Association between the FABP2 Ala54Thr, PPARα Leu162/Val, and PPARα intron7 polymorphisms and blood lipids ApoB and ApoCIII in hypertriglyceridemic subjects in Tehran

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BACKGROUND: The alanine to threonine substitution at codon 54 in the FABP2 gene and PPARα Val162 allele have been associated with hypertriglyceridemia.

OBJECTIVE: We sought to determine the prevalence of the Ala54Thr polymorphism of fatty acid binding protein (FABP) 2 gene and the Leu162/Val in exon 5 and G/C in intron7 polymorphism of peroxisome proliferator-activated receptor alpha (PPARα) gene in hypertriglyceridemic patients and their associations with blood lipid concentrations.

METHODS: A total of 170 hypertriglyceridemic subjects were enrolled and genotyped for Ala54Thr, Leu162Val, and intron 7 polymorphism by the use of a polymerase chain reaction-restriction fragment length polymorphism method. Fasting blood triglyceride, total cholesterol (TC), low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, apolipoprotein (Apo)B, and ApoCIII also were determined.

RESULTS: We found frequency of 81.2% for the Thr54 polymorphism among hypertriglyceridemic subjects. Positive associations were observed between this polymorphism and greater blood triglyceride, very low-density lipoprotein, and ApoCIII levels and lower blood high-density lipoprotein cholesterol concentration both in men and women. However, no association was found between the Thr54 polymorphism and TC, low-density lipoprotein cholesterol, ApoB, and body mass index. Frequency of the Leu162Val polymorphism was 21.8%. The Leu162Val polymorphism was not associated with lipid and lipoprotein concentrations in hypertriglyceridemic subjects (both in men and women). The frequency of intron7 polymorphism was 55.3% in subjects studied and, except for body mass index and TC, no association was found between the intron7 allele and blood lipids ApoB, and ApoCIII.

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Increasing experimental and clinical evidence suggests that triglyceride (TG)-rich lipoproteins play a significant role in the pathogenesis of atherosclerosis. In addition, the ratio of blood TG to high-density lipoprotein cholesterol (HDL-C) has been identified as a strong predictor of myocardial infarction compared with either total cholesterol (TC)/HDL-C or low-density lipoprotein cholesterol (LDL-C)/HDL-C. Very low-density lipoprotein (VLDL), the major carrier of plasma TG, is composed of the lipoproteins apolipoprotein (Apo)CII, CIII, and ApoE. ApoB100 in VLDL and ApoB48 in chylomicrons are essential components for synthesis and secretion. ApoCIII is one of the major determinants of the metabolism of VLDL in plasma, and increased plasma ApoCIII concentration is associated with the acceleration of atherosclerosis. 

It is now well recognized that the formation of TG-rich lipoproteins within enterocytes is a multistep process that includes the uptake of lipolytic products and their translocation to the endoplasmic reticulum by fatty acid binding proteins, followed by TG synthesis transfer to ApoB48 and posttranslational modification of various added apolipoproteins. This leads ultimately to the secretion of chylomicrons into the intestinal lymph. The fatty acid binding protein 2 (FABP2) gene encodes an intestinal fatty acid binding protein, which is a member of a family of small intracellular lipid-binding proteins. 

Although up-regulation of FABP2 has been proposed to influence the formation of TG-rich lipoproteins, some recent data suggest that the normal physiologic role of intestinal FABP in healthy subjects may actually be to reduce fatty acid uptake and chylomicron secretion. In studies of healthy subjects, a relationship between the presence of the Thr54 polymorphism in FABP2 protein and the frequency of intron7 polymorphism may be greater than Leu162Val in hypertriglyceridemic patients. 

**CONCLUSION:** Frequency of the Thr54 polymorphism is high in hypertriglyceridemic subjects, and the presence of this allele may increase some blood lipid and lipoprotein concentrations. In addition, the frequency of intron7 polymorphism may be greater than Leu162Val in hypertriglyceridemic patients.

