Genetic association between ICAM-1 gene variants and susceptibility to ischemic cardiomyopathy

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Research Article

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Abstract

Objective: 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 susceptibility to Ischemic Cardiomyopathy (ICM).

Methods: The control group underwent a Hardy-Weinberg equilibrium test. The associations of genotypes and alleles with susceptibility to ischemic cardiomyopathy were then analyzed using logistic regression. 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.

Results: The incidence of ICM was significantly higher among individuals carrying the T allele of rs3093032 (OR = 2.032, 95% CI = 1.275–3.241, \( P = 0.003 \)) in relative to those with the C allele. Additionally, 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, three SNPs (rs3093032, rs923366, rs3093030) exhibited a strong interaction with each other, while rs281437 showed no interaction with the other three 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, \( P < 0.001 \)).

Conclusion: Regarding rs3093032, individuals carrying the T allele exhibited a higher risk of ICM than those with the C allele. Moreover, CT genotype carriers were more susceptible to ICM than CC genotype carriers. Furthermore, individuals carrying the C\(_{rs3093032}\)-T\(_{rs923366}\)-C\(_{rs3093030}\) and T\(_{rs3093032}\)-C\(_{rs923366}\)-C\(_{rs3093030}\) haplotypes presented an elevated risk of developing ICM compared to carriers of the C\(_{rs3093032}\)-C\(_{rs923366}\)-C\(_{rs3093030}\) haplotype. These findings provide valuable insights into the effects of ICAM-1 gene variants on the intricate pathogenic mechanisms underlying ICM.

1. Introduction

Cardiovascular diseases (CVDs) constitute a leading reason for cardiogenic death worldwide\(^1\). Particularly, ischemic heart disease (IHD) is a significant contributor to global mortality and morbidity\(^1,2\), primarily driven by coronary artery atherosclerosis. Coronary artery disease (CAD) 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 (NHANES I)\(^3\). In addition, other vascular disorders can also obstruct blood flow into heart tissues\(^4\). CVDs often 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 USA\[6\]. Globally, it is estimated that around 26 million cases suffer from cardiac insufficiency, leading to more than $30 billion in costs for global health systems\[7, 8\]. Moreover, cardiac disease patients have reported a mortality rate of over 50% in the past five years\[9, 10\]. Therefore, there is an urgent need to investigate the etiology of ICM to enhance early diagnosis and treatment.

Atherosclerotic lesions of multi-coronary 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 (CHD) 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 leukocyte integrin lymphocyte ability\[3–5\]. 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 and the risk and prognosis of ICM\[13, 14\]. However, since 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 between these SNPs.

2. Materials and Methods

2.1 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 two or more experienced cardiologists, revealed more than 50% luminal stenosis in at least one 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. Additionally, cases with < 50% coronary artery luminal stenosis, as verified by coronary angiography conducted by two experienced cardiologists, and (2) those without angina on exertion were also excluded from the study.

2.2 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 Xinjiang Medical University for examination.

2.3 DNA Isolation

After conducting laboratory tests, DNA extraction from venous blood was performed. The blood was subjected to a 10-min centrifugation with anticoagulant ethylene diamine tetraacetic acid (EDTA) at 1500rpm 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 (Xiamen Kaishuo Biotechnology Corporation, China), following relevant protocols, and stored at − 80°C before genotyping.

2.4 ICAM-1 Gene genotyping

Subsequently, 1µL of DNA was amplified through PCR following specific protocols. Then, SNP genotyping was performed on the amplified samples with a SNaPshot multiplex SNP genotyping kit (Application Binary Interface Company, USA) following the instructions of the manufacturer.

2.5 Statistical Analysis

The control group underwent a Hardy-Weinberg equilibrium (HWE) test based on the chi-square 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 SPSS 25.0.

To identify optimal interaction combinations among the SNPs of the ICAM-1 gene, the present study employed generalized multifactor dimensionality reduction (GMDR)\cite{15}, and certain parameters were determined. The consistency of the ideal interaction model was assessed using the cross-validation consistency score, while 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 four SNPs was plotted using multifactor dimensionality reduction (MDR) software\cite{16}.

