SCN5A Main gene mutations with LQT3

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1. **Mutation:** Deletion of amino acids 1,505–1,507 (ΔKPQ) (**Wang 1995**). Delta KPQ (N1325S and R1644H), **(Dumaine 1998; Nagatomo 2000; Windle 2001; Potet 2015)** LQT3 DeltaKPQ mutant has normalization of ventricular repolarization with class IC antiarrhythmic flecainide.
2. **Mutation:** R1623Q (**Kambouris 1998**) severe LQT3 phenotype increased the probability of long openings and caused early reopenings, producing a threefold prolongation of sodium current decay. Lidocaine restored rapid decay of the R1623Q macroscopic current. These findings explain the unusual lidocaine sensitivity of R1623Q and provide a general and unanticipated mechanism for understanding how Na+ channel-blocking agents may suppress the pathologic, sustained Na current induced by LQT3 mutations.
3. **Mutation:** R1623Q, S4 segment of domain (**Makita1998**). Severe form of LQT3. have significantly prolonged open times with bursting behavior, suggesting a novel mechanism of pathophysiology in Na+ channel-linked LQTS.
4. **Mutation:** single nucleotide substitution in SCN5A exon 28 that caused the substitution of Glu1784 by Lys (E1784K). (**Wei 1999**) The mutation occurs in a highly-conserved domain within the C-terminus of the cardiac sodium channel containing multiple, negatively charged amino acids. Two-electrode voltage-clamp recordings of a recombinant E1784K mutant. The C-terminus suggest that the molecular mechanism of channel dysfunction involves an allosteric rather than a direct effect on channel gating.
5. **Mutation:** a novel missense mutation, T1645M, in the DIV; S4 voltage sensor immediately adjacent to mutation R1644H. novel mutation, T1304M, at the voltage-sensing region DIII; S4. . We also examined all of the additional pore-forming regions and voltage-sensing regions and discovered another novel mutation, T1304M, at the voltage-sensing region DIII; S4. Neither T1645M nor T1304M

were seen in a panel of unaffected control individuals. Five of six T1304M gene carriers were symptomatic. In contrast to previous studies, QT (onset-c) was not a sensitive indicator of SCN5A-associated LQTS, at least in this family. These data suggest that mutations of SCN5A are responsible for only a small proportion of LQTS cases. (**Wattanasirichaigoon 1999**)

6. **Mutation:** 1795insD has opposite effects on two distinct kinetic components of Na^+ channel gating (fast and slow inactivation) that render unique, simultaneous effects on cardiac excitability. The mutation disrupts fast inactivation, causing sustained Na^+ current throughout the AP plateau and prolonging cardiac repolarization at slow heart rates. At the same time, 1795insD augments slow inactivation, delaying recovery of Na^+ channel availability between stimuli and reducing the Na^+ current at rapid heart rates. This findings reveal a novel molecular mechanism for the BrS and identify a new dual mechanism whereby single SCN5A mutations may evoke multiple cardiac arrhythmia syndromes by influencing diverse components of Na^+ channel gating function. (**Veldkamp 2000**)
7. **Mutation:** D1790G (DG), **(Abriel 2000)** responsive to flecainide. The authors (1) demonstrate that the DG mutation confers a unique pharmacological response on expressed channels; (2) suggest that flecainide use-dependent block of DG channels underlies its therapeutic effects in carriers of this gene mutation; and (3) suggest a role of the Na^+ channel alpha-subunit C-terminus in the flecainide/ channel interaction.
8. **Mutation:** Deletion of amino-acid residues 1505-1507 (KPQ) (**Nuyens 2001**) Unexpectedly, sudden accelerations in heart rate or premature beats caused lengthening of the AP with EADs and triggered arrhythmias in SCN5A (Delta/+) mice. Adrenergic agonists normalized the response to rate acceleration in vitro and suppressed arrhythmias upon premature stimulation in vivo.
9. **Mutation:** (**Bezzina 2001**) Severe form overlap syndromes Cardiac arrest LQT3 with bradycardia-dependent QT-prolongation +BrS+ Progressive cardiac conduction defect (PCCD).
10. **Mutation:** SCN5A-linked disorder (1795insD) **Phenotype:** LQT_3,+ BrS and familial conduction system disease. Prophylactic pacemaker is indicating (**van den Berg 2002**).
11. **Mutation:** Missense mutation, M1766L (**Valdivia 2002**). Severe form of LQT3 in infants Mexiletine partially 'rescued' the defective expression. The double-mutation M1766L/H558R in the hH1a

background restored normal trafficking and current including persistent late I(Na) current, suggesting the disease phenotype was the result of a "double hit" that included the common polymorphism, H558R. The choice of background clone must be carefully considered in mutagenesis studies.(**Ye 2003**)

