Table S1. Genetic SNV and CNV events from the Simons Simplex Collection used as input for NETBAG. See attached Excel spreadsheet.

Table S2. Implicated ASD network genes and associated prioritization annotations (average $\log_2$ brain expression and truncating SNV status). See attached Excel spreadsheet.

Table S3. Gene Ontology (GO) terms associated with the functional clusters			
Postsynaptic density (Fig. 1, cyan)			
GO ID	**Ontology**	**Term**	**P-value**
GO:0045202	CC	Synapse	$1x10^{-9}$
GO:0044456	CC	synapse part	$3x10^{-7}$
GO:0014069	CC	postsynaptic density	$4x10^{-6}$
GO:0045211	CC	postsynaptic membrane	$4x10^{-5}$
GO:0004385	MF	guanylate kinase activity	0.0009
GO:0019201	MF	nucleotide kinase activity	0.002
GO:0007268	BP	synaptic transmission	0.002
GO:0019226	BP	transmission of nerve impulse	0.003
GO:0016776	MF	phosphotransferase activity, phosphate group as acceptor	0.003
GO:0019205	MF	nucleobase, nucleoside, nucleotide kinase activity	0.004
GO:0048489	BP	synaptic vesicle transport	0.008
GO:0050808	BP	synapse organization	0.02
GO:0003001	BP	generation of a signal involved in cell-cell signaling	0.03
Channel activity (Fig. 1, blue)			
GO ID	**Ontology**	**Term**	**P-value**
GO:0046873	MF	metal ion transmembrane transporter activity	$1x10^{-14}$
GO:0005216	MF	ion channel activity	$3x10^{-14}$
GO:0022838	MF	substrate specific channel activity	$3x10^{-14}$
GO:0005261	MF	cation channel activity	$4x10^{-14}$
GO:0022836	MF	gated channel activity	$5x10^{-14}$
GO:0005262	MF	calcium channel activity	$2x10^{-12}$
GO:0006816	BP	calcium ion transport	$6x10^{-11}$
GO:0015674	BP	di-, tri-valent inorganic cation transport	$2x10^{-10}$
GO:0005245	MF	voltage-gated calcium channel activity	$7x10^{-9}$
GO:0022843	MF	voltage-gated cation channel activity	$2x10^{-8}$
GO:0034702	CC	ion channel complex	$2x10^{-8}$
GO:0022832	MF	voltage-gated channel activity	$1x10^{-7}$
GO:0005244	MF	voltage-gated ion channel activity	$1x10^{-7}$
GO:0022834	MF	ligand-gated channel activity	$1x10^{-5}$
GO:0015276	MF	ligand-gated ion channel activity	$1x10^{-5}$
GO:0034703	CC	cation channel complex	$3x10^{-5}$
GO:0005891	CC	voltage-gated calcium channel complex	$8x10^{-5}$
GO:0034704	CC	calcium channel complex	0.0001
GO:0044456	CC	synapse part	0.0003
GO:0045211	CC	postsynaptic membrane	0.0005
GO:0007187	BP	G-protein signaling, coupled to cyclic nucleotide second messenger	0.0009
GO:0019932	BP	second-messenger-mediated signaling	0.0009
GO:0019935	BP	cyclic-nucleotide-mediated signaling	0.001
GO:0042383	CC	sarcolemma	0.001
GO:0005230	MF	extracellular ligand-gated ion channel activity	0.002

