Metabolism Open 26 (2025) 100364

Contents lists available at ScienceDirect

Metabolism Open

journal homepage: www.sciencedirect.com/journal/metabolism-open

Truncated variant rs373056577 confers increased risk of type 2 diabetes and missense variant rs121912717 is associated with hypertriglyceridemia in Bangladeshi population

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ARTICLE INFO

Keywords:
APOA1
APOA2
Type 2 diabetes
Polymorphism
Bangladeshi population

ABSTRACT

This study investigates the association of allelic and genotypic variations of rs121912717 and rs373056577 within APOA1 and APOA2 genes, respectively with the risk of type 2 diabetes (T2D). In this cross-sectional study, real-time quantitative PCR with specific Taqman probes was used to determine the genotypic and allelic frequencies of rs121912717 and rs373056577 in 300 unrelated Bangladeshi individuals (Healthy = 144, T2D patients = 156). Logistic regression analysis was performed to investigate the association of genotypic and allelic frequencies of these SNPs with respect to T2D under different inheritance models. Neither allelic nor genotypic frequencies of rs121912717 within APOA1 showed any significant association with T2D. Genotypes with respect to rs373056577 within APOA2 showed significant association with the risk of T2D under co-dominant heterozygous model (GG vs GA) [OR (95 %CI): 2.64 (1.32–5.59), p = 0.008], dominant [OR (95 %CI): 2.31 (1.24–4.49), p = 0.01] and over-dominant [OR (95 %CI): 2.62 (1.31–5.53), p = 0.008] models without adjusting for age, gender and BMI. After adjusting for age, gender and BMI, the A allele of rs373056577 showed significant association with T2D only in the dominant model [OR (95 %CI): 3.20 (1.12–10.51), p = 0.04]. Also, A allele of rs373056577 demonstrated significant association with the risk of T2D compared to allele G with [OR (95 %CI): 2.90 (1.15–8.14), p = 0.03] and without adjusting for confounders [OR (95 %CI): 1.97 (1.14–3.52), p = 0.02]. The genotypic frequency was significantly associated with T2D in codominant, dominant, and overdominant models in male participants when a gender-stratified analysis was conducted for rs373056577. However, when the logistic regression analysis was adjusted for age and BMI, the association was not significant in any of the models with respect to rs373056577 for male participants. On the other hand, gender-stratified regression analyses revealed no significant association with T2D before and after adjusting for age and BMI with respect to both allelic and genotypic frequencies of rs121912717. Individuals with CT genotype of rs121912717 had significantly higher triglyceride levels (322.2 mg/dL) compared to those harboring CC genotype (202.8 mg/dL) with or without adjusting for age, gender, BMI and disease status of the study participants. In conclusion, this study revealed that individuals harboring the allele A of rs373056577 possessed an increased risk of developing T2D and individuals having CT genotype of rs121912717 had increased triglyceride levels. The result of this study needs to be validated in a larger cohort for a more robust assessment.

1. Introduction

Diabetes mellitus is a metabolic disorder caused by insulin deficiency and/or insulin resistance characterized by hyperglycemia, polyphagia, polydipsia and weight loss [1]. The International Diabetes Federation (IDF) projects that 783 million people worldwide—roughly 1 in 8 adults, will be living with diabetes and 3 out of 4 of these adults are living in the low and middle-income countries [2]. As of 2021, the age-adjusted prevalence of diabetes of people aged 20–79 years was 14.2 % and the number was 13.1 million in Bangladesh [2]. Type 2 diabetes (T2D), the most predominant form of diabetes, is polygenic in nature and many genes contribute to the complex pathogenesis of T2D. Genome Wide

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https://doi.org/10.1016/j.metop.2025.100364
Received 8 February 2025; Received in revised form 29 March 2025; Accepted 13 April 2025
Available online 14 April 2025

Association Studies (GWAS) have played a major role in identifying genetic mutations that are associated with the risk of T2D. A recent multi-ancestry GWAS conducted by the DIAMANTE (DIAbetes Meta-ANalysis of Trans-Ethnic association studies) consortium revealed 238 significant T2D candidate loci corresponding to 338 association signals [3]. Based on the GWAS findings, the common missense variants within the candidate genes have been investigated more rigorously [4–6]. The number of studies that focus on exploring the contribution of infrequent and rare genetic variants to the polygenic disease mechanism of T2D is inadequate. But rare variants such as nonsense mutations can play a significant role in polygenic diseases. A study conducted in Saudi population found a nonsense polymorphism (R392X) in Toll Like Receptor-5 (TLR5) which conferred risk of diabetes but provided a protective role towards obesity [7]. Another study focused on Caucasian population revealed the link of a rare stop-gained mutation in the membrane glycoprotein CD36 with the risk of T2D and impaired insulin sensitivity [8]. A strong association of partial or total loss variants of Melatonin Receptor 1B (MTNR1B) with the risk of diabetes was evident in European population [9]. Such studies emphasize the necessity to investigate the link between rare genetic variants with the risk of developing a polygenic disorder such as T2D.

