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Detection of the 5HT2C polymorphism in myocardial infarction and cardiovascular event patients

Miyokard infarktüsü ve kardiyovasküler olay geçiren hastalarda 5HT2C polimorfizminin saptanması

İbrahim Açıkbaş, Ayşen Buket Er Urgancı, Dursun Dursunoğlu, Asuman Kaftan

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Abstract

Purpose: Deaths from cardiovascular (CV) disease are prevalent worldwide. Genetics, environment, nutritional habits, and lifestyle are major factors in the etiology of Coronary artery disease (CAD). Certain genes (that play roles in lipid, homocysteine, glucose metabolism, renin-angiotensin, fibrinolytic, and inflammation systems) have been found in association with CAD by genome-wide association studies. The present genes are not important for direct and independent prediction. A recent study on the rs6318 polymorphism of the serotonin receptor 2C (5HT2C) gene in the prediction of CAD and myocardial infarction (MI) can meet the expected criteria. The aim of our study is to determine the predictive and risk alleles of the rs6318 polymorphism of the 5HT2C gene by comparing healthy subjects with patients diagnosed with MI and CAD.

Materials and Methods: The study consisted of two groups: 142 patients and 100 controls. DNA was isolated from venous blood and "melting curve genotyping" analysis was performed.

Results:GC genotype was 4.9% in the case group and 27% in the control group. The GC genotype is protective against CV disease (p=0.01). In addition, the observation that no GC genotyped subjects were diagnosed with MI suggests that the GC genotype is protective for MI in our study. Also, among cases with MI, it was found that only 1 patient (0.9%) was CC homozygote, while there were 12 patients (11%) that were C hemizygotes.

Conclusion: The results suggest that the C allele has a protective effect against CV diseases, although no clear statistical significance is found.

Key Words: 5HT2C, myocardial infarction, coronary artery disease, polymorphism, cardiovascular.

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Özet

Amaç: Kardiyovasküler hastalıklardan (KV) ölümler dünya genelinde ilk sırada yer almaktadır. Etiyolojide genetik, çevre, beslenme ve yaşam tarzının etkileri bulunmaktadır. Genom tarama çalışmaları, koroner arter hastalıklarıyla (KAH) ilişkili çeşitli genler (Lipid, homosistein, glukoz, metabolizmaları, renin-anjiyotensin, fibnolitik, inflamasyon sistemlerinde rol alan genler) ortaya çıkarmıştır. Bunların arasında tek başına direk ve bağımsız bir prediktif faktör olarak öne çıkan yok gibidir. Son zamanlarda yapılan bir çalışmada 5HTR2C genine ait rs6318 polimorfizminin, KAH ve miyokard infarktüsü (Mİ) riskini belirlemede beklenen özellikleri karşılayabileceği ortaya çıkmıştır. Çalışmamızın amacı Mİ ve KAH tanısı alan hastalarda 5HTR2C genindeki rs6318 polimorfizmini belirlemek ve sağlıklı bireylerle karşılaştırarak koruyucu ve riskli allelleri tespit etmektir.

Gereç ve Yöntem:Çalışmamız 142 hasta ve 100 kontrol olmak üzere iki gruptan oluşmaktadır. Venöz kandan DNA izolasyonu yapıldı ve 'erime eğrisi genotiplemesi' analizi gerçekleştirildi.

Bulgular: GC genotipi, olgu grubunda %4,9, kontrol grubunda %27 idi. GC genotipi, KV hastalığına karşı koruyucu olarak bulundu (p=0,01). Ek olarak, GC genotipli deneklere Mİ tanısı konmadığı gözlemi, çalışmamızda GC genotipinin Mİ için koruyucu olduğunu düşündürdü. Ayrıca Mİ'li olgularda sadece 1 hastanın (%0,9) CC homozigot olduğu, 12'sinde (%11) ise C hemizigot olduğu saptandı.

Sonuç:C allelinin belirgin bir istatistiksel anlamlılık olmamasına rağmen, KV hastalıklarına karşı koruyucu bir etkiye sahip olduğunu göstermektedir.

Anahtar Kelimeler: 5ht2c, miyokard infarktüsü, koroner arter hastalığı, polimorfizm, kardiyovasküler.

