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A Novel Non-Sense Mutation in a Senegalese Patient with Hermansky-Pudlak Type 1 Syndrome

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Abstract

Hermansky-Pudlak syndrome (HPS) is a rare inherited multisystem disorder characterized by oculocutaneous albinism and diathesis, and in some patients with pulmonary fibrosis. It is caused by defective biogenesis and trafficking of lysosome-related organelles. Genetically HPS is heterogeneous, and ten loci have been identified as causative genes. The majority of these genes encode subunits of multi-protein complexes named biogenesis of lysosomes-related organelles complex. Mutations within *HPS1* and *HPS4* genes lead to pulmonary fibrosis in HPS type1 and type 4 patients respectively and are the leading cause of mortality. A 14 years Senegalese boy who was initially diagnosed with oculocutaneous albinism was recruited with his father after informed consent for genetic analysis. In his clinical history, there was no bleeding tendency or clinical episodes of hemorrhagic diathesis. One of his sisters had albinism and died from lung complications at the age of 15 years. The patient was referred to the pneumology department of Fann Hospital in Dakar for further explorations. The high-resolution computed tomography (HRCT) scans of the lungs revealed no evidence of diffuse interstitial lung disease, pleuropericardial effusion, bronchiectasis, pulmonary hypertension, intra pulmonary/mediastinal mass or lymphadenopathy. Mutation screening by Albinism NGS panel identified a homozygous mutation located in exon 6 of the *HPS1* gene, c.421C>T (p.Gln141*), in the Proband while his father showed heterozygosity for this mutation. The parents of the proband are not consanguineous and this may suggest a common allele of *HPS1* among Senegalese people. Patients with oculocutaneous albinism should therefore be evaluated for Hermansky-Pudlak syndrome by mutational screening within the ten *HPS* genes.

Keywords: Hermanski-Pudlak; HPS1 gene; Mutation; Senegal

Introduction

Hermansky-Pudlak syndrome (HPS) is an autosomal recessive disorder characterized by oculocutaneous albinism and diathesis [1]. Some HPS patients present additional symptoms, including granulomatous colitis, immunodeficiency, cardiomyopathy, renal failure and pulmonary fibrosis [2-5]. HPS is a multisystem disorder due to disruption of the biogenesis of the lysosomes and related organelles such as melanosomes in melanocytes, dense bodies in platelets, lamellar bodies in type-2 pneumocytes (2PC) and lytic granules in cytotoxic T lymphocytes.

Genetically, HPS is a heterogeneous disorder. Almost ten loci have been linked to this mendelian trait [6]. Among these genes, *HPS1* and *HPS4* encode subunits of a multi-protein complex named biogenesis of lysosome-related organelles complex 3 (BLOC-3) [7]. The localization and functions of this multi-protein complex have not yet been well defined. It has been shown that BLOC-3 plays a role in the movement of late endocytic organelles by time-lapse fluorescence microscopy [8].

Patients with HPS type 1 or HPS type 4 have an increased risk of developing lung fibrosis [9,10]. This particular clinical feature seems to be the result of the disruption in the biogenesis organelles of the lysosomal system, particularly in lamellar bodies in 2PCs, involved in the storage and the secretion of pulmonary surfactant [11]. The deleterious lesion of 2PCs, could lead to the activation of fibroblasts that produce and secrete excess extracellular matrix leading to lung fibrosis [12]. The average age of the occurrence of pulmonary symptoms was estimated at 35 years [9]. Molecular characterization and different HPS1 phenotypes suggested that differentially truncated HPS1 polypeptides may have different effects on the cellular function [13].

Here we report a novel non-sense mutation of *HPS1* gene in a Senegalese patient with Hermansky-Pudlak type 1 syndrome.