Apolipoproteins are the lipid transporting proteins and polymorphic anomalies in them have been found to be associated with resultant altered lipid profile, obesity, and T2D [10,11]. Among these apolipoproteins, only APOE polymorphisms have been extensively studied to elucidate more about the sex-specific polymorphic changes and the risk of diabetes found to differ based on dissimilarity in sex [12,13].

Apolipoprotein A-1 (APOA1) (11q23-q24) and A-2 (APOA2) (1q23.3) are the first and second major constituents of HDL, respectively. APOA1 containing HDL, interacts with peripheral tissues to acquire cholesterol through a transport process facilitated by ATP-binding cassette protein 1 (ABC1) [14]. APOA2 impairs the reverse cholesterol function and antioxidant activity of HDL [15]. Among APOA1 SNPs, two missense variants G75A and C83T are the most extensively studied [16]. G75A exhibited protective effect against CVDs in Chinese population [17] but was linked to Schizophrenia in a Korean Population [18]. AA genotype of this MSP1 polymorphism was also linked with T2D in Spanish Population [19]. There have been few studies where the risk association of APOA1 polymorphisms with metabolic syndrome was investigated within gender-based sub-groups [20,21]. For instance, in a Turkish population, the G75A polymorphism was found to be linked with atherogenic dyslipidemia and elevated blood pressure only in the male [20]. Another study conducted on Caucasian population reported both the G75A and C83T to exert significant effect on plasma Apo-A1 protein variation only in male [21]. These studies suggest that the effect of APOA1 polymorphisms can be gender specific. The C83T polymorphism has also been found to be associated with metabolic indices like levels of ApoA1 protein level [21], HDL [22], higher body mass index (BMI) and waist-to-hip ratio (WHR) in obesity [23] and early-onset of T2D [24]. Our SNP of interest, missense variant rs121912717 hasn't been studied in any ethnicities in association with T2D; but had been mentioned in an Austrian study with an aim to investigate its link to premature atherosclerosis [25]. Strobl et al. identified five additional individuals with rs121912717 (C > T) among 20 family members (spanning three generations) of a 15-year-old girl with type IIa hyperlipoproteinemia, who carried the mutated allele [25]. Recently in a study conducted among the Korean population, this missense variant was found to be linked with metabolic syndrome [26]. NGS analysis conducted by Lee et al. identified 10 rare variants in four genes (APOA1, APOA4, APOC2, and LMF1) associated with hypertriglyceridemia. Among the 10 rare variants, rs121912717 (C > A) was one of them [26].

Association of T2D with the chromosomal location of 1q21-q23 harboring APOA2 has been comprehensively investigated in British [10], French [27], Pima Indians [28] and US European [29] populations. T265C (rs5082) in APOA2 gene has been reported to be associated with altered lipid profiles [10] in patients with T2D and exacerbation towards risk of obesity [11]. rs373056577 (G > A) within APOA2 is a nonsense SNP, which has not been studied so far in any population. Genome Wide Association Studies (GWAS) have been focusing more on the possible link between nonsense novel SNPs and multifactorial diseases like T2D [28–31]. Due to the association of excess bodyweight with insulin resistance and resultant T2D, we perceive the necessity to focus more on rare and infrequent SNPs which are located within apolipoproteins as they are involved with lipid transportation. To the best of our knowledge, the associations of the two SNPs (rs121912717 and rs373056577) have not been studied with the risk of T2D in Bangladeshi population. Therefore, we aim to investigate the associations of rs121912717in APOA1 and rs373056577 in APOA2 with T2D and further investigate their associations on the basis of gender differences.

2. Methods

2.1. Subject selection and sample collection

This case-control study consisted of 300 unrelated Bangladeshis. Among them, 156 individuals (52 %) suffering from T2D were recruited from BIRDEM (Specialized Diabetes Hospital). The remaining 144 (48 %) subjects without diabetes (healthy controls) were teachers, graduate students and hospital personnel without any history of diabetes or any other chronic diseases of kidney or liver. This study was approved by the ethical review committee of Department of Biochemistry and Molecular Biology, University of Dhaka. All participants were recruited only after getting their full consent. Each participant filled up a structured questionnaire with details about their age, gender, height, weights, systolic and diastolic blood pressure. T2D patients were confirmed clinically using the levels of fasting plasma glucose (FPG) (≥7.0 mmol/L or 126 mg/dL) and HbA1C (≥6.5 %), according to World Health Organization (WHO) criteria.

With the help of an expert phlebotomist, approximately 4–5 ml venous blood was collected into EDTA (Ethylene Di-amine Tetra-acetic Acid) containing tubes from all participants. The EDTA tubes were centrifuged at 4000 rpm for 10 min. Plasma and cellular parts were separated and stored at −80 °C. The separated cellular and plasma portions have been used for genomic DNA extraction and biochemical parameters [lipid profiling] testing, respectively.

2.2. Assay of biochemical parameters

FPG (Fasting Plasma Glucose) and HbA1C (Glycated Hemoglobin) were measured using standard GOD-PAP and HPLC methods (Bio-Rad Laboratories, USA)], respectively. Levels of triglyceride (TG), total cholesterol and HDL were measured using CHEMELEX kit. (S.A. Pol. Ind. Can Castells) with spectrophotometric method in the Thermo-Scientific GENESYS-20 at 505 nm. LDL was determined according to Friedewald's formula [32].

