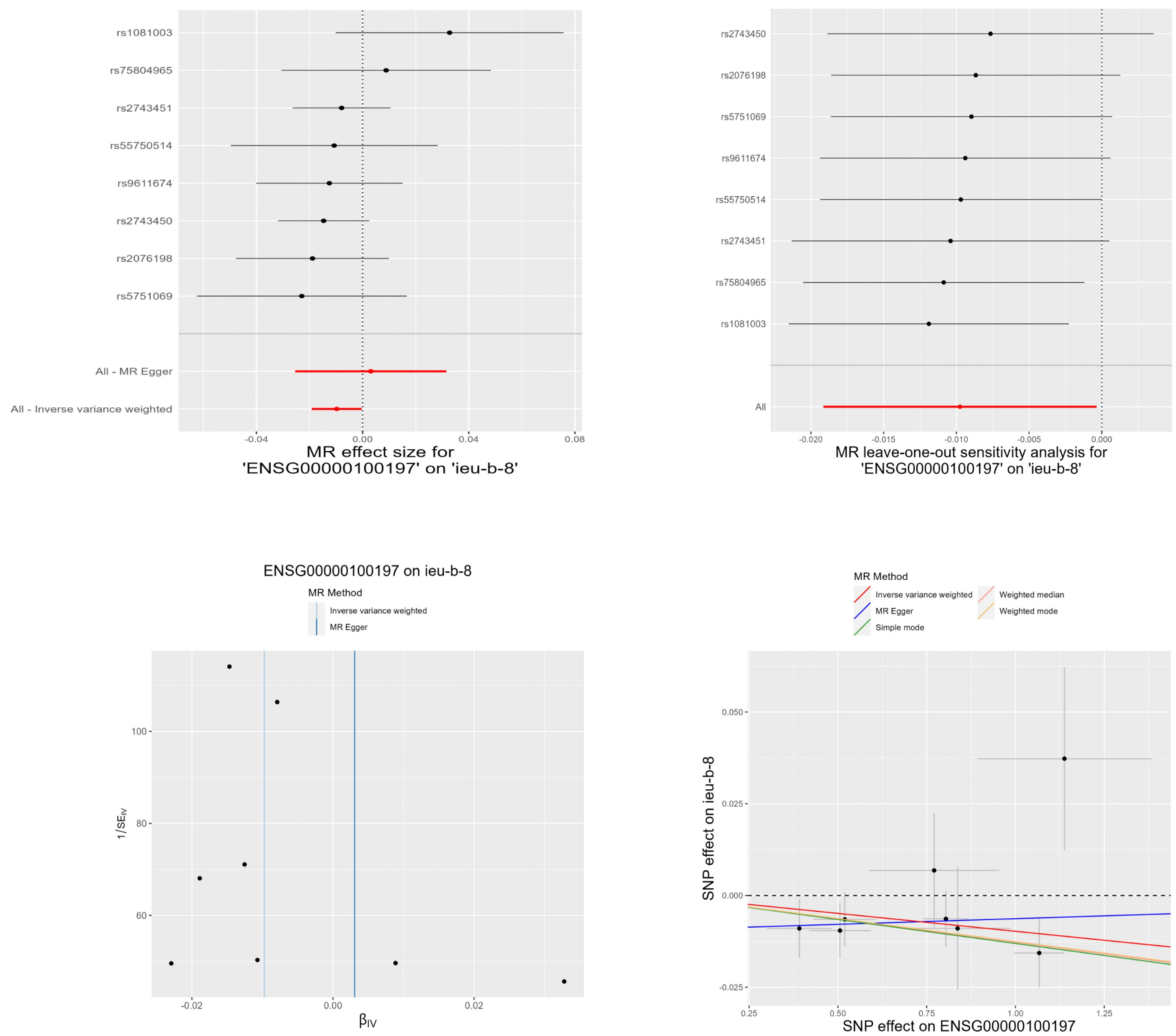
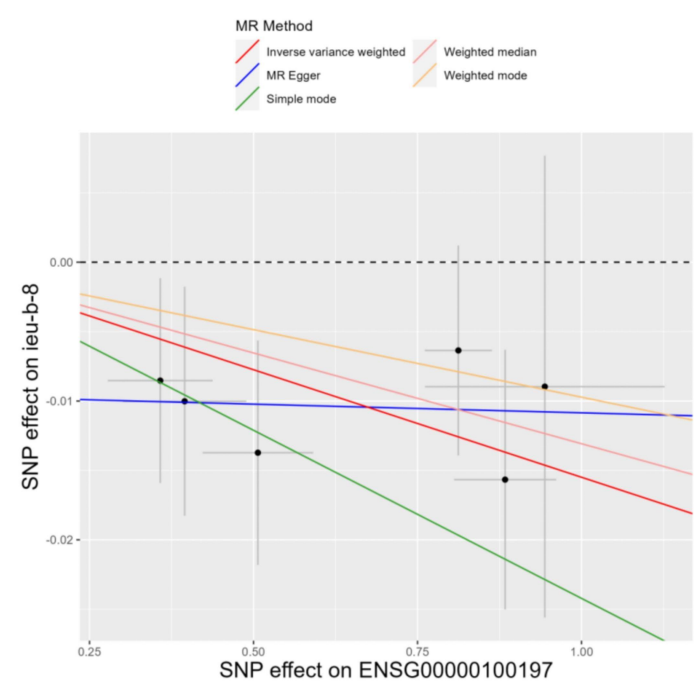
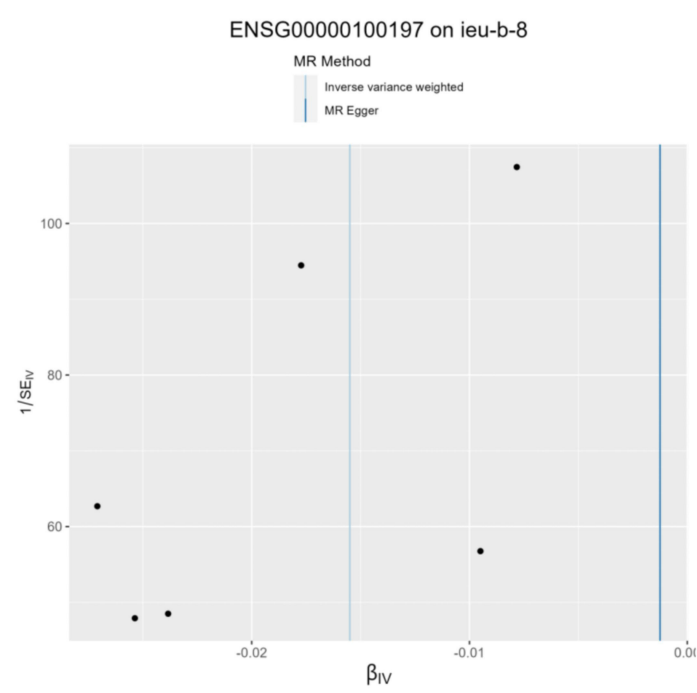
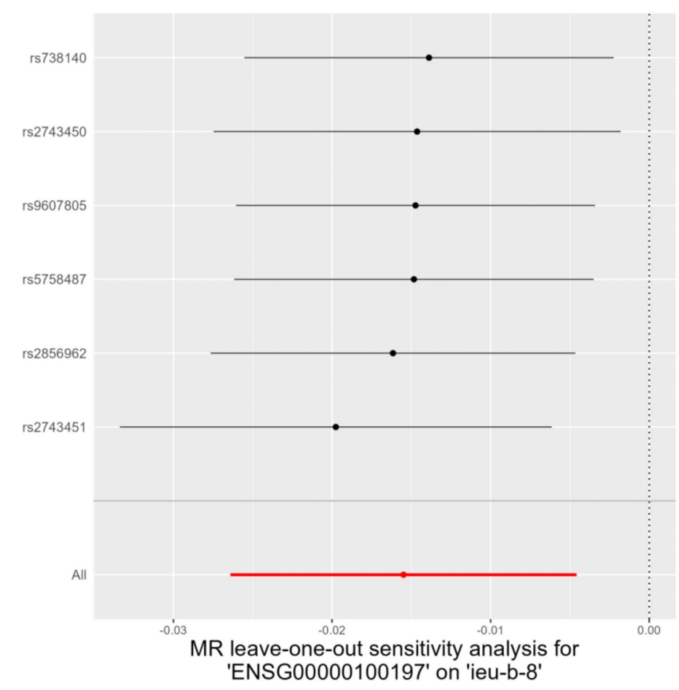
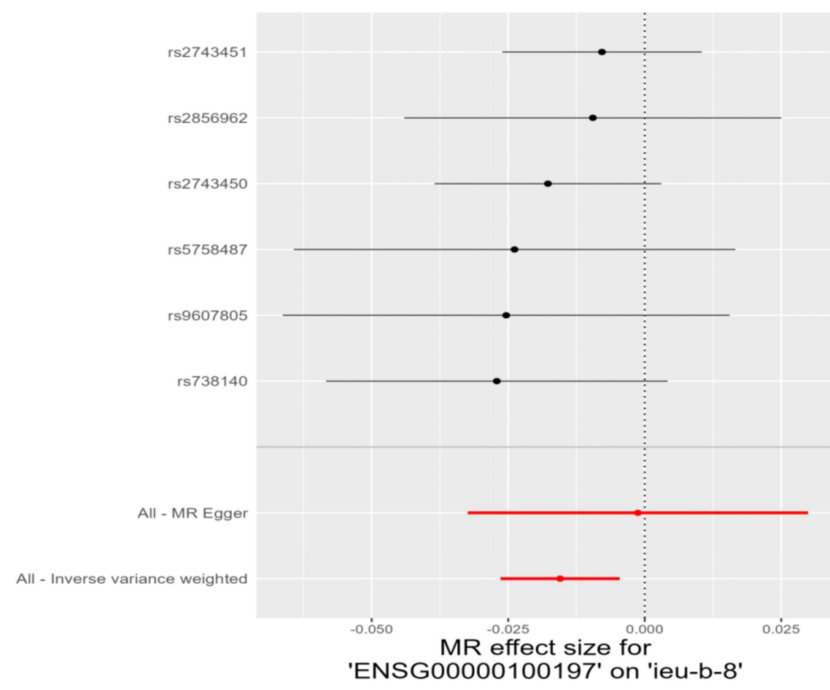
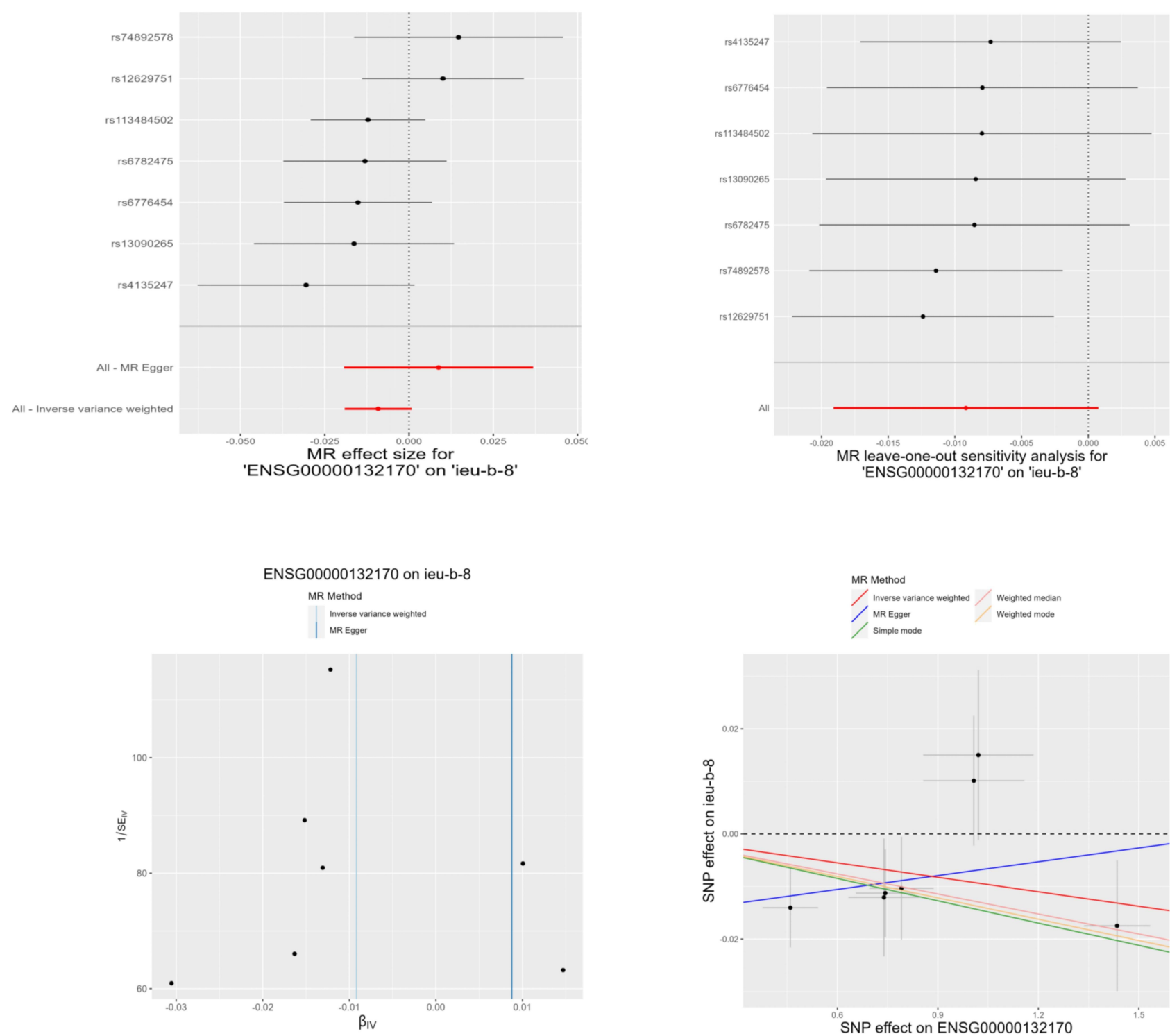




