



## Review article

## Overview of genetics and obsessive–compulsive disorder

Humberto Nicolini<sup>a,b,\*</sup>, Paul Arnold<sup>c</sup>, Gerald Nestadt<sup>d</sup>, Nuria Lanzagorta<sup>a</sup>, James L. Kennedy<sup>e</sup><sup>a</sup> Carracci Medical Group, Mexico City, Mexico<sup>b</sup> Posgrado en Ciencias Genómicas, Universidad Autónoma de la Ciudad de México, Mexico<sup>c</sup> Department of Psychiatry, Hospital for Sick Children, Toronto, Ontario, Canada<sup>d</sup> Department of Psychiatry and Behavioral Sciences, Johns Hopkins Hospital, Baltimore, MD, United States<sup>e</sup> Psychiatric Neurogenetics Section, Centre for Addiction and Mental Health, Toronto, Ontario, Canada

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## ABSTRACT

This paper reviews the current state of research into the genetics of obsessive–compulsive disorder (OCD). Heredity has a major role in OCD etiology. This evidence comes from several methodological approaches such as family, twin, and segregation analysis studies. A major single gene effect as well as a polygenic hypothesis has been suggested based on segregation studies. In addition, candidate gene association and linkage analyses have shown not only one gene, but a few interesting genes and areas of the genome that may be relevant in OCD. In this search for genes, new definitions of the OCD phenotype have emerged, and some of them may be considered intermediate phenotypes between the gene effect and OCD–DSM–IV diagnosis. The phenotypic and genetic heterogeneity of OCD magnifies the challenge of locating susceptibility genes; at the same time, the identification of vulnerability genes will elucidate the identification of subtypes or dimensions of the disorder. Therefore research strategies that take advantage of clinical subtyping and that redefine the OCD phenotype in the context of genetic studies may potentially contribute to the nosology of OCD and ultimately pathophysiology. There is a lack of understanding about how genes and environment interact in OCD. However, there are some reports that will be discussed, which have attempted to evaluate how the environment contributes to OCD.

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\* Corresponding author. Carracci Medical Group, 107 Carracci St., 03740, Mexico City, Mexico. Tel.: +52 55 5611 3028; fax: +52 55 3330 0108.  
E-mail address: [nicolini\\_humberto@yahoo.com](mailto:nicolini_humberto@yahoo.com) (H. Nicolini).

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## 1. Introduction

Ultimately nosology ought to be guided by etiology. The development of classification systems in psychiatry is a complex task, but it is critical for both research and clinical practice. Therefore, there is interest in the prospects that genetic studies may be a useful approach for understanding the place of obsessive-compulsive disorder (OCD) in future psychiatric nomenclatures such as the DSM-V. For a revised and refined classification to be most effective, ambiguities in the diagnostic criteria, the possibility of distinct clinical subtypes, and the high rate of comorbidity need to be resolved, and then we will have better phenotypes for genetic research.

OCD is heterogeneous, symptoms are experienced within multiple potentially overlapping dimensions, and it will be important to document their presence as specifiers in DSM-V (Mataix et al., 2007). This remarkably diverse clinical presentation hampers the interpretation of findings and complicates the search for vulnerability genes. Variability in clinical subtypes in genetic research translates into variability of phenotypic expression. A combined symptom dimensional approach within distinctive clinical subgroups is proposed as probably the most effective way of helping to identify the heritable components of OCD (Miguel et al., 2005). Therefore, we need indicators of processes mediating between phenotype and genotype, the so-called endophenotypes or intermediate phenotypes, which in turn may be less influenced by environmental factors (Gottesman and Gould, 2003).

The following sections discuss what has been learned from the different molecular genetic/family studies of OCD to date. Several of these approaches provide information relevant for diagnostic refinements. The additional sections provide an overview of additional genetic studies in OCD. Finally, there is a review of some data derived from attempts to evaluate the environmental contribution to OCD, by means of epidemiological, family and twin studies.

