Research Article

APOE and FABP2 Polymorphisms and History of Myocardial Infarction, Stroke, Diabetes, and Gallbladder Disease

Ikuko Kato, Susan Land, Jill Barnholtz-Sloan, and Richard K. Severson

1 Karmanos Cancer Institute, School of Medicine, Wayne State University, 4100 John R. Street, Detroit, MI 48201, USA
2 Department of Pathology, School of Medicine, Wayne State University, Detroit, MI 48201, USA
3 Department of Obstetrics and Gynecology, School of Medicine, Wayne State University, Detroit, MI 48201, USA
4 Case Comprehensive Cancer Center, Case Western Reserve University School of Medicine, Cleveland, OH 44106, USA
5 Department of Family Medicine and Public Health Sciences, School of Medicine, Wayne State University, Detroit, MI 48201, USA

Correspondence should be addressed to Ikuko Kato, katoi@karmanos.org

Received 24 February 2011; Revised 11 May 2011; Accepted 20 June 2011

Academic Editor: Bruce Griffin

Copyright © 2011 Ikuko Kato et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Dysfunctional lipid metabolism plays a central role in pathogenesis of major chronic diseases, and genetic factors are important determinants of individual lipid profiles. We analyzed the associations of two well-established functional polymorphisms (FABP2 A54T and APOE isoforms) with past and family histories of 1492 population samples. FABP2-T54 allele was associated with an increased risk of past history of myocardial infarction (odds ratio (OR) = 1.51). Likewise, the subjects with APOE4, compared with E2 and E3, had a significantly increased risk of past history myocardial infarction (OR = 1.89). The OR associated with APOE4 was specifically increased in women for past history of myocardial infarction but decreased for gallstone disease. Interactions between gender and APOE isoforms were also significant or marginally significant for these two conditions. FABP2-T54 allele may be a potential genetic marker for myocardial infarction, and APOE4 may exert sex-dependent effects on myocardial infarction and gallbladder disease.

1. Introduction

Dysfunctional lipid metabolism plays a central role in pathogenesis of major chronic diseases, including cardiovascular diseases, insulin-independent diabetes, and gallbladder disease [1, 2]. While environmental factors, such as diet, are important determinants of circulating lipid concentrations, heritabilities of lipid profiles have been well elucidated in twin studies [3–6]. Because of the well-established association between circulating cholesterol levels and cardiovascular diseases, genes involved in cholesterol synthesis and transport have been more extensively studied than the others involved in long-chain fatty acids (LCFAs) and phospholipids [2, 7–11].

Among a number of genetic loci that have been examined thus far, APOE isoforms are the first common genetic polymorphisms that were linked to cardiovascular diseases (CVDs) and Alzheimer’s disease [9, 12–14]. ApoE is a multifunctional protein that is synthesized by the liver and several peripheral tissues and cell types, including macrophages, and a major component of several classes of plasma lipoproteins including triglyceride-rich very-low-density lipoprotein (VLDL) [13]. The protein is involved in the efficient hepatic uptake of lipoprotein particles, stimulation of cholesterol efflux from macrophage foam cells in the atherosclerotic lesion, and the regulation of immune and inflammatory responses and thus has key roles in lipid transport in the plasma and in the central nervous system as well as in responses to the dietary fat content and fatty acid compositions [13–15]. Three isoforms, E2, E3, and E4, are defined by combinations of amino acid (cysteine/arginine) substitutions at codons 112 and 158 [12–14]. The most recent meta-analysis by Bennet et al. demonstrated approximately linear relationships of APOE genotype (E2 through E4) with both LDL cholesterol levels and coronary risk, highlighting the effect of E2 [16], while two earlier analyses emphasized the adverse effect of E4 on coronary risk [17, 18]. Some studies also suggest that genetic effects of APOE on several lipid parameters may be modified by gender [19–25]. FABP2 encodes intestinal fatty acid binding protein,
2.1. Study Design. This study was secondary data analysis of the parent study have been described elsewhere [42]. The recruitment, and characteristics of the study subjects of Detroit, Mich, USA. Details concerning the ascertainment, case-control study for colorectal cancer in Metropolitan Detroit, Mich, USA. These subjects consisted of 57% of females, 43% of males, 26.5% of African Americans, 69.2% of Non-Hispanic Caucasians, and 4.3% of other racial groups. The subjects were interviewed over the telephone using structured questionnaires regarding their usual diet and other risk factors for colorectal cancer (e.g., demographics, smoking, physical activity, medication/supplement use, and own and family history of major chronic diseases) for the time-period preceding cancer diagnosis for the cases (approximately 2 years prior to the interview). Specifically, a semiquantitative food frequency questionnaire (FFQ), Block 98.2 (Block Dietary Data Systems, Berkeley, Calif), that was validated against multiple diet records [43, 44] was used to estimate daily nutrient intake. This questionnaire was chosen based on its superiority to categorize individuals on energy from fat as compared to the Willett instrument [45] as dietary fat was a main focus of the study. The residual method described by Willett and Stampfer was used to calculate energy-adjusted nutrient intake [46]. The study participants provided either peripheral blood (71%) or buccal cell samples (29%) for TaqMan genotyping for ApoE and FABP2 polymorphisms. Both polymorphisms were found to be in Hardy-Weinberg equilibrium using $P = 0.05$ as the threshold.

2.2. Statistical Analysis. Out of the 1547 controls originally consented to the study, 1492 with all study parameters were included in this analysis. The following histories of diseases were queried for subjects themselves as well as for their first degree of family members (parents, children, and siblings): myocardial infarction/heart attack, stroke and transitional ischemic attack, diabetes, and gallstone/gallbladder surgery. Odds ratios (ORs) and 95% confidence intervals (CIs) for history (own, family, or both) of these diseases associated with FABP2 and APOE polymorphisms were estimated using an unconditional logistic regression model [47], adjusting for selected covariates, which included demographic variables (age, sex, race (African American versus others), and educational level), family size (numbers of own siblings and children), common risk factors for major chronic diseases (pack-years of cigarette smoking, body mass index (body weight (kg)/body height (m$^2$)), and alcohol intake), and dietary covariates (energy-adjusted saturated fat, cholesterol, dietary fiber, and total calcium intakes) that were known risk factors for the diseases of interest and differed by either FABP2 or APOE genotype. For the FABP2 polymorphism, the AA genotype was used as the reference to calculate the ORs for AT, TT, or those combined. E3 homozygotes were used as the reference for APOE to calculate ORs associated with E2/E2, E2/E3, and E2/E4 and E4 (E4/E4 and E4/E3) isoforms, while the ORs were also calculated for E4 compared with E2 and E3 combined. The decision to include E2/E4 to E2 was based on the meta-analysis by Bennet et al. that clearly demonstrated that total and LDL cholesterol levels were lower in the E2/E4 genotype than in the wild-type E3/E3 group [16]. Tests for linear trend in the logit of risk associated with these ordinal categorical genotypes were performed using equally spaced scores to the categories. In addition, the ORs were calculated stratified by gender, and the interactions between the polymorphisms and gender were tested by including their multiplicative interaction terms. All statistical analyses were performed using SAS version 9.

