Enhancing Discovery of Genetic Variants for Posttraumatic Stress Disorder Through Integration of Quantitative Phenotypes and Trauma Exposure Information

Supplement 1

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Construction of a LTE count in the UKBB

Participating cohorts typically provided trauma exposure as a count variable for the number of traumas. This variable did not exist in the UKBB data, which had item level data but no sum score. We constructed a count measure of LTE from 8 trauma items of the self-reported retrospective trauma screener from the UKBB mental-health questionnaire, including exposure to combat or war zone (UKBB Item: 20527), life threatening accident (UKBB Item: 20526), life threatening illness (UKBB Item: 20528), physical violence by partner or ex-partner as an adult (UKBB Item: 20523), victim of sexual assault (UKBB Item: 20531), sexual interference by partner as an adult (UKBB Item: 20524), victim of violent crime (UKBB Item: 20529), and witnessed death (UKBB Item: 20530). For our measure of LTE, items were re-coded based on the presence or absence of trauma, where 'Prefer not to answer' was coded as NA, 'never' was coded as 0, and any amount of endorsement of trauma was coded as 1. The LTE score was taken as the sum of these 8 dichotomously coded items, yielding a score of 0-8. As PTSD prevalence may be conditional on trauma type, as a sensitivity analysis, we also created a LTE phenotype where items were weighted by the trauma specific conditional prevalences of PTSD given in Yehuda et al. and analyzed it in the same manner.

Parameters for FUMA analysis

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GTEx/v8/Brain_Substantia_nigra.txt.gz

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eqtlMapChr15Meth	NA
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eqtlMapAnnoMeth	NA
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ciMapChr15Meth	NA
ciMapAnnoDs	NA
ciMapAnnoMeth	NA

MTAG maxFDR statistic

Violation of a primary assumption of the MTAG model, i.e. that the variance-covariance matrix of effects is identical across SNPs, can lead to an inflated false discovery rate. MTAG simulates false discovery rate under a worst case scenario to provide an upper bound of how severely deviations will affect FDR. The max FDR statistic generated by MTAG was 0.0157, indicating that any violations from MTAG model assumptions would still result in an acceptable (commonly used acceptable false discovery rates are 5%) false discovery rate.

eQTL analyses

Considering the nine and the six GWS variants associated with PTSD (five from GWAS and 4 from MTAG; Table 1) and LTE, we tested their effect on transcriptomic regulation of the surrounding genes (± 1 Mb of the gene transcription starting site) leveraging GTEx v8 resources. Applying a genome-wide false discovery rate correction, we observed that seven PTSD-associated and four LT-trauma associated loci were related to multiple tissue-specific expression quantitative trait loci (eQTL; Supplementary Table S8).

Among the PTSD-associated loci, a widespread transcriptomic regulatory effect was observed for rs146918648 (33 gene-tissue combinations) and rs7264419 (38 gene-tissue combinations). A pervasive cross-tissue effect was observed between rs146918648 and *ZNF603P* where FDR-significant transcriptomic effect was across 16 tissues and in the multi-tissue analysis a posterior probability >90% was observed with respect to 40 out the 42 tested (multi-tissue eQTL p = 1.97e-96). Rs7264419 showed a similar cross-tissue transcriptomic regulation with respect to *ARFGEF2* (10 FDR-significant tissues; multi-tissue eQTL p = 8.66e-86) and *CSE1L* (18 FDR-significant tissues; multi-tissue eQTL p = 1.03e-138). Although transcriptomic regulation is present across PTSD-associated loci, we observed only a limited number (11%) of FDR-significant eQTLs in tissues that are expected to be relevant in PTSD pathogenesis (i.e., brain regions, 7 gene-tissue combinations, top-result *DFNA5*-rs2721816 p=2.50E-06; pituitary gland, 2 gene-tissue combinations, top-result *FOXP2*-rs10266297 p=5E-06; adrenal gland, 2 gene-tissue combinations, top-result *SGCD*-rs6896669 p=5.50E-10). Similar trend was also present with respect to splicing QTLs (sQTL; Supplementary Table S9) where only 5 out 76 gene-tissue combinations (~7%) were related to tissues expected to be involved in PTSD pathogenesis. Four of these sQTL were related to the cross-tissue effect of rs7264419 across CSE1L (10 FDR significant tissues), STAU1 (22 FDR significant tissues), ZFAS1 (25 FDR significant tissues), and ZNFX1 (2 FDR significant tissues).

Among LT-associated loci, Rs6661135 was associated with the transcriptomic regulation of 15 genes across 19 different tissues. Among them, rs6661135 regulates HORMAD1 gene expression with concordant effect across eight tissues (multi-tissue eQTL p = 1.48e-69). A similar cross-tissue effect was observed with respect to PNMAL1-rs770444611 eQTL concordant and significant across 26 tissues (multi-tissue eQTL p=4.11e-191) and SGCD-rs4704792 eQTL with concordant and significant across 6 tissues (multi-tissue eQTL p=3.8e-57). Conversely, rs1476535*T allele was associated with FOXP2 transcriptomic down-regulation in the pituitary gland (normalized effect size=-0.27, p=2e-6) and upregulation in the adrenal gland (normalized effect size=0.38, p=2.5e-5). In addition to its cross-tissue eQTL effect, rs6661135 was associated with sQTL related to three surrounding genes (Supplemental Table S9): *CDC42SE1* (p<1.8e-6), *GOLPH3L* (p<1.3e-7), and *SEMA6C* (p<3.3e-6).

PheWAS

To understand further how significant loci are associated with human traits and diseases, we conducted a PheWAS of PTSD and LTE. Considering a Bonferroni multiple testing correction accounting for the number of phenotypes available (p<1.05e-5), we identified 97 phenome-wide significant (PWS) associations with respect to LTE- loci and 200 PWS associations with respect to PTSD loci (Supplementary Table S12).

