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Case Report

Differences in Gene Mutations Between Chinese and Caucasian Cystic Fibrosis Patients

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Summary. Cystic fibrosis (CF) is rarely seen in Asian populations. We diagnosed two CF cases. One of them had a novel mutation c.870-1G>C in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. There have been 38 Chinese CF patients reported in literature from 1974 until the present (2016), 25 different mutations were identified. Only one of these mutations (R553X) is in the Caucasian CF screening panel. The mutations identified in Chinese CF patients are very different from the common Caucasian gene mutations. The CFTR gene mutation spectrum for the Chinese population requires further investigation. **Pediatr Pulmonol. 2017;52: E11–E14.** © 2016 The Authors. *Pediatric Pulmonology* Published by Wiley Periodicals, Inc.

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CASE REPORT

Case One

Five-year-old boy, born in Shandong province of China, was admitted in our hospital for recurring coughing and wheezing over a 5-year period. At 4-month-old, the child began to cough. Two months later, he began to periodically wheeze 4–5 times per year, sometimes accompanied by fever, green and yellow sputum. The child received small bowel resection due to intestinal atresia after birth. He defecated 7–8 times per day, and intestinal obstruction occurred three times.

He suffered from malnutrition. Physical examination revealed respiratory distress with dyspnea, tachypnea, and wheezing. Pulmonary auscultation revealed fine rales and wheezing rales. In his abdomen, the liver was palpable two finger-breadth below the right costal margin.

Total IgE was 1,301 Ku/L, the specific IgE for aspergillus fumigatus was strongly positive, the sputum cultures were positive for *Pseudomonas aeruginosa*. The Sudan III dye test of fecal matter was positive. The sweat check showed an elevated sweat ion level of 140 mmol/L (equivalent NaCl) (Macroduct 3700 & Sweat-Check3120, Wescor, America). The lung function revealed obstructive lung disease with a forced expiratory volume in 1 sec (FEV1) of 66.1% of predicted. The chest HRCT (Fig. 1A) confirmed the presence of central bronchiectasis, especially in the upper lung zones. The paranasal CT (Fig. 1C) showed nasosinusitis. The abdominal CT showed the pancreas had fat density (Fig. 1B). The mutations in the CFTR included c.3196C>T (p.R1066C) and c.870-1G>C, which originated from his father and mother respectively. Thus, we diagnosed the child as having CF with ABPA.

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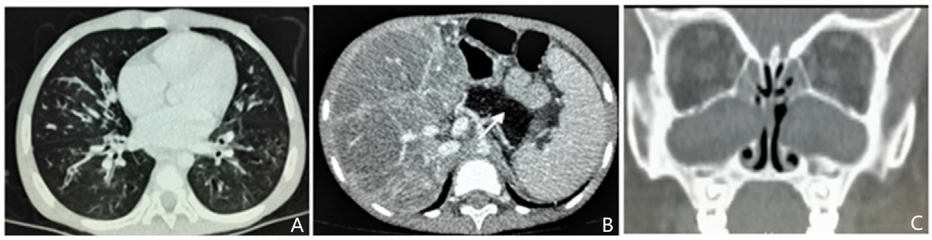

Fig. 1. (A) There is bronchial wall thickening, bronchiectasis, and areas of mucous plugging. (B) Enhanced CT demonstrate the low density of pancreas (small arrow) and liver. The entire pancreas demonstrated as fat density (CT value = −90HU). (C) Maxillary sinuses and ethmoid sinus were fully filled with secretions symmetrically.

Other than hypertonic saline (7%) nebulization, high frequency chest wall oscillation, pancreatic enzyme replacement therapy, and the supplement of vitamins A, D, E, K, the child was prescribed ciprofloxacin to deal with *P. aeruginosa*. We also used itraconazole and prednisone to treat ABPA. The symptoms abated, lung function improved. The FEV1 rose to 116.5% of predicted.

Case Two

Five-year-old girl was admitted in our hospital for recurrent coughing over a 3-year period. Three years ago, the child began to cough, no obvious sputum and dyspnea, roughly 1–2 times per year, which lasted 15 days each occurrence. The symptoms could be relieved through antibiotics.

From 4 years ago, she began to have rectocele, and defecated 3–5 times per day, oil drops could sometimes be seen. She was thin and sweaty, saline traces could be observed on her face. She had clubbed fingers and toes. The sputum cultures tested positive for *P. aeruginosa*. The Sudan III dye test of fecal matter was positive. The sweat ion level was 109 mmol/L (equivalent NaCl). The chest HRCT (Fig. 2A) showed bronchiectasis, especially in the upper lung zones. The paranasal CT (Fig. 2C) showed nasosinusitis, the abdominal CT (Fig. 1B) showed the pancreas had fat density (Fig. 2). The mutations in the CFTR included c.3G>A (p.M1I) and c.1572C>A (p.Cys524X) which originated from her father and mother, respectively.

Other than hypertonic saline (7%) nebulization, high frequency chest wall oscillation, pancreatic enzyme replacement therapy, the child was prescribed intravenous antibiotics including cefepime and ciprofloxacin. The respiratory symptoms improved.

DISCUSSION

Cystic fibrosis is the most frequently occurring life-limiting autosomal recessive disorder among Caucasians populations, with a carrier frequency of about 1:25, resulting in a disease incidence of 1 in 2,500 live births.[1] However, CF is quite rare in Asian populations, and an epidemiological study of the Japanese population found the incidence of CF to be about 1 in 350,000.[2] In China, there are no epidemiological statistics in incidence of this disease. There have been only 36 cases report from 1974 until the present.

