International Journal of Preventive Medicine

Original Article Open Access

Association Study Between Metabolic Syndrome and rs8066560 Polymorphism in the Promoter Region of Sterol Regulatory Element-binding Transcription Factor 1 Gene in Iranian Children and Adolescents

Hajar Miranzadeh-Mahabadi[1,2], Modjtaba Emadi-Baygi[1,3], Parvaneh Nikpour[2,4,5], Roya Kelishadi[2]

[1]Department of Genetics, School of Basic Sciences, Shahrekord University, Shahrekord, Iran, [2]Child Growth and Development Research Center, Research Institute for Primordial Prevention of Non-communicable Disease, Isfahan University of Medical Sciences, Isfahan, Iran, [3]Research Institute of Biotechnology, Shahrekord University, Shahrekord, Iran, [4]Applied Physiology Research Center, Isfahan University of Medical Sciences, Isfahan, Iran, [5]Department of Genetics and Molecular Biology, Faculty of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran

Correspondence to:
Dr. Parvaneh Nikpour, Department of Genetics and Molecular Biology, Faculty of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran.
E-mail: pnikpour@med.mui.ac.ir

How to cite this article: Miranzadeh-Mahabadi H, Emadi-Baygi M, Nikpour P, Kelishadi R. Association study between metabolic syndrome and rs8066560 polymorphism in the promoter region of sterol regulatory element-binding transcription factor 1 gene in Iranian children and adolescents. Int J Prev Med 2016;7:41.

ABSTRACT

Background: Metabolic syndrome (MetS) is a prevalent disorder in pediatric age groups, described by a combination of genetic and environmental factors. Sterol regulatory element-binding transcription factor 1 (*SREBF-1*) induces the expression of a family of genes involved in fatty acid synthesis. Moreover, dysregulation of *miR-33b*, which is located within the intron 17 of the *SREBF-1* gene, disrupts fatty acid oxidation and insulin signaling, thus leading to MetS. The aim of the present study was to investigate the association between *SREBF-1* rs8066560 polymorphism and MetS in Iranian children and adolescents.

Methods: This study includes 100 MetS and 100 normal individuals aged 9–19 years. Anthropological and biochemical indexes were measured. The -1099G > A polymorphism was genotyped by TaqMan real-time polymerase chain reaction.

Results: Significant differences were observed in anthropometric measurements and lipid profiles between MetS and normal children. There were no differences in the genotype frequencies or allele distribution for -1099G > A polymorphism between MetS and control groups. High-density lipoprotein cholesterol levels were significantly higher in the MetS GG group than in the A allele carrier group. The genotype AA controls had significantly increased cholesterol and low-density lipoprotein cholesterol levels than AG genotypes. By logistic regression using different genetic models, no significant association was observed between *SREBF-1* rs8066560 polymorphism and the risk of MetS.

Conclusions: We conclude that the -1099G > A variant on *SREBF-1* gene associated with serum lipid profiles, however, it may not be a major risk factor for the MetS in Iranian children and adolescents.

Keywords: Children and adolescents, metabolic syndrome, miR-33b, polymorphism, sterol regulatory element-binding transcription factor 1

Access this article online	
Quick Response Code:	**Website:** www.ijpvmjournal.net/www.ijpm.ir
	DOI: 10.4103/2008-7802.177314

INTRODUCTION

Metabolic syndrome (MetS) is a complex disorder resulting from the interaction of both genetic and environmental factors.[1,2] The prevalence of the syndrome is 1–2% in Iranian children and adolescents much higher than that reported for other ethnicities.[3-5] Individuals affected with MetS are most likely to develop heart attack and type 2 diabetes mellitus (T2DM), the two main causes of death worldwide.[6] Although the core components of the syndrome include central obesity, dyslipidemia, insulin resistance, and hypertension, there is no unique definition for the MetS.[6] In Iranian children and adolescents, MetS is being diagnosed by low levels of high-density lipoprotein cholesterol (HDL-C) and high triglyceride (TG).[3]

