Clinical Characteristics and Genetic Analysis of Birt-Hogg-Dubé Syndrome With Congenital Contractural Arachnodactyly in a Family

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Research

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Abstract

Background Birt-Hogg-Dubé Syndrome (BHD syndrome) and congenital contractural arachnodactyly (CCA) or Beals Hecht Syndrome (BHS) are clinically rare autosomal dominant genetic diseases. In this study, we find an extremely rare family with BHD Syndrome with CCA.

Objective To investigate the clinical and genetic variation characteristics of a family with BHD Syndrome with CCA.

Methods The patient was examined for chest Computed Tomography (CT), abdominal and heart color ultrasound, rheumatism immune-related indexes, and hand Direct Digital Radiography (DR), and Whole Exome Sequencing (WES) was performed on family members.

Results The proband, male, developed symptoms of chest tightness and shortness of breath, accompanied by irritant cough 2 years ago, and then repeated spontaneous pneumothorax four times. Chest CT showed: spontaneous pneumothorax on the right side, emphysema in both lungs, and bullae in both lungs. No manifestations of kidney tumors and skin lesions. His son had a history of pulmonary bullobes and occurred spontaneous pneumothorax twice. He, his mother, and his son were all born with a hand deformity. Sequencing results showed that both the proband and his son were folliculin (FLCN) gene c.1015C>T（p.Gln339Ter） heterozygous variation, Fibrillin 2 gene (FBN2) gene c.3485G>A （p.Cys1162Tyr） heterozygous variation, associated with BHD syndrome and CCA.

Conclusion For patients with chest tightness, shortness of breath, recurrent spontaneous pneumothorax, and congenital hand deformity without inducement, genetic testing should be carried out as soon as possible to make a clear diagnosis, which can guide treatment and genetic counseling.

1 Introduction

Birt-Hogg-Dubé Syndrome (BHD syndrome) is a rare autosomal dominant genetic disease. Folliculin (FLCN) is its causative gene (located on chromosome 17p11. 2). Its common features include multiple skin fibro cystadenoma, bullae (spontaneous pneumothorax) and kidney Tumor, etc. [1]. This condition exhibits extensive phenotypic variation. Even in the same family, affected individuals may have any combination of skin, lung, or kidney manifestations of varying severity [2]. Spontaneous pneumothorax is usually the first manifestation of BHD syndrome [3], and maybe the only one [4], and skin findings usually appear in the fourth decade of FLCN mutation carriers, and gradually increase with age becomes more obvious [5]. Compared with lung cyst/pneumothorax, the renal manifestations of BHD also occur later [6]. Congenital contractural arachnodactyly (CCA) or Beals Hecht Syndrome (BHS) is a rare autosomal dominant connective tissue disease, which is associated with disease-causing Fibrillin 2 (FBN2) gene. The main clinical features of CCA are spider fingers (toes), flexion fingers, major joint contractures, scoliosis, pectus excavatum, and helix shrinkage [7]. In this paper, we find an extremely rare family with BHD Syndrome with CCA.

2 Materials And Methods

2.1 A rare family with BHD Syndrome with CCA

A 55-year-old male patient had chest tightness, shortness of breath, and irritating cough without obvious triggers in the past 2 years. He was repeatedly admitted to the hospital for spontaneous pneumothorax (4 times in total). Physical examination: weak breathing sounds in the right lung and thick breathing sounds in the left lung. No dry and wet rales were heard, right lung percussion drum sounds, left lung percussion voiceless, bilateral finger deformities, bilateral asymmetrical, incomplete extension. He had a history of "hypertension" for more than one month, and his blood pressure was as high as 180/120mmHg. The blood pressure was lowered by oral administration of "amlodipine besylate, valsartan, and bisoprolol fumarate", and the blood pressure could be controlled. No bad habits of tobacco and alcohol.

Family history: The patient's parents were married to non-consanguineous relatives, and both were deceased. The father has no bullae and hand malformations; the mother has congenital hand malformations and no history of bullae; the unmarried son has congenital hand malformations, a history of bullae, and spontaneous pneumothorax 2 times, closed-chest in the local hospital He improved after drainage and was physically fit. Denies history of other family genetic diseases. This family is considered as a family hereditary disease, possibly BHD syndrome. The blood samples of the patient and his son were sent to the Henan Rare Disease Research Center for genetic sequencing.

Computed tomography (CT) of the chest, color Doppler ultrasound of the abdomen and heart, rheumatism-related indicators and digital radiography (DR) of the hands were performed on the patients. The study was approved by the hospital ethics committee (2021-03-B024), and the family members signed an informed consent form.