Considering the PTSD PheWAS, more than half of the significant associations were related to two domains: psychiatry (34%) and metabolism (18%). Several PTSD-associated loci showed widespread pleiotropy across multiple psychiatric traits: rs10266297 (35 PWS associations, 40% psychiatric domain, top psychiatric result: risk taking p=1.27e-11), rs10821140 (37 PWS associations, 38% psychiatric domain, top psychiatric result: loneliness p=1.11e-11), rs146918648 (44 PWS associations, 48% psychiatric domain, top psychiatric result: tenseness/restlessness p=2.13e-9). Conversely, among its 58 PWS associations, rs7264419 showed an enrichment for metabolic domain (40%, top result trunk fat-free mass p=1.3e-16) over psychiatric domain (14%, top result well-being spectrum p=1.92e-8).

In the LT PheWAS, 38 phenotypic associations were related to rs1476535 and 50% of them were with psychiatric traits including sleep duration as the strongest association (p=5.8e-11). Similarly, rs4665501 showed mainly associations with psychiatric traits (9 out of 10 reaching phenome-wide significance) with strongest significance for schizophrenia-bipolar disorder meta-analysis (p=2.97e-7). Conversely, we observed that rs2933196, rs6661135, and rs4665501 were mostly associated with metabolic traits with most significant associations for body mass index (p=9.48e-15), trunk predicted mass (p=1.26e-10), and waist-hip ratio (p=1.63e-7),

respectively. The results highlight how LT loci show pleiotropy with different phenotypic domains.

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Vietnam Era Twin Study of Aging (VETS) (ST1#24)

This research was supported by National Institute on Aging R01 AG018386, AG022982, AG050595 (W.S.K.), R01 AG018384 (M.J.L.), R03 AG046413 (C.E.F), and K08 AG047903 (M.S.P), and the VA San Diego Center of Excellence for Stress and Mental Health Healthcare System. The content is the responsibility of the authors and does not necessarily represent official views of the NIA, NIH, or VA. The Cooperative Studies Program of the U.S. Department of Veterans Affairs provided financial support for development and maintenance of the Vietnam Era Twin Registry. We would also like to acknowledge the continued cooperation and participation of the members of the VET Registry and their families.

The Women and Children's Health Study (WACH)(ST1#43)

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Yale-Penn Study (GSDC)(ST1#6)

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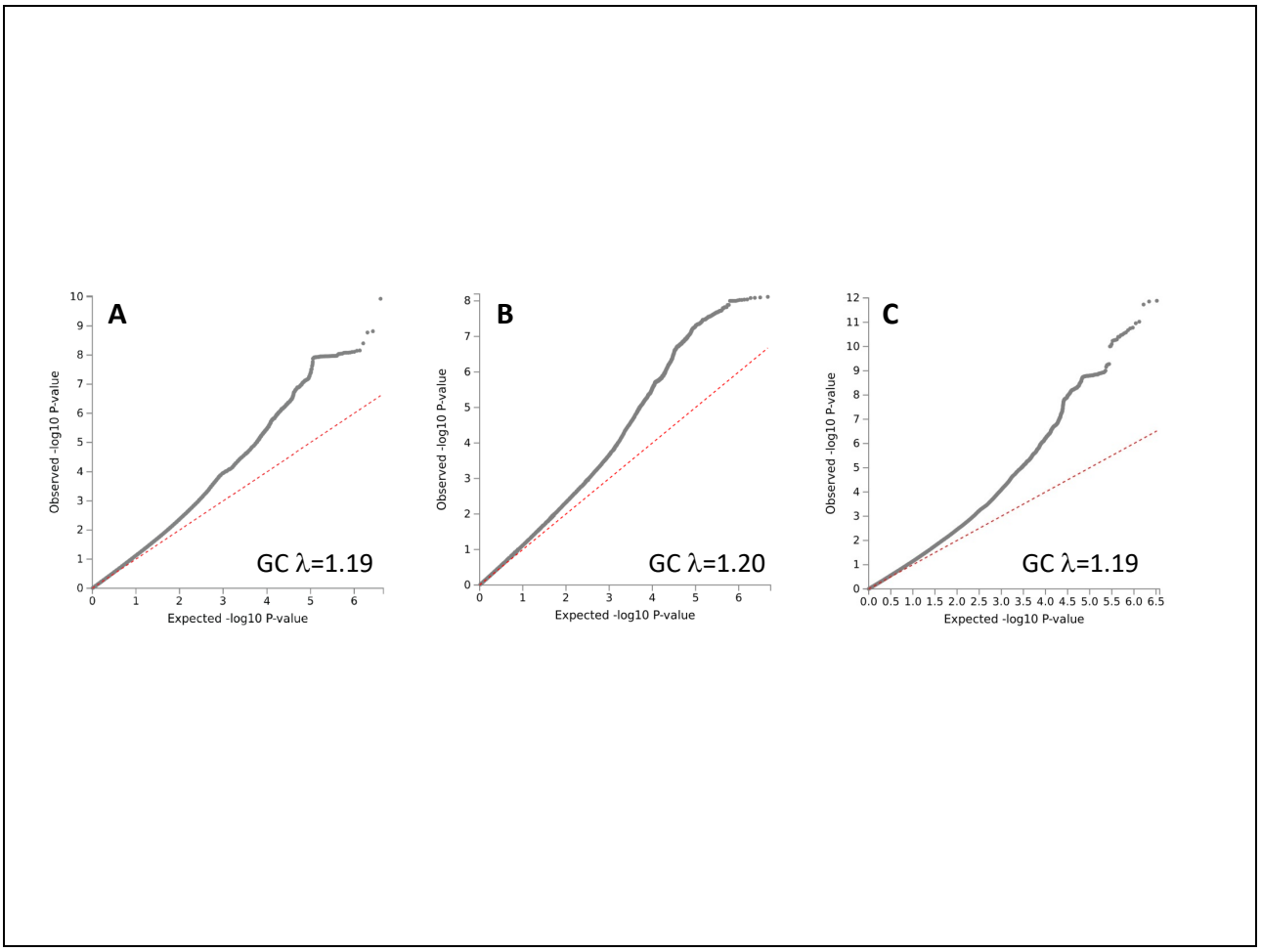
Million Veteran Program (MVP) (replication cohort)

