RESEARCH PAPER

Association of Genetic Polymorphisms in ABCA1 (rs2230806 and rs141420090) Gene and Their Association with the Risk of Type 2 Diabetes and Coronary Artery Disease: A Case-Control Study

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ABSTRACT

Background: CAD is linked to T2DM through common pathways in the metabolism and genome. The ATP-binding cassette transporter A1 (ABCA1) gene is a key component in cholesterol efflux, high-density lipoprotein (HDL) metabolism, and glucose-lipid balance. Genetic polymorphisms of ABCA1 could affect insulin sensitivity and lipid transport and consequently affect the susceptibility to both T2DM and CAD.

Objective: To assess the relationship of ABCA1 polymorphisms: (rs2230806:R219K and rs141420090) with the risk of T2DM and CAD in north Indian population.

Methods: The study comprised 600 unrelated cases (150 controls, 150 T2DM, 150 CAD, 150 T2DM+CAD). The PCR-RFLP technique was used for genotyping. The chi-square test was utilised to compare genotypic and allelic frequencies, and odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. All groups were found to be at Hardy-Weinberg equilibrium (HWE).

Results: For rs2230806, the GG genotype frequency was significantly lower in T2DM patients (26%) compared to controls (37.3%) (χ^2=6.39, p=0.041). The G allele frequency was significantly reduced in T2DM+CAD patients versus controls (49.7% vs 60.3%; OR=1.54, 95% CI: 1.22–2.13, p=0.014). Under the dominant model, the risk genotype (GA+AA) conferred significantly higher odds for T2DM (OR=1.98; p=0.012), CAD (OR=1.80; p=0.040), and T2DM+CAD (OR=2.62; p=0.002). However, in comparison, there was no significant association observed between rs141420090 and T2DM, CAD or T2DM+CAD in any genetic model (all p>0.05).

Conclusion: ABCA1 rs2230806 is a potential genetic risk factor for T2DM and comorbid CAD in the Haryana population. rs141420090 does not appear to be associated with cardiometabolic disease susceptibility. The results need to be confirmed in larger multicenter studies.

Keywords: ABCA1; Genetic polymorphism; rs2230806; rs141420090; Type 2 diabetes mellitus; Coronary artery disease; PCR-RFLP; North India.

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1. Introduction

Diabetes mellitus (DM) is a common non-communicable metabolic disease and a public health emergency in the world. It is projected that there existed 537 In 2021, there were millions of adults with diabetes globally, and this number is projected to rise to 783 million by 2045, with type 2 diabetes mellitus (T2DM) comprising almost 90–95% of all instances (IDF 2021) [1]. Urbanisation, a sedentary lifestyle, dietary changes and population ageing are driving the rapid increase in the burden of disease in low- and middle-income nations, especially India. T2DM is a chronic hyperglycemia disorder due to insulin resistance and inadequate insulin levels, resulting in progressive insulin dys-regulation [2]. Chronic hyperglycemia leads to a substantial mortality risk and decreased morbidity from micro and macrovascular complications [3].

Coronary artery disease (CAD) is the most prevalent and severe macrovascular consequence of type 2 diabetes mellitus (T2DM) and constitutes the primary cause of mortality globally. Individuals with Type 2 Diabetes Mellitus (T2DM) possess a 2-4 fold increased risk for Coronary Artery Disease (CAD) compared to those without T2DM.In India, particularly among the northern population, CAD has been documented to present with a more severe phenotype and earlier onset, attributed to a combination of genetic predisposition and environmental risk factors [4].

ATP-binding cassette transporter A1 (ABCA1) is a key gene for reverse cholesterol transport and cardiovascular homeostasis. ABCA1 facilitates the translocation of cholesterol and phospholipids from cells to apolipoprotein A-I (ApoA-I), which is the first and limiting step in the generation of HDL-C [6]. Defective ABCA1 causes decreased HDL-C and disregulated lipid accumulation, which promotes insulin resistance, β-cell dysfunction and atherosclerosis.SNPs within the ABCA1 gene may affect the stability of the protein, or the activity of the transporter, and thus the efficiency of cholesterol efflux, which can affect metabolic risk [7]. Of these, rs2230806 (R219K) is a well characterised non-synonymous polymorphism in exon 7, and a functional variant within the extracellular domains of the ABCA1 protein is rs141420090. A number of international studies have been reported to show that polymorphisms of ABCA1 are associated with changes in HDL-C level, T2DM and CAD, but with inconsistent results in different ethnic groups [8].

