Case Report

# A novel cystic fibrosis gene mutation c.2490insT in a Palestinian patient: A case report and review of the literature

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**Abstract:**

We report the case of a 19-year-old male patient of Palestinian descent, who presented with a 1-year history of recurrent *Pseudomonas aeruginosa* respiratory infections, weight loss, chronic diarrhea, and a normal chloride sweat test. A panel for common cystic fibrosis transmembrane conductance regulator (*CFTR*) gene mutations test was also negative. Cystic fibrosis (CF) was still clinically suspected thus, full *CFTR* gene sequencing was performed, which revealed a homozygous unreported mutation c.2490insT (GenBank accession number: BankIt2019289 seq1 MF167456). Both parents were also found to be heterozygous for this mutation. This case highlights the importance of clinical evaluation and the need for extensive genetic investigation when dealing with a genetic disease with wide variability in a clinical presentation such as CF.

**Keywords:**

Atypical cystic fibrosis, conductance transmembrane regulatory gene, genetics, new mutation, normal chloride sweat test

Cystic fibrosis (CF) is one of the most common inherited genetic disorders in the Caucasian population with an estimated incidence of 1 in 2500 live birth. While more than 1800 CF transmembrane conductance regulator (*CFTR)* mutations have been identified, delta F508del mutation is the most common mutation (86.5%).[1]

In the Arab population, CF is less common with an incidence ranging between 1 in 2560 and 1 in 15,876.[2-5] The delta F508del mutation along with some other native Arab mutations are described to be common mutations.[6-8]

The introduction of newborn screening worldwide allowed for early detection and better management of this life-threatening disease. In 2014, 63.4% of the newly diagnosed CF cases were detected by newborn screening and 66.4% were diagnosed in the 1st year of life.[1] Patients presenting in adulthood have a milder variant of the disease, with lung diseases being the most common first presentation.[9] Diagnosis of CF in these patients is more challenging and a high level of clinical suspicion is required as they are associated with rare mutations that may fail detection while using the recommended *CFTR* gene mutation panel.[10,11]

We report the case of a 19-year-old male of Palestinian origins, presenting with CF symptoms and a normal sweat chloride test, who was found to be homozygous for a novel *CFTR* gene mutation.

## Case Report

A 19-year-old male patient of Palestinian origins, presented with persistent productive



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cough of 1-year duration, exertional dyspnea, and unintentional weight loss. He also reported a history of chronic diarrhea and a previous sputum culture performed more than 1 year ago which grew *Pseudomonas aeruginosa*. His parents are healthy, consanguineous, and of Palestinian descent. He had a sibling deceased at a younger age following a complicated respiratory infection and another healthy younger brother. No systemic symptoms, joint pain, or skin/mucosal symptoms were present.

On physical examination, the patient looked younger than stated age, confortable, and not in distress. Oxygen saturation was 95% on room air with otherwise normal vital signs. Cardiovascular examination was normal. Lungs demonstrated scattered ronchi with bilateral decrease in breath sounds. Abdominal examination showed an enlarged liver. There were no signs of digital clubbing or cyanosis on extremities. A chest computerized tomography (CT) scan showed diffuse bronchiectasis with a "tree-in-bud" pattern along with liver cirrhosis, cholestasis, and splenomegaly but no ascites. Sputum culture grew pansensitive *Klebsiella* for which ciprofloxacin was started. He was also treated with inhaled bronchodilators and with pancreatic enzymes supplementations (pancrelipase) for steatorrhea.

A week later, the patient reported significant improvement of his cough. Sinus CT scan showed evidence of chronic sinusitis. Quantitative immunoglobulin levels, acid-fast bacillus cultures, liver enzymes, and liver function tests were all normal. Sweat chloride test by pilocarpine iontophoresis showed normal conductivity (<9mmol/L).

*CFTR* gene analysis for mutations known to be common in the local Lebanese population was normal. A full *CFTR* sequencing was performed later on and showed a homozygous unclassified variant c.2490insT [Figure 1 GenBank accession number: BankIt2019289 seq1 MF167456]. Sequencing of *CFTR* gene in parents and a healthy sibling showed both parents to be heterozygous for the same insertion and the sibling to be homozygous normal [Figure 2].

