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RESEARCH ARTICLE
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Molecular and Bioinformatic Analysis of *CFTR* Gene Mutations in Azerbaijani Patients with Cystic Fibrosis

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ABSTRACT

This study identified five CFTR (Cystic Fibrosis Transmembrane Regulator gene) gene mutations, which show high-frequency significance. We set a goal to study CFTR gene mutations in a population of the Azerbaijan Republic. Between 2015 and 2020, 1,344 (1,144 experimental and 200 control group) individuals from the Baku, Sheki-Zagatala, Guba-Khachmaz, and Lankaran-Astara zones of Azerbaijan participated in this study. A family study was conducted to identify cases similar to those with cystic fibrosis. Of these, only 18 patients in the experimental group were found to have various mutations in the *CFTR* gene. Sweat tests were done. To address the task at hand, we employed the molecular-genetic method. Blood samples of patients diagnosed with cystic fibrosis were analyzed using exome and Sanger sequencing. We found 5 mutations for the CFTR gene. They are as follows: Phe508del, R117H, R334W, R553X, İVS8-5T and L322P (novel mutation). We were the first to describe mutation L322P (965 T>C (Leu322Pro)) in Azerbaijan, which has no reference sequence results in NCBI. Thus, in the studied samples, two mutations—R334W and L322P—were found in exon 4 of the CFTR gene, one new mutation (L322P) in exon 7, the ΔF508 mutation in exon 10, and the R553X mutation in exon 11. The protein structure was analyzed using the Swiss Model program (www.swiss-prot.org). The novel L322P mutation, detected in exon 7 of the CFTR gene, was accompanied by the substitution of thymine with cytosine at position 965 of the gene, substituting leucine with proline in the protein structure. A novel mutation was detected in 1 patient from 1344 samples. Early molecular genetic screening of newborns is essential for preventing cystic fibrosis. In this regard, our research is of great importance.

Keywords: Cystic fibrosis, Bioinformatic Analysis, CFTR gene, Enzymes, Novel mutation

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INTRODUCTION

Cystic fibrosis (CF) is particularly prevalent in European countries and the US. A defect in the secretion of chloride and bicarbonate carrier proteins in multiple organs characterizes this inherited disorder. This absence can produce excessive mucus, dehydrating the generated bronchial mucus and causing obstruction, chronic infections, and subsequent tissue damage. The main aspects of CF are chronic pulmonary inflammation and reduced mucociliary clearance (Taulan et al., 2007; Malhotra et al., 2019; Innocenti et al., 2023).

Nowadays, diagnosis is made through neonatal screening programs in many countries by determining trypsinogen in dried blood. The diagnosis is confirmed by determining the electrophysiological measurements of the affected pathways after administering isoprenaline, as well as through electrophysiological or molecular genetic tests (Guo et al., 2022).

The genotypic variability is mirrored by phenotypic heterogeneity, concerning not only the life expectancy of a patient but also the prognosis of their disease. *CFTR* is responsible for the epithelial transport of chloride and bicarbonate and is regulated by a complex signaling network. This signaling network is very sensitive and well spatially and temporally organized. Due to the influence of

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CFTR gene alterations, dysregulation of this network may be responsible for multiple dysfunctions in CF. Considering how this disease and its alterations can be presented asymptomatically or with mild phenotypic relevance, as in some heterozygous or healthy carriers, one can appreciate the importance of the CFTR gene in health and disease and the significance of resolving these alterations to be translated into clinical practice. The studies of CF caused by a malfunctioning of the *CFTR* channel have helped to clarify some aspects of other less common diseases in which genes are malfunctioning ion-transporting proteins (Deignan et al., 2020).

CF is characterized by two pathological processes: duct obstruction and periductal fibrosis. The role was first reported in 1989. At least 1,880 mutational changes have been reported, many likely due to founder effects. It is known that the clinical manifestations of cystic fibrosis can exhibit significant differences across different populations due to the extremely high level of allelic heterogeneity in the CFTR gene and the influence of other genes and environmental factors on the clinical course. Cystic fibrosis is mainly observed in the Caucasian population (1:1700). In other populations, such as the African American and Asian populations, the occurrence rates are relatively low. It is impossible to explain this phenomenon for genetic reasons alone. The life-threatening autosomal recessive condition cystic fibrosis has no possible survival benefit to explain variant *CFTR* allele persistence either and the public's exposure to tobacco (Raraigh et al., 2022).