The data on the genetic variants of ABCA1 in Indian population are scarce and particularly in the north Indian population where there is high prevalence of T2DM and CAD. Studies conducted in other ethnic groups of India have shown conflicting results, highlighting the importance of conducting genetic studies in individual populations [9]. This study sought to assess the correlation between ABCA1 rs2230806 and rs141420090 with the risk of T2DM and CAD within a North Indian demographic from Haryana, India. This hypothesized that the A allele of rs2230806 can be significantly associated with increased susceptibility to T2DM and CAD, and rs141420090 can have population specific effect which might be neutral.

2. Materials and Methods

2.1 Study Design and Ethics

This is a case-control study performed at Kurukshetra University in collaboration with several hospitals in Haryana, India. Ethical approval was secured from the ethics council of Kurukshetra University, with all samples obtained by authorised medical professionals under supervision a physician who had gained authorisation from the Medical Council of India (MCI) in accordance with ICMR guidelines.

2.2 Sample Size and Power Calculation

A minimum sample size of 130 per group was determined based on a two-tailed chi-square test of 80% power, α=0.05, and an expected OR of 1.5–2.0 for the rs2230806 variant. A total of 150 subjects per group was enrolled, to cater for possible exclusions, for a total of 600 subjects.

2.3 Study Participants

(150) Indian subjects were recruited, 150 healthy controls, 150 patients with T2DM, 150 patients with CAD and 150 patients with T2DM +CAD to form the four groups. Total of 600 unrelated individuals aged more than 35 years were recruited which included 150 healthy controls and 150 subjects each with T2DM, CAD and T2DM+CAD. Qualified doctors have made diagnosis based on ICMR and ADA standards. The diagnosis of T2DM was based on fasting blood glucose levels ≥126 mg/dL and/or HbA1c levels ≥6.5%. CAD was diagnosed by coronary angiography, electrocardiography, and/or cardiac biomarker testing.

Inclusion Criteria: (1) Age>35 years; (2) confirmed diagnosis of T2DM and/or CAD; (3) participants give written consent to participate. Exclusion criteria: (i) Type 1 diabetes mellitus; (ii) gestational diabetes; (iii) maturity-onset diabetes of the young (MODY); (iv) other major systemic diseases (renal failure, liver diseases, malignancy); (v) unstable angina or recent myocardial infarction which required acute intervention; (vi) refusal of consent.

2.4 Blood Sampling and Biochemical Analysis

All anthropometric and clinical data were taken by trained persons with the help of standard proforma and record through the physicians verification. Upon

enrolment, height, weight, and blood pressure were assessed. The Body Mass Index (BMI) was calculated using weight (kg)/height (m²). Blood was drawn in EDTA coated tubes. HbA1c, a standard enzymatic method and fasting blood glucose (FBG), a turbidimetric method, were used to measure these parameters. The insulin concentration was measured using enzyme-linked immunosorbent assay (ELISA) of plasma insulin. Automated analysers employed standard enzymatic techniques to assess the lipid profile, which included total cholesterol (TC), triglycerides (TG), HDL-C, and LDL-C.

2.5 DNA Extraction and Genotyping

Peripheral blood leukocytes (PBL) were used to extract genomic DNA with MDi Genomic DNA Miniprep Kit according to the manufacturer's instructions. The purity and content of DNA was determined by UV spectrophotometry (260/280 nm), and preserved at -20°C for further analysis. The method of PCR-RFLP was used for genotyping the polymorphisms of ABCA1 genes: rs2230806 and rs141420090 .The PCR reaction volume was made up of 25 µL of GoTaq Green Master Mix, forward and reverse primers, template DNA, and nuclease-free water. 'Thermal cycling was carried out as follows: initial denaturation at 95°C for 5 min, then 35 cycles denaturation (95°C, 30 s), annealing (50–60°C, 30 s) and extension (72°C, 45 s); final extension at 72°C for 10 min. PCR products and restriction fragments were run on 1.5% agarose gels stained with ethidium bromide. For rs2230806, digestion with EcoNI distingu
(185 bp and 124 bp), and GA
124 bp) genotypes'. HpyCH4
characteristic banding pattern
genotype in the case of rs1414200090.

