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Genetics of early-onset obsessive-compulsive disorder — Source link

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REVIEW

Genetics of early-onset obsessive–compulsive disorder

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Abstract Obsessive–compulsive disorder (OCD) is characterized by recurrent, intrusive and disturbing thoughts as well as by repetitive stereotypic behaviors. Epidemiological data are similar in children and adults, i.e., between 1 and 3% of the general population suffer from OCD. Children with OCD are often seriously impaired in their development. OCD, especially of early onset, has been shown to be familial. Several candidate genes of predominantly neurotransmitter systems have been analyzed and a total of three genome-wide linkage scans have been performed until now. Analyses of candidate genes in linkage regions have not provided evidence for their involvement in OCD, with the exception of the glutamate transporter gene *SLC1A1* on 9p24. Genome-wide association analyses are in progress and the results will promote further independent replication studies. The consideration of subtypes regarding age of onset, symptom dimensions and/or comorbid disorders is needed.

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Introduction

Obsessive–compulsive disorder (OCD) is a heterogeneous psychiatric disorder characterized by clinically significant recurrent, intrusive and disturbing thoughts (obsessions) as well as by repetitive stereotypic behaviors, which are usually associated with anxiety or dread (compulsions). OCD affects up to 3% of the population and an early age of symptom onset has been observed in many patients [18, 38, 49]. According to the National Comorbidity Survey Replication, OCD has a median age at onset of 19 years, with 21% of all cases starting by the age of 10 years [27]. Furthermore, OCD often follows a chronic course and has a poor long-term prognosis. Pooled mean persistence rates were 41% for full OCD and 60% for full or subthreshold OCD [48]. Kessler et al. [27] have found OCD to be the anxiety disorder with the highest percentage (50%) of serious cases. Converging evidence from various lines of research supports a causal role of the cortico-basal ganglia-thalamo-cortical loops that involve the orbitofrontal cortex and the anterior cingulate cortex. A review of the neurobiology of OCD is given by Grados and Wilcox [19] in their research update of genetics in OCD.

Formal genetic findings

Twin and family studies have led to a better understanding of the contribution of both genetic and environmental factors to the development of OCD. Knowledge of the

formal genetic aspects of OCD is a prerequisite for the understanding of the results of numerous molecular genetic studies.

Twin studies

There are only a very limited number of twin studies regarding early-onset OCD and OC symptoms (see Table 1). In a study of anxiety-related behaviors, Eley et al. [15] observed a heritability of OC behavior of 0.65 in 4,564 preschool twins. Hudziak et al. [26] studied the Child Behaviour Checklist Obsessive Compulsive Scale (CBCL-OCS) in a sample of the Netherlands Twins Registry (NTR) and in a second sample of the Missouri Twin Study. In the NTR sample, the authors assessed twin pairs, whose parents reported on their behavior via CBCL when they were 7, 10 or 12 years of age. A total of 4,246, 2,841 and 1,562 twin pairs were available for analysis at ages 7, 10 and 12 years, respectively. The 10- and 12-year-old samples were subsets of the 7-year-old sample. In the Missouri Twin Study sample, the twins were aged 8.8–9.5 years. A total of 1,461 twin pairs were available for the analysis of CBCL-OCS. Analysis of the twin correlations yielded evidence for the influence of both genetic and environmental factors. Across age groups and the two cultures (Netherlands and USA), the additive genetic influence on the CBCL-OCS varied from 45 to 58%. The variance accounted for by non-shared environmental factors ranged from 42 to 55%. Only in the 12-year-old group of the NTR sample, the magnitude of the shared environmental influences was about 16%.

