Genetic association studies in obsessive-compulsive disorder

Aline Santos Sampaio1, Rita Maria Pacheco Lins3, Renato Dal tro-Oliveira2, Lucas de Castro Quarantini4, Maria Conceição do Rosário5, Eurípedes Constantino Miguel1, Ana Gabriela Hounie1

1 Departamento e Instituto de Psiquiatria, Faculdade de Medicina da Universidade de São Paulo (FMUSP).
2 Serviço Médico Universitário Or. Rubens Brasil, Universidade Federal da Bahia (UFBA).
3 Departamento de Neurociências e Saúde Mental, Faculdade de Medicina, UFBA.
4 Pós-graduação em Medicina e Saúde, UFBA.
5 Departamento de Psiquiatria, Universidade Federal de São Paulo (Unifesp).

Institution where the study was elaborated: Instituto de Psiquiatria do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo.

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Abstract

Background: Obsessive-compulsive disorder (OCD) segregates in families. It follows a complex model of genetic transmission, which involves the influence of several small effect genes interacting with the environment. Methods: A systematic review of genetic association studies in OCD was performed. Articles published until 2012 were searched in the databases PubMed, Embase and Scielo using the terms of MeSH and its associates or synonyms for “obsessive-compulsive disorder”, “gene” and “genetic association studies”. Results: We selected 105 papers and described their main results grouped as genes related to: serotonin, dopamine, glutamate, GABA, white matter, immune system, hormones and other genes. Discussion: There is high variability between findings of association studies among the several candidate genes studied in OCD. Glutamate-related genes are promising candidates for OCD, but there is no conclusive association between any of the candidate genes studied and OCD. Association studies with large sample size, evaluation of more homogeneous subgroups of phenotype and meta-analyses are still needed.

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Introduction

Obsessive-compulsive disorder (OCD) is the fourth most common psychiatric disorder with a lifetime prevalence between 2.0% and 2.5%. According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria, OCD is characterized by obsessions and/or compulsions. These obsessions/compulsions occur for at least an hour a day, cause functional interference and significant distress or social impairment. OCD is a chronic disorder and manifests regardless of sex, race, intelligence, marital status, socioeconomic status, religion or nationality. The cross-cultural studies show that the OCD symptoms are similar in different population and cultures, supporting the idea that biological and genetic factors can contribute to its etiology. Although psychological theories have grounded the emergence of the OCD concept there is increasing evidence that it is mediated by a genetic-environmental interaction. In fact, the involvement of genetic factors in the etiology of OCD has been emphasized since the first descriptions of OCD. Studies in Human Genetics Psychiatric genetics seeks to understand how biological and environmental factors interact to cause a specific psychiatric disorder. The study designs in human genetics assessing etiologic factors of psychiatric disorders are divided into two groups: genetic-epidemiological studies and molecular genetic studies.

Genetic-epidemiological studies

Genetic-epidemiological psychiatry is a science that deals with “causes, distribution and control of disease among family groups and with genetic causes of diseases in populations”. Genetic epidemiology uses as methodology the family studies, twin or adoption studies, or segregation analyses.

Family studies

Uses the case-control study design. Thus, there is a comparison between the frequency of the disorder in relatives of patients with the
Association studies
Are designed to detect specific genes involved in a disorder. With the case-control design, whether there is a significant difference in an allelic variant distribution among affected (cases) and unaffected (controls) is evaluated. The main limitation of the case-control association analysis is population stratification bias, which is when cases and controls are not ethnically matched. Family-based association studies, comparing the proband with the own biological parents, a "trio", controls the population stratification bias. These analyses, called Transmission Disequilibrium Test (TDT) and the Haplotype Relative Risk (HRR), compare the frequency of transmitted and untransmitted alleles from parents to the proband.

Several markers covering the entire genome can be evaluated in a Genomewide association study. However, most association studies evaluate polymorphisms located in candidate genes. Polymorphism is a DNA sequence variation found that is present in more than 1% of the population. The polymorphisms may be by exchange of one nitrogenous base (single nucleotide polymorphism – SNP) or by varying the number of repetitions of a sequence of bases in a particular loci (variable number of tandem repeats – VNTR). The choice of a candidate gene to be investigated on a particular disorder can be based on clinical features or pathophysiology.

This review aims to present the results of studies of the association between candidate genes and OCD.

Methods
We performed a systematic review by searching for articles published up to May 4, 2012 in databases: PubMed, Embase and SciELO using MeSH terms, its associates or synonyms for "obsessive-compulsive disorder", "gene" and "genetic association studies".

Each term was searched separately (PubMed: term1 = 1,662,401 results; term 2 = 14,124; term 3 = 14,124; Embase: term 1 = 227,040 results; term 2 = 19,244; term 3 = 16,843; SciELO: term 1 = 4719 results, term 2 = 209, 3 = 181 term results) and later the three searches were combined using the word "AND" resulting in 202 references in PubMed, 49 references in Embase and 7 references in SciELO. References were sent to the reference management program EndNote® duplicates were discarded. References were selected and two independent researchers (ASS and RPL) assessed the full texts based on the inclusion criteria, which were: 1) Original studies or reviews about the association with candidate genes 2) The probands were required to meet criteria for DSM III or DSM IV to obsessive-compulsive disorder, 3) Studies should be written in English, Portuguese or Spanish (Figure 1): flowchart of search and selection of articles. The list of references of selected studies was examined to evaluate studies not found in the database.

