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Genotype and allele frequencies of the intestinal fatty acid binding protein gene in two Arab populations

[İki Arap topluluğunda barsak yağ asidi bağlayıcı proteini genotipi ve alel frekansı]*

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ABSTRACT

Objective: Intestinal fatty acid binding protein (IFAPB) participates in the uptake, intracellular metabolism and/or transport of long chain fatty acids. A polymorphism at codon 54 in exon 2 of FABP2 gene, which encodes for the IFAPB, exchanges an Alanine for Threonine. FABP2 gene polymorphism could modify the uptake of fatty acids, and it could correlate with risk of several diseases. In the light of the potential role of the FABP2 polymorphism, the aim of this study was to determine the frequency of the Ala54Thr FABP2 polymorphism in two Middle Eastern Arab Populations.

Materials and Methods: Genotyping was investigated in 182 and 120 unrelated healthy subjects from Bahrain and Jordan, respectively. A PCR-RFLP assay was applied for determination of Ala54Thr (rs1799883) FABP2 polymorphism. Allele frequencies were calculated by direct counting. Hardy Weinberg Equilibrium was evaluated using a Chi-square goodness of fit test.

Results: In the studied Bahraini subjects, 52.8% were homozygous for the Ala54/Ala54 genotype, 35.7% were heterozygous for the Ala54/Thr54 genotype and 11.5% were homozygous for the Thr54/Thr54 genotype. The gene frequencies obtained in Jordanians were: 48.3%, 43.3% and 8.4% for Ala54/Ala54; Ala54/Thr54 and Thr54/Thr54 genotypes, respectively. The frequencies of the allele Ala54 and the allele Thr54 of the FABP2 gene were found to be 0.706 and 0.294 for Bahrainis and 0.700 and 0.300 for Jordanians. These results revealed a similar population polymorphism frequency as in previous European and Arab populations' studies.

Conclusion: This is the first study to investigate the population frequency of the Thr54 allele in Bahraini and Jordanian populations.

Key Words: FABP2 gene polymorphism, Bahrainis, Jordanians, human population genetics

Conflict of Interest: The author declares no conflict of interest

ÖZET

Amaç: Barsak yağ asidi bağlayıcı proteini (IFAPB) uzun zincirli yağ asitlerinin taşınması ve hücre içine alınması ve/veya metabolizmasında görev alır. FABP2 geninde gözlenen bir polimorfizmde ikinci ekzonda yer alan 54. kodon Alanin ile treonin yer değiştirir. FABP2 polimorfizmi yağ asitlerinin tutulumunu değiştirip çeşitli hastalıkların oluşum riski ile korelasyon gösterebilir. Bu potansiyel etki göz önüne alınarak bu çalışmada iki Ortadoğu Arap topluluğunda Ala54Thr FABP2 polimorfizmin sıklığı incelenmiştir.

Gereç ve Yöntemler: Genotipleme aralarında akrabalık ilişkisi olmayan 182 Bahreyn'li, ve 120 Ürdün'lü sağlıklı kişide gerçekleştirildi. Ala54Thr (rs1799883) FABP2 polimorfizmi belirlenmesi PCR-RFLP ile gerçekleştirildi. Alel frekansları doğrudan sıyım ile hesaplanmıştır. Hardy Weinberg Dengesi Chi kare ile değerlendirilmiştir.

Bulgular: İncelenen Bahreyn'li kişilerin % 52.8'i Ala54/Ala54 genotipi için homozigot, % 35.7'si Ala54/Thr54 genotipi için heterozigot ve % 11.5'i Thr54/Thr54 homozigot genotipine ait bulunmuştur. Ürdün'lü kişiler için elde edilen gen frekansları Ala54/Ala54; Ala54/Thr54 ve Thr54/Thr54 genotipleri için sırası ile % 48.3, % 43.3 ve % 8.4 olarak bulunmuştur. FABP2 geni alel Ala54 ve allel Thr54 frekansları Bahreyn'li kişilerlerde sırası ile 0.706 ve 0.294 iken Ürdün kökenlilerde 0.700 ve 0.300 olarak saptanmıştır. Bulgular daha önce yapılan Avrupa ve Arab toplumu çalışmalarında elde edilen polimorfizm frekanslarına benzemektedir.

