Common variants in IL-17A/IL-17RA axis contribute to predisposition to and progression of congestive heart failure

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Abstract
Heart failure is characterized by immune activation leading to production and release of proinflammatory cytokines. Interleukin 17A (IL-17A) is a proinflammatory cytokine and multiple lines of evidence from animal and human studies suggest crucial roles of IL-17A in heart failure. Therefore, we investigated whether common polymorphisms of genes IL17A and IL17RA (coding interleukin 17 receptor A) contribute to genetic predisposition to heart failure and adverse clinical outcomes associated with it.

A total of 1713 adult patients with congestive heart failure and 1713 age- and sex-matched controls were genotyped for promoter single nucleotide polymorphisms (SNPs), rs2275913 and rs8193037 in IL17A and rs4819554 in IL17RA, to assess the relationship between individual SNPs and the risk of congestive heart failure. Results showed that rs8193037 in IL17A was associated with the risk of congestive heart failure (odds ratio [OR] = 0.76; 95% confidence interval [CI] 0.63–0.90, adjusted P = 0.002) after adjustment for multiple cardiovascular risk factors including age, sex, smoking status, diabetes, hypertension, and dyslipidemia. This association was evident in both ischemic and nonischemic heart failure (P = 0.005 and P = 0.05, respectively). Furthermore, prospective follow-up of 12.7 months for the occurrence of adverse clinical outcomes showed that rs4819554 in IL17RA was significantly associated with cardiovascular mortality (hazard ratio [HR] = 1.28; 95% CI = 1.02–1.59, adjusted P = 0.03) after adjustments for multiple cardiovascular risk factors and New York Heart Association functional class.

This study demonstrated associations of rs8193037 in the promoter of IL17A with the risk of congestive heart failure, and of rs4819554 in the promoter of IL17RA with the risk of cardiovascular mortality in patients with congestive heart failure. These data lend further support to the notion that immune activation and genetic polymorphisms contribute to heart failure pathogenesis and progression.

Abbreviations: CAD = coronary artery disease, CHF = congestive heart failure, CI = confidence interval, DCM = dilated cardiomyopathy, ESRD = end-stage renal disease, HR = hazard ratio, IL-17A = interleukin 17A, IQR = interquartile range, NFAT = nuclear factor activated T cells, OR = odds ratio, SNP = single nucleotide polymorphism.

Keywords: congestive heart failure, IL-17A, IL-17RA, single nucleotide polymorphism

1. Introduction
Heart failure is a systemic disease with a multifactorial etiology including genetic factors and immune factors.\textsuperscript{[1–3]} Immune activation leads to production and release of proinflammatory cytokines, activation of the complement system, and production of autoantibodies.\textsuperscript{[2]} Yandestad and colleagues\textsuperscript{[4]} have reported that gene expression of chemokines is upregulated in T cells from patients with heart failure, which activates the immune system through binding to the tumor necrosis factor superfamily and their...
receptors, the inflammatory cytokines interferon-gamma, and interleukin-18 with similar pattern in ischemic and idiopathic cardiomyopathy. Th1/Th2 cytokine imbalance has also been identified to play a role in heart failure pathogenesis.\textsuperscript{[14–21]} Circulating levels of proinflammatory cytokines such as TNF-alpha, soluble TNF receptors (sTNF-R1 and sTNF-R2), IL-6 and sCD14 have been shown to be independent predictors of mortality in patients with advanced heart failure.\textsuperscript{[19,20]} Interleukin 17A (IL-17A) is a proinflammatory cytokine produced mainly by Th17 lymphocytes, but also by natural killer T cells, γδ T cells, cytotoxic CD8\textsuperscript{+} T cells, and neutrophils.\textsuperscript{[11–13]} Multiple lines of evidence from animal and human studies suggest crucial roles of IL-17A and its receptor interleukin 17 receptor A (IL-17RA) in ischemic heart disease.\textsuperscript{[14–21]} Similarly, animal studies have provided evidence that IL-17A plays an important role in dilated cardiomyopathy (DCM).\textsuperscript{[22–26]} Previous studies have identified Th17/Treg imbalance with upregulation of IL-17A that plays important roles in heart failure pathogenesis.\textsuperscript{[27–31]}

