

## CASE REPORT

# A rare CFTR mutation associated with severe disease progression in a 10-year-old Hispanic patient

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## Introduction

Cystic fibrosis (CF, OMIM 219700) is a life-shortening autosomal recessive disease that affects one in 3900 individuals in the United States (US). The highest incidence of CF worldwide has been observed in European whites and Ashkenazi Jews, at one in 2500 and one in 2270, respectively [1–3].

A wide ethnic variation of CFTR mutations has been reported, indicating the need for diverse and ethnic-specific mutations to be included in diagnostic and carrier screening conducted in the diverse US population [1, 4]. Many of the mutations identified by temporal temperature gradient electrophoresis (TTGE) and/or DNA sequencing in the US Hispanic population are not detected in the standard ACMG/ACOG-recommended 23-mutation screening panel, despite several of these having a relative frequency over 1% [1].

Here, we report a case of a 10-year-old Hispanic boy diagnosed with cystic fibrosis by positive sweat chloride test, who was found to have two rare CFTR gene mutations, c.233dupT and 7T/12TG. This is the first homozygous case

### Key Clinical Message

Cystic fibrosis is a life-shortening multisystem genetic disease. While readily tested, few tests analyze rare gene mutations prevalent among ethnic minorities. This case of a Hispanic child with a rare CF-causing c.233dupT mutation and severe disease emphasizes the need for broad CFTR mutation analyses and genotyping particularly in minority populations.

### Keywords

Cystic fibrosis, cystic fibrosis genetic testing.

of c.233dupT and only the second case described in the literature with this mutation, with only six in the Clinical and Functional Translation of CFTR (CFTR2) database to date [5]. We describe the aggressive progression of his disease, indicative of the phenotypic severity of this particular mutation. We reinforce the recommendation for a wide mutation screening panel for patients with CF in this ethnic population, due to the potential benefits of early recognition and treatment.

## Case Presentation

A ten-year-old Hispanic boy with history of cystic fibrosis (CF) diagnosed at 2 months of age presented to the pulmonology clinic with worsening pulmonary function and recurrent pulmonary infections. The patient's birth history was unremarkable; he was born at term, with no history of consanguinity. The patient's family history is significant only for the paternal side having diabetes mellitus, but no known family history of CF.

The patient's newborn screen was positive for elevated IRT, but a subsequent 97-CFTR mutation panel was

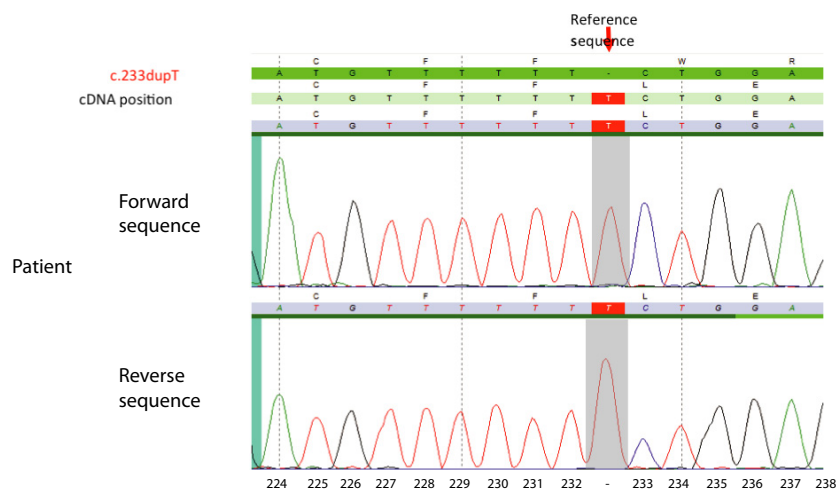
negative. At 2 months of age, a history of failure to thrive, sweat chloride concentration of 94 mmol/L, repeat level 84 mmol/L, and fecal elastase levels (<100), led to his diagnosis of cystic fibrosis with pancreatic insufficiency. The patient was reported to have sporadic follow-up with the pulmonologist in his birth state. Full CFTR gene sequencing (John Hopkins Mutation Analysis Program [MAP]) identified a novel mutation, c.233dupT on exon 3 of the CFTR gene (Fig. 1) and a 7T/12TG polymorphism several years later, with no other mutations identified. After his diagnosis, his mother tested negative for 23 mutations, and younger sister's sweat test and 40-mutation analysis were negative, suggesting that the most common mutations were unlikely to be present in their family. His father and older brother were also healthy.

