Research Paper

CFTR Variant Analysis of Patients With Cystic Fibrosis in Mazandaran Province, North of Iran

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ABSTRACT

Background: Cystic fibrosis (CF) is a monogenic autosomal recessive disorder caused by pathogenic variants in the CF transmembrane conductance regulator (*CFTR*) gene on chromosome 7. While the ΔF508 mutation is globally predominant, accounting for about 70% of CF cases, Iran exhibits a highly heterogeneous CFTR mutation spectrum.

Objectives: This study aimed to investigate the molecular profile of CF in people from Mazandaran Province, northern Iran.

Methods: We included 17 patients with CF (7 males and 10 females) from unrelated families in Mazandaran Province. The polymerase chain reaction (PCR)-Sanger sequencing was used to find common CFTR pathogenic variants in 14 patients, while whole exome sequencing (WES) and confirmatory Sanger testing were used to identify rare or novel variants in three patients.

Results: Nine distinct pathogenic variants were identified, with c.19911del emerging as the most frequent (25% of mutant alleles), surpassing the globally dominant ΔF508 variant.

Conclusions: The findings highlight the region-specific genetic landscape of CF and emphasize the need for tailored diagnostic strategies in Iran.

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Introduction:

Cystic fibrosis (CF) is a monogenic disorder with autosomal recessive inheritance, primarily affecting people of Northern European ancestry [1]. First described in 1949, this common life-limiting disease arises from deleterious variants in the CF transmembrane conductance regulator (*CFTR*) gene on chromosome 7 [2, 3]. More than 72,000 cases of CF have been reported worldwide [4], and the frequency of the disease varies significantly among different ethnic groups, with the highest incidence observed in individuals of Caucasian descent [5]. In contrast, CF is extremely rare in Japan, with an estimated incidence of approximately one in every 350,000 live births [6]. In Europe, the incidence ranges widely from 1 in 97,000 in Latvia to 1 in 3,400 in Ireland, highlighting notable regional differences in prevalence [7]. According to the American Cystic Fibrosis Foundation Patient Registry (CFFPR), more than 40,000 individuals are currently diagnosed with CF in the United States [8]. More than 75% of individuals with CF are diagnosed by age 2, although the mean age at diagnosis is around 3 years [1].

The *CFTR* gene, located at chromosomal position 7q31.2, comprises 27 exons and encodes the CFTR protein. This protein functions as a chloride ion channel in epithelial cell membranes, playing a critical role in maintaining fluid balance across tissues. Pathogenic variants in the *CFTR* gene disrupt the protein's structure or function, leading to impaired ion transport and the clinical manifestations of CF [9-11]. Over 2,000 unique mutations in the *CFTR* gene have been reported, according to the Cystic Fibrosis Mutation Database, underscoring the genetic heterogeneity of CF [12]. Globally, the ΔF508 mutation represents the most common pathogenic variant in the *CFTR* gene, with an estimated frequency of about 70% among individuals diagnosed with CF [13]. Previous research has indicated that ΔF508 is among the most common *CFTR* mutations in the Iranian population. However, the overall mutation spectrum in Iran is highly heterogeneous, with numerous distinct variants contributing to CF cases across different regions and ethnic groups [14].

Iran, located in the Middle East, has a population of over 92 million with significant ethnic diversity. The majority of the population comprises Persians, followed by Azerbaijanis, Kurds, Lurs, Balochs, Arabs, Turkmens, and other ethnic groups, each contributing to the country's complex social fabric and regional identities [15, 16]. Previous studies on thalassemia and deafness [17-19] have demonstrated a gradient shift in mutation types and frequencies, moving from northwest to southeast parts. This suggests that the northwestern Iranian population is more similar to Turkish and East Europeans compared to the south and southeast populations. Because of this ethnic diversity, some genetic disorders are far more common in specific areas. For example, thalassemia is more common in the North (especially Mazandaran Province) and the South of Iran [20, 21].

