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Prevalence of eNOS 3 Gene Polymorphism in Family Members of Patients with Familial Bronchial Asthma in the Uzbek Population

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Abstract The frequency of distribution of alleles and genotypes of the polymorphic variant of the eNOS3 gene has been studied in patients with bronchial asthma and healthy individuals in a family of Uzbek ethnicity. In this, 193 individuals in the family were under surveillance. Patient testing was carried out according to the International Classification of the World Health Organization (ICD-10) and the relevant diagnostic criteria of the global strategy for treatment and Prevention of BA (GINA 2021). A polymorphic variant of the eNOS3 gene was investigated by the polymerase chain reaction (PCR) method at the center of "Medical Genetics" of the Institute of Biochemistry of the Academy of Sciences of the Republic of Uzbekistan. In the Uzbek population, patients with family asthma were more commonly encountered in the family carrying the 4b/4b genotype and 4b allele of the eNOS3 gene, and they were more common in allergic types of the disease, mild disease, Disease Control, and women. Homozygous genotype carriers of 4a/4a in the family have been noted to be a non-allergic type of family BA, severe course, and abundant in those with uncontrolled disease. This suggests that the eNOS3 gene in the Uzbek population has a higher risk of developing the disease in these genotypes and allele carriers, which makes it possible to identify the disease early in the family, make a comparative diagnosis and create new methods of treatment.

Keywords Familial bronchial asthma, eNOS3 gene, 4b/4b, 4b/4a, 4a/4a genotype

1. Introduction

Family – specific genetico-epidemiological studies have found a high incidence of bronchial asthma (BA) among family – members. If one parent has bronchial asthma the risk of developing the disease in their children is three times higher than in a healthy family, if both parents have bronchial asthma it has been found that their children have a six times higher risk of getting it [Didkowski N.A., Jarów M.A. 2005., Bochkov N. P. 2018].

Literature records that 46.3% of individuals in the family were diagnosed with bronchial asthma [Asanov A.Yu.2018]. In Russia I. A study by Cherkashinai et al showed that 18% of family members were diagnosed with BA disease.

Ubaydullaev A. M, Yakimova M. A. in a genetic study conducted by a family of patients with bronchial asthma in the Uzbek population for the first time, they studied the prevalence and hereditary predisposition of the disease in Uzbek families. In this, inbred found that in a family with a marriage, bronchial asthma is severe, and the disease occurs early.

The distribution of eNOS3 gene genotypes and alleles in different ethnic populations in the world has been studied. In the Turkish population, 4b/4b - 69.0%, 4b/4a- 28.2%, 4a/4a- 2.8% were found [Senkal N.2023]. In Europe, whites are more likely to have a b allele, and their citation is respectively: 4b/4b - 0.41; 4b/4a- 0.46; 4a/4a- 0.13. Among people living in the northwest of Russia, 4b/4b - 63.7%; ba4b/4a- 34.5%; 4a/4a-1.8% were found, while Novosibirsk was found to be represented by 4b/4b - 67.9%; 4b/4a-28.9%; 4a/4a-3.3% distribution [Pozdnyakov N.O. 2015].

eNOS3 and other genes calculated from candidate genes among individuals in the family – families of patients with hereditary predisposition to bronchial asthma in different ethnic groups are in the cluster of distribution of genotypes and alleles [Kelembet n. A. 2005., Sardaryan I. S. 2009., Cherkashina I.I. 2010., Pasieshvili T. M.2012., Bezrukov L.A. 2015., Shakhanov A. V. 2017., Cortez e Castro M. 2020., Dai X., Inna K. 2021., Agache I, Aline E., Aytac H. M. 2022.] a number of scientific studies have been conducted.

In particular, in Saint Petersburg the N.A. Kelembet eNOS3 gene is abundant in the 4a allele and the 4a/4a genotype in the BA medium-heavy species, known as in Astrakhan. X. A. Akhminayev., L.P. Varoninain a study conducted by and co-authors, BA reported a high incidence of 4a/4b polymorphism in patients. Of the 150 patients

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with BA who spent in Tomsky, 4b/4b - 65.33-63.7%; 4b/4a-32.67-34.5%; 4a/4a-2.00-1.8% were observed [Babushkina N.P. 2015].

In patients with bronchial asthma in Uzbekistan, the eNOS3 gene has not been studied before studies on the distribution of genotypes and alleles.

2. Research Objective

Family eNOS3 gene studies the occurrence of bronchial asthma in genotype and allele-carrying individuals.

