Molecular Psychiatry (2002) 7, 919–920

www.nature.com/mp

GUEST EDITORIAL

The role of Reelin in pathology of autism

Molecular Psychiatry (2002) **7,** 919–920. doi:10.1038/sj.mp.4001248

Autism is a severe neurodevelopmental disorder with childhood onset and a rising prevalence rate of 16–20 per 10 000 which is characterized by severe problems in communication, social skills and repetitive behavior. The causes for autism may be genetic[1] and/or environmental.[2] The preponderance of evidence, however, supports genetic causes for evolution of this disabling disorder,[3] with high linkage between autism and several markers on chromosome 7.[4] Many areas of the brain exhibit abnormalities in autism, including cerebellum, hippocampus, parietal and frontal cortices.[5–7] Courchesne and coworkers[5] studied the MRIs of 60 autistic and 52 normal boys and showed brain abnormalities such as hyperplasia of cerebellar white matter, neocortical gray matter, and cerebral white matter at the earliest ages, with slowed growth thereafter. These investigators also described evidence of slowed growth in the cerebellar hemispheres and a reduction in the size of vermal gray matter.[5] Saitoh *et al*[6] studied the MRIs of 59 autistic and 51 healthy normal controls and showed hypoplasia of the area dentata in the autistic subjects during the earliest years of the disorder (age 29 months–4 years), consistent with previous neuroanatomic work showing increased pyramidal cell packing density and reduced neuronal cell size[7] with small dendritic neuronal cell branching.[8] Recent biochemical evidence shows significant alterations in levels of several important neuroregulatory proteins affecting growth of central nervous system, in brains of age, sex and postmortem interval-matched (PMI) autistic subjects *vs* controls; these changes include deficits in Bcl2,[9,10] glutamic-acid decarboxylase proteins of 65 and 67 kDa,[11] and Reelin[10], and increases in p53[12] and glial fibrillary acidic proteins.[13]

Reelin is an extracellular matrix protein with serine protease activity,[14] which is responsible for correct lamination of the brain during the embryonic period and cell signaling and synaptic plasticity in the adult life.[15] Recent emerging evidence points to pathologic involvement of Reelin in several neuropsychiatric disorders and in several animal models of brain development.[16] Costa and coworkers were the first investigators to report deficits in brain levels of Reelin mRNA and protein, in subjects with schizophrenia and psychotic bipolar disorder.[17] These reports were later confirmed[18,19] and extended to involve patients with nonpsychotic bipolar disorder,[17] major depression,[19] lissencephaly[20] and autism.[10] These reports clearly indicated that Reelin protein deficiency may be a common phenomenon subserving cognitive deficits (including psychotic thinking) in multiple neuropsychiatric disorders. A recent report[21] also implicates Reelin signaling system in the neuropathology of Alzheimer's disease. These authors showed the presence of Reelin immunostaining in association with amyloid deposits in brains of double-transgenic mice that expressed both human mutant β-amyloid precursor protein and human mutant presenelin-1.[21]

Several recent genetic studies describe the association of polymorphisms in the RELN gene with three neurodevelopmental disorders: lissencephaly,[20] schizophrenia[22] and autism.[23,24] The study by Grayson and coworkers[22] described a polymorphic GGC repeat in the 5′ UTR of the human RELN gene, upstream of the ATG initiation codon.

Polymorphisms in this repeat were also described by Persico *et al*.[23] In that study, six distinct alleles (containing 8–14 copies of the repeats) were found in the general population, and four additional alleles (containing 4,7,15 or 23 repeats) were found in the autistic subjects and their first-degree relatives.[23] Alleles containing 8–10 repeats were most common in the general population, although the genotypic and allelic distributions were different for different ethnic groups. Individuals with autism, however, tended to have more repeats. For Caucasians of Italian descent, 17.9% of autistic individuals *vs* 9.1% unaffected had at least one allele containing 11 or more repeats and the frequencies of 'long' alleles were twice as high in affected individuals compared to normal individuals.

Preferential transmission of 'long' alleles (11 or more repeats) was also found in a study of 89 Caucasian Americans of European descent and their first-degree relatives.[23] In addition to the polymorphic GGC repeat, Persico *et al*,[23] also described two additional polymorphisms eg (i) a A/G transversion predicted to affect RNA splicing immediately 5′ to exon 6; (ii) a conservative T/C transversion in the codon for histidine 2682 in exon 50. Haplotype analysis using these three genetic markers revealed statistically significant increases in the frequency of occurrence in autistic patients *vs* controls for several specific combinations of alleles.[23] Now, in a recent report (see the current issue) Zhang and coworkers,[24] test the hypothesis that an instability in the number of repeats in the RELN gene, or an altered distribution in these alleles, may be associated with increased susceptibility towards development of autism. These investigators examined the distribution of GGC repeat numbers in affected members from 126 multiplex and 68 simplex families and found no evidence for expansion, or instability of transmission of this repeat in the autistic subjects. The authors discovered 14 alleles of variable number of GGC repeats (3–

16 repeats) in the affected and control subjects;[24] there were no differences in the case-control studies for the most common alleles ie, 8 or 10 alleles or genotypes.