With a history of chronic congestion, his long-term therapy at this early stage included a bronchodilator, dornase alfa daily, airway clearance with chest percussion therapy, vitamins, and pancreatic enzyme replacement. At 6 months of age, he was admitted for his first CF exacerbation, at which time his sputum culture was positive for *Pseudomonas*, treated with chronic tobramycin inhalation. By 2 years of age, he had multiple CF exacerbations and had received several weeks of IV and inhaled antibiotics. Chest X-rays beginning at 3 months of age, followed by CT scan, showed significant bronchiectasis, and consolidation of the right middle lobe and inferior segment of the lower lobe. These persisted despite aggressive airway clearance. Bronchoscopy and bronchoalveolar lavage (BAL) were unable to resolve the significant mucous plugging. The patient underwent thoroscopic right middle lobe and right lower lobectomies. At the age of four, he demonstrated persistent right upper lobe atelectasis

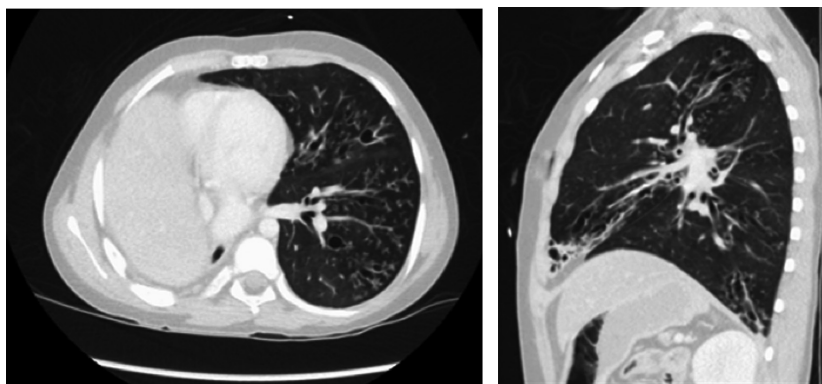
versus infiltrate, with flexible and rigid bronchoscopy revealing purulent fluid in the right bronchi that grew *Staphylococcus aureus*. The right upper lobe infiltrate persisted, however, and a ventilation-perfusion (VQ) scan measured only 3% pulmonary perfusion to the right upper lobe, leading to a right completion pneumonectomy.

After the pneumonectomy, the patient continued to have recurrent CF exacerbations with respiratory infections despite being fully immunized. Immune workup was unremarkable, with normal immunoglobulin levels and expected *Streptococcus pneumoniae* IgG antibody levels. His sputum and respiratory cultures have been positive for *Stenotrophomonas maltophilia*, methicillin-resistant *Staphylococcus aureus* (MRSA), and *Pseudomonas aeruginosa*. In the past 3 years, he has been admitted to the hospital four times per year and required IV antibiotics for one-month duration on multiple occasions. He has been maintained on rotating antibiotics. His most recent exacerbation failed to respond to IV antibiotics. Flexible bronchoscopy showed obstruction of the stump by thick material, and BAL and brush biopsy were positive for *Candida parapsilosis* that responded well to caspofungin.

His last chest CT showed hyperinflated left lung with moderately severe changes of cystic fibrosis, bronchiectasis, bronchial wall thickening, mucus plugging, atelectasis, scarring in the lingula, and stable changes of prior right pneumonectomy (Fig. 2). His pulmonary function tests showed severe mixed restrictive and obstructive lung disease. His best forced vital capacity (FVC) was 0.97 L, best forced expiratory volume in the first second (FEV1) was 0.61 L, with FEV1s ranging from 20% to 40% of



**Figure 1.** Genomic sequencing identifying the C.233dupT frameshift mutation in exon 3 of the CFTR gene in our patient. He also has 7T/12TG repeats.



**Figure 2.** Chest CT with contrast after right pneumonectomy shows a hyperinflated left lung with stable moderate-to-severe bronchiectasis. A marked rightward mediastinal and cardiac shift is seen with elevation of the right hemidiaphragm. Additionally are tree-in-bud densities consistent with peripheral airway occlusion, patchy areas of air trapping within the inferior lingula, and chronic subsegmental collapse and fibrosis with marked focal cystic bronchiectasis.

predicted value. His  $O_2$  saturation on room air was 94%, with venous  $O_2$  saturation 70%, and venous partial pressure  $O_2$  40 mmHg, total  $CO_2$  33 mmHg at last examination. His most recent echocardiogram revealed no evidence of increased pulmonary artery pressure. The patient currently takes levalbuterol tartrate and dornase alfa and uses a saline nebulizer, positive pressure device to help mucociliary clearance, and high-frequency chest wall oscillation (VEST) treatments.

