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REVIEW ARTICLE

Gender differences in obsessive-compulsive disorder: a literature review

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DESCRIPTORS:
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Abstract

Introduction: Obsessive-compulsive disorder (OCD) is a heterogeneous condition, in which subtypes have been proposed. Previous studies suggested that gender plays a relevant role in OCD phenotypic expression. This study aimed to review the literature on gender differences in clinical, genetic or familial aspects of OCD. *Method*: A conventional review was conducted, including all papers that investigated demographic, clinical, and genetic aspects of OCD according to gender. The search was based on data available in Medline and PsycINFO databases in the last 20 years, using as keywords: obsessive-compulsive disorder; and: gender, sex, male, female, demographic characteristics, clinical features, clinical characteristics, genetic, genes, genetics gender OCD, genes OCD, genes OCD males, genes OCD females. *Results*: Sixty three of 487 phenotypical and genetics studies were selected. Most studies indicate that male patients are more likely than females to be single, present early onset of symptoms and chronic course of the disorder, greater social impairment, more sexual-religious and aggressive symptoms, and greater comorbidity with tic and substance use disorders. Female patients present more contamination/cleaning symptoms and greater comorbidity with eating and impulse-control disorders. Genetic and family studies are inconclusive, but suggest that gender may play a role in the disease expression. *Conclusions*: Gender is a relevant factor that should be taken into account when evaluating OCD patients. More studies are necessary to determine whether in fact it defines a homogeneous and particular group in OCD.

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DESCRITORES:
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Genética.

Diferenças de gênero no transtorno obsessivo-compulsivo: uma revisão da literatura

Resumo
Introdução: O transtorno obsessivo-compulsivo (TOC) é um quadro heterogêneo, no qual subtipos têm sido propostos. Estudos anteriores sugerem que gênero desempenha papel relevante na expressão fenotípica. O objetivo foi realizar uma revisão convencional da literatura sobre diferenças de gênero em relação a aspectos clínicos e genéticos ou familiares do TOC. *Método*: Realizou-se uma revisão convencional da literatura incluindo todos os artigos que investigaram aspectos sociodemográficos, clínicos e genéticos do TOC, de acordo com o gênero. A pesquisa foi baseada em publicações disponíveis nas bases de dados Medline e PsycInfo nos últimos 20 anos, usando como palavras-chave: obsessive-compulsive disorder (OCD), e: gender, sex, male, female, demographic characteristics, clinical features, clinical characteristics, genetic, genes, genetics gender OCD, genes OCD, genes OCD males, genes OCD females. *Resultado*: Sessenta e três artigos de fenótipo e genética foram selecionados. Na maioria dos estudos, o sexo masculino associou-se mais que o feminino com: ser solteiro, apresentar início mais precoce dos sintomas, maior prejuízo social, mais sintomas sexuais, religiosos e de agressão, e mais comorbidade com transtorno de tiques e abuso de substâncias. Pacientes do sexo feminino apresentam mais sintomas de contaminação/limpeza e mais comorbidade com transtornos alimentares e do controle de impulsos. Estudos genéticos e familiares são controversos, mas indicam que o gênero pode desempenhar um papel na expressão da doença. *Conclusão*: Gênero é um fator relevante a ser considerado na avaliação de pacientes com TOC. São necessários mais estudos para determinar se este fator define de fato um grupo homogêneo e particular de TOC.
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Introduction

Obsessive-Compulsive Disorder (OCD) is the fourth most prevalent psychiatric disorder in the United States.[1] Epidemiological studies conducted in several countries reported current prevalence around 1% and lifetime prevalence ranging from 2% to 3%.[2] Regarding gender, a bimodal distribution of age of onset has been described. Studies assessing pediatric samples report male preponderance (70%), whereas adult studies report equal gender distribution or a slight female preponderance.[3] Males usually report early-onset of obsessive-compulsive symptoms (OCS) and association with tic disorders, attention deficit, and hyperactivity disorder (ADHD).[4,5]

OCD is a very heterogeneous disorder, and gender differences may help identify more homogeneous subgroups. This strategy may enhance our understanding of the pathophysiology of OCD, including gene-environment interactions.[6] Also, as a considerable proportion of OCD patients is not responsive to first line treatments,[7] the identification of more homogeneous subgroups may lead to more tailored and effective treatments.[8] Until now, some OCD subgroups have been proposed based on age of OCS onset, presence of tics, and history of streptococcal infection.[8,9]