Lipotoxicity may result in T2DM, obesity, and insulin resistance.[7,8] Sterol regulatory element-binding factors (*SREBFs*) are transcription factors playing central roles in the regulation of the carbohydrate and lipid metabolism.[9,10] This family consists of three isoforms, designated *SREBF-1a*, *SREBF-1c*, and *SREBF-2*. *SREBF-1a* and *-1c* are encoded by *SREBF-1* gene and *SREBF-2* isoform is encoded by the *SREBF-2* gene, which are located on human chromosomes 17p11.2 and 22q13, respectively.[11]

SREBF-1a and *SREBF-2* are expressed in all tissues and most cultured cell lines, whereas *SREBF-1c* is the main isoform produced in the liver and adipocytes.[12,13] *SREBF-1a* and *-1c* isoforms both regulate the genes involved in cholesterol, TG, and fatty acid synthesis.[13] *SREBF-2* isoform has a functional overlap with *SREBF-1* proteins in a way that it mediates the activation of genes involved in the uptake and biosynthesis of cholesterol. As the *SREBF-1c* expression is under the control of insulin, it can be, therefore, considered a main coordinator of insulin-related regulation of lipid and carbohydrate biosynthesis.[13-16]

Furthermore, *SREBF-1* and *-2* are host genes for miR-33b and miR-33a, respectively.[17] These two microRNAs contribute to the regulation of cholesterol metabolism, β-oxidation of fatty acids, and insulin signaling as well.[18]

Several studies have so far investigated the relationship between *SREBF-1* gene polymorphisms, glucose and lipid dysregulation in humans.[19-35] In 2006, Harding *et al*.[22] genotyped six *SREBF-1* single nucleotide polymorphisms (SNPs) to test their association with type 2 diabetes. They reported a significant association between three SNPs (rs2236513, rs6502618, and rs1889018) and diabetes risk. As these three polymorphisms are located in the 5′ region of *SREBF-1* gene, 7.8–20.4 kb before the start of exon 1c, they concluded that these SNPs are probably too distant to be considered as promoter SNPs. Furthermore, another SNP (rs8066560) introduced by HapMap project, which is more probably located in the promoter region of the *SREBF-1* gene (-1099G > A), was in high linkage disequilibrium with the above mentioned polymorphisms in the 5′ region. Due to the role of the *SREBF-1* gene in the biosynthesis of TG and cholesterol and linkage of -1099G > A variant with other studied 5′ region SNPs which have been shown a positive association with diabetes risk, we aimed to assess the association of rs8066560 and the risk of MetS and its components in Iranian children and adolescents.

METHODS

Study population

The experimental design conformed to the Code of Ethics of the World Medical Association (Declaration of Helsinki) and was approved by the Ethics Committee of Isfahan University of Medical Sciences. Oral assent was obtained from participants and written informed consent from their parents. This case–control study consisted of 100 healthy and 100 MetS subjects with an age range of 9–19 years. MetS was defined according to the modified adult treatment panel III criteria.[3] Accordingly, an individual was considered as a MetS case if she/he had at least three of the following criteria: (a) Fasting TG ≥100 mg/dl; (b) HDL-C <50 mg/dl; (c) waist circumference >75th percentile for age and gender in the studied population; (d) systolic blood pressure/diastolic blood pressure >90th percentile for gender, age, and height,[36] and (e) fasting blood sugar ≥100 mg/dl. Control individuals were examined to have normal weight without any signs of MetS, cardiovascular disorders, and diabetes. Peripheral blood samples were collected in ethylenediaminete-traacetic acid-treated tubes and stored at −20°C for genetic analyses.

Laboratory analyses

After at least 10 h overnight fasting, 5 mL of venous blood were obtained for laboratory analyses from all the children. Plasma was then separated by immediate centrifugation. Lipid profiles and fasting glucose concentration were measured enzymatically using a Hitachi 7070 analyzer (Diamond Diagnostics, USA) with reagents from Pars Azmoon (Pars Azmoon, Iran). Fasting insulin concentration was measured by a chemiluminescent assay (DiaSorin, Italy) on the LIAISON® analyzer (DiaSorin, Italy).

