

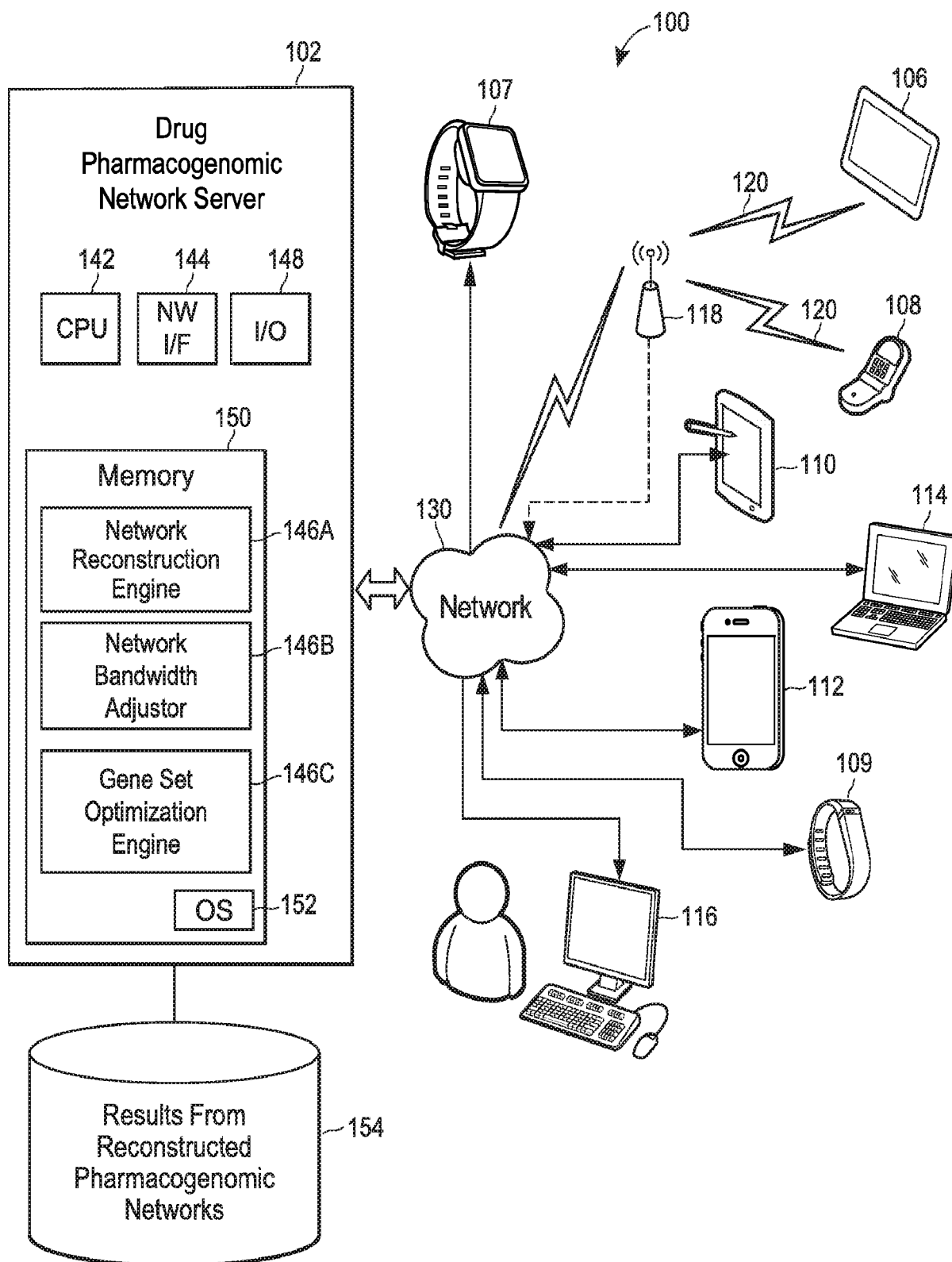
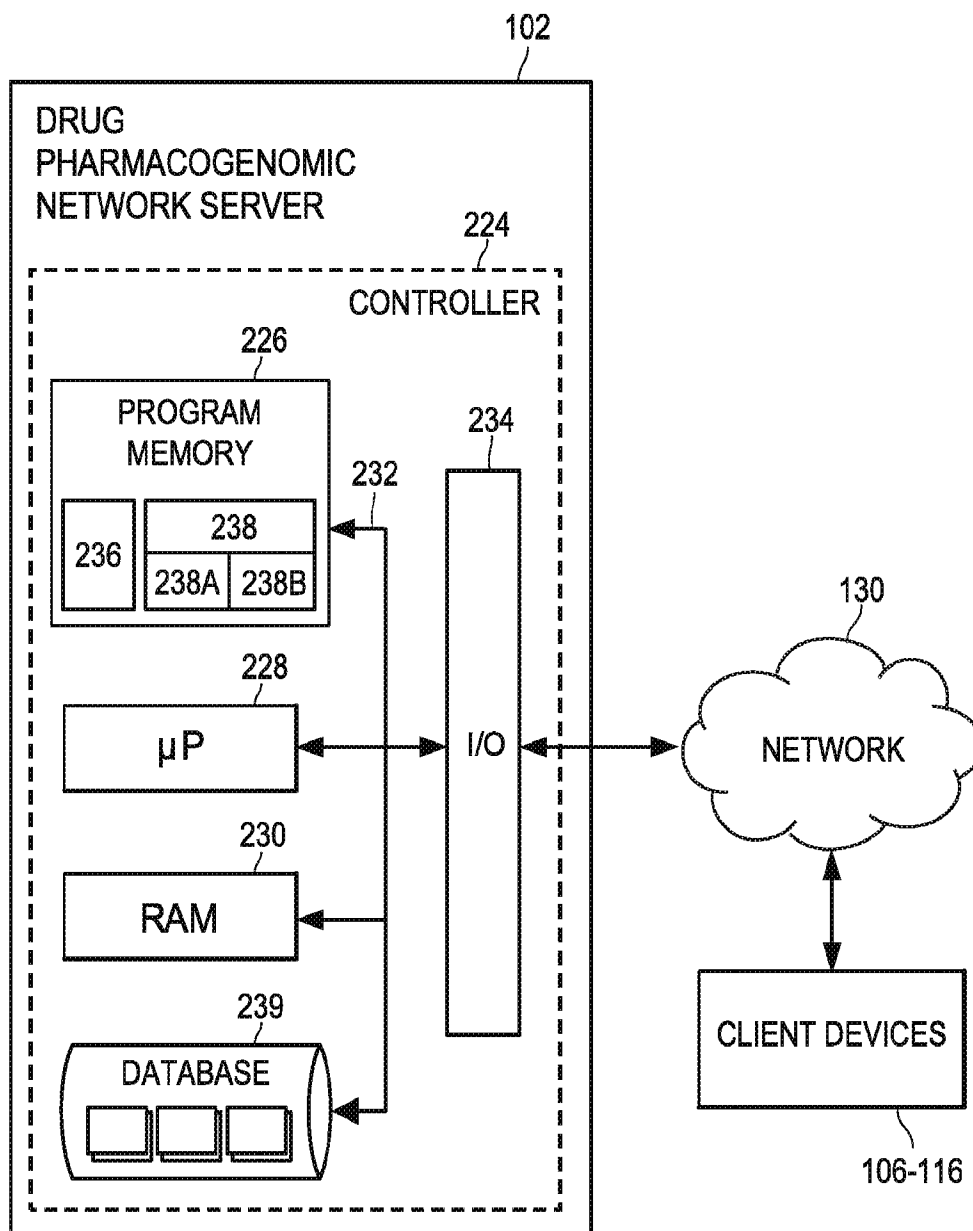
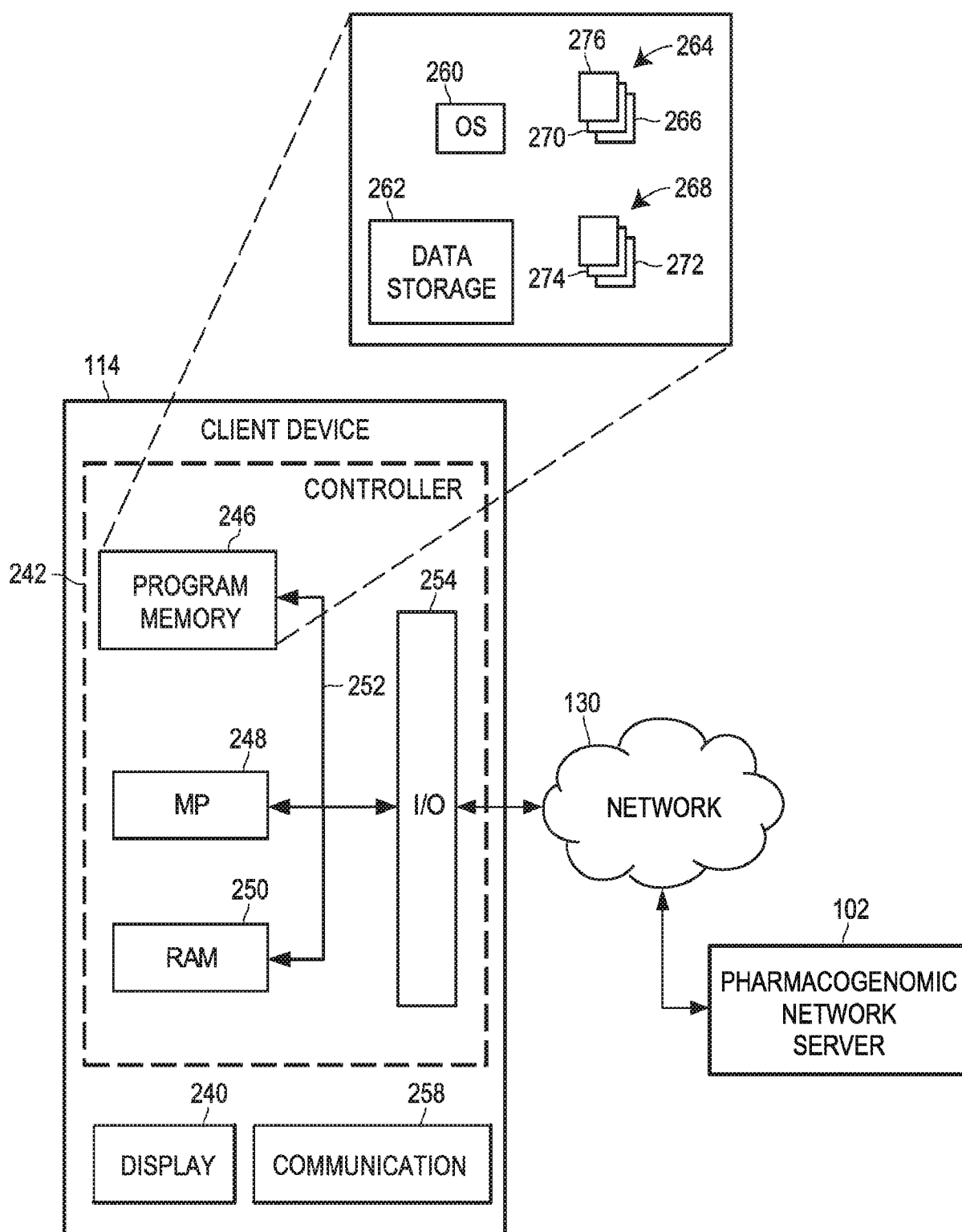


FIG. 1A

**FIG. 1B**

**FIG. 1C**

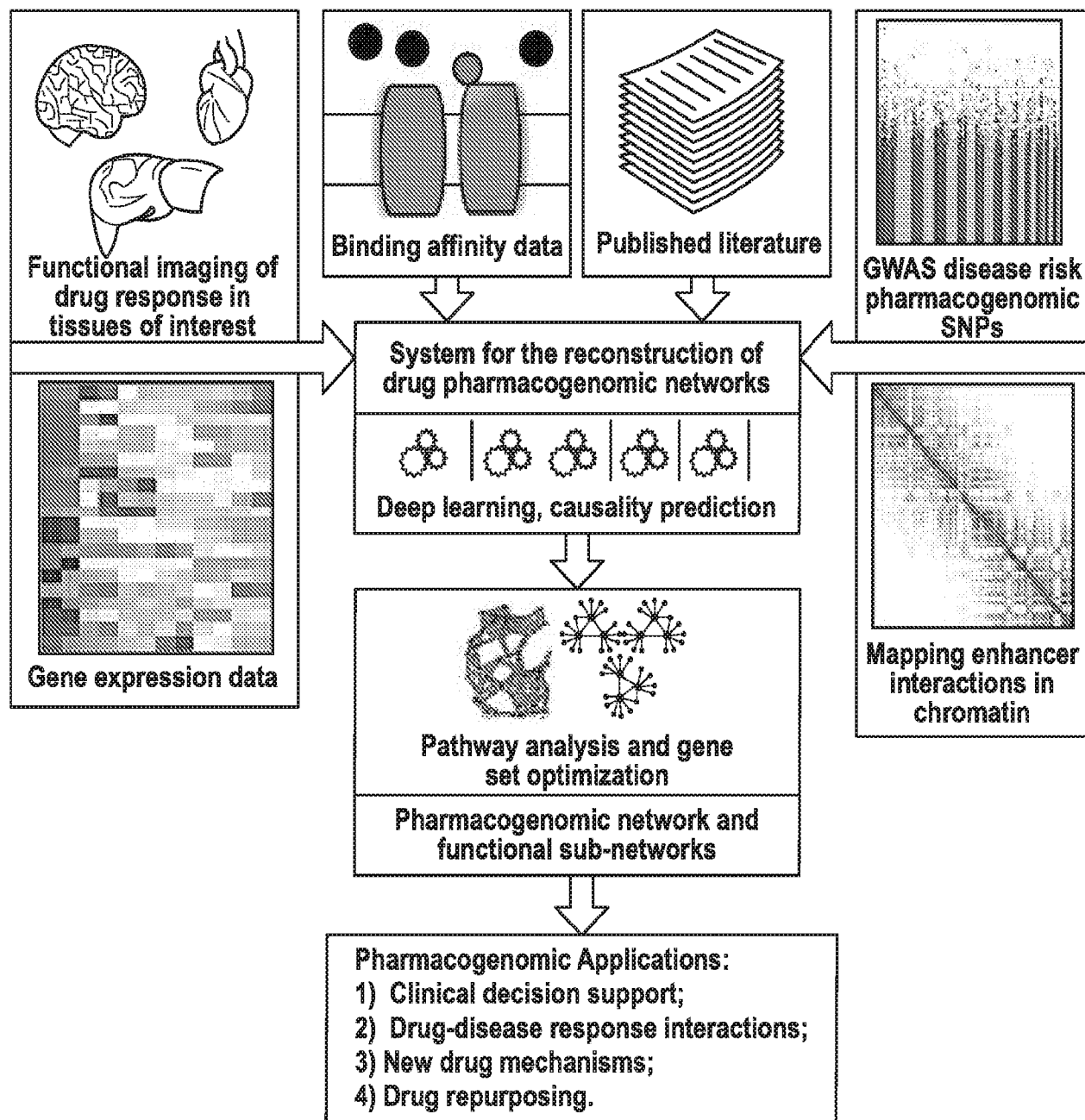


FIG. 2

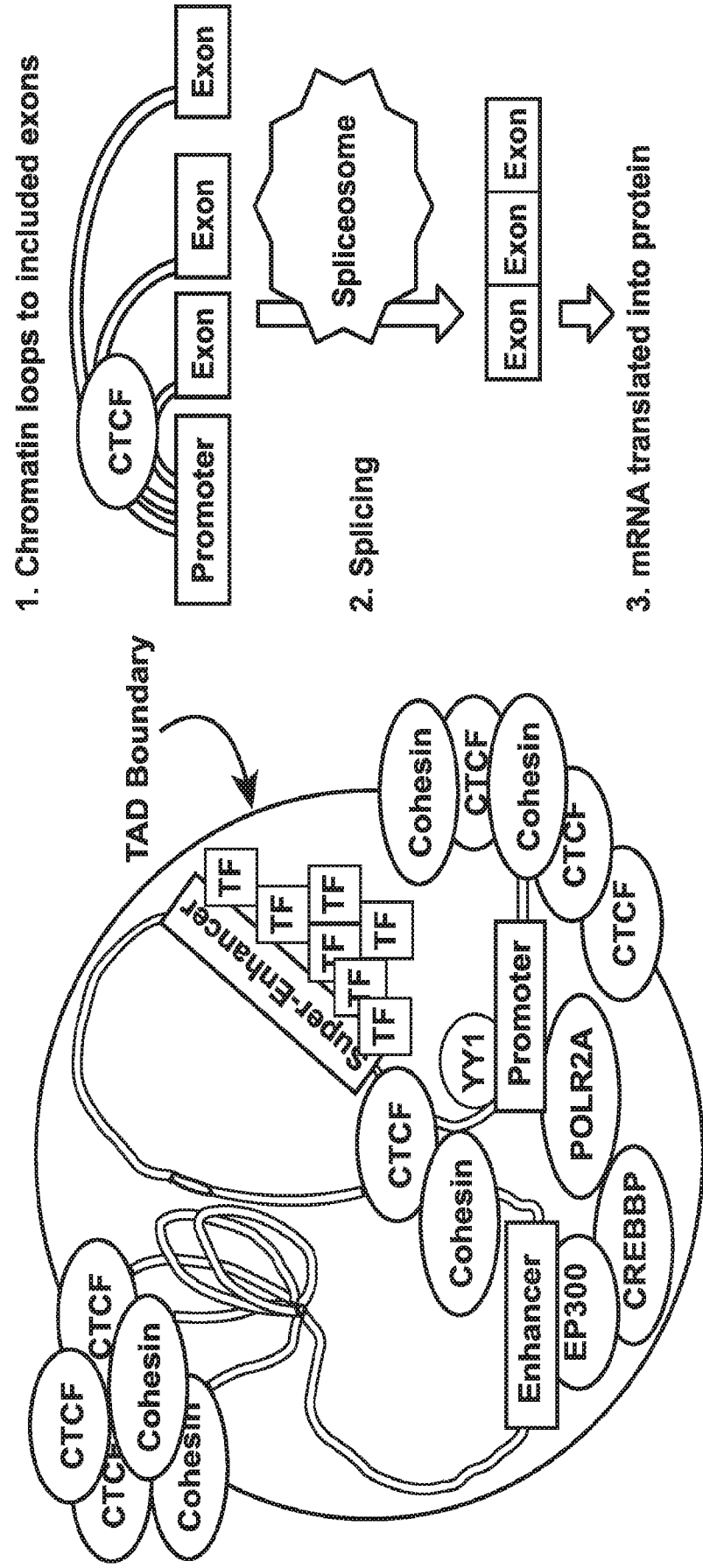


FIG. 3

Topologically-associated domains (TADs) are geometrically condensed

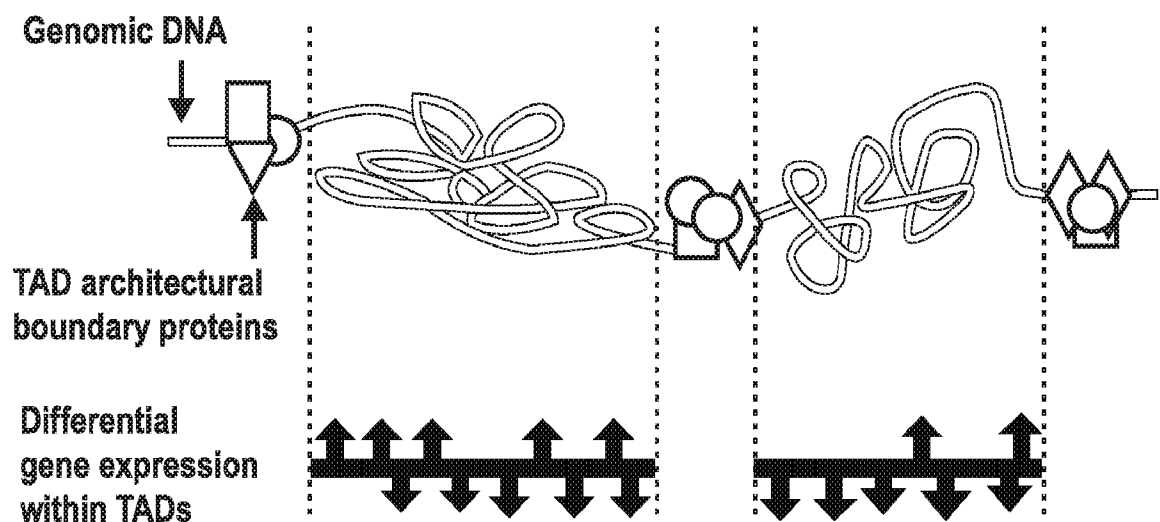


FIG. 4A

Specific Tads are geometrically expanded, and specific intra-TAD gene expression is activated or suppressed by enhancer(s)-gene promoters contacts

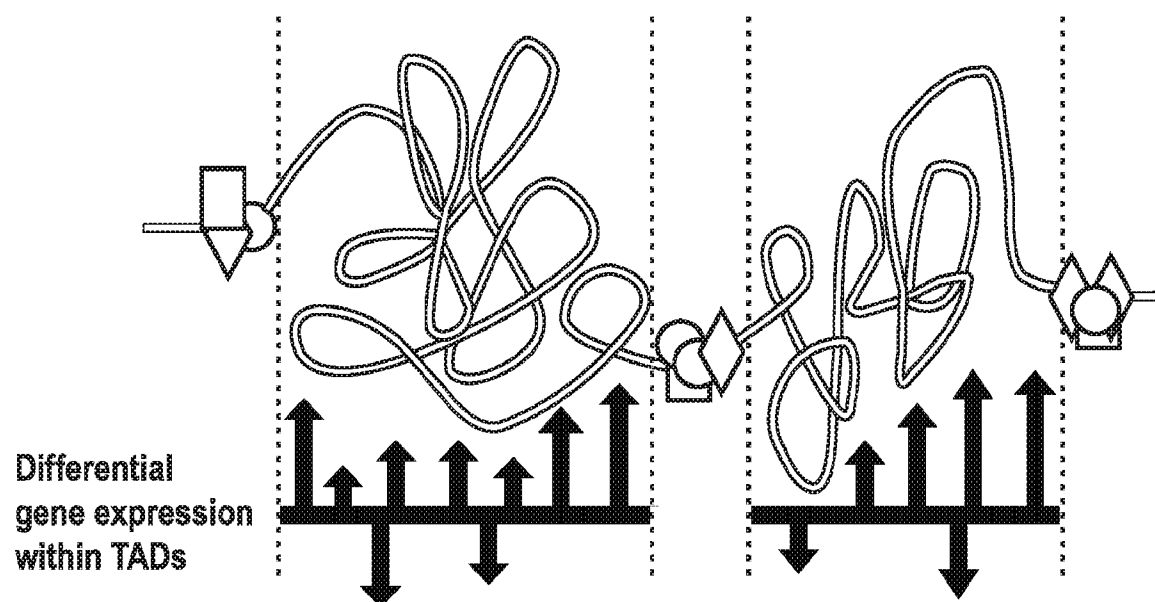


FIG. 4B

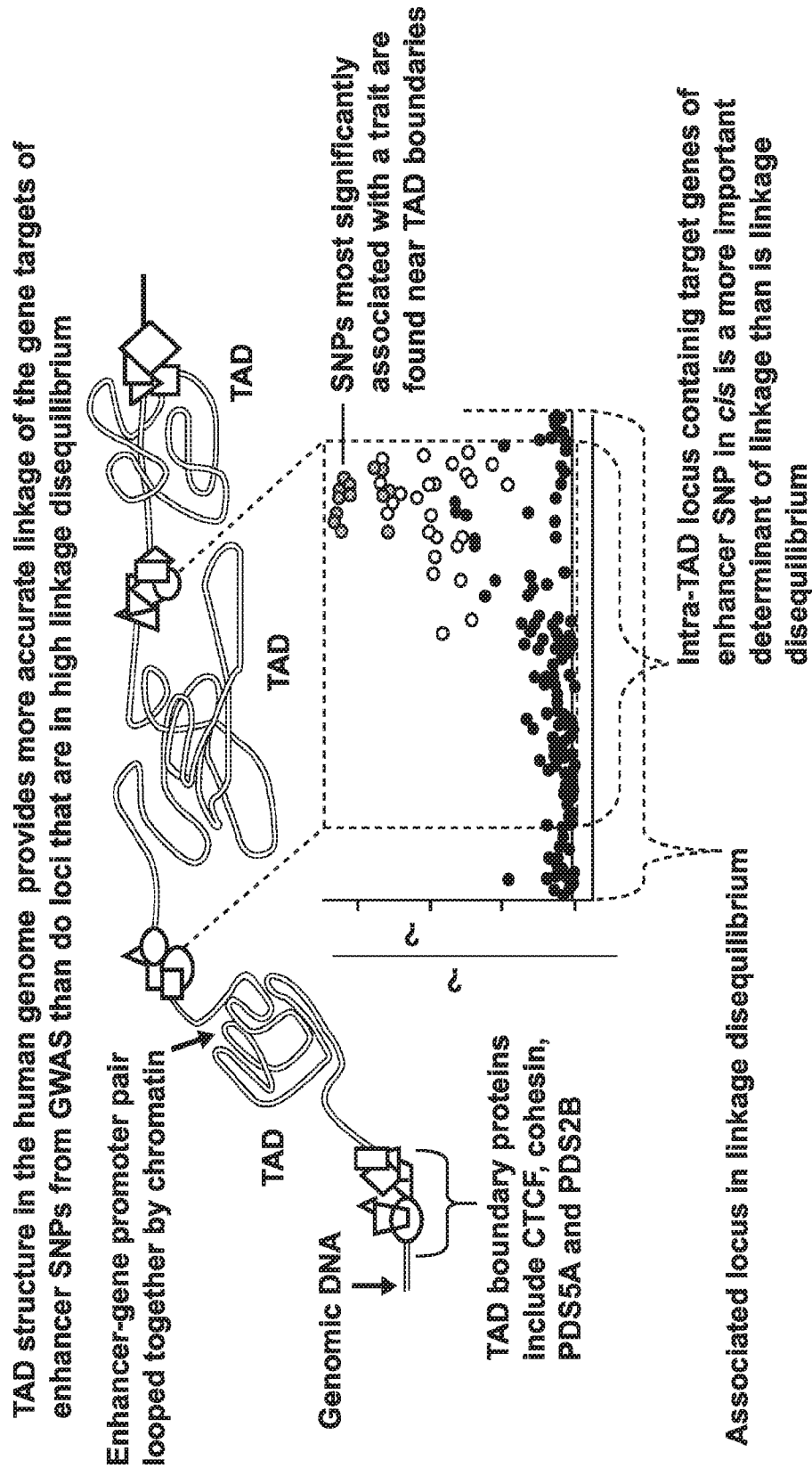


FIG. 4C

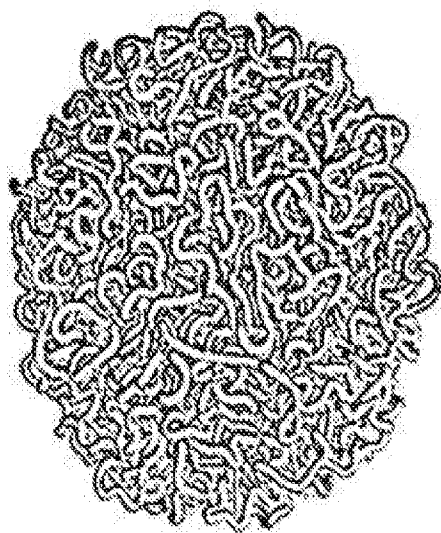


FIG. 5A

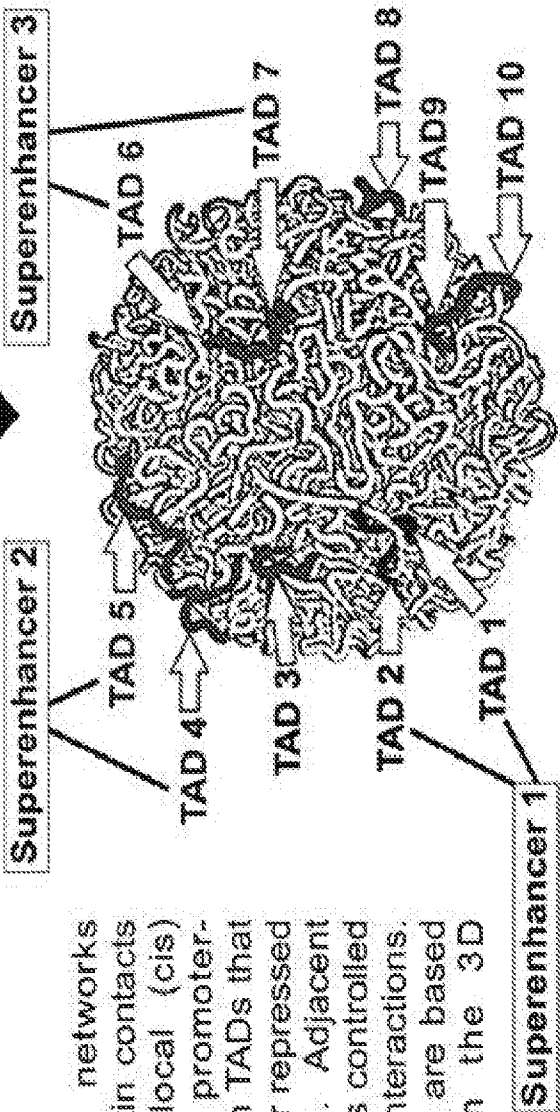


FIG. 5B

Chromatin is organized with the three-dimensional (3D) architecture of the human genome in a manner that resembles a "ball-of-yarn", including pre-existing and drug-induced changes in spatial contacts.

