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Genetics of Obsessive-Compulsive Disorder and Related Disorders

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Synopsis

Twin and family studies support a significant genetic contribution to obsessive-compulsive disorder (OCD) and related disorders such as chronic tic disorders, trichotillomania, skin picking disorder, body dysmorphic disorder, and hoarding disorder. Recently, population-based studies and novel laboratory-based methods have confirmed substantial heritability in OCD. Genome-wide association studies and candidate gene association studies have provided information on specific genes that may be involved in the pathobiology of OCD and also of related disorders, particularly chronic tic disorders, though these genes each contribute only a small portion of the total genetic risk and a substantial portion of the specific genetic risk profile in OCD is still unknown. Nevertheless, there are some examples of genes for which perturbations produce OCD-like phenotypes in animal model systems, allowing a laboratory platform for investigating the pathobiology of --- and new treatments for --- OCD and related disorders. Future work promises to continue to clarify the specific genes involved in risk for OCD as well as their interaction with environmental variables.

Keywords

OCD; genetics; heritability; twin study; familial recurrence; GWAS; candidate gene; model system

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Overview

Obsessive-compulsive disorder (OCD) is a disorder that can onset during childhood or during adult life. As a result, OCD is a disorder of interest to both child and adult psychiatrists. There are several other disorders that either commonly co-occur with OCD or have overlapping or similar features and symptoms. Tourette syndrome (TS) is characterized by the presence of both motor and vocal tics that onset in childhood and last at least 12 months. A related condition, chronic tic disorder (CT; defined by the presence of motor tics or vocal tics, but not both, and also lasting more than one year) is thought to be an alternate phenotype to TS and shares genetic and biological underpinnings with TS. There is a substantial body of literature focused on the twin, familial and genetic aspects of TS and CT a summary of which is presented elsewhere in this issue in the article “Tics and Tourette’s Disorder” by Shaw and Coffey. Of relevance here is that chronic tic disorders (TS and CT) are often seen in conjunction with childhood-onset OCD. This is reflected in the recent addition of a *tic-related* specifier for OCD in DSM-5. Other OCD related disorders beyond TS and CT, namely trichotillomania (TTM), skin picking disorder, body dysmorphic disorder, and hoarding disorder, occur across the lifespan. While compared to TS and CT there is less specific genetic evidence that these other related disorders share pathobiology with OCD there is growing evidence that overlapping genetic risk factors do exist across OCD, TTM, skin picking disorder, body dysmorphic disorder, and hoarding disorder.

The earliest studies to support a role for genetic factors in OCD demonstrated a higher concordance rate for OCD among monozygotic twins compared to dizygotic twins. While fewer studies have focused on TTM, skin picking disorder, body dysmorphic disorder, and hoarding disorder, there is emergent evidence that some portion of risk for these related disorders is also rooted in genetic factors. These twin studies and subsequent family studies provide estimates of heritability in OCD and related disorders as high as 50%. Recently, powerful population-based epidemiological studies and new molecular methods have confirmed significant heritability, indicating that genetics contribute substantially to risk for these disorders. Because OCD and related disorders show substantial heritability, familial recurrence risk is high. Over the past several years, several genome-wide association studies (GWAS), candidate gene association studies and other studies have identified specific gene variants that seem to contribute to risk for OCD and related disorders. Each variant likely contributes only a small percentage of total risk, indicating that many different gene variations compose the genetic risk architecture for these disorders. Much of the specific genetic risk for OCD remains unknown. Nevertheless, there are examples of genes for which perturbations produce OCD-like phenotypes in animal model systems, allowing a laboratory platform to study the pathobiology and treatment of OCD and related disorders. Future work promises to continue to clarify the specific genes involved in risk for OCD as well as their interaction with environmental risk architecture.

Twin Studies and Heritability of OCD

Although the familial nature of many core features of OCD is apparent to most seasoned clinicians the first formal evidence for a genetic contribution to OCD came in 1965 from a case series that found monozygotic twins had a higher concordance for OCD than dizygotic

twins.[1] Earlier studies had examined concordance rates in twins, but this was first to compare the concordance rates between monozygotic twins, so-called “identical twins” who share all their genes, and dizygotic twins, so-called “fraternal twins”, who share on average about 50% of their genes. A higher concordance rate among monozygotic twins compared to dizygotic twins is thus indicative of a significant genetic basis for the disorder under study.

