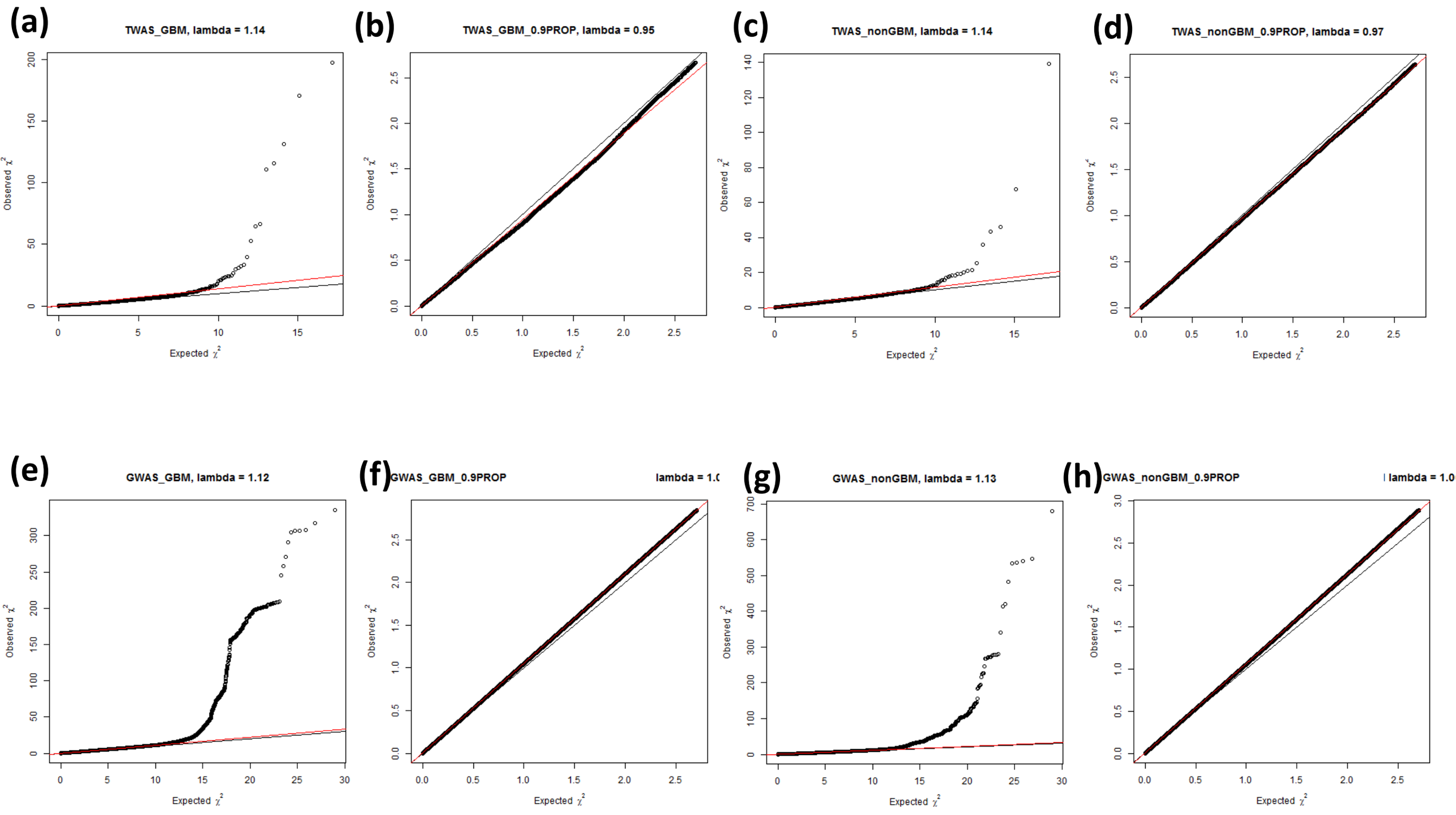
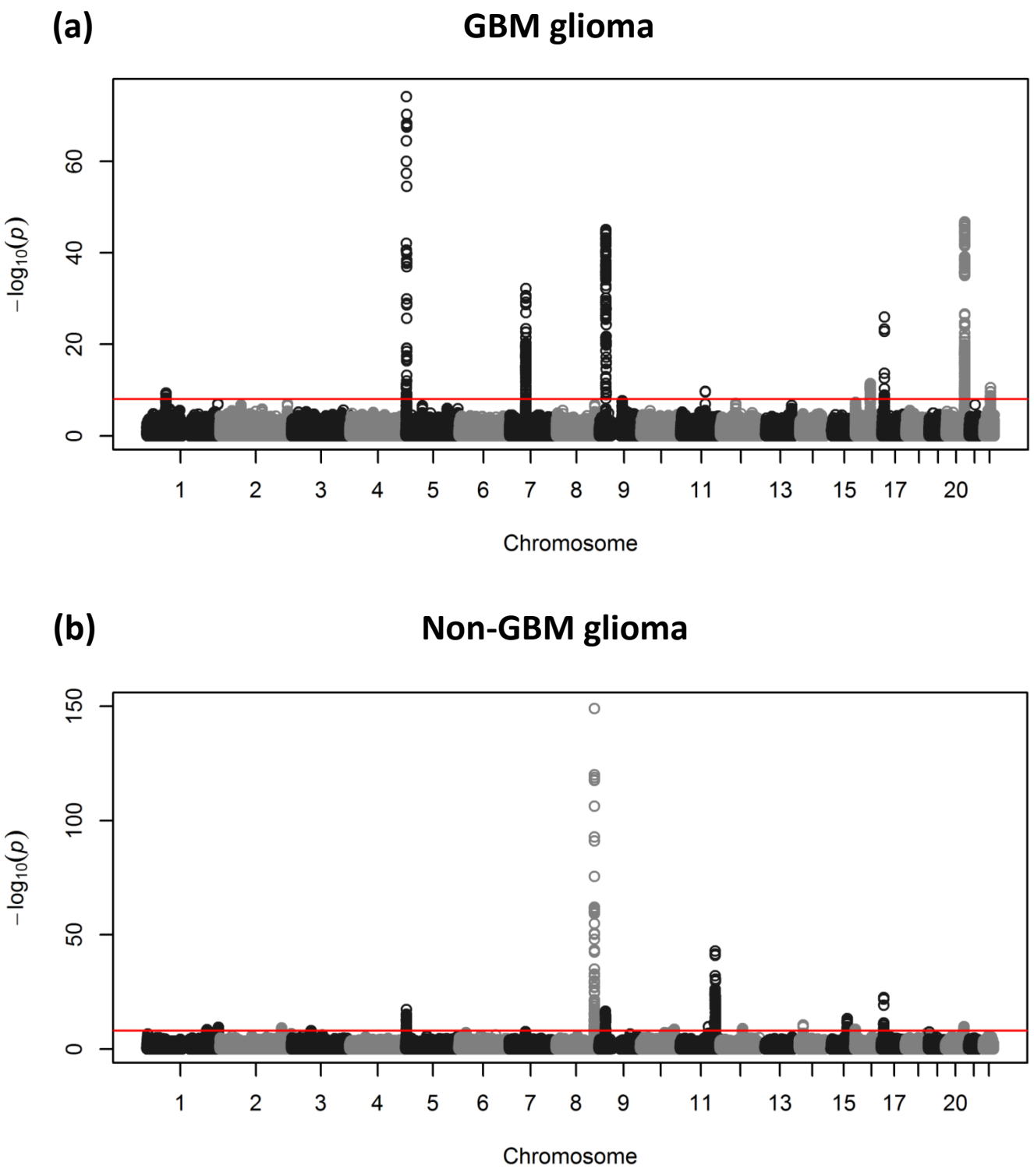
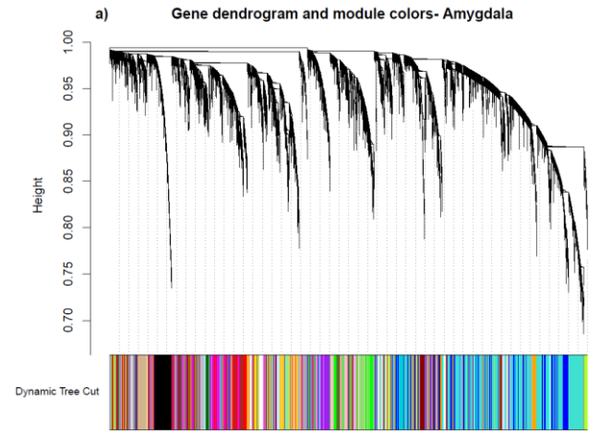
Supplementary Figure 1: Quantile-Quantile Plots of $-\log_{10}$(*P*-value) associations. (a) TWAS for GBM glioma; (b) TWAS for GBM glioma (lower 90% of associations); (c) TWAS for non-GBM glioma; (d) TWAS for non-GBM glioma (lower 90% of associations); (e) GWAS meta-analysis for GBM glioma; (f) GWAS meta-analysis for GBM glioma (lower 90% of associations); (g) GWAS meta-analysis for non-GBM glioma; (h) GWAS meta-analysis for non-GBM glioma (lower 90% of associations).