Sonuçlar: Bu rapor, Bahreyn ve Ürdün toplumunda Thr54 allel populasyon frekansının incelendiği ilk çalışmadır.

Anahtar kelimeler: FABP2 gen polimorfizmi, Bahreyn, Ürdün, insan populasyon genetiği

Çıkar Çatışması: Yazarların çıkar çatışması bulunmamaktadır.

Introduction

Fatty acid binding proteins (FABPs) are intracellular proteins which are involved in fatty acid transfer and metabolism [1]. The FABPs are a family of 14-15 kDa proteins which are found in abundance in the cytoplasm of numerous cell types of different tissues [2]. Approximately 10 separate mammalian FABP have been identified [3]. FABP2 are expressed only in intestinal epithelial cells and are encoded by a family of different genes. The FABP2 gene encodes intestinal FABP (I-FABP) [4]. The FABP2 gene consists of approximately 3.4 kilobases located in chromosomal region 4q28-4q31 and has the conserved 4 exons and 3 introns that are characteristic of this family of genes [5]. Their primary role is to mediates the absorption and transport of fatty acids inside the intestinal epithelial cells where they bind long chain fatty acids [6].

The G to A polymorphism at codon 54 in exon 2 of the human FABP2 gene exchanges an Alanine (Ala) for Threonine (Thr). Thr-containing protein has been shown to have 2-fold greater affinity for long chain fatty acids than does Ala-containing protein suggesting that the Ala-to-Thr substitution is in fact a functional mutation [7]. This greater affinity has been suggested to cause increased absorption and processing of fatty acids [7, 8]. If the FABP2 gene polymorphism modifies the uptake of fatty acids, it could in turn affect the lipid metabolism and/or correlate with cardiovascular disease risk. Previous studies have shown that the IFABP Thr54 allele is significantly associated with higher total cholesterol, increased stroke incidence [9], elevation of fasting and postprandial triglyceride [10, 11], higher nonesterified fatty acid concentrations [12], dyslipidemia [13], obesity [14], and insulin resistance [7, 11, 15]. Ala54Thr polymorphism of FABP2 was associated with a risk of hearing impairment [16]. The risk of colorectal cancer associated with this polymorphism is higher in the subjects with lower fat intake [17]. Also, the Thr allele has been associated with visceral fat in Japanese subjects [18], diabetic nephropathy in Japanese patients with type 2 diabetes [19], triglycerides in Finnish hyperlipidemic males [20] and Body Mass Index (BMI) and percent body fat in Aboriginal Canadians [15]. However, there are many contradicting studies that have found non-significant association with these parameters [11, 21, 22].

The frequencies of the FABP2 alleles have been studied in many ethnic groups, and demonstrated interethnic variations in their distribution. The frequency of the wild-type Alanine allele was highest in Tongans (Polynesians) [23] and lowest in the East Asians [24-26]. However, these studies have focused on Asians, Europeans, and North Americans and the data have been reported for Arab populations is lacking [27]. In the light of the potential role of the FABP2 polymorphism, the goal of this study was to determine the frequency of the Thr54 allele in the Bahraini and Jordanian populations and to compare our results with similar studies in other ethnic groups.

Materials and Methods

Subjects

This study is a population-based prospective study which included 302 participants. The blood samples studied were collected from 182 unrelated healthy subjects (without a prior history of diabetes and hypertension and none of the participants were receiving continuous medical treatment) from the Arabian Gulf University, Manama, Bahrain and from 120 unrelated healthy subjects from the city of Amman, Jordan. All participants are Arabs, aged between 18 and 65 years, and non-Arab or recently naturalized were excluded. A written informed consent from all participants included in this study was done under institutionally approved internal review board protocols (Protocol number: 60/2009) according to the Helsinki Declaration.