Based on DSM-IV criteria, Bolton et al. [10] recently investigated a community sample of 854 6-year-old twins (see Table 1), whose mothers were interviewed after positive screening at age 4 using a maternal-informant composite questionnaire on anxiety related behaviors and tics. The study aimed to address whether individual differences in early-onset OCD, tics and anxiety disorders show familial aggregation effects due to either genetic or environmental influences. For the final analysis, a child was assigned a "symptom syndrome" on meeting the full DSM-IV symptom criteria for the disorder regardless of the degree of impairment, defined by the interview schedule rules [Anxiety Disorders Interview Schedule for Children and Parents (ADIS-C/P)]. To maximize the numbers, a phenotype termed "subthreshold for symptom syndrome" was also included (for more details see Bolton et al. [10]. Additive genetic effects accounted for 29% of the variance of the OCD phenotype including subthreshold cases. The estimation of familial effects due to both combined additive genetic effects and shared environmental factors, which could not be distinguished in this study, was 47%. In this pediatric population, significant within-twin associations between OCD and tics as well as OCD and anxiety disorders were observed.

A review of the findings based on twin studies of children and adults was compiled by Van Grootheest et al. [50]. The authors concluded that the heritability for obsessive–compulsive symptoms ranges from 0.45 to 0.65 in children and from 0.27 to 0.47 in adults.

Family studies

First-degree relatives of patients with OCD have elevated rates of OCD as well as anxiety, mood, attention deficit/hyperactivity and tic disorders. In earlier studies, family members were not investigated using standardized interviews. Familial rates were described using the family history method with one person (the index patient) or, in the case of children, with the mother or father providing

Table 1 Twin studies of early-onset OCD or OC symptoms

Number of twins	Age at investigation (years)	Heritability	Instruments	Studies
4,564	4	0.65 for OC behavior	Mother-reported anxiety-related behaviors	Eley et al. [15]
4,246[a]	7[a]	0.45–0.58	CBCL-OCS[b]	Hudziak et al. [26]
2,841[a]	10[a]			
1,562[a]	12[a]			
1,461[c]	8.8–9.5[c]			
854	6	0.47 for subthreshold OCD	DSM-IV ADIS-C/P[d]	Bolton et al. [10]

[a] The Netherlands sample was divided into three age groups

[b] CBCL-OCS: Child Behaviour Checklist Obsessive–Compulsive Scale

[c] Missouri Twin study, average age of 9 years

[d] Anxiety disorders interview schedule for children and parents

information about all first-degree relatives. Although this kind of assessment probably underestimated the rate of affected relatives, the findings suggested that OCD was familial. Since the 1980s, direct interview studies have been performed, investigating as many first- and second-degree family members as possible. Family studies showed that first-degree relatives of patients with OCD were affected by OCD considerably more frequently than relatives of healthy control subjects (see Table 2).

Family studies based on children and adolescents with OCD

Among the parents of children with severe OCD, Lenane et al. [30] detected OCD in 25% of the fathers and in 9% of the mothers. Riddle et al. [45] reported that 15 out of 21 (71%) OCD children had a parent with either OCD ($N = 4$) or obsessive–compulsive symptoms ($N = 11$). Chabane et al. [11] did not find elevated rates of OCD among family members of patients with an age of onset of >16 years. These authors concluded that some children with OCD may show a high degree of familiality, while a considerable number show no familiality. Hanna et al. [21] examined first- and second-degree relatives of 35 children with OCD and of 17 healthy controls. The lifetime prevalences of definite OCD were significantly higher in first-degree relatives than in control relatives (22.5% vs. 2.6%; ratio: 8.65). The difference between case and control first-degree relatives increased on inclusion of subthreshold OCD (27.4% vs. 2.6%), yielding a relative risk of 10.54. In contrast to these findings based on first-degree relatives, there were no significant differences between case and control second-degree relatives. This study, however, probably underestimated the true rate of OCD in second-degree relatives, since the majority of them were not directly interviewed. According to the same study of Hanna et al. [21], an increase in lifetime OCD and subthreshold OCD was observed in relatives of patients with ordering compulsions compared to the relatives of OCD patients without these compulsions (45.4% vs. 18.8%). Furthermore lifetime prevalence of definite OCD was significantly higher in the case of first-degree relatives with a history of tics than in the case of first-degree relatives without a tic history (57.1% vs. 20.9%).

