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THE PATHOPHYSIOLOGY AND GENETICS OF OBSESSIVE-COMPULSIVE DISORDER

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Multiple converging lines of evidence suggest that neurobiology plays a significant role in the etiology of obsessivecompulsive disorder (OCD). During the past decade, there has been considerable progress in the identification of neuroanatomic substrates involved in the expression of OCD. The brain areas most frequently identified by in vivo neuroimaging studies as potentially involved in the manifestation of OCD are the orbitofrontal cortex (OFC), the anterior cingulate area (ACA), and the head of the caudate nucleus (1). Furthermore, pharmacologic and neurobiological studies have implicated several central neurotransmitter systems in the pathophysiology of OCD and related conditions. The strongest pharmacologic evidence concerns the serotonergic system and the well-established efficacy of potent serotonin reuptake inhibitors in the treatment of OCD (2,3); however, other systems have also been implicated. A growing body of evidence suggests that the pathophysiology OCD is complex and that, despite the fundamental role played by serotonin (5-HT) in the pathogenesis of obsessions and compulsions, a serotonergic dysfunction may explain no more than 50% of the variability of the disease. The most widely accepted alternative neurochemical theory for OCD suggests that the dopamine (DA) neurotransmission system also may be important in the pathophysiology of some cases of OCD (3-6). Specifically, the DA hypothesis has been proposed for those cases of OCD that appear to be related to Gilles de la Tourette syndrome (GTS) or other tics disorders, and/or those that occur with schizotypal personality disorder and/or poor insight. There is also a new etiologic hypothesis for OCD involving an autoimmune mechanism, particularly relevant for early-onset cases.

At the same time, there has been considerable research that has documented the familial nature of OCD (7). These family data, when taken together with twin studies, suggest that genetic factors are important in the manifestation of this illness. Segregation, linkage, and association studies have begun and the results are similar to those observed for other major psychiatric disorders: The mode of transmission within families is complex and the precise genetic mechanism is not known.

In this chapter the main pathophysiologic findings for OCD are reviewed as well as the evidence that genetic factors are of etiologic importance. Finally, the findings from studies examining candidate genes proposed as the result of several lines of investigation that implicate both the serotonergic and dopaminergic neurotransmitter systems are summarized.

THE PATHOPHYSIOLOGY OF OCD

The Serotonin Hypothesis

Historically, the serotonin (5-HT) hypothesis has its basis in the pharmacology of OCD. In the late 1960s it was observed that clomipramine, the only tricyclic antidepressant with potent 5-HT reuptake blocking properties, had antiobsessional activity (8,9). Subsequently, several studies have shown that clomipramine and several other selective serotonin reuptake inhibitors (SSRIs) are effective antiobsessional agents. In fact, results were taken as evidence that serotonin plays a fundamental role in the pathogenesis of OCD (10-18). These observations have led to the examination of the serotonin system and its function in OCD patients. Peripheral markers for the 5-HT system and a number of parameters of the 5-HT function have been investigated. These include CSF 5-hydroxyindoleacetic acid (the major metabolite of serotonin) (19-22), whole blood levels of 5-HT (23-25), platelet 5-HT concentrations (26),

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and platelet imipramine binding (thought to be reflective of 5-HT uptake) (27–30). The results of these studies, although not definitive, suggest that a 5-HT dysfunction is present in OCD. More detailed information has come from pharmacologic challenge studies in which compounds were administered that, acting presynaptically or postsynaptically, stimulate 5-HT transmission. In these studies behavioral and neuroendocrine responses in OCD patients were assessed after challenges with meta-chloro-phenyl-piperazine (mCPP) (20,31–36), intravenous clomipramine (37, 38), the 5-HT precursor tryptophan (39,40), the 5-HT releasing agent fenfluramine (41-45), ipsapirone (46), buspirone (47), and sumatriptan (48,49). These studies have also yielded conflicting results, similar to those derived from the challenge studies employing the 5-HT antagonist metergoline (50,51) and tryptophan depletion (53). Overall, about 50% of the OCD patients challenged acutely with proserotonergic compounds experienced a transient worsening of obsessive symptoms. These results suggest that for some OCD patients there would be a basal hyperactivity of the 5-HT neurotransmission system, owing either to a hypersensitivity of the postsynaptic receptors or to a hypoactivity of the presynaptic ones, which usually provide self-regulation (54). This could explain both the worsening of OCD symptoms after acute 5-HT stimulation and the clinical efficacy (i.e., improvement of OCD symptoms) after chronic administration of proserotonergic compounds (37,

