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Differential Diagnosis of Pulmonary Veno-Occlusive Disease and/or Pulmonary Capillary Hemangiomatosis after Identification of Two Novel *EIF2AK4* Variants by Whole-Exome Sequencing

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Established Facts

- The clinical presentations of pulmonary arterial hypertension and pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis are similar.
- Treatment options for pulmonary hypertension depend upon correct identification etiology in each individual patient.

Novel Insights

- Whole-exome sequencing or panel sequencing allows to rapidly and correctly identify the genetic cause of the pulmonary hypertension.
- Knowing the genetic cause of pulmonary hypertension can lead to effective treatment choices.

Keywords
Pulmonary capillary hemangiomatosis · *EIF2AK4* · Exome sequencing

Abstract
Background: Pulmonary veno-occlusive disease (PVOD) and/or pulmonary capillary hemangiomatosis (PCH) are rare causes of pulmonary hypertension. Pulmonary arterial hypertension (PAH) and PVOD/PCH are clinically similar, but there is a risk of drug-induced pulmonary edema when PCH patients receive the PAH therapy. Therefore, early diagnosis of PVOD/PCH is important. ***Objectives:*** We report the first case in Korea of PVOD/PCH in a patient carrying compound heterozygous pathogenic variants in the *EIF2AK4* gene. ***Case Description and Method:*** A 19-year-old man who was previously diagnosed with idiopathic PAH suffered from dyspnea on exertion for 2 months. He had a reduced lung diffusion

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capacity for carbon monoxide (25% predicted). Chest computed tomography images showed diffusely scattered ground-glass opacity nodules in both lungs with an enlarged main pulmonary artery. For the molecular diagnosis of PVOD/PCH, whole-exome sequencing was performed for the proband. ***Results:*** Exome sequencing identified two novel *EIF2AK4* variants, c.2137_2138dup (p.Ser714Leufs*78) and c.3358-1G>A. These two variants were classified as pathogenic variants according to the 2015 American College of Medical Genetics and Genomics guidelines. ***Conclusions:*** We identified two novel pathogenic variants (c.2137_2138dup and c.3358-1G>A) in the *EIF2AK4* gene. Identification of possible pathogenic gene variants by whole-exome sequencing or panel sequencing is recommended as a guide to adequate treatment of patients with pulmonary hypertension.

Introduction

Pulmonary veno-occlusive disease (PVOD) and/or pulmonary capillary hemangiomatosis (PCH) are rare causes of pulmonary hypertension, and they share a similar clinical presentation to pulmonary arterial hypertension (PAH). PVOD/PCH, categorized into a subgroup 1′ of PAH, has an estimated incidence and prevalence less than 1 case per million [Galie et al., 2016]. PVOD and PCH were initially described as two distinct diseases. Recently, it has been proposed that PCH could be a secondary angioproliferative process caused by the post-capillary obstruction of PVOD [Simonneau et al., 2013]. PAH and PVOD/PCH are clinically similar, but there is a risk of drug-induced pulmonary edema when PCH patients receive the PAH therapy [Humbert et al., 1998]. Therefore, early diagnosis of PVOD/PCH is important.

In 2014, biallelic autosomal recessive mutations of *EIF2AK4* were first identified in PVOD/PCH families [Best et al., 2014; Eyries et al., 2014]. *EIF2AK4* encodes a serine/threonine kinase that regulates angiogenesis in response to cellular stress [Berlanga et al., 1999]. *EIF2AK4* mutations were identified in all 13 PVOD families and 5/20 (25%) sporadic cases [Eyries et al., 2014]. In the past, definite diagnosis of PVOD/PCH required a pathologic examination of tissue from a lung biopsy or postmortem lung samples. However, because lung biopsy was dangerous for patients with severe pulmonary hypertension, noninvasive diagnostic tools have been established that combine clinical suspicion, physical examination, bronchoscopy, and radiological findings [Montani et al., 2008]. Recently, identification of a biallelic *EIF2AK4* mutation is recommended to confirm a diagnosis of heritable PVOD/PCH without histological confirmation [Galie et al., 2016]. Here, we report the first case of PVOD/PCH in Korea in a patient carrying compound heterozygous pathogenic variants (PVs) in the *EIF2AK4* gene.

