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Reporting Two Novel Mutations in Two Iranian Families with Cystic Fibrosis, Molecular and Bioinformatic Analysis

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ABSTRACT

Background: Cystic fibrosis is the most common heredity disease among the Caucasian population. More than 350 known pathogenic variations in the *CFTR* gene (NM_000492.4) cause CF. Herein, we report the outcome of our investigation in two unrelated Iranian families with CF patients.

Methods: We conducted phenotypic examination, segregation, linkage analysis, and *CFTR* gene sequencing to define causative mutations.

Results: We found two novel mutations in the present study. The first one was a deletion causing frameshift, c.299delT p.(Leu100Profs*7), and the second one was a missense mutation, c.1857G>T, at nucleotide binding domain 1 of the CFTR protein. Haplotype segregation data supported our new mutation findings.

Conclusion: Findings of this study expand the spectrum of *CFTR* pathogenic variations and can improve prenatal diagnosis and genetic counseling for CF.

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Keywords: Cystic fibrosis, Cystic fibrosis transmembrane conductance regulator, Genetic linkage, Haplotype, Sequence analysis

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INTRODUCTION

Cystic fibrosis (OMIM: #219700), a congenital disease with an autosomal recessive mode of inheritance, is caused by mutations in the *CFTR* gene (OMIM: *602421; cytogenetic location: 7q31.2)[1]. These mutations affect the function of the CFTR protein in ion channels in epithelial tissues, leading to unusually viscous secretions. This abnormality gives rise to obstruction in lung airways and pancreatic ducts. Individuals with *CFTR* mutations have shown susceptibility to bacterial infections[2,3].

CF is the most frequent fatal autosomal recessive heredity disease among the Caucasian population with an average incidence of 1 out of 3,500 individuals in Europe[4]. Besides, one in every 2,500, 3,600, and 4,000 children in Australia, Canada, and the US are respectively born with CF[5]. So far, CF Mutation Database has reported more than 2,000 *CFTR* gene variations, of which only 352 have been verified to be pathogenic.

New advances in genetic technology and availability of powerful predictive tools have accelerated the findings of disease-causing mutations, including alterations in the *CFTR* gene in CF patients and carriers[6]. Furthermore, the discovery of novel variants supplements the information about the spectrum of the *CFTR* mutations. These findings are essential for geneticists and clinicians working on CF diagnosis, prevention, and treatment, as well as for those seeking for new therapeutic approaches. Currently, there are powerful tools for the identification and characterization of newly discovered mutations or variants. Both *in silico* and molecular findings may be necessary to verify a mutation as pathogenic or nonpathogenic.

Consanguineous marriage plays a crucial role in the relatively high incidence of CF in Iran, as observed in

List of Abbreviations:
ACMG, American College of Medical Genetics; NBD1, nucleotide-binding domain 1; **CF,** cystic fibrosis; **CFTR,** cystic fibrosis transmembrane conductance regulator; **NBD,** nucleotide-binding domain; **STR,** short tandem repeat;

several other autosomal recessive disorders[7-11]. While CF is believed to be rare in Iran, an earlier investigation has suggested that it might be an underdiagnosed disorder in the country[12].

The present study aimed to investigate nine individuals from two unrelated families who had affected children with CF. To this end, we performed phenotypic examination, pedigree study, and genetic analysis by Sanger sequencing and haplotyping using the *CFTR*-linked STR markers.

MATERIALS AND METHODS

Subjects

Two Iranian families with children suspected of being affected with CF were referred to Dr. Zeinali's Medical Genetic Lab., Kawsar Human Genetics Research Center (KHGRC) for *CFTR* gene analysis. Each family had four members. The affected child who belonged to the family I was a four-month-old male infant at the time of counseling. The affected child from family II was a female infant who had died at two months of age. Peripheral blood samples were collected in EDTA-containing tubes.

DNA extraction and genotyping

DNA samples were extracted by salting-out method[13]. The concentration of the isolated DNA was measured by Nanodrop spectrophotometry (Thermo Fisher Scientific, Foster City, CA, USA). Genetic analysis of the DNA samples was performed using direct sequencing of the *CFTR* gene exons. Primers for sequencing were designed to target all exons, and 200 flanking intronic regions were used based on a previously reported method[14]. Sequences of primers are available upon request. DNA sequencing was carried out using BigDye Terminator Cycle Sequencing Kit (Thermo Fisher Scientific) and analyzed on 3130/XL Genetic Analyzer. By using bioinformatics tools such as MutationTaster[15], PolyPhen-2[16], CADD[17], FATHMM[18], SIFT[19], and PROVEAN[20], we investigated the pathogenicity of the detected variations, including novel variants[21]. Mutation nomenclature was compiled in accordance with the Human Genome Variation Society guidelines[22]. Novelty and pathogenicity of the mutations were also investigated in the Human Gene Mutation (http://www. hgmd.cf.ac.uk/ac/all.php), Clinical and Functional Translation of CFTR (http://cftr2.org), and CF mutation (http://www.genet. sickkids.on.ca) databases, and also in literature review. The protein tertiary structure was predicted by Swiss-MODEL software[23,24].