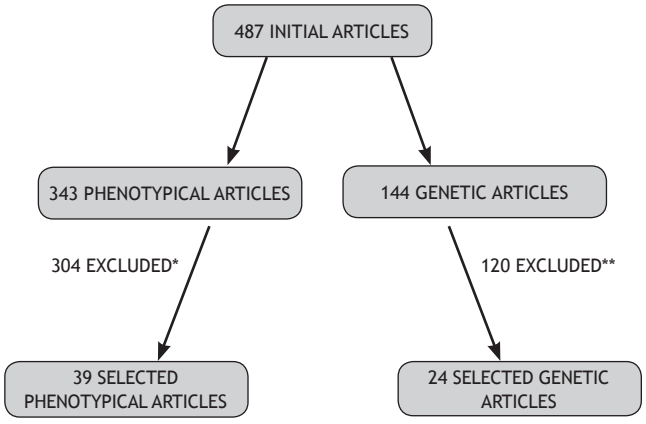
Gender has been shown to play a vital role in neurobiological aspects, psychosocial factors, and behavioral patterns in several psychiatric disorders. Whereas sex is a concept focused on biological aspects, gender is a broader concept, including a range of psychosocial aspects (e.g. attitudes, feelings, values, behaviours, and activities) that, through a process of social construction, differentiate men and women.[10] Recent studies of OCD clinical samples suggest that gender moderates the genetic expression of this complex disorder, resulting in specific phenotypes.[11-14]

The aim of this study was to conduct a two-decade conventional literature review of gender differences in demographic, clinical, and genetic aspects of OCD.

Method

A conventional review of gender (or sex) differences in OCD patients was conducted, including all epidemiological, clinical, neuropsychological, and genetic or familial studies available in Pubmed and PsycINFO databases between January 1990 and August 2010. Only articles published in English and Portuguese were included. The phenotypical studies search strategy included the following keywords: obsessive-compulsive disorder (OCD) and: gender, sex, male, female, demographic characteristics, clinical features, clinical characteristics. Initially, 343 studies were found, but only 39 of them were included in the present review, as most articles (N = 304) did not specifically address gender differences and were therefore excluded. A few references cited in the selected articles that had not been previously found and that were considered pertinent were also included.

To investigate genetic or familial aspects, the following key words were used: obsessive-compulsive disorder (OCD) and genetic(s), genes, gender OCD, genes OCD, genes OCD males, genes OCD female, gene OCD male. Twenty-four genetic studies from a pull of 144 articles were finally included in this study (Figure 1).



* Did not specifically address sex or gender differences.
** Did not specifically address genetic differences.

Figure 1 Fluxogram of the articles included in this revision.

Results

Phenotypical Studies

Several studies describe an earlier OCD onset among male patients, compared to femaless.[14,15] Approximately one third of adult patients refer symptom onset in childhood[26] and, among children, two thirds of cases are boys.[3,13,27-28] Fontenelle et al. evaluated possible differences in Brazilian patients with early (up to 17 years of age) and late onset, confirming the predominance of men in the first group, which presented higher clinical severity when compared to the latter.[20] In another study conducted in Brazil of 330 patients, men also prevailed in the early onset group (up to 11 years of age).[29] An Italian study found a higher frequency of insidious onset and chronic course among male sufferers and more episodic course among females.[19]

According to Noshirvani et al.,[17] similarly to schizophrenia, OCD cases with an early onset are usually more severe, reflecting the influence of cerebral lesions or constitutional aspects to which men are more vulnerable than women. Likewise, Bogetto et al.[19] consider that early OCD onset is not strongly related to the impact of stressful life events but, conversely, could indicate a higher influence of biological lesions to which men are more predisposed. Biological theories propose that damage occurring during pregnancy is more global than that occurring after birth, and that the rapid growing organs are more vulnerable. Boys would be more susceptible than girls to developmental damage because among humans and other animals females are biologically stronger compared to males.[30] A more accelerated growth of the prefrontal cortex (PFC) was observed between 8 and 14 years of age,[31] a period in which most cases of OCD begin in childhood. This finding indicates that abnormal development of these structures could be related to early onset of symptoms.[32] As the PFC continues to mature throughout adult life, abnormalities in later maturation processes could be related to late-onset OCD. Because the development of the caudate nucleus and the orbitofrontal cortex (OFC) — two central components of the OFC/ACC (anterior cingulate cortex) loop — is different for boys and girls, this could explain, at least in part, the higher prevalence of early-onset OCD among boys.[32]

Sobin et al.[33] found some indirect indicators of a higher negative impact of OCD among male sufferers. For example, two thirds remain single versus only one third of women. Moreover, almost half of male patients continued to live with their original families or in assisted homes, compared with only 20% of women. Torresan et al.[25] described earlier age of symptom interference among Brazilian men, who were also more likely than women to be single, which is consistent with findings from other countries.[18,23,34] Several other authors have also described that women with OCD are more frequently married than men.[14,22-24] Matsunaga et al.,[34] evaluating 94 Japanese patients, found higher social interference of OCS among men, whereas women more frequently involved family members in their rituals. Therefore, an early onset among males can lead to a higher impact on several areas of daily life, including social adjustment and interpersonal relationships, which may be indirectly indicated by the lower rates of marriage in this population.

