ISSN 2307-8960 (online)

# World Journal of *Clinical Cases*

*World J Clin Cases* 2019 August 6; 7(15): 1908-2133

Published by Baishideng Publishing Group Inc

World Journal of Clinical Cases

Contents

Semimonthly Volume 7 Number 15 August 6, 2019

**Contents**

*World Journal of Clinical Cases*

**Volume 7 Number 15 August 6, 2019**



**AIMS AND SCOPE**

*World Journal of Clinical Cases* (*World J Clin Cases*, *WJCC*, online ISSN 2307-8960, DOI: 10.12998) is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

The primary task of *WJCC* is to rapidly publish high-quality Case Report, Clinical Management, Editorial, Field of Vision, Frontier, Medical Ethics, Original Articles, Meta-Analysis, Minireviews, and Review, in the fields of allergy, anesthesiology, cardiac medicine, clinical genetics, clinical neurology, critical care, dentistry, dermatology, emergency medicine, endocrinology, family medicine, gastroenterology and hepatology, *etc*.

**INDEXING/ABSTRACTING**

The *WJCC* is now indexed in PubMed, PubMed Central, Science Citation Index Expanded (also known as SciSearch®), and Journal Citation Reports/Science Edition. The 2019 Edition of Journal Citation Reports cites the 2018 impact factor for *WJCC* as 1.153 (5-year impact factor: N/A), ranking *WJCC* as 99 among 160 journals in Medicine, General and Internal (quartile in category Q3).

**RESPONSIBLE EDITORS FOR THIS ISSUE**

**Responsible Electronic Editor:** *Yan-Xia Xing*

**Proofing Production Department Director:** *Yun-Xiaojian Wu*

**NAME OF JOURNAL**
*World Journal of Clinical Cases*

**ISSN**
ISSN 2307-8960 (online)

**LAUNCH DATE**
April 16, 2013

**FREQUENCY**
Semimonthly

**EDITORS-IN-CHIEF**
Dennis A Bloomfield, Sandro Vento

**EDITORIAL BOARD MEMBERS**
https://www.wjgnet.com/2307-8960/editorialboard.htm

**EDITORIAL OFFICE**
Jin-Lei Wang, Director

**PUBLICATION DATE**
August 6, 2019



**INSTRUCTIONS TO AUTHORS**
https://www.wjgnet.com/bpg/gerinfo/204

**GUIDELINES FOR ETHICS DOCUMENTS**
https://www.wjgnet.com/bpg/GerInfo/287

**GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH**
https://www.wjgnet.com/bpg/gerinfo/240

**PUBLICATION MISCONDUCT**
https://www.wjgnet.com/bpg/gerinfo/208

**ARTICLE PROCESSING CHARGE**
https://www.wjgnet.com/bpg/gerinfo/242

**STEPS FOR SUBMITTING MANUSCRIPTS**
https://www.wjgnet.com/bpg/GerInfo/239

**ONLINE SUBMISSION**
https://www.f6publishing.com

World Journal of Clinical Cases

Submit a Manuscript: https://www.f6publishing.com

*World J Clin Cases* 2019 August 6; 7(15): 2110-2119

DOI: 10.12998/wjcc.v7.i15.2110

ISSN 2307-8960 (online)

CASE REPORT

# c.753_754delAG, a novel *CFTR* mutation found in a Chinese patient with cystic fibrosis: A case report and review of the literature

Yu-Qing Wang, Chuang-Li Hao, Wu-Jun Jiang, Yan-Hong Lu, Hui-Quan Sun, Chun-Yan Gao, Min Wu

**ORCID number:** Yu-Qing Wang (0000-0002-4153-3984); Chuang-Li Hao (0000-0002-1342-8175); Wu-Jun Jiang (0000-0002-1538-9069); Yan-Hong Lu (0000-0002-9447-6493); Hui-Quan Sun (0000-0002-1200-0812); Chun-Yan Gao (0000-0001-6875-9652); Min Wu (0000-0001-9758-9517).

**Author contributions:** Wang YQ wrote the main manuscript text; Hao CL and Wang YQ designed the study and revised the manuscript; Jiang WJ and Lu YH carried out the initial analyses; Sun HQ did the bronchoscopy and microbiological detection; Gao CY and Wu M did the data collection. All authors read and approved the final manuscript.

**Supported by** the National Natural Science Foundation of China, No. 81573167; Science and Technology Project of Jiangsu, No. BE2017657; Livelihood Science and Technology Project of Suzhou, No. SYS201640.

**Informed consent statement:** This study was approved by the Ethics Committee of Children's Hospital of Soochow University, and written informed consent was obtained from the parents of the patient.

**Conflict-of-interest statement:** The authors declare that they have no conflict of interest.

**CARE Checklist (2016) statement:** The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE

**Open-Access:** This article is an

**Yu-Qing Wang, Chuang-Li Hao, Wu-Jun Jiang, Yan-Hong Lu, Hui-Quan Sun, Chun-Yan Gao, Min Wu,** Department of Respiratory Medicine, Children's Hospital of Soochow University, Suzhou 215000, Jiangsu Province, China

**Corresponding author:** Yu-Qing Wang, MD, Chief Doctor, Deputy Director, Department of Respiratory Medicine, Children's Hospital of Soochow University, No. 303, Jingde Road , Suzhou 215000, Jiangsu Province, China. wang_yu_qing@126.com
**Telephone:** +86-512-67788313
**Fax:** +86-512-67786316

## Abstract

### *BACKGROUND*

Cystic fibrosis (CF) is rare in Asian populations relative to the Caucasian population. In this paper, we report the cystic fibrosis transmembrane conductance regulator (CFTR) variation in a family of Chinese CF patients, and systematically review the previous literature.