Drug pharmacogenomic networks consist of specific chromatin contacts that are comprised of local (cis) enhancer-promoter and promoter-promoter interactions within TADs that are activated (expanded) or repressed (contracted) by the drug. Adjacent TADs may have their genes controlled by superenhancers in cis-interactions. Distant (trans) interactions are based on spatial proximity in the 3D genome.

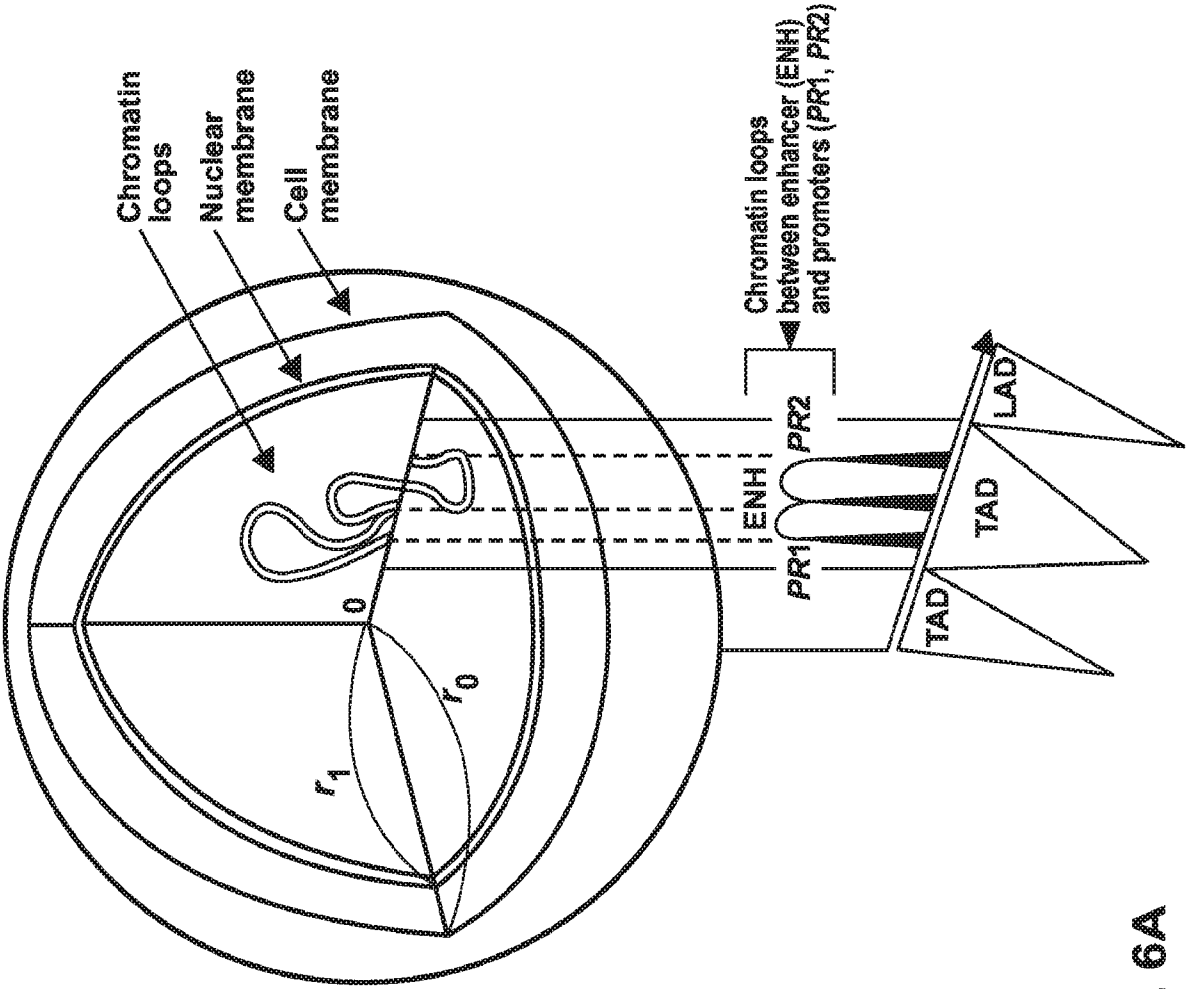
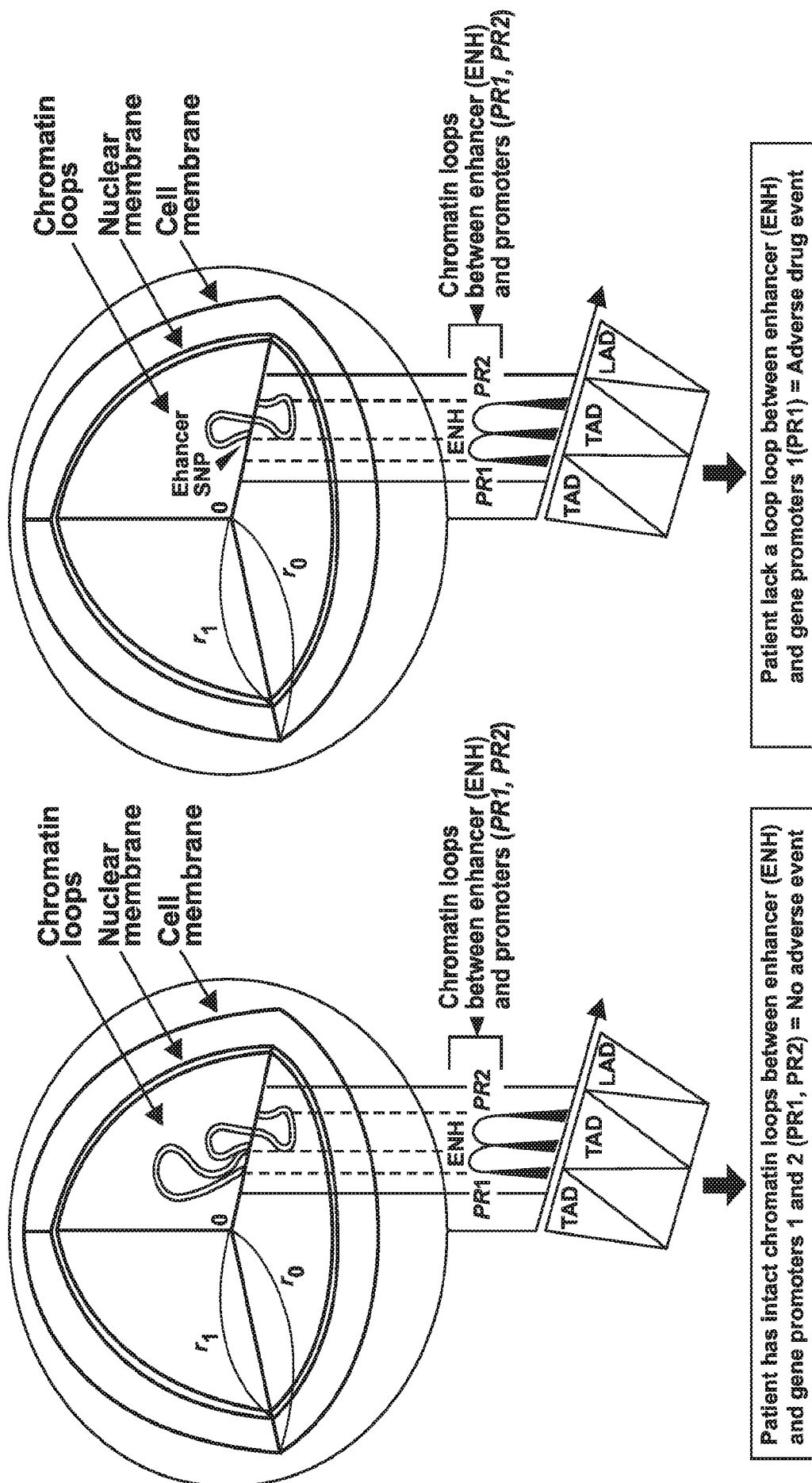


FIG. 6A

MEASURES

1. **Three-dimensional (3D) nuclear architecture:** Develop 3D model of cell type-specific nucleus, map drug-induced difference in chromatin contacts using Euclidian spatial coordinates (x, y, z). May be performed using FISH and high resolution microscopic analysis;
2. **Matrix mapping of TADs activated / repressed by input drug** using both chromosome conformation capture and gene expression methods. Convert for 2D for comparative analysis using deep learning;
3. Apply known chromosome conformation capture methods for inference of differential TAD activation / repression and chromatin loop contacts.



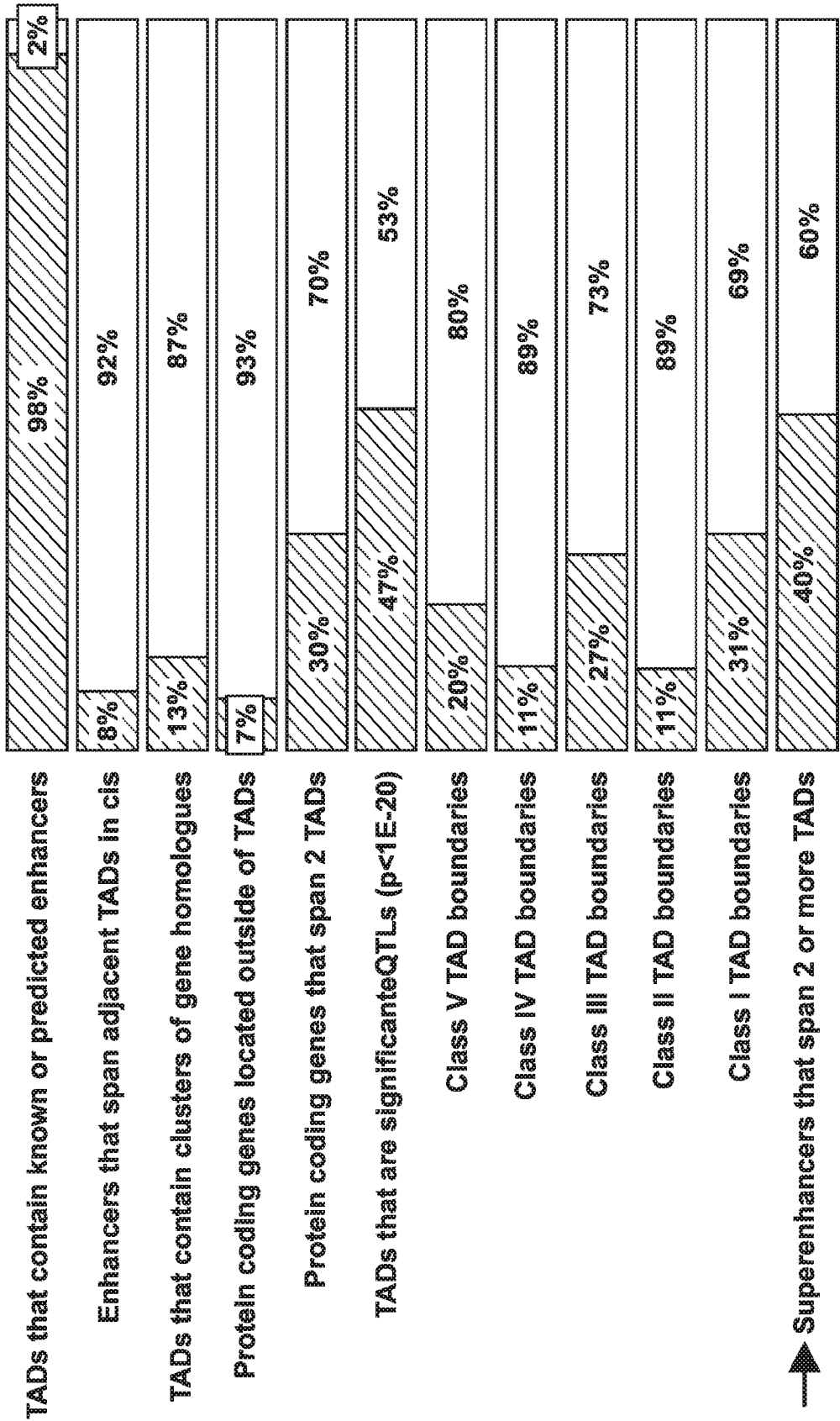


FIG. 7

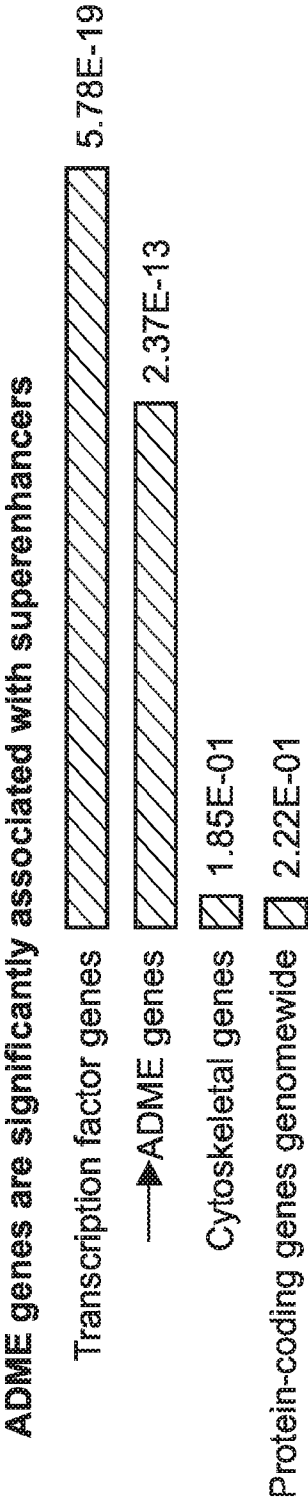


FIG. 8A

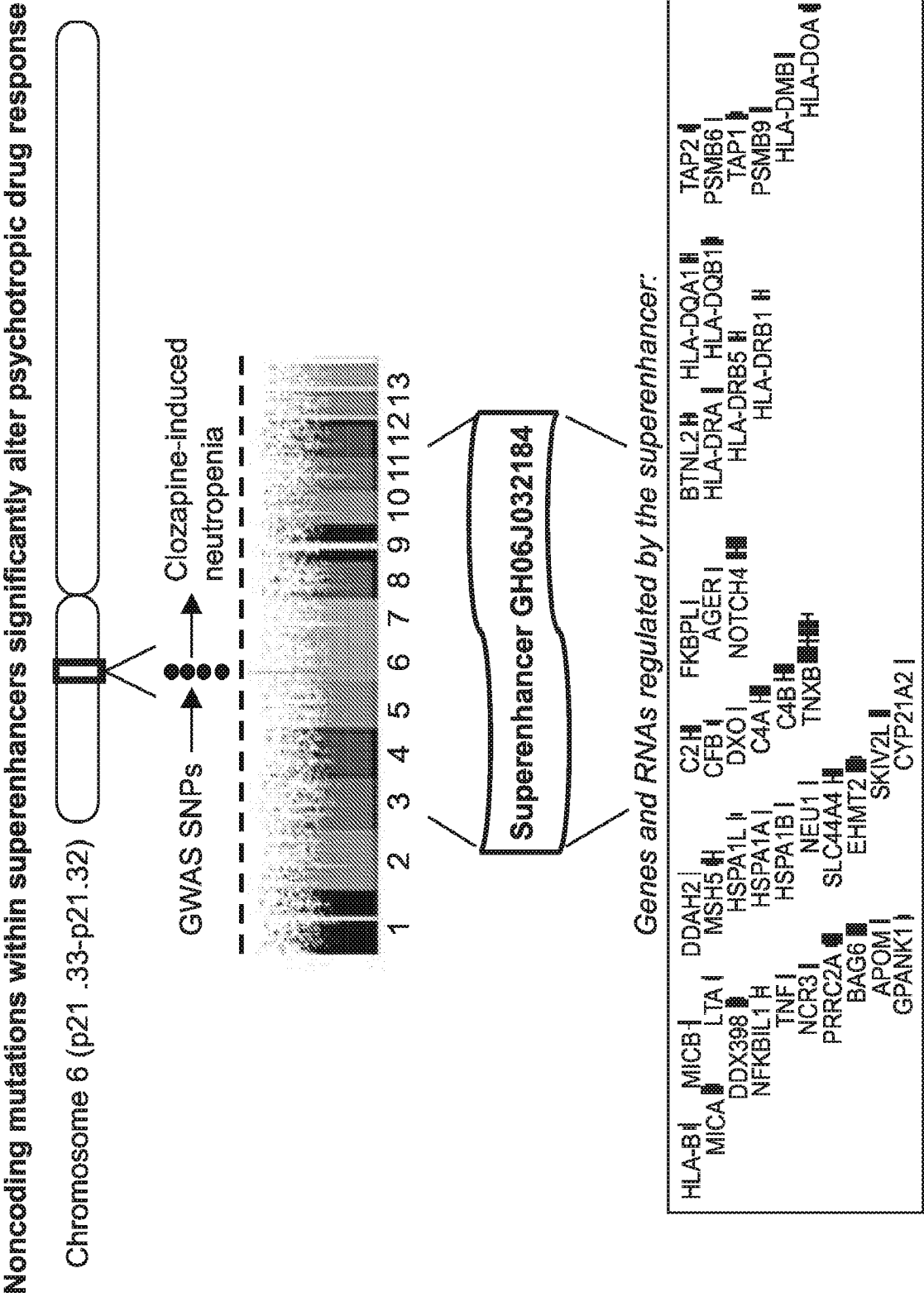


FIG. 8B

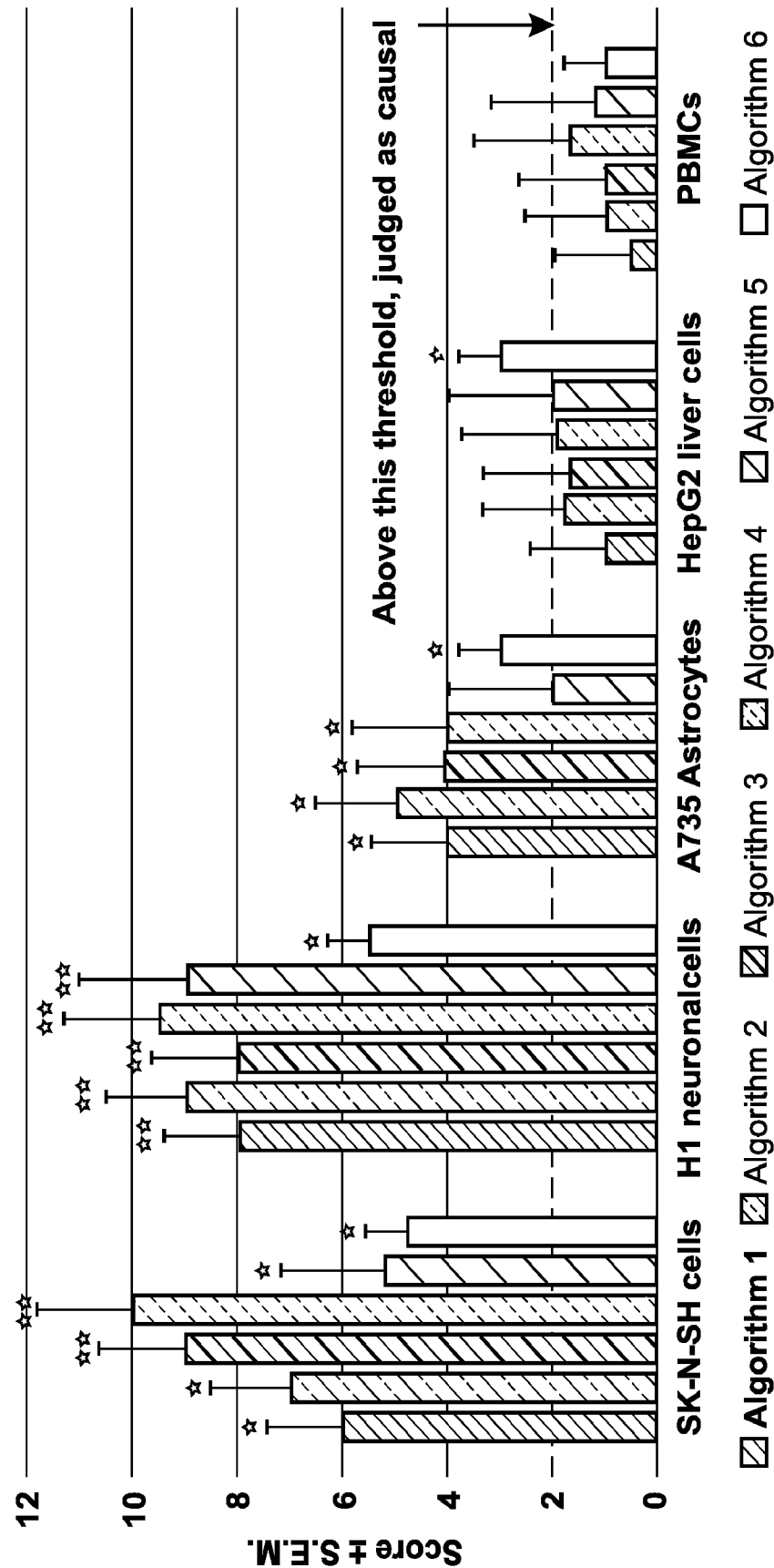


FIG. 9

GENES	TAD COORDINATES (Human GRch 37/hg19)	NUMBER OF GENES IN TAD	TAD SIZE	MOST SIGNIFICANT BIOLOGICAL PROCESS OF ENTIRE TAD	TAD BOUNDARY STRENGTH
EXAMPLES OF PHARMACOKINETIC GENES					
CYP1A1, CYP1A2, CYP11A1	15:74652947-75252947	17	600 KB	Dibenzo-p-dioxin metabolic process, P=9.4E-04	V
CYP2A6, CYP2A7, CYP2B6, CYP2A13, CYP2C9, CYP2C18, CYP2C19	19:41348160-4248160	24	1.08 MB	Epoxygenase P450 pathway, P=8.39E-10	V
CYP2C8, CYP2C9, CYP2C18, CYP2C19	10:96330010-98130010	18	1.8 MB	Omega-hydroxylase P450 pathway, P=6.55E-04	V
CYP2D6, CYP2D7	22:42030054-42950056	21	920 KB	Drug catabolic process, P=4.41E-03	III
CYP3A4, CYP3A5, CYP3A7	7:99042064-100482064	51	1.44 MB	Lipid hydroxylation, P=3.24E-03	V
CYP4F2, CYP4F3, CYP4F11, CYP4F12, CYP4F22	19:14619000-1633900	42	1.72 MB	Leukotriene metabolic process, P=1.56E-04	V
UGT1A1, UGT1A3, UGT1A4, UGT1A5, UGT1A7, UGT1A9, UGT1A10, UGT1A11	2:234375261-234735261	13	360 KB	Xenobiotic glucuronidation, P=3.0E-24	V
UGT2A3, UGT2B7, UGT2B10, UGT2B11	4:69590555-70085411	5	494 KB	Cellular glucuronidation, P=3.00E-05	V
UGT2A1, UGT2B4, UGT2B28, SULT1B1, SULT1E1	4:70085411-70841136	7	755 KB	Xenobiotic metabolic process, P=7.83E-09	V
SULT1A1, SULT1A2, SULT1A3, SULT1A4	16:27492499-28652499	24	2.4 MB	Xenobiotic metabolic process, P=5.63E-05	V
NAT1, NAT2	8:17795720-18675720	5	880 KB	Arylamine N-acetyltransferase activity, P=1.35E-04	V
EXAMPLES OF ADVERSE DRUG EVENT GENES					
HLA-DRA, HLA-DRB1, HLA-DRB5, HLA-DQA1, HLA-DQA2, HLA-DQB1, HLA-DQB2, HLA-DMA, HLA-DMB, HLA-DOA, HLA-DOB, HLA-DP1, HLA-DPB1	6:32172022-33252022	31	1.08 MB	Antigen processing and presentation of exogenous peptide antigen, P=2.69E-20	V
HCP5, HLA-A, HLA-B, HLA-C, MICA, MICB	6:30972499-31532499	21	560 KB	Antigen processing and presentation of exogenous peptide antigen, P=4.01E-09	V

FIG. 10

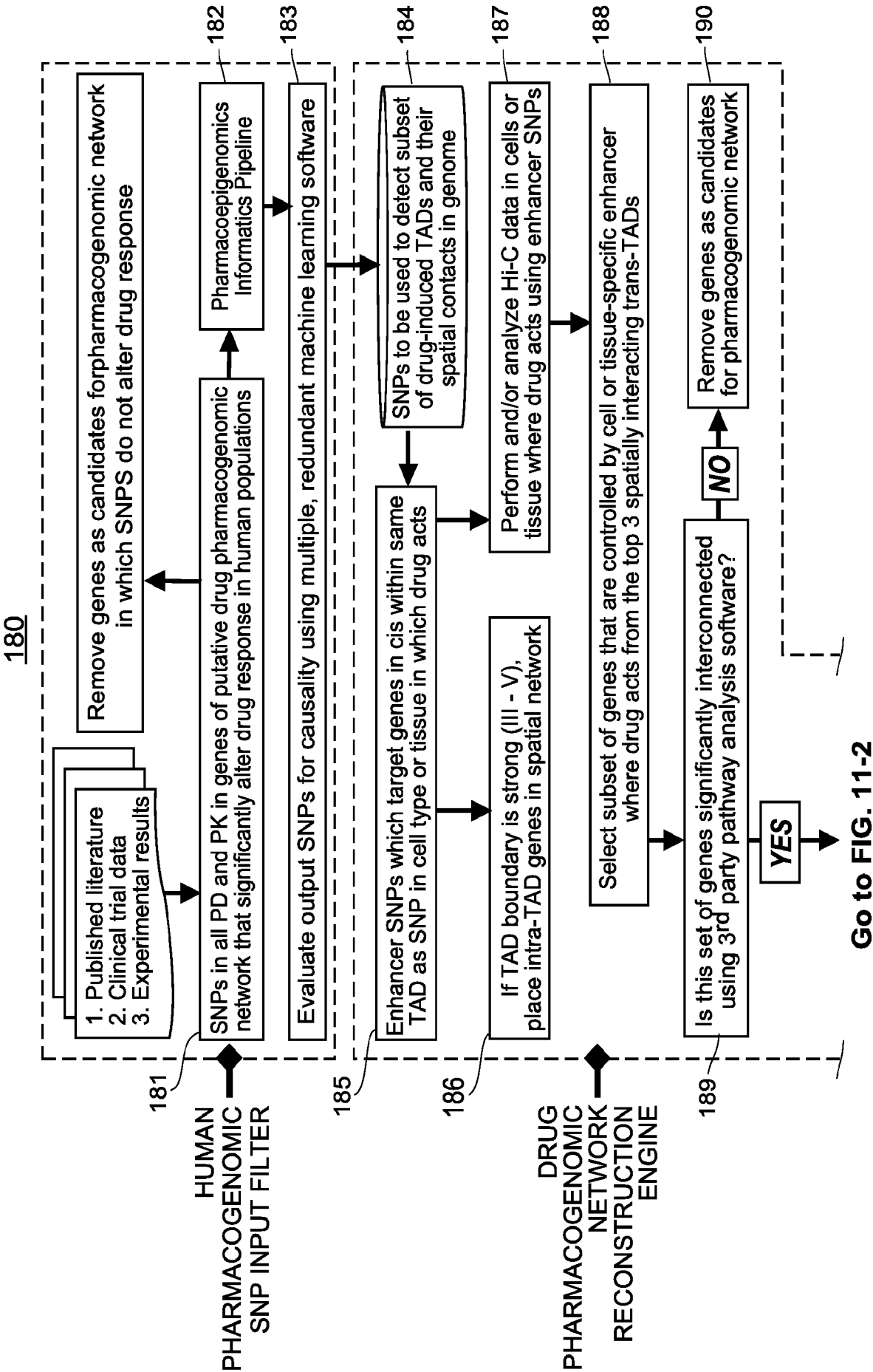
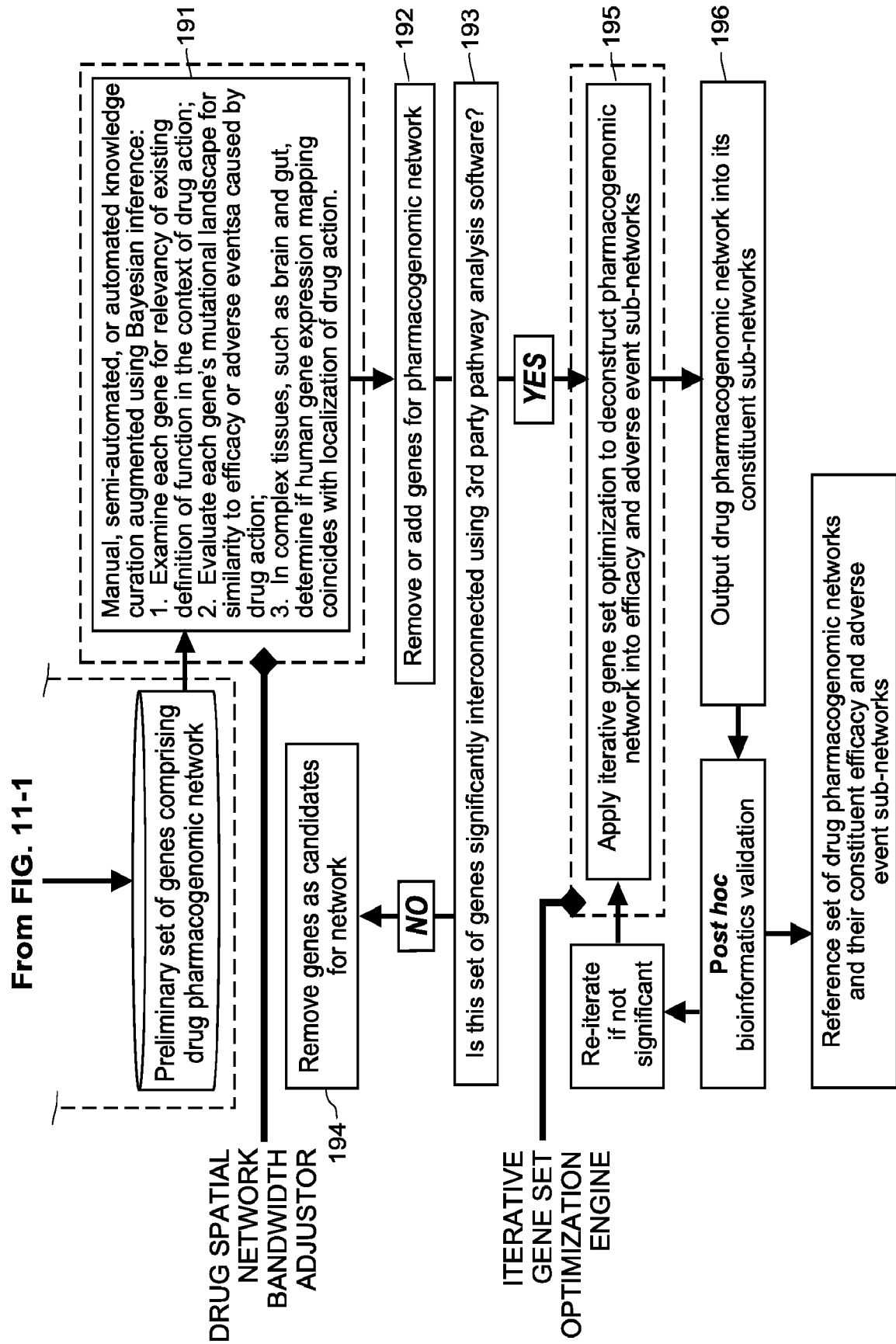


