

## NEW *RELN* MUTATION ASSOCIATED WITH LISSENCEPHALY AND EPILEPSY

### Autosomal Recessive Lissencephaly with Cerebellar Hypoplasia is Associated with Human *RELN* Mutations.

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Normal development of the cerebral cortex requires long-range migration of cortical neurons from proliferative regions deep in the brain. Lissencephaly (“smooth brain,” from “lissos,” meaning smooth, and “encephalos,” meaning brain) is a severe developmental disorder in which neuronal migration is impaired, leading to a thickened cerebral cortex whose normally folded contour is simplified and smooth. Two identified lissencephaly genes do not account for all known cases, and additional lissencephaly syndromes have been described. An autosomal recessive form of lissencephaly (LCH) associated with severe abnormalities of the cerebellum, hippocampus, and brainstem maps to chromosome 7q22, and is associated with two independent mutations in the human gene encoding reelin (*RELN*). The mutations disrupt splicing of *RELN* cDNA, resulting in low or undetectable amounts of reelin protein. LCH parallels the reeler mouse mutant (*Reln<sup>rl</sup>*), in which *Reln* mutations cause cerebellar hypoplasia, abnormal cerebral cortical neuronal migration, and abnormal axonal connectivity. *RELN* encodes a large (388 kD) secreted protein that acts on migrating cortical neurons by binding to the very low density lipoprotein receptor (VLDLR), the apolipoprotein E receptor 2 (ApoER2),  $\alpha$ 3 $\beta$ 1 integrin and protocadherins. Although reelin was previously thought to function exclusively in brain, some humans with *RELN* mutations show abnormal neuromuscular connectivity and congenital lymphoedema, suggesting previously unsuspected functions for reelin in and outside of the brain.

### COMMENTARY

Lissencephaly is a severe developmental brain malformation characterized by loss of the normal gyral patterns in the cerebral hemispheres, marked disorganization of the cerebral cortical cytoarchitecture, and a high association with profound neurologic deficits and epilepsy. The lissencephalic cortex is thickened and is reduced from the normal hexalaminar structure to a four layered pattern containing a population of neurons with abnormal cell morphologies. Two lissencephaly genes have been identified including LIS-1 (Miller-Dieker syndrome) and doublecortin (X-linked lissencephaly). However, other lissencephaly syndromes exist that do not result from mutations at these loci.

The article by Hong et al. describes two consanguineous pedigrees, one British and one Saudi Arabian, in which an autosomal recessive lissencephaly syndrome associated with cerebellar hypoplasia, was mapped to chromosome 7q22 by linkage analysis. All affected patients exhibited severe delay in cognitive development and epilepsy and brain magnetic resonance imaging (MRI) demonstrated profound cerebellar hypoplasia and lissencephaly. These investigators postulated that the mutational locus for this syndrome would be at or near 7q22 since this chromosomal region contains the reelin (*RELN*) gene and mutations in this gene in mice results in neocortical migration abnormalities and cerebellar hypoplasia similar to the patient cohort.

Reelin is a secreted protein that modulates neuronal migration by binding to several cell surface molecules including the very low density lipoprotein receptor, the apoprotein E receptor 2,  $\alpha$ 3 $\beta$ 1 integrin, and protocadherins. *RELN* is encoded by 65 exons and spans more than 400 kilobasepairs of genomic DNA. Using select primers, Hong et al. used RT-PCR to identify a precise 85 basepair deletion corresponding to exon 36 in the Saudi Arabian pedigree. This deletion resulted in abnormal splicing of exon 35 to exon 37. In the British pedigree, a second distinct mutation was identified in which 148 basepairs corresponding to exon 42 were deleted. Both mutations produced a translational frameshift followed by a premature termination codon and resembled naturally occurring

mouse reelin alleles. Western analysis of serum from affected patients demonstrated reduced or absent reelin protein expression. This report provides a new candidate molecule to study in all patients with lissencephaly as well as those with associated cerebellar hypoplasia. Genetic screening for mutations in *RELN* may be helpful in individuals in whom mutations in LIS-1 or doublecortin cannot be identified.

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