The gene encoding the cystic fibrosis transmembrane regulator is important to determining lung disease severity. Symptoms of cystic fibrosis are seen at birth or shortly thereafter. The most common symptom is immobility owing to blockage of the intestines, a condition called meconium ileus. Salty skin, chronic cough, and recurring lung and sinus infections are typical symptoms. All these signs and symptoms develop similarly in adults but are less severe. In addition, adults may have difficulty gaining weight despite a normal appetite, infertility, feces that are bulky and foul-smelling, and frequent, oily stools. Other symptoms include liver disease and gallbladder disease. The classic quality of the salty sweat generally makes diagnosing cystic fibrosis relatively straightforward. Lung disease is the most severe symptom and is often the primary cause of significant health issues in patients. In the first few weeks of life, 10–20% of children are hospitalized for a flu-like illness. About 90–95% of adults have chronic lung disease. Treatment can relieve some of the diseases and improve the well-being of patients, but most patients die with significant and continuing lung damage.

Furthermore, CF leads directly to malnutrition because patients produce thick secretions in the intestine, blocking the passage of important enzymes from the pancreas to the intestine. These enzymes are necessary for the intestine to enter the bloodstream. After the intestinal section is blocked, the tissue is damaged. Then, excessive fluid from the intestine is lost into the bowel and excreted as diarrhea. Small intestine surgery is necessary for approximately 15% of newborns. These problems often lessen with time in cystic fibrosis. However, lifelong pancreas malfunctions occur. Also, the bile ducts can be blocked, and the liver can be damaged. CF is a chronic and progressive disease (Frost et al., 2022; Guo et al., 2022; Gryspeert et al., 2025).

From his pioneering conclusions, much new information has continued to be produced throughout the years. It has already been found that almost all patients with certain forms of chronic sinus, lung, liver, gastrointestinal, and male reproductive system disease have the disease. Although many of these patients are also classified as positive for CF, some are not. The currently accepted level of certainty for a diagnosis of CF has recently been established at 50mosm/L; a higher level, 70mosm/L, when expressed under certain circumstances, is consistent with the finding that heavy loss of electrolytes from a child younger than the fourth or fifth day of life almost always indicates CF disease. Data are presented that lactate could serve as the normalized developmental metabolic fuel and that a low plasma concentration of this organic acid appears to indicate defective regulatory mechanisms that may impinge upon growth, electrolyte transport, and exocytosis at mucosal surfaces such as those lining the lung, pancreas, liver, bowel, paranasal sinuses, and epididymis (Ratbi et al., 2007; Jain & Goralski, 2025).

Up to 90% of patients with cystic fibrosis died in the last century at an early age. Optimized treatment means that today, individuals born in developed countries live on average past the third decade. However, two in three newborns in developed countries are diagnosed with cystic fibrosis (Roe et al., 2023).

MATERIALS & METHODS

Ethical Consent/Approval

All participants provided written informed consent affirming their voluntary participation in the study. This commitment ensured ethical transparency and protected patient rights. The study underwent review and approval by the Azerbaijan Medical University Ethics Committee (approval number AMU/EC/16/04/2021/N16), providing additional ethical assurance for this research undertaking.

Patients

From 2015 to 2020, 1,344 people from different zones of Azerbaijan participated in the study. To identify CFTR gene mutations, we performed a sweat test on all of them and used a molecular-genetic method.

DNA Extraction

Blood (2mL) was taken from the patients, and leukocytes were obtained through centrifugation. To isolate DNA from leukocytes, QIAamp genomic DNA (200mL) and RNA kit (QIAGEN, Germany), buffer solution (200mL) of venous blood, and 20mL of protease enzyme (QIAGEN) were used.

Electrophoresis

Positive PCR samples were checked by electrophoresis on 1.5% agarose gel. For this purpose, Power PacBasic Gel DocIM EZ (BioRad. USA) electrophoresis and Lambda DNA

Mixed Digest marker were used. DNA fragments were stained in an aqueous solution of ethidium bromide (Fig. 1).

