A genetic association study of heart failure: more evidence for the role of BAG3 in idiopathic dilated cardiomyopathy

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Abstract

Aims Few investigations have been conducted to identify genetic determinants of common, polygenetic forms of heart failure (HF), and only a limited number of these genetic associations have been validated by multiple groups.

Methods and results We performed a case–control study to further investigate the potential impact of 14 previously reported candidate genes on the risk of HF and specific HF sub-types. We also performed an exploratory genome-wide study. We included 799 patients with HF and 1529 controls. After adjusting for age, sex, and genetic ancestry, we found that the C allele of rs2234962 in BAG3 was associated with a decreased risk of idiopathic dilated cardiomyopathy (odds ratio 0.42, 95% confidence interval 0.25–0.68, \( P = 0.0005 \)), consistent with a previous report. No association for the other primary variants or exploratory genome-wide study was found.

Conclusions Our findings provide independent replication for the association between a common coding variant (rs2234962) in BAG3 and the risk of idiopathic dilated cardiomyopathy.

Keywords Heart failure; Genetics; B-cell lymphoma 2-associated anthanogene protein

Background

Heart failure (HF) and various associated characteristics, including neurohormonal activation and left ventricular structure, are heritable complex phenotypes.1,2 Yet few investigations have been conducted to identify genetic determinants of common, polygenetic forms of HF. In recent years, a small number of common variants have been associated with unselected cases of HF, HF with reduced left ventricular ejection fraction (LVEF; HF-REF), and non-familial cases of dilated cardiomyopathy.3,4 Few of these genetic associations have been validated by other groups. Thus, we performed a case–control study to further investigate the potential impact of previously reported candidate genes on the risk of HF and specific HF sub-types.

Methods

Study design and study participants

We conducted a case–control study that included participants from the Montreal Heart Institute (MHI) Hospital Cohort.5 Cases were individuals who had a prior history of HF and a document LVEF prior to the baseline inclusion visit.
in the MHI Hospital Cohort. The control group consisted of individuals who had no history of HF or any other established cardiac or valvular diseases, coronary artery disease, any clinically significant arrhythmia, stroke, or deep vein thrombosis. The study was limited to unrelated individuals of genetically determined Caucasian ancestry. In addition, as a sensitivity analysis for the BAG3 replication, we conducted a matched case–control analysis where cases were matched with up to three controls from the MHI Hospital Cohort based on sex, age (±2 years), history of myocardial infarction and diabetes, and smoking status. All patients provided written consent to participate in the MHI Hospital Cohort. The MHI Hospital Cohort and this study were approved by the Scientific and Ethics Review Boards of the MHI.

Genetic analyses

Patients were genotyped using a custom Agena MassArray (San Diego, CA) panel that included genetic variants that had been associated with HF susceptibility (e.g. CLCNKA and BAG3), HF drug response, or HF-related pathways such as genes coding for the angiotensin-converting enzyme (ACE), adrenergic receptors (e.g. ADRB1), and B-type natriuretic peptide (NPPB), and with the HumanExome-12 v1.1 and HumanExome-24 v1.0 array by Illumina (San Diego, CA), which include >240 000 exonic variants according to methods previously described. Data clean-up and imputation were performed according to published methods.

Statistical analyses

The significance threshold for replication of the 14 primary variants (listed in Table 2) was set at a $P < 0.0045$, as the effective number of independent tests was calculated to be of 11 ($P = 0.05/11 = 0.0045$). Because the Bonferroni correction assumes independence among the tests, we have applied this multiple testing correction that takes into account the linkage disequilibrium between single nucleotide polymorphisms (SNPs). Associations with $P$-values between 0.05 and 0.0045 presenting a concordant risk direction with previous reports were deemed as suggestive of a replication of the association. We also performed an exploratory genome-wide study. All genetic association analyses were performed using a logistic regression, with a log additive genetic model, controlling for age, sex, and genetic ancestry (10 principal components). Genetest 0.3.0 and SAS 9.4 were used to conduct the statistical analyses.