On follow-up, 1 month later, the patient was found to be hyperglycemic and was started on short and long-acting insulin. The patient was maintained on nutritional supplements, nasal saline washes, nebulized hypertonic saline, chest physiotherapy, inhaled tobramycin, and recombinant human deoxyribonuclease (Pulmozyne) with significant improvement in his respiratory symptoms and rare respiratory infections.

## Discussion

Despite a better understanding of the genetics behind CF, atypical cases still present a diagnostic challenge. Diagnosis of these patients is usually delayed until the development of severe complications that could be prevented or minimized by early detection and treatment. Current guidelines set by the American College of Medical Genetics in 2004, recommend screening through a sweat chloride test and a 23-*CFTR*-gene mutation panel (ΔF508; ΔI507; G542X; G551D; N1303K; R553X; 621+1G>T; 1717-1G>A; A455E; R560T; G85E; R334W; R347P; 711+1G>T; 2184delA; 3849+10kbC>T; 3659delC; 3120+1G>A; 2789+5G>A; 1898+1G>A; R1162X; W1282X; R117H). The sensitivity of this panel varies among different ethnic groups with the highest sensitivity in Ashekenazi Jews (94%) and the lowest in Asian Americans (49%).[12-14] Expanding this panel to include ethnicity-specific mutations can increase the test sensitivity.[15,16] A 64-mutation-panel suggested by Heim *et al*. increases the sensitivity of CF screening to 84.1%

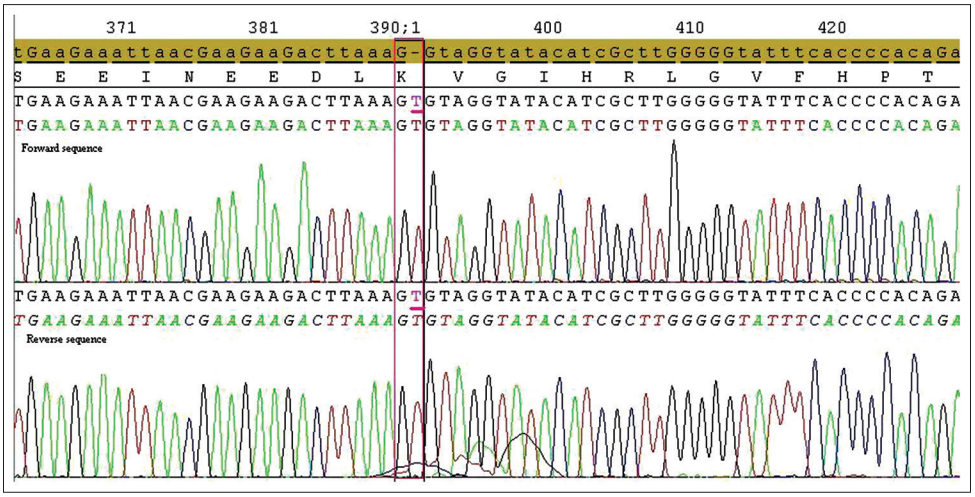


**Figure 1:** Cystic fibrosis transmembrane conductance regulator gene sequence of the patient (child affected with cystic fibrosis) showing c.2490insT underlined in red, in both directions (forward and reverse)

