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A novel mutation causes Hermansky-Pudlak syndrome type 4 with pulmonary fibrosis in 2 siblings from China

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Abstract

Hermansky-Pudlak syndrome (HPS) is a rare autosomal recessive multisystem disorder characterized by oculocutaneous albinism (OCA) and bleeding diathesis, although it displays both genetic and phenotypic heterogeneity. Several genetic subtypes of HPS have been identified in human; however, the characterizations of HPS type 4 (HPS-4) genotype and phenotype remain unclear. This study was aimed to identify gene mutation responsible for HPS-4 with pulmonary fibrosis (PF).

Two Chinese siblings in their 50s afflicted with OCA and progressive dyspnea were recruited and underwent clinical and genetic examinations. In both patients, chest high-resolution computerized tomography showed severe interstitial PF in bilateral lung fields, and the pulmonary function test indicated restrictive lung disease. A novel homozygous frameshift mutation (NM_022081: c.630dupC; p.A211fs) in the *HPS4* gene was identified by whole-exome sequencing analysis followed by Sanger DNA sequencing, and it segregated with the phenotypes. The c.630dupC mutation was not found in unaffected healthy controls. The patients were considered as HPS-4 with interstitial PF and eventually died of respiratory failure.

This is the first report on the genotype and clinical phenotype of HPS-4 in China. Our results demonstrate the association between a novel frameshift mutation in *HPS4* and severe PF with poor prognosis in HPS is presented.

Abbreviation: HPS = Hermansky-Pudlak syndrome, HRCT = high-resolution computerized tomography, LRO = lysosome-related organelle, OCA = oculocutaneous albinism, PF = pulmonary fibrosis.

Keywords: Hermansky-Pudlak syndrome, *HPS4*, oculocutaneous albinism, pulmonary fibrosis, whole exome sequencing

1. Introduction

Hermansky-Pudlak syndrome (HPS) is a rare autosomal recessive disease with characteristic symptoms, including oculocutaneous albinism (OCA) and bleeding tendency. HPS is genetically heterogeneous. Thus far, 10 genetically distinct subtypes (HPS-1 to HPS-10) have been reported to share the common symptoms; furthermore, each subtype has >1 genetic variant. Furthermore, HPS phenotype is heterogeneous. In addition to OCA and bleeding diathesis, HPS subtypes are usually associated with ≥1 clinical features, including granulomatous colitis, neutropenia, recurrent infection, and pulmonary fibrosis (PF).[1] Genetic mutations have not been identified in all HPS patients, largely because of the phenotypic heterogeneity and technical limitations of genetic analysis. Thus, it is likely that some genetic defects responsible for HPS among diverse populations will only be revealed after advanced genetic techniques became available.[2,3]

Most of the clinical manifestations of HPS can be explained by HPS gene mutations resulting in abnormalities in the formation and intracellular trafficking of lysosome-related organelles (LROs) in specific cell types. For example, LRO defects in melanocytes (melanosomes) and platelets (platelet-dense granules) are responsible for albinism and bleeding tendency, respectively. However, the detailed mechanisms by which HPS gene mutations lead to alterations in intercellular signaling and clinical phenotypes remain incompletely understood.[1,4,5] The exploration of clinical features and their underlying genetic bases is indispensable for diagnosis, treatment, and preventive health care of HPS.

PF, a common clinical imaging feature of interstitial pneumonia, is the most life-threatening complication of HPS, although so far it has been found only in the HPS-1, HPS-2, and HPS-4 subtypes with high penetrance.[6] HPS-1 is generally the most common and most severe subtype in Puerto Rican and other ethnic populations. Almost all patients with HPS-1 develop

