Received: 16 December 2020 | Revised: 19 January 2021 | Accepted: 21 January 2021

DOI: 10.1002/ajmg.b.32837

ORIGINAL ARTICLE

AMERICAN JOURNAL OF medical genetics PART B Neuropsychiatric Genetics WILEY

# "The Heidelberg Five" personality dimensions: Genome-wide associations, polygenic risk for neuroticism, and psychopathology 20 years after assessment

Urs Heilbronner[1] | Sergi Papiol[1,2] | Monika Budde[1] | Till F. M. Andlauer[3] | Jana Strohmaier[4] | Fabian Streit[4] | Josef Frank[4] | Franziska Degenhardt[5,6] | Stefanie Heilmann-Heimbach[5] | Stephanie H. Witt[4] | Andreas J. Forstner[5,7,8] | Adrian Loerbroks[9] | Manfred Amelang[10] | Til Stürmer[11] | Bertram Müller-Myhsok[12] | Markus M. Nöthen[5] | Marcella Rietschel[4] | Thomas G. Schulze[1,13]

[1]Institute of Psychiatric Phenomics and Genomics (IPPG), University Hospital, LMU Munich, Munich, Germany

[2]Department of Psychiatry and Psychotherapy, University Hospital, LMU Munich, Munich, Germany

[3]Department of Neurology, Klinikum rechts der Isar, School of Medicine, Technical University of Munich, Munich, Germany

[4]Department of Genetic Epidemiology in Psychiatry, Central Institute of Mental Health, Medical Faculty Mannheim, University of Heidelberg, Mannheim, Germany

[5]Institute of Human Genetics, School of Medicine & University Hospital Bonn, University of Bonn, Bonn, Germany

[6]Department of Child and Adolescent Psychiatry, University Hospital Essen, University of Duisburg-Essen, Essen, Germany

[7]Centre for Human Genetics, University of Marburg, Marburg, Germany

[8]Department of Biomedicine, University of Basel, Basel, Switzerland

[9]Institute of Occupational, Social and Environmental Medicine, Center for Health and Society, Faculty of Medicine, University of Düsseldorf, Düsseldorf, Germany

[10]Department of Psychology, University of Heidelberg, Heidelberg, Germany

[11]Department of Epidemiology, UNC Gillings School of Global Public Health, Chapel Hill, North Carolina

[12]Department of Translational Psychiatry, Max Planck Institute of Psychiatry, Munich, Germany

[13]Department of Psychiatry and Behavioral Sciences, Upstate University Hospital, Syracuse, New York

**Correspondence**
Urs Heilbronner, Institute of Psychiatric Phenomics and Genomics (IPPG), University Hospital, LMU Munich, Nussbaumstr. 7, 80336 Munich, Germany.
Email: urs.heilbronner@med.uni-muenchen.de

**Funding information**
BONFOR Programme of the University of Bonn; Bundesministerium für Bildung und Forschung, Grant/Award Numbers: 01ZX1614K, 01ZX1614G, 01ZX1614A, 01ZX1614J, 01EE1404H : 01ZZ1804A; Deutsche Forschungsgemeinschaft, Grant/Award Numbers: SCHU 1603/4-1, SCHU 1603/5-1, SCHU 1603/7-1, FA241/16-1 : FOR2107 : RI908/11-2 : WI3429/3-2; Dr. Lisa

## Abstract

HeiDE is a longitudinal population-based study that started in the 1990s and, at baseline, assessed an array of health-related personality questionnaires in 5133 individuals. Five latent personality dimensions (The Heidelberg Five) were identified and 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, 3268 HeiDE participants (post-QC) were genotyped on single nucleotide polymorphism (SNP) arrays. To further characterize The Heidelberg Five, we analyzed genomic underpinnings, their relations to the genetic basis of the Big Five trait Neuroticism, and longitudinal associations with psychiatric symptoms at follow-up. SNP-based heritability was significant for ELAB (34%) and LBCN (29%). A genome-wide

Oehler Foundation, Kassel; ERA-NET Neuron, Grant/Award Numbers: 01EW1810, 01EW1904; European Union's Horizon 2020 Research and Innovation Programme, Grant/Award Number: RIA 7331; National Institutes of Health, Grant/Award Number: R01 AG056479: R01 HL118255: R01 MD011680; UNC Clinical and Translational Science Award, Grant/Award Number: UL1TR002489

association study for each personality dimension was conducted; only the phenotype PSYC yielded a genome-wide significant finding ($p < 5 \times 10^{-8}$, top SNP rs138223660). Gene-based analyses identified significant findings for ELAB, TYAB, and PSYC. Polygenic risk scores for Neuroticism were only associated with ELAB. Each of The Heidelberg Five was related to depressive symptoms at follow-up. ELAB, LBCN, and PSYC were also associated with lifetime anxiety symptoms. These results highlight the clinical importance of health-related personality traits and identify LBCN as a heritable "executive function" personality trait.

**KEYWORDS**
control, executive, longitudinal, psychoticism

## 1 | INTRODUCTION

In its widest sense, personality can be conceptualized as "relatively enduring patterns of thoughts, feelings, and behaviors" (Sanchez-Roige et al., 2018) that constitute hallmarks of individuality. The "Big Five" personality traits (reviewed by Goldberg, 1993) have become the prevailing scientific taxonomy, and an individual's personality can be comprehensively characterized along these latent dimensions. A related but somewhat different scientific approach has been to characterize specific health-related personality dimensions (see Capitanio, 2008; Friedman & Booth-Kewley, 1987), hypothesized to be related to somatic disease such as cardiovascular disease (CVD) and cancer. The longitudinal HeiDE study ("Heidelberger Langzeitstudie zu Risikofaktoren und Diagnose chronischer Erkrankungen") pursues the latter approach (Stürmer et al., 2006). Since the early 1990s, this epidemiological study assesses personality, health, lifestyle, and cognitive variables in a population-based sample of 5133 individuals from the German city of Heidelberg and surroundings. Several follow-up assessments have been conducted, to evaluate the association of psychological factors and disease. Based on an array of questionnaires completed at baseline that assessed depressive symptoms, resilience factors, as well as some broad personality factors (Extraversion, Neuroticism, and Psychoticism), five personality dimensions, named "The Heidelberg Five," were subsequently extracted using exploratory factor analysis (Amelang et al., 2004). These were named Emotional Lability (ELAB, defined by Neuroticism, depression, a tendency to suppress anger, low social support, low optimism, and a low sense of coherence, as well as low Extraversion), Lack of Behavioral Control (LBCN, characterized by low social desirability and low anger control), Type A Behavior (TYAB, defined by high time urgency, exaggerated social control and high Extraversion), Locus of Control over Disease (LOCC, characterized by a high internal locus of control), and Psychoticism (PSYC, defined by high psychoticism). ELAB appears to tap the combination of risk factors for psychopathology, and the absence of resilience factors. LBCN characterizes a low capacity to self-regulate and may thus be regarded as an "executive function" personality trait, primarily defined by a lack of inhibitory control of emotions. Consistently, the dimension LBCN encompasses behaviors associated with executive function during development (e.g., Rohlf et al., 2018), high expression of which resemble some clinical conditions of the prefrontal cortex (e.g., Szczepanski & Knight, 2014; Tate, 1999). The personality dimension TYAB is highly correlated with psychological tests measuring time urgency, exaggerated social control, and Extraversion (for details see Supporting Information). The construct TYAB is "characterized primarily by a chronic incessant struggle to achieve more and more in less and less time" (Smith et al., 1996) and was initially hypothesized to be associated with CVD (Friedman & Rosenman, 1959), but this assumption was later found to have little empirical support (for review see Kuper et al., 2002). In line with this finding, prospective research in the HeiDE study did not identify TYAB as a predictor of the incidence of CVD (Amelang et al., 2004). LOCC is a construct based on Rotter's influential social learning theory (Rotter, 1966) that assesses cognitions of control over health (e.g., Wooldridge et al., 1992). Briefly, social learning theory postulates that individuals differ in their perception of reinforcements and classify these either as being controlled externally, that is, by chance or the specific situation, or internally, by the person's own actions. According to Rotter, generalized expectancies differ between individuals and this constitutes a personality dimension, Locus of Control. The personality dimension determines whether individuals perceive outcomes as rather externally or internally controlled (Weiner et al., 2009). High internal Locus of Control has been shown to be important for a variety of health behaviors including smoking, alcohol consumption, exercise, diet (Steptoe & Wardle, 2001; Strudler Wallston & Wallston, 1978), and medication adherence (Náfrádi et al., 2017). Finally, PSYC is one of the three personality factors in Eysenck's influential theory-based model of personality (Eysenck & Eysenck, 1976) and has been discussed as a core element of maladaptive personality, resembling schizotypy (Chapman et al., 1994; van Kampen, 2009; Wright et al., 2012). Initially, Psychoticism was conceptualized as a continuous dimension, predisposing individuals to psychosis, but a 10-year longitudinal study did not confirm this association (Chapman et al., 1994). The latter study, however, also reported that individuals scoring high on Psychoticism "exceeded controls on ratings of psychotic-like experiences and on symptoms of schizotypal and paranoid personality

disorder." Furthermore, based on a number of analyses, Psychoticism was described as encompassing "impulsivity, lack of socialization and responsibility, aggression, a strong need for independence, and sensation seeking," with clinical extremes (Zuckerman, 1989).

