Association between Six CETP Polymorphisms and Metabolic Syndrome in Uyghur Adults from Xinjiang, China

Huixian Hou †, Rulin Ma †, Heng Guo, Jia He, Yunhua Hu, Lati Mu, Yizhong Yan, Jiaolong Ma, Shugang Li, Jingyu Zhang, Yunhua Hu, Lati Mu, Yizhong Yan, Jiaolong Ma, Shugang Li, Jingyu Zhang, Yusong Ding, Mei Zhang, Qiang Niu, Jiaming Liu and Shuxia Guo *

Department of Public Health and Key Laboratory of Xinjiang Endemic and Ethnic Diseases of the Ministry of Education, Shihezi University School of Medicine, Shihezi 832002, China; sjzhx06@sina.com (H.H.); marulin@126.com (R.M.); guoheng@shzu.edu.cn (H.G.); hejia123.shihezi@163.com (J.H.); hyh6133@sina.com (Y.H.); murat08123@163.com (L.M.); erriu19880215@sina.com (Y.Y.); jiaojiaolong881202@163.com (J.M.); liushugang@ymail.com (S.L.); yfyxxzjy@126.com (J.Z.); 13399931625@163.com (Y.D.); zmberry@foxmail.com (M.Z.); niuqiang1214@163.com (Q.N.); liujiaming@shzu.edu.cn (J.L.)
* Correspondence: gsxshzu@sina.com; Tel.: +86-180-0993-2625; Fax: +86-993-2057-153
† These authors contributed equally to this work

Academic Editor: William Chi-shing Cho
Received: 8 May 2017; Accepted: 15 June 2017; Published: 18 June 2017

Abstract: Objective: To explore the association between CETP gene polymorphisms and metabolic syndrome (MS), as well as the relationship between the CETP gene polymorphisms and each component of MS. Methods: A total of 571 individuals which were randomly selected from 5692 Uyghur adults were subdivided into two groups, including 280 patients with MS and 291 control subjects, using the group-matching method after matching for gender. We detected CETP polymorphisms (rs5882, rs1800775, rs3764261, rs12149545, rs711752, and rs708272) by using the Snapshot method. Results: (1) Significant differences were found involving the frequency distribution of genotypes and alleles of rs1800775, rs3764261, rs12149545, rs711752, and rs708272 between the control and MS groups (all \( p < 0.05 \)). (2) rs1800775, rs3764261, rs12149545, rs711752, and rs708272 polymorphisms were significantly related to the risk of MS (all \( p < 0.05 \)). (3) The rs1800775 polymorphism was associated with high fasting blood glucose levels and low high density lipoprotein cholesterol (HDL-C); rs3764261 and rs12149545 polymorphisms were associated with all components of MS except high blood pressure; rs711752 and rs708272 polymorphisms were associated with low HDL-C (all \( p < 0.05 \)). (4) Complete linkage disequilibrium (LD) was identified for two pairs of single nucleotide polymorphisms (SNPs) (rs3764261 and rs12149545 (\( D' = 1.000, r^2 = 0.931 \), rs711752 and rs708272 (\( D' = 1.000, r^2 = 0.996 \))). (5) The A-G-G-G-C (\( p = 0.013 \), odds ratio [OR] = 0.622, 95% confidence interval [95% CI] = 0.427–0.906) and A-T-A-A-T (\( p < 0.001 \), OR = 0.519, 95% CI = 0.386–0.697) haplotypes were more frequent in the control group than in the case group. Conclusions: The rs1800775, rs3764261, rs12149545, rs711752, and rs708272 polymorphisms of CETP were associated with MS and its components among the Uyghur ethnic group. Complete LD was found between two pairs of SNPs (rs3764261 and rs12149545, rs711752, and rs708272). The A-G-G-G-C and A-T-A-A-T haplotypes might be protective factors for MS.

Keywords: CETP gene; polymorphism; metabolic syndrome; Uyghur

1. Introduction

Metabolic syndrome (MS), which is perceived as a chronic and complex disease, has become a worldwide public health challenge for its concomitant complications over recent years [1]. Its clinical
Symptoms include three or more of the following factors: central obesity, raised blood pressure, elevated glucose, high triglyceride (TG) levels, and depressed high density lipoprotein cholesterol (HDL-C) [2]. At present, reaching a consensus on the definition of MS is further complicated by the fact that it is a progressive disorder [3], in that its several components tend to worsen over time. In addition, the prevalence of MS is generally high globally. In the United States, from 2003 to 2012, the overall prevalence of MS was 33% [4]. In Australia, the prevalence of MS was 30.7% [5]. In Japan, the prevalence of MS among 2113 subjects was 22.8% for males and 8.7% for females [6]. In China, a meta-analysis with a total population of 226,653 Chinese subjects from mainland China showed that the pooled prevalence of MS was 24.5% [7]. Our preliminary findings indicated that MS prevalence in the Uyghur population in Xinjiang was 21.2% [8]. This was lower than the 23.3% reported for adults in Northern China through an age-scale epidemiological investigation [9]. Later, another epidemiological survey in Xinjiang also showed a high prevalence of MS among the Uyghur [10]. The age-standardized prevalence of MS was 27.9%, which was slightly lower than that in the Han population in the same area (31.3%). However, the cause of MS remains ambiguous, involving a combination of age, race, genetic factors, diet, behavior, and environmental factors [11]. Genetic factors increasingly attract the attention of scholars.

Cholesteryl ester transfer protein (CETP) is mainly secreted by the spleen, liver, and adipose tissue. CETP is considered a key protein for the process of reverse cholesterol transport, and mediates the exchange and transfer of cholesterol esters (CEs) and triglycerides (TGs). CE generated by lecithin cholesterol acyltransferase (LCAT) in HDL is transferred to other lipoproteins by CETP. CETP promotes the removal of CE from HDL in exchange for TGs derived primarily from very low density lipoprotein (VLDL) or chylomicrons [12]. High CETP activity lowers the concentration of HDL-C [13], regulated by the CETP gene and the availability of substrates for transfer. The CETP gene is highly polymorphic. Some variants in the CETP gene are associated with decreased plasma CETP protein activity and protein levels, thereby resulting in greater HDL-C concentrations [14,15]. Among the CETP polymorphisms, rs708272 has been widely studied. Meta-analyses have shown that carriers of the B2 allele, associated with lower CETP, have higher HDL-C concentrations than B1B1 homozygotes [16]. The rs5882 and rs1800775 variants are also related to CETP abundance, activity, and lipid levels [17]. At present, the study of the CETP gene is mainly related to dyslipidemia. At the same time, the relevance between CETP gene polymorphisms and MS components, such as hypertension, type 2 diabetes, and low HDL-C has been studied [18–21]. We previously demonstrated that five of the eight functional CETP polymorphisms (rs1800775, rs3764261, rs12149545, rs711752, and rs708272) are closely linked to dyslipidemia among the Uyghur and Kazakh populations [22]. The studies above showed that CETP gene polymorphisms may be related to components of MS. The association between CETP and MS has been assessed by many scholars; the results were different in different populations and ethnic groups [23,24], and most were single locus polymorphism studies. Furthermore, there are insufficient data to draw conclusions regarding any association between polymorphisms of CETP and MS among the Uyghur ethnicity.

Xinjiang is a multi-ethnic settlement in China, and the Uyghur is the largest population present. It has a unique culture and unique life customs. Because the unique national characteristics and relatively low prevalence of MS, on the basis of previous research, we chose six single nucleotide polymorphisms (SNPs) (rs5882, rs1800775, rs3764261, rs12149545, rs711752, and rs708272) to study associations between CETP polymorphisms and MS and its components among the Uyghur. The findings may provide a scientific basis for the study of genetic susceptibility of MS among the Uyghur in Xinjiang.

