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REVIEW

RAAS and adrenergic genes in heart failure: Function, predisposition and survival implications

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Abstract

It is well appreciated that several neurohormones and signaling cascades are activated that promote long-term deterioration of cardiac function and structure. Activation of the renin-angiotensin-aldosterone system (RAAS) and the adrenergic system is closely related to heart failure. Common gene variants that encode neurohormonal, adrenergic and intracellular proteins have been demonstrated to modulate the course and consequences of heart failure. However, the literature is replete with conflicting results and it remains uncertain as to whether particular gene variants predispose heart failure. Therefore, the main purpose of this review was to discuss the effects of single nucleotide polymorphisms (SNPs) that are located in genes encoding elements of the RAAS and the adrenergic system on the predisposition to and survival from heart failure. Most studies indicate that common SNPs encoding elements of the RAAS and the adrenergic system do not predispose individuals to heart failure. Conversely, it has been demonstrated that ARB1 Arg389Gly, GRK5 Gln41Leu, ACE I/D, CYP11B2 C-344T and AGTR1 A+1166C modulate pharmacological responses and have a considerable impact on cardiac-related survival. It should not be expected, however, that a single polymorphism determines survival, given that multiple gene products and environmental factors contribute to the pathogenesis of heart failure. Therefore, future studies should consider the interaction effects of multiple genes in populations that are as homogeneous as possible with respect to environmental characteristics.

Key words: Cardiac failure; Polymorphisms; Susceptibility; Mortality

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INTRODUCTION

In recent years, the incidence of heart failure has continued to increase along with sustained elevated rates of morbidity and mortality[1]. It is now well appreciated that several neurohormonal and signaling cascades are activated that promote long-term deterioration of cardiac function and structure[2] (Figure 1). These changes, collectively referred to as cardiac remodeling, are modulated by genetic factors[3].

The renin-angiotensin-aldosterone system (RAAS) plays a pivotal role in the processes of heart failure. In response to sustained activation of the RAAS, the angio-

tensin-II receptors are deregulated in the human failing heart[4]. Several downstream intracellular signaling effectors are overexpressed and activated in tandem with cardiac hypertrophy[5]. The adrenergic system is also closely related to heart failure. Adrenergic receptors are deregulated in human heart failure in concert with impaired ventricular contraction and relaxation[6].

It seems that the molecular portrayal of heart failure is incomplete as molecular and genetic studies continue to recognize genes and signaling cascades that participate in the development and progression of heart failure[7]. In addition to the discovery of disease-causing (rare) mutations, common variants in genes that encode neurohormonal, adrenergic, intracellular and interstitial proteins have been demonstrated to modulate the course and consequences of heart failure. The literature, however, is replete with conflicting results and intense debate exists as to whether gene polymorphisms determine susceptibility to developing heart failure. Considering the prominent role of the RAAS and adrenergic receptors in the pathophysiology of heart failure, this review focuses on functional single nucleotide polymorphisms (SNPs) that appear to be related to the predisposition to and the survival from heart failure.

FUNCTIONAL PROPERTIES OF GENE POLYMORPHISMS

β-adrenergic receptors

The gene encoding the β_1-adrenergic receptor is located on chromosome 10q24-26 and contains no introns. Several SNPs have been described in this gene, with two having been demonstrated to be functional and relevant for heart failure[8,9]. One of these polymorphisms is derived from a transition between the amino acids arginine and glycine in residue 389 (*Arg*389*Gly*)[10]. Given that this variant is located in the carboxyl terminal, it follows that variant alleles may have a distinct binding to G proteins and thus may have distinct signaling characteristics. The other variant is located at residue 49, wherein amino-acid serine is replaced by glycine (*Ser*49*Gly*)[11]. The functional properties of these SNPs have been demonstrated in transgenic animals as well as studies *in vitro*, *ex vivo* and *in vivo*. For example, numerous *in vitro* studies have demonstrated that cells expressing the human variant *Arg*389 have increased adenylyl cyclase activity in response to agonists compared to those expressing *Gly*389[10,12]. Upon agonist activation, the former variant appears more prone to desensitization and may predispose to heart failure under certain conditions; e.g. increased catecholamine stimulation[13]. These findings have been substantiated in numerous *ex vivo* and *in vivo* human and animal studies[10,14-16] in which mice expressing *Arg*389 have increased contractile responses to agonists and exhibited faster and greater desensitization upon activation[17]. Nonetheless, most human studies have shown identical hemodynamic responses to exercise in both variants[18,19]. While not in all studies, it has been demonstrated that *Gly*49 has similar characteristics to *Arg*389, showing increased contractile responses and desensitization upon stimulation with agonists[11,20]. Together, these data indicate that individuals who harbor *Arg*389 and *Gly*49 may have increased cardiac remodeling under adverse conditions.