Recently, a subset of HeiDE participants was genotyped on whole-genome arrays, and here, we examine genomic underpinnings of The Heidelberg Five. To establish genetic similarities to and differences from the well-established Big Five trait Neuroticism, we also examined associations of The Heidelberg Five with polygenic risk scores (PRS) for Neuroticism. Also, we research associations of The Heidelberg Five with psychopathological symptoms about 20 years after their initial assessment.

## 2 | METHODS

Data were analyzed using R (v3.1 or higher; R Core Team, 2014), PLINK 1.9 (GWAS and calculation of PRS; Chang et al., 2015), SHAPEIT/IMPUTE2 (imputation; Delaneau et al., 2012; Howie et al., 2009), MAGMA (v1.07; gene, gene-set, and tissue expression analyses; de Leeuw et al., 2015), and GCTA (v1.92.1beta6, estimation of SNP-based heritabilities and genetic correlations; Yang et al., 2011).

The analyses are covered by an ethics vote of the Medical Faculty of the University of Heidelberg (# 026/2001).

### 2.1 | Heidelberg Cohort Study of the Elderly

The HeiDE study is a population-based longitudinal cohort study of the inhabitants of Heidelberg (Germany) and was designed to prospectively research the association of personality and somatic diseases. Details on the baseline sample, assessed from 1992 to 1994, can be found in Amelang et al. (2004). The final baseline sample consisted of 5114 individuals (52.2% female) aged between 28 and 74 (99.6% between 40 and 68). Data analyzed in this study are from the baseline assessment (personality phenotypes; see below), the first follow-up (on average 8.5 years later; collection of biomaterials), and from a follow-up conducted in 2013 (psychiatric phenotypes).

### 2.2 | Personality assessment, principal components factor analysis, and generation of factor scores

At baseline, participants completed an array of personality and health-related questionnaires (see Data S1). We used the original dataset of Amelang et al. (2004) and re-analyzed it using principal components followed by varimax rotation using the R *psych* library, obtaining a virtually identical solution. Regression factor scores were calculated for each latent personality dimension.

### 2.3 | Genotyping and imputation

DNA from saliva collected with mouthwash samples was extracted on a chemagic platform (PerkinElmer chemagen Technologie GmbH, Germany). DNA collected with Oragene OG500 Kits (DNA Genotek Inc., Canada) was extracted using DNA Genotek's prepIT kit (DNA Genotek Inc., Canada). Samples were genotyped using two different Illumina microarrays (Illumina, San Diego, CA). One subsample ($HeiDE_1$) was genotyped using the Infinium PsychArray-24 BeadChip ($n$ = 2734) and another one using the InfiniumOmniExpressExome-8v1-3_A BeadChip ($HeiDE_2$; $n$ = 1000). The combined dataset ($n$ = 3734 pre-QC) was imputed to the 1000 Genomes phase 3 reference panel. Details on quality control (QC) and imputation can be found in the Supporting Information.

### 2.4 | Descriptive statistics of the genotyped sample

Of 3320 genotyped HeiDE participants (post-QC), 34 had missing personality phenotypes, and 18 were excluded because the phenotypic sex at baseline was either missing or did not match the sex recorded at follow-up. Thus, 3268 genotyped ($HeiDE_1$: $n$ = 2387, $HeiDE_2$: $n$ = 881) were contained in the final sample. At baseline, these individuals were 52.8 ± 7.0 (mean ± *SD*) years old (range 28–70; 99.6% were between 40 and 68 years old), 52.3% of them were female.

### 2.5 | Genome-wide association studies

We conducted a genome-wide association study (GWAS) for each personality phenotype. The covariates for each phenotype were the following: age, sex, and the first four multidimensional scaling (MDS) components of the pairwise identity-by-state distance matrix calculated on the nonimputed genotype data.

### 2.6 | Gene-set and gene property analyses

MAGMA gene-set and gene property tissue-specific expression analysis (GTEx v7, 53 tissue types) were performed as part of the FUMA (Watanabe et al., 2017) pipeline.

### 2.7 | SNP-based heritabilities and genetic correlation

For each of The Heidelberg Five personality traits, we estimated the aggregate proportion of variance explained by the additive effects of all genetic SNPs/variants and genetic correlations between pairwise combinations of personality traits using GCTA GREML. We estimated the genetic relationships among all HeiDE participants, excluding cryptically related individuals with genetic similarity $\hat{\pi} > 0.025$, and

using the same covariates as in the GWAS analyses. We used the –grm-adj 0 flag and thus assumed that causal loci have a similar distribution of allele frequencies as the genotyped SNPs.

### 2.8 | Calculation of PRS

We used summary statistics of a large GWAS on Neuroticism (Okbay et al., 2016) by the Social Science Genetic Association Consortium ($n$ = 170911) as training data. PRS were calculated as the sum of the imputation dosage for each risk allele multiplied by the effect size of each genetic variant. SNPs overlapping between the Neuroticism GWAS and the HeiDE sample were clumped with an LD threshold of 0.2 within a 500 kb window. Subsequently, PRS were calculated at 12 different $p$-value thresholds (from $1 \times 10^{-6}$ to 1). For each of The Heidelberg Five personality traits, we first evaluated a baseline linear regression model that predicted the factor scores of each individual personality dimension by age, sex, and the first four MDS components. We subsequently regressed residuals of the latter model onto Neuroticism PRS.

### 2.9 | The Heidelberg Five and psychiatric phenotypes at follow-up

We evaluated whether The Heidelberg Five, assessed at baseline, were associated with current depressive symptoms and lifetime anxiety phenotypes about 20 years later. The HeiDE subsample used in these analyses consisted of $n$ = 2888 individuals, were 71.5 ± 6.6 (mean ± $SD$, approximated by year of birth) years old (range 53–87), and 47.4% were female ($n$ = 2718 and $n$ = 2660 individuals without missing data were used for analyses of depressive and anxiety symptoms, respectively). Current (past 3 months) depressive symptoms were assessed using the German version of the 15-item CES-D questionnaire (Radloff, 1977; Hautzinger & Bailer, 1993; range of sum scores: 15–60). Using linear regression, we evaluated whether current depressive symptoms were associated with year of birth, sex, and factor scores of each of The Heidelberg Five measured at baseline. Visual inspection of the residuals indicated that these were not normally distributed (data not shown). We therefore log-transformed depression sum scores and subsequent visual inspection of the residuals of this model did not show obvious deviation from normality (see Supporting Information). We also tested, using logistic regression, whether a positive answer to at least one of six yes/no screening questions for lifetime anxiety symptoms (see Supporting Information) at the second follow-up was associated with year of birth, sex, and the factor scores of each of The Heidelberg Five measured at baseline. The $R^2$ of both models was calculated using the R *rsq* package. For anxiety symptoms, we used a variance-function-based $R^2$ for generalized linear models (Zhang, 2017).

### 2.10 | Correction procedures for multiple testing

When analyzing each of The Heidelberg Five personality dimensions separately by GWAS, gene-based, gene-set, and gene property analyses, we used the conservative Bonferroni threshold to correct $p$-values, to minimize false-positives. In the analyses that compared PRS across different $p$-value thresholds, and in the analyses in which SNP-based heritabilities were compared across all personality dimensions, we used the more powerful false-discovery rate (FDR; Benjamini & Hochberg, 1995). The latter method was also used when adjusting the $p$-values of the longitudinal associations of depressive and anxiety symptoms, due to the inherent dependency of both phenotypes.

## 3 | RESULTS

### 3.1 | The Heidelberg Five personality dimensions

We extracted the five personality dimensions ELAB, LBCN, TYAB, LOCC, and PSYC (Figure S1). These explained 22%, 14%, 10%, 8%, and 7% of the total variance (cumulative variance explained: 61%). The resulting factor scores had the following ranges: ELAB: −2.78 to 5.07; LBCN: −3.08 to 3.61; TYAB: −3.01 to 4.69; LOCC: −4.12 to 3.66; PSYC: −2.19 to 8.56.

### 3.2 | Genomic underpinnings of The Heidelberg Five

Tables 1 and 2 detail the results of SNP-based heritability analyses of and genetic correlation analyses between The Heidelberg Five. Nominally significant negative genetic correlations were found between ELAB and LBCN (Table 2) and ELAB and PSYC (Table 3), but these did not remain significant after correction for multiple testing.

### 3.3 | Emotional Lability

The GWAS of ELAB did not yield a genome-wide significant result (for details see Supporting Information). Gene-based tests identified the gene *Integrin Subunit Beta 5* (*ITGB5*) as significantly associated ($z$ = 4.66, $p = 1.56 \times 10^{-6}$, $n$ = 3268; see Figure 1). Tissue expression and gene-set analyses did not yield significant results (for details see Data S1). The SNP-based heritability was significant (33.9%, Table 1).

