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Human Genome Epidemiology (HuGE) Review

Genetic Variation associated with Ischemic Heart Failure: A HuGE Review and Meta-Analysis

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The ischemic etiology of heart failure is an independent prognostic factor associated with worse long-term outcome. Recent evidence indicates a role for genetic susceptibility to ischemic heart failure. The authors systematically reviewed all known case-control studies that investigated the association between genetic variants and ischemic heart failure. Twenty-two articles, which examined 24 gene polymorphisms, were identified. In 22 polymorphisms, the variant form had a functional effect. Twenty-two polymorphisms were variants of genes involved in the maladaptive neurohormonal activation. Seven polymorphisms (*ACE I/D, AGT M235T, ADRA2C Del322-325, ADRB2 Arg16Gly, ADRB2 Gln27Glu, EDN1 Lys198Asn, VEGF G-405C*) showed a significant association in individual studies. Five polymorphisms (*ACE I/D, ADRB1 Arg389Gly, ADRB2 Arg16Gly, ADRB2 Gln27Glu, TNF G308A*) were examined by more than one study, and meta-analyses were performed. The meta-analyses showed no significant sign of heterogeneity. In all settings, there was no significant association, except for polymorphism *ADRB2 Arg16Gly* under a recessive model (fixed-effects odds ratio = 1.32, 95% confidence interval: 1.05, 1.65). Taking into account that ischemic heart failure is a complex disease with multifactorial etiology, a minor contributing pathogenetic role of the investigated gene polymorphisms cannot be totally excluded. Case-control studies that investigate gene-gene and gene-environment interactions might further elucidate the genetics of ischemic heart failure.

epidemiology; heart failure, congestive; meta-analysis; myocardial ischemia; polymorphism, genetic; variation (genetics)

Abbreviations: CI, confidence interval; HWE, Hardy-Weinberg equilibrium; IHF, ischemic heart failure; SNP, single nucleotide polymorphism.

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Heart failure is a complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood (1). Heart failure is a relatively common disorder, and the diagnosis is clinical (2). Patients with heart failure are classified broadly into two groups on the basis of the etiology of the left ventricular dysfunction: patients with ischemic (40–74 percent) and nonischemic (26–35 percent) heart disease (3–5). Ischemic etiology has been shown to be independently associated with worse long-term outcome in heart failure patients in a variety of studies (6, 7). Clinically,

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patients are classified as having heart failure of ischemic etiology on the basis of a history of myocardial infarction or on objective evidence of coronary artery disease such as angiography or functional testing, although a more standardized definition for ischemic heart failure (IHF) has been proposed for use in research (8).

Although significant progress has been made in elucidating the genetics of coronary artery disease/myocardial infarction with a large number of family-based (whole-genome scans) and association studies (9–11), the evidence for a genetic basis of IHF susceptibility is limited (12). Nevertheless, a genetic basis could be indicated by the ethnic diversity in disease prevalence (13), the interindividual variability in IHF susceptibility (14, 15), the familial clustering of heart failure (16), and the experimental data from animal models (17, 18).

The genetic association studies of IHF under the ''candidate gene'' approach have produced inconclusive or inconsistent results so far. To address this issue, we reviewed the literature for genetic studies investigating the association of genetic variation with the risk of developing clinically evident IHF.

MATERIALS AND METHODS

Selection of studies

Literature for this review was systematically identified by searching PubMed (National Library of Medicine, Bethesda, Maryland) for all English-language articles published up to November 2006 related to IHF and genetic polymorphisms. As search criteria, we used combinations of the following terms: ''ischemic heart failure,'' ''IHF,'' ''ischemic cardiomyopathy,'' ''heart failure,'' ''cardiac failure,'' ''cardiomyopathy,'' ''polymorphism,'' ''gene variant,'' ''genetic variant,'' ''susceptibility,'' and ''genetic association study.'' Bibliographies in articles provided further references.

Our review included genetic association studies fulfilling the following inclusion criteria: 1) providing cases with clinically diagnosed IHF and controls free of heart failure, 2) providing information on genotype frequency or risk estimates, 3) using validated molecular methods for genotyping, and 4) including subjects who were human. Studies investigating progression, severity, phenotype modification, response to treatment, or survival were excluded from our study. Case reports, editorials, and review articles were also excluded. Finally, family-based studies were excluded because of different design settings (19).

Data extraction

From each study, the following information was extracted: first author, journal, year of publication, ethnicity of the study population, demographics, definition of cases and controls, matching, blinded genotyping, validity of the genotyping method, and number of cases and controls for each genotype. The frequencies of the alleles and the genotypic distributions were extracted or calculated for both the cases and the controls. The two investigators independently extracted data, discussed all disagreements, and reached consensus on all items.

Data synthesis

In this review, the associations are indicated as odds ratios with the corresponding 95 percent confidence intervals. When more than one genetic association study investigated the same polymorphism, a meta-analysis of published results was carried out. The meta-analysis examined the overall association of the allele contrast and the recessive and dominant models for the allele of interest. For a polymorphism with two alleles (A and a), the allele contrast is defined as $*a$ *vs.* $*A$, the recessive model for allele a is defined as aa *vs.* $Aa + AA$, and the dominant model is defined as $aa + Aa$ *vs.* AA (20, 21). In the meta-analysis, then, pooled odds ratios were estimated based on the individual odds ratios produced by the individual studies. Heterogeneity between studies was tested by using the Q statistic, a weighted sum of squares of the deviations of individual study odds ratio estimates from the overall (pooled) estimate (22, 23). If $p < 0.10$, then heterogeneity was considered statistically significant. Heterogeneity was quantified with the I^2 metric, which is independent of the number of studies in the meta-analysis. I^2 takes values between 0 percent and 100 percent, with higher values denoting a greater degree of heterogeneity (19, 24).

The pooled odds ratio was estimated by using fixed-effects (Mantel-Haenszel) and random-effects (DerSimonian and Laird) models (25). Random-effects modeling assumes a genuine diversity in the results of various studies, and it incorporates into the calculations a between-study variance. Hence, when there is heterogeneity between studies, the pooled odds ratio is preferably estimated by using the random-effects model (26). Studies with controls not in Hardy-Weinberg equilibrium (HWE; $p \geq 0.05$) (27) were subjected to a sensitivity analysis (26, 28). Analyses were performed by using Meta-Analyst (Joseph Lau, Tufts-New England Medical Center, Boston, Massachusetts), StatsDirect (Microsoft Corporation, Redmond, Washington), and CVF90 with the IMSL library (26, 29, 30).

RESULTS

The literature review identified 693 titles in PubMed that met the search criteria. The abstracts of these articles were independently read by the two investigators to assess their appropriateness for this review. The results were compared, and disagreements were resolved by consensus. Sixty-four articles remained after abstract selection. The full articles for the remaining studies were evaluated for compliance with the inclusion criteria. Data from 22 articles describing 37 studies that investigated the association between polymorphisms and IHF met the inclusion criteria (31–52), and they were included in our review. The diagnosis criteria were similar in the reviewed studies, although not standardized ((8), table 1). Overall, 17 candidate genes and 24 polymorphisms were found to have been investigated in association with IHF (table 2).