Recent studies have identified single nucleotide polymorphisms (SNPs) in IL-17A/IL-17RA axis contribute to various cancers, autoimmune diseases, diabetes, and end-stage renal disease (ESRD). The A allele of rs2275913 (G>A) has been reported to show an association with immune-mediated disorders such as giant cell arteritis,\textsuperscript{[32]} primary antiphospholipid syndrome,\textsuperscript{[33]} ulcerative colitis,\textsuperscript{[34]} etc. A allele carriers of rs4819554 (A>G) has been reported to be associated with immune-mediated clinical phenotypes such as aspirin hypersensitivity in asthma and age of onset in alopecia as well as ESRD and development of new onset diabetes in renal transplant recipients\textsuperscript{[35–39]} in Asian population. The G allele carriers of rs8193037 (G>A) were reported to be at higher risk of metabolic syndrome in a large Mexican study.\textsuperscript{[40]} A large angiography-based study in a Chinese Han population suggested G allele carriers rs8193037 are at significantly higher risk of coronary artery disease (CAD) risk.\textsuperscript{[41]} However, whether these SNPs in IL-17A/IL-17RA axis are associated with risk stratification of heart failure has never been investigated.

Considering the crucial roles of IL-17A and its receptor IL-17RA in heart failure, we enrolled 1713 patients with congestive heart failure (CHF) and 1713 matched control subjects and aimed to investigate whether common polymorphisms of IL17A and IL17RA gene contribute to genetic predisposition to heart failure and adverse clinical outcomes associated with it.

2. Methods
2.1. Study participants
Patients referred to cardiology department of Tongji Medical College between September 2008 and August 2014 were screened for potential inclusion. Patients diagnosed with CHF based on medical history, physical examination, and relevant investigations were included as cases. Patients with ≥50% stenosis of major coronary arteries on coronary angiography were classified as ischemic heart failure, and those without angiographic evidence of coronary stenosis were classified as nonischemic heart failure. Ethnically and geographically matched individuals without evidence of CHF were included as controls. Anthropometric measurements, clinical characteristics, and clinical events were recorded at planned follow-up clinic visits, from questionnaires, medical records, and telephone calls.

The investigation conformed to the principles of the Declaration of Helsinki. All protocols and methods were approved by the ethics committee of the local hospital (Ethics Committee of Tongji Hospital). Written informed consents were obtained from all the participants.

2.2. Clinical endpoints
The endpoints included all-cause mortality, cardiac mortality, and hospitalization for heart failure.

2.3. SNP Selection and genotyping
Polymorphisms with minor allele frequencies >0.01, based on HapMap Beijing data, located in the promoter region and recently reported to be associated with immune-mediated diseases were selected for genotyping. Polymorphisms were genotyped using the TaqMan assay (Applied Biosystems, Foster City, CA). Primers and probes are presented in Supplementary Table 1, http://links.lww.com/MD/B104. Polymorphism genotyping adheres to a rigorous quality control program including blind replicate genotype assessment on 5% of the total samples.

2.4. Enzyme-linked immunosorbent assay
Blood samples collected in tubes containing EDTA were centrifuged at 3000g for 15 min at 4°C to isolate the plasma. Plasma samples were stored at −80°C till further use. Plasma levels of IL-17A were measured in duplicate using Legend MaxTM Human IL-17A ELISA kit (No. 433917, BioLegend, San Diego, CA). The detection limit was 0.8 pg/mL and the lowest concentration for standard sample was 3.9 pg/mL. The mean intraassay and the mean interassay coefficients of variation were 5.4% and 7.9%, respectively. High sensitivity C reactive protein (hs-CRP) levels were obtained from medical records.

2.5. Statistical analysis
Continuous variables were compared between groups by Mann–Whitney U test or independent sample t test. Categorical variables were compared by Chi-square test. The polymorphisms were tested for Hardy–Weinberg equilibrium among the heart failure patients and the controls using a Chi-square test with 1 degree of freedom. The association between the individual SNPs and heart failure risk was estimated by computing odds ratios (ORs) and 95% confidence intervals (CIs)\textsuperscript{[9]} from the multivariate logistic regression analyses. An unconditional logistic model was used to adjust for multiple cardiovascular risk factors. Clinical outcome analyses were performed using Kaplan–Meier curve and Cox proportional hazards regression model. All statistical analyses were performed with SPSS 15.0 (SPSS, Inc., Chicago, IL) for Windows and the level of statistical significance was set at P ≤ 0.05.

