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SPECIAL ISSUE

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Genetic and environmental influences on obsessive-compulsive disorder

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Abstract It is important to understand how genetic and environmental factors interact in the development of obsessive-compulsive disorder (OCD) in order to provide a cohesive model of the underlying pathogenic mechanisms. In this article, we provide an overview of the current knowledge of possible genetic and environmental contributions to the development of OCD. We consider the significant challenges for identifying risk factors for OCD as well as promising avenues for overcoming these obstacles in future research. In particular, we discuss the value of focusing on certain phenotypes, applying a dimensional approach, and investigating possible endophenotypes. We also describe innovative study designs that may be used in future research to explore the interaction between genetic vulnerability and environmental risk factors for OCD.

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Introduction

Obsessive-compulsive disorder (OCD) is characterized by recurrent obsessions or compulsions that provoke distress and/or interfere significantly with everyday functioning. The disorder affects approximately 1–3% of adults [48] and is ranked by the World Health Organization as among the ten most disabling medical conditions [66]. Although there is strong evidence that OCD has a genetic component [43], definitive single-domain or integrative models have not yet been established [86]. Similar to other anxiety disorders [14], the etiology of OCD is likely to involve both environmental and genetic factors and interactions between them.

For this reason, gene by environment (G × E) studies of OCD are essential. These studies need to be based on (1) evidence that there is genetic liability for the disorder, (2) an understanding of the mode of transmission of this genetic liability including the primary candidate genes, and (3) information about environmental risks for the disorder and how they interact with genes. In this article, we will review evidence regarding how genetics may make an individual vulnerable to OCD and consider possible environmental triggers that may lead to the development of OCD in a vulnerable individual. We will then address obstacles to G × E research in OCD and suggest possible ways to overcome these obstacles in future research.

What evidence is there for a genetic liability for OCD?

Although there is substantial evidence that genetic factors can increase an individual's vulnerability to OCD, the specific nature of this vulnerability is still unclear [5]. Estimates of heritability and familial aggregation vary (see review by Grados et al. [37]) due to methodological differences across studies in the participants used (child vs. adult), the ascertainment

of cases, the use of control/comparison groups, the diagnostic criteria/dimensional measures by which OCD is operationalized, and the use of direct interviews with cases (or parental informants).

Conservative estimates of genetic liability can be derived from Hettema et al.'s [43] review and meta-analysis of genetic epidemiology of anxiety disorders. For OCD, they identified only five family studies (and no twin studies) with operationalized diagnostic criteria, systematic ascertainment of cases, direct interviews using interviewers blind to case status, and inclusion of a comparison group. They found significant association between OCD in the probands and OCD in their first-degree relatives (odds ratio = 4). An unadjusted aggregate risk of 8.2% to first-degree relatives of OCD probands (based on n = 1,209) was observed, compared to 2.0% in relatives of comparisons (n = 746). Using more inclusive criteria, van Grootheest et al. [90] have reviewed child and adult twin studies published to date. In examining studies with dimensional assessment of OCD symptoms using questionnaires, genetic liability ranging between 45 and 65% for OCD symptoms in children was observed. For adults, results were suggestive of a genetic influence between 27 and 47%, but the authors concluded that larger studies with continuous data are needed to confirm this.

What is the pattern of disease transmission?

Results of segregation studies for OCD suggest that, in part, disease transmission is due to genetic factors. Some studies supported a dominant Mendelian mode of transmission [17, 39, 67], while one study supported a mixed model involving major gene effect(s) and polygenic background [25]. Sex and age-dependent penetrance have been observed across studies. For example, Nestadt et al. [67] found that the transmission of OCD in female probands was compatible with a Mendelian major locus (either dominant or codominant) model, while this model was less evident in the male-proband families. More studies are needed, however, before a specific genetic mode of transmission can be indisputably identified.

What genes are likely to be involved?

Identifying gene(s) involved in complex diseases can be achieved using both linkage and association study approaches. To date, few studies have conducted a genome-wide linkage analysis of OCD. Using seven pedigrees, Hanna et al. [40] found the candidate region 9p24 at marker D9S288 to be suggestive of linkage. This region was then largely supported by a replication study using 50 pedigrees [92]. More recently, a study including 219 families found evidence for susceptibility loci on chromosomes 3q, 7p, 1q, 15q and 6q [84]. Across studies, however, none of the observed findings exceeded the suggested logarithm of odds (LOD) cut-score of 3, and therefore replication with larger samples is warranted.