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İbrahim Açıkbaş, Prof. Dr. Pamukkale Üniversitesi Tıp Fakültesi Tıbbi Biyoloji Anabilim Dalı, DENİZLİ, e-mail: iacikbas@pau.edu.tr (orcid.org/0000-0001-7483-1147) (Sorumlu yazar)

Ayşen Buket Er Urgancı, Arş. Gör. Dr. Pamukkale Üniversitesi Tıp Fakültesi Tıbbi Biyoloji Anabilim Dalı, DENİZLİ, e-mail: aber@pau.edu.tr (orcid.org/0000-0002-5339-3835)

Dursun Dursunoğlu, Prof. Dr. Pamukkale Üniversitesi Tıp Fakültesi Kardiyoloji Anabilim Dalı, DENİZLİ, e-mail: ddursunoglu@pau.edu.tr (orcid.org/0000-0002-5232-7078)

Asuman Kaftan, Prof. Dr. Pamukkale Üniversitesi Tıp Fakültesi Kardiyoloji Anabilim Dalı, DENİZLİ, e-mail: akaftan@pau.edu.tr (orcid.org/0000-0002-5073-7348)

Introduction

Deaths from coronary artery disease (CAD) are the most common in the world and in our country [1-3]. CAD etiology is multifactorial [4]. Physiological factors for the development of CAD include dyslipidemia (DL), hypertension (HT)/ renin-angiotensin system, metabolic syndrome, diabetes, obesity, and the fibrinolytic system. Family history and environmental factors such as nutrition, sedentary lifestyle, work, and stressful life come to the forefront. When we look at the genetic component, although there are several variants closely related to CAD, there is no gene directly responsible for CAD [4, 5].

In order to elucidate the genetic etiology of CAD, mutations and polymorphisms were screened for in various genes (LL6, CRP, APOE, NOS, ACE, CYPs, MTHFR, PAI-1, HSP70, and MYBPC3) and different study groups achieved different results in different ethnic groups [5, 6]. However, their effects on increasing the risk of CAD alone are small and controversial. Various formulas have been developed to determine the genetic factors associated with CAD. One of the formulas is the total genetic risk burden, a multi-locus genetic risk score (mGRS) analysis and evaluation of all the markers together. In this way, the total/combined/compound risk coefficient is increasing [7-11]. It turns out that there is a great need to make risk estimation directly and simply with a single genetic parameter (Gne/ polymorphism/marker). To make a genome-based prediction of cardiovascular (CV) disease, it is necessary to identify more genetic variants with significant effects on CAD risk [12, 13]000 individuals with a 10-year CHD incidence of 10%. For each combination of model parameters (number of variants, genotype frequency and odds ratio [OR].

In a recent study, serotonin receptor 2C (5HT2C) is described as a new independent predictor of CAD and myocardial infarction (MI) and an independent predictor of morbidity for patients [14]. 5HT2C is involved in the stress response. 5HT2C mRNA shows alternate splicing and editing specific to the tissue, which determines the shape and level of the stress response.

The purpose of this study is to determine the rs6318 polymorphism in the 5HT2C gene in patients with CAD and MI and compare with healthy subjects. Besides that, we aim to detect protective and risk alleles to find out whether the rs6318 polymorphism of the 5HT2C gene is an independent marker of CAD and MI.

Materials and methods

Subjects

Patients and control groups were composed of individuals who underwent angiography and were grouped according to the results of angiography. Written informed consent was obtained from individuals prior to their inclusion in this work.

The study consisted of two groups: 142 Patients and 100 controls. The case group consisted of individuals with one or more coronary vessels, 40% and over obstructed, and have stents, balloons, etc., according to coronary angiography results. The control group was selected from those without obstructed vessels, no more than 30% obstruction, no stent, balloon, etc. [included in the control group in anatomical variation (bridge) individuals with coronary vessels open]. Participants diabetes, HT, DL, triglycerides (TG), total cholesterol (TK), low-density lipoprotein (LDL), high-density lipoprotein (HDL) information were recorded.

In the case group, there were 44 females and 98 males, while the control group consisted of 54 females and 46 males. The mean age was 64.21±11.73 years and 59.22±12.02 years in case and control groups, respectively.

Polymorphism Assay

DNA was isolated from venous blood with a High Pure PCR Template Preparation Kit (Roche) performed according to manufacturer's instructions. Polymorphism was assayed using a LightCycler® FastStart DNA Master HybProbe (Roche) kit. Primers and probes with F1: TGATCCATGAAGAAGCAGTTGTT, R 1 : C T G G G A A T T T G A A G C G T C , FL:CTATTGGTTTGGCAATCTGAT-FL-3',LC:5'-LC-640TTCTGTGAGCCCAGTAGCAGCTATAG TAACT-Ph-3 sequences were diluted according to the user's manual and reactions were performed

In LightCycler 480 software, Tm (Melting temperature) was made in calling mode and was checked whether all the cases were different. The samples with different Tm were identified as

GG, CC, and GC genotypes. Afterward, "melting curve genotyping" analysis was performed, and these allele groups were determined for each sample.

