Loss of Metabotropic Glutamate Receptor 2 Escalates Alcohol Consumption: Genomic Discovery and Functional Validation

Supporting Information

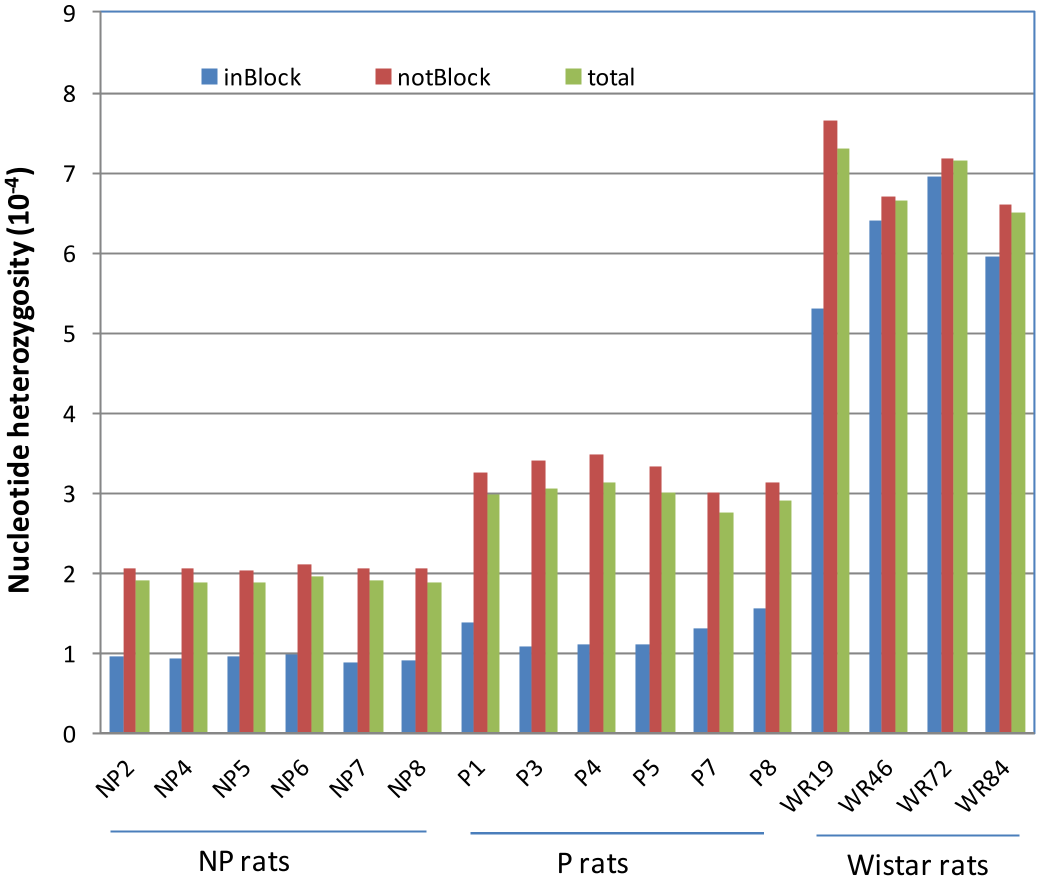


Figure S1. Nuceotide heterozygosity in P, NP, and Wistar rats showing overall genetic fixation in P and NP rats and genetic fixation occurring in large genomic blocks. The fixation is attributable to both inbreeding and selection. The heterozygosities are calculated using sequences of all bases covered by exome sequencing and presented as heterozygousbases per 10^4 nucleotides. The average heterozygosities in all regions, in large fixed blocks, and in regions outside the large blocks are coded as green, blue, and red respectively. As shown in Supplemental 2, the large fixed blocks tend to be fixed in opposite configuration in P and NP rats.

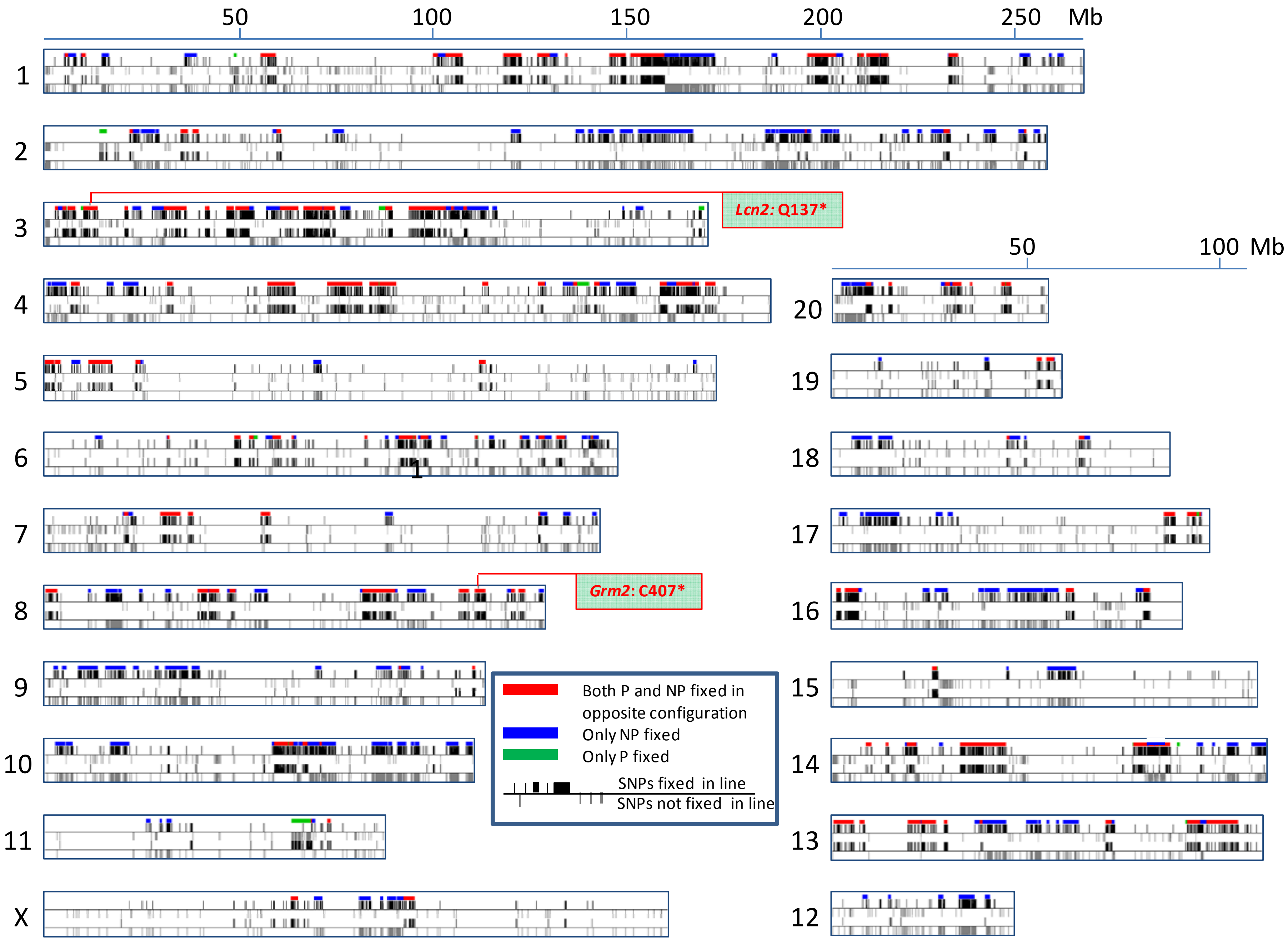

50
100
150
200
250
Mb
1
2
3
Lcn2: Q137*
50
100
Mb
4
20
5
19
6
1
18
7
17
8
Grm2: C407*
16
9
15
10
14
11
13
X
12
Both P and NP fixed in opposite configuration
Only NP fixed
Only P fixed
SNPs fixed in line
SNPs not fixed in line

Figure S2. Distributions of SNPs and their allelic segregation between P and NP rats across the genome. All SNPs (vertical lines) that are either fixed (upward) or not fixed (downward) in NP (upper horizontal line) and P rats (lower horizontal line) are marked at their positions on each chromosome. Genomic regions containing SNPs that are fixed in both P and NP and in opposite allelic configurations are highlighted in red, those fixed in NP are in blue, and those fixed in P are in green. The locations of two stop codon variants, *Grm2* C407* and *Lcn2* Q137* are highlighted, and both are located in large blocks fixed in opposite configuration.

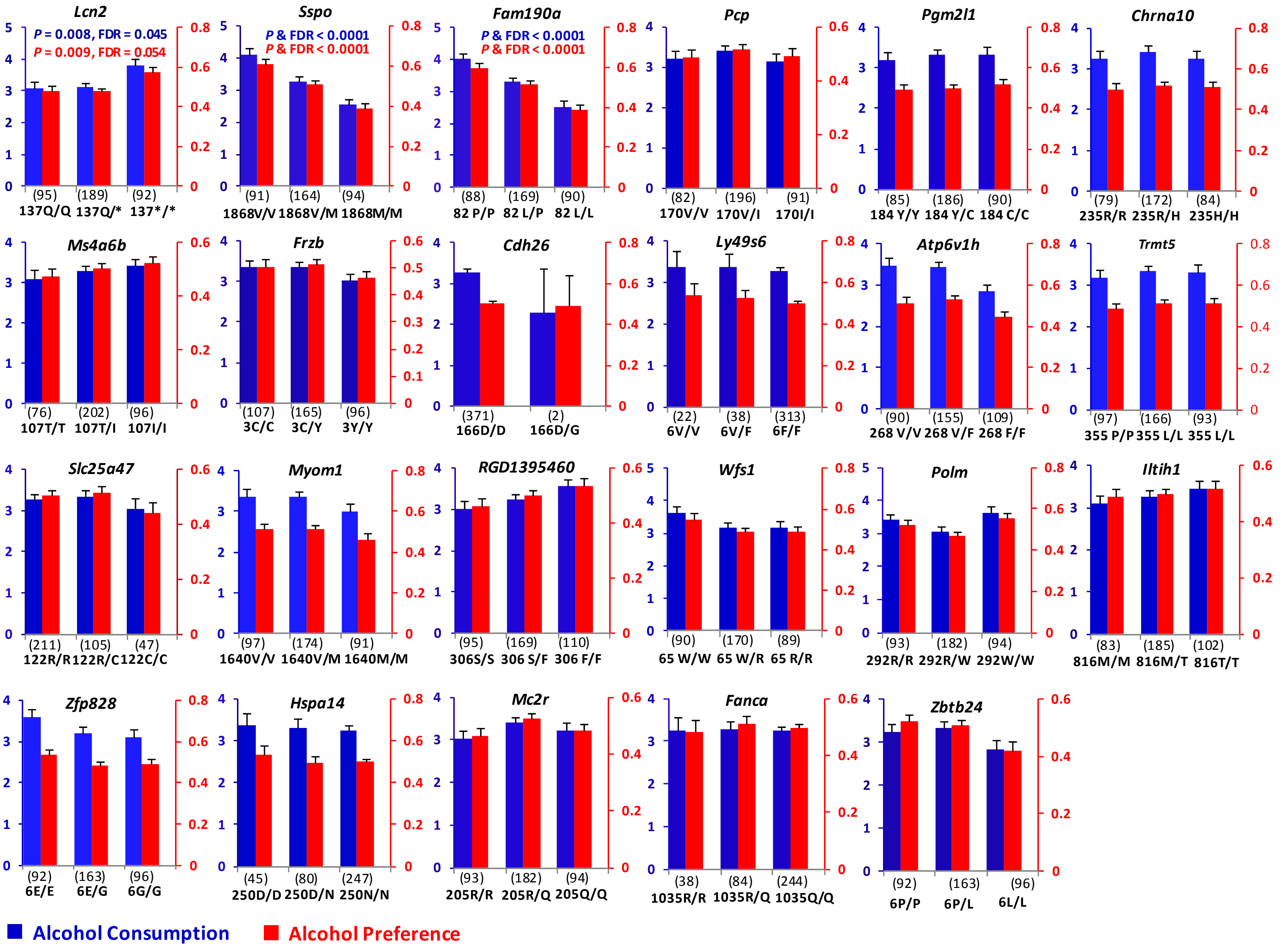

Lcn2
P = 0.008, FDR = 0.045
P = 0.009, FDR = 0.054
(95) 137Q/Q
(189) 137Q/*
(92) 137*/*
Sspo
P & FDR < 0.0001
P & FDR < 0.0001
(91) 1868V/V
(164) 1868V/M
(94) 1868M/M
Fam190a
P & FDR < 0.0001
P & FDR < 0.0001
(88) 82 P/P
(169) 82 L/P
(90) 82 L/L
Pcp
(82) 170V/V
(196) 170V/I
(91) 170I/I
Pgm2l1
(85) 184 Y/Y
(186) 184 Y/C
(90) 184 C/C
Chrna10
(79) 235R/R
(172) 235R/H
(84) 235H/H
Ms4a6b
(76) 107T/T
(202) 107T/I
(96) 107I/I
Frzb
(107) 3C/C
(165) 3C/Y
(96) 3Y/Y
Cdh26
(371) 166D/D
(2) 166D/G
Ly49s6
(22) 6V/V
(38) 6V/F
(313) 6F/F
Atp6v1h
(90) 268 V/V
(155) 268 V/F
(109) 268 F/F
Trmt5
(97) 355 P/P
(166) 355 L/L
(93) 355 L/L
Slc25a47
(211) 122R/R
(105) 122R/C
(47) 122C/C
Myom1
(97) 1640V/V
(174) 1640V/M
(91) 1640M/M
RGD1395460
(95) 306S/S
(169) 306 S/F
(110) 306 F/F
Wfs1
(90) 65 W/W
(170) 65 W/R
(89) 65 R/R
Polm
(93) 292R/R
(182) 292R/W
(94) 292W/W
Iltih1
(83) 816M/M
(185) 816M/T
(102) 816T/T
Zfp828
(92) 6E/E
(163) 6E/G
(96) 6G/G
Hspa14
(45) 250D/D
(80) 250D/N
(247) 250N/N
Mc2r
(93) 205R/R
(182) 205R/Q
(94) 205Q/Q
Fanca
(38) 1035R/R
(84) 1035R/Q
(244) 1035Q/Q
Zbtb24
(92) 6P/P
(163) 6P/L
(96) 6L/L
Alcohol Consumption
Alcohol Preference

