

Supplementary Tables

Table S1. A detailed feature description. This table includes all features used in our model. These features are grouped into three levels: gene, functional/genomic segment and sequence. A brief description along with references is described on each feature.

Feature category	Feature set	Description	Feature type	References
Gene level (N = 61)	Cell essential and nonessential genes	CRISPR/Cas9 screens identified essential genes in human cell lines. Curated in ²	discrete	1
	ClinGen curated genes and genomic regions	Genes and genomics regions were rated from 0 to 3, indicating an increased evidence on dosage sensitivity. Additional two levels (40,30) suggest unlikely dosage sensitive and genes associated with autosomal recessive phenotype.	discrete	3
	DDG2P database	A curated list of genes linked to developmental disorders compiled by clinicians as part of the DDD study to facilitate clinical feedback on likely causal variants	discrete	4
	Dosage sensitive genes	Predicted score on dosage sensitive genes (i.e., haploinsufficiency or triplosensitivity)	discrete	5, 34
	FDA proved drug target	Genes with protein products that are mechanistic targets of FDA-approved drugs. Curated in ²	discrete	6
	G protein-coupled receptor	GPCR list curated in ²	discrete	32, 33, 35
	Mouse heterozygous LoF lethal	Genes that are lethal in mouse models when inactivated heterozygous. Curated by ²	discrete	7
	Neurodevelopmental process related genes	Genes associated with various phenotypes from HPO: Abnormality of the nervous system (HP:0000707)-associated genes Abnormality of nervous system physiology (HP:0012638)-associated	discrete	8

		<p>genes</p> <p>Behavioral abnormality (HP:0000708)-associated genes</p> <p>Abnormality of nervous system morphology (HP:0012639)-associated genes</p> <p>Abnormality of the immune system (HP:0002715)-associated genes</p> <p>Neurodevelopmental abnormality (HP:0012759)-associated genes</p> <p>Autoimmunity (HP:0002960)-associated genes</p> <p>Morphological abnormality of the central nervous system (HP:0002011)-associated genes</p> <p>Schizophrenia (HP:0100753)-associated genes</p> <p>Autistic behavior (HP:0000729)-associated genes</p> <p>Abnormality of movement (HP:0100022)-associated genes</p> <p>Seizures (HP:0001250)-associated genes</p> <p>Autism (HP:0000717)-associated genes</p> <p>Hyperactivity (HP:0000752)-associated genes</p> <p>Abnormality of prenatal development or birth (HP:0001197)-associated genes</p> <p>Impairment in personality functioning (HP:0031466)-associated genes</p> <p>Abnormality of the digestive system (HP:0025031)-associated genes</p> <p>Growth abnormality (HP:0001507)-associated genes</p> <p>Abnormal fear/anxiety-related behavior (HP:0100852)-associated genes</p> <p>Abnormality of brain morphology (HP:0012443)-associated genes</p> <p>Abnormality of higher mental function (HP:0011446)-associated genes</p>		
	Olfactory receptors	Any HUGO-recognized family of olfactory receptor genes	discrete	⁹
	SFARI gene	Genes implicated in autism susceptibility	discrete	¹⁰

Functional/genomic segment level (N = 121)	Chromatin states	Brain related chromatin states inferred by the extended 18-way ChromHMM model across 98 tissues from the Roadmap Epigenomics Project	discrete	11
	CTCF binding sites	Genome wide observed CTCF binding sites from Brain	continuous	12
		Genome wide CTCF binding sites from 7 cell lines generated by ChIP-seq. Curated by UCSC	continuous	13
	DNA Accessibility	ATAC-seq from brain and neurosph.	continuous	13
	DNase hypersensitive sites	Observed DNase I hypersensitive areas from brain and neurosph.	continuous	13
		DNase hypersensitive sites assayed from a collection of cell types. Download from UCSC table browser NAR 2004	continuous	14
		RoadmapDNasePromCount	discrete	15
	Enhancers	Brain cell type-specific enhancers identified by PLAC-seq	discrete	16
		dbSUPER: Super enhancers from Brain Angular Gyrus; Brain Anterior Caudate; Brain Cingulate Gyrus; Brain Hippocampus Middle; Brain Inferior Temporal Lobe	discrete	17
		EpiMap: enhancers from the brain and neurosph.	discrete	12
		EnhancerAtlas 2.0: Enhancer predictions in 197 human cell lines & tissues	discrete	18
		FANTOM Enhancers: Enhancer predictions for human tissues and cell types from the FANTOM5 consortium	discrete	19
		HACER: Active enhancer predictions in human cell lines & tissues based on PRO-seq, GRO-seq, or CAGE data	discrete	20
PsychENCODE: PEC EnhancersDER-03a_hg19_PEC_enhancers_clean.bed		discrete	21	
SEA: Super enhancer predictions from 143 human cell lines and tissues (mapped back to hg19 using liftOver with minimum 75% match)		discrete	23	

