

Genetic Association Between *ICAM-1* Gene Variants and Susceptibility to Ischemic Cardiomyopathy

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Abstract: The current work was aimed at exploring the association between single nucleotide polymorphisms (SNPs) in the *ICAM-1* gene, along with the identification of additional haplotypes and their potential role in the susceptibility to ischemic cardiomyopathy (ICM). The control group underwent a Hardy–Weinberg equilibrium test. The associations of genotypes and alleles with susceptibility to ICM were then analyzed using logistic regression analysis. Subsequently odds ratios (ORs) along with 95% confidence intervals (95% CI) were calculated. Interaction analysis was conducted between these SNPs. Furthermore, linkage disequilibrium analysis and haplotype analysis were performed on SNPs that showed interactions with each other. The incidence of ICM was significantly higher among individuals carrying the T allele of rs3093032 (OR = 2.032, 95% CI, 1.275–3.241, $P = 0.003$) relative to those with the C allele. In addition, CT genotype carriers had a higher susceptibility to ICM than CC genotype carriers (OR = 2.490, 95% CI, 1.445–4.29, $P = 0.001$). Furthermore, 3 SNPs (rs3093032, rs923366, rs3093030) exhibited a strong interaction with each other, whereas rs281437 showed no interaction with the other 3 SNPs. Individuals carrying the $C_{rs3093032}-T_{rs923366}-C_{rs3093030}$ haplotype had an elevated risk of ICM compared with those carrying the $C_{rs3093032}-C_{rs923366}-C_{rs3093030}$ haplotype (OR = 2.280, 95% CI, 1.568–3.315, $P < 0.001$). Moreover, individuals carrying the $T_{rs3093032}-C_{rs923366}-C_{rs3093030}$ haplotype were more susceptible to

ICM than those carrying the $C_{rs3093032}-C_{rs923366}-C_{rs3093030}$ haplotype (OR = 2.388, 95% CI, 1.469–3.880, $P < 0.001$). Regarding rs3093032, the minor alleles and haplotypes are associated with an increased ICM risk: 3 SNPs (rs3093032, rs923366, rs3093030) in *ICAM-1* have strong interaction with each other.

Key Words: ischemic cardiomyopathy (ICM), *ICAM-1* gene, gene polymorphism, interaction, haplotype analysis

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INTRODUCTION

Cardiovascular diseases (CVDs) constitute a leading reason for cardiogenic death worldwide.¹ Particularly, ischemic heart disease is a significant contributor to global mortality and morbidity,^{1,2} primarily driven by coronary artery atherosclerosis. Coronary artery disease accounts for more than 60% of all heart failure (HF) cases, with diabetes and hypertension contributing to 3% and 10%, respectively, as suggested by the first National Health and Nutrition Examination Survey.³ In addition, other vascular disorders can also obstruct blood flow into heart tissues.⁴ CVDs result from reduced or halted blood flow into the myocardium, causing myocardial damage.⁵ Ischemic cardiomyopathy (ICM) is a common etiology of CVDs and represents a significant risk factor for HF occurrence in the United States.⁶ Globally, it is estimated that around 26 million cases experience cardiac insufficiency, leading to more than \$30 billion costs for global health systems.^{7,8} Moreover, cardiac disease patients have reported a mortality rate of more than 50% in the past 5 years.^{9,10} Therefore, there is an urgent need to investigate the etiology of ICM to enhance early diagnosis and treatment.

Atherosclerotic lesions of multicoronary arteries, particularly diffuse lesions, play a pivotal role in causing severe myocardial dysfunction, a major factor leading to ICM.¹¹ The presence of intercellular adhesion molecule-1 (*ICAM-1*) in the blood has been used as a marker for coronary artery atherosclerosis and coronary heart disease progression.^{1,2,12} *ICAM-1*, a member of the immunoglobulin superfamily, is widely distributed within leukocytes and endothelial cells, playing a critical role as a receptor for antigen-1 and Mac-1 associated with the lymphocyte ability of leukocyte integrin.^{3–5} *ICAM-1* is a crucial factor in the pathogenesis of atherosclerosis, facilitating the recruitment of mononuclear cells to the vasculature basement membrane.^{6,7} Therefore, *ICAM-1* is known to significantly impact ICM and atherosclerosis.

