Int J Clin Exp Med 2018;11(6):6293-6301
www.ijcem.com /ISSN:1940-5901/IJCEM0065112

Case Report

Chinese data of the CFTR mutation: a report from West China Hospital and literature review

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Received June 15, 2017; Accepted March 11, 2018; Epub June 15, 2018; Published June 30, 2018

Abstract: Background and objective: Cystic fibrosis (CF) is a serious genetic disorder that is caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. Little is known about the genetic information of the CFTR mutation in the Chinese population. The objective of this study is to report a new CFTR mutation in a Chinese CF patient and describe the CFTR mutations and clinical manifestations of this group in China. Methods: We studied a 20-year-old Chinese CF patient and performed DNA sequencing of the CFTR gene. We also analyzed published data on CFTR mutations in the Chinese population. Results: After sequencing the CFTR gene, we identified two mutations of the CFTR gene in the CF patient: one was c.263T>G (p.L88X) in exon 3 from her father and the other one was c.2335C>T (p.Q779X) in exon 14 from her mother. We found c.2335C>T to be a possible novel mutation. After we reviewed all the reported mutations in the Chinese CF patients, we found that nearly half of the reported mutations were located on splice junction sites and vary in their frequency and distribution from Caucasian groups. Conclusions: The current study reported a novel CFTR mutation in the Chinese CF patient. There is an urgent need to understand the mutation spectrum in China in order to establish a mutation panel for providing patients with earlier and more comprehensive treatment and genetic counseling.

Keywords: Cystic fibrosis, cystic fibrosis transmembrane conductance regulator, China, mutation

Introduction

Cystic fibrosis (CF) is a serious genetic disorder that is caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene located on chromosome 7. The CFTR gene encodes a large transmembrane protein composed of 1480 amino acids. As of now, more than 2000 mutations that might be associated with CF have been identified in the CFTR gene (www.genet.sickkids.on.ca/cftr/). Mutations in the CFTR gene produces a defect in chloride transport in most exocrine glands, which leads to an abnormally thick mucus secretion, and results in elevated sweat chloride level, meconium ileus, chronic bacterial airway infection, pancreatic insufficiency and steatorrhea [1]. Male patients diagnosed late usually present with infertility due to congenital bilateral absence of the vas deferens (CBAVD).

CF is the most common fatal autosomal recessive disease among Caucasians, with an incidence of approximately 1 in 2,500 live births and a carrier frequency of about 1 in 25 [2]. The disease is rare, however, in Asia and little is known about the spectrum of CFTR mutations in this race. Although this rate was probably underestimated, Yamashiro' team [3] reported an incidence rate of only 1 in 350,000 in the Japanese population. As for the Chinese population, only a few CF patients were reported so far and a portion of these cases were not confirmed by genetic analysis [4-21]. Even though CF is rare in China, with a total population of about 1.3 billion, an incidence rate of 1 in a million would predict almost 3 million carriers of CFTR mutations. The lower number of reported CF patients in the Chinese population may suggest that a large number of CF patients were not diagnosed.

In this study, we performed a genetic analysis for the CFTR gene in a 20-year-old CF female to determine the CFTR mutations of this patient. In addition, we analyzed the CFTR mutations

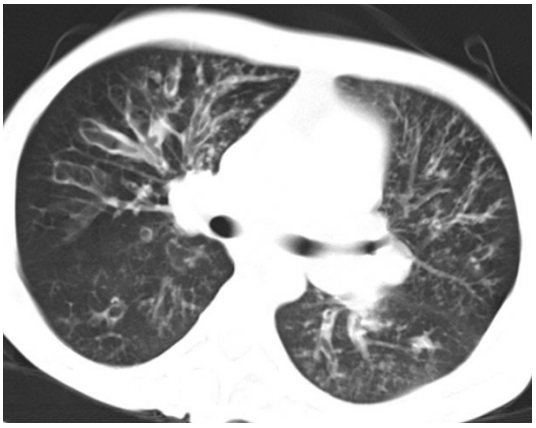

Figure 1. Chest computed tomography (CT) scan showed the severe bronchiectasis and peribronchial infiltration in both lung fields.

