GENES AND SCHIZOPHRENIA

Genes and Schizophrenia: From a Festschrift Seminar Honoring
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Recent data have begun to elucidate the genetic architecture of schizophrenia, as well as provide new insights into the relationships of specific genetic factors across diagnostic boundaries, with specific symptom domains, and in the prediction of antipsychotic treatment response. Not surprisingly, work conducted at the Maryland Psychiatric Research Center (MPRC), led by Dr William Carpenter, has helped to guide the thinking behind much of this work, as well as contributed valuable data toward these efforts. In this article, I will briefly summarize some of the major findings emerging from these lines of research and highlight the role of the Dr Carpenter and his colleagues at the MPRC in this area.

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Molecular Genetic Overlap Across Psychiatric Disorders

Although the development of DSM-III and its successors greatly enhanced the reliability of psychiatric nosology, it has become increasingly clear that its clinical syndromes do not cleanly “carve nature at the joints.” For example, overlap between schizophrenia and bipolar disorder has been documented at multiple levels; including neuroanatomic and neurofunctional abnormalities,1 as well as clinical characteristics (ie, presence of psychotic features and response to second-generation antipsychotics).2 At the same time, other patients with psychosis are not adequately captured by either category, receiving nonspecific diagnoses.3 These limitations in the current nosology may be impeding attempts to understand the pathophysiology of psychotic illness and develop clinically useful biomarkers.

Recently, large-scale genome-wide association studies (GWAS) have provided new data on the overlap across psychiatric disorders. In 2009, the International Schizophrenia Consortium4 published results from a GWAS of 3322 subjects with schizophrenia and 3587 controls, in which, although only a limited number of loci achieved genome-wide significance, the authors were able to detect evidence for a polygenic component to illness through use of a novel score test. Essentially, as increasingly liberal thresholds of significance (as high as $P < .50$) were utilized to identify potential risk alleles in an arbitrarily selected discovery data set, these putative risk alleles were able to differentiate schizophrenia cases from controls in additional target data sets, including independently collected data sets derived from different ethnic groups. Most notably, however, these alleles also explained significant, albeit modest, amounts of the variance in risk for bipolar disorder in 2 independent data sets, with no significant evidence observed for overlap with multiple nonschizophrenic disorders including diabetes and rheumatoid arthritis. These data suggesting polygenic overlap are supported by candidate gene studies implicating a bipolar disorder risk gene, CACNA1C, in risk for schizophrenia,5 as well as a recent study from the Psychiatric Genomics Consortium (PGC) of over 60 000 subjects identifying shared loci across 5 disorders (autism spectrum disorders, attention deficit hyperactivity disorder, major depressive disorder, bipolar disorder, and schizophrenia), including CACNA1C.6 Taken together, these recent studies provide considerable evidence that a proportion of alleles that increase risk for schizophrenia are not specific to schizophrenia but also impart risk for other psychiatric disorders, including bipolar disorder.

Interestingly, Carpenter and colleagues’ early work in the area of symptomatic overlap between psychiatric disorders anticipates these molecular genetic results. In the study by Carpenter et al,7 the authors investigated the incidence of Schneider’s first rank symptoms (hallucinations, delusions, thought disorder etc.) commonly believed to be pathognomonic for schizophrenia, in a
cohort of 131 psychiatrically ill subjects, including bipolar disorder patients, systematically characterized with a structured interview with established reliability. Results indicated that although first rank symptoms were present in the majority of the patients diagnosed with schizophrenia, that there was still a substantial proportion of schizophrenia subjects who did not exhibit these symptoms, and that even among patients carefully diagnosed with nonschizophrenia diagnoses, there was a substantial incidence (23%) of these key symptoms. Carpenter stated “we conclude that the postulated pathogenomicity of first rank symptoms is refuted,” solidly supporting the hypothesis that symptomatic overlap could be observed across disorders.

Genetics of Symptom Domains: The Importance of Negative Symptoms

Data suggesting the overlap of symptoms across diagnostic groups have suggested an alternative to diagnosis-based genetic studies. For many years, the MPRC group has been at the forefront of clinical and neurobiological investigations of a particularly important symptom domain of illness, the negative symptoms. The negative symptoms include blunted affect, avolition, and alogia and have been shown to be enduring trait-like characteristics, relatively resistant to pharmacotherapy, and linked to brain structural abnormalities. Carpenter and colleagues developed the concept that these symptoms can be primary, compared to secondarily associated with medication or mood state, and introduced assessment scales that could reliably rate these symptoms in a wide range of patient populations.

