

Gene A	Gene B	p value	Count patient carriers	Count control carriers	Patient	Variant A cDNA	Variant A protein	Variant B cDNA	Variant B protein	Epilepsy type	Seizure type	MRI	EEG
MACF1	RELN	0.001	6	0	#17	NM_012090.5: c.2444G>T	NP_036222.3: p.(C815F)	NM_005045.4: c.5108C>G	NP_005036.2: p.(P1703R)	GGE	Generalized tonic-clonic seizures	Normal	Generalized spike waves
					#18	NM_012090.5: c.2444G>T	NP_036222.3: p.(C815F)	NM_005045.4: c.7438G>A/ c.19G>T	NP_005036.2: p.(G2480S)/ p.(A7S)	NAFE	Focal seizures with impaired consciousness	Normal	Left temporal spike waves
					#19	NM_012090.5: c.1163G>A	NP_036222.3: p.(G388D)	NM_005045.4: c.9415G>A	NP_005036.2: p.(V3139I)	NAFE	Focal seizures with preserved and impaired consciousness, focal-to-bilateral tonic-clonic seizures	Mild ventricular dilatation, right frontal porencephalic cyst	Right temporal sharp waves
					#20	NM_012090.5: c.16131T>G/ c.8987T>A	NP_036222.3: p.(F5377L)/ p.(V2996E)	NM_005045.4: c.7114G>A	NP_005036.2: p.(V2372M)	GGE	Myoclonic seizures, generalized tonic-clonic seizures	NA	Generalized epileptiform discharges
					#21	NM_012090.5: c.16131T>G/ c.8987T>A	NP_036222.3: p.(F5377L)/ p.(V2996E)	NM_005045.4: c.6353C>T	NP_005036.2: p.(P2118L)	NAFE	Focal seizures	Normal	Left temporal epileptiform discharges
DMXL2	MACF1	0.014	5	1	#22	NM_012090.5: c.15824G>A	NP_036222.3: p.(R5275H)	NM_005045.4: c.9751G>A	NP_005036.2: p.(E3251K)	NAFE	Focal seizures with impaired consciousness	Cerebellar atrophy	Bilateral temporal spikes
					#23	NM_001378457.1: c.23C>G	NP_001365386.1: p.(T8S)	NM_012090.5: c.8940A>C	NP_036222.3: p.(Q2980H)	DEE	Absence, atonic and myoclonic seizures	Normal	Generalized spike waves and slow waves
					#24	NM_001378457.1: c.23C>G	NP_001365386.1: p.(T8S)	NM_012090.5: c.16131T>G	NP_036222.3: p.(F5377L)	NAFE	Focal-to-bilateral tonic-clonic seizures	Right temporal hippocampal sclerosis	Right temporal spikes
					#11	NM_001378457.1: c.2512G>A	NP_001365386.1: p.(A838T)	NM_012090.5: c.7867A>G	NP_036222.3: p.(S2623G)	NAFE	Focal seizures with impaired consciousness, and nocturnal hypermotor seizures	Normal	Right temporal spikes, spike-waves and slow waves
					#25	NM_001378457.1: c.6376C>T	NP_001365386.1: p.(R2126C)	NM_012090.5: c.2444G>T	NP_036222.3: p.(C815F)	NAFE	Focal seizures, focal-to-bilateral tonic-clonic seizures	Normal	Normal
COQ9	MMACHC	0.031	3	0	#26	NM_001378457.1: c.7186C>A	NP_001365386.1: p.(P2396T)	NM_012090.5: c.4009C>G	NP_036222.3: p.(Q1337E)	GGE	Absence seizures, generalized tonic-clonic seizures	Mild left hippocampal malrotation	Generalized spike waves
					#27	NM_020312.4: c.*622A>G	NP_064708.1: p.?	NM_015506.3: c.181C>T	NP_056321.2: p.(R61W)	GGE	Myoclonic seizures, generalized tonic-clonic seizures	Normal	Generalized spike waves and slow waves
					#28	NM_020312.4: c.892G>C	NP_064708.1: p.(V298L)	NM_015506.3: c.67G>T	NP_056321.2: p.(V23F)	GGE	Generalized tonic-clonic seizures	Left hippocampal malrotation	Normal
