Lung (2014) 192:625–627
DOI 10.1007/s00408-014-9580-y

BRIEF REPORT

BMPR2 Germline Mutation in Chronic Thromboembolic Pulmonary Hypertension

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Received: 15 December 2013 / Accepted: 21 March 2014 / Published online: 13 April 2014

Abstract
Introduction Heterozygous germline mutations of the bone morphogenetic protein type II receptor (BMPR2) gene *BMPR2* are the most important predisposing factors for heritable pulmonary arterial hypertension. *BMPR2* mutation was occasionally reported in pulmonary veno-occlusive disease, appetite suppressant-related pulmonary arterial hypertension (PAH), and PAH with congenital heart disease.
Materials and Methods In this study we identified a missense mutation (c.2296A > G) located in *BMPR2* exon 12 in a patient with chronic thromboembolic pulmonary hypertension (CTEPH).
Conclusion It is the first report of a *BMPR2* mutation in CTEPH. Our study provides innovative insight into etiology of CTEPH. The genetic predisposing factor is an important component in the process of this CTEPH patient.

Drs Yu-Xuan Feng and Dong Liu contributed equally to this study.

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Keywords Bone morphogenetic protein receptor 2 · Gene mutation · Chronic thromboembolic pulmonary hypertension

Chronic thromboembolic pulmonary hypertension (CTEPH) is an important cause of pulmonary hypertension that is commonly considered to be the consequence of acute pulmonary embolic disease [1]. Following an acute event, unresolved residual thrombus becomes organized and fibrosed, leading to ongoing obstruction to pulmonary blood flow and progressive pulmonary hypertension, right ventricular dysfunction, and death [2].

Heterozygous germline mutations of *BMPR2* are the most important predisposing factors for heritable pulmonary arterial hypertension (HPAH). *BMPR2* mutation was occasionally reported in pulmonary veno-occlusive disease (PVOD) [3], appetite suppressant-related PAH [4], and PAH with congenital heart disease [5]. In this study we identified a missense mutation (c.2296A > G) located in *BMPR2* exon 12 in a patient with CTEPH. This is the first report of a *BMPR2* mutation in CTEPH. The genetic predisposing factor is an important component in the process of this CTEPH patient.

Case Report

A 29-year-old female complained of progressive shortness of breath and chest tightness on exertion over 6 years. Past medical history consisted of an acute pulmonary embolism 6 years prior and an appendectomy. Physical examination revealed elevated jugular venous pressure, wet rale from the bottom of the left lung, a prominent second heart sound, and grade 3/6 systolic murmur in the tricuspid area. Serology for collagen vascular disease was negative. A

chest radiograph showed the right atrium and ventricular enlargement and dilated main pulmonary arteries. The cardiothoracic ratio was 0.67 (Fig. 1). Lung perfusion scanning revealed multiple, bilateral perfusion defects of the blood with only about 34.65 % perfusion in the left lung. Right heart catheterization demonstrated a mean pulmonary arterial pressure of 46 mmHg, mean pulmonary capillary wedge pressure of 9 mmHg, cardiac output of 3.08 L/min, pulmonary vascular resistance of 12.01 Wood units, and the negative response to the acute vasodilator drug testing after inhaling iloprost. Pulmonary angiography revealed multiple stenoses from the beginning of the bilateral segment, and subsegmental arteries scattered perfusion defects in peripheral vessels (Fig. 2). After undergoing a series of examinations, the patient was diagnosed with CTEPH and was treated with sildenafil and beraprost to reduce the pulmonary hypertension and with warfarin for anticoagulation. Unfortunately, the patient died of right heart failure 3 years later.