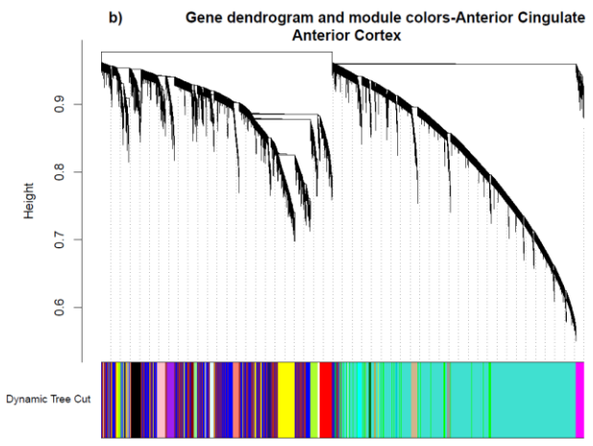


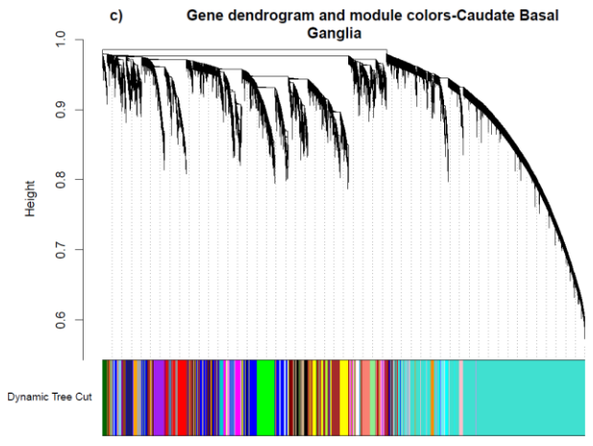
Supplementary Figure 2: Manhattan Plots of SNP genomic co-ordinates against GWAS meta-analysis $-\log_{10}$(*P*-value). (a) GBM glioma; (b) Non-GBM glioma. The red line represents the Bonferroni-corrected threshold of $P \leq 5 \times 10^{-8}$.

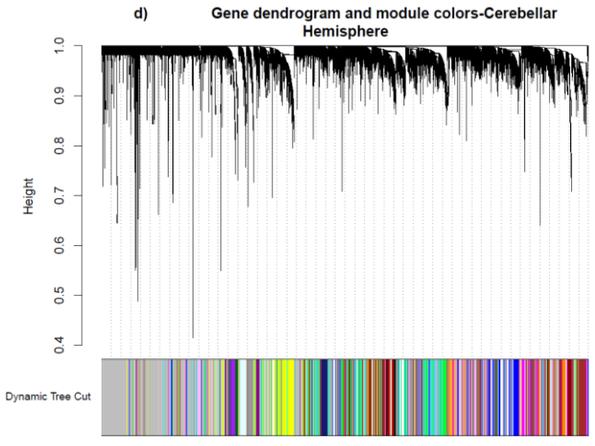


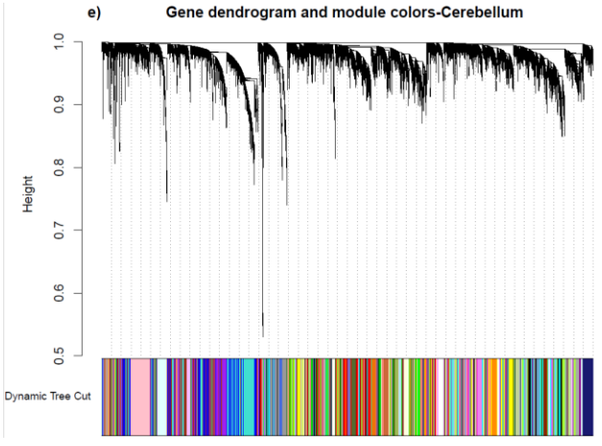
Supplementary Figure 3: Dendograms to display gene module clustering in brain tissues. Clustering was performed using the WGCNA[11] package for each tissue. (a) Amygdala; (b) Anterior cingulate cortex (BA24); (c) Caudate (basal ganglia); (d) Cerebellar Hemisphere; (e) Cerebellum; (f) Cortex; (g) Frontal Cortex (BA9); (h) Hippocampus; (i) Hypothalamus; (j) Nucleus accumbens (basal ganglia); (k) Putamen (basal ganglia); (l) Spinal cord (cervical c-1); (m) Substantia nigra.