For linkage disequilibrium analysis and haplotype testing, this study utilized SHEsis\cite{17}, where D'-values of SNPs > 0.75 indicated severe linkage disequilibrium\cite{18}. 
3. Results

3.1 HWE test

This study included totally 532 participants, consisting of 252 cases with ICM and 280 controls (Figure 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.

3.2 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% versus 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 two groups concerning alleles and genotypes of rs923366, rs281437, and rs3093030 (Table 1).
<table>
<thead>
<tr>
<th>SNP</th>
<th>Control (n = 280)</th>
<th>Case (n = 252)</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs3093032</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CC</td>
<td>254 (90.7)</td>
<td>204 (81.0)</td>
<td>1.000</td>
<td></td>
</tr>
<tr>
<td>CT</td>
<td>22 (7.9)</td>
<td>44 (17.5)</td>
<td>2.490 (1.445–4.29)</td>
<td>0.001</td>
</tr>
<tr>
<td>TT</td>
<td>4 (1.4)</td>
<td>4 (1.6)</td>
<td>1.245 (0.308–5.04)</td>
<td>0.759</td>
</tr>
<tr>
<td>CT+TT</td>
<td>26 (9.3)</td>
<td>48 (19.0)</td>
<td>2.3 (1.378–3.834)</td>
<td>0.001</td>
</tr>
<tr>
<td>C</td>
<td>530 (94.6)</td>
<td>452 (89.7)</td>
<td>1.000</td>
<td></td>
</tr>
<tr>
<td>T</td>
<td>30 (5.4)</td>
<td>52 (10.3)</td>
<td>2.032 (1.275–3.241)</td>
<td>0.003</td>
</tr>
<tr>
<td>rs923366</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CC</td>
<td>84 (30.0)</td>
<td>60 (23.8)</td>
<td>1.000</td>
<td></td>
</tr>
<tr>
<td>CT</td>
<td>132 (47.1)</td>
<td>128 (50.8)</td>
<td>1.358 (0.900–2.048)</td>
<td>0.145</td>
</tr>
<tr>
<td>TT</td>
<td>64 (22.9)</td>
<td>64 (25.4)</td>
<td>1.400 (0.867–2.261)</td>
<td>0.169</td>
</tr>
<tr>
<td>CT+TT</td>
<td>196 (70.0)</td>
<td>192 (76.2)</td>
<td>1.37 (0.932–2.018)</td>
<td>0.11</td>
</tr>
<tr>
<td>C</td>
<td>300 (53.6)</td>
<td>248 (49.2)</td>
<td>1.000</td>
<td></td>
</tr>
<tr>
<td>T</td>
<td>260 (46.4)</td>
<td>256 (50.8)</td>
<td>1.191 (0.936–1.516)</td>
<td>0.155</td>
</tr>
<tr>
<td>rs281437</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CC</td>
<td>212 (75.7)</td>
<td>180 (71.4)</td>
<td>1.000</td>
<td></td>
</tr>
<tr>
<td>CT</td>
<td>54 (19.3)</td>
<td>60 (23.8)</td>
<td>1.309 (0.862–1.987)</td>
<td>0.207</td>
</tr>
<tr>
<td>TT</td>
<td>14 (5.0)</td>
<td>12 (4.8)</td>
<td>1.010 (0.455–2.238)</td>
<td>0.981</td>
</tr>
<tr>
<td>CT+TT</td>
<td>68 (24.3)</td>
<td>72 (28.6)</td>
<td>1.25 (0.847–1.835)</td>
<td>0.238</td>
</tr>
<tr>
<td>C</td>
<td>478 (85.4)</td>
<td>420 (83.3)</td>
<td>1.000</td>
<td></td>
</tr>
<tr>
<td>T</td>
<td>82 (14.6)</td>
<td>84 (16.7)</td>
<td>1.166 (0.837–1.624)</td>
<td>0.364</td>
</tr>
<tr>
<td>rs3093030</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CC</td>
<td>118 (42.1)</td>
<td>124 (49.2)</td>
<td>1.000</td>
<td></td>
</tr>
<tr>
<td>CT</td>
<td>122 (43.6)</td>
<td>96 (38.1)</td>
<td>0.749 (0.519–1.081)</td>
<td>0.123</td>
</tr>
<tr>
<td>TT</td>
<td>40 (14.3)</td>
<td>32 (12.7)</td>
<td>0.761 (0.449–1.292)</td>
<td>0.312</td>
</tr>
<tr>
<td>CT+TT</td>
<td>162 (57.9)</td>
<td>128 (50.8)</td>
<td>0.752 (0.534–1.059)</td>
<td>0.103</td>
</tr>
<tr>
<td>C</td>
<td>358 (63.9)</td>
<td>344 (68.3)</td>
<td>1.000</td>
<td></td>
</tr>
</tbody>
</table>
3.3 Interaction analysis of SNPs