Additionally, Zhang *et al*,[24] did not observe an increased frequency of large alleles (more than or equal to 11 repeats) in the autistic cases *vs* controls. Later, using a family-based association test, these authors showed that the larger alleles (more than or equal to 11 repeats) were transmitted higher than expected in the affected children (S = 43, E(S) = 34.5, $P = 0.035$) and in particular with the 13 repeat allele (S = 22, E(S) = 16, $P = 0.034$).[24] This increased risk of developing autism supports Persico *et al*'s[23] findings, without evidence of increased allele sharing previously described in the siblings of the autistic children.[23] While Zhang *et al*'s[24] case-control studies did not replicate Persico *et al*'s[23] data, their family-based data support Persico *et al*'s[23] study, adding to the weight of genetic evidence implicating RELN in the etiology of autism.[23,24] Despite these positive findings, a recent study,[29] could not show any association between a polymorphic GGC repeat in the 5′ untranslated region of the RELN gene and autism in a population of mixed European descent emphasizing the need for more future rigorous genetic studies to establish a definitive link between the RELN gene and autism.

Recently, Fatemi *et al*[25] measured blood levels of unprocessed Reelin (410 kDa) and its proteolytic cleavage products (Reelin 330 and 180 kDa) as well as albumin and ceruloplasmin in 28 autistic monozygotic twins (AGRE consortium), their parents (13 fathers, 13 mothers), six normal siblings, and eight normal controls using SDS-PAGE and Western blotting. Results obtained indicated significant reductions in 410 kDa Reelin species in autistic twins (–70%, $P < 0.01$), their fathers (–62%, $P < 0.01$), their mothers (–72%, $P < 0.01$) , and their phenotypically normal siblings (–70%, $P < 0.01$) *vs* controls.[25]

Additionally, autistic cerebellar Reelin 410 kDa protein deficits[10] have now been extended to parietal cortices of matched autistic subjects (Fatemi, Stary, Halt, unpublished observations) *vs* controls, showing further evidence for Reelin deficiency in brains and sera of autistic subjects. These biochemical data[10,25] confirm the recent genetic data,[23,24] implicating Reelin as a vulnerability factor in the etiopathology of autistic disorder.

Finally, supportive experimental animal data,[16,26–28] also extend the important role of Reelin glycoprotein, in normal brain development and synaptic plasticity, as exemplified in various rodent models which exhibit Reelin deficits in association with development of abnormal brain structure, leading to the genesis of abnormal behavior. Future studies should focus on and expand the scope of postmortem, genetic and animal model studies to better define the etiology and potential treatments for autism.

Acknowledgements

This work was supported by grants by Stanley Foundation, March of Dimes, NARSAD and Kunin Fund of St Paul Foundation. The generous use of brain samples by the Autism Tissue Foundation and its affiliated brain banks (Harvard, Maryland and Miami University brain banks), and sera by the AGRE Consortium is greatly appreciated.

SH Fatemi, MD, PhD
Division of Neuroscience Research
Department of Psychiatry
University of Minnesota Medical School
Minneapolis, MN, USA

References

1 Folstein SE, Rosen-Sheidley B. *Nat Rev Nat Gen* 2001; **2**: 943–955.
2 Rodier PM. *Sci Am* 2000; **282**: 56–63.
3 Korvatska E *et al. Neurobiol Dis* 2002; **9**: 107–125.
4 Badner JA, Gershon ES. *Mol Psychiatry* 2002; **7**: 56–66.
5 Courchesne E *et al. Neurology* 2001; **57**: 245–254.
6 Saitoh O *et al. Brain* 2001; **124**: 1317–1324.
7 Bauman ML, Kemper TL. *Neurology* 1985; **35**: 866–874.
8 Raymond GV *et al. Acta Neuropathol (Berl)* 1996; **91**: 117–119.
9 Fatemi SH *et al. NeuroReport* 2001; **12**: 929–933.
10 Fatemi SH *et al. J Aut Devel Dis* 2001; **31**: 529–535.
11 Fatemi SH *et al. Biol Psychiatry* 2002; **52**: 805–810.
12 Fatemi SH, Halt AR. *Synapse* 2001; **42**: 281–284.
13 Fatemi SH *et al. Int J Neuropsychopharmacol* 2002; **5**(S1): S163–S164.
14 Quattrochi CC *et al. J Biol Chem* 2002; **277**: 303–309.
15 Costa E *et al. Mol Interventions* 2002; **2**: 47–57.
16 Fatemi SH. *Mol Psychiatry* 2001; **6**: 129–133.
17 Impagnatiello F *et al. Proc Natl Acad Sci (USA)* 1998; **95**: 15718–15723.
18 Guidotti AR *et al. Arch Gen Psychiatr* 2000; **57**: 1061–1069.
19 Fatemi SH *et al. Mol Psychiatr* 2000; **5**: 654–663.
20 Hong SE *et al. Nat Genet* 2000; **26**: 93–96.
21 Wirths O *et al. Neurosci Lett* 2001; **316**: 145–148.
22 Grayson DR *et al. Biol. Psychiatr* 2000; **47**: 41S.
23 Persico AM *et al. Mol Psychiatry* 2001; **6**: 150–159.
24 Zhang H *et al. Mol Psychiatry* 2002; **7**: 1012–1017.
25 Fatemi SH *et al. Cell Mol Neurobiol* 2002; **22**: 139–162.
26 Magdaleno S *et al. Neuron* 2002; **33**: 573–586.
27 Ohshima T *et al. J Neurosci* 2002; **22**: 4036–4044.
28 Fatemi SH *et al. Cell Mol Neurobiol* 2002; **22**: 25–33.
29 Kreas MO *et al. Mol Psychiatry* 2002; **7**: 801–804.