**TABLE 1** Single nucleotide polymorphism (SNP)-based heritabilities of The Heidelberg Five personality dimensions ($n$ = 2948 for each phenotype)

| Phenotype | $h^2_{SNP}$ | *SE* | Nominal *p* | *p*FDR |
|---|---|---|---|---|
| ELAB | 0.339 | 0.131 | 0.004 | 0.019 |
| LBCN | 0.294 | 0.134 | 0.014 | 0.034 |
| TYAB | 0.063 | 0.132 | 0.320 | 0.320 |
| LOCC | 0.093 | 0.128 | 0.229 | 0.320 |
| PSYC | 0.079 | 0.131 | 0.275 | 0.320 |

Abbreviations: ELAB, Emotional Lability; *p*FDR, FDR-corrected *p*-value; LBCN, Lack of Behavioral Control; LOCC, Locus of Control over Disease; PSYC, Psychoticism; *SE*, standard error; $h^2_{SNP}$, SNP-based heritability; TYAB, Type A Behavior.

**TABLE 2** Bivariate genetic correlations between The Heidelberg Five personality dimensions (1-tailed test, $n$ = 5896 for each phenotype pair)

| Phenotype 1 | Phenotype 2 | $r_G$ | *SE* | Nominal *p* | *p*FDR |
|---|---|---|---|---|---|
| ELAB | LBCN | −0.497 | 0.345 | 0.0489 | 0.197 |
| ELAB | LOCC | −0.901 | 1.015 | 0.059 | 0.197 |
| ELAB | PSYC | −1.000 | 0.942 | 0.044 | 0.197 |
| ELAB | TYAB | −0.700 | 0.982 | 0.164 | 0.329 |
| LBCN | LOCC | −0.400 | 0.731 | 0.274 | 0.391 |
| LBCN | PSYC | −0.677 | 0.847 | 0.157 | 0.329 |
| LBCN | TYAB | 0.808 | 1.340 | 0.246 | 0.391 |
| TYAB | LOCC | −1.000 | 2.679 | 0.5 | 0.500 |
| TYAB | PSYC | 1.000 | 2.095 | 0.5 | 0.500 |
| LOCC | PSYC | −1.000 | 1.717 | 0.5 | 0.500 |

*Note:* None of the correlations survived FDR correction.
Abbreviations: ELAB, Emotional Lability; FDR, false-discovery rate; $r_G$, genetic correlation; LBCN, Lack of Behavioral Control; LOCC, Locus of Control over Disease; PSYC, Psychoticism; *SE*, standard error; TYAB, Type A Behavior.

**TABLE 3** Top 10 SNPs from the GWAS of the phenotype PSYC

| SNP | CHR | BP | A1 | A2 | FRQ | INFO | BETA | *SE* | *p*-value |
|---|---|---|---|---|---|---|---|---|---|
| rs138223660 | 8 | 130801535 | T | C | 0.9861 | 0.8937 | −0.6671 | 0.1087 | 9.58e-10 |
| rs112196460 | 8 | 130842384 | C | T | 0.9869 | 0.9353 | −0.6669 | 0.1092 | 1.139e-09 |
| rs113875761 | 8 | 130787390 | C | G | 0.9859 | 0.8883 | −0.6568 | 0.1082 | 1.447e-09 |
| rs117161072 | 8 | 131417500 | G | A | 0.9868 | 0.9033 | −0.6697 | 0.1109 | 1.745e-09 |
| rs142975048 | 8 | 130743235 | A | G | 0.9848 | 0.8279 | −0.6466 | 0.1081 | 2.472e-09 |
| rs147237681 | 8 | 131027478 | C | A | 0.9863 | 0.9766 | −0.6113 | 0.1047 | 5.761e-09 |
| rs139795768 | 8 | 131314036 | T | A | 0.9877 | 0.8709 | −0.6609 | 0.117 | 1.748e-08 |
| rs9882438 | 3 | 36776413 | A | G | 0.0225 | 0.8547 | 0.4916 | 0.0879 | 2.414e-08 |
| rs143320762 | 8 | 130749679 | C | T | 0.9892 | 0.8892 | −0.6883 | 0.1237 | 2.827e-08 |
| rs187876956 | 8 | 130953808 | C | T | 0.9873 | 0.9854 | −0.5949 | 0.1082 | 4.172e-08 |

Abbreviations: A1, allele 1; A2, allele 2; BP, position; CHR, chomosome; FRQ, allele 1 frequency; GWAS, genome-wide association study; INFO, $R^2$ quality metric/information content; PSYC, Psychoticism; *SE*, standard error of effect estimate; SNP, single nucleotide polymorphism.

### 3.4 | Low Behavioral Control

GWAS, gene-based tests, tissue expression, and gene-set analyses did not show significant results (for details see Supporting Information). We observed, however, a significant SNP-based heritability (29.4%, Table 1). Apart from the nominally significant genetic correlation with ELAB mentioned above, none of the genetic correlations between LBCN and the other personality dimensions were significant.

### 3.5 | Type A Behavior

There was no genome-wide significant result for TYAB (for details see Supporting Information). The gene-based analysis identified the gene *Coiled-coil Domain Containing 83* (*CCDC83*) as significantly associated ($z$ = 4.63, $p = 1.81 \times 10^{-6}$, $n$ = 3268; see Figure 2) and three SNPs in the *CCDC83* gene (rs56160063, rs35944027, and rs60894727) were among the top 10 SNPs in the GWAS (all $p < 2.07 \times 10^{-6}$; see Supporting Information). Tissue expression and gene-set analyses did not yield significant results, neither did the SNP-based heritability analysis nor analyses of genetic correlations between The Heidelberg Five personality dimensions (for details see Supporting Information).

### 3.6 | Locus of Control over Disease

For LOCC, neither GWAS, gene-based, gene-set, tissue expression, SNP-based heritability, nor genetic correlation analyses yielded significant results (for details see Supporting Information).

### 3.7 | Psychoticism

The GWAS of PSYC identified a significantly associated locus on chromosome (top SNP rs138223660, $p = 9.58 \times 10^{-10}$; Figure 3). Genes at this locus include *Gasdermin C* (*GSDMC*), *Family With Sequence*

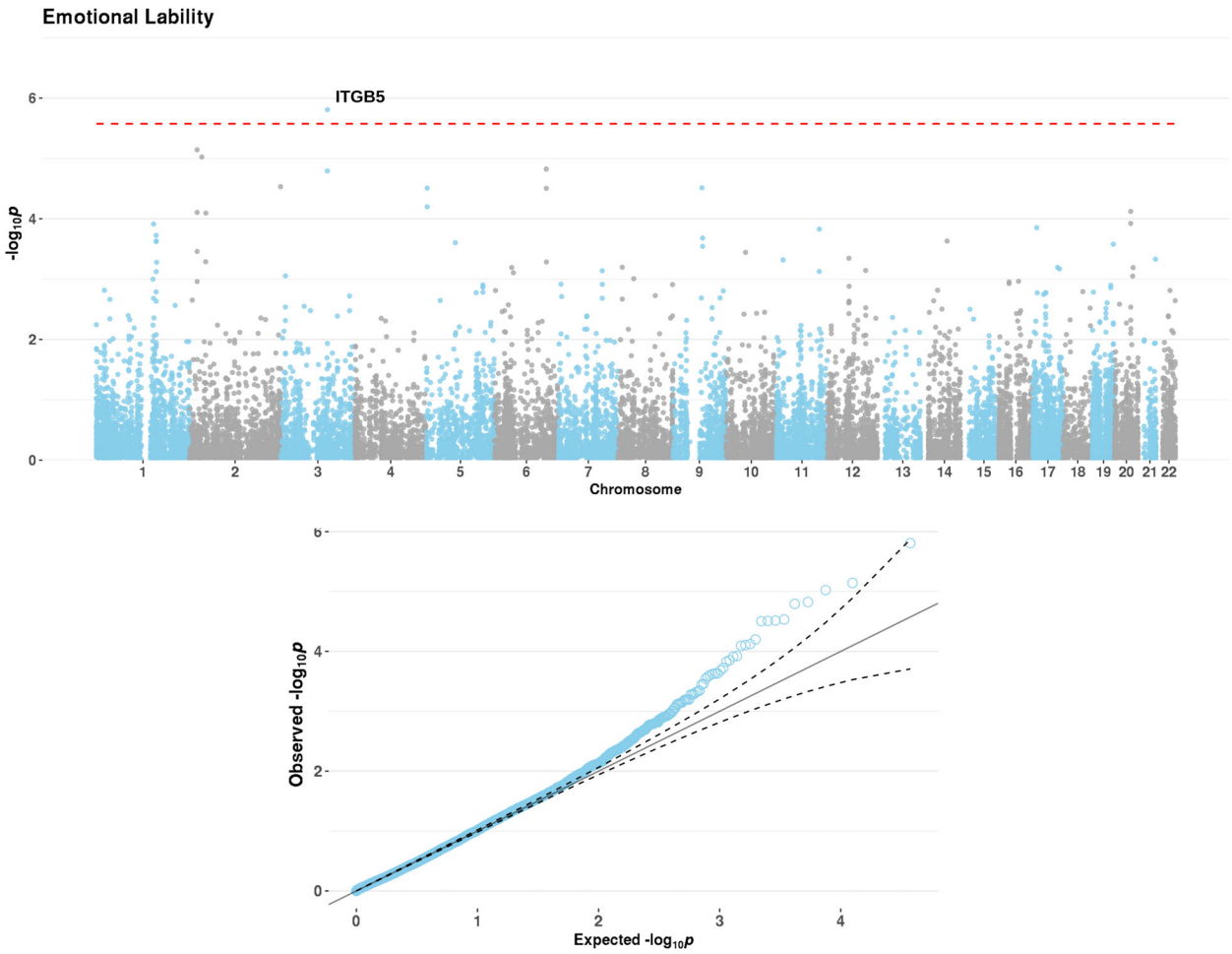


**FIGURE 1** Manhattan (top) and Q–Q plots (bottom) of the gene-based test of the phenotype ELAB. Genome-wide significance level (Bonferroni-corrected for 18,776 genes) is indicated by the red dashed line