		Sedb: Super enhancer and typical enhancer predictions from 541 human cell lines and tissues	discrete	22
		VISTA: Experimentally-validated mammalian enhancers	discrete	24
	Genomic segmentations	All autosomal, protein-coding genes; CDS; exon; Selenocysteine; start_codon; stop_codon; transcript UTR	discrete	25
	Histone markers	H2AFZ, H2AK5ac, H2AK9ac, H2BK120ac, H2BK12ac, H2BK15ac, H2BK20ac, H2BK5ac, H3F3A, H3K27ac, H3K4ac, H3K4me1, H3K4me2, H3K4me3, H3K9ac, H3K9me1, H3K9me2, H3K9me3 from the brain or neurosph	continuous	12
		H3K27ac peaks for the Prefrontal Cortex, the Temporal Cortex, and the Cerebellar Cortex	continuous	21
	Long range probable genes	Target genes by prediction on GWAS hits and 3D chromatin structures	discrete	26
	Loop anchors and topological associated domains in higher-order chromatin structure	TAD boundaries (defined as the start and end coordinates for each TAD \pm 5kb) from 30 samples meeting our ENCODE data inclusion criteria available for download from the ENCODE Data Portal	continuous	14
		Selected "derived" datasets from PsychENCODE Integrated Analysis Package, including cortex enhancers, transcriptionally active regions, TAD boundaries, and H3k27ac peaks	continuous	21
		Yue labs	continuous	27
	Methylation	MeDIP/MRE (mCRF) methylation calls	continuous	15
	Transcript active regions	Cortex Transcriptionally Active Regions are found within at least 70% of the individuals	continuous	21
	Transcript factor binding sites	SNP-SELEX	discrete	28
	Transcript starting sites	The 2000bp flanking regions about transcript starting sites	discrete	36

Sequence level (N = 7)	Blacklisted regions	Genome regions have anomalous, unstructured, high signal/read counts (DacMapExclude), problematic regions for short sequence tag signal detection (DukeMapExclude)	discrete	²⁹
	Cross species conservation score	The conservation scoring (phylop46way, phastcon46way) for multiple alignments of 45 vertebrate genomes to the human genome	continuous	²⁹
	GC content	GC content calculated with a "span" size of 5 bases	continuous	²⁹
	Heterochromatin positions	It is calculated based on H3K9me3 enrichment regions	discrete	³⁰
	Human accelerated regions	Human accelerated regions are conserved genomic loci with elevated divergence in humans	discrete	³¹

Table S2. Individual feature comparisons. This table compares all of the features used in the copy number loss and copy number gain models. The comparisons were made using the two-tailed Wilcoxon rank-sum test, with a significant cut off of $P = 0.05$. All the feature names were reformatted as followed: feature type (Fun_level/Gen_level/Seq_level)_feature names(original sources)_tissue type (if applicable). Fun: Function; Gen: Gene; Seq: Sequence.

Source	Features in copy number loss model	P value	Source	Features in copy number gain model	P value
Functional/ genomic segment level	<i>Fun_level_significant features are 80 out of 120</i>		Functional/ genomic segment level	<i>Fun_level_significant features are 75 out of 120</i>	
Chromatin states from Roadmap Epigenomic s Project	Fun_level_1_TssA_chromHMM_brain	~0	Chromatin states from Roadmap Epigenomic s Project	Fun_level_1_TssA_chromHMM_brain	~0
	Fun_level_10_EnhA2_chromHMM_brain	~0		Fun_level_10_EnhA2_chromHMM_brain	~0
	Fun_level_11_EnhWk_chromHMM_brain	~0		Fun_level_11_EnhWk_chromHMM_brain	~0
	Fun_level_12_ZNF_chromHMM_brain	~0		Fun_level_12_ZNF_chromHMM_brain	0.0003
	Fun_level_13_Het_chromHMM_brain	~0		Fun_level_13_Het_chromHMM_brain	~0
	Fun_level_14_TssBiv_chromHMM_brain	0.1050		Fun_level_14_TssBiv_chromHMM_brain	~0
	Fun_level_15_EnhBiv_chromHMM_brain	~0		Fun_level_15_EnhBiv_chromHMM_brain	~0
	Fun_level_16_ReprPC_chromHMM_brain	~0		Fun_level_16_ReprPC_chromHMM_brain	0.9910
	Fun_level_17_ReprPCWk_chromHMM_brain	0.0498		Fun_level_17_ReprPCWk_chromHMM_brain	~0
	Fun_level_18_Quies_chromHMM_brain	~0		Fun_level_18_Quies_chromHMM_brain	~0
	Fun_level_2_TssFlnk_chromHMM_brain	~0		Fun_level_2_TssFlnk_chromHMM_brain	~0
	Fun_level_3_TssFlnkU_chromHMM_brain	~0		Fun_level_3_TssFlnkU_chromHMM_brain	~0
	Fun_level_4_TssFlnkD_chromHMM_brain	~0		Fun_level_4_TssFlnkD_chromHMM_brain	~0
	Fun_level_5_Tx_chromHMM_brain	~0		Fun_level_5_Tx_chromHMM_brain	~0
	Fun_level_6_TxWk_chromHMM_brain	~0		Fun_level_6_TxWk_chromHMM_brain	~0
	Fun_level_7_EnhG1_chromHMM_brain	~0		Fun_level_7_EnhG1_chromHMM_brain	~0