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

<table>
<thead>
<tr>
<th>Model</th>
<th>Test accuracy</th>
<th>Cross-validation consistency</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs3093032</td>
<td>0.5452</td>
<td>10/10</td>
<td>0.0107</td>
</tr>
<tr>
<td>rs923366×rs3093030</td>
<td>0.5662</td>
<td>10/10</td>
<td>0.0547</td>
</tr>
<tr>
<td>rs3093032×rs923366×rs3093030</td>
<td>0.5988</td>
<td>10/10</td>
<td>0.0010</td>
</tr>
<tr>
<td>rs3093032×rs923366×rs281437×rs3093030</td>
<td>0.5930</td>
<td>10/10</td>
<td>0.0107</td>
</tr>
</tbody>
</table>

The findings revealed there are significant differences (P<0.05) among the three models, with consistent cross-validation consistency observed in three of the models (10/10). However, the three-loci model demonstrated higher test accuracy (0.5988) compared to the other two models. Thus, the three-loci model emerged as the most favorable among the multiloci models (test accuracy = 0.5988, P = 0.001). Additionally, an interaction map of the four SNPs was plotted using the MDR software (Figure 2).

Based on the color of the illustration, it is evident that rs281437 exhibits minimal interaction with the other three SNPs. On the other hand, the other three SNPs (rs3093032, rs923366, rs3093030) display strong interactions with each other. Specifically, rs923366 and rs3093030 show positive interaction with each other, while rs3093032 demonstrates a negative correlation with the other two SNPs (rs923366, rs3093030).

3.4 LD and haplotype analyses in ICM, between two groups and relations with ICM

Using the SHEsis online software, we conducted linkage disequilibrium (LD) analysis and haplotype analysis on three SNPs (rs3093032, rs923366, rs3093030) that exhibited strong interactions with each other. The analysis revealed a significant level of linkage disequilibrium (D' >0.75) among these three SNPs (Figure 3).

Haplotype analysis was further conducted on these three SNPs, revealing five haplotypes (Table 3). The C<sub>rs3093032</sub>T<sub>rs923366</sub>C<sub>rs3093030</sub> and T<sub>rs3093032</sub>C<sub>rs923366</sub>C<sub>rs3093030</sub> haplotypes were discovered to be
more prevalent in the case group in relative to the control group (19.0% versus 10.4% and 10.3% versus 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 compared to 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 two groups, with a frequency of 0.0% in both the control and case groups. Therefore, this haplotype was not further analyzed.

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

### 4. Discussion

Single nucleotide polymorphisms (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[20]. Assessing the strength of association between SNPs through LD analysis is a valuable approach to detect genetic variations associated with complex human disorders[21]. Additionally, 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[21].