The genotypes obtained by melting curve analysis from real-time genotyping results were confirmed by the classical PCR-RFLP (Polymerase Chain Reaction-Restriction Fragment Length Polymorphism method. For this, four samples with genotypes GG, GC, and CC according to the melting curve analysis were randomly selected.

The reaction was prepared in a total volume of 50 µl using 150 ng gDNA, 10 pmol primers, and 1× Master Mix (Genaid). PCR was performed using primers F: TGATCCATGAAGAAGCAGTTGTT, R: CTGGGAATTTGAAGCGTC in a thermal cycler (Hybaid PCR-Sprint). The amplification products (208 base pair) were checked by electrophoresis. A total of 10 µl PCR product was digested with 1 U BrsDI (NEB) at 65°C/20 minutes. The results showed that genotype GG has one cutting site to produce two bands (128 bp, 80 bp) and genotype GC has two cutting sites to produce three bands (208 bp, 128 bp, and 80 bp) and genotype CC has no cutting site, thus only a single band (208 bp) was observed.

Statistical Analysis

Relationships between demographic, clinical, and genotype parameters of the cases were tested. Chi-square test was applied when relations between categorical variables were determined.

Since diabetes, HT, DL were etiologic and comorbid diseases contributory to CV diseases, regression analysis was used on both these diseases and the effects of rs6318 on CV disease. Statistical significance was determined as $p \leq 0.05$.

Results

There was a statistically significant difference between the age of the case and control groups (p=0.001). The mean age±SD for patients and controls were 64.22±11.73 and 59.22±12.03, respectively. However, there was no significant difference between the genders (p>0.05).

Clinical Parameters and Comorbid Disease Analysis

The number of individuals with diabetes in the control group was 21 (21%) and 49 (34.5%) in the case group, and the difference between the groups was statistically significant (p=0.03).

Regarding the presence of HT, there were 56 individuals (56%) in the control group and 71 individuals (50%) in the case group (p>0.05).

Regarding the presence of DL, there were 20 individuals (20%) in the control group and 30 individuals (21.1%) in the case group (p>0.05).

However, when the clinical parameters were compared according to gender in the case and control groups, significant differences were found between diabetes and DL comorbidities in male individuals. In male patients, Diabetes was found in 37.7% of male patients, whereas, 15.2% of control group males had diabetes (p=0.011). Also, DL was found in 25.5% of male patients, while 10.9% of control group males had DL (p=0.049).

rs6318 Polymorphism Analysis

5HT2C gene located in X-chromosome q23 and men are hemizygous for genotypes. The genotype distributions in the case and control groups were all in Hardy-Weinberg equilibrium.

Also, allele frequencies between case and control groups were compared and the frequency of the G allele was higher in the case group (Table 1).

When the genotype frequencies in the case and control groups were compared, the GG genotype was found in 24.7% of the case group and in 26% of the control group. The CC genotype was found in 1.4% of the case group and in 10% of the control group, while the GC genotype was found in 4.9% of the case group and in 27% of the control group. GC genotype was found to have a relatively high frequency in the control group. The G- genotype was found in 54.9% of the case group and in 35% of the control group, and the C- genotype was found in 14.1% of the case group and in 11% of the control group. Regression analysis by removing the effects of age and diabetes showed that the GC genotype is protective against CV disease (OR:0.179, 0.067-0.473, CI:0.95, p=0.01).

Table 1. Allele frequencies between case and control groups.

Group		Allele* G	Allele* C	Total	*p*
Control	**Count**	114	40	154	**0.036**
	Frequency	0.740	0.260	1	
Case	**Count**	155	31	186	
	Frequency	0.833	0.167	1	

*5HT2C is an X-linked gene.

Myocardial Infarction Analysis

In the case group, 33 subjects (23.2%) had MI while 109 subjects (76.8%) subjects did not have MI (p>0.05)

Also, it was found that the average age of individuals experiencing MI was older than those that did not experience MI (p=0.003), the mean age±SD were 62.63±11.44 and 69.45±11.30, respectively.

When the clinical parameters of cases with MI were analyzed, there was a significant correlation of MI with HT (p=0.003) and diabetes (p=0.05) comorbidities (Table 2 and 3).

There is no GC genotype in cases with MI. This suggests that the GC genotype is protective for MI, which would the “end point” for CAD (Table 4).

Table 2. Relationship between MI (Myocardial Infarction) and HT (Hypertension).

MI		HT HT negative	HT HT positive	Total	*p*
None	**Count**	62	47	109	**0.003**
	%	56.9	43.1	100.0	
Present	**Count**	9	24	33	
	%	27.3	72.7	100.0	
Total	**Count**	71	71	142	
	%	50.0	50.0	100.0	

Table 3. Relationship between MI (Myocardial Infarction) and DL (Dyslipidemia).

