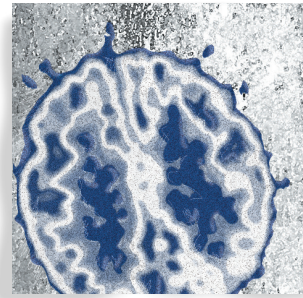# Translational research

The genetics of obsessive-compulsive disorder: a review
David L. Pauls, PhD

Obsessive-compulsive disorder (OCD) is a serious psychiatric disorder that affects approximately 2% of the populations of children and adults. Family aggregation studies have demonstrated that OCD is familial, and results from twin studies demonstrate that the familiality is due in part to genetic factors. Only three genome-wide linkage studies have been completed to date, with suggestive but not definitive results. In addition, over 80 candidate gene studies have been published. Most of these studies have focused on genes in the serotonergic and dopaminergic pathways. Unfortunately, none have achieved genome-wide significance, and, with the exception of the glutamate transporter gene, none have been replicated. Future research will require the collaboration of multidisciplinary teams of investigators to (i) achieve sufficiently large samples of individuals with OCD; (ii) apply the state-of-the-art laboratory techniques; and (iii) perform the bioinformatic analyses essential to the identification of risk loci.

Obsessive-compulsive disorder (OCD) is a prevalent psychiatric disorder that is characterized by disabling obsessions (intrusive unwanted thoughts and/or images) and/or compulsions (ritualized repetitive behaviors).[1] OCD was originally thought to be rare, but a number of studies have reported a lifetime prevalence that ranges between approximately 1% to 3% worldwide.[2-3] Thus, it is one of the more common and serious mental conditions.[4]

Twin and family studies provide convincing evidence for the importance of genetic factors for the expression of OCD. The author has previously reviewed these data.[5] In this paper, the historic evidence is again summarized and updated with recent results. Thus, sections of this manuscript will be similar to those previously published reviews. Supporting results from twin and family aggregation studies, functional neuroimaging, pharmacological, and molecular genetic studies provide compelling data that suggest that biochemical/biological factors are important for the manifestation of OCD.

Twin studies

Twin studies are useful in determining whether genetic factors are important in the etiology of complex disorders. The difference in concordance rates between monozygotic and dizygotic twins can be used to estimate the percentage of the phenotypic variance observed for a specific trait that can be accounted for by genetic factors.

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Translational research

There are a number of published twin studies for OCD. Results from the early studies should be interpreted with caution, given the limitations of those studies: most are case reports, others have small sample sizes, still others used different criteria to diagnose individuals, and in most cases the investigator evaluating the cotwin was not blind to the diagnosis of the index twin.

In the most comprehensive review to date, van Grootheest et al[6] summarized all published twin studies from 1929 through 2005 (Table I). Of note is that five of the six twin studies with adequate sample sizes[32-36] (~100 twin pairs or more) attempted to estimate the heritability of obsessive-compulsive (OC) symptoms, not OCD. Only two studies[29-30] were able to estimate the heritability of OCD as determined by DSM diagnostic criteria.

There have been only two additional twin study OCD published since 2005.[29-30] The first study[29] included 854 6-year-old twins who had been identified in a community sample and subsequently diagnosed using *DSM-IV* criteria with information obtained in a maternal-informant

Study type	No of twin pairs	MZ concordance	DZ concordance
Case studies			
Lange[7]	3	1/2	-
Le Gras[8,9]	1	1/1	-
Lewis[10]	3	2/3	-
Tarozzi[11]	1	1/1	-
Rüdin[12]	1	-	0/1
Tienari[13]	11	10/11	-
Parker[14]	2	0/2	-
Wooddruff & Pitts[15]	1	1/1	-
Inouye[16]	14	8/10	1/4
DSM-III/DSM-III-R OCD			
Marks et al[17]	1	1/1	-
Tarsh[18]	1	-	1/1
Hoaken & Schurr[19]	1	0/1	-
McGuffin & Mawson[20]	2	2/2	-
Carey & Gottesman[21]	30	13/15	7/15
Torgerson[22]	12	0/3	0/9
McKeon et al[23]	1	0/1	-
Mahgroub et al[24]	1	1/1	-
Kim et al[25]	1	1/1	-
Andrews et al[26]	48	0/18	0/30
Lewis et al[27]	3	3/3	-
Cryan et al[28]	1	1/1	-
DSM-IV		MZ tetrachoric r	DZ tetrachoric r
Bolton et al[29]	854	0.57 (0.24-0.80)	0.22 (-0.02-0.43)
Tambs et al[30]			
OC behaviors		h²	
Young et al[31]	32	0	
Torgerson[32]	99	0.18 (men); 0.23(women)	
Clifford et al[33]	419	0.44(traits); 0.47(symptoms)	
Jonnal et al[34]	527	0.33(obsessions); 0.26(compulsions)	
Eley et al[35]	4 564	0.65 (OC behavior)	
Hudziak et al[36]	4 246	0.45 – 0.61	

Table I. Twin studies of OCD.

interview. This was the first study with sufficient sample size to adequately evaluate the influence of genetic factors on OCD, not just OC symptoms in the general population of twins. The Bolton et al[29] findings are consistent with the majority of studies with sufficient sample sizes *(Table I)* in that the results support the hypothesis that genetic factors play a significant role in the etiology of OC behaviors as well as OCD.

