Research Article

Association between functional FABP2 promoter haplotypes and body mass index: Analyses of 8072 participants of the KORA cohort study

Mike Böhme[1], Harald Grallert[2], Maja Klapper[1], Christian Gieger[2], Alexandra Fischer[1], Iris Heid[2], H.-Erich Wichmann[2], Frank Döring[1] and Thomas Illig[2]

[1] Institute of Human Nutrition and Food Science, Molecular Nutrition, Christian-Albrecht-University, Kiel, Germany
[2] Institute of Epidemiology, German Research Centre for Environmental Health, Helmholtz Centre Munich, Munich, Germany

Studies in relatively small cohorts provide preliminary evidence that functional fatty acid binding protein 2 (FABP2) promoter haplotypes are associated with type 2 diabetes and BMI. Here, we studied the influence of the haplotypes on BMI by using 8072 male and female participants of the Kooperative Gesundheitsforschung in der Region Augsburg (KORA) cohort. By linear regression analysis, we found in males a reduction of −0.39 BMI units (95% CI: −0.73, −0.05, $p = 0.024$) in homozygous FABP2 promoter haplotype B carriers. Carriers of haplotype B showed a significant decrease in BMI of −0.19 BMI units (95% CI: −0.35, −0.02, $p = 0.027$). In accordance, a significant reduction in BMI of the minor haplotype carriers in the BMI point categories of 25–30 (BMI units: −0.10, 95% CI: −0.18, −0.01, $p = 0.03$) and <30 (BMI units: −0.37, 95% CI: −0.67, −0.07, $p = 0.02$) were found. In summary, the minor FABP2 promoter haplotype B contributes to a reduced BMI in men. This provides evidence that functional FABP2 contributes to multifactorialy regulated body weight.

Keywords: BMI / FABP2 gene / KORA / Promoter polymorphism

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1 Introduction

The human fatty acid binding protein 2 (FABP2) gene (*FABP2*, NM_000134.2) is exclusively expressed in the intestine during development and cell differentiation in absorptive cells of the upper villus region [1–3]. Although the specific function of FABP2 is still not fully elucidated, the protein is proposed to be involved in fat absorption by binding and intracellular transport of newly absorbed non-esterified long-chain free fatty acids, which are finally assembled and secreted in triglyceride-rich chylomicrons [4, 5]. FABP2 also mediates fatty acid signalling by transferring fatty acids to the nucleus as ligands for transcription factors, such as peroxisome proliferator-activated receptors (PPARs) [6, 7] and seems to be involved in regulation of cell proliferation and differentiation [8, 9]. More recently, an antioxidant function was shown [10, 11].

Based on a huge number of association studies in different human populations, *FABP2* is described as a candidate gene for the metabolic syndrome [12–16]. Sequencing studies [13, 14, 16] revealed that the 5′ upstream promoter region of *FABP2* contains insertion/deletion sites c.–80_-79insT (rs5861422), c.–136_-132delAGTAG (rs5861423) and c.–168_-166delAAGinsT (rs1973598) as well as c.–260G > A (rs6857641), c.–471G > A (rs2282688) and c.–778G > T (rs10034579) single nucleotide polymorphisms (SNPs). For explanation of sequence variation nomenclature refer to den Dunnen and Antonarakis, 2000 [17]. These six variants are in complete linkage disequilibrium resulting in only two haplotypes A > B. As demonstrated by us [16] and others [14] the rare *FABP2* promoter haplotype B, with an allele frequency in Caucasians of 44% [16], showed almost 2–3-fold lower transcriptional activity than haplotype A in Caco2 cells. Recently, we showed that this different activity is due to decreased binding affinity of GATA-5 and -6 to the c.–80_-79insT polymorphism [18]. The *FABP2* promoter haplotypes were associated with postpran-

Correspondence: Professor Frank Döring, Molecular Nutrition, Institute for Human Nutrition and Food Science, University of Kiel, Heinrich-Hecht-Platz 10, 24118 Kiel, Germany
E-mail: sek@molnut.uni-kiel.de
Fax: +49-431-880-5658

Abbreviations: FABP2, fatty acid binding protein 2; **KORA,** Kooperative Gesundheitsforschung in der Region Augsburg; **MONICA,** multinational MONItoring of trends and determinants in Cardiovascular disease; **PPAR,** peroxisome proliferator-activated receptor

dial triglyceride levels [15], type 2 diabetes [16] and BMI [13]. Since, these studies were done in relatively small cohorts composed of 500 – 1000 participants and functional intervention studies are still lacking, the associations remain disputable. In the present study, we analysed the data of a large (n = 8072) population-based survey from 1994 to 2001 of the Kooperative Gesundheitsforschung in der Region Augsburg (KORA) study cohort regarding the association between *FABP2* promoter haplotypes and BMI.

