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The Association of PLA2G7 Gene Polymorphisms with Serum Lp-PLA2 Activity and Lipid Profile in Han Chinese Patients with Coronary Heart Disease

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Purpose: This study aimed to investigate the distribution patterns of PLA2G7 gene variants in Han Chinese patients with coronary heart disease (CHD), and their relationships with serum lipoprotein-associated phospholipase A2 (Lp-PLA2) levels and lipid profiles.

Methods: A total of 93 han Chinese CHD patients were recruited. Serum Lp-PLA2 levels were determined using enzyme-linked immunosorbent assay (ELISA), while comprehensive analysis of PLA2G7 gene polymorphisms was conducted through whole-exome sequencing. Concurrently, multiple lipid parameters were measured and analyzed.

Results: Among these Han Chinese CHD patients, the PLA2G7 gene rs1051931 (c.1136T>C p.Val379Ala) rare variant was highly prevalent (variant rate: 94.62%) among the study population, and showed negative correlation with serum Lp-PLA2 activity. The rs1765208290 (c.233G>A p.Gly78Asp) rare variant showed positive correlation with TG, ApoA, ApoB, HDL, LDL and TCHO levels in the serum. Strong linkage disequilibrium was observed between the rs1805018 (c.593T>C p.Ile198Thr) and rs76863441 (c.835G>T p.Val279Phe), both of which were related to lower Lp-PLA2 activity.

Conclusion: In these Han Chinese CHD patients, the rs1051931 (c.1136T>C p.Val379Ala) rare variant in the PLA2G7 gene is closely linked to decreased Lp-PLA2 activity, whereas the rs1765208290 (c.233G>A p.Gly78Asp) rare variant influences lipid homeostasis. The strong LD between rs1805018 (c.593T>C p.Ile198Thr) and rs76863441 (c.835G>T p.Val279Phe) loci may act synergistically to reduce Lp-PLA2 activity.

Keywords: PLA2G7 gene, coronary artery atherosclerotic heart disease, serum Lp-PLA2, lipid profile

Introduction

Coronary Heart Disease (CHD) has emerged as a major cause of mortality worldwide, including in China,[1] with a higher prevalence particularly among males. According to the "China Cardiovascular Report 2018", there were about 11 million CHD patients in the country,[2] and both the incidence and mortality rates were steadily increasing, with a death rate surpassing 1‰. CHD primarily results from coronary artery atherosclerosis, causing vessel narrowing or obstruction, ultimately leading to ischemic and hypoxic myocardial necrosis. Extensive evidence indicates that the interplay between genetic and environmental factors significantly exacerbates the risk of CHD, with high cholesterol levels, hypertension, smoking status, and diabetes being among the numerous risk factors tightly linked to CHD onset and progression.[3] Inflammation plays a pivotal role in the atherosclerotic process, driving coronary plaque formation and coronary artery disease development, and AT1R and PLA2G7 gene polymorphisms may increase CHD risk by influencing inflammatory and lipid metabolic processes.[4]

Lipoprotein-Associated Phospholipase A2 (Lp-PLA2), an emerging inflammatory biomarker, has been shown to play a crucial role in the formation of atherosclerosis and the progression of cardiovascular diseases, making it a research focus

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in the field of cardiovascular and cerebrovascular diseases.[5–7] Studies suggest that Lp-PLA2 is involved in the inflammatory process of coronary atherosclerosis and could serve as a significant biomarker for assessing CHD risk.[8] Lp-PLA2 plays a significant role in CHD. Lp-PLA2 is an enzyme that associates with low-density lipoprotein (LDL) and primarily participates in inflammation and atherosclerosis. Studies have shown that Lp-PLA2 activity is positively correlated with the severity of CHD.[9] This finding supports the role of Lp-PLA2 in the rupture and erosion of atherosclerotic plaques.[10] Additionally, elevated Lp-PLA2 levels are associated with endothelial dysfunction and arterial stiffness in patients with stable CHD, independent of typical risk factors for CHD, statin use, antihypertensive treatment, and disease duration.[11]