	Fun_level_8_EnhG2_chromHMM_brain	~0		Fun_level_8_EnhG2_chromHMM_brain	~0
	Fun_level_9_EnhA1_chromHMM_brain	~0		Fun_level_9_EnhA1_chromHMM_brain	~0
Enhancers	Fun_level_dbsuper_Brain_Angular_Gyrus	~0	Enhancers	Fun_level_dbsuper_Brain_Angular_Gyrus	~0
	Fun_level_dbsuper_Brain_Anterior_Caudate	~0		Fun_level_dbsuper_Brain_Anterior_Caudate	~0
	Fun_level_dbsuper_Brain_Cingulate_Gyrus	~0		Fun_level_dbsuper_Brain_Cingulate_Gyrus	~0
	Fun_level_dbsuper_Brain_Hippocampus_Middle_150	~0		Fun_level_dbsuper_Brain_Hippocampus_Middle_150	~0
	Fun_level_dbsuper_Brain_Hippocampus_Middle	~0		Fun_level_dbsuper_Brain_Hippocampus_Middle	~0
	Fun_level_dbsuper_Brain_Inferior_Temporal_Lobe	~0		Fun_level_dbsuper_Brain_Inferior_Temporal_Lobe	~0
	Fun_level_dbsuper_Brain_Mid_Frontal_Lobe	0.0293		Fun_level_dbsuper_Brain_Mid_Frontal_Lobe	0.0266
	Fun_level_famton_astrocyte	0.0004		Fun_level_famton_astrocyte	0.0230
	Fun_level_famton_brain	0.4890		Fun_level_famton_brain	0.6620
	Fun_level_famton_CL:0000127	0.0001		Fun_level_famton_CL:0000127	~0
	Fun_level_famton_count	~0		Fun_level_famton_count	~0
	Fun_level_famton_neuronal_stem_cell	0.3280		Fun_level_famton_neuronal_stem_cell	0.6990
	Fun_level_famton_permssive	~0		Fun_level_famton_permssive	~0
	Fun_level_enhancerAtlas_Astrocyte_EP	~0		Fun_level_enhancerAtlas_Astrocyte_EP	~0
	Fun_level_enhancerAtlas_Cerebellum_EP	~0		Fun_level_enhancerAtlas_Cerebellum_EP	~0
	Fun_level_enhancerAtlas_ESC_neuron_EP	~0		Fun_level_enhancerAtlas_ESC_neuron_EP	~0
	Fun_level_gene_enhancer_links_brain_enhcenter	~0		Fun_level_gene_enhancer_links_brain_enhcenter	~0
	Fun_level_gene_enhancer_links_neurosph_enhcenter	~0		Fun_level_gene_enhancer_links_neurosph_enhcenter	~0
	Fun_level_hacer_T1	~0		Fun_level_hacer_T1	~0
	Fun_level_SE_ele	~0		Fun_level_SE_ele	~0

	Fun_level_SEA00101	~0		Fun_level_SEA00101	~0
	Fun_level_nott_Astrocyte_enhancers	~0		Fun_level_nott_Astrocyte_enhancers	~0
	Fun_level_nott_Astrocyte_promoters	~0		Fun_level_nott_Astrocyte_promoters	~0
	Fun_level_nott_H3K4me3_around_TSS	~0		Fun_level_nott_H3K4me3_around_TSS	~0
	Fun_level_nott_Microglia_enhancers	~0		Fun_level_nott_Microglia_enhancers	~0
	Fun_level_nott_Microglia_promoters	~0		Fun_level_nott_Microglia_promoters	~0
	Fun_level_nott_Neuronal_enhancers	~0		Fun_level_nott_Neuronal_enhancers	~0
	Fun_level_nott_Neuronal_promoters	~0		Fun_level_nott_Neuronal_promoters	~0
	Fun_level_nott_Oligo_enhancers	~0		Fun_level_nott_Oligo_enhancers	~0
	Fun_level_nott_Oligo_promoters	~0		Fun_level_nott_Oligo_promoters	~0
	Fun_level_nott_superEnhancer	1		Fun_level_nott_superEnhancer	1
	Fun_level_vista	~0		Fun_level_vista	~0
CTCF binding sites	Fun_level_ctcf	~0	CTCF binding sites	Fun_level_ctcf	~0
	Fun_level_CTCF_observed_Brain	~0		Fun_level_CTCF_observed_Brain	~0
DNase hypersensitive sites	Fun_level_DNaseClusterd	~0	DNase hypersensitive sites	Fun_level_DNaseClusterd	~0
	Fun_level_DnaseMaster	~0		Fun_level_DnaseMaster	~0
	Fun_level_DNase-seq_observed_Brain	~0		Fun_level_DNase-seq_observed_Brain	~0
	Fun_level_DNase-seq_observed_Neurosp	~0		Fun_level_DNase-seq_observed_Neurosp	~0
Genomic segmentations from Gencode	Fun_level_EncodeAvgTfbsBroadNhaCtcf	~0	Genomic segmentations from Gencode	Fun_level_EncodeAvgTfbsBroadNhaCtcf	~0
	Fun_level_EncodeRegTfbsClustered	~0		Fun_level_EncodeRegTfbsClustered	~0
	Fun_level_gencode_CDS	~0		Fun_level_gencode_CDS	~0
	Fun_level_gencode_exon	0.5440		Fun_level_gencode_exon	~0
	Fun_level_gencode_gene	~0		Fun_level_gencode_gene	~0
	Fun_level_gencode_Selenocysteine	0.5450		Fun_level_gencode_Selenocysteine	0.6280
	Fun_level_gencode_start_codon	0.2450		Fun_level_gencode_start_codon	~0