Differences in the content of OCS between genders have also been described in studies conducted in Spain, Italy, France, India, and Turkey. Women are more prone to contamination obsessions,[22] usually associated with cleaning rituals;[6,19,23,24] whereas sexual obsessions are more common among men.[19,22,23,35] Several studies combine rates of sexual and religious symptoms, which are more frequent in males.[6,24,36] Results are inconclusive regarding aggressive obsessions, with studies showing varying predominance between genders.[22,36,37] In male, symmetry obsessions would be more common,[23,24,38] as well as ordering,[36,38] repeating,[19] checking,[23] and hoarding compulsions.[39,40,41]

Torresan et al.[25] found among Brazilian men more sexual, religious, and symmetry obsessions, as well as more mental rituals. Chacon et al.[42] evaluated OCD symptom dimensions in 40 pairs of Brazilian siblings with OCD. When both siblings were male, there was a significant correlation with contamination obsessions and cleaning rituals; and when both siblings were female, a correlation was found with hoarding symptoms.

The higher frequency of aggressive obsessions among women,[37] which are usually characterized by fear of losing control, could be related to motherhood and fear of causing some harm to the newborn.[37] Different ways of clustering symptoms hamper the comparisons between OCD studies to some extent. Some of them, for example, analyze aggressive obsession along with sexual and religious obsessions,[36,38-42] which are more common among males. Such symptoms are called by some authors “forbidden” or “taboo” thoughts,[43] usually manifested as ego-dystonic impulses. Aspects related to sexuality are particularly complex, involving a constant interaction between biological, psychosocial, and cultural factors, which are remarkably divergent between genders.

Likewise, the predominance of contamination-cleaning symptoms among females, a finding almost universal in OCD phenomenological studies, probably involve biological, psychological, and sociocultural aspects related to the female role in different societies. Mataix-Cols et al.,[44] in a functional neuroimaging study during a provocation task of

cleaning symptoms, described a greater activation of areas such as ventromedial prefrontal regions, medium temporal gyrus, right caudate nucleus, medium frontal gyrus, and left cingulus antero-dorsal gyrus in OCD patients, when compared to normal controls. A study of individuals without any psychiatric disorder suggested that the same cerebral areas contain a large number of sex hormone receptors, with relevant sexual dimorphism, with women presenting larger volumes of these structures.[45] According to Labad et al.,[6] this finding could at least partially explain the greater proportion of women with these symptoms.

Regarding psychiatric comorbidities in OCD, some of them seem to be more associated with one gender than the other.[46] According to some authors, more women present co-occurring major depressive disorder.[6,23,33] On the other hand, several studies found no gender differences regarding major depression comorbidity, which is the most common Axis I disorder in both genders.[21,22,24,25,37,47] In an Italian study,[19] men presented more social phobia, tic disorders, and hypomania episodes. In Brazil, Torresan et al.[25] found more posttraumatic stress disorder and tic disorders among men, whereas women presented more simple phobias, eating disorders (anorexia nervosa), as well as more impulse control disorders in general, particularly skin picking and "compulsive" shopping.[25] Another Brazilian study[47] compared OCD patients with and without alcohol use disorders and found more men in the first group, in accordance with other studies.[19,33] Men also presented more chronic tics and Tourette syndrome (TS), a clinical aspect that overlaps with early onset of OCS.[9] Besides substance use disorders, men were more likely to present attention deficit, hyperactivity, social phobia, affective, and anxiety disorders in general.[24,25,48]

Some gender-related comorbidity findings in OCD, such as substance use and social phobia among men, and eating and impulse control disorders among women, seem to reflect a general trend of clinical samples with other mental disorders, as well as community samples. Therefore, it is noteworthy that major depression usually does not predominate among women with OCD, possibly indicating that depressive symptoms are intrinsically linked to OCS regardless of gender.

The results of the main clinical studies assessing OCD clinical features and gender are summarized in Table 1.