Among family studies based on children with OCD, Rosario-Campos et al. [14] also reported a high rate of first-degree relatives affected by OCD (22.7%). The average age of the index patients was very low (onset less than 7 years) in comparison to the age of index patients in other family studies (see Table 2). Moreover, the age of onset of OCD in the index patients was correlated with that in the affected first-degree relatives [14]. In this study, the patients had high co-morbidity rates with Tourette syndrome (33%) and tic disorders (13.2%).

In contrast, an earlier study of Reddy et al. [44] reported a prevalence rate of 4.96% in first-degree relatives of

Table 2 Familiality in children and adults with OCD

OCD in first-degree relatives of index patients with onset ≤18 years (%)	OCD in first-degree relatives of index patients with onset >18 years (%)	OCD in first-degree relatives of controls (%)	Studies
25 in mothers			Lenane et al. [30][a]
9 in fathers			
8.8			Bellodi et al. [7]
	2.5	2.3	Black et al. [8]
	4.9		Nicolini et al. [39]
19			Riddle et al. [45][a]
52[b]			
10.3		1.9	Pauls et al. [42][c]
7.9[b]		2.0[b]	
11.7	0	2.7	Nestadt et al. [38]
4.96		0	Reddy et al. [44][a]
	3.5		Albert et al. [1]
22.7		0.9	do Rosario-Campos et al. [14][a]
29.2[d]		2.4[d]	
16.1	2.9		Chabane et al. [11][a]
22.5		2.6	Hanna et al. [21][a]
27.4[d]			

[a] Studies performed in samples ascertained through children with OCD

[b] Subthreshold OCD using DSM-III-R

[c] 82% of the patients had an onset prior to 18 years of age

[d] Including subthreshold OCD using DSM-IV

juvenile patients with OCD (aged 16 years or less), while no OCD was observed among the relatives of controls. In contrast to other studies, none of the siblings of the index patients received a diagnosis of OCD and none of the first-degree relatives had subthreshold OCD. The authors concluded that most juvenile cases of OCD were non-familial and unrelated to tic disorders. A limitation of this study was the small sample size (35 patients and 34 age-matched controls). Furthermore, the authors discussed that their findings of a relatively low rate of OCD in the first-degree relatives could be related to the only moderate clinical symptomatology and the relatively short duration of the illness in their index patients.

Family studies based on adults with childhood or adolescent-onset OCD

Bellodi et al. [7] investigated families based on index patients whose OCD commenced at different ages (21 patients with age of onset of <14 years of age, and 71 patients with age of onset of >14 years of age). The risk for OCD of all first-degree relatives was 3.4% and increased to 8.8% when patients had an onset of OCD earlier than 14 years of age. Pauls et al. [42] interviewed all available first-degree relatives of 100 patients, whose OCD onset was mainly in childhood and adolescence: 82 reported onset of OCD symptoms at or before the age of 18 years. OCD and subthreshold OCD were significantly more frequent in the patients' families in comparison to families of healthy controls (10.3 and 7.9% and 1.9 and 2.0%, respectively). The rate of OCD and subthreshold OCD was approximately twice as high among the relatives of the patients with early-onset as compared with the relatives of patients with late-onset OCD (20.1% vs. 10.9%). It is of note that most of this difference was due to the more common occurrence of subthreshold OCD among the relatives of the cases. Pauls et al. also found that first-degree relatives of patients with OCD had higher frequencies of tic disorders (4.6%) than relatives of the controls (1%). Nestadt et al. [38] reported an OCD prevalence rate of 11.7% in first-degree relatives of OCD patients and of 2.7% in relatives of controls. There were no affected first-degree relatives of patients with an OCD onset after the age of 17 years.