Results
We selected 105 studies whose main findings are summarized below.

Genes related to serotonin
Gene serotonin transporter (SLC6A4, 5-HTT, SERT, 5HTTLPR)

Chromosome: 17; location: 17q11.1-q12

The serotonin transporter gene is an important candidate gene, since it represents the primary target for serotonin reuptake inhibitors (SSRI). Hanna et al. reported an association between blood levels of serotonin and specific genotypes of 5HTT in families of patients with OCD11.

A polymorphic region, comprising repeated elements 16, is described next to the start of zone 5HTT gene transcription, the 5-HTT-LP polymorphism is an insertion or deletion of 44-bp elements involving repeated 6 to 8 times generating two functional alleles: A short allele (S) and the long allele (L)12. However, Hu and co-workers...
reported that 5-HTTLPR polymorphism is functionally triallelic, resulting from the substitution of A for G in the G allele. Other polymorphisms of this gene that correspond to a variable number of tandem repeats (VNTR) in the 17 base pair (bp) are termed the VNTR STin2 and involve different alleles. Studies of the gene 5HTT are described in Table 1.

Table 1. Association studies between obsessive-compulsive disorder and polymorphisms of the serotonin transporter gene (5HTT) and the promoter of the serotonin transporter (5HTTLPR)

| Study design | Genotype | Population | Phenotype | Sample Cases/ Controls | Results | Reference |
|--------------|----------|------------|-----------|------------------------|---------|-----------|
| CC           | 5HTTLPR  | Italian    | OCD       | 180/112                | NS      | (158)     |
| CC           | 5HTTLPR  | Brazilian  | OCD       | 79/202                 | NS      | (23)      |
| CC/FB        | 5HTTLPR  | French/German | OCD   | 106 families 86/171   | NS      | (159)     |
| CC/FB        | 5HTTLPR  | Mexican    | OCD       | 43 families 115/136    | NS      | (160)     |
| FB           | 5HTTLPR  | German     | Early onset OCD | 64 families      | NS      | (28)      |
| CC           | 5HTTLPR, VNTR | Indian  | OCD       | 93/92                  | Association between 5-HTTLPR and OCD severity ($p = 0.036$); VNTR: NS | (161)     |
| CC           | 5HTTLPR, VNTR | Korean  | OCD       | 148/157                | NS      | (21)      |
| CC           | 5HTTLPR, VNTR | Caucasian | OCD    | 295/657                | NS      | (89)      |
| CC           | 5HTTLPR, VNTR | Spanish Caucasians | OCD | 97 OCD/570 psychiatric controls /406 healthy controls | More 12/12 e 12/10 genotypes in patients with OCD. | (162)     |
| CC           | 5HTTLPR  | Spanish Caucasians | OCD    | 99 OCD/466 psychiatric controls /420 healthy controls | 5HTTLPR: NS; VNTR: More 12/12, 12/10 and 12/9 genotypes in patients with OCD | (19)      |
| CC           | 5HTTLPR  | Han Chinese | OCD    | 207/275                | NS      | (163)     |
| CC           | 5HTTLPR  | Korean     | OCD       | 124/171                | The L allele in OCD presented higher scores on symptoms religious/somatic ($p = 0.005$) | (164)     |

OCD: obsessive-compulsive disorder; NS: nonsignificant; CC: case-control; FB: family-based; 5-HTTLPR: polymorphism of the promoter region of the serotonin transporter gene.
Serotonin receptor type 2A (HTR2A, 5-HT2A)

Chromosome: 13; location: 13q14-q21

Evidence suggests that an action of the serotonin 2A receptor in OCD run reports of benefit in the use of hallucinogens (potent stimulants of 5HT2A) and the tendency of clozapine trigger SOC in patients with schizophrenia25.

The two most studied polymorphisms in OCD are -1438 A/G and T102C. Some studies show an association between OCD and AA allele polymorphism -1438 G/A in women16,17 and in a sample of children and adolescents18. These results were not replicated in other studies19,20. Liu et al. studied a sample of 103 Chinese trios and found a significant association between OCD and 5HT2A polymorphism -1438G/A (p = 0.0389), and a transmission disequilibrium in the late-onset group (p = 0.0132) and in the male group (p = 0.0255)20. Regarding the T102C variant, several studies found no significant association with OCD15,21. Tot et al. found that genotypes and T102T variant -1438 AA genotype A/G were associated with an increased severity of OCD22. Meira-Lima et al. also found that silent C516T variant was associated with OCD23.

Serotonin receptor type 1B (HTR1B, 5HT1B)

Chromosome: 6; location: 6q13

The beneficial effects of atypical antipsychotic drugs and hallucinogens in 5HT1B were seen in some OCD patients, suggesting that this receptor may be involved in the neurobiology of OCD.

