Obsessive-Compulsive Symptoms in a Genetic Epidemiological Twin Family sample: Genome - Wide Association and Beyond

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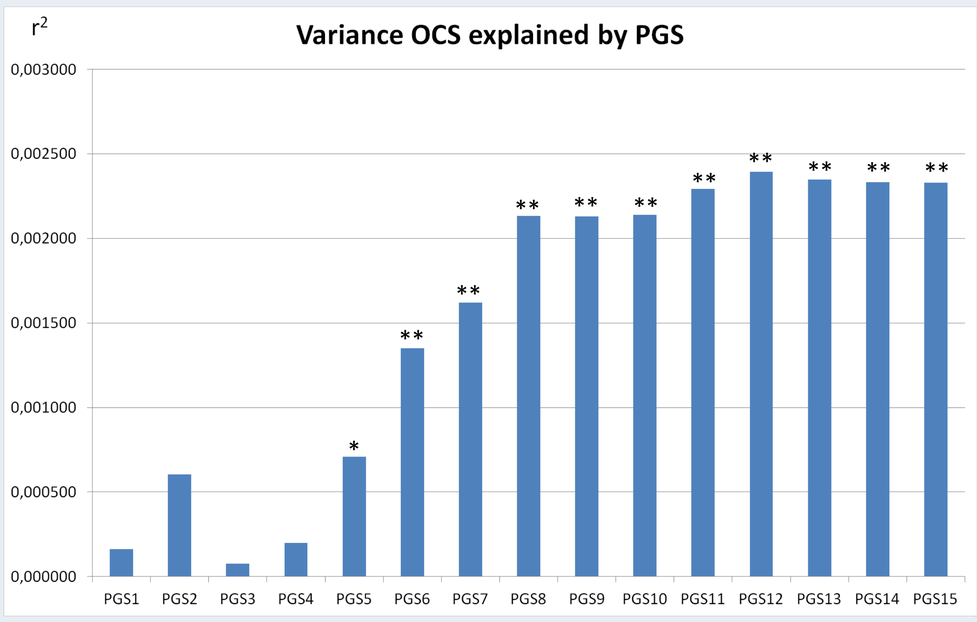
Introduction

The heritability of Obsessive–Compulsive symptoms (OCS) has been estimated at 40%. Genetic association studies have thus far not yielded consistent findings, though discovery samples were not large. We aimed to gain further insights into the genetic basis of OCS by performing a series of genetic analyses in a homogeneous, population-based twin sample from the Netherlands.

Methods

- First, we estimated phenotypic and genetic stability of OCS by modeling of twin-sibling data (n = 5478 adults, mean age (SD) = 33 (11.5) years). OCS were measured using the Padua Inventory-Revised Abbreviated *.
- Second, we calculated polygenic scores (PGS) for subjects with OCS scores and genome-wide SNP data (n= 6931) based on meta-analysis results from Stewart and colleagues **, to investigate the predictive value of this PGS.
- Third, we estimated the proportion of the phenotypic variance explained by all autosomal SNPs in a subset of unrelated subjects (n=3618).
- Lastly, we performed an explorative GWAS on OCS scores from the 6931 subjects, testing for SNP and gene based associations.



PGS	P
1	0 - 0.00001
2	0 - 0.0001
3	0 - 0.001
4	0 - 0.01
5	0 - 0.05
6	0 - 0.1
7	0 - 0.2
8	0 - 0.3
9	0 - 0.4
10	0 - 0.5
11	0 - 0.6
12	0 - 0.7
13	0 - 0.8
14	0 - 0.9
15	0 - 1.000

Figure 1. *Proportion of variance in OCS scores, as measured in the NTR sample, explained by polygenic scores obtained from European case-control sample by Stewart et al. 2013, with a range of 15 statistical cutoffs for SNP inclusion in the score (p<0.00001, p<0.0001, p<0.001, p<0.01, p<0.05, p<0.1, p<0.2, p<0.3, p<0.4, p<0.5, p<0.6, p<0.7, p<0.8, p<0.9, p<=1).PGS=polygenic score; *=p<0.05; **=p<0.01.*