					#29	NM_020312.4: c.835G>A	NP_064708.1: p.(D279N)	NM_015506.3: c.*2085C>T	NP_056321.2: p.?	NAFE	Myoclonic seizures, generalized tonic-clonic seizures	Normal	NA
PCNT	STIL	0.031	3	0	#21	NM_006031.6: c.5582C>T	NP_006022.3: p.(A1861V)	NM_001048166.1: c.200G>A	NP_001041631.1: p.(R67H)	NAFE	Focal seizures	Normal	Left temporal epileptiform discharges
					#30	NM_006031.6: c.4675A>T	NP_006022.3: p.(M1559L)	NM_001048166.1: c.1136C>T	NP_001041631.1: p.(S379F)	NAFE	Focal seizures with preserved and impaired consciousness, focal-to-bilateral tonic-clonic seizures	Left temporal hippocampal sclerosis and abnormal gyration	Left temporal epileptiform discharges
					#31	NM_006031.6: c.3446A>G	NP_006022.3: p.(N1149S)	NM_001048166.1: c.3157G>A	NP_001041631.1: p.(G1053S)	GGE	Absence, myoclonic and generalized tonic-clonic seizures	Normal	Generalized spike waves

CACNA1H	KLHL41	0.031	3	0	#32	NM_021098.3: c.347C>T	NP_066921.2: p.(T116I)	NM_006063.3: c.1279T>C	NP_006054.2: p.(W427R)	NAFE	Focal seizures with impaired consciousness	Normal	Left hemispheric sharp waves
					#33	NM_021098.3: c.307G>A	NP_066921.2: p.(E103K)	NM_006063.3: c.398G>A	NP_006054.2: p.(G133D)	NAFE	Focal seizures with impaired consciousness, focal-to-bilateral tonic- clonic seizures	Left parietal small periventricular hypersignal	Frontal spike waves
					#34	NM_021098.3: c.212C>G	NP_066921.2: p.(P71R)	NM_006063.3: c.863T>G	NP_006054.2: p.(L288R)	GGE	Generalized tonic-clonic seizures	NA	Generalized spike waves
PCCB	PLCB1	0.032	3	0	#35	NM_001178014.2: c.932G>A	NP_001171485.1: p.(C311Y)	NM_015192.4: c.1469A>G	NP_056007.1: p.(Y490C)	NAFE	Focal-to-bilateral tonic- clonic seizures	NA	NA
					#36	NM_001178014.2: c.971C>T	NP_001171485.1: p.(T324I)	NM_015192.4: c.3550C>T	NP_056007.1: p.(L1184F)	NAFE	Focal seizures with preserved and impaired consciousness, focal-to- bilateral tonic-clonic seizures	Left temporal hippocampal sclerosis	NA
HADH	KMT2D	0.035	3	0	#9	NM_001178014.2: c.655C>T	NP_001171485.1: p.(P219S)	NM_015192.4: c.1982A>G	NP_056007.1: p.(H661R)	DEE	Lennox-Gastaut syndrome, with spasms, tonic and tonic-clonic seizures	Normal	Generalized epileptiform discharges, frontal slow waves
					#37	NM_005327.7: c.275T>G	NP_005318.6: p.(F92C)	NM_003482.4: c.4020+13C>G	NP_003473.3: p.?	NAFE	Focal seizures with impaired consciousness	NA	Right temporal spikes
					#38	NM_005327.7: c.275T>G	NP_005318.6: p.(F92C)	NM_003482.4: c.6811C>T	NP_003473.3: p.(P2271S)	NAFE	Atonic seizures, focal seizures with impaired consciousness	Normal	Generalized spike waves and slow waves
MACF1	PCNT	0.036	9	6	#39	NM_005327.7: c.456G>T	NP_005318.6: p.(Q152H)	NM_003482.4: c.15797G>A	NP_003473.3: p.(R5266H)	GGE	Absence and myoclonic seizures	NA	Generalized spike waves
					#20	NM_012090.5: c.16131T>G/ c.8987T>A	NP_036222.3: p.(F5377L)/ p.(V2996E)	NM_006031.6: c.931G>A	NP_006022.3: p.(A311T)	GGE	Myoclonic seizures, generalized tonic-clonic seizures	NA	Generalized epileptiform discharges
					#21	NM_012090.5: c.16131T>G/ c.8987T>A	NP_036222.3: p.(F5377L)/ p.(V2996E)	NM_006031.6: c.5582C>T	NP_006022.3: p.(A1861V)	NAFE	Focal seizures	Normal	Left temporal epileptiform discharges
