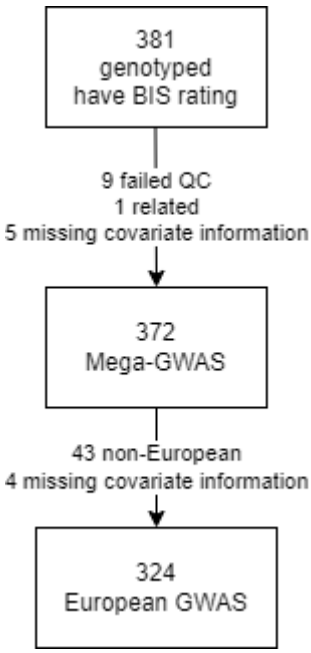
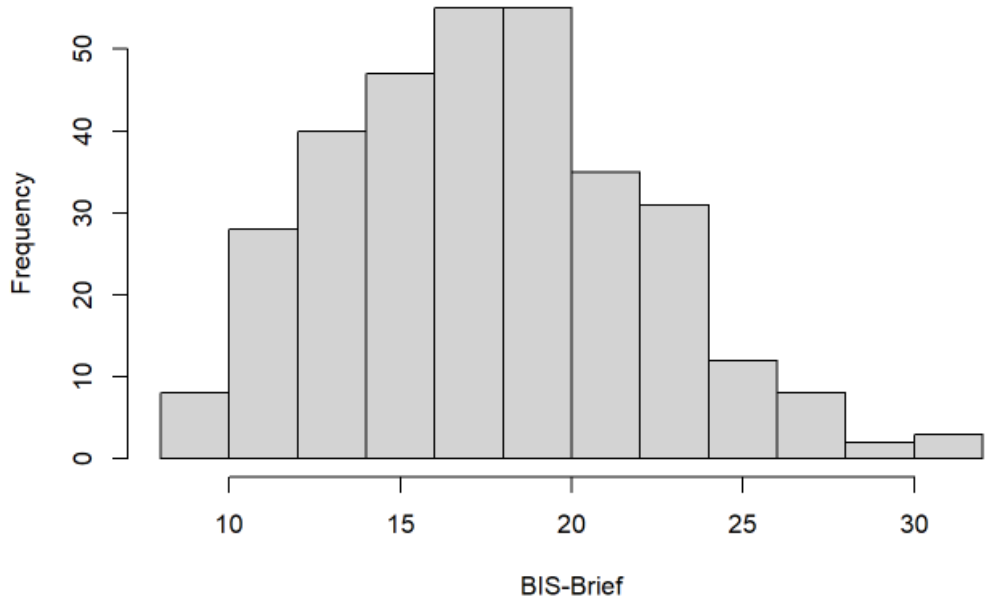
Supplementary Figures

Supplementary Figure 1. Flowchart of inclusion for the mega-GWAS and the European GWAS



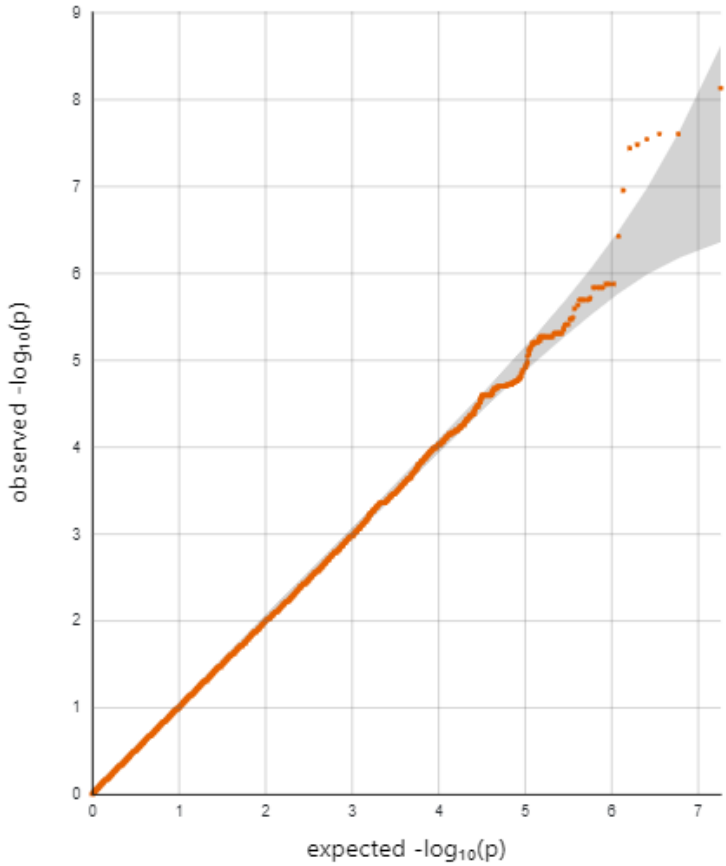
The mega-GWAS includes individuals of all ethnic backgrounds, while the main European GWAS includes those individuals within six standard deviations from the 1000 Genomes-defined European cluster.

Supplementary Figure 2. The distribution of BIS-Brief



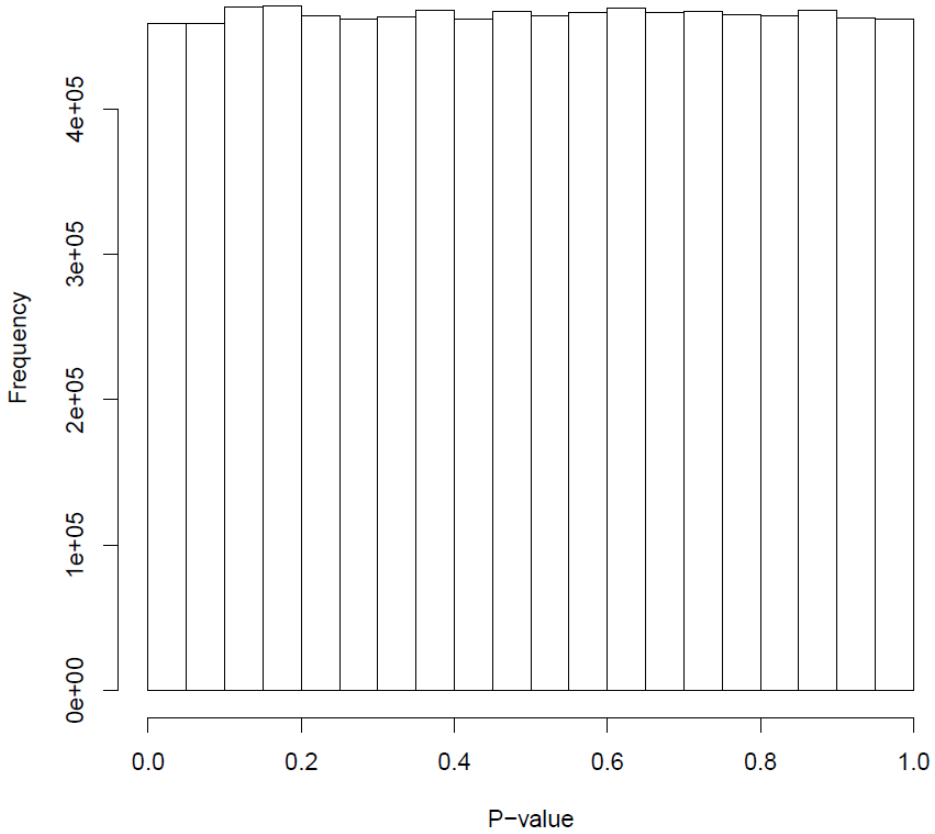
The plot shows the distribution of BIS-Brief in 324 European subjects with JME.