Genetics studies

Several genes of serotoninergic, dopaminergic, and other systems have been implicated in OCD pathogenesis, based on theories derived from treatment response to medications that exert effects on those pathways.

Table 2 presents the main findings for genetic differences between genders in OCD. The discussion will not focus on each individual study, as the main findings for each individual are summarized in the above-mentioned table. As for methodological details, they can be found in the original articles. For some studies, when genotypic data was available, we reanalyzed the allelic frequencies. Thus, some findings published as "trends" were not included by us as positive results (e.g., study 50) if after our reanalysis they turned to be negative (Izbicki et al., submitted).

The results of association or family-based studies are inconclusive, with some rendering positive associations with one gender, others negative and even some with positive findings for the opposite sex regarding several polymorphisms of candidate genes. Candidate genes in the serotonergic pathway were more frequently studied due to the consistent response of OCD to selective serotonin reuptake inhibitors (SSRI). However, findings have not been conclusive. For example, the same polymorphism of the gene 5HT1Dbeta [Single Nucleotide Polymorphism (SNP) G861C] was associated with OCD in males in two studies, one found association with the C allele,[21] and the other with the G allele.[49] However, the second study[49] evaluated only males, not allowing an unequivocal association. On the other hand, OCD in women, but not in men, was associated with the A allele of the -1438G>A polymorphism of the promoter region of 5-HT2A[50] and the short allele of 5-HTTLPR.[51] However Wendland et al.[52] found no association between OCD, gender and three other functional polymorphisms of the serotonin transporter gene (5-HTTLPR, STin2, and rs25531),[52] despite using a larger sample than the one used by Denys et al.,[53] which also found an association between the short allele of 5-HTTLPR and women with OCD.[53]

Dickel et al.[54] also found an association between woman with OCD and the 5-HTTLPR long allele polymorphism, although, after correction for multiple testing, the finding lost significance.[54] Although no individual study has been replicated, a pooled analysis of five TDT replication studies of the SLC6A4 5-HTTLPR polymorphism supports association ($p = 0.02$) between OCD and this polymorphism.

In the most recent study of SLC6A4 in OCD, Voyiaziakis et al.[55] genotyped 1241 individuals from 278 families for 13 SNPs in the polymorphic region (LPR) indel (insertion/deletion) including haplotypes of the rs25531, VNTR polymorphisms in introns 2 and 7, and for a 381 bp deletion in the 3´ portion of LPR. Data were analyzed with the Family Based Association Test (FBAT) and after sex stratification, women were associated with alleles 9/10 of the Int2 ($p < 0.0002$).[55] This was the most significant finding in terms of statistical outcomes, which remained significant even after correction for multiple markers. The authors mentioned that many alleles related to the Int2 marker are associated with neuropsychiatric disorders, and as the majority of the affected individuals were women (66%) and there were differences due to gender in the prevalence of several Axis I disorders (women more affected with major depressive and panic disorders), it is plausible that the association observed with 9/10 alleles of Int2 VNTR in the sample may be explained by other Axis I disorder rather than by OCD. The most plausible explanation so far for the discrepancy in the findings lies in the small size of the sample.

An interesting finding is the association between MAOA gene variants and OCD. The monoamine oxidase is responsible for the oxidation of biogenic amines. Additionally, the gene encoding MAO-A is located on the X chromosome. There are few functional MAOA polymorphisms that have been studied in OCD: one is a 30 bp VNTR in the encoding region (intron 1); another is a T to G substitution in the exon 8 (T941G) that, despite not leading to aminoacid change, results in high enzymatic activity; and a third is a T to C silent substitution in exon 14, in which the T allele is related to lower enzymatic activity (C1460T/EcoRV). Karayiorgou et al.[56] and Lochner et al.[21] have found an association, in independent studies and with independent polymorphisms, between men with OCD

Table 1 Main results of the clinical studies on obsessive-compulsive disorder and gende