	Fun_level_gencode_stop_codon	~0		Fun_level_gencode_stop_codon	~0
	Fun_level_gencode_transcript	0.8590		Fun_level_gencode_transcript	0.8330
	Fun_level_gencode_UTR	~0		Fun_level_gencode_UTR	~0
	Fun_level_miRNA	~0		Fun_level_miRNA	~0
	Fun_level_non-codingRNAs	~0		Fun_level_non-codingRNAs	0.0010
Histone markers	Fun_level_ATAC-seq_observed_Brain	~0	Histone markers	Fun_level_ATAC-seq_observed_Brain	~0
	Fun_level_H2AFZ_imputed_Brain	~0		Fun_level_H2AFZ_imputed_Brain	~0
	Fun_level_EP300_imputed_Brain	~0		Fun_level_EP300_imputed_Brain	~0
	Fun_level_EP300_imputed_Neurosph	~0		Fun_level_EP300_imputed_Neurosph	~0
	Fun_level_H2AFZ_imputed_Neurosph	~0		Fun_level_H2AFZ_imputed_Neurosph	~0
	Fun_level_H2AFZ_observed_Brain	~0		Fun_level_H2AFZ_observed_Brain	~0
	Fun_level_H3k27ac	~0		Fun_level_H3k27ac	~0
	Fun_level_H3K27ac_imputed_Brain	~0		Fun_level_H3K27ac_imputed_Brain	~0
	Fun_level_H3K27ac_imputed_Neurosph	~0		Fun_level_H3K27ac_imputed_Neurosph	~0
	Fun_level_H3K27ac_observed_Brain	~0		Fun_level_H3K27ac_observed_Brain	~0
	Fun_level_H3K27ac_observed_Neurosph	~0		Fun_level_H3K27ac_observed_Neurosph	~0
	Fun_level_H3K27me3_imputed_Brain	~0		Fun_level_H3K27me3_imputed_Brain	~0
	Fun_level_H3K27me3_imputed_Neurosph	~0		Fun_level_H3K27me3_imputed_Neurosph	~0
	Fun_level_H3K27me3_observed_Brain	~0		Fun_level_H3K27me3_observed_Brain	~0
	Fun_level_H3k4me1	~0		Fun_level_H3k4me1	~0
	Fun_level_H3K4me1_imputed_Brain	~0		Fun_level_H3K4me1_imputed_Brain	~0
	Fun_level_H3K4me1_imputed_Neurosph	~0		Fun_level_H3K4me1_imputed_Neurosph	~0
	Fun_level_H3K4me1_observed_Brain	~0		Fun_level_H3K4me1_observed_Brain	~0
	Fun_level_H3K4me1_observed_Neurosph	~0		Fun_level_H3K4me1_observed_Neurosph	~0
	Fun_level_H3K4me2_observed_Brain	~0		Fun_level_H3K4me2_observed_Brain	~0

	Fun_level_H3k4me3	~0		Fun_level_H3k4me3	~0
	Fun_level_H3K4me3_imputed_Brain	0.0580		Fun_level_H3K4me3_imputed_Brain	0.4680
	Fun_level_H3K4me3_imputed_Neurosph	~0		Fun_level_H3K4me3_imputed_Neurosph	~0
	Fun_level_H3K4me3_observed_Brain	0.0592		Fun_level_H3K4me3_observed_Brain	0.4710
	Fun_level_H3K4me3_observed_Neurosph	~0		Fun_level_H3K4me3_observed_Neurosph	~0
	Fun_level_H3K9ac_imputed_Brain	~0		Fun_level_H3K9ac_imputed_Brain	~0
	Fun_level_H3K9ac_imputed_Neurosph	~0		Fun_level_H3K9ac_imputed_Neurosph	~0
	Fun_level_H3K9me3_imputed_Brain	~0		Fun_level_H3K9me3_imputed_Brain	~0
	Fun_level_H3K9me3_imputed_Neurosph	~0		Fun_level_H3K9me3_imputed_Neurosph	~0
	Fun_level_H3K9me3_observed_Brain	~0		Fun_level_H3K9me3_observed_Brain	~0
	Fun_level_H3K9me3_observed_Neurosph	~0		Fun_level_H3K9me3_observed_Neurosph	~0
	Fun_level_H4K20me1_imputed_Neurosph	~0		Fun_level_H4K20me1_imputed_Neurosph	~0
	Fun_level_H4K20me1_observed_Brain	~0		Fun_level_H4K20me1_observed_Brain	~0
	Fun_level_POLR2A_imputed_Neurosph	~0		Fun_level_POLR2A_imputed_Neurosph	~0
	Fun_level_RAD21_imputed_Brain	~0		Fun_level_RAD21_imputed_Brain	~0
	Fun_level_RAD21_imputed_Neurosph	~0		Fun_level_RAD21_imputed_Neurosph	~0
	Fun_level_SMC3_imputed_Brain	~0		Fun_level_SMC3_imputed_Brain	~0
	Fun_level_SMC3_imputed_Neurosph	~0		Fun_level_SMC3_imputed_Neurosph	~0
Long range probable genes	Fun_level_liu_csbj_targetgene	~0	Long range probable genes	Fun_level_liu_csbj_targetgene	~0
Methylation	Fun_level_methMCRF	~0	Methylation	Fun_level_methMCRF	~0
Loop anchors and topological	Fun_level_PsychENCODE_CBC_H3K27ac	~0	Loop anchors and topological	Fun_level_PsychENCODE_CBC_H3K27ac	~0
	Fun_level_PsychENCODE_HiC_EP	~0		Fun_level_PsychENCODE_HiC_EP	~0
	Fun_level_PsychENCODE_loops_interRegion	~0		Fun_level_PsychENCODE_loops_interRegion	0.1890

associated domains in higher-order chromatin structure	Fun_level_PsychENCODE_PEC_Enhancers	~0	associated domains in higher-order chromatin structure	Fun_level_PsychENCODE_PEC_Enhancers	~0		
	Fun_level_PsychENCODE_PFC_H3K27ac	~0		Fun_level_PsychENCODE_PFC_H3K27ac	~0		
	Fun_level_PsychENCODE_TAR	~0		Fun_level_PsychENCODE_TAR	~0		
	Fun_level_PsychENCODE_TC_H3K27ac	~0		Fun_level_PsychENCODE_TC_H3K27ac	~0		
	Fun_level_TAD56	~0		Fun_level_TAD56	~0		
DNase hypersensitive sites	Fun_level_RoadmapDNasePromCount	~0	DNase hypersensitive sites	Fun_level_RoadmapDNasePromCount	~0		
Transcript factor binding sites from snp-selex	Fun_level_snp_selex	0.0860	Transcript factor binding sites from snp-selex	Fun_level_snp_selex	0.0403		
Transcript starting sites	Fun_level_tss2000bp	~0	Transcript starting sites	Fun_level_tss2000bp	0.1450		
Higher-order chromatin structure from Yue lab	Fun_level_yue_loops_hippo	~0	Higher-order chromatin structure from Yue lab	Fun_level_yue_loops_hippo	~0		
Gene level		<i>The Gen_level_significant features are 34 out of 45</i>		Gene level		<i>The Gen_level_significant features are 25 out of 45</i>	
ClinGen curated	Gen_level_ClinGen_haploinsufficiency_gene_0	0.0013	ClinGen curated	Gen_level_ClinGen_region_curation_Triplosensitivity_0	0.4450		