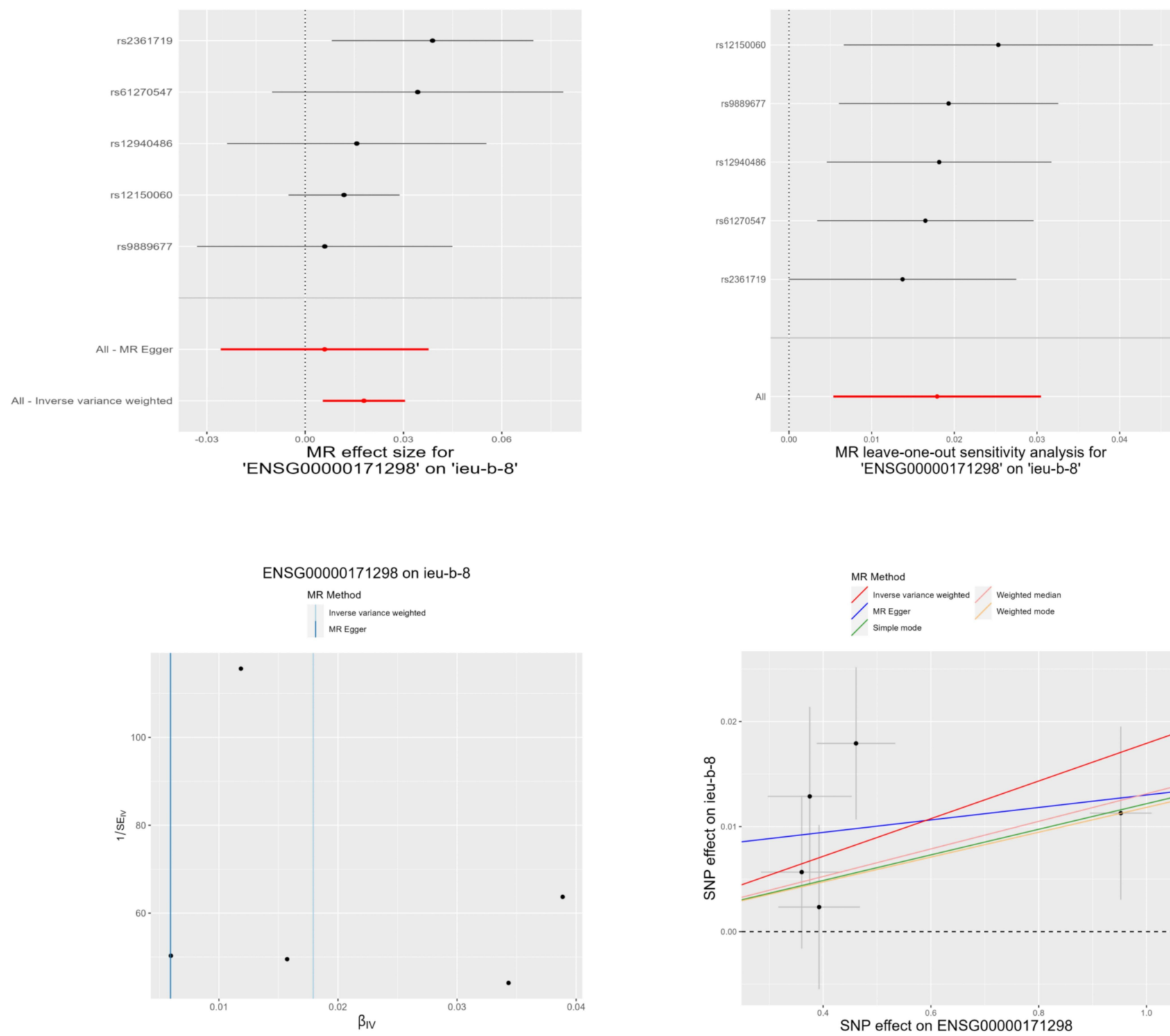
Supplement figure 1. Mendelian randomization assessment of CYP2D6 expression in the brain-cerebellum and epilepsy risk.