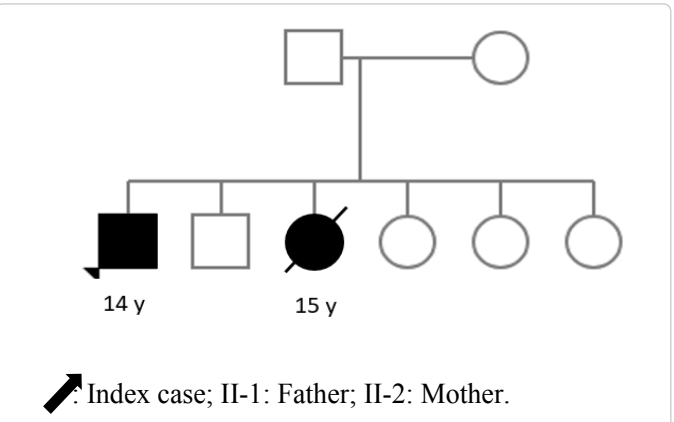

Figure 1: Pedigree of the patient's family.

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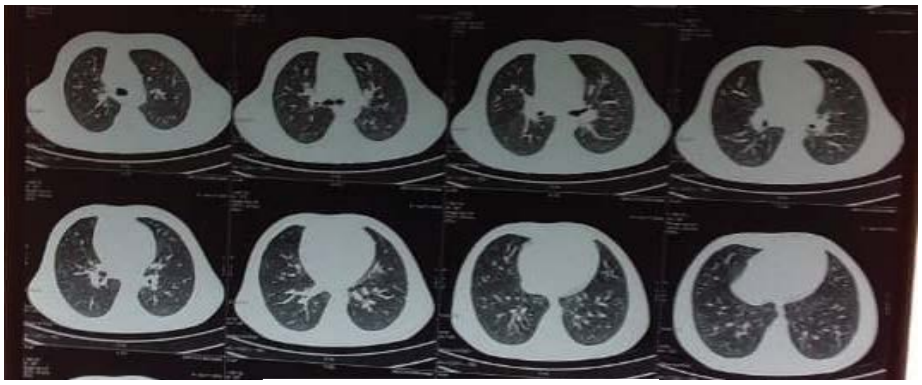

Figure 2: Patient's HRCT scan of the chest.

Note: The red box indicates the variant nucleotide C/T at heterozygous state in the father and the proband.

Figure 3: Chromatogram of the genomic region surrounding the mutation identified in *HPS1* gene.

Population and Methods

Patient information

After informed consent from his father, a 14 years old boy clinically diagnosed with oculocutaneous albinism was recruited for molecular characterization. In his clinical history, there was no bleeding tendency or clinical episodes of hemorrhagic diathesis. He presented additional symptoms including cough and dyspnea. One of his sisters had albinism and died from lung complications at the age of 15 years. Three sisters and one brother showed no symptoms. His parents were not consanguineous (Figure 1).

The patient was referred to the pneumology department of Fann Hospital in Dakar for further explorations. The high-resolution computed tomography (HRCT) scans of the lungs showed no evidence of diffuse interstitial lung disease, pleuropericardial effusion, bronchiectasis, pulmonary hypertension, intra pulmonary/mediastinal mass or lymphadenopathy (Figure 2).

Methods

Blood samples were collected from the patient and his father for genetic analyses. Informed consent was obtained from the patient and his father. Genomic DNA was extracted using Qiagen Kit (Qiagen, Hildel, Germany).

DNA were analyzed by Next Generation Sequencing (NGS) of a multigene panel that includes *TYR, OCA2, TYRP1, SLC45A2, SLC24A5, C10orf11/LRMDA, GPR143, SLC38A8, HPS1, AP3B1, HPS3, HPS4, HPS5, HPS6, DTNBP1, BLOC1S3, BLOC1S6, AP3D1,* and *LYST*. The mutations identified by NGS, were confirmed by Sanger sequencing method.

Results

Screening of the 19 known albinism-related genes identified a homozygous mutation located in exon 6 in the *HPS1* gene, c.421C>T (p.Gln141*) in the proband, while his father showed heterozygosity for this mutation (Figure 3).This mutation is neither present in the ClinVar database (http://www.ncbi.nlm.nih.gov/clinvar/) nor in a large series of 990 patients with albinism [14,15]. It therefore constitutes a novel nonsense mutation in the *HPS1* gene.