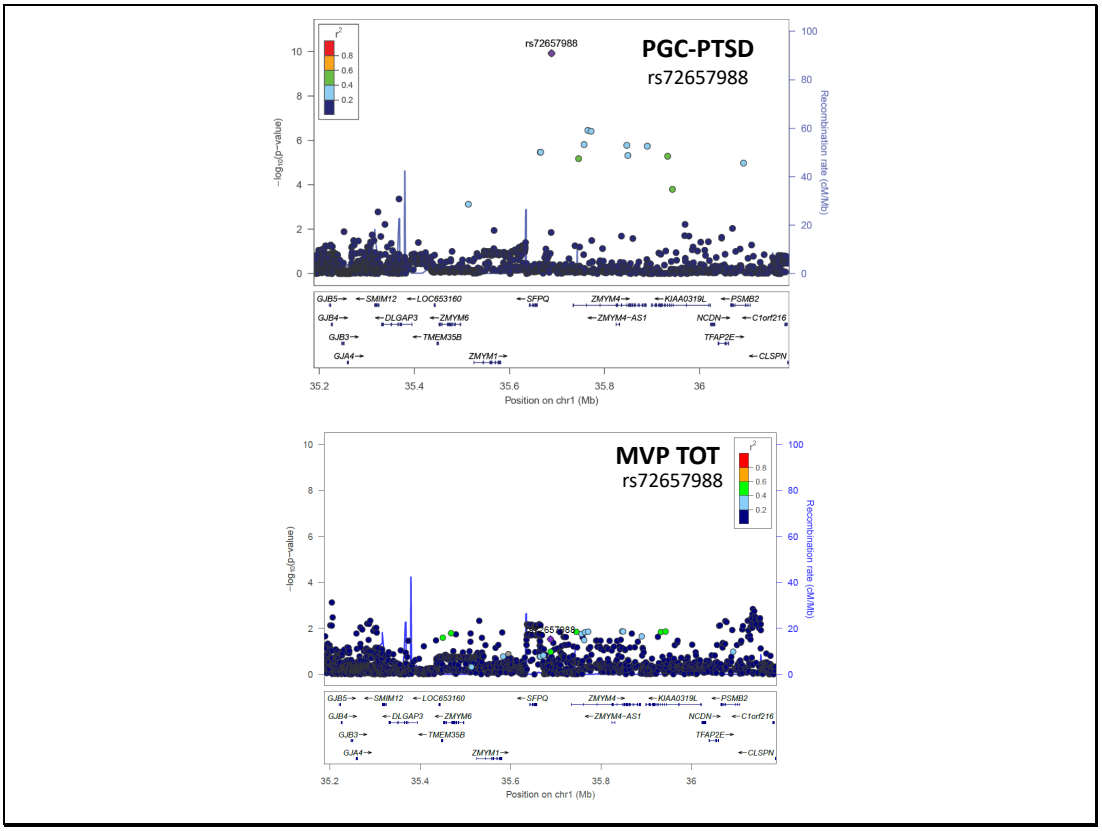
This research includes data from the Million Veteran Program (MVP), Office of Research and Development, Veterans Health Administration, and was supported by MVP and the VA Cooperative Studies Program (CSP) study #575B.

Supplementary Figures



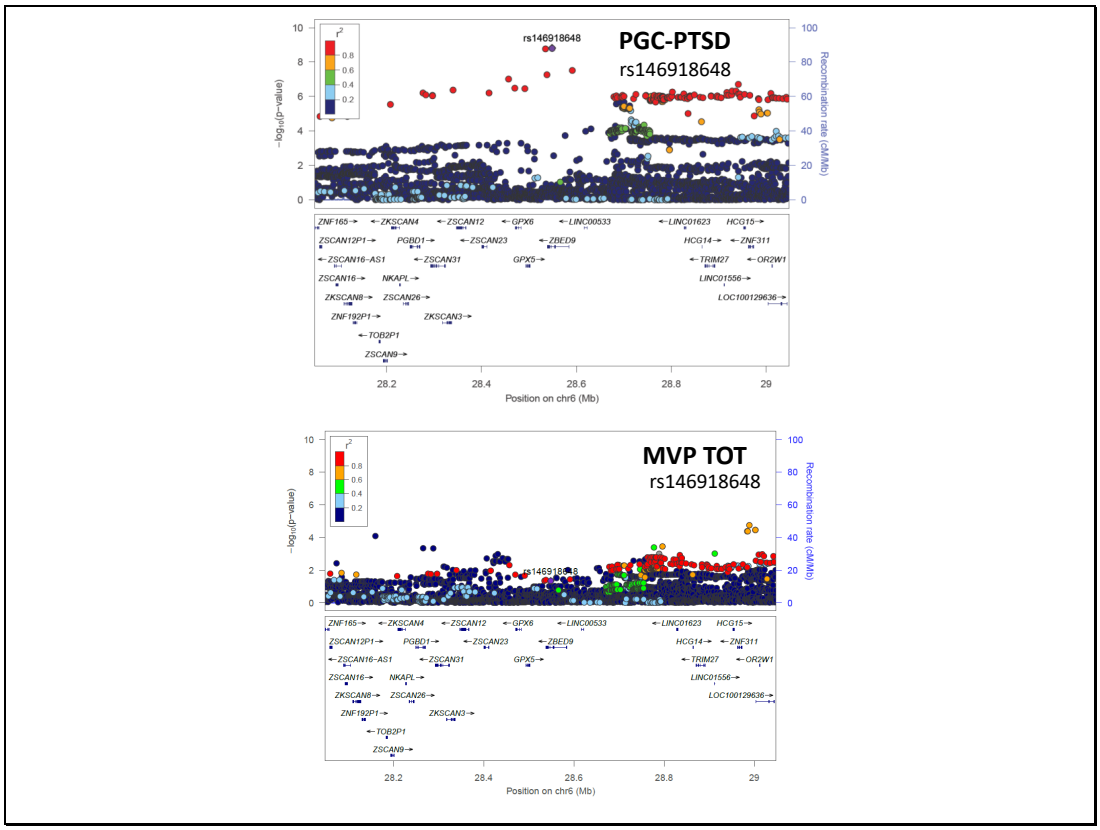
Supplementary Figure S1.