2. Materials and Methods

2.1. Study Population

We designed a case-control study that included 571 individuals, resident in Jiashi County, Xinjiang Uyghur Autonomous Region, China, and subdivided into two groups including 280 MS patients and
291 healthy control individuals. All subjects in this study were randomly selected from our previous stratified randomized cluster samples using the group-matching method [25].

2.2. Epidemiological Survey and Biochemical Detection

Using a self-developed questionnaire, detailed information on demographic and personal lifestyles for each participant was collected during a face-to-face interview by trained investigators. The questionnaire included personal profile, details of disease, family medical history, diet, current alcohol consumption, smoking status, and physical exercise. Height, weight, waist circumference, hip circumference, and blood pressure were measured by trained field workers according to standardized methods [26]. Biochemical tests of blood samples included tests for fasting TG, total cholesterol (TC), HDL-C, LDL-C, and fasting plasma glucose (FPG). All blood detections were analyzed using an automatic biochemical analyzer (AU400, Olympus, Tokyo, Japan). Each subject signed an approved informed consent form. All experiments were performed in accordance with relevant guidelines and regulations. This study was approved by the Institutional Ethics Review Board (IERB) of the First Affiliated Hospital of Shihezi University School of Medicine (IERB No. SHZ2010LL01).

2.3. MS Diagnostic Criteria

MS was diagnosed using a new harmonizing definition formulated by the Joint Interim Statement criteria (JIS criteria) [2], which requires that the participants have three or more of the following five components: (1) central obesity (defined as waist circumference ≥85 cm in male subjects and ≥80 cm in female subjects, Chinese population waist circumference cutoffs); (2) elevated triglycerides: TG >150 mg/dL (1.7 mmol/L); (3) reduced HDL-C: HDL-C <40 mg/dL (1.0 mmol/L) in male subjects and <50 mg/dL (1.30 mmol/L) in female subjects; (4) elevated blood pressure: systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥85 mmHg; (5) elevated fasting glucose: fasting plasma glucose ≥100 mg/dL (5.6 mmol/L).

2.4. DNA Extraction and Genotyping Analysis

Fasting venous blood (200 µL) was taken from each study subject, and a blood genomic DNA isolation kit (Non-centrifugal columnar, Tiangen, Beijing, China) was used to isolate the genomic DNA. The extracted DNA was verified by gel electrophoresis (0.7% agarose). A NanoDrop spectrophotometer (Thermo Scientific, Waltham, MA, USA) was used for quantitative determination of DNA concentration and purity: concentration ≥30 ng/µL and purity levels (optical density [OD]: OD260/OD280) of 1.7–2.0 were considered acceptable. Samples that met these criteria were diluted to 10–30 ng/µL using double-distilled water and then stored at −80 °C. The sequences of the forward and reverse primers designed using the Mysequenom tool (www.mysequenom.com/Home) and AssayDesigner3.0 software (Sequenom, Inc., San Diego, CA, USA) are shown in Table 1. The process of polymerase chain reaction (PCR) amplification, purification, and single-base extension were consistent with previous research [22]. All representative SNP genotyping experiments were performed using TaqMan technology on an ABI3730xl system (Applied Biosystems, Foster City, CA, USA). ABI GeneMapper was used to complete the classification and present the results.

Table 1. Sequences of forward and reverse primers for genotyping of the CETP gene.

| Single Nucleotide Polymorphisms (SNPs) | Forward Sequence | Reverse Sequence | PCR Product | Allele |
|----------------------------------------|------------------|------------------|-------------|--------|
| rs5882                                 | TCACCATGGGCAATTTAGTGG | TATCAATGACTGGGAAGAGGG | 211 bp | A/G |
| rs1800775                              | CGACCTGTAGTTAAGAGTCATG | CAGTCCCTACTCTGACTACCTCC | 210 bp | A/C |
| rs3764261                              | AGGCCACCATGCGCTGCTTATG | GTTCCCTGACTGGCCAAGGGCTTC | 360 bp | G/T |
| rs1214954                              | AGGCCACCATGCGCTGCTTATG | GTTCCCTGACTGGCCAAGGGCTTC | 360 bp | G/A |
| rs711752                               | GCCTCCCTACACTGAGCTTCTGATG | ATGGGGCTGAGTGGAGCCTGCTCA | 276 bp | G/A |
| rs708272                               | GCCTCCCTACACTGAGCTTCTGATG | ATGGGGCTGAGTGGAGCCTGCTCA | 276 bp | C/T |
2.5. Statistical Analysis

We used EpiData3.02 software to establish a database and adopted a double entry method for data input and logic error detection. SPSS statistical software version 17.0 for Windows (SPSS, Inc. Chicago, IL, USA) was used for basic statistical analysis. Non-normally distributed continuous variables such as age, height, weight, body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), TG, TC, HDL-C, and LDL-C were presented as median and interquartile ranges (25th, 75th percentile). We conducted the Wilcoxon rank sum test to compare the differences of the means from two groups of measurement data. Categorical data such as gender, smoking status, and alcohol consumption were evaluated using the chi-square test. To estimate the association between the SNPs in CETP and MS, we conducted a logistic regression analysis to evaluate the odds ratios (OR) and 95% confidence intervals (95% CI). MS (0 = no, 1 = yes), central obesity (0 = no, 1 = yes), high blood pressure (0 = no, 1 = yes), high fasting glucose (0 = no, 1 = yes), high TG (0 = no, 1 = yes), and low HDL-C (0 = no, 1 = yes) were used as dependent variables, respectively. Independent variables included age, gender (1 = male, 2 = female), smoking (0 = no, 1 = yes), alcohol consumption (0 = no, 1 = yes), rs5882 (AA = 1, AG = 2, GG = 3), rs1800775 (AA = 1, AC = 2, CC = 3), rs3764261 (GG = 1, GA = 2, AA = 3), rs12149545 (GG = 1, GA = 2, AA = 3), and rs708272 (CC = 1, CT = 2, TT = 3).

SHEsis software was used to perform the Hardy–Weinberg equilibrium test, haplotype construction, and statistical analysis [27]. The criterion for significance was set at $p < 0.05$ for all tests.

3. Results

3.1. Assessment of Demographic and Clinical Characteristics of Study Subjects

Table 2 presents the demographic and clinical characteristics of the study population. The distribution of gender and height were well-matched ($p > 0.05$). The average age, weight, BMI, waist circumference, hip circumference, blood pressure, FPG, TG, TC, and LDL-C levels were higher in the case group than the control group (all $p < 0.001$), while the HDL-C levels were lower in the case group. There was no significant difference on current smokers and current alcohol drinkers between the two groups ($p > 0.05$).

| Characteristics          | Control ($n = 291$) | Case ($n = 280$) | Z/$\chi^2$ | $p$       |
|--------------------------|---------------------|-----------------|------------|-----------|
| Male/female              | 152/139             | 140/140         | 0.285      | 0.593     |
| Age, years               | 40 (29–56)          | 50 (38–60)      | −4.914     | $<0.001$  |
| Height, cm               | 158 (153–166)       | 160 (153–167)   | −1.066     | 0.286     |
| Weight, kg               | 55 (48–60.5)        | 64 (55–73)      | −10.002    | $<0.001$  |
| BMI, kg/m$^2$            | 21.03 (19.63–23.03) | 24.79 (22.20–27.64) | −12.065 | $<0.001$  |
| Waist circumference, cm  | 78 (74–82)          | 91.5 (85–99)    | −15.706    | $<0.001$  |
| Hip circumference, cm    | 92 (88–96)          | 99 (94–104)     | −11.341    | $<0.001$  |
| SBP, mmHg                | 118 (110–126)       | 132 (120–150)   | −10.118    | $<0.001$  |
| DBP, mmHg                | 74 (68–80)          | 82 (76–92)      | −8.346     | $<0.001$  |
| FPG, mmol/L              | 4.24 (3.85–4.69)    | 4.63 (4.11–5.25) | −6.310     | $<0.001$  |
| TC, mmol/L               | 0.78 (0.58–0.96)    | 2.31 (1.76–3.01) | −17.678    | $<0.001$  |
| TG, mmol/L               | 4.15 (3.65–4.60)    | 4.75 (4.00–5.63) | −6.980     | $<0.001$  |
| HDL-C, mmol/L            | 1.34 (1.23–1.49)    | 0.90 (0.78–1.02) | −17.940    | $<0.001$  |
| LDL-C, mmol/L            | 2.15 (1.80–2.62)    | 2.66 (2.05–3.22) | −6.258     | $<0.001$  |
| Current smoker, n (%)    | 40 (13.7)           | 36 (12.9)       | 0.098      | 0.735     |
| Current alcohol drinker, n (%) | 7 (2.4)       | 9 (3.2)      | 0.343      | 0.558     |

Notes: BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; FPG: fasting plasma glucose; TG: triglyceride; TC: total cholesterol; HDL-C: high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol.