Other comorbid conditions included chronic sinusitis obstructive sleep apnea. A gastrostomy tube was placed when the patient was 7 years old to meet his caloric goals with complete liquid tube feeding formula. He was also found to have CF-related diabetes mellitus that is managed with insulin, vitamin D deficiency, and CF-related liver disease, for which he receives ursodiol. His regimen includes a multivitamin, mineral supplement, and pancrelipase.

Other laboratories showed normal hemoglobin, platelets and electrolytes, elevated BUN of 40 but normal creatinine 0.3 mg/dL. Iron levels were normal. Alpha-1-Antitrypsin level, ANA, and anti-smooth muscle antibody were normal. He had a positive IgE to *Alternaria*, but not to *Aspergillus*. His IgE level was 9.52 kU/L (reference range <78 kU/L). Dual-energy X-ray absorptiometry (DEXA) scan showed bone density consistent with chronological age and total body less head Z-score of -1.9.

On his most recent examination, he coughed occasionally and had few crackles on the left and hollow tubular breath sounds on the right chest, 2+ clubbing, notable chest wall deformity with scoliosis, 2+ tonsils, and cobblestoning of the posterior pharynx. He reported dyspnea with exertion. His frequent exacerbations, moderately severe lung disease on imaging studies and consistently poor

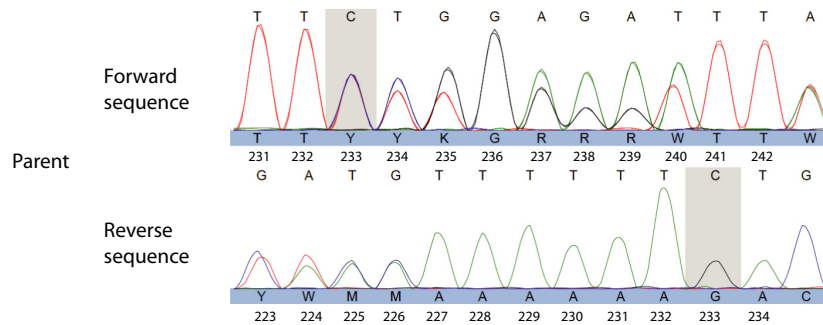
postpneumonectomy pulmonary function tests, have led his clinical care team and family to begin discussing the possibility of lung transplant.

More extensive genomic sequencing of the patient's mother and father suggests this patient is homozygous for the c.233dupT mutation as both parents are carriers of this rare mutation on exon 3 of the CFTR gene. Both the patient and his mother carry the 7T/12TG polymorphism. In addition, his mother also carries a 5T/12TG polymorphism that was not passed on to the patient (Fig. 3).

## Discussion

Cystic fibrosis is caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene on chromosome 7q31. This encodes a transmembrane chloride ion channel protein that requires adenosine triphosphate (ATP) binding and hydrolysis to function. Deficiency or dysfunction of this protein has systemic downstream effects on exocrine glands that lead to elevated sweat chloride levels, thick mucus in the lungs, and in 85% of patients, severely impaired gastrointestinal absorption due to exocrine pancreatic insufficiency [6, 7]. Typically, other complications including CF-related diabetes and CF liver disease are seen in the second decade of life. Median predicted survival age has consistently increased since 1986 to 39.3 years in 2014 [8].

Although mutations in the deltaF508 CFTR gene allele are the most common and account for nearly two-thirds of CFTR mutations, the Cystic Fibrosis Mutation Database and CFTR2 database currently list over 2000 CFTR mutations seen in individuals with CF, with ongoing work to identify the disease-causing mutations [2, 5, 9, 10]. To the best of our knowledge to date, this is the first case describing a cystic fibrosis patient homozygous for c.233dupT, with



**Figure 3.** Sequencing results showed the C.233dupT mutation on exon 3 of the CFTR gene on exon 3 in the patient's mother and father. The patient's mother was found to be heterozygous for both the c.233dupT mutation, 5T/12TG and 7T/12TG polymorphism. The patient's father was found to be heterozygous for the c.233dupT mutation with 7T/7T.

only six cases of the c.233dupT (p.Phe77 fs) CFTR mutation reported in the CFTR2 database [10].

