Study of the association of 17 lipid-related gene polymorphisms with coronary heart disease

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Abstract

Objective: Blood lipids are well-known risk factors for coronary heart disease (CHD). The aim of this study was to explore the association between 17 lipid-related gene polymorphisms and CHD.

Methods: The current study examined with 784 CHD cases and 739 non-CHD controls. Genotyping was performed on the MassARRAY iPLEX® assay platform.

Results: Our analyses revealed a significant association of APOE rs7259620 with CHD (genotype: $\chi^2=6.353$, df=2, $p=0.042$; allele: $\chi^2=5.05$, df=1, $p=0.025$; recessive model: $\chi^2=5.57$, df=1, $p=0.018$). A further gender-based subgroup analysis revealed significant associations of APOE rs7259620 and PPAP2B rs72664392 with CHD in males (genotype: $\chi^2=8.379$, df=2, $p=0.015$; allele: $\chi^2=5.190$, df=1, $p=0.023$; recessive model: $\chi^2=19.3$, df=1, $p<0.001$) and females (genotype: $\chi^2=9.878$, df=2, $p=0.007$), respectively. Subsequent breakdown analysis by age showed that CETP rs4783961, MLXIPL rs35493868, and PON2 rs12704796 were significantly associated with CHD among individuals younger than 55 years of age (CETP rs4783961: $\chi^2=8.966$, df=1, $p=0.011$ by genotype; MLXIPL rs35493868: $\chi^2=4.87$, df=1, $p=0.027$ by allele; $\chi^2=4.88$, df=1, $p=0.027$ by dominant model; PON2 rs12704796: $\chi^2=6.511$, df=2, $p=0.039$ by genotype; $\chi^2=6.210$, df=1, $p=0.013$ by allele; $\chi^2=5.03$, df=1, $p=0.025$ by dominant model). Significant allelic association was observed between LEPR rs656451 and CHD among individuals older than 65 years of age ($\chi^2=4.410$, df=1, $p=0.036$).

Conclusion: Our study revealed significant associations of APOE, PPAP2B, CETP, MLXIPL, PON2, and LEPR gene polymorphisms with CHD among the Han Chinese. (Anatol J Cardiol 2018; 19: 360-7)

Keywords: coronary heart disease, APOE, PPAP2B, CETP, MLXIPL, PON2, LEPR

Introduction

Coronary heart disease (CHD) is characterized by atherosclerosis, which leads to vascular stenosis and occlusion. Dyslipidemia is known as a risk factor for CHD (1). Blood lipids have been reported to predict the risk of CHD (2, 3), which encouraged us to examine the association of lipid-related gene polymorphisms with CHD (4).

In this study, we selected seven adipocytokine signaling pathway genes, including three peroxisome proliferator-activated receptor (PPAR) signaling pathway genes [angiopoietin-like 4 (ANGPTL4), adiponectin (ADIPOQ), and apolipoprotein A-V (APOA5)], leptin (LEP), leptin receptor (LEPR), adiponectin receptor 1 (ADIPOR1), and 5′-AMP-activated protein kinase subunit gamma-1 (PRKAG1). PPAR or adipocytokine signaling pathway genes have been reported to be significantly upregulated in ruptured plaques (5). Of the remaining lipid-related genes, angiopeptin-like 3 (ANGPTL3) is a member of the angiopeptin-like protein family, which can regulate the activity of lipoprotein lipase in the lipolytic processing of triglyceride (TG)-rich lipoproteins (6). Apolipoprotein E (APOE) regulates plasma low-density lipoprotein (LDL) levels (7-9). Paraoxonase 2 (PON2) and paraoxonase 3 (PON3) are antioxidants against atherosclerosis (10). Very-low-density-lipoprotein receptor (VLDLR) can affect the metabolism of VLDL-TGs, which are associated with CHD (11). MLX-interacting protein-like (MLXIPL) gene encodes carbohydrate response element-binding protein that has been found to be significantly associated with CHD (12). Scavenger receptor class B type 1 (SCARB1) can regulate the levels of high-density lipoprotein cholesterol (HDL-C) and thus might influence CHD incidence (13). Cholesteryl ester transfer protein (CETP) has been shown to increase the risk of CHD by disrupting the balance of...
HDL-C and LDL-cholesterol levels in the plasma (14). Proprotein convertase subtilisin/kexin type 9 (PCSK9) can reduce blood cholesterol levels and is associated with CHD (15). Phosphatidic acid phosphatase type 2B (PPAP2B), which catalyzes phosphoric acid hydrolysis and thus contributes to glycerophospholipid and triacylglycerol syntheses, has been shown to be associated with CHD (16, 17).