In addition, these investigators also examined the relation between OCD and two commonly occurring comorbid disorders: tic disorder and anxiety disorders. Their findings support the hypothesis that there are shared etiologic factors for OCD and tics, as well as OCD and other anxiety disorders, and are consistent with the hypothesis that there may be different subtypes of OCD that may have different underlying risk factors.[37-41] This hypothesis will be discussed in more depth in the Family Studies section below.

The second study, published in 2009,[30] obtained data from 2801 young-adult Norwegian twins by means of the Composite International Diagnostic Interview (CIDI). This study examined the heritability of five anxiety disorders (Generalized Anxiety Disorder, Panic Disorder, Phobias, Obsessive-Compulsive Disorder, and Post-Traumatic Stress Disorder.) Valid anxiety data were available for 1385 twin pairs; however, there were only 57 pairs where one twin had a diagnosis of OCD. Because the prevalence of OCD was so low in this sample, the investigators included individuals who met criteria or subthreshold OCD (the number of pairs where at least one had a diagnosis of OCD or subthreshold OCD was 165). The estimate of heritability was 29%. However, these investigators reported that 55% of this heritability was due to a common factor shared by all five anxiety disorders. On the other hand, 45% appear to be due to factors that were specific to OCD.

In summarizing the studies published prior to 2006, van Grootheest and colleagues[6] concluded that "in children, obsessive-compulsive (OC) symptoms are heritable, with genetic influences in the range of 45% to 65%. In adults, studies are suggestive for a genetic influence on OC symptoms, ranging from 27% to 47%…" The findings from the two most recent studies[29,30] are remarkably similar when cotwins who met criteria for subclinical OCD were included in the analyses. Both studies reported that additive genetic effects accounted for 29% of the variance for OCD and subclinical OCD. In the Bolten study,[29] familial aggregation due to combined additive genetic and shared environmental effects accounted for 47% of the phenotypic variance. Unfortunately, these investigators were unable to estimate the effects of additive genetic and shared environmental separately.[29]

Family studies

Numerous family studies on OCD and obsessional neurosis have been published since 1930 *(Table II)*. Results from the majority of these studies demonstrate that at least some forms of OCD are familial, and the findings from twin studies summarized above provide evidence that this familiality is due in part to genetic factors. However, it is also evident that environmental/cultural factors influence OC behaviors and are also transmitted within families.[29] These nongenetic factors unquestionably influence the manifestation of OC behaviors as evidenced from twin studies that consistently demonstrate that the concordance rate of MZ twins for OC behaviors and OCD is always less than 1.0. Understanding the impact of these environmental/cultural factors will be critical to the eventual elucidation of the risk factors important for the manifestation of complex disorders such as OCD. However, while it is clear that genes alone will not explain all of the observed inheritance of OCD, demonstrating familiality is an important step for the eventual determination of the importance of genetic risk factors.

Family history studies

Studies in which all diagnostic data about family members are obtained from one or two informants are referred to as family history studies. Prior to 1987, all studies of the familiality of OC illness and/or OC features relied on family history data. It has been shown that, in general, family history data yields underestimates of the true rates of illness within families.[42-43] Hence, it is significant that these early family history studies reported findings suggesting that OC illness and/or OC features were familial *(Table II)*. An important shortcoming of all of these early studies was that no control samples were obtained to estimate the rate of OC illness or OC features in the general population. Thus, all of these data need to be interpreted with that caveat in mind.

In only one study,[49] results were reported that were not consistent with OC illness and/or features being familial. In this study, a relative was considered affected only

if they had been hospitalized for OC illness. Using this criterion, no significant increase of OC illness among first-degree relatives of 144 obsessional neurotics was observed, although an increased rate of psychiatric illness among these relatives was reported. Unfortunately, no information about OC symptomatology among relatives who were not hospitalized was provided.

Direct interview family studies

Subsequent to 1986, all family studies collected direct interview from at least some of the relatives in the family. With the exception of one study,[52] all available relatives were directly interviewed. In the study by McKeon and Murray[52] all family members of adult probands with OCD were given the Leyton Obsessional Inventory

(LOI), and only those relatives who scored high on the LOI were directly interviewed. Only one of the interviewed relatives met criteria for OC neurosis, suggesting that the disorder is not familial.

It is possible that some relatives with OCD may not have been identified with this ascertainment scheme. Low scores on the LOI can be observed in individuals having only a few obsessions and/or compulsions which consume significant time and cause considerable distress and result in a diagnosis of OCD. Thus, it is possible that some of the noninterviewed relatives could have scored low on the LOI yet still met criteria for a diagnosis of OCD. In should be noted, however, that these investigators did observe an increased rate of mental illness overall among the relatives of these OCD probands.