Detection of the polymorphism

Genomic DNA was extracted from peripheral blood mononuclear cells using diatome kit according to the manufacturer's instruction (Isogen Laboratory, Russia).

Quantity and quality of the genomic DNA were assessed by a spectrophotometer (Biochrom Ltd, UK) and agarose gel electrophoresis, respectively. Allelic discrimination for rs8066560 was performed using TaqMan® SNP genotyping assay on the Applied Biosystems StepOnePlus™ real-time polymerase chain reaction (PCR) system. TaqMan Genotyping Master Mix (number 4351379) and TaqMan SNP genotyping assay (number 4027774) were obtained from Applied Biosystems (Grand Island, USA). Each reaction was 10 μL consisting of 4.5 μL of 20 ng DNA, 5 μL of 2X TaqMan Genotyping Master Mix, and 0.5 μL of 20X TaqMan SNP genotyping assay (diluted by 1X TE buffer, pH = 8). PCR cycling conditions were as follows: 60°C for 30 s; 95°C for 10 min; followed by 40 cycles of 95°C for 15 s, 60°C for 1 min. The fluorescence intensity in the VIC and FAM channels was measured at the end of each cycle. Results were analyzed by StepOnePlus software (Applied Biosystems, Grand Island, USA). Hardy–Weinberg equilibrium (HWE) was evaluated by Chi-square test.

Statistical methods

All statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) version 16.0 (SPSS Inc., Chicago, IL, USA) and reported as means ± standard error of the mean. Comparison of continuous variables was examined by Student's *t*-test or ANOVA. Following ANOVA, *post-hoc* analysis was performed with Least Significant Difference test. Statistical analysis of categorical variables was performed using the Chi-squared test. Simple and multivariable adjusted odds ratios (ORs) and 95% confidence intervals (CI) were computed using the logistic regression. In the multivariable model, the adjustment was performed for age (continuous) and gender. $P < 0.05$ was considered statistically significant.

RESULTS

Different genotypes for rs8066560 was determined using TaqMan® SNP genotyping assay on the Applied Biosystems StepOnePlus™ real-time PCR system. Different genotypes including AA, GG, and AG were easily detectable in the allele discrimination plot [Figure 1].

The anthropometric and biochemical characteristics of the MetS and control groups are listed in Table 1. No statistically significant differences were found in the mean age ($P = 0.096$) and sex ($P = 0.335$) between the groups. Body mass index (BMI), serum levels of TG, total cholesterol (TC), and low-density lipoprotein cholesterol (LDL-C) were significantly higher in MetS cases than controls. The HDL-C serum levels were lower in MetS cases ($P < 0.001$).

The genotype and allele frequencies distribution of *SREBF-1* rs8066560 are indicated in Table 2. No significant differences were found between the MetS and control groups in genotype or allele frequencies. The genotype frequencies in both MetS and control groups were in HWE.

Stratification of the laboratory parameters of the control and MetS subjects according to different genotypes of the rs8066560 (A/G) are given in Tables 3 and 4. There was no statistically significant difference in mean age, BMI, TG, TC, and LDL-C between the three genotypes; however, the HDL-C levels of the GG group were significantly higher than the AA ($P = 0.017$) and AG ($P = 0.023$) carriers in MetS groups.

In the control group, there was no significant difference in BMI, TG, HDL-C, and LDL-C between different genotypes [Table 4]. However, *post-hoc* analysis showed that subjects with the AA genotype had higher cholesterol ($P = 0.016$) and LDL-C levels ($P = 0.034$) than AG genotypes.

