Supplementary Information

Sample Collection

The ascertainment of samples for this study has been previously described.[1] Samples for this study were collected from the Scottish participants who had been approved by the Research Ethics Committee. Case samples were unrelated schizophrenia (SCZ), bipolar disorder (BD) and recurrent major depressive disorder (rMDD) hospital patients diagnosed based on DSM-IV criteria as described previously.[2] The Lothian Birth Cohort of 1936 (LBC1936) samples, which had quantitative measures of mood and cognitive aging, were used as the controls in this study.[3,4] The LBC1936 includes 1 091 community-dwelling individuals without dementia (548 males and 543 females), residing in or around the city of Edinburgh, Scotland.[3,5] The majority of the LBC1936 had participated in the Scottish Mental Survey 1947 at a mean age of 10.9 years and then at a mean age of 69.5 years (standard deviation=0.8) in a follow-up assessment approximately 59 years later. These assessments are referred to as ages 11 and 70 throughout.

In total, 1 543 samples, including 241 cases of SCZ, 221 cases of BD, 192 cases of rMDD and 889 controls from the LBC1936 were sequenced in the present study.

Phenotypes

Clinical diagnoses

Affected individuals were inpatients or outpatients of hospitals in South East or South Central Scotland. Subjects were interviewed by an experienced psychiatrist and a venous blood sample was given for DNA extraction. Diagnoses were made according to

Diagnostic and Statistical Manual (DSM)-IV criteria[6] based on case note review and personal interview using The Schedule for Affective Disorders and Schizophrenia – lifetime version (SADS-L).[7] Final diagnoses were reached by consensus between two experienced psychiatrists.

Cognitive variables - LBC1936

The majority of LBC1936 participants undertook the Moray House Test (MHT) at about age 11 years.[3] They retook the same MHT at about age 70. The MHT is a group-administered, paper-and-pencil test that has a time limit of 45 minutes. The questions are mainly verbal reasoning items with some arithmetical and abstract items. MHT scores were converted into an IQ-type scale, with a mean of 100 and standard deviation of 15.[8] Cognitive change between ages 11 and 70 were calculated by adjusting each test for age at testing and then regressing age 70 MHT on age 11 MHT and using the unstandardized residual. A General Fluid (gf) Intelligence at age 70 was derived from principal components analysis of 6 Wechsler Adult Intelligence Scale–III UK nonverbal subtests[9] (Matrix Reasoning, Letter Number Sequencing, Block Design, Symbol Search, Digit Symbol, Digit Span Backward), as described previously.[10] Crystallized intelligence at age 70 was measured using the National Adult Reading Test (NART).[11] Cognitive measures were adjusted for age at testing and sex.

Mood and personality trait - LBC1936

The mood states of anxiety and depression were assessed using the Hospital Anxiety Depression Scale (HADS).[12] The personality trait of neuroticism were measured using

the NEO Five-Factor Inventory.[13] Personality measures were adjusted for age at testing and sex.

Gene Selection

A total of 213 genes that directly or indirectly interact with DISC1 were selected for targeted resequencing in the study Genes were grouped into following categories.

1. **DISC1 Interactome**: A set of 59 genes consisting of *DISC1* locus (*Disrupted in Schizophrenia 1* (*DISC1*); *Translin-associated factor X* (*TSNAX*); *TSNAX-DISC1 readthrough*) and direct DISC1 Protein-Protein Interacting (PPI) genes based on annotations in the protein interaction databases IntAct and Mentha.[14,15]
2. **DISC1 Regulome**: 154 genes based on the following criteria:

   a) prior evidence of genetic association with psychiatric illness (GWAS, CNV and candidate genes studies.[16–18]

   b) expression altered in hippocampus of DISC1 mutant mice.[19]

   c) expression patterns dysregulated in lymphoblastoid cell lines of DISC1 t(1:11) translocation carriers (see below).

   d) expression regulated by risk variants in DISC1 or DISC1 interactors.[20]

   e) proteins that directly interact with other Interactome gene proteins.

All genes selected were required to meet criterion a) and one other from b-e. The full list of 213 DISC1 Interactome plus Regulome genes targeted for this study are listed in in Supplementary Table 1.

Differential gene expression in lymphoblastoid cell lines of t(1;11) translocation carriers

This experiment has been published as part of a PhD Thesis. Full details can be found in Briggs, Gareth James, “Investigating putative pathogenic mechanisms within a family in which a chromosomal translocation confers risk of major mental illness”. PhD Thesis, University of Edinburgh (www.era.lib.ed.ac.uk). Gene expression from Epstein-Barr virus transformed lymphblastoid cell lines was assessed using a proprietary Rosetta chip in a study implemented by Maerk Sharp Dohme. Gene expression was detected for 10 923 genes. Differential expression was analysed between translocation carriers and family controls with techinical replicates (fold change ±1.3 and $P \leq 0.05$). 1 010 genes were differentially expressed (9.2%) and functional enrichment analyses showed a clear signature for cell cycle and DNA replication as well as possible effects on immune function and inflammation pathways.

Target Design

A custom solution capture probe set (Roche NimbleGen) was developed to target approximately 11.7Mbp (0.38%) of the human genome (hg18) representing the exons (3.3 Mbp) and promoters of all 213 DISC1 Interactome plus Regulome genes as well as conserved regions 20kb upstream, downstream and across each gene. The exon coordinates of every isoform of each gene were extracted from the RefSeq and UCSC Gene lists (hg18). The promoters were defined as 2kb upstream regions of transcription start site of all selected genes. The conserved regions were defined as runs of at least 10bps with an average score ≥0.3 using phastCons 44-vertebrate alignment.[21]

Expanding our analysis to include 100bp flanking each of the 67 551 targets represents 21.5 Mbp (0.70%) of the human genome, taking into account overlaps between flanking targets.

Targeted Resequencing

Genomic DNA (1ug) extracted from blood samples of each individual was sheared to create fragments with an average size of 250bp using a Covaris S2 sonicator system (temperature: 4°C, duty cycle: 10%, intensity: 5, cycles per burst: 200, time: 90 s). The fragment size distribution of the DNA was checked using a DNA 1000 Bioanalyzer chip (Agilent Technologies), and the DNA was concentrated using Agencourt Ampure XP beads (Beckman Coulter). The NEXTflex DNA Sequencing Kit (Bioo Scientific) was used for sequencing library preparation including end repair, size selection (~400bp insert size), adenylation, and adaptor ligation. The DNA was purified using Ampure XP beads, and amplified using LM-PCR. The DNA was then quantified using a Quant-iT fluorometric assay and the Agilent Technologies 2100 Bioanalyzer DNA 1000 Kit. The library was hybridized with the custom solution capture probes described above. The hybridization was performed, according to the NimbleGen SeqCap User's Guide, for 72 hours at 47°C with the barcode-blocking oligo. The captured DNA was recovered using Streptavidin Dynabeads. The post-capture sample library amplifications were performed using two LM-PCR reactions per sample to reduce PCR bias followed by an Ampure XP bead clean-up. The post-capture PCR enriched library was quantified by using a qPCR library quantification kit (KAPA Biosystems). The library fragment distribution was determined using a High Sensitivity DNA kit on the Agilent Bioanalyzer system, and the

results suggested that the samples have broad peaks ranging from 250bp to 850bp with the highest peak at around 400bp. The sequencing flow cells were generated using a CBot reagent plate (Illumina), in total 16 barcoded samples were sequenced across three lanes of a flowcell using HiSeq2000 (Illumina) with paired-end 101 reads. In total 1464 (95%) samples with 80% of the targets at ≥20x read depth were used in the downstream analysis, and the other 79 samples were excluded from the further analyses. The average mean target coverage of the samples was 116x read depth (Supplementary Table S2), and no evidence of significant sequencing bias was observed between the case and control groups (Supplementary Table S2 & Supplementary Figure S1).

Variant Calling

Variant calling was performed using our standardized variant calling pipeline. Paired-end reads were aligned to the human NCBI Build 36 (hg18) reference using BWA.[22] SAMtools[23] was used to convert to bam format, sort, index and merge the aligned sequencing files. Picard was applied to remove duplicate read pairs, which were an artifact of the PCR amplification during sample preparation. BamTools[24] was used to filter for properly paired reads and for mapping quality of >=20. The Genome Analysis Toolkit (GATK)[25] was used to recalibrate base quality scores, realign indel regions and call single nucleotide variants (SNVs) and small insertions and deletions (INDELs) located in the targets as well as in the 100bp flanking regions of each target. The SNVs located in called INDEL regions were masked. Standardized filtering parameters (minimum mapping quality 40, minimum confidence score 30, minimum depth 6,

clusterWindowSize 10, clusterSize 3) were applied to select the SNVs with high confidence. Additional filters used in SNV calling included "HaplotypeScoreFilter" (HaplotypeScore>13.0), "QDFilter" (QD<2.0), "FSFilter" FS>60.0 MQRankSumFilter (MQRankSum<-12.5) and "ReadPosRankSumFilter" (ReadPosRankSum<-8.0). To establish the filtering criteria for SNVs with high quality, we compared the SNV calling results with our previous Sanger sequencing validations[1] in the TRAX/DISC1 region. The SNVs with filters “PASS” or “HaplotypeScoreFilter” were selected for further analysis, and showed good agreement with 100% and 98% sensitivity for detecting the true exonic and rare SNVs in the TRAX/DISC1 region. VCFtools[26] was used to merge the VCF files and convert from VCF to PLINK format (ped and map files), and multi-allelic SNVs were excluded for further analysis. GATK[25] was also used to generate “coverage” VCF files including calls at all sites from the recalibrated bam files. An in-house Perl script was applied to extract the genotypes of reference allele homozygotes from the VCF files to fill missing information in the merged VCF file, and the genotypes were set as missing if they had a coverage of <6X.

Case-Control Quality Control

To reduce the number of potential false-positive and false-negative associations, we performed several data quality control analyses using PLINK[27,28] to remove poor quality samples and SNVs. The detailed quality control strategy is illustrated in Supplementary Figure S2.

Sample Quality Control

1. To minimize issues with population stratification that can confound case-control studies, we performed multidimensional scaling (MDS) analysis of our samples together with genotype data from HapMap (release 23). We removed four samples that deviated from the Hapmap European population and the samples sequenced in this study (Supplementary Figure S3).
2. To exclude samples of low quality,[28] we removed three samples with a missing genotype rate>7.5% (Supplementary Figure S4, vertical dashed line) and three samples with an outlying heterozygosity rate ± 4 s.d. from the mean (Supplementary Figure S4, horizontal dashed lines),
3. Two samples with inconsistency between chrX heterozygous SNV rates and reported gender were removed.
4. Finally, three samples with cryptic relatedness (PI_HAT>0.3) identified based on pairwise Identity by Descent (IBD) using PLINK default settings were excluded.

SNV Quality Control

Following the removal of poor quality and unreliable samples, SNVs were filtered as follows to minimize issues with coverage, and genotyping errors:

1. SNVs with a genotype missing rate >0.2 were removed (Supplementary Figure S5, vertical dashed line).
2. SNVs with a Hardy-Weinberg equilibrium P-value <0.00001 (Supplementary Figure S6, horizontal dashed lines) were removed.

3. SNVs with a minor allele frequency equal to zero due to sample elimination were excluded.
4. Finally singleton variants with high strand bias ("FSFilter" FS>30.0) were excluded as these singletons showed high false positive rate in validation.

Variant Annotation

The SNVs were matched to hg19 coordinates using liftOver from UCSC. ANNOVAR[29] was used to predict the mutational class (exon, splice site, nonsense, missense, silent, UTR, etc.) of each variant based on RefSeq (hg19). ANNOVAR uses the precedence (exonic=splicing>ncRNA>UTR5/UTR3>intron>upstream/downstream>intergenic) to decide what function to print out when a variant fit multiple functional categories. Analysis was restricted to variants located within 5kb upstream and downstream of each gene. ANNOVAR was used to identify the SNVs that present in dbSNP144 and determine the allele frequency of SNVs in the 1000 Genomes Project (2015aug version). Rare variants were classified as SNVs with a minor allele frequency (MAF) <1% in the combined case-control samples, and singleton variants were SNVs observed in only one sample. The functional effect of each variant was predicted based on five *in silico* algorithms (SIFT[30], PolyPhen2 HumDiv and HumVar[31], LRT[32] and MutationTaster[33]) using ANNOVAR. We applied a strategy similar to that used in previous studies[34,35] to classify the coding variants into three damaging mutation classes: (1) disruptive mutations including nonsense and splice-site variants; (2) non-synonymous strict damaging mutations (NS_{strict}) including disruptive variants plus missense variants predicted as damaging by all five algorithms above; and (3) non-synonymous broad

damaging mutations (NS_{broad}) including disruptive plus missense variants predicted as damaging by at least one of the five algorithms listed above.