The gene encoding the β_2-adrenergic receptor is located on chromosome 5q31-32. Among numerous gene variants, two non-synonymous polymorphisms, namely *Arg*16*Gly* and *Gln*27*Glu,* have to some extent been related to cardiac functional changes[8,9]. Although consistent evidence has shown that these SNPs have no influence on agonist-mediated contractile responses, *in vitro* studies have reported that *Gly*16 and *Gln*27 are more prone to desensitization than *Arg*16 and *Glu*27[21]. Thus, these variants might be relevant to heart failure. However, some *ex vivo* and *in vivo* human studies showed that *Gly*16 is more resistant to agonist-mediated desensitization than *Arg*16[22]. The contrasting results are not easily explained, but may stem from the predominant desensitization of *Gly*16 from endogenous catecholamines[9,23]. In contrast, another SNP (*Thr*164*Ile*) has been shown to modulate cardiac contractile responses *in vitro* and *in vivo*. Consistent evidence indicates that *Ile*164 presents reduced basal and agonist-mediated intracellular effector activation, contractile response and heart rate as compared to *Thr*164[24-26]. However, most humans possess two copies of threonine, casting doubts as to whether this variant is relevant to heart failure.

α-adrenergic receptors

The α_1-adrenergic receptors encompass three subtypes, the genes for which are located in different chromosomes. Nonetheless, only α_{1A} and α_{1B} receptors seem to be translated and are functional in the human heart[27]. Several gene variants have been reported, though many are uncommon or non-functional (for a review, see reference[28]). A common variant of α_{1A} receptors, resulting from the substitution of arginine for cysteine, is located in the residue 347 (*Arg*347*Cys*) and has been expressed *in vitro*[29]. There were no differences with respect to antagonist and agonist binding affinities, intracellular calcium concentrations or receptor desensitization upon stimulation with noradrenaline. In contrast, another gene polymorphism located in the intracellular loop seems functional; the *Gly*247*Arg* variant enhances G-protein binding, inositol phosphate production and cellular growth[30]. Moreover, non-synonymous polymorphisms located in transmembrane domains have been reported to decrease ligand binding and receptor activation, including the *Arg*166*Lys* and *Val*311*Ile*[30]. To our knowledge, however, these three polymorphisms have never been studied in patients with heart failure.

The α_2 adrenergic receptors also comprise three subtypes. The α_{2A} and α_{2C} are encoded by single genes and are both important in controlling noradrenaline release in pre-synaptic nerve terminals[31]. Among the α_{2A} receptors, a particular gene polymorphism appears to be functional