3. Results

Overall, a total of 452 subjects reported previous diagnosis or treatment for one of the diseases specified above, while 1095 reported family history of these diseases. Out of these 452, 357 had additional family history. Subjects who had been diagnosed with these diseases were older than those who had not. While diabetes and gallbladder disease were common as past histories, heart attack was most prevalent as a family history (Table 1).

As shown in Table 2, the subjects who carried at least one FABP2-T54 allele were at an increased risk of past history of myocardial infarction (OR = 1.51, 95% CI: 1.01–2.27). There was no difference between homozygotes and heterozygotes. The risk of myocardial infarction was further increased if they had family history (OR = 1.93, 95% CI: 1.15–3.23).
Table 1: The numbers of study subjects who reported past or family history of selected chronic diseases and their mean ages at study enrolment.

| Diseases                  | Own No. | Own Mean age | Medical history | Family No. | Family Mean age | Both No. | Both Mean age |
|---------------------------|---------|--------------|----------------|------------|-----------------|----------|---------------|
| Myocardial infarction     | 110     | 66.7         |                | 663        | 62.8            | 66       | 66.3          |
| Stroke                    | 74      | 68.2         |                | 444        | 62.6            | 21       | 66.0          |
| Diabetes                  | 204     | 64.7         |                | 573        | 62.1            | 123      | 64.6          |
| Gallbladder disease       | 203     | 64.7         |                | 280        | 60.8            | 53       | 63.7          |
| Any of the above          | 452     | 65.0         |                | 1095       | 62.4            | 357      | 65.0          |
| None of the above         | 1040    | 61.3         |                | 397        | 62.5            | 1135     | 61.6          |

Table 2: Odds ratios (ORs) and 95% confidence intervals (CIs) for history of selected chronic diseases according to FABP2 genotypes.

| Diseases                  | Genotype | Own Yes/No | OR 95% CI | Medical history | Both Yes/No | OR 95% CI |
|---------------------------|----------|------------|-----------|-----------------|-------------|-----------|
| Myocardial infarction     | AA       | 51/777     | 1.00 —    | 358/470         | 27/801      | 1.00 —    |
|                           | AT       | 51/509     | 1.55 1.02–2.35 | 262/298     | 43/61       | 0.94 0.62–1.43 |
|                           | TT + TT  | 59/605     | 1.11 1.01–2.27 | 305/359     | 4/100       | 1.30 0.44–3.87 |
|                           | P        | 0.089      |           | 0.595           | 0.051       |           |
| Stroke                    | AA       | 41/787     | 1.00 —    | 258/570        | 13/815      | 1.00 —    |
|                           | AT       | 30/530     | 1.11 0.67–1.84 | 158/402    | 8/552       | — —       |
|                           | TT + TT  | 33/631     | 1.05 0.64–1.70 | 186/478    | 8/656       | 0.80 0.32–1.97 |
|                           | P        | 0.869      |           | 0.220           | 0.406       |           |
| Diabetes                  | AA       | 118/710    | 1.00 —    | 298/530        | 75/753      | 1.00 —    |
|                           | AT       | 76/484     | 0.94 0.68–1.31 | 234/326    | 44/516      | 0.88 0.59–1.32 |
|                           | TT + TT  | 86/578     | 0.90 0.66–1.24 | 275/389    | 48/616      | 0.82 0.55–1.21 |
|                           | P        | 0.335      |           | 0.029           | 0.168       |           |
| Gallbladder disease       | AA       | 112/716    | 1.00 —    | 148/680        | 30/798      | 1.00 —    |
|                           | AT       | 81/479     | 1.05 0.76–1.44 | 118/442    | 21/539      | 0.93 0.52–1.68 |
|                           | TT + TT  | 91/573     | 1.00 0.73–1.36 | 132/532    | 23/641      | 0.88 0.50–1.56 |
|                           | P        | 0.710      |           | 0.876           | 0.512       |           |

ORs were adjusted for age, sex, race, educational levels, cigarette smoking (pack-years), alcohol intake, body mass index, energy-adjusted dietary saturated fat, cholesterol, fiber and total calcium intakes, and family size. P values for a linear trend for the number of T-alleles.

For other diseases, there were no consistent associations with the T54 allele, except an increased risk of family history of diabetes (P value for trend = 0.029). Likewise, the subjects with the APOE4 genotypes had a significantly increased risk of past history of myocardial infarction compared with E2 and E3 combined (OR = 1.89; 95% CI: 1.24–2.88) (Table 3). The similar trend was observed for the subjects with both past and family histories of myocardial infarction, but it remained marginally statistically significant (OR = 1.64, 95% CI: 0.97–2.80). There were no statistically significant associations between APOE genotypes and the rest of the diseases. Although the information was available only for the subjects themselves, the prevalence of high blood cholesterol or use of cholesterol-reducing medication increased progressively from E2 through E4 with a significant linear trend (P = 0.002) (data not shown).

