S38G single-nucleotide polymorphism at the KCNE1 locus is associated with heart failure

S38G single-nucleotide polymorphism at the *KCNE1* locus is associated with heart failure

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BACKGROUND Prolongation of the action potential duration, whose major determinants are the delayed-rectifier potassium currents, is a hallmark of failing ventricular myocardium. Genetic variants in the *KCNE1* gene, encoding for the β-subunit (minK) of a slowly activated cardiac potassium channel (I_{ks}), may impair myocardial repolarization. Experimental data demonstrated a higher *KCNE1* expression in heart failure (HF).

OBJECTIVE The purpose of this study was to investigate the association between a *KCNE1* S38G single-nucleotide polymorphism (SNP) and HF.

METHODS We genotyped 197 out of 323 previously investigated patients and 352 healthy controls comparable for age and sex. This study was replicated in 186 HF patients and in 200 healthy subjects comparable for age and sex and recruited from the Department of Cardiovascular Medicine of the National Research Council, Pisa, Italy.

RESULTS A significant difference in genotype distribution and allele frequency between patients and controls was observed for the *KCNE1* S38G SNP ($P = .002$ and $P = .0008$, respectively). The *KCNE1* 38G variant was associated with a significant predisposition to HF under a dominant (odds ratio [OR] = 2.22 [1.23–3.28]; $P = .008$) and additive (OR = 2.13 [1.09–4.15]; $P = .03$) model, after adjustment for age, sex, and traditional cardiovascular risk factors. No difference in genotype distribution and allele frequency for the *KCNE1* S38G SNP according to functional New York Heart Association class was found ($P = .4$ and $P = .3$, respectively). In the HF replication study, the *KCNE1* 38G allele frequency was significantly higher in comparison with that observed in the control population (38G = 0.59 vs. 0.49; $P = .004$). The 38G allele was associated with HF predisposition under the recessive (OR [95% confidence interval (CI)] = 2.49 [1.45–4.29]; $P = .001$) and additive models (OR [95% CI] = 2.63 [1.29–5.35]; $P = .008$), after adjustment for traditional risk factors.

CONCLUSION *KCNE1* S38G SNP is associated with HF predisposition in two study populations. Nevertheless, further studies performed in larger populations and aimed to better define the role of this locus are required.

KEYWORDS Heart failure; KCNE1 gene; S38G SNP

ABBREVIATIONS **APD** = action potential duration; **CAD** = coronary artery disease; **EF** = ejection fraction; **HC** = hypertensive cardiomyopathy; **HF** = heart failure; **HC** = hypertensive cardiomyopathy; **LVEDD** = left ventricular end-diastolic diameter; **LVESD** = left ventricular end-systolic diameter; **NYHA** = New York Heart Association; **SNP** = single-nucleotide polymorphism

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Introduction

Heart failure (HF) results from any structural or functional cardiac disorder that impairs heart function. Ventricular arrhythmias are a common cause of sudden death in HF patients;[1] nevertheless, the underlying mechanism of arrhythmia is poorly understood. Prolongation of the action potential duration (APD) is a hallmark of a failing ventricular myocardium,[2] in particular in the setting of an increased dispersion of repolarization.[3] The rapid (I_{Kr}) and slow (I_{Ks}) components of the delayed-rectifier potassium current are the major determinants of APD.[4] The slow component of the potassium current is related to minK and KCNQ1 channel subunits function. The minK protein is encoded by the *KCNE1* gene located on chromosome 21q22.12, and mutations in this gene may impair the slowly activating cardiac delayed-rectifier (I_{Ks}) current,[5] thus contributing to modulating myocardial repolarization. An experimental study performed on human endomyocardial

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biopsy samples demonstrated a higher *KCNE1* gene expression in HF patients.[6]

The *KCNE1* locus has been investigated in nonvalvular atrial fibrillation patients,[7,8] but to the best of our knowledge no data concerning its influence on HF susceptibility are available. Accordingly, in the present study we investigated the association between the *KCNE1* S38G single-nucleotide polymorphism (SNP) and HF patients, and we validated data in a different HF population.