A large number of association studies assessing likely candidate genes have now been conducted. As a thorough review of these findings is beyond the scope of this article, interested readers are directed to Hemmings and Stein [42] for a recent review. Generally, association studies have focused on genes that are important to the serotonin and dopaminergic neurotransmitter systems, while some have pursued genes associated with CNS developmental pathways. Most candidates have been selected on the basis of animal models, clinical case observations, and drug efficacy in the treatment of OCD. Under the serotonergic system, the serotonin transporter, serotonin receptor types (2A, 2C, 1Dβ), and tryptophan hydroxylase have been studied. Under the dopaminergic system, dopamine receptors 2, 3 and 4, the dopamine transporter gene, Monoamine oxidase A, and Catechol-*O*-methyltransferase have been investigated. Other candidates of interest include genes encoding glutamate, glutamate ionotropic kainite receptors (1 and 3), GABA Type B receptor 1, brain derived neurotrophic factor, and myelin oligodendrocyte glycoprotein. Hemmings et al. [42] concluded that "the preliminary and frequently inconsistent nature of the data represented in the majority of OCD psychiatric genetic-association studies may seem discouraging" (p. 435). They described several reasons why difficulty with replication exists, including population admixture, clinical heterogeneity of OCD, and small sample sizes. Even when vulnerability gene(s) for OCD are identified, the functional variants and interactive genes will need to be identified, the associated endophenotypes clarified and any gender effects considered [52].

What are the environmental risk factors for OCD?

Very little is known about environmental triggers for OCD. Further, some factors that were previously considered to be purely environmental are now considered to have a heritable component, such as family life, parent–child interaction, divorce, and life events [72]. Some of the limited information we do have about environmental risk factors for OCD has been obtained from patients with Tourette's Syndrome (TS), which is considered etiologically related to certain forms of OCD [70, 80, 83]. When investigating potential G × E interactions for OCD, environmental risk should include not only psychosocial experiences, but also perinatal injuries, infections, and toxic pathogens associated with elevated rates of the disorder [65]. Vasconcelos et al. [91] conducted a retrospective study of environmental risk factors for OCD and found that prolonged labor and edema during pregnancy predicted OCD later in life.

Due to reports of higher prevalence of OCD among patients with Sydenham's chorea, several studies have

examined the possible relationship between streptococcus infection and OCD. Swedo [87] proposed that in a subgroup of children, exposure to streptococcal infection led to abrupt onset of OCD and TS symptoms. She referred to this group of children as having "pediatric autoimmune neuropsychiatric disorder associated with streptococcal infection" (PANDAS). According to some authors, their OCD may represent an abnormal immune response to the infection, with the production of self-antibodies and inflammatory changes in the basal ganglia [88]. Although it was initially proposed that exposure to streptococcus represented an environmental cause of OCD, this does not appear to be the case given that familial aggregation for OCD/TS has been described in relatives of PANDAS probands [57]. The relevance of PANDAS to OCD in general, however, remains unclear and additional research is needed to clarify this relationship.

There is also some evidence that stressful or traumatic events may be a risk factor for OCD. Brown et al. [15] reported that statistically significant covariation between lifetime PTSD and OCD was attributable to cases in which a principal diagnosis of PTSD was followed by a secondary diagnosis of OCD. This finding indicates the possibility that precipitants or features of PTSD may act as causal factors in OCD. Other studies suggest that OCD may be linked to a history of physical and sexual abuse during childhood [e.g., 55]. One study found that children with OCD had significantly more total life events and more negative life events in the year before onset than normal controls, and they perceived the life events as having more impact [34]. Another study found that the only difference between familial and non-familial OCD was that individuals with non-familial OCD reported more common and more severe life events prior to the onset of OCD [4]. Finally, Cromer et al. [20] examined traumatic events among a sample of individuals diagnosed with OCD and found that the presence of one or more traumatic life events was associated with increased OCD symptom severity.