3.2. Genotype and Allele Frequencies Distribution

The six SNPs genotypes and alleles frequency distributions for CETP between the control and case group are shown in Table 3. No obvious difference was found regarding the frequency distribution of the genotypes of rs5882 between the two groups ($p > 0.05$). We were pleasantly surprised to find
that there were significant differences for the other five SNPs between the two groups (all \( p < 0.05 \)). Similar to the allele frequency distribution analysis result, no obvious difference was found for rs5882 between the two groups \( (p > 0.05) \). After further investigation, we found that the T allele of rs3764261 \((24.6 \text{ vs. } 36.3, p < 0.001, \text{OR} = 0.575, 95\% \text{ CI} = 0.445–0.743)\) and rs708272 \((42.1 \text{ vs. } 51.2, p = 0.002, \text{OR} = 0.694, 95\% \text{ CI} = 0.550–0.877)\), and the A allele of rs12149545 \((22.5 \text{ vs. } 35.4, p < 0.001, \text{OR} = 0.530, 95\% \text{ CI} = 0.408–0.688)\) and rs711752 \((42.3 \text{ vs. } 51.2, p = 0.003, \text{OR} = 0.699, 95\% \text{ CI} = 0.554–0.883)\) had a lower frequency in the case group than in the controls. However, we observed that rs1800775-C more frequently appeared in the case group than in the control group \((45.7 \text{ vs. } 38.3, p = 0.011, \text{OR} = 1.356; 95\% \text{ CI} = 1.071–1.716)\). We also calculated the Hardy–Weinberg equilibrium \( p \)-value for each SNP to evaluate the sample’s representativeness. Six CETP SNPs were in the Hardy–Weinberg equilibrium \((all \ p > 0.05)\).

### 3.3. Association of Six SNPs and MS Subjects

We conducted multivariate logistic regression analysis to detect any associations between six CETP SNPs and MS. The results are shown in Table 4. The logistic regression analysis confirmed the results of the \( \chi^2 \) test of independence on the genotype frequencies of the CETP polymorphisms between cases and controls, following adjustment for age, gender, smoking, and alcohol consumption.

### 3.4. Risk Factor Analysis between Six CETP SNPs and Five Components of MS

We detailed a risk factor analysis between the six CETP SNPs and five components in MS after finding the association of six SNPs and MS subjects (Table 5). SNP rs5882 had no effect on the five components of MS \((all \ p > 0.05)\). For rs1800775, compared with AA genotype carriers, rs1800775-AC \((p = 0.026, \text{OR} = 0.540, 95\% \text{ CI} = 0.314–0.929)\) and rs1800775-CC \((p = 0.043, \text{OR} = 0.448, 95\% \text{ CI} = 0.206–0.976)\) carriers had a lower risk of high fasting glucose, whereas rs1800775-AC \((p = 0.031, \text{OR} = 1.557, 95\% \text{ CI} = 1.041–2.330)\) and rs1800775-CC \((p = 0.003, \text{OR} = 2.205, 95\% \text{ CI} = 1.316–3.696)\) carriers were at a higher risk of low HDL-C. For rs3764261, the risk of rs3764261-GT carriers in central obesity \((p = 0.004, \text{OR} = 0.631, 95\% \text{ CI} = 0.460–0.865)\) and high TG \((p = 0.022, \text{OR} = 0.667, 95\% \text{ CI} = 0.472–0.943)\) patients were lower than that of rs3764261-GG carriers, while rs3764261-GT \((p = 0.001, \text{OR} = 2.652, 95\% \text{ CI} = 1.526–4.609)\) carriers had a higher risk of high fasting glucose. For rs12149545, the risk of rs12149545-AG carriers in central obesity \((p = 0.001, \text{OR} = 0.597, 95\% \text{ CI} = 0.435–0.819)\), high TG \((p < 0.001, \text{OR} = 0.587, 95\% \text{ CI} = 0.413–0.833)\) and low HDL-C \((p = 0.018, \text{OR} = 0.633, 95\% \text{ CI} = 0.434–0.924)\) patients was lower than that of rs12149545-GG carriers, while rs12149545-AG \((p = 0.006, \text{OR} = 2.125, 95\% \text{ CI} = 1.245–3.629)\) carriers had a higher risk of high fasting glucose. For rs711752, compared with the GG genotype, rs711752-AA \((p = 0.007, \text{OR} = 0.500, 95\% \text{ CI} = 0.303–0.824)\) carriers had a lower risk of low HDL-C. Compared with rs708272-CC, rs708272-TT \((p = 0.006, \text{OR} = 0.498, 95\% \text{ CI} = 0.302–0.821)\) might reduce the risk of low HDL-C.
| SNPs  | Group | Genotype Distribution n (%) | HWE-P | Allelic Distribution | MAF n (%) | χ² | p | OR (95% CI) |
|-------|-------|----------------------------|-------|----------------------|-----------|----|---|-------------|
| rs5882 | Control | 122 (41.9) | CR 122 (43.6) | RR 42 (14.4) | 0.489 | 0.783 | 0.341 | R: 211 (36.3) | 0.400 | 0.527 | 1.000 (0.925–1.179) |
|       | Case    | 127 (43.6) | CR 123 (43.9) | RR 35 (12.5) | 0.645 |       |       | R: 193 (34.5) |       |       | |
| rs1800775 | Control | 111 (38.1) | CR 137 (47.1) | RR 43 (14.8) | 6.388 | 0.041 | 0.945 | R: 223 (38.3) | 6.415 | 0.011 | 1.000 (1.356–1.716) |
|        | Case    | 85 (30.4)  | CR 134 (47.9) | RR 61 (21.8) |       |       |       | R: 256 (45.7) |       |       | |
| rs3764261 | Control | 114 (39.2) | CR 143 (49.1) | RR 34 (11.7) | 18.966 | < 0.001 | 0.323 | R: 211 (36.3) | 18.132 | < 0.001 | 1.000 (0.575–0.743) |
|        | Case    | 156 (55.7) | CR 110 (39.3) | RR 14 (5.0)  |       |       |       | R: 138 (24.6) |       |       | |
| rs12149545 | Control | 117 (40.2) | CR 142 (48.8) | RR 32 (11.0) | 23.911 | < 0.001 | 0.253 | R: 206 (35.4) | 23.015 | < 0.001 | 1.000 (0.530–0.688) |
|        | Case    | 167 (59.6) | CR 100 (35.7) | RR 13 (4.6)  |       |       |       | R: 126 (22.5) |       |       | |
| rs711752  | Control | 69 (23.7)  | CR 146 (50.2) | RR 76 (26.1) | 8.998 | 0.011 | 0.945 | C: 284 (48.8) | 9.040 | 0.003 | 1.000 (0.554–0.883) |
|        | Case    | 93 (33.2)  | CR 137 (48.9) | RR 50 (17.9) |       |       |       | R: 237 (42.3) |       |       | |
| rs708272 | Control | 69 (23.7)  | CR 146 (50.2) | RR 76 (26.1) | 9.346 | 0.009 | 0.947 | C: 284 (48.8) | 9.410 | 0.002 | 1.000 (0.694–0.877) |
|        | Case    | 94 (33.6)  | CR 136 (48.6) | RR 50 (17.9) |       |       |       | R: 236 (42.1) |       |       | |

