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The Genetics of Obsessive-Compulsive Disorder

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Abstract

OCD is a psychiatric disorder with a lifetime prevalence of 1–3% and is a significant cause of disability worldwide. Family studies indicate that OCD has a significant heritable component, with relatives of OCD cases being 4 times more likely to develop the disorder than the general population. Linkage studies in OCD have generally been underpowered and have failed to reach the statistical threshold for genome-wide significance, but they have nevertheless been useful for revealing potential regions of interest for future candidate gene studies. Candidate gene studies in OCD have thus far focused on genes involved in the serotonergic, dopaminergic, and glutamatergic pathways. These studies have been for the most part inconclusive, and failures to replicate have been the norm until very recently. The only genetic association replicated by multiple groups was with a glutamate transporter gene (*SLC1A1*). Genome-wide association studies in OCD are in progress, but final results have not yet been reported. As with the study of many other psychiatric disorders, an improved understanding of OCD will only be achieved (1) with larger collaborative efforts involving more probands, (2) the use of probands and controls drawn from epidemiologically-based populations rather than clinical samples, (3) developing a more precise phenotypic description of OCD and (4) measuring important environmental influences that affect OCD pathogenesis and severity.

Keywords

Obsessive-compulsive disorder; genetics

Introduction

Obsessive-compulsive disorder (OCD) is a psychiatric illness characterized by obsessions (bothersome, intrusive thoughts, images and impulses) and compulsions (stereotyped mental or physical rituals designed to relieve the anxiety associated with obsessions). OCD has a lifetime prevalence of 1–3% and represents a substantial source of disability worldwide (1, 2). OCD symptom type and structure is remarkably similar across development and cross-culturally (3). OCD has a bimodal distribution of onset and affects both children and adults (4, 5).

Effective pharmacological and behavioral treatments for OCD have been developed over the past three decades. First-line treatments for OCD, such as selective-serotonin reuptake inhibitors (SSRIs) and cognitive behavioral therapy significantly, benefit one-half to two-

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thirds of children and adults with OCD (6, 7). Although our current treatments for OCD substantially improve symptoms in a majority of cases, they cannot be considered adequate, for several reasons. Most individuals with OCD still experience substantial residual symptoms, even after successful initial treatment. A sizeable proportion of OCD patients, at least a quarter, do not improve with current treatments. Finally, currently available treatments for OCD take a long time to work (typically 2–3 months in the case of SSRIs and CBT). Novel therapies, and the new insights into the pathophysiology of the disorder that will generate them, are urgently needed. Understanding the genetics of OCD will provide one important route towards this goal.

Here we review genetic studies conducted to date in obsessive-compulsive disorder (OCD). We will begin by discussing the heritability of OCD, by reviewing twin and family studies of OCD. Linkage studies have identified chromosomal regions of potential interest in OCD; we review these, and candidate gene association studies that have largely focused on genes in these identified regions. Until recently, positive associations with OCD risk have not been replicated and must be viewed as tentative. We conclude by discussing collaborative genome-wide association studies currently underway and addressing methods for improving the overall quality genetic studies in OCD.

Heritability of OCD

Twin Studies

Twin studies use the fact that monozygotic (MZ) twins are genetically identical, while dizygotic (DZ) twins share on average 50% of their segregating genes (similar to any set of non-twin siblings). Since twins typically experience similar environments, any difference in concordance rates between MZ and DZ twins is indicative of genetic influence on a trait.

Three epidemiologic twin studies have been conducted in OCD (8). Carey and Gottesman recruited thirty consecutive twin pairs (15 MZ and 15 DZ) from the Maudsley Twin Register in which at least 1 member had obsessional symptoms according to DSM-III criteria (9). They reported an 87% concordance rate for MZ twins and a 47% concordance rate for DZ twins for “obsessional symptoms or features with or without treatment (9).” For “obsessional symptoms were required to be severe enough to warrant treatment,” concordance rates were 33% for MZ twins and 7% for DZ twins (9). These concordance rates suggest a heritable component of OCD, but methodological limitations of this study such as lack of interviewer blinding to zygosity status of the pair introduces the potential of a detection bias. Smaller epidemiological twin studies designed to measure the heritability of anxiety disorders in general failed to uncover any concordant MZ or DZ twin pairs and thus were unable to measure the heritability for OCD (10, 11). The low prevalence of OCD in epidemiologically-based samples limits the statistical power of this approach.

More recent epidemiologically-based twin studies have employed dimensional approaches to quantitatively assess the heritability of obsessive and compulsive symptoms in non-affected twin pairs (8). One study used 20 items from the Padua Inventory to assess the heritability of 527 adult female twin pairs from the Virginia Twin Registry (12). This study used structural equation modeling to attribute 33% of obsessiveness and 26% of compulsiveness to heritability and the remainder to environmental effects (12). Hudziak et al. examined the heritability of obsessive-compulsive symptoms in children using the Obsessive-Compulsive Scale of the Child Behavioral Checklist (CBCL) (13). This study included 5707 twin pairs from the Netherlands Twin Registry and the Missouri Twin Study Sample. Across age groups and cultures, 45–61% of the CBCL OCS was attributed to genetic heritability (13). Taken together these twin studies suggest a significant genetic contribution to the pathogenesis of OCD.

Family Studies

Family studies can also be used to determine the heritability of disorders. However, increased rates of transmission within families can be due to either shared genetic or shared environmental factors; thus family studies can provide only circumstantial evidence of heritability of psychiatric disorders (14). They can, however, provide an accurate representation of risk for OCD in relatives and offspring of probands with OCD. Adoption studies would be more definitive in teasing apart genetic and environmental contributions to OCD pathogenesis, but no such studies have been conducted in OCD to date (14).