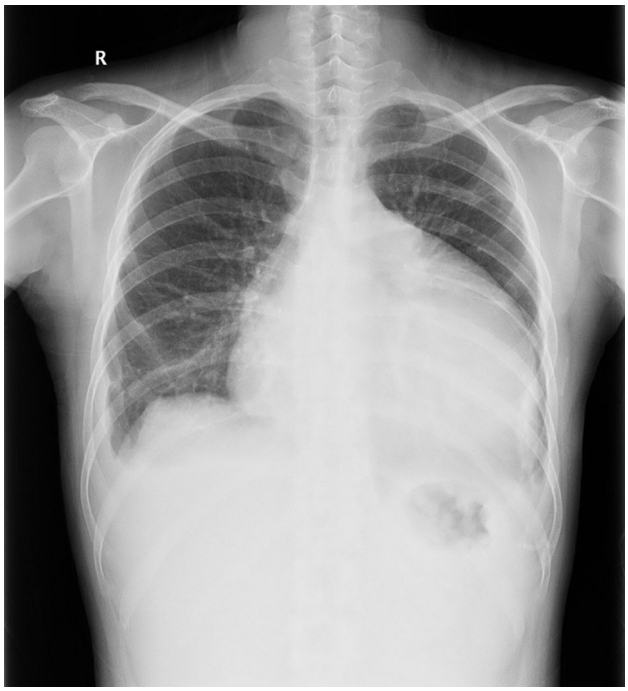

Fig. 1 Chest X-ray of patient shows the enlarged right atrium and ventricular and dilated main pulmonary arteries. Cardiothoracic ratio was 0.67

Molecular Methods

The patient gave her written informed consent for genetic analyses prior to participation. The study was approved by the Ethics Committee of Shanghai Pulmonary Hospital (k10–036). Direct screening using an ABI 3730 (Applied Biosystems, Foster City, CA, USA) was adopted to detect the point mutations in the coding regions and intron/exon boundaries of *BMPR2*. Genomic DNA was isolated from peripheral blood leukocytes. Fifteen pairs of PCR primers were designed to amplify 13 exons and the 5′, 3′ untranslated region of the *BMPR2* gene [6]. The results were compared with the reference sequence of the *BMPR2* gene (accession No. NM-001204.5) using the ABI SeqScape software ver. 2.5 (Applied Biosystems). The mutation nomenclature followed current guidelines as recommended by the Human Genome Variation Society (http://www.hgvs.org/mutnomen/). The mutation numbering employed in this report is based on the cDNA sequence, where +1 designates the A of the ATG initiation codon (Fig. 3).

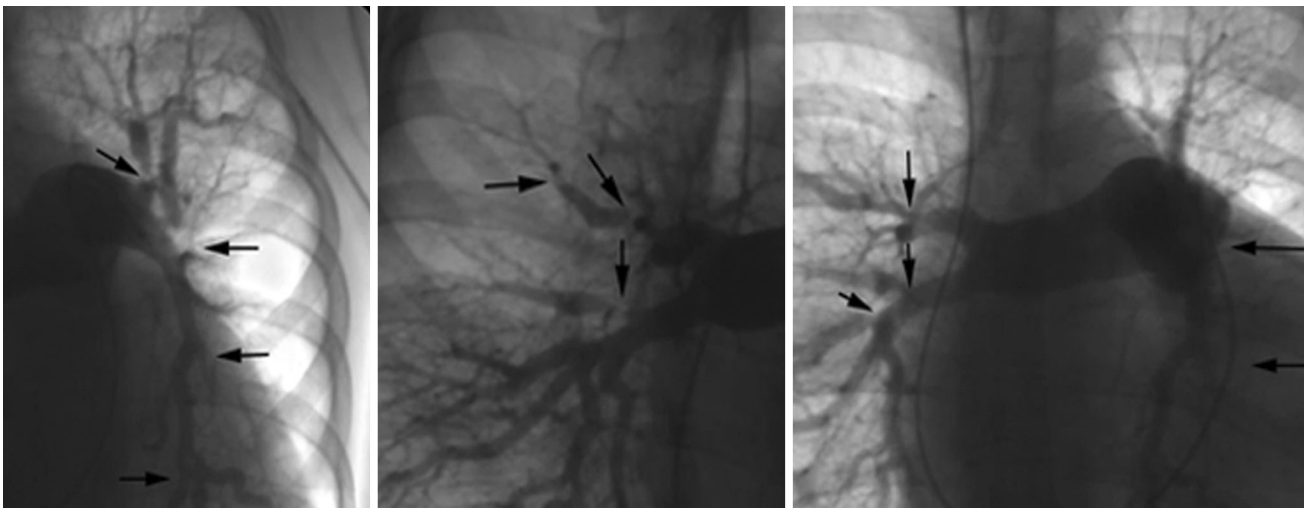

Fig. 2 Pulmonary angiographies of the patient in different positions reveal multiple stenoses from the beginning of the bilateral segment and subsegmental arteries (*arrows*) scattered perfusion defects in peripheral vessels