On the basis of previous studies, the aim of this study was to assess the association of 17 lipid-related gene polymorphisms with CHD in the Han Chinese.

Methods

Sample collection

A total of 784 CHD cases and 739 non-CHD controls were enrolled in the current study. The enrolled cases were classified on the basis of the findings of standardized coronary angiography according to the Seldinger’s method (18). The classification details have been reported in our previous studies (19-21). The study protocol was approved by the ethical committees of Ningbo First Hospital and Ningbo University. Written informed consent was obtained from all the participants.

Single nucleotide polymorphism (SNP) genotyping

DNA extraction and quantification were performed as previously described (22, 23). Genotyping was performed on the MassARRAY iPLEX® assay platform (Sequenom, San Diego, CA, USA). The primer sequences and the details of the selected SNPs are presented in Table 1.

| Gene   | SNP     | Primer sequences                  |
|--------|---------|-----------------------------------|
| PCSK9  | rs2479409 | 1st primer: ACGTTGGATGTTGCCTACCATAGAATTCTG; |
|        |         | 2nd primer: ACGTTGGATGGCTATCATGCTTTAAGGGG; |
|        |         | Extend primer: tTTCAGGTTTTAAGTTTGCAAAGA; |
| PPAP2B | rs72664392 | 1st primer: ACGTTGGATCCATATTGTCAGTTGCC; |
|        |         | 2nd primer: ACGTTGGATGAAGGGCTTCCCTTTGATCT; |
|        |         | Extend primer: tcTCTTTATAGTGCCTAGCA; |
| ANGPTL3| rs11207997 | 1st primer: ACGTTGGATGATTAGTAAATTACCCC; |
|        |         | 2nd primer: ACGTTGGATGAAAAGCCGGCTCAGCTGTTC; |
|        |         | Extend primer: tcctCATGGATTAGTCTCCTCATCT; |
| LEPR   | rs6656451 | 1st primer: ACGTTGGATGCAATTACCATCAGCGCTGGG; |
|        |         | 2nd primer: ACGTTGGATGAAGGGCTTCCCTCTGATCT; |
| ADIPO1 | rs7523903 | 1st primer: ACGTTGGATGTACAAAGTGCAGCTGGGAAG; |
|        |         | 2nd primer: ACGTTGGATGTGCCCAGGCTGTCAAAAATG; |
|        |         | Extend primer: GGTTGAGAAAGATTCAAGAAGACC; |
| ADIPOQ | rs266729 | 1st primer: ACGTTGGATGATGTGTGGCTTGCAAGAACC; |
|        |         | 2nd primer: ACGTTGGATGTTGGCTTTGCAAGAAGACC; |
|        |         | Extend primer: CACGCTCATGTTTTTGGTTTGAAG; |
| MLXIPL | rs35493868 | 1st primer: ACGTTGGATGTCAAGCGATTCTCCCTCTATCT; |
|        |         | 2nd primer: ACGTTGGATGCTTTCGAGGCGCTTACC; |
|        |         | Extend primer: GCATGTAGTCCTAGCTACT; |
| PON3   | rs11770903 | 1st primer: ACGTTGGATGAGGAAAAGACAGCGCTGGGAAG; |
|        |         | 2nd primer: ACGTTGGATGCTAGGAGAAAGAGGCGCTCAG; |
|        |         | Extend primer: caCTACCTCGCCAAGGAA; |
| PON2   | rs12704796 | 1st primer: ACGTTGGATGTTGGAGAGCAGTGTAGCTGGTTT; |
|        |         | 2nd primer: ACGTTGGATGCAGGCAAGAGAGGGCTTAC; |
determined by odds ratios (ORs) and 95% confidence intervals (CIs). Hardy-Weinberg equilibrium (HWE) test was used to assess the consistency of genotypic distribution in the controls. A two-tailed p<0.05 was considered significant. A power analysis was performed using the Power and Sample Size Calculation software (v3.1.2, Nashville, USA).