## 2. Evidence from family studies in OCD

There have been many family studies on OCD over the past 75 years. The majority of them, in particular those prior to 1991, used the “family history” method, an approach that indirectly gathers information in all relatives. The “family study” method may also rely on direct structured interviews that obtain information directly from the subjects assessed (Nicolini et al., 1999; Pauls et al., 1999). The general conclusion of these family studies is that rates of OCD are significantly greater in relatives. In addition, the type of obsessions and compulsions displayed by probands (e.g. ordering, checking and symmetry) adds homogeneity to the phenotype, increasing as a consequence rates of OCD in relatives (Alsobrook et al., 1999; Hanna et al., 2005b; Miguel et al., 2005).

The concept of a spectrum it is not new in psychiatry. The schizophrenia spectrum disorders have been well documented and mainly supported in family studies (Barch, 2008). There may be an “OCD spectrum” (OCSO) of related disorders that share some of the same vulnerability genes, but the extent of this “spectrum” remains unknown. Similarities in symptomatology, course of illness, patient population, and neurocircuitry of OCD and OCSO are supported by comorbidity, family, and neurological studies, which also offer a critical re-evaluation of the relationship between OCD and anxiety disorders (Hollander et al., 2007). However, there is compelling evidence supporting the family genetic OCD spectrum association, among OCD, tic disorders, body dysmorphic disorder, somatoform disorders and grooming behaviors (Pauls et al., 1995; Grados et al., 2001; Bienvenu et al., 2000; Phillips et al., 2005).

The prevalence of OCD in relatives of probands is clearly elevated: 12% in first-degree relatives compared to 2% in relatives of normal controls (Pauls et al., 1995; Alsobrook et al., 1999). For the anxiety disorders, there is no elevation in rates for specific or social phobia, but there are higher rates of generalized anxiety disorder (GAD), separation anxiety disorder, panic, and agoraphobia in first-degree relatives of probands with OCD (Nestadt et al., 2000b; Grabe et al., 2006; Grados et al., 2003). When one controls for the presence of these disorders in the probands, GAD and agoraphobia still remain significantly higher in first-degree relatives, suggesting that GAD and agoraphobia are strongly related to the OCD phenotype (Nestadt et al., 2000b). While major depressive disorder (MDD) is elevated (in contrast to bipolar and dysthymic disorders), the elevation is no longer significant when adjusted for MDD in the probands, suggesting that MDD in relatives may be secondary to OCD (Nestadt et al., 2000b; Arnold et al., 2004; Grabe et al., 2006). This could be taken as a further hint that a specific gene does not cause OCD, but that a disposition to develop any anxiety disorder may be genetically based.

The rates of affected relatives with OCD tend to vary depending on several factors related to proband definition, such as comorbidity with tics or earlier age-at-onset, that significantly increase such rates (Nestadt et al., 2000b; Rosario-Campos et al., 2006; Hanna et al., 2005c). There were higher rates of tics in relatives of probands with OCD, and rates of OCD were higher in relatives of probands with tics (Pauls et al., 1995; Nestadt et al., 2000b). The familiarity of OCD is even stronger when there is comorbidity with tics and an earlier onset (Miguel et al., 2005). Family members are also more likely to have the types of obsessions and compulsions displayed by the probands such as ordering, checking, and symmetry (Alsobrook et al., 1999; Mataix-Cols et al., 2004). In addition, age at onset was associated with a higher probability of having comorbidity with tic, anxiety, somatoform, eating and impulse-control disorders (de Mathis et al., 2008).

It has been hypothesized that genetic and environmental factors relate to psychiatric disorders through the effect of intermediate vulnerability traits called endophenotypes. One example of this kind of research is the work of Delorme et al. (2005), who investigated blood serotonin abnormalities in the unaffected parents of OCD patients. They found lower whole blood 5-HT concentration, fewer platelet 5-HTT binding sites, and higher platelet IP3 content in OCD probands and their unaffected parents compared to controls. The only parameter that appeared to discriminate affected and unaffected subjects was 5-HT2A receptor-binding characteristics, with increased receptor number and affinity in parents and no change in OCD probands.

In summary, published family studies support the contention that OCD, alone or co-morbid with other disorders, is a condition influenced by genetic factors.