The criticality of negative symptoms is underscored by the wealth of data linked negative symptom severity to illness outcome. Palmer et al. assessed functional status in 83 patients with schizophrenia and found that more severe negative symptoms were associated with poorer outcome in terms of work history, independent living status, and driving status. Bowie et al. measured real-world outcome in 78 patients with schizophrenia using the Specific Level of Function Scale and reported a significant influence of negative symptoms on interpersonal skills but no significant effect on community activities or work skills. These data in chronic subjects are consistent with baseline negative symptom severity. Analyses of data collected at the Zucker Hillside Hospital (ZHH) are consistent with this; in a longitudinal study of 250 patients with schizophrenia enrolled within 6 months after hospital discharge and followed for 18 months, we found that general cognitive ability and negative symptomatology are significant correlates of overall disability. Zero-order correlations for each of these 2 predictors with global functioning were −.33 and −.35, respectively (Ps < .001) (figure 1). By contrast, severity of positive and depressive symptoms was not significantly correlated with functional disability. Similarly, in a separate cohort of 185 stable subjects with schizophrenia, we demonstrated that negative symptoms specifically predicted work and social functioning.

Notably, negative symptoms may be influenced by genetic factors. Ross et al. found that there was a significant sibling correlation for primary negative symptoms, indicating a familial and therefore a potential genetic contribution. To date, the majority of genetic studies of negative symptoms have been candidate gene based, predicated on the idea that genes implicated in risk for schizophrenia may have more pronounced effects on specific symptom domains. For example, the gene DTNBP1 or dysbindin codes for a 40–50kDa protein that binds to β-dystrobrevin, a component of the dystrophin glycoprotein complex in the brain, and has been linked to schizophrenia in several genetic studies. Notably, studies suggest that DTNBP1 genotype may also influence the severity of negative symptoms in schizophrenia. Fanous et al. examined 755 subjects in the Irish Study of High Density Schizophrenia and reported that a DTNBP1 schizophrenia risk haplotype was significantly overtransmitted to subjects with greater negative symptom ratings. Factors for hallucinations, delusions, and depressive and manic symptoms were not related to the high-risk DTNBP1 haplotype, and no other haplotype within the sample was associated with negative symptoms. This relationship was not observed in a separate study in an Irish case-control sample; however, the symptom factor structure differed between the 2 Irish samples.

We also assessed the role of DTNBP1 variation in schizophrenia and reported that 3 individual single nucleotide polymorphisms and a single 6-locus haplotype were associated with schizophrenia and schizoaffective disorder in Caucasian subjects, albeit with a modest odds ratio. Moreover, we observed that our DTNBP1 risk haplotype was also associated with significantly (P = .001) greater negative symptoms in schizophrenia subjects. Risk haplotype carriers displayed significantly higher ratings than noncarriers on each of the three 3 SCID-IV negative symptom items: avolition (P = .039), alogia (P = .014), and flattened affect (P = .016) (figure 2). The relationship was independent of an effect of the risk haplotype on neurocognition, as a global neurocognitive measure and WRAT-3 performance were included as covariates in these analyses. These data provide evidence that DTNBP1 risk haplotypes may be associated with a greater degree of negative symptoms in schizophrenia.

In addition to DTNBP1, other schizophrenia risk variants, including a variant near the microRNA 137
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gene, have been implicated in negative symptom severity. Moreover, larger scale efforts are now underway to assess the contribution of specific genetic factors to key symptom domains. The PGC is amassing data from thousands of subjects with more refined symptomatic assessments to conduct a comprehensive genome-wide analysis of symptom domains including negative symptoms. Finally, relatively large-scale studies within academia and the Veterans Administration system are focusing their efforts on the identification of genes that influence functional disability and may further highlight the important role of genes that influence negative symptom severity. In all of this work, the contributions of Dr. Carpenter and colleagues toward the identification and characterization of this critical domain of psychopathology are notable and provide further evidence of his key role in advancing our understanding of the genetics of mental illness.

Pharmacogenetics of Schizophrenia

The advances in molecular genetics have also provided the impetus for renewed attempts to identify antipsychotic drug-response predictors or pharmacogenetics. Some of the earliest work focused on the prototypic atypical antipsychotic agent clozapine for several reasons. First, a number of important studies including some conducted by the MPRC group highlighted the fact that clozapine, among all other antipsychotic agents, appeared to offer superior antipsychotic efficacy on poorly responsive or treatment-resistant patients. Second, clozapine has affinities in the nanomolar range for dopaminergic, serotonergic, noradrenergic, muscarinic, and histaminic receptors, suggesting a number of potential candidate systems for investigation in pharmacogenetic studies of clozapine’s enhanced efficacy. Finally, clozapine’s association with the potentially fatal side effect of agranulocytosis required that treated patients undergo regular venipuncture for white blood cell counts, and therefore access to peripheral blood samples from which to extract DNA was improved.