Table 1 shows the study characteristics and the results of association between the different polymorphisms and the risk of IHF for each individual study. Table 2 shows gene polymorphism characteristics. Table 3 shows the meta-analysis results. In summary, seven genetic polymorphisms (angiotensin-converting enzyme insertion/deletion (*ACE I/D*), angiotensinogen (*AGT*) *M235T,* α2C subtype-adrenergic receptor (*ADRA2C*) *Del322-325,* β2-adrenergic receptor (*ADRB2*) *Arg16Gly, ADRB2 Gln27Glu,* endothelin-1 (*EDN1*) *Lys198Asn*, and vascular endothelial growth factor (*VEGF*) *G-405C*) showed significant association (31, 36, 37, 40, 41, 46). The genotype distribution in controls was not in HWE in three studies (37, 39, 40), whereas, in 10 studies (31, 38, 43, 48–50), information was not provided. The genotyping personnel were reported to be blinded to phenotype in four studies (33, 36, 52), and the reliability of the genotyping procedure was controlled in nine studies (33, 35, 36, 41, 45, 47).

A meta-analysis was performed for polymorphisms *ACE I/D* (31–35), β1-adrenergic receptor (*ADRB1*) *Arg389Gly* (37, 39), *ADRB2 Arg16Gly* (39, 40), *ADRB2 Gln27Glu* (39, 40), and tumor necrosis factor-α (*TNF*) *G-308A* (42, 44). Overall, only one polymorphism, *ADRB2 Arg16Gly*, was found to have a significant association with IHF in the meta-analysis. The results from the remaining studies were very consistent, with only the *ACE I/D* polymorphism, when examined under the recessive model, showing significant heterogeneity. The results from each individual meta-analysis are described below. We now analyze and further discuss the findings for each gene polymorphism in turn.

Candidate genes and biologic mechanisms

The high allele frequency of the studied genes (table 2) suggests low genotype relative risk. Such genes may contribute to the development of heart failure only in conjunction with exogenous and endogenous exposures (53). Susceptibly genes can be identified by studying the biochemical or physiological pathways postulated to be involved in heart failure pathophysiology.

IHF begins with an initial myocardial insult, for example, myocardial infarction, which sets into motion a destructive cycle in which the remaining normal myocardium undergoes changes in cell metabolism and morphology, leading to hypertrophy and fibrosis (54). Alternatively, chronic, low-grade myocardial ischemia may also result in such changes (55). These cellular changes gradually alter the ultrastructural properties of the ventricle through a process called remodeling. Although remodeling initially occurs as an adaptive response to improve cardiac performance, over time, the response becomes counterproductive and maladaptive (54). A key mediator of this process is the neurohormonal activation, including regulators such as the renin-angiotensin-aldosterone system, the sympathetic nervous system, growth factors, and inflammatory molecules. Considering the fundamental role of neurohormonal factors in the pathophysiology and progression of cardiac dysfunction and remodeling, variants of neurohormonal genes are logical candidate genes in heart failure (12).

The genes identified by the literature search can be classified in five main categories: renin-angiotensin-aldosterone system, sympathetic nervous system, genes encoding growth factors or endothelial proteins, inflammatory genes, and miscellaneous genes.

For 22 of the studied polymorphisms, functional implications are reported in the literature (table 2). In two cases, the polymorphisms were not functional (endothelin A receptor (*EDNRA*) *C69T, VEGF C-590T*), but even nonfunctional polymorphisms are likely to be in linkage disequilibrium with causative alleles (56). The reference single nucleotide polymorphism (SNP) identification numbers (rs numbers) from the Database of Single Nucleotide Polymorphisms (57), the chromosomal gene position, the nucleotide base change, the average heterozygosity, and the amino acid substitution for each polymorphism are shown on table 2.

Renin-angiotensin-aldosterone system

The role of the renin-angiotensin-aldosterone system in heart failure is well known (58). Angiotensin-converting enzyme catalyzes the production of angiotensin II and the degradation of bradykinin. A functional intronic *I/D* polymorphism of the *ACE* gene has been studied for several cardiovascular-renal outcomes (59–61). Five case-control studies to date have addressed whether the variant form of the *ACE* gene alters the risk of IHF. Raynolds et al. (31) reported the only, to date, positive association. Two small-scale studies were conducted among Chinese subjects, but no increased risk of IHF under any model was found (32, 35). However, in Chinese, the frequency of the *DD ACE* genotype is lower than in other populations; thus, any negative conclusion could be due to low statistical power (62). One study in Turks (33) and one in Whites (34) also failed to show a significant genetic effect.

Overall, the meta-analysis of the five published studies (31–35) for the recessive model showed high heterogeneity ($p = 0.09$; $I^2 = 0.51$), which is attributable mainly to Whites ($p = 0.01$; $I^2 = 0.85$) since there is no significant sign of heterogeneity ($p \geq 0.10$; $I^2 = 0$) for East Asians. Then, overall and for Whites, the random-effects odds ratios were 0.95 (95 percent confidence interval (CI): 0.60, 1.52) and 1.16 (95 percent CI: 0.40, 3.37), respectively; for East Asians, the fixed-effects odds ratio was 0.67 (95 percent CI: 0.30, 1.50). The allele contrast and the dominant model consisted of four studies (32–35) because one study of Whites (31) did not provide enough data. For these models, the analysis showed no significant sign of heterogeneity overall, and the associations were not significant. In a sensitivity analysis (exclusion of the study with no information on HWE) (31), the pattern of results was not altered (table 3).

Angiotensinogen is the precursor of the hormone angiotensin II. Two functional SNPs of the *AGT* gene, a nonsynonymous SNP designated as *M235T* (63) and a promoter SNP symbolized as *G-6A* (64, 65), have been investigated in a heart failure cohort of 158 White cases (60 percent ischemic) and 200 controls (36). The results were significant for only *M235T* because the estimated odds ratio under the allele contrast model in the entire heart failure group was 1.35 (95 percent CI: 1.1, 1.6).