Authors and year (Country)	N total (n ♂; ♀) [age range]	Diagnostic Criteria	Men	Women
Minichiello et al.[16]	138 (67; 71) [6 - 68]	No information	Earlier onset of OCD, more obsessions without compulsions	More cleaning compulsions
Noshirvani et al.[17]	307 (137; 170) [16 - 67]	DSM-III	Earlier onset of OCD, more likely to be single, more checking compulsions and alcohol dependence	More cleaning compulsions, depression, and anorexia
Castle et al.[14]	219 (93; 126) [no information]	DSM-III-R	Earlier onset of OCD	More cleaning compulsions, more likely to be married and to have children
Hantouche et al.[36]	646 (261; 385) [no information]	DSM-III-R	Higher severity of OCS/OCD, more sexual, religious and aggressive obsessions, symmetry-ordering rituals, hypochondriasis and paraphilias	More checking compulsions, eating disorders, and "compulsive" shopping
Lensi et al.[37]	263 (112; 151) [11 - 71]	DSM-III-R	Earlier onset of OCD, More sexual and symmetry-exactness symptoms, bizarre rituals, hypomania, and alcohol abuse	More aggressive obsessions, cleaning compulsions, and panic attacks post OCD
Bogetto et al.[19]	160 (76; 84) [> 18]	DSM-IV, Y-BOCS ≥ 16	OCS and OCD earlier onset, higher severity of obsessions, more sexual and repetitive symptoms, social phobia, hypomania, depersonalization, and substance use disorders	More contamination and cleaning symptoms, anorexia and impulse control disorders
Sobin et al.[33]	100 (44; 56) [adults]	DSM-IV	More likely to be single and living with the original families or in assisted homes, more sexual obsessions, and substance use disorders	More depression
Fontenelle et al.[20]	69 (32; 37) [18 - 65]	ICD-10	Earlier onset of OCD and higher global severity at the onset (CGI)	Higher severity of depressive symptoms at the onset (BDI)
Lochner et al.[21]	220 (107; 113) [18 - 75]	DSM-IV	Earlier onset of OCD, more unemployment, aggressive obsessions, and substance use disorders	More anorexia, bulimia, simple phobia, and depression
Tukel et al.[22]	169 (73; 96) [16 - 60]	DSM-III-R or DSM-IV	Earlier onset of OCD, higher educational level, more sexual, aggressive, and checking symptoms, social phobia and schizophrenia	More likely to be married, higher severity of compulsions (YBOCS), and more contamination and cleaning symptoms
Karadag et al.[23]	141 (41; 100) [16 - 73]	DSM-IV	Earlier onset of OCD, more sexual, symmetry, and checking symptoms, tics and bipolar disorder	More likely to be married, more contamination and cleaning symptoms, and depression
Labad et al.[57]	186 (114; 72) [no information]	DSM-IV	More sexual and religious obsessions	Higher severity of OC (YBOCS), depressive (HAM-D) and anxious (HAM-A) symptoms, more contamination and cleaning symptoms, and depression
Jaisoorya et al.[24]	231 (166; 65) [no information]	DSM-IV	Earlier onset of OCD, more religious and symmetry symptoms, and ADHD	More likely to be married, more cleaning rituals and trichotillomania
Li et al.[38]	139 [no information]	DSM-IV	More symptoms of the symmetry-ordering dimension	More symptoms of the contamination-cleaning dimension
Torresan et al.[25]	330 (182; 148) [10 - 72]	DSM-IV	Earlier onset and interference of OCS, more likely to be single, higher educational level, more sexual and religious obsessions, symmetry and mental rituals, PTSD and tics	Higher severity of depressive (BDI) and anxious symptoms (BAI), more simple phobia, anorexia, impulse control disorders, "compulsive" buying, and skin picking

BDI: Beck Depression Inventory; BAI: Beck Anxiety Inventory; HAM-A; Anxiety Hamilton Scale; HAM-D: Depression Hamilton Scale; OCS: Obsessive-compulsive symptoms; OCD: Obsessive-compulsive disorder; PTSD: Posttraumatic Stress Disorder; ADHD: Attention deficit and hyperactivity disorder.

and high activity alleles of the MAO-A gene. Camarena et al.[58] and Lochner et al.,[21] pointed towards an association between low activity MAO-A alleles and woman with OCD. These findings depict a probable example of sexual dimorphism, although its significance is currently not clear, as IMAOs are not as effective as SSRIs in OCD treatment and the outcomes found were based on small samples and different populations. Another explanation for the disparity of the findings is that the studied polymorphisms were close to the "true" polymorphism possibly associated with OCD, although they are not, per se, responsible for OCD.

