## Genome-wide association study of the sensitivity to environmental stress and adversity neuroticism cluster

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## Research Letter

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Neuroticism is a highly heritable personality trait, characterized by emotions such as guilt, loneliness, embarrassment, and being easily hurt. Individuals with high levels of neuroticism are at increased risk of developing mental disorders, depression in particular (1). Neuroticism is commonly measured using the 12-item version of the Eysenck Personality Questionnaire (EPQ) (2). A recent genome-wide association study (GWAS) of approximately 370 000 EPQ responders by Nagel *et al*. (3) identified two genetically distinct neuroticism clusters: 'depressed affect' and 'worry', each defined by four of the 12 EPQ questions. Based on clustering of the pairwise genetic correlations, we hypothesize that three of the remaining four questions, namely 'Are your feelings easily hurt?', 'Do you worry too long after an embarrassing experience?', and 'Are you often troubled by feelings of guilt?', define a third genetic cluster (marked by blue color in Fig. 1a). Due to the common theme of the three items, we call this cluster 'sensitivity to environmental stress and adversity' (SESA). Such a cluster would be of particular interest due to the likely role of environmental stress and adversity in the etiology of depression.

Previously, we used data from the UK Biobank (4) to perform a GWAS for each of the 12 EPQ items, for their sum, and for the depressed affect and worry clusters (3, 5). For the study reported here, we performed an additional GWAS using 351 827 individuals of European descent from the UK Biobank, where each individual's phenotype is the number of 'YES' answers to the three SESA questions (field IDs 1950, 2000, and 2030). We use the same procedure as for our previous works (3, 5), testing each SNP using linear regression, including 14 covariates (age, sex, Townsend deprivation index, genotyping array, and ten principal components). In total, there are 7 259 579 autosomal SNPs with minor allele frequency ≥0.01, info ≥0.9, missingness ≤0.05, and with results for all 16 GWAS (i.e., the 15 published previously plus the GWAS focusing on the SESA cluster). The genome-wide significance threshold was 5e-8. We defined two SNPs as independent if they are more than 1cM apart, or have squared correlation <0.05. We assigned SNPs to genes using GENCODE annotations (www.gencodegenes.org) and estimated genetic correlations using SumHer (www.ldak.org) (6)

The Manhattan plot for the GWAS of the SESA cluster is shown in Fig. 1b. In total, there were 4 419 genome-wide significant SNPs, spanning 47 independent loci and 125 genes. Details of the 47 independent loci are shown in Table S1, while genome-wide results as well as postanalysis from FUMA (7) are available at https://ctg.cncr.nl/software/summary_statistics and http://fuma.ctglab.nl respectively (see a description of the FUMA analysis in the online supplement). The estimated genetic correlation between SESA and depressed affect was 0.68 (standard deviation (SD) = 0.01) and 0.75 (SD = 0.01) between SESA and worry, in both cases significantly less than one ($P$ < 1e-10). For comparison, the estimated genetic correlation between depressed affect and worry is 0.62 (SD = 0.01), while the phenotypic correlations between the three clusters were 0.48 (SESA and depressed affect), 0.52 (SESA and worry), and 0.45 (depressed affect and worry). Table 1 lists the 12 significant genes (8 distinct loci) not within the major histocompatibility complex (Chr6:25-34Mb) that are 'unique' (not genome-wide significant in any of the other 15 GWAS of neuroticism/clusters/items).

We have shown that three of the EPQ items define a third genetic cluster under neuroticism—sensitivity to environmental stress and adversity (SESA)—that is significantly different from the two previously established clusters (3). Furthermore, our analysis identified genome-wide significant associations between SESA and a series of genes not previously associated with neuroticism, among which *FAM19A4* (part of a family of genes that encodes for proteins that most likely function as brain-specific chemokines/neurokines) and *KCNH3* (encodes a voltage-gated potassium channel alpha subunit expressed in the forebrain that has been linked to cognitive function) seem of particular interest. Given the overall content of the SESA items, we expect that polygenic risk