3. Results
3.1. Baseline characteristics of study participants
Baseline characteristics of heart failure cases and control participants are shown in Table 1. Heart failure and control participants were well matched in age and sex. More participants in heart failure group had diabetes, hypertension, dyslipidemia, smoking habit, but slightly lower level of triglycerides, total cholesterol, and low-density lipoprotein (LDL) cholesterol owing to lipid lowering therapy. The distribution of allele and genotype frequencies of the 3 SNPs is shown in Table 2. All the SNPs investigated are in Hardy–Weinberg equilibrium.
3.2. Association between IL-17A/IL-17RA polymorphisms and risk of congestive heart failure

No significant difference was detected in genotype and allele frequency of rs2275913 and rs4819534 between cases and controls suggesting these SNPs are not associated with the risk of heart failure. However, a statistically significant association was observed for rs8193037 (G>A). The frequency of GG and GA genotype was significantly higher in heart failure subjects than controls (Table 2). The distribution of genotype frequency was similar across ischemic and nonischemic heart failure and differed significantly from the controls (Table 3 and Supplementary Tables 2 and 3, http://links.lww.com/MD/B104). A allele was associated with a decreased risk of heart failure compared with G allele (OR=0.76; 95% CI=0.63–0.90, P=0.002) after adjustment for multiple cardiovascular risk factors including age, sex, smoking status, diabetes, hypertension, and dyslipidemia. Results of the stratified analysis suggested the effect size to be comparable between ischemic (OR=0.79; 95% CI=0.65–0.97, P=0.021) and nonischemic heart failure (OR=0.80; 95% CI=0.65–0.99, P=0.044). After adjustment for age, sex, smoking status, diabetes, hypertension, and dyslipidemia, these associations were still highly significant for ischemic heart failure (OR=0.74; 95% CI=0.60–0.91, P=0.005) and retained borderline significance for nonischemic heart failure (OR=0.80; 95% CI=0.61–1.00, P=0.050).

3.3. Association between IL-17A/IL-17RA polymorphisms and clinical outcomes of heart failure

In total, 1515 CHF patients were prospectively followed for a mean of 12.7 months. Survival analyses were conducted on these patients stratified by the genotype of SNPs in IL17-A/IL-17RA axis. No significant differences were noted between the investigated SNPs and all-cause mortality (Supplementary Figure 1, http://links.lww.com/MD/B104). Among these investigated SNP, only rs4819554 (G being the minor allele, with a frequency of 45.2% in this CHF cohort) exhibited a highly significant association with the diversity of cardiovascular mortality (log rank=0.027) (Fig. 1). The deaths from cardiovascular causes occurred in 69 patients (14.3%) in AA genotype group, 77 patients (11.3%) in AG genotype group, and 29 patients (8.3%) in GG genotype group. Cox-regression analysis showed that the A allele is significantly associated with an increased risk of cardiovascular mortality (hazard ratio

| Table 1 |

Baseline characteristics of the study population.

| Characteristics       | Controls (N=1713) | Cases (N=1713) |
|-----------------------|-------------------|---------------|
| Men, %                | 64.4              | 65.7          |
| Age, y                | 57.47±10.28       | 57.98±13.63   |
| Glucose, mmol/L       | 4.75±1.9          | 6.64±3.01*    |
| TG, mmol/L            | 1.61±1.33         | 1.4±1.09*     |
| TC, mmol/L            | 4.42±0.98         | 3.92±1.18*    |
| LDL-C, mmol/L         | 2.52±0.89         | 2.36±0.88*    |
| Hypertension, %       | 20.7              | 33.9          |
| Glucose, mmol/L       | 4.75±1.9          | 6.64±3.01*    |
| Smoking status, %     | 30.2              | 37.7          |

*P<0.05 vs control.

| Table 2 |

Association of the IL17A and IL17RA polymorphisms with chronic heart failure.

| Groups              | Genotype, n (%) | Per copy of the minor allele |
|---------------------|-----------------|-------------------------------|
|                     | MM | Mm | mm | MAF (%) | Unadjusted OR (95% CI), P | Adjusted OR (95% CI), P |
| IL17A rs2275913     |     |    |    |         |                            |                         |
| Controls            | 461 | 876 | 376 | 21.9 | 47.5 | 0.97 (0.88–1.06), 0.47 | Reference |
| Cases               | 494 | 840 | 379 | 21.1 | 46.6 | 0.95 (0.85–1.05), 0.30 |                     |
| IL17A rs8193037     |     |    |    |         |                            |                         |
| Controls            | 1389 | 303 | 21 | 1.2 | 10.1 | 0.80 (0.68–0.94), 0.007 | Reference |
| Cases               | 1445 | 256 | 12 | 0.7 | 8.2 | 0.76 (0.63–0.90), 0.002 |                     |
| IL17A rs4819654     |     |    |    |         |                            |                         |
| Controls            | 560 | 780 | 373 | 21.8 | 44.5 | 1.03 (0.94–1.12), 0.59 | Reference |
| Cases               | 554 | 769 | 390 | 22.8 | 45.2 | 1.04 (0.94–1.46), 0.46 |                     |