The ORs were calculated for allelic (G vs. A), additive 1 (AG vs. AA), additive 2 (GG vs. AA), dominant (GG + AG vs. AA), and recessive (GG vs. AA + AG) models [Table 5]. Overall, no association was observed between *SREBF-1* rs8066560 polymorphism and the risk of MetS in any of genetic models before and after adjustment.

DISCUSSION

As a master regulator of genes encoding for central rate-limiting enzymes of cholesterol and lipid metabolism, *SREBF-1* appears to be a biological principle with clinical implications.[37] Among the SNPs in the promoter region of this gene, there is no study assessing the association of rs8066560 (-1099G > A) with MetS. The current study is the first investigating the correlation of a *SREBF-1* variant with MetS. In the control group, *SREBF-1* -1099G > A polymorphism had the same frequencies as what reported

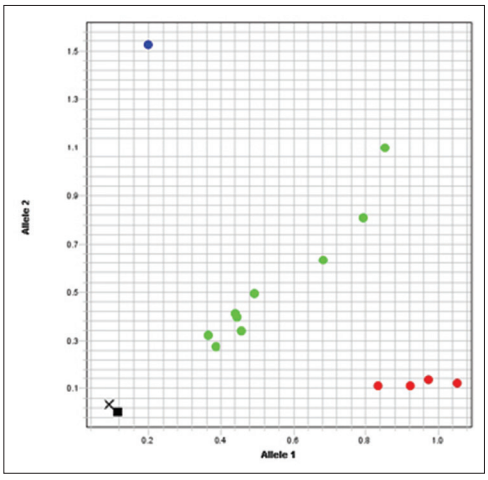

Figure 1: Allelic discrimination plot of rs8066560 (-1099G>A). Red dots show the homozygous AA, green dots show heterozygous GA, and the blue dot shows a person with homozygous GG genotype

Table 1: Anthropometric and biochemical data in case and control groups

	Case group (n=100)		Control group (n=100)		t	P
	Mean	SEM	Mean	SEM		
Age (years)	12.86	0.22	13.31	0.26	1.30	0.096
Boys/girls	46/54		49/51		0.18 (χ^2)	0.335
BMI (kg/m^2)	26.63	0.39	19.91	0.55	10.21	<0.001
TG (mg/dl)	112.42	4.914	78.93	3.02	5.80	<0.001
TC (mg/dl)	162.79	3.24	148.60	6.16	2.03	0.021
HDL-C (mg/dl)	43.62	0.54	49.54	1.20	4.48	<0.001
LDL-C (mg/dl)	90.52	2.11	82.59	4.10	1.71	0.043

Values are expressed as mean±SEM. BMI=Body mass index, TG=Triglyceride, TC=Total cholesterol, HDL-C=High-density lipoprotein cholesterol, LDL-C=Low-density lipoprotein cholesterol, SEM=Standard error of the mean

Table 2: Genotype and allele frequencies for rs8066560 in MetS and control groups

Group	Genotype frequency						Allele frequency				
	Total (n)	A/A (n)	A/G (n)	G/G (n)	χ^2	P	Total (n)	A n (%)	G n (%)	χ^2	P
Case	100	21	43	36	1.79	0.20	200	85 (42)	115 (58)	1.97	0.8
Control	100	27	45	28			200	99 (49)	101 (51)		

MetS=Metabolic syndrome

Table 3: The *SREBF-1* rs8066560 genotypes and their correlation with anthropometric and biochemical parameters in the MetS group

	AA (n=21)		AG (n=43)		GG (n=36)		t	P
	Mean	SEM	Mean	SEM	Mean	SEM		
Age (years)	12.24	0.37	12.95	0.36	13.11	0.37	1.04	0.168
BMI (kg/m^2)	26.06	0.79	26.86	0.60	26.72	0.67	0.56	0.347
TG (mg/dl)	108.71	8.87	120.93	8.74	104.42	7.02	1.08	0.155
TC (mg/dl)	165.38	9.84	162.44	4.16	161.69	5.05	5.05	0.458
HDL-C (mg/dl)	42.19	1.37	42.91	0.767	45.31	0.81	1.73	0.027
LDL-C (mg/dl)	90.10	5.64	91.93	3.06	89.08	3.30	0.42	0.418