The comparatively high familiality in early versus late OCD [1, 8, 39] is illustrated in Table 2 based on both childhood and adult index patients. The wide range of prevalence rates of OCD in first-degree relatives across different studies merits discussion. Heterogeneity of the phenotype, the absence of a control group, the young age of siblings in studies of childhood OCD patients and too few directly interviewed relatives may result in over/underestimation of the prevalence of OCD in relatives. Investigators were in some studies not blinded with respect to whether or not they were assessing relatives of cases or controls or relatives of patients with early- versus late-onset of OCD [7, 44, 45].

Molecular genetic findings in OCD

Linkage studies

Three genome-wide linkage studies of OCD have so far been published. In two of these studies, the samples were ascertained through patients with early-onset OCD (<18 years of age, Hanna et al. [22, 23]). In all three studies, no significant genome-wide evidence for linkage was detected according to standard guidelines for linkage studies [28]. However, several loci displayed suggestive evidence for linkage and have provided valuable starting points for follow-up association studies.

The first genome scan was performed by Hanna et al. [22]. These authors analyzed 56 family members from seven pedigrees, each ascertained via a child with OCD. Of the relatives, 27 also had a lifetime diagnosis of OCD. As much as 349 microsatellite markers were used (with an average between-marker distance of 11.3 cM). The maximum multipoint LOD (logarithm of the odds) score was found to be 2.25 on 9p24 (marker D9S288) using a dominant model. Evidence for linkage to 9p24 was also supported by Willour et al. [58], who in order to replicate the findings of Hanna et al. [22] genotyped 50 pedigrees based on OCD index patients (42 sib pairs, 8 trios; altogether 193 subjects), using microsatellite markers spanning only the 9p24-region [58]. These authors found their strongest results for two markers (D9S1792, D9S1813) located within 0.5 cM of the initial marker D9S288 [22]. Although the eight trio pedigrees were not informative for the linkage analysis, they were included in the 9p24 association analysis, which identified two markers (D9S288 and GATA62F03) with p-values of <0.05 (Willour et al. [58]) using the pedigree-disequilibrium test. It is noteworthy that 93% of the probands of this study had an early age of onset (<16 years of age), which was comparable to that (<14 years of age) in the sample of Hanna et al. [22].

Shugart et al. [46] studied a sample of 219 families (sib pairs and extended families). Multipoint analysis uncovered several suggestive linkage signals on chromosomes 3q27–28, 6q, 7p, 1q and 15q. Covariate linkage analyses implicated a possible role of a gene variant(s) on chromosome 1 in increasing the risk for an early-onset form of OCD [46]. The authors differentiated between the broad and narrow phenotypes and found linkage to 3q27–28 using the broad phenotype definition, which included definite and probable cases of OCD. The 3q27–28 region

harbors, among others, the serotonergic genes *HTR3C* (5-hydroxytryptamine [serotonin] receptor 3, family member C), *HTR3D* and *HTR3E*. Hanna et al. [23] undertook another genome-wide linkage scan based on a total of 121 subjects, who were ascertained through 26 independent index patients with "early-onset" OCD (onset of OC symptoms before the age of 18 years). The maximum nonparametric log of odds (NLOD) score was 2.43 on chromosome 10p15 (marker D10S1745). However, the NLOD score on 10p15 decreased to 1.8 on inclusion of the data of their first genome scan [22]. Family-based association tests conducted with 35 SNPs in the 10p15 region provided evidence for association and linkage disequilibrium with three adjacent single-nucleotide polymorphisms (SNPs) in the 3′ region of the adenosine deaminase acting on RNA 3 gene (*ADAR3*). Interestingly, drosophila deletion mutants lacking ADAR activity have been observed to spend an inordinate amount of time in grooming throughout their life span [40]. The second highest NLOD score was 1.54 on chromosome 1 (at 126 cM), which was approximately 45–50 cM proximal to the region 1q implicated in the genome scan of Shugart et al. [46].

