with a pericentric chromosome 7 inversion that interrupts the *RELN* gene. The proband, with a homozygous inversion, demonstrates the typical clinical and radiological features of LCH [Hong et al., 2000], including developmental delay, severe hypotonia, seizures, diffuse pachygyria, and severe cerebellar hypoplasia. Her phenotype is essentially indistinguishable from that of previously reported patients who have *RELN* point mutations. Those reported mutations were presumed to be null alleles due to the presence of identical clinical and radiological phenotypes in the two respective pedigrees [Hong et al., 2000]. Here, we demonstrate absent reelin serum expression in our proband and presume that the homozygous inversion in this individual has a complete loss-of-function effect as well.

RELN-Associated LCH Compared to Classical Lissencephaly

The distinctive radiological phenotype associated with *RELN* mutations distinguishes this disorder from other, more common forms of lissencephaly including those associated with the genes *DCX* and *LIS1* (Fig. 2). Although slight cerebellar hypoplasia can be seen in patients with *DCX*- or *LIS1*-associated lissencephaly [Ross et al., 2001], the cardinal feature of those disorders is pachygyria or agyria [Pilz et al., 1998; Dobyns et al., 1999], with any cerebellar abnormalities relatively mild in comparison. The *RELN*-associated malformation, by contrast, features profound cerebellar hypoplasia, with preservation of only a small superior band of tissue with no other discernible cerebellar structures or foliation. The cerebral abnormality is best characterized as a mild or moderate pachygyria, which is usually worse anteriorly.

RELN-Associated LCH Compared to Other Forms of LCH

Several similar conditions involving both pachygyria/agyria and cerebellar hypoplasia have been described. Kato et al. [1999] described cases in which the degree of cerebral pachygyria appears more severe than in *RELN*-associated LCH while the degree of cerebellar hypoplasia appears slightly less severe. Kerner et al. [1999] described two siblings in whom pathological study suggested nearly complete agyria (unlike in *RELN*-associated LCH), more severe cerebellar hypoplasia, and other associated malformations. Finally, the brain malformation seen in the Hutterite dysequilibrium syndrome, a condition recently found to be associated with mutations in the gene for the VLDL receptor, one of the cell surface receptors for reelin, appears to feature a milder degree of cerebral gyral simplification and less severe cerebellar hypoplasia than is seen in *RELN*-associated LCH [Boycott et al., 2005]. The identification and characterization of patients with mutations in other reelin signaling pathway molecules may help to differentiate LCH subtypes even further and allow for critical genotype–phenotype correlations.

The Role of *RELN* in Other Neuropsychiatric Disorders

Although there is evidence from postmortem human brain tissue and behavioral studies of heterozygous mutant mice to suggest that reelin may play a role in schizophrenia, bipolar disorder, and autism [Impagnatiello et al., 1998; Tueting et al., 1999; Fatemi et al., 2000, 2005; Guidotti et al., 2000; Fatemi, 2001; Carboni et al., 2004], we found no evidence to support the diagnosis of any of these disorders in the homozygous proband or in the four known heterozygous individuals in this family, despite detailed evaluation by a psychiatrist. This is consistent with the absence of major psychiatric disease in the previously reported individuals who were homozygous or heterozygous for *RELN* mutations [Hong et al., 2000]. Including both the mutation cases and the individuals from this report, 7 total homozygous patients and 11 total heterozygous patients with mutations or inversions at the *RELN* locus have now been described, and none have demonstrated clinical signs of primary psychotic disorders or autism.

However, these patients still represent a relatively small sample and the families were ascertained on the basis of neuroanatomical and clinical neurological phenotype, while reports of association between *RELN* expression and psychiatric disorders have included patients selected based on psychopathology. In addition, while our data imply that there is no simple gene dosage correlation between *RELN* and psychosis, it is theoretically possible that a heterozygous state of *RELN* disruption could still result in normal reelin protein expression. Three heterozygous patients did have anxiety or adjustment disorders, raising the possibility of a relationship between *RELN* and these conditions or other affective disorders, although in two of those cases the diagnosis was associated with a clear external precipitant.

It is also possible, of course, that unusual or missense mutations in *RELN* could cause a different human phenotype that has not been established yet, one distinct from the null presentation and from the largely normal phenotype that we see in heterozygous individuals. The identification and characterization of patients carrying such mutations would potentially expand our understanding of the function of *RELN* in neural development. Similarly, the identification of patients with mutations in other downstream molecules in the reelin signaling cascade would also help to shed light on the molecular pathogenesis of the LCH phenotype.

ACKNOWLEDGMENTS

We thank the patients in this family for participating in the study. We thank A. James Barkovich, M.D., (University of California San Francisco) for providing the images used in Figure 2D. We thank André M. Goffinet, M.D., Ph.D. (University of Louvain Medical School, Brussels), for providing the anti-reelin antibody. FISH was performed at the Cytogenetics Core of the Dana Farber Harvard Cancer Center (P30 CA006516 from the National Cancer Institute). An agreement form for the International Transfer of Biological Material was accepted by both institutions and confirmed by the Turkish Ministry of Health. B.S.C. and C.A.W. were supported by the National Institute of Neurological Disorders and Stroke (K23 NS049159 and R37 NS35129, respectively). C.A.W. is an Investigator of the Howard Hughes Medical Institute.

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