Results The peak I_{Na} densities did not differ between WT and mutant channels containing R800L-SCN5A, A261V-SNTA1 or R800L-SCN5A plus A261V-SNTA1. However, late I_{Na} for either mutant channel was moderately increased 2–3 fold compared to WT. The combined mutations of R800L-SCN5A plus A261V-SNTA1 significantly enhanced the I_{Na} late/peak ration by 5.6–fold compared with WT. The time constants of current decay of combined mutant channel were markedly increased. The 'gain-of-function' effect could be blocked by the NG-monomethyl-L-arginine (L-NMMA), a nNOSinhibitor.

Conclusions We conclude that novel mutations inSCN5A and SNTA1synergistically exert a nNOS dependent 'gain-of-function' on SCN5A channels, which may consequently prolong the action potential duration (APD) and lead to LQTS phenotype.

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SYNERGISTIC EFFECT OF THE NOVEL MUTATIONS IN SCN5A AND SNTA1 ON LATE INA CONTRIBUTING TO LQT SYNDROME

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Objectives SCN5A and SNTA1 are reported susceptible genes for long QT syndrome (LQTS). This study was designed to elucidate a plausible pathogenic arrhythmiamechanism for the combined novel mutations R800L-SCN5Aand A261V-SNTA1 on cardiac sodium channels.

Methods A Caucasian family with syncope and marginally prolonged QT interval was screened for LQTS-susceptibility genes and found to harbour the R800L mutation in SCN5A and A261V mutation in SNTA1. The mutations were engineered into the most common splice variant of human SCN5Aand SNTA1 cDNA respectively and sodium current (I_{Na}) was characterised in HEK293 cells co-transfected with neuronal nitric oxide synthase (nNOS) and the cardiac isoform of the plasma membrane Ca-ATPase (PMCA4b).