·Basic Research·

A novel mutation of SGK-1 gene in central serous chorioretinopathy

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Abstract

• AIM: To investigate the association of serum glucocorticoid kinase gene-1 (SGK-1) DNA variants with chronic central serous chorioretinopathy (CSC).

• METHODS: We enrolled 32 eyes of 32 patients who were diagnosed with chronic CSC and composed 32 normal eyes as a control group. Peripheral blood was used for DNA extraction and polymerase chain reaction amplification. SGK1 gene was sequenced by using BigDye® Terminator v3.1 cycle sequencing Kit (Applied Biosystems, Foster City, CA, USA). The SGK-1 gene and its variants were investigated in CSC patient group and control group.

• RESULTS: We identified a new polymorphism M32V in two person in the patient group [Minor allele frequency (MAF)=0.009] on the region of 1-60 amino acids. The rs1057293 was located in the encoder region of the SGK- 1 gene but not associated with CSC (P=0.68). An intrinsic rs1743966 is also not associated (P=0.28).

• CONCLUSION: The new polymorphism M32V is located on the region of 1-60 amino acids which is necessary for localization to the mitochondria in CSC patient. This mutation is probably important for the energy metabolism and plays an important role in the cellular response to hyperosmotic stress and other stress stimuli. Both rs1057293 and rs1743966 are not associated with CSC.

• **KEYWORDS:** central serous chorioretinopathy; mutation; polymerase chain reaction; serum glucocorticoid kinase gene-1
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INTRODUCTION

Central serous chorioretinopathy (CSC) is characterized by fluid accumulation underneath the neurosensory retina in the macular area with or without concomitant retinal pigment epithelium (RPE) detachment. Focal source of dye leakage into the detachment area is seen in fluorescein angiography. Although attacks are generally unilateral, RPE changes are often seen in fellow eye [1]. Additionally, it was demonstrated the increase in choroidal thickness not only in affected but also in unaffected eye [2]. These data suggest that CSC is diffuse, multifocal and a systemic disease.

Although exact pathogenesis of CSC is not completely understood, choroidal hyperpermeability at foci of subretinal fluorescein leakage is a frequent finding. But choroidal hyperpermeability secondary to choroidal ischemia also be found without associated fluorescein leakage, suggesting more generalized RPE or choroidal vascular disturbance[3-5].

The RPE has a very high capacity for removing subretinal fluid, even when it contains serum proteins. It has been shown that opening the tight junctions between RPE cells mechanically or with a toxin does not cause serous detachment experimentally, but rather allows fluid to leave the sub retinal space even more quickly because of intraocular pressure and choroidal osmotic pressure [6]. These data suggest that there is broad dysfunction of the RPE transport system in CSC that cause accumulation of fluid in the sub-retinal space, if a leakage occurs. The cause of such transport dysfunction still remains unknown, and may be secondary to underlying disease of the choroid and choriocapillaris.

The serum glucocorticoid inducible kinase gene-1 (SGK-1) was originally cloned as an immediate early gene transcriptionally stimulated by glucocorticoids and mineralocorticoid in rat mammary tumour cells. The human isoform has been explored as a gene up regulated by cell shrinkage. More recent studies showed the involvement of SGK-1 in the regulation of a variety of channels and transporters, such as the renal epithelial Na^+ channel EnaC; the voltage-gated Na^+ channel SCN5A; the K^+ channels ROMK1, KCNE1/KCNQ1 and Kv1.3; the Na^+/H^+ exchanger NHE3; and Na^+/K^+-ATPase[7-11].

Multifocal serous detachments can be induced in animals by long-term administration of systemic adrenalin and corticosteroids. Notably, CSC is actually worsened, by glucocorticoids. Systemic or local glucocorticoids are known risk factors for CSC and may be the presenting symptom of Cushing disease. However, the role of glucocorticoids in the pathogenesis of CSC remains unknown. Plasma cortisol levels are not usually elevated in patients with CSC [12,13]. Instead, the disorder may be caused by inappropriate activity of a downstream signalling element. SGK-1 is a signalling molecule downstream of glucocorticoid receptors. Thus, a SGK-1 gene variant leading to increased SGK-1 activity would trigger glucocorticoid actions without the need for stimulation by enhanced plasma glucocorticoid concentrations. Furthermore, SGK-1 which has an important role in many epithelial ion transport system may have a role in RPE pump function whose disturbance is one of the main mechanism in development of CSC. Based on this knowledge, we conducted a study to explore whether there is a relationship between SGK-1 gene and CSC.

