

Appendix 1 to Stacey D, Lourdusamy A, Ruggeri B, et al. A translational systems biology approach in both animals and humans identifies a functionally related module of accumbal genes involved in the regulation of reward processing and binge drinking in males. *J Psychiatry Neurosci* 2015.

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Supplementary methods

Quality control of human genotype data. SNPs with call rates of <98%, minor allele frequency <1% or deviation from the Hardy-Weinberg equilibrium ($P \leq 1 \times 10^{-4}$) were excluded from the analyses. Individuals with an ambiguous sex code, excessive missing genotypes (failure rate >2%), and outlying heterozygosity (heterozygosity rate of 3 SDs from the mean) were also excluded. Identity-by-state similarity was used to estimate cryptic relatedness for each pair of individuals using PLINK software¹. Closely related individuals with identity-by-descent (IBD > 0.1875) were eliminated from the subsequent analysis. Population stratification for the GWAS data was examined by principal component analysis (PCA) using EIGENSTRAT software². The four HapMap populations were used as reference groups in the PCA analysis and individuals with divergent ancestry (from CEU) were also excluded.

Mouse gene coexpression network analysis and module characterization. Unlike the standard gene co-expression network analysis, WGCNA assigns a connection weight to each gene pair using soft-thresholding and thus is robust to parameter selection. The determination of weighted co-expression starts by calculating a correlation matrix containing all pairwise Pearson correlations between all probe sets across all samples. It then uses the power function parameter $\beta \geq 1$ to convert correlation matrix into an adjacency matrix. For this data set, we select the smallest β ($= 8$) that leads to an approximately scale-free network with the truncated scale-free fitting index $R^2 > 0.8$. To explore the modular structures of the co-expression network, the adjacency matrix is further transformed into a topological overlap matrix TOM and then modules of highly correlated transcripts were identified using average linkage hierarchical clustering followed dynamic tree-cut algorithm. Once modules were identified, each module was represented by the module eigengene (ME; i.e., first principal component of the expression values across subjects). The MEs were then correlated to relevant phenotypes using the Pearson correlation. Within-module connectivity (kWithin) for each probe set was determined by summing the connectivity of that probe set with each other probe set in that module.

We used the following strategies to characterize the modules: first, the MEs were associated with KO status and *Rasgrf2* gene expression levels; second, significantly associated modules obtained from the first step were annotated using gene ontology (GO) terms, marker genes for astrocytes, microglia, neurons, and oligodendrocytes obtained from the mouse gene expression data³, mouse quantitative trait loci (QTL) for alcohol preference⁴. To determine whether the modules are biologically meaningful, GO enrichment analyses were conducted using Gene Codis⁵. For each module, we examined enrichment of GO terms as compared to the list of reference genes using a Hypergeometric test. FDR < 0.05 were considered significant.

Module-based GWAS signal enrichment analysis. We utilized the following procedures to run the enrichment test⁶. First the max $-\log(P\text{-value})$ of a SNP located at 100kb upstream or downstream of a gene was assigned to represent the gene, then gene set's enrichment scores (ES) were calculated based the gene's rank. Here, the list of genes in each module was considered as a single gene set. SNP label level permutation was used to generate a distribution of the ES, and then the distribution was normalized by multiplying the ratio of the proportion of significant

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genes of the gene set and the proportion of significant genes of the total genes in the GWAS. FDR values were calculated if multiple gene sets were included in enrichment test.

Kernel based association measure. In brief, a kernel based canonical correlation analysis (CCA) is to solve a following eigen-problem between two joint Gaussian variables Y and X :

$$\begin{pmatrix} (K_Y + \lambda I)^2 & K_Y K_X \\ K_Y K_X & (K_X + \lambda I)^2 \end{pmatrix} \begin{pmatrix} \zeta_Y \\ \zeta_X \end{pmatrix} = (1 + \rho) \begin{pmatrix} (K_Y + \lambda I)^2 & 0 \\ 0 & (K_X + \lambda I)^2 \end{pmatrix} \begin{pmatrix} \zeta_Y \\ \zeta_X \end{pmatrix},$$

where K_Y and K_X are the Gram matrix of the sample calculated using the kernel function, and λ is a small regularization parameter to avoid overfitting. The kernel generalized variance statistics ('regularized kernel association' would be a more preferable name) is then defined as

$$rkassoc^{(k)} = -\sum_{i=1}^k \log(1 - \rho_i^2),$$

where ρ_i is the i^{th} leading eigenvalue of the regularized eigenproblem (minus one from the eigenvalue calculated directly from the matrices!!!). This is justified by the fact that the rest eigenvalues converge rapidly to 0, and therefore retaining these eigenvalues will not only contribute little to the association but also sacrifice the numerical stability. The thus defined kernel generalized variance approximates the mutual information between variables Y and X to the second level when the variables in question follow arbitrary distributions and 'near independency' (please refer to Bach & Jordan⁷ for a detailed proof), and therefore $rkassoc^{(k)} \approx 0$ if Y and X are independent.

To get the p-value under the NULL hypothesis, we used the permutation procedure. The columns of X were permuted for B times, and the permuted kernel generalized variance statistics were calculated and recorded. The empirical p-value was then calculated as the percent of permuted statistics exceeding the original one. We found that a gamma fit of the permuted statistics approximates the NULL distribution of statistics quite well and is especially useful when one is performing screening where statistical correction is required. We truncated the left most 2% tail of the permuted NULL to get a stable fit of the gamma distribution. A diagnostic QQ-plot was also produced along with the approximated p-value in case of deviation from the gamma fit, which happens if inappropriate regularization parameter or kernel function is chosen, or the distribution from the original space is too irregular given a small sample size. Intensive numerical simulations reveal no sign of inflated false positive rate of the kernel association measure (data not shown). Nevertheless, in this paper we only report the empirical p-values.

To control for the covariates, we eliminate the covariate effect from the original space of the data. As we expect no interactions between the covariates in this study, we enforce only the linear covariate removal procedure, where a linear model was applied on the main variables, e.g. SNPs and phenotypes, to regress out the covariates, e.g. research sites and gender, and the residual terms were then used to represent the corresponding main variable in the kernel based association analysis. A more general nonlinear covariate removal scheme should be enforced when nonlinear interaction between the covariates is expected and will be detailed in a separated article for more general applications. Simulation studies indicate that removing covariates from

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either phenotype or SNP is more conservative than removing covariates from both of them, while both procedures show no sign of inflated false positives (data not shown).

For our current application, Gaussian kernels were used, and the determination of kernel bandwidth followed the recipe of ⁷, the regularization parameter was set to 0.1. We permuted the sample 1, 000 times to get the empirical p-value. After the covariate removal procedure, the data were transformed to its rank divided by sample size before testing for the kernel association to smooth out possible outliers that might destabilize the algorithm.