Table 1. Primer sequences, product lengths, annealing temperatures, and restriction enzymes used for genotyping of ABCA1 SNPs rs2230806 and rs141420090.

SNP	Primer Sequence (5'→3')	Product Length	Annealing Temp.	Restriction Enzyme
rs2230806	F: 5'-AAAGACTTCAAGGACCCAGCTT-3' R: 5'-CCTCACATTCCGAAAGCATTA-3'	309 bp	58°C	EcoNI
rs141420090	F: 5'-TCTGCTGCAGCCAGTTTCTTC-3' R: 5'-GCATTGGACTGTTGCAATGGA-3'	300 bp	56°C	HpyCH4IV

2.6 Statistical Analysis

All SNPs were assessed in all groups for Hardy Weinberg equilibrium (HWE) using chi-square goodness of fit test. The genotypic and allelic frequencies were compared between the groups by using the chi-square test. An odds ratio (OR) and 95% confidence interval (CI) was used to evaluate the association with the disease. Genetic model analyses (additive, dominant, recessive, and heterozygous) were carried out. The Student's independent t test method was used for analysing the relationship between SNP genotypes and clinical indicators. The Bonferroni correction was used for multiple comparisons ($p<0.017$). The analysis of data was performed in SPSS version 26.0 (IBM Corp, Armonk, NY, USA). P-values <0.05 were considered significant, unless otherwise mentioned.

3. Results

3.1 Clinical and Demographic Characteristics

All four groups have clinical parameters as shown in Table 2. There was no significant difference in age between groups (all $p>0.05$), which shows that proper age matching was achieved. All three disease groups had significantly high systolic and diastolic blood pressure levels as compared to controls. The FBG and HbA1c were significantly higher in T2DM and T2DM+CAD groups, suggesting glycaemic dysregulation. For lipid parameters, TC, TG and LDL-C also demonstrated a gradual upwards trend, and HDL-C decreased with disease groups. The largest changes were seen in T2DM+CAD patients. Differences in the rates of hypertension, smoking and family history were found to be significant, and confirmed the expected clinical profiles.

Table 2. Clinical and demographic parameters of healthy controls

Clinical Parameter	Control (n=150) Mean ± SD	T2DM (n=150) Mean ± SD	CAD (n=150) Mean ± SD	T2DM+CAD (n=150) Mean ± SD	p-value (T2DM vs Control)	p-value (CAD vs Control)	p-v (T2 Co
Age (Years)	54.85 ± 12.35	55.55 ± 13.08	54.85 ± 12.34	57.23 ± 11.64	0.634	0.086	0.37
DBP (mmHg)	81.17 ± 4.65	84.86 ± 8.06	83.25 ± 4.75	83.17 ± 6.19	<0.05	<0.05	<0.0
SBP (mmHg)	121.72 ± 4.84	130.53 ± 14.31	123.74 ± 10.01	126.00 ± 11.34	<0.05	<0.05	<0.0
FBG (mg/dL)	93.91 ± 10.03	161.63 ± 49.68	94.38 ± 12.30	166.67 ± 58.00	<0.05	0.621	<0.0
TC (mg/dL)	177.78 ± 73.98	188.01 ± 48.21	243.35 ± 52.11	250.03 ± 42.06	0.025	<0.05	<0.0
TG (mg/dL)	105.61 ± 54.46	170.71 ± 34.02	154.00 ± 39.64	191.76 ± 72.02	<0.05	<0.05	<0.0
HDL C (mg/dL)	46.44 ± 12.40	40.16 ± 11.30	42.77 ± 11.81	31.62 ± 14.01	0.009	<0.05	<0.0
LDL C (mg/dL)	104.22 ± 78.75	123.11 ± 44.27	171.51 ± 46.55	177.73 ± 54.17	0.025	<0.05	<0.0
HbA1c (%)	4.74 ±	7.72 ±	4.71 ±	7.46 ± 1.82	<0.05	0.982	<0.0

