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Review article

Overview of genetics and obsessive–compulsive disorder

Humberto Nicolini [a,b,*], Paul Arnold [c], Gerald Nestadt [d], Nuria Lanzagorta [a], James L. Kennedy [e]

[a] Carracci Medical Group, Mexico City, Mexico
[b] Posgrado en Ciencias Genómicas, Universidad Autónoma de la Ciudad de México, Mexico
[c] Department of Psychiatry, Hospital for Sick Children, Toronto, Ontario, Canada
[d] Department of Psychiatry and Behavioral Sciences, Johns Hopkins Hospital, Baltimore, MD, United States
[e] 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 (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 classicication 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” (OCSD) 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 OCSD 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 familiality 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

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