Recent Findings in the Genetics of OCD

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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. *(J Clin Psychiatry 2002;63[suppl 6]:30–33)*

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. OCD is not unique in this regard, since all psychiatric disorders are defined only descriptively and the molecular mechanisms of illness remain unclear.

To address these dilemmas, the session on genetics at the 5th International Obsessive Compulsive Disorder Conference attempted to explore both of these areas. Foci were alternative phenotypic classification schemes that included both the notion of subtypes and the idea that OCD could be comprised of independently heritable components that make up the more complex disorder, the results of candidate gene studies, and additional endophenotypic models that might help guide future genotypic exploration.

PHENOTYPIC CLASSIFICATION IN OCD

Symptom dimensions may be valuable as quantitative phenotypes in studies of OCD. Leckman et al.[1] have 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.[2] Based on data from the Tourette Syndrome Association International Consortium for Genetics Affected Sibling Pair Study, Leckman and colleagues[3] 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.[3]

Links between OCD and eating disorders are another area of phenotype interest. Halmi 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.[4] 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.[4]

In a similar vein, Bellodi and colleagues have conducted research on several different but related disorders

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including OCD, OCD plus tics, Gilles de la Tourette's syndrome, idiopathic focal dystonia, and OCD plus idiopathic focal dystonia.[5] A family study[6] 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.[7] 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.[8]

Family studies have also examined the relationship of OCD to spectrum disorders including pathological gambling and trichotillomania. Black et al.[9] 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[10] 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[11] 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[12,13] 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.[14] However, genotype 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.[14] Recent candidate gene research in OCD has also included studies of GABA-A-γ2,[15] monoamine oxidase A,[16] and the use of single nucleotide polymorphism analysis.[17] 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.

Table 1. Candidate Genes in Obsessive-Compulsive Disorder[a]

Candidate Gene	Positive Findings	Negative Findings
5-HT_{2A}	Enoch et al,[18] 1998	Nicolini et al,[19] 1996, Pato et al,[20] 2001; Bellodi et al,[5] 2001
SLC6A4	McDougle et al,[21] 1998; Bengel et al,[22] 1999	Billett et al,[23] 1997; Ohara et al,[24] 1998
TPH		Han et al,[25] 1999; Frisch et al,[26] 2000
5-HT_{2C}		Nicolini et al,[19] 1996; Cavallini et al,[27] 1998
5-HTT	Bengel et al,[22] 1999; McDougle et al,[21] 1998	Pato et al,[20] 2001; Billett et al,[28] 1998
5-$HT_{1D\beta}$	Mundo et al,[29] 2000; Pauls,[30] 2001	Bellodi et al,[5] 2001
DRD2		Nicolini et al,[19] 1996; Billett et al,[28] 1998; Novelli et al,[31] 1994
DRD3		Nicolini et al,[19] 1996; Billett et al,[28] 1998; Catalano et al,[32] 1994
DRD4	Cruz et al,[33] 1997; Billett et al,[28] 1998	
DAT-1		Frisch et al,[26] 2000; Billett et al,[28] 1998
COMT	Karayiorgou et al,[12] 1997; Alsobrook et al,[34] 1999; Schindler et al,[14] 2000	
MAO-A	Camarena et al,[16] 2001	
MOG-2		Kennedy et al,[35] 2001
MOG-4	Kennedy et al,[35] 2001	
HLA-CAR		Kennedy et al,[35] 2001
GABA-A-γ2		Richter et al,[15] 2001

[a]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.

Pauls[30] has reported on a family-based association study of the 5-$HT_{1D\beta}$ 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,[5] while Mundo and coworkers[29] have had some similar preliminary findings. Functional polymorphisms like the one in 5-$HT_{1D\beta}$ 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.[35] 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

