New Insights Into the Genetic Architecture of Obsessive-Compulsive Disorder: Another Step Along the Way

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Using data from Swedish nationwide administrative registries, an international group of scholars conducted a population-based cohort study to estimate the heritability of obsessive-compulsive disorder (OCD) from common genetic variants, which Mahjani et al. report on in this issue (1). The sample consisted of 2,090 Swedish-born individuals diagnosed with OCD and 1,263 control subjects. DNA from all the participants were genotyped for more than 400,000 single-nucleotide polymorphisms (SNPs). The proportion of phenotypic variance due to additive genetic variation was found to be 29% (SE=4%). This proportion of the variance is referred to as the "narrow-sense" heritability. This estimate was robust and clearly indicates that these common genetic variants contribute meaningfully to the heritability of OCD within this genetically homogeneous sample. Rare genetic variation was also found to contribute to the heritability of OCD, but to a lesser degree.

Of interest, the authors also conducted a heritability analysis partitioned by individual chromosomes. With one exception, they found that the size of the chromosome was a good predictor of the chromosome's contribution to total heritability of OCD. This finding is consistent with the prediction that the SNPs affecting risk appear to be distributed at random over each of the chromosomes. The exception was chromosome 13, which has a very low gene density compared to most other chromosomes.

Overall, these results clearly demonstrate that the genetic risk for OCD is influenced by a large number of loci across the genome, which is consistent with an "infinitesimal model." The infinitesimal model is a simple and robust model for the inheritance of quantitative traits. It is the sum of both the genetic and environmental components. The genetic component follows a normal distribution around the average of the individual's parents. Hopefully, comparable analyses will be feasible for additional OCD cohorts from more diverse populations in the not-too-distant future (2).

OCD is clearly highly heritable, and it is often comorbid with other psychiatric disorders. However, the genetic heterogeneity of OCD in relation to specific comorbid conditions has not yet been exhaustively explored. Several cross-disorder analyses have previously evaluated the genetic overlap across a number of these disorders, revealing broad genetic correlations (3). Most recently, as part of the Psychiatric Genomics Consortium (PGC), a data-driven meta-analysis of genome-wide association studies (GWASs) was performed across several neuropsychiatric disorders for which large GWAS data sets are available, including attention deficit hyperactivity disorder, autism spectrum disorder (ASD), and Tourette's syndrome (4, 5).

In addition to genes, the environment also plays a key role in the pathogenesis of OCD. As noted in the introductory section of Mahjani and colleagues' article, members of this research team have already identified several environmental risk factors associated with an increased risk for developing OCD—smoking 10 or more cigarettes per day during pregnancy, a breech presentation, delivery by cesarean section, a shorter gestational age, lower birth weight, and a family history of an autoimmune condition (6–10). It will be important to see which genetic risk variants are associated with specific environmental risk factors.

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It is fascinating that "environmental events" and "maternal effects" very early in neural and somatic development often play an important role. Maternal effects are influences on the offspring phenotype that result from maternal genotypes and from the maternal environment (6). These effects are distinct from the child's genetic endowment. They include maternal genotypes that alter the expression and transmission of critical messenger RNA or proteins to the developing embryo and have genetic or environmental effects on the child's environment in utero. Interestingly, maternal factors have been shown to increase risk for multiple psychiatric phenotypes in offspring (6, 11–16). Epigenetic effects are also likely part of this emerging story (17, 18). Fortunately, both maternal and paternal factors can also have a protective role and foster resilience (19).

We are also in the midst of recognizing the important role that the "immune system" plays in very early somatic and neural development as well as in the pathobiology of OCD and Tourette's syndrome and other neuropsychiatric disorders

(16, 20–22). For example, microglia play an important role in circuit formation from very early in neural development (23). Given these realities, there may be real potential in monitoring the developmental progression of patient-specific brain organoids. However, to date, very few protocols include patient-specific microglia (24, 25). In addition to inherited genetic variants and epigenetic effects, somatic mosaicism also needs to be considered (25). Somatic mosaicism refers to the occurrence of two or more genetically distinct populations of cells within specific regions of an individual's body derived from postzygotic mutations. Somatic mutations may be present in an individual's germline. As a result, these genetic alterations can lead to the transmission of mutant genes from one generation to the next. These mutations can be key in assessing an individual's risk as well as in providing accurate genetic counseling. Next-generation sequencing is now available. This will facilitate the identification of clinically significant mutations that previously would never have been detected (26).

There are several other interrelated areas of science that merit our attention as we move forward as a field to gain a deeper understanding of OCD and related conditions. They include the role of the individual's microbiome and the gut-brain axis (27). The microbiota-gut-brain axis provides a bidirectional nervous, endocrine, and immune communication between these two organs. They are connected through a variety of pathways, including the vagus nerve, the immune system, microbial metabolites, the enteric nervous system, and various hormones. An individual's environment from birth onward, their diet, the use of antibiotics, and many other factors influence the composition of their microbiome, and this complex system may contribute to the emergence of neuropsychiatric disorders. Time will tell.

The more we learn, the more we recognize the complexities that affect the mental health and well-being of our patients with OCD and related conditions. That said, we can be confident that the outstanding international group of scholars who crafted this study will continue to advance our understanding of OCD in its various forms across the course of development. We can also be optimistic that their findings will contribute to effective patient-specific interventions and possibly even prevention.

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The author reports no financial relationships with commercial interests.

Accepted January 11, 2022.

Am J Psychiatry 2022; 179:177–179; doi: 10.1176/appi.ajp.22010027

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