Associations of polymorphisms in the apolipoprotein A1/C3/A4/A5 gene cluster with familial combined hyperlipidaemia in Hong Kong Chinese

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A R T I C L E   I N F O

Article history:
Received 18 March 2009
Received in revised form 30 June 2009
Accepted 9 August 2009
Available online 15 August 2009

Keywords:
Familial combined hyperlipidaemia
APOA1/C3/A4/A5 gene cluster
Single nucleotide polymorphisms
Triglycerides
Chinese

A B S T R A C T

Background: Familial combined hyperlipidaemia (FCH) is the most common genetic dyslipidaemia associated with coronary artery disease. Single nucleotide polymorphisms (SNPs) and haplotypes in the APOA1/C3/A4/A5 gene cluster are associated with FCH in Caucasians and with elevated triglycerides (TG) in various ethnic groups. We examined these associations with FCH in Hong Kong Chinese.

Methods: Fifty-six Chinese FCH patients and 176 unrelated controls were studied. Thirteen SNPs in the APOA1/C3/A4/A5 cluster were genotyped.

Results: Four alleles in APOA5 were associated with FCH (P < 0.001). The −1131T>C (rs662799) and −3A>G (rs651821) SNPs in APOA5 were in almost complete linkage disequilibrium (LD, r² = 0.99), and their minor alleles were more frequent (P < 0.001) in FCH than controls (0.60 vs. 0.24). The odds ratio (OR) for FCH was 6.2 (95% CI, 2.6–14.8) and 6.1 (2.6–14.6) per copy of −1131C and −3G, respectively, and 24.6 (8.4–72.0) and 24.4 (8.4–70.9) in −1131C and −3G homozygotes, respectively, as compared to wild-type homozygotes. The 1891T>C (rs2266788) SNP was in LD (r² = 0.68) with −1131T>C and −3A>G, and the minor allele was more frequent in FCH than controls (0.42 vs. 0.19, P < 0.001). The 553G>T (rs2075291) nonsynonymous variant was also associated with FCH (0.15 vs. 0.04, P = 0.001) and, along with −3A>G (or −1131T>C) and 1891T>C, contributed to haplotypes predicting FCH. The two tightly linked SNPs, −1131T>C and −3A>G polymorphism were significantly associated with lipid traits in all subjects combined, with variant homozygous subjects having higher TG and LDL-C and lower HDL-C levels.

Conclusions: Some common polymorphisms and haplotypes in APOA5 are closely associated with FCH in Hong Kong Chinese, and these differ from those found in Caucasians.

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1. Introduction

Familial combined hyperlipidaemia (FCH), with a prevalence of 2% or more in Caucasians, is thought to be the most common genetic dyslipidaemia and is associated with an increased risk of coronary artery disease (CAD) [1]. FCH is a ‘multiple-type hyperlipidaemia’ and can be classified into three phenotype groups: elevated TC (phenotype IIA), elevated TG and TC (phenotype IIB), and elevated TG (phenotype IV) [2]. It has also been shown that the hyperlipidaemia phenotype within an individual may change over time in relation to changes in obesity or other factors, a phenomenon that complicates the diagnosis due to the combination of genetic and environmental factors [3]. The diagnosis of FCH requires affected first-degree relatives and may be best predicted by absolute apoB levels combined with elevated TG and TC levels adjusted for age and gender, which also predicted CAD risk [4].

FCH represents multiple phenotypes as the consequence of environmental impact on metabolic pathways, each of which is regulated by particular genes [5]. This polygenic lipid disorder overlaps considerably with the metabolic syndrome and central obesity [1,6]. Several candidate genetic regions, including APOE, the lipoprotein lipase gene and the chromosome 1q21–23 region, have been associated with FCH, but the APOA1/APOC3/APOA4 gene cluster on chromosome 11q23, coding for apoAI/CIII/AIV, has received the most attention recently [7]. A newly identified gene (APOA5) located proximal to the APOA1/C3/A4 gene cluster was found to be associated with TG levels [8], and population studies and genome-wide association studies have identified certain variants in APOA5 strongly related to TG levels [9–11]. The APOA5 56C>G (rs19W, rs3135506) and −1131T>C (rs662799) polymorphisms have been studied extensively and have been associated with a range of lipid phenotypes linked by hypertriglyceridaemia, including FCH [12].
The APOA5 56C > G polymorphism is almost absent in Chinese [13], but the –1131T > C allele is more common in Chinese than in Caucasians, thus this polymorphism may have more impact on lipid phenotypes among Chinese [14]. However, to our knowledge, no published study has examined the relationship between FCH and polymorphisms in the APOA1/C3/A4/A5 gene cluster in Chinese. In the present study, we examined whether 13 SNPs identified in the APOA1/C3/A4/A5 gene cluster (GenBank accession no. AY555191) were associated with FCH in Hong Kong Chinese. Concomitantly, we also investigated the relationship between these polymorphisms and lipid profiles and measures of obesity in the FCH patients and control subjects.