FIG. 11-1

**FIG. 11-2**

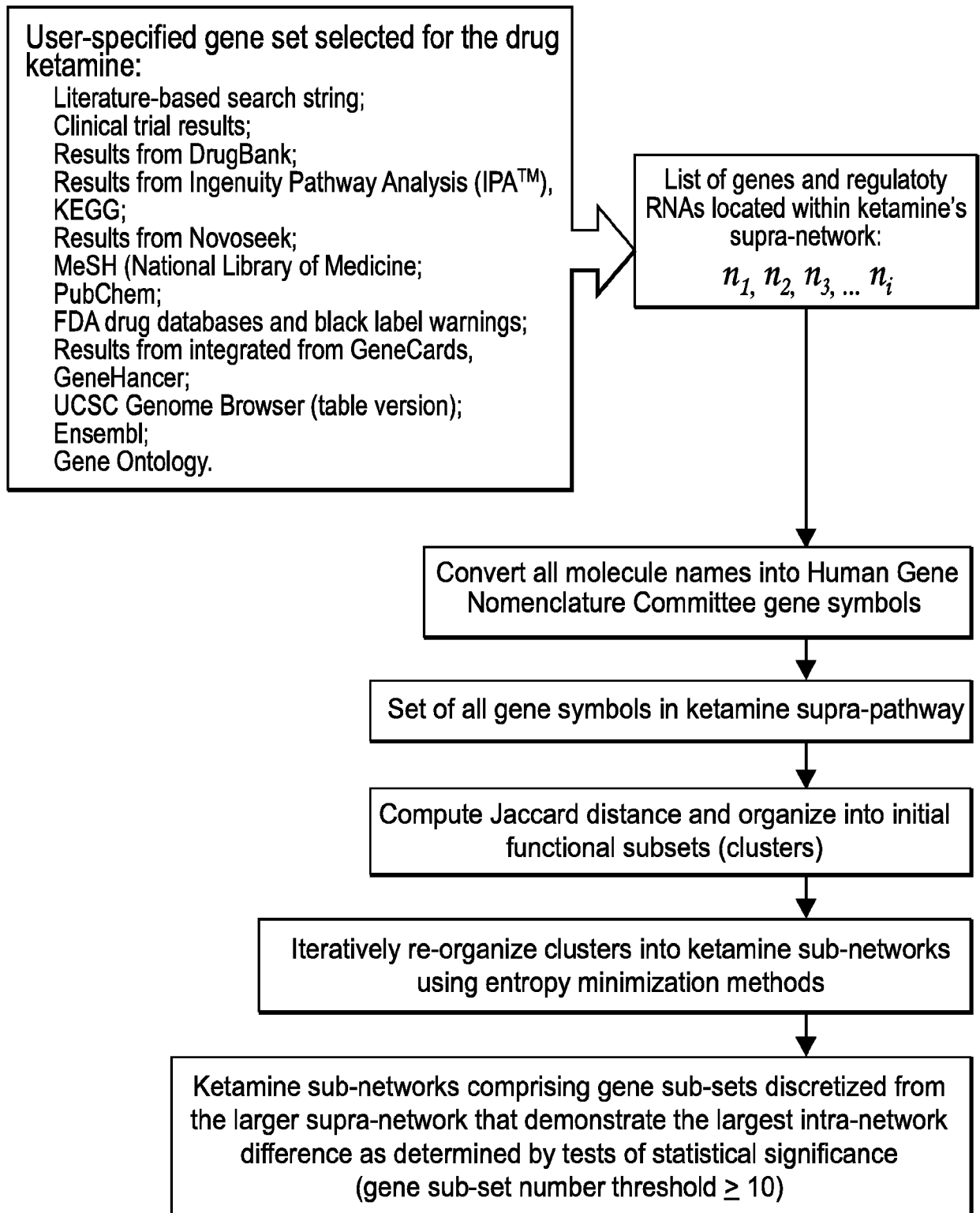


FIG. 12

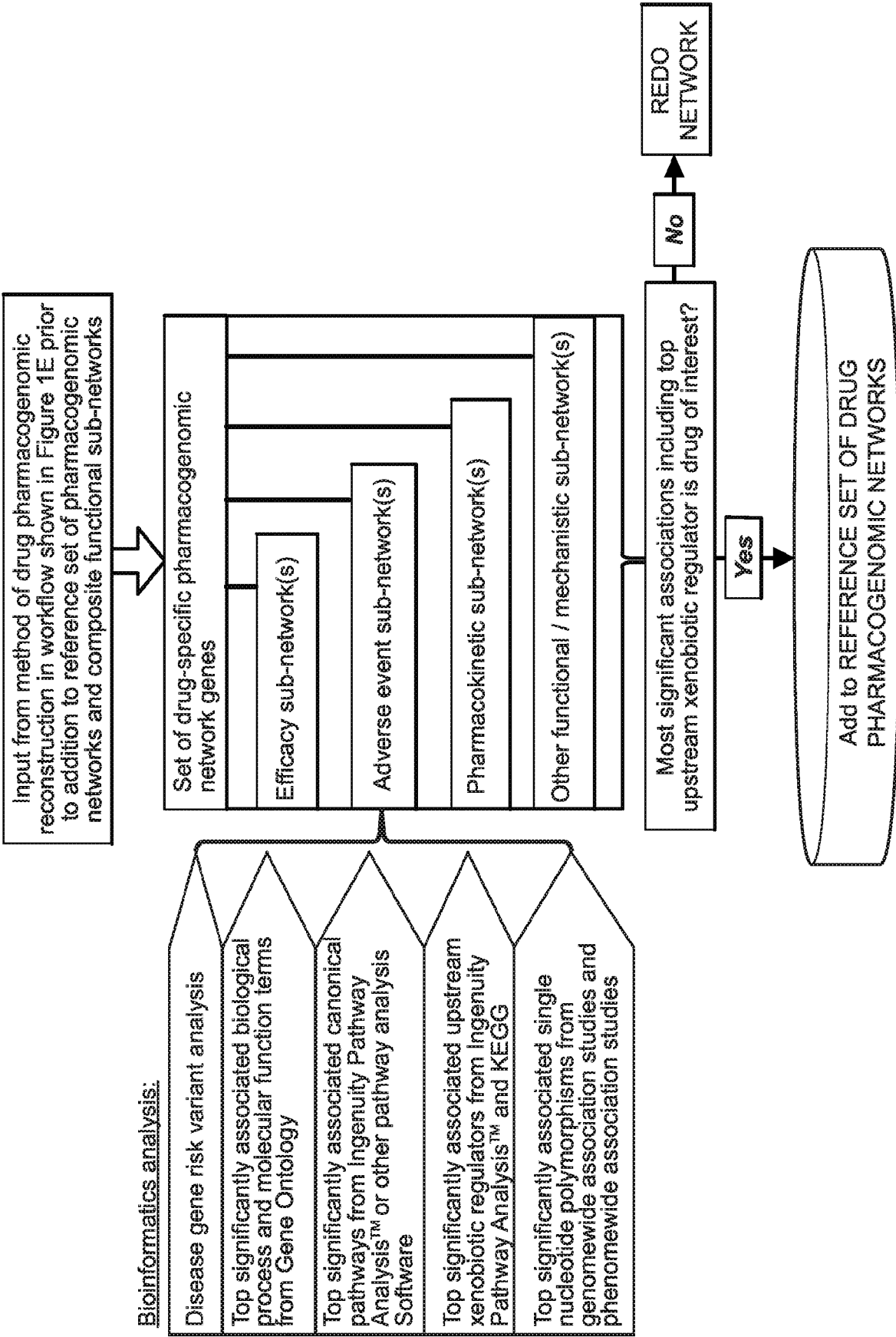


FIG. 13

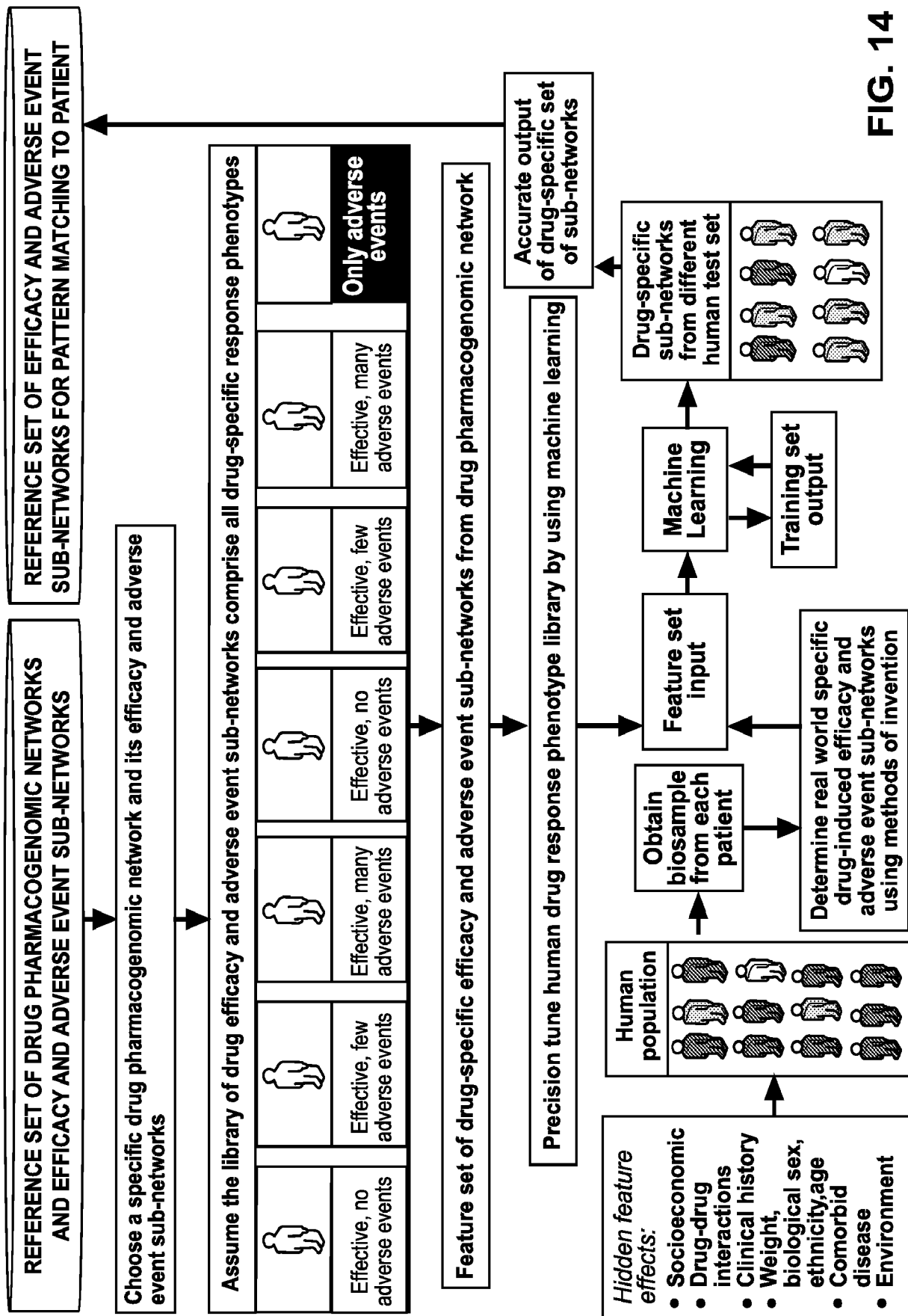


FIG. 14

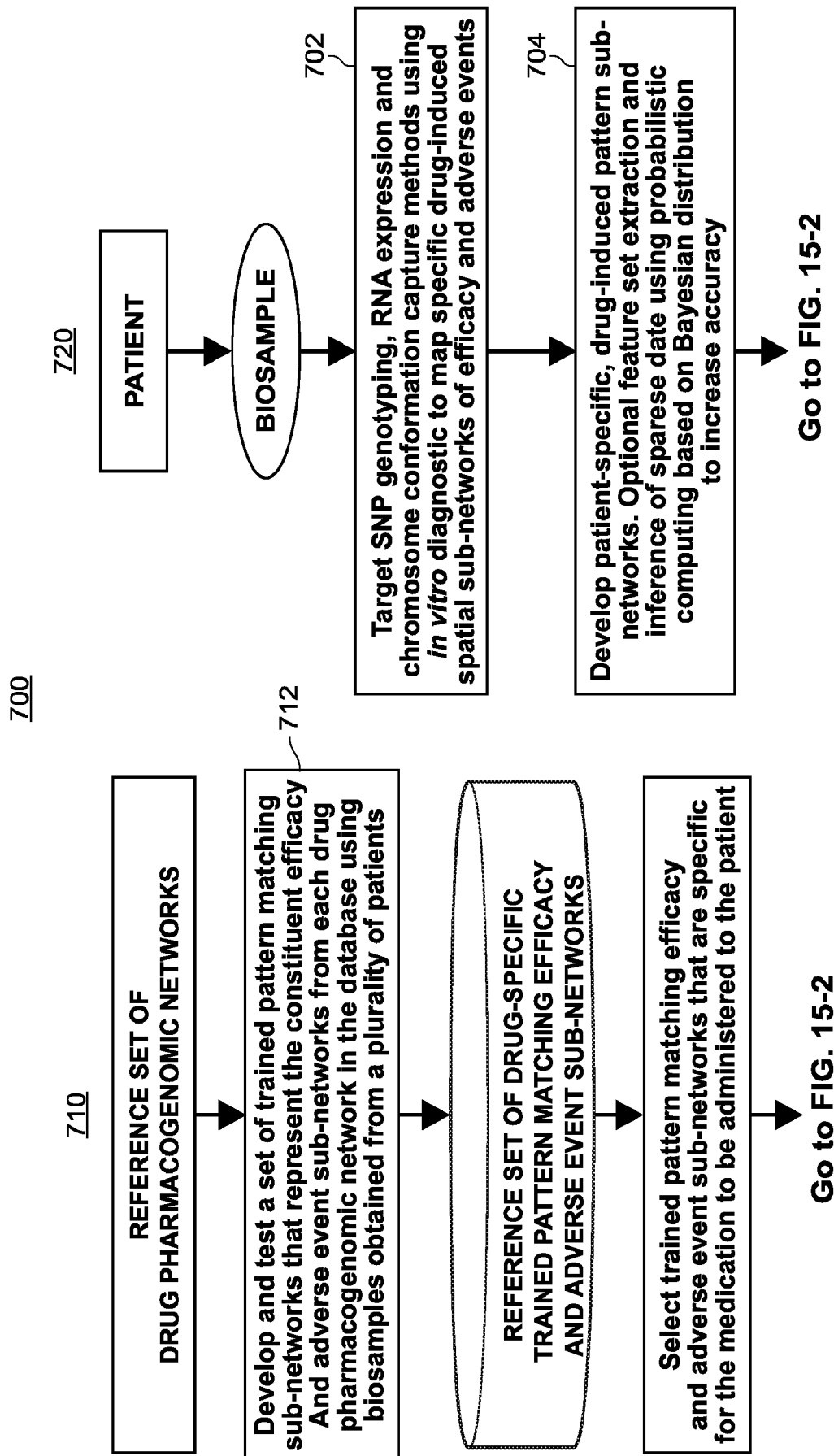


FIG. 15-1

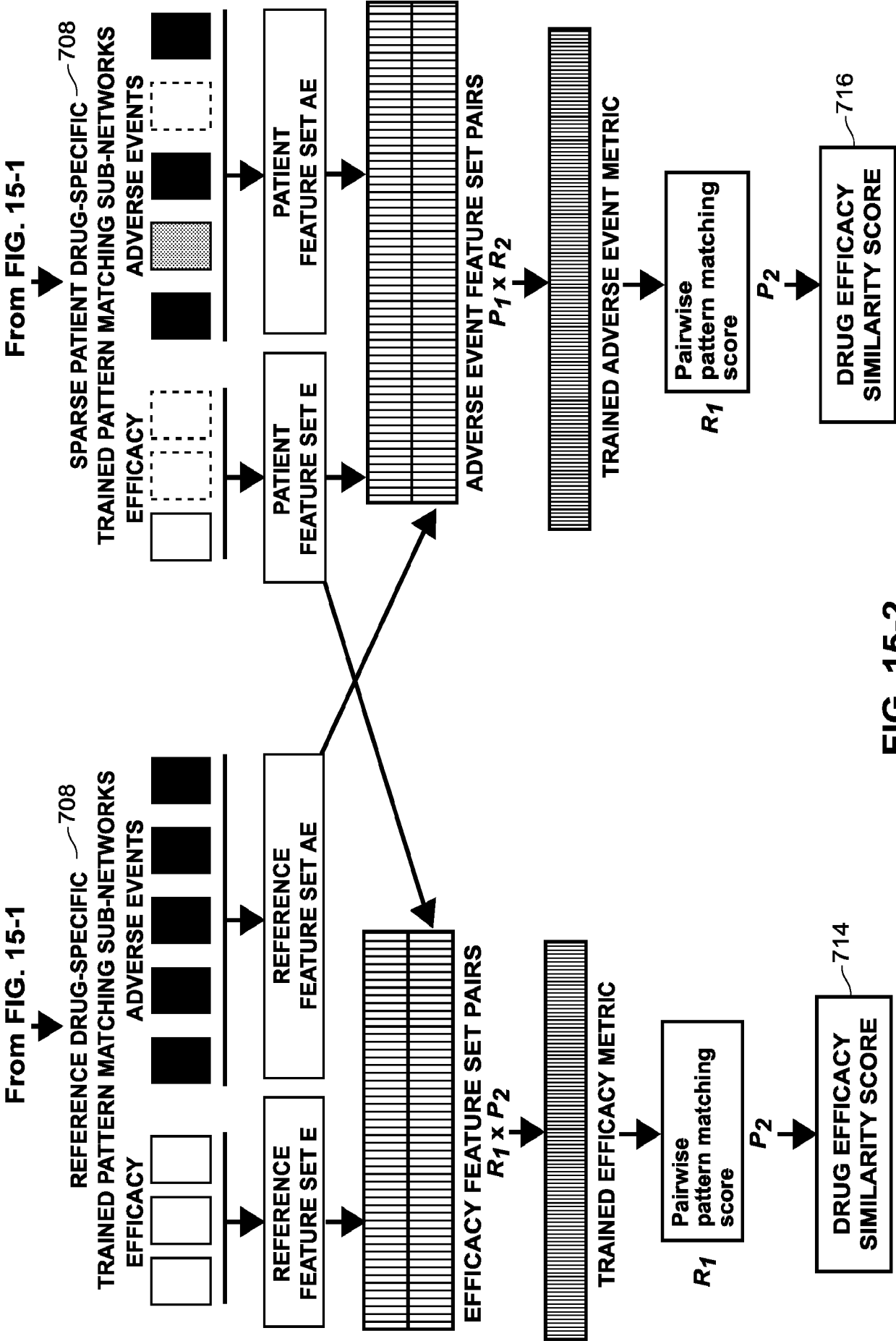


FIG. 15-2

800

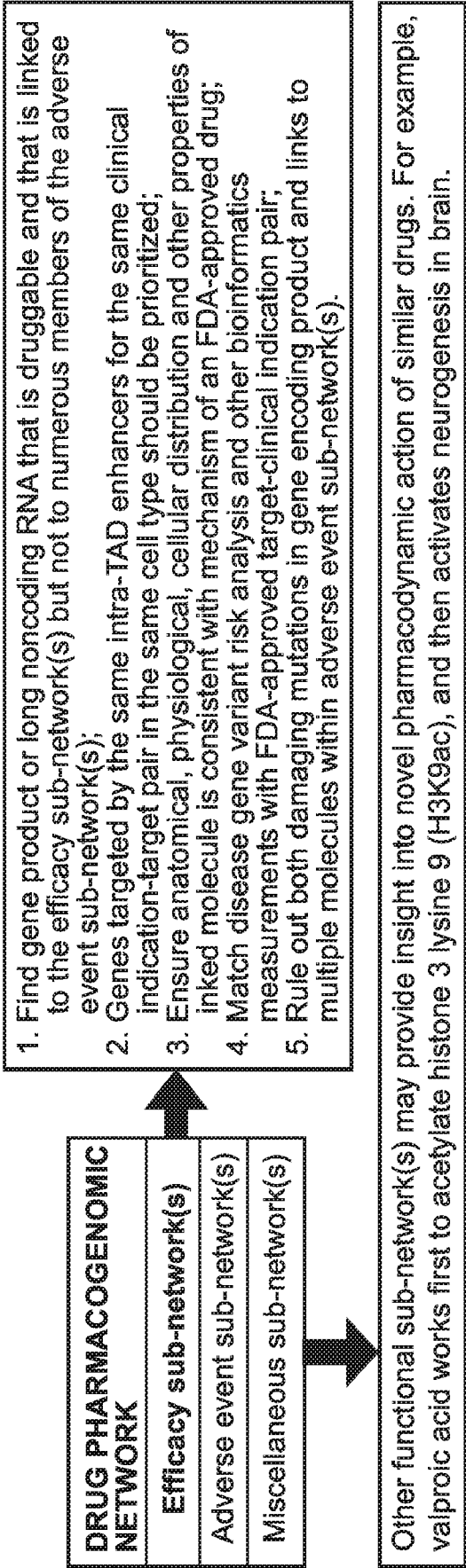


FIG. 16A

INTRA-TAD GENES CONTROLLED BY SAME ENHANCERS

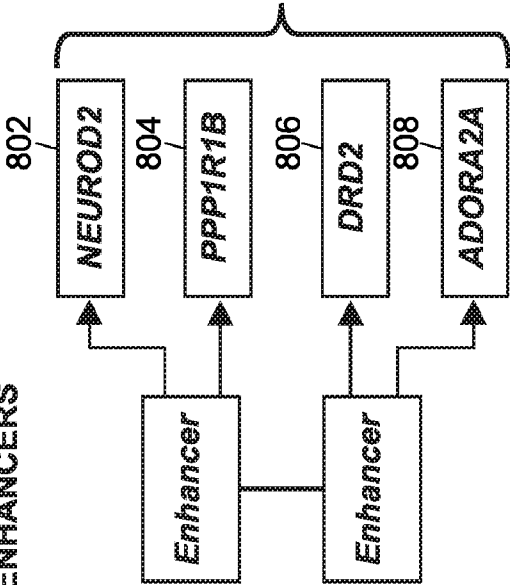
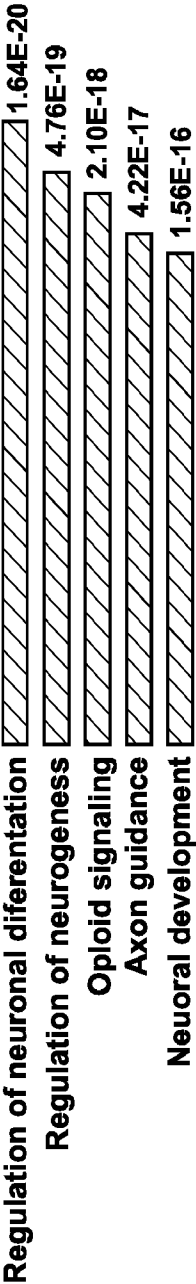


