

Association transient receptor potential melastatin channel gene polymorphism with primary open angle glaucoma

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Purpose: Genetic factors are shown to have a role in the development of primary open angle glaucoma (POAG). The aim of this study was to determine the effects of genetic polymorphisms of transient receptor potential melastatin (TRPM) channel genes on the risk of POAG in a Turkish population.

Methods: Genomic DNA was extracted from the leukocytes of the peripheral blood, and 26 single nucleotide polymorphisms in the TRPM channel genes were analyzed in 179 patients with POAG and in 182 healthy controls of similar age by using the BioMark HD dynamic array system.

Results: There were marked changes in the genotype (TT, 26.8%; CT, 66.7%; CC, 6.5%) and allele (T, 60.1%; C, 39.9%) frequencies for the *TRPM5* gene rs34551253 (Ala456Thr, in exon 9) polymorphism in patients when compared to the controls (TT, 11.3%; CT, 74.6%; CC, 14.1%, $p=0.0009$; T, 48.6%; A, 51.4%, $p=0.0063$). However, no associations with the other 25 polymorphisms studied were found.

Conclusions: This is the first study to examine the involvement of *TRPM* channel gene variations in the risk of incident POAG. This study demonstrated that the *TRPM5* gene rs34551253 (Ala456Thr) polymorphism may be associated with increased risk of developing POAG in the Turkish population.

Glaucoma is a complex and heterogeneous disease characterized by a progressive degeneration of the axons of the retinal ganglion cells (RGCs), but the mechanisms causing the RGC loss are still undetermined. Glaucoma is the second most common cause of blindness worldwide [1]. Primary open angle glaucoma (POAG), the most common form of glaucoma, is a complex chronic degenerative disease with a multifactorial etiology including mechanical damage due to elevated intraocular pressure (IOP), increased glutamate levels, mutations in specific genes, toxic effects and oxidative damage caused by reactive oxygen species (ROS) [2], and apoptosis [3]. Elevation of IOP also causes retinal ischemia and neuronal cell death. However, most of the molecular mechanisms leading to POAG development are still unknown. Several genetic loci that contribute to the susceptibility of eyes to POAG have been identified. Genome-wide association studies showed that only two identified genes, myocilin (*MYOC*) and optineurin (*OPTN*), are well-established glaucoma-causing genes [4].

Transient receptor potential (TRP) channels are a highly diverse group of ion channels with widely diverging functional properties. Various stimuli can regulate the gating of the TRP channels, such as physical stimuli (temperature, voltage, mechanical stress), exogenous ligands, intracellular cations, and lipid components of the plasma membrane [5]. There are 28 mammalian TRP channels, which are subdivided into six subfamilies based on protein sequence homology: TRPA (ankyrin), TRPC (canonical), TRPM (melastatin), TRPML (mucolipin), TRPP (polycystin), and TRPV (vanilloid) [6]. The TRPM subfamily consists of eight members (TRPM1–8). Three members of the TRPM subfamily (TRPM2, TRPM6, and TRPM7) have enzymatic activity. Moreover, TRPM4 and TRPM5 are impermeable to Ca^{2+} [6]. TRPM1 is the founding member of the TRPM subfamily of TRP channels, and was initially identified by differential display as a potential suppressor of tumor metastasis (and originally named melastatin because it is downregulated in metastatic melanoma) [7]. TRPM2 forms a non-selective cation channel gated by adenosine diphosphate-ribose, hydrogen peroxide, and intracellular Ca^{2+} [8,9]. TRPM3 is activated by sphingolipids [9], and shown to function in insulin secretion [10]. TRPM4 controls pressure-mediated smooth muscle cell depolarization and vasoconstriction of cerebral arteries, so it may participate in autoregulating cerebral blood flow [11,12]. TRPM5 is

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activated by Ca^{2+} released from intracellular stores, and has a role in taste transduction [13]. TRPM6 and TRPM7 are close members of the TRP superfamily of ion channels with ion channel and protein kinase activities and have been shown to play important roles in magnesium homeostasis. TRPM6 and TRPM7 are highly permeable to magnesium [14,15]. TRPM8 is involved in thermosensation [16]. However, the role of TRPM channels in POAG is not known.