World et al. found a preferential transmission of the G861 allele for OCD24 and confirmed these findings in a longitudinal study25. Camarena et al. also found a preferential transmission of the variant G861 C861 compared to the group with the highest scores of the YBOCS (Yale-Brown Obsessive Compulsive Scale), although no association was found with OCD25. Liu et al. found an association of this gene with early-onset OCD (p = 0.0389)26. Meanwhile, other studies have two negative findings27,28. Preliminary findings of an association between allele G861 and symptoms of order/arrangement/symmetry let the suggestion for more refined phenotypic analyses in genetic studies29.

Receptor 5-hydroxytryptamine (serotonin) type 2C (HTR2C, 5HT2C)

Chromosome: X; location: Xq24

Chronic treatment of OCD with SSRIs may result in reduced dopamine transmission through activation of mesocorticolimbic 5HT2C, which may represent an important event for the therapeutic efficacy of SSRIs20.31. Study in mice, which presented 5HT2C gene deletion, showed similar behavior to compulsive symptoms32. Tsaltas et al. showed similar behavior to compulsive symptoms32. Tsaltas and T102C. Some studies show an association between OCD and TPH2 polymorphism, which considered its 3 allele (OR: 1.251, 95% CI: (1.048-1.492), p = 0.001), and two polymorphisms of the 5-THR2A rs6311 and 6313 (OR: 1.219, 95% CI: (1.037 to 1.433), p = 0.002) were statistically significant, strengthening its possible contribution in the etiology of OCD30.

Dopamine related genes

The serotonergic system has many interrelationships with other neuronal circuits and neurotransmitters31. Dopamine plays an important role in the pathophysiology of OCD32 and is involved in an interaction with the dopaminergic system in the fronto-thalamic-base ganglion33. Such modulation of dopamine transmission made by SSRIs indirectly influences the development and OCD.34. Pharmacological studies have found that dopamine antagonists in combination with SSRIs were effective in treating OCD. Animal studies have found that the use of dopamine agonists induces stereotypic movements similar to some SOC35.

Dopamine transporter gene (DAT1 or SLC6A3)

Chromosome: 5; location: 5p15.3

The dopamine transporter gene has a central role in the removal of midbrain dopamine synapses. The diffusion and uptake of dopamine by DAT1 changes the magnitude, duration, and spatial configuration of the receptor activation induced by the transmitter, thereby modifying dopaminergic neurotransmission36. Mice with deletion of DAT sequential display stereotypic behaviors37; similar to those observed in basal ganglia disorders such as OCD and Tourette syndrome. DAT1 has a VNTR polymorphism in the 40bp repeat having 3 to 11 repetitions in the 3 "untranslated" that can influence gene expression and protein levels in brain DAT146. The studies that investigated the association between DAT and TOC were negative findings37,38 (Table 2).

Dopamine receptor D2 (DRD2)

Chromosome: 11; location: 11q23

The dopamine D2 receptor (DRD2) is found at high levels in the basal ganglia, which makes it a candidate gene for the pathophysiology of OCD. Although some studies have found no association between this gene and OCD, Nicolini et al. found a higher frequency of the variant in the DRD2 A2A2 OCD + tics (p = 0.008)46. In another study, Nicolini et al. found an association between the A allele of the DRD2 TaqA2 (p = 0.01) and TOC and an excess of homozygotes A2A2 in OCD + tics group (p = 0.001)46. Denys et al. found a higher frequency of the DRD2 A2 allele only in men with OCD (p = 0.02)46 (Table 2).
Table 2. Association studies between obsessive-compulsive disorder and genes of dopamine receptors 2, 3 and 4 (DRD2, DRD3 and DRD4) and dopamine transporter (DAT1)

| Study Design | Population | Phenotype | Samples | Results | Reference |
|--------------|------------|-----------|---------|---------|-----------|
| CC           | Canadian   | OCD       | 100/18  | Association between OCD and the DRD4 gene \(p = 0.02\) which was not found after correction for multiple testing; no associations with DAT1, DRD2 or DRD3 | (52) |
| CC           | Afrikaners | OCD       | 71/129  | NS      | (165)     |
| CC           | Ashkenazi and nonnon-Ashkenazi Jews | OCD | 75/172 | NS | (37) |
| FB CC        | French     | OCD       | 55 trios| DRD4: No transmission of the 2 repeats allele/ Lower frequency of the 2 repeats allele in patients with OCD without tic \(p = 0.005\) | (55) |
| CC           | Afrikaners | OCD       | 252/180 | DRD4: the allele of 7 repeats was associated with early onset OCD \(p = 0.02\) | (56) |
| CC           | Korean     | OCD       | 115/160 | Higher frequency of the 2 repeats allele in patients with OCD \(p = 0.04\) | (158) |
| CC           | Mexican    | OCD + tics| 49 OCD-tics/12 OCD + tics/63 controls | DRD4: higher frequency of the 7 repeats allele \(p = 0.02\) | (54) |
| CC           | Mexican    | OCD + tics| 54 OCD-tics/12 OCD + tics/54 | DRD2: Association between OCD and the most frequent allele, A2 \(p = 0.01\); Excess of allele A2 homozygosis \(p = 0.001\); DRD4: higher frequency of the 7 repeats allele \(p = 0.02\) and of the haplotype A2R7 \(p = 0.02\) in the OCD + tics group | (50) |
| CC           | Mexican    | OCD       | 67 (12 with tics)/54 | DRD2: higher frequency of A2 homozygosis in OCD + tics group \(p = 0.008\), nonsignificant for DRD3 | (49) |
| CC           | Dutch      | OCD       | 150 (56 male)/150 (79 male) | Higher frequency of DRD2 A2 allele in male OCD patients \(p = 0.02\) | (51) |
| CC           | Caucasian  | OCD       | 97/97   | NS      | (166)     |
| CC,FB        | Mexican    | OCD       | 210/202 | DRD4: lower frequency of the 4 repeats allele \(p = 0.0027\) | (57) |
| FB           | Caucasian  | OCD + tics| 38/202  | Higher frequency of the 6 repeats allele in OCD + tics group \(p = 0.0016\) | (58) |
| FB           | Chinese    | Early onset OCD | 69 trios | NS | (20) |

