Progress in the elucidation of the genetic mechanisms involved in the expression of obsessive-compulsive disorder (OCD) has been hampered by 2 factors: heterogeneity of the clinical phenotype and lack of understanding of the molecular mechanism of the disorder. Efforts to narrow the phenotype have included identification of 4 symptom dimensions as well as investigation into comorbid and perhaps related illnesses such as Gilles de la Tourette’s syndrome, eating disorders, and impulse-control disorders. A number of familial studies have been conducted to explore the relationship of OCD to these illnesses and the possible existence of independently heritable components that make up the more complex disorder. Candidate gene studies are also being conducted, with the goal of understanding the molecular mechanisms of OCD.

From the Laboratory of Psychiatric and Molecular Genetics, SUNY at Buffalo (Drs. M. T. Pato and C. N. Pato) and the Unit of Psychiatric and Neurodevelopmental Genetics, Massachusetts General Hospital, Harvard Medical School, Charlestown (Dr. Pauls).

Presented at the symposium “Exploring the Boundaries of Obsessive-Compulsive Disorder and Other Anxiety Disorders: New Developments and Practical Approaches From the Fifth International OCD Conference,” which was held March 29–April 1, 2001, in Sardinia, Italy, and supported by an unrestricted educational grant from Solvay Pharmaceuticals.

Corresponding author and reprints: David L. Pauls, Ph.D., Unit of Psychiatric and Neurodevelopmental Genetics, Massachusetts General Hospital, Harvard Medical School, 149 13th St., 10th Floor, Charlestown, MA 02129 (e-mail: pauls@psych.mgh.harvard.edu).

Identified 4 symptom dimensions, or factors, in OCD: (1) aggressive, sexual, and religious obsessions and checking compulsions; (2) symmetry and ordering obsessions and compulsions; (3) contamination obsessions and cleaning compulsions; and (4) hoarding obsessions and compulsions. These 4 factors have recently been validated by Cochran et al. Based on data from the Tourette Syndrome Association International Consortium for Genetics Affected Sibling Pair Study, Leckman and colleagues found that factors 1 and 2 were significantly correlated in sib pairs concordant for Gilles de la Tourette’s syndrome. Mother-child correlations were also significant on these 2 factors. Further work in this dimensional approach, along with research in specific comorbid and perhaps related illnesses, could help to narrow phenotypes.

Links between OCD and eating disorders are another area of phenotype interest. Halmy and colleagues’ research has focused on patients with anorexia nervosa, who often exhibit OCD symptoms. In collaboration with an international multicenter group studying the genetics of anorexia nervosa, Halmi et al. have demonstrated a high frequency of obsessions and compulsions in patients with anorexia nervosa. Sixty-eight percent of anorexia nervosa restrictors (AN-R; anorexics who restrict food intake but do not binge/purge) and 79% of anorexia nervosa binge-purgers (AN-BP; anorexics who binge, then purge to get rid of the food) reported at least 1 obsession or compulsion. The preliminary findings of this study suggest that principle component analyses for AN-R, AN-BP, and OCD could be useful in identifying components of eating behaviors that might be independently heritable. One suggested approach to further genetic study is to look across DSM-IV diagnoses at clusters of traits and then at clusters of genes that might be related to the traits.

In a similar vein, Bellodi and colleagues have conducted research on several different but related disorders...
including OCD, OCD plus tics, Gilles de la Tourette’s syndrome, idiopathic focal dystonia, and OCD plus idiopathic focal dystonia. A family study by this group found that the morbidity risk for obsessive-compulsive spectrum disorders (OCD and tic disorders) was significantly higher among first-degree relatives of 136 eating disorder probands than among first-degree relatives of comparison subjects (9.7% vs. 0.0%). Segregation analysis is also being explored comparing subject samples with and without movement disorders and eating disorders. After conducting complex segregation analysis to test for models of genetic transmission in 107 OCD probands and their families, Cavallini et al. concluded that the OCD phenotype probably has a higher level of heterogeneity than the Tourette’s syndrome phenotype and could be regulated through different etiologic pathways. Complex segregation analysis on eating disorder probands and their relatives revealed that eating disorders and OCD followed a Mendelian dominant model of transmission, which suggests that a common genetic liability could account for eating disorders and OCD.

Family studies have also examined the relationship of OCD to spectrum disorders including pathological gambling and trichotillomania. Black et al. assessed the prevalence of eating disorders and pathological gambling in first-degree relatives of subjects with OCD and found no familial relationship between OCD and eating disorders or pathological gambling. Another study found higher rates of pathological grooming conditions (e.g., nail biting, skin picking, trichotillomania) in OCD probands and their first-degree relatives than in controls, but did not find higher rates of impulse-control disorders (e.g., kleptomania, pathological gambling, pyromania) in probands or their relatives. Wax and colleagues found a comorbidity rate of 44% for trichotillomania and OCD in 25 trichotillomania probands. Furthermore, an elevated rate of OCD (32%) was found among 75 first-degree relatives of the probands.