Results

As shown in the Table 2, 17 SNPs were detected in the upstream regions of lipid-related genes. LEPR rs6656451 was located in the upstream region of a transcript isoform. Among the tested SNPs, APOE rs7259620 was significantly associated with CHD [genotype p=0.042 (df=2), allele p=0.025 (df=1), OR (95% CI)=1.196 (1.023-1.398); recessive model (GG+GA versus AA) p=0.018, df=1, OR (95% CI)=1.54(1.07-2.21)]. PON2 rs12704796, ADIPOQ rs266729, VLDLR rs7852409, and PPAP2B rs72664392 were excluded from further analyses since their genotypic distributions did not meet HWE in the controls (data not shown). In addition, the association of the remaining 12 SNPs with CHD could not be evaluated in the total samples (p>0.05).

Further, subgroup analyses by gender were performed. PON2 rs12704796 and ADIPOQ rs7523903 were excluded from the analyses since they did not meet HWE in the male subgroup; ADIPOQ rs266729 and ADIPOQ rs7523903 were excluded since they did not meet HWE in the female subgroup. APOE rs7259620 was significantly associated with CHD only in males ($\chi^2=8.397$, df=2, p=0.015 by genotype; $\chi^2=5.190$, df=1, p=0.023 by allele; $\chi^2=19.3$, df=1, p<0.0001 by recessive model (GG + GA versus AA), Table 3). In addition, PPAP2B rs72664392 showed a genotype-level association with CHD in females ($\chi^2=9.878$, df=2, p=0.007, Table 3).

Age-based subgroup analyses revealed that CETP rs4783961, MLXIPL rs35493868, and PON2 rs12704796 were significantly as-

| Table 1. Cont. |
|----------------|
| **Gene SNP** | **Primer sequences** |
| LEP rs13228377 | 1st primer: ACGTTGGATGAAACCATAACATAAAGCGG; 2nd primer: ACGTTGGATGTGTTGGAATTCCCAAGGG; Extend primer: atTGGCAGGCTGGTTACCC; |
| VLDLR rs7852409 | 1st primer: ACGTGAGATGGGCAAGCCTGTTGATGTC; 2nd primer: ACGTTGGATGTGTTGGAATTCCCAAGGG; Extend primer: ggttAAATTAGGACAGGCACC; |
| APOA5 rs10750097 | 1st primer: ACGTGGAATGGGATAGGCTATTTCAAGCAG; 2nd primer: ACGTTGGATGTGTTGGAATTCCCAAGGG; Extend primer: caccctCCCTCCCCCGGGCTCTC; |
| PRKAG1 rs2293446 | 1st primer: ACGTGGAATGGGCAAGCCTGTTGATGTC; 2nd primer: ACGTTGGATGTGTTGGAATTCCCAAGGG; Extend primer: TCCCTGGGAAGAAGCCCC; |
| SCARB1 rs59358115 | 1st primer: ACGTGGAATGGGCAAGCCTGTTGATGTC; 2nd primer: ACGTTGGATGTGTTGGAATTCCCAAGGG; Extend primer: GCTCTGGCAAGACCC; |
| CETP rs4783961 | 1st primer: ACGTGGAATGGGCAAGCCTGTTGATGTC; 2nd primer: ACGTTGGATGTGTTGGAATTCCCAAGGG; Extend primer: GGTCCCTGGCTTACCC; |
| ANGPTL4 rs4076317 | 1st primer: ACGTGGAATGGGCAAGCCTGTTGATGTC; 2nd primer: ACGTTGGATGTGTTGGAATTCCCAAGGG; Extend primer: aataCAGACTTCCCTCCGCCCACCT; |
| APOE rs7259620 | 1st primer: ACGTGGAATGGGCAAGCCTGTTGATGTC; 2nd primer: ACGTTGGATGTGTTGGAATTCCCAAGGG; Extend primer: GGTCCCTGGCAAGACCC; |