Short tandem repeat-based homozygosity mapping

We examined the pattern of inheritance by CFTR-linked STR markers using GT Hapscreen CFTR kit (Genetek Biopharma, Berlin, Germany). As per the kit user manual, we drew and interpreted each person's haplotype. We also performed multiplex PCR using the GT Hapscreen CFTR kit, and the fragments were analyzed on the ABI 3130/XL Genetic Analyzer. The resulting files were converted to PDF using GeneMapper IDX 1.5, and fragment sizes were used to draw haplotypes according to the manufacturer's user manual.

RESULTS

Clinical presentation

Family I

The family had been referred to Kawsar Human Genetics Research Center (KHGRC) for prenatal diagnosis. The parents were not consanguineous (Fig. 1A). The proband's (II-1) sweat test was positive for CF. Also, the proband manifested classic CF-related symptoms, i.e. salty-tasting skin from birth and greasy stools. The elastase activity in his stool was severely insufficient (50 µg/g), and microscopic analysis of the stool had revealed many fatty acid droplets. At the time of our examination, the infant had already surgical treatment for ileal atresia. The infant's father, mother, and sister displayed no sign of CF. Haplotyping and mutation analysis of proband's sister (II-2) indicated that she is carrier of mutation inherited from her father.

Family II

A consanguineous couple of Kurdish origin (Fig. 1B) was referred to HGRC for prenatal diagnosis. The mother, a 29-year-old woman, was at 12 weeks of gestation at the time of blood sampling. The deceased female child (i.e., II2, Fig. 1B) had been affected with CF as the positive sweat test confirmed the diagnosis. The family had an 11-year-old son with no CF-associated complications. He also participated in this study.

Sanger sequencing and identification of two novel variants in the *CFTR* gene

The analysis of sequencing revealed three mutations in the studied participants. In family I, we identified two mutations that one of them was a previously described pathogenic deletion, c.1911delG[25] p.(Gln637Hisfs *26), in exon 13 of the proband's sample. His father and sister were heterozygous for this mutation. Another heterozygote mutation, c.299delT p.(Leu100 Profs*7), was detected in exon 4 of the proband. This mutation shared by his mother

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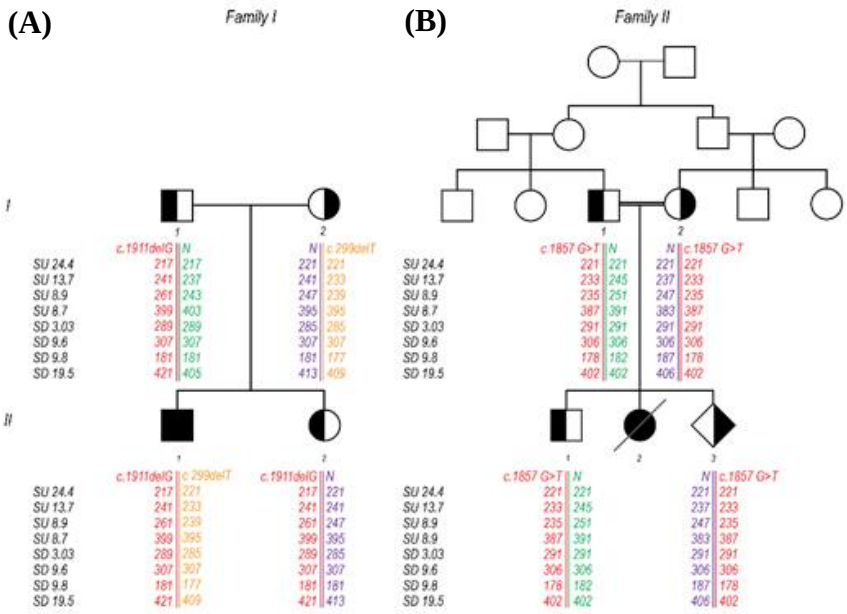

Fig. 1. Pedigree of two families with novel CFTR variants. (A) In family I, the I1, II1, and II2 share the same haplotype and mutation. The II1 shares a similar haplotype with I2, as well. Therefore, the defective haplotypes in the II2 have come from the father even if we do not show the mutation. (B) In family II, I1 and I2 are cousins and share the same mutation and haplotype. Their affected child (II2) has died, and the other two children are carriers based on mutation and haplotype results. II1 has received the defective haplotype from the mother and II3 from the father.

confirmed to be a novel mutation associated with the patient's phenotype, since we did not find any record of c.299delT mutation in the CF Mutation Databases or the literature. Therefore, this mutation can be regarded as a novel genetic variation.