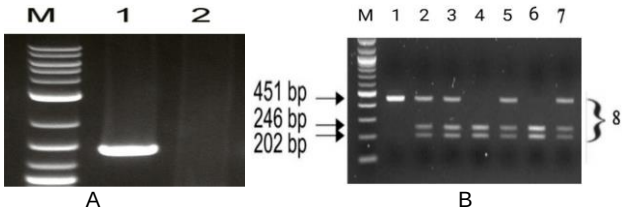

Fig. 1: a) Gel electrophoresis image of the IVS8-5T mutation in intron 8 of the CFTR gene: M-DNA marker; 1-mutation (134bp); 2-control sample (250 bp). b) Gel electrophoresis image of the delF508 mutation detected in the CFTR gene: M-DNA marker; 1-healthy; 2,3,5,7-heterozygous form; 4,6-homozygous form; 8-mutant region.

Polymerase Chain Reaction

All four studied genes were amplified using the PCR method, which was performed using the "T100TM Thermal Cycler" (BIO-RAD, Germany). A pair of Forward (F) and Reverse (R) primers was used for each genome fragment (Aghayeva et al., 2021).

Sequencing

The purified product was preceded by the exome sequencing and Sanger analysis, for the exome sequencing was carried out using a HiSeq2500 sequencer. Variations were screened with indicators Sift Pred=Damaging. The sequence of DNA fragments was studied on the "Applied Biosystems (Hitachi) 3130xl Genetic Analyzer Sequencing" sequencer. The data obtained in Sanger sequencing were compared with the reference gene using the "SeqScape TM" program (Huseynova et al., 2021).

In silico Modeling

For the simulated mutations in the studied genes, the following steps were taken in silico modeling: the sequences for these genes were obtained from the NCBI databases. We used ClinVar and HGMD databases to identify specific mutations and experimental structures were used from PDB (Protein Data Bank) to restore protein structure. To introduce mutations into the 3D structure, I used the software PyMOL. To predict the effect of mutations, PolyPhen-2 was used. To learn how mutations affect protein stability, use FoldX. The AutoDock program was used to simulate interactions of the mutant protein with cofactors or substrates. GROMACS molecular dynamics were used to simulate the behavior of wild-type and mutant proteins, and stability, flexibility, and conformational changes were analyzed. Mutations and structural effects were visualized with PyMOL, and mutation modeling and Missense3D databases were used for automated structural impact predictions. We used KBase to study how mutations in the *BCKDH* complex genes affect protein structure.

Statistical Analysis

Pearson Chi-square (X^2) Test was applied to the analysis of the study results. $P \leq 0.05$ indicated a significant association between the variables.

RESULTS

In this research, five mutations —Phe508del, R117H, R334W, R553X, and IVS8-5 T, as well as L322P — for the CFTR gene were identified in the Azerbaijan population. We were the first to describe the novel mutation L322P (965 T>C (Leu322Pro)) in Azerbaijan. It has been recorded that the frequency of cystic fibrosis among the population of Azerbaijan is 0.0074. The *CFTR* gene mutation was not detected in the 200 control samples. Various mutations of the *CFTR* gene were identified in 18 of the 1,144 samples from the experimental group. It was found that there was no significant difference (χ^2=3.140; df=1; P=0.076) in the number of patients between the control and experimental groups.

Of the 18 patients, 12 were homozygous (66.7%), 4 were heterozygous (22.2%), and 2 were compound heterozygous (11.1%). Complex homozygosity was not observed among the examined patients. There was a significant difference between the identified homozygous, heterozygous, and compound heterozygous conditions (χ^2=6.545; df=2; P=0.038). Of the 18 patients with *CFTR* gene mutations, 7 were men (38.9%), and 11 were women (61.1%) (χ^2=0.596; df=1; P=0.440).

Based on symptoms and results of biochemical and molecular genetic analysis of patients with cystic fibrosis, the disease was classified into severe and mild forms. A moderate form of the disease was not observed. In 11 out of 18 patients, the disease manifested with more severe symptoms (χ^2=0.148; df=1; P=0.700).

