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Common *FABP4* Genetic Variants and Plasma Levels of Fatty Acid Binding Protein 4 in Older Adults

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Abstract

We examined common variants in the fatty acid binding protein 4 gene (*FABP4*) and plasma levels of FABP4 in adults aged 65 and older from the Cardiovascular Health Study. We genotyped rs16909187, rs1054135, rs16909192, rs10808846, rs7018409, rs2290201, and rs6992708 and measured circulating FABP4 levels among 3190 European Americans and 660 African Americans. Among European Americans, the minor alleles of six single nucleotide polymorphisms (SNP) were associated with lower FABP4 levels (all $p \leq 0.01$). Among African Americans, the SNP with the lowest minor allele frequency was associated with lower FABP4 levels ($p = 0.015$). The C-A haplotype of rs16909192 and rs2290201 was associated with lower FABP4 levels in both European Americans (frequency = 16 %; $p = 0.001$) and African Americans (frequency = 8 %; $p = 0.04$). The haplotype combined a SNP in the first intron with one in the 3'untranslated region. However, the alleles associated with lower FABP4 levels were associated with higher fasting glucose in meta-analyses from the MAGIC consortium. These results demonstrate associations of common SNP and haplotypes in the *FABP4* gene with lower plasma FABP4 but higher fasting glucose levels.

Keywords

Fatty acid binding proteins; Metabolism; Genetics

Introduction

Adipose tissues produce multiple adipokines that influence inflammation, thrombogenicity, insulin resistance, and other metabolic pathways [1]. One of these adipokines is fatty acid binding protein 4 (FABP4 or aP2), a carrier for fatty acids and other lipophilic substances between extra- and intra-cellular membranes [2]. FABP4 is expressed by macrophages and adipocytes [3, 4]. FABP4 expression in adipocytes has been associated with insulin resistance in animal and human studies [5, 6]. FABP4 effects on insulin and glucose metabolism are thought to result from its effects on fatty acid release and transport, insulin secretion from beta-cells, and inflammation [4, 5, 7, 8]. We have previously demonstrated a positive association between plasma FABP4 and incident diabetes in the Cardiovascular Health Study (CHS) [9]. Plasma FABP4 levels were also associated with increased risk of diabetes in a prospective case-control study from the Physicians' Health Study [10].

Expression of FABP4 is modulated by the *FABP4* gene. A functional mutation (T-87C) in the *FABP4* gene reduces expression of FABP4 in adipocytes and is associated with a lower risk of type 2 diabetes (especially among obese subjects) [6]. Recently however, the Women's Health Initiative (WHI) reported null results for common variants across the *FABP4* gene in relation to diabetes risk, which included the T-87C SNP [11]. Among children, a variant in exon 4 has been related to obesity and FABP4 plasma levels in obese and non-obese children, but the T-87C variant was not assessed [12]. The exon 4 SNP (rs1054135) was not associated with T2D risk in the WHI [11]. It is unknown whether other polymorphisms in the *FABP4* gene influence plasma FABP4 concentrations.

Because CHS participants underwent measurement of plasma FABP4 levels and genotyping for *FABP4* single-nucleotide polymorphisms as part of the candidate gene association resource (CARE) project [13], it offers a unique opportunity to evaluate their association in a large cohort of older adults. Data on eight SNP in or near the gene on chromosome 8 were available from CARE, but the T-87C was not genotyped. The current project examined whether common *FABP4* polymorphisms are associated with plasma levels of FABP4 in older adults. Additionally, we examined published GWAS results from the MAGIC and GIANT consortia to determine the relation of these SNP to fasting glucose, fasting insulin, and body mass index.

Materials and Methods

CHS is a population-based cohort study of 5,201 adults aged 65 years and older that began in 1989–1990; a supplemental cohort of 687 predominantly African-Americans was enrolled in 1992–1993 [14]. Participants in the current study are limited to those included in the CARE genotyping project and who had a blood sample from the 1992–1993 examination available for the measurement of plasma FABP4. These totaled 3,190 European Americans [mean (SD) age 75.2 ± 5.2 years, 43 % male] and 660 African Americans (73.3 ± 5.7 years, 37 % male). All CHS participants provided written informed consent and participants included in this study provided additional consent for analysis of genetic data. Plasma FABP4 concentration was measured using BioVendor ELISA kits. Genotyping was performed using an Illumina custom SNP array with 50,000 SNP, which has been previously described [15]. In the current project, we evaluated the eight SNP near the *FABP4* gene, one of which had a minor allele occurring only twice in the CHS participants, and thus was too rare for further analysis.