Supplementary tables

Table S1. M5 module genes with differential gene expression between WT and *Rasgrf2*^{-/-} and module membership. logFC: fold change on log₂ scale between WT and *Rasgrf2*^{-/-}; MM: module membership; kWithin: number of connections between a gene and other genes in a module

Mouse Gene Symbol	Differential Expression			Module Membership			Human Gene Symbol
	logFC	t	P value	MM	P value	kWithin	
Glr1	3	38.27	2.67E-20	0.99	2.29E-16	76.61	
LOC666403	4.48	59.71	3.67E-24	0.99	7.83E-16	76.23	
1200015F23Rik	2.15	42.63	3.11E-21	0.99	1.23E-15	75.97	
Tmem87a	-2.38	-42.17	3.86E-21	-0.99	3.11E-15	75.47	TMEM87A
Lrrc57	2.44	34.6	1.98E-19	0.99	5.85E-15	75.23	LRRC57
Ccndbp1	1.43	24.13	2.40E-16	0.99	2.59E-14	73.6	CCNDBP1
9930021D14Rik	1.31	22.86	6.85E-16	0.99	9.43E-14	72.98	
Slc25a18	2.25	23.78	3.19E-16	0.98	4.12E-13	72.8	SLC25A18
2810410P22Rik	1.84	19.75	1.17E-14	0.98	4.50E-13	71.23	
Pla2g4b	0.43	11.35	3.29E-10	0.98	7.04E-13	70.12	PLA2G4B
Gfer	0.66	14.77	2.81E-12	0.98	2.45E-12	68.74	GFER
Cops8	-2.91	-21.1	3.26E-15	-0.98	3.08E-12	67.93	COPS8
Adamts9	0.85	15.38	1.33E-12	0.98	3.24E-12	67.84	ADAMTS9
Eme2	-1.74	-20.75	4.50E-15	-0.98	5.20E-12	68	EME2
C920004C08Rik	-0.98	-16.06	5.90E-13	-0.98	5.72E-12	66.72	
Slc39a9	0.65	12.83	3.71E-11	0.97	9.06E-12	66.17	SLC39A9
Arrdc3	2.07	16.82	2.47E-13	0.97	9.55E-12	68.47	ARRDC3
2810423A18Rik	1.51	17.65	9.99E-14	0.97	1.27E-11	68.02	
Mad	1.21	17.31	1.44E-13	0.97	1.33E-11	68.05	
A330021E22Rik	1.28	16.43	3.86E-13	0.97	1.52E-11	64.42	C7orf63
Arl5a	1.7	16.24	4.80E-13	0.97	1.85E-11	66.31	ARL5A
LOC229810	-1.64	-18.56	3.83E-14	-0.97	2.81E-11	68.29	
Zap3-pending	0.58	13.07	2.65E-11	0.97	3.22E-11	65.62	
Clstn1	-1.51	-18.54	3.91E-14	-0.97	4.05E-11	66.34	CLSTN1
Per3	-0.77	-13.83	9.50E-12	-0.97	6.43E-11	64.12	PER3
Vrk1	0.85	13.51	1.45E-11	0.96	1.15E-10	62.83	VRK1
2310002B06Rik	-0.6	-12.66	4.71E-11	-0.96	1.27E-10	61.92	
Polr3f	-0.38	-9.54	6.39E-09	-0.96	1.96E-10	61.86	POLR3F

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Gpr19	0.81	11.99	1.24E-10	0.96	2.02E-10	62.33	GPR19
Mid1	1.61	17.27	1.50E-13	0.96	2.98E-10	62.82	MID1
A630064P09Rik	-0.46	-10.17	2.20E-09	-0.96	3.42E-10	59.67	
Ccl27	-1.79	-15.52	1.12E-12	-0.96	4.35E-10	60.68	
8430432M10Rik	0.67	11.92	1.38E-10	0.95	1.13E-09	59.82	
Ndufb10	1.09	15.91	7.03E-13	0.95	1.74E-09	59.86	NDUFB10
Ube2i	-1.04	-12.22	8.89E-11	-0.95	3.01E-09	56.05	UBE2I
Tubgcp4	0.62	10.28	1.82E-09	0.95	3.11E-09	55.84	TUBGCP4
Bub1b	0.36	8.56	3.79E-08	0.94	6.11E-09	53.49	BUB1B
Ehd4	0.67	9.79	4.19E-09	0.94	6.77E-09	54.66	EHD4
Rps2	-0.51	-10.47	1.33E-09	-0.94	7.38E-09	53.67	RPS2
Arhgap12	1.12	11.84	1.57E-10	0.94	8.00E-09	53.33	ARHGAP12
Atm	-0.54	-9.67	5.10E-09	-0.94	8.80E-09	52.53	ATM
Nubp2	0.69	9.87	3.67E-09	0.94	1.00E-08	53.57	NUBP2
Neol	0.61	9.99	2.99E-09	0.93	1.61E-08	51.98	NEO1
6430553K24Rik	0.36	7.66	2.15E-07	0.93	2.58E-08	51.24	
Clcn7	-0.57	-9.35	9.06E-09	-0.93	2.83E-08	50.28	CLCN7
LOC100043919	-1.44	-10.29	1.80E-09	-0.93	3.23E-08	49.33	
B830006A16Rik	-0.37	-8.35	5.60E-08	-0.93	3.30E-08	48.96	
EG434402	0.72	10.44	1.40E-09	0.92	5.00E-08	49.21	
Rnd3	0.89	9.15	1.28E-08	0.92	5.20E-08	48.74	RND3
Gins4	0.5	8.15	8.31E-08	0.92	6.18E-08	48.92	GIN54
Slc45a1	-0.52	-8.97	1.79E-08	-0.92	6.38E-08	47.62	SLC45A1
Exoc6b	0.32	6.98	8.65E-07	0.92	6.79E-08	44.1	EXOC6B
Eif2ak2	0.65	8.68	3.03E-08	0.92	7.05E-08	47.23	EIF2AK2
Osbp11a	1.01	9.15	1.28E-08	0.92	7.46E-08	46.08	OSBPL1A
2700017A04Rik	0.54	8.3	6.24E-08	0.92	8.34E-08	42.87	
LOC329506	0.38	7.57	2.60E-07	0.92	1.03E-07	42.98	
LOC331139	-0.64	-8.79	2.49E-08	-0.91	1.10E-07	42.81	
0610010D24Rik	0.27	6.7	1.53E-06	0.91	1.20E-07	45.64	
Dbpht2	-1.36	-9.09	1.42E-08	-0.91	1.81E-07	45.51	FLJ45079
Anxa4	-0.3	-6.96	8.93E-07	-0.91	2.21E-07	43.5	ANXA4
Alg9	-0.4	-8.31	6.04E-08	-0.9	2.53E-07	44.68	ALG9
Ivd	0.45	7.51	2.93E-07	0.9	2.62E-07	38.97	IVD
Tatdn3	-0.36	-7.2	5.41E-07	-0.9	2.72E-07	42.82	TATDN3
A930004K21Rik	0.43	7.46	3.21E-07	0.9	2.83E-07	41.51	
2310007O11Rik	0.62	8.17	7.89E-08	0.9	3.23E-07	41.14	
Msh2	0.45	8.33	5.81E-08	0.9	3.69E-07	41.62	MSH2
Tsc2	-0.67	-8.43	4.81E-08	-0.9	3.90E-07	41.37	TSC2
Chl1	-1.18	-8.53	4.02E-08	-0.9	4.76E-07	41.8	CHL1
Eif4el3	-0.57	-8.43	4.81E-08	-0.9	5.10E-07	39.08	
Gnptg	-0.45	-7.35	4.04E-07	-0.89	5.73E-07	38.63	GNPTG
3110021A11Rik	0.44	7.03	7.73E-07	0.89	6.14E-07	36.91	
Pigf	-0.25	-6.02	6.74E-06	-0.89	6.92E-07	38.72	PIGF
Rbbp9	-0.88	-9.4	8.19E-09	-0.89	7.51E-07	40.43	RBBP9
Cml1	0.5	7.31	4.34E-07	0.89	7.67E-07	39.15	
Dhrsx	-0.88	-8.6	3.52E-08	-0.89	7.88E-07	36.82	DHR5X
Abca8a	0.34	6.69	1.57E-06	0.89	8.36E-07	36.01	