Notes: C–R: rs5882 (A–G), rs1800775 (A–C), rs3764261 (G–T), rs12149545 (G–A), rs711752 (G–A), rs708272 (C–T); HWE-P: Hardy–Weinberg equilibrium p-value; MAF: minor allele frequency.
Table 4. The relationship between six CETP SNPs and metabolic syndrome (MS).

| SNP     | Genotype | B    | SE   | Wals $\chi^2$ | df | $p$   | OR   | 95% CI       |
|---------|----------|------|------|---------------|----|-------|------|--------------|
| rs5882  | AA       | 1    |      |               |    |       |      |              |
|         | AG       | -0.099 | 0.185 | 0.285         | 1  | 0.593 | 0.906 | 0.630–1.303 |
|         | GG       | -0.120 | 0.268 | 0.200         | 1  | 0.654 | 0.887 | 0.524–1.501 |
| rs1800775 | AA      | 1    |      |               |    |       |      |              |
|         | AC       | 0.238 | 0.193 | 1.518         | 1  | 0.218 | 1.269 | 0.869–1.854 |
|         | CC       | 0.654 | 0.252 | 6.752         | 1  | 0.009 | 1.922 | 1.174–3.147 |
| rs3764261 | GG      | 1    |      |               |    |       |      |              |
|         | GT       | -0.594 | 0.181 | 10.714        | 1  | 0.001 | 0.552 | 0.387–0.788 |
|         | TT       | -1.242 | 0.350 | 12.605        | 1  | $p < 0.001$ | 0.289 | 0.145–0.573 |
| rs12149545 | GG     | 1    |      |               |    |       |      |              |
|         | AG       | -0.725 | 0.182 | 15.783        | 1  | $p < 0.001$ | 0.484 | 0.339–0.693 |
|         | AA       | -1.284 | 0.360 | 12.743        | 1  | $p < 0.001$ | 0.277 | 0.137–0.560 |
| rs711752  | GG       | 1    |      |               |    |       |      |              |
|         | AG       | -0.329 | 0.202 | 2.634         | 1  | 0.105 | 0.720 | 0.484–1.071 |
|         | AA       | -0.702 | 0.247 | 8.054         | 1  | 0.005 | 0.496 | 0.305–0.805 |
| rs708272  | CC       | 1    |      |               |    |       |      |              |
|         | CT       | -0.344 | 0.202 | 2.899         | 1  | 0.089 | 0.709 | 0.477–1.053 |
|         | TT       | -0.712 | 0.247 | 8.288         | 1  | 0.004 | 0.491 | 0.302–0.797 |

**Notes:** B: regression coefficient; SE: Standard error; OR: odds ratio; CI: confidence interval. The rs5882-AA, rs1800775-AA, rs3764261-GG, rs12149545-GG, rs711752-GG, and rs708272-CC were used as reference genotypes for the risk analysis.
Table 5. Risk factor analysis between six CETP SNPs and five components in MS.

| SNP    | Central Obesity | High Blood Pressure | High Fasting Glucose | High TG | Low HDL-C |
|--------|-----------------|---------------------|----------------------|---------|-----------|
|        | p               | OR (95% CI)         | p                    | OR (95% CI) | p          | OR (95% CI) |
| rs5882 | AA              | 1                   | 1                    | 1        | 1         | 1          |
|        | AG              | 0.549               | 0.906 (0.657–1.250)  | 0.376    | 0.854 (0.601–1.212) | 0.933 | 0.977 (0.572–1.670) | 0.693 | 1.073 (0.755–1.525) | 0.151 | 0.754 (0.513–1.109) |
|        | GG              | 0.953               | 0.986 (0.624–1.560)  | 0.481    | 1.194 (0.729–1.955) | 0.947 | 0.974 (0.441–2.150) | 0.121 | 0.663 (0.395–1.115) | 0.489 | 0.827 (0.483–1.416) |
| rs1800775 | AA           | 1                   | 1                    | 1        | 1         | 1          |
|        | AC              | 0.864               | 1.030 (0.738–1.435)  | 0.498    | 0.882 (0.615–1.267) | 0.026 | 0.540 (0.314–0.929) | 0.285 | 1.224 (0.845–1.773) | 0.031 | 1.557 (1.041–2.330) |
|        | CC              | 0.255               | 1.286 (0.834–1.985)  | 0.874    | 1.038 (0.653–1.650) | 0.043 | 0.448 (0.206–0.976) | 0.093 | 1.491 (0.936–2.377) | 0.003 | 2.205 (1.316–3.696) |
| rs3764261 | GG             | 0.004               | 0.631 (0.460–0.865)  | 0.972    | 0.994 (0.707–1.398) | 0.001 | 2.652 (1.526–4.609) | 0.022 | 0.667 (0.472–0.943) | 0.061 | 0.699 (0.481–1.017) |
|        | GT              | 0.074               | 0.624 (0.372–1.047)  | 0.161    | 0.664 (0.375–1.177) | 0.550 | 1.339 (0.514–3.490) | 0.042 | 0.539 (0.297–0.978) | 0.013 | 0.443 (0.234–0.841) |
|        | TT              | 0.001               | 0.597 (0.435–0.819)  | 0.953    | 1.010 (0.717–1.423) | 0.006 | 2.125 (1.245–3.629) | 0.014 | 0.567 (0.413–0.833) | 0.018 | 0.633 (0.434–0.924) |
| rs12149545 | GG            | 0.070               | 0.615 (0.363–1.041)  | 0.059    | 0.566 (0.313–1.023) | 0.680 | 1.220 (0.475–3.135) | 0.078 | 0.583 (0.320–1.063) | 0.007 | 0.410 (0.214–0.788) |
|        | AG              | 0.900               | 0.738 (0.519–1.049)  | 0.717    | 1.072 (0.735–1.563) | 0.089 | 1.699 (0.923–3.125) | 0.116 | 0.756 (0.518–1.103) | 0.364 | 0.624 (0.543–1.251) |
| rs711752 | GG              | 0.194               | 0.758 (0.499–1.151)  | 0.407    | 0.826 (0.526–1.297) | 0.499 | 1.291 (0.616–2.703) | 0.061 | 0.646 (0.409–1.020) | 0.007 | 0.500 (0.303–0.824) |
|        | AG              | 0.076               | 0.728 (0.512–1.034)  | 0.608    | 1.104 (0.757–1.609) | 0.082 | 1.710 (0.934–3.162) | 0.126 | 0.745 (0.511–1.086) | 0.351 | 0.820 (0.540–1.245) |
| rs708272 | CC              | 0.181               | 0.752 (0.495–1.142)  | 0.451    | 0.841 (0.536–1.320) | 0.487 | 1.300 (0.620–2.723) | 0.056 | 0.641 (0.406–1.111) | 0.006 | 0.496 (0.302–0.821) |

Notes: All the regression analysis was carried out after adjustment for age, gender, smoking, and alcohol drinking. Analysis of high blood pressure and high fasting glucose was then carried out after adjustment for central obesity. The analysis involving high TG was carried out after adjustment for central obesity and low HDL-C. Analysis concerning low HDL-C was carried out after adjustment for central obesity and high TG. The cut-off values (low-high) for the five parameters were as follows: central obesity: waist circumference ≥85 cm in male subjects and ≥80 cm in female subjects; (2) high TG: TG > 150 mg/dL (1.7 mmol/L); (3) low HDL-C: HDL-C < 40 mg/dL (1.0 mmol/L) in male subjects and <50 mg/dL (1.30 mmol/L) in female subjects; (4) elevated blood pressure: SBP ≥130 mm Hg and/or DBP ≥85 mm Hg; (5) high fasting glucose: fasting plasma glucose ≥100 mg/dL (5.6 mmol/L). The rs5882-AA, rs1800775-AA, rs3764261-GG, rs12149545-GG, rs711752-GG, and rs708272-CC were used as reference genotypes for the risk analysis of each component.
3.5. Linkage Disequilibrium (LD) and Hardy–Weinberg Equilibrium Testing

In our study, we calculated pairwise linkage disequilibrium (LD) between six SNPs, and the result is shown in Table 6. The value of $D'$ ranged from 0.060 to 1.000, and the value of $r^2$ spanned 0.003 to 0.996. Complete LD was observed for two pairs of SNPs: rs3764261 and rs12149545 ($D' = 1.000$, $r^2 = 0.931$) and rs711752 and rs708272 ($D' = 1.000$, $r^2 = 0.996$).