Odds ratios (ORs) and 95% confidence intervals (CI) were obtained by logistic regression, with and without adjustment for age, sex, hypertension, diabetes, dyslipidemia, and smoking status. rs22759123, M=G, m=A; rs8193037, M=G, m=A; rs4819654 M=A, m=G. MAF=minor allelic frequency.

| Table 3 |

Association of rs8193037 (G>A) with chronic heart failure with an ischemic or nonischemic etiology.

| Groups          | Genotype, n (%) | Per copy of the risk allele |
|-----------------|-----------------|----------------------------|
|                 | GG | GA | AA | MAF (%) | Unadjusted OR (95% CI), P | Adjusted OR (95% CI), P |
| Ischemic etiology |    |    |    |         |                            |                         |
| Controls        | 1389 | 303 | 21 | 1.2 | 10.1 | 0.79 (0.65–0.97), 0.021 | Reference |
| Cases           | 1445 | 256 | 12 | 0.7 | 8.2 | 0.74 (0.60–0.91), 0.005 |                     |
| Nonischemic etiology |    |    |    |         |                            |                         |
| Controls        | 1389 | 303 | 21 | 1.2 | 10.1 | 0.80 (0.65–0.99), 0.044 | Reference |
| Cases           | 796  | 139 | 7  | 0.7 | 8.1 | 0.80 (0.61–1.00), 0.050 |                     |

Odds ratios (ORs) and 95% confidence intervals (CI) were obtained by logistic regression, with and without adjustment for age, sex, hypertension, diabetes, dyslipidemia, and smoking status. MAF=minor allelic frequency.
Association of the IL17A and IL17RA polymorphisms with cardiac mortality in chronic heart failure.

| SNPs | MM vs mm | Dominant model | Recessive model | Additive model |
|------|----------|----------------|----------------|---------------|
|      | HR (95% CI) | P | HR (95% CI) | P | HR (95% CI) | P | HR (95% CI) | P |
| IL17A rs2275913 | | | | | | | | |
| Unadjusted | 0.93 (0.76–1.15) | 0.519 | 0.88 (0.64–1.21) | 0.433 | 0.97 (0.81–1.16) | 0.735 | 0.03 (0.76–1.14) | 0.491 |
| Adjusted | 0.94 (0.75–1.17) | 0.574 | 0.88 (0.62–1.19) | 0.368 | 0.98 (0.83–1.18) | 0.897 | 0.03 (0.75–1.16) | 0.526 |
| IL17A rs8193037 | | | | | | | | |
| Unadjusted | 1.28 (0.48–3.43) | 0.621 | 1.04 (0.70–1.55) | 0.854 | 1.28 (0.48–3.42) | 0.624 | 1.05 (0.72–1.54) | 0.799 |
| Adjusted | 1.47 (0.54–3.98) | 0.445 | 1.07 (0.72–1.60) | 0.730 | 1.42 (0.53–3.81) | 0.483 | 1.01 (0.66–1.55) | 0.949 |
| IL17RA rs4819554 | | | | | | | | |
| Unadjusted | 1.35 (1.08–1.67) | 0.007 | 1.57 (1.05–2.34) | 0.027 | 1.18 (1.02–1.38) | 0.029 | 1.32 (1.07–1.62) | 0.008 |
| Adjusted | 1.25 (0.98–1.56) | 0.053 | 1.51 (1.01–2.25) | 0.045 | 1.21 (1.04–1.41) | 0.014 | 1.28 (1.02–1.59) | 0.030 |