DRD2: gene of Dopamine Receptor D2; DRD3: gene of Dopamine Receptor D3; DRD4: gene of Dopamine Receptor D4; NS: nonsignificant; CC: case-control; FB: family-based; OCD: obsessive-compulsive disorder; OCD + tics: obsessive-compulsive disorder in association with tic disorder.

Dopamine D3 receptor (DRD3)

Chromosome: 3; Location: 3q13.3

The antagonism at dopamine D3 receptor has an anxiolytic effect. The function and expression of DRD3 is decreased during stress and depression, while chronic treatment with SSRI drugs or noradrenergic DRD3 mRNA increases, offsetting the effect of the initial stress\(^{15}\). The SNP variant most studied is one that leads to the substitution of glycine for serine at codon 9 (Ser9Gly), but studies with this gene and TOC were found to be negative\(^{49,52}\) (Table 2).

Dopamine receptor D4 (DRD4)

Chromosome: 11; location: 11p15.5

The dopamine receptor D4 (DRD4) is involved in higher brain functions, modulation of synthesis and turnover of brain dopamine. In the DRD4 gene encoding there is a VNTR polymorphism (48PB 2 to 10 tandem repeats) in the third exon, which is of great interest for psychiatric studies\(^{35}\). The results of studies of the association between DRD4 and TOC are not conclusive. Some studies have found a higher frequency of allele 7 repeats in patients with OCD and tics\(^{50,54}\). Millet \textit{et al.} found no transmission of allele 2 repetitions \(p = 0.005\) and in a case-control study, they found an allele frequency of 2 replicates significantly lower in OCD patients \(p = 0.02\)\(^{55}\). Hemmings \textit{et al.} found an association between allele 7 repeats and early-onset OCD \(p = 0.02\)\(^{56}\). Camarena \textit{et al.} found lower frequency allele of the DRD4 4 replicates in OCD patients \(p = 0.0027\) and higher frequency of the 6 repeats allele in the group with tics \(p = 0.0016\)\(^{57}\). Walitza \textit{et al.} found, in a family-based study, lower transmission of allele 4 repetitions \(p = 0.003\)\(^{59}\) (Table 2).

Despite evidence of involvement of dopamine in the pathophysiology of OCD, the findings of association studies with dopamine-related genes were mostly negative. The DRD4 gene has been the most studied in OCD with divergent findings. A recent meta-analysis found no association between OCD and the genes DAT1, DRD2, DRD3 and DRD4\(^{40}\).
Glutamate related genes

Neuroimaging studies in animal models and pharmacological studies of candidate gene association reinforce the hypothesis of the involvement of glutamate in the pathophysiology of OCD. Functional neuroimaging studies showed metabolic hyperactivity in the cortico-striatal-thalamic-cortical circuits. Abnormal levels of glutamate have been reported in OCD patients, predominantly in prefrontal regions such as the orbitofrontal cortex and its projection areas in the striatum. Glutamate levels in the CSF were also significantly higher in patients with OCD compared to controls (p = 0.014). Drugs that modulate glutamate have been recently used as boosters of pharmacological treatment of OCD in adults and children. In addition, glutamate-related genes as well as serotonin-related genes had more positive association results replicated until date. Given this, the investigation of glutamatergic genes as candidates for OCD has been seen as a promising field.

Gene associated protein SAP90/PSD95- 3 - SAPAP3/ DLGAP3

Chromosome: 1; location: 1p35.3-p34.1

The family of proteins associated with SAP90/PSD95 (SAPAP) is a component of postsynaptic density that interacts with other proteins in a complex key-lock glutamatergic synapses. Results from studies in mice suggest that SAPAP3 may be involved in the pathophysiology of OCD and trichotillomania. The mouse with SAPAP3 deletion self-developed facial injuries caused secondary to excessive grooming behavior, and showed dysfunction in cortical-striatal synapses. After these rats received SSRIs, such behavior improved. The selective striatal expression SAPAP3, mediated by lentivirus, recovered synaptic and behavioral changes of the mutant mice.