A meta-analysis of family studies in OCD suggested that first-degree relatives of individuals with OCD were approximately four-fold more likely to develop OCD than relatives of unaffected controls (15). Family studies suggest that early-onset OCD may be particularly heritable form of the disorder, with relatives of early-onset OCD cases being ten-fold more likely than control relatives to develop the disorder (16). Similarly, within adulthood OCD cohorts, earlier age of onset has been associated with increased heritability of symptoms (17–19). First-degree relatives of OCD patients also appear to be at higher risk of developing tic symptoms, body focused repetitive behaviors such as compulsive skin picking and trichotillomania, body dysmorphic disorder, and somatoform disorders, suggesting a shared vulnerability among these conditions (20, 21). Some evidence from family studies suggests that the ordering/symmetry symptoms of OCD may be particularly heritable (22).

Genetic Segregation Analyses

Once the genetic basis of a disorder is established through twin and family based studies, segregation analysis is often utilized to determine specific patterns of genetic transmission of disorders within families. Segregation analysis test the goodness of fit of specific genetic and non-genetic patterns of inheritance compared to the observed patterns (14). Five segregation analyses have been conducted to date in OCD (23–27). While all of these studies are supportive of the genetic transmission of OCD within families, these studies differ with regard to the suggested mode of inheritance.

Initial segregation analyses involving a relatively small number of probands suggested an autosomal dominant transmission pattern for OCD (23, 27). Alsobrook and colleagues conducted a segregation of 96 families that were further phenotyped according to the four principle symptom dimensions of OCD. Their findings were supportive of the genetic transmission of OCD, most specifically, ordering and symmetry symptoms, although no specific model of inheritance could be specified (24). Two more recent segregation analyses (25, 26), have suggested gender differences in modes of inheritance with female probands showing greater penetrance and favoring dominant modes of inheritance. Results from segregation analyses in OCD universally support the genetic inheritance of OCD and taken together suggest a complex, polygenetic pattern of inheritance. These studies also highlight that differences in phenotype definition (i.e. OCD symptom dimensions) and recruitment of probands (in terms of gender, early vs. late-onset OCD, tic-related OCD) can have profound effects on the results of OCD genetic studies.

Genetic Linkage Studies

Genetic linkage studies are used to identify regions that the genome that predispose to disease. Linkage studies are often the first stage in the genetic investigation of a disorder, because they can identify broad areas of the genome that might contain a disease gene, even in the absence of a biological understanding of the underlying pathophysiology (28). To date, three genome-wide linkage studies have been conducted in OCD (26, 29, 30). All three

studies were underpowered and failed to achieve genome-wide significance. However, they have suggested regions of interest that have been studied further in candidate gene studies, as we will further review below.

The first linkage study involved 56 OCD cases from 7 families obtained through childhood-onset OCD probands. The genome scan consisted of 349 microsatellite markers with an average between-marker distance of 11.3 centiMorgan (cM). The maximum LOD score was 2.25 for marker D9S288 on chromosome 9p; this falls below the threshold for genome-wide significance but identified this region as being of potential interest (26). In order to substantiate this finding, 50 sib pairs with one member with OCD were genotyped using microsatellite markers that spanned the 9p24 region. Evidence for suggestive linkage was reported at markers D9S1792 (HLOD=2.26) and D9S1813 (NPL=2.52), which are within 0.5cM of the original 9p24 linkage signal (31); likewise, pedigree-based association analysis at these markers supported association of polymorphisms at 9p24 with OCD. In both the original genome scan and this confirmatory analysis, the greatest significance was found when the OCD phenotype was construed narrowly (that is, 'definite OCD').

The largest linkage study of OCD to date was conducted by the OCD Collaborative Genetics Study, which recruited from six sites in the USA (30). This study involved 219 OCD families, totaling slightly under 1000 individuals. The genome scan consisted of 386 microsatellite markers with an average between-marker distance of 9 cM. Suggestive linkage was demonstrated on chromosomes 3q27-28, 6q, 7p, 1q and 15q. The most suggestive evidence for linkage was achieved when a broad OCD phenotype was used, in contrast to the earlier studies implicating the 9p24 locus. The highest LOD score was demonstrated at D3S1261 and D3S2398 on 3q27-28. No linkage was observed at 9p24. When data in this sample were further examined to determine linkage with compulsive hoarding behaviors, an additional region of suggestive linkage was observed for D14S588 on chromosome 14q (32).

An additional genome-wide linkage scan was recently completed on 121 individuals from 26 pedigrees with early-onset OCD probands (29). Suggestive linkage (NLOD=2.43) was demonstrated on chromosome 10p15 (29). No evidence of linkage was again reported for the 9p24 region.

It is noteworthy that these three linkage scans have produced suggestive linkage to a number of different chromosomal regions but have failed to replicate one another. The causes for this are unclear. Certainly all three studies had limited statistical power, rendering them subject to both Type 1 and Type 2 errors. This is particularly true given that none of the three studies achieved the usual criterion for statistically significant genome-wide significance. It is also possible that the underlying genetic heterogeneity of OCD contributed to this discrepancy between studies, and that the studies are finding true linkage peaks but are characterizing somewhat different patient populations. Certainly the linkage peaks found in these various studies merit further exploration.

Candidate Gene Studies

Candidate gene studies aim to detect an association between a genetic polymorphism of interest and a trait (33). Selection of candidate genes for OCD studies has occurred based on (1) the mechanism of action of effective pharmacological agents for OCD, (2) molecular genetic target suggested by animal models for OCD or (3) proximity to a genetic loci implicated by the linkage studies reviewed above. Initial candidate gene studies focused primarily on genes involved in the serotonin and dopamine neurotransmitter systems. More recently, candidate gene studies have begun to focus on the glutamate system as well. With a

few notable exceptions, initial promising results from candidate gene studies have failed to replicate in the field (34).