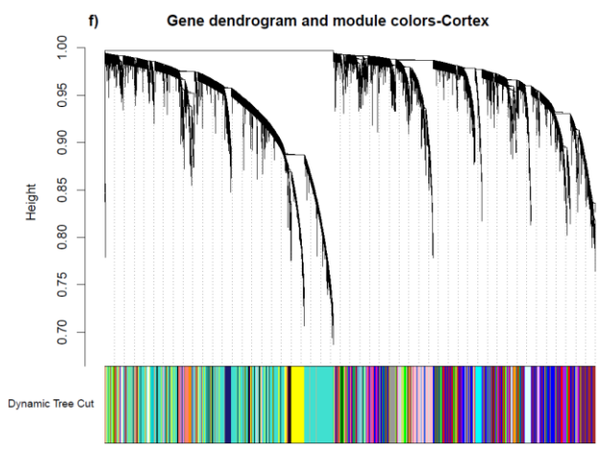


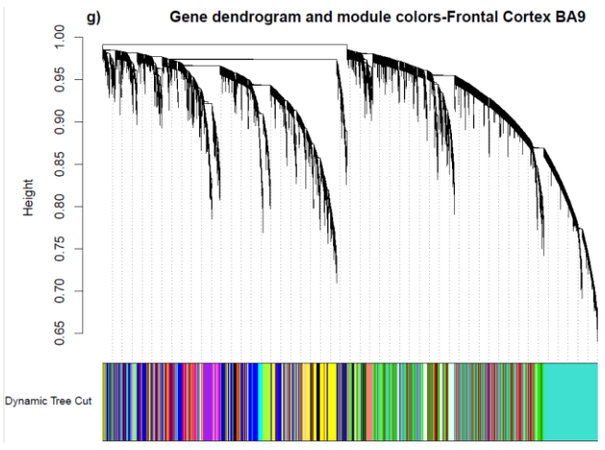


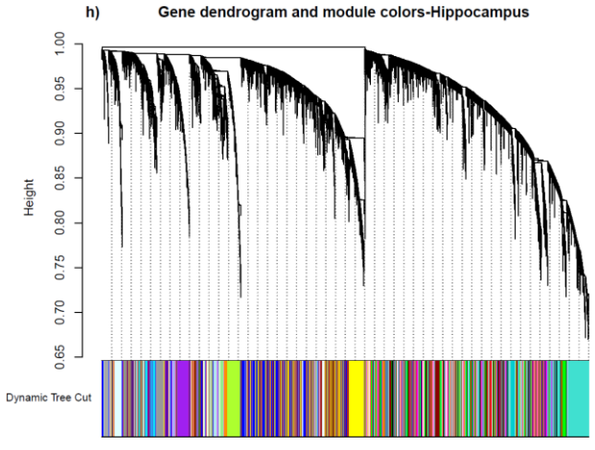


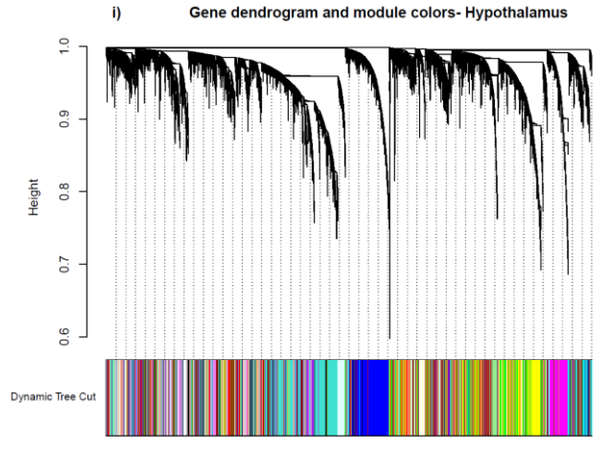


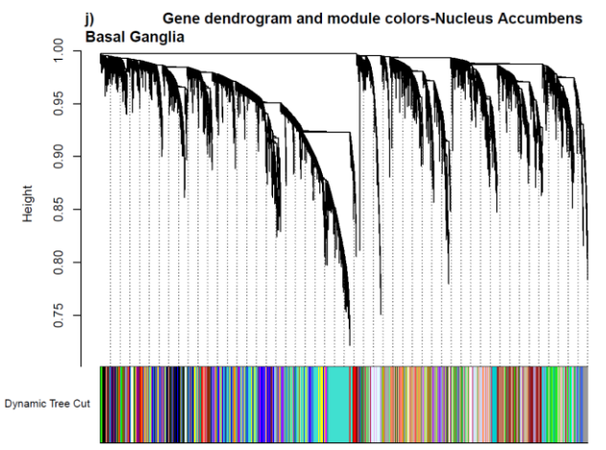


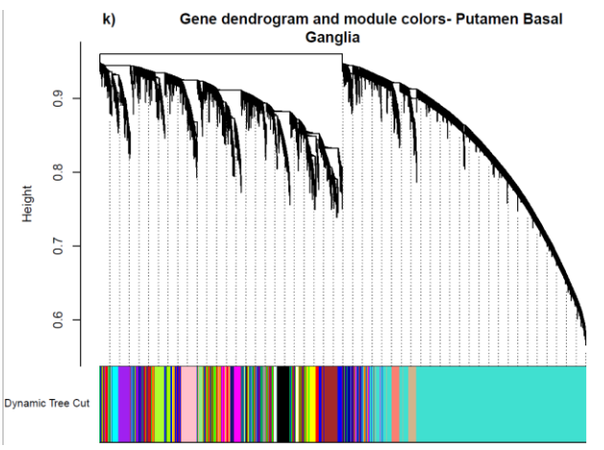


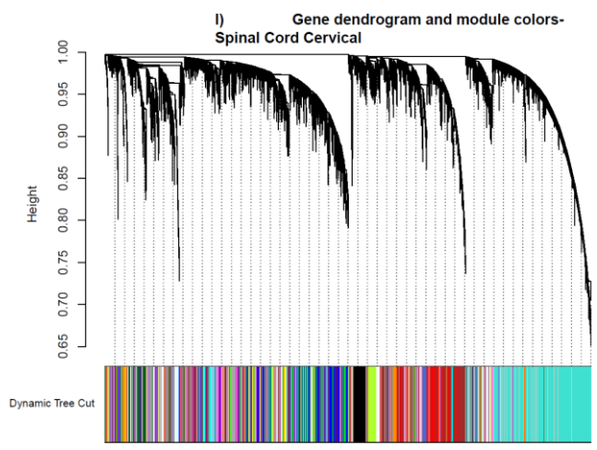


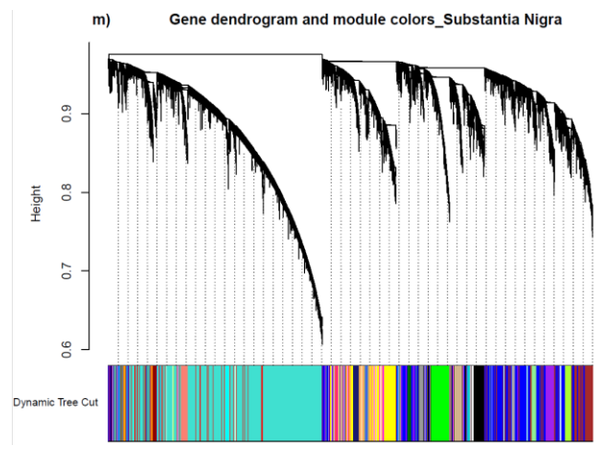




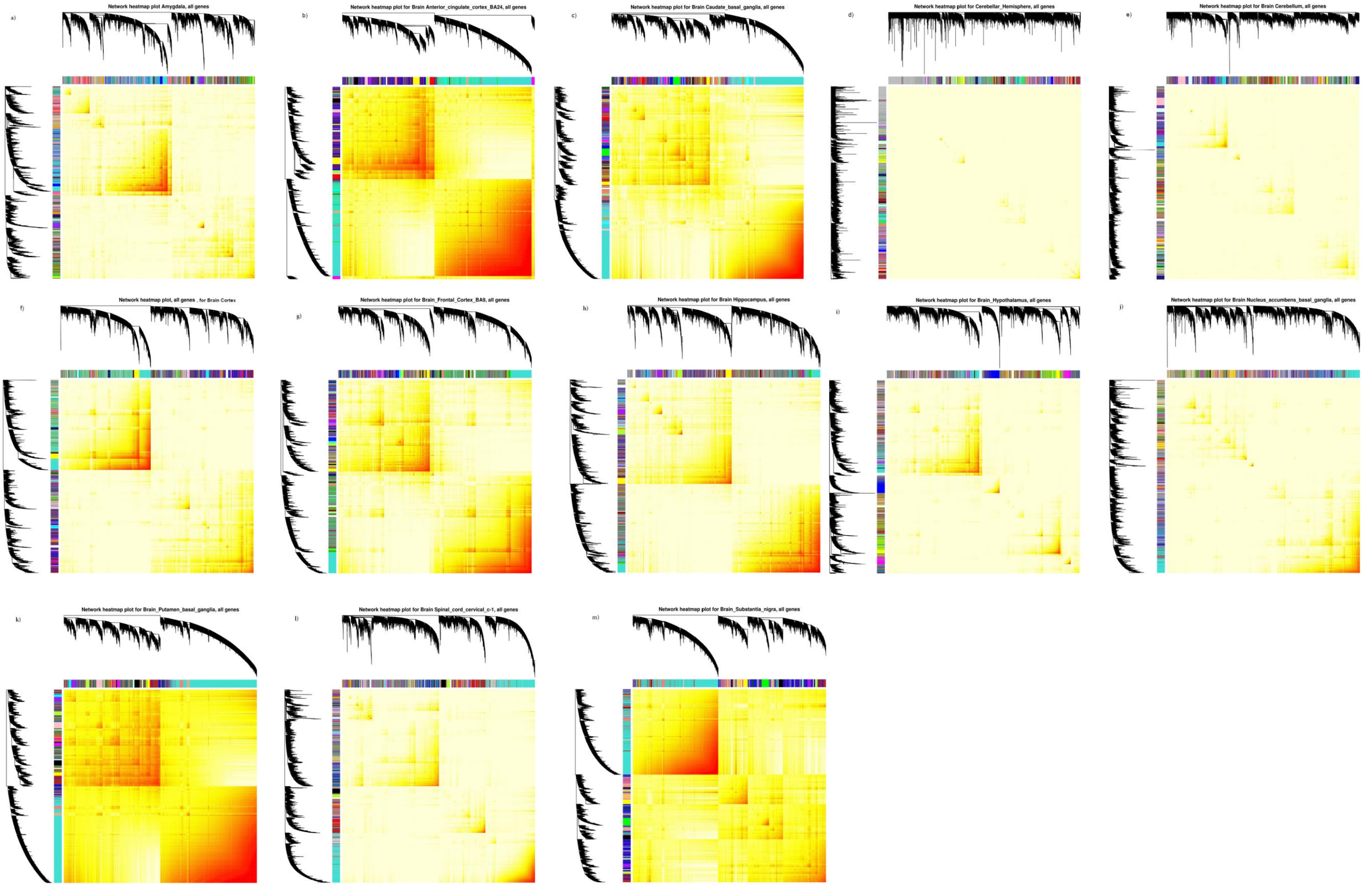




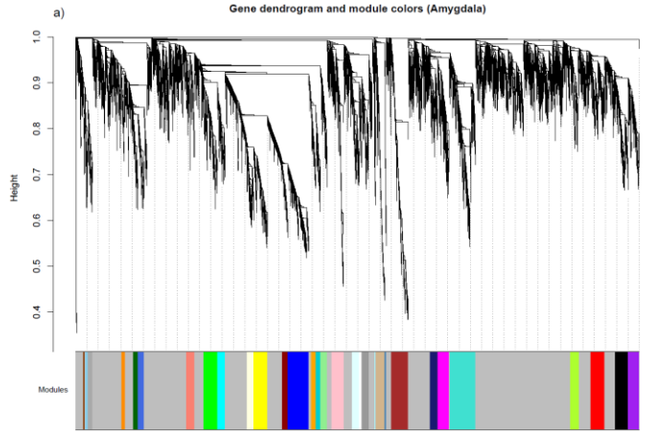


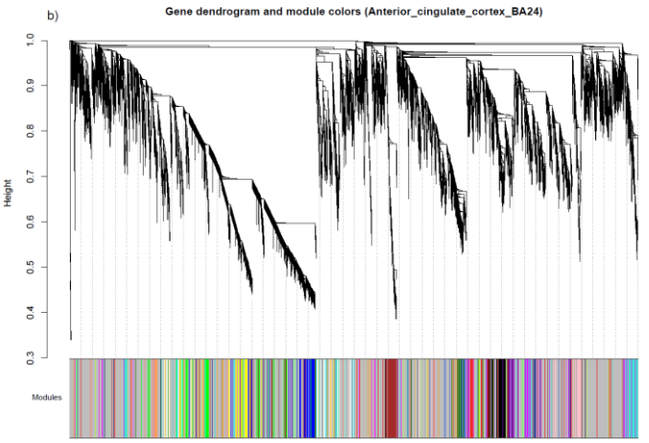


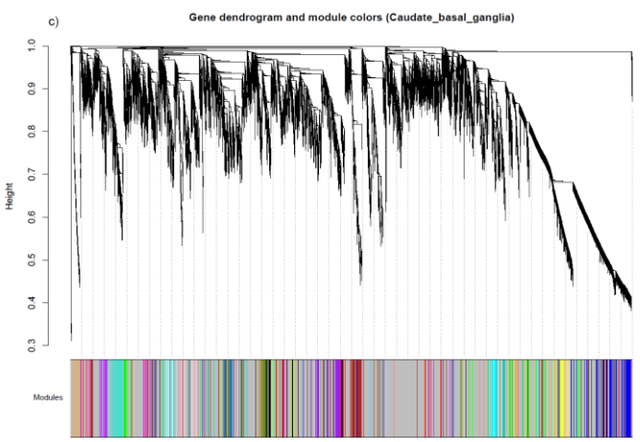
Supplementary Figure 4: Heatmaps illustrating gene module correlations in brain tissues. Darker colors indicate stronger associations. (a) Amygdala; (b) Anterior cingulate cortex (BA24); (c) Caudate (basal ganglia); (d) Cerebellar Hemisphere; (e) Cerebellum; (f) Cortex; (g) Frontal Cortex (BA9); (h) Hippocampus; (i) Hypothalamus; (j) Nucleus accumbens (basal ganglia); (k) Putamen (basal ganglia); (l) Spinal cord (cervical c-1); (m) Substantia nigra.

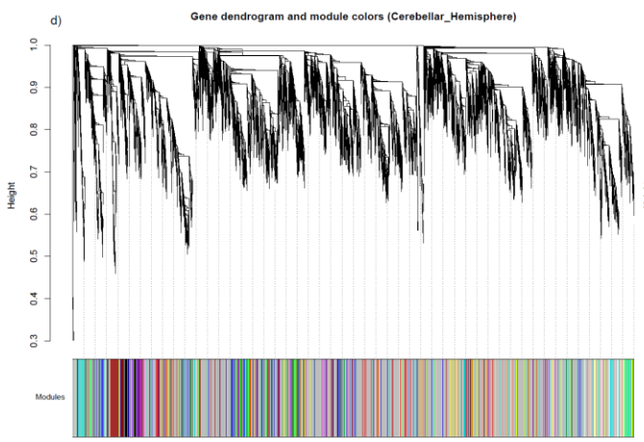


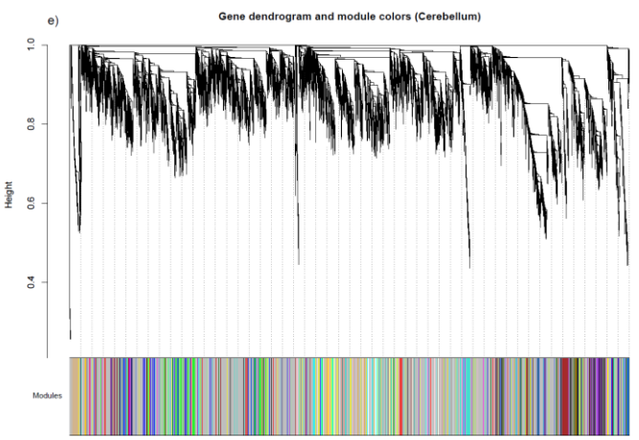
Supplementary Figure 5: Module clustering of brain tissues with amygdala. Modules were created by clustering according to the amygdala tissue using WGCNA[11]. These modules were applied to each tissue in turn and the Z statistic is a quantitative measure of module preservation. (a) Amygdala (reference); (b) Anterior cingulate cortex (BA24); (c) Caudate (basal ganglia); (d) Cerebellar Hemisphere; (e) Cerebellum; (f) Cortex; (g) Frontal Cortex (BA9); (h) Hippocampus; (i) Hypothalamus; (j) Nucleus accumbens (basal ganglia); (k) Putamen (basal ganglia); (l) Spinal cord (cervical c-1); (m) Substantia nigra.

