

# FABP2 *Ala54Thr* polymorphism and diabetes in Chilean elders

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## Abstract

**Objective:** The FABP2 *Ala54Thr* polymorphism has been associated with insulin resistance and diabetes in several populations. The aim of this study was to estimate the prevalence of FABP2 genotypes in 223 Chilean subjects (136 women and 87 men aged 65–79 years) and its association with type 2 diabetes in a 4 years follow-up.

**Methods:** Glucose, Insulin and lipids were measured in fasting plasma samples. Insulin resistance was estimated through the homeostasis model assessment. Diabetes was diagnosed according ADA criteria. The *Ala54Thr* allelic variant was determined by polymerase chain reaction and restriction fragment-length polymorphism analysis. Logistic regression techniques were used to assess gene–disease associations.

**Results:** Genotype frequencies were estimated as 30.5, 49.3 and 20.2% for the *Ala/Ala*, *Ala/Thr* and *Thr/Thr*, respectively. The crude OR for the association between *Thr54* carriers and diabetes was estimated as 2.18 (1.12–4.24). The corresponding OR for the association between *Thr54* carriers with Metabolic Syndrome was 1.06 (0.59–1.88). After adjustment by BMI and age, a significant association persists for *Thr54Thr* carriers and diabetes (OR 2.70; 95% CI 1.113–6.527). The 4-year cumulative incidence of diabetes was higher in *Thr* carriers than in non-carriers (20.1% versus 8.5%;  $p < 0.04$ ). The adjusted association between *Thr54Thr* polymorphism and diabetes incidence was OR 3.84 (95% CI: 1.140–12.910)

**Conclusion:** Our results strongly suggest an association between the *Ala54Thr* polymorphism of FABP2 with diabetes, revealing a genetic dosage effect regarding its association with diabetes in Chilean elders

**Keywords:** FABP2 polymorphism; Diabetes; Elders

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## 1. Introduction

The fatty acid binding protein 2 (FABP2) is an intracellular protein expressed in the villus tips of the small intestine, involved in the absorption and transport of dietary long chain fatty acids (FA) [1].

A single nucleotide polymorphism (G-to-A) in codon 54 of exon 2 resulting in an alanine to threonine substitution was first associated with insulin resistance in Pima Indians without type 2 diabetes [2]. The *Ala54Thr* polymorphism of the FABP2 is relatively common occurring in 30% to 35% of the studied populations [2,3]. Individuals carrying at least one copy of the *Thr54* allele have a two-fold greater affinity for the long-chain FA than those with the *Ala54*-containing FABP2 [2]. A resulting increased flux of dietary fatty acids in the circulation may lead to an impairment of

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sensitivity of glucose metabolism to insulin, supporting the role of the FABP2 *Ala54Thr* polymorphism in the aetiology of metabolic disorders [3,4]. FABP2 *Ala54Thr* variant has been associated with an increased fasting insulin concentration, an increased rate of fat oxidation, reduced insulin-stimulated glucose uptake and increased concentrations of fasting and postprandial triglyceride-rich lipoprotein [4–9]. Previous studies have found contradictory associations between FABP2 genotypes and the occurrence of type 2 diabetes, obesity or decreased insulin sensitivity [4,9–13].

The aim of this study was to estimate the prevalence of FABP2 genotypes in a population-based sample of Chilean subjects and to evaluate their association with type 2 diabetes in a 4-year follow up.

## 2. Subjects and methodology

The present study is part of a cross sectional study conducted in the year 2000 in a representative sample of 1301 subjects  $\geq 60$  years and older residing in Santiago, Chile, described elsewhere [14,15] to study health and wellbeing of the elderly (SABE Study). From the SABE original sample, 1202 subjects had complete measurements from which 909 frozen blood samples were available to study *Ala54Thr* genotypes of FABP2. Of these 909 individuals, four years later 151 were reported to have died, 594 subjects were accessible and 164 were lost to follow-up. Our study sample is a sub-sample selected, regardless of disease status, from the 594 accessible subjects. We studied 223 individuals, 136 women and 87 men, aged 65–79 years. This sample size provides a statistical power of 80% and a confidence level of 95% to find differences between FABP2 genotypes and the incidence of type 2 diabetes, assuming a 4-year incidence of 10% for the reference group, and a hypothesized incidence probability of 0.20 for genetic high-risk group.