2. Subjects, materials and methods

2.1. Study population

Fifty-six genetically unrelated FCH patients (11 phenotype IIA, 35 phenotype IIB, 10 phenotype IV) and 176 unrelated age-matched control subjects were identified based on lipid levels and evidence of affected family members from a database of 392 patients with combined hyperlipidaemia attending the lipid clinic at the Prince of Wales Hospital in Hong Kong. All participants were of Han Chinese origin without known ancestors of other ethnicity, and lived in the Hong Kong Special Administrative Region (SAR) of China. They all gave written informed consent to join the study, which was approved by the local Clinical Research Ethics Committee. They all had elevated TC levels (TC > 6.2 mmol/L) and/or moderately elevated TG levels (2 mmol/L < TG ≤ 15 mmol/L). All patients had at least one first-degree relative confirmed to have phenotype IIB, or an abnormal lipid phenotype different to the proband. Patients with diabetes (fasting plasma glucose (FPG) > 7.0 mmol/L) or with renal, liver or thyroid disorders were excluded. Control subjects were recruited from hospital staff and their relatives and friends who were thought to be generally healthy with no history of significant chronic illness. The control subjects selected for this study did not have hypertension (blood pressure <140/90 mmHg) or diabetes and had normal TC (<5.2 mmol/L) and TG levels (<2.0 mmol/L). Body weight, height, waist and hip circumference, and blood pressure were measured, and body mass index (BMI) was calculated in kg/m².

2.2. Biochemical analysis

Fasting lipid concentrations were determined by enzymatic methods for TC and TG (Centrichem chemistry system, Baker Instruments Co., AllenTown) and fractional precipitation for HDL-cholesterol (HDL-C). LDL-C concentrations were calculated using the Friedewald formula when TG levels were below 4.5 mmol/L. Fasting plasma glucose (FPG) levels were measured using the standard oxidase method.

2.3. DNA extraction, SNP selection and genotype analysis

The traditional phenol chloroform method or High Pure PCR Template Preparation Kits (Roche) were used to extract DNA samples from the blood specimens. Thirteen SNPs at the APOA1/C3/A4/A5 gene cluster (APOA5 SNP1 [1891T > C, rs2266788], SNP3 [–1131T > C, rs662799], 553G > T [rs2075291], –3A > G [rs651821], [rs6589567], [rs6589568], and [rs1729410]; APOA4 360C > A [Q360H, rs5110] and 347T > A [T347S, rs675]; APOC3 –455T > C [rs2854116], SstI [rs5128] and 1100C > T [rs4520]; and APOA1 84T > C [rs5070]) were selected based on prior associations with FCH or triglyceride levels in other ethnic groups and two novel common SNPs (rs6589567 and rs6589568) in this cluster were also selected from the HapMap. Genotyping was performed in the Genome Research Centre, University of Hong Kong using the mass-spectroscopy based, high-throughput MassARRAY iPLEX platform (Sequenom, San Diego, CA).

2.4. Statistical analyses

The Haploview program (Daly Lab) was used to estimate pairwise linkage disequilibrium (LD) and construct haplotypes. Analysis of haplotypes was performed using the program PLINK (version 1.0.4). All other data analyses were performed with the SPSS 13.0 statistical package (SPSS Inc., Chicago, IL). Continuous variables were expressed as means ± SD, and skewed variables were logarithmically transformed before comparison using the Student’s t-test or by ANOVA. Mann–Whitney U-test or Kruskal–Wallis H-test was used for the comparison of non-normally distributed variables. A chi-square test was used to assess whether the genotypes were in Hardy–Weinberg equilibrium (HWE) in cases and controls and to compare the differences of genotypic distribution and allelic frequency between cases and controls. The heterozygotes and homozygotes for the minor allele were pooled together for some polymorphisms (rs5070 in APOA1; rs2075291 and rs2266788 in APOA5) in the analysis because of a low frequency of the minor allele. Binary logistic regression was used to determine the odds ratio (OR) for FCH (with 95% confidence interval [95% CI]) with adjustment for age, gender and BMI. The Bonferroni correction was used to adjust for multiple comparisons.

