Update Genetic Congenital SQTS variants 2021

Dr. Andrés R. Pérez Riera

SQT Variants	QTc duration	Gene symbol and effect	Author
SQT 1	260-280 ms	hERG (human ether-a-go-go-related gene KCNH2) (I_{ks}) Gain Of Function mutation	Brugada R et al. Circulation. **2004** Jan 6;109(1):30-5
SQT 2		e (I_{k1}) Gain-Of Function mutation GOF KCNH2 Potassium Voltage-Gated Channel Subfamily H Member 2 (hERG or Kv11.1) SQTS Prevalence 15%	Bellocq C, et al. Circulation. **2004**;109:2394
SQT 3	315-320 ms 172 ms	*KCNJ12 (Kir2*.2) gain-of function mutation KCNJ2 mutation, M301K	Priori SG et al. Circ Res. **2005** Apr 15;96(7):800-7. Tetsuhisa Hattori et al, GOF KCNJ2

SQT 4	331-370 ms BrS+ SQTS phenotypes QTc < 350ms	CACNA1C($I_{Ca^{2+}}$) Protein: Subunit α2/d1	Antzelevitch C et al. Circulation **2007;1**15:442
SQT 5	346-360 ms BrS+ SQTS phenotypes	CACNB2b (ICa2+) loss-of-function Calcium Voltage-Gated Channel Subunit Alpha1 C (Cav1.2) Calcium Voltage-Gated Channel Auxiliary Subunit Beta 2 (CavB2)	Antzelevitch C et al. Circulation **2007**;115:442.
SQT 6	329 ms 7q21.11 BrS+ SQTS phenotypes	CACNA2D1 ($I_{Ca^{2+}}$) Protein Calcium Voltage-Gated Channel Auxiliary	Templin C et al. Eur Heart J. **2011** May; 32(9):1077-88. **Not conclusive diagnosis.**
SQT 7 ?	320ms,	SCN5A gene heterozygous missense Mutation G to at nucleotide site 2066 that resulted in a amino-acid substitution of arginine to histidine at amino-acid site 689 (R689H).	**No conclusive data concerning the association of this variant with SQTS.** Hong K, Hu J, Yu J, Brugada R.Concomitant Brugada-like and short QT electrocardiogram linked to SCN5A mutation. Eur J Hum Genet. 2012 Nov; 20(11):1189-92. doi: 10.1038/ejhg.2012.63.

SQT 8 ?	? ms	Gene Solute Carrier Family 4 Member 3 (SLCA4A3) Loss-of-activity-mutation in the cardiac chloride-bicarbonate exchanger AE3	Thorsen K. et al 2017 **No conclusive data concerning the association of this variant with SQTS.**

1. **SQT 1: Brugada R, et al. Sudden death associated with short-QT syndrome linked to mutations in HERG. *Circulation.* 2004;109:30–35. doi: 10.1161/01.CIR.0000109482.92774.3A.** *KCNH2* gene
2. **SQT 2: Bellocq C, van Ginneken ACG, Bezzina CR, Alders M, Escande D, Mannens MMAM, et al. Mutation in the KCNQ1 gene leading to the short QT-interval syndrome. *Circulation*. 2004;109(20):2394–7. 10.1161/01.CIR.0000130409.72142.FE**
3. **SQT 3: Priori SG, Pandit SV, Rivolta I, Berenfeld O, Ronchetti E, Dhamoon A, et al. A novel form of short QT syndrome (SQT3) is caused by a mutation in the KCNJ2 gene. *Circ Res*. 2005;96(7):800–7. 10.1161/01.RES.0000162101.76263.8c)(Tetsuhisa Hattori et al. A novel gain-of-function(GOF) KCNJ2 mutation associated with short-QT syndrome impairs inward rectification of Kir2.1 currents. Case Reports Cardiovasc Res. 2012 Mar 15;93(4):666-73. doi: 10.1093/cvr/cvr329.**
4. **SQT 4**/Antzelevitch C,
5. **SQT 5: Antzelevitch C, Pollevick GD, Cordeiro JM, Casis O, Sanguinetti MC, Aizawa Y, et al. Loss-of-function mutations in the cardiac calcium channel underlie a new clinical entity characterized by ST-segment elevation, short QT intervals, and sudden cardiac death. *Circulation*. 2007;115(4):442–9. 10.1161/CIRCULATIONAHA.106.668392 (Carlo Napolitano 1, Katherine W Timothy 2, Raffaella Bloise 3, Silvia G Priori 1CACNA1C-Related Disorders Margaret P Adam, Holly H Ardinger, Roberta A Pagon, Stephanie E Wallace, Lora JH Bean, Ghayda Mirzaa, Anne Amemiya , editors. In: GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993–2021.2006 Feb 15 [updated 2021 Feb 11].**
6. **SQT 6 Templin C et al. Identification of a novel loss-of-function calcium channel gene mutation in short QT syndrome (SQTS6) Eur Heart J. 2011 May;32(9):1077-88. doi: 10.1093/eurheartj/ehr076.**