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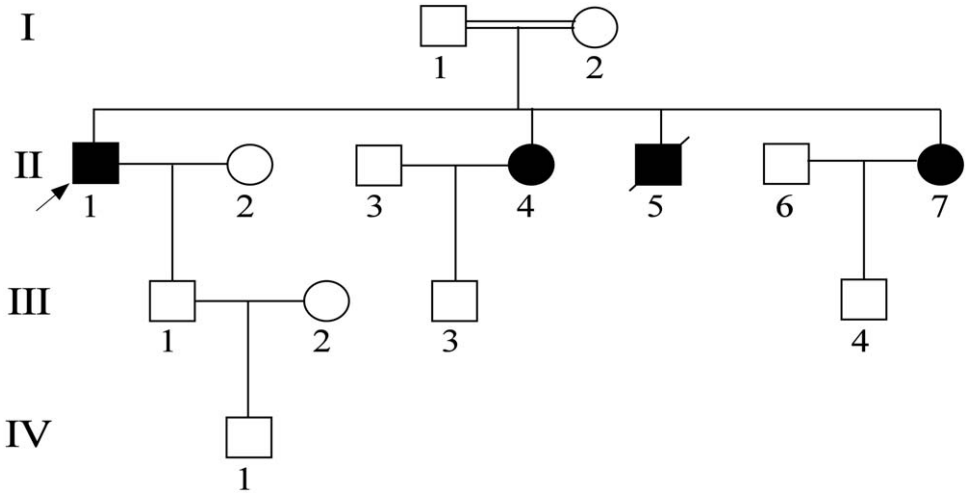

Figure 1. The pedigree of the Chinese family. The proband (II.1) and his siblings (II.4, II.5, II.7) have been recorded to show albinism and dyspnea. The younger brother (II.5) of the proband die at 35 years because of expiratory failure. Their parents (I.1 and I.2) are first cousins. The dark filled symbols indicate affected individuals. The white-filled symbols indicate other family members without albinism. The double line indicates a consanguineous marriage. The arrow indicates the proband.

progressive PF affecting middle-aged adults with about a 50% mortality rate.[5] In contrast to HPS-1, PF usually affects children with HPS-2.[7] The clinical manifestations and severity of HPS-4 are generally considered to be similar to those of HPS-1. A possible explanation is that the HPS1 and HPS4 proteins together form the BLOC-3 complex; therefore, genetic defects in either protein would disrupt the formation of the complex, thus leading to similar clinical consequences.[8] However, the number of HPS-4 cases is too small to prove this idea.

HPS-4 has been found in patients with a variety of ethnic backgrounds in the America, Europe, and Asia. However, only a few cases of HPS-4 with PF have been described in the literature, and the frequency and risk of PF in HPS-4 remain unclear. Approximately a dozen cases of HPS have been identified in China, which includes HPS-1, HPS-3, HPS-5, and HPS-6,[3,9,10] although HPS-4 has not been reported in China. Here, we describe a novel frameshift mutation in the *HPS4* gene that underlies the HPS-4 with PF in 2 Chinese siblings in their 50s.

2. Materials and methods

2.1. Participants

Three individuals from a Chinese family (the family pedigree is shown in Fig. 1) with Han ethnic background, including the proband (II.1), his younger sister (II.4) and his son (III.1), were enrolled in this study. The enrollment protocol was in accordance with the Declaration of Helsinki (1964) and approved by the ethics review board of the Second Affiliated Hospital of Kunming Medical University. Patients were candidates for HPS diagnosis if an HPS mutation was identified. Informed consent was obtained from the 3 participants. However, the other family members were not available for the present study.

The parents (I.1 and I.2) had a consanguineous marriage. All 4 siblings had congenital albinism. The proband (II.1), a 53-year-old male farmer, nonsmoker, with no allergic history, complained of progressive dyspnea and dry cough for approximately 15 years, frequent skin bruising, and bleeding tendency. His younger sister (II.4), who had similar clinical manifestations, complained of expiratory symptoms starting from her 30s. In addition, she has abdominal complications without blood in the stool. Another young sister (II.7) also experienced dyspnea for years, but she was not available for diagnosis. His younger brother (II.5) died of respiratory failure at the age of 35 without known causes.

2.2. Clinical assessment

We performed a physical examination, blood tests including blood cells count, liver function, blood fatty acids, autoimmune antibodies, coagulation functions, and biochemical examinations. Chest high-resolution CT (HRCT) and abdominal ultrasound scans were implemented. The primary diagnosis was albinism and PF for the proband and his younger sister (II.4). A regular dose (0.75 mg/kg body weight/day) of prednisone acetate had been prescribed in their treatment.