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

1. Leckman JF, Zhang H, Alsobrook JP, et al. Symptom dimensions in obsessive-compulsive disorder: toward quantitative phenotypes. Am J Med Genet 2001;105:28–30
2. Cochran LW, Smith MJ, Greenberg BD, et al. Factor analysis of symptoms in obsessive-compulsive disorder. Presented at the 5th International Obsessive Compulsive Disorder Conference; March 29–April 1, 2001; Sardinia, Italy
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
6. Bellodi L, Cavallini MC, Bertelli S, et al. Morbidity risk for obsessive-compulsive spectrum disorders in first-degree relatives of patients with eating disorders. Am J Psychiatry 2001;158:563–569
7. Cavallini MC, Pasquale L, Bellodi L, et al. Complex segregation analysis for obsessive compulsive disorder and related disorders. Am J Med Genet 1999;88:38–43
8. Cavallini MC, Bertelli S, Chiapparino D, et al. Complex segregation analysis of obsessive-compulsive disorder in 141 families of eating disorder probands, with and without obsessive-compulsive disorder. Am J Med Genet 2000;96:384–391
9. Black DW, Goldstein RB, Noyes R Jr, et al. Compulsive behaviors and obsessive-compulsive disorder (OCD): lack of a relationship between OCD, eating disorders, and gambling. Compr Psychiatry 1994;35:145–148
10. Bienvenu OJ, Samuels JF, Riddle MA, et al. The relationship of obsessive-compulsive disorder to possible spectrum disorders: results from a family study. Biol Psychiatry 2000;48:287–293
11. 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. Karayiorgou M, Altemus M, Galke BL, et al. Genotype determining low catechol-*O*-methyltransferase activity as a risk factor for obsessive-compulsive disorder. Proc Natl Acad Sci U S A 1997;94:4572–4575
13. Karayiorgou M, Sobin C, Blundell ML, et al. Family-based association studies support a sexually dimorphic effect of COMT and MAO-A on genetic susceptibility to obsessive-compulsive disorder. Biol Psychiatry 1999;45:1178–1189
14. Schindler KM, Richter MA, Kennedy JL, et al. Association between homozygosity at the COMT gene locus and obsessive compulsive disorder. Am J Med Genet 2000;96:721–724
15. Richter MA, Mundo E, Sam F, et al. The $GABA_A$-γ2 receptor gene in OCD and social phobia. Presented at the 5th International Obsessive Compulsive Disorder Conference; March 29–April 1, 2001; Sardinia, Italy
16. Camarena B, Rinetti G, Cruz C, et al. Additional evidence that genetic variation of MAO-A gene supports a gender subtype in obsessive-compulsive disorder. Am J Med Genet 2001;105:279–282
17. 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

18. Enoch MA, Kaye WH, Rotondo A, et al. 5-HT_{2A} promoter polymorphism: 1438G/A, anorexia nervosa, and obsessive-compulsive disorder. Lancet 1998;351:1785–1786
19. Nicolini H, Cruz C, Camarena B, et al. DRD2, DRD3, and 5-HT_{2A} receptor gene polymorphisms in obsessive-compulsive disorder. Mol Psychiatry 1996;1:461–465
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
21. McDougle CJ, Epperson CN, Price LH, et al. Evidence for linkage disequilibrium between serotonin transporter protein gene (SLC6A4) and obsessive compulsive disorder. Mol Psychiatry 1998;3:270–273
22. Bengel D, Greenberg BD, Cora-Locatelli G, et al. Association of the serotonin transporter promoter regulatory region polymorphism and obsessive compulsive disorder. Mol Psychiatry 1999;4:463–466
23. Billett EA, Richter MA, King N, et al. Obsessive compulsive disorder, response to serotonin reuptake inhibitors and the serotonin transporter gene. Mol Psychiatry 1997;2:403–406
24. Ohara K, Nagai M, Suzuki Y, et al. Association between anxiety disorders and a functional polymorphism in the serotonin transporter gene. Psychiatry Res 1998;81:277–279
25. Han L, Nielsen DA, Rosenthal NE, et al. No coding variant of the tryptophan hydroxylase gene detected in seasonal affective disorder, obsessive-compulsive disorder, anorexia nervosa, and alcoholism. Biol Psychiatry 1999;45:615–619
26. Frisch A, Michaelovsky E, Rockah R, et al. Association between obsessive-compulsive disorder and polymorphism of genes encoding components of the serotonergic and dopaminergic pathways. Eur Neuropsychopharmacol 2000;10:205–209
27. Cavallini MC, Di Bella D, Pasquale L, et al. 5-HT_{2C} CYS23/SER23 polymorphism is not associated with obsessive-compulsive disorder. Psychiatry Res 1998;77:97–104
28. Billett EA, Richter MA, Sam F, et al. Investigation of dopamine system genes in obsessive-compulsive disorder. Psychiatric Genet 1998;8: 163–169
29. Mundo E, Richter MA, Sam F, et al. Is the 5-HT1Dβ receptor gene implicated in the pathogenesis of obsessive-compulsive disorder? Am J Psychiatry 2000;157:1160–1161
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
31. Novelli E, Nobile M, Diaferia G, et al. A molecular investigation suggests no relationship between obsessive-compulsive disorder and the dopamine D2 receptor. Neuropsychobiology 1994;29:61–63
32. Catalano M, Sciuto G, Di Bella D, et al. Lack of association between obsessive-compulsive disorder and the dopamine D3 receptor gene: some preliminary considerations. Am J Med Genet 1994;54:253–255
33. Cruz C, Camarena B, King N, et al. Increased prevalence of the seven-repeat variant of the dopamine D4 receptor gene in patients with obsessive-compulsive disorder with tics. Neuroscience Lett 1997;231:1–4
34. Alsobrook JP II, Leckman JF, Goodman WK, et al. Segregation analysis of obsessive-compulsive disorder using symptom-based factor scores. Am J Med Genet 1999;88:669–675
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
36. Risch N, Merikangas K. The future of genetic studies of complex human diseases. Science 1996;273:1516–1517