2.3. Genomic DNA extraction and genotyping

Genomic DNA was extracted from stored cellular fractions of blood samples by organic method as described previously [33,34]. Both APOA1 missense variant rs121912717 and APOA2 nonsense variant rs373056577 were genotyped using Applied Biosystems™ TaqMan® SNP Genotyping Assay Mix (APOA1: C_161029974_10, APOA2: C_357391154_10). PCR reaction volume of 10 μL consisted of 2.5 μL TaqMan genotyping master mix, 0.125 μL TaqMan genotyping assay mix, 2.625 μL PCR- H_2O and 4.7 μL template DNA. In control, PCR- H_2O was used in place of template DNA. Amplification took place in Applied Biosystems 7500 fast real-time PCR instrument in a condition of 1 cycle of initial denaturation for 10 min at 95 °C followed by 35 cycles of denaturation for 15 s at 60 °C, annealing and elongation at 60 °C for 1

min and cooling down for at least 10 min at 4 °C. Genotyping analyses were programmed in Applied Biosystems 7500 software v2.3 via allelic discrimination plot. The quality of each experiment was controlled using appropriate negative controls and repetition of samples. The overall call rate of each genotype was 98 %.

2.4. Statistical analyses

For association studies, a web-based tool SNPStats (https://www.snpstats.net/start.htm) based on R packages [35] and haplo.stats [36] was used under different genetic inheritance models: codominant, dominant, recessive and over dominant models. The data have been summarized as genotype and allele frequencies, proportions, and OR with a 95 % CI. Demographic data and clinical parameters were analyzed using R programming language where the results were expressed as mean ± SD for continuous variables and as percentages or frequencies for categorical variables. Independent student's t-test was conducted to determine the significance of the mean difference between two groups. Univariate linear regression analysis was used to evaluate the association of the level of lipid profile parameters (cholesterol, triglyceride, HDL and LDL) with the genotypes of rs121912717 and rs373056577. Multivariate linear regression was done to adjust for other confounders like age, gender, BMI and the disease status. Univariate logistic regression analysis was done to evaluate the association of the disease status with the allelic and genotypic frequencies of rs121912717 and rs373056577. Multivariate logistic regression analysis was done to adjust for other possible confounders like age, gender and BMI.

3. Results

3.1. Demographic, anthropometric and biochemical characteristics of the study participants

Demographic data of the study participants has been demonstrated in Table 1. Out of 300 study participants, 144 (48 %) were healthy individuals and the rest of the 156 (52 %) were individuals with T2D. Among healthy individuals, 77 (53.47 %) were male and 67 (46.53 %) were female while 80 (51.28 %) male and 76 (48.72 %) female patients had T2D. Among the anthropometric parameters, age and BMI varied significantly between control and T2D patients (Table 1). Age varied significantly between control and T2D patients in gender-specific male and female groups. BMI varied significantly when the total participants were concerned, but in terms of gender-specific classification, this parameter varied significantly among the control and T2D patients only in female group. Again, such sex-specific variability was observed in terms of systolic blood pressure (SBP) which did not vary significantly between control and T2D groups in male participants whereas the difference in SBP was significantly different between controls and T2D in female participants. Contrary to SBP, diastolic blood pressure (DBP) varied significantly between the two groups in both male and female groups. Among the lipid profile parameters, the levels of TG and LDL varied significantly between healthy individuals and patients with T2D. When patients were stratified according to male and female participants, the mean level of TG varied significantly between these two groups in only female participants while the mean levels of LDL varied significantly only in case of males. For HDL and total cholesterol, the differences were not statistically significant between control and T2D patients (Table 1).

3.2. Frequency distribution and disease risk evaluation of APOA1 rs121912717 and APOA2 rs373056577 genotypes and alleles in the study participants

The associations of genotypic and allelic frequencies with T2D in terms of both SNPs are shown in Table 2. The frequency distributions of homozygous (CC), heterozygous (CT) and mutant homozygous (TT) with respect to rs121912717 were found to be 284, 15 and 1, respectively when all 300 participants were considered. The distribution of the different genotypes within healthy individuals and T2D is shown in Table 2. On the other hand, frequency distribution of wild type (GG), heterozygous (GA) and double mutant homozygous (AA) genotypes with respect to rs373056577 were 249, 42 and 9 in the study participants (Table 2).