The purpose of this study was to characterize the molecular spectrum of CF in Mazandaran Province, north of Iran. By identifying the types and frequencies of *CFTR* gene mutations in this region, we aim to improve understanding of the regional genetic profile of CF, contribute to genotype–phenotype correlation data, and support the development of more accurate diagnostic, screening, and genetic counseling strategies tailored to the local population.

Materials and Methods

Participants were 17 patients clinically diagnosed with CF referred to the CF center at Boali Sina Children's Hospital in Mazandaran Province. CF diagnosis was established by specialists based on elevated sweat chloride concentrations (>60 mEq/L) measured on two separate occasions using the pilocarpine iontophoresis method, in accordance with clinical guidelines, and the presence of characteristic clinical manifestations, including recurrent or persistent respiratory symptoms (chronic cough, dyspnea, sputum production) and/or gastrointestinal features (malabsorption, chronic diarrhea, failure to thrive).

Demographic and clinical variables, including age at diagnosis, sex, family history, consanguinity, and primary clinical manifestations, were first recorded for all participants. Peripheral venous blood samples (3–5 mL) were collected in EDTA-containing tubes. Genomic DNA was extracted from leukocytes using the phenol–chloroform method following standard laboratory protocols. DNA concentration and purity were assessed using spectrophotometry and agarose gel electrophoresis to ensure suitability for downstream analyses.

Fourteen patients were initially screened for known CFTR pathogenic variants using a polymerase chain reaction (PCR)–Sanger sequencing approach. Mutation-specific primers previously described in the literature [17] were employed. Target exons were amplified in a 25 µL reaction containing 100 ng genomic DNA, 10 pmol of each primer, and 2× PCR Master Mix (Amplicon, Den-

mark). PCR amplification was performed with an initial denaturation at 95 °C for 5 minutes, followed by 35 cycles of denaturation at 95 °C for 30 seconds, annealing at 60 °C for 45 seconds, and extension at 72 °C for 1 minute, with a final extension at 72 °C for 7 minutes. Amplified products were visualized on a 1% agarose gel and subsequently purified for bidirectional Sanger sequencing using the Applied Biosystems 3130xl Genetic Analyzer. Sequence chromatograms were analyzed against the CFTR reference sequence (NM_000492.4) to identify pathogenic variants.

Whole exome sequencing (WES) was performed for three patients to identify rare or novel CFTR variants. Genomic DNA was fragmented, and exonic regions were captured using a commercial exome enrichment kit, followed by library preparation with indexed adaptors. Libraries were sequenced on an Illumina platform using paired-end 150 bp reads, targeting a mean coverage depth of ≥100×, with >85% of bases achieving a Phred quality Q score ≥30. Raw reads were aligned to the human reference genome (GRCh38, NM_000492.4) using the BWA tool, and duplicates were marked with Picard. Variant calling was performed using the Genome Analysis Toolkit following best-practice workflows, and variants were annotated and filtered based on minor allele frequency (<1%), predicting functional impact, and known clinical significance in ClinVar and CFTR-specific databases. Candidate CFTR variants were confirmed by PCR–Sanger sequencing, and pathogenic variants were classified according to ACMG/AMP guidelines before inclusion in the study analysis.

Results

A total of 17 patients with CF from unrelated families of Mazandarani origin were included in this study, comprising 7 males and 10 females, aged 3-44 years. Pathogenic variants were identified on both alleles in 13 out of 17 patients. In two patients, a single heterozygous mutation was detected, while no mutation was found in the remaining two patients. Among the 13 patients with biallelic mutations, 9 were homozygous and 4 were compound heterozygous (Table 1).

A total of nine distinct pathogenic variants were identified across the patients, encompassing 28 mutant alleles. The most frequent variant was c.19911del, accounting for 25% of all alleles. The F508del and c.175_176del variants were each detected in three homozygous patients, representing the second most common variants with an allelic frequency of 21.4%. The c.2T>C and c.3230T>C variants were each identified in one patient in the homozygous state. The c.350G>A variant was observed in two patients as part of a compound heterozygous genotype with c.19911del. Additionally, the c.3889dup, c.710A>G, and c.2657+5G>A variants were each detected in a single allele as part of a compound heterozygous genotype (Table 2).