Variant Validation and Evaluation

We used Sanger sequencing to validate variants. PCR primers flanking the SNV regions were picked by Primer3 and manufactured by Sigma. LongAmp PCR was used to amplify the sample DNA. Sanger sequencing was performed using the primers and the Big Dye terminator sequencing kit (Life Technologies) on an Applied Biosystems 3730XL DNA sequencer. Sequenced reads were then assembled with the corresponding region of the reference genome (exported from UCSC genome browser hg19) and SNVs were confirmed using the CONSED package.[36] All false positive SNVs identified in validation were removed from further analyzes.

The final dataset used for association analyses included 196 005 SNVs and 1 446 samples consisting of 575 cases of patients (211 cases of SCZ, 169 cases of rMDD and 195 cases of BD) and 871 controls from the LBC1936.

Evaluation of Variant Detection and False Discovery Rates

Using validated data from our recent sequence analysis of DISC1[1] which included all 1446 samples that passed the quality control filters in the current study, we established a set of gold standard DISC1 variants to evaluate the quality and reliability of filtered SNV calls detected by targeted re-sequencing. In total, 1 202 gold standard DISC1 variants and 1 482 DISC1 target sequence variants were called in non-repeat regions common to both studies. Of the 1 202 gold standard DISC1 variants, 1 168 were

detected by targeted resequencing estimating the sensitivity of variant detection by targeted sequencing to be approximately 97% (Supplementary Table S3). There were 314 variants specific to the targeted re-sequencing call set. Of these 314, 251 had sequence read evidence in our previous DISC1 analysis, but were not called or did not pass filtering in that study. Following Sanger validations the False Discovery Rate of variant calling by targeted sequencing was reduced to 4%. A similar FDR was achieved by randomly selecting 96 variants for Sanger validation across the entire Interactome. For the purposes of downstream variant analyses, all nonsense and splice site variants were Sanger validated and, as expected, had a higher FDR rate of 11%.

As a final measure of call quality, we contrasted the minor allele frequency (MAF) spectrum of the LBC1936 control SNVs to the MAF spectrum in the European Ancestry subset of the 1000 Genomes Project (1000G_EU). Supporting the performance of our filtering measures, the MAF spectrum of control SNVs highly correlated with the MAF spectrum in the 1000G_EU (R^2=0.982, Supplementary Figure S6), which was a significant improvement over the correlation between the unfiltered control and 1000G_EU MAF spectra (R^2=0.926).

Rare Variant Burden Analysis

We carried out general burden test (BURDEN) and sequence kernel association test (SKAT) implemented in the R package 'SKAT' to assess the burden of rare variants.[37] BURDEN test was used for the gene-wide burden analysis for the genes with multiple variants (Supplementary Table S8, S11, S14, S16). BURDEN approach collapses the minor alleles across all samples into a single variable, and compares the cumulative

effects in cases vs controls within a gene to evaluate the significance of the difference. However, at the gene set level, the variants in different genes affect the phenotype in different directions and most rare variants have little effect on phenotype. SKAT[37] test is particularly designed for solving this problem. It uses a kernel machine regression approach to aggregate the associations between variants in a gene region and a phenotypic trait. SKAT is powerful for the genes with many non-causal variants or both protective and deleterious variants. Thus, we used SKAT test to evaluate the burden of rare variants at gene set level (Supplementary Table S6, S9, S13, S15).

We used a bootstrap resampling method (n.Resampling=10 000) to calculate the p-values and estimate the adjusted *P*-values using Family Wise Error Rate (FWER) correction within each trait (SCZ or BD or rMDD) ($FWER_{within}$) and across all traits ($FWER_{across}$). The FWER gives the probability of having at least one false-positive result when the null hypothesis (H0) is true for all M tests at α=0.05. The adjusted *P*-value is calculated by $P=(m + 1)/(n + 1)$, where n is the total number of resampling tests (n=10 000) and m is the number of tests with a smallest *P*-value smaller than the unadjusted *P*-value from the original data set. The FWER corrections were carried out for all burden tests (functional class and frequency) within the trait ($FWER_{within}$ *P*) and all tests across all traits ($FWER_{across}$ *P*). The effect size (Beta) and standard error (SE) were computed using the 'burdenMeta' function implemented in the R package 'seqMeta' for both gene-wide and gene set levels, and the odds ratio (OR) was estimated by taking exponential function of the beta value.

Due to the relatively small sample size in this study, we evaluated the rates of singleton and rare variants in each functional mutation class using the Exact Poisson

test under a Poisson distribution (the sample variance is the same as the mean in our data) in cases compared to controls in each functional mutation class (Supplementary Table S7 & S10). The unadjusted *P*-value was calculated using the 'poisson.test' function implemented in R. As for the burden tests, we used a bootstrapping method to determine the adjusted $FWER_{within}$ and $FWER_{across}$ *P*-values for each test.

The case-control burden analysis was carried out on each of three diagnoses (SCZ, BD and rMDD) and the sum of all three diagnoses (Supplementary Table S6-S11). The quantitative trait association analyses using LBC1936 controls were performed on eight traits including five cognitive measures and three personality traits described in Phenotypes section (Supplementary Table S13-S16). The cognitive measures were Moray House Test at age 11 (a verbal reasoning and IQ-type test), Moray House Test at age 70, Moray House Test at age 70 adjusted for the Moray House Test score at age 11, National Adult Reading Test and General Fluid Intelligence. The personality traits were Hospital Anxiety Depression Scales - Depression, Hospital Anxiety Depression Scales - Anxiety and NEO Five-Factor Inventory - Neuroticism. Both case-control and quantitative trait burden analyzes were carried out for three damaging mutation classes (Disruptive, NS_{strict} and NS_{broad}) on all rare variants as well as singletons as described in Variant Annotation section. The quantile-quantile plots showed that most of gene-wide association tests in case-control and quantitative trait association analysis follow the expected null distribution (Supplementary Figures S7 & S8).

GO Enrichment Analysis

Gene ontology (GO) enrichment analyses were performed using GoRilla[38] against a background list of known protein coding genes.[39,40] Comparison of enriched GO terms was performed using GOView.[41] The Interactome shows significant enrichment for genes involved in cytoskeletal binding and the centrosome, particularly microtubule organization and the G2/M transition of mitotic cell cycle (Supplementary Tables S17). In contrast, the genes in the Regulome are enriched for synaptic transmission and peripheral nervous system development, particularly extracellular-glutamate-gated ion channel activity (Supplementary Tables S18). Comparison of the GO terms associated with both the DISC1 Interactome and Regulome reveals largely independent GO term associations with a very limited set of intersecting terms focused on negative regulation of cellular process, protein binding, and cell projections (Supplementary Figures S9-S11).

URLS

Picard: http://picard.sourceforge.net

UCSC Hg18: http://genome.ucsc.edu/

PLINK 1.90 beta: https://www.cog-genomics.org/plink2

ANNOVAR: http://www.openbioinformatics.org/annovar/

1000 Genomes Project: http://www.1000genomes.org/

Primer3: http://primer3.sourceforge.net

SKAT: https://cran.r-project.org/web/packages/SKAT/

seqMeta: http://cran.r-project.org/web/packages/seqMeta/

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Supplementary Tables

Supplementary Table S1: DISC1 Interactome and Regulome Gene List

The full list of 213 gene symbols and coordinates (hg18 & hg19).

See: “S1.GeneList” sheet in supplementary tables.xlsx

Supplementary Table S2: Sequencing Summary Statistics

Averages for Mean Target Coverage and Percentage of the Target Bases at 2x, 10x, 20x and 30x are shown for all samples (ALL) as well as individually for schizophrenia (SCZ), recurrent major depressive disorder (rMDD), bipolar (BD), and the Lothian Birth Cohort of 1936 (LBC1936) samples. The samples with 80% of the targets at ≥20x read depth were used for further analysis. The case control quality control filters (Supplementary Figure S2) were applied to generate the final data set.

	ALL	SCZ	rMDD	BD	LBC1936
All Sequenced Sample					
Total Number	1543	241	192	221	889
Mean Target Coverage	115	105	107	111	120
Percentage of Target Bases at ≥2x	96.96%	96.43%	96.55%	96.90%	97.21%
Percentage of Target Bases at ≥10x	94.21%	92.82%	92.51%	93.56%	95.11%
Percentage of Target Bases at ≥20x	90.11%	87.79%	87.00%	88.71%	91.76%
Percentage of Target Bases at ≥30x	85.23%	82.09%	81.02%	83.05%	87.53%
Samples with 80% of the Targets at ≥20x					
Total Number	1464	217	173	199	875
Mean Target Coverage	118	111	113	117	121
Percentage of Target Bases at ≥2x	97.15%	97.08%	97.03%	97.03%	97.22%
Percentage of Target Bases at ≥10x	94.84%	94.42%	94.19%	94.23%	95.21%
Percentage of Target Bases at ≥20x	91.27%	90.35%	89.91%	90.17%	92.02%
Percentage of Target Bases at ≥30x	86.84%	85.35%	84.74%	85.28%	87.98%
Samples in the Final Data Set					
Total Number	1446	211	169	195	871
Mean Target Coverage	118	111	113	117	121
Percentage of Target Bases at ≥2x	97.15%	97.08%	97.04%	97.04%	97.22%
Percentage of Target Bases at ≥10x	94.85%	94.42%	94.22%	94.28%	95.21%
Percentage of Target Bases at ≥20x	91.30%	90.35%	89.95%	90.25%	92.03%
Percentage of Target Bases at ≥30x	86.88%	85.35%	84.76%	85.40%	87.99%

Supplementary Table S3: Variant Summary Statistics

Class	# SNV	% Rare (MAF<1%)	% Singleton
All Identified SNVs	196080	78%	50%
Common (MAF ≥ 1%)	42789		
Rare (MAF<1%)	153291		
Singleton	97786		
Reported in Public Databases			
1000G_EU[a]	77593		
dbSNP144	124268		
Functional Anotations			
Intronic	169905	78%	50%
5'/3' UTR	5410	84%	53%
Exonic	4523	86%	57%
Silent	1893	79%	51%
Missense	2569	91%	62%
Nonsense	41	100%	71%
Unknown[b]	20	90%	65%
Splice Site	24	92%	75%
Damaging Mutations[c]			
Disruptive	65	97%	72%
NS_{strict}	374	98%	73%
NS_{broad}	2057	94%	66%

[a]Based on ANNOVAR filter for 1000 Genomes Project (2015 Aug) European subset annotations.

[b]Unknown refers to exonic variants in genes with incomplete or unavailable ORF information. These variants were not included in the analysis.

[c]Disruptive, nonsense and splice site variants; NS_{strict}, Non-synonymous strict damaging mutations were defined as disruptive plus missense variants predicted as damaging by all five algorithms (PolyPhen2 HumDiv and HumVar, SIFT, LRT and MutationTaster); NS_{broad}, Non-synonymous broad damaging mutations were defined as disruptive plus missense variants predicted as damaging by at least one algorithm above.

Supplementary Table S4: Sensitivity and Specificity of DISC1 Variant Discovery by Capture Sequencing

The DISC1 Locus (DL) variants were obtained from the recent DISC1 locus sequence analysis[1] and validated using Sanger sequencing. The DISC1 Interactome (DI) variants identified in the present study were filtered by case control quality control filters (Supplementary Figure S2). Both DL and DI variants were called in *DISC1* non-repeat regions common to both studies.

