Diagnostic Pathology

CASE REPORT Open Access

Compound heterozygous CFTR variants (*Q1352H and 5T; TG13*) in a Chinese patient with cystic fibrosis

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Abstract

Cystic fibrosis (CF) is an autosomal recessive inherited disease caused by variants of *cystic fibrosis transmembrane conductance regulation (CFTR)* gene. This report presents a case of a Chinese boy diagnosed with CF, attributed to the presence of two specific CFTR gene variations: *4056G > C (NM_000492.4) (p.Gln1352His*, *legacy: Q1352H)* and *c.1210-34TG[13]T[5] (NM_000492.4)(legacy: 5T; TG13)*. A ten-year-old boy was admitted to the hospital due to recurrent pneumonia, cough, and intermittent fever for seven years. Lung auscultation revealed rales, and a lung CT scan indicated parenchymal transformation with infection in both lungs. Whole Exome Sequencing (WES) identified two CFTR gene variants, *Q1352H* and *5T; TG13*, which were significantly associated with clinical phenotype. Following a two-year course of azithromycin combined with inhalation therapy with budesonide, the patient experienced no further episodes of respiratory infections. Moreover, significant improvements were observed in pulmonary function, pulmonary infection, and bronchiectasis. The occurrence of combined variations, *Q1352H* and *5T; TG13*, in the *CFTR* gene is rare and specific to Chinese populations. WES proves to be a valuable diagnostic tool for detecting *CFTR* gene variants.

Keywords Cystic fibrosis, *CFTR variants*, Whole exome sequencing (WES), Compound heterozygous, Chinese population, Case report, Recurrent pneumonia, Genetic diagnosis

Introduction

Cystic fibrosis (CF) is a genetic disease inherited in an autosomal recessive manner, primarily affecting organs such as the lung, pancreas, gonads. It is caused by variations in the *CF transmembrane conduction regulator (CFTR)* gene. Clinical manifestations of CF include recurrent lung infections, chronic cough with sputum production, pancreatic dysfunction, and male infertility. The majority of CF cases are reported among Caucasian populations. The measurement of sweat chloride ion levels serves as the gold standard for CF diagnosis. [1, 2] Compared to the prevalence rate of 1 in 3000 among Caucasians, [2] CF is much less common in the Chinese population, with an estimated occurrence of 1 in 128,434. [3] This report presents a case study detailing the clinical features and diagnostic procedures employed in a boy with compound heterozygous variants (*c.4056G > C [NM_000492.3]* (*p.Gln1352His*, legacy: *Q1352H)* and *c.1210-34TG[13]T[5] [NM_ 000492.3] (legacy: 5T; TG13))* of the *CFTR* gene.

We present the following case in accordance with the CARE reporting checklist.

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Case report

A ten-year-old boy was admitted to our hospital on September 17, 2020, presenting with a history of recurrent pneumonia for seven years, accompanied by a persistent cough and intermittent fever for the past ten months. Over the past seven years, he experienced episodes of pneumonia once or twice per year. Treatment with either intravenous or oral cephalosporin (specific drugs and dosages unknown) for one week would typically alleviate his symptoms. It is worth noting that he never had severe pneumonia requiring intensive intervention. The boy also has a history of recurrent rhinitis, sinusitis, and otitis media since the age of three. There was no complication during childbirth, and the parents of the child are not blood relatives. Furthermore, the absence of siblings and a lack of similar symptom history among other family members have been reported.

Upon admission, the patient's physical examinations revealed normal body temperature, pulse, and blood pressure. He had a thin build, measuring 135 cm in height and weighing 25.4 kg, with not clubbed-fingers. His breathing was stable, with a respiratory rate of 18 breaths per minute and no signs of cyanosis. Auscultation of both lungs detected symmetrical breath sounds, characterized by rales. No abnormalities were observed during the examination of the heart, liver, and spleen. A lung CT scan exhibited inflammatory consolidation in the middle lobes of both the left and right lungs (Fig. 1A).

Various laboratory tests, including blood routine, C-reactive protein, liver function, kidney function, electrolytes, immunoglobulin, and blood flow cytology, showed no abnormalities. The serum procalcitonin (PCT) level was 0.07ng/ml, and the erythrocyte sedimentation rate was 27 mm/h. Tests for *Mycoplasma pneumoniae* antibodies, TB-PPD (tuberculin purified protein derivative), and sputum cultures all yielded negative results. Pulmonary function analysis indicated mild obstructive ventilatory dysfunction, with the forced expiratory volume in the first second (FEV1) at 73.7% of predicted value and a FEV1/forced vital capacity (FEV1/FVC) ratio of 82.16%. The peak expiratory flow (PEF) was 67.9% of the predicted value. Fractional exhaled nitric oxide (FeNO) was at 4ppb, and the alveolar exhaled carbon monoxide (CaNO) at 3.6ppb.