Supplementary Figure 3. QQ plot of BIS-Brief GWAS (GC lambda = 0.998)



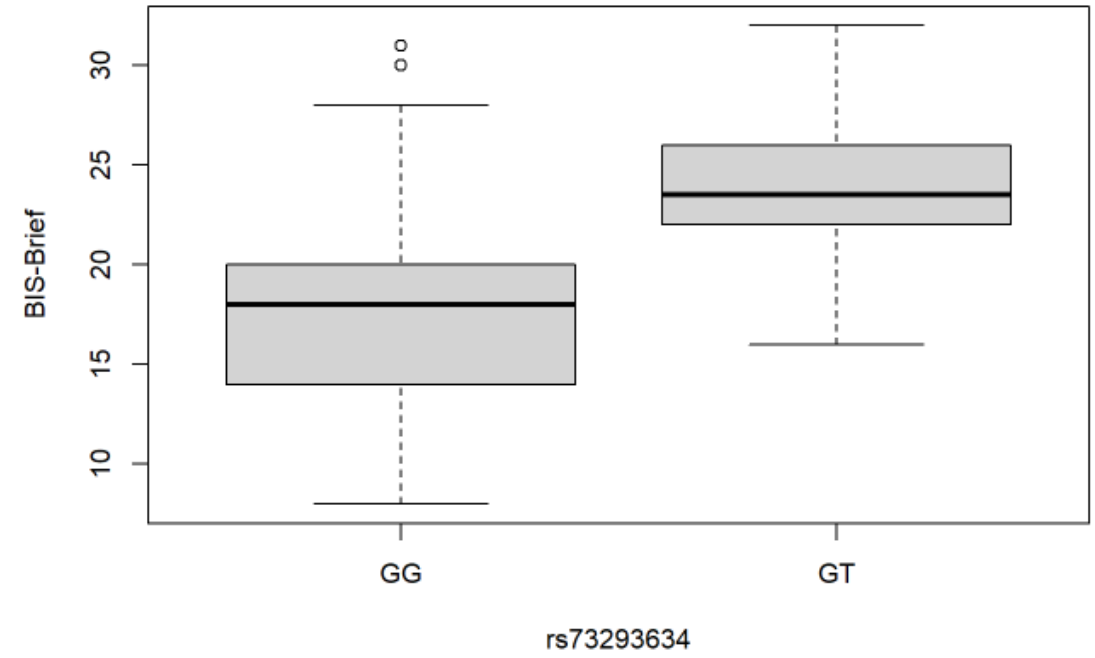
Linear regression was used to test association of each SNP with BIS-Brief. Sex, genotyping batch, age at consent, first 3 PCs, and the frequency of myoclonus or absence seizures were included as covariates in the model.

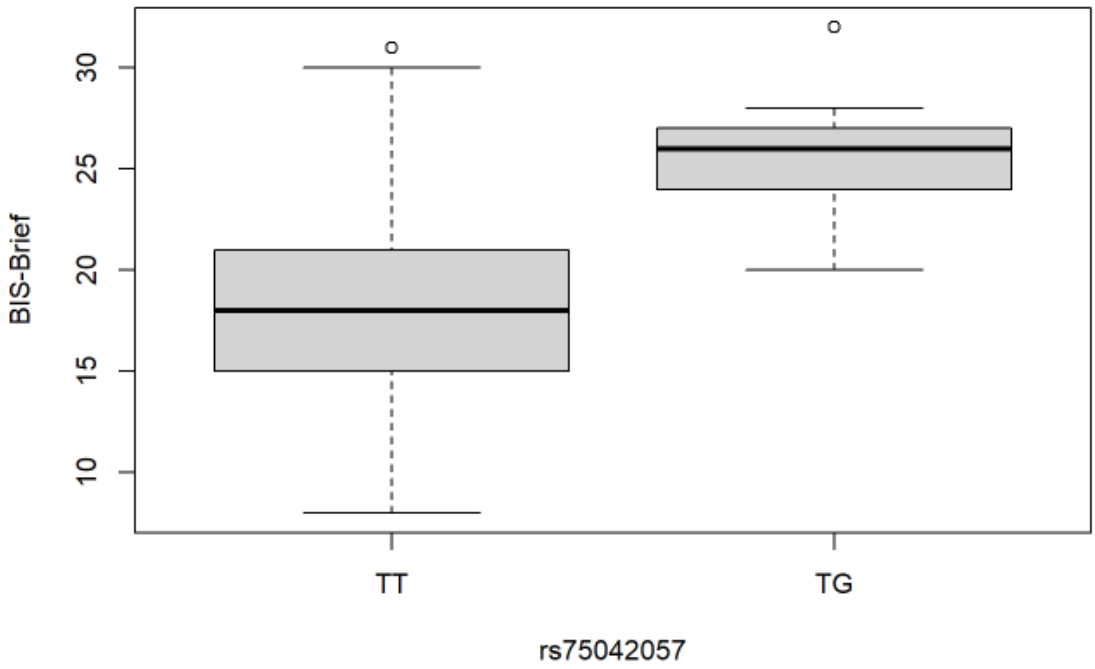
Supplementary Figure 4. Histogram of p-values for BIS-Brief GWAS



Linear regression was used to test association of each SNP with BIS-Brief. Sex, genotyping batch, age at consent, first 3 PCs, and the frequency of myoclonus or absence seizures were included as covariates in the model.