(Hong K et al. Concomitant Brugada-like and short QT electrocardiogram linked to SCN5A mutation., Eur J Hum Genet. 2012 Nov; 20(11):1189-92.) not conclusive diagnosis.

7. SQT 7 Hong K, Hu J, Yu J, Brugada R.Concomitant Brugada-like and short QT electrocardiogram linked to SCN5A mutation. Eur J Hum Genet. 2012 Nov;20(11):1189-92. doi: 10.1038/ejhg.2012.63. In 2012, it was identified as the p.R689H variant in the SCN5A gene (ID: 6331). This gene encodes the sodium channel protein type 5-subunit alpha (Nav1.5) which mediates the voltage-dependent sodium ion permeability of myocyte membranes. it has also been associated with BrS. Concerning SQTS, the reported patient was an asymptomatic 40-year-old male with family history of SCD of unknown origin who had a Brugada-ECG pattern + short QT intervals(overlap phenotypes). No conclusive data exist concerning the association of this variant with SQTS. Despite this fact, it is so-called SQTS type 7, and potentially responsible for < 1% of all cases. Campuzano O, et al. point of view, mentioned that genetic translation of SCN5A variants in SQTS patients should be done with caution due to its ambiguous role.

8. SQT 8 Kasper Thorsen, et al.Loss-of-activity-mutation in the cardiac chloride-bicarbonate exchanger AE3 causes short QT syndrome. Nat Commun. 2017 Nov 22;8(1):1696. doi: 10.1038/s41467-017-01630-0. The mutation causes reduced surface expression of AE3 and reduced membrane bicarbonate transport. Slc4a3 knockdown in zebrafish causes increased cardiac pH_i, short QTc, and reduced systolic duration, which is rescued by wildtype but not mutated SLC4A3. Mechanistic analyses suggest that an increase in pH_i and decrease in $[Cl^-]_i$ shortened the action potential duration. However, other mechanisms may also play a role. Altered anion transport represents a mechanism for development of arrhythmia and may provide new therapeutic possibilities. This gene (Solute Carrier Family 4 Member 3) encodes a plasma membrane anion exchange protein 3 (AE3). It mediates a part of the Cl-/HCO3- exchange in cardiac myocytes. To date, only one rare variant (p.R370H) have been identified in the *SLC4A3* gene associated with SQTS. It follows an autosomal dominant pattern of inheritance. The pathogenic variant leads to a trafficking defect, decreased Cl,HCO3-exchange over the cell membrane and increased intracellular pH, shortened the APD and it reduces QT interval. This variant has not been identified in global databases, reinforcing its potential deleterious role. However, no conclusive data exist concerning the association of this variant with SQTS. **Priori SG et al. European Society of Cardiology Guidelines for the**

management of patients with ventricular arrhythmias and the prevention of sudden cardiac death *Eur Heart J. 2015 Nov 1; 36(41):2757-9*.