SUBJECTS AND METHODS

Subjects Consecutive patients diagnosed with chronic CSC at the Ophthalmology Department of Antalya Educational and Training Hospital between August 2012 and August 2013 were enrolled. The study was approved by the ethics committee of our institution and an Institutional Review Board was obtained. It has been performed in accordance with the ethical standards laid down in the Declaration of Helsinki. The patients agreed to participate after explanation of the nature and possible consequences of the study and gave their informed consent prior to their inclusion in the study.

Thirty two chronic CSC patients and 32 healthy individuals were included in the study. Body mass index was calculated according to the World Health Organization guidelines[14]. All subjects underwent a complete ophthalmic examination including best-corrected visual acuity, slit-lamp biomicroscopy and dilated fundus examination. CSC was confirmed by fundus fluorescein angiography (FFA Visucam NM/FA, Carl Zeiss, Germany) and fundus autofluorescence. Neurosensory or RPE detachment was also evaluated by optical coherence tomography imaging (Cirrus HD-OCT Model4000, Carl Zeiss Meditec Inc, Dublin, CA, USA). Indocyanine angiography (Visucam NM/FA, Carl Zeiss, Germany) was applied to make definite diagnosis in doubtful cases.

Inclusion criteria for patients was chronic CSC (more than six months of symptoms) characterized by serous retinal detachment, RPE detachment or dysfunction without evidence of any other possible cause of fluid exudation, such as choroidal neovascularization, inflammation, infiltration or polypoidal choroidal vasculopathy. Exclusion criteria for both patients and controls were: concurrent ocular and retinal disease, history of coagulation abnormalities such as thromboembolism, pregnancy, congestive heart failure, diabetes mellitus, coronary artery disease, uncontrolled arterial hypertension, smoking, hyperlipidemia, cancer, autoimmune inflammatory diseases, renal and hepatic abnormalities, endocrine pathology, and concomitant treatment affecting fibrinolysis metabolism (such as glucocorticoids and oral contraceptives), drug and/or alcohol intake.

DNA Extraction and Sequencing From each group, to determine SGK-1 gene analysis 2 mL of whole blood was taken in EDTA tubes, and stored at 80℃. The DNA extraction was performed with MagNa Pure LC DNA Isolation System using MagNa pure LC DNA Isolation Kit (ROCHE, Mannheim, Germany). Polymerase chain reaction (PCR) primers were designed using the online Exon Primer Program (http://ihg.gsf.de/ihg/ExonPrimer.html). All primers are listed in Table 1.

PCR amplifications were performed with Qiagene HotStartTaq DNA Polymerase Kit (Qiagene, Hilden, Germany) using a standard application protocol of manufacturer's instructions in a total volume of 12 mL for 40 cycles. Each cycle consists of heating 10min at 95℃ and for the 40 times cycling of 15s at 95℃, 45s at specific Tm and 1min at 72℃ - as a last step 10min at 72℃ on a thermal cycler (Applied bio systems, Forester City, CA, USA). For the PCR cleanup Exouclease 1 and Schrimpalkalaen phosphatase purification protocol was applied. The cleaned PCR products were submitted for sequencing using a BigDyeTerminator v3.1 cycle sequencing Kit (Applied bio systems, Forester City, CA, USA). Then, sequenced products run on the Applied Bio systems AB3100 (Applied Bio Systems, Forester City, CA, USA). Mutation analysis and was performed using the Seqscape v2.7software package (Applied bio systems, Forester City, CA, USA).

Statistical Analysis We tested for differences in base-line characteristics; we used two-tailed Student's t-test for continuous variables and Pearson's Chi-squared test (χ^2) for discontinuous variables. A two-tailed P value of less than 0.05 ($P<0.05$) was considered statistically significant. All calculations were performed with SPSS statistical software (version 16.0; SPSS Inc., Chicago, Illinois, USA).