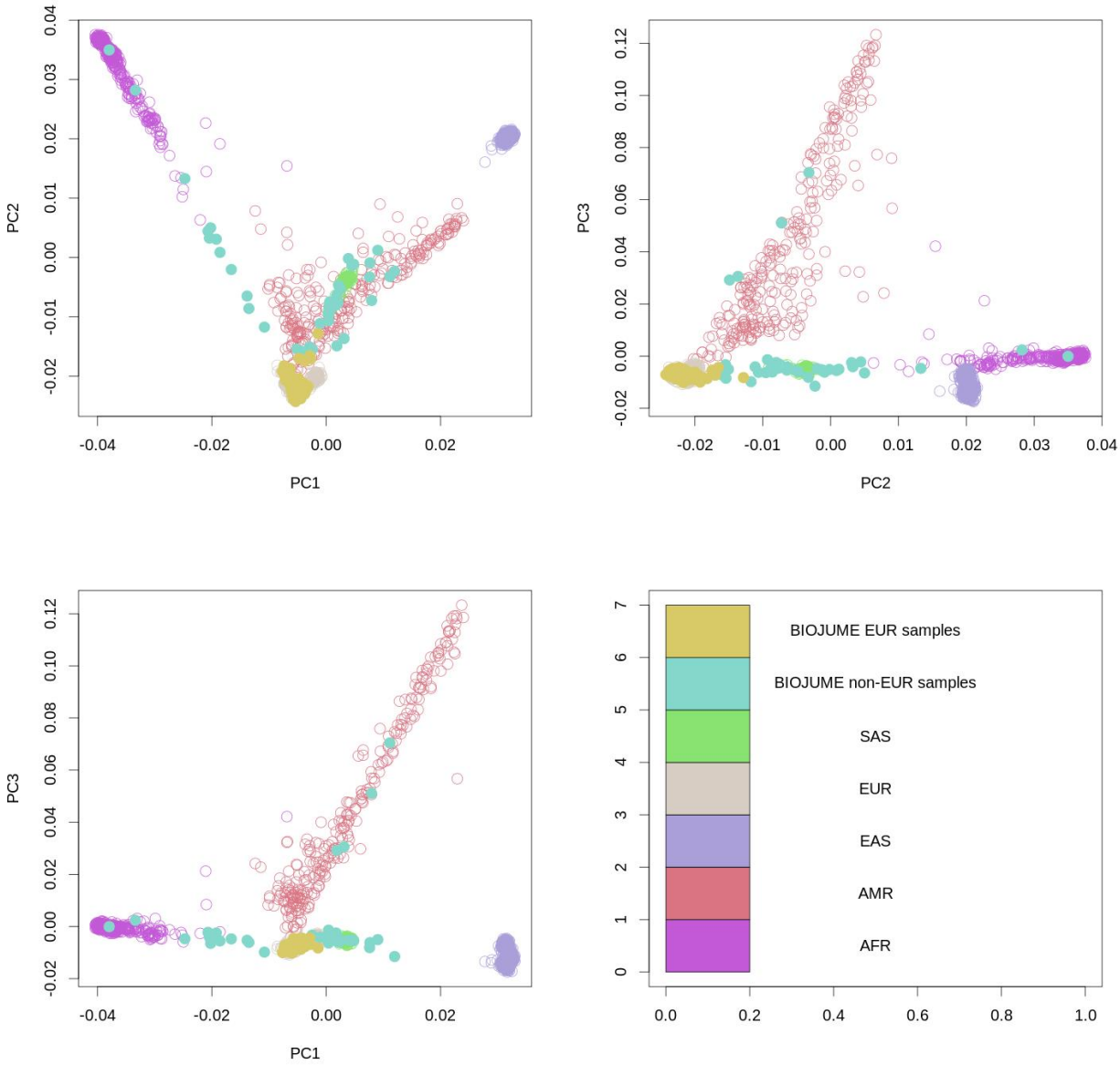
Supplementary Figure 5. Distribution of BIS-Brief by rs73293634 and rs75042057 genotypes





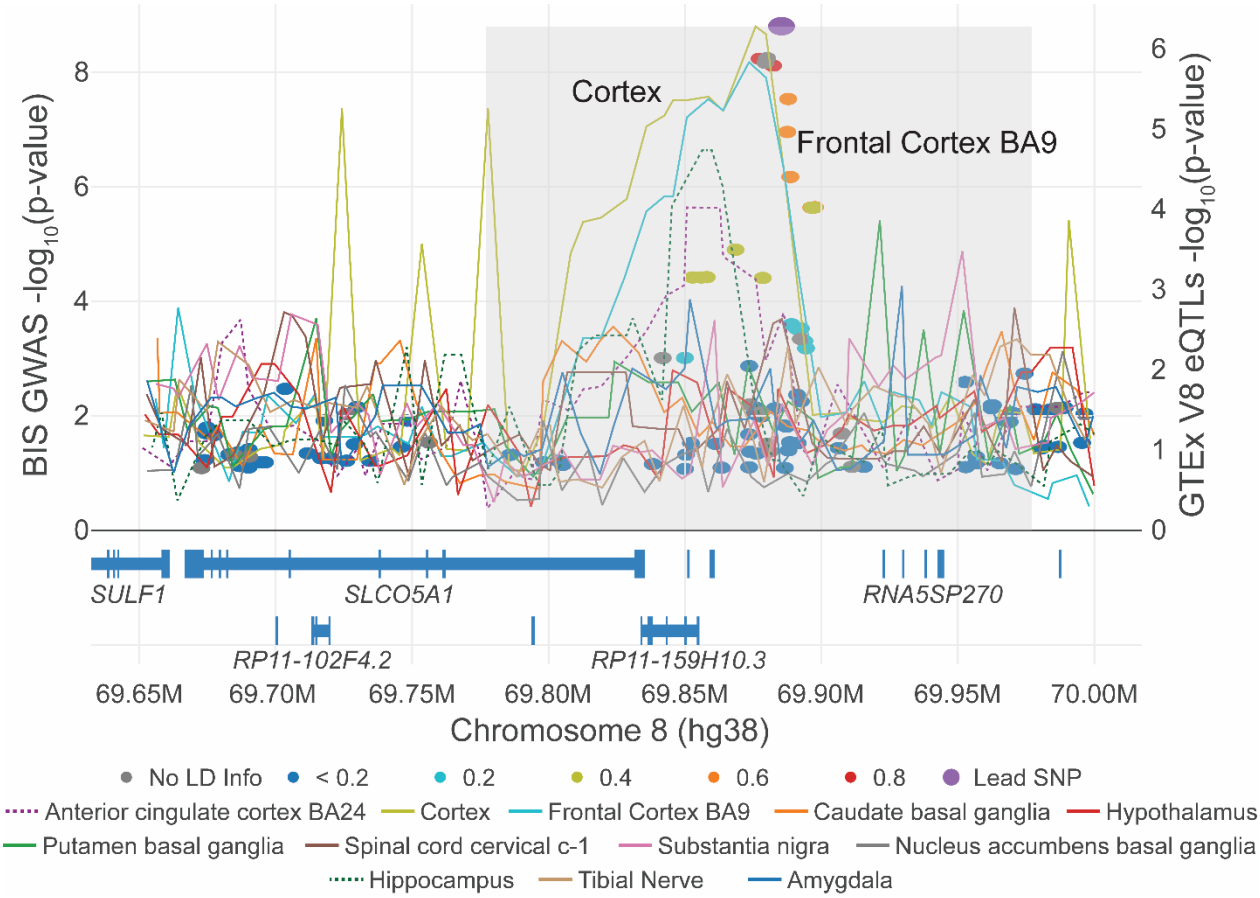
The center lines represent the 50th percentile (median) and the bounds of the boxes are the 75th and 25th percentiles (interquartile range) with the whiskers being the largest value within 1.5 times the interquartile range above the 75th percentile and smallest values within 1.5 times the interquartile range below the 25th percentile.