**CANDIDATE GENE RESEARCH IN OCD**

A number of candidate gene studies have been conducted with the goal of helping to elucidate the molecular mechanisms of OCD. Karayiorgou and colleagues reported positive findings in association studies of the catechol O-methyltransferase low enzyme activity (COMT-L) allele with OCD. A recent investigation of the role of COMT in OCD showed no significant association between a particular allele and the diagnosis of OCD. However, genotyped results from this study demonstrated a tendency for association between homozygosity at the COMT locus and OCD, suggesting a potential role for homozygosity in relation to OCD. Recent candidate gene research in OCD has also included studies of GABA-A-γ2, monoamine oxidase A, and the use of single nucleotide polymorphism analysis. In these reports, and in the world literature, there have been findings for candidate genes in serotonin, dopamine, and other regions (Table 1). Unfortunately, few findings have been positive, and most positive findings have been accompanied by negative ones.

Pauls has reported on a family-based association study of the 5-HT1D gene. G and C alleles of this gene differ by a single base pair, which changes the amino acid coded for and has some functional significance. In a sample of patients with Gilles de la Tourette’s syndrome and OCD, the G allele seemed to be transmitted with those patients who had obsessive-compulsive symptoms preferentially. Bellodi’s group has not found such an association in their work, while Mundo and coworkers have had some similar preliminary findings. Functional polymorphisms like the one in 5-HT1D and the one in COMT have generated enthusiasm because of the role they could play in understanding the mechanism of the illness.

Recent work by Kennedy et al. has focused on the myelin oligodendrocyte glycoprotein (MOG) gene rather than the typical candidates in the serotonin and dopamine systems. MOG, which is adjacent to the human leukocyte antigen (HLA) region and located close to the GABA-B

| Table 1. Candidate Genes in Obsessive-Compulsive Disorder

<table>
<thead>
<tr>
<th>Candidate Gene</th>
<th>Positive Findings</th>
<th>Negative Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-HT2A</td>
<td>Enoch et al., 1998</td>
<td>Nicolin et al., 1996; Pato et al., 2001; Bellodi et al., 2001; Billett et al., 1997; Ohara et al., 1998</td>
</tr>
<tr>
<td>SLC6A4</td>
<td>McDougle et al., 1999; Bengel et al., 1999</td>
<td></td>
</tr>
<tr>
<td>TPH</td>
<td>Han et al., 2000; Frisch et al., 2000</td>
<td></td>
</tr>
<tr>
<td>5-HT2C</td>
<td>Nicolin et al., 1996; Cavallini et al., 1998</td>
<td></td>
</tr>
<tr>
<td>5-HTT</td>
<td>McDougle et al., 1999; Bengel et al., 1999; Mundo et al., 2000; Pauls, 2001</td>
<td></td>
</tr>
<tr>
<td>5-HT1D</td>
<td>Bellodi et al., 2001</td>
<td></td>
</tr>
<tr>
<td>DRD2</td>
<td>Nicolin et al., 1996; Billett et al., 1998; Novelli et al., 1994</td>
<td></td>
</tr>
<tr>
<td>DRD3</td>
<td>Nicolin et al., 1996; Billett et al., 1998; Catalano et al., 1994</td>
<td></td>
</tr>
<tr>
<td>DRD4</td>
<td>Cruz et al., 1997; Billett et al., 1998</td>
<td></td>
</tr>
<tr>
<td>DAT-1</td>
<td>Frisch et al., 2000; Billett et al., 1998</td>
<td></td>
</tr>
<tr>
<td>COMT</td>
<td>Karayiorgou et al., 1997; Alsobrook et al., 1999; Schindler et al., 2000</td>
<td></td>
</tr>
<tr>
<td>MAO-A</td>
<td>Camarena et al., 2001</td>
<td></td>
</tr>
<tr>
<td>MOG-2</td>
<td>Kennedy et al., 2001</td>
<td></td>
</tr>
<tr>
<td>MOG-4</td>
<td>Kennedy et al., 2001</td>
<td></td>
</tr>
<tr>
<td>HLA-CAR</td>
<td>Kennedy et al., 2001; Richter et al., 2001</td>
<td></td>
</tr>
<tr>
<td>GABA-A-γ2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: COMT = catechol O-methyltransferase, DAT-1 = dopamine transporter, HLA-CAR = human leukocyte antigen–CA repeat, MAO-A = monoamine oxidase A, MOG = myelin oligodendrocyte glycoprotein, TPH = tryptophan hydroxylase.
gene, is implicated as an activator of complement and as such may be involved in a number of autoimmune processes, including those involved in the evolution of the pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) subtype of OCD. Kennedy’s group looked at 2 markers of the MOG locus (MOG-2 and MOG-4) and identified a significant association with the MOG-4 but not the MOG-2 locus. These findings are only preliminary, but they highlight the importance of looking beyond the typical OCD candidates based on treatment and diagnostic categories. It is also important to note that studying candidate genes related only to the sites of drug action, serotonin or dopamine, may not actually lead to a better understanding of the etiology or treatment of OCD.