## 3. Evidence from twin studies in OCD

There have been only a few twin studies of OCD, and these all support the presence of significant genetic influence. Most of the largest studies have been based on samples of non-clinical twins in which obsessive-compulsive symptoms have been assessed through self-report measures and not through a psychiatric diagnosis. Hettema et al. (2001) conducted a meta-analysis of data from family and twin studies of panic disorder, GAD, phobias, and OCD to explore the roles of genetic and environmental factors in their etiology. For family studies, odds ratios predicting association of illness in first-degree relatives with affection status of the proband (disorder present or absent) were homogeneous across studies for all disorders. Panic disorder, GAD, phobias, and OCD all have significant familial

aggregation. The role of non-shared environmental experience was relevant, underscoring the importance of identifying putative environmental risk factors that predispose individuals to anxiety. In the most recent study of adults, Jonnal et al. (2000) studied 527 pairs from the Virginia Twin Registry. Principal component analyses suggested two meaningful factors corresponding roughly to obsessions and compulsions, with heritabilities of 33 and 26%, respectively. Van Grootheest et al. (2005) conducted an extensive review of over 70 years of twin research of OCD. The authors concluded that only the studies using Structural Equation Modeling have convincingly shown that, in children, obsessive-compulsive (OC) symptoms are heritable, with genetic influences in the range of 45% to 65%. In contrast, adult studies have suggested a somewhat lower genetic influence on OC symptoms, ranging from 27% to 47%.

#### 4. Evidence from segregation analyses in OCD

The purpose of segregation analyses is to statistically assess the mode of inheritance for a particular disorder. In this case, segregation analysis has been used to assess the mode of inheritance of OCD in families ascertained through OCD and OCD-subtype probands. Segregation analysis has suggested that there is evidence of a single gene (autosomal dominant) for the following OCD subtypes: symptom-based groupings such as symmetry and ordering (Alsobrook et al., 1999), OCD with eating disorders (Cavallini et al., 2000), gender-specific OCD (Nestadt et al., 2000a), and early age at onset (Nicolini et al., 1991; Hanna et al., 2005a). Somewhat surprisingly, the main results provided by this methodology supported the hypothesis that OCD may be caused by the effect of a single major gene, with residual family effects (possibly caused by polygenic influences). This is true when ascertaining via paediatric or adult probands (Nicolini et al., 1991; Cavallini et al., 1999; Nestadt et al., 2000a; Hanna et al., 2005a). Nonetheless, Mendelian factors only partially explain the familial aggregation of the phenotype. It is important to note that the results cannot determine whether the same genetic locus is segregating across all families, or the number of genetic loci segregating in OCD, or the extent to which genetic heterogeneity is present in the disorder. However, stratification of the sample by the sex of probands provides further evidence of genetic heterogeneity (Nestadt et al., 2000a). In the specific case of tics or Gilles de la Tourette syndrome (TS) comorbidity with OCD, when probands are primary TS with comorbid OCD, the most parsimonious model is an autosomal dominant gene (Pauls et al., 1990); however, when probands are diagnosed with primary OCD, this finding does not hold true (Cavallini et al., 1999). In conclusion, segregation analyses suggest both evidence for genes of major effect and/or a polygenic inheritance.

#### 5. Genome scans

There are only two published genome scans of OCD per se conducted to date (Hanna et al., 2002; Shugart et al., 2006). Hanna and colleagues found suggestive linkage on chromosome 9p24. This finding was replicated in a linkage study of the 9p24 region by Willour et al. (2004). However, this 9p24 finding was not replicated in the genome-wide screen conducted with the sample that included the subset of families in the Willour sample. This is a demonstration of an important lesson in genetic studies; namely, that this could therefore be considered either evidence of non-replication, or it may demonstrate evidence for heterogeneity and that a subset of the larger sample had a different genetic etiology from that of the entire larger sample.

The strongest linkage signal in the second genome scan (300 families) was in 3q27-28 (Shugart et al., 2006), a region which contains the gene encoding the serotonin 3C receptor, suggesting a candidate gene not previously investigated in OCD. There were several additional linkage signals that deserve further follow-up. Also a genome-wide linkage scan was performed for the phenotype of

compulsive hoarding (Samuels et al., 2007), and significant linkage was found on chromosome 14. It is important to point out that the hoarding study used a subset of the sample that had been reported for the OCD genome scan.

#### 6. Candidate gene studies

There have been many reports over the last 10 years regarding genetic polymorphisms associated with OCD. However, a great majority of these studies had small sample sizes that may have led to false positives. Methodologies to assess association have varied from case-control to family-based transmission tests (TDT). Also, in many of these studies, positive results are obtained only if the cases are subtyped into smaller and supposedly more homogenous sub-samples. The following genes are among the main ones that have been studied thus far.