Discussion

Most studies on the identification and prevalence of CFTR variants have mostly been conducted in European and American countries [22], with limited research available in other countries, including Iran, which is home to approximately 1% of the global population, making it the second most populous nation in the Middle East [23, 24]. It has been located on the historic Silk Road route and has witnessed several waves of migration as a result of various historical events, which brings attention to the valuable genetic insights embedded in the Iranian population [25]. Iran's population is composed of diverse ethnic groups, each with its own dialects, languages, and religious beliefs. Recent research reveals that the Iranian population exhibits high genetic diversity while maintaining distinct genetic characteristics [26]. The present study investigated the distribution of CFTR mutations in CF patients from Mazandaran Province, a region situated in northern Iran on the southern shore of the Caspian Sea.

To date, a total of 101 distinct *CFTR* gene variants have been reported among Iranian patients with CF. The most prevalent variant is p.Phe508del (c.1521_1523delCTT), accounting for 21.22% of cases [14]. In the present study, 9 different CFTR variants were identified in CF patients. The c.19911del variant was the most common, followed by the p.Phe508del and c.175_176del variants. Although the frequency of the F508del variant in our study is consistent with previous reports in Iran [27], it remains lower than the rates reported in most Western European countries (~60%), and significantly below those in Albania (81.4%), Croatia (81.3%), and Denmark (81.4%) [28]. In Iran, approximately 54% of F508del alleles are found in patients from the northwest and western regions bordering Turkey. In contrast, in Mazandaran Province, F508del was the second most common variant after c.19911del. This regional variation may reflect genetic heterogeneity across different parts of Iran [26], as well as the unique genetic continuity of populations in the Northern Iranian Plateau, as previously reported [29]. A study on 56 CF patients from Northeastern Iran investigated the frequency of common CFTR mutations using ARMS-PCR, PCR-RFLP, and PCR-sequencing of exons 11 and 12. Among 112

Table 1. Clinical characteristics of patients with CF in Mazandaran Province

Patient[#]	Sex	Age (y)	Sweat Chloride	Pancreatic Insufficiency	Age of Onset (months)	First Clinical Symptom	Consanguinity	Pathogenic Variant
1	M	12	130	+	0	Ileus meconium	First cousin	c.175_176 del/ c.175_176 del
2	F	16	110	+	0	Ileus meconium, Steatorrhea	Distant relative	c.175_176 del/ c.175_176 del
3	F	3	77	+	11	FTT, steatorrhea, recurrent pneumonia	First cousin	c.175_176 del/ c.175_176 del
4	F	6	96	+	6	FTT, steatorrhea	First cousin	F508del/ F508del
5	M	22	118	+	0	Ileus meconium, FTT, steatorrhea	First cousin	F508del/ F508del
6	F	10	120	+	0	Ileus meconium, steatorrhea	No	F508del/ F508del
7	M	9	84	+	0	Ileus meconium, steatorrhea	First cousin	c.19911del/ c.19911del
8	M	10	100	+	10	NA	No	c.19911del/ c.350 G>A
9	M	4	80	+	11	FTT, steatorrhea, recurrent pneumonia	Distant relative	c.19911del/ c.350 G>A
10	M	13	110	+	0	Ileus meconium, FTT, steatorrhea	Distant relative	c.1911del/ c.3889Dup
11	F	5	110	+	9	FTT, Steatorrhea	First cousin	c.2T>C/ c.2T>C
12	F	16	86	NA	3	NA	NO	c.710A>G/ c.2657+5G>A
13	F	8	125	+	4	NA	Distant relative	c.3230T>C/ c.3230T>C
14	F	17	134	+	0	Ileus meconium, FTT, steatorrhea	Distant relative	c.1911del/ unknown
15	F	26	111	NA	NA	NA	NO	c.1911del/ Unknown
16	M	14	119	+	1	Ileus meconium, FTT, steatorrhea	First cousin	Unknown
17	F	44	93	+	0	Ileus meconium, FTT, steatorrhea	No	Unknown

FFT: Failure to thrive. NA: Not answered.

