BMC Pediatrics

RESEARCH Open Access

Clinical and genetic characteristics of diseases caused by *CFTR* gene mutations in 15 Chinese children: a retrospective analysis

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Abstract

Objective This study aimed to summarize and analyze the clinical and genetic characteristics of diseases caused by cystic fibrosis transmembrane conduction regulator (*CFTR*) gene mutations in Chinese children and to improve our understanding of cystic fibrosis (CF).

Methods We retrospectively analyzed the clinical data of 15 children with *CFTR* mutations who were admitted to Children's Hospital of Chongqing Medical University from January 2012 to January 2023.

Results 15 Chinese patients were included in our study, among which 9 had a confirmed diagnosis of CF. The median age of onset was 1.00 years (IQR 0.11–5.08 years, range 0-13.17 years). The median age of diagnosis was 5.33 years (IQR 0.43–11.33, range 0.09–14.17 years). Among those confirmed CF patients, 66.7% had bronchiectasis, 88.9% had malnutrition, and 66.7% had fatty stools. Across all hospitalizations, P. aeruginosa (6 patients), Haemophilus influenzae (6 patients), Staphylococcus aureus (5 patients), and Klebsiella pneumoniae (3 patients) were the most common bacterial infections. We identified 27 variants (two patients had three variants and one patient had single variant) from 15 individuals. The common variants included c.1521_1523delcTT (3 patients), c.2909G > A (2 patients), c.1766 + 5G > T (2 patients), and c.374T > C (2 patients). Four novel variants were found, namely c.2476_2477AACG ins, c.3104 A > G, c.884delT and c.4137-35G > A.

Conclusion Our study demonstrated that the clinical phenotypes associated with *CFTR* gene mutations are diverse. *CFTR* gene variants are rare in China, and the pathogenicity of over half of the associated loci remains unclear. Enhancing sweat chloride detection should be applied to facilitate the diagnosis of these conditions and clarify the pathogenicity of these variants.

Keywords Cystic fibrosis transmembrane conductance regulator, Cystic fibrosis, CFTR-related disorders, Phenotype, Gene variants, Children

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Introduction

The cystic fibrosis transmembrane conductance regulator gene *CFTR* on chromosome 7's long arm (7q31), spans a 230 kb genomic sequence comprising 27 exons [1]. It encodes the CFTR protein, a cyclic adenosine monophosphate (cAMP) dependent chloride channel in ion and fluid transport across the apical membrane of epithelial cells in various organs including lungs, intestine, pancreas, hepatobiliary system, reproductive system and sweat glands. Dysfunction of CFTR leads to impaired ions transport, resulting in thick mucus secretion by exocrine glands, which leads to obstruction and damaging defense mechanisms, and culminates in tissue destruction [2]. In fact, CF diagnosis in China is underestimated due to the unavailability of CFTR functional tests (sweat test, NPD or ICM) and different genetic spectrum and phenotypes from CF patients in Europe [3–5]. It is particularly important for the diagnosis of CF in China to analyze *CFTR* gene variants. Here, we retrospectively summarized the clinical data and *CFTR* gene variants of patients with *CFTR* gene mutations screened by next-generation sequencing at the Children's Hospital of Chongqing Medical University from January 2012 to January 2023.

Table 1 Clinical features of cystic fibrosis or CFTR-related disorders [12]

	Cystic fibrosis manifestations	CFTR-related disorders
Lungs	Recurrent or chronic bacterial and fungal infections, bronchiectasis, pneumothorax, haemoptysis and respiratory failure	Bronchiectasis (non-cystic fibrosis)
Upper airways	Chronic sinusitis and nasal polyps	Chronic sinusitis and nasal polyps
Pancreas	Pancreatic insufficiency, and pancreatitis	Recurrent pancreatitis
Liver	Neonatal jaundice, liver disease, fatty liver, cirrhosis, and biliary calculi	Primary sclerosing cholangitis
Gut	Meconium ileus, distal intestinal obstruction syndrome, malnutrition, and dyslipidaemia	
Kidneys	Urinary tract calculi	
Male genitals	Congenital bilateral absence of the vas deferens, and azoospermia and infertility	Congenital bilateral absence of the vas deferens
Female genitals	Cervical mucus abnormality	
Endocrine	Cystic fibrosis-related diabetes	
Sweat glands and skin	Hypochloremic metabolic alkalosis, dehydration, and aquagenic palmoplantar keratoderma	Aquagenic palmoplantar keratoderma

Patients and methods

Study objects

Fifteen hospitalized patients were admitted from Children's Hospital of Chongqing Medical University between January 2012 and January 2023. The patients received the (suspected) diagnosis of CF or CFTR-RDs prior to inclusion in the study due to the presence of clinical features consistent with the disease and at least one rare *CFTR* variant identified by next generation sequencing.

Diagnosis for CF or CFTR-RDs

In regions without newborn screening, diagnostic criteria for CF are suggestive clinical manifestations (Table 1), or familial history and evidence of CFTR dysfunction, or familial history and two disease causing *CFTR* variants [5–7]. However, there are CF cases with only one *CFTR* variant in Europe [8]. Sweat testing remains the gold standard test of CFTR function (≥ 60 mmol/L, diagnostic; 30–59 mmol/L, intermediate; < 30 mmol/L, normal). In our study, not everyone conducted sweat test.

The diagnosis of CFTR-related disorder has been defined as a mono or combined single organ disease (Table 1) associated with CFTR dysfunction that does not fulfill the diagnostic criteria for CF [9, 10]. After inconclusive sweat testing (30-59mmol/L) or genetic testing (uncharacterized or varying clinical consequence), nasal potential difference (NPD) and intestinal current measurement (ICM) can further be applied to detect the CFTR function [11]. CFTR-related disorders will frequently have intermediate values indicating a degree of CFTR dysfunction. In our study, nobody conducted NPD or ICM.