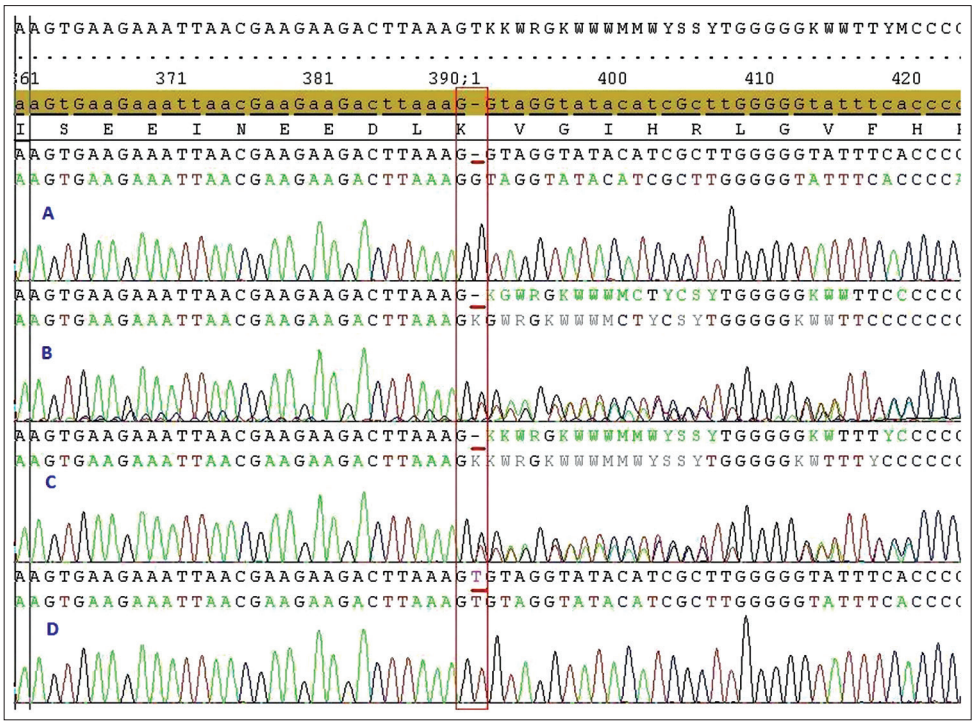


**Figure 2:** Cystic fibrosis transmembrane conductance regulator gene sequences of the 4 family members aligned from top to bottom. (A) Sequence of the healthy brother, no insertion c.2490insT. (B) Sequence of the father, carrier heterozygous for the insertion c.2490insT. (C) Sequence of the child affected with cystic fibrosis, homozygous for the insertion c.2490insT. (D) Sequence of the child affected with cystic fibrosis, homozygous for the insertion c.2490insT

and covers CF gene mutations with a frequency ≥0.1% in the general population.[16] Hubert *et al*. suggest testing for 31 common *CFTR* mutations when the sweat chloride test is normal or borderline with a clinical presentation highly suggestive of CF.[17]

The genetic laboratory at our medical center, tests for the ACMG recommended panel of 23 mutations in addition to 8 mutations previously described in the Lebanese population: S4X; 4010del4; 2043delG; 4016insG; 4096-28G>A; E672del; M952I and S549N.[6]

Data from Arab countries show that delta F508del mutation along with other mutations, such as 1548delG and H139L thought to originate from the native Arab population, to be the most common mutations.[6-8] Among the Lebanese population F508del, N1303K, and W1282X account for most of the mutations.[2,6] While studies on the Palestinian population showed c.1393-1G>A, F508del, N1303K, W1282X, 3120+1Kbdel8.6Kb, and G85E mutations to be the most common.[18-20]

The c.2490insT variant found in this patient was not previously described. It consists of an insertion of a T nucleotide before the G typically positioned at 2490+1 (2490+1G), and is predicted to interfere with the *CFTR*-mRNA splicing leading to a frameshift truncated protein (p. Lys830Asnfs*6) explaining the disease severity presentation.

This case sheds light on the limitation of the standardized genetic testing for CF, as per current recommendations, which may lead to delay in diagnosis and possible misdiagnosis.

It also emphasizes the importance of high level of clinical suspicion and full *CFTR* sequencing in atypical presentations.

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## Conflicts of interest
There are no conflicts of interest.