Limitations are noted with the above studies, including the fact that they are correlational in design and therefore cannot provide conclusive evidence on causation. In addition, studies reliant on self-report are constrained by methodological issues related to the fallibility of memory, same-rater bias, and the emotional state of the reporter. Finally, most of these studies lack an appropriate clinical comparison group, such as a group of individuals diagnosed with another anxiety disorder, which would allow us to determine whether the risk factors are specific to OCD. In one of the few studies of prospective predictors of OCD conducted with the Dunedin Multidisciplinary Health and Development Cohort [24], individuals who were assessed as having OCD at age 18 were significantly more depressed and anxious and had a higher level of substance use than comparison groups at age 15. Additional developmental studies are underway with the Dunedin Cohort to evaluate whether substance abuse, traumatic experiences, including childhood physical and sexual abuse, or other psychosocial stressors contribute risk to the future development of OCD.

As described in the previous section, there is evidence that OCD is a familial disorder and that the transmission of OCD is in part genetic. There is still uncertainty, however, about the precise mode of genetic transmission of OCD and the exact gene(s) involved. As with other anxiety and mood disorders, we must think not only about *which* genes are related to OCD, but also about *how* genes may influence anxiety in general and OCD in particular [27]. Environmental risks, such as traumatic or stressful life events, may also be important in the development of OCD. At this time, however, designing a G × E study for OCD is somewhat difficult due to the tentative findings observed in some areas. In the following section, we identify some of the challenges for G × E studies of OCD and discuss various findings and approaches that may facilitate this type of research in the future.

Challenges for G × E Research in OCD

One of the greatest obstacles to examining G × E interactions in OCD is that it is a heterogenous disorder, rather than a unitary diagnostic entity [10, 12, 16, 51]. Different variants of the OCD clinical phenotype may have different etiologic pathways [18] and signify variability in genetic, neural, and neuropsychological correlates. OCD may comprise several overlapping syndromes that share causative factors but also have unique causative factors. If this is the case, researchers must identify the specific clinical and phenomenological characteristics of OCD that may be associated with an independent pattern of inheritance. They may then investigate the common and specific causative factors implicated in each OCD subtype. If we can identify a subtype of OCD that is distinctively transmitted within families and might be due to unique genetic factors, that subtype could be more easily identified with genetic linkage studies.

OCD symptom subtypes

Several approaches have been used to subdivide the broader OCD phenotype into subgroups that are potentially more etiologically and genetically homogenous. One strategy has been to classify OCD symptoms into different symptom themes or dimensions. Factor or cluster analyses of OCD symptoms have consistently identified four or five OCD symptom dimensions, including symmetry/order, contamination/cleaning, obsessions/checking, and hoarding [60]. Some studies include a fifth dimension consisting of somatic, sexual, religious obsessions and mental rituals ("pure obsessionals") [58]. These subtypes may be relevant for

linking particular genetic variations to OCD. For example, one recent study suggested that the 5-HTTLPR polymorphism may be relevant for the religious/somatic obsessions subtype of OCD. Patients with OCD carrying the long allele were found to have higher scores for religious and somatic obsessions [49].

Compulsive hoarding may also constitute a distinct OCD symptom dimension with a particular genetic vulnerability. Recent studies using quantitative traits have provided especially promising leads with regard to the hoarding obsessive-compulsive phenotype. Zhang et al. [95] conducted a genome scan of patients with TS using the hoarding factor as a quantitative phenotype. They observed significant allele sharing for the hoarding factor for markers at 4q34, 5q35.2, and 17q25. The 4q site is in proximity to a region previously linked to the TS phenotype. Although the chromosome 4 and 17 sites have been previously implicated in TS, the chromosome 4 site may be specific to hoarding [63]. Similarly, Hasler et al. [41] examined several OCD symptom dimensions and found that hoarding showed the highest familiality. Another factor consisting of sexual, aggressive, religious, and somatic obsessions and checking compulsions was also familial. Finally, in a study of 11 multigenerational families with OCD and hoarding, Mathews et al. [61] found that hoarding was highly heritable, although they did not have sufficient power to detect regions of interest for hoarding. Although findings regarding the familiality of hoarding are promising, the relevance of these findings to OCD is debatable due to the uncertain diagnostic status of hoarding. Some have argued against the inclusion of hoarding within OCD after finding strong intercorrelations for classic OCD symptoms such as checking, rituals, and contamination and only moderate correlations between these symptoms and hoarding [94]. In addition, hoarding is notorious for its poor treatment response to pharmacological and behavioral treatments that are efficacious for OCD [1, 12, 59, 93].