The T deletion at nucleotide 299 (Fig. 2A) causes a frameshift and changes the amino acids (aa) frames, p.(Leu100Profs*7). The frameshift caused by this deletion led to substituting the isoleucine codon with a stop codon at aa 106 (p. I106*). MutationTaster predicted this variant as deleterious. No other mutation in other exons merited the same criteria. All pedigree members in family II, who participated in the study, carried a heterozygous mutation c.1857G>T (Fig. 2B), located in exon 13. This missense mutation caused the substitution of leucine to phenylalanine at position 619 (p.Leu619Phe). There is no previous report on c.1857G>T mutation in the CF Mutation Databases and literature; therefore, it is novel. The *in silico* tools predicted this mutation to be damaging and disease-causing, and its CADD score was 23.0. This mutation is in the NBD1 of the CFTR (Fig. 3). Also, *CFTR*-linked STR markers showed that the parents shared the same haplotype and none of the healthy members,

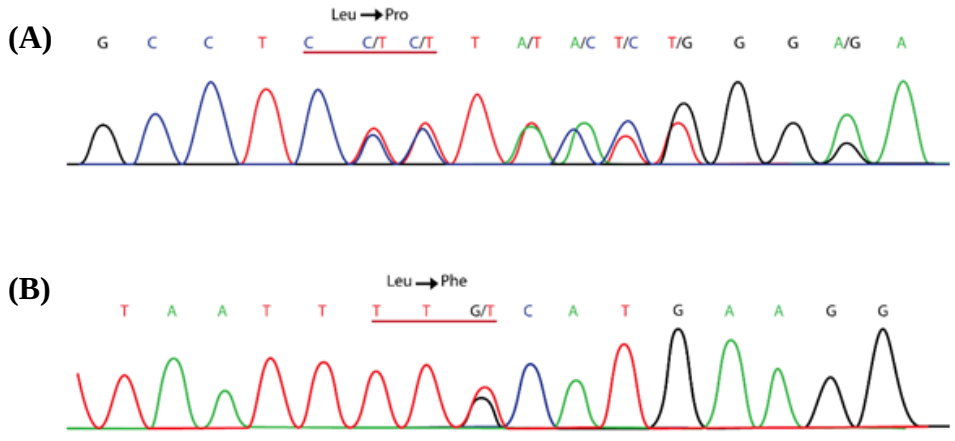

Fig. 2. Result of Sanger sequencing of studied probands. The CFTR variant of (A) c.299delT p.(Leu100Profs*7) and (B) c.1857G>T p.L619F were found in family I and II, respectively.

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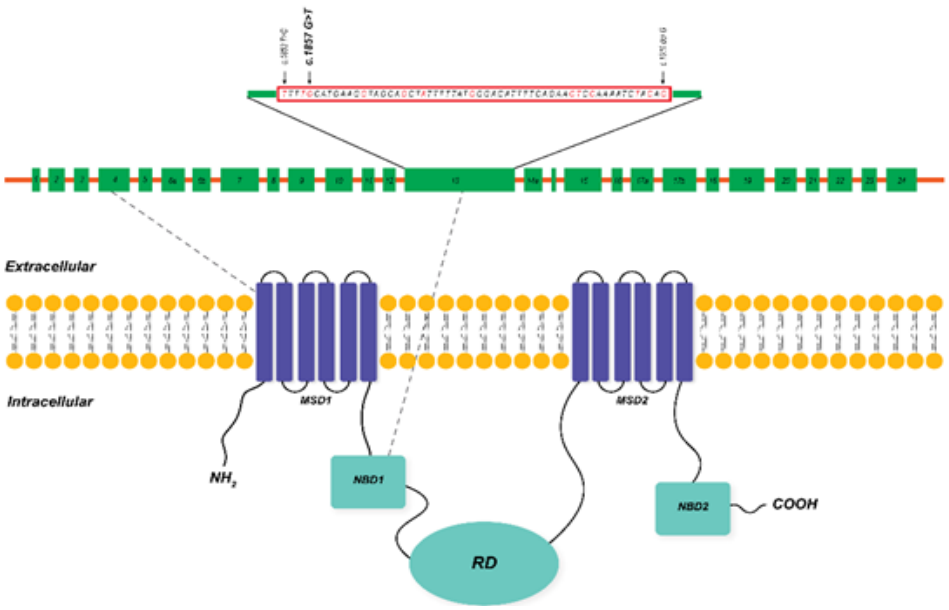

Fig. 3. Exon structure of the CFTR gene and domain structure of the CFTR protein. The mutation hot spot in exon 13. The mutation point is indicated with red line. The position of variants c.299delT p.(Leu100Profs*7) and c.1857G>T (p.L619F) is shown in the three-dimensional structure of CFTR protein. RD, regulatory domain.

including the carrier infant, was homozygote for this haplotype (Fig. 1B). Thus, the segregation analysis of the STR markers suggests an association of c.1857G>T mutation with CF phenotypes in the deceased infant. The Swiss-MODEL predicted the three-dimensional structure of the CFTR protein (Fig. 4). This amino acid substitution in position 619 might affect the stability of the protein.