Assessment of pathogenicity of variants on the CFTR gene

Whole-exome sequencing (Beijing Mai Kino Gene Technology, Guangzhou Jiajian Medical Testing, and Beijing Joy Orient Translational Medicine Research Center) was performed on the patients' peripheral blood samples. Four patients did sanger sequencing. And the pathogenicity of the variants was evaluated by the American College of Medical Genetics and Genomics (ACMG) [13, 14]. Novel ones have never been reported in CFTR1, CFTR2, CFTR-France and dbSNP databases.

Use of database

We refered to three genetic databases of CF patients, namely (a) CFTR2 database (25 December 2024) (http://www.cftr2.org/) included 122 935 individuals and 1167 annotated variants: 1085 CF-causing; 55 varying clinical consequence; 27 non-CF-causing. (b) CFTR-France Database (https://cftr.iurc.montp.inserm.fr/) included 5855 individuals and 1004 variants. (c) Cystic Fibrosis Mutation Database (http://www.genet.sickkids.on.ca/). (d) db SNP database (https://www.ncbi.nlm.nih.gov/snp

/). (e) UCSC Genome browser (https://genome.ucsc.edu/).

Computational methods (in-silico analysis)

The following predictors were applied to evaluate the pathogenicity of the variants identified in the *CFTR*: (a) MutationTaster (http://www.mutationtaster.org/). (b) REVEL (https://genome.ucsc.edu/). (c) PolyPhen-2 (Polymorphism Phenotyping v2) (http://genetics.bwh.harvard.edu/pph2/). (d) CADD (Combined Annotation Dependent Depletion) (https://cadd.gs.washington.edu/). (e) MutPred-2 (Mutation Prediction 2) (http://mutpred.mutdb.org/index.html). (f) MutPred-LOF (Loss-of-function) (http://mutpred2.mutdb.org/mutpredlof/). (g) Human Splicing Finder version 3.1 (http://www.umd.be/HSF3/).

Statistical analysis

For the descriptive analysis, quantitative non-normally distributed data are presented as the median (P25–P75). The data were analyzed using R 4.1.3.

Table 2 Description of clinical features of the 15 included patients

Variables	CF (n = 9)	Suspected CF or CFTR-RDs (n = 6)	All patients (n = 15)
Sex			
Female	4/9	3/6	7/15
Male	5/9	3/6	8/15
Age at onset (years) [a]	0.42(0.17–5.00)	0.44(0.05–5.17)	1.00 (0.11–5.08)
Age at diagnosis (years) [a]	8.17(0.55–12.37)	0.61(0.11–5.33)	5.33 (0.43–11.33)
Respiratory manifestations			
Recurrent respiratory infections	66.7% (6)	0% (0)	40.0% (6)
Chronic sinusitis	33.3% (3)	16.7% (1)	26.7% (4)
Bronchiectasis	66.7% (6)	16.7% (1)	46.7% (7)
Respiratory failure	11.1% (1)	33.3% (2)	20.0% (3)
Digestive manifestations			
Fatty stools	66.7% (6)	33.3% (2)	53.2% (8)
Meconium ileus	22.2% (2)	0% (0)	13.3% (2)
Distal intestinal obstruction syndrome	22.2% (2)	16.7% (1)	20.0% (3)
Liver cirrhosis	11.1% (1)	16.7% (1)	13.3% (2)
Pancreatitis	11.1% (1)	0% (0)	6.7% (1)
Endocrine manifestations			
Pseudo-Bartter syndrome	44.4% (4)	33.3% (2)	40.0% (6)
Hypoglycemia	0% (0)	16.7% (1)	6.7% (1)
Malnutrition	88.9% (8)	16.7% (1)	60.0% (9)
Salt crystal on skin	22.2% (2)	0% (0)	13.3% (2)

[a]median (P25-P75)

Results

Study population

As shown in Table 1, a total of 15 individuals (8 males and 7 females) were submitted to this study from 14 families in Southwest China. The median age of onset was 1.00 years (IQR 0.11–5.08 years, range 0-13.17 years). The median age of diagnosis was 5.33 years (IQR 0.43–11.33, range 0.09–14.17 years).

Among the 15 patients, 9 had a confirmed diagnosis of CF (P1,2,3,4,5,6,7,8,10), 3 had a suspected CF diagnosis (P9,12,14), 3 had a suspected CFTR-RDs (P11,13,15). Regarding to those suspected CF or CFTR-RDs patients, additional CFTR functional tests (sweat chloride, NPD or ICM) were suggested.

Clinical characteristic and genotypes of the patients

Among the 15 patients, 11 had mainly respiratory manifestations, 3 had mainly gastrointestinal manifestations, and 1 had mainly electrolyte disorders. One patient had only respiratory manifestations, one had only liver cirrhosis, and the rest had multisystem involvement. Among those confirmed CF patients, 66.7% (6/9) had bronchiectasis, 88.9% (8/9) had malnutrition, 66.7% (6/9) had fatty stools (Table 2; Fig. 1).

Bacterial pathogens of the respiratory tract were examined in 13 patients, and Pseudomonas aeruginosa (P. aeruginosa) was detected in 6. Across all hospitalizations, in addition to P. aeruginosa, Haemophilus influenzae (6 patients), Staphylococcus aureus (5 patients) and Klebsiella pneumoniae (3 patients) were the three most common pathogens.

Seven patients underwent pulmonary function tests at first admission: 1 had severe ventilation dysfunction (FEV1% pred < 35%), 1 had moderately severe ventilation dysfunction (50% ≤ FEV1% pred ≤ 59%), and 1 had moderate ventilation dysfunction (60% ≤ FEV1% pred ≤ 69%). Five patients in the CF group were examined for the fractional nasally exhaled nitric oxide (FnNO), and three had a concentration below the normal value.

All patients received symptomatic treatment according to their clinical manifestations. As for chronic respiratory symptoms, long-term macrolide therapy (azithromycin), bronchodilators (salbutamol), and hypertonic saline were used. One patient underwent liver transplantation due to cirrhosis. Two patients had meconium ileus; one underwent partial small bowel resection, subtotal colectomy, and ileostomy, and the other underwent ileostomy.