Table 4 presents gender-specific ORs for past history of these conditions according to the APOE polymorphism. The increasing risk of myocardial infarction from E2 through E4 was only observed in women. Compared with E3 homozygotes, the ORs associated with E2 and E4 were 0.52 (95% CI: 0.17–1.62) and 1.93 (95% CI: 1.00–3.70), respectively, in women, while in men both ORs were equally elevated. As a result, the interaction between gender and APOE isoforms was statistically significant (P = 0.01). There were no statistically significant differences in the association...
of APOE with diabetes by gender. The association of APOE isoforms with gallbladder disease was the opposite in men and women. In women the OR was the lowest with E4 (0.67, 95% CI 0.43–1.06) and the highest with E2 (1.28, 95% CI: 0.79–2.08) (P value for trend = 0.025), but in men it was the highest with E4 (1.14, 95% CI: 0.58–2.26) and the lowest with E2 (0.58, 95% CI: 0.22–1.58) (P value for trend = 0.244). The interaction with gender was marginally statistically significant (P = 0.088). There were no significant interactions between FABP2 polymorphism and gender for any medical conditions (data not shown).

### 4. Discussion

The results of the present study are consistent with those in a few other studies that reported the significant effect of FABP2-T54 on the risk of myocardial infarction or coronary heart disease with the ORs ranging from 1.41 to 2.50 [36–38]. It is interesting to note that the positive associations in these earlier studies were found in patients who were diagnosed with metabolic syndrome or had one of the conditions of the syndrome. Although we did not collect the information about hypertension, 59.5% of our study subjects had at least one condition that satisfied or was indicative of the criteria for metabolic syndrome, that is, obesity (BMI (kg/m²) ≥ 30), history of diabetes, or a history of high blood cholesterol (a surrogate marker for atherogenic dyslipidemia) [48]. Thus, these results suggest that other cardiovascular risk factors may be important effect modifiers of the FABP2 polymorphism and warrant further studies in populations with diverse risk profiles for CVD.

We also confirmed the association between APOE polymorphism and risk of myocardial infarction reported by many others [16–18], especially for E4 genotypes. Although the latest meta-analysis showed stepwise increases in total and LDL cholesterol levels and in risk of coronary heart disease from E2 homozygotes, E2 heterozygotes, E3/E3 wild-type, E4/E3, and E4 homozygotes [16], there were not enough subjects in each of the combinations, E2/E2 (N = 11), E2/E4 (N = 43), and E4/E4 (N = 42), to analyze them separately in our study. The exclusion of E2/E4 from the E2 group, however, had only nominal effects on the OR estimates associated with E2 genotypes. For example the OR for past history of MI changed from 1.14 (0.62–2.08) to 1.11 (0.58–2.13). Furthermore, our study and others suggest that the effects of APOE genotypes were greater in women than in men [19–25]. APOE is primarily produced in the liver, while it has been well documented that the liver is a sexually dimorphic organ. Hepatic gene expression is often sex specific, mediated through sex-dependent activation of several liver-enriched transcription factors in response to sex-specific secretion patterns of pituitary growth hormone [49, 50]. In fact, higher circulating levels of APOE in

---

### Table 3: Odds ratios (ORs) and 95% confidence intervals (CIs) for history of selected chronic diseases according to APOE genotypes.

| Diseases               | Genotype | Own                          | Medical history                        | Both                          |
|------------------------|----------|------------------------------|---------------------------------------|-------------------------------|
|                        |          | Yes/No OR 95% CI             | Yes/No OR 95% CI                      | Yes/No OR 95% CI             |
| Myocardial infarction   | E2       | 16/223 1.14 0.62–2.08        | 113/126 1.16 0.86–1.55                | 9/230 0.99 0.46–2.13         |
|                        | E3       | 51/810 1.00 —                | 378/483 1.00 —                        | 33/828 1.00 —                |
|                        | E4       | 43/349 1.95 1.25–3.04        | 172/220 1.01 0.79–1.29                | 24/368 1.64 0.94–2.86        |
|                        | E4 versus E2E3 | 1.89 1.24–2.88 | 0.98 0.77–1.24 | 1.64 0.97–2.80 |
|                        |          | P = 0.022                    | P = 0.477                             | P = 0.119                     |
| Stroke                 | E2       | 15/224 1.28 0.67–2.45        | 77/162 1.11 0.81–1.52                 | 3/236 0.75 0.20–2.74         |
|                        | E3       | 37/824 1.00 —                | 255/606 1.00 —                        | 12/849 1.00 —                |
|                        | E4       | 22/370 1.10 0.63–1.93        | 112/280 0.94 0.72–1.23                | 6/386 0.87 0.31–2.42         |
|                        | E4 versus E2E3 | 1.03 0.61–1.76 | 0.92 0.71–1.19 | 0.93 0.35–2.49 |
|                        |          | P = 0.764                    | P = 0.382                             | P = 0.904                     |
| Diabetes               | E2       | 36/203 0.98 0.64–1.51        | 98/141 1.09 0.81–1.47                 | 26/213 1.35 0.81–2.23         |
|                        | E3       | 121/740 1.00 —               | 323/538 1.00 —                        | 64/797 1.00 —                |
|                        | E4       | 47/345 0.73 0.50–1.07        | 152/240 1.00 0.78–1.28                | 33/359 1.02 0.64–1.61         |
|                        | E4 versus E2E3 | 0.73 0.51–1.06 | 0.98 0.77–1.25 | 0.94 0.61–1.46 |
|                        |          | P = 0.173                    | P = 0.645                             | P = 0.395                     |
| Gallbladder disease     | E2       | 36/203 1.09 0.72–1.67        | 49/190 1.20 0.83–1.74                 | 11/228 1.38 0.66–2.90         |
|                        | E3       | 121/740 1.00 —               | 157/704 1.00 —                        | 29/832 1.00 —                |
|                        | E4       | 46/346 0.80 0.55–1.17        | 74/318 1.12 0.81–1.53                 | 13/379 0.98 0.50–1.95         |
|                        | E4 versus E2E3 | 0.79 0.55–1.13 | 1.07 0.79–1.45 | 0.91 0.47–1.75 |
|                        |          | P = 0.187                    | P = 0.866                             | P = 0.473                     |

ORs were adjusted for age, sex, race, educational levels, cigarette smoking (pack-years), alcohol intake, body mass index, energy-adjusted dietary saturated fat, cholesterol, fiber and total calcium intakes, and family size, E2 includes E2/E2, E2/E3, and E2/E4, and E4 includes E4/E3, and E4/E4. P values for a linear trend for E2, E3 and E4.
females, female-predominant hepatic expression of fatty acid translocase and differential fatty acid compositions between males and females have been demonstrated in both humans and rodents [51–53]. Thus, effects of genetic polymorphisms may be more articulated in females through such transcriptional upregulation. This also explains the absence of the interaction between gender and FABP2 (intestinal type), whereas sex-dimorphic effects of FABP1 (liver-type) knockout have been noted in rodent models [54, 55].

