Table Supplement 2. Summary of $Na_v1.5$ phosphorylation sites identified in the present and previous studies.

Phosphorylation site (mouse sequence)	Previous MS identification(s)	Kinase	Genetic variant(s) in the general population (human sequence)	Genetic variant(s) in cardiac arrhythmias (human sequence)	Reference(s)
S11	Herren et al, 2015		S11R (MAF=0.000007)		
S12	Herren et al, 2015				
T17	Herren et al, 2015		F16L (MAF=0.000004) R18W (MAF=0.00009) R18Q (MAF=0.00004)	F16L (CCD) R18W or Q (LQT3) R18Q (Br)	Denham et al, 2019 Zimmer et al, 2008 Kapplinger et al, 2009
S20	Herren et al, 2015		S20F (MAF=0.000004)		
S36	Marionneau et al, 2012 Burel et al, 2017	PKA	S36L (MAF=0.000007)	G35S (Br)	Zimmer et al, 2008
S39	Marionneau et al, 2012 Burel et al, 2017				
S42	Marionneau et al, 2012 Herren et al, 2015 Burel et al, 2017			R43Q (LQT3)	Kapplinger et al, 2009
S61	Herren et al, 2015				
Y68		Fyn	Y68C (MAF=0.000007)		Iqbal et al, 2018
Y87		Fyn			Iqbal et al, 2018
T101		AMPK	T101I (MAF=0.000004)		Liu et al, 2019
Y112		Fyn	Y112C (MAF=0.000004)		Iqbal et al, 2018
T455	Herren et al, 2015				
S457	Marionneau et al, 2012 Herren et al, 2015 Burel et al, 2017				
S459			S459G (MAF=0.000004) S459T (MAF=0.000007)		
S460	Marionneau et al, 2012 Herren et al, 2015 Burel et al, 2017				
S464	Herren et al, 2015				
S471 (only in human)	Herren et al, 2015				
S483	Marionneau et al, 2012 Herren et al, 2015 Burel et al, 2017				
S484	Marionneau et al, 2012 Herren et al, 2015 Burel et al, 2017	SGK3			
T486	Burel et al, 2017		T486A (MAF=0.000004) T486S (MAF=0.000004)		
S497	Marionneau et al, 2012 Herren et al, 2015 Burel et al, 2017		S497C (MAF=0.000007)		
S499	Herren et al, 2015 Burel et al, 2017		S499L (MAF=0.000007)		
S510	Marionneau et al, 2012 Herren et al, 2015 Burel et al, 2017				
S516	Herren et al, 2015 Burel et al, 2017	CaMKII			
S525	Marionneau et al, 2012 Burel et al, 2017	PKA	S525G (MAF=0.000007)	R526H (BrS)	Denham et al, 2019
S528	Herren et al, 2015	PKA	S528R (MAF=0.000008)		Marionneau and Abriel, 2015
S539	Herren et al, 2015 Burel et al, 2017				
S549					
S560					
T570 (only in human)	Herren et al, 2015		T570N (MAF=0.000004)	R569W (LQT3)	Kapplinger et al, 2009
S571	Marionneau et al, 2012 Herren et al, 2015 Burel et al, 2017	CaMKII	S571I (MAF=0.00003)	S571I (LQT3) A572D, S or V (CCD, LQT3)	Kapplinger et al, 2009 Denham et al, 2019 Zimmer et al, 2008
S577 (only in human)	Herren et al, 2015		S577N (MAF=0.000004)		
S581			S581L (MAF=0.000007)		
S593				N592K (BrS)	Juang et al, 2015
T594		CaMKII			Marionneau and Abriel, 2015

Table Supplement 2 (continues). Summary of $Na_V1.5$ phosphorylation sites identified in the present and previous studies.