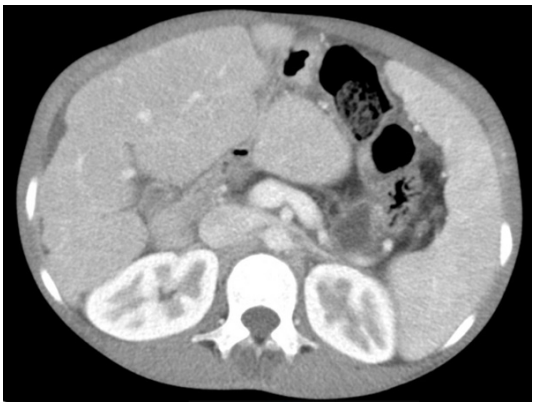

Figure 2. Contrast-enhanced CT of the upper abdomen demonstrated cirrhotic liver with splenomegaly and ascites.

and clinical manifestations of reported Chinese CF patients, in order to characterize the specific mutational pattern of the CFTR gene in the Chinese population.

Materials and methods

Patient

A 20-year-old female was admitted to our hospital with complaints of dyspnea, productive cough, and edema. She presented with neonatal growth retardation, steatorrhea since the age of 2 months, and subsequently with chronic cough, dyspnea and bronchopulmonary colonization with pseudomonas. The patient had been treated for several episodes of pneumonia and malnutrition, necessitating frequent hospital admissions. The patient was born from unrelated Chinese parents. There was no history of delayed passage of meconium. Her feeding history was unremarkable; however, frequent foul-smelling stools with fat droplets had been noted since her birth.

On admission, the patient looked lethargic and had generalized edema. Her vital signs were as follows: body temperature, 37.0°C; heart rate, 100 beats/minute with a regular rhythm; respiratory rate, 20 breaths/minute; and blood pressure, 118/72 mmHg. Her body mass index was 14.6 kg/m^2. Diffused crackles and wheezing were heard throughout the entire lung field. The liver was palpated 6 cm below the right subcostal margin and the spleen was palpable 2 cm below the left costal margin. Digital clubbing was also noted.

Routine laboratory tests showed leukocytosis, with a white blood cell count of 20,650/mm^3 (86.6% neutrophils and 8.0% lymphocytes). The serum albumin level was 25.6 g/L. Liver and renal function tests were below normal limits. Her arterial blood gas analysis revealed hypercapnia and respiratory acidosis with compensatory metabolic alkalosis. The sweat check showed an elevated sweat ion level of 118 mmol/L. Sputum culture was positive for pseudomonas. The chest computed tomography (CT) scan showed severe bronchiectasis and peribronchial infiltration in both lung fields (**Figure 1**). Contrast-enhanced CT of the upper abdomen demonstrated a cirrhotic liver with splenomegaly and ascites (**Figure 2**).

Mutation analysis

We have sought and obtained approval from our hospital to use patients' records for our study. Informed consent was obtained from the proband and her parents. The patient confidentiality has been maintained. Genomic DNA of the patient and her family members were extracted from peripheral blood leukocytes by using the TianGene Genomic DNA Purification Kit according to the manufacturer's instructions. All 27 exons and exon-intron splice junctions of the CFTR gene were assessed for the presence of mutations by polymerase chain reaction (PCR) and DNA sequencing using primer pairs designed by the author. Gel purified PCR products were sequenced by using the ABI3730XL Sequencer and the results were