Methods

Study populations

Florence HF patients

One hundred ninety-seven (156 males/39 females, age 73 [20–95] years) HF Caucasian patients from Tuscany who were previously investigated[9] were genotyped for the *KCNE1* S38G polymorphism. Inclusion criteria were diagnosis of HF according to the Framingham criteria[10] and the presence of a left ventricular dysfunction defined as an ejection fraction (EF) <40% by echocardiography performed on hospital admission. The cause of HF was determined in each patient by clinical assessment and echocardiography. The etiology of HF was classified as coronary artery disease (CAD; n = 103), hypertensive cardiomyopathy (HC; n = 2), or idiopathic dilated cardiomyopathy (IDCM; n = 92) on the basis of disease history and coronary angiographic evaluation. Owing to the role of the *KCNE1* gene in influencing the susceptibility to atrial fibrillation,[7,8] in this study atrial fibrillation patients (n = 39) were excluded. Moreover, the exclusion criterion for patients was the presence of familial cardiomyopathy (n = 1), as gene mutations involved in modulating arrhythmogenic disorders may be related to the pathogenesis of ventricular cardiomyopathies, in particular polymorphisms in the *KCNE1* gene.[11]

Pisa HF patients

One hundred eighty-six HF Caucasian patients (134 males and 52 females, age 72 [24–97] years) from Tuscany, enrolled from the Department of Cardiovascular Medicine of the National Research Council, Pisa, were investigated to perform the replication study. Inclusion criteria were diagnosis of HF according to the Framingham criteria[10] and the presence of a left ventricular dysfunction defined as an EF <40% by echocardiography performed on hospital admission. The cause of HF was determined in each patient by clinical assessment and echocardiography. The etiology of HF was classified as CAD (n = 99), HC (n = 14), or IDCM (n = 73) on the basis of disease history and coronary angiographic evaluation. Exclusion criteria were the presence of familial cardiomyopathy (n = 0) and atrial fibrillation (n = 46).

The subjects were considered to have hypertension according to the guidelines of the European Society of Hypertension/European Society of Cardiology[12] or if they were taking antihypertensive drugs. Dyslipidemia was defined according to the Third Report of the National Cholesterol Education Program,[13] and diabetes was defined in agreement with the American Diabetes Association.[14] All subjects gave informed consent, and the study complies with the Declaration of Helsinki and was approved by the local ethics committee.

Control subjects (Florence and Pisa)

Three hundred fifty-two Caucasian control subjects, comparable for age and gender, were invited to participate in the study and consisted of partners or friends of patients and subjects from a population study, "Progetto Nutrizione per la Salute e la Prevenzione di Malattia," conducted between 2002 and 2004 and aimed to evaluate the lifestyle and dietary habits of clinically healthy persons living in Florence, Italy. Exclusion criteria for the controls were personal and family history of cardiovascular disease. A detailed interview addressed to personal and familial history was performed in the framework of a physical examination by expert physicians to identify symptom-free subjects and to exclude those who were suspected of having any form of vascular disease.

Two hundred Caucasian control subjects enrolled from healthy persons living in Pisa were used for the replication study. Exclusion criteria for the controls were personal and family history of cardiovascular disease. A detailed interview addressed to personal and familial history was performed in the framework of a physical examination by expert physicians to identify symptom-free subjects and to exclude those who were suspected of having any form of vascular disease.

Detection of KCNE1 S38G polymorphism

The S38G (112A>G) *KCNE1* gene SNP was analyzed through polymerase chain reaction-Restriction Fragment Length Polymorphism (RFLP) analysis as described elsewhere.[8]

Statistical analysis

Statistical analysis was performed by using the SPSS (Statistical Package for Social Sciences, Chicago) software for Windows (version 11.5). The χ^2-test was used to test for deviation of genotype distribution from Hardy-Weinberg equilibrium. The association between *KCNE1* SNP and HF was assessed using logistic regression analysis under a dominant, recessive, and additive genetic model.

The dominant genetic model compares individuals with one or more polymorphic alleles with a baseline group with no polymorphic alleles (e.g., *KCNE1* 38GG + GS vs. SS). The recessive genetic model compares the 38GG genotype with the combined GS + SS genotypes, which form the baseline group. The additive genetic model assumes that there is a linear gradient in risk between the 38GG, 38GS, and 38SS genotypes (38SS genotype baseline). This is equivalent to a comparison of the 38G allele versus the 38S allele (baseline). $P < .05$ was considered statistically significant (two-sided P-value).