The COMT gene (catecol-O-metil transferase) encodes a homonymous enzyme, which also metabolizes monoamines, with particular importance for dopamine in the prefrontal cortex.[59] The COMT gene has several allelic variations, including the most studied polymorphism Val158Met, which is a functional SNP(G158A) of this gene, resulting in a substitution of valine (high activity allele) to methionine (low activity allele). In a study of 110 OCD families, Karayiorgou et al.[56] found a sexually dimorphic association between a low enzymatic activity variant of the COMT gene and OCD males. This finding is consistent with a previous study[11] in which the same association between OCD and Met allele was mentioned, although in a smaller sample. However Schindler et al.,[60] Alsobrook et al.,[61] Katerberg et al.,[59] and Denys et al.[51] have not found differences due to gender in the allelic or genotypic frequencies, although Katerberg et al.,[59] found that women with the val-met genotype had lower scores in somatic- sensorial phenomena. Pooley et al.[62] found a trend towards a higher frequency of the Met allele in OCD males, although genotypic data were not published, which did not allow us to confirm the finding.[62] But this meta-analyses, based on data from all case-control studies published (n = 1,908 patients) showed association between the 158met allele and OCD in males (OR = 1.88, 95% CI 1.45-2.44, p < 0.001). Wang et al. (2009) in a COMT gene expression study found that not only did OCD patients present a lower expression of the COMT gene, in relation to controls, but also women had lower expression than men.[63] The main controversial point of this study is that plasma levels of COMT do not necessarily reflect what occurs in the CNS, leaving the interpretation of the present results for future studies. Kinnear et al.[64] failed to detect statistical significance in their sample stratified by gender when studying the association between a new polymorphism (Cà T transition) in the COMT gene, its levels of enzymatic activity, and the regulation by estrogen through the estrogen responsive elements in the promoter region of this gene in OCD patients.[64] The positive findings are biologically plausible: compared to val-COMT, met-COMT individuals performed less well on tests of task shifting, had an electrophysiological profile indicative of decreased flexibility of prefrontal neural processing, and showed greater amygdala-orbitofrontal connectivity in response to negative emotional stimuli suggestive of inflexible emotional processing. It may be speculated that the stability and relative inflexibility of neural processing associated with met-COMT may become excessive, and thereby render the individual vulnerable to obsessions and compulsions. Anatomically, although COMT functionality is thought to be predominantly cortical, the val158met polymorphism also influences striatal dopamine activity, and may thus influence both cortical and subcortical levels, signaling within the corticostriatal loops that underlie the pathophysiology of OCD.

Denys et al.,[53] studying dopamine gene receptors in a sample of 300 patients, half of them with OCD and half controls, concluded that male OCD patients expressed a predominance of A2A2 genotypes (p = 0.049), as well as the A2 DRD2 allele (p = 0.020).[53] This genetic link, supporting the association of the dopaminergic system with the pathophysiology of OCD and a dimorphic pattern due to gender, was not found while investigating the association between the polymorphism located in the intron 8 of the dopamine transporter gene (SLC6A3 or DAT1) and OCD in a Brazilian sample of 208 patients and 865 healthy controls.[65] The positive finding of Denys et al. (2006) needs replication as it is difficult to interpret: the association of the A2 allele with the OCD sample was unexpected and the A1 allele of the DRD2 TaqI A system has been found to be associated with a variety of addictive, impulsive, and compulsive disorders.

The studies of the genes in the glutamatergic system found a positive association between OCD, several SNPs, and haplotypes in the gene encoding the glutamate transporter, more associated with men with OCD, according to family-based studies. Although the associated SNPs have not been the same, all of them point towards the need for biological validation of the findings, as these have been the most consistent findings in the genetic research of OCD.[66-69] Moreover, although the stratified analysis by gender status in Shugart et al.[69] indicated that the male-only analysis showed more significant results than the female-only analysis in our samples, the pooled data set showed the strongest results. Therefore, their finding may not strongly support the results reported by the other three independent groups in which only the families with male probands contributed to the significant association of signs, which generally suggests an association with OCDl. Increasing evidence from several lines of study implicate a role for glutamatergic neurotransmission in OCD. Cerebrospinal fluid levels of glutamate have been shown to be increased in a sample of adult OCD patients compared to controls, and decreased glutamate levels have been reported following a successful paroxetine trial. Furthermore, successful preliminary open-label trials of two glutamatergic modulating agents (riluzole and n-acetylcysteine) have been reported.[66]

Finally, a few studies that searched for association between BDNF gene polymorphism and OCD also reported controversial findings.