Previous studies have shown a connection between the *ICAM-1* gene and ICM and atherosclerosis. Our earlier work demonstrated a correlation between *ICAM-1* polymorphism

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T. Naman and R. Abuduhaliq performed coronary angiography and coronary intervention (if necessary) on all subjects and performed statistical analysis and write the paper, should be regarded as cofirst authors. A. Abudouwayiti, M. Abudoureyimu, and J. Sun collect data and performed the experiment. A. Mahemuti designed the project and revised the final manuscript.

The present work was approved by the Ethics Committee of First Affiliated Hospital of the Xinjiang Medical University (Approval No. 2021D01D17). Our participants provided their informed consents. Written informed consents were also provided by individuals for publishing any data or identifiable images in this manuscript.

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and the risk as well as prognosis of ICM.^{13,14} However, because that research also considered other environmental factors, a detailed analysis of the effect of the *ICAM-1* gene and its haplotypes on ICM was not conducted. Thus, in this study, we specifically analyze the relationship between ICM and the *ICAM-1* gene, including the genotypes, alleles, and haplotypes of *ICAM-1* (rs3093032, rs923366, rs281437, rs3093030) and investigate the interactions among these single nucleotide polymorphisms (SNPs).

MATERIALS AND METHODS

Study Design and Populations

This study recruited participants from the First Affiliated Hospital of Xinjiang Medical University between January 2013 and December 2015. Totally, 758 subjects were initially considered for the study, out of which 532 met the eligibility criteria. This group included 252 individuals with ICM and 280 controls (Fig. 1). During the study, all participants underwent coronary angiography either during their final hospital stay or while in the hospital.

The diagnosis of ICM was based on the following criteria: (1) coronary angiography, verified by 2 or more experienced cardiologists, revealed more than 50% luminal stenosis in at least 1 coronary artery, with a leading branch, in patients who had undergone previous coronary artery bypass grafting or percutaneous coronary intervention. (2) Myocardial impairment, characterized by N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels exceeding 125 ng/mL.

Patients who had the following conditions were excluded from the study: acute decompensated HF; unstable hemodynamics, hepatic/nephritic/hematologic/autoimmune

diseases, noncardiac disorders with a predicted survival of less than 1 year, cachexia, and those who declined to participate. In addition, cases with <50% coronary artery luminal stenosis, as verified by coronary angiography conducted by 2 experienced cardiologists, and those without angina on exertion were also excluded from the study.

Blood Sampling and Laboratory Tests

Upon admission, blood samples were collected from each ICM cases and controls and sent to the Laboratory of the First Affiliated Hospital of the Xinjiang Medical University for examination.

DNA Isolation

After conducting laboratory tests, DNA extraction from venous blood was performed. The blood was subjected to a 10-minute centrifugation with anticoagulant ethylenediaminetetraacetic acid at 1500 rpm to separate blood cells from plasma using the Eppendorf high-speed centrifuge. Subsequently, DNA was extracted from peripheral leukocytes with a whole-blood genome extraction kit (Kaishuo Biotechnology Corporation, Xiamen, China), following relevant protocols and stored at -80°C before genotyping.

ICAM-1 Gene Genotyping

Subsequently, 1 μL of DNA was amplified through polymerase chain reaction following specific protocols. Then, SNP genotyping was performed on the amplified samples with an SNaPshot multiplex SNP genotyping kit (Application Binary Interface Company, Santa Cruz, CA) following the instructions of the manufacturer.