Among those participating in the study, various mutations of the *CFTR* gene were found only in the population of the Guba-Khachmaz zone and Baku city. Of the 18 patients, 11 are from the Guba-Khachmaz zone, and 7 are from Baku (χ^2=0.596; df=1; P=0.440). No significant difference exists in the number of patients in the Guba-Khachmaz zone and Baku city. Mutations of the *CFTR* gene were not detected among the examined patients in the Sheki-Zagatala and Lankaran-Astara zones (Table 1).

There is no previous report of the L322P (965 T>C (Leu322Pro)) mutation in exon 7 in the CFTR databases, Human Gene Mutation Database, and literature. Thus, it can be regarded as a novel mutation. Results from this study expand the mutation spectrum of CF disease and will greatly help prenatal diagnosis and carrier detection of this disorder worldwide (Fig. 2).

Table 1: Comparison of genotype, geographical and gender distribution, and disease severity of patients

Comparison	Number of cases		χ^2 Value	df	P Value
CFTR Mutation (Experimental and Control)	Exp: 18/1,144	Control: 200	3.140	1	0.076
Gender Distribution	Female: 11	Male: 7	0.596	1	0.440
Disease Severity	Severe: 10	Mild: 8	0.148	1	0.700
Geographical Distribution (Guba-Khachmaz and Baku)	GK: 11	Baku: 7	0.596	1	0.440

P value P<0.05 or P<0.001 indicates a statistically significant difference. Geographical Distribution (Sheki-Zagatala and Lankaran-Astara) does not have any positive case of mutation.

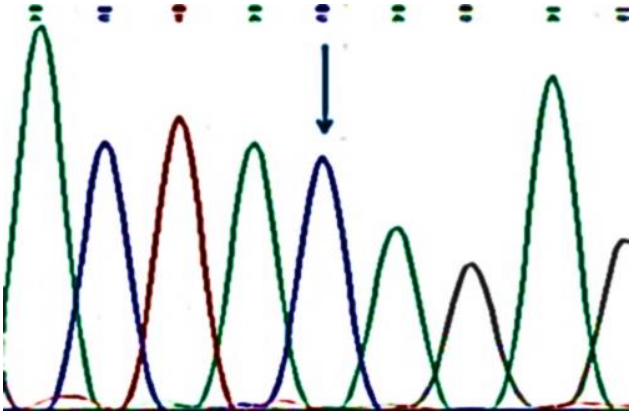

Fig. 2: Sequence of the *CFTR* gene: Homozygous form of the 965T>C (Leu322Pro) mutation.

The genetic pedigree of the patient with the L322P mutation is shown in Fig. 3. The grandparents are cousins. The first child of this family also had the same symptoms. She died within the first few months of life (Fig. 3).

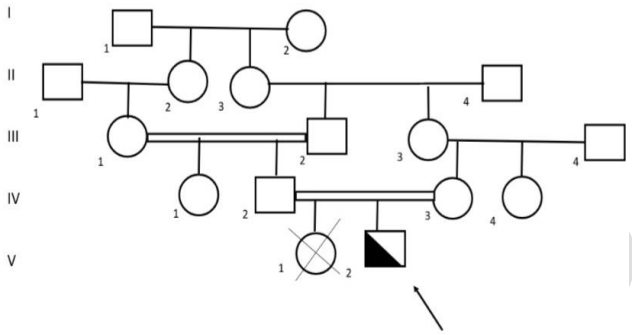

Fig. 3: Genetic pedigree of a patient with the 965T>C (Leu322Pro) mutation: I, II, III- grandparents; III-1, 2-father's parents (cousin); IV-1-father's sister; IV-2,3- close relatives married mother and father (cousin); IV-4- mother's sister; V-1- proband's newborn sister died due to the same symptoms.; V-2-proband.

Based on the proband's pedigree, the kinship coefficient is 0.75, and the inbreeding coefficient is 0.375.

We analyzed the protein structure using Swiss-Model software (www.swiss-prot.org). The novel L322P mutation detected in exon 7 of the *CFTR* gene was accompanied by the substitution of thymine with cytosine in position 965 of the gene, resulting in the substitution of leucine with proline in the protein structure (Fig. 4).