	0.96	1.94	0.83		GG	56 (37.3%)	39 (26.0%)	6.39	-	0.041	39 (26.0%)	5.32	-	0.070	26 (17.3%)	9.1
ulin	13.10 ± 10.76	19.93 ± 18.96	14.78 ± 9.75	25.31 ± 21.72	<0.05		0.158		<0.05							
					GA	69 (46.0%)	89 (59.3%)				82 (54.6%)				97 (64.6%)	
	82/68	88/62	95/55	91/59	0.387		0.118		0.204							
					AA	25 (16.7%)	22 (14.7%)				29 (19.3%)				27 (18.0%)	
%)	18 (12%)	29 (19.3%)	47 (31.3%)	43 (28.7%)	0.049		<0.001		<0.001							
					HWE p-value	0.724	0.681				0.708				0.693	
(n,	22 (14.7%)	61 (40.7%)	68 (45.3%)	74 (	**Allelic Distribution**											
					G allele	181 (60.3%)	159 (53.0%)	3.96	1.35 (1.02–1.78)	0.047	160 (53.3%)	3.22	1.33 (0.96–1.86)	0.073	149 (49.7%)	6.0
tory %)	19 (12.7%)	38 (25.3%)	49 (32.7%)	57 (38%)	<0.05		<0.05		<0.05							
					A allele	119 (39.7%)	141 (47.0%)				140 (46.7%)				151 (50.3%)	
					Genetic Model Analysis											
					Additive (GA vs GG)	56 (37.3%)	89 (59.3%)	8.29	2.13 (1.27–3.59)	0.004	82 (54.6%)	4.65	1.70 (1.05–2.77)	0.031	97 (64.6%)	13.
					Dominant (GG vs GA+AA)	56 (37.3%)	115 (76.7%)	6.25	1.98 (1.16–3.38)	0.012	111 (74.0%)	4.23	1.80 (1.03–3.15)	0.040	124 (82.7%)	9.7
					Recessive (AA vs GG+GA)	25 (16.7%)	22 (14.7%)	0.53	1.28 (0.79–2.96)	0.456	29 (19.3%)	1.32	1.53 (0.79–2.96)	0.250	27 (18.0%)	0.9
					Heterozygous (GA vs GG+AA)	89 (59.3%)	69 (46.0%)	5.51	1.85 (1.11–3.09)	0.019	82 (54.6%)	4.17	1.73 (1.02–2.93)	0.200	97 (64.6%)	7.4

Patients with T2DM, CAD and T2DM+CAD (N=150 each). Data is presented as Mean ± SD (continuous data) and frequency (%) (categorical data). For comparison of the control group vs. each patient group, statistically significant results are those with a p value <0.05.

3.2 Genotypic and Allelic Distribution of rs2230806

There was no deviation from Hardy-Weinberg equilibrium for the rs2230806 in all groups (HWE p>0.05; Table 3). There was a significant difference between the T2DM patients (26%) and controls (37.3%) regarding the GG genotype (χ^2=4.39, p=0.041). 'A similar trend was observed in CAD patients (26%; χ^2=5.32, p=0.070) and was strongest in T2DM+CAD patients (17.3%; χ^2=9.11, p=0.011). At the allelic level, the G allele frequency was significantly reduced in T2DM+CAD patients compared to controls (49.7% vs 60.3%; OR=1.54, 95% CI: 1.22–2.13, p=0.014)'.

'Significant associations were found with the genetic model analysis under both the dominant and heterozygote model. The GA genotype conferred significantly elevated risk for T2DM (OR=2.13, 95% CI: 1.27–3.59, p=0.004), CAD (OR=1.70, 95% CI: 1.05–2.77, p=0.031), and T2DM+CAD (OR=2.85, 95% CI: 1.61–5.05, p=0.001). Under the dominant model (GG vs GA+AA), significant associations were observed for T2DM (OR=1.98, p=0.012), CAD (OR=1.80, p=0.040), and T2DM+CAD (OR=2.62, p=0.002). There were no significant associations when the recessive model was used'.