### *CASE SUMMARY*

Here we report a 30-month-old Chinese girl who was diagnosed with CF based on her history and symptoms such as recurrent productive cough, wheezing with repeated infection of *Pseudomonas aeruginosa*, and parasinusitis. Chest computed tomography (CT) scanning revealed obvious exudative lesions and bilateral bronchiectasis. Liver CT scanning revealed a low-density lesion in the left lobe of the liver. A diagnosis of CF was made based upon *CFTR* gene tests. The *CFTR* gene was sequenced using the blood samples of her and her parents and showed a heterozygous novel missense mutation of c.753_754delAG in exon 7. In addition, a heterozygous c.1240 C>T mutation was found in exon 10 of the *CFTR*. The mutation c.753_754delAG was verified to have been inherited from her mother, and the c.1240 C>T mutation was from her father who was diagnosed with congenital absence of vas deferens.

### *CONCLUSION*

A novel mutation of CFTR, c.753_754delAG, was found in a Chinese CF child. c.2909G>A is the most common mutation among Chinese CF patients.

**Key words:** Cystic fibrosis; Cystic fibrosis transmembrane conductance regulator; Mutation; Chinese children; Case report

**Manuscript source**: Unsolicited manuscript

**Received:** February 28, 2019
**Peer-review started:** March 4, 2019
**First decision:** May 31, 2019
**Revised:** June 23, 2019
**Accepted:** July 2, 2019
**Article in press:** July 2, 2019
**Published online:** August 6, 2019

**P-Reviewer:** Brecelj J
**S-Editor:** Dou Y
**L-Editor:** Wang TQ
**E-Editor:** Xing YX

**Core tip:** Cystic fibrosis (CF) is an autosomal recessive inherited disease caused by mutations in the CF transmembrane conduction regulator (*CFTR*) gene. CF is rare in Chinese. ΔF508 is the most common mutation, accounting for greater than two-thirds of CF alleles worldwide, though it is not a predominant mutation in Chinese CF patients. In this paper, we report a novel homozygous complex rearrangement involving *CFTR* exon 7 deletion (c.753_754delAG chr7-117176607-117176608) in a Chinese child with CF and describe the clinical feature. Moreover, we further review the literature regarding gene mutations in Chinese CF cases from the 1970s to 2017.

**Citation:** Wang YQ, Hao CL, Jiang WJ, Lu YH, Sun HQ, Gao CY, Wu M. c.753_754delAG, a novel *CFTR* mutation found in a Chinese patient with cystic fibrosis: A case report and review of the literature. *World J Clin Cases* 2019; 7(15): 2110-2119
**URL**: https://www.wjgnet.com/2307-8960/full/v7/i15/2110.htm
**DOI**: https://dx.doi.org/10.12998/wjcc.v7.i15.2110

## INTRODUCTION

Cystic fibrosis (CF) is an autosomal recessive inherited disease caused by mutations in the CF transmembrane conduction regulator (*CFTR*) gene. CF is most common in the Caucasian population, with a prevalence of 1/2500-3500 among those with Northern European ancestry[1,2]. CF was once considered extremely rare among the Chinese population, and to date, only about 60 cases of CF have been diagnosed in China[3]. CFTR is responsible for regulating the flow of chloride ions across the epithelial membrane. Since *CFTR* was first identified as the pathogenic gene of CF in 1989, more than 2000 mutations have been found in CF patients, according to the Cystic Fibrosis Mutation Database (http://www.genet.sickkids.on.ca). ΔF508 is the most common mutation, accounting for greater than two-thirds of CF alleles worldwide, though it is not a predominant mutation in Chinese CF patients[4]. The most common gene mutation in Chinese children with CF is c.2909G-A[5]. With increased awareness of this disease and improvements in diagnostic techniques, we have found that CF is not as rare as once believed in the Chinese population. The novel variants c.699 C-A, c.579+1_579+2insACAT, c.1117-1G>C c.3140-454_c.3367+249del931ins13, and p.R1048_G1123del have been reported in CF patients from China in recent years[6-8]. Interestingly, the gene mutation spectrum of CFTR in Chinese patients with CF is significantly different from that in Caucasian patients. Therefore, it is necessary to establish the Chinese *CFTR* gene mutation database, which will facilitate the genetic diagnosis of CF patients in China. In the present study, we identified a novel homozygous complex rearrangement involving CFTR exon 7 deletion (c.753_754delAG chr7-117176607-117176608) using multiplex ligation-dependent probe amplification analysis in a Chinese child with CF. We further review the literature regarding Chinese CF patients from the 1970s to 2017. The clinical data of all identified CF patients are summarized.

## CASE PRESENTATION

### *Chief complaints*

A girl aged 2 years and 10 months was admitted to Children's Hospital of Soochow University in May 2018 due to recurrent productive cough and wheezing lasting for 1 month.

### *History of past illness*

She had experienced recurrent pneumonia (2-3 times every year) beginning 4 mo after birth, with repeated infection by *Pseudomonas aeruginosa* and parasinusitis, but without a history of chronic diarrhea or pancreatic involvement.

### *Personal and family history*

The child was conceived through *in vitro* fertilization. Her father had been diagnosed with congenital absence of vas deferens, and her mother was healthy.

### *Physical examination*

She weighed 11 kg, her height was 89 cm, her body mass index was 13.9, and she

presented with shortness of breath and dyspnea. Crackles and wheezing rales were present in bilateral lungs. The heart and abdomen were normal. No clubbed digits were found.