##### 6.1. Catechol-O-methyltransferase (COMT)

COMT is an enzyme which metabolizes monoamine neurotransmitters; it is encoded by a gene in the 22q11 region. Interestingly, microdeletions of 22q11 have been associated with obsessive-compulsive symptoms in adults (Gothelf et al., 2004) and children (Arnold et al., 2001). The first finding of an association between COMT and OCD was reported by Karayiorgou et al. (1997) who described a functional allele of this gene, Val158met, wherein the met variant results in a 3- to 4-fold reduction in enzyme activity. The met allele was significantly associated in a recessive manner with susceptibility to OCD, particularly in males. After this publication there have been several others with mixed results (Niehaus et al., 2001; Alsobrook et al., 2002; Meira-Lima et al., 2004). Azzam and Mathews (2003) conducted a systematic review and meta-analysis of both the published literature and unpublished data. Available data were stratified according to the original study design as either case-control or family-based, and two separate meta-analyses were conducted. These analyses showed insufficient evidence to support an association between the COMT gene polymorphism and OCD. Subgroup stratification based on gender generated no statistically significant associations. Finally, Poyurovsky et al. (2005) could not support the hypothesis that the COMT Val158Met polymorphism is associated with liability to schizo-obsessive syndrome. Additional work is required to definitively rule in or out the role of COMT, particularly using newer markers and haplotypes that provide more extensive information regarding the participation of this gene in the etiology of OCD.

##### 6.2. Monoamine oxidase A (MAO-A)

MAO-A is a major catabolic enzyme for monoamines, and thus influences levels of serotonin, dopamine, and norepinephrine in the brain. Regarding OCD, the literature suggests a significant association of the MAO-A low enzymatic activity allele in OCD, particularly in females with comorbid depression (Camarena et al., 1998; Karayiorgou et al., 1999; Camarena et al., 2001a; Hemmings et al., 2003). However, these studies are not large enough to provide compelling evidence to support this association.

##### 6.3. Dopamine system

The dopamine system has been implicated in OCD from pharmacologic studies using dopamine receptor blocking agents that ameliorate some symptoms of the disorder. Several genes in this system have been studied in OCD such as the dopamine transporter (DAT), and dopamine receptors (DRD1, DRD2, DRD3 and DRD4) with some positive associations, particularly with DRD4. However, findings have been mixed, with no conclusively identified markers (Nicolini et al., 1996; Cruz-Fuentes et al., 1997; Billett et al., 1998; Hemmings et al., 2003; Millet et al., 2003).

#### 6.4. Serotonin system

The serotonin transporter (SERT) is probably the most widely studied gene in psychiatry (Graff-Guerrero et al., 2005). In particular, the most widely studied SERT variant consists of an insertion (long allele, “L”) or deletion (short allele, “S”) of a 44 base pair sequence in the promoter region. Although the results in OCD suggest an effect of the “L” allele, the literature still remains controversial (Bengel et al., 1999; Camarena et al., 2001b; Meira-Lima et al., 2004; Hu et al., 2006). In the case of Hu et al. (2006) a single nucleotide polymorphism (SNP) that converts the long allele to a functionally short one was important in determining the significance of the SERT gene in OCD. The long allele containing the A variant of the SNP was associated with OCD, while the long-G and short alleles were not. Thus other groups should investigate this SNP in their analyses. Other genes such as the 5-HT<sub>2A</sub> receptor promoter polymorphism and 5HT1B have been extensively studied, although for only a small number of SNPs, with positive associations for both of them (Mundo et al., 2000, 2002; Walitza et al., 2002; Hemmings et al., 2003; Camarena et al., 2004; Meira-Lima et al., 2004; Hu et al., 2006; Levitan et al., 2006); but also negative findings (Frisch et al., 2000; Di Bella et al., 2002a,b; Walitza et al., 2004).