Table 1 The all PCR primers

Primer	5'-------->3'	PCR Product Size (bp)
SGK1_Exon 01_1-F	GATATGCACTAACCAGGCGG	202
SGK1_Exon 01_1-R	TCAGGCAAACATTCAAAAGC	
SGK1_Exon 02-F	CCCCAATAAACATCAAAGGG	490
SGK1_Exon 02-R	TGCTGTGAACTTAAAGCTGCTC	
SGK1_Exon 03-F	TTCAGCCTTGGAATCCTTTC	256
SGK1_Exon 03-R	CCAAACCTTGCCTTTGTGTAG	
SGK1_Exon 01_2-F	CGCAATGGGGAGAATAAATG	347
SGK1_Exon 01_2-R	ATGCCAAGTAACCCCAAATC	
SGK1_Exon 01_3-F	TGAAATGCAGATTGTACTTCTTCC	389
SGK1_Exon 01_3-R	GCCGCTCTGGGGAAGTG	
SGK1_Exon 01_4-04-F	GTAGCCGCCAGCAAACC	590
SGK1_Exon 01_4-04-R	GAAGAAGTCTTCGCCTTCCC	
SGK1_Exon 05-F	ACTTTTGATGTTGGTGTGCC	204
SGK1_Exon 05-R	AGGAATACTAACTGACTCCCTTACAG	
SGK1_Exon 06-07-F	CATCGTTTATGTTATAGATGTCTTCC	448
SGK1_Exon 06-07-R	TCAACTTGGCACCAACATTC	
SGK1_Exon 08-09-F	GATTCTGGAATGTTGGTGCC	616
SGK1_Exon 08-09-R	ACAGCCAGTGCTACGTCTCC	
SGK1_Exon 10-F	TGAACCTAAAATGCCTCTAATACC	283
SGK1_Exon 10-R	CATCTCTCTCTTGGAAGGCG	
SGK1_Exon 11-F	ATGTGTGGTCGTGGGATTG	233
SGK1_Exon 11-R	AAGCATGGGCTGTGTGAAG	
SGK1_Exon 12-13-F	CGAGCCTAATATTTATTGCCG	544
SGK1_Exon 12-13-R	GTATTCCTTCCAACCCTCCC	
SGK1_Exon 14-F	TCAAGATTTCCCTGTCCTGTG	308
SGK1_Exon 14-R	GGCTCCACCAAAAGGCTAAC	

RESULTS

The CSC patient group consisted of 26 males and 6 females who had a mean age of 44.72±9.23 (range 32-60y). Control group consisted of 24 male and 8 female healthy subjects with mean age of 42.8±8.75 (range 30-55y). Age, sex and body mass index did not differ significantly between two groups (P<0.05; Table 2).

As a result of the analysis with the program Seqscape v2.7 of the sequenced coding exons of SGK-1 gene, a new heterozygous allele Met 32 Val is determined in two patients (6.25%) in CSC patients group, which is located in the encoder region of the SGK-1 gene, was found to have an AG genotype frequency of 0.066 (HWE P=0.86; Figure 1).

Additionally rs1743966 (intronic) and rs1057293 (Asp335Asp) were observed in our study. In our study group, observed genotypes of rs1743966 were AA in 20 patients (6.25%), AG in 10 patients (31.25%) and GG in 2 patients (6.6%); (P=0.27 and HWE P=0.62). Rs1743966 was not associated with CSC (P=0.27). Rs1057293 was also in HWE (HWE P=0.70) and not associated with CSC (P=0.68). Genotypes of rs1057293 were CC in 28 patients (62.5%), CT in 4 patients (31.25%) and but not TT (0%) (Table 3).

DISCUSSION

In our study we identified a new polymorphism M32V in two CSC patients. The region of 1-60 amino acids is necessary for localization to the mitochondria [15]. It is known that the expression, localization and activity of the SGK-1, are regulated by multiple hormonal and environmental cause including cellular stress. Stress-induced SGK-1 localizes to the mitochondria, which permits access to physiologically appropriate mitochondrial interacting proteins and substrates. Cordas *et al* [16] concluded that the mitochondria matrix protein IF-1 is as a part of the cellular stress induced program is a new SGK-1 binding partner, which probably plays an important role in the cellular response to hyperosmotic stress and other stress stimuli that promote SGK-1 localization into the mitochondria. Oztekin *et al* [17] showed another mutation (Arg97Ile 1/28) in the SGK-1 in patients with transient tachypnea of the newborn.