Overall, the follow-up compliance was poor. Among the 15 patients, 2 patients discontinued treatment because of their critical condition, and 2 did not attend follow-up visits. The remaining 11 patients were followed up for 1 month to 4 years and 9 months; 4 patients were subsequently lost, and 1 patient died from coronavirus disease 2019 infection in the community after

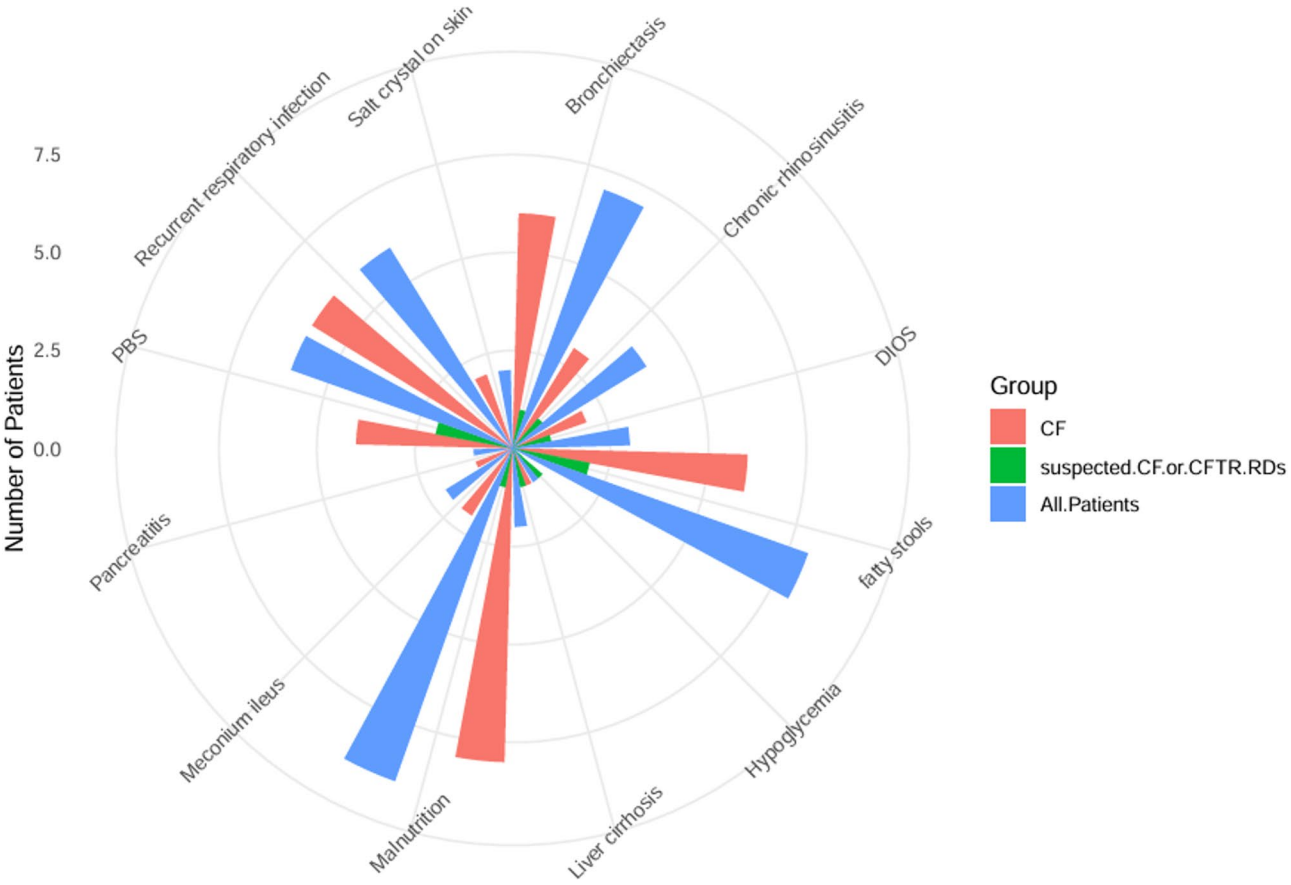

Fig. 1 Clinical manifestations of the 15 included patients. CF: cystic fibrosis; CFTR-RDs: CFTR-related disorders; PBS: pseudo-Bartter syndrome; DIOS: distal intestinal obstruction syndrome

1 year of follow-up. Except for one patient who underwent liver transplantation and was followed up regularly, most of the other patients were followed up only during short-term exacerbations or the recovery period after exacerbation.

Case 1

In this male patient, c.1766 + 5G>T and F508del CF-causing variants were identified, both in a heterozygote form. CF diagnosis was established in this patient at the age of 8 years. His old sister (case2) also had a diagnosis of CF. Before diagnosis, the patient suffered from recurrent respiratory infections, fever, chronic wet cough and wheezing. He had salt frost on the skin and clubbing fingers. He also had a diagnosis of chronic sinusitis, bronchiectasis and severe malnutrition. Bronchoalveolar lavage fluid culture was positive for Staphylococcus aureus, Pseudomonas aeruginosa, Haemophilus influenza and Aspergillus fumigatus through next-generation sequencing (NGS). Chest CT indicated pulmonary inflammation and bilateral bronchiectasis, with reduced inflammatory exudation after treatment. FnNO decreased (166ppb). Pulmonary function decreased (moderately severe) [15]: FVC, 51.7% and FEV1, 56.0%. Urinary amylase levels were elevated (861 U/L). Urine vitamin C was positive (3+)。This patient was followed up for a total of 3 years.