The chronic administration of clomipramine or SSRIs induces an enhanced 5-HT release in the orbitofrontal cortex, probably as a consequence of the desensitization of the terminal 5-HT autoreceptors, and this has been hypothesized to be the neurobiological substratum for the effects of SSRIs in the treatment of OCD. The involvement of the presynaptic desensitization as a key step for the neurobiological mechanism of the antiobsessional response to proserotonergic compounds is also suggested by both the long latency of clinical efficacy (6 to 8 weeks, longer than the latency for the antidepressant response induced by the same compounds) and the high doses required (54).

Nevertheless, the fact that not all OCD patients respond to clomipramine or SSRIs and approximately 40% of them have no clinical improvement (55,56) may reflect the biological heterogeneity of the OCD phenotype already suggested by the variability of the response to acute 5-HT challenges. Thus, consideration of more homogeneous subgroups of OCD patients defined by response to biological challenges or different symptom subtypes could lead to clarification of the pathogenesis of the disease and the role of alternative hypotheses to the serotonergic one.

The Dopamine Hypothesis

There is now considerable evidence that some forms of OCD are etiologic related to GTS (57). GTS appears to

be predominantly dopaminergically mediated, as evidenced by the well-documented clinical response to haloperidol and other dopamine antagonists (58), by the exacerbation with L-dopa and central nervous system stimulants (such as amphetamines) (59,60), and reports of lower CSF levels of the dopamine metabolite homovanillic acid (HVA) (61). Moreover, OCD patients with comorbid tic disorder or GTS are usually resistant to conventional pharmacotherapy with proserotonergic compounds, and may benefit from adjuvant treatment with dopamine (DA) or DA/5-HT blockers (6,55,56,62,63). This body of evidence suggests that there is an involvement of DA in at least some OCD patients.

With respect to the peripheral markers of the DA transmission, normal CSF levels of HVA have been reported (19, 64), whereas the administration of fenfluramine produced increased inhibition of HVA secretion (33,65). The DA involvement has been assessed by measures of growth hormone response to apomorphine (66,67), and challenge with *d*-amphetamine (68) and methylphenidate (69), with conflicting results.

The serotonin and dopamine systems interact extensively, particularly in the basal ganglia (31), an area that has been implicated in the pathogenesis of obsessive-compulsive phenomenology by several studies (1,70–72). Indirect support for the involvement of both transmitter systems includes the observation of the emergence of *de novo* OC symptoms in patients on clozapine or risperidone, atypical antipsychotics with both D2 and 5-HT2 blocking properties (73–75), together with the demonstrated antidopaminergic activity of two antiobsessional agents, clomipramine and fluoxetine (76,77).

Other Neurobiological Hypotheses

Alternative neurobiological mechanisms have been proposed for OCD but they are in need of further confirmation. As already reported, functional neuroimaging studies have demonstrated dysfunction in the orbitofrontal cortex, basal ganglia and striatum, which normalize with successful treatment (78,79). Neuroendocrine mechanisms were implicated in the pathogenesis of obsessions and compulsions, based on studies employing oxytocin, vasopressin, and somatostatin (64,80–82). These studies also need further replication.