TABLE 1. Studies of genetic polymorphisms and ischemic heart failure

First author, year (reference no.)	Study area, ethnicity	Cases: no. (no. of males/no. of females, mean age in years (standard deviation)), diagnosis criteria*	Controls: no. (no. of males, no. of females, mean age in years (standard deviation)), matching, diagnosis criteria†	Gene (polymorphism)‡	Genotype distribution: mtmt/mtwt/wtwt§	Association	Comparison	OR§	95% CI§	HWE§
Raynolds, 1993 (31)	United States, Whites	$n = 102$ (96/6, 53.7 (0.8)), criteria: 1	$n = 79$ (50/29, 33 (1.8)), no, criteria: i	*ACE (I/D)*	Cases: N/A§; controls: N/A	Yes	*DD* vs. *DI/II*	2.01	1.1, 3.7	No
							DD/DI vs. *II*	N/A	N/A	
							DD vs. *DI*	N/A	N/A	
							**D* vs. **I*	N/A	N/A	
Sanderson, 1996 (32)	Hong Kong, Chinese	$n = 53$ (39/14, 64 (12)), criteria: 1	$n = 183$ (106/77, 40 (12)), no, criteria: ii	*ACE (I/D)*	Cases: 6/21/26; controls: 24/88/71	No	*DD* vs. *DI/II*	0.83	0.4, 1.9	Yes
							DD/DI vs. *II*	0.67	0.4, l.2	
							DD vs. *DI*	1.02	0.4, 2.5	
							**D* vs. **I*	0.76	0.5, 1.2	
Akbulut, 2003 (33)	Turkey, Turks	$n = 84$ (68/16, 59.5 (10.4)), criteria: 2	$n = 125$ (105/20, 57.2 (10.5)), no, criteria: iii	*ACE (I/D)*	Cases: 28/41/15; controls: 43/59/23	No	*DD* vs. *DI/II*	0.95	0.5, 1.7	Yes
							DD/DI vs. *II*	1.04	0.5, 2.1	
							DD vs. *DI*	0.94	0.5, 1.7	
							**D* vs. **I*	0.99	0.7, 1.5	
Covolo, 2003 (34)	Italy, Whites	$n = 107$ (nr§), criteria: 3	$n = 230$ (115/115, 62.4 (7.8)), age matched, criteria: ii	*ACE (I/D)*	Cases: 31/57/19; controls: 86/105/39	No	*DD* vs. *DI/II*	0.68	0.4, 1.2	Yes
							DD/DI vs. *II*	0.95	0.5, 1.7	
							DD vs. *DI*	0.66	0.4, 1.1	
							**D* vs. **I*	0.83	0.6, 1.1	
Huang, 2004 (35)	China, Chinese	$n = 26$ (nr), criteria: 1	$n = 102$ (nr), no, criteria: ii	*ACE (I/D)*	Cases: 2/14/10; controls: 17/48/37	No	*DD* vs. *DI/II*	0.40	0.1, 1.9	Yes
							DD/DI vs. *II*	0.91	0.4, 2.2	
							DD vs. *DI*	1.05	0.4, 2.9	
							**D* vs. **I*	0.79	0.4, 1.5	
Goldbergova, 2003 (36)	Czech Republic, Whites	n¶ $= 158$ (nr), criteria: 4	$n = 200$ (nr, 54 (nr)), no, criteria: ii	*AGT (M235T)*	Cases: 37/83/38; controls: 37/100/63	Yes	*TT/MT* vs. *MM*	1.33	0.8, 2.1	Yes
							**T* vs. **M*	1.35	1.1, 1.6	
				AGT (G-6A)	Cases: 37/53/68; controls: 38/89/73	No	*AA/AG* vs. *GG*	0.76	0.5, 1.2	Yes
							**A* vs. **G*	0.96	0.8, 1.1	
Small, 2002 (37)	United States, Whites	n¶ $= 81$ (nr), criteria: 4	$n = 105$ (nr), no, criteria: ii	*ADRA2C (Del322-325)*	Cases: 6/5/70; controls: 2/4/99	Yes	*DelDel* vs. *wtwt/wtDel*	3.94	0.5, 31.1	No
							**Del* vs. **wt*	2.97	2.0, 4.4	
	United States, Blacks	n¶ $= 78$ (nr), criteria: 4	$n = 84$ (nr), no, criteria: ii		Cases: 41/14/23; controls: 14/41/29	Yes	*DelDel* vs. *wtwt/wtDel*	5.65	2.7, 11.9	Yes
							**Del* vs. **wt*	2.29	1.9, 2.7	
	United States, Whites	n¶ $= 81$ (nr), criteria: 4	$n = 105$ (nr), no, criteria: ii	*ADRB1 (Arg389Gly)*	Cases: 43/34/4; controls: 63/34/8	No	*ArgArg* vs. *GlyGly/GlyArg*	0.80	0.4, 1.7	Yes
							**Arg* vs. **Gly*	0.89	0.7, 1.1	
	United States, Blacks	n¶ $= 78$ (nr), criteria: 4	$n = 84$ (nr), no, criteria: ii		Cases: 23/36/19; controls: 23/48/13	No	*ArgArg* vs. *GlyGly/GlyArg*	0.90	0.4, 1.8	Yes
							**Arg* vs. **Gly*	0.87	0.7, 1.1	
Metra, 2006 (38)	Italy, Whites	$n = 126$ (nr), criteria: 4	$n = 230$ (nr), no, criteria: ii	*ADRA2C (Del322-325)*	Cases: N/A; controls: N/A	No	*DelDel* vs. *wtwt/wtDel*	1.0	0.4, 2.5	N/A
							**Del* vs. **wt*	N/A	N/A	
				ADRB1 (Arg389Gly)	Cases: N/A; controls: N/A	No	*ArgArg* vs. *GlyGly/GlyArg*	0.8	0.5, 1.2	N/A
							**Arg* vs. **Gly*	N/A	N/A	