Follow-up studies have consistently found monozygotic twins to have higher concordance rates for OCD and obsessive-compulsive (OC) symptoms than dizygotic twins, confirming an important genetic contribution to OCD (Table 1).[2-8] Beyond formal OCD diagnoses, a recent study determined that monozygotic twins have higher concordance than dizygotic twins on 5 obsessive-compulsive symptom dimensions.[9] From these studies, heritability estimates have ranged from 27-65%.[10] Early twin studies on OCD typically had small sample sizes, were likely adversely influenced by ascertainment bias, and often utilized sub-optimal statistical analysis. A more robust approach, Structural Equation Modeling (SEM), is a newly developed multivariate approach, that allows for more conclusive evidence about heritability rates.[9] To date, the largest and most statistically robust twin study found a monozygotic twin concordance rate of 0.52 and a dizygotic concordance rate of 0.21, with overall heritability for OCD estimated to be 48%.[8]

Twin Studies and Heritability of Related Disorders

There are few twin studies of TTM, skin-picking disorder, BDD and hoarding disorder. With such a limited body of evidence it is difficult to draw substantial conclusions about heritability, genetic architecture and risk for these disorders. The field awaits larger and thus more decisive studies. Renewed interest in trans-diagnostic symptoms/phenotypes may be an innovative way forward to understand genetic risk factors. Available studies are summarized here.

Trichotillomania

To date, only two studies have compared TTM concordance rates between monozygotic and dizygotic twins.[8,11] Both studies found a significant difference in concordance rates based on DSM-IV criteria for TTM. One study estimated heritability to be 76%.[11] Interestingly, there were no significant differences between monozygotic and dizygotic twin pairs for either skin-picking or hair manipulation, suggesting that different genetic mechanisms may underlie those two behaviors compared to TTM. Another study estimated heritability to be only 32%,[8] and did find TTM and skin-picking disorder to be clustered in cross-trait correlations.

Skin-picking Disorder

One group has shown skin-picking disorder concordance rates to be higher in monozygotic than dizygotic twin pairs.[6,8] In a population-based study comparing concordance rates of persistent skin picking disorder in female monozygotic and dizygotic twin pairs, the heritability estimate was 40%.[6] A follow-up study found a slightly higher heritability with an estimate of 47%.[8]

Hoarding Disorder

The Twins UK registry was used to assess the genetic correlation of hoarding disorder.[8,12] There was a greater correlation between monozygotic than between dizygotic twins for two of the main features of hoarding: difficulty discarding and excessive acquisition. The estimated heritability for these traits was 45% and 49% respectively.[12] The overall heritability for hoarding disorder was estimated to be 51%.[8] In contrast, another study found that hoarding had the least amount of genetic liability compared to other OC symptom dimensions.[9] Interestingly, a Swedish study of 1,987 twin pairs found a greater correlation of hoarding in male monozygotic pairs than male dizygotic pairs (0.44 vs. 0.17), but no difference in concordance between female monozygotic and female dizygotic twin pairs, suggesting a gender effect may impact risk.[13]

Body Dysmorphic Disorder

Only one study has compared monozygotic and dizygotic twin concordance rates for body dysmorphic disorder (BDD). This study found higher concordance rates for monozygotic twins than dizygotic twins and estimated heritability at 43%.[8] Another study compared the genetic and environmental covariance between BDD and OCD traits.[14] In a sample of 1,074 twin pairs, recruited from the Twins UK adult twin registry, 64% of the phenotypic correlation between OCD and BDD was explained by shared genetic factors. When examining specific OCD symptom dimensions (using the Obsessive-Compulsive Inventory - Revised), 82% of the correlation between symmetry/ordering symptoms and the obsessing dimensions were explained by common genetic factors. Modeling in a follow-up study suggests that OCD, hoarding disorder, and BDD are clustered together.[8] These results suggest a partial genetic overlap for OCD and BDD.