Statistical Analysis

The control group underwent a Hardy–Weinberg equilibrium (HWE) test based on the χ^2 test. Categorical data, presented as numbers and proportions, were analyzed with logistic regression to identify correlations between alleles, genotypes, and ICM susceptibility. Odds ratios (ORs) along with 95% confidence intervals (95% CIs) were calculated to evaluate the correlation between gene polymorphism and ICM. Data analysis was conducted using Statistical Product and Service Solutions 25.0 (SPSS 25.0) software.

To identify optimal interaction combinations among the SNPs of the *ICAM-1* gene, this study employed generalized multifactor dimensionality reduction,¹⁵ and certain parameters were determined. The consistency of the ideal interaction model was assessed using the cross-validation consistency score, whereas the optimal combination was identified based on the score size. The test balance accuracy indicated the accuracy of the interaction in predicting the degree of case–control status, with scores between 0.5 and 1.0 denoting no superiority to chance and the best interaction combinations, respectively. Furthermore, *P* values were used for measuring the significance of these interaction combinations. The interaction map between the 4 SNPs was plotted using multifactor dimensionality reduction software.¹⁶

For linkage disequilibrium (LD) analysis and haplotype testing, this study used SHEsis,¹⁷ where *D'* values of SNPs of >0.75 indicated severe LD.¹⁸

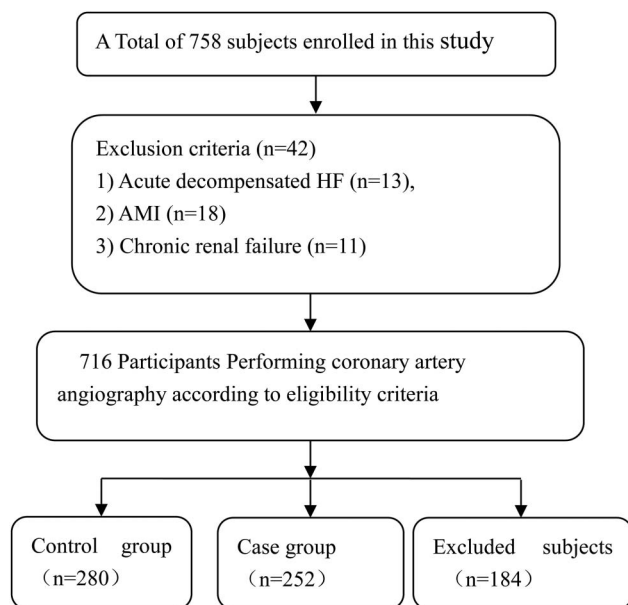


FIGURE 1. Roadmap of screening and grouping the study cohorts.

RESULTS

HWE Test

This study included totally 532 participants, consisting of 252 cases with ICM and 280 controls (Fig. 1). The genotype distribution frequencies of the SNPs (rs3093032, rs923366, rs281437, rs3093030) in the *ICAM-1* gene for the control group were found to be in accordance with the HWE test. This result indicates that our control group appropriately represented the study population and was included in this investigation.

Genotype and Alleles Frequency Comparison Between Two Groups and Relations with ICM

The results revealed a significant elevation in the T-allele frequency of the rs3093032 variant in the case group when compared with the control group (10.3% vs. 5.4%). The logistic regression model indicated that individuals carrying the T allele were associated with an elevated risk of ICM in comparison to those carrying the C allele (OR = 2.032, 95% CI, 1.275–3.241, $P = 0.003$). Moreover, CT genotype carriers were more prevalent in the patient group when compared with controls (17.5% vs. 7.9%), and CT genotype carriers exhibited a higher susceptibility to ICM than CC genotype carriers (OR = 2.490, 95% CI, 1.445–4.29, $P = 0.001$). Under the dominant model, individuals carrying the CT+TT genotype had an increased risk of ICM in relative to those carrying the CC genotype (OR = 2.3, 95% CI, 1.378–3.834, $P = 0.001$). However, no statistically significant differences were found between the 2 groups concerning alleles and genotypes of rs923366, rs281437, and rs3093030 (Table 1).