Figure S3. QTL analysis of nonsense (see main paper for *Grm2* C407*) and missense variants for alcohol consumption and preference in F2 rats. The 22 missense variants evaluated for linkage were all predicted to affect protein function. The left Y axis represents alcohol consumption (g/kg body weight/day) and the right Y axis represents alcohol preference (ethanol/total fluid) for each genotype group. The numbers of F2 rats in each genotype group are shown in parentheses. Comparisons were analyzed by one-way ANOVA and FDR (Benjamini) was calculated for multiple testing correction.

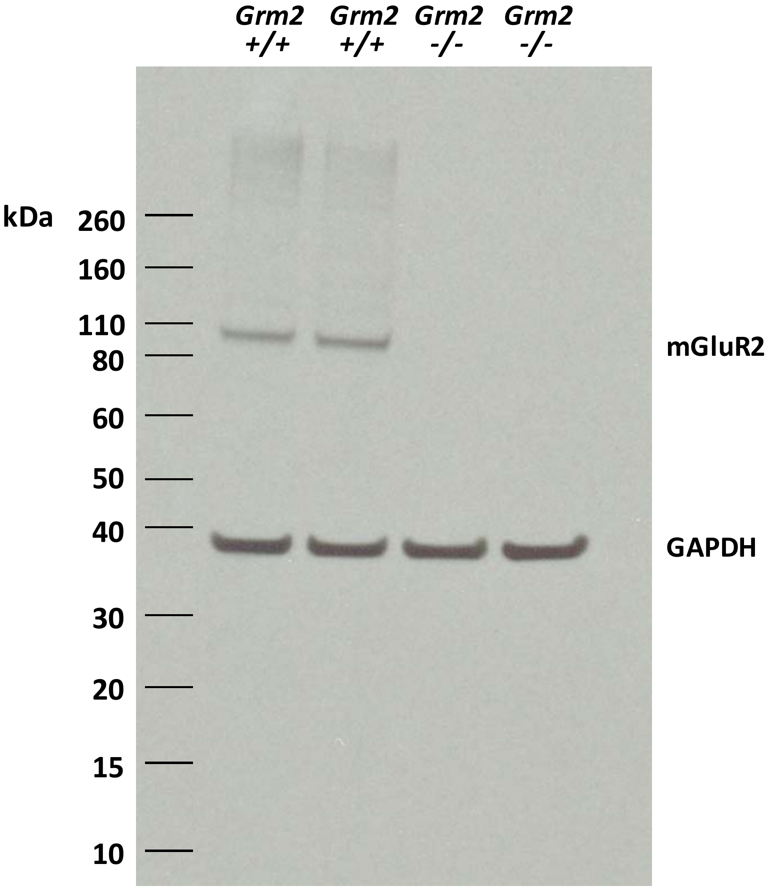
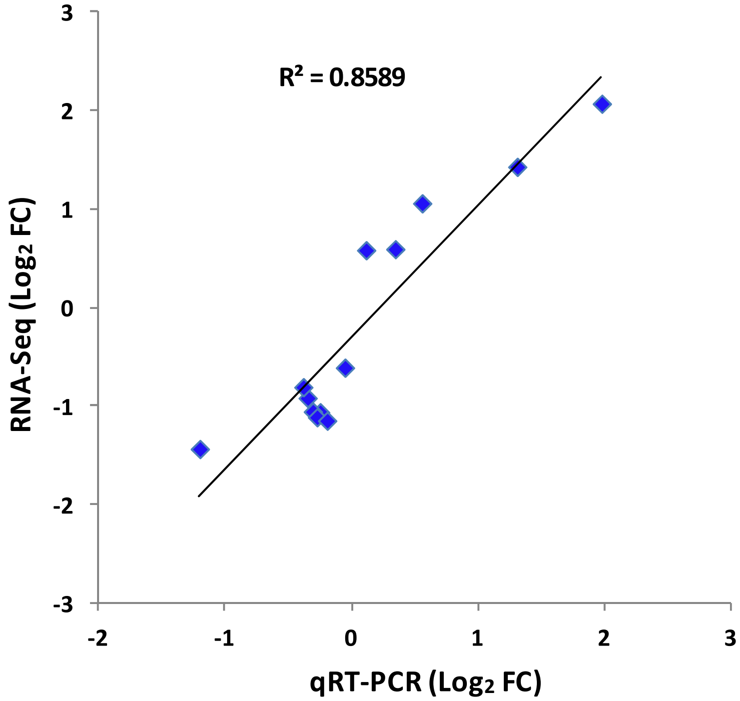


Figure S4. Western blot of hippocampal mGluR2 protein in *Grm2+/+* and *Grm2-/-* mice. A mouse monoclonal anti-mGluR2 N-terminal antibody (ab15672, Abcam) was used. A GAPDH antibody (MAB374, Millipore) was used as control. Two individual *Grm2+/+* and *Grm2-/-* mice in each group were analyzed.



Gene Symbol	RNAseq (Log_2 FC)	qRT-PCR (Log2 FC)
Slit1	1.44	1.31
Syn1	-0.79	-0.38
Gsta4	-1.42	-1.20
Gabra3	0.60	0.11
Gabbr1	-0.91	-0.35
Slc6a1	-0.60	-0.05
Akr1b10	1.07	0.56
Atp2b2	-1.04	-0.31
Gria4	0.61	0.34
Nrxn2	-1.10	-0.27
Thrsp	-1.13	-0.19
Nrgn	-1.05	-0.25
Vegfb	2.08	1.98

Figure S5. Correlation between RNA-Seq and qRT-PCR measures of differential hippocampal gene expression in P and NP rats. The log2 based fold differences in RNA levels (P vs. NP) were measured for 13 genes by qRT-PCR and RNA-Seq The numerical values are listed in the table on right.

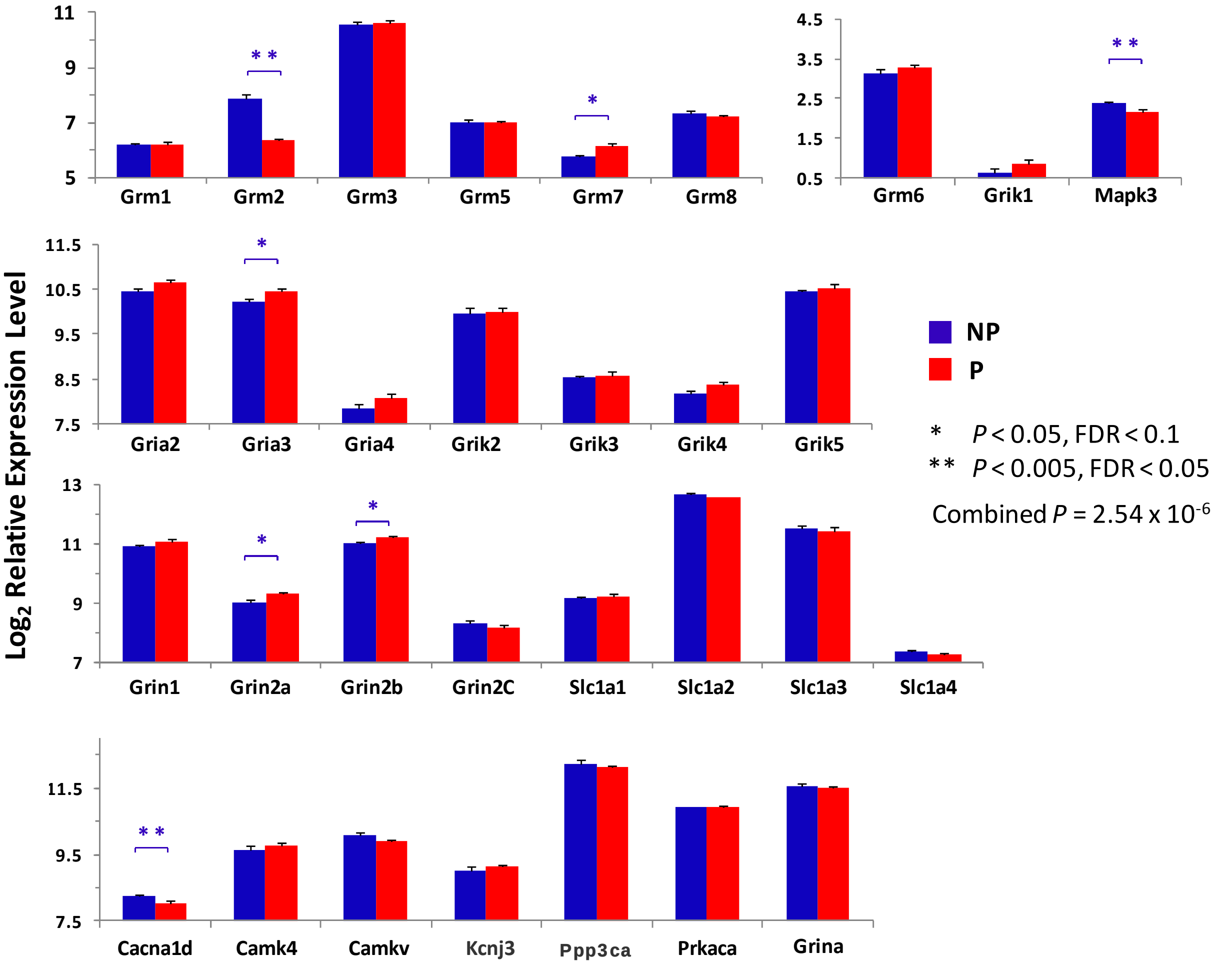


Figure S6. Expression of genes involved in synaptic glutamatergic functions in the striatum of P and NP rats. Total RNA extracted from striatum was reverse transcribed and quantified by PCR. Log2 relative expression levels were analyzed by one-way ANOVA . Genes that were differentially expressed between P and NP rats are indicated ($P < 0.05$ or $P < 0.005$). The combined P value ($p = 2.54 \times 10^{-6}$) was calculated using the Truncated Product Method (Zaykin, D.V. et al. *Genetic Epidemiology* **22**, 170-185, 2002).