Supplementary Figure 6. Principal component analysis (PCA) of all study samples with the 1000 Genomes (phase 3)



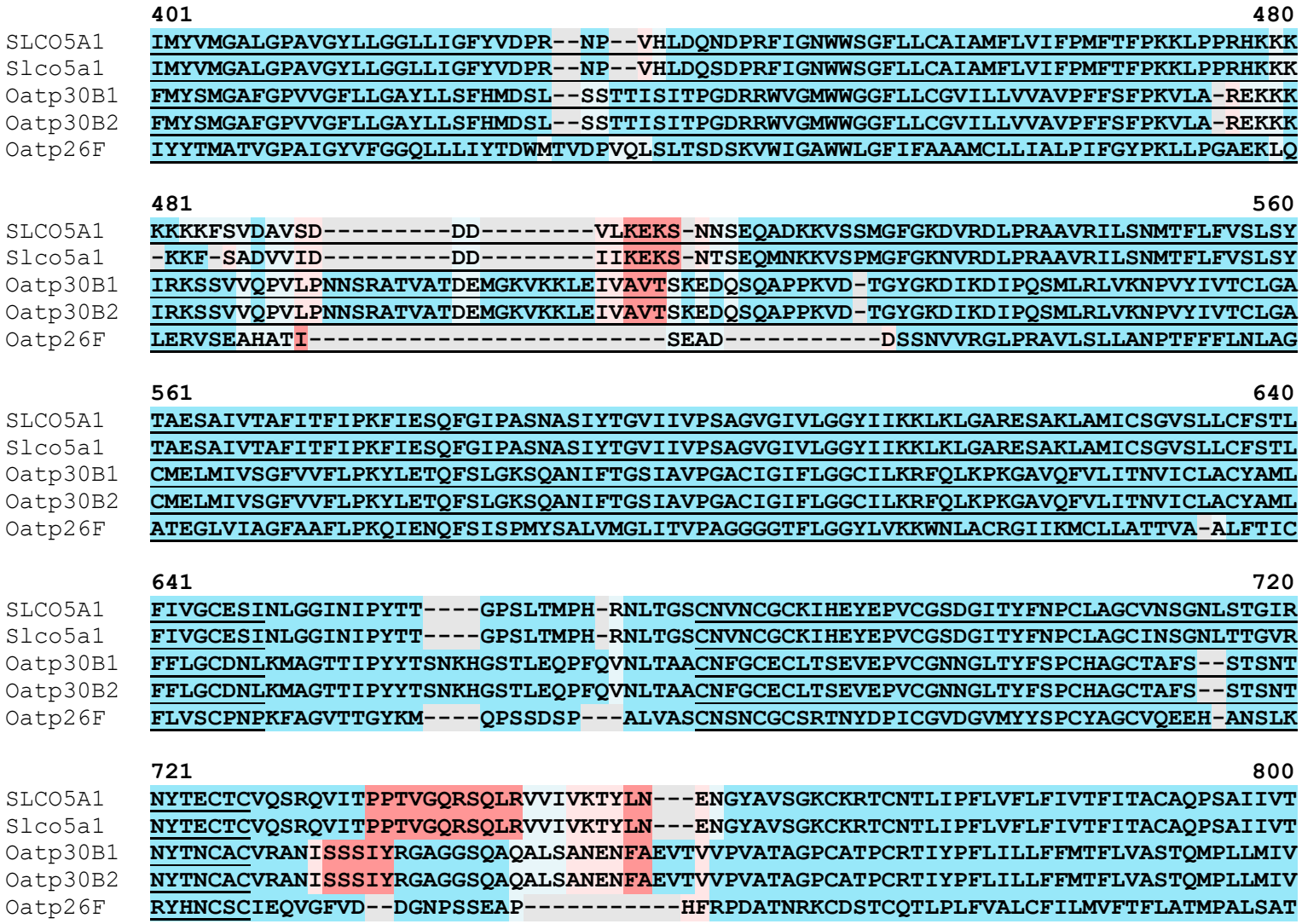
BIOJUME samples who were admixed or AMR were kept if they were within 6 standard deviations from the European cluster. SAS, South Asian; EUR, European; EAS, East Asian; AFR, African; AMR, Ad Mixed American.