3. Results

3.1. Subject characteristics

The general characteristics of the study subjects are summarized in Table 1. There were 27 male and 29 female patients with FCH,
and they were age–matched with the control group consisting of 61 males and 115 females. As expected, FCH patients had significantly higher TC, TG, and LDL-C levels and lower HDL-C levels compared with those of the controls (all \( P < 0.001 \)), and the FCH patients also had higher BMI, FPG, and blood pressure (all \( P < 0.05 \)).

### 3.2. Allele frequency and linkage disequilibrium

Thirteen SNPs in the APOA1/C3/A4/A5 gene cluster were successfully genotyped in 98.2% of FCH cases and 98.3% of controls. The genotype error rate was less than 1.0% on the replicated samples. No variant allele was found in two SNPs in \( \text{APOA4} \) (rs675, rs5110). The genotype distributions of the other 11 SNPs were all in HWE for both FCH cases and controls (all \( P < 0.05 \)). The frequencies of the minor alleles in controls were similar to those in Han Chinese in HapMap except for rs5128, which had a significantly lower minor allele frequency compared to Han Chinese in HapMap (0.265 vs. 0.389, \( P = 0.037 \)). To determine the extent of LD in this group of subjects, standardised LD coefficients were calculated (Fig. 1). Two SNPs (rs651821, and rs662799) in \( \text{APOA5} \) were in almost complete LD (\( r^2 = 0.99 \)).

### 3.3. Association with lipid profiles and obesity

The individual associations between each polymorphism and lipid levels were examined in FCH cases and controls separately, and no significant association between TG, HDL-C or LDL-C levels with any polymorphism examined was observed before or after adjustment for age and gender, although some of these SNPs did show a tendency to gene-dose effects with TG levels in FCH cases (Supplementary material Table 1). When FCH cases and controls were combined, there were significant associations between the lipid traits and polymorphisms in \( \text{APOA5} \). Subjects with \( \text{APOA5} \) variants tended to have higher TG and LDL-C and lower HDL-C levels. In linear regression analysis, \(-1131T>C\) (rs662799) (or \(-3A>G\)) was the only SNP associated with all of these three lipid traits, with CC subjects having higher TG and LDL-C but lower HDL-C levels compared to those with one or two copies of the T allele (TG: 3.28 mmol/L vs. 1.54 mmol/L, \( P < 0.001 \); LDL-C: 4.19 mmol/L vs. 3.15 mmol/L, \( P < 0.001 \); HDL-C: 1.25 mmol/L vs. 1.34 mmol/L, \( P = 0.002 \)).

There were no significant associations or consistent trends between any polymorphism and body weight or BMI in FCH cases or controls, but four polymorphisms in \( \text{APOA5} \) (rs2266788, rs651821, rs662279 and rs6589567) and one in \( \text{APOC3} \) (rs5128) were found to be associated (\( P < 0.05 \)) with waist/hip circumference ratio (WHR) in the control group, with subjects carrying minor alleles having lower WHR, but this was no longer significant after adjusting for multiple tests (data not shown).

### 3.4. Association of the APOA1/C3/A4/A5 variants with FCH

Of the 11 SNPs evaluated in \( \text{APOA1/C3/A4/A5} \) with variants observed in this study, 4 SNPs in \( \text{APOA5} \) showed significant associations (\( P < 0.001 \)) with FCH after adjustment for multiple testing (Table 2). The minor alleles of the 2 tightly linked \( \text{APOA5} \) SNPs, \(-1131T>C\) (rs651821) and \(-3A>G\) (rs662799), were more frequent (\( P < 0.001 \)) in FCH than controls (0.60 vs. 0.24), with OR 6.2 (3.0–12.6, \( P < 0.001 \)) for subjects with either one or two copies of variant alleles compared with homozygotes for the major allele. The 553G>T (rs2075291) SNP in \( \text{APOA5} \) was not in significant LD with the other \( \text{APOA5} \) SNPs, but the T allele was more frequent in FCH than controls (0.15 vs. 0.04, \( P = 0.001 \)), with OR of 4.4 (1.9–10.4, \( P = 0.001 \)) for subjects with either one or two copies of T compared with CC.
Table 2
Associations between FCH and polymorphisms in the APOA1/C3/A4/A5 gene cluster.