Phosphorylation site (mouse sequence)	Previous MS identification(s)	Kinase	Genetic variant(s) in the general population (human sequence)	Genetic variant(s) in cardiac arrhythmias (human sequence)	Reference(s)
S664	Marionneau et al, 2012 Herren et al, 2015 Burel et al, 2017	SGK3	S664G (MAF=0.000007)		
S667	Marionneau et al, 2012 Herren et al, 2015		S667N (MAF=0.000007)		
T670					
S671			S671C (MAF=0.000004) S671R (MAF=0.000007)		
T999					
S1001					
S1005	Herren et al, 2015			C1004R (LQT3)	Kapplinger et al, 2009
S1012	Burel et al, 2017				
S1056 and/or T1058			T1056A (MAF=0.000004)	E1053K (BrS, LQT3) D1055G (BrS)	Denham et al, 2019 Kapplinger et al, 2009
T1105					
S1107			S1104Y (MAF=0.000007)		
S1138			S1135I (MAF=0.00003)		
Y1498		Fyn		Y1495S (LQT3)	Marionneau and Abriel, 2015 Kapplinger et al, 2009
S1506	Herren et al, 2015	PKC	S1503Y (MAF=0.000004)		Ahern et al, 2005
T1809					
Y1814		Fyn			Iqbal et al, 2018
S1868	Herren et al, 2015				
S1888	Herren et al, 2015 Burel et al, 2017				
Y1892		Fyn	Y1889C (MAF=0.0001)		Iqbal et al, 2018
S1923	Herren et al, 2015		S1919C (MAF=0.00003)		
S1928	Herren et al, 2015		S1924F (MAF=0.000004) S1924A (MAF=0.000007)	A1923T (BrS)	Denham et al, 2019
S1937	Herren et al, 2015 Burel et al, 2017			G1934S (BrS)	Denham et al, 2019
S1938	Burel et al, 2017			G1934S (BrS)	Denham et al, 2019
S1941	Herren et al, 2015		S1936A (MAF=0.000004)	S1936F (BrS) E1937K (BrS)	Denham et al, 2019
S1964					
S1969			S1964N (MAF=0.000004) S1664G (MAF=0.000004)	S1963F (BrS)	Denham et al, 2019
S1971				I1967S (BrS)	Denham et al, 2019
S1973					
S1974			S1969-S1971del (MAF=0.000007)		
S1989	Burel et al, 2017				
S2002	Herren et al, 2015				
S2011	Herren et al, 2015			P2005A (LQT3, CCD)	Remme et al, 2008

The phosphorylation sites and genetic variants are numbered on the mouse (Reference sequence NP_001240789.1) and human (NP_000326.2) $Na_V1.5$ sequences, respectively. The phosphorylation sites highlighted in grey are not detected in the present study. Out of the 42 phosphorylation sites identified, 19 are novel, and 23 were previously identified in mass spectrometric (MS) analyses of native mouse ventricular (Marionneau *et al*, 2012, PMID: 23092124; Burel *et al*, 2017, PMID: 28882890) or heterologously-expressed human $Na_V1.5$ channels (Herren *et al*, 2015, PMID: 25815641), and/or in *in silico* and/or *in vitro* analyses (reviewed in Marionneau and Abriel, 2015, PMID: 25748040; Iqbal et al, 2018, PMID: 29734505; Liu et al, 2019, PMID: 30759345). Three sites, at positions S471, T570 and S577 are present in the human $Na_V1.5$ sequence, but are not conserved in mouse. The genetic variants matching to the phosphorylation sites and causing missense or inframe deletion (del) mutations in the general population were provided in the v3 and v2 short variant data sets of the gnomAD database (Genome Aggregation Database). The Minor Allele Frequency (MAF) is reported in parentheses. The genetic variants in Brugada Syndrome (BrS), Long-QT syndrome type 3 (LQT3) and Cardiac Conduction Defect (CCD) were extended to the amino acids directly adjacent to the phosphorylation sites identified (Zimmer *et al*, 2008, PMID: 19027780; Remme *et al*, 2008, PMID: 18436145; Kapplinger *et al*, 2009, PMID: 19716085; Juang *et al*, 2015, PMID: 26154754; and Denham *et al*, 2019, PMID: 30203441). Abbreviations: PKA, Protein Kinase A; AMPK, Adenosine Monophosphate-activated Protein Kinase; SGK3, Serum- and Glucocorticoid-inducible Kinase 3; CaMKII, Ca^{2+}/Calmodulin-dependent protein Kinase II; PKC, Protein Kinase C.