Supplementary Table 1: Paralogue annotation for missense variants, identified in CPVT cohort, that have been previously or subsequently been reported to be associated with CPVT.

RYR2 variant		Region	Cases (n=155)	Exon	Paralogue	Paralogue mutation	Paralogue disease	Consensus
CDS	Protein							
c.7159G>A	p.A2387T	Central hotspot	3	47	RYR1	A2421P	Congenital myopathy with cores	9
c.7202G>A	p.R2401H	Central hotspot	1	47	RYR1	R2435H	Central core disease	9
					RYR1	R2435L	Central core disease	9
c.7207G>A	p.A2403T	Central hotspot	1	47	RYR1	A2437V	Malignant hyperthermia	9
c.14011G>C	p.G4671R	Channel hotspot	1	97	RYR1	G4743D	Multiminicore disease	9
c.14311G>A	p.V4771I	Channel hotspot	2	100	RYR1	V4842M	Congenital myopathy with cores	9

Supplementary Table 2: Paralogue annotations for missense variants, identified in BrS patients, that have previously/subsequently been reported as pathogenic.

SCN5A variant		Region	Cases (n=2111)	Exon	Paralogue	Paralogue variant	Paralogue disease	Consensus
CDS	Protein							
c.311G>A	p.R104Q	N-terminus	3	3	SCN1A	R101W	Myoclonic epilepsy of infancy	7
					SCN1A	R101Q	Myoclonic epilepsy of infancy	7
c.310C>T	p.R104W	N-terminus	2	3	SCN1A	R101W	Myoclonic epilepsy of infancy	7
					SCN1A	R101Q	Myoclonic epilepsy of infancy	7
c.361C>T	p.R121W	N-terminus	1	3	SCN1A	R118S	Myoclonic epilepsy of infancy	9
c.665G>A	p.R222Q	TM domain 1	1	6	SCN4A	R222W	Hypokalaemic periodic paralysis	9
c.673C>T	p.R225W	TM domain 1	3	6	SCN2A	R223Q	Neonatal-infantile seizures	9
					SCN4A	R225W	Non-dystrophic myotonia	9
c.677C>T	p.A226V	TM domain 1	2	6	SCN1A	A223E	Dravet syndrome	9
c.1066G>A	p.D356N	TM domain 1	8	9	SCN1A	D366E	Myoclonic epilepsy of infancy	9
c.1099C>T	p.R367C	TM domain 1	2	9	SCN1A	R377Q	Generalized epilepsy with febrile seizures	9
					SCN1A	R377L	Dravet syndrome	9
c.1100G>A	p.R367H	TM domain 1	6	9	SCN1A	R377Q	Generalized epilepsy with febrile seizures	9
					SCN1A	R377L	Dravet syndrome	9
c.1106T>A	p.M369K	TM domain 1	1	9	SCN1A	M379R	Dravet syndrome	9
c.2314G>A	p.D772N	TM Domain 2	1	15	CACNA1H	G848S	Childhood absence epilepsy	9
c.2423G>C	p.R808P	TM Domain 2	1	15	SCN1A	R859C	Generalized epilepsy with febrile seizures	9
					SCN4A	R669H	Hypokalaemic periodic paralysis	9
					CACNA1S	R528G	Hypokalaemic periodic paralysis	9
					CACNA1S	R528H	Hypokalaemic periodic paralysis	9
					CACNA1A	R583Q	Hemiplegic migraine and ataxia	9

					SCN1A	R859H	Generalized epilepsy with febrile seizures plus	9
c.2516T>C	p.L839P	TM Domain 2	1	16	SCN1A	L890P	Dravet syndrome C ?	9
c.2632C>T	p.R878C	TM Domain 2	1	16	SCN1A	R931C	Myoclonic epilepsy of infancy	8
					SCN9A	R896Q	Congenital indifference to pain	8
					SCN1A	R931H	Epilepsy ?	8
c.3673G>A	p.E1225K	TM Domain 3	4	21	SCN1A	E1238D	Myoclonic epilepsy of infancy	9
c.3694C>T	p.R1232W	TM Domain 3	3	21	SCN1A	R1245Q	Myoclonic epilepsy of infancy	7
c.3784G>A	p.G1262S	TM Domain 3	1	21	SCN1A	G1275V	Dravet syndrome	9
c.3823G>A	p.D1275N	TM Domain 3	3	21	CACNA1F	D944Y	Night blindness, congenital stationary, incomplete	9
					SCN1A	D1288N	Dravet syndrome C ?	9
c.3995C>T	p.P1332L	TM Domain 3	1	23	SCN4A	P1158S	Hypokalaemic periodic paralysis	9
					SCN9A	P1308L	Erythermalgia, primary	9
c.4018G>A	p.V1340I	TM Domain 3	1	23	SCN1A	V1353L	Generalized epilepsy with febrile seizures plus	9
c.4145G>T	p.S1382I	TM Domain 3	1	23	SCN1A	T1394I	Dravet syndrome C ?	4
c.4313C>T	p.P1438L	TM Domain 3	1	25	SCN1A	P1451L	Myoclonic epilepsy of infancy	9
					SCN1A	P1451S	Dravet syndrome C ?	9
c.4501C>G	p.L1501V	Interdomain Linker III-IV	1	26	SCN1A	L1514S	Dravet syndrome	2
c.4868G>A	p.R1623Q	TM Domain 4	1	28	SCN1A	R1636Q	Lennox-Gastaut syndrome	6
					SCN4A	R1448S	Paramyotonia congenita	6
					SCN4A	R1448C	Paramyotonia congenita	6
					SCN4A	R1448H	Paramyotonia congenita	6
					SCN4A	R1448P	Myotonia	6
					SCN4A	R1448L	Paramyotonia congenita	6
					CACNA1F	R1296S	Night blindness, congenital stationary, incomplete	6

					CACNA1A	R1662H	Episodic ataxia 2	6
c.4978A>G	p.I1660V	TM Domain 4	5	28	CACNA1A	V1696I	Hemiplegic migraine	9
					CACNA1A	V1696F	Hemipl. migraine/alternating hemipl. of childhood	9
					SCN1A	I1673T	Dravet syndrome C ?	9
c.5218G>A	p.G1740R	TM Domain 4	1	28	SCN1A	G1754R	Dravet syndrome	3