### Laboratory examinations

Blood routine examination showed a white blood cell count of 15.59 × $10^9$/L, a C reactive protein concentration of 55.4 mg/L, and positivity for *Pseudomonas aeruginosa* on bronchoalveolar lavage fluid culture. Findings on other tests, including serum electrolyte measurement, fungus culture, Glactomannan test, T-SPOT tuberculosis test, allergic bronchopulmonary aspergillosis and aspergillus fumigatus specific IgE detection were all negative.

### Imaging examinations

Chest computed tomography (CT) scanning revealed obvious exudative lesions and bilateral bronchiectasis (Figures 1 and 2). Sinus CT scanning revealed bilateral parasinusitis. Liver CT scanning revealed a low-density lesion in the left lobe of the liver. In patients with CF, the liver is also the organ affected by the dense secretion of digestive juice. Bile secreted by the liver can clog bile ducts and damage the liver. Ultrasonography of the pancreas was negative.

### CFTR gene sequence analysis

Two heterozygous mutations were found in the CF patient by Sanger sequencing analysis. A heterozygous novel missense mutation of c.753_754delAG chr7-117176607-117176608 was identified in exon 7 (Figure 3), which was inherited from her mother based on its identification in the mother's sample as well (Figure 3). This novel mutation has not yet been recorded in the *CFTR* mutation database (http://www.genet.sickkids.on.ca). In addition, a heterozygous c.1240 C>T mutation in exon 10 was observed in *CFTR* of the CF patient (Figure 4), which was inherited from her father and had already been included in the *CFTR* mutation database.

## FINAL DIAGNOSIS

CF.

## TREATMENT

Her symptoms improved after antibiotic treatment with ceftazidime for 3 wk, expectorant, and nutritional support treatment including fat-soluble vitamins and powdered milk with high calorie.

## OUTCOME AND FOLLOW-UP

After being discharged from our hospital, the children were followed monthly in the outpatient clinic. We gave low dose azithromycin anti-inflammatory treatment to eradicate *P. aeruginosa* infection. We did regular examinations of respiratory rate, oxygen saturation, and high-resolution CT of the chest to evaluate the pulmonary disease regression/progression. We introduced regular atomized bronchodilators such as terbutaline and oral secretion expellant including acetylcysteine to help remove respiratory secretions. She had one time of pulmonary infection. The general situation remained well up to date. She weighed 13 kg, her height was 95 cm, and her body mass index was 14.4.

## DISCUSSION

CF is characterized by the abnormal transport of ions and fluid across epithelial cell membranes, resulting from mutations on both alleles in the gene encoding the CFTR[9,10]. *CFTR* mutations can cause secretions to obstruct the airway, pancreatic tract, and biliary tract and lead to abnormal secretion by the sweat glands. The most important organ to be invaded in CF is the lung, and lung disease is the most lethal factor (85%)[11]. The pancreas is also an important affected organ in CF. Disorders caused by CF include nutritional disorders (fat, protein malabsorption, and fatty diarrhea) and growth retardation. Low body weight caused by pancreatic insufficiency is negatively correlated with lung function and survival rate, and thus,

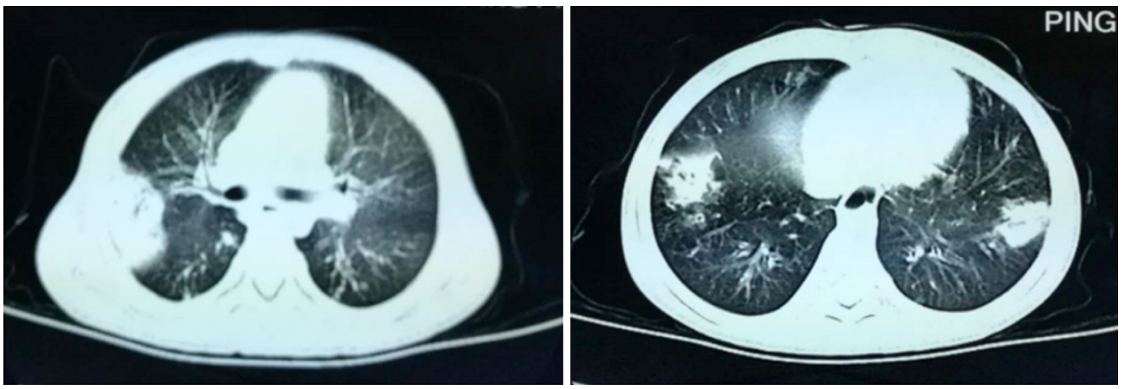


**Figure 1 Chest computed tomography images of the cystic fibrosis patient.** A chest computed tomography scan showed obvious exudative lesions and bilateral bronchiectasis in the lung of the cystic fibrosis patient.

an important factor for poor prognosis[12]. Malnutrition and gastrointestinal symptoms are relatively mild and atypical in Chinese CF patients. Therefore, it is easy for CF diagnosis to be missed or delayed.

For patients with one or more clinical characteristics, such as chronic sinopulmonary disease, gastrointestinal and nutritional abnormalities, genital abnormalities in males resulting in obstructive azoospermia, and/or a family history of CF, the measurement of sweat electrolyte concentrations has been the mainstay of CF diagnosis since the standardized procedure was introduced[13]. In the CF case reported here, the patient had chronic sinopulmonary disease, and her father had a CF mutation with obstructive azoospermia. These patients should undergo repeat sweat chloride testing and further evaluation, including detailed clinical assessment and more extensive *CFTR* gene mutation analysis. CF in Chinese patients is difficult to diagnose, due to insufficient understanding and because sweat examination as well as genetic testing cannot be carried out in most hospitals. It is necessary to educate Chinese pediatricians concerning the clinical manifestations and diagnostic criteria for CF and to promote the implementation of the sweat chloride test.