The Autoimmune Hypothesis

Allen, Leonard, and Swedo first proposed the intriguing autoimmune hypothesis of OCD (83) after a thoughtful review of the literature. An association was drawn between infection with group A B-hemolytic Streptococcus (as well as other agents, including viruses), and the onset or the exacerbation of OCD in some children. The observation of an association between Sydenham's chorea (an involuntary

movement disorder related to group A B-hemolytic Streptococcus-induced autoantibodies reacting with the basal ganglia) and OCD led to the characterization of the "pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections" (PANDAS) by Swedo and colleagues (84,85), including OCD. Similar links between group A B-hemolytic Streptococcus and GTS have been observed (86,87). A monoclonal antibody that identifies Blymphocyte antigen (D8/17) has been shown to be a marker for susceptibility to rheumatic fever, PANDAS, and earlyonset OCD in general (88,89). Moreover, D8/17 levels have been found to follow a segregation pattern most consistent with autosomal recessive inheritance in rheumatic fever families (89,90). There is evidence that PANDAS is familial, with dramatically increased rates of clinical and subclinical OCD observed in parents of children with PANDAS (91).

The importance of this hypothesis cannot yet be determined, however, because it is not known how many child-hood-onset cases of OCD are associated with this autoimmune process. It is possible that inherited genetic factors interact with the autoimmune mechanisms, making a subject more or less susceptible to the cross reaction created by the infection. Genetic variants in the human leukocyte antigen (HLA) system may be interesting candidates to examine in this group of OCD subjects.

THE GENETICS OF OCD

There has been considerable controversy regarding the inheritance of OCD. This is surprising since the familial nature of OCD has been documented since the 1930s and twin studies have provided evidence for the importance of genetic factors in the manifestation of OCD.

Twin Studies

In 1986, Rasmussen and Tsuang (92) reviewed the literature on OCD twins and found 32 of 51 (63%) MZ twins were concordant for OCD. Furthermore, when those twins where zygosity was in doubt were eliminated from the sample, 13 of 20 (65%) were concordant for OCD. These MZ concordance rates are similar to those reported for affective and anxiety disorders. However, the results need to be interpreted with caution because no data from DZ twins were available for comparisons.

This shortcoming was addressed by Carey and Gottesman (93) who studied a consecutive series of 15 MZ and 15 DZ twins ascertained from the Maudsley Twin Register. The index twin in each pair had received a psychiatric diagnosis of obsessional neurosis, obsessional personality, or phobic neurosis at local hospitals during a 32-year interval (1948 to 1979). Each twin pair was followed-up by personal interview and assessment of psychiatric status. The hospitals' notes on the index cases and family members were also

used to assign diagnoses. When a diagnosis of obsessive symptoms was used, these investigators found that 87% of the MZ twins were pair wise concordant compared to 47% of DZ twins, yielding a heritability estimate of approximately 80%.

In a more recent study, Torgersen (94) investigated the concordance of anxiety disorders (including obsessive-compulsive disorder) in the co-twins of 32 MZ and 53 DZ samesex Norwegian twins. The sample consisted of all twins born between 1910 and 1955 who were admitted for treatment of neurotic or borderline psychotic disorders at any time before 1977. After ascertainment each twin was interviewed using a structured psychiatric interview that recorded lifetime occurrence of psychiatric symptoms; this information was then combined with the hospital records to make DSM-III lifetime diagnoses. A group of six DSM-III anxiety disorders was examined: panic disorder, agoraphobia with and without panic, social phobia, OCD, and generalized anxiety disorder (GAD). No twins were found to be concordant for the same anxiety disorder. Thus, the author examined concordances in the larger context of an "anxiety spectrum." When the category that included only panic disorder, agoraphobia, social phobia, and OCD was, a statistically significant difference in concordance rates was seen: 45% in MZ pairs compared to 15% in DZ pairs (P < .02). This difference was not seen when considering GAD alone, nor when a combined proband diagnostic category including GAD

Two important aspects of these studies critically limit their usefulness. The first limitation is the lack of standardized diagnostic criteria across studies. It is difficult to interpret results when different diagnostic criteria are used in the different studies being compared. The second limitation is the lack of blindness in evaluating the twins. The investigators doing the evaluations of the co-twin, knew the diagnosis of the index case. The lack of any procedural blind for obtaining diagnostic information or for making the actual diagnoses of a co-twin is a serious source of bias that could lead to spurious results.