On the other hand, we showed that rs1743966 and rs1057293 were in HWE and not associated with CSC. Even though Busjahn and Luft [18] had previously reported an association between two single nucleotide polymorphisms (SNPs rs1743966- rs1057293 and systolic blood pressure and diastolic blood pressure in German twins. It was confirmed these results in unrelated Caucasians[19]. The previous study of Dahlberg *et al* [20] showed the similar association between these two SNPS and ischemic stroke.

Table 2 Demographic characteristic of CSC patients and healthy controls group

Parameters	CSC Patients	Control	*P*
Mean age ±SD	44.72±9.23	42.8±8.75	0.642
Gender (F/M)	6/26	8/24	0.576
Mean BMI (kg/m^2) ±SD	24.0±2.7	24.7±2.4	0.234

F: Female; M: Male; BMI: Body mass index.

Table 3 Observed of rs1743966 (intronic) and rs1057293 (Asp335Asp) were listed

Parameters	Groups	Genotype, *n* (%)			MAF	Global MAF	HWE (*P*)
		AA	AG	GG			
Met 32 Val	CSC patients	30 (93.75)	2 (6.25)	0	0.03	0	0.86
	Control	32 (100)	0	0	0		-
		AA	AG	GG			
Rs1743966	CSC patients	20 (62.5)	10 (31.25)	2 (6.25)	0.22	0.23 (23)	0.62
	Control	24 (75)	8 (25)	0	0.12		0.41
		CC	CT	TT			
RS1057293 (Asp335Asp)	CSC patients	28 (87.5)	4 (12.5)	0	0.06	0.11 (11)	0.70
	Control	29 (90.6)	3 (9.3)	0	0.05		0.78

Global minor allele frequency (MAF): dbSNP is reporting the minor allele frequency for each rs included in a default global population. Since this is being provided to distinguish common polymorphism from rare variants, the MAF is actually the second most frequent allele value (www.ncbi.nlm.nih.gov/projects/SNP/); HWE: Hardy-Weinberg equilibrium.

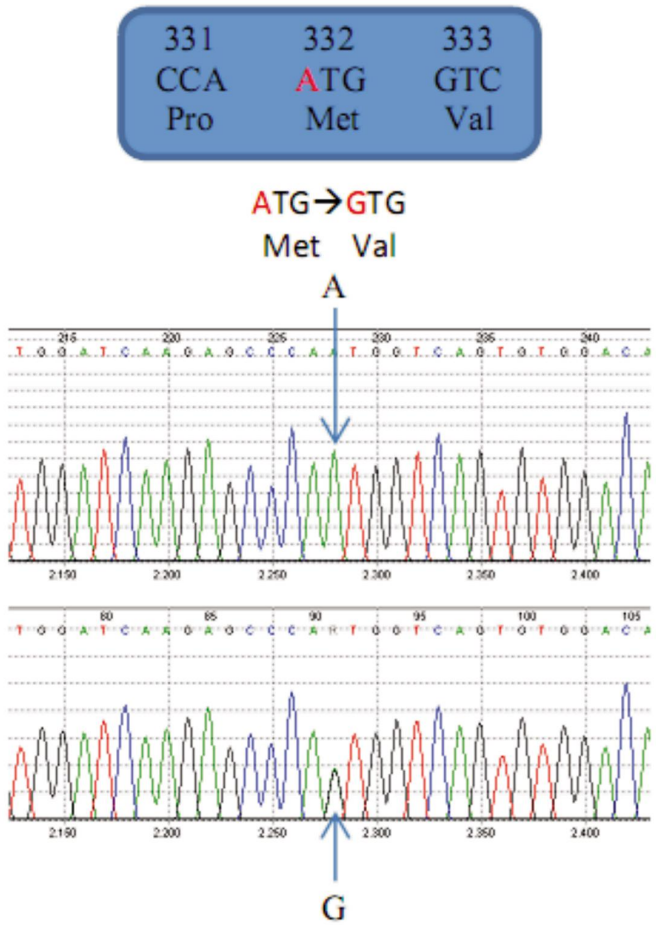

Figure 1 The new heterozygous allele Met 32 Val was found to have a AG genotype.