Surprisingly few studies have addressed the association between the APOE polymorphism and risk of diabetes. However, our marginally significant inverse association with E4 genotypes and past history of diabetes was consistent with a mouse model demonstrating that APOE deficiency abrogates insulin resistance [56] and with the observations in humans that the E4 genotypes were associated with a decreased risk and E2 genotypes with an increased risk of diabetes [57, 58]. On the other hand, the associations between the FABP2 polymorphism and diabetes remain inconsistent [59] despite the fact that the polymorphism has been associated with postprandial glucose and insulin levels [26, 34, 35].

Our study found the only modest association between T54 allele and family history, which was not confirmed with own history and thus likely to be a chance finding.

Excessive biliary cholesterol in conjunction with decreased bile acid output is the requisite for the formation of gallstones, particularly for cholesterol stones which account for the vast majority of this disease in Western countries and which are much more common in females than in males [60]. APOE plays a role not only in cholesterol metabolism but also in bile acid synthesis. Fecal bile acid output has been reported to be lowest in the subjects with E4 allele, highest in the subjects with E2 allele, and intermediate in the subjects with E3 homozygotes [61–65]. While the results of earlier studies are very mixed, some with a positive association with E4 [66–70], others with no association [71–74], and one with an inverse association [75, 76], the current study indicates that the effects of APOE may also be sex dependent, that is, a significantly reduced risk in women with E4, but not in men. This corresponds to the APOE knockout mouse model where bile acid synthesis markedly varies by gender [77].

There are several limitations in this study. We realize that a certain degree of misclassification exists in self-reported past and family history of diseases, which is likely to bias the results toward a null association. As far as the medical conditions selected for this study are concerned, moderate to high agreement (0.55–0.91 as kappa statistics) has been observed between self-reports and in medical records [78–80]. In addition, more than 50% of our study subjects had some college education [42], which further ensures the quality of self-reported data. Therefore, the magnitude of underestimation of the ORs is likely to be relatively small. Another concern is the coverage of disease spectra. Fatal cases of their own could not be included in this study, whereas fatal cases in their families may have been recalled more accurately. Thus, the interpretation of the ORs for

### Table 4: Odds ratios (ORs) and 95% confidence intervals (CIs) for past history of selected chronic diseases according APOE genotypes and gender.

| Diseases              | Genotype | Females | Males | P values for interaction |
|-----------------------|----------|---------|-------|--------------------------|
|                       |          | Yes/No  | OR    | 95% CI                   | Yes/No  | OR    | 95% CI | P          |
| Myocardial infarction | E2       | 4/129   | 0.52  | 0.17–1.62                | 12/94   | 1.70  | 0.81–3.56 | 0.009      |
|                       | E3       | 22/475  | 1.00  | —                        | 29/335  | 1.00  | —       | 0.463      | 0.008      |
|                       | E4       | 21/205  | 1.93  | 1.00–3.70                | 22/144  | 1.92  | 1.03–3.58 | 0.025      | 0.002      |
|                       | E4       | 2.18    | 1.16–4.09 | 1.68 | 0.94–3.00 | 0.772    | 0.846    | 0.762    | 0.244      | 0.088      |
| Stroke                | E2       | 9/124   | 1.34  | 0.57–3.15                | 6/100   | 1.22  | 0.42–3.55 | 0.706      | 0.002      |
|                       | E3       | 21/476  | 1.00  | —                        | 16/348  | 1.00  | —       | 0.81       | 0.008      |
|                       | E4       | 13/213  | 1.11  | 0.53–2.33                | 9/157   | 1.05  | 0.42–2.61 | 0.324      | 0.706      |
|                       | E4       | 1.03    | 0.51–2.06 | 1.00 | 0.42–2.38 | 0.244    | 0.244    | 0.762    | 0.706      |
| Diabetes              | E2       | 22/111  | 0.99  | 0.56–1.73                | 14/92   | 0.93  | 0.47–1.87 | 0.706      | 0.002      |
|                       | E3       | 68/429  | 1.00  | —                        | 53/311  | 1.00  | —       | 0.81       | 0.008      |
|                       | E4       | 32/194  | 0.89  | 0.55–1.44                | 15/151  | 0.50  | 0.26–0.97 | 0.324      | 0.706      |
|                       | E4       | 0.89    | 0.56–1.42 | 0.51 | 0.27–0.97 | 0.772    | 0.846    | 0.762    | 0.706      |
| Gallbladder disease   | E2       | 31/102  | 1.28  | 0.79–2.08                | 5/101   | 0.58  | 0.22–1.58 | 0.706      | 0.002      |
|                       | E3       | 92/405  | 1.00  | —                        | 29/335  | 1.00  | —       | 0.81       | 0.008      |
|                       | E4       | 31/195  | 0.67  | 0.43–1.06                | 15/151  | 1.14  | 0.58–2.26 | 0.324      | 0.706      |
|                       | E4       | 0.64    | 0.41–0.99 | 1.27 | 0.66–2.46 | 0.772    | 0.846    | 0.762    | 0.706      |

ORs were adjusted for age, race, educational levels, cigarette smoking (pack-years), alcohol intake, body mass index, energy-adjusted dietary saturated fat, cholesterol, fiber and total calcium intakes, and family size. E2 includes E2/E2, E2/E3, and E2/E4, and E4 includes E4/E3 and E4/E4. P values for a linear trend for E2, E3 and E4.
past and family histories may differ particularly for CVD. Exclusion of fatal cases as well as cases who had severe complications especially in their speech may account for the small number of past histories of stroke reported in this study. Third, these chronic conditions stay asymptomatic for a long period of time. Thus, diagnoses of such asymptomatic cases depend on their preventive care or the presence of other conditions that require routine follow-up visits to health care professionals. Accordingly, some undiagnosed cases of diabetes and gallstones and subjects who underwent cardiac bypass or angioplasty without a heart attack were classified as a negative history in this study, which would further reduce potential differences between cases and noncases. Fourth, there is significant likelihood that some of the associations observed in this study were chance findings due to multiple comparisons in terms of outcome variables, although we focused on the two well-established functional polymorphisms. Finally, we acknowledge reverse temporal associations between the disease outcomes and some of the covariates included in the model, that is, smoking, BMI, and alcohol and dietary intake, which may have changed due to the diagnosis. However, these yielded predicted directions with histories of all diseases combined, that is, significant positive associations with cigarette smoking and BMI and inverse association with alcohol and calcium intake (data not shown). Although these adjustments may not have fully controlled confounding, it is less likely that the genotype distributions were affected by these covariates.