Bronchoscopy revealed bilateral bronchial mucosal inflammation with pale mucus attached white secretions. Culture of alveolar lavage fluid yielded negative results. High-throughput sequencing of pathogens in the bronchoalveolar lavage fluid (BALF) suggested the presence of Haemophilus influenzae. However, a sweat chloride ion test was not performed because no hospital can do it in Beijing and Tianjing area in China. In differential diagnosis, diseases such as primary ciliary dyskinesia (PCD), chronic pancreatitis, and immunodeficiency were excluded. To further elucidate the etiology, Whole Exome Sequencing (WES) was performed after obtaining informed consent from the boy's parents. The results revealed two *CFTR* gene variants significantly associated with clinical phenotype: a heterozygous variant of *Q1352H* of *CFTR* (Fig. 2A) [4, 5], derived from his mother, resulting in an amino acid variant *p.Q1352H*; and a heterozygous variant of *5T; TG13* of *CFTR* (Fig. 2B) [6], derived from his father. Consequently, a diagnosis of CF was established based on the genetic test report. The patient was 10 years old and consequently did not undergo fertility analysis.

Four and seven months after being discharged, the boy experienced two hospitalizations due to fever, cough and sputum. A lung CT scan conducted at the fourth month after discharge revealed inflammatory consolidation in both the left and lung right middle lobes, as well as bronchiectasis in the right middle lobe and left lung (Fig. 1B). Pulmonary function analysis tests showed normal results. Bronchoscopy confirmed inflammation of the bronchial mucous membranes in both lungs, along with a significant amount of white secretions. High-throughput sequencing of pathogens in the BALF identified *Streptococcus pneumoniae* and *Pseudomonas aeruginosa*.

At the seventh month after discharge, a lung CT scan indicated an exacerbation of inflammatory consolidation

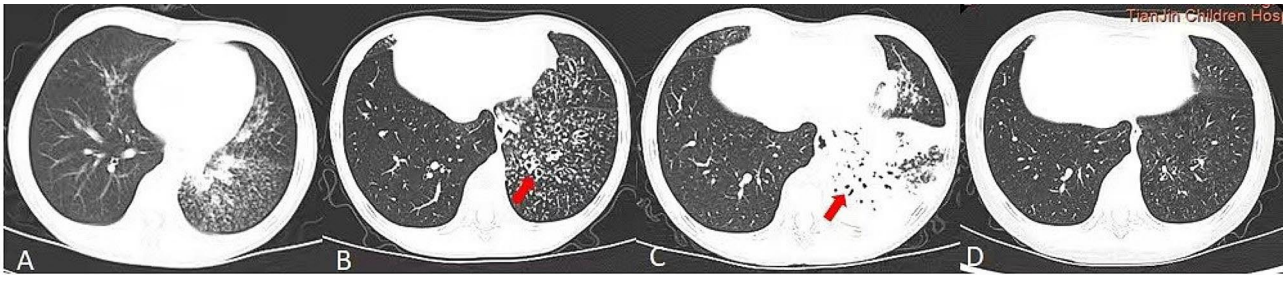

Fig. 1 Compound Heterozygous CFTR Variants in a Boy with CF: Lungs CT Scan Findings. **A**, the lungs CT scan indicates inflammatory consolidation in both the left and right middle lobes of lung. **B**, at the four-month follow-up, the lungs CT scan shows inflammatory consolidation in the left and right middle lungs, along with bronchiectasis in the right middle and left lungs (indicated by arrowed). **C**, at the seven-month follow-up, the CT scan demonstrates more advanced left lung lesions and accompanying bronchiectasis in the left lung (arrowed). D, at the twenty-two months follow-up, the lungs CT scan indicated a notable improvement in distal bronchiectasis in the right middle lobe and left lung compared with previous scans

