Alleviating Effects of Long-QT Syndrome Type 2 by Allele-Specific Inhibition of the *KCNH2* Mutant Allele

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It was recently demonstrated that the effects of long-QT syndrome type 1 can be alleviated by allele-specific 40–60% inhibition of mutant *KCNQ1*. This gene encodes the pore-forming Kv7.1 α-subunit of the tetrameric ion channel carrying the slow delayed rectifier potassium current (I_{Ks}). We questioned whether the effects of long-QT syndrome type 2 (LQT2) can similarly be alleviated by 60% downregulation of mutant *KCNH2*, encoding the pore-forming Kv11.1 α-subunit of the tetrameric ion channel carrying the rapid delayed rectifier potassium current (I_{Kr}).

We investigated the effect of 60% inhibition of mutant *KCNH2* through computer simulations with the O'Hara–Rudy human ventricular cardiomyocyte model, updated with the I_{Kr} Markov model from Li et al. (2017; PMID: 28202629). The model cell was stimulated at 1 Hz.

In a situation where mutant and wild-type Kv11.1 proteins are equally expressed and co-assemble randomly, only 6.25% of the I_{Kr} channels will completely consist of wild-type subunits. Inhibition of the mutant *KCNH2* allele by 60% decreases the overall number of I_{Kr} channels by 30%. However, if only I_{Kr} channels entirely built of wild-type subunits are conductive, as in severe LQT2 mutations, the amount of conductive I_{Kr} channels increases almost threefold. The associated increase in I_{Kr} results in a reduction of the mutation-induced prolongation of the action potential duration at 90% repolarization (APD_{90}) from 357 ms (+135%) to 236 ms (+89%). If the mutant *KCNH2* allele can be inhibited by as much as 80%, the amount of conductive I_{Kr} channels will increase 4.6-fold and the prolongation in APD_{90} will be further reduced to 177 ms (+67%).

We conclude that allele-specific inhibition of the *KCNH2* mutant allele in case of long-QT syndrome type 2 may alleviate the disease.