*PCSK9* - proprotein convertase subtilisin/kexin type 9; *PPAP2B* - phosphatidic acid phosphatase type 2B; *ANGPTL4* - angiopoietin-like 4; *LEP* - leptin receptor; *ADIPOR1* - adiponectin receptor 1; *ADIPOQ* - adiponectin; *MLXIPL* - MLX-interacting protein-like; *PON3* - paraoxonase 3; *PON2* - paraoxonase 2; *CETP* - lepin; *VLDLR* - very-low-density-lipoprotein receptor; *APOE* - apolipoprotein E; *APOA5* - apolipoprotein A-V; *PRKAG1* - 5'-AMP-activated protein kinase subunit gamma-1; *SCARB1* - scavenger receptor class B type 1; *CETP* - cholesteryl ester transfer protein; *ANGPTL4* - angiopoietin-like 4; *APOE* - apolipoprotein E.
associated with CHD among participants younger than 55 years of age (CETP rs4783961; \( \chi^2 = 8.966, df=2, p=0.011 \) by genotype; MLXIPL rs35493368; \( \chi^2 = 4.870, p=0.027 \) by allele; \( \chi^2 = 4.88, df=1, p=0.027 \) by dominant model; PON2 rs12704796; \( \chi^2 = 6.511, df=2, p=0.039 \) by genotype; \( \chi^2 = 6.210, df=1, p=0.013 \) by allele, \( \chi^2 = 5.03, df=1, p=0.025 \) by dominant model, Table 4). In addition, LEPR rs6656451 was associated with CHD in participants older than 65 years of age (\( \chi^2 = 4.10, df=1, p=0.036 \) by allele, Table 4). No other SNPs were associated with CHD in the age-based subgroup analyses.

**Discussion**

In the present study, we examined the association of 17 lipid-related SNPs with CHD among 784 CHD cases and 739 non-CHD controls. We identified a male-specific association of APOE rs7259620 with CHD. Meanwhile, we also found a significant association of PON2 rs12704796 with CHD among participants younger than 55 years of age. On the genotypic level, we identified a significant association of CHD with MLXIPL rs35493368 in participants younger than 55 years of age and LEPR rs6656451 in participants older than 65 years of age.

Previous studies have indicated that APOE is significantly associated with CHD. APOE e2 was shown to reduce the risk of CHD by 20% (24), whereas e4 was shown to increase the risk of CHD by approximately 42% compared with e3/e3 genotype (25). Epidemiological evidence has shown that males are at a higher risk of CHD than females worldwide (26). Gender disparity has been found in APOE-related cardiovascular disease (27). In the previous studies, we have shown that CHD risk was gender-dependent in the Han Chinese and that APOE rs4420638 polymorphism was significantly associated with increased CHD risk in male Han Chinese (28). This observation might be explained by the differences of hormonal profiles, smoking status, alcohol-drinking, occupation, and dietary habits between males and females (29, 30). In the present study, we also identified a novel genetic variant of APOE associated with CHD in males.

PPAR2B is a negative regulator of inflammatory cytokines, leukocyte adhesion, cell survival, and migration in human primary aortic endothelial cells (31), suggesting that PPAR2B can protect blood vessel against inflammation (32). Mechanosensitive PPAP2B plays a critical role in promoting anti-inflammatory phenotype and maintaining the vascular integrity of endothelial monolayer under atheroprotective flow (33). However, discrepancies exist regarding the association of PPAP2B with CHD (34). PPAP2B rs1759752 is associated with increased CHD risk in males, while PPAP2B rs12566304 is associated with increased CHD risk in females and PPAP2B - phosphatidic acid phosphatase type 2B; ANGPTL3 - angiopoietin-like 3; LEPR - leptin receptor; ADIPOQ1 - adiponectin receptor 1; ADIPOQ2 - adiponectin; MLXIPL - MLX-interacting protein-like; PON2 - paraoxonase 2; HDL - high-density lipoprotein; CETP - cholesteryl ester transfer protein; ANGPTL4 - angiopoietin-like 4; APOE - apolipoprotein E. Genotypic distributions of PON2 rs1704796, ADIPOQ1 rs266729, CETP rs1704796, and PPAP2B rs12566304 did not meet HWE in the controls. N.S. - not significant; N.A. - not analyzed; HWD in controls: did not meet HWE in the controls; 95% CI - 95% confidence interval; OR - odds ratio. APOE rs7259620, G/A) was significant in recessive model [GG+GA vs. AA, \( \chi^2 = 5.57, p=0.018 \). OR (95% CI)=1.54(1.07-2.21).]
associated with a decreased CHD risk in females (34). Other studies have shown that PPAP2B rs17114036-A is associated with CHD (35, 36). In contrast, PPAP2B rs17114036 is not associated with CHD after adjustments for gender (16, 35). Here, we identified a novel
Table 4. Comparison of genotype and allele frequencies of genes between CHD cases and non-CHD controls by age*