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Methods

Subjects

One hundred seventy hypertriglyceridemic adults (112 men and 58 women) were enrolled in this study. The inclusion criteria was serum TG >200 mg/dl (>2.3 mmol/l), and blood fasting glucose concentration less than 110 mg/dl (<6.2 mmol/l). Those who received lipid-lowering agents, oral contraceptive pills, diuretics, sex hormones, thyroid medications, and omega-3 supplement; those patients with a history of gastrointestinal diseases; and smokers were excluded from the study.

A blood sample was taken after 14 hours of overnight fasting. Height and weight were measured by Seca scale (Seca, Hamburg, Germany) with patients wearing light clothing and no shoes. Body mass index (BMI) was calculated. The waist circumference was measured with a flexible tape midway between the lowest rib and the iliac crest and the hip circumference at the widest part of the gluteal region. The study was approved by the ethics committee of the Endocrinology and Metabolism Research Center (EMRC), Tehran University of Medical Sciences (TUMS). All participants were informed of the nature of the study and gave written consent. The biochemical analyses were performed at EMRC laboratory, TUMS. Genetic studies were conducted at the Department of Medical Genetics, TUMS, Tehran, Iran.

Laboratory analyses

Plasma and serum were isolated from the blood samples by centrifuging at 4 °C and 1800g for 15 min and transferred into sterile tubes in aliquots of 1 ml and stored at −80 °C until used. Serum TG and total cholesterol levels were measured by use of the photometric method with commercial kits (Pars-Azmoon, Tehran, Iran), LDL-C and HDL-C were measured by the use of an enzymatic method (Pars-Azmoon, Tehran, Iran) with a HITACHI 902 autoanalyzer (Roche, Mannheim, Germany). Serum VLDL (d < 1.006 g/l) was isolated by ultracentrifugation (Optima TL X fixed-angle, Beckman Instruments, Fullerton, CA), at 100,000 rpm and 16°C for 2 hours; the TG concentration of the isolated fraction was then determined. ApoB concentrations were measured by use of the immunoturbidimetric method (Pars-Azmoon, Tehran, Iran). ApoCIII concentrations were measured by an immunoturbidimetric method (Randox Laboratories, Antrim, UK).

Genotyping

Ala 54 Thr (gene ID = 2169)

Genomic DNA was extracted from whole blood by use of the Flexi Gene DNA kit (QIAGEN, GmbH, Hilden, Germany). A 180-bp DNA fragment containing the G → A nucleotide substitution in exon 2 (codon 54) of the FABP2 gene (A1a54Thr) was genotyped by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) as follows. The exon 2 of FABP 2 gene was amplified by PCR. The PCR amplification of the genomic DNA fragment for FABP2 was performed by the forward primer of, 5’-ACA GGT GTT GTA ATA GTG AAA (BIONEER, GmbH, Korea). The PCR was performed in a total volume of 20 μl containing 0.5 μM of each primer, 200 ng DNA, and 10 μl of Taq DNA polymerase 2X master mix (Ampliqon, Copenhagen, Denmark).

The amplification protocol consisted of an initial denaturation step at 95°C for 3 minutes, followed by 30 cycles of denaturation at 95°C for 40 seconds, annealing at 56°C for 40 seconds, and extension at 72°C for 50 seconds and a final extension at 72°C for 5 minutes. Digestion was performed with 1 μl of the PCR product incubated with 0.2 μl of HinfI (2000 U, Fermentase, Germany) and 2 μl of 10X restriction Tango buffer (in a total 20-μl reaction) overnight at 37°C and then inactivated at 0°C for 5 minutes. The digested product was then separated by electrophoresis on a 4% agarose gel (Boehringer-Mannheim, GmbH, Mannheim, Germany), stained with ethidium bromide (Sinagene, Tehran, Iran), and visualized on a Gel Doc. System (U.V.P. Company, Cambridge, UK). A 50-bp ladder (MBI, Fermentas, Germany) was used to determine the length of the digested products. The presence of Thr54 allele appeared as a 180-bp fragment after electrophoresis, whereas the Ala54 allele was cleaved by the restriction enzyme and appeared as 99- and 81-bp fragments.