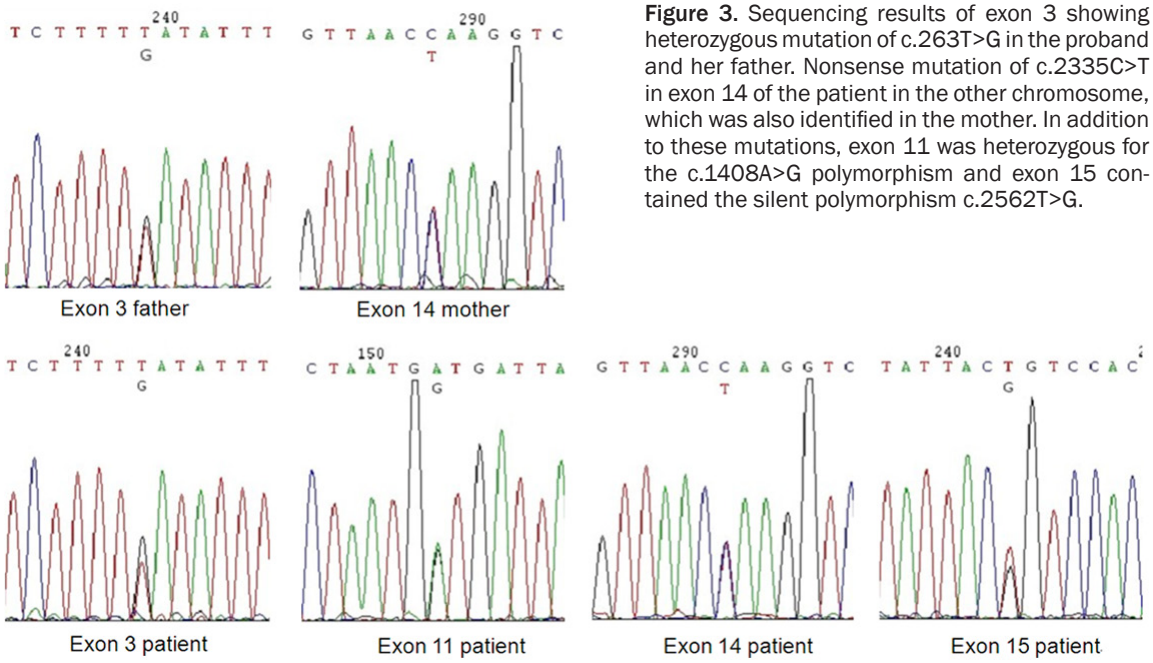

Figure 3. Sequencing results of exon 3 showing heterozygous mutation of c.263T>G in the proband and her father. Nonsense mutation of c.2335C>T in exon 14 of the patient in the other chromosome, which was also identified in the mother. In addition to these mutations, exon 11 was heterozygous for the c.1408A>G polymorphism and exon 15 contained the silent polymorphism c.2562T>G.

compared with the sequence of wild type CFTR gene (www.genet.sickkids.on.ca/cftr/).

Literature review

Up until 30 August 2017, two investigators (Wang YT, Liu JH) independently searched PubMed, Embase, Wanfang and CNKI databases. Disagreements were resolved through discussion or adjudicated by a third author (Yang XD). The search terms were as follows: 'CF or cystic fibrosis' in combination with 'mutation' and with 'Chinese or China'. All studies that reported CFTR mutations were included. All mutations were summarized.

Results

Clinical diagnosis of the patient

The recent Cystic Fibrosis Foundation consensus statement on the criteria for a diagnosis of CF requires clinical CF symptoms in at least one organ system as well as some evidence of CFTR dysfunction [22]. This can be determined with functional testing (such as sweat chloride measurement) or with genetic testing for CFTR mutations. As for the current patient, she presented with typical clinical features, perspired chloride evidence of CFTR dysfunction, and had other diseases excluded, so as a result, a clinical diagnosis was established.

Genetic study for the patient

Genetic confirmation was initiated in order to confirm the disease. The analysis of the direct sequencing of both DNA strands demonstrated that the proband possessed two heterozygous nonsense mutations in her CFTR gene: c.263T>G (p.L88X) in exon 3 from her father and c.2335C>T (p.Q779X) in exon 14 from her mother (**Figure 3**). Both are considered Class I mutations, which is the most severe group of CFTR mutations [23]. A literature search of the Sick Kids Cystic Fibrosis Mutation database showed no prior report of the c.2335C>T mutation. This novel mutation we identified has been submitted to the Cystic Fibrosis Mutation Database (http://www.genet.sickkids.on.ca/cftr/). In addition to these mutations, exon 11 was heterozygous for c.1408A>G (p.M470V) polymorphism and exon 15 contained the silent polymorphism c.2562T>G (T854T) (**Figure 3**).

Summary results of the CFTR mutations in Chinese population

After our careful search of the databases, a total of 18 studies, including 63 cases which met our inclusion criteria, were identified. Two of them were Chinese documents and their full texts were retrieved from both CNKI and Wanfang databases [13, 16]. There were also fifteen English documents, which were obtained

from PubMed and Embase databases [4, 6-12, 14, 15, 17-21]. Only one document was very difficult to obtain [5]. In the end, we were able to obtain this document with the assistance of online help after posting on the Internet. We found that nearly half of the reported mutations were located on splice junction sites and it seemed that the 1898+5G>T, c.2909G>A and 3068T>G were the most identified mutations in Chinese CF patients. We found that these mutations are very different from those of Caucasian populations and some of them have never been reported. In addition, we also found that all of these Chinese CF patients presented with typical features of the disease and that the median age of this population was 10.55 years old.