	DISC1 Locus (DL) Validated Variants		**Total**
DISC1 Interactome (DI) Filtered Variants	**DI in DL**	**DI not in DL**	1482
	1168	314	
	DL not in DI	**Not in DL or DI**	136173
	34	136139	
Total	1202	136453	137655

Supplementary Table S5: Summary of Validated Disruptive Variants

Gene	Chr	Pos (hg18)	Ref base	Alt base	dbSNP144	1000G-Eur Frequency	Case MAF	Control MAF	SCZ[a]	rMDD[a]	BP[a]	CTL[a]
						Nonsense						
AP4B1	1	114246002	G	A	NA	NA	0.0009	0.0006	0/0/211	0/0/169	0/1/194	0/1/870
DISC1	1	229924937	G	A	rs201177890	NA	0.0000	0.0006	0/0/211	0/0/169	0/0/195	0/1/870
DISC1	1	230211206	C	T	rs190975963	NA	0.0009	0.0006	0/0/211	0/1/168	0/0/195	0/1/870
NRXN1	2	50704217	G	C	NA	NA	0.0009	0.0000	0/1/210	0/0/169	0/0/195	0/0/871
NRXN1	2	51108309	T	A	NA	NA	0.0009	0.0000	0/1/210	0/0/169	0/0/195	0/0/871
DCTN1	2	74454963	G	A	NA	NA	0.0000	0.0006	0/0/211	0/0/169	0/0/195	0/1/870
SH3BP5	3	15286253	G	A	NA	NA	0.0009	0.0000	0/0/211	0/1/166	0/0/193	0/0/871
KALRN	3	125786386	C	T	rs56407180	0.0010	0.0009	0.0023	0/0/211	0/0/169	0/1/194	0/4/867
NEK1	4	170582394	G	C	rs199947197	NA	0.0000	0.0006	0/0/211	0/0/169	0/0/195	0/1/870
DPYSL3	5	146775486	G	A	NA	NA	0.0009	0.0000	0/0/211	0/1/168	0/0/195	0/0/871
DTNBP1	6	15632694	G	A	rs144524387	NA	0.0009	0.0006	0/1/210	0/0/169	0/0/195	0/1/870
DTNBP1	6	15771061	C	A	NA	NA	0.0000	0.0006	0/0/211	0/0/168	0/0/192	0/1/869
DST	6	56593325	G	A	rs577972555	NA	0.0009	0.0000	0/0/211	0/0/169	0/1/194	0/0/871
SYNE1	6	152587381	G	A	rs778445117	NA	0.0000	0.0006	0/0/211	0/0/169	0/0/195	0/1/870
NUDT1	7	2256028	G	T	rs370549369	NA	0.0010	0.0000	0/0/196	0/0/148	0/1/166	0/0/839
MCPH1	8	6289896	T	A	rs377204886	NA	0.0009	0.0000	0/0/211	0/0/169	0/1/194	0/0/871
PCM1	8	17882493	G	T	rs148806955	0.0050	0.0035	0.0029	0/3/208	0/1/168	0/0/195	0/5/866
DMRT2	9	1046377	C	T	NA	NA	0.0009	0.0000	0/0/211	0/1/168	0/0/195	0/0/871
KCNQ1	11	2746687	C	T	rs17215500	NA	0.0018	0.0000	0/0/205	0/0/157	0/2/178	0/0/859
CEP290	12	86995171	C	A	rs137852832	NA	0.0000	0.0006	0/0/211	0/0/169	0/0/195	0/1/870
CEP290	12	87001844	T	A	rs137852834	NA	0.0009	0.0017	0/0/211	0/0/169	0/1/194	0/3/868
CEP290	12	87032396	G	A	rs386834152	NA	0.0000	0.0011	0/0/211	0/0/169	0/0/195	0/2/869
CEP290	12	87049117	G	A	rs757641323	NA	0.0000	0.0011	0/0/211	0/0/169	0/0/195	0/2/869
APPL2	12	104113408	C	T	NA	NA	0.0017	0.0006	0/2/209	0/0/169	0/0/195	0/1/870
APPL2	12	104115860	T	A	NA	NA	0.0000	0.0006	0/0/211	0/0/169	0/0/195	0/1/870
MAP1A	15	41609340	C	T	NA	NA	0.0000	0.0006	0/0/210	0/0/169	0/0/194	0/1/870
CHRNA5	15	76666084	C	T	NA	NA	0.0009	0.0000	0/1/210	0/0/169	0/0/195	0/0/871

SV2B	15	89602698	G	A	NA	NA	0.0000	0.0006	0/0/211	0/0/169	0/0/195	0/1/870
EEF2K	16	22181932	G	T	rs139935693	NA	0.0009	0.0011	0/1/210	0/0/169	0/0/195	0/2/869
PRKCB	16	24110023	G	T	NA	NA	0.0009	0.0000	0/1/210	0/0/169	0/0/195	0/0/871
TSNAXIP1	16	66405794	C	T	rs146214814	0.0030	0.0054	0.0041	0/6/200	0/0/163	0/0/189	0/7/854
PCNT	21	46656167	G	T	NA	NA	0.0000	0.0006	0/0/176	0/0/137	0/0/164	0/1/845
PCNT	21	46688165	C	T	NA	NA	0.0009	0.0000	0/1/210	0/0/169	0/0/195	0/0/871
TRIOBP	22	36449548	C	T	rs118204026	NA	0.0000	0.0006	0/0/211	0/0/163	0/0/188	0/1/870
Splice site												
BLZF1	1	167604205	G	A	rs187961364	0.0030	0.0113	0.0138	0/5/206	0/3/166	0/5/190	0/24/847
LPIN1	2	11771390	G	T	NA	NA	0.0009	0.0000	0/0/211	0/1/168	0/0/195	0/0/871
SYN2	3	12186408	T	G	rs773718233	NA	0.0000	0.0006	0/0/211	0/0/169	0/0/195	0/1/870
SNAP91	6	84347024	T	C	NA	NA	0.0009	0.0006	0/0/211	0/1/168	0/0/195	0/1/870
SYNE1	6	152991092	C	A	NA	NA	0.0009	0.0000	0/0/211	0/1/168	0/0/195	0/0/871
PCM1	8	17824978	G	A	rs375662391	NA	0.0009	0.0000	0/1/209	0/0/169	0/0/195	0/0/870
PCM1	8	17826500	A	T	NA	NA	0.0009	0.0000	0/1/210	0/0/169	0/0/195	0/0/871
PCM1	8	17826570	G	T	rs747885172	NA	0.0009	0.0000	0/0/211	0/0/169	0/1/194	0/0/871
RAD21	8	117948182	C	T	rs16889042	0.0040	0.0009	0.0023	0/0/211	0/1/168	0/0/195	0/4/867
SLC1A2	11	35300683	C	T	rs56205617	0.0338	0.0339	0.0276	0/21/190	0/5/164	0/13/182	0/48/823
DIXDC1	11	111358273	G	A	NA	NA	0.0000	0.0006	0/0/211	0/0/169	0/0/195	0/1/870
DIXDC1	11	111371043	G	A	rs200500225	NA	0.0000	0.0006	0/0/211	0/0/169	0/0/195	0/1/870
CEP290	12	87038904	C	A	NA	NA	0.0000	0.0006	0/0/211	0/0/169	0/0/195	0/1/870
APPL2	12	104147133	T	C	NA	NA	0.0000	0.0006	0/0/211	0/0/169	0/0/195	0/1/870
EEF2K	16	22169514	G	A	rs200670923	NA	0.0009	0.0000	0/1/210	0/0/169	0/0/195	0/0/871
TSNAXIP1	16	66419156	G	C	NA	NA	0.0009	0.0000	0/0/210	0/1/163	0/0/189	0/0/868
STAT5A	17	37705293	A	T	NA	NA	0.0000	0.0006	0/0/211	0/0/169	0/0/195	0/1/870
CDK5RAP3	17	43413801	G	C	rs184760380	0.0010	0.0000	0.0006	0/0/211	0/0/169	0/0/195	0/1/870
PCNT	21	46642354	A	G	rs760664460	NA	0.0009	0.0006	0/0/210	0/1/167	0/0/195	0/1/870
BCR	22	21986153	A	C	NA	NA	0.0009	0.0000	0/1/209	0/0/164	0/0/189	0/0/870

[a]Genotype counts are shown for Schizophrenia (SCZ), bipolar (BD), recurrent major depressive disorder (rMDD) cases and the Lothian Birth Cohort of 1936 controls (CTL).

Supplementary Table S6. Gene Set Burden Analysis of Rare Functional Variants in the DISC1 Interactome for Case-Control Traits

Trait[a]	Mutation Class[b]	MAFbin	N.SNP.Test	Unadjusted *P*	$FWER_{within}$ *P*	$FWER_{cross}$ *P*	OR	SE
SCZ	Disruptive	Singleton	11	0.8085	0.9992	1.0000	0.9021	0.1201
SCZ	Disruptive	Rare	19	0.8270	0.9996	1.0000	0.8487	0.0746
SCZ	NS_{strict}	Singleton	94	0.7180	0.9915	1.0000	0.9768	0.0405
SCZ	NS_{strict}	Rare	147	0.9091	0.9998	1.0000	0.9818	0.0242
SCZ	NS_{broad}	Singleton	451	0.2572	0.7552	0.9962	1.0124	0.0178
SCZ	NS_{broad}	Rare	721	0.7876	0.9967	1.0000	0.9959	0.0095
rMDD	Disruptive	Singleton	13	0.2484	0.7102	0.9952	1.0736	0.1030
rMDD	Disruptive	Rare	21	0.4635	0.8953	1.0000	1.0154	0.0644
rMDD	NS_{strict}	Singleton	97	0.1955	0.5473	0.9747	1.0344	0.0369
rMDD	NS_{strict}	Rare	150	0.3592	0.8258	0.9997	1.0110	0.0225
rMDD	NS_{broad}	Singleton	441	0.1232	0.4167	0.9012	1.0262	0.0174
rMDD	NS_{broad}	Rare	708	0.2849	0.7605	0.9979	1.0002	0.0090
BD	Disruptive	Singleton	11	0.7858	0.9986	1.0000	0.9130	0.1172
BD	Disruptive	Rare	20	0.3831	0.8461	0.9997	0.9946	0.0674
BD	NS_{strict}	Singleton	91	0.8326	0.9994	1.0000	0.9639	0.0396
BD	NS_{strict}	Rare	144	0.9167	1.0000	1.0000	0.9605	0.0239
BD	NS_{broad}	Singleton	436	0.5918	0.9723	1.0000	0.9971	0.0181
BD	NS_{broad}	Rare	700	0.4302	0.8832	0.9998	0.9910	0.0094
Combined	Disruptive	Singleton	15	0.7145	0.9968	1.0000	0.9396	0.1271
Combined	Disruptive	Rare	24	0.6307	0.9881	1.0000	0.9219	0.0776
Combined	NS_{strict}	Singleton	126	0.6553	0.9905	1.0000	0.9857	0.0431
Combined	NS_{strict}	Rare	181	0.9209	1.0000	1.0000	0.9740	0.0259
Combined	NS_{broad}	Singleton	612	0.2355	0.7185	0.9905	1.0184	0.0192
Combined	NS_{broad}	Rare	888	0.3625	0.8827	0.9997	0.9929	0.0101

[a]Schizophrenia (SCZ); bipolar disorder (BD); recurrent major depressive disorder (rMDD); Combined Cases (Combined).
[b]Non-synonymous strictly damaging mutations (NS_{strict}); Non-synonymous broadly damaging mutations (NS_{broad}).
The odds ratio (OR) and standard error (SE).