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

### 2.1. Anthropometric measurements

Height and weight were measured in light clothing, without shoes. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Obesity was defined according World Health Organization (WHO) criteria as a BMI  $\geq 30$  kg/m<sup>2</sup> [16]. Waist circumference was measured in a horizontal plane around the abdomen at level of iliac crest. Elevated waist circumference was defined as  $\geq 102$  cm in men and  $\geq 88$  cm in women [17]. Blood pressure was measured using a sphygmomanometer after at least a 5-min rest. Two readings were taken from the left arm, systolic pressure and diastolic pressure were estimated and the average was used. Hypertension was defined according 1999 World Health Organization—International Society of Hypertension guidelines for the management of hypertension [18], as the

proportion of subjects with systolic blood pressure at least 140 mmHg or diastolic blood pressure at least 90 mmHg or presently using hypertension medication. Diagnosis of diabetes was made with a fasting plasma glucose  $\geq 126$  mg/dl or presently taking oral hypoglycemic drugs [19].

### 2.2. Biochemical measurements

Blood samples were taken in the morning after a 12 h overnight fast. Serum fasting glucose was measured by the glucose oxidase technique and serum fasting insulin was determined by means of radioimmunoassay (RIA Diagnostic Corporation, USA). The lipid profile total cholesterol, HDL-cholesterol and triglycerides were determined with enzymatic colorimetric methods using commercial kits (Boehringer Mannheim, Germany). Insulin resistance was assessed by the relationship between fasting glucose and insulin concentrations, and analyzed by the homeostasis model assessment (HOMA) [20].

### 2.3. Genetic analysis of FABP2 gene

Genomic DNA was extracted from leukocytes by the phenol/chloroform method followed by proteinase K (GIBCO BRL, USA). Amplification of the FABP2 gene sequence was performed by polymerase chain reaction (PCR) in a volume of 25  $\mu$ l containing 0.5 U of Taq DNA polymerase (Invitrogen, USA), 10 mmol/l Tris–HCl pH 8.3, 50 mmol/l KCl, 1.5 mmol/l of MgCl<sub>2</sub>, 100  $\mu$ mol/l of dNTPs 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  $\mu$ l) of PCR products were analyzed on 2% agarose gels (Invitrogen, USA). The amplified PCR product (180 bp) was digested with 2U HhaI (Invitrogen, USA) in 10 mmol/l Tris–HCl pH 7.9, 50 mmol/l NaCl, 10 mmol/l MgCl<sub>2</sub> 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 visualized 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.

### 2.4. Statistical methods

Genotype frequencies were estimated by gene counting. Hardy–Weinberg equilibrium was evaluated through Chi-square goodness-of-fit test. Differences in frequencies of dichotomous variables among study groups were assessed through Chi-square tests. Logistic regression techniques were used to assess gene–disease associations after adjustment by confounding variables. All statistical analyses were performed with STATA 8.0 package (Statacorp. 2003).

## 3. Results

Genotype and allele frequencies for the FABP2 polymorphism in the sample by gender are given in

Table 1  
Genotype and allele frequencies for the FABP2 polymorphism in the total sample by gender (N = 223)

	Men (N = 87), frequency (%)	Women (N = 136), frequency (%)	Total (N = 223), frequency (%)
Genotype			
Ala54Ala	30 (34.5)	38 (27.9)	68 (30.5)
Ala54Thr	45 (51.7)	65 (47.8)	110 (49.3)
Thr54Thr	12 (13.8)	33 (24.3)	45(20.2)
Allele			
Ala	105 (60.3)	141(51.8)	246 (55.2)
Thr	69 (39.7)	131(48.2)	200 (44.8)

Table 2  
Characteristics of the study group according FABP2 X/Thr genotype

Genotype	Ala54Ala mean $\pm$ S.D. (N = 68)	Ala54Thr mean $\pm$ S.D. (N = 110)	Thr54Thr mean $\pm$ S.D. (N = 45)	Total mean $\pm$ S.D. (N = 223)
Age (years)	72.1 $\pm$ 4.6	71.3 $\pm$ 4.3	71.5 $\pm$ 4.0	70.5 $\pm$ 3.9
BMI (kg/m <sup>2</sup> )	28.9 $\pm$ 3.9	29.5 $\pm$ 5.3	28.7 $\pm$ 4.2	29.2 $\pm$ 4.7
WC (cm)	98.7 $\pm$ 10.8	96.9 $\pm$ 11.6	95.5 $\pm$ 9.9	97.1 $\pm$ 11.1
TC (mg/dl)	204.4 $\pm$ 44.0	211.3 $\pm$ 43.2	210.0 $\pm$ 45.0	208.9 $\pm$ 43.7
TG (mg/dl)	173.1 $\pm$ 92.7	196.6 $\pm$ 167.3	184.8 $\pm$ 117.5	187.0 $\pm$ 138.9
HDLc (mg/dl)	37.2 $\pm$ 10.7	40.9 $\pm$ 14.8	40.4 $\pm$ 13.2	39.7 $\pm$ 13.4
SBP (mmHg)	137.3 $\pm$ 20.2	138.9 $\pm$ 22.1	137.6 $\pm$ 17.2	138.1 $\pm$ 20.5
DBP (mmHg)	81.3 $\pm$ 12.8	80.5 $\pm$ 10.2	81.6 $\pm$ 10.4	80.9 $\pm$ 11.2
Glucose (mg/dl)	101.4 $\pm$ 41.0	108.0 $\pm$ 43.9	107.0 $\pm$ 44.3	105.8 $\pm$ 43.0
Insulin ( $\mu$ UI/ml)	9.7 $\pm$ 8.2	10.3 $\pm$ 8.5	7.9 $\pm$ 5.4	9.6 $\pm$ 7.9
HOMA	2.4 $\pm$ 2.3	3.0 $\pm$ 3.8	2.1 $\pm$ 1.5	2.6 $\pm$ 3.0