5. Conclusions

Despite the limitations discussed above, the results of the present study suggest that FBBP2-T54 allele is potential genetic marker for myocardial infarction and that the APOE4 isof orm may exert opposite effects on myocardial infarction and gallstone disease in women, increasing risk for the former and decreasing risk for the later.

Conflict of Interests

The authors declare no Conflict of interests.

Acknowledgment

This work was supported by a Research Grant from the US National Institutes of Health R01-CA93817.

References

[1] D. B. Jump, D. Botolin, Y. Wang, J. Xu, and B. Christian, “Fatty acids and gene transcription,” Scandinavian Journal of Food and Nutrition, vol. 50, no. 2, pp. 5–12, 2006.
[2] C. J. Willer, S. Sanna, A. U. Jackson et al., “Newly identified loci that influence lipid concentrations and risk of coronary artery disease,” Nature Genetics, vol. 40, no. 2, pp. 161–169, 2008.
[3] M. Beekman, B. T. Heijmans, N. G. Martin et al., “Heritabilities of apolipoprotein and lipid levels in three countries,” Twin Research, vol. 5, no. 2, pp. 87–97, 2002.
[4] D. I. Boomsma, H. J. M. Kempen, J. A. Gevven Leuven, L. Havekes, P. De Kniff, and R. R. Frants, “Genetic analysis of sex and generation differences in plasma lipid, lipoprotein, and apolipoprotein levels in adolescent twins and their parents,” Genetic Epidemiology, vol. 13, no. 1, pp. 49–60, 1996.
[5] D. A. Heller, U. de Faire, N. L. Pedersen, G. Dahlén, and G. E. McClearn, “Genetic and environmental influences on serum lipid levels in twins,” The New England Journal of Medicine, vol. 328, no. 16, pp. 1150–1156, 1993.
[6] A. Iliadou, P. Lichtenstein, U. de Faire, and N. L. Pedersen, “Variation in genetic and environmental influences in serum lipid and apolipoprotein levels across the lifespan in Swedish male and female twins,” American Journal of Medical Genetics, vol. 102, no. 1, pp. 48–58, 2001.
[7] G. V. Z. Dedoussis, “Apolipoprotein polymorphisms and familial hypercholesterolemia,” Pharmacogenomics, vol. 8, no. 9, pp. 1179–1189, 2007.
[8] A. M. Minihane, “Fatty acid-genotype interactions and cardiovascular risk,” Prostaglandins Leukotrienes and Essential Fatty Acids, vol. 82, no. 4–6, pp. 259–264, 2010.
[9] P. Perez-Martinez, J. Lopez-Miranda, E. Perez-Jimenez, and J. M. Ordovas, “Influence of genetic factors in the modulation of postprandial lipemia,” Atherosclerosis Supplements, vol. 9, no. 2, pp. 49–55, 2008.
[10] S. Kathiresan, O. Melander, C. Guiducci et al., “Six new loci associated with blood low-density lipoprotein cholesterol, high-density lipoprotein cholesterol or triglycerides in humans,” Nature Genetics, vol. 40, no. 2, pp. 189–197, 2008.
[11] S. Kathiresan, C. J. Willer, G. M. Peloso et al., “Common variants at 30 loci contribute to polygenic dyslipidemia,” Nature Genetics, vol. 41, no. 1, pp. 56–63, 2009.
[12] J. E. Eichner, S. T. Dunn, G. Perveen, D. M. Thompson, K. E. Stewart, and B. C. Stroehla, “Apolipoprotein E polymorphism and cardiovascular disease: a HuGE review,” American Journal of Epidemiology, vol. 155, no. 6, pp. 487–495, 2002.
[13] K. Greenow, N. J. Pearce, and D. P. Ramji, “The key role of apolipoprotein e in atherosclerosis,” Journal of Molecular Medicine, vol. 83, no. 5, pp. 329–342, 2005.
[14] D. M. Hatters, C. A. Peters-Libeu, and K. H. Weisgraber, “Apolipoprotein E structure: insights into function,” Trends in Biochemical Sciences, vol. 31, no. 8, pp. 445–454, 2006.
[15] A. M. Minihane, L. Jofre-Monseny, E. Olano-Martin, and G. Rimbach, “ApoE genotype, cardiovascular risk and responsiveness to dietary fat manipulation,” Proceedings of the Nutrition Society, vol. 66, no. 2, pp. 183–197, 2007.
[16] A. M. Bennet, E. Di Angelantonio, Z. Ye et al., “Association of apolipoprotein e genotypes with lipid levels and coronary risk,” Journal of the American Medical Association, vol. 298, no. 11, pp. 1300–1311, 2007.
[17] P. W. Wilson, E. J. Schaef er, M. G. Larson, and J. M. Ordovas, “Apolipoprotein E alleles and risk of coronary disease. A meta-analysis,” Arteriosclerosis, Thrombosis, and Vascular Biology, vol. 16, no. 10, pp. 1250–1255, 1996.
[18] Y. Song, M. J. Stampfer, and S. Liu, “Meta-analysis: apolipo- protein E genotypes and risk for coronary heart disease,” Annals of Internal Medicine, vol. 141, no. 2, pp. 137–147, 2004.
[19] G. D. Kolovou, D. Damaskos, K. Anagnostopoulou, and D. V. Cokkinos, “Apolipoprotein E gene polymorphism and gender,” Annals of Clinical and Laboratory Science, vol. 39, no. 2, pp. 120–133, 2009.
[20] D. Gómez-Coronado, J. J. Alvarez, A. Entrala, J. M. Olmos, E. Herrera, and M. A. Lasunción, "Apolipoprotein E polymorphism in men and women from a Spanish population: allele frequencies and influence on plasma lipids and apolipoproteins," *Atherosclerosis*, vol. 147, no. 1, pp. 167–176, 1999.

