

A Primary Candidate Gene for Obsessive-compulsive Disorder

ALTHOUGH DOZENS OF genes have been linked to psychiatric disorders, connecting the dots between behavioral phenotypes and genetic variations has not been easy. In this issue of the ARCHIVES, 2 groups of investigators report that statistically significant associations between the transmission of obsessive-compulsive disorder (OCD) for male but not female offspring, and a genetic locus on chromosome 9p24 that codes for a high-affinity neuronal/epithelial excitatory amino acid transporter (ECCA-1) known in the genetic world as *SLC1A1* (solute carrier family 1, member 1; Online Mendelian Inheritance in Man [OMIM] 133550).^{1,2} In the brain, this transporter is crucial in terminating the action of the excitatory neurotransmitter glutamate and in maintaining extracellular glutamate concentrations within a normal range.

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These data add to a growing body of work that suggest that *SLC1A1* is perhaps a primary candidate gene for OCD. This evidence includes the results from 2 independent genome scans that identified a region of chromosome 9p24 that had a suggestive linkage to early-onset OCD.^{3,4} Other suggestive data include location in the brain where the gene is expressed (cortex, striatum, and thalamus), cerebrospinal fluid studies, brain imaging findings, medication effects, and other candidate gene studies.⁵⁻¹⁰

We concur with the authors that their findings are promising. Efforts to replicate these findings in larger samples (with additional single nucleotide polymorphisms [SNPs] from the region) are clearly warranted. With the recent accel-

eration of SNP identification from the HapMap Project, many more polymorphisms within *SLC1A1* are available that have not been tested in OCD. Further, the use of these markers in genotyping these and additional markers within the large multigenerational families that were part of the original genome scans to find enhanced evidence for linkage would be particularly noteworthy. We hope to obtain a logarithm-of-odds ratio greater than 6.0, which has been found for schizophrenia and *DISC1* (disrupted in schizophrenia 1).¹¹ But before beginning the celebration, we would like to note where these findings, if true, might lead. We close with a few reflections of the limitations of these 2 studies.

If it is true that *SLC1A1* is a vulnerability gene for OCD, then there is a lot of work to be done. The following are a few questions that would need to be addressed: What are the functional variants? What are the interactive genes? How do we understand the robust sex effect? How does it effect neural development? What endophenotypes are most closely associated with these variants? Can we create a valid animal model? What might it tell us vis-a-vis therapeutics?

What are the functional variants? Further research, including sequencing of the putative susceptibility region is surely warranted in order to locate the actual functional variant(s) contributing to the OCD phenotype. The identification of these sequence variants will set the stage for understanding how they effect *SLC1A1* expression and ultimately central nervous system function.

What are the interactive genes? Our list is surely idiosyncratic and includes glutamate transporter EAAC1-associated protein (*GTRAP3-18*), Slit and Trk-like 1

(*SLITRK1*), the serotonin transporter (*SLC6A4*), the glutamate receptor, ionotropic, NMDA subunit 2B gene (*GRIN2B*), and the glutamate receptor ionotropic kainate receptor 2 gene (*GRIK2*). The *GTRAP3-18* gene is expressed in numerous tissues, localizes to the cell membrane and cytoplasm, and specifically interacts with the carboxy-terminal intracellular domain of EAAC1 (the gene product of *SLC1A1*).¹² Increasing the expression of *GTRAP3-18* in cells reduces EAAC1-mediated glutamate transport by lowering substrate affinity. As a consequence, functional variants of *GTRAP3-18* could well potentiate the effects of the functional variants of *SLC1A1*. Although likely premature at present, it might be worthwhile to identify SNPs at the *GTRAP3-18* locus and haplotyping individuals with OCD to determine if there are gene-gene interactions. Likewise, functional variants at the *SLITRK1* locus are associated with Tourette syndrome,¹³ a condition closely associated with early-onset OCD.^{14,15} Its gene product is also expressed in overlapping brain regions. Functional variants of the serotonin transporter have also been identified in OCD.¹⁶ Although these are quite rare, Sutcliffe et al¹⁷ have recently found 4 coding substitutions at highly conserved positions and 15 other variants in 5' noncoding and other intronic regions of *SLC6A4* transmitted in autistic families exhibiting increased rigid-compulsive behaviors. Again, given the overlapping phenotypes of OCD and autism and other pervasive developmental disorders, a search for gene-gene interactions with some of these functional variants may be worthwhile.¹⁸ Further genetic evidence implicating glutamate neurotransmission in OCD has been provided by preliminary candidate gene findings for *GRIN2B* and *GRIK2*.^{9,10}