Lp-PLA2, also known as Platelet-Activating Factor Acetylhydrolase (PAF-AH), is a key inflammation-related enzyme secreted by inflammatory cells such as macrophages and lymphocytes, belonging to the PLA2 superfamily. Physiologically, this enzyme catalyzes the hydrolysis of oxidized phospholipids and assumes a vital function in the atherosclerotic process. The encoding gene for Lp-PLA2, PLA2G7, is located on human chromosome 6, spanning 31,378 base pairs, encompassing 12 exons, and translating into a 441-amino-acid protein with a molecular weight of approximately 45 kD.[12] In cardiovascular disease research, several studies have reported multiple variant sites in the PLA2G7 gene associated with Lp-PLA2 function, including but not limited to rs1805017 (c.275G>A p.Arg92His), rs76863441 (c.835G>T p.Val279Phe), rs1805018 (c.593T>C p.Ile198Thr), rs1051931 (c.1136T>C p.Val379Ala), rs4498351 (Q28R), and variants such as rs7756935, rs1421368, and rs4498351.[13–16] However, the analysis of rare variants across the entire length of the PLA2G7 gene remains incomplete and warrants further investigation. Numerous studies on PLA2G7 screened by single nucleotide polymorphism (SNP) tests have revealed substantial differences in the biological functions of similar variations among different ethnic groups;[17–20] for instance, Hou et al[18] found that elevated Lp-PLA2 activity is independently associated with CHD and MI in the Chinese Han population, with the rs13210544 T allele significantly increasing the risk of MI, whereas rs76863441 and rs1805018 rare variants, despite reducing Lp-PLA2 activity, do not influence CHD risk. The relationship between PLA2G7 gene polymorphisms, serum Lp-PLA2 activity, and lipid indicators in the Han CHD patient population in Inner Mongolia requires further investigation.

To comprehensively elucidate the distribution characteristics of PLA2G7 gene variants and their biological effects in Han CHD patients from Inner Mongolia, we performed extensive, deep, full-length sequencing of the PLA2G7 gene, aiming to reveal its status of variants across its entire length and to thoroughly investigate potential associations between these gene variants, Lp-PLA2 activity in the serum of CHD patients, and key lipid profile indices. This study endeavors to provide robust theoretical underpinnings and scientific evidence for uncovering the genetic background and pathogenic mechanisms of CHD.

Materials and Methods

General Information

Data was collected from 93 patients admitted to the Department of Cardiology at the First Hospital of Hohhot between June 2022 and August 2023. Patients met the 2007 American College of Cardiology/American Heart Association (ACC/AHA) clinical diagnostic criteria for coronary heart disease (CHD): ① At least one coronary artery with >50% stenosis; ② History of angioplasty; ③ History of coronary artery bypass surgery. Any patient fulfilling one of these criteria was included, while those with pulmonary embolism, congenital heart disease, leukemia, cardiomyopathy, valvular disease, autoimmune disorders, or severe infectious diseases were excluded. All study participants provided written informed consent, and the study was approved by the Ethics Committee of the First Hospital of Hohhot (IRB2021074-1.0, approved on Oct 12, 2021). The study was proceeded in compliance with the Declaration of Helsinki. Blood biochemical indicators, including total cholesterol, low-density lipoprotein, high-density lipoprotein, apolipoproteins, triglycerides, and creatinine, were collected for all subjects, with all testing performed by the Clinical Laboratory of the First Hospital of Hohhot using Roche Diagnostics (Shanghai) Co., Ltd. instruments and reagents provided by the same company.

Human Lipoprotein-Associated Phospholipase A2 (Lp-PLA2) Assay

Serum Lp-PLA2 levels were determined using an enzyme-linked immunosorbent assay (ELISA). During the test, samples and diluent were added to the sample well of the detection card. Sample Lp-PLA2 first binds to anti-human Lp-PLA2 antibodies

labeled with up-converting phosphor (UCP) materials. The resulting complex then binds to mouse anti-human Lp-PLA2 antibodies immobilized on the reaction area, forming a sandwich complex of antibody 1-antigen-UCP-labeled antibody 2-UCP particles. In the control zone, a solid-phase goat anti-mouse-Lp-PLA2 antibody 2-UCP particle complex forms. UCP particles emit visible light signals upon excitation, and the ratio of the reaction zone signal to the control zone signal is directly proportional to the concentration of Lp-PLA2 in the sample. By inserting the detection card into a chemiluminescence immunoassay analyzer, the content of Lp-PLA2 in the tested sample was obtained. This portion of the testing was carried out by the Hohhot Dian Medical Testing Institute.

PLA2G7 Whole Exome Sequencing

After obtaining informed consent, 5 mL of venous blood was collected from probands and their parents using EDTA anticoagulant tubes. Genomic DNA was extracted using the QIAamp DNA Blood Midi Kit (Qiagen, Hilden, Germany). Genomic DNA was fragmented to 200–250 bp using a Bioruptor Pico ultrasonic disruptor, followed by purification, end repair, "A" tailing, and adapter ligation to construct individual sample DNA libraries.

Hybrid capture of the prepared libraries was performed using the SureSelect Human All Exon V6 kit (Agilent, USA). Amplified libraries were quality-checked using the Agilent 2100 Bioanalyzer and ABI StepOne, and qualified libraries were subjected to paired-end 150-bp sequencing on an Illumina HiSeq X Ten Analyzer (Illumina, San Diego, USA). Raw sequencing data were read using Illumina Pipeline software.

