

The Role of Neurodevelopmental Genes in Infectious Etiology of Autism

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Abstract: Autism is a neurodevelopmental disorder with both genetic and environmental etiologies. Prenatal infections may play a role in evolution of autism. Experimental evidence shows human influenza viral infection in pregnancy leads to significant deleterious effects in brain structure and function in the developing mouse progeny. Several brain genes of interest in this animal model are also involved in the pathology of autism. The roles of these genes in brain development are discussed in this review.

Key words: Autism, influenza, viral model, brain genes, mouse

INTRODUCTION

Autism is an important neurodevelopmental disorder which is characterized by deficits in social relatedness, communication, and cognition^[1]. Onset of unusual behavior typically occurs in infancy and is fully present by the child's 30th month. The incidence is approximately 1-2 in 1000 live births with a 4:1 predominance of males to females. The severity of disease may vary widely. Autism is not a single disease, but a syndrome most likely brought on by a variety of causes. While autism is a highly familial disorder, environmental causes can contribute to its genesis^[2]. Here, I will describe some of our findings in pathology of autism using postmortem autistic and matched brains and contributions of a potential mouse model to studies of the etiopathology of autism.

Reelin Signaling System In Autism: Many brain proteins participate in the early orderly growth and development of the mammalian central nervous system. Reelin is an important glycoprotein that helps guide brain development in an orderly fashion^[3]. Changes in the level of this protein or its receptors or downstream proteins cause abnormal corticogenesis^[4].

Reelin gene (Reln) is localized to chromosome 7 in man. Reelin protein product has a relative molecular mass of 388 kDa^[5, 6]. Reelin appears as several protein bands, ranging from 410 to 330 to 180 kDa, and several smaller fragments^[7]. Reelin is an extracellular matrix protein secreted by GABAergic neurons or

Cajal-Retzius cells of layer I^[8, 9], which binds several receptors, including apolipoprotein E receptor 2 (ApoER2), very low-density lipoprotein receptor (VLDLR) and $\alpha 3\beta 1$ integrin protein^[4] on cortical pyramidal cells^[10]. Reelin binding to ApoER2 and VLDLR receptors induces clustering of the latter receptors, causing oligomerization of the adaptor protein, disabled-1 (Dab-1), with eventual tyrosine phosphorylation of Dab-1 protein. Phosphorylation of Dab-1 enables this protein to become the substrate for various kinases leading to a number of important events, such as synaptic and dendritic spine plasticity^[10], neurotransmission and inhibition of glycogen synthase-kinase 3 β and final modulation of pathways of cell survival and growth^[11]. Recently, Reelin signaling has been implicated in enhancement of long term potentiation (LTP), memory formation, and synaptic plasticity^[12, 13].

Disruption of Reelin signaling pathway by mutations^[5, 14] and selective hypermethylation of the Reelin gene promoter^[15, 16], or following various pre or postnatal insults^[9, 17] leads to cognitive deficits in several neuropsychiatric disorders, like autism^[18, 19, 20], schizophrenia^[21, 22, 23], or lissencephaly^[24].

Research over the last several years has helped in providing a preliminary description of several steps in Reelin signaling which may be impaired in autism^[20]. Measurement of Reelin protein and mRNA, its adaptor molecule Dab-1, and Reelin receptor VLDLR mRNA in three brain sites (areas 9 and 40 and cerebellum) in autistic subjects and matched controls showed

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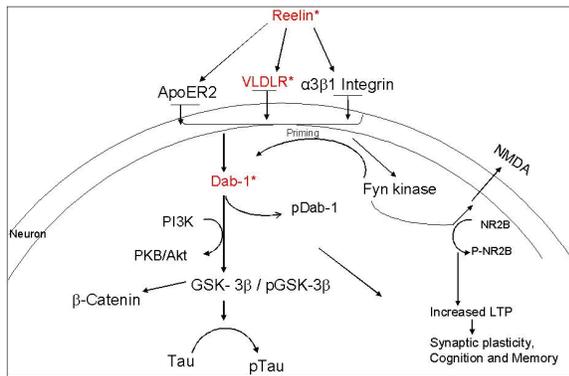


Fig. 1: The role of Reelin signaling system in autism

impairment in three steps: 1) Reelin is not produced adequately as evident by reductions in mRNA and protein levels; 2) Reelin receptor VLDLR mRNA is upregulated in response to reduced levels of its ligand, Reelin; and 3) Dab-1 mRNA is also reduced, potentially due to reductions in levels of Reelin^[20]. It is thus proposed that alterations in these three steps may interfere with normal Reelin signaling affecting LTP, synaptic plasticity, and memory/cognition in autism^[20] (Fig. 1). Three positive genetic association studies also support the involvement of Reelin gene in autism^[25]. Simultaneously, several other linkage studies have been negative^[3, 25].