3. Materials and Methods

Accordingly, we studied the distribution of allele and genotype frequencies of the polymorphic variant of the eNOS3 gene in patients with bronchial asthma and healthy individuals of Uzbek nation. 193 individuals were examined in the family. All patients with family BA underwent extensive clinical, functional and laboratory tests. Patients were examined according to the WHO International Classification (ICD-10) and the diagnostic criteria of the global strategy for treatment and Prevention of BA (GINA, 2021).

At the "center of Medical Genetics" of the Institute of Biochemistry of the Academy of Sciences of the Republic of Uzbekistan (director, Doctor of medical sciences, professor Mukhamedov R.S.) analysis of the polymorphic variant of the eNOS3 gene was done through the PCR method.

The control group is made up of 45 (of which 23 are male and 22 are female) practically healthy people aged 17-62 (average age 28.64) living in the Republic of Uzbekistan.

Polymorphisms of genes under study in asthma patients and the control group coincided with The Hardy-Weinberg equilibrium, where the distribution of genotypes was expected. The difference in allele and genotype frequency distribution was evaluated through the $\chi 2$ criterion. To assess the Association of alleles and genotypes with the results, the relative risk (OR) was calculated with a 95% confidence interval (CI). Online calculator for statistical processing of molecular genetic verification data (https://medstatistic.ru/index.php).

4. Conclusions and Discussion

Based on the results obtained, when the frequency of occurrence of eNOS3 gene genotypes and alleles in 49 family individuals was assessed, the following distribution in 173 individuals in the family was 4b/4b genotype - 152(87.9%), 4b/4a genotype - 17(9.8%), 4a/4a genotype - 4 (2.3%), 4b allele - 321 (92.8%), 4a allele - 25 (7.2%). In 45 practically healthy individuals examined as a control group, however, 4b/4b genotype - 38(84.5%), 4b/4a genotype - 6(13.3%), 4a/4a genotype - 1 (2.2%), 4b allele - 82 (91.1%), 4a allele - 8 (8.9%) were reported [Table 1].

Table 1. Frequency of eNOS3 gene occurrence in family individuals

Genotype and allele	People in the family (173)	Control (45)	$\chi 2$	p	OR[95% CI]
4b/4b	152(87,9%)	38(84,5%)	0.46	p=0.793	1.33[0.53-3.37]
4b/4a	17(9,8%)	6(13,3%)			0.71[0.26- 1.91]
4a/4a	4 (2,3%)	1 (2,2%)			1.04[0.11- 9.55]
4b	321 (92,8%)	82 (91,1%)	0.28	p=0.596	1.25[0.54-2.88]
4a	25 (7,2%)	8 (8,9%)			0.79[0.34-1.81]

Table 2. eNOS3 gene polymorphism between individuals in the family can occur genotype and alleles

Genotype and allele	Control group (n=45)		BA (n=116)				
	n	%	n	%	$\chi 2$	p	OR[95%CI]
4b/4b	38	84,5	105	90,5	1.70	p=0.429	1.76[0.64- 4.86]
4b/4a	6	13,3	8	6,9			0.48[0.16- 1.48]
4a/4a	1	2,2	3	2,6			1.17 [0.12- 11.53]
4b	82	91,1	218	94,0	0.83	p=0.363	1.52[0.61- 3.75]
4a	8	8,9	14	6,0			0.66[0.27- 1.63]
			BA unspecified relatives (n=57)				
4b/4b	38	84,5	47	82,5	0.14	p=0.931	0.87 [0.30- 2.49]
4b/4a	6	13,3	9	15,8			1.22 [0.39- 3.72]
4a/4a	1	2,2	1	1,7			0.79[0.05-12.92]
4b	82	91,1	103	90,4	0.03	p=0.853	0.91[0.35- 2.38]
4a	8	8,9	11	9,6			1.09 [0.42- 2.85]

The polymorphism of the eNOS3 gene identified in the subjects included in the study was studied by assigning the genotype and alleles of 4b/4a to a group of BA-infected and BA-undetected individuals. In this, it was noted that homozygous genotype carriers consisting of 4b/4b alleles were found to be abundant in patients with familial BA compared to 105(90.5%) control group 38(84.5%) (OR=1.76, $\chi2$=1.70, p=0.429). In contrast, family BA was 47(82.5%) in undetected family heterozygous genotype carriers consisting of family 4b/4a alleles were found to be 8 (6.9%) in familial BA patients, twice as rare as 9(15.8%) in BA undetected individuals. In the control group, it was 6 (13.3%). Patients with familial BA carrying the homozygous genotype 4a/4a allele in the family were noted to have a significant incidence when compared to 3(2.6%), control group 1 (2.2%) (OR=1.17, $\chi2$=1.70, p=0.429). In the family, BA was 1(1.7%) of those not identified.