Leu162Val (gene ID = 5465)

The Leu162 Val mutation of the PPARγ gene is caused by a C to G transversion at nucleotide 484 in exon 5. Mismatch PCR method was performed with the following primers: forward 5’- GAC TCA AGC TGG TGT ATG ACA AGT-3’ and reverse-mismatch 5’- CGT TGT GTG ACA CAA GGC-3’ (BIONEER) with the mismatch nucleotide in the reverse primer underlined. The PCR was performed in a mixture containing 0.5 μM of each primer, 200 ng of DNA, 10 μl of Taq DNA Polymerase 2X Master Mix (Ampliqon) in a total volume of 20 μl. The thermal cycler program was as follows: denaturation at 95°C for 2 min; followed by 30 cycles of denaturation at 95°C for 30 seconds, annealing at 61°C for 30 seconds, extension at 72°C for 20 seconds, and a final extension 72°C for 5 minutes. Amplification results in a 117-bp fragment including a HinfI restriction site for the mutated allele C to G at position 484 in exon 5 of the PPARγ gene.

The PCR product was digested with HinfI (2000 U, Fermentase, Germany), in which 7 μl of the PCR product was incubated with 2 μl of 10X restriction red buffer and 0.2 μl of HinfI in a total volume of 20 reaction at 37°C overnight and then inactivated at 0°C for 5 minutes. The mutated allele can be cleaved into a 24-bp and 93-bp fragment, whereas the normal allele will not digest. The digested product was resolved on 4% agarose gel at 80 V for 3 hours (Boehringer-Mannheim), stained with ethidium bromide (Sinagene), and visualized on a Gel Doc. System (U.V.P. Company).

Intron 7

The PCR-RFLP method was performed to determine intron7 mutation. The intron7 of the PPARγ gene was
amplified by PCR using forward primer 5'-ACA ATC ACT CCT TAA ATA TGG TGG-3' and the reverse primer 5'-AAG TAG GGA CAG ACA GGA CCA GTA-3' (BIONEER).24 The PCR was conducted in 20-μl reaction volume containing 0.5 μM of each primer, 200 ng of DNA, and 10 μl of Taq DNA Polymerase 2X Master Mix (Ampliqon). The thermal cycler condition was as follows: initial denaturation at 95°C for 2 min, followed by 30 cycles of denaturation at 95°C for 30 seconds, annealing at 56°C for 30 seconds, extension at 72°C for 30 seconds, and a final extension 72°C for 5 min. The PCR product (266 bp) was digested by TaqI (2000 U, Fermentase, Germany) to 216 bp and 50 -bp. Digestion was performed by adding 0.2 μl of TaqI and 2 μl of restriction red buffer to 7 μl of PCR product in total volume of 20 μl, which incubated at 65°C for 1 hour and then inactivated at 0°C for 5 minutes. For length determination, separation was done on 4% agarose gel at 80 V for 3 hours (Boehringer-Mannheim), stained with ethidium bromide (Sinagene), and visualized on a Gel Doc. System (U.V.P. Company).

Statistical analyses

The normality of distribution of continuous variables was tested by the use of the one-sample Kolmogorov-Smirnov test. To normalize the continuous variables not normally distributed, a log transformation was applied. A potential relationship between blood lipid levels and plasma lipids and lipoproteins was studied, and 21.8% of subjects were Leu162 carriers. No significant differences were observed in plasma lipid and lipoprotein concentrations in Leu162 and Val162 carriers. Association between greater BMI and Val allele was found only in men (Table 3). Intron7 polymorphism was found to be 55.3% in these subjects. No significant association was found between intron7 and plasma lipid and lipoprotein concentrations except for total cholesterol (Table 3). The intron7 polymorphism also was associated with greater BMI in men (data are not shown).

Frequency of Leu162 was found to be 78.2% in subjects studied, and 21.8% of subjects were Leu162/Val carriers. No significant differences were observed in plasma lipid and lipoprotein concentrations in Leu162 and Val162 carriers. Association between greater BMI and Val allele was found only in men (Table 3). The frequency of FABP2 Thr54 carriers, PPARα Leu162Val carriers in exon 5, and intron 7 was 79.5% and 84.4% (for FABP2), 21.4% and 22.4% (for PPARα), and 59.8% and 46.6% (for intron7 C) in men and women, respectively. (The PCR-RFLP results of subjects are shown in Figures 1 and 2.)