Two studies were completed that used twins ascertained through twin registries. Furthermore, the evaluations of the twins were done blindly. Clifford (95) and Clifford and associates (96) analyzed data collected from 419 pairs of unselected twins who had been given the Eysenck Personality Questionnaire (EPQ) and the 42-item version of the Leyton Obsessional Inventory (LOI). Multivariate analyses provided separate heritability estimates of 44% for obsessional traits (as defined by the 10-item "Trait Scale" of the LOI) and 47% for obsessional symptoms necessary for a diagnosis of OCD (as defined by the 32-item "Symptom Scale" of the LOI). In a separate study using twins from the Australian Twin Registry, Andrews and associates (97) administered structured psychiatric interviews to 186 MZ and 260 DZ twin pairs. Ascertainment was not based on psychiatric caseness. Lifetime data for OCD, GAD, panic disorder, social phobia, and major depressive disorder were obtained. The findings were similar to those of Torgersen in that, no differences in MZ/DZ concordances were observed when individual disorders were examined. However, when the diagnoses were combined into a single category of "neuroticism," the MZ correlations were significantly higher than for the DZ twins; (0.58 versus 0.31) for female twins and (0.44 versus 0.27) for male twins.

In summary, all twin studies to date are consistent with the hypothesis that genetic factors are important for the expression of OCD and the specific symptoms necessary for a diagnosis of OCD. Furthermore, the two most recent studies (94,97) suggest that some of the same genetic factors may be important for the manifestation of some other anxiety symptoms.

Family Studies

Data from the majority of family studies completed over the past 60 years suggest that OCD is familial (7); however, rates of illness among relatives vary from study to study. Many of the studies completed prior to 1990 are difficult to interpret because of differences in diagnostic criteria and assessment methodologies and the lack of control samples or reliable estimates of population prevalence. Some of the shortcomings of this early research were addressed in six recent studies (57,98–102). All of these studies demonstrate that OCD and related conditions are familial.

Lenane and colleagues (98) studied families of 46 children and adolescents and found that 17% of the parents had OCD (25% of fathers and 9% of mothers). In a second study of the families of children and adolescents, Leonard and co-workers (99) found that 13% of first-degree firstdegree relatives of OCD probands met DSM criteria for OCD. Bellodi and associates (100) reported that 3.4% of the relatives in 92 families had OCD. Although this rate is somewhat lower than other studies, it nevertheless represents a twofold increase over available population prevalence estimates. Of note is that when probands were separated on the basis of age at onset, the morbid risk for OCD among relatives of early onset (before age 14) probands was 8.8% compared to 3.2% among the relatives of later onset probands. A shortcoming of these three studies is that none included a control sample. However, assessments in all of them were done using structured interviews that were used in epidemiologic surveys. The best estimate of the population prevalence for OCD from the most recent epidemiologic study (103) is 2.3 \pm 0.3% in Baltimore (both of the Lenane and Leonard studies were done at the NIH in Washington, DC). Using this estimate of prevalence, the relative risk (γ) (the ratio of illness among relatives to the population prevalence) (103) for these two studies ranged between 4.4 and 10.2.

The three remaining family studies included control samples. Black and colleagues (101) studied families of 32