genes and genomic regions	Gen_level_ClinGen_haploinsufficiency_gene_1	0.0086	genes and genomic regions	Gen_level_ClinGen_region_curation_Triplosensitivity_1	0.4030
	Gen_level_ClinGen_haploinsufficiency_gene_2	0.5950		Gen_level_ClinGen_region_curation_Triplosensitivity_2	0.0603
	Gen_level_ClinGen_haploinsufficiency_gene_3	~0		Gen_level_ClinGen_region_curation_Triplosensitivity_3	0.3880
	Gen_level_ClinGen_haploinsufficiency_gene_30	~0		Gen_level_ClinGen_region_curation_Triplosensitivity_40	~0
	Gen_level_ClinGen_haploinsufficiency_gene_40	0.7010		Gen_level_ClinGen_triplosensitivity_gene	0.7800
	Gen_level_ClinGen_region_curation_Haploinsufficiency_0	0.8020		Gen_level_ClinGen_triplosensitivity_gene_0	~0
	Gen_level_ClinGen_region_curation_Haploinsufficiency_1	0.8830		Gen_level_ClinGen_triplosensitivity_gene_1	0.9070
	Gen_level_ClinGen_region_curation_Haploinsufficiency_2	0.8130		Gen_level_ClinGen_triplosensitivity_gene_2	0.9410
	Gen_level_ClinGen_region_curation_Haploinsufficiency_3	0.0011		Gen_level_ClinGen_triplosensitivity_gene_3	1.0000
	Gen_level_ClinGen_region_curation_Haploinsufficiency_30	0.9290		Gen_level_ClinGen_triplosensitivity_gene_30	1.0000
	Gen_level_ClinGen_region_curation_Haploinsufficiency_40	~0		Gen_level_ClinGen_triplosensitivity_gene_40	1.0000
	Gen_level_loss_of_function_score1	0.0026		Gen_level_gain_activating_score1	0.8030
	Gen_level_loss_of_function_score2	~0		Gen_level_gain_activating_score2	0.6810
	Gen_level_loss_of_function_score3	~0		Gen_level_gain_activating_score3	0.2840

Dosage sensitive genes	Gen_level_Collins_rCNV_PLIgenes_PHI	~0	Dosage sensitive genes	Gen_level_Collins_rCNV_PLIgenes PTS	~0
DDG2P database	Gen_level_ddg2p_loss	~0	DDG2P database	Gen_level_ddg2p_gain	0.0690
Cell essential and nonessential genes	Gen_level_Essential_in_culture_CRISPR	0.0001	Cell essential and nonessential genes	Gen_level_Essential_in_culture_CRISPR	~0
	Gen_nonEssential_in_culture_CRISPR	0.3020		Gen_nonEssential_in_culture_CRISPR	0.6100
FDA proved drug target	Gen_level_FDA-approved_drug_targets	0.0013	FDA proved drug target	Gen_level_FDA-approved_drug_targets	~0
G protein-coupled receptor	Gen_level_gpcr_union	0.4010	G protein-coupled receptor	Gen_level_gpcr_union	0.0003
Neurodevelopmental process related genes	Gen_level_HP_0000707	~0	Neurodevelopmental process related genes	Gen_level_HP_0000707	~0
	Gen_level_HP_0000708	~0		Gen_level_HP_0000708	~0
	Gen_level_HP_0000717	0.0008		Gen_level_HP_0000717	0.0032
	Gen_level_HP_0000729	~0		Gen_level_HP_0000729	~0
	Gen_level_HP_0000752	~0		Gen_level_HP_0000752	~0
	Gen_level_HP_0001197	~0		Gen_level_HP_0001197	~0
	Gen_level_HP_0001250	~0		Gen_level_HP_0001250	~0
	Gen_level_HP_0001507	~0		Gen_level_HP_0001507	~0
	Gen_level_HP_0002011	~0		Gen_level_HP_0002011	~0
Gen_level_HP_0002715	~0	Gen_level_HP_0002715	~0		

	Gen_level_HP_0002960	0.7040		Gen_level_HP_0002960	0.3470
	Gen_level_HP_0011446	~0		Gen_level_HP_0011446	~0
	Gen_level_HP_0012443	~0		Gen_level_HP_0012443	~0
	Gen_level_HP_0012638	~0		Gen_level_HP_0012638	~0
	Gen_level_HP_0012639	~0		Gen_level_HP_0012639	~0
	Gen_level_HP_0012759	~0		Gen_level_HP_0012759	~0
	Gen_level_HP_0025031	~0		Gen_level_HP_0025031	~0
	Gen_level_HP_0031466	~0		Gen_level_HP_0031466	~0
	Gen_level_HP_0100022	~0		Gen_level_HP_0100022	~0
	Gen_level_HP_0100753	0.1320		Gen_level_HP_0100753	0.8250
	Gen_level_HP_0100852	~0		Gen_level_HP_0100852	0.0009
Mouse heterozygous LoF lethal	Gen_level_mgi_essential_gene	~0	Mouse heterozygous LoF lethal	Gen_level_mgi_essential_gene	~0
Olfactory receptors	Gen_level_Olfactory_receptors_mainland	0.0066	Olfactory receptors	Gen_level_Olfactory_receptors_mainland	0.6100
Sfari gene	Gen_level_sfari_gene	~0	Sfari gene	Gen_level_sfari_gene	~0
Sequence level	<i>The Seq_level_significant features are 7 out of 7</i>		Sequence level	<i>The Seq_level_significant features are 6 out of 7</i>	
Blacklisted regions	Seq_level_DacMapExclude	~0	Blacklisted regions	Seq_level_DacMapExclude	~0
Sfari gene	Seq_level_DukeMapExclude	~0	Sfari gene	Seq_level_DukeMapExclude	~0
GC content	Seq_level_GC	~0	GC content	Seq_level_GC	~0
Human	Seq_level_HAR	0.0085	Human	Seq_level_HAR	0.2010

