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The effect of *APOA5* and *APOC3* variants on lipid parameters in European Whites, Indian Asians and Afro-Caribbeans with type 2 diabetes

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Abstract

Common variants in *APOA5* and *APOC3* have been associated with differences in plasma triglyceride (TG) levels in healthy individuals. The aim of this study was to examine the association of *APOA5* (−1131T>C, S19W) and *APOC3* (−482C>T, 1100C>T) polymorphisms in patients with type 2 diabetes (T2D) of European White (EW) (n=931), Indian Asian (IA) (n=610) and Afro-Caribbean (AC) (n=167) origin, with lipid and T2D parameters. Rare allele frequencies and linkage disequilibrium differed significantly amongst ethnic groups. Compared to *APOA5* −1131T and 19S homozygotes, −1131C and 19W carriers had higher TGs in all groups, but this effect was only statistically significant for the −1131C in the EWs (P=0.04) and 19W in the IAs (P<0.001). *APOC3* SNPs showed no significant association with lipid levels in any ethnic group. While haplotypes carrying −1131C allele showed significant TG-raising in the EWs only, the 19W defined haplotype showed significant TG-raising in both IAs and EWs. Comparing all four SNPs in EW T2D subjects with healthy EWs (n=2579), the *APOC3* 1100C>T frequency was significantly higher in T2D [0.26 (0.24, 0.28)] vs. healthy EWs [0.22 (0.20, 0.23)], P=0.001. While the variable size effects of the two *APOA5* SNPs on TG levels may result from ethnically different gene–gene or gene–environment interactions, *APOA5* and *APOC3* variants did not affect parameters of T2D. However, comparison between EWs with T2D and healthy EWs suggest *APOC3* 1100C>T is associated with increased risk of diabetes probably through mechanisms other than direct effects on TG.
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1. Introduction

Type 2 diabetes (T2D) is a global pandemic increasing and already affecting over 150 million people worldwide [1]. There is considerable ethnic variation in the prevalence, incidence and disease progression with adult T2D being about three to five times greater in Afro-Caribbeans (ACs) and South Asians compared to European Whites (EWs) [2].

Heart disease is 3–5 times more common in T2D. Patients have a typical atherogenic dyslipidemia profile characterised by raised fasting triglyceride (TG) levels, excessive postprandial lipaemia and low HDL cholesterol. Patients with T2D also tend to have a preponderance of atherogenic small dense LDL [3]. Since raised TG levels are an independent risk factor for cardiovascular disease [4], the genetic determinants of TGs might play a part in the hypertriglyceridemia prevalent in T2D. The *APOA5/A4/C3/A1* gene cluster on chromosome 11 is of interest, as common single nucleotide polymorphisms (SNPs) in *APOC3* and *APOA5* have been associated with differences in plasma TG levels in healthy individuals [5–8]. *APOA5* is a hepatically expressed minor constituent of HDL, which in the postprandial state transfers to VLDL [9,10]. *APOC3*, a component of TG-rich lipoproteins and HDL, is mainly synthesized in the liver and to some extent in the intestine [11].

Linkage disequilibrium (LD) structure and haplotype patterns between *APOA5* and *APOC3* have been studied [5,12–14]. Two

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APOA5 TG-raising haplotypes have been identified, *APOA5**2, defined by five SNPs, −1131T>C, −3A>G, IVS3+, 476G>A, 1259T>C and *APOA5**3, defined by the rare allele of the 56C>G SNP (S19W) [6,7]. Thus, −1131T>C and S19W essentially act as tagging SNPs for these two TG-raising haplotypes. Haplotype analysis of the chromosome 11 gene cluster suggests that while S19W independently affects TG levels [13] and has been shown to be functional [15], *APOA5**2 is significantly associated with the rare alleles of the *APOC3* Sst I (3238G>C) and the two promoter SNPs, −482C>T and −455T>C [12], of which the −482C>T has been shown to be functional [16].

Very few studies have looked at the relationship between *APOA5* [17–20] and *APOC3* gene polymorphisms and lipid traits [19,21,22] in patients with T2D in different ethnic groups [20,23]. Since no data are available for the *APOA5* S19W or *APOC3* 1100C>T variants in patients with T2D, the purpose of this study was to examine the association of two *APOA5* (−1131T>C and S19W) and two *APOC3* SNPs (−482C>T and 1100C>T) with lipid traits, primarily TG levels, in European White (EW), Indian Asian (IA) and Afro-Caribbean (AC) patients with T2D. These effects in the EWs with T2D were also compared to healthy EWs who had participated in the prospective Northwick Park Heart Study II and in whom the effects of *APOA5* [13] and *APOC3* [8] variants had been previously reported. Association with other indicators of risk of T2D was also examined, namely age of onset, duration of diabetes (calculated from reported age of diabetes onset to age at entry into the study), and obesity as measured by body mass index (BMI).

2. Materials and methods

2.1. Population studies

2.1.1. UCL diabetes and cardiovascular disease study; UDACS

This is a cross-sectional sample of subjects designed to study the association between common variants in inflammatory/metabolic genes and biochemical risk factors implicated in CHD in patients with diabetes [24,25]. Briefly, 1100 consecutive patients were recruited from the diabetes clinic at University College London Hospitals NHS Trust in Central London between the years 2001 and 2002. Ethical approval was granted by the institutional ethics committee, and all participants gave written informed consent before recruitment. Analyses were confined to 781 patients with T2D (EWs n=600, IAs n=107 and ACs n=74).