Table S1. Distributions of SNVs with homozygously segregating alleles between P and NP rats

	Number of Segregating SNPs	Number of Genes Containing Segregating SNPs
CDS	2579	1068
Synonymous	2204	1107
Missense	879	495
Affect Functions*	36	33
Non-sense	2	2
UTR	608	424
Near Splicing Site (within 10 n.t.)	550	417
Intron	10752	1672
Upstream (1 kb)	408	264
Downstream (1 kb)	213	144
Intergenic	10840	

Table S2. Nonsense and missense variants segregating between P and NP rats and predicted to affect protein functions

Chr	post	Ref Base	Alt Base	Gene Symbol	Gene Name	Transcript	Amino Acid Sub	Rat with Alt Allele	Polyphen		SIFT		QTL Analysis¶
									Prediction*	Prob	Prediction	Score	
3	11512622	G	A	*Lcn2*	Lipocalin2	NM_130741	Q137*	P					Y
8	111844799	G	T	*Grm2*	Glutamate receptor, metabotropic 2	NM_001105711	C407*	P					Y
1	149749858	G	A	*Prcp*	Lysosomal Pro-X carboxypeptidase precursor	NM_001106281	V170I	NP	Poss Dam	0.827	Deleterious	0.02	Y
1	157634616	A	G	*Pgm2l1*	Glucose 1,6-bisphosphate synthase	NM_001109454	Y184C	NP	Prob Dam	0.999	Deleterious	0	Y
1	157812662	C	T	*C2cd3*	C2 domain-containing protein 3	NM_001191602	S212F	NP	Prob Dam	0.992	Deleterious	0.05	
1	159592812	C	T	*Chrna10*	Neuronal acetylcholine receptor subunit alpha-10 precursor	NM_022639	R235H	NP	Prob Dam	1	Deleterious	0.01	Y
1	214017149	C	T	*Ms4a2*	High affinity immunoglobulin epsilon receptor subunit beta	NM_012845	P213L	P	Poss Dam	0.454	Deleterious	0.02	
1	214214271	G	A	*Ms4a6b*	Membrane-spanning 4-domains subfamily A member 6B	NM_001006975	T107I	P	Poss Dam	0.742	Deleterious	0.01	Y
1	233681974	G	A	*Il33*	Interleukin-33 precursor	NM_001014166	G171S	P	Prob Dam	0.963	Deleterious	0.03	
3	10029374	C	T	*Dyt1*	Torsin-1A precursor	NM_153303	G179S	NP	Prob Dam	1	Deleterious	0.03	
3	63382438	C	T	*Frzb*	Secreted frizzled-related protein 3 precursor	NM_001100527	C3Y	NP	Poss Dam	0.827	Deleterious	0.02	Y
3	167547084	A	G	*Cdh26*	Cadherin-like protein 26 precursor	NM_001191745	D166G	P	Prob Dam	1	Deleterious	0.01	Y
4	76550783	G	A	*Sspo*	SCO-spondin precursor	NM_001007016	V1868M	NP	Prob Dam	0.98	Deleterious	0.01	Y
4	77105531	G	C	*Svs1*	Seminal vesicle-secreted protein I precursor	NM_199095	G214R	NP	Prob Dam	0.984	Deleterious	0	
4	78888170	A	G	*Npvf*	Fmrfamide-related peptides precursor	NM_023952	L153S	NP	Prob Dam	0.999	Deleterious	0	
4	87347648	C	T	*LOC500148*	Similar to 40S ribosomal protein S7 (S8)	NM_001035253	D35N	NP	Prob Dam	0.992	Deleterious	0	
4	90254140	C	T	*Fam190a*	Protein FAM190A	NM_001134622	P82L	NP	Prob Dam	0.958	Deleterious	0	Y
4	167956645	C	A	*Ly49s6*	Ly49 stimulatory receptor 6	NM_001009488	V6F	P	Prob Dam	0.998	Deleterious	0.02	Y

5	14621693	C	A	*Atp6v1h*	V-type proton ATPase subunit H	NM_001013929	V268F	NP	Poss Dam	0.845	Deleterious	0.03	Y
6	95709737	G	A	*Trmt5*	Trna (guanine-N(1)-)-methyltransferase	NM_001108713	P355L	NP	Prob Dam	0.967	Deleterious	0.01	Y
6	133196293	C	T	*Slc25a47*	Solute carrier family 25 member 47	NM_001001509	R122C	P	Prob Dam	1	Deleterious	0	Y
9	110340396	G	A	*Myom1*	Myomesin-1 isoform 1	NM_001191584	V1640M	P	Prob Dam	1	Deleterious	0	Y
14	33108957	C	T	*RDG1359460*		NM_001006959	S306F	P	Prob Dam	0.976	Deleterious	0.01	Y
14	33113513	G	A	*RDG1359460*		NM_001006959	G536R	NP	Prob Dam	0.959	Deleterious	0.02	
14	79387445	T	C	*Wfs1*	Wolframin	NM_031823	W65R	P	Poss Dam	0.948	Deleterious	0.1	Y
14	86493947	G	A	*Polm*	DNA-directed DNA/RNA polymerase mu	NM_001011912	R292W	P	Prob Dam	1	Deleterious	0	Y
16	6365006	A	G	*Itih1*	Inter-alpha-trypsin inhibitor heavy chain H1 precursor	NM_001107291	M816T	P	Prob Dam	0.988	Deleterious	0.02	Y
16	80573644	T	C	*Zfp828*	Zinc finger protein 828	NM_001107329	E6G	NP	Prob Dam	0.992	Deleterious	0.04	Y
17	85862715	G	A	*Hspa14*	Heat shock 70 kda protein 14 isoform 1	NM_001004257	D250N	NP	Poss Dam	0.756	Deleterious	0	Y
18	63896710	T	C	*Cidea*	Cell death activator CIDE-A	NM_001170467	F214S	P	Poss Dam	0.454	Deleterious	0.01	
18	64601568	G	A	*Mc2r*	Adrenocorticotropic hormone receptor	NM_001100491	R205Q	NP	Poss Dam	0.517	Deleterious	0.04	Y
19	53589560	C	T	*Fanca*	Fanconi anemia group A protein homolog	NM_001108455	R1035Q	NP	Prob Dam	0.999	Deleterious	0.03	Y
20	45410281	C	T	*Zbtb24*	Zinc finger and BTB domain-containing protein 24	NM_001098667	P6L	NP	Prob Dam	0.958	Deleterious	0	Y

*Prob Dam = Probably damaging; Poss Dam = Possibly damaging. ¶ Y = yes. Genomic positions refer to Baylor 3.4/rn4

Table S3. Differentially Expressed (FDR < 0.05) Genes in the Hippocampus of P and NP Rats

Gene Symbol	Gene Name	Ave Exp Level	Log2 FC (P/NP)	P value	FDR
Fam111a	Family with sequence similarity 111, member A	3.37	4.54	2.6E-16	2.9E-12
Mpeg1	Macrophage expressed gene 1	3.41	-2.19	6.8E-13	3.8E-09
Vegfb	Vascular endothelial growth factor B	3.45	2.08	1.1E-12	4.1E-09
Plac9	Placenta-specific 9	2.64	2.21	9.3E-12	2.7E-08
LOC501110	Similar to Glutathione S-transferase A1 (GTH1) (HA subunit 1) (GST-epsilon) (GSTA1-1) (GST class-alpha)	2.14	2.62	8.4E-10	1.9E-06
Thrsp	Thyroid hormone responsive	4.50	-1.13	2.3E-09	4.4E-06
Fbp2	Fructose-1,6-bisphosphatase 2	0.59	0.91	7.0E-08	1.1E-04
Slit1	Slit homolog 1 (Drosophila)	3.46	1.44	9.2E-08	1.3E-04
Gsta4	Glutathione S-transferase alpha 4	3.38	-1.42	4.2E-07	5.3E-04
Necap1	NECAP endocytosis associated 1	6.45	-0.77	5.7E-07	6.6E-04
Ccdc50	Coiled-coil domain containing 50	6.38	-0.83	1.2E-06	1.3E-03
Dcn	Decorin	4.04	1.42	1.3E-06	1.3E-03
Abcb1b	ATP-binding cassette, sub-family B (MDR/TAP), member 1B	3.05	1.44	2.6E-06	2.2E-03
Zmiz1	Zinc finger, MIZ-type containing 1	4.32	-1.01	3.3E-06	2.7E-03
Ms4a2	Membrane-spanning 4-domains, subfamily A, member 2 (Fc fragment of ige, high affinity I, receptor for; beta polypeptide)	0.70	0.89	3.6E-06	2.8E-03
Bace1	Beta-site APP cleaving enzyme 1	5.03	0.85	4.3E-06	3.1E-03
Chchd2	Coiled-coil-helix-coiled-coil-helix domain containing 2	3.95	2.14	4.6E-06	3.1E-03
Immt	Inner membrane protein, mitochondrial	5.59	0.88	5.9E-06	3.7E-03
Akr1b10	Aldo-keto reductase family 1, member B10 (aldose reductase)	3.05	1.07	6.2E-06	3.7E-03
Centg2	Arfgap with gtpase domain, ankyrin repeat and PH domain 1	4.22	-0.82	7.0E-06	4.0E-03
Aebp1	AE binding protein 1	2.88	-1.09	7.8E-06	4.2E-03
Arf4	ADP-ribosylation factor 4	6.17	0.77	8.3E-06	4.3E-03
Slc35d3	Solute carrier family 35, member D3	1.74	-1.28	8.9E-06	4.3E-03
Pter	Phosphotriesterase related	2.07	-0.87	9.1E-06	4.3E-03
Trappc2	Trafficking protein particle complex 2	6.53	1.02	1.1E-05	5.1E-03
Gas2	Growth arrest-specific 2	2.18	1.06	1.6E-05	6.6E-03
LOC100134871	Beta globin minor gene	0.58	0.89	1.6E-05	6.6E-03
Pgam1	Phosphoglycerate mutase 1 (brain)	2.59	0.87	1.8E-05	7.3E-03
Riok2	RIO kinase 2 (yeast)	4.45	0.89	2.1E-05	8.3E-03

Psmg1	Proteasome (prosome, macropain) assembly chaperone 1	4.63	0.77	2.7E-05	9.7E-03
Serpina3n	Serine (or cysteine) peptidase inhibitor, clade A, member 3N	0.93	-1.15	2.7E-05	9.7E-03
Sptb	Spectrin, beta, erythrocytic	5.70	-0.83	2.7E-05	9.7E-03
Camkv	Cam kinase-like vesicle-associated	7.68	0.63	2.8E-05	9.7E-03
Bscl2	Bernardinelli-Seip congenital lipodystrophy 2 homolog	4.20	-0.85	3.0E-05	9.9E-03
Depdc7	DEP domain containing 7	2.73	0.79	3.2E-05	1.1E-02
Camta2	Calmodulin binding transcription activator 2	6.13	-0.94	3.7E-05	1.2E-02
Mfap3l	Microfibrillar-associated protein 3-like	6.95	-0.69	3.9E-05	1.2E-02
Taf9	TAF9 RNA polymerase II, TATA box binding protein (TBP)-associated factor	5.00	0.65	4.5E-05	1.3E-02
RGD1306284	Similar to RIKEN cdna 1110005A03	2.67	0.83	4.7E-05	1.3E-02
Asam	Adipocyte-specific adhesion molecule	4.46	-0.78	4.9E-05	1.3E-02
Trim8	Tripartite motif-containing 8	5.58	-0.94	5.0E-05	1.3E-02
Ehd3	EH-domain containing 3	5.05	-1.46	5.3E-05	1.3E-02
Sptbn2	Spectrin, beta, non-erythrocytic 2	7.24	-0.71	5.4E-05	1.3E-02
Synpo	Synaptopodin	3.29	-0.81	5.6E-05	1.3E-02
Syn1	Synapsin I	6.09	-0.79	5.7E-05	1.3E-02
Nomo1	Nodal modulator 1	5.67	-0.80	5.8E-05	1.3E-02
Cog2	Component of oligomeric golgi complex 2	4.93	0.57	6.0E-05	1.3E-02
Atp5c1	ATP synthase, H+ transporting, mitochondrial F1 complex, gamma polypeptide 1	6.85	0.57	6.1E-05	1.3E-02
Pak6	P21 protein (Cdc42/Rac)-activated kinase 6	3.53	-1.01	6.1E-05	1.3E-02
Incenp	Inner centromere protein	2.68	-0.89	6.2E-05	1.3E-02
Fgf2	Fibroblast growth factor 2	2.71	-0.60	6.3E-05	1.3E-02
Add2	Adducin 2 (beta)	5.27	-0.90	6.3E-05	1.3E-02
Snrpb	Small nuclear ribonucleoprotein polypeptides B and B1	5.62	0.70	6.4E-05	1.3E-02
Eml1	Echinoderm microtubule associated protein like 1	2.59	-0.96	6.6E-05	1.3E-02
Atp5o	ATP synthase, H+ transporting, mitochondrial F1 complex, O subunit	7.61	0.60	6.7E-05	1.3E-02
Scaf1	SR-related CTD-associated factor 1	6.08	-1.12	6.9E-05	1.3E-02
Hsbp1	Heat shock factor binding protein 1	7.06	0.89	6.9E-05	1.3E-02
Myh7	Myosin, heavy chain 7, cardiac muscle, beta	2.02	-0.99	6.9E-05	1.3E-02
Ppp2r2d	Protein phosphatase 2, regulatory subunit B, delta isoform	5.85	0.89	6.9E-05	1.3E-02
Pex5l	Peroxisomal biogenesis factor 5-like	5.24	-0.70	7.4E-05	1.4E-02
Itpkc	Inositol 1,4,5-trisphosphate 3-kinase C	2.40	-0.57	7.4E-05	1.4E-02
Wdr45l	Wdr45 like	4.58	0.79	7.5E-05	1.4E-02