TRPM1 is a visual transduction channel in retinal ON bipolar cells. Four recent articles reported an association between mutations in the TRPM1 gene and autosomal recessive congenital stationary night blindness in humans [17-20]. In the complete form of congenital stationary night blindness, various mutations, including deletions and nonsense mutations, leading to loss of function were found. Since TRPM channels are present in the vascular and ocular cells, vasoconstriction may lead to optic nerve head ischemia and subsequent development of visual field defects during the course of glaucoma; we hypothesize that TRPM channels gene variants play a role in the risk of POAG development. The purpose of the present study was to investigate a possible association between TRPM gene polymorphisms and POAG in a Turkish population.

METHODS

Study population: A total of 179 unrelated Turkish patients (91 males and 88 females; age range, 33-79 years old) and 182 healthy controls (93 males and 89 females; age range, 29-80 years old) evaluated at University of Gaziantep, Faculty of Medicine, Department of Ophthalmology, Gaziantep, Turkey were recruited into this study. Routine ophthalmologic evaluations were performed on all subjects. Patients with POAG underwent a complete eye examination including visual acuity testing, slit-lamp biomicroscopy with and without dilation, fundus examination with 90-diopter lens, IOP measurement with Goldmann applanation tonometry, central corneal thickness (CCT) measurement with ultrasonic pachymetry, and gonioscopy. The criteria for classifying a patient as having POAG were as follows: IOP > 22 mmHg in each eye without antiglaucoma drugs, pathological cupping of the optic disc including the quantitative assessment of cup-to-disc (C/D) ratio > 0.7 in each eye, visual field defects determined with automated perimetry (Octopus 900, Haag-Streit, Switzerland) and/or Humphrey visual field analysis consistent with the glaucomatous cupping in at least 1 eye, and an open anterior chamber angle. We checked the IOP on at least three visits, and the measurements were made during the daylight hours. Patients with a history of eye surgery before the diagnosis of glaucoma, or with evidence of secondary glaucoma, such as

exfoliation, pigment dispersion, trauma-, uveitis-, or steroid-induced glaucoma, were excluded. Patients with malignant or autoimmune diseases were also excluded. A control group of age- and sex-matched individuals was chosen randomly from a sample of patients admitted to the ophthalmology outpatient department for refractive errors, conjunctivitis, blepharitis, burning, itching, presbyopia, senile cataracts, routine ophthalmic examinations, or medical staff with no ocular problems. The control subjects had the following characteristics: IOP < 22 mmHg, normal optic discs, with a C/D ratio of ≤ 0.3 and glaucoma hemifield test within normal limits, and no family history of glaucoma. The study was approved by the local Ethics Committee, in compliance with the Declaration of Helsinki.

Blood samples and deoxyribonucleic acid isolation: Peripheral venous blood samples (5 ml) were obtained and collected in sterile siliconized vacutainer tubes with 2 mg/ml disodium EDTA. Immediately after collection, all samples were stored at -20°C until use. Genomic DNA was extracted from whole blood with the salting-out method and stored at -20°C .

Genotyping: The genotype was determined in all patients and controls with the Fluidigm dynamic array system. Polymorphisms were analyzed in genomic DNA with a 96.96 dynamic array on the BioMark HD system (Fluidigm, South San Francisco, CA). Digital PCR Analysis software (Fluidigm) was used to process the data after the reaction. Chambers that yielded signals were detected and counted.