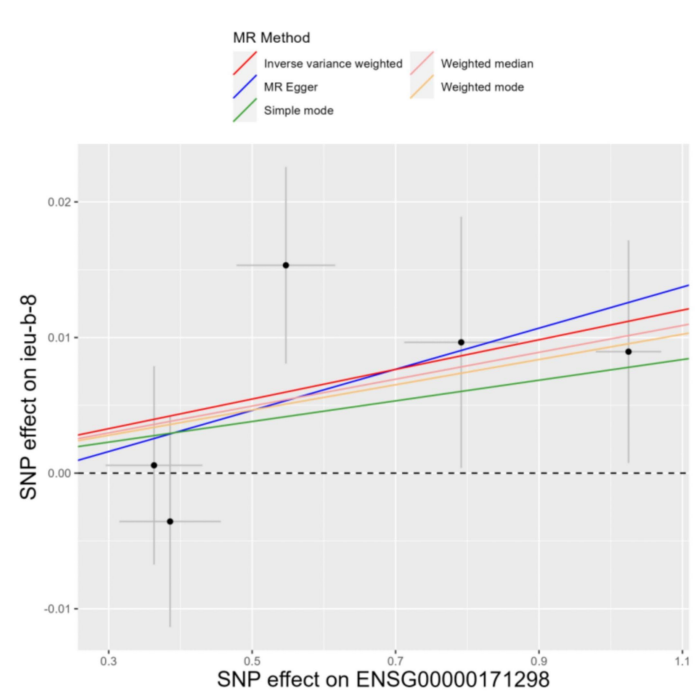
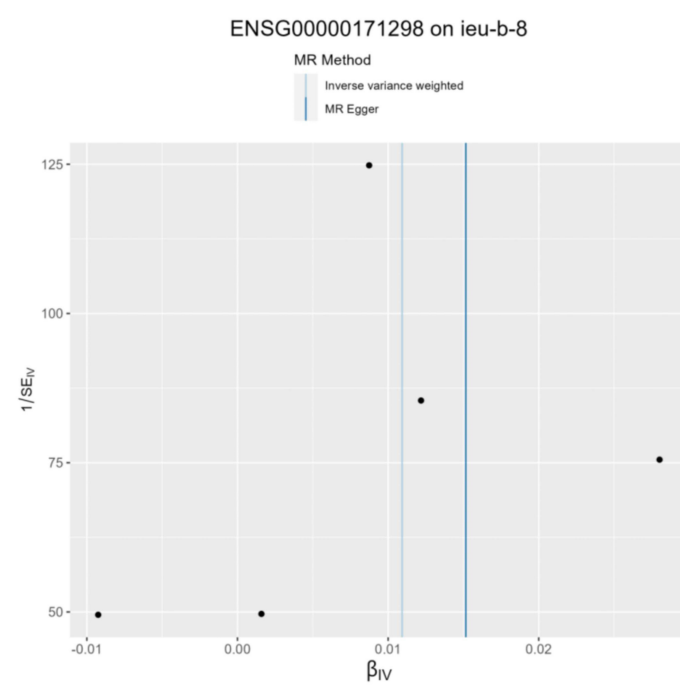
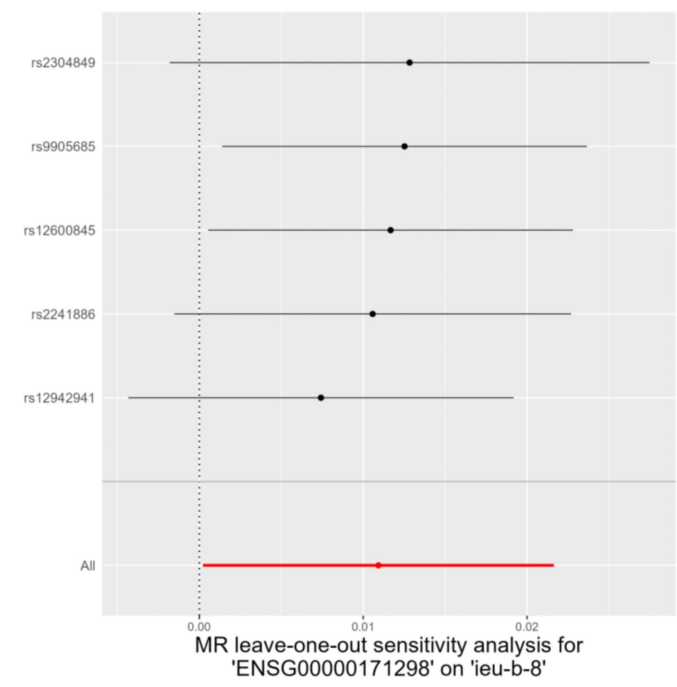
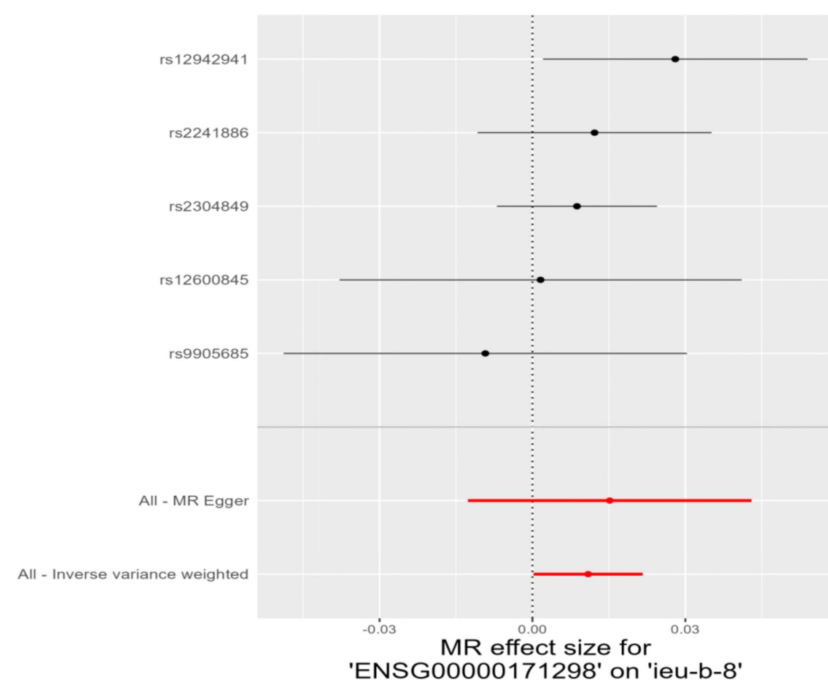
Supplement figure 2. Mendelian randomization assessment of CYP2D6 expression in the brain-cortex and epilepsy risk.



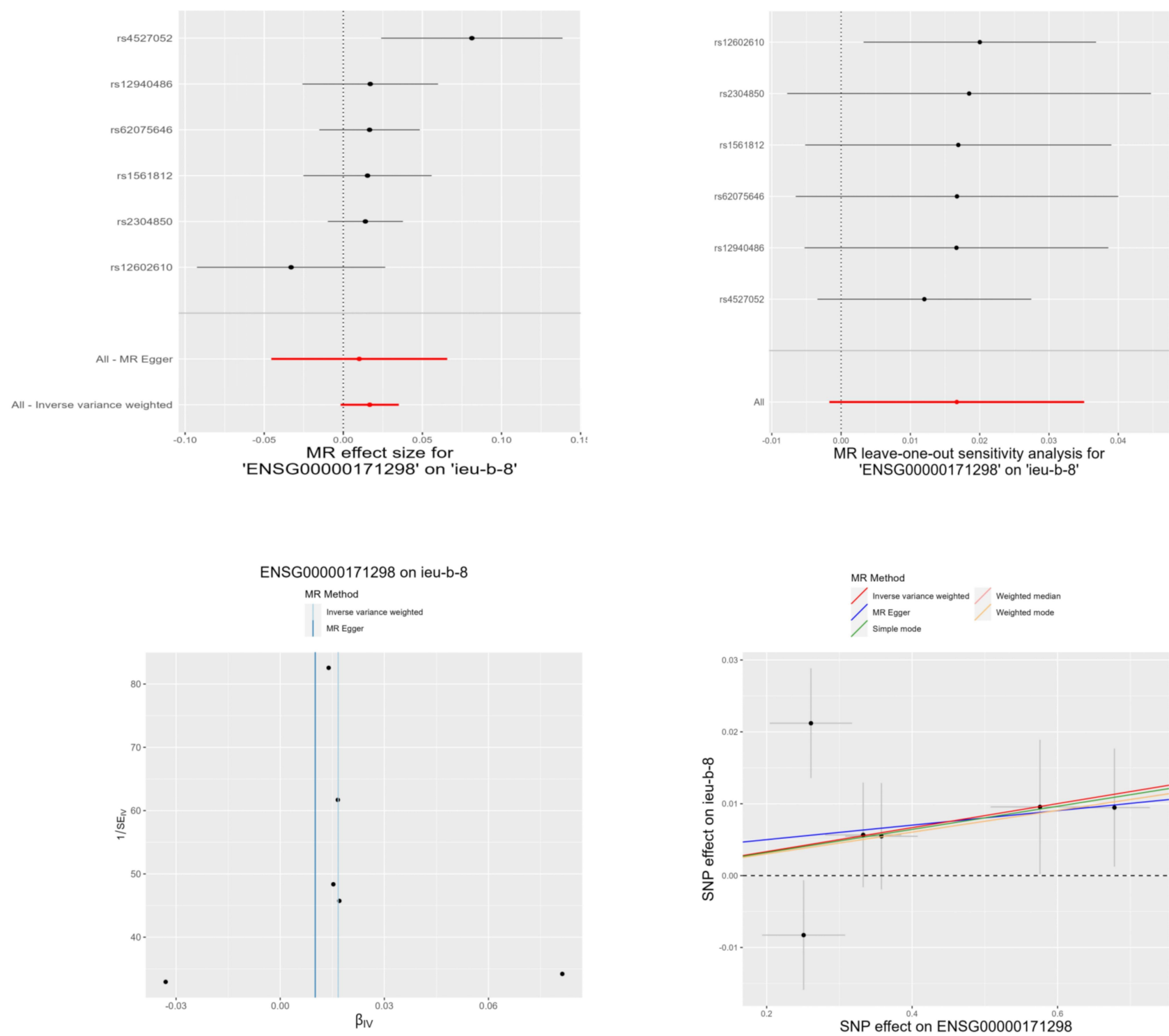
Supplement figure 3. Mendelian randomization assessment of PPARG expression in the brain-cerebellum and epilepsy risk.