Covolo, 2004 (39)	Italy, Whites	$n = 130$ (nr), criteria: 4	$n = 230$ (nr), no, criteria: ii	*ADRB1 (Arg389Gly)*	Cases: 60/55/11; controls: 122/90/18	No	*ArgArg* vs. *GlyGly/GlyArg*	0.8	0.5, 1.2	Yes
							**Arg* vs. **Gly*	0.86	0.6, 1.2	
							ArgGly vs. *GlyGly*	1.3	0.8, 2.1	
							ArgArg vs. *GlyGly*	1.0	0.4, 2.3	
				ADRB2 (Arg16Gly)	Cases: 49/56/21; controls: 81/115/34	No	*GlyGly/GlyArg* vs. *ArgArg*	0.87	0.5, 1.6	Yes
							**Gly* vs. **Arg*	1.17	0.8, 1.6	
							GlyGly vs. *ArgGly*	1.24	0.8, 2.0	
							GlyGly vs. *ArgArg*	0.98	0.5, 1.9	
				ADRB2 (Gln27Glu)	Cases: 16/52/58; controls: 31/79/120	No	*GluGlu/GlnGlu* vs. *GlnGln*	1.28	0.8, 1.9	No
							**Glu* vs. **Gln*	1.13	0.8, 1.6	
							GluGlu vs. *GlnGlu*	0.78	0.4, 1.6	
							GluGlu vs. *GlnGln*	1.1	0.5, 2.5	
Leineweber, 2006 (40)	Germany, Whites	n¶ = 520, (380/140, 59 (11)), criteria: 4	$n = 328$ (216/112, 31 (11)), no, criteria: ii	*ADRB2 (Arg16Gly)*	Cases: 216/215/89; controls: 108/170/50	Yes	*GlyGly/GlyArg* vs. *ArgArg*	1.36	0.9, 2.0	Yes
							**Gly* vs. **Arg*	2.35	1.3, 4.1	
							GlyGly vs. *ArgGly*	1.58	1.2, 2.1	
							GlyGly vs. *ArgArg*	1.12	0.7, 1.7	
				ADRB2 (Gln27Glu)	Cases: 108/224/188; controls: 51/162/115	Yes	*GluGlu/GlnGlu* vs. *GlnGln*	0.95	0.7, 1.3	No
							**Glu* vs. **Gln*	1.09	0.6, 1.9	
							GluGlu vs. *GlnGlu*	1.53	1.0, 2.3	
							GluGlu vs. *GlnGln*	1.29	0.9, 1.9	
				ADRB2 (Thr164Ile)	Cases: 0/10/510; controls: 0/7/321	No	*ThrIle* vs. *ThrThr*	0.89	0.3, 2.4	N/A
							**Ile* vs. **Thr*	0.90	0.7, 1.2	
Colombo, 2006 (41)	Italy, Whites	n¶ = 122 (nr), criteria: 2	$n = 216$ (nr), age matched, criteria: iv	*EDN1 (Lys198Asn)*	Cases: 16/46/60; controls: 7/72/114	Yes	*AsnAsn* vs. *LysLys*	4.34	1.7, 11.1	Yes
							AsnAsn vs. *LysLys/Lys Asn*	4.01	1.6, 10.1	
							**Asn* vs. **Lys*	1.64	1.1, 2.4	
				EDNRA (C69T)	Cases: 8/49/65; controls: 15/87/114	No	*CC* vs. *TT/CT*	0.94	0.4, 2.3	Yes
							**C* vs. **T*	0.98	0.7, 1.4	
Holweg, 2005 (47)	The Netherlands, Whites	$n = 167$ (156/11, 51.1 (7.6)), criteria:4	$n = 169$ (nr), no, criteria: v	*HMOX1* $(GT)_n$	Cases: 63/79/25; controls: 64/85/20	No	*LL/LS*§ vs. *SS*¶	0.76	0.4, 1.4	Yes
							**L* vs. **S*	0.93	0.7, 1.3	
van der Meer, 2005 (46)	The Netherlands and United Kingdom, mixed	$n = 417$ (nr), criteria: 2	$n = 187$(nr), age and sex matched, criteria: ii	*VEGF (G-405C)*	Cases: 55/189/173; controls: 24/75/88	Yes	*CC/CG* vs. *GG*	1.25	0.9, 1.8	Yes
							**C* vs. **G*	1.32	1.0, 1.7	
				VEGF (C-460T)	Cases: 98/212/103; controls: 53/89/45	No	*TT/CT* vs. *CC*	0.87	0.6, 1.3	Yes
							**T* vs. **C*	1.13	0.9, 1.4	
Kubota, 1998 (44)	United States, mixed	n¶ = 124 (nr), criteria: 4	$n = 139$ (nr), age matched, criteria: ii	*TNF (G-308A)*	Cases: 8/57/164; controls: 3/38/98	No	*AA/AG* vs. *GG*	0.95	0.6, 1.5	Yes
							AA vs. *AG/GG*	1.64	0.4, 6.3	
							**A* vs. **G*	1.00	0.7, 1.5	
				LTA (G-252A)	Cases: 103/102/24; controls: 65/58/16	No	*AA/AG* vs. *GG*	1.11	0.6, 2.2	Yes
							**A* vs. **G*	0.98	0.7, 1.4	

Table continues

TABLE 1. Continued

First author, year (reference no.)	Study area, ethnicity	Cases: no. (no. of males/no. of females, mean age in years (standard deviation)), diagnosis criteria*	Controls: no. (no. of males, no. of females, mean age in years (standard deviation)), matching, diagnosis criteria†	Gene (polymorphism)‡	Genotype distribution: mtmt/mtwt/w ⁄t§	Association	Comparison	OR	95% CI	HWE
Densem, 2002 (43)	United Kingdom, Whites	$n = 106$ (nr), criteria: 4	$n = 212$ (nr), no, criteria: ii	*TNF (G-308A)*	Cases: N/A; controls: N/A	No	*AA/AG* vs. *GG*	N/A	N/A	N/A
							**A* vs. **G*	0.95	0.5, 1.9	
Alikasifoglu, 2003 (42)	Turkey, Turks	n¶ = 63 (nr), criteria: 1	$n = 93$ (60/33, 56.2 (9.1)), sex and age matched, criteria: ii	*TNF (G-238A)*	Cases: 2/15/46; controls: 3/22/68	No	*AA/AG* vs. *GG*	0.86	0.4, 1.8	Yes
							**A* vs. **G*	1.00	0.5, 1.9	
				TNF (G-308A)	Cases: 3/16/44; controls: 4/20/69	No	*AA/AG* vs. *GG*	1.24	0.6, 2.5	Yes
							AA vs. *AG/GG*	0.99	0.2, 4.6	
							**A* vs. **G*	1.19	0.6, 2.2	
Holweg, 2001 (45)	The Netherlands, Whites (>95%)	$n = 144$ (135/9, 50.8 (7.7)), criteria:4	$n = 94$ (49/45, 36.7 (10.3)), no, criteria: ii	*TGFB1 (Leu10Pro)*	Cases: 14/70/60; controls: 14/43/37	No	*ProPro/LeuPro* vs. *LeuLeu*	0.91	0.5, 1.5	Yes
							**Pro* vs. **Leu*	0.85	0.6, 1.2	
				TGFB1 (Arg25Pro)	Cases: 3/18/123; controls: 0/15/79	No	*ProPro/ArgPro* vs. *ArgArg*	0.89	0.4, 1.8	Yes
							**Pro* vs. **Arg*	1.04	0.5, 2.1	
Bijlsma, 2001 (48)	The Netherlands, Whites	$n = 35$ (nr), criteria: 4	$n = 29$, (nr), no, criteria: vi	*IL10 (G-1082A)*	Cases: N/A; controls: N/A	No	**A* vs. **G*	1.54	0.8, 3.1	N/A
				IL10(C-592A)	Cases: N/A; controls: N/A	No	**C* vs. **A*	1.16	0.6, 2.1	N/A
Bijlsma, 2002 (49)	The Netherlands, Whites	$n = 35$ (nr), criteria: 4	$n = 36$, (nr), no, criteria: vi	*IL4 (C-590T)*	Cases: N/A; controls: N/A	No	**T* vs. **C*	0.64	0.3, 1.3	N/A
Kruger, 2005 (51)	Germany, Whites	$n = 51$ (nr, 62 (3)), criteria: 5	$n = 100$, (nr), age and sex matched, criteria: ii	*CD14 (C-260T)*	Cases: 7/25/19; controls: 28/40/32	No	*TT/CT* vs. *CC*	0.79	0.4, 1.6	Yes
							**T* vs. **C*	0.66	0.4, 1.2	
Kolek, 2005 (50)	United States, mixed	$n = 605$ (nr), criteria: 5	$n = 605$ (nr), no, criteria: iii	*AMPD (C34T)*	Cases: N/A; controls: N/A	No	*TT/CT* vs. *CC*	0.87	0.4, 1.8	N/A
		$n = 605$ (nr), criteria: 5	$n = 433$ (nr), no, criteria: iv		Cases: N/A; controls: N/A	No	*TT/CT* vs. *CC*	0.94	0.5, 1.9	N/A
Nakatani, 2005 (52)	Japan, Japanese	$n = 70$ (nr), criteria: 6	$n = 2,389$ (nr), no, criteria: vii	*SLC6A4 (I/D)*	Cases: 47/22/1; controls: 1,533/754/102	No	*DD/DI* vs. *II*	3.08	0.4, 22.4	Yes
							**D* vs. **I*	1.23	0.8, 1.9	