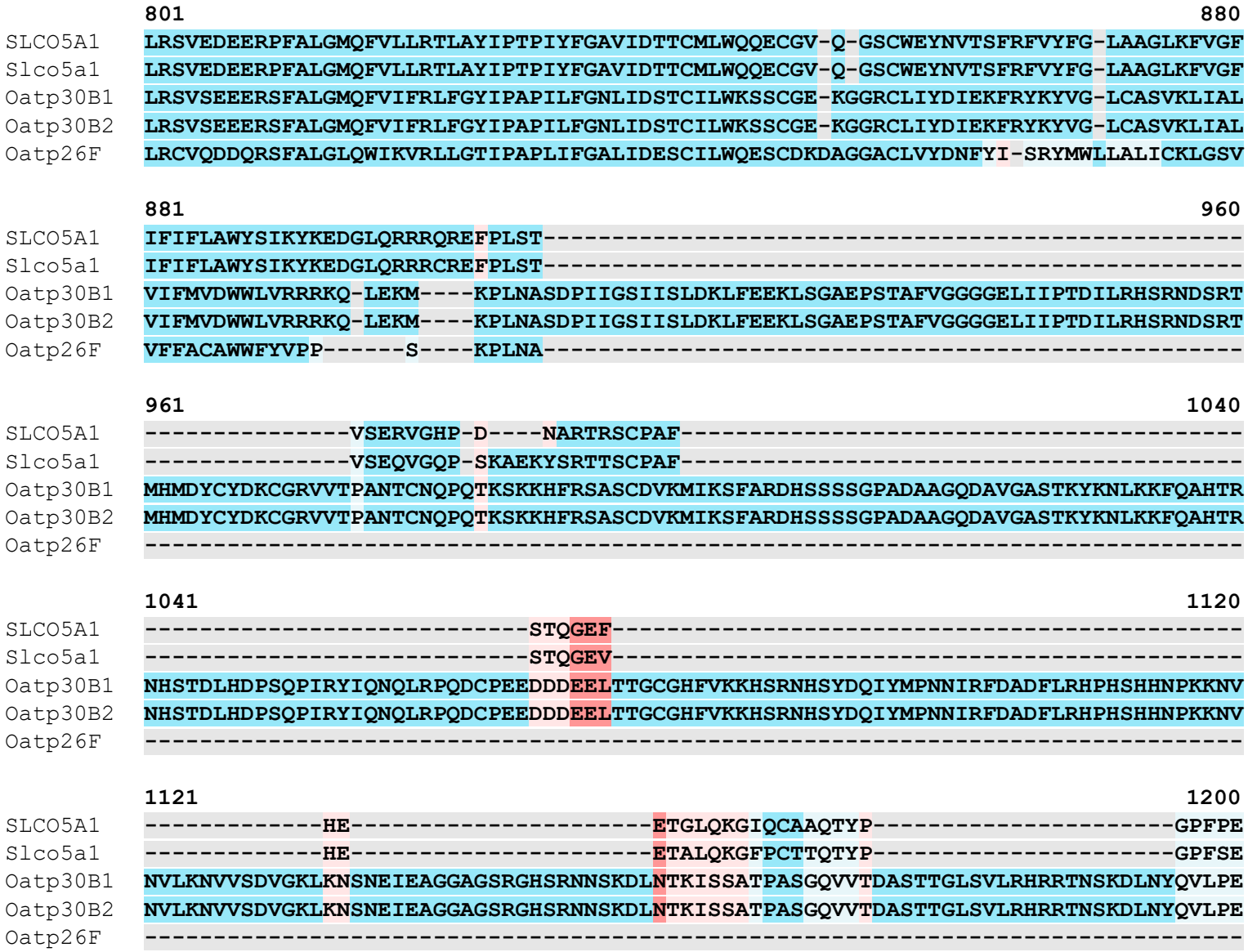
Supplementary Figure 7: Colocalization figure from LocusFocus[1] for the *SLCO5A1* gene

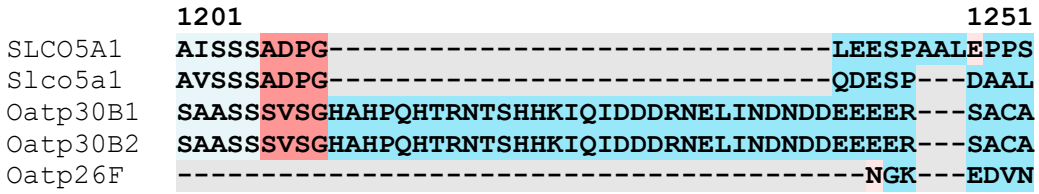


Same as in main Figure 2a, but circles depict the GWAS with BIS-Brief in the European subset (n=324). Colocalization analysis results reveal colocalization with GTEx[2] V8 brain cortex ($-\log_{10}$ Simple Sum P-value (SSP) = 1.36), although this colocalization does not pass the multiple testing significance threshold of $-\log_{10}$SSP=2.0 for testing colocalization across eQTLs from GTEx[2], PsychENCODE[3] and fetal brain eQTLs from O'Brien *et al.*[4]

Supplementary Figure 8. Multiple sequence alignment of putative homologous sequences to human *SLCO5A1* (first row): mouse *Slco5a1* (88.60% identity), *Oatp30B* from fly (*D. melanogaster*; 37.43% identity), and *Oatp26F* from fly (34.63% identity).