Materials and Methods

Case Description

A 19-year-old man with dyspnea on exertion for 2 months visited the Samsung Medical Center for a second opinion. Ambrisentan and sildenafil were prescribed from outside hospital with diagnosis of idiopathic PAH; however, treatment response was poor. The concentration of brain natriuretic peptide was 513.9 pg/mL. The echocardiogram revealed a dilated right ventricular (RV) cavity, decreased RV systolic function, normal left ventricular systolic function, and an estimated RV systolic peak pressure of 53.5 mm Hg. The 6 min walk distance was 371 m. Chest computed tomography images showed diffusely scattered ground-glass opacity nodules in both lungs with an enlarged main pulmonary artery (shown in Fig. 1). He had a reduced lung diffusion capacity for carbon monoxide (25% predicted). Right heart catheterization showed severe PAH with a mean pulmonary artery pressure at 57 mm Hg and pulmonary capillary wedge pressure of 8 mm Hg. A video-assisted thoracoscopic wedge resection was performed for PCH evaluation, and histological examination showed interstitial capillary proliferation, mild interlobular septal fibrosis, and extensive interlobular septal edema, compatible with PCH. Imatinib treatment was started for PCH.

Genetic Analysis

For the molecular diagnosis of PVOD/PCH, whole-exome sequencing was performed for the proband. After obtaining informed consent, the patient's genomic DNA was extracted, enriched by using the Agilent SureSelect Human All Exon v5 Kit (Agilent Technologies, Santa Clara, CA, USA) and sequenced on a HiSeq 2000 platform (Illumina, Inc., San Diego, CA, USA).

Results

Nine genes (*BMPR2*, *ATP13A3*, *KCNK3*, *SMAD9*, *CAV1*, *EIF2AK4*, *ENG*, *ACVRL1*, and *GDF2*) known to be associated with pulmonary hypertension were analyzed. Two novel variants were identified only in the *EIF2AK4* gene, NM_001013703.3:c.2137_2138dup (p.Ser^{714}Leufs*78) and c.3358-1G>A, and no variants were identified in the other genes. These variants were absent in the large population database gnomAD (https://gnomad.broadinstitute.org/). Genetic examination of the patient's parents confirmed that the c.3358-1G>A variant was inherited from the father, and c.2137_2138dup was inherited from the mother (shown in Fig. 2). These two variants were

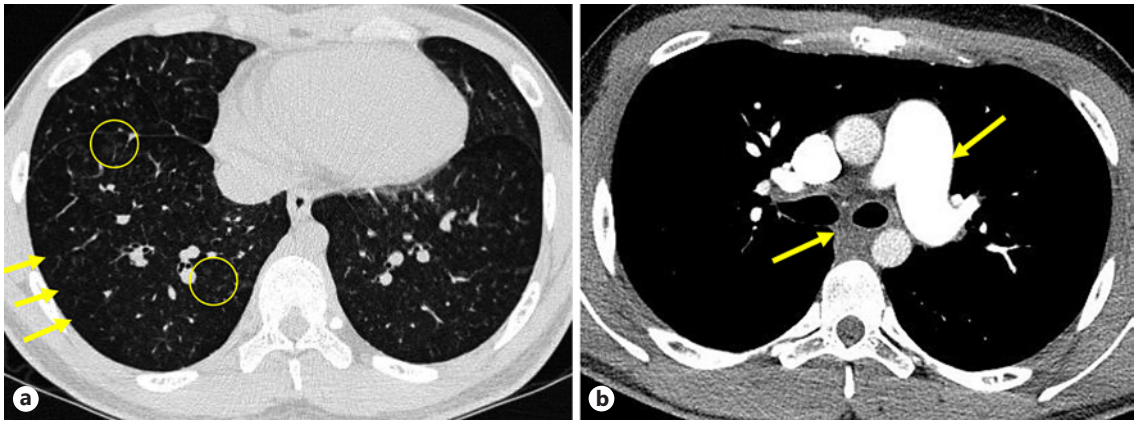

Fig. 1. Chest computed tomography. **a** Diffuse ground-glass opacity nodules (yellow circles) were seen with sparing of subpleural regions in both lungs (arrows). **b** Mediastinal and hilar lymphadenopathy (left arrow) were noticed bilaterally. Note main pulmonary arterial dilation (right arrow). Ground-glass opacity nodules and mediastinal and hilar lymphadenopathy are observed in pulmonary capillary hemangiomatosis.