Interaction Analysis of SNPs

Using generalized multifactor dimensionality reduction software, we conducted an interaction analysis involving selected SNPs (rs3093032, rs923366, rs281437, rs3093030) (Table 2).

The findings revealed that there are significant differences ($P < 0.05$) among the 3 models, with consistent cross-validation consistency observed in 3 of the models (10/10). However, the 3-loci model demonstrated higher test accuracy (0.5988) compared with the other 2 models. Thus, the 3-loci model emerged as the most favorable among the multiloci models (test accuracy = 0.5988, $P = 0.001$). In addition, an interaction map of the 4 SNPs was plotted using the multifactor dimensionality reduction software (Fig. 2).

Based on the color of the dendrogram, it is evident that rs281437 exhibits minimal interaction with the other 3 SNPs (rs3093032, rs923366, rs3093030). Conversely, the correlation degree of other 3 SNPs in each other bigger than the correlation degree of rs281437 with other 3 SNPs. Specifically, rs923366 and rs3093030 show positive interaction with each other, whereas rs3093032 demonstrates a negative correlation with the other 2 SNPs (rs923366, rs3093030). The specific correlation statuses (positive or negative) and correlation value are shown in circular map (Fig. 2).

TABLE 1. The Genotype and Allele Frequencies Comparison of *ICAM-1* Polymorphisms Between Two Group

SNP	Control (n = 280)	Case (n = 252)	OR (95% CI)	P
rs3093032				
CC	254 (90.7)	204 (81.0)	1.000	
CT	22 (7.9)	44 (17.5)	2.490 (1.445–4.29)	0.001
TT	4 (1.4)	4 (1.6)	1.245 (0.308–5.04)	0.759
CT+TT	26 (9.3)	48 (19.0)	2.3 (1.378–3.834)	0.001
C	530 (94.6)	452 (89.7)	1.000	
T	30 (5.4)	52 (10.3)	2.032 (1.275–3.241)	0.003
rs923366				
CC	84 (30.0)	60 (23.8)	1.000	
CT	132 (47.1)	128 (50.8)	1.358 (0.900–2.048)	0.145
TT	64 (22.9)	64 (25.4)	1.400 (0.867–2.261)	0.169
CT+TT	196 (70.0)	192 (76.2)	1.37 (0.932–2.018)	0.11
C	300 (53.6)	248 (49.2)	1.000	
T	260 (46.4)	256 (50.8)	1.191 (0.936–1.516)	0.155
rs281437				
CC	212 (75.7)	180 (71.4)	1.000	
CT	54 (19.3)	60 (23.8)	1.309 (0.862–1.987)	0.207
TT	14 (5.0)	12 (4.8)	1.010 (0.455–2.238)	0.981
CT+TT	68 (24.3)	72 (28.6)	1.25 (0.847–1.835)	0.238
C	478 (85.4)	420 (83.3)	1.000	
T	82 (14.6)	84 (16.7)	1.166 (0.837–1.624)	0.364
rs3093030				
CC	118 (42.1)	124 (49.2)	1.000	
CT	122 (43.6)	96 (38.1)	0.749 (0.519–1.081)	0.123
TT	40 (14.3)	32 (12.7)	0.761 (0.449–1.292)	0.312
CT+TT	162 (57.9)	128 (50.8)	0.752 (0.534–1.059)	0.103
C	358 (63.9)	344 (68.3)	1.000	
T	202 (36.1)	160 (31.7)	0.824 (0.639–1.064)	0.137

LD and Haplotype Analyses in ICM, Between Two Groups and Relations with ICM

Using the SHEsis online software, we conducted LD analysis and haplotype analysis on 3 SNPs (rs3093032, rs923366, rs3093030), which are incorporated in 3-loci model. The analysis revealed a significant level of LD ($D' > 0.75$) among these 3 SNPs (Fig. 3).

