Genetic polymorphisms associated with heart failure: A literature review

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Abstract
Objective: To review possible associations reported between genetic variants and the risk, therapeutic response and prognosis of heart failure.
Methods: Electronic databases (PubMed, Web of Science and CNKI) were systematically searched for relevant papers, published between January 1995 and February 2015.
Results: Eighty-two articles covering 29 genes and 39 polymorphisms were identified.
Conclusion: Genetic association studies of heart failure have been highly controversial. There may be interaction or synergism of several genetic variants that together result in the ultimate pathological phenotype for heart failure.

Keywords
Heart failure, genetic polymorphism, susceptibility, therapy, prognosis

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Introduction
Heart failure (HF) is a multifactorial disease, which is the leading cause of morbidity and mortality worldwide.¹ There are various etiologies for HF, such as coronary artery disease, hypertension, valvular heart disease, arrhythmia, dilated cardiomyopathy (DCM), infection and inflammation. Neurohormonal factors play a fundamental role in the pathophysiology of structural changes of the heart (cardiac remodeling), and the subsequently deterioration of cardiac function (heart failure),² including activation of the sympathetic nervous system and the renin-angiotensin-aldosterone system, altered expression of endothelin, vascular endothelial growth factor, inflammatory cytokines, pro-oxidant and antioxidant factors, as well as signal transduction components. A number of drugs are available for HF including angiotensin-converting enzyme inhibitors (ACEI), β-blockers, aldosterone antagonists, diuretics and inotropic agents.³

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However, the risk, severity and therapeutic response of HF is variable among individuals, which may be related to genetic variation.4

The aim of this study was to review the literature for any genetic association with the susceptibility, therapeutic response or prognosis of HF. These findings could then be used to identify risk factors and pharmacogenetic mechanisms of HF, providing information to prevent future cases and to ensure effective therapeutic decisions.

Methods

Literature retrieval

All available articles about HF and gene polymorphisms published between January 1995 and February 2015 were searched for from electronic databases, PubMed, Web of Science and the Chinese National Knowledge Infrastructure (CNKI). The following terms were used as search criteria: ‘heart failure’, ‘HF’, ‘cardiomyopathy’, ‘polymorphism’, ‘variant’, ‘genetic polymorphism’, ‘genetic variant’, ‘susceptibility,’ ‘therapy response’, ‘cardiac remodeling’, ‘severity’, ‘survival’, ‘mortality’, ‘death’, ‘prognosis’ and ‘genetic association study’. Bibliographies in articles provided further references.

Inclusion criteria

Inclusion criteria were defined as: 1) clinical research of cases of HF; 2) publication between January 1995 and February 2015; 3) diagnosis of HF defined: (a) left ventricular ejection fraction (LVEF) ≤45% or abnormal diastolic function and (b) classic HF signs/symptoms, 4) assessment of ≥10 cases; 5) detailed information about morbidity, therapeutic response, and/or prognosis of HF.

Literature analysis

The investigators reviewed data from the published literature independently, and all disagreements were resolved by joint review and consensus.

Results

This study retrieved 793 publications and, following co-author reviews and discussions, 82 articles covering 29 genes and 54 polymorphisms were finally included. An overview of the genetic polymorphisms that were included and their impact on HF is given in Table 1. Papers were divided into those that looked at susceptibility to HF, those that assessed therapeutic response in HF and those that examined the impact of the polymorphism on HF prognosis.

Gene polymorphisms and susceptibility to HF

Renin-angiotensin-aldosterone system. Angiotensin converting enzyme (ACE), as a key enzyme catalyzing the production of angiotensin II and the degradation of bradykinin, and plays an important role in the development of HF. A functional intragenic I/D polymorphism of the ACE gene was studied in association with serum and cardiac ACE, and its role in HF susceptibility.5–15 A meta-analysis16 of the studies failed to find any significant association of the polymorphism with the risk of ischemic or idiopathic DCM.