We performed a replication study in different Caucasian HF and control populations to further strengthen the claim of predisposition for the *KCNE1* S38G polymorphism in HF

Table 1 Demographic and clinical characteristics of study populations (Florence HF and controls)

	Florence HF (n = 195)	Florence controls (n = 352)
Age, years, median (range)	73 (20–95)	72 (36–93)
Males/females	156/39	259/94
Hypertension	103 (52.8)	116 (33.0)
Dyslipidemia	58 (29.4)	72 (20.5)
Diabetes	58 (29.4)	25 (7.1)
Smoking habit	92 (46.7)	64 (18.2)
CAD	103 (52.2)	—
IDCM	92 (46.7)	—
HC	2 (1.01)	—
LVEF <40%	149 (75.6)	—
Chronic renal failure	33 (16.7)	—
NT-proBNP, pg/mL, median (range)	3564 (52–37,940)	—
NYHA class:		
II	51 (25.8)	—
III	73 (37.1)	—
IV	73 (37.1)	—
KCNE1 S38G genotype distribution[a] and allele frequency[b]:		
KCNE1 38GG	71 (36.0)	98 (27.8)
*KCNE1*38SG	99 (50.3)	161 (45.7)
*KCNE1*38SS	27 (13.7)	93 (26.4)
KCNE1 38G	0.61	0.51

Note: Values are n (%) unless otherwise indicated. LVEF: left ventricular ejection fraction.
[a]$P = .002$.
[b]$P = .0008$.

patients. The same healthy control population was used in this replication study.

Results

The demographic and clinical characteristics of the study populations are reported in Tables 1 and 2. The prevalence of traditional cardiovascular risk factors was significantly higher in Florence HF patients in comparison with that observed in the control group ($P < .05$). In the Pisa HF patients, we observed a significant difference in the prevalence of all traditional risk factors between patients and controls ($P < .05$).

No deviation from the expected population genotype proportions predicted by the Hardy-Weinberg equilibrium was detected at the *KCNE1* locus. A significant difference in genotype distribution and allele frequency between patients and controls was observed for the *KCNE1* S38G SNP in both the populations investigated (Tables 1 and 2).

Florence HF patients

The *KCNE1* S38G genotype distribution and allele frequency were investigated in relation to a HF clinical subset (Table 3). A significantly higher prevalence of the *KCNE* 38G variant was observed in HF hypertensives, diabetics, smokers, and HF patients with a history of CAD than in controls (Table 3). The *KCNE1* 38G variant was associated with a significant predisposition to HF under all three genetic models of inheritance (dominant, recessive, and additive; Table 4). After adjustment for age, sex, and traditional cardiovascular risk factors, the *KCNE1* 38G allele significantly and independently influenced the susceptibility to HF under a dominant and additive but not recessive model (Table 4).

No difference in genotype distribution and allele frequency for the *KCNE1* S38G SNP according to functional New York Heart Association (NYHA) class was found ($\chi^2 = 5.3$, $P = .4$ and $\chi^2 = 3.4$, $P = .3$, respectively).

The role of *KCNE1* S38G SNP has been analyzed according to parameters related to the severity of HF, such as EF, left ventricular end-diastolic diameter (LVEDD), and left ventricular end-systolic diameter (LVESD); a relationship, even not significant, between the *KCNE1* 38G allele and altered hemodynamic parameters (EF 38G = 0.62, LVEDD 38G = 0.64, and LVESD 38G = 0.63, respectively) was observed.

Pisa HF patients

To validate our results, we have replicated this study in different Caucasians HF and control populations enrolled from the Department of Cardiovascular Medicine of the National Research Council, Pisa. Data from the replication study demonstrated similar findings concerning the role of the *KCNE1* S38G polymorphism in modulating susceptibility to HF. The *KCNE1* 38G variant significantly influenced the predisposition to HF under the recessive and additive but not dominant model of inheritance after adjustment for age, sex, and cardiovascular risk factors (Table 5).