The remaining 15 family studies of OCD interviewed all

Family history studies	Obsessive-compulsive illness	Obsessive-compulsive features	Controls	
Luxenburger[44]	0.08	0.08	---	
Lewis[45]	---	0.327	---	
Brown[46]	0.073	---	---	
Rüdin[47]	0.040	0.070	---	
Kringlen[48]	0.198		---	
Rosenburg[49]	0.004	---	---	
Insel et al[50]	0	0.150	---	
Rasmussen & Tsuang[51]	0.045	0.114	---	
Adult family studies	**OCD**	**Subclinical OCD**	**OCD**	**Subclinical OCD**
Mckeon & Murray[52]	0.007	---	0.007	
Bellodi et al[53]	0.034	---	---	---
Black et al[54]	0.025	0.156	0.023	0.029
Nicolini et al[55]	0.049	---	---	---
Pauls et al[38]	0.103	0.079	0.019	0.020
Nestadt et al[56]	0.117	0.046	0.027	0.030
Albert et al[57]	0.035	---	---	---
Fyer et al[58]	0.062	0.084	0	0
Lipsitz et al[59]*	0.026	0.057	0.013	0.013
Grabe et al[60]**	0.064	0.055	0.012	0.030
Child family studies	**OCD**	**Subclinical OCD**	**OCD**	**Subclinical OCD**
Lenane et al[61]	0.170	---	---	---
Riddle et al[62]	0.095	---	---	---
Leonard et al[63]	0.130	---	---	---
Reddy et al[64]	0.050	---	0	---
Chabane et al[65]	0.170	---	---	---
Hanna et al[40]	0.225	---	0.026	---
Rosario-Campos et al[41]	0.227	0.065	0.009	0.015

Table II. Family studies of OCD. The rates shown refer to the frequency of these conditions among first-degree relatives.
Adapted from ref 5: Pauls DL. The genetics of obsessive compulsive disorder: a review of the evidence. *Am J Med Genetics C: Sem Med Genet*. 2008;148:133-139. Copyright © Wiley-Liss 2008

available first-degree relatives with structured psychiatric interviews.[38,40-41,53-65] In some of these studies, additional information was obtained from all interviewed relatives about the presence of OCD in all of their first-degree relatives; even those relatives that had been directly interviewed. Thus, both direct interview data and family history data were available for all interviewed individuals in those family studies.

While there were some inconsistent results, most of these studies provided data that are consistent with the hypothesis that some forms of OCD are familial *(Table II)*. In seven studies ascertainment was through children and/or adolescents with OCD *(Table II)*. In the remaining eight studies, ascertainment was through adults with OCD *(Table II)*.

Studies of families ascertained through child/adolescent probands

In all of the studies in which all available relatives of children and/or adolescents with OCD were interviewed,[40-41,61-65] the rates of OCD and subclinical OCD were significantly higher than the population prevalence and/or the rate obtained in controls assessed in the same way. While the frequency of OCD and subclinical OCD differed within families across studies, the overall conclusion was the same: OCD and subclinical OCD are familial. Furthermore, the recurrence risks within these families were considerably higher than the rates observed in families ascertained through adults (see below). While the rate of OCD among relatives of adults with OCD was approximately two times that among controls, the rate of OCD among relatives of children and adolescents with OCD was increased approximately 10-fold in those studies where comparison with controls was possible.

Studies of families ascertained through adult probands

The results from studies of families ascertained through adults with OCD in which all available relatives were interviewed were not as consistent as those family studies of child and/or adolescent probands summarized above. As noted above, the study by McKeon and Murray[52] did not observe an increased rate of OCD among relatives of adult OCD probands. In addition, Black et al[54] reported results of a study examining 120 first-degree relatives of 32 adult OCD probands and 129

relatives of 33 psychiatrically age-matched normal controls. This was the first controlled study of OCD in which all relatives were assessed using structured interviews and all interviewers were blind to the diagnostic status of the proband. *DSM-III* criteria were used to assign all diagnoses from the direct interview data. While family history data had been obtained from all interviewed relatives about other first-degree relatives, none of those data were included in the diagnostic process. These investigators reported an age-corrected rate of *DSM-III* OCD of 2.5% among relatives of probands compared with 2.3% in controls. These data suggest that OCD is not familial. However, when a more broadly defined OCD was used in the analyses the rate among parents of OCD probands was 15.6%. In contrast to the rate among the parents of control individuals was 2.9%. It is noteworthy that these investigators also reported an increased rate of non-OCD anxiety among the relatives. It is possible that, since in this study only direct interview data were used in the diagnostic process, the estimated recurrence risks could have been biased. Lipsitz et al[59] examined whether using informant information influenced the recurrence risk estimates. In most family studies of OCD diagnoses are based on all direct interview and family history data collected from informants in the family. When only data from the direct interviews were used to assign diagnoses, there was not a significant increase in the occurrence of OCD among the relatives. The rate of OCD and subclinical OCD for interviewed relatives when no informant information was used in the diagnostic process was 5.4% compared with 1.7% among controls (*P*=0.17). On the other hand, the rate of OCD and subclinical OCD among interviewed relatives when additional informant data were used was 8.9% compared with only 1.7% among controls (*P*=0.02). These investigators concluded that "evidence of familial transmission of OCD was found only when diagnoses were made using information from the proband about the relative." As an explanation for these differences, these authors suggest that since individuals with OCD can be quite secretive about their symptoms, it is possible that upon direct interview, they might deny OC symptomatology. This could be particularly important in the case when the individual being interviewed has never sought treatment for their OC symptoms. On the other hand, it is also possible that an affected relative who has sought treatment or proband may "over-report" symptoms in their relatives. In the Lipsitz et al[59] study, family history informa-