The study published by Iijima *et al* [21] noticed that the abnormality of the choroidal circulation in CSC seems to be analogous to the angiographic abnormality in the retinal circulation of branch retinal vein occlusion. This was also supported by the case report of a patient with coexistent branch retinal vein occlusion and CSC both probably due to anti phospholipid antibody syndrome [22]. Iijima *et al* [21] also demonstrated the increased plasminogen activator inhibitor (PAI-1) concentrations in patients with CSC and hypothesized that the choroidal hyper permeability was a result of thrombotic occlusion of choroidal vessels. Accordingly in the literature there have been several reports that focused on the thrombotic mechanism in the pathogenesis of CSC [23-25]. More recently, Sari *et al* [26] also showed the increased PAI concentration in patients with CSC and they hypothesized that CSC patients could have genetic predisposition to thrombosis. SGK-1 stimulates coagulation by stimulating tissue factor expression and increases the reagibility of blood platelets by up-regulation of NFκB and subsequent expression of the platelet Ca^{2+} channel Orai1/STIM1 [27]. Enhanced coagulation and platelet reagibility predispose to the occurrence of thrombosis. When this knowledge was taken into account CSC may be associated with SGK-1 gene polymorphism.

Several risk factors for development of CSC were described in the literature as male gender, glucocorticoid use, smoking, type A personality, disorders with increased endogenous steroids and hormones [23-29]. Additionally, psychological disorders were suggested among them. Higher levels of emotional distress and alexithymia in CSC patients have been reported in a previous study [30]. The proneness to stress is suggested to be a predisposing factor for the development of CSC. A recent study showed poorer quality of life and higher psychological problems in acute CSC patients [31]. Furthermore, Fok *et al* [32] conclude that a history of psychiatric illness is associated with an increased risk of CSC

recurrence. Recently, Anacker *et al* [33] analyzed SGK1 gene expression in the peripheral blood of drug-free depressed patients, and in the hippocampus of rats exposed to unpredictable chronic mild stress or prenatal stress. They found that expression of SGK-1 in both models increased. When we look in this aspect we can see that there is possibility of association between CSC and SGK-1 gene.

A previous study showed us that mineralocorticoid receptors are effective in the development of serous chorioretinopathy in human beings and animals. Furthermore, it is reported that the MR antagonist epleronon was effective in treatment of 2 chronic CSC patients and it is also reported that it is not relapsed in six months treatment [34]. In another study, 13 patients with chronic CSC, the treatment is started with 25 mg of epleronon per day in a week and then it is continued with 50 mg of epleronon per day for 3mo and it is reported that the central macular thickness decreased and the vision increased (on 13 patients with chronic CSC [35]. However, on 3 patients it wasn't seen an evident effect on central macula thickness. One of the reasons of epleronon which is affective on CSC patients might be that it has inhibitory effect on SGK-1[36].

There are a lot of studies which show us the togetherness of CSC with gastroesophageal reflux disease, obstructive sleep apnea, sleep disorder, Helicobacter pylori infection [37-41]. Recently, Rao *et al* [42] studied with 113 patients with CSC and they showed that there is a meaningful relation with chronic CSC. Chronic CSC has only a statistical relationship with hypertension. It is shown that SGK has an important role in the development of hypertension both keeping (retention) water and sodium in the body and regulating the water and salt appetite [42]. When we take this into account, it might be thought that SGK-1 assists in the development of CSC. It is important to understand gene polymorphisms in CSC. Recently, Miki *et al* [43] identified a novel association between CSC and common complement factor H (CFH) gene polymorphisms.

Having a small patient population and having neglected the serum SGK-1 level might be a weakness of our study & the weak side of our study. Despite this, 2 of the 32 patients have a non-identified mutation of the SGK-1 gene and this will be hindsight to the understanding of the pathogenesis and will lead to a new therapeutic target. A greater patient's population with testing the SGK-1 gene levels is needed in further studies.

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2) Drafting the article or revising it critically for important intellectual content: Mahmut Akyol, Muhammet Kazım Erol and Ozdemir Ozdemir.

3) Final approval of the version to be submitted: Ozdemir Ozdemir.

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