Supplementary Table S7. Gene Set Exact Poisson Tests of Rare Functional Variants in the DISC1 Interactome for Case-Control Traits

Trait[a]	Mutation Class[b]	MAFbin	Unadjusted *P*	$FWER_{within}$ *P*	$FWER_{cross}$ *P*	Case/Control Ratio	Control Rate	Case Rate
SCZ	Disruptive	Singleton	0.7397	0.9981	1.0000	0.4128	0.0115	0.0047
SCZ	Disruptive	Rare	**0.0188**	0.1683	0.5666	0.1474	0.0321	0.0047
SCZ	NS_{strict}	Singleton	0.6440	0.9948	1.0000	0.8468	0.0896	0.0758
SCZ	NS_{strict}	Rare	0.4505	0.9504	1.0000	0.8819	0.2526	0.2227
SCZ	NS_{broad}	Singleton	0.4850	0.9711	1.0000	1.0723	0.4110	0.4408
SCZ	NS_{broad}	Rare	0.5994	0.9926	1.0000	0.9686	1.5511	1.5024
rMDD	Disruptive	Singleton	0.4508	0.9539	1.0000	1.5462	0.0115	0.0178
rMDD	Disruptive	Rare	0.6690	0.9908	1.0000	1.1044	0.0321	0.0355
rMDD	NS_{strict}	Singleton	0.3022	0.8348	0.9994	1.2554	0.0896	0.1124
rMDD	NS_{strict}	Rare	0.5916	0.9842	1.0000	1.0776	0.2526	0.2722
rMDD	NS_{broad}	Singleton	0.1051	0.4827	0.9612	1.1949	0.4110	0.4911
rMDD	NS_{broad}	Rare	1.0000	1.0000	1.0000	0.9995	1.5511	1.5503
BD	Disruptive	Singleton	0.7329	0.9992	1.0000	0.4467	0.0115	0.0051
BD	Disruptive	Rare	1.0000	1.0000	1.0000	0.9571	0.0321	0.0308
BD	NS_{strict}	Singleton	0.3379	0.9124	0.9999	0.7444	0.0896	0.0667
BD	NS_{strict}	Rare	0.0633	0.3401	0.8611	0.7309	0.2526	0.1846
BD	NS_{broad}	Singleton	0.8669	1.0000	1.0000	0.9732	0.4110	0.4000
BD	NS_{broad}	Rare	0.2272	0.7571	0.9971	0.9290	1.5511	1.4410
Combined	Disruptive	Singleton	0.6966	0.9994	1.0000	0.7574	0.0115	0.0087
Combined	Disruptive	Rare	0.2433	0.8779	0.9985	0.7033	0.0321	0.0226
Combined	NS_{strict}	Singleton	0.6761	0.9988	1.0000	0.9322	0.0896	0.0835
Combined	NS_{strict}	Rare	0.1843	0.8146	0.9938	0.8882	0.2526	0.2243
Combined	NS_{broad}	Singleton	0.2548	0.8975	0.9987	1.0747	0.4110	0.4417
Combined	NS_{broad}	Rare	0.2915	0.9118	0.9993	0.9643	1.5511	1.4957

[a]Schizophrenia (SCZ); bipolar disorder (BD); recurrent major depressive disorder (rMDD); Combined Cases (Combined).
[b]Non-synonymous strictly damaging mutations (NS_{strict}); Non-synonymous broadly damaging mutations (NS_{broad}).
Bold, P<0.05; Case/Control Ratio is calculated using Case Rate divided by Control Rate.

Supplementary Table S8. Gene-Wide Burden Analysis of Rare Functional Variants in the DISC1 Interactome for Case-Control Traits

See: “S8.CaseControlGeneInteractome” sheet in supplementary tables.xlsx

[a]Schizophrenia (SCZ); bipolar disorder (BD); recurrent major depressive disorder (rMDD); Combined Cases (Combined).
[b]Non-synonymous strictly damaging mutations (NS_{strict}); Non-synonymous broadly damaging mutations (NS_{broad}).
Bold, $P<0.05$. Tests are sorted in ascending order of the unadjusted *P*-value. The odds ratio (OR) and standard error (SE).

Supplementary Table S9. Gene Set Burden Analysis of Rare Functional Variants in the DISC1 Regulome for Case-Control Traits

Trait[a]	Mutation Class[b]	MAFbin	N.SNP.Test	Unadjusted *P*	$FWER_{within}$ *P*	$FWER_{cross}$ *P*	OR	SE
SCZ	Disruptive	Singleton	16	**0.0019**	**0.0069**	**0.0339**	1.3162	0.0941
SCZ	Disruptive	Rare	22	**0.0061**	**0.0228**	0.0863	1.2992	0.0584
SCZ	NS_{strict}	Singleton	136	**0.0314**	0.1106	0.3852	1.0776	0.0335
SCZ	NS_{strict}	Rare	186	**0.0398**	0.1385	0.4694	1.0685	0.0227
SCZ	NS_{broad}	Singleton	570	0.1032	0.3424	0.8302	1.0227	0.0158
SCZ	NS_{broad}	Rare	883	0.1063	0.3504	0.8384	1.0081	0.0090
rMDD	Disruptive	Singleton	11	0.1580	0.4736	0.9378	1.1188	0.1119
rMDD	Disruptive	Rare	17	0.3287	0.7683	0.9989	1.0054	0.0684
rMDD	NS_{strict}	Singleton	122	0.2557	0.6828	0.9920	1.0259	0.0328
rMDD	NS_{strict}	Rare	172	0.1281	0.3933	0.8843	1.0209	0.0220
rMDD	NS_{broad}	Singleton	536	0.5029	0.9301	1.0000	1.0036	0.0152
rMDD	NS_{broad}	Rare	842	0.8302	0.9985	1.0000	0.9924	0.0086
BD	Disruptive	Singleton	11	0.2107	0.5821	0.9795	1.0974	0.1172
BD	Disruptive	Rare	17	0.2527	0.7082	0.9915	0.9266	0.0741
BD	NS_{strict}	Singleton	116	0.8479	0.9990	1.0000	0.9654	0.0353
BD	NS_{strict}	Rare	165	0.7288	0.9923	1.0000	0.9477	0.0235
BD	NS_{broad}	Singleton	553	0.2796	0.7375	0.9945	1.0110	0.0155
BD	NS_{broad}	Rare	858	0.2574	0.7172	0.9921	0.9978	0.0088
Combined	Disruptive	Singleton	22	**0.0127**	**0.0461**	0.2112	1.2503	0.1006
Combined	Disruptive	Rare	28	0.8971	1.0000	1.0000	1.1515	0.0666
Combined	NS_{strict}	Singleton	176	0.1623	0.5365	0.9492	1.0410	0.0368
Combined	NS_{strict}	Rare	227	0.8261	0.9989	1.0000	1.0228	0.0250
Combined	NS_{broad}	Singleton	765	0.1455	0.5003	0.9228	1.0206	0.0168
Combined	NS_{broad}	Rare	1084	0.1972	0.6431	0.9733	0.9995	0.0096

[a]Schizophrenia (SCZ); bipolar disorder (BD); recurrent major depressive disorder (rMDD); Combined Cases (Combined).
[b]Non-synonymous strictly damaging mutations (NS_{strict}); Non-synonymous broadly damaging mutations (NS_{broad}).
Bold, $P<0.05$. The odds ratio (OR) and standard error (SE).

Supplementary Table S10. Gene Set Exact Poisson Tests of Rare Functional Variants in the DISC1 Regulome for Case-Control Traits

Trait[a]	Mutation Class[b]	MAFbin	Unadjusted *P*	$FWER_{within}$ *P*	$FWER_{cross}$ *P*	Case/Control Ratio	Control Rate	Case Rate
SCZ	Disruptive	Singleton	**9.00E-04**	**0.0185**	0.0965	4.1280	0.0092	0.0379
SCZ	Disruptive	Rare	**1.68E-06**	**1.00E-04**	**0.0022**	3.4675	0.0287	0.0995
SCZ	NS_{strict}	Singleton	**0.0136**	0.1249	0.5022	1.5428	0.1137	0.1754
SCZ	NS_{strict}	Rare	**0.0013**	**0.0304**	0.1434	1.4624	0.2560	0.3744
SCZ	NS_{broad}	Singleton	0.1631	0.6385	0.9892	1.1359	0.5132	0.5829
SCZ	NS_{broad}	Rare	0.4477	0.9501	1.0000	1.0408	1.6119	1.6777
rMDD	Disruptive	Singleton	0.2044	0.6908	0.9972	1.9327	0.0092	0.0178
rMDD	Disruptive	Rare	0.8195	0.9996	1.0000	1.0308	0.0287	0.0296
rMDD	NS_{strict}	Singleton	0.3605	0.9047	1.0000	1.1974	0.1137	0.1361
rMDD	NS_{strict}	Rare	0.2873	0.8662	0.9997	1.1556	0.2560	0.2959
rMDD	NS_{broad}	Singleton	0.7882	0.9995	1.0000	1.0262	0.5132	0.5266
rMDD	NS_{broad}	Rare	0.2496	0.8163	0.9990	0.9287	1.6119	1.4970
BD	Disruptive	Singleton	0.2670	0.8207	0.9993	1.6750	0.0092	0.0154
BD	Disruptive	Rare	0.3936	0.9287	1.0000	0.5360	0.0287	0.0154
BD	NS_{strict}	Singleton	0.3374	0.9000	0.9998	0.7670	0.1137	0.0872
BD	NS_{strict}	Rare	**0.0087**	0.0910	0.4004	0.6410	0.2560	0.1641
BD	NS_{broad}	Singleton	0.5483	0.9842	1.0000	1.0592	0.5132	0.5436
BD	NS_{broad}	Rare	0.5165	0.9826	1.0000	0.9608	1.6119	1.5487
Combined	Disruptive	Singleton	**0.0012**	0.0616	0.1211	2.6509	0.0092	0.0243
Combined	Disruptive	Rare	**0.0043**	0.1328	0.2593	1.7571	0.0287	0.0504
Combined	NS_{strict}	Singleton	0.1543	0.7456	0.9860	1.1782	0.1137	0.1339
Combined	NS_{strict}	Rare	0.2485	0.8941	0.9990	1.0936	0.2560	0.2800
Combined	NS_{broad}	Singleton	0.1806	0.8043	0.9921	1.0776	0.5132	0.5530
Combined	NS_{broad}	Rare	0.5765	0.9954	1.0000	0.9807	1.6119	1.5809

[a]Schizophrenia (SCZ); bipolar disorder (BD); recurrent major depressive disorder (rMDD); Combined Cases (Combined).
[b]Non-synonymous strictly damaging mutations (NS_{strict}); Non-synonymous broadly damaging mutations (NS_{broad}).
Bold, *P*<0.05; Case/Control Ratio is calculated using Case Rate divided by Control Rate.

Supplementary Table S11. Gene-Wide Burden Analysis of Rare Functional Variants in DISC1 Regulome for Case-Control Traits

See: “S11.CaseControlGeneRegulome” sheet in supplementary tables.xlsx

[a]Schizophrenia (SCZ); bipolar disorder (BD); recurrent major depressive disorder (rMDD); Combined Cases (Combined).
[b]Non-synonymous strictly damaging mutations (NS_{strict}); Non-synonymous broadly damaging mutations (NS_{broad}).
Bold, $P<0.05$. Tests are sorted in ascending order of the unadjusted *P*-value. The odds ratio (OR) and standard error (SE).

Supplementary Table S12. Translin-Associated Factor X Interacting Protein 1 (*TSNAXIP1*) Rare Mutations

Mutation[a]	Exon[a]	Chr	Pos (hg18)	Ref base	Alt base	dbSNP144	1000G-Eur Frequency	Case MAF	Control MAF	SCZ[b]	rMDD[b]	BD[b]	Control[b]
R46X*	exon2	16	66405794	C	T	rs146214814	0.0030	0.0054	0.0041	0/6/200	0/0/163	0/0/189	0/7/854
S60Y*	exon3	16	66412274	C	A	NA	NA	0.0009	0.0000	0/0/200	0/1/156	0/0/180	0/0/843
R75Q	exon3	16	66412319	G	A	rs761157513	NA	0.0000	0.0006	0/0/194	0/0/157	0/0/177	0/1/837
R95C	exon4	16	66412525	C	T	rs747610440	NA	0.0010	0.0000	0/1/181	0/0/148	0/0/157	0/0/814
D246G	exon7	16	66416599	A	G	rs74684664	0.0050	0.0035	0.0052	0/1/210	0/2/166	0/1/191	0/9/862
L349P	exon9	16	66417382	T	C	rs150340970	NA	0.0000	0.0006	0/0/205	0/0/158	0/0/179	0/1/860
R374W	exon9	16	66417456	C	T	rs61999337	0.0010	0.0009	0.0000	0/1/198	0/0/156	0/0/181	0/0/846
Q402L*	exon10	16	66417616	A	T	rs201147559	0.0010	0.0010	0.0000	0/0/178	0/1/140	0/0/163	0/0/812
P432L*	exon11	16	66417860	C	T	rs763142409	NA	0.0009	0.0000	0/1/209	0/0/164	0/0/190	0/0/868
R436W*	exon11	16	66417871	C	T	rs758788310	NA	0.0018	0.0000	0/2/207	0/0/165	0/0/189	0/0/869
R519Q	exon13	16	66418368	G	A	rs140006528	NA	0.0036	0.0006	0/1/205	0/1/163	0/2/181	0/1/867
P605S	exon15	16	66418898	C	T	rs146474803	NA	0.0000	0.0012	0/0/210	0/0/166	0/0/192	0/2/865
Splice*	exon16	16	66419156	G	C	NA	NA	0.0009	0.0000	0/0/210	0/1/163	0/0/189	0/0/868
G645D	exon16	16	66419192	G	A	rs190858166	NA	0.0009	0.0000	0/0/211	0/1/164	0/0/192	0/0/870
S671L	exon16	16	66419270	C	T	rs763671210	NA	0.0009	0.0000	0/1/209	0/0/166	0/0/189	0/0/871
R694W	exon16	16	66419338	C	T	rs140308084	NA	0.0000	0.0006	0/0/210	0/0/166	0/0/189	0/1/869
R702C*	exon16	16	66419362	C	T	rs150288850	NA	0.0009	0.0000	0/0/211	0/1/166	0/0/190	0/0/871

*Non-synonymous strict damaging mutations (NS_{strict}): disruptive plus missense variants predicted as damaging by all five algorithms (PolyPhen2 HumDiv and HumVar, SIFT, LRT and MutationTaster)
[a]Variant annotation is based on NM_001288990.
[b]Genotype counts are shown for Schizophrenia (SCZ), bipolar disorder (BD), recurrent major depressive disorder (rMDD) cases and the Lothian Birth Cohort of 1936 controls (CTL).