<table>
<thead>
<tr>
<th>SNP</th>
<th>Genotype</th>
<th>Genotype distribution (n)</th>
<th>OR (95% CI)</th>
<th>P valuea</th>
</tr>
</thead>
<tbody>
<tr>
<td>APOA5 SNP1, 1891T &gt; C, rs2266788</td>
<td>TT</td>
<td>17</td>
<td>1</td>
<td>&lt;0.001b</td>
</tr>
<tr>
<td></td>
<td>TC/CC</td>
<td>39</td>
<td>6.18 (3.05, 12.56)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Minor allele frequency</td>
<td>0.429</td>
<td>0.187</td>
<td>&lt;0.001b</td>
</tr>
<tr>
<td>APOA5 553 G &gt; T, rs2075291</td>
<td>GG</td>
<td>40</td>
<td>1</td>
<td>0.001b</td>
</tr>
<tr>
<td></td>
<td>GT/TT</td>
<td>15</td>
<td>4.40 (1.86, 10.42)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Minor allele frequency</td>
<td>0.145</td>
<td>0.038</td>
<td>&lt;0.001b</td>
</tr>
<tr>
<td>APOA5 −3A &gt; G, rs651821</td>
<td>AA</td>
<td>9</td>
<td>1</td>
<td>&lt;0.001b</td>
</tr>
<tr>
<td></td>
<td>AG</td>
<td>26</td>
<td>6.13 (2.57, 14.63)</td>
<td>&lt;0.001b</td>
</tr>
<tr>
<td></td>
<td>GG</td>
<td>20</td>
<td>24.35 (8.36, 70.94)</td>
<td>&lt;0.001b</td>
</tr>
<tr>
<td></td>
<td>Minor allele frequency</td>
<td>0.6</td>
<td>0.237</td>
<td>&lt;0.001b</td>
</tr>
<tr>
<td>APOA5 SNP3, −1131T &gt; C, rs662799</td>
<td>TT</td>
<td>9</td>
<td>1</td>
<td>&lt;0.001b</td>
</tr>
<tr>
<td></td>
<td>TC</td>
<td>27</td>
<td>6.23 (2.62, 14.85)</td>
<td>&lt;0.001b</td>
</tr>
<tr>
<td></td>
<td>CC</td>
<td>20</td>
<td>24.60 (8.40, 72.03)</td>
<td>&lt;0.001b</td>
</tr>
<tr>
<td></td>
<td>Minor allele frequency</td>
<td>0.598</td>
<td>0.24</td>
<td>&lt;0.001b</td>
</tr>
<tr>
<td>APOA5 C &gt; A, rs6589567</td>
<td>CC</td>
<td>24</td>
<td>1</td>
<td>0.066</td>
</tr>
<tr>
<td></td>
<td>CA</td>
<td>23</td>
<td>1.88 (0.96, 3.70)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>AA</td>
<td>9</td>
<td>3.58 (1.27, 10.11)</td>
<td>0.016</td>
</tr>
<tr>
<td></td>
<td>Minor allele frequency</td>
<td>0.366</td>
<td>0.225</td>
<td>0.003</td>
</tr>
<tr>
<td>APOA5 A &gt; G, rs6589568</td>
<td>AA</td>
<td>23</td>
<td>1</td>
<td>0.72</td>
</tr>
<tr>
<td></td>
<td>AG</td>
<td>21</td>
<td>1.13 (0.57, 2.24)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>GG</td>
<td>12</td>
<td>3.89 (1.48, 10.23)</td>
<td>0.006</td>
</tr>
<tr>
<td></td>
<td>Minor allele frequency</td>
<td>0.402</td>
<td>0.277</td>
<td>0.013</td>
</tr>
<tr>
<td>APOC3 1100 C &gt; T, rs4520</td>
<td>CC</td>
<td>7</td>
<td>1</td>
<td>0.685</td>
</tr>
<tr>
<td></td>
<td>CT</td>
<td>19</td>
<td>0.81 (0.29, 2.26)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TT</td>
<td>30</td>
<td>2.21 (0.80, 6.11)</td>
<td>0.125</td>
</tr>
<tr>
<td></td>
<td>Minor allele frequency</td>
<td>0.295</td>
<td>0.401</td>
<td>0.044</td>
</tr>
</tbody>
</table>

CI: confidence interval; FCH: familial combined hyperlipidaemia; OR: odds ratio.