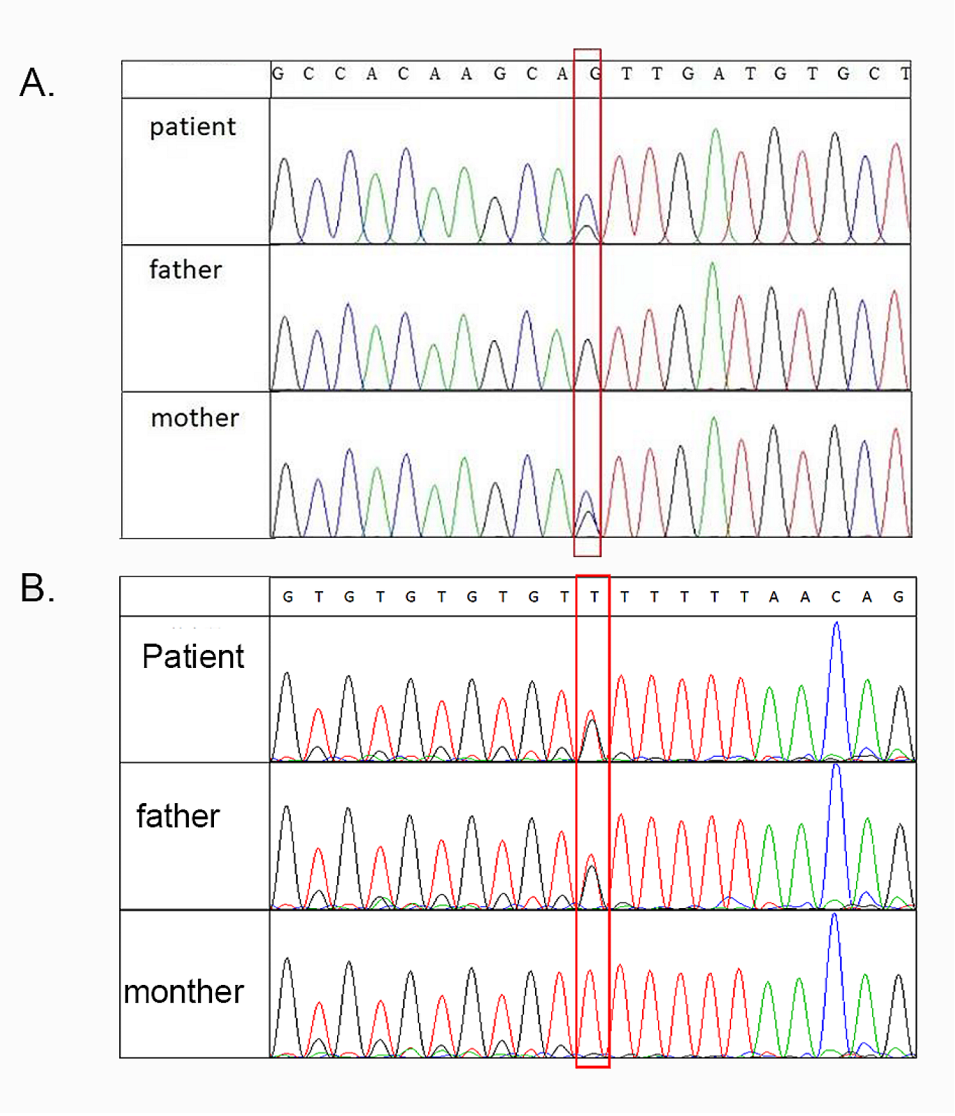

Fig. 2 Whole Exome Sequencing (WES) reveals CFTR (NM_000492.4) variants. **A**, The results of WES result revealed that both the boy (patient) and his mother carry the *c.4056G> C (Q1352H)/p.Gln1352His* variants. **B**, The results of WES indicated that both the boy (patient) and his father carry the *c.1210-34TG[13]T[5]* (*legacy: 5T; TG13*) variant. Both variant codes are highlighted in red boxes

in the left lung lesion compared to previous scans (Fig. 1C). Pulmonary function test indicated mild obstructive ventilatory dysfunction, with the FEV1 at 61.7% of the predicted value, FEV1/ FVC ratio at 96%, And PEF at 60.3% of the predicted value. Both recurrences were treated with a 10- to 11-day course of intravenous infusion of 60 mg/(kg.d) Cefoperazone sodium and sulbactam sodium, combined with inhalation of budesonide suspension.

After discharge, the boy continued taking 10 mg/(kg.d) of azithromycin (Pfizer) orally for three days, followed by a four-day break, orally, and received twice-daily inhalation of budesonide and formoterol fumarate powder for Inhalation (80 μg/4.5 μg) (Symbicort Turbuhaler, AstraZeneca AB, Sdertlje, Sweden) twice a day.

During the two-year follow-up period after discharge, the boy did not experience any further episodes of respiratory infection. At the age of twelve, he measured 143.8 cm in height and weighed 38.1 kg. His pulmonary function gradually improved and normalized over the two-year period after discharge. The most recent pulmonary function test results showed 96.3% of the predicted FEV1 value, 85% of the predicted FEV1/FVC ratio, and 83.6% of the predicted PEF predicted value. At twenty-two months after discharge, a lung CT scan indicated significant improvement in the bronchiectasis of the right middle lobe and distal bronchiectasis of the left lung compared to previous scans (Fig. 1D).

