Common genetic variants associated with personality dimensions in the Heidelberg Cohort Study of the Elderly (HeiDE): an update

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Abstract

Here, we present an update on our genetic analyses of personality phenotypes in the HeiDE study, a longitudinal study of the inhabitants of Heidelberg, Germany (n=5,114). We investigated five latent personality dimensions (*The Heidelberg Five*), derived from principal components factor analysis: *Emotional Lability, Lack of Behavioral Control*, *Type-A-Behavior*, *Locus of Control over Disease,* and *Psychoticism*. Previously, in the first HeiDE subsample for which genetic data became available, a GWAS had identified a variant on chromosome 5 (rs79136259) to be associated with *Emotional Lability*. Recently, genetic data for a second HeiDE subsample became available, which we have now jointly analyzed and combined with the first sample using meta-analysis (n_1=2,387 and n_2=881; post-QC). We were not able to confirm our initial result of the phenotype *Emotional Lability* in the combined sample. However, we found a genome-wide significant hit for the phenotype Type-A-Behavior. Also, we estimated SNP-based heritabilities of and genetic correlations between *The Heidelberg Five* using the GCTA software. *Emotional Lability*, *Lack of Behavioral Control*, and *Psychoticism* showed significant FDR-corrected SNP-based heritabilities (all p=0.047). Genetic correlations between *The Heidelberg Five* were not significant, mirroring phenotypic orthogonality on the genomic level.

Introduction

The HeiDE study is an ongoing longitudinal investigation that started in the 1990s and, at baseline, assessed an array of personality tests in 5,114 individuals (e.g. Amelang et al., 2004). Principal components factor analysis was used to identify five latent personality dimensions (*The Heidelberg Five*), interpreted as *Emotional Lability* (ELAB), *Lack of Behavioral Control* (LBCN), *Type-A-Behavior* (TYAB), *Locus of Control over Disease* (LOCC), and *Psychoticism* (PSYC). At follow-up, a subset of responding participants were genotyped using Illumina SNP arrays. We conducted five initial GWAS, analyzing common genetic variants underlying the previously identified orthogonal personality dimensions with factor scores as phenotypes. For ELAB, we observed a locus that was genome-wide significant (rs79136259; $p=8.2\times10^{-9}$). Recently, genome-wide data from another subsample of the HeiDE study became available and we have now jointly analyzed both samples and combined results using meta-analysis (n_1=2,387 and n_2=881; post-QC). Furthermore, we have extended our analysis by assessing SNP-based heritabilities of and genetic correlations between *The Heidelberg Five*.

Methods

Both samples were genotyped on Illumina SNP arrays. We imputed common variants (MAF≥0.01) using the 1000 Genomes Phase 3 reference panel. Data were analyzed using PLINK 1.07 (http://zzz.bwh.harvard.edu/plink/) with sex, age and the first four ancestry principal components as covariates. Fixed-effects meta-analysis was conducted using METAL (http://genome.sph.umich.edu/wiki/METAL). SNP-based heritability estimates and genetic correlations were calculated using GCTA (http://cnsgenomics.com/software/gcta/index.html), jointly on all available individuals.

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Results

Meta-analysis of both HeiDE samples

The association of SNP rs79136259 with ELAB, discovered in the first HeiDE subsample, did not replicate in the second subsample. Association strength in the fixed-effects meta-analysis of both samples decreased to a nominal level ($p=1.3\times10^{-4}$). For TYAB, an InDel variant on chromosome 8 (rs58535027, $p=1.1\times10^{-8}$) that was not significant in either sample alone reached genome-wide significance in the meta-analysis (Figure 1). No genome-wide significant associations were found in the meta-analyses for LBCN, LOCC or PSYC.