Familial Recurrence Risk in OCD and Related Disorders

The likelihood that a biologically-related family member, such as a child, will be affected with a disorder that is already present in a family is captured in recurrence risk. While recurrence risk is derived from the study of families and not the study of genes or DNA, it is not uncommon to interpret recurrence risk as a proxy for genetic risk for a disorder. If substantial familial recurrence risk is documented in conjunction with twin and/or other family studies this provides a solid rational for follow up molecular genetic analyses. For OCD, a large number of studies have included first-degree family members of individuals with OCD or related disorders in order to estimate the recurrence rates, typically by administering structured interviews such as the Structured Clinical Interview for DSM or the Schedule for Affective Disorders and Schizophrenia and assigning diagnoses by best-estimate diagnostic procedures.[15] These studies, which range in size from about 30 probands with OCD to over 300 probands with OCD and all available first-degree relatives, have estimated recurrence risk among first-degree relatives for lifetime OCD as low as 6% to as high as 55%, with the majority of estimates falling between about 10 and 20%.[16-22] These estimates are significantly higher than the lifetime prevalence for OCD in the general population, which is estimated to be 0.7-3%,[23,24] and in each study the familial recurrence risk in affected families was significantly higher than the risk for OCD among relatives of controls. One earlier and smaller study failed to find an increased risk among first-degree

family members, though when the authors considered a broader definition of OCD (including individuals who had obsessions and/or compulsions but did not meet formal criteria for OCD), family members of probands with OCD were at increased risk, with 15.6% of relatives of probands with OCD affected versus 2.9% of relatives of controls.[25] Indeed, when OC symptoms and behaviors are considered as a broader phenotype, familial recurrence risk estimates are even higher among first-degree family members of probands with OCD.[16,18,20,21] Taken together, the increased risk for OCD and OC behaviors among first-degree relatives of individuals with OCD strongly supports a significant genetic contribution to both sub-diagnostic OC symptoms and OCD itself.

Additionally, there is evidence that pediatric-onset OCD may have a higher degree of familial aggregation compared to adult-onset OCD. Several studies have found that first-degree relatives of individuals with pediatric-onset OCD have higher rates of OCD compared to first-degree relatives of those with adult-onset OCD[16,17] or that age of onset in probands is correlated with age of onset in relatives.[18] A recent review examined twelve prior studies which compared familial recurrence risk between pediatric and adult-onset probands, and found a mean odds ratio of greater than one, in support of higher risk among relatives of pediatric-onset probands.[26] Of note, each of the studies except for one had confidence intervals for the odds ratio that included one, and indeed not all studies have agreed that age of onset of OCD is associated with familiality.[20] Thus is it possible that genetic factors play a greater role in pediatric-onset OCD compared to late-onset OCD, but more research needs to be done to clarify this possibility.

Multiple studies have also supported the familial relationship between OCD and several related disorders including body dysmorphic disorder, TTM, and other grooming disorders such as pathologic nail biting and pathologic skin picking. For example, it has been reported that first-degree relatives of probands with OCD are more likely than relatives of controls to have each of these disorders, with estimates of risk among relatives of probands with OCD as high as 6% for body dysmorphic disorder, 4% for TTM, 15% for pathologic nail biting, and 17% for pathologic skin picking.[22,27,28] Moreover, it has been shown in two studies that first-degree relatives of individuals with chronic hair pulling have not only an increased risk for hair pulling disorders but also an increased risk for OCD, with recurrence risk estimates of 6.4% and 17%.[29,30] Moreover, one study showed that some relatives of probands with hair pulling and OCD also had both disorders, but no relatives of probands with only hair pulling had both disorders. The authors thus suggest that there may be familial subtypes of OCD that are particularly associated with certain other related disorders.[30] Finally, there is also evidence that tic disorders, specifically TS and CT, are more common among first-degree relatives of individuals with OCD compared to relatives of controls, with recurrence risk estimates ranging from approximately 4% to 14%.[17-19,22,28] Taken together, these results support the possibility of overlapping genetic risk between OCD and several related disorders.

Though the family studies described herein are valuable and have moved the field ahead in important ways, the majority of these studies have used clinic-based and other convenience (i.e., non-population-based) samples, rendering them vulnerable to ascertainment bias and questionable generalizability. Moreover, the relatively small sample sizes result in low