Quality assessment of the raw sequencing data was conducted using After QC, with low-quality reads and those contaminated by adapters removed. Filtered data were aligned to the human hg19 reference genome using BWA software (Burrows-Wheeler Aligner). Subsequently, the capture efficiency was evaluated, and single nucleotide variants (SNVs) and insertions/deletions (Indels) in the genome were analyzed using GATK software (Genome Analysis Toolkit). Identified SNVs and Indels were filtered against population databases, including 1000 Genomes, Genome AD, and ExAC. The pathogenicity of missense and splice site rare variants was predicted using the dbNSFP database. Known variants were screened using the Human Gene Mutation Database (HGMD) and ClinVar. All sites of rare variants were classified according to ACMG guidelines for the interpretation of genetic variants. Potentially pathogenic variants were validated by Sanger sequencing.

Statistical Analysis

Power analysis was calculated using Gpower software. Initial processing of vcf data was performed using awk and grep commands in the Linux system. The results of rare variant were formatted using plink software (https://www.cog-genomics.org/plink).[21] Linkage disequilibrium (LD) analysis was conducted using Haploview 4.2 software (https://www.broadinstitute.org/haploview/).[22] Two SNPs were considered to be in LD if D′>0.9 and r2>0.3.[23]

Results

Biochemical Characteristics of the Study Population

This study enrolled a total of 93 patients, comprising 62 males and 31 females. The age, serological indicators (total cholesterol, low-density lipoprotein, high-density lipoprotein, apolipoprotein A, apolipoprotein B, triglycerides, serum creatinine), and serum Lp-PLA2 levels of all patients are detailed in Table 1 below. Among the 93 patients, SNP analysis of the PLA2G7 gene identified four common variant sites: rs1051931, rs1805017, rs1805018, rs76863441.

To evaluate the effects of gene polymorphisms on serum Lp-PLA2 activity and blood lipids, we performed an efficacy analysis. Based on an effect size of 0.7 and a significance level of 0.05, our sample size was 93 cases. The calculated statistical power is 0.99, indicating that with this sample size, there is a 99% probability that the effect size we set will be detected. This suggests that our study has sufficient statistical power to explore the relationship between gene polymorphism and serum Lp-PLA2 activity and blood lipids (Figure S1).

Distribution of PLA2G7 Gene Polymorphisms

The PLA2G7 gene has a full length of 31,521 bp. In this study, a comprehensive screening of rare variant was conducted for the PLA2G7 gene in 93 patients. Among the 93 analyzed samples from Han Chinese coronary heart disease patients

Table 1 General Characteristics of the Study Population

Indicator	Median	Mean ± Standard Deviation
Age (years)	63.5	61.51 ± 10.20
Total Cholesterol (mmol/L)	5.18	5.08 ± 1.55
Low-Density Lipoprotein (mmol/L)	2.93	2.87 ± 1.22
High-Density Lipoprotein (mmol/L)	1.26	1.30 ± 0.36
Apolipoprotein A (mg/L)	1.50	1.59 ± 0.41
Apolipoprotein B (g/L)	0.82	0.88 ± 0.35
Triglycerides (mmol/L)	1.59	2.07 ± 1.76
Serum Creatinine (mmol/L)	73.68	81.85 ± 59.23
Serum Lp-PLA2 (ng/mL)	149.94	180.54 ± 128.48
PLA2G7 SNP Detection		rs1051931 (c.1136T>C p.Val379Ala), rs1805017 (c.275G>A p.Arg92His), rs1805018 (c.593T>C p.Ile198Thr), rs76863441 (c.835G>T p.Val279Phe)

in the Inner Mongolia region, the rs1051931 (c.1136T>C p.Val379Ala) variant exhibited the highest variant frequency among the study population, reaching 94.62%, followed by rs1805017 (c.275G>A p.Arg92His) at 26.88%, rs1805018 (c.593T>C p.Ile198Thr) at 10.75%, and rs76863441 (c.835G>T p.Val279Phe) at 5.38%. The variant frequencies of rs201842579 (c.950T>A p.Ile317Asn), rs147252565 (c.833C>T p.Thr278Met) and rs1765208290 (c.233G>A p.Gly78Asp) were relatively low (Figure 1). Additionally, higher proportions of c*78_*89del and c*76_*91del, as well as the −67C>G, were observed within the PLA2G7 gene.

