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Association of a Common *KCNE1* Variant with Heart Failure

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Heart failure is a common multifactorial disease with substantial morbidity and mortality. The main clinical manifestations of heart failure include limited exercise tolerance, fluid retention with predisposition to edematous states and acute pulmonary edema, and other organ dysfunction such as hepatic and renal insufficiency. Heart failure is associated with a shortened life expectancy with a median survival of 1.7 years in men and 3.2 years in women according to epidemiological data from the Framingham Heart Study.¹ A significant cause of mortality in heart failure is sudden cardiac death caused in many cases by ventricular arrhythmias. Cardiac myocytes from failing hearts exhibit abnormal repolarization suggesting a predisposition to reentrant arrhythmia.² Understanding risk factors for heart failure should promote the development of improved therapies and preventive measures to lessen this public-health burden.

A genetic basis for heart failure has been well established for rare familial monogenetic forms of cardiomyopathy but there is less evidence for a genetic contribution to the risk for more common acquired forms of this disease.^{3,4} Genetic factors have also been identified that predispose to underlying conditions such as coronary artery disease and hypertension that predispose to heart failure.⁵ However, there have been few studies addressing whether genetic factors independent of underlying disease processes are associated with the risk of heart failure.

In this issue of *Heart Rhythm*, Fatini, *et al.* report a candidate gene association study performed in Italian subjects with heart failure.⁶ The investigators utilized a case-control study design to investigate the association of a non-synonymous single nucleotide polymorphism (SNP) in *KCNE1* with the occurrence of heart failure. This particular SNP causes substitution of serine for a glycine residue in the extracellular domain of the encoded potassium channel accessory subunit originally named “minK”. Previous genetic studies have demonstrated association of this common *KCNE1* variant with the occurrence of atrial fibrillation.^{7–9} Because heart failure is a known risk factor for atrial fibrillation, these previous genetic associations could conceivably represent associations with heart failure instead. This would appear to be a rationale for the present study by Fatini and colleagues.

By using a case-control study design, the investigators tested association between *KCNE1* and heart failure in two separate cohorts of Italian heart failure subjects. In both case-control populations, they found significant association of the common allele (encoding Gly-38) with the occurrence of heart failure. This association remained significant even after adjusting for

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Disclosures

There are no relevant disclosures.

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age, sex and known risk factors for heart failure. The odds ratios for heart failure risk conferred by the variant ranged from 2.2 to 2.6 depending on the cohort and the genetic model used in the analysis. Interesting, the study did not demonstrate an association between the *KCNE1* variant and clinical severity of heart failure in either population. The replication of an association in two independent populations of similar ethnicity helps diminish the possibility that the result is a spurious association caused by population stratification or admixture. But, further replication of this association in larger independent populations will be required to solidify the finding.

The specific *KCNE1* variant investigated by Fatini, *et al.* involves a single nucleotide change in codon 38. The more common allele is a guanine nucleotide in the first base position of codon 38 (GGT) that encodes a glycine (G) residue whereas the minor allele encodes serine (S) because of adenine substitution (AGT). Interestingly, serine is present at codon 38 in most reference sequences hence the misleading notation of S38G (i.e., G38S is more appropriate given the glycine is encoded by the predominant allele). This variant has been detected worldwide in many distinct populations.¹⁰ In Caucasians of European ancestry used for the HapMap Project, the common allele frequency is 0.62 and this value approximates the allele frequency observed among heart failure cases in both cohorts reported by Fatini, *et al.* This raises some concern that control subjects utilized for this association study might in some way be skewed toward a lower common allele frequency. Further replication studies in other populations will be necessary to alleviate this concern.

As with most genetic association studies the results do not demonstrate a causal relationship between the genetic variant and the disease. The association of *KCNE1*-G38S with heart failure could arise because this common variant is in linkage disequilibrium with another causal variant in this gene or within a neighboring genomic region. If this non-synonymous variant was causal for heart failure in some way, the mechanism linking a potassium channel accessory subunit with contractile dysfunction is not clear. The authors of the study speculate that the *KCNE1* protein might interact with sarcomeric contractile elements and that this could alter the response to biomechanical stress possibly predisposing to heart failure.

An alternative hypothesis is that *KCNE1*-G38S provides a survival advantage to heart failure subjects. A case-control association study is inherently cross-sectional and therefore all cases are living subjects, a potential ascertainment bias for a disease with a high mortality rate. Heart failure is associated with a higher mortality due to ventricular arrhythmias and sudden cardiac death. Could *KCNE1*-G38S provide a survival advantage by affecting cardiomyocyte repolarization? This hypothesis is reminiscent of lower mortality in the settings of heart failure and myocardial ischemia observed in African Americans who carry a G-protein receptor kinase-5 (GRK5) polymorphism that alters cardiac β_1 -adrenergic receptor desensitization.¹² A previous *in vitro* investigation demonstrated that heterologous co-expression of KCNQ1 potassium channels with these two variant *KCNE1* subunits generated slow delayed rectifier current (I_{Ks}) with different current densities.¹¹ Specifically, I_{Ks} generated from channels containing the less common (minor) allele *KCNE1*-S38 exhibited higher current density. Therefore, the *in vitro* evidence demonstrated that the common allele (G38), which was associated with heart failure in the Fatini study, is associated with lower I_{Ks} density. Although, it seems counterintuitive to propose that reduced I_{Ks} density would confer protection from ventricular arrhythmias, the behavior of this allele *in vivo* could be different than in heterologous cells.

In the future, additional replication studies using independent populations should reexamine the association of *KCNE1*-G38S with heart failure. Longitudinal studies of subjects with heart failure should also be studied to determine if *KCNE1*-G38S is associated with a survival advantage. Finally, electrophysiological studies of human ventricular cardiac myocytes

homozygous for either of the two genotypes, possibly obtained from patient-derived induced pluripotent stem cells, would be valuable to determine the effects of the variant on native repolarizing currents.

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