Table 6. Linkage disequilibrium test for the six CETP SNPs.

| SNP          | rs5882 | rs1800775 | rs3764261 | rs12149545 | rs711752 | rs708272 |
|--------------|--------|-----------|-----------|------------|----------|----------|
| rs5882       | -      | 0.545     | 0.069     | 0.060      | 0.455    | 0.457    |
| rs1800775    | 0.117  | -         | 0.860     | 0.862      | 0.833    | 0.833    |
| rs3764261    | 0.004  | 0.235     | -         | 1.000      | 0.880    | 0.874    |
| rs12149545   | 0.003  | 0.220     | 0.931     | -          | 0.979    | 0.972    |
| rs711752     | 0.129  | 0.442     | 0.387     | 0.446      | -        | 1.000    |
| rs708272     | 0.130  | 0.440     | 0.383     | 0.441      | 0.996    | -        |

Notes: The upper triangle is $D'$ value and the lower triangle is $r^2$ value.

3.6. Haplotype Analysis

Since rs5882 was obviously not in LD with the other SNPs, it was excluded during the process of haplotype construction. The remaining five SNPs above formed 11 kinds of haplotypes among the 32 types of possible haplotypes identified through SHEsis software. The results of four haplotypes analyses, in which frequencies were greater than 0.001, are presented in Table 7. The global haplotype frequencies in the case group were significantly different from the control group ($p < 0.001$). The A-G-G-G-C ($p = 0.013$, OR = 0.622, 95% CI = 0.427–0.906) and A-T-A-A-T ($p < 0.001$, OR = 0.519, 95% CI = 0.386–0.697) haplotypes were more frequent in the controls than in the case group. Compared with the C-G-G-G-C haplotype, A-G-G-G-C and A-T-A-A-T haplotypes might reduce the risk of MS.

Table 7. The discrepancy of haplotype frequencies of five CETP SNPs between the control and case group in the Uyghur.

| Haplotype     | Case (Freq)  | Control (Freq) | $\chi^2$ | $p$     | OR (95% CI) |
|---------------|--------------|----------------|----------|---------|-------------|
| C-G-G-G-C     | 245.72 (0.439)| 193.44 (0.332)  | -        | 1       | -           |
| A-G-G-A-T     | 103.92 (0.186)| 83.76 (0.144)   | 0.027    | 0.868   | 0.971 (0.689–1.370) |
| A-G-G-G-C     | 65.27 (0.117) | 81.99 (0.141)   | 6.176    | 0.013   | 0.622 (0.427–0.906) |
| A-T-A-A-T     | 123.00 (0.220)| 186.19 (0.320)  | 19.113   | $p < 0.001$ | 0.519 (0.386–0.697) |

Notes: Global chi2 is 23.149 (frequency <0.03 in both control & case has been dropped.); global $p < 0.001$. The C-G-G-G-C was used as a reference haplotype for obtaining the odds ratio calculations. The order of five SNPs in haplotypes is (from left to right): rs1800775 (A/C), rs3764261 (G/T), rs12149545 (G/A), rs711752 (G/A), and rs708272 (C/T).

4. Discussion

In China, the prevalence of MS is generally high. The rate in the Uyghur ethnic group was lower than that of Han and Kazak populations in the same area [10,28]. This may be related to Uyghur characteristics and genetic susceptibility. Therefore, we chose the Uyghur to study any relationships between CETP gene polymorphisms and MS. Since CETP is a key factor in the process of reverse cholesterol transport (RCT) and plays an important role in lipoprotein metabolism, it has attracted the attention of many scholars [29]. Some studies proved that CETP mutations may affect the abundance of serum CETP, which, in turn, affects lipid metabolism [17].

The results in this study showed that the levels of average age, BMI, waist circumference, blood pressure, FPG, and TG were higher in the case group than in the controls, while the level of HDL-C was lower in cases than in the control group. Some studies showed that the risk of MS increases with age [30], so the variable of age should be adjusted for in risk factor analysis. Central obesity,
elevated TG, reduced HDL-C, elevated blood pressure, and elevated fasting glucose are clinical symptoms of MS. Consistent with other studies [31], the levels of TC and LDL-C in the case group were higher than in the controls. Other studies [32] have shown that normal or slightly elevated LDL-C levels are characteristics of dyslipidemia among MS patients. However, differing results have appeared in other research [33]. This might be caused by ethnic differences. The distribution of gender between the two groups was well matched, and SNPs were all in accordance with Hardy–Weinberg equilibrium. The results above indicated that the genotypic frequencies were representative of their respective populations.

No obvious difference was found between the control and MS group including the frequency distribution of the genotypes and alleles of rs5882. Combined with the results of regression analysis, this SNP may not be involved in MS among the Uyghur population for the ethnic difference. Furthermore, meta-analyses [17] showed that rs5882 was related to the CETP abundance, activity, or lipid levels. Hence, further study is needed. For the other five SNPs, significant differences were found regarding the frequency distribution of genotypes and alleles between the control and MS groups. Our research showed that rs1800775-C frequency (41.9%) was lower than that in the Latvian (44.3%) [21] and European (51%) [34]. Compared with rs1800775-A carriers, individuals who carried rs1800775-C were more likely to develop MS. This SNP may increase the risk of MS. This is consistent with Radovica et al. [21], who also hold the view that rs1800775 can increase the risk of low HDL-C levels. For rs3764261, we discovered statistically significant association between T allele and MS. Furthermore, the rs3764261-T frequency (30.6%) was higher in Uyghur individuals than that in the Han population (16%) [35]. For the rs12149545 and rs711752 polymorphisms, the risk of MS was reduced among the A allele carriers. The rs12149545-A frequency was 29.1%, and the rs711752-A frequency (46.8%) was similar to that in Latvians (46.2%) [21]. For rs708272, the rs708272-T frequency (46.8%) was higher than that in Austria (41.3) [36], Turkey (43%) [37], or Southern Thailand (37.43%) [38]. Moreover, rs708272-T plays an inactive role in the development of MS. This is consistent with Anton et al. [36] who hold that the risk of MS was reduced by 32% ($p = 0.005$, OR = 0.68) in carriers of the B2 variant. However, this was different from observations by Jeenduang [38] and Maroufi [39].