Hazard ratio (HR) and 95% confidence intervals (CIs) were obtained by Cox regression, with and without adjustment for sex, age, BMI, hypertension, diabetes, hyperlipidemia, smoking status, NYHA class, and left ventricular ejection fraction. rs2275913, M = S, m = A; rs8193037, M = G, m = A; rs4819554 M = A, m = G. SNP = single nucleotide polymorphism.
associated with lower IL-17A level in plasma, which suggested patients carrying A allele exhibited lower inflammatory response in CHF. This, at least, partly explain why A allele is significantly associated with a decreased risk of heart failure. Stratified analysis revealed that this SNP was associated with ischemic as well as nonischemic heart failure, which was in line with the crucial roles of IL-17A in heart failure of various forms and etiologies. Further, A allele of rs4819554 exhibited a statistically significant association with higher cardiovascular mortality in cases of heart failure after adjustment for multiple cardiovascular risk factors, baseline NYHA class and left ventricular ejection fraction suggesting an important role of this SNP in the occurrence of fatal cardiac events for heart failure patients.

4.1. IL-17A/IL-17RA axis in heart failure

Heart failure is the end stage of adverse cardiac remodeling initiated by a wide variety of cardiac injuries. DCM, ischemic cardiomyopathy, and hypertensive heart disease are among the leading causes of heart failure. IL-17A is the prototype cytokine in IL-17 family that acts through IL-17RA to activate proinflammatory signaling pathways. There is a vast body of evidence from previous studies demonstrating crucial roles of IL-17A/IL-17RA axis in atherosclerosis suggesting that it may contribute to the risk of ischemic heart failure. In a T-cell receptor transgenic mouse model of DCM, IL-17A plays an essential role in progression of myocarditis to DCM. These data suggest that IL-17A plays an essential role in progression of myocarditis to DCM. IL-17A was shown to contribute to inflammatory DCM pathogenesis by stimulating cardiac fibroblast-GM CSF-monocyte macrophage pathway. Collectively, these findings suggest crucial roles of IL-17A in heart failure of various forms and etiologies.

4.2. IL17A/IL17RA genes and SNPs

The most extensively investigated polymorphism of IL-17A/IL-17RA axis is rs2275913 with an association reported with acute graft versus host disease, childhood asthma, age related macular degeneration, infections, autoimmune disorders, inflammatory bowel disease, and various cancers, albeit usually in smaller studies. However, there is no evidence to support its role in cardiovascular diseases. Two of the previous studies investigating rs2275913 showed no association with CAD in a Chinese Han population or with premature CAD in a Mexican population. Another small scale study in a Chinese Han population failed to detect any association with DCM. Our findings provide further confirmation of a lack of association of rs2275913 with ischemic or nonischemic heart failure. Collectively, these results argue against a significant role of this polymorphism in heart failure, at least in Chinese Han population.

Another SNP rs8193037 represents G to A single-base substitution in the promoter at position 121 of IL17A gene. To our knowledge, only 2 studies have investigated this SNP with the risk of CAD. Zhang et al studied 5 IL-17A polymorphisms (rs4711998, rs3819024, rs2275913, rs8193037, and rs3819025) in 1031 CAD cases and 935 controls. They observed a significant association of rs8193037 with the risk of CAD in the Han population from northern China. Vargas-Alarcon et al studied four IL17A gene polymorphisms (rs8193036, rs3819024, rs2275913, and rs8193037) in 1031 CAD cases and 935 controls. They observed a significant association of rs8193037 with the risk of CAD in the Han population from northern China. Vargas-Alarcon et al studied four IL17A gene polymorphisms (rs8193036, rs3819024, rs2275913, and rs8193037) in 1031 CAD cases and 935 controls. They observed a significant association of rs8193037 with the risk of CAD in the Han population from northern China. Vargas-Alarcon et al studied four IL17A gene polymorphisms (rs8193036, rs3819024, rs2275913, and rs8193037) in 1031 CAD cases and 935 controls. They observed a significant association of rs8193037 with the risk of CAD in the Han population from northern China. Vargas-Alarcon et al studied four IL17A gene polymorphisms (rs8193036, rs3819024, rs2275913, and rs8193037) in 1031 CAD cases and 935 controls. They observed a significant association of rs8193037 with the risk of CAD in the Han population from northern China. Vargas-Alarcon et al studied four IL17A gene polymorphisms (rs8193036, rs3819024, rs2275913, and rs8193037) in 1031 CAD cases and 935 controls. They observed a significant association of rs8193037 with the risk of CAD in the Han population from northern China. Vargas-Alarcon et al studied four IL17A gene polymorphisms (rs8193036, rs3819024, rs2275913, and rs8193037) in 1031 CAD cases and 935 controls. They observed a significant association of rs8193037 with the risk of CAD in the Han population from northern China.
though the individual SNPs showed no direct association with premature CAD. In our study with 1713 CHF cases and 1713 controls, rs8193037 was found to be significantly associated with the risk of CHF in a Han population from southern China. This association holds true in both ischemic and nonischemic heart failure suggesting that rs8193037 could play a central role in cardiac remodeling induced by diverse stimuli. To our knowledge, this is the first study demonstrating an association between rs8193037 and the risk of heart failure, although there was no significant effect of this SNP on major adverse clinical outcomes in CHF.

