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Differential effects of five risk variants for atrial fibrillation at the 4q25 region on L-type calcium current and transient inward currents in human atrial myocytes

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Background: An increasing number of single nucleotide polymorphisms (SNPs) at the chromosomal region 4q25 have been associated with risk of atrial fibrillation (AF) and we have recently reported that carriers of the rs13143308 risk variant have an increased incidence of spontaneous calcium release-induce transient inward currents (ITI). However, it is not known if different 4q25 variants have similar effects.

Purpose: This study aimed to compare the effects of five SNPs at 4q25 on L-type calcium current (ICa) and ITI frequency, features that are altered in patients with AF.

Methods: To avoid confounding effects of AF on calcium homeostasis, atrial samples from 63 patients without AF were genotyped and divided into groups according to the genotype of the SNPs rs1448818, rs6817105, rs13143308, rs6843082, rs3853443 ordered according to their location and identified by the three last digits + an R for risk or N for normal variants. ICa density and ITI frequency were measured with perforated patch clamp technique in atrial myocytes from these patients.

Results: Three SNPs 818, 308 and 443 segregated independently of the genotype at the other loci. The 105 and 082 loci always co-segregated with 308 but never together. The ICa density was smaller in carriers of 818R and 443N variants (–1.6±0.3pA/pF, p=0.01) or 818N and 443R variants (–1.6±0.4pA/pF, p=0.02) than in patients with 818N and 443N variants (–3.2±0.4pA/pF), independently of the genotype at 105, 308 and 082 (these loci did not affect ICa). In contrast, to this, the ITI frequency was increased only in myocytes from patients carrying 105R, 308R and 082N (1.4±0.2events/min, $p<0.001$) or 105N, 308R and 082R (1.6±0.5events/min, p=0.002) when compared to patients with 105N, 308N and 082N (0.36±0.09events/min) independently of the genotypes at 818 and 443, or when compared to patients without risk at any of the five loci (0.55±0.30events/min). The table shows schematically the qualitative effects of the different risk variants.

Conclusion: Different SNPs at the chromosomal region 4q25 are associated with differential pathological changes in intracellular calcium homeostasis. Risk variants at rs1448818 or rs3853445 cause loss of ICa without affecting ITI frequency while a risk variant at rs13143308 elevates the ITI frequency without affecting ICa. These findings afford a framework for stratification of pharmacological therapy based on the functional effects of the 4q25 risk variants

Risk variant	rs1448818C	rs6817105C	rs13143308T	rs6843082T	rs3853445C
I_{Ca}	Decreased	Unchanged	Unchanged	Unchanged	Decreased
I_{TI}	Unchanged	Increased	Increased	Increased	Unchanged