12. **Mutation:** nonsense mutation (W156X), missense mutation (R225W), (**Bezzina 2003**) Overlap DCM+ severe degenerative abnormalities of the conduction system.
13. **Mutation:** Veldkamp et al. (**Veldkamp 2003**) studied the effect of the 1795insD mutation on sinoatrial node(SAN). Activity of 1795insD channels during SAN was confirmed by AP clamp experiments, and the previously characterized persistent inward current (I-pst) and negative shift were implemented into SAN (AP) models. The -10 mV shift decreased the sinus rate by decreasing the diastolic depolarization rate, whereas the I-pst decreased the sinus rate by AP prolongation, despite a concomitant increase in the diastolic depolarization rate. In combination, a moderate I-pst (1 to 2%) and the shift reduced the sinus heart rate by about 10%
14. **Mutation:** A novel missense mutation (L1825P) was identified within the C-terminus region of the cardiac Na+ channel. Subclinical mutations in the LQTS-related gene SCN5A may predispose certain individuals to drug-induced cardiac arrhythmias. L1825P exhibited loss of function Na+ channel features characteristic of BrS. (**Miura 2003**)
15. **Mutation:** A-->G substitution at codon 1768, close to the C-terminal end of domain IVS6, which changes an isoleucine to a valine. (**Groengage 2003**).
16. **Mutation:** L619F (LF), located in the domain I-II linker. heterozygous missense mutation (L619F). sever form in infant (**Wehrens 2003**.)
17. **Mutation:** beta3-V54G/ beta3-V36M; beta4-S206L (**Tan BH 2010**). Phenotype: Sudden infant death syndrome (SIDS)
18. **Mutation:** V411M (**Home 2011**) Severe form of LQT3 in newborn with a QTc of 640 ms and 2:1 atrioventricular block (AVB). (**Miura 2003**)
19. **Mutation:** T1620K **(Surber 2008).** Overlapping syndrome: Concomitant occurrence of PPCD and LQT3.
20. **Mutation:** Approximately 5-10% of LQTS cases are due to mutations in *SCN5A* gene with the triggering factors associated with arrhythmic events at rest or during sleep without emotional arousal in ≈ 65% of cases, (**Ruan 2008**) It is also observed that *SCN5A* mutations often

produce distinct clinical features including bradycardia. (**Qureshi 2015**).

21. **Mutation:** *SCN5A* (L409P) and a homozygous common variant (R558). Fetal LQTS. The fetus presented with episodes of ventricular ectopy progressing to incessant VT and hydrops fetalis. Genetic analysis disclosed a novel, *de novo* heterozygous mutation in *SCN5A* (L409P) and a homozygous common variant (R558). (**Murphy 2012**)
22. **Mutation:** S1787N; Q1077del; Q1077 splice variant (**Hu 20015**) LQT3 acidosis-induced arrhythmia mechanisms.
23. **Mutation:** Missense mutation, V2016M, (**Chen 2016**). Phenotype: Sinus node dysfunction and epinephrine-induced QT prolongation, which is an atypical phenotype for LQT3.
24. **Mutation:** missense mutation-pQ371E **(Kimura 2016).** Phenotype: Overlapping syndrome: LQT3+ DCM.
25. **Mutation:** H558R+ E1784K. (**Veltmann 2016**)**.** Phenotype: Overlap syndromes LQT3+BrS+ Progressive cardiac conduction defect (PCCD). The last
26. **Mutation:** Missense **m**utation Thr1709MetDomain I–IV and Segments 1 to 6 of SCN5A. between S5 and S6. **(Lakshmanadoss 2016);**
27. **Mutation:** E1784K **(Hohmann 2017)** Ajmaline challenge was positive in 75% mutation carriers, but negative in all non-carriers (**Hohmann 2011**) a significant shortening of the JT (JTc) interval was observed in mutation carriers. The baseline JTc interval was significantly longer in mutation carriers with a positive ajmaline challenge compared with those with a negative one.