Angiotensin type1 receptor (AT1R), as the major receptor of angiotensin II, mediates most of the physiologic actions of angiotensin II. Polymorphism AT1R I1166C has been studied in relation to diastolic HF,13 coronary artery disease17 and incidence of HF.10,18 Wu, et al.13 reported that AT1R I1166C carriers were associated with a higher risk of diastolic HF, and Mishra, et al.17 showed that AT1R A1166C heterozygote patients with coronary artery disease were susceptible to left ventricular dysfunction. In contrast, two further studies failed to find any significant relationship
between A1166C polymorphisms and incidence of HF.\textsuperscript{10,18}

Angiotensinogen (AGT) gene alleles AGT 174M and AGT 235 T have been studied in systolic HF patients\textsuperscript{10} and in relation to susceptibility to DCM.\textsuperscript{6,15} Zakrzewski-Jakubiak, \textit{et al.}\textsuperscript{10} reported an increased frequency of the AGT 174M allele and AGT 235
T allele in systolic HF patients, however, Tirt, et al. and Tiago, et al. failed to find evidence for an involvement of either polymorphism in the susceptibility to DCM.

Sympathetic nervous system. The pivotal role of sympathetic activation in HF and the benefit of anti-adrenergic therapy are well-known. This study has focused on several functional single nucleotide polymorphisms (SNPs) of the \( b_1 \)-adrenergic receptor gene (\( ADRB1 \) Arg389Gly, Ser49Gly), \( b_2 \)-adrenergic receptor gene (\( ADRB2 \) Arg16Gly, Gln27Glu, Thr164Ile) and \( \alpha_2 \) c subtype of the adrenergic receptor gene (\( ADRAC2 \) Del322–325).

A meta-analysis from Liu, et al. found no significant association between the \( ADRB1 \) Arg389Gly polymorphism and HF risk in the general population. However, Asian Gly389Gly homozygotes were significantly more susceptible to HF, while the risk of HF in homozygote Caucasians decreased. No robust association was found for the Ser49Gly polymorphism.

The \( b_2 \)-adrenergic receptor polymorphism \( ADRB2 \)Gly16Gly has been studied in relation to DCM and HF. Forleo, et al. demonstrated significant association of \( ADRB2 \)Gly16Gly homozygotes with DCM. Leineweber, et al. showed that the Gly16Gly genotype, which was in linkage disequilibrium with the Glu27Glu genotype, was more prevalent in patients with end-stage HF and those who underwent heart transplantation (HTX). The remaining studies failed to find any relationship between HF risk and \( ADRB2 \) gene polymorphisms (Arg16Gly, Gln27Glu, Thr164Ile).

The \( \alpha_2 \) c-adrenergic receptor (\( \alpha_2 \) C-AR) polymorphism \( ADRAC2 \) Del322–325 effect appears linked to race: African-American \( ADRAC2 \) Del322–325 homozygotes, but not Caucasian homozygotes are more susceptible to HF. Nonen, et al. found that the Del322–325 allele frequency of Del322–325 homozygotes among Japanese.

Inflammatory genes. Tumor necrosis factor alpha (TNF-\( \alpha \)) is one of the most studied inflammatory cytokines in the pathogenesis of HF. TNF-\( \alpha \) causes endothelial dysfunction, muscle contractility reduction and myocardial hypertrophy.

A meta-analysis of eight studies demonstrated that the TNFA-308 GA/AA genotype was more prevalent among DCM patients. Cytotoxic T-lymphocyte antigen 4 (CTLA4) is an inhibitory receptor expressed on activated T lymphocytes, which acts as an important negative regulator of T-cell activation. A promoter SNP (−318 C/T) and a functional SNP (+49 A/G) of the CTLA4 gene were investigated in two independent cohorts of DCM patients and healthy controls. In patients with DCM, the +49GG genotype predicted high susceptibility for DCM.

The nuclear factor kappa B family (NF-\( \kappa B \)) of transcription factors, major mediators of inflammation, have been implicated in cardioprotection and in detrimental effects on the heart. The prevalence of NFKB1-94 ATTG2 in DCM patients was higher in those at risk of HF was explored. Zhou B, et al. observed a higher prevalence of NFKB1-94 ATTG2 carriers in DCM patients, however, Santos, et al. failed to find any association between the NFKB1-94 ATTG polymorphism and HF risk.

Mahmoudi, et al. has investigated three interleukin-4 polymorphisms with regard to their influence on the risk of ischemic HF (IHf). Polymorphisms of IL-4 −590CC, −33TT and −33CC were positively associated with the risk of IHf, while −1098TG, −590 TC and −33CC genotypes were negatively related.

