6. Overview of previously described candidate modifier genes and variants in them detected in the current cohort

Previously described candidate gene	**Described effect**	**Reference**	**Number of variants (CADD[a] >20) in current cohort**				
			Variants in only mild or severe member of families with varying phenotypes (MAF<0.01, CADD>20)	*Type A variants (MAF[b]<0.01, CADD>20)*		*Type D variants (MAF<0.5, all CADD scores)*	
				Mild patients (n)	Severe patients (n)	Mild patients (n)	Severe patients (n)
SCN9A	Pathogenic variants present in multipe Dravet syndrome patients	Singh 2009		1	2	2	3
SCN8A	SCN8A pathogenic variants rescue SCN1A-phenotype in mice; increased resistance for induces seizures in mice with GEFS+ variants	Martin, 2007; Hawkins, 2012		1		1	1
HLF	Decreased survival in HLF/SCN1A double knockout mice	Hawkins, 2016					
POLG	POLG variants may increase susceptibility to focal brain injury during prolonged seizures in Dravet syndrome	Gaily,2013			1		4
CACNB4	Pathogenic variant in Dravet syndrome patient who died after status epilepticus	Ohmori, 2008					
CACNA1G	Decreased Cacna1g expression led to partial amelioration in SCN1A+/− mice	Calhoun, 2017			1	2	2
CACNA1A	More severe phenotype in Dravet syndrome patients who also have CACNA1A variants	Ohmori, 2013			1		3

GABRA2	Potential candidate gene at locus linked to premature lethality in Scn1a+/− mice	Miller, 2014					
GABRG3	" "	Miller, 2014				1	
GABRB3	" "	Miller, 2014					
GABRA6	" "	Miller, 2014		1		2	2
GABRB2	" "	Miller, 2014					1
CACNA1A	" "	Miller, 2014					
CACNA2D1	" "	Miller, 2014					1
CLCN3	" "	Miller, 2014					
KCNJ11	" "	Miller, 2014				1	
ATP1A3	" "	Miller, 2014			1		2
LGI2	" "	Miller, 2014					2
MAPK10	" "	Miller, 2014					
RELN	" "	Miller, 2014					3
SLC7A10	" "	Miller, 2014				1	
KCNQ2	Variants present in 3/12 severe Dravet syndrome patients, not in mild patients; More severe phenotype in GEFS+ mice that also carry KCNQ2 variant	Hammer, 2017; Hakwins, 2012				1	3
SCN2A	More severe phenotype in GEFS+ mice that also carry SCN2A variant	Hawkins, 2012			1		1
Top ranking EE genes in common epilepsy							
DEPDC5	Enriched in common epilepsies	Epi4K consortium, 2017	2 variants in more severe brother of family 3; both are however mildly affected			4	5
LGI1	" "	Epi4K consortium, 2017					
PCDH19	" "	Epi4K consortium,					

		2017					
GRIN2A	" "	Epi4K consortium, 2017					2
KCNA2	" "	Epi4K consortium, 2017				2	1
GABRB3	" "	Epi4K consortium, 2017					
GABRA1	" "	Epi4K consortium, 2017					
KCNQ2	Enriched in common epilepsies	Epi4K consortium, 2017				1	3
GABRG2	Enriched in common epilepsies	Epi4K consortium, 2017					
SCN1B	" "	Epi4K consortium, 2017					
SLC6A1	" "	Epi4K consortium, 2017	1 variant in mildly affected grandmother of Dravet syndrome patients (family 6)				
EEF1A2	" "	Epi4K consortium, 2017					

[a] PHRED-scaled CADD (Combined Annotation Dependent Depletion). A score of >20 represents the top 1% deleterious substitutions in the human genome.

[b]Minor allele frequency; only variants with a frequency below this threshold in both the exomes and genomes in the gnomAD database are included.