Another two SNPs (rs6589567, rs6589568) in LD (r² = 0.78) in APOA5 and one SNP (rs4520) in APOC3 were also associated with FCH, but the associations were no longer significant after correction for multiple comparisons (Table 3).

On the basis of the three adjacent APOA5 polymorphisms (1891T > C, 553G > T, and −3A > G), three common haplotypes (frequency >2%) were inferred, which represented >98% of the sample. Two haplotypes (CGG, TTG), each containing 2 out of 3 variant alleles, were strongly associated with FCH compared with the reference haplotype (TGA) defined by the wild-type alleles at all three polymorphic sites (Table 3). The haplotype associated with highest ORs for FCH carried both the APOA5 −3A > G and 553G > T rare alleles, which suggested that these two independent polymorphisms provide a major contribution to genetic susceptibility to FCH in the Chinese population.

4. Discussion

From the 13 SNPs examined, no variant allele was found in two SNPs in APOA4 (rs675, rs5110), which is consistent with previous reports in Asian populations. Four of the SNPs in APOA5 were significantly associated with FCH. Previous studies have shown that the minor allele of −1131T > C was associated with elevated TG levels and increased CAD risk in Chinese [14–17] as well as in other ethnic groups [11,18]. This polymorphism was the only one out of 158 in 133 candidate genes found to be related to the metabolic syndrome in Japanese [19], and in a case–control study in Caucasians, having one C allele was associated with over 3-fold increase in risk (compared to TT homozygotes) of the metabolic syndrome [20].

A study in Romania also showed that the risk of metabolic syndrome was associated with the −1131C allele and that carriers had higher BMI, triglycerides, and glucose and lower HDL-C [21]. However, in a large study in Austria and Germany, the minor alleles of variants −1131T > C, −3A > G, 56C > G, 476G > A, and 1259T > C were all associated with higher plasma TG, but only the 56C > G variant and not −1131T > C was associated with the metabolic syndrome [22]. The association of APOA5 SNPs with the metabolic syndrome appears to be mediated largely through effects on triglycerides rather than on obesity, but one study in Caucasians did show an interaction between the −1131T > C SNP, but not the 56C > G variant, and BMI, with subjects homozygous for the −1131T major allele having increased BMI with increased total fat intake, which was not seen in the −1131C carriers [23]. The present finding that

Table 3
Haplotype associations with FCH.

<table>
<thead>
<tr>
<th>Haplotypes in APOA5</th>
<th>Haplotype frequencies OR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs2266788 1891 T &gt; C</td>
<td>rs2075291 553 G &gt; T</td>
<td>rs651821 −3A &gt; G</td>
</tr>
<tr>
<td>T</td>
<td>G</td>
<td>A</td>
</tr>
<tr>
<td>C</td>
<td>G</td>
<td>G</td>
</tr>
<tr>
<td>T</td>
<td>T</td>
<td>G</td>
</tr>
</tbody>
</table>

CI: confidence interval; FCH: familial combined hyperlipidaemia; OR: odds ratio.
control subjects with the −1131T allele and some other SNPs in APOA5 and APOC3 tended to have increased WHR, which may represent a similar relationship, which would require confirmation in a larger study population with assessments of dietary fat intake.

A number of studies in Caucasians have shown associations with FCH and APOA5 variants such as the Msel enzymatic restriction site [24] or the 56C>G and −1131T>C variants [12,25,26]. The 56C>G variant, which is in LD with other SNPs in the APOA1/C3/A4/A5 cluster such as APOA1 −3031C>T but not with −1131T>C or the other common APOA5 variants, defines the APOA5*3 haplotype [12,25,27] and is the predominant SNP associated with FCH in most Caucasian studies, probably because of its higher frequency. In the present study, we found that the two tightly linked SNPs, −1131T>C and −3A>G SNPs were most strongly associated with FCH in Chinese and also influenced the lipid parameters significantly when data from all subjects were combined. The 56C>G variant is almost absent in Asians, but the minor alleles of −1131T>C or −3A>G are more common (~20–30%) than in Caucasians (<10%) and these were the more frequent alleles in the Chinese FCH patients, being nearly 2.5-fold more common than in controls.