					#40	NM_012090.5: c.8940A>C	NP_036222.3: p.(Q2980H)	NM_006031.6: c.4675A>T	NP_006022.3: p.(M1559L)	NAFE	Focal seizures with impaired consciousness, focal-to-bilateral tonic- clonic seizures	Normal	NA
					#41	NM_012090.5: c.3731G>T/ c.8941G>T	NP_036222.3: p.(R1244L)/ p.(A2981S)	NM_006031.6: c.9707G>A	NP_006022.3: p.(R3236Q)	NAFE	Focal seizures with impaired consciousness	Left temporal hippocampal sclerosis, cerebellar atrophy	Left temporal sharp waves and slow waves
					#42	NM_012090.5: c.2444G>T	NP_036222.3: p.(C815F)	NM_006031.6: c.9707G>A	NP_006022.3: p.(R3236Q)	NAFE	Focal seizures with impaired consciousness, focal-to-bilateral tonic- clonic seizures	Normal	Right temporal sharp waves
					#18	NM_012090.5: c.2444G>T	NP_036222.3: p.(C815F)	NM_006031.6: c.9707G>A	NP_006022.3: p.(R3236Q)	NAFE	Focal seizures with impaired consciousness	Normal	Left temporal spike waves
					#17	NM_012090.5: c.2444G>T	NP_036222.3: p.(C815F)	NM_006031.6: c.6884C>T/ c.9273+4G>A	NP_006022.3: p.(P2295L)/ p.?	GGE	Generalized tonic-clonic seizures	Normal	Generalized spike waves
					#43	NM_012090.5: c.2444G>T	NP_036222.3: p.(C815F)	NM_006031.6: c.8924T>C/ c.6986C>G	NP_006022.3: p.(L2975P)/ p.(P2329R)	NAFE	Focal seizures with impaired consciousness, focal-to-bilateral tonic- clonic seizures	Normal	Left frontal spike waves and slow waves
					#44	NM_001394062.1: c.17566-6A>T	NP_001380991.1: p.?	NM_006031.6: c.8924T>C/ c.6986C>G	NP_006022.3: p.(L2975P)/ p.(P2329R)	NAFE	Focal seizures with impaired consciousness, focal-to-bilateral tonic- clonic seizures	Cerebral atrophy, periventricular leucoencephalopathy	Right temporal slow waves

MMACHC	MTHFR	0.036	3	0	#27	NM_015506.3: c.181C>T	NP_056321.2: p.(R61W)	NM_005957.5: c.3673+141C>T	NP_005948.3: p.?	GGE	Myoclonic seizures, generalized tonic-clonic seizures	Normal	Generalized spike waves and slow waves
					#28	NM_015506.3: c.67G>T	NP_056321.2: p.(V23F)	NM_005957.5: c.3848+39G>A	NP_005948.3: p.?	GGE	Generalized tonic-clonic seizures	Left hippocampal malrotation	Normal
					#45	NM_015506.3: c.440G>C/ c.*2085C>T	NP_056321.2: p.(G147A)/ p.?	NM_005957.5: c.3673+159C>G	NP_005948.3: p.?	GGE	Myoclonic seizures, generalized tonic-clonic seizures	Normal	Generalized sharp waves
CACNA1G	SCN1B	0.039	3	0	#46	NM_018896.5: c.1367G>A	NP_061496.2: p.(R456Q)	NM_001037.5: c.287G>A	NP_001028.1: p.(R96Q)	GGE	Absence and generalized tonic-clonic seizures	NA	Generalized spike waves and slow waves
					#47	NM_018896.5: c.1367G>A	NP_061496.2: p.(R456Q)	NM_199037.5: c.641G>A/ c.641G>A	NP_950238.1: p.(R214Q)/ p.(R214Q)	NAFE	Focal seizures with impaired consciousness, focal-to-bilateral tonic- clonic seizures	Normal	Left temporal spike waves and slow waves
					#48	NM_018896.5: c.1367G>A	NP_061496.2: p.(R456Q)	NM_001037.5: c.448+605G>A	NP_001028.1: p.?	NAFE	Focal seizures with preserved and impaired consciousness, focal-to- bilateral tonic-clonic seizures	Bilateral mineralization of basal ganglia	Normal
