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EDITORIAL

Progress in the genetics of autism

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Autism (OMIM 209850) is a pervasive developmental disorder characterized by impairments in reciprocal social interactions and communications, and by unusually restricted, repetitive, and stereotyped patterns of behaviors and interests. The sex-ratio is 4:1 male to female, and the prevalence is 2–5 in 10 000.

While the role of the environment remains unclear, the role of genetic factors in autism is increasingly evident. It appears that autism is a syndrome of heterogeneous etiology. The most common specific etiology appears to be maternally inhertited duplications of 15q11–q13; however, these only account for 1–3% of cases. In most cases, estimates of no fewer than two and possibly over 20 autism susceptibility genes acting in convert have been proposed based on the available data. For scholarly reviews of the genetics of autism, please see references.[1,2]

Molecular Psychiatry has received articles with the latest findings in the area of autism genetics and that work is being published in our 2002 issues. In our January 2002 issue, Badner and Gershon described an interesting approach to regional meta-analysis, the multiple-scan probability (MSP).[3] They applied this new method of meta-analysis to autism and demonstrated evidence for a susceptibility locus at 7q. However, the identification of specific genes within that region remains elusive. In this issue Bonora *et al* report work aimed at identifying relevant genes in 7q32 using a positional candidate gene approach (pages 289–301). They studied four adjacent genes localized to a 800-kb region of 7q32 that contains an imprinted domain: PEG1/MEST, COPG2, CPA1 and CPA5. The analysis of these four genes strongly suggested that they do not have a role in autism. The authors are now examining additional candidate genes mapping to the 7q locus.

Because autism is far more common in boys than in girls, it is reasonable to look for clues in the Y chromosome. In our last issue, Jamain *et al* used informative Y-polymorphic markers and defined Y chromosome haplotypes of 111 autistic subjects from France, Sweden and Norway, as well of appropriate controls.[4] No significant difference in Y-haplotype distribution was observed. These results are not suggestive of a Y chromosome effect in autism.

In this issue, we have three articles with positive genetic findings in autism. Jamain *et al* report data indicating that the glutamate receptor 6 (GluR6) is in linkage disequilibrium with autism (pages 302–310). The GluR6 gene is localized in 6q21, a candidate region. Glutamate, the main excitatory neurotransmitter in the CNS, has a key role in cognition. Jamain and colleagues studied a large number of subjects and used both the affected sib-pair method and the transmission disequilibrium test. Both approaches showed a significant linkage and association of GluR6 with autism. GluR6 is highly expressed in brain regions involved in learning and memory (hippocampus) and in motor and motivational aspects of behavior (basal ganglia and cerebellum). Additionally, GluR6 function regulates the seizure threshold. Thus, alterations in GluR6 gene function could explain not only cognitive, motor, and motivational impairments, but also the high occurrence of seizures in autistic children.

Gamma-aminobutiric acid (GABA) is an aminoacid neurotransmitter that regulates the seizure threshold. GABA is a key modulator of anxiety. Rates of anxiety disorders are higher in first-degree relatives of autistic subjects. The GABA type-A receptor β3 subunit gene (GABRB3) is localized in the Pader–Willi/Angelman syndrome critical region (15q11–13), where cytogenetic abnormalities have been described in several patients with autism.[5] In this issue (pages 311–316) Buxbaum *et al* present data that strongly support a role for genetic variants within the GABA receptor gene complex (GABRB3) in autism.

Serotonin is thought to be implicated in autism because whole blood serotonin levels are increased in patients and serotonin transporter inhibitors reduce rituals and aggression in autism. The paper by Kim and colleagues (pages 278–288) provides the first comprehensive screening of introns and exons of the serotonin transporter for polymorphisms in this disorder. A key finding is that the TDT peaks at a location other than the most commonly typed polymorphisms in the gene, the 5-HTTLPR and an intron 2 VNTR. It will be interesting to see if the new variants lead to more consistent results across autism samples and whether they help in understanding the variable association with other phenotypes ranging from neuroticism to bipolar mood disorder.

The six articles on autism published to date in the current volume of *Molecular Psychiatry* contribute to enhance our understanding of this devastating disorder. We look forward to continuing to publish the latest advances in autism research.

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