2.3. Molecular genetic analyses

Genomic DNA was isolated from ethylenediaminetetraacetic acid-antagonized peripheral blood cells using the blood genomic DNA isolation kit (Axgene, Shuzou, China). Causal genetic variants were screened using high-throughput whole-exome sequencing analysis at 100× coverage by Berry Genomics Corporation (Beijing, China) using the Agilent SureSelect Target Enrichment System (Human V6) and the Illumina Hiseq2500 NGS platform, which employed PE150 (150 bp paired-end) sequencing. The sequencing reads were aligned to the GRCH38/hg19 (human reference genome, NCBI build 37 at UCSC). Pathogenic variants were filtered and evaluated using standard methods, including identifying rare alleles from the 1000 Genomes and the Exome Aggregation Consortium population databases, in silico predicting pathogenic variants and their functional effects using the Polyphen2 (http://genetics.bwh.harvard.edu/pph2/), Mutation Taster (www.mutationtaster.org/), and SIFT (https://sift.bii.a-star.edu.sg/) programs. PredictProtein online server (www.predictprotein.org) was used for protein secondary structure and protein function prediction.

Table 1

Clinical findings in the Chinese siblings with Hermansky-Pudlak syndrome.

	Brother	Sister	Normal reference
Age	53 y	50 y	
Age at start of lung symptoms	~38 y	~35 y	
Main complaints		Progressive dyspnea, dry cough, bleeding tendency	
Physical examination			
Skin and hair		White skin, brown hair	
Eye		Light gray irides, iris transillumination Horizontal nystagmus, squint, amblyopia	
Lung auscultation		Velcro rale in bilateral lung lobes	
Finger		Finger clubbing	
Blood analysis			
White blood cell, 10^9 cells/L	8.51	9.54	3.50–9.50
Hemoglobin, g/L	145	86 ↓	130–175 (brother) 115–150 (sister)
Hematocrit, L/L	0.447	0.324	0.400–0.500 (brother) 0.350–0.450 (sister)
Platelet, 10^9 cells/L	135	260	125-350
Ferrum, μmol/L	21.4	3.4 ↓	10.6–36.7 (brother) 7.8–32.2 (sister)
Alanine aminotransferase, U/L	42	10	5–40
Aspartate aminotransferase, U/L	31		
Triglycerides, mmol/L	4.11	1.34	3.49–5.18
Lactate dehydrogenase, U/L	173	240	109–245
Autoimmune antibodies (ANA, PCNA, AHA, SS-A, SS-B, dsDNA)	(-)	(-)	
Prothrombin time, s	13.5	13.6	11.0–15.0
International normalized ratio	1.04	1.06	0.82–1.15
Activated partial thromboplastin time, s	33.6	36.7	28.0–43.5
Fibrinogen, g/L	3.46	3.26	2.00–4.00
Pulmonary function test			
FVC (% predicted)	32% ↓	48%↓	≥80%
FEV_1 (% predicted)	38%↓	56%↓	≥80%
FEV1/FVC (%)	93% ↑	99% ↑	82%
Chest HRCT		Pulmonary fibrosis	
B-mode ultrasonography	Normal Intestinal wall diffuse thickening and reduced peristalsis were found from the sigmoid colon to the rectum		

↓: the detected value is lower than the normal reference value; ↑: the detected value is higher than the normal reference value. FVC = forced vital capacity, FEV_1 = forced expiratory volume in 1 second, HRCT = high-resolution computerized tomography.

SWISS-MODEL (https://swissmodel.expasy.org/interactive) web-based services were used to build protein homology model.

The causal mutation was further confirmed using PCR and Sanger DNA sequencing. In addition, gene frequency of new mutation was evaluated by searching genome data of Chinese Han ethnic population in both 1000 genome (http://phase3 browser.1000genomes.org/) and the International HapMap project (http://www.hapmap.org) databases, and by screening DNA samples from 100 unaffected individuals of the same ethnic background and same living region as the patients using Sanger DNA sequencing. The DNA samples were obtained from the DNA bank of Chinese ethnic populations (Institute of Medical Biology, Chinese Academy of Medical Sciences. Kunming, China)

3. Results

3.1. Clinical findings

The major clinical findings of the 2 Chinese sibling patients are outlined in Table 1. The hypopigmentation of skin, hair, and iris showed typical OCA. Velcro rale in the bilateral lower lobes suggested interstitial pneumonia, and the representative images of chest HRCT are presented in Figure 2. The HRCT images demonstrated advanced, bilateral interstitial PF in the lungs, predominantly in the lower lobes. Lung function tests showed significantly decreased forced vital capacity (FVC) and forced expiratory volume in one second (FEV_1) values, whereas the value of the FEV_1/FVC ratio increased, indicating a severe restrictive ventilatory functional disturbance. The observed clubbed fingers implied hypoxemic lung disease.