The first generation of clozapine pharmacogenetic studies was conducted by just a few groups, including a collaborative group that included NIMH, NIAAA, and MPRC investigators, and were candidate gene studies focused on loci in the dopamine and serotonin receptor systems. Arranz and colleagues initially attracted interest in the serotonin 5-HT2A T102C polymorphism with a report of a significant association between the 102C allele and failure to respond to clozapine in a cohort of 149 patients with chronic schizophrenia who were retrospectively assessed with a Global Assessment Scale. These data were not replicated in a series of clozapine studies from independent laboratories as well as in a study that included typical antipsychotic agents. 5-HT2A T102C could be considered a relatively weak candidate polymorphism because it does not result in an amino acid substitution at the protein level, and there is little evidence that it produces significant functional effects on 5-HT2A receptor function. A less common polymorphism within the 5-HT2A gene, His452Tyr, not in significant linkage disequilibrium with T102C has also not consistently been found to be associated with clozapine response.

Another obvious candidate for pharmacogenetic studies of antipsychotic drug response is the D2 receptor gene (DRD2). To date, all known antipsychotic drugs have potent affinities for the D2 receptor, and functional brain imaging studies have suggested that D2 receptor binding by antipsychotic agents may be “necessary and sufficient” for antipsychotic efficacy. Even more recently developed drugs that have targeted non-D2 receptors without at least some element of D2 blockade have unfortunately failed to treat schizophrenia effectively, despite early promise. However, there are few common polymorphisms within the coding regions of DRD2 and thus, fewer studies of DRD2 and antipsychotic drug response have been conducted compared with the 5-HT system.

Some of the earliest studies of DRD2 polymorphisms, specifically, the −141C Ins/Del and Taq1A variants,
revealed promising associations with antipsychotic efficacy, including data from the MPRC group. Although the subsequent literature has been marked by mixed results and small sample sizes, a pharmacogenetic meta-analysis composed of 687 patients reported that the 141C Ins/Del polymorphism significantly influences antipsychotic drug response, whereas there was not a significant relationship between clinical response and the Taq1A variant. It can be argued that these data, providing evidence that the strongest candidate gene for antipsychotic drug response is linked with clinical outcomes, provide proof of principle for these types of pharmacogenetic studies, including larger scale GWAS studies, and it is notable that, once again, Dr Carpenter and his group were critically involved at the outset of this line of research.

Pharmacogenetic studies of antipsychotic drug-induced adverse events have also been a focus of current research. Clozapine-induced agranulocytosis is a rare, but potentially serious adverse effect that limits clozapine’s clinical utilization despite its enhanced efficacy in treating refractory schizophrenia. A candidate gene-based pharmacogenetic study found an association between an allele at the HLA-DQB1 locus with risk of agranulocytosis in 2 independent clozapine-treated cohorts. Effect sizes were extremely high (OR = 16.86); nearly 90% of allele carriers developed agranulocytosis. Unfortunately, the overall sensitivity of the marker was only 21%, which indicates that a majority of individuals who develop agranulocytosis are not carriers of the allele and presumably have other genetic risk factors. Thus, a more comprehensive risk profile would be necessary in order to obviate the need for invasive monitoring.

Unlike agranulocytosis, weight gain is a much more common adverse effect of antipsychotic medications. Recently, our group has found a strong genetic signal in predicting antipsychotic-induced weight gain. An initial GWAS of antipsychotic-induced weight gain identified a top signal on chromosome 18q21 in a pediatric sample prescribed antipsychotic drugs for the first time. Risk allele homozygotes gained twice as much weight as other patients after 12 weeks of treatment, with consistent effects observed on key metabolic parameters. This result was replicated in 3 other independent samples, with strikingly similar effect sizes.

This locus is approximately 150kb downstream from MC4R, the melanocortin 4 receptor gene, which has been previously found to be associated with obesity in the general population. MC4R-expressing neurons in the ventromedial hypothalamus are regulated by circulating levels of leptin via pathways in the arcuate nucleus. These leptin-sensitive pathways are regulated by 5-HT2C receptors, which have also implicated in weight gain in pharmacogenetic studies. The consistency of the HTR2C-MC4R findings increases the possibility that pharmacogenetically mediated intervention strategies may soon be feasible.

Conclusions
Emerging data from psychiatric genetics research suggests a better understanding of the contribution of genetic variation to susceptibility to multiple psychiatric disorders, to clinical symptom severity, and to the interindividual variability in antipsychotic drug response. In each of these domains, the contributions of Dr William Carpenter and his colleagues at the MPRC have been instrumental, and our field has been greatly enhanced by his leadership in these, as well as many others, areas of scientific inquiry.

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