* Diagnosis criteria for ischemic heart failure: 1) history of myocardial infarction or severe coronary artery disease on arteriogram, left ventricular ejection fraction (LVEF) <40% and left ventricular enlargement on echocardiogram; 2) New York Heart Association class II–IV functional capacity, LVEF <40%, coronary stenosis >50% for at least one vessel on arteriogram; 3) LVEF <40%, structured questionnaire for the definition of the heart failure cause; 4) nonspecified ischemic etiology definition; 5) New York Heart Association class II–III functional capacity, LVEF <35%, coronary stenosis >0% for at least one vessel on arteriogram; and 6) new-onset ischemic heart failure cases in a cohort of myocardial infarction survivors (Osaka Acute Coronary Insufficiency Study).

† Diagnosis criteria for controls: i) actual or prospective heart donors with normal donor-screening echocardiograms and normal coronary arteriograms; ii) healthy subjects, randomly selected, without evidence of heart disease; iii) patients with stable angina pectoris with angiographic evidence of coronary stenosis >50% for at least one vessel, LVEF ≥40%; iv) hospitalized patients with normal arteriogram and LVEF >50%; v) cardiac donors with no transplant coronary artery disease; vi) cardiac donors without transplant rejection; and vii) myocardial infarction survivors who did not develop postmyocardial infarction heart failure in a 12-month follow-up period.

‡ Defined in the Materials and Methods section of the text.

§ mt, mutant type; wt, wild type; OR, odds ratio; CI, confidence interval; HWE, Hardy-Weinberg equilibrium; N/A, not available; nr, not reported; *L*, long allele (>27 repeats); *S*, short allele (≤27 repeats).

¶ Heart failure population including all etiologies, but ischemic etiology is the leading cause and the authors state that there is no difference in genotype distribution between the heart failure etiologies.

TABLE 2. Genetic polymorphisms investigated in relation to ischemic heart failure risk

dbSNP* rs no.	Gene†	Chromosomal position	Base change‡	Average heterozygosity (standard error)	Amino acid change§	Detection method	Functional effect (reference no.)
rs4646994	*ACE*	17q23	Intron 16: 287 base pair insertion/deletion	0.460 (0.136)	None	PCR¶ fragment size	Increased plasma ACE levels (59, 60)
rs699	*AGT*	1q42-43	Exon 2: C704T	0.469 (0.121)	Met235Thr	RFLPs¶: creates *AspI* site	Increased AGT levels (63)
rs5051	*AGT*	1q42-43	Promoter: G-6A	0.304 (0.244)	None	RFLPs: creates *BstNI* site	Affected promoter activity (64, 65)
rs2234888	*ADRA2C*	4p16.1	Exon 1: in-frame 12-nucleotide (GGGGCGGGGCCG) deletion in nucleotide 964	N/A¶	Positions 322–325: deletion Gly-Ala-Gly-Pro	RFLPs: loss of a *NciI* site	Substantial loss of agonist-mediated receptor function-enhanced presynaptic release of norepinephrine (68)
rs1801253	*ADRB1*	10q24-q26	Exon 1: G1165C	0.427 (0.177)	Arg389Gly	RFLPs: creates *BcgI* site	Threefold higher maximal isoproterenol-stimulated levels of adenylate cyclase activities (69)
rs1042713	*ADRB2*	5q31-q32	Exon 1: A46G	0.488 (0.078)	Arg16Gly	RFLPs: creates *BsrD I* site	Controversial data regarding down-regulation, desensitization (72, 73)
rs1042714	*ADRB2*	5q31-q32	Exon 1: C79G	0.368 (0.221)	Gln27Glu	RFLPs: creates *Fnu4H I* site	Resistance to down-regulation (71)
rs1800888	*ADRB2*	5q31-q32	Exon 1: C740T	0.007 (0.059)	Thr134Ile	SSOP¶	Signaling defects (75)
rs5370	*EDN1*	6p24.1	Exon 5: G61T	0.346 (0.231)	Lys198Asn	RFLPs: creates *Cac8 I* site	Higher plasma levels of endothelin (77, 78)
rs5333	*EDNRA*	4q31.23	Exon 6: C69T	0.464 (0.129)	None (synonymous)	SSOP	No functional studies available
rs361525	*TNF*	6p21.3	Promoter: G-238A	0.127 (0.218)	None	RFLPs: creates *BamHI* site	Greater transcription rate (89)
rs1800629	*TNF*	6p21.3	Promoter: G-308A	0.161 (0.233)	None	RFLPs: loss of NcoI site	Greater transcription rate, higher constitutive and inducible levels (90)
rs4986978	*LTA*	6p21.3	Intron 1: G252A	0.010 (0.069)	None	RFLPs: loss of *NcoI* site	High tumor necrosis factor-α production (91)
rs1982073	*TGFB1*	19q13	Exon 1: T869C	0.397 (0.202)	Leu10Pro	SSOP	High TGF β production in vitro (94)
rs1800471	*TGFB1*	19q13	Exon 1: G915C	0.112 (0.209)	Arg25Pro	SSOP	High TGF β production in vitro (95)
rs2010963	*VEGF*	6p21.3	Promoter: G-405C	0.460 (0.136)	None	RFLPs: loss of *BsmFI* site	Lower VEGF production (85, 86)
rs833061	*VEGF*	6p21.3	Promoter: C-460T	0.214 (0.247)	None	RFLPs: loss of *BsrUI* site	Unlikely (85, 86)
rs3074372	*HMOX1*	22q12	Promoter: $(GT)_n$ repeats	N/A	None	PCR fragment size	No. of repeats is inversely related to the activity (82)
rs1800896	*IL-10*	1q31-q32	Promoter: G-1082A	0.417 (0.186)	None	SSOP	Low IL-10 production (99)
rs1800872	*IL-10*	1q31-q32	Promoter: C-592A	0.467 (0.124)	None	SSOP	Low IL-10 production (98)
rs2243250	*IL-4*	5q31.1	Promoter: C-590T	0.500 (0.012)	None	SSOP	Increases promoter strength (97)
rs17602729	*AMPD*	1p13-p21	Exon 2: C34T	0.069 (0.172)	Gln12 - nonsense (termination)	RFLPs: creates *NspI* site	Severely truncated protein that loses its catalytic activity (103)
rs5744455	*CD14*	5q31	Promoter: C-260T	0.315 (0.241)	None	SSOP	Enhanced transcriptional activity (101)
rs4795541	*SLC6A4*	17q11.2-q12	Promoter: 44 base pair insertion/deletion	N/A	None	PCR fragment size	Reduced transcriptional activity (106)