#### 6.5. Glutamate system

The glutamate NMDA subunit receptor gene was associated with OCD in a family-based association study (Arnold et al., 2004). The glutamate transporter gene SLC1A1 is a promising positional and functional candidate gene given its location within a linkage peak on 9p24 and its potential functional significance due to its role in glutamate neurotransmission. Three groups have now identified associations with this gene (Arnold et al., 2006; Dickel et al., 2006; Stewart et al., 2007c) with no negative findings reported to date. Delorme et al. (2004) recently examined the kainate receptor genes GRIK2 and GRIK3, resulting in a weak association with GRIK2 that requires replication.

Other genes that have been less studied but may be promising are: BDNF with both positive (Hall et al., 2003) and negative (Mossner et al., 2000; Zai et al., 2005b) findings; GABA type B receptor 1 (Zai et al., 2005a); the myelin oligodendrocyte glycoprotein gene (MOG; Zai et al., 2004); the Mu opioid receptor (Urraca et al., 2004); and the myelin regulatory gene Olig2 (Stewart et al., 2007a). On the other hand interesting genes that have been studied with negative results are TNF- $\alpha$  (Zai et al., 2006) and ApoE (Nicolini et al., 2001). Also, it is noteworthy that no genetic studies with prospective measures of medication response in OCD have been done. This is a very interesting endophenotype, possibly more homogeneous and more closely connected to the biological function of the candidate genes.

Over 60 candidate gene studies have been conducted. Most studies have focused on genes in the serotonergic and dopaminergic pathways. Unfortunately, none have achieved genome-wide significance and, with the exception of the glutamate transporter gene, none have been reliably replicated (Pauls, 2008). Future research will require much larger samples and the collaboration of researchers to be able to identify susceptibility loci for OCD.

While OCD appears to have a genetic component, additional innovative research, such as whole genome association studies, are needed to unravel the genetic influences in the disorder. Two whole genome association scans that cover the entire genome with more than 1,200,000 SNP markers in one experiment are in progress. This methodology is purported to be more useful in detecting common genetic variants with only moderate effect size.

### 7. Alternate and intermediate phenotypes

Results from family studies have suggested that OCD is a genetically heterogeneous disorder and have emphasized the importance of

identifying valid subgroups of patients, such as early onset, sex effects, symptom clustering, neuropsychological performance, neuroimaging, and response to treatment. Such clinical subgroups, also called alternate phenotypes, do not necessarily represent true biological entities. However, a major challenge in OCD genetic research is to demonstrate processes mediating between “DSM-IV OCD phenotype” and genotype, becoming true intermediate phenotypes or endophenotypes (Miguel et al., 2005). Endophenotypes represent simpler clues to genetic underpinnings than the disease syndrome itself. The interaction between genes and environment (epigenetics) may also be of critical importance for modifying the development of the OCD phenotype. Endophenotypes would ideally have genetic routes. A clinical subtype or a biological marker may not necessarily reflect genetic underpinnings but may rather reflect associated findings. Therefore, the endophenotype is heritable, is state-independent, co-segregates with the illness, and is found in unaffected family members at a higher rate than in the general population (Gottesman and Gould, 2003).

#### 7.1. Early onset

Early-onset OCD appears to be a particular subtype that exhibits distinct clinical features and is associated with greater familial loading (Hemmings et al., 2004; Chabane et al., 2005; Do Rosario-Campos et al., 2005). In addition, in an early-onset form of the disorder triggered by infection (OCD-PANDAS), which is more of an environmental form of the disorder, it has been shown that rates of tic disorders and OCD in first-degree relatives of pediatric probands with PANDAS are higher than those reported in the general population, and are similar to those reported for tic disorders and OCD (Lougee et al., 2000).

#### 7.2. Neuropsychology and neuroimaging

Chamberlain et al. (2007) demonstrated deficits in cognitive flexibility and motor inhibition that were present in both OCD-affected individuals and their unaffected relatives, suggesting another potential endophenotype. Other neuropsychological tasks associated with OCD might serve as endophenotypes, although there are no published reports based on unaffected relatives. Examples include executive functioning (Kuelz et al., 2004), procedural or implicit learning (Joel et al., 2005), or visual memory encoding (Penades et al., 2005).

