Clinical characteristics and genetic analysis of familial spontaneous pneumothorax in China

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Research Article

Keywords: words Familial spontaneous pneumothorax, Birt-Hogg-Dubé, syndrome, Clinical characteristics, Folliculin, Next-generation sequencing technology

Posted Date: May 12th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-504907/v1

Abstract

Familial spontaneous pneumothorax (FSP) is a hereditary disease, and Birt-Hogg-Dubé (BHD) syndrome is its main cause. FSP is an autosomal dominant genetic disease related to folliculin (FLCN). The goal of this study was to investigate the clinical characteristics and possible causes of FSP in China compared with those of primary spontaneous pneumothorax (PSP). We reviewed the detailed clinical data of 8 FSP patients in a family and analyzed the clinical characteristics of FSP combined with literatures. The FLCN gene of these 8 FSP patients was sequenced by the next-generation sequencing technology (NGS). The results showed that the clinical features of FSP were significantly different from those of PSP: the incidence of pneumothorax in women is significantly higher, and the age of pneumothorax is later, most of them are two generations, which may be related to heredity. And the effect of surgical treatment is the best. Novel nonsense mutation was found in the 8 patients, and the 8 patients had the same mutation, thus demonstrating the diversity of mutation spots along the gene. Therefore, the FLCN gene screening and early surgical intervention is recommended for FSP patients.

Introduction

Primary spontaneous pneumothorax (PSP, OMIM 173600) is defined as the spontaneous occurrence of pneumothorax in patients without clinically obvious potential lung disease. There are tens of thousands of patients with PSP every year [1–3]. Spontaneous pneumothorax is usually not considered a hereditary disease, but about 11.5%–16.2% of patients with spontaneous pneumothorax had a positive family history [4–5]. At present, the pathogenesis of PSP is not clear. Most familial spontaneous pneumothorax (FSP) cases are caused by the germ line mutation of folliculin (FLCN), which is the pathogenic gene of Birt-Hogg-Dubé syndrome (BHD, OMIM 135150). BHD is an autosomal dominant genetic disease characterized by follicular hamartomas, renal tumors, pulmonary cysts and spontaneous pneumothorax [6]. This research based on the clinical data of 8 patients with FSP, we reviewed the recent literature in China and discussed the clinical features and possible causes of FSP.

Materials And Methods

One patient with spontaneous pneumothorax was treated in our department in April 2018. By inquiring about the medical history, we found that 8 patients in their family had suffered from spontaneous pneumothorax and were hospitalized nearby. General information, diagnosis and treatment of these 8 patients were obtained through the proband and their families.

Because FSP is rare in clinic, in order to further analyze its clinical characteristics, we searched all the literatures about FSP before 2018 in China National Knowledge Infrastructure (CNKI) and Wanfang Data. The keywords of "familial spontaneous pneumothorax" were used to search and summarize literatures (excluding cases with incomplete clinical data), We obtained 23 related literatures, 75 families, plus this case, a total of 76 families, 265 patients with FSP. The clinical characteristics of FSP patients were analyzed combined with literature.

We used the target region probe capture technology and next-generation sequencing technology (NGS) based on illumina sequencing platform to detect FLCN gene in 8 patients of this family (details are available upon request). The results were compared in a large population database, and the previously unreported mutations were defined as new mutations.

The project was approved by the Research Ethics Committee of the Fourth Hospital of Hebei Medical University, Shijiazhuang, China (2015mECD35). All patients gave written informed consent. All methods were carried out in accordance with relevant guidelines and regulations. The responses in all of the experiments were quantified based upon the percentage of the baseline value of muscle strip tone relative to the nadir of the response.

Results

The clinical information of 8 patients with pneumothorax are listed in Table 1. We also made a simple family pedigree for this family (the spouse is omitted) as shown in Fig. 1.

Table 1
Clinical information of family members with pneumothorax

Family Index No.	Sex	Height (cm)	Weight (kg)	Somking history	Chest CT	Treatment opinion	
						Left lung	Right lung
-1	M	172	65	Y	NA	TH, TH	
-1	M	174	73	Y	NA	TD, TB	TD, TB
-2	M	178	78	N	NA		TH
-6	F	160	66	Y	MPC	TD, VB	
-2	M	173	77	N	MPC		TD, TB
-14	M	177	82	Y	MPC	TB	TB
-16	F	165	58	N	MPC	TH, VB + MP	
-25	M	177	63	N	MPC	VB + MP	

CP: chemical pleurodesis; CT: computed tomography; MP: mechanical pleurodesis; MPC: multiple pulmonary cysts; NA: not available; TB: thoracotomy bullectomy; TD: tube drainage; VB: VATS bullectomy; TH: thoracentesis; M: male; F: female; Y: yes; N: no.