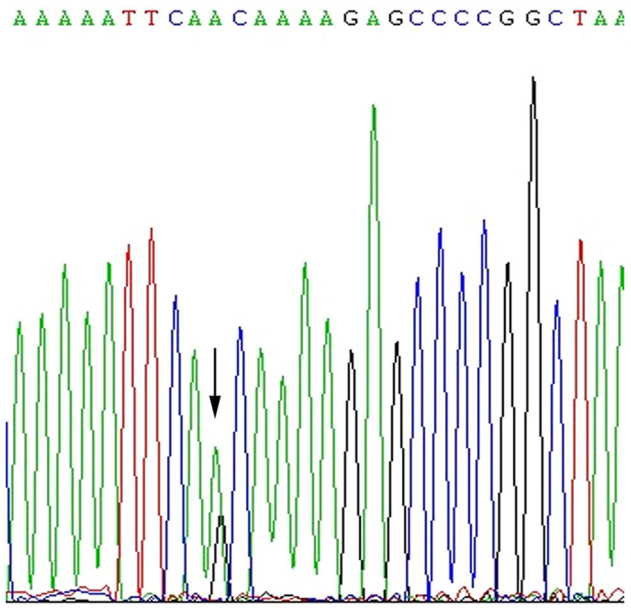

Fig. 3 Sequencing analysis of PCR product indicated a variation (A → T change) at codon 766 in exon 12 of the *BMPR2* gene in the patient

Discussion

Although a number of *BMPR2* mutations have been reported in a variety of diseases, mutation in CTEPH has not been previously studied. Our study provides innovative insight into etiology of CTEPH. The early onset and fast progress of CTEPH in this patient indicates the damaging effect of this variant.

The patient in our study had an acute pulmonary embolism 6 years before diagnosis of CTEPH. Her *BMPR2* mutation may be a genetic risk factor in triggering the onset of the disease. The patient's age at diagnosis was 29 years old, about 20 years younger than the average age of the patients in Pengo's study [7], and she died 3 years after CTEPH confirmation. *BMPR2* mutation may play an important role in the early onset of the disease and accelerated her pulmonary artery occlusion.

BMPR2 encodes the protein BMPR II, a member of the transforming growth factor-β (TGF-β) cell signaling superfamily, which is a constitutively active serine/threonine receptor kinase whose downstream signaling has profound effects on developmental processes, including vasculogenesis [8]. Mutations of *BMPR2* result in down-regulation Smad signaling in pulmonary arterial smooth muscle cells, with resultant loss of the antiproliferative effect. The imbalance of proproliferative and antiapoptotic effects promotes the development of PAH [9]. Exon 12 is the largest exon of the gene and forms part of the intracytoplasmic tail domain which is important for interactions of BMPR-II with β-actin. It has been previously demonstrated that a missense mutation or a truncated mutation in exon 12 decreases activity to phosphorylate the protein cofilin and inhibits the interaction with downstream mediators of BMPR-II signaling, e.g., Smad1 and $P38^{MAPK}$ [9, 10]. In this patient, unresolved thrombus combined with *BMPR2* mutation may contribute to the elevated pulmonary vascular resistance and accelerated the progress of the disease.

Although our study is the first report that identifies the *BMPR2* mutation in CTEPH, a larger number of patients is needed to access the mutation rate and to define the role of the *BMPR2* mutation in the pathogenesis of CTEPH.

Conflict of interest ZCJ has relationships with drug companies, including Actelion, Bayer Schering, Pfizer, and United Therapeutics, in addition to being an investigator in trials sponsored by these companies; relationships include consultancy services and membership of scientific advisory boards. None of the other authors has any conflict of interest to declare regarding the content of this article.

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