*CFTR* mutations are divided into five general classes: mutations affecting biosynthesis, mutations interfering with protein maturation, mutations influencing $Cl^-$ channel regulation, mutations intervening $Cl^-$ conductance or channel gating, and mutations that reduce CFTR synthesis[14]. Different types of *CFFR* mutations can cause different clinical phenotypes: I, II, and III mutations are prone to cause pancreatic insufficiency with more serious clinical manifestations. In contrast, because normal $Cl^-$ channel function is partially retained, the clinical symptoms of IV and V mutations are relatively mild with pancreatic function remaining normal.

Several studies have demonstrated that p.F508del is the most common mutation in Caucasian CF patients, accounting for approximately 70% of cases[4,5]. The p. F508del mutation is a type II mutation. We review 82 different mutations among 69 Chinese CF patients (40 females and 29 males) reported from the 1970s to 2017. Among them, 53 were from mainland China, 9 from Taiwan, and 4 from Hongkong, with the remaining patients being of Chinese and Vietnamese descent, Chinese and Portuguese descent[7,8,15-40] (Table 1). The age at diagnosis ranged from 0.17 months to 23 years.

Among the Chinese CF patients, the c.2909 G>A variant was the most common mutation type (11%), followed by 1898+5G>T (7.3%), c.293A>G (6.1%), and 2215insG+G2816A and c.263T>G (both 4.9%). Nevertheless, no p.F508del mutation was found in the Chinese patients (Table 1). In addition, with the exceptions of c.3909 C>G, R553X, and c.1000 C>T, none of the *CFTR* mutations in the Chinese patients were present in the common Caucasian *CFTR* mutation-screening panels, indicating that the mutations identified in Chinese CF patients are obviously different from the common gene mutations in Caucasian CF patients. Further, pulmonary lesions were more prominent in Chinese CF patients with or without pancreatic insufficiency[6-8,26,27]. Therefore, it is necessary to establish a Chinese gene mutation database to facilitate genetic diagnosis of CF in China to clarify the relationship between genotype and clinical phenotype.

In the case reported herein, the c.1240C>T mutation resulted in the alteration of amino acid p.Q414* (glutamine > termination). This mutation type has been reported already as a pathogenic mutation in the HGMD pro database[14]. c.753_754A del A.G is a novel mutation (deletion mutation) that results in amino acid changes P.R251Sfs * 6 (frame-shifting mutation - 6 termination). According to the ACMG guidelines, the mutation site c.753_754delAG could be classified as a pathogenic mutation[39]. Both

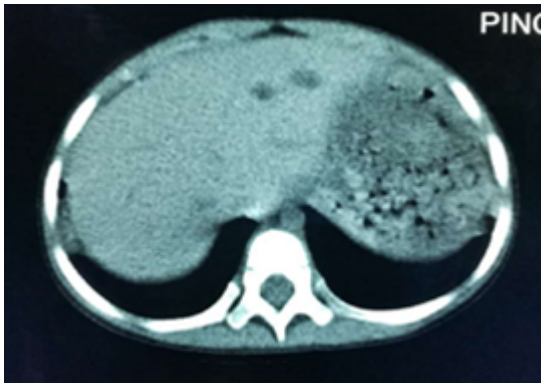

**Figure 2 Liver computed tomography image of the cystic fibrosis patient.** A liver computed tomography scan revealed a low-density lesion in the left lobe of the liver.

mutations could result in the early termination of CFTR protein translation, which might have a great impact on protein function. The double heterozygous mutation came from the patient's parents separately. As a compound heterozygous mutation, it is consistent with autosomal recessive inheritance and is a theoretically possible cause of disease. This case expands the mutation spectrum of *CFTR* in patients of Chinese origin. Several studies have shown that only pancreatic function correlates well with *CFTR* genotypes[40,41]. According to the pancreatic status of patients, CF mutations can be subdivided into two groups: mild and severe mutations[40]. Patients with pancreatic insufficiency are homozygous or compound heterozygous with two "severe" mutations, whereas patients with pancreatic sufficiency have at least one "mild" allele. As it is not clear from the case if the patient had pancreatic sufficiency or insufficiency, we cannot deduce whether the two mutations were severe mutations or not. Elevated serum lipase, which has not been mentioned before, is not a sign of severe mutation, more of possible pancreatitis which is more commonly seen in heterozygous CF carriers or in those with milder mutations and pancreatic sufficiency.

## CONCLUSION

In conclusion, a novel compound heterozygous c.753_754delAG mutation was found in exon 7 of *CFTR* in the case reported herein. The common *CFTR* mutation spectrum in Chinese CF patients is quite different from that in Caucasian patients. Therefore, the Chinese common *CFTR* mutation spectrum provides valuable data for CF diagnosis in Chinese patients and the development of a commercial Chinese *CFTR* genetic screening kit. The relevant Chinese gene mutation database is urgently needed.