Among 265 FSP patients from 76 families,(1) The ratio of male to female is 1.55:1. (2) 51.70% patients were ≤ 40 years old. 48.30% were 40 years old. (3) Family status: The incidence of the same generation was 17.11% (13/76), two generations were 67.10% (51/76), and three generations were 14.47% (11/76). In this case, was four generations (1.31%) (1/76). The phenomenon of skipped a generation was not found. (4) Treatment methods and recurrence rate: Conservative treatment (bed rest, oxygen inhalation) was given 37 times, with a recurrence rate of 21.62% (8/37); Thoracentesis was performed in 62 cases,

with a recurrence rate of 48.39% (30/62); There were 90 cases of closed thoracic drainage, and the recurrence rate was 38.89% (35/90). Surgical treatment was performed in 100 cases, and the recurrence rate was 4% (4/100). (Tables 2 and 3)

Table 2
Characters of patients with pneumothorax

Index	number of cases	constituent ratio (%)
Sex		
male	161	60.75
female	104	39.25
Year of first episode		
≤ 40	137	51.70
40	128	48.30
Generation	(Number of families)	
the same generation	13	17.11
two generations	51	67.10
three generations	11	14.47
four generations	1	1.31

Table 3
Treatment methods and recurrence rates with pneumothorax

Treatment methods	case times	recurrence case times	recurrence rates(%)
OB	37	8	21.62
TH	62	30	48.39
TD	90	35	38.89
SO	100	4	4
OB: observation; TD: tube drainage; TH: thoracentesis; SO: surgical operation.			

Sequence analysis of the FLCN gene revealed a novel nonsense mutation (c.558G A) in exon 6, and 8 patients in the family harbored the same mutation, thus demonstrating the diversity of mutation spots along the gene. (Fig. 2)

Discussion

PSP sporadic cases are common among young people, most of whom are 20–30 years old, and the incidence rate is 9/ 100,000 [7]. There are more men than women, with a ratio of 4–6:1. Among smokers, the incidence rate increased. FSP was first reported by Faber in 1921 [8]. The right side is slightly more than the left side, and 10% of patients are bilateral. However, through literature review, we found that the ratio of male to female FSP was 1.55:1. This result is consistent with the male to female ratio of 61 cases of FSP in 22 families reported by Wilson et al. In 1979[9], which is significantly different from that of sporadic cases of PSP. Although men are still the majority, the incidence rate of women is significantly higher. Among them, the incidence rate over 40 years old is 48.3%, while the PSP sporadic cases are mostly high and thin men between 10 and 30 years old [1].

PSP is caused by the rupture of pulmonary bullae. FSP is a special kind of PSP, and its causes are the same. Liu and other studies found that FSP patients had more bilateral, multiple, and pulmonary bullae in the lung parenchyma. Because of the deep bullae, the time of pneumothorax caused by rupture is often later than that of the patients with pneumothorax in other superficial locations. This is the reason for the older age of the first onset of pneumothorax in FSP patients [10]. Combining with the previous literature, we found that there are still quite a few relatives of patients in FSP family who have pulmonary bullae but have not yet developed the disease, and these people need our close monitoring.

The results of this study show that 13 families (17.11%) in the same generation, 51 families (67.10%) in two generation and 11 families (14.47%) in three generation. However, in this report, 8 people in four generations suffered from pneumothorax, with a large number of patients, both male and female, suggesting that it may be related to genetic factors. Combined with previous literature, it is suggested that several monogenic diseases are associated with FSP, including Marfan syndrome, homocystinuria, Ehlers Danlos syndrome, α 1-antitrypsin deficiency and BHD syndrome [11]. We found that a large proportion of reported FSP cases are closely related to FLCN gene mutations in BHD syndrome [12–15]. In this study, novel nonsense mutation of FLCN gene was found in the proband and other patients in the family. Further, we found that Amino acid 186 of FLCN gene was mutated from tryptophan to terminator. Premature terminator may lead to nonsense mediated mRNA degradation (NMD), resulting in loss of protein expression. The mutation has not been found in large population databases (including gnomad, exac, 1000genome, etc.), suggesting that it is a rare mutation. Whether there are FLCN mutations in other members of the family needs further genetic testing to determine.