Statistical analysis revealed neither allelic nor genotypic frequencies (under any model of inheritance) with respect to rs121912717 had any significant association with T2D. On the other hand, genotypic frequencies with respect to rs373056577 showed significant association with the risk of developing T2D under co-dominant heterozygous model (GG vs GA) [OR (95 %CI): 2.64 (1.32–5.59); p = 0.008], dominant [OR, 95 %CI: 2.31 (1.24–4.49); p = 0.01] and over-dominant [OR, 95 %CI: 2.62 (1.31–5.53); p = 0.008] models without adjusting for age, gender and BMI. After adjusting for age, gender and BMI, the A allele of rs373056577 showed significant association with T2D only in the dominant model [OR (95 %): 3.30 (1.15–10.91); p = 0.04]. Also, mutant A allele of rs373056577 showed significant association with the risk of developing T2D [OR, 95 %CI: 1.97 (1.14–3.52); p = 0.02] as shown in Table 2. The association remained significant even after adjusting for confounding factors [OR, 95 %CI: 2.90 (1.15–8.14), p = 0.03].

3.3. Frequency distribution and disease risk evaluation of APOA1 rs121912717 and APOA2 rs373056577 genotypes and alleles in male and female study participants

In case of rs121912717, neither the allelic nor the genotypic

Table 1
Demographic and anthropometric characteristics of all study participants.

Parameters	Control (total), n = 144	T2D (total), n = 156	p	Male (control), n = 77	Male (T2D), n = 80	p	Female (CN), n = 67	Female (T2D), n = 76	p
Age (years)	32.48 ± 12.55	51.38 ± 10.41	<0.01	33.53 ± 12.38	52.83 ± 9.88	<0.01	31.06 ± 12.82	50.07 ± 10.73	<0.01
BMI (weight/m^2)	24.33 ± 3.52	26.26 ± 2.62	<0.01	24.82 ± 3.54	25.08 ± 1.97	0.64	23.68 ± 3.43	27.49 ± 2.67	<0.01
SBP (mmHg)	118.90 ± 9.35	124.39 ± 10.01	<0.01	121.96 ± 8.06	124.00 ± 9.76	0.21	114.86 ± 9.51	124.80 ± 10.31	<0.01
DBP (mmHg)	78.27 ± 8.98	85.32 ± 5.76	<0.01	80.65 ± 8.98	85.25 ± 5.56	<0.01	75.14 ± 8.09	85.39 ± 5.99	<0.01
FPG (mmol/L)	5.07 ± 0.33	9.54 ± 3.38	<0.01	5.08 ± 0.34	9.05 ± 2.71	<0.01	5.05 ± 0.33	10.06 ± 3.92	<0.01
HbA1c (%)	5.55 ± 0.32	8.92 ± 1.96	<0.01	5.60 ± 0.24	8.85 ± 1.84	<0.01	5.49 ± 0.38	9.00 ± 2.08	<0.01
Triglyceride (mg/dL)	179.39 ± 92.00.	217.77 ± 136.67	0.03	202.11 ± 102.07	233.61 ± 171.41	0.26	151.5 ± 70.50	200.10 ± 84.27	0.01
Total cholesterol (mg/dL)	180.10 ± 34.54	189.29 ± 54.03	0.16	185.11 ± 36.86	185.17 ± 49.96	1.00	173.95 ± 31.20	193.63 ± 58.02	0.04
HDL(mg/dL)	39.92 ± 11.10	40.91 ± 17.65	0.64	36.04 ± 7.29	39.67 ± 16.77	0.12	44.68 ± 13.15	42.22 ± 18.55	0.49
LDL(mg/dL)	120.98 ± 38.15	104.82 ± 55.29	0.02	128.76 ± 41.49	98.78 ± 54.36	<0.01	111.45 ± 31.99	111.19 ± 55.91	0.98

CN: Healthy Individuals; T2D: Type 2 Diabetes; BMI: Body Mass Index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; FPG: Fasting plasma glucose; HbA1c: Glycated hemoglobin; HDL: High density lipoprotein; LDL: Low density lipoprotein.

Table 2
Association of genotypic and allelic frequencies with respect to rs121912717 (APOA1) and rs373056577 (APOA2) in the study participants.

rs121912717							
Models	Genotypes	CN (n = 144)	T2D (n = 156)	OR (95 % CI)	p	OR[a] (95 % CI)	p[a]
Co-dominant	CC	139	145	1			
	CT	5	10	1.92 (0.84–6.28)	0.25	3.60(0.48–80.1)	0.29
	TT	0	1	NA (0.00 – NA)	0.99	NA (0.00 – NA)	0.99
Dominant	CC	139	145	1		1	
	CT + TT	5	11	2.11(0.75–6.84)	0.18	3.75 (0.51–82.49)	0.27
Recessive	CC + CT	144	155	1		1	
	TT	0	1	NA(0-NA)	0.99	NA(0-NA)	0.99
Over-dominant	CC + TT	139	146	1			
	CT	5	10	1.9 (0.66–6.24)	0.25	3.60 (0.48–80.33)	0.29
Allele	C/T	283/5	300/12	2.26 (0.83–7.19)	0.13	3.80 (0.55–81.5)	0.26
rs373056577							
Co-dominant	GG	128	121	1		1	
	GA	12	30	2.64 (1.32–5.59)	0.008	3.31 (1.03–13.09)	0.06
	AA	4	5	1.32 (0.34–5.45)	0.68	2.86 (0.39–31.86)	0.34
Dominant	GG	128	121	1		1	
	GA + AA	16	35	2.31 (1.24–4.49)	0.01	3.20 (1.12–10.51)	0.04
Recessive	GG + GA	140	151	1		1	
	AA	4	5	1.15 (0.30–4.76)	0.83	2.51 (0.34–28.44)	0.41
Over-dominant	GG + AA	132	126	1		1	
	GA	12	30	2.62 (1.31–5.53)	0.008	3.18 (0.99–12.54)	0.07
Allele	G/A	268/20	272/40	1.97 (1.14–3.52)	0.02	2.90 (1.15–8.14)	0.03