* dbSNP, Database of Single Nucleotide Polymorphisms. Bethesda, Maryland: National Center for Biotechnology Information, National Library of Medicine. (dbSNP Build ID: 126). Available at the following website: http://www.ncbi.nlm.nih.gov/SNP/.

† Defined in the Materials and Methods section of the text.

‡ Base change symbolized as locus: wild-type allele, nucleotide position, mutant allele. The nucleotide substitution for promoter polymorphism is symbolized as number of nucleotides before the transcription initiation site.

§ Amino acid substitution for nonsynonymous polymorphisms symbolized as wild-type amino acid (three-letter coding), amino acid position, mutant amino acid (three-letter coding).

¶ PCR, polymerase chain reaction; RFLPs, restriction fragment length polymorphisms; N/A, not available; SSOP, sequence specific oligonucleotide probing.

Sympathetic nervous system

The pathophysiological relevance of α- and β-adrenergic receptors (α-AR and β-AR, respectively) and the benefit of antiadrenergic strategies in heart failure have been thoroughly studied (66, 67). Two case-control studies (37, 38) have investigated an in-frame deletion (symbolized *Del322-325*) (68) in the gene coding *ADRA2C* for susceptibility to IHF. Under the recessive model, a positive association was found by Small et al. (37) for Black subjects only, because the respective odds ratio was 5.65 (95 percent CI: 2.67, 11.95).

A nonsynonymous functional SNP of the β1-AR gene (*ADRB1*), symbolized *Arg389Gly* (69), has been genotyped by three case-control studies (37–39). All of them report lack of association of the *Arg389Gly* polymorphism with IHF, although two (38, 39) possibly used a completely overlapping set of White cases. The meta-analysis of two studies (37, 39) showed no significant sign of heterogeneity ($p \geq 0.10$), and the allele contrast, the recessive model, and the dominant model produced no significant results (table 3).

Three nonsynonymous functional SNPs of the β2-AR gene (*ADRB2*), designated *Arg16Gly, Gln27Glu*, and *Thr134Ile* (66, 70–75), have been investigated for a potential role in IHF risk (39, 40). Covolo et al. (39) studied the possible association of the *Gly16Arg* and *Gln27Glu* polymorphisms with IHF, but no significant effect was observed. Leineweber et al. (40) genotyped the three aforementioned SNPs in a heart failure cohort consisting of 80 percent IHF cases. A positive association for **Gly* under the allele contrast and a marginal association of *Glu* homozygotes versus heterozygotes were found. The meta-analysis for the *Arg16Gly* polymorphism showed no significant sign of heterogeneity ($p \geq 0.10$; $I^2 \leq 12$) and that the recessive model reaches marginal significance with a fixed-effects odds ratio equal to 1.32 (95 percent CI: 1.05, 1.65) (table 3). The meta-analysis for the *Gln27Glu* polymorphism showed no significant sign of heterogeneity ($p \geq 0.10$; $I^2 \leq 7$), and the allele contrast, the recessive model, and the dominant model produced no significant results (table 3).

Growth factors and endothelial proteins

A multitude of data suggests that the endothelin system is intricately involved in the pathophysiology of heart failure (76). A functional nonsynonymous SNP (*Lys198Asn*) of the *EDN1* gene (77, 78), and a nonfunctional synonymous SNP (*C69T*) (79) of the endothelin A receptor gene (*EDNRA*), have been genotyped by Colombo et al. (41) in 122 White heart failure (79 percent ischemic) cases and 216 controls. In comparison with that for *Lys* homozygotes, the odds ratio for heart failure associated with the *AsnAsn* genotype was 4.34 (95 percent CI: 1.7, 11.1).

Heme oxygenase-1 is a rate-limiting enzyme in heme degradation, leading to the generation of by-products that exert potent antiproliferative and antiinflammatory effects (80, 81). A functional promoter dinucleotide repeat polymorphism [(*GT*)n] (82) of the heme oxygenase-1 gene (*HMOX1*) was investigated in relation to IHF (47). No association was found for the long (>27 repeats) or the short (≤27 repeats) version of this polymorphism.

Vascular endothelial growth factor plays a key role in angiogenesis and endothelial integrity and seems to be involved in the microvasculature abnormalities in heart failure (83, 84). Two functional promoter SNPs (*G-405C* and *C-460T*) (85, 86) of the *VEGF* gene have been examined by van der Meer et al. (46) in 417 IHF patients enrolled in the Metoprolol CR/XL Randomized Intervention Trial in Heart Failure study (5) and in 187 healthy controls. Only a marginal association for the *−405C* allele was obvious under the allele contrast.

Inflammatory genes

Evidence is accumulating that inflammation plays an important role in the development of left ventricular remodeling (87, 88).

The gene for proinflammatory cytokine tumor necrosis factor-α (*TNF*) is arranged in tandem with the tumor necrosis factor-β or lymphotoxin alpha (*LTA*) gene. Three genetic association studies of Whites (42–44) have shown lack of association of IHF with two functional promoter SNPs (*G-238A* and *G-308A*) (89, 90) of the *TNF* gene and a functional intronic SNP (*G252A*) (91) of the *LTA* gene. Accordingly, the meta-analysis of two published studies of the *TNF G308A* polymorphism (42, 44) showed no significant sign of heterogeneity ($p \geq 0.10$; $I^2 = 0$), and the allele contrast, the recessive, and the dominant model produced no significant results (table 3).

Transforming growth factor-beta (TGFβ) is a multifunctional cytokine involved in the production and degradation of the extracellular matrix, important during the healing process after myocardial infarction and the transition from stable hypertrophy to heart failure (92, 93). Investigation of two functional nonsynonymous SNPs (*Leu10Pro* and *Arg25Pro*) (94, 95) of the *TGFB1* gene in 144 heart transplant recipients with IHF and 94 healthy controls has shown no significant results (45).