The expression of FLCN mRNA plays a role in the transformation of surfactant in phagocytosis and is expressed in alveolar macrophages, it is speculated that FLCN protein may have endocytosis or phagocytosis [16]. It is speculated that when FLCN gene mutation occurs, a large number of inflammatory factors are secreted by macrophages and fibroblasts to induce inflammation, which eventually leads to the destruction of elastic fibers in the lung, which may also be the cause of pneumothorax. Therefore, it is speculated that when FLCN gene is mutated, a large number of inflammatory factors are secreted by macrophages and fibroblasts, which induce inflammation, and finally cause the destruction of elastic fibers in the lung and lead to pneumothorax, which may also be

the cause of pneumothorax. Whether it belongs to BHD syndrome requires further genetic testing to make a definite diagnosis.

Combined with literature review, we found that the surgical treatment of FSP is the best, with a recurrence rate of only 4%, followed by medical conservative treatment with a recurrence rate of 21.62%, while the recurrence rates of thoracic puncture and closed thoracic drainage are higher, which are 48.39% and 38.89%, respectively. However, the recurrence rate of PSP sporadic patients undergoing non-surgical treatment, including follow-up observation, puncture aspiration and closed thoracic drainage, is about 30% [17]. The difference of recurrence rate may be due to the fact that FSP patients often complicated with multiple pulmonary bullae, and the number and size of pulmonary bullae in these patients will develop with the extension of time, and eventually rupture and cause pneumothorax; Therefore, if the imaging data of FSP patients clearly have pulmonary bullae, surgical treatment is recommended; sometimes when patients have a large number of diffuse pulmonary vesicles, the operation is difficult to achieve the intended result and there is still a chance of pneumothorax recurrence. Mechanical or chemical pleurodesis is used in the operation to promote pleural cavity adhesion. According to Japanese reports, bioabsorbable pleura coverings have successfully protected patients from intractable pneumothorax [18–19]. This method enables patients to safely receive video-assisted thoracoscopic (VATS) treatment after several years of other lung diseases; However, there is still a lack of effective measures and follow-up data collection to support the treatment of pneumothorax with pleural covering technology, which needs to be verified by a large number of cases.

Although the study of FLCN gene mutation in FSP is more concerned than before, the development of pulmonary cysts in BHD syndrome is still unknown, we need to further study the relationship between these diseases. If BHD syndrome is diagnosed, the risk of renal tumor will be increased by 7 times, and the risk of pneumothorax will be increased by 50 times [20–21]. FSP patients may be more likely to develop kidney tumors. It is recommended that these patients should be regularly screened for renal ultrasound or nuclear magnetic resonance imaging.

This study has some limitations. First of all, we only tested the gene of the patients in the family. We need to further verify whether other members of the family have the same gene mutation. Secondly, we only made a retrospective analysis of this study, and the conclusion may be biased. Therefore, we need to conduct a large number of prospective studies to verify our conclusions.

Conclusion

In conclusion, this study shows that BHD syndrome is one of the most common causes of FSP. Patients with FSP should be recommended for mutation screening for the FLCN gene to facilitate early diagnosis and surgical intervention. Further studies are warranted to better understand the nature of this disease.

Declarations

Data availability

Data are available upon reasonable request.

Acknowledgments

Not applicable.

Funding

This work was supported by Key topics of medical science research of Hebei Provincial Health Commission (No.20201053)

Authors' contributions

FY, YL and WW performed the experiments and drafted the manuscript. LC, ML and FY was involved in research design, literature review and data examination. YL participated in the statistical analysis. All authors read and approved final manuscript.

Competing interests

The authors declare that they have no competing interests.