2.1.2. Ealing diabetes study of coagulation; EDSC

Patients were recruited consecutively from a diabetes clinic at Ealing Hospital in Central London at the same time as UDACS over a 2-year period from 2001 (n=1270). Approval was given for the study from Ealing Hospital Ethics Committee and all individuals gave written informed consent. The study was designed to address genotype/phenotype associations (particularly in haemostatic and anti-inflammatory pathways) in T2D and to identify risk factors for CHD primarily in three ethnic groups, IAs, EWs and ACs [26]. Analysis was restricted to patients with T2D (total of 927 patients, EWs n=331, IAs n=503 and ACs n=93). Biochemical, disease related and demographic results for each patient, specific to the recruitment date, were retrieved from clinic.

UDACS and EDSC were recruited simultaneously from London hospitals with a view to combining genetic analysis and all patients were diagnosed with T2D using the same diagnostic criteria [27].

2.1.3. Northwick park heart study; NPHSII

NPHSII is a prospective study of healthy men aged 50–64 years at baseline, who were clinically free of cardiovascular disease at that time. The cohort is well documented in peer-reviewed literature [28,29]. The study commenced in 1989 and is based within nine general medical practices in England and Scotland. Of 4600 men, 4141 were eligible for study and 3052 were recruited. Blood was taken in the non-fasting state for haemostatic factors and other biochemical markers. In the current analysis, non-Caucasian subjects were excluded, as well as 75 men, who were diabetic at baseline and 174 men, who developed diabetes during follow up, leaving 2735 of whom 2350 individuals were successfully genotyped, as published elsewhere [8,13]. Briefly, lipid characteristics were: TG levels 1.76±0.92 mmol/l, total cholesterol levels 5.72±1.00 mmol/l, LDL levels 3.99±0.95 mmol/l and HDL levels 0.81±0.24 mmol/l and BMI were 26±3.3 kg/m^2 (mean±SD, Table 1).

In all three studies, UDACS, EDSC and NPHSII, non-fasting blood samples were taken.

2.1.4. APOA5 genotyping

DNA was extracted using the salting out method [30]. The two *APOA5* SNPs, −1131T>C and S19W, in the UDACS, EDSC and NPHSII studies were assayed using PCR and restriction enzyme digest as previously reported [13]. In the NPHSII study, *APOC3* SNPs (−482C>T and 1100C>T) were assayed using PCR and restriction enzyme digest as previously reported in [31]. *APOC3* SNPs in the UDACS/EDSC samples were genotyped with Taqman (Applied

Table 1
Baseline characteristic in UDACS and EDSC for patients with T2D and NPSHII

	Baseline characteristics (T2D)							
	EWs (N=587)	IAs (N=354)	ACs (N=108)	P value EWs v IAs	P value ACs v EWs	P value ACs v IAs	NPHSII (N=2578)	P value EWs T2D v NPHSII
Male (%)	59.6 (554)	59.6 (361)	63.9 (106)	0.79	0.48	0.96	100 (2578)	
BMI (kg/m^2)*	29.3 (5.5)	27.7 (4.5)	28.4 (4.9)	<0.001	0.004	0.005	26.0 (3.3)	<0.001
Age of onset diabetes (y)	54.6 (13.2)	47.8 (11.5)	50.8 (10.6)	<0.001	0.20	0.08	–	
Age of recruitment (y)	65.6 (12.1)	58.5 (11.5)	61.6 (11.2)	<0.001	0.002	<0.001	–	
Duration of diabetes (y)$^+$	9 [4–15]	10 [5–16]	10 [5–15]	0.08	0.44	0.77	–	
Chol (mmol/l)	5.01 (1.10)	4.91 (1.14)	4.99 (1.04)	0.23	0.87	0.48	5.72 (1.00)	<0.001
HDL-Chol (mmol/l)*	1.24 (0.37)	1.14 (0.28)	1.40 (0.41)	0.02	<0.001	<0.001	0.81 (0.24)	<0.001
TG (mmol/l)*	1.90 (1.10)	2.04 (1.06)	1.44 (0.77)	0.38	<0.001	<0.001	1.76 (0.92)	<0.001
LDL-Chol (mmol/l)^x	2.72 (0.92)	2.73 (0.93)	2.76 (0.92)	0.63	0.998	0.64	3.99 (0.95)	<0.001
Glucose (mmol/l)$^+$	10.7 [7.9–14.6]	11.7 [8.6–15]	10.2 [7.4–14.5]	0.15	0.03	0.12	–	
HbA1c (%)	8.03 (1.82)	8.66 (2.08)	8.40 (2.07)	0.10	0.17	0.42	–	
SBP (mm Hg)	140.8 (20.1)	136.9 (20.7)	144.0 (20.9)	0.74	0.17	0.42	137.8 (19.1)	<0.001
DBP (mm Hg)	77.3 (11.6)	76.0 (11.3)	79.5 (12.1)	0.42	0.003	0.006	84.5 (11.4)	<0.001

Data is presented as * geometric means±approximately standard deviation or $^+$median (interquartile range).

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