CN: Healthy Individuals; T2D: Type 2 Diabetes; OR: Odds ratio; CI: Confidence intervals; OR[a]: Odds ratio adjusted for age, gender and bmi, p[a]: p-value adjusted for age, gender and bmi.

distributions were associated with T2D in males or females with or without adjustments for possible confounders. The A allele of rs373056577 in male study participants was found to be significantly associated with T2D in codominant heterozygous, dominant and over-dominant models (Table 3) without any adjustments. However, after adjusting for confounders there was no significant association of the genotypic distribution of rs373056577 in the male participants under any genetic inheritance model. The A allele of rs373056577 was not found to be significantly associated with T2D in female participants with or without adjusting for confounders in any of the genetic inheritance models (Table 4).

The alleles T and A of rs121912717 and rs373056577, respectively were not significantly associated with T2D in male participants with or without adjusting for confounders (Table 3). The T allele of rs121912717 was not found to be significantly associated with T2D in female participants with or without adjusting for confounders. However, the A allele of rs373056577 was found to be significantly associated with T2D after adjusting for age and BMI in female participants [Table 4; OR (95 %CI): 7.04 (1.37–48.17), p = 0.03].

3.4. Evaluation of the association of the lipid profile parameters with the genotypes of rs121912717 and rs373056577

The mean (±SD) levels of cholesterol, triglyceride, HDL and LDL with respect to genotypic distributions of rs121912717 and rs37305677 are shown in Table 5 There was a significant association between the

Table 3
Association of genotypic and allelic frequencies with respect to rs121912717 (APOA1) and rs373056577 (APOA2) in male participants.

rs121912717							
Models	Genotypes	CN (n = 77)	T2D (n = 80)	OR (95 % CI)	p	OR[a] (95 % CI)	p[a]
Co-dominant	CC	73	74	1		1	
	CT	4	5	1.23 (0.31–5.15)	0.76	2.34 (0.20–67.75)	0.55
	TT	0	1	NA (0-NA)	0.99	NA (0-NA)	0.99
Dominant	CC	73	74	1		1	
	CT + TT	4	6	1.48 (0.41–5.99)	0.56	2.42 (0.22–69.07)	0.53
Recessive	CC + CT	77	79	1		1	
	TT	0	1	NA (0-NA)	0.99	NA (0-NA)	0.99
Over-dominant	CC + TT	73	75	1		1	
	CT	4	5	1.22 (0.31–5.08)	0.78	2.34 (0.20–68.03)	0.55
Allele	C/T	150/4	153/7	1.72 (0.51–6.66)	0.4	2.47 (0.24–67.49)	0.52
rs373056577							
Co-dominant	GG	68	60	1		1	
	GA	7	18	2.91 (1.18–7.94)	0.03	3.14 (0.73–17.32)	0.15
	AA	2	2	1.13 (0.13–9.68)	0.9	0.94 (0.07–22.73)	0.96
Dominant	GG	68	60	1		1	
	GA + AA	9	20	2.52 (1.09–6.21)	0.04	2.43 (0.66–10.77)	0.2
Recessive	GG + GA	75	78	1		1	
	AA	2	2	0.96 (0.11–8.18)	0.99	0.80 (0.06–19.33)	0.87
Over-dominant	GG + AA	70	62				
	GA	7	18	2.90 (1.18–7.89)	0.03	3.15 (0.74–17.32)	0.15
Allele	G/A	143/11	138/22	2.07 (0.99–4.59)	0.06	1.89 (0.61–6.85)	0.29

CN: Healthy Individuals; T2D: Type 2 Diabetes; OR: Odds ratio; CI: Confidence intervals; OR[a]: Odds ratio adjusted for age and BMI, p[a]: p-value adjusted for age and BMI.

Table 4
Association of genotypic and allelic frequencies with respect to rs121912717 (APOA1) and rs373056577 (APOA2) in female participants.