In patients with familial BA, 4b allele carriers of the eNOS3 gene were found to be 218 (94.0%), significantly higher when compared to control group 82 (91.1%) (OR=1.52, $\chi2$=0.83, p=0.363). In the family, BA was recorded in 103(90.4%) in unidentified individuals. In the family, it was noted that 11(9.6%) of BA undefined individuals had significantly higher incidence when compared to control group 8 (8.9%) (OR=1.09, $\chi2$=0.03, p=0.853). In patients with familial BA, 4a allele carriers of the eNOS3 gene accounted for 14 (6.0%) [Table 2].

An analysis of the occurrence of genotypes and alleles of the eNOS3 gene on pathogenetic types of disease was conducted in patients with familial BA. In the family, it was noted that the eNOS3 gene was significantly more abundant when homozygous genotype carriers consisting of 4b/4b alleles compared with the family BA allergic type 89(95.7%) control group 38 (84.5%) (OR=4.10, $\chi2$=5.44, p=0.066). In the family, the eNOS3 gene was noted to occur twice as often as heterozygous genotype carriers consisting of 4b/4a alleles compared with the family BA non-allergic type 4(28.6%) control group 6(13.3%) (OR=2.17, $\chi2$=5.54, p=0.063). Also in the family, the eNOS3 gene was six times more abundant than the homozygous genotype carriers of 4a/4a alleles compared to the family BA non-allergic type 2(14.3%) control group 6 (13.3%) (OR=7.33, $\chi2$=5.54, p=0.063). Also in the family, it was noted that the eNOS3 gene was significantly more abundant when homozygous genotype carriers consisting of 4b/4b alleles compared the family BA mixed type with 8(88.9%) control group 38 (84.5%) (OR=1.47, $\chi2$=0.25, p=0.885).

In patients with familial BA, 4b allele carriers of the eNOS3 gene were recorded as having a reliable incidence of 181 (97.3%) in the familial BA allergic type, compared to 82 (91.1%) in the control group (OR=3.53, $\chi2$=5.20, p<0.05). In patients with familial BA, 4a allele carriers of the eNOS3 gene were recorded as having a more reliable incidence of familial BA in the non-allergic type than 8 (28.6%) in the control group of 8 (8.9%) (OR=4.10, $\chi2$=7. 06, p<0.01). Also in patients with familial BA, it was noted that 4b allele carriers of the eNOS3 gene had 17 (94.4%) in a mixed type of familial BA, significantly higher incidence than 82 (91.1%) in the control group (OR=1.66, $\chi2$=0.25, p=0.641). [Table 3].

Table 3. By pathogenetic types of disease, the eNOS3 gene meets the genotype and alleles

Genotype and allele	Control group (n= 45)		Allergic (n=93)				
	n	%	n	%	$\chi2$	p	OR[95%CI]
4b/4b	38	84,5	89	95,7	5.44	p=0.066	4.10 [1.13-14.83]
4b/4a	6	13,3	3	3,2			0.22 [0.05- 0.91]
4a/4a	1	2,2	1	1,1			0.48 [0.03- 7.83]
4b	82	91,1	181	97,3	5.20	p<0.05 p=0.023	3.53 [1.12- 11.12]
4a	8	8,9	5	2,7			0.28 [0.09- 0.89]
			Non-allergic (n=14)				
4b/4b	38	84,5	8	57,1	5.54	p=0.063	0.25 [0.06- 0.93]
4b/4a	6	13,3	4	28,6			2.17 [0.52- 8.97]
4a/4a	1	2,2	2	14,3			7.33 [0.61-87.91]
4b	82	91,1	20	71,4	7.06	p<0.01 p=0.008	0.24 [0.08 -0.73]
4a	8	8,9	8	28,6			4.10 [1.37- 12.26]
			Mixed (n=9)				
4b/4b	38	84,5	8	88,9	0.25	p=0.885	1.47 [0.16-13.70]
4b/4a	6	13,3	1	11,1			0.81 [0.09- 7.70]
4a/4a	1	2,2	0	0			
4b	82	91,1	17	94,4	0.21	p=0.641	1.66[0.19-14.15]
4a	8	8,9	1	5,6			0.60 [0.07- 5.14]

In patients with familial BA, a distribution analysis of occurrence of eNOS3 gene genotypes and alleles in terms of disease rejection severity was conducted. In the family, the eNOS3 gene was noted to be abundant when homozygous genotype carriers consisting of 4b/4b alleles compared to 51 (96.2%) control group 38 (84.5%) at mild levels of disease (OR=4.70, $\chi2$=4.27, p=0.118). In patients with familial BA, it was noted that 4b allele carriers of the eNOS3 gene were reliably abundant when compared with 104 (98.1%) control group 82 (91.1%) at a mild level of familial BA (OR=5.07, $\chi2$=4.93, p<0.05).