DISCUSSION

Cystic fibrosis (CF) is a life-threatening inherited disease that can have different consequences, in terms of frequency and severity, among various ethnic populations and is connected with mutations of the CFTR gene (Frost et al., 2022; Kececi Ozgur et al., 2024; Gryspeert et al., 2025). The CFTR gene is the gene that codes for making a CFTR protein, which regulates the functions of sweat glands and mucus production. CFTR mutations have been discovered, characterized by either a specific or clinical effect on CF patients. However, not all the identified mutations have the same clinical importance. Most mutations are specific to a disease in the population, while mutations may vary due to ethnic and racial factors in terms of mutation frequency. Even if the mutations are rare, in the case of clinical effects, the mutation may have an impact on different populations. As of April 2018, 500 different CFTR mutations have been reported in Azerbaijani CF patients, and CFTR gene mutations identified in Azerbaijani CF patients have been divided into seven main groups. In the case of clinical disease heterogeneity, some discussion about the CFTR gene is closely related to the development of a worldwide known fatal, autosomal recessive genetic disorder, CF. As of April 2018, 2,190 mutations in total were described in the CFTR gene, and 23,864 Caucasian CF patients were included in the database (Mammadova & Huseynova, 2024; Bustamante, 2024; Yousaf et al., 2024; Kasmi et al., 2024).

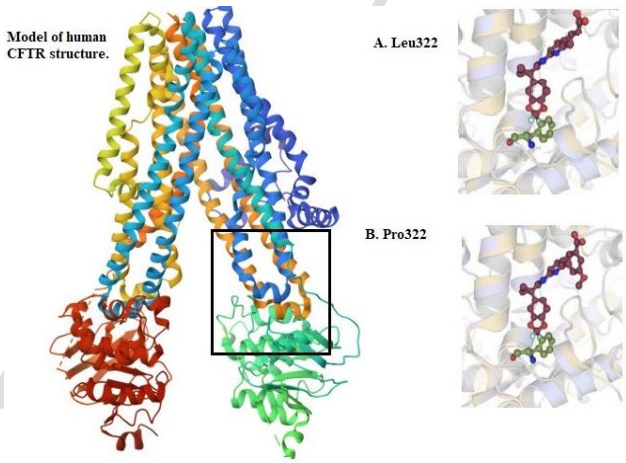

Fig. 4: The *CFTR* protein tertiary structure predicted by Swiss-MODEL software. Different structures caused by amino acid changes are shown in position 322 of CFTR. On the right top, the wild-type leucine, and on the right bottom, the mutant proline is shown.

Understanding the genotype-phenotype connection makes it possible to think about personalized therapeutic strategies susceptible to therapeutic modulation related to different variations. More than 2,000 mutations have been described with varying frequencies in various populations. Although most mutations are rare, some common mutations are the same in different populations, and other mutations are present in only specific geographic regions. A comparison of the results of *CFTR* gene mutation studies in neighboring countries with Azerbaijan was conducted by us (Huseynova et al., 2021).

Jalalirad et al. (2004) performed molecular genetic analysis of seven mutations (ΔF508, G542X, W1282X, G551D, N1303K, 1717-1G→A and 621-1G→T) in exons 4 and 7 of the *CFTR* gene in 37 Iranian patients diagnosed with cystic fibrosis using PCR. This study identified 26.8% of all *CFTR* alleles. During the study, mutations ΔF508 (16.2%), W1282X (4%), G542X (2.7%), R117H (1.3%), R347H (1.3%) and A120T (1.3%) were detected. The obtained data showed the heterogeneity of the Iranian population and demonstrated the need to attract attention to sequence analysis to identify population-specific mutations (Jalalirad et al., 2004).

Radpour et al. (2008) characterized *CFTR* gene mutations in 106 asymptomatic patients to investigate cystic fibrosis in an Iranian population at the molecular level. They also analyzed the 5T DNA variant, which was

identified in 5 of 106 patients and one 5T allele in 46 of 85 patients (two alleles in 11 cases and only one allele of 5T in 35 cases). Thus, various forms of the disease were registered according to the degree of severity, and it was also found that they occur with high frequency in infertile men (Radpour et al., 2008).

Bonyadi et al. (2011) first determined the spectrum of *CFTR* gene mutations in 100 patients with cystic fibrosis from the Azeri Turkic ethnic group in Iran and identified 17 known mutations and one new mutation—K1302X. During their study, researchers determined that the frequency of the DelF508 mutation was 23% (Bonyadi et al., 2011).

