

# Genome-wide association analysis of composite sleep health scores in 413,904 individuals

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## Supplement

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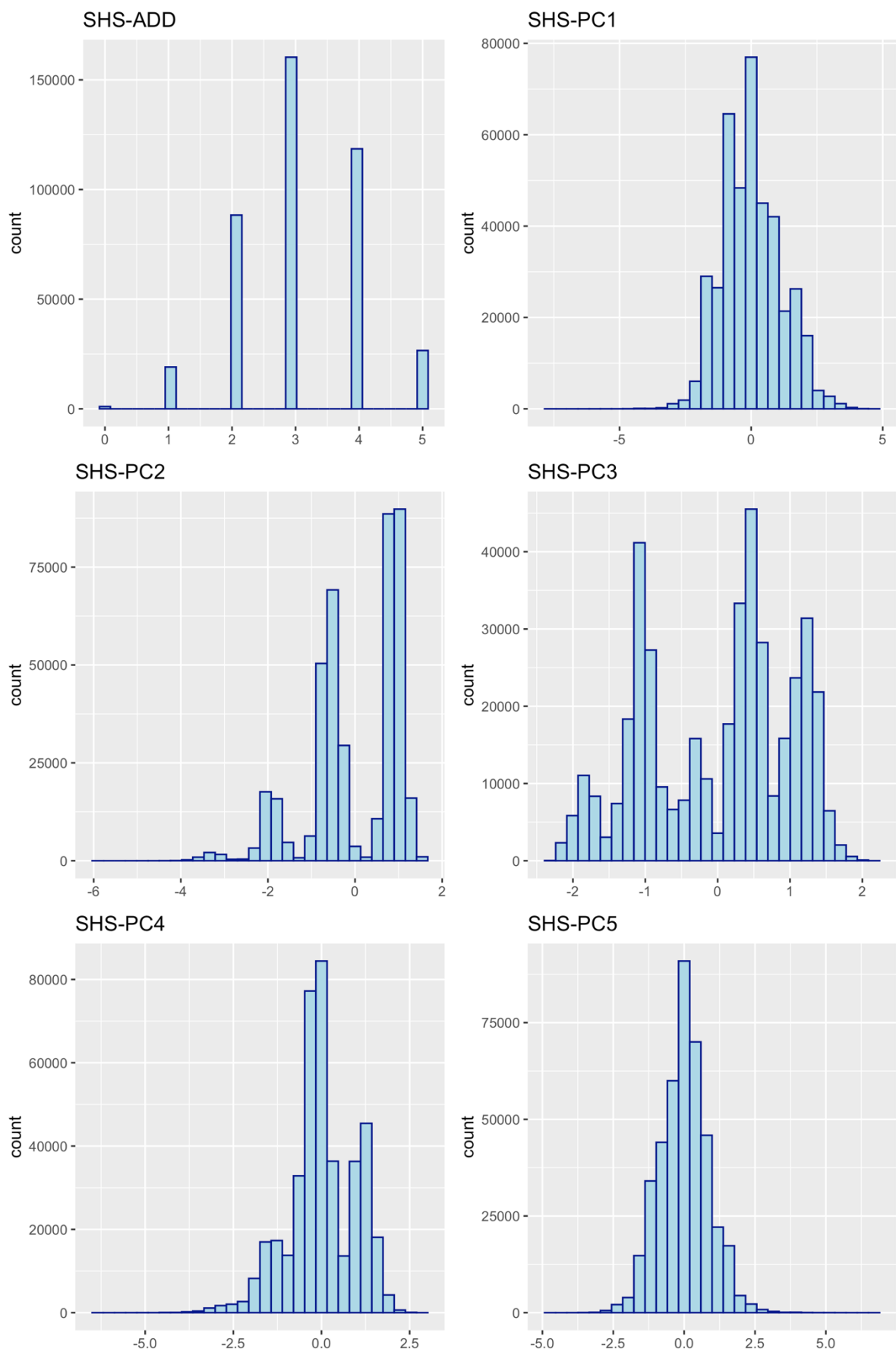
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## Supplementary Note 1

### **Additional results of genetic risk score analysis**

Both individual loci and GRS associated with SHS tended to associate with multiple self-reported sleep traits from which they were derived, as well as objective accelerometry-derived sleep traits, which were not used in SHS construction. For example, the *MEIS1* locus (SHS-ADD, SHS-PCs 1, 3, and 5) was associated with accelerometry-derived circadian/sleep timing, sleep duration, efficiency, and regularity, and the *PAX8* (SHS-PCs 1, 2, and 5) locus was associated with accelerometry sleep duration, efficiency, and daytime inactivity ( $p < 5 \times 10^{-8}$ ; Supplementary Table 9). Similarly, GRSs for SHS-ADD and SHS-PC1 associated with longer accelerometry-derived sleep duration, and higher sleep efficiency and regularity, while GRS of SHS-PC2 associated with shorter accelerometry-assessed daytime inactivity ( $p < 0.05/15/6 = 5.6 \times 10^{-4}$ ; Supplementary Table 10).

Supplementary Fig. 1. Histograms of SHS traits.

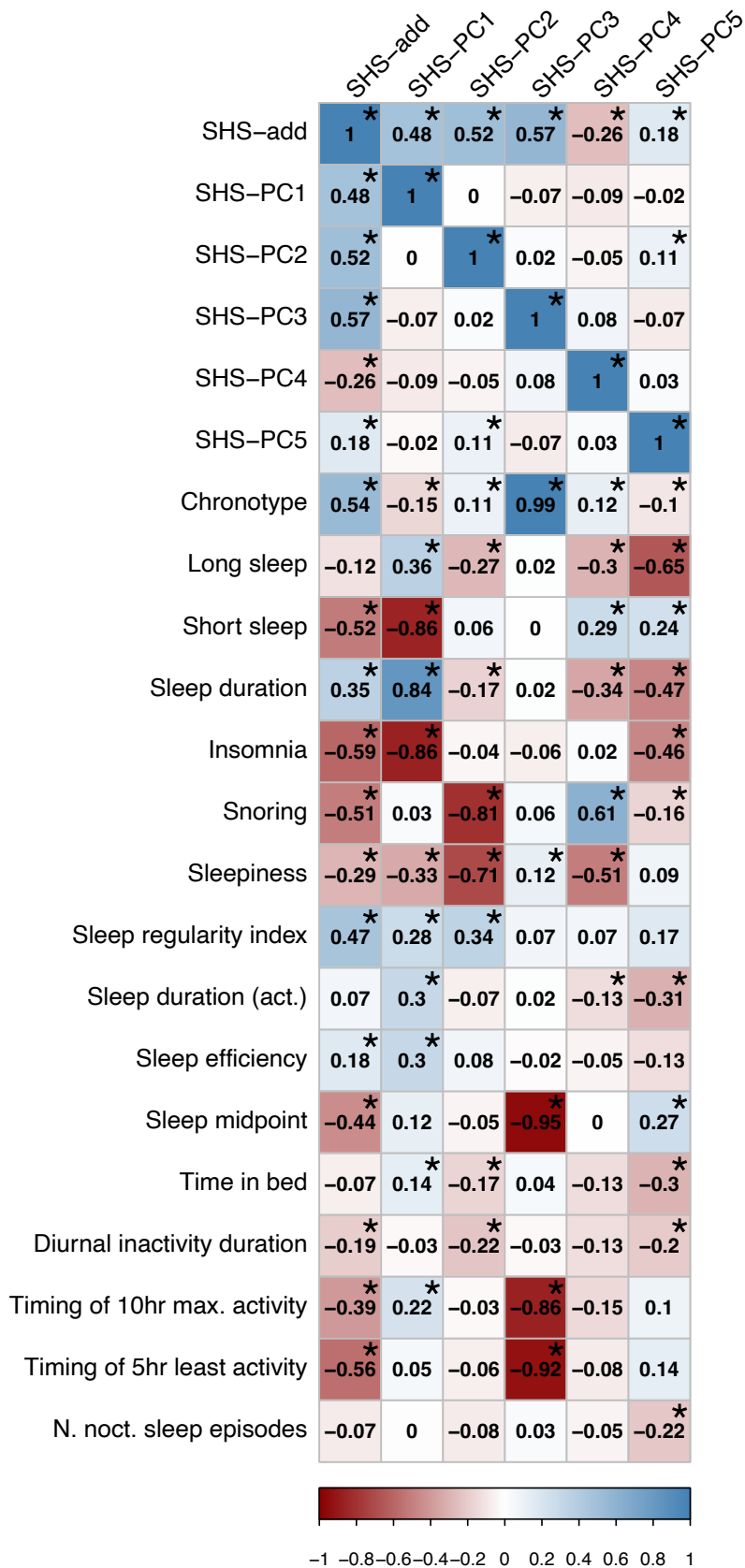


Supplementary Fig. 2. Phenotypic and genetic correlations between SHS traits with self-reported and accelerometry sleep traits in UKB.

a. Spearman correlations with self-reported and accelerometry sleep traits (\*:  $p < 3.8 \times 10^{-4}$ ).