Early versus late onset OCD

Some evidence suggests that individuals with early onset of OC symptoms may represent a more etiologically and genetically homogeneous subset of patients and that heredity may play a stronger role in early-onset OCD [23, 26, 32, 74]. Although the threshold for defining "early-onset" varies across studies, data from a family study revealed that onset of OCD symptoms before age 18 was significantly associated with higher familial loading [67]. Other characteristics associated with the early-onset phenotype are a male preponderance [29, 97], a higher frequency of compulsions not preceded by obsessions [32], higher comorbidity with tics and TS [26, 31, 75], and worse response to monotherapy with clomipramine or serotonin reuptake inhibitor (SRI) [2, 3, 26]. In a genome scan by Hanna et al. [40] based on probands with OCD, a region of suggestive linkage was found in chromosome 9p24, a linkage finding that was replicated by Willour et al. [92]. Both Hanna et al. [40] and Willour et al. [92] achieved their strongest results based on a narrow phenotype model in samples ascertained largely through probands with early-onset disorder. Another recent genome-scan analysis of OCD conducted by Shugart et al. [84] indicated a role of gene(s) on chromosome 1 in increasing the risk for an earlier onset form of OCD, whereas linkage on chromosome 7 increased the risk for a later onset form of OCD.

Comorbid TS or tics

Obsessive-compulsive disorder with comorbid tic disorders may also be a potentially important clinical subtype with a different etiology and neurobiological mechanisms. In a study completed on 466 first-degree relatives of OCD adult probands, probands with OCD and comorbid tic disorders had a higher familial loading for OCD [69]. Other studies have found that the lifetime prevalence of OCD was significantly higher in first-degree relatives with a history of tics than in first-degree relatives without a tic history [39] and that OCD probands and relatives had a greater lifetime prevalence of tics than control participants [36], suggesting that tic disorders may constitute an alternate expression of the familial OCD phenotype. Younger age-at-onset and male gender have been found to be associated with increased tic disorders in relatives of OCD probands [36]. Cruz et al. [21] reported an association between the sevenfold variant of the 48bp VNTR polymorphism of the DRD4 gene and OCD with tics. This finding was replicated 1 year later by the same research group suggesting that the sevenfold variant of the DRD4 gene could explain the phenotypic variance of comorbid tic disorders in OCD patients [68], although another recent study failed to confirm these results [64].

Several studies have found that although OC symptoms in patients with TS are integral to TS [73], they are both clinically and phenomenologically different from those encountered in OCD [30, 33]. George et al. [33] demonstrated that patients with TS plus OCD had significantly more violent, sexual, and symmetry-related obsessions and more touching, blinking, counting, and self-damaging compulsions than patients with OCD alone, who had more obsessions concerning dirt or germs and more compulsions related to cleaning. The participants with both disorders reported that their compulsions arose spontaneously, while those with OCD alone reported that their compulsions were frequently preceded by cognitions. Other groups have also found phenomenological differences between the repetitive behaviors in TS and those in OCD [62]. Leckman et al. [53] found that obsessions/checking and symmetry/ordering

were significantly correlated in sibling pairs that were concordant for Tourette's disorder.

Sexual dimorphism

There is evidence of sex dimorphism of clinical features of OCD. Women with OCD may have more aggressive and contamination obsessions and cleaning rituals, while men tend to report more frequently primary obsessive slowness, sexual, exactness and symmetry obsessions and odd rituals [96]. Accordingly, several studies have examined sex-specific genetic effects for OCD [42]. Sexually dimorphic associations in OCD have been found with COMT, MAO-A, and 5-HT 2A genes [56]. Two studies have found a possible association between the L allele of COMT gene, which appears to be gender-related, being present only in males [47, 82]. Other studies have found different results and a meta-analysis conducted on data from the different studies showed little evidence to support an association between OCD and the COMT gene [9]. Arnold et al. [7] also found a specific haplotype association of SLC1A1 that was statistically significant in transmissions to male but not female offspring. Finally, another recent association study found evidence for the SLC6A4 JT transporter gene-linked polymorphic region (5-HTTLPR) polymorphism for female participants only [22]. Although the underlying explanation for these gender effects is unknown, one possibility concerns exposure of the developing brain in utero and during early postpartum to high levels of androgens [71].