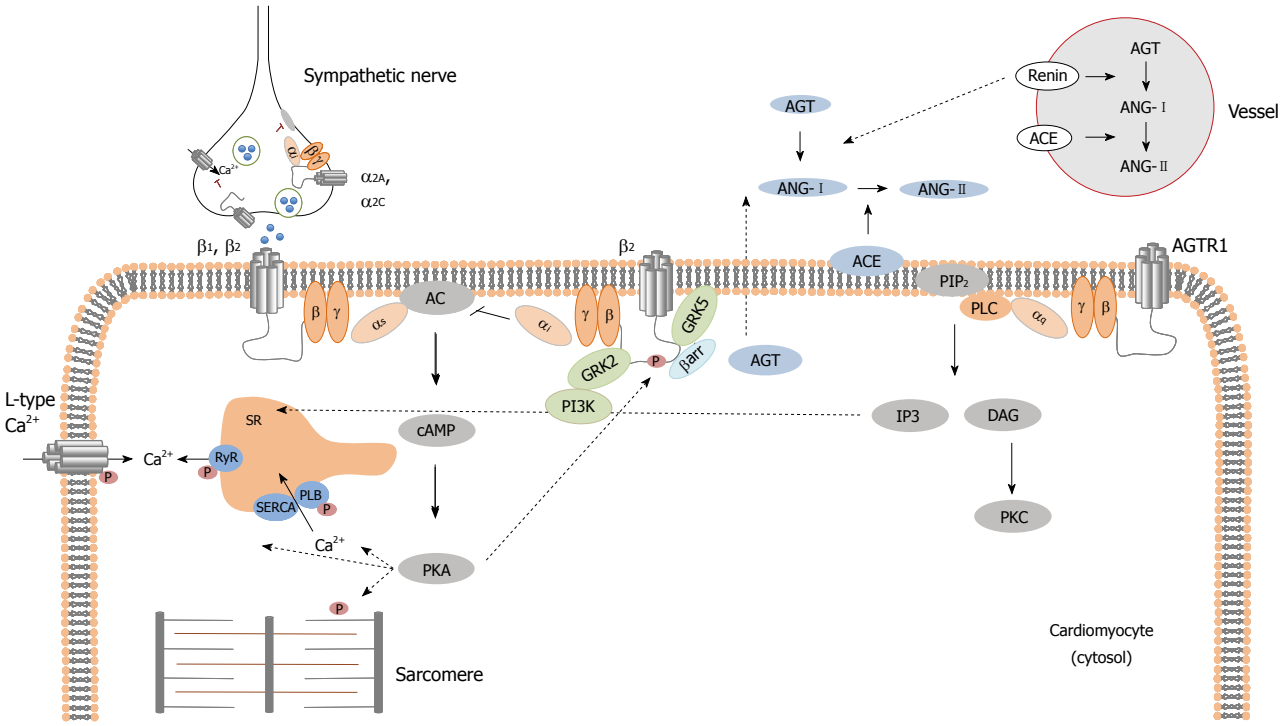

Figure 1 Adrenergic and renin-angiotensin-aldosterone system signaling pathways. AC: Adenylyl cyclase; ACE: Angiotensin-converting enzyme; AGT: Angiotensinogen; ANG: Angiotensin; cAMP: Cyclic Adenosine Monophosphate; βarr: β-arrestin; DAG: Diaglycerol; GRK2: G-protein coupled receptor kinase 2; GRK5: G-protein coupled receptor kinase 5; IP3: Inositol trisphosphate; PI3K: Phosphoinositide 3-kinase; PIP2: Phosphatidylinositol 4,5-biphosphate; PKA: Protein kinase A; PKC: Protein kinase C; PLC: Phospholipase C; SR: Sarcoplasmic reticulum.

and has been described in the context of heart failure. This polymorphism is located in a cytoplasmic domain and occurs in amino acid 251, where an asparagine or lysine is present (*Asn*251*Lys*)[32]. Transfected cells with *Lys*251 have shown enhanced coupling to Gi-proteins, effective inhibition of adenylyl cyclase and activation of mitogen-activated protein kinases[32]. Thus, this variant could reduce noradrenaline release and confer protection under conditions of increased catecholamine stimulation, such as heart failure. In α_{2C} receptors, a polymorphism has been demonstrated to be functional and related to heart failure. The Del322-325 derives from a 12 nucleic acid deletion and generates a receptor that lacks four amino acids (glycine, alanine, glycine, proline) in the third intracellular loop[33]. As a result, the generated receptors have reduced ligand-binding affinity, adrenaline-promoted coupling to Gi-proteins, inositol phosphate production and stimulation of mitogen-activated protein kinases[33].

G-protein receptor kinases

Besides second-messenger protein kinases, the particular class of G-protein coupled receptors kinases (GRK) modulates agonist-promoted desensitization and internalization of G-protein coupled receptors[34]. Among seven isoforms, GRK2 and GRK5 predominate in the myocardium and have been demonstrated to be important during heart failure[34]. While GRK2 showed no non-synonymous polymorphisms, four non-synonymous variants have been found in GRK5[35]. Of these, the substitution of leucine by glutamine in amino acid 41 (*Gln*41*Leu*) enhanced isoproterenol-promoted desensitization and decreased signaling of β_1-adrenergic receptors. Consistent with these observations, the *Leu*41 allele has shown a protective effect against experimental cardiomyopathy induced by catecholamines. Nonetheless, this gene polymorphism is extremely uncommon in Caucasians[35].

RAAS POLYMORPHISMS AND HEART FAILURE

Activation of the RAAS is one of the earlier and critical steps in heart failure. Although important to maintaining circulatory homeostasis, unremitting activation imposes a significant load on the heart and activates an immense and intricate signaling pathway[36]. As a consequence, several elements of this system are deregulated in heart failure, including angiotensinogen, angiotensin-converting enzyme (ACE), angiotensin-Ⅱ receptors and aldosterone[2,4].

Angiotensinogen

The gene encoding angiotensinogen is located on chromosome 1q42-q43 and contains various gene polymorphisms[37]. Two of these polymorphisms have been investigated particularly in heart failure[38]. A polymorphism on exon 2 causes the substitution of methionine to threonine in amino acid 235 (*M*235*T*). This polymorphism is in close linkage disequilibrium with another polymorphism in the promoter region, the -6 G/A variant, and is associated with plasma angiotensinogen concentrations[39].

Another polymorphism results from a threonine to methionine substitution in position 174. This polymorphism has been related to changes in cardiac function in patients with heart failure, although its functional implications remain unknown[38].