Gjd2	Gap junction protein, delta 2	3.03	0.87	8.0E-05	1.4E-02
Afaf	Acrosome formation associated factor	1.10	1.01	8.0E-05	1.4E-02
Zfp365	Zinc finger protein 365	6.20	-0.85	8.4E-05	1.5E-02
Rpl23a	Ribosomal protein l23a	5.25	0.76	8.5E-05	1.5E-02
Dlg4	Discs, large homolog 4 (Drosophila)	5.66	-0.81	8.6E-05	1.5E-02
Ociad1	OCIA domain containing 1	6.67	0.59	8.7E-05	1.5E-02
Zdhhc2	Zinc finger, DHHC-type containing 2	4.33	0.83	8.8E-05	1.5E-02
Atp5g3	ATP synthase, H+ transporting, mitochondrial F0 complex, subunit C3 (subunit 9)	6.10	0.86	9.1E-05	1.5E-02
Cacna1i	Calcium channel, voltage-dependent, T type, alpha 1I subunit	2.83	-0.77	9.4E-05	1.5E-02
Lysmd2	Lysm, putative peptidoglycan-binding, domain containing 2	3.95	0.79	9.4E-05	1.5E-02
RGD1562351	Similar to chromosome 7 open reading frame 23	1.99	0.65	9.5E-05	1.5E-02
Ddn	Dendrin	9.27	-0.83	9.8E-05	1.5E-02
Ctnnal1	Catenin (cadherin associated protein), alpha-like 1	4.25	0.74	9.8E-05	1.5E-02
Skp1	S-phase kinase-associated protein 1	9.27	0.57	9.9E-05	1.5E-02
Mfsd2	Major facilitator superfamily domain containing 2	3.81	0.82	1.0E-04	1.5E-02
Rcn2	Reticulocalbin 2, EF-hand calcium binding domain	5.96	0.66	1.0E-04	1.5E-02
Fam36a	Family with sequence similarity 36, member A	4.38	0.67	1.0E-04	1.5E-02
Grin2b	Glutamate receptor, ionotropic, N-methyl D-aspartate 2B	4.76	-0.74	1.1E-04	1.5E-02
Atp2b2	Atpase, Ca++ transporting, plasma membrane 2	6.23	-1.04	1.1E-04	1.5E-02
Wash2	WAS protein family homolog 2	3.37	-0.68	1.1E-04	1.5E-02
Paqr8	Progestin and adipoq receptor family member VIII	6.31	-0.62	1.1E-04	1.5E-02
Ucp3	Uncoupling protein 3 (mitochondrial, proton carrier)	0.51	-0.76	1.1E-04	1.5E-02
Grm2	Glutamate receptor, metabotropic 2	1.87	-0.73	1.1E-04	1.5E-02
Freq	Frequenin homolog (Drosophila)	6.67	-0.89	1.1E-04	1.5E-02
Gdap1	Ganglioside-induced differentiation-associated-protein 1	5.67	0.59	1.1E-04	1.5E-02
Bpnt1	3'(2'), 5'-bisphosphate nucleotidase 1	5.62	1.13	1.1E-04	1.5E-02
Lmbrd1	LMBR1 domain containing 1	6.68	0.72	1.2E-04	1.5E-02
Prss23	Protease, serine, 23	4.08	-0.60	1.2E-04	1.5E-02
Tapbpl	TAP binding protein-like	2.36	-0.83	1.2E-04	1.5E-02
RGD1566130	Similar to mkiaa1940 protein	3.89	-0.78	1.2E-04	1.5E-02

H2afz	H2A histone family, member Z	4.90	1.03	1.2E-04	1.5E-02
Ppp1r9b	Protein phosphatase 1, regulatory subunit 9B	8.02	-0.62	1.2E-04	1.5E-02
Prdx1	Peroxiredoxin 1	3.09	0.82	1.2E-04	1.5E-02
Tmem41b	Transmembrane protein 41B	4.62	0.73	1.3E-04	1.5E-02
Ophn1	Oligophrenin 1	3.69	0.69	1.3E-04	1.5E-02
LOC498685	Similar to UPF0308 protein c9orf21	2.64	0.92	1.3E-04	1.5E-02
Psmc6	Proteasome (prosome, macropain) 26S subunit, atpase, 6	7.16	0.57	1.3E-04	1.5E-02
Slc17a5	Solute carrier family 17 (anion/sugar transporter), member 5	4.07	0.87	1.4E-04	1.5E-02
Tmem119	Transmembrane protein 119	2.02	-0.72	1.4E-04	1.6E-02
Mtx2	Metaxin 2	4.84	0.95	1.4E-04	1.6E-02
Lrrc20	Leucine rich repeat containing 20	2.27	0.89	1.4E-04	1.6E-02
Scn7a	Sodium channel, voltage-gated, type VII, alpha	1.62	0.96	1.4E-04	1.6E-02
Cdk5r2	Cyclin-dependent kinase 5, regulatory subunit 2 (p39)	3.15	-0.86	1.5E-04	1.7E-02
Trim41	Tripartite motif-containing 41	4.99	-0.80	1.5E-04	1.7E-02
Vamp2	Vesicle-associated membrane protein 2 (synaptobrevin 2)	8.66	-1.01	1.6E-04	1.7E-02
Clic2	Chloride intracellular channel 2	1.38	0.70	1.6E-04	1.7E-02
Irf2bp1	Interferon regulatory factor 2 binding protein 1	3.11	-0.99	1.6E-04	1.7E-02
Kcnj6	Potassium inwardly-rectifying channel, subfamily J, member 6	5.65	-0.59	1.7E-04	1.8E-02
Cmc1	COX assembly mitochondrial protein homolog (S. Cerevisiae)	3.05	-0.79	1.7E-04	1.8E-02
Memo1	Mediator of cell motility 1	4.18	0.83	1.8E-04	1.8E-02
Ndufc2	NADH dehydrogenase (ubiquinone) 1, subcomplex unknown, 2	6.12	0.63	1.8E-04	1.8E-02
Ccl6	Chemokine (C-C motif) ligand 6	0.64	0.79	1.8E-04	1.8E-02
Man2a2	Mannosidase 2, alpha 2	3.75	-0.81	1.9E-04	1.9E-02
Rarres2	Retinoic acid receptor responder (tazarotene induced) 2	3.19	-0.88	1.9E-04	1.9E-02
Glrx5	Glutaredoxin 5	5.41	-0.79	1.9E-04	1.9E-02
Slco2b1	Solute carrier organic anion transporter family, member 2b1	3.71	-0.77	2.0E-04	1.9E-02
RT1-N1	RT1 class Ib, locus N1	1.09	1.92	2.1E-04	1.9E-02
RT1-N2		1.09	1.92	2.1E-04	1.9E-02
Mmp15	Matrix metallopeptidase 15	3.03	-0.97	2.1E-04	1.9E-02
Pdzd11	PDZ domain containing 11	4.12	0.71	2.1E-04	1.9E-02
Imp3	IMP3, U3 small nucleolar ribonucleoprotein, homolog (yeast)	3.04	0.70	2.2E-04	1.9E-02

Pcdhgb7	Protocadherin gamma subfamily B, 7	5.77	-1.04	2.2E-04	1.9E-02
RGD1311946	Similar to RIKEN cdna 1810055G02	2.72	-0.90	2.2E-04	1.9E-02
Pcdhga1	Protocadherin gamma subfamily A, 1	5.74	-1.10	2.3E-04	1.9E-02
Pcdhga10	Protocadherin gamma subfamily A, 10	5.74	-1.10	2.3E-04	1.9E-02
Pcdhga11	Protocadherin gamma subfamily A, 11	5.74	-1.10	2.3E-04	1.9E-02
Pcdhga12	Protocadherin gamma subfamily A, 12	5.74	-1.10	2.3E-04	1.9E-02
Pcdhga2	Protocadherin gamma subfamily A, 2	5.74	-1.10	2.3E-04	1.9E-02
Pcdhga3	Protocadherin gamma subfamily A, 3	5.74	-1.10	2.3E-04	1.9E-02
Pcdhga5	Protocadherin gamma subfamily A, 5	5.74	-1.10	2.3E-04	1.9E-02
Pcdhga7	Protocadherin gamma subfamily A, 7	5.74	-1.10	2.3E-04	1.9E-02
Pcdhga8	Protocadherin gamma subfamily A, 8	5.74	-1.10	2.3E-04	1.9E-02
Pcdhga9	Protocadherin gamma subfamily A, 9	5.74	-1.10	2.3E-04	1.9E-02
Pcdhgb8	Protocadherin gamma subfamily B, 8	5.74	-1.10	2.3E-04	1.9E-02
Pcdhgc3	Protocadherin gamma subfamily C, 3	5.74	-1.10	2.3E-04	1.9E-02
Rbm9	RNA binding motif protein 9	5.50	-0.58	2.3E-04	1.9E-02
RT1-CE14	RT1 class I, locus CE14	1.14	1.11	2.3E-04	1.9E-02
Drg1	Developmentally regulated GTP binding protein 1	4.63	0.67	2.3E-04	1.9E-02
Lsm5	LSM5 homolog, U6 small nuclear RNA associated (S. Cerevisiae)	3.37	1.06	2.4E-04	1.9E-02
Taok2	TAO kinase 2	4.37	-0.62	2.4E-04	1.9E-02
Angel2	Angel homolog 2 (Drosophila)	5.59	0.70	2.4E-04	1.9E-02
Slc48a1	Solute carrier family 48 (heme transporter), member 1	4.67	-0.75	2.4E-04	1.9E-02
Sort1	Sortilin 1	7.77	-0.96	2.4E-04	1.9E-02
Rps7	Ribosomal protein S7	5.47	-1.09	2.4E-04	1.9E-02
Bsn	Bassoon	5.86	-0.89	2.5E-04	1.9E-02
Dpysl5	Dihydropyrimidinase-like 5	2.60	-0.81	2.5E-04	1.9E-02
Gabbr1	Gamma-aminobutyric acid (GABA) B receptor 1	8.02	-0.91	2.6E-04	2.0E-02
Pcdhgc5	Protocadherin gamma c5	5.64	-1.16	2.6E-04	2.0E-02
Snx14	Sorting nexin 14	4.95	0.63	2.6E-04	2.0E-02
Plau	Plasminogen activator, urokinase	0.73	0.73	2.7E-04	2.0E-02
Mobkl3	MOB1, Mps One Binder kinase activator-like 3 (yeast)	6.24	0.88	2.7E-04	2.0E-02
Srp19	Signal recognition particle 19	4.07	0.60	2.8E-04	2.1E-02
Pls3	Plastin 3 (T-isoform)	6.36	0.53	2.8E-04	2.1E-02
Tmem22	Transmembrane protein 22	3.64	0.67	2.9E-04	2.1E-02
Psmd10	Proteasome (prosome, macropain) 26S subunit, non-atpase, 10	3.20	0.72	3.0E-04	2.1E-02
Ndn	Necdin homolog (mouse)	5.24	0.54	3.0E-04	2.1E-02

MGC94199	Similar to RIKEN cdna 2610301B20; EST AI428449	5.54	0.85	3.0E-04	2.1E-02
Gatad2b	GATA zinc finger domain containing 2B	4.41	-0.65	3.0E-04	2.1E-02
Tusc3	Tumor suppressor candidate 3	4.78	1.01	3.1E-04	2.1E-02
Thumpd2	THUMP domain containing 2	2.70	0.83	3.1E-04	2.1E-02
Rfk	Riboflavin kinase	2.16	0.96	3.1E-04	2.1E-02
LOC501038	Ab2-060	3.49	-0.95	3.1E-04	2.2E-02
Kcnj11	Potassium inwardly rectifying channel, subfamily J, member 11	2.63	-0.87	3.2E-04	2.2E-02
Adrbk1	Adrenergic, beta, receptor kinase 1	5.68	-0.92	3.2E-04	2.2E-02
Ndufab1	NADH dehydrogenase (ubiquinone) 1, alpha/beta subcomplex, 1	7.19	0.57	3.2E-04	2.2E-02
Dock5	Dedicator of cytokinesis 5	2.73	0.63	3.3E-04	2.2E-02
Impa1	Inositol (myo)-1(or 4)-monophosphatase 1	5.14	0.63	3.3E-04	2.2E-02
Gins1	GINS complex subunit 1 (Psf1 homolog)	0.71	0.68	3.3E-04	2.2E-02
Map2k4	Mitogen activated protein kinase kinase 4	5.62	0.50	3.4E-04	2.3E-02
Slc31a1	Solute carrier family 31 (copper transporters), member 1	2.92	0.69	3.5E-04	2.3E-02
LOC691431	Similar to mitochondrial carrier protein MGC4399	3.49	0.73	3.6E-04	2.3E-02
Cno	Cappuccino homolog (mouse)	2.76	0.68	3.6E-04	2.3E-02
Dscr3	Down syndrome critical region gene 3	1.97	0.53	3.6E-04	2.4E-02
Wdr61	WD repeat domain 61	5.01	0.54	3.7E-04	2.4E-02
Cct5	Chaperonin containing Tcp1, subunit 5 (epsilon)	7.18	0.54	3.7E-04	2.4E-02
Oprm1	Opioid receptor, mu 1	1.91	0.76	3.7E-04	2.4E-02
Anxa11	Annexin A11	4.69	-0.93	3.8E-04	2.4E-02
Sec22a	SEC22 vesicle trafficking protein homolog A (S. Cerevisiae)	3.46	0.83	3.9E-04	2.4E-02
Rnh1	Ribonuclease/angiogenin inhibitor 1	3.69	0.72	3.9E-04	2.4E-02
Mrpl3	Mitochondrial ribosomal protein L3	4.12	0.50	4.0E-04	2.5E-02
RGD1562218	Similar to RIKEN cdna 0610039J04	4.36	-0.71	4.0E-04	2.5E-02
Riok3	RIO kinase 3 (yeast)	6.38	0.80	4.0E-04	2.5E-02
Btf3	Basic transcription factor 3	4.92	0.63	4.0E-04	2.5E-02
Ncbp1	Nuclear cap binding protein subunit 1, 80kda	5.93	0.56	4.1E-04	2.5E-02
Gja1	Gap junction protein, alpha 1	7.71	-0.49	4.2E-04	2.6E-02
Pno1	Partner of NOB1 homolog (S. Cerevisiae)	4.36	0.73	4.4E-04	2.7E-02
Slc30a3	Solute carrier family 30 (zinc transporter), member 3	4.27	-1.19	4.6E-04	2.8E-02
Tp53	Tumor protein p53	2.28	-0.64	4.6E-04	2.8E-02
Phf15	PHD finger protein 15	3.67	-0.67	4.6E-04	2.8E-02
Hs2st1	Heparan sulfate 2-O-sulfotransferase 1	5.02	-0.71	4.7E-04	2.8E-02