In combination, the studies described in the preceding section provide evidence for the notion that different OCD phenotypes may have different genetic susceptibilities. Particular symptom phenotypes, such as hoarding, counting/repeating rituals, and pure obsessions, appear particularly promising for future research identifying gene-disorder associations in OCD [41], as well as perhaps OCD with tic disorders and OCD with obsessional slowness. It is also possible that a combination of several of these subtypes may be involved in a particularly heritable form of OCD. Blanes and McGuire [13] suggested that there is a "neurodevelopmental" subtype of OCD, with a male-preponderance, early onset, high frequency of motor tics, soft neurological signs, and poor performance on neuropsychological tests of visuospatial functioning.

Future directions

Dimensional approach

Given evidence of clinical heterogeneity described in the previous section, it seems appropriate to examine symptom subtypes when examining vulnerability to OCD. Attempts to classify OCD patients into subtypes have had limited success, however, because OCD patients are rarely monosymptomatic and recruitment of sufficient sample sizes of each subtype is difficult [60]. For this reason, Mataix-Cols et al. [60] have recommended a dimensional approach for OCD symptoms. Symptom dimensions constitute a spectrum of potentially overlapping vulnerabilities that cut across diagnostic boundaries and do not establish a boundary between normal and abnormal. Dimensional approaches to OCD resolve some of the difficulties associated with subtyping by more accurately characterizing individual differences among OCD patients and allowing researchers to detect the genetic susceptibility loci that contribute to the heterogeneous OCD presentations. In addition, a dimensional approach will allow family members presenting with OCD symptoms that fall below DSM-IV threshold to be included in genetic studies. Finally, Miguel et al. [63] suggest that a combined dimensional approach within specific subgroups may best identify the susceptibility loci for OCD.

Several studies have applied a dimensional approach to examining risk for OCD (see [90] for a discussion of using this type of approach in twin studies). Alsobrook et al. [5] found that the relatives of OCD probands who scored highly on obsessions/checking and symmetry/ordering were at greater risk for OCD than were relatives who had low scores on those factors. Similarly, Leckman et al. [53] found that obsessions/checking and symmetry/ordering factors were significantly correlated in sib-pairs concordant for TS. Cavallini et al. [18] also performed a candidate gene study with a functional polymorphism in the promoter region of the serotonin transporter locus at 17q11. They found a significant association of the long/long haplotype in patients with tics and high scores on the repeating/counting factor. In an effort to provide an instrument capable of properly assessing the dimension-specific OCD symptoms severity, Rosario-Campos et al. [76] developed the Dimensional Yale-Brown Obsessive-Compulsive Scale (DY-BOCS). Initial findings using the DY-BOCS suggest it is a reliable and valid instrument for assessing multiple aspects of OCD symptom severity when administered by trained assessors [76]. This scale should enhance the phenotypic characterization of different OCD symptom dimensions.

Identifying endophenotypes

Although it will be useful to examine genetic vulnerability for specific OCD dimensions or symptom subtypes, it is also becoming clear that approaching OCD exclusively in terms of top-level overt symptoms is limited. Another approach that has been suggested is using endophenotypes [35]. The rationale for using endophenotypes (traits associated with OCD that do not include any aspect of its clinical manifestation) is that the number of genes required to produce variations in OCD traits may be fewer than those involved

in producing the OCD diagnosis. In addition, these intermediate phenotypes would be less influenced by environmental factors and may be a better way to define affected and non-affected individuals in a given family. Ideal endophenotypes should be developmental precursors of OCD that are heritable and share genetic influences with OCD. It also may be important to look at disorders where OCD shares endophenotypes, such as neurocircuitry, including TS, body dysmorphic disorder (BDD), and autism.

Neuropsychological characteristics may constitute possible endophenotypes, such as failures in cognitive inhibition. Chamberlain et al. [19] argue that top-level OCD symptoms are strongly suggestive of inhibitory failures. Obsessions may be characterized as failures to inhibit or shift attention from intrusive thoughts to other, less distressing cognitions. Similarly, compulsions may be conceptualized as lack of control over behavior, e.g., ritualistic checking behavior. OCD has also been related to altered action monitoring and target detection processes that may be related to hyperactive striatal–cortical circuits [38, 46].