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Psmb5	-0.85	-7.91	1.30E-07	-0.89	8.51E-07	37.1	PSMB5
Mela	-0.9	-8.63	3.32E-08	-0.88	1.13E-06	35.54	
Serpina3n	-0.94	-8.95	1.84E-08	-0.88	1.21E-06	37.18	SERPI3
Stk25	-1.1	-7.6	2.43E-07	-0.88	1.28E-06	34.54	STK25
Vps39	-0.47	-7.78	1.71E-07	-0.88	1.29E-06	36.81	VPS39
LOC666621	0.16	3.99	7.16E-04	0.88	1.83E-06	32.33	
Itgb3bp	0.61	6.95	9.19E-07	0.88	1.89E-06	35.53	ITGB3BP
Serpina3h	-0.58	-8.15	8.30E-08	-0.88	1.93E-06	34.07	
Rnase4	0.87	8.37	5.38E-08	0.87	2.13E-06	36.07	RSE4
AB041568	0.23	5.07	5.70E-05	0.87	3.07E-06	29.43	
Ugt1a10	-0.3	-5.96	7.71E-06	-0.87	3.29E-06	31.41	
2310045N01Rik	0.33	5.93	8.23E-06	0.86	4.10E-06	28.85	MEF2BNB
Prdm16	0.55	6.94	9.34E-07	0.86	4.12E-06	32.03	PRDM16
Supt16h	-1.94	-7.43	3.39E-07	-0.86	4.50E-06	31.14	SUPT16H
Mertk	-0.36	-6.05	6.29E-06	-0.86	4.52E-06	29.82	MERTK
Ang	-0.45	-6.72	1.48E-06	-0.86	4.66E-06	29.48	ANG
Pgm2	-0.26	-5.71	1.34E-05	-0.86	5.14E-06	28.79	PGM1
1700047117Rik1	0.59	6.16	4.97E-06	0.85	6.21E-06	26.33	
Spata7	0.45	6.17	4.81E-06	0.85	6.38E-06	22.97	SPATA7
Snx5	-0.33	-5.88	9.05E-06	-0.85	6.64E-06	29.48	SNX5
Ints7	-0.33	-5.97	7.50E-06	-0.85	6.74E-06	29.03	INTS7
Ajap1	-0.4	-6.42	2.79E-06	-0.85	7.16E-06	28.49	AJAP1
Catsper2	-0.25	-5.22	4.01E-05	-0.85	7.32E-06	26.81	CATSPER2
Bid	0.38	5.95	7.86E-06	0.85	8.20E-06	26.65	BID
Exdl1	-0.22	-5.05	5.95E-05	-0.85	8.53E-06	26.02	
Pgpep1	0.45	6	6.94E-06	0.85	9.40E-06	29.74	PGPEP1
H2afv	-0.89	-6.88	1.06E-06	-0.85	9.45E-06	25.84	H2AFV
8030462N17Rik	-0.32	-5.85	9.74E-06	-0.85	9.72E-06	28.92	C18orf25
Zfp706	0.37	6.12	5.37E-06	0.85	9.98E-06	27.53	ZNF706
Rfesd	-0.29	-5.63	1.60E-05	-0.84	1.11E-05	26.48	RFESD
D330027H18Rik	1.16	6.62	1.85E-06	0.84	1.14E-05	24.51	
LOC100048331	-0.43	-6.33	3.38E-06	-0.84	1.16E-05	27.19	
Rpp25	-0.51	-6.7	1.55E-06	-0.84	1.23E-05	27.53	RPP25
Evpl	0.38	5.71	1.33E-05	0.84	1.33E-05	25.81	EVPL
LOC100046129	0.36	5.81	1.07E-05	0.84	1.39E-05	24.04	
Ppp1r3f	0.38	6.08	5.92E-06	0.84	1.48E-05	27.1	PPP1R3F
LOC667034	-0.49	-5.96	7.64E-06	-0.84	1.58E-05	22.82	
Dapk1	-0.3	-5.04	6.08E-05	-0.84	1.60E-05	24.45	DAPK1
2410004L22Rik	0.41	5.74	1.26E-05	0.84	1.61E-05	25.69	
Dcp1b	0.58	6.24	4.13E-06	0.83	1.78E-05	28.68	DCP1B
Dguok	0.38	5.55	1.91E-05	0.83	1.99E-05	26.55	DGUOK
Itfg2	0.63	6.54	2.15E-06	0.83	2.07E-05	27	ITFG2
Cryab	-0.7	-6.16	4.97E-06	-0.83	2.17E-05	25.62	CRYAB
Hnrpc	0.29	4.82	1.02E-04	0.83	2.21E-05	24.65	
Gpr68	0.33	5.12	5.06E-05	0.83	2.22E-05	26.1	GPR68
Map4k5	0.23	4.63	1.57E-04	0.83	2.25E-05	24.66	MAP4K5
Gm288	0.3	5.45	2.39E-05	0.82	2.62E-05	24.26	
Snpc3	0.38	5.43	2.53E-05	0.82	2.75E-05	22.87	SPC3

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C130002N06	0.35	5.14	4.90E-05	0.82	2.77E-05	24.87	
Prkd3	0.64	6.2	4.54E-06	0.82	2.89E-05	24.04	PRKD3
Esco1	-0.17	-3.95	7.78E-04	-0.82	3.02E-05	21.06	ESCO1
Thtpa	0.24	4.83	9.85E-05	0.82	3.23E-05	21.24	THTPA
Alg6	-0.44	-5.94	7.96E-06	-0.82	3.42E-05	20.05	ALG6
A130082M07Rik	0.41	5.19	4.39E-05	0.82	3.51E-05	24.53	
Cdc21l	-0.34	-5.38	2.80E-05	-0.82	3.59E-05	21.66	
Pts	-0.62	-6.47	2.49E-06	-0.82	3.60E-05	24.97	PTS
Snapc1	0.42	5.22	4.08E-05	0.81	4.12E-05	24.82	SPC1
LOC218206	0.25	5.11	5.16E-05	0.81	4.14E-05	21.87	
Bcdo2	-0.21	-4.48	2.23E-04	-0.81	4.41E-05	21.03	
Shhrs	-0.15	-3.67	1.51E-03	-0.81	4.85E-05	19.39	
Polr3k	0.28	4.67	1.44E-04	0.81	4.94E-05	21.66	POLR3K
Kcnu1	-0.29	-4.8	1.07E-04	-0.81	5.07E-05	19.84	KCNU1
Abca3	0.39	5.18	4.48E-05	0.81	5.13E-05	22.66	ABCA3
Chd8	0.26	4.93	7.98E-05	0.81	5.26E-05	20.66	CHD8
4930570C03Rik	-0.5	-5.89	8.89E-06	-0.81	5.49E-05	21.96	
Gadd45gip1	-0.25	-4.9	8.49E-05	-0.8	5.83E-05	19.85	GADD45GIP1
Plcb2	0.17	3.94	7.94E-04	0.8	6.68E-05	18.68	PLCB2
Cdh15	0.78	5.92	8.43E-06	0.79	8.67E-05	18.16	CDH15
Rpl21	0.22	4.4	2.69E-04	0.79	8.86E-05	17.93	RPL21
ENSMUSG0000043795	-0.21	-4.5	2.14E-04	-0.79	9.41E-05	18.79	
Dio2	0.26	4.45	2.44E-04	0.79	9.67E-05	16.6	DIO2
Emp2	0.44	4.88	8.81E-05	0.79	9.71E-05	18.76	EMP2
Lypd6b	0.39	4.87	9.12E-05	0.79	9.78E-05	14.14	LYPD6B
Zmat5	-0.32	-4.67	1.43E-04	-0.79	1.00E-04	17.46	ZMAT5
LOC100040525	0.65	5.73	1.28E-05	0.79	1.01E-04	18.85	
2410076I21Rik	0.26	4.52	2.07E-04	0.79	1.03E-04	19.23	C15orf60
Nfam1	0.16	3.7	1.42E-03	0.79	1.03E-04	17.72	NFAM1
Sfrp1	0.39	5.08	5.60E-05	0.79	1.09E-04	16.88	SFRP1
LOC100046232	0.22	4.12	5.19E-04	0.79	1.13E-04	17.08	
Dbnl	0.31	4.63	1.60E-04	0.78	1.21E-04	14.47	DBNL
BC030867	0.16	3.74	1.27E-03	0.78	1.21E-04	15.77	C17orf53
Rbm28	0.66	5.89	8.86E-06	0.78	1.24E-04	16.79	RBM28
LOC386486	0.47	5.49	2.20E-05	0.78	1.28E-04	19.13	
Lsm8	-0.27	-4.49	2.18E-04	-0.78	1.28E-04	16.42	
Ndrg2	-0.59	-5.51	2.11E-05	-0.78	1.29E-04	17.55	NDRG2
Fkbp11	0.38	5.03	6.21E-05	0.78	1.29E-04	18.07	FKBP11
Lpcat2	0.22	4.21	4.26E-04	0.78	1.29E-04	14.88	LPCAT2
2900016B01Rik	-0.26	-4.21	4.21E-04	-0.78	1.38E-04	17.49	
Pygb	-0.75	-5.31	3.29E-05	-0.78	1.43E-04	13.34	PYGB
Ubfd1	0.26	4.34	3.12E-04	0.78	1.45E-04	14.72	UBFD1
Jdp2	0.19	3.89	8.93E-04	0.78	1.45E-04	15.42	JDP2
Rusc1	0.22	4.25	3.85E-04	0.78	1.46E-04	16.12	RUSC1
Nuded3	0.16	3.43	2.62E-03	0.78	1.46E-04	13.61	NUDCD3
Tnks	-0.13	-3.12	5.36E-03	-0.78	1.46E-04	13.39	TNKS
Col4a3bp	-0.17	-3.85	9.78E-04	-0.78	1.54E-04	16.61	COL4A3BP