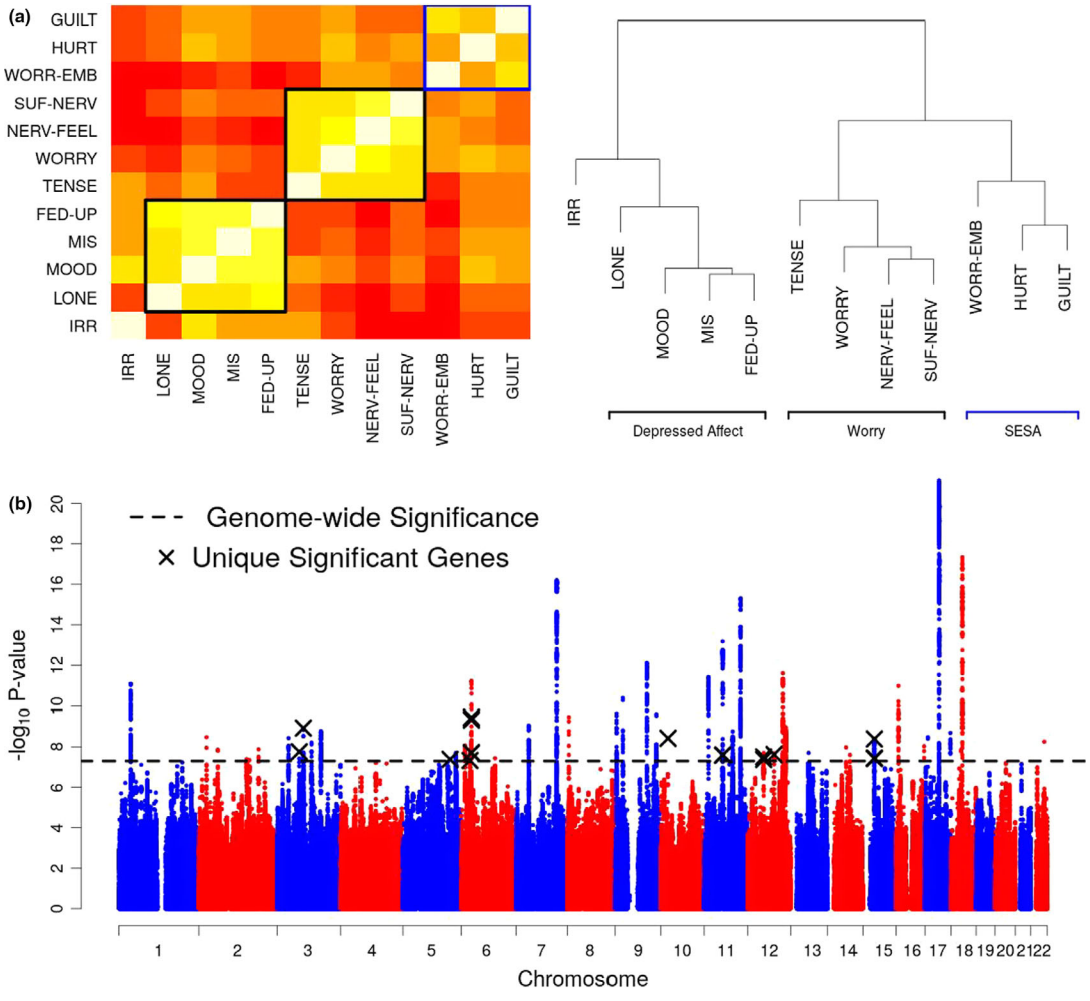


*Fig. 1.* Clustering of Eysenck Personality Questionnaire items and association analysis for the sensitivity to environmental stress and adversity (SESA) cluster. (a) The plot (left) shows genetic correlations between pairs of items. Colors indicate values between zero (red) and one (white). The SESA cluster is marked by blue color, while the depressed affect and worry clusters are marked by black color. The dendrogram (right) clusters the 12 neuroticism items based on their genetic correlations. (b) Points indicates the −log10 *P*-value from regressing the SESA phenotype (the number of YES responses to the three SESA items) on each SNP. The horizontal line marks genome-wide significance ($P < 5e\text{-}8$), while the crosses mark the unique significant genes (see main text). [Colour figure can be viewed at wileyonlinelibrary.com]

Table 1. Genes uniquely associated with the sensitivity to environmental stress and adversity (SESA) neuroticism cluster

| Gene | | *P*-values | | | | |
|---|---|---|---|---|---|---|
| Name | Location | SESA cluster | Depressed affect cluster | Worry cluster | Neuroticism score | Top neuroticism item |
| FAM19A4 | 3:68780917-69002448 | 2e-08 | 7e-05 | 0.002 | 3e-04 | 3e-07 |
| GBE1 | 3:81538850-81811312 | 1e-09 | 1e-06 | 7e-04 | 1e-06 | 1e-07 |
| PPP2R2B | 5:145960709-146464347 | 4e-08 | 0.001 | 4e-04 | 2e-04 | 1e-06 |
| PIP4K2A | 10:22823778-23003484 | 4e-09 | 0.01 | 1e-04 | 8e-05 | 2e-07 |
| SERPING1 | 11:57364860-57382326 | 3e-08 | 3e-04 | 0.003 | 4e-07 | 1e-06 |
| OR9Q1 | 11:57791353-57949088 | 2e-08 | 1e-04 | 6e-05 | 5e-06 | 3e-06 |
| KCNH3 | 12:49932940-49952091 | 3e-08 | 7e-04 | 3e-06 | 2e-06 | 4e-07 |
| PRPF40B | 12:49962001-50038449 | 4e-08 | 3e-04 | 3e-06 | 2e-06 | 3e-07 |
| LINC02426 | 12:82347498-82386912 | 2e-08 | 0.007 | 0.002 | 7e-04 | 5e-06 |
| AQR | 15:35143983-35262040 | 4e-09 | 0.006 | 4e-05 | 9e-07 | 4e-06 |
| ZNF770 | 15:35270542-35280488 | 4e-08 | 0.02 | 0.001 | 7e-06 | 2e-05 |
| AC114546 | 15:35285847-35295422 | 4e-08 | 0.04 | 3e-05 | 4e-06 | 2e-06 |

For each gene, we report *P*-values from GWAS for the SESA, depressive affect and worry phenotypes (constructed by summing the number of 'YES' answers to the 3, 4 and 4 corresponding Eysenck Personality Questionnaire items respectively) and from the full neuroticism score (the sum of all 12 items), and the smallest *P*-value from the 12 GWAS of individual items.

scores based on the results reported here will be of relevance in the search for gene-environment interactions in depression, where environmental stress and adversity has been suggested to play a key role.


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## Declaration of interest

The authors report no conflicts of interest.

## Data availability statement

The data used for this study are available upon application to the UK Biobank Resource.


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## Supporting Information

Additional Supporting Information may be found in the online version of this article:

**Table S1.** Description of the FUMA analysis & Independent genome-wide significant loci from SESA GWAS.