|                              | SHS_add | SHS_PC1 | SHS_PC2 | SHS_PC3 | SHS_PC4 | SHS_PC5 |
|------------------------------|---------|---------|---------|---------|---------|---------|
| SHS_add                      | 1       | 0.36    | 0.46    | 0.49    | -0.29   | 0.19    |
| SHS_PC1                      | 0.36    | 1       | -0.19   | 0.05    | -0.07   | 0.09    |
| SHS_PC2                      | 0.46    | -0.19   | 1       | 0.1     | -0.06   | 0.06    |
| SHS_PC3                      | 0.49    | 0.05    | 0.1     | 1       | 0.01    | 0.03    |
| SHS_PC4                      | -0.29   | -0.07   | -0.06   | 0.01    | 1       | 0.04    |
| SHS_PC5                      | 0.19    | 0.09    | 0.06    | 0.03    | 0.04    | 1       |
| chronotype                   | 0.45    | -0.1    | 0.25    | 0.96    | 0.11    | -0.06   |
| Long sleep                   | -0.21   | 0.34    | -0.19   | 0.03    | -0.22   | -0.33   |
| Short sleep                  | -0.44   | -0.58   | 0.21    | -0.07   | 0.28    | 0.34    |
| Sleep duration               | 0.25    | 0.7     | -0.29   | 0.09    | -0.39   | -0.5    |
| Insomnia                     | -0.43   | -0.8    | 0.09    | -0.16   | -0.01   | -0.62   |
| Snoring                      | -0.49   | 0.09    | -0.76   | 0.03    | 0.65    | -0.11   |
| Sleepiness                   | -0.15   | -0.27   | -0.54   | 0.15    | -0.52   | 0.21    |
| Sleep regularity index       | 0.1     | 0.06    | 0.06    | 0.02    | 0       | 0       |
| Sleep duration (act.)        | 0.04    | 0.09    | 0       | 0.02    | -0.07   | -0.16   |
| Sleep efficiency             | 0.08    | 0.08    | 0.06    | 0       | -0.06   | -0.1    |
| Sleep midpoint               | -0.11   | 0.03    | -0.08   | -0.27   | -0.04   | 0.02    |
| Diurnal inactivity duration  | -0.08   | 0       | -0.1    | -0.01   | -0.03   | -0.03   |
| Timing of 10hr max. activity | -0.12   | 0.06    | -0.07   | -0.29   | -0.03   | 0.02    |
| Timing of 5hr least activity | -0.15   | 0.02    | -0.1    | -0.3    | -0.05   | 0.02    |
| N. noct. sleep episodes      | -0.01   | 0.04    | -0.03   | 0       | -0.01   | -0.06   |

b. LDSC genetic correlations with self-reported and accelerometry sleep traits (\*:  $p < 3.8 \times 10^{-4}$ ).

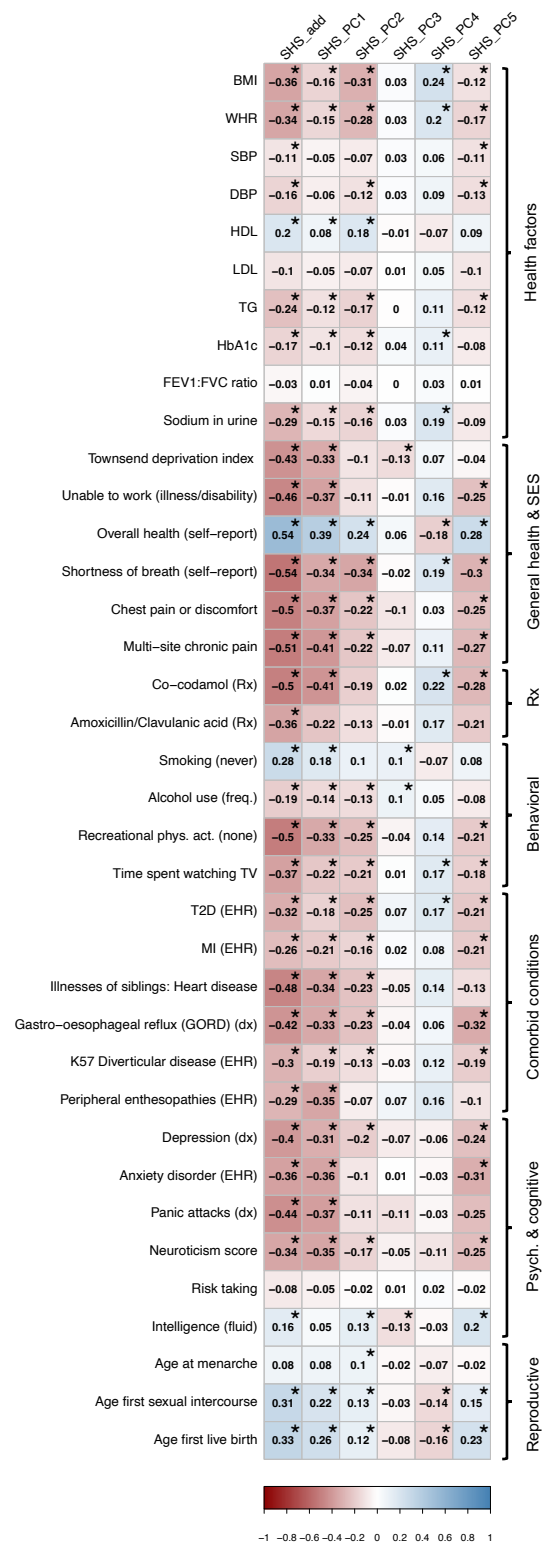


Supplementary Fig. 3. Phenotypic and genetic correlation plots of SHS traits with selected representative traits

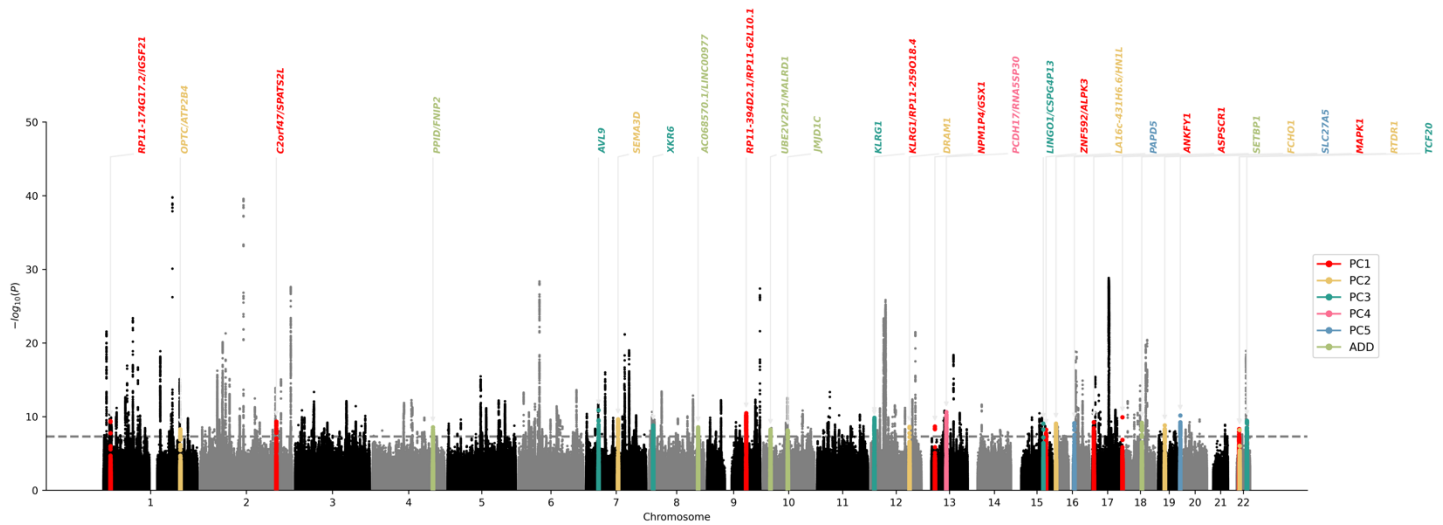
a. Spearman rank correlations of SHSs with phenotypic traits of interest (\*:  $p < 2.2 \times 10^{-5}$ ).