| Group | Gene (SNP, allele)          | Genotype counts (Cases vs. Controls) | Genotype ($\chi^2$, $P$) | Allele ($\chi^2$, $P$) | OR (95% CI)          |
|-------|-----------------------------|-------------------------------------|---------------------------|-------------------------|----------------------|
| ≤55   | CETP (rs4783961, G/A)        | 99/76/4 vs. 147/73/16               | 8.966, 0.011              | N.S.                    | N.S.                 |
|       | APOA5 (rs1075009, G/A)       | 55/82/43 vs. 80/112/47              | N.S.                      | N.S.                    | N.S.                 |
|       | PCSK9 (rs2479409, G/A)       | 84/77/19 vs. 121/99/19              | N.S.                      | N.S.                    | N.S.                 |
|       | SCARB1 (rs53958115, G/A)     | 131/46/3 vs. 177/58/4               | N.S.                      | N.S.                    | N.S.                 |
|       | PRKAG1 (rs2293446, G/A)      | 64/78/37 vs. 88/109/39              | N.S.                      | N.S.                    | N.S.                 |
|       | PON3 (rs11770903, A/G)       | 129/45/5 vs. 173/58/8               | N.S.                      | N.S.                    | N.S.                 |
|       | MLXIPR (rs35493868, G/C)     | 131/45/3 vs. 194/40/2               | N.S.                      | N.S.                    | 4.87, 0.027          | 0.619 (0.403-0.951)  |
|       | ADIPOR1 (rs7523903, G/C)     | 112/60/7 vs. 133/94/9               | N.S.                      | N.S.                    | N.S.                 |
|       | LEP (rs13228377, A/G)        | 102/68/10 vs. 131/94/14             | N.S.                      | N.S.                    | N.S.                 |
|       | VLDLR (rs7852409, C/G)       | 116/53/11 vs. 165/61/11             | N.S.                      | N.S.                    | N.S.                 |
|       | ANGPTL4 (rs4076317, C/G)     | 96/67/15 vs. 123/92/21              | N.S.                      | N.S.                    | N.S.                 |
|       | LEP (rs6656451, C/T)         | 149/29/0 vs. 213/22/1               | N.S.                      | N.S.                    | N.S.                 |
|       | ANGPTL3 (rs11207997, C/T)    | 94/73/11 vs. 144/81/11              | N.S.                      | N.S.                    | N.S.                 |
|       | PON2 (rs12704796, G/A)       | 74/86/20 vs. 73/124/42              | 6.511, 0.039              | 6.210, 0.013            | 1.431 (1.079–1.879)  |
|       | APOE (rs7259620, G/A)        | 88/80/11 vs. 121/88/30              | HWD in controls           | N.A.                    | N.A.                 |
|       | ADIPOQ (rs266729, C/G)       | 83/71/24 vs. 138/76/22              | HWD in controls           | N.A.                    | N.A.                 |
|       | PPAP2B (rs72664392, T/C)     | 129/47/3 vs. 187/44/8               | HWD in controls           | N.A.                    | N.A.                 |
| 55-65 | CETP (rs4783961, G/A)        | 164/95/11 vs. 160/92/11             | N.S.                      | N.S.                    | N.S.                 |
|       | APOA5 (rs10750097, G/A)      | 82/134/55 vs. 82/137/49             | N.S.                      | N.S.                    | N.S.                 |
|       | PCSK9 (rs2479409, G/A)       | 139/118/14 vs. 122/123/23           | N.S.                      | N.S.                    | N.S.                 |
|       | SCARB1 (rs53958115, G/A)     | 214/54/3 vs. 198/64/7               | N.S.                      | N.S.                    | N.S.                 |
|       | PRKAG1 (rs2293446, G/A)      | 91/126/53 vs. 94/126/44             | N.S.                      | N.S.                    | N.S.                 |
|       | PON3 (rs11770903, A/G)       | 190/70/11 vs. 189/76/3              | N.S.                      | N.S.                    | N.S.                 |
|       | MLXIPR (rs35493868, G/C)     | 222/44/3 vs. 214/46/2               | N.S.                      | N.S.                    | N.S.                 |