MI		DL DL negative	DL DL positive	Total	*p*
None	**Count**	90	19	109	**0.05**
	%	82.6	17.4	100.0	
Present	**Count**	22	11	33	
	%	66.7	33.3	100.0	
Total	**Count**	112	30	142	
	%	78.9	21.1	100.0	

Table 4. Genotype relationship of MI (Myocardial infarction) status.

			Genotype					Total
			GG	GC	CC	G	C	
MI	None	Count	28	7	1	61	12	109
		%	25.7	6.4	0.9	56.0	11.0	100.0
	Present	Count	7	0	1	17	8	33
		%	21.2	0	3.0	51.5	24.2	100.0
Total		Count	35	7	2	78	20	142
		%	24.6	4.9	1.4	54.9	14.1	100.0

Discussion

According to the Turkish Adult Risk Factor (TARF) study (1990-2014), the death rate due to CAD is 7.64 per 1000 in males per year and 3.84 per 1000 in females per year in Turkish patients [15]. While the general prevalence of CAD is 3.8%, the age-related prevalence is over 12% in Turkey [16].

Genetic markers of CAD are usually related to markers such as fibrin, fat, carbohydrate metabolism, and certain comorbid diseases such as HT, diabetes, and metabolic syndrome (MS) [17]. For this reason, CAD has multifactorial pathophysiology and genetic characteristics. Since physical pathology in coronary arteries is apparently atherosclerosis, researchers are usually focused on lipid metabolism and vascular atheroma formation.

The triggering and actualization of CV events leading to mortality, such as MI, at the site of the vascular-atherosclerotic component is the risk associated with physical and psychological stress and stress physiology.

Although familial hypercholesterolemia, which is an inherited autosomal dominant disorder, is associated with 14 variants of CAD, estimating low value in risk analysis tests. In the Greek-EPIC study, which is relatively close in terms of geographical and lifestyle, combined genetic risk score (GRS) was found to be high for 9 genetic markers (PCSK9, CELSR2-PSRC1-SORT1, MIA3, WDR12, PHACTR1, CXCL12, LDLR, SCL5A3-MRPS6, KCNE2, and 9p21) [18].

The addition of new biomarkers to the classical risk calculation has led to an increase in the work done in recent years. The American Heart Association (AHA) has introduced new proposals and work plans that suggest the inadequacy of the existing combination formula [19] Marrugat et al. [20] suggest that this high rate of CAD patients in low and moderate risk groups indicate that Framingham criteria are not sufficient to identify risk accurately and need new and effective markers.

Given the genetic marker study conducted in China, it is thought that myocyte enhancer factor-2A (MEF2A, transcription factor) gene may be an independent marker for CAD in the Chinese population [21]a mutation in the human myocyte enhancer factor-2A (MEF2A.

Like other members of the serotonin receptor gene family, 5HT2C exhibits alternate tissue and individual splicing and editing processes. Its manifestations in life and in the clinic lead to unusual differences in responses to psychiatric disorders and drugs [22-25]. While 5HT2C has direct physiological effects in CAD and MI, some variants of 5HT2C (rs6318, rs498207, rs3813928, and rs3813929) have an indirect contribution to weight gain [26]. On the contrary, in another study with healthy individuals, rs6318, Ser23C, and rs3813929 -759 T variants were found to be more frequent in women with low body mass index (BMI<20) [27]and 2 single nucleotide polymorphisms in this gene (HTR2C.

After the first study of serotonin receptors on insulin metabolism [28], Brummett et al. [14] published the second study that identifies 5HT2C as a new and powerful marker for CAD and MI in the literature for the first time. Its reported that the rs6318 polymorphism (68C, Ser23) of *5HT2C* gene has a high risk for CAD and the Ser23C variant is reported to have an independent and strong predictive value for CAD, MI, and patient morbidities in this study.

242 subjects in our study is consistent with Brummett et al. [14] regarding clinical parameters, such as history of MI, and the CAD rates that increases with history of diabetes. Brummett et al. indicated that males hemizygous for Ser23C and females homozygous for Ser23C allele had an increase in cardiovascular disease event (death and/or MI) risk compared to those with other rs6318 genotypes. On the contrary, our regression analysis concluded that the GC genotype is protective against CAD.

Furthermore, patients with MI, males hemizygous for Ser23C were 12 (11%), females homozygous for Ser23C allele was only 1 (0.9%) and the lack of the GC genotype in MI cases shows that the C allele can be protective agaist myocardial infarction.

In conclusion, the rs6318 polymorphism of 5HT2C might have a protective effect against CV diseases and MI, which should be supported by large-scale studies.

Conflict of Interest: The authors declare that there is no conflict of interest.

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