FLNA	PTEN	0.042	3	0	#49	NM_001110556.2: c.4232C>T	NP_001104026.1: p.(S1411L)	NM_000314.8: c.1130A>T	NP_000305.3: p.(Y377F)	GGE	Generalized tonic-clonic seizures	Normal	Generalized spike waves and slow waves
					#50	NM_001110556.2: c.5830C>T	NP_001104026.1: p.(P1944S)	NM_001304717.5: c.382C>T	NP_001291646.4: p.(Q128*)	NAFE	Focal seizures with impaired consciousness, focal-to-bilateral tonic- clonic seizures	Normal	Right temporal spike waves
					#51	NM_001110556.2: c.6871G>A	NP_001104026.1: p.(G2291S)	NM_000314.8: c.*75T>A	NP_000305.3: p.?	NAFE	Focal seizures with preserved and impaired consciousness	Normal	Right temporal sharp waves
FLNA	PTCH1	0.045	3	0	#52	NM_001110556.2: c.2725G>A/ c.2725G>A	NP_001104026.1: p.(V909I)/ p.(V909I)	NM_000264.5: c.4240G>A	NP_000255.2: p.(V1414M)	NAFE	Focal seizures with impaired consciousness	Diffuse supratentorial white matter lesions	Left temporal spikes
					#49	NM_001110556.2: c.4232C>T	NP_001104026.1: p.(S1411L)	NM_000264.5: c.3247G>A	NP_000255.2: p.(V1083M)	GGE	Generalized tonic-clonic seizures	Normal	Generalized spike waves and slow waves
					#50	NM_001110556.2: c.5830C>T	NP_001104026.1: p.(P1944S)	NM_000264.5: c.109G>A	NP_000255.2: p.(G37R)	NAFE	Focal seizures with impaired consciousness, focal-to-bilateral tonic- clonic seizures	Normal	Right temporal spike waves
CDK5RAP2	PCNT	0.018	0	10	C1	NM_018249.6: c.*47C>T	NP_060719.4: p.(=)	NM_006031.6: c.4345C>G	NP_006022.3: p.(Q1449E)	None			
					C2	NM_018249.6: c.5452-8C>T	NP_060719.4: p.?	NM_006031.6: c.8702C>T	NP_006022.3: p.(P2901L)	None			
					C3	NM_018249.6: c.412G>A	NP_060719.4: p.(G138S)	NM_006031.6: c.4285C>T	NP_006022.3: p.(R1429C)	None			
					C4	NM_018249.6: c.901G>A	NP_060719.4: p.(E301K)	NM_006031.6: c.9800G>A	NP_006022.3: p.(R3267H)	None			
					C5	NM_018249.6: c.2655C>G	NP_060719.4: p.(F885L)	NM_006031.6: c.8231A>T	NP_006022.3: p.(Q2744L)	None			
					C6	NM_018249.6: c.2809C>T	NP_060719.4: p.(R937C)	NM_006031.6: c.2247A>C/c.5710G>A	NP_006022.3: p.(E749D)/p.(A1904T)	None			
					C7	NM_018249.6: c.-159G>A	NP_060719.4: p.(=)	NM_006031.6: c.8671G>A	NP_006022.3: p.(A2891T)	None			
					C8	NM_018249.6: c.4222C>G	NP_060719.4: p.(R1408G)	NM_006031.6: c.1457-8T>C	NP_006022.3: p.?	None			

C9	NM_018249.6: c.3062C>G	NP_060719.4: p.(P1021R)	NM_006031.6: c.8753G>A	NP_006022.3: p.(R2918Q)	None
C10	NM_018249.6: c.2939C>T	NP_060719.4: p.(T980I)	NM_006031.6: c.9556C>T/c.1370A>G	NP_006022.3: p.(R3186W)/p.(E457G)	None

Table S2. Gene combinations. Selection of 12 biologically relevant gene pairs that were significantly more frequent in cases compared to controls. They were present in at least three more cases than controls. For each case, the variants in the two genes and the phenotype of the patient are detailed. The thirteenth gene pair is the unique biologically relevant combination that was significantly more frequent in controls compared to cases. DEE, Developmental and Epileptic Encephalopathy. GGE, Generalized Genetic Epilepsy. NA, not available. NAFE, Non Acquired Focal Epilepsy.