BMI=Body mass index, TG=Triglyceride, TC=Total cholesterol, HDL-C=High-density lipoprotein cholesterol, LDL-C=Low-density lipoprotein cholesterol, SEM=Standard error of the mean, MetS=Metabolic syndrome, *SREBF-1*=Sterol regulatory element-binding transcription factor 1

Table 4: The *SREBF-1* rs8066560 genotypes and their correlation with anthropometric and biochemical parameters in the control group

	AA (n=27)		AG (n=45)		GG (n=28)		t	P
	Mean	SEM	Mean	SEM	Mean	SEM		
Age (years)	13.44	0.51	13.24	0.39	13.29	0.52	0.22	0.47
BMI (kg/m^2)	20.12	1.10	20.86	0.93	18.88	0.85	1.11	0.10
TG (mg/dl)	80.93	5.49	81.84	5.22	72.37	4.22	0.967	0.198
TC (mg/dl)	170.67	19.96	138.51	5.43	143.54	5.09	1.58	0.043
HDL-C (mg/dl)	52.37	3.08	48.73	1.40	48.11	2.13	1.02	0.177
LDL-C (mg/dl)	93.89	14.04	75.64	2.62	82.86	3.46	1.3	0.095

BMI=Body mass index, TG=Triglyceride, TC=Total cholesterol, HDL-C=High-density lipoprotein cholesterol, LDL-C=Low-density lipoprotein cholesterol, SEM=Standard error of the mean, *SREBF-1*=Sterol regulatory element-binding transcription factor 1

Table 5: Logistic regression analyzes of association between *SREBF-1* rs8066560 and risk of MetS

Allele/genotype	Crude OR (95% CI)	P	Adjusted[a] OR (95% CI)	P
G versus A	1.326 (0.894-1.967)	0.161	1.338 (0.900-1.991)	0.150
AG versus AA	1.229 (0.606-2.492)	0.568	1.242 (0.607-2.543)	0.552
GG versus AA	1.653 (0.777-3.315)	0.192	1.680 (0.779-3.619)	0.186
GG + AG versus AA	1.391 (0.724-2.673)	0.322	1.403 (0.726-2.711)	0.314
GG versus AA + AG	1.446 (0.796-2.630)	0.226	1.468 (0.805-2.680)	0.211

[a]Adjusted for age and sex. OR=Odds ratio, CI=Confidence interval, MetS=Metabolic syndrome, *SREBF-1*=Sterol regulatory element-binding transcription factor 1

by 1000 genomes project.[38] Furthermore, there was no significant difference between the MetS and control groups in genotype and allele frequencies. We found that in MetS group, the HDL-C levels were significantly higher in GG individuals. Moreover, control subjects with the AA genotype had higher TC and LDL-C levels. This finding is in agreement with findings of Lu *et al*.[35] which showed rs8066560 is significantly associated with TC levels. Previous studies have shown a reverse correlation between miR-33a and miR-33b expressions and HDL-C levels and a direct association with TC.[18,39,40] Thus, we may hypothesize that having two copies of G allele in the -1099 location, may have a negative regulatory effect on miR-33b transcription and consequently increasing the HDL-C and decreasing TC and LDL-C levels. Further studies to analyze the promoter of the human sterol regulatory element-binding protein 1 to test this hypothesis is demanding. So far, numerous studies have investigated the associations between other *SREBF-1* genetic polymorphisms and lipid profiles. A significant correlation of -36del-G variant of the *SREBF-1* gene with TC and LDL-C has been indicated in a study by Vedie *et al*.[34] but other studies did not observe such a correlation.[25,33] Previous studies analyzing 54 G/C polymorphism (rs2297508) in *SREBF-1* gene reported a significant association with LDL-C[21,30,32] but not with TC, HDL-C, and TG levels.[21,24,29,30] Although Eberle *et al*. reported a correlation of this SNP with TG only in male subjects.[24] Rs11868035 variant in the *SREBF-1* gene has also shown a correlation with LDL-C and TC.[28-30,32] By logistic regression using different genetic models, we found no evidence for a statistically significant association between the *SREBF-1* rs8066560 polymorphism and the risk of MetS. Currently, data on the association of polymorphisms in the promoter/coding regions of the *SREBF-1* gene and MetS, as an entity, are lacking.