Discussion

CF is a congenital, recessively inherited disorder that reflects mutations in the CFTR gene. Since the CFTR gene was first identified in 1989 [23], more than 1900 mutations have been identified (www.genet.sickkids.on.ca/cftr/). The majority of these mutations were identified in Caucasian populations. Little is known, however, about the CFTR mutations in many populations, especially in Asians. This may be due to the fact that the disease incidence of CF is particularly low in Asians and that the disease might be misdiagnosed or underdiagnosed due to economic or medical factors in Asia. In this study, we identified and recorded an unreported mutation in a Chinese CF patient. The disease-causing mutations on both alleles of this patient, along with two polymorphisms, were also described.

c.2335C>T (p.Q779X)

The new CFTR allele is the nonsense mutation c.2335C>T in exon 14 involving the substitution of C to T at nucleotide position 2335. This nonsense mutation produces dramatically changed CFTR polypeptides that are located at the regulatory region, which is predicted to result in null CFTR function [24]. Many previous studies have shown that there is a strong relationship between the CF genotype and pancreatic status: Class I-III mutations (also called 'severe' mutations) tend to be associated with pancreatic insufficiency [25]. We speculate that this mutation (Class I mutation) contributes to the symptoms of malnutrition and steatorrhea. Therefore, further testing is required to confirm the causality of this mutation.

c.263T>G (p.L88X)

The second mutation is a heterozygous nonsense mutation of c.263T>G (p.L88X) in exon 3 on the other chromosome. This mutation was also found in two CF patients of Korean origin [26, 27], but it was not detected in Caucasians. We suspect this mutation arose in ancestors of Chinese and Korean descent. One of the Korean patients was a compound heterozygote of two mutations: c.263T>G and c.2089_2090insA [27]. Similar to our patient, compound heterozygous for class I mutations predicted earlier and more severe deterioration of lung function, higher incidence of malnutrition, and liver disease. In contrast, however, the Korean patient showed no evidence of pancreatic insufficiency. It is likely that this variation can be explained by the influence of non-CFTR gene modifiers and environmental factors.

Polymorphisms

In contrast with the mutations, both of the polymorphisms observed are widespread. The single nucleotide polymorphism (SNP) c.2562T>G has no known consequence. The threonine at codon 854 remains unchanged, so it is likely to be a silent polymorphism. Huang's team investigated the c.1408A>G polymorphisms in 132 healthy unrelated subjects in China and compared its distribution with that in Caucasians and other Asian populations. They found that c.1408A>G distributions were similar to those in other East Asians, but they had marked differences in frequency from single haplotype polymorphisms and linkage haplotypes in Caucasians [28]. Consequently, their study may be able to explain the low incidence of CF in Asians.

The present situation of Chinese

As shown in **Table 1**, we reviewed clinical manifestations and CFTR mutations of Chinese CF patients. It is evident that all of these Chinese CF patients were diagnosed when they presented with typical features of the disease. As we all know, the clinical manifestations of a portion of CF patients are mild or atypical. So therefore, we believed that a number of Chinese CF patients were misdiagnosed.