In the family, it was noted that the eNOS3 gene was abundant when homozygous genotype carriers consisting of 4b/4b alleles compared the disease to 38 (90.5%) control group 38 (84.5%) at the middle severe level (OR=1.75, $\chi2$=1.30, p=0.523). In patients with familial BA, 4b allele carriers of the eNOS3 gene were noted to be abundant when family BA was compared at moderate severity with 80 (95.2%) control group 82 (91.1%) (OR=1.95, $\chi2$=1.15, p=0.284).

In the family, the eNOS3 gene was noted to be abundant when homozygous genotype carriers consisting of 4a/4a alleles compared the disease at severe levels with 3 (14.3%) control group 1 (2.2%) (OR=7.33, $\chi2$=3.73, p=0.155). In patients with familial BA, it was noted that 4a allele carriers of the eNOS3 gene were abundant when compared with 8 (14.3%) control group 8 (8.9%) at a severe level of familial BA (OR=2.28, $\chi2$=2.43, p=0.120) [Table 4].

Table 4. Whether the eNOS3 gene meets genotypes and alleles by disease severity

Genotype and allele	Control group (n= 45)		Mild (n=53)				
	n	%	n	%	$\chi2$	p	OR[95%CI]
4b/4b	38	84,5	51	96,2	4.27	p=0.118	4.70[0.92-23.89]
4b/4a	6	13,3	2	3,8			0.25[0.05-1.33]
4a/4a	1	2,2	0	0			
4b	82	91,1	104	98,1	4.93	p<0.05 p=0.027	5.07[1.04-24.54]
4a	8	8,9	2	1,9			0.20[0.04-0.95]
			Moderate (n=42)				
4b/4b	38	84,5	38	90,5	1.30	p=0.523	1.75[0.47-6.47]
4b/4a	6	13,3	4	9,5			0.68[0.17-2.62]
4a/4a	1	2,2	0	0			
4b	82	91,1	80	95,2	1.15	p=0.284	1.95[0.56-6.74]
4a	8	8,9	4	4,8			0.52[0.14-1.76]
			Severe (n=21)				
4b/4b	38	84,5	16	76,2	3.73	p=0.155	0.59[0.16-2.14]
4b/4a	6	13,3	2	9,5			0.68[0.13-3.71]
4a/4a	1	2,2	3	14,3			7.33[0.71-75.27]
4b	82	91,1	36	85,7	2.43	p=0.120	0.43[0.15-1.26]
4a	8	8,9	8	14,3			2.28[0.79-6.54]

Table 5. Whether the eNOS3 gene meets genotypes and alleles in terms of Disease Control

Genotype and allele	Control group (n=45)		Controlled BA (n=76)				
	n	%	n	%	$\chi2$	p	OR[95%CI]
4b/4b	38	84,5	73	96,1	5.45	p=0.066	4.48 [1.10-18.33]
4b/4a	6	13,3	3	3,9			0.27 [0.06-1.13]
4a/4a	1	2,2	0	0			
4b	82	91,1	149	98,0	6.23	p<0.05 p=0.013	4.85[1.25-18.77]
4a	8	8,9	3	2,0			0.20 [0.05-0.80]
			Uncontrolled BA (n=40)				
4b/4b	38	84,5	32	80,0	1.32	p=0.518	0.74 [0.24-2.25]
4b/4a	6	13,3	5	12,5			0.93 [0.26-3.31]
4a/4a	1	2,2	3	7,5			3.57[0.36-35.76]
4b	82	91,1	69	86,3	1.008	p=0.316	0.61 [0.23-1.61]
4a	8	8,9	11	13,7			1.63 [0.62-4.29]

Table 6. Whether the eNOS3 gene by male sex in the family meets the genotype and alleles

