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# Basigin rs8259 Polymorphism Confers Decreased Risk of Chronic Heart Failure in a Chinese Population

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**Abstract:** Left ventricular remodeling is an essential risk factor contributing to the pathogenesis of chronic heart failure (CHF). Basigin (BSG) promotes cardiovascular inflammation and myocardial remodeling processes by induction of extracellular matrix metalloproteinases and inflammatory cytokines. BSG rs8259 polymorphism was associated with BSG expression and risk of acute coronary syndrome. Therefore, we investigated whether rs8259 polymorphism contributes to risk and prognosis of CHF in Chinese patients. In total 922 adult patients with CHF and 1107 matched healthy controls were enrolled. BSG rs8259 polymorphism was genotyped using PCR-restriction fragment length polymorphism. Whole blood BSG mRNA expression data from Genotype-Tissue Expression project was accessed. Evaluation of follow-up data was performed in only 15.2% (140) of the patients with CHF. BSG rs8259 TT genotype was associated with a decreased risk of CHF (OR = 0.83, 95% CI = 0.72–0.96,  $p = 0.010$ ), especially in patients with hypertension (OR = 0.80, 95% CI = 0.68–0.95,  $p = 0.011$ ) and coronary heart disease (OR = 0.81, 95% CI = 0.69–0.96,  $p = 0.013$ ) after adjustment for multiple cardiovascular risk factors. Rs8259 T allele was associated with decreased BSG mRNA in whole blood from 338 healthy normal donors ( $p = 1.31 \times 10^{-6}$ ). However, rs8259 polymorphism failed to exhibit an association with cardiovascular mortality ( $p = 0.283$ ). BSG rs8259 polymorphism may contribute to decreased risk of CHF in a Chinese Han population.

**Keywords:** Basigin; polymorphism; chronic heart failure; prognosis

## 1. Introduction

Heart failure is a complex clinical syndrome of insufficient cardiac output resulting from myocardial injury. To date, heart failure remains a leading cause of morbidity and mortality worldwide [1]. Chronic heart failure (CHF) is the most common form of heart failure. Whilst most cases of CHF are caused by hypertension, coronary heart disease, and diabetes mellitus, genetic association studies revealed that genetic predispositions contribute greatly to risk and prognosis of CHF [2–10]. Nevertheless, the genetic background for sporadic CHF has been poorly characterized yet, and identification of novel risk loci of CHF may help to foster early diagnosis and therapeutic intervention for this disease.

Basigin (BSG), also known as CD147 and extracellular matrix metalloproteinase inducer (EMMPRIN), is a member of the immunoglobulin super family and expressed in tumour cells, tumour-associated fibroblasts, and cardiovascular cells [11]. BSG is a multifunctional glycoprotein that promotes cell proliferation, myofibroblast differentiation, and matrix metalloproteinases (MMPs) activation and inhibits autophagy [12]. BSG is an essential receptor for multiple ligands such as pathogens, cyclophilin A, and soluble BSG (sBSG) itself [12]. BSG is highly expressed in tumors and promotes progression, invasion and metastasis of multiple tumors [12]. Recent evidence suggested an important role for BSG in thrombosis and cardiovascular disease [13]. BSG and MMPs are upregulated in monocytes of acute myocardial infarction [14,15]. Also, BSG is highly expressed in left ventricle (LV) of patients with myocardial infarction [16,17], inflammatory cardiomyopathy [18], and dilated cardiomyopathy [19]. Serum levels of sBSG were significantly elevated in patients with heart failure and were predictive of poor prognosis [20]. In mice model, persistent cardiomyocyte-specific overexpression of BSG increases MMPs levels and promotes cardiac fibrosis, adverse LV remodeling, and heart failure in response to chronic pressure overload and during aging [20,21]. On the contrary, BSG knockdown contributes to decrease in MMPs levels and resistance to pressure overload induced cardiac hypertrophy [20,22]. Cardiac BSG knockdown also improves adverse remodeling induced by IL-18 in the post-infarcted mice heart [23].

