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I/D Polymorphism of the ACE Gene in Kazakh Origin Patients with Mitral Heart Disease

Mitral Kapak Hastalığı Olan Kazak Orjinli Olgularda ACE Geninde I/D Polimorfizmi

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ABSTRACT

Purpose: Purpose of study is to reflect the characteristics of the comparative between Kazakh nationality in patients with mitral heart disease, healthy people and literature data of the ACE gene I/D polymorphism

Material and Methods: Total of 138 individual were included in our study. Of these, 70 were patients with mitral valvular disease (42,83 ± 1,06 years) and 68 were healthy (40,24 ± 0,87 years). All subjects were of Kazakh origin and was not involved with each other in terms of kinship.

Result: 70 patients and 68 healthy people, all of whom were Kazakh origin, were genotyped for I/D polymorphism of ACE gene. In healthy individuals, the frequency of carriers having only genotype II was 35,29% (n = 24), only ID was 50,00% (n = 34), and only DD genotype was 14,71% (n = 10). Among patients with mitral valvular disease the heart rate of people with carriers II genotype was only 25,72% (n = 18), only the ID genotype carriers were 61,43% (n = 43), and DD genotype were 12,86% (n = 9) . I allele frequency equal to 56,50% (n = 79), D alleles - 43,60% (n = 61). Differences between the frequency distribution of genotypes in patients compared to healthy individuals were insignificant. I allele frequency in all healthy individuals was 60,30% (n = 82), D allele - 39,70% (n = 54), patients with mitral valvular disease were - 56.50% and 43.60%, respectively. Difference in distribution of alleles of the ACE gene was also not reliable. The frequency distribution of genotypes and alleles of the ACE gene we have studied was comparable with the data distribution of healthy Kazakhs and Kazakhs population from other authors, as well as Kazakhs living in Xinjiang province in China.But, our data on the genotypes and alleles did not differ significantly from those of the Uighurs, Yakuts, Hindus. The difference of the frequency distribution of genotypes and alleles of our data was with the Czechs, Greeks, British, Turks, and alleles, which was statistically significant

Conclusion: Thus, the results of a study of the frequency distribution of genotypes and alleles of the ACE gene in Kazakhs - healthy individuals and patients with mitral valvular disease significant differences between them are not identified, and the results are depended on the distribution of ethnicity. The data obtained from healthy Kazakhs were comparable to published data from other researches including Kazakhs people, e.g. Kazakhs living in Xinjiang province in China, Uighurs, Yakuts, Hindus, which is statistically significantly different from the Uzbeks, Turks, Czechs, English, and Greeks. Few reference data on the ACE gene polymorphism in patients with mitral valvular disease does not allow for statistical comparison of our data in Kazakhs patients with data of world literature.

Key Words: I/D polymorphism of the ACE gene, mitral valvular heart disease, gene polymorphisms of the RAS, the frequency distribution of genotypes and alleles.

ÖZET

Amaç: Mitral kalp hastalığı olan Kazak milliyet hastalarda, sağlıklı insanlar ve literatür verileri ile ACE gen I / D polimorfizminin karşılaştırılmalı karakteristiğini yansıtmak.

Materyal ve Method: Çalışmamıza toplam 138 birey dahil edildi. Bunların 70'i (42,83±1,06 yaşlarında) mitral kapak hastası iken 68'i sağlıklıydı. Birbiriyle arkaba olmayan 138 bireyin hepsi Kazak kökenliydi.