Case 2

In this female patient, c.1766 + 5G>T and F508del CF-causing variants were identified, both in a heterozygote form. CF diagnosis was established in this patient at the age of 12 years. Her young brother (case1) also had a diagnosis of CF. Before diagnosis, she suffered from recurrent upper respiratory infections. she also had a diagnosis of chronic sinusitis, bronchiectasis and mild live fibrosis. Bronchoalveolar lavage fluid culture was positive for Staphylococcus aureus and Haemophilus influenzae through NGS. Chest CT indicated bronchiectasis in the left upper lobe. FnNO was normal (367ppb). Pulmonary function was normal: FVC, 83.1%, FEV1, 87.5%. Urine vitamin C was positive (+). Fat droplets were found in the stool.

Case 3

A recently defined rare CF-causing variant c.3988_3989del was detected in this male patient in one

copy of the *CFTR* gene. In another allele, a known CF-causing variant G970D was identified. CF diagnosis was established in this patient at the age of 4 months. Before diagnosis, he suffered from chronic wet cough. He also had a diagnosis of electrolyte disturbances, secondary Bartter's syndrome and malnutrition. Chest CT indicated thickening of the bronchial walls and partial occlusion. Sputum culture was positive for Staphylococcus aureus and Haemophilus influenzae. Fat droplets were found in the stool. Hydrocele of the tunica vaginalis in the right testis was found. This patient was followed up for a total of 2.5 months.

Case 4

A novel pathogenic variant c.2476_2477AACG ins was detected in this male patient in one copy of the *CFTR* gene. In another allele, a known CF-causing variant c.3123_3124dupA was identified. He suffered from recurrent respiratory infections, wheezing and fatty stools. He also had a diagnosis of bronchiectasis, liver cirrhosis, hypokalemia and malnutrition. He had salt frost on the skin. Chest CT indicated bilateral bronchiectasis with infections. Sputum culture was positive for Pseudomonas aeruginosa. Fat droplets were found in the stool. This patient was followed up for a total of 3 years. c.2476_2477AACG ins variant is predicated to be pathogenic according to ACMG and in-silico predictors, which is also similar to the CF-causing variant c.2476G > T. Thus CF diagnosis was established in this patient at the age of 11 years.

Case 5

In this female patient, two CF-causing variants (G970D and c.264_268del) and novel variant c.3104 A > G were identified, all in a heterozygote form. CF diagnosis was established in this patient at the age of 14 years. Before diagnosis, this patient suffered from chronic cough for 1 year. She had clubbing fingers. She also had a diagnosis of chronic pneumonia, bronchiectasis, malnutrition, renal insufficiency, electrolyte disturbances and pancreatic atrophy. Bronchoalveolar lavage fluid culture was positive for Pseudomonas aeruginosa and Haemophilus influenza through NGS. Chest CT indicated pulmonary inflammation and bilateral bronchiectasis. FnNO10 was normal (300ppb). Electrolyte tests: K+, 2.95 mmol/L, Cl-, 96.2 mmol/L. Blood lipase levels were elevated (227). No follow-up was conducted.

Case 6

In this male patient, c.2052del and R1066C CF-causing variants were identified, both in a heterozygote form. CF diagnosis was established in this patient at the age of 5 months. Before diagnosis, he suffered from wheezing, vomiting and diarrhea. He also had a diagnosis of severe malnutrition, respiratory failure, hypothyroidism and liver function impairment. Chest CT indicated bilateral lung inflammation. Sputum culture was positive for Escherichia coli. During hospitalization, the patient had two ICU admissions. No follow-up was conducted due to his critical conditions.

Case 7

In this preterm female patient, CF-causing variant c.2547 C > A, reported variant E217G and novel variant c.884del were identified, all in a heterozygote form. High sweat chloride levels were presented (133mmol/L). CF diagnosis was established in this patient at the age of 7 months. Before diagnosis, she suffered from recurrent respiratory infections, vomiting and diarrhea. She also had a diagnosis of distal intestinal obstruction syndrome, Hirschsprung's disease (postoperative), electrolyte disturbances, pancreatic enzyme deficiency and severe malnutrition. Chest CT indicated bilateral interstitial pneumonia. Sputum culture was positive for Haemophilus influenzae. Fat droplets were found in the stool. The patient was followed up for a total of 4 years.

Case 8

In this female patient, R851X and S945L CF-causing variants were identified, both in a heterozygote form. CF diagnosis was established in this patient at the age of 6 years. High sweat chloride levels were presented (75mmol/L). Before diagnosis, she suffered from chronic cough, wheezing, recurrent respiratory infections and delayed passage of meconium. She had clubbing fingers. She also had a diagnosis of bronchiectasis and malnutrition. During the follow-up, the patient was hospitalized three times due to pneumonia, with subsequent diagnosis of respiratory failure, liver function impairment, acute pancreatitis and sinusitis. Chest CT indicated diffuse bronchiectasis. Pulmonary function decreased (severe) [15]: FVC%, 65.0%, FEV1, 45.4%. Sputum culture was positive for Pseudomonas aeruginosa, Acinetobacter baumannii and methicillin-resistant Staphylococcus aureus. FnNO10 decreased (189 ppb). Serum K + decreased (3mmol/L). The patient was followed up for a total of 6 years.

Case 9

In this male patient, c.3267G > A (W1089X) and c.91 C > T variants were detected, both in a heterozygote form. He had a diagnosis of congenital central hypoventilation syndrome, respiratory failure, bronchopulmonary dysplasia, allied disorders of Hirschsprung's disease, electrolyte disturbances and neonatal hypoglycemia at age of 1 month. Chest CT indicated bilateral lung inflammation. Sputum culture was positive for Acinetobacter baumannii and Klebsiella pneumoniae. No follow-up was

conducted thereafter. Similarly, c.3266G > A (W1089X) was reported to be CF-causing in the CFTR2 database. Although c.91 C > T was considered to be non CF-causing in the CFTR2 and VUS in the CFTR-France databases, given that the patient's typical lung and intestinal manifestations and poor clinical prognosis, this patient was suspected with CF. However, diagnosis of CF still requires CFTR functional tests.