(WES)

WES was performed at Fuzhou Furui Medical Laboratory (Beijing, China). Peripheral blood samples were collected from the child and his parents, and genomic DNA extraction was carried out using the TGuide S32 blood genome DNA extraction kit (Tiangen Biochemical Technology, Beijing, China). WES was conducted using coding+flanking regions method and on the illumina Novaseq 6000 platform (illumina, USA). Due to the rarity of CF patients in China, major hospitals in Tianjin and Beijing have not conducted sweat chloride testing analysis. Therefore, no sweat chloride testing was performed.

Discussion

Cystic fibrosis (CF) is a genetic disorder caused by variants in the *CFTR* gene, leading to dysfunction of chloride and sodium ion transport in epithelial tissues. This dysfunction affects various organs, including the lung, liver, pancreas, respiratory tract, intestinal tract, biliary tract, reproductive tract, heart and vascular smooth muscle. Over 1800 CFTR variants associated with CF have been identified, with the most common variants being ΔF508, resulting in impaired CFTR function or insufficient quantities of CFTR [7, 8].

The compound heterozygous variants *Q1352H* and *5T; TG13* reported in this case are exceptionally rare, with only three cases reported in the Chinese population so far [9–13]. It appears that this compound heterozygous variant of CFTR has a distinct distribution pattern in the Chinese population [10, 11]. CFTR variants in the Chinese population exhibit a different spectrum compared to Caucasian population. For example, *G970D (c.2909G>A)* variants of *CFTR* is the most common type in Chinese populations, but not found in Caucasians. This highlights the higher haplotype diversity and distinct variants patterns in Chinese individuals with CF compared to Caucasians [14]. Two cases of Chinese CF with *Q1352H* variant of *CFTR* were reported so far. Experimental analysis showed that *p.Q1352H* cariant can significantly reduce the protein expression of mature glycosylated CFTR. Compared with the wild-type, the varianted protein expression level decreased by 73%, and the chloride ion channel current decreased by 71% [15]. In studies on patients with congenital *vas* deferens deficiency and CF, it was found that compared to the control group, *T5* was only found in patients [12].

The majority *CFTR* variants in Caucasian individuals are located in nucleotide binding domain one of *CFTR*. However, the first two of the most common pathogenic/likely pathogenic (P/LP) variants (G970D and D979A) are located in the transmembrane domain two of *CFTR* in Chinese population. Compared to Caucasians, Chinese people with CF have higher haplotype diversity [3]. In addition, Ni et al. compared 140 Caucasian's specific CFTR P/LP variants with 53 Chinese P/LP variants and found that only 21 variants were shared each other. Therefore, the CF screening panels for the Caucasian population may not be suitable for the Chinese population [3].

In handling this case, there were regrettable shortcomings, as we did not strictly follow the CF Clinical Care Guidelines. Instead, we impatiently applied azithromycin and budesonide for anti-inflammatory treatment. This serves as a lesson for doctors in areas where CF is rare. However, after long-term treatment with azithromycin and budesonide, the cough symptoms, bronchiectasis, and lung function of the patient have all improved. More time for follow-up is needed to investigate whether this treatment will further benefit the patient.

In conclusion, this case highlights the rarity of the compound heterozygous variants *Q1352H* and *5T; TG13* in the *CFTR* gene, particularly in the Chinese population. The Chinese population exhibits a distinct spectrum of *CFTR* variants compared to Caucasians, necessitating different screening panels. The long-term treatment regimen involving azithromycin and inhalation therapy resulted in improved pulmonary function without significant adverse effects in the patient. However, further research is needed to determine the optimal duration and efficacy of azithromycin treatment in CF patients.

Acknowledgements

None.

Author contributions

RG and YZ contributed to the study conception and design. All authors collected the data and performed the data analysis. All authors contributed to the interpretation of the data and the completion of figures and tables. All authors contributed to the drafting of the article and final approval of the submitted version.

Funding

The funding was supported by the Tianjin Key Medical Discipline (specialty) Construction Project (No. TJYXZDXK-040 A).

Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Ethical approval was given by the Ethics Committee of Tianjin Children's Hospital (Children's Hospital of Tianjin University) Machang compus (L2021-08). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Written informed consent was obtained from the guardian of the participant.

Consent for publication

All data published here are under the consent for publication. Written informed consent was obtained from all individual participants included in the study.

Competing interests

The authors declare no competing interests.

Received: 19 April 2024 / Accepted: 29 July 2024
Published online: 06 August 2024

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