There are some studies that have assessed brain imaging as an endophenotype in OCD. Using magnetic resonance imaging (MRI) and behavioral performance on a response inhibition task (Stop-Signal), Menzies et al. (2007) found that OCD patients and their relatives both had delayed response inhibition on the Stop-Signal task compared with healthy controls. This finding was significantly associated with reduced grey matter in orbitofrontal and right inferior frontal regions and increased grey matter in cingulate, parietal and striatal regions. A novel permutation test indicated significant familial effects on variation of the MRI markers of inhibitory processing, supporting the candidacy of these brain structural systems as endophenotypes of OCD. These authors concluded that structural variation in large-scale brain systems related to motor inhibitory control may mediate genetic risk for OCD, providing evidence for a neurocognitive endophenotype of OCD.

Obsessive–compulsive hoarding may be a well-defined subgroup or variant of OCD in addition to its symptoms, but also compelling data supported by neuroimaging studies suggest that the ‘compulsive hoarding syndrome’ may be a neurobiologically distinct entity (Saxena et al., 2004; Mataix et al., 2007; An et al., 2008).

#### 7.3. Gender

It has been suggested that gender may contribute to the clinical and biological heterogeneity of OCD. Besides different clinical



presentations, gender has been associated with distinct candidate gene associations for at least four genes: MAO-A, COMT, 5HT1DBeta and SLC1A1, as well as one linkage study which detected a significant linkage signal in the region of 11p15 at D11S4146 in the families of male probands (Karayiorgou et al., 1999; Camarena et al., 2001a, 2004; Lochner et al., 2004; Arnold et al., 2006; Dickel et al., 2006; Wang et al., 2009).

#### 7.4. Symptom

There have been several factor-analytic studies of OCD that consistently found three to five factors that explained nearly 70% of the variance (Do Rosario-Campos et al., 2005; Cullen et al., 2008; Pinto et al., 2008). These symptom factors are consistent between adult and child samples (Stewart et al., 2007b). Those dimensions are: cleaning and contamination, hoarding, symmetry and ordering, and sexual and religious obsessions. There is a high familial risk if probands present high scores on obsessions/checking and symmetry/ordering factors for OCD and TS, as well as an increased allele sharing at three loci in chromosomes 4, 5 and 17 in hoarder patients (Alsobrook et al., 1999; Leckman et al., 2003; Lochner et al., 2005). As noted above, hoarding has also been associated with distinct findings on a genome scan on OCD (Samuels et al., 2007). In addition there is an association with the serotonin transporter in patients with OCD and tics which also presents the repeating/counting factor (Cavallini et al., 2002).

#### 7.5. Personality

Little is known about personality disorders and normal personality dimensions in relatives of patients with OCD or if personality may serve as an endophenotype. However, there are some interesting data. Neuroticism and obsessive-compulsive personality disorder may share a common familial etiology with OCD (Samuels et al., 2000). Perfectionism appears to be more closely associated with obsessive-compulsive personality symptoms rather than OCD (Halmi et al., 2005), and there is a relation of temperament and character dimensions with the severity of obsessive-compulsive symptoms. On the Temperament and Character Inventory, OCD subjects displayed increased harm avoidance and lower self-directedness and cooperativeness (Cruz-Fuentes et al., 2004). There is an extensive amount of research that shows associations with personality and several candidate genes, some of which have also been associated with OCD (Ebstein, 2006), although the usefulness of personality as an endophenotype remains to be further studied.

#### 7.6. Drug response

There are not many studies exploring the pharmacogenetics of OCD. However, this may be a useful endophenotype for future research (Billett et al., 1997). OCD symptoms respond differently to drug treatments (Shetti et al., 2005); moreover, there are polymorphisms associated with the mechanism of action of anti-obsessional drugs that may in fact be vulnerability genes to the disorder. Also, genes associated with susceptibility to OCD may represent future targets for drug development.

The most studied polymorphism is again the promoter region of the serotonin transporter. However, no differences among the genotypes and response to serotonin reuptake inhibitors (SRI) have been demonstrated (Di Bella et al., 2002a,b). On the other hand, there is some evidence that response in venlafaxine-treated OCD patients is associated with the S/L genotype of the 5-HTTLPR polymorphism and in paroxetine-treated OCD patients with the G/G genotype of the 5-HT2A polymorphism (Denys et al., 2007). Nonetheless, there is still a lack of studies in this area; additional research is needed to better understand if treatment response may constitute an endophenotype.