Serotonergic Candidate Genes

Serotonin Transporter Gene

The most effective pharmacological treatment for OCD is the use serotonin reuptake inhibitors (SRIs) (35, 36). After release from synaptic terminals, serotonin (5-HT) is removed from the synaptic cleft by the serotonin transporter (5-HTT), which is encoded by the *SLC6A4* gene. SRIs increase brain levels of serotonin by decreasing its reuptake by 5-HTT. Based on this observation, polymorphisms in the *SLC6A4* have been extensively studied in OCD.

A well-characterized 44-bp insertion/deletion polymorphism (5-HTTLPR) in the promoter region of the *SLC6A4* gene has been found to influence transcriptional activity of the gene and hence the amount of protein made and presumably efficiency with which 5-HT is removed from the synaptic cleft. In *in vitro* but not *in vivo* studies, the long variant (l-allele) of the gene has been demonstrated to be more than twice as efficiently transcribed as the short variant (s-allele) and therefore leads to more efficient reuptake of 5-HT (37–42). Nineteen studies involving 2283 individuals have examined the association between this 5-HTTLPR polymorphism and OCD. Despite the positive results of initial association studies, a recent meta-analysis indicated no association between OCD and the 5-HTTLPR polymorphism (43). In post-hoc analysis a significant association between the l-allele and OCD case status was found when studies were family-based or involved children, leaving open the possibility that the polymorphism may be associated with a subset of OCD cases (43).

A third variant of the 5-HTTLPR gene promoter has been identified more recently. The L_g allele has a single nucleotide polymorphism compared to the previous characterized long form of the allele (L_A). This single nucleotide polymorphism of the L_g allele results in lower transcriptional activity of the gene, rendering it functionally similar to the s-allele despite having similar length to the L_A allele (44). This functional polymorphism between the L_A and L_g alleles was not distinguished until recent genetic studies (44) and therefore was neglected in the majority of the studies reviewed above (43). This novel polymorphism is a potential source of genetic misclassification in previous candidate gene studies of 5-HTTLPR. This source of genetic misclassification could dramatically reduce power to detect a significant association at this locus even with a fairly low prevalence. Indeed, the study that first characterized the L_g allele found no association between OCD and 5-HTTLPR when using a biallelic classification (i.e. grouping both subtypes of the L allele together) but demonstrated an association of gain-of-function alleles with OCD when the L_g alleles were correctly identified (44). More studies that correctly account for the triallelic structure of this locus will be needed to determine whether the negative results studies based on a biallelic classification require revision (43).

Serotonin Receptor Genes

The serotonin 2A receptor (5-HT_{2A}) has been studied in candidate gene studies of OCD based on the clinical observation that (1) clozapine, an atypical antipsychotic and 5-HT_{2A} receptor antagonist can exacerbate or cause OCD symptoms in schizophrenic patients and (2) chronic use of hallucinogenic drugs such as LSD and psilocin have ameliorated OCD symptoms in some patients (45–47).

In initial case-control association studies, a polymorphism near the promoter region of the 5-HT_{2A} gene (–1438 A/G) was associated with OCD (48, 49). The first case-control

demonstrated an association of the A-allele of the -1438 A/G polymorphism with OCD among women but failed to demonstrate an association among the entire 239 subject sample (48). A subsequent study reported an association of the A-allele with OCD in a group of 278 German children (49). Four subsequent case-control studies in Turkish, Jewish, Afrikaner and Mexican samples have failed to demonstrate an association of the -1438 A/G polymorphism with OCD (50–53).

A number of candidate gene studies have also examined the T102C polymorphism in exon 1 of the 5-HT2A gene. This polymorphism is believed to represent a silent mutation in the gene and candidate gene studies for this polymorphism have been consistently negative (50–54).

The serotonin 2C receptor role in OCD has been implicated by animal studies that have demonstrated compulsive symptoms in 5-HT2C knockout mice and some pharmacological challenge studies that have demonstrated acute exacerbation of OCD symptoms with administration of m-CPP which is a 5-HT2C agonist (55–58). A genetic polymorphism that results in a cysteine to serine substitution at the extracellular N-terminal region of the receptor has been studied in several candidate gene studies but failed to demonstrate any significant association with OCD (50, 59).

The serotonin 1D β receptor (also known as 5-HT1B) was examined as a candidate gene for OCD after animal studies that suggested that the enhanced release of serotonin in the orbito-frontal cortex upon SRI treatment was mediated through 5-HT1D β autoreceptor desensitization (60). Additionally, pharmacological challenges with 5-HT1D agonists such as m-CPP and sumatriptan have been demonstrated to exacerbate OCD symptoms in some studies (55, 57, 58). Candidate gene studies have focused on a silent G681C allelic variant of the 5-HT1D β receptor gene (34). Although initial family-based association studies in Italian subjects suggested an association of the G-allele with an OCD diagnosis several subsequent studies have failed to replicate this finding (61–64).

Tryptophan Hydroxylase Genes

Tryptophan hydroxylase (TPH) catalyzes the rate-limiting step in the synthesis of serotonin from tryptophan. There are two isoforms of TPH: TPH1, expressed primarily in the skin, pineal gland and gut; and TPH2, expressed exclusively in the central nervous system. Both TPH isoforms have been studied in candidate gene studies of OCD. Candidate gene studies investigating TPH1 demonstrated no association with OCD (49, 50). A family-based association study examined two common single nucleotide polymorphisms (SNPs) of TPH2 in the putative transcriptional control region and in intron 2 of the TPH2 gene in 71 early-onset OCD trios. Analysis of the single nucleotide polymorphisms (SNPs) rs4570625 and rs4565946, revealed a significant preferential transmission of haplotype G-C to children and adolescents with OCD (65). This association awaits replication.