Plekhb1	Pleckstrin homology domain containing, family B (evectins) member 1	8.26	-0.77	4.7E-04	2.8E-02
Prr18	Proline rich region 18	4.28	-0.53	4.7E-04	2.8E-02
Kcna6	Potassium voltage gated channel, shaker related subfamily, member 6	4.13	-0.63	4.7E-04	2.8E-02
Terf2ip	Telomeric repeat binding factor 2, interacting protein	5.27	0.56	4.9E-04	2.8E-02
RGD1565584	Similar to tyrosine kinase-associated leucine zipper protein lazipii	4.71	0.85	5.0E-04	2.9E-02
Rab14	RAB14, member RAS oncogene family	5.45	0.58	5.1E-04	2.9E-02
Rad1	RAD1 homolog (S. Pombe)	1.89	0.72	5.1E-04	2.9E-02
Tmem178	Transmembrane protein 178	7.27	-1.13	5.1E-04	2.9E-02
Upf3a	UPF3 regulator of nonsense transcripts homolog A (yeast)	4.81	-0.54	5.1E-04	2.9E-02
Chrm4	Cholinergic receptor, muscarinic 4	2.19	-0.77	5.1E-04	2.9E-02
Mylip	Myosin regulatory light chain interacting protein	3.77	-0.55	5.1E-04	2.9E-02
Tbkbp1	TBK1 binding protein 1	3.65	-0.51	5.2E-04	2.9E-02
Jun	Jun oncogene	6.39	-0.81	5.2E-04	2.9E-02
Nus1	Nuclear undecaprenyl pyrophosphate synthase 1 homolog (S. Cerevisiae)	4.45	0.62	5.2E-04	2.9E-02
Rpl37a	Ribosomal protein l37a	8.47	0.58	5.3E-04	2.9E-02
Pnrc1	Proline-rich nuclear receptor coactivator 1	4.92	0.87	5.5E-04	3.0E-02
Camk4	Calcium/calmodulin-dependent protein kinase IV	4.15	-0.61	5.6E-04	3.0E-02
Tmem69	Transmembrane protein 69	3.75	0.75	5.6E-04	3.0E-02
Pols	Polymerase (DNA directed) sigma	4.19	0.76	5.6E-04	3.0E-02
Tspan5	Tetraspanin 5	5.26	-0.70	5.6E-04	3.0E-02
Cotl1	Coactosin-like 1 (Dictyostelium)	5.30	-0.92	5.6E-04	3.0E-02
Usmg5	Up-regulated during skeletal muscle growth 5 homolog (mouse)	6.32	0.56	5.7E-04	3.0E-02
Ntan1	N-terminal asparagine amidase	4.37	0.68	5.8E-04	3.0E-02
Yipf5	Yip1 domain family, member 5	4.67	0.75	5.8E-04	3.0E-02
Pik3r2	Phosphoinositide-3-kinase, regulatory subunit 2 (beta)	4.81	-0.99	5.8E-04	3.0E-02
Il12a	Interleukin 12a	1.46	0.48	5.9E-04	3.0E-02
Tfg	Trk-fused gene	3.89	0.60	5.9E-04	3.0E-02
LOC290595		0.51	-0.69	5.9E-04	3.0E-02
Pcgf3	Polycomb group ring finger 3	3.33	-0.68	5.9E-04	3.0E-02
Acad9	Acyl-Coenzyme A dehydrogenase family, member 9	4.86	0.64	5.9E-04	3.0E-02
Lztfl1	Leucine zipper transcription factor-like 1	4.66	0.72	5.9E-04	3.0E-02

RGD1311605	Similar to apoptosis related protein APR-3; p18 protein	2.57	0.55	6.0E-04	3.0E-02
Zfp469	Zinc finger protein 469	4.27	-0.75	6.0E-04	3.0E-02
Rplp2	Ribosomal protein, large P2	6.22	0.57	6.1E-04	3.1E-02
Kdm1	Lysine (K)-specific demethylase 1	5.69	0.64	6.2E-04	3.1E-02
Nudcd2	Nudc domain containing 2	3.10	0.65	6.2E-04	3.1E-02
Golga7	Golgi autoantigen, golgin subfamily a, 7	5.99	0.69	6.3E-04	3.1E-02
Rnf208	Ring finger protein 208	2.80	-0.70	6.3E-04	3.1E-02
Otop3	Otopetrin 3	2.36	-0.68	6.3E-04	3.1E-02
Acsm5	Acyl-coa synthetase medium-chain family member 5	2.10	-0.77	6.3E-04	3.1E-02
Slc6a8	Solute carrier family 6 (neurotransmitter transporter, creatine), member 8	5.73	-0.59	6.3E-04	3.1E-02
Psd	Pleckstrin and Sec7 domain containing	5.74	-1.13	6.4E-04	3.1E-02
Ndufa2	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 2	4.87	0.48	6.6E-04	3.2E-02
Rpgr	Retinitis pigmentosa gtpase regulator	3.30	0.71	6.6E-04	3.2E-02
Sae1	SUMO1 activating enzyme subunit 1	4.57	0.66	6.6E-04	3.2E-02
Ubl3	Ubiquitin-like 3	5.90	1.29	6.6E-04	3.2E-02
Spna2	Alpha-spectrin 2	7.99	-0.69	6.6E-04	3.2E-02
Wdr37	WD repeat domain 37	4.96	0.67	6.7E-04	3.2E-02
RGD1560350	Similar to proteasome subunit iota	0.92	1.11	6.8E-04	3.2E-02
Gtf2b	General transcription factor IIB	5.63	0.53	6.8E-04	3.2E-02
Taok1	TAO kinase 1	6.84	-0.51	6.8E-04	3.2E-02
Arvcf	Armadillo repeat gene deleted in velo-cardio-facial syndrome	3.96	1.04	6.8E-04	3.2E-02
RT1-CE1	RT1 class I, locus1	1.08	0.89	6.9E-04	3.2E-02
Cox7c	Cytochrome c oxidase, subunit viic	6.05	0.63	6.9E-04	3.2E-02
Ppa1	Pyrophosphatase (inorganic) 1	5.00	0.53	6.9E-04	3.2E-02
Iqsec3	IQ motif and Sec7 domain 3	5.82	-0.54	6.9E-04	3.2E-02
Ctxn1	Cortexin 1	4.63	-0.77	6.9E-04	3.2E-02
RGD1559496	Similar to hypothetical protein	4.88	-0.71	6.9E-04	3.2E-02
Agap2	Arfgap with gtpase domain, ankyrin repeat and PH domain 2	8.13	-0.66	7.0E-04	3.2E-02
Slbp	Stem-loop binding protein	1.88	0.75	7.0E-04	3.2E-02
MGC94335	Similar to hypothetical protein FLJ22555	4.43	0.96	7.0E-04	3.2E-02
St3gal6	ST3 beta-galactoside alpha-2,3-sialyltransferase 6	3.46	0.88	7.0E-04	3.2E-02
Sfxn5	Sideroflexin 5	4.56	-0.60	7.1E-04	3.2E-02
Map1a	Microtubule-associated protein 1A	9.66	-0.51	7.1E-04	3.2E-02

Cbfa2t3	Core-binding factor, runt domain, alpha subunit 2; translocated to, 3	2.74	-0.53	7.1E-04	3.2E-02
Cilp	Cartilage intermediate layer protein, nucleotide pyrophosphohydrolase	0.68	0.63	7.3E-04	3.2E-02
Cnot7	CCR4-NOT transcription complex, subunit 7	6.44	0.89	7.3E-04	3.2E-02
Psma6	Proteasome (prosome, macropain) subunit, alpha type 6	6.13	0.69	7.4E-04	3.2E-02
Znf710	Zinc finger protein 710	2.06	-0.69	7.5E-04	3.3E-02
Ide	Insulin degrading enzyme	3.76	0.93	7.6E-04	3.3E-02
Sh3pxd2a	SH3 and PX domains 2A	3.28	-0.74	7.6E-04	3.3E-02
LOC100233176	Hypothetical protein LOC100233176	6.84	0.47	7.6E-04	3.3E-02
Moap1	Modulator of apoptosis 1	6.84	0.47	7.6E-04	3.3E-02
Rph3a	Rabphilin 3A	6.18	-0.53	7.7E-04	3.3E-02
Nfix	Nuclear factor I/X (CCAAT-binding transcription factor)	3.81	-0.54	7.7E-04	3.3E-02
Hba-a2	Hemoglobin alpha, adult chain 2	4.89	-0.88	7.8E-04	3.3E-02
Cct8	Chaperonin containing Tcp1, subunit 8 (theta)	7.35	0.49	7.8E-04	3.3E-02
Znf513	Zinc finger protein 513	3.98	-0.68	7.8E-04	3.3E-02
Arid1a	AT rich interactive domain 1A (SWI-like)	4.87	-0.46	7.9E-04	3.3E-02
Nudt19	Nudix (nucleoside diphosphate linked moiety X)-type motif 19	4.82	0.57	7.9E-04	3.3E-02
Azi1	5-azacytidine induced 1	3.69	-0.51	7.9E-04	3.3E-02
Yap1	Yes-associated protein 1	3.44	-0.91	8.0E-04	3.3E-02
Mmp17	Matrix metallopeptidase 17	4.24	-0.89	8.0E-04	3.3E-02
Fabp4	Fatty acid binding protein 4, adipocyte	0.97	0.75	8.1E-04	3.4E-02
3367353600		5.26	0.51	8.2E-04	3.4E-02
Ncan	Neurocan	5.69	-0.54	8.3E-04	3.4E-02
Bag1	BCL2-associated athanogene	4.66	0.56	8.3E-04	3.4E-02
Gpr84	G protein-coupled receptor 84	1.44	-0.56	8.3E-04	3.4E-02
C1ql3	Complement component 1, q subcomponent-like 3	6.76	-0.67	8.4E-04	3.4E-02
Mical1	Microtubule associated monoxygenase, calponin and LIM domain containing 1	2.61	-0.65	8.5E-04	3.4E-02
Alg13	Asparagine-linked glycosylation 13 homolog (S. Cerevisiae)	2.97	0.78	8.5E-04	3.4E-02
Gtf3c2	General transcription factor IIIC, polypeptide 2, beta	3.46	-0.57	8.5E-04	3.4E-02
Ufm1	Ubiquitin-fold modifier 1	3.21	0.81	8.6E-04	3.4E-02
Lrsam1	Leucine rich repeat and sterile alpha motif containing 1	3.20	-0.56	8.6E-04	3.4E-02
Snph	Syntaphilin	6.86	-0.58	8.6E-04	3.4E-02

