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The Genetic Spectrum of Cystic Fibrosis in Different Populations

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Abstract: Cystic fibrosis (CF) is a hereditary disease caused by mutations in the CFTR gene, which regulates chloride ion transport in epithelial cells. To date, more than 1,500 CFTR mutations have been identified, with their prevalence varying among different ethnic groups. This article reviews data on the frequency and spectrum of CFTR mutations in various populations, including Iran, Turkey, Russia, the USA, Australia, and Europe. Special attention is given to neonatal CF screening programs, their effectiveness, challenges related to false-negative results, and the need to adapt mutation panels based on ethnic characteristics. Studies confirm that expanding genetic panels, lowering IRT threshold values, and implementing a differentiated screening approach can significantly improve diagnostic accuracy and patient outcomes.

Keywords: Cystic fibrosis, children, lungs, CFTR gene.

Introduction: To date, more than 1,500 mutations in the CFTR gene have been identified, with their prevalence varying among different ethnic groups. Several studies have been conducted in Iran to examine the distribution of CFTR mutations among cystic fibrosis (CF) patients. In northeastern Iran, an analysis of 56 patients identified 24 mutant alleles (21.42%), with the most common being ΔF508 (10.71%) (1). Another study in Mazandaran Province found only one mutation, ΔF508, among 30 CF patients, accounting for 21.7% (2). Similarly, an analysis of CFTR mutations in 70 Iranian patients showed that ΔF508 was present in 17.8% of alleles, N1303K in 4.3%, and G542X in 3.6% (3).

The CFTR gene is located on chromosome 7 (locus 7q31) and encodes the cystic fibrosis transmembrane conductance regulator, which controls chloride ion transport. Mutations in this gene lead to thickened secretions from exocrine glands, causing dysfunction in the respiratory, digestive, and reproductive systems (4).

According to WHO data, the incidence of cystic fibrosis (CF) among newborns ranges from 1:600 to 1:1200, with approximately 300 children diagnosed with CF annually in Russia. In recent years, due to early neonatal screening and improved therapy, the average life expectancy of CF patients has increased from 5 to 40 years in developed countries and up to 23 years in Moscow and St. Petersburg (4).

In Russia, the most common mutation is F508del, found in over 60% of patients. However, more than 1,200 CFTR gene mutations have been identified, including rare regional variants such as L138ins in the Middle Urals (5) and c.1545_1546del in Chechnya (6).

A study conducted in Turkey revealed that the prevalence of CF in Central Anatolia is similar to that in Northern Europe, with an incidence rate of 2.9 per 10,000 live births in Konya and 2.8 per 10,000 in Kayseri. Among 30 CF patients, the F508del mutation was the most frequent (17/30), with half of the patients being homozygous and the other half compound heterozygous (7).

A comparative study in Australia evaluated three neonatal screening strategies between 1989 and 2008.

It was found that incorporating a CFTR 12-mutation panel increased diagnostic sensitivity from 86.6% (using only IRT) to 95.8% (8).

In the United States, the newborn screening program for cystic fibrosis (CF NBS) has evolved over two decades. An analysis of false-negative cases in New Jersey revealed that some patients with severe respiratory diseases were not detected during initial testing. This led to an update of the CF NBS algorithm, which now includes a lower IRT threshold and an expanded panel covering 139 CFTR variants (9).

In the U.S., expanded CFTR panels include up to 402 mutations; however, high false-negative rates persist among Asian and African American populations (10).

In Australia, a study by Lee & Orton (2025) found that the sensitivity of CFTR panels among South Asians was 64%, the lowest among all ethnic groups. In Europe, the prevalence of the F508del mutation is higher among Northern Europeans (95.6%) compared to Southern European populations (12).

In Turkey, a national CF NBS program has been in place since 2015, based on a two-step measurement of immunoreactive trypsinogen levels (IRT-1/IRT-2). A study by Çoksüer et al. (2025) showed that this method has low sensitivity (80.3%) and a positive predictive value (PPV) of 23.3%, along with high rates of false-negative (FNP) and false-positive results. Among 66 infants diagnosed with CF, 19.7% were identified solely based on clinical suspicion, highlighting the need to revise IRT threshold values and explore alternative strategies to improve screening accuracy.

In the French-speaking community of Belgium, an improved IRT-DNA screening algorithm has been implemented since 2020, incorporating a 12-variant CFTR panel and a fail-safe IRT/IRT method. A four-year evaluation (14) demonstrated a sensitivity of 95% and a median diagnosis age of 23 days, indicating a high level of early detection and timely treatment.