Normally, extracellular Reelin is secreted by Cajal-Retzius cells and certain GABAergic cells to bind its receptors, VLDLR, ApoER2 and $\alpha3\beta1$ integrin on effector cells. Following binding of Reelin to its receptors, Dab-1 protein is oligomerized and phosphorylated. In autistic brain, Reelin signaling system appears to be impaired in 3 steps (marked in red with an asterisk character (*)): 1) Reelin ligand is not produced adequately as is evident by reductions in mRNA and protein levels is superior frontal cortex and cerebellum; 2) Reelin receptor VLDLR mRNA is upregulated, potentially in response to reduced levels of its ligand, Reelin; 3) Dab-1 mRNA is also reduced, potentially due to reduction in levels of Reelin which normally activate Dab-1 phosphorylation via a positive-feedback loop. Alternatively, Dab-1 levels may be reduced in response to increases in levels of VLDLR, acting via a negative-feedback loop. Alterations on levels of Reelin, its receptor VLDLR and adaptor protein Dab-1 interfere with the Reelin signaling system affecting LTP, synaptic plasticity, cognition, and memory modalities involved in autism (Fatemi *et al.*, 2005).

Our laboratory has also demonstrated Reelin deficiency in hippocampi of subjects with schizophrenia, bipolar disorder and major

depression^[22], connecting this deficit with cognitive problems as seen in these disorders and confirming a previous landmark finding of similar deficits in schizophrenic subjects^[21]. These data have been extended to the cerebella of subjects with schizophrenia and bipolar disorder^[26, 27]. Additionally, we have also shown that Reelin levels are abnormal in blood of subjects with schizophrenia and autism^[19]. Reelin gene deficit is considered to be a replicated and robust marker of schizophrenia, autism, and mood disorders^[15, 16, 20].

Virally-induced brain disorder in mouse: a potential animal model for autism. There is significant support for genetic contributions to development of autism^[25]. However, epidemiologic studies have also indicated an environmental contribution to the genesis of this disorder^[28]. Infections and, specifically, viral etiologies for this disorder have been suspected and implicated^[29, 30, 31, 32, 33]. Recent reports by several groups have provided the first experimental evidence that prenatal infection of rodents with human influenza virus or administration of a viral mimic on day 9 of pregnancy causes deleterious effects in brains of the exposed mouse progeny^[9, 34, 35, 36]. Interestingly, some of the accumulated published data show correlations between brain biochemical, structural, and behavioral indices in the virally-exposed mouse progeny^[17] and those seen in schizophrenic and autistic subjects^[37, 38].

Research over the last decade provided the first evidence that intranasal administration of human influenza virus (H1N1) at day 9 of pregnancy in mouse leads to defective corticogenesis and reduced levels of Reelin in day 0 virally exposed mouse brains^[9]. The exposed mice exhibit decreases in neocortical and hippocampal thickness^[9]. The same animals also show reduced prepulse inhibition (PPI) and other behavioral abnormalities analogous to PPI deficits seen in schizophrenic and autistic subjects^[35, 39, 63, 64]. This work has been replicated by several groups and is considered as one of the best animal models for schizophrenia and autism^[36, 40, 41, 42, 43]. Additional work by our group shows that several important brain genes involved in pathology of autism are also affected by the viral insult (see Table 1). We have already documented that viral infections *in utero* at E9 of pregnancy cause abnormal corticogenesis at various postnatal dates leading to atrophy of brain^[9, 35] (Table 2), pyramidal cell atrophy^[35], ventricular size abnormalities^[35], and neuronal and glial cell number alterations^[17, 35]. Several important brain genes involved in the viral insult include nNos, SNAP-25, glutamic acid decarboxylase (GAD), and myelin basic protein^[17] (Fatemi unpublished data, 2007), which are also involved in

Table 1: Mouse model of viral infection; genes differentially changed in progeny of E9 maternal infection and positive associations with autism in humans

Genes	Brain*	References
Adenosine Deaminase	+↓	Bottini <i>et al.</i> ^[48]
Ceruloplasmin	+↓	Fatemi <i>et al.</i> ^[19] , Torsdottir <i>et al.</i> ^[49] , Chauhan <i>et al.</i> ^[50] , Chauhan and Chauhan ^[51]
Forkhead Box P2	+↑	Gong <i>et al.</i> ^[53]
GABA A receptor subunit α5	+↑	McCauley <i>et al.</i> ^[55]
GAD 65/67	+↑	Fatemi <i>et al.</i> ^[56] , Blatt <i>et al.</i> ^[57]
GFAP	+↑	Vargas <i>et al.</i> ^[58] , Laurence and Fatemi ^[59]
Oxytocin	+↑	Hollander <i>et al.</i> ^[61] , Green <i>et al.</i> ^[62]
Reelin	+↓	Fatemi <i>et al.</i> ^[20]