In both patients, the platelet counts were normal, and the prothrombin time, international normalized ratio, activated partial thromboplastin time, and fibrinogen values were in the normal ranges, indicating normal coagulation function. Lung infection, autoimmune disorders, abnormal liver function, and lipid metabolism were excluded based on the normal values of white blood cells, alanine aminotransferase and aspartate aminotransferase, autoantibodies and lactate dehydrogenase (LDH), respectively. In the younger sister (II.4), hemoglobin and ferrum tests indicated iron-deficiency anemia, and abdominal B-ultrasound findings suggested colitis. Regular doses of corticosteroids led to reduced lung symptoms, including dyspnea and cough, for the sibling patients during their hospitalization, but the drug did not effectively

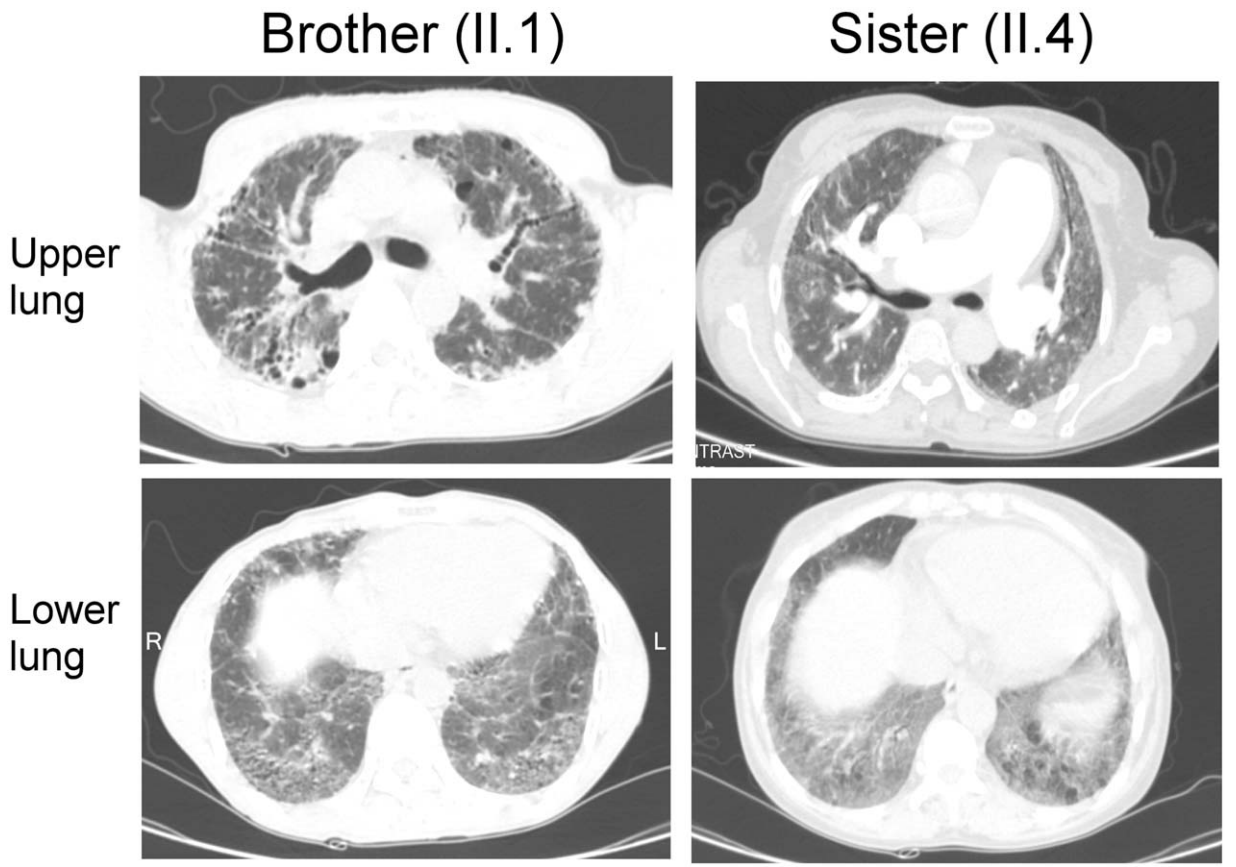

Figure 2. High-resolution computed tomography scans of the 2 Chinese siblings' lungs at the time of admission. The images show subpleural septal thickening, traction bronchiectasis, obvious ground-glass opacities and reticular opacities with a honeycomb pattern in the bilateral lung fields.

prevent exacerbation of the expiratory symptoms. One year after admission, both patients died of respiratory failure in their 50s.