2 Materials and methods

2.1 Study population

In the Southern German region of Augsburg including the city of Augsburg and the two surrounding counties, population-based surveys of the 25 – 74 years old population in groups of age range of 5 years were implemented in 1984 as part of the WHO multinational MONItoring of trends and determinants in CArdiovascular disease (MONICA) project and continued since, 1996 within the KORA platform. The aims of the surveys were to describe the prevalence of common diseases and their risk factors in a representative sample of the adult general population. The current study included the survey of the years 1994 – 1995 (MONICA S3) including 4856 participants and the survey of the years 1999 – 2001 (KORA S4) including 4261 participants yielding 9117 recruited participants. The study population of S3 and S4 consisted of all German residents of the Augsburg region who were born between 1920 and 1975 identified through the public record office. More than 99.5% of the participants were Caucasian. The high standards of the WHO MONICA project applied to both surveys. All study participants underwent a standardized interview, a physical examination and blood withdrawal by trained staff and signed a consent form of the Bavarian Ethics committee and the Ethics committee of the University of Munich. For determination of body weight and height, participants were asked to remove shoes and heavy clothing. The weight measurements were done with a calibrated body weight scale (SECA 709) and were carried out with an accuracy of 0.1 kg. The body height was read to the nearest 0.5 cm on a body height scale. BMI (kg/m^2) was calculated as weight in kilograms divided by height in square meters. The pooled data analysis included 8072 individuals with complete information on age, sex, BMI and genotypes. The range of BMI was 14 – 57 kg/m^2 and the gender distribution was equal. There was no overlap between the two surveys by design. Detail characteristics of the study cohorts were described elsewhere [19, 20].

2.2 Genotyping

The 5′ upstream promoter region of *FABP2* containing insertion/deletion sites c. – 80_-79insT (rs5861422), c. – 136_-132delAGTAG (rs5861423) and c. – 168_-166delAAGinsT (rs1973598) as well as c. – 260G > A (rs6857641), c. – 471G > A (rs2282688) and c. – 778G > T (rs10034579) SNPs which are in complete linkage disequilibrium resulting in only two haplotypes A > B. *FABP2* promoter haplotypes were genotyped based on htSNP c. – 260G > A (rs6857641) using a MALDI TOF MS system (Sequenom, Mass EXTEND, San Diego, USA), with the 5′ Capture Primer ACGTTGGATGAACAATCTTCAGACGGCATG and the 3′ Capture Primer ACGTTGGATGTGAGAAGCATACCTATTCTG.

2.3 Statistical methods

We used a linear regression model with BMI as continuous outcome for both studies combined; the unit change in BMI by the DNA variants was estimated. Haplotype analysis was carried out with the statistical software R (V. 2.3.1. including haplo.stats package) using the haplo.glm procedure. This procedure performs an iterative two-step estimation-maximization (EM)-algorithm, with the posterior probabilities of pairs of haplotypes *per* subject used as weights to update the regression coefficients, and the regression coefficients used to update the posterior probabilities. Haplotypes were included into the regression model all at once except the most common haplotype. Using the expected number of copies of haplotype implies an additive model for each haplotype. Statistics were gender-stratified because sex-specific associations of FABP2 polymorphisms were described [21, 22].

3 Results and discussion

As shown in Table 1, in the whole study population as well as in female subjects no associations between *FABP2* promoter haplotypes and BMI were found. In male subjects, we observed a significant reduction in BMI of –0.39 BMI units (95% CI: –0.73, –0.05, p = 0.024) for the homozygous *FABP2* promoter haplotype B compared with homozygous haplotype A (wild type). Carriers of haplotype B (A/B + B/B) showed a significant decrease in BMI of –0.19 BMI units (95% CI: –0.35, –0.02, p = 0.027). These findings were congruent with a significant reduction in BMI of the minor haplotype carriers (A/B + B/B) in the BMI point categories of 25 – 30 (BMI units: –0.10, 95% CI: –0.18, –0.01, p = 0.03) and <30 (BMI units: –0.37, 95% CI: –0.67, –0.07, p = 0.02).

The presented analysis of 8072 participants confirmed and extended previously data in humans that the rare *FABP2* promoter haplotype B has a protective effect on metabolic traits like type 2 diabetes [16]. Though, previously an increase in BMI was found in female non-Hispanics from Colorado (USA) [13] and no decrease in male whites similar to our results. These differences may partly

Table 1. Frequencies of FABP2 promoter genotypes (AA, AB, BB) and their associations with BMI as continuous variable *via* linear regression