**Table 1 Characteristics of *CFTR* gene mutations in 69 Chinese cystic fibrosis patients**

| Reference | Location | *n* | Gender | Age (yr) | Mutation |
|---|---|---|---|---|---|
| Wang *et al*[15], 1993 | Taiwan China | 1 | F | 0.5 | 1898+5 G-->T, 2215insG+G2816A |
| Chen *et al*[16],1995 | Mainland China | 1 | F | – | E2 del about 30 bp |
| Zielenski *et al*[17], 1995 | Taiwan China | 1 | F | 8 | 1898+5 G-->T, 1898+5 G-->T |
| Crawford *et al*[18], 1995 | Chinese and Portuguese | 1 | F | 3 | 1898 + 1G>T |
| Wagner *et al*[19], 1999 | Chinese | 1 | F | 23 | c.319-326delGCTTCCTA, c. 2909G>A |
| Wu *et al*[20], 2000 | Taiwan China | 2 | F | 14 | 1898+5 G>T, 2215insG+G2816A |
| | | | M | 17 | 1898+5 G>T, 2215insG+G2816A |
| Alper *et al*[21], 2003 | Chinese and Vietnamese | 2 | M | 1.5 | G151T, 989-992insA |
| | Taiwan China | | F | 0.5 | 1898+5G>T, 2215insG+G2816A |
| Chen *et al*[22], 2005 | Taiwan China | 1 | M | 3 | R553X, R553X |
| Li *et al*[6], 2006 | Mainland China | 1 | F | 14 | 699C>A, 3821-3823delT |
| Wang *et al*[23], 2012 | Mainland China | 1 | F | 14 | W679X |
| Liu *et al*[24], 2012 | Mainland China | 2 | F | 13 | 2909G>A, 362T>G |
| | | | F | 10 | 3196C>T, 3196C>T |
| Cheng *et al*[25], 2013 | Mainland China | 1 | F | 12 | W679X, 1342-11TTT>G, 3120+2T>C |
| Liu *et al*[26], 2015 | Mainland China | 7 | M | 12 | c.95T>C, c.1657C>T |
| | | | M | 10 | c.293A>G, c.558C>G |
| | | | M | 16 | c.2052 dupA, E18-E20(c.2909-?_3367 + ?del) |
| | | | F | 16 | c.2909G>A, E7-E11†(c.744-?_1584 + ?del) |
| | | | F | 10 | c.1679 + 2T>C, c.2658-1G>C |
| | | | F | 21 | c.293A>G, c.293A>G |
| | | | F | 28 | c.1666A>G |
| Shen *et al*[27], 2016 | Mainland China | 19 | M | 11.58 | c.1699G>T, c.3909C>G |
| | | | F | 10.58 | c.263T>G, c.1766+5G>T, c.110C>G |
| | | | M | 13.25 | c.3700A>G, c.960_961insA |
| | | | F | 13.67 | c.263T>G, c.2909G>A |
| | | | M | 7.17 | c.326A>G, c.1000C>T, c.1666A>G |
| | | | F | 10.67 | c.595C>T |
| | | | F | 7.75 | c.223C>T, c.326A>G |
| | | | F | 7.33 | c.1000C>T |
| | | | F | 10.17 | c.263T>G |
| | | | F | 11.08 | c.1666A>G |
| | | | M | 8.25 | c.293A>G, c.558C>G |
| | | | F | 4.17 | c.326A>G, c.2374C>T |
| | | | M | 3.67 | c.1666A>G |
| | | | F | 12.67 | c.293A>G |
| | | | M | 11 | c.648G>A, c.2491-126T>C |
| | | | F | 10.33 | c.3196C>T |
| | | | M | 11.17 | c.414_415insCTA |
| | | | F | 3.42 | c.1075C>T, c.3307delA |
| | | | F | 14 | c.2909G>A |
| Chu *et al*[28], 2016 | Mainland China | 1 | M | 9 | C.579+2insACAT, C.F481766+5G>T |
| Xu *et al*[29], 2016 | Mainland China | 1 | M | 0.67 | c.595C>T, C.2290C>T |
| Li *et al*[30], 2016 | Mainland China | 1 | M | 0.42 | c.214G>G/A, c.650A>A/G,c.3406G>G/A |
| Tian *et al*[31], 2016 | Mainland China | 8 | F | 15 | c.2909G>A, c.2374C>T |
| | | | F | 1 | c.2909G>A, c.2125C>T |
| | | | M | 13 | c.3700A>G, c.959–960insA |
| | | | M | 15 | c.3635delT |
| | | | F | 4 | c.2909G>A, c.263T>G |
| | | | F | 13 | c.2909G>A, c.2907A>C |
| | | | M | 20 | c.2909G>A, c.1521_1523delCTT |
| | | | F | 22 | c.2909G>A, c.1997T>G |

| | | | | | |
|---|---|---|---|---|---|
| Leung *et al*[32], 2017 | HongKong China | 4 | M | 17 | c.1766+5G>T, c.3068T>G |
| | | | M | 0.5 | c.1766+5G>T, c.3140-26A>G |
| | | | M | 0.17 | c.868C>T, c.3068T>G |
| | | | F | 0.75 | c.1657C>T, c.3068T>G |
| Xie *et al*[33], 2017 | Mainland China | 2 | M | 12 | c.865A>T,c.3651_3652insAAAT |
| | | | M | 15 | c.865A>T,c.3651_3653insAAAT |
| Zheng *et al*[34], 2017 | Mainland China | 2 | M | 5 | c.3196C>T, c.870-1G>C |
| | | | F | 5 | c.3G>A , c.1572C>A |
| Xu *et al*[7], 2017 | Mainland China | 4 | M | 9 | c.579+1_579+2insACAT, c.1766+5G>T |
| | | | M | 5 | c.595C>T |
| | | | F | 6 | c.1117-1G>C, c.2909G>A |
| | | | M | 13 | c.4056G>C |
| Liu *et al*[8], 2017 | Mainland China | 1 | M | 11 | c.3140-454_c.3367+249del931ins13 |
| Yao *et al*[35], 2017 | Mainland China | 1 | F | 0.5 | c.532G>A |
| Sun *et al*[36], 2017 | Mainland China | 1 | F | 2 | C.1 666A>G |
| Guo *et al*[37], 2017 | Mainland China | 1 | F | 0.75 | c.1373G>A(p.G458E), c.271G>A(p.G91R) |
| Li *et al*[38], 2017 | Mainland China | 1 | F | 1.33 | R709X, G970D |


**Figure 3 Genomic sequence of exon 7 of *CFTR*.** *CFTR* genomic sequencing results for exon 7 showed a heterozygous mutation of c.753_754delAG chr7-117176607-1171766 08 p.R251Sfs*6 in the cystic fibrosis patient and her mother. Exon 7 of *CFTR* was normal in her father.