|                                       | SHS_A04 | SHS_PC1 | SHS_PC2 | SHS_PC3 | SHS_PC4 | SHS_PC5 |                      |
|---------------------------------------|---------|---------|---------|---------|---------|---------|----------------------|
| Age                                   | -0.03   | -0.05   | -0.07   | 0.09    | -0.08   | -0.1    | Health factors       |
| Male                                  | -0.07   | 0.08    | -0.17   | 0.01    | 0.14    | 0.12    |                      |
| BMI                                   | -0.17   | -0.04   | -0.19   | 0       | 0.12    | -0.02   |                      |
| WHR                                   | -0.15   | 0.02    | -0.22   | 0       | 0.13    | 0.04    |                      |
| SBP                                   | -0.07   | -0.01   | -0.09   | 0.04    | 0.05    | -0.04   |                      |
| DBP                                   | -0.09   | 0       | -0.1    | 0.01    | 0.09    | -0.03   |                      |
| HDL                                   | 0.1     | -0.03   | 0.16    | 0       | -0.08   | -0.04   |                      |
| LDL                                   | -0.06   | -0.02   | -0.06   | 0       | 0.03    | -0.05   |                      |
| TG                                    | -0.12   | -0.01   | -0.14   | -0.01   | 0.07    | -0.03   |                      |
| HbA1c                                 | -0.08   | -0.05   | -0.09   | 0.02    | 0.01    | -0.03   |                      |
| FEV1:FVC ratio                        | 0.01    | 0.01    | 0.02    | -0.01   | 0.03    | 0.01    | General health & SES |
| Townsend deprivation index            | -0.05   | -0.05   | -0.01   | -0.02   | -0.02   | 0.02    |                      |
| Age completed education               | 0.06    | 0.06    | 0.04    | -0.07   | 0.03    | 0.04    |                      |
| Unable to work (illness/disability)   | -0.1    | -0.06   | -0.05   | -0.03   | -0.06   | -0.04   |                      |
| Recent stress                         | 0.07    | 0.07    | 0.02    | 0.04    | -0.01   | 0.01    |                      |
| Overall health rating                 | 0.21    | 0.15    | 0.12    | 0.08    | 0       | 0.08    |                      |
| Number of treatments/meds taken       | -0.12   | -0.11   | -0.09   | 0       | -0.05   | -0.11   |                      |
| Shortness of breath (EHR)             | -0.03   | -0.02   | -0.02   | 0       | -0.01   | -0.01   |                      |
| Chest pain or discomfort              | -0.11   | -0.09   | -0.06   | -0.04   | -0.01   | -0.03   |                      |
| Multi-site chronic pain               | -0.16   | -0.16   | -0.07   | -0.05   | -0.01   | -0.07   | Rx                   |
| Taking analgesic (OTC med.)           | -0.09   | -0.1    | -0.04   | -0.02   | -0.02   | -0.06   |                      |
| Co-codamol (Rx)                       | -0.05   | -0.05   | -0.02   | -0.01   | -0.02   | -0.03   |                      |
| Amoxicillin (Rx)                      | 0       | 0       | 0       | 0       | 0       | 0       |                      |
| Smoking (ever)                        | -0.08   | -0.02   | -0.06   | -0.06   | 0.03    | -0.02   | Behavioral           |
| Alcohol use (freq.)                   | -0.01   | 0.04    | -0.03   | -0.05   | 0.06    | -0.01   |                      |
| Physical activity (METS)              | 0.07    | 0.01    | 0.06    | 0.06    | 0       | 0.03    |                      |
| Recreational phys. act. (none)        | -0.08   | -0.05   | -0.03   | -0.04   | -0.01   | -0.01   |                      |
| Time spent watching TV                | -0.13   | -0.06   | -0.11   | -0.01   | -0.02   | -0.09   | Comorbid conditions  |
| Time spent using computer             | -0.02   | 0.02    | -0.02   | 0.01    | 0.11    | 0.07    |                      |
| Diabetes (dx)                         | -0.05   | -0.02   | -0.06   | 0       | -0.02   | -0.02   |                      |
| MI (UKB)                              | -0.04   | -0.02   | -0.05   | 0.01    | -0.01   | -0.01   |                      |
| Stroke (UKB)                          | -0.03   | -0.01   | -0.03   | 0       | -0.02   | -0.01   |                      |
| COPD (UKB)                            | -0.06   | -0.04   | -0.03   | -0.01   | -0.02   | -0.01   |                      |
| Gastro-oesophageal reflux (GORD) (dx) | -0.05   | -0.04   | -0.03   | -0.01   | 0       | -0.03   |                      |
| Diverticular dis. (dx)                | -0.02   | -0.02   | -0.01   | 0       | -0.01   | -0.02   |                      |
| Osteoarthritis                        | -0.05   | -0.07   | -0.02   | 0.01    | -0.02   | -0.04   |                      |
| Alzheimer's (fam. hx)                 | -0.01   | -0.02   | -0.01   | 0       | -0.01   | -0.02   | Psych. & cognitive   |
| Anxiety disorder dx                   | -0.01   | -0.03   | 0.01    | -0.02   | -0.01   | -0.03   |                      |
| Bipolar dx                            | -0.02   | 0.01    | -0.02   | -0.01   | -0.02   | -0.01   |                      |
| Depression dx                         | -0.03   | -0.03   | 0       | -0.03   | -0.01   | -0.03   |                      |
| Manic episodes                        | -0.03   | -0.02   | -0.02   | -0.01   | 0       | 0       |                      |
| Migraine                              | -0.01   | -0.02   | 0.01    | -0.01   | -0.02   | -0.01   |                      |
| Panic attacks (dx)                    | -0.02   | -0.02   | 0       | -0.02   | 0       | -0.02   |                      |
| Neuroticism score                     | -0.18   | -0.22   | -0.06   | -0.08   | -0.05   | -0.13   |                      |
| Risk taking                           | -0.03   | 0.01    | -0.04   | -0.01   | 0.05    | 0.04    |                      |
| Intelligence (fluid)                  | 0.03    | 0.02    | 0.02    | -0.06   | 0.04    | 0.03    | Reproductive         |
| Age at menarche                       | 0.01    | 0.02    | 0.01    | -0.01   | -0.03   | -0.01   |                      |
| Age start oral contraceptives         | 0       | -0.03   | -0.02   | 0.04    | -0.04   | -0.02   |                      |
| Age first live birth                  | 0.09    | 0.09    | 0.03    | -0.03   | -0.01   | 0.06    |                      |

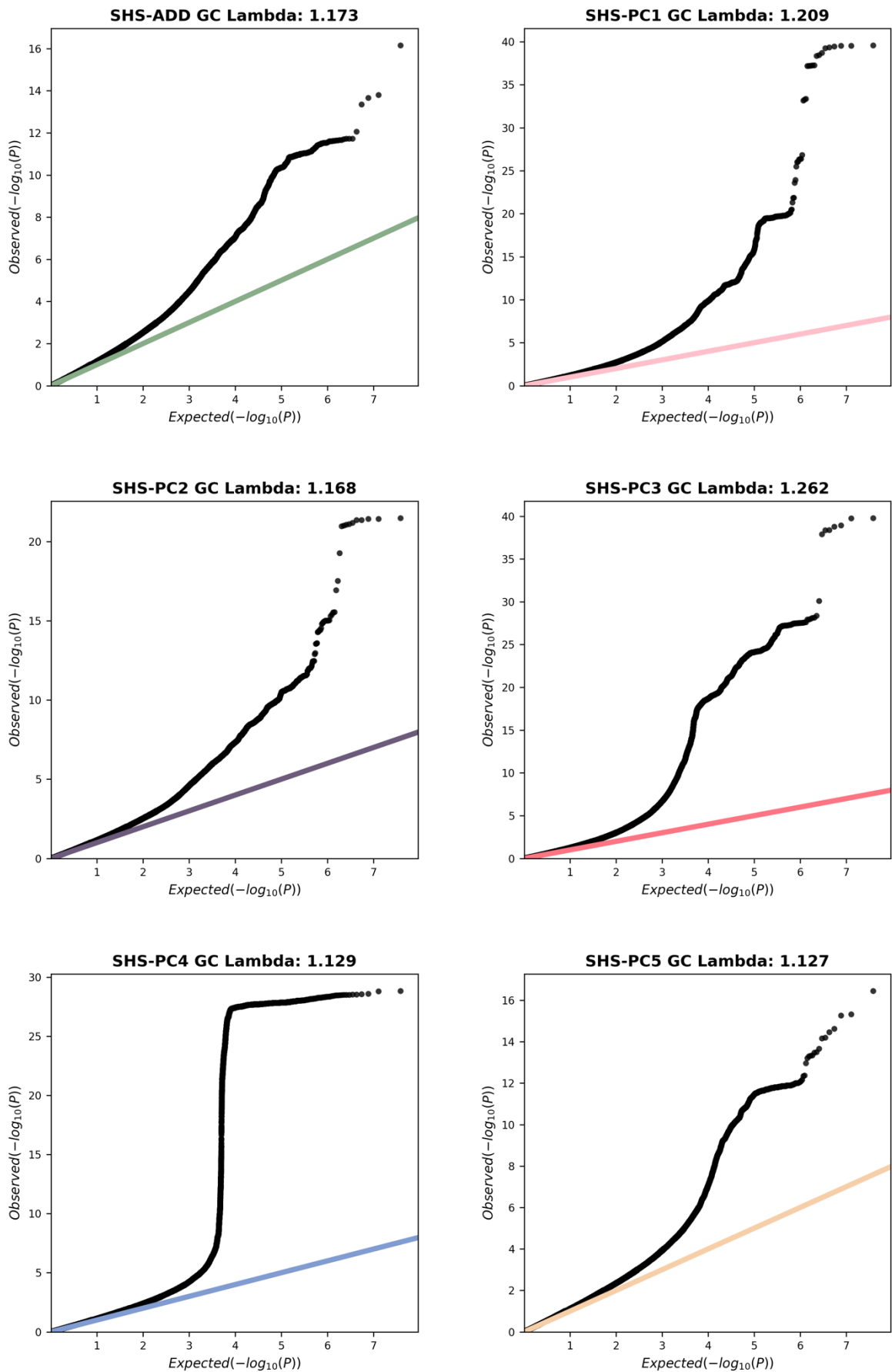
b. Genetic correlations with phenotypic traits of interest from LD score regression (\*: p<2.2e-05).



Supplementary Fig. 4. Composite Manhattan plot for SHS traits.



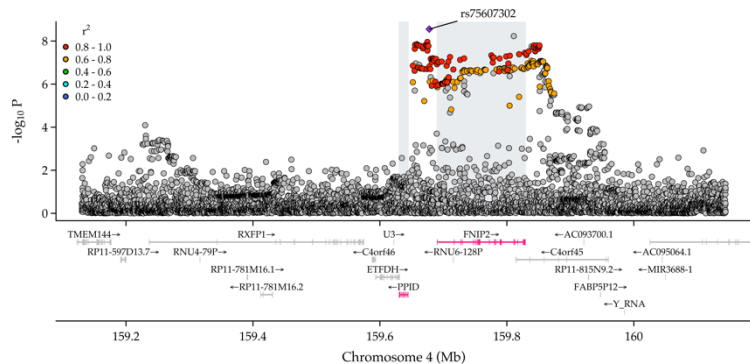
Supplementary Fig. 5. QQ plots for SHS GWASs.



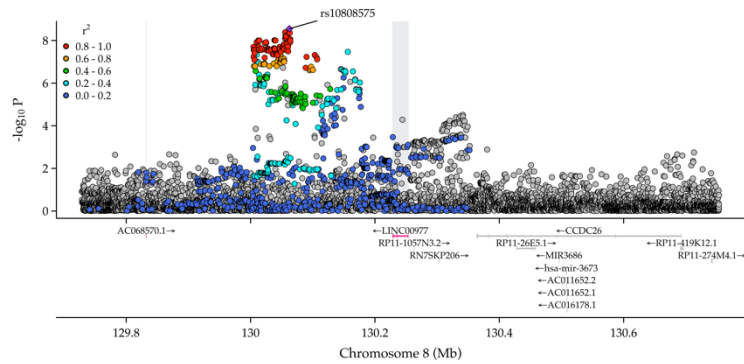
# Supplementary Fig. 6. Locus zoom plots. Note: Below regional association plots created from locuszoomr are depicted if rsID is available (Table 1).

Primary genes mapped to each variant (Table 1) are highlighted in pink with their spanning regions shown in light grey background. Scatter is colored based on linkage disequilibrium information (R<sup>2</sup>) retrieved from LDLink and FUMA SNP2GENE (Methods). The lead SNP for each locus is depicted as a dark purple diamond.