Carriers of wild-type Ala54 comprised only 18.8% of total hypertriglyceridemic subjects in our study, and 81.2% of subjects were carriers of Thr54 allele. Because the sample size for Thr54 homozygous subjects was small, data from those subjects were pooled with data from heterozygous subjects for comparisons of FABP2 genotype groups (Table 2). In Thr54 carriers, plasma concentrations of TG, VLDL, and APOCIII levels were greater and HDL-C concentration was lower than Ala54 carriers (Table 2). Stratification on the basis of sex showed that, in Thr54 carriers, LDL-C concentration was greater in men (data are not shown).

Table 1 Characteristics of hypertriglyceridemic subjects at the baseline

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Men</th>
<th>Women</th>
<th>Independent t test, P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 170 (%)</td>
<td>112 (68.9)</td>
<td>58 (34.1)</td>
<td>–</td>
</tr>
<tr>
<td>Thr54 carriers (%)</td>
<td>89 (79.5)</td>
<td>49 (84.4)</td>
<td>NS</td>
</tr>
<tr>
<td>V162 carriers (%)</td>
<td>24 (21.4)</td>
<td>13 (22.4)</td>
<td>NS</td>
</tr>
<tr>
<td>C 7 carriers (%)</td>
<td>67 (59.8)</td>
<td>27 (46.6)</td>
<td>NS</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>45.18 ± 10.19</td>
<td>46.43 ± 11.74†</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.77 ± 3.05</td>
<td>29.04 ± 4.80†</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>TG (mg/dl)</td>
<td>426.42 ± 162.61</td>
<td>338.4 ± 123.8†</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>TC (mg/dl)</td>
<td>214.44 ± 39.04</td>
<td>220.87 ± 47.08</td>
<td>NS</td>
</tr>
<tr>
<td>LDL-C (mg/dl)</td>
<td>109.72 ± 25.22</td>
<td>116.62 ± 32.87</td>
<td>NS</td>
</tr>
<tr>
<td>HDL-C (mg/dl)</td>
<td>32.74 ± 9.34</td>
<td>38.34 ± 14.31†</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>VLDL (mg/dl)</td>
<td>85.28 ± 32.52</td>
<td>67.68 ± 24.76†</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>FBS (mg/dl)</td>
<td>98.43 ± 15.36</td>
<td>99.62 ± 19.33</td>
<td>0.66</td>
</tr>
<tr>
<td>APOB (mg/dl)</td>
<td>117.76 ± 28.05</td>
<td>123.40 ± 28.45</td>
<td>2.17</td>
</tr>
<tr>
<td>APOCIII (mg/dl)</td>
<td>17.49 ± 4.99</td>
<td>15.46 ± 3.10†</td>
<td>&lt;.01</td>
</tr>
</tbody>
</table>

Values are shown as means ± SD unless otherwise noted. Analyses were performed by SPSS® for Windows®. Values with P < .05 were considered as statistically significant.

*Carriers are expressed as the frequency (percentage), and an independent t test was performed between blood parameters and men and women. †Significant difference between the men and women groups.

Discussion

The Ala54/Thr polymorphism of the FABP2 gene is a prevalent polymorphism in several populations,7 ie, up to
30% to 40% reported in Caucasian, Japanese, and Native American populations. The results of this study imply that Thr54 genotype is even more prevalent in hypertriglyceridemic subjects living in Iran. These subjects had a frequency of 81.2%, which is much greater than those reported in previous studies. This discrepancy might be the result of subject selection criteria because in our study all the subjects were hypertriglyceridemic whereas previous studies determined the frequency without considering triglyceride concentrations as inclusion criteria.