2.2 Family Whole Exome Sequencing

With full notification and informed consent, 3ml of peripheral blood from the patient and his son was drawn and sent to a third-party company for whole-exome gene sequencing (WES). First, the DNA is interrupted, and the library is prepared, then the Agilent V6 probe is used to hybridize and capture the DNA in the whole exome and part of the Untranslated Region (UTR) region and enrich it, and finally use the high-throughput sequencing platform for mutation detection. Analyze the pathogenic genes of single-gene genetic diseases that have been identified in Online Mendelian Inheritance in Man (OMIM) (2019.06), refer to the American College of Medical Genetics and Genomics (ACMG) genetic variation interpretation standards and guidelines, and indicate the ACMG variation grade. Separate clinical analysis of different samples, including clinical symptom matching, disease recommendations, etc.

3 Results

Patient's Chest CT showed: spontaneous pneumothorax on the right side, emphysema in both lungs, and bullae in both lungs (see Fig. 1a). Ask the thoracic surgery consultation to provide closed thoracic

drainage to drain air to promote lung recruitment. DR in both hands suggests changes in both hands and wrists, consider degenerative changes or chronic inflammatory lesions (see Fig. 1b). Both the patient and his son have a history of hand deformities and pulmonary bullae formation (see Fig. 1c for the appearance of the patient's hands and Fig. 1d for the appearance of the son's hands). Abdominal and cardiac color Doppler ultrasound, rheumatism-related indicators (including Antinuclear antibody profile, Anti-Neutrophil Cytoplasmic Antibodies (ANCA)-related antibodies, Rheumatoid factor, High-sensitivity C-reactive protein) were not abnormal. No manifestations of kidney tumors and skin lesions. After treatment, part of the patient's lungs were re-expanded, the pneumothorax improved, and air bubbles were still visible in the closed thoracic drainage bottle after the chest tube was intermittently clamped. He was transferred to thoracic surgery for thoracoscopic right lung volume reduction + pleural adhesion cauterization + pleural fixation, and the postoperative recovery was good. No spontaneous pneumothorax recurred during regular telephone follow-up.

The results of WES showed that the proband and the son were heterozygous variants in FLCN gene c.1015C > T (p. Gln339Ter) and FBN2 gene c.3485G > A (p. Cys1162Tyr) (See Fig. 2). The sample found a heterozygous nonsense mutation in the exon region of the FLCN gene: c.1015C > T, resulting in an amino acid change: p. Gln339Ter. The Human Gene Mutation Database (HGMD) Professional database report situation: the mutation site is reported as a pathogenic variant. The mutation is not included in the ClinVar database. According to ACMG guidelines, the variant was judged to be pathogenic (PVS1 + PM2 + PP5). The sample found a heterozygous missense mutation in the exon region of the FBN2 gene: c.3485G > A, resulting in an amino acid change: p. Cys1162Tyr. Neither the HGMD Professional database nor the ClinVar database included this mutation. According to ACMG guidelines, the variant was judged to be potentially pathogenic (PM1 + PM2 + PM5 + PP3). The FLCN gene-associated disease is BHD syndrome, which is an autosomal dominant genetic disease. The proband and sons are consistent with the phenotype of this disease. The FBN2 gene-associated disease is CCA, which is an autosomal dominant genetic disease. The proband, mother, and son are phenotypically consistent with this disease. The final diagnosis was BHD syndrome with CCA.

4 Discussion

In this study, we find an extremely rare family with BHD Syndrome with CCA for the first time. The family of BHD syndrome combined with CCA has not been reported at home and abroad till now. Some data show that compared with white people, Asian patients with BHD syndrome have a lower incidence of skin and kidney manifestations, but a higher rate of recurrence of pneumothorax [8]. The risk of lung collapse (pneumothorax) in BHD patients is 50 times higher than that of the general population [9]. Pulmonary cysts (multiple and bilateral) occur in 80%-100% of patients with BHD syndrome, and 76% of them have a pneumothorax. BHD syndrome is one of the most common causes of familial spontaneous pneumothorax [10]. Family history of pneumothorax is an important clue, suggesting the diagnosis of BHD [11]. The pulmonary manifestations of BHD disease need to be distinguished from other diseases related to diffuse cystic lung diseases (DCLD), such as Lymphangioleiomyomatosis, Langerhans cell histiocytosis, and Lymphocytic interstitial pneumonia [12]. Unlike other cystic lung diseases, BHD disease

does not cause progressive loss of lung function and chronic respiratory insufficiency [10]. According to reports in the literature, the prevalence of renal involvement in BHD patients ranges from 6.5–34% [13]. Furuya et al. [14] found that 25.8% of BHD patients have renal damage, especially renal cell carcinoma, the most common histology in chromophobe renal cell carcinoma (43.6%), and all patients with renal involvement also have Lung cyst. Kidney cancer is the most serious manifestation of BHD.