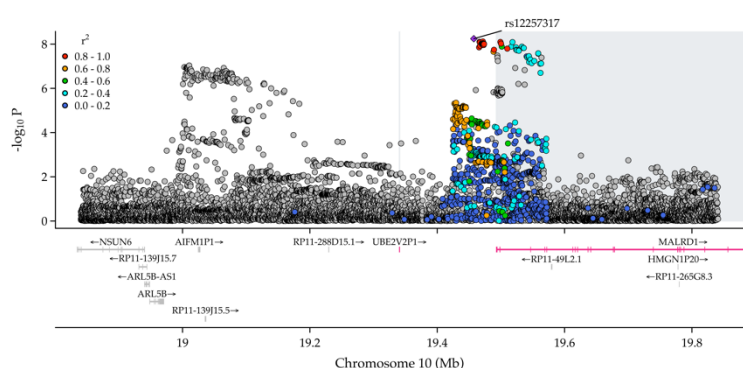
## Locus 1: rs75607302, SHS-ADD



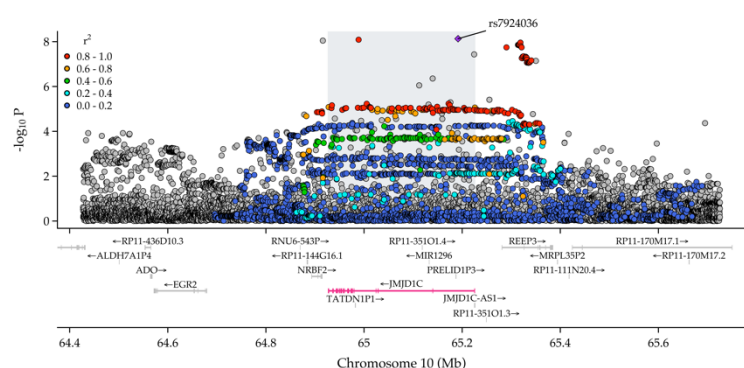
## Locus 2: rs10808575, SHS-ADD



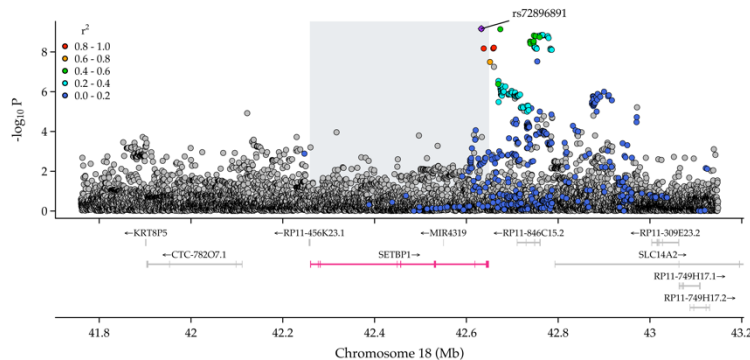
## Locus 3: rs12257317, SHS-ADD



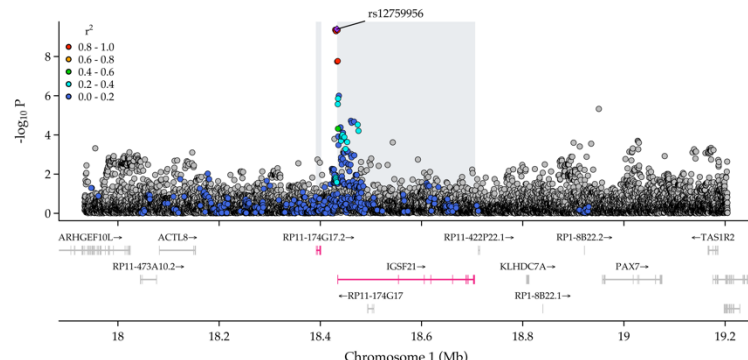
## Locus 4: rs7924036, SHS-ADD



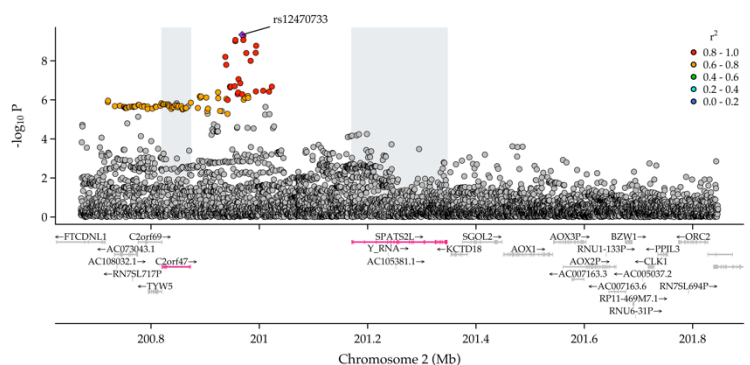
## Locus 5: rs72896891, SHS-ADD



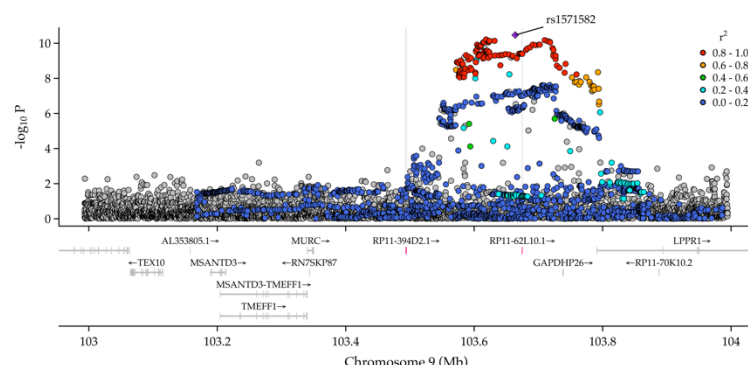
## Locus 6: rs12759956, SHS-PC1



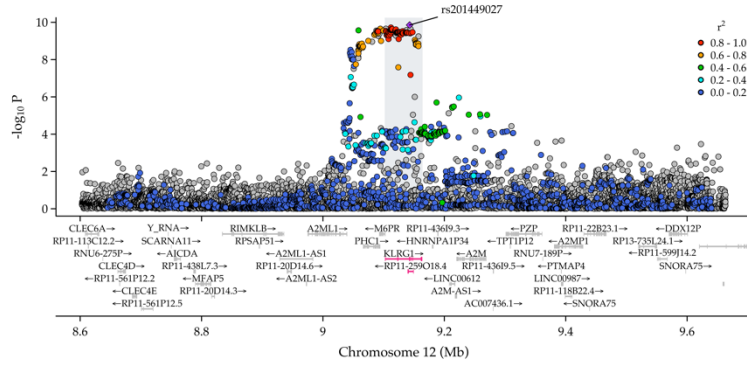
## Locus 7: rs12470733, SHS-PC1



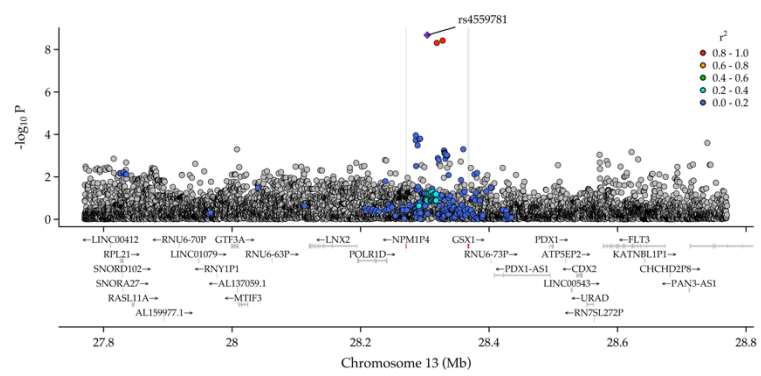
## Locus 8: rs1571582, SHS-PC1



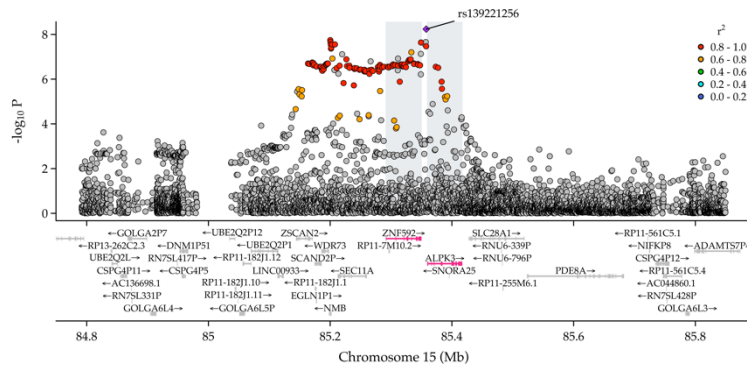