Genotype analysis

Genomic DNA was isolated from blood samples by phenol-chloroform extraction followed by ethanol precipitation. The DNA samples were analyzed using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method [28]. A 180-bp fragment was amplified. DNA was amplified in a total volume of 25 µl, with the forward primer: 5'-ACAGGTGTTAATATAGTGAAAAG-3' and the reverse primer: 5'-TACCCTGAGTTCAGTTCCGTC-3' [8]. PCR amplification was carried out using 50–100 ng of target DNA, 40 pM of each oligonucleotide primer, 200mM dNTPs in 50mM KCl, 1.5mM $MgCl_2$, 10mM Tris–HCl pH 8.4 and Taq DNA polymerase (1.25 U) as recommended by the supplier (Life Technologies). The PCR program consisted of an initial denaturation step at 94°C for 5 min followed by 32 cycles of denaturation at 94°C for 1 min, annealing at 55°C for 1 min, and extension at 72°C for 1 min. The final extension step was performed at 72°C for 10 min. For Restriction Fragment length Polymorphism (RFLP) analysis, 5 µl of PCR product were incubated with 0.4 µl of enzyme *Hha*I (GCG/C) (10 U/µl, New England *Biolabs*) in a final volume of 10 µl overnight at 37°C. The products were run on 3% agarose gel containing 1mg/mL ethidium bromide, electrophoresed for 45 min at 120 volts, and photographed under ultraviolet light. The PCR products that lack the *Hha*I site migrate as one 180-bp fragment (those carrying the Thr54), but PCR products containing the *Hha*I site are cleaved into two fragments (a 99-bp and an 81-bp).

Sample Size Calculation

The samples size was calculated according to the following formula: $n = \{t^2 \times p\ (1-p)\}/\ m^2$

Where n = sample size; t = confidence level at 95%

(standard value of 1.96); p = estimated prevalence of *Thr* allele in the population (0.267 in Egyptian population; Salem, 2009); m = margin of error at 5% (standard value of 0.05).

$n = \{(1.96)^2 \times 0.267\ (1-0.267)\}/\ (0.05)^2 = 300.74 = \sim 301$ individuals

Statistical analysis

Genotype and allele frequencies were calculated by direct counting and were evaluated using the chi square test for goodness of fit. The significant deviation from Hardy-Weinberg equilibrium (HWE) was evaluated by an exact test provided by the Arlequin program (version 3.0) [29]. The confidence limits were calculated by the online statistic tool [30] according to Wilson score method without continuity correction [31].

Results

In this study 302 volunteers were investigated (aged between 18 and 65 years, mean age 42 years) from Bahraini and Jordanian Arab populations. The Bahraini sample included 70 men (aged between 19 and 58 years, mean age 40) and 112 women (aged between 18 and 60 years, mean age 41) and the Jordanian sample included 44 men (aged between 20 and 62 years, mean age 43) and 76 women (aged between 18 and 65 years, mean age 44). The mean BMI for all participants was 23.24 kg/m^2 and the mean BMI for Bahraini samples was 23.29 kg/m^2 (22.92 for men and 23.65 for woman) and for Jordanians was 23.19 kg/m^2 (22.83 for men and 23.54 for woman). There were no significant differences between the mean ages, gender and BMI in the studied populations.

The genotype and allele frequencies of Ala54/Thr54 mutation in the Bahraini and Jordanian populations have been shown in Table 1. The studied populations were found to be in Hardy–Weinberg equilibrium. As regard Bahraini population, the data showed that the Ala54/Ala54 genotype is the most prevalent (52.8%) followed by Ala54/Thr54 (35.7%) and Thr54/Thr54 (11.5%). In this Bahraini population sample, the frequencies of allele Ala54 and allele Thr54 were 0.706 (95% CI, 0.636-0.767) and 0.294 (95% CI, 0.233-0.364), respectively. For Jordanians, the results showed that the Ala54/Ala54 genotype is the most prevalent (48.3%) followed by Ala54/Thr54 (43.3%) and Thr54/Thr54 (8.4%). Among Jordanians, the frequencies of allele Ala54 and allele Thr54 were 0.700 (95% CI, 0.612-0.774) and 0.300 (95% CI, 0.225-0.387), respectively. Figure 1 shows the electrophoresis patterns for FABP2 genotypes by PCR-RFLP based assay.