Quantile-Quantile plots. The x-axis is the expected -log10 P value under the null distribution. The y-axis is the observed -log10 p value. The dotted red line is where x = y. The grey dots denote the -log 10 P values of a given SNP. Panel A depicts the QQ plot for the PTSD GWAS. Panel B depicts the QQ plot for the LT GWAS. Panel C depicts the QQ plot for the MTAG GWAS.



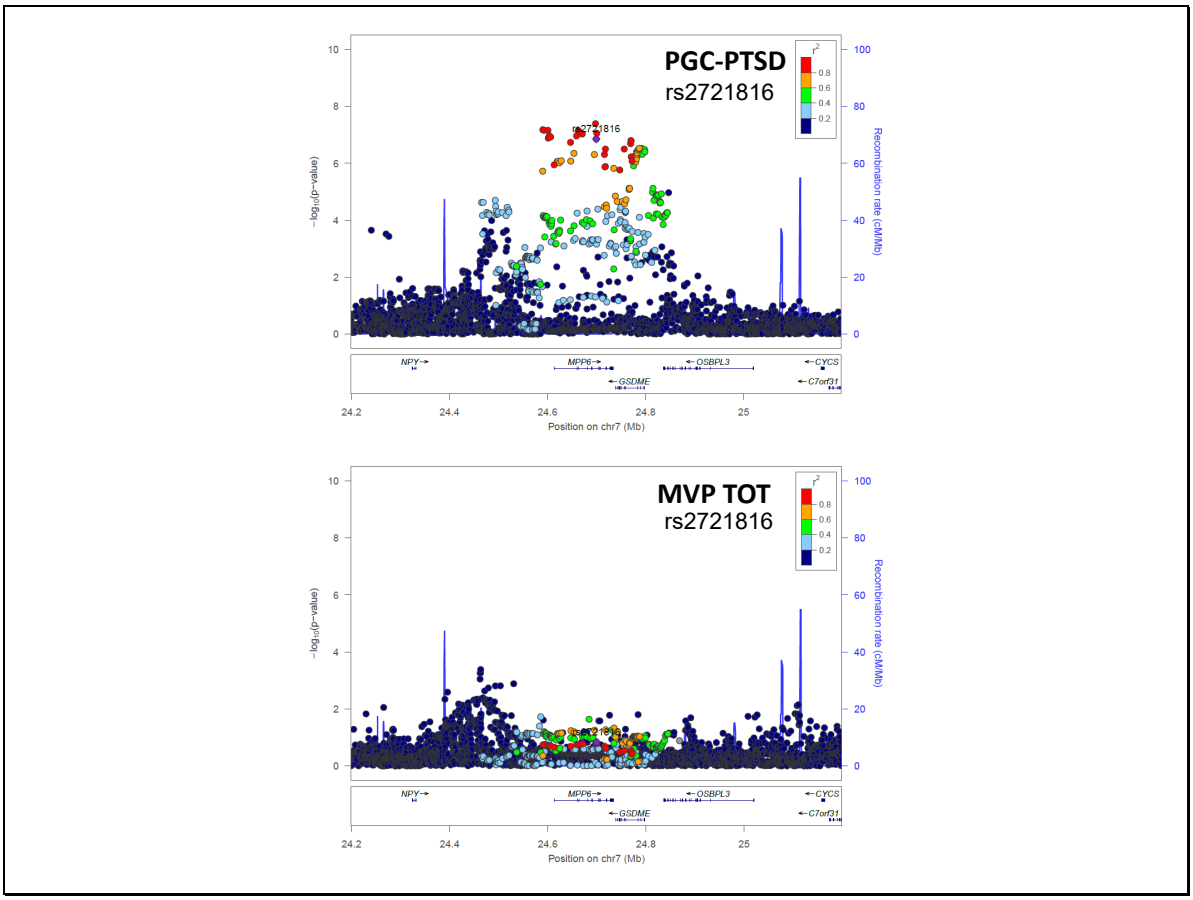
Supplementary Figure S2.

Regional plots (Locus zoom) of the top hit rs72657988. The top panel depicts the region in the PGC PTSD meta-analysis. The bottom panel depicts the region in the MVP PCL Total Severity Score cohort.