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Tmem59l	0.45	5.28	3.57E-05	0.78	1.56E-04	16.64	TMEM59L
EG232599	0.3	4.45	2.43E-04	0.78	1.56E-04	19.15	
Ocell1	-0.75	-5.16	4.68E-05	-0.78	1.58E-04	19.79	OCEL1
4933431K14Rik	0.22	4.3	3.43E-04	0.78	1.58E-04	15.48	
Kctd5	0.19	3.91	8.54E-04	0.77	1.62E-04	15.45	KCTD5
Zcchc3	-0.58	-4.92	8.03E-05	-0.77	1.64E-04	14.62	ZCCHC3
2410026K10Rik	0.27	4.82	1.01E-04	0.77	1.64E-04	17.34	
Coq9	0.3	4.58	1.78E-04	0.77	1.66E-04	14.78	COQ9
9.33E+12	0.17	3.84	1.02E-03	0.77	1.67E-04	16.42	
Thap4	-0.92	-5.62	1.64E-05	-0.77	1.72E-04	18.09	THAP4
A330029H11Rik	-0.19	-3.94	7.94E-04	-0.77	1.92E-04	15.59	
Clec16a	-0.5	-4.8	1.06E-04	-0.77	1.98E-04	16.02	CLEC16A
Mcp1	0.14	3.23	4.20E-03	0.77	1.99E-04	15.6	MCPH1
6330583M11Rik	-0.33	-4.62	1.63E-04	-0.77	2.04E-04	15.56	
3010022N24Rik	0.64	5.61	1.66E-05	0.77	2.08E-04	16.57	
Klcl	0.78	5	6.71E-05	0.77	2.08E-04	17.05	KLC1
Hebp1	-0.32	-4.42	2.60E-04	-0.77	2.11E-04	13.81	HEBP1
Pkm2	-0.37	-4.41	2.67E-04	-0.77	2.11E-04	15.2	
1500012F01Rik	0.33	4.95	7.63E-05	0.76	2.17E-04	16.76	
B2m	0.35	4.69	1.39E-04	0.76	2.25E-04	13.55	B2M
Ganc	-0.42	-4.47	2.32E-04	-0.75	2.93E-04	14.05	GANC
Prdx2	1.27	5.24	3.83E-05	0.75	2.99E-04	13.95	PRDX2
Galt	-0.31	-4.55	1.91E-04	-0.75	3.00E-04	12.6	GALT
Rnase6	-0.24	-4.25	3.83E-04	-0.75	3.21E-04	12.77	RSE6
Tmco5	0.18	3.56	1.96E-03	0.75	3.23E-04	12.89	TMCO5A
Rhoq	-0.22	-4.08	5.71E-04	-0.75	3.32E-04	14.62	RHOQ
Spsb3	-0.38	-4.82	1.03E-04	-0.75	3.36E-04	13.66	SPSB3
4732469G06Rik	-0.2	-4	6.99E-04	-0.75	3.41E-04	12.39	
2310047M10Rik	0.27	4.41	2.63E-04	0.75	3.66E-04	12.97	C17orf59
Slc5a5	1.23	4.74	1.22E-04	0.74	4.31E-04	14.19	SLC5A5
LOC100048384	0.25	4.35	3.06E-04	0.74	4.33E-04	14.21	
Kns2	1.28	4.61	1.65E-04	0.74	4.36E-04	15.72	
5730405I09Rik	0.37	4.21	4.25E-04	0.74	4.52E-04	11.08	
Usp2	-0.41	-4.1	5.43E-04	-0.74	4.65E-04	14.19	USP2
Tmem22	0.39	4.3	3.47E-04	0.74	4.67E-04	12.88	SLC35G2
6330562C20Rik	0.21	3.76	1.22E-03	0.74	4.86E-04	11.72	
E030045B01Rik	-0.26	-4.03	6.43E-04	-0.74	4.96E-04	12.59	
Spsb1	0.27	4.07	5.88E-04	0.74	4.98E-04	12.05	SPSB1
Gtpbp3	-0.26	-4.13	5.09E-04	-0.74	5.01E-04	11.06	GTPBP3
6430561B16Rik	-0.12	-2.95	7.84E-03	-0.73	5.18E-04	11.27	
Ncan	-0.36	-4.4	2.70E-04	-0.73	5.22E-04	13.94	NCAN
AU019823	0.19	3.62	1.68E-03	0.73	5.32E-04	11.39	C11orf57
Zfp609	0.14	3.17	4.80E-03	0.73	5.38E-04	10.5	ZNF609
Btdb6	0.34	4.02	6.68E-04	0.73	5.74E-04	14.16	BTBD6
Pcdhb7	-0.24	-3.86	9.63E-04	-0.73	5.90E-04	11.13	
Ccl9	-0.35	-4.47	2.32E-04	-0.73	5.93E-04	11.86	
Igf2r	0.15	3.39	2.91E-03	0.73	6.01E-04	11.58	IGF2R
Gpr176	0.32	3.91	8.61E-04	0.73	6.12E-04	13.42	GPR176