Alternatively, the prevalence of this polymorphism might be high in Iranian people. We designed our study in a specific group with abnormal lipids and did not have access to a representative sample of the general population for measurement of this polymorphism. If the presence of the Thr54 allele has a causative relationship to the hypertriglyceridemia, the mechanism is not clear. It has been reported that this fatty acid binding protein is very abundant in enterocytes, and the allele appears to produce FAB2 with increased affinity for long-chain fatty acids. One might postulate an increased absorption of fatty acids and, consequently, increased levels of free fatty acid, are reaching the plasma as TGs.

Baier et al hypothesized that the Ala54/Thr polymorphism results in increased fatty acid uptake from the intestinal lumen and that Thr 54 carrying enterocytes secreted a 5- to 6-fold greater amount of TG compared with Ala54 cells. However, this would not explain the increased VLDL unless the additional calories might stimulate VLDL production in liver. The results of a previous study showed that subjects with the Ala54/Thr and Thr54/Thr variant had 1.56 and 2.011 times greater risk for developing hypertriglyceridemia, respectively, and increased TG-rich lipoprotein levels in vivo. Another in vitro study showed a 2- to 3-fold increase in intestinal TG secretion by Caco-2 cells transfected with the codon 54Thr allele.

However, it seems unlikely that increased absorption of fatty acids and, consequently, increased incorporation of absorbed free fatty acids into chylomicrons, would contribute to increased plasma TGs because there is no evidence that the Ala54 wild type is associated with fat malabsorption. Increased absorption of fat could result in abnormally high postprandial plasma fatty acid concentrations as they are released from chylomicrons by lipoprotein lipase. Another possibility is that the altered FABP plays a role in synthesis of fatty acids from various substrates and their conversion into TGs so that VLDL production rates are increased as well.

One study reporting differences in fasting plasma TGs between the Thr 54 carrier vs the wild type was performed
In Canadian aboriginals. It is of interest that the level of plasma TG in homozygotes was approximately twice that present in the wild type. The results of our study suggests that serum TG, VLDL, and APOCIII concentrations in Thr54 (Thr54 heterozygous, homozygous or combined) are greater and HDL-C levels are lower than in Ala54 both in men and women. Thr54 also was associated with fasting and postprandial TG levels in a mostly Caucasian population of type 2 diabetics.

In addition to effects on serum TG, this polymorphism has been shown to play an important role on TC and LDL-C among Caucasian women. In contrast, findings of a large population study in Tangan showed association between FABP2 Thr54 with lower TC and LDL-C in men and women. However, we did not find any significant association between TC, LDL-C, ApoB concentrations, and Ala54/Thr and Thr54/Thr polymorphism in this hypertriglyceridemic Iranian population.

The results of these studies may be discrepant for several reasons. First, the effect of the FABP2 genotype on blood lipids may be more evident in Thr54 homozygous subjects. Because we had too few Thr54-homozygous carriers we did not compare them with Ala54 carriers. Some previous studies have shown that the FABP2 Thr54/Thr genotype is more strongly related to postprandial lipemia compared with the Ala54/Thr group. Furthermore, in addition to genotype, other confounding factors such as physical activity and diet could affect levels of blood lipids. Data on these issues were not collected in or included in analyses in our study or previous ones. In the present study, the BMI did not differ in Ala54 or Thr54 carriers, a finding that is consistent with the results of the Framingham Offspring study. Sex-dependent differences in the association of the FABP2 polymorphism and fat metabolism have been recently reported, suggesting that this polymorphism may have a sex-dependent role in body fat distribution, possibly mediated through differences in the hormonal milieu of men and women.