Ndufaf3	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, assembly factor 3	4.37	0.64	8.7E-04	3.4E-02
Bat2	HLA-B associated transcript 2	6.18	-1.05	8.7E-04	3.4E-02
Smarca2	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a, member 2	6.68	-0.73	8.8E-04	3.4E-02
Il1rl2		0.63	-0.78	8.8E-04	3.4E-02
Laptm4a	Lysosomal protein transmembrane 4 alpha	7.65	0.61	8.8E-04	3.4E-02
Tf	Transferrin	7.74	-0.62	8.8E-04	3.4E-02
Cep78	Centrosomal protein 78kda	3.14	0.60	8.9E-04	3.4E-02
Cyp26b1	Cytochrome P450, family 26, subfamily b, polypeptide 1	2.48	-0.64	8.9E-04	3.4E-02
Hnrnpul1	Heterogeneous nuclear ribonucleoprotein U-like 1	5.12	-0.62	8.9E-04	3.4E-02
Ube2d3	Ubiquitin-conjugating enzyme E2D 3 (UBC4/5 homolog, yeast)	6.11	0.57	8.9E-04	3.4E-02
Kif21b	Kinesin family member 21B	4.16	-0.68	8.9E-04	3.4E-02
Nfic	Nuclear factor I/C	2.71	-0.50	8.9E-04	3.4E-02
Ifit2	Interferon-induced protein with tetratricopeptide repeats 2	2.69	0.56	9.0E-04	3.4E-02
Hspc159	Galectin-related protein	4.93	0.60	9.1E-04	3.4E-02
Ivd	Isovaleryl coenzyme A dehydrogenase	3.47	-0.63	9.2E-04	3.5E-02
Egr4	Early growth response 4	2.15	0.61	9.3E-04	3.5E-02
RGD1304587	Similar to RIKEN cdna 2310033P09	4.93	-0.49	9.3E-04	3.5E-02
Dnajc18	Dnaj (Hsp40) homolog, subfamily C, member 18	5.12	-0.51	9.3E-04	3.5E-02
Kcnj4	Potassium inwardly-rectifying channel, subfamily J, member 4	4.74	-0.60	9.3E-04	3.5E-02
Arl6ip1	ADP-ribosylation factor-like 6 interacting protein 1	5.35	0.46	9.3E-04	3.5E-02
Cox7b	Cytochrome c oxidase subunit viib	4.17	0.64	9.4E-04	3.5E-02
Gtpbp10	GTP-binding protein 10 (putative)	3.66	0.49	9.4E-04	3.5E-02
Camk2b	Calcium/calmodulin-dependent protein kinase II beta	8.30	-0.60	9.4E-04	3.5E-02
Slc43a2	Solute carrier family 43, member 2	5.34	-0.41	9.4E-04	3.5E-02
RT1-CE7	RT1 class I, locus CE7	2.27	-1.35	9.4E-04	3.5E-02
Mageh1	Melanoma antigen, family H, 1	4.09	0.45	9.5E-04	3.5E-02
Med11	Mediator complex subunit 11	2.64	0.63	9.5E-04	3.5E-02
Amotl1	Angiomotin-like 1	3.28	-0.72	9.6E-04	3.5E-02
Myh9	Myosin, heavy chain 9, non-muscle	4.55	-0.50	9.7E-04	3.5E-02
Gabrg3	Gamma-aminobutyric acid (GABA) A receptor, gamma 3	1.65	0.76	9.7E-04	3.5E-02

Ccdc56	Coiled-coil domain containing 56	3.57	0.65	9.8E-04	3.5E-02
Pygb	Phosphorylase, glycogen; brain	5.84	0.50	9.8E-04	3.5E-02
Apc2	Adenomatosis polyposis coli 2	3.97	-0.50	9.9E-04	3.5E-02
LOC683504	Similar to zinc finger protein 639	2.73	0.64	1.0E-03	3.5E-02
Cyb5r1	Cytochrome b5 reductase 1	3.31	-0.70	1.0E-03	3.6E-02
Lsm3	LSM3 homolog, U6 small nuclear RNA associated (S. Cerevisiae)	6.89	0.60	1.0E-03	3.7E-02
Dscaml1	Down syndrome cell adhesion molecule-like 1	3.65	0.61	1.0E-03	3.7E-02
Dek	DEK oncogene	6.84	0.58	1.1E-03	3.7E-02
Pnmal1	PNMA-like 1	4.91	-0.76	1.1E-03	3.7E-02
Pnlip	Pancreatic lipase	2.86	0.60	1.1E-03	3.7E-02
Dsn1	DSN1, MIND kinetochore complex component, homolog (S. Cerevisiae)	1.88	0.59	1.1E-03	3.7E-02
Carm1	Coactivator-associated arginine methyltransferase 1	2.76	-0.61	1.1E-03	3.7E-02
Mettl9	Methyltransferase like 9	4.90	0.86	1.1E-03	3.8E-02
Glt8d1	Glycosyltransferase 8 domain containing 1	3.56	0.53	1.1E-03	3.8E-02
Rab40b	Rab40b, member RAS oncogene family	4.36	0.68	1.1E-03	3.8E-02
Sf3a3	Splicing factor 3a, subunit 3	6.29	0.57	1.1E-03	3.8E-02
RGD1309077	Similar to putative RNA methyltransferase	1.69	0.49	1.1E-03	3.8E-02
Lyn	V-yes-1 Yamaguchi sarcoma viral related oncogene homolog	3.47	0.86	1.1E-03	3.8E-02
Nhlh2	Nescient helix loop helix 2	1.48	0.82	1.1E-03	3.8E-02
Dpt	Dermatopontin	1.57	0.80	1.1E-03	3.8E-02
Abhd12	Abhydrolase domain containing 12	5.13	-1.11	1.1E-03	3.8E-02
Myst3	MYST histone acetyltransferase (monocytic leukemia) 3	5.14	-0.56	1.1E-03	3.8E-02
Vcp	Valosin-containing protein	6.54	0.52	1.1E-03	3.8E-02
Nfia	Nuclear factor I/A	3.82	-0.59	1.1E-03	3.8E-02
C1galt1c1	C1GALT1-specific chaperone 1	5.23	0.60	1.2E-03	3.9E-02
Eif3s6ip	Eukaryotic translation initiation factor 3, subunit 6 interacting protein	5.75	0.51	1.2E-03	3.9E-02
Kcnc3	Potassium voltage gated channel, Shaw-related subfamily, member 3	4.83	-1.12	1.2E-03	3.9E-02
3366144000		1.57	0.57	1.2E-03	3.9E-02
Tm7sf3	Transmembrane 7 superfamily member 3	3.85	0.57	1.2E-03	3.9E-02
Ndufs1	NADH dehydrogenase (ubiquinone) Fe-S protein 1	7.09	0.57	1.2E-03	3.9E-02
Pcdhb9	Protocadherin beta 9	3.76	0.56	1.2E-03	3.9E-02
Pcna	Proliferating cell nuclear antigen	5.22	0.69	1.2E-03	3.9E-02

Ephx2	Epoxide hydrolase 2, cytoplasmic	3.01	0.62	1.2E-03	3.9E-02
Mrps15	Mitochondrial ribosomal protein S15	5.30	0.66	1.2E-03	3.9E-02
Pde10a		4.09	-0.50	1.2E-03	3.9E-02
Aard	Alanine and arginine rich domain containing protein	3.01	0.81	1.2E-03	3.9E-02
Nipsnap3b	Nipsnap homolog 3B (C. Elegans)	3.30	0.72	1.2E-03	3.9E-02
Numbl	Numb homolog (Drosophila)-like	3.33	-0.84	1.2E-03	3.9E-02
Nos3	Nitric oxide synthase 3, endothelial cell	2.75	-0.99	1.2E-03	4.0E-02
Ppp3ca	Protein phosphatase 3 (formerly 2B), catalytic subunit, alpha isoform	8.44	-0.47	1.3E-03	4.0E-02
Mlh1	Mutl homolog 1 (E. Coli)	2.36	0.54	1.3E-03	4.0E-02
A2ld1	AIG2-like domain 1	4.53	0.86	1.3E-03	4.0E-02
Ccl27	Chemokine (C-C motif) ligand 27	3.50	-0.88	1.3E-03	4.0E-02
Xrcc5		5.06	0.69	1.3E-03	4.0E-02
Sirt3	Sirtuin (silent mating type information regulation 2 homolog) 3 (S. Cerevisiae)	3.88	-0.70	1.3E-03	4.0E-02
Tmem214	Transmembrane protein 214	2.74	-0.62	1.3E-03	4.0E-02
Tpo1	Developmentally regulated protein TPO1	5.87	-0.46	1.3E-03	4.1E-02
Kcnh3	Potassium voltage-gated channel, subfamily H (eag-related), member 3	3.72	-0.69	1.3E-03	4.1E-02
Slc1a2	Solute carrier family 1 (glial high affinity glutamate transporter), member 2	9.04	-0.60	1.3E-03	4.1E-02
Cdh18	Cadherin 18, type 2	2.86	0.97	1.3E-03	4.1E-02
Sirpa	Signal-regulatory protein alpha	5.69	-0.61	1.3E-03	4.1E-02
Shank1	SH3 and multiple ankyrin repeat domains 1	5.44	-0.74	1.3E-03	4.1E-02
Polr3d	Polymerase (RNA) III (DNA directed) polypeptide D	5.63	0.75	1.3E-03	4.1E-02
Ostc	Oligosaccharyltransferase complex subunit	5.41	0.49	1.3E-03	4.1E-02
Robo1	Roundabout homolog 1 (Drosophila)	4.90	-0.49	1.3E-03	4.1E-02
Man1a1	Mannosidase, alpha, class 1A, member 1	4.31	-0.96	1.3E-03	4.1E-02
RGD1307947	Similar to RIKEN cdna C430008C19	5.27	0.52	1.4E-03	4.1E-02
Ttc19	Tetratricopeptide repeat domain 19	6.35	0.52	1.4E-03	4.2E-02
Kcnj9	Potassium inwardly-rectifying channel, subfamily J, member 9	4.78	-0.83	1.4E-03	4.2E-02
LOC689852	Similar to Proteasome inhibitor PI31 subunit	3.63	0.62	1.4E-03	4.2E-02
Rsl1d1	Ribosomal L1 domain containing 1	5.31	0.59	1.4E-03	4.2E-02
Zfyve19	Zinc finger, FYVE domain containing 19	2.97	-0.64	1.4E-03	4.2E-02
Cacng8	Calcium channel, voltage-dependent, gamma subunit 8	4.68	-0.92	1.4E-03	4.2E-02
Atf5	Activating transcription factor 5	3.97	-0.74	1.4E-03	4.2E-02
Lpl	Lipoprotein lipase	5.93	0.54	1.4E-03	4.2E-02

Cyp2j4	Cytochrome P450, family 2, subfamily j, polypeptide 4	1.88	0.53	1.4E-03	4.3E-02
Tle3	Transducin-like enhancer of split 3 (E(sp1) homolog, Drosophila)	3.50	-0.61	1.4E-03	4.3E-02
Mrpl55	Mitochondrial ribosomal protein L55	4.88	0.50	1.4E-03	4.3E-02
Dlgap4	Discs, large homolog-associated protein 4 (Drosophila)	3.77	-0.62	1.4E-03	4.3E-02
Sdk2	Sidekick homolog 2 (chicken)	2.50	-0.49	1.5E-03	4.3E-02
Kctd3	Potassium channel tetramerisation domain containing 3	4.70	-0.57	1.5E-03	4.3E-02
Kcng1	Potassium voltage-gated channel, subfamily G, member 1	3.74	-0.90	1.5E-03	4.3E-02
Ilf3	Interleukin enhancer binding factor 3	4.92	-0.63	1.5E-03	4.3E-02
Nphp1	Nephronophthisis 1 (juvenile) homolog (human)	4.32	-0.53	1.5E-03	4.3E-02
Arhgef11	Rho guanine nucleotide exchange factor (GEF) 11	3.90	-0.71	1.5E-03	4.3E-02
Tmem14a	Transmembrane protein 14A	5.32	-0.65	1.5E-03	4.3E-02
RGD1560070		6.54	-0.70	1.5E-03	4.4E-02
Nsmce4a	Non-SMC element 4 homolog A (S. Cerevisiae)	5.02	0.65	1.5E-03	4.4E-02
Ralb	V-ral simian leukemia viral oncogene homolog B (ras related; GTP binding protein)	5.04	-0.68	1.5E-03	4.4E-02
Lysmd3	Lysm, putative peptidoglycan-binding, domain containing 3	2.54	0.93	1.5E-03	4.4E-02
Fhl1	Four and a half LIM domains 1	5.25	0.56	1.5E-03	4.4E-02
Clu		8.99	-0.63	1.5E-03	4.4E-02
Ankh	Ankylosis, progressive homolog (mouse)	4.43	-0.69	1.6E-03	4.5E-02
Rbm18	RNA binding motif protein 18	5.67	0.91	1.6E-03	4.5E-02
B3galnt1	Beta-1,3-N-acetylgalactosaminyltransferase 1	3.23	0.66	1.6E-03	4.5E-02
Gria4	Glutamate receptor, ionotropic, AMPA4	6.11	0.61	1.6E-03	4.5E-02
Ppcs	Phosphopantothenoylcysteine synthetase	2.71	0.46	1.6E-03	4.6E-02
Cnpy2	Canopy 2 homolog (zebrafish)	5.51	0.45	1.6E-03	4.6E-02
Brd2	Bromodomain containing 2	5.23	-0.45	1.6E-03	4.6E-02
Pik3r4	Phosphoinositide-3-kinase, regulatory subunit 4	4.45	0.62	1.7E-03	4.6E-02
Bid	BH3 interacting domain death agonist	2.53	-0.68	1.7E-03	4.6E-02
Gtf2e2	General transcription factor IIE, polypeptide 2, beta	4.04	0.64	1.7E-03	4.6E-02
Supt4h1	Suppressor of Ty 4 homolog 1 (S. Cerevisiae)	4.58	0.50	1.7E-03	4.6E-02
Snapap	SNAP-associated protein	5.32	0.67	1.7E-03	4.6E-02
Stard3nl	STARD3 N-terminal like	4.02	0.47	1.7E-03	4.6E-02
Gspt2	G1 to S phase transition 2	5.90	0.51	1.7E-03	4.6E-02