Dopaminergic Candidate Genes

Several lines of evidence suggest the importance of the dopaminergic system in OCD: (1) the efficacy of dopamine antagonists for treatment-refractory OCD, (2) functional neuroimaging studies suggesting abnormalities in the dopamine system in OCD and (3) the high comorbidity of OCD with Tourette syndrome.

Dopamine Transporter Genes

The dopamine transporter gene (SLC6A3) has been studied as a candidate gene in OCD. A 40-bp variable number tandem repeats (VNTR) polymorphism located at the 3' end of the

gene with unknown functional significance has been studied in OCD. Four separate studies have failed to demonstrate a significant association with OCD (50, 53, 66, 67).

Dopamine Receptor Genes

The Dopamine receptor 2 (DRD2) has been studied sparingly in OCD candidate gene studies. Support for the importance of DRD2 in OCD comes from the demonstration of lower DRD2-binding ratios, as measured by SPECT imaging, in the left caudate of subjects with OCD compared to unaffected controls (68). The TaqIA polymorphism, a serine-to-cysteine missense mutation occurring in exon 7 of DRD2, was examined in a population-based case-control study in OCD. No significant association between this polymorphism and OCD was demonstrated in this 220 subject sample (66).

Several studies have examined a single-nucleotide polymorphism in the dopamine receptor 3 (DRD3) that results in a glycine-to-serine amino acid substitution in the third exon. Several studies have failed to demonstrate a significant association with this polymorphism (52, 66, 69).

The dopamine receptor 4 (DRD4) has been well studied in psychiatric genetics. A polymorphism in exon 3 of the DRD4 gene, within the third cytoplasmic loop of the receptor, consists of a variable number repeats of a 48-bp motif (VNTR); different alleles contain 2–10 repeats. Studies have demonstrated that the seven-repeat allele expresses a receptor with a blunted response, such that at least 3-fold more dopamine is required to induce a response, relative to other versions of the receptor. A case-control study in 245 Ashkenazi Jews demonstrated a significantly lower frequency of A7 alleles in cases than controls (50), but this finding did not withstand statistical correction for multiple hypothesis testing. Another study, which used both family-based and case-control designs, demonstrated a significantly higher frequency of the A2 allele in OCD cases compared to controls but did not find an association with A7 (70). A family-based association study examining 69 early-onset OCD trios demonstrated an increased transmission of both A7 and A2 alleles in OCD cases (71). However, an additional case-control study from South Africa failed to demonstrate a significant association between DRD2 VNTR and OCD (53). This polymorphism merits further study.

Monoamine Oxidase A

Monoamine oxidase A (MAO-A) degrades epinephrine, norepinephrine, serotonin and dopamine and is the target of monoamine oxidase inhibitor drugs (MAOIs) such as tranylcypromine and phenelzine. Two polymorphisms that have both been shown to affect the activity level of the enzyme have been studied in OCD. A family-based association study of 110 trios demonstrated an association between the low-activity form of the exon 8 T/G polymorphism in the MAO-A gene and OCD in males (72). A later study, using both case-control and family-based association analyses in a Mexican sample, suggested that the other, high-activity variant was associated with OCD in females (73). A subsequent study within the Afrikaner population showed no evidence of association with OCD, even after stratifying for gender in a different polymorphism that also affects enzyme activity level, T1046C in exon 14 (53). The potential contribution of MAO-A polymorphisms, in both males and females, requires further elucidation.

Catechol-O-methyltransferase Gene

Catechol-O-methyltransferase (COMT) is also involved in the inactivation of catecholamines (norepinephrine, epinephrine and dopamine), by methylation rather than oxidation; COMT is thought to be relatively more important for terminating dopamine neurotransmission in the frontal lobes, while MAO has a larger role in subcortical structures.

A SNP encoding for a valine-to-methionine substitution at codon 158 (val158met) has been demonstrated to affect the activity of the enzyme (74). Despite several initially promising results, a meta-analysis of 7 studies involving 413 OCD cases and 865 controls found no evidence of association between the COMT val158met polymorphism and OCD (75). A subsequent meta-analysis, involving the addition of 1 case-control study with 414 additional samples, suggested that there may indeed be an association of the COMT met158 allele and OCD, but only in males (76). As in the case of MAO-A, further investigations are needed to better elucidate this intriguing potential sex-specific effect.

Glutamatergic Candidate Genes

There has been significant interest recently in the possible role of perturbations of glutamatergic neurotransmission in OCD (77). While early evidence for such a role came from neuroimaging studies (78) and small open-label pharmacological trials (79, 80), this view gained credibility and broader interest with the replicated association in the past few years of glutamatergic genes with OCD.

The neuronal glutamate transporter EAAT3

As reviewed above, the first genomic linkage scan performed in OCD, and a follow-up replication study, suggested linkage of OCD risk with polymorphisms at 9p24 (26, 31). The identified region contained many known and predicted genes, including the primary neuronal glutamate transporter, Slc1A1 (also EAAT3, EAAC1). Further suggestive evidence for an OCD susceptibility gene on chromosome 9 derived from the description of a patient with both OCD and Tourette syndrome with a monosomy of chromosome 9 (81).

In 2006, a pair of well-powered association studies lent credence to SLC1A1 as an OCD risk gene. An early association study from Hanna's group showed no association with two markers in two SNPs in intron 3 of the SLC1A1 gene (82); but a larger family-based association study using more markers revealed significant association between OCD and two SNPs in the 3' region of the gene (83). These authors also described a multi-generational pedigree in which the disorder was associated with a small deletion in the 3' flanking region of Slc1A1; while the functional consequence of this deletion remains unclear, it lends further credence to the conclusion that dysregulation of Slc1A1 may contribute to risk for OCD (83). Simultaneously, Arnold and colleagues published an independent family-based association study examining 9 SNPs spanning the SLC1A1 locus. They found two markers, within the same haplotype block (albeit one distinct from that found in the previous study), significantly associated with transmission of OCD (84).

