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COMPARATIVE ANALYSIS OF POLYMORPHISM OF THE CFTR GENE IN UZBEK POPULATION

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ABSTRACT

One of the factors of male infertility is cystic fibrosis. This is a monogenic autosomal recessive disease caused by a mutation of the cystic fibrosis transmembrane conduction regulator gene, characterized by lesions of the exocrine glands of vital organs and usually with a severe course and prognosis. The severity of the disease and symptoms may vary depending on the type of mutation. Different mutations and polymorphisms of the CFTR gene have a pronounced population specificity, reflecting the genetic processes that are emerging.

KEYWORDS: cystic fibrosis, mutation, gene, polymorphism, population.

INTRODUCTION

Genetic factors are one of the common causes of developmental abnormalities and dysfunction of the organs of the reproductive system.[10] The frequency of their occurrence correlates with the severity of reproductive pathology. Thus, at least 1/3 of cases of severe forms of infertility in men is due to genetic factors.[9] Infertility in men can be caused by chromosomal abnormalities, microstructural reorganizations and gene mutations that lead to impaired sex determination, differentiation and / or development of the reproductive system, its hormonal disregulation, impaired spermatogenesis and / or sperm function.[1] In some cases, infertility in men is due to the presence of a genetic syndrome, while in the clinical picture, infertility either comes to the fore or is not the main symptom.[10]

One of the factors of male infertility is cystic fibrosis (CF). This is a monogenic autosomal recessive disease caused by a mutation of the cystic fibrosis transmembrane conduction regulator gene (CFTR - Cystic Fibrosis Transmembrane conductance Regulator), characterized by lesions of the exocrine glands of vital organs and having usually a severe course and prognosis. The same name has the gene encoding this protein.[1,2,4] The CFTR gene, located on the long arm of chromosome 7, was identified in 1989 by L.-Ch. Tsui, F. Collins, J. Riordan. It has a length of about 250 thousand bp. and includes 27 exons. It has been established that the CFTR gene refers to "housekeeping genes" that function at all stages of the life cycle of an organism.[3,7]

The pathogenesis of CF is associated with a defect in protein synthesis that acts as a chloride channel that is involved in the water-electrolyte metabolism of the epithelial cells of the respiratory tract, gastrointestinal tract, pancreas, liver, and reproductive system. Due to the inability of the defective protein to adequately perform the work of the chloride channel, Cl– ions accumulate inside the cell. The electrical potential in the lumen of the excretory ducts changes, and sodium ions rush into the cell. The latter, in turn, serves as a pump, which leads to increased water absorption from the extracellular space. As a result, the secret of most glands of external secretion thickens, its evacuation is impeded, secondary changes occur in the organs.[3,6] Nearly all male CF patients (97%) develop azoospermia, associated with congenital absence, atrophy or obstruction of the spermatic cord. Accordingly, most men with CF are not able to have offspring. These abnormalities are also found in some males from among carriers of the CF gene.[5.8]

To date, about 2,000 mutations of the gene responsible for the development of symptoms of CF have been identified, and developing methods for detecting mutations make it possible to replenish the international database with new genetic disorders every month. Mutations that lead to a severe form, as well as mutations causing a milder course of the disease, have been found. The severity of the disease and symptoms may vary depending on the type of mutation.[1,6,8]

Depending on the primary damaging effect, all mutations of the gene are divided into 6 classes.[2,4,6]

I class: The violation of protein synthesis (G542X, W1282X, 394delTT, R553X, 1717-1G → A);

II class: The violation of processing or transport (F508del, dI507, N1303K, S541I, S549R);

III class: dysregulation of protein regulation (G551D, G1224E, S1255P);
IV class: reduced conduction channel (R117H, R334W, R347P);
V class: reduction of the level of normal protein molecules or RNA (A455E, 3849 + 10kbC → T);
VI class: reduced protein stability.

Different mutations and polymorphisms of the CFTR gene have a pronounced population specificity, reflecting the genetic processes that are emerging.

THE AIM OF THE STUDY

The aim of the study was to conduct a population comparative analysis of 3 main polymorphisms of the CFTR gene in men: F508del; N1303K; W1282X.