GO:0045202	CC	synapse	0.002
GO:0007268	BP	synaptic transmission	0.002
GO:0019226	BP	transmission of nerve impulse	0.003
GO:0030315	CC	T-tubule	0.004
GO:0042165	MF	neurotransmitter binding	0.004
GO:0006873	BP	cellular ion homeostasis	0.004
GO:0055082	BP	cellular chemical homeostasis	0.004
GO:0043176	MF	amine binding	0.005
GO:0007188	BP	G-protein signaling, coupled to cAMP nucleotide second messenger	0.005
GO:0045761	BP	regulation of adenylate cyclase activity	0.006
GO:0019933	BP	cAMP-mediated signaling	0.006
GO:0031279	BP	regulation of cyclase activity	0.007
GO:0051339	BP	regulation of lyase activity	0.007
GO:0030817	BP	regulation of cAMP biosynthetic process	0.007
GO:0030814	BP	regulation of cAMP metabolic process	0.007
GO:0008066	MF	glutamate receptor activity	0.007
GO:0030799	BP	regulation of cyclic nucleotide metabolic process	0.007
GO:0030802	BP	regulation of cyclic nucleotide biosynthetic process	0.007
GO:0030808	BP	regulation of nucleotide biosynthetic process	0.007
GO:0006140	BP	regulation of nucleotide metabolic process	0.008
GO:0016529	CC	sarcoplasmic reticulum	0.01
GO:0016528	CC	sarcoplasm	0.01
GO:0007613	BP	memory	0.02
GO:0031674	CC	I band	0.02
GO:0006874	BP	cellular calcium ion homeostasis	0.03
GO:0055074	BP	calcium ion homeostasis	0.03
GO:0006875	BP	cellular metal ion homeostasis	0.03
GO:0031280	BP	negative regulation of cyclase activity	0.03
GO:0007194	BP	negative regulation of adenylate cyclase activity	0.03
GO:0051350	BP	negative regulation of lyase activity	0.03
GO:0055065	BP	metal ion homeostasis	0.03
GO:0030005	BP	cellular di-, tri-valent inorganic cation homeostasis	0.04
GO:0055066	BP	di-, tri-valent inorganic cation homeostasis	0.04
Neuronal signaling / cytoskeleton (Fig. 1, green)			
GO ID	**Ontology**	**Term**	**P-value**
GO:0051015	MF	actin filament binding	$6x10^{-9}$
GO:0032989	BP	cellular component morphogenesis	$3x10^{-7}$
GO:0030036	BP	actin cytoskeleton organization	$3x10^{-7}$
GO:0015629	CC	actin cytoskeleton	$4x10^{-7}$
GO:0030029	BP	actin filament-based process	$5x10^{-7}$
GO:0005913	CC	cell-cell adherens junction	$6x10^{-7}$
GO:0031252	CC	cell leading edge	$9x10^{-7}$
GO:0003779	MF	actin binding	$2x10^{-6}$
GO:0004713	MF	protein tyrosine kinase activity	$3x10^{-6}$
GO:0000902	BP	cell morphogenesis	$3x10^{-6}$
GO:0030030	BP	cell projection organization	$4x10^{-6}$
GO:0005911	CC	cell-cell junction	$6x10^{-6}$
GO:0031175	BP	neuron projection development	$7x10^{-6}$
GO:0005912	CC	adherens junction	$1x10^{-5}$
GO:0048666	BP	neuron development	$1x10^{-5}$
GO:0007167	BP	enzyme linked receptor protein signaling pathway	$1x10^{-5}$
GO:0004714	MF	transmembrane receptor protein tyrosine kinase	$2x10^{-5}$