adult OCD probands. First-degree relatives over the age of 18 of 32 probands with OCD and 33 controls were systematically interviewed using the Diagnostic Interview Schedule (DIS). Altogether, 249 relatives (nearly 60%) were directly interviewed. Although the prevalence of OCD was not significantly increased among relatives of OCD probands, the results support the concept of an OCD spectrum. In particular, there was an increase in the rate of "subclinical" OCD among parents of OCD probands when compared to parents of controls. The following caveat should be noted when interpreting these findings. In most studies of psychiatric disorders, direct interviews, family history data, and medical record data are used to make "best estimate" diagnoses (104). In this study, Black and colleagues used only data collected from direct interviews of the relatives about themselves to assign diagnoses. Given the secrecy of many OCD patients and their tendency to hide their illness, it is possible that some family members denied symptomatology on direct interview. As noted in the report, family history data were collected by Black and colleagues but were not used in the diagnostic assignment reported. When those family history data are included, the recurrence risk among first-degree relatives is 9.8%; a rate not significantly different from recurrence risks reported in other studies. Using this estimate for the risk to relatives, the γ ranges between 1.8 and 12.1.

In 1995, Pauls and colleagues (57) reported the results of a study of 466 first-degree relatives of 100 OCD probands and 113 control subjects. The age corrected rate of OCD (10.3%) was significantly higher in the relatives of OCD probands when compared to controls (1.9%). A familial relationship has been reported between OCD and GTS and chronic tics (CT) (105) and it has been speculated that familial OCD is that type that is related to GTS. Although the rates of GTS and chronic tics were also significantly higher among relatives of OCD probands than among controls in this study, the patterns within the families suggested that much of OCD is not related to GTS; the majority of OCD individuals did not have a personal or family history of GTS or tics; however, many did have a positive family history of OCD. Thus, some forms of OCD that appear to be unrelated to tics or GTS are familial.

Finally, in the most recent and methodologically sound family study of OCD, Nestadt and colleagues (102) reported that 11.7% of 326 first-degree relatives of 85 OCD probands met DSM-III-R criteria for OCD compared to only 2.7% of controls. The methods used in this study were essentially identical to those used in the Pauls and associates (57) study. That is, the investigators directly interviewed all available first-degree relatives and obtained family history data for all first-degree relatives. Best estimate procedures were used in assigning diagnoses. The difference between the Pauls and Nestadt study is that, the latter was able to interview many more first-degree relatives than the former. Nevertheless, it is remarkable that the estimates of recur-

rence risk obtained in the two studies were not significantly different. Using available population prevalence estimates from each site and the recurrence risks reported for first-degree relatives, the estimated γ ranges between 3.4 and 27.8.

Clinical Heterogeneity and Its Relationship to Familiality

Although the assessment and diagnosis of OCD is highly reliable and valid, it has also become clear over the last decade that there is considerable variability of symptomatology across individuals who have a diagnosis of OCD. Given this variability, a number of investigators have begun research to explore the possibility that subtypes/components of OCD might be distinguished on the basis of some features of the disorder. Several analyses have been completed to determine whether more homogeneous groups of OCD patients could be identified that were also more likely to be familial. One way of grouping individuals that has helped identify heritable subtypes in other conditions has been to examine age at onset. Analyses of age at onset of OCD indicate that early-onset OCD is more likely to be familial (57,102). However, there is still considerable familial heterogeneity within this group because a substantial proportion of early-onset OCD cases are not familial (7).

Another approach that has proven useful in identifying components of the phenotype rather than subtypes of patients is factor analysis. A number of investigators have completed factor analyses on at least four independent samples of individuals with OCD (106–109). In all of these analyses similar factors emerged that accounted for a substantial amount of the variance in each data set. One factor was best characterized by aggressive, sexual, religious, and somatic obsessions and related checking behavior (in the most recent set of analyses, this factor appeared to split into two separate factors). Another factor was characterized by the need for symmetry or exactness, repeating rituals, counting compulsions, and ordering/arranging compulsions. Another factor was characterized by contamination obsessions and washing/cleaning compulsions. And a final factor was characterized by hoarding obsessions and compulsions.