Supplementary Table S13. Gene Set Burden Analysis of Rare Functional Variants in the DISC1 Interactome for Quantitative Traits

Trait[a]	Mutation Class[b]	MAFbin	N.SNP.Test	Unadjusted *P*	$FWER_{within}$ *P*	$FWER_{cross}$ *P*	Beta	SE
Cognitive Measures								
MHT11	Disruptive	Singleton	10	**9.35E-05**	**0.0005**	**0.0043**	-7.1141	3.6863
MHT11	Disruptive	Rare	18	0.0541	0.2367	0.8785	-2.9891	2.2262
MHT11	NS_{strict}	Singleton	76	**0.0003**	**0.0017**	**0.0122**	-2.7865	1.2877
MHT11	NS_{strict}	Rare	126	**0.0326**	0.1564	0.7266	-0.9314	0.7755
MHT11	NS_{broad}	Singleton	344	**0.0447**	0.2043	0.8296	-0.8037	0.5970
MHT11	NS_{broad}	Rare	595	0.5013	0.9187	1.0000	0.0223	0.3087
MHT70	Disruptive	Singleton	9	**0.0056**	**0.0294**	0.2209	-6.6785	2.7886
MHT70	Disruptive	Rare	17	0.3384	0.7995	0.9999	-1.5651	1.6838
MHT70	NS_{strict}	Singleton	77	**0.0287**	0.1354	0.6835	-2.3177	0.9725
MHT70	NS_{strict}	Rare	128	0.0994	0.3882	0.9728	-0.9408	0.5864
MHT70	NS_{broad}	Singleton	354	0.3898	0.8460	0.9999	-0.4608	0.4516
MHT70	NS_{broad}	Rare	610	0.6196	0.9665	1.0000	0.2453	0.2334
MHT70-11	Disruptive	Singleton	9	0.5837	0.9563	1.0000	-1.7825	1.8772
MHT70-11	Disruptive	Rare	17	0.9126	0.9997	1.0000	0.1731	1.1339
MHT70-11	NS_{strict}	Singleton	75	0.4291	0.8770	1.0000	-0.7946	0.6551
MHT70-11	NS_{strict}	Rare	125	0.9219	0.9997	1.0000	-0.1955	0.3950
MHT70-11	NS_{broad}	Singleton	340	0.3724	0.8309	1.0000	0.0603	0.3041
MHT70-11	NS_{broad}	Rare	591	0.9444	0.9998	1.0000	0.3243	0.1573
NART	Disruptive	Singleton	10	**0.0051**	**0.0289**	0.2012	-6.9970	2.6307
NART	Disruptive	Rare	18	0.2523	0.6872	0.9998	-2.3257	1.5884
NART	NS_{strict}	Singleton	78	0.0874	0.3417	0.9606	-2.2643	0.9175
NART	NS_{strict}	Rare	129	0.4730	0.9036	1.0000	-0.9683	0.5532
NART	NS_{broad}	Singleton	356	0.5297	0.9318	1.0000	-0.1771	0.4260
NART	NS_{broad}	Rare	612	0.5258	0.9291	1.0000	-0.0910	0.2202

Gf	Disruptive	Singleton	10	**0.0293**	0.1378	0.6911	-0.5152	0.3097
Gf	Disruptive	Rare	18	0.3673	0.8262	0.9999	-0.1573	0.1870
Gf	NS_{strict}	Singleton	75	0.1554	0.5186	0.9966	-0.1703	0.1080
Gf	NS_{strict}	Rare	126	0.1551	0.5184	0.9965	-0.1002	0.0651
Gf	NS_{broad}	Singleton	350	0.4616	0.8995	1.0000	-0.0449	0.0502
Gf	NS_{broad}	Rare	605	0.1938	0.5891	0.9991	-0.0046	0.0259
Psychiatric Symptoms								
Neuroticism	Disruptive	Singleton	8	**0.0154**	0.0754	0.4765	6.5671	2.2564
Neuroticism	Disruptive	Rare	15	0.1581	0.5215	0.9969	1.7280	1.3624
Neuroticism	NS_{strict}	Singleton	68	0.1688	0.5429	0.9978	0.2127	0.7869
Neuroticism	NS_{strict}	Rare	117	0.2502	0.6863	0.9998	-0.2497	0.4745
Neuroticism	NS_{broad}	Singleton	320	0.3592	0.8204	0.9999	0.2554	0.3654
Neuroticism	NS_{broad}	Rare	569	0.4616	0.8978	1.0000	-0.3550	0.1889
Anxiety	Disruptive	Singleton	10	0.5153	0.9235	1.0000	2.0461	0.9927
Anxiety	Disruptive	Rare	18	0.6085	0.9614	1.0000	0.3739	0.5994
Anxiety	NS_{strict}	Singleton	78	0.3098	0.7584	0.9999	0.8798	0.3462
Anxiety	NS_{strict}	Rare	129	**0.0349**	0.1561	0.7500	0.1394	0.2087
Anxiety	NS_{broad}	Singleton	356	0.6432	0.9713	1.0000	0.2508	0.1607
Anxiety	NS_{broad}	Rare	612	0.2737	0.7060	0.9999	-0.0917	0.0831
Depression	Disruptive	Singleton	10	0.4476	0.8900	0.9999	0.4975	0.7151
Depression	Disruptive	Rare	18	0.1088	0.4023	0.9800	0.1265	0.4318
Depression	NS_{strict}	Singleton	77	0.2971	0.7513	0.9999	0.2985	0.2494
Depression	NS_{strict}	Rare	128	0.7048	0.9842	1.0000	0.1120	0.1504
Depression	NS_{broad}	Singleton	355	**0.0431**	0.1911	0.8167	0.2587	0.1158
Depression	NS_{broad}	Rare	611	0.7032	0.9840	1.0000	0.0492	0.0599

[a]Moray House Test at age 11 (MHT11); Moray House Test at age 70 (MHT70); Moray House Test at age 70 adjusted for the Moray House Test score at age 11 (MHT70-11); National Adult Reading Test (NART); General Fluid Intelligence (Gf); Hospital Anxiety Depression Scales - Depression (Depression); Hospital Anxiety Depression Scales - Anxiety (Anxiety); NEO Five-Factor Inventory Neuroticism (Neuroticism).

[b]Non-synonymous strictly damaging mutations (NS_{strict}); Non-synonymous broadly damaging mutations (NS_{broad}).

Bold, $P<0.05$. The effect size (Beta) and standard error (SE).

Supplementary Table S14. Gene-Wide Burden Analysis of Rare Functional Variants in the DISC1 Interactome for Quantitative Traits

See: "S14.QuantitativeGeneInteractome" sheet in supplementary tables.xlsx

[a]Moray House Test at age 11 (MHT11); Moray House Test at age 70 (MHT70); Moray House Test at age 70 adjusted for the Moray House Test score at age 11 (MHT70-11); National Adult Reading Test (NART); General Fluid Intelligence (Gf); Hospital Anxiety Depression Scales - Depression (Depression); Hospital Anxiety Depression Scales - Anxiety (Anxiety); NEO Five-Factor Inventory Neuroticism (Neuroticism).
[b]Non-synonymous strictly damaging mutations (NS_{strict}); Non-synonymous broadly damaging mutations (NS_{broad}).
Bold, *P*<0.05. Tests are sorted in ascending order of the unadjusted *P*-value. The effect size (Beta) and standard error (SE).

Supplementary Table S15. Gene Set Burden Analysis of Rare Functional Variants in the DISC1 Regulome for Quantitative Traits

Trait[a]	Mutation Class[b]	MAFbin	N.SNP.Test	Unadjusted *P*	$FWER_{within}$ *P*	$FWER_{cross}$ *P*	Beta	SE
Cognitive Measures								
MHT11	Disruptive	Singleton	8	0.9765	1.0000	1.0000	3.6344	4.1177
MHT11	Disruptive	Rare	14	0.9593	0.9999	1.0000	0.4846	2.3509
MHT11	NS_{strict}	Singleton	93	0.5367	0.9357	1.0000	-0.6650	1.1353
MHT11	NS_{strict}	Rare	141	0.4442	0.8861	1.0000	-0.8979	0.7527
MHT11	NS_{broad}	Singleton	428	0.4343	0.8794	1.0000	-0.6673	0.5190
MHT11	NS_{broad}	Rare	719	0.3258	0.7787	1.0000	-0.5767	0.2916
MHT70	Disruptive	Singleton	8	0.8481	0.9979	1.0000	5.3886	3.1132
MHT70	Disruptive	Rare	14	0.7998	0.9950	1.0000	2.4608	1.7762
MHT70	NS_{strict}	Singleton	99	**0.0014**	**0.0079**	0.0609	-1.7895	0.8596
MHT70	NS_{strict}	Rare	146	**0.0142**	0.0688	0.4392	-1.1343	0.5704
MHT70	NS_{broad}	Singleton	444	**0.0093**	**0.0451**	0.3160	-0.7885	0.3927
MHT70	NS_{broad}	Rare	736	0.1417	0.4727	0.9942	-0.4136	0.2205
MHT70-11	Disruptive	Singleton	8	0.8646	0.9977	1.0000	3.2670	2.0973
MHT70-11	Disruptive	Rare	14	0.2644	0.6969	0.9999	2.2696	1.1966
MHT70-11	NS_{strict}	Singleton	93	**0.0131**	0.0657	0.4143	-1.4338	0.5777
MHT70-11	NS_{strict}	Rare	140	0.3453	0.7940	1.0000	-0.5199	0.3834
MHT70-11	NS_{broad}	Singleton	425	**0.0014**	**0.0075**	0.0617	-0.3175	0.2644
MHT70-11	NS_{broad}	Rare	715	**0.0280**	0.1294	0.6687	-0.0010	0.1485
NART	Disruptive	Singleton	8	0.6397	0.9706	1.0000	3.6591	2.9369
NART	Disruptive	Rare	14	0.9836	1.0000	1.0000	1.1720	1.6756
NART	NS_{strict}	Singleton	99	0.2747	0.7099	1.0000	-0.6962	0.8109
NART	NS_{strict}	Rare	147	**0.0457**	0.1978	0.8297	-0.9724	0.5381
NART	NS_{broad}	Singleton	447	0.1256	0.4341	0.9892	-0.5452	0.3704
NART	NS_{broad}	Rare	740	0.3995	0.8455	1.0000	-0.4607	0.2080