Results

We included 799 patients with HF and 1529 controls. As anticipated, HF patients were older and were more likely to be male and present cardiovascular risk factors (Table 1). In patients with idiopathic dilated cardiomyopathy (IDC; LVEF: 38.6 ± 14.5%; lowest LVEF documented: 24.6 ± 12.0%), we found that the allele C of rs2234962 in BAG3 was associated with a decreased risk of IDC [odds ratio (OR) 0.42, 95% confidence interval 0.25–0.68, $P = 0.0005$], after adjusting for age, sex, and genetic ancestry, which is consistent with a previous report of sporadic dilated cardiomyopathy. No association was found between this BAG3 variant and the risk of HF in the overall population or for the HF-REF subgroup. No association for the other primary variants was found significant according to the pre-established threshold (Table 2). In the matched case–control sensitivity analysis (102 cases and 283 matched controls; Supporting Information, Table S1), BAG3 was also significantly associated with a reduction of the risk of idiopathic cardiomyopathy (effect allele: C; effect allele frequency IDC: 0.088; effect allele frequency matched controls: 0.223; OR 0.39, 95% confidence interval 0.23–0.68, $P = 0.0008$).

We further explored whether other variants genotyped or imputed in BAG3 were associated with idiopathic cardiomyopathy. Although other variants were associated with the

| Table 1 Characteristics of the study population |
|---------------------------------------------|
| Characteristic                              | Cases  | Controls | $P$-   |
| n = 799                                     | (n = 1529) |          | value$^a$ |
| Female                                     | 183 (22.9%) | 878 (57.4%) | <0.01 |
| Age                                        | 66.3 ± 10.0 | 59.7 ± 11.6 | <0.01 |
| Body mass index                            | 29.6 ± 5.9 | 28.3 ± 5.4 | <0.01 |
| Diabetes                                   | 288 (36.1%) | 144 (9.4%)  | <0.01 |
| Hypertension                               | 582 (72.8%) | 589 (38.5%) | <0.01 |
| Atrial fibrillation/flutter                 | 395 (49.4%) | 0 (0.0%)   | <0.01 |
| Previous myocardial infarction              | 462 (57.8%) | 0 (0.0%)   | <0.01 |
| Left ventricular ejection fraction          | 39.3 ± 14.8 | NA        |
| Heart failure aetiology                     | NA     |
| Ischaemic cardiomyopathy                    | 444 (55.6%) | 117 (14.6%) | NA    |
| Valvular                                    | 107 (13.4%) | 24 (3.0%)  | NA    |
| Hypertrophic                               | 24 (3.0%)  |
| Myocarditis                                 | 24 (3.0%)  |
| Tachyarrhythmic                            | 21 (2.6%)  |
| Hypertension                               | 10 (1.3%)  |
| Alcoholic                                   | 8 (1.0%)   |
| Post-partum                                 | 2 (0.3%)   |
| Post-chemotherapy                           | 3 (0.4%)   |
| Other                                       | 39 (4.9%)  |

$^a$Not applicable.

$^b$Value corresponds to comparison between cases and controls using Fisher for categorical variables or Kruskal–Wallis for continuous variables.

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phenotype, all were intronic and in strong linkage disequilibrium with rs2234962 (all \( r^2 > 0.99 \); Table S2). The associations with the two other exonic variants were not statistically significant.

We found multiple nominal associations with HF or tested subgroups (\( P = 0.05–0.0045 \)). The HF-REF sub-phenotype provided the greatest number of findings that were consistent with previous reports of IDC or HF-REF. Indeed, four of the 14 primary SNPs were nominally (\( P < 0.05 \), Table 2) associated with HF-REF with risk associations consistent with previous reports (\( HSPB7, CLCNKA,^3 MLIP^3 \) and \( ALPK3^3 \)). \( ALPK3 \) and \( SLC39A8 \) also showed a similar trend in the investigation of the overall HF group, while \( ALPK3 \) was also nominally associated with IDC (Table 2).^3 The exploratory genome-wide investigations did not provide significant results (data not shown).