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[#]Patient number.

alleles, 24 mutations (21.42%) were detected, with c.1521_1523delCTT (p.Phe508del) being the most prevalent (10.71%), followed by c.1677delTA (p.Tyr559Ter) and c.1397C>G (p.Ser466Ter) each with 3.57% prevalence, while c.3909C>G (p.Asn1303Lys), c.1624G>T (p.Gly542Ter), c.1030C>T (p.Arg344Trp), and c.1400C>T (p.Leu467Phe) were rare (each with 0.89% prevalence) [30]. These findings highlight the regional spectrum of CFTR mutations in Iran, emphasizing the importance of population-specific genetic screening for accurate diagnosis and genetic counseling.

Establishing a robust genotype–phenotype correlation in CF patients is crucial for advancing personalized medicine, improving prognostic accuracy, and guiding therapeutic decisions. Different CFTR mutations can lead to different clinical manifestations, ranging from classic CF with severe pulmonary and pancreatic involvement to milder or atypical CF. Understanding how specific genetic variants influence disease severity, organ involvement, and response to CFTR modulators enables clinicians to tailor treatment strategies more effectively. Moreover, genotype–phenotype insights are essential for genetic counseling, early diagnosis through newborn screening, and the development of mutation-specific therapies, particularly in populations with diverse or regionally unique mutation spectra.

The findings from Mazandaran Province in our study highlight a distinct CFTR mutational spectrum shaped by

Table 2. Distribution of pathogenic variants in the *CFTR* gene among patients with CF in Mazandaran Province

Variant	Zygosity	Allele Count	Allelic percentage
c.19911del	Homozygous/Compound heterozygous	7	25
F508del	Homozygous	6	21.4
c.175_176del	Homozygous	6	21.4
c.2T>C	Homozygous	2	7.1
c.3230T>C	Homozygous	2	7.1
c.350G>A	Compound heterozygous	2	7.1
c.3889dup	Compound heterozygous	1	3.6
c.710A>G	Compound heterozygous	1	3.6
c.2657+5G>A	Compound heterozygous	1	3.6
Undetected	Homozygous/Compound heterozygous	6	21.4

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founder effects and high consanguinity. Future studies in neighboring provinces such as Guilan and Golestan can be useful for regional comparisons, helping to map population-specific allele frequencies and identify shared or unique variants. Such data can improve genetic counseling, early diagnosis, and targeted carrier screening programs across northern Iran. Moreover, larger, multi-province analyses can clarify genotype–phenotype correlations, reveal potential founder mutations, and guide personalized treatment strategies, including emerging CFTR-modulator therapies. Ultimately, these efforts will contribute to a comprehensive understanding of CF in the Iranian population and inform public health initiatives tailored to local needs.

There were some limitations in this study. The relatively small sample size limited to a single province may limit the generalizability of the findings to other regions of Iran. Two patients showed no detectable CFTR mutations, which may reflect technical limitations of the detection method, including the inability to identify deep intronic variants, large rearrangements, or regulatory region mutations. The absence of comprehensive functional analyses also limits interpretation of rare variants, particularly c.19911del. Additionally, undiagnosed mild or atypical cases cannot be excluded, potentially affecting the representation of the regional mutation spectrum. Larger, multicenter studies using comprehensive sequencing approaches are recommended to validate and expand these findings.

Conclusion

In Mazandaran Province, northern Iran, our analyses revealed a distinct spectrum of CFTR variants, reflecting both genetic heterogeneity and a likely founder effect. The c.1991del variant is the most prevalent mutation in this region, surpassing the globally dominant p.Phe508del (ΔF508), which was the second most common variant in the region. These findings underscore the importance of region-specific genetic screening and contribute to a broader understanding of CF in the Iranian population.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the Ethics Committee of Mazandaran University of Medical Sciences, Sari, Iran (Code: IR.MAZUMS.REC.1403.343). Written informed consent was obtained from the participants or their parents following a counseling session regarding the implications of genetic testing for CF.

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Authors contributions

All authors equally contributed to preparing this article.

Conflicts of interest

The authors declared no conflict of interest.

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