3.2. Molecular genetic analyses

The whole-exome sequencing revealed a novel homozygous allele with a duplication of a C residue in codon 211 in exon 8 of the *HSP4* gene (NM_022081): c.630 dupC:p.A211fs, which resulted in interruption of the reading frame. This frameshift mutation was confirmed by Sanger DNA sequencing (Fig. 3 A). The c.630 dupC p.A211fs mutation causes not only a shift of amino acid codons but also a premature stop codon at codon 257 (257X), leading to a truncated HPS4 protein with a length of 256-amino acids (Fig. 3 B), which is much shorter than the wild-type protein (708 amino acids). This novel variant was predicted to be "damaging" to the protein function by SIFT algorithm program. In addition, according to MutationTaster, the frameshift mutation (A211fs) causing a premature termination codon and ultimately leading to nonsense-mediated mRNA decay (NMD) was predicted to be "disease causing" status with probability value equal to 1, which indicates the highest confidence of the prediction. Secondary structure analyses using Predictprotein server show significant change when compared to the truncated and wild types of HPS4 protein (see Figure, Supplemental Content, http://links.lww.com/MD/D183, which demonstrates the effects of the mutation on the secondary structure), indicating the loss-of-function effects resulted from the mutation. No overlapping homologous superfamilies were retrieved from protein databases, and no HPS4 protein homology model was built with confident quality using SWISS-MODEL.

Sanger sequencing confirmed that the proband (II.1) and his younger sister (II.4) were both homozygous for the mutation, and his son (III.1) was a heterozygotic carrier of the mutant allele. The search for the mutation by using both the genome databases from Chinese Han ethnic populations and the Sanger DNA sequencing of 100 unaffected individuals indicated that the mutation is a novel mutation of *HSP4* gene. Based on the DNA analysis, clinical data, and family history, the 2 patients were diagnosed as having HPS type 4. The inheritance pattern of HPS-4 in the Chinese family was consistent with an autosomal recessive model.

4. Discussion

In the present study, our findings reveal a novel *HPS4* mutation as the cause of OCA and PF in 2 Chinese siblings. The 2 patients were diagnosed as having HPS-4 based on the genetic and clinical findings. Our findings demonstrate a strong association between the *HPS4* mutation and severe PF in patients with HPS-4. In addition, to the best of our knowledge, this is the first report of HPS-4 in China.

HPS is rarely distributed in a variety of different ethnic people around the world, except for Puerto Ricans, who have the highest incidence (approximately 1:4000) because of the genetic founder effect.[1,11] As a type of syndromic OCA, HPS is very likely overlooked in China and other countries where the common