The following criteria were used to choose the single nuclear polymorphisms (SNPs): (1) relatively high minor allele frequencies in Caucasian populations; (2) location within the promoter region, and exonic and intronic sites that could potentially impact TRPM expression and function; and (3) suitable for the Fluidigm dynamic array chip designing, i.e., with no high G/C levels. In the present study, 26 SNPs [TRPM1: [rs28441327](#) in intron 1, [rs11070811](#) in intron 1, [rs2241493](#) (Ser32Asn) in exon 5; TRPM2: [rs1618355](#) in intron 18, [rs9978351](#) (Arg1189=) in exon 24; TRPM3: [rs113652718](#) (Val104Ala) in exon 6, [rs1328142](#) in intron 9; TRPM4: [rs3760663](#) in 5'-untranslated region, [rs71352737](#) (Trp525Ter) in exon 11; TRPM5: [rs34364959](#) (Gly900Ser) in exon 18, [rs4929982](#) (Arg578Gln) in exon 11, [rs34551253](#) (Ala456Thr) in exon 9, [rs886277](#) (Asn235Ser) in exon 5, [rs3986599](#) (Val254Ala) in exon 6; TRPM6: [rs3750425](#) (Val1388Ile) in exon 28, [rs2274924](#) (Lys1579Glu) in exon 29; TRPM7: [rs77165588](#) in promoter; TRPM8: [rs1016062](#) in intron 21, [rs2362294](#) in intron 21, [rs6431648](#) in intron 1, [rs2362295](#) in intron 22, [rs10803666](#) in intron 2, [rs10490018](#) in intron 24, [rs2052029](#) in 3'-untranslated region, [rs2215173](#)

in intron 7, and rs6740118 in intron 9] were studied for *TRPM* gene polymorphisms.

Statistical analyses: Results are expressed as mean±standard deviation (SD) or percentage. Differences in genotype and allele frequencies among the cases and controls were tested with the chi-square test for independence and the chi-square test with Yate's correction or Fisher's exact tests. For comparisons of the differences between the mean values of two groups, the unpaired Student *t* test was used. The original significance level was set at a *p* value of 0.05. All probability values were based on two-tailed tests. To conclude the association, we used the Bonferroni method to correct the *p* values for multiple testing, using a stringent threshold. For correcting *p* values in model-based analysis, including the allele and full model, a *p* value of <0.0019 (0.05/26) was considered statistically significant. The odds ratio (OR) and 95% confidence intervals (CIs) were also calculated using logistic regression analysis. The SPSS statistical package (SPSS, version 17.0, Chicago, IL) and GraphPad Instat version 3.05 (GraphPad Software, San Diego, CA) were used for statistical analysis.

RESULTS

Clinical characteristics of the study population are presented in Table 1. In this study, 179 patients with POAG admitted to the ophthalmology clinic were investigated. The mean age and gender of the patients and control groups were similar. In glaucoma group, the mean IOP was 28.6±6.2 mmHg within a range between 22 and 55 mmHg, and the C/D ratio was 0.7±0.2. The mean CCT value was 557.8±37.7 μm within a range between 470 and 670 μm.

Table 2 and Table 3 show the distributions of the genotypes and alleles between the case and control groups. There were marked associations for the genotype (*p*=0.0009) frequencies of the *TRPM5* gene rs34551253 (Ala456Thr) polymorphism between the patients and the control group.

TABLE 1. CLINICAL CHARACTERISTICS OF THE STUDY POPULATION.

Parameters	Controls	Cases with POAG	P value
	(n=182)	(n=179)	
Age (years) ^a	51.3±11.2	53.2±8.4	0.0694
Gender			
Male (n, %)	93 (51.1)	91 (50.8)	0.9605
Female (n, %)	89 (48.9)	88 (49.2)	
IOP (mmHg) ^a	13.3±3.4	28.6±6.2	<0.0001

^aData are mean±SD. POAG, primary open-angle glaucoma; IOP, intraocular pressure.

The TT genotype frequency (26.8%) of this polymorphism was significantly higher in patients with POAG than in the controls (TT, 11.3%). We performed a logistic regression analysis model for the association between the minor allele of *TRPM5* rs34551253 (Ala456Thr) polymorphism and POAG. The TT genotype was significantly associated as a risk factor for POAG (OR: 4.93; 95% CI=1.89–12.87, *p*=0.001) after adjustment for gender and age. However, the CT genotype was not markedly associated with POAG (OR: 1.79; 95% CI=0.79–4.05, *p*=0.157). There were no marked associations with the other 25 *TRPM* polymorphisms studied (Table 2 and Table 3).