FIG. 16B

BIOINFORMATICS ANALYSIS OF PP1R1B GENE NETWORK — 810

Top Gene Ontology terms



Top canonical pathways

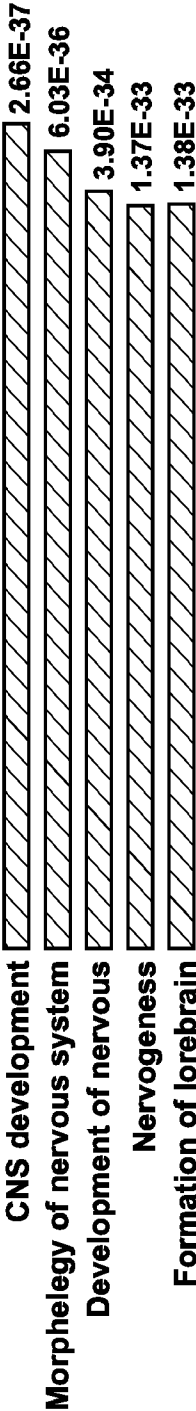


FIG. 16C

SAME PATTERNS OF GENE EXPRESSION IN THE HUMAN BRAIN: ANTERIOR CAUDATE, NUCLEUS ACCUMENS AND PUTAMEN

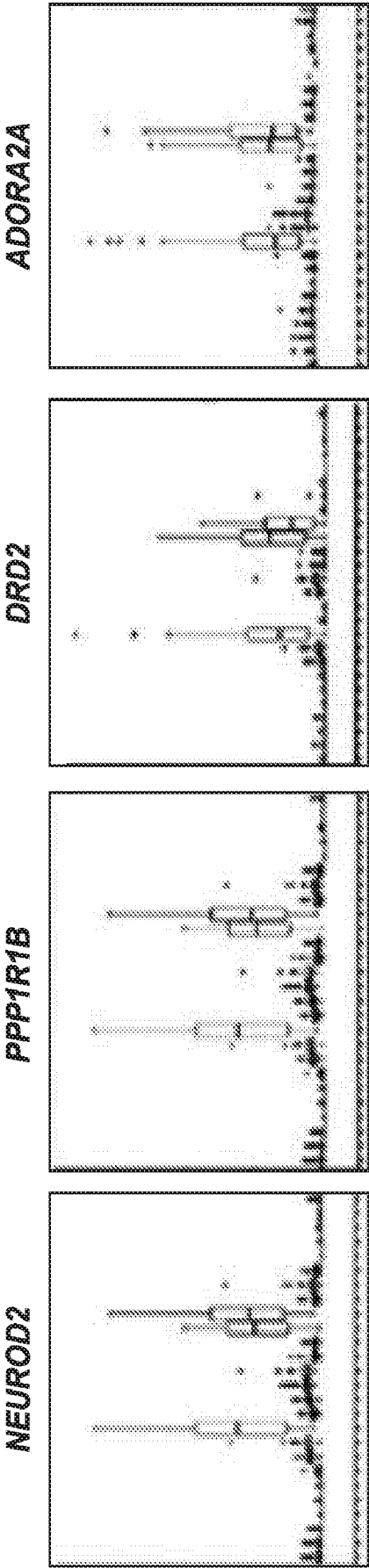


FIG. 16D

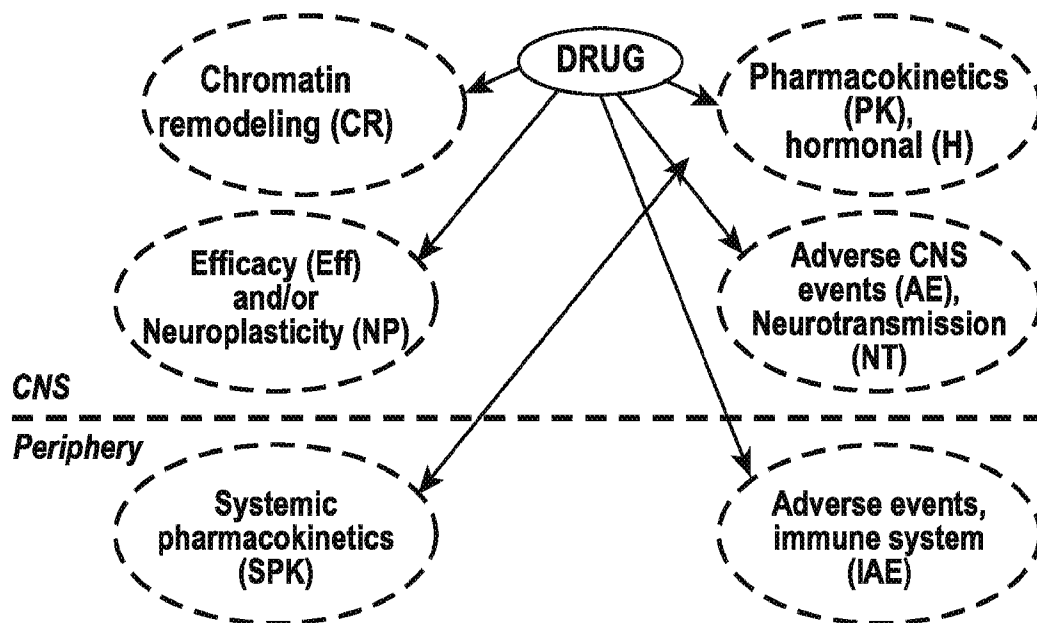
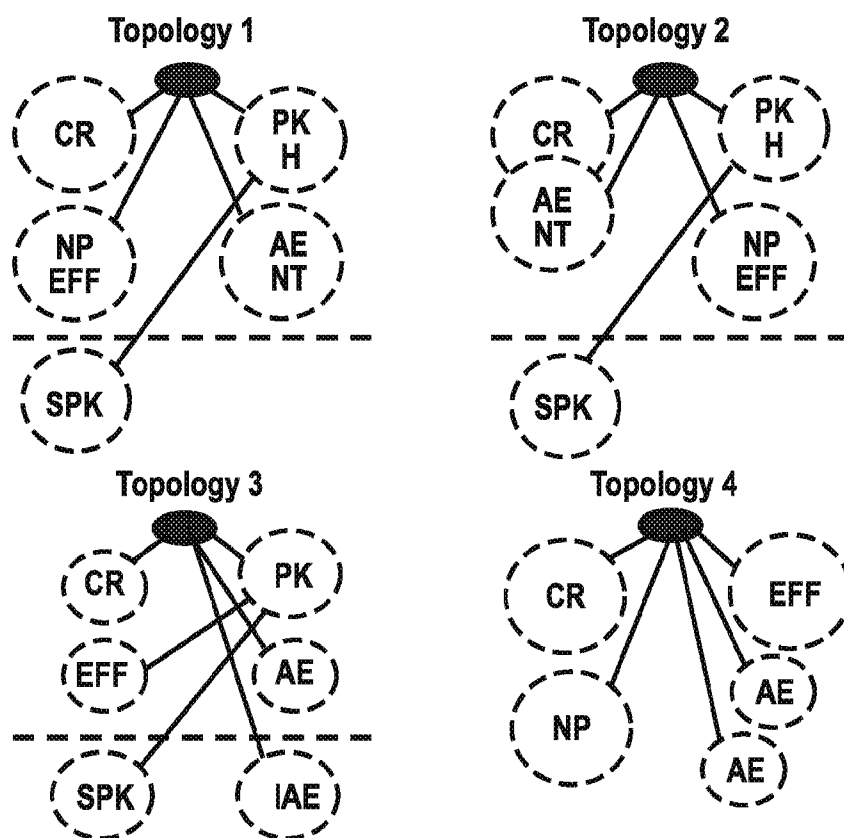


FIG. 17A



Medications, Topology 1	Medications, Topology 2	Medications, Topology 3	Medications, Topology 4
Valproic acid Bexarotene Trichostatin A	Ketamine Esketamine Lamotrigine	Clozapine Chlorpromazine Carbamazine	Lithium Lithium carbonate Fluoxetine

FIG. 17B



Neurogenesis and anti-epileptic, anti-mania and anti-migraine properties

Diseases Annotation	p-value of overlap
Epilepsy or neurodevelopmental disorder	2.19E-31
Cognitive impairment	5.29E-25
Mood disorders	1.35E-21
Migraine	1.78E-19
Mania	4.26E-19

FIG. 19A

Upstream Regulator	p-value of overlap
valproic acid	5.20E-114
trichostatin A	3.21E-35
nicotine	5.57E-21
curcumin	6.15E-20
lithium chloride	6.66E-15
clozapine	3.99E-11
morphine	5.32E-11
resveratrol	5.52E-11
lithium	1.02E-10
carbamazepine	5.93E-10

FIG. 19B

Network topology

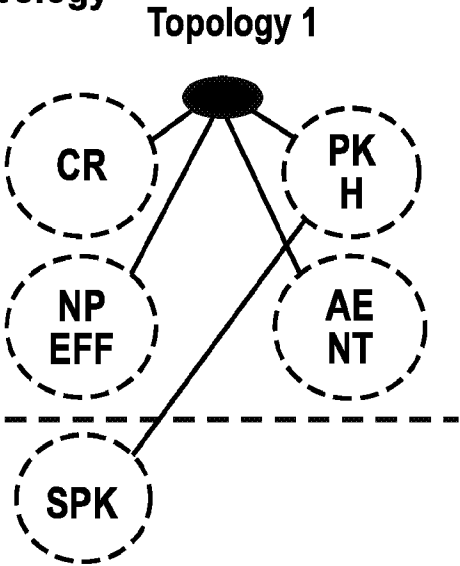
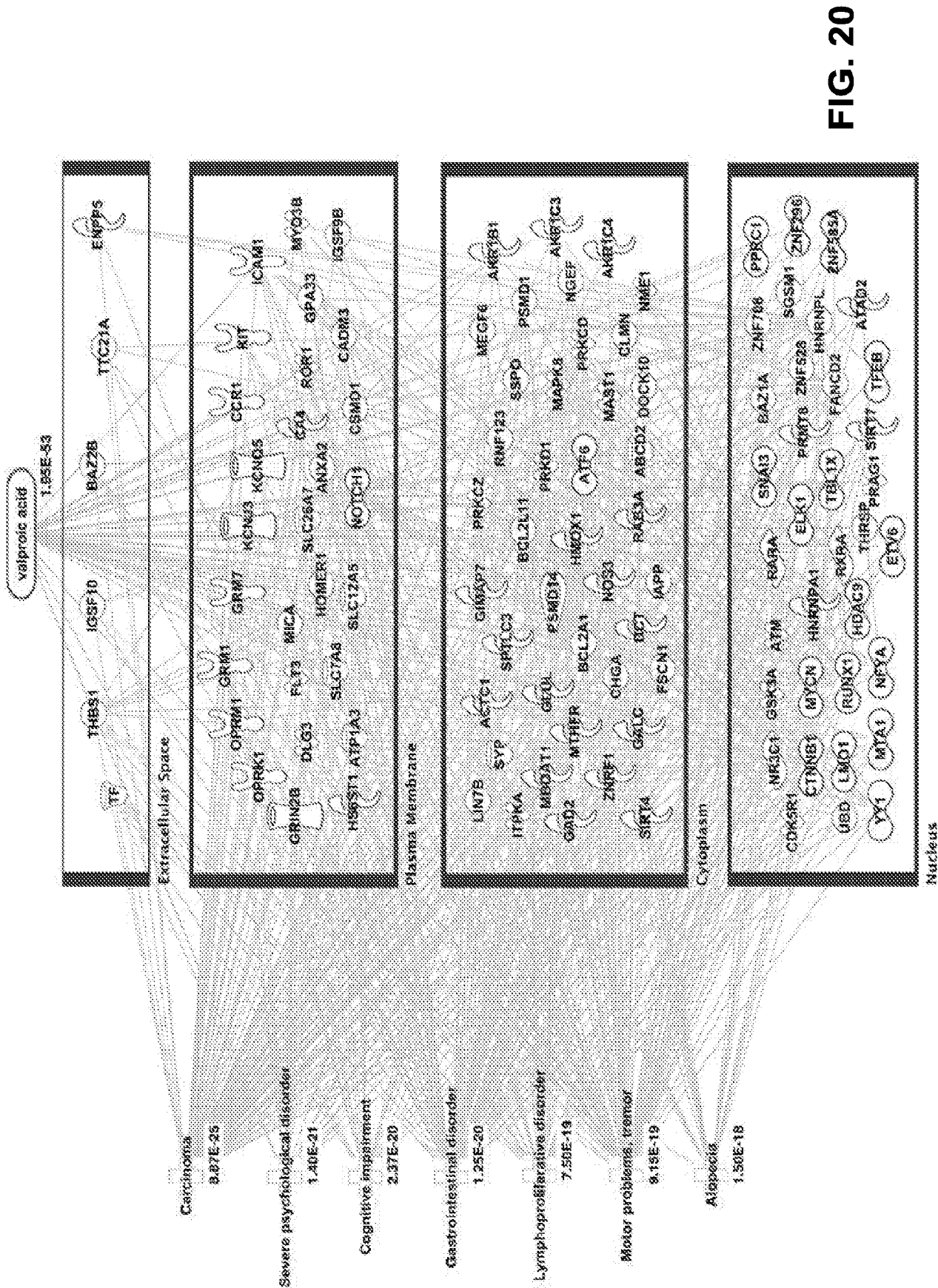
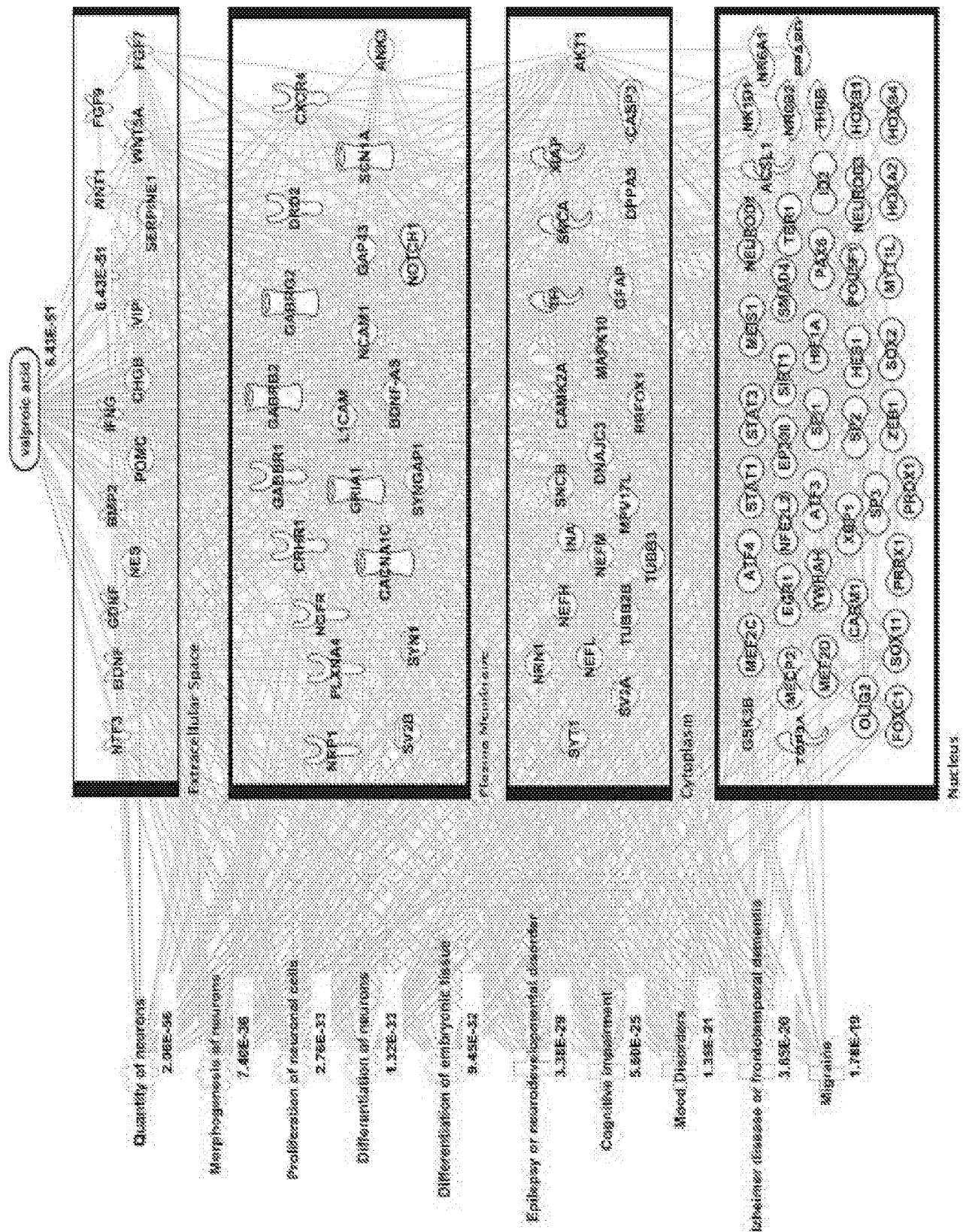


FIG. 19C





The valproic acid adverse event sub-network							
GWAS SNP	Populations	Gene(s)	Reported trait	Reported P-value	Enhancer, cell type	Hi-C score: Human brain	PMID
rs71530654	EUR	HDAC9	Alopecia	5E-70	Neuron	1E-10: Temporal cortex	28196072
rs13300218	EUR	NOTCH1	Inflammatory bowel disease	5E-29	Neuron	1E-10: Dorsal root	26192919
rs13300218	EUR	NOTCH1	Crohn's disease	7E-16	Neuron	1E-10: Dorsal root	26192919
rs13300218	EUR	NOTCH1	Ulcerative colitis	2E-10	Neuron	1E-10: Dorsal root	26192919
rs77945277	EUR	BAZ1A	Reduced efficacy, bupropion, bipolar depression	3E-08	Biopolar Neuron	1E-10: Cingulate cortex	27622933
rs34102224	EUR	CSMD1	Reduced efficacy, bupropion, bipolar depression	7E-06	Biopolar Neuron	1E-10: Frontal cortex	27622933
rs68088846	EUR	RUNX1	Alopecia	3E-19	Epithelial cell: Astrocyte	1E-10: Cingulate cortex	29146897

FIG. 22A

The valproic acid neurogenesis sub-network								
GWAS SNP	Populations	Gene(s)	Reported trait	Reported P-value	Enhancer, cell type	Hi-C score: Human brain	PMID	
rs1925950	EUR	MEF2D	Chronic migraine	9E-22	Neuron	1E-10: Cingulate cortex	27182965	
rs1050316	EUR	MEF2D	Headache	2E-11	Biopolar Neuron	1.00E-15: Temporal cortex	29397368	
rs6432877	EUR	SCN1A	Epilepsy	2E-13	Neuron	1E-05: Temporal cortex	30531953	
rs6732655	EUR	SCN1A	Epilepsy	9E-10	Biopolar Neuron	1E-05: Temporal cortex	30531953	
rs7587026	EUR	SCN1A	Epilepsy	3E-09	Neuron	1E-20: Temporal cortex	24014518	
rs1006737	EUR	CACNA1C	Bipolar I disorder (F31.0 - F31.64)	6E-13	Biopolar Neuron	1E-10: Cingulate cortex	24280982	
rs10744560	EUR	CACNA1C	Bipolar I disorder (F31.0 - F31.64)	4E-10	Biopolar Neuron	1E-10: Cingulate cortex	31043756	
rs10998815	EUR	ANK3	Bipolar I disorder (F31.0 - F31.64)	7E-11	Biopolar Neuron	1E-19: Frontal cortex	31096178	
rs10994338	EUR	ANK3	Bipolar I disorder (F31.0 - F31.64)	9E-09	Biopolar Neuron	1E-19: Frontal cortex	31096178	
rs1051730	ASN, EUR	XBP1	Efficacy, valproic acid in mania	6E-27	Neuron	1E-23: Frontal cortex	25910213	

FIG. 22B

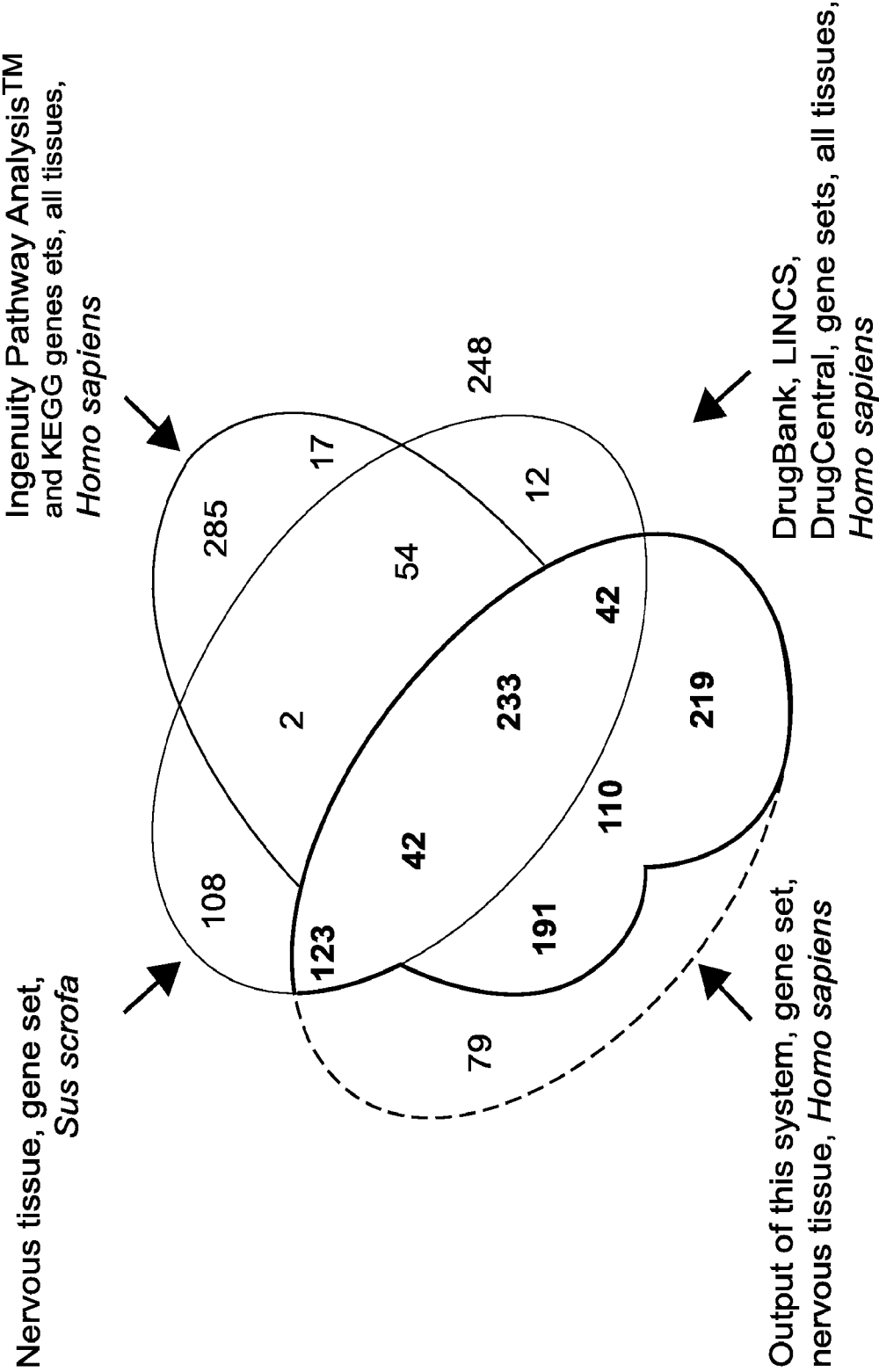


FIG. 23

Symbol	Entrez Gene Name
ACTL6A	actin like 6A
ACTL6B	actin like 6B
ARID1A	AT-rich interaction domain 1A
ARID1B	AT-rich interaction domain 1B
ARID2	AT-rich interaction domain 2
BCL11A	BAF chromatin remodeling complex subunit BCL11A
HDAC1	histone deacetylase 1
HDAC10	histone deacetylase 10
HDAC2	histone deacetylase 2
HDAC3	histone deacetylase 3
HDAC4	histone deacetylase 4
HDAC5	histone deacetylase 5
HDAC6	histone deacetylase 6
HDAC7	histone deacetylase 7
HDAC8	histone deacetylase 8
HDAC9	histone deacetylase 9
HST1H3G	histone cluster 1 H3 family member g
HST2H3C	histone cluster 2 H3 family member c
HST3H2A	histone cluster 3 H2A
HST3H2BB	histone cluster 3 H2B family member b
HST4H4	histone cluster 4 H4
INO80	INO80 complex subunit
PBRM1	polybromo 1
SMARCA2	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a, member 2
SMARCA4	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a, member 4
SMARCB1	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily b, member 1
SMARCC1	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily c, member 1
SMARCD1	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily d, member 1
SMARCD2	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily d, member 2
SMARCE1	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily e, member 1
SOX10	SRY-box 10
SS18L1	SS18L1 subunit of BAF chromatin remodeling complex
ST18	ST18, C2HC-type zinc finger

FIG. 24

Symbol	Entrez Gene Name
ACSL1	acyl-CoA synthetase long chain family member 1
AKT1	AKT serine/threonine kinase 1
ANK3	ankyrin 3
ATF3	activating transcription factor 3
ATF4	activating transcription factor 4
BDNF	brain derived neurotrophic factor
BDNF-AS	BDNF antisense RNA
BMP2	bone morphogenetic protein 2
CACNA1C	calcium voltage-gated channel subunit alpha 1 C
CAMK2A	calcium/calmodulin dependent protein kinase II alpha
CARM1	coactivator associated arginine methyltransferase 1
CASP3	caspase 3
CCL2	C-C motif chemokine ligand 2
CHGB	chromogranin B
CRHR1	corticotropin releasing hormone receptor 1
CXCR4	C-X-C motif chemokine receptor 4
DNAJC3	DnaJ heat shock protein family Hsp40) member C3
DRD1	dopamine receptor D2
EGR1	early growth response 1
EP300	E1A binding protein p300
FGF7	fibroblast growth factor 7
FGF9	fibroblast growth factor 9
FOXC1	forkhead box C1
FRS2	fibroblast growth factor receptor substrate 2
GABBR1	gamma-aminobutyric acid type B receptor subunit 1
GABRB2	gamma-aminobutyric acid type A receptor beta2 subunit
GABRG2	gamma-aminobutyric acid type A receptor gamma2 subunit
GAP43	growth associated protein 43
GDNF	glial cell derived neurotrophic factor
GFAP	glial fibrillary acidic protein
GRIA1	glutamate ionotropic receptor AMPA type subunit 1
GSK3B	glycogen synthase kinase 3 beta
HES1	hes family bHLH transcription factor 1
HIF1A	hypoxia inducible factor 1 subunit alpha
HOXA2	homeobox A2
HOXB1	homeobox B1
HOXB4	homeobox B4
ID2	inhibitor of DNA binding 2
INA	internexin neuronal intermediate filament protein alpha
KIT	KIT proto-oncogene, receptor tyrosine kinase
L1CAM	L1 cell adhesion molecule
MAPK10	mitogen-activated protein kinase 10
MECP2	methyl-CpG binding protein 2
MEF2C	myocyte enhancer factor 2C
MEF2D	myocyte enhancer factor 2D
MEIS1	Meis homeobox 1
MYT1L	myelin transcription factor 1 like
NCAM1	neural cell adhesion molecule 1
NEFH	neurofilament heavy

FIG. 25A

NEFL	neurofilament light
NEFM	neurofilament medium
NES	nestin
NEUROD1	neuronal differentiation 1
NEUROG3	neurogenin 3
NFE2L2	nuclear factor, erythroid 2 like 2
NOTCH1	notch receptor 1
NR0B2	nuclear receptor subfamily 0 group B member 2
NR1D1	nuclear receptor subfamily 1 group D member 1
NR6A1	nuclear receptor subfamily 6 group A member 1
NRN1	neuritin 1
NTF3	neurotrophin 3
OLIG2	oligodendrocyte transcription factor 2
PAX6	paired box 6
PLXNA4	plexin A4
POMC	proopiomelanocortin
POU5F1	POU class 5 homeobox1
PPARD	Peroxisome proliferator activated receptor delta
PROX1	prospero homeobox 1
PRRX1	paired related homeobox 1
RBFOX1	RNA binding fox-1 homolog 1
RUNX1	runt related transcription factor 1
SCN1A	sodium voltage-gated channel alpha subunit 1
SERPINE1	serpin family E member 1
SIRT1	sirtuin 1
SMAD4	SMAD family member 4
SNCA	synuclein alpha
SNCB	synuclein beta
SOX11	SRY-box 11
SOX2	SRY-box 2
SP2	Sp2 transcription factor
SP3	Sp3 transcription factor
SPI1	Spi-1 proto-oncogene
STAT1	signal transducer and activator of transcription 1
STAT3	signal transducer and activator of transcription 3
SV2A	synaptic vesicle glycoprotein 2A
SV2B	synaptic vesicle glycoprotein 2B
SYN1	synapsin I
SYNGAP1	synaptic Ras GTPase activating protein 1
SYT1	synaptotagmin 1
TBR1	T-box, brain 1
TH	tyrosine hydroxylase
THRB	thyroid hormone receptor beta
TOP2A	DNA topoisomerase II alpha
TUBB2B	tubulin beta 2B class IIb
TUBB3	tubulin beta 3 class III
VIP	vasoactive intestinal peptide
WNT1	Wnt family member 1
WNT5A	Wnt family member 5A
XIAP	X-linked inhibitor of apoptosis
XBP1	X-box binding protein 1
YWHAH	tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein eta
ZEB1	zinc finger E-box binding homeobox 1