Interestingly, both of these studies found the association between SLC1A1 genotype and transmission of OCD to be significant for male probands but not female probands (83, 84). There was also a suggestion that the association was strongest when probands had early-onset OCD. Dickel and colleagues ascertained specifically for early-onset OCD (83) (as had the original genome scan that identified 9p24 as a region of interest; (26)). Arnold and colleagues did not specifically recruit subjects with early-onset disease; but a secondary analysis of their data suggested association only within the early onset group (84; this finding did not, however, survive correction for multiple comparisons). These observations are intriguing in light of the fact that early-onset OCD is thought to be genetically distinct from adult-onset disease (85) and to be more heritable (17–19). (Indeed, this higher heritability motivated the focus on pediatric-onset probands in several studies; (26, 83).)

Association of SLC1A1 with OCD risk has now been replicated in a number of other studies. Stewart and colleagues genotyped 66 OCD probands and their families at 18 SNPs spanning the 3' end of the Slc1A1 gene (86). They found association of OCD risk with the

same 3' haplotype reported by Dickel et al (83), distinct from but close to that reported by Arnold and colleagues (84). Association was again more significant in males. Interestingly, the pattern of overtransmission of a specific haplotype in this replication study was opposite that reported in the original association; this has been interpreted as evidence that the tested SNPs are not themselves causative of the increased risk for OCD but rather are in linkage disequilibrium with a causative SNP (86). Despite these differences in the studies, the replication of association at the same locus stands in contrast to the history of non-replication that has plagued many earlier genetic findings in OCD (34).

More recent studies have followed this pattern: while failing to replicate overtransmission of precisely the same haplotype as was identified in the original studies (83, 84), they have by and large continued to report association of OCD risk with polymorphisms at the SLC1A1 locus. Shugart and colleagues genotyped 13 SNPs spanning the Slc1A1 gene in members of 378 families with OCD probands, using somewhat different methodology and more extended pedigrees than earlier studies the locus. They did not replicate association of OCD risk with the specific SNPs found in earlier studies, but they did find highly significant association of OCD risk with a distinct SNP, 7.5 kb outside the SLC1A1 gene. They hypothesize that, although it is beyond the gene proper, this SNP (or another causative SNP in linkage disequilibrium with it) may disrupts EAAT3 expression or function (87). Further evidence supporting a role for SLC1A1 in OCD comes from a recent case-control study of 325 OCD probands and 662 controls, in which specific SLC1A1 haplotypes were again found to be associated with OCD risk (88). This latter study did not find increased association in males and provided evidence for causative polymorphisms both in the 3' region of the gene, as suggested by previous family-based studies, and closer to the 5' end; the authors tentatively interpret this as evidence for multiple causative polymorphisms (88).

These association studies have produced increasing confidence that polymorphisms at the SLC1A1 locus contribute to OCD risk; but they have shed little light on the causative polymorphism. Two recent studies have sought to elucidate this issue. Wang and colleagues screened the coding regions of SLC1A1 from 378 patients with OCD, and controls, for potentially functional polymorphisms. They found several synonymous substitution mutations in OCD probands and one nonsynonymous mutation, whose functional significance remains unclear (87).

Wendland and colleagues screened known SNPs at the Slc1A1 locus, including all those associated with the OCD phenotype in earlier studies, for their correlation with Slc1A1 expression in lymphoblasts and in postmortem brain tissue (from normal controls or patients with other, non-OCD psychiatric conditions). They found that three polymorphisms predicted Slc1A1 expression in immortalized lymphoblasts, and that SNP rs301430 predicted expression in brain tissue. Furthermore, in an *in vitro* assay this SNP was found to influence expression of a reporter gene (88). This SNP was associated with OCD risk in two of the previous genetic association studies (83, 86).

These exciting data provide the clearest evidence to date for a direct connection between known polymorphisms at the Slc1A1 locus and the function of the gene. It is to be hoped that further investigations along these lines will lead to hypotheses as to how the gene is perturbed in OCD, and how this perturbation leads to the circuit dysfunction and symptomatology of the disorder.

The glutamatergic synapse: SAPAP and glutamate receptor genes

The glutamatergic synapse is a complicated and highly regulated structure. Postsynaptically, several subtypes of glutamate receptor are organized spatially by direct and indirect interactions with the cytoskeleton of the postsynaptic cell. In particular, glutamate receptors

of the NMDA and AMPA classes interact with the meshwork of proteins that makes up the postsynaptic density (PSD) and are therefore localized on dendritic spines. Physiological or pathological postsynaptic changes in glutamatergic neurotransmission can thus be produced by changes in the receptors themselves or in the PSD in which they are embedded.

Significant attention has focused in recent years on a critical component of the PSD, termed 'synapse associated protein associated protein', or SAPAP. In particular, SAPAP3, which is highly expressed in the basal ganglia circuitry implicated in OCD, has emerged as a potential OCD candidate gene. In contrast to the case of SLC1A1, in which a candidate gene emerged as a result of gene linkage scans and subsequent targeted association studies, interest in SAPAP3 derives from studies in mice. Feng and colleagues found knockout of SAPAP3 in mice to produce a behavioral phenotype reminiscent of important aspects of OCD, including anxiety and compulsive grooming (89). Importantly, both of these phenotypes reversed with treatment with the selective serotonin reuptake inhibitor fluoxetine, which is an established treatment for OCD. Furthermore, the knockout produced dysregulation of glutamatergic synaptic transmission in the striatum; again, such a dysregulation has been suggested to occur in OCD (77, 78).