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Figures

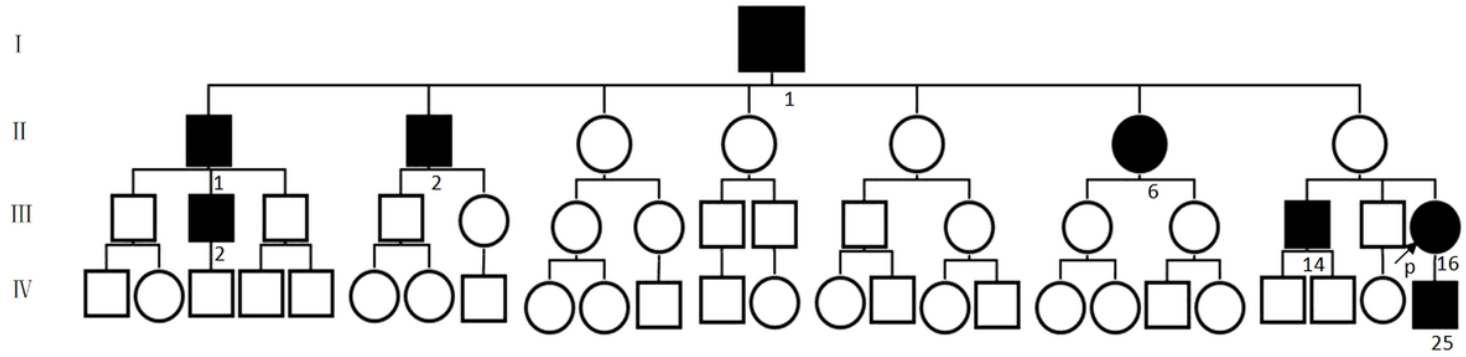

Figure 1

Simplified family pedigree (spouses are omitted due to space limitation). The index number of generations is listed on the left using Roman numerals. The index number of certain individuals in each generation is listed on the lower using Arabic numerals. The proband is indicated by an arrow with a “P” on the lower left. Patients with pneumothorax are highlighted in black.

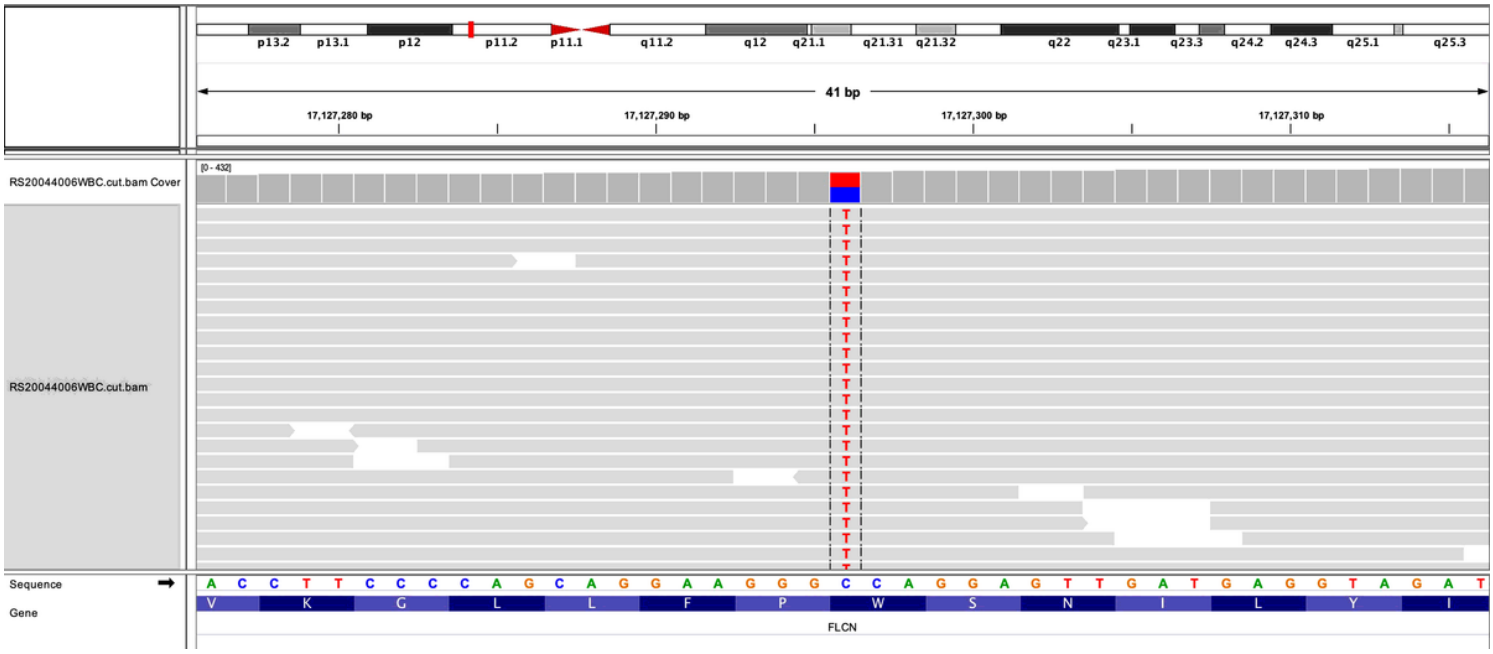

Figure 2

Sequence analysis revealed a Nonsense mutation c.558G>A in exon 6 of the FLCN gene.