Genetic alterations in bone morphogenic protein receptor 2 in Polish patients diagnosed with idiopathic pulmonary arterial hypertension

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INTRODUCTION

Pulmonary arterial hypertension (PAH) is a rare vascular disorder characterized by structural changes in the pulmonary vessels and elevated pressure in the pulmonary artery, leading to right ventricular hypertrophy and right heart failure [1–3]. Idiopathic PAH (IPAH) is diagnosed by excluding other potential causes of pulmonary hypertension. The most commonly mutated gene in PAH codes the bone morphogenic protein receptor 2 (BMPR2), a transmembrane receptor involved in cell-specific BMP signaling [4, 5]. In this study, we present the first comprehensive analysis of BMPR2 gene alterations in Polish patients diagnosed with IPAH.

METHODS

Patients

We recruited consecutive patients with IPAH between June 2009 and June 2020. Eligible participants had precapillary pulmonary hypertension defined by a pulmonary vascular resistance (PVR) >3 Wood units (WU) and a mean pulmonary artery pressure (mPAP) >25 mm Hg, in the absence of other known causes of precapillary pulmonary hypertension. All enrolled participants provided written informed consent. The study protocol was approved by the Bioethics Committee of the Jagiellonian University (approval No. 122.6120.125.2016).

At baseline, we collected demographic, clinical, and hemodynamic data including World Health Organization functional class (WHO FC), 6-minute walk distance, N-terminal pro-B-type natriuretic peptide (NT-proBNP), mPAP, right atrial pressure, pulmonary arterial wedge pressure, cardiac output, and PVR [6]. Patients with no detectable genetic variants served as the control group. Genomic DNA was extracted from whole blood using the Maxwell 16 LEV Blood DNA Kit (Promega, Madison, WI, US). Quality was assessed with the TapeStation 2200 (Agilent, Santa Clara, CA, US), with all samples showing a DNA Integrity Number >7. Concentration was measured using a NanoDrop 2000 spectrophotometer. Large genomic rearrangements in BMPR2 were detected using the SALSA multiplex ligation-dependent probe amplification P093-C2 HHT/HPAH Probemix and Reagent Kit (MRC-Holland, Amsterdam, Netherlands), with 100 ng DNA per reaction; healthy donor DNA served as reference. Libraries were prepared with the SureSelect XT Low Input Target Enrichment system (Agilent) and sequenced on an Illumina NextSeq 500 (v2.5 kit, 2 × 150 bp). Variants were evaluated using MutationTaster [7], which applies a Bayes classifier based on HGMD Professional and the 1000 Genomes Project (D — disease-causing, A — automatic disease-causing, N — benign polymorphism, P — automatic benign polymorphism). Variants classified as A or D were