Interleukin 4 (IL-4) and interleukin 10 (IL-10) are antiinflammatory cytokines that inhibit the synthesis of proinflammatory cytokines (96). Three published studies by the same group of investigators in the Netherlands examined whether genetic variability in the *IL-4* and *IL-10* genes affects individual susceptibility to IHF (48, 49). One promoter SNP (*C-590T*) for *IL-4* (97) and two promoter SNPs (*G-1082A* and *C-592A*) for *IL-10* (98, 99) were examined, but no positive association was reported. Cluster of differentiation (CD) surface molecules mediate cell activation and signaling (100). The functional promoter SNP (*C-260T*) of the *CD14* gene (101) was genotyped by Kruger et al. (51) in 51 IHF cases and 100 healthy controls, but no increased risk of IHF was found.

Miscellaneous genes

Kolek et al. (50) hypothesized that carriers of the *C34T* nonsense mutation of the adenosine monophosphate deaminase gene (*AMPD1*) might have a relative advantage, since this mutation results in a beneficial increase in the cardioprotective molecule adenosine (102–104). They genotyped 605 IHF patients in the Beta-Blocker Evaluation of Survival Trial compared with two control groups from the

Intermountain Heart Collaborative Study Registry. No protective effect of the *C34T* mutation was detected for carriers when compared with both the first and the second control groups.

The serotonin transporter is considered one of the determinants of depressive symptoms, which is an independent predictor of increased morbidity and mortality in patients with acute myocardial infarction (105). Nakatani et al. (52) published a cohort study from the Osaka Acute Coronary Insufficiency Study group, in which they investigated the influence of a functional *I/D* polymorphism of the serotonin transporter gene (*SLC6A4*) (106). The *D* allele did not confer an increased risk of developing new-onset heart failure in myocardial infarction survivors within 1 year of follow-up.

Interactions

As with other complex traits, development of IHF is likely determined by several genes that act collectively, and allelic variants at different genes may have either additive or contrasting effects (epistasis) (56, 107). Additionally, there are several possible interactions between genetic polymorphisms and effect modifiers such as age, gender, treatment, hypertension, or other environmental factors (108).

Gene-gene interactions. Four studies (37–39, 41) investigated possible gene-gene interactions. Small et al. (37) examined the possible interaction of the *ADRA2C*, *Del322-325*, and *ADRB1 Arg389Gly* polymorphisms. In Black subjects, homozygosity for **Del322-325* and **Arg* was associated with a substantially increased risk of heart failure, and the estimated odds ratio was 10.11 (95 percent CI: 2.11, 48.53). A possible biologic explanation for this synergistic effect is that the combination of receptor variance results in increased synaptic norepinephrine release and in enhanced receptor function at the cardiomyocyte (37). The lack of association of this combined genotype in Whites was reported by two studies (37, 38). Covolo et al. (39) investigated the possibility of an interaction between the *ADRB1* and *ADRB2* polymorphisms, that is, whether homozygosity for *ADRB1*Arg* combined with the *ADRB2 *Gly*Gln* haplotype confers an increased risk. Despite their negative findings, these should be carefully interpreted because the per-stratum sample size and the associated statistical power are reduced when the number of examined genes is increased (109).

Colombo et al. (41) investigated the potential synergistic effect between the genes of the endothelin system signal transduction pathway. A two-locus analysis indicated that homozygosity for *EDN1 AsnAsn* and *EDNRA TT* was associated with a substantially increased risk of heart failure because the odds ratio was 8.6 (95 percent CI: 1.5, 48.1).

Gene-environment interactions. The conflicting results among studies investigating genetic polymorphisms and the risk of IHF may be due to the lack of information on the possible interactions with environmental factors. Akbulut et al. (33) used coronary artery disease patients without heart failure as controls, but there was a significant difference in the positive history of myocardial infarction between the cases and the controls ($p < 0.05$). Because the *ACE DD* genotype was not associated with an increased risk of myocardial infarction ($p = 0.6$), the *DD* genotype was not overrepresented in cases because of the positive history of myocardial infarction. The presence of hypertension could promote the progression of heart failure. However, Small et al. (37) demonstrated that the distribution of the risk-associated dual genotype (**Del322-325* and **Arg*) was not different between hypertensive and normotensive heart failure cases (chi-square = 0.34, $p = 0.95$). Goldbergova et al. (36) detected an increased risk of the *G-6A* polymorphism of the *AGT* gene, only after adjustment for sex. Furthermore, for women carrying the combined genotype *GGMT* for the *AGT* gene, the odds ratio was 15.5 (95 percent CI: 1.86, 129.42) in contrast to the nonsignificant odds ratio observed for men. Such a sex-specific influence could result from the effect of steroid hormones, which affect *AGT* expression in a variety of tissues (110).

DISCUSSION

Understanding the role that genes play in developing IHF is essential to creating more effective screening tests for predicting which individuals are at risk of developing the disease, to implementing appropriate early-intervention preventive and therapeutic strategies, and to developing gene therapy approaches in the future (111). So far, IHF genetic association studies have been highly inconsistent. The complex nature of heart failure implies that, for individual polymorphisms, associations are likely to be modest (12). To detect such modest genetic effects, a series of important research priorities must be implemented.

Power improvement

There is clearly a loss of statistical power when the genetic effect is reduced (107). Most of the studies we analyzed included few cases and controls and consequently did not have adequate power to detect a modest genetic effect. Apart from the need for larger sample sizes, selecting cases that are genetically loaded may also improve power. By selecting cases with very early onset disease and a strong family history, cases will be weighted toward those individuals whose disease has a strong genetic etiology (112).

Stratification

Small et al. (37) were able to detect the strongest to-date genetic association in Blacks, but not in Whites. Lack of stratification in this study could have led to blurring of the genetic effect. On the contrary, there is serious concern about the possible effects of population stratification on the results of case-control studies (113). Unequal genetic admixture in the control and patient populations can result in spurious associations. An approach proposed to minimize this potential problem is to measure and adjust for genetic markers not linked to the disease under investigation (114).

Prospective design

All the analyzed studies except for one (52) were of case-control design and were retrospective. If a genetic variant not only significantly increases the risk of IHF but also

TABLE 3. Odds ratios with the corresponding 95% confidence intervals and heterogeneity tests results (I^2, *Q* test) for genetic contrasts of *ACE I/D, ADRB1 Arg389Gly, ADRB2 Arg16Gly, ADRB2 Gln27Glu* and *TNF G308A* polymorphisms* for ischemic heart failure