Genotype and allele	Control group (n=24)		BA (n=49)				
	n	%	n	%	χ2	p	OR[95%CI]
4b/4b	21	46,6	43	37,1	0.57	p=0.753	1.02 [0.23-4.50]
4b/4a	3	6,7	5	4,3			0.79[0.17- 3.64]
4a/4a	0	0	1	0,9			
4b	45	93,8	91	39,3	0.04	p=0.841	0.87 [0.21- 3.51]
4a	3	6,2	7	3,0			1.15 [0.28- 4.64]
			BA unspecified relatives (n=24)				
4b/4b	21	46,6	18	31,5	1.23	p=0.268	0.43 [0.09- 1.96]
4b/4a	3	6,7	6	10,5			2.33 [0.51-10.69]
4b	45	93,8	42	87,5	1.10	p=0.294	0.47 [0.11- 1.99]
4a	3	6,2	6	12,5			2.14 [0.50- 9.12]

Table 7. Whether the eNOS3 gene by female sex in the family meets the genotype and alleles

Genotype and allele	Control group (n=21)		BA (n=67)				
	n	%	n	%	χ2	p	OR[95%CI]
4b/4b	17	37,8	62	53,4	2.64	p=0.267	2.92 [0.70 -12.07]
4b/4a	3	6,7	3	2,6			0.28 [0.05- 1.51]
4a/4a	1	2,2	2	1,7			0.61 [0.05- 7.15]
4b	37	88,1	127	54,7	2.25	p=0.134	2.45 [0.73- 8.18]
4a	5	11,9	7	3,0			0.41 [0.12- 1.36]
			BA unspecified relatives (n=33)				
4b/4b	17	37,8	29	50,8	1.69	p=0.430	1.71[0.38-7.72]
4b/4a	3	6,7	4	7,0			0.83 [0.17- 4.13]
4a/4a	1	2,2	0	0			
4b	37	88,1	62	93,9	1.19	p=0.285	2.09[0.52- 8.30]
4a	5	11,9	4	6,0			0.48[0.12- 1.89]

A distribution analysis of the occurrence of eNOS3 gene genotypes and alleles on the rate of Disease Control was conducted in patients with familial BA. Homozygous genotype carriers consisting of 73(96.1%) 4b/4b alleles in family BA controlled patients were noted to have a reliable increase compared to control group 38(84.5%) (OR=4.48, $\chi2$=5.45, p=0.066). It was noted that familial BA had 149(98.0%) eNOS3 gene 4b allele carriers in controlled patients, with reliable multiple observations compared to control group 82(91.1%) (OR=4.85, $\chi2$=6.23, p<0.05).

Homozygous genotype carriers consisting of 3(7.5%) 4a/4a alleles in familial BA uncontrolled patients were noted to have reliably increased compared to control group 1(2.2%) (OR=3.57, $\chi2$=1.32, p=0.518). It has been noted that family BA has 11(13.7%) occurrence of 4a allele carriers of the eNOS3 gene in uncontrolled patients, with multiple observations compared to control group 8(8.9%) (OR=1.63, $\chi2$=1.008, p=316) [Table 5].

An analysis of the distribution of the occurrence of eNOS3 gene genotypes and alleles by sex of patients with familial BA was conducted. In males with no family BA detection, heterozygous genotype carriers consisting of 4b/4a alleles were noted to be abundant when compared to 6 (10.5%) control group 3(6.7%) (OR=2.33, $\chi2$=1.23, p=268). It was noted that there was a high incidence of 4a allele carriers 6(12.5%;) compared to control group 3(6.2%;) in males with no BA detection in the family (OR=2.14, $\chi2$=1.10, p=294) [Table 6].

The eNOS3 gene in the family was noted to be abundant in 62(53.4%) women with a homozygous genotype carrier BA consisting of 4b/4b alleles compared to the control group 17(37.8%) (OR=2.92, $\chi2$=2.64, p=267). In the family, it was noted that 29(50.8%) women with an undefined BA had high incidence compared to control group 17(37.8%) (OR=1.71, $\chi2$=1.69, p=430). The 4b allele – carrying BA of the eNOS3 gene in the family was noted to be abundant in undefined 62(93.9%;) females compared to control group 37(88.1%) (OR=2.09, $\chi2$=1.19, p=285) [Table 7].

5. Conclusions

Thus, in the family, eNOS3 gene 4b/4b genotype and 4b allele carriers were more common for those with familial BA and were more likely to diagnose the disease by allergic type, mild degree of disease, in those with Disease Control, and in women. In homozygous genotype carriers with 4a/4a alleles

in the family, those with familial BA were poorly identified and the disease was reported by a not allergic type, those with severe illness, and those without control. This can lead to early detection of the disease in the family, comparative diagnosis and the creation of new treatments, indicating that the eNOS3 gene in the Uzbek population is high in disease progression in carriers of this genotype and allele.

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