Locus 9: rs201449027, SHS-PC1



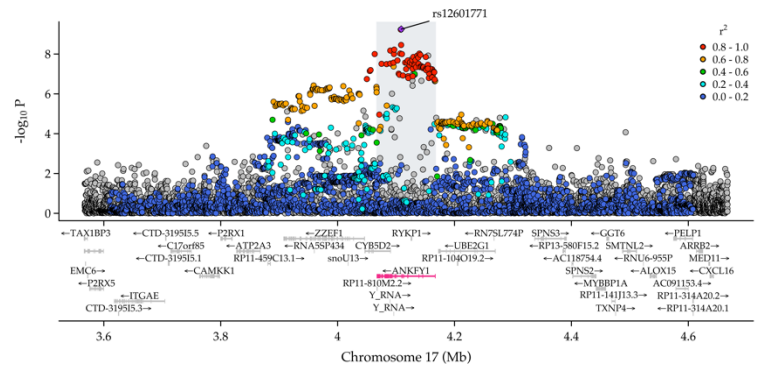
Locus 10: rs4559781, SHS-PC1



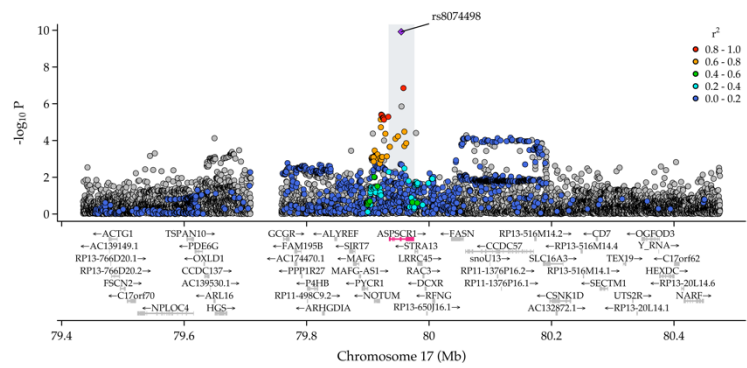
Locus 11: rs139221256, SHS-PC1



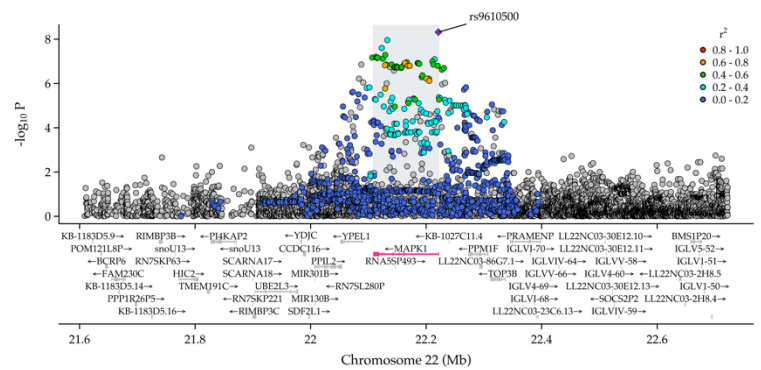
Locus 12: rs12601771, SHS-PC1



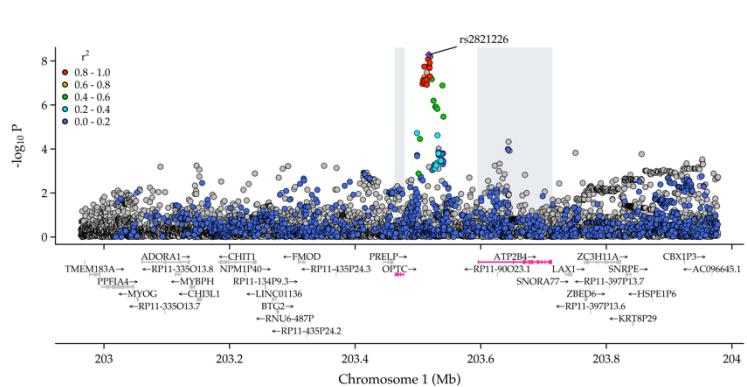
Locus 13: rs8074498, SHS-PC1



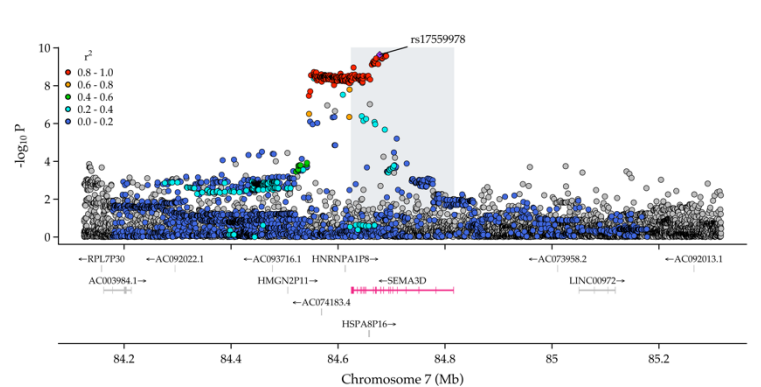
Locus 14: rs9610500, SHS-PC1



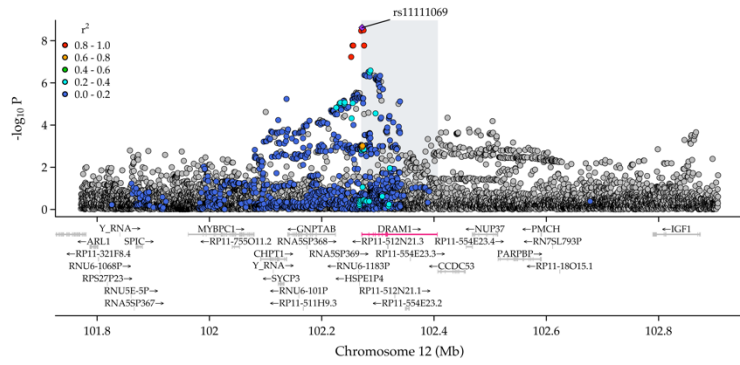
Locus 15: rs2821226, SHS-PC2



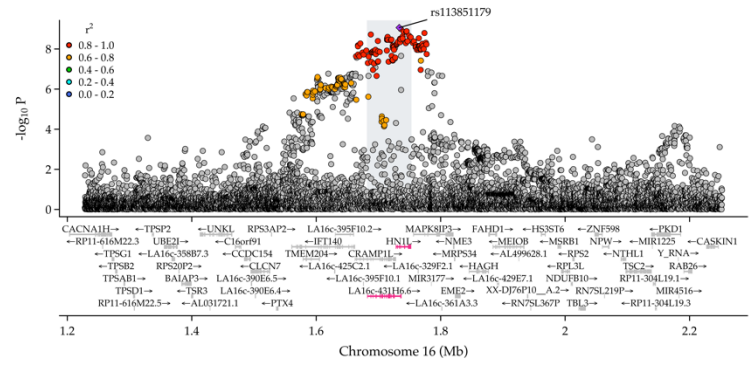
Locus 16: rs17559978, SHS-PC2



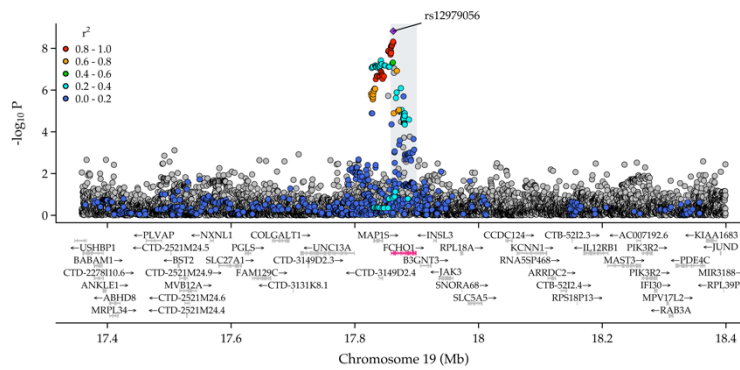
Locus 17: rs11111069, SHS-PC2