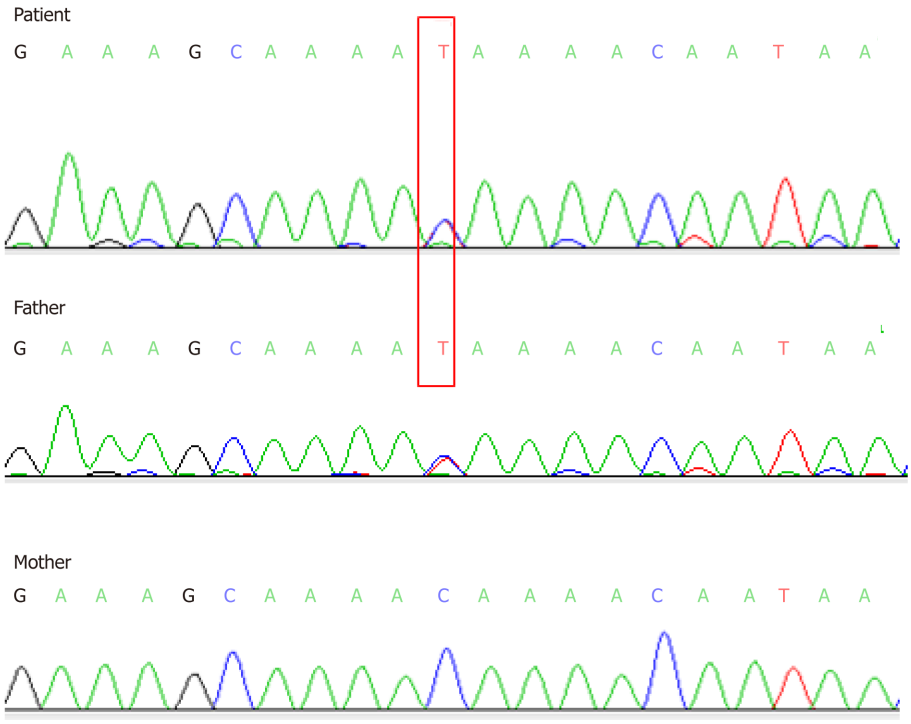


**Figure 4 Genomic sequence of exon 10 of *CFTR*.** *CFTR* genomic sequencing results of exon 10 revealed a heterozygous mutation of c.1240C>T chr7-117188725 p.Q414* in the cystic fibrosis patient and her father. Exon 10 of her mother was normal.

## ACKNOWLEDGEMENTS

The authors are grateful to all technicians of the Diagnostic Microbiology Laboratory, the Children's Hospital of Soochow University, for technical contributions and Beijing Precision Gene Technology Company (Beijing, China).

## REFERENCES

1 **Salvatore D**, Buzzetti R, Baldo E, Forneris MP, Lucidi V, Manunza D, Marinelli I, Messore B, Neri AS, Raia V, Furnari ML, Mastella G. An overview of international literature from cystic fibrosis registries. Part 3. Disease incidence, genotype/phenotype correlation, microbiology, pregnancy, clinical complications, lung transplantation, and miscellanea. *J Cyst Fibros* 2011; **10**: 71-85 [PMID: 21257352 DOI: 10.1016/j.jcf.2010.12.005]

2 **Southern KW**, Munck A, Pollitt R, Travert G, Zanolla L, Dankert-Roelse J, Castellani C; ECFS CF Neonatal Screening Working Group. A survey of newborn screening for cystic fibrosis in Europe. *J Cyst Fibros* 2007; **6**: 57-65 [PMID: 16870510 DOI: 10.1016/j.jcf.2006.05.008]

3 **Singh M**, Rebordosa C, Bernholz J, Sharma N. Epidemiology and genetics of cystic fibrosis in Asia: In preparation for the next-generation treatments. *Respirology* 2015; **20**: 1172-1181 [PMID: 26437683 DOI: 10.1111/resp.12656]

4 **Tabaripour R**, Niaki HA, Douki MR, Bazzaz JT, Larijani B, Yaghmaei P. Poly thymidine polymorphism and cystic fibrosis in a non-Caucasian population. *Dis Markers* 2012; **32**: 241-246 [PMID: 22430190 DOI: 10.3233/DMA-2011-0880]

5 **Boyle MP**, De Boeck K. A new era in the treatment of cystic fibrosis: correction of the underlying CFTR defect. *Lancet Respir Med* 2013; **1**: 158-163 [PMID: 24429096 DOI: 10.1016/S2213-2600(12)70057-7]

6 **Li N**, Pei P, Bu DF, He B, Wang GF. A novel CFTR mutation found in a Chinese patient with cystic fibrosis. *Chin Med J (Engl)* 2006; **119**: 103-109 [PMID: 16454991 DOI: 10.3901/JME.2006.11.103]

7 **Xu J**, Yin Y, Zhang L, Zhang J, Yuan S, Zhang H. Four case reports of Chinese cystic fibrosis patients and literature review. *Pediatr Pulmonol* 2017; **52**: 1020-1028 [PMID: 28608624 DOI: 10.1002/ppul.23744]

8 **Liu K**, Liu Y, Li X, Xu KF, Tian X, Zhang X. A novel homozygous complex deletion in CFTR caused cystic fibrosis in a Chinese patient. *Mol Genet Genomics* 2017; **292**: 1083-1089 [PMID: 28620757 DOI: 10.1007/s00438-017-1334-0]