Association studies

As described above, linkage studies have implicated several chromosomal regions, but the results have mostly been inconsistent. Only SNPs in the glutamate transporter gene *SLC1A1* on 9p24 have been found to be associated with OCD, as based on a linkage finding. Otherwise, association studies have primarily focused on neurobiologically and pharmacologically plausible candidate genes such as *SERT* [*SLC6A4*], *HTR1D*, *HTR2A*, *HTR2C*, *DRD4*, *DRD2*, *SLC1A1*, *GRIN2B*, *GABBR1*, *COMT*, *MAOA*, *TPH1*, *TPH2*, *BDNF*, *NTRK2*, *OLIG2* and *MOG*. Two reviews including candidate gene studies have recently been published by Pauls et al. [41] and Grados and Wilcox [19]. In contrast to both these publications, the next paragraph will focus on results based on children with OCD (see Table 3).

Serotonergic system

Selective serotonin re-uptake inhibitors block the serotonin transporter (SERT) and represent the most effective pharmacological treatment for OCD. Most association studies in OCD have therefore investigated serotonergic genes. The most frequently studied gene is *SERT* [*SCL6A4*] with its functional polymorphism in the upstream region termed 5-HTTLPR, which involves an insertion (L-[long] allele)/deletion (S-[short] allele) polymorphism. In comparison with the S-allele, the L-allele has been reported to exert an increased transcriptional activity and an increased basal re-uptake of 5-HT in vitro [24, 31, 37]. The L-allele is therefore referred to as the gain-of-function variant of the serotonin transporter. Bloch et al. [9] reported a stratified meta-analysis investigating whether mean age of the sample (child vs. adult), ethnicity (Caucasian/Asian) and study design (case–control/family-based association studies) moderated any association. These authors found a significant association between the L-allele and OCD in family-based association studies (OR = 1.31; 95% CI: 1.02–1.69) and in studies involving Caucasian children (OR = 1.41; 95% CI: 1.00–1.99), which might point to its specificity in early-onset OCD in Caucasians. In our own sample, we found a trend toward an association between the L-allele and early-onset OCD [53].

The 5-HTTLPR has been functionally refined by subdividing L-alleles into the high-functioning L_A-alleles and low-functioning L_G-alleles. When this new classification is used, approximately 5–10% of L-alleles (depending on ethnicity) are low functioning and need to be grouped with the S-alleles for comparison purposes [25]. In our own sample of early-onset OCD patients, we observed a significant overtransmission of the L_A-allele to affected offspring in 104 trios ($p = 0.0054$, OR = 2.06; Wendland et al. under review [57]).

Serotonin receptor subtypes

The so-called HTR2 family consists of G-protein coupled receptors known as HTR2A and HTR2C. They are primarily associated with phospholipase C, which catalyzes the hydrolysis of phosphatidylinositol bisphosphate (PIP2) and generates the second messenger molecules inositol triphosphate 3 (IP3) that mobilizes calcium from intracellular stores resulting in PKC activation and diacylglycerol (which potentiates PKC activation). PKC regulates numerous processes of cell function. For example, PKC activation causes a reduction in 5HT uptake capacity by phosphorylation and sequestration of 5HT transporter proteins [3]. The HTR2 subcategories have a widespread distribution in the brain [3].

Studies regarding association studies of the *HTR2A* polymorphisms (13q14–q21) in early-onset OCD are rare. In our sample of children and adolescents with OCD, we found in a case–control study an association of the A-allele of the −1438A/G (rs6311) locus with OCD [54]. These results pointed in the same direction as those of Enoch et al. [16, 17]. These authors also described a correlation between the −1438A-allele and a retrospectively determined early onset of the disease [16, 17]. The results of these studies were more pronounced in female patients [17, 54].