The skin manifestations of BHD include fibrofollicular tumors, hair discomfort, and peri-follicular fibroids. These three types are clinically indistinguishable between 2–4 mm flesh-colored and light gray-white, smooth dome-shaped papules. These papules are commonly found on the face, neck, and trunk [7]. The most common skin manifestation of BHD is fibrofollicular tumors, the number of which can range from 2 to more than 100. Fibrofollicular tumors are rare and unique to BHD syndrome and can be diagnosed by needle biopsy [15]. This patient's family currently has no skin and kidney manifestations, but it needs regular review and follow-up.

The diagnosis of BHD disease needs to be combined with family history, clinical and/or skin histopathological criteria. Management mainly includes early pleurodesis in the case of pneumothorax, regular kidney imaging for tumor detection, and diagnostic tests to find BHD among the patient’s relatives [11]. For patients diagnosed with BHD syndrome, follow-up should be strengthened, with special attention to the condition of the kidneys. Currently, pneumothorax is usually treated symptomatically, and methods such as electrocoagulation, laser, and curettage are generally used for skin lesions. Both the proband and the son in this family have a recurrent spontaneous pneumothorax. First of all, we must be alert to the possibility of familial pneumothorax. After a clear diagnosis, kidney tumors and skin lesions should be ruled out. If corresponding symptoms occur, seek medical attention in time. It is recommended to screen the genetic locus for members of the subject's blood-related family, establish a follow-up plan for carriers as soon as possible, and conduct genetic counseling when there is a need for fertility. At present, there is no special treatment for this disease and regular follow-up observation.

The main clinical features of CCA are spider finger (toe), flexion finger, major joint contracture, scoliosis, pectus excavatum, and helix shrinkage [16]. Marfan syndrome (MFS) is a rare autosomal dominant multi-system disease, manifested by bone, eye, skin, and cardiovascular symptoms [17]. CCA and MFS have many common clinical features, including the so-called Marfan-like appearance, which is composed of tall, slender, and weak appearance and skeletal features, including spider fingers, bipedal deformities, pectus excavatum, and kyphosis [18]. However, most patients with CCA have helix shrinkage, flexion contracture, and muscle hypoplasia [19]. Two similar syndromes, MFS and CCA, are caused by mutations in genes FBN1 and FBN2, respectively [20]. It is difficult to distinguish between MFS and CCA based on clinical symptoms alone [21], and the best way to distinguish between the two diseases is genetic testing.

The clinical manifestations of CCA patients are different, involving the heart, bones, lens, and other parts, requiring individualized treatment for the patients. Flexion contractures of the large joints of the extremities often do not require targeted treatment, while hand joint contractures can loosen joints and skin grafts to improve appearance and function. Kyphosis and scoliosis deformity can be corrected by

surgery if it affects life. Severe heart deformities often require early surgical treatment, and regular follow-up monitoring is required for non-severe ones [22]. The proband, mother, and son in this family all have congenital hand deformities with mild symptoms and do not affect normal functions. Since the mother of the proband also has hand deformities, and because the mother is deceased, it is recommended to send samples from the maternal relatives of the proband for screening at this site and establish a follow-up plan for carriers as soon as possible. Genetic counseling when there is a need for fertility.

5 Conclusions

WES is currently the gold standard for diagnosing these two familial genetic diseases. For patients with chest tightness, shortness of breath, recurrent spontaneous pneumothorax, and congenital hand deformity without inducement, genetic sequencing should be carried out as soon as possible to make a clear diagnosis, which can guide treatment and genetic counseling. Lifelong follow-up after the diagnosis is made to control the patient's progress in time and reduce complications.

List Of Abbreviations

Birt-Hogg-Dubé Syndrome, BHD syndrome

Congenital contractural arachnodactyly, CCA

Beals Hecht Syndrome, BHS

Computed Tomography, CT

Digital Radiography, DR

Whole Exome Sequencing, WES

Folliculin, FLCN

Fibrillin 2 gene, FBN2

Online Mendelian Inheritance in Man, OMIM

American College of Medical Genetics and Genomics, ACMG

Untranslated Region, UTR

Anti-Neutrophil Cytoplasmic Antibodies, ANCA

The Human Gene Mutation Database, HGMD

Marfan syndrome, MFS

Declarations

Ethical Approval and Consent to participate

This study was approved by the Ethics Committee of the First Affiliated Hospital of Henan University of Science and Technology (2021-03-B024), and the family members signed an informed consent form.