DISCUSSION

By investigating molecular defects causing CF in our patients, we found two novel mutations, c.299delT and c.1856G>T, in two unrelated families. There is no previous report on these two mutations in the CFTR databases, Human Gene Mutation Database, and literature; thus, they can be regarded as novel

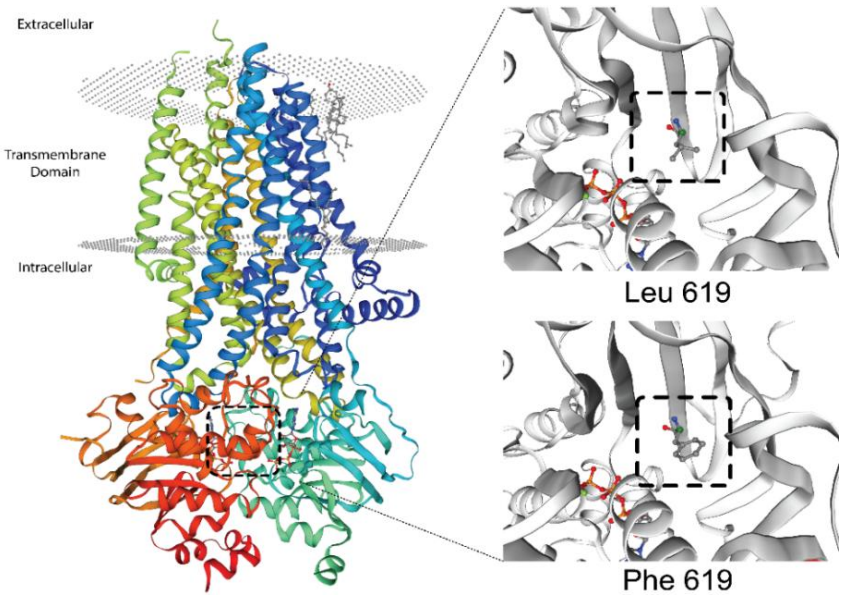

Fig. 4. The CFTR protein tertiary structure predicted by Swiss-MODEL software. Different structures caused by amino acid changes are shown in position 619 of CFTR. On the right top the wild-type leucine and on the right bottom, the mutant phenylalanines are shown.

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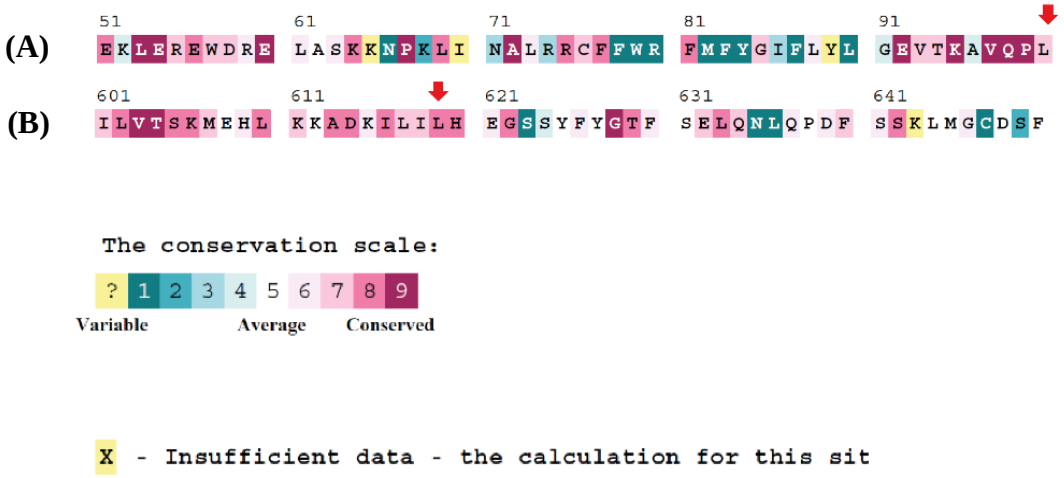

Fig. 5. Conservation score of CFTR protein by ConSurf software. Conservation score of the amino acids (A) 51-100 and (B) 601-650 (B); red arrows indicate the position of 100th and 619th amino acid, respectively.

mutations. Results from this study expand the mutation spectrum of CF disease and will be of great help for prenatal diagnosis and carrier detection of this disorder worldwide.