CONCLUSIONS

Our study is the first exploring the association between a *SREBF-1* variant and MetS. Our results showed that the rs8066560 of the *SREBF-1* gene may not be a major risk factor for the MetS in Iranian children and adolescents.

However, our preliminary results obtained from a small population sample should be interpreted with caution and will require confirmation in larger populations.

ACKNOWLEDGEMENTS

This study was partly supported by a research fund from Isfahan University of Medical Sciences, Isfashan, Iran. The authors thank Prof. Mahin Hashemipour and Ms. Ghazaleh Fatemi for helping in sample collection and experiments.

Received: 30 Apr 15 **Accepted:** 22 Sep 15
Published: 23 Feb 16

REFERENCES

1. Poulsen P, Vaag A. The impact of genes and pre- and postnatal environment on the metabolic syndrome. Evidence from twin studies. Panminerva Med 2003;45:109-15.
2. Ordovas JM, Shen J. Gene-environment interactions and susceptibility to metabolic syndrome and other chronic diseases. J Periodontol 2008;79 8 Suppl: 1508-13.
3. Kelishadi R, Ardalan G, Gheiratmand R, Adeli K, Delavari A, Majdzadeh R; Caspian Study Group. Paediatric metabolic syndrome and associated anthropometric indices: The CASPIAN study. Acta Paediatr 2006;95:1625-34.
4. Schwandt P, Kelishadi R, Haas GM. Ethnic disparities of the metabolic syndrome in population-based samples of german and Iranian adolescents. Metab Syndr Relat Disord 2010;8:189-92.
5. Schwandt P, Kelishadi R, Ribeiro RQ, Haas GM, Poursafa P. A three-country study on the components of the metabolic syndrome in youths: The BIG study. Int J Pediatr Obes 2010;5:334-41.
6. Alberti KG, Zimmet P, Shaw J. Metabolic syndrome – A new world-wide definition. A Consensus Statement from the International Diabetes Federation. Diabet Med 2006;23:469-80.
7. Jacob S, Machann J, Rett K, Brechtel K, Volk A, Renn W, *et al.* Association of increased intramyocellular lipid content with insulin resistance in lean nondiabetic offspring of type 2 diabetic subjects. Diabetes 1999;48:1113-9.
8. Unger RH, Zhou YT. Lipotoxicity of beta-cells in obesity and in other causes of fatty acid spillover. Diabetes 2001;50 Suppl 1:S118-21.
9. Brown MS, Goldstein JL. The SREBP pathway: Regulation of cholesterol metabolism by proteolysis of a membrane-bound transcription factor. Cell 1997;89:331-40.
10. Osborne TF. Sterol regulatory element-binding proteins (SREBPs): Key regulators of nutritional homeostasis and insulin action. J Biol Chem 2000;275:32379-82.
11. Horton JD, Goldstein JL, Brown MS. SREBPs: Activators of the complete program of cholesterol and fatty acid synthesis in the liver. J Clin Invest 2002;109:1125-31.
12. Shimomura I, Shimano H, Horton JD, Goldstein JL, Brown MS. Differential expression of exons 1a and 1c in mRNAs for sterol regulatory element binding protein-1 in human and mouse organs and cultured cells. J Clin Invest 1997;99:838-45.
13. Raghow R, Yellaturu C, Deng X, Park EA, Elam MB. SREBPs: The crossroads of physiological and pathological lipid homeostasis. Trends Endocrinol Metab 2008;19:65-73.