Preliminary analyses have been undertaken to examine whether any of these factors are related to family risk patterns (110). One of the samples included in the factor analyses reported by Leckman and associates (107) consisted of the probands for the family study of OCD reported by Pauls and co-workers (57). Additional factor analyses of the family data, which included all first-degree relatives, demonstrated that the relatives showed the same factor structure as the probands. Further analyses suggested that there were different recurrence risks for OCD among relatives of probands with different combinations of factors scores. The age-corrected recurrence risk among relatives of probands who had positive scores on the factor characterized by aggressive, sex-

ual, religious and somatic obsessions and related checking behavior was 23.6% compared to only 13.9% among relatives of probands who had negative scores on that factor $(\chi^2 = 7.57, P < .006)$. For the factor characterized by the need for symmetry or exactness, repeating rituals, counting compulsions and ordering/arranging compulsions, the agecorrected recurrence risk among relatives of probands who had positive scores was 22.7% compared to 13.5% among relatives of probands who had negative scores on that factor $(\chi^2 = 7.57, P < .019)$. There was no relationship between risk to relatives and proband factor scores for the other factors. As discussed, results of complex segregation analyses that incorporated these factors scores suggested that there were different patterns of transmission within families that were related to the factor scores of the probands. Unfortunately, the number of affected relatives for whom it was possible to generate factor scores was too small to allow meaningful analyses designed to determine whether the factor scores of affected relatives were correlated with the factor scores of the probands.

Family patterns demonstrate that OCD is a complex disorder with different familial patterns being associated with different clinical characteristics of OCD. Given these familial patterns, it is likely that several genes contribute to the manifestation of the disorder. It is quite plausible that unique genes could be involved in the expression of different domains of symptomatology. Separately examining these component parts of the phenotypic spectrum with regard to their transmission within families and the possible role of genetic factors could facilitate the identification of the genes involved in the manifestation of OCD.

Segregation Analyses

Together, the family and twin study data provide compelling evidence that some forms of OCD are familial and genetic. Furthermore, segregation analyses reveal that the patterns within families are consistent with genetic models that include genes of major effect. Nicolini and colleagues (111) performed segregation analyses on data collected from 24 OCD families and Cavallini and co-workers (112) completed complex segregation analyses with data from a sample 107 families ascertained through an OCD proband. In both studies, the most parsimonious result suggested that the mode of transmission within families was most similar to an autosomal dominant pattern; however, other major gene solutions could also adequately explain the observed familial patterns.

More recently, complex segregation analyses were completed (110) on the family study data reported on by Pauls and associates (57). Analyses were done using the computer program POINTER (113). One hundred families with 466 first-degree relatives composed of 191 parents (95 fathers and 96 mothers), 217 siblings (105 brothers and 112 sis-

ters), and 58 offspring (39 sons and 19 daughters) were included in the analysis.

Analyses were performed on: (a) the complete data set; (b) a subset of clearly familial families; and (c) family subsets based on the previously described symptom factor structure in order to explore the possibility that these factors represent homogeneous heritable components of OCD.

Using the entire data set, only the model of no transmission could be rejected (χ^2 (4) = 135.49, $P < 10^{-6}$). No specific genetic models could be ruled out. The lack of definitive results with the total sample could be due to the fact that approximately half of the families in this sample did not have any relatives affected with OCD. This pattern of familiality has also been observed in at least three other studies: Nicolini and associates (111) reported that 11 of 24 probands in their study did not have a family history of OCD; Eapen and co-workers (114) observed that approximately half of the probands in their study were isolated cases; and Cavallini and colleagues (112) reported that 54 of their 107 probands were sporadic cases.

Given these findings, the next analyses included only the subset of families in which there were at least two individuals (the proband and one other first-degree relative) affected with OCD. A total of 52 families were included in these analyses. Because OCD in another family member was a criterion for inclusion of a family, one of the affected first-degree relatives in each family was randomly assigned as a secondary proband and the analyses were appropriately corrected for this ascertainment. In these analyses, all transmission models could be rejected except a multigenic model that included both a gene of major effect and polygenic background.