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Sh3glb1	-0.18	-3.63	1.65E-03	-0.73	6.15E-04	11.04	SH3GLB1
LOC224532	0.32	4.29	3.53E-04	0.73	6.31E-04	13.02	
Slc9a3r2	0.23	3.93	8.23E-04	0.72	6.66E-04	9.14	SLC9A3R2
Wnt2	0.64	4.37	2.90E-04	0.72	6.70E-04	10.65	WNT2
Rasl12	0.27	4.01	6.78E-04	0.72	6.91E-04	10.36	RASL12
Pelo	0.26	3.92	8.35E-04	0.72	6.99E-04	9.76	PELO
Agpat5	-0.59	-4.6	1.69E-04	-0.72	7.05E-04	10.53	AGPAT5
Ppp1r3e	-0.13	-2.98	7.39E-03	-0.72	7.17E-04	10.17	PPP1R3E
Xkr8	0.35	4.52	2.04E-04	0.72	7.30E-04	10.18	XKR8
LOC100045567	0.38	4.16	4.81E-04	0.72	7.49E-04	9.76	
Fancc	0.18	3.55	1.99E-03	0.72	7.62E-04	11.45	FANCC
Ccdc124	0.49	4.47	2.29E-04	0.72	7.71E-04	11.69	CCDC124
Slc39a2	-0.41	-4.05	6.13E-04	-0.72	7.71E-04	10.01	SLC39A2
Rtbdn	0.18	3.54	2.05E-03	0.72	7.77E-04	9.67	RTBDN
Dci	-0.28	-4.14	4.98E-04	-0.72	7.79E-04	10.03	
Pkd2l1	-0.57	-4.48	2.28E-04	-0.72	7.97E-04	10.27	PKD2L1
Uncx	0.14	3.15	5.00E-03	0.72	8.50E-04	8.95	UNCX
Ccdc66	-0.11	-2.69	1.40E-02	-0.71	8.82E-04	9.29	CCDC66
D330040L23Rik	-0.19	-3.47	2.39E-03	-0.71	9.47E-04	8.17	
D8Ert82e	0.24	3.71	1.38E-03	0.71	9.96E-04	10	SGK223
4833418A01Rik	-0.16	-3.29	3.61E-03	-0.71	1.01E-03	7.21	
EG623661	0.13	3.07	5.97E-03	0.71	1.03E-03	10.26	
Dscr3	0.16	3.22	4.30E-03	0.71	1.04E-03	7.4	DSCR3
AU021838	0.21	3.56	1.95E-03	0.71	1.05E-03	10.26	
A930017G19Rik	0.14	2.97	7.49E-03	0.71	1.05E-03	8.12	
AU014645	-0.16	-3.31	3.44E-03	-0.71	1.07E-03	8.99	
Xpnpep1	-0.29	-4.16	4.79E-04	-0.7	1.09E-03	10.88	XPNPEP1
Trfp	0.24	3.63	1.67E-03	0.7	1.10E-03	10.9	
C730046C01Rik	-0.19	-3.4	2.80E-03	-0.7	1.12E-03	10.26	
Xpa	-0.3	-3.98	7.30E-04	-0.7	1.14E-03	9.56	XPA
Dgkq	0.28	4.07	5.83E-04	0.7	1.23E-03	10.14	DGKQ
Stmn1	0.29	3.67	1.52E-03	0.7	1.24E-03	6.85	STMN1
Plvap	-0.52	-4.11	5.39E-04	-0.7	1.28E-03	10.55	PLVAP
Atg16l1	-0.24	-3.74	1.29E-03	-0.7	1.29E-03	10.14	ATG16L1
Fam122b	0.15	3.04	6.44E-03	0.7	1.29E-03	8.06	FAM122B
Pycrl	0.19	3.71	1.37E-03	0.7	1.31E-03	10.39	PYCRL
Nin	-0.31	-3.82	1.05E-03	-0.7	1.33E-03	8.55	NIN
Upp1	0.28	3.94	8.04E-04	0.69	1.39E-03	8.57	UPP1
Ogfrl1	-0.73	-3.89	8.97E-04	-0.69	1.47E-03	9.3	OGFRL1
Ntn2l	0.22	3.64	1.60E-03	0.69	1.51E-03	8.76	
Ppp1r13b	0.41	4	6.99E-04	0.69	1.55E-03	9.81	PPP1R13B
Flnc	0.13	2.86	9.55E-03	0.69	1.61E-03	7.67	FLNC
Ap1g2	0.28	3.48	2.31E-03	0.69	1.63E-03	7.85	APIG2
A1256775	-0.26	-3.87	9.51E-04	-0.69	1.67E-03	8.16	
L3mbtl2	-0.15	-3.19	4.61E-03	-0.69	1.69E-03	7.99	L3MBTL2
Fgl1	-0.25	-3.63	1.63E-03	-0.68	1.76E-03	7.77	FGL1
Pdk4	-0.36	-3.96	7.61E-04	-0.68	1.80E-03	6.77	PDK4
Brunol6	0.34	3.99	7.06E-04	0.68	1.81E-03	8.77	

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Adhfe1	0.12	2.76	1.20E-02	0.68	1.82E-03	7.8	ADHFE1
LOC381596	-0.11	-2.58	1.79E-02	-0.68	1.86E-03	5.59	
Trappc6b	0.43	3.73	1.31E-03	0.68	1.89E-03	7.2	TRAPPC6B
4930563F16Rik	-0.13	-2.93	8.32E-03	-0.68	1.92E-03	7.46	
Gng10	-0.22	-3.35	3.14E-03	-0.68	1.99E-03	5.98	GNG10
2410006H16Rik	0.21	3.39	2.87E-03	0.68	2.02E-03	8.11	
Sytl4	0.68	3.74	1.27E-03	0.68	2.05E-03	7.79	SYTL4
Mt2	-0.25	-3.86	9.75E-04	-0.68	2.09E-03	7.27	MT2A
Rpap3	-0.26	-3.84	1.01E-03	-0.67	2.15E-03	9.13	RPAP3
Mrpl9	0.31	3.7	1.42E-03	0.67	2.15E-03	7.65	MRPL9
LOC100044294	-0.23	-3.42	2.68E-03	-0.67	2.17E-03	7.31	
Zbtb46	0.12	2.61	1.67E-02	0.67	2.17E-03	8.44	ZBTB46
Ifrd2	-0.12	-2.69	1.39E-02	-0.67	2.32E-03	6.32	IFRD2
Pbx4	0.24	3.45	2.51E-03	0.67	2.43E-03	5.86	PBX4
2810402K13Rik	0.14	2.86	9.72E-03	0.66	2.65E-03	5.77	
Nola2	-0.29	-3.78	1.17E-03	-0.66	2.69E-03	6.54	
2810422J05Rik	0.15	2.92	8.44E-03	0.66	2.70E-03	7.52	
Capn3	0.17	3.11	5.53E-03	0.66	2.72E-03	6.21	CAPN3
B230396K19Rik	-0.11	-2.45	2.36E-02	-0.66	2.78E-03	6.49	
Erdr1	-0.81	-3.48	2.32E-03	-0.66	2.97E-03	6.57	
C230078M08Rik	-0.3	-3.61	1.75E-03	-0.66	3.01E-03	5.91	
Dnajc2	-0.23	-3.3	3.53E-03	-0.66	3.02E-03	6.79	DJC2
Pawr	0.12	2.63	1.59E-02	0.66	3.04E-03	6.1	PAWR
LOC330052	0.13	2.72	1.32E-02	0.66	3.06E-03	4.42	
C630016C03Rik	0.17	3.02	6.72E-03	0.65	3.22E-03	6	
LOC381420	0.12	2.67	1.46E-02	0.65	3.31E-03	5.76	
D8Erd738e	-0.21	-3.32	3.37E-03	-0.65	3.37E-03	5.83	C19orf53
Adamtsl2	0.19	3.2	4.51E-03	0.65	3.38E-03	4.48	ADAMTSL2
EG668831	0.15	2.83	1.04E-02	0.65	3.45E-03	6.69	
AI316807	-0.24	-3.48	2.35E-03	-0.65	3.63E-03	5.92	C8orf40
Bcl2l2	0.11	2.48	2.19E-02	0.65	3.73E-03	5.53	BCL2L2
Sdccag33l	0.25	3.3	3.59E-03	0.65	3.80E-03	5.96	
Abhd4	-0.32	-3.51	2.18E-03	-0.64	4.00E-03	6.31	ABHD4
Fos	0.52	3.63	1.65E-03	0.64	4.06E-03	4.46	FOS
6330500D04Rik	-0.39	-3.54	2.02E-03	-0.64	4.11E-03	6.68	
Rps4y2	0.35	3.37	3.03E-03	0.64	4.16E-03	4.83	
Phf13	0.15	2.79	1.13E-02	0.64	4.40E-03	4.2	PHF13
1110003P22Rik	0.15	2.91	8.69E-03	0.64	4.47E-03	5.17	
Zswim4	0.13	2.66	1.49E-02	0.64	4.57E-03	5.21	ZSWIM4
Eif3s1	-0.17	-3.02	6.66E-03	-0.63	4.77E-03	4.17	
LOC384104	-0.19	-3.19	4.59E-03	-0.63	4.84E-03	5.19	
mt-Nd4	-0.26	-3.18	4.71E-03	-0.63	5.13E-03	5.05	ND4
Ccl17	0.35	3.22	4.22E-03	0.63	5.23E-03	4.84	CCL17
Zfp709	0.1	2.32	3.09E-02	0.63	5.24E-03	4.62	ZNF14
Ift122	0.15	2.84	1.01E-02	0.63	5.28E-03	5.53	IFT122
A830093I24Rik	0.11	2.47	2.24E-02	0.63	5.43E-03	5.6	
Pcm1	-0.19	-3.06	6.09E-03	-0.62	5.83E-03	5	PCM1
Pou6f1	-1.15	-3.65	1.57E-03	-0.62	5.91E-03	4.05	POU6F1