precision with associated wide confidence intervals and variability between studies. An approach that has become available only in recent years to circumvent these issues is to use national health registries, available in several countries such as Denmark and Sweden. These national registries provide a wealth of data for epidemiologic analyses including refined examination of familiality with high precision and very low ascertainment bias. One recent such study, for example, accessed Swedish registries to identify over 24,000 individuals with OCD with matched controls from a total population of over 13 million, as well as all first, second, and third-degree relatives. The authors showed with high precision that recurrence risk for OCD was higher for first, second, and third-degree relatives of probands with OCD compared to risk in the family members of controls. Moreover, risk was higher in first-degree relatives than second-degree relatives, and higher in second-degree relatives than third-degree relatives. Recurrence risk estimates were on the lower end of previous reports, as seen from the family studies described above, with odds ratios of approximately 4.5-5 for first-degree relatives. The authors also assessed risk in family members of pediatric-onset probands compared to adult-onset probands, reporting that relatives of pediatric-onset probands had slightly but non-significantly higher familial risk, lower than what has been reported in previous studies.[7] A similar population-based study performed using Danish national registries also confirmed that having a first-degree relative (mother, father, sibling, or offspring) was a risk factor for OCD.[31] A second research group also utilizing the Danish registries focused on relative recurrence risk (RRR) which takes into account any fluctuations in population prevalence during the study period. Averaged over all birth years, the sibling RRR of OCD was 4.9 and the sibling RRR for tic disorders (TD; including TS and CT) was 18.6. When examining risk to offspring of affected parents even greater risk was documented with a parent-offspring RRR for OCD at 6.3 and for TD at 61.0 [96]. These large, unbiased studies have thus supported the familial nature of OCD and rendered strong yet indirect evidence indicative of a substantial genetic contribution to this disorder.

Heritability of OCD and Related Disorders via Novel Methods

In recent years, genetic researchers have developed methods for estimating disease heritability directly from genome-wide genotyping data through the use of linear mixed models.[32,33] Using these methods, as implemented in the statistical genetics package Genome-wide Complex Trait Analysis (GCTA) one can estimate narrow-sense heritability (h^2), i.e. the proportion of the disease phenotype that can be explained by additive genetic factors.[34] Conceptually, the method determines the amount of genome-wide shared genetic variation between case-case and control-control pairs compared to case-control pairs. Of note, this estimate represents a lower bound of the true heritability of the disorder, since it does not capture gene-gene or gene-environment interactions well and can only detect common variation of the type found in single nucleotide polymorphism (SNP) genotyping arrays (commonly known as GWAS arrays); these estimates therefore do not capture heritability attributable to (1) genomic copy number variation (see below), (2) rare to very rare genetic variation, or (3) *de novo* genetic variation. Nonetheless, it is an extremely powerful tool for complex genetic traits (such as psychiatric disorders in general and of relevance here, OCD and related disorders), as it provides direct genetic evidence of disease

heritability, which can be compared to traditional heritability estimates based on phenotypic concordance in twin or family studies.

Recently, the International OCD Foundation Genetics Consortium (IOCDFGC) and Tourette Syndrome Association International Consortium for Genetics (TSAICG) used linear mixed models to estimate the additive heritability of OCD and TS derived from GWAS data.[35] Encouragingly, both disorders were confirmed to be highly heritable (OCD h^2=0.37, SE=0.07; TS h^2=0.58, SE=0.08). In addition, these direct heritability estimates were in the same range as the twin-based heritability estimates of OCD and TS, suggesting that the vast majority of OCD and TS heritability may be explained by genetic variants captured by GWAS arrays. Davis and colleagues subsequently partitioned the genome both by chromosome and by variant frequency to further dissect the underlying genetic architecture. For TS, the genetic variation contributing to heritability appeared to be nearly equally distributed across all autosomal chromosomes, with ~80% of variation explained by "common" genetic variants that are present in at least 5% of the general population, and ~20% explained by rare variants (<5% minor allele frequency). In contrast, OCD had a marked proportion of heritability present on chromosome 15, with the remaining genetic variation equally distributed across the rest of the genome. Surprisingly, the OCD heritability appeared to be limited to common variants present in >30% of the general population. If verified in independent samples, these data together suggest that OCD and TS are both "polygenic" disorders, in that they arise due to the combination of many genetic variants (possibly hundreds or thousands), each of small to modest effect and individually present in a large proportion of the general population, but when combined together, likely in combination with rarer, large effect variation and/or non-genetic/environmental risk factors, surpass a threshold and result in disease. An extrapolation of these observations would be the prediction that individuals in the general population with non-interfering OC symptoms may carry a small number of OCD risk variants and represent one end of a continuous OC phenotypic spectrum, while individuals with clinically significant OCD lie at the other end and harbor a large number of OCD risk alleles. Future analyses in population-based cohorts will be needed to examine this hypothesis directly.[10]