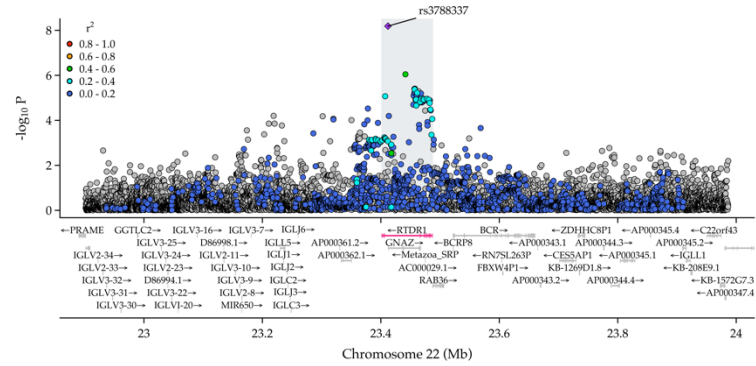
Locus 18: rs113851179, SHS-PC2



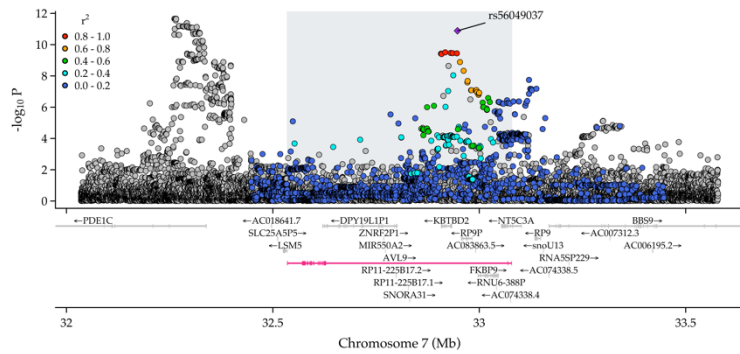
Locus 19: rs12979056, SHS-PC2



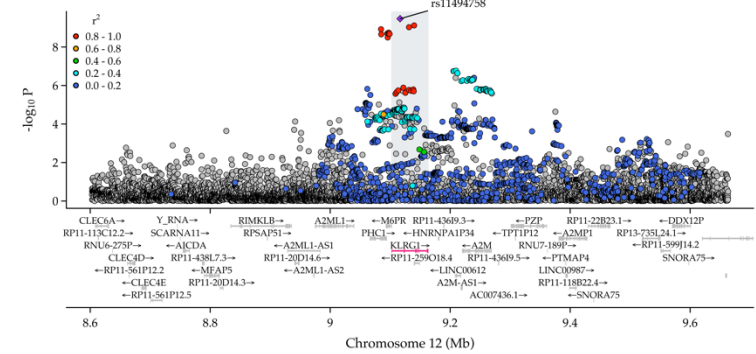
Locus 20: rs3788337, SHS-PC2



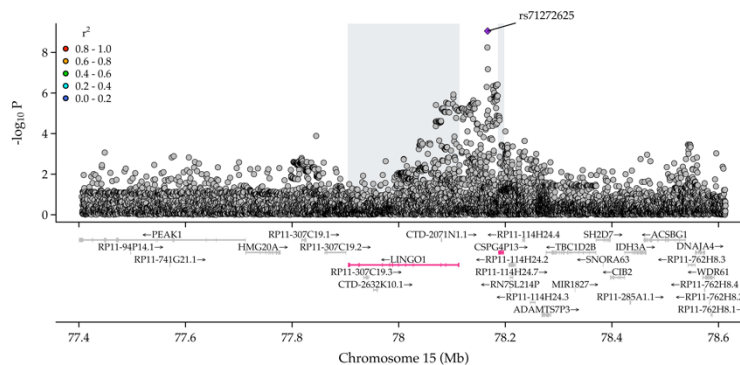
Locus 21: rs56049037, SHS-PC3



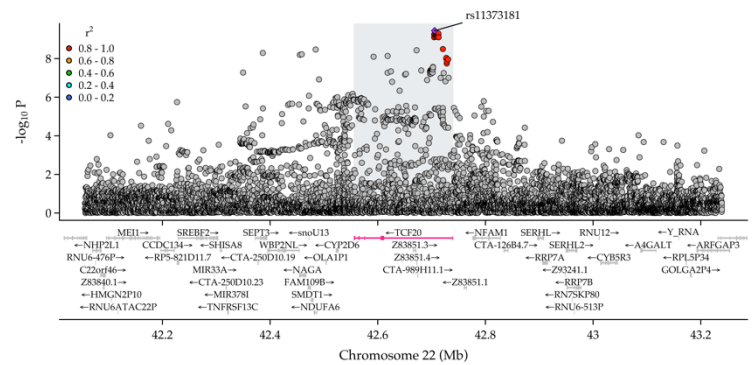
Locus 23: rs11494758, SHS-PC3



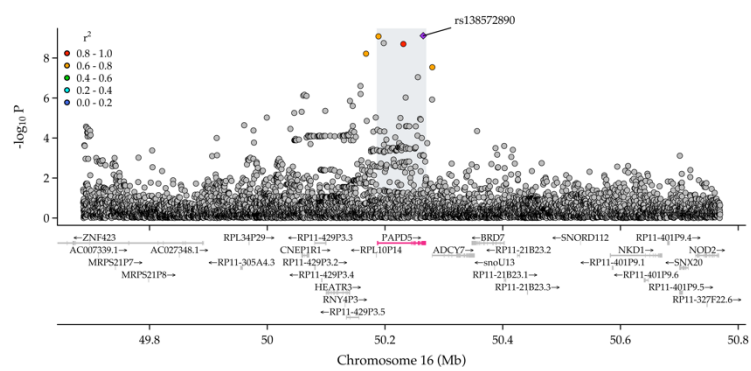
Locus 24: rs71272625, SHS-PC3



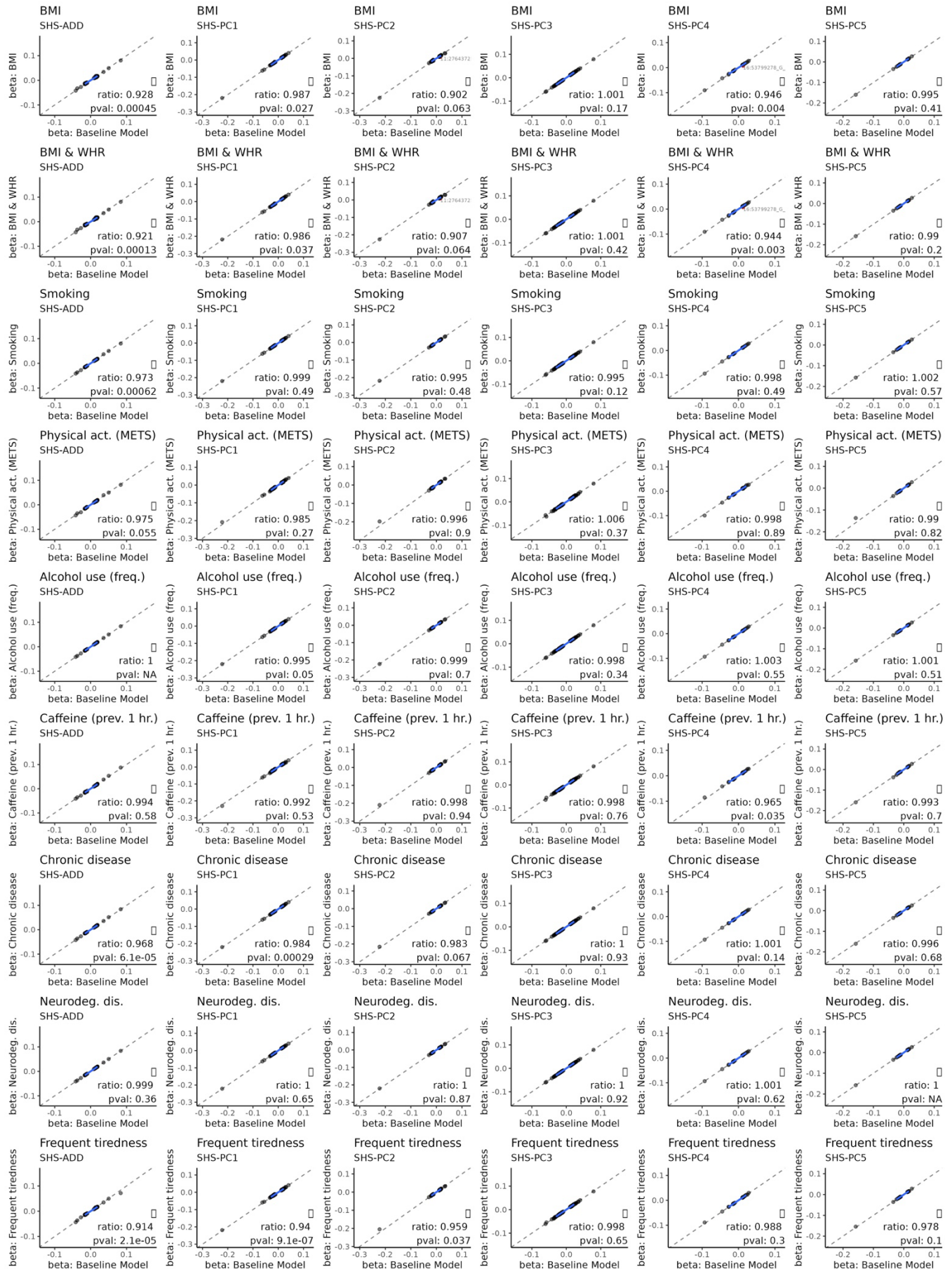
Locus 25: rs11373181, SHS-PC3

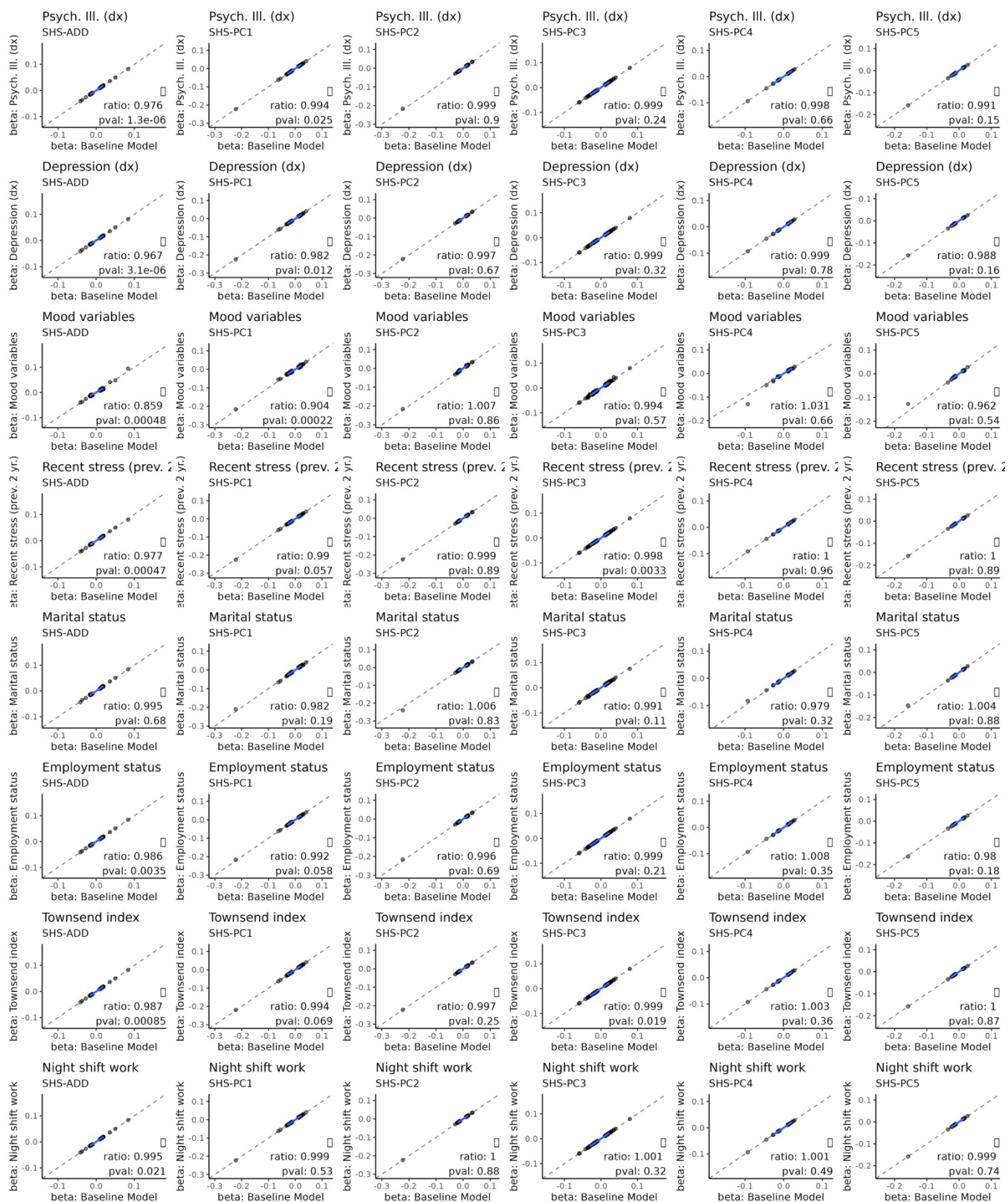


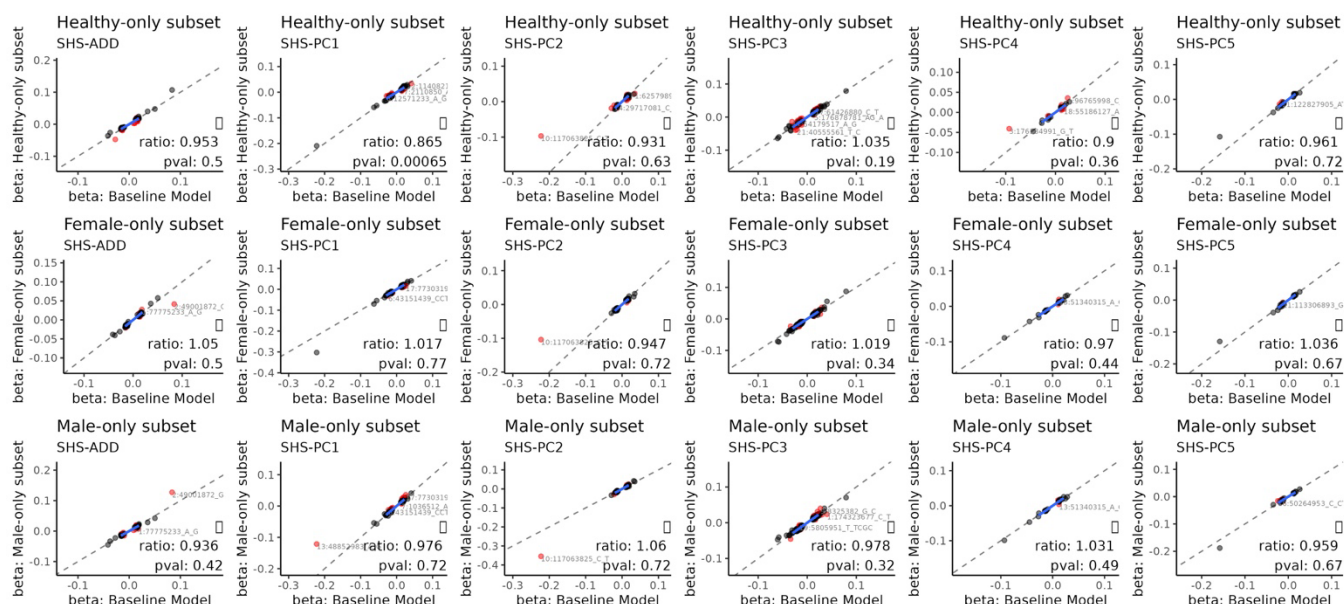
Locus 27: rs138572890, SHS-PC5



