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Lack of association between the fatty acid binding protein 2 (FABP2) polymorphism with obesity and insulin resistance in two aboriginal populations from Chile

Abstract The aim of this study was to assess the frequency of fatty acid binding protein 2 (FABP2) Ala54Thr genetic polymorphism and to evaluate its association with obesity and insulin resistance in Chilean aboriginal populations. A sample of 96 urban Aymara and 111 urban Mapuche subjects aged 20–80 years were recruited for this cross-sectional study. Glucose, insulin and lipid profile were measured in fasting plasma samples. Insulin resistance was estimated through the HOMA-IR model. FABP2 Ala54Thr genotypes were determined by PCR followed by RFLP analysis. The allele frequency of Thr54 variant was estimated as 18.2% in Aymara subjects, which is one of the lowest reported to date. The corresponding frequency in Mapuche subjects was 31.9% (p<0.002). Regarding genotype–phenotype associations, no significant differences were found in any of the anthropometric or metabolic variables according to Ala54Thr genotypes. After adjustment by BMI and metabolic variables through a logistic regression analysis, the association of the FABP2 polymorphism with ethnic group persisted (Mapuche group: OR=2.37, 95% CI 1.319–4.277, p=0.004) It is unlikely that Ala54Thr polymorphism of the FABP2 gene plays a relevant role in obesity and insulin resistance in Chilean ethnic groups.

Key words BMI • Genotype • Fatty acids • Ethnic background • Amerindians

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Introduction

The important variability in the prevalence of type 2 diabetes and obesity among different populations and ethnic groups has been the focus of many epidemiologists. The impact of both diseases on personal and public health is already considerable, and is increasing in several areas of the world [1]. Both conditions are complex traits influenced by multiple genetic and environmental factors. Obesity and type 2 diabetes have been shown to cluster within families, suggesting a genetic component for their aetiology [2].

The gene for fatty acid binding protein 2 (FABP2) is located in the long arm of chromosome 4. The G to A polymorphism of codon 54 results in the substitution of threonine (Thr) for alanine (Ala) [3]. The associations between the FABP2 Ala54Thr polymorphism and increased fasting insulin (FI) concentration, fasting fatty acid oxidation and reduced glucose uptake were identified in Pima Indians, an extreme population with high prevalence rates of obesity and type 2 diabetes [3]. Furthermore, the linkage analysis of the FABP2 locus with insulin resistance was also found in a study in Mexican–Americans, who are a mixture of Amerindian

and European ancestry [4]. FABP2 plays a key role in the absorption and intracellular transport of dietary long-chain fatty acids. Carriers of the Thr54 allele in FABP2 have a twofold greater affinity to the absorption for the long-chain fatty acids than those with the Ala54-containing FABP2 [5], which supports the role of the FABP2 Ala54Thr polymorphism in the aetiology of obesity and metabolic disorders. *In vitro* experiments have shown that this substitution increases the affinity of FABP2 for long-chain fatty acids and is associated with increased triglyceride transport in human intestinal cells [6, 7].

The Chilean population is formed by a mixture of Amerindian native groups and descendants of several European migrants. Mapuche subjects are the largest native group in the country; they are descendants of Asian migrants that settled in the southern part of Chile up to Patagonia. Nowadays the Mapuche population lives in rural areas and in the main urban cities such as Santiago. According to the last Chilean census, the total Mapuche population was 604 309 inhabitants distributed in the entire country (4.5% of total population). Nearly 40% of these natives live in urban cities [8]. On the other hand, the Aymara population lives in Northern Chile, on the western slopes of the Andes, near the Bolivian and Peruvian borders. The majority of Aymara subjects are dependent on agriculture for at least part of their subsistence, animal husbandry being the secondary activity. This population preserves distinctive ethnic and cultural characteristics [9, 10] that are very different from those of the population of European origin living in Chile. Moreover, the Aymara population has yet to experience the massive transition from traditional ways of living to the modern lifestyles characteristic of industrialised countries. In recent reports both populations, living in rural areas, show a low prevalence of type 2 diabetes: 1.5% in Aymaras (mean age 47.0±8.4, range: 20–87 years) and 3.2% in Mapuches (mean age 47.7±16.2, range: 20–88 years) despite high frequency of obesity [11, 12]. Since the frequency of the Ala54Thr polymorphism has shown a high variability among several populations, the aim of this study was to assess the frequency of FABP2 Ala54Thr genetic polymorphism and to evaluate its association with obesity and insulin resistance in Chilean aboriginal populations.