accelerated regions Heterochromatin positions			accelerated regions Heterochromatin positions		
Human accelerated regions Heterochromatin positions Cross species conservation score	Seq_level_HetDomain Seq_level_phastCons46way	~0	Human accelerated regions Heterochromatin positions Cross species conservation score	Seq_level_HetDomain Seq_level_phastCons46way	~0
Human accelerated regions	Seq_level_phyloP46way	~0	Human accelerated regions	Seq_level_phyloP46way	~0

p-values: when $P < 1 \times 10^{-4}$, it is shown as ~0, and when $1 \times 10^{-4} < P < 1$, it is shown as a decimal mode.

Table S3. Feature importancy. All the feature names were shown as feature names (original sources)_tissue type (if applicable). p-values: when $P < 1 \times 10^{-4}$, it is shown as ~0, and when $1 \times 10^{-4} < P < 1$, it is shown as a decimal mode. $P = 0.05$ is set as the significant level.

Features in copy number loss model	Feature importancy	Features in copy number gain model	Feature importancy
1_TssA_chromHMM_brain	0.0053	1_TssA_chromHMM_brain	0.0056
10_EnhA2_chromHMM_brain	0.0078	10_EnhA2_chromHMM_brain	0.0049
11_EnhWk_chromHMM_brain	0.0138	11_EnhWk_chromHMM_brain	0.0093
12_ZNF_chromHMM_brain	0.0046	12_ZNF_chromHMM_brain	0.0049
13_Het_chromHMM_brain	0.0058	13_Het_chromHMM_brain	0.0058
14_TssBiv_chromHMM_brain	0.0043	14_TssBiv_chromHMM_brain	0.0041
15_EnhBiv_chromHMM_brain	0.0057	15_EnhBiv_chromHMM_brain	0.0062
16_ReprPC_chromHMM_brain	0.0043	16_ReprPC_chromHMM_brain	0.0041
17_ReprPCWk_chromHMM_brain	0.0054	17_ReprPCWk_chromHMM_brain	0.0055
18_Quies_chromHMM_brain	0.0062	18_Quies_chromHMM_brain	0.0073
2_TssFlnk_chromHMM_brain	0.0045	2_TssFlnk_chromHMM_brain	0.0043
3_TssFlnkU_chromHMM_brain	0.0047	3_TssFlnkU_chromHMM_brain	0.0046
4_TssFlnkD_chromHMM_brain	0.0073	4_TssFlnkD_chromHMM_brain	0.0053
5_Tx_chromHMM_brain	0.0046	5_Tx_chromHMM_brain	0.0051
6_TxWk_chromHMM_brain	0.0050	6_TxWk_chromHMM_brain	0.0048
7_EnhG1_chromHMM_brain	0.0045	7_EnhG1_chromHMM_brain	0.0044
8_EnhG2_chromHMM_brain	0.0047	8_EnhG2_chromHMM_brain	0.0054
9_EnhA1_chromHMM_brain	0.0055	9_EnhA1_chromHMM_brain	0.0048
ATAC-seq_observed_Brain	0.0058	ATAC-seq_observed_Brain	0.0060
Brain_Angular_Gyrus_dbSUPER	0.0042	Brain_Angular_Gyrus_dbSUPER	0.0035
Brain_Anterior_Caudate_dbSUPER	0.0043	Brain_Anterior_Caudate_dbSUPER	0.0051
Brain_Cingulate_Gyrus_dbSUPER	0.0040	Brain_Cingulate_Gyrus_dbSUPER	0.0039

Brain_Hippocampus_Middle_150_dbsuper	0.0045	Brain_Hippocampus_Middle_150_dbsuper	0.0063
Brain_Hippocampus_Middle_dbsuper	0.0039	Brain_Hippocampus_Middle_dbsuper	0.0042
Brain_Inferior_Temporal_Lobe_dbsuper	0.0035	Brain_Inferior_Temporal_Lobe_dbsuper	0.0054
Brain_Mid_Frontal_Lobe_dbsuper	0.0050	Brain_Mid_Frontal_Lobe_dbsuper	0.0070
ClinGen_haploinsufficiency_gene_0	0.0037	ClinGen_region_curation_Triplosensitivity_0	0.0022
ClinGen_haploinsufficiency_gene_1	0.0059	ClinGen_region_curation_Triplosensitivity_1	0.0071
ClinGen_haploinsufficiency_gene_2	~0	ClinGen_region_curation_Triplosensitivity_2	0.0061
ClinGen_haploinsufficiency_gene_3	0.0094	ClinGen_region_curation_Triplosensitivity_3	0.0054
ClinGen_haploinsufficiency_gene_30	0.0048	ClinGen_region_curation_Triplosensitivity_40	0.0101
ClinGen_haploinsufficiency_gene_40	0.0011	ClinGen_triplosensitivity_gene	~0
ClinGen_region_curation_Haploinsufficiency_0	0.0046	ClinGen_triplosensitivity_gene_0	0.0062
ClinGen_region_curation_Haploinsufficiency_1	~0	ClinGen_triplosensitivity_gene_1	~0
ClinGen_region_curation_Haploinsufficiency_2	0.0026	ClinGen_triplosensitivity_gene_2	~0
ClinGen_region_curation_Haploinsufficiency_3	0.0048	ClinGen_triplosensitivity_gene_3	~0
ClinGen_region_curation_Haploinsufficiency_30	~0	ClinGen_triplosensitivity_gene_30	~0
ClinGen_region_curation_Haploinsufficiency_40	0.0105	ClinGen_triplosensitivity_gene_40	~0
Collins_rCNV_PLIgenes_PHI	0.0524	Collins_rCNV_PLIgenes PTS	0.0653
ctcf	0.0053	ctcf	0.0045
CTCF_observed_Brain	0.0043	CTCF_observed_Brain	0.0051
DacMapExclude	0.0057	DacMapExclude	0.0089
ddg2p_loss	0.0075	ddg2p_gain	0.0035
DNaseIClusterd	0.0042	DNaseIClusterd	0.0045
DnaseMaster	0.0055	DnaseMaster	0.0050
DNase-seq_observed_Brain	0.0111	DNase-seq_observed_Brain	0.0108
DNase-seq_observed_Neurosph	0.0230	DNase-seq_observed_Neurosph	0.0224

