**Supplemental Note: Investigation of convergent and divergent genetic influences underlying schizophrenia and alcohol use disorder**

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**Methods**

***Meta-analysis of PGC Alcdep and MVP AUD African-ancestries samples***

We used METAL1 to meta-analyze the summary statistics from the MVP1 AUD2 and PGC alcohol dependence3 (Alcdep) African-ancestries GWAS using an inverse variance-weighted fixed-effects model, excluding SNPs with INFO score < 0.8 and/or minor allele frequency (MAF) < 0.01 within either sample.

***Association analysis based on SubSETs (ASSET)***

ASSET is a generalized version of fixed-effects meta-analysis; it allows a subset of the input GWAS to have no effect on a given SNP, and explores all possible subsets of “non-null” GWAS inputs to identify the strongest association signal in positive and/or negative directions. The final test-statistic thus accounts for both positive and negative (or null) directions of association at each SNP in the input file, combining the p-values from both positive and negative associations using Fisher’s method4 to create an overall Z-score and p-value. Thus, ASSET also permits the addition of a covariance term for the adjustment of overlapping samples. We selected ASSET for its ability to identify not only convergent pleiotropic variants (i.e. SNPs with the same direction of effect on each disorder) but also divergent pleiotropic SNPs, its conservative effect estimates and minimal inflation, and previous use in the literature5.

As ASSET searches for and determines the most likely subset for each SNP (i.e., classifying SNPs as having an effect only on AUD, only on SCZ, or having an effect on both disorders), the ASSET-identified pleiotropic SNPs were not necessarily significant in both single-disorder GWAS. For a more conservative description of pleiotropic loci, we further considered only the lead SNPs that had p < 0.05 in both disorders; after excluding SNPs with p 0.05 in either disorder, there were 8 divergent lead SNPs and 55 convergent lead SNPs (the lead SNPs in the genome-wide loci for the convergent subset already had p < 0.05 in both disorders; **Supplemental Table 3**).

***MAGMA analyses conducted through FUMA***

We used the FUMA6 v1.3.6a platform to conduct gene-based analyses in MAGMA v1.087. Specifically, we conducted the gene-based test, which simply assigns SNPs to genes based on physical location. We also performed the competitive gene-set analysis, which uses curated gene sets and GO terms from MsigDB8. Finally, we conducted gene-property analyses in MAGMA, which test the relationship between tissue-specific gene expression profiles and disease-gene associations. The gene-property analyses are performed using the average expression of genes per tissue type as a gene covariate, where the gene expression values are log2 transformed average RPKM per tissue type after winsorization based on GTEx RNA-seq data. This test was performed in FUMA using the result of the MAGMA gene analysis (i.e., the gene-based p-values) and a one-sided test (testing for greater association between disease-gene associations and tissue specificity), conditioning on average expression across all tissue types.

***Differential Gene Expression***

For differential gene expression analyses, we used whole-genome transcriptomic data from Kapoor et al.9, specifically comparing differential gene expression in the prefrontal cortex (PFC) of 65 alcoholics versus 73 controls (post-mortem brain samples from New South Wales Tissue Resource Centre at the University of Sydney (http://sydney.edu.au/medicine/pathology/btrc/)) and in the PFC of 258 SCZ cases versus 279 controls (data obtained from the CommonMind consortium.) We used Fisher’s exact test to determine whether pleiotropic genes with p < 0.05 in our cross-disorder GWAS showed enrichment10 for differentially-expressed genes.

***GeNetic cOVariance Analyzer (GNOVA)***

GNOVA11 uses the method of moments to provide annotation-stratified covariance

estimates that are robust to LD and sample overlap. The MAF quartiles for annotation were determined using the 1000 Genomes Phase 3 European reference panel after filtering SNPs with MAF < 0.05. GenoCanyon12 is a functional annotation approach which utilizes unsupervised statistical learning to integrate genomic conservation measures and biochemical annotation data to predict functional potential across the entire genome. GenoSkyline and GenoSkyline-Plus13,14 utilize transcriptomic and epigenomic data from ENCODE15 and the Roadmap Epigenomics Project16 to predict tissue-specific functional regions for seven broad tissue categories: brain, cardiovascular, epithelium, gastrointestinal, immune, muscle, and other tissues; these annotations were used for the tissue-specific genetic covariance partitioning. We first filtered the summary statistics to only include common HapMap3 SNPs as described previously, removed the MHC region (chr6:26000885 - chr6:33999991), then used GNOVA to estimate the attributable to each category in the MAF, functionality, and tissue-specific functionality annotations.

We also included alternative annotations that were defined using GTEx17 data on 13 specific brain regions (created using annotation files from the LDSC cell-type specific analyses18: <https://github.com/bulik/ldsc/wiki/Cell-type-specific-analyses>).

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