Genome-wide Association Studies in OCD and Related Disorders

To date, two GWAS of OCD have been conducted (1465 cases, 5557 controls, 400 parent-proband trios in the IOCDFGC study and 1406 cases in 1065 families in the OCD Collaborative Genetic Association Study (OCGAS) GWAS) and one GWAS of TS (1285 cases, 4964 controls)[36-38] None of these studies identified a specific genetic variant in the final analysis surpassing the stringent threshold needed to achieve genome-wide significance ($p \leq 5 \times 10^{-8}$).[39,40] Scharf and colleagues identified supportive evidence for the top TS GWAS SNP variant within an intron of the collagen Type XXVIIa gene (*COL27A1*) in an additional 211 TS cases and 285 matched controls from two Latin American population isolates (combined p-value 3.6×10^{-7}).[36] Stewart and colleagues detected a genome-wide significant variant in SNP rs6131295 near *BTBD3* ($p=3.8 \times 10^{-8}$) in the subset of 400 parent-proband trios within the IOCDFGC OCD study, though this signal decreased to $p=3.6 \times 10^{-5}$ in the final meta-analysis of all samples.[37] Matthiesen and colleagues reported a top signal from the OCGAS study ($p=4.1 \times 10^{-7}$) upstream of *PTPRD*, a tyrosine phosphatase that has been

shown previously to be involved in regulation of both glutamatergic and GABAergic synapse formation.[38] Interestingly, the top signals from the initial IOCDFGC OCD GWAS were enriched in the OCGAS GWAS (p=0.018), suggesting that a subset of these variants may represent true OCD susceptibility loci.

Given the sample sizes needed to discover definitive common disease variants in other neuropsychiatric disorders, the absence of genome-wide significant results in the initial OCD, and TS, GWAS is not surprising in retrospect.[41] However, the GCTA heritability study described above provides strong evidence that additional GWAS of OCD and TS with larger sample numbers should identify definitive OCD and TS genes. The current OCD/TS results parallel early GWAS of bipolar disorder and schizophrenia in which initial experiments did not produce genome-wide significant results, yet the first definitive susceptibility genes were detected in GWAS of approximately 4000-5000 cases.[42-45] Furthermore, as a result of worldwide collaborative efforts in the Psychiatric Genomics Consortium (PGC), the most recent schizophrenia GWAS with 35,000 cases has identified 108 independent associations in 97 genes, including known drug targets (dopamine D2 receptor, *DRD2*), syndromic causes of psychosis (*TCF4*, previously known to cause Pitt-Hopkins Syndrome), and novel druggable targets (T-type calcium channel genes, *CACNA1C*).[46,47]

GWAS data have also been used to examine the genetic relationship between OCD and TS/CT. As noted above, numerous family studies have suggested that OCD and TS/CT are genetically related,[48,49] though this relationship has never been verified at the molecular level. Using linear mixed models, Davis and colleagues identified a significant genetic correlation between OCD and TS cases (r=0.41), though they could not exclude within-subject co-morbidity as the source of this shared signal.[35] A subsequent combined OCD/TS analysis also supported the presence of overlapping genetic signals between the two disorders.[50] In addition, using a second technique to examine the aggregated, polygenic signal within and across GWAS, Yu and colleagues demonstrated that while a polygenic risk score derived from a “discovery sample” of 1154 OCD cases without known tics could predict OCD case/control status in a second “target” sample, the addition of 345 OCD cases with co-occurring TS/CT (increasing the total discovery sample to 1499 OCD cases) significantly decreased the ability of the OCD discovery sample to predict OCD case/control status in the target sample. These data suggest that OCD with co-occurring TS/CT may have a subset of distinct genetic loci compared to OCD without tics and offers biological support for the “tic-related” specifier for OCD discussed above.

CNV Studies in OCD and Related Disorders

Submicroscopic deletions and duplications of DNA segments throughout the genome, collectively known as copy number variants (CNVs), have emerged in recent years as another major component of the genetic architecture of a wide range of developmental neuropsychiatric disorders.[51] In particular, these studies have reported the presence of recurrent, large (>500 kb), rare (often *de novo*) CNVs in multiple regions of the genome in which the same deletions and duplications can be found in individuals with different neurodevelopmental disorders, including schizophrenia, autism, intellectual disability (ID),

developmental delay (DD), epilepsy, bipolar disorder and attention deficit hyperactivity disorder (ADHD).[51-53] Two CNV studies of specific chromosomal regions have been conducted in OCD[54,55] as well as three moderately sized (each <500 cases) genome-wide CNV analyses of TS.[56-58] While none of the studies identified a genomic region statistically associated with either OCD or TS, exonic *NRXN1* deletions were found in two of the TS studies[56,58] and Fernandez and colleagues identified an enrichment of CNVs in histamine-signaling pathway genes in the other TS study.[57]