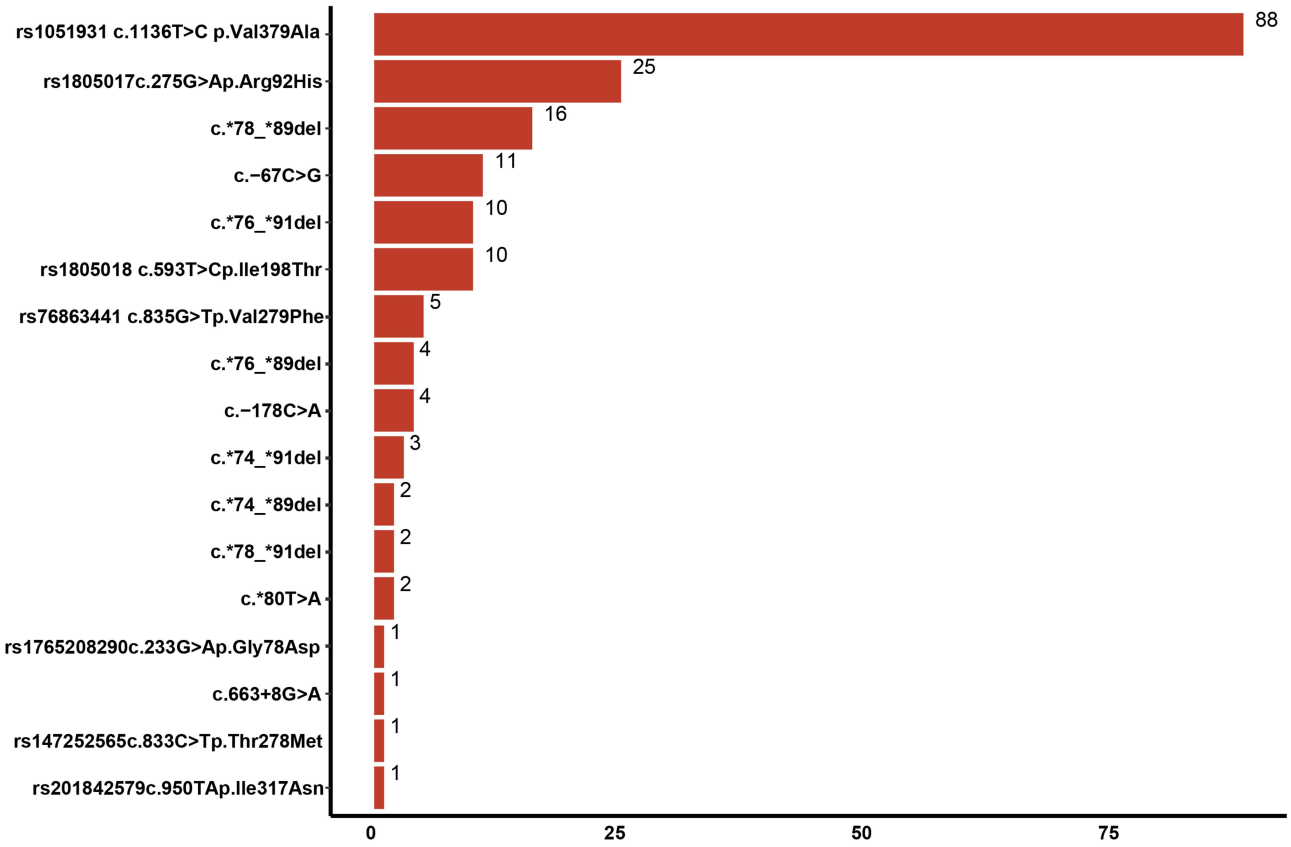

Figure 1 Distribution of PLA2G7 Gene Polymorphisms. The horizontal axis represents the number of patients in the cohort with corresponding variants, while the vertical axis represents the detected polymorphism types. *Represents a frameshift or deletion caused by a mutation, representing the termination site of a coding sequence.

Correlation Between PLA2G7 Gene Polymorphisms and Serum Lp-PLA2 Activity and Lipid Profile

Spearman correlation analysis was employed to investigate the associations between PLA2G7 gene polymorphisms and serum Lp-PLA2 activity, LDL, HDL, apolipoprotein A, apolipoprotein B, triglycerides, and serum creatinine. The results (Figure 2) indicate that rs1805017 (c.275G>A p.Arg92His) is positively correlated with serum Lp-PLA2 activity, while other variants including the common variant rs1051931 (c.1136T>C p.Val379Ala) in PLA2G7 show negative correlations with serum Lp-PLA2 activity. Contrary to Lp-PLA2, TCHO is positively correlated with all variants except rs147252565 (c.833C>T p.Thr278Met). APOA and APOB are positively correlated with rs1765208290 (c.233G>A p.Gly78As) and rs201842579 (c.950T>A p.Ile317Asn), and negatively correlated with rs147252565 (c.833C>T p.Thr278Met) and