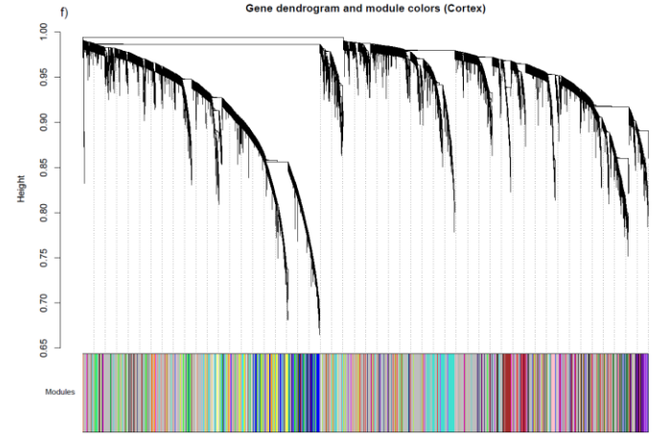


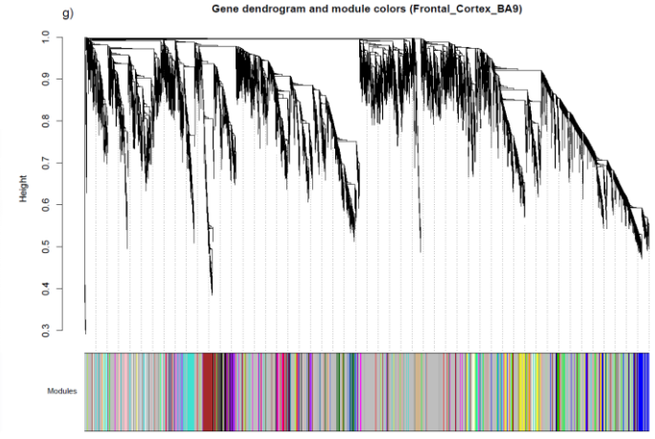


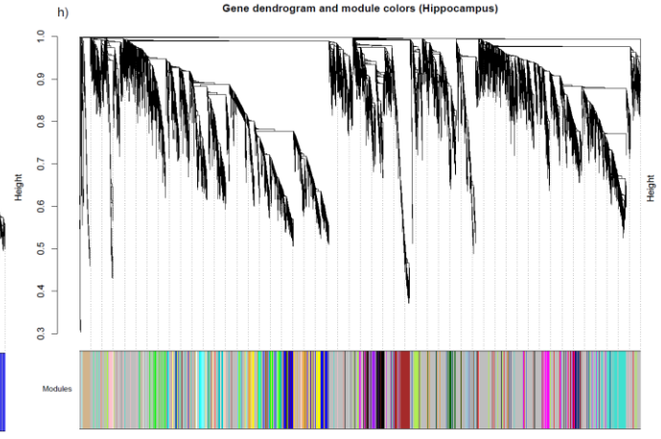


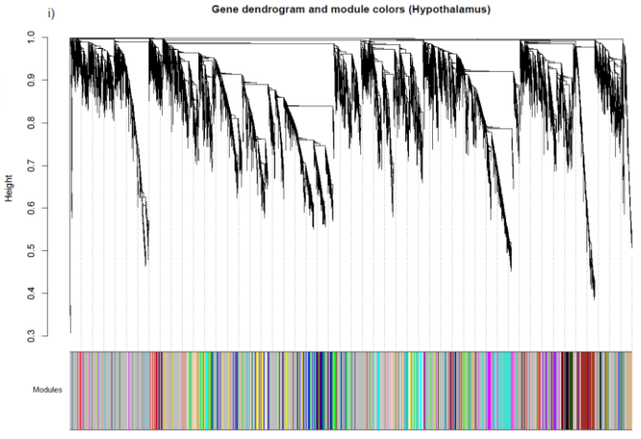


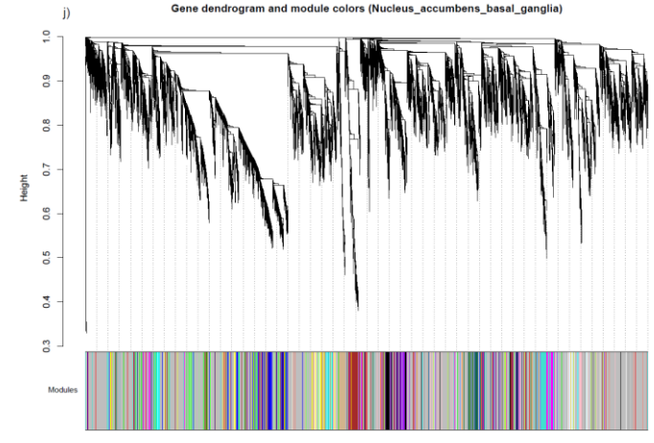


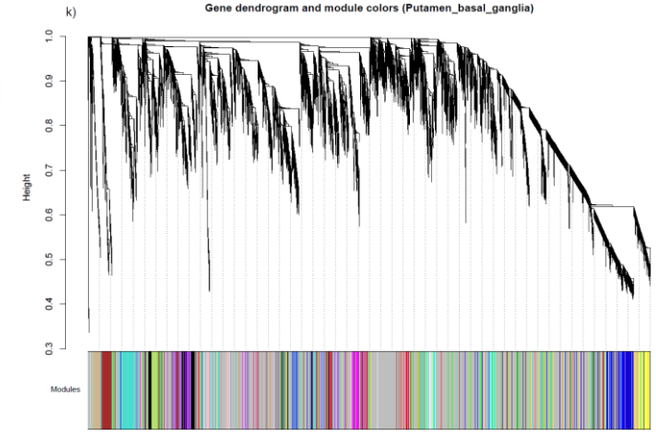


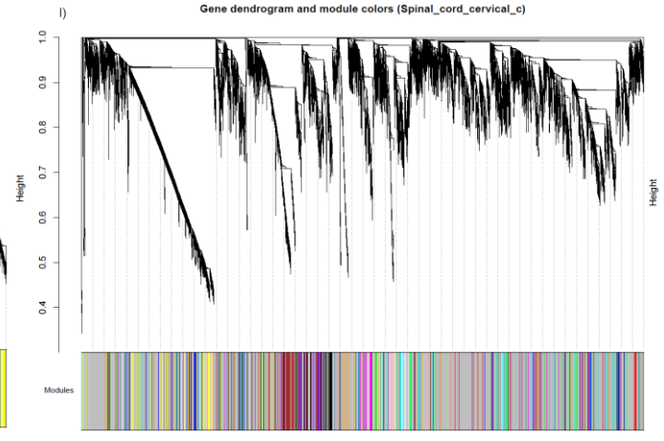


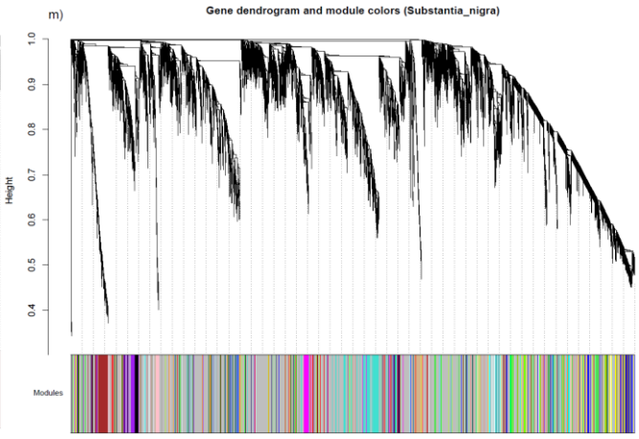




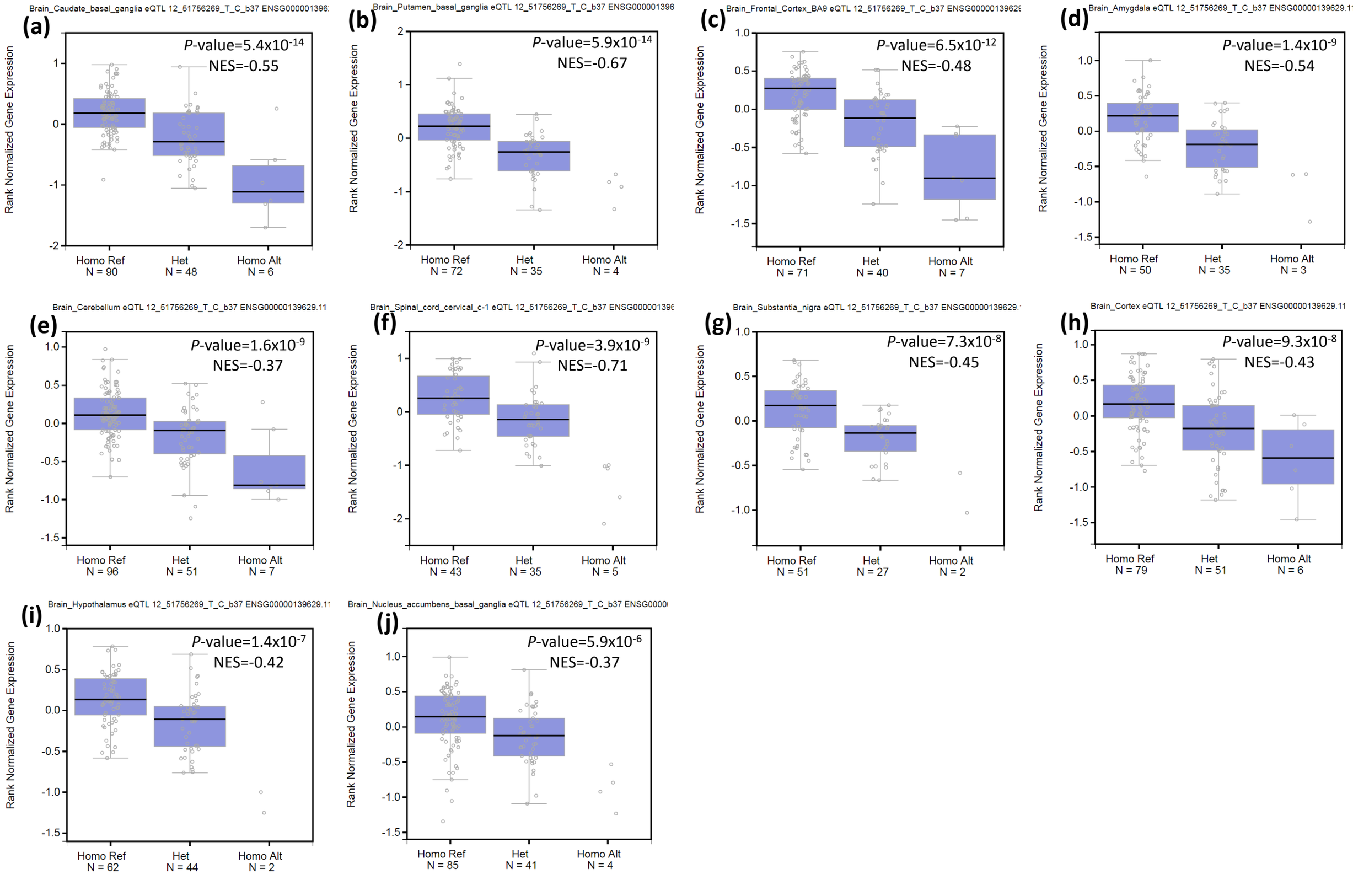




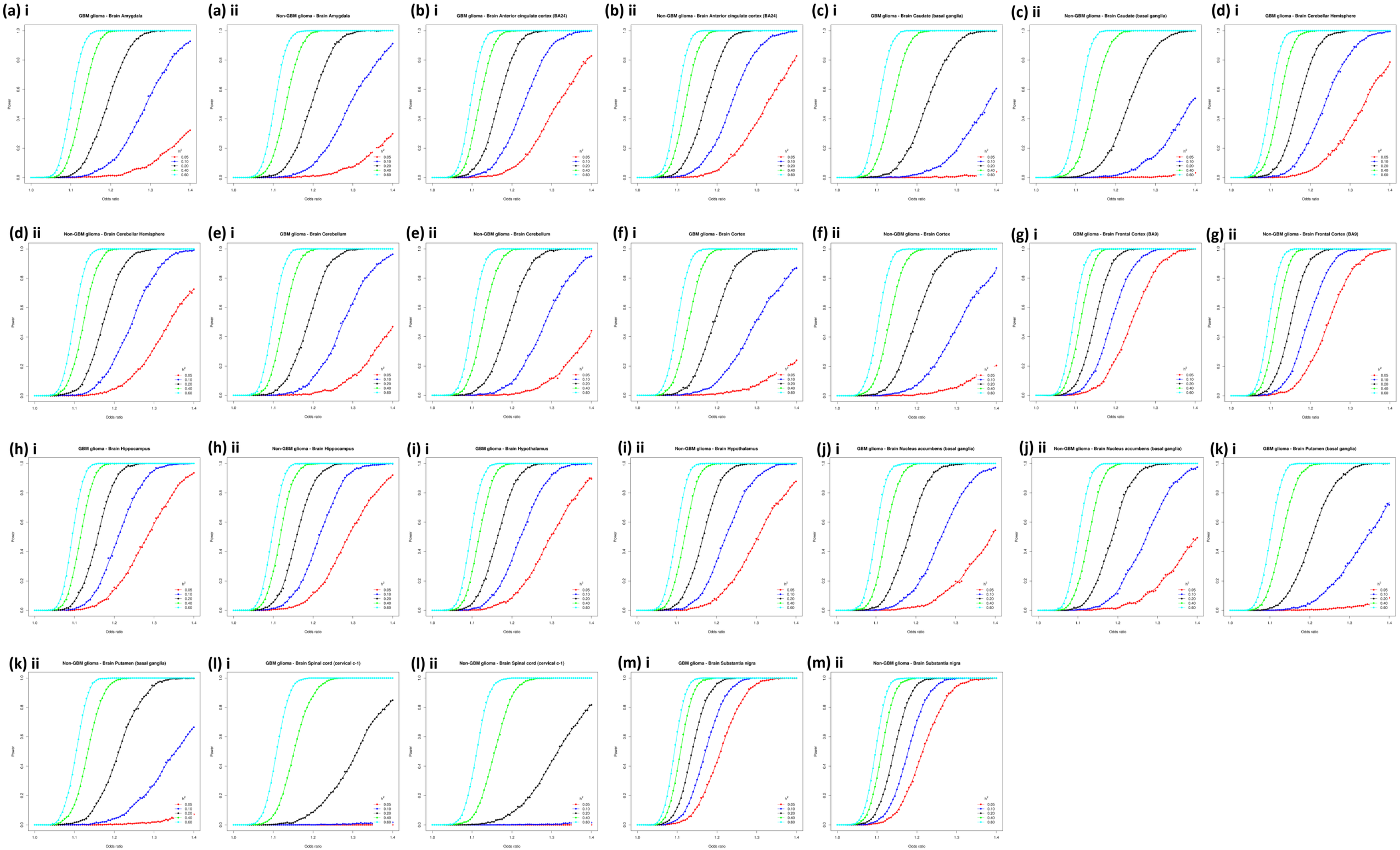




Supplementary Figure 6: Association between rs3782473 genotype and *GALNT6* expression in GTEx v7 brain tissue. Reference and alternate alleles for rs3782473 are T and C respectively. (a) Caudate (basal ganglia); (b) Putamen (basal ganglia); (c) Frontal Cortex (BA9); (d) Amygdala; (e) Cerebellum; (f) Spinal cord (cervical c-1); (g) Substantia nigra; (h) Cortex; (i) Hypothalamus; (j) Nucleus accumbens (basal ganglia).



Supplementary Figure 7: TWAS power plots. Simulation analysis based on 12,488 glioma cases (6,183 GBM, 5,820 non-GBM) and 18,169 controls. Gene expression was generated from the distribution of gene expression levels from the respective brain tissue. Statistical power was calculated at $P<5.69\times10^{-6}$ (the significance threshold used in the main TWAS analysis) according to various cis-heritability (h^2) thresholds which are assumed to be equivalent to gene expression prediction models (R^2). Power calculations were per 1 s.d. increase or decrease in gene expression based on 1,000 replicates. i) GBM glioma; ii) Non-GBM glioma; (a) Brain Amygdala; (b) Brain Anterior cingulate cortex (BA24); (c) Brain Caudate (basal ganglia); (d) Brain Cerebellar Hemisphere; (e) Brain Cerebellum; (f) Brain Cortex; (g) Brain Frontal Cortex (BA9); (h) Brain Hippocampus; (i) Brain Hypothalamus; (j) Brain Nucleus accumbens (basal ganglia); (k) Brain Putamen (basal ganglia); (l) Brain Spinal cord (cervical c-1); (m) Brain Substantia nigra.