9 **Riordan JR**, Rommens JM, Kerem B, Alon N, Rozmahel R, Grzelczak Z, Zielenski J, Lok S, Plavsic N, Chou JL. Identification of the cystic fibrosis gene: cloning and characterization of complementary DNA. *Science* 1989; **245**: 1066-1073 [PMID: 2475911 DOI: 10.1126/science.2475911]

10 **Kerem B**, Rommens JM, Buchanan JA, Markiewicz D, Cox TK, Chakravarti A, Buchwald M, Tsui LC. Identification of the cystic fibrosis gene: genetic analysis. *Science* 1989; **245**: 1073-1080 [PMID: 2570460 DOI: 10.1016/0168-9525(89)90156-X]

11 **Davis PB**. Cystic fibrosis since 1938. *Am J Respir Crit Care Med* 2006; **173**: 475-482 [PMID: 16126935 DOI: 10.1164/rccm.200505-840OE]

12 **Stallings VA**, Stark LJ, Robinson KA, Feranchak AP, Quinton H; Clinical Practice Guidelines on Growth

and Nutrition Subcommittee; Ad Hoc Working Group. Evidence-based practice recommendations for nutrition-related management of children and adults with cystic fibrosis and pancreatic insufficiency: results of a systematic review. *J Am Diet Assoc* 2008; **108**: 832-839 [PMID: 18442507 DOI: 10.1016/j.jada.2008.02.020]

13 **Farrell PM**, Rosenstein BJ, White TB, Accurso FJ, Castellani C, Cutting GR, Durie PR, Legrys VA, Massie J, Parad RB, Rock MJ, Campbell PW; Cystic Fibrosis Foundation. Guidelines for diagnosis of cystic fibrosis in newborns through older adults: Cystic Fibrosis Foundation consensus report. *J Pediatr* 2008; **153**: S4-S14 [PMID: 18639722 DOI: 10.1016/j.jpeds.2008.05.005]

14 **Dörk T**, Fislage R, Neumann T, Wulf B, Tümmler B. Exon 9 of the CFTR gene: splice site haplotypes and cystic fibrosis mutations. *Hum Genet* 1994; **93**: 67-73 [PMID: 7505767 DOI: 10.1007/BF00218916]

15 **Wang MC**, Shu SG, Chang SM, Ho WL, Chi CS. Cystic fibrosis in two Chinese infants in Taiwan. *Zhonghua Min Guo Xiao Er Ke Yi Xue Hui Za Zhi* 1993; **34**: 314-321 [PMID: 8213163]

16 **Chen BH**, Zhang SZ, Yang Y. The first case of CF in Mainland China identified by DNA analysis. *Zhonghua Yi Xue Yi Chuan Xue Za Zhi* 1995; **12**: 5-9

17 **Zielenski J**, Markiewicz D, Lin SP, Huang FY, Yang-Feng TL, Tsui LC. Skipping of exon 12 as a consequence of a point mutation (1898 + 5G-->T) in the cystic fibrosis transmembrane conductance regulator gene found in a consanguineous Chinese family. *Clin Genet* 1995; **47**: 125-132 [PMID: 7543385 DOI: 10.1111/j.1399-0004.1995.tb03944.x]

18 **Crawford J**, Labrinidis A, Carey WF, Nelson PV, Harvey JS, Morris CP. A splicing mutation (1898 + 1G-->T) in the CFTR gene causing cystic fibrosis. *Hum Mutat* 1995; **5**: 101-102 [PMID: 7537147 DOI: 10.1002/humu.1380050115]

19 **Wagner JA**, Vassilakis A, Yee K, Li M, Hurlock G, Krouse ME, Moss RB, Wine JJ. Two novel mutations in a cystic fibrosis patient of Chinese origin. *Hum Genet* 1999; **104**: 511-515 [PMID: 10453741 DOI: 10.1007/s004390050996]

20 **Wu CL**, Shu SG, Zielenski J, Chiang CD, Tsui LC. Novel cystic fibrosis mutation (2215insG) in two adolescent Taiwanese siblings. *J Formos Med Assoc* 2000; **99**: 564-567 [PMID: 10925568 DOI: 10.1016/S0885-3924(00)00150-0]

21 **Alper OM**, Shu SG, Lee MH, Wang BT, Lo SY, Lin KL, Chiu YL, Wong LJ. Detection of novel CFTR mutations in Taiwanese cystic fibrosis patients. *J Formos Med Assoc* 2003; **102**: 287-291 [PMID: 12874665 DOI: 10.1016/S0885-3924(03)00065-4]

22 **Chen HJ**, Lin SP, Lee HC, Chen CP, Chiu NC, Hung HY, Chern SR, Chuang CK. Cystic fibrosis with homozygous R553X mutation in a Taiwanese child. *J Hum Genet* 2005; **50**: 674-678 [PMID: 16283068 DOI: 10.1007/s10038-005-0309-x]

23 **Wang B**, Yang L. Cystic Fibrosis Involving Multisystem: A Case Report and Literature Review. *Huaxi Yixue* 2012; **6**: 852-854

24 **Liu JR**, Peng Y, Zhao YH, Wang W, Guo Y, He JX, Zhao SY, Jiang ZF. [Clinical manifestations and gene analysis of 2 Chinese children with cystic fibrosis]. *Zhonghua Er Ke Za Zhi* 2012; **50**: 829-833 [PMID: 23302613 DOI: 10.1007/s11783-011-0280-z]