The novel brain-specific tryptophan hydroxylase-2 (TPH2), the rate-limiting enzyme in 5-HT synthesis in the brain, was studied for association in OCD [35]. In this first study of *TPH2* in OCD, rs4570625 and rs4565946 were significantly overtransmitted as a G–C haplotype in

Table 3 Results of association studies and meta-analyses in early-onset OCD

Patient group, study design	Gene SNP or variant	Association	Studies
Children/adolescents, case control	**5-HT2A** −1438A/G rs6311	Positive	Walitza et al. [54]
Adults with early onset[a], case control	**5-HT2A** −1438A/G rs6311	Positive	Enoch et al. [16, 17]
Children/adolescents, family based	**5-HTTLPR** L-allele	Only a trend	Walitza et al. [53]
Meta-analysis adults and children, case control and family based	**5-HTTLPR** L-allele	Positive for Caucasian children and in family-based studies	Bloch et al. [9]
Children/adolescents, family based	**5-HTTLPR** L_A-allele	Positive	Wendland et al. under review [57]
Children/adolescents, family based	**TPH2** rs4570625 rs4565946	Overtransmission	Mossner et al. [35]
Children/adolescents, family based	**DRD4 VNTR** 4-repeat allele	Undertransmission	Walitza et al. [52]
Children/adolescents, family based	**COMT** Val158Met rs4680	No association	Walitza et al. [52]
164 triads including 38 children and adolescents	**BDNF** Val66Met rs6265	Positive	Hall et al. [20]
Children/adolescents, family based	**BDNF**	No association	Mossner et al. [36]
138 adults and 19 children/adolescents, family based	**SLC1A1** rs301434	Positive	Arnold et al. [6]
Children/adolescents, family based	**SLC1A1** rs3780412 rs301430	Overtransmission	Dickel et al. [13]
Children/adolescents	**SLC1A1** rs3780412 rs2228622 haplotype including rs12682807 rs20772657 rs3011430	Overtransmission to male offspring Positive association	Stewart et al. [47]

[a] The patients retrospectively had predominately reported an early onset of OCD

children and adolescents with OCD. Moreover, a trend toward preferential transmission of the C-allele of rs4565946 in affected offspring was found. The genotype relative-risk estimate for homozygous C-allele carriers of rs4565946 was 2.58 (95% CI: 0.98–6.82).

Dopaminergic system

Obsessive–compulsive disorder patients, who are non-responders to SSRIs, sometimes show clinical improvement following low-dose neuroleptic treatment, suggesting a dopaminergic role in OCD and therefore justifying the investigation of dopamine-related candidate genes. Several studies analyzed the variable number of tandem repeats (VNTR) of the dopamine-receptor D4 (*DRD4*) gene based on a 48-base pair repeat in exon III. In early-onset OCD, the most commonly observed four-repeat allele was found to be undertransmitted in trios, while no significant finding was observed for the seven-repeat allele [52]. Catecholamine-*O*-methyltransferase (*COMT*) is an

enzyme involved in the metabolism of dopamine and a key modulator of dopaminergic neurotransmission. A G > A substitution in codon 158 of *COMT* (Val158Met, rs4680) causes a three- to four-fold reduction of COMT activity and has been extensively studied for its association with OCD. We detected no evidence of transmission disequilibrium for *COMT* in early-onset OCD [52]. Another study of 261 adult patients with OCD (reported age at onset range: 2–51 years, mean age at investigation: 17.8 years) described an association of early-onset OCD and Met/Met genotype of *COMT* in a symptom cluster termed "Obsessional/checking" according to the Yale-Brown Obsessive–Compulsive Symptoms Checklist [33]. This symptom cluster included sexual, religious, somatic and harm-related obsessions as well as a variety of related compulsions (e.g., checking).