## 8. Environment and OCD

There are some reports that have attempted to evaluate environment contribution to OCD. One important strategy has been through twin studies, which can assess genetic as well as environment contributions to the OCD phenotype. For instance, Santangelo et al. (1996), in a study of TS patients, found that labor complications, excessive consumption of caffeine or alcohol by the mother, and maternal smoking all correlated with the development of OCD. Hudziak et al. (2004) assessed cultural differences in a large twin dataset by determining whether the genetic/environmental contributions differ by country (USA or Netherlands). They found a unique environmental contribution of the non-shared type using non-clinical measures of DSM-V OCD, and concluded that some environmental possibilities that may lead to the expression of OCD are PANDAS, differences in parenting, and school activities. However, they did not directly test for them. Other researchers evaluated prenatal, perinatal and postnatal risk factors in OCD. They concluded that edema during pregnancy and prolonged labor were the most significant risk factors (Salema et al., 2007). Also there is some evidence that shows an increase in postpartum obsessive-compulsive disorder (OCD). However, most studies are retrospective in nature, thus not answering questions about the overall prevalence of such symptoms. In addition, the neurobiological basis of this phenomenon remains unknown (Abramowitz et al., 2003).

## 9. Discussion

As we can see from the numerous studies listed above, multiple genetic and environmental factors may be involved in OCD etiology. This is complicated by the probability of genetic heterogeneity for this phenotype which needs further exploration of gene-gene and gene-environment interactions. In addition, the exploration of alternate phenotypes based on symptom expression, age at onset or comorbid conditions may be crucial in finding good candidate genes. However, there is some compelling evidence. First OCD is a Spectrum disorder phenotype, with many alternate forms that deserve further research; based on family genetic studies, OCD, tics, BDD and grooming behaviors seem to be part of it. In addition there is good evidence that a polygenic etiology is supported by segregation analysis. This evidence is further supported by the signals of genome scans. Many candidate genes have been found in association with OCD; however, the glutamate and serotonin system genes have been the most replicated. Among all alternative phenotypes described, the most compelling evidence to be considered endophenotypes points to neuroimaging studies and the Hoarding subtype and performance on a response inhibition task as well as deficits in cognitive flexibility and motor inhibition. Finally, environment needs further study since it contributes to several interesting forms of the disorder (e.g., PANDAS).

OCD is remarkably diverse, and can vary both within and across patients over time. This variability in the phenotypic expression means that OCD is a heterogeneous disorder and this heterogeneity complicates the search for vulnerability genes. In order to find valid endophenotypes for OCD we need several approaches. Phenotype needs to be narrowed by identifying biologically valid subgroups of patients, such as the ones reviewed before. By identifying heritable components of OCD, it should be possible to find genes for these separate components.

A goal of genetic research is to provide improved and earlier diagnosis of OCD. It may be that multiple genes combined together in an algorithm will be used for prediction, or risk models that include both genetic and environmental factors. Once risk genes for OCD are confirmed, “high-risk” individuals (e.g. children who are exhibiting early symptoms or have a strong family history) could be genotyped for risk alleles and followed prospectively. Such an approach would be the most valid design for identifying environmental factors that

interact with genotype to confer susceptibility to OCD. Furthermore, prevention programs could be designed and targeted to children with high genetic risk, a more cost-effective strategy than offering it to all children or even all children with a positive family history of OCD. Identification of susceptibility genes, and a better understanding of how environment interacts with them, should refine our classification of OCD and OC spectrum disorders, since our current syndrome-based diagnosis likely represents a heterogeneous group of disorders that may have different associated features and respond to different treatment approaches. This is analogous to infectious diseases, in which a variety of conditions that could only previously be identified by non-specific symptoms (e.g. fever) were found to be the result of different infectious agents and to respond to different medications. Conversely, the identification of susceptibility genes will likely be enhanced by more refined definition of the clinical phenotype. For example, as noted above, factor analyses have identified symptom dimensions that may have distinct genetic correlates.

In summary, genetic findings have already informed our understanding of the diagnosis of OCD and OC spectrum disorders, and future research promises to enhance our diagnostic system even more. Genetic technology is rapidly advancing, making it feasible to genotype most of human genetic variation. This capability will allow us not only to understand genes better but also how environment interacts with the genome.

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