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Schizophrenia Genetics

Variations in the neuregulin 1 (*NRG1*) gene appear to contribute to the heritable risk for developing schizophrenia, and may contribute to difficulties in filtering sensory information that are associated with schizophrenia. Sensory filtering can be measured using the prepulse inhibition (PPI) test. PPI is the ability of a weak warning "prepulse" to inhibit a subsequent startle response to a louder sound. **Hong *et al.*** (pages 17–23) report that a missense mutation on the neuregulin 1 gene may have a functional effect on PPI in both schizophrenia and healthy control populations.

Dysbindin, a known risk gene for schizophrenia, is part of a protein complex called BLOC-1. **Morris *et al.*** (pages 24–31) have performed the first comprehensive association study of the seven other genes that encode BLOC-1 proteins, incorporating a novel method for testing gene-gene interaction. This work has identified effects associated with single genes and interactions between genes that increase schizophrenia risk. These findings suggest that dysbindin may mediate its effect on schizophrenia pathogenesis via the BLOC-1 protein complex.

Proitsi *et al.* (pages 13–16) combined genome wide meta-analysis with bioinformatics to search for genes involved in the regulation of glycogen synthase kinase-3 (GSK-3) through the wnt pathway as putative susceptibility loci for schizophrenia. In a case-control study in a Chinese population, they found that one of these genes, DKK4, is associated with the disease and confirmed this in a replication group.

Campbell *et al.* (pages 32–41) report that differential effectiveness of antipsychotic treatment was predicted, in a subset of patients with schizophrenia, by variants of the gene encoding for the regulator of G-protein signaling 4 (RGS4), a protein that regulates the functional consequences of activating neurotransmitter receptors. The findings presented will require replication, but they indicate that RGS4 contributes to both the severity of schizophrenia symptoms and the response to antipsychotic treatment. These data raise the possibility that, in the future, genotyping for *RGS4* variants and other genetic attributes may help to guide individualized treatment strategies for schizophrenia.

Negative symptoms of schizophrenia have been associated with low serum folate levels. **Roffman *et al.*** (pages 42–48) report that a version of a gene that influences folate metabolism, the 6C77T allele of the methylenetetrahydrofolate reductase (*MTHFR*) gene, was associated with worse negative symptoms, but with milder positive symptoms. The association of genotype and negative symptoms was particularly prominent in the setting of low serum folate. These data suggest that diet and genetic factors may interact to shape the features of schizophrenia.

Facial & Auditory Processing Deficits

Oxytocin is a hormone that has been linked to the capacity for intimacy and social affiliation. **Guastella *et al.*** (pages 3–5) tracked the eye-movements of male volunteers presented with neutral human faces after intranasal administration of oxytocin or placebo. Results showed that oxytocin increased gaze toward the eye-region of the faces, suggesting a mechanism for how oxytocin enhances emotion recognition in humans and a role for its use in the treatment of disorders characterized by facial processing deficits.

22q11.2 deletion syndrome (22q11DS) substantially increases the risk for developing a schizophrenia-like disorder. **Andersson *et al.*** (pages 49–57) show that in 22q11DS, regions of the brain involved in interpreting faces or the facial expression of emotion are altered in their function. These results provide a link between brain circuits involved in interpreting facial expressions and the social and emotional problems associated with schizophrenia.

Schizophrenia is associated with impairments in attention. **Todd *et al.*** (pages 58–64) provide evidence that as schizophrenia progresses, attention problems associated with schizophrenia become more complex. The authors show that early in the course of schizophrenia, individuals show deficits in detecting changes in the duration and intensity, but not frequency of auditory stimulation. As the disease progresses, the ability to detect subtle changes in the frequency of auditory stimuli also becomes compromised.

Cognitive Impairments in Schizophrenia

Wobrock *et al.* (pages 65–71) observed a reduction in magnetic resonance imaging (MRI) volume of the anterior limb of the right internal capsule, a brain region containing neural pathways connecting the cortex and thalamus, in individuals with schizophrenia and their unaffected relatives as compared to healthy controls. This volume reduction, suggestive of reduced brain connections, was associated with poorer performance on some cognitive tasks.