Numerous evidences have suggested that pathological ventricular remodeling is an essential risk factor contributing to the pathogenesis of CHF [24]. Considering the crucial roles of BSG in promotion of LV remodeling, BSG may be a potential candidate gene associated with risk of CHF. However, there is no report about association between BSG polymorphisms and risk of CHF yet. Notably, a miR-492 binding-site polymorphism (rs8259 A > T) in BSG 3'UTR was associated with decreased BSG mRNA and protein levels in peripheral blood mononuclear cells (PBMCs) or plasma from healthy subjects and patients with psoriasis and acute coronary syndrome (ACS) [25,26]. Also, rs8259 T allele was associated with decreased psoriasis and ACS susceptibility and lower rate of major adverse cardiac events in ACS [25,26]. To make clear the clinical relevance of BSG rs8259 polymorphism, we herein performed a case-control study to investigate the association between rs8259 polymorphism and risk of CHF in a Chinese population.

## 2. Materials and Methods

### 2.1. Study Participants

Patients referred to Department of Cardiovascular Medicine, Xiangya Hospital, Central South University between November 2011 and December 2014 were screened for potential inclusion in the study. The eligibility criteria were described previously [6]. Eligible patients were men and women aged 18–80 years, with clinical evidence of heart failure as demonstrated by New York Heart Association class II–IV, for more than three months before enrollment. Major exclusion criteria included tumors or malignant diseases, severe hepatic or renal dysfunctions, and pregnancy. Consequently, 922 patients were enrolled for analysis. During the planned follow-up clinic visits, clinical events in only 15.2% (140) of the patients were recorded from questionnaires, medical records, and telephone interviews.

Control individuals with similar age and gender were selected from physical examination center of the same hospital. According to the inclusion criteria, these subjects were unrelated to one another and apparently healthy as assessed by physical examination, serum biochemical testing, and electrocardiogram. Hypertension was defined by systolic blood pressure (SBP)  $\geq$  140 mmHg and/or diastolic blood pressure (DBP)  $\geq$  90 mmHg and/or being on antihypertensive therapy. Coronary heart disease (CHD) was defined as luminal stenosis  $\geq$ 50% in at least one major coronary artery branch or myocardial infarction. Type 2 diabetes mellitus was defined as a fasting plasma glucose  $\geq$ 7.0 mmol/L and/or on antidiabetic medication. The healthy subjects were free of a history or symptoms of hypertension, CHD, diabetes mellitus, or any other cardiovascular diseases. All subjects

were Han Chinese origin as ascertained by their resident identity cards. The study protocol was approved by the ethic committee of School of Pharmaceutical Sciences, Central South University and registered in Chinese Clinical Trial Registry (registration number: ChiCTR-RCC-12002817). Statement of informed consent was obtained from all participants.

## 2.2. Polymorphism Genotyping

The venous blood samples were collected into tubes containing EDTA and stored at  $-20\text{ }^{\circ}\text{C}$  until analysis. The standard phenol/chloroform protocol was used to extract genomic DNA from whole blood. *BSG* rs8259 polymorphism was genotyped by PCR-restriction fragment length polymorphism as described previously [25]. The target fragment of 162 bp was amplified using primers 5'-gagtcactcccagtgcttg-3' and 5'-ctcgtgaacacttcagaaggaaaaca-3' (forward/reverse). Five microliters of PCR products were digested with *Bse*I restriction enzyme (Thermo Fisher Scientific, Waltham, MA, USA) at  $55\text{ }^{\circ}\text{C}$  overnight. The digested PCR products were then analyzed on an agarose gel followed by ethidium bromide staining. In addition, a random selection of 5% of the samples was also genotyped by Sanger sequencing with the ABI PRISM 3730XL DNA sequencer (Applied Biosystems, Foster City, CA, USA) and the genotyping were confirmed in 100%.