In Italy, the incidence of cystic fibrosis (CF) among Caucasian newborns is estimated at 1/2500–1/3000. A study by Dell'Edera et al. (2014) analyzed the prevalence of CFTR mutations among CF patients and infertile couples in the Basilicata region. CFTR mutations were detected in 6.85% of individuals screened, exceeding the hypothetical carrier frequency (4%). While F508del was the most common cause of CF, rare regional mutations were also identified. The study highlighted the need for expanded screening panels to improve diagnostic accuracy and disease prevention.

In the United States, neonatal screening is mandatory and includes IRT level measurement, a CFTR variant panel, and CFTR sequencing if a single variant is detected. However, a study by McGarry et al. (2024) revealed significant racial and ethnic disparities in NBS sensitivity. Asian (OR 6.3) and Black infants (OR 2.5) were more likely to receive false-negative results, attributed to low IRT levels or incomplete mutation panels. The introduction of an expanded CFTR panel covering 402 variants improved CF detection across all racial and ethnic groups.

The spectrum of CFTR mutations in cystic fibrosis (CF) patients of Pakistani origin differs significantly from Western populations. A study by Majid et al. (2025) reported a high frequency of rare mutations, emphasizing the need to adapt screening programs for this ethnic group.

The prevalence of CRMS/CFSPID varies by geographic region and the neonatal screening (NBS) algorithms used. A study conducted in six Italian centers found that the ratio of CF patients to infants with CRMS/CFSPID was 1:1.30, higher than in countries with a greater prevalence of the F508del mutation (18). In the United States, the frequency of CRMS is estimated to be higher than expected due to the inclusion of expanded gene sequencing in NBS protocols (21).

Children with CRMS/CFSPID generally have a milder clinical course compared to those with a confirmed CF diagnosis. The Italian study (18, 19) found that infants with CRMS/CFSPID had significantly lower levels of immunoreactive trypsinogen (IRT) and sweat chloride concentrations, with the F508del mutation present in only 20% of alleles.

Another study (20) demonstrated that by the age of seven, children with CRMS/CFSPID showed less severe lung involvement compared to CF patients. They experienced fewer hospitalizations, had better lung function, and had lower rates of complications such as Pseudomonas aeruginosa and Staphylococcus aureus infections. However, in 44% of these children, the diagnosis was later revised to CF, highlighting the need for careful long-term monitoring.

Additionally, according to Barben et al. (2021), despite the generally favorable prognosis for most patients with CRMS/CFSPID, some may develop CF or CFTR-related disorders (CFTR-RD) during adolescence or adulthood. Therefore, educating families about potential risks and disease symptoms is crucial.

The lack of a standardized approach to managing children with CRMS/CFSPID has led to significant variations in clinical practice across different centers (18). For example, the frequency of sweat testing ranged from 8% to 100%, while recommendations for salt supplementation varied from 11% to 90%.

The updated international guidelines (21) introduced a

key recommendation for a detailed assessment of children with CRMS/CFSPID at the age of six. This evaluation includes lung function tests and chest imaging, allowing for informed decisions regarding further monitoring. Families are also advised to receive clear instructions on symptoms that require medical attention.

In Uzbekistan, studies by Barataeva L. and Rakhmonova Sh. (2024) confirm that the intestinal form of CF is predominant among newborns. However, data on specific CFTR mutations in this region remain limited.

Thus, the study of CFTR gene mutations across different populations demonstrates significant ethnic and geographic variations in their prevalence. Data on mutation frequencies are essential for optimizing newborn screening programs, prenatal testing, and genetic counseling. Advancements in diagnostic methods, including expanded mutation panels and lower IRT threshold values, contribute to earlier disease detection, which is crucial for improving patient outcomes.

CONCLUSIONS

1.The genetic variability of CFTR differs significantly by ethnicity, necessitating the adaptation of screening programs for various populations.

2.The F508del mutation is the most common in Europe and Russia but is less frequent in Asia and among African Americans. Some regions have specific rare mutations.

3.Neonatal CF screening programs have demonstrated varying effectiveness, with expanded mutation panels and lower IRT thresholds improving diagnostic sensitivity.

4.The false-negative rate remains high among Asian and African American infants, highlighting the need to refine NBS algorithms.

5.Patients with CRMS/CFSPID require long-term monitoring, as some may develop classical CF over time.

6.Genetic studies and CFTR mutation analysis play a key role in optimizing screening, prenatal testing, and genetic counseling.

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