[21] K. E. Zerba, R. E. Ferrell, and C. F. Sing, "Genotype-environment interaction: apolipoprotein E (APOE) gene effects and age as an index of time and spatial context in the human," *Genetics*, vol. 143, no. 1, pp. 463–478, 1996.

[22] R. Eloosua, J. M. Ordovas, L. A. Cupples et al., "Association of APOE genotype with carotid atherosclerosis in men and women: the Framingham Heart Study," *Journal of Lipid Research*, vol. 45, no. 10, pp. 1868–1875, 2004.

[23] R. Frikke-Schmidt, B. G. Nordestgaard, B. Agerholm-Larsen, P. Schnohr, and A. Tybjaerg-Hansen, "Context-dependent and invariant associations between lipids, lipoproteins, and apolipoproteins and apolipoprotein E genotype," *Journal of Lipid Research*, vol. 41, no. 11, pp. 1812–1822, 2000.

[24] C. Lahoz, E. J. Schafer, L. A. Cupples et al., "Apolipoprotein E genotype and cardiovascular disease in the Framingham Heart Study," *Atherosclerosis*, vol. 154, no. 3, pp. 529–537, 2001.

[25] R. W. Mahley, J. Pépin, K. E. Palaoglu, M. J. Malloy, J. P. Kane, and T. P. Bersot, "Low levels of high density lipoproteins in Turks, a population with elevated hepatic lipase. High density lipoprotein characterization and gender-specific effects of apolipoprotein E genotype," *Journal of Lipid Research*, vol. 41, no. 8, pp. 1290–1301, 2000.

[26] L. J. Baier, J. C. Sacchettini, W. C. Knowler et al., "An amino acid substitution in the human intestinal fatty acid binding protein is associated with increased fatty acid binding, increased fat oxidation and insulin resistance," *Journal of Clinical Investigation*, vol. 95, no. 3, pp. 1281–1287, 1995.

[27] L. J. Baier, C. Bogardus, and J. C. Sacchettini, "A polymorphism in the human intestinal fatty acid binding protein alters fatty acid transport across Caco-2 cells," *Journal of Biological Chemistry*, vol. 271, no. 18, pp. 10892–10896, 1996.

[28] A. Georgopoulos, O. Aras, and M. Y. Tsai, "Codon-54 polymorphism of the fatty acid-binding protein 2 gene is associated with elevation of fasting and postprandial triglyceride in type 2 diabetes," *Journal of Clinical Endocrinology and Metabolism*, vol. 85, no. 9, pp. 3155–3160, 2000.

[29] R. A. Hegele, P. W. Connelly, A. J. G. Hanley, F. Sun, S. B. Harris, and B. Zimman, "Common genomic variants associated with variation in plasma lipoproteins in young aboriginal Canadians," *Arteriosclerosis, Thrombosis, and Vascular Biology*, vol. 17, no. 6, pp. 1060–1066, 1997.

[30] J. Pihlajamäki, J. Rissanen, S. Heikkinen, L. Karjalainen, and M. Laakso, "A codon 54 polymorphism of the human intestinal fatty acid binding protein 2 gene is associated with dyslipidemias but not with insulin resistance in patients with familial combined hyperlipidemia," *Arteriosclerosis, Thrombosis, and Vascular Biology*, vol. 17, no. 6, pp. 1039–1044, 1997.

[31] H. M. Vidgren, R. H. Sipiläinen, S. Heikkinen, M. Laakso, and M. I. J. Uusitupa, "Threonine allele in codon 54 of the fatty acid binding protein 2 gene does not modify the fatty acid composition of serum lipids in obese subjects," *European Journal of Clinical Investigation*, vol. 27, no. 5, pp. 405–408, 1997.

[32] J. J. Ågren, R. Valve, H. Vidgren, M. Laakso, and M. Uusitupa, "Postprandial lipemic response is modified by the polymorphism at codon 54 of the fatty acid-binding protein 2 gene," *Arteriosclerosis, Thrombosis, and Vascular Biology*, vol. 18, no. 10, pp. 1606–1610, 1998.

[33] J. J. Ågren, H. M. Vidgren, R. S. Valve, M. Laakso, and M. I. Uusitupa, "Postprandial responses of individual fatty acids in subjects homozygous for the threonine- or alanine-encoding allele in codon 54 of the intestinal fatty acid binding protein 2 gene," *American Journal of Clinical Nutrition*, vol. 73, no. 1, pp. 31–35, 2001.

[34] K. Yamada, X. Yuan, S. Ishiyama et al., "Association between Ala54Thr substitution of the fatty acid-binding protein 2 gene with insulin resistance and intra-abdominal fat thickness in Japanese men," *Diabetologia*, vol. 40, no. 6, pp. 706–710, 1997.

[35] R. A. Hegele, T. K. Young, and P. W. Connelly, "Are Canadian Inuit at increased genetic risk for coronary heart disease?" *Journal of Molecular Medicine*, vol. 75, no. 5, pp. 364–370, 1997.

[36] A. Georgopoulos, H. Bloomfield, D. Collins et al., "Codon 54 polymorphism of the fatty acid binding protein (FABP) 2 gene is associated with increased cardiovascular risk in the dyslipidemic diabetic participants of the Veterans Affairs HDL intervention trial (VA-HIT)," *Atherosclerosis*, vol. 194, no. 1, pp. 169–174, 2007.

[37] K. Nishihama, Y. Yamada, H. Matsuo et al., "Association of gene polymorphisms with myocardial infarction in individuals with or without conventional coronary risk factors," *International Journal of Molecular Medicine*, vol. 19, no. 1, pp. 129–141, 2007.

[38] M. Oguri, K. Kato, K. Yokoi et al., "Association of genetic variants with myocardial infarction in Japanese individuals with metabolic syndrome," *Atherosclerosis*, vol. 206, no. 2, pp. 486–493, 2009.

[39] P. Wanby, P. Palmquist, I. Rydén, L. Brattström, and M. Carlsson, "The FABP2 gene polymorphism in cerebrovascular disease," *Acta Neurologica Scandinavica*, vol. 110, no. 6, pp. 355–360, 2004.

