Genetic association studies in obsessive-compulsive disorder

Estudos de associação genética no transtorno obsessivo-compulsivo

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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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Keywords: Association, gene, obsessive-compulsive disorder, review.

Resumo

Contexto: O caráter familial do transtorno obsessivo-compulsivo (TOC) já é bem estabelecido. Ele segue o modelo complexo de transmissão genética que envolve a influência de diversos genes de pequeno efeito em interação com o ambiente. **Métodos:** Foi realizada uma revisão sistemática de estudos de associação genética com o TOC mediante busca de artigos publicados até 2012 nas bases de dados: PubMed, Embase e SciELO, usando os termos MeSH, seus associados ou sinônimos para "*obsessive-compulsive disorder*", "*gene*" e "*genetic association studies*". **Resultados:** Foram selecionados 105 artigos cujos principais resultados foram agrupados em grupos de genes relacionados a serotonina, dopamina, glutamato, GABA, substância branca, hormônios, sistema imune e outros genes (MAO-A, BNDF, COMT). **Conclusão:** Há grande variabilidade nos achados de estudos de associação entre os diversos genes candidatos estudados e o TOC. Genes relacionados às vias glutamatérgicas são candidatos promissores, porém não há associação conclusiva entre nenhum dos genes candidatos estudados e o TOC. Estudos de associação com grande tamanho amostral, avaliação de subgrupos mais homogêneos do fenótipo e metanálises ainda são necessários.

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Palavras-chave: Associação, gene, transtorno obsessivo-compulsivo, revisão.

Introduction

Obsessive-compulsive disorder (OCD) is the fourth most common psychiatric disorder with a lifetime prevalence between 2.0% and 2.5%[1]. 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[2]. OCD is a chronic disorder and manifests regardless of sex, race, intelligence, marital status, socio-economic status, religion or nationality. The cross-cultural studies show that the OCD symptoms are similar in different population and cultures[3], supporting the idea that biological and genetic factors can contribute to its etiology. Although psychological theories have grounded the emergence of the OCD concept[4] 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[5]. 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"[6]. 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

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investigated phenotype (case probands) and the frequency of that disorder in relatives of individuals who do not have the investigated phenotype (control probands). If the frequency of the studied phenotype is significantly higher in the group of case probands' relatives, it can be said that there is familial aggregation[6]. A meta-analysis of studies in OCD families, involving 312 probands and their 1209 first-degree relatives, found a cumulative risk of 8.2% among "case" relatives and 2% among "control" family members, with an odds ratio of 4 (95% CI = 2.2, 7.1) to present OCD[7].

Twin studies compare the concordance for certain phenotypes between monozygotic (MZ), with the correlation observed between dizygotic (DZ) twins. The assumption is that MZ and DZ twins suffer similar environmental influence; however MZ twins share 100% of genome, while DZ twins share about 50%. Thus, in phenotypes more influenced by the environment, the concordance rates between MZ and DZ were similar; whereas in phenotypes more influenced by a genetic component, the MZ concordance rate would be higher than in DZ[8]. Furthermore, twin studies also allow us to estimate heritability (h2), that is, the size of the genetic effect in determining the studied phenotype. Data from 28 twin studies in OCD have shown that obsessive-compulsive symptoms (OCS) have genetic contributions with heritability rates of 45% to 65% in children and 27% to 47% in adults[9].

Adoption studies

Allow greater separation between genetic and environmental factors in the disorder etiology, since children do not share the home with their biological parents. Its main limitation is that the homes that embrace the adopted children do not represent higher risk environments (*e.g.*, environments of extreme poverty and deprivation)[8]. Generally adoption studies assess the history of mental disorders in the biological family and correlate with psychosocial protective or risk factors in the adoptive family[8]. As far as we know, there is no adoption study in OCD.

Segregation analysis

Assesses whether the transmission of a studied phenotype, over the family generations, can be explained by a Mendelian genetic model. Some of the models evaluated by genetic segregation analysis are: no transmission, autosomal dominant, autosomal recessive, polygenic (multiple genes of small effect); multifactorial or mixed (multiple genes of small effect added to environmental influences). The most accepted segregation model for OCD is the complex or mixed model, which involves the influence of many genes of small effect interacting with the environment[6].

