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Co-occurrence of Neurodevelopmental genes in etiopathogenesis of autism and schizophrenia

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Neurodevelopmental disorders schizophrenia and autism are set apart by their respective behavioral manifestations and course of development of pathology. Recently, a number of published reports indicate a potential involvement of certain brain genes in the etiology of both schizophrenia and autism (see Table 1).

One gene that has recently attracted significant attention is reelin (Fatemi, 2005). Reelin deficits have been documented in the brain and blood of patients with autism and their relatives (reviewed in Fatemi, 2005). Reelin deficiency is also present in brains of subjects with schizophrenia, bipolar disorder, and major depression (Guidotti et al., 2000; Fatemi, 2005). Reelin plays a major role in synaptic plasticity, which may explain its involvement in such diverse neuropsychiatric disorders such as autism and schizophrenia.

Investigations in the past decade have repeatedly shown multiple abnormalities involving various aspects of the GABAergic neurotransmission in autism and schizophrenia. One such deficit involves the activity of an enzyme system composed of two isoforms of the glutamic acid decarboxylase (GAD). It has been shown consistently that GAD 67 is reduced in brains of subjects with schizophrenia (Guidotti et al., 2000). Moreover, GAD65 and 67 are significantly reduced in multiple brain sites in subjects with autism (Fatemi et al., 2002). As levels of glutamate and GABA play such important roles in modulation of various brain functions, including the release of dopamine, it is not surprising that these enzymes may be involved in both of these disorders. Furthermore, receptors for the GABA system are also known to be abnormally regulated both in autism (Fatemi et al., 2010; Oblak et al., 2009) and schizophrenia (Bullock et al., 2008). Changes in levels of GABA receptors can impact multiple domains involving learning, sleep/wake cycles, and seizure induction.

Another molecule of importance is 6-cyclic adenosine monophosphate (cAMP). cAMP is involved in transmission of signals intracellularly in various cell types and tissues including the brain. One way of controlling the levels of cAMP is via the phosphodiesterases (PDEs). In a recent study, Fatemi et al. (2008) identified several nucleotide polymorphisms and a 2-SNP haplotype in PDE4B to be associated with an increased incidence in schizophrenia in two large populations of Caucasian and African American patients (Fatemi et al., 2008).

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These authors also observed specific decreases in PDE4B isoforms in brain tissue obtained postmortem from subjects diagnosed with schizophrenia and bipolar disorder. The same laboratory had previously shown abnormal expression of PDE4A and 4B in multiple brain areas of subjects with autism (Braun et al., 2007). These observations clearly showed that dysregulation of intracellular signaling of cAMP mediated by PDE4B and 4A may be considered as significant factors in the causation of schizophrenia, bipolar disorder, and autism and that PDE regulated signaling pathways may yield new therapeutic avenues for treatment of these disorders.

A further molecule of interest is glial fibrillary protein (GFAP), which is the primary intermediate filament in astrocytes. GFAP has multiple functions, including the maintenance of astrocyte morphology, integrity of blood-brain barrier, and a marker for astrocyte maturation. Importantly, GFAP up-regulation is a hallmark of gliosis, in response to injury to the centralnervous system. GFAP levels are known to be increased in subjects with autism (Laurence & Fatemi, 2005; Vargas et al., 2005).

A number of additional genes have been proposed to be involved in etiopathogenesis of schizophrenia and autism, including forkhead box P2, ceruloplasmin, and nude 1, however, they have been less adequately studied. Future studies are needed to carefully study these genes for potential roles in neuropsychiatric disorders.

I conformed to all ethical principles in the writing of this editorial.

Sincerely,

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Table 1

Selected Genes Involved in the Etiopathogenesis of Autism and Schizophrenia

Gene/Protein	Schizophrenia	Autism	Author(s)
GAD 65/67	+	+	Guidotti et al., 2000; Fatemi et al., 2002
GFAP	+	+	Lawrence & Fatemi (2005); Vargas et al., 2005
PDE 4A/4B	+	+	Braun et al., 2007; Fatemi et al., 2008a
RELN	+	+	Guidotti et al., 2000; Fatemi, 2005