Neuroimaging may also be a useful tool for identifying potential candidates for characterizing OCD endophenotypes. Attempts have been made to use indices of brain structure in the classification of OCD, such as regional volumes. A number of volumetric studies of individuals with OCD have identified alterations in several brain structures, including the basal ganglia [77], thalamus and orbitofrontal cortex [8], and amygdala [89]. One recent study by Soriano-Mas et al. [85] successfully identified OCD patients on the basis of whole-brain anatomical alterations. These whole-brain anatomical alterations were positively correlated with the severity of symptoms reported by the OCD patients, and gender specific analyses improved OCD-control classification in this study [85]. Future studies may consider whether any observed sexually dimorphic endophenotypic brain structural differences in OCD patients are related to the apparent sexually dimorphic genetic influences on OCD, whether certain structural profiles can identify OCD subtypes, and whether unaffected relatives of OCD patients also have structural differences.

Functional indices may also be used characterize OCD endophenotypes, such as regional metabolism at rest, regional concentrations of neurochemical and metabolic product, and regional indices of receptor binding potentials. Although findings of functional abnormalities in OCD have been somewhat ambiguous thus far, one consistent finding has been that of orbitofrontal hypermetabolism [81], which may be considered as an endophenotypic marker of OCD that could reduce the effect of heterogeneity in future studies. To date, both structural and functional findings support continued focus on the orbitofrontal cortex-anterior cingulate cortex-striatum-thalamus brain circuit in the search for endophenotypic markers for the genetic study of OCD.

Another approach to examining the heritability of OCD is investigating the heritability of quantitative personality traits associated with the disorder, such as neuroticism, obsessionality, and perfectionism. Enoch et al. [28] found that -1438 G/A polymorphism might contribute to a behavioral trait (perfectionism or obsessionality) common to both anorexia nervosa and OCD. DSM-IV lists OCD as an anxiety disorder, and there is evidence that a polymorphism in the promoter region for the serotoninergic reuptake transporter (5-HTTLPR promoter region) accounts for a portion of the variation in anxiety-related personality traits in the healthy background population [54]. Knock-out of this gene in mice causes abnormal behavioral phenotypes consistent with increased anxiety and reduced aggression [45].

Some researchers have suggested that the best way to enhance the endophenotyping effort with respect to OCD is to broaden the phenotype by including other disorders that may have an etiopathological link with OCD [44]. From a phenotypic spectrum perspective, spectrum disorders should occur more commonly among the relatives of case probands. Disorders that are posited to be linked to OCD, based on their similarities with OCD in a variety of domains, including symptoms, demographic features, course of illness, comorbidity, joint familial loading and presumed etiology, are referred to as OC spectrum disorders [44]. These disorders include those associated with bodily preoccupation (BDD, anorexia nervosa, and hypochondriasis), neurological disorders, including TS and autism, and impulse control disorders, including pathological gambling, kleptomania, and trichotillomania. Results from a recent family study on 80 cases and 73 controls showed a possible genetic relationship between OCD, somatoform disorders (BDD, hypochondriasis), eating disorders, and impulse control disorder. In particular, BDD appeared to be part of the familial OCD spectrum [11]. In a family study of OCD probands by Bienvenu et al. [11], either BDD alone or BDD with hypochondriasis occurred significantly more frequently in first-degree relatives of OCD probands than community control probands.

Pooling across samples

Although assessing symptom dimensions and examining endophenotypes may advance genetic investigations of OCD, researchers continue to face the challenge of having inadequate power to detect genes for OCD, which is a relatively low-prevalence disorder. Dickel et al. [22] pointed out that low power across individual association studies in OCD may lead to a false acceptance of the null hypothesis. One obvious solution to this dilemma is to increase power by pooling DNA across sites. Dickel et al. [22] conducted a pooled analysis of five replication studies that supported the role of the SLC64A 5-HTTLPR

polymorphism in OCD. Another solution is to conduct multi-site collaborative studies to obtain sufficiently large samples of patients and families. This strategy has been implemented by the OCD Collaborative Genetics Study (OCGS), which commenced in 2001. The OCGS is an ongoing collaboration between investigators at six sites in the USA [79]. This study has produced a number of important advances in understanding the genetics of OCD, including the importance of OCD symptom dimensions as refined phenotypes for genetic studies of OCD [41]. Accumulation of evidence from multiple studies will increase the number of families and cases that may be used to evaluate the potential role for specific genes in contributing vulnerability to OCD, as well as allowing for cross-fertilization of ideas about diagnosis and phenotype [79].