Haplotype analysis was further conducted on these 3 SNPs, revealing 5 haplotypes (Table 3). The $C_{rs3093032}-T_{rs923366}-C_{rs3093030}$ and $T_{rs3093032}-C_{rs923366}-C_{rs3093030}$ haplotypes were discovered to be more prevalent in the case group in relative to the control group (19.0% vs. 10.4% and 10.3% vs. 5.3%, respectively).

Carrying the $C_{rs3093032}-T_{rs923366}-C_{rs3093030}$ haplotype was related to a 2.28-fold increase in the risk of ICM

TABLE 2. The Interaction Analysis of SNPs and Best Model for ICM

Model	Test Accuracy	Cross-Validation Consistency	P
rs3093032	0.5452	10/10	0.0107
rs923366 × rs3093030	0.5662	10/10	0.0547
rs3093032 × rs923366 × rs3093030	0.5988	10/10	0.0010
rs3093032 × rs923366 × rs281437 × rs3093030	0.5930	10/10	0.0107

compared with individuals carrying the C_{rs3093032}-C_{rs923366}-C_{rs3093030} haplotype (OR = 2.280, 95% CI, 1.568–3.315, P < 0.001). Similarly, carrying the T_{rs3093032}-C_{rs923366}-C_{rs3093030} haplotype was related to a 2.388-fold increase in ICM risk relative to individuals carrying the C_{rs3093032}-C_{rs3093030} haplotype (OR = 2.388; 95% CI, 1.469–3.880, P < 0.001). In addition, the C_{rs3093032}-T_{rs923366}-T_{rs3093030} haplotype did not exhibit any obvious difference between the 2 groups, with a frequency of 0.0% in both the control and case groups. Therefore, this haplotype was not further analyzed.

DISCUSSION

SNPs are common and fundamental genetic variations within the genome, known to impact the susceptibility to various complex disorders.¹⁹ These SNPs not only correlate with diseases individually but also interact with each other during the disease development, either positively or negatively influencing the function of other SNPs. Gene–gene interactions have been increasingly recognized as critical factors in determining susceptibility to prevalent human diseases, making them essential components in the genetic structure.¹⁹ Assessing the strength of association between SNPs through LD analysis is a valuable approach to detect genetic variations associated with complex human disorders.²⁰ In addition, haplotype-based methods that consider several SNPs on a single inherited chromosome can help map disease genes and shed light on the factors influencing dependency across diverse genetic markers.²⁰

To specifically investigate the correlation between ICM and SNPs, as well as haplotypes, and to identify gene–gene interactions, this study analyzed the relationship of SNPs (rs3093032, rs923366, rs281437, rs3093030) within the *ICAM-1* gene with ICM susceptibility. The study further explored the interactions between these SNPs and performed LD analysis on the SNPs that showed interaction with each other. Haplotype analysis was also performed to assess the influence of the SNPs on susceptibility to ICM.

In the analysis of gene polymorphisms and their association with ICM susceptibility, we observed that in rs3093032, individuals carrying the T allele had a 2.03 times higher risk of ICM in relative to those carrying the C allele. Similarly, CT genotype carriers had a 2.49 times higher susceptibility to ICM than CC genotype carriers. Under the dominant model, individuals carrying the CT+TT genotype had a 2.30 times higher risk of developing ICM than those with the CC genotype. However, we found no statistically significant differences between the 2 groups for the other 3 SNPs (rs923366, rs281437, and rs3093030). In the interaction analysis among the SNPs, except for rs281437, the other 3 SNPs (rs3093032, rs923366, rs3093030) displayed strong interactions with each other. This suggests that although some SNPs may not directly correlate with ICM, they can influence ICM risk through their interaction with rs3093032. Furthermore, we conducted LD analysis on these 3 SNPs, and the results indicated a strong LD (D' > 0.75) (Fig. 3). Subsequently, haplotype analysis revealed 5 haplotypes (Table 3). The ICM risk was found to be 2.28 times higher