25 **Cheng Y**, Ning G, Song B, Guo YK, Li XS. A Chinese girl with cystic fibrosis: a case report identified by sweat and genetic tests. *Chin Med J (Engl)* 2012; **125**: 719 [PMID: 22490504 DOI: 10.3760/cma.j.issn.0366-6999.2012.04.031]

26 **Liu Y**, Wang L, Tian X, Xu KF, Xu W, Li X, Yue C, Zhang P, Xiao Y, Zhang X. Characterization of gene mutations and phenotypes of cystic fibrosis in Chinese patients. *Respirology* 2015; **20**: 312-318 [PMID: 25580864 DOI: 10.1111/resp.12452]

27 **Shen Y**, Liu J, Zhong L, Mogayzel PJ, Zeitlin PL, Sosnay PR, Zhao S. Clinical Phenotypes and Genotypic Spectrum of Cystic Fibrosis in Chinese Children. *J Pediatr* 2016; **171**: 269-76.e1 [PMID: 26826884 DOI: 10.1016/j.jpeds.2015.12.025]

28 **Chu JL**, Wang Y, Qian J. Cystic fibrosis with severe pneumonia in children. *Chin Pediatr Emerg Med* 2016; **23**: 501-504 [DOI: 10.3760/cma.j.issn.1673-4912.2016.07.018]

29 **Xu BP**, Wang H, Zhao YH, Liu J, Yao Y, Feng XL, Shen KL. [Molecular diagnosis of two Chinese cystic fibrosis children and literature review]. *Zhonghua Er Ke Za Zhi* 2016; **54**: 344-348 [PMID: 27143075 DOI: 10.3760/cma.j.issn.0578-1310.2016.05.007]

30 **Li L**, Wang NL, Gong JY, Wang JS. [Infantile cholestasis caused by CFTR mutation: case report and literature review]. *Zhonghua Er Ke Za Zhi* 2016; **54**: 851-855 [PMID: 27806795 DOI: 10.3760/cma.j.issn.0578-1310.2016.11.013]

31 **Tian X**, Liu Y, Yang J, Wang H, Liu T, Xu W, Li X, Zhu Y, Xu KF, Zhang X. p.G970D is the most frequent CFTR mutation in Chinese patients with cystic fibrosis. *Hum Genome Var* 2016; **3**: 15063 [PMID: 27081564 DOI: 10.1038/hgv.2015.63]

32 **Leung GK**, Ying D, Mak CC, Chen XY, Xu W, Yeung KS, Wong WL, Chu YW, Mok GT, Chau CS, McLuskey J, Ong WP, Leong HY, Chan KY, Yang W, Chen JH, Li AM, Sham PC, Lau YL, Chung BH, Lee SL. CFTR founder mutation causes protein trafficking defects in Chinese patients with cystic fibrosis. *Mol Genet Genomic Med* 2016; **5**: 40-49 [PMID: 28116329 DOI: 10.1002/mgg3.258]

33 **Xie Y**, Huang X, Liang Y, Xu L, Pei Y, Cheng Y, Zhang L, Tang W. A new compound heterozygous CFTR mutation in a Chinese family with cystic fibrosis. *Clin Respir J* 2017; **11**: 696-702 [PMID: 26471113 DOI: 10.1111/crj.12401]

34 **Zheng B**, Cao L. Differences in gene mutations between Chinese and Caucasian cystic fibrosis patients. *Pediatr Pulmonol* 2017; **52**: E11-E14 [PMID: 27717243 DOI: 10.1002/ppul.23539]

35 **Yao Y**, Feng XL, Xu BP, Shen KL. Pseudo-Bartter Syndrome in a Chinese Infant with Cystic Fibrosis Caused by c.532G>A Mutation in CFTR. *Chin Med J (Engl)* 2017; **130**: 2771-2772 [PMID: 29133775 DOI: 10.4103/0366-6999.218015]

36 **Sun Y**, Zhong YM, Zhu M, Wang SY, Wang J, Zhang H, Zhang L, Shao H. Clinical and radiological manifestations of 5 pediatric cases with cystic fibrosis. *J Clin Pediatr* 2017; **35**: 837-840 [DOI: 10.3969/j.issn.1000-3606.2017.11.009]

37 **Guo ZY**, Shi YY, Qian LL, Wang LB. A case report of infantile cystic fibrosis with pseudo-Bartter syndrome. *Zhongguo Xunzheng Erke Zazhi* 2017; **12**: 471-473 [DOI: 10.3969/j.issn.1673-5501.2017.06.014]

38 **Li J**, Zhang Y, Wang W, Wan WL, Qiu ZQ. One case of cystic fibrosis in children with pseudoBartter syndrome and literature review. *Shandong Yiyao* 2017; **57**: 48-50 [DOI: 10.3969/j.issn.1002-266X.2017.04.015]

39 **Richards S**, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL; ACMG Laboratory Quality Assurance Committee. Standards and guidelines for

the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med* 2015; **17**: 405-424 [PMID: 25741868 DOI: 10.1038/gim.2015.30]

40 **Kristidis P**, Bozon D, Corey M, Markiewicz D, Rommens J, Tsui LC, Durie P. Genetic determination of exocrine pancreatic function in cystic fibrosis. *Am J Hum Genet* 1992; **50**: 1178-1184 [PMID: 1376016]

41 **Ferrari M**, Cremonesi L. Genotype-phenotype correlation in cystic fibrosis patients. *Ann Biol Clin (Paris)* 1996; **54**: 235-241 [PMID: 8949420 DOI: 10.1016/S0065-2423(08)60428-X]


Published By Baishideng Publishing Group Inc
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: bpgoffice@wjgnet.com
Help Desk:https://www.f6publishing.com/helpdesk
https://www.wjgnet.com