[40] Y. Yamada, K. Kato, M. Oguri et al., "Association of genetic variants with atherothrombotic cerebral infarction in Japanese individuals with metabolic syndrome," *International Journal of Molecular Medicine*, vol. 21, no. 6, pp. 801–808, 2008.

[41] C. Albala, A. Villarroel, J. L. Santos et al., "FABP2 Ala54Thr polymorphism and diabetes in Chilean elders," *Diabetes Research and Clinical Practice*, vol. 77, no. 2, pp. 245–250, 2007.

[42] I. Kato, S. Land, A. P. Majumdar, J. Barnholtz-Sloan, and R. K. Severson, "Functional polymorphisms to modulate luminal lipid exposure and risk of colorectal cancer," *Cancer Epidemiology*, vol. 34, no. 3, pp. 291–297, 2010.

[43] G. Block, M. Woods, A. Potosky, and C. Clifford, "Validation of a self-administered diet history questionnaire using multiple diet records," *Journal of Clinical Epidemiology*, vol. 43, no. 12, pp. 1327–1335, 1990.

[44] G. Block, F. E. Thompson, A. M. Hartman, F. A. Larkin, and K. E. Guire, "Comparison of two dietary questionnaires validated against multiple dietary records collected during a 1-year period," *Journal of the American Dietetic Association*, vol. 92, no. 6, pp. 686–693, 1992.

[45] A. K. Wirfalt, R. W. Jeffery, and P. J. Elmer, "Comparison of food frequency questionnaires: the reduced Block and Willett questionnaires differ in ranking on nutrient intakes," *American Journal of Epidemiology*, vol. 148, no. 12, pp. 1148–1156, 1998.

[46] W. Willett and M. J. Stampfer, "Total energy intake: implications for epidemiologic analyses," *American Journal of Epidemiology*, vol. 124, no. 1, pp. 17–27, 1986.

[47] N. E. Breslow and N. E. Day, "Statistical methods in cancer research, vol 1, the analysis of case-control studies," *International Aerial Robotics Competition Scientific Publications*, no. 32, pp. 5–338, 1980.
Y. A. Kes „äniemi, C. Ehnholm, and T. A. Miettinen, “Intestinal
D. E. Johnston and M. M. Kaplan, “Pathogenesis and treat-
A. T avridou, K. I. Arvanitidis, A. Tiptiri-Kourpeti et al.,
N. St ˚ahlberg, E. Rico-Bautista, R. M. Fisher et al., “Female-
Y. Kawashima, J. Chen, H. Sun et al., “Apolipoprotein E
gene ablation potentiates hepatic cholesterol accumulation in
cholesterol-fed female mice,” American Journal of Physiology—
Gastrointestinal and Liver Physiology, vol. 290, no. 1, pp. G36–
G48, 2006.
J. Oscarsson, S. O. Olofsson, K. Vikman, and S. Ed ´en,
“Sex differences in fatty acid composition of rat liver
phosphatidylcholine are regulated by the plasma pattern of
growth hormone,” Biochimica et Biophysica Acta, vol. 959, no. 3, pp. 280–287,
1988.
G. G. Martin, B. P. Atshaves, A. L. McIntosh, J. T. Mackie,
A. B. Kier, and F. Schroeder, “Liver fatty acid binding protein
genotype in middle aged subjects,” Gut, vol. 43, no. 11, pp. 1434–
1441, 2009.
Y. Kawashima, J. Chen, H. Sun et al., “Apolipoprotein E
deficiency in a mouse model of type 2 diabetes mellitus,” Diabetologia,
v. 52, no. 7, pp. 1434–
1441, 2009.
L. A. Profenno and S. V. Faroone, “Diabetes and overweight
associate with non-APOE4 genotype in an Alzheimer’s disease
population,” American Journal of Medical Genetics—Part B,
v. 147B, no. 6, pp. 822–829, 2008.
F. I. Errera, M. E. Silva, E. Yeh et al., “Effect of polymorphisms of
the MTHFR and APOE genes on susceptibility to diabetes
and severity of diabetic retinopathy in Brazilian patients,”
Brazilian Journal of Medical and Biological Research, v. 39,
no. 7, pp. 883–888, 2006.
A. Tavridou, K. I. Arvanitisid, A. Tiptiri-Kourpeti et al.,
“Thr54 allele of fatty-acid binding protein 2 gene is associated
with obesity but not type 2 diabetes mellitus in a Caucasian
population,” Diabetes Research and Clinical Practice, v. 84,
no. 2, pp. 132–137, 2009.
D. E. Johnston and M. M. Kaplan, “Pathogenesis and treat-
ment of gallstones,” The New England Journal of Medicine,
v. 328, no. 6, pp. 412–421, 1993.
Y. A. Kes „äniemi, C. Ehnholm, and T. A. Miettinen, “Intestinal
cholesterol absorption efficiency in man is related to apopro-
tein E phenotype,” Journal of Clinical Investigation, v. 80,
no. 2, pp. 578–581, 1987.

