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Candidate gene association studies constitute a major approach to understanding the relationship between particular genes and traits or disorders. However, the ability to replicate findings across studies that use this approach is not as good as one would hope. **Sullivan** (pages 1121–1126) used simulated data to explore this problem. The author reports that candidate gene studies may produce many false positive findings when the standard for significance is set at the common standard, i.e., a 5% chance of finding the result by accident ($p<.05$). This paper also highlights steps to improve the reliability of candidate gene association studies.

McIntosh *et al.* (pages 1127–1134) provide important new data adding to evidence that variation in the catechol-O-methyltransferase (COMT) gene is related to the risk for schizophrenia and has effects on prefrontal cortex structure and function in association with familial schizophrenia.

The 22q11.2 Deletion Syndrome (22qDS) is associated with schizophrenia risk and is associated with the loss of one copy of a gene associated with schizophrenia risk, the COMT gene. **Bassett *et al.*** (pages 1135–1140) now report that the versions of the remaining copy of the COMT gene are related to the function of the prefrontal cortex in individuals with 22qDS, but not to the risk to develop schizophrenia in this population.

Bonner-Jackson *et al.* (pages 1141–1147) provide new evidence that by providing individuals at increased genetic risk for schizophrenia, siblings of individuals diagnosed with schizophrenia, with helpful strategies for encoding memory, the differences in memory performance between this group and a group of individuals without relatives diagnosed with schizophrenia may be minimized or eliminated. Despite the improved performance, the siblings of individuals with schizophrenia show increased cortical activation than the other group when performing the memory tasks. These persisting differences may be related to factors that influence the extent of cortical excitation or the "efficiency" of cortical function that might be related to the heritable risk for schizophrenia.

There is an urgent need to have a biological marker that identifies the subgroup that will progress to schizophrenia from among the larger group of individuals who are at increased risk to develop this disorder. **Borgwardt *et al.*** (pages 1148–1156) report that the group "at risk" for developing schizophrenia had reductions in the volume of cortical gray matter in several brain regions compared to individuals who did not show any signs of an incipient psychiatric disorder. Within the group with the "at risk mental state", deficits in the frontal and temporal cortex on the right side of the brain distinguished subjects that became psychotic during a follow-up period from those that did not.

McClure *et al.* (pages 1157–1160) conducted a four-week, double-blind, placebo-controlled study of the effectiveness of guanfacine, an agonist for the noradrenergic alpha-2A receptor, for the treatment of cognitive deficits associated with schizophrenia in 29 individuals with schizotypal personality disorder (SPD). The authors showed that, relative to placebo, guanfacine reduced impairments in "context processing."

Combining *in situ* radioligand binding and *in situ* hybridization in brain tissue from individuals who had been schizophrenic, **Scarr *et al.*** (pages 1161–1170) showed that reduced hippocampal [^{3}H]pirenzepine binding to muscarinic cholinergic receptors was accompanied by decreased messenger ribonucleic acid (mRNA) levels for the muscarinic M4 receptor. These data further implicate muscarinic cholinergic mechanisms in cognitive impairments associated with schizophrenia.

Functional neuroimaging studies implicate the medial prefrontal cortex (MPFC) in psychological functions pertaining to self-reference and social information processing. **Taylor *et al.*** (pages 1171–1178) report that patients with schizophrenia or schizoaffective disorder who had symptoms of reality distortion showed hyperactivity of the MPFC compared to patients who did not experience reality distortion.

Mittal *et al.* (pages 1179–1186) provide evidence that among individuals with schizotypal personality disorder, minor physical abnormalities are associated with subtle signs of movement disorder and activation of the hypothalamo-pituitary adrenal axis, as reflected in elevated cortisol levels. These findings lend further support to the hypothesis that schizophrenia is a disorder of early development that is not limited to the brain.

As in the prior paper, there is interest in better understanding schizophrenia in the context of organismal development. **Hennessy *et al.*** (pages 1187–1194) use three dimensional imaging to quantitatively demonstrate that individuals with schizophrenia show subtle alterations in facial shape that may not be apparent upon visual inspection.

Deficits in N-methyl d-aspartate (NMDA) glutamate receptor function may play an important role in the neurobiology of schizophrenia, but the sources of NMDA receptor dysfunction in schizophrenia is not yet clear. D-amino oxidase (DAO) is an enzyme that metabolizes D-serine, a facilitator of NMDA glutamate receptor function. Lower functioning versions of the gene that codes for DAO have been linked to the risk for developing schizophrenia. In this report, **Wood *et al.*** (pages 1195–1199) examine several genes previously associated with schizophrenia and, based on this analysis, provide strong additional evidence that variation in DAO is related to the vulnerability for schizophrenia.

Another gene that codes for a protein involved in the metabolism of D-serine, serine racemase, also has been implicated in schizophrenia. D-serine racemase converts L-serine to D-serine, the form of this amino acid that facilitates NMDA glutamate receptor function. **Morita *et al.*** (pages 1200–1203) now report evidence that a less functional variant of this gene, which reduces transcription, was associated with the susceptibility to schizophrenia.

Investigators have long hypothesized that increased distractibility in schizophrenia might reflect deficient filtering of sensory input. **Braff *et al.*** (pages 1204–1207) now show that the two best-studied forms of "filter deficits" in schizophrenia are unrelated. In other words, the deficient tendency to inhibit the rapid neural response to click pairs (P50 gating) and the reduced capacity of a quiet warning pulse to suppress the acoustic startle response (pre-pulse inhibition) are not correlated within individuals. This finding suggests that these deficits may have distinctive neurobiological underpinnings and heritability.

The Disrupted in Schizophrenia 1 gene (*DISC1*) has been implicated in the risk for schizophrenia spectrum disorders. **DeRosse *et al.*** (pages 1208–1210) now report exciting new data implicating variation in the *DISC1* gene with the lifetime severity of delusions in 199 patients with schizophrenia and schizoaffective disorder.

There is an ongoing effort to study endophenotypes, i.e., traits that are associated with schizophrenia but which may be more directly connected to particular genotypes than the overall

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disorder. **Selch *et al.*** (pages 1211–1214) now report that variations in components (introns, promotor region) of the *MLC1* gene are associated with periodic catatonia, a trait present in a subgroup of patients with schizophrenia.

There remains interest in the possibility that brain infections might contribute to the development of schizophrenia. **Amminger *et al.*** (pages 1215–1217) report a new link in this regard. They found that, among people who appeared to be in a prodromal phase for schizophrenia and who showed evidence of exposure to an infectious agent, *Toxoplasma gondii,* increased immunoglobulin-G (IgG) antibody levels to *Toxoplasma gondii* were associated with more severe positive symptoms.