rs121912717							
Models	Genotypes	CN (n = 67)	T2D (n = 76)	OR (95 % CI)	p	OR[a] (95 % CI)	p[a]
Co-dominant	CC	66	71	1		1	
	CT	1	5	4.65 (0.71–90.29)	0.17	NA (0-NA)	0.99
	TT	0	0	–	–	–	–
Dominant	CC	66	71	1	0.17	1	
	CT + TT	1	5	4.65 (0.71–90.29)		NA (0-NA)	0.99
Recessive	CC + CT	67	76	1	–	1	–
	TT	0	0	–		–	
Over-dominant	CC + TT	66	71	1	0.17	1	0.99
	CT	1	5	4.65 (0.71–90.29)		NA (0-NA)	
Allele	C/T	133/1	147/5	4.52 (0.72–87.3)	0.17	NA (0-NA)	0.99
rs373056577							
Co-dominant	GG	60	61				
	GA	5	12	2.36 (0.82–7.79)	0.13	3.09 (0.44–62.69)	0.33
	AA	2	3	1.48 (0.24–11.50)	0.68	13.69 (0.68–464.62)	0.1
Dominant	GG	60	61	1			
	GA + AA	7	15	2.11 (0.83–5.86)	0.13	2.56 (0.69–11.52)	0.1
Recessive	GG + GA	65	73	1			
	AA	2	3	1.34 (0.21–10.38)	0.76	12.73 (0.62–428.39)	0.11
Over-dominant	GG + AA	62	64	1			
	GA	5	12	2.33 (0.81–7.66)	0.13	2.81 (0.41–56.52)	0.36
Allele	G/A	125/9	134/18	1.87 (0.83–4.50)	0.14	7.04 (1.37–48.17)	0.03

CN: Healthy Individuals; T2D: Type 2 Diabetes; OR: Odds ratio; CI: Confidence intervals; OR[a]: Odds ratio adjusted for age, gender and BMIi, p[a]: p-value adjusted for age, gender and BMI.

Table 5
Association of genotypes of rs121912717 and rs373056577 with parameters of lipid profile.

rsID	Genotypes	Lipid profile parameters (Mean ± SD)											
		Cholesterol (mg/dL)	p	p[b]	Triglyceride (mg/dL)	p	p[b]	HDL (mg/dL)	p	p[b]	LDL (mg/dL)	p	p[b]
rs121912717	CC	186.72 (±50.72)	–	–	202.83 (±91.37)	–	–	40.72 (±16.64)	–	–	109.66 (±50.17)	–	–
	CT	197.64 (±39.83)	0.48	0.52	322.21 (±398.28)	0.003	0.004	39.38 (±10.26)	0.79	0.69	93.81 (±81.84)	0.33	0.48
	TT	144.00 (±NA)	0.4	0.34	72.00 (±NA)	0.3	0.24	46.00 (±NA)	0.75	0.45	83.60 (±NA)	0.62	0.48
rs373056577	GG	178.90 (±51.28)	–	–	193.85 (±42.02)	–	–	31.78(±9.24)	–	–	108.35 (±44.34)	–	–
	GA	199.69 (±48.00)	0.12	0.15	241.69 (±98.55)	0.11	0.25	41.52 (±17.08)	0.81	0.79	112.36 (±55.62)	0.66	0.38
	AA	184.85 (±50.44)	0.79	0.71	202.50 (±134.32)	0.88	0.62	40.77 (±16.31)	0.23	0.25	107.97 (±51.86)	0.99	0.87

HDL: High density lipoprotein, LDL: Low density lipoprotein, p_b: p-value adjusted for age, gender, BMI and the disease status (control or T2D).

triglyceride (TG) level and the genotypic distribution of rs121912717. The individuals harboring the CT genotype of rs121912717 had significantly higher TG levels compared to those harboring CC genotype with or without adjusting for confounders like age, gender, BMI and disease status of the study participants (Table 5).

4. Discussion

Early detection and management of diabetes will facilitate reduction of the mortality rate and cost related liabilities associated with the disease. For speeding up proper management and treatment of this disease and associated complications, identification of risk factors is a prerequisite. It is now well evident that both genetic and environmental factors like lifestyle, obesity etc. are the pivotal risk elements that cause T2D [1]. Being a polygenic disease, population-based studies focus more on elucidating the link of common genetic markers associated with risk of diabetes. But the contribution of rare novel variants in T2D is often overlooked. Rare variants are suggested to play a significant role in complex diseases [37,38]. The synergistic effect of multiple rare variants from different genes can confer a detectable risk for a polygenic disorder according to the 'common disease-rare variant' hypothesis [39]. Another important fact is that the effect of rare variants can be very population specific as they often are caused by genetic drift. For instance, the rare variant rs200185429 in SLC30A8 conferred a protective role against diabetes in Finnish population [40] but no such association was found in Bangladeshi populations [41]. For these reasons, we had investigated less-studied rare variants with the risk of T2D in Bangladeshi population. The associations of rs121912717 and rs373056577 with T2D were investigated in Bangladesh population under different genetic models of inheritances (co-dominant, dominant, over-dominant, recessive). As apolipoproteins are involved in fat distribution [42], obesity [10] and concomitantly with insulin resistance [11], we perceived the necessity to focus more on the polymorphisms present in the major HDL apolipoproteins.