Supplementary Figure 8: Association plots at glioma risk regions before and after adjusting for eSNPs at significant TWAS genes. (a) 1p31.3 (GBM): i) unadjusted ii) JAK1 eSNP; (b) 5p15.33 (GBM): i) unadjusted ii) TERT eSNP iii) NKD2 eSNP iv) combined eSNP; (c) 5p15.33 (non-GBM): i) unadjusted ii) TERT eSNP; (d) 7p11.2 (GBM): i) unadjusted ii) EGFR eSNP; (e) 9p21.3 (GBM): i) unadjusted ii) CDKN2B eSNP; (f) 11q23.3 (non-GBM): i) unadjusted ii) PHLDB1 eSNP iii) RPL5P30 eSNP iv) TMEM25 eSNP v) TREH eSNP vi) combined eSNP; (g) 12q13.1 (GBM): i) unadjusted ii) GALNT6 eSNP; (h) 16p13.3 (GBM): i) unadjusted ii) IL9RP3 eSNP; (i) 16q12.1 (GBM): i) unadjusted ii) HEATR3 eSNP; (j) 20q13.33 (GBM): i) unadjusted ii) ARFRP1 eSNP iii) DIDO1 eSNP iv) GMEB2 eSNP v) HAR1A eSNP vi) LIME1 eSNP vii) OPRL1 eSNP viii) PCMTD2 eSNP ix) SLC2A4RG eSNP x) STMN3 eSNP xi) TCEA2 eSNP xii) ZGPAT eSNP xiii) combined eSNP; (k) 20q13.33 (non-GBM): i) unadjusted ii) LIME1 eSNP iii) SLC2A4RG eSNP iv) ZGPAT eSNP v) combined eSNP; (l) 22q13.1 (GBM): i) unadjusted ii) BAIAP2L2 eSNP iii) CTA-228A9.3 eSNP iv) PICK1 eSNP v) SLC16A8 eSNP vi) combined eSNP. Each plot shows association results of both genotyped (triangles) and imputed (circles) SNPs in the GWAS samples. −log10 *P* values (y axes) of the SNPs are shown according to their chromosomal positions (x axes). The lead SNP is shown as a large circle. The color intensity of each symbol reflects the extent of LD with the top genotyped SNP, white (r^2 = 0) through to dark red (r^2 = 1.0). Genetic recombination rates, estimated using HapMap samples from Utah residents of western and northern European ancestry (CEU), are shown with a light blue line. Physical positions are based on NCBI build 37 of the human genome. Below each plot the location of gene eSNPs are indicated, as well as the relative positions of GENCODE v19 genes mapping to the region of association.

		Sample numbers		
Study	**Reference (PMID)**	**Cases (GBM/non-GBM)**	**Controls**	**Imputed SNPs**
UK-GWAS	19578367	631 (270/361)	2,699	8,954,681
French-GWAS	21531791	1,423 (430/993)	1,190	9,113,681
German-GWAS	21531791	846 (431/415)	1,310	9,012,806
MDA-GWAS	19578367	1,175 (652/523)	2,236	9,043,003
SFAGS	19578366	677 (511/166)	3,940	10,679,291
GliomaScan	22886559	1,653 (903/472)	2,725	9,161,499
GICC	28346443	4,564 (2,460/1,898)	3,265	10,783,269
UCSF/Mayo	28346443	1,519 (526/992)	804	6,915,238[a]
TOTAL		12,488 (6,183/5,820)	18,169	
		SNP numbers		
		All glioma	**GBM**	**Non-GBM**
Meta-analysis				
All SNPs		6,887,412	6,790,270	6,769,856

Supplementary Table 1: Details of glioma GWAS and SNPs imputed. Successfully imputed SNPs in each discovery series GWAS were those with INFO > 0.4, case and control MAF > 0.01, P_{HWE} in controls > $1x10^{-8}$. For the meta-analysis we considered all SNPs meeting the above criteria in all eight studies as well as having heterogeneity I^2 < 75 in GBM/non-GBM glioma. [a] For the UCSF/Mayo study an imputation threshold of > 0.8 was applied.

		Number of genes tested per R^2 threshold										
Tissue	**Number of participants**	**Total**	**0.1**	**0.2**	**0.3**	**0.4**	**0.5**	**0.6**	**0.7**	**0.8**	**0.9**	**1.0**
Brain – Amygdala	88	2,356	874	848	337	171	87	28	10	1	0	0
Brain – Anterior cingulate cortex (BA24)	109	3,295	1,361	1,022	445	245	126	72	22	2	0	0
Brain – Caudate (basal ganglia)	144	4,171	1,881	1,198	533	272	153	92	36	6	0	0
Brain – Cerebellar Hemisphere	125	4,746	1,739	1,426	725	390	264	132	56	14	0	0
Brain – Cerebellum	154	6,076	2,398	1,715	956	493	331	139	43	1	0	0
Brain – Cortex	136	4,318	1,709	1,344	587	332	190	109	40	7	0	0
Brain – Frontal Cortex (BA9)	118	3,590	1,472	1,102	480	280	147	75	29	5	0	0
Brain – Hippocampus	111	2,808	1,191	880	372	200	93	55	17	0	0	0
Brain – Hypothalamus	108	2,827	1,176	925	353	207	115	41	19	0	0	0
Brain – Nucleus accumbens (basal ganglia)	130	3,623	1,554	1,097	456	266	142	80	23	5	0	0
Brain – Putamen (basal ganglia)	111	3,168	1,226	1,011	462	240	146	63	18	2	0	0
Brain – Spinal cord (cervical c-1)	83	2,515	861	879	408	207	101	48	9	2	0	0
Brain – Substantia nigra	80	2,032	660	786	335	148	70	24	7	2	0	0
Combined (S-MultiXcan)		14,485										

Supplementary Table 2: Brain tissue prediction models trained on GTEx v7 data and covariance files obtained from http://predictdb.org/. Genes were retained if nested cross-validated correlation between predicted and actual levels > 0.10 (R^2>1%) and *P*-value of the correlation test < 0.05.

SNP	Locus	Position (b37)	Risk allele	Other allele	Reference
rs12752552	1p31.3	65229299	T	C	[1]
rs4252707	1q32.1	204508147	A	G	[1]
rs12076373	1q44	243851947	G	C	[1]
rs7572263	2q33.3	209051586	A	G	[1]
rs11706832	3p14.1	66502981	C	A	[1]
rs10069690	5p15.33	1279790	T	C	[1,3]
rs723527	7p11.2 (1)	55134872	A	G	[1,4]
rs75061358	7p11.2 (2)	54916280	G	T	[1,4]
rs55705857	8q24.21	130645692	G	A	[3,5,6]
rs634537	9p21.3	22032152	G	T	[1,3,7]
rs11598018	10q24.33	105661315	C	A	[1]
rs11599775	10q25.2	114459697	G	A	[1,8]
rs11233250	11q14.1	82397014	C	T	[1]
rs7107785	11q21	95747337	T	C	[1]
rs648044	11q23.2	114030799	A	G	[8]
rs12803321	11q23.3	118480115	G	C	[1,3]
rs1275600	12q21.2	76263551	T	A	[1,8]
rs10131032	14q12	33250081	G	A	[1]
rs77633900	15q24.2	76538459	C	G	[1,8]
rs2562152	16p13.3 (1)	123896	T	A	[1]
rs3751667	16p13.3 (2)	1004554	T	C	[1]
rs10852606	16q12.1	50128872	C	T	[1]
rs78378222	17p13.1	7571752	G	T	[9]
rs2297440	20q13.33	62312299	C	T	[1,3]
rs2235573	22q13.1	38477930	G	A	[1]

Supplementary Table 3: Previously reported glioma risk SNPs.

1. Melin, B.S. *et al.* Genome-wide association study of glioma subtypes identifies specific differences in genetic susceptibility to glioblastoma and non-glioblastoma tumors. *Nat Genet* **49**, 789-794 (2017).
2. Walsh, K.M. *et al.* Variants near TERT and TERC influencing telomere length are associated with high-grade glioma risk. *Nat Genet* **46**, 731-5 (2014).
3. Shete, S. *et al.* Genome-wide association study identifies five susceptibility loci for glioma. *Nat Genet* **41**, 899-904 (2009).
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Tissue	Soft Power	Number of Independent Genes
Amygdala	9	9,009
Anterior cingulate cortex (BA24)	6	10,209
Caudate (basal ganglia)	7	8,151
Cerebellar Hemisphere	24+	15,981+
Cerebellum	13+	10,835+
Cortex	10	10,066
Frontal Cortex (BA9)	8	8,661
Hippocampus	10	8,781
Hypothalamus	13	10,027
Nucleus accumbens (basal ganglia)	14	10,749
Putamen (basal ganglia)	5	7,986
Spinal cord (cervical c-1)	11	7,749
Substantia nigra	6	6,317
Median	9	8,781

Supplementary Table 5: Brain tissue, soft power threshold and number of independent genes. Soft power thresholds were chosen at the 90% threshold unless otherwise indicated. + For Cerebellar Hemisphere and Cerebellum, the 90% threshold was not achieved and 80% was imposed. For this reason such tissues were excluded from median calculations for soft power and number of independent genes.

