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APOE, *CETP* and *LPL* genes show strong association with lipid levels in Greek children☆

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Abstract *Background and aims:* Studies have consistently demonstrated that variants in a number of candidate genes are significant determinants of lipid levels in adults. However, few studies have investigated the impact of these variants in children. Therefore, in the present investigation we examined the influence of ten common variants in the genes for lipoprotein lipase (*LPL* – S447X), cholesterol ester transfer protein (*CETP* – *Taq*1B) apolipoprotein (*APO*) E (ε2, ε3, ε4), *APOA5* (−1131C > T and S19W), *APOA4* (S347T) and *APOC3* (−482C > T; 1100C > T and 3238G > C) on lipoprotein levels children from the Gene–Diet Attica Investigation on childhood obesity (GENDAI).

Methods and results: The ten variants selected were genotyped in 882 Greek children, mean age: 11.2 ± 0.7 years (418 females and 464 males). Genotypes were assessed using *Taq*Man technology. Significantly higher total cholesterol (TC) ($p = 0.0001$) and low-density lipoprotein cholesterol (LDL-C) ($p < 0.0001$) were observed in *APOE* ε4 carriers compared to ε3/ε3 homozygotes and ε2 carriers. The association of *APOE* genotype with TC and high-density lipoprotein cholesterol (HDL-C) ratio ($p = 0.0008$) was further modulated by body mass index. Carriers of the *CETP Taq*IB B2 allele had significantly higher HDL-C ($p < 0.0001$) and significantly lower

Abbreviations: T2D, type 2 diabetes; GENDAI, Gene–Diet Attica Investigation on childhood obesity; APO, apolipoprotein; TG, triglyceride; LPL, lipoprotein lipase; CETP, cholesterol ester transfer protein; BMI, body mass index; SNPs, single nucleotide polymorphisms; HWE, Hardy–Weinberg equilibrium; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; PCA, principal component analysis; PC1, first principal component; PC2, second principal component; MAF, minor allele frequency; GWAS, genome wide association studies; TGRL, triglyceride rich lipoproteins; NS, not statistically significant; CI, confidence intervals; IQR, inter quartile range; AA, amino acid.

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TC: HDL-C ratio ($p < 0.0001$) compared to B1/B1 individuals. No significant associations were observed between *APOA4*, *APOA5* and *APOC3* variants and serum lipids.
Conclusion: This study demonstrates that these common variants are associated with lipid levels in this healthy paediatric cohort, suggesting that even in these young children there may be potential in predicting their lifelong exposure to an adverse lipid profile.
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Introduction

In parallel with the increase in adult obesity, childhood obesity is a rapidly growing health problem worldwide [1]. Obesity in childhood is linked to many serious health complications usually seen in adulthood [2]. Co-morbidities include elevated blood pressure, increased prevalence of factors associated with type 2 diabetes (T2D) and lipid abnormalities [1]. The Gene—Diet Attica Investigation on childhood obesity (GENDAI) [3] was established to specifically explore the contribution of genetics and environmental factors in the development of childhood obesity. The GENDAI cohort consists of young children of both sexes attending school in the area of Attica, Greece. Preliminary assessment provided the impetus for a more detailed study of the metabolic syndrome phenotype in the GENDAI cohort with particular focus on the genetic contribution to inter-individual variation in plasma lipids in the young and the potential modulation of these genetic associations by environmental influences.

Genetic factors are considered to be important determinants of plasma lipoprotein levels in adults; however, the role of genetics in determining plasma lipoproteins in children and adolescents is less clear. The apolipoprotein (*APO*) cluster including *APOA5*, *APOAIV*, *APOC3* and *APOA1* on chromosome 11 is associated with variation in triglycerides (TG) in both children and adults and across a range of ethnic groups [4,5]. Variation in the *APOE*, lipoprotein lipase (*LPL*) and cholesterol ester transfer protein (*CETP*) genes has been consistently associated with variation in lipid levels in adults [6,7]. However, genetic variation in these gene loci explain only a modest proportion of inter-individual variability in fasting lipid levels [8]. We genotyped the GENDAI cohort for ten variants in the *APOE*, *LPL*, *CETP* genes and the *APOA5/A4/C3* cluster, to examine if the reported effects could be replicated in children and assess if these associations could be further modulated by body mass index (BMI).

Methods

Study population

Participants were drawn from the children recruited in the GENDAI study. Briefly, a random sample of 2492 children attending school in the Attica region in Greece were invited to join the study. A total of 1138 children were recruited from November 2005 to June 2006. Due to the heterogeneity in allele frequencies between Greek and non-Greek Caucasians, only children of Greek nationality, mean age: 11.2 ± 0.7 years ($n = 882$; 418 males and 464 females), were included in the present study. Details of recruitment and data collection have been previously described [3]. All persons gave their informed consent prior to inclusion in the study. The study was approved by the Institutional Review Board of Harokopio University and the Greek Ministry of Education [3].

Experimental procedures

Single nucleotide polymorphism selection and genotyping

A salting-out procedure [9] was used to isolate DNA samples from whole blood. Ten single nucleotide polymorphisms (SNPs) in six candidate genes; *LPL* S447X (rs328), *CETP* *Taq*1B (rs708272), *APOE* (rs7412, rs429358), *APOA5* −1131C > T (rs662799) and S19W (rs3135506), *APOA4* S347T (rs675) and *APOC3* −482C > T (rs2854117), 1100C > T (rs4520) and 3238C > G (rs5128) were genotyped using *Taq*Man technology (Applied Biosciences, ABI, Warrington UK). Reactions were performed on 384-well microplates and analysed using ABI *Taq*Man 7900HT software. Primers and MGB probes are available upon request.

Statistical methods

Hardy—Weinberg equilibrium (HWE) was examined by chi-square goodness of fit test. A p value of <0.05 was taken as deviation from HWE. Plasma levels of insulin, TG, total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) and all anthropometric measures were natural log-transformed. For association studies a p value of <0.01 was taken as statistically significant. Setting a threshold of significance was the chosen method above Bonferroni corrections, since the candidate genes studied had been selected for based on a *priori* hypothesis and biological plausibility. A p value of <0.05 was taken as statistically significant in Principal Component Analysis (PCA). The majority of statistical analyses were performed using Intercooled Stata 8.2 for Windows (StataCorp LP, Texas, USA). Haplotype association analysis was carried out using Thesias [10]. PCA was carried out using SAS (SAS Institute Inc., Cary, NC). Throughout this study we used the first principal component (PC1) and the second principal component (PC2) because both components explained more than 80% of the variation and their eigenvalues were greater than the average eigenvalue [11].

Results

Subjects were classified as obese, overweight and non-overweight according to the International Obesity Task

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