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EDITORIAL

Back to where it all started: monoamines and behavior—from drug responses to genes

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Early research in biological psychiatry addressed the mechanism of action of serendipitously discovered psychotropic drugs. Because such drugs were found to act on central monoaminergic systems, the role of those systems became evident, and led to groundbreaking work that resulted in two Nobel prizes, awarded in 1970 to Ulf von Euler and Julius Axelrod (http://www.nobel.se/medicine/laureates/1970/index.html) and in 2000 to Arvid Carlsson (http://www.nobel.se/medicine/laureates/2000/index.html). Dysregulation of monoaminergic function cannot, however, fully explain psychiatric disorders. Depression is not simply a dysfunction of serotonin and norepinephrine. Schizophrenia is not just the outcome of dysregulation of dopaminergic systems. The advent of molecular biology, contemporary genetics and genomics promised to offer novel and exciting targets for study and drug discovery. Yet, as genetic research unfolds, well-replicated findings include associations of psychiatric disorders with polymorphisms in genes involved in monoaminergic neurotransmission.

One of the most replicated findings in psychiatric genetics is the association of attention deficit hyperactivity disorder (ADHD) with the dopamine D4 receptor—this was first published in our journal in 1996.[1] Now, 8 years later, we publish new findings of association with another element of the dopaminergic system, the dopamine D1 receptor. In this issue (pp 500–509), Misener *et al* tested for linkage of DRD1 to ADHD by examining the inheritance of four bi-allelic DRD1 polymorphisms in a sample of 156 ADHD families. Using the transmission/disequilibrium test (TDT), they observed a strong bias for transmission of a specific haplotype from heterozygous parents to their affected children. Additionally, using quantitative trait TDT analyses, they found significant and positive relationships between transmission of that haplotype and clinical presentation. These findings support the involvement of DRD1 in ADHD.

An exciting article on monoaminergic genes in schizophrenia by Xu *et al* (pp 510–521) shows a novel approach that is being taken by various groups. Rather than examining one candidate at a time, an entire pathway system is tested. In this exciting work that is further commented on by Irizarry and Galbraith (pp 431–432) 85 single-nucleotide polymorphisms (SNPs) present in 23 genes for the dopamine metabolism pathway were genotyped in patients with paranoid schizophrenia and controls. Two new multi-locus approaches were used, and showed that three susceptibility genotype combinations were associated with schizophrenia. These results were also validated in a family-based cohort consisting of 95 family trios with paranoid schizophrenia. The concept of approaching various elements along a pathway is becoming increasing important. A useful resource for the study of genetic variations along critical biological pathways can be found at http://www.pharmgkb.org, specifically at http://www.pharmgkb.org/search/pathway/pathway.jsp. We particularly encourage submissions of papers that test multiple genes along pathways.

Using either a traditional candidate approach, or a pathway approach, components of monoaminergic neurotransmission emerge as key candidates in psychiatric disorders. As these disorders are polygenic, they cannot of course be reduced solely to disruption in dopaminergic function. In this issue, a highly interesting article by Gharani *et al* (pp 474–484) shows a new association between the homeobox transcription factor ENGRAILED 2 (EN2) and autism spectrum disorder. Mouse mutants of EN2 and autistic individuals display similar cerebellar morphological abnormalities, which include hypoplasia and a decrease in the number of Purkinje cells. Human EN2 maps to 7q36, a chromosomal region that has demonstrated linkage to autism spectrum disorder (ASD). The work of Gharani and colleagues indicates that two intronic SNPs of EN2 have significant association with autism. The analysis was then extended to include 167 small nuclear autism pedigrees and significant association was again only observed under both narrow and broad diagnostic criteria. These new findings suggest a role for EN2 as a susceptibility locus and support a neurodevelopmental defect hypothesis in the etiology of autism.

As pathways that are a part of old and of emerging new hypotheses of mental illnesses are explored, it will certainly be discovered that complex patterns of polygenic susceptibility loci interact with environmental factors to result in psychiatric phenotypes. The challenge now is to unravel the identity of and model the interactions among specific polygenic loci and environmental factors that converge to cause psychiatric disorders.

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1 LaHoste GJ, Swanson JM, Wigal SB, Glabe C, Wigal T, King N *et al*. *Mol Psychiatry* 1996; **1**: 121–124.