Polymorphism	Population	Fixed effects		Random effects		No. of studies (reference no.)	I^2 (%)	*p* value, *Q* test
		OR†	95% CI†	OR	95% CI			
ACE I/D								
**D* vs. **I*	All	0.85	0.69, 1.05	0.85	0.69, 1.05	4 (32–35)	0	0.84
	East Asians	0.77	0.53, 1.12	0.77	0.53, 1.12	2 (32, 35)	0	0.94
Recessive model	All	0.94	0.70, 1.27	0.95	0.60, 1.52	5 (31–35)	51	0.09
	Sensitivity‡	0.76	0.54, 1.07	0.77	0.55, 1.08	4 (32–35)	0	0.71
	Whites	1.02	0.70, 1.50	1.16	0.40, 3.37	2 (31, 34)	85	0.01
	East Asians	0.67	0.30, 1.50	0.70	0.31, 1.56	2 (32, 35)	0	0.44
Dominant model	All	0.86	0.61, 1.21	0.86	0.61, 1.21	4 (32–35)	0	0.77
	East Asians	0.73	0.44, 1.21	0.73	0.44, 1.21	2 (32, 35)	0	0.56
ADRB1 Arg389Gly								
**Arg* vs. **Gly*	All	0.87	0.69, 1.10	0.87	0.69, 1.10	3 (37, 39)	0	0.99
	Whites	0.87	0.66, 1.14	0.87	0.66, 1.14	2 (37, 39)	0	0.89
Recessive model	All	0.85	0.62, 1.15	0.85	0.62, 1.15	3 (37, 39)	0	0.67
	Whites	0.79	0.56, 1.12	0.79	0.56, 1.12	2 (37, 39)	0	0.86
Dominant model	All	0.82	0.50, 1.34	0.81	0.49, 1.35	3 (37, 39)	0	0.37
	Whites	1.06	0.55, 1.04	1.05	0.54, 2.03	2 (37, 39)	0	0.44
ADRB2 Arg16Gly								
**Gly* vs. **Arg*	Whites	1.03	0.81, 1.30	1.03	0.81, 1.30	2 (39, 40)	0	0.78
Recessive model	Whites	1.32	1.05, 1.65	1.31	1.03, 1.67	2 (39, 40)	12	0.29
Dominant model	Whites	0.89	0.66, 1.21	0.90	0.66, 1.21	2 (39, 40)	0	0.82
ADRB2 Gln27Glu								
**Glu* vs. **Gln*	Whites	1.07	0.84, 1.37	1.07	0.84, 1.33	2 (39, 40)	0	0.68
Recessive model	Whites	1.28	0.95, 1.72	1.27	0.93, 1.74	2 (39, 40)	7	0.30
Dominant model	Whites	1.03	0.82, 1.29	1.03	0.82, 1.29	2 (39, 40)	0	0.40
TNF G308A								
**A* vs. **G*	All	1.04	0.77, 1.39	1.04	0.77, 1.39	2 (42, 44)	0	0.86
Recessive model	All	1.40	0.52, 3.79	1.39	0.51, 3.81	2 (42, 44)	0	0.71
Dominant model	All	1.03	0.70, 1.52	1.03	0.70, 1.52	2 (42, 44)	0	0.53

* Defined in the Materials and Methods section of the text.
† OR, odds ratio; CI, confidence interval.
‡ Exclusion of a study with no data on Hardy-Weinberg equilibrium (31).

influences survival, it is possible that risk-allele carriers will have advanced heart failure and die prematurely, leading to an underrepresentation of the risk genotype at the time of enrollment (115). Consequently, prospective studies are needed.

Case selection

The inclusion criteria for cases could also be another source of bias. Firstly, all studies except for one (40) included cases with impaired systolic function only. However, there are accumulating data indicating that as much as 50 percent of heart failure is associated with a normal left ventricular ejection fraction (116). Additionally, myocardial hibernation could introduce an issue of misclassification because revascularization could improve, and even normalize, left ventricular ejection fraction and heart failure symptoms in patients with hibernating myocardium (117).

Standardization of the definition of IHF based on angiographic criteria, as proposed by Felker et al. (8), could limit variability in defining etiologic subgroups in heart failure cohorts.

Appropriateness of controls

The majority of the control groups consisted of healthy or nonischemic and non–heart failure subjects. However, the absence of coronary artery disease in controls could lead to spurious associations. The use of two control groups, with and without coronary artery disease as in the study by Kolek et al. (50), establishes the appropriate contrast to detect a possibly true genetic effect.

HWE and genotyping

In the studies with the controls not in HWE (37, 39, 40), the lack of HWE indicates genotyping errors, population stratification, and selection bias (118). In addition, lack of HWE in a population implies continued selection, migration, mutation, and absence of random mating (119, 120). Thus, the validity of the genotyping method, and the selection of controls, are questioned (119, 121). Furthermore, the lack of reporting blindness in genotyping personnel in 33 studies (31, 32, 34, 35, 37–51) and the possible lack of a validated genotyping procedure in 28 studies (31, 32, 34, 37–40, 42–44, 46, 48–52) could be potential sources of biases.

Candidate gene selection

In addition to candidate gene approaches, genomic or proteomic expression analyses can assist in the selection of candidate variants by ranking those genes that appear to be the most active in the disease process (107, 122). Recent studies have identified gene expression profiles that could accurately distinguish ischemic and nonischemic cardiomyopathy (123). This overlapping of independent sources of information has been termed ''genomic convergence'' and is expected to provide new insights into the cellular mechanisms involved in cardiac dysfunction (124).

Gene-environment interactions

Many environmental factors have been associated with increased risk of IHF, such as age, obesity, hypertension, myocardial infarction, anemia, diabetes mellitus, hyperlipidemia, and thyroid disorders, while a number of pharmacological and nonpharmacological interventions have been shown to alter the natural history of the syndrome (125). Despite difficulties in study design and assessment of the exposures, such parameters should be incorporated in future studies (126).

Gene-gene interactions

The search for susceptibility loci has probably been complicated by the increased number of contributing loci and susceptibility alleles (127). Elucidating the pathogenesis of the disorder would demand investigation of association for many variants of genes that constitute distinct pathophysiological pathways (128).

Large-scale genetic association studies and meta-analyses

IHF cases are usually aged (table 1), which means that recruiting large numbers of affected sib pairs or family trios, needed for wide-genome scans and family-based association studies, might be problematic (10, 129). Consequently, elucidating the genetics of IHF largely relies upon designing and undertaking rigorous genetic association studies. Moreover, future studies should be planned with the idea of their being incorporated into other similar studies in a meta-analysis. The opportunities offered by a meta-analysis are enhancement of power; the ability to place each study in the context of all others, particularly early spurious results; and the possibility of examining why studies reach different conclusions (120).

In summary, there is no evidence of strong association between genetic variants and the risk of developing IHF in the individual studies and meta-analyses. These findings suggest that the risk of IHF is not related to genes or that research to date has been insufficient to identify such associations. However, conclusions reached in the present analysis were based on relatively small numbers of studies and participants for each gene polymorphism, and their interpretation has to be cautious. Taking into account that IHF is a complex disease with multifactorial etiology, a minor contributing pathogenetic role of the investigated gene polymorphisms in specific cases, and in cooperation with other factors, cannot be totally excluded. Therefore, the relation between genetic variation and IHF still remains an unresolved issue. The results of long-term prospective and case-control studies (118, 130), designed to investigate gene-gene and gene-environment interactions, and utilizing the vast amount of data produced by genomic studies (122) might produce more conclusive claims about the genetics of IHF.

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