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Transgenic Short QT Syndrome Type 1 Rabbits (HERG-N588K) Exhibit Shortened Cardiac Repolarization, Ventricular Fibrillation, and Sudden Death

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Abstract

Background and Objective: Short QT syndrome is an inherited ion channelopathy with an accelerated cardiac repolarization due to gain-of-function mutations in K^+ channel genes. Patients are prone to ventricular tachycardia and sudden cardiac death (SCD). Detailed knowledge about mechanisms of arrhythmogenesis is lacking. We aimed at generating transgenic SQT1 rabbits as novel tool to investigate these mechanisms.

Methods: FLAG-HA-tagged HERG-N588K cDNA and the β-MyHC promoter were integrated into a pBSII SK vector. To generate transgenic rabbits, these SQT1 constructs were microinjected in rabbit oocytes. SQT1 rabbits and their wildtype littermates (WT) were subjected to *in vivo* ECG and *ex vivo* monophasic action potential (AP) measurements. Electrical remodeling was investigated using real-time PCR.

Results: We successfully generated 3 transgenic SQT1 founder rabbits. One of the founders died suddenly at the age of 60 days. In SQT1 rabbits not subjected to any experiments 3/11 died around day 40 vs. 0/8 WT animals ($p<0.05$). SQT1 founder rabbits and their offsprings demonstrated a shortened QT interval compared to WT (QT, ms, SQT1, n=44, 147.8±1.7 vs. WT, n=24, 166.4±2.9, $p<0.0001$, heart-rate corrected QTi, %, 91.6±0.7 vs. 98.1±1.1, $p<0.0001$) with a steeper QT/RR ratio (0.17±0.03 vs. 0.04±0.01, $p<0.05$) and no gender differences among SQT1 rabbits. Moreover, in SQT1, AP duration was shortened in all segments of LV base, mid, and apex (LV base-lat, APD_{90}, ms, SQT1, n=7, 118.6±5.1 vs. WT, n=9, 154.4±2.2, $p<0.0001$; APD_{75}, 93.1±6.8 vs. 127.1±1.9, $p<0.0001$). Ventricular fibrillation (VF) occurred more often during AP measurements in SQT1 than in WT rabbits (SQT1 5/11 vs. WT 0/8, p<0.05).

FLAG-HA-HERG-N588K channels demonstrated increased I_{Kr} steady currents and impaired inactivation indicative of a gain-of-function. Remodeling of ion channels and Ca^{2+} handling proteins occurred in SQT1 rabbits with a downregulation of L-type Ca^{2+} channel mRNA in LV septum-mid (SQT1, n=4, 0.84±0.1 vs. WT, n=6, 1.03±0.1, $p<0.05$) and of RyR2 in LV septum-apex (0.85±0.1 vs. 1.08±0.1, $p<0.05$).

Conclusion:

Transgenic SQT1 rabbits over-expressing HERG-N588K gain-of-function mutation mimic the human phenotype with shortening of QT and APD, a higher rate of VF and SCD. These rabbits are thus a useful tool to explore arrhythmogenic mechanisms in SQTS.

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