Case 10

In this male patient, c.405_406dupAC and c.49_50del CF-causing variants were identified, both in a heterozygote form. High sweat chloride levels were presented (126mmol/L). CF diagnosis was established in this patient at the age of 12 years. Before diagnosis, he suffered from chronic wet cough, wheezing, fatty stools and recurrent respiratory infections. He also had a diagnosis of bronchiectasis and severe malnutrition. He had clubbing fingers. Chest CT indicated diffuse inflammation and bronchiectasis. Bronchoalveolar lavage fluid culture was positive for Pseudomonas aeruginosa and Staphylococcus aureus. Pulmonary function decreased (moderate) [15]: FVC: 78.8%, FEV1: 66.8%. FnNO decreased (156 ppb). Fat droplets were found in the stool. The patient was followed up for a total of 1 month.

Case 11

In this female patient, N287K and c.−152G > C variants were detected, both in a heterozygote form. Intermediate sweat chloride levels were presented (33mmol/L). She suffered from chronic wet cough and recurrent respiratory infections. She had a diagnosis of bronchiectasis and bronchiolitis obliterans. Chest CT indicated bronchiectasis. Bronchoalveolar lavage fluid culture was positive for Staphylococcus aureus and Klebsiella pneumoniae. FnNO was normal (339 ppb). The patient was followed up for a total of 3 years and 8 months. Considering the single organ disease, two uncharacterized *CFTR* variants and intermediate sweat chloride level, this patient was suspected to have CFTR-RDs at age of 11 years, though this diagnosis still requires additional CFTR functional tests (NPD or ICM).

Case 12

In this male patient, c.374T > C variant was detected in this patient in one copy of the *CFTR* gene. In another allele, a known CF-causing variant F508del was identified. He had a diagnosis of severe malnutrition, hyperkalemia and right cryptorchidism. The patient also had symptoms of diarrhea. No follow-up was conducted. Variant c.374T > C is reported to be associated with hereditary pancreatitis and congenital bilateral absence of the vas deferens (CBAVD) [16, 17]. Considering suggestive CF clinical features and one uncharacterized *CFTR* variant (c.374T > C), his suspected diagnosis of CF still requires other CFTR functional tests.

Case 13

In this male patient, c.4137-35G > A and c.374T > C were detected, both in a heterozygote form. He was admitted due to a chronic cough and wheezing for 3 months, and diagnosed with chronic pneumonia and sinusitis at the age of 1 year. Chest CT indicated infectious lesions in both lungs. Sputum culture was positive for Streptococcus pneumoniae and Klebsiella pneumoniae. The patient was followed up for a total of 1 year and 6 months. Considering the single organ disease and two uncharacterized *CFTR* variants, with variant c.374T > C associated with hereditary pancreatitis and CBAVD [16, 17], this patient was suspected to have CFTR-RD, though this diagnosis still requires other CFTR functional tests.

Case14

In this female patient, three variants (c.3062 C > T, c.1393–4 C > A and c.1352G > T) were detected, all in a heterozygote form. She was admitted due to intermittent abdominal pain for 1 year, and diagnosed with liver cirrhosis at the age of 5 years and underwent a liver transplant. The patient was followed up for a total of 4 years and 5 months, with all liver function and coagulation indicators normal. Though c.3062 C > T and c.1352G > T were both reported to be CF-causing variants and pathogenic with in-silico predictors, considering single organ disease and good prognosis, her suspected diagnosis of CF still requires CFTR functional tests [18, 19].

Case15

In this preterm female patient, c.592G > C variant was detected in a heterozygote form. At the age of 1 month, she was diagnosed with severe pneumonia, respiratory failure, bronchiectasis, hypothyroidism and hyponatremia with hypochloremia. Sputum culture was positive for Klebsiella pneumoniae, Escherichia coli, Streptococcus pneumoniae and Enterococcus faecalis. Chest CT showed interstitial lesions in both lungs. After one year of follow-up, the patient passed away. Considering one uncharacterized variant and poor prognosis, her suspected diagnosis of CF or CFTR-RDs still requires CFTR functional tests. If CF established, MLPA or others can be applied to detect other variants in *CFTR* gene.

Variants identified in the CFTR

A total of 27 variants were identified in the CF patients (Tables 3 and 4), and three patients had three variants as follow: (i) c.[2909G > A;3104 A > G]; [264_268delATATT]; (ii) c.[650 A > G;884delT]; [2547 C > A]; (iii) c. [3062 C > T; 1393–4 C > TA]; [1352G > T]. 1 patient had a single *CFTR*

Table 3 Full description of CFTR variants screened in cystic fibrosis patients considering the alleles