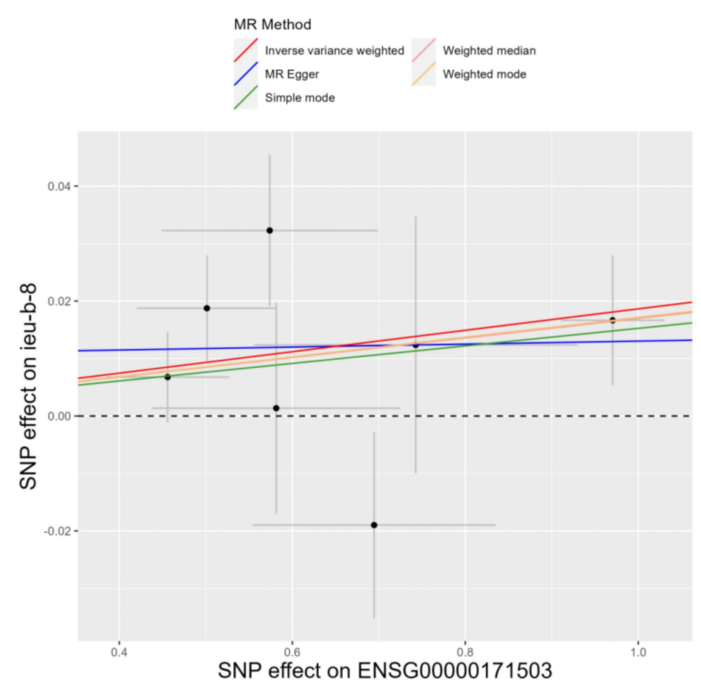
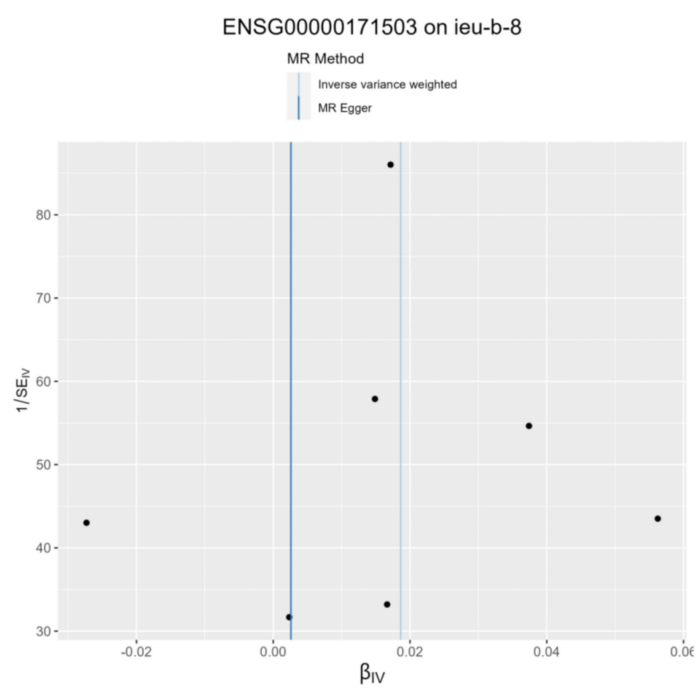
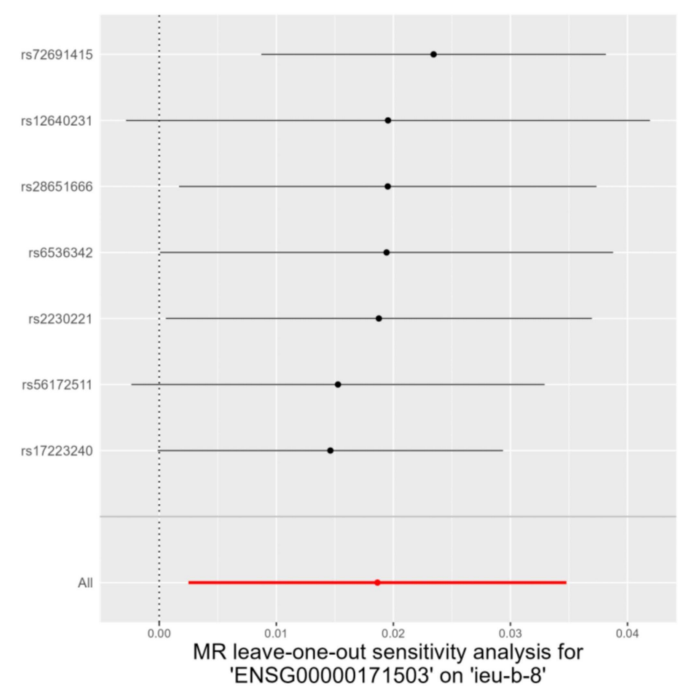
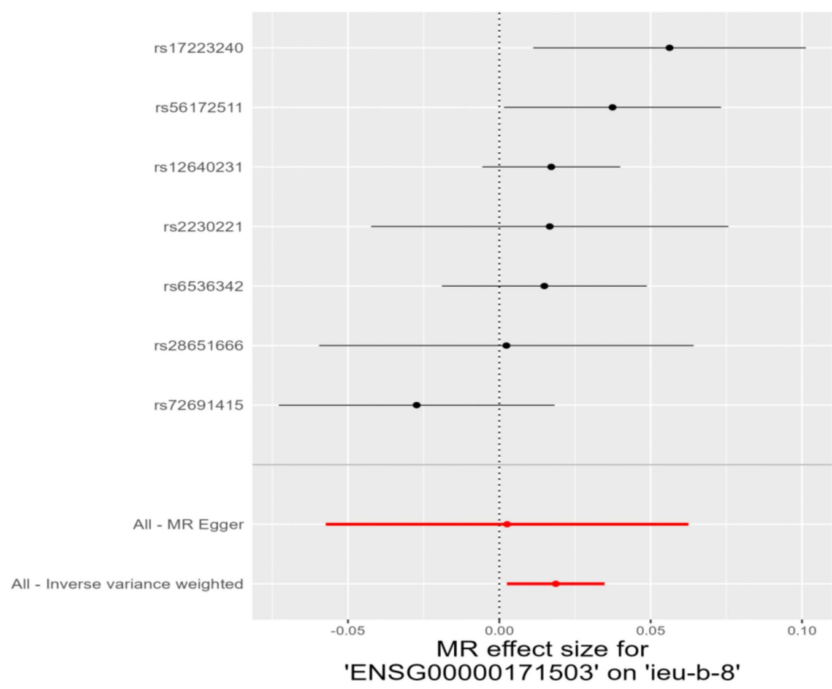
Supplement figure 4. Mendelian randomization assessment of GAA expression in the brain-cerebellar-hemisphere and epilepsy risk.



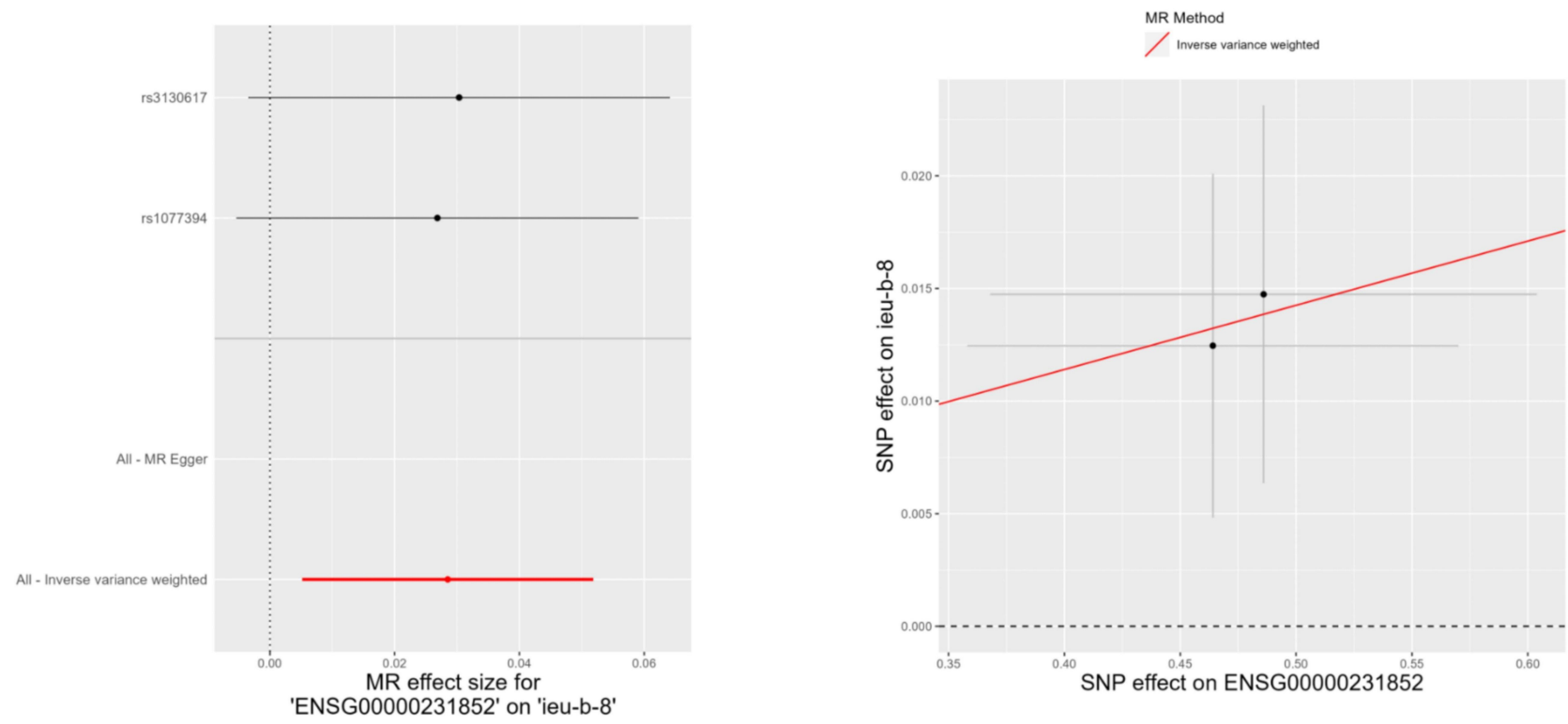
Supplement figure 5. Mendelian randomization assessment of GAA expression in the brain-cerebellum and epilepsy risk.