Molecular genetic studies

Several studies in genetic epidemiology have been consistent in stating that OCD is a familial disorder. With the advent of modern molecular biology techniques, there has been growing interest in identifying which genes are involved in OCD etiology. Most genetic studies in OCD evaluate its association with genes involved in OCD-related brain circuits.

Linkage studies

Evaluate whether a particular genetic marker with known location co-segregates with the studied phenotype over generations. When two loci, located on the same chromosome, are very close to each other, they tend to be transmitted together (linked) as there are low odds of recombination between homologous chromosomes (crossing over). So, if the affected family members always inherit the studied genetic marker, the gene responsible for the disease is probably located near the marker. The main limitation of the study is the need to evaluate several family generations, with multiple affected members, in "complex" disorders such as OCD[6].

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 individuals (controls)[10] 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)[6], 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 *locus* (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: term 1 = 1,662,401 results; term results 2 = 14,124; term results 3 = 14 124; Embase: term 1 = 227,040 results; term results 2 = 19,244; term results 3 = 16 843; SciELO: term 1 = 4719 results, 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® and duplicates were discarded. References were selected and two independent researchers (ASS and RPL) assessed the full texts based on the inclusion criteria, which are: 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 (SRI). Hanna *et al.* reported an association between blood levels of serotonin and specific genotypes of 5HTT in families of patients with OCD[11].

A polymorphic region, comprising repeated elements 16, is described next to the start of zone 5HTT gene transcription, the 5-HTTLPR 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[13]. 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[14]. Studies of the gene 5HTT are described in table 1.

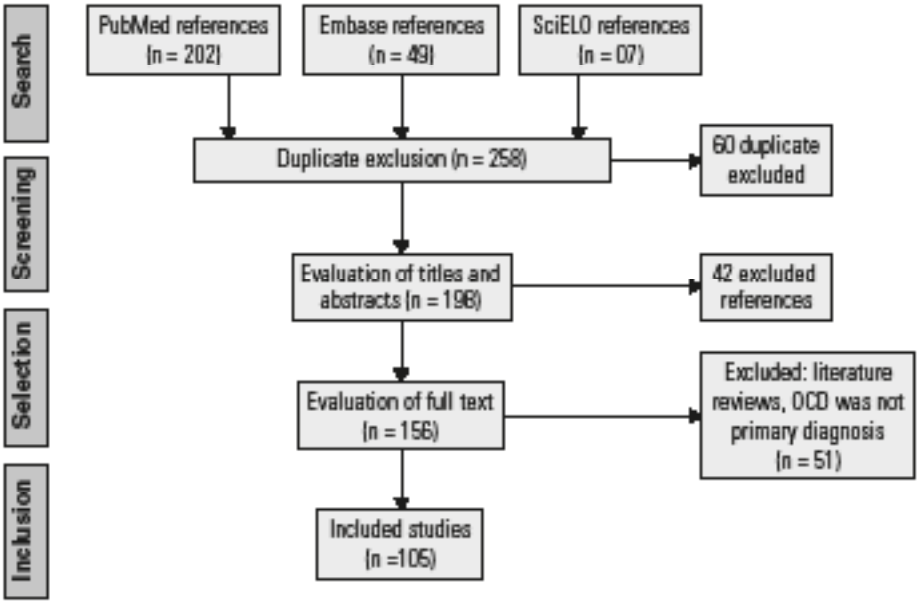

Figure 1. Flowchart of studies search and selection.

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/456 psychiatric controls /420 healthy controls	5HTTLPR: NS; VNTR: More 12/12, 12/10 and 12/9 genotypes in patients with OCD	(19)
CC	5HTLLPR	Han Chinese	OCD	207/275	NS	(163)
CC	5HTLLPR	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 schizophrenia[15].

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 women[16,17] and in a sample of children and adolescents[18]. These results were not replicated in other studies[15,19]. 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 OCD[15,21]. Tot *et al.* found that genotypes and T102T variant -1438 AA genotype A/G were associated with an increased severity of OCD[22]. Meira-Lima *et al.* also found that silent C516T variant was associated with OCD[23].