tion was only collected from the affected probands, all of whom had sought treatment, so it is possible that there was "projection" of their own behaviors onto their relatives, resulting in over-reporting of affected status. However, in other studies where family history data were collected from all interviewed relatives,[3,8,56] information was collected from both affected and unaffected relatives, and therefore it is less likely that there would be over-reporting of OC symptomatology, since unaffected relatives would not be "projecting" their own behavior onto their relatives. Of note is that in the study of Lipsitz et al,[59] an increased rate of other non-OCD anxiety disorders was observed. Finally, Black and colleagues did report that a number of family members were reported to have OC symptomatology by their relatives. Thus, it is possible that, if all available information had been used to assign diagnoses, the recurrence risk for OCD among first-degree relatives could have been higher than reported.

All of the remaining studies of families ascertained through adult individuals with OCD provide evidence that OCD is a familial disorder.[38,53,55-58,60] In these studies, the rate of OCD among relatives of affected individuals was significantly higher than either the estimated population prevalence or rate among controls. In the most recently published study,[60] the investigators ascertained affected individuals from both a population sample and a clinic sample. They observed a significant increase in both relatives of individuals who were ascertained through an OCD clinic and individuals who were identified through a population study of OCD. The study by Grabe et al was the first controlled study of OCD in Europe, and confirmed the results of earlier studies completed in the US[38,56,58] with families ascertained through treatment facilities. The finding that relatives of both clinic patients and individuals identified in a population based study is important. As the authors nicely summarize, "the finding of a comparable familial aggregation of definite OCD and a higher familial aggregation of subclinical OCD in relatives of never treated persons with OCD from the community strongly supports the impact of familial-genetic factors in OCD."

Associated conditions

As noted in the discussion of twin studies, a number of investigators have examined family data to test the hypothesis that other disorders may be significantly increased among relatives of OCD probands. Additional analyses of the Hopkins OCD Family Study[56] were reported.[66-67] Bienvenu et al[66] explored OC-spectrum disorders among proband relatives and found significantly higher rates of BDD (OR=5.4), somatoform disorders (OR 3.9), grooming disorders (OR=1.8), and all spectrum disorders combined (OR=2.7). Similarly, Grados et al[67] explored OCD comorbidity and found an increased prevalence of tic disorders among proband relatives versus control relatives. There was also an association between earlier age of OCD onset and tic comorbidity. These findings are consistent with those reported earlier.[29,38,41] These findings suggest that there may be at least three different types of OCD: (i) one that is inherited and related to TS; (ii) one that is inherited and not related to TS but possibly related to anxiety; and (iii) one that is not familial.

In sum, these studies of OCD probands and their relatives cumulatively provide strong evidence that some but possibly not all forms of OCD are familial. This was confirmed in a meta-analysis of five family studies of OCD probands published prior to 2001 involving 1209 first-degree relatives[68] in which a significantly increased risk of OCD among relatives of probands was observed (Mantel-Haenszel summary OR=4.0 (95% CI=2.2-7.1)). The unadjusted aggregate risk for relatives of OCD probands was 8.2%, compared with 2.0% for relatives of relatives. Although these family study findings are consistent with a genetic etiology of OCD, by themselves they only demonstrate that OCD is familial; not that genetic factors are necessary for the manifestation of the illness. However, taken together with the evidence from twin studies, there is compelling evidence that genetic factors play an important role in the manifestation of some forms of OCD.

Segregation analyses

Given that the majority of studies demonstrated that OCD is familial, and twin studies suggest that this familiality is in part due to genetic factors, the next step has been to examine whether the mode of transmission in these families can be explained by specific genetic models. Complex segregation analyses allow an examination of specific genetic models by estimating the "goodness-of-fit" of the pattern of transmission specified by an hypothesized genetic model to that of the observed patterns of transmission within families. While complex segregation analyses do not prove the existence of genes

that are associated with OCD, results of these analyses can reveal patterns of transmission within families that may be helpful in future molecular genetic studies.