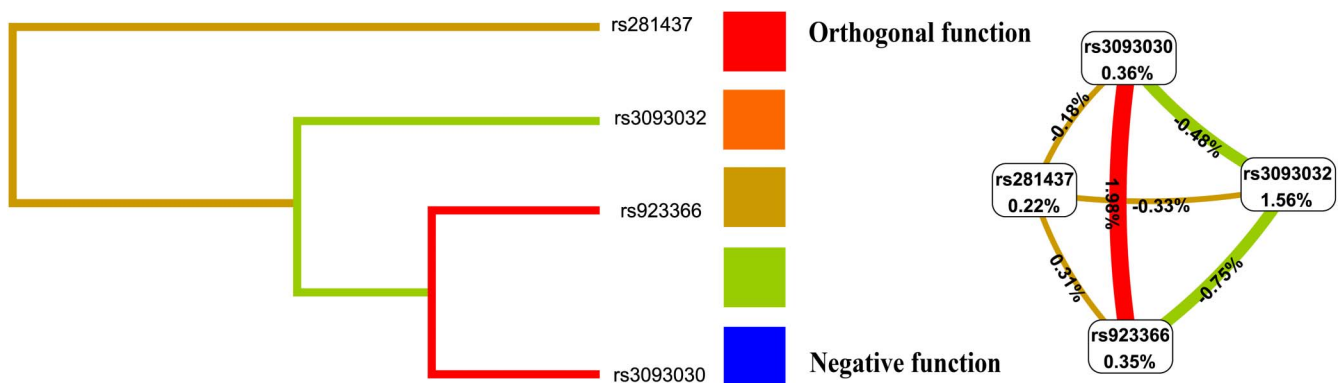


FIGURE 2. The dendrogram and circular map for the interactions of SNPs (rs3093032, rs923366, rs281437, rs3093030). In the dendrogram, the gold vein color represents the smallest correlation degree, yellow and red represents the positive correlation: the correlation degree of red is bigger than yellow. Green and blue represents negative correlation: the correlation degree of blue is bigger than green. The circular map shows the specific correlation statuses (positive or negative) and correlation value.

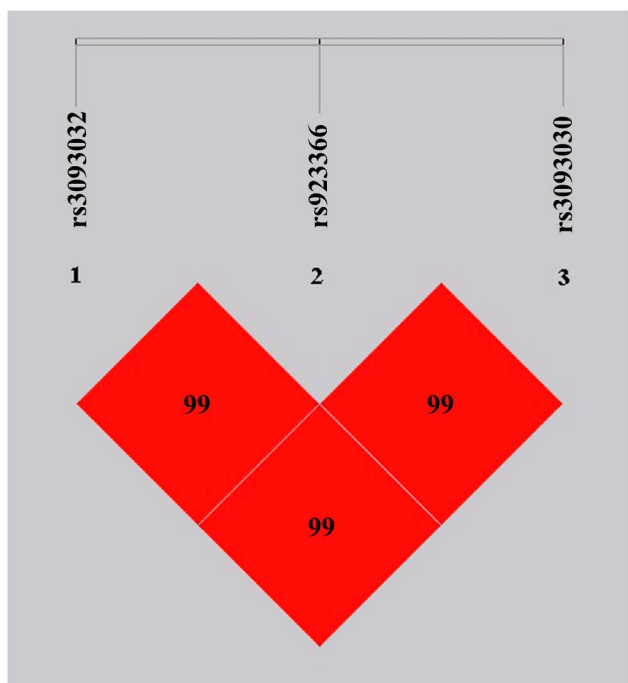


FIGURE 3. LD test of SNPs (rs3093032, rs923366, rs3093030).

in individuals carrying the $C_{rs3093032}-T_{rs923366}-C_{rs3093030}$ haplotype relative to those carrying the $C_{rs3093032}-C_{rs923366}-C_{rs3093030}$ haplotype. In addition, individuals carrying the $T_{rs3093032}-C_{rs923366}-C_{rs3093030}$ haplotype had a 2.39 times higher risk of developing ICM when compared with those carrying the $C_{rs3093032}-C_{rs923366}-C_{rs3093030}$ haplotype.