We analyzed the association between seven genotyped SNP and natural log transformed plasma FABP4 levels using race-specific linear regression models adjusted for age, sex, body mass index (BMI), and clinic. SNP were analyzed using an additive genetic model coding for the minor allele, which in two instances differed by race. Linkage disequilibrium (LD) was evaluated using Haploview [16] to determine the number of independent tests for Bonferroni correction. Haplotypes were analyzed using PLINK [17], which estimates phased haplotypes using an Expectation–Maximization algorithm. Linear models with the same covariates were implemented, and each haplotype was tested against a collapsed group of the other haplotypes. The SNP with the strongest association in race-specific single-SNP models was paired with each of the other SNP to evaluate 2-SNP haplotypes. The best 2-SNP haplotype was then evaluated with each of the remaining SNP.

To address the potential for *FABP4* SNP to influence glycemic traits and obesity, we accessed GWAS results from three large consortia meta-analyses. For fasting glucose and insulin, we examined results from the MAGIC consortium, downloaded from www.magicinvestigators.org, which were generated from analyses of 46,186 non-diabetic participants [18]. For BMI, we examined results from the GIANT consortium, downloaded from http://www.broadinstitute.org/collaboration/giant/index.php/GIANT_consortium_data_files, which analyzed over 122,800 participants at each of the *FABP4* SNP [19].

Results

Mean levels of FABP4 were higher in African Americans (38.3 ± 24.3 ng/mL) than European Americans (33.3 ± 17.4 ng/mL), as was the prevalence of obesity and diabetes. In the European American sample, all SNP were consistent with Hardy–Weinberg equilibrium (HWE) and had over 98 % successful genotyping (call rate). In the African American

sample, three SNP (SNP 2–4) exhibited departure from HWE with p -values 0.013–0.016, and all SNP had over 99 % call rate.

In European Americans, we observed a nominal association ($p = 0.05$) with six of the seven SNP examined and the minor alleles were all associated with lower *FABP4* levels (Table 1). In an LD plot (Fig. 1), we observed two sets of SNP with $r^2 > 0.8$ among them (SNP 1–3–5 and 4–6–7), and SNP 2 was independent of the others. Therefore, we set a Bonferroni threshold of 0.017 to account for the three comparisons, and both sets of correlated SNP met this criterion. The strongest association was observed for SNP 5 (rs7018409), which had a minor allele (T) related to lower *FABP4* levels. This SNP explained 0.006 of the variance and was located in an intron (Fig. 2).

In African-Americans, the smaller sample size reduced power and there was considerably less LD among the SNP (Fig. 1b), which would require a more stringent correction for multiple testing. The minor allele for two SNP (SNP 4 and 6) was opposite from that observed in European Americans. SNP 3 was nominally associated with *FABP4* levels ($p = 0.015$) but not statistically significant after correction for multiple testing, although it provides independent replication of the effect observed in European Americans. The C allele of SNP 3 (rs16909192) was associated with lower *FABP4* levels. This SNP explained 0.009 of the variance and was located in the 3' untranslated region of *FABP4*.

In general, haplotype analyses did not identify combinations of SNP with stronger effects than observed in single SNP analyses. For both races, the best haplotype combination came from combining the strongest individual SNP result with SNP6 (rs2290201), which is one that had inverse allele frequencies between the races. We present the result for the 2-SNP haplotype of SNP 3 and 6 (rs16909192-rs2290201) for comparison between the races (Table 2). In both races, the C-A haplotype was associated with lower *FABP4* levels.

We examined results from the MAGIC and GIANT consortia to identify association between *FABP4* SNP and diabetes-related traits (Table 3). None of the *FABP4* SNP studied in the current project were associated with fasting insulin (smallest p value = 0.12), but for fasting glucose, five SNP were nominally associated. The LD block that included SNP 1-3-5 had p -values for association between 0.012 and 0.017, meeting our criteria for Bonferroni corrected statistical significance, and the alleles associated with lower *FABP4* levels were associated with higher fasting glucose concentrations. For BMI, none of the SNP were statistically significant, but the same block of SNP [1–3] had p -values between 0.08 and 0.1 and the alleles associated with lower *FABP4* levels were related to lower BMI.

Discussion

Common variants in the *FABP4* gene are associated with plasma *FABP4* levels measured in a sample of European American older adults. Although the sample size among African Americans was smaller, we observed larger effect sizes in African-Americans. Among African-Americans, the SNP with the smallest minor allele frequency was nominally associated with a beta estimate of -0.09 , compared to an effect of -0.04 in European Americans. Haplotype results were driven by the effects observed in single SNP results, and we observed some consistent effects across races despite large differences in allele frequency.