Reduced plasma concentration of HDL and low plasma levels of APOA1 are one of the hallmarks of insulin resistance [43]. Among the APOA1 polymorphisms, 2 MSP1 polymorphisms (G75A, rs1799837 and C83T, *rs*5069) were found to have inconsistent findings with respect to their association with dyslipidemia and accompanying heart diseases in Chinese [16], Assamese [44], Finnish [45] and Omani [46] ethnicities. Liao et al. found association of G75A, rs1799837 with the lower risk of heart diseases in Chinese population because of its effect on higher

serum concentrations of APOA1 and HDL-C [16] whereas Bora et al. found no effect of rs1799837 (G75A) and rs5069 (C83T) on HDL concentration but found them to be possible modulator of CVD risk factors in Assamese people [44]. In Finnish population, rs5069 polymorphism was found to be associated with elevated levels of apolipoprotein and HDL in non-diabetic patients [45] but in Omani population the elevated levels of those parameters were associated with diabetes [46]. The exact mechanism of how these polymorphisms work is still not clearly elucidated but, epigenetic changes such as hypomethylation, which occur in the T and/or A substitution can possibly increase APOA1 expression [47]. Such incongruous findings in different populations can also be influenced by anthropometric and environmental factors [43,48]. A possible link between the rs1799837 and T2D may lie in the hormonal and metabolic signaling pathways that regulate APOA1 expression at transcriptional level. The A allele carriers had higher transcription efficiency compared to G allele containing homozygotes. The inconsistency in the promoter region may contribute to enhanced binding of glucose which would suppress the expression of APOA1 protein [49]. In contrast to the well-studied rs1799837 and *rs*5069, our study interest rs121912717 is a less studied SNP which has not been investigated any ethnicities so far with respect to T2D. The population genetic data with respect to rs121912717 was not concordant among different databases (Supplementary Table 1). Allele Frequency Aggregator (ALFA) and ExAC (Exome Aggregation Consortium) databases showed the mutant T allele to be absent in the Asian population [50]. The frequency of the T allele was very low as found in two GWAS studies on Japanese population. There is also discrepancy about the presence of this variant in African and European sub-groups. According to the population frequency data in ALFA database, the mutant T allele was absent in European population but was present in African population. Whereas the data in ExAC database, listed the presence of the mutant T allele in European population but found it to be absent in African sub-group [50].

In a recent study in Korean population, next-generation sequencing revealed the missense SNP rs121912717 (c.664C > A) to be linked with hypertriglyceridemia [26]. Their findings corroborated our findings observed in Bangladeshi population. Similar to their discovery we observed that individuals harboring the CT genotype of rs121912717 had significantly higher levels of triglyceride compared to those harboring CC genotype with and without adjusting for confounders like age, gender, BMI and disease status of the study participants (Table 5). Another important finding is that neither allelic nor genotypic frequencies of rs121912717 within APOA1 showed any significant association with T2D in Bangladeshi population. Further, gender-based stratification showed no significant risk association under any inheritance models among healthy and T2D populations in either of the male or female groups for rs121912717.

Strobl et al. investigated the effect of the rs121912717 mutation with dyslipidemia and risk of premature atherosclerosis within Austrian population and found hyperlipoproteinemia of types IIa, IIb, or IV in most of the affected kindred [25]. The association between rs121912717 and hyperlipoproteinemia was not consistent [25]. Strobl et al. also concluded that the HDL level is not significantly influenced by this variant although the level of HDL was found to be decreased in individuals with the heterozygous genotypes [25]. In the Bangladeshi cohort, we didn't observe HDL levels to vary significantly among the different genotypes with or without adjusting for confounders (Table 5). In contrast to our study, Strobl et al. and Lee et al. didn't conduct gender specific investigation of rs121912717 with T2D [25,26]. But gender-specific link of other APOA1 polymorphisms in Turkish and Caucasian populations with dyslipidemia were already reported [20,21]. Such findings encouraged us to investigate whether such gender-specific patterns occur for this rare novel APOA1 variant in Bangladeshi population.

The protein APOA2 impairs the reverse cholesterol transport. According to dbSNP database, there are 1842 SNPs located within APOA2 gene [51]. But only the association of one polymorphism in the promoter region −265T/C (rs5082) has been studied rigorously with respect to T2D [24–26]. Lara-Castro et al. found that T265C in APOA2 was associated with amount of abdominal fat deposition in women [52] and Erfan et al. found the SNP to be associated with waist circumference in men [53]. Animal model studies also provided evidence for the role of ApoA2 proteins in glucose homeostasis. ApoA2 deficient mice showed improved insulin sensitivity [54], while transgenic mice overexpressing murine ApoA2 showed insulin resistance and obesity [55]. Such studies insinuate a link among APOA2, obesity and insulin responses. APOA2 containing genomic region was found to be a candidate locus for T2D in diverse populations, but these studies did not focus on any SNP of APOA2 [27–29]. Although most GWAS studies put more emphasis on SNPs in coding regions, a meta-analysis of 4 European populations showed that SNPs located in the non-coding regions of APOA2 can also be linked to T2D [56–58]. These findings corroborate our findings of possible link between nonsense SNP within APOA2 with T2D. The rs373056577 is a rare APOA2 variant and according to different databases, it has been found within European population across all of them (Supplementary Table 2) [59]. The ALFA and the PAGE databases found the presence of the mutant allele in Asian population, but the ExAC study reported the absence of the mutant allele in their Asian sub-group. Again, these inconsistent findings may arise due to the heterogeneity across the sample populations. The mutant A allele showed significant association with the risk of developing T2D as shown in Table 2. The association remained significant even after adjusting for confounding factors (Table 2). Further gender-based genotypic frequency analysis showed this SNP to be associated with the risk of T2D in crude analysis when only male participants were concerned. Gender-specific roles have already been observed in terms of other genetic loci [60,61], but the underlying mechanism is still obscured. One possible explanation of such gender-specific association can be attributed to the influence of environmental factors such as dietary intake. In the current study we didn't investigate the association of any environmental factors on genotypes. But dietary intake has been found to be an influencing factor of APOA2 polymorphic variants in different populations. For instance, higher quantity of saturated fat intake showed significant differences of anthropometric variable in different genotypes of APOA2 promoter (−265T/C) variant in Mediterranean and Asian populations. But lower saturated fat intake did not confer such effect on different genotypes [62]. So, the possibility that difference of dietary intake between male and female population can affect their risk of T2D in different genotypes cannot be dismissed.