The functional effect of the −1131T>C polymorphism is incompletely understood but may be related to the almost complete LD with −3A>G, which is in a functionally important part of the kozak sequence potentially influencing APOA5 mRNA translation [27], or to linkage with other SNPs in APOA5 and in some ethnic groups with SNPs in APOC3, such as 386C>G [25]. The 1891T>C (rs2266788) SNP has been reported to be in 100% LD with −1131T>C, −3A>G, and 751A>G (rs2072560) in Caucasians, and carriers of the rare alleles have the APOA5*2 haplotype [27]. We found 68% LD between 1891T>C and −1131T>C or −3A>G in this study, which would probably account for the association of the 1891T>C polymorphism with FCH, which became insignificant after adjusting for −1131T>C.

The 553G>T (rs2075291, G185C) variant is rare in Caucasian and results in the substitution of cysteine for glycine at residue 185 in APOA5. The minor allele frequencies were 0.145 and 0.038 (P=0.001) for FCH patients and controls, respectively, which compares with frequencies of 0.078 and 0.040 in another study in Chinese patients with CAD and controls, where the polymorphism was associated with CAD and hypertriglyceridaemia [28]. The 553G>T SNP was not in significant LD with −1131T>C or −3A>G or other SNPs in the cluster. A large study in Japan found that both the 553G>T and −3A>G SNPs were significantly associated with the prevalence of metabolic syndrome and plasma TG and HDL-C levels [29]. The 553G>T SNP also contributed to the effects of the haplotype association with FCH. Likewise, a study in Taiwanese Chinese showed that people carrying the haplotype with both minor alleles of APOA5 −1131C and 553T had 116% higher plasma TG concentration compared with those carrying only the common alleles [30].

The two other novel SNPs in APOA5 (rs6589567, rs6589568) selected from HapMap were in close LD with each other but not with any other SNP, and the minor allele frequencies were higher in FCH patients than those in controls (0.366 vs. 0.225 and 0.402 vs. 0.277, respectively), but differences were not significant after correction for multiple comparisons. A small contribution of these SNPs to FCH cannot be excluded as the study was not adequately powered to demonstrate a weak association, and further studies with larger sample sizes are required to determine if these associations really exist. A recent genome-wide association study showed that the rs6589567 polymorphism, which has a frequency of about 8% in Caucasians, tends to have some effect on modulating TC levels [31].

The relationship between SNPs in APOA5 and TG or other lipids was not significant in the FCH cases and controls analysed separately, probably due to insufficient power with the small number of FCH cases and the relatively low TG values in controls. However, combining the subjects together did produce significant results, consistent with previous studies. Gender and other environmental and genetic factors are thought to influence these relationships [32].

It is also worth noting that the lipid phenotype of FCH may overlap with that of familial hypercholesterolaemia (FH), which is characterized by markedly elevated LDL-C levels, sometimes with mild to moderate elevation of triglycerides, resulting from mutations in the LDL-receptor (LDLR), apolipoprotein B or protein convertase subtilisin/keratin type 9 (PCSK9) genes. A recent study showed that some patients with a clinical diagnosis of FCH had functional LDLR mutations, which indicates potential difficulties with the distinction between FH and FCH on clinical diagnosis [33,34]. It is possible that some of the cases considered as FCH in this study may also disclose a functional mutation in the LDLR or other FH genes and should be classified as FH, but we did not examine for LDLR mutations in this study, which is one of the limitations. The inclusion of subjects with monogenic FH might be expected to weaken the relationship of these FCH subjects with APOA5 polymorphisms.

In conclusion, this study showed that of 11 variants identified in the APOA1/C3/A4/A5 gene cluster, the two tightly linked SNPs, −1131T>C (rs662799) and −3A>G (rs651821), from which the rare alleles constitute the APOA5*2 haplotype along with the 1891T>C (rs2266788) variant, were most significant for association with FCH in Hong Kong Chinese subjects. The less frequent nonsynonymous 553G>T (rs2075291) variant also showed an association with FCH in SNP and haplotype analyses. These differ from the pattern of associations in Caucasians. These effects are probably mediated through the influence of APOA5 on plasma TG, but there may be additional effects through modulation of obesity.

Conflict of interest
None.

Acknowledgements
We thank Emily Poon for laboratory assistance and Claudia Tam for help with the haplotype analysis. This study was partially supported by the grants from the Research Grants Council of the Hong Kong Special Administrative Region, China (Project nos. CUHK 4095/00M and CUHK 4438/03M).

Appendix A. Supplementary data
Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.atherosclerosis.2009.08.013.

References