Wendland et al.[52] and Dickel et al.[54] found no association between BDNF gene polymorphism and OCD, even after gender stratification.[52,54] However, Alonso et al.[70] in a sample of 215 OCD patients and 342 controls, found a significant association between the SNP (rs2378672) in the BDNF receptor gene (neurotrophic tyrosine kinase receptor type 2- NTRK2) and OCD in women (p < 0.0001).[70] Katerberg et al.[59] found that the BDNF's genotype Met66Met might be associated with a mild phenotype in Dutch women (but not in South Africans), and that the BDNF Val66Val genotype and the Val66 allele may have a role in sexual and religious obsessions.[59]

Hemmings et al.,[71] who investigated the variant val66met in the BDNF gene, showed an association between the met66 allele and the male gender, as well as an association with early onset OCD. However, the genotype val66val was associated with more

Table 2 Main results of genetics studies on obsessive-compulsive disorder and gender

Author; Year	Males	Females
Karayiorgou et al.[56]	- Men with OCD associated with the low activity allele in a recessive form - High activity G allele (MAOA*297CGG) in a subsample of male OCD patients with depression (n = 47)	- No significant association was found with females (n = 56)
Schindler et al.[60]	-No difference in genotypes was found between genders regarding the gene SLC1A1 (males n = 101) (females n = 115)	
Kinnear et al.[64]	- The C-T transition adjacent to ERE 6 in the promoter area of COMT and OCD was not significantly associated with OCD (p = 0.93) or gender (p = 0.67) (males n = 45) (females n = 51)	
Enoch et al.[50]	- No significant differences between male probands and controls in (-1438G>A) (n = 53 OCD x 61 controls)	- Female probands associated with A allele of polymorphism (-1438G>A) of 5-HT2A (n = 48 OCD x 77 controls)
Camarena et al.[58]	- OCD men associated with allele 2 but not confirmed by TDT (n = 63)	- Women with OCD and depression associated with allele 1 of MAOA/EcoRV (T, low activity) (n = 59)
Alsobrook et al.[61]	- No significant differences found in male probands compared to controls (males n = 104) (females n = 120)	
Lochner et al.[21]	- Caucasians expressed high activity T allele of EcoRV variant of MAO-A-(C1460T/EcoRV) gene (n = 52 OCD x 21 controls) - Afrikaners frequently homozygous for C allele (variant G861C) of 5HT1Dbeta gene. (n = 37 OCD x 20 controls)	- Caucasians: most homozygous for low activity C allele of MAOA (C1460T/EcoRV) gene. (n = 43 OCD x 73 controls)
Arnold et al.[68]	-2 SNPs (rs301434; rs301435) - Located in the SLC1A1gene area (glutamate transporter) were associated with OCD transmission - (Haplotype C-G) was associated with transmission in OCD (n = 191)	- No significant association was found in studied areas (n = 285)
Denys et al.[53]	- No association was found with 5-HTTLPR polymorphism (n = 56 OCD)	- Short allele (S) of 5-HTTLPR was associated with OCD in females (n = 100 OCD)
Denys et al.[51]	- Predominance of genotype A2A2 of dopamine receptor (DRD2) (n = 51 OCD x 67 controls) - Predominance of A2 allele (DRD2) expression - No differences found between male probands and controls for COMT gene	- No differences were found between female probands and controls for DRD2 (n = 88 OCD x 66 controls) and COMT (n = 99 OCD x 71 controls)
Dickel et al.[54]	- Probands presented significant association with SNP rs3780412 in SLC1A1 gene (p = 0.002) and association with T/C haplotype of SNPs rs301430; rs301979 (p = 0.003) (n = 373)	- no differences found in females (n = 375)
Miguita et al.[65]	- No association nor differences between sexes in relation to polymorphism of dopamine gene transporter (SLC6A3) and OCD (males n = 720) (females n = 353)	
Wendland et al.[52]	- No differences between sexes according to serotonin transporter gene (SLC6A4) (and its functional polymorphisms 5-HTTLPR, STin2 and rs25531) and BDNF gene. ((n = 347 OCD x 749 controls)	
Dickel et al.[67]	- No significant differences in genes SLC6A4,HTR1B,HTR2A and BDNF n = 54 trios	
Stewart et al.[66]	- Three haplotypes related to SCL1A1 gene: rs12682807/ rs2072657/ rs301430, higher transmission of a/a/t in OCD males (n = 47)	- No significant differences found between female probands and controls (n = 19)
Pooley et al.[62]	-Trend to a higher frequency of the met allele of the COMT gene in men with OCD (n = 30 OCD x 137 controls)	- No association between met COMT allele gene in women with OCD (n = 57 OCD x 190 controls)
Hemmings et al.[71]	- 66met allele of the codifying gene of BDNF was associated with early-onset OCD in males (n = 140)	-Val66val genotype was associated with severe OCD in females (n = 140)
Alonso et al.[70]	- No significant differences found between male probands and controls (n = 103 OCD x 202 controls)	- The SNP (rs2378672) of gene (NTRK2) was higher in women with OCD compared to controls (n = 112 OCD x 140 controls)
Shugart et al.[69]	- Strong association (p < 0.0001) between SNP rs301443 (gene SLC1A1) and relatives of male OCD probands (n = 379)	- Trend of association (p = 0.076) with SNP rs301443 (gene SLC1A1) in relatives of female OCD probands (n = 627)
Katerberg et al.[59]	- Polymorphism Val/met of BDNF in association with men (n=200 OCD x 278 controls)	-In females with OCD, the Met66Met genotype was associated with later age of onset and a trend for a negative family history, whereas the Val66Val genotype showed a trend for association with lower YBOCS severity scores. (n=219 OCD x 372 controls)
Katerberg et al.[72]	-No association with 158Met COMT allele gene in OCD males (n = 151 OCD x 235 controls)	- No association with 158Met of COMT gene in females - Women with Val-Met genotype presented lower scores in somatic symptoms and sensory phenomena (n = 222 OCD x 227 controls)
Wang et al.[63]	- Men presented increased COMT gene expression compared to females - OCD males had 38% of downregulation in expression of COMT genes compared with controls (n = 36)	- Women presented decreased COMT gene expression compared to males - OCD women presented 27% of downregulation in COMT gene expression compared with controls (n = 30)
Kim et al.[49]	- Increased expression of allele G861 of receptor 5-HT1Dbeta in male probands (n = 167 OCD x 107 controls)	- Study was not conducted with females (n = 0)
Voyiaziakis et al.[55]	- No association with polymorphism in SLC6A4 (n = 484)	- Females were associated with 9/10 of Int2 alleles (p < 0.0002) (n = 742)