G × E interaction models

As previously discussed, another important direction for future research on risk for OCD is considering the interaction between genes and environment. Despite the evidence that environmental factors contribute to psychological disorders, most gene research on OCD has ignored the role of the environment. This is one of the possible explanations for the difficulties in replicating specific genes for OCD. As Moffitt [65] suggested, "ignoring nurture may have handicapped the field's ability to understand nature" (p. 478). Attempts to rectify this problem will involve several steps toward developing appropriate G × E models. First, investigators must identify appropriate candidate susceptibility genes. These genes must have polymorphic variants that are relatively common in the population, evidence suggestive of a gene-to-disorder association, and a functional significance in relation to the environmental pathogen.

Next, we must consider possible environmental risk factors for G × E models, including some of the risk factors previously discussed in the current paper. Moffitt et al. [65] suggested several criteria for environmental risk factors: variability in response among people exposed to the risk factor, credible effect of the environmental risk on biological systems implicated in the disorder, and evidence that it is a true environmental pathogen having causal effects. In addition, proximal risk factors (like parent child relationships) are more relevant for G × E research than distal environmental risk factors (such as SES) because they are more likely to meet criteria for pathogen status and are credible candidates for hypotheses about their impact on neurobiological systems that mediate psychiatric symptoms. Unfortunately, most genotyped studies have only distal measures, such as participants' educational attainment, and lack good proximal measures. Age specific environmental pathogens, such as infectious exposure in childhood, are also important, as there may be sensitive periods in the development of OCD. Finally, we must also consider the effects of multiple environmental influences on the development of the OCD since the cumulative effect of multiple pathogens can be large.

Although the most obvious type of research to test G × E models is a longitudinal cohort design, there are other possible strategies. One alternate option is to test G × E within a pool of individuals exposed to a known environmental pathogen. For example, researchers may select one of the strongest candidate genes for OCD and utilize an exposed sample to test the hypothesis that genotype-risk individuals develop psychopathology but genotype controls do not. As an example of this approach, Kotb et al. [50] conducted a study that began with hospital patients exposed to streptococcal infection and found that variation in leukocyte antigen class II haplotypes associated with histocompatibility explained which patients developed severe toxic systemic syndrome as opposed to merely a sore throat. Similarly, it is possible that patients with a certain genotype-risk that are exposed to streptoccoal infection develop OCD while others do not. A related research avenue for identifying G × E would be to recruit individuals who are pregnant, assess for the genetic markers and then evaluate whether those developing post-natal OCD symptoms can be attributed to a genotype, suggesting the effect of childbirth is dependent on (moderated by) genetic susceptibility. When collecting longitudinal data is not possible, several alternative study designs may be employed. For example, it may be useful to examine retrospective reports of perinatal experiences of affected subjects. Although retrospective data from this type of study would have significant methodological limitations, these data may complement findings from prospective OCD studies. Finally, a future study could test G × E interaction models with a population at higher risk for OCD, such as younger siblings of OCD affected children.

Another exciting possible area for G × E research is to examine whether there is a genetic influence on cognitive biases proposed by cognitive-behavioral theorists to be associated with OCD, such as an inflated sense of responsibility [78] or a high degree of thought-action-fusion (TAF) [6]. TAF refers to a tendency to believe that thinking about a particular negative event makes it more likely to happen in reality, and thinking about a catastrophic event is morally equivalent to letting the event take place [6]. It would be interesting to investigate whether there is a genetic or cognitive neurobiological vulnerability to these types of thinking styles. From a G × E perspective, these genetically predisposed cognitive biases may interact with environmental stressors and lead to OCD.

Conclusion

Despite exciting advances in OCD genetic research, a single gene or single genetic model is unlikely to

provide the best and most parsimonious explanation for the patterns of transmission of OCD. Like most psychiatric disorders, OCD is a complex disease and environmental and genetic factors are both likely to be included in its pathogenetic mechanisms. For example, a functional polymorphism in the promoter region of SLC6A4 might moderate the risk for developing OCD following exposure to a traumatic experience. Another possibility is that a functional polymorphism in a particular gene may lead to a neurocognitive profile (e.g., problems with cognitive inhibition) or a personality profile (perfectionism, excessive responsibility) that would predispose an individual to develop OCD symptoms after certain types of environmental stress. Future approaches to identifying risk for OCD should consider the heterogeneity of OCD, include more dimensional conceptualizations, focus on possible endophenotypes, and pool data across samples. These approaches will allow us to test developmental models of OCD that include both genetic and environmental risk. Ultimately, this type of research is our best hope for understanding the etiology and pathophysiology of this chronic and disabling disorder.

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