The affected child in our first case (family I) had typical CF symptoms and was compound heterozygote for c.299delT p.(Leu100Profs*7), and c.1911delG (p.Gln637Hisfs*26) mutations. The novel p.(Leu100Profs*7) mutation was located in the first membrane spanning domain of the CFTR protein and a *CFTR* gene mutation hotspot[26,27] (Fig. 3). The mutation causes a six-amino-acid alteration, and a termination codon follows the frameshift caused by this deletion. The nonsense-mediated mRNA decay targets the transcribed mRNA after this premature termination[28]. This process results in the loss of CFTR protein activity and is consistent with the patient's classical CF phenotypes. The c.299delT p.(Leu100 Profs*7) mutation is classified as pathogenic based on the ACMG guidelines because it meets PVS1, PM2, PM3, and PP3 criteria. It has formerly been classified as class I mutation, as well[29]. *In vitro* analysis can verify the effect of this variant in CF. The patient also carried a second mutation, a previously known deletion, the c.1911delG (p.Gln637Hisfs*26) in exon 13. This mutation has been reported in patients with pancreatic insufficiency and pathological lung conditions[30,31]. The c.1911delG, legacy name c.2043delG, is a common mutation in the north of Iran, where the patients are originally from[31]. Furthermore, several studies have reported this mutation in a number of areas with geographical proximity to Iran, e.g. Russia[32,33] and the Middle Eastern countries such as Bahrain[34], Turkey[35,36], Lebanon[37], and Saudi Arabia[38].

We found a second novel missense mutation in another family having c.1857G>T (p.L619F) mutation. This mutation has a length of 58 nucleotides and is positioned in a mutation hot spot in exon 13, which harbors 15 mutations (12 missense mutations and three deletions) as reported in the CF Mutation Database so far. The mutation is also close to another nonsense mutation hotspot region in exon 13. The altered amino acid is placed in the NBD1 of CFTR protein[39]. The NBD1 is a key player in the CFTR gating control because of its interaction with ATP[40,41]. This mutation introduces an amino acid with different properties, affecting the structural stability and gating function of the protein. Also, the wild-type amino acid, which is leucine and the mutant amino acid, phenylalanine, differs in size. The mutant residue is bigger than the wild type; therefore, its bulky side chain might lead to bumps (Fig. 4). H-loop is a conserved structure[40] in CFTR protein, which is involved in ATP recognition[42]. The c.1857G>T substitution is located seven amino acids downstream of h-loop. All the *in silico* tools predicted this mutation to be damaging, and based on the ACMG guidelines, this mutation is likely pathogenic as it meets PP1, PP2, PP5, and PP3 criteria. *In vitro* as well as *in vivo* confirmatory studies can assess the pathogenic effect of c. 1857G>T in CF patients.

We may here note another adjacent mutation, c.1856T>C (p.L619S), detected in other studies[43-45]. This mutation also changes leucine at position 619 and has been found in a patient with pancreatic insufficiency[43]. Furthermore, when c.1856T>C mutation was introduced in mammalian HEK 293 cells. The transformed cells displayed no Cl^- channel activity in the electrode voltage clam test. The mutated

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cells failed to process the CFTR protein correctly; as a result, the protein was mislocalized[44]. Moreover, nine other mutations approximate to this mutation (aa 601-619) led to CFTR protein processing defects[45]. This high number of pathogenic mutations is consistent with the highly conserved amino acid sequences neighboring the aa position 619 between various species (Fig. 5) and highlights the crucial role of this region, particularly the leucine at position 619 in protein function.

The infant family II had been diagnosed with CF and died very early at two months of age. Although a small population makes it challenging to make a genotype and phenotype connection, haplotyping indicated that c.1857G>T is probably the cause of CF in the infant. Therefore, we can deduce that the mutated allele segregates with a specific haplotype using *CFTR* linked STR markers.

In the present study, we discovered two novel mutations (c.299delT and c.1857G>T) and another missense mutation, c.1911delG of CF disease. Introducing these two novel mutations to the *CFTR* mutation spectrum will help genetic specialists and clinicians better diagnose CF patients and provide more effective medical care. Applying haplotyping will increase the accuracy of findings, particularly in families with few children or consanguinity.

DECLARATIONS

Acknowledgments

The authors would like to thank the families who participated in this study.

Ethical statement

The above-mentioned sampling protocols were approved by the Institutional Review Board of the Kawsar Human Genetics Research Center, Tehran, Iran (ethical code: 1400-6328). All participants or their parents signed informed consent forms prior to blood sampling.

Data availability

The raw data supporting the conclusions of this article are available from the authors upon reasonable request.