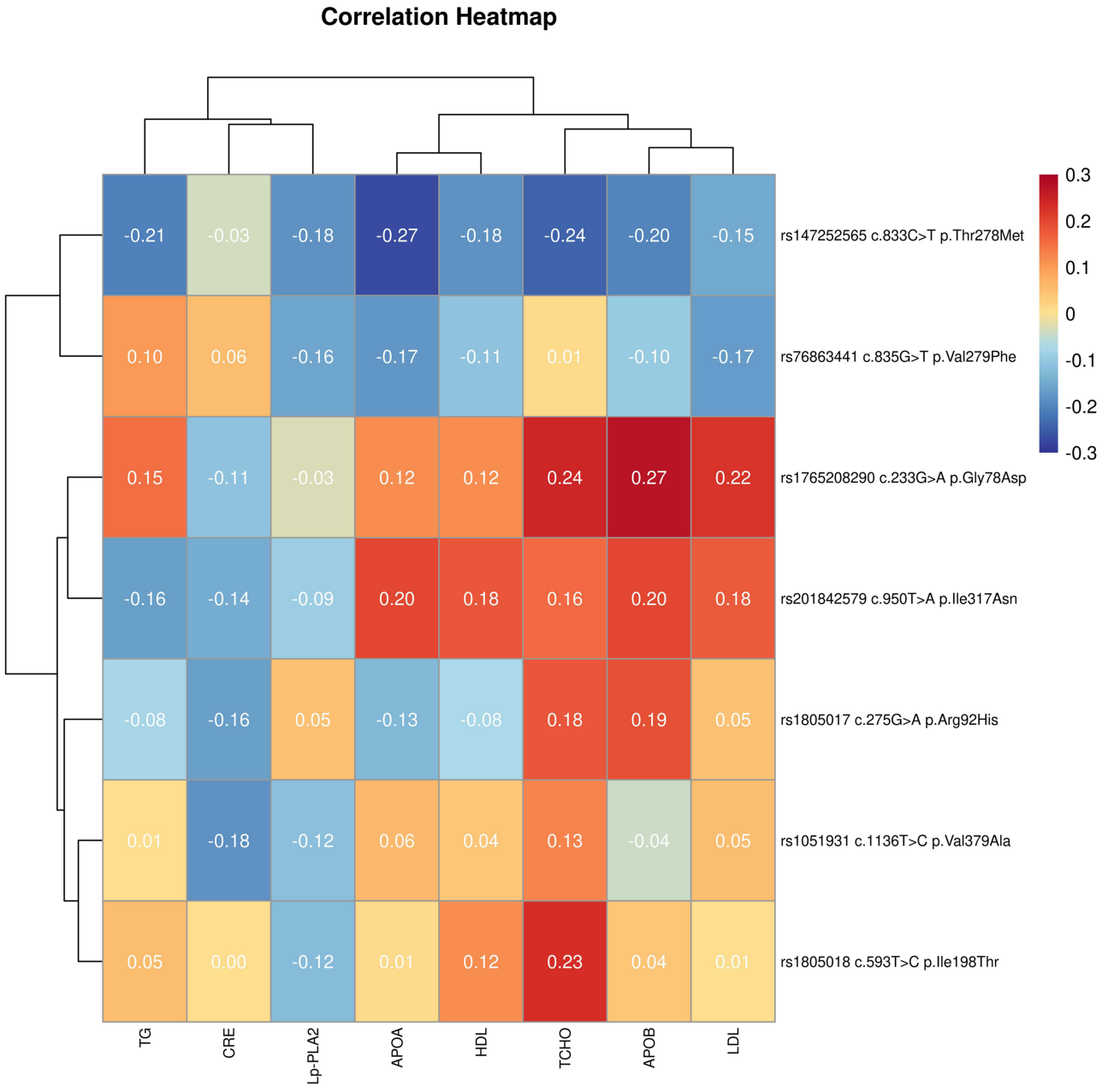

Figure 2 Correlation Between PLA2G7 Gene Polymorphisms and Serum Lp-PLA2 Activity and Lipid Profile. Horizontal axis represents serum Lp-PLA2 activity and lipidomics profile, while the vertical axis denotes PLA2G7 Gene Polymorphisms. Colors indicate correlation coefficients ranging from −0.3 (negative correlation) to +0.3 (positive correlation), with darker colors indicating stronger correlations.

rs76863441 (c.835G>T p.Val279Phe). Apart from APOA and APOB, HDL, LDL, and TCHO are also positively correlated with rs1765208290 (c.233G>A p.Gly78As) and rs201842579 (c.950T>A p.Ile317Asn). Interestingly, rs147252565 (c.833C>T p.Thr278Met) showed negative correlations with all the indicators. However, none of these correlations reached statistical significance, highlighting the need for a more extensive study with a larger sample size.

Linkage Disequilibrium Analysis

Linkage disequilibrium refers to the nonrandom association between allele of different loci. We used linkage disequilibrium analysis to reveal whether the different loci in the PLA2G7 gene are inherited independently or related to each other in the population. Seven variant sites in the PLA2G7 gene were identified in this study, all located on chromosome 6. The linkage disequilibrium analysis results for the seven PLA2G7 gene sites are presented in Table 2. Haploview software was utilized for linkage disequilibrium analysis. The analysis results (Figure 3) show that two variant sites exhibit linkage disequilibrium. Notably, the linkage disequilibrium between rs76863441 (c.835G>T p.Val279Phe) and rs1805018 (c.593T>C p.Ile198Thr) on chromosome 6 is particularly prominent, with $r^2 = 0.446$.