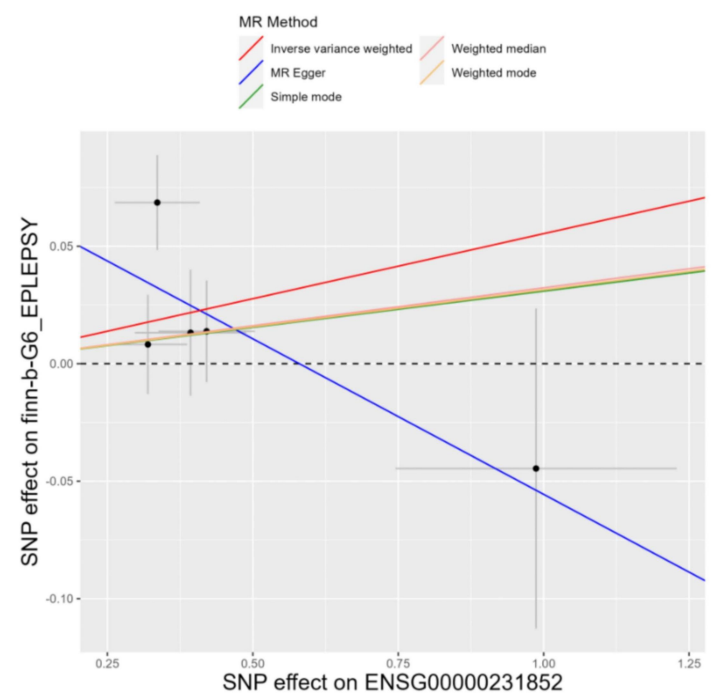
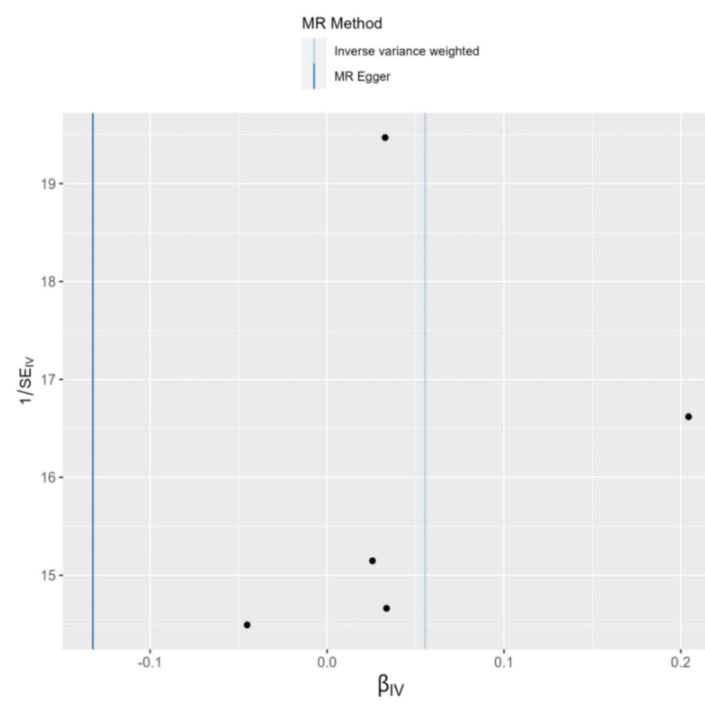
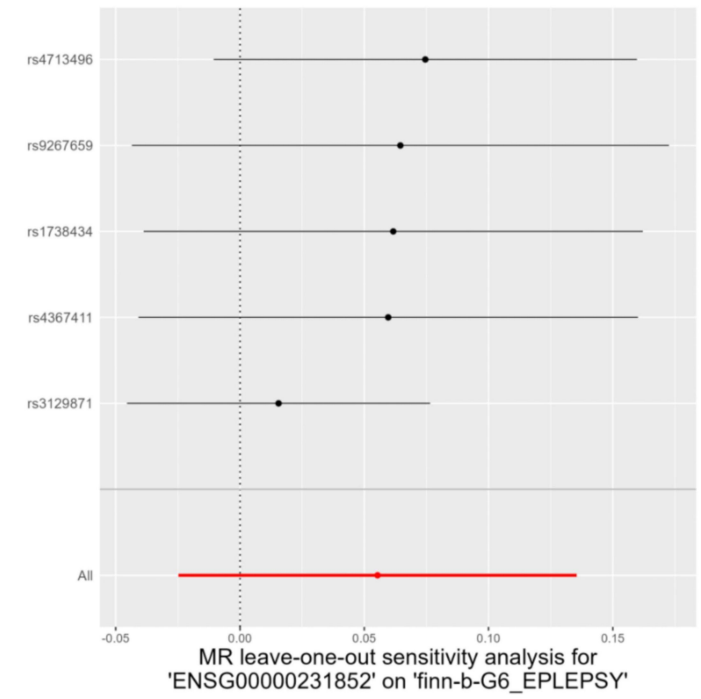
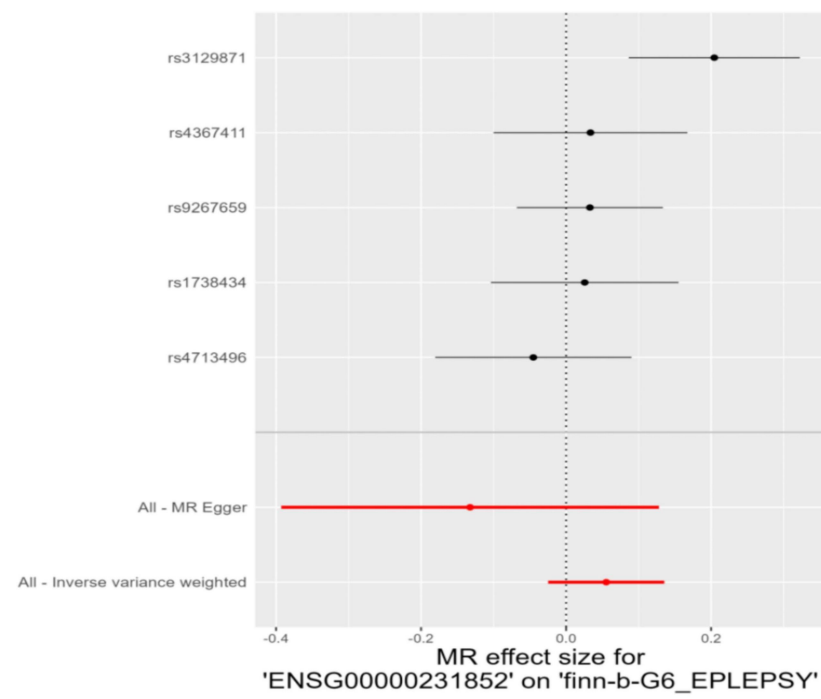
Supplement figure 6. Mendelian randomization assessment of GAA expression in the brain-cerebellum and epilepsy risk.



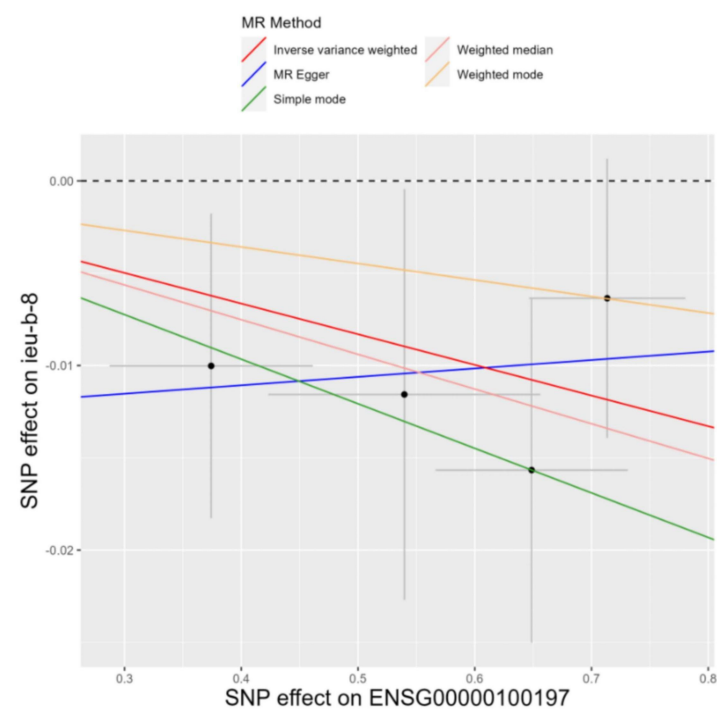
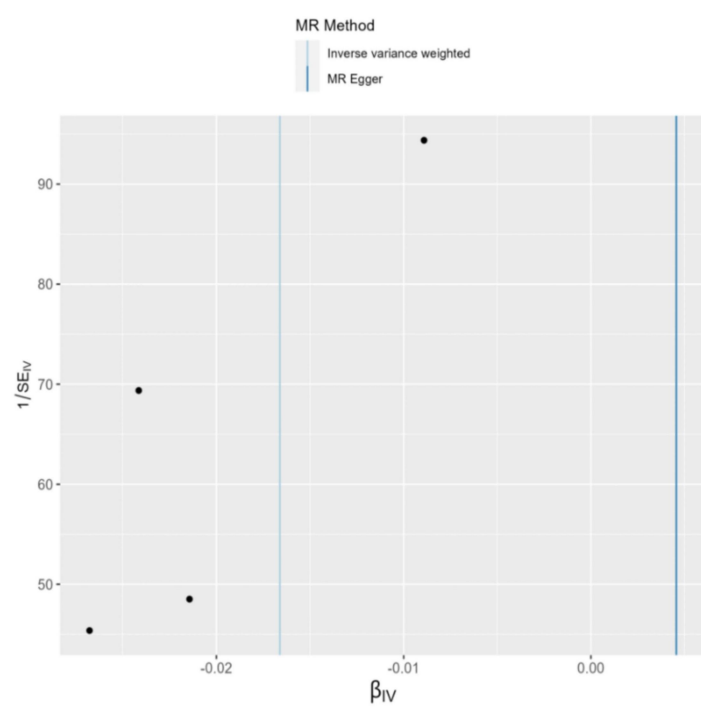
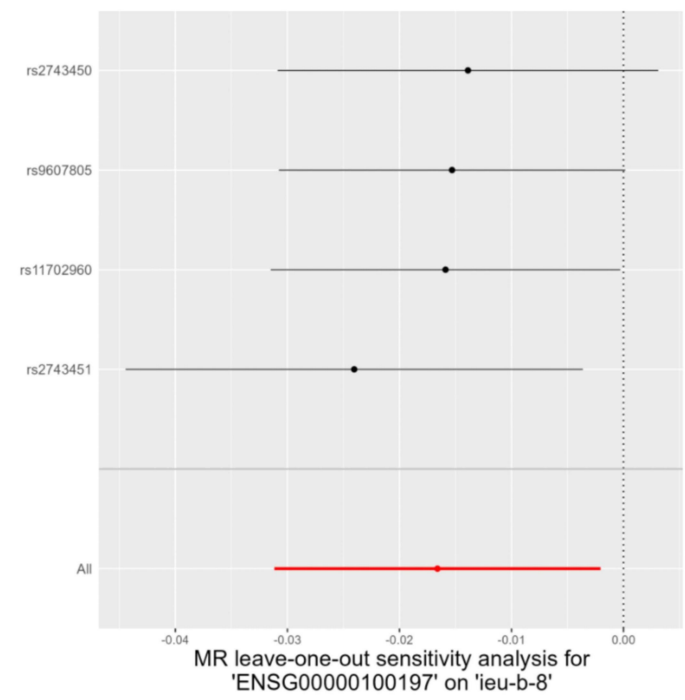
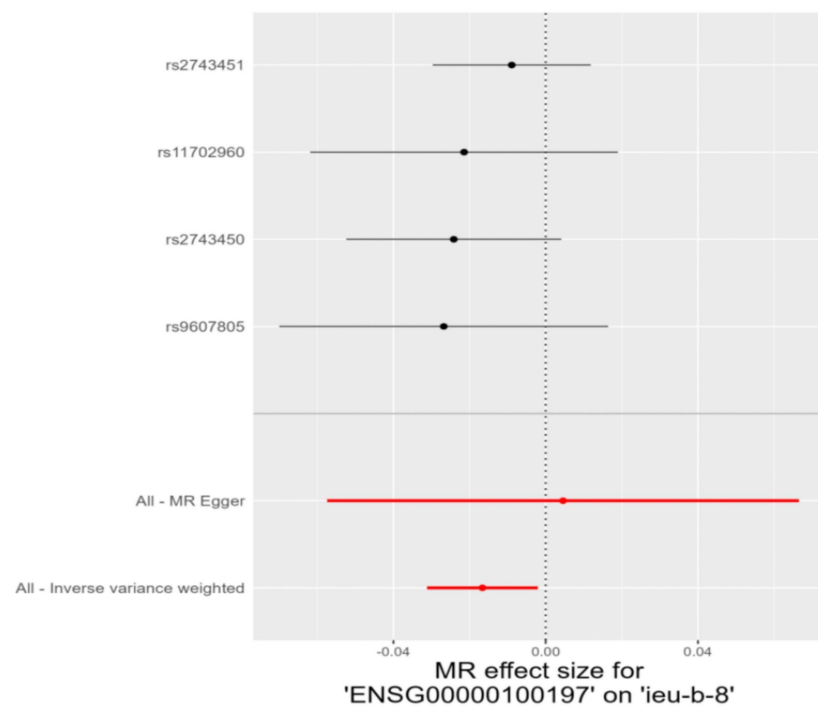
Supplement figure 7. Mendelian randomization assessment of ETFDH expression in the brain-cerebellar-hemisphere and epilepsy risk.