Author contributions

AHN: performed and designed experiments, collected and analyzed the data, and AHN wrote the manuscript and prepared figures; MK supervised the study; SZ: conceived the idea, initiated the study, provided the material including patients samples, designed experiments, and supervised the study; All authors have read and edited the manuscript.

Conflict of interest

SZ reports a relationship with Kawsar Human Genetics Research Center (KHGRC), Tehran, Iran that includes board membership. SZ is the CEO of Kawsar Biotech Co., which commercialize the haplotyping kit used in this study. However, the manuscript is not advertising the kits or implying their superiority.

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REFERENCES

1. Ratjen F, Bell SC, Rowe SM, Goss CH, Quittner AL, Bush A. Cystic fibrosis. *Nature reviews. Disease primers* 2015; **1**: 15010.
2. Cutting GR. Cystic fibrosis genetics: from molecular understanding to clinical application. *Nature reviews. Genetics* 2015; **16**(1): 45-56.
3. Allan KM, Farrow N, Donnelley M, Jaffe A, Waters SA. Treatment of Cystic Fibrosis: from gene- to cell-based therapies. *Frontiers in pharmacology* 2021; **12**: 639475.
4. De Boeck K. Cystic fibrosis in the year 2020: A disease with a new face. *Acta paediatr* 2020; **109**(5): 893-899.
5. Scotet V, L'Hostis C, Férec C. The Changing epidemiology of Cystic Fibrosis: Incidence, survival and impact of the CFTR gene discovery. *Genes (Basel)* 2020; **11**(6): 589.
6. Zhao S, Cheng X, Wen W, Qiu G, Zhang TJ, Wu Z, Wu N. Advances in clinical genetics and genomics. *Intelligent medicine* 2021; **1**(3): 128-133.
7. Ajallouyan M, Radfar S, Nouhi S, Tavallaie SA, Amirsalari S, Yousefi J, Hasanali Fard M. Consanguinity among parents of Iranian deaf children. *Iranian Red Crescent medical journal* 2016; **18**(11): e22038.
8. Rahimi Z. Genetic epidemiology, hematological and clinical features of hemoglobinopathies in Iran. *BioMed research international* 2013; **2013**: 803487.
9. Mehrjoo Z, Fattahi Z, Beheshtian M, Mohseni M, Poustchi H, Ardalani F, Jalalvand K, Arzhangi S, Mohammadi Z, Khoshbakht S, Najafi F, Nikuei P, Haddadi M, Zohrehvand E, Oladnabi M, Mohammadzadeh A, Jafari MH, Akhtarkhavari T, Gooshki ES, Haghdoost A, Najafipour R, Niestroj LM, Helwing B, Gossmann Y, Toliat MR, Malekzadeh R, Nürnberg P, Kahrizi K, Najmabadi H, Nothnagel M. Distinct genetic variation and heterogeneity of the Iranian population. *PLoS genetics* 2019; **15**(9): e1008385.
10. Behjati F, Ghasemi Firouzabadi S, Kahrizi K,

[Downloaded from ibj.pasteur.ac.ir on 2026-09-04]
[DOR: 20.1001.1.1028852.2022.26.5.4.3]
[DOI: 10.52547/ibj.3713]