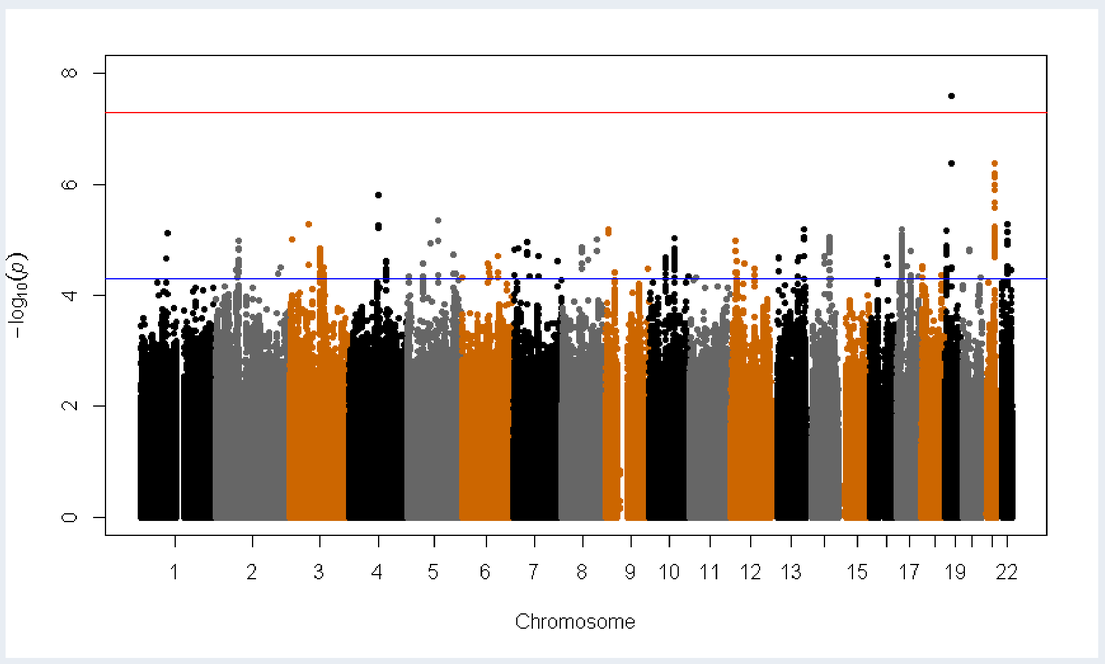


Figure 2. *Manhattan plots of all genotyped single-nucleotide polymorphisms (SNPs). Red and blue lines indicate significance thresholds of 5 x 10^{-8} and 1 x 10^{-5}, respectively.*

Results

- Stability in OCS (0.64 over a 6-year period) was mainly explained by genetic factors (56%).
- PGS obtained from a European case-control set predicted OCS in this population sample with 0.2% explained variance at p=0.07 ***(Figure 1)***.
- One SNP (rs8100480), located within the MEF2BNB gene, showed to be associated with OCS (p=2.56x10^{-8}) ***(Figure 2)***.
- Additional gene-based testing resulted in 4 significantly associated genes (RFXANK, MEF2BNB, MEF2BNB-MEF2B and MEF2B), all located in the same chromosomal region (19p13.11).

Discussion

Significantly associated genes are expressed in the brain and involved in development and control of immune system functions (RFXANK) and the regulation of gene expression of muscle specific genes (MEF2BNB). The MEF2BNB gene also showed a suggestive association with OCD in a previous gene based study using a case-control design***. These results, indicate an important role for the 19p13.11 region in OCS. The fact that we were able to replicate the association of the MEF2BNB gene with OCS, might be the beginning of a breakthrough in OCD. Therefore, future genetic studies should investigate this area in association with OCD into depth. Further, our data shows that well phenotyped population cohorts could contribute to the understanding of the underlying architecture of common complex disorders such as OCS, and that these partly overlap with results from case-control studies . Therefore, future studies could benefit from combining case-control and population-based samples.

* Cath DC et al.. Environmental factors in obsessive-compulsive behavior: evidence from discordant and concordant monozygotic twins. Behav Genet 2008 Mar;38(2):108-20.
** Stewart SE et al. Genome-wide association study of obsessive-compulsive disorder. Mol Psychiatry 2013 Jul;18(7):788-98.
*** Mattheisen M et al. Genome-wide association study in obsessive-compulsive disorder: results from the OCGAS. Mol Psychiatry 2014 May 13.