FIG. 25B

Symbol	Entrez Gene Name
ABCD2	ATP binding cassette subfamily D member 2
ACTC1	actin alpha cardiac muscle 1
ALR1B1	aldo-keto reductase family 1 member B
AKR1C3	aldo-keto reductase family 1 member C3
AKR1C4	aldo-keto reductase family 1 member C4
ANXA2	annexin A2
ATAD2	ATPase family AAA domain containing 2
ATF3	activating transcription factor 3
ATF4	activating transcription factor 4
ATF6	activating transcription factor 6
ATM	ATM serine/threonine kinase
ATP1A3	ATPase Na ⁺ /K ⁺ transporting subunit alpha 3
BAZ1A	bromodomain adjacent to zinc finger domain 1A
BAZ2B	bromodomain adjacent to zinc finger domain 2B
BCL2A1	BCL2 related protein A1
BCL2L11	BCL2 like 11
BRDT	bromodomain testis associated
CA4	carbonic anhydrase 4
CADM3	cell adhesion molecule 3
CARM1	coactivator associated arginine methyltransferase
CCR1	C-C motif chemokine receptor 1
CDK5R1	cyclin dependent kinase 5 regulatory subunit 1
CEBPA	CCAAT enhancer binding protein alpha
CHAF1B	chromatin assembly factor 1 subunit B
CHGA	chromogranin A
CLMN	calmin
DCT	dopachrome tautomerase
DLG3	discs large MAGUK scaffold protein 3
DOCK10	dedicator of cytokinesis 10
EDNRB	endothelin receptor type B
ELK1	ETS transcription factor ELK1
ENPP5	econucleotide pyrophosphatase/phosphodiesterase 5 (putative)
EP300	E1A binding protein p300
ETV6	ETS variant 6
FLT3	fms related tyrosine kinase 3
FSCN1	fascin actin-bundling protein 1
GAD2	glutamate decarboxylase 2
GALC	galactosylceramidase
GLUL	glutamate-ammonia ligase
GRIN2B	glutamate ionotropic receptor NMDA type subunit 2B
GRM1	glutamate metabotropic receptor 1
GRM7	glutamate metabotropic receptor 7
GSK3A	glycogen synthase kinase 3 alpha
HMOX1	heme oxygenase 1
HNRNPA1	heterogeneous nuclear ribonucleoprotein A1
HOMER1	homer scaffold protein 1
HS6ST1	heparan sulfate 6-O-sulfotransferase 1
IAPP	islet amyloid polypeptide precursor

FIG. 26-1

ICAM1	intercellular adhesion molecule 1
ITPKA	inositol-trisphosphate 3-kinase A
KAT2A	lysine acetyltransferase 2A
KCNJ11	potassium voltage-gated channel subfamily J member 11
KCNJ3	potassium voltage-gated channel subfamily J member 3
KCNQ5	potassium voltage-gated channel subfamily Q member 5
KIT	KIT proto-oncogene, receptor tyrosine kinase
KMT2A	lysine methyltransferase 2A
LIN7B	lin-7 homolog B, crumbs cell polarity complex component
LMO1	LIM domain only 1
MAPK8	mitogen-activated protein kinase 8
MAST1	microtubule associated serine/threonine kinase 1
MBOAT1	membrane bound O-acyltransferase domain containing 1
MICA	MHC class I polypeptide sequence A
MTA1	metastasis associated 1
MTHFR	methylenetetrahydrofolate reductase
MYCN	MYCN proto-oncogene, bHLH transcription factor
NFYA	nuclear transcription factor Y subunit alpha
NGEF	neuronal guanine nucleotide exchange factor
NME1	NME/NM23 nucleoside diphosphate kinase 1
NOS3	nitric oxide synthase 3
NR3C1	nuclear receptor subfamily 3 group C member 1
OPRK1	opioid receptor kappa 1
OPRM1	opioid receptor mu 1
PPRC1	peroxisome proliferator-activated receptor gamma, coactivator-related 1
PREG1	PEAK1 related, kinase-activating pseudokinase 1
PRKCD	protein kinase C delta
PRKCZ	protein kinase C zeta
PRKD1	protein kinase D1
PRMT8	protein arginine methyltransferase 8
PSMD1	proteasome26S subunit, non-ATPase 1
PSMD14	proteasome26S subunit, non-ATPase 14
RAB3A	RAB3A, member RAS oncogene family
RARA	retinoic acid receptor alpha
RUNX1	runt related transcription factor 1
ROR1	receptor tyrosine kinase like orphan receptor 1
RXRA	retinoid X receptor alpha
SERPINH1	serpin family H member 1
SIRT4	sirtuin 4
SIRT7	sirtuin 7
SLC12A5	solute carrier family 12 member 5
SLC7A8	solute carrier family 7 member 8
SYN	synaptophysin
TBL1X	transcription beta like 1 X-linked
TF	transferrin
TFEB	transcription factor EB
THBS1	thrombospondin 1
UBD	ubiquitin D
YY1	YY1 transcription factor
ZNF296	zinc finger protein 296
ZNF585A	zinc finger protein 585A
ZNRF1	zinc and ring finger 1

FIG. 26-2

Symbol	Entrez Gene Name
<i>AR</i>	androgen receptor
<i>CYP2B6</i>	cytochrome P450 family 2subfamily B member 6
<i>CYP2C8</i>	cytochrome P450 family 2subfamily C member 8
<i>CYP2C9</i>	cytochrome P450 family 2subfamily C member 9
<i>ESR1</i>	estrogen receptor 1
<i>UGT1A1</i>	UDP glucuronosyltransferase family 1 member A1
<i>UGT1A3</i>	UDP glucuronosyltransferase family 1 member A3
<i>UGT1A4</i>	UDP glucuronosyltransferase family 1 member A4
<i>UGT1A6</i>	UDP glucuronosyltransferase family 1 member A6
<i>UGT2B17</i>	UDP glucuronosyltransferase family 2 member B17
<i>UGT2B7</i>	UDP glucuronosyltransferase family 2 member B7

FIG. 27

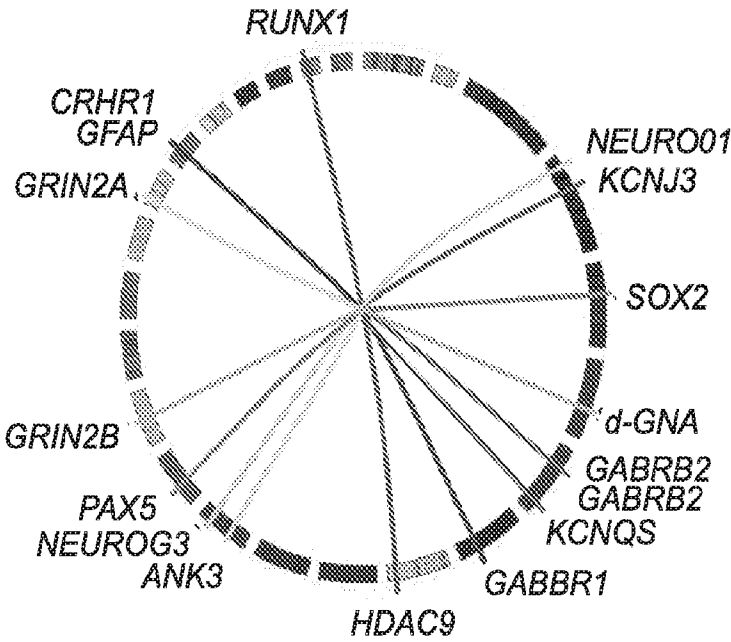


FIG. 28A

FIG. 28B

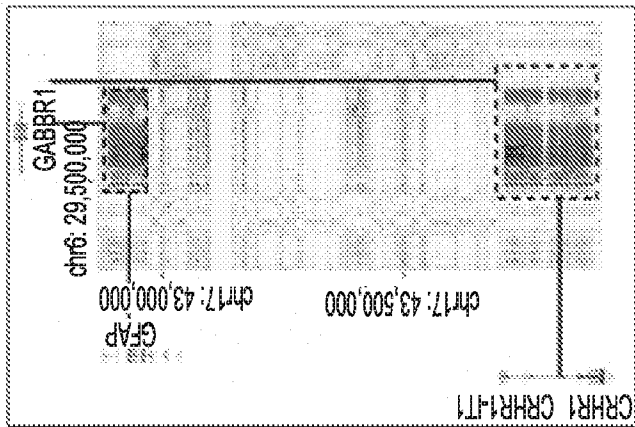


FIG. 28C

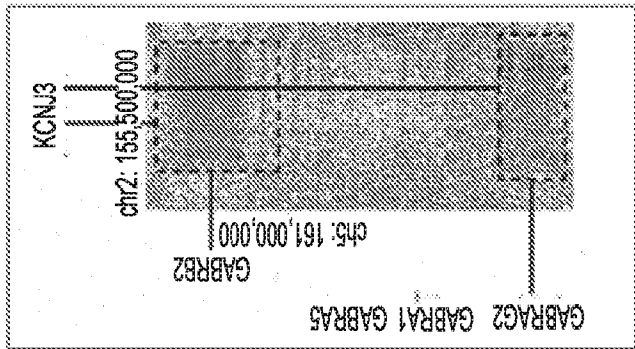


FIG. 28D

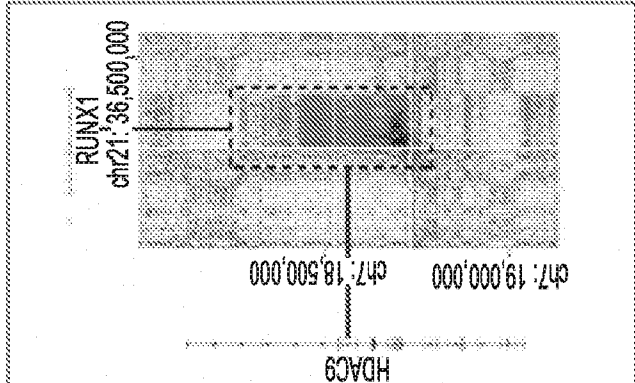


FIG. 28E

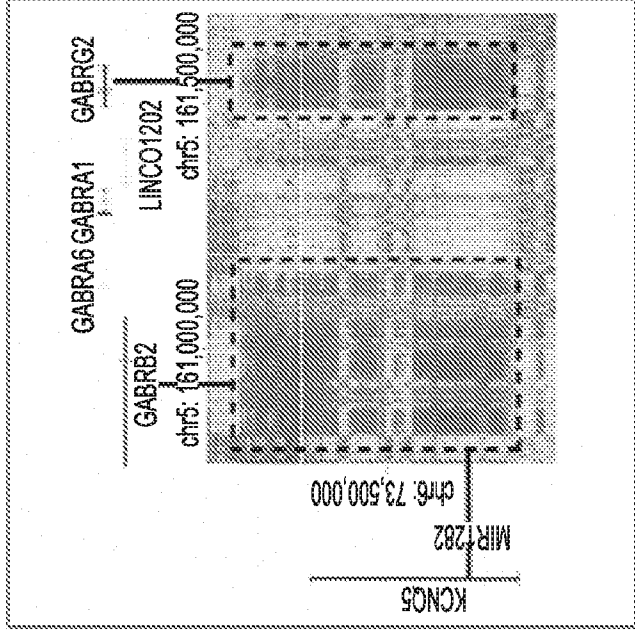


FIG. 28F

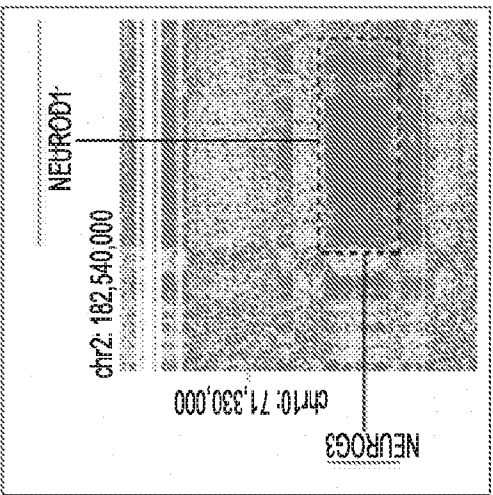


FIG. 28G

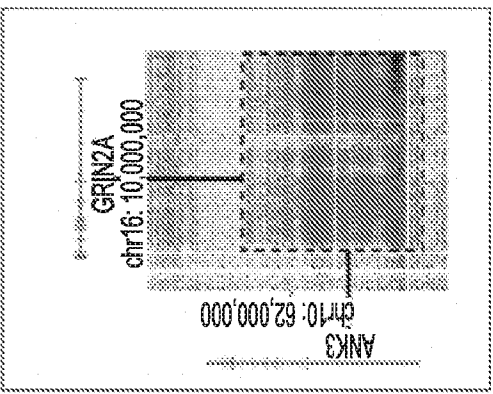


FIG. 28H

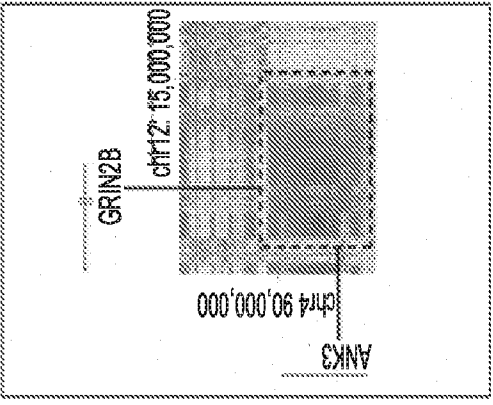
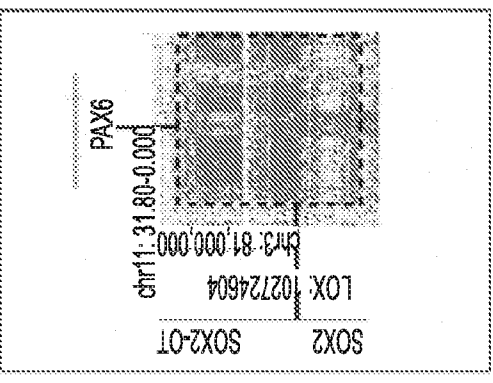


FIG. 28I



Diseases Annotation	p-value
Schizophrenia	3.45E-41
Refractory depression	1.33E-40
Bipolar disorder	8.44E-40
Postoperative delirium	4.47E-39
Postoperative pain	3.20E-38

FIG. 29A

Upstream Regulator	p-value
ketamine	6.26E-33
morphine	1.97E-17
nicotine	6.62E-17
cocaine	6.92E-17
haloperidol	1.32E-14

FIG. 29B

Network topology

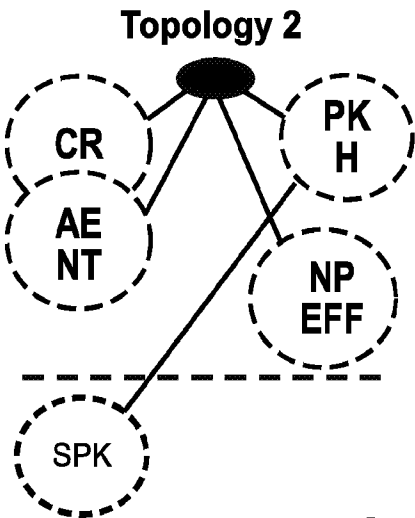


FIG. 29C

The ketamine glutamate receptor sub-network

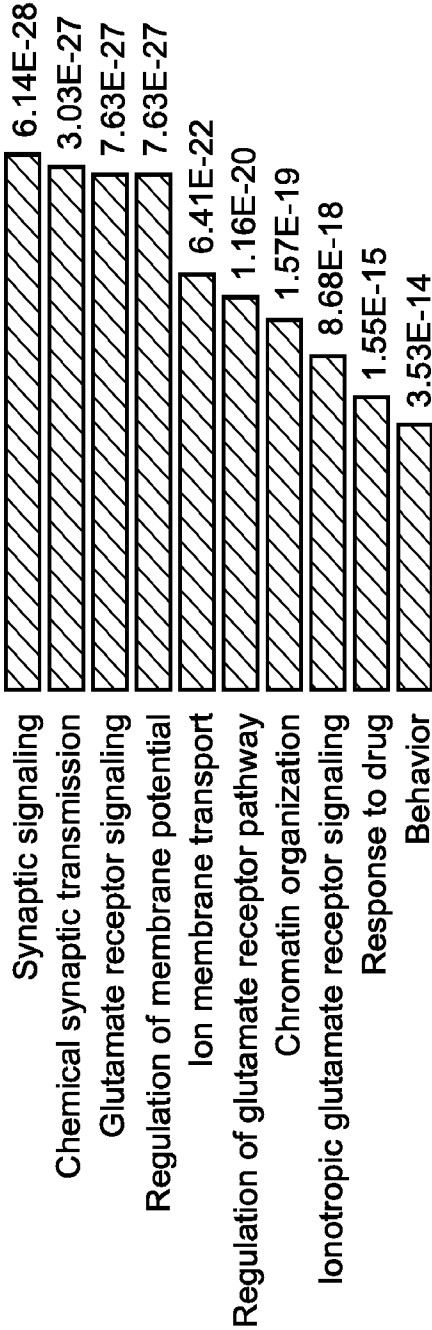


FIG. 30A

The ketamine neuroplasticity sub-network

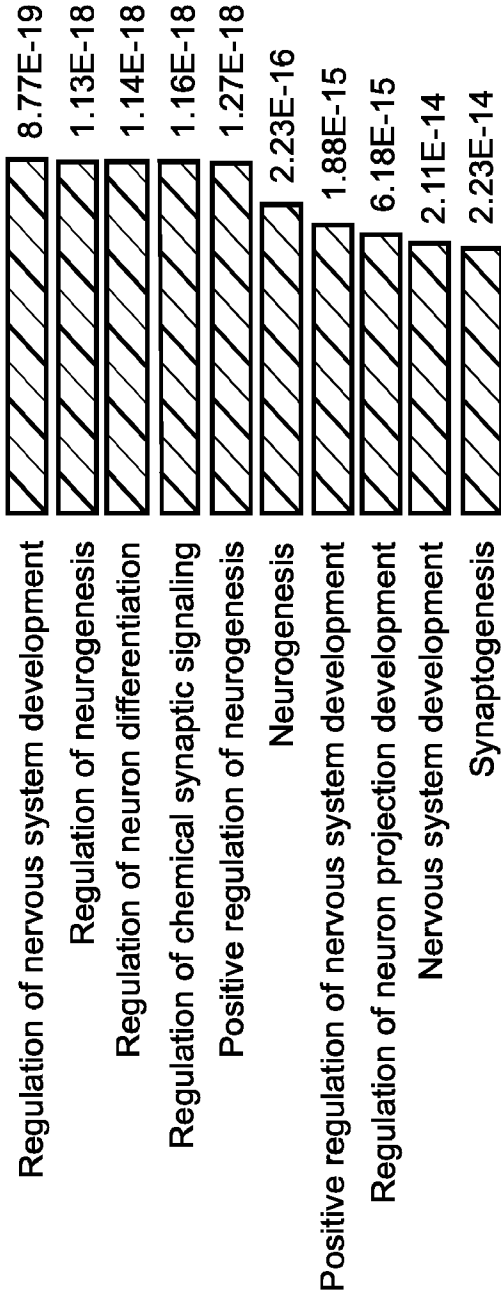
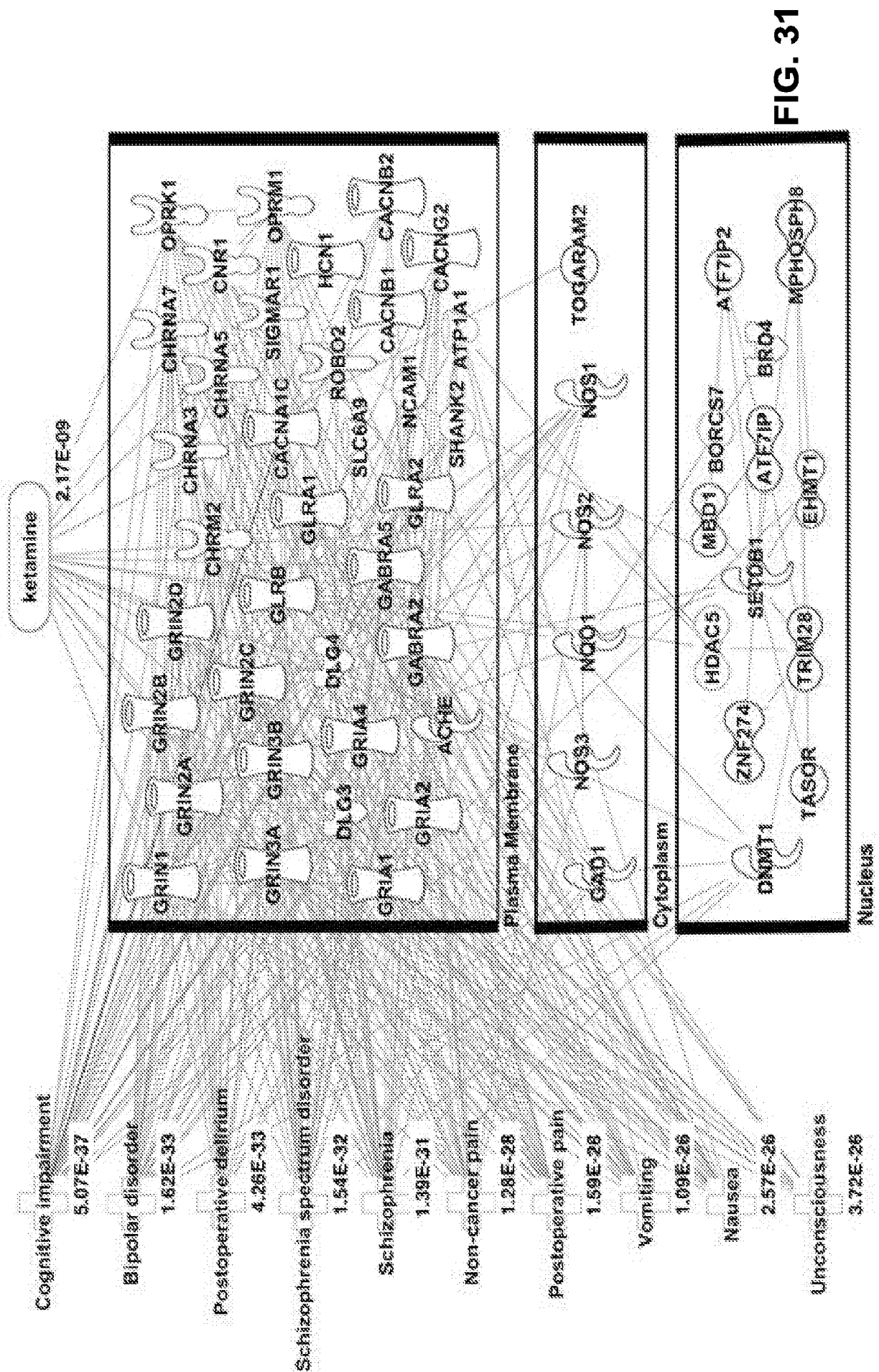


FIG. 30B



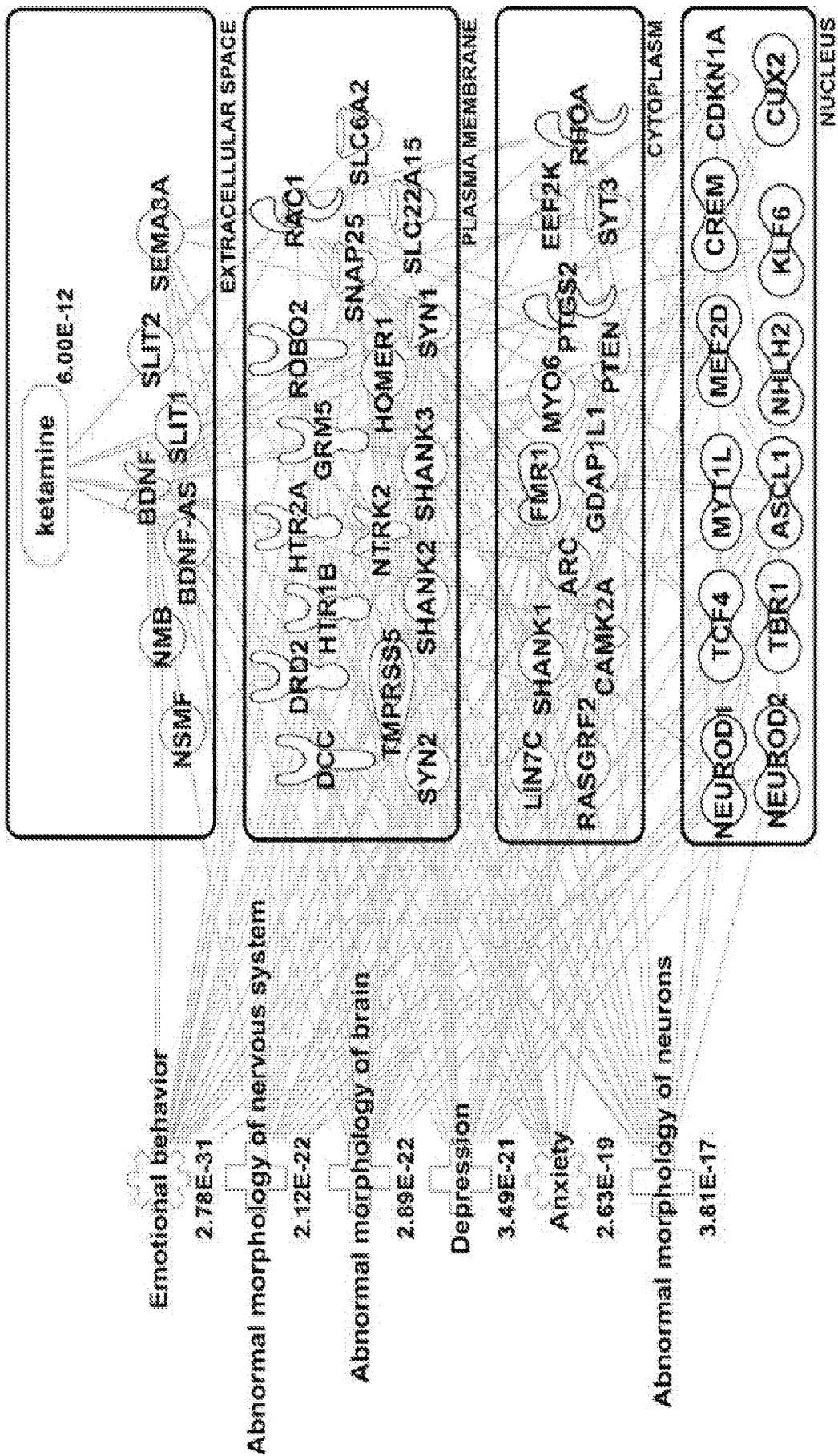


FIG. 32

The ketamine glutamate receptor sub-network

GWAS SNP	Populations	Gene(s)	Reported trait	Reported P-value	Enhancer, cell type	Hi-C score: Human brain	PMID
rs1051730	ASN, EUR	<i>CHRNA5</i> , <i>CHRNA3</i>	Smoking status	6E-121	Neuron	1E-27: Nucleus accumbens	30617275
rs28681284	ASN	<i>CHRNA5</i> , <i>CHRNA3</i>	Schizophrenia, chronic (F20)	6E-13	Neuron	1E-27: Nucleus accumbens	30285260
rs2007044	ASN	<i>CACNA1C</i>	Schizophrenia, chronic (F20)	6E-20	Bipolar neuron	1E-10: Cingulate cortex	29483656
rs7192140	EUR	<i>GRIN2A</i>	Smoking status	2E-15	Bipolar neuron	1E-19: Frontal cortex	30643251
rs11647445	EUR	<i>GRIN2A</i>	Bipolar 1 disorder (F31.0 - F31.64)	1E-10	Bipolar neuron	1E-19: Frontal cortex	31043756
rs7893279	ASN, EUR	<i>CACNB2</i>	Schizophrenia, chronic (F20)	9E-14	Neuron	1E-10: Frontal cortex	30285260
rs111294930	EUR	<i>LINCO1470</i> , <i>GRIA1</i>	Schizophrenia, chronic (F20)	9E-12	Bipolar neuron	1E-12: Cingulate cortex	29483656
rs9292918	ASN	<i>HCN1</i>	Schizophrenia, chronic (F20)	4E-11	Bipolar neuron	1E-10: Frontal cortex	28991256
rs62367520	EUR	<i>HCN1</i>	Smoking status	1E-10	Bipolar neuron	1E-10: Frontal cortex	29283656

FIG. 33A**The ketamine neuroplasticity sub-network**

GWAS SNP	Populations	Gene(s)	Reported trait	Reported P-value	Enhancer, cell type	Hi-C score: Human brain	PMID
rs61902811	EUR	<i>TMPRSS5</i> , <i>DRD2</i>	Recurrent depression (F33)	4E-39	Neuron	1E-04: Hippocampus	30718901
rs4936277	EUR	<i>TMPRSS5</i> , <i>DRD2</i>	Alcohol use disorder, alcohol dependence	1E-13	Bipolar neuron	1.00E-06: Nucleus Accumbens	29942085
rs7227069	EUR	<i>DCC</i>	Recurrent depression (F33)	2E-28	Neuron	1E-10: Cingulate cortex	30718901
rs12967143	EUR	<i>TCF4</i>	Recurrent depression (F33)	2E-27	Neuron	1E-10: Frontal cortex	30718901
rs7932640	EUR	<i>GRM5</i>	Recurrent depression (F33)	2E-25	Neuron	1E-04: Cingulate cortex	30718901
rs139438618	AFR	<i>SEMA3A</i>	Major depression and alcoholism	2E-11	Bipolar neuron	1E-10: Nucleus Accumbens	29071344
rs775766	EUR	<i>ROBO2</i>	Recurrent depression (F33)	2E-08	Neuron	1E-14: Cingulate cortex	29942085
rs1400237	EUR	<i>ROBO2</i>	Response to ketamine in depression	8E-06*	Neuron	1E-14: Cingulate cortex	30552316