Since the Welch et al. study have shown an animal model for OCD and pathological grooming with knockout SAPAP3 gene mice, the correlate human gene (DLGAP1) began to be studied as a candidate in OCD. Boardman et al. evaluated seven polymorphisms in the gene encoding the SAPAP3 in individuals with OCD (n = 172), trichotillomania (n = 45) and controls (n = 153), and found no association. Among the group with OCD, early onset of the disorder and ATAT haplotype (rs11583978-rs7541937-rs6662980-rs4652867) was positively associated. Bienvenu et al. evaluated 383 families and found an association between four SAPAP3 polymorphisms and pathological grooming (onychophagia, dermatotilexomania and/or trichotillomania), but not with OCD. Another study sequenced the gene SAPAP3 in 44 patients with OCD and trichotillomania, 44 OCD patients and 178 controls without trichotillomania, genotyped 6 polymorphisms in an additional sample of 281 OCD patients and 751 individuals from the general population, and noted an association between OCD and A189Y polymorphism (p = 0.045). The SLC1A1, encoding the glutamate transporter high affinity neuronal/epithelial (GLT1), is a strong candidate gene located on 9p24 region. Studies related to the SLC1A1 gene are described in table 3.

Table 3. Association studies between obsessive-compulsive disorder and the gene SLC1A1

| Study design | Population   | Phenotype            | Sample Cases/Controls | Results                                                                 | Reference |
|-------------|--------------|----------------------|-----------------------|--------------------------------------------------------------------------|-----------|
| FB          | North American | Early onset OCD      | 71 trios              | Association between two adjacent SNPs of the rs301430 on 3′ region (p = 0.03) in whole sample and rs3780412 (p = 0.002) in the male sample | (153)     |
| FB          | Caucasian    | OCD                  | 157 trios             | rs301434 (χ² = 12.04; p = 0.006) and rs301435 (χ² = 9.24; p = 0.03)        | (152)     |
| FB          | North American and French | OCD | 66 families | rs12682807/rs2072657/rs301430, with higher transmission of A/T/T in whole sample (p = 0.0015) and the male sample (p = 0.0031) | (142)     |
| FB          | North American | OCD                  | 378 families          | Strong association with the SNP RS301443 (p = 0.000067; Bonferroni correction p = 0.0167) | 154       |
| CC          | Caucasian    | OCD                  | 325/662               | rs7956819/rs3087879/rs301430 – associated with OCD even after correction for multiple testing. The haplotype C/C/G was two times higher in OCD when compared with controls. rs38333321 was associated with hoarding | (167)     |

OCD: obsessive-compulsive disorder, NS: nonsignificant, CC: case-control, FB: family-based.
Glutamate receptor, ionotropic, kainato 2 and 3 (GRIK2/EA44 and GRIK3/EA45)

Chromosome: 6; location: 6q16.3-q21, and chromosome: 1, location: 1p34-p33, respectively

GRIK2 and GRIK3 contribute to the regulation of inhibitory and excitatory transmission and have important roles in physiology and plasticity of synapses93. These GRIK2 messenger RNA abundance in pyramidal neurons in the caudate, which are involved in the pathophysiology of OCD. Animal studies have shown that mice with deletion of GRIK2 have significant reduction of fear memory, less anxiety behaviors, more exposure to risk and aggressiveness94. Genes of GRIK2 and GRIK3 were investigated in a study of 156 OCD patients, 141 controls and 124 trios, found that SNP rs2238076 allele of GRIK2 was less transmitted than expected for OCD patients (p < 0.03). Sampaio et al. also found a significant association between the SNP rs1556995 of GRIK2 (p = 0.03), and between rs1556995/rs1417182 haplotype (p = 0.01) and OCD. The glutamatergic system has been the preferred target of the current association studies. The association with OCD was identified in five regions, genes related to GABA deserve to continue to be evaluated in future studies.

GABA-aminobutyric acid (GABA) related genes

GABA receptor (GABBR1)

Chromosome: 6; location: 6q13-q16.3

In the only study evaluating this gene in OCD, Zai et al. evaluated five polymorphisms in the GABA receptor type 1 (GABBR1) in 159 families and found a greater transmission of the A allele of A-7265G polymorphism in OCD93.

Taking into account that functional neuroimaging studies in OCD showed hyperactivity in regions of the orbitofrontal cortex, striatum, thalamus, and anterior cingulate81 and that there is an inhibitory GABAAergic pathways on glutamatergic pathways in these regions, genes related to GABA deserve to continue to be evaluated in future studies.