How do we understand the robust sex effect? As noted by these authors, the patient's sex appears to be interactive with many of the features of OCD including age at onset, precipitating events at onset of OCD, the range of obsessive-compulsive symptoms, comorbid disorders, and personality traits.¹⁹ There have also been numerous genetic studies showing gender dimorphism in OCD.²⁰⁻²⁴ Although the precise mechanisms underlying these effects remains in doubt, given that early-onset OCD appears well before puberty, our favorite explanation concerns the exposure of the developing brain in utero and during the early postpartum period to high levels of androgens.²⁵ Given the major advances in genomic science, it is now possible to also ask fundamentally interesting questions of the genome. For example, does the *SLC1A1* locus have any conserved androgen receptor binding sites in its promoter region? According to our colleague Matthew W. State, MD, PhD (oral communication, January 2006), and the Web site www.genome.ucsc.edu, it appears that among the approximately 45 predicted transcription factor binding sites, there are 3 potential androgen receptor binding sites. The prediction algorithms based on conserved sequences always yield multiple hits, therefore, it is not possible without experimentation to confirm them. In contrast, around *GTRAP3-18*, no potential androgen receptor binding sites were predicted among the potential transcription factor binding sites. However, it has been confirmed by others that there is a functional retinoic acid receptor binding site as well as another for Sex-Determining Region Y (*SRY*) in the promoter region of *GTRAP3-18*. The *SRY* encodes a transcription factor that is a member of the high mobility group-box family of DNA binding proteins, and there is a predicted androgen binding site upstream of the *SRY* coding region on the Y chromosome. There may be a story here regarding these data.

How do these variants affect neural development? Some of the most exciting developments in psychiatric genetics concern our deepening understanding of how the func-

tional variants of vulnerability like *DISC1* and *SLITRRK1* influence neural development. Reports on these topics were judged by the editors of *Science* to be "hot runners-up" for the honor of being the breakthrough of the year for 2005.²⁶ One Japanese research team found that *DISC1* is a component of the microtubule-associated dynein motor complex and is essential for normal microtubular dynamics. Inhibition of *DISC1* alters brain development causing subtle abnormalities in the animals' cerebral cortices similar to those seen in postmortem brains from schizophrenia patients.²⁷ Another team from Scotland linked *DISC1* to the cAMP molecular signaling pathways important in brain development and in regulating neurotransmitter levels.²⁸ Similarly, we described multiple functional variants of *SLITRK1* that may cause a very small percentage of cases of Tourette syndrome. We also documented that *SLITRK1* influences branch formation by neurons and is active during development in brain regions thought to be altered in Tourette syndrome and other conditions, including OCD.¹³

What endophenotypes are most closely associated with these variants? Careful consideration of the heterogeneity of the OCD phenotype is also needed. For example, there is clear evidence from factor-analytic studies that OCD across the age span consists of a small number of overlapping symptom dimensions rather than a unitary disorder.^{29,30} Future association and linkage studies of OCD should include separate analyses of these symptom dimensions based on the assumption that they are endophenotypes that are likely to be more etiologically homogeneous and closely linked to the action of genes compared with the DSM-IV OCD diagnosis. Structural and functional neuroimaging findings may also prove to be robust endophenotypes for genetic association studies of OCD. The combination of genotypic characterization with detailed phenotypic and in vivo anatomical data will be a particularly powerful combination as we move to the next level of translational research in psychiatry.^{31,32} Our pick for

the most promising biologically mediated endophenotype for OCD and related forms of Tourette syndrome will be electrophysiological in nature.^{33,34}

Can we create a valid animal model? Needless to say, the development of valid animal models will be a key aspect in the development of novel therapeutics. While this may be true at least to some degree for *DISC1*, it is less clear that creating a null mutation of *SLC1A1* will prove to be a valid model of OCD.³⁵ It may be an entirely different story once the functional variants are identified, if they exist.

What might it tell us vis-a-vis therapeutics? While serotonin reuptake inhibitors are mainstays for the pharmacological treatment of OCD,^{36,37} it is clear that these agents often fall short of the mark. At least 40% to 60% of OCD patients do not respond adequately to therapy using serotonin reuptake inhibitors and an even greater proportion of patients fail to experience a remission.³⁸ Even those patients who are judged to be "clinical responders" based on the usual criteria (ie, typically a greater than 25% or 35% decline in symptoms) continue to experience significant impairment. Although neuroleptic augmentation of treatment using serotonin reuptake inhibitors has been shown to be beneficial,³⁸ many other agents have been exhausted. Recently, Coric et al³⁹ found in an open trial that riluzole augmentation shows real promise. Riluzole is a potent ant glutamatergic agent that reduces glutamatergic neurotransmission in several ways, including inhibition of glutamate release, inactivation of voltage-dependent sodium channels in cortical neurons, and blockade of gamma-aminobutyric acid reuptake.^{40,41} If functional variants at the *SLC1A1* locus are forthcoming, then genotyping individuals may be of value on predicting their response to riluzole augmentation and related measures of brain glutamate levels.^{7,8}

The authors of these 2 reports are quite circumspect and well aware of the limitations of their studies. Although some of the same SNPs were used in both studies, the findings for

specific SNPs did not replicate across the studies nor is it clear that any of the polymorphisms are likely by themselves to confer susceptibility. It is also unclear if combining the data from these 2 studies would produce significant results. The authors credibly discuss these issues. It is also possible, as pointed out by Deckel et al,² that if linkage is present in this chromosomal region, then this finding alone may confer a significant result⁴² even in the absence of a true association with *SLC1A1*.

As pointed out by Insel and Quirion,⁴³ genomics and neuroscience have come of age during the past 2 decades. Yet methods of diagnosis and treatment for patients with mental disorders have remained relatively unchanged. This may be about to change for OCD, Tourette syndrome, schizophrenia, and the rest of our field.

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