DISCUSSION

In this case-control study, we showed that the *TRPM5* gene rs34551253 (Ala456Thr) polymorphism was significantly associated with POAG and could be a risk factor for developing POAG. This is the first study to examine the association of the *TRPM* gene polymorphisms with the risk of developing POAG. Our results suggest the TT genotype of the rs34551253 (Ala456Thr) polymorphism may increase susceptibility to POAG.

Increased IOP in most cases is due to increased resistance to the outflow of aqueous humor through the trabecular meshwork, which also leads to optic nerve damage [21]. Reduction in blood flow to the optic nerve head could also be an important risk factor involved in the damage to the RGCs [22]. All eight members of the TRPM subfamily are present in vascular smooth muscle cells. Expression of all the TRPM channel proteins except TRPM5 has been reported in endothelial cells [9,11,23,24]. TRPM5 currents are Ca²⁺ and voltage dependent. In the presence of high levels of intracellular Ca²⁺, depolarization strongly increases the opening of the TRPM5 channel [9,25,26]. TRPM5 channels are blocked by an external pH of 6.0 or lower [27]. TRPM5 is highly permeable to monovalent cations and impermeable to divalent cations (i.e., Ca²⁺, Mg²⁺) [25,26,28]. This is the first study showing a marked association between TRPM5 and glaucoma. TRPM5 channel localization in ocular tissue, physiologic function of this channel, and the contribution of this channel to the glaucoma pathogenesis are currently unknown, and require further studies. In addition, the structure and function of the channel affected with the rs34551253 polymorphism is currently unknown.

Several searches have been made for associations between phenylthiourea (phenylthiocarbamide) tasting and glaucoma. Becker and Morton [29] found that the number of individuals unable to recognize the bitter taste of phenylthiourea was 28% in a "normal" eye clinic population (446

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 POAG	n*	P value
TRPM1 rs28441327	CC/CT/TT C/T	112/60/10 284/80	182	119/47/13 285/73	179	0.3399 0.6667
TRPM1 rs11070811	GG/GA/AA G/A	112/60/10 284/80	182	117/51/10 285/71	178	0.6721 0.5627
TRPM1 rs2241493 (Ser32Asn)	AA/AG/GG A/G	107/62/13 276/88	182	104/61/14 269/89	179	0.969 0.8987
TRPM2 rs1618355	TT/TG/GG T/G	97/72/11 266/94	180	95/73/11 263/95	179	0.9876 0.9644
TRPM2 rs9978351 (Arg1189=)	CC/CT/TT C/T	180/1/0 362/2	182	178/0/0 356/0	178	0.4987 0.4994
TRPM3 rs113652718 (Val104Ala)	TT/TC/CC T/C	181/1/0 363/1	182	179/0/0 358/0	179	1 1
TRPM3 rs1328142	CC/CA/AA C/A	132/44/6 308/56	182	128/42/9 298/60	179	0.7106 0.6879
TRPM4 rs3760663	CC/CT/TT C/T	85/73/24 243/121	182	93/67/18 253/103	178	0.4893 0.2427
TRPM4 rs71352737 (Trp525Ter)	GG/GA/AA G/A	178/4/0 360/4	182	165/10/0 340/10	175	0.1055 0.1088
TRPM5 rs34364959 (Gly900Ser)	CC/CT/TT C/T	151/30/0 332/30	181	143/33/3 319/39	179	0.1874 0.2885
TRPM5 rs4929982 (Arg578Gln)	CC/CT/TT C/T	55/84/42 194/168	181	55/90/31 200/152	176	0.4076 0.4286
TRPM5 rs34551253 (Ala456Thr)	CC/CT/TT C/T	20/106/16 146/138	142	10/102/41 122/184	153	0.0009 0.0063
TRPM5 rs886277 (Asn235Ser)	AA/AG/GG A/G	65/87/30 214/147	182	68/82/28 218/138	178	0.8869 0.7126
TRPM5 rs3986599 (Val254Ala)	GG/GA/AA G/A	100/67/15 267/97	182	96/68/12 260/92	176	0.8513 0.9437