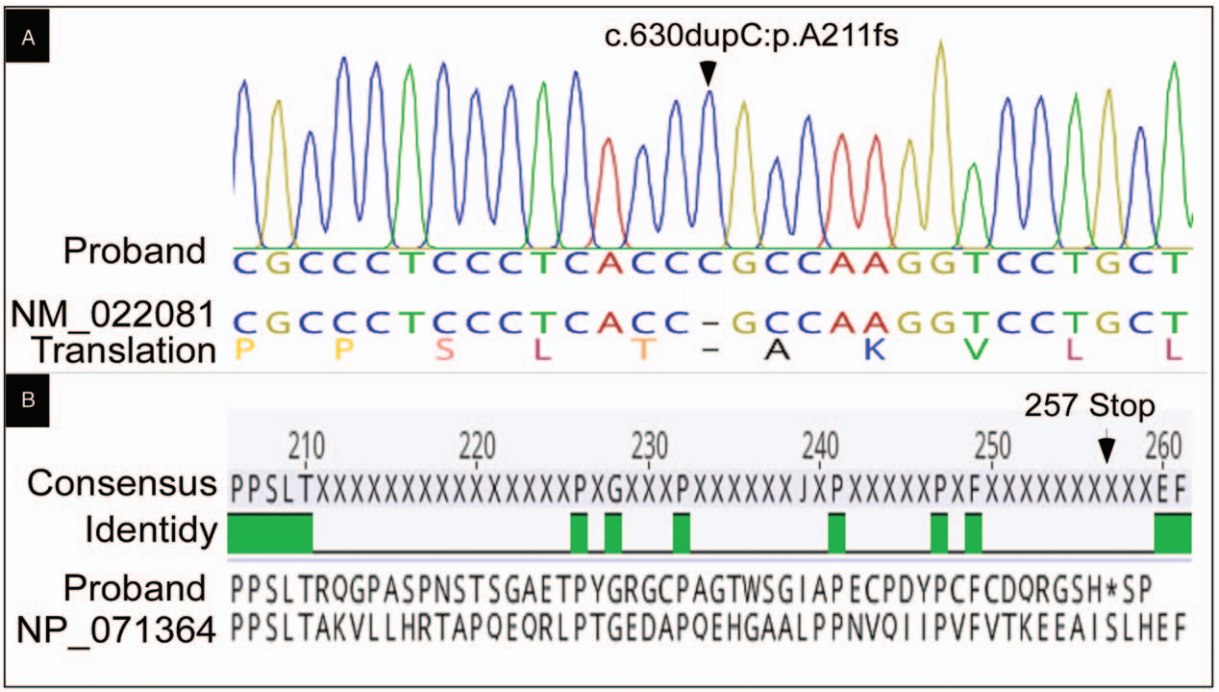

Figure 3. The *HPS4* gene mutation identified in the proband (II.1) and its predicted consequence on the protein sequence. (A) The Sanger DNA sequence chromatogram identifies a C residue duplication at nucleotide 630 of the *HPS4* cDNA (NM_022081, c.630dupC:p.A211fs), which leads to a frameshift starting from Codon 211 A (Ala) in the translation. (B) The protein sequence alignment indicates that the mutation causes a frameshift of the amino acid sequence after amino acid 211 and a premature translational stop at amino acid 257, resulting in an abnormally truncated protein compared with wild-type HPS4 protein (NP_071364), which contains 708 amino acid residues.

types of albinism are usually nonsyndromic OCA1 (*TYR*) and OCA2 (*P* GENE).[12] HPS is genetically and phenotypically heterogenous. Ten genetic subtypes of HPS have been found with variable clinical features, severities, and prognoses. Therefore, molecular genetic analysis serves an essential role in HPS diagnosis and therapy. Our results reveal an undescribed *HPS4* mutation in the patients, thus expanding the HPS mutation spectrum. In addition, 4 HPS subtypes, HPS-1, HPS-3, HPS-5, and HPS-6, have been found in 12 patients with OCA in China to date, but no HPS-4 has been described.[3,9,10,13] Here, we diagnosed 2 patients with HPS-4 and provided the first proof that an *HPS4* gene mutation was associated with OCA in China. Therefore, it is recommended that HPS-4 should be taken into account when encountering patients with recessive OCA in China. Moreover, HPS-4 has been identified in Western countries and some Asian countries, including India, Sri Lanka, and Japan.[14–18] The HPS-4 cases identified in the present study were from southwest China, and our findings add to a growing body of evidence showing that *HPS4* mutations are distributed across a variety of populations with different ethnic backgrounds.

HSP-4 is genetically heterogeneous. According to the Hermansky-Pudlak Syndrome Database (www.genelab-bch.com.cn/HPSD/) and recent reports,[17–19] 16 mutations distributed in exons 2–3, 6–8, 11, and 13–14 of *HPS4* have been found so far in 21 HPS-4 patients. Coincidentally, 14 of the 16 mutations lead to premature stop codons because of nonsense mutations (9) and frameshift mutations (5), which resulted in truncated HPS4 proteins with a size range of 5 to 693 amino acids, all shorter than the wild-type protein with 708 amino acids. The frameshift mutations commonly led to a very N-terminal (codon 15X) or to a very C-terminal stop codon (codon 703X) in *HPS4*. Our results identified a novel frameshift mutation (dupC:p.A211fs) in exon 8 leading to an N-terminal stop codon (257X) and a C-terminally truncated HPS4 protein (Fig. 2). In silico analyses suggested that the novel insertion variant is a pathogenic mutation. This mutation results in loss of most of the region required for the HPS1: HPS4 interaction, which would consequently prevent the formation of the BLOC-3 complex and leads to the clinical manifestations of HPS-4.[8] Our results add a frameshift mutation, bringing the total number of *HPS4* mutations to 17. It is worth noting that not all of the genetic variants in the *HPS4* exons are associated with HPS-4. For example, 2 missense mutations, rs713998 G/A (p.G229E) in exon 8 and rs2014410 C/G in exon 11 (p.L443 V), are not pathogenic but are rather polymorphic loci in the *HPS4* gene associated with susceptibility to schizophrenia in some Japanese populations.[20,21]