Table 2 Demographic and clinical characteristics of study populations (Pisa HF and controls)

	Pisa HF (n = 186)	Pisa controls (n = 200)
Age, years, median (range)	72 (24–97)	71 (36–96)
Males/females	134/52	129/71
Hypertension	79 (42.5)	65 (32.5)
Dyslipidemia	69 (37.0)	45 (22.5)
Diabetes	47(25.3)	16 (8.0)
Smoking habit	72 (38.7)	35 (17.5)
CAD	99 (53)	—
IDCM	73 (39)	—
HC	14 (8)	—
LVEF <40%	143 (77)	—
Chronic renal failure	73 (39)	—
NT-proBNP, pg/mL, median (range)	1211 (10–38,200)	—
NYHA class:		
II	115 (62.0)	—
III	52 (28.0)	—
IV	19 (10)	—
KCNE1 S38G genotype distribution[a] and allele frequency[b]:		
KCNE1 38GG	65 (34.9)	47 (23.5)
*KCNE1*38SG	90 (48.4)	101 (50.5)
*KCNE1*38SS	31 (16.7)	52 (26.0)
KCNE1 38G	0.59	0.49

Note: Values are n (%) unless otherwise indicated. LVEF = left ventricular ejection fraction.
[a]$P = .01$.
[b]$P = .004$.

Table 3 *KCNE1* S38G polymorphism genotype distribution and allele frequency according to subsets of Florence HF patients

	Hypertension, n = 103	Dyslipidemia, n = 58	Diabetes, n = 58	Smoking habit, n = 92	CAD, n = 103	IDCM, n = 92	LVEF<40%, n = 149	Chronic renal failure, n = 33
KCNE1 38GG	34 (33.0)	21 (36.2)	21 (36.2)	38 (41.3)	35 (34.0)	34 (37.0)	56 (37.6)	10 (30.3)
KCNE1 38SG	57 (55.3)	28 (48.3)	30 (51.7)	41 (44.6)	53 (51.5)	39 (42.4)	73 (49.0)	14 (42.4)
KCNE1 38SS	12 (11.7)	9 (15.5)	7 (12.1)	13 (14.1)	15 (14.6)	19 (20.6)	20 (13.4)	9 (27.3)
KCNE1 38G	0.61	0.60	0.62	0.64	0.60	0.58	0.62	0.51
Allele frequency (*P*-value)[a]	.01	.05	.02	.002	.02	.07	.001	.9
Genotype distribution (*P*-value)[a]	.007	.2	.05	.01	.04	.2	.003	.9

Note: Values are n (%) unless otherwise indicated. LVEF = left ventricular ejection fraction.
[a]χ^2-test: allele frequency and genotype distribution vs. controls.

Discussion

This is the first study in which the effect of the *KCNE1* gene has been evaluated as a potential predisposing factor to HF. The results of the present study provide evidence of its role in predisposing to HF apart from cardiovascular risk factors but not in modulating the severity of the disease. These findings have been replicated in a separate HF population with the same genetic background and recruited from the Department of Cardiovascular Medicine of Pisa.

Data from the replication study confirmed the role of the *KCNE1* 38G allele in influencing the predisposition to the disease, independently of the presence of traditional cardiovascular risk factors. The two study populations investigated were comparable for sex and age but not for the percentage of cardiovascular risk factors. Accordingly, these findings stressed the role of the *KCNE1* gene in modulating HF susceptibility *per se*, despite the presence or absence of traditional cardiovascular risk factors.

Little information is available on the genetic modulation of delayed-rectifier potassium currents in humans.[15,6] Data from experimental studies performed in rabbit and human hearts demonstrated a prolongation of the APD in left ventricular myocytes isolated from failing rabbit ventricles[16] and that *KCNE1* gene expression was significantly higher in myocytes from HF patients in comparison with controls, thus contributing to the prolongation of the QT interval through reducing the net outward current during the plateau of the action potential.[6]

The *KCNE1* gene encodes for a single transmembrane domain protein (minK), which represents the β-subunit of a potassium channel able to conduct the slow component (I_{Ks}) of the delayed-rectifier current, which is relevant in the repolarization of cardiac myocytes. The minK protein cytoplasmatic domain is also able to interact with regulatory proteins, such as the sarcomeric Z-line component T-cap (telethonin), which is involved in cardiac muscle contraction. Indeed, it has been reported that the biomechanical stress during myocardium contraction-relaxation cycles may contribute to determining an altered ion channel localization, thus possibly influencing the ionic properties of cardiac tissue.[17,18]

An SNP in the *KCNE1* gene (A to G at position 112), leading to a glycine substitution for serine at amino acid position 38, has been identified.[19] The functional significance of the S38G polymorphism in the *KCNE1* gene remains unclear. An experimental study documented that the minK 38G isoform was associated with reduced I_{Ks} current, thus resulting in increased APD,[20] whereas data from the KORA study[21] did not evidence its modifying effect on the QT interval. Indeed, the *KCNE1* S38G SNP might not have a causal effect on the I_{Ks} current, but it could be a marker in linkage disequilibrium with another functional variant. An association between the *KCNE1* S38G SNP and atrial fi-