14. Sewter C, Berger D, Considine RV, Medina G, Rochford J, Ciaraldi T, *et al.* Human obesity and type 2 diabetes are associated with alterations in SREBP1 isoform expression that are reproduced *ex vivo* by tumor necrosis factor-alpha. Diabetes 2002;51:1035-41.
15. Le Lay S, Lefrère I, Trautwein C, Dugail I, Krief S. Insulin and sterol-regulatory element-binding protein-1c (SREBP-1C) regulation of gene expression in 3T3-L1 adipocytes. Identification of CCAAT/enhancer-binding protein beta as an SREBP-1C target. J Biol Chem 2002;277:35625-34.
16. Foretz M, Pacot C, Dugail I, Lemarchand P, Guichard C, Le Lièpvre X, *et al.* ADD1/SREBP-1c is required in the activation of hepatic lipogenic gene expression by glucose. Mol Cell Biol 1999;19:3760-8.
17. Najafi-Shoushtari SH, Kristo F, Li Y, Shioda T, Cohen DE, Gerszten RE, *et al.* MicroRNA-33 and the SREBP host genes cooperate to control cholesterol homeostasis. Science 2010;328:1566-9.
18. Dávalos A, Goedeke L, Smibert P, Ramírez CM, Warrier NP, Andreo U, *et al.* MiR-33a/b contribute to the regulation of fatty acid metabolism and insulin signaling. Proc Natl Acad Sci U S A 2011;108:9232-7.
19. Musso G, Bo S, Cassader M, De Michieli F, Gambino R. Impact of sterol regulatory element-binding factor-1c polymorphism on incidence of nonalcoholic fatty liver disease and on the severity of liver disease and of glucose and lipid dysmetabolism. Am J Clin Nutr 2013;98:895-906.
20. Choukem SP, Boudou P, Sobngwi E, Villette JM, Ibrahim F, Moulin P, *et al.* The polymorphism Arg585Gln in the gene of the sterol regulatory element binding protein-1 (SREBP-1) is not a determinant of ketosis prone type 2 diabetes (KPD) in Africans. Diabetes Metab 2009;35:20-4.
21. Felder TK, Oberkofler H, Weitgasser R, Mackevics V, Krempler F, Paulweber B, *et al.* The SREBF-1 locus is associated with type 2 diabetes and plasma adiponectin levels in a middle-aged Austrian population. Int J Obes (Lond) 2007;31:1099-103.
22. Harding AH, Loos RJ, Luan J, O'Rahilly S, Wareham NJ, Barroso I. Polymorphisms in the gene encoding sterol regulatory element-binding factor-1c are associated with type 2 diabetes. Diabetologia 2006;49:2642-8.
23. Laaksonen R, Thelen KM, Päivä H, Matinheikki J, Vesalainen R, Janatuinen T, *et al.* Genetic variant of the SREBF-1 gene is significantly related to cholesterol synthesis in man. Atherosclerosis 2006;185:206-9.
24. Eberlé D, Clément K, Meyre D, Sahbatou M, Vaxillaire M, Le Gall A, *et al.* SREBF-1 gene polymorphisms are associated with obesity and type 2 diabetes in French obese and diabetic cohorts. Diabetes 2004;53:2153-7.
25. Salek L, Lutucuta S, Ballantyne CM, Gotto Jr AM, Marian AJ. Effects of SREBF-1a and SCAP polymorphisms on plasma levels of lipids, severity, progression and regression of coronary atherosclerosis and response to therapy with fluvastatin. J Mol Med (Berl) 2002;80:737-44.
26. Adams LA, Marsh JA, Ayonrinde OT, Olynyk JK, Ang WQ, Beilin LJ, *et al.* Cholesteryl ester transfer protein gene polymorphisms increase the risk of fatty liver in females independent of adiposity. J Gastroenterol Hepatol 2012;27:1520-7.
27. Zhang Z, Gong RR, Du J, Xiao LY, Duan W, Zhou XD, *et al.* Associations of the SREBP-1c gene polymorphism with gender-specific changes in serum lipids induced by a high-carbohydrate diet in healthy Chinese youth. Appl Physiol Nutr Metab 2011;36:226-32.