DukeMapExclude	0.0063	DukeMapExclude	0.0085
EncodeAvgTfbsBroadNhaCtcf	0.0051	EncodeAvgTfbsBroadNhaCtcf	0.0048
EncodeRegTfbsClustered	0.0049	EncodeRegTfbsClustered	0.0056
enhancerAtlas_Astrocyte_EP	0.0034	enhancerAtlas_Astrocyte_EP	0.0068
enhancerAtlas_Cerebellum_EP	0.0042	enhancerAtlas_Cerebellum_EP	0.0049
enhancerAtlas_ESC_neuron_EP	0.0033	enhancerAtlas_ESC_neuron_EP	0.0045
EP300_imputed_Brain	0.0048	EP300_imputed_Brain	0.0040
EP300_imputed_NeurospH	0.0051	EP300_imputed_NeurospH	0.0055
Essential_in_culture_CRISPR	0.0039	Essential_in_culture_CRISPR	0.0051
famton_astrocyte	0.0039	famton_astrocyte	0.0070
famton_brain	0.0067	famton_brain	0.0053
famton_CL:0000127	0.0035	famton_CL:0000127	0.0038
famton_count	0.0054	famton_count	0.0062
famton_neuronal_stem_cell	0.0046	famton_neuronal_stem_cell	0.0032
famton_permssive	0.0046	famton_permssive	0.0050
FDA-approved_drug_targets	0.0040	FDA-approved_drug_targets	0.0046
GC	0.0065	gain_activating_score1	~0
gencode_CDS	0.0092	gain_activating_score2	~0
gencode_exon	0.0077	gain_activating_score3	0.0018
gencode_gene	0.0074	GC	0.0059
gencode_Selenocysteine	~0	gencode_CDS	0.0096
gencode_start_codon	0.0208	gencode_exon	0.0211
gencode_stop_codon	0.0035	gencode_gene	0.0072
gencode_transcript	0.0047	gencode_Selenocysteine	0.0005
gencode_UTR	0.0058	gencode_start_codon	0.0086

gene_enhancer_links_brain_enhcenter	0.0056	gencode_stop_codon	0.0043
gene_enhancer_links_neurosph_enhcenter	0.0064	gencode_transcript	0.0051
gpcr_union	0.0040	gencode_UTR	0.0043
H2AFZ_imputed_Brain	0.0043	gene_enhancer_links_brain_enhcenter	0.0043
H2AFZ_imputed_Neurosph	0.0047	gene_enhancer_links_neurosph_enhcenter	0.0061
H2AFZ_observed_Brain	0.0052	gpcr_union	0.0035
H3k27ac	0.0049	H2AFZ_imputed_Brain	0.0045
H3K27ac_imputed_Brain	0.0046	H2AFZ_imputed_Neurosph	0.0060
H3K27ac_imputed_Neurosph	0.0051	H2AFZ_observed_Brain	0.0056
H3K27ac_observed_Brain	0.0045	H3k27ac	0.0054
H3K27ac_observed_Neurosph	0.0058	H3K27ac_imputed_Brain	0.0063
H3K27me3_imputed_Brain	0.0050	H3K27ac_imputed_Neurosph	0.0066
H3K27me3_imputed_Neurosph	0.0065	H3K27ac_observed_Brain	0.0047
H3K27me3_observed_Brain	0.0067	H3K27ac_observed_Neurosph	0.0062
H3k4me1	0.0061	H3K27me3_imputed_Brain	0.0051
H3K4me1_imputed_Brain	0.0041	H3K27me3_imputed_Neurosph	0.0064
H3K4me1_imputed_Neurosph	0.0053	H3K27me3_observed_Brain	0.0077
H3K4me1_observed_Brain	0.0056	H3k4me1	0.0072
H3K4me1_observed_Neurosph	0.0043	H3K4me1_imputed_Brain	0.0057
H3K4me2_observed_Brain	0.0052	H3K4me1_imputed_Neurosph	0.0060
H3k4me3	0.0077	H3K4me1_observed_Brain	0.0058
H3K4me3_imputed_Brain	0.0061	H3K4me1_observed_Neurosph	0.0053
H3K4me3_imputed_Neurosph	0.0051	H3K4me2_observed_Brain	0.0053
H3K4me3_observed_Brain	0.0054	H3k4me3	0.0053
H3K4me3_observed_Neurosph	0.0054	H3K4me3_imputed_Brain	0.0053