[48] S. M. Grundy, J. I. Cleeman, S. R. Daniels et al., “Diagnosis
and management of the metabolic syndrome: an American
Heart Association/National Heart, Lung, and Blood Institute
Scientific Statement,” Circulation, v. 112, no. 17, pp. 2735–
2752, 2005.
[49] C. A. Wiwi and D. J. Waxman, “Role of hepatocyte nuclear
factors in growth hormone-regulated, sexually dimorphic
expression of liver cytochromes P450,” Growth Factors, v. 22,
no. 2, pp. 79–88, 2004.
[50] D. J. Waxman and C. O’Connor, “Growth hormone regulation
of sex-dependent liver gene expression,” Molecular Endocrinol-
yogy, v. 20, no. 11, pp. 2613–2629, 2006.
[51] J. Oscarsson, S. O. Olofsson, K. Vikman, and S. Ed ´en,
“Growth hormone regulation of serum lipoproteins in the
rat: different growth hormone regulatory principles for
apolipoprotein (apo) B and the sexually dimorphic apo E
concentrations,” Metabolism, v. 40, no. 11, pp. 1191–1198,
1991.
[52] N. St ¸ahlberg, E. Rico-Bautista, R. M. Fisher et al., “Female-
predominant expression of fatty acid translocase/CD36 in rat
and human liver,” Endocrinology, v. 145, no. 4, pp. 1972–
1979, 2004.
[53] J. Oscarsson and S. Ed ´en, “Sex differences in fatty acid
composition of rat liver phosphatidylethanolamine are regu-
lated by the plasma pattern of growth hormone,” Biochimica et
Biophysica Acta, vol. 959, no. 3, pp. 280–287,
1988.
[54] G. G. Martin, B. P. Atshaves, A. L. McIntosh, J. T. Mackie,
A. B. Kier, and F. Schroeder, “Liver fatty acid binding protein
genotype in Alzheimer’s disease population,” American Journal of
Physiology—Gastrointestinal and Liver Physiology, vol. 290, no. 1, pp. G36–
G48, 2006.
[55] Y. Xie, E. P. Newberry, S. M. Kennedy, I. Luo, and N. O.
Davidson, “Increased susceptibility to diet-induced gallstones in
liver fatty acid binding protein knockout mice,” Journal of
Lipid Research, v. 50, no. 5, pp. 977–987, 2009.
[56] M. Niemi, K. Kervinen, A. Rantalai et al., “The role of
apolipoprotein E and glucose intolerance in gallstone disease
in middle aged subjects,” Gut, vol. 44, no. 4, pp. 557–562, 1999.
[57] A. Bertomeu, E. Ros, D. Zambrón et al., “Apolipoprotein E
genotype and gallstones,” Gastroenterology, vol. 111, no. 6,
p. 1603–1610, 1996.
[58] S. Fischer, M. H. Dolu, B. Zündt, G. Meyer, S. Geisler, and
D. Jüngst, “Apolipoprotein E polymorphism and ligandogene
factors in gallbladder bile,” European Journal of Clinical
Investigation, vol. 31, no. 9, pp. 789–795, 2001.
[59] K. J. van Erpecum, P. Portincasa, M. H. Dohlu, G. P. van
Berge-Henegouwen, and D. Jüngst, “Biliary pronucleating
proteins and apolipoprotein E in cholesterol and pigment-
stone patients,” Journal of Hepatology, vol. 39, no. 1, pp. 7–11,
2003.
[60] P. Portincasa, K. J. van Erpecum, P. C. van De Meeberg, G.
M. Dallinga-Thie, T. W. A. De Bruin, and G. P. van Berge-
Henegouwen, “Apolipoprotein E4 genotype and gallbladder
motility influence speed of gallstone clearance and risk of
recurrence after extracorporeal shock-wave lithotripsy,”
Hepatology, vol. 24, no. 3, pp. 580–587, 1996.
[61] M. Dixit, G. Choudhuri, and B. Mittal, “Association of
APOE-C1 gene cluster polymorphisms with gallstone disease,”
Digestive and Liver Disease, vol. 38, no. 6, pp. 397–403, 2006.
[62] Z. Y. Jiang, T. Q. Han, G. J. Suo et al., “Apolipoprotein E
genotype in middle aged subjects,” Gut, vol. 44, no. 4, pp. 557–562, 1999.
[63] A. B. Kier, and F. Schroeder, “Liver fatty acid binding protein
genotype in Alzheimer’s disease population,” American Journal of
Physiology—Gastrointestinal and Liver Physiology, vol. 290, no. 1, pp. G36–
G48, 2006.
[64] Y. Xie, E. P. Newberry, S. M. Kennedy, I. Luo, and N. O.
Davidson, “Increased susceptibility to diet-induced gallstones in
liver fatty acid binding protein knockout mice,” Journal of
Lipid Research, vol. 50, no. 5, pp. 977–987, 2009.
[65] M. Niemi, K. Kervinen, A. Rantalai et al., “The role of
apolipoprotein E and glucose intolerance in gallstone disease
in middle aged subjects,” Gut, vol. 44, no. 4, pp. 557–562, 1999.
[66] A. Bertomeu, E. Ros, D. Zambrón et al., “Apolipoprotein E
genotype and gallstones,” Gastroenterology, vol. 111, no. 6,
p. 1603–1610, 1996.
[67] S. Fischer, M. H. Dolu, B. Zündt, G. Meyer, S. Geisler, and
D. Jüngst, “Apolipoprotein E polymorphism and ligandogene
factors in gallbladder bile,” European Journal of Clinical
Investigation, vol. 31, no. 9, pp. 789–795, 2001.
[68] K. J. van Erpecum, P. Portincasa, M. H. Dohlu, G. P. van
Berge-Henegouwen, and D. Jüngst, “Biliary pronucleating
proteins and apolipoprotein E in cholesterol and pigment-
stone patients,” Journal of Hepatology, vol. 39, no. 1, pp. 7–11,
2003.
[76] L. L. Boland, A. R. Folsom, E. Boerwinkle et al., “Atherosclerosis Risk in Communities (ARIC) Study Investigators. Apolipoprotein E genotype and gallbladder disease risk in a large population-based cohort,” *Annals of Epidemiology*, vol. 16, no. 10, pp. 763–769, 2006.

[77] H. B. Hartman, S. J. Gardell, C. J. Petucci, S. Wang, J. A. Krueger, and M. J. Evans, “Activation of farnesoid X receptor prevents atherosclerotic lesion formation in LDLR-/- and apoE-/- mice,” *Journal of Lipid Research*, vol. 50, no. 6, pp. 1090–1100, 2009.

[78] C. Bosetti, A. Tavani, E. Negri, D. Trichopoulou, and C. La Vecchia, “Reliability of data on medical conditions, menstrual and reproductive history provided by hospital controls,” *Journal of Clinical Epidemiology*, vol. 54, no. 9, pp. 902–906, 2001.

[79] O. H. Klungel, A. de Boer, A. H. P. Paes, J. C. Seidell, and A. Bakker, “Cardiovascular diseases and risk factors in a population-based study in The Netherlands: agreement between questionnaire information and medical records,” *Netherlands Journal of Medicine*, vol. 55, no. 4, pp. 177–183, 1999.

[80] F. Kee, L. Tiret, J. Y. Robo et al., “Reliability of reported family history of myocardial infarction,” *British Medical Journal*, vol. 307, no. 6918, pp. 1528–1530, 1993.