Subjects and methods

Subjects

The participants were recruited from 3 Chilean cities: Arica, a northern city near the Andean "altiplano" zone were Aymara people originally used to live, Temuco, from the Mapuche living area in the south of the country, and Santiago, the capital city.

The enrolment of participants was done through an open invitation to city residents with at least 2 last names of Mapuche (Temuco and Santiago) or Aymara (Arica) origin, through advertising in local community organisations, church groups and primary health care centres. The appointment was concurrent with health exams that are carried out periodically by national health-care programmes in the adult population.

A sample of apparently 207 healthy subjects >20 years were recruited in both study areas: 96 Aymara subjects (77 women and 19 men; mean age: 50.6±12.9, range: 21–80 years) and 111 Mapuche subjects (82 women and 29 men; mean age: 43.7±13.5, range: 20–71 years). In this sample, the percentage of participants with blood type O in the ABO system was higher than 95%, which indicates a low admixture with Caucasian populations. Coincidentally, we observed that the subjects with A or B blood groups had European surnames and Caucasoid anthropometric traits. For this reason, besides the 2 last names criteria, we included only participants with O blood group. Those inclusion criteria are not absolutely accurate, as sometimes Spanish last names are merely a translation of a common Mapuche surname, although the high prevalence of O blood group (>95%) reported in both groups and the very low frequency of the A and B alleles in the ABO groups sustained the identification of the target population [13].

The study protocol was approved by the Institutional Review Board at INTA, University of Chile, and all subjects gave written informed consent.

Anthropometric measurements

Blood pressure was measured using a sphygmomanometer after at least a 5-min rest. Two readings were taken from the right arm: systolic pressure (SP) and diastolic pressure (DP) were estimated and the average was used. Height and weight were measured in light clothing, without shoes. Waist circumference at the umbilicus level and hip circumference at the maximum girth were tabulated. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in metres. Nutritional status was determined according to the World Health Organization (WHO) standard BMI categories (normal BMI 18.5–24.9 kg/m^2, overweight BMI 24.9–29.9 kg/m^2 and obese BMI ≥30 kg/m^2) [14].

Biochemical measurements

Blood samples were drawn in the morning between 07:00 and 09:00 h after an overnight fast. A standard 75-g oral glucose tolerance test (OGTT) was performed in each subject, after which subjects were classified into normal, impaired glucose tolerant (IGT) and diabetic on the basis of the WHO Criteria. Serum fasting glucose (FG) was measured by the glucose oxidase technique and serum FI was determined by means of radioimmunoassay (RIA Diagnostic Corporation, USA). The lipid profile: total cholesterol (TC), HDL-cholesterol (HDL-C) and triglycerides (TG), were determined with enzymatic colorimetric methods using commercial kits (Boehringer Mannheim, Germany). Insulin resistance was assessed by the relationship between FG and insulin concentrations, and analysed by the homeostasis model assessment (HOMA-IR) [15].

Determination of the polymorphism of the FABP2 gene

Genomic DNA was extracted from leukocytes by the phenol/chloroform method followed by proteinase K (GIBCO BRL, USA). A total of 100 ng of genomic DNA was used to amplify a specific FABP2 gene sequence by polymerase chain reaction (PCR) in a volume of 25 µl containing 0.5 U of Taq DNA polymerase (Invitrogen, USA). The reaction mix was composed by: tris HCl (10 mmol/l), pH 8.3, KCl (50 mmol/l), $MgCl_2$ (1.5 mmol/l), dNTPs (100 µmol/l) using the following primers: 5'-AC AGG TGT TAA TAT AGT GAA AAG-3' and 5'-TA CCC TGA GTT CAG TTC CGT C-3'. After 35 cycles of 1 min at 94°C, 1 min at 58°C and 1 min at 72°C, aliquots (7 µl) of PCR products were analysed on 2% agarose gels (Invitrogen, USA). The amplified PCR product (180 bp) was digested with 2 U HhaI (Invitrogen, USA) in 10 mmol/l Tris HCl pH 7.9, 50 mmol/l NaCl, 10 mmol/l $MgCl_2$ and 1 mmol/l dithiothreitol. After incubation at 37°C for 3 h, the digested samples were separated by electrophoresis through 3% agarose gel and visualised by staining with ethidium bromide. PCR products having an intact HhaI site are cleaved into 99 and 81 bp fragments; whereas the Ala54Thr substitution abolishes the restriction site.