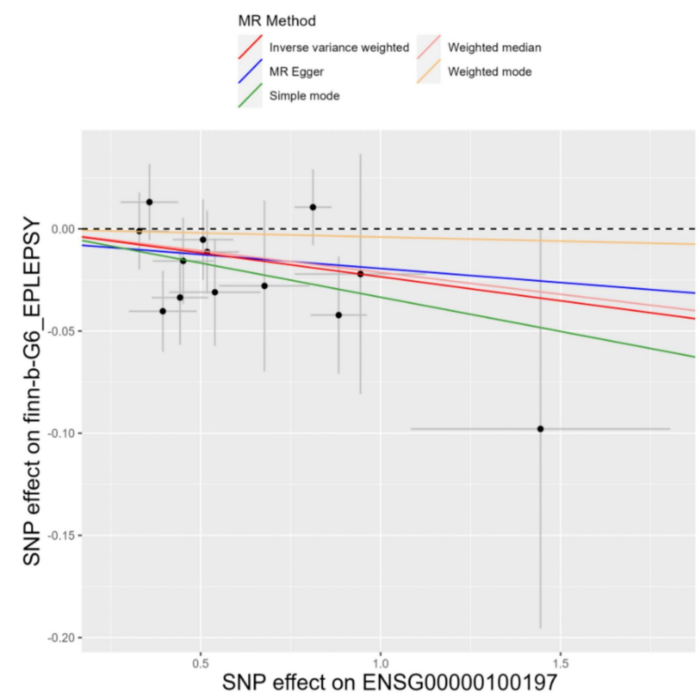
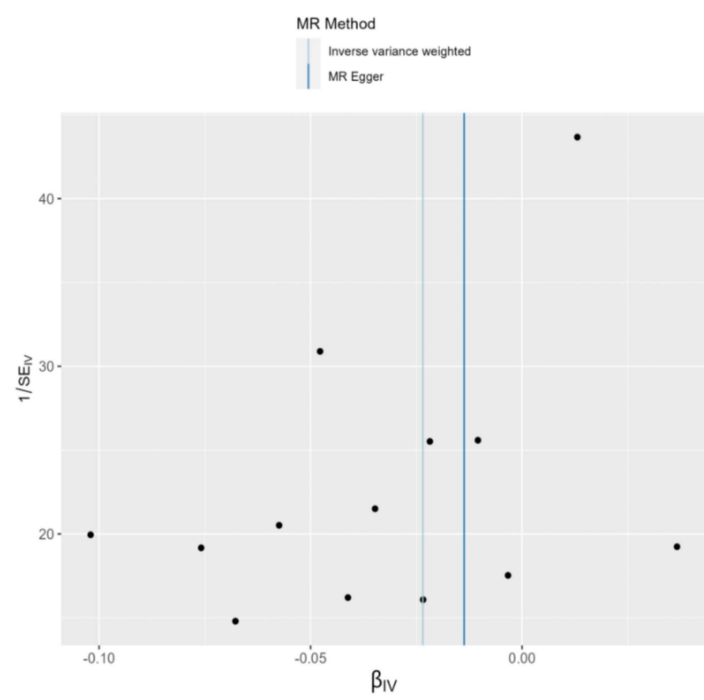
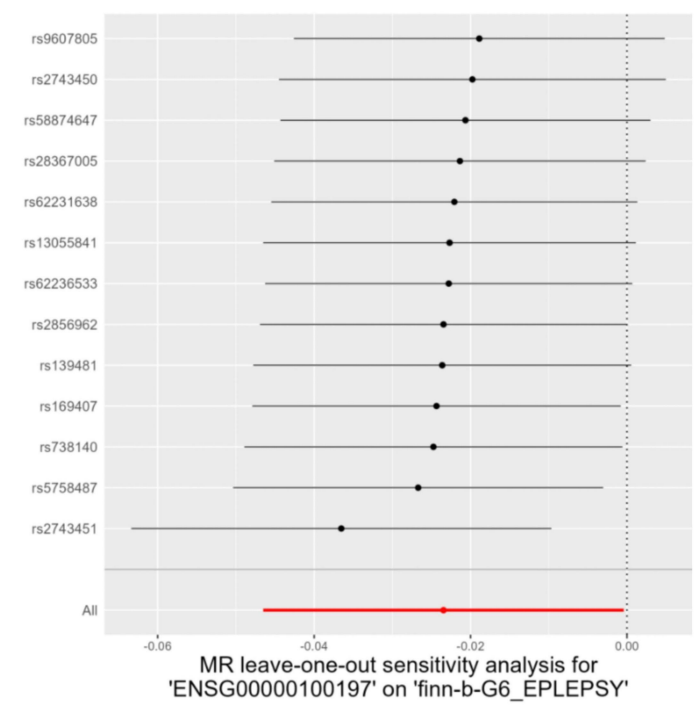
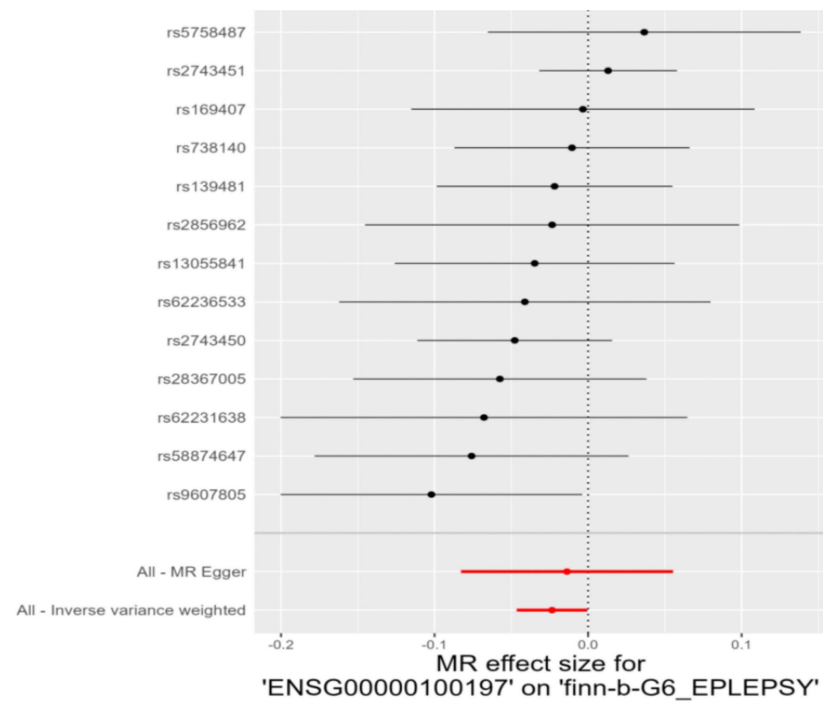
Supplement figure 8. Mendelian randomization assessment of the CYP21A2 expression in brain_cerebellum and epilepsy risk in ILAE.