Allele Frequency Analysis

Gene frequencies for each locus were calculated based on the various variants, along with genotype counts and frequencies (Table 3). Notably, the GG type of rs1051931 (c.1136T>C p.Val379Ala) and CC type of rs1805017 (c.275G>A p.Arg92His) loci exhibit relatively high allele frequencies, at 0.763 and 0.645, respectively. In contrast,

Table 2 Results of Linkage Disequilibrium Analysis for Seven PLA2G7 Gene Sites

L1	L2	D′	LOD	r^2	CIlow	CIhi	Dist	T-int
rs1051931	rs201842579	1	0.06	0.001	0.04	0.97	2875	1.11
rs1051931	rs76863441	1	0.11	0.006	0.04	0.97	4155	–
rs1051931	rs147252565	1	0.06	0.001	0.04	0.97	4157	–
rs1051931	rs1805018	1	0.6	0.012	0.09	0.99	6360	–
rs1051931	rs1805017	0.888	0.28	0.028	0.06	0.97	11,279	–
rs1051931	rs1765208290	1	0.06	0.001	0.04	0.97	11,321	–
rs201842579	rs76863441	1	0.02	0	0.04	0.97	1280	1.58
rs201842579	rs147252565	1	0	0	0.04	0.96	1282	–
rs201842579	rs1805018	1	0.04	0	0.04	0.97	3485	–
rs201842579	rs1805017	1	0.41	0.022	0.07	0.98	8404	–
rs201842579	rs1765208290	1	0	0	0.04	0.96	8446	–
rs76863441	rs147252565	1	0.02	0	0.04	0.97	2	9.13
rs76863441	rs1805018	1	6.95	0.446	0.67	1	2205	–
rs76863441	rs1805017	1	0.69	0.01	0.1	0.99	7124	–
rs76863441	rs1765208290	1	0.02	0	0.04	0.97	7166	–
rs147252565	rs1805018	1	0.04	0	0.04	0.97	2203	9.19
rs147252565	rs1805017	1	0.1	0.001	0.04	0.97	7122	–
rs147252565	rs1765208290	1	0	0	0.04	0.96	7164	–
rs1805018	rs1805017	1	1.21	0.022	0.2	1	4919	3.58
rs1805018	rs1765208290	1	0.81	0.062	0.12	0.99	4961	–
rs1805017	rs1765208290	1	0.1	0.001	0.04	0.97	42	0.93

Note: L1 and L2: single nucleotide polymorphism names; D′: represents the D′ value, a statistical measure of the degree of linkage disequilibrium between genetic markers, ranging from 0 to 1, where 1 indicates complete linkage disequilibrium. LOD: LOD score, representing the connection score between two genetic markers and used to estimate the strength of linkage (linkage). r^2: r-squared (r-squared), also a statistical measure for assessing the degree of association between two genetic markers, with a range from 0 to 1, where 1 indicates complete correlation. CIlow and CIhi: lower and upper limits of confidence intervals. In LD analysis, they may be used to indicate the statistical significance of D′ or r^2 values. Dist: physical distance or genetic distance between genetic markers. T-int is a statistic used by the HapMap Project to measure the completeness of information represented by a set of markers in a region.

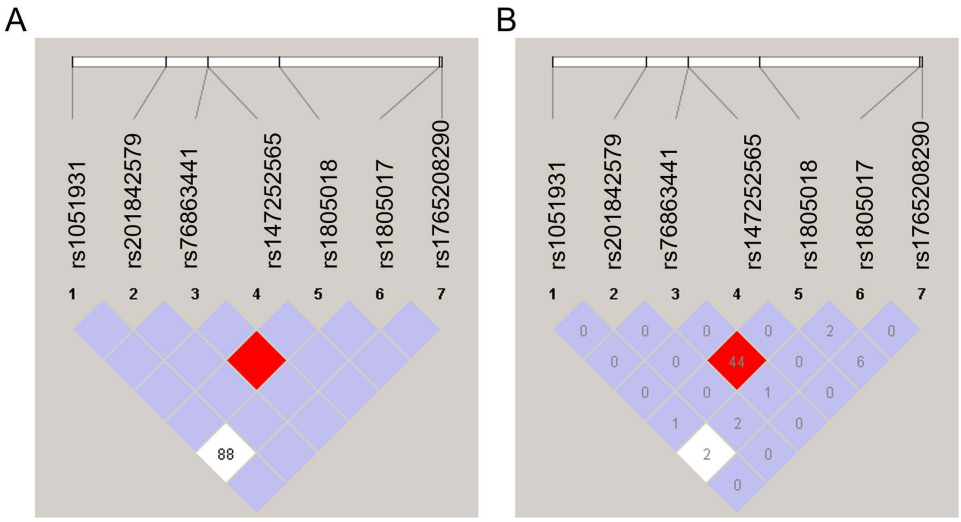

Figure 3 Linkage Disequilibrium Map of PLA2G7 Gene variants. (**A**) D′ values, it depicts the localization of the selected in single nucleotide polymorphism tests along the gene; (**B**) r^2 values, it presents the Haploview-generated linkage disequilibrium map for the seven variant sites.