A recent joint CNV analysis of OCD and TS (2699 subjects with either disorder) found a 3.3-fold increased burden of large (>500kb) deletions within the subset of neurodevelopmental loci previously reported to harbor large, recurrent pathogenic CNVs.[59] Five of the 10 neurodevelopmental deletions were located within the 16p13.11 locus previously associated with ID/DD, seizures and autism; 4 of 5 deletions were in OCD cases, while one subject had TS. Three of the OCD/TS 16p13.11 deletions were found to be *de novo* events: one in an OCD subject without tics, one with TS without OCD, and one with OCD and CT. These results support the hypothesis that OCD and TS/CT have some shared genetic susceptibility, though these observations require replication given the small number of observed events. In addition, McGrath and colleagues found three 22q11 duplications and one *de novo* 22q11 deletion in subjects with OCD. Given prior reports of three TS subjects with 22q11 duplications, this region may also prove to be a shared genetic locus for both disorders.[57,58,60,61]

Candidate Gene Studies in OCD and Related Disorders

Although a large number of candidate genes have been reported to be associated with OCD and related disorders, no single gene has acquired the stringent level of statistical evidence to be considered a definitive risk gene. The strongest OCD candidate gene to date is the neuronal glutamate transporter gene, *SLC1A1*, though a recent meta-analyses of existing genetic association data did not find nominal significance following correction for multiple hypothesis testing.[62] A separate meta-analysis reported significant associations for three loci: the serotonin transporter promoter variant (*5-HTTLPR*) L_a vs. (L_g+S) alleles; *COMT* Met/Val; and the serotonin 2A receptor (*HTR2A)*.[63] While these three loci met the pre-specified corrected significance threshold of $\alpha<0.05$, it is important to note that these three signals are still below the standard genome-wide significant threshold of 5×10^{-8} for conclusive evidence of a disease susceptibility gene. Whether a candidate gene study should meet genome-wide evidence is a matter of debate, however, the history of psychiatric genetics has made it clear that many candidate genes study of nominal significance are not readily replicated.

Rare variation has been studied first in TS and this led to interesting follow up findings in OCD and related disorder. In TS, rare variation in two genes, *SLITRK1* and *HDC* have been identified in individual TS families.[64,65] A frameshift mutation in *SLITRK1* was initially found in one TS proband and his mother who had TTM as well as two individuals with a rare variation in an miRNA-binding site in the 3′UTR of the gene that was not found in 3600 control chromosomes. Based on these findings, subsequent association studies,looking at common variation, have produced conflicting results,[66-72] and the recent TS GWAS found

no association with *SLITRK1*, although one of the top statistical signals was located in the 2 Mb region between *SLITRK1* and the adjacent gene *SLITRK6*.[36] Of note, preliminary sequencing studies of *SLITRK1* in patients with OCD and TTM have suggested that rare variation may also be associated with these two related disorders.[73-75] With the advent of genome and exome sequencing, new appreciation of the high frequency of amino-acid altering variations in the general population now supports the need for follow-up studies in larger case-control samples and/or studies of *de novo* variation in parent-proband trios to determine the significance of these results.[76]

A frameshift mutation in the histidine carboxylase gene, *HDC*, the rate-limiting enzyme in histamine biosynthesis, has been identified in one family consisting of a father and eight offspring all with TS.[65] While rare variants in *HDC* have not been identified in additional TS cases, Fernandez and colleagues found an enrichment of histamine signaling pathway genes in their TS CNV analysis,[57] and a recent association study in 520 TS nuclear families reported a significant association of two *HDC* SNPs with TS ($p=0.0018$).[77] Future analyses in additional samples will be needed to examine both common and rare *HDC* variation in TS, OCD and related disorders.