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 OCD[24] and confirmed these findings in a longitudinal study[25]. 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 OCD[26]. Liu *et al.* found an association of this gene with early onset OCD (p = 0.0389)[20]. Meanwhile, other studies have two negative findings[27,28]. Preliminary findings of an association between allele G861 and symptoms of order/arrangement/symmetry let the suggestion for more refined phenotypic analyses in genetic studies[29].

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 SSRIs[30,31]. Study in mice, which presented 5HT2C gene deletion, showed similar behavior to compulsive symptoms[32]. Tsaltas and co-workers showed exacerbation of SOC after administration of m-CPP (5HT2C agonist)[33]. Two studies of the association between a structural variant in the N-terminal extracellular region of the receptor and the 5HT2C TOC findings were negative[34,35]. This variant resulting from the substitution of the amino acid cysteine for serine at position 23[36], but does not have a defined function[34,37].

Tryptophan hydroxylase 1 (TPH1)

Chromosome: 11; location: 11p15.3-p14

Tryptophan hydroxylase (TPH) is an important step in the synthesis of 5HTT, and in this way is an important candidate gene. There are two forms of expression: TPH1 and TPH2.

The TPH1 is detected in blood and peripherally in the duodenum, but is not found in the brain. Two association studies found no significant findings between this gene and OCD[28,37].

Tryptophan hydroxylase 2 (TPH2)

Chromosome: 12; location: 12q21.1

The TPH2 is detected exclusively in the brain. One study found an association between this gene and early-onset OCD[38]. A Brazilian study with 107 patients and 214 controls found no association between the 8 SNPs evaluated in the TPH2 gene and OCD, but found higher prevalence of T-C-T (rs4448731, rs4565946, rs10506645) e C-A-T (rs4565946, rs7955501, rs10506645) haplotypes among OCD patients[39]. Among the most studied genes are the genes of the serotonin transporter (5-HTT) and its promoter region (5-HTTLPR). A recent meta-analysis assessed the studies with the 5-HTT gene, 5-HTTLPR, HTR1B, HTR2A and HTR2C in OCD and found that the association between OCD and 5HTTLPR polymorphism, when 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 OCD[40].

Dopamine related genes

The serotonergic system has many interrelationships with other neuronal circuits and neurotransmitters[41]. Dopamine plays an important role in the pathophysiology of OCD[42] and is involved in an interaction with the dopaminergic system in the fronto-thalamic-base ganglion[43]. Such modulation of dopamine transmission made by SSRIs indirectly influences the development and OCD[43]. 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 SOC[44].

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 neurotransmission[15]. Mice with deletion of DAT sequential display stereotypic behaviors[45]; 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 DAT1[46]. The studies that investigated the association between DAT and TOC were negative findings[47,48] (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)[49]. In another study, Nicolini *et al.* found an association between the A allele of the DRD2 TaqIA2 (p = 0.01) and TOC and an excess of homozygotes A2A2 in OCD + tics group (p = 0.001)[50]. Denys *et al.* found a higher frequency of the DRD2 A2 allele only in men with OCD (p = 0.02)[51] (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 Cases/Controls	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 49 OCD (17 OCD + tics)/63 controls	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 ($p = 0.04$)	(156)
CC	Mexican	OCD + tics	49 OCD-tics/12 OCD + tics	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 OCD	38/202 86 families	Higher frequency of the 6 repeats allele in OCD + tics group ($p = 0.0016$)	(58)
FB	Chinese	Early onset OCD OCD	69 trios 103 trios	NS DRD4: lower frequency in transmission of the 4 repeats allele ($p = 0.003$) 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[53]. 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 *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 *et al.* found an association between allele 7 repeats and early-onset OCD ($p = 0.02$)[56]. Camarena *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 *et al.* found, in a family-based study, lower transmission of allele 4 repetitions ($p = 0.003$)[58] (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[59-61]. Glutamate levels in the CSF were also significantly higher in patients with OCD compared to controls (p = 0.014)[62]. Drugs that modulate glutamate have been recently used as boosters of pharmacological treatment of OCD in adults[63,64], adolescents and children[65]. 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 (PSD) 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[66]. 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 SSRI, such behavior improved. Also, the selective striatal expression SAPAP3, mediated by lentivirus, recovered synaptic and behavioral changes of the mutant mice. The TOC and pathological grooming such as trichotillomania, have similar phenomenological characteristics[67].