Gsk3b	Glycogen synthase kinase 3 beta	4.47	-0.53	1.7E-03	4.6E-02
Pkia	Protein kinase (camp-dependent, catalytic) inhibitor alpha	5.88	0.54	1.7E-03	4.6E-02
Mprip	Myosin phosphatase Rho interacting protein	5.65	-0.46	1.7E-03	4.6E-02
RGD1306508		6.73	0.75	1.7E-03	4.6E-02
Zfp709l1	Zinc finger protein 709-like 1	1.89	0.70	1.7E-03	4.6E-02
Cox18	COX18 cytochrome c oxidase assembly homolog (S. Cerevisiae)	2.55	0.86	1.7E-03	4.6E-02
Anks1a	Ankyrin repeat and sterile alpha motif domain containing 1A	2.59	0.51	1.7E-03	4.7E-02
Reln		3.38	0.76	1.7E-03	4.7E-02
Rasd2	RASD family, member 2	3.56	-0.55	1.7E-03	4.7E-02
RGD1308215		4.58	-0.74	1.7E-03	4.7E-02
Accn2	Amiloride-sensitive cation channel 2, neuronal	3.79	-0.65	1.7E-03	4.7E-02
Rere	Arginine-glutamic acid dipeptide (RE) repeats	4.62	-0.48	1.7E-03	4.7E-02
Cstb	Cystatin B (stefin B)	3.09	0.63	1.7E-03	4.7E-02
Gucy1b3		6.23	0.56	1.7E-03	4.7E-02
Sp100	SP100 nuclear antigen	1.64	0.63	1.7E-03	4.7E-02
Fam101b	Family with sequence similarity 101, member B	2.41	-0.61	1.8E-03	4.7E-02
Mael	Maelstrom homolog (Drosophila)	0.44	0.62	1.8E-03	4.7E-02
Map1b	Microtubule-associated protein 1B	8.87	-0.58	1.8E-03	4.7E-02
Pigt	Phosphatidylinositol glycan anchor biosynthesis, class T	3.75	-0.74	1.8E-03	4.7E-02
Usp14	Ubiquitin specific peptidase 14	6.50	0.67	1.8E-03	4.7E-02
Adam11	ADAM metallopeptidase domain 11	4.96	-0.88	1.8E-03	4.8E-02
RGD1565096	Similar to TSG118.1	4.27	-0.49	1.8E-03	4.8E-02
Sacm1l		5.59	0.42	1.8E-03	4.8E-02
Fam164a	Family with sequence similarity 164, member A	3.57	0.52	1.8E-03	4.8E-02
Fam168a	Family with sequence similarity 168, member A	6.13	-0.60	1.8E-03	4.8E-02
Nudt3	Nudix (nucleoside diphosphate linked moiety X)-type motif 3	7.76	-0.76	1.8E-03	4.8E-02
LOC293103	Similar to RIKEN cdna 0610007P06	3.76	0.84	1.8E-03	4.8E-02
Necab1	N-terminal EF-hand calcium binding protein 1	5.36	0.64	1.8E-03	4.8E-02
Kalrn	Kalirin, rhogef kinase	5.66	-0.78	1.9E-03	4.8E-02
Bbs5	Bardet-Biedl syndrome 5	3.77	0.64	1.9E-03	4.8E-02
Mettl6	Methyltransferase like 6	3.82	0.48	1.9E-03	4.8E-02

Necap2	NECAP endocytosis associated 2	2.75	-0.64	1.9E-03	4.8E-02
Acvr1	Activin A receptor, type I	3.13	-0.56	1.9E-03	4.8E-02
Nell1	NEL-like 1 (chicken)	4.27	0.46	1.9E-03	4.8E-02
LOC690102		0.82	0.74	1.9E-03	4.8E-02
Vars	Valyl-trna synthetase	3.73	-0.73	1.9E-03	4.8E-02
Paics	Phosphoribosylaminoimidazole carboxylase, phosphoribosylaminoimidazole succinocarboxamide synthetase	3.48	0.53	1.9E-03	4.8E-02
Cmip	C-Maf-inducing protein	4.07	-0.57	1.9E-03	4.8E-02
Rab6b	RAB6B, member RAS oncogene family	6.95	-0.57	1.9E-03	4.8E-02
Eno2	Enolase 2, gamma, neuronal	7.49	-1.03	1.9E-03	4.8E-02
Fam134b	Family with sequence similarity 134, member B	6.45	0.70	1.9E-03	4.8E-02
Rab15	RAB15, member RAS oncogene family	6.25	-0.87	1.9E-03	4.8E-02
Fam89a	Family with sequence similarity 89, member A	2.02	-0.61	1.9E-03	4.8E-02
Wdr47	WD repeat domain 47	6.69	0.63	1.9E-03	4.8E-02
Plxnb3	Plexin B3	2.68	-0.51	1.9E-03	4.8E-02
Idi1	Isopentenyl-diphosphate delta isomerase 1	5.25	0.73	1.9E-03	4.8E-02
Acsl6	Acyl-coa synthetase long-chain family member 6	6.96	-0.69	1.9E-03	4.8E-02
Cited2	Cbp/p300-interacting transactivator, with Glu/Asp-rich carboxy-terminal domain, 2	3.98	0.62	1.9E-03	4.8E-02
Npc2	Niemann-Pick disease, type C2	5.24	-0.77	2.0E-03	4.8E-02
Klhl26	Kelch-like 26 (Drosophila)	4.48	-0.57	2.0E-03	4.8E-02
Il22ra2	Interleukin 22 receptor, alpha 2	1.04	0.79	2.0E-03	4.9E-02
Ccdc126	Coiled-coil domain containing 126	4.29	0.51	2.0E-03	4.9E-02
Pnpt1	Polyribonucleotide nucleotidyltransferase 1	3.30	0.59	2.0E-03	4.9E-02
Slc8a2	Solute carrier family 8 (sodium/calcium exchanger), member 2	5.41	-0.64	2.0E-03	4.9E-02
Nup62	Nucleoporin 62	3.21	-0.57	2.0E-03	4.9E-02
Gng7	Guanine nucleotide binding protein (G protein), gamma 7	4.81	-0.57	2.0E-03	4.9E-02
Btg1	B-cell translocation gene 1, anti-proliferative	4.36	-0.52	2.0E-03	4.9E-02
LOC362419	Similar to CG33331-PA	3.70	0.55	2.0E-03	4.9E-02
Tmem49	Transmembrane protein 49	5.50	0.47	2.0E-03	4.9E-02
Rab4b	RAB4B, member RAS oncogene family	4.47	-1.02	2.0E-03	4.9E-02
Filip1	Filamin A interacting protein 1	4.70	-0.51	2.0E-03	4.9E-02
Efnb1	Ephrin B1	2.20	-0.56	2.0E-03	4.9E-02
Ttrap	Traf and Tnf receptor associated protein	4.24	0.71	2.0E-03	4.9E-02
Slc12a5	Solute carrier family 12 (potassium-chloride transporter), member 5	5.68	-0.43	2.0E-03	4.9E-02
Pogk	Pogo transposable element with KRAB domain	4.18	-0.44	2.1E-03	4.9E-02

Prdm2		4.48	-0.43	2.1E-03	4.9E-02
Tspan12	Tetraspanin 12	4.56	0.80	2.1E-03	4.9E-02
Slc16a1	Solute carrier family 16, member 1 (monocarboxylic acid transporter 1)	5.45	-0.80	2.1E-03	4.9E-02
Ube2d2	Ubiquitin-conjugating enzyme E2D 2	6.06	0.59	2.1E-03	4.9E-02
Shc2		4.82	0.74	2.1E-03	4.9E-02
Zc3h7a	Zinc finger CCCH type containing 7 A	4.94	0.53	2.1E-03	4.9E-02
Ptdss2	Phosphatidylserine synthase 2	4.50	-0.73	2.1E-03	4.9E-02

Table S4. Enrichment of segregating (P vs NP rat) coding sequence (CDS) and UTR SNPs in genes differentially expressed in the hippocampus of P and NP rats

	Number of Segregating SNPs					Number of Genes				
	In all Expressed Genes	In Differentially Expressed Genes	Fraction	χ^2* (Pearson)	*P* value	All Expressed Genes	Differentially Expressed Genes	Fraction	χ^2* (Pearson)	*P* value
CDS and UTR	2158	130	0.060	12.924	0.0003	881	58	0.066	9.129	0.003
CDS	1698	97	0.057	6.734	0.01	739	50	0.068	8.886	0.003
Synonymous	1177	66	0.056	3.708	0.054	612	43	0.070	8.972	0.003
Mis-sense	517	30	0.058	2.082	0.149	311	16	0.051	0.322	0.57
Non-sense	2	1				2	1			
UTR	460	33	0.072	7.423	0.006	327	23	0.070	4.69	0.03
Gene	11364	485	0.043			11364	485	0.043		

*df = 1

Table S5. Functional domains (GO Term) with over-representation of differentially expressed genes (FDR < 0.05) in the hippocampus of P and NP rats

GO Term	Count	Fold Enrichment	*P* Value	Adj. *P* (Benjamini)
GO:0005516~calmodulin binding	12	4.86	3.39E-05	5.03E-03
GO:0045202~synapse	25	2.37	1.42E-04	9.34E-03
GO:0030054~cell junction	28	2.30	8.45E-05	1.11E-02
GO:0030425~dendrite	18	2.76	2.79E-04	1.37E-02
GO:0043005~neuron projection	25	2.06	1.08E-03	4.65E-02

Table S6. Genes differentially expressed in the hippocampus of P and NP rats and classified in the function domains of calmodulin binding, synapse, and neuronal projection

Gene Symbol	Gene Name	Ave Exp	log2 FC	P Value	FDR	Function* Domain
Abcb1b	ATP-binding cassette, sub-family B (MDR/TAP), member 1B	3.05	-1.44	2.6E-06	2.2E-03	2
Add2	Adducin 2 (beta)	5.27	0.90	6.3E-05	1.3E-02	1
Adrbk1	Adrenergic, beta, receptor kinase 1	5.68	0.92	3.2E-04	2.2E-02	2,3
Amotl1	Angiomotin-like 1	3.28	0.72	9.6E-04	3.5E-02	2
Asam	Adipocyte-specific adhesion molecule	4.46	0.78	4.9E-05	1.3E-02	2
Atp2b2	Atpase, Ca++ transporting, plasma membrane 2	6.23	1.04	1.1E-04	1.5E-02	1,3
Bace1	Beta-site APP cleaving enzyme 1	5.03	-0.85	4.3E-06	3.1E-03	3
Bsn	Bassoon	5.86	0.89	2.5E-04	1.9E-02	2
Camk2b	Calcium/calmodulin-dependent protein kinase II beta	8.30	0.60	9.4E-04	3.5E-02	1
Camk4	Calcium/calmodulin-dependent protein kinase IV	4.15	0.61	5.6E-04	3.0E-02	1
Camkv	Cam kinase-like vesicle-associated	7.68	-0.63	2.8E-05	9.7E-03	1
Chrm4	Cholinergic receptor, muscarinic 4	2.19	0.77	5.1E-04	2.9E-02	2,3
Ddn	Dendrin	9.27	0.83	9.8E-05	1.5E-02	3
Dlg4	Discs, large homolog 4 (Drosophila)	5.66	0.81	8.6E-05	1.5E-02	2
Dlgap4	Discs, large homolog-associated protein 4 (Drosophila)	3.77	0.62	1.4E-03	4.3E-02	2
Dpysl5	Dihydropyrimidinase-like 5	2.60	0.81	2.5E-04	1.9E-02	3
Efnb1	Ephrin B1	2.20	0.56	2.0E-03	4.9E-02	2
Freq	Frequenin homolog (Drosophila)	6.67	0.89	1.1E-04	1.5E-02	2,3
Gabbr1	Gamma-aminobutyric acid (GABA) B receptor 1	8.02	0.91	2.6E-04	2.0E-02	2
Gabrg3	Gamma-aminobutyric acid (GABA) A receptor, gamma 3	1.65	-0.76	9.7E-04	3.5E-02	2
Gja1	Gap junction protein, alpha 1	7.71	0.49	4.2E-04	2.6E-02	2
Gjd2	Gap junction protein, delta 2	3.03	-0.87	8.0E-05	1.4E-02	2
Gria4	Glutamate receptor, ionotropic, AMPA4	6.11	-0.61	1.6E-03	4.5E-02	2,3
Grin2b	Glutamate receptor, ionotropic, N-methyl D-aspartate 2B	4.76	0.74	1.1E-04	1.5E-02	2,3
Grm2	Glutamate receptor, metabotropic 2	1.87	0.73	1.1E-04	1.5E-02	2,3
Gsk3b	Glycogen synthase kinase 3 beta	4.47	0.53	1.7E-03	4.6E-02	3
Itpkc	Inositol 1,4,5-trisphosphate 3-kinase C	2.40	0.57	7.4E-05	1.4E-02	1
Kalrn	Kalirin, rhogef kinase	5.66	0.78	1.9E-03	4.8E-02	3
Kcnj4	Potassium inwardly-rectifying channel, subfamily J, member 4	4.74	0.60	9.3E-04	3.5E-02	3
Lyn	V-yes-1 Yamaguchi sarcoma viral	3.47	-0.86	1.1E-03	3.8E-02	2