The catechol-o-methyltransferase (COMT) gene influences the metabolism of dopamine, a neurotransmitter implicated in schizophrenia and cognitive function. **Diaz-Asper *et al.*** (pages 72–79) show that variability (polymorphisms) in several regions of the COMT gene interact, i.e., form a haplotype, in a way that influences cognitive function in healthy individuals and in people with schizophrenia.

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Schizophrenia is a heritable disorder associated with abnormal brain development. **Stanfield *et al.*** (pages 80–85) show subtle clinical symptoms that are associated with schizophrenia in otherwise healthy people, schizotypal personality disorder, are also associated with abnormal folding of the frontal cortex. These data provide additional evidence that clinical and neurobiological features in even subtle aspects of the heritable risk for schizophrenia are rooted in altered brain development.

Receptor Manipulations in Animal Models of Schizophrenia

Olszewski *et al.* (pages 86–91) tested a novel drug that inhibits the breakdown of the transmitter N-acetylaspartylglutamate, which activates a receptor that reduces schizophrenia-like behaviors in some animal models. Their findings indicate that this drug is effective in an animal model of schizophrenia, and that it may represent a new therapeutic approach to treatment.

Hashimoto *et al.* (pages 92–97) demonstrated that repeated administration of the N-methyl-D-aspartate (NMDA) receptor antagonist phencyclidine (PCP) decreased the density of α7 nicotinic receptors (α7 nAChRs) in the mouse brain, and that the novel α7 nAChR agonist SSR180711 could ameliorate PCP-induced cognitive deficits in mice. These findings suggest that α7 nAChR agonists including SSR180711 would be potential therapeutic drugs for cognitive deficits in schizophrenic patients.

Semenova *et al.* (pages 98–105) show that a recently discovered brain receptor for serotonin (5-HT_7) might be of importance for understanding certain aspects of schizophrenia. The study focused on sensory input processing, which is often impaired in schizophrenia, and finds that blockade of this particular serotonin receptor in mice alleviates this impairment. The findings also provide important new tools to study the role of the 5-HT_7 receptor in the action of atypical antipsychotic drugs.

Brain Volume Loss in Schizophrenia

Some individuals diagnosed with schizophrenia experience progressive reductions in brain volume over the span of their illness. **Van Haren *et al.*** (pages 106–113) sought to examine the trajectory of the volume changes over time by performing two MRI scans over a 5-year interval in schizophrenia patients and healthy controls. They found that volume reductions were most pronounced among patients who had poorer clinical outcomes.

PET & MRI Findings in Unaffected Relatives of Schizophrenia Patients

Huttunen *et al.* (pages 114–117) report that, like patients with schizophrenia, non-psychotic first-degree relatives of patients with schizophrenia have increased rates of dopamine synthesis in the striatum, as assessed using positron emission tomography (PET).

Fan *et al.* (pages 118–124) found that healthy family members of people diagnosed with schizophrenia show a profile of regional brain volume deficits, as measured with MRI, that overlaps substantially with the pattern of regional brain structural deficits associated with schizophrenia. These findings provide evidence that high-dimensional pattern analysis and classification can identify complex and subtle structural correlates of the genetic risk for schizophrenia, i.e., endophenotypes.

Sarcosine Treatment for Acute Schizophrenia

Lane *et al.* (pages 9–12) studied sarcosine, a glycine reuptake inhibitor that enhances NMDA neurotransmission, in patients with acute schizophrenia and found that patients administered 2 grams/day were more likely to respond to treatment, particularly for those who were antipsychotic-naïve. Sarcosine represents a new therapeutic approach distinct from currently available antipsychotics.

Lamotrigine: An Effective Treatment for Bipolar Disorder

Mood stabilizers for bipolar disorder are often evaluated based on their ability to treat or prevent affective episodes, but in routine practice, clinicians often target weekly or daily variation in mood. **Goldberg *et al.*** (pages 125–130) used prospective life charting to compare deviations from euthymia on a weekly basis during a 26-week randomized comparison of lamotrigine or placebo. Results showed nearly a two-fold greater likelihood for achieving euthymia with lamotrigine than placebo.