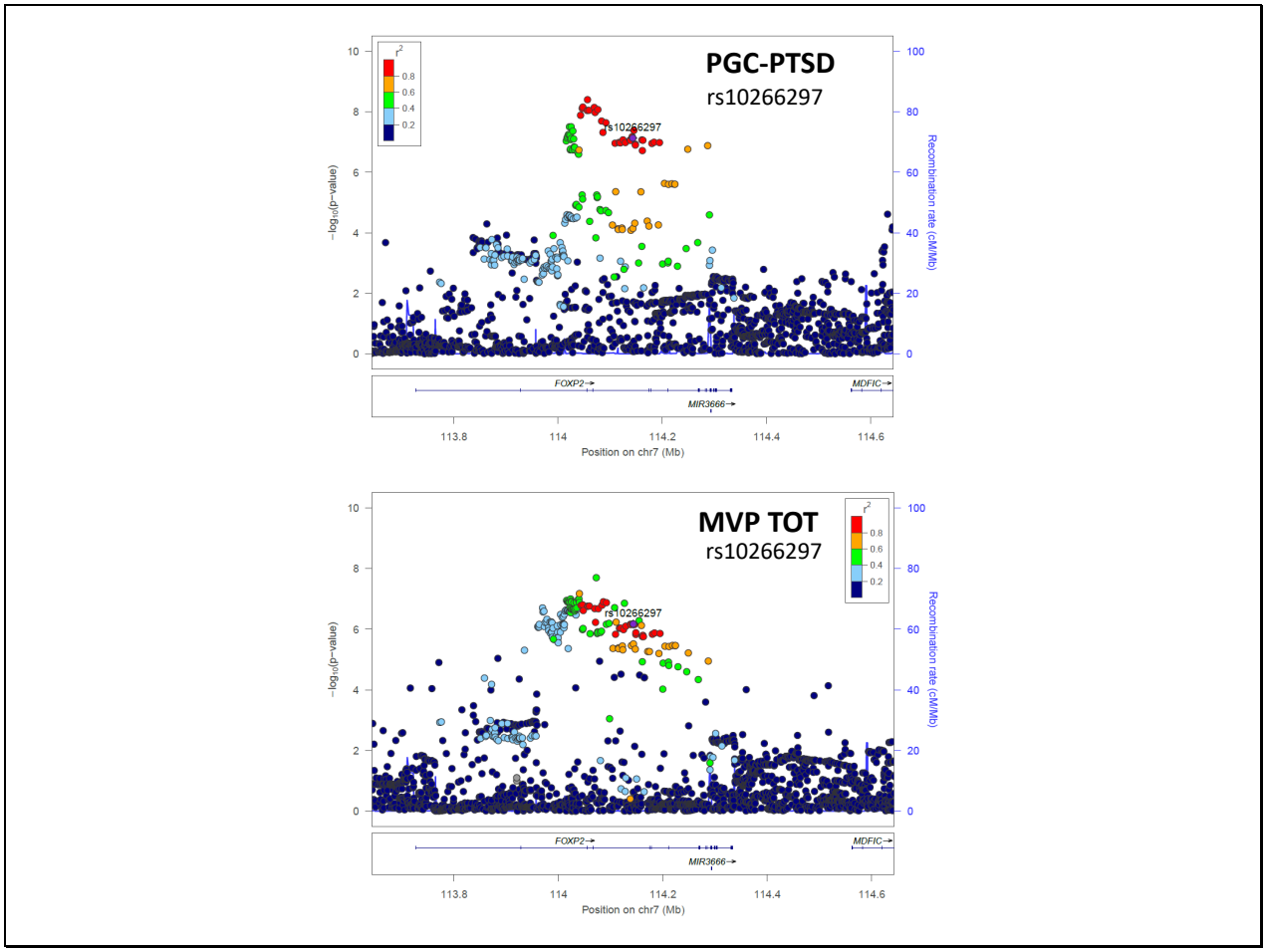
Supplementary Figure S3.

Regional plots (Locus zoom) of the top hit rs146918648. The top panel depicts the region in the PGC PTSD meta-analysis. The bottom panel depicts the region in the MVP PCL Total Severity Score cohort.



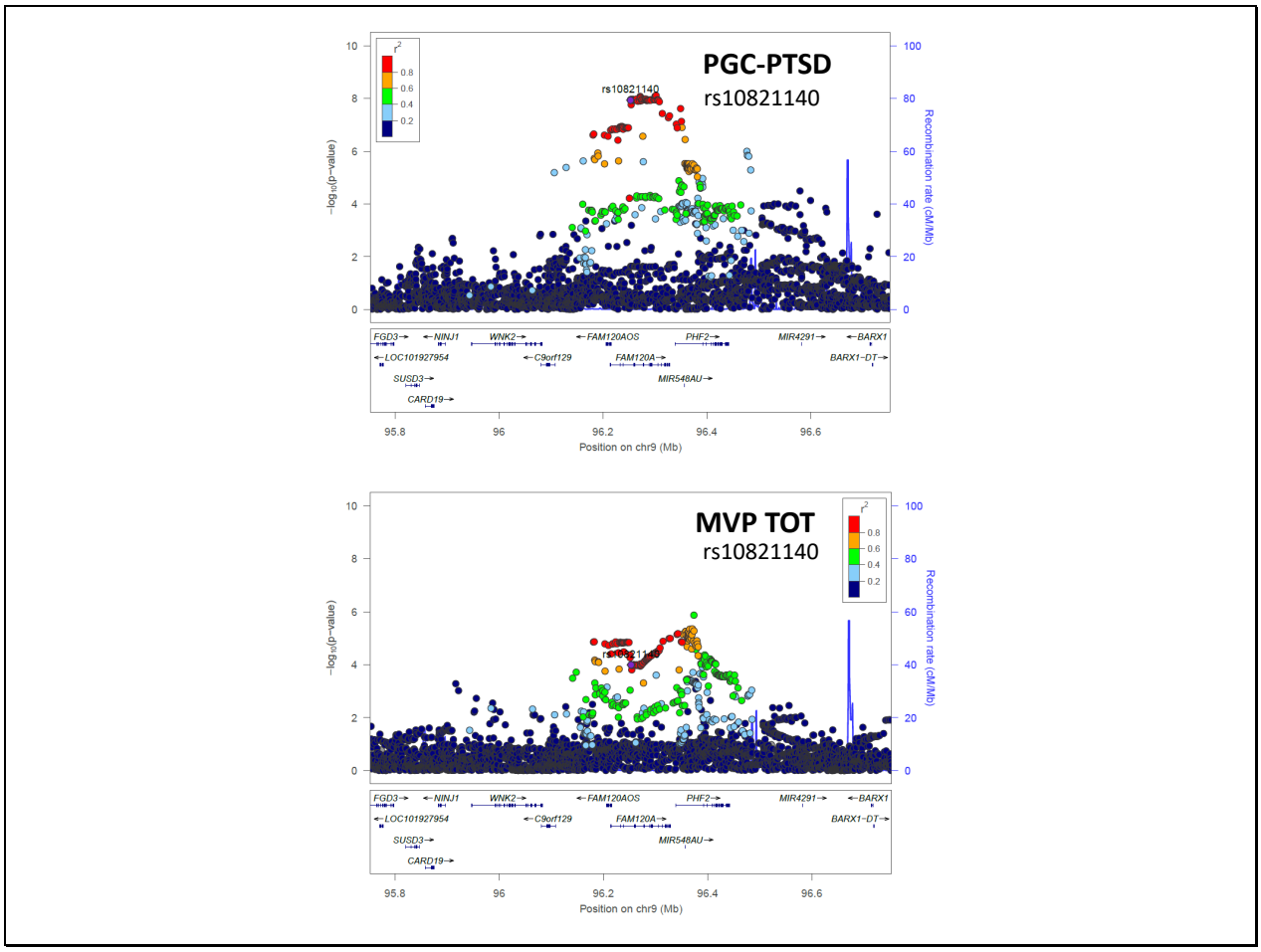
Supplementary Figure S4.