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LOC100041567	0.42	3.53	2.08E-03	0.62	6.01E-03	4.74	
Mrps7	0.18	2.95	7.87E-03	0.62	6.06E-03	5.59	MRPS7
Slc35f3	-0.19	-2.87	9.48E-03	-0.62	6.34E-03	4.72	SLC35F3
Tulp3	-0.11	-2.41	2.56E-02	-0.62	6.43E-03	4.19	TULP3
Spns1	0.16	2.91	8.68E-03	0.61	6.79E-03	3.73	SPNS1
Sdf2l1	0.15	2.73	1.28E-02	0.61	7.41E-03	3.59	SDF2L1
Diap3	0.18	3.09	5.76E-03	0.61	7.46E-03	4.31	DIAPH3
2310005E10Rik	0.15	2.72	1.32E-02	0.61	7.49E-03	5.14	
Socs2	-0.21	-2.96	7.67E-03	-0.61	7.64E-03	3.85	SOCS2
Tra2a	0.3	3.39	2.88E-03	0.6	8.27E-03	4.41	TRA2A
Bmx	0.12	2.5	2.13E-02	0.6	8.95E-03	3.71	BMX
Nicn1	0.18	2.62	1.62E-02	0.59	1.04E-02	4.05	NICN1
Cog3	-0.13	-2.5	2.13E-02	-0.59	1.04E-02	3.24	COG3
LOC385792	0.12	2.43	2.46E-02	0.59	1.05E-02	3.36	
2410075B13Rik	0.1	2.16	4.30E-02	0.59	1.06E-02	3.06	
Zfp593	0.15	2.64	1.58E-02	0.58	1.25E-02	3.31	ZNF593
Dhps	0.11	2.26	3.53E-02	0.57	1.28E-02	2.56	DHPS
Fabp6	0.11	2.26	3.52E-02	0.57	1.42E-02	2.73	FABP6
Fam171b	-0.17	-2.54	1.92E-02	-0.56	1.54E-02	3.51	FAM171B
Tpmt	-0.15	-2.72	1.32E-02	-0.56	1.66E-02	2.45	TPMT
Mat2b	0.21	2.86	9.54E-03	0.55	1.70E-02	3.35	MAT2B
Akr1e1	0.27	3.06	6.10E-03	0.55	1.73E-02	1.94	AKR1E2
LOC383579	0.12	2.22	3.80E-02	0.55	1.78E-02	2.23	
Zbtb43	-0.12	-2.11	4.80E-02	-0.55	1.87E-02	2.98	ZBTB43
Tcerg1	-0.16	-2.54	1.96E-02	-0.54	1.97E-02	2.09	TCERG1
Nt5dc2	-0.12	-2.3	3.25E-02	-0.54	1.97E-02	2.05	NT5DC2
Coq3	0.14	2.37	2.78E-02	0.54	2.01E-02	2.15	COQ3
Ankrd35	0.1	2	5.94E-02	0.54	2.01E-02	2.72	ANKRD35
1110038F14Rik	-0.17	-2.38	2.75E-02	-0.54	2.13E-02	2.11	C8orf33
Nupr1	-0.26	-2.66	1.51E-02	-0.53	2.25E-02	2.43	NUPR1
LOC100039175	-0.1	-2.17	4.22E-02	-0.53	2.34E-02	1.64	
AI837181	0.15	2.27	3.44E-02	0.53	2.42E-02	1.79	C11orf68
Rbbp5	0.12	2.18	4.11E-02	0.52	2.58E-02	2.83	RBBP5
Birc5	0.09	2.02	5.73E-02	0.52	2.69E-02	1.6	BIRC5
Cd97	0.11	2.15	4.41E-02	0.52	2.72E-02	1.78	CD97
5430400L16Rik	0.09	1.83	8.22E-02	0.51	3.06E-02	1.88	
Lass5	-0.11	-2.11	4.75E-02	-0.51	3.10E-02	1.74	CERS5
Vps35	0.16	2.23	3.70E-02	0.5	3.28E-02	1.51	VPS35
Rpl13a	0.12	2.14	4.50E-02	0.5	3.34E-02	1.38	RPL13A
Stxbp4	-0.14	-2.11	4.80E-02	-0.5	3.42E-02	1.9	STXBP4
Ap1s3	0.09	1.92	6.92E-02	0.5	3.63E-02	0.93	AP1S3
Fbxl17	-0.11	-2	5.93E-02	-0.49	3.68E-02	1.24	FBXL17
LOC674707	0.12	2.08	5.00E-02	0.49	3.80E-02	1.25	
Pak1	-0.49	-2.72	1.31E-02	-0.49	4.01E-02	1.3	PAK1
4933436C20Rik	-0.11	-2.04	5.44E-02	-0.48	4.18E-02	1.22	
Grb2	0.09	1.82	8.34E-02	0.46	5.27E-02	0.61	GRB2
Dynlrb1	-0.16	-2.07	5.13E-02	-0.46	5.34E-02	0.89	DYNLRB1
Madcaml	0.07	1.47	1.58E-01	0.43	7.25E-02	0.78	MADCAM1

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Mgl2	0.08	1.56	1.35E-01	0.4	9.97E-02	0.61	CLEC10A
L1td1	-0.08	-1.47	1.57E-01	-0.39	1.07E-01	0.36	L1TD1
Epha4	0.06	1.31	2.05E-01	0.35	1.55E-01	0.43	EPHA4
Il6st	-0.14	-1.29	2.13E-01	-0.28	2.54E-01	0.54	IL6ST

Table S2. Significantly enriched gene ontology (GO) terms for genes in M5 module. Count, number of genes from the input list in the term; Size, number of genes in each term; *p*-value, raw *p*-value from hypergeometric test; FDR, false discovery rate for multiple test adjustment.