There are currently 2006 mutations listed in the Cystic Fibrosis Mutation Database,[3] but not all can be conclusively categorized as disease-causing,[4] and only the 32 most frequent mutations are listed in the recommended CFTR gene mutation screening panel.[5] The most common mutation, p.F508del, occurred in about 70% of Caucasian CF patients,[1] other disease-causing mutations often occur with low frequencies.[6] But the p.F508del is not a common mutation in Asian CF patients, there have been no cases where a p.F508del mutation was found in China.

We identified four different mutations in the two CF patients, three of these mutations (R1066C, p.Cys524X, p.M1I) are present in the Cystic Fibrosis Mutation

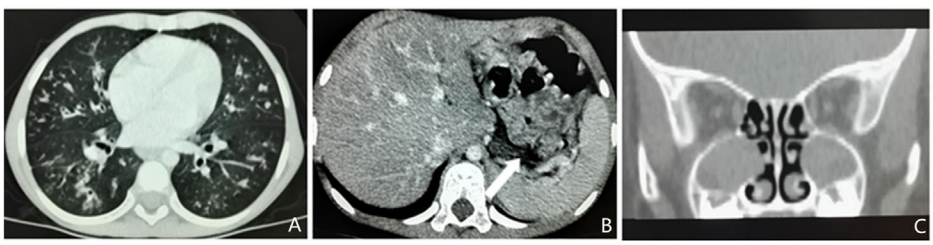

Fig. 2. (A) Central bronchiectasis and wall thickening. (B) The pancreas (large arrow) was small in this case. The entire pancreas demonstrated as fat density (CT value = −90HU). (C) Maxillary sinuses were fully filled with secretions symmetrically.

TABLE 1— Characteristics of *CFTR* Gene Mutations in 22 Chinese CF Patients

cDNA name (frequency %[1])	Protein name	Areas (number)
c.1766 + 5G>T (27)	NA	Taiwan (4), Australia (1), Canada (1)
c. 2909G>A (13)	p.G970D	Mainland China (2), America (1)
c.2083dupG (13)	p.E695GfsX35	Taiwan (3)
c.2684G>A (13)	p.S895N	Taiwan (3)
c.1657C>T (9)	p.R553X	Mainland China (1), Taiwan (1)
c.3196C>T (9)	p.R1066C	Mainland China (2)
c.293A>G (9)	p.Q98R	Mainland China (2)
E2 del about 30 bp (4)	NA	Mainland China (1)
c.319-326delGCTTCCTA (4)	p.Ala107X	America (1)
c.19G>T (4)	p.Glu7X	Taiwan (1)
c.857-858insA (4)	p.Asn287LysfsX21	Taiwan (1)
c.567C>A (4)	p.N189K	Mainland China (1)
△E7-E11 (c.744-?_1584 + ?del) (4)	p.Arg248_Glu528delinsArgfsX	Mainland China (1)
c.263T>G (4)	p.L88X	Mainland China (1)
c.1666A>G (4)	p.I556V	Mainland China (1)
c.3G>A (4)	p.M1I	Mainland China (1)
c.1572C>A (4)	p.Cys524X	Mainland China (1)
c.3691delT (4)	p.S1231PfsX4	Mainland China (1)
c.95T>C (4)	p.L32P	Mainland China (1)
c.558C>G (4)	p.N186K	Mainland China (1)
c.1679 + 2T>C (4)	NA	Mainland China (1)
c.2658-1G>C (4)	NA	Mainland China (1)
c.870-1G>C (4)	NA	Mainland China (1)
c.2052 dupA (4)	p.Q686TfsX3	Mainland China (1)
△E18-E20(c.2909-?_3367 + ?del) (4)	p.Gly980_Thr1112delinsGly	Mainland China (1)

[1]The frequency was calculated through the number of patients who carried the gene mutation/22.

Database.[7] But none of them are common in Caucasian CF patients. Among the 36 Chinese CF together with our two patients, 26 were diagnosed in mainland China, eight in Taiwan, the remaining patients were diagnosed in Singapore, Australia, Canada, and America, respectively. Twenty-two patients had their CFTR gene tested, and 25 different mutations were identified (Table 1).[8–10] c.1766 + 5G>T was the most common mutation among Chinese, with a detection rate as high as 27% as shown in Table 1, mainly reported in Taiwan. p.G970D was primarily detected in Chinese, its frequency in the 22 patients was 13%, which was found in America by Wine et al.[11] in 2001. The frequency of p.E695GfsX35 and p.S895N mutation were also 13%, but only found in Taiwan. p.Q98R is a mutation that was first reported in Southern France,[12] and primarily reported in Koreans and Japanese, with a detection rate as high as 9% in the 22 patients. p.R1066C had been reported in Italy and Spain. c.870-1G>C is the first report by us. Only two patients carried the R553X mutation included in the CF screening panel for Caucasians. All the other mutations are uncommonly seen in Caucasians. In conclusion, the spectrum of CFTR mutations in Chinese is highly different from that of Caucasian.

In China, CF is difficult to diagnose because of a combination of low awareness, atypical clinical symptoms, and a lack of sweat and genetic testing facilities in most hospitals.[8] It is a pity that our two patients were only tested for sweat ion level instead of the sweat chloride concentration for there is no standardized instrument to test the sweat chloride in China now. Furthermore, the mutations identified in Chinese CF patients are different from the common Caucasian gene mutations. We should further investigate the CFTR gene mutation spectrum for the Chinese population, and the relationship between the Chinese genotype and clinical phenotypes.

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