Regional plots (Locus zoom) of the top hit rs2721816. The top panel depicts the region in the PGC PTSD meta-analysis. The bottom panel depicts the region in the MVP PCL Total Severity Score cohort.



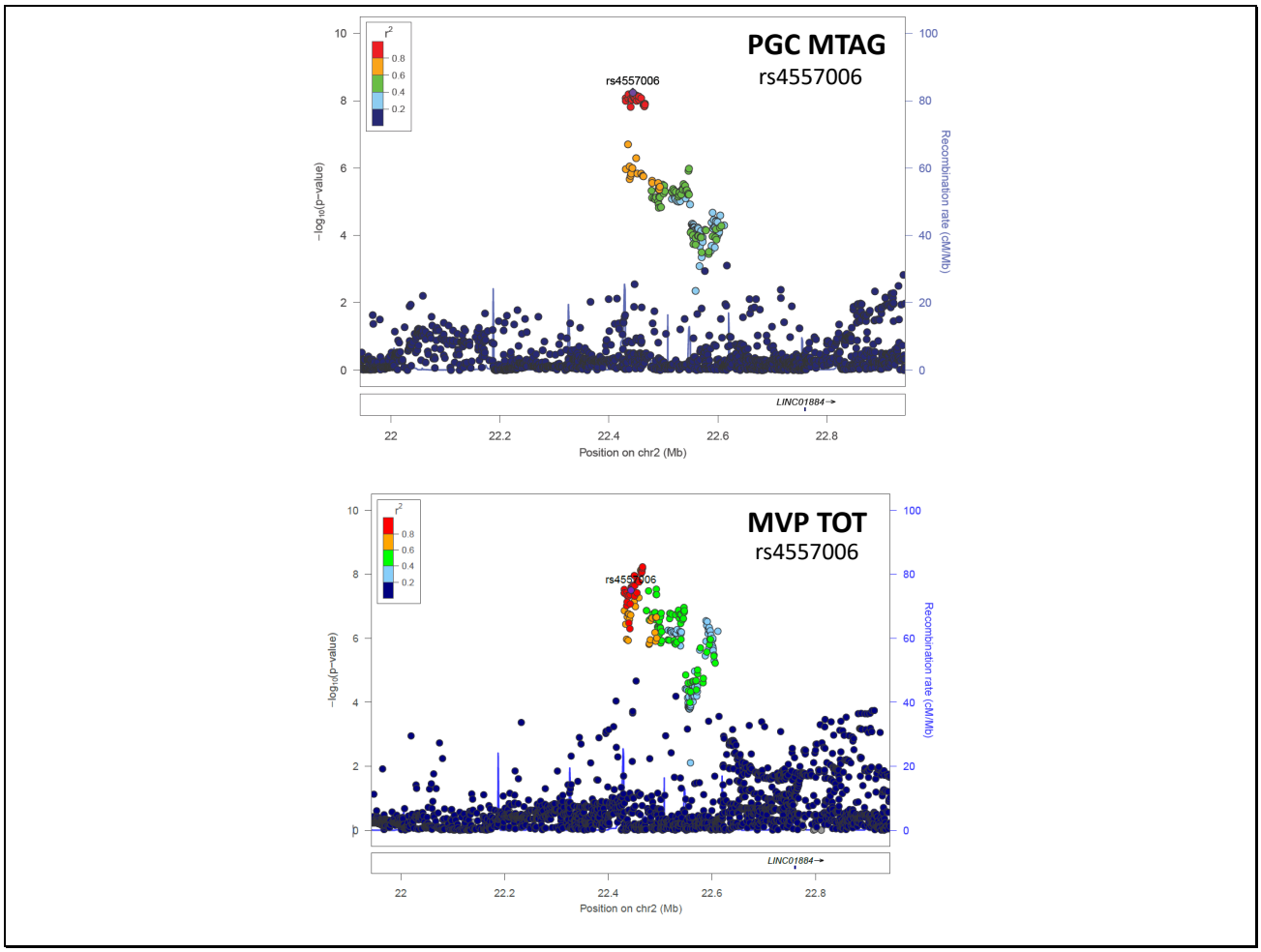
Supplementary Figure S5.

Regional plots (Locus zoom) of the top hit rs10266297. The top panel depicts the region in the PGC PTSD meta-analysis. The bottom panel depicts the region in the MVP PCL Total Severity Score cohort.