Bulgular: 70 hastanın ve 68 sağlıklı bireylerin hepsi Kazak kökenliydi ve ACE geni I/D polimorfizmi için genotiplendirildiler. Sağlıklı bireylerde, taşıyıcıların genotip II frekansı %35,29 iken (n:24), genotip ID frekansı %50 (n:34) ve DD genotip frekansı ise %14,71 (n:10) idi. Mitral kapak rahatsızlığına sahip bireyler arasında, taşıyıcıların genotip II oranları %25,72 (n:18), genotip ID %61,43 (n:43) iken genotip DD frekansı %12,86 idi. I allel frekansı %56,50 (n: 79), D allel frekansı ise %43,60 (n: 61) idi. Hastalarda ki genotiplerin frekans dağılımı sağlık bireylere nazaran daha önemsizdi. Sağlıklı bireylerde I allel frekansı %60,30 (n: 82), D alleli %39,70 (n: 54) idi. Mitral kapak hastalarında ki oranlar ise sırasıyla %56,50 ve %43,60 idi. ACE gen allellerin bu dağılımlarında ki farklılık aynı zamanda anlamlı değildi. Çalıştığımız ACE gen allelleri ve genotiplerin dağılım frekansları, Çin'in Xinjiang ilinde yaşayan Kazakların yanı sıra sağlıklı Kazaklar ve diğer araştırmacıların dahil ettiği Kazak populasyonlarına göre karşılaştırıldı. Bizim verilerimizde ki alleller ve genotipler Uygur, Yakuts, Hindu populasyonlarından çokta farklı değildi. Ancak; Türk, Çek, İngiliz, Yunan populasyonlarına göre aralarında istatistiksel olarak anlamlı bir fark vardı

Sonuç: Böylece; Kazaklar da ACE gen allelleri ve genotiplerinin dağılım frekansları üzerine yapılan çalışmamızın sonuçlarına göre, sağlıklı bireyler ve nitral kapak hastaları arasında önemli farklılıklar belirlenmedi. Ancak; etnik kökene göre farklılık gösterdiği bulundu. Sağlıklı Kazaklardan elde edilen veriler, diğer araştırmacıların çalışmalarına dahil ettiği Kazak populasyonlarına göre, Çin'de yaşayan Kazaklara göre, Uygur, Yakut, Hindu populasyonlarına göre ve Kazak populasyona göre aralarında istatistiksel olarak önemli fark olan Özbek, Türk, Çek, İngiliz ve Yunan populasyonlarına göre karşılaştırıldı. Mitral kapak hastalığı olan hastalarda ACE gen polimorfizmi ile ilgili birkaç referans veri, bizim Kazak hastal verilerinin istatistiksel olarak karşılaştırmasına izin vermez.

Anahtar Kelimeler: ACE geninin I/D polimorfizmi, Allellerin ve genotiplerin frekans dağılımları, Mitral kapak kalp hastalığı, RAS'ın gen polimorfizmleri

INTRODUCTION

Genetic predisposition to the development of various diseases is currently a mostly accepted concept but the mechanisms and putative candidate genes are not exactly understood. For instance, in a study made by Taiwanese scientists Chou HT. et al. (2004) about the RHD, a significant difference was found between the frequency distribution of genotypes C-509T gene polymorphisms T869S and TGF-beta1 in patients with rheumatic heart disease ($p < 0.0001$)[1]. Currently, the genetic aspects of the RAS gene in several pathologies are of great importance. Since it is the gene that determines the structure of the encoded proteins, the RAS gene polymorphisms may affect the function of the RAS in various diseases.

ACE human gene is located on chromosome 17q23[2]. I / D polymorphism of the ACE gene in intron 16, due to the presence of Alu-repeat, has 287 base pairs[3]. Its presence defines I allele and absence of D allele. Accordingly, I/D polymorphism of the ACE gene determines the presence of three genotypes: homozygotes II, heterozygotes and homozygotes, ID and DD, respectively. Studies have shown that the DD genotype and D-allele of the ACE gene are associated with a higher functional activity of circulating ACE and control up to 44% of the variability of circulating levels of ACE[4].

According to the references, the RAS gene polymorphisms may influence the development of various cardiac valvular lesions.

Thus, Turkish researchers Ertas F.S. et al (2007) showed that the I / D polymorphism of the ACE gene may be associated with severe calcification of the aortic valve, which is not associated with rheumatism, while the frequency of II genotype in these patients was significantly reduced[5].