## 2.3. Statistical Analysis

The results were presented as the mean  $\pm$  SD for continuous variables and as numbers and percentages for categorical data. Chi-square test was used for comparison of the categorical variables and Mann-Whitney U test or independent sample *t*-test for continuous variables. Deviation from Hardy-Weinberg equilibrium was assessed by means of a Chi-square test. Logistic regression method was used to analyze the effect of *BSG* polymorphism on the risk of heart failure adjusting for multiple cardiovascular risk factors. In genetic association analysis, three genetic models (additive, dominant, and recessive) were generally used. Kaplan-Meier curve and Cox proportional hazards regression model were used to assess the effect of *BSG* polymorphism on disease survival. All of the above analyses were performed with SPSS software (version 13.0, SPSS Inc., Chicago, IL, USA). A two-sided *p*-value  $< 0.05$  was considered as statistically significant.

## 3. Results

### 3.1. Population Characteristics

The demographic and clinical characteristics of study participants are reported in Table 1. CHF and control participants were well matched in gender and age. According to the inclusion criteria, controls had no hypertension, CHD, or diabetes mellitus. Patients with CHF exhibited higher levels of SBP, DBP, total cholesterol, triglyceride, low-density lipoprotein cholesterol, but lower level of high-density lipoprotein cholesterol compared to the controls. The prevalence of dyslipidemia and smoking was greater in patients with CHF in comparison with that observed in the control group.

### 3.2. Association of *BSG* rs8259 Polymorphism with Risk of CHF

The distribution of genotype frequencies of *BSG* rs8259 polymorphism is presented in Table 2. Rs8259 polymorphism was in Hardy-Weinberg equilibrium in both CHF and control groups ( $p = 0.263$  and  $0.634$ , respectively). The frequency of rs8259 TT genotype was significantly lower in heart failure subjects than controls (Table 2). Logistic regression analysis showed that rs8259 TT genotype was associated with decreased risk of CHF (additive model: OR = 0.84, 95% CI = 0.73–0.97,  $p = 0.019$ ; recessive model: OR = 0.87, 95% CI = 0.76–1.00,  $p = 0.042$ ). After adjustment for age, gender, smoking status, and dyslipidemia, the association was still significant (additive model: OR = 0.83, 95% CI = 0.72–0.96,  $p = 0.010$ ; recessive model: OR = 0.86, 95% CI = 0.75–0.98,  $p = 0.027$ ).

**Table 1.** Baseline characteristics of the study population.

Characteristics	CHF (n = 922)	Control (n = 1107)	p
Male (%)	563 (61.1)	647 (58.4)	0.232
Age (years)	61 ± 11	60 ± 8	0.173
SBP (mmHg)	133.3 ± 25.6	114.4 ± 10.3	<0.001
DBP (mmHg)	79.4 ± 14.4	73.5 ± 7.3	<0.001
TC (mmol/L)	4.7 ± 1	3.9 ± 1.4	<0.001
TG (mmol/L)	1.8 ± 1.9	1.5 ± 1.3	<0.001
HDL-C (mmol/L)	1.3 ± 1	1.7 ± 0.7	<0.001
LDL-C (mmol/L)	2.4 ± 0.9	2.1 ± 0.6	<0.001
Cigarette smoker within the past year (%)	313 (33.9)	283 (25.6)	<0.001
Dyslipidemia (%)	266 (28.9)	216 (19.5)	<0.001
Hypertension (%)	596 (64.6)	0 (0)	<0.001
Coronary heart disease (%)	690 (74.8)	0 (0)	<0.001
Diabetes mellitus (%)	232 (25.2)	0 (0)	<0.001

CHF: chronic heart failure; SBP: systolic blood pressure; DBP: diastolic blood pressure; TC: total cholesterol; TG: triglyceride; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol.