ACE

The ACE converts angiotensin-Ⅰ into angiotensin-Ⅱ, which activates angiotensin-Ⅱ receptors for modulating various cardiovascular responses, including vasoconstriction and cardiac growth[36]. The gene that encodes ACE is located on chromosome 17q23. Despite the fact that more than 100 polymorphisms have been found in the ACE gene, a variant based on the presence (insertion) or absence (deletion) of 287 base pairs in intron 16 have been described and tested more than any other polymorphism[37]. An initial study demonstrated that the *ACE I/D* polymorphism accounts for more than 40% of the total variance in serum ACE, with subjects harboring *D* alleles having increased concentrations[40]. Nonetheless, its functional role *in vivo* is still under strong debate, as numerous studies have reported no association between *ACE I/D* genotypes and hypertension[41].

Aldosterone

Another important element is aldosterone, whose synthesis is stimulated by angiotensin-Ⅱ[42]. Aldosterone is synthesized in the adrenal gland by aldosterone synthase, whose gene (CYP11B2) is located on chromosome 8q22[43]. A common polymorphism at position -344 within the promoter region (*C*-344*T*) has been described to be functional *in vitro* and determines concentrations of aldosterone[44,45]. In particular, the -344*C* allele has four times more binding affinity to the steroidogenic transcription factor 1 than the *T* allele and has been associated with increased production of aldosterone[45,46].

Angiotensin-Ⅱ receptors

Two distinct subtypes of angiotensin-Ⅱ receptors mediate the predominant actions of the renin-angiotensin system[47]. The gene encoding the type Ⅰ receptor (AGT1R) is located on chromosomes 3q21-3q25. A particular gene polymorphism (*A*+1166*C*) in the 3' untranslated region has been demonstrated to determine receptor expression and has been associated with hypertension. In particular, the presence of the +1166*C* allele seems to eliminate a particular microRNA (mir-155) binding site, preventing the receptors downregulation that occurs in the +1166*A* allele. The net result is increased receptor expression in +1166C[48]. Aligned with these observations, the +1166*C* allele has been associated with hypertension[49].

THE ROLE OF GENE POLYMORPHISMS ON THE PREDISPOSITION TO HEART FAILURE

To determine whether gene polymorphisms increase the chances of developing heart failure, several studies have investigated whether the proportion of functional alleles differs among affected and unaffected populations. Although contrasting results are abundant, most studies have found no differences in allele frequencies among patients and the general population (Tables 1 and 2).

Adrenergic receptors and G-protein receptor kinases

Given their role in β_1-adrenoceptors signaling and receptor desensitization, *Arg*389 and *Gly*49 alleles have been hypothesized to predispose heart failure. However, most studies to date have found no differences in allele frequencies between patients and healthy individuals[50-58]. Likewise, numerous investigations have demonstrated a similar genotype within β_2 adrenergic receptors in heart failure patients and the general population[51,59]. On the other hand, two studies reported that *Gly*16 and *Glu*27 were more frequent in end-stage heart failure patients[52,60]. Given that these variants are more resistant to desensitization, patients could be more exposed to intracellular signaling and maladaptive cardiac hypertrophy. However, this association remains to be established. In addition, a foremost study advocated that genetic variation in α_{2C} adrenoreceptors might predispose people to heart failure[54]. African Americans who are homozygous for the *Del*322-325 allele presented five times the odds for developing heart failure. The odds were augmented markedly among persons who were homozygous for both *Del*322-325 and *Arg*389. It makes reasonable sense that these variants predispose for heart failure by combining increased noradrenaline release with increased adrenergic signaling. However, more recent studies have not replicated these observations[53,56]. Furthermore, the GRK5 functional polymorphism also seems unrelated to heart failure predisposition. In a leading study, the proportion of *Gln*41 alleles was similar among African- and European-American patients and controls[35]. Together, these data show that most, if not all, polymorphisms play no role in the predisposition to heart failure. These observations have been substantiated in a recent large-scale genome-wide scan association study[74]. This study included more than 23 000 individuals, among whom almost 3000 developed heart failure during a 13-year follow-up, and assessed almost 2.5 million markers. Only two markers exceeded the genome-wide threshold for significance. One SNP was found in individuals with European ancestry and was located near the ubiquitin-specific protease gene 3. The other one was detected in individuals of African ancestry and was located close to the leucine-rich repeats and immunoglobulin-like domains 3 gene. Fourteen additional loci were identified, one of which is located in the GNA15 gene, which codes for a Gq-protein. The Gq-proteins are important mediators of α-adrenergic, endothelin and angiotensin-receptors signal transduction.