ID	TERM	Count	Size	<i>p</i> -value	FDR
GO Biological Process					
0006468	protein phosphorylation	17	532	1.04E-04	4.01E-02
0016310	phosphorylation	19	642	1.12E-04	2.89E-02
0005975	carbohydrate metabolic process	9	168	1.13E-04	2.18E-02
0006006	glucose metabolic process	6	47	1.28E-05	9.90E-03
GO Molecular Function					
0016740	transferase activity	36	1298	4.47E-07	1.49E-04
0004672	protein kinase activity	16	454	5.33E-05	5.92E-03
0016301	kinase activity	20	643	3.76E-05	6.26E-03
0000166	nucleotide binding	38	1857	1.98E-04	1.65E-02
0005515	protein binding	51	2814	3.08E-04	2.05E-02
0004518	nuclease activity	6	91	5.30E-04	2.94E-02
0016772	transferase activity, transferring phosphorus-containing groups	14	463	7.18E-04	3.42E-02
0008092	cytoskeletal protein binding	4	40	9.81E-04	3.63E-02
GO Cellular Component					
0005737	cytoplasm	103	4708	1.48E-12	2.92E-10
0005634	nucleus	93	4536	9.81E-10	9.67E-08
0005622	intracellular	45	1751	1.27E-07	8.37E-06
0005794	Golgi apparatus	25	866	1.43E-05	7.06E-04
0005829	cytosol	24	843	2.67E-05	1.05E-03
0005739	mitochondrion	32	1391	8.17E-05	2.68E-03
0005768	endosome	12	315	2.25E-04	6.32E-03
0016020	membrane	81	5262	9.07E-04	2.23E-02
0005694	chromosome	9	240	1.50E-03	3.28E-02
0005813	centrosome	10	301	2.05E-03	4.04E-02

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Table S3. List of neuron-marker genes in M5 module. The list of genes known to be preferentially expressed in mouse astrocytes, microglia, neurons, and oligodendrocytes were obtained from (Cahoy et al. 2008).

Probe ID	Gene Symbol
ILMN_2511868	2310002B06Rik
ILMN_2465905	2310007O11Rik
ILMN_2749747	2410004L22Rik
ILMN_1230834	A930004K21Rik
ILMN_2847950	AI837181
ILMN_1242540	Alg6
ILMN_3160212	AU021838
ILMN_2774007	Bub1b
ILMN_2771518	Capn3
ILMN_1232067	Ccdc124
ILMN_2973089	Coq3
ILMN_2638914	D330027H18Rik
ILMN_2583454	E030045B01Rik
ILMN_2546510	EG434402
ILMN_2731999	Gnptg
ILMN_2663585	Jdp2
ILMN_1216575	LOC329506
ILMN_1216281	Map4k5
ILMN_2901903	Pigf
ILMN_2848548	Pts
ILMN_2747754	Pygb
ILMN_2763772	Rpap3
ILMN_2704027	Slc25a18
ILMN_1248132	Stmn1
ILMN_1232065	Tmem22
ILMN_3123657	Vrk1
ILMN_2703621	Zfp593

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Table S4. List of M5 genes located within mouse QTLs for alcohol preference. Chr, chromosome; Loci, gene location in Mb on mouse genome.

Gene Symbol	Gene Name	Chr	Loci
<i>2410076I21Rik</i>	RIKEN cDNA 2410076I21 gene	9	58.65
<i>4933431K14Rik</i>	RIKEN cDNA 4933431K14 gene	9	85.75
<i>6330562C20Rik</i>	RIKEN cDNA 6330562C20 gene	3	95.31
<i>Adamtsl2</i>	ADAMTS-like 2	2	27.08
<i>Alg6</i>	asparagine-linked glycosylation 6 (alpha-1,3,-glucosyltransferase)	4	99.72
<i>Alg9</i>	asparagine-linked glycosylation 9 (alpha 1,2 mannosyltransferase)	9	50.78
<i>Ampd1</i>	adenosine monophosphate deaminase 1	3	103.07
<i>Ankrd35</i>	ankyrin repeat domain 35	3	96.67
<i>Arl5a</i>	ADP-ribosylation factor-like 5A	2	52.40
<i>Atm</i>	ataxia telangiectasia mutated homolog (human)	9	53.44
<i>AU019823</i>	expressed sequence AU019823	9	50.61
<i>Bco2</i>	beta-carotene oxygenase 2	9	50.53
<i>Celf6</i>	CUGBP, Elav-like family member 6	9	59.58
<i>Cryab</i>	crystallin, alpha B	9	50.75
<i>Dcaf17</i>	DDB1 and CUL4 associated factor 17	2	71.06
<i>Dixdc1</i>	DIX domain containing 1	9	50.66
<i>Ggtal</i>	glycoprotein galactosyltransferase alpha 1, 3	2	35.40
<i>Gm5617</i>	predicted gene 5617	9	48.50
<i>Gm9387</i>	predicted pseudogene 9387	3	128.95
<i>Itgb3bp</i>	integrin beta 3 binding protein (beta3-endonexin)	4	99.77
<i>Lypd6b</i>	LY6/PLAUR domain containing 6B	2	49.79
<i>Mrpl9</i>	mitochondrial ribosomal protein L9	3	94.44
<i>Mtnr1b</i>	melatonin receptor 1B	9	15.86
<i>Neol</i>	neogenin	9	58.87
<i>Pgm2</i>	phosphoglucomutase 2	4	99.93
<i>Pkm</i>	pyruvate kinase, muscle	9	59.66
<i>Ppcdc</i>	phosphopantothencysteine decarboxylase	9	57.41
<i>Pts</i>	6-pyruvoyl-tetrahydropterin synthase	9	50.52
<i>Rasl12</i>	RAS-like, family 12	9	65.40
<i>Rnd3</i>	Rho family GTPase 3	2	51.13
<i>Rpp25</i>	ribonuclease P/MRP 25 subunit	9	57.50
<i>Rusc1</i>	RUN and SH3 domain containing 1	3	89.08
<i>Sapcd2</i>	suppressor APC domain containing 2	2	25.37
<i>Usp2</i>	ubiquitin specific peptidase 2	9	44.07
<i>Zbtb43</i>	zinc finger and BTB domain containing 43	2	33.45
<i>Zfp609</i>	zinc finger protein 609	9	65.69

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Table S5. The phases of haplotype block 3 in *EHD4* and corresponding frequencies in adolescent boys from the IMAGEN study.

	rs1704394	rs4923919	rs1648821	rs4924588	rs6493012	rs1025226	Freq
Hap1	T	G	T	A	T	A	0.06
Hap2	T	G	C	A	T	C	0.10
Hap3	G	A	C	G	C	C	0.34
Hap4	G	G	C	G	C	C	0.06
Hap5	G	G	C	A	C	C	0.45

Table S6. Haplotype analysis of haplotype block 3 in *EHD4*. Analyses are with binge drinking in 14 year old boys (n=905) and ventral striatal (VS) activity for contrast 10 (reward anticipation) of the monetary incentive delay (MID) task in 14 year old boys (n=608). The omnibus test results were acquired after 10000 permutations.

Test	MID task		
	Binge drinking	Left VS	Right VS
Hap1	4.11E-04	9.60E-01	8.39E-01
Hap2	6.96E-01	4.89E-01	1.74E-01
Hap3	1.73E-01	9.90E-03	2.49E-04
Hap4	4.76E-01	5.99E-01	5.61E-01
Hap5	7.66E-01	2.31E-02	6.87E-03
Omnibus	1.09E-02	9.24E-02	6.07E-03