Model Systems in OCD and Related Disorders

Genetic manipulations that produce compulsive-like behaviors in animals provide a valuable model system for understanding the neurobiological underpinnings of OCD and related disorders, as well as a platform in which to generate and test novel treatments. Because of the paucity of information on specific genes that contribute to risk for OCD in humans, these models tend to rely on genetic manipulations that produce behavioral phenotypes in animals that appear analogous to human compulsions; in some instances the specific genetic manipulation has been found to confer risk for human OCD, and in other examples the specific gene has not been validated in human OCD. Frequently these genes are highly expressed in cortico-striatal circuits, dysfunction in which is thought to mediate compulsive behaviors and tics.[78-81] In their review on animal models of OC spectrum disorders, Camilla d'Angelo et al. describe standard criteria used to assess these models, including face validity (phenotypic similarity between the model and the human condition), predictive validity (how well the animal model predicts efficacy of treatment for the disorder being modeled), and construct validity (how close the underlying mechanism of the model mimics the underlying mechanism of the disorder).[82]

One such animal model is the *Sapap3* knockout mouse. Interestingly, Sapap3 is expressed highly in striatum, and electrophysiological and biochemical studies of these animals reveal abnormalities in cortico-striatal synapses. An in-depth characterization of these mice show that they reliably exhibit both increased anxiety in behavioral testing as well as excessive self-grooming behaviors that lead to facial hair loss and skin lesions. The self-grooming is considered reminiscent of the compulsive behaviors seen in OCD and also bears commonalities with features seen in human grooming disorders such as TTM and pathologic skin picking, giving the model face validity. Moreover, the abnormal self-grooming and anxiety behaviors are reduced by sub-chronic treatment (six days) with fluoxetine (an empirically based treatment for OCD in humans) but not by a single dose of fluoxetine,

making the model even more reminiscent of human OCD[83] and giving the model predictive validity. Not only does the *Sapap3* knockout mouse thus provide a useful model for potentially characterizing the neuropathology of and evaluating novel treatments for OCD and related disorders, but *SAPAP3* has also been shown to be a promising candidate for these disorders in humans, thus giving the model construct validity. Studies have now shown that SNPs and other variants in *SAPAP3* appear to be enriched in individuals with grooming disorders (pathologic nail biting, pathologic skin picking, or TTM) compared to controls,[84] and in at least one study variants in *SAPAP3* were enriched in individuals with OCD as well.[85] Distinct variants in *SAPAP3* have also been reported in TS.[86]

A similar animal model, with face, predictive, and construct validity, exists with the *Slitrk5* knockout mouse (Slitrk1-6 is a family of related proteins, see Candidate Gene Studies in OCD and Related Disorders, above). Similarly to the *Sapap3* knockout mice, these animals exhibit increased anxiety in behavioral testing. Additionally, they exhibit excessive self-grooming, which leads to facial hair loss and skin lesions, akin to pathological grooming behavior specifically and perhaps compulsive behavior more generally. These behaviors also improve with fluoxetine treatment. Moreover, the knockout mice show selective over-activation of the orbitofrontal cortex, much like what has been shown in human imaging studies of OCD, and neuronal electrophysiological recordings from these animals reveal abnormal cortico-striatal neurotransmission.[87] The *Slitrk5* knockout mouse thus provides a useful model for OCD and related disorders both in terms of neuropathophysiology and in terms of behavioral abnormalities. It is notable that variations in the related protein, Slitrk1, have been found in cases of human OCD and TS.[64,75] However, the *Slitrk5* knockout mouse seems to be a more useful model for studying OCD and related disorders, as the *Slitrk1* knockout mouse has been shown to have increased anxiety behaviors but studies have not detected additional behavioral abnormalities consistent with OCD behaviors such as excessive self-grooming.[88]

In other genetic mouse models of OCD and related disorders, the manipulated genes have not been studied and/or shown to contribute to risk in human OCD. Nevertheless, these too can provide additional tools to study the pathobiology of OCD. For example, mice with loss of function disruptions of the gene *HOXB8* show excess self-grooming leading to hair loss and skin lesions; unlike the *Sapap3* and *Slitrk5* knockout mice, these mice also excessively groom their normal cagemates. Though *HOXB8* has not been shown to contribute to human OCD, it is interesting to note that the gene is highly expressed in brain regions thought to be involved in OCD, including the orbitofrontal cortex, anterior cingulate cortex, and striatum.[89] Thus the model may have some construct validity, disrupting pathways similarly to other genetic causes of OCD even if the gene is not involved in human OCD, as well as face validity given the compulsive behaviors of the animals. Similarly, the 5HT2C receptor knockout mouse provides a promising model of compulsive behavior with face validity; compared to controls, the mice show more repetitive and organized behaviors, chewing more non-nutritive clay, producing a distinctly organized chewing pattern on plastic screens, and showing increased perseveration of a head dipping activity in a behavioral assay.[90] Finally, male aromatase knockout mice develop compulsive behaviors such as excessive barbering, grooming, and wheel running. Interestingly, these mice have low catechol-O-

methyltransferase (COMT) protein expression in the hypothalamus,[91] and in human males, low COMT activity is associated with a higher risk of developing OCD.[92,93] Thus this model again provides both face validity and possibly construct validity.