Endothelial system. The endothelial system plays an important role in the pathogenesis of HF. The endothelin-1 genes (\( ET-1 \))
regulate ET-1 production and endothelin-A receptor genes (ETA) regulate ET-1-induced activation of the target receptor. The TT genotype of the ETA +1363C/T polymorphism was related to an increased risk for DCM.41 The TT genotype of the ETA +1363C/T polymorphism and those homozygous for ET-1 198Asn have a 3-fold higher risk of HF than those of a different genotype.42

Vascular endothelial growth factor (VEGF) is a multifunctional protein, inducing receptor-mediated endothelial proliferation, angiogenesis and endothelial integrity. It is involved in microvascular abnormalities of HF.43,44 Douvaras et al.45 studied patients after acute myocardial infarction, and found that those with the VEGF −634CC genotype alone or co-inherited with the rare alleles VEGF-7 +1612, −1190 or −2549 were at higher risk for HF.

Miscellaneous genes. G-protein coupled receptor kinases (GRKs), a large family of receptor-regulating proteins, play pivotal roles in signal transduction of G-protein coupled receptors, especially the β-receptor. The common variant, GRK5 Glu41Leu, is in a putative regulatory domain and confers enhanced agonist-promoted desensitization, phosphorylation and internalization of β1-AR responses. Studies have assessed the prevalence of this variant in patients with left ventricular apical ballooning syndrome (LVABS), an idiopathic but reversible stress cardiomyopathy.46,47 Spinelli, et al.46 showed that patients with LVABS exhibited a higher prevalence of the GRK5 41Leu variant, although this finding was not confirmed in a larger cohort study.47

Manganese superoxide dismutase (MnSOD), a mitochondrial antioxidant enzyme, may be induced by increased inflammatory cytokines in cardiomyopathy or myocarditis.48 Overexpression of MnSOD might protect cardiac cells from damage by these cytokines.49 A substitution (Val16Ala) might neutralize superoxide radicals in the cells.50 Homozygosity for 16Val in the MnSOD gene is an independent predictor for development of DCM among Japanese.51

A common intronic variant in heat shock protein (HSP) gene HSPB27 member 7 (HSPB7 +245 G/A), which encodes cardiovascular small HSP, has been investigated in two studies.54,55 These found that the minor A allele of the HSPB7 +245 G/A variant was protective against HF in Caucasians, but not in African-Americans. The activation of matrix metalloproteinases (MMPs), a family of proteolytic enzymes, might contribute to the progressive cardiac remodeling process in HF by degrading the myocardial extracellular matrix. There is a significant increase of the MMP-2 −735 C allele and −790 T allele among congestive HF patients.52 In addition, MMP-2 −1575A carriers show a lower risk of systolic HF among Han Chinese.53

Micro-RNA sequences. There are several studies focusing on the effects of DNA variants within or adjacent to micro-RNA sequences (miRs). These miRs are short, endogenous, noncoding RNAs that bind to the 3'-untranslated region (3'-UTR) of their target mRNA and regulate the subsequent translation of proteins. MiR-499 u17c was first described in association with human HF,56 with the c17 mutant misdirecting recruitment of a subset of miR-499 target mRNAs, thus altering steady-state cardiac mRNA and proteins to favorably impact cardiac function.56 The rs7223247 polymorphism, located within the 3'-UTR of a nonfunctional TLCD2 gene downstream from miR-22 has been implicated in left ventricular hypertrophy (as a strong independent predictor of HF).57 HCM patients and healthy controls had similar frequencies of the polymorphisms rs45489294 in miRNA 208b and rs13136737 in miRNA 367.58 However, re998532 in miRNA 1-2, the only variant not detected in the healthy controls, was a rare SNP but not necessarily an HCM-associated mutation.58
Gene polymorphisms and therapeutic response

Renin-angiotensin-aldosterone system. Several studies have demonstrated that patients with ACE DD genotype benefited more significantly from therapies with ACE inhibitors (greater improvement in left ventricular ejection fraction and cardiac remodeling), but did not apparently respond to β-blocker therapy. Patients with non-DD genotypes were found to have better responses to spironolactone therapy than those of other genotypes.

Sympathetic nervous system. A variety of studies have been performed to evaluate the impact of the β-AR polymorphisms on response to β-blocker therapy. The meta-analysis of Liu, et al. showed that ADRB1 389Arg homozygotes were associated with more improvement of left ventricular ejection fraction (LVEF), left ventricular end diastolic diameter (LVEDd) and left ventricular end systolic diameter (LVESd) than those with different genotypes. Moreover, the benefits appeared significantly towards selective β-blockers rather than non-selective β-blockers.