*Changes observed in various brain areas of autistic subjects

Table 2: Comparison of area measurements (mm²) between prenatally-infected and sham-infected brain areas

Animals	Cerebral cortical Layer I	Cerebral cortex (layers II-VI and IZ ^a)	Hippocampus (all Layers) and IZ ^a	Total unilateral brain hemisphere
Control (n=9)	0.56±0.07	4.44±1.08	0.99±0.33	10.3±1.58
Infected (n=12)	0.34±0.09*	3.23±1.26**	0.81±0.35	7.57±1.97*
% Change	↓39.3%	↓27.2%	↓18.1%	↓26.5%

Values have been expressed as mean±SD., (adapted from Fatemi *et al.*^[9])

*P<0.0001 (unpaired t-test); **P<0.0015 (unpaired t-test); IZ^a= Intermediate zone

pathology of schizophrenia and autism in humans^[18, 19, 44, 45] and in a mouse model^[17]. Two potential mechanisms purported to be involved in the viral effects include maternal and fetal cytokine-related brain injury and fetal brain gene modulation by viral antigens^[17, 46]. Evidence for both mechanisms being responsible for brain changes in the exposed mouse progeny is accumulating. Recent data from our laboratory shows that prenatal infection of Balb/c E9 pregnant mice with a sublethal dose of H1N1 causes alterations in levels of multiple transcription factors and important genes which affect cell differentiation, apoptosis, cell cycle progression, and myelination in the exposed brains of the offspring^[47].

Correlation of virally-affected mouse genes and genes implicated in the genesis of schizophrenia and autism show parallel mechanisms involved in the etiopathogenesis of abnormal brain development (see Table 1). Similarities in genes involved suggest new avenues in studies of environmental contributions to genesis of both disorders.

Several important brain genes affected by prenatal viral infection in the exposed offspring of mice^[47] are also associated with autism in humans (Table 1): 1) Adenosine deaminase is an enzyme that catalyzes the hydrolysis of adenosine to inosine and NH₃. This enzyme is also involved in the degradation of adenosine and the formation of uric acid. Reduction in levels of this enzyme may be a way to reduce inflammation and provide better survival for the neurons. Polymorphisms in this gene have been associated with autism^[48]; 2) Ceruloplasmin is a copper-containing enzyme and a

marker for antioxidant activity^[49, 50], which has been reported to be either decreased^[50, 51] or same in autism^[19, 49]; 3) Forkhead box P2 (FOXP2) is a trinucleotide repeat-containing gene with putative transcription factor activity containing a polyglutamine tract and a forkhead binding domain and is involved in development of speech and language^[52]. This gene is involved in embryogenesis; its mutation causes cerebellar abnormalities^[52]. Significant genetic associations have been found between FOXP2 gene polymorphisms and subjects with autism^[53] and schizophrenia^[54]; 4) GABA A receptor, subunit α5 is involved in startle response, associative learning and postsynaptic inhibitory circuitry of the brain. This receptor has been linked to autism^[55]; 5) Glutamic acid decarboxylase 65 and 67 kDa (GAD65 and GAD67) proteins are involved in conversion of glutamate to GABA. Cells containing these enzymes also colocalize Reelin. Significant decreases have been reported in levels of GAD 65 and 67 kDa proteins and mRNAs in autistic brains^[56, 57]. Similar deficits have also been reported in cerebella of schizophrenic subjects^[26]; 6) Glial fibrillary acidic protein (GFAP) is a glial cell marker whose upregulation signifies inflammation and reactive injury in the brain. Levels of GFAP are increased in autistic brains^[58, 59] and in virally exposed offspring^[60], reflecting inflammatory and immune response; and 7) Oxytocin is an important hormone involved with prosocial appropriate behavior generation and social memory. Lack of oxytocin has been associated with a lack of ability to develop social memory. Published reports indicate an involvement of oxytocin in autism^[61, 62].

CONCLUSIONS

Autism is an important genetic disorder with environmental contributions. A viral model of mental illness developed by our laboratory results in abnormalities in several brain genes, causes abnormal corticogenesis, and provides behavioral deficits also seen in autism and schizophrenia. Future research should help facilitate use of this animal model for studies of mechanisms responsible for genesis of neurodevelopmental disorders like autism and schizophrenia.

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