It remains unclear whether these mice are best characterized as exhibiting OCD-like behaviors, or whether they might be better described as recapitulating trichotillomania or some other disorder of repetitive, compulsive behavior and anxiety. Indeed, interpretative difficulties of this sort inevitably accompany any attempt to model psychiatric conditions, with their complex and inevitably subjective symptomatology, in animals. Despite this, several groups have begun to investigate SAPAP3 in OCD, and grooming disorders, in humans.

A study from the Obsessive-Compulsive Disorder Collaborative investigated this question in 383 families with OCD; 32% of the subjects had trichotillomania or another grooming disorder. Several SNPs within the SAPAP3 gene were significantly associated with a grooming disorder, using a family-based association test. No SAPAP3 SNPs were associated with OCD independent of grooming disorders (87).

More recently, a group based at Miami, the NIH and Duke described complete sequencing of SAPAP3 in patients with OCD, TTM, or both, and a group of normal controls. Seven novel mutations, one of which was seen twice, were identified in patients with OCD and/or TTM (4.2%), while only two mutations were found in control subjects (1.1%; 90). While the functional significance of these mutations is unclear, and *in silico* analysis suggested that most of them are likely to be benign, the authors suggest that an accumulated load of minor mutations may have the aggregate effect of increasing risk for OCD and/or grooming disorders (90).

The evidence for a role for SAPAP3 in human disease remains very preliminary; it is perhaps stronger for grooming disorders than for OCD itself. Regardless, this gene remains an intriguing candidate for future studies; and the OCD-like phenotype of the knockout mouse (89) has created new interest in modeling OCD-like behaviors in animals through manipulations of glutamate-related genes.

Candidate gene studies have examined several other glutamate-related genes as potential risk alleles for OCD. Two studies have examined the potential contribution of the NMDA receptor subunit GRIN2B to OCD. Arnold and colleagues examined SNPs in the GRIN2B gene in 178 adult OCD patients and 211 unaffected family member controls; they reported association of a single SNP with OCD transmission (91). More recently, an association was observed between GRIN2B alleles and the concentration of glutamate and related molecules, as measured by magnetic resonance spectroscopy (MRS), in the anterior

cingulate cortex (92); MRS has previously revealed perturbation of glutamate and related molecules in this region in patients with OCD (93). While the association of GRIN2B genotype with OCD risk remains to be replicated and clarified, studies of this sort demonstrate a new approach to linking genetics, neurochemical endophenotypes, and psychiatric diagnosis to better elucidate both genetics and pathophysiology.

One early study examined the kainate-class glutamate receptors GRIK2 and GRIK3 in 156 OCD cases with matched controls as well as 124 parent-offspring trios. Association between SNPs in these genes and the OCD phenotype was by and large negative, though nominally significant association was reported with a single SNP in GRIK2 (94). The potential association of OCD with GRIK2 has not been further examined to date.

Other Candidate Genes

Brain Derived Neurotrophic Growth Factor

Brain-derived neurotrophic factor (*BDNF*) is important in neuronal survival, maturation, and plasticity (44, 95). The Val66Met polymorphism in the *BDNF* gene has been extensively studied in various psychiatric conditions. The polymorphism influences *BDNF* processing and its activity-dependent release from neurons. It has been associated in humans with hippocampal size, cognitive function, and mood and anxiety phenotypes. (44, 96). Similarly, a mouse in which the *BDNF* gene has been mutated to recapitulate the human Met allele exhibits increased anxiety-related behaviors (97).

This polymorphism is therefore a natural candidate for OCD, and other anxiety disorders. Initial case-control association studies suggested, in post-hoc analysis, that the Val66Met polymorphism was associated with increased OCD risk in the subgroup with early-onset disease (98). However, several subsequent candidate gene studies in early-onset or all OCD cases failed to replicate this association (99–103).

Oligodendrocyte Lineage Transcription Factor 2

Oligodendrocyte lineage transcription factor 2 (*OLIG2*) is an essential regulator in the development of oligodendrocytes, the cells that myelinate axons in the central nervous system. The *OLIG2* gene is highly expressed in the amygdala, thalamus, and caudate nuclei—brain regions implicated in OCD (104, 105). Furthermore, white matter abnormalities have been demonstrated in OCD by diffusion tensor imaging (DTI) (106, 107). In a family-based association study of 57 early-onset OCD trios, 3 SNPs (rs762178, rs1059004 and rs9653711) within the *OLIG2* gene were associated with OCD (105). The *OLIG2* gene represents a promising candidate gene in early-onset OCD, however, the results of this study have yet to be replicated.

Immune-related genes

It has been hypothesized that some cases of OCD may be related to autoimmune dysfunction. In particular, some cases of episodic OCD symptoms in the pediatric population appear to be associated with an autoimmune reaction to Group A streptococcal infection; this syndrome, whose details remain somewhat controversial, has been named “pediatric autoimmune neuropsychiatric disorder associated with *Streptococcus*,” or PANDAS (108). The existence of this syndrome, and the possibility that a broader subset of OCD cases may be attributable to perturbed immune function, has motivated investigation of candidate immunological genes in OCD in a few association studies.

Myelin oligodendrocyte glycoprotein (MOG) is a key component of the complement cascade. Four polymorphisms in the *MOG* gene, a dinucleotide CA repeat (MOG2), a

tetranucleotide TAAA repeat (MOG4), and 2 intronic single nucleotide polymorphisms, C1334T and C10991T, were investigated for the possibility of association with OCD using 160 nuclear families with OCD probands (91). Analysis revealed a significantly increased transmission of allele 2 of MOG4 to affected probands. This association remains to be replicated.