### Table 2 Genetic associations of candidate variants in all-cause HF, HF-REF, and idiopathic HF

| Ref | SNP   | Gene | Chr | Position^a | Ref allele | OR (95% CI) | P    | Ref allele | OR (95% CI) | P    | Ref allele | OR (95% CI) | P    |
|-----|-------|------|-----|------------|------------|-------------|------|------------|-------------|------|------------|-------------|------|
| Esslinger et al. ^3 | rs848210 | SPEN | 1   | 16 259 813 | G A        | 0.424       | 1.06 | 0.4090.44 | 1.04       | 0.6250.457 | 1.14       | 0.377       |
| Esslinger et al. ^3 | rs10927875 | ZBTB17 | 1   | 16 299 312 | C T        | 0.319       | 0.96 | 0.5620.284 | 0.90       | 0.2600.298 | 0.94       | 0.690       |
| Cappola et al. ^14 | rs1739843 | HSPB7 | 1   | 16 343 254 | C T        | 0.394       | 0.88 | 0.0770.344 | 0.81       | 0.0200.327 | 0.78       | 0.107       |
| Cappola et al. ^15 | rs10927887 | CLCNKA | 1   | 16 351 275 | G A        | 0.427       | 0.89 | 0.0910.373 | 0.82       | 0.0240.35 | 0.77       | 0.082       |
| Esslinger et al. ^3 | rs3829746 | TTN  | 2   | 179 427 536 | T C        | 0.235       | 1.03 | 0.7130.230 | 0.97       | 0.7640.207 | 0.85       | 0.371       |
| Cappola et al. ^14 | rs6787362 | FRMD4B | 3   | 69 227 379 | A G        | 0.114       | 0.94 | 0.5550.113 | 1.00       | 0.9880.144 | 1.32       | 0.193       |
| Esslinger et al. ^3 | rs13107325 | SLC39A8 | 4   | 103 188 709 | C T        | 0.077       | 1.28 | 0.0440.103 | 1.26       | 0.1290.115 | 1.43       | 0.134       |
| Esslinger et al. ^3 | rs4712056 | MLIP | 6   | 53 989 526 | A G        | 0.369       | 1.13 | 0.0910.399 | 1.21       | 0.0380.423 | 1.33       | 0.066       |
| Esslinger et al. ^3 | rs2291569 | FLNC | 7   | 128 488 734 | G A        | 0.080       | 1.08 | 0.5600.098 | 1.20       | 0.2530.067 | 0.77       | 0.386       |
| Villard et al. ^8 | rs2234962 | BAG3 | 10  | 121 429 633 | T C        | 0.201       | 0.97 | 0.7550.167 | 0.88       | 0.2570.087 | 0.42       | 0.0005      |
| Esslinger et al. ^3 | rs3188055 | INPP5F | 10  | 121 586 882 | A G        | 0.342       | 1.12 | 0.1410.369 | 1.09       | 0.340.380 | 1.17       | 0.306       |
| Esslinger et al. ^3 | rs1051168 | NMB  | 15  | 85 200 520 | G T        | 0.292       | 1.11 | 0.1910.315 | 1.16       | 0.1160.346 | 1.25       | 0.153       |
| Esslinger et al. ^3 | rs3803403C | ALPK3 | 15  | 85 383 145 | C G        | 0.286       | 1.20 | 0.0160.325 | 1.26       | 0.0170.363 | 1.38       | 0.038       |
| Esslinger et al. ^3 | rs2303510 | FHOD3 | 18  | 34 324 091 | G A        | 0.309       | 1.14 | 0.6000.313 | 1.00       | 0.9690.279 | 0.85       | 0.315       |

Chr, chromosome; CI, confidence interval; EAF, effect allele frequency; HF, heart failure; HF-REF, HF with a reduced left ventricular ejection fraction; OR, odds ratio; Ref, reference; SNP, single nucleotide polymorphism.

Association in same direction as previously reported and \( P < 0.0045 \) (yellow highlight) or \( P = 0.05–0.0045 \) (blue highlight).

^aPosition of variants from NCBI Build 37 assembly.

^bFor the 'all HF', all patients with a history of HF were included, even if they had since undergone heart transplantation. Patients who had undergone heart transplant (\( n = 53 \)) were excluded from all other sub-type analyses. All analyses were performed using a logistic regression controlling for age, sex, and 10 principal components.

^cImputed variant.
Conclusions

Our findings provide independent replication for the association between a common non-synonymous variant (rs2234962; c.451T>C, p.Cys151Arg) in BAG3 and the risk of IDC. This association was consistent when using controls without cardiac disease or a matched population (OR 0.42 and 0.39, respectively). This genetic variant has been associated with the risk of sporadic IDC in patients of European descent, initially by Villard et al., which they ultimately validated in six populations of European Ancestry. More recently, a large case–control study of the Heart Failure Molecular Epidemiology for Therapeutic Targets (HERMES) consortium has also identified BAG3 as a likely HF genetic determinant. Consistent with these results, a genome-wide analysis of 16,923 European UK Biobank participants found that BAG3 was associated with LVEF as well as LV end-systolic and end-diastolic volumes.