To date, four complex segregation analyses of OCD transmission in families ascertained through OCD probands have been reported.[69-72] All studies provided evidence that the transmission of OCD within families is consistent with genetic transmission. However, the genetic model that best explained the transmission within families differed from study to study. Given the variability of recurrence risks observed in the family studies and the clinical heterogeneity that is evident in OCD, this result is not surprising. Nevertheless, it is noteworthy that the conclusions of the authors in all of these reports were that there are some genes of major effect important for the manifestation of OCD. Given the variability in the estimates of recurrence risks in the reported studies, it is quite likely that OCD is an oligogenic disorder (ie, a number of genes are important for the expression of the disorder).

In addition to advances in understanding regarding familiality and genetic mechanisms that are likely to be involved in OCD, there have also been dramatic gains in our understanding of the phenotype of OCD. Perhaps most important for genetic research are new ways to assess the phenotype dimensionally, moving beyond traditional categorical diagnostic classifications. Over the last decade, results from a number of independent studies have demonstrated that there are different clusters of symptoms that comprise the OCD phenotype[73-77] and that they appear to be heritable.[73,76] It follows then that there may be several genes that could influence the different components of OCD.

Candidate gene studies

Given current theoretical understanding of mechanisms that may be implicated in the emergence and maintenance of OCD symptoms and the treatment of the disorder, a number of investigators have pursued genetic studies of specific genes that are known to be involved in systems implicated in the pathogenesis of OCD. In particular, because of the efficacy of serotonin reuptake in treating OCD,[78-79] a number of genes important in the serotonergic system have been examined. In addition, genes in the dopaminergic, glutamatergic, and opioid systems have also been studied to determine if they also contribute to the risk of OCD.[80]

Over 80 candidate gene studies have been published over the last decade *(Table III)*. As noted above, association studies have examined candidate genes that function within the serotonergic and dopaminergic systems and more recently the glutamatergic system based on knowledge of the pathophysiology and pharmacology of OCD. However, with the exception of the glutamate transporter gene *SLCL1A1*,[81-84] none have been consistently replicated. While some of the more recent published studies have larger sample sizes, all have inadequate sample sizes to achieve genome-wide significance (ie, 5×10^{-8}). Some recent studies have moved beyond simply documenting that individuals with OCD are more likely to have a specific allele or candidate gene that other nonaffected individuals (ie, association studies) and have begun to explore the function of some of the genes being studied. Preliminary results suggest that may be a promising approach.[85] However, none of these studies have yet been replicated, so it is too early to reach any definite conclusions.

Given the complexity of the OCD phenotype, it is highly unlikely that any of the candidate genes examined to date will be significant, unique risk factors for OCD. Thus, although they may truly be associated with the onset, severity, or persistence of OCD symptoms, they are unlikely to cause OCD without the presence of other risk genes. On the other hand, since most current effective pharmacologic agents target the serotonergic and dopaminergic systems, it is possible that some of the genes in those systems could play a role in treatment response. Knowing which genes impact treatment response would be a major advance in the treatment of OCD and is consistent with the primary goal of the emerging field of pharmacogenetics. However, it would not necessarily demonstrate that those genes are involved in the etiology of OCD. Genes involved in response to treatment may not be involved in the etiology of a disorder.

Genetic linkage studies

Only three genome-wide linkage studies of OCD have been completed to date.[135-137] No study yielded genome-wide significance; however all studies suggested regions of interest for future research. Hanna et al[136] completed a genome scan on seven families which included 66 individuals. All families had been identified through childhood OCD probands. All but one of the relatives were

