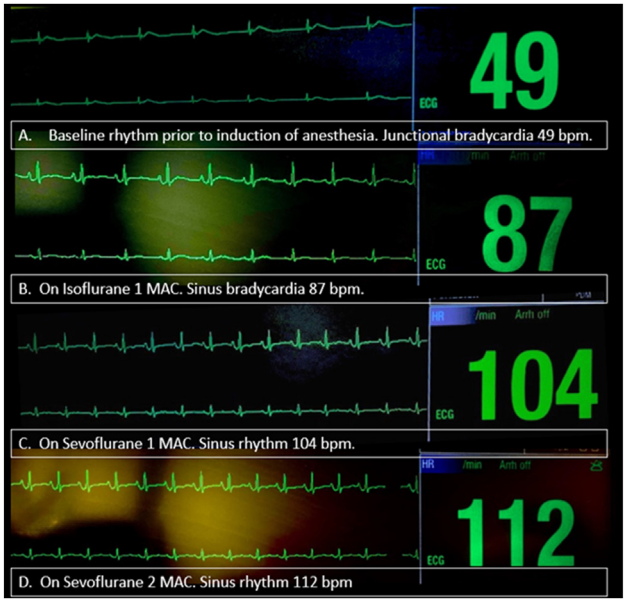
could thereby inhibit overactive K^+ channels and result in improvement in sinus bradycardia. There are no effective IV medications to treat SQTS and associated sinus bradycardia is often refractory to sympathomimetic medications. It is possible that inhaled anesthetics may provide a temporizing rescue therapy for Short QT patients with hemodynamically significant and drug-refractory bradycardia.



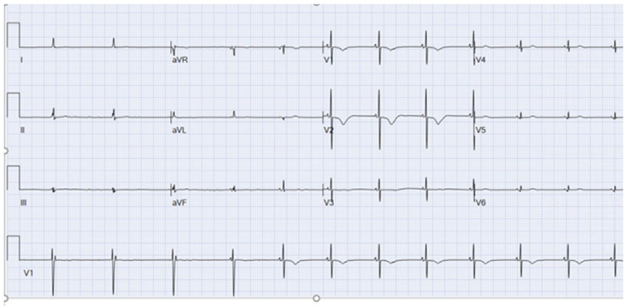


Figure 1. Baseline ECG at 1 day of age demonstrating junctional bradycardia transitioning to sinus rhythm with marked T wave abnormality. QT 280msec, QTc 317msec

AP-517-03

WHOLE EXOME SEQUENCING IDENTIFIES TWO NOVEL EXTREMELY RARE CANDIDATE VARIANTS ASSOCIATED WITH THE SHORT QT SYNDROME IN TWO LARGE PEDIGREES

Boldizsar Kovacs MD

Background: Short QT syndrome (SQTS) is caused by pathogenic variants predominantly in the *KCNQ1*, *KCNH2*, *KCNJ2* genes and genes encoding for different subunits of the L-type calcium channel. Recently, a variant in the *SLC4A3* gene has been associated with the SQTS as well.

Objective: To identify the genetic background causing SQTS using whole exome sequencing (WES) and co-segregation analysis in two large pedigrees.

Methods: Genetic testing of the index patient 1 and molecular autopsy of the index patient two was performed using NGS. Family screening was performed with cardiologic work-up and genetic cascade screening.

Results: Index case 1 was diagnosed with SQTS at the age of 28 years after a syncopal event. Work-up revealed a markedly shortened QTc interval (340ms). Family history revealed peripartum death of one relative. Genetic testing of all known implicated genes was initially negative. WES was performed, which revealed a novel rare heterozygous missense variant (p.(Arg370Cys)) in a highly conserved region of the *SLC4A3* gene. Cardiac and genetic work-up of 5 relatives suggested co-segregation of the candidate variant (pedigree 1) with the SQTS. Index case 2 had sudden cardiac death (SCD) at 17 years of age and had a positive family history for SCD before the age of 40 in three cases. A previously recorded 12-lead ECG revealed a QTc of 340ms in the index patient. Post-mortem genetic testing of all known implicated genes was initially negative. In light of our previous findings, reanalysis was performed including the *SLC4A3*gene, which revealed a second rare novel heterozygous missense variant(p.(Ser1039Arg)). Cardiac and genetic work-up of 10 relatives suggested co-segregation of the candidate variant with the SQTS (pedigree 2).

Conclusion: WES and co-segregation analysis in two families with the SQTS revealed two novel candidate variants in the *SLC4A3* gene with high penetrance. Alteration of the protein encoded by the *SLC4A3* gene may lead to increased intracellular pH and shortened action potential duration leading to the SQTS. Functional work-up of these two variants is under way.