In a study made by Ozisik K. et al (2004) in 50 patients with rheumatic fever frequency of MHD II and DD homozygotes ACE gene polymorphism was 60%, whereas in healthy subjects it was 74%, which is in favor of a interaction between the I / D genotype of the ACE gene and rheumatic MHD[6]. In this article, an association between the AT1R gene polymorphisms and ATG MHD was also confirmed.

Davutoglu V., Nacak M., (2005) studied the frequency distribution of genotypes of I / D polymorphism of the ACE gene in 82 patients with MHD rheumatism, and they found that the frequency of II genotype of the ACE gene was higher in patients compared to 154 healthy persons[7].

Atalar E. et al (2003) aimed to determine how much I / D polymorphism of the ACE gene is associated with the development of valvular heart damage as a result of an attack of rheumatism[8]. The study included 165 patients, who had been exposed to verified diagnosis of rheumatic fever between the years 1975-1988. Results showed that healthy heart valves were found in 39 patients, and in 126 patients showed a confirmed valvular heart disease. In both group of patients with and without heart disease, baseline clinical characteristics of signs of the initial manifestation of rheumatic fever were identical and therefore could not affect the prediction of valvular heart disease. In patients with valvular heart disease, the presence of DD genotype of the ACE gene is likely more important than patients, in whom a valve defect, after the initial attack of rheumatic fever, has not developed ($p = 0.02$) and for the development of heart defects DD genotype was 2,7 (CI 95% 1,15-6,50) .The authors found no difference frequency distribution of genotypes of the ACE gene by comparing patients with different localization of rheumatic: patients with isolated MPS compared with patients which had involved the aortic valve.

RAS gene polymorphisms may play a role in the development of the clinical symptoms of the RHD. Davutoglu V., Nacak M., Turkey (2005) investigated the effect of ACE gene polymorphism on clinical and echocardiographic indices. The authors found that a genetic predisposition to the CPF was significantly lower in patients with DD genotype of ACE gene. The relationship between the ACE gene polymorphism and the severity of mitral defect, degree of mitral regurgitation and left atrial diameter were detected. A higher degree of mitral valve calcification was associated with significantly higher incidence of II genotype ID genotype compared to DD genotype. Thus, II genotype was associated with a higher risk of more severe calcification of the mitral valve.

In this regard, the purpose of this study was to determine the I / D polymorphism of the ACE gene in patients with Kazakh origin; with regards to mitral heart disease in comparison with healthy and with the data of world literature

Material and methods. Total of 138 individual were included in our study. Of these, 70 were patients with mitral valvular disease (42,83 ± 1,06 years) and 68 were healthy (40,24 ± 0,87 years). All subjects were of Kazakh origin and was not involved with each other in terms of kinship. The survey was conducted on the basis of a manual "Methods of mapping survey of patients with cardiovascular disease, diabetes and cerebral blood flow in order to conduct research" approved by the Ministry of Health of the Republic of Kazakhstan dated May 11, 2005.

The result of the study. 70 patients and 68 healthy people, all of whom were Kazakh origin, were genotyped for A/G polymorphism of AT2R gene. The distribution of genotypes and alleles of the ACE gene in healthy individuals and patients with mitral valvular disease are presented in Table 1.The frequency distribution of genotypes and alleles of the ACE gene in Kazakhs - healthy individuals and patients with mitral valvular disease.

Table 1.

	Healthy (n=68)		Sick (n=70)		χ2, p
	n	%	n	%	
Genotypes					
II	24	35,29	18	25,72	χ2=1,933, p=0,380
ID	34	50,00	43	61,43	
DD	10	14,71	9	12,86	
Alleles					
Iallele	82	60,30	79	56,50	χ2=0,280, p=0,590
D allele	54	39,70	61	43,50	

In healthy individuals, the frequency of carriers having only genotype II was 35,29% (n = 24), only ID was 50,00% (n = 34), and only DD genotype was 14,71% (n = 10).

Among patients with mitral valvular disease the heart rate of people with carriers II genotype was only 25,72% (n = 18), only the ID genotype carriers were 61,43% (n = 43), and DD genotype were 12,86% (n = 9) . I allele frequency equal to 56,50% (n = 79), D alleles - 43,60% (n = 61).