Supplement figure 9. Mendelian randomization assessment of the CYP21A2 expression in brain_nucleus_accumbens_basal_ganglia and epilepsy risk in Finn Gen.



Supplement figure 10. Mendelian randomization assessment of the CYP2D6 expression in brain_anterior_cingulate_cortex and epilepsy risk in ILAE.



Supplement figure 11. Mendelian randomization assessment of the CYP2D6 expression in brain_cortex and epilepsy risk in Finn Gen.

Name	Drugbank ID	Target genes	Ensembl ID
Ebselen	DB12610	EPHX2	ENSG00000120915
INCB13739	DB05064	HSD11B1	ENSG00000117594
PSN357	DB05044	PYGL	ENSG00000100504
Bisegliptin	DB06127	DPP4	ENSG00000197635
NOX- 700	DB05464	NFKB2	ENSG00000077150
		NFKB1	ENSG00000109320
CLX- 0921	DB05854	PPARG	ENSG00000132170
Reglitazar	DB04971	PPARA	ENSG00000186951
		PPARG	ENSG00000132170
ISIS 113715	DB05506	PTPN1	ENSG00000196396
AT1391	DB05120	INSR	ENSG00000171105
NN344	DB05115	INSR	ENSG00000171105
		CYP1A2	ENSG00000140505
APD668	DB05166	GPR119	ENSG00000147262
Dutogliptin	DB11723	DPP4	ENSG00000197635
MB-07803	DB05053	FBP1	ENSG00000165140
PSN9301	DB05001	DPP4	ENSG00000197635
Gliquidone	DB01251	ABCC8	ENSG00000006071
		KCNJ8	ENSG00000121361
		CYP2C9	ENSG00000138109
Albiglutide	DB09043	GLP1R	ENSG00000112164
Pramlintide	DB01278	CALCR	ENSG00000004948
		RAMP1	ENSG00000132329
		RAMP2	ENSG00000131477
		RAMP3	ENSG00000122679
Voglibose	DB04878	MGAM	ENSG00000257335
Dapagliflozin	DB06292	SLC5A2	ENSG00000140675
		CYP1A1	ENSG00000140465
		CYP1A2	ENSG00000140505
		CYP2A6	ENSG00000255974
		CYP2C9	ENSG00000138109
		CYP2D6	ENSG00000100197
		CYP3A4	ENSG00000160868
		UGT1A9	ENSG00000241119
		UGT2B4	ENSG00000156096
		UGT2B7	ENSG00000171234
Miglitol	DB00491	MGAM	ENSG00000257335
		GAA	ENSG00000171298
		GANAB	ENSG00000089597
		GANC	ENSG00000214013
		AMY2A	ENSG00000243480
Vildagliptin	DB04876	DPP4	ENSG00000197635
Dulaglutide	DB09045	GLP1R	ENSG00000112164
Phenformin	DB00914	PRKAA1	ENSG00000132356
		KCNJ8	ENSG00000121361
		CYP2D6	ENSG00000100197
AMG- 131	DB05490	PPARG	ENSG00000132170
Acarbose	DB00284	MGAM	ENSG00000257335
		GAA	ENSG00000171298
		SI	ENSG00000090402
		AMY2A	ENSG00000243480
Sitagliptin	DB01261	DPP4	ENSG00000197635
		CYP3A4	ENSG00000160868
		CYP2C8	ENSG00000138115
Acetohexamide	DB00414	KCNJ1	ENSG00000151704
		CBR1	ENSG00000159228
		CYP2C9	ENSG00000138109
Canagliflozin	DB08907	SLC5A2	ENSG00000140675
		UGT1A9	ENSG00000241119
		UGT2B4	ENSG00000156096
		CYP3A4	ENSG00000160868
Pioglitazone	DB01132	PPARG	ENSG00000132170
		MAOB	ENSG00000069535

		CYP2C8	ENSG00000138115
		CYP3A4	ENSG00000160868
		CYP1A1	ENSG00000140465
Glisoxepide	DB01289	KCNJ8	ENSG00000121361
Glipizide	DB01067	CYP2C9	ENSG00000138109
		ABCC8	ENSG00000006071
		PPARG	ENSG00000132170
		CYP2C9	ENSG00000138109
Insulin Glargine	DB00047	UGT1A1	ENSG00000241635
		INSR	ENSG00000171105
		IGF1R	ENSG00000140443
Insulin Degludec	DB09564	CYP1A2	ENSG00000140505
		INSR	ENSG00000171105
		IGF1R	ENSG00000140443
Chlorpropamide	DB00672	CYP1A2	ENSG00000140505
		ABCC8	ENSG00000006071
		CYP2C9	ENSG00000138109
		CYP2C19	ENSG00000165841
Linagliptin	DB08882	PTGS1	ENSG00000095303
		DPP4	ENSG00000197635
		CYP3A4	ENSG00000160868
Repaglinide	DB00912	ABCC8	ENSG00000006071
		PPARG	ENSG00000132170
		CYP2C8	ENSG00000138115
		CYP3A4	ENSG00000160868
Insulin Pork	DB00071	INSR	ENSG00000171105
		IGF1R	ENSG00000140443
		IDE	ENSG00000119912
		CYP1A2	ENSG00000140505
Nateglinide	DB00731	CYP1A2	ENSG00000140505
		ABCC8	ENSG00000006071
		PPARG	ENSG00000132170
		CYP2C9	ENSG00000138109
		CYP3A4	ENSG00000160868
		CYP3A5	ENSG00000106258
		CYP3A7	ENSG00000160870
		PTGS1	ENSG00000095303
		UGT1A9	ENSG00000241119
Insulin Aspart	DB01306	CYP2D6	ENSG00000100197
		INSR	ENSG00000171105
		IGF1R	ENSG00000140443
Insulin Detemir	DB01307	CYP1A2	ENSG00000140505
		INSR	ENSG00000171105
		IGF1R	ENSG00000140443
Saxagliptin	DB06335	CYP1A2	ENSG00000140505
		DPP4	ENSG00000197635
		CYP3A4	ENSG00000160868
Insulin Glulisine	DB01309	CYP3A5	ENSG00000106258
		INSR	ENSG00000171105
		IGF1R	ENSG00000140443
Tolbutamide	DB01124	CYP1A2	ENSG00000140505
		ABCC8	ENSG00000006071
		KCNJ1	ENSG00000151704
		CYP2C9	ENSG00000138109
		CYP2C8	ENSG00000138115
		CYP2C19	ENSG00000165841
Rosiglitazone	DB00412	CYP2C18	ENSG00000108242
		PPARG	ENSG00000132170
		ACSL4	ENSG00000068366
		PPARA	ENSG00000186951
		PPARD	ENSG00000112033
		RXRA	ENSG00000186350
		RXRB	ENSG00000204231
		RXRG	ENSG00000143171
		CYP2C8	ENSG00000138115

		CYP2C9	ENSG00000138109
		PTGS1	ENSG00000095303
		CYP1A2	ENSG00000140505
		CYP3A4	ENSG00000160868
		CYP2B6	ENSG00000197408
		CYP2D6	ENSG00000100197
		CYP2E1	ENSG00000130649
Mitiglinide	DB01252	ABCC8	ENSG0000006071
		PPARG	ENSG00000132170
		UGT1A3	ENSG00000243135
		UGT2B7	ENSG00000171234
Insulin Human	DB00030	INSR	ENSG00000171105
		IGF1R	ENSG00000140443
		CPE	ENSG00000109472
		NOV	NA
		LRP2	ENSG00000081479
		IGFBP7	ENSG00000163453
		IDE	ENSG00000119912
		PCSK2	ENSG00000125851
		PCSK1	ENSG00000175426
		CYP1A2	ENSG00000140505
Insulin Lispro	DB00046	INSR	ENSG00000171105
		IGF1R	ENSG00000140443
		CYP1A2	ENSG00000140505
		IDE	ENSG00000119912
Lixisenatide	DB09265	GLP1R	ENSG00000112164
Metformin	DB00331	PRKAB1	ENSG0000011725
		ETFDH	ENSG00000171503
		GPD1	ENSG00000167588
Lobeglitazone	DB09198	PPARG	ENSG00000132170
		CYP1A2	ENSG00000140505
		CYP2C9	ENSG00000138109
		CYP2C19	ENSG00000165841
		CYP3A4	ENSG00000160868
Managlinat dialanetil	DB05518	FBP1	ENSG00000165140
Levoketoconazole	DB05667	CYP11B1	ENSG00000160882
		CYP51A1	ENSG00000001630
		CYP3A4	ENSG00000160868
		CYP3A5	ENSG00000106258
		CYP51A1	ENSG00000001630
		CYP17A1	ENSG00000148795
		CYP21A2	ENSG00000231852
		CYP11B1	ENSG00000160882
Tesaglitazar	DB06536	PPARA	ENSG00000186951
		PPARG	ENSG00000132170
Ertiprotafib	DB06521	PTPN1	ENSG00000196396
		IKBKB	ENSG00000104365
		PPARA	ENSG00000186951
		PPARG	ENSG00000132170
Glycodiazine	DB01382	KCNJ1	ENSG00000151704
		ABCC8	ENSG0000006071
Muraglitazar	DB06510	PPARA	ENSG00000186951
		PPARG	ENSG00000132170
		CYP1A2	ENSG00000140505
		UGT1A3	ENSG00000243135
		UGT1A1	ENSG00000241635
		CYP2C8	ENSG00000138115
Troglitazone	DB00197	PPARG	ENSG00000132170
		ACSL4	ENSG00000068366
		SERPINE1	ENSG00000106366
		SLC29A1	ENSG00000112759
		ESRRG	ENSG00000196482
		ESRRA	NA