Table 3. Genotypic and allelic distribution, and genetic model analysis of SNP rs2230806 in ABCA1 gene among he CAD, and T2DM+CAD after Bonferroni correctio

ealthy ontrols n=150)	T2DM Patients (n=150)	χ^2	OR (95% CI)	p	CAD Patients (n=150)	χ^2	OR (95% CI)	p	T2DM+CAD (n=150)	χ^2
bution										
					AA	53 (35.3%)	47 (31.3%)	0.49	-	0.782	51 (34.0%)	0.08	-	0.961	46 (30.7%)	0.9
					CA	72	75				73				75 (50.0%)	

3.3 Genotypic and Allelic Distribution of rs141420090

In all groups, HWE was confirmed for the following marker: rs141420090 (Table 4). No substantial differences were seen between the genotype or allele frequencies of any illness group and the control group (all p>0.05). No significant associations were found using genetic model analysis for the additive, dominant, recessive or heterozygous models. The results of these analyses were similar following Bonferroni correction.

Table 4. Genotypic and allelic distribution, and genetic model analysis of SNP rs141420090 in ABCA1 gene among healthy controls, T2DM, CAD, and T2DM+CAD patients. All comparisons were non-significant (p>0.05).

SNP rs141420090	Healthy Controls (n=150)	T2DM Patients (n=150)	χ^2	OR (95% CI)	p	CAD Patients (n=150)	χ^2	OR (95% CI)	p	T2DM+CAD (n=150)	χ^2
Genotype Distribution											
AA	53 (35.3%)	47 (31.3%)	0.49	-	0.782	51 (34.0%)	0.08	-	0.961	46 (30.7%)	0.9
CA	72	75				73				75 (50.0%)	

48.0%)	(50.0%)				(48.7%)				
5 16.7%)	28 (18.7%)				26 (17.3%)				29 (19.3%)
.711	0.694				0.720				0.707
tion									
78 59.3%)	169 (56.3%)	0.52	1.13 (0.86–1.49)	0.470	175 (58.3%)	0.04	1.04 (0.79–1.37)	0.841	167 (55.7%)
22 40.7%)	131 (43.7%)				125 (41.7%)				133 (44.3%)
Analysis (all p > 0.05 after Bonferroni correction)									
3 35.3%)	75 (50.0%)	0.36	1.12 (0.70–1.80)	0.548	73 (48.7%)	0.02	1.04 (0.65–1.67)	0.900	75 (50.0%)
3 35.3%)	103 (68.7%)	0.49	0.98 (0.66–1.46)	0.782	99 (66.0%)	0.08	1.01 (0.68–1.51)	0.961	104 (69.3%)
5 16.7%)	28 (18.7%)	0.20	0.87 (0.48–1.58)	0.652	26 (17.3%)	0.01	0.97 (0.53–1.77)	0.920	29 (19.3%)
2 48.0%)	75 (50.0%)	0.12	1.08 (0.70–1.66)	0.721	73 (48.7%)	0.01	1.02 (0.66–1.58)	0.920	75 (50.0%)

3.4 Association of rs2230806 Genotypes with Clinical Parameters

Analysis of rs2230806 genotypes with clinical parameters in T2DM patients revealed significant associations with BMI (GG: 26.34±3.34 vs GA+AA: 28.54±2.54; p=0.0001), FBG (p=0.020), and HbA1c (p=0.006). The BMI (p=0.0002) and HbA1c (p<0.0001) were significant in the T2DM+CAD group. The control and CAD groups showed no significant association between the genotypes of the rs2230806 polymorphism and clinical parameters (Table 5).

Table 5. Association of SNP rs2230806 genotypes (GG vs GA+AA) with clinical parameters across all groups. Values are Mean ± SD. *Statistically significant (p<0.05).