Discussion

The clinical features of HPS result from defects in proteins

required for the normal assembly, maturation, or structure of different organelles. Until now, ten loci have been identified and each lead to an HPS subtype. HPS1 is the most common subtype of Hermansky–Pudlak syndrome [16-18]. The present study reports a nonsense mutation, c.421C >T (p.Gln141*) of *HPS1* gene in a 14 years old Senegalese boy. This mutation introduces a premature stop codon in the *HPS1* transcript and predictably leads to the synthesis of a truncated protein of 141 residues or a nonsense-mediated mRNA decay (NMD) which results in degradation of a gene at RNA level without producing protein.

This mutation is neither present in the ClinVar database, nor in a large series of 990 patients with albinism [14,15]. It therefore constitutes a novel nonsense mutation of the *HPS1* gene. The parents of the proband are not consanguineous. While the mother wasn't available for testing, the heterozygosity of the father suggests this may represent a common allele of *HPS1* among Senegalese people.

HPS1 is common in many populations worldwide. In fact, 55 *HPS1* mutations have been described. In Africa, HPS patients have not been reported so far, to the best of our knowledge [19]. However, in northwest of Puerto Rico, a 16-pb duplication in exon 15 of *HPS1* with a founder effect is the most common pathogenic variant [16,19]. This variant is not prevalent in other countries. Other HPS1 frameshift mutations, missense mutations and splice site mutations have been reported worldwide [13,16,20]. These mutations may generate a protein with predictably compromised function. Non-sense mutation does not always produce truncated protein, it could also induce nonsense-mediated mRNA decay (NMD), which results in degradation at RNA level without producing protein. NMD is a translation-coupled mechanism that eliminates mRNAs containing premature translation-termination codons [21].

HPS1 and *HPS4* are components of a heterodimer named BLOC-3 complex, which shares no homology with other known proteins [7]. The N and C-terminal domains of *HPS1* interact with the N-terminal and middle region of *HPS4* to form the complex [22]. The precise function of BLOC-3 is not well known, but it is believed to be involved in lysosome and late endosome biogenesis and transport [11].

Besides oculocutaneous albinism, HPS1 and HPS4 patients have an increased risk of developing lung fibrosis [9]. HPS1 patients generally manifest symptoms of pulmonary fibrosis in middle age [9]. The HRCT of the studied proband revealed no evidence of diffuse interstitial lung disease, bronchiectasis, pulmonary hypertension, intra pulmonary/mediastinal mass or lymphadenopathy. The absence of pulmonary fibrosis in the proband might be due to his relatively young age. Carmona-Rivera described a 16-year-old boy with no pulmonary symptoms in HPS-1 [16]. The reason for lung fibrosis is unclear, but it probably reflects the relevant role of BLOC-3 in the biogenesis and function of lamellar bodies of 2PC [11]. The clinical phenotypes associated with differentially truncated HPS polypeptides may suggest different functional consequences at the subcellular level [13]. The truncated HPS1 polypeptide might be less likely to interact with HPS 4 polypeptide in BLOC-3. Another mechanism that might explain the onset of lung fibrosis in HPS1 and HPS4 patients is the interaction between Galectin-3 and chitinase-like protein chitinase 3-like-1(CHI3L1). The prototypic CHI3L1 plays a protective role in the lung by ameliorating cell death and stimulating fibroproliferative repair [23]. Galectin-3 contributes to the exaggerated injury and fibroproliferative repair responses in HPS 1 patients by altering the antiapoptotic and fibroproliferative effects of CHI3L1 and its receptor complex in a tissue compartment-specific manner [24]. It is therefore relevant to do regular clinical monitoring in HPS1 patients, starting in early adulthood.

Conclusion

The prevalence of HPS is unknown in the Senegalese population. Senegalese patients with oculocutaneous albinism should therefore be evaluated for Hermansky-Pudlak syndrome by mutational screening of the ten *HPS* genes (AP3B1, *AP3D1* BLOC1S3, BLOC1S6, DTNBP1, HPS1, HPS3, HPS4, HPS5, HPS6). The identification of a recessive mutation in a non-consanguineous family may suggest a common allele of *HPS1* among Senegalese people. Meanwhile, this need to be confirmed in a large cohort of health controls from Senegalese population.

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Competing Interests

The authors declare that they do not have any competing interests.

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