		activity	
GO:0070161	CC	anchoring junction	$2x10^{-5}$
GO:0001725	CC	stress fiber	$7x10^{-5}$
GO:0032432	CC	actin filament bundle	$9x10^{-5}$
GO:0042641	CC	actomyosin	0.0001
GO:0007507	BP	heart development	0.0001
GO:0007169	BP	transmembrane receptor protein tyrosine kinase signaling pathway	0.0001
GO:0005916	CC	fascia adherens	0.0002
GO:0030027	CC	lamellipodium	0.0002
GO:0000904	BP	cell morphogenesis involved in differentiation	0.0003
GO:0022604	BP	regulation of cell morphogenesis	0.0003
GO:0014704	CC	intercalated disc	0.0005
GO:0005938	CC	cell cortex	0.0006
GO:0048812	BP	neuron projection morphogenesis	0.0007
GO:0030425	CC	dendrite	0.0009
GO:0005516	MF	calmodulin binding	0.001
GO:0045296	MF	cadherin binding	0.001
GO:0044449	CC	contractile fiber part	0.001
GO:0043005	CC	neuron projection	0.001
GO:0043531	MF	ADP binding	0.001
GO:0043292	CC	contractile fiber	0.002
GO:0048858	BP	cell projection morphogenesis	0.002
GO:0032990	BP	cell part morphogenesis	0.002
GO:0007409	BP	axonogenesis	0.003
GO:0016477	BP	cell migration	0.003
GO:0008285	BP	negative regulation of cell proliferation	0.004
GO:0048667	BP	cell morphogenesis involved in neuron differentiation	0.004
GO:0007243	BP	protein kinase cascade	0.004
GO:0050839	MF	cell adhesion molecule binding	0.005
GO:0008013	MF	beta-catenin binding	0.005
GO:0048870	BP	cell motility	0.006
GO:0051674	BP	localization of cell	0.006
GO:0030898	MF	actin-dependent ATPase activity	0.007
GO:0007265	BP	Ras protein signal transduction	0.007
GO:0030017	CC	sarcomere	0.007
GO:0043010	BP	camera-type eye development	0.007
GO:0001568	BP	blood vessel development	0.008
GO:0007611	BP	learning or memory	0.008
GO:0030018	CC	Z disc	0.008
GO:0001944	BP	vasculature development	0.009
GO:0017048	MF	Rho GTPase binding	0.009
GO:0051271	BP	negative regulation of cell motion	0.009
GO:0019903	MF	protein phosphatase binding	0.009
GO:0044433	CC	cytoplasmic vesicle part	0.01
GO:0030016	CC	myofibril	0.01
GO:0042692	BP	muscle cell differentiation	0.01
GO:0030426	CC	growth cone	0.01
GO:0016328	CC	lateral plasma membrane	0.01
GO:0030427	CC	site of polarized growth	0.01
GO:0031674	CC	I band	0.01
GO:0040012	BP	regulation of locomotion	0.01
GO:0051270	BP	regulation of cell motion	0.01

GO:0019902	MF	phosphatase binding	0.01
GO:0016337	BP	cell-cell adhesion	0.01
GO:0009798	BP	axis specification	0.01
GO:0001654	BP	eye development	0.01
GO:0010035	BP	response to inorganic substance	0.02
GO:0010769	BP	regulation of cell morphogenesis involved in differentiation	0.02
GO:0016459	CC	myosin complex	0.02
GO:0001726	CC	ruffle	0.02
GO:0005083	MF	small GTPase regulator activity	0.02
GO:0031594	CC	neuromuscular junction	0.02
GO:0007423	BP	sensory organ development	0.02
GO:0000146	MF	microfilament motor activity	0.03
GO:0030424	CC	axon	0.03
GO:0048593	BP	camera-type eye morphogenesis	0.03
GO:0043025	CC	cell soma	0.03
GO:0030334	BP	regulation of cell migration	0.04
GO:0019992	MF	diacylglycerol binding	0.04
GO:0030111	BP	regulation of Wnt receptor signaling pathway	0.04
GO:0018108	BP	peptidyl-tyrosine phosphorylation	0.04
GO:0045859	BP	regulation of protein kinase activity	0.04
GO:0018212	BP	peptidyl-tyrosine modification	0.04
GO:0007163	BP	establishment or maintenance of cell polarity	0.04
GO:0003774	MF	motor activity	0.04
GO:0043549	BP	regulation of kinase activity	0.04
GO:0048729	BP	tissue morphogenesis	0.04
GO:0019904	MF	protein domain specific binding	0.05
GO:0030705	BP	cytoskeleton-dependent intracellular transport	0.05
Chromatin modification/regulation (Fig. 1, red)			
GO ID	**Ontology**	**Term**	**P-value**
GO:0016568	BP	chromatin modification	$3x10^{-13}$
GO:0006325	BP	chromatin organization	$1x10^{-12}$
GO:0004386	MF	helicase activity	$4x10^{-10}$
GO:0016887	MF	ATPase activity	$2x10^{-5}$
GO:0016569	BP	covalent chromatin modification	$4x10^{-5}$
GO:0016585	CC	chromatin remodeling complex	$7x10^{-5}$
GO:0042623	MF	ATPase activity, coupled	0.0002
GO:0003712	MF	transcription cofactor activity	0.0003
GO:0016570	BP	histone modification	0.0003
GO:0000123	CC	histone acetyltransferase complex	0.0003
GO:0008026	MF	ATP-dependent helicase activity	0.0004
GO:0070035	MF	purine NTP-dependent helicase activity	0.0004
GO:0016573	BP	histone acetylation	0.001
GO:0006473	BP	protein amino acid acetylation	0.001
GO:0000122	BP	negative regulation of transcription from RNA polymerase II promoter	0.001
GO:0016564	MF	transcription repressor activity	0.002
GO:0043543	BP	protein amino acid acylation	0.002
GO:0003678	MF	DNA helicase activity	0.003
GO:0042393	MF	histone binding	0.004
GO:0000118	CC	histone deacetylase complex	0.004
GO:0017053	CC	transcriptional repressor complex	0.004
GO:0000398	BP	nuclear mRNA splicing, via spliceosome	0.004