Other genes

Brain-derived neurotrophic factor (BDNF)

Chromosome: 11; location: 11p13

The brain-derived neurotrophic factor (BDNF) promotes regeneration of brain connectivity and proliferation during development and participates in the maintenance and plasticity of neurons even during adulthood82. Hall et al. evaluated the BDNF gene in 164 trios of probands with OCD and found that the Met66 allele, which alters the sequence of pro-BDNF protein was overtransmitted, and may confer a protective effect against OCD82. Alonso et al. evaluated SNPs in BDNF in 215 OCD patients and 342 controls, and found a significant association with a haplotype containing five val66met polymorphism markers (p = 0.006 after permutation test, which minimizes the risk of false-positive)40. Hemmings et al. found that Met66 allele was associated with the OCD in men with early onset OCD however, genotype Val66/Val66 was associated with more severe OCD in women83. Dicel et al. found no association of polymorphisms of genes SLCA4A, HTR1B, HTR2A, and BDNF in 54 trios of probands with early-onset OCD84. Kartcerberg and employees, trying to replicate these findings, evaluated 419 OCD patients and 650 controls, but found no significant association between the polymorphism val66met (rs6265) and OCD, or any dimension of OCD symptoms84. The studies of Mosnner and employees, and Wendland et al. were also negative84,85. A meta-analysis found no association between the polymorphism and OCD val66met (OR: 1.013, 95% CI: (0.765 to 1.342), p = 0.904)40.

Neurotrophic tyrosine kinase receptor of (NTRK) types 1, 2 and 3

Chromosome: 1; location: 1q21-q22; chromosome: 9 location: 9q22.1; chromosome: 15; location: 15q25 (respectively)

Neurotrophic tyrosine kinase receptor of type 3 (NTRK3), high affinity receptor for the neurotrophin 3 (NT-3), was evaluated by Alonso et al. in 120 OCD patients and 342 controls, and an association was found between the SNP rs7176429 (p = 0, 0001) and hoarding40. Alonso et al. also studied the gene of Neurotrophic tyrosine kinase receptor type 2 (NTRK2) in 215 OCD patients and 342 controls and found an intronic haplotype with a protective effect against OCD (p = 0.001) and also that an intronic SNP of NTRK2 (rs2378672) was associated with OCD in women (p < 0.0001)43.

Monoamine oxidase A (MAO A)

Chromosome: X; location: Xp11.21

The monoamine oxidase (MAO) is a mitochondrial enzyme that degrades various biogenic amines, including serotonin, epinephrine, norepinephrine and dopamine. Two functional polymorphisms were studied in OCD. A polymorphism consists of a 30 bp VNTR located above the 1.2kb coding sequences of MAO-A (MAO-Au VNTR) and the other is a substitution of T for C (EcoRV) with the T allele associated with low enzymatic activity94. There was no association between the polymorphism and OCD EcoRV in a meta-analysis40. Studies on the MAO-A gene are described in table 4.

Catechol-O-methyltransferase (COMT)

Chromosome: 22; location: 22q11.21

The catechol-O-methyltransferase (COMT) is an enzyme that metabolizes catecholamines, including the neurotransmitters norepinephrine, epinephrine and dopamine. The most studied polymorphism in the COMT gene is an exchange of single nucleotide (SNP) (val158met or rs4680) G to A, which leads to an amino acid substitution of valine for methionine at codon 158 of the enzyme. This variation is associated with thermolabile form (low activity – 158met allele, allele A or allele G) or thermostable (high activity – val158, allele G allele or H) of the enzyme95,96. A recent study has shown that OCD patients with the G allele of COMT have low levels of 3-O-methyl-DOPA, which results from methylation of L-DOPA in plasma97, showing that there is a decrease in the activity of the COMT enzyme in OCD patients carrying the polymorphism of low activity.

The homozygosity of allele G rs4680 of COMT polymorphism results in a decrease to half the enzyme activity and dopamine catabolism98,99, with subsequent increase in the availability of dopamine88,100, particularly in the prefrontal cortex.

Four meta-analyses of studies of the association between the rs4680 polymorphism and OCD had discordant results. The first, carried out in 2003101 included case-control and family-based studies and found no significant association. The second, made in 2007, only with case-control studies (n = 1,908 individuals) found an association between OCD and L allele in men but not in women102. This finding was replicated in the third meta-analysis that included published case-control and family-based studies103. However, a fourth meta-analysis, with only studies based on families, also found no association with OCD102. Studies related to the COMT are described in table 5.

A common feature among BDNF, NTRK, COMT and MAO-A is that their functions lead to neuronal pathways in various implications. The lack of specificity of their functions may contribute to the inconsistent findings in studies of these genes in association with OCD.
Table 5. Association studies between obsessive-compulsive disorder and the gene of catecol O-methyltransferasis