RAAS

The association between the *ACE I/D* polymorphism and heart failure was suggested in a leading study[62]. In that study, the proportion of *ACE DD* genotype was

Table 1 Effect of adrenergic gene polymorphisms on the predisposition to patients with heart failure

Gene/SNP	Ref.	Cases/controls	Ethnic group	Association	Risk allele frequency
β adrenergic receptor type 1					
Arg389Gly	[50]	201/141	Mixed	No	0.74 *vs* 0.76
	[51]	256/230	Italian	No	0.69 *vs* 0.73
	[52]	189/378	Italian	Yes	0.74 *vs* 0.67
	[53]	91/119	Japanese	No	0.80 *vs* 0.81
	[54]	78/84	African-American	No	0.52 *vs* 0.56
	[54]	81/105	Caucasians	No	0.74 *vs* 0.76
	[55]	426/395	French	No	0.77 *vs* 0.75
	[56]	403/429	South Africans	No	0.70 *vs* 0.69
	[57]	260/230	Italian	No	0.69 *vs* 0.73
Ser49Gly	[50]	201/141	Mixed	No	0.15 *vs* 0.15
	[58]	184/77	Swedish	No	0.18 *vs* 0.13
	[52]	189/378	Italian	Yes	0.14 *vs* 0.08
	[53]	91/119	Japanese	No	0.16 *vs* 0.16
β adrenergic receptor type 2					
Gly16Arg	[51]	256/230	Italian	No	0.61 *vs* 0.60
	[52]	189/378	Italian	Yes	0.67 *vs* 0.59
	[59]	259/212	Mixed	No	0.60 *vs* 0.63
	[60]	520/328	Mixed	Yes	0.62 *vs* 0.59
Gln27Glu	[51]	256/230	Italian	No	0.32 *vs* 0.31
	[52]	189/378	Italian	No	0.38 *vs* 0.33
	[59]	259/212	Mixed	No	0.44 *vs* 0.42
	[60]	520/328	Mixed	No	0.42 *vs* 0.40
	[61]	58/111	Canadians	No	0.41 *vs* 0.47
Thr164Ile	[52]	189/378	Italian	No	0.02 *vs* 0.01
	[59]	259/212	Mixed	No	0.02 *vs* 0.01
	[60]	520/328	Mixed	No	0.01 *vs* 0.01
5′LC-Arg19Cys	[52]	189/378	Italian	No	0.36 *vs* 0.31
α adrenergic receptor type 2					
Del 322-325	[53]	91/119	Japanese	Yes	0.04 *vs* 0.11
	[54]	78/84	African-Americans	Yes	0.61 *vs* 0.41
	[54]	81/105	Caucasians	No	0.10 *vs* 0.04
	[56]	403/429	South Africans	No	1.00 *vs* 1.00
G-protein receptor kinase 5					
Gln41Leu	[35]	242/107	African-Americans	No	0.76 *vs* 0.77
	[35]	568/406	European-Americans	No	0.98 *vs* 0.99

SNP: Single nucleotide polymorphism.

more than 50% higher in end-stage heart failure patients than in healthy controls. However, these observations have been called into question by numerous subsequent studies[63-69,75]. Likewise, the angiotensinogen *M*235 variant has not been associated with a predisposition to heart failure in most studies[61,66,70-72]. Similar results were reported for *T*174 and -6G/A variants[70-72]. One single study reported an association for these variants, although its small sample size precludes solid conclusions[61]. The aldosterone synthase polymorphism (-344*C*) is not more frequent in patients than controls[66,61,70], and neither are the AGT1R (+1116*C*) and AGT2R (*G*1675) polymorphisms[61,70,73]. Collectively, these data indicate that gene polymorphisms encoding elements of the RAAS also do not indicate predisposition for heart failure, at least in Caucasians.

THE ROLE OF GENE POLYMORPHISMS IN SURVIVAL FROM HEART FAILURE

Although most studies have shown that gene polymorphisms do not increase the risk for heart failure, functional gene polymorphisms might determine survival once heart failure develops. Stimulation of neurohormonal and interstitial proteins increases once the disease onsets. Hence, instead of predisposing to the disease, genetic variants might compromise heart function and survival by increasing function and expression of adverse proteins and/or by suppressing the favorable ones. However, even here the results are somewhat diverse and conflicting (Tables 3 and 4).