401 480
SLCO5A1 IMYVMGALGPAVGYLLGGLLIGFYVDPR--NP--VHLDQNDPRFIGNWWSGFLLCAIAMFLVIFPMFTFPKKLPPRHKKK
Slco5a1 IMYVMGALGPAVGYLLGGLLIGFYVDPR--NP--VHLDQSDPRFIGNWWSGFLLCAIAMFLVIFPMFTFPKKLPPRHKKK
Oatp30B1 FMYSMGAFGPVVGFLLGAYLLSFHMDSL--SSTTISITPGDRRWVGMWWGGFLLCGVILLVVAVPFFSFPKVLA-REKKK
Oatp30B2 FMYSMGAFGPVVGFLLGAYLLSFHMDSL--SSTTISITPGDRRWVGMWWGGFLLCGVILLVVAVPFFSFPKVLA-REKKK
Oatp26F IYYTMATVGPAIGYVFGGQLLLIYTDWMTVDPVQLSLTSDSKVWIGAWWLGFIFAAAMCLLIALPIFGYPKLLPGAEKLQ
481 560
SLCO5A1 KKKKFSVDAVSD---------DD--------VLKEKS-NNSEQADKKVSSMGFGKDVRDLPRAAVRILSNMTFLFVSLSY
Slco5a1 -KKF-SADVVID---------DD--------IIKEKS-NTSEQMNKKVSPMGFGKNVRDLPRAAVRILSNMTFLFVSLSY
Oatp30B1 IRKSSVVQPVLPNNSRATVATDEMGKVKKLEIVAVTSKEDQSQAPPKVD-TGYGKDIKDIPQSMLRLVKNPVYIVTCLGA
Oatp30B2 IRKSSVVQPVLPNNSRATVATDEMGKVKKLEIVAVTSKEDQSQAPPKVD-TGYGKDIKDIPQSMLRLVKNPVYIVTCLGA
Oatp26F LERVSEAHATI----------SEAD----------DSSNVVRGLPRAVLSLLANPTFFFLNLAG
561 640
SLCO5A1 TAESAIVTAFITFIPKFIESQFGIPASNASIYTGVIIVPSAGVGIVLGGYIIKKLKLGARESAKLAMICSGVSLLCFSTL
Slco5a1 TAESAIVTAFITFIPKFIESQFGIPASNASIYTGVIIVPSAGVGIVLGGYIIKKLKLGARESAKLAMICSGVSLLCFSTL
Oatp30B1 CMELMIVSGFVVFLPKYLETQFSLGKSQANIFTGSIAVPGACIGIFLGGCILKRFQLKPKGAVQFVLITNVICLACYAML
Oatp30B2 CMELMIVSGFVVFLPKYLETQFSLGKSQANIFTGSIAVPGACIGIFLGGCILKRFQLKPKGAVQFVLITNVICLACYAML
Oatp26F ATEGLVIAGFAAFLPKQIENQFSISPMYSALVMGLITVPAGGGGTFLGGYLVKKWNLACRGIIKMCLLATTVA-ALFTIC
641 720
SLCO5A1 FIVGCESINLGGINIPYTT----GPSLTMPH-RNLTGSCNVNCGCKIHEYEPVCGSDGITYFNPCLAGCVNSGNLSTGIR
Slco5a1 FIVGCESINLGGINIPYTT----GPSLTMPH-RNLTGSCNVNCGCKIHEYEPVCGSDGITYFNPCLAGCINSGNLTTGVR
Oatp30B1 FFLGCDNLKMAGTTIPYYTSNKHGSTLEQPFQVNLTAACNFGCECLTSEVEPVCGNNGLTYFSPCHAGCTAFS--STSNT
Oatp30B2 FFLGCDNLKMAGTTIPYYTSNKHGSTLEQPFQVNLTAACNFGCECLTSEVEPVCGNNGLTYFSPCHAGCTAFS--STSNT
Oatp26F FLVSCPNPKFAGVTTGYKM----QPSSDSP---ALVASCNSNCGCSRTNYDPICGVDGVMYYSPCYAGCVQEEH-ANSLK
721 800
SLCO5A1 NYTECTCVQSRQVITPPTVGQRSQLRVVIVKTYLN---ENGYAVSGKCKRTCNTLIPFLVFLFIVTFITACAQPSAIIVT
Slco5a1 NYTECTCVQSRQVITPPTVGQRSQLRVVIVKTYLN---ENGYAVSGKCKRTCNTLIPFLVFLFIVTFITACAQPSAIIVT
Oatp30B1 NYTNCACVRANISSSIYRGAGGSQAQALSANENFAEVTVVPVATAGPCATPCRTIYPFLILLFFMTFLVASTQMPLLMIV
Oatp30B2 NYTNCACVRANISSSIYRGAGGSQAQALSANENFAEVTVVPVATAGPCATPCRTIYPFLILLFFMTFLVASTQMPLLMIV
Oatp26F RYHNCSCIEQVGFVD--DGNPSSEAP----------HFRPDATNRKCDSTCQTLPLFVALCFILMVFTFLATMPALSAT


801 880
SLCO5A1 LRSVEDEERPFALGMQFVLLRTLAYIPTPIYFGAVIDTTCMLWQQECGV-Q-GSCWEYNVTSFRFVYFG-LAAGLKFVGF
Slco5a1 LRSVEDEERPFALGMQFVLLRTLAYIPTPIYFGAVIDTTCMLWQQECGV-Q-GSCWEYNVTSFRFVYFG-LAAGLKFVGF
Oatp30B1 LRSVSEEERSFALGMQFVIFRLFGYIPAPILFGNLIDSTCILWKSSCGE-KGGRCLIYDIEKFRYKYVG-LCASVKLIAL
Oatp30B2 LRSVSEEERSFALGMQFVIFRLFGYIPAPILFGNLIDSTCILWKSSCGE-KGGRCLIYDIEKFRYKYVG-LCASVKLIAL
Oatp26F LRCVQDDQRSFALGLQWIKVRLLGTIPAPLIFGALIDESCILWQESCDKDAGGACLVYDNFYI-SRYMWLLALICKLGSV
881 960
SLCO5A1 IFIFLAWYSIKYKEDGLQRRRQREFPLST----------
Slco5a1 IFIFLAWYSIKYKEDGLQRRRCREFPLST----------
Oatp30B1 VIFMVDWWLVRRRKQ-LEKM----KPLNASDPIIGSIISLDKLFEEKLSGAEPSTAFVGGGGELIIPTDILRHSRNDSRT
Oatp30B2 VIFMVDWWLVRRRKQ-LEKM----KPLNASDPIIGSIISLDKLFEEKLSGAEPSTAFVGGGGELIIPTDILRHSRNDSRT
Oatp26F VFFACAWWFYVPP------S----KPLNA----------
961 1040
SLCO5A1 ----------VSERVGHP-D----NARTRSCPAF----------
Slco5a1 ----------VSEQVGQP-SKAEKYSRTTSCPAF----------
Oatp30B1 MHMDYCYDKCGRVVTPANTCNQPQTKSKKHFRSASCDVKMIKSFARDHSSSSGPADAAGQDAVGASTKYKNLKKFQAHTR
Oatp30B2 MHMDYCYDKCGRVVTPANTCNQPQTKSKKHFRSASCDVKMIKSFARDHSSSSGPADAAGQDAVGASTKYKNLKKFQAHTR
Oatp26F ----------
1041 1120
SLCO5A1 ----------STQGEF----------
Slco5a1 ----------STQGEV----------
Oatp30B1 NHSTDLHDPSQPIRYIQNQLRPQDCPEEDDDEELTTGCGHFVKKHSRNHSYDQIYMPNNIRFDADFLRHPHSHHNPKKNV
Oatp30B2 NHSTDLHDPSQPIRYIQNQLRPQDCPEEDDDEELTTGCGHFVKKHSRNHSYDQIYMPNNIRFDADFLRHPHSHHNPKKNV
Oatp26F ----------
1121 1200
SLCO5A1 ----------HE----------ETGLQKGIQCAAQTYP----------GPFPE
Slco5a1 ----------HE----------ETALQKGFPCTTQTYP----------GPFSE
Oatp30B1 NVLKNVVSDVGKLKNSNEIEAGGAGSRGHSRNNSKDLNTKISSATPASGQVVTDASTTGLSVLRHRRTNSKDLNYQVLPE
Oatp30B2 NVLKNVVSDVGKLKNSNEIEAGGAGSRGHSRNNSKDLNTKISSATPASGQVVTDASTTGLSVLRHRRTNSKDLNYQVLPE
Oatp26F ----------