	related oncogene homolog					
Map1b	Microtubule-associated protein 1B	8.87	0.58	1.8E-03	4.7E-02	2,3
Map2k4	Mitogen activated protein kinase kinase 4	5.62	-0.50	3.4E-04	2.3E-02	3
Myh7	Myosin, heavy chain 7, cardiac muscle, beta	2.02	0.99	6.9E-05	1.3E-02	1,2
Myh9	Myosin, heavy chain 9, non-muscle	4.55	0.50	9.7E-04	3.5E-02	1,2
Nos3	Nitric oxide synthase 3, endothelial cell	2.75	0.99	1.2E-03	4.0E-02	1
Ophn1	Oligophrenin 1	3.69	-0.69	1.3E-04	1.5E-02	2,3
Oprm1	Opioid receptor, mu 1	1.91	-0.76	3.7E-04	2.4E-02	2
Pcdhga12	Protocadherin gamma subfamily A, 12	5.74	1.10	2.3E-04	1.9E-02	2
Pcdhgc3	Protocadherin gamma subfamily C, 3	5.74	1.10	2.3E-04	1.9E-02	2
Pex5l	Peroxisomal biogenesis factor 5-like	5.24	0.70	7.4E-05	1.4E-02	3
Ppp1r9b	Protein phosphatase 1, regulatory subunit 9B	8.02	0.62	1.2E-04	1.5E-02	2,3
Ppp3ca	Protein phosphatase 3 (formerly 2B), catalytic subunit, alpha isoform	8.44	0.47	1.3E-03	4.0E-02	1
Pygb	Phosphorylase, glycogen; brain	5.84	-0.50	9.8E-04	3.5E-02	3
Robo1	Roundabout homolog 1 (Drosophila)	4.90	0.49	1.3E-03	4.1E-02	3
Rph3a	Rabphilin 3A	6.18	0.53	7.7E-04	3.3E-02	2
Sae1	SUMO1 activating enzyme subunit 1	4.57	-0.66	6.6E-04	3.2E-02	1
Shank1	SH3 and multiple ankyrin repeat domains 1	5.44	0.74	1.3E-03	4.1E-02	2,3
Slc12a5	Solute carrier family 12 (potassium-chloride transporter), member 5	5.68	0.43	2.0E-03	4.9E-02	3
Slc1a2	Solute carrier family 1 (glial high affinity glutamate transporter), member 2	9.04	0.60	1.3E-03	4.1E-02	2,3
Slc30a3	Solute carrier family 30 (zinc transporter), member 3	4.27	1.19	4.6E-04	2.8E-02	2
Slc8a2	Solute carrier family 8 (sodium/calcium exchanger), member 2	5.41	0.64	2.0E-03	4.9E-02	1
Snapap	SNAP-associated protein	5.32	-0.67	1.7E-03	4.6E-02	2
Snph	Syntaphilin	6.86	0.58	8.6E-04	3.4E-02	2
Sort1	Sortilin 1	7.77	0.96	2.4E-04	1.9E-02	3
Spna2	Alpha-spectrin 2	7.99	0.69	6.6E-04	3.2E-02	1,2
Syn1	Synapsin I	6.09	0.79	5.7E-05	1.3E-02	2
Synpo	Synaptopodin	3.29	0.81	5.6E-05	1.3E-02	2,3

* 1. Calmodulin binding; 2. Synapse; 3. Neuronal Projection

Supplementary Materials and Methods

Exome and cDNA sequencing library construction

Exome sequencing libraries were constructed using Agilent SureSelect protocols. Briefly, P and NP rat genomic DNA was fragmented to the 150 – 300 base-pair range by sonication. The genomic fragments were ligated with universal adaptors and amplified by PCR for 6 cycles. Exonic regions were captured by hybridization with the Mouse All Exon bait library at 60C for 24 hours. The captured exome genomic libraries were amplified again by PCR for 13 cycles before sequencing. For cDNA library construction, total RNA was extracted from hippocampal tissue and treated with DNase I (Qiagen) to eliminate residual genomic DNA contamination. Fifty ng of mRNA isolated with Dynabeads oligo $(dT)_{25}$ magnetic beads (Invitrogen) was fragmented to the 150 – 500 base pair range in fragmentation buffer (Ambion) at 70 C for 3 min. Fragmented mRNA was treated with Antarctic phosphatase (New England Biolab) and then phosphorylated with polynucleotide kinase (NEB). The treated mRNA was ligated with 3' RNA adaptor (Illumina) using truncated T4 RNA ligase 2 (NEB) and then with 5' RNA adaptor (Illumina). The adaptor-ligated mRNA was then reverse transcribed to first strand cDNAs, using a universal primer (Illumina) and Superscript II reverse transcriptase (Invitrogen), and then amplified for 12 cycles with Phusion DNA Polymerase. Fragments of 170 – 300 base-pair in size were purified using a 2% agarose gel and recovered.

Sequencing base-calling, mapping, and SNP calling, and RNA-Seq data analysis

Sequencing of exome and cDNA libraries was carried out on an Illumina GAIIx sequencer. Sequences of 75 x 2 paired-end reads for exome and 36 base-pair single reads for RNA-Seq were called from image files with the Illumina GApipeline and aligned to the rat reference genome (Baylor 3.4/rn4) using Extended Eland in CASAVA-1.8.1. An average of 40 million uniquely mapped exome reads and 7.8 million RNA-seq reads for each sample were retrieved and parsed with in-house Perl scripts to generate base coverage in WIG file format. SNPs from exome-seq reads were called with CASAVA-1.8.1 with default setting except with "—variantsNoCovCutoff" option to turn off high-coverage filtration of SNPs. The sequenced base counts at individual SNP locations for each sample were parsed from the mapped reads. RNA-Seq data analysis, including peak identification, quantification and normalization has been previously described (Zhou et al., 2011). The group comparisons of log transformed data between the P and NP rats were performed using t-tests, FDR q value was calculated for each P value using the Benjamini-Hochberg method. For gene ontology and functional annotation analysis, the genes that were significantly different in expression (FDR < 0.05) between the P and NP rat lines were analyzed with the Functional Annotation Tool of the DAVID Bioinformatics Resources 6.7, National Institute of Allergy and Infectious Diseases (NIAID), NIH (http://david.abcc.ncifcrf.gov).

Sanger sequencing validation, genotyping, QTL analysis, and quantitative RT-PCR

Nonsense and missense variants were validated by Sanger sequencing of PCR-amplified genomic DNA using specific primers and BigDye Terminator mix v3.1 (Applied Biosystems) and analyzed on an ABI 3730 or 3100 capillary sequencer. TaqMan assays on an ABI 7900 instrument were used for genotyping P, NP and Wistar rats. For QTL analysis, quantitative measures of ethanol consumption and preference of all F2 rats were analyzed together with genotypes as predictor variables by ANOVA. For RT-PCR, first strand cDNA was reverse transcribed from mRNA with random priming using Superscript RT II (Invitrogen). Quantitative PCR was carried out with SYBR Green master mix (Applied Biosystems) on an ABI 7900 instrument. Relative gene expression level was calculated using the ΔCT value. Expression differences were analyzed by one-way ANOVA. Combined P value was calculated using the Truncated Product Method (Zaykin et al., 2002).

Western blots

Fifty μg of total protein extracted from hippocampus of P and NP rats was separated on 4-12% Bis-Tris denaturing polyacrylamide gel together with the Novex Sharp protein standard and then dry-transferred to nitrocellulose membrane using the iBlot system (Invitrogen). Membranes were incubated with 32 μg of a mouse monoclonal anti-mGluR2 N-terminal antibody (ab15672, Abcam) in 5% milk/TBST solution at room temperature for 7 hr, followed by incubation with 0.15 μg of mouse anti-Gapdh antibody (MAB374, Millipore) at 4C for 40 min. 0.5 μl of an goat anti-mouse IgG (A4415, SIGMA) conjugated with HRP was then incubated with blots at room temperature for 1 hr before chemi-luminescent detection was performed.

Field potential recording in brain slices

Rats (2-3 month old) and mGluR+/+ and -/- mice (10 wks old) were anesthetized and decapitated. Brains were blocked and mounted on the stage of a Leica BT1200S brain slicer in cold cutting solution, and sliced in coronal sections of 300-320 μm thickness containing the dorsal hippocampus, or the striatum posterior to the head of the caudate nucleus. Slices were then placed on netting in a beaker filled with artificial cerebrospinal fluid (aCSF) at 32^{o}C for 1 hour, after which the slice-containing beaker was moved to the bench top and allowed to cool to room temperature. Individual slices were moved to a Plexiglas recording chamber and constantly superfused with carbogen-bubbled aCSF at 30^{o}C at a flow rate of ~2 mL/min. Under visualization with a stereomicroscope, the tips of a twisted pair of Teflon-coated tungsten wires were placed into the slices in the white matter separating the cortex from the dorsolateral striatum, or in the middle third of the molecular layer of the dentate gyrus (DG) for afferent stimulation. A glass microelectrode (~1 MOhm tip resistance) filled with 0.9% NaCl was placed in the slices within ~300 μm of the stimulating electrode tips (in dorsolateral striatum or molecular layer middle third in DG) to record stimulus-evoked field potentials. Field potentials evoked at a rate of 0.033 Hz were amplified 1000 x using an Axoclamp 2A amplifier and a Warner Instruments DP-301 differential AC preamplifier, filtered at 1 Hz high-pass and 1KHz low-pass, and digitized at 20 KHz using a Digidata 1322A (Molecular Devices, Sunnyvale CA). Stimulus amplitude was set to evoke a population spike or fEPSP ~80% of the maximum that could be induced. Data were stored, displayed and analyzed using pClamp v8.2 software (Molecular Devices). The fEPSP Slope in DG recordings was measured by a linear fit between cursors placed across the middle third of the initial negative-going component of the field potential. The PS amplitude in stiratum was measured as the difference in values obtained from cursors placed at the onset (peak positivity) and negative peak of the negative-going field potential that occurs 4-8 msec post-stimulus. Once recording was initiated and a stable field potential obtained, the group II mGluR agonist LY379268 (200 nM) was applied to the slice for 5 min via whole-bath superfusion.

Following agonist application, superfusion was switched back to aCSF. To validate the involvement of group II mGluR in the agonist action, in some experiments the group II mGluR antagonist LY341495 was applied throughout the recording at a 1 μM concentration, and agonist was applied as described above. The agonist effect was completely prevented in the presence of LY341495. For the graph in Figure 3, the fEPSP Slope or PS amplitude values in the 0-10 min range of the experiment were averaged and this average was used to set the baseline level of 100%. All subsequent values were then normalized to this average within each slice and means +/- SEM were calculated for all slices in the group and plotted as the percent of baseline value at each time point.

Alcohol self-administration in Wistar rats

Male Wistar rats weighing 300-400 g at the outset of the experiment were housed on a reverse 12 h light/dark cycle. Food and water were available ad libitum. Experiments were conducted during the dark cycle. Rats were trained in operant conditioning chambers to self-administer 20% alcohol (v/v) in 30 min daily sessions on a fixed ratio 1 (FR-1) schedule of reinforcement, in which each response on the active lever resulted in delivery of 0.03 ml of fluid. Experiments were initiated after 14 days of training when response rates reached stability. Rats were injected intraperitoneal (i.p.) with vehicle or LY341495 (3 mg/kg), 30 min prior to 30 min sessions for five consecutive days.

Alcohol consumption and preference in Grm2-/- mice

The *Grm2-/-* mice were generated on a CD1 background by homologous recombination as previously described (Linden et al., 2005). At the start of the experiment mice were 10 weeks old. The mGluR2+/+ and mGluR2 -/- mice were on a 12 hour on / 12 hour off dark/light cycle with food and water available *ad libitum*. Animals were single housed and trained to drink in a two-bottle choice procedure with one bottle containing water and the other containing increasing concentrations of alcohol (3, 6, 9, 11, 13, 15 and finally 17%; v/v) providing a free choice situation. Alcohol and water intake were measured on Monday, Wednesday, and Friday, for 10 weeks. To measure the loss of righting reflex (LORR), mice were injected with a high dose of alcohol (4 g/kg intraperitoneal (i.p.) then returned to their home cage until they exhibited LORR. LORR is defined as the inability to right from the supine position, and recovery was considered to be when the mouse was able to turn around on 4 paws 3 times in 1 min after being placed in the supine position on a v-shaped trough. LORR measurement was calculated by subtracting the time (in minutes) of onset of LORR from the time at recovery from LORR. To measure alcohol metabolism, mice were injected with 4 g/kg i.p. of alcohol. Tail blood was collected at either 10, 30, 60, 120, or 180 min post injection. Blood alcohol levels (BALs) were determined by a gas chromatograph system (Agilent Technologies, Fort Worth, TX, USA).