#Family		cDNA and AA change	db SNP	Het/Hom	Origin	ACMG	genomeAD (global)[a]	genomeAD (East Asians)[a]	CFF(%)	CFTR2[b]	CFTR-France[c]	CFTR1[d]
#1	P1	c.1766 + 5G>T(splicing)	rs121908796	het	paternal	P(PVS1 + PM3_Strong)	3.75E-06	1.12E-04	0.0081	CF-causing	CF-causing	Found
		c.1521_1523delCTT(p.F508del)	rs113993960	het	maternal	P(PS3 + PM1 + PM3_Strong + PM4)	0.01	2.23E-05	65.0683	CF-causing	CF-causing	Found
#1	P2	c.1766 + 5G>T(splicing)	rs121908796	het	paternal	P(PVS1 + PM3_Strong)	3.75E-06	1.12E-04	0.0081	CF-causing	CF-causing	Found
		c.1521_1523delCTT(p.F508del)	rs113993960	het	maternal	P(PS3 + PM1 + PM3_Strong + PM4)	0.01	2.23E-05	65.0683	CF-causing	CF-causing	Found
#2	P3	c.2909G > A(p.G970D)	rs386134230	het	paternal	P(PM1 + PM2_Supporting + PM3_Strong + PP3_Strong)	5.94E-06	1.58E-04	0.0142	CF-causing	CF-causing	Found
		c.3988_3989delCA(p.Q1330Vfs*6)	rs1057516457	het	maternal	P(PVS1 + PM2_Supporting + PM3_Strong)	/	/	0.0005	CF-causing	CF-causing	/
#3	P4	c.3123_3124dupA(p.Q1042Tfs*5)	Not found	het	paternal	P	6.20E-07	2.23E-05	0.0005	CF-causing	Not found	Found
		c.2476_2477AACG ins(p.E827Rfs*10)	Not found	het	maternal	P	/	/	Not found	Not found	Not found	/
#4	P5	c.2909G > A (p.G970D)	rs386134230	het	paternal	P(PM1 + PM2_Supporting + PM3_Strong + PP3_Strong)	5.94E-06	1.58E-04	0.0142	CF-causing	VUS	Found
		c.264_268delATATT(p.Leu88Phefs*21)	rs2484975593	het	maternal		/	/	0.0005	CF-causing	Not found	Found
		c.3104 A > G(p.Q1035R)	Not found	het	paternal	LP(PVS1 + PM2_Supporting) Uncertain(PM1 + PM2_Supporting + PM3_Trans + BP4)	/	/	Not found	Not found	Not found	/
#5	P6	c.2052delA(p.Lys684Asnfs*38)	rs121908746	het	paternal	LP	5.08E-05	0.00	0.1999	CF-causing	CF-causing	Found
		c.3196 C > T(p.R1066C)	rs78194216	het	maternal	LP	2.17E-05	0.00	0.2520	CF-causing	CF-causing	Found
#6	P7	c.2547 C > A(p.Y849X)	rs397508394	het	paternal	P	6.20E-07	0.00	0.0099	CF causing	CF causing	Found
		c.650 A > G(p.E217G)	rs121909046	het	maternal	LP	2.06E-03	0.01	Not found	Not found	VUS	Found
		c.884delT(p.L295Rfs*7)	Not found	het	maternal	LP	/	/	Not found	Not found	Not found	/
#7	P8	c.2551 C > T(p.R851X)	rs121909012	het	paternal	P(PVS + PS1 + PM2 + PM3)	2.48E-06	0.00	0.0284	CF-causing	CF-causing	Found
		c.2834 C > T(p.S945L)	rs397508442	het	maternal	LP(PS1 + PM2 + PM3 + PP3)	4.09E-05	0.00	0.1402	CF-causing	VUS	Found
#8	P9	c.3267G > A(p.W1089X)	rs150020260	het	/	P	/	/	not found	Not found	Not found	/
		c.91 C > T(p.R31C)	rs1800073	het	/	LP	1.51E-03	6.76E-03	0.0166	None CF-causing	VUS	Found
#9	P10	c.405_406dupAC(p.L136Hfs*18)	rs1554379846	het	paternal	P(PVS1 + PM2 + PM3_Strong)	/	/	0.0009	CF-causing	Not found	Found
		c.49_50delTT(p.F17Qfs*27)	Not found	het	maternal	P(PVS1 + PM2 + PM3_Trans)	/	/	0.0014	CF-causing	Not found	/
#10	P11	c.861 C > G(p.N287K)	rs112162204	het	paternal	LP(PS1 + PM1 + BS2)	3.23E-05	9.61E-04	Not found	Not found	VUS	Found
		c.−152G > C	rs551681003	het	maternal	Uncertain	1.03E-04	2.5E-03	Not found	Not found	Not found	/
#11	P12	c.374T > C(p.I125T)	rs141723617	het	paternal	Uncertain	1.96E-04	6.04E-03	Not found	Not found	Not found	Found
		c.1521_1523delCTT(p.F508del)	rs113993960	het	maternal	Pathogenic	0.01	2.23E-05	65.0683	CF-causing	CF-causing	Found
#12	P13	c.4137-35G > A(splicing)	Not found	het	paternal	Uncertain(PM2_Supporting	/	/	Not found	Not found	Not found	/
		c.374T > C(p.I125T)	rs141723617	het	maternal	Uncertain(PM1 + PP3)	1.96E-04	6.04E-03	Not found	Not found	Not found	Found

Table 3 (continued)

#Family		cDNA and AA change	db SNP	Het/Hom	Origin	ACMG	genomeAD (global)[a]	genomeAD (East Asians)[a]	CFF(%)	CFTR2[b]	CFTR-France[c]	CFTR1[d]
#13	P14	c.3062 C > T(p.P1021L)	rs1554392023	het	paternal	LP	/	/	Not found	Not found	Not found	/
		c.1393–4 C > A(splicing)	rs1799416194	het	paternal	Uncertain	0.00	0.00	Not found	Not found	Not found	/
		c.1352G > T(p.G451V)	rs1554382653	het	maternal	LP	/	/	Not found	Not found	Not found	/
#14	P15	c.592G > C(p.A198P)	rs193922529	het	maternal	LP(PM1 + PM2_Supporting + PM5 + PP3)	6.20E-07	2.23E-05	Not found	Not found	Not found	Found

dbSNP Single Nucleotide Polymorphism database, *CFF* Cystic Fibrosis Foundation, *CFTR* Cystic fibrosis transmembrane conductance regulator

[a] *UCSC Genome Browser (https://genome.ucsc.edu/)*

[b] Based on the current CFTR2 database (25 December 2024) (http://www.cftr2.org/) with 122 935 included patients, and 1167 annotated variants: 1085 CF-causing; 55 varying clinical consequence; 27 non-CF-causing

[c] Based on list of current CFTR-France Database (https://cftr.iurc.montp.inserm.fr)

[d] Based on list of current Cystic Fibrosis Mutation Database (http://www.genet.sickkids.on.ca/)

Table 4 Description of CFTR variants without inclusion in the CFTR2 database, or with uncertain interpretations of pathogenicity, or novel variants screened in the CFTR gene considering the in-silico