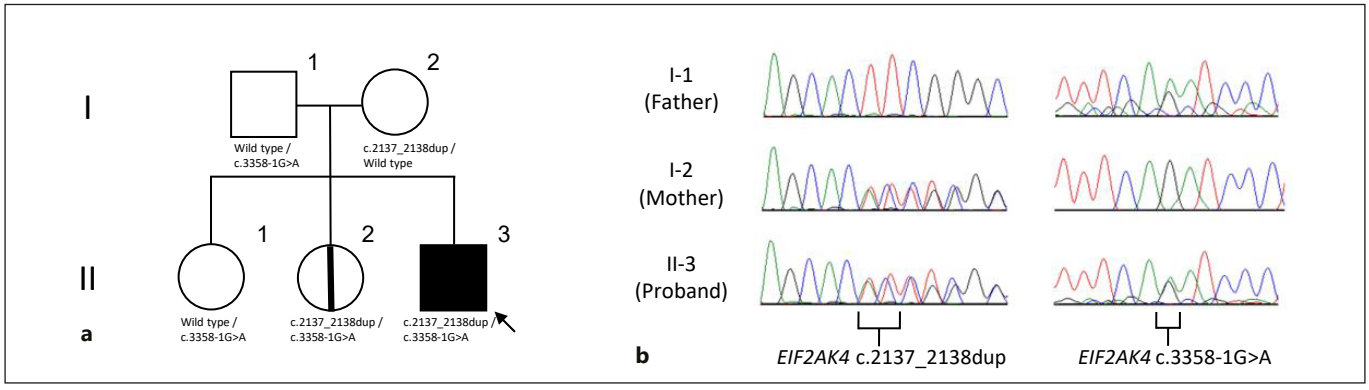

Fig. 2. Pedigree and sequence chromatogram of the *EIF2AK4* variant identified in the family of the present case. **a** The family pedigree shows 1 affected patient. Male, square; female, circle; filled symbols, affected; half-filled symbols, heterozygous carriers; circle with vertical line symbols, asymptomatic compound heterozygous carrier; arrow, proband. **b** The patient was compound heterozygous for two *EIF2AK4* variants (c.2137_2138dup and c.3358-1G>A), while both parents were heterozygous carriers of the same variant.

classified as PVs according to the 2015 American College of Medical Genetics and Genomics and the Association for Molecular Pathology guidelines [Richards et al., 2015]. Additional family studies for the two PVs were conducted in the patient's two sisters. The second sister had two PVs, but she had no PVOD-related symptoms.

Discussion

The clinical features observed in patients with PVOD/PCH include a low diffusing capacity of the lung for carbon monoxide, hypoxemia, and radiological abnormalities on high-resolution computed tomography (centrilobular ground-glass opacification, interlobular septal thickening, and mediastinal lymphadenopathy) [Montani et al., 2017]. However, it is difficult to distinguish between PVOD/PCH and idiopathic PAH because the clinical and radiological features are similar. Unlike other types of PAH, PVOD/PCH patients have a poor prognosis due to the progressive nature of pulmonary vascular involvement and fatal pulmonary edema caused by vasodilating PAH-targeted drugs such as PDE5 inhibitors [Szturmowicz et al., 2018]. Patients with a clinical diagnosis of PAH who carried biallelic *EIF2AK4* mutations had a reduced transfer coefficient for carbon monoxide (KCO:

33% [interquartile range, 30–35%] predicted), younger age at diagnosis (29 years [interquartile range, 23–38 years]), and shorter survival compared to PAH patients without *EIF2AK4* mutations [Hadinnapola et al., 2017]. Like the patient, the second sister also has two PVs. However, the second sister does not have PVOD-related symptoms, so it is presumed that the disease did not occur before the onset or due to incomplete penetration. Nevertheless, due to the genetic predisposition to the disease, we continue to monitor the second sister. Clinical genetic testing can have an important role in identification of this high-risk group and enables to facilitate early referral for lung transplantation and appropriate management.

Conclusion

In conclusion, we identified two novel PVs (c.2137_2138dup and c.3358-1G>A) in the *EIF2AK4* gene. Identification of possible pathogenic gene variants by whole-exome sequencing or panel sequencing is recommended as a guide to adequate treatment of patients with pulmonary hypertension. This report is expected to contribute to a better understanding of the genetic background of Korean PVOD/PCH patients.

Acknowledgments

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Statement of Ethics

Samples from the patient and parents were obtained in accordance with the Helsinki Declarations. Written informed consent for genetic testing, publication of other medical information, and photographs was obtained from patient and parents. This study protocol was reviewed and approved by Samsung Medical Center, approval number SMC 2016-11-039.

Conflict of Interest Statement

The authors have no conflicts of interest to report.

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Author Contributions

All the authors have contributed significantly and approved the final content of the manuscript. Conceptualization: S.A.C., K.S.L., and D.K.K. Investigation: J.E.P. and S.Y.J. Writing – original draft preparation: J.E.P. Writing – review and editing: S.A.C., K.S.L., D.K.K., C.S.K.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author.

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