Genotypic frequencies with respect to rs373056577 showed significant association with the risk of developing T2D under co-dominant heterozygous model (GG vs GA), dominant and over-dominant models without adjusting for age, gender and BMI. After adjusting for age, gender and BMI, the A allele of rs373056577 showed significant association with T2D only in the dominant model. Also, mutant A allele of rs373056577 showed significant association with the risk of developing T2D which remained significant even after adjusting for confounding factors. The codominant and overdominant models might be more sensitive to confounders compared to the dominant model. Moreover, the dominant model deals with the presence of the A allele as a risk factor which reflects the true effect of genetic variant after confounder adjustment. Since dominant model combines homozygotes and heterozygotes together compared to co-dominant and overdominant models, this might result in increased statistical power compared to the other two models and hence retaining of statistical significance after adjustment.

In this study, the A allele of rs373056577 in male study participants was found to be significantly associated with T2D in codominant heterozygous, dominant and over-dominant models (Table 3) without any adjustments. However, after adjusting for confounders there was no significant association of the genotypic distribution of rs373056577 in the male participants under any genetic inheritance model. The loss of significance of the association of genotypic frequencies of rs373056577

with T2D after confounder adjustment in males might imply that the initial significant association was confounded by age and BMI in male participants. The genotypic frequency of rs373056577 was not found to be significantly associated with T2D under any genetic inheritance models in female participants with or without adjusting for confounders (Table 4).The A allele of rs373056577 was found to be significantly associated with T2D after adjusting for age and BMI in female participants. The emergence of significant association after adjusting for confounders implies a stronger influence of the confounders with respect to the association of A allele of rs373056577 with T2D when age and BMI were considered. This depicts a possible gene-environment interaction in case of female participants where the environmental factors (age, BMI) might interact with the rs373056577 to increase the risk of T2D in female participants.

In this study, the truncated variant rs373056577 was found to be linked with the risk of type 2 diabetes and the variant rs121912717 was found to be associated with hypertriglyceridemia in Bangladeshi population. This study offers great insights into the role of APOA1 and APOA2 variants in type 2 diabetes (T2D) and their association with metabolic factors such as triglyceride levels. However, it is important to mention the limitations of the study. The sample size of the study was not calculated prior to the study, which might impact the generalizability of the findings. However, the adjustment for possible confounders in the underlying statistical analyses employed increased the robustness of the study. Our study is a cross-sectional study and hence the causal relationship between the genetic variants and T2D or hypertriglyceridemia cannot be established. Longitudinal studies are required to establish the causal relationship between the variants and T2D or any metabolic parameters. However, our study provides the underlying foundation for future studies that certain variants within APOA1 and APOA2 genes might be associated with metabolic conditions like T2D and hypertriglyceridemia. The gender-stratified analyses resulted in decreased sample size in each group which increased the risk of both Type II (false negative) and Type I (false positive) errors. Hence the results obtained in male and female subgroups should be considered with caution. Moreover, an expanded study with a larger number of study participants and meta-analyses will help to solidify the findings. Large scale studies along with the quantification of ApoA1 and ApoA2 proteins in serum will help to elucidate whether these SNPs are affecting the lipoproteins in serum.

CRediT authorship contribution statement

Shomoita Sayed: Writing – original draft, Methodology, Investigation. **Abdullah Al Saba:** Writing – review & editing, Validation, Formal analysis. **Imrul Hasan:** Validation, Methodology. **Rafia Rahat:** Investigation, Data curation. **Mohammad Sayem:** Visualization, Project administration. **Akio Ebihara:** Resources, Funding acquisition. **A.H.M. Nurun Nabi:** Writing – review & editing, Writing – original draft, Supervision, Funding acquisition, Conceptualization.

Data availability statement

The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgement

Part of this study was supported by the United Graduate School of Agricultural Sciences, Gifu University, Japan (Grant#2019–2020). Shomoita Sayed received student fellowship from the Ministry of Science and Technology, Government of People's Republic of Bangladesh (Grant#2018–2019). Authors want to thank the participants of the study who willingly donated their blood to carry on the research work smoothly.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.metop.2025.100364.

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