Table 1. CFTR mutations and clinical manifestations of Chinese CF patients

Patient [reference]	Mutation†	Sweat test	Current clinical conditions	Age at diagnosis	Sex	Family history
1. [4]	c.699C>A/c.3821-3823delT	108.9±3.3 mmol/L	Recurrent pneumonia, parasinusitis and otitis media. productive cough with bronchiectasis in bilateral upper lobes.	14	F	No family history
2. [5]	c.1898+5G>T	194.5 mmol/L	Dehydration, electrolyte imbalance, pancreatic insufficiency and respiratory symptoms.	0.5	F	Older brother with the same symptoms died at 6 months.
3. [6]	c.1898+1G>T	"High"	Pancreatic insufficiency and respiratory symptoms.	5	F	Older sister had cystic fibrosis.
4. [7]	c.1898+5G>T	"High"	Respiratory symptoms, FFT and clubbing fingers.	8	F	Consanguineous marriage.
5. [8]	c.3041G>A/c.ΔGCTTCCTA	104 mmol/L	Sputum cultures positive for Staphylococcus aureus and Burkholderia cepacia, and ABPA.	23	F	No family history.
6. [9]	c.2215insG, c.1898+5G>T	327 mmol/L	Respiratory symptoms, poor weight gain and clubbing fingers.	17	M	Sibling of patient 6.
7. [9]	c.2215insG, c.1898+5G>T	276 mmol/L	Respiratory symptoms, poor weight gain and clubbing fingers.	14	F	Sibling of patient 5.
8. [10]	c.151G>T, c.989-992insA	89 mEq/L	Pancreatic insufficiency, FFT and respiratory symptoms.	1.5	M	Older sister had cystic fibrosis.
9. [10]	p.S895N, /c.2215insG, c.1898+5G>T	135 mEq/L	Dehydration,electrolyte imbalance,recurrent pancreatitis and deteriorated pulmonary function.	10	F	Older brother with recurrent pneumonia died at 6 months.
10. [11]	p.R553X	90 mEq/L	Rectal prolapse, dehydration, electrolyte imbalance,chronic diarrhea, FFT, pancreatic insufficiency and respiratory symptoms.	3.5	M	No family history
11. [12]	p.W679X/c.1342-11TTT>G,c.3120+2T>C	115.8 mmol/L	Respiratory symptoms, liver disease, chronic nasal congestion, and pancreatic insufficiency.	12	F	No family history
12. [13]	c.263T>G,c.2909G>A	98.53 mmol/L	Respiratory symptoms, sinus polypus.	13.8	F	Father suffers from emphysema
13. [13]	c.3196C>T	NA	Respiratory symptoms and nasosinusitis.	10	F	No family history
14. [14]	c.293A>G	154 mmol/L	Respiratory symptoms including ABPA.	21	F	No family history
15. [14]	c.95T>C, c.1657C>T	66 mmol/L	Respiratory symptoms including ABPA and abdominal distension.	12	M	No family history
16. [14]	c.293A>G, c.558C>G	135 mmol/L	Recurrent pneumonia.	10	M	No family history
17. [14]	c.2052 dupA, c.2909-?_3367+?del	132 mmol/L	Recurrent pneumonia.	16	M	No family history
18. [14]	c.2909G>A, c.744-?_1584+?del	130 mmol/L	Respiratory symptoms.	16	F	No family history
19. [14]	c.1666A>G	100 mmol/L	Respiratory symptoms and recurrent diarrhoea.	28	F	No family history
20. [14]	c.1679+2T>C, c.2658-1G>C	154 mmol/L	Respiratory symptoms including ABPA.	10	F	The patient's older sister died at the age of 11 as a result of pneumonia.
21. [15]	c.865A>T, c.3651_3652 insAAAT	NA	Recurrent respiratory infection and productive cough of yellow-green sputum.	15	M	Sibling of patient 22.
22. [15]	c.865A>T, c.3651_3652insAAAT	NA	Frequent productive cough and shortness of breath.	12	M	Sibling of patient 22.
23. [16]	c.595C>T	306.8 mmol/L	Recurrentcough with expectoration and associated with cirrhosis.	10	F	No family history
24. [16]	c.595C>T, c.2290C>T	ND	Recurrentpneumonia from neonate, FFT and fatty diarrhea.	0.8	M	No family history
25. ‡[17]	c.263T>G, c.1666A>G, c.326A>G	101 mmol/L	Bronchiectasis, sinusitis, ABPA and liver disease.	11.58	M	NA
26. ‡[17]	c.2909G>A	103 mmol/L	Bronchiectasis, sinusitis, ABPA and pancreatitis.	10.58	F	NA
27. ‡[17]	c.293A>G	101 mmol/L	Bronchiectasis, sinusitis, ABPA, hemoptysis, nasal polyps and FTT.	13.25	M	NA
28. ‡[17]	c.414_415insCTA	99 mmol/L	Bronchiectasis, sinusitis, ABPA, hemoptysis and finger clubbing.	13.67	F	NA
29. ‡[17]	c.648G>A	106 mmol/L	Bronchiectasis, sinusitis and ABPA.	7.17	M	NA
30. ‡[17]	c.1000C>T	127 mmol/L	Bronchiectasis, sinusitis, hepatocirrhosis and finger clubbing.	10.67	F	NA
31. ‡[17]	c.2491-126T>C	118 mmol/L	Bronchiectasis, sinusitis and saltytasting skin.	7.75	F	NA
32. ‡[17]	c.3196C>T	105 mmol/L	Bronchiectasis, recurrent pneumonia, FTT and finger clubbing.	10.17	F	NA