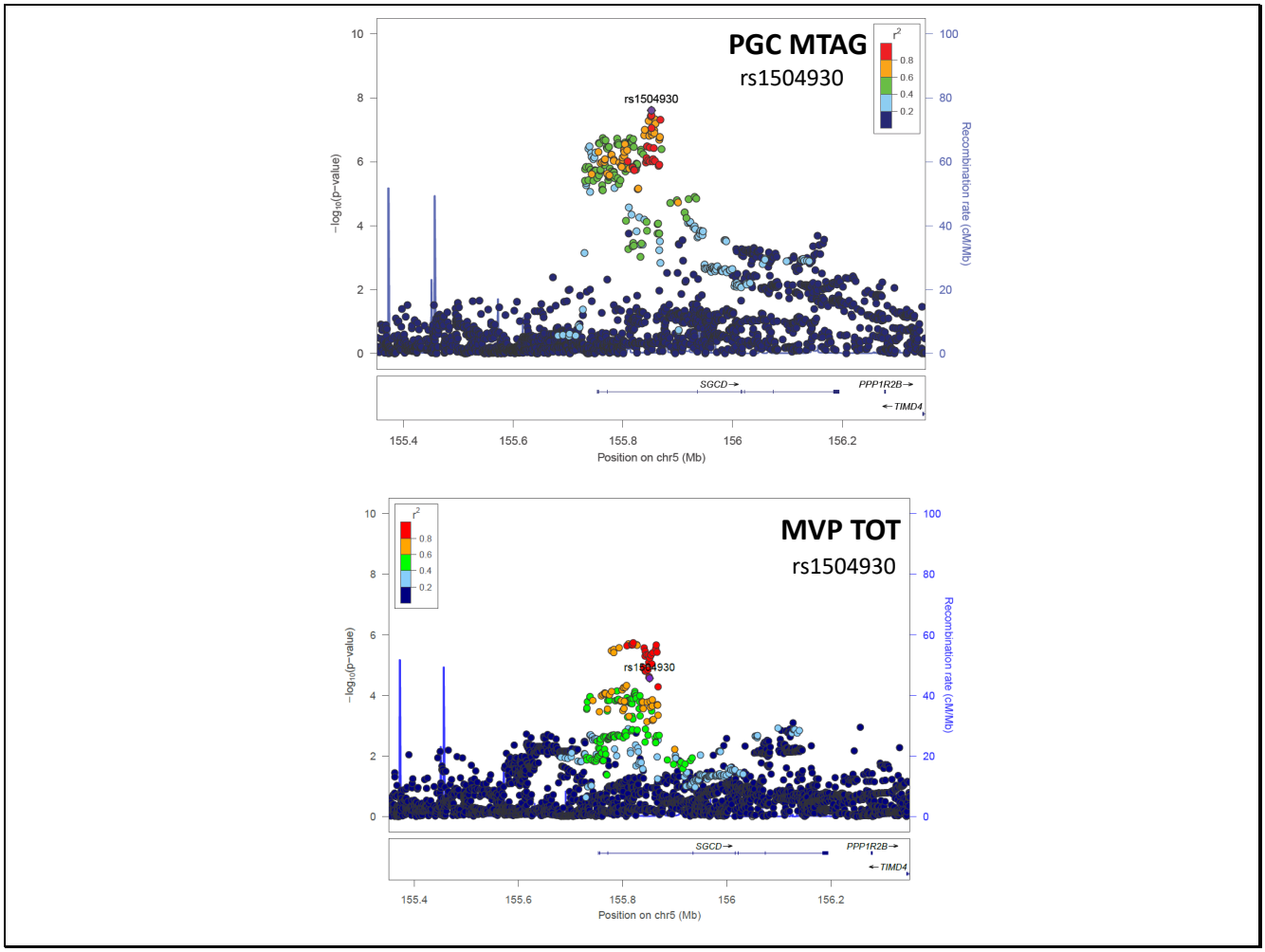
Supplementary Figure S6.

Regional plots (Locus zoom) of the top hit rs10821140. The top panel depicts the region in the PGC PTSD meta-analysis. The bottom panel depicts the region in the MVP PCL Total Severity Score cohort.



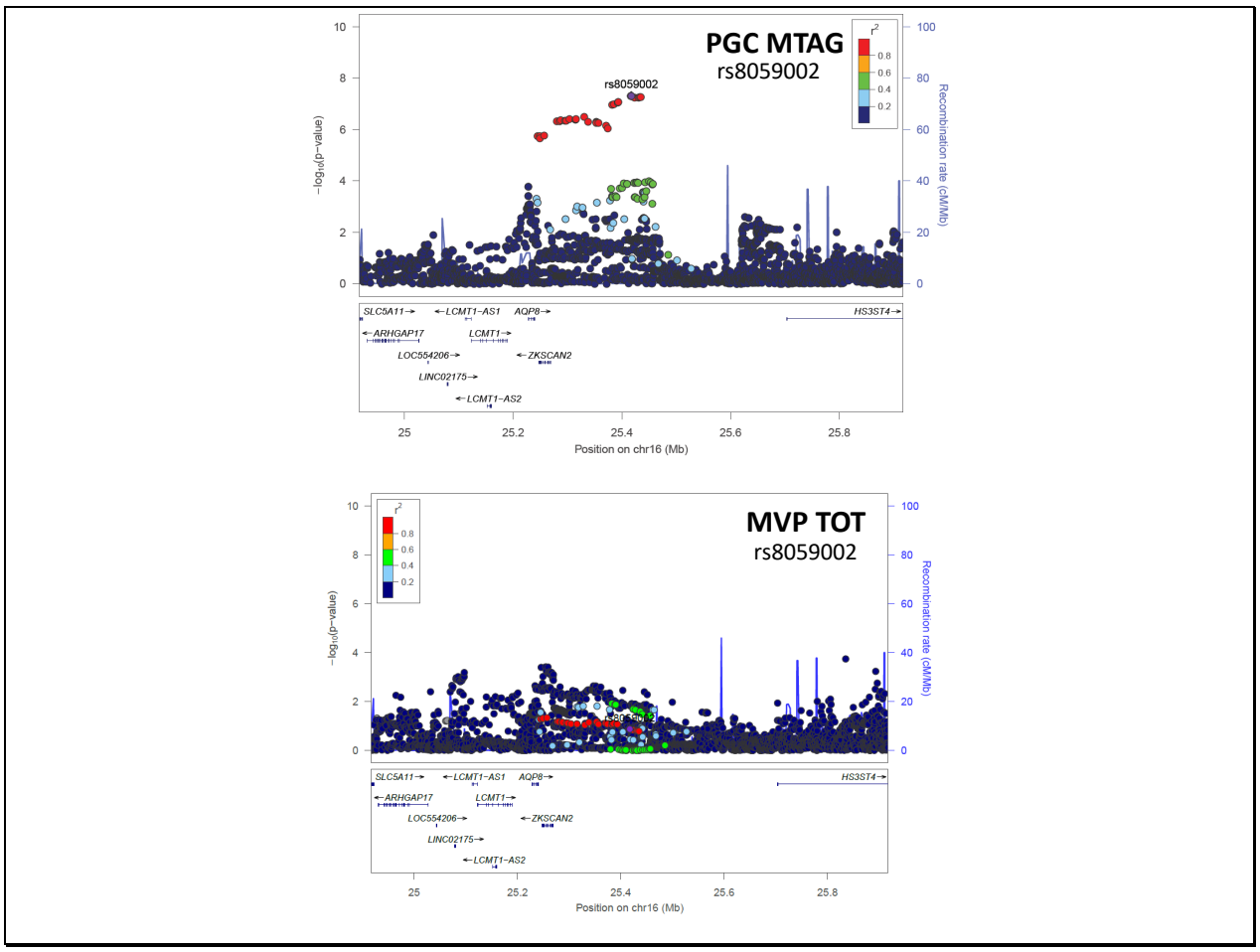
Supplementary Figure S7.