PPARα has been considered as a candidate gene involved in metabolic diseases such as obesity, type 2 diabetes, or dyslipidemia. Because it is expressed mainly in tissues with high capacity for fatty acid β-oxidation and target genes of

Table 2: BMI, blood lipid, and lipoprotein levels of hypertriglyceridemic subjects according to the FABP2 genotype

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Parameter</th>
<th>n (%)</th>
<th>BMI (kg/m²)</th>
<th>TG (mg/dl)</th>
<th>TC (mg/dl)</th>
<th>LDL-C (mg/dl)</th>
<th>HDL-C (mg/dl)</th>
<th>VLDL (mg/dl)</th>
<th>APOB (mg/dl)</th>
<th>APOCIII (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ala/Ala</td>
<td></td>
<td>32 (18.8)</td>
<td>27.802 ± 2.75</td>
<td>333.01 ± 122.73</td>
<td>213.54 ± 31.32</td>
<td>119.19 ± 22.74</td>
<td>37.66 ± 8.84</td>
<td>66.60 ± 24.55</td>
<td>119.31 ± 19.75</td>
<td>14.18 ± 3.85</td>
</tr>
<tr>
<td>Ala/Thr</td>
<td></td>
<td>125 (73.5)</td>
<td>28.24 ± 3.87</td>
<td>404.95 ± 164.00</td>
<td>214.32 ± 43.87</td>
<td>109.38 ± 29.25</td>
<td>34.01 ± 12.48</td>
<td>80.99 ± 32.80</td>
<td>118.50 ± 29.93</td>
<td>17.31 ± 4.57</td>
</tr>
<tr>
<td>Thr/Thr</td>
<td></td>
<td>12 (7.6)</td>
<td>28.87 ± 5.03</td>
<td>470.02 ± 88.54</td>
<td>246.54 ± 35.95</td>
<td>120.47 ± 26.47</td>
<td>33.46 ± 6.16</td>
<td>94.00 ± 17.71</td>
<td>131.99 ± 27.96</td>
<td>18.27 ± 3.48</td>
</tr>
</tbody>
</table>

Values are shown as mean ± SD. Because the Thr54/Thr group was small, data of Ala54/Thr group were combined with data of Thr54/Thr, and an independent t-test was performed between the combined groups data and data of group Ala/Ala.

*Number and percentage of subjects in each group, NS not significant.
†Significant difference between Ala/Ala and Ala/Thr.
‡Significant difference between two groups.

Table 3: BMI, blood lipid, and lipoprotein levels of hypertriglyceridemic subjects according to Val162 and GG and GC genotypes

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Parameter</th>
<th>n (%)</th>
<th>BMI (kg/m²)</th>
<th>TG (mg/dl)</th>
<th>TC (mg/dl)</th>
<th>LDL-C (mg/dl)</th>
<th>HDL-C (mg/dl)</th>
<th>VLDL (mg/dl)</th>
<th>APOB (mg/dl)</th>
<th>APOCIII (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leu162/Lue</td>
<td></td>
<td>133 (78.2)</td>
<td>28.11 ± 3.81</td>
<td>397.37 ± 158.89</td>
<td>217.39 ± 44.02</td>
<td>112.55 ± 30.09</td>
<td>37.71 ± 12.52</td>
<td>79.47 ± 31.78</td>
<td>120.54 ± 29.99</td>
<td>16.87 ± 4.60</td>
</tr>
<tr>
<td>Leu162/Val</td>
<td></td>
<td>37 (21.8)</td>
<td>28.55 ± 3.69</td>
<td>392.86 ± 146.37</td>
<td>213.91 ± 33.75</td>
<td>110.38 ± 19.95</td>
<td>34.43 ± 7.42</td>
<td>78.52 ± 29.27</td>
<td>116.59 ± 20.78</td>
<td>16.55 ± 4.32</td>
</tr>
<tr>
<td>GG</td>
<td></td>
<td>76 (44.7)</td>
<td>27.28 ± 2.44 †</td>
<td>375.99 ± 142.18</td>
<td>206.09 ± 36.04 †</td>
<td>107.10 ± 27.09</td>
<td>32.22 ± 10.31</td>
<td>75.20 ± 28.44</td>
<td>115.87 ± 25.95</td>
<td>16.20 ± 4.48</td>
</tr>
<tr>
<td>GC</td>
<td></td>
<td>94 (55.3)</td>
<td>28.94 ± 4.57 &lt;.01</td>
<td>412.88 ± 164.97</td>
<td>225.17 ± 44.54 &lt;.002</td>
<td>116.1 ± 28.50</td>
<td>35.81 ± 12.4</td>
<td>82.57 ± 32.99</td>
<td>122.77 ± 29.72</td>
<td>17.28 ± 4.54</td>
</tr>
</tbody>
</table>

Values are shown as mean ± SD. Because the Thr54/Thr group was small, data of Ala54/Thr group were combined with data of Thr54/Thr, and an independent t-test was performed between the combined groups data and data of group Ala/Ala.