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Supplementary figures

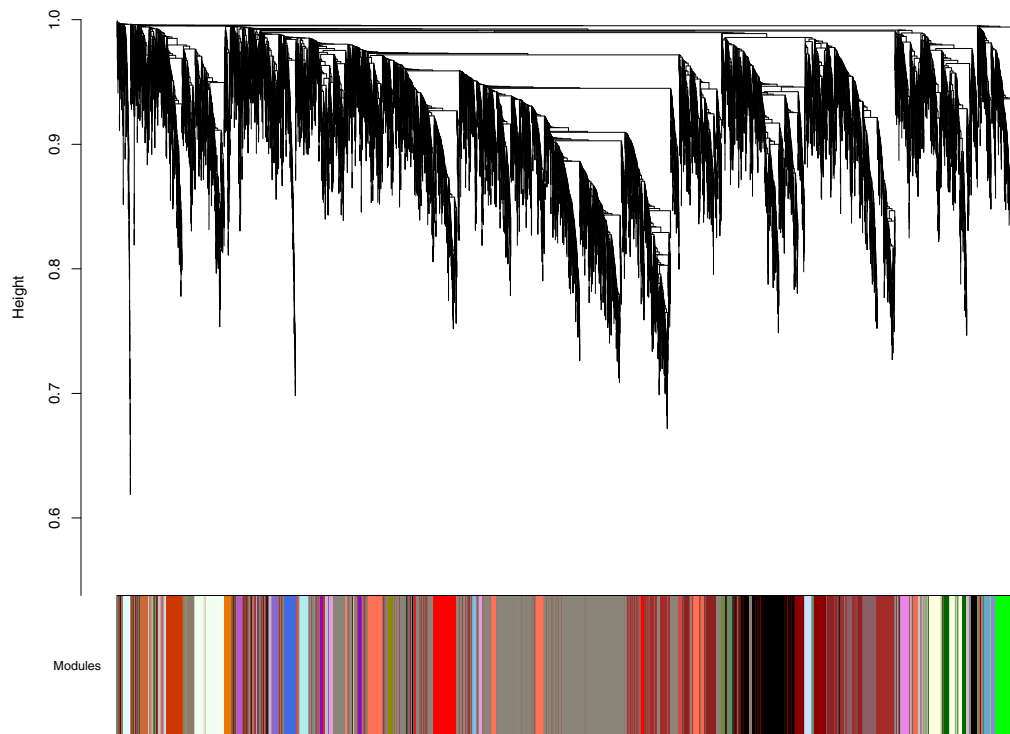


Fig. S1. Weighted gene co-expression network analysis of mouse VS expression data. Cluster dendrogram generated by hierarchical clustering of genes on the basis of topological overlap. Modules of correlated genes were assigned colors and are indicated by the horizontal bar beneath the dendrogram, where all unassigned genes were placed in the gray module

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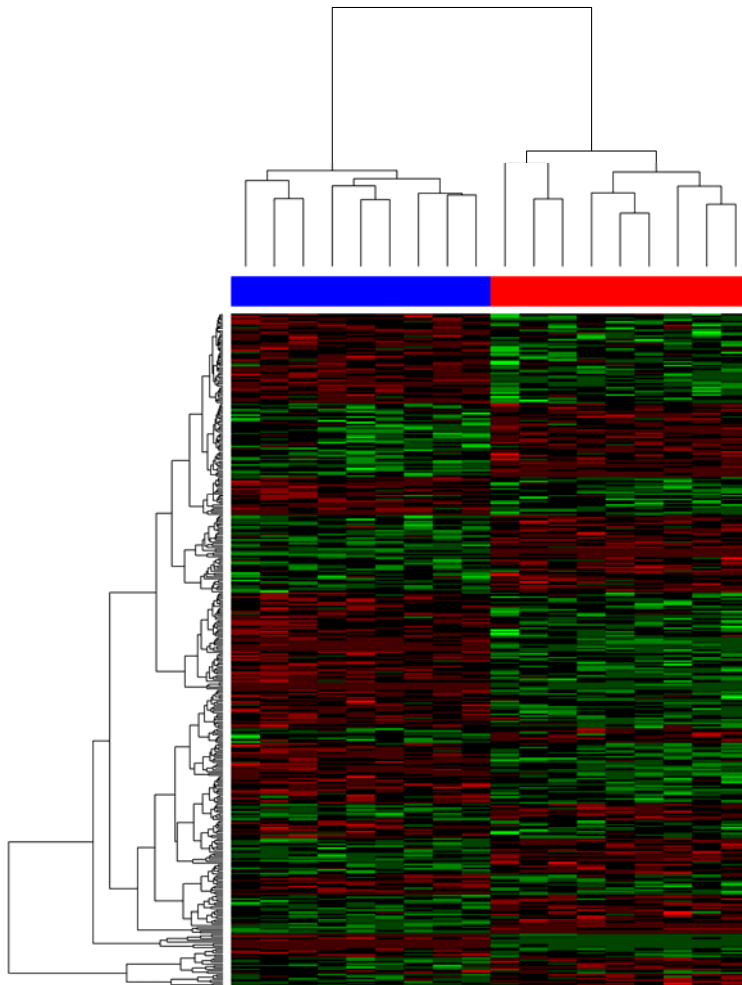


Fig. S2. Heatmap of genes in the M5 module. In the heatmap, red represents lower expression whereas green represents higher expression values. Top bar indicates samples: blue, Wild type mice; red, *Rasgrf2*^{-/-} mice.

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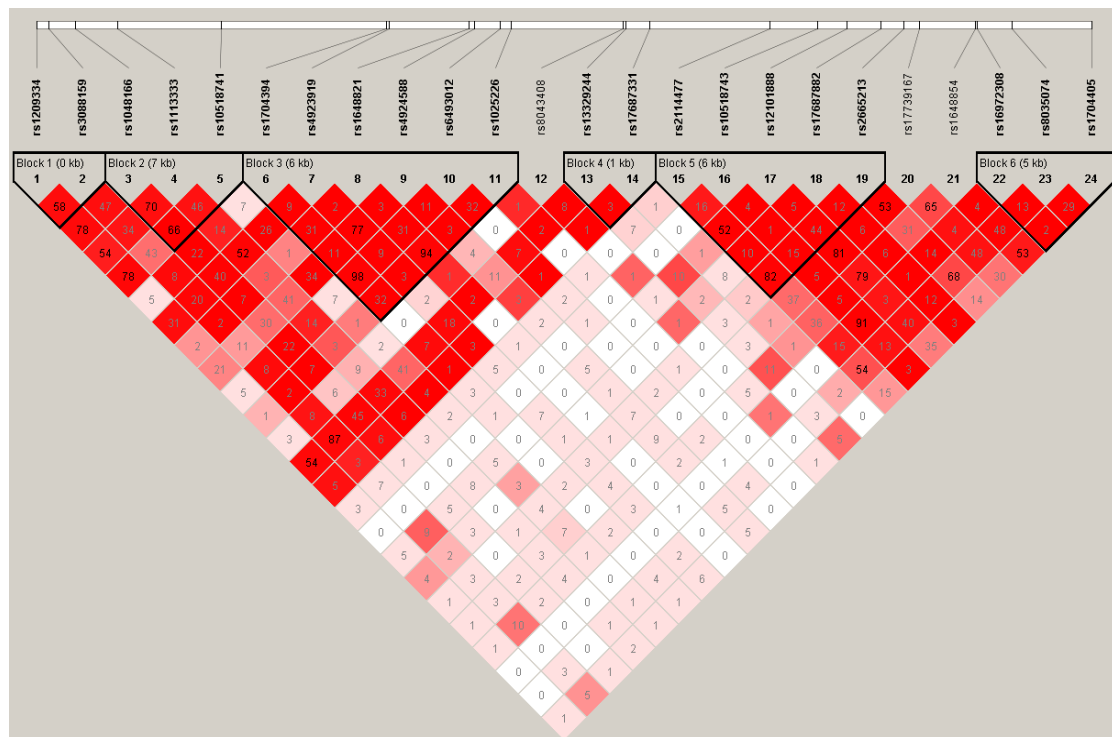


Fig. S3. Linkage disequilibrium (LD) plot covering the *EHD4* gene. Results are generated from Haploview. The degree of red in each block indicates the adjusted linkage disequilibrium (LD') between the corresponding pair of SNPs, and their r^2 is given in each block. The haplotype blocks in *EHD4* are also indicated (numbered 1-6).

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