The mutation identified in our patient, 365\_366insT (c.233dupT, p.Phe77 fs, p.Trp79LeufsX32), is a rare frameshift mutation and truncation on exon 3 that causes no CFTR protein to be produced. The complete loss of this protein rather than merely a partial dysfunction as seen with many other mutations may help predict the mechanism of increased disease severity. Phenotypic penetrance appears to be dependent on homozygosity of the c.233dupT mutation, as both parents are heterozygous and asymptomatic, yet this patient has severe disease. The CFTR2 database recently updated classification of this mutation to CF-causing [10]. Alper et al. described the only other case of this mutation reported in the literature in a 10-year-old Hispanic female who was diagnosed with CF at 10 months of age after presenting with recurrent respiratory tract infections and failure to thrive, and a sweat chloride concentration of 84 mmol/L [5]. She was found to have a compound heterozygous mutation identified as c.233dupT (p.Phe77 fs, 360\_365insT) with 1756G>T (p.Gly542Ter) by temporal temperature gradient gel electrophoresis (TTGE) scanning of all CFTR gene coding exons. She had no family history of CF and, by 10 years old, had developed moderate obstructive lung disease and clubbing [5]. Both our patient and the patient in the Alper case are Hispanic without a family history of CF. Although definitive conclusions cannot be drawn from two cases alone due to low power, these cases suggest that this rare mutation has a higher incidence in the Hispanic population and is associated with higher clinical severity.

The 7T/12TG variant that our patient demonstrates may also influence the expression of his disease. Common variants of the polythymidine (poly T) tract in intron 8 of the CFTR gene include 5T, 7T (most common polymorphic variant), and 9T. Based on their size, they have been associated with CFTR-related disorders including

cystic fibrosis and congenital absence of the vas deferens. The TG tract adjacent to the poly T tract typically includes 11, 12, or 13 TG repeats, where longer TG repeats (12 or 13, as in our patient) tend to correlate with an abnormal phenotype. In combination, a shorter poly T tract (5T) and longer TG tract lead to the most decreased efficiency of intron 8 splicing, which may contribute the wide range of clinical presentations [11, 12].

The severity and unrelenting nature of this patient's disease is suggested by his history of lobectomies and eventually a total pneumonectomy due to persistent atelectasis and mucous plugging, despite more conservative management. In addition, our patient has early-onset CF-related diabetes and CF liver disease. In retrospect, it is difficult to judge whether the decision to perform the initial lobectomies at 2 years of age was too aggressive. Additionally, psychosocial and financial circumstances, including language barrier (parents spoke limited English) and poor adherence, may have contributed to his severe progressive disease [13].

A wide range in CFTR allele mutation frequency has been observed in different ethnic groups, as well as regional heterogeneity worldwide [5, 14]. TTGE was found to increase the detection rate of CF mutations in Hispanic patients from 58.0% to 97.5% after common mutation analysis [5]. Previous studies have reviewed the distribution of CFTR mutation in the US Hispanic and African American population and noted an increased frequency of mutations that are not detected by the standard 87-mutation panel as well as many with variable expression [1, 4, 15]. In fact, the 23-mutation panel (American College of Medical Genetics and Genomics) that is used for diagnosis and newborn screening in the general population detects fewer than half of the molecular mutations of patients with CF who are neither Caucasian nor Native American [15]. Thus, prior studies have recommended a diverse mutation screen analysis including ethnic-specific mutations testing when screening for mutations in the

diverse US population, with additional benefits to testing deletion/duplication rearrangements in Hispanics [1, 4, 15, 16]. The current case supports this recommendation, as our patient initially tested negative for 97 different mutations before full-gene sequencing detected his rare mutation.

Early detection and treatment of CF has shown to significantly improve outcomes in children, with treatment initiation before 2 months of age associated with improvement in respiratory and digestive outcomes before 6 years of age. In fact, treatment initiation advanced by 4–13 months appeared to affect outcomes throughout childhood [17]. Advances in treatment options have also allowed for significantly improved disease control and increased life expectancy over time.

## Conclusion

Cystic fibrosis is a life-shortening autosomal recessive disease caused by mutations in the CFTR gene, in which over 2000 mutations have been identified. Recent literature has proposed a number of ethnic-specific mutations, which this case supports. This points to the need for a broad range of CFTR mutation analyses or even full genotyping for patient populations who do not have their mutations identified with the standard mutation panels. This case also suggests a severe disease course associated with this particular mutation, for which early detection and treatment has the potential to improve outcomes.

## Consent

Written informed consent was obtained from the guardian for publication of this case report and any accompanying laboratory values and images. A copy of the written consent is available for review by the Editor of this journal on request.

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## Conflict of Interest

None declared.

## Authorship

KS: gathered data and drafted the initial manuscript; MMGB: supervised, assisted in data collection, critically reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspect of the work.

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