28. Laudes M, Barroso I, Luan J, Soos MA, Yeo G, Meirhaeghe A, *et al.* Genetic variants in human sterol regulatory element binding protein-1c in syndromes of severe insulin resistance and type 2 diabetes. Diabetes 2004;53:842-6.
29. Grarup N, Stender-Petersen KL, Andersson EA, Jørgensen T, Borch-Johnsen K, Sandbaek A, *et al.* Association of variants in the sterol regulatory element-binding factor 1 (SREBF1) gene with type 2 diabetes, glycemia, and insulin resistance: A study of 15,734 Danish subjects. Diabetes 2008;57:1136-42.
30. Liu JX, Liu J, Li PQ, Xie XD, Guo Q, Tian LM, *et al.* Association of sterol regulatory element-binding protein-1c gene polymorphism with type 2 diabetes mellitus, insulin resistance and blood lipid levels in Chinese population. Diabetes Res Clin Pract 2008;82:42-7.
31. Song Y, Li N, He L, Chen Q, Tang X, Chen DF, *et al.* An association study of abdominal obesity and polymorphisms of UCP2 and SREBP1c genes. Beijing Da Xue Xue Bao 2009;41:302-6.
32. Liu JX, Liu J, Guo Q, Liu J. Association of sterol regulatory element binding protein-1c genetic polymorphisms rs2297508 and rs11868035 with type 2 diabetes mellitus in Gansu Han and Dongxiang population. Zhonghua Yi Xue Yi Chuan Xue Za Zhi 2012;29:328-33.
33. Rios DL, Vargas AF, Torres MR, Zago AJ, Callegari-Jacques SM, Hutz MH. Interaction between SREBP-1a and APOB polymorphisms influences total and low-density lipoprotein cholesterol levels in patients with coronary artery disease. Clin Genet 2003;63:380-5.
34. Védie B, Jeunemaitre X, Mégnien JL, Atger V, Simon A, Moatti N. A new DNA polymorphism in the 5' untranslated region of the human SREBP-1a is related to development of atherosclerosis in high cardiovascular risk population. Atherosclerosis 2001;154:589-97.
35. Lu Y, Feskens EJ, Boer JM, Imholz S, Verschuren WM, Wijmenga C, *et al.* Exploring genetic determinants of plasma total cholesterol levels and their predictive value in a longitudinal study. Atherosclerosis 2010;213:200-5.
36. Update on the 1987 Task Force Report on High Blood Pressure in Children and Adolescents: A working group report from the National High Blood

Pressure Education Program. National High Blood Pressure Education Program Working Group on Hypertension Control in Children and Adolescents. Pediatrics 1996;98 (4 Pt 1):649-58.
37. Müller-Wieland D, Kotzka J. SREBP-1: Gene regulatory key to syndrome X? Ann N Y Acad Sci 2002;967:19-27.
38. Genomes Project Consortium, Abecasis GR, Altshuler D, Auton A, Brooks LD, Durbin RM, *et al.* A map of human genome variation from population-scale sequencing. Nature 2010;467:1061-73.
39. Rayner KJ, Sheedy FJ, Esau CC, Hussain FN, Temel RE, Parathath S, *et al.* Antagonism of miR-33 in mice promotes reverse cholesterol transport and regression of atherosclerosis. J Clin Invest 2011;121:2921-31.
40. Rayner KJ, Suárez Y, Dávalos A, Parathath S, Fitzgerald ML, Tamehiro N, *et al.* MiR-33 contributes to the regulation of cholesterol homeostasis. Science 2010;328:1570-3.

Source of Support: Isfahan University of Medical Sciences, Isfahan, Iran, **Conflict of Interest:** None declared.