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[66]. 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[68]. Among the group with OCD, early onset of the disorder and ATAT haplotype (rs11583978-rs7541937-rs6662980-rs4652867) was positively associated[68]. 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[69]. 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 A189V polymorphism (p = 0.045)[70].

Ionotropic glutamate receptor N-methyl D-aspartate 2B (GRIN2B, NMDAR2B)

Chromosome: 12; location: 12p12

GRIN2B is the gene which encodes one subunit of the NMDA receptor[71]. Arnold *et al.* studied 130 families of OCD patients and found that a haplotype consisting of two polymorphisms GRIN2B - 5072T/G (p = 0.014) and 5072G-5988T was associated with susceptibility to OCD (p = 0.002) (29). Later they evaluated 16 patients with treatment-naive OCD with magnetic resonance imaging and genotyped four polymorphisms GRIN2B (rs1019385, rs890, rs1805476 and rs1805502), and found that rs1019385 was associated with lower concentrations of glutamate in the anterior cingulate cortex[29].

Glutamate transporter high affinity neuronal/epithelial (SLC1A1, EAAC1)

Chromosome: 9; location: 9p24

The SLC1A1, encoding the glutamate transporter high affinity neuronal/epithelial (SLC1A1, EAAC1), is a strong candidate gene is located on 9p24 region[72]. Hanna *et al.* studied seven families of patients with early-onset OCD, found evidence of linkage in the region 9p[73]. In a replication study, Willour *et al.* genotyped 50 families with OCD and found peak connecting two markers: D9S1792 (alpha p = 0.59) and D9S1813 (p = 0.006) in the 9p24 region[74], only 0, 5 cM (< 350 kb) marker found by Hanna *et al.*[73]). 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 (χ^2 = 12.04; p = 0.006) and rs301435 (χ^2 = 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	rs7858819/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. rs3933331 was associated with hoarding	(167)

OCD: obsessive-compulsive disorder; NS: nonsignificant, CC: case-control; FB: family-based.

Glutamate receptor, ionotropic, kainatos 2 and 3 (GRIK2/ EAA4 and GRIK3/EAA5)

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 has important roles in physiology and plasticity of synapses[75]. There 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 had significant reduction of fear memory, less anxiety behaviors, more exposure to risk and aggressiveness[76]. 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[77].

The gutamatergic system has been the preferred target of the current association studies. The association with OCD was identified in five studies and a meta-analysis[78], but another recent meta-analysis did not confirm this association[40]. A large genome scan study including 1,465 cases, 5,557 controls matched for ethnicity and 400 trios of OCD patients found an association with polymorphisms in the gene-associated protein SAP90/PSD95- 1 - DLGAP-1, also related to glutamate[79].

Gama-aminobutyric acid (GABA) related genes

GABA receptor (GABRR1)

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 OCD[80].

Taking into account that functional neuroimaging studies in OCD showed hyperactivity in regions of the orbitofrontal cortex, striatum, thalamus, and anterior cingulate[81] and that there is an inhibitory GABAergic 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 adulthood[82]. 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 OCD[83]. 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)[84]. 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 women[85]. Dickel *et al.* found no association of polymorphisms of genes SLC6A4, HTR1B, HTR2A, and BDNF in 54 trios of probands with early-onset OCD[86]. Karterberg 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 symptoms[87]. The studies of Mossner and employees, and Wendland *et al.* were also negative[88,89].

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 hoarding[90]. 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 ($p < 0.0001$)[84].

Monoamine oxidase A (MAO A)

Chromosome: X; location: Xp11.3

The monoamine oxidase (MAO) is a mitochondrial enzyme that degradetes 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 activity[47]. There was no association between the polymorphism and OCD EcoRV in a meta-analysis[40]. 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[91]. The most studied polymorphism in the COMT gene is an exchange of single nucleotide (SNP) (val 158met 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 enzyme[92-94]. 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 plasma[95], 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 catabolism[96,97], with subsequent increase in the availability of dopamine[96,98,99], 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 2003[100] 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 women[101]. This finding was replicated in the third meta-analysis that included published case-control and family-based studies[40]. However, a fourth meta-analysis, with only studies based on families, also found no association with OCD[102]. Studies related to the COMT are described in table 5.