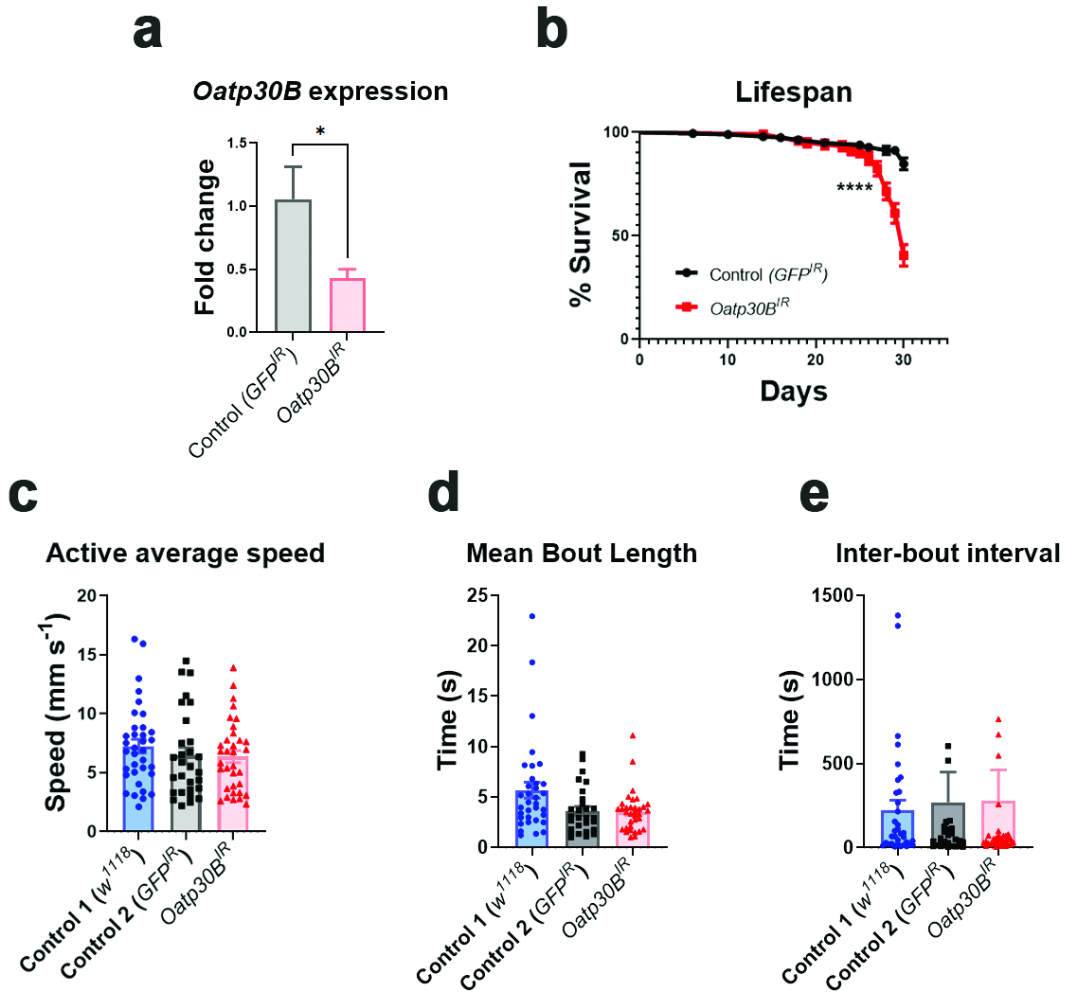
Alignment confidence (per residue): high **9876543210** low

Domain	Corresponding residues in human *SLCO5A1* (source: Pfam)
MFS_1	135-529
OATP	129-734
Kazal	549-603

Overlapping domain regions are underlined.

The multiple sequence alignment was performed using MUSCLE5.[5] All sequences have a Kazal-like domain (shown in red).

Supplementary Figure 9. (a) *Oatp30B* mRNA levels as measured by qPCR (b) Reduced lifespan in flies with *Oatp30B* knock-down. (c) Unchanged speed during action. (d) Unaffected duration of single action bouts. (e) Unaffected rest interval in between single action bouts.



a: The *UAS-Oatp30B*^{IR} (GD12775) transgenic or the control *UAS-GFP*^{IR} were driven with *Tub-Gal4* and *Ubi-Gal80ts*. The graph reports data from 3 biological samples (n=10 flies, both males and females) and 5 technical replicates. Mean +/- SEM * P<0.05, Unpaired t-test, one-tailed.

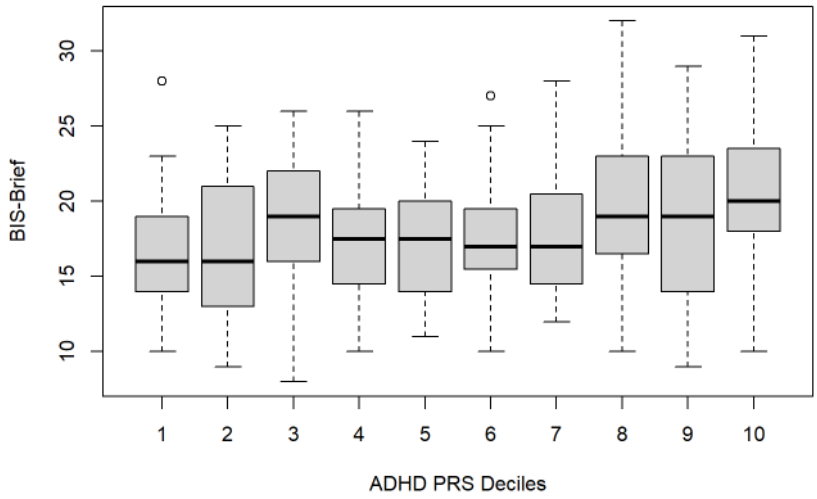
b: The *UAS-Oatp30B*^{IR} (GD12775) transgenic or the control *UAS-GFP*^{IR} were driven with *nSyb-Gal4* and *Ubi-Gal80ts*. Percent +/- SE **** P<0.0001, Log-rank (Mantel-Cox) test, χ^2 51.74 for 1 df, n=119-194.

c: The *UAS-Oatp30B*^{IR} (GD12775) transgenic or the control *UAS-GFP*^{IR} were driven with *nSyb-Gal4* and *Ubi-Gal80ts*. The *w*^{1118} strain is a control for the genetic background in absence of transgenes.

d: Flies as in c.

e: Flies as in c.