Table 4 Univariate and multivariate analysis for cardiovascular risk factors and *KCNE1* S38G polymorphism according to dominant, recessive and additive genetic models (Florence HF patients and controls)

Univariate analysis	Odds ratio (95% CI)	*P*
Age	0.99 (0.97–1.004)	.2
Sex	0.69 (0.45–1.05)	.08
Hypertension	2.28 (1.59–3.26)	<.0001
Smoking habit	2.12 (1.41–3.18)	<.0001
Diabetes	5.54 (3.23–9.22)	<.0001
Dyslipidemia	1.65 (1.10–2.46)	.01

	Dominant model		Recessive model		Additive model	
Genetic polymorphism	Odds ratio (95% CI)	*P*	Odds ratio (95% CI)	*P*	Odds ratio (95% CI)	*P*
Univariate analysis, *KCNE1* S38G	2.40 (1.48–3.89)	<.0001	1.45 (1.00–2.12)	.049	2.62 (1.53–4.89)	<.0001
Multivariate analysis,[a] *KCNE1* S38G	2.22 (1.23–3.98)	.008	1.13 (0.72–1.78)	.6	2.13 (1.09–4.15)	.03

Note: CI: confidence interval.
[a]Adjusted for age, sex, and cardiovascular risk factors.

Table 5 Univariate and multivariate analysis for cardiovascular risk factors and *KCNE1* S38G polymorphism according to dominant, recessive and additive genetic models (Pisa HF patients and controls)

Univariate analysis	Odds ratio (95% CI)	*P*
Age	0.99 (0.97–1.01)	.2
Sex	0.70 (0.46–1.09)	.1
Hypertension	1.53 (1.01–2.32)	.04
Smoking habit	2.98 (1.86–4.76)	<.0001
Diabetes	3.89 (2.12–7.15)	<.0001
Dyslipidemia	2.03 (1.30–13.7)	.002

	Dominant model		Recessive model		Additive model	
Genetic polymorphism	Odds ratio (95% CI)	*P*	Odds ratio (95% CI)	*P*	Odds ratio (95% CI)	*P*
Univariate analysis, *KCNE1* S38G	1.76 (1.07–2.89)	.03	1.75 (1.12–2.73)	.01	2.32 (1.29–4.15)	.005
Multivariate analysis,[a] *KCNE1* S38G	1.54 (0.84–2.81)	.2	2.49 (1.45–4.29)	.001	2.63 (1.29-5.35)	.008

Note: CI: confidence interval.
[a]Adjusted for age, sex, and cardiovascular risk factors.

brillation has been investigated,[7,8] but no data are available on HF susceptibility. We previously demonstrated that the *KCNE1* gene was associated with atrial fibrillation, possibly by modulating the ionic properties of the atria and in turn their irregular activation.[8] The present study, in which patients with atrial fibrillation have been excluded, provides evidence for a role of the same gene in modulating HF predisposition. Therefore, we could hypothesize that the *KCNE1* gene, through the modulation of I_{Ks} current, may affect alterations in ionic properties in both atrial and ventricular myocytes, thus determining two different clinical phenotypes.

A limitation of this study is the lack of information concerning electrocardiogram data, and in particular QTc values, as the *KCNE1* gene has been demonstrated to be associated with QT interval prolongation in HF.[6]

Our results failed to demonstrate the influence of the *KCNE1* locus on the severity of the disease, as no difference in *KCNE1* 38G allele frequency has been observed according to NYHA class. This datum possibly strengthens the observation that the *KCNE1* locus could be involved in the electrical damage in HF but not in its progression.

Findings from the present study, which have been replicated in a different population, are intriguing for the novelty of the data. Nevertheless, owing to the limited sample size, further studies performed in larger populations are required to better define the role of the *KCNE1* S38G SNP in influencing not only HF susceptibility but also the severity of the disease.

Conclusion

This preliminary study shows an association between the *KCNE1* gene, which is involved in the modulation of I_{Ks} delayed-rectifier potassium current, and HF, thus providing new highlights for investigating the contribution of cardiac potassium channels.

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