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**Commentary**

# Reelin, a Marker of Stress Resilience in Depression and Psychosis

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Reelin protein is an extracellular matrix protease responsible for normal lamination of the brain during embryogenesis, and is involved in cell signaling and synaptic plasticity in adult life. The Reelin gene (*RELN*) is localized to chromosome 7 in humans and chromosome 5 in mice, and produces a protein product with relative molecular mass of 388 kDa. Reelin protein is localized to a number of brain sites, specifically Cajal–Retzius cells located in layer 1 of neocortex, GABAergic interneurons, and cerebellar granule cells. Activation of the Reelin signaling pathway leads to various, important functions such as enhancement of long-term potentiation, cell proliferation, cell migration, and more importantly dendritic spine morphogenesis.

Spontaneous mutation of the *RELN* gene in the reeler homozygous mutant mouse leads to the development of ataxia and a reeling gait and reversal of the normal layering of the brain (Goffinet, 1979). The reeler cerebellum is hypoplastic and the Purkinje cell number is diminished potentially explaining the ataxic gait. Historically, comparative studies of the homozygous and heterozygous reeler mutant mice and the similarities in their cognitive, anatomic, and biochemical abnormalities to mental diseases caused an upsurge in generation of new information about Reelin's involvement in various neuropsychiatric disorders.

Multiple postmortem studies have implicated a pathologic involvement of *RELN* gene in several neuropsychiatric disorders, namely, schizophrenia, bipolar disorder, autism, major depression, lissencephaly, and Alzheimer's disease. Erminio Costa and coworkers reported on deficits in brain levels of Reelin mRNA and the protein in patients suffering from schizophrenia and psychotic bipolar disorder (Impagnatiello *et al*, 1998). Later reports by Fatemi (2005) confirmed and extended these findings to patients with non-psychotic bipolar disorder, major depression, and autism. Additional reports by other investigators showed that Reelin deficits are common phenomena subserving cognitive deficits in multiple disorders including lissencephaly, Alzheimer's disease, and temporal lobe epilepsy. The causative factors may include a mutation in the *RELN* gene (lissencephaly) to variable expression of the molecule due to hypermethylation of the promoter region of the *RELN* gene or other unknown mechanisms. Moreover, several non-CNS disorders have been associated with changes in expression of Reelin including several forms of cancers and otosclerosis.

In the current issue, Teixeira and colleagues evaluated the effects of overexpression of Reelin in a transgenic mouse model as compared with wild-type mice and to heterozygous reeler mutant mice using a battery of behavioral tests (Texeira *et al*, 2011). These investigators tested the hypothesis that if downregulation of Reelin production could lead to various behavioral abnormalities, upregulation of this molecule could lead to reversal of these deficits. The effects of Reelin overexpression on (1) anxiety (open field, novelty-suppressed feeding, black and white box), (2) depression (forced-swim test in presence or absence of the stress-associated hormone corticosterone), (3) mania and positive symptoms of schizophrenia (cocaine sensitization and cocaine self-administration), and (4) gating abnormalities in schizophrenia (prepulse inhibition) were assessed at 8 weeks of age in presence or absence of the NMDA antagonist MK-801. Additionally, all animals were subjected to electrophysiological recordings to evaluate for functionality of the NMDA-NR2B glutamatergic transmission. The results demonstrated that although heterozygous reeler mice did not show any behavioral abnormalities, mice overexpressing Reelin exhibited several salient and novel findings ie, (1) increased brain levels of Reelin protected the transgenic mice from developing depression-like behavior in the forced-swim test, (2) stress induced NMDA NR2B—mediated synaptic transmission (a marker of depression) was reduced in transgenic mice, and lastly (3) evidence for positive symptoms of schizophrenia ie, behavioral sensitization to cocaine and gating deficits (PPI abnormalities) were reduced in transgenic mice. These findings are both positive and potentially important as they point to Reelin as a therapeutic agent to treat some aspects of depression, psychosis, and autistic behavior. Previous

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findings of Reelin production induced by various psychotropic medications including citalopram support these results (Jaako *et al*, 2011). Additionally, in a previous work by the same laboratory, it was demonstrated that Reelin overexpression in the hippocampus of the transgenic mice resulted in potentiation of synaptic strength and hypertrophy of dendritic spine morphology, albeit with no change in dendritic spine density (Pujadas *et al*, 2010). These changes in the hippocampus reflect Reelin's ability to act as an antidepressant by both increasing neurogenesis and improving learning and memory.

As Reelin abnormalities are pervasive and span a range of neuropsychiatric disorders, future studies should focus on and expand the scope of genetic, biochemical, and clinical studies to better define the etiopathologic and therapeutic roles of this important and evolutionary conserved molecule.

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## DISCLOSURE

The author declares no conflict of interest.

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