FUTURE RESEARCH

The success of future research on the genetics of OCD will be dependent upon clarification of the inherited phenotype. At the present time, the DSM-IV and ICD-10 diagnostic classification of OCD is too broad and the resultant patient samples are extremely clinically heterogeneous. Given this clinical heterogeneity, it is likely that the underlying etiologic mechanisms are also quite diverse. To deal with this problem, investigators have turned to symptom clusters and spectrum or related disorders to try to narrow the phenotype as well as to recognize the multidimensional nature of the disorder. Other methods besides diagnosis are being investigated to “phenotypically” define samples; these methods include considering age at onset (could some forms of OCD be neurodevelopmental and others neurodegenerative?), functional neuroimaging, and neuropsychological testing (such as continuous performance tasks).

Technical matters in genetic research of OCD include the value of pedigree versus trio studies. Many researchers agree that families tend to be more informative. However, recent advances in statistical analysis suggest that trios may be more powerful than has been thought and that both types of samples, pedigree and trio, can inform results from the other type. 36

To date, there is no worldwide brain bank for OCD that would allow for testing transcription of mRNA, and the ability to easily collaborate with other sites to enhance sample sizes and replicate data is not yet a reality.

In conclusion, while it is clear that some forms of OCD are familial, the underlying genetic mechanisms are not clearly understood. This situation is not unique in psychiatric genetics. Most psychiatric disorders are familial, but the specific genetic mechanisms have not yet been elucidated. With the advent of more sophisticated analytic approaches and the completion of the human genome project, though, there is reason for optimism. However, large samples of families and patients will be needed to have enough statistical power to identify genomic regions that harbor susceptibility loci and/or genes that increase the risk for the manifestation of OCD. Thus, large collaborative efforts will be necessary to obtain sufficiently large samples of patients and families.

Disclosure of off-label usage: The authors have determined that, to the best of their knowledge, no investigational information about pharmaceutical agents has been presented in this article that is outside U.S. Food and Drug Administration–approved labeling.

REFERENCES

3. Leckman JF, Zhang H, Pauls DL. Obsessive-compulsive symptom dimensions in affected sibling pairs diagnosed with Gilles de la Tourette syndrome. Presented at the 5th International Obsessive Compulsive Disorder Conference; March 29–April 1, 2001; Sardinia, Italy
4. Halmi KA, Sunday S, Klump K, et al. Obsessions and compulsions in anorexia nervosa. Presented at the 5th International Obsessive Compulsive Disorder Conference; March 29–April 1, 2001; Sardinia, Italy
5. Bellodi L, Cavallini MC, Di Bella D. The genetics of obsessive-compulsive disorder and related disorders in Italian population. Presented at the 5th International Obsessive Compulsive Disorder Conference; March 29–April 1, 2001; Sardinia, Italy
9. Wax MA, Smith M, Murphy DL. Prevalence of obsessive-compulsive disorder in probands with trichotillomania and their first degree relatives: a preliminary study. Presented at the 5th International Obsessive Compulsive Disorder Conference; March 29–April 1, 2001; Sardinia, Italy
12. Richter MA, Mundo E, Sam F, et al. The GABA_Aγ2 receptor gene in OCD and social phobia. Presented at the 5th International Obsessive Compulsive Disorder Conference; March 29–April 1, 2001; Sardinia, Italy
14. Lesch K-P. Genetic dissection of obsessive-compulsive disorder (OCD). Presented at the 5th International Obsessive Compulsive Disorder Conference; March 29–April 1, 2001; Sardinia, Italy
Recent Findings in the Genetics of OCD

20. Pato CN, Schindler KM, Richter M, et al. Serotonin genes in OCD. Presented at the 5th International Obsessive Compulsive Disorder Conference; March 29–April 1, 2001; Sardinia, Italy
30. Pauls DL. The genetics of obsessive compulsive disorder. Presented at the 5th International Obsessive Compulsive Disorder Conference; March 29–April 1, 2001; Sardinia, Italy
35. Kennedy JL, Bezchlibnyk J, Barr CL, et al. Investigation of the myelin/oligodendrocyte glycoprotein (MOG) and HLA region CA repeat loci in obsessive compulsive disorder. Presented at the 5th International Obsessive Compulsive Disorder Conference; March 29–April 1, 2001; Sardinia, Italy