Association between the transient receptor potential (TRP) channel gene polymorphisms and metabolic syndrome

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OBJECTIVES

Metabolic syndrome (MetS) is characterized by a combination of visceral obesity, hypertension, insulin resistance, dyslipidemia, and impaired glucose tolerance. It is a prominent risk factor for cardiovascular morbidity and mortality. The etiology of MetS is complex. The progression of MetS is influenced by genetic susceptibility and environmental factors. The aim of this study was to investigate a possible association between transient receptor potential (TRP) channels gene polymorphisms and MetS in a Turkish population.

METHODS

A total of 308 unrelated Turkish subjects, 142 with obesity-related MetS and 166 non-MetS controls evaluated at Division of Endocrinology, Department of Internal Medicine, Faculty of Medicine, Gaziantep University, Gaziantep, Turkey were recruited into this study. The study was approved by the local Ethics Committee, and written informed consent prior to participation in the study was obtained from patients and healthy volunteers according to the Declaration of Helsinki. MetS was defined by using modified criteria proposed by the Third Report of the National Cholesterol Education Program Adult Treatment Panel. All sex and age-matched controls were healthy and had no symptoms of MetS. The selection criteria of the controls were that all control subjects were from the same geographical area with a similar socioeconomic and ethnic background and were admitted to outpatient clinic. Genomic DNA from the participants was analyzed by a BioMark 96.96 dynamic array system (Fluidigm, South San Francisco, CA, USA). For calculation of the significance of differences in genotype and allele frequencies, the chi-square test or Fisher's exact test was used. A p value of <0.002 (0.05/25) was considered statistically significant after Bonferoni correction for multiple testing.

Table 1. Baseline demographic and clinical characteristics of MetS patients and controls

	Patients (n=142)	Controls (n=166)	*P* value
Age (years)[a]	42.25±12.22	41.89±9.42	0.7708
Gender			
Male (n, %)	15 (10.6)	29 (17.5)	0.1025
Female (n, %)	127 (89.4)	137 (82.5)	
Smoking status			
Current (n, %)	19 (13.4)	20 (12.1)	0.9383
Never (n, %)	114 (80.3)	135 (81.3)	
Past (n, %)	9 (6.3)	11 (6.6)	
Alcohol intake	6 (4.2)	9 (5.4)	0.7920
BMI (kg/m^2)[a]	40.19±6.32	22.61±2.00	<0.0001
Waist circumference (cm)[a]	118.10±12.99	82.12±8.23	<0.0001
Systolic BP (mm Hg)[a]	131.81±15.69	117.95±8.65	<0.0001
Diastolic BP (mm Hg)[a]	86.39±13.69	74.88±5.36	<0.0001
Diabetes mellitus (n, %)	37 (26.1)	-	
Fasting plasma glucose (mg/dl)[a]	116.62±58.52	86.64±6.89	<0.0001
HbA1c (%)[a]	6.33±1.81	-	
Creatinine (mg/dl)[a]	0.68±0.14	0.71 ±0.15	0.0722
Alanine aminotransferase (IU/l)[a]	24.83±14.56	23.86 ±13.38	0.5430
Total cholesterol (mg/dl)[a]	198.46±45.46	152.64±18.77	<0.0001
Low density lipoprotein cholesterol (mg/dl)[a]	129.60±32.63	96.12±14.37	<0.0001
High density lipoprotein cholesterol (mg/dl)[a]	40.68±8.15	43.12±5.75	0.0024
Triglyceride (mg/dl)[a]	174.04±66.43	123.46±26.45	<0.0001
Uric acid (mg/dl)[a]	4.94±1.30	-	
High-sensitive C-reactive protein	1.92±3.62	0.27±0.18	<0.0001
Insulin (pmol/l)[a]	22.10±16.43	-	
HOMA-IR[a]	6.00±4.68	-	

[a]Data are mean±S.D. BMI, body mass index. BP, blood pressure. Fasting glucose and insulin plasma levels are used to calculate homeostasis model assessment of insulin resistance (HOMA-IR).

Table 2. Distributions of genotypes and alleles for the *TRPM1, TRPM2, TRPM3, TRPM4,* and *TRPM5* gene polymorphisms between the case and control groups.