*Similarity 49 Member B (FAM49B)*, and *ArfGAP With SH3 Domain, Ankyrin Repeat And PH Domain 1 (ASAP1)*. Another SNP on chromosome 3 (rs9882438, $p = 2.41 \times 10^{-8}$), located in an intron of the *Doublecortin Like Kinase 3 (DCLK3)* gene was also significantly associated with PSYC. The 10 SNPs with the lowest *p*-values are shown in Table 3. Gene-based analyses identified the gene *Nuclear Receptor Subfamily 1 Group H Member 4* (*NR1H4*, $z = 4.983$, $p = 3.13 \times 10^{-7}$; Figure 4) on chromosome 12 as associated with PSYC. Also, gene-set analysis identified the gene-set *GO_mf:go_bile_acid_binding* as over-represented in the GWAS results ($p_{Bon} < 0.05$, see Supporting Information). Neither tissue expression nor SNP-based heritability analysis yielded significant results.

## 3.8 | Associations of The Heidelberg Five with polygenic risk for neuroticism

We assessed the extent to which each of The Heidelberg Five personality dimensions shares a genetic basis with the clinically relevant Big Five personality trait Neuroticism by explaining the residuals of baseline regression models (each containing age, sex, and the first four ancestry principal components) by PRS for Neuroticism. Neuroticism PRS were significantly associated with ELAB (Figure 5), but not with the remaining personality dimensions (see Supporting Information). The direction of the association was positive, and the adjusted $R^2$s of FDR-significant *p*-value thresholds (0.01, 0.05, 0.1, 0.2, 0.3, 0.4, 0.5, 1) were 0.0024, 0.0031, 0.0025, 0.0030, 0.0027, 0.0029, 0.0026, and 0.0027 (see the legend of Figure 5 for *p*-values).

## 3.9 | Associations of The Heidelberg Five and psychopathology at follow-up

Table 4 lists the result of the regression analyses. All personality dimensions showed significant longitudinal associations with current depressive symptoms about 20 years after assessment. Regarding lifetime anxiety symptoms, ELAB, LBCN, and PSYC, but not LOCC or TYAB, were significantly associated.

# 4 | DISCUSSION

The aim of this work was to further characterize The Heidelberg Five using information on common genetic variants and long-term follow-

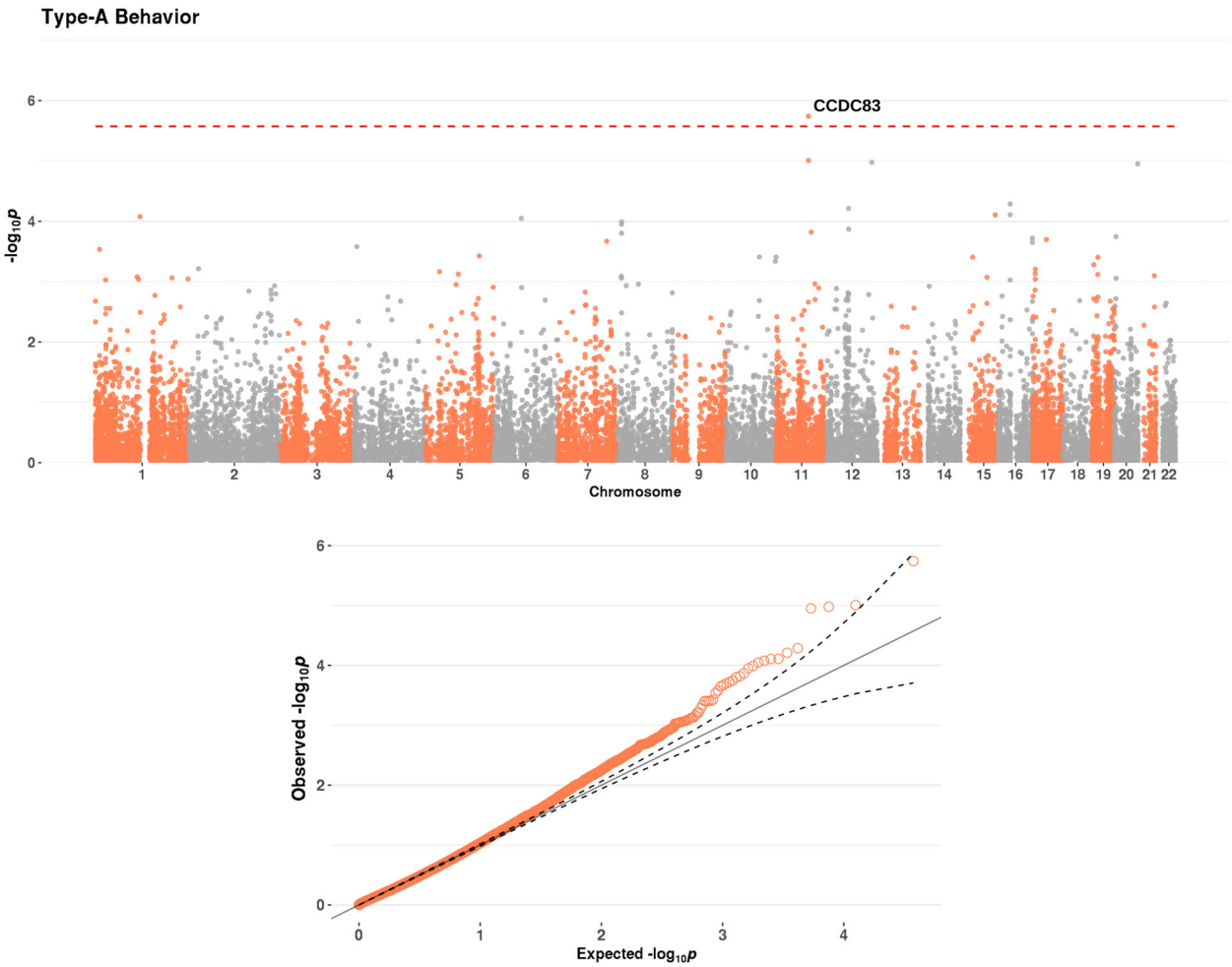


**FIGURE 2** Manhattan (top) and Q–Q plots (bottom) of the gene-based test of the phenotype TYAB. Genome-wide significance level (Bonferroni-corrected for 18,776 genes) is indicated by the red dashed line

up data, to gain a more comprehensive understanding of both their biological basis and their putative importance in predicting longitudinal outcomes. Regarding the follow-up analysis, it was surprising that each of The Heidelberg Five (high ELAB, low behavioral control, high TYAB, low internal LOCC, and high PSYC) was associated with more severe depressive symptoms, measured at the 20-year follow-up. These findings alone corroborate the importance of health-related personality traits, providing justification for further research.

Different SNP-based heritabilities across The Heidelberg Five furthermore suggest a varying importance of common genetic variants, albeit this may depend on the population under study (Moore & Shenk, 2017). Specifically, both ELAB and LBCN showed substantial SNP-based heritabilities. Studies that researched SNP-based heritability of Neuroticism, both phenotypically and genetically related to ELAB, report substantially lower heritability estimates around 15% (Docherty et al., 2016; Power & Pluess, 2015). Thus, in an elderly population-based sample, ELAB appears to tap a combination of characteristics that have a relatively strong common genetic basis. Interestingly, high Neuroticism, low Extraversion, and increased age have been also found to be associated with depression scores in a large Norwegian population-based study (Grav et al., 2012), supporting the ELAB construct. Our finding thus underscores the relevance of clinically valid personality dimensions for genetic research. It is conceivable that, in the elderly, ELAB defines a personality dimension having a strong genetic background, being jointly defined by a combination of two Big Five personality factors (Neuroticism and Extraversion).

