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Review

# Reelin down-regulation in mice and psychosis endophenotypes

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**Abstract**

Reelin, a large glycoprotein secreted by telencephalic GABAergic neurons, plays an important role in neuronal guidance embryonically and in synaptic plasticity postnatally. The reeler heterozygous mouse (+/rl) appears superficially normal but has been of interest as an animal model for psychosis since the discovery that reelin is 50% down-regulated in postmortem psychotic brain. Brain abnormalities in +/rl are similar to psychotic brain and include a reduction in glutamic acid de carboxylase 67 ($GAD_{67}$), dendritic arbors and spine density in cortex and hippocampus, and abnormalities in synaptic function including long-term potentiation (LTP). In spite of these abnormalities, behavioral abnormalities in +/rl are subtle and controversial. Recent findings indicate that the reelin (*RELN*) and $GAD_{67}$ promoters are hypermethylated in GABAergic neurons of psychotic postmortem brain and that DNA methyltransferase 1 (DNMT1) is up-regulated. Hypermethlyation of *RELN* and $GAD_{67}$ promoters can be induced by treating mice with methionine, and these mice display brain and behavioral abnormalities similar to +/rl. Thus, an animal model that combines genetic heterozygocity with epigenesis holds promise for understanding the role of Reelin down-regulation in psychosis


*Keywords:* Epigenetic; $GAD_{67}$; Prepulse inhibition of startle; *RELN*; GABA; NMDA receptor; Methionine; Methylation; Reelin; Reeler heterozygous mouse; Endophenotype

**Contents**



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## 1. Introduction

Reelin is a large extracellular protein playing a significant role in neuronal guidance during neurodevelopment and an important role in early postnatal development and in synaptic plasticity and memory in the adult. Thus, reelin is pleiotropic, having one function during embryonic development (neuronal guidance) and other related functions in the developing and mature nervous system (in dendritic spine morphology, N-methyl-D-aspartic acid (NMDA) receptor function, and synaptic plasticity). Reelin signal transduction is mediated by a receptor complex that may include the α3β1 integrin receptor (Rodriguez et al., 2000), the apolipoprotein E receptor 2 (Apoer2) and the low-density lipoprotein receptor (VLDR) (Weeber et al., 2002), and the cytoplasmic adapter protein drosophila disabled 1(Dab1) (Howell et al., 1997).

Postnatally, reelin is important in dendrite development (Niu et al., 2004) and in neural stem cell migration (Kim et al., 2002). The dendritic spine is a principal target of extracellular matrix reelin. In the cerebellum, reelin is secreted by glutamatergic granule cells (Lacor et al., 2000) and the principal target is presumably the dendritic spine of the GABAergic Purkinje cell. Importantly for cognition, in the cortex and hippocampus, reelin is secreted by specific types of GABAergic interneurons and surrounds dendritic spines of cortical pyramidal neurons where glutamatergic receptors are located. Reelin binds to receptors located in dendritic spine postsynaptic densities (PSD) of pyramidal neurons (Pappas et al., 2001; Rodriguez et al., 2000) where it interacts with transcription factors (Erbel-Sieler et al., 2004) and influences the rapid translation of dendritic resident mRNAs involved in dendritic spine morphology and synaptic function, e.g., activity regulated cytoskeletal protein (Arc) (Dong et al., 2003).

Reelin has been shown to modulate NMDA activity by enhancing glutamate-stimulated $Ca^{2+}$ influx through NMDA receptors in cortical neuron cultures (Chen et al., 2005), and to positively regulate long-term potentiation (LTP) in the mouse hippocampus (Weeber et al., 2002). Modulation of synaptic plasticity and memory by Reelin involves differential splicing of Apoer2, a component of the NMDA receptor complex (Beffert et al., 2005; D'Arcangelo, 2005), and in a recent report, multiple electrophysiological abnormalities in hippocampal CA1 synapses were attributed to reelin down-regulation (Qui et al., 2005). Further, reelin control of the NMDA receptor developmental switch from NR1/2B to NR1/2A subunits has been demonstrated in hippocampal neuronal cultures of mice indicating a pivotal role for reelin in orchestrating stages of postnatal cognitive development (Sinagra et al., 2005).

Reelin messenger RNA (mRNA) and protein are down-regulated in cortical GABAergic neurons of schizophrenia and psychotic bipolar disorder patients and a down-regulation of glutamic acid decarboxylase 67 ($GAD_{67}$) messenger is associated with the reelin down-regulation (Guidotti et al., 2000; Impagnatiello et al., 1998). These findings have been replicated in other brain cohorts and by other laboratories (Abdolmaleky et al., 2005; Akbarian et al., 1995; Eastwood, 2004; Fatemi et al., 2000, 2005; Knable et al., 2001; Lewis et al., 2004; Woo et al., 2004), and are considered to be the most consistent findings to date in schizophrenia postmortem brain tissue (Torrey et al., 2005). Significantly, the decreases in reelin and $GAD_{67}$ expression in the cortex of psychotic patients are related to an increased expression of DNA-methyltransferase (DNMT1) in these same cortical GABAergic interneurons (Grayson et al., 2005, 2006; Veldic et al., 2004, 2005), thereby implicating epigenetic hypermethylation in their down-regulation in psychosis. Reelin down-regulation has also been found in other disorders involving cognitive dysfunction, most notably autism (Fatemi et al., 2005; Serajee et al., 2006).

Because reelin mRNA was approximately 50% down-regulated in our initial study of psychotic postmortem brain (Impagnatiello et al., 1998), the heterozygous reeler mouse (+/rl) became of immediate interest as a possible animal model for psychosis (Tueting et al., 1999). It is well known that the inheritance of schizophrenia is not Mendelian and the reelin gene locus 7q22 (*RELN*) is only one of several loci reported to be potentially involved in the polygenetic inheritance of psychosis (Ekelund et al., 2000; Goldberger et al., 2005). Thus, the +/rl mouse was never considered to be an uncomplicated model for schizophrenia vulnerability. However, once it was determined that the down-regulation of reelin and $GAD_{67}$ in frontal cortex and hippocampus of +/rl was similar in magnitude to that observed in psychotic postmortem brain (Carboni et al., 2004; Costa et al., 2001; Liu et al., 2001), +/rl became a logical starting point for a preliminary working animal model aimed at understanding the implications of down-regulated reelin. Moreover, the model was consistent with current thinking about psychosis vulnerability since +/rl appears relatively normal on cursory observation similar to many human patients before the onset of psychosis and during lasting symptom remission. In addition, the model fit the growing realization that abnormalities in GABAergic neurodevelopment may be at the core of the etiology of schizophrenia. It is known that reelin, secreted by GABAergic Cajal-Retzius cells during embryogenesis, is a major player in determining projection neuron positioning after migration into areas of the telencephalon. Further, psychoses in general, and schizophrenia in particular, are most certainly disorders associated with deficits in synaptic plasticity (Eastwood, 2004; Gisabella et al., 2005). Since reelin is involved in dendritic arborization, dendritic spine dynamics, and NMDA receptor function (Costa et al., 2001; Dong et al., 2003; Niu et al., 2004; Qiu et al., 2005), a deficit in synaptic plasticity is an important research focus in +/rl. Significantly, reelin has been shown to be critical for cognitive functions involving learning and memory and for the LTP underlying these important adaptive processes (Carboni et al., 2004; Larson et al., 2003; Qui et al., 2005; Rothblat et al., 2004; Weeber et al., 2002).