Magnusson, et al. demonstrated that ADRB1 49Gly carriers had similar survival rates with different doses of β-blockers, while Ser49Ser homozygotes had better response only with a high dose of β-blocker. A previous report showed that the survival rate of 49Gly carriers without β-blockers was of the same magnitude as that of Ser49Ser patients with β-blockers (all doses combined). This finding is consistent with an “internal blockade” theory that strong and fast desensitization of the ADRB1 receptor plays a protective role in development of HF.

For the ADRB2 polymorphisms, Metra, et al. and Kaye, et al. demonstrated that the Gln27Glu SNP was a predictor of the LVEF variation in response to carvedilol. Conversely, de Groote, et al. failed to find significant difference of LVEF improvement in patients with Gln27Glu genetic variations, neither with carvedilol nor bisoprolol therapy. Moreover, β-blocker therapy seemed to have negative influence on survival rates of Thr164Ile heterozygotes, but a positive influence on Thr164Thr homozygotes. The ADRA2C Wt322–325 carriers were also found to respond better to β-blockers compared with other genotypes.

Miscellaneous genes. In the general Chinese population, GRK5 Gln41Leu variants were not associated with the risk of systolic HF, but this genotype did significantly reduce the morbidity of those with systolic HF using β-blockers. Liggett, et al. showed that GRK5 41Leu carriers taking β-blocker therapy had significantly longer transplant-free survival time, revealing pharmacogenetic interactions between the GRK5 41Leu allele and β-blocker therapy in Africans only.

Cytochrome P4502D6 (CYP2D6) plays an important role in hepatic metabolism, clearing lipophilic β-blocker from the body. CYP2D6 phenotypes are classified as poor metabolizers, intermediate metabolizers, extensive metabolizers and ultrarapid metabolizers. Poor metabolizers have no functional alleles, intermediate metabolizers have two hypofunctional alleles, while ultrarapid and extensive metabolizers have two fully functional alleles. Previous studies found no association between CYP2D6 genotype and clinical effects of β-blockers, despite the CYP2D6 poor metabolizers exhibiting increased plasma concentration of β-blocker during long-term treatment.

Gene polymorphisms and prognosis of HF

Renin-angiotensin-aldosterone system. Although the ACED variants have been associated with an increase of adverse events, the
negative influence of the $D$ allele might be diminished in those receiving ACEIs, suggesting genetic variants in the genes of the renin-angiotensin system could be modified by ACEIs.\textsuperscript{59,82}

**Sympathetic nervous system.** From the meta-analysis of Liu, \textit{et al.}\textsuperscript{21}, no differences were found in the prognosis of HF among \textit{ADRB1 Arg389Gly} and \textit{Ser49Gly} polymorphisms. Several studies\textsuperscript{63,83–85} have revealed that differences in survival rates between 389Gly carriers and 389Arg homozygotes, as well as between 49Gly carriers and 49Ser homozygotes, could be diminished by $\beta$-blocker therapy. The results indicated that standardized or individualized therapy might have greater effects on the course of HF, and this may partially, if not totally, make up for the genetic deficiency.

Several studies aimed to find linkage between the \textit{ADRB2 Arg16Gly} and/or \textit{Gln27Glu} polymorphisms with HF survival. Forleo, \textit{et al.}\textsuperscript{86} demonstrated that both 16Arg and 27Gln alleles were associated with better prognosis among DCM patients. Leineweber, \textit{et al.}\textsuperscript{87} found that end-stage HF patients who were homozygous for Gly16Gly tended to have a lower incidence of death or HTX. In contrast, two other studies\textsuperscript{88,89} failed to find a significant association between the two genetic polymorphisms and HF survival. Liggett, \textit{et al.}\textsuperscript{89} and Barbato, \textit{et al.}\textsuperscript{90} both reported that having the \textit{ADRB2 Thr164Ile} polymorphism blunted the $\beta_2$ adrenergic-mediated myocardial contractile response, adversely affecting the outcome of congestive HF. In addition, the effect of \textit{ADRA2C Del322–325} polymorphisms on HF prognosis has been investigated in two studies,\textsuperscript{71,91} revealing that the wild type might be the favorable genotype against exacerbation of HF conditions.