33. ‡[17]	c.223C>T	96 mmol/L	Bronchiectasis, sinusitis and recurrent pneumonia.	11.08	F	NA
34. ‡[17]	c.558C>G	115 mmol/L	Bronchiectasis, ABPA, recurrent pneumonia and FTT.	8.25	M	NA
35. ‡[17]	c.595C>T	101 mmol/L	Bronchiectasis and FTT.	4.17	F	NA
36. ‡[17]	c.960_961insA	99 mmol/L	Sinusitis, recurrent pneumonia and bronchopulmonary dysplasia.	3.67	M	NA
37. ‡[17]	c.1075C>T	122 mmol/L	Bronchiectasis, sinusitis, ABPA, liver disease and finger clubbing	12.67	F	NA
38. ‡[17]	c.1699G>T	120 mmol/L	Bronchiectasis, recurrent pneumonia, hemoptysis, Pancreatitis and finger clubbing.	12.75	M	NA
39. ‡[17]	c.1766+5G>T	137 mmol/L	Bronchiectasis, sinusitis and recurrent pneumonia	10.75	M	NA
40. ‡[17]	c.2374C>T	ND	Bronchiectasis, sinusitis, recurrent pneumonia, hepatocirrhosis, FTT, finger clubbing and salty-tasting skin.	11	M	NA
41. ‡[17]	c.3307delA	ND	Bronchiectasis, sinusitis, recurrent pneumonia, FTT, steatorrhea, atrophy of pancreas, finger clubbing and salty-tasting skin.	10.33	F	NA
42. ‡[17]	c.3700A>G	ND	Bronchiectasis, ABPA, liver disease and salty-tasting skin.	11.17	M	NA
43. ‡[17]	c.3909C>G	ND	Bronchiectasis, sinusitis, FTT, steatorrhea, purulent appendicitis, finger clubbing and salty-tasting skin	3.42	F	NA
44. ‡[17]	c.110C>G	115 mmol/L	Bronchiectasis, sinusitis, ABPA, FTT, Steatorrhea, finger clubbing and salty-tasting skin.	14	F	NA
45. [18]	c.3196C>T, c.870-1G>C	140 mmol/L	Recurring cough and wheeze.	5	M	NA
46. [18]	c.3G>A, c.1572C>A	109 mmol/L	Recurrent cough and diarrhoea. clubbed fingers and toes.	5	W	NA
47.	c.1766+5G>T, c.3068T>G	123.5 mmol/L	Chronic productive cough.	17	M	NA
48. [19]	c.1766+5G>T, c.3140-26A>G	106 mmol/L	Two episodes of pneumonia.	0.5	M	NA
49. [19]	c.868C>T, c.3068T>G	110 mmol/L	Recurrent pneumonia; CT chest shows bronchiectasis, segmental left lingular collapse.	0.2	M	NA
50. [19]	c.1657C>T, c.3068T>G	123 mmol/L	Recurrent pneumonia; HRCT chest shows bronchiectasis.	9	W	NA
51. [19]	c.3068T>G; c.3068T>G	123 mmol/L	Recurrent pneumonia and rhinosinusitis; HRCT chest shows bronchiectasis.	1.1	W	NA
52. [20]	c.2909G>A; c.1521_1523delCTT	137 mmol/L	Bronchiectasis, Recurrent diarrhea, marasmus.	20	M	No family history
53. [20]	c.2909G>A; c.2374C>T	140 mmol/L	Bronchiectasis, marasmus and steatorrhea.	15	F	No family history
54. [20]	c.2909G>A; c.2125C>T	108.4 mmol/L	Recurrent diarrhea; meconium ileus suspected and Bartter Syndrome.	1	F	Have a family history
55. [20]	c.3700A>G;, c.959_960insA	95.2 mmol/L	Bartter Syndrome and bronchiectasis.	13	M	No family history
56. [20]	c.3635delT	106.5 mmol/L	Bronchiectasis.	15	M	Have a family history
57. [20]	c.2909G>A, c.1997T>G	101.9 mmol/L	Bronchiectasis and marasmus.	22	F	Have a family history
58. [20]	c.2909G>A, c.263T>G	122.1 mmol/L	Bronchiectasis and malnutrition.	4	F	No family history
59. [20]	c.2909G>A, c.2907A>C	62 mmol/L	ABPA and malnutrition.	13	F	No family history
60. [21]	c.579+1_579+2insACAT; c.1766+5G>T	ND	Bronchiectasis.	9	M	No family history
61. [21]	c.595C>T	ND	Bronchiectasis.	5	M	No family history
62. [21]	c.1117-1G>C; c.2909G>A	ND	Bronchiectasis and clubbed fingers.	6	F	No family history
63. [21]	c.4056G>C	ND	Bronchiectasis and steatorrhea.	13	M	No family history
64. (our patient)	c.263T>G, c.2335C>T	118.4 mmol/L	Respiratory symptoms, liver disease, clubbing fingers, and pancreatic insufficiency.	20	F	No family history