Adrenergic receptors and G-protein receptor kinases

Several lines of evidence have led to the belief that genes encoding β_1-receptors have no effect on clinical endpoints, including survival, hospitalization or heart transplantation[76-78]. Nonetheless, many clinical trials have not accounted for mortality for cardiac reasons and/or have not controlled for potential pharmacological confounding effects. For example, Liggett *et al*[15] demonstrated that patients who are homozygous for *Arg*389 and treated with bucindolol survive longer than patients treated with a placebo. In contrast, patients with *Gly*389 have not benefited from treatment with bucindolol. Biolo *et al*[50] also demonstrated that treatment dosage modulates survival in

Table 2 Effect of renin-angiotensin-aldosterone system gene polymorphisms on the predisposition to patients with heart failure

Gene/SNP	Ref.	Cases/controls	Ethnic group	Association	Risk allele frequency
Angiotensin-converting enzyme					
I/D	[62]	214/79	Caucasian	Yes	0.58 *vs* 0.56
	[63]	193/77	Swedish	No	0.57 *vs* 0.56
	[64]	229/230	Italian	No	0.58 *vs* 0.60
	[65]	99/364	Caucasian	No	0.57 *vs* 0.54
	[66]	157/225	South-Africans	No	0.64 *vs* 0.69
	[67]	90/287	Czech	No	0.54 *vs* 0.57
	[68]	79/102	Chinese Han	No	0.43 *vs* 0.40
	[69]	104/183	Chinese	No	0.36 *vs* 0.37
	[70]	433/401	French	No	0.54 *vs* 0.57
	[71]	88/122	Japanese	No	0.39 *vs* 0.36
	[61]	58/111	Canadians	No	0.64 *vs* 0.62
Angiotensinogen					
M235T	[66]	157/225	South-Africans	No	0.83 *vs* 0.87
	[72]	158/200	Czech	No	0.51 *vs* 0.43
	[72]	40/63 (women)	Czech	Yes	0.56 *vs* 0.39
	[70]	433/401	French	No	0.40 *vs* 0.43
	[71]	88/122	Japanese	No	0.80 *vs* 0.80
	[61]	58/111	Canadians	Yes	0.48 *vs* 0.31
T174M	[70]	433/401	French	No	0.12 *vs* 0.14
	[71]	88/122	Japanese	No	0.05 *vs* 0.10
	[61]	58/111	Canadians	Yes	0.18 *vs* 0.10
G(-6)A	[72]	158/200	Czech	No	0.59 *vs* 0.58
Angiotensin-Ⅱ type 1 receptor					
A1166C	[70]	433/401	French	No	0.28 *vs* 0.28
	[61]	58/111	Canadians	No	0.31 *vs* 0.33
	[73]	193/77	Swedish	No	0.29 *vs* 0.30
A-153G	[70]	433/401	French	No	0.16 *vs* 0.19
Aldosterone					
T-344C	[66]	157/225	South-Africans	No	0.21 *vs* 0.18
	[70]	433/401	French	No	0.43 *vs* 0.46
	[61]	58/111	Canadians	No	0.39 *vs* 0.45

SNP: Single nucleotide polymorphism; T174M: Threonine to methionine substitution in position 174.

patients harboring *Arg*389. Once again, all patients carrying *Gly*389 survived irrespective of treatment conditions. These data indicate that medication attenuates the negative impact that variant *Arg*389 has on survival. In contrast, mounting evidence shows that *Gly*49 has no impact on survival or heart transplantation endpoints, irrespective of medication[77,79]. Moreover, most studies to date have reported that *Gly*16 and *Glu*27 are not associated with survival related to heart failure[59,77,79]. Nonetheless, it may be that, rather than single polymorphisms, the haplotype may determine the chances of survival. Indeed, one investigation reported that patients carrying two copies of *Gly*16 and *Gln*27 have an increased risk of adverse events[78].

A number of studies have reported that individuals carrying the *Thr*164*Ile* variant have a worse prognosis than those carrying the *Thr*164 homozygous variant[59,80]. Even though *Thr*164*Thr* patients have improved survival rates upon treatment with β-blockers, individuals who carry the *Thr*164*Ile* variant seem to present the opposite response[81].

Similarly, *GRK5* gene variants are associated with different responses to medication and impact on survival. Liggett *et al*[35] showed that survival times were longer in *Gln*41 patients under treatment with β-blockers than medication naïve patients. Nonetheless, survival times were similar to Leu41 carriers who were not under treatment. These findings prompted the authors to conclude that the *Leu*41 variant provides similar effects as β-blockers (genetic β-blockade). A large prospective study supported these outcomes[88]. Among untreated African Americans, *Leu*41 carriers had longer survival times than those who were *Gln*41 homozygous. On the contrary, there were no differences in survival times among African Americans treated with β-blockers, indicating that medication attenuated the negative impact of the *Gln*41 variant. Even though GRK5 variants seem to be associated with pharmacological responses and survival rates in African-Americans, they are uncommon in Caucasians. However, since recent evidence points out that Caucasians who are homozygous for *Gln*41 and *Gly*389 have shown prolonged survival with treatment, as is the case with African Americans, future studies should consider gene-gene interaction effects.