the rs147252565 (c.833C>T p.Thr278Met), rs1765208290 (c.233G>A p.Gly78Asp), and rs201842579 (c.950T>A p. Ile317Asn) loci display significantly lower mutant allele frequencies.

Discussion

Coronary heart disease (CHD) is currently understood as a chronic inflammatory condition, with inflammation playing a role throughout the disease's progression. In recent years, several inflammatory factors and genes associated with both the onset and prognosis of CHD have been identified, some of which hold promise as therapeutic targets for the management and control of the disease.[24–27]

Table 3 Genotype Counts and Frequencies for PLA2G7 Gene Polymorphisms

Variants	Genotype	Number	Frequency	Gene	Frequency
rs1051931	A A	1	0.011	A	0.124
	G A	21	0.226	G	0.876
	G G	71	0.763		
rs1805017	C C	60	0.645	C	0.801
	T C	29	0.312	T	0.199
	T T	4	0.043		
rs76863441	A A	1	0.011	A	0.038
	A C	5	0.054	C	0.962
	C C	87	0.935		
rs1805018	A A	79	0.849	A	0.855
	G A	13	0.140	G	0.081
	G G	1	0.011		
rs147252565	A G	1	0.011	A	0.005
	G G	92	0.989	G	0.995
rs1765208290	C C	92	0.989	C	0.995
	T C	1	0.011	T	0.005
rs201842579	A A	92	0.989	A	0.995
	T A	1	0.011	T	0.005

Lipoprotein-associated phospholipase A2 (Lp-PLA2), in particular, has garnered substantial attention as an inflammatory factor in recent times.[25] Secreted by inflammatory cells within atherosclerotic plaques, Lp-PLA2 concentrations are significantly elevated in advanced plaques. It primarily associates with low-density lipoprotein (LDL) in circulation and hydrolyzes oxidized phosphatidylcholine products formed during LDL oxidation, generating two potent pro-inflammatory substances.[24] Studies have consistently demonstrated a strong association between Lp-PLA2 levels and both the incidence and prognosis of CHD.[28–30] Lp-PLA2 is encoded by the PLA2G7 gene located in the chromosomal region 6p21-p12. Prior research has revealed that multiple missense variants within this gene influence Lp-PLA2 activity. Reported polymorphic sites linked to Lp-PLA2 activity include rs76863441 (c.835G>T p.Val279Phe), rs1805017 (c.275G>A p.Arg92His), rs1805018 (c.593T>C p.Ile198Thr), and rs1051931 (c.1136T>C p.Val379Ala), yet the relationships between these sites and enzyme activity have been highly inconsistent.[4,12–16,19] One plausible explanation is that different patterns of linkage disequilibrium exist among these gene loci across populations. The present study lays the groundwork for investigating PLA2G7 gene polymorphisms in Han Chinese CHD patients from Inner Mongolia, as well as their correlations with serum Lp-PLA2 levels and lipid-related indices.

In the Han Chinese population with coronary heart disease in Inner Mongolia region, the polymorphism characteristics of the PLA2G7 gene are particularly prominent. Specifically, the rs1051931 (c.1136T>C p.Val379Ala) variant is highly prevalent among this population, accounting for up to 94.62% of cases, and this variant exhibits negative correlation with serum Lp-PLA2 activity, suggesting that the rs1051931 (c.1136T>C p.Val379Ala) variant may lead to a weakened or decreased function and activity of Lp-PLA2, which in turn could potentially affect the progression of coronary atherosclerosis. Moreover, the rs1765208290 (c.233G>A p.Gly78Asp) variant causing a change from glycine to aspartic acid at position 78 (G78D) demonstrates a significant positive correlation with TG, ApoA, ApoB, HDL, LDL and TCHO levels, implying that this particular variant might contribute, to some extent, to an adverse lipid profile associated with coronary heart disease development.