		PPARD	ENSG00000112033
		PPARA	ENSG00000186951
		GSTP1	ENSG00000084207
		CYP3A4	ENSG00000160868
		CYP2C19	ENSG00000165841
		UGT1A1	ENSG00000241635
		CYP2C8	ENSG00000138115
		CYP19A1	ENSG00000137869
		CYP1A1	ENSG00000140465
		CYP2B6	Enzyme
		CYP2C9	ENSG00000138109
		CYP3A5	ENSG00000106258
		CYP3A7	ENSG00000160870
		UGT1A3	ENSG00000243135
		UGT1A4	ENSG00000244474
		UGT1A6	ENSG00000167165
		UGT1A7	ENSG00000244122
		UGT1A8	ENSG00000242366
		UGT1A9	ENSG00000241119
		UGT1A10	ENSG00000242515
		UGT2B7	ENSG00000171234
		UGT2B15	ENSG00000277132
Ertugliflozin	DB11827	SLC5A2	ENSG00000140675
		UGT1A9	ENSG00000241119
		UGT2B7	ENSG00000171234
		UGT1A1	ENSG00000241635
		UGT1A4	ENSG00000244474
Exenatide	DB01276	GLP1R	ENSG00000112164
		DPP4	ENSG00000197635
Naveglitazar	DB12662	PPARG	ENSG00000132170
Alogliptin	DB06203	DPP4	ENSG00000197635
		CYP3A4	ENSG00000160868
		CYP2D6	ENSG00000100197
Liraglutide	DB06655	GLP1R	ENSG00000112164
		DPP4	ENSG00000197635
		MME	ENSG00000196549
Semaglutide	DB13928	GLP1R	ENSG00000112164
		DPP4	ENSG00000197635
		MME	ENSG00000196549
		LPL	ENSG00000175445
		AMY1A	ENSG00000237763
Glimepiride	DB00222	KCNJ11	ENSG00000187486
		KCNJ1	ENSG00000151704
		ABCC8	ENSG00000006071
		CYP2C9	ENSG00000138109
Sarpogrelate	DB12163	HTR2C	ENSG00000147246
		HTR2A	ENSG00000102468
Glyburide	DB01016	ABCC9	ENSG00000069431
		ABCB11	ENSG00000073734
		ABCA1	ENSG00000165029
		CFTR	ENSG00000001626
		CPT1A	ENSG00000110090
		TRPM4	ENSG00000130529
		CYP2C9	ENSG00000138109
		CYP2C19	ENSG00000165841
		CYP3A4	ENSG00000160868
		CYP3A7	ENSG00000160870
		CYP3A5	ENSG00000106258
	DB01120	ABCC8	ENSG00000006071
		VEGFA	ENSG00000112715
		CYP2C9	ENSG00000138109
		CYP2C19	ENSG00000165841
Empagliflozin	DB09038	SLC5A2	ENSG00000140675
		UGT2B7	ENSG00000171234

		UGT1A3	ENSG00000243135
		UGT1A8	ENSG00000242366
		UGT1A9	ENSG00000241119
Glymidine	DB01382	KCNJ1	ENSG00000151704
		ABCC8	ENSG00000006071
Balaglitazone	DB12781	CYP3A4	ENSG00000160868
		CYP2C8	ENSG00000138115
Glibornuride	DB08962	CYP2C9	ENSG00000138109
Rivoglitazone	DB09200	CYP3A4	ENSG00000160868
		CYP2C8	ENSG00000138115
AB192	DB06111	MPO	ENSG00000005381
Lisofylline	DB12406	CYP1A2	ENSG00000140505

Supplementary Tale1. The names of 74 drugs and information on 96 drug target genes

Drug trarget	id.outcome	outcome	tissue	method	nsnp	b	se	pval
CYP2E1	ieu-b-8	epilepsy	Brain_Anterior_cingulate_cortex	Wald ratio	1	-0.079855248	0.026147801	0.00225816
CFTR	ieu-b-8	epilepsy	Brain_Caudate_basal_ganglia	Inverse variance weighted	2	0.079143397	0.027501063	0.004004203
GAA	ieu-b-8	epilepsy	Brain_Cerebellar_Hemisphere	Inverse variance weighted (fixed effects)	5	0.017924063	0.006407333	0.005151101
CYP2D6	ieu-b-8	epilepsy	Brain_Cortex	Inverse variance weighted (fixed effects)	6	-0.015492395	0.005566947	0.005387131
MGAM	ieu-b-8	epilepsy	Brain_Frontal_Cortex	Inverse variance weighted	2	-0.033189999	0.012156427	0.006328768
CYP17A1	ieu-b-8	epilepsy	Brain_Cortex	Wald ratio	1	-0.040868245	0.015014033	0.006488751
ETFDH	ieu-b-8	epilepsy	Brain_Cerebellar_Hemisphere	Inverse variance weighted (fixed effects)	7	0.018642276	0.007145262	0.009079654
NFKB2	ieu-b-8	epilepsy	Brain_Nucleus_accumbens_basal_ganglia	Wald ratio	1	0.109857736	0.042236687	0.009295173
GAA	ieu-b-8	epilepsy	Brain_Frontal_Cortex	Inverse variance weighted (fixed effects)	4	0.028127937	0.011488759	0.014353179
CYP21A2	ieu-b-8	epilepsy	Brain_Cerebellum	Inverse variance weighted	2	0.028507761	0.011902962	0.016619733
FBP1	ieu-b-8	epilepsy	Brain_Hypothalamus	Wald ratio	1	0.030394679	0.012706828	0.01675703
CYP3A5	ieu-b-8	epilepsy	Brain_Nucleus_accumbens_basal_ganglia	Inverse variance weighted	2	-0.037077993	0.015735013	0.018453006
HTR2A	ieu-b-8	epilepsy	Brain_Caudate_basal_ganglia	Wald ratio	1	-0.055011716	0.023349593	0.018472758
SLC5A2	ieu-b-8	epilepsy	Brain_Cerebellar_Hemisphere	Wald ratio	1	-0.053197137	0.022782439	0.019543097
ABCC8	ieu-b-8	epilepsy	Brain_Anterior_cingulate_cortex	Inverse variance weighted (fixed effects)	3	0.041078161	0.017667724	0.020069829
MGAM	ieu-b-8	epilepsy	Brain_Caudate_basal_ganglia	Wald ratio	1	-0.04242295	0.018729773	0.023512632
CYP2D6	ieu-b-8	epilepsy	Brain_Anterior_cingulate_cortex	Inverse variance weighted (fixed effects)	4	-0.01660883	0.007426274	0.025319323
CYP2E1	ieu-b-8	epilepsy	Brain_Cortex	Wald ratio	1	0.034699016	0.015539214	0.025549157
CYP17A1	ieu-b-8	epilepsy	Brain_Frontal_Cortex	Wald ratio	1	-0.042643412	0.019392158	0.027877712
GAA	ieu-b-8	epilepsy	Brain_Cortex	Inverse variance weighted (fixed effects)	6	0.016693594	0.00760106	0.02807626
CYP2D6	ieu-b-8	epilepsy	Brain_Nucleus_accumbens_basal_ganglia	Inverse variance weighted (fixed effects)	4	-0.017242958	0.007852281	0.028097872
GAA	ieu-b-8	epilepsy	Brain_Amygdala	Inverse variance weighted	2	0.026280734	0.012045202	0.029121158
IGF1R	ieu-b-8	epilepsy	Brain_Cerebellar_Hemisphere	Wald ratio	1	-0.0563649	0.026010552	0.030234754
CYP2E1	ieu-b-8	epilepsy	Brain_Caudate_basal_ganglia	Wald ratio	1	0.051453394	0.024201978	0.033503299
KCNJ11	ieu-b-8	epilepsy	Brain_Caudate_basal_ganglia	Wald ratio	1	0.042721232	0.020142102	0.0339225
MGAM	ieu-b-8	epilepsy	Brain_Putamen_basal_ganglia	Wald ratio	1	-0.041252116	0.019569307	0.035030916
CYP2D6	ieu-b-8	epilepsy	Brain_Cerebellum	Inverse variance weighted (fixed effects)	8	-0.009752104	0.004791349	0.041815024
LPL	ieu-b-8	epilepsy	Brain_Cerebellum	Wald ratio	1	-0.078744183	0.038905217	0.04297009
CYP2D6	ieu-b-8	epilepsy	Brain_Caudate_basal_ganglia	Inverse variance weighted (fixed effects)	3	-0.027489153	0.013629994	0.043714995
MGAM	ieu-b-8	epilepsy	Brain_Cerebellar_Hemisphere	Inverse variance weighted	2	-0.021391146	0.010662218	0.044828871
CYP3A5	ieu-b-8	epilepsy	Brain_Cerebellum	Inverse variance weighted (fixed effects)	4	-0.02706016	0.013490931	0.044877189
GAA	ieu-b-8	epilepsy	Brain_Cerebellum	Inverse variance weighted (fixed effects)	5	0.010929471	0.00546373	0.04546055
PPARG	ieu-b-8	epilepsy	Brain_Cerebellum	Inverse variance weighted (fixed effects)	7	-0.009173489	0.004635833	0.047836032
CYP2D6	ieu-b-8	epilepsy	Brain_Spinal_cord_cervical	Inverse variance weighted	2	-0.013564195	0.006886384	0.048871344

Supplementary Table 2. MR estimation of antiglycemic drug target genes with the International League Against Epilepsy GWAS during the preliminary analysis phase. “Drug trarget” is the exposure in the MR study, “epilepsy” is the outcome in the MR study, “tissue” is the location of antiglycemic drug target gene expression, “nsnp” refers to the number of instrumental variables used, “method” refers to the meta method we used, “beta” refers to the effect size in MR analysis, “se” refers to the standard error in MR analysis, and “P” is the statistical significance of MR analysis.