Furthermore, in our study, the novel dupC:p.A211fs mutation was associated with HPS and the fetal PF in the patients who died in their 50s. A previous study reported a frameshift mutation (Q698insAAGCA), which putatively produced a truncated HPS4 protein (703X) only 5 amino acids shorter than the wild type (708AA), that was associated with the death of the affected patient at age 61 owing to PF,[14] demonstrating the significant functional importance of the far C-terminus of the HPS4 protein. Another report showed an association between a nonsense mutation (p.Q620X) and interstitial pneumonia in a Japanese HPS-4 patient.[18] Taken together with our results, we speculate that mutations shortening the C-terminus of HPS4 are strongly associated with PF. However, more cases and molecular analyses are needed to evaluate the causal relationship between *HPS4* mutations and PF, other clinical manifestations and prognosis.

High-penetrance PF is one major clinical feature of HPS, usually associated with HPS-1, HPS-2, and HPS-4. HPS-1 is the most common subtype reported with PF. Nearly 100% of HPS-1 patients develop PF, typically restrictive lung disease with onset in middle age. It has been noted that HPS-1 PF is predominantly in the middle and lower sections of the lung, resulting in decreased lung capacity.[22] PF in HPS-1 usually is severe, and >70% of patients die in their 50s. Several cases of HPS-4 with variable manifestations, such as PF and elevated LDH, have been reported.[15,16] However, the features of PF associated with HPS-4 remain poorly described. One study showed that the course HPS-4 is similar to that of HPS-1 because mutations in both HPS1 and HPS4 could interrupt HPS1: HPS4 interaction and BLOC-3 complex formation, therefore leading to the same kinds of clinical manifestations.[15] Another report, however, showed that HPS-4 is less severe than HPS-1,[16] which suggested that HPS phenotypes could be modified by genetic or environmental factors.[5] Our study showed the clinical features of 2 HPS-4 patients, including onset age (~40 years old), the severity of PF (HRCT honeycomb pattern in lung field), and prognosis (~15 years survival time after onset), were very similar to those of typical HPS-1. Our findings provided additional descriptions of HPS-4 clinical features and further strengthened the evidence linking fetal PF with HPS-4. In addition, in our study, clinical examination suggested colitis in the young sister (II.4) but not in the brother (II.1). Our findings demonstrate phenotypical heterogeneity in HPS-4 and support the notion that different factors may contribute to the variable phenotypes. For instance, age is a major factor affecting fibrosis development of HPS-4,[1,5] and this relationship is a good explanation for why PF is rarely observed in most under-age patients with nonsense mutations in *HPS4*.[14,17,18,23]

There is no effective treatment for HPS PF except lung transplantation.[5,24] In our patients, regular doses of corticosteroid improved their respiratory symptoms but did not significantly slow the fibrosis progression, which is in agreement with a previous report.[16] The antifibrotic drug pirfenidone, a small molecular TGF-beta inhibitor, shows effectiveness in delaying the progression of PF and dysfunction,[16,22] although the efficiency for pirfenidone use could be considered on a case-by-case basis.[25] However, efficacy remains controversial.[26] Pirfenidone was not used in our patient's treatment because HPS had not been considered during their hospitalization. Our report demonstrates the need for molecular genetic tests for early diagnosis and treatment of HPS.

In summary, we report a novel frame-shift mutation in 2 Chinese patients with HPS-4 that expands the mutation spectrum of HPS and proves that HPS-4 occurs in China. In addition, the descriptions of the clinical features of our patients further demonstrated the close association between HPS-4 and PF and poor prognosis. However, there are several limitations in our study. For example, we were unable to evaluate the clinical effect of the causal mutation in more patients; moreover, photomicrographs from biopsy or autopsy materials showing the lung pathology, and some other clinical data assisting in the diagnosis, were not available. Platelet-dense granules were not examined using an electron microscope, and PF and granulomatous colitis were not evaluated using appropriate biopsies of affected organs. Overall, our findings have highlighted the need for early genetic diagnosis of HPS subtypes when encountering patients with ocular albinism and the urgent requirement for the development of effective drugs and therapy strategies to substantially improve PF and other manifestations of HPS.

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