MATERIALS AND RESEARCH METHODS

The collection of clinical material was carried out on the basis of the Institute of Immunology and Human Genomics, Academy of Sciences of Uzbekistan from 2014-2018. The study included 165 men belonging to the Uzbek population aged 28 to 45 years. Genetic examinations were carried out in the Reproduction Immunology Laboratory of the Institute of Immunology and Human Genomics, Academy of Sciences of Uzbekistan. DNA preparations were used to type polymorphic variants of the CFTR gene. The DNA isolation was carried out from whole blood leukocytes with the "DNA-EXPRESS-blood" reagent "produced by Litech LLC. Genotyping was performed by PCR using a test system to determine the number of mutations in the CFTR gene of scientific and production company Litech LLC (Moscow).

The obtained results were processed statistically in accordance with the observed frequency distributions of genotypes theoretically expected, according to the Hardy-Weinberg equation using the $\chi 2$ criterion.

RESULTS AND DISCUSSION

Among the most common mutations in the CFTR gene is the F508del mutation, caused by the deletion of three nucleotides in exon 10, leading to a phenylalanine loss at 508 of the transmembrane regulatory protein. This mutation belongs to the first class of CFTR gene mutations, characterized by a violation of protein maturation. Thus, analysis of the frequency distribution of alleles for the F508del polymorphism of the CFTR gene among the Uzbek population, by Germans, Romanians, Hungarians, Brazilians, and Colombians, revealed significantly significant differences: with Colombians $\chi 2 = 8.42$ $p < 0.01$, and with Germans $\chi 2 = 61, 2$ $p < 0.01$ (table number 1). While with Ashkenazi Jews and Turks there were no statistically significant differences ($p > 0.05$).

Table 1: Population comparison of the Uzbek population.

Polymorphisms	Populations	Alleles	
		Norm	Risk
		CTT	
F508del	Uzbeks	83	17
	Germans	28	72
	Romanians	43,7	56,3
	Hungarians	35,7	64,3
	Ashkenazi Jews	72	28
	Turks	75,5	24,5
	Brazilians	52,3	47,7
	Colombians	64,6	35,4
		G	T
		C	G
N1303K	Uzbeks	100	0
	Germans	97,7	2,3
	Romanians	99,2	0,8
	Hungarians	98,8	1,2
	Ashkenazi Jews	97	3
	Turks	97,1	2,9
	Brazilians	97,6	2,4
	Colombians	97,9	2,1
		G	A
W1282X	Uzbeks	100	0
	Germans	99,3	0,7
	Romanians	97,7	2,3
	Hungarians	98,8	1,2
	Ashkenazi Jews	52	48
	Turks	97,4	2,6
	Brazilians	98,7	1,3
	Colombians	99,3	0,7

N1303K mutation also belongs to the second class of mutations, but which is characterized by the replacement of the nucleotide in exon 21, leading to the replacement of the amino acid asparagine by lysine. Investigating the N1303K polymorphism, there were no significant differences in alleles of the Uzbek population with all considered populations: from $\chi2 = 0$ $p > 0.05$ Romanians and Hungarians to $\chi2 = 1.354$ $p > 0.05$ in Ashkenazi Jews.

The W1282X belongs to the first class of mutations leading to nucleotide replacement in exon 20. This mutation is characteristic of blocking protein synthesis, which leads to the formation of a stop codon. Studying the W1282X polymorphism, the differences between the Uzbeks and Ashkenazi Jews ($\chi2 = 60.554$ $p < 0.01$) were identified, and with the other populations in question, no statistically significant differences were found ($p > 0.05$).

CONCLUSION

Thus, during a population comparison of the Uzbek population with representatives of the German, Romanian, Hungarian, Jewish, Brazilian, Colombian, Turkish populations, the prevalence of the risk allele of this polymorphism was found to be statistically significant differences with all except Ashkenazi Jews and Turks.

Population analysis of the CFTR gene showed that the F508del polymorphism in exon 10 is of practical importance in the Uzbek population.

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