**Inflammatory genes.** Tiret, \textit{et al.}\textsuperscript{15} found that the \textit{TNFA–308 G/A} polymorphism was not associated with the severity of HF (assessed by LVEF and LVESd) or incidence of HTX. The TNF receptor gene \textit{TNFRSF1B 587 G} allele was not associated with a worse prognosis or more severe phenotype of congestive HF,\textsuperscript{92} although increased prevalence of the 587 \textit{G} allele compared with the 587 \textit{T} allele has been observed in various inflammatory diseases.\textsuperscript{93,94} Several genes of inflammatory cytokines were investigated in the study of Adamopoulos, \textit{et al.},\textsuperscript{95} who showed an association between worse cardiac function and adverse prognosis with the \textit{TT} genotype of transforming growth factor-\textit{\textbeta} \textit{1 (TGF\textbeta1) +869 T/C} polymorphism, the \textit{C} variant of \textit{TGF\textbeta1 +915 G/C} polymorphism, the \textit{GG} homozygote of the interleukin-6 (IL-6) -174 \textit{G/C} polymorphism and the \textit{AA} homozygote for interferon-\textgamma (IFN) +874 T/A polymorphism.

**Endothelial system.** Van der Meer, \textit{et al.}\textsuperscript{96} found that the \textit{VEGF +405CC} genotype might exacerbate the process of HF by down-regulating serum VEGF levels, while the \textit{VEGF -460 C/T} polymorphism, which does not affect VEGF levels, had no impact on prognosis. The \textit{T} allele of \textit{ETA, H323H (T/C)} was found to be a pronounced independent predictor of reduced survival in DCM patients.\textsuperscript{97}

In the endothelial cell, nitric oxide is synthesized by nitric oxide synthases (NOS). It might exert direct toxic effects on the myocardium and mediate the negative inotropic effects of some inflammatory cytokines.\textsuperscript{98} McNamara, \textit{et al.}\textsuperscript{99} showed that the \textit{NOS3 298Asp} variant was associated with poorer event-free survival among systolic HF patients. However, Maiolino, \textit{et al.}\textsuperscript{100} argued that the \textit{NOS3 -786 C} variant, which was in linkage disequilibrium with the Asp298 variant, might act as a more determinable predictor for HF patients.

**Miscellaneous genes.** Adenosine monophosphate deaminase1 (AMPD1) can convert...
adenosine monophosphate (AMP) to inosine monophosphate (IMP). Changes of T to C at exon 2 of AMPD1 result in a truncated, inactive enzyme and an accumulation of adenosine, which plays an important role in the cardiovascular system. Except for Gastmann, et al., other studies all found no significant relationship between the C34T polymorphism and HF mortality. There were also controversial discoveries of both potentially beneficial and deleterious impacts of adenosine and the T mutation.

Hua, et al. showed that MMP-2 -1059A carriers had lower mortality for systolic HF in northern Han Chinese. Mizon-Gerard, et al. revealed that the MMP-3 (−1171)5 A/5 A genotype was independently associated with cardiac survival in non-ischemic HF patients, but not in IHF patients. The MMP-9 1562T allele was also an independent predictor of cardiac mortality in patients with diverse HF etiologies.

Gene-gene interaction

Susceptibility to HF has been demonstrated with the synergistic action of the ACE D variant with either the AT1R 1166C allele or the ATG 235 T allele. Although the ADRB1 389Arg allele alone showed no significant effects on HF development, when combined with ADR2A C Del322–325 homozygotes or ADRB1 Gly49 variants the associations are pronounced. Moreover, the ADRB2 Gly16Gly-Glu27Glu-Thr164Thr haplotype also significantly increases the incidence of HF as compared with the individual risk genotype. In the endothelial system, the co-existence of ET-1 IVS-4 G and who are Asn198 homozygotes, which are in tight linkage disequilibrium, also have better β-blocker therapeutic responses than those of different genotypes.

Andersson, et al. found a significant trend toward poorer HF survival in patients carrying ACE DD genotype and the AT1R 1166C variant. Combination ADRB1 and ADRB2 polymorphisms, such as Arg389/Ser49, Arg16/Gln27 and Gly589Gly/Gly49Gly/Thr164Ile were found to confer lower HF-related mortality than other haplotypes. In addition, Adamopoulos, et al. showed that combination of the TGFB1+869 T/C and TGFB1+915 G/C genotypes was associated with worse cardiac function and adverse prognosis than other genotypes.

Discussion and conclusion

Genetic association studies of HF have been highly controversial; there may be interaction or synergism of several genetic variants which together result in an ultimate pathological phenotype for HF. Understanding the role that genetic variants play in HF development is essential for individualized preventive and therapeutic strategies.

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Declaration of conflicting interest

The authors declare that there are no conflicts of interest.

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