Another study was conducted by Morteza et al. (2017) to analyze the influence of the genetic model of cystic fibrosis on the age, sex, and mortality of Azerbaijanis living in Iran. This study was conducted on Azerbaijani cystic fibrosis patients living in Iran from 2001 to 2014. The spectrum of *CFTR* gene mutations was examined in 263 of 331 patients, and the frequency of demographic and genetic data of patients was summarized. The frequency of consanguineous marriages showed a significant difference: 196 (59.2%) positive and 135 (40.8%) negative (P=0.001). In addition to the DelF508 mutation, R553X, R117H, and R334W mutations were frequently observed among Azerbaijanis living in Iran (Morteza et al., 2017).

Alibakhshi et al. (2008) identified 37 mutations. They suggested that 81.9% (113/138) of *CFTR* gene mutations obtained from Iranian cystic fibrosis patients could be characterized as disease-causing mutations. The most common mutations in the Iranian population are F508del (ΔF508) (18.1%), c.2183_2184delAAinsG (2183AANG) (6.5%), S466X (5.8%), N1303K (4.3%), c.2789 It was +5GNA (4.3). %), G542X (3.6%), c.3120+1GNA (3.6%), R334W (2.9%) and c.3130delA (2.9%). These 9 mutations accounted for 52% of all *CFTR* gene mutations obtained from 69 Iranian cystic fibrosis patients. They have identified 8 more mutations — c.406-8TNC, A566D, c.2576delA, c.2752-1_2756delGGTGGCinsTTG, T1036I, W1145R, c.3850-24GNA, c.1342X-154X. The authors identified 37 *CFTR* mutations in 69 Iranian cystic fibrosis patients, obtaining a *CFTR* mutation detection rate of 81.9%, which was estimated to be the highest detection rate achieved so far in the Iranian population (Alibakhshi et al., 2008).

In a study by Karimi et al. (2020) to determine the spectrum and frequency of disease-causing mutations in Iranian cystic fibrosis patients, mutational analysis was performed on the *CFTR* gene, including the complete coding region and intron-exon regions, using direct sequencing. The authors identified 10 mutations in 27 patients. Two of which are new (754delT and GGTGGCdel/TTGins), the most frequently observed in patients are R334W (40.74%), ΔF508 (18.5%), K710X (12.96%), D110H (5.5%), 1897C>G (1.85%).), R1162X (1.85%), S466X (1.8%), and T1036I (1.85%) mutations were identified among the population living in Western Iran (Karimi et al., 2020).

Mohammad & Helal (2020) found 54 variants, including 5 deletions in 345 Iranian patients. In these studies, in 25 patients (3.62%) 2043delG, in 15 patients (2.17%) - c.2051_2052delAAinsG, in 15 patients (2.17%), 2183AA>G, in 12 patients (1.74%) c .1624G>T(G542X), in 12 patients (1.74%) c.1697C>A (A566D), in 9 patients (1.30%) c.1210-12T, in 7 patients (1.01%) c.3196C>T (R1066C) mutations were detected. The frequency of other options is less than 1%, it was recorded by the authors (Mohammad & Helal, 2020).

Mehdizadeh et al. (2020) investigated the frequency of several *CFTR* mutations in cystic fibrosis patients in North-Eastern Iran and examined exon 11 of the *CFTR* gene to detect R344W and R347P mutations in 56 patients. The authors identified 24 mutated alleles among 112 alleles—delF508 (10.71%), 1677delTA (3.57%), S466X (3.57%), N1303K (0.89%), G542X (0.89%), R347P (80%), L467F (0.89%) [26].DelF508, IVS85T, R334W, G542X, D110H, R352Q, and R117H mutations, which were identified with the highest frequency among the *CFTR* gene mutations in the Iranian population, were also studied in the Azerbaijani population. Among these mutations, delF508 (83.3%), R117H (5.5%), R334W (5.5%), and IVS85T (5.5%) were identified in the patients diagnosed with cystic fibrosis studied in the Azerbaijani population. G542X, D110H, and R352Q mutations were not identified in the population of Azerbaijan (Mehdizadeh et al., 2020).