Statistical methods

Genotype frequencies were tested for Hardy–Weinberg equilibrium after the estimation of allele and genotype frequencies. Continuous variables were expressed as means, standard deviations and 95% confidence intervals or ranges. Differences among study groups were assessed through the two-sample Wilcoxon rank-sum (Mann–Whitney) test. The association between Thr54Ala genotypes and obesity-related variables and ethnic group was assessed through logistic regression techniques. All statistical analyses were performed with the STATA 9.1 package.

Results

The frequency of the Thr54 allele was higher in the Mapuche subjects compared with the Aymara group (31.9% *vs*. 18.2%, $p<0.002$). In both groups, genotype frequencies were concordant with Hardy–Weinberg expectations. Table 1 shows genotype and allele frequencies for the FABP2 polymorphism in Mapuche and Aymara subjects jointly with previously published FABP2 genotype frequencies for several populations around the world.

Table 2 shows the distribution of anthropometric variables stratified by gender in relation to the observed genotypes of FABP2 in each ethnic group. No differences were found between Thr carriers in comparison with non-carriers either in the Mapuche group or the Aymara group in any of the anthropometric variables. In the Aymara group, among the obese the Thr54 allele was more frequent (0.51) than the Ala allele (0.33), $p=0.074$.

In the Mapuche group, the prevalence of obesity was 29.4%. The frequency of impaired glucose tolerance (IGT)

Table 1 FABP2 genotype and allelic frequency in several populations (HWE, Hardy–Weinberg equilibrium)

	Ala/Ala	Ala/Thr	Thr/Thr	Ala	Thr	*p*-value, HWE
Aymara (*n*=96)	0.66	0.31	0.03	0.82	0.18	0.73
Mapuche (*n*=111)	0.46	0.44	0.10	0.69	0.31	0.95
Japanese[22] (*n*=237)	0.44	0.45	0.11	0.65	0.35	0.39
Korean[20] (*n*=96)	0.45	0.42	0.13	0.66	0.34	0.45
Pima Indians[3] (*n*=457)	0.48	0.45	0.07	0.70	0.30	0.07
Sweden[7] (*n*= 59)	0.42	0.46	0.12	0.70	0.30	0.34
USA women[19] (*n*=60)	0.61	0.30	0.09	0.76	0.24	0.21
Chilean women[21] (*n*=63)	0.37	0.47	0.16	0.60	0.40	0.38

Table 2 Anthropometric variables according to FABP2 genotype in Aymara and Mapuche natives

	Aymara, mean±SD (95% CI)		Mapuche, mean±SD (95% CI)	
Men	Ala/Ala (*n*=9)	X/Thr (*n*=10)	Ala/Ala (*n*=11)	X/Thr (*n*=18)
BMI (kg/m^2)	26.7±2.2 (24.9–28.4)	26.8±6.3 (22.2–31.3)	28.1±2.8 (26.2–30.0)	29.0±5.2 (26.3–31.5)
Waist/hip ratio	0.90±0.10 (0.80–0.98)	0.93±0.02 (0.91–0.95)	0.90±0.1 (0.82–0.97)	0.92±0.05 (0.89–0.95)
Waist (cm)	92.6±10.4 (84.5–100.6)	95.4±12.1 (86.7–104.0)	97.5±8.5 (91.7–103.2)	98.4±9.8 (93.5–103.2)
Women	Ala/Ala (*n*=55)	X/Thr (*n*=22)	Ala/Ala (*n*=40)	X/Thr (*n*=42)
BMI (kg/m^2)	29.9±5.8 (28.2–31.4)	31.6±4.7 (29.4–33.6)	30.5±4.8 (28.9–32.0)	31.6±5.8 (29.7–33.4)
Waist/hip ratio	0.87±0.04 (0.86–0.89)	0.88±0.05 (0.86–0.90)	0.87±0.05 (0.85–0.89)	0.86±0.04 (0.84–0.87)
Waist (cm)	96.2±13.1 (92.7–99.8)	97.4±9.9 (92.9–101.8)	95.9±11.1 (92.3–99.4)	96.8±11.9 (93.1–100.5)