BAG3, which encodes the B-cell lymphoma 2-associated anarthrogenene (BAG3) protein, is most prominently expressed in the heart and serves as a co-chaperone of the heat shock protein family. Reduced myocardial levels have been associated with HF. BAG3 appears critical in autophagy to maintain cardiac protein homeostasis, in decreasing apoptosis, and is involved in myocardial contraction by stabilizing the Z-disk and through coupling with the L-type calcium channel and the β1-adrenergic receptor. The cysteine to arginine substitution associated with rs2234962 may modulate autophagy because of its location between two conserved Ile-Pro-Val motifs that are involved in complex formation between BAG3 and HSPB6 and HSPB8. This potential mechanism requires investigation. Our results also suggest that BAG3 does not have a major impact on the risk of HF of other aetiologies, although, given our sample size, an effect of a smaller magnitude cannot be excluded. This potential difference also supports the possibility that preventive treatment for HF could be personalized according to genetic factors.

Rare coding mutations have also been associated with familial dilated cardiomyopathies. Interestingly, Myers et al. have found that rare variants in BAG3 contributing to dilated cardiomyopathy differed considerably between individuals of European and African ancestry. Unfortunately, rs2234962 was not investigated in that study and, to our knowledge, in any dilated cardiomyopathy association study of patients of African Ancestry. Given the fact that rs2234962 is relatively common in African-Americans (0.03 allele frequency), investigations of its impact in individuals of African and other ancestry do appear warranted.

Our study also provides supporting evidence for the association of HSPB7, CLCNKA, MLIP, ALPK3 with HF-REF, and SLC39A8 with all cases of HF, even though these associations did not meet our significance threshold. Yet the magnitude of the allelic effect was consistent with previous reports. The pathophysiological mechanisms by which these genes modulate the risk of HF remain uncertain. In particular, whether these variants actually predispose to LV dysfunction or in fact modulate HF risk factors, such as coronary artery disease, remains to be determined. Nonetheless, the current study provides further evidence to support future investigations focusing on the contribution of these genes and their proteins in the development of HF.

It should also be highlighted that we were not able to validate some previously reported associations. One immediate potential cause is our relatively small sample size. Yet the magnitude of the effect observed for some of the variants was surprisingly consistent with some of the original reports, even if the association did not reach statistical significance. For example, in the subgroup of patients with idiopathic cardiomyopathy, in addition to the significant and nominal association with BAG3 and ALPK3, the ORs observed were remarkably consistent with the original report for SNPs in the TTN gene (0.85 vs. 0.81), SLC39A8 (1.43 vs. 1.35), NMB (1.25 vs. 1.27), FHOD3 (0.85 vs. 0.82), SPEN (1.14 vs. 1.18), and FLNC (0.77 vs. 0.65). Given that only a limited number of these common variants have been validated in multiple cohorts, further investigations are required to validate the association between these common variants and the various types of HF. In fact, the importance of validating newly discovered variants and genes has recently been highlighted in the largest study of sequenced monogenic dilated cardiomyopathy. In this study, Mazzarotto et al. found that of 56 commonly tested genes, a clear implication was demonstrated for only 12 genes, including BAG3.

In summary, we have replicated the association between a genetic variant rs2234962 in BAG3 and IDC, and we observed many other signals concordant with previous genetic association studies of HF. The replication of genetic associations in well-characterized HF patient populations is essential to support advances in our understanding of the contribution of genetic factors in HF. More importantly, the identification of novel pathways involved in HF can lead to new therapeutic targets to prevent the development and progression of this deadly disease.

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Conflict of interest

S.d.D. was supported through grants from Pfizer, AstraZeneca, Roche Molecular Science, DalCor, and Novartis. J.R. reports being a consultant for AstraZeneca and Novartis. J.C.T. reports grants from Amarin, AstraZeneca, DalCor, Esperion, Ionis, Sanofi, and Servier; honoraria from Amarin, DalCor, Sanofi, and Servier; minor equity in DalCor; and is an author of a patent on pharmacogenomics-guided CETP inhibition. M.-P.D. reports being an author of a patent pertaining to pharmacogenomics-guided CETP inhibition; minor equity interest in DalCor; honoraria from Dalcor; and research support (access to samples and data) from AstraZeneca, Pfizer, Servier, Sanofi, and GlaxoSmithKline.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Sex and age for the matched cases and controls groups.

Table S2. Genetic associations of BAG3 variants in idiopathic dilated cardiomyopathy (position from build37 121,410,859 to 121,437,331 bp).

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