Dayangaç-Erden et al. (2020) examined *CFTR* gene mutations by directly sequencing exon-intron regions in 51 Turkish patients diagnosed with cystic fibrosis at Ankara Hacettepe University. In 72.5% of the alleles studied by the authors, 27 different mutations were identified. Two predominant mutations—IVS8-5T and D1152H—account for more than a third of the alleles. For the first time, five new mutations were identified (Dayangaç-Erden et al., 2020).

Onay et al. (2001) studied the entire coding region of the *CFTR* gene in 122 individuals from 73 Turkish families to determine the spectrum of cystic fibrosis-causing mutations in the Turkish population. They identified three new mutations - 3172delAC, P1013L, and M1028I. The ΔF508 mutation was identified in 18.8% of patients. The second most common mutation identified by the authors was the 1677delTA mutation, with a frequency of 7.3%, and the third and fourth were the G542X and 2183AA→G mutations, with a frequency of 4.9% (Onay et al., 2001). They found *CFTR* mutations causing cystic fibrosis. A comprehensive screening was carried out in Turkey to evaluate the molecular basis of this disease and develop prenatal diagnostic and genetic counseling strategies. In this study, a total of 27 different mutations were identified, accounting for almost 60% of the disease genes in the Turkish population (Onay et al., 2001).

According to Yilmaz et al. (1995), the most common mutation in the Turkish population was ΔF508 (28.4%). Two other mutations (R347H: 3.0%; N1303K: 3.7%) also accounted for 6.7% of the occurring alleles (Yilmaz et al., 1995). Of the mutations IVS8-5T, DelF508, G542X, R553X, R117H, R334W, and S492F identified in the *CFTR* gene in the Turkish population, mutations IVS8-5T, DelF508, R553X, R117H, R334W were identified in the Azerbaijani population. In addition to the DelF508 mutation, the frequency of other mutations was different. Unlike the

Turkish population, the G542X and S492F mutations were not identified in the Azerbaijani population.

Bulegenova et al. (2022) and her colleagues conducted a molecular genetic analysis of the *CFTR* gene in 58 cystic fibrosis patients to study the frequency and spectrum of *CFTR* gene variants in different ethnic groups of Kazakhstan and identify genotype-phenotype correlations. During the study, 28 specific variants were identified. DelF508 mutation, the most common variant in the European population, was identified in 30 patients (51.7%). The authors also found a number of specific variants typical for the population of Kazakhstan. Among these variants, the most common, along with the DelF508 mutation, were R553X, R117H, and R334W mutations (Bulegenova et al., 2022). DelF508, R553X, R117H, and R334W mutations in the *CFTR* gene identified in different ethnic groups of Kazakhstan were also found in the population of Azerbaijan (Bulegenova et al., 2022). The frequency of DelF508 mutation in the population of Kazakhstan was 51.7%, and in Azerbaijan, it was relatively high - 66.6%.

Kiseleva et al. (2020) using a diagnostic panel that allows simultaneous analysis of 60 variants of the *CFTR* gene in the Russian population, found mutations F508del (rs113993960) with a frequency of 2.02%, L138ins (rs397508686) and 394delTT (rs121908769) with a frequency of 0.47%, CF502.5 (CF50212), p.S18Rfs*16 with a frequency of 0.31%, R117H (rs78655421) and G542X (rs113993959) with a frequency of 0.16% among 642 patients diagnosed with cystic fibrosis and identified 23 carriers of mutations. The frequency of heterozygotes in the Russian population was 3.58% or 1:28 (Kiseleva et.al., 2020).

Gorinova et al. (2020) used the new-generation sequencing method to identify 71 CFTR gene mutations in 191 cystic fibrosis patients in the Russian population. Authors, along with these mutations, have identified 14 new mutations: c.580G>A, c.4298A>G, c.613C>A, c.1526G>A, p.252T>A, c.237G>A, c.1488G>A, c.353del, c.1708_1712del, c.3927_3938del, c.1219del, c.1853_1863del, c*1279del, c.2619+1G>A (Gorinova et al., 2020). Of the delF508, R117H, and G542X mutations found in the CFTR gene in the Russian population, delF508 and R117H mutations were identified in the Azerbaijani population. The frequency of the intensified delF508 mutation was observed at a higher frequency in the Azerbaijani population than in the Russian population.

