



## Commentary

## Genetic and Environmental Contribution to Major Depressive Disorder and Self-declared Depression



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Major depressive disorder (MDD) is a high-prevalence disease (~15%) that is the fifth leading disease contributing to disability-adjusted life years (DALYs) in the US (Murray et al., 2013). The pathogenesis of MDD is still partially unknown, consequently diagnosis is based on clinical criteria. However, MDD is a clinically heterogeneous disorder and this probably reflects heterogeneity in the underlying biology. Since ~20 years, genetic variants are known to be involved in MDD biology thanks to family studies (Sullivan et al., 2000) and recently genome-wide association studies (GWAS) (Hyde et al., 2016). The estimation of genetic variants contribution and the identification of specific variants involved have been difficult partly because of the heterogeneity and high prevalence of MDD (Gratten et al., 2014). The consequent large sample sizes required to provide adequate statistical power are difficult to recruit and self-declared depression (SDD) is an interesting option to face this issue.

The study by (Zeng et al., 2016) used a family-based cohort to estimate the contribution of genetic and environmental factors to MDD and SDD. This study suggested that common genetic variants ( $h^2_g$ ), pedigree associated variants ( $h^2_p$ ) and common environmental effect shared by couples ( $e^2_c$ ) are the major contributors to both MDD and SDD. The proportion of total additive genetic determinant ( $h^2_n$ ) was 30% for MDD and 72% for SDD when environmental effects were also considered in the model. The former finding is in line with other studies (e.g. 37% in (Sullivan et al., 2000)) while for the latter there are not comparable data in literature. This study proposed a framework for comparing phenotypically related traits but replication is pivotal. In particular, the high difference between the estimated  $h^2_n$  for MDD and SDD requires further consideration since no clear biological explanation can be hypothesized. Despite the relative contribution of  $h^2_p$  to MDD (20%) and SDD (50%) is similar (i.e. ~1/3 of  $h^2_n$ ), the high absolute contribution of rare variants

to SDD also needs clarification of the underlying biological mechanisms. Examples of psychiatric disorders with high heritability and a wide gap between  $h^2_n$  and  $h^2_g$  are schizophrenia (Sullivan et al., 2003; Loh et al., 2015) and bipolar disorder (Barnett and Smoller, 2009; Moser et al., 2015). This observation suggests that SDD may overlap with major psychiatric disorders different from MDD, since negative symptoms of schizophrenia may resemble depression and major depression is the phase of bipolar disorder with the highest personal impact. It should be kept in mind that the high correlation among the matrices representing  $h^2_g$ ,  $h^2_p$  and the environmental components and/or assortative mating may have influenced the results in a relatively limited sample size. Results found for SDD may have been influenced to a larger extent by these possible sources of bias since the total variance explained for this trait was very high (98%, SE = 9%), despite no evidence of genetic relatedness was found analyzing genome-wide data and evidence of collinearity between the model components was similar between SDD and MDD.

For both MDD and SDD the contribution of rare variants finds poor support in literature since previous studies were mainly focused on common variants (e.g. (Gratten et al., 2014; Hyde et al., 2016)). Recent and not replicated evidence supported that rare variants in the PPH21B gene (Wong et al., 2016), in the CAV2-adaptor gene set and a network involved in actin polymerization and dendritic spine formation (Pirooznia et al., 2016) may be over-represented in MDD.

The contribution of common variants to MDD variance was estimated to be 21% (SE = 2%) in a meta-analysis of nine cohorts including 9381 cases (Cross-Disorder Group of the Psychiatric Genomics et al., 2013), that is quite higher than  $h^2_g$  found by Zeng et al. (10%, SE = 5%). This may be explained by the relatively low genetic correlation across different MDD samples (Gratten et al., 2014), as confirmed by a recent meta-analysis (Hyde et al., 2016) that included ~120K subjects with MDD or self-reported depression (23andMe sample) and found heritability was 5% or 6% depending on the considered population prevalence (15% and 25%, respectively). The heritability score estimated in the 23andMe cohort was also low (4%).

Previous family-based studies did not take into account  $e^2_c$  but the overall evidence suggested that shared environment between twins did not contribute to MDD (Sullivan et al., 2000) in line with Zeng et al. that did not identify any effect of shared environment between siblings or family members. On the other hand, individual-specific environmental factors were found to affect significantly MDD (63%, 95% CI = 58–67% (Sullivan et al., 2000)) but this association could not be investigated by Zeng et al. because these data were lacking.

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The final interesting point is the correlation among the genetic and environmental factors contributing to MDD and SDD. Zeng et al. reported that there was a high correlation between the common genetic variants involved in the two phenotypes, while moderate correlation was found for pedigree-associated variants and environmental factors common to the couple (1, 0.57 and 0.52, respectively). These estimations need replication in independent samples since there are not similar data in previous literature. If replicated, they may have relevant implications for future studies in both the genetic and epidemiological fields since SDD may become a validated proxy of MDD. On the clinical level, the good correlation between the two phenotypes may reflect a good level of psychoeducation, thus patients' better insight of disease. It is worth of note that this can vary in different clinical settings or countries and SDD might include sub-threshold forms of depression or (para)-physiological stress responses.

In conclusion, the study by Zeng et al. was the first to estimate the contribution of common genetic variants, pedigree associated variants and different environmental factors to both MDD and SDD. The results need replication in independent samples before any definitive statement, particularly the effect of pedigree-associated variants and environmental effects shared by couples. The high correlation between common genetic variants involved in MDD and SDD suggested that SDD may serve as adequate proxy of MDD in future studies.

## Disclosure

The author declared no conflicts of interest.

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