*Numbers do not always add up to total numbers because of missing values on the BioMark dynamic array system. SNP, single nucleotide polymorphism. POAG, primary open-angle glaucoma.

individuals) and 53% in 211 patients with primary open angle glaucoma in Caucasian patients. This finding has been further confirmed in patients with open angle glaucoma [30,31]. Becker and Ballin [32] demonstrated that 60% of the offspring of patients with POAG were non-tasters. Thus, patients with POAG are less likely to detect a bitter taste on the phenylthiourea test. The overall results show a raised incidence of non-tasters among patients with POAG.

TRPM5 is coexpressed with taste receptors, and functions as a common downstream component in sweet, bitter, and umami taste signal transduction [13,33]. Our results may

suggest that *TRPM5* is a gene associated with the detection of bitter taste in patients with POAG. However, the role of the TRPM5 channel in the development of POAG is not known, and requires further studies. The *TRPM5* gene is located on chromosome 11p15.5, and our results for the TRPM gene polymorphisms add new loci of susceptibility to POAG. Our findings suggest that the *TRPM5* gene polymorphism may be involved in POAG pathogenesis.

In conclusion, this study demonstrated that a TRPM gene polymorphism is associated with POAG in the Turkish population, and the *TRPM5* polymorphism also plays a role

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 POAG	n*	P value
TRPM6	GG/GA/AA	114/64/4	182	123/52/4	179	0.4588
rs3750425 (Val1388Ile)	G/A	292/72		298/60		0.3403
TRPM6	GG/GA/AA	56/73/52	181	35/88/52	175	0.0463
rs2274924 (Lys1579Glu)	G/A	185/177		158/192		0.1293
TRPM7	CC/CG/GG	179/3/0	182	179/0/0	179	0.248
rs77165588	C/G	361/3		358/0		0.249
TRPM8	CC/CT/TT	125/51/6	182	124/53/2	179	0.3646
rs1016062	C/T	301/63		301/57		0.689
TRPM8	CC/CT/TT	58/86/38	182	66/74/39	179	0.4955
rs2362294	C/T	202/162		206/152		0.6314
TRPM8	CC/CT/TT	100/67/14	181	99/63/16	178	0.8885
rs6431648	C/T	267/95		261/95		0.9603
TRPM8	AA/AG/GG	116/58/8	182	111/63/5	179	0.6113
rs2362295	A/G	290/74		285/73		0.9837
TRPM8	GG/GC/CC	125/50/7	182	129/44/6	179	0.7796
rs10803666	G/C	300/64		302/56		0.5484
TRPM8	GG/GA/AA	96/66/20	182	79/85/15	179	0.0939
rs10490018	G/A	258/106		243/115		0.427
TRPM8	GG/GA/AA	105/63/14	182	108/61/10	179	0.699
rs2052029	G/A	273/91		277/81		0.5083
TRPM8	CC/CT/TT	125/50/6	181	130/41/8	179	0.5318
rs2215173	C/T	300/62		301/57		0.7376
TRPM8	GG/GA/AA	126/50/6	182	128/42/8	178	0.621
rs6740118	G/A	302/62		298/58		0.8676

*Numbers do not always add up to total numbers because of missing values on the BioMark dynamic array system. SNP, single nucleotide polymorphism. POAG, primary open-angle glaucoma.

in the pathogenesis of this glaucoma. However, the exact roles of particular TRP channels in POAG require future analysis. Further investigations of *TRPM* gene polymorphisms in different ethnic populations would be helpful in understanding the pathogenesis of POAG.

ACKNOWLEDGMENTS

This work was supported by a project (BAP TF.12.06) from the University of Gaziantep.

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Articles are provided courtesy of Emory University and the Zhongshan Ophthalmic Center, Sun Yat-sen University, P.R. China. The print version of this article was created on 24 August 2013. This reflects all typographical corrections and errata to the article through that date. Details of any changes may be found in the online version of the article.