Considering that hypertension and CHD are important risk factors for heart failure [27], association analyses stratified by hypertension and CHD were performed. Rs8259 TT genotype was associated with decreased risk of CHF in hypertensive patients after adjusting for age, gender, smoking status, and dyslipidemia (additive model: OR = 0.80, 95% CI = 0.68–0.95,  $p = 0.011$ ; recessive model: OR = 0.84, 95% CI = 0.72–0.98,  $p = 0.030$ ). Moreover, when the patients were stratified by CHD, rs8259 TT genotype still exhibited a significant association with decreased risk of CHF in patients with CHD (additive model: OR = 0.81, 95% CI = 0.69–0.96,  $p = 0.013$ ; recessive model: OR = 0.85, 95% CI = 0.73–0.99,  $p = 0.033$ ). However, no association was observed between rs8259 polymorphism and risk of CHF in patients without hypertension and CHD (Table 2).

### 3.3. Association of BSG rs8259 Polymorphism with BSG Expression

The Genotype-Tissue Expression (GTEx) Project is a resource project designed to develop expression quantitative trait loci (eQTL) on the basis of data from 900 relatively healthy donors over 53 sampled sites [28]. The analysis methods of eQTL were described in detail in the GTEx project (<http://www.gtexportal.org/home/documentationPage>). Briefly, associations between genotypes and gene expression levels were determined by linear regression on quantile normalized gene-level expression values, after correction for known and inferred technical covariates, using Matrix eQTL [28]. Based on the GTEx project (<http://www.gtexportal.org>), we accessed the database to determine whether rs8259 polymorphism was associated with BSG expression in multi-tissue (<http://www.gtexportal.org/home/eqtls/bySnp?snpId=rs8259&tissueName=All>). As shown in Figure 1, rs8259 T allele was associated with decreased BSG mRNA in whole blood from 338 healthy normal donors ( $p = 1.31 \times 10^{-6}$ ).

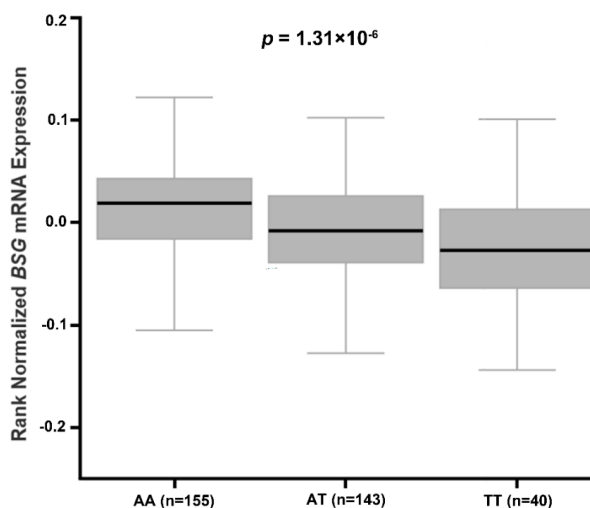
**Table 2.** Association of BSG rs8259 polymorphism with risk of CHF.