GO:0000377	BP	RNA splicing, via transesterification reactions with bulged adenosine as nucleophile	0.004
GO:0000375	BP	RNA splicing, via transesterification reactions	0.004
GO:0045892	BP	negative regulation of transcription, DNA-dependent	0.005
GO:0051253	BP	negative regulation of RNA metabolic process	0.005
GO:0016071	BP	mRNA metabolic process	0.006
GO:0010553	BP	negative regulation of specific transcription from RNA polymerase II promoter	0.007
GO:0008380	BP	RNA splicing	0.008
GO:0006281	BP	DNA repair	0.008
GO:0008094	MF	DNA-dependent ATPase activity	0.008
GO:0035267	CC	NuA4 histone acetyltransferase complex	0.01
GO:0003743	MF	translation initiation factor activity	0.01
GO:0043189	CC	H4/H2A histone acetyltransferase complex	0.01
GO:0032582	BP	negative regulation of gene-specific transcription	0.01
GO:0043968	BP	histone H2A acetylation	0.01
GO:0003714	MF	transcription corepressor activity	0.01
GO:0006397	BP	mRNA processing	0.01
GO:0003682	MF	chromatin binding	0.01
GO:0006974	BP	response to DNA damage stimulus	0.03
GO:0043967	BP	histone H4 acetylation	0.03
GO:0070647	BP	protein modification by small protein conjugation or removal	0.03
GO:0040029	BP	regulation of gene expression, epigenetic	0.03
GO:0008135	MF	translation factor activity, nucleic acid binding	0.03
GO:0005876	CC	spindle microtubule	0.04
GO:0000785	CC	chromatin	0.04
GO:0035064	MF	methylated histone residue binding	0.04

Table S3. Gene Ontology (GO) terms enriched in functional clusters of the implicated network (Fig. 1), as identified by DAVID (david.abcc.ncifcrf.gov). P-values shown in the table were corrected for multiple hypotheses testing using the Benjamini procedure available in DAVID. The ontology column indicates GO domain: BP for biological process, MF for molecular function, and CC for cellular component. Non-specific terms, i.e. terms associated with more than 400 human genes, are not shown.