severe OCD in females. BDNF has been implicated in neuronal survival and in activity-dependent neuroplasticity. Studies in knockout mice as well as those using B cell lines suggest that BDNF modulates the serotonin transporter function. Although the BDNF gene is an attractive OCD candidate gene, from both brain development and neurotransmitter perspectives, the findings are still controversial.

Despite the fact that almost ten years have passed since the beginning of the Genome Project and the hope that genes involved in several diseases would be easily found, the results of genetic psychiatric studies remain inconclusive. These dissonant findings are typical of association studies of complex diseases carried out in different populations. The low rate of replication of these studies could be explained by methodological problems, such as differences in phenotypical definition and small statistical power of the studies. It has become clear over time that without establishing more homogeneous and valid subgroups and without the correct identification of the inherited phenotypes, molecular genetics by itself will not be able to identify the susceptible genes for OCD. Moreover, not only larger samples are required for association studies of the entire genome, but also a search for psychopathological and clinical inherited features and the characterization of homogeneous subgroups with consistent genetic validation. Finally, it should be borne in mind that genetic studies are the key to understanding the interaction between genes and environment, and that all efforts towards molecular studies are in vain if the phenotype and environmental factors are not carefully examined in advance.

Conclusions

This literature review points to some consistent differences between genders regarding OCD phenomenology, as well as to possible genetic differences regarding susceptible polymorphisms. The study of these differences may lead to the definition of more homogeneous phenotypes and contribute to the elucidation of etiological factors and development of new treatments. The investigation of OCS using the recently developed dimensional approach,[73] which combines obsessions and compulsions that more frequently co-occur, may bring relevant contributions to the understanding of this heterogeneous disorder.[6] The importance of such investigation is reinforced by studies that described considerable differences in neuroimaging results for different OCD symptom dimensions.[74,75]

In summary, gender may be a relevant factor to determine OCD clinical presentation and course, and may be considered to define more homogeneous subgroups. Although the reasons why OCD presentation differs between genders are not clear, one may speculate that they result from both biological and psychosocial influences. Among the biological factors, sex-linked genetic features and hormonal differences may be cited. Considering psychosocial aspects, gender-related social roles may affect the content of obsessions and compulsions. While age of onset seems to be a more genetic characteristic influenced by family history of OCD, the occurrence of sexual and aggression symptoms may be influenced by hormonal characteristics, as well as by gender role. For instance, it is widely accepted that testosterone levels influence sexual drive and preoccupations, impulsivity and aggressive behavior. Thus, regardless of the causes of gender differences found in patients, it is important to address this issue when it comes to the evaluation and treatment of OCD. Further studies are necessary to determine whether in fact gender defines a particular OCD subgroup. Phenotypical, epidemiological, genetic, family, neuroimaging, neuropsychological, and intervention studies taking into account aspects of gender differences may add to the understanding of OCD etiological mechanisms and possibly also to the development of more specific and effective therapeutic approaches.

Disclosures

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