Candidate gene	Investigator	Study design	Sample size			Significance	Associated allele
			Cases	Controls	Families		
Serotonin transporter							
	McDougle et al[86]	FB	---	---	35	P<0.03	L allele
	Bengel et al[87]	CC	75	397	---	P=0.023	LL genotype
	Frisch et al[88]	CC	75	172	---	ns	---
	Kinnear et al[89]	CC	54	82	---	ns	---
	Denys et al[90]	CC	156	134	---	ns	---
	Dickel et al[91]	FB	---	---	54	ns	---
	Saiz et al[92]	CC	99	420	--	ns	---
	Wendland et al93	CC	347	749	---	ns	---
	Wendland et al[84]	CC	295	657	--	P<0.018	3 marker haplotype
Serotonin transporter promoter							
	Kinnear et al[94]	CC	129	479	---	ns	---
	Camarena et al[95]	CC/FB	115	136	43	ns	---
	Cavallini et al[96]	CC	180	112	---	ns	---
	Walitza et al[97]	FB	---	---	63	ns	---
	Meira-Lima et al[98]	CC	79	202	---	ns	---
	Chabane et al[99]	CC/FB	106	171	86	ns	---
Serotonin receptor 2A							
	Nicolini et al[100]	CC	67	54	---	ns	---
	Enoch et al[101]	CC	62	144	---	P<0.05	A allele
	Enoch et al[102]	CC	101	138	---	P=0.015	A allele
	Frisch et al[88]	CC	75	172	---	ns	---
	Walitza et al[103]	CC	55	223	---	ns	---
	Hemmings et al[104]	CC	71	129	---	ns	---
	Tot et al[105]	CC	??	??	---	ns	---
	Hemmings et al[106]	CC	58	83	---	ns	---
	Meira-Lima et al[98]	CC	79	202	---	P<0.00007	C - Allele
	Denys et al[90]	CC	156	134	---	ns	---
	Dickel et al[91]	FB	---	---	54	ns	---
	Saiz et a[92]	CC	99	420	---	P=0.02	---
Serotonin receptor 2C							
	Cavallini et al[107]	CC	109	107	---	ns	---
	Frisch et al[88]	CC	75	172	---	ns	---
	Meira-Lima et al[98]	CC	79	202	---	ns	---
	Cavallini et al[107]	CC	109	107	---	ns	---
	Frisch et al[88]	CC	75	172	---	ns	---
	Meira-Lima et al[98]	CC	79	202	---	ns	---
Serotonin receptor 1B (1Dβ)							
	Mundo et al[108]	FB	---	---	32	P<0.006	G allele
	Mundo et al[109]	FB	---	---	121	P=0.023	G allele
	DiBella et al[110]	FB	---	---	48	ns	---
	Hemmings et al[104]	CC	77	129	---	ns	---
	Camarena et al[111]	FB	---	---	47	ns	---
	Walitza et al[97]	FB	---	---	63	ns	---

Table III. Candidate gene studies of OCD. *Association with the hoarding phenotype
Adapted from ref 134 (and updated through 11/2009): Hanna GL, Veenstra-VanderWeele J, Cox NJ, et al. Genome-wide linkage analysis of families with obsessive-compulsive disorder ascertained through pediatric probands. *Am J Med Genet.* 2002;114:541-552. Copyright © Wiley-Liss 2002

Candidate gene	Investigator	Study design	Sample size			Significance	Associated allele
			Cases	Controls	Families		
	Denys et al[90]	CC	156	134	---	ns	---
	Dickel et al[91]	FB	---	---	54	ns	---
Tryptophan hydroxylase							
	Frisch et al[88]	CC	75	172	---	ns	---
	Walitza et al[97]	FB	---	---	63	ns	---
	Mössner et al[112]	FB	---	---	71	P=0.035	G-C Haplotype
Dopamine receptor 4							
	Cruz et al[113]	CC	12	49	---	P= 0.018	
	Billet et al[114]	CC	118	118	---	P= 0.021	
	Frisch et al[88]	CC	75	172	---	P=0.04	7 allele less frequent
	Millet et al[115]	CC/FB	49	63	34	P=0.03	2 allele protective
	Hemmings et al[104]	CC	71	129	---	ns	---
	Hemmings et al[106]	CC	95	85	---	P=0.013	early vs late onset
Dopamine receptor 2							
	Nicolini et al[100]	CC	67	54	---	ns	---
	Billet et al[114]	CC	110	110	---	P=0.014	CC genotype
Dopamine receptor 3							
	Catalano et al[116]	CC	97	97	---	ns	---
	Nicolini et al[100]	CC	67	54	---	ns	---
	Billet et al[114]	CC	103	103	---	ns	---
Dopamine transporter							
	Billet et al[114]	CC	103	103	---	ns	---
	Frisch et al[88]	CC	75	172	---	ns	---
	Hemmings et al[104]	CC	71	129	---	ns	---
Dopamine receptor 2							
	Nicolini et al[100]	CC	67	54	---	ns	---
	Billet et al[114]	CC	110	110	---	P=0.014	CC genotype
Dopamine receptor 3							
	Catalano et al[116]	CC	97	97	---	ns	---
	Nicolini et al[100]	CC	67	54	---	ns	---
	Billet et al[114]	CC	103	103	---	ns	---
Dopamine transporter							
	Billet et al[114]	CC	103	103	---	ns	---
	Frisch et al[88]	CC	75	172	---	ns	---
	Hemmings et al[104]	CC	71	129	---	ns	---
Monamine oxidase A							
	Karayiorgou et al[117]	FB	---	---	110	P=0.019 (males)	G allele
	Camarena et al[95]	CC/FB	122	124	51	CC: P=0.024 FB: P=0.022	T allele
	Hemmings et al[104]	CC	71	129	---	ns	---
Catechol O-methyl transferase							
	Karayiorgou et al[118]	CC	73	148	---	P=0.0002	L allele in males
	Karayiorgou et al[117]	FB	---	---	110	P=0.0079	L allele
	Schindler et al[119]	FB	---	---	67	P=0.006	L allele

Table III. Continued

directly assessed with structured psychiatric interviews and 32 received diagnosis of lifetime OCD.