The observed genotype results did not differ significantly from the expected genotypes for a population in Hardy Weinberg equilibrium (Table 1) ($p > 0.05$, Chi squared goodness of fit). Comparison of the results with data reported for other ethnic groups using the Chi square test for goodness of fit is shown in Table 2.

Discussion

The present study described for the first time the frequency of the Ala54Thr polymorphism in FABP2 gene in two Arab populations; Bahraini and Jordanians. We determined the genotype and allelic polymorphisms of FABP2 gene among 182 Bahrainis and 120 Jordanians.

This study showed that there were no statistically significant differences of the allelic frequencies of FABP2 gene between Bahraini and Jordanian populations. The available data regarding the allelic frequencies of Ala54Thr polymorphism in FABP2 gene among Arab populations is deficient. The observed frequency of the Thr54 allele in Bahraini and Jordanian subjects is similar to that reported for Egyptians [27]. The Ala54Thr polymorphism of FABP2 is in a Hardy Weinberg equilibrium which suggests that there is no significant natural selection pressure acting against individuals with the Thr54 FABP2 variant living in Bahrain and Jordan.

The frequencies of FABP2 polymorphism varies between different ethnic groups, i.e. from 0.22 in the African Americans [32] to 0.35 in Japanese [24], and approximately 0.30 in Caucasians [33]. The results of this study are within the range reported in the literature.

Table 1. Distribution of the FABP2 genotype and allele frequencies among the Bahraini and Jordanian populations.

Study Population	FABP2 Genotype	Number Observed (and percentage)	FABP2 Allele Frequency		Heterozygosity	
			Ala54	*Thr54*	Observed	Expected
Bahrainis (n) = 182	Ala54/Ala54	96 (52.8)	0.706	0.294	0.357	0.416
	Ala54/Thr54	65 (35.7)				
	Thr54/Thr54	21 (11.5)				
Jordanians (n) = 120	Ala54/Ala54	58 (48.3)	0.700	0.300	0.433	0.421
	Ala54/Thr54	52 (43.3)				
	Thr54/Thr54	10 (8. 4)				

n = sample size

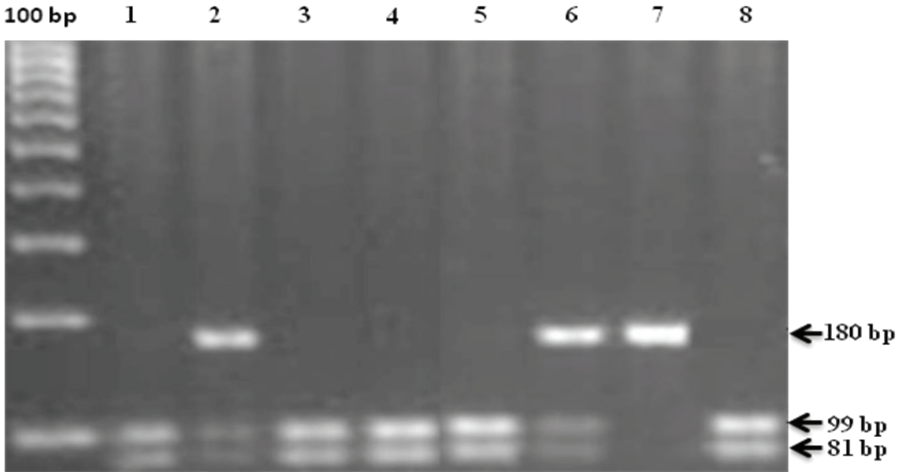

Figure 1. Electrophoresis patterns for FABP2 genotypes by PCR-RFLP based assay, persons with homozygous genotype (Ala54/Ala54) (lanes 1, 3, 4, 5, and 8), homozygous genotype (Thr54/Thr54) (lane 7) and heterozygous genotype (Ala54/Thr54) (lanes 2 and 6), are shown. 100 bp DNA marker.