Finally, these investigators divided all families on the basis of four dichotomous classification schemes that were derived from the probands' factor scores obtained from the factor analyses described in the preceding (107). For the analyses performed on families whose probands had positive scores for hoarding obsessions and compulsions, contamination obsessions and compulsions, or aggression/checking obsessions and compulsions, only the hypothesis of no transmission could be rejected. That is, there was no genetic model that could be identified as the most parsimonious. On the other hand, analyses of families whose probands had positive scores on the factor characterized by symmetry (counting obsessions and compulsions) yielded results consistent with a model that included genes of major effect.

The results of these segregation analyses demonstrate that the transmission of OCD is generally difficult to model (at least within the confines of current methods for complex segregation analysis). In most cases, no single genetic model provided the most parsimonious solution to the patterns of transmission. This could be owing to the fact that OCD is etiologically heterogeneous with only half of the cases representing familial forms. It is noteworthy that when analyses were limited to those families in which the disorder

was clearly familial (i.e., families in which there are at least two individuals with OCD), the most parsimonious explanation of transmission was that it was multigenic, with at least one gene of major effect on a polygenic background.

OCD is clinically heterogeneous and most likely is also genetically heterogeneous. Although it is possible that there is at least one locus that has an appreciable impact on the manifestation of OCD, it is highly likely that it is not a single-gene disease. The familial transmission patterns are not consistent with single-gene inheritance. As reviewed in the section on pathophysiology, it appears that there are several different neurochemical pathways that are involved in the expression of OCD. Thus, it is likely that there are a number of different molecular paths to the behavioral outcome; each influenced by a different gene or genes.

In summary, there is compelling evidence from twin, family, neuroanatomic, and neurobiological studies that biological/genetic factors are important in the expression of OCD. A more complete understanding of the genetic basis and of the interactions between relevant genotypes and relevant environmental factors will be important for eventual clarification of the etiology and pathogenesis of this complex disorder. Results from all segregation analyses suggest that the underlying genetic mechanisms for OCD involve genes of major effect. The next necessary step in our goal of understanding the genetics of OCD is to localize and characterize the genes that confer susceptibility.

MOLECULAR GENETIC STUDIES

Genetic linkage has long been recognized as one of the methods useful in clarifying the role of genetic and environmental factors in the expression of complex disorders like OCD. Historically, the method has had limited applicability because of the small number of sufficiently polymorphic genetic markers available for study in humans. With the sequencing of the human genome, this situation has changed dramatically. Theoretical and empirical work suggests linkage studies can identify the location and thereby verify the existence of genetic loci important in the expression of these disorders; however, multiple strategies need to be employed in the study of complex non-mendelian disorders (115,116). Although the sib-pair approach has been available for some time, only recently has it become evident that its application is increasingly important in the genetic study of disorders where there may be genetic heterogeneity and where the mode of inheritance is complex (116). An important advantage in the use of sib-pairs is that no prior assumptions regarding specific genetic model parameters are required. Furthermore, with the increasing number of polymorphic markers available, association studies may prove feasible in the search for susceptibility genes

Given the family patterns observed and the findings from

segregation analyses regarding the mode of transmission of OCD, a methodologic approach that does not require specification of a particular genetic model should be more efficacious in identifying some of the OCD susceptibility genes. Furthermore, as discussed by Pauls (118) exclusive reliance on large multigenerational families for the detection of linkage is not indicated when the disorder is common and the most likely mode of transmission is multigenic.

At the present time, there are no published linkage studies of OCD. Thus, the remainder of this chapter focuses on association studies of candidate genes.

Association Studies

Genes of the Serotonergic System

Gene testing in OCD has begun, focusing on candidates derived from the hypothesized etiologic importance of the serotonin and dopamine systems. With respect to the serotonin system, the serotonin transporter gene (SLC6A4) has been implicated in OCD as the site at which SSRIs initially exert their effects. Lesch and co-workers (119) evoked considerable interest in the transporter gene by demonstrating an association between the short allele of the 44bp insertion/ deletion polymorphism in the promoter region and the anxiety-related personality traits of Neuroticism and Harm Avoidance in 505 individuals. This polymorphism has been shown to affect gene function in vitro; the longer allele (l) is associated with threefold increases in gene expression (120). Furthermore, the *l* allele of this polymorphism has been associated with elevated blood SLC6A4 levels in a sample of 70 OCD subjects (121). The first study of the promoter polymorphism revealed a trend toward increased homozygosity (//l and s/s) in OCD patients, but the overall results were indeterminate (122). Subsequent investigation of OCD trios revealed significantly increased transmission of the l allele to OCD probands (123).