Glutamatergic system

The neuronal glutamate transporter gene (*SLC1A1*) on 9p24 is one of the few candidate genes for OCD that was investigated due to its localization within a linkage peak (see above). The role of this glutamate transporter gene in OCD is supported by the observation that the anti-glutamatergic drug riluzole can be beneficial in the treatment of OCD [43] and by the finding of elevated glutamate levels in the cerebrospinal fluid of OCD patients [12]. Shortly before *SLC1A1* was proposed as a 9p24 positional candidate, Veenstra-VanderWeele [51] performed a mutation screen and family-based association of *SLC1A1* with primarily negative results. Five years later, Arnold et al. [6] detected an association of several markers spanning *SLC1A1* with OCD in a sample of mostly adults and Dickel et al. [13] in children and adolescents. The association of *SLC1A1* with OCD was corroborated at the haplotype and single-marker level by three other studies [32, 47, 56]. It should be noted, however, that all of the five positive *SLC1A1* association studies in OCD used markers that only partially overlapped, and the findings regarding some of the few markers that were genotyped in more than one study were not consistently replicated. This inconsistency and the fact that the association described by Stewart et al. [47] in children and Wendland et al. [56] in adults pertains to haplotypes suggest that there are additional functional and possibly causal variants within the *SLC1A1* region for OCD. It should further be noted that SLC1A1 also acts as a cysteine transporter and that transgenic mice with the disrupted orthologous gene *Slc1a1* display grooming abnormalities with increasing age [4]. It is also noteworthy that Arnold et al. [5] have reported an association of a glutamatergic receptor gene (*GRIN2B*) with early-onset OCD. Further studies of glutamatergic neurons and SLC1A1, in particular, are therefore warranted in early- and adult-onset OCD.

Neurotrophic factors and transcription factors

Brain-derived neurotrophic factor (BDNF) promotes neuronal proliferation, regeneration and connectivity during development and participates in the plasticity and maintenance of neurons throughout adulthood. In addition, the neurotrophic tyrosine kinase (Trk) receptor type 2 (NTRK2) is highly linked to the activation of BDNF. Of special interest is the *BDNF* Val66Met (rs6265) polymorphism, since this substitution may either influence the processing of the mature form or affect the interaction of the secreted and extracellularly processed pre–pro form with p75 NTR, thus modulating apoptotic signaling through this alternate pathway. Hall et al. [20] studied a number of four SNPs including Val66Met (rs 6165) spread over a distance of 56 kb at the *BDNF* gene in 164 triads with OCD. They described evidence of association for all the markers. This finding is also of interest because the sample included 38 cases of early-onset OCD. Only in the group of early-onset OCD and in the total group, but not in the group consisting only of late-onset OCD, significant associations were observed. However, later studies did not find an association between OCD and BNDF [2, 36, 55, 59].

Additional evidence for the possible involvement of neurotrophic pathways stems from the association of two SNPs in the 3′ downstream region of *NTRK2* (rs1017412 and rs7176429) with OCD (OR = 2.16 and 2.78, respectively) [2].

The gene for oligodendrocyte lineage transcription factor 2 (*OLIG2*), located on 21q22.11, is an essential regulator in the development of human cells that produce white matter (myelin). In a family-based association study, three SNPs (rs762178, rs1059004 and rs9653711) within *OLIG2* were associated with OCD without Tourette syndrome [47]. This finding awaits confirmation in future studies.

Conclusion

Like other psychiatric disorders, OCD is a complex disorder and its pathogenesis is most likely influenced by both genetic and environmental factors. Ongoing genome-wide association studies may shed new insight into the molecular genetic etiology of OCD. Possible gene–environment interactions include the moderation by a functional polymorphism of the risk for developing OCD following exposure to a traumatic event or an effect of a functional polymorphism on the development of a personality/neurocognitive profile that may predispose a person to OCD following environmental stress. An improved understanding of the OCD phenotype and the underlying etiological mechanisms may require novel approaches in the

conceptualization of the disorder. These approaches include (1) narrowing the phenotype to identify categorically defined more homogeneous and mutually exclusive subtypes of OCD, (2) considering OC symptom dimensions as quantitative components of the more complex OCD phenotype and (3) broadening the phenotype to include other etiologically related conditions [34]. More elaborate phenotyping including age at onset, disease severity and dimensional measures [29] are therefore needed. Finally, the definition of endophenotypes through neuropsychological, neurophysiological and neuroimaging studies may contribute to the understanding of the genetic factors underlying OCD.

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