Traditional name	Mutation Taster[a]	REVEL[b]	PolyPhen-2[c]	CADD Phred[d]	MutPred-2[e]	MutPred-LOF[f]	human splicing finder[g]
Novel variants							
c.2476_2477dupAACG(p.E827Rfs*10)	disease causing	/	/	/	/	0.7698	/
c.3104 A > G(p.Q1035R)	polymorphism	0.284	benign	13.53	0.163	/	no significant splicing motif
c.884delT(p.L295Rfs*7)	disease causing	/	/	/	/	0.7676	/
c.4137-35G > A(splicing)	polymorphism	/	/	3.094	/	/	no significant splicing motif
P/LP variants and described in the literature							
c.650 A > G(p.E217G)[22]	disease causing	0.546	benign	23.1	0.475	/	alteration of ESE/ESS motifs ratio (−3); new acceptor site; new donor site
c.3267G > A(p.W1089X)[23]	disease causing	0.677	/	41	/	0.7621	no significant splicing motif
c.861 C > G(p.N287K)	disease causing	0.324	benign	18.07	0.482		new acceptor site; new donor site
c.3062 C > T(p.P1021L)[18]	disease causing	0.778	probably damaging	29.1	0.85	/	alteration of ESE/ESS motifs ratio (−2)
c.1352G > T(p.G451V)[19]	disease causing	0.979	probably damaging	29.2	0.844	/	alteration of ESE/ESS motifs ratio (−10)
c.592G > C(p.A198P)	disease causing	0.859	probably damaging	24	0.885	/	no significant splicing motif
Uncertain variants							
c.374T > C(p.I125T)[16, 17]	disease causing	0.668	possibly damaging	22.2	0.598	/	no significant splicing motif
c.1393–4 C > A	disease causing	/	/	4.924	/	/	No significant impact on splicing signals

[a]MutationTaster (http://www.mutationtaster.org/)

[b]UCSC Genome Browser (https://genome.ucsc.edu/)

[c]PolyPhen-2 (Polymorphism Phenotyping v2) (http://genetics.bwh.harvard.edu/pph2/)

[d]CADD (Combined Annotation Dependent Depletion) (https://cadd.gs.washington.edu/)

[e]MutPred-2 (Mutation Prediction 2) (http://mutpred.mutdb.org/index.html)

[f]MutPred-LOF (Loss-of-function) (http://mutpred2.mutdb.org/mutpredlof/)

[g]Human Splicing Finder version 3.1 (http://www.umd.be/HSF3/)

allele mutation, and 14 patients had compound heterozygous mutations.

In our study, three of the fifteen patients harbored the c.1521_1523del variant. The other frequent variants are c.2909G > A (2 patients), c.1766 + 5G > T (2 patients) and c.374T > C (2 patients). Two patients from the same family had the same variants.

Of the variants identified, 13 are identified as CF-causing according to the CFTR2 database, 1 non CF-causing, and 13 not characterized. Four novel variants were found: c.2476_2477AACG ins, c.3104 A > G, c.884delT and c.4137-35G > A.

The variant c.2476_2477AACG ins (p.E827Rfs*10) is determined to be pathogenic according to ACMG, leading to premature termination. This variant is predicated to be disease causing and have a score of 0.7698 according to Mutation taster and MutPred-LOF respectively. Additionally, this variant is similar to the variant c.2476G > T (p.E826X), which is CF-causing in the CFTR2 database. The variant c.884delT (p. L295Rfs*7) of CF patient is determined to be likely pathogenic according to ACMG, leading to premature termination. This variant is predicated to be disease causing and have a score of 0.7676 according to Mutation taster and MutPred-LOF

respectively. The two variants c.3104 A > G and c.4137-35G > A are both determined to be uncertain according to ACMG. These two variants are both predicated to be polymorphism according to Mutation taster.

Discussion

In recent years, with the increasing awareness of CF and the continuous improvement of genetic testing technology, the number of Chinese individuals diagnosed with CF has increased. The number of CF Chinese patients in the past 10 years has exceeded 2.5 times the total in the previous 30 years [24], indicating that the number of CF patients may be underestimated in the past. This underestimated diagnosis can be attributed to several factors, including limitations in detection methods and the differences in the genotypes and phenotypes between Chinese and people from other regions [25–27].

The methods used for CFTR function detection are limited in China. Currently, there is no established newborn screening program in China. Sweat testing is not popular, and nasal potential difference (NPD) and intestinal current measurements (ICM) are difficult to obtain. Therefore, the diagnosis of CF and CFTR-RDs still relies on clinical manifestations and genetic testing. However, the genetic spectrum of CF in China is different from that observed in Caucasians [25, 28]. c.1521_1523delCTT (p. F508del) is the most common variant in Caucasians, accounting for approximately 70% of the mutated variants in general [29], but it accounted for only 11% of the variants in our study. The variant c.2909G > A (p.G970D), the most common variant in the Chinese population [30], has rarely been reported in the Caucasian CF population. Nearly half of the detected *CFTR* variants have uncertain significance [1]. Thus, it is necessary to establish a *CFTR* genetic spectrum of Chinese and promote the use of sweat chloride in China.

Many studies suggested significant differences of clinical phenotypes between Chinese and Caucasian patients [31, 32]. Among Chinese CF patients, 70.8% had bronchiectasis, higher than CF patients in Europe, which is consistent with our study (66.7%, 6/9). Late CF diagnosis may contribute to the high incidence of bronchiectasis in China. Among Caucasian CF patients, other than respiratory manifestations, approximately 85% had pancreatic insufficiency, higher than Chinese CF patients (12.4%), as a result of different genomic backgrounds [33]. Additionally, Chinese CF patients had a lower incidence of meconium ileus and higher incidence of malnutrition. Totally, the clinical manifestations of Chinese CF patients are relatively mild and nonspecific [3, 34].