Models	Genotypes	CHF, n (%)	Control, n (%)	Unadjusted OR (95% CI)	<i>p</i>	* Adjusted OR (95% CI)	<i>p</i>
Entire cohort							
Additive	AA	388 (42.1)	422 (38.1)	1.00 (reference)		1.00 (reference)	
	AT	432 (46.8)	529 (47.8)	0.89 (0.74–1.07)	0.215	0.88 (0.73–1.07)	0.199
	TT	102 (11.1)	156 (14.1)	0.84 (0.73–0.97)	0.019	0.83 (0.72–0.96)	0.010
Dominant	AA	388 (42.1)	422 (38.1)	1.00 (reference)		1.00 (reference)	
	AT/TT	534 (57.9)	685 (61.9)	0.85 (0.71–1.01)	0.070	0.84 (0.70–1.01)	0.056
Recessive	AA/AT	820 (88.9)	951 (85.9)	1.00 (reference)		1.00 (reference)	
	TT	102 (11.1)	156 (14.1)	0.87 (0.76–1.00)	0.042	0.86 (0.75–0.98)	0.027
Hypertension							
Additive	AA	253 (42.4)	422 (38.1)	1.00 (reference)		1.00 (reference)	
	AT	279 (46.8)	529 (47.8)	0.88 (0.71–1.09)	0.238	0.86 (0.69–1.07)	0.182
	TT	64 (10.7)	156 (14.1)	0.83 (0.70–0.98)	0.024	0.80 (0.68–0.95)	0.011
Dominant	AA	253 (42.4)	422 (38.1)	1.00 (reference)		1.00 (reference)	
	AT/TT	343 (57.6)	685 (61.9)	0.84 (0.68–1.02)	0.082	0.81 (0.66–1.00)	0.049
Recessive	AA/AT	532 (89.3)	951 (85.9)	1.00 (reference)		1.00 (reference)	
	TT	64 (10.7)	156 (14.1)	0.86 (0.73–1.00)	0.050	0.84 (0.72–0.98)	0.030
Nonhypertension							
Additive	AA	135 (41.4)	422 (38.1)	1.00 (reference)		1.00 (reference)	
	AT	153 (46.9)	529 (47.8)	0.90 (0.69–1.18)	0.455	0.91 (0.69–1.20)	0.501
	TT	38 (11.7)	156 (14.1)	0.87 (0.71–1.07)	0.186	0.88 (0.72–1.09)	0.247
Dominant	AA	135 (41.4)	422 (38.1)	1.00 (reference)		1.00 (reference)	
	AT/TT	191 (58.6)	685 (61.9)	0.87 (0.68–1.12)	0.284	0.88 (0.68–1.14)	0.333
Recessive	AA/AT	288 (88.3)	951 (85.9)	1.00 (reference)		1.00 (reference)	
	TT	38 (11.7)	156 (14.1)	0.90 (0.74–1.08)	0.259	0.91 (0.75–1.10)	0.314

Table 2. Cont.

Models	Genotypes	CHF, n (%)	Control, n (%)	Unadjusted OR (95% CI)	<i>p</i>	* Adjusted OR (95% CI)	<i>p</i>
CHD							
Additive	AA	290 (42.0)	422 (38.1)	1.00 (reference)		1.00 (reference)	
	AT	324 (47.0)	529 (47.8)	0.89 (0.73–1.09)	0.268	0.87 (0.71–1.07)	0.193
	TT	76 (11.0)	156 (14.1)	0.84 (0.72–0.98)	0.031	0.81 (0.69–0.96)	0.013
Dominant	AA	290 (42.0)	422 (38.1)	1.00 (reference)		1.00 (reference)	
	AT/TT	400 (58.0)	685 (61.9)	0.85 (0.70–1.03)	0.100	0.82 (0.67–1.01)	0.056
Recessive	AA/AT	614 (89.0)	951 (85.9)	1.00 (reference)		1.00 (reference)	
	TT	76 (11.0)	156 (14.1)	0.87 (0.75–1.01)	0.059	0.85 (0.73–0.99)	0.033
Non-CHD							
Additive	AA	98 (42.2)	422 (38.1)	1.00 (reference)		1.00 (reference)	
	AT	108 (46.6)	529 (47.8)	0.88 (0.65–1.19)	0.403	0.89 (0.65–1.21)	0.455
	TT	26 (11.2)	156 (14.1)	0.85 (0.67–1.07)	0.166	0.86 (0.68–1.09)	0.218
Dominant	AA	98 (42.2)	422 (38.1)	1.00 (reference)		1.00 (reference)	
	AT/TT	134 (57.8)	685 (61.9)	0.84 (0.63–1.12)	0.242	0.86 (0.64–1.15)	0.300
Recessive	AA/AT	206 (88.8)	951 (85.9)	1.00 (reference)		1.00 (reference)	
	TT	26 (11.2)	156 (14.1)	0.88 (0.70–1.09)	0.245	0.89 (0.71–1.12)	0.314

