Nonsyndromic Peripheral Pulmonary Artery Stenosis Is Associated With Homozygosity of \textit{RNF213} p.Arg4810Lys Regardless of Co-occurrence of Moyamoya Disease

Sung-A Chang, MD, PhD; Ju Sun Song, MD; Taek Kyu Park, MD; Jeong Hoon Yang, MD, PhD; Woo Chan Kwon, MD; So Ree Kim, MD; Sung Mok Kim, MD, PhD; Jihoon Cha, MD, PhD; Shin Yi Jang, PhD; Young Seok Cho, MD, PhD; Tae Jung Kim, MD, PhD; Oh Young Bang, MD, PhD; Jin Young Song, MD, PhD; Chang-Seok Ki, MD, PhD; and Duk-Kyung Kim, MD, PhD

**BACKGROUND:** Peripheral pulmonary arterial stenosis (PPAS) in childhood is frequently associated with other syndromes; however, PPAS in adolescents and adults is rare and its etiology is not well understood. We report the clinical characteristics of adult-onset non-syndromic PPAS associated with the p.Arg4810Lys variant of the \textit{RNF213} gene.

**METHODS:** We recently encountered an index case of severe pulmonary hypertension with multiple PPAS and intra- and extracranial arteriopathy. Because of a family history of Moyamoya disease (MMD), genetic analysis was performed, and revealed that this patient was homozygous for \textit{RNF213} p.Arg4810Lys. We searched for PPAS by reviewing the pulmonary hypertension registry and the MMD registry, and found four more cases of PPAS. Clinical features of the five patients and their families were analyzed.

**RESULTS:** Mean age at diagnosis of pulmonary hypertension was 26 years, and the male to female ratio was 4:1. Genetic analysis of four patients revealed that all these patients were homozygous for the \textit{RNF213} p.Arg4810Lys variant. Pulmonary angiograms showed a string of beads pattern and/or diffuse stenosis of peripheral pulmonary arteries. Notably, three patients had MMD, whereas two patients did not. The three MMD patients had multiple stenoses of extracranial arteries other than the pulmonary artery.

**CONCLUSIONS:** PPAS in segmental or subsegmental arteries in adulthood with multiple extracranial vasculopathies was found to be associated with homozygosity for \textit{RNF213} p.Arg4810Lys. \textit{RNF213} variant-associated vasculopathy should be categorized as a discrete disease entity of adulthood-onset PPAS regardless of the presence of MMD.

**KEY WORDS:** homozygote; Moyamoya disease; peripheral pulmonary arterial stenosis; pulmonary hypertension

**ABBREVIATIONS:** MRA = magnetic resonance angiography; MMD = Moyamoya disease; PAH = pulmonary arterial hypertension; PPAS = peripheral pulmonary arterial stenosis

**AFFILIATIONS:** From the Division of Cardiology, Department of Medicine, Heart Vascular Stroke Institute (Drs Chang, Park, Yang, Kwon, S. R. Kim, Jang, and D.-K. Kim); the Departments of Laboratory Medicine and Genetics (Drs J. S. Song and Kí); the Departments of Radiology, Heart Vascular Stroke Institute (Drs S. M. Kim, Cha, and T. J. Kim); the Departments of Nuclear Medicine and Molecular Imaging (Dr Cho); the Departments of Neurology, Heart Vascular Stroke Institute (Dr Bang); and the Departments of Pediatrics, Heart Vascular Stroke Institute (Dr J. Y. Song), Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea.

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Peripheral pulmonary arterial stenosis (PPAS) is usually found in pediatric patients with associated congenital anomalies or chromosomal syndromes, including Williams syndrome, Noonan syndrome, and Allagile syndrome. In adulthood, PPAS is rarer than in childhood, and most cases affect the main and lobar arteries, and occasionally produce right ventricular failure with severe pulmonary hypertension.

Moyamoya disease (MMD) is a genetic disease that affects the cerebrovascular arteries because of progressive occlusion with intimal hyperplasia of vascular smooth muscle cells and luminal thrombosis. Reduced blood flow to the cerebral artery stimulates the collateral small vessels, which appear as puffs of smoke on cerebral angiography. The p.Arg4810Lys variant (rs112735431) of RNF213 on chromosome 17q25.3 has been identified as a susceptibility variant for MMD.

Materials and Methods

Participants

Because the index case had PPAS, MMD, and was homozygous for RNF213 p.Arg4810Lys, we reviewed the pulmonary hypertension registry in our pulmonary hypertension clinic (Samsung Medical Center, Seoul, Korea) and found three more patients with an undiagnosed cause of severe pulmonary hypertension and unusual pulmonary angiography results showing PPAS. Next, in light of a possible link between the RNF213 variant and PPAS, we reviewed patients in the MMD registry and searched for right ventricular hypertrophy or pulmonary hypertension in 1,195 ECGs or 219 patients in the MMD registry and found four more cases of PPAS. Here, we describe PPAS with a string of beads pattern and/or diffuse stenosis of peripheral pulmonary arteries that develops during adolescence and adulthood related to homozygosity for the RNF213 gene. This form of PPAS can occur independently of MMD.

Identification of the RNF213 p.Arg4810Lys Variant

After obtaining informed consent, genomic DNA was extracted from peripheral blood leukocytes using a Wizard Genomic DNA Purification kit (Promega) following the manufacturer’s instructions. The c.14429G>A (p.Arg4810Lys) variant of the RNF213 gene (GenBank accession No.: NM_001256071.2) was amplified using primer sets designed by the authors (available on request). Polymerase chain reaction was performed with a thermal cycler (model Verti; Applied Biosystems), and direct sequencing was performed with a Big-Dye Terminator Cycle Sequencing Ready Reaction kit (Applied Biosystems) on an ABI Prism 3730xl genetic analyzer (Applied Biosystems).

Imaging Studies

Transthoracic echocardiography, lung perfusion scan, right heart catheterization, chest CT scan, and pulmonary angiography were performed in all patients. CT angiography of the coronary artery and the aorta was obtained for the three patients who were alive at the time of the study. Brain MRI scan with magnetic resonance angiography (MRA) was reviewed.

Family Study

The pedigree of the patients was acquired except for the deceased patients (cases 2 and 5). Family history of MMD, pulmonary hypertension, cerebral vascular disease, and other vascular disease was reviewed. Peripheral blood from parents, siblings, and children was sampled when available with written informed consent. Heterozygous family members were evaluated for the presence of intra- and extracranial arteriopathy, including PPAS. Transcranial echocardiography, CT angiography of the coronary artery and the aorta, and brain MRI scan and MRA were performed.

Results

Clinical characteristics, hemodynamic data, and vascular involvement of multiple organs and presence of the RNF213 p.Arg4810Lys variant in the five patients are summarized in Tables 1 to 3. Mean age at diagnosis of pulmonary hypertension was 26 years (range, 13-36 years). Four patients were men. The follow-up duration of pulmonary hypertension was < 11 years. World Health Organization functional class at diagnosis was II or III. On physical examination, bruits across all the lung fields were noticed in three patients (cases 1, 2, and 3). Their presumptive diagnosis of pulmonary hypertension was chronic thromboembolic pulmonary
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