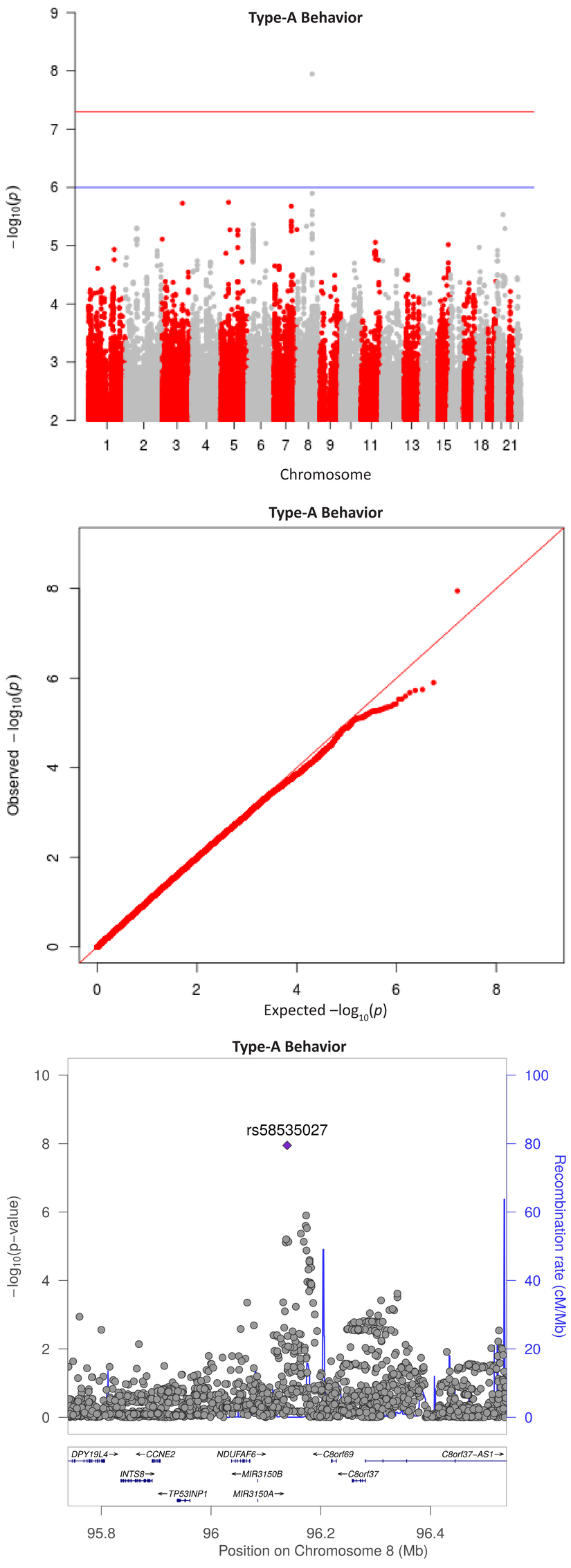

Figure 1. Manhattan (A) and Q-Q (B) plots of the meta-analysis investigating the phenotype Type-A Behavior. We observed a genome-wide significant variant (rs58535027, $p=1.1\times10^{-8}$) on chromosome 8 (C).

SNP-based heritabilities of The Heidelberg Five

SNP-based heritability estimates of the joint genotype data are: 28.8% (ELAB; FDR p=0.047), 27.3% (LBCN; FDR p=0.047), 8.4% (TYAB; FDR p=0.269), 8.4% (LOCC; FDR p=0.269) and 23.6% (PSYC; FDR p=0.047).

Genetic correlations between The Heidelberg Five

The genetic correlation matrix is visualized in Figure 2. No genetic correlation reached nominal significance.

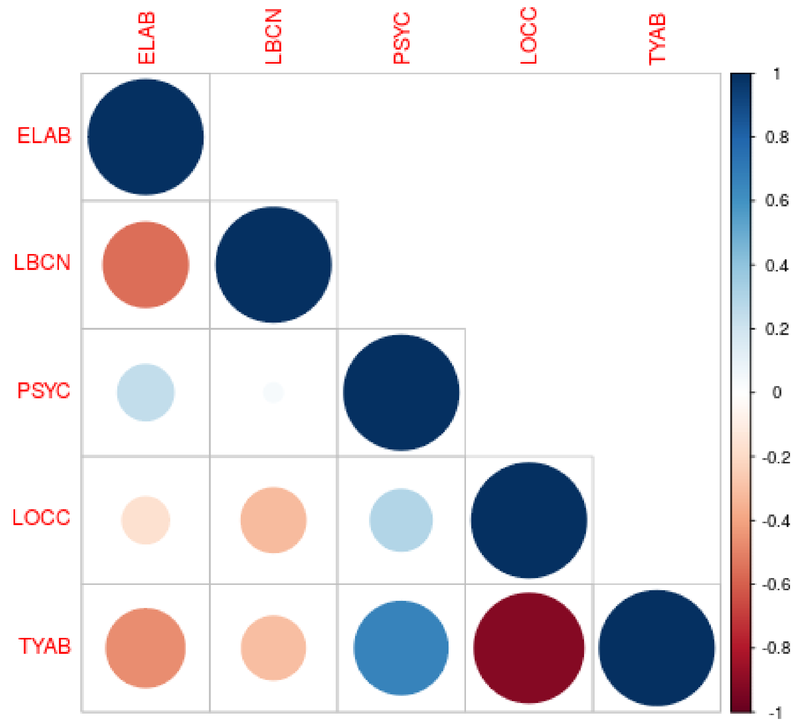

Figure 2. Graphical display of the genetic correlation matrix of *The Heidelberg Five* personality phenotypes. No correlation was nominally significant.

Discussion

The HeiDE study is a unique opportunity to study the association of personality and genetics. Meta-analysis of both subsamples did not find evidence for our previously reported association of rs79136259 with ELAB but found evidence for a genetic variant influencing TYAB (rs58535027). Biological consequences of this variant are yet unknown.

There is a large body of behavioral genetic literature investigating personality (see e.g. Krueger and Johnson, 2008, for review), that has lead to the phenotypic null hypothesis that all personality traits are equally heritable (Turkheimer et al., 2014). Here, we show that heritability of some clinically relevant personality traits such as ELAB (closely related to neuroticism), LBCN (related to executive function) and PSYC can also be demonstrated using genomic data. Moreover, heritability estimates of these personality traits were around 25% and are thus close to heritabilities of personality traits estimated by traditional behavioral genetics (around 40%; Turkheimer et al., 2014). This points to a highly polygenic structure of these personality traits. Other personality traits such as TYAB and LOCC appear to refute the notion that all personality traits are heritable, at least when using genomic data.

Genetic correlations between *The Heidelberg Five* were mostly low and no correlation was even nominally significant. This indicates that the orthogonal structure of *The Heidelberg Five* personality traits on the phenotypic level is mirrored on the genomic level.

References

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