	Frequencies			Unit change in BMI in kg/m^2 [95% confidence interval] (*p*-values)		
	All	Men	Women	All	Men	Women
By genotype						
All	8072	4002	4070			
AA	2695	1293	1402			
AB	3974	1997	1977	−0.047 [−0.26, 0.16] (0.66)	−0.140 [−0.4, 0.12] (0.29)	0.048 [−0.28, 0.38] (0.78)
BB	1403	712	691	−0.206 [−0.49, 0.07] (0.15)	**−0.392 [−0.73, −0.05] (0.024)**	−0.004 [−0.44, 0.43] (0.99)
B[a)]	5377	2709	2668	−0.094 [−0.23, 0.04] (0.18)	**−0.188 [−0.35, −0.02] (0.027)**	0.007 [-0.21, 0.22] (0.95)
By WHO BMI cat.[a)]						
18.5–25	2729	1044	1685	−0.041 [−0.12, 0.04] (0.33)	0,011 [−0.11, 0.13] (0.86)	−0.072 [−0.18, 0.04] (0.21)
25–30	3507	2105	1402	−0.067 [−0.13, 0] (0.049)	**−0.098 [−0.18, −0.01] (0.025)**	−0.021 [−0.13, 0.09] (0.71)
30–35	1355	695	660	0.037 [−0.07, 0.14] (0.51)	0.056 [−0.09, 0.2] (0.46)	0.017 [−0.14, 0.17] (0.83)
35–40	334	116	218	0.029 [−0.19, 0.24] (0.79)	0.111 [−0.28, 0.5] (0.57)	−0.011 [−0.27, 0.25] (0.93)
By obesity status[a)]						
≤30	6282	3159	3123	−0.16 [−0.39, 0.07] (0.17)	**−0.37 [−0.67, −0.07] (0.017)**	0.01 [−0.33, 0.36] (0.94)
>30	1790	843	947	−0.06 [−0.15, 0.03] (0.17)	−0.10 [−0.22, 0.02] (0.10)	−0.02 [−0.16, 0.12] (0.76)

Results are the β estimate (linear regression) with 95% confidence interval and *p*-values. All calculations were adjusted for age and sex. The main results are in bold.
a) Additive model.

be due to different diet composition, especially fatty acids, in the two cohorts. Additional, neither this nor the study from Damcott *et al*. 2003 [13] were adjusted for medicament treatment of participants, which might have an impact on fatty acid metabolism and lead to divergent results.

Differences in associations of the *FABP2* promoter haplotypes with metabolic traits may result from strong but not total linkage disequilibrium of the promoter haplotype B with the Thr allele of the *FABP2* Ala54Thr polymorphism with an LD = 0.9 [13]. Associations with the Thr allele and metabolic traits showed controversial results. The Thr allele was associated with increased fasting lipid metabolism, intra-abdominal fat, C reactive protein, IL6, lipoprotein a, fasting insulin concentration, fasting fatty acid oxidation and decreased insulin sensitivity, reduced glucose uptake and obesity [23–29]. Further studies showed no influence of the Ala54Thr polymorphism on fasting and postprandial insulin, glucose or triglyceride levels, fat distribution and weight loss [30–35]. Other studies found associations with reduced subcutaneous adipose tissue, systolic blood pressure and glucose levels [31, 36]. These studies were carried out in populations with different ethnic, phenotypic and lifestyle backgrounds. This contributes in addition to putative changes in LD between the promoter and exon polymorphism in these different races to diverse associations.

Further, our data revealed a reduced BMI for nonobese but not for obese males carrying haplotype B. Hence, the *FAPB2* promoter haplotype B may bear prevention against overweight as long as obesity has not been occurred.

At a first glance, the observed sexual dimorphism shows inconsistencies with the phenotype of *FABP2* knock out mice [37]. Male mice lacking FABP2 have higher body weight than wild type animals [37]. Here, a reduced BMI is associated with the *FABP2* promoter haplotype B which showed lower basal activity than haplotype A in cell culture experiments [13, 14, 16, 18, 38]. Assuming a functional connection of *FABP2* gene expression and BMI we tempt to speculate that the *FABP2* promoter haplotype B is *in vivo* more active in males than in females. This is supported by reports demonstrating higher activity of PPARs in male animals compared to females [39, 40] and higher responsiveness of *FABP2* promoter haplotype B than A to PPARg/RXRa as recently stated by us and others [41, 42]. The physiological mechanism by which the *FABP2* promoter influences BMI remains obscure. A possible pathway is the complex and still incomplete understood interaction between diabetes type 2 and obesity [27, 43]. FABP2 is not solely expressed in enterocytes but also in GLP expressing intestinal epithelial L-cells [44]. The anti-diabetic hormones GLP-1 and GLP-2 are expressed after fat ingestion and could influence insulin sensitivity and *via* glucose metabolism the triglyceride metabolism in peripheral cells. Of course our hypothesis has to be tested by comparing the FABP2 expression levels from human males and females.

4 Concluding remarks

We obtained evidence in a population-based sample comprising 8072 participants that the minor *FABP2* promoter haplotype B contribute to a reduced body weight in men.

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