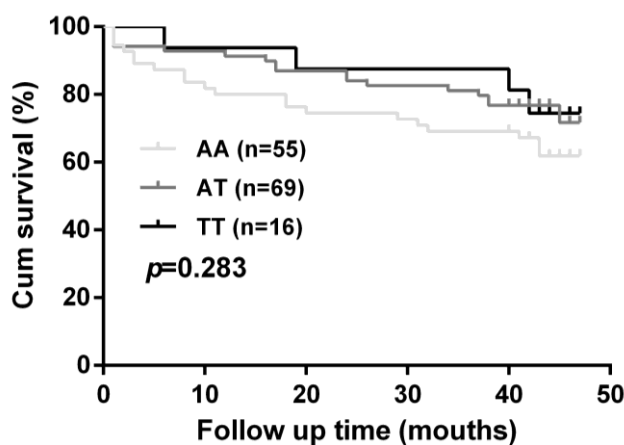
OR: odd ratio; CI: confidence interval. CHD: Coronary heart disease. \* Adjusted for age, gender, smoking status, and dyslipidemia.



**Figure 1.** Effect of *BSG* rs8259 polymorphism on *BSG* mRNA expression in whole blood from healthy normal donors.

#### 3.4. Association of *BSG* rs8259 Polymorphism with Progression of CHF

In order to evaluate whether *BSG* rs8259 polymorphism affects CHF prognosis, only 15.2% (140) of the patients were followed up for a median period of 38.7 months. No significant difference was observed for cardiovascular mortality between rs8259 genotype groups ( $p = 0.283$ , Figure 2).



**Figure 2.** Effect of *BSG* rs8259 polymorphism on cardiovascular mortality in heart failure patients.

## 4. Discussion

To our knowledge, this is the first case-control study involving 922 CHF patients and 1107 healthy subjects to investigate a potential association of *BSG* rs8259 polymorphism with the risk and prognosis of CHF. Our results demonstrated that rs8259 TT genotype was associated with a decreased risk of CHF in Chinese Han populations. Stratified analyses demonstrated that this polymorphism was only associated with CHF in patients with hypertension and CHD. However, rs8259 polymorphism failed to exhibit an association with cardiovascular mortality in CHF patients.

It has been reported that *BSG* is highly expressed in monocytes and LV of patients with myocardial infarction [14–17]. *BSG* also exhibited high expression in LV of patients with cardiomyopathy [18,19]. Moreover, upregulation of serum or plasma s*BSG* was observed in patients with heart failure and ACS [20,26]. High expression of s*BSG* indicates an unfavorable prognosis in heart failure [20]. In aging mice, cardiac-restricted overexpression of *BSG* caused adverse myocardial remodeling consisting of

LV dilatation, hypertrophy, and fibrosis along with increase and activation of MMPs [21]. BSG has recently been proved to promote cardiac fibroblasts proliferation and inflammatory cytokines secretion, resulting in MMPs activation [20]. Activated MMPs cleave extracellular BSG and release sBSG. Finally, inflammatory cytokines and sBSG promote cardiac hypertrophy, fibrosis, and heart failure under pathological conditions such as pressure overload [20]. Collectively, these data may suggest a crucial role of BSG in heart failure caused by pathological myocardial remodeling.

Currently, few studies have investigated the association of BSG polymorphisms with phenotypic traits. We and others showed that rs8259 T allele was associated with decreased level of BSG expression and sBSG, as well as decreased risk of psoriasis and ACS [25,26]. It was also demonstrated that the rs8259 polymorphism was located in a potential miR-492 binding site. The sequence carrying rs8259 T allele seems to match miRNA-492 better, and in contrast, associated with lower BSG protein expression, compared with sequence carrying A allele. [25]. Therefore, rs8259 polymorphism may decrease these diseases susceptibility through downregulating BSG expression. Our present study found that rs8259 T allele was associated with decreased risk of CHF. We also assessed the mRNA expression data from GTEx project and found that rs8259 T allele was significantly associated with decreased BSG mRNA in whole blood. As we did not detect the BSG expression of different rs8259 genotypes in CHF patients, whether rs8259 T allele contributes to decreased risk of CHF by downregulation of BSG expression deserves further investigation.