Rs4819554 represents A to G single-base substitution in the promoter at position 947 of IL17RA gene. Rs4819554 is in linkage disequilibrium with 2 other promoter polymorphisms, rs4819553 and rs917864, defining an IL17RA risk haplotype.[58] It has been recently linked to immune-mediated clinical phenotypes such as aspirin hypersensitivity in asthma, alopecia, papillary carcinoma of thyroid, ESRD and risk of new onset diabetes in ESRD.[33–35,56,57] Interestingly, the homozygous AA genotype showed a statistically significant higher risk of cardiovascular mortality compared to GG homozygotes, suggesting this polymorphism could have a prognostic role in CHF. Although a statistically significant association with rehospitalization for heart failure was not observed, differences in treating physician’s preferences and socioeconomic condition of the patient may have influenced the results.

4.3. Functional studies

Gene expression is sophisticatedly regulated by a complex of transcriptional activators or inhibitors with transcriptional machinery, and is subjected to influence by SNPs contributing to inter individual variations.[58] Kim et al.[58] identified IL17A variants exerting allele-specific effects on gene expression in peripheral blood mononuclear cells by regulating their binding affinities for transcription factor complexes or CpG methylation profiles in inflammatory bowel disease. In this study, we have observed that GA heterozygotes of rs8193037 have lower circulating levels of IL-17A than GG homozygotes, which is consistent with previous study based on a CAD population.[40] Our data provide further confirmation of an IL-17A-mediated adaptive immune response in a subpopulation of heart failure patients suggesting that the presence of G allele of rs8193037 could potentially contribute to trigger this response especially during inflammation. Elevated levels of inflammatory mediators have been identified in patients with heart failure, and experimental studies have shown repeatedly that activation of inflammation in the heart provokes left ventricular remodeling and left ventricular dysfunction.[59] Lower circulating level of IL-17A in A allele carriers of rs8193037 could explain, at least in part, the lower risk of heart failure as observed in this study. Our findings also suggest that subtle differences in expression of IL-17A due to differences in promoter sequences may account for significant differences over a lifetime, and potentially the difference between a balanced inflammatory response and a slightly too enthusiastic response that will exacerbate the inflammation rather than transition to a healing response following a cardiac event.

Other polymorphisms in IL-17A/IL-17RA system have also been reported to modulate the expression of the inflammatory cytokine IL-17A and its receptor IL-17RA, such as rs2275913 G>A locating within a binding motif for the nuclear factor-κB (NFκB) which shows a higher affinity to this transcription factor and regulates IL-17A expression.[44,60] However, data on rs2275913 and IL17A secretion remain conflicting and we did not detect the association between rs2275913 and plasma IL-17A level.[44,48] Park et al have provided evidence that rs4819554 predisposes to asthma by upregulating IL17RA gene expression. IL-17A mRNA and protein expression in CD14(+) peripheral blood monocytes and mononuclear cells are significantly higher in AA homozygotes compared with the GG homozygotes in line with the lower frequency of the minor allele G in asthmatics.[55] However, it is great challenge to access the effect of a single SNP on the level of gene expression and regulation of cytokines is a complex network. Further studies are needed to define the underlying molecular mechanisms regulating IL-17A and IL-17RA expression by rs8193037 and rs4819554, respectively.

Drawbacks pertinent to the current study include: Low event rate and lower frequency of AA genotype of rs8193037 limited the power to assess the effect of this polymorphism on clinical outcomes and IL-17A levels. Relatively short mean follow-up period. Single center study.

5. Conclusions

The current study provides the first clinical evidence for an association of rs8193037 in IL-17A with the risk of heart failure, and of rs4819554 in IL17RA with the risk of cardiovascular mortality. Collectively, these data lend further support to the notion that immune activation and genetic polymorphisms contribute to heart failure pathogenesis and progression. These findings require replication in diverse ethnicities.

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