Tumor necrosis factor α (TNFA) is a proinflammatory cytokine involved in rheumatic fever and other autoimmune diseases (109). Polymorphisms in the promoter region of the *TNFA* gene have been associated with rheumatic fever. Obsessive-compulsive symptoms are common in individuals with rheumatic fever, and OCD is overrepresented in the relatives of individuals with rheumatic fever (110). The -308 G/A polymorphism in the *TNFA* gene promoter is believed to affect transcription of the gene (111). An initial examination of this polymorphism in a Canadian sample failed to detect any significant association with OCD (112). However, a subsequent study from Brazil, examining both the -308G/A polymorphism and a separate -238G/A polymorphism in 111 patients and 250 controls, found significant associations with both polymorphisms. This candidate gene clearly merits further investigation (113).

CONCLUSIONS

Genetic studies of OCD have taught us several important points about the disorder over the past two decades. Twin and family studies demonstrate that OCD has a significant hereditary component, although and environmental factors appear equally or more important in most studies. Genetic linkage studies have demonstrated that OCD is a complex genetic disorder that likely has many susceptibility genes, each of small effect. Of the three genome-wide linkage scans published to date, none has identified a locus that reached the statistical threshold for genome-wide significance; and the three have provided suggestive evidence of linkage to distinct genomic regions. The likelihood of finding susceptibility genes that are both common and of large effect is becoming exceedingly small.

Association studies and failures of replication

Despite the publication of nearly 100 candidate gene association studies from over 2 dozen groups of investigators over the past 2 decades, we have few convincing, replicated associations of specific genetic polymorphisms with OCD risk. Initial positive studies followed by repeated failures to replicate and negative findings upon meta-analysis have been the norm, as summarized in multiple specific cases above. Frustration and confusion has developed over the frequency with which initial positive candidate gene studies in OCD and other psychiatric conditions are not replicated (114).

There are several possible explanations for this difficulty in replication. Broadly speaking, it can derive either from false-positive findings (Type 1 error) in initial studies, from false-negative findings (Type 2 error) in replication studies, or from complexities in the genetics of the disorder that render replication challenging even if the initial positive finding is valid. Going forward, investigations of the genetics of OCD, as of all complex disorders, must grapple with these sources of complexity.

Several characteristics of individual candidate gene association studies may contribute to false-positive results. (1) Statistically, false positive results may result from inadequate control for multiple hypothesis testing; this is particularly likely to be problematic when a single, valuable repository of well-characterized DNAs is tested, in separate studies, for multiple candidate genes. (2) Publication bias can magnify this effect; statistically significant findings, even in post-hoc analyses of subgroups, are more likely to be published than negative association findings. (3) Genotyping error can also contribute; while it is

perhaps more likely to contribute to false negative results, genotyping error can also lead to false positive results (114). Case-control studies are particularly prone to false-positive error when there are batch differences in error rates and case and control samples are treated differently. Family-based association studies are also inherently biased towards false-positive results as error rate increases. (4) False positive results can derive from population stratification – the presence of systematic differences in allele frequency between subpopulations due to differences in ancestry. If cases are not optimally matched to controls, by sex and ancestry (as measured either by genetic criteria or by surrogate markers), systematic differences may emerge that are not actually related to the condition of interest.

Failure to replicate a valid initial finding can derive from false-negative error in replication studies, which can derive from any of several sources. (1) Inadequate sample size and statistical power can readily lead to a false negative result, especially when rigorous statistical criteria are (appropriately) employed. (2) Genotyping error can easily lead to a false negative result; traditionally, very few journals have required reporting of genotyping error rate. Genotyping error rates, even in well run laboratories are not uncommon (often 1–3% in the case of SNPs) (115). High genotyping error rates can greatly reduce the power of genetic studies. A 1% increase in error rates might require a 2–8% increase in sample size to maintain consistent statistical power (116).

Perhaps most interestingly – failures to replicate a valid initial finding can derive from the complexity of the disorder itself. Population stratification between studies, rather than within them, may contribute to such a phenomenon, especially as candidate gene studies have been performed by groups around the world, on widely different ethnic populations. Since allele frequencies inevitably differ at many loci in ancestrally distinct populations, and since the effect size of an OCD susceptibility gene may be moderated by its interactions with alleles at other genetic loci, the effect size of any given candidate gene may differ substantially between different populations and hence between different studies. If so, a positive association finding in one population, in which the effect size of the candidate polymorphism is large due to such epistatic interactions, may be hard to replicate in a distinct population in which the effect size is smaller.

Finally, the heterogeneity of the disorder itself may contribute to differences between studies. OCD is a clinically complex disorder, and two patients with the diagnosis can have completely non-overlapping symptomatology (117). There has been substantial interest recently in characterizing overlapping but distinct dimensions of symptomatology (3). It may be that risk genes are associated with one dimension more than others; indeed, there is evidence that this is the case, at least for hoarding symptoms (118). If the clinical characteristics of the patients in a replication study differs substantially from those of the patients in the original study, due to differences in ascertainment or the environment from which they are drawn, the effect size of a given risk allele may again be affected.

Positive candidate gene associations

Despite these challenges and the multiple failures to replicate candidate gene association studies, at least one reasonably convincing susceptibility gene for OCD has been identified. SLC1A1, which encodes the neuronal glutamate transporter EAAT3 (also EAAC1), falls under the linkage peak on chromosome 9 identified in the first genome scan (26). Its plausibility as a functional candidate gene derives from the increasing evidence that glutamate dysregulation may contribute to the pathophysiology of OCD (77). SNPs in or adjacent to this gene, primarily at its 3' end, have now been associated with OCD in five separate association studies (83, 84, 86–88).

As summarized above, other associations have been less convincing. Replication has yet to be attempted for several candidate genes, such as OLIG2 (105), and initial positive findings must therefore be interpreted with caution. Secondary analysis and meta-analyses have suggested association of some candidates with specific subpopulations, but confirmatory studies in which such subpopulations were identified in the primary analysis have not yet been performed. Clarity on whether any of the other candidate genes described above represent bona fide OCD risk genes must await further study.