Therefore, people with the same *CFTR* variants, same genetic background, may exhibit different phenotypes [1, 35–37]. In our study, two siblings (P1 and P2) from the same family had the same genotype (c.1521_1523del, c.1766 + 5G > T) exhibited different clinical manifestations. P1 experienced recurrent respiratory infections since infancy, accompanied by growth retardation, severe malnutrition and bilateral bronchiectasis. However, his old sister (P2) just had respiratory manifestations. Bronchiectasis was found by chest CT, and mild liver fibrosis and polycystic pancreas were found by ultrasound. Other than genetic variants, environmental factors and modifying genes may be involved in the phenotype of CF [4, 37]. Given the similar living environments of these two patients, modifying genes may play a role in the phenotype difference of the two patients. If possible, we will continue to follow up in the future and perform further exploration through transcriptional sequencing and other methods.

P. aeruginosa is considered to be one of the most critical pathogens causing respiratory tract infection in CF patients, but it was not the most common pathogen in our study [38, 39]. Among the seven patients without *P. aeruginosa* detected, five were younger than 8 months, and one was treated with a full course of cefoperazone sodium and sulbactam sodium before admission. These may be the reason for low incidence of *P. aeruginosa* in our study. Interestingly, in our study, among the six patients with *P. aeruginosa*, three (P1,8,10) had persistent infection (*P. aeruginosa* detected in the sputum or lung lavage fluid during hospitalization on at least two consecutive occasions due to exacerbation of acute pulmonary infection), while no persistent infection was observed for other common pathogenic bacteria. Early infection with *P. aeruginosa* is one of the risk factors for low predicated % in CF patients aged 6–7 years [40], and persistent infection with *P. aeruginosa* also significantly increases the risk of lung deterioration [41, 42]. In our study, the pulmonary function of the three patients with persistent *P. aeruginosa* infection all indicated varying degrees of obstructive ventilation dysfunction during the acute infection interval. Therefore, it is necessary to conduct eradication treatment in the early stage of acute *P. aeruginosa* infection. Currently, the international treatment guidelines for *P. aeruginosa* recommends inhaled antibiotics alone or in combination with systemic antibiotics (oral or intravenous) [43]. One RCT showed that, regarding inhaled antibiotic treatment, the combination of intravenous medication has no more clinical benefit than the combination of oral medication [44]. There is no evidence that one scheme is superior to the other. There are no relevant studies in China due to the small size of CF patients.

Recently, CFTR modulators are all in clinical trials including potentiators for mutations with cell surface protein, and correctors for aiding trafficking of misfolded protein, read-through reagents for premature mutations, gene and mRNA-based therapies, novel anti-infective

therapies and anti-inflammatory therapies [45–51]. In our study, all patients received symptomatic treatment. For G970D, the most common *CFTR* variant in China, CFTR modulators are in clinical trials in Europe [20, 21, 30]. Thus, clinical trials of those molecular reagents in China are promoted. However, availability and adoption of those reagents are still limited in China.

For those novel variants or variants of uncertain clinical significance identified in our study, their pathogenicity remains to be identified from these aspects: (i) construction of WT and mutant *CFTR* plasmid to detect their effect on protein function or mRNA splicing. (ii) detection of CFTR protein or transcriptional expression in patients' sample. (iii) CFTR function test on those CF (suspected) patients.

Over diagnosis will increase the burden of patients and their families, whereas a missed diagnosis could delay treatment. Therefore, clinicians must strictly control the indications for genetic testing and be cautious about the diagnosis according to genetic reports. It is suggested that patients whose genetic testing results fail to meet the diagnostic criteria for CF but cannot be completely excluded should be followed up regularly, and sweat test results should be collected when possible to provide additional diagnostic clues.

There are still some limitations in our study. One is the small sample size, which is due to the underdiagnosis of CF. The second one is the fact that not all patients underwent sweat chlorine testing. The third one is the poor follow-up.

Conclusions

Our study expands the spectrum of genotypes for CF of Chinese origin, which differs significantly from that of Europe and other regions. As to those uncertain gene variants, sweat chloride test can aid in the diagnosis process and serve as a reference for identifying the pathogenicity of variants. It is hoped that with the continuous improvement in our understanding of such diseases, the rate of misdiagnosis and missed diagnosis will decrease, patients with a definite diagnosis receiving regular follow-up and treatment, and a disease spectrum within Chinese population established.

Abbreviations

CF	Cystic fibrosis
CFTR	Cystic fibrosis transmembrane conductance regulator
CFTR-RDs	CFTR-related disorders
NPD	Nasal potential difference
ICM	Intestinal current measurements
ACMG	American College of Medical Genetics and Genomics
PBS	Pseudo-Bartter syndrome
DIOS	Distal intestinal obstruction syndrome
P. aeruginosa	*Pseudomonas aeruginosa*
VUS	Variant of unknown clinical significance
CBAVD	Congenital bilateral absence of the vas deferens
ECFs	European Cystic Fibrosis Society

Acknowledgements

We thank LetPub for its linguistic assistance during the preparation of this manuscript.

Authors' contributions

D.T., D.W., J.D., L.Y., Y.L. and T.Y. contributed to the study's conception and design. T.Y., H.B, J.L. and D.Z. contributed to the data collection and analysis. T.Y. and H.B. drafted the manuscript. H.B, T.G., S.L. and D.T. revised the manuscript. D.T. provided financial support. Huaqin Bu and Tian Yang should be listed as co-first authors. All authors have read and approved the final manuscript.

Funding

This work was supported by the National Natural Science Foundation of China (Grant: 81870012, 82171712), Program for Youth Innovation in Future Medicine, Chongqing Medical University (Number: W0063), and General Program of Natural Science Foundation of Chongqing (Number: CSTB2022NSCQMSX0822).

Data availability

The data are available upon reasonable request. The raw data without personal identifiers are available from the corresponding author upon reasonable request.

Declarations

Ethical approval and consent to participate

This study was approved by the Ethics Committee of the Children's Hospital of Chongqing Medical University (File No. (2023)295). The need for written informed consent was waived by the Ethics Committee of the Children's Hospital of Chongqing Medical University due to retrospective nature of the study.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Received: 8 April 2024 / Accepted: 7 August 2025
Published online: 02 October 2025

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