In summary, the T-allele gene and CT genotype in rs3093032 are associated with ICM susceptibility. Moreover, carriers of the $C_{rs3093032}-T_{rs923366}-C_{rs3093030}$ and $T_{rs3093032}-C_{rs923366}-C_{rs3093030}$ haplotypes have a higher risk of developing ICM. Although the genotypes and alleles of the other SNPs (rs923366, rs3093030) did not show significant differences, their interactions with other SNPs and the presence of heavy LD ($D' > 0.75$) suggest their potential role in ICM susceptibility. However, further studies are required to investigate the specific mechanisms of these SNPs in relation to ICM.

ICAM-1, a member of the immunoglobulin superfamily, is a transmembrane single-chain glycoprotein with a molecular mass of 90–115 kD. It contains 1

transmembrane and 5 immunoglobulin architectures and is present in various cell types, including leukocytes, epithelial cells, and fibroblasts.²¹ The level of ICAM-1 in the blood has been identified as a marker for coronary artery atherosclerosis and the progression of ICM.²

The *ICAM-1* gene is located on chromosome 19p13.2 and consists of 6 introns, 7 exons, a 1.5-kb 3'-noncoding RNA sequence, and a 2.4-kb upstream sequence. The rs3093032 site is found at position 10,285,660 bp in the 3'-UTR region of ICAM-1, which is considered the potential junction between hsa-miR-4648 and the 3'-UTR in ICAM-1.

SNPs are DNA variations that occur in individuals and play a significant role in complex diseases like coronary artery disease, as well as in different drug responses among individuals.²² They can occur within coding regions, affecting amino acid synthesis, or in noncoding regions, influencing gene and protein levels.²³ Understanding gene variations and their impact are crucial for exploring disease mechanisms and the relationship between gene variations and diseases and for developing effective preventive and treatment measures.

Although rs3093032 is an SNP located in the non-coding region of *ICAM-1* and does not code for amino acids, it is still associated with ICM susceptibility. Although its specific mechanism in ICM development is not yet known, it is likely to interact with other SNPs, particularly those located in the coding region of ICAM-1, influencing their abilities and functions. Further research is required to understand the mechanisms through which these SNPs affect ICAM-1 levels and function in the development of ICM.

This research provides valuable insights into the association between *ICAM-1* variants and ICM. However, there are some limitations in this study. At first, the participants were recruited from a single hospital, which may lead to recruitment bias, and the sample size is limited. Second, the potential roles of these *ICAM-1* gene variants still require further analysis. Therefore, large-scale prospective studies with biological functional analysis are necessary for validation.

To summarize, our findings suggest that minor alleles, mutant genotypes, and haplotypes of rs3093032 correlated with high susceptibility to ICM, and 3 SNPs (rs3093032, rs923366, and rs3093030) in *ICAM-1* gene have strong correlation with each other. Our findings may be useful for insight into the contribution of *ICAM-1* variants to the complex pathogenesis of ICM. However,

TABLE 3. Haplotype Frequency of rs3093032, rs923366, rs3093030 SNPs and Correlation With ICM

Haplotype	Control (n = 280)	Case (n = 252)	OR (95% CI)	P
C-C-C	270 (48.2)	196 (38.9)	1.000	—
C-T-C	58 (10.4)	96 (19.0)	2.280 (1.568–3.315)	<0.001
C-T-T	202 (36.1)	160 (31.7)	1.091 (0.827–1.440)	0.538
T-C-C	30 (5.3)	52 (10.3)	2.388 (1.469–3.880)	<0.001
T-T-T	0 (0.0)	0 (0.0)	—	—

further studies are needed to find the specific mechanism of it.

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