Table S4. Gene Ontology (GO) terms using brain-expressed background genes			
GO ID	**Ontology**	**Term**	**P-value**
GO:0045202	CC	Synapse	$6x10^{-5}$
GO:0051015	MF	actin filament binding	$9x10^{-5}$
GO:0016887	MF	ATPase activity	0.0005
GO:0005938	CC	cell cortex	0.0008
GO:0005911	CC	cell-cell junction	0.0009
GO:0005913	CC	cell-cell adherens junction	0.0009
GO:0031252	CC	cell leading edge	0.001
GO:0045211	CC	postsynaptic membrane	0.001
GO:0007611	BP	learning or memory	0.002
GO:0005262	MF	calcium channel activity	0.002
GO:0044456	CC	synapse part	0.004
GO:0004386	MF	helicase activity	0.005
GO:0030036	BP	actin cytoskeleton organization	0.006
GO:0030029	BP	actin filament-based process	0.006
GO:0014069	CC	postsynaptic density	0.006

GO:0016568	BP	chromatin modification	0.008
GO:0030425	CC	Dendrite	0.02
GO:0015629	CC	actin cytoskeleton	0.02
GO:0043005	CC	neuron projection	0.02

Table S4. Gene Ontology (GO) terms enriched in the implicated network (Fig. 1), as identified by DAVID using brain-expressed background genes. Background genes used are genes in the top half of all human genes in terms of their average brain expression levels based on the Human Brain Transcriptome database. Notably, the average expression level of human genes selected in this way is very similar to the average expression level of genes in the implicated network. P-values shown in the table were corrected for multiple hypotheses testing using the Benjamini procedure available in DAVID. Non-specific terms, i.e. terms associated with more than 400 human genes, are not shown.

Table S5. Overlap between ASD gene sets and additional FMRP targets or PSD proteins					
Gene set	Number of genes	Ascano *et al.* FMRP targets		Bayes *et al.* PSD proteins	
		Expected : observed	P-value	Expected : observed	P-value
Network genes	159	17.5 : 32 (1 : 1.83)	0.0008	8.52 : 29 (1 : 3.4)	$7x10^{-9}$
Truncating SNV genes	108	11.9 : 13 (1 : 1.09)	0.8	5.79 : 11 (1 : 1.9)	0.05
Network non-truncating-SNV genes	138	15.2 : 25 (1 : 1.65)	0.013	7.4 : 22 (1 : 2.97)	$5x10^{-6}$
Neuronal signaling/cytoskeleton cluster genes	69	7.59 : 13 (1 : 1.71)	0.05	3.7 : 15 (1 : 4.06)	$3x10^{-6}$
Chromatin modification/regulation cluster genes	50	5.5 : 12 (1 : 2.18)	0.01	2.68 : 2 (1 : 0.746)	1
Postsynaptic density cluster genes	11	1.21 : 2 (1 : 1.65)	0.3	0.59 : 7 (1 : 11.9)	$3x10^{-7}$
Channel activity cluster genes	21	2.31 : 1 (1 : 0.43)	0.7	1.13 : 3 (1 : 2.66)	0.1
Non-network SNV genes	449	49.4 : 45 (1 : 0.91)	0.5	24.1 : 14 (1 : 0.582)	0.04
Sibling SNV genes	355	39.1 : 47 (1 : 1.20)	0.2	19 : 20 (1 : 1.05)	0.8

Table S5. The expected and observed number of FMRP targets[30] and PSD-localized proteins[31] among different sets of implicated genes. The expected numbers of FMRP targets or PSD proteins were obtained based on the proportion of rare synonymous variants observed in a recent large-scale survey of human genetic variation[29]. The significances of the overlaps were established using the two-tail binominal test.

Table S6. Overlap between ASD gene sets and FMRP targets compared to matched null sets			
Gene set	**Number of genes**	**Expected : observed (Ratio)**	**P-value**
Network genes	159	29.6 : 48 (1 : 1.62)	< 0.0001
Truncating SNV network genes	21	4.1 : 8 (1 : 1.94)	0.02
Non-truncating SNV network genes	138	25.4 : 40 (1 : 1.57)	0.0004
Truncating SNV genes	108	14.9 : 25 (1 : 1.68)	0.0014
Non-network SNV genes	449	44.6 : 40 (1 : 0.90)	0.8
Sibling SNV genes	355	38.9 : 47 (1 : 1.21)	0.1

Table S6. The expected and observed number of FMRP targets proteins from Darnell *et al.* (2008). The expected numbers of FMRP targets were obtained by comparing overlap with sets of random genes of similar protein length and network connectivity to the genes in various sets. The test P-values reflect the probability of observing a matched gene set with the FMRP overlap greater or equal overlap to the one observed in real data.