Gene	Ensembl ID	Band	Subtype	Z-score	*P*-value	r^2
JAK1	ENSG00000162434.7	1p31.3	GBM	5.31	$1.09x10^{-7}$	0.0096
TERT	ENSG00000164362.14	5p15.33	GBM	15.30	$7.54x10^{-53}$	0.00050
NKD2	ENSG00000145506.9	5p15.33	GBM	NA	NA	NA
EGFR	ENSG00000146648.11	7p11.2	GBM	NA	NA	NA
CDKN2B	ENSG00000147883.9	9p21.3	GBM	2.32	0.020	0.21
GALNT6	ENSG00000139629.11	12q13.13	GBM	2.45	0.014	0.30
HEATR3	ENSG00000155393.8	16q12.1	GBM	6.43	$1.31x10^{-10}$	0.27
IL9RP3	ENSG00000226942.2	16p13.3	GBM	NA	NA	NA
ZGPAT	ENSG00000197114.7	20q13.33	GBM	12.96	$2.15x10^{-38}$	0.0032
SLC2A4RG	ENSG00000125520.9	20q13.33	GBM	-5.11	$3.25x10^{-7}$	0.076
ARFRP1	ENSG00000101246.15	20q13.33	GBM	8.92	$4.53x10^{-19}$	0.0070
STMN3	ENSG00000197457.5	20q13.33	GBM	7.40	$1.32x10^{-13}$	0.18
GMEB2	ENSG00000101216.6	20q13.33	GBM	-6.47	$1.01x10^{-10}$	0.070
LIME1	ENSG00000203896.5	20q13.33	GBM	-8.82	$1.18x10^{-18}$	0.18
HAR1A	ENSG00000225978.2	20q13.33	GBM	NA	NA	NA
OPRL1	ENSG00000125510.11	20q13.33	GBM	2.92	$3.50x10^{-3}$	0.25
PCMTD2	ENSG00000203880.7	20q13.33	GBM	3.31	$9.48x10^{-4}$	0.13
DIDO1	ENSG00000101191.12	20q13.33	GBM	0.55	0.58	0.17
TCEA2	ENSG00000171703.12	20q13.33	GBM	-5.57	$2.62x10^{-8}$	0.088
BAIAP2L2	ENSG00000128298.12	22q13.1	GBM	-0.41	0.68	0.068
SLC16A8	ENSG00000100156.6	22q13.1	GBM	NA	NA	NA
CTA-228A9.3	ENSG00000272720.1	22q13.1	GBM	NA	NA	NA
PICK1	ENSG00000100151.11	22q13.1	GBM	1.48	0.14	0.51
TERT	ENSG00000164362.14	5p15.33	Non-GBM	7.23	$4.79x10^{-13}$	0.00050
PHLDB1	ENSG00000019144.12	11q23.3	Non-GBM	-9.52	$1.81x10^{-21}$	0.0067
TREH	ENSG00000118094.7	11q23.3	Non-GBM	NA	NA	NA
RPL5P30	ENSG00000243431.1	11q23.3	Non-GBM	NA	NA	NA
TMEM25	ENSG00000149582.11	11q23.3	Non-GBM	4.37	$1.25x10^{-5}$	0.0067
ZGPAT	ENSG00000197114.7	20q13.33	Non-GBM	5.60	$2.11x10^{-8}$	0.0032
SLC2A4RG	ENSG00000125520.9	20q13.33	Non-GBM	-0.36	0.72	0.076

Supplementary Table 8: S-PrediXcan results for 31 genes in 922 whole-blood samples from the Depression Genes and Networks (DGN) study.

				Cosmic cancer gene census			Copy number in glioma (n=1,048)		Copy number across all cancers (n=15,062)	
Gene	**Subtype**	**Band**	**TWAS direction**	**Tier**	**Mode**	**Role**	**Gain (%)**	**Loss (%)**	**Gain (%)**	**Loss (%)**
JAK1	GBM	1p31.3	POSITIVE	1	Dom	Oncogene, TSG	-	-	348 (2.3)	617 (4.1)
TERT	GBM/ Non-GBM	5p15.33	POSITIVE	1	Dom	Oncogene, TSG	6 (0.6)	1 (0.1)	1,017 (6.8)	291 (1.9)
NKD2	GBM	5p15.33	POSITIVE				3 (0.3)	-	1,007 (6.7)	355 (2.4)
EGFR	GBM	7p11.2	NEGATIVE	1	Dom	Oncogene	376 (36)	-	1,346 (8.9)	184 (1.2)
*CDKN2B**	GBM	9p21.3	NEGATIVE	1	Rec	TSG	1 (0.1)	367 (35)	193 (1.3)	2,609 (17)
PHLDB1	Non-GBM	11q23.3	POSITIVE				4 (0.4)	-	372 (2.5)	854 (5.7)
TREH	Non-GBM	11q23.3	POSITIVE				4 (0.4)	-	371 (2.5)	855 (5.7)
RPL5P30	Non-GBM	11q23.3	NEGATIVE				-	-	-	-
TMEM25	Non-GBM	11q23.3	POSITIVE				4 (0.4)	-	366 (2.4)	850 (5.6)
GALNT6	GBM	12q13.13	POSITIVE				1 (0.1)	-	559 (3.7)	467 (3.1)
IL9RP3	GBM	16p13.3	NEGATIVE				-	-	-	-
HEATR3	GBM	16q12.1	POSITIVE				-	-	317 (2.1)	553 (3.7)
ZGPAT	GBM/ Non-GBM	20q13.33	POSITIVE				1 (0.1)	2 (0.2)	953 (6.3)	190 (1.3)
SLC2A4RG	GBM/ Non-GBM	20q13.33	POSITIVE				1 (0.1)	2 (0.2)	948 (6.3)	187 (1.2)
ARFRP1	GBM	20q13.33	POSITIVE				1 (0.1)	2 (0.2)	950 (6.3)	195 (1.3)
STMN3	GBM	20q13.33	NEGATIVE				1 (0.1)	2 (0.2)	950 (6.3)	182 (1.2)
GMEB2	GBM	20q13.33	NEGATIVE				1 (0.1)	1 (0.1)	958 (6.4)	182 (1.2)
LIME1	GBM/ Non-GBM	20q13.33	BOTH				1 (0.1)	2 (0.2)	948 (6.3)	187 (1.2)
HAR1A	GBM	20q13.33	POSITIVE				-	-	-	-
OPRL1	GBM	20q13.33	NEGATIVE				1 (0.1)	4 (0.4)	926 (6.1)	198 (1.3)
PCMTD2	GBM	20q13.33	POSITIVE				1 (0.1)	8 (0.8)	836 (5.6)	367 (2.4)
DIDO1	GBM	20q13.33	POSITIVE				1 (0.1)	-	893 (5.9)	167 (1.1)
TCEA2	GBM	20q13.33	POSITIVE				1 (0.1)	3 (0.3)	930 (6.2)	190 (1.3)
BAIAP2L2	GBM	22q13.1	POSITIVE				-	-	368 (2.4)	861 (5.7)
SLC16A8	GBM	22q13.1	POSITIVE				-	-	361 (2.4)	851 (5.6)
CTA-228A9.3	GBM	22q13.1	POSITIVE				-	-	-	-
PICK1	GBM	22q13.1	POSITIVE				-	-	360 (2.4)	853 (5.7)

Supplementary Table 9: Annotation of identified genes by presence within COSMIC cancer gene census and overlap with tumor copy number changes. *Cosmic cancer gene census annotation for *CDKN2A* was used.