## References

1. Registry CFFP. 2014 Annual Data Report. Cystic Fibrosis Foundation; 2015.
2. Desgeorges M, Mégarbané A, Guittard C, Carles S, Loiselet J, Demaille J, *et al*. Cystic fibrosis in Lebanon: Distribution of CFTR mutations among Arab communities. Hum Genet 1997;100:279-83.
3. Jonsdottir B, Bergsteinsson H, Baldursson O. Cystic fibrosis - Review. Laeknabladid 2008;94:831-7.
4. Programme HG. Chronic Diseases and Health Promotion. World Health Organization. The Molecular Genetic Epidemiology of Cystic Fibrosis. Genoa, Italy: World Health Organization.
5. Shah U, Frossard P, Moatter T. Cystic fibrosis: Defining a disease under-diagnosed in Pakistan. Trop Med Int Health 2009;14:542-5.
6. Farra C, Menassa R, Awwad J, Morel Y, Salameh P, Yazbeck N, *et al*. Mutational spectrum of cystic fibrosis in the Lebanese population. J Cyst Fibros 2010;9:406-10.

7. Wei S, Feldman GL, Monaghan KG. Cystic Fibrosis testing among Arab-Americans. Genet Med 2006;8:255-8.
8. Shoshani T, Augarten A, Yahav J, Gazit E, Kerem B. Two novel mutations in the CFTR gene: W1089X in exon 17B and 4010delTATT in exon 21. Hum Mol Genet 1994;3:657-8.
9. Gilljam M, Ellis L, Corey M, Zielenski J, Durie P, Tullis DE. Clinical manifestations of cystic fibrosis among patients with diagnosis in adulthood. Chest 2004;126:1215-24.
10. Stewart B, Zabner J, Shuber AP, Welsh MJ, McCray PB Jr. Normal sweat chloride values do not exclude the diagnosis of cystic fibrosis. Am J Respir Crit Care Med 1995;151:899-903.
11. Gaskin K, Gurwitz D, Durie P, Corey M, Levison H, Forstner G. Improved respiratory prognosis in patients with cystic fibrosis with normal fat absorption. J Pediatr 1982;100:857-62.
12. Richards CS, Bradley LA, Amos J, Allitto B, Grody WW, Maddalena A, *et al*. Standards and guidelines for CFTR mutation testing. Genet Med 2002;4:379-91.
13. Genetics ACoM. Technical Standards and Guidlines for CFTR Mutation Testing. Approved by the Board of Directors of the American College of Medical Genetics October 26, 2002. Genetics in Medicine 2002. p. 3.
14. Watson MS, Cutting GR, Desnick RJ, Driscoll DA, Klinger K, Mennuti M, *et al.* Cystic fibrosis population carrier screening: 2004 revision of American College of Medical Genetics mutation panel. Genet Med 2004;6:387-91.
15. Sugarman EA, Rohlfs EM, Silverman LM, Allitto BA. CFTR mutation distribution among U.S. Hispanic and African American individuals: Evaluation in cystic fibrosis patient and carrier screening populations. Genet Med 2004;6:392-9.
16. Heim RA, Sugarman EA, Allitto BA. Improved detection of cystic fibrosis mutations in the heterogeneous U.S. Population using an expanded, pan-ethnic mutation panel. Genet Med 2001;3:168-76.
17. Hubert D, Fajac I, Bienvenu T, Desmazes-Dufeu N, Ellaffi M, Dall'Ava-Santucci J, *et al.* Diagnosis of cystic fibrosis in adults with diffuse bronchiectasis. J Cyst Fibros 2004;3:203.
18. Siryani I, Jama M, Rumman N, Marzouqa H, Kannan M, Lyon E, *et al.* Distribution of Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) mutations in a cohort of patients residing in palestine. PLoS One 2015;10:e0133890.
19. Chiba-Falek O, Nissim-Rafinia M, Argaman Z, Genem A, Moran I, Kerem E, *et al.* Screening of CFTR mutations in an isolated population: Identification of carriers and patients. Eur J Hum Genet 1998;6:181-4.
20. Laufer-Cahana A, Lerer I, Sagi M, Rachmilewitz-Minei T, Zamir C, Rivlin JR, *et al.* Cystic fibrosis mutations in Israeli Arab patients. Hum Mutat 1999;14:543.