LBCN also showed a relatively high SNP-based heritability which is supported by previous twin studies that found differences in executive control functions to be almost entirely genetic in origin (Friedman et al., 2008), lending support to the notion of LBCN as a latent "executive function" personality trait. Indeed, the unity/diversity framework for executive functions (Friedman & Miyake, 2017) describes inhibition as a key element. The loadings of low values on Anger Control and Social Desirability scales, and high values on Aggression, Irritability, and Anger Out scales (Amelang et al., 2004) onto the LBCN factor appear to fit well with this interpretation. Furthermore, as described in the case of ELAB, LBCN may define a clinically valid personality dimension for genetic research. Further research is necessary to determine whether an association of LBCN with cognitive tests of

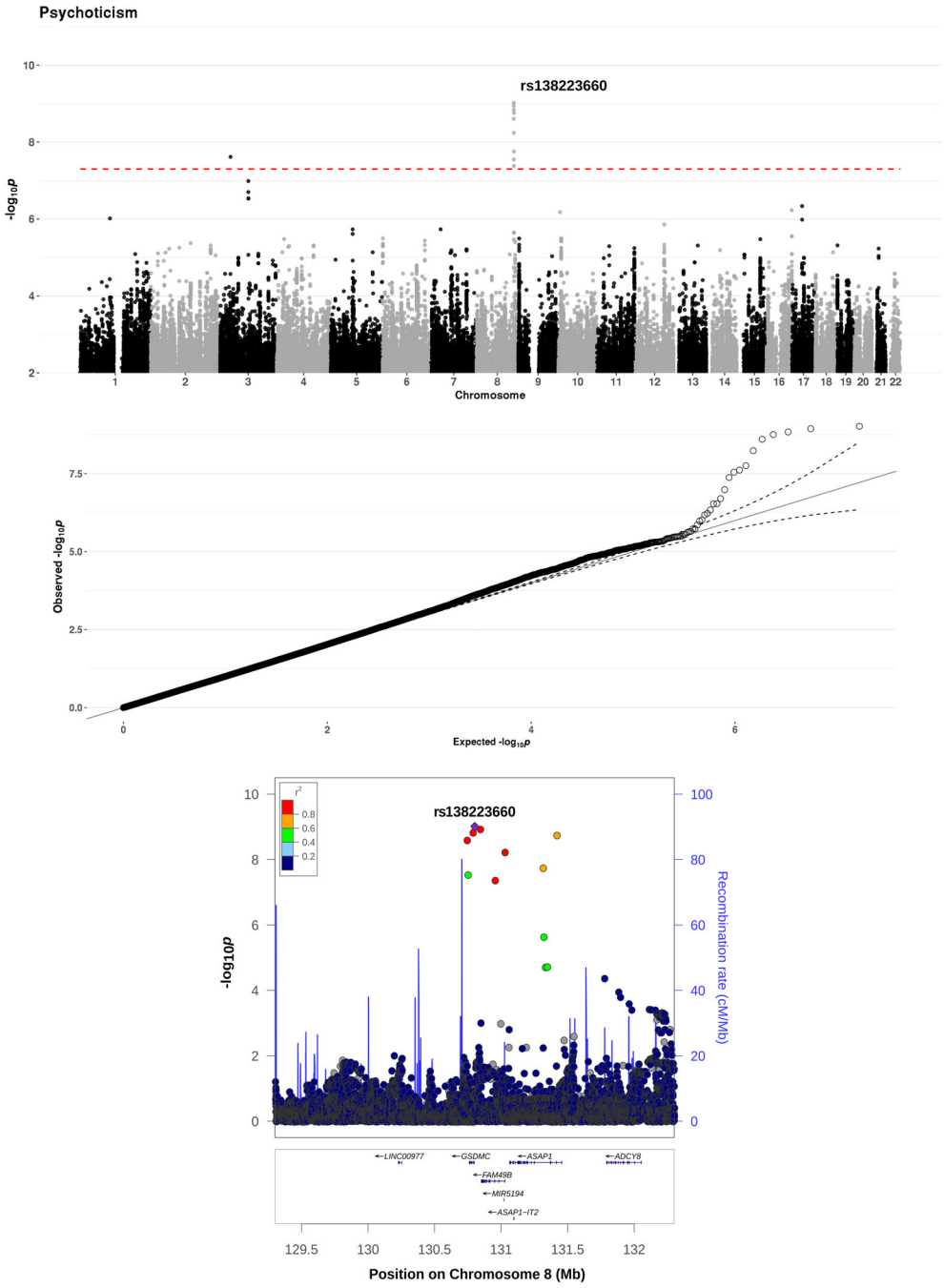


**FIGURE 3** Manhattan (top), Q–Q (middle, $\lambda$ = 1.008), and regional association (bottom) plots of the GWAS of the phenotype PSYC

executive function holds, as has been found for other behavioral constructs (Friedman et al., 2018; Morgan & Lilienfeld, 2000).

In the present study, we did not detect significant $h^2_{SNP}$ for TYAB, LOCC, or PSYC. Similar to Power and Pluess (2015), who found significant SNP-based heritabilities for only two Big Five traits (Neuroticism and Openness), this may be interpreted as emphasizing the putative importance of rare or structural variants for these personality dimensions, as all personality phenotypes are heritable to some degree (Turkheimer et al., 2014). Also, it is possible that unknown environmental covariates exist that explain more phenotypic variance of TYAB, LOCC, and PSYC, and accounting for these would result in larger observed SNP-based heritabilities also for these personality dimensions.

The orthogonality of The Heidelberg Five on the phenotype level is reflected by nonsignificant genetic correlations between them. Conversely, both the phenotypic and genotypic relatedness of Neuroticism and ELAB is reflected in substantial SNP-based heritabilities of both traits (see above) and by the result that Neuroticism PRS explain variation of ELAB. This was not the case for the remaining Heidelberg Five personality dimensions. Gene-based analysis of the ELAB phenotype identified *ITGB5*, encoding a transmembrane protein. The family of integrins, to which *ITGB5* belongs, are membrane proteins that translate intracellular signaling to extracellular interactions. They have been associated with neuropsychiatric disease (Carneiro, 2010) and coordinate both synaptic structure and function (Park & Goda, 2016).

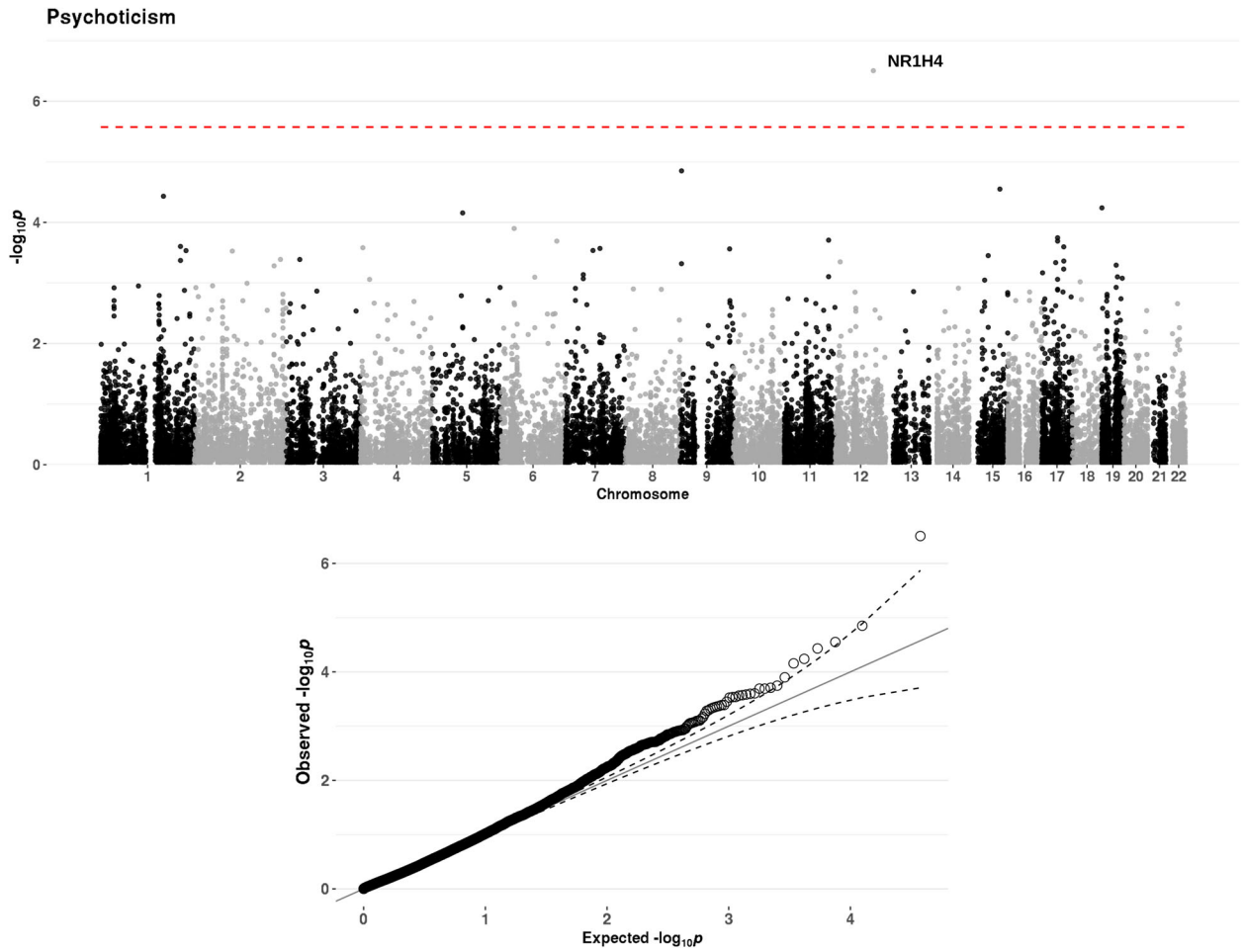


**FIGURE 4** Manhattan (top) and Q–Q plots (bottom) of the gene-based test of the phenotype PSYC. Genome-wide significance level (Bonferroni-corrected for 18,776 genes) is indicated by the red dashed line

