

# 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<sup>1,2</sup>, Modjtaba Emadi-Baygi<sup>1,3</sup>, Parvaneh Nikpour<sup>2,4,5</sup>, Roya Kelishadi<sup>2</sup>

<sup>1</sup>Department of Genetics, School of Basic Sciences, Shahrekord University, Shahrekord, Iran, <sup>2</sup>Child Growth and Development Research Center, Research Institute for Primordial Prevention of Non-communicable Disease, Isfahan University of Medical Sciences, Isfahan, Iran, <sup>3</sup>Research Institute of Biotechnology, Shahrekord University, Shahrekord, Iran, <sup>4</sup>Applied Physiology Research Center, Isfahan University of Medical Sciences, Isfahan, Iran, <sup>5</sup>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

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## 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

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## INTRODUCTION

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

Lipotoxicity may result in T2DM, obesity, and insulin resistance.<sup>[7,8]</sup> Sterol regulatory element-binding factors (SREBFs) are transcription factors playing central roles in the regulation of the carbohydrate and lipid metabolism.<sup>[9,10]</sup> 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.<sup>[11]</sup>

*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.<sup>[12,13]</sup> *SREBF-1a* and *-1c* isoforms both regulate the genes involved in cholesterol, TG, and fatty acid synthesis.<sup>[13]</sup> *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.<sup>[13–16]</sup>

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

Several studies have so far investigated the relationship between *SREBF-1* gene polymorphisms, glucose and lipid dysregulation in humans.<sup>[19–35]</sup> In 2006, Harding *et al.*<sup>[22]</sup> 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.<sup>[3]</sup> Accordingly, an individual was considered as a MetS case if she/he had at least three of the following criteria: (a) Fasting TG  $\geq$  100 mg/dl; (b) HDL-C < 50 mg/dl; (c) waist circumference > 75<sup>th</sup> percentile for age and gender in the studied population; (d) systolic blood pressure/diastolic blood pressure > 90<sup>th</sup> percentile for gender, age, and height,<sup>[36]</sup> and (e) fasting blood sugar  $\geq$  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 ethylenediamine-tetraacetic acid-treated tubes and stored at  $-20^{\circ}\text{C}$  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<sup>®</sup> 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.

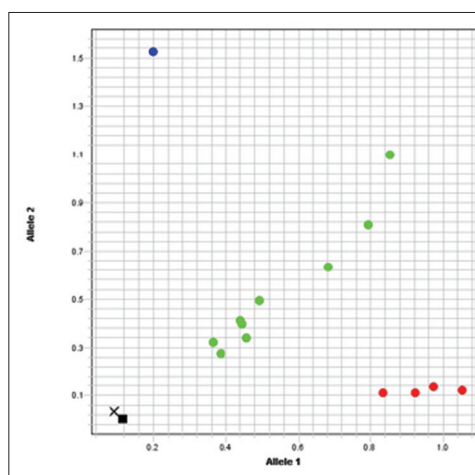
Stratification of the laboratory parameters of the control and MetS subjects according to different genotypes of the rs8066560 (A/G) are given in Tables 3 and 4. There was no statistically significant difference in mean age, BMI, TG, TC, and LDL-C between the three genotypes; however, the HDL-C levels 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.<sup>[37]</sup> 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 ( $\chi^2$ )	0.335
BMI (kg/m <sup>2</sup> )	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)	$\chi^2$	P	Total (n)	A n (%)	G n (%)	$\chi^2$	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 <sup>2</sup> )	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 I

by 1000 genomes project.<sup>[38]</sup> 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.*<sup>[35]</sup> 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.<sup>[18,39,40]</sup> 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

**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 <sup>2</sup> )	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 I

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

Allele/genotype	Crude OR (95% CI)	P	Adjusted <sup>a</sup> 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

<sup>a</sup>Adjusted for age and sex. OR=Odds ratio, CI=Confidence interval, MetS=Metabolic syndrome, SREBF-1=Sterol regulatory element-binding transcription factor I

the HDL-C and decreasing TC and LDL-C levels. Further studies to analyze the promoter of the human sterol regulatory element-binding protein I 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 Vedio *et al.*<sup>[34]</sup> but other studies did not observe such a correlation.<sup>[25,33]</sup> Previous studies analyzing 54 C/C polymorphism (rs2297508) in SREBF-1 gene reported a significant association with LDL-C<sup>[21,30,32]</sup> but not with TC, HDL-C, and TG levels.<sup>[21,24,29,30]</sup> Although Eberle *et al.* reported a correlation of this SNP with TG only in male subjects.<sup>[24]</sup> Rs11868035 variant in the SREBF-1 gene has also shown a correlation with LDL-C and TC.<sup>[28-30,32]</sup> 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.

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