The 5-HT2A-receptor gene has been investigated in an association study, including 67 OCD patients (124) with inconclusive results. Kim and associates sequenced the 5-HT2B-receptor (125). One single nucleotide polymorphism was found in intron 1 of the gene, but no evidence for a functional mutation was found. Finally, another association study by Cavallini and colleagues (126) of a 5-HT2C polymorphism in 109 OCD subjects and matched controls also gave negative results.

Very recently, an association between OCD and a polymorphism of the 5-HT1DB receptor gene has been reported (127). This result appears to be particularly interesting with respect to the pathogenesis of OCD and surely deserves further investigation. The 5-HT1DB receptor is a terminal autoreceptor involved in the regulation of 5-HT transmission, and challenge studies with selective ligands (i.e., sumatriptan) (48) showed an acute worsening of OC symptoms, whereas chronic treatment with the same com-

pound can induce improvement in OCD patients resistant to conventional pharmacotherapy (128).

Genes of the Dopaminergic System

Turning to dopamine system genes, two early case—control studies showed a lack of association with polymorphic sites in the dopamine D2 and D3 receptor genes (129,130). These negative results also have been replicated (124). The most promising gene in the dopamine system appears to be the D4 receptor gene. Preliminary investigations have shown a positive association between a 48-bp VNTR polymorphism and OCD (131); Cruz and co-workers (132) reported an association between the seven-repeat variant of the same polymorphism and the subtype of OCD with co-morbid tic disorders.

Additional Genes

There are preliminary investigations of two enzymes involved in the metabolism of biogenic amines, catechol-Omethyltransferase (COMT) and monoamine oxidase A (MAO-A). Camarena and associates (133) found increased frequency of the low activity MAO-A allele in females, among a total sample of 41 OCD patients and controls. COMT modulates dopaminergic and noradrenergic neurotransmission via inactivation of catecholamines. Support for involvement of this gene derives from observations of an association between velo-cardio-facial syndrome, a rare congenital malformation associated with a microdeletion on chromosome 22q11, and obsessive-compulsive symptoms (134,135). Of significant interest, the COMT gene maps to this region. Two studies by Karayiorgou and colleagues (136,137) have shown an association between susceptibility to OCD in males and a common functional COMT allele that leads to a reduced enzyme activity. In an attempt to replicate this finding, Alsobrook and associates (138) completed family based association studies in 50 OCD trios and found no significant association in the total sample or in male probands; however, these investigators found an association in female probands (P = 0.051). Schindler and colleagues (139) have found evidence for association between homozygosity of either COMT allele and OCD. In sum, these COMT results are difficult to understand at this point. It is possible that genetic heterogeneity and population stratification may be contributing to the complexity of the findings.

CONCLUSION

The identification and characterization of genes important in the expression of OCD will be a major step forward in understanding the genetic and biological risk factors important for the expression of this disorder. In addition, this work will allow the potential identification of other nongenetic factors associated with the manifestation or amelioration of the symptoms of the disorders. On the one hand, the identification of a linked marker will permit the design of much more incisive studies to illuminate the physiologic/ biochemical etiology of OCD by examination of the gene product and its impact on the development of the disorders. On the other hand, by controlling for genetic factors, through the genetic case-control research paradigm, it will be possible to document more carefully the environmental and nongenetic factors important for the expression of OCD and other possibly related conditions. Studying genetic marker data together with data characterizing phenotypic expression in the context of specific environments should allow a more complete examination of the cocontribution of genetic and nongenetic factors.

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