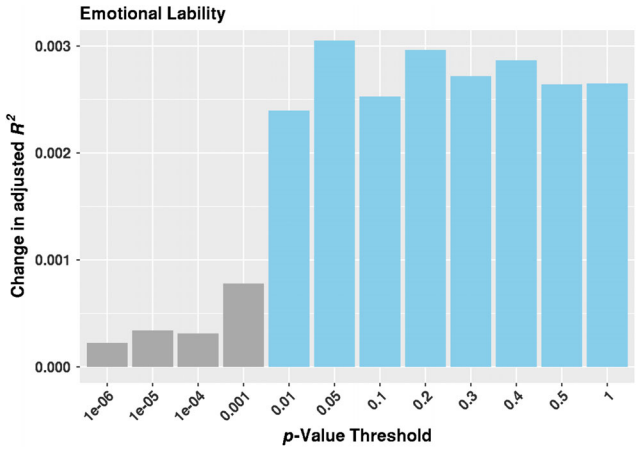


**FIGURE 5** Effects (adjusted $R^2$s) of PRS for neuroticism at different *p*-value thresholds on the residuals of a model regressing the personality dimension ELAB onto a set of baseline variables (see section 2). FDR-corrected *p*-values of the PRS were 0.187, 0.168, 0.168, 0.078, 0.004, 0.004, 0.004, 0.004, 0.004, 0.004, 0.004, and 0.004

Furthermore, SNPs in the *ITGB5* gene are associated with blood pressure (Giri et al., 2019) and coronary artery disease (Nelson et al., 2017). Interestingly, an association between ELAB and the incidence of CVD was previously identified in longitudinal analyses (Amelang et al., 2004) and thus may suggest a common genetic basis of both. Concerning the longitudinal associations of high ELAB scores with both depressive and anxiety symptoms, observed in the present study, confirm the well-known clinical importance of this Neuroticism-like phenotype (Gale et al., 2016), and are in line with meta-analyses of longitudinal studies of Neuroticism (Hakulinen et al., 2015; Jeronimus et al., 2016).

Regarding TYAB, gene-based analysis pointed to the protein-coding gene *Coiled-coil Domain Containing 83* (*CCDC83*). In European populations, this gene has been linked to urinary tract infection frequency (Tian et al., 2017), but not to behavioral phenotypes.

While no significant SNP-based heritability of PSYC was detected in the present study, GWAS and gene-based analysis revealed significant loci on chromosomes 3, 8, and 12. Of the genes in these loci, a SNP in *FAM49B* showed a suggestive association with post-traumatic

**TABLE 4** Regression analyses of current depressive and lifetime anxiety symptoms approximately 20 years after assessment of The Heidelberg Five

| **Current depressive symptoms** | | | | | |
|---|---|---|---|---|---|
| | **Estimate** | ***SE*** | ***t*-value** | ***p*-value** | $p_{FDR}$ |
| Intercept | 8.5428550 | 1.1990121 | 7.125 | 1.33e-12 | 5.317157e-12 |
| Year of birth | *−0.0027880* | *0.0006175* | *−4.515* | *6.60e-06* | *1.056070e-05* |
| Sex (male) | *−0.0234999* | *0.0080501* | *−2.919* | *0.00354* | *4.717726e-03* |
| ELAB | *0.1315498* | *0.0040296* | *32.646* | *<2e-16* | *<2e-16* |
| LBCN | *0.0363260* | *0.0041415* | *8.771* | *<2e-16* | *<2e-16* |
| TYAB | *0.0200983* | *0.0040783* | *4.928* | *8.80e-07* | *1.564546e-06* |
| LOCC | *−0.0084948* | *0.0040523* | *−2.096* | *0.03615* | *4.131205e-02* |
| PSYC | *0.0162838* | *0.0039524* | *4.120* | *3.90e-05* | *5.675753e-05* |
| **Lifetime anxiety symptoms** | | | | | |
| | **Estimate** | ***SE*** | ***z*-value** | ***p*-value** | $p_{FDR}$ |
| Intercept | −64.069467 | 12.953826 | −4.946 | 7.58e-07 | 1.556365e-06 |
| Year of birth | *0.032959* | *0.006671* | *4.941* | *7.78e-07* | *1.556365e-06* |
| Sex (male) | *−0.450115* | *0.085660* | *−5.255* | *1.48e-07* | *3.954736e-07* |
| ELAB | *0.613520* | *0.045513* | *13.480* | *<2e-16* | *<2e-16* |
| LBCN | *0.295001* | *0.044516* | *6.627* | *3.43e-11* | *1.097851e-10* |
| TYAB | *0.047679* | 0.042997 | 1.109 | 0.2675 | 2.853136e-01 |
| LOCC | 0.006232 | 0.042799 | 0.146 | 0.8842 | 8.842379e-01 |
| PSYC | *0.110470* | *0.043120* | *2.562* | *0.0104* | *1.281183e-02* |

*Note:* The adjusted $R^2$ of the model (see text) was 31.1% for current depressive symptoms and 11.2% for lifetime anxiety symptoms. FDR-significant regressors are in italics.
Abbreviations: ELAB, Emotional Lability; $p_{FDR}$, FDR-adjusted *p*-value; LBCN, Lack of Behavioral Control; LOCC, Locus of Control over Disease; PSYC, Psychoticism; *SE*, standard error of the estimate; TYAB, Type A Behavior.

stress disorder (Xie et al., 2013). Furthermore, SNPs in *ASAP1* were suggestively associated with autism spectrum disorder (Grove et al., 2019) and, in individuals with Ashkenazi Jewish ancestry, suggestively associated with schizophrenia (Goes et al., 2015). Finally, the gene-set *GO_mf:go_bile_acid_binding* was overrepresented among the PSYC results. The 10 genes in this gene set include *NR1H4* (also significant in the gene-based analysis), and the *Vitamin-D Receptor*, both of which are ligand-inducible transcription factors. The genes regulated by these transcription factors may thus contribute to the personality dimension PSYC.

## 5 | CONCLUSIONS

Several findings emerge from the present analyses of The Heidelberg Five. First, each personality dimension is associated with psychiatric phenotypes, measured some 20 years later, which underlines their clinical significance. Second, ELAB is genetically related to Neuroticism. As ELAB explained most of the phenotypic variance in the factor analysis, the behavioral importance of this clinical personality dimension is further underscored. Third, LBCN, a previously unknown latent "executive function" personality dimension has emerged as a heritable trait of clinical importance, warranting further investigation.

Our results need to be interpreted keeping the following limitations in mind: While based on longitudinal data, we used cross-sectional analyses ignoring accrual and mortality. If any of the traits or SNPs are associated with accrual or mortality, this will introduce selection bias. Results of the effects of psychological traits on CVD and cancer, including cause-specific mortality, are reassuring, however, insofar as most had no major impact on these outcomes (Stürmer et al., 2006). Finally, both the sample size, and the lack of a replication sample should be borne in mind when interpreting GWAS results.

## ACKNOWLEDGMENTS

The authors are grateful to all investigators and participants of the HeiDE study. Thomas G. Schulze was supported by the Deutsche Forschungsgemeinschaft (DFG) within the framework of the projects www.kfo241.de and www.PsyCourse.de (SCHU 1603/4-1, 5-1, 7-1, FA241/16-1) and by the German Federal Ministry of Education and Research (BMBF) through the Integrated Network IntegraMent (Integrated Understanding of Causes and Mechanisms in Mental Disorders), under the auspices of the e:Med Programme with grants awarded to Thomas G. Schulze (01ZX1614K), Marcella Rietschel (01ZX1614G), Markus M. Nöthen (01ZX1614A), and Bertram Müller-Myhsok (01ZX1614J). Thomas G. Schulze received additional support from the BMBF within the framework of the BipoLife network

(01EE1404H) and the Dr. Lisa Oehler Foundation, Kassel (Germany). Marcella Rietschel was additionally supported by the ERA-NET NEURON grants "SynSchiz" (01EW1810) and "EMBED" (01EW1904), and the DFG (FOR2107, RI908/11-2). Franziska Degenhardt received support from the BONFOR Program of the University of Bonn, Germany. Stephanie H. Witt was supported by the DFG (FOR2107, WI3429/3-2). Till F. M. Andlauer was supported by the BMBF through the DIFUTURE consortium of the Medical Informatics Initiative Germany (01ZZ1804A) and the European Union's Horizon 2020 Research and Innovation Programme (MultipleMS, EU RIA 733161). Til Stürmer received investigator-initiated research funding and support as Principal Investigator (R01 AG056479) from the National Institute on Aging (NIA), and as Co-Investigator (R01 HL118255, R01 MD011680), National Institutes of Health (NIH). He also received salary support as Director of Comparative Effectiveness Research (CER), NC TraCS Institute, UNC Clinical and Translational Science Award (UL1TR002489), the Center for Pharmacoepidemiology (current members: GlaxoSmithKline, UCB BioSciences, Takeda, AbbVie, Boehringer Ingelheim), from pharmaceutical companies (Novo Nordisk), and from a generous contribution from Dr. Nancy A. Dreyer to the Department of Epidemiology, University of North Carolina at Chapel Hill. Open Access funding enabled and organized by Projekt DEAL.