Clinical Parameter	Healthy (GG)	Healthy (GA+AA)	p	T2DM (GG)	T2DM (GA+AA)	p	CAD (GG)	CAD (GA+AA)	p	T2DM+CAD (GG)	T2DM+CAD (GA+AA)	p
Age (Years)	55.48 ±11.51	55.46 ±10.95	0.90	55.25 ±11.33	57.12 ±10.54	0.2	58.94 ±10.88	57.99 ±10.27	0.58	55.25 ±12.97	57.70 ±9.13	0.8
BMI (kg/m²)	26.46 ±3.08	27.60 ±2.33	0.0001*	26.34 ±3.34	28.54 ±2.54	0.0002*	27.79 ±3.89	27.57 ±3.03	0.690	25.67 ±3.51	23.73 ±2.71	0.0002*
DBP (mmHg)	78.44 ±5.48	77.55 ±6.40	0.3	79.17 ±5.85	76.27 ±6.48	0.006	79.48 ±6.51	78.20 ±7.34	0.259	80.82 ±6.56	82.88 ±6.40	0.053
SBP (mmHg)	128.34 ±4.01	127.41 ±4.00	0.14	123.70 ±3.74	124.90 ±3.94	0.698	124.27 ±4.40	123.91 ±3.70	0.589	124.23 ±3.66	123.46 ±3.61	0.691
FBG (mg/dL)	92.97 ±9.80	92.93 ±10.69	0.888	91.91 ±9.41	88.11 ±10.32	0.020*	95.09 ±9.23	94.30 ±10.21	0.621	92.79 ±9.52	90.84 ±9.34	0.206
TC (mg/dL)	174.92 ±74.97	175.18 ±70.52	0.982	175.78 ±73.98	177.88 ±75.75	0.864	179.53 ±70.46	179.47 ±69.31	0.996	175.91 ±79.16	176.14 ±72.15	0.985
TG (mg/dL)	103.66 ±51.31	104.33 ±52.59	0.937	103.61 ±51.38	102.42 ±53.52	0.890	103.61 ±51.38	102.42 ±53.52	0.955	100.96 ±46.87	101.58 ±59.27	0.943
HDL-C (mg/dL)	48.89 ±10.95	47.30 ±9.66	0.728	48.34 ±10.40	47.56 ±9.80	0.637	51.32 ±9.47	51.07 ±11.62	0.885	49.92 ±11.81	49.10 ±9.88	0.922

mg/dL)												
LDL-C (mg/dL)	101.45±76.02	101.37±70.79	0.994	102.34±75.78	103.47±76.92	0.928	101.16±70.67	99.80±83.93	0.914	101.91±70.56	102.31±90.31	0.976
HbA1c (%)	5.08±1.10	5.49±2.24	0.164	5.74±1.21	6.52±2.12	0.006*	7.36±1.37	7.33±2.40	0.910	4.33±1.16	2.55±1.98	<0.0001*
Fasting Insulin (µIU/mL)	10.70±9.06	10.54±8.88	0.915	11.10±8.76	12.34±9.54	0.408	11.54±8.72	12.81±9.54	0.397	9.83±9.21	9.48±10.07	0.822

No significant associations were observed between rs141420090 genotypes and clinical parameters in any group (all p>0.05; data not shown in Table 6 for brevity).

3.5 Haplotype Analysis

Four haplotypes (A–C, A–T, G–C and G–T) were found in the two polymorphic sites (rs2230806, rs141420090) in the haplotype analysis. There were no significant differences with the frequencies of the haplotypes between healthy controls, T2DM, CAD, or T2DM+CAD groups (Table 6). All haplotype ORs were near unity, indicating that there was no association at the haplotype level.

Table 6. Haplotype analysis of ABCA1 SNPs rs2230806 and rs141420090 in healthy controls, T2DM, CAD, and T2DM+CAD patients . CI = Confidence Interval.