Contrasting results have been reported for α_{2C} adrenoceptor polymorphisms. The variant *Del*322-325 was surprisingly associated with a decreased event rate and reduced death rate in patients with dilated cardiomyopathy[82]. However, more than 90% of the patients were Caucasians, and similar to previous studies, had no individuals who were homozygous for the deletion variant.

Table 3 Effect of adrenergic gene polymorphisms on survival of patients with heart failure

Ref.	Sample, design[1]	Endpoints	Follow-up (mo)	Mortality rate (%)	SNP	Main findings
β adrenergic receptor type 1						
[15]	1040[2]	AD, HZ	48	19	Arg389Gly	Increased survival in Arg389 homozygous treated with bucindolol
[58]	184[3]	AD, HT	24-60	38	Ser49Gly	Decreased survival in Ser49Ser patients
[76]	600[2]	AD, HZ	7-17	26	Arg389Gly	No association with endpoints
[50]	201[3]	AD, CD	18-62	28	Arg389Gly, Ser49Gly	Increased survival in Arg389 allele carriers on high dose beta-blockers
[77]	444[3]	CD, HT	41 (median)	25	Arg389Gly, Ser49Gly	No association with endpoints
[78]	227[3]	AD, HT	48	18	Arg389Gly, Ser49Gly	No association with endpoints
[79]	637[3]	AD, HT	35 (mean)	23	Arg389Gly, Ser49Gly	No association with endpoints
β adrenergic receptor type 2						
[59]	259[3]	AD, HT	22 (mean)		Gly16Arg, Gln27Glu, Thr164Ile	Increased risk of death in Thr164Ile patients
[77]	444[3]	CD, HT	41 (median)	25	Gly16Arg, Thr164Ile	No association with endpoints
[78]	227[3]	AD, HT	48	18	Gly16Arg, Gln27Glu	Increased risk of death (haplotype)
[80]	31[3]	AD, HT	24	3	Thr164Ile	Worsening HF in Thr164Ile patients
[81]	443[3]	AD	36 (median)		Thr164Ile	Improved survival in Thr164Thr patients treated with beta-blockers
α adrenergic receptor type 2						
[78]	227[3]	AD, HT	48	18	Del322-325	No association with endpoints
[79]	637[3]	AD, HT	35 (median)	23	Del322-325	No association with endpoints
[82]	345[3]	AD, HT	60 (mean)	18	Del322-325	Reduced risk of death and end-points
G-protein kinase receptor 5						
[35]	375[2]	AD, HT	30 (mean)		Gln41Leu	Increased survival in Leu41 African-American patients treated with beta-blockers. No impact on Caucasians

[1]Study design; [2]Placebo controlled randomized trial; [3]Non-randomized, single group assignment. SNP: Single nucleotide polymorphism; AD: All cause mortality; CD: Cardiac mortality; HT: Heart transplantation; HZ: Hospitalizations.

Table 4 Effect of renin-angiotensin-aldosterone system gene polymorphisms on survival of patients with heart failure

Ref.	Sample, design[1]	Endpoints	Follow-up (mo)	Mortality rate (%)	SNP	Main findings
Angiotensinogen						
[75]	82[2]	AD, HZ	12	24	M235T	No association with endpoints
[78]	227[3]	AD, HT	48	18	M235T	No association with endpoints
[83]	451[3]	AD	48	49.7	M235T, T174M	Increased mortality in 174M patients
Angiotensin-converting enzyme						
[75]	82[2]	AD, HZ	12	24	I/D	No association with endpoints
[73]	194[3]	AD, HT	60	42	I/D	Increased risk of death in DD patients
[78]	227[3]	AD, HT	48	18	I/D	No association with endpoints
[84]	328[3]	AD, HT	3-38	23	I/D	Decreased survival in D allele patients untreated with beta-blockers. No differences in treated patients
[85]	479[3]	AD, HT	3-62	28.6	I/D	Decreased survival in D allele patients untreated with β-blockers. No differences in treated patients and decreased impact with high dose ACE inhibitors
[86]	323[3]	AD, HZ	10 (median)	9.6	I/D	Associated with severity of disease (NYHA class)
Angiotensin-Ⅱ receptor type 1						
[73]	194[3]	AD, HT	60	42	A1166C	Not associated with end-points. Increased risk of mortality as haplotype (ACE DD)
[75]	82[2]	AD, HZ	12	24	A1166C	No correlation with mortality rate
[78]	227[3]	AD, HT	48	18	A1166C	No association with endpoints
Aldosterone						
[87]	354[2]	AD, HZ	12	3.4	-344 T/C	Decreased survival in C allele patients. Isosorbide dinitrate and hydralazine improved composite score in TT genotype but had no impact on C allele

[1]Study design; [2]Placebo controlled randomized trial; [3]Non-randomized, single group assignment. SNP: Single nucleotide polymorphism; AD: All cause mortality; CD: Cardiac mortality; HT: Heart transplantation; HZ: Hospitalizations; ACE: Angiotensin-converting enzyme.