FABP4 levels have been associated with a higher risk of incident diabetes in the CHS cohort and in the Physicians' Health Study [9, 10]. However, a search of the NHGRI catalog of published genome-wide association studies (<http://www.genome.gov/gwastudies/> accessed 6/26/2012) [20] does not identify the *FABP4* gene as being associated with diabetes, which

is consistent with the results from the WHI [11]. One of the SNP examined here, rs1054135 (SNP2) was previously shown to be associated with FABP4 levels in children [12], but we could not replicate that association. Our meta-analyses identified an association between *FABP4* SNP and fasting glucose levels, but not fasting insulin or BMI.

The association between the *FABP4* SNP and lower FABP4 levels but higher fasting glucose appears to be paradoxical in relation to the observed association between higher FABP4 levels and higher risk of diabetes. While SNP in the *FABP4* gene exhibit association to plasma levels, variants in other genes may also influence FABP4 levels, both through gene expression and metabolism. The SNP examined in the current analysis account for only a small amount of the variability in FABP4 levels, and given the observed association of FABP4 levels with diabetes, genome-wide studies of FABP4 levels are warranted.

Important limitations of our work include its restriction to previously genotyped SNP, the small sample size of African-Americans, and lack of circulating FABP4 levels outside of CHS. Nonetheless, our results confirm the structure of the genetic association between *FABP4* SNP and *FABP4* levels and illustrate the complexity of relating these to metabolic traits.

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Abbreviations

BMI	Body mass index
CARe	Candidate gene association resource
CHS	Cardiovascular Health Study
FABP4	Fatty acid binding protein 4
GWAS	Genome-wide association study
HWE	Hardy-Weinberg equilibrium
LD	Linkage disequilibrium
SNP	Single nucleotide polymorphism
WHI	Women's Health Initiative

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Fig. 1.
a Linkage disequilibrium in European Americans presented as r^2 values, and **b** linkage disequilibrium in African Americans presented as r^2 values

*2 SNP in bold (square box) are located in exonic region. Color of dot represents LD value.

Fig. 2.
FABP genetic region, association with FABP4 levels in CHS (European) and r^2 for LD with top-associated SNP (rs7018409)

Table 1

SNP association to FABP4 levels adjusted for age, sex, BMI and clinic

#	SNP	European American				African-American			
		Minor allele	MAF	Beta	p-value	Minor allele	MAF	Beta	p-value
1	rs16909187	A	0.17	-0.044	1.6E-04*	A	0.16	-0.042	0.16
2	rs1054135	T	0.10	0.023	0.11	T	0.25	0.015	0.57
3	rs16909192	C	0.17	-0.042	3.8E-04*	C	0.08	-0.093	1.5E-02
4	rs10808846	T	0.27	-0.024	1.5E-02*	G	0.46	0.013	0.57
5	rs7018409	T	0.17	-0.050	2.4E-05*	T	0.16	-0.053	7.8E-02
6	rs2290201	A	0.27	-0.026	1.0E-02*	G	0.34	0.002	0.93
7	rs6992708	C	0.29	-0.027	5.7E-03*	C	0.47	-0.014	0.52

Beta estimate from in-transformed FABP4 levels in ng/mL

* Statistically significant after Bonferroni correction for multiple testing

Table 2

rs16909192-rs2290201 haplotype association to FABP4 levels

Haplotype	<u>European American omnibus p-value = 0.001</u>			<u>African-American omnibus p-value = 0.04</u>		
	Freq	Beta	p -value	Freq	Beta	p -value
C-A	0.163	-0.049	4.4E-05	0.076	-0.0954	1.3E-02
A-A	0.108	0.018	0.23	0.58	0.0311	0.17
A-G	0.722	0.022	2.7E-02	0.343	0.00205	0.93

Table 3*FABP4* SNP results for diabetes-related traits from MAGIC [18] and GIANT [19]

#	SNP	MAGIC(18) N = 46,186 non-diabetic ^a				GIANT[19] N C 122,804 ^b		
		Effect allele	Fasting glucose		Fasting insulin		BMI	
			Effect	p-value	Effect	p-value	Allele decreasing BMI	p-value
1	rs16909187	A	0.012	0.013	0.0003	0.96	A	0.08
2	rs1054135	T	0.0014	0.83	0.011	0.12	T	0.91
3	rs16909192	A	-0.012	0.012	-0.001	0.85	C	0.09
4	rs10808846	T	0.008	0.06	0.0041	0.35	T	0.25
5	rs7018409	T	0.012	0.017	0.0011	0.84	T	0.10
6	rs2290201	A	0.0085	0.04	0.0045	0.29	A	0.15
7	rs6992708	A	-0.0086	0.04	-0.0054	0.22	C	0.22

^aData on glycemic traits have been contributed by MAGIC investigators and downloaded from www.magicinvestigators.org^bhttp://www.broadinstitute.org/collaboration/giant/index.php/GIANT_consortium_data_files