Based on these findings, to verify the authenticity, we conducted a logistic regression analysis adjusting for covariates such as age, gender, smoking, and alcohol consumption. We found that the association remained. The results showed that rs3764261-GT/TT, rs12149545-AG/AA, rs711752-AA, and rs708272-TT might reduce the risk of MS on different levels. This suggested that the four SNPs may be associated with MS in the Uyghur population. The rs708272 polymorphism was one of the loci with high variant frequency, and it is the most widely studied CETP gene polymorphism. Compared with the CC genotype, the risk of MS among the rs708272-CC carriers was reduced. Similarly, a previous study showed that MS patients have a higher prevalence of the B1B1(CC) genotype in Egypt [40]. This also explained why the prevalence of MS among the Uyghur is lower than that among other ethnic groups in the same area [10]. However, compared with AA genotype carriers, rs1800775-CC increased the risk of MS. Hence, we suspected that rs1800775-CC might be a risk factor for MS. The association of rs1800775 with MS has not been previously reported, while the relationship between rs1800775 and low HDL-C has been well established in a systematic in-depth review [41]. It has the potential to increase the risk of low HDL-C and may serve as a basis for MS. These studies above indicated that the correlation between CETP gene polymorphisms and MS has racial and ethnic differences.

After analyzing the association between six SNPs and MS, we further investigated the relationship between the six SNPs and five components of MS, respectively. Compared with the relevance between six SNPs and MS, we found that the relevance was slightly different among the five components. For central obesity, we found that rs3764261-GT and rs12149545-AG might reduce the risk of this disease. However, in another adult Chinese population, Ruan et al. [42] discovered that less common alleles of Taq1b (rs708272) and I405V (rs5882) polymorphisms of CETP are moderately associated with risk of obesity. For high blood pressure, no significant correlation was found among the six SNPs. For high fasting glucose, rs1800775-AC/CC might reduce the risk of this disease, but rs3764261-GT
and rs12149545-AG might increase the risk. However, another study showed that the rs3764261 polymorphism of \textit{CETP} is not associated with type 2 diabetes in patients with clinically manifest vascular disease [43]. For high TG, rs3764261-GT/TT and rs12149545-AG might reduce the risk of elevated TG. However, a statistically significant association was not discovered between rs3764261 and high TG in another Chinese population [44]. For low HDL-C, we found that all of the SNPs we studied, except rs5882, had an effect on the risk of low HDL-C. The rs1800775-AC/CC increased the risk of low HDL-C, while the other four SNPs reduced the risk of low HDL-C. In accordance with our observation, the effect of the six SNPs on the risk of low HDL-C was previously verified in other populations [21,22,37,42,43,45,46]. Combined with functional \textit{CETP} gene variants effects and serum HDL-C concentration [34,47], we suspected that low HDL-C might be the most relevant component to \textit{CETP} gene polymorphisms among the five components of MS.

Complete LD was found for two pairs of SNPs, and strong LD was identified between other SNPs. Similarly, strong LD was found between rs708272 and rs1800775 in Europeans [48] and in other parts of China [49]. Some reports suggest that the rs708272 polymorphism acts through LD to a second SNP in the promoter of the \textit{CETP} gene at position rs1800775 from the transcription start site [50]. Therefore, the discovery of complete LD may provide direction for further studies.

The association of four haplotypes of the \textit{CETP} gene and MS disease was analyzed using SHEsis software. We observed that the A-G-G-G-C and A-T-A-A-T haplotypes were more frequent in the controls than in the case group. Thus, we suspected that the two haplotypes, especially the A-T-A-A-T haplotype, were protective factors that can reduce the risk of MS and protect people from the harm of MS. Similarly, the common A-A-T haplotype defined by the G-2708A, rs1800775, and rs708272 polymorphisms was consistently associated with reduced \textit{CETP} activity and increased HDL-C levels in another study [51]. However, haplotype formation was influenced by many aspects and we just demonstrated \textit{CETP} gene SNP haplotypes in a small random sample of the Uyghur population. Therefore, this complex relationship needs to be further explored and verified.

5. Study Limitations

Despite our comprehensive analysis, there are still potential limitations in our study. First, more than 180 SNPs exist in the \textit{CETP} gene. In our study, we only selected six major functional SNPs to study the relationship between \textit{CETP} and MS. Therefore, the analysis and results of our study may be unilateral. In addition, we investigated the association of six SNPs with MS and its components, but did not study the interaction between genes and genes, or between genes and environmental factors in MS. Therefore, we need further research into the effects of these interactions.

6. Conclusions

The rs1800775, rs3764261, rs12149545, rs711752, and rs708272 polymorphisms of \textit{CETP} were associated with MS and its components among the Uyghur ethnic group. Complete LD was found for two pairs of SNPs (rs3764261 and rs12149545, and rs711752 and rs708272). The A-G-G-G-C and A-T-A-A-T haplotypes might be protective factors for MS.

Acknowledgments: This research was supported by grants from the National Natural Science Foundation of China (No. 81560551) and the National Natural Science Foundation of Shihezi University (0305KX0161).

Author Contributions: We thank all the individuals who participated in the present study. Shuxia Guo, Huixian Hou, and Rulin Ma had the original idea for the study and all co-authors carried out the design. Heng Guo, Jia He, Yunhua Hu, Lati Mu, Yizhong Yan, and Jiaolong Ma were responsible for recruitment and follow-up of study participants. Shugang Li and Jingyu Zhang were responsible for data cleaning, and Yusong Ding, Mei Zhang, Qiang Niu, and Jiaming Liu carried out the analyses. Huixian Hou and Rulin Ma drafted the manuscript, which was revised by all authors. All authors read and approved the final manuscript.

Conflicts of Interest: The authors declare no conflict of interest.
References

1. Maury, E.; Brichard, S.M. Adipokine dysregulation, adipose tissue inflammation and metabolic syndrome. *Mol. Cell. Endocrinol.* 2010, 314, 1. [CrossRef] [PubMed]

2. Alberti, K.G.; Eckel, R.H.; Grundy, S.M.; Zimmet, P.Z.; Donato, K.A.; Fruchart, J.C; James, W.P.; Loria, C.M.; Smith, S.C., Jr.; et al. Harmonizing the metabolic syndrome: A joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International A. *Circulation* 2009, 120, 1640. [CrossRef] [PubMed]

3. Grundy, S.M. Metabolic syndrome: A multiplex cardiovascular risk factor. *J. Clin. Endocrinol. Metab.* 2007, 92, 399–404. [CrossRef] [PubMed]

4. Aguilar, M.; Bhuket, T.; Torres, S.; Liu, B.; Wong, R.J. Prevalence of the metabolic syndrome in the United States, 2003–2012. *JAMA* 2015, 313, 1973–1974. [CrossRef] [PubMed]

5. Cameron, A.J.; Magliano, D.J.; Zimmet, P.Z.; Welborn, T.; Shaw, J.E. The metabolic syndrome in Australia: Prevalence using four definitions. *Diabetes Res. Clin. Pract.* 2007, 77, 471–478. [CrossRef] [PubMed]

6. Nishimura, R.; Nakagami, T.; Tominaga, M.; Yoshiike, N.; Tajima, N. Prevalence of metabolic syndrome and optimal waist circumference cut-off values in Japan. *Diabetes Res. Clin. Pract.* 2007, 78, 77–84. [CrossRef] [PubMed]

7. Li, R.; Li, W.; Lun, Z.; Zhang, H.; Sun, Z.; Sam, K.J.; Qiu, S.; Cheng, Y.; Liu, Y. Prevalence of metabolic syndrome in mainland China: A meta-analysis of published studies. *BMC Public Health* 2016, 16, 296. [CrossRef] [PubMed]

8. Li, C.; Guo, S.; Ma, R.; Ding, Y.; Guo, H.; Liu, J.; Xu, S.; Zhang, J.; Li, S.; Zhang, M. Prevalence of metabolic syndrome in Uygur population in Xinjiang. Kashi, 2010. *J. Chin. Prev. Med.* 2012, 46, 419–423.

9. Gu, D.; K, R.; Yang, W.; Chen, S.; Wu, X.; Duan, X.; Pu, X.; Xu, L.; Wu, X.; Chen, X.; et al. Prevalence of metabolic syndrome in Chinese adults. *J. Chin. Diabetes* 2005, 13, 181–186.