Further linkage disequilibrium analysis of seven variant sites reveals pronounced disequilibrium among these sites, with the strongest linkage observed between positions 46677098 and 46679303 on chromosome 6. The study also uncovers linkage disequilibrium between the rs1805018 (c.593T>C p.Ile198Thr) and rs76863441 (c.835G>T p.Val279Phe) sites within the PLA2G7 gene, both of which are associated with decreased serum Lp-PLA2 activity. An independent study[31] confirm that both the rs76863441 (c.835G>T p.Val279Phe) and rs1805018 (c.593T>C p.Ile198Thr) polymorphisms significantly reduce Lp-PLA2 activity. Sutton et al[32] in a tagSNP haplotype study in Caucasians, suggest an association between the rs1805018 (c.593T>C p.Ile198Thr) site and PLA2G7 gene expression in large arteries. Hong et al[19] and Hou et al[18] find that the Lp-PLA2 gene rs76863441 (c.835G>T p.Val279Phe) and rs1805018 (c.593T>C p.Ile198Thr) polymorphisms in Han Chinese are associated with lower Lp-PLA2 activity, but not significantly with CHD risk, whereas the T allele at rs13210554 site is significantly related to increased myocardial infarction (MI) risk. Hong et al[19] in a study on Southern Han Chinese demonstrate that the rs1805017 (c.275G>A p.Arg92His) polymorphism in PLA2G7 gene is significantly associated with CHD risk, with RH/HH genotypes conferring increased risk. The study also detects differential effects of haplotypes on CHD risk, associating rs1805017 (c.275G>A p.Arg92His) polymorphism with decreased HDL-C levels. Wang et al,[20] through a meta-analysis, report that the rs1805017 (c.275G>A p.Arg92His) polymorphism in PLA2G7 gene is significantly related to CHD risk under a recessive model, indicating that the 92H allele may increase CHD risk in Han Chinese. Conversely, rs1051931 (c.1136T>C p.Val379Ala) and rs76863441 (c.835G>T p.Val279Phe) polymorphisms do not show significant associations with CHD risk. Collectively, these findings and the current study emphasize the potential role of PLA2G7 gene polymorphisms in modulating Lp-PLA2 activity and influencing CHD risk, with rs1805017 (c.275G>A p.Arg92His) polymorphism consistently demonstrating an association with increased CHD risk in Han Chinese populations.

These observations collectively point to individuals carrying rs1805018 (c.593T>C p.Ile198Thr) and rs76863441 (c.835G>T p.Val279Phe) alleles potentially having lower PLA2G7 gene expression and Lp-PLA2 activity, thereby increasing their risk for CHD. These studies collectively highlight the crucial role played by PLA2G7 gene polymorphisms in regulating Lp-PLA2 activity and in the development of coronary artery disease, providing new genetic insights for CHD prevention and treatment. Given that Lp-PLA2 has been established as a participant in the inflammatory processes of coronary atherosclerosis and its activity is closely tied to CHD incidence and prognosis, elucidating the

impact of PLA2G7 gene polymorphisms on Lp-PLA2 activity not only helps uncover genetic factors underlying CHD development but also holds promise for guiding personalized treatment strategies for patients with specific genotypes or for developing novel therapies targeting Lp-PLA2 activity to reduce CHD risk.

However, despite the fact that this study has made some meaningful findings, some of the results cannot be statistically supported more strongly due to the lack of control group results. Future research should investigate this issue more comprehensively and deeply. Future research can build upon these results by expanding sample sizes and further refining the precise relationships between different genotypes and clinical phenotypes/prognosis of CHD, ultimately providing more precise genetic foundations for CHD prevention and management strategies.

This study reveals a significant association between the PLA2G7 gene rs1051931 (c.1136T>C p.Val379Ala) variant and decreased Lp-PLA2 activity in Han Chinese CHD patients from Inner Mongolia, with the rs1765208290 (c.233G>A p.Gly78Asp) variant affecting lipid homeostasis and the linkage disequilibrium between rs1805018 (c.593T>C p.Ile198Thr) and rs76863441 (c.835G>T p.Val279Phe) sites potentially synergistically reducing Lp-PLA2 activity. These findings deepen our understanding of the role of PLA2G7 gene polymorphisms in the pathogenesis of CHD in this population, particularly how variants influence Lp-PLA2 activity and lipid metabolic pathways, providing new leads for CHD risk assessment, early prevention, and personalized therapy.

Future research can build upon these results by expanding sample sizes and further refining the precise relationships between different genotypes and clinical phenotypes/prognosis of CHD, ultimately providing more precise genetic foundations for CHD prevention and management strategies.

Data Sharing Statement

The datasets generated and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request. All the variants were reviewed and annotated using dbSNP (ncbi.nlm.nih.gov/snp).

Ethics Approval and Informed Consent

The study was approved by the Ethics Committee of the First Hospital of Hohhot (IRB2021074-1.0, approved on Oct 12, 2021). And all study participants provided written informed consent. The study was proceeded in compliance with the Declaration of Helsinki.

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Disclosure

The authors report no conflicts of interest in this work.

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