Three hundred forty-nine microsatellite markers were genotyped on these families. Twenty-four additional markers included in the fine-mapping subsequent to the initial genome scan. In the initial analyses a LOD score of 2.25 for marker D9S288 on chromosome 9p was observed. However, after finemapping the LOD score dropped to 1.97. In general, LOD scores above 3.6 are considered to be genome-wide significant.

In an attempt to replicate these findings, Willour et al[138] genotyped microsatellite markers on all available relatives in 50 pedigrees which had been ascertained through persons with OCD. The largest LOD scores observed in this study were for markers D9S1792 (HLOD=2.26) D9S1813 (NPL=2.52, P=0.006). D9S1813 and D9S1792 are within 350 kb of marker D9S288, the marker yielding the largest LOD score reported by Hanna et al.

The second genome-wide linkage study included a total of 219 families. Both affected sib-pair and multigenerational families were genotyped.[136] Suggestive evidence was observed for susceptibility loci on chromosomes 3q, 7p, 1q, 15q, and 6q. The strongest linkage evidence was obtained for markers on chromosome 3q27-28 when both definite and probable cases of OCD were considered affected. The maximum overall Kong and Cox LODall score (2.67) occurred with markers D3S1262

Candidate gene	Investigator	Study design	Sample size			Significance	Associated allele
			Cases	Controls	Families		
	Niehaus et al[120]	CC	54	54	---	P=0.0017	HL genotype
	Alsobrook et al[121]	FB	---	---	56	P=0.048	L allele in females
	Ohara et al[122]	CC	17	35	---	ns	---
	Erdal et al[123]	CC	59	114	---	ns	---
	Azzam et al[124]	CC	144	337	---	ns	---
	Meira-Lima et al[98]	CC	79	202	---	ns	---
	Katerberg et al[125]	CC	373	462	---	ns	---
Glutamate receptor subtype 2B	Arnold et al[126]	FB	---	---	130	P=0.002	5072G-5988T haplotype
Kainite glutamate receptor 2	Delorme et al[127]	CC/FB	156	156	141	CC: ns FB: P=0.03	867I allele undertransmitted
Gamma-Amino-butyric acid type B receptor 1	Zai et al[128]	FB	---	---	159	P=0.006	A-7265G
Brain-derived neurotropic factor							
	Hall et al[129]	FB	---	---	164	P<0.020	Multiple SNPs
	Dickel et al[91]	FB	---	---	54	ns	---
	Wendland et al[93]	CC	347	749	---	ns	---
Myelin oligo-dendrocyte							
	Zai et al[130]	FB	---	---	160	P=0.022	MOG4 2-repeat allele
Glutamate transporter							
	Arnold et al[81]	FB	---	---	157	P=0.006	2 marker haplotype (males)
	Dickel et al[82]	FB	---	---	71	P=0.030	2 marker haplotype (males)
	Stewart et al[83]	FB	---	---	66	P=0.0015	3 marker haplotype
	Wendland et al[84]	CC	325	662	---	P<0.001	3 marker haplotype
Oligo-dendrocyte lineage transcription factor 2	Stewart et al[131]	FB	---	---	66	P=0.004	5 marker haplotype
Neurotrophin-3 receptor gene (NTRK3)*	Muiños-Gimeno et al[132]	CC	153	324		P=0.005	---
Extraneuronal monoamine transporter, EMT (SLC22A3)	Lazar et al[133]	CC	84	204		ns	---

Table III. Continued

(P=0.0003) and D3S2398 (P=0.0004). The method proposed by Kong and Cox estimates the degree of allele sharing between affected individuals and provides using a maximum likelihood approach. When there is no linkage there should be no allele sharing greater than expected by chance.

In a second set of analyses of 219 families, Samuels et al[139] examined whether compulsive hoarding behavior was linked to different markers across the genome. These investigators reported suggestive evidence for linkage for D14S588 (KAC(all)=2.9) on chromosome 14. When families which included two or more hoarding relatives were analyzed separately, the Kong and Cox LODall score increased to 3.7.

In the third genome-wide linkage study,[137 121] individuals in 26 multigenerational families were genotyped with markers with an average spacing of 10 centimorgans (cM). (Note: a centimorgan is defined as the distance on a chromosome in which 1% crossing over occurs. Given the success of the human genome project, this metric is rarely used any more, since it is now possible to determine precisely the number of base pairs between markers.) As in the first study published by these investigators,[135] all relatives were assessed with a semistructured psychiatric interview, and best estimate lifetime psychiatric diagnoses were made using data from these interviews and all other available sources of information. The maximum nonparametric LOD (NLOD) score observed was 2.43 for markers on chromosome 10p15. When data from Hanna et al's first genome scan were analyzed together with the current marker data, the maximum NLOD score in the 10p15 region was decreased to 1.79. These investigators followed up the linkage findings with a family-based association analysis which examined 35 single-nucleotide polymorphisms (SNPs) in this 10p15 region. Association was detected on 10p15 with three adjacent SNPs, including the amino acid variant rs2271275 in the 3' region of adenosine deaminase acting on RNA 3 (ADAR3) (P<.05).