Thus several animal models of OCD and related disorders exist and provide valuable preclinical systems for exploring neurobiological mechanisms of these disorders as well as potential novel treatments. As our knowledge of specific genetic factors that contribute to risk for human OCD expands it will inform a richer understanding of the biological underpinnings of OCD and render preclinical models even more powerful tools.

Conclusion / Summary

Twin and family studies as well as newer population-based approaches and novel laboratory-based investigations have provided powerful insights into the substantial heritability in OCD and related disorders, supporting a significant genetic contribution to these disorders. GWAS and candidate gene studies have identified specific gene variants that may contribute a small portion of the total genetic risk to OCD and related disorders, allowing for the development of model systems in which to study the pathobiology and treatment of these disorders. Nevertheless, a substantial portion of the genetic risk lies in genes that remain unidentified. Ongoing and future work will continue to clarify the genetic architecture and risk profile in OCD and related disorders to allow improved assessment of individualized risk and the development of novel therapeutics.

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Glossary

ADHD	Attention Deficit Hyperactivity Disorder
BDD	Body Dysmorphic Disorder
CNVs	Copy Number Variants
COMT	Catechol-O-methyltransferase
CT	Chronic Tic Disorder
DD	Developmental Delay
GCTA	Genome-wide Complex Trait Analysis
GWAS	Genome-Wide Association Study
ID	Intellectual Disability
IOCDFGC	International OCD Foundation Genetics Consortium

OC	Obsessive-Compulsive
OCD	Obsessive-Compulsive Disorder
OCGAS	OCD Collaborative Genetic Association Study
PGC	Psychiatric Genomics Consortium
RRR	Relative Recurrence Risk
SEM	Structural Equation Modeling
SNP	Single Nucleotide Polymorphism
TS	Tourette Syndrome
TSAICG	Tourette Syndrome Association International Consortium for Genetics
TTM	Trichotillomania

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Key Points: "takeaway" point for readers (≤125 words)

1. While most genetic studies focus primarily on obsessive-compulsive disorder (OCD) and Tourette Syndrome (TS), twin and family studies support a significant genetic contribution to OCD and also to related disorders including chronic tic disorders (e.g. TS), trichotillomania, skin picking disorder, body dysmorphic disorder, and hoarding disorder.
2. Recently, population-based studies and novel laboratory-based methods have confirmed substantial heritability in OCD and Tourette syndrome.
3. Genome-wide association studies and candidate gene studies have provided information on specific genes that may be involved in the pathobiology of OCD and related disorders, and for some genes model systems have supported a likely role in OCD.
4. A substantial portion of the genetic contribution to OCD is still unknown.

Table 1

Twin Studies of OCD Comparing Monozygotic and Dizygotic Concordance Rates

Authors, Year	Number of Twin Pairs	MZ concordance rate	DZ concordance rate	Heritability Estimate
Innouye, 1965[1]	14	0.80	0.25	-
Torgersen, 1980[94]	99	-	-	18% (male) 23% (female)
Carey and Gottesman, 1981[95]	30	0.87	0.47	-
Clifford et al., 1984[2]	419	0.50 (male) 0.44 (female)	0.22 (male) 0.11 (female)	47%
Jonnal et al., 2000[3]	527	0.34 (female)	0.14 (female)	33% (compulsiveness) 26% (obsessiveness)
Eley et al., 2003[4]	4,564	0.59 (male) 0.58 (female)	0.19 (male) 0.28 (female)	54%
Hudziak et al., 2004[5]	4,246	0.51-0.59 (male) 0.46-0.57 (female)	0.30-0.35 (male) 0.10-0.40 (female)	45-58%
Iervolino et al., 2011[9]	2,053	0.47	0.28	38-47% (OCS)
Monzani et al., 2012[6]	1,474	0.51	0.25	51%
Mataix-Cols et al., 2013[7]	16,383	0.4 (male) 0.5 (female)	0.2 (male) 0.15 (female)	47%
Monzani et al., 2014[8]	5,409	0.52	0.21	48%

MZ= monozygotic; DZ= dizygotic. Summary of results from twin studies that compared rates of obsessive-compulsive disorder (OCD) or obsessive-compulsive symptoms (OCS) in monozygotic and dizygotic twins.