Regional plots (Locus zoom) of the top hit rs4557006. The top panel depicts the region in the PGC MTAG analysis. The bottom panel depicts the region in the MVP PCL Total Severity Score cohort.



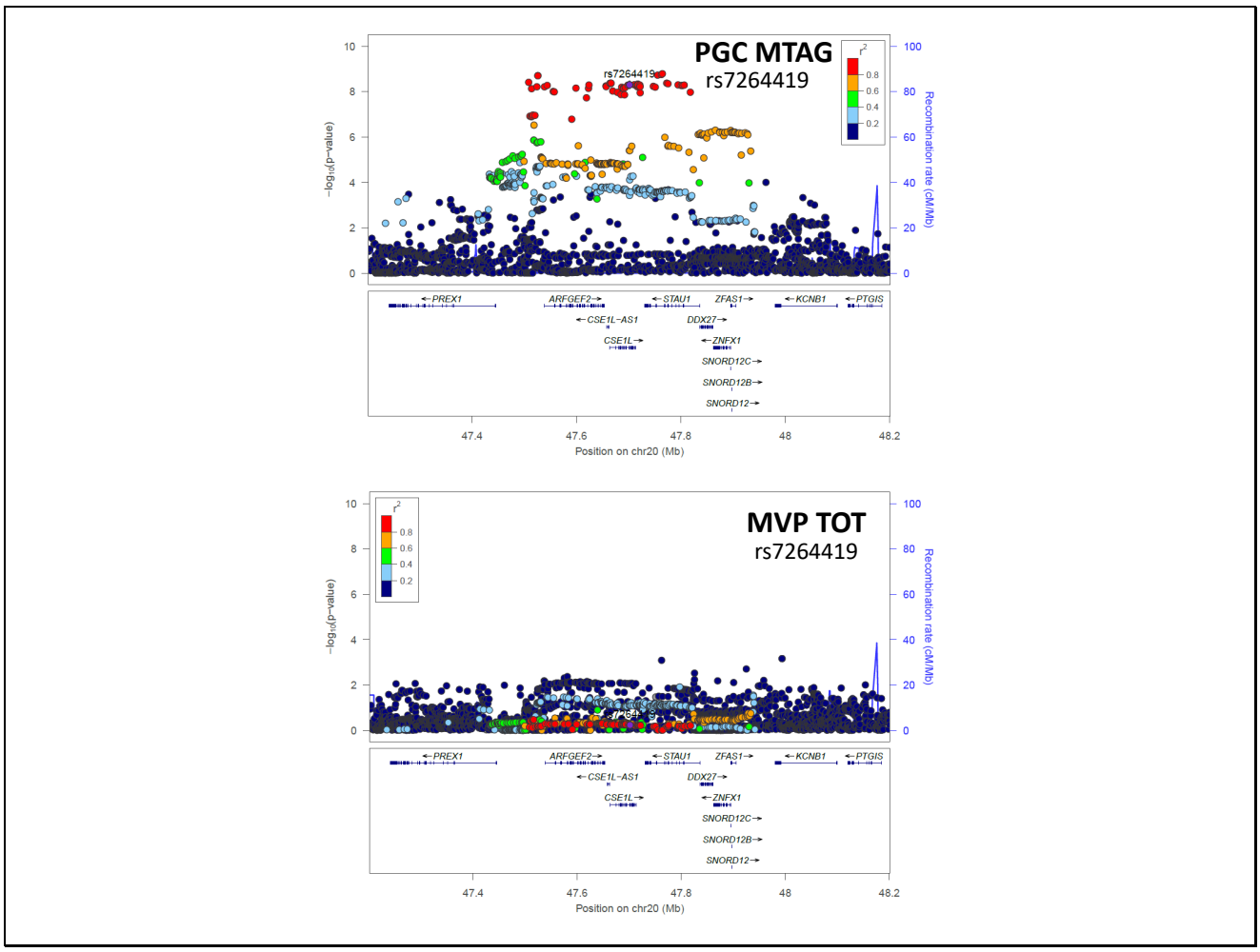
Supplementary Figure S8.

Regional plots (Locus zoom) of the top hit rs1504930. The top panel depicts the region in the PGC MTAG analysis. The bottom panel depicts the region in the MVP Re-experiencing cohort.



Supplementary Figure S9.

Regional plots (Locus zoom) of the top hit rs8059002. The top panel depicts the region in the PGC MTAG analysis. The bottom panel depicts the region in the MVP PCL Total Severity Score cohort.



Supplementary Figure S10.

Regional plots (Locus zoom) of the top hit rs7264419. The top panel depicts the region in the PGC MTAG analysis. The bottom panel depicts the region in the MVP PCL Total Severity Score cohort.