Kariminejad R, Bagherizadeh I, Ansari J, Fallah M, Mojtahedi F, Darvish H, Bahrami Monajemi G, Abedini SS, Jamali P, Mojahedi F, Zadeh-Vakili A, Najmabadi H. Chromosome abnormality rate among Iranian patients with idiopathic mental retardation from consanguineous marriages. *Archives of medical science : AMS* 2011; **7**(2): 321-325.
11. Asadi-Pooya AA, Doroudchi M. Thalassemia major and consanguinity in Shiraz city, Iran. *Turkish journal of haematology* 2004; **21**(3): 127-130.
12. Elahi E, Khodadad A, Kupershmidt I, Ghasemi F, Alinasab B, Naghizadeh R, Eason RG, Amini M, Esmaili M, Esmaeili Dooki MR, Sanati MH, Davis RW, Ronaghi M, Thorstenson YR. A haplotype framework for cystic fibrosis mutations in Iran. *The Journal of molecular diagnostics* 2006; **8**(1): 119-127.
13. Miller SA, Dykes DD, Polesky HF. A simple salting out procedure for extracting DNA from human nucleated cells. *Nucleic acids research* 1988; **16**(3): 1215.
14. Zafarghandi Motlagh F, Fallah MS, Bagherian H, Shirzadeh T, Ghasri S, Dabbagh S, Jamali M, Salehi Z, Abiri M, Zeinali S. Molecular genetic diagnosis of Glanzmann syndrome in Iranian population; reporting novel and recurrent mutations. *Orphanet journal of rare diseases* 2019; **14**(1): 87.
15. Schwarz JM, Cooper DN, Schuelke M, Seelow D. Mutation taster2: mutation prediction for the deep-sequencing age. *Nature methods* 2014; **11**(4): 361-362.
16. Adzhubei IA, Schmidt S, Peshkin L, Ramensky VE, Gerasimova A, Bork P, Kondrashov AS, Sunyaev SR. A method and server for predicting damaging missense mutations. *Nature methods* 2010; **7**(4): 248-249.
17. Kircher M, Witten DM, Jain P, O'Roak BJ, Cooper GM, Shendure J. A general framework for estimating the relative pathogenicity of human genetic variants. *Nature genetics* 2014; **46**(3): 310-315.
18. Shihab HA, Gough J, Cooper DN, Stenson PD, Barker GL, Edwards KJ, Day IN, Gaunt TR. Predicting the functional, molecular, and phenotypic consequences of amino acid substitutions using hidden Markov models. *Human mutation* 2013; **34**(1): 57-65.
19. Sim N-L, Kumar P, Hu J, Henikoff S, Schneider G, Ng PC. SIFT web server: predicting effects of amino acid substitutions on proteins. *Nucleic acids research* 2012; **40**(W1): W452-W457.
20. Choi Y, Chan AP. PROVEAN web server: a tool to predict the functional effect of amino acid substitutions and indels. *Bioinformatics* 2015; **31**(16): 2745-2747.
21. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American college of medical genetics and genomics and the association for molecular pathology. *Genetics in medicine* 2015; **17**(5): 405-424.
22. Den Dunnen JT, Dalgleish R, Maglott DR, Hart RK, Greenblatt MS, McGowan-Jordan J, Roux AF, Smith T, Antonarakis SE, Taschner PE. HGVS Recommendations for the description of sequence variants: 2016 Update. *Human mutation* 2016; **37**(6): 564-569.
23. Waterhouse A, Bertoni M, Bienert S, Studer G, Tauriello G, Gumienny R, Heer FT, de Beer TAP, Rempfer C, Bordoli L, Lepore R, Schwede T. SWISS-MODEL: homology modelling of protein structures and complexes. *Nucleic acids research* 2018; **46**(W1): W296-w303.
24. Biasini M, Bienert S, Waterhouse A, Arnold K, Studer G, Schmidt T, Kiefer F, Gallo Cassarino T, Bertoni M, Bordoli L, Schwede T. SWISS-MODEL: modelling protein tertiary and quaternary structure using evolutionary information. *Nucleic acids research* 2014; **42**(Web Server issue): W252-258.
25. Fanen P, Ghanem N, Vidaud M, Besmond C, Martin J, Costes B, Plassa F, Goossens M. Molecular characterization of cystic fibrosis: 16 novel mutations identified by analysis of the whole cystic fibrosis conductance transmembrane regulator (CFTR) coding regions and splice site junctions. *Genomics* 1992; **13**(3): 770-776.
26. Sharma H, Mavuduru RS, Singh SK, Prasad R. Heterogeneous spectrum of mutations in CFTR gene from Indian patients with congenital absence of the vas deferens and their association with cystic fibrosis genetic modifiers. *Molecular human reproduction* 2014; **20**(9): 827-835.
27. Kerem B, Kerem E. The Molecular basis for disease variability in cystic fibrosis. *European journal of human genetics* 1996; **4**(2): 65-73.
28. Lykke-Andersen S, Jensen TH. Nonsense-mediated mRNA decay: an intricate machinery that shapes transcriptomes. *Nature reviews molecular cell biology* 2015; **16**(11): 665-677.
29. Veit G, Avramescu RG, Chiang AN, Houck SA, Cai Z, Peters KW, Hong JS, Pollard HB, Guggino WB, Balch WE, Skach WR, Cutting GR, Frizzell RA, Sheppard DN, Cyr DM, Sorscher EJ, Brodsky JL, Lukacs GL. From CFTR biology toward combinatorial pharmacotherapy: expanded classification of cystic fibrosis mutations. *Molecular biology of the cell* 2016; **27**(3): 424-433.
30. el-Harith EA, Dörk T, Stuhrmann M, Abu-Srair H, al-Shahri A, Keller KM, Lentze MJ, Schmidtke J. Novel and characteristic CFTR mutations in Saudi Arab children with severe cystic fibrosis. *Journal of medical genetics* 1997; **34**(12): 996-999.
31. Esmaeili Dooki MR, Tabaripour R, Rahimi R, Akhavan-Niaki H. Mutation and new polymorphisms insight in introns 11 to 14a of CFTR gene of northern Iranian cystic fibrosis patients. *Gene* 2015; **564**(2): 193-196.
32. Petrova NV, Kashirskaya NY, Vasilyeva TA, Kondratyeva EI, Zhekaite EK, Voronkova AY, Sherman VD, Galkina VA, Ginter EK, Kutsev SI, Marakhonov AV, Zinchenko RA. Analysis of CFTR mutation spectrum in ethnic russian cystic fibrosis patients. *Genes (Basel)* 2020; **11**(5):554.
33. Ivanov M, Matsvay A, Glazova O, Krasovskiy S, Usacheva M, Amelina E, Chernyak A, Ivanov M, Musienko S, Prodanov T, Kovalenko S, Baranova A,