†Protein or cDNA name. ‡Spectrum of CFTR variants detected in 19 of these patients. ABPA, allergic bronchopulmonary aspergillosis; FTT, failure to thrive; F, female; M, male; NA, not available; ND, not done.

The median age of the Chinese patients, confirmed by genetic analysis, is 10.55, which is much older than CF patients in Western countries with national CF screenings for newborns (Australia-1.8 months, US--6 months, UK--4 months, France--4 months) [25]. This difference is due to different diagnostic methods. As a result of the low incidence of CF in China, we did not have newborn screening tests for this disease and the genetic testing for this disease was not popularized in most of the provinces in China, especially for those in the poorer western areas. Thus, many patients are not diagnosed until a typical clinical symptom occured in adulthood.

In reality, considerable numbers of CF carriers do exist in the Chinese population. Li's team [29] sequenced the entire coding regions and the splice sites of 27 exons of the CFTR gene in 146 chromosomes from the 73 Chinese CBAVD patients. Nine novel mutations along with nineteen previously reported mutations and polymorphism sites were found [29]. It has long been known that CFTR mutations vary in their frequency and distribution in different groups [25]. The F508del mutation accounts for 70-90% of cases of CF in Northern Europe and Norther America, while it accounts for less than 50% in the Mediterranean region [30]. The F508del, however, might not be the predominant mutation in Asian CF patients [3] since it has yet to be reported in China. It seems that the 1898+5G>T, c.2909G>A and 3068T>G are recurrent mutations in Chinese CF patients, as shown in **Table 1**. **Table 1** summarizes the mutations identified in Chinese CF patients and some of them (c.699C>A, c.451-458delGCTTCCTA, c.3041G>A, c.151G>T, c.989-992insA, c865A>T, c.780G>A, c.1092insA, c.1075C>T, c.1699G>T, c.2623-126T>C, c.3439delA, c.4575+110C>G, c.870-1G>C, c.3635delT, c.1997T>G, c.2907A>C, c.579+1_579+2insACAT; c.1117-1G>C) had never been reported in Caucasian patients. China has a population of about 1.3 billion, so an incidence of 1 in a million would predict 3 million carriers of CFTR mutations. In the sixty-four reported cases, nineteen novel mutations were found, which indicated that large pools of Chinese CF mutations are novel.

Since CF is considered extremely rare in China, the present study would suggest that carriers of CF alleles do exist in the Chinese population and are often associated with rare genotypes. Thus, mutational analysis cannot be overlooked. Direct sequencing of the CFTR gene generally includes all exons and their splice junction sites, so it is an effective methodology that is not constrained to known mutations, unlike many commercial kits, and can therefore help detect novel mutations not included on existing panels. Increasing recognition of CFTR mutations as an etiology for different phenotypes of patients with productive cough, pancreatic insufficiency, and male infertility will provide the potential to identify the Chinese CFTR mutation spectrum and will provide earlier and more comprehensive treatment and genetic counseling.

Acknowledgements

We thank the patient for her assistance with the report.

Disclosure of conflict of interest

None.

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