10. Yang, T.; Ma, Y.; Yang, Y.; Yu, Z.; Liu, F.; Li, X.; Xiang, Y.; Huang, Y.; Chen, B. The prevalence of metabolic syndrome in Han and Uygur in adults from Xinjiang. *J. Xinjiang Med. Univ.* 2011, 34, 129–132.

11. Shi, Y.; Zhang, P.; Jiao, S. Research Progress on prevalence and risk factors of metabolic syndrome. *J. Chin. Chronic Dis. Prev. Control* 2007, 15, 615–617.

12. Matsuura, F.; Wang, N.; Chen, W.; Jiang, X.C.; Tall, A.R. HDL from CETP-deficient subjects shows enhanced ability to promote cholesterol efflux from macrophages in an apoE- and ABCG1-dependent pathway. *J. Clin. Investig.* 2006, 116, 1435–1442. [CrossRef] [PubMed]

13. Papp, A.C.; Pinsonneault, J.K.; Wang, D.; Newman, L.C.; Gong, Y.; Johnson, J.A.; Pepine, C.J.; Kumari, M.; Hingorani, A.D.; Talmud, P.J.; et al. Cholesteryl Ester Transfer Protein (CETP) Polymorphisms Affect mRNA Splicing, HDL Levels, and Sex-Dependent Cardiovascular Risk. *PLoS ONE* 2012, 7, e31930. [CrossRef] [PubMed]

14. Lu, H.; Inazu, A.; Moriyama, Y.; Higashikata, T.; Kawashiri, M.A.; Yu, W.; Huang, Z.; Okamura, T.; Mabuchi, H. Haplotype analyses of cholesteryl ester transfer protein gene promoter: A clue to an unsolved mystery of TaqIB polymorphism. *J. Mol. Med.* 2003, 81, 246–255. [CrossRef] [PubMed]

15. Frisdal, E.; Klerko, A.H.E.M.; Goff, W.L.; Tanck, M.W.T.; Lagarde, J.P.; Jukema, J.W.; Kastelein, J.J.P.; Chapman, M.J.; Guerin, M. Functional interaction between -629C/A, -971G/A and -1337C/T polymorphisms in the CETP gene is a major determinant of promoter activity and plasma CETP concentration in the REGRESS Study. *Hum. Mol. Genet.* 2005, 14, 2607–2618. [CrossRef] [PubMed]

16. Boekholdt, S.M.; Sacks, F.M.; Jukema, J.W.; Shepherd, J.; Freeman, D.J.; McMahan, A.D.; Cambien, F.; Nicaud, V.; de Grooth, G.J.; Talmud, P.J.; et al. Cholesteryl ester transfer protein TaqIB variant, high-density lipoprotein cholesterol levels, cardiovascular risk, and efficacy of pravastatin treatment: Individual patient meta-analysis of 13,677 subjects. *Circulation* 2005, 111, 278. [CrossRef] [PubMed]

17. Thompson, A.; Angelantonio, E.D.; Sarwar, N.; Erqou, S.; Saleheen, D.; Dullaart, R.P.F.; Kearney, B.; Zheng, Y.; Danesh, J. Association of Cholesteryl Ester Transfer Protein Genotypes With CETP Mass and Activity, Lipid Levels, and Coronary Risk. *JAMA* 2008, 299, 2777. [CrossRef] [PubMed]

18. Su, Y.; Wu, K.; Zhang, Y.; Sun, Y.; Xia, R.; Zhang, Y.; Qiu, Y. Association between CETP H405 V polymorphism and hypertension in Hainan Han population. *J. Chin. Gerontol.* 2016, 36, 4458–4459.
19. Schechter, C.B.; Barzilai, N.; Crandall, J.P.; Atzmon, G. Cholesteryl Ester Transfer Protein (CETP) Genotype and Reduced CETP Levels Associated with Decreased Prevalence of Hypertension. *Mayo Clin. Proc.* 2010, 85, 522. [CrossRef] [PubMed]

20. Li, H.; Xiao, H.; Zhang, Y.; Zheng, Y.; Wang, X. Relationship between CETP gene polymorphism and type 2 diabetes in Uygur. *Chin. Public Health* 2009, 25, 1430–1432.

21. Radovica, I.; Fridmanis, D.; Vaivade, I.; Nikitina-Zake, L.; Klovins, J. The association of common SNPs and haplotypes in CETP gene with HDL cholesterol levels in Latvian population. *PLoS ONE* 2013, 8, e64191. [CrossRef] [PubMed]

22. Guo, S.; Hu, Y.; Ding, Y.; Liu, J.; Zhang, M.; Ma, R.; Guo, H.; Wang, K.; He, J.; Yan, Y.; et al. Association between Eight Functional Polymorphisms and Haplotypes in the Cholesterol Ester Transfer Protein (CETP) Gene and Dyslipidemia in National Minority Adults in the Far West Region of China. *Int. J. Environ. Res. Public Health* 2015, 12, 15979–15992. [CrossRef] [PubMed]

23. Cañhua-Pablo, J.Á.; Cruz, M.; Méndez-Palacios, A.; Antúnez-Ortiz, D.L.; Vences-Velázquez, A.; Alarcón-Romero, L.D.C.; Parra, E.J.; Tello-Flores, V.A.; Leyva-Vázquez, M.A.; Villadarest-Salgado, A.; et al. Polymorphisms in the LPLandCETPGenes and Haplotype in theESR1Gene Are Associated with Metabolic Syndrome in Women from Southwestern Mexico. *Int. J. Mol. Sci.* 2015, 16, 21539–21554. [CrossRef] [PubMed]

24. Wang, L.; Xiao, H.; Zhang, Y.; Zheng, Y.; Wang, X. Relationship between CETP gene polymorphism and type 2 diabetes in Uygur. *Chin. Public Health* 2009, 25, 1430–1432.

25. Radovica, I.; Fridmanis, D.; Vaivade, I.; Nikitina-Zake, L.; Klovins, J. The association of common SNPs and haplotypes in CETP gene with HDL cholesterol levels in Latvian population. *PLoS ONE* 2013, 8, e64191. [CrossRef] [PubMed]

26. Guo, S.; Hu, Y.; Ding, Y.; Liu, J.; Zhang, M.; Ma, R.; Guo, H.; Wang, K.; He, J.; Yan, Y.; et al. Association between Eight Functional Polymorphisms and Haplotypes in the Cholesterol Ester Transfer Protein (CETP) Gene and Dyslipidemia in National Minority Adults in the Far West Region of China. *Int. J. Environ. Res. Public Health* 2015, 12, 15979–15992. [CrossRef] [PubMed]

27. Cañhua-Pablo, J.Á.; Cruz, M.; Méndez-Palacios, A.; Antúnez-Ortiz, D.L.; Vences-Velázquez, A.; Alarcón-Romero, L.D.C.; Parra, E.J.; Tello-Flores, V.A.; Leyva-Vázquez, M.A.; Villadarest-Salgado, A.; et al. Polymorphisms in the LPL and CETP genes and haplotype in the ESR1 gene are associated with metabolic syndrome in women from southwestern Mexico. *Int. J. Mol. Sci.* 2015, 16, 21539–21554. [CrossRef] [PubMed]

28. He, J.; Guo, S.; Liu, J.; Zhang, M.; Ding, Y.; Zhang, J.; Li, S.; Xu, S.; Niu, Q.; Guo, H.; et al. Ethnic differences in prevalence of general obesity and abdominal obesity among low-income rural Kazakh and Uyghur adults in far western China and implications in preventive public health. *PLoS ONE* 2014, 9, e106723. [CrossRef] [PubMed]

29. World Health Organization. Obesity: Preventing and managing the global epidemic. Report of a WHO consultation. *World Health Organ. Tech. Rep.* 2000, 894, 1–253.