## CONFLICT OF INTEREST

Til Stürmer owns stock in Novartis, Roche, and Novo Nordisk, but does not accept personal compensation of any kind from any pharmaceutical company. All other authors declare no Conflict of Interest.

## AUTHOR CONTRIBUTIONS

**Urs Heilbronner**: Conceptualization; formal analysis; visualization; writing – original draft. **Sergi Papiol**: Supervision; writing – review and editing. **Monika Budde**: Conceptualization; writing – review and editing. **Till F. M. Andlauer**: Formal analysis; writing – review and editing. **Jana Strohmaier**: Resources; writing – review and editing. **Fabian Streit**: Resources; writing – review and editing. **Josef Frank**: Resources; writing – review and editing. **Franziska Degenhardt**: Resources; writing – review and editing. **Stefanie Heilmann-Heimbach**: Investigation; resources; writing – review and editing. **Stephanie Witt**: Resources; writing – review and editing. **Andreas J. Forstner**: Writing – review and editing. **Adrian Loerbroks**: Investigation; resources; writing – review and editing. **Manfred Amelang**: Investigation; writing – review and editing. **Til Stürmer**: Investigation; resources; writing – review and editing. **Bertram Müller-Myhsok**: Writing – review and editing. **Markus M. Nöthen**: Resources; writing – review and editing. **Marcella Rietschel**: Conceptualization; resources; project administration; writing – review and editing. **Thomas G. Schulze**: Conceptualization; funding acquisition; project administration; writing – review and editing.

## DATA AVAILABILITY STATEMENT

Due to the sensitivity of individual-level genetic data, these data and the corresponding analysis scripts are available from the authors based on reasonable request. Summary statistics of each GWAS are available online (GWAS Catalog, www.ebi.ac.uk/gwas/home), accession numbers GCST90013452 (ELAB), GCST90013453 (LBCN), GCST90013454 (TYAB), GCST90013455 (LOCC), and GCST90013456 (PSYC).

## ORCID

*Urs Heilbronner* https://orcid.org/0000-0001-7135-762X
*Till F. M. Andlauer* https://orcid.org/0000-0002-2917-5889
*Fabian Streit* https://orcid.org/0000-0003-1080-4339

## REFERENCES

Amelang, M., Hasselbach, P., & Stürmer, T. (2004). Personality, cardiovascular disease, and cancer: First results from the Heidelberg cohort study of the elderly. *Zeitschrift für Gesundheitspsychologie*, *12*(3), 102–115.

Benjamini, Y., & Hochberg, Y. (1995). Controlling the false discovery rate: A practical and powerful approach to multiple testing. *Journal of the Royal Statistical Society: Series B (Methodological)*, *57*(1), 289–300. https://doi.org/10.1111/j.2517-6161.1995.tb02031.x

Capitanio, J. P. (2008). Personality and disease. *Brain, Behavior, and Immunity*, *22*(5), 647–650. https://doi.org/10.1016/j.bbi.2008.02.002

Carneiro, A. M. D. (2010). The emerging role of integrins in neuropsychiatric disorders. *Neuropsychopharmacology*, *35*(1), 338–339. https://doi.org/10.1038/npp.2009.134

Chang, C. C., Chow, C. C., Tellier, L. C., Vattikuti, S., Purcell, S. M., & Lee, J. J. (2015). Second-generation PLINK: Rising to the challenge of larger and richer datasets. *GigaScience*, *4*, 7. https://doi.org/10.1186/s13742-015-0047-8

Chapman, J. P., Chapman, L. J., & Kwapil, T. R. (1994). Does the Eysenck psychoticism scale predict psychosis? A ten year longitudinal study. *Personality and Individual Differences*, *17*(3), 369–375. https://doi.org/10.1016/0191-8869(94)90284-4

de Leeuw, C. A., Mooij, J. M., Heskes, T., & Posthuma, D. (2015). MAGMA: Generalized gene-set analysis of GWAS data. *PLoS Computational Biology*, *11*(4), e1004219. https://doi.org/10.1371/journal.pcbi.1004219

Delaneau, O., Marchini, J., & Zagury, J.-F. (2012). A linear complexity phasing method for thousands of genomes. *Nature Methods*, *9*(2), 179–181. https://doi.org/10.1038/nmeth.1785

Docherty, A. R., Moscati, A., Peterson, R., Edwards, A. C., Adkins, D. E., Bacanu, S. A., … Kendler, K. S. (2016). SNP-based heritability estimates of the personality dimensions and polygenic prediction of both neuroticism and major depression: Findings from CONVERGE. *Translational Psychiatry*, *6*(10), e926–e926. https://doi.org/10.1038/tp.2016.177

Eysenck, H. J., & Eysenck, S. B. G. (1976). *Psychoticism as a dimension of personality*. London, England: Hodder and Stoughton.

Friedman, H. S., & Booth-Kewley, S. (1987). Personality, type A behavior, and coronary heart disease: The role of emotional expression. *Journal of Personality and Social Psychology*, *53*(4), 783–792. https://doi.org/10.1037//0022-3514.53.4.783

Friedman, M., & Rosenman, R. H. (1959). Association of specific overt behavior pattern with blood and cardiovascular findings; blood cholesterol level, blood clotting time, incidence of arcus senilis, and clinical coronary artery disease. *Journal of the American Medical Association*, *169*(12), 1286–1296. https://doi.org/10.1001/jama.1959.03000290012005

Friedman, N. P., & Miyake, A. (2017). Unity and diversity of executive functions: Individual differences as a window on cognitive structure. *Cortex*, *86*, 186–204. https://doi.org/10.1016/j.cortex.2016.04.023

Friedman, N. P., Miyake, A., Young, S. E., DeFries, J. C., Corley, R. P., & Hewitt, J. K. (2008). Individual differences in executive functions are almost entirely genetic in origin. *Journal of Experimental Psychology. General*, *137*(2), 201–225. https://doi.org/10.1037/0096-3445.137.2.201

Friedman, N. P., Rhee, S. H., Ross, J. M., Corley, R. P., & Hewitt, J. K. (2018). Genetic and environmental relations of executive functions to antisocial personality disorder symptoms and psychopathy. *International Journal of Psychophysiology*. https://doi.org/10.1016/j.ijpsycho.2018.12.007

Gale, C. R., Hagenaars, S. P., Davies, G., Hill, W. D., Liewald, D. C. M., Cullen, B., … Harris, S. E. (2016). Pleiotropy between neuroticism and physical and mental health: Findings from 108038 men and women in UK Biobank. *Translational Psychiatry*, *6*, e791. https://doi.org/10.1038/tp.2016.56

Giri, A., Hellwege, J. N., Keaton, J. M., Park, J., Qiu, C., Warren, H. R., … Edwards, T. L. (2019). Trans-ethnic association study of blood pressure determinants in over 750,000 individuals. *Nature Genetics*, *51*(1), 51–62. https://doi.org/10.1038/s41588-018-0303-9

Goes, F. S., McGrath, J., Avramopoulos, D., Wolyniec, P., Pirooznia, M., Ruczinski, I., … Pulver, A. E. (2015). Genome-wide association study of schizophrenia in Ashkenazi Jews. *American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics*, *168*(8), 649–659. https://doi.org/10.1002/ajmg.b.32349

Goldberg, L. R. (1993). The structure of phenotypic personality traits. *American Psychologist*, *48*(1), 26–34. https://doi.org/10.1037//0003-066x.48.1.26

Grav, S., Stordal, E., Romild, U. K., & Hellzen, O. (2012). The relationship among neuroticism, extraversion, and depression in the HUNT study: In relation to age and gender. *Issues in Mental Health Nursing*, *33*(11), 777–785. https://doi.org/10.3109/01612840.2012.713082

Grove, J., Ripke, S., Als, T. D., Mattheisen, M., Walters, R. K., Won, H., … Børglum, A. D. (2019). Identification of common genetic risk variants for autism spectrum disorder. *Nature Genetics*, *51*(3), 431–444. https://doi.org/10.1038/s41588-019-0344-8

Hakulinen, C., Elovainio, M., Pulkki-Råback, L., Virtanen, M., Kivimäki, M., & Jokela, M. (2015). Personality and depressive symptoms: individual participant meta-analysis of 10 cohort studies: Personality and depression. *Depression and Anxiety*, *32*(7), 461–470. https://doi.org/10.1002/da.22376

Hautzinger, M., & Bailer, M. (1993). *Allgemeine Depressions Skala: ADS*. Weinheim, Germany: Beltz.