Gf	Disruptive	Singleton	8	0.4882	0.9138	1.0000	0.2448	0.3458
Gf	Disruptive	Rare	14	0.4246	0.8753	1.0000	0.0172	0.1973
Gf	NS_{strict}	Singleton	95	0.3744	0.8327	1.0000	-0.0947	0.0955
Gf	NS_{strict}	Rare	143	0.2384	0.6650	0.9999	-0.0957	0.0634
Gf	NS_{broad}	Singleton	440	0.1647	0.5327	0.9976	-0.0385	0.0436
Gf	NS_{broad}	Rare	732	0.3885	0.8469	1.0000	-0.0119	0.0245
Psychiatric Symptoms								
Neuroticism	Disruptive	Singleton	7	0.2730	0.7135	1.0000	-2.6295	2.5190
Neuroticism	Disruptive	Rare	13	0.3603	0.8151	1.0000	-0.2165	1.4372
Neuroticism	NS_{strict}	Singleton	91	0.8691	0.9993	1.0000	0.3354	0.6955
Neuroticism	NS_{strict}	Rare	136	0.8089	0.9952	1.0000	0.1261	0.4616
Neuroticism	NS_{broad}	Singleton	400	0.8478	0.9982	1.0000	-0.4638	0.3177
Neuroticism	NS_{broad}	Rare	682	0.8925	0.9997	1.0000	-0.2167	0.1784
Anxiety	Disruptive	Singleton	8	0.4673	0.9006	1.0000	-2.2912	1.1082
Anxiety	Disruptive	Rare	14	0.7084	0.9844	1.0000	-0.4895	0.6323
Anxiety	NS_{strict}	Singleton	99	0.6367	0.9711	1.0000	0.3305	0.3060
Anxiety	NS_{strict}	Rare	147	0.9529	1.0000	1.0000	0.1551	0.2031
Anxiety	NS_{broad}	Singleton	447	0.5648	0.9486	1.0000	0.0332	0.1398
Anxiety	NS_{broad}	Rare	740	0.6768	0.9809	1.0000	-0.0890	0.0785
Depression	Disruptive	Singleton	8	0.9594	1.0000	1.0000	-0.3317	0.7984
Depression	Disruptive	Rare	14	0.9879	1.0000	1.0000	-0.1067	0.4555
Depression	NS_{strict}	Singleton	98	0.6834	0.9812	1.0000	0.3950	0.2204
Depression	NS_{strict}	Rare	146	0.6177	0.9663	1.0000	0.2661	0.1463
Depression	NS_{broad}	Singleton	446	0.9579	0.9999	1.0000	-0.0391	0.1007
Depression	NS_{broad}	Rare	738	0.9988	1.0000	1.0000	-0.0760	0.0565

[a]Moray House Test at age 11 (MHT11); Moray House Test at age 70 (MHT70); Moray House Test at age 70 adjusted for the Moray House Test score at age 11 (MHT70-11); National Adult Reading Test (NART); General Fluid Intelligence (Gf); Hospital Anxiety Depression Scales - Depression (Depression); Hospital Anxiety Depression Scales - Anxiety (Anxiety); NEO Five-Factor Inventory Neuroticism (Neuroticism).

[b]Non-synonymous strictly damaging mutations (NS_{strict}); Non-synonymous broadly damaging mutations (NS_{broad}).

Bold, $P<0.05$. Tests are sorted in ascending order of the unadjusted *P*-value. The effect size (Beta) and standard error (SE).

Supplementary Table S16. Gene-Wide Burden Analysis of Rare Functional Variants in the DISC1 Regulome for Quantitative Traits

See: “S16.QuantitativeGeneRegulome” sheet in supplementary tables.xlsx

[a]Moray House Test at age 11 (MHT11); Moray House Test at age 70 (MHT70); Moray House Test at age 70 adjusted for the Moray House Test score at age 11 (MHT70-11); National Adult Reading Test (NART); General Fluid Intelligence (Gf); Hospital Anxiety Depression Scales - Depression (Depression); Hospital Anxiety Depression Scales - Anxiety (Anxiety); NEO Five-Factor Inventory Neuroticism (Neuroticism).
[b]Non-synonymous strictly damaging mutations (NS_{strict}); Non-synonymous broadly damaging mutations (NS_{broad}).
Bold, $P<0.05$. Tests are sorted in ascending order of the unadjusted *P*-value. The effect size (Beta) and standard error (SE).

Supplementary Table S17. Gene Ontology Enrichment Analyses of the DISC1 Interactome

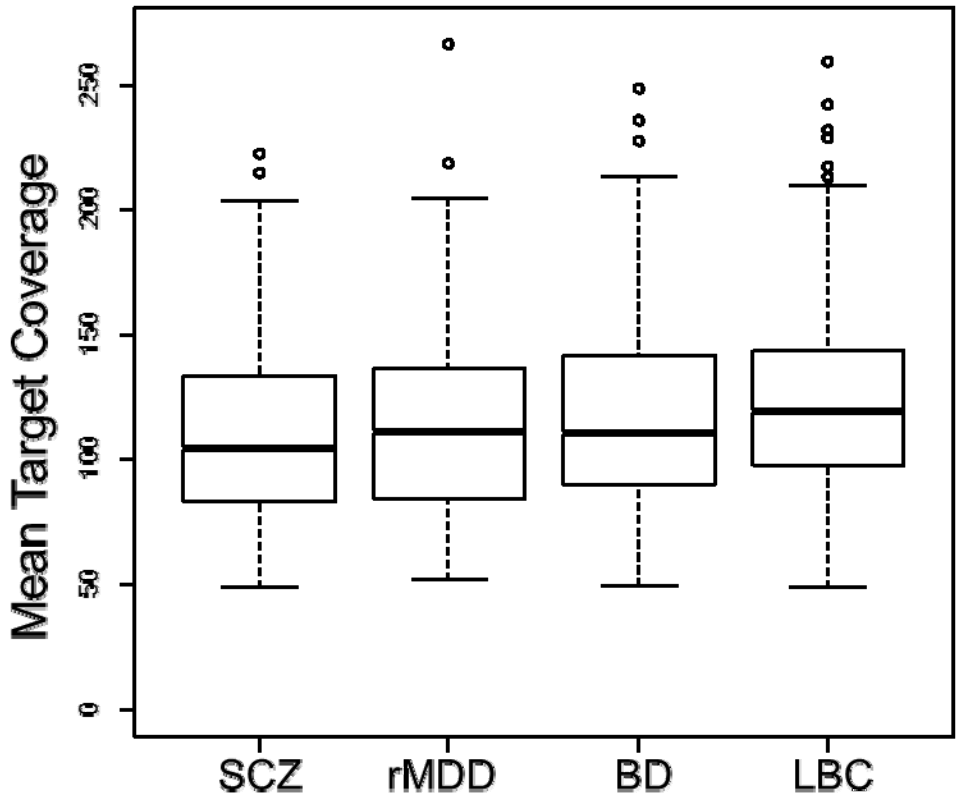
See: “S17.GeneOntologyInteractome” sheet in supplementary tables.xlsx

Supplementary Table S18. Gene Ontology Enrichment Analyses of the DISC1 Regulome

See: “S18.GeneOntologyRegulome” sheet in supplementary tables.xlsx

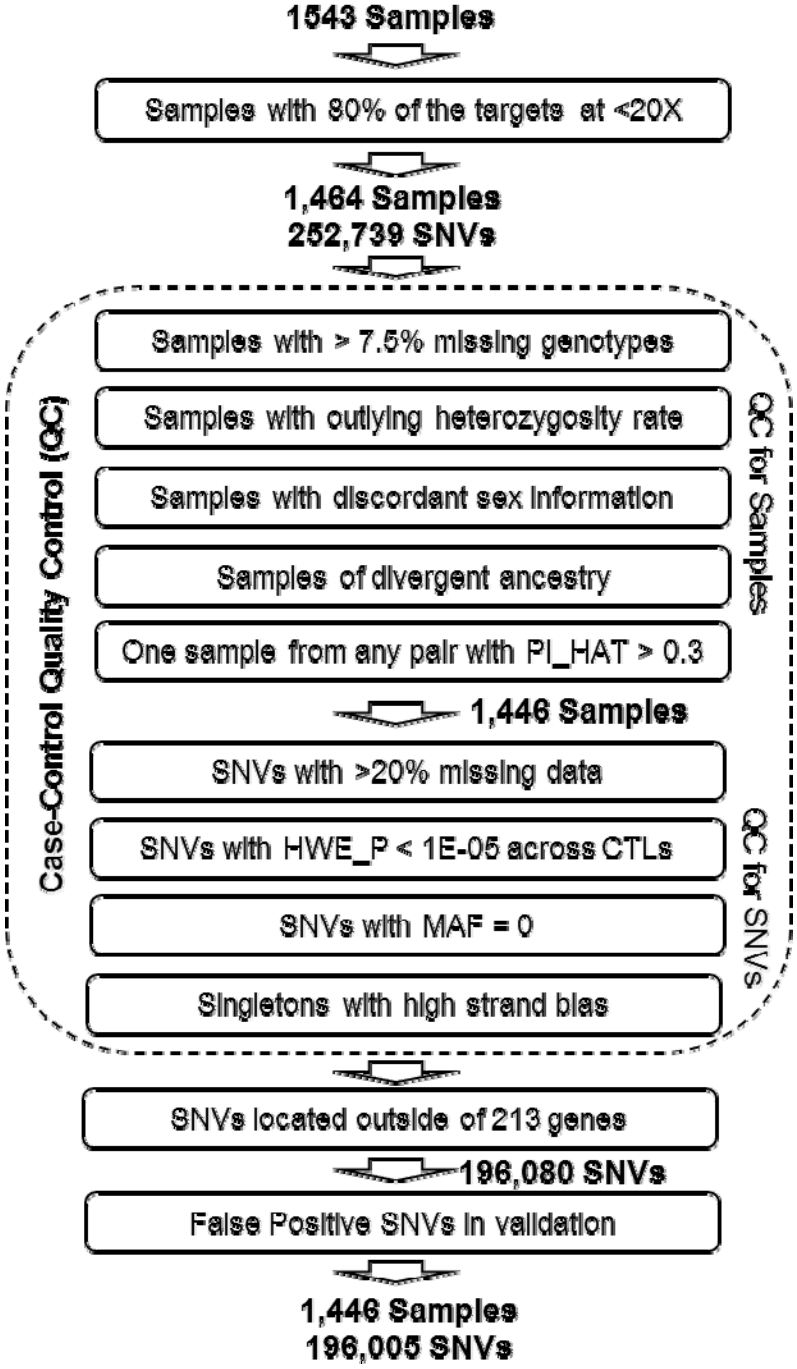
Supplementary Figures

Supplementary Figure S1: Distribution of Coverage in Samples



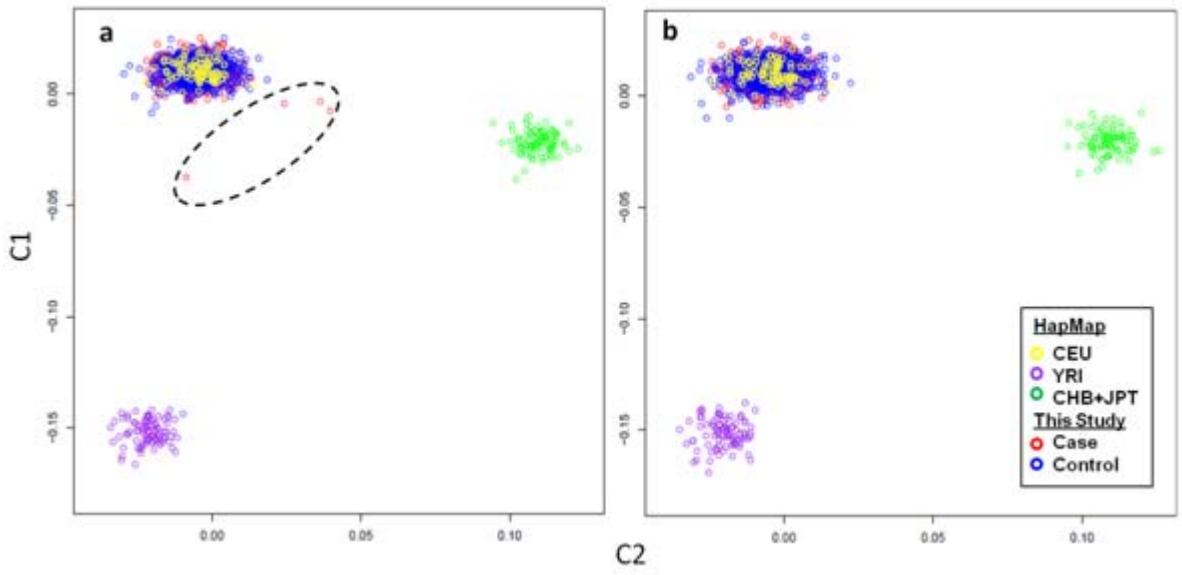
The distribution of the mean target coverage for samples with 80% of the targets at ≥20x depth in schizophrenia (SCZ), recurrent major depressive disorder (rMDD), bipolar disorder (BD) and the Lothian Birth Cohort of 1936 (LBC1936). No evidence of sequencing bias was observed between cases (SCZ, BD and rMDD) and controls (LBC1936).