Table 3 Metabolic variables according to FABP2 genotype and nutritional status in Aymara and Mapuche natives

	Aymara, mean±SD (ranges)		Mapuche, mean±SD (ranges)	
Normal	Ala/Ala (*n*=43)	X/Thr (*n*=17)	Ala/Ala (*n*=28)	X/Thr (*n*=28)
Fasting insulin (pmol/l)	82.1±72.1 (10–402.2)	78.8±76.4 (12.1–269.3)	72.8±77.1 (8.5–300)	69.3±65 (11.4–271.5)
HOMA-IR	2.5±2.6 (0.2–13.5)	2.3±2.1 (0.2–7.1)	1.5±1.5*[¢] (0.1–5.9)	2.9±4.8 (0.2–20.4)
Triglycerides (mmol/l)	1.3±0.5 (0.4–2.59)	1.1±0.5 (0.5–2.5)	1.2±0.7 (0.5–3.4)	1.1±0.5 (0.4–2.4)
Obese	Ala/Ala (*n*=20)	X/Thr (*n*=15)	Ala/Ala (*n*=23)	X/Thr (*n*=32)
Fasting insulin (pmol/l)	137.9±142.9 (11.4–613)	184.3±127.1 (48.5–436.5)	104.3±76.4 (12.1–44.3)	105.7±155.7**[¥] (11.4–683.7)
HOMA-IR	5.2±0.6 (0.3–22.5)	5.3±3.4 (1.2–10.9)	2.5±1.7 (0.2–6.2)	3.0±4.2**[£] (0.2–18.1)
Triglycerides (mmol/l)	1.4±0.6 (0.5–3.2)	1.6±0.6 (0.9–2.7)	1.5±0.8 (0.5–3.9)	1.5±1.0 (0.5–4.7)

*p<0.05, **p<0.01 two-sample Wilcoxon rank-sum (Mann–Whitney) test; [¢]Homa-IR between normal Aymara Ala/Ala *vs*. normal Mapuche Ala/Ala; [¥]Fasting insulin between obese Aymara X/Thr *vs*. obese Mapuche X/Thr; [£]Homa-IR between obese Aymara X/Thr *vs*. obese Mapuche X/Thr

Table 4 Logistic regression for FABP2 genotype with BMI, ethnic group, triglycerides and HOMA-IR as contributing variables

Parameter	FABP2 genotype (*n*=207) (Thr/X)		
	OR	(95% CI)	*p*
BMI	0.867	(0.367–2.043)	0.744
Mapuche ethnic	2.37	(1.319–4.277)	0.004
Triglycerides	0.99	(0.994–1.003)	0.722
HOMA-IR	1.04	(0.964–1.133)	0.279

was 5.51% and the prevalence of type 2 diabetes was 6.31%. In Aymara subjects the respective frequencies were 28.7% for obesity, 4.8% for IGT and 10.4% for type 2 diabetes.

Table 3 shows obesity-related variables according to the FABP2 genotype. No differences were detected for Thr carriers compared with the non-carriers in any of the metabolic variables either in the Mapuche group or the Aymara group. However, when we compared Aymara *vs*. Mapuche natives, HOMA-IR was statistically different in normal weight status between Ala/Ala genotype (p<0.05). In the obese status, significant differences were detected between Aymara X/Thr *vs*. Mapuche X/Thr to FI and HOMA-IR (p<0.01).

After adjustment by BMI and metabolic variables through a logistic regression analysis (Table 4), the association of the FABP2 polymorphism with ethnic group persisted (Mapuche group: OR=2.37, 95% CI 1.319–4.277, p=0.004).

Discussion

In Chile, although both Aymara and Mapuche aboriginal populations living in rural areas are still characterised by traditional lifestyles, it is remarkable that the prevalence of obesity (BMI≥30 kg/m^2) is relatively high, especially among women. However, the low prevalence of insulin resistance and type 2 diabetes would indicate a special protective genetic background regarding some candidate genes [16].