FIG. 33B

Symbol	Entrez Gene Name
ARC	activity regulated cytoskeleton associated protein
ASCL1	achaete-scute family bHLH transcription factor 1
BDNF	brain derived neurotrophic factor
BDNF-AS	BDNF antisense RNA
CAMK2A	calcium/calmodulin dependent protein kinase II alpha
CDKN1A	cyclin dependent kinase inhibitor 1A
CREM	cAMP responsive element modulator
CUX2	cut like homeobox 2
DCC	DCC netrin 1 receptor
DRD2	dopamine receptor D2
EEF2K	eukaryotic elongation factor 2 kinase
FMR1	fragile X mental retardation 1
GDAP1L1	ganglioside induced differentiation associated protein 1 like 1
GRM5	glutamate metabotropic receptor 5
HOMER1	homer scaffold protein 1
HTR1B	5-hydroxytryptamine receptor 1B
HTR2A	5-hydroxytryptamine receptor 2A
KLF6	Kruppel like factor 6
LIN7C	lin-7 homolog C, crumbs cell polarity complex component
LOC105379109	
MEF2D	myocyte enhancer factor 2D
MYO6	myosin VI
MYT1L	myelin transcription factor 1 like
NEUROD1	neuronal differentiation 1
NEUROD2	neuronal differentiation 2
NHLH2	nascent helix-loop-helix 2
NMB	neuromedin B
NSMF	NMDA receptor synaptonuclear signaling and neuronal migration factor
NTRK2	neurotrophic receptor tyrosine kinase 2
PTEN	phosphatase and tensin homolog
PTGS2	prostaglandin-endoperoxide synthase 2
RAC1	Rac family small GTPase 1
RASGRF2	Ras protein specific guanine nucleotide releasing factor 2
RHOA	ras homolog family member A
ROBO2	roundabout guidance receptor 2
RP11_360A181	
SEMA3A	semaphorin 3A
SHANK1	SH3 and multiple ankyrin repeat domains 1
SHANK2	SH3 and multiple ankyrin repeat domains 2
SHANK3	SH3 and multiple ankyrin repeat domains 3
SLC22A15	solute carrier family 22 member 15
SLC6A2	solute carrier family 6 member 2
SLIT1	slit guidance ligand 1
SLIT2	slit guidance ligand 2
SNAP25	synaptosome associated protein 25
SYN1	synapsin I
SYN2	synapsin II
SYT3	synaptotagmin 3
TBR1	T-box, brain 1
TCF4	transcription factor 4

FIG. 34

Symbol	Entrez Gene Name
<i>ACHE</i>	acetylcholinesterase (Cartwright blood group)
<i>ATF7IP</i>	activating transcription factor 7 interacting protein
<i>ATF7IP2</i>	activating transcription factor 7 interacting protein 2
<i>ATP1A1</i>	ATPase Na ⁺ /K ⁺ transporting subunit alpha 1
<i>BORCS7</i>	BLOC-1 related complex subunit 7
<i>BRD4</i>	bromodomain containing 4
<i>CACNA1C</i>	calcium voltage-gated channel subunit alpha1 C
<i>CACNB1</i>	calcium voltage-gated channel auxiliary subunit beta 1
<i>CACNB2</i>	calcium voltage-gated channel auxiliary subunit beta 2
<i>CACNG2</i>	calcium voltage-gated channel auxiliary subunit gamma 2
<i>CHRM2</i>	cholinergic receptor muscarinic 2
<i>CHRNA3</i>	cholinergic receptor nicotinic alpha 3 subunit
<i>CHRNA5</i>	cholinergic receptor nicotinic alpha 5 subunit
<i>CHRNA7</i>	cholinergic receptor nicotinic alpha 7 subunit
<i>CNR1</i>	cannabinoid receptor 1
<i>DLG3</i>	discs large MAGUK scaffold protein 3
<i>DLG4</i>	discs large MAGUK scaffold protein 4
<i>DNMT1</i>	DNA methyltransferase 1
<i>EHMT1</i>	euchromatic histone lysine methyltransferase 1
<i>GABRA2</i>	gamma-aminobutyric acid type A receptor alpha2 subunit
<i>GABRA5</i>	gamma-aminobutyric acid type A receptor alpha5 subunit
<i>GAD1</i>	glutamate decarboxylase 1
<i>GLRA1</i>	glycine receptor alpha 1
<i>GLRA2</i>	glycine receptor alpha 2
<i>GLRB</i>	glycine receptor beta
<i>GRIA1</i>	glutamate ionotropic receptor AMPA type subunit 1
<i>GRIA2</i>	glutamate ionotropic receptor AMPA type subunit 2
<i>GRIA4</i>	glutamate ionotropic receptor AMPA type subunit 4
<i>GRIN1</i>	glutamate ionotropic receptor NMDA type subunit 1
<i>GRIN2A</i>	glutamate ionotropic receptor NMDA type subunit 2A
<i>GRIN2B</i>	glutamate ionotropic receptor NMDA type subunit 2B
<i>GRIN2C</i>	glutamate ionotropic receptor NMDA type subunit 2C
<i>GRIN2D</i>	glutamate ionotropic receptor NMDA type subunit 2D
<i>GRIN3A</i>	glutamate ionotropic receptor NMDA type subunit 3A
<i>GRIN3B</i>	glutamate ionotropic receptor NMDA type subunit 3B
<i>HCN1</i>	hyperpolarization activated cyclic nucleotide gated potassium channel 1
<i>HDAC5</i>	histone deacetylase 5
<i>MBD1</i>	methyl-CpG binding domain protein 1
<i>MPHOSPH8</i>	M-phase phosphoprotein 8
<i>NCAM1</i>	neural cell adhesion molecule 1
<i>NOS1</i>	nitric oxide synthase 1
<i>NOS2</i>	nitric oxide synthase 2
<i>NOS3</i>	nitric oxide synthase 3
<i>NQO1</i>	NAD(P)H quinone dehydrogenase 1
<i>OPRK1</i>	opioid receptor kappa 1
<i>OPRM1</i>	opioid receptor mu 1
<i>ROBO2</i>	roundabout guidance receptor 2
<i>SETDB1</i>	SET domain bifurcated histone lysine methyltransferase 1
<i>SHANK2</i>	SH3 and multiple ankyrin repeat domains 2
<i>SIGMAR1</i>	sigma non-opioid intracellular receptor 1
<i>SLC6A9</i>	solute carrier family 6 member 9
<i>TASOR</i>	transcription activation suppressor
<i>TOGARAM2</i>	TOG array regulator of axonemal microtubules 2
<i>TRIM28</i>	tripartite motif containing 28
<i>ZNF274</i>	zinc finger protein 274

FIG. 35

Symbol	Entrez Gene Name
ANAPC2	anaphase promoting complex subunit 2
CYP2A6 (<i>includes others</i>)	cytochrome P450 family 2 subfamily A member 6
CYP2B6	cytochrome P450 family 2 subfamily B member 6
CYP3A4	cytochrome P450 family 3 subfamily A member 4
DLG4	discs large MAGUK scaffold protein 4
EEF2K	eukaryotic elongation factor 2 kinase
ESR1	estrogen receptor 1
GRIA1	glutamate ionotropic receptor AMPA type subunit 1
GRIA4	glutamate ionotropic receptor AMPA type subunit 4
GRIN1	glutamate ionotropic receptor NMDA type subunit 1
GRIN2B	glutamate ionotropic receptor NMDA type subunit 2E
MYO6	myosin VI
ROBO2	roundabout guidance receptor 2
SHANK2	SH3 and multiple ankyrin repeat domains 2
TCERG1	transcription elongation regulator 1

FIG. 36

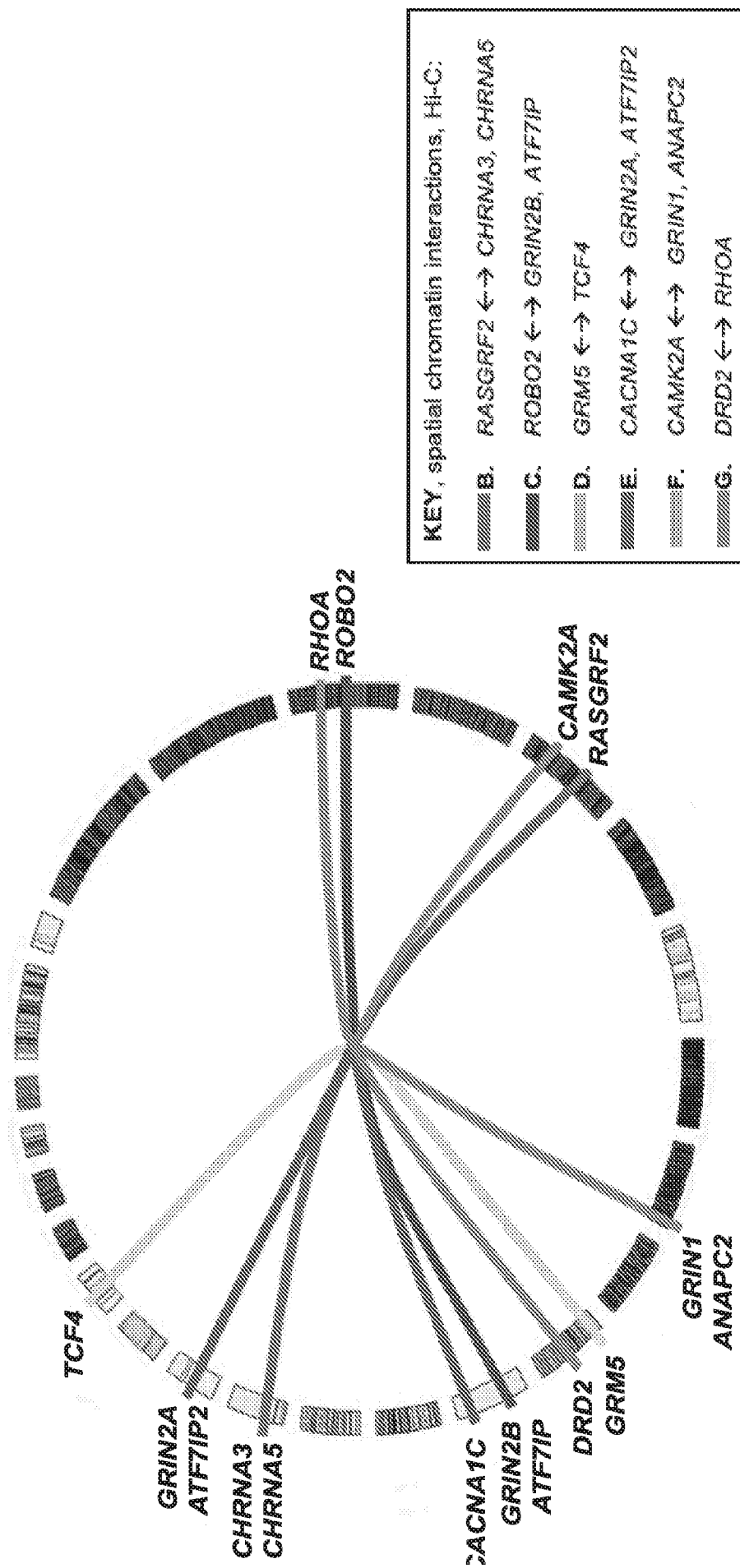


FIG. 37A

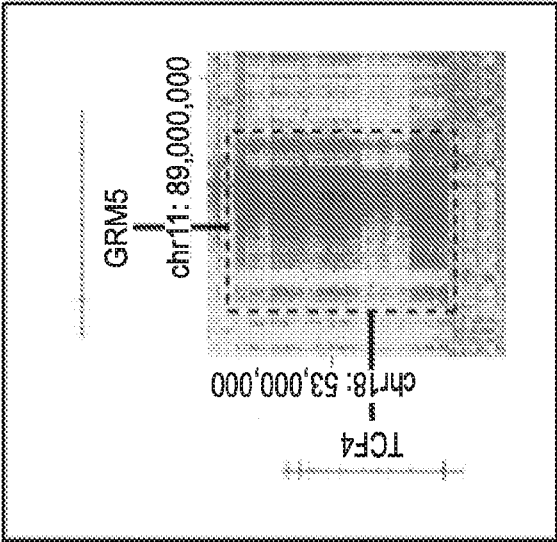


FIG. 37D

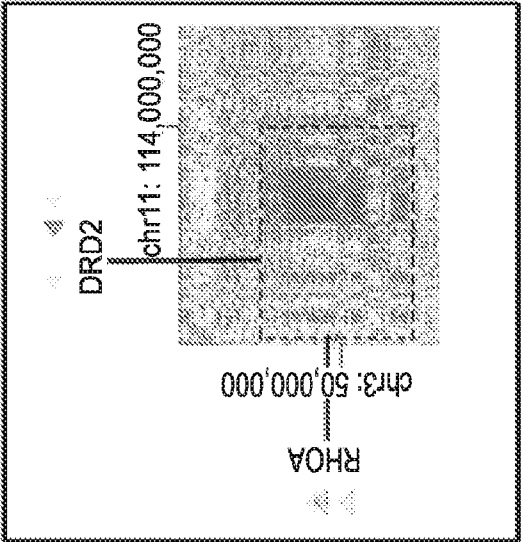


FIG. 37G

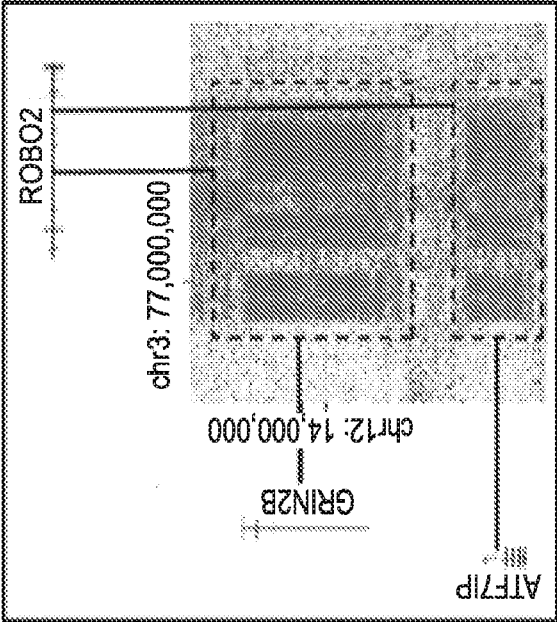


FIG. 37C

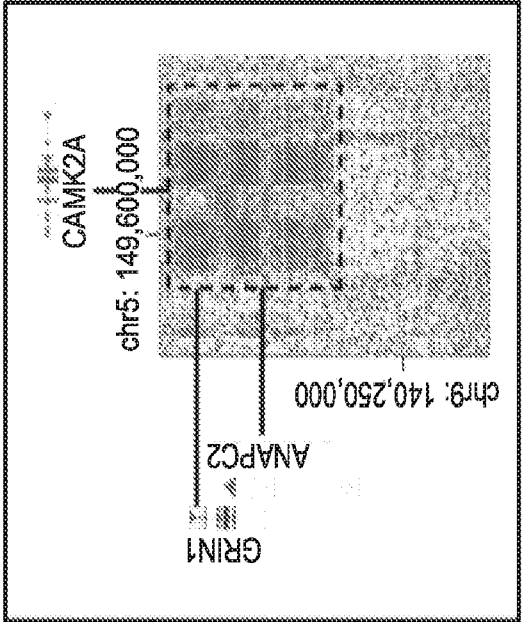


FIG. 37F

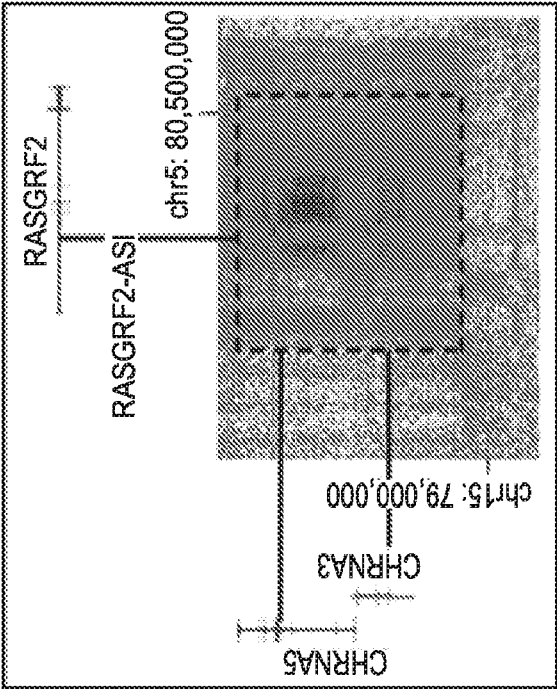


FIG. 37B

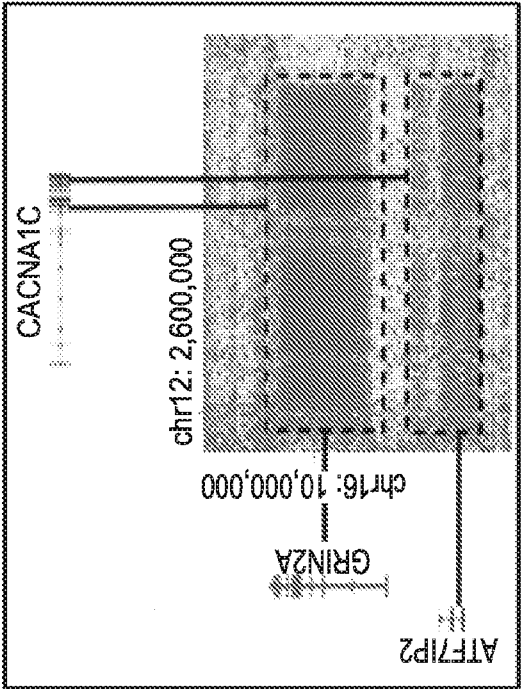
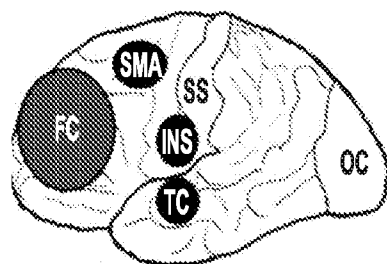
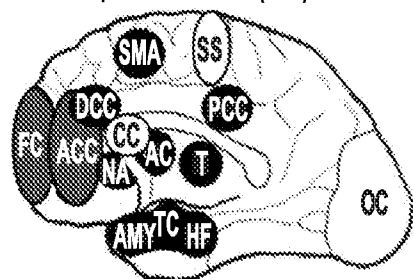


FIG. 37E

Ketamine activation:
Anterior cingulate cortex (ACC)
Frontal cortex (FC)



No Ketamine activation:
Somatosensory cortex (SS)
Occipital cortex (OC)
Corpus callosum (CC)



KEY

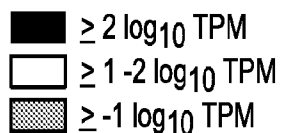


FIG. 38

GENES	ACC	FC	SS	OC	CC	GENES	ACC	FC	SS	OC	CC
ACHE						GRIN3A					
ANAPC2						GRIN3B					
ARC						GRM5					
ASCL1						HCN1					
ATF7IP						HDAC5					
ATF7IP2						HOMER1					
ATP1A1						HTR1B					
BDNF						HTR2A					
BORCS7						KLF6					
BRD4						LIN7C					
CACNA1C						MBD1					
CACNB1						MEF2D					
CACNB2						MYO6					
CACNG2						MYT1L					
CAMK2A						NCAM1					
CDKN1A						NEUROD1					
CHRM2						NEUROD2					
CHRNA3						NHLH2					
CHRNA5						NMB					
CHRNA7						NOS1					
CNR1						NOS2					
CREM						NOS3					
CUX2						NQO1					
CYP2A6						NSMF					
CYP2B6						NTRK2					
CYP3A4						OPRK1					
DCC						OPRM1					
DLG3						RAC1					
DLG4						RASGRF2					
DNMT1						RHOA					
DRD2						ROBO2					
EEF2K						SEMA3A					
EHMT1						SETDB1					
ESR1						SHANK1					
FMR1						SHANK2					
GABRA2						SHANK3					
GABRA5						SIGMAR1					
GAD1						SLC6A2					
GDAP1L1						SLC6A9					
GLRA1						SLIT1					
GLRA2						SLIT2					
GLRB						SNAP25					
GRIA1						SYN1					
GRIA2						SYN2					
GRIA4						SYT3					
GRIN1						TBR1					
GRIN2A						TCERG1					
GRIN2B						TCF4					
GRIN2C						TRIM28					
GRIN2D						ZNF274					

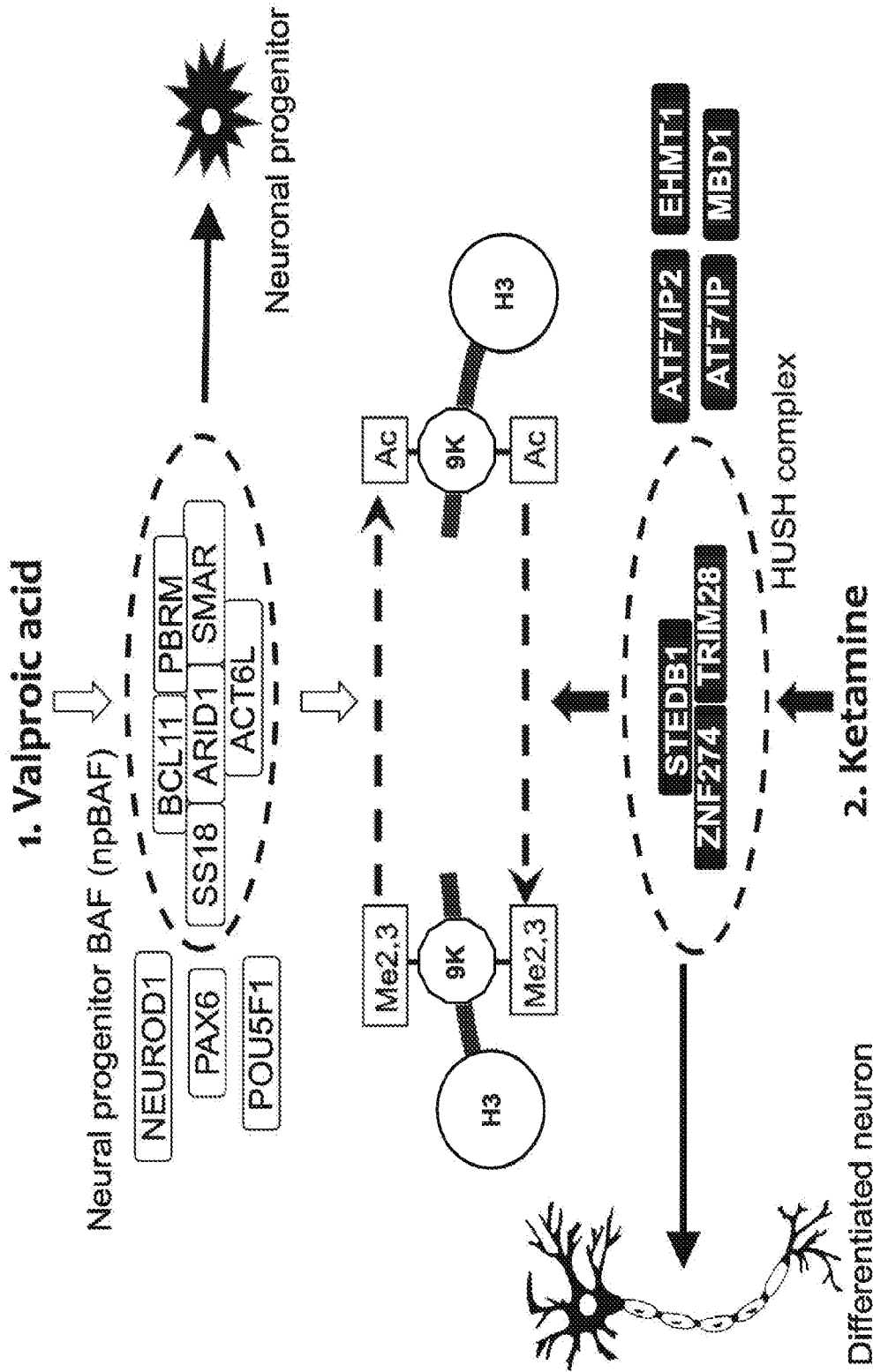


FIG. 39

Valproic acid pharmacogenomic network

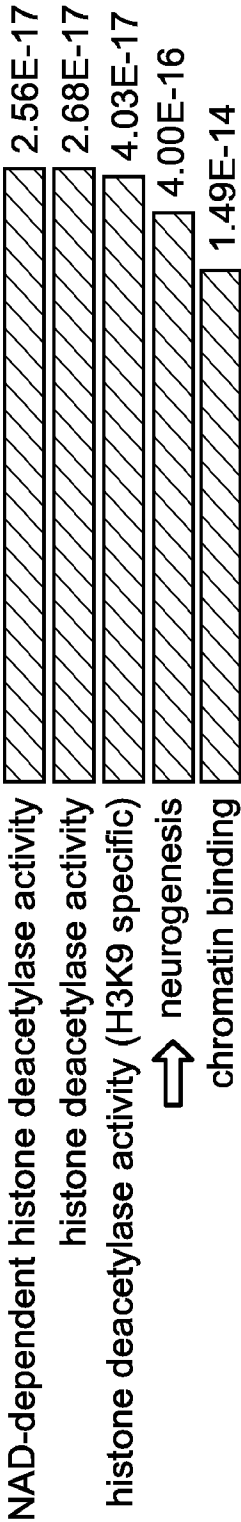


FIG. 40A

Ketamine pharmacogenomic network

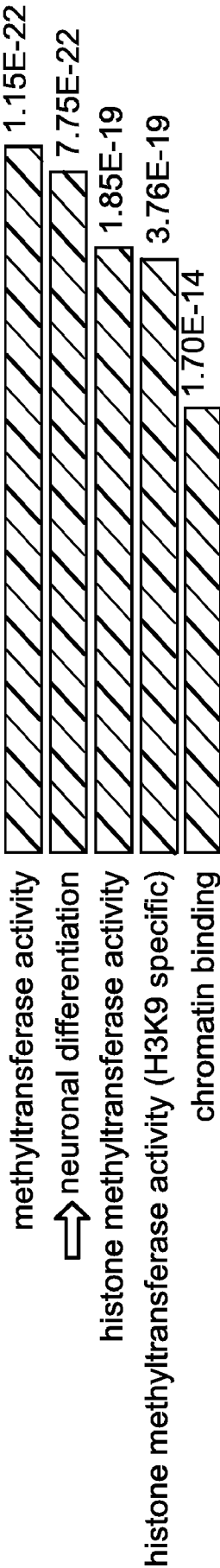


FIG. 40B

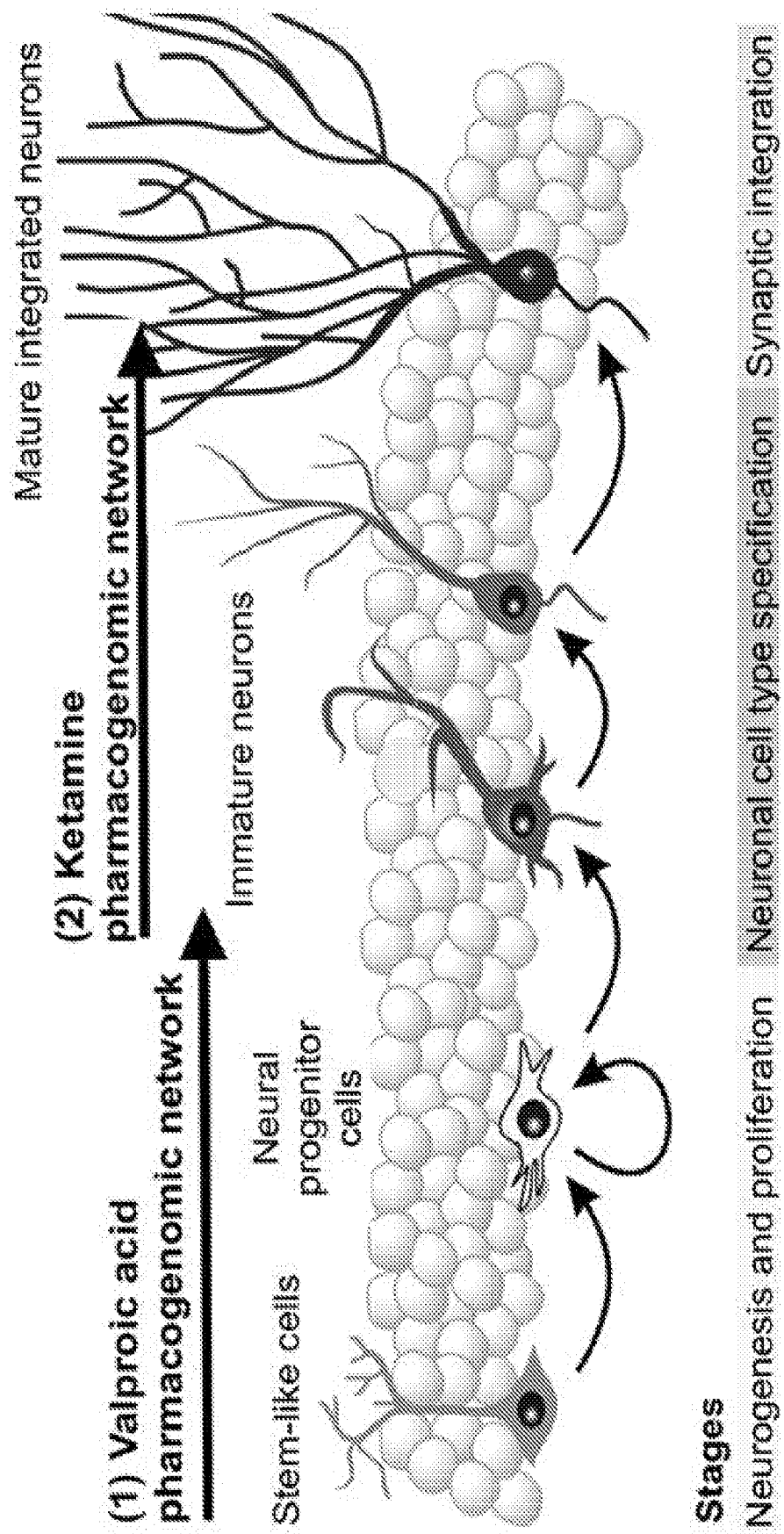
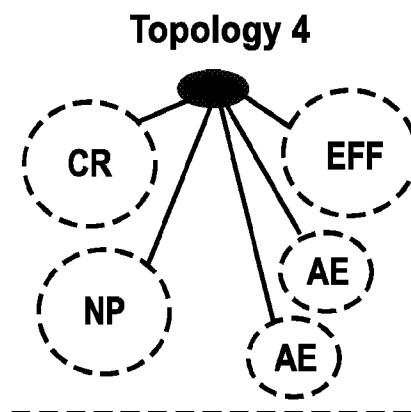