Table S7. Probands versus siblings expression biases across brain regions		
Brain region	**Network genes**	**Truncating SNVs**
Amygdala	0.98	0.63
Cerebellum	0.96	0.59

Frontal	1.00	0.67
Hippocampus	0.98	0.68
Occipital	1.01	0.67
Parietal	1.01	0.66
Striatum/ganglia	1.00	0.64
Temporal	1.01	0.66
Thalamus	0.90	0.57

Table S7. Probands versus siblings expression biases for network genes and for truncating SNV genes across different brain regions. Human expression data used to calculate the biases were obtained from the HBT database. To quantify the expression bias for each brain region, we calculated the difference between the average $\log_2$ expression of implicated genes and the average $\log_2$ expression of genes harboring SNVs in unaffected siblings. For all comparisons in the table, the Wilcoxon rank-sum one-tail test P-values after the Bonferroni correction were lower than $1x10^{-20}$.

Table S8. Probands versus siblings expression biases across CNS cell types

Primary cell type	Network genes		Recurrent truncating SNVs		Corrected Stouffer's P-value	Corrected Fisher's P-value
	Bias	P-value	Bias	P-value		
Astroglia (includes Bergman Glia)	0.01	0.3	−0.08	0.4	1	1
Astroglia (reactive and non-reactive, JD130 line)	0.02	0.2	0.68	0.2	1	1
Astroglia (reactive and non-reactive, JD133 line)	−0.01	0.2	0.76	0.15	1	1
Bergman Glia	0.14	0.2	0.53	0.3	1	1
Cholinergic Neurons (corpus striatum)	−0.01	0.3	0.91	0.05	1	1
Cholinergic Projection Neurons (basal forebrain)	0.01	0.3	1.07	**0.05**	1	1
Drd1 Positive Medium Spiny Neurons (striatum)	0.40	**0.007**	2.09	**0.0005**	**0.0006**	**0.001**
Drd2 Positive Medium Spiny Neurons (striatum)	0.42	**0.01**	1.30	**0.03**	**0.04**	0.07
Granule Cell Layer Interneurons (Inner Golgi Cells)	−0.14	0.2	0.39	0.2	1	1
Granule Cells, Deep Cerebellar Nuclei	0.40	**0.007**	1.24	**0.04**	**0.03**	0.06
Interneurons (cortex)	0.30	0.04	2.12	**0.001**	**0.008**	**0.012**
Layer 5a Corticostriatal Pyramidal Neurons	0.45	**0.02**	2.31	**0.0015**	**0.005**	**0.008**
Layer 5b Corticospinal, Corticopontine Pyramidal Neurons, and Small Pyramidal Neurons	0.35	0.04	2.14	**0.002**	**0.014**	**0.02**
Layer 6 Corticothalamic Pyramidal Neurons	0.36	0.03	2.41	**0.0006**	**0.004**	**0.005**
Mature Oligodendrocytes (cerebellum)	0.13	0.2	0.87	0.1	1	1
Mature Oligodendrocytes (cortex)	0.04	0.3	1.44	**0.02**	0.8	0.9
Mature Oligodendrocytes and Progenitors (cerebellum)	0.02	0.3	0.33	0.4	1	1
Mature Oligodendrocytes and Progenitors (cortex)	0.005	0.4	1.09	0.07	1	1
Mixed Neurons (cortex)	0.37	**0.01**	2.35	**0.0004**	**0.0008**	**0.0014**
Motor Neurons, Cholinergic Interneurons	−0.20	0.7	0.17	0.4	1	1
Motor Neurons, Midbrain Cholinergic Neurons	−0.16	0.5	0.23	0.4	1	1
Neurons (cortex)	0.12	0.05	1.43	**0.007**	**0.04**	0.08
Purkinje Cells	0.03	0.04	0.38	0.16	0.6	0.9
Stellate and Basket Cells	0.15	0.14	0.36	0.5	1	1
Unipolar Brush Cells (mGluR1 subtype)	0.19	0.16	1.62	**0.02**	0.4	0.5

