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NEWS AND COMMENTARY

Polygenic risk scores for schizophrenia and depression linked to OCD

Polygenic prediction of obsessive compulsive symptoms

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Obsessive compulsive disorder (OCD) is a common neuropsychiatric disorder, causing considerable social impairment and disease burden worldwide.[1] OCD is characterized by the presence of a heterogeneous array of 'clinically significant' obsessions and compulsions, in a permanent uncontrollable cycle. It is widely recognized, similarly to what is observed for other psychiatric disorders, that individual differences in the susceptibility to OCD are at least partly genetic.[1]

Twin and family studies estimate the heritability of OCD to be between 0.27 and 0.50. Molecular genetic studies in epidemiological samples offer evidence for the highly polygenic nature of OCD, i.e., OCD is influenced by large numbers of (common) genetic variants with small-effects.[1] This polygenicity is within the expectations, considering the findings on the genetic architecture of other psychiatric traits.

Polygenic risk scores (PRS) offer an opportunity to test if results from large meta-analyses for psychiatric disorders can predict OCD. PRS are a measure of an individual's genetic risk to develop a certain disorder, calculated by summing all genotype scores for a person after weighting them by their estimated effect size for a trait as obtained from a genetic association analysis. These scores can be used to test the predictive value of a PRS towards the disorder in independent samples, or towards another disorder of interest. This approach allows one to simultaneously (1) tackle the inherent culprit of polygenicity surrounding complex traits—that true genetic variance is captured by the full set of measured SNPs not only significant signals, and (2) assess to which extent the individual genetic risk to a trait has predictive value for another trait—serving as measure of genetic correlation between disorders, even in the absence of phenotype measurements for multiple disorders.[2]

Recently, large GWASs for psychiatric traits have been completed and we constructed polygenic scores based on the summary statistics from a series of disorders that are epidemiologically related to OCD, namely: Attention Deficit Hyperactivity Disorder (ADHD), Bipolar Disorder (BD), Schizophrenia (SCZ), major depressive disorder (MDD), Autism, and Migraine. In addition we had at our disposal summary statistics from a meta-analysis performed on clinically-derived OCD samples from the International OCD Foundation Genetic Collaborative (IOCDFGC) and OCD Collaborative Genetics Association Study (OCGAS).[3,4] We investigated the power of each of these scores to effectively predict obsessive compulsive symptoms (OCS) in a population-based sample, considering different values for genetic correlations between the score and OCS, following the method proposed by Dubridge.[2]

Table 1 summarizes the results. The polygenic scores for OCD, SCZ ($P = 1.4 \times 10^{-6}$), MDD ($P = 5.6 \times 10^{-5}$) and BP-SCZ combined ($P = 8.1 \times 10^{-7}$) were significant after correcting for multiple testing ($\alpha = 0.006$). This last result is probably driven by the

Table 1. Results of the GEE association analyses between OCS and different polygenic scores ($N = 6506$)

Polygenic score	P- *value*	R^2 *(%)*	*N-GWAS*	h^2 *LDSC*	*Power* ($r_g = 0.2$)	*Power* ($r_g = 0.4$)	*Power* ($r_g = 0.6$)	*Power* ($r_g = 0.8$)
OCD[3,4]	**3.0×10^{-4}**	0.57	9761	0.14	0.18	0.54	0.87	0.99
ADHD[5]	0.85	0.39	51 306	0.23	0.84	0.84	1	1
Bipolar Disorder (BD)[6]	0.015	0.48	63 766	0.43	0.29	0.29	0.98	1
Schizophrenia[7]	**1.4×10^{-6}**	0.71	79 845	0.45	0.97	0.97	1	1
BD & Schizophrenia[6]	**8.1×10^{-7}**	0.79	39 202	0.37	0.48	0.48	0.99	1
BD vs Schizophrenia[6]	0.025	0.44	16 381	0.33	0.11	0.11	0.78	1
MDD (PGC and 23andMe)[8]	**5.6×10^{-5}**	0.57	370 973	0.07	0.78	0.98	1	1
Autism[9]	0.47	0.38	10 263	0.46	0.12	0.12	0.81	1
Migraine[10]	0.16	0.41	196 685	0.04	0.03	0.03	0.31	0.99

Abbreviations: ADHD, attention deficit hyperactivity disorder; GEE, generalized estimation equations; MDD, major depressive disorder; OCD, obsessive compulsive disorder; OCS, obsessive compulsive symptoms. The third column also indicates the proportion (in percentage of variance explained in OCS by each polygenic risk score (R^2). N-GWAS gives sample size and h^2 the heritability estimates (h^2 LDSC) of the GWAS summary statistics from LD score regression. The last 4 columns give the power to detect an association between OCS and the polygenic scores given a genetic correlation (r_g) of 0.2, 0.4, 0.6 and 0.8. Bold font indicates significant *P*-values after multiple testing correction ($\alpha = 0.05/9 = 0.006$); gray color font indicates nominally significant *P*-values ($\alpha = 0.05$). The reference for the provenance of each summary statistics is given alongside the respective score.

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genetic component that Schizophrenia shares with BD. Overall, the polygenic scores explained between 0.38–0.79% of the total variance of OCS—in line with what is observed for most PRS analysis. The score 'BD vs Schizophrenia'—which includes the genetic component that differentiates between BD and Schizophrenia, did not significantly predict OCS, which indicates that genetic variation unique to SCZ or BIP is not related to OCS. MDD scores also showed a strong genetic association with OCS. Among the most co-occurring disorders with OCD are major depression (31%) and BD (7%), while for schizophrenia rates for co-occurrence are rare. These results indicate that the reason for comorbidity partly is genetic, with a shared genetic liability to OCS.

These results show that population-based OCS can be predicted with the help of clinically based GWAS, which in turn reveals that psychiatric genetic risk factors can lead to the presence of sub-clinical OC symptoms. The risk scores also indicate that OCS are clinically relevant markers of other psychiatric disorders related to OCD. In other words, sub-clinical OCS shares genetic variance that underlies OCD, Schizophrenia and MDD.

The relevance of PRS lies within their predictive value. PRS have a better predictive value than the individual GWASs' top hits. Their application may in many cases be clinically useful when applied to population-based samples (as herein shown), and predict the development of psychiatric traits such as OCD. Our results regarding the predictive value of MDD and Schizophrenia for OCS should be looked into in further studies.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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