Consent for publication

Subject agrees

Availability of data and materials

None

Competing interests

None

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Authors' contributions

Yimin Mao and Hongwei Jiang designed the study, performed the research. Jiayong Qiu and Yao Lou analysed data and wrote the paper. Huifang Peng collected the data. All authors discussed the results and revised the manuscript.

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None

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Figures

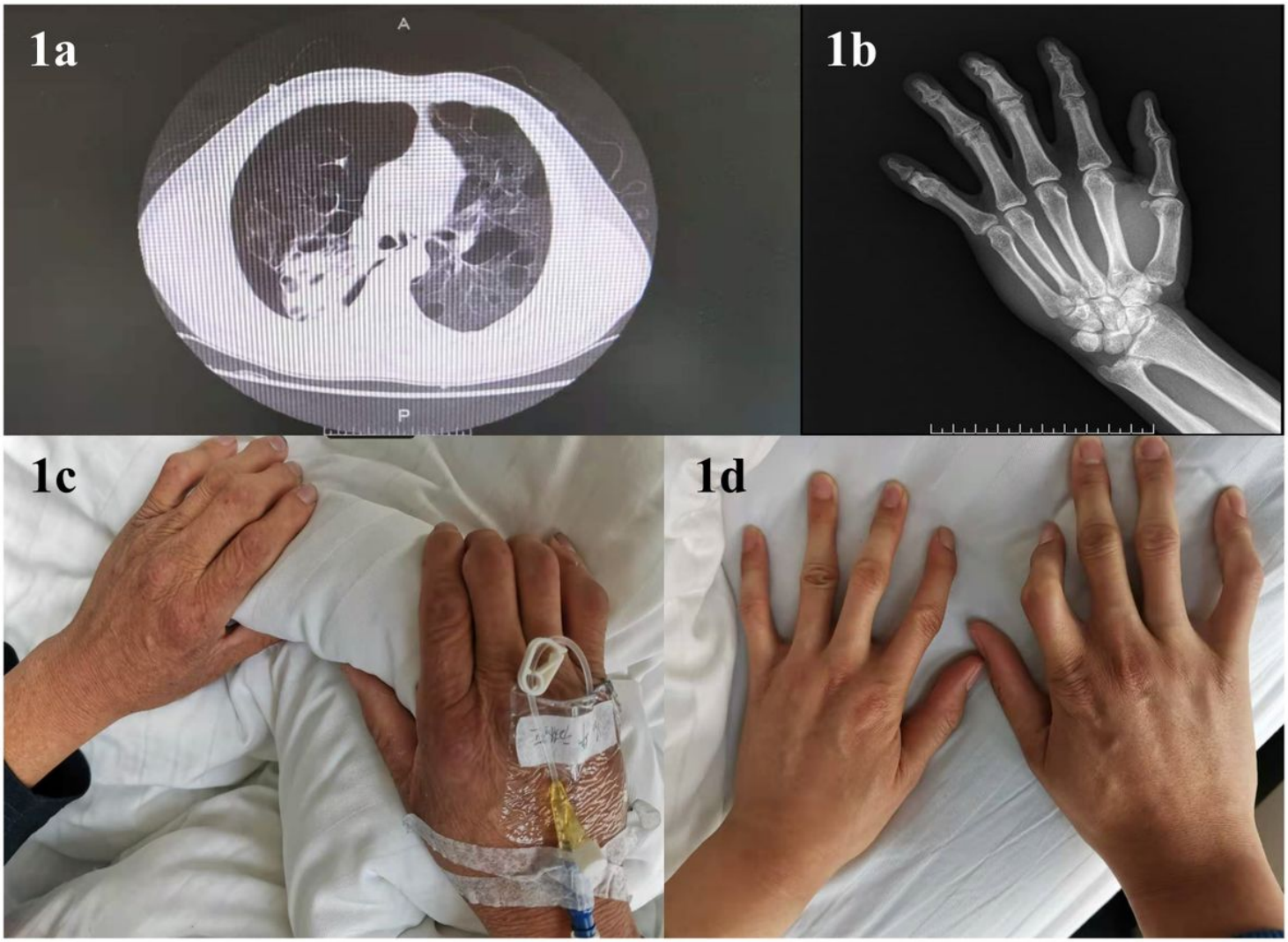

Figure 1

1a: CT of the patient’s chest showed: spontaneous pneumothorax on the right side, emphysema in both lungs, and bullae in both lungs; 1b: DR in both patient’s hands suggests changes in both hands and wrists, consider degenerative changes or chronic inflammatory lesions; 1c: Appearance picture of the patient's hands; 1d: Appearance picture of the patient's son.