A common feature among BDNF, NKTR, 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 4. Association studies between obsessive-compulsive disorder and the gene of monoamine oxidase-A

Study design	Genotype	Population	Phenotype	Sample Cases/Controls	Results	Reference
FB	Exon 8 T/G	North American	OCD OCD + TD *vs.* OCD – TD	110 families 25 families	Allele G as a risk factor for OCD in men *(p* = 0.02) Allele G as a risk factor for OCD (*p* = 0.0004)	(150)
FB CC	Exon 8 T/G	North American	OCD	51 families 122/124	Allele T as a risk factor for women with OCD (CC: *p* = 0.02; FB: *p* = 0.02)	(160)
CC	MAO-Au VNTR	Korean	OCD	121/276	Higher frequency of the 3 repeats allele in men with OCD	(47)
CC	Exon 14 T/G (EcoRV)	Afrikaners	OCD	71/129	NS	(165)

MAO-A: monoamine oxidase-A, OCD: obsessive-compulsive disorder; NS: nonsignificant, CC: case-control; FB: family-based.

Table 5. Association studies between obsessive-compulsive disorder and the gene of catecol O-methyltransferasis

Study design	Population	Phenotype	Sample Cases/Controls	Results	Reference
CC	White South Africans	Hoarding	298/307	NS	(136)
CC	Israeli	OCD + EQZ	113 OCD + EQZ /79 OCD/171 controls	NS	(168)
CC	White North Americans	OCD	73/148	LL Genotype and the L allele as risk factors for OCD in men (*p* = 0.0002)	(149)
FB	White North Americans	OCD	110 families	L Allele as risk factor for OCD in men (*p* = 0.008)	(150)
FB	Canadian and North American	OCD	67 families	Homozygosis for both alleles as risk factor for OCD (p = 0.006)	(169)
CC	White South Africans	OCD	54/54	Heterozygosis as risk factors for OCD (*p* = 0.002)	(170)
FB	Israeli + French + North American	OCD	56 families	L Alelle as risk factor for OCD in women (*p* = 0.05)	(151)
CC	Japanese	OCD	17/35	NS	(171)
CC	Turkish	OCD	59/114	NS	(172)
CC	Turkish	OCD	79/202	NS	(23)
CC	Dutch	OCD	320 cases	LL genotype protects against "Tabu" dimension of OCD symptoms (*p* = 0.06)	(173)
CC	Dutch and North American	OCD	373/462	Higher frequency of L allele in women from control group	(155)
CC	Dutch	OCD	87/327	Higher frequency of the L allele in men with OCD	(101)
FB	Chinese	OCD	103 trios	NS	(20)
CC	Dutch	OCD	159/151	Association between L allele and men with OCD (*p* = 0.035)	(51)

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 relatd 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), rs1059004 (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. 2 = 6.426, p = $\chi 2$ = 5.255, p = 0.022) and the MOG4 haplotype C1334T.MOG2. C10991T.MOG4: 1.13.2.2 (Zai *et al.* found a preferential transmission of the 459-bp allele (allele 2: 0.011)[110]. Atmaca *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 telated 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[111] patients with OCD and 250 controls and found an association between OCD and the A allele from the -238 A/G polymorphism (Chi2 = 12.05, p = 0.0005), the A allele of the -308 G/A polymorphism (Chi2 = 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[122].

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 rs34535804 SNP and haplotype of ESR1 five SNPs were significantly associated with extent of contamination/cleaning (p = 0.0001) and the frequency of the haplotype rs34535804 * 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[49,50,57]. OCD also is genetically linked to Tourette syndrome[139,140] which was associated with dopamine-related genes such as the gene for dopamine D2 receptor (DRD2)[141-143], dopamine receptor D4 (DRD4)[144], dopamine transporter (DAT)[145], and monoamine oxidase A (MAO-A)[144]. 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[16,17,51,85,101, 146-155]. The same is seen when the sample is divided according to age at onset of TOC[18,20,56,68,86,153,156]. These two characteristics are used to group individuals with OCD in more homogeneous subgroups[131].

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 OCD[157]. The definition of endophenotypes by neuroimaging studies, neurophysiology and neuropsychology are essential in guiding genetic studies[157].

Conclusion

The amount of available data does not allow us to pinpoint a gene responsible for the etiology of OCD. Establishing groups with more homogeneous 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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