30. Shi, Y.Y.; Lin, H.E. SHEsis, a powerful software platform for analyses of linkage disequilibrium, haplotype construction, and genetic association at polymorphism loci. *Cell Res.* 2005, 15, 97–98. [CrossRef] [PubMed]

31. Nakano, S.; Kuboki, K.T.; Nishimura, C.; Yoshino, G. Small, dense LDL and high-sensitivity C-reactive protein (hs-CRP) in metabolic syndrome with type 2 diabetes mellitus. *J. Atheroscler. Thromb.* 2010, 17, 410–415. [CrossRef] [PubMed]

32. Ginsberg, H.N.; Zhang, Y.L.; Hernandez-Ono, A. Metabolic Syndrome: Focus on Dyslipidemia. *Obesity* 2006, 14, 41S–49S. [CrossRef] [PubMed]

33. Mascarenhas-Melo, F.; Sereno, J.; Teixeira-Lemos, E.; Marado, D.; Palavra, F.; Pinto, R.; Rocha-Pereira, P.; Teixeira, F.; Reis, F. Implication of low HDL-C levels in patients with average LDL-c levels and adiponectin. *Mediat. Inflamm.* 2013, 2013, 612038. [CrossRef] [PubMed]

34. Kathiresan, S.; Melander, O.; Guiducci, C.; Surti, A.; Burtt, N.P.; Rieder, M.J.; Cooper, G.M.; Roos, C.; Voight, B.F.; Havulinna, A.S.; et al. Six new loci associated with blood low-density lipoprotein cholesterol, high-density lipoprotein cholesterol or triglycerides in humans. *Nat. Genet.* 2008, 40, 189. [CrossRef] [PubMed]

35. Zhou, L.; He, M.; Mo, Z.; Wu, C.; Yang, H.; Yu, D.; Yang, X.; Zhang, X.; Wang, Y.; Sun, J.; et al. A genome wide association study identifies common variants associated with lipid levels in the Chinese population. *PLoS ONE* 2012, 8, e82420. [CrossRef] [PubMed]
36. Anton, S.; Tobias, T.; Markus, L.; Andreas, R.; Susanne, K.; Bernhard, P.; Ebenbichler, C.F.; Patsch, J.R. The Taq1B-variant in the Cholesteryl Ester–Transfer Protein Gene and the Risk of Metabolic Syndrome. *Obesity* 2008, 16, 919–922.

37. Ozsait, B.; Kömürçü, B.E.; Poda, M.; Can, G.; Hergenci, G.; Onat, A.; Humphries, S.E.; Erginol, U.N. CETP TaqIB polymorphism in Turkish adults: Association with dyslipidemia and metabolic syndrome. *Anatol. J. Cardiol.* 2008, 8, 324–330.

38. Jeenduang, N.; Porntadavity, S.; Nuinoon, M.; Horpet, D.; Thapkwam, N.; Thaworn, P.; Theanmontri, S. Studies of the CETP TaqIB and ApoE Polymorphisms in Southern Thai Subjects with the Metabolic Syndrome. *Biochem. Genet.* 2015, 53, 184–199. [CrossRef] [PubMed]

39. Maroufi, N.F.; Farzaneh, K.; Alibabrdel, M.; Zarei, L.; Cheraghi, O.; Soltani, S.; Montazersaheb, S.; Akbarzadeh, M.; Nouri, M. Taq1B Polymorphism of Cholesteryl Ester Transfer Protein (CETP) and Its Effects on the Serum Lipid Levels in Metabolic Syndrome Patients. *Biochem. Genet.* 2016, 54, 894–902. [CrossRef] [PubMed]

40. Elsammak, M.Y.; Al-Sharkaweey, R.M.; Fahmy, M.; Reda, A.A.; Farid, W.; Emara, A.; Hassan, H.; Kandil, M.H. Taq 1B polymorphism of cholesteryl ester transfer protein (CETP) in Egyptian patients with metabolic syndrome. *Diabetes Metab. Syndr. Clin. Res. Rev.* 2011, 5, 61–65. [CrossRef] [PubMed]

41. Boes, E.; Coassin, S.; Kollerits, B.; Heid, I.M.; Kronenberg, F. Genetic-epidemiological evidence on genes associated with HDL cholesterol levels: A systematic in-depth review. *Exp. Gerontol.* 2009, 44, 136–160. [CrossRef] [PubMed]

42. Ruan, X.; Ma, L.; Wang, S.; Lindpaintner, K.; Liu, X.; Wang, B.; Peng, Z.; Ma, X.; Cheng, M.; Zhang, J.; et al. TAQIB and I405V polymorphisms of CETP are moderately associated with obesity risk in the Chinese adult population. *Acta Diabetol.* 2010, 47, 217–224. [CrossRef] [PubMed]

43. Koopal, C.; Graaf, Y.V.D.; Asselbergs, F.W.; Westerink, J.; Visseren, F.L.J. Association between CETP gene polymorphism, insulin resistance and risk of diabetes mellitus in patients with vascular disease. *Atherosclerosis* 2015, 242, 605–610. [CrossRef] [PubMed]

44. Liu, Y.; Zhou, D.; Zhang, Z.; Song, Y.; Zhang, D.; Zhao, T.; Chen, Z.; Sun, Y.; Zhang, D.; Yang, Y.; et al. Effects of genetic variants on lipid parameters and dyslipidemia in a Chinese population. *J. Lipid Res.* 2011, 52, 354–360. [CrossRef] [PubMed]

45. Wang, B.; Tan, X.; Yang, L. The Correlation Study of Dyslipidemia and CETP rs3764261 Gene Polymorphism. *J. Shihezi Univ.* 2012, 30, 345–350.

46. Chen, S.N.; Cilingiroglu, M.; Todd, J.; Lombardi, R.; Willerson, J.T.; Gotto, A.M., Jr.; Ballantyne, C.M.; Marian, A.J. Candidate genetic analysis of plasma high-density lipoprotein-cholesterol and severity of coronary atherosclerosis. *BMJ Med. Genet.* 2009, 10, 111. [CrossRef] [PubMed]

47. Barbosa, E.J.; Glad, C.A.; Nilsson, A.G.; Filipsson, N.H.; Götherström, G.; Svensson, P.A.; Vinotti, L.; Bengtsson, B.A.; Nilsson, S.; Boguszewski, C.L. Genotypes associated with lipid metabolism contribute to differences in serum lipid profile of GH-deficient adults before and after GH replacement therapy. *Eur. J. Endocrinol.* 2012, 167, 353–362. [CrossRef] [PubMed]

48. Sofat, R. Separating the mechanism-based and off-target actions of cholesteryl ester transfer protein inhibitors with CETP gene polymorphisms. *Circulation* 2010, 121, 52. [CrossRef] [PubMed]

49. Wang, J.; Li, J.W.; Yong, Z.; Ping, G.; Jia, Q.S.; Shi, S.J.; Jian, B.G. CETP gene polymorphisms and risk of coronary atherosclerosis in a Chinese population. *Lipids Health Dis.* 2013, 12, 176. [CrossRef] [PubMed]

50. Klerkx, A.H.; Tanck, M.W.; Kastelein, J.J.; Molhuizen, H.O.; Jukema, J.W.; Zwinderman, A.H.; Kuivenhoven, J.A. Haplotype analysis of the CETP gene: Not Taq1B, but the closely linked -629C→A polymorphism and a novel promoter variant are independently associated with CETP concentration. *Hum. Mol. Genet.* 2003, 12, 111. [CrossRef] [PubMed]

51. Mccaskie, P.A.; Beilby, J.P.; Chapman, C.M.; Hung, J.; Mcquillan, B.M.; Thompson, P.L.; Palmer, L.J. Cholesteryl ester transfer protein gene haplotypes, plasma high-density lipoprotein levels and the risk of coronary heart disease. *Hum. Genet.* 2007, 121, 401–411. [CrossRef] [PubMed]

© 2017 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (http://creativecommons.org/licenses/by/4.0/).