Differences between the frequency distribution of genotypes in patients compared to healthy individuals were insignificant (χ 2 = 1.933, p = 0.380).

I allele frequency in all healthy individuals was 60,30% (n = 82), D allele - 39,70% (n = 54), patients with mitral valvular disease were - 56.50% and 43.60%, respectively. Difference in distribution of alleles of the ACE gene was also not reliable (χ 2 = 0.280, p = 0.590).

The results of the frequency distribution of genotypes and alleles of the ACE gene in our study were comparable to the literature data. (Table 2, 3).

The frequency distribution of genotypes of the ACE gene in healthy individuals of Kazakhs origin in comparison to literature data

Table 2.

Practically healthy people	II		ID		DD		χ2	p
	n	%	n	%	n	%		
Kazakhs (G.K. Bakhtiyarova., 2010) (n=68)	24	35,29	34	50,00	10	14,71		
Kazakhs (A.T. Musagalieva, 2000) (n=32)	12	37,5	16	50,00	4	12,5	0,105	0,949
Kazakhs (Shalharova J.S, 2001) (n=60)	24	40,01	29	48,33	7	11,66	0,428	0,807
Xinjiang Kazakhs (WangXF, 2003) (n=151)	60	40,00	65	43,00	26	17,00	0,923	0,630
Kazakhs (Kozhanova O.V,1999) (n=72)	24	33,33	32	44,44	16	22,23	1,332	0,514
Kazakhs (Baitasova N.B,2003) (n=112)	37	33,33	50	44,4	25	22,3	1,586	0,453
Uighurs (Baitasova N.B., 2003) (n=95)	39	41,4	38	40,00	18	18,6	1,652	0,438

Hindus (Joseph A., 1998) (n= 201)	54	26,86	100	49,75	47	23,38	3,051	0,218
Yakuts (Grigorieva L.V, 2009) (n=152)	51	33,55	62	40,79	39	25,66	3,485	0,175
Czechs (Hubacek JA, 2000) (n=302)	66	21,8	149	49,4	87	28,8	8,337	0,015
Greeks (Tziakas DN, 2007) (n=332)	74	22,3	158	47,6	100	30,1	8,812	0,012
British (Samani NJ, 1996) (n=537)	118	22,00	258	48,00	161	30,00	9,593	0,008
Uzbeks (Abdullayeva G.J.,2005) (n=60)	34	56,7	14	23,3	12	20,00	9,777	0,008
Turks (Davutoglu, 2005) (n=154)	28	18,8	69	44,81	57	37,00	13,949	0,000

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The frequency distribution of genotypes and alleles of the ACE gene we have studied was comparable with the data distribution of healthy Kazakhs and Kazakhs population from other authors (Musagalieva AT, Shalharova JC, Kozhanova OV, Baitasova NB), as well as Kazakhs living in Xinjiang province in China (Wang XF).

Our data on the genotypes and alleles did not differ significantly from those of the Uighurs, Yakuts, Hindus (Baitasova NB, Grigorieva L., Joseph A.). The difference of the frequency distribution of genotypes and alleles of our data was with the Czechs, Greeks, British, Turks, and alleles, which was statistically significant (Hubacek JA., Tziakas DN., Samani NJ., Davutoglu).

Compared to the Uzbeks, the allele differences were not significant, while the difference in genotype distribution was statistically significant, as compared to the Uzbeks, and Kazakhs had commonly genotype II.

The frequency distribution of alleles of the ACE gene in healthy individuals Kazakhs compared with literature data.

Table 3.