Supplementary Fig. 7. Sensitivity results.



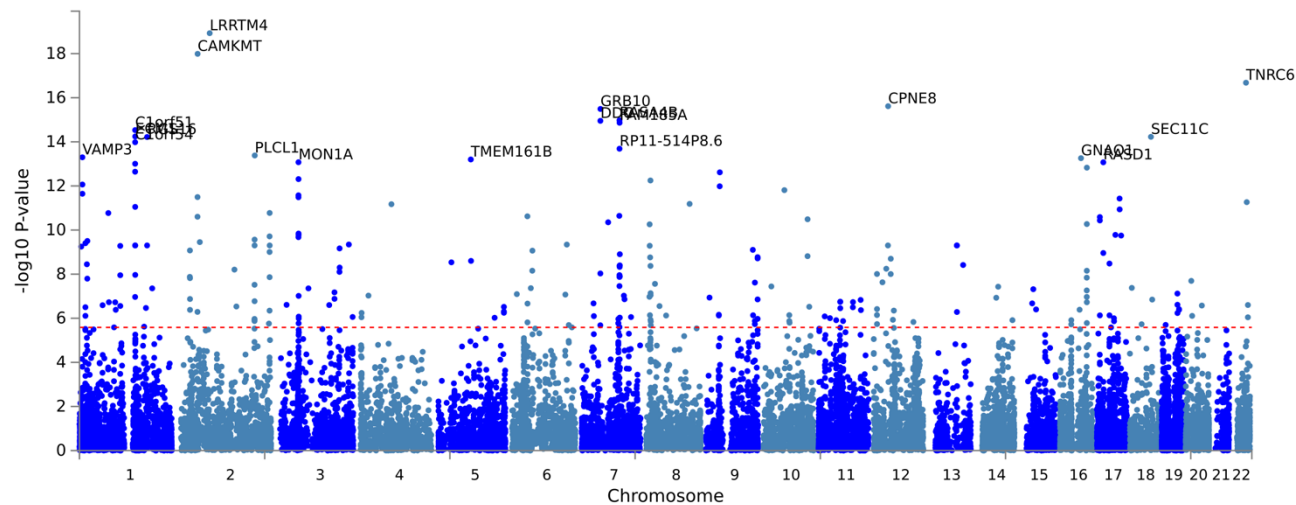




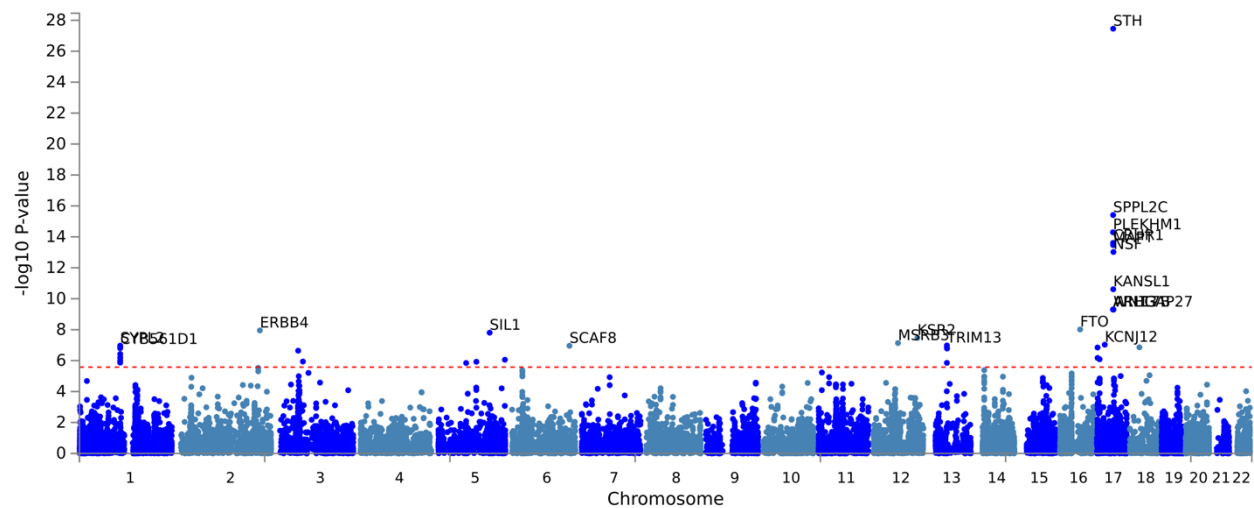
Plots of genetic effect size beta (log odds ratio) comparing baseline model with sensitivity models controlling for additional covariates. Corresponding variant-level results shown in Supplementary Table 12. Ratio: 90% truncated mean ratio of betas from sensitivity model compared with betas from baseline model. P-value: p-value for null hypothesis  $H_0$ : Ratio = 1. Variants shown in red have adjusted effect size in the sensitivity model that differs from the baseline model by at least two standard errors.