To specifically investigate the correlation between ICM and SNPs, as well as haplotypes, and to identify gene-gene interactions, the present 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 linkage disequilibrium analysis on the SNPs that showed interaction with each other. Haplotype analysis was also carried out 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 2.032 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 2.3 times higher risk of developing ICM than those with the CC genotype. However, we found no statistically significant differences between the two groups for the other three SNPs (rs923366, rs281437, and rs3093030). In the interaction analysis among the SNPs, except for rs281437, the other three 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. Further, we conducted linkage disequilibrium analysis on these three SNPs, and the results indicated a strong linkage disequilibrium ($D' > 0.75$) (Figure 3). Subsequently, haplotype analysis revealed five haplotypes (Table 3). The ICM risk was found to be 2.28 times higher in individuals carrying the $C_{rs3093032}-T_{rs923366}-C_{rs3093030}$ haplotype relative to those carrying the $C_{rs3093032}-C_{rs923366}-C_{rs3093030}$ haplotype. Additionally, individuals carrying the $T_{rs3093032}-C_{rs923366}-C_{rs3093030}$ haplotype had a 2.388 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 linkage disequilibrium ($D' > 0.75$) 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 90–115kD. It contains one transmembrane and five immunoglobulin architectures and is present in various cell types, including leukocytes, epithelial cells, and fibroblasts [22]. 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 10285660 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 CAD, as well as in different drug responses among individuals [23]. They can occur within coding regions, affecting amino acid synthesis, or in noncoding regions, influencing gene and protein levels [24]. Understanding gene variations and their impact is crucial for exploring disease mechanisms and the
relationship between gene variations and diseases, and for developing effective preventive and treatment measures.

While rs3093032 is an SNP located in the noncoding 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.

The findings from these studies could potentially lead to the development of new and efficient SNP markers for medical tests, enabling individualized diagnosis and customized treatment for ICM cases. Early detection and preventive measures can be facilitated, offering a promising approach in the medical field.

This research provides valuable insights into the association between ICAM-1 variants and ICM. However, there are some limitations in the present study. At first, the participants were recruited from a single hospital, which may lead to recruitment bias, and the sample size is limited. Secondly, 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.

In summary, our findings suggest that individuals carrying the T allele in rs3093032 have an elevated risk of ICM in relative to those carrying the C allele. CT genotype carriers also show higher susceptibility to ICM compared to CC genotype carriers. Moreover, we observed strong interactions among three SNPs (rs3093032, rs923366, and rs3093030). In the haplotype analysis, individuals carrying the C\textsubscript{rs3093032}-T\textsubscript{rs923366}-C\textsubscript{rs3093030} and T\textsubscript{rs3093032}-C\textsubscript{rs923366}-C\textsubscript{rs3093030} haplotypes have a higher risk of developing ICM in relative to carriers of the C\textsubscript{rs3093032}-C\textsubscript{rs923366}-C\textsubscript{rs3093030} haplotype.

**Declarations**

**Conflict of interest**

All authors read the final revision and agreed to submit in this journal, and claim no competing interest.

**Author contribution statement**

Tuersunjiang Naman and RefuaitiAbuduhalike performed coronary angiography and coronary intervention (if necessary) on all subjects and performed statistical analysis and write the paper, should be regarded as co-first authors.

AihaidanAbudouwayiti, MuyassarAbudoureyimu and Juan Sun collect data and performed the experiment.

Ailiman Mahemuti design the project and revised the final manuscript.
**Funding**

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**Ethics Statement**

The present work was approved by the Ethics Committee of First Affiliated Hospital of 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 the present manuscript.

**Data availability statement**

Data used in this study can be available by the submitting author on request.

**References**


Figures
Altogether 758 cases were recruited in the study.

Exclusion criteria (n=42):
1) Acute decompensated HF (n=13),
2) AMI (n=18),
3) Chronic renal failure (n=11)

716 Participants Performing coronary artery angiography according to eligibility criteria

Control group (n=280)
Case group (n=252)
Excluded subjects (n=184)

Figure 1
Flowchart of the patient selection process

Figure 2
Dendrogram for the interactions of SNPs (rs3093032, rs923366, rs281437, rs3093030). The red and blue colors represent positive and redundant interactions, respectively.

Figure 3

LD test of SNPs(rs3093032, rs923366, rs3093030)