Supplementary Figure S2: A Flowchart of Quality Control



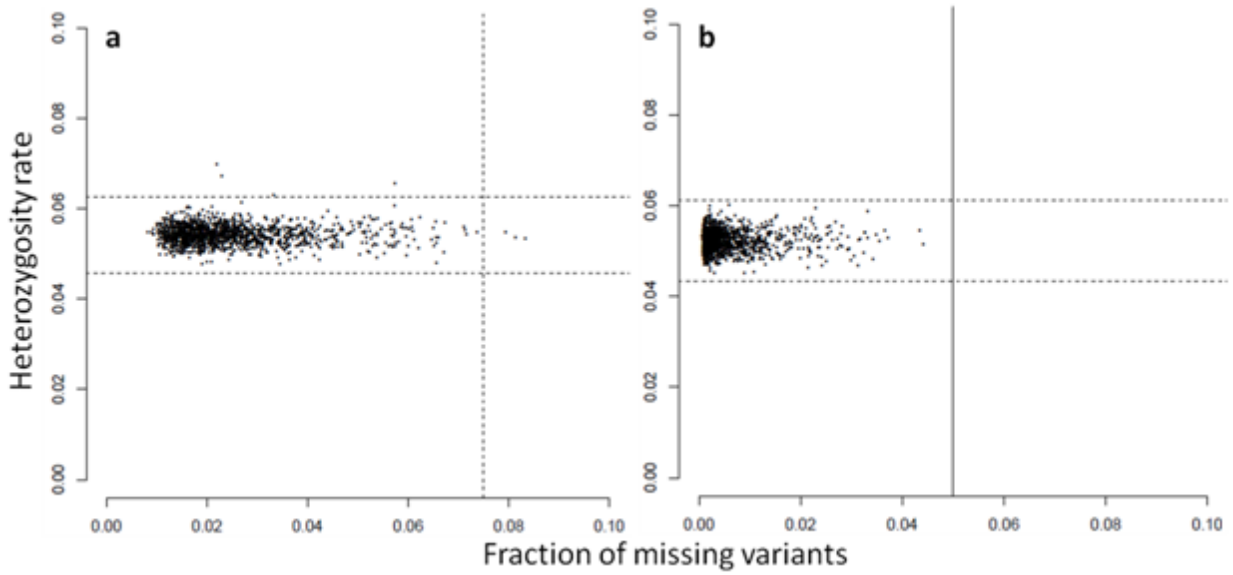
Flowchart depicting the filtering strategy involved in removal of outlying samples and single nucleotide variants (SNVs) that introduce bias (rounded rectangles).

Supplementary Figure S3: Multidimensional Scaling Plots



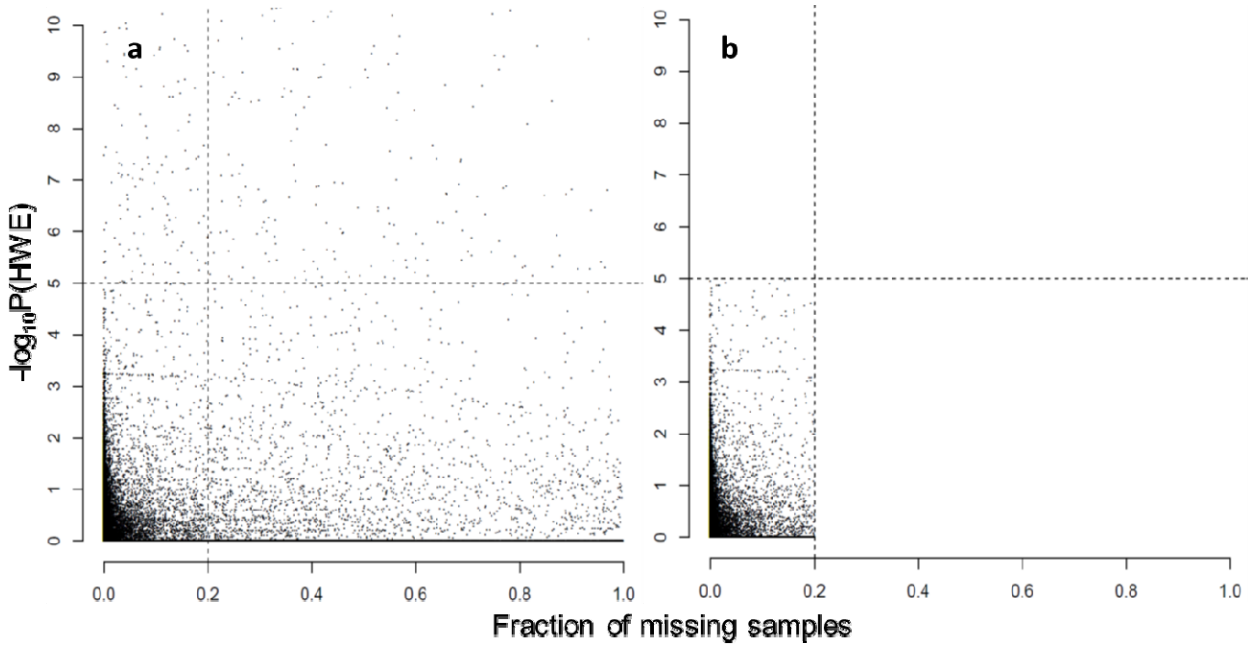
Multidimensional scaling (MDS) plots for the samples in the (a) raw dataset and (b) final dataset. The four samples (within dashed circle) which clustered away from the HapMap European population (CEU, yellow) were removed from further analysis.

Supplementary Figure S4: Missing Variant Rate versus Heterozygosity Rate across all Samples



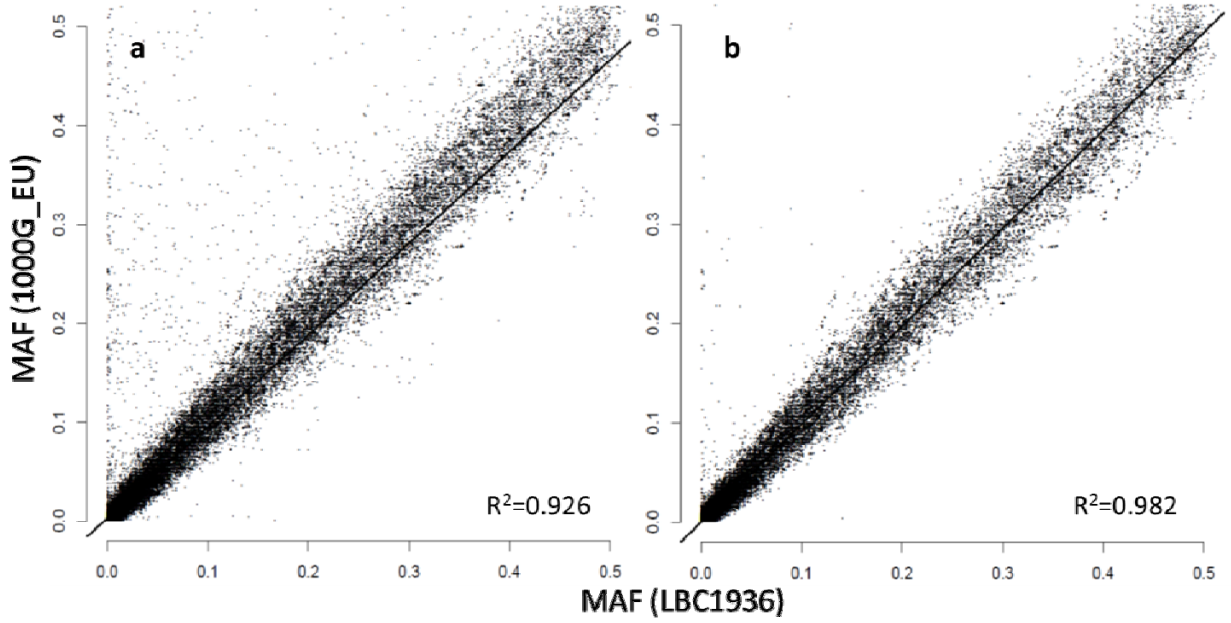
Missing variant rate versus heterozygosity rate across all samples in the (a) raw dataset and b) final dataset. The samples with a missing variant rate>0.75 (vertical dashed line) and/or a heterozygosity rate ± 4 standard deviation from the mean (horizontal dashed lines) were excluded from further analysis. These samples usually have low DNA quality or concentration.[28]

Supplementary Figure S5: Missing Sample Rate versus Hardy-Weinberg equilibrium *P*-values across all SNVs



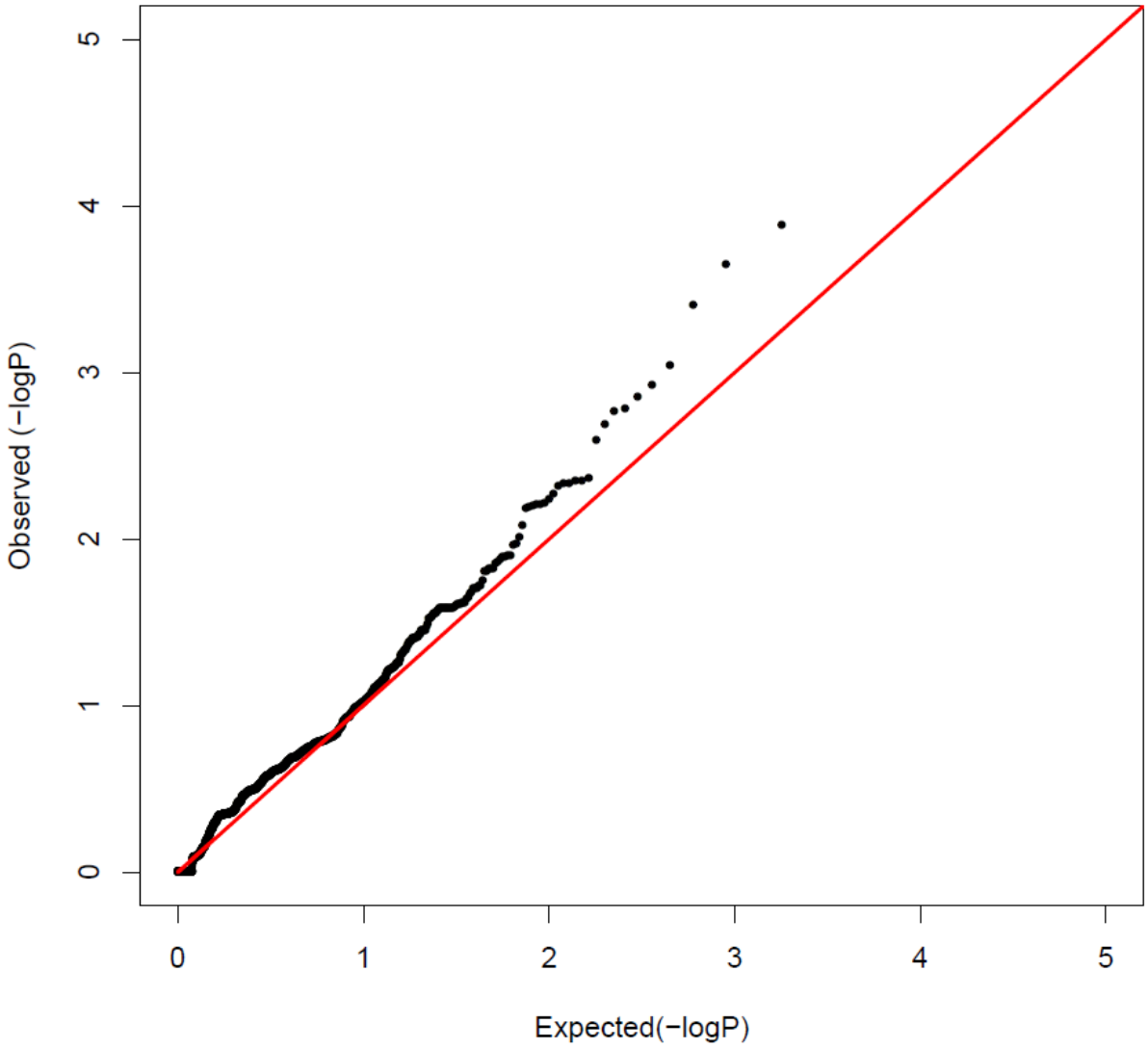
Missing sample rate versus Hardy-Weinberg equilibrium (HWE) *P*-values across all SNVs in the (a) raw dataset and (b) final dataset. The SNVs with a missing sample rate>0.2 (vertical dashed line) and/or Hardy-Weinberg equilibrium *P*-values<0.00001 (horizontal dashed lines) in controls were excluded from further analysis. These variants represent false positives and genotyping errors.[28]

Supplementary Figure S6: Minor Allele Frequencies in the 1000 Genomes Project and LBC1936 controls