Table 2. Genotype percentages and allele frequencies of FABP2 polymorphism in various ethnic groups

Study Population	Sample Size	Genotype Percentage			Allele Frequency		Reference
		Ala/Ala	**Ala/Thr**	**Thr/Thr**	**Ala**	**Thr**	
Bahrainis	182	52.8	35.7	11.5	0.703	0.297	This study
Jordanians	120	48.3	43.3	8.4	0.700	0.300	This study
Egyptians	180	56.7	33.3	10	0.733	0.267	[27]
Finnish	170	49.4	45.3	5.3	0.725	0.275	[21]
Sweden	59	52	36	12	0.703	0.297	[9]
British	69	62.3	31.9	5.8	0.783	0.217	[34]
Middle Europeans #	102	51.0	43.1	5.9	0.726	0.275	[34]
South Europeans *	90	56.7	36.7	6.6	0.750	0.250	[34]
Indians	899	53.6	39.3	7.1	0.732	0.268	[35]
Japanese	258	45	41	14	0.655	0.345	[24]
Chinese	165	45	44	11	0.670	0.330	[26]
Koreans	96	45	42	13	0.660	0.340	[25]
Argentineans	202	52.0	40.6	7.4	0.723	0.277	[28]
African Americans	1831	60	35	5	0.775	0.225	[32]
Pima Indians	457	48	45	7	0.700	0.300	[7]
Native Canadians	188	74	24	2	0.860	0.140	[15]
Tongans	1022	76	23	1	0.876	0.124	[23]

Middle Europeans are from Denmark, Germany, Belgium and Switzerland
* Southern Europeans are from Portugal, Italy, Spain and Greece

The frequency of the Thr54 allele in Bahrainis and Jordanians is similar to that reported in different European populations [9, 21, 34]. Also, it is similar to that reported for Argentineans, who are mostly of Europeans descent [28]. It is also similar to that reported for south-east Asians [24-26, 35]. Interestingly, no statistically significant differences were seen between Jordanians, and African Americans [32] or Pima Indians [7]. Statistically significant differences were seen between Bahrainis, and African Americans [32] and Pima Indians [7] ($p < 0.029$).

The frequency of the wild Ala54 allele among Bahrainis and Jordanians is significantly different from that reported for Native Canadians ($p < 0.001$) [15] and Tongans (Polynesians) ($p < 0.001$) [23].

It is well known that the Ala54Thr polymorphism of FABP2 is a missense variant that has a definite effect on the primary structure of the protein and affects its fatty acid binding properties. It is not clear whether this change can affect the lipid metabolism of carriers [36]. Previous studies have reported associations between this polymorphism and insulin resistance, BMI, dyslipidemia,

hypertriglyceridemia, obesity, hearing impairment, stroke, and metabolic syndromes [4, 7, 11-16, 35]. The Thr polymorphism has been associated with diabetes related variables in Mexican Americans [37], Pima Indians [7], Japanese men [18, 24], Indian migrants [38], and various Caucasian populations [38, 39]. In contrast, other studies report no association with the same parameters [20, 28, 39]. The contradictory results among the different studies may come from the different dietary habits of the analyzed populations [32, 41].

Thr-containing protein has been shown to have 2-fold greater affinity for long-chain fatty acids than does Ala-containing protein which may lead to increase absorption and processing of fatty acids [7]. Subjects with the Thr-encoding allele have been shown to be more insulin resistant and more obese than carriers of the Ala-encoding allele [9]. In the present study, about 11% of Bahraini subjects and 8% of Jordanians were homozygous for the Thr54 allele with their Thr-containing proteins may have greater affinity to long-chain fatty acids which may lead to increase absorption and processing of fatty acids in those subjects. This group of population may be liable to different types of diseases associated with increase absorption of the long-chain fatty acid including; cardiovascular diseases, stroke, obesity, diabetes, etc. Association studies between Thr54 allele of FABP2 gene and these diseases among Bahraini and Jordanians are needed.

Conclusion

This study is the first description of Thr54 allele of FABP2 gene in Bahraini and Jordanian populations which does not exclude the possibility of the presence of new SNPs unique to these populations. The population frequency of the Thr54 allele in Bahrain and Jordan does not differ from previously reported frequencies in European and Arab populations.

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