Of the mutations IVS8-5T, DelF508, G542X, R553X, R117H, R334W, and S492F identified in the *CFTR* gene in the Turkish population, mutations IVS8-5T, DelF508, R553X, R117H, R334W were identified in the Azerbaijani population. In addition to the DelF508 mutation, the frequency of other mutations found in the Azerbaijani population is lower than in the Turkish population. Unlike the Turkish population, the G542X and S492F mutations were not identified in the Azerbaijani population (Onay et al., 2001; Mammadova & Huseynova, 2024; Yıldız et al., 2024).

In order to carry out a molecular-genetic study of cystic fibrosis in the Azerbaijan population, the most common mutations of the *CFTR* gene in neighboring countries were taken into account in the Baku city, Sheki-Zagatala, Guba-Khachmaz, and Lankaran-Astara zones the 4th exon - R117H(350G > A), D110H(328G> C), 7th exon - R334W (1000G>T), R352Q(1055G>A), 10 exon S492F(1475C>T), delF508(1521-1523del), 11 exon G542X(1624G > T), R553X(3846G>A) and 8 intron IVS8-5T(1210-1211T>G) mutations of CFTR gene were studied. İn the examined patients, various mutations in exons 4, 7, 10, and intron 8 of the *CFTR* gene. Thus, in the studied population of Azerbaijan, 4th exon-R117H(350G > A), 7th exon R334W (1000G>T), new L322P(965T>C) mutation, 10th exon delF508(1521-1523del) and 8th intron IVS8-5T(1210-1211T>G) mutations of CFTR gene were identified. No mutation was identified in exon 11 of the *CFTR* gene among the studied samples. Early molecular diagnostics of newborns is very important for preventing cystic fibrosis.

Identifying the new mutational patterns of a specific CFTR gene is crucial both in population studies and in clinical practice. This is why searches must be conducted, particularly in a population where the researcher's interest encompasses the country where they are currently working. According to the Clinical and Functional Traits of CFTR data, the analysis of these mutations that were detected both in homozygous and compound heterozygous states could be of importance not only in establishing genotype-phenotype correlations of cystic fibrosis in Azerbaijan but also in any other future studies or practically oriented examinations involving this gene. Certain results have been obtained regarding the analysis of specific CFTR gene mutations prevalent among the populations of Turkey (Dayangaç-Erden et al., 2020; Yıldız et al., 2024), Iran, Russia, and other countries neighboring Azerbaijan.

A comprehensive study involving 87 Iranian families from diverse ethnic backgrounds revealed the following prevalent CFTR mutations (Hosseini Nami et al., 2023). In the Russian Federation, several CFTR mutations have been identified with varying frequencies across different federal districts. Thus, CFTRdele2,3 (Slavic deletion) is present in 6.11% of cases, with regional frequencies ranging from 1.6 to 7.8%. The E92K mutation was found in 3.46% of cases, with a higher prevalence in the Volga (9.2%) and North Caucasus (7.3%) federal districts. 1677delTA deletion is notably prevalent in the North Caucasus (28.4%), especially among Chechen individuals (67.3%). The W1282X mutation, originating from the Middle East, has a frequency of 13.5% in the North Caucasus, with higher rates among the Karachay (88.9%) and Ossetians (37.5%) (Kondratyeva et al., 2024).

While specific data from 2021 to 2025 are limited, studies have identified several CFTR mutations in the Turkish population. These findings underscore the genetic diversity of CFTR mutations within these populations, influenced by historical migration patterns and regional genetic factors.

Raising awareness about cystic fibrosis aims to refocus attention on the condition, as new methods and techniques are being considered for prenatal and early newborn diagnostics and physiotherapeutically directed

treatment applications. Individuals born in this millennium must know about this disease and the specific signs and symptoms of CF-related illnesses.

Conclusion

During 2015-2020, 1344 people from Baku, Sheki-Zagatala, Guba-Khachmaz, and Lankaran-Astara zones of Azerbaijan participated in this study. We found 5 mutations (Phe508del, R117H, R334W, R553X, IVS8-5T, and L322P (novel mutation)) in the CFTR gene of cystic fibrosis patients. We described the L322P mutation for the first time in Azerbaijan, which does not have a reference sequence result in NCBI. In this study, we analyzed the structure of the cystic fibrosis transmembrane regulator protein.

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