Practically healthy people	I		D		χ^2	p
	n	%	n	%		
Kazakhs (Bakhtiyarova G.K., 2010) (n=68)	82	60,30	54	39,70		
Uighurs (Baitasova N.B., 2003) (n=95)	116	61,00	74	39,00	0,001	0,981
Kazakhs (MusagalievaA.T., 2000) (n=32)	40	62,5	24	37,5	0,020	0,886
Kazakhs (Shalharova J.S., 2001) (n=60)	77	64,17	43	35,83	0,258	0,611
Xinjiang Kazakhs (WangXF, 2003) (n=151)	85	56,00	66	44,00	0,321	0,571
Kazakhs (Kozhanova O.V,1999) (n=72)	80	56,00	64	44,00	0,464	0,496
Uzbeks (Abdullayeva GJ, 2005) (n=60)	79	65,8	41	34,2	0,618	0,432
Kazakhs (Baitasova N.B, 2003) (n=112)	124	56,00	100	56,00	0,653	0,419
Yakuts (Grigorieva L.V, 2009) (n=152)	82	53,95	70	46,05	0,935	0,334
Hindus (Joseph A., 1998) (n= 201)	104	51,74	97	48,26	2,066	0,151

Czechs (Hubacek JA, 2000) (n=302)	140	46,52	162	53,48	6,740	0,009
Greeks (Tziakas DN, 2007) (n=332)	153	46,08	179	53,92	7,234	0,007
British (Samani NJ, 1996) (n=537)	247	46,00	290	54,00	8,315	0,004
Turks (Davutoglu, 2005) (n=154)	62	40,58	92	59,42	10,808	0,001

For comparison of our data, the frequency distribution of genotypes and alleles of the ACE gene in patients with mitral valvular disease, we have analyzed the literature data. We found only three studies, in which the ACE gene polymorphism was studied in patients with rheumatic heart disease - two Turkish researchers and one researcher from the U.S.A.

Previously, it was shown that the distribution of genotypes and alleles of the ACE gene in healthy Kazakhs differed significantly from those of Turkish researchers Davutoglu (2005) (Table 4). We also found exact same statistical differences when comparing data of Davutoglu (2005) in patients with chronic rheumatic heart disease and the distribution of genotypes and alleles of the ACE gene in patients of Kazakh origin with mitral valvular disease (Table 3), and the Turks in patients with chronic rheumatic heart disease was more common homozygous II and DD. The distribution of genotypes and alleles of the ACE gene in patients with mitral valvular disease according to another Turkish researchers Ozisik (2004) was similar Davutoglu (2005), therefore not presented for comparison.

The frequency distribution of genotypes of the ACE gene in patients with mitral valvular disease Kazakh origin data Turkish researchers

Table 4.

	Kazakhs (Bakhtiyarova G.K., 2010) (n=70)		Turks (Davutoglu, 2005) (n=82)		$\chi 2$, p
	n	%	n	%	
II	18	25,72	26	31,7	$\chi 2=17,481$, $p<0,001$
ID	43	61,43	25	30,5	
DD	9	22,86	31	37,8	
Iallele	79	56,50	77	46,95	$\chi 2=2,349$, $p=0,125$
Dallele	61	43,50	87	53,05	

Chou et al (2004), however, observed a different picture; when healthy individuals were compared to patients with chronic rheumatic heart disease, patients were found to have significantly more allele I and II genotype of the ACE gene, however, since their publication did not include the distribution of genotypes and allels of the ACE gene, it would be hard to infer its statistical significance.

CONCLUSION

Thus, the results of a study of the frequency distribution of genotypes and alleles of the ACE gene in Kazakhs - healthy individuals and patients

with mitral valvular disease significant differences between them are not identified, and the results are depended on the distribution of ethnicity. The data obtained from healthy Kazakhs were comparable to published data from other researches including Kazakhs people, e.g. Kazakhs living in Xinjiang province in China, Uighurs, Yakuts, Hindus, which is statistically significantly different from the Uzbeks, Turks, Czechs, English, and Greeks. Few reference data on the ACE gene polymorphism in patients with mitral valvular disease does not allow for statistical comparison of our data in Kazakhs patients with data of world literature.

Mitral heart defects are the most common cause of disability and poor prognosis in young, still in adulthood, regardless of ethnic predisposition. in this connection, the purpose of research is the study of the spread MPS in the Kazakhs as a function of I / D polymorphism of the ACE gene in comparison with healthy and data world literature.

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