# Modelling the Effects of Propafenone on Human Atrial Patho-electrophysiology Associated with hERG-Linked Short QT Syndrome

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**Introduction:** The N588K mutation to the *human Ether-à-go-go-Related Gene* (hERG) underlies short QT syndrome variant 1 (SQT1), which is associated with increased incidence of atrial fibrillation (AF). However, mechanisms and pharmacological management of AF in the context of SQT1 remain poorly understood.

**Methods:** In this study, multi-scale computational modelling was used as a means of investigating mechanisms of human atrial arrhythmogenesis consequent to the N588K-hERG mutation, as well as pharmacotherapeutic effects of the class Ic drug propafenone. A Markov chain formulation of rapid delayed rectifier potassium current, $I_{Kr}$, describing wild type (WT), and N588K mutant hERG channel currents was incorporated into a contemporary model of the human atrial action potential (AP), which was subsequently integrated into a three-dimensional (3D) heterogeneous, anisotropic anatomical model of the human atria. Effects of multi-channel block by propafenone, including binding kinetics and altered potency of $I_{Kr}$/hERG block in SQT1 and state-dependent block of sodium channels, were simulated on single- and multi-cellular electrophysiology models.

**Results:** At the single cell level, propafenone at clinically-relevant concentrations (0.2, 0.5, 0.8 μM) prolonged the AP duration, which was shortened by ~50 ms under heterozygous SQT1 (WT-N588K) conditions, in a dose-dependent manner. In tissue, propafenone prolonged the effective refractory period and excitation wavelength, whilst reducing the conduction velocity. In simulations of re-entrant excitation waves in the 3D anatomical model, propafenone partially reversed the SQT1-mediated increase in dominant frequency of re-entry (from ~4.2 Hz in the WT condition to ~5.0 Hz in the heterozygous SQT1 condition) and demonstrated some efficacy in pharmacological conversion of re-entry.

**Conclusion:** Our findings show that propafenone has efficacious effects in reversing human AF associated with hERG-linked short QT syndrome. Further studies are warranted to establish whether propafenone represents a useful SQT1-specific pharmacotherapy for AF.