Howie, B. N., Donnelly, P., & Marchini, J. (2009). A flexible and accurate genotype imputation method for the next generation of genome-wide association studies. *PLoS Genetics*, *5*(6), e1000529. https://doi.org/10.1371/journal.pgen.1000529

Jeronimus, B. F., Kotov, R., Riese, H., & Ormel, J. (2016). Neuroticism's prospective association with mental disorders halves after adjustment for baseline symptoms and psychiatric history, but the adjusted association hardly decays with time: A meta-analysis on 59 longitudinal/prospective studies with 443 313 participants. *Psychological Medicine*, *46*(14), 2883–2906. https://doi.org/10.1017/S0033291716001653

Kuper, H., Marmot, M., & Hemingway, H. (2002). Systematic review of prospective cohort studies of psychosocial factors in the etiology and prognosis of coronary heart disease. *Seminars in Vascular Medicine*, *2*(3), 267–314. https://doi.org/10.1055/s-2002-35401

Moore, D. S., & Shenk, D. (2017). The heritability fallacy. *Wiley Interdisciplinary Reviews Cognitive Science*, *8*(1–2), e1400. https://doi.org/10.1002/wcs.1400

Morgan, A. B., & Lilienfeld, S. O. (2000). A meta-analytic review of the relation between antisocial behavior and neuropsychological measures of executive function. *Clinical Psychology Review*, *20*(1), 113–136. https://doi.org/10.1016/S0272-7358(98)00096-8

Náfrádi, L., Nakamoto, K., & Schulz, P. J. (2017). Is patient empowerment the key to promote adherence? A systematic review of the relationship between self-efficacy, health locus of control and medication adherence. *PLoS One*, *12*(10), e0186458. https://doi.org/10.1371/journal.pone.0186458

Nelson, C. P., Goel, A., Butterworth, A. S., Kanoni, S., Webb, T. R., Marouli, E., … Deloukas, P. (2017). Association analyses based on false discovery rate implicate new loci for coronary artery disease. *Nature Genetics*, *49*(9), 1385–1391. https://doi.org/10.1038/ng.3913

Okbay, A., Baselmans, B. M. L., De Neve, J.-E., Turley, P., Nivard, M. G., Fontana, M. A., … Cesarini, D. (2016). Genetic variants associated with subjective well-being, depressive symptoms, and neuroticism identified through genome-wide analyses. *Nature Genetics*, *48*(6), 624–633. https://doi.org/10.1038/ng.3552

Park, Y. K., & Goda, Y. (2016). Integrins in synapse regulation. *Nature Reviews. Neuroscience*, *17*(12), 745–756. https://doi.org/10.1038/nrn.2016.138

Power, R. A., & Pluess, M. (2015). Heritability estimates of the Big Five personality traits based on common genetic variants. *Translational Psychiatry*, *5*, e604. https://doi.org/10.1038/tp.2015.96

R Core Team. (2014). *R: A language and environment for statistical computing*. Vienna, Austria: R Foundation for Statistical Computing. Retrieved from http://www.R-project.org

Radloff, L. S. (1977). The CES-D scale: A self-report depression scale for research in the general population. *Applied Psychological Measurement*, *1*(3), 385–401. https://doi.org/10.1177/014662167700100306

Rohlf, H. L., Holl, A. K., Kirsch, F., Krahé, B., & Elsner, B. (2018). Longitudinal links between executive function, anger, and aggression in middle childhood. *Frontiers in Behavioral Neuroscience*, *12*, 27. https://doi.org/10.3389/fnbeh.2018.00027

Rotter, J. B. (1966). Generalized expectancies for internal versus external control of reinforcement. *Psychological Monographs*, *80*(1), 1–28.

Sanchez-Roige, S., Gray, J. C., MacKillop, J., Chen, C.-H., & Palmer, A. A. (2018). The genetics of human personality. *Genes, Brain, and Behavior*, *17*(3), e12439. https://doi.org/10.1111/gbb.12439

Smith, D. F., Sterndorff, B., Røpcke, G., Gustavsen, E. M., & Hansen, J. K. (1996). Prevalence and severity of anxiety, depression and Type A behaviors in angina pectoris. *Scandinavian Journal of Psychology*, *37*(3), 249–258. https://doi.org/10.1111/j.1467-9450.1996.tb00657.x

Steptoe, A., & Wardle, J. (2001). Locus of control and health behaviour revisited: A multivariate analysis of young adults from 18 countries. *British Journal of Psychology (London, England: 1953)*, *92*(Pt 4), 659–672. https://doi.org/10.1348/000712601162400

Strudler Wallston, B., & Wallston, K. A. (1978). Locus of control and health: A review of the literature. *Health Education Monographs*, *6*(1), 107–117. https://doi.org/10.1177/109019817800600102

Stürmer, T., Hasselbach, P., & Amelang, M. (2006). Personality, lifestyle, and risk of cardiovascular disease and cancer: Follow-up of population based cohort. *BMJ (Clinical Research Ed.)*, *332*(7554), 1359. https://doi.org/10.1136/bmj.38833.479560.80

Szczepanski, S. M., & Knight, R. T. (2014). Insights into human behavior from lesions to the prefrontal cortex. *Neuron*, *83*(5), 1002–1018. https://doi.org/10.1016/j.neuron.2014.08.011

Tate, R. L. (1999). Executive dysfunction and characterological changes after traumatic brain injury: Two sides of the same coin? *Cortex*, *35*(1), 39–55. https://doi.org/10.1016/s0010-9452(08)70784-6

Tian, C., Hromatka, B. S., Kiefer, A. K., Eriksson, N., Noble, S. M., Tung, J. Y., & Hinds, D. A. (2017). Genome-wide association and HLA region fine-mapping studies identify susceptibility loci for multiple common infections. *Nature Communications*, *8*(1), 599. https://doi.org/10.1038/s41467-017-00257-5

Turkheimer, E., Pettersson, E., & Horn, E. E. (2014). A phenotypic null hypothesis for the genetics of personality. *Annual Review of Psychology*, *65*, 515–540. https://doi.org/10.1146/annurev-psych-113011-143752

van Kampen, D. (2009). Personality and psychopathology: A theory-based revision of Eysenck's PEN model. *Clinical Practice and Epidemiology in Mental Health*, *5*, 9–21. https://doi.org/10.2174/1745017900905010009

Watanabe, K., Taskesen, E., van Bochoven, A., & Posthuma, D. (2017). Functional mapping and annotation of genetic associations with FUMA. *Nature Communications*, *8*(1), 1826. https://doi.org/10.1038/s41467-017-01261-5

Weiner, B., Reisenzein, R., & Pranter, W. (2009). *Motivationspsychologie*. Weinheim, Germany: Beltz, Psychologie-Verl.-Union.

Wooldridge, K. L., Wallston, K. A., Graber, A. L., Brown, A. W., & Davidson, P. (1992). The relationship between health beliefs, adherence, and metabolic control of diabetes. *Diabetes Educator*, *18*(6), 495–500. https://doi.org/10.1177/014572179201800608

Wright, A. G. C., Thomas, K. M., Hopwood, C. J., Markon, K. E., Pincus, A. L., & Krueger, R. F. (2012). The hierarchical structure of DSM-5 pathological personality traits. *Journal of Abnormal Psychology*, *121*(4), 951–957. https://doi.org/10.1037/a0027669

Xie, P., Kranzler, H. R., Yang, C., Zhao, H., Farrer, L. A., & Gelernter, J. (2013). Genome-wide association study identifies new susceptibility loci for posttraumatic stress disorder. *Biological Psychiatry*, *74*(9), 656–663. https://doi.org/10.1016/j.biopsych.2013.04.013

Yang, J., Lee, S. H., Goddard, M. E., & Visscher, P. M. (2011). GCTA: A tool for genome-wide complex trait analysis. *American Journal of Human Genetics*, *88*(1), 76–82. https://doi.org/10.1016/j.ajhg.2010.11.011

Zhang, D. (2017). A coefficient of determination for generalized linear models. *American Statistician*, *71*(4), 310–316. https://doi.org/10.1080/00031305.2016.1256839

Zuckerman, M. (1989). Personality in the third dimension: A psychobiological approach. *Personality and Individual Differences*, *10*(4), 391–418. https://doi.org/10.1016/0191-8869(89)90004-4

## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

**How to cite this article:** Heilbronner U, Papiol S, Budde M, et al. "The Heidelberg Five" personality dimensions: Genome-wide associations, polygenic risk for neuroticism, and psychopathology 20 years after assessment. *Am J Med Genet Part B*. 2021;186B:77–89. https://doi.org/10.1002/ajmg.b.32837