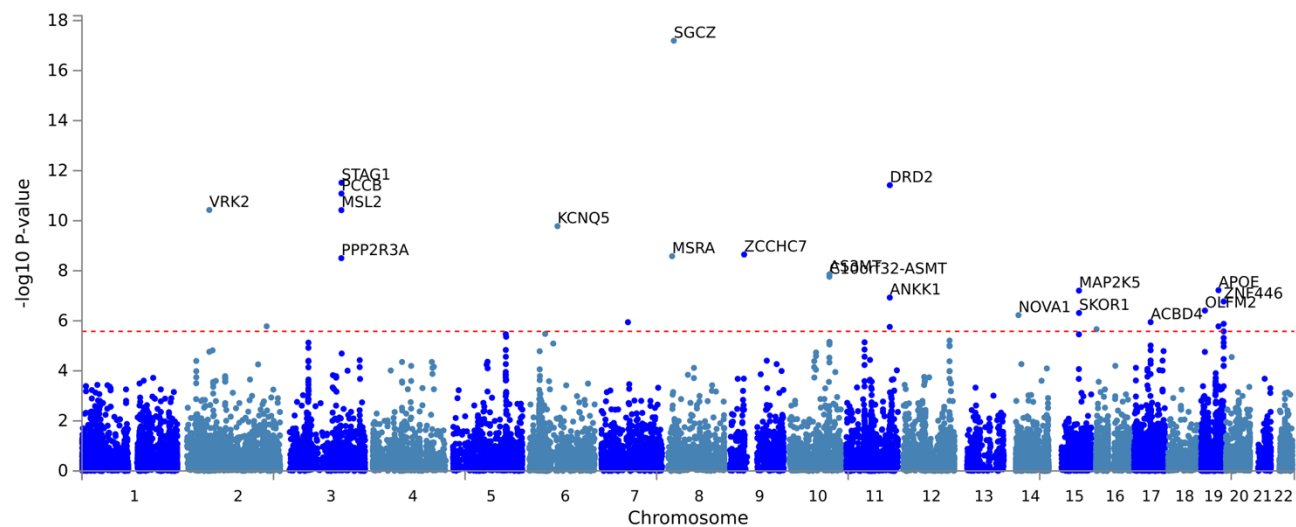
d. SHS-PC3



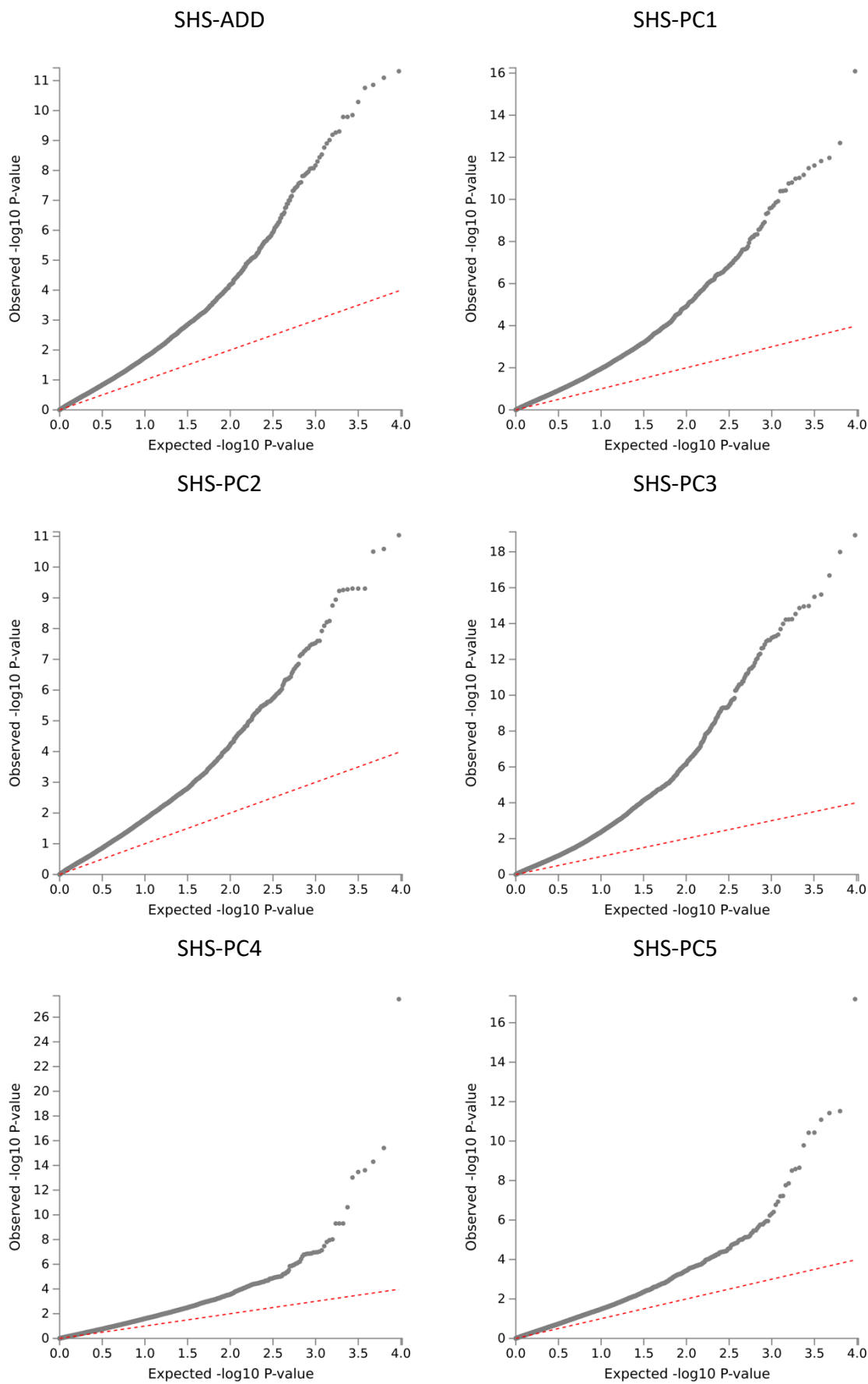
e. SHS-PC4



f. SHS-PC5

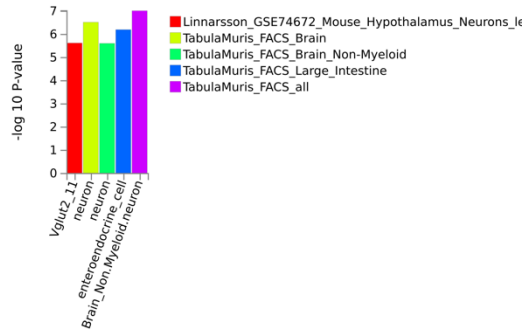


Supplementary Fig. 9. QQ plots of genome-wide gene-based analysis using FUMA MAGMA.

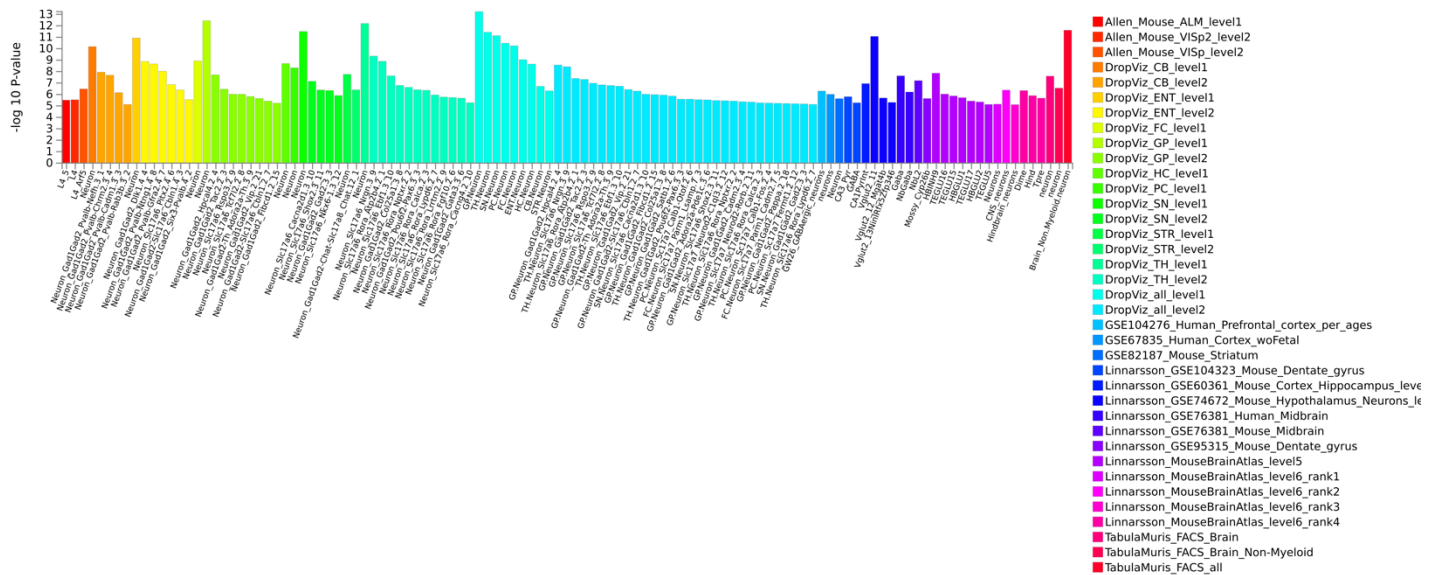


Supplementary Fig. 10. Significant cell types enriched for SHS genes in expression.

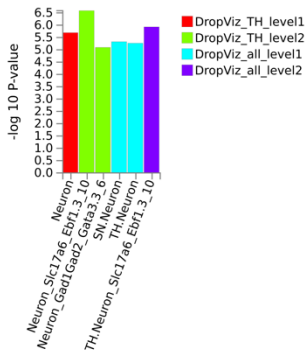
a. SHS-ADD



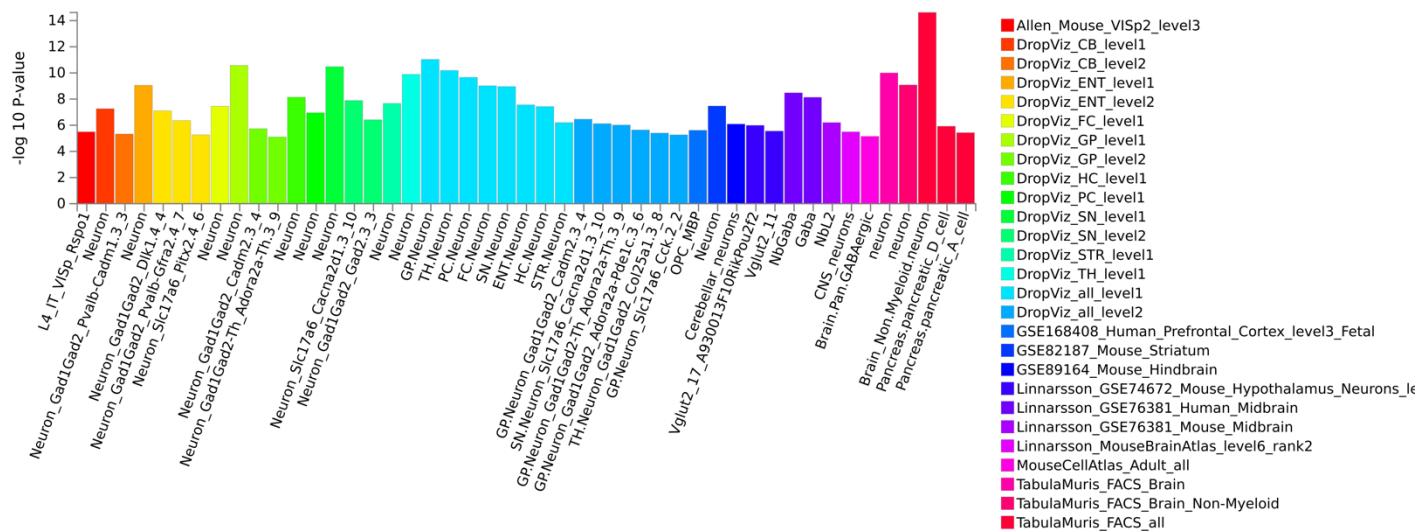
b. SHS-PC1



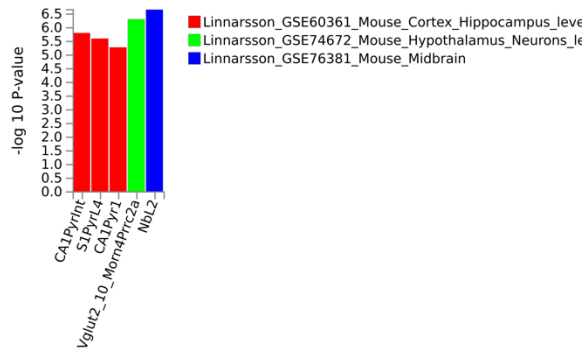
c. SHS-PC2



d. SHS-PC3



e. SHS-PC4



f. SHS-PC5

