Mutation site-specific risk profile in patients with Type 1 Long QT Syndrome

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Background: Type 1 Long QT Syndrome (LQT1) is an arrhythmogenic disorder, caused by loss-of-function mutations on KCNQ1 gene, coding for Kv7.1 potassium channel. Although LQT1 is described as the most benign form of LQTS, patients still experience arrhythmic events and there is an unmet need for personalized risk stratification. Attempts have been made to correlate the location of mutations with outcome, but the results are unequivocal.

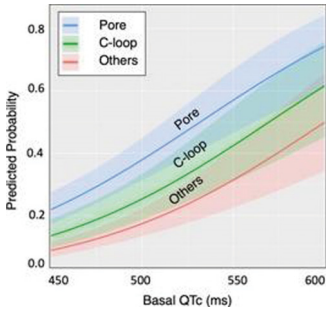
Purpose: We provide in the present study a new mutation site-specific risk profile obtained from a large cohort of LQT1 patients.

Methods: We gathered data on 963 patients with the diagnosis of LQT1 and divided the Kv7.1 channel into 5 functional regions: the N-terminus (NT), the voltage sensor (VS, including transmembrane segments S1 to S4), the cytoplasmic loops (CL), the pore (PO, including the transmembrane segments S5, S6 and the S5-S6 extracellular linker), the C-terminus (CT).

Results: We studied 963 LQT1 patients: 518 (54%) females; average age 20±17 years; mean QTc at baseline ECG 465±38ms. During a mean follow-up of 8±7 years, 172 (18%) patients experienced arrhythmic events: 31 (3%) experienced one or more cardiac arrests, while 141 (15%) experienced one or more syncopal spells. We identified 188 different variants in the KCNQ1 gene, with the following distribution: 15 (8%) in the NT, 33 (18%) in the VS, 27 (14%) in the CL, 43 (23%) in the PO, 70 (37%) in the CT. The frequency of pathogenic variants per number of amino acids (a.a.) was higher in the CL region, as compared to the other domains (1 mutation every 1.4 a.a.). The duration of QTc interval was significantly longer for patients with mutations in the PO region (473±40 ms) and in the CL region (468±38 ms) as compared to the other regions ($p<0.01$).

Importantly, in a multivariate analysis PO and CL regions were associated with a higher probability of experiencing arrhythmic events (OR 2.89, 95% CI 1.95–4.29, p=0.019 and OR 1.61, 95% CI 1.0–2.49, p=0.05, respectively. Figure) than the other regions. Interestingly, the risk was independent from QTc interval duration.

Conclusions: Mutations affecting the PO and the CL region of the Kv7.1. channel are associated with a higher probability of experiencing arrhythmic events. This finding is clinically relevant, because it will allow for a more personalized, mutation site-specific risk stratification.



Mutation site and arrhythmic events