|       | ADIPOR1 (rs7523903, G/C)     | 169/92/9 vs. 171/82/10              | N.S.                      | N.S.                    | N.S.                 |
|       | LEP (rs13228377, A/G)        | 156/96/19 vs. 147/106/15             | N.S.                      | N.S.                    | N.S.                 |
|       | VLDLR (rs7852409, C/G)       | 196/65/10 vs. 193/64/9              | N.S.                      | N.S.                    | N.S.                 |
|       | ANGPTL4 (rs4076317, C/G)     | 129/116/24 vs. 127/119/17           | N.S.                      | N.S.                    | N.S.                 |
|       | LEP (rs6656451, C/T)         | 240/29/1 vs. 222/41/0               | N.S.                      | N.S.                    | N.S.                 |
|       | ANGPTL3 (rs11207997, C/T)    | 158/100/10 vs. 157/92/13            | N.S.                      | N.S.                    | N.S.                 |
|       | PON2 (rs12704796, G/A)       | 157/86/44 vs. 88/144/37             | HWD in controls           | N.A.                    | N.A.                 |
|       | APOE (rs7259620, G/A)        | 140/106/25 vs. 125/112/31           | N.S.                      | N.S.                    | N.S.                 |
|       | ADIPOQ (rs266729, C/G)       | 138/115/17 vs. 151/88/24            | HWD in controls           | N.A.                    | N.A.                 |
|       | PPAP2B (rs72664392, T/C)     | 198/68/4 vs. 203/55/10              | HWD in controls           | N.A.                    | N.A.                 |
| ≥65   | CETP (rs4783961, G/A)        | 204/110/14 vs. 145/75/12            | N.S.                      | N.S.                    | N.S.                 |
|       | APOA5 (rs10750097, G/A)      | 98/162/73 vs. 75/106/50             | N.S.                      | N.S.                    | N.S.                 |
|       | PCSK9 (rs2479409, G/A)       | 169/131/33 vs. 115/94/21            | N.S.                      | N.S.                    | N.S.                 |
|       | SCARB1 (rs53958115, G/A)     | 238/86/9 vs. 171/56/4               | N.S.                      | N.S.                    | N.S.                 |
|       | PRKAG1 (rs2293446, G/A)      | 115/158/54 vs. 97/96/38             | N.S.                      | N.S.                    | N.S.                 |
polymorphism (rs72664392) in PPAP2B promoter associated with CHD in females. This finding could be partly explained by the particular genetic background. Aging is a pivotal risk factor for CHD (37, 38). The incidence of CHD in people younger than 40 years of age is 0.6%, and it increases two-fold or more with every 10-year increase in age (39). High adiponectin concentration has been shown to be associated with a lower risk of CHD in people younger 65 years of age (40). In people younger than 55 years of age, PON2 rs12704796-A has been shown to increase the risk of CHD by 43.1%, whereas MLXIPL rs35493886-G has been shown to reduce the risk of CHD by 38.1%. In addition, LEPR rs6656451-T has been reported to reduce the risk of CHD by 45.5% among people older than 65 years of age.

Study limitations
Our results did not demonstrate a significant association of 11 of the tested SNPs with CHD. A power analysis revealed that these SNPs showed a minimal or moderate power to detect a significant association in the current study (power=0.074-0.425). In addition, several SNPs did not present reliable association results in gender- and age-based subgroup analyses since their genotype distributions did not meet HWE in the controls. Future association study of these SNPs with CHD is warranted in other cohorts.

Conclusion
Our study demonstrated the gender- or age-dependent association of six SNPs (APOE rs7259620, PPAP2B rs72664392, CETP rs4783961, PON2 rs12704796, MLXIPL rs35493886, and LEPR rs6656451) CHD in Han Chinese population. However, future replication is required to validate our findings.

Conflict of interest: None declared.

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