FIG. 41

Diseases Annotation	p-value
Cognitive impairment	9.45E-20
Mood disorders	7.93E-18
Drug-induced tremor	2.46E-16
Drug-induced weight gain	1.08E-15
Schizophrenia	1.00E-12

FIG. 42A

Upstream Regulator	p-value
Lithium chloride	2.04E-23
Lithium	4.20E-19
Fluoxetine	2.94E-14
Haloperidol	2.59E-12
Valproic acid	1.04E-11

FIG. 42B**Network topology****FIG. 42C**

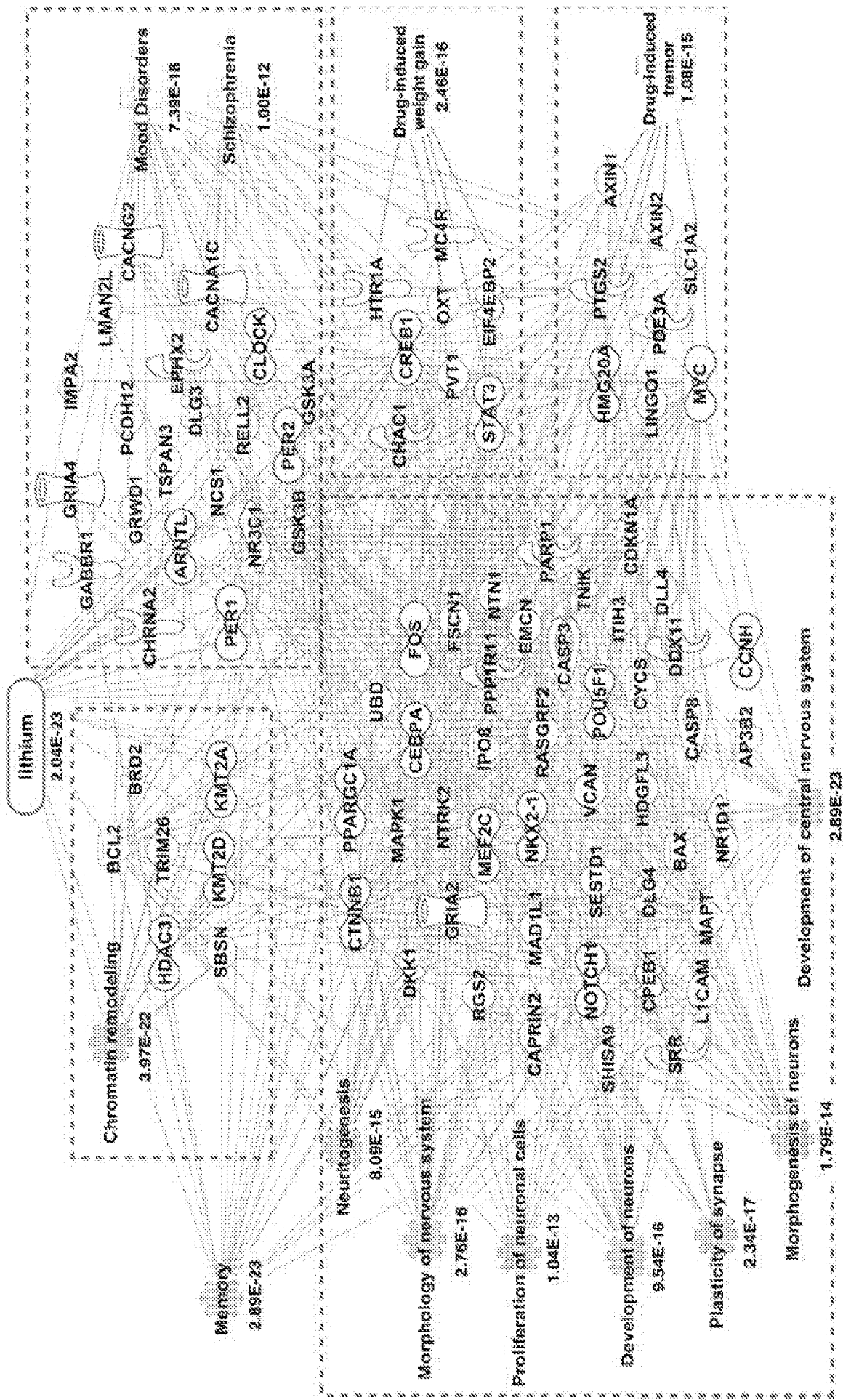


FIG. 43

Symbol	Entrez Gene Name
<i>BCL2</i>	BCL2 apoptosis regulator
<i>BRD2</i>	bromodomain containing 2
<i>HDAC3</i>	histone deacetylase 3
<i>KMT2A</i>	lysine methyltransferase 2A
<i>KMT2D</i>	lysine methyltransferase 2D
<i>SBSN</i>	suprabasin
<i>TRIM26</i>	tripartite motif containing 26

FIG. 44

Symbol	Entrez Gene Name
AKR1C3	aldo-keto reductase family 1 member C3
ANK3	ankyrin 3
AP3B2	adaptor related protein complex 3 subunit beta 2
BAX	BCL2 associated X, apoptosis regulator
CAPRIN2	caprin family member 2
CASP3	caspase 3
CASP8	caspase 8
CCNH	cyclin H
CDKN1A	cyclin dependent kinase inhibitor 1A
CEBPA	CCAAT renhancer binding protein alpha
CPEB1	cytoplasmic polyadenylation element binding protein 1
CTNNB1	catenin beta 1
CYCS	cytochrome c, somatic
DDX11	DEAD/H-box helicase 11
DKK1	diokkopf WNT signaling pathway inhibitor 1
DLG4	discs large MAGUK scaffold protein 4
DLL4	delta like caronical Notch ligand 4
EMCN	endomucin
FOS	FOS proto-oncogene, AP-1 transcription factor subunit
FSCN1	fascin actin-bundling protein 1
GRIA2	glutamate ionotropic receptor AMPA type subunit 1
HDGFL3	HDGF like 3
IPO8	importin 8
ITIH3	inter-alpha-trypsin inhibitor heavy chain 3
L1CAM	L1 cell adhesion molecule
MAD1L1	mitotic arrest deficient 1 like 1
MAPK1	mitogen- activated protein kinase 1
MAPT	microtubule associated protein tau
MEF2C	myocyte enhancer factor 2C
NKX2-1	NK2 homeobox 1
NOTCH1	notch receptor 1
NR1D1	nuclear receptor subfamily 1 group D member 1
NTN1	netrin 1
NTRK2	neurotrophic receptor tryosine kinase 2
PARP1	poly (ADP-ribose) polymerase 1
POU5F1	POU class 5 homeobox 1
PPARGC1A	PPARO coactivator 1 alpha
PPP1R11	protein phosphatase 1 regulatory inhibitor subunit 1
RASGRFF2	Ras protein specific guanine nucleotide releasing factor 2
RGS2	regulator of G protein signaling 2
SESTD1	SEC14 and spectrin domain containing 1
SHISA9	shisa family member 9
SRR	serine racemase
TNIK	TRAF2 and NCK interacting kinase
UBD	ubiquillin D
VCAN	versican

FIG. 45

Symbol	Entrez Gene Name
<i>ARNTL</i>	aryl hydrocarbon receptor nuclear translocator like
<i>CACNA1C</i>	calcium voltage-gated channel subunit alpha 1 C
<i>CACNG2</i>	calcium voltage-gated channel auxillary subunit gamma 2
<i>CHRNA2</i>	cholinergic receptor nicotinic alpha 2 subunit
<i>CLOCK</i>	clock circadian regulator
<i>DLG3</i>	discs large MAGUK scaffold protein 3
<i>EPHX2</i>	epoxide hydrolase 2
<i>GABBR1</i>	gamma-aminobutyric acid type B receptor subunit 1
<i>GRIA4</i>	glutamate ionotropic receptor AMPA type subunit 4
<i>GRWD1</i>	glutamate rich WD repeat containing 1
<i>GSK3A</i>	glycogen synthase kinase 3 alpha
<i>GSK3B</i>	glycogen synthase kinase 3 beta
<i>IMPA2</i>	inositol monophosphatase 2
<i>LMAN2L</i>	lectin, mannose binding 2 like
<i>NCS1</i>	neuronal calcium sensor 1
<i>NR3C1</i>	nuclear receptor subfamily 3 group C member 1
<i>PER1</i>	period circadian regulator 1
<i>PER2</i>	period circadian regulator 2
<i>PCDH12</i>	protocadherin 12
<i>RELL2</i>	RELT like 2
<i>TSPAN3</i>	tetraspanin 3

FIG. 46

Symbol	Entrez Gene Name
<i>CHAC1</i>	ChaC glutathione specific gamma-glutamylcyclotransferase 1
<i>CREB1</i>	cAMP response element binding protein 1
<i>EIF4EBP2</i>	eukaryotic translation initiation factor 4E binding protein 2
<i>HTR1A</i>	5-hydroxytryptamine receptor 1A
<i>MC4R</i>	melanocortin 4 receptor
<i>OXT</i>	oxytocin/neurophysin I prepropeptide
<i>PDE3A</i>	phosphodiesterase 3A
<i>PVT1</i>	Pvt1 oncogene
<i>STAT3</i>	signal transducer and activator of transcription 3

FIG. 47

Symbol	Entrez Gene Name
<i>AXIN1</i>	axin 1
<i>AXIN2</i>	axin 2
<i>HMG20A</i>	high mobility group 20A
<i>LINGO1</i>	leucine rich repeat and Ig domain containing 1
<i>MYC</i>	MYC proto-oncogene, bHLH transcription factor
<i>PTGS2</i>	prostaglandin-endoperoxide synthase 2
<i>SLC1A2</i>	solute carrier family 1 member 2

FIG. 48

Diseases Annotation	p-value
Epilepsy	1.95E-21
Fibromyalgia	9.75E-21
Bipolar 1 disorder	2.62E-19
Mania	3.12E-19
Treatment-resistant schizophrenia	9.83E-46

FIG. 49A

Upstream Regulator	p-value
Lamotrigine	1.08E-10
Carbamazepine	3.51E-08
Mirtazapine	1.06E-07
Fluoxetine	7.11E-06
Haloperidol	1.01E-05

FIG. 49B

Network topology

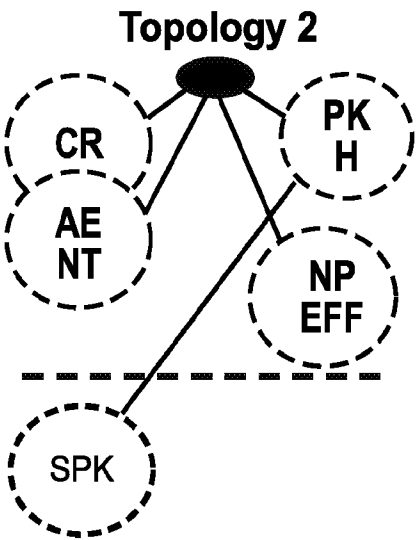
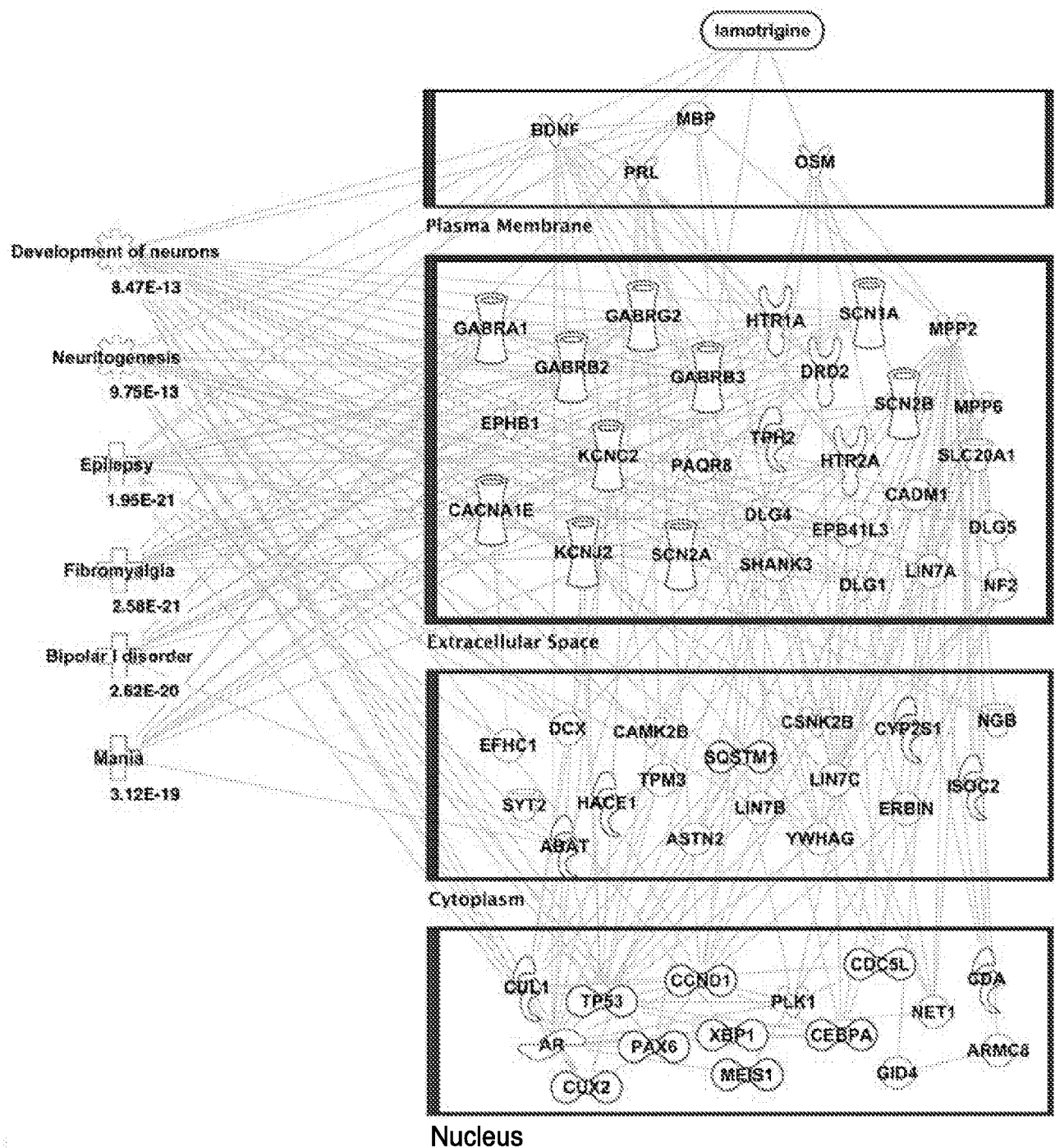


FIG. 49C

**FIG. 51**

Symbol	Entrez Gene Name
ACTL6B	actin like 6B
ANKRA2	ankyrin repeat family A member 2
ARID2	AT-rich interaction domain 2
ARID2	AT-rich interaction domain 4A
ARID4A	AT-rich interaction domain 4B
BRD1	bromodomain containing 1
BRD7	bromodomain containing 7
CHD2	chromodomain helicase DNA binding protein 2
GATAD2A	GATA zinc finger domain containing 2A
GATAD2B	GATA zinc finger domain containing 2B
HDAC2	histone deacetylase 2
HDAC3	histone deacetylase 3
HDAC5	histone deacetylase 5
KAT6A	lysine acetyltransferase 6A
KDM5C	lysine demethylase 5C
MBD3	methyl-CpG binding domain protein 3
PBRM1	polybromo 1
SMARCA2	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a, member 2
SMARCA4	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a, member 4
SMARCC2	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily c, member 2
SMARCD1	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily d, member 1
SMARCD3	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily d, member 3
SMARCE1	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily e, member 1

FIG. 52

Symbol	Entrez Gene Name
<i>AEAT</i>	4-aminobutyrate aminotransferase
<i>AR</i>	androgen receptor
<i>ARMC8</i>	armadillo repeat cotaining 8
<i>ASTN2</i>	astrotactin 2
<i>BDNF</i>	brain derived neurotrophic factor
<i>CACNA1E</i>	calcium voltage-gated channel subunit alpha 1 E
<i>CADM1</i>	cell adhesion molecule 1
<i>CAMK2B</i>	calcium/calmodulin dependent protein kinase II beta
<i>CCND1</i>	cyclin D1
<i>CDA</i>	cytidine deaminase
<i>CDC5L</i>	cell division cycle 5 like
<i>CEBPA</i>	CCAAT enhancer binding protein alpha
<i>CSNK2B</i>	casein kinase 2 beta
<i>CUL1</i>	cullin 1
<i>CUX2</i>	cut like homeobox 2
<i>CYP2S1</i>	cytochrome P450 family 2 subfamily S member 1
<i>DCX</i>	doublecortin
<i>DLG1</i>	discs large MAGUK scaffold protein 1
<i>DLG4</i>	discs large MAGUK scaffold protein 4
<i>DLG5</i>	discs large MAGUK scaffold protein 5
<i>DRD2</i>	dopamine receptor D2
<i>EFHC1</i>	EF-hand domain containing 1
<i>EPB41L3</i>	erythrocyte membrane protein band 4.1 like 3
<i>EPHB1</i>	EPH receptor B1
<i>ERBIN</i>	erbb2 interacting protein
<i>GABRA1</i>	gamma-aminobutyric acid type A receptor alpha1 subunit
<i>GABRB2</i>	gamma-aminobutyric acid type A receptor beta2 subunit
<i>GABRB3</i>	gamma-aminobutyric acid type A receptor beta3 subunit
<i>GABRG2</i>	gamma-aminobutyric acid type A receptor gamma2 subunit
<i>GID4</i>	GID complex subunit 4 homolog

FIG. 53-1

<i>HACE1</i>	HECT domain and ankyrin repeat containing E3 ubiquitin protein ligase 1
<i>HTR1A</i>	5-hydroxytryptamine receptor 1A
<i>HTR2A</i>	5-hydroxytryptamine receptor 2A
<i>ISOC2</i>	isochorismatase domain containing 2
<i>KCNC2</i>	potassium voltage-gated channel subfamily C member 2
<i>KCNJ2</i>	potassium inwardly rectifying channel subfamily C member 2
<i>LIN7A</i>	lin-7 homolog A, crumbs cell polarity complex component
<i>LIN7B</i>	lin-7 homolog B, crumbs cell polarity complex component
<i>LIN7C</i>	lin-7 homolog C, crumbs cell polarity complex component
<i>MBP</i>	myelin basic protein
<i>MEIS1</i>	Meis homeobox 1
<i>MPP2</i>	membrane palmitoylated protein 2
<i>MPP6</i>	membrane palmitoylated protein 6
<i>NET1</i>	neuroepithelial cell transforming 1
<i>NF2</i>	neurofibromin 2
<i>NGB</i>	neuroglobin
<i>OSM</i>	oncostatin M
<i>PAQR8</i>	progesterone and adipoQ receptor family member B
<i>PAX8</i>	paired box 6
<i>PLK1</i>	polo like kinase 1
<i>PRL</i>	prolactin
<i>SCN1A</i>	sodium voltage-gated channel alpha subunit 1
<i>SCN2A</i>	sodium voltage-gated channel alpha subunit 2
<i>SCN2B</i>	sodium voltage-gated channel beta subunit 2
<i>SHANK3</i>	SH3 and multiple ankyrin repeat domains 3
<i>SLC20A1</i>	solute carrier family 20 member 1
<i>SQSTM1</i>	sequestosome 1
<i>SYT2</i>	synaptotagmin 2
<i>TP53</i>	tumor protein p53
<i>TPH2</i>	tryptophan hydroxylase 2
<i>TPM3</i>	tropomyosin 3
<i>XBP1</i>	X-box binding protein
<i>YWHAG</i>	tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein gamma

FIG. 53-2

Symbol	Entrez Gene Name
ABCB1	ATP binding cassette subfamily B member 1
ABRA	actin binding Rho activating protein
ADAT2	adenosine deaminase tRNA specific 2
APP	amyloid beta precursor protein
C11orf154	chromosome 11 open reading frame 54
CALML4	calmodulin like 4
CFDP1	craniofacial development protein 1
CLTC	clathrin heavy chain
CRAMP1	cramped chromatin regulator homolog 1
DHRX	dehydrogenase/reductase X-linked
DNAJB14	DnaJ heat shock protein family (Hsp40) member B14
DNAJB7	DnaJ heat shock protein family (Hsp40) member B7
DNAJC4	DnaJ heat shock protein family (Hsp40) member C4
DNAJC5B	DnaJ heat shock protein family (Hsp40) member C5 beta
FAM53A	family with sequence similarity 53 member A
FHIT	fragile histidine triad diadenosine triphosphatase
GUSB	glucuronidase beta
HDAC9	histone deacetylase 9
HIF1A	hypoxia inducible factor 1 subunit alpha
HLA-A	major histocompatibility complex, class I, A
HLA-B	major histocompatibility complex, class I, B
HNF4A	hepatocyte nuclear factor 4 alpha
HNRNPL	heterogeneous nuclear ribonucleoprotein L
HTT	huntingtin
IFNA1/IFNA13	interferon alpha 1
IFNA6	interferon alpha 6
IFO8	importin 8
KCNJ2	potassium inwardly rectifying channel subfamily J member 2
MAPK10	mitogen-activated protein kinase 10
MCTP2	multiple C2 and transmembrane domain containing 2
MEF2C	myocyte enhancer factor 2C
NDUFB2	NADH:ubiquinone oxidoreductase subunit B2
NDUFV2	NADH:ubiquinone oxidoreductase core subunit V2
PNPLA7	patatin like phospholipase domain containing 7
PTCHD3	patched domain containing 3
RAB18	RAB18, member RAS oncogene family
RNF14	ring finger protein 14
SYT2	synaptotagmin 2
TMCC1	transmembrane and coiled-coil domain family 1
ZDHHC14	zinc finger DHHC-type containing 14
ZNF236	zinc finger protein 236
ZNF385B	zinc finger protein 385B
ZNF449	zinc finger protein 449
ZNF706	zinc finger protein 706
ZNF839	zinc finger protein 839

FIG. 54

Symbol	Entrez Gene Name
<i>SLC22A1</i>	solute carrier family 22 member 1
<i>UGT1A1</i>	UDP glucuronosyltransferase family 1 member A1
<i>UGT1A3</i>	UDP glucuronosyltransferase family 1 member A3
<i>UGT1A4</i>	UDP glucuronosyltransferase family 1 member A4
<i>UGT1A6</i>	UDP glucuronosyltransferase family 1 member A6
<i>UGT2B7</i>	UDP glucuronosyltransferase family 2 member B7

FIG. 55

Diseases Annotation	p-value
Psychosis	2.66E-57
Agitation	1.01E-49
Bipolar spectrum disorder	5.99E-48
Non-affective psychosis	3.33E-47
Treatment-resistant schizophrenia	9.83E-46

FIG. 56A

Upstream Regulator	p-value
Clozapine	8.85E-110
Haloperidol	1.45E-42
Chlorpromazine	6.59E-20
Ollanzapine	2E-19
Risperidone	5.45E-13

FIG. 56B

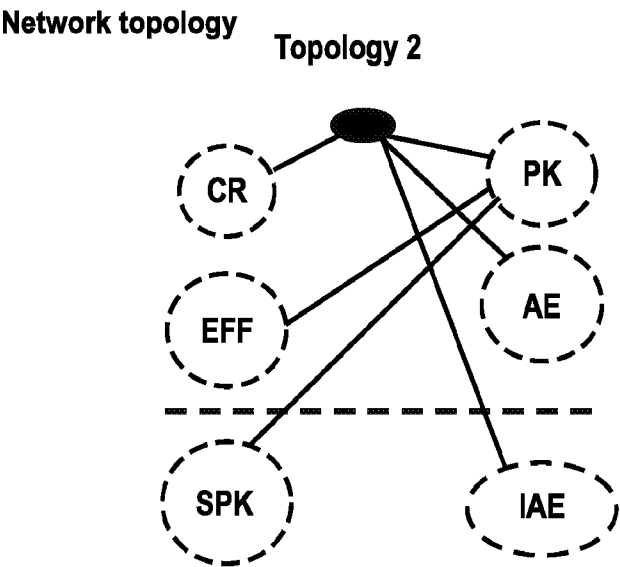


FIG. 56C

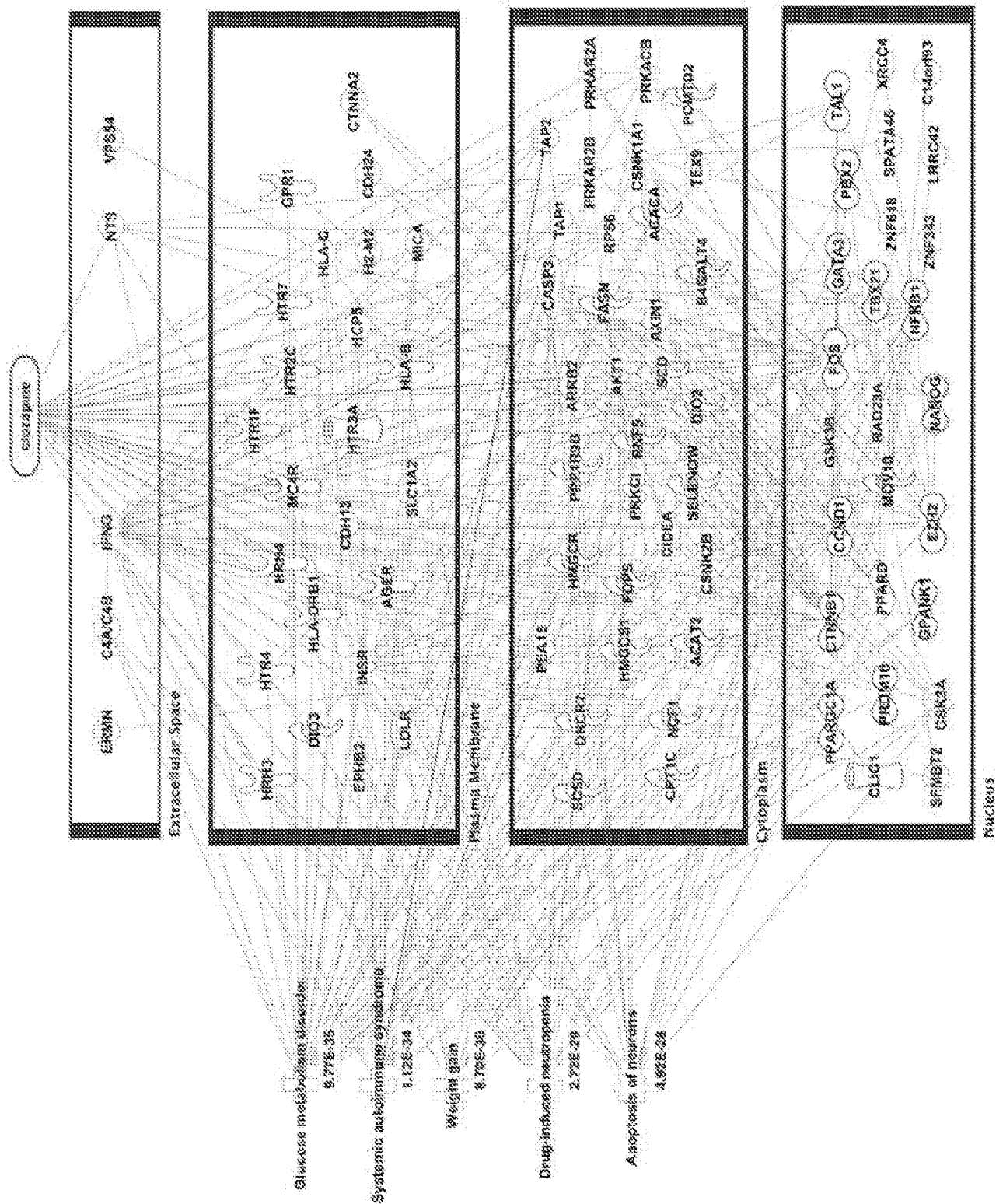
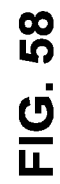