| Study design | Genotype | Population | Phenotype | Sample Cases/Controls | Results | Reference |
|--------------|----------|------------|-----------|-----------------------|---------|-----------|
| CC           | Exon 14 T/G | Afrikaners | OCD       | 71/129                | NS      | (165)     |
| FB           | Exon 14 T/G | North Americans | OCD       | 113 OCD + EQZ/79 OCD/171 controls | Allele G as a risk factor for OCD in men (p = 0.0004) | (173)     |
| FB           | Exon 8 T/G | North Americans | OCD + TD vs. OCD – TD | 110 families | Allele G as a risk factor for OCD (p = 0.02) | (160)     |
| FB           | Exon 8 T/G | North Americans | OCD       | 51 families | Allele T as a risk factor for women with OCD (CC: p = 0.02; FB: p = 0.02) | (149)     |
| CC           | MAO-Au VNTR | Korean | OCD       | 121/276 | Higher frequency of the 3 repeats allele in men with OCD | (169)     |
| CC           | Exon 8 T/G | White South Africans | OCD       | 298/307 | NS | (139)     |
| FB           | Exon 8 T/G | Israeli | OCD       | 122/124 | Allele T as a risk factor for women with OCD (CC: p = 0.02; FB: p = 0.02) | (160)     |
| CC           | Exon 14 T/G | French + North American | OCD       | 17/35 | NS | (179)     |
| CC           | Exon 14 T/G | Turkish | OCD       | 59/114 | NS | (179)     |
| CC           | Exon 14 T/G | Turkish | OCD       | 20/79 | NS | (179)     |
| CC           | Exon 14 T/G | Dutch | OCD       | 320 cases | LL genotype protects against “Tabu” dimension of OCD symptoms (p = 0.06) | (173)     |
| CC           | Exon 14 T/G | Dutch and North American | OCD       | 373/462 | Higher frequency of L allele in women from control group | (155)     |
| CC           | Exon 14 T/G | Dutch | OCD       | 87/327 | Higher frequency of the L allele in men with OCD | (101)     |
| CC           | Exon 14 T/G | Chinese | OCD       | 103 trios | NS | (20)      |

L: met allele of the val158met of the COMT gene; H: val allele of the val158met of the COMT gene; COMT: catecol-O-metiltransferase; OCD: obsessive-compulsive disorder; FB: family-based; YBOCS: Yale-Brown Scale of Obsessive-Compulsive Symptoms; Val: Valine; Met: methionine; EQZ: schizophrenia; NS: nonsignificant.

White matter related genes

Transcription factor of the oligodendrocyte lineage (OLIG2; BHLHB1 OLIGO2, PRKCBP2, RACK17)

Chromosome: 21; location: 21q22.11

OCD is associated with decreased volume and structural abnormalities of white matter\(^{103,104}\), reflecting a decrease in fractional anisotropy\(^{105}\). The transcription factor of the oligodendrocyte lineage 2 (OLIG2) is involved in myelination and neurogenesis and is essential in regulating the development of cells producing white substance (myelin)\(^{106}\). OLIG2 is highly expressed in the amygdala, caudate nucleus and thalamus, regions involved in OCD\(^{107,108}\). Stewart et al. evaluated 66 families with OCD with or without tic disorders (TT) and 33 families of probands with OCD without tic disorders. They found an association between OCD without tics in 3 SNP: rs762178 (p < 0.001), rs1059094 (p = 0.005) and rs9653711 (p = 0.004) in addition to the association with a haplotype of 5 markers (p = 0.008 after permutation test)\(^{109}\). These findings have not been replicated.
Myelin oligodendrocyte glycoprotein (MOG)

**Chromosome: 6; location: 6p22.1**

OCD may be related to autoimmune processes such as what occurs with children who have early symptoms after streptococcal infection. Furthermore, white matter abnormalities have been reported in patients with OCD. One of the candidate genes involved in the immune response is myelin oligodendrocyte glycoprotein (MOG), which is the mediator of the complement cascade and also plays an important role in the formation of white substance. \( \chi^2 = 5.255, p = 0.022 \) and the MOG4 haplotype C134T:MOG2. C10991T:MOG4: 1.13.2.2 (Zai et al. found a preferential transmission of the 459-bp allele (allele \( \text{G} \): 0.011)\(^{109} \). Attmaca et al. evaluated genotypes MOG G511C (Val142Leu) and magnetic resonance imaging in 30 patients with OCD and 30 controls and found that the total white matter volume was greater in patients with OCD who had Val/Val genotype of MOG G511C (Val142Leu)\(^{111} \). Genes related to white matter in OCD have been studied little and his findings are interesting. The evaluation of the association between these genes and the change of white matter as an OCD endophenotype, deserve to be studied more.

**Immune system related genes**

There is evidence to support the involvement of the immune system in OCD, as the emergence of OCD associated with rheumatic fever\(^{112-114} \). Pediatric Autoimmune Neuropsychiatric Disease with Associated Streptococcus (PANDAS)\(^{115,116} \) and evidence that disorders of the obsessive-compulsive spectrum aggregate in families of patients with rheumatic fever\(^{117-119} \).

**Tumor necrosis factor alpha (TNF-alpha)**

**Chromosome: 6; location: 6p21.3**

TNF-alpha is a pro-inflammatory cytokine involved in autoimmune diseases such as rheumatic fever. Polymorphisms in the promoter region of this gene have been associated with clinical forms of fever\(^{120} \). Hounie et al. evaluated\(^{121} \) patients with OCD and 250 controls and found an association between OCD and the A allele from the -238 A/G polymorphism (Chisq2 = 12.05, p = 0.0005), the A allele of the -308 G/A polymorphism (Chisq2 = 7.09, p = 0.007) and AA haplotype of these two markers (p = 0.0099)\(^{121} \). Cappi et al. evaluated the same polymorphisms in an OCD 83 trios sample, and found that the G allele of TNFA 238G/A was overtransmitted to OCD probands (p = 0.007) (122). However, Zai et al. found no association between TNFA and OCD\(^{123} \).

**Nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor-like 1 (NFKBIL1)**

**Chromosome: 6; location: 6p21.3**

Lamb et al. assessed the polymorphism -62A/T NFKBIL1 in 111 OCD patients and 272 controls and found no significant association\(^{124} \).

**Interleukin-6 (IL-6)**

**Chromosome: 1; location: 1q21**

Cappi et al. evaluated 83 trios with OCD as the rs1800795 polymorphism in the promoter region of IL-6 and found no association\(^{125} \). The TNFA was associated with OCD in two studies, but with different alleles. Therefore, this association has yet to be replicated in future studies. There is a small number of association studies of genes related to immune response and more studies are needed in this area.

**Hormone-related genes**

**Estrogen receptor alpha (ESR)**

**Chromosome: 6; location: 6q25.1**

There is the hypothesis that estrogen-related genes influence the clinical presentation of OCD. The postpartum period is a risk for the development of obsessive-compulsive symptoms\(^{125} \). Several clinical and genetic studies in OCD showed different results for the two genders. Among the sex steroids there is evidence that estrogens modulate monoamines and neuropeptides (including those more related to OCD such as serotonin, dopamine, glutamate and GABA) regulate emotional responses, promote neuroprotective effects and improve cognition\(^{126} \). Alonso et al. evaluated the gene estrogen receptor 1 and 2 (ESR1 and ESR2) in 236 cases with OCD and 296 healthy controls; they found that the rs34538504 SNP and haplotype of ESR1 five SNPs were significantly associated with extent of contamination/cleaning (p = 0.0001) and the frequency of the haplotype rs3453804 A/rs488133 C/rs9478245 C/rs2234693 C/ rs9340799 G * was significantly lower in patients with this symptom dimension (p = 0.018)\(^{127} \).

Studies evaluating the association of genes related to estrogen in specific subtypes of OCD, such as of early postpartum OCD or late onset OCD in females as well as the investigation of genes related to oxytocin could help in understanding the mechanisms by which there is an increased risk of developing OCD after the birth of a child or in the postpartum period\(^{128-130} \).

**Discussion**

There is a body of evidence that biological/genetic expression is important in OCD. The genetic segregation model that best explained OCD is the complex model in which the influences of several genes with small effects are in interaction with environmental factors. Several studies with candidate genes have been performed for various reasons and their findings are not conclusive.

Possible explanations for the diversity of results and low replicability are its small sample size and the low statistical power of most studies. Moreover, many of them conducted multiple analyses without adequate statistical correction to its results, which increases the chance of false positives.

Another possible explanation for the diversity of results is the phenotypic heterogeneity of OCD. There is a hypothesis that different subgroups of TOC can receive influence from different genes. The subgroups of OCD can be organized by gender, age at onset of symptoms and comorbid tics\(^{131,132} \). There is also an attempt to subdivide the TOC according to the size of symptoms because they would relate to a different neurobiological substrate. Hoarding, for example, has specific features on the epidemiology, treatment response in neuroimaging findings\(^{133-136} \) and genetic findings\(^{137} \). As for comorbid tics, there is evidence of involvement of the dopaminergic system in OCD\(^{138} \) and there were even found positive findings of association between certain genes related to dopamine and OCD with comorbid tic disorders\(^{139-142} \). OCD also is genetically linked to Tourette syndrome\(^{140,141} \) which was associated with dopamine-related genes such as the gene for dopamine D2 receptor (DRD2)\(^{142-145} \), dopamine transporter (DAT)\(^{145} \), and monoamine oxidase A (MAO-A)\(^{146} \). It is possible that OCD in comorbid tic disorders configure a separate subgroup with susceptibility associated with polymorphisms in genes related to dopamine. OCD can also be heterogeneous between genders. Several genetic association studies showed there were differences when analyzed separately by gender\(^{146,147,148,149,150} \). The same is seen when the sample is divided according to age at onset of TOC\(^{151,152,153,154,155} \). These two characteristics are used to group individuals with OCD in more homogeneous subgroups\(^{151} \).

The use of quantitative traits (such as severity scores of YBOCS), endophenotypes, studies of gene-environment interaction and
epigenetic studies are the next steps in association studies in OCD. Possible investigations of interaction between genes and environment in OCD include the role of polymorphisms in the development of OCD after traumatic events, or streptococcus infection, or even the influence of polymorphisms in the development of personality traits risk for OCD10. The definition of endophenotypes by neuroimaging studies, neurophysiology and neuropsychology are essential in guiding genetic studies11.

Conclusion
The amount of available data does not allow us to pinpoint a gene responsible for the etiology of OCD. Establishing groups with more homogenous phenotypes may improve the accuracy of results. Association studies with a large sample size, sometimes achieved through consortia and meta-analyses are still needed.

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