In addition to rs8259 polymorphism, other polymorphisms in BSG were included in previous genetic association studies. BSG rs11473 polymorphism within miR-483-5p binding site was reported to be associated with increased risk of esophageal cancer in a Chinese population [29]. Other studies failed to demonstrate an association between BSG polymorphisms and risk of schizophrenia [30], cerebral malaria [31], and atherosclerotic cerebral infarction [32].

As hypertension and CHD remain the major causes of CHF [27], stratified analysis was performed to control these confounding factors. Stratified analysis based on hypertension showed that rs8259 TT genotype was associated with CHF in hypertensive patients. LV hypertrophy, the most visible manifestation of target organ damage in hypertension, eventually predisposes to heart failure [33]. Given the crucial role of BSG in promoting ventricular remodeling consisting of LV dilatation, hypertrophy, and fibrosis, BSG may exhibit an important role in the development of CHF in hypertensive patients. Meanwhile, rs8259 TT genotype was associated with decreased risk of CHF in patients with CHD. Recent research has shown that rs8259 T allele can decrease risk of ACS, a subtype of CHD [26]. It was proven that BSG contributes to atherosclerosis and atherothrombosis [34], the basic pathological manifestations of CHD. Hence, rs8259 polymorphism may also affect the risk of CHF in patients with CHD.

Despite considerable advances in early diagnosis and therapeutic interventions for heart failure, the survival estimates for heart failure are only 50% and 10% at 5 and 10 years, respectively [1]. Therefore, identifying novel CHF susceptibility genes may help to foster future prevention and treatment of CHF. We firstly indicated that BSG rs8259 polymorphism may be a protective factor for CHF in a Chinese Han population. However, this variant exhibited no association with prognosis of CHF, which may be accounted by our limited sample size. Further studies performed in larger populations are required to better defining the role of this polymorphism in risk and prognosis of CHF. It has been reported that there were geographic differences in allele frequencies of susceptibility polymorphisms for cardiovascular diseases [35], including rs8259 polymorphism. According to the allele frequencies of 1000 Genomes Project (<http://browser.1000genomes.org>), the frequency of rs8259 T allele ranges from 0.31 to 0.44 in East Asian, South Asian, and African populations. As a comparison, the frequency of rs8259 T allele ranges from 0.62 to 0.70 in American and European populations. It will be interesting to investigate whether rs8259 polymorphism exhibit an association with CHF in different ethnic groups.

The present study had several limitations. We only enrolled a relatively limited sample size of Chinese Han subjects. Considering the minor allele and its frequency of rs8259 varies with race,



whether the findings of the present study are generalized to other ethnicity still needs to be clarified on the basis of larger sample size. In addition, only rs8259 polymorphism was investigated in the present study, other potentially functional polymorphism in *BSG* should be evaluated for their association with CHF. Finally, functional study of rs8259 polymorphism was not performed. Therefore, further research is necessary to elucidate the exact relationship between this variant and heart failure.

## 5. Conclusions

In conclusion, our study firstly demonstrated that *BSG* rs8259 polymorphism was associated with decreased risk of CHF. Further investigations in larger cohorts may be required to verify our findings. More comprehensive survey and functional experiments are also needed to illuminate the exact mechanism behind our findings.

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**Author Contributions:** Xiao-Ping Chen, Jie Tang, and Mu-Peng Li designed the study; Mu-Peng Li, Xiao-Lei Hu, and Yong-Long Yang performed the genotyping; Mu-Peng Li, Yan-Jiao Zhang, Ji-Peng Zhou, and Li-Ming Peng collected blood samples and clinical data; Mu-Peng Li performed statistical analysis and drafted the manuscript; Xiao-Ping Chen and Jie Tang revised the manuscript critically. All authors agreed on the final version of the manuscript.

**Conflicts of Interest:** The authors declare no conflict of interest.

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