Values are means  $\pm$  S.D.;  $p$  = NS.

**Table 1.** The frequency of *Thr* carriers was 44.8%, being the frequencies for the *Thr54Thr* 20.2 %. Genotype frequencies agreed with Hardy–Weinberg expectations.

In **Table 2** are described the anthropometric, biochemical and metabolic characteristic of the study group according FABP2 genotype. No significant genotype–phenotype associations with the genotype were observed.

The crude association of FABP2 polymorphism with obesity, diabetes, hypertension and elevated waist circumference is presented in **Table 3**. There was significant association between *Ala54Thr* polymorphism and diabetes (OR = 2.18; 95% CI 1.12–4.24), but

not with hypertension nor with obesity neither with elevated waist circumference.

From the subsample of 223 subjects, 190 subjects were free of diabetes in 2000. The 4-year cumulative incidence of diabetes for that group, presented in **Table 4**, was 8.5% for the *Ala/Ala* carriers 17.4% for *Ala/Thr* carriers and 28.2% for *Thr/Thr* carriers (Pearson  $\chi^2$  = 6.5647 Pr = 0.038).

Finally, in **Table 5** is presented a multivariate analysis to adjust the association between FABP2 polymorphism with diabetes by other possible contributing variables as gender, age, BMI. The analysis demonstrated a significant association between *Thr54Thr* genotype with diabetes for both prevalent

Table 3  
Crude association between FABP2 X/Thr genotype and obesity, diabetes, hypertension and elevated waist circumference

	Ala54Ala (N = 68)	X54Thr (N = 155)	OR (95% CI)	$p$ -Value
Obesity	27	62	1.25 (0.73–2.15)	0.236
Diabetes	14	56	2.18 (1.12–4.24)	0.022
Hypertension	34	93	1.50 (0.85–2.66)	0.850
Elevated Waist Circumference	44	83	0.64 (0.34–1.19)	0.134

Table 4  
Risk of type 2 diabetes according FABP2 genotype

	4-Year risk	Relative risk	95%
Ala54ala	0.0847	Reference	–
Ala54Thr	0.1739	2.05	0.79–5.30
Thr54Thr	0.2821	3.33	1.25–8.84

cases (OR = 2.70; 95% CI 1.11–6.53) and incident cases (OR = 3.84; 95% CI 1.14–12.91).

#### 4. Discussion

The genotype frequencies for FABP2 *Ala54Thr* polymorphism in the study group, shows that allele frequencies (0.45) were slightly higher than those reported for other populations. It must be stated that the study group is mostly of Caucasian origin arising from a representative sample from the city of Santiago where, according the 2002 Chilean census, only 2% of this age group population have aboriginal ethnic ancestries [21].

The frequencies of FABP2 *Ala54Thr* polymorphism described in others populations fluctuate between 0.30 and 0.35 as in non-diabetic Pima Indians (0.30), Korean (0.34), Japanese (0.35), Swedish (0.30) and Caucasian individuals from USA (0.32) [2,3,13,22,23].

Several studies have reported the association between the *Ala54Thr* polymorphism of FABP2 with insulin resistance and diabetes [2,13,22–26]. In the present study we have not found differences in glycemia, insulin, and serum lipids between FABP2 *X/Thr* and *Ala54Ala* genotype groups although significant differences in type 2 diabetes were attained. Multiple gene/environment interactions such as diet, exercise, body composition and life style modification [27,28] would determine a potential effect not examined in the present study. However the apparent contradiction may in part be explained by the pharmacologic management of hyperglycemia in diabetics and the therapies directed

to accompanying conditions such as dyslipidemia and hypertension. Glycemia in diabetic patients are extremely variables depending on diet, physical activity and pharmacotherapy adherence; on the other side a confirmed diagnosis of diabetes reveals more accurately a metabolic disturbance.

