How additive effects of small changes in repolarising currents can increase the risk for atrial fibrillation – a modelling study

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Atrial fibrillation (AF) is the most common cardiac arrhythmia and a frequent complication of cardiac and systemic disorders. Community-based studies have demonstrated familial aggregation of AF (Fox *et al.*, 2004; Arnar *et al.*, 2006) with the heritability of AF estimated to be 60% in one twin cohort (Christophersen *et al.*, 2009).

While these studies indicate that genetic factors have an important role in AF pathogenesis, the genes involved and mechanistic links with atrial arrhythmogenesis are incompletely understood. AF is predicted to be a complex trait in which one or more genetic variants, together with acquired "environmental" factors that alter atrial size and/or function, are involved in most cases (Fatkin, Otway & Vandenberg, 2007). Genome-wide association studies have been used to define common variants that modify susceptibility to AF in the general population (Milan *et al.*, 2010). Because of their frequency, common variants have a significant population impact but the effect size of individual variants is generally only small. Combinations of variants with small effect size may have additive, opposing, or synergistic actions, and the net effects of multiple variants are difficult to predict or demonstrate experimentally.

We performed *in silico* modelling using the Courtemanche human atrial action potential model (Courtemanche, Ramirez & Natte, 1998) to assess the effects of combinations of multiple potassium variants on atrial action potential properties. For this we simultaneously altered the conductances of each of the five potassium channel components of the Courtemanche model by +10 or −10 percent of their original values. For each of the resulting 243 combinations we performed 1000 simulation runs - with additional random noise added to the potassium conductances - and measured the resulting action potential duration variabilities.

Our data demonstrate that multiple K^+ variants of small effect size can have collective effects that are functionally equivalent to those attributable to single-gene mutations.

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