The process of modernisation and urbanisation undergone in several aboriginal communities has brought new nutritional and physical activity patterns that may have contributed to the high prevalence of obesity and type 2 diabetes in such populations. In contrast with other aboriginal populations such as Pima Indians in North America, it is interesting to note that Aymara and Mapuche populations as well as Mexican Pima Indians have not completely adopted lifestyles from industrialised Western societies [17, 18].

The frequency of the Thr54 allele variant was estimated as 0.32 in the Mapuche group and 0.18 in Aymaras. The frequency of this polymorphism has been described in several populations, such as non-diabetic Pima Indians (0.30), Korean people (0.34), Japanese subjects (0.35), Swedish (0.30) and Caucasian individuals from USA (0.32) [5, 6, 19, 20]. The frequency observed in those populations, including our recent publication on Chilean women (0.39) [21], is similar to that reported in the Mapuche group.

However, the frequency observed in the Aymara natives is very low, only comparable with the recently reported frequency in the Tongan population (0.12) [22].

Previous studies have found a significant association between the FABP2 genotype and occurrence of type 2 diabetes or decreased insulin sensitivity [3, 23]. In Japanese men, the Thr54Thr genotype was associated with higher insulin levels at baseline and 2 h after a glucose challenge [7]. Similar results were found in the presence of the Thr54 allele in fasting samples after correcting for BMI in Pima Indians [3]. Other studies reported significant associations between the FABP2 locus and increased prevalence of insulin resistance in some populations [3, 6, 19–21]. None of these associations were found in the present study.

In addition to its association with insulin resistance and diabetes, it has been proposed that gain of function mutations of FABP2 could result in postprandial lipid abnormalities [24]. The Ala54Thr polymorphism, which results in a higher affinity of FABP2 for long-chain fatty acids, has been linked with increased total body fat oxidation and a small elevation of plasma FFA levels, however these results have been inconsistent. An association with higher postprandial triglyceride levels and lipoprotein extrusion has also been observed [24, 25]. This observation may indicate the existence of complex unmeasured gene–gene or gene–environment interactions that may enhance metabolic abnormalities [26–28]. As is well known, elevated FFA increases the accumulation of TG in the liver, associated with high levels of FI.

On the other hand, it is possible that the Thr/Thr homozygous genotype confers some degree of susceptibility to obesity, associated with an influence of the genotype on parameters related to lipid metabolism [29].

The wide variation in the prevalence of obesity and diabetes among Aymara, Mapuche and other aboriginal populations of the Americas is difficult to interpret.

The present study has shown a high prevalence of type 2 diabetes in both ethnic groups, Mapuche (6.31 %) and specially in the Aymara group (10.4%), when comparing with our previous studies conducted in rural areas (Mapuche 4.1% and Aymara 1.5%) [11, 12]. In a first approach, we would expect that the low frequency of the Thr54 variant in Aymara subjects could exert a protective role for obesity and type 2 diabetes when this ethnia is exposed to western diets and unhealthy environments. However, we pointed out that this was not the case. Besides, the X/Thr obese subjects in this ethnic group were more insulin-resistant (high FI and HOMA-IR) compared to X/Thr obese Mapuche individuals.

Multiple dietary factors and gene/environment interactions may determine a potential epigenetic effect. The low prevalence of type 2 diabetes in Aymara and Mapuche subjects found in our previous studies however, was in sharp contrast with the high prevalence of this condition in most aboriginal groups in North America, including the Pima Indians from Arizona and Mexican–American minorities in the USA. Like most aboriginal populations, nowadays Mapuche and Aymara people have changed their diet and physical activity patterns to fit an industrialised country model. They now derive their intake completely or in large part from western diets and live mostly sedentary lifestyles in large cities. Under these circumstances, they develop high rates of obesity, insulin resistance and type 2 diabetes.

In conclusion, although the FABP2 polymorphism is a suitable candidate gene for insulin resistance, obesity and type 2 diabetes, no relevant differences were found in the assessment of its association with these abnormalities in each ethnic group. However, when we compared both ethnias, the Ala54Thr polymorphism of the FABP2 gene seems to play a major role in obesity and insulin resistance in the Aymara ethnic groups, despite its low frequency, compared to Mapuche Amerindians.

Acknowledgements This work was supported by grant Fondecyt 1020703 to C. Albala and DI Grant 022 to E. Carrasco.

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