All of these findings should be interpreted with caution. The sample sizes in all three studies were quite small. Nevertheless, given that Willour et al[138] observed suggestive linkage to the same chromosome 9p region as reported by Hanna et al is noteworthy. In addition, as discussed above, four independent studies have reported an association of OCD and the glutamate transporter which is located in this region on 9p. Thus, the findings from the two studies by Hanna and colleagues[135,137] and

the one reported by Willour et al[138] suggest that there may be a susceptibility locus in this region of 9p. Unfortunately, this region did not show any evidence for linage in the study completed by Shugart et al.[136]

Future work

The twin and family studies summarized in this review demonstrate that at least some forms of OCD have a genetic basis. However, given that none of the linkage studies and essentially all of the candidate genes studies provide only suggestive evidence for risk genes of moderate-to-large effect, whole-genome association studies of OCD are warranted as the next step in our understanding of the genetic basis of the disorder. Whole-genome association studies are preferred over more traditional linkage studies or candidate gene studies because they provide more power to identify risk genes of relatively small effect. The primary difference between genome-wide linkage studies and genome-wide association studies (GWASs) is that with linkage the investigator is looking for cotransmission of a specific DNA marker within a family, while in a genome-wide association study the investigator is looking for a population association between a DNA marker and disease. Linkage studies are better suited to identifying genes that have large effects, and GWASs are better when attempting to identify genes that have relatively small effects on the phenotype. These GWASs should examine both common markers as well a copy number variants and other rare genetic events. It is becoming evidence that complex disorders may be "caused" by both rare genes of major effect and a combination of common genes of lesser effect.

Given the limited state of knowledge about the pathophysiological pathways important for the manifestation of OCD, it is premature at this time to restrict focus on the association of specific candidate genes with OCD. Instead, a GWAS with a sample of sufficient size is the most promising approach for the identification of genomic regions that most likely harbor OCD risk genes. Once these regions have been identified, then more informed candidate gene studies could be undertaken. Given the variability of recurrence risks and the results from the most recent twin study, it is clear that, like other neuropsychiatric conditions, OCD is etiologically heterogeneous. Given this high likelihood of etiologic heterogeneity, it is critical to study a sufficiently large sam-

ple of affected individuals so that homogeneous clinical subgroups more likely to be etiologically homogenous can be identified from within the larger sample.[140-141] In order to obtain these large samples, it is imperative that investigators interested in the genetics of OCD collaborate. A collaboration of this type (the International OCD Foundation Genetics Collaborative) is currently conducting a GWAS of OCD on samples contributed from 21 different research sites from around the world. ❑

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La genética del trastorno obsesivo-compulsivo: una revisión

El trastorno obsesivo-compulsivo (TOC) es un serio trastorno psiquiátrico que afecta aproximadamente al 2% de la población de niños y adultos. Los estudios de agregación familiar han demostrado que el TOC es familiar y los resultados de los estudios en gemelos demuestran que el carácter familiar se debe en parte a factores genéticos. A la fecha se han terminado sólo tres estudios del ligamiento de genoma completo, con resultados sugerentes, pero no definitivos. Además, se han publicado más de 80 estudios de genes candidatos. La mayoría de estos estudios se han focalizado en genes de las vías serotoninérgica y dopaminérgica. Lamentablemente, ninguno de ellos ha logrado una significación para el genoma completo y, con excepción del gen del transportador de glutamato, ninguno ha sido replicado. La investigación a futuro requerirá de la colaboración de equipos multidisciplinarios para: 1) conseguir muestras suficientemente grandes de individuos con TOC, 2) aplicar las técnicas de laboratorio más actualizadas y 3) realizar los análisis bioinformáticos esenciales para la identificación de los loci de riesgo.

Génétique du trouble obsessionnel compulsif : revue de la littérature

Le trouble obsessionnel compulsif (TOC) est un trouble psychiatrique grave affectant environ 2 % de la population enfant et adulte. Des études d'agrégation familiale ont montré que le TOC est d'origine familiale, le résultat d'études sur les jumeaux ayant mis en évidence que le caractère familial serait dû en partie à des facteurs génétiques. Seules trois études de liaison du génome entier sont terminées à ce jour, avec des résultats évocateurs mais pas définitifs. De surcroît, plus de 80 études sur les gènes candidats ont été publiées. La plupart des études se sont intéressées aux gènes des voies sérotoninergiques et dopaminergiques. Malheureusement, aucune n'a pu être significative sur génome entier et, mis à part le gène transporteur du glutamate, aucune n'a pu être reproduite. La recherche ultérieure nécessitera la collaboration d'équipes pluridisciplinaires d'investigateurs pour 1) obtenir des échantillons suffisamment importants de sujets atteints de TOC ; 2) appliquer des techniques de laboratoires optimales ; et 3) réaliser des analyses bio-informatiques essentielles à l'identification des loci à risque.

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