*Number and percentage of subjects in each group, NS not significant.
†Significant difference between Ala/Ala and Ala/Thr + Thr/Thr.
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PABPz participate in many aspects of lipid metabolism. Among reported polymorphisms for the PABPz gene, Leu162Val polymorphism is the most prevalent with frequency of 10.45% in diabetic and non-diabetic patients. 13 It is also associated with alterations in lipoprotein concentrations in both diabetic and non-diabetic subjects. 19,36

We found a prevalence of 21.8% for the Leu162/Val polymorphism in these Iranian hypertriglyceridemic. There was no difference in the frequency of Leu162/Val between men and women. This polymorphism has been previously found to be associated with greater blood TC, 15 LDL-C, 17,19,23 TG levels, 36,37 and lower HDL-C concentration 17 depending on the population studied. Most studies that have found an association between the Leu162Val polymorphism and greater blood lipid concentrations were conducted in diabetic subjects; few studies have found a positive association in healthy subjects. 11

In a normolipidemic population, Leu162Val polymorphism was associated with increased plasma concentrations of TC, LDL-C, ApoB, and ApoCIII. 19 It has also been reported that this polymorphism is associated with decreased concentrations of fasting serum TG among healthy Caucasian subjects. 18 In our study, Leu162Val polymorphism was not associated with any of the blood lipid levels, or with ApoB and ApoCIII, which is in contrast to the study of Jamshidi, 24 who reported an association between this polymorphism and increased fasting serum triglyceride and TC levels in non-diabetic hypertriglyceridemic subjects. A possible explanation for this discrepancy might be small sample size of the polymorphic subjects in our study.

The Leu162Val polymorphism also has been associated with some measures of adiposity. 38 In the present study, a significant positive association was found between the presence of the Leu162Val and BMI in men but not in women (data are not shown). Our results are in agreement with those of Uthrralt’s et al, 39 who suggested that PABPz Leu162Val alleles have strong statistical significance with greater BMI in young Caucasian men. 39 In contrast, the two previous reports have found association of the Leu162Val allele with lower BMI, in overweight and diabetic women. 38 Vohl et al 23 found no significant association between Leu162Val polymorphism and greater BMI, either in patients with type 2 diabetic or in non-diabetic subjects. Discrepancies among these studies may originate from differences in the population studied with most studies focusing on older or unhealthy populations and also may be due to differences in methods of measuring both regional and total adiposity. 39

The intron7 allele has been shown to be associated with increased progression of atherosclerosis. The Val162 allele and intron7 allele are in strong allelic association, such that 78% of Val162 carriers are found in combination with the intron7. 40 In our study the frequency of the intron7 polymorphism was 55.3%, which are much greater than frequency of Leu162Val polymorphism in studied subjects, and all of the subjects who were Leu162/Val carriers had also intron7 allele. Except for blood TC level, there were no significant associations between intron7 allele and blood lipid, ApoB, or ApoCIII concentrations. Similar results have been observed in Foucher’s study in which intron7 polymorphism was only associated with blood TC levels. 41

In conclusion, the frequency of the Thr54 polymorphism is high in hypertriglyceridemic subjects, and presence of this allele may increase some of the blood lipid and lipoprotein concentrations. Frequency of intron7 polymorphism is greater than Leu162Val and all hypertriglyceridemic subjects with Leu162 polymorphism might be carriers of the intron7 polymorphism.

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Authors’ contributions

HP carried out the design and performed all experiments and prepared the manuscript. SAM provided assistance in the design and coordination of the study. PM coordinated the PCR experiment. MRE helped with the statistical analysis. JMA helped with DNA extraction and PCR-RFLP experiments. SH helped with the revising of the manuscript. MR helped with patient selection and data collection.

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