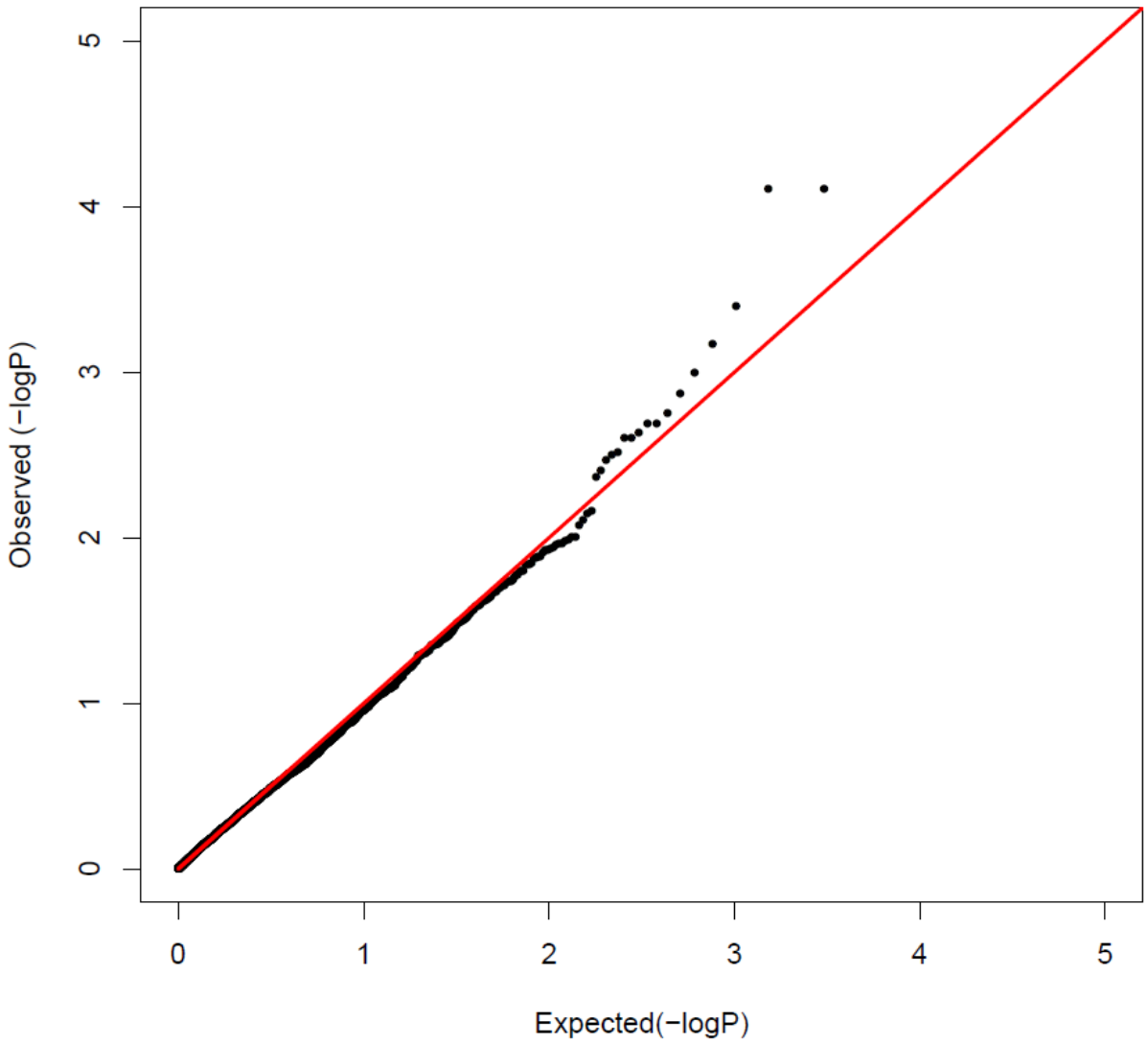


Minor allele frequencies (MAFs) in the 1000 Genomes Project (2015 Aug annotations) and LBC1936 controls in the (a) raw dataset and (b) final dataset. The variant MAFs identified in the European subset of the 1000 Genomes Project (1000G_EU) versus healthy controls (LBC1936) data set are more correlated after applying quality control filters (R^2=0.982).

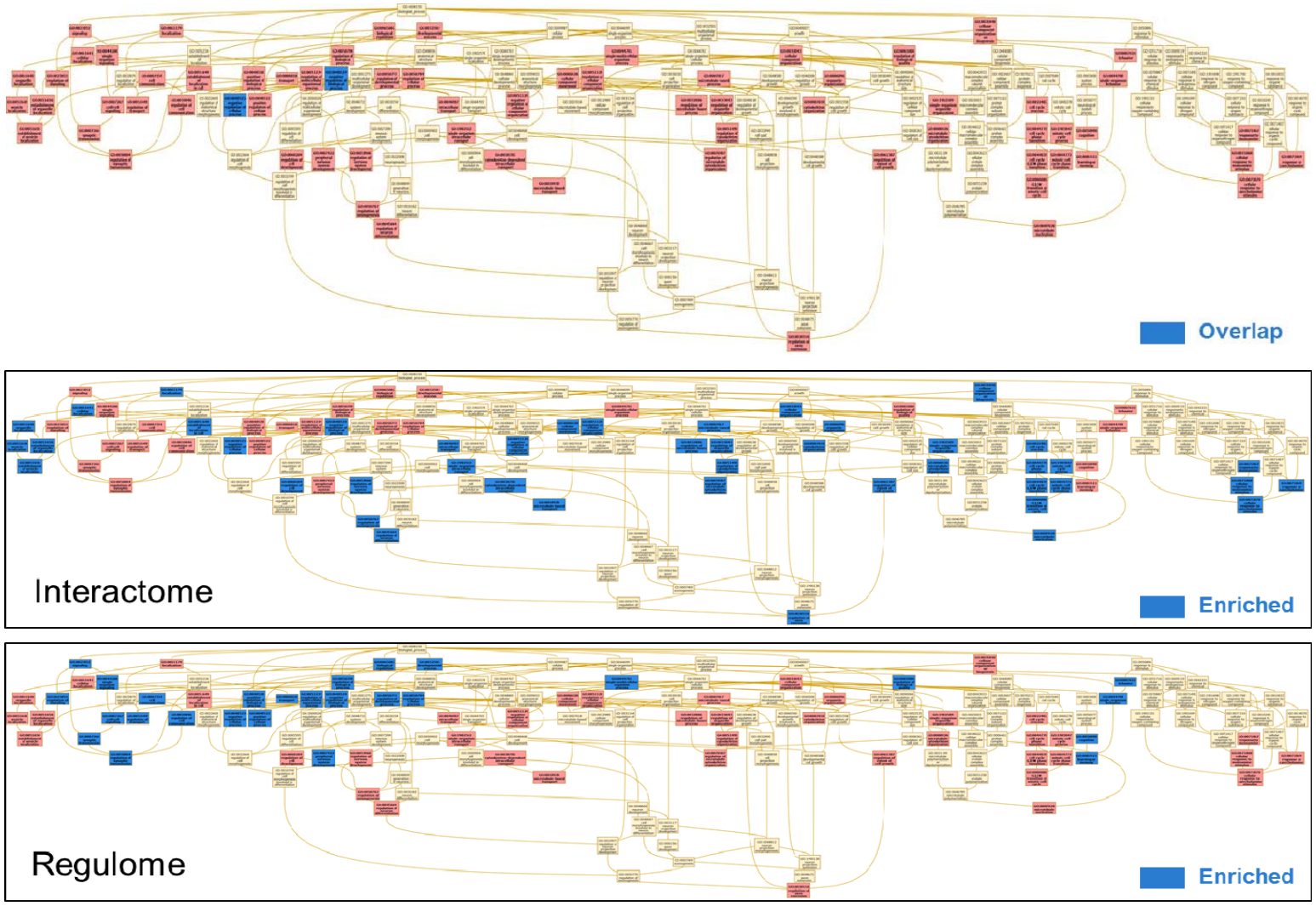
Supplementary Figure S7: Quantile-Quantile Plots of Gene-wide Burden Analysis of Rare Damaging Mutations for Case-Control Traits



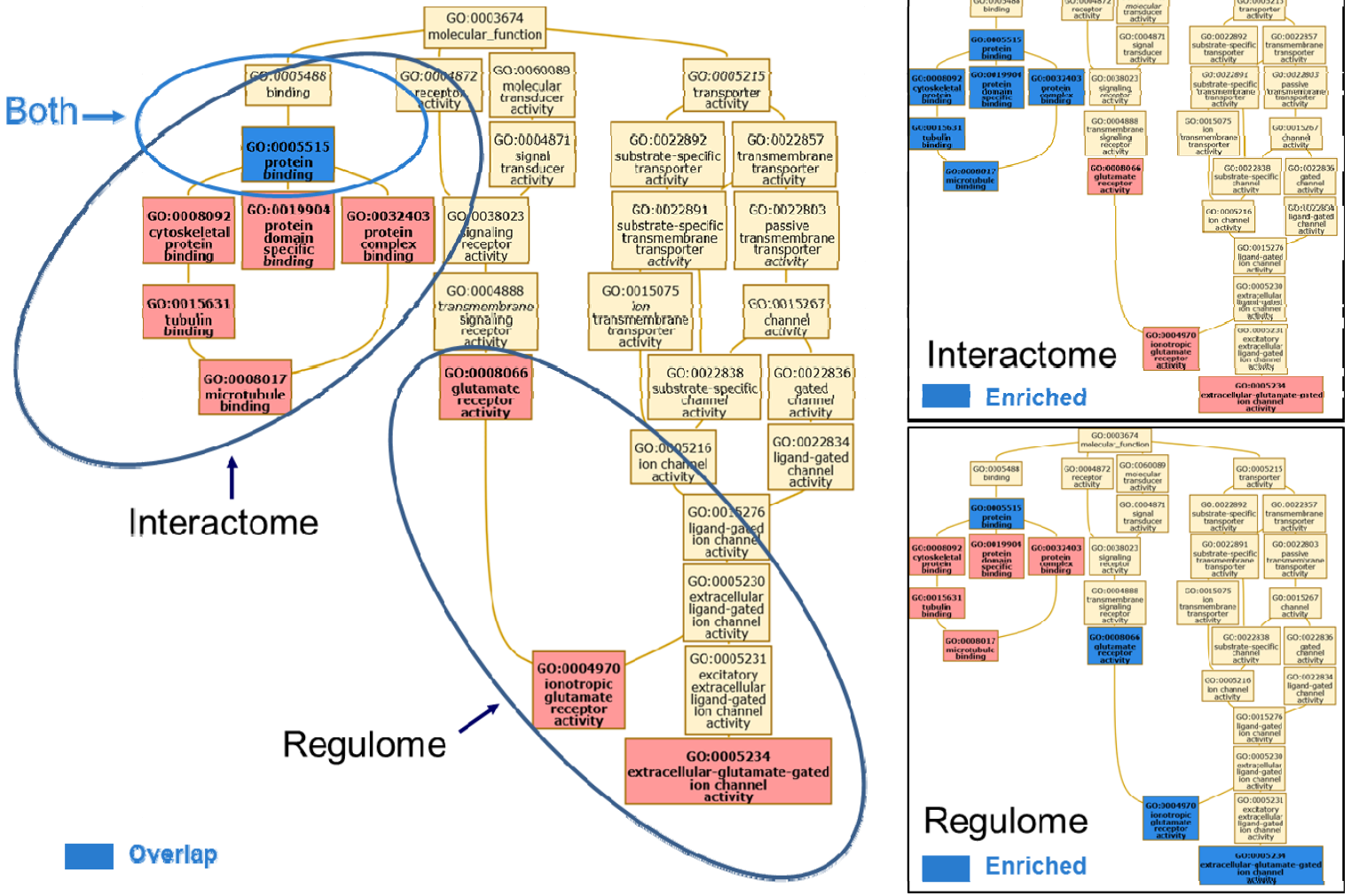
Supplementary Figure S8: Quantile-Quantile Plots of Gene-wide Burden Analysis of Rare Damaging Mutations for Quantitative Traits



Supplementary Figure S9: Gene Ontology Enrichment Analyses for Biological Process



Supplementary Figure S10: Gene Ontology Enrichment Analyses for Molecular Function



Supplementary Figure S11: Gene Ontology Enrichment Analyses for Cellular Component