More recent studies disputed these observations, among which there was no association between this variant and survival related to heart failure[75,78,79]. It is not reasonable to expect that a single polymorphism will exert a marked

influence on survival, given that multiple gene products and environmental factors contribute to the pathogenesis of the disease. Therefore, future studies should consider the combined effect of several genes involved in the progression of heart failure in populations that are as homogeneous as possible in regard to their environmental characteristics.

RAAS

Even though the RAAS genes are not associated with a predisposition for heart disease, numerous genes encoding elements of the RAAS have been associated with varied responses to pharmacological treatment and survival. One such example concerns the *ACE I/D* polymorphism. An initial investigation reported that survival was lower in patients harboring the *DD* genotype[63] and numerous subsequent studies have supported these observations. McNamara *et al*[84,85] demonstrated that survival was lower in untreated *DD* patients, *albeit* similar among those who received β-blockers and ACE inhibitors. Hence, in tandem with other polymorphisms, the adverse effects induced by the *ACE DD* genotype seem to be attenuated by standard heart failure medication. However, other studies have not replicated these findings[75,78,86]. The same group showed that the aldosterone -344*C* polymorphism has a scaled impact on survival, being considerably poorer in *CC* genotype patients[87]. Unlike other polymorphisms, *TT* patients, rather than *CC*, were the ones who benefited the most with isosorbide dinitrate and hydralazine. Therefore, individuals with the *CC* genotype might be at particular risk of death once they develop heart failure. Once more, allele frequencies were different between African-Americans and Caucasians.

The angiotensin-Ⅱ receptor polymorphisms also are expected to have a negative impact upon survival following heart failure, because their sustained activation has serious cellular and cardiovascular consequences. Nonetheless, the results are contradictory. Evidence exists that 1166*C* is associated with a more severe disease condition and increased risk of death when combined with *ACE DD*[73]. However, in a recent study, survival and heart transplantation endpoints were not associated with either 1166*C* or 1166*A*[78]. In addition, studies are unanimous in demonstrating that the angiotensinogen *M*235*T* polymorphism does not influence survival from heart failure[75,78,83]. On the other hand, the *M*174 allele was associated with increased mortality[83]. Overall, angiotensinogen polymorphisms seem to have a slight effect on survival, however, thus far, studies have included somewhat small samples and are of insufficient number for drawing definitive conclusions. In addition, some of these studies have not taken into consideration the potential attenuating effects that medication has on certain gene variants.

CONCLUSION

Although gene products related to the RAAS and the adrenergic system are strongly implicated in the pathogenesis of heart failure, functional genetic variations that enhance or suppress their function and/or expression do not seem to predispose the development of heart failure. These observations are not entirely unexpected as the production of these end products markedly increases once heart failure onsets. In contrast, when the disease develops, genetic variants that adversely modify the function/expression of proteins are expected to lead to a worse outcome and possibly to poorer prognosis. Indeed, numerous studies have demonstrated that some SNPs not only modify responses to medication but also have implications for survival related to heart failure. This has been the case for ARB1 *Arg*389*Gly*, GRK5 *Gln*41*Leu*, ACE *I/D*, CYP11B2 *C*-344*T* and AGTR1 *A*+1166*C*.

However, conflicting results abound in the literature, wherein positive associations reported in initial studies often were not supported by subsequent investigations. Several reasons may explain these discrepant results, including limitations in design, technical procedures (mistyping) and analysis (unconditional). Numerous studies have included small sample sizes, which may compromise the power to detect common small effects in genetic association studies of multifactorial traits, such as heart failure[38]. In addition, numerous studies have not matched or grouped sample cohorts according to the severity of heart failure. With respect to survival, many studies were retrospective and have not controlled for potential confounding pharmacological effects. As outlined previously, standard heart failure medications (e.g. β-blockers and ACE inhibitors) appear to offset the adverse impact that some gene variants exert on survival. Furthermore, several studies involved various SNPs and multiple testing may generate false-positive results[8]. On the other hand, the impact of one SNP on survival is expected to be small and can be counteracted by the presence of other SNPs, at least in theory. Given that multiple gene products and environmental factors contribute to heart failure, future studies should consider studying haplotypes and the interacting effects of multiple genes implicated in the pathogenesis of heart failure. Future studies should be carried out in populations that are as homogeneous as possible regarding etiology, gender, race and environmental characteristics.

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