H3K9ac_imputed_Brain	0.0055	H3K4me3_imputed_Neurosph	0.0041
H3K9ac_imputed_Neurosph	0.0055	H3K4me3_observed_Brain	0.0068
H3K9me3_imputed_Brain	0.0057	H3K4me3_observed_Neurosph	0.0065
H3K9me3_imputed_Neurosph	0.0059	H3K9ac_imputed_Brain	0.0050
H3K9me3_observed_Brain	0.0055	H3K9ac_imputed_Neurosph	0.0069
H3K9me3_observed_Neurosph	0.0047	H3K9me3_imputed_Brain	0.0068
H4K20me1_imputed_Neurosph	0.0044	H3K9me3_imputed_Neurosph	0.0066
H4K20me1_observed_Brain	0.0050	H3K9me3_observed_Brain	0.0066
hacer_T1	0.0051	H3K9me3_observed_Neurosph	0.0079
HAR	0.0044	H4K20me1_imputed_Neurosph	0.0055
HetDomain	0.0113	H4K20me1_observed_Brain	0.0054
HP_0000707	0.0034	hacer_T1	0.0063
HP_0000708	0.0047	HAR	0.0053
HP_0000717	0.0092	HetDomain	0.0069
HP_0000729	0.0031	HP_0000707	0.0041
HP_0000752	0.0032	HP_0000708	0.0046
HP_0001197	0.0047	HP_0000717	0.0045
HP_0001250	0.0038	HP_0000729	0.0053
HP_0001507	0.0042	HP_0000752	0.0056
HP_0002011	0.0056	HP_0001197	0.0045
HP_0002715	0.0077	HP_0001250	0.0026
HP_0002960	0.0090	HP_0001507	0.0058
HP_0011446	0.0053	HP_0002011	0.0043
HP_0012443	0.0068	HP_0002715	0.0045
HP_0012638	0.0034	HP_0002960	0.0040

HP_0012639	0.0051	HP_0011446	0.0063
HP_0012759	0.0074	HP_0012443	0.0028
HP_0025031	0.0045	HP_0012638	0.0045
HP_0031466	0.0055	HP_0012639	0.0029
HP_0100022	0.0065	HP_0012759	0.0058
HP_0100753	~0	HP_0025031	0.0079
HP_0100852	0.0043	HP_0031466	0.0058
liu_csbj_targetgene	0.0052	HP_0100022	0.0035
loss_of_function_score1	0.0059	HP_0100753	0.0046
loss_of_function_score2	0.0033	HP_0100852	0.0052
loss_of_function_score3	0.0055	liu_csbj_targetgene	0.0050
methMCRF	0.0065	methMCRF	0.0075
mgi_essential_gene	0.0044	mgi_essential_gene	0.0139
miRNA	0.0049	miRNA	0.0053
non-codingRNAs	0.0058	non-codingRNAs	0.0049
nonEssential_in_culture_CRISPR	0.0047	nonEssential_in_culture_CRISPR	0.0043
nott_Astrocyte_enhancers	0.0040	nott_Astrocyte_enhancers	0.0051
nott_Astrocyte_promoters	0.0045	nott_Astrocyte_promoters	0.0063
nott_H3K4me3_around_TSS	0.0060	nott_H3K4me3_around_TSS	0.0056
nott_Microglia_enhancers	0.0047	nott_Microglia_enhancers	0.0051
nott_Microglia_promoters	0.0057	nott_Microglia_promoters	0.0052
nott_Neuronal_enhancers	0.0123	nott_Neuronal_enhancers	0.0109
nott_Neuronal_promoters	0.0047	nott_Neuronal_promoters	0.0054
nott_Oligo_enhancers	0.0049	nott_Oligo_enhancers	0.0058
nott_Oligo_promoters	0.0061	nott_Oligo_promoters	0.0048

nott_superEnhancer	~0	nott_superEnhancer	~0
Olfactory_receptors_mainland	0.0068	Olfactory_receptors_mainland	0.0025
phastCons46way	0.0062	phastCons46way	0.0070
phyloP46way	0.0051	phyloP46way	0.0057
POLR2A_imputed_Neurosph	0.0067	POLR2A_imputed_Neurosph	0.0043
PsychENCODE_CBC_H3K27ac	0.0067	PsychENCODE_CBC_H3K27ac	0.0049
PsychENCODE_HiC_EP	0.0050	PsychENCODE_HiC_EP	0.0046
PsychENCODE_loops_interRegion	0.0043	PsychENCODE_loops_interRegion	0.0043
PsychENCODE_PEC_Enhancers	0.0104	PsychENCODE_PEC_Enhancers	0.0079
PsychENCODE_PFC_H3K27ac	0.0062	PsychENCODE_PFC_H3K27ac	0.0047
PsychENCODE_TAR	0.0058	PsychENCODE_TAR	0.0052
PsychENCODE_TC_H3K27ac	0.0047	PsychENCODE_TC_H3K27ac	0.0047
RAD21_imputed_Brain	0.0055	RAD21_imputed_Brain	0.0061
RAD21_imputed_Neurosph	0.0057	RAD21_imputed_Neurosph	0.0060
RoadmapDNasePromCount	0.0048	RoadmapDNasePromCount	0.0049
SE_ele	0.0043	SE_ele	0.0052
SEA00101	0.0046	SEA00101	0.0056
sfari_gene	0.0046	sfari_gene	0.0043
SMC3_imputed_Brain	0.0060	SMC3_imputed_Brain	0.0054
SMC3_imputed_Neurosph	0.0047	SMC3_imputed_Neurosph	0.0069
snp_selex	0.0084	snp_selex	0.0045
TAD56	0.0079	TAD56	0.0072
tss2000bp	0.0178	tss2000bp	0.0146
vista	0.0047	vista	0.0045
yue_loops_hippo	0.0051	yue_loops_hippo	0.0066

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