Haplotype (rs2230806 – rs141420090)	Healthy Controls	T2DM	χ^2	OR (95% CI)	p	CAD	χ^2	OR (95% CI)	p	T2DM+CAD	χ^2	OR (95% CI)	p
A–C	44.8 (14.9%)	46.2 (15.4%)	0.21	1.03 (0.75–1.41)	0.790	45.6 (15.2%)	0.18	1.01 (0.74–1.39)	0.860	47.4 (15.8%)	0.31	0.98 (0.71–1.36)	0.858
A–T	41.4 (13.8%)	39.6 (13.2%)	0.26	0.95 (0.67–1.36)	0.780	40.8 (13.6%)	0.22	0.98 (0.69–1.39)	0.830	38.4 (12.8%)	0.27	1.05 (0.74–1.50)	0.652
G–C	138.6 (46.2%)	135.6 (45.2%)	0.34	0.96 (0.77–1.21)	0.740	136.8 (45.6%)	0.29	0.99 (0.79–1.24)	0.810	134.4 (44.8%)	0.38	1.04 (0.82–1.34)	0.534
G–T	75.2 (25.1%)	78.6 (26.2%)	0.33	1.07 (0.82–1.39)	0.620	76.8 (25.6%)	0.31	1.02 (0.78–1.34)	0.720	79.8 (26.6%)	0.33	0.96 (0.73–1.26)	0.819

4. Discussion

In the present case control study, the association of ABCA1 gene polymorphisms rs2230806 (R219K) and rs141420090 with susceptibility to the development of T2DM and CAD was evaluated in a North Indian population of Haryana state. A strong association was found for rs2230806 towards T2DM, especially in the dominant and additive genetic models, but not for rs141420090.

ABCA1 is an essential component of reverse cholesterol transport, responsible for the cholesterol and phospholipids exit from peripheral cells to ApoA-I, the initial step in the biogenesis of HDL.

The negative consequences of diminished ABCA1 activity encompass intracellular cholesterol buildup in pancreatic β-cells, resulting in endoplasmic reticulum stress, impaired insulin production, and ultimately β-cell demise, thus directly relating cholesterol dysregulation to T2DM. The R219K variant (G→A at codon 219) affects the conformation of the transporter, and diminishes the efficiency of cholesterol efflux, which may increase the risk of dyslipidaemia and insulin resistance in carriers.

The discovery of the association of rs2230806 with T2DM in Haryana population is similar to the report from other South-East Asian populations which showed similar association. The R219K variant has been associated with changes of HDL-C levels and insulin sensitivity in the Chinese Han [9] and Japanese populations [10] and has been reported to have a direct association with cardiometabolic risk. However, the results from the European studies differ from others [11] which found that K allele was protective against CAD and metabolic syndrome. In the current study, rs141420090 did not show any significant association with T2DM, CAD and their combination. The minor allele frequency of rs141420090 in the population studied may account for this finding as it has a relatively low minor allele frequency resulting in compromised powers to detect modest effect sizes. However, the rs141420090 may be a neutral variant in the North Indian genetic background. There is limited literature on this particular SNP and most of the large genome-wide association studies (GWAS) find no association with lipid traits or cardiometabolic outcomes.

Strenghts-The advantages of the present study are the well-characterized, multi-group case-control design with 600 cases in four clinically distinct groups, HWE confirmation for all SNPs, extensive genetic model analyses using Bonferroni correction and genotypic correlation with multiple biochemical parameters.

Limitations the case control design (cross sectional) with limited causal inference, the absence of genome wide ancestry data for full exclusion of population stratification, genotype confirmation based on gel image which is missing, and lack of in-vitro functional validation of the observed SNP effects.

5. Conclusion

The present study illustrates a significant association between the ABCA1 rs223086 (R219K) polymorphism and type 2 diabetes mellitus (T2DM), whereas the rs141420090 did not exhibit association with T2DM, CAD, T2DM with C polymorphisms in case and control individuals. The results indicate that the rs2230806 variant may affect the susceptibility to diabetes, mediated by the alteration of the ABCA1 cholesterol transport and glucose–lipid homeostasis. This result suggests that the lack of association with CAD may be because of the fact that the rs2230806 variant is more important for glucose metabolism than for the progression of atherosclerosis. In addition, the result of the absence of significant involvement of variant rs141420090 may underscore the variant-specific nature of ABCA1 genetic effects. In general, this study points to the potential use of ABCA1 rs2230806 as a genetic marker for T2DM, and highlights the importance of larger, multi-ethnic and functional studies to further clarify the contribution of ABCA1 polymorphisms to cardiometabolic diseases

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