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[DOR: 20.1001.1.1028852.2022.26.5.4.3]
[DOI: 10.52547/ibj.3713]

Khafizov K. Targeted sequencing reveals complex, phenotype-correlated genotypes in cystic fibrosis. *BMC medical genomics* 2018; **11**(Suppl 1): 13.
34. Eskandarani HA. Cystic fibrosis transmembrane regulator gene mutations in Bahrain. *Journal of tropical pediatrics* 2002; **48**(6): 348-350.
35. Onay T, Topaloglu O, Zielenski J, Gokgoz N, Kayserili H, Camcioglu Y, Cokugras H, Akcakaya N, Apak M, Tsui LC, Kirdar B. Analysis of the CFTR gene in Turkish cystic fibrosis patients: identification of three novel mutations (3172delAC, P1013L and M1028I). *Human genetics* 1998; **102**(2): 224-230.
36. Onay T, Zielenski J, Topaloglu O, Gokgoz N, Kayserili H, Apak MY, Camcioglu Y, Cokugras H, Akcakaya N, Tsui LC, Kirdar B. Cystic fibrosis mutations and associated haplotypes in Turkish cystic fibrosis patients. *Human biology* 2001; **73**(2): 191-203.
37. Farra C, Menassa R, Awwad J, Morel Y, Salameh P, Yazbeck N, Majdalani M, Wakim R, Yunis K, Mroueh S, Cabet F. Mutational spectrum of cystic fibrosis in the Lebanese population. *Journal of cystic fibrosis* 2010; **9**(6): 406-410.
38. Banjar HH, Tuleimat L, El Seoudi AAA, Mogarri I, Alhaider S, Nizami IY, AlMaghamsi T, Alkaf SA, Moghrabi N. Genotype patterns for mutations of the cystic fibrosis transmembrane conductance regulator gene: a retrospective descriptive study from Saudi Arabia. *Annals of Saudi medicine* 2020; **40**(1): 15-24.
39. Liu F, Zhang Z, Csanády L, Gadsby DC, Chen J. Molecular structure of the human CFTR ion channel. *Cell* 2017; **169**(1): 85-95.e88.
40. Lewis HA, Buchanan SG, Burley SK, Conners K, Dickey M, Dorwart M, Fowler R, Gao X, Guggino WB, Hendrickson WA, Hunt JF, Kearins MC, Lorimer D, Maloney PC, Post KW, Rajashankar KR, Rutter ME, Sauder JM, Shriver S, Thibodeau PH, Thomas PJ, Zhang M, Zhao X, Emtage S. Structure of nucleotide-binding domain 1 of the cystic fibrosis transmembrane conductance regulator. *The EMBO journal* 2004; **23**(2): 282-293.
41. Clancy JP, Hong JS, Bebök Z, King SA, Demolombe S, Bedwell DM, Sorscher EJ. Cystic fibrosis transmembrane conductance regulator (CFTR) nucleotide-binding domain 1 (NBD-1) and CFTR truncated within NBD-1 target to the epithelial plasma membrane and increase anion permeability. *Biochemistry* 1998; **37**(43): 15222-15230 .
42. Kloch M, Milewski M, Nurowska E, Dworakowska B, Cutting GR, Dołowy K. The H-loop in the second nucleotide-binding domain of the cystic fibrosis transmembrane conductance regulator is required for efficient chloride channel closing. *Cellular physiology and biochemistry* 2010; **25**(2-3): 169-180.
43. Dörk T, Mekus F, Schmidt K, Bosshammer J, Fislage R, Heuer T, Dziadek V, Neumann T, Kälin N, Wulbrand U. Detection of more than 50 different CFTR mutations in a large group of German cystic fibrosis patients. *Human genetics* 1994; **94**(5): 533-542.
44. Pasyk EA, Morin XK, Zeman P, Garami E, Galley K, Huan LJ, Wang Y, Bear CE. A conserved region of the R domain of cystic fibrosis transmembrane conductance regulator is important in processing and function. *The Journal of biological chemistry* 1998; **273**(48): 31759-31764.
45. Vankeerberghen A, Wei L, Jaspers M, Cassiman JJ, Nilius B, Cuppens H. Characterization of 19 disease-associated missense mutations in the regulatory domain of the cystic fibrosis transmembrane conductance regulator. *Human molecular genetics* 1998; **7**(11): 1761-1769.

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