Table S8. Probands versus siblings cell expression biases across 25 cell types of the central nervous system for implicated network genes and for genes with recurrent truncating *de novo* SNVs. The biases were calculated using *Mus. musculus* expression data obtained from the study by Doyle *et al*.[17] To quantify the expression bias for each cell type, we calculate the difference between the average $\log_2$ expression of mouse orthologs of human implicated genes and the average $\log_2$ expression of ortholog genes harboring SNVs in unaffected siblings. The significances of the cell type expression biases were calculated using a one-tail Wilcoxon rank-sum test and corrected for multiple hypothesis testing using the Benjamini-Hochberg procedure with FDR = 10%; the significant tests are shown in bold. To combine P-values from the two independent approaches — one based on network genes and the other

based on genes affected by recurrent truncating mutations — we used Fisher's and Stouffer's meta-analysis methods. The combined P-values, shown in the last two columns, were corrected for multiple-hypothesis testing using the Bonferroni method; significant tests are shown in bold.

Table S9. Effect size significance of brain expression bias				
Prenatal versus postnatal bias				
Gene set	**P-value**	**Bias**	**Null bias**	
			Mean	**Std. dev.**
Network genes	< 0.0001	0.16	–0.004	0.028
Truncating SNV genes	< 0.0001	0.18	–0.004	0.041
Embryonic bias				
Network truncating SNV genes	< 0.0001	0.59	–0.02	0.11
Network CNV genes	< 0.0001	0.87	–0.02	0.10
Non-network SNV genes	0.3	0.001	0.001	0.030
Sibling SNV genes	0.2	0.02	–0.01	0.033
Female versus male bias				
Truncating SNV genes	0.002	0.58	–0.008	0.19
Non-network SNV genes	0.7	–0.05	0.0006	0.088
Phenotype bias				
Truncating SNVs, low vs. high IQ	< 0.0001	0.95	0.007	0.18
Truncating SNVs, high vs. low ADIR-S	0.002	0.53	–0.002	0.17
Truncating SNVs, high vs. low ADIR-R	0.08	0.24	$4x10^{-5}$	0.17
Network genes, low vs. high IQ	0.01	0.28	0.002	0.12
Network genes, high vs. low ADIR-S	0.3	0.072	–0.004	0.12
Network genes, high vs. low ADIR-R	0.02	0.25	0.004	0.12

Table S9. The significance of the temporal, gender, and phenotype biases using randomly generated expression probe sets. The biases were calculated using human expression data obtained from the HBT database. To quantify the temporal brain expression biases, we calculated the difference between the average $\log_2$ expression during early developmental periods (prenatal or embryonic) and the average $\log_2$ expression during the later periods. To quantify the gender brain expression bias, we calculated the difference between the average $\log_2$ expression of genes with mutations in female probands and male probands. To quantify the phenotype expression bias, we calculated the difference between the average $\log_2$ expression of genes with mutations in probands of greater phenotypic severity and of less severity. The significances of various biases were computed using randomly generated probe sets. The numbers of probe sets sampled in random trials were equal to the numbers of probes sets in corresponding original datasets. Analogous to the procedure used to process the original HBT data, we computed the median probe set expression values in each of 10000 randomly generated probe sets; expression biases were calculated by taking the difference between the corresponding expression averages. The final P-values obtained using the random trials reflect the probability to obtain a bias greater or equal to the one observed in the original data.