Future directions: increasing power and reliability

The sources of failures to replicate listed above lead to clear ways in which the genetics of OCD can be clarified in future studies, all of which are being pursued by investigators in the field.

Increasing the sample size and power of future genetic studies is imperative, as it is clear that OCD is a multifactorial disorder determined by environmental influences as well as many susceptibility genes of small effect (14). Single-site studies are typically not large enough to detect susceptibility genes of small effect. Towards this end, two collaborative multi-site efforts for the elucidation of the genetics of OCD have been established. The OCD Genetics Collaborative collects samples from 6 US sites (Brown University, Columbia University/New York State Psychiatric Institute, Johns Hopkins University, Massachusetts General Hospital, University of California at Los Angeles, and the National Institute of Mental Health). This 6-site collaboration effort has studied several hundred families with OCD and has produced a number of important findings, as summarized above (19, 30, 32, 87).. A more recently formed group, the Obsessive Compulsive Foundation Genetics Collaborative is a collaboration of over 50 investigators from more than 20 sites in North America, South America, Europe and Africa. Established in 2002, the Collaborative has been able to pool over 3000 existing samples together to run the first genome-wide association study in OCD. The results of this study are eagerly anticipated and will hopefully significantly further our understanding of the genetics of OCD. Such collaborative efforts will need to be maintained in the future in order provide the necessary power for replication of initial findings and for ongoing investigations of adequate power to provide reliable results.

Improved selection of cases and controls will also improve the reliability of genetic studies. Family-based association studies, which collect trios of probands and their immediate relatives, adequately account for most of problems with control selection, since a ghost-control for each case can be created from the non-transmitted alleles of each parent (33). However, the advantages associated with this experimental design are partially counteracted by the increased difficulty associated with recruiting trios for genetic studies. In case-control genetic association studies, the use of genetic markers can now ensure proper matching by ethnicity and account for issues of population stratification (119). However, the current selection of cases for OCD genetics studies primarily involves recruitment from tertiary academic centers engaged in OCD research. Subjects reaching tertiary academic centers often differ in intelligence, socioeconomic status, responsive to treatment and impairment compared to population-based samples of OCD..

Refinement of how OCD cases are ascertained and described at the phenotypic level may increase the power of genetic studies. It may prove more fruitful to seek genetic contributors to obsessiveness as a continuous trait, rather than clinical OCD as a dichotomous factor. This would permit the inclusion of individuals with symptoms not severe enough to produce impairment or merit clinical attention. Several studies have suggested a higher heritability when OCD is construed broadly in this way (i.e. not requiring the impairment that is necessary for a clinical diagnosis) (12, 13).

Enriching the phenotype of OCD cases for genetic studies to increase homogeneity and enhance heritability in samples may be further beneficial to OCD genetic studies. Clinical characteristics such as age of onset and comorbid conditions such as tics may identify more homogenous subpopulations on which to do genetic analyses. Indeed, OCD with comorbid tics has been shown to have a different longitudinal course and differential pharmacological response relative to OCD without tics, suggesting that it may represent a distinct subsyndrome (120–122). Similarly, insofar as different symptomatic types of OCD represent distinct (though overlapping) dimensions of pathology, increasing homogeneity by focusing on specific symptomatic groups such as hoarding or washing may enhance our ability to identify causative polymorphisms (3).

Advancing genetic technologies will allow us to conduct larger, more powerful studies examining the genetics of OCD. Larger, collaborative studies are crucial given that OCD is a complex genetic trait with multiple susceptibility genes of small effect. Combining these technologies with sound experimental techniques from the field of epidemiology such as proper selection of controls and correction for multiple hypothesis testing will aid in the advancement. Improved characterization of the phenotype of OCD and the use of endophenotypes in genetic studies will provide further help in the effort.

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TABLEStudies implicating the *Slc1a1* gene in OCD.

Authors	Design	Subjects	Principal findings	Reference
Taylor et al, 1991	Case report	1 subject with Tourette syndrome, OCD, and ADHD	Deletion of terminal portion of 9p	81
Hanna et al, 2002	Genome-wide linkage analysis	56 individuals from 7 families, with pediatric-onset probands	Maximum linkage score (LOD = 2.25) on at 9p24	26
Veenstra-Vander Weele et al, 2001	Analysis of the genomic structure of <i>Slc1a1</i> and sequencing of coding sequence	7 probands from ref. 26	Several SNPs identified; no clear functional SNP	82
Willour et al, 2004	Sib-pair analysis	50 sib-pairs, 42 with narrow-phenotype OCD	Replication of linkage at 9p24	31
Dickel et al, 2006	Family-based candidate gene association study	71 trios with early-onset probands; one multigenerational OCD pedigree	Linkage to 2 SNPs within <i>Slc1a1</i> ; significance at one of these was limited to male probands	83
Arnold et al, 2006	Family-based candidate gene association study	157 probands and their first-degree relatives	Significant linkage to 2 SNPs and one haplotype within <i>Slc1a1</i> ; haplotype linkage was significant only with male probands.	84
Stewart et al, 2007	Family-based candidate gene association study	66 probands and their first-degree relatives	Significant association with a three-marker haplotype in both males and females, and with two individual markers	86
Shugart et al, 2009	Family-based candidate gene association study	378 families	Significant association with a marker outside the <i>Slc1a1</i> gene	87
Wendland et al, 2009	Case-control association study; <i>in vitro</i> expression study	325 subjects with OCD; 662 matched controls	Significant association with 2 haplotypes within <i>Slc1a1</i> , and one novel 5' haplotype associated with hoarding; stronger association in males	88