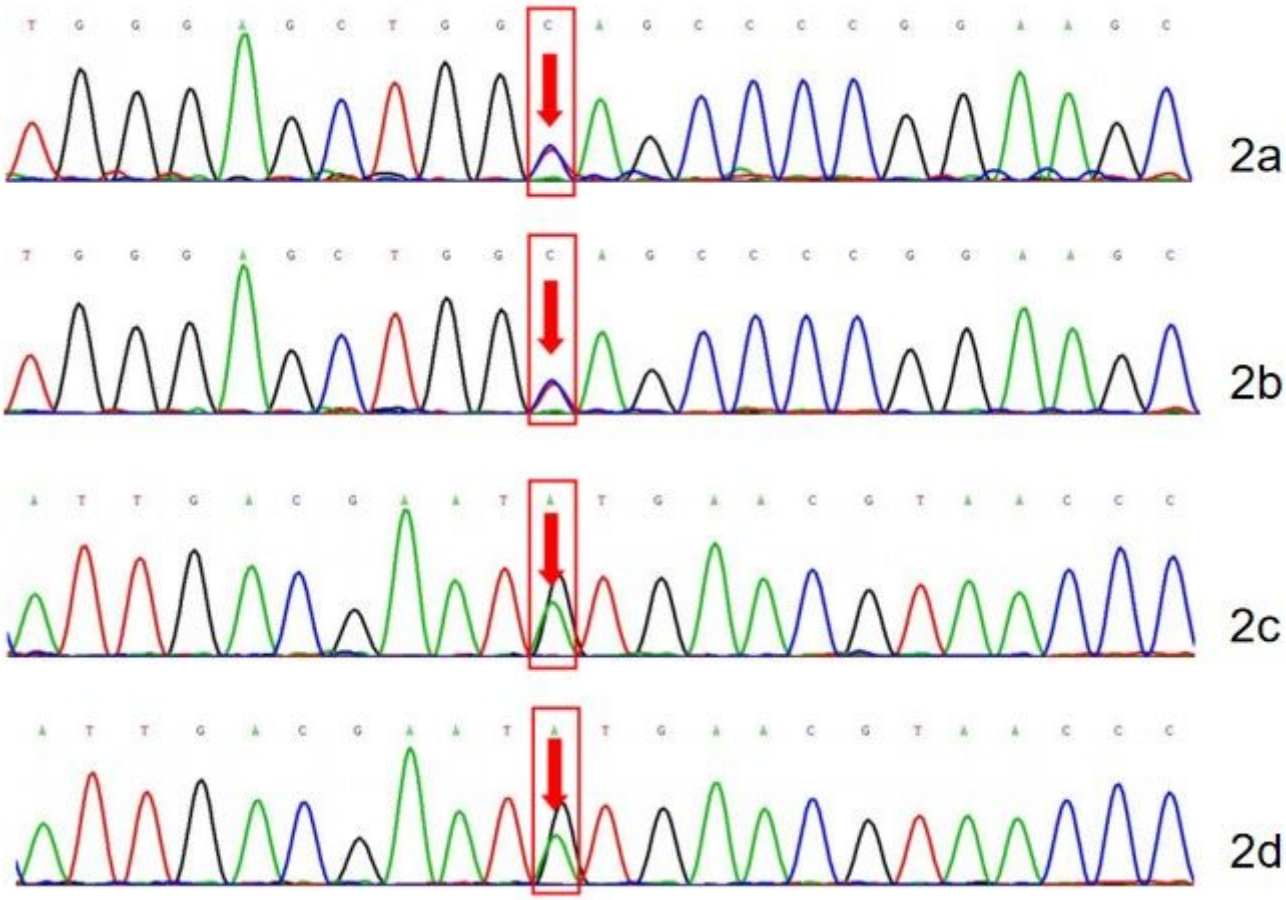

Figure 2

FLCN gene c.1015C>T (p. Gln339Ter) mutation sequencing results 2a: proband, heterozygous mutation; 2b: son, heterozygous mutation FBN2 gene c.3485G>A (p. Cys1162Tyr) mutation sequencing results 2c: proband, heterozygous mutation; 2d: son, heterozygous mutation

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