Gene SNP	Genotypes/ Alleles	Controls	n*	Cases with MetS	n*	*P* value
TRPM1	CC/CT/TT	109/43/14	166	91/31/16	138	0.5684
rs28441327	C/T	261/71		213/63		0.7426
TRPM1	GG/GA/AA	105/48/8	161	93/37/10	140	0.6337
rs11070811	G/A	258/64		223/57		0.9641
TRPM1	AA/AG/GG	86/52/20	158	87/35/17	139	0.3065
rs2241493 (Ser71Asn)	A/G	224/92		209/69		0.2791
TRPM1	CC/CT/TT	157/5/0	162	132/6/0	138	0.7596
rs111649153 (Arg1518His)	C/T	319/5		270/6		0.7619
TRPM2	TT/TG/GG	93/47/23	163	93/27/18	138	0.1376
rs1618355	T/G	233/93		213/63		0.1343
TRPM3	CC/CA/AA	130/22/9	161	109/20/6	135	0.8787
rs1328142	C/A	282/40		238/32		0.8998
TRPM4	CC/CT/TT	91/44/24	159	65/46/20	131	0.3575
rs3760663	C/T	226/92		176/86		0.3569
TRPM5	CC/CT/TT	157/0/4	161	134/0/5	139	0.7376
rs34364959 (Gly900Ser)	C/T	314/8		268/10		0.4774
TRPM5	AA/AG/GG	51/6/52	109	68/10/35	113	0.0354
rs4929982 (Arg578Gln)	A/G	108/110		146/80		**0.0019**
TRPM5	AA/AG/GG	68/57/34	129	63/44/25	132	0.6914
rs886277 (Asn235Ser)	A/G	193/125		170/94		0.4055
TRPM5	CC/CT/TT	52/2/6	60	70/2/5	77	0.7236
rs34551253 (Ala456Thr)	C/T	106/14		144/12		0.3016
TRPM5	GG/GA/AA	115/23/18	156	102/14/18	134	0.5203
rs3986599 (Val254Ala)	G/A	253/59		218/50		0.9379

*Numbers do not always add up to total numbers because of missing values on the BioMark dynamic array system. SNP, single nucleotide polymorphism. MetS, metabolic syndrome.

Table 3. Distributions of genotypes and alleles for the *TRPM6, TRPM7,* and *TRPM8* gene polymorphisms between the case and control groups.

Gene SNP	Genotypes/ Alleles	Controls	n*	Cases with MetS	n*	*P* value
TRPM6	GG/GA/AA	120/35/7	162	98/32/8	138	0.7771
rs3750425 (Val1388Ile)	G/A	275/49		228/48		0.5217
TRPM6	AA/AG/GG	159/1/0	160	133/1/0	134	1.0000
rs62569677 (Asn877Asp)	A/G	319/1		267/1		1.0000
TRPM7	TT/TC/CC	159/3/0	162	135/1/0	136	0.6282
rs55924090 (Ile159Thr)	T/C	321/3		271/1		0.6295
TRPM8	CC/CT/TT	119/35/5	159	100/27/5	132	0.9153
rs1016062	C/T	273/45		227/37		0.9626
TRPM8	TT/TC/CC	61/42/56	159	44/40/58	142	0.3902
rs2362294	T/C	164/154		128/156		0.1306
TRPM8	AA/AG/GG	98/51/15	164	75/39/19	133	0.3841
rs2362295	A/G	247/81		189/77		0.2833
TRPM8	GG/GA/AA	97/52/14	163	81/44/12	137	0.9973
rs10190018	G/A	246/80		206/68		0.9374
TRPM8	GG/GA/AA	98/49/17	164	81/40/16	137	0.9352
rs2052029	G/A	245/83		202/72		0.8586
TRPM8	CC/CT/TT	93/55/12	160	91/34/14	139	0.1593
rs6431648	C/T	241/79		216/62		0.5560
TRPM8	GG/GC/CC	131/27/3	161	118/18/3	139	0.6472
rs10803666	G/C	289/33		254/24		0.5771
TRPM8	CC/CT/TT	132/27/2	161	78/57/2	137	**<0.0001**
rs12472151	C/T	291/31		213/61		**<0.0001**
TRPM8	CC/CT/TT	108/41/10	159	103/24/6	133	0.1944
rs2215173	C/T	257/61		230/36		0.0863
TRPM8	GG/GA/AA	108/42/11	161	101/25/7	133	0.2472
rs6740118	G/A	258/64		227/39		0.1220

*Numbers do not always add up to total numbers because of missing values on the BioMark dynamic array system. SNP, single nucleotide polymorphism. MetS, metabolic syndrome.

RESULTS

Demographic and clinical characteristics of the study population are presented in Table 1. Genotype and allele frequencies of *TRPM1, TRPM2, TRPM3, TRPM4, TRPM5 TRPM6, TRPM7,* and *TRPM8* gene polymorphisms in MetS and control groups are presented in Tables 2 and 3. There was an increase in A allele (64.6% in patients vs. 49.5% in controls) and decrease in G allele frequencies (35.4% in patients vs. 50.5% in control, *P*=0.0019) of the *TRPM5* gene rs4929982 (Arg578Gln) polymorphism. No significant differences were noted in genotype distribution. We also observed that the distribution of genotype and allele frequencies of the *TRPM8* gene rs12472151 in MetS patients were significantly different from controls (*P*<0.0001). However, no associations were found with the other 23 polymorphisms studied.

CONCLUSIONS

In conclusion, to the best of our knowledge, the present case-control study is the first to examine the potential involvement of TRP channel gene variations in the risk of incident MetS. Our data showed that genetic polymorphisms in *TRPM5* and *TRPM8* genes may modify individual susceptibility to MetS in the Turkish population.

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