FIG. 57



Symbol	Entrez Gene Name
<i>BRD2</i>	bromodomain containing 2
<i>EHMT2</i>	euchromatic histone lysine methyltransferase 2
<i>HDAC2</i>	histone deacetylase 2
<i>HDAC3</i>	histone deacetylase 3
<i>KDM1A</i>	lysine demethylase 1A
<i>KDM6A</i>	lysine demethylase 6A
<i>KMT2A</i>	lysine methyltransferase 2A
<i>KMT2D</i>	lysine methyltransferase 2D
<i>MYT1</i>	myelin transcription factor 1
<i>SOX2</i>	SRY-box transcription factor 2
<i>WDR5</i>	WD repeat domain 5

FIG. 59

Symbol	Entrez Gene Name
<i>ADH7</i>	alcohol dehydrogenase 7 (class IV), mu or sigma polypeptide
<i>ADRA1A</i>	adrenoceptor alpha 1A
<i>ADRA1B</i>	adrenoceptor alpha 1B
<i>ADRA1D</i>	adrenoceptor alpha 1D
<i>ADRA2A</i>	adrenoceptor alpha 2A
<i>ADRA2B</i>	adrenoceptor alpha 2B
<i>ADRA2C</i>	adrenoceptor alpha 2C
<i>AGER</i>	advanced glycosylation end-product specific receptor
<i>BCAS1</i>	breast carcinoma amplified sequence 1
<i>BCL9</i>	BCL9 transcription coactivator
<i>BCL9L</i>	BCL9 like
<i>BDNF</i>	brain derived neurotrophic factor
<i>C11orf98</i>	chromosome 11 open reading frame 98
<i>CACNB2</i>	calcium voltage-gated channel auxillary subunit beta 2
<i>CASKIN2</i>	CASK interacting protein 2
<i>CASP3</i>	caspase 3
<i>CERS4</i>	Ceramide synthase 4
<i>CHRM1</i>	cholinergic receptor muscarinic 1
<i>CHRM3</i>	cholinergic receptor muscarinic 3
<i>CHRM4</i>	cholinergic receptor muscarinic 4
<i>CHRM5</i>	cholinergic receptor muscarinic 5
<i>COL16A1</i>	collagen type XVI alpha 1 chain
<i>COMT</i>	catechol-O-methyltransferase
<i>CYTH4</i>	cytohesin 4
<i>DLGAP1</i>	DLG associated protein 1
<i>DLGAP2</i>	DLG associated protein 2
<i>DRD1</i>	dopamine receptor D1
<i>DRD2</i>	dopamine receptor D2
<i>DRD3</i>	dopamine receptor D3
<i>DRD4</i>	dopamine receptor D4
<i>DRD5</i>	dopamine receptor D5
<i>DVL3</i>	dishevelled segment polarity protein 3
<i>EFHD1</i>	EF-hand domain family member D1
<i>EGR1</i>	early growth response 1
<i>ESR2</i>	estrogen receptor 2
<i>EVX1</i>	even-skipped homeobox 1
<i>FAM50A</i>	family with sequence similarity 50 member A
<i>FARP1</i>	FERM, ARH/RhoGEF and pleckstrin domain protein 1
<i>FOS</i>	Fos proto-oncogene, AP-1 transcription factor subunit
<i>FOXA1</i>	forkhead box A1
<i>GATA3</i>	GATA binding protein 3
<i>GRIA1</i>	glutamate ionotropic receptor AMPA type subunit 1
<i>GRIA2</i>	glutamate ionotropic receptor AMPA type subunit 2
<i>GRIN2B</i>	glutamate ionotropic receptor NMDA type subunit 2B
<i>HOMER1</i>	homer scaffold protein 1
<i>HRH1</i>	histamine receptor H1
<i>HTR1A</i>	5-hydroxytryptamine receptor 1A

FIG. 60-1

<i>HRT1B</i>	5-hydroxytryptamine receptor 1B
<i>HRT1D</i>	5-hydroxytryptamine receptor 1D
<i>HRT2A</i>	5-hydroxytryptamine receptor 2A
<i>HRT2B</i>	5-hydroxytryptamine receptor 2B
<i>HRT3A</i>	5-hydroxytryptamine receptor 3A
<i>HRT3B</i>	5-hydroxytryptamine receptor 3B
<i>HRT5A</i>	5-hydroxytryptamine receptor 5A
<i>HRT6</i>	5-hydroxytryptamine receptor 6
<i>KCNC2</i>	potassium voltage-gated channel subfamily C member 2
<i>KCNH2</i>	potassium voltage-gated channel subfamily H member 2
<i>KIRREL3</i>	kirre like nephrin family adhesion molecule 3
<i>LEP</i>	leptin
<i>MEIS2</i>	Meis homeobox 2
<i>MICA</i>	MHC class I polypeptide-related sequence A
<i>MISP3</i>	MISP family member 3
<i>MTERF4</i>	mitochondrial transcription termination factor 4
<i>MTNR1B</i>	melatonin receptor 1B
<i>NOTCH4</i>	notch receptor 4
<i>NR4A1</i>	nuclear receptor subfamily 4 group A member 1
<i>NR4A2</i>	nuclear receptor subfamily 4 group A member 2
<i>NR4A3</i>	nuclear receptor subfamily 4 group A member 3
<i>NRXN1</i>	neurexin 1
<i>NSUN5</i>	NOP2/Sun RNA methyltransferase 5
<i>NTRK2</i>	neurotrophic receptor tyrosine kinase 2
<i>PCDH19</i>	protocadherin 19
<i>PRDM15</i>	PR/SET domain 15
<i>PRDM16</i>	PR/SET domain 16
<i>PRKAA1</i>	Protein kinase AMP-activated catalytic subunit alpha 1
<i>PRL</i>	prolactin
<i>PRR12</i>	proline rich 12
<i>PVALB</i>	parvalbumin
<i>RGS14</i>	regulator of G protein signaling 14
<i>RIC3</i>	RIC3 acetylcholine receptor chaperone
<i>SDK1</i>	sidekick cell adhesion molecule 1
<i>SGK1</i>	serum/glucocorticoid regulated kinase 1
<i>SHANK1</i>	SH3 and multiple ankyrin repeat domains 1
<i>SLITRK1</i>	SLIT and NTRK like family member 1
<i>SNN</i>	Stannin
<i>SOX2</i>	SRY-box transcription factor 2
<i>SREBF1</i>	sterol regulatory element binding transcription factor 1
<i>SREBF2</i>	sterol regulatory element binding transcription factor 2
<i>SYP</i>	synaptophysin
<i>TAC1</i>	tachykinin precursor 1
<i>UCP1</i>	uncoupling protein 1
<i>WNT5A</i>	Wnt family member 5A
<i>ZNF618</i>	zinc finger protein 618
<i>ZNF652</i>	zinc finger protein 652
<i>ZNF787</i>	zinc finger protein 787

FIG. 60-2

Symbol	Entrez Gene Name
ACAC2	acetyl-CoA carboxylase alpha
ACAT2	acetyl-CoA acetyltransferase 2
AGER	advanced glycosylation end-product specific receptor
AKT1	AKT serine/threonine kinase 1
ARRB2	arrestin beta 2
AXIN1	axin 1
B4GALT4	beta-1,4 galactosyltransferase 4
C14ORF93	chromosome 14 open reading frame 93
C4A/C4B	complement C4B (Chido blood group)
CASP3	caspase 3
CCND1	cyclin D1
CDH13	cadherin 13
CDH24	cadherin 24
CIDEA	cell death inducing DFFA like effector a
CL/C1	chloride intracellular channel 1
CPT1C	carnitine palmitoyltransferase 1C
CSNK1A1	casein kinase 1 alpha 1
CSNK2B	casein kinase 2 beta
CTNNA2	catenin alpha 2
CTNNB1	catenin beta 1
DHCR7	7-dehydrocholesterol reductase
DIO2	iodothyronine deiodinase 2
DIO3	iodothyronine deiodinase 3
EPHB2	EPH receptor B2
ERMN	ermin
EZH2	enhancer of zeste 2 polycomb repressive complex 2 subunit
FASN	fatty acid synthase
FDPS	farnesyl diphosphate synthase
FOS	Fos proto-oncogene, AP-1 transcription factor subunit
GATA3	GATA binding protein 3
GPANK1	G-patch domain and ankyrin repeats 1
GPR1	G protein-coupled receptor 1
GSK3A	glycogen synthase kinase 3 alpha
GSK3B	glycogen synthase kinase 3 beta
H2-M2	histocompatibility 2, M region locus 2
HCP5	HLA complex P5
HLA-B	major histocompatibility complex, class I, B
HLA-C	major histocompatibility complex, class I, C
HLA-DRBB1	major histocompatibility complex, class II, DR beta 1
HMGCR	3-hydroxy-3-methylglutaryl-CoA reductase 1
HMGCS1	3-hydroxy-3-methylglutaryl-CoA synthase 1
HRH3	histamine receptor H3

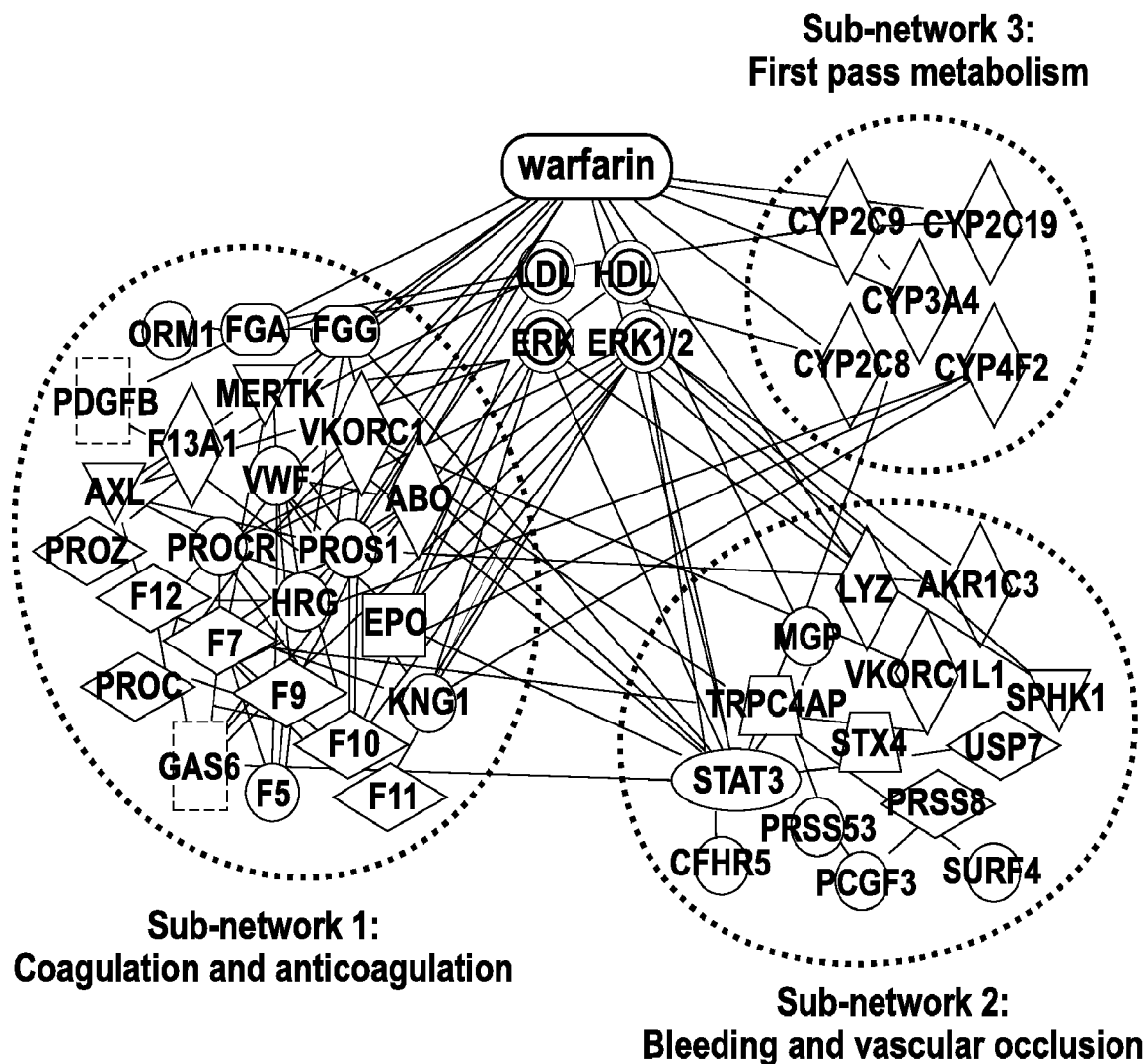
FIG. 61-1

<i>HRH4</i>	histamine receptor H4
<i>HTR1F</i>	5-hydroxytryptamine receptor 1F
<i>HTR2C</i>	5-hydroxytryptamine receptor 2C
<i>HTR3A</i>	5-hydroxytryptamine receptor 3A
<i>HTR4</i>	5-hydroxytryptamine receptor 4
<i>HTR7</i>	5-hydroxytryptamine receptor 7
<i>IFNG</i>	interferon gamma
<i>INSR</i>	insulin receptor
<i>LDLR</i>	low density lipoprotein receptor
<i>LRRC42</i>	leucine rich repeat containing 42
<i>MC4R</i>	melanocortin 4 receptor
<i>MICA</i>	MHC class I polypeptide-related sequence A
<i>MOV10</i>	Mov10 RISC complex RNA helicase
<i>NANOG</i>	Nanog homeobox
<i>NCF1</i>	neutrophil cytosolic factor 1
<i>NFKB1</i>	nuclear factor kappa B subunit 1
<i>NTS</i>	neurotensin
<i>PBX2</i>	PBX homeobox 2
<i>PCMTD2</i>	protein-L-isoaspartate (D-aspartate) O-methyltransferase domain containing 2
<i>PEA15</i>	proliferation and apoptosis adaptor protein 15
<i>PPARD</i>	peroxisome proliferator activated receptor delta
<i>PPARGC1A</i>	PPARG coactivator 1 alpha
<i>PPP1R9B</i>	protein phosphatase 1 regulatory subunit 9B
<i>PRDM16</i>	PR/SET domain 16
<i>PRKACB</i>	protein kinase cAMP-activated catalytic subunit beta
<i>PRKAR2A</i>	protein kinase cAMP-dependent type II regulatory subunit alpha
<i>PRKAR2B</i>	protein kinase cAMP-dependent type II regulatory subunit beta
<i>PRKCI</i>	protein kinase C iota
<i>RAD23A</i>	RAD23 homolog A, nucleotide excision repair protein
<i>RNF5</i>	ring finger protein 5
<i>RPS6</i>	ribosomal protein S6
<i>SC5D</i>	sterol-C5-desaturase
<i>SCD</i>	stearoyl-CoA desaturase
<i>SELENOW</i>	selenoprotein W
<i>SFMBT2</i>	Scm like with four mbt domains 2
<i>SLC1A2</i>	solute carrier family 1 member 2
<i>SPATA46</i>	spermatogenesis associated 46
<i>TAL1</i>	TAL bHLH transcription factor 1, erythroid differentiation factor
<i>TAP1</i>	transporter 1, ATP binding cassette subfamily B member
<i>TAP2</i>	transporter 2, ATP binding cassette subfamily B member
<i>TBX21</i>	t-box transcription factor 21
<i>TEX9</i>	testis expressed 9
<i>VPS54</i>	VPS54 subunit of GARP complex
<i>XRCC4</i>	X-ray repair cross complementing 4
<i>ZNF343</i>	zinc finger protein 343
<i>ZNF618</i>	zinc finger protein 618

FIG. 61-2

Symbol	Entrez Gene Name
<i>CYP1A1</i>	cytochrome P450 family 1 subfamily A member 1
<i>CYP1A2</i>	cytochrome P450 family 1 subfamily A member 2
<i>CYP2C19</i>	cytochrome P450 family 2 subfamily C member 19
<i>CYP2C8</i>	cytochrome P450 family 2 subfamily C member 8
<i>CYP2C9</i>	cytochrome P450 family 2 subfamily C member 9
<i>CYP2D6</i>	cytochrome P450 family 2 subfamily D member 6
<i>CYP2E1</i>	cytochrome P450 family 2 subfamily E member 1
<i>CYP3A4</i>	cytochrome P450 family 3 subfamily A member 4
<i>UGT1A4</i>	UDP glucuronosyltransferase family 1 member A4
<i>UGT1A7</i>	UDP glucuronosyltransferase family 1 member A9
<i>UGT2B10</i>	UDP glucuronosyltransferase family 2 member B10

FIG. 62

Warfarin pharmacogenomic network**FIG. 63A**

Warfarin pharmacogenomic network - gene set enrichment

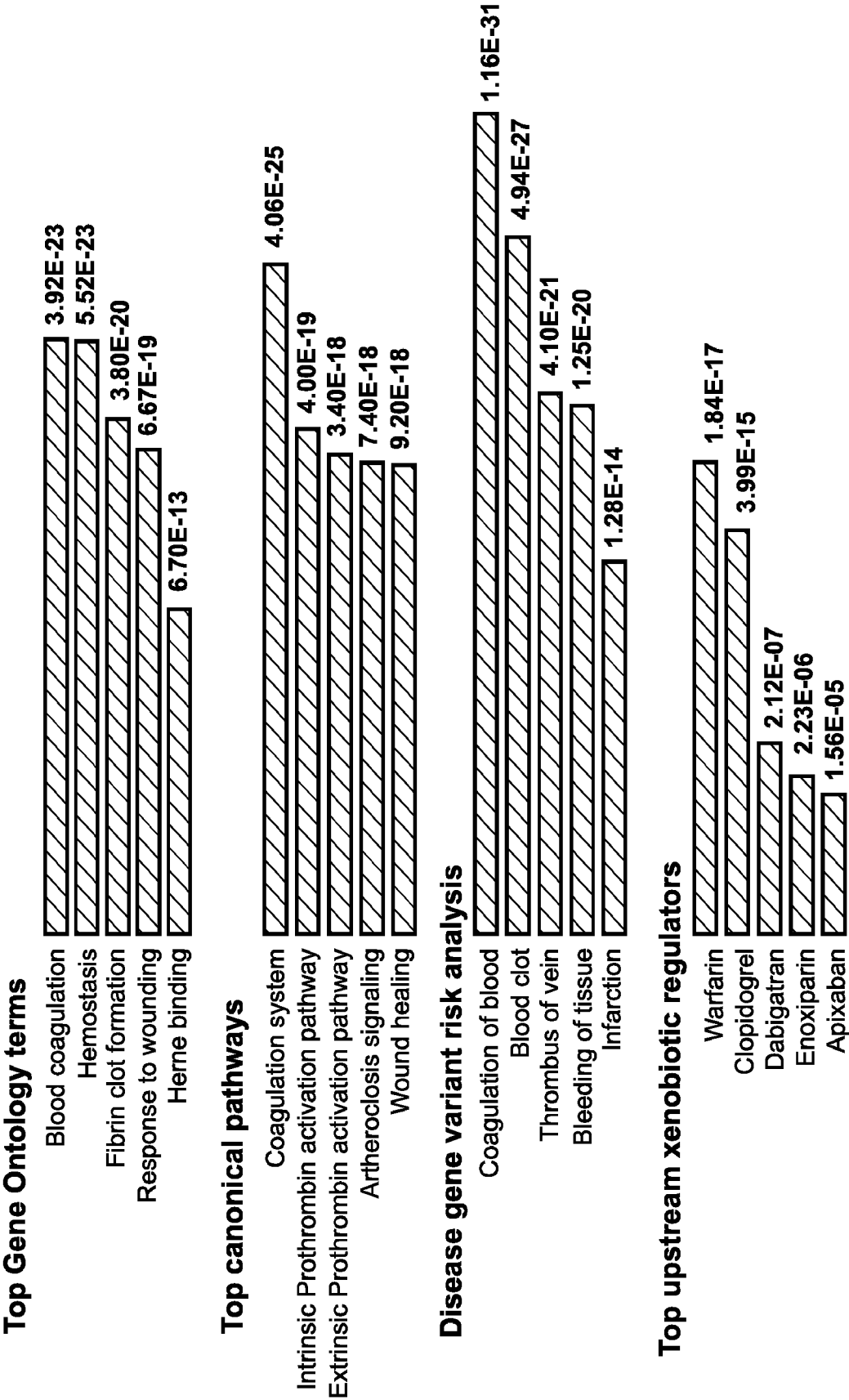
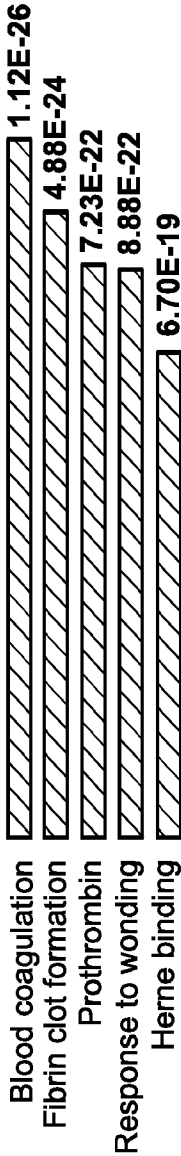


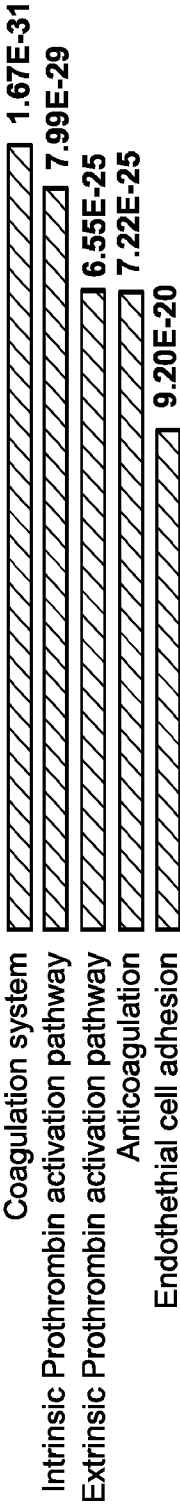
FIG. 63B

Sub-network 1: Coagulation and anticoagulation

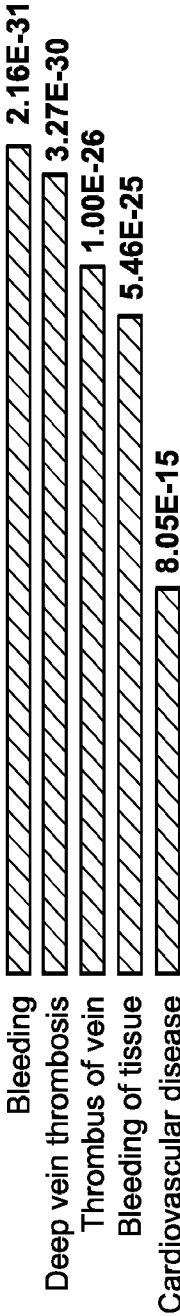
Top Gene Ontology terms



Top canonical pathways



Disease gene variant risk analysis



Top upstream xenobiotic regulators

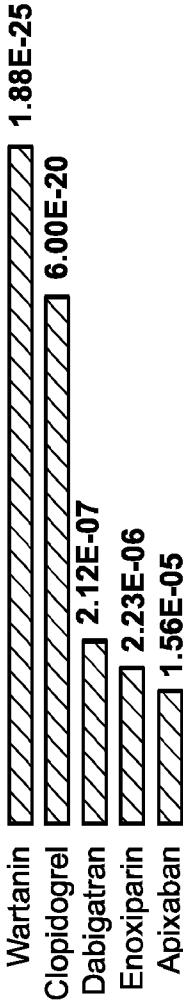


FIG. 63C

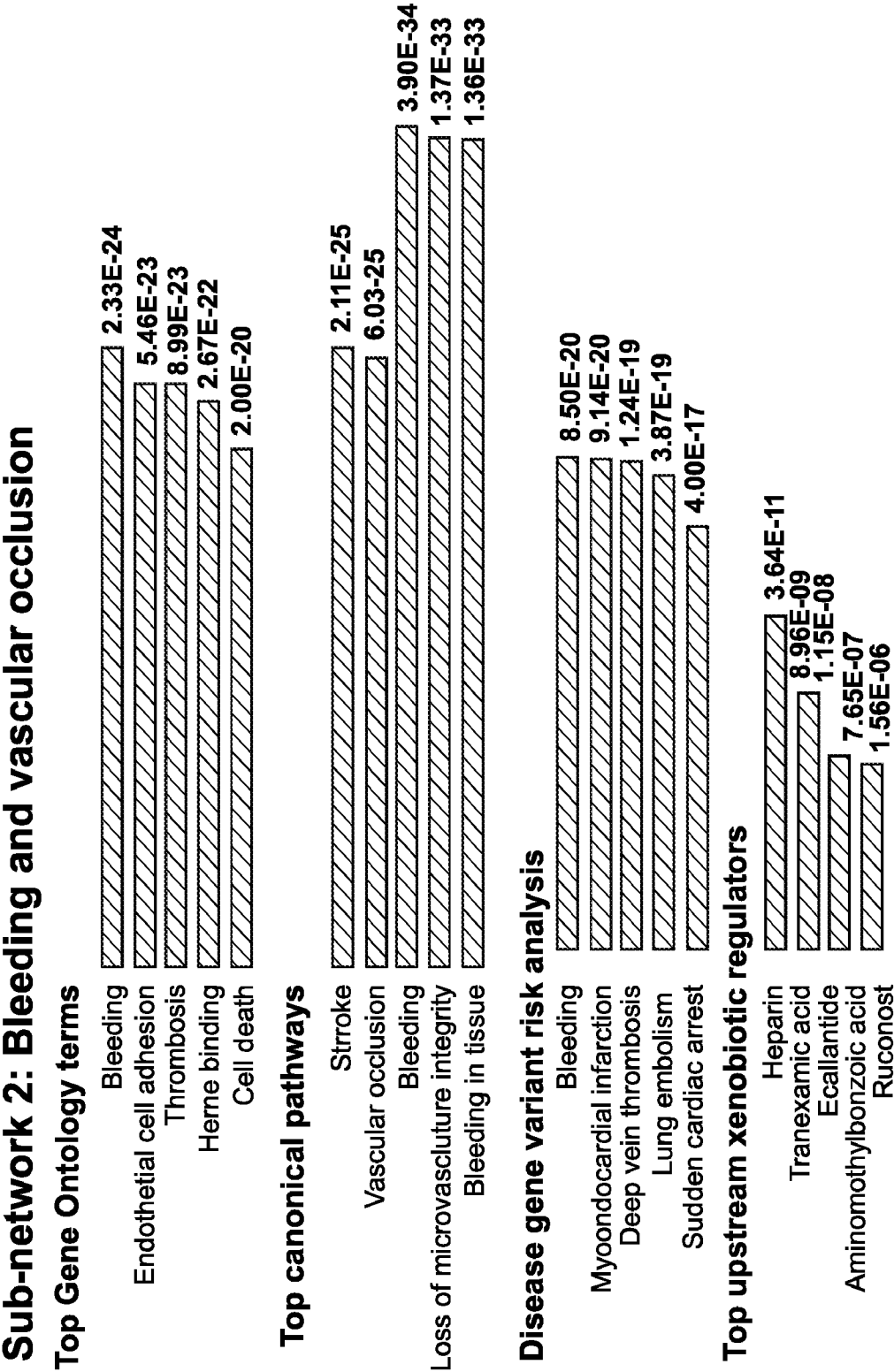


FIG. 63D