The results of the present study are consistent with an association between the *Ala54Thr* polymorphism of FABP2 with Diabetes (OR 2.18; 95%CI 1.12–4.24) but not with serum lipid alterations, nor with obesity neither hypertension. The 4-year cumulative incidence of diabetes demonstrates a higher risk in individuals carrying at least 1 copy of the *Thr54* allele. The highest incidence of diabetes was observed in individuals homozygous for the *Thr* allele suggesting an allelic-dosage effect.

In a previous study, we have described an association between the *Ala54Thr* polymorphism of FABP2 with insulin resistance and obesity in women [13]. Other studies reported significant associations between the FABP2 locus and increased prevalence of insulin resistance, type 2 diabetes or decreased insulin sensitivity [2,9,23–26,29]. In Japanese men, the *Thr54Thr* genotype was associated with higher insulin levels at baseline and 2 h after a glucose challenge [23]. Similar results were found in the presence of the *Thr54* allele in fasting samples after correcting for body mass index in Pima Indians [2].

In addition to its association with insulin resistance and diabetes, it has been proposed that the heavyweight of dosage of functional mutations of FABP2, the higher postprandial lipid abnormalities [7]. The *Ala54Thr* polymorphism, which results in a higher affinity of FABP2 for long chain fatty acids, has been associated with increased total body fat oxidation and a small elevation of plasma FFA level; however these results have been inconsistent. An association with higher postprandial triglyceride levels and lipoprotein extrusion has also been observed [7,24]. Moreover, in

Table 5  
Logistic regression for prevalent cases and 4-year incident cases of Diabetes as outcome and FABP2 genotype, gender, BMI and age as contributing variables

Parameter	Diabetes prevalence (n = 222)		Diabetes incidents (n = 190)	
	OR (95% CI)	p-Value	OR (95% CI)	p-Value
Gender (male)	0.02 (0.000–1415)	0.497	0.45 (0.00–73644)	0.913
Age (continuous variable)	0.90 (0.811–1.010)	0.070	0.92 (0.810–1.044)	0.197
BMI	1.11 (1.036–1.183)	0.003	1.13 (1.027–1.233)	0.012
Ala54Thr genotype	1.84 (0.885–3.810)	0.103	2.03 (0.681–6.043)	0.204
Thr54Thr genotype	2.70 (1.113–6.527)	0.028	3.84 (1.140–12.910)	0.030
Interaction age/gender	1.06 (0.907–1.244)	0.455	1.01 (0.827–1.244)	0.892

patients with type 2 diabetes, *Thr54* FABP2 polymorphism results in increased concentrations of fasting and postprandial triglyceride and dyslipidemia [8].

It is possible that *Thr/Thr* homozygous genotype confers some degree of susceptibility to obesity, associated with an influence of the genotype on parameters related to lipid metabolism [29–31]. As it is well known, elevated FFA increase the accumulation of triglycerides in the liver (related to compensatory hyperinsulinemia), this effect is associated with high levels of fasting insulin. This observation may indicate the existence of complex unmeasured gene-gene or gene-environment interactions that may enhance metabolic abnormalities [30,31].

It has been observed that disturbances in glucose metabolism, dyslipidemias, obesity and elevated blood pressure are all conditions linked to a higher risk in several candidate genes. The evidence for a causal association linking adaptive responses in complex diseases should be analysed in the context of gene-environmental and/or gene-gene interaction [27,32]. Two functional variations in FABP2 gene have been described. The *Ala54Thr* variant, that affects binding and transport and allelic variants in the promoter region leading to alterations of gene expression. Recent findings in Caucasian population, suggest that the FABP promoter haplotype may contribute to type 2 diabetes in a sex-specific manner [33]. It has been also proposed ethnic-specific effects on metabolic characteristics determined by variation in the FABP2 promoter region [29,30]. In Pima Indians, complete genotypic concordances were found between promoter variants and the *Ala54Thr* polymorphism [32]. On the other hand, in a sample of non-diabetic Hispanic and non-Hispanic white subjects, a promoter variant was associated with alterations in body composition and lipid metabolism in the later but not in the former [34]. However, it would be possible that such functional variants are not in genotypic concordance in other populations and may interact differently on the development of obesity-related phenotypes.

The cohort old age and accordingly low male representation is a characteristic that might pose some limitation to the present study. Although the possible exercise effects on diabetes incidence have not been controlled, this factor probably is not determinant taking in consideration that according the 2003 National Health Survey 95.7% of the Chilean population >64 year is sedentary [35].

In conclusion, our findings strongly suggest an association between the *Ala54Thr* polymorphism of FABP2 with diabetes, revealing a genetic dosage effect regarding its association with diabetes in Chilean elders.

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