Supplementary Figure 10. BIS-Brief score vs. ADHD PRS deciles



The center lines represent the 50th percentile (median) and the bounds of the boxes are the 75th and 25th percentiles (interquartile range) with the whiskers being the largest value within 1.5 times the interquartile range above the 75th percentile and smallest values within 1.5 times the interquartile range below the 25th percentile.

Supplementary Tables

Supplementary Table 1: Methods applied for the computation of PRS.

	Summary statistics				BIOJUME	Clumping + Thresholding	
Disease	**Study**	**Sample size**	**Ethnicity**	**Variant filtering**	**Variant Filtering**	**Clumping**	**p-value Threshold**
ADHD	Demontis et al., 2019[6]	19,099 cases & 34,194 controls	European	MAF ≤0·05 r^2 ≤0·8 Indels Ambiguous SNPs Multi-allelic SNPs MHC region	r^2 ≤0·5	r^2: 0·3 radius: 500 kb	0·1
Risk Taking	UK Biobank[7]	348,549	European	MAF ≤0·05 Info ≤0·8 Indels Ambiguous SNPs Multi-allelic SNPs	r2 ≤0·5	r2: 0·1 radius: 500 kb	0·05*
Bipolar Disorder	Stahl et al., 2019[8]	20,352 cases and 31,358 controls	European	MAF ≤0·05 Info ≤0·9 Indels Ambiguous SNPs Multi-allelic SNPs MHC region except for the most significant associated SNP (rs36034627, Chr6:27,269,584, T>G)	r^2 ≤0·5	r^2: 0·1 radius: 500 kb	0·2
Generalized epilepsy	ILAE Consortium, 2018[9]	15,212 cases & 29,677 controls	Majority European	MAF ≤0·02 r^2 ≤0·3 Ambiguous SNPs	r^2 ≤0·5	r^2: 0·1 radius: 500 kb	0·5
Focal epilepsy	ILAE Consortium, 2018[9]	15,212 cases & 29,677 controls	Majority European	MAF ≤0·02 r^2 ≤0·3 Ambiguous SNPs	r^2 ≤0·5	r^2: 0·1 radius: 500 kb	0·5

Clumping and thresholding were used to calculate ADHD, risk taking, bipolar disorder, generalized epilepsy, and focal epilepsy PRS in individuals of European ancestry using PLINK v1·9.[10] PRS values were generated by weighting selected SNPs after clumping and thresholding by the additive scale effect ($\log_{10}$(OR)/Beta), and then summing over the variants.

For generalized and focal epilepsy PRSs, we tested 10 different p-value thresholds (5E-8, 1E-6, 1E-4, 1E-3, 1E-2, 0·05, 0·1, 0·2, 0·5, 1), and 0.05 explained the highest proportion of variation in BIS-Brief score (R^2 = 0·016).

MHC region: The major histocompatibility complex region, chr6:25-34Mbp
ILAE: International League Against Epilepsy
The methods applied to calculated generalized and focal epilepsy PRS are based on Leu et al. 2019.[11]

Supplementary Table 2: Univariate analysis with BIS-Brief

Variable	Beta	Standard Error	P-value
Sex	-1·36	0·51	$8{\cdot}0 \times 10^{-3}$
Age at consent	0·042	0·028	0·13
Myoclonus or absence seizure frequency	1·09	0·25	$2{\cdot}2 \times 10^{-5}$
PC1	3·96	5·05	0·43
PC2	-4·48	5·42	0·41
PC3	4·30	4·39	0·33
Cohort 2	1·41	0·78	0·071
Cohort 3	1·49	0·92	0·10
Cohort 4	1·66	0·79	0·035

Linear regression was used to test association of each variable with BIS-Brief in 324 European individuals with JME. We have previously shown the association of sex and seizure frequency with BIS-Brief.[12] Seizure frequency was used as a marker of controlled seizures and was defined as missing if there was no reported myoclonus frequency; otherwise, it was the maximum observed frequency for myoclonus or absence seizure as follows: daily seizures=3; weekly=2; less than weekly=1; none (currently or ever)=0. Cohort refers to the genotyping batch; samples recruited were genotyped in four batches at different time points.

Supplementary Table 3: Association of top BIS-Brief GWAS SNPs with inverse rank normal transformed BIS-Brief (N = 324)

Variant ID	Position (hg38)	Alleles	Beta	SE	P-value
rs73293634	chr8:69,884,968	G/T	1.2	0.2	3.1E-8
rs75042057	chr10:34,202,650	T/G	1.6	0.3	1.4E-7

Linear regression was used to test association of each SNP with inverse rank normal transformed BIS-Brief. Sex, genotyping batch, age at consent, first 3 PCs, and the frequency of myoclonus or absence seizures were included as covariates in the model.

Supplementary Table 4: Association of ADHD, bipolar disorder, and focal and general epilepsy PRS with BIS-Brief

PRS	β	SE	P
ADHD	0.09	0.03	1.60E-3
Risk Taking	2.14	0.90	1.83E-2
Bipolar Disorder	0.07	0.04	0.080
Generalized Epilepsy PRS	-0.03	0.03	0.33
Focal Epilepsy PRS	0.002	0.045	0.96

Association of each PRS with BIS-Brief was tested using linear regression with age, sex, and frequency of absence/myoclonic seizure as covariates in the model.

References

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7 *Neale's Lab UK Biobank GWAS Results Round 2 (Imputed v3 - File Manifest Release 20180731)*, <http://www.nealelab.is/uk-biobank> (

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10 Purcell, S. *et al.* PLINK: a tool set for whole-genome association and population-based linkage analyses. *Am J Hum Genet* **81**, 559-575, doi:10.1086/519795 (2007).

11 Leu, C. *et al.* Polygenic burden in focal and generalized epilepsies. *Brain* **142**, 3473-3481, doi:10.1093/brain/awz292 (2019).

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