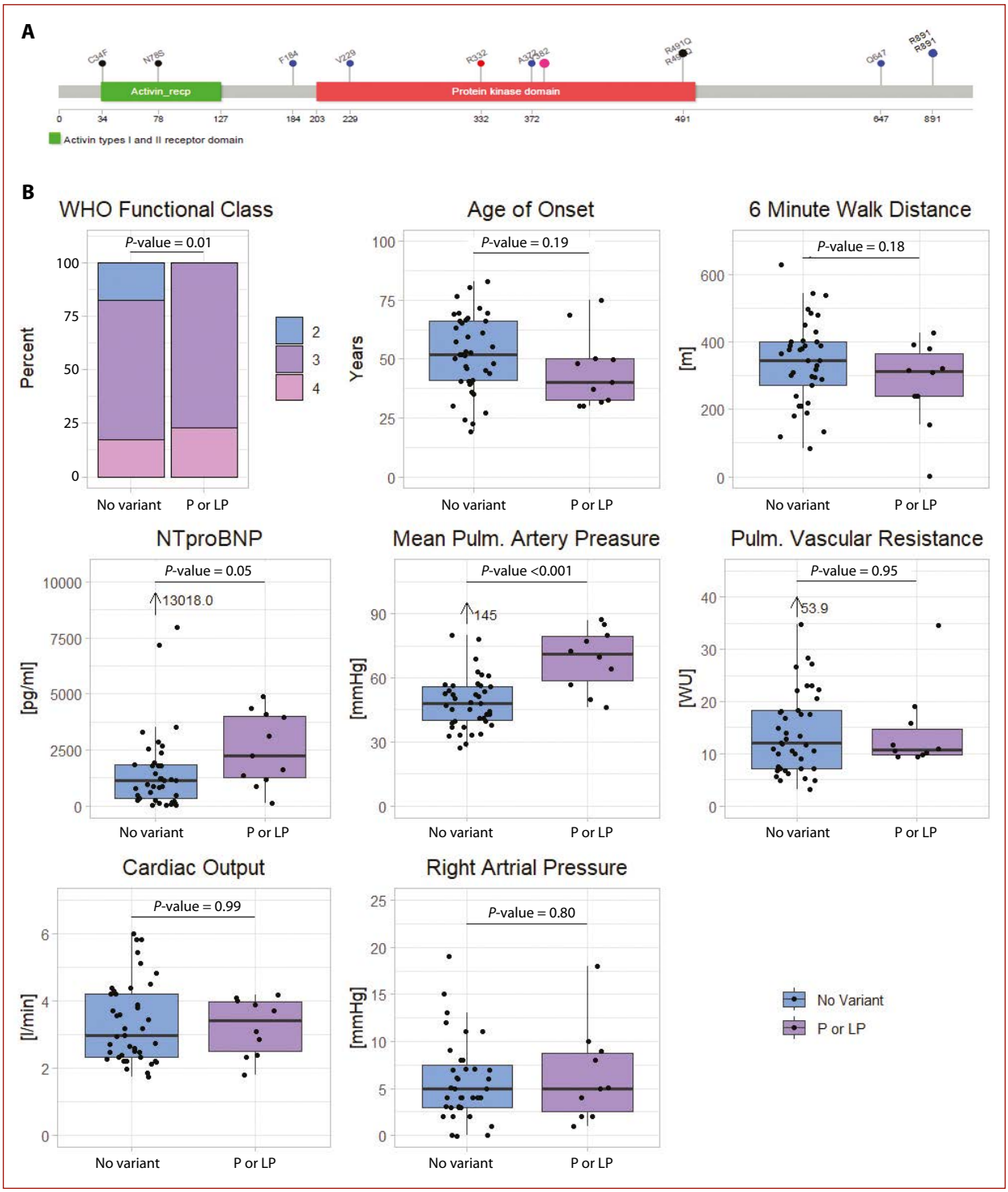

Figure 1. A. Predicted effects of genetic variants on BMPR2 amino acid alterations in the study population. Variant locations and corresponding amino acid changes are shown on a linear representation of the BMPR2 protein, with functional domains indicated. The figure was generated using lollipops [13]. Each 'lollipop' represents an affected amino acid; color indicates the type of alteration (black — missense, blue — frameshift, red — stop gain, pink — homozygous stop gain); lollipop height reflects the number of affected individuals. **B.** Clinical characteristics of patients with pathogenic or likely pathogenic BMPR2 variants compared to controls

Abbreviations: BMPR2, bone morphogenic protein receptor 2; NT-proBNP, N-terminal pro-B-type natriuretic peptide; P or LP – pathogenic or likely pathogenic

further assessed using the ACMG Guidelines [8] *via* the Franklin (Genoox, Palo Alto, CA, US) platform and classified into 'pathogenic', 'likely pathogenic', 'variant of unknown significance', 'likely benign', and 'benign'[8].

Statistical analysis

Categorical variables were presented as counts (percentages) while continuous variables as medians and interquartile ranges. To assess differences in continuous and categorical variables between the two groups, we used the Mann–Whitney U test and χ^2 test, respectively. The significance level was set at $P < 0.05$. Statistical analyses were conducted in the R software environment.

RESULTS

We enrolled 93 Caucasian IPAH patients (69.9% female; mean age 53 years, range 41–69), most in advanced WHO FC (III: 62.4%, IV: 24.7%). Median NT-proBNP was 1236 (462––3161) pg/ml, 6-minute walk distance 319.0 (210.7–400.0) m, mPAP 55.0 (44.2–71.2) mm Hg, right atrial pressure 5.0 (3.0–9.0) mm Hg, pulmonary arterial wedge pressure 8.0 (5.0–10.2) mm Hg, cardiac output 3.25 (2.46–4.35) l/min, and PVR 11.0 (7.2–17.9) WU.

We identified 10 distinct BMPR2 variants in 12 individuals (12.9% of the cohort), including 2 pathogenic, 6 likely pathogenic, and 1 variant of unknown significance. One additional variant had varying classification, depending on the pedigree information (patients 835, 269). Three variants (likely pathogenic) in 4 patients (10, 44, 608, 3273) were not previously reported. Detailed characteristics of variants are presented in Supplementary material, *Table S1*. No large genomic rearrangements were detected by multiplex ligation-dependent probe amplification.

As shown in Figure 1 and Supplementary material, *Table S2*, at the time of diagnosis patients with pathogenic or likely pathogenic BMPR2 variants had higher WHO FC, mPAP, and NT-proBNP levels than controls (n = 44).

DISCUSSION

The frequency of genetic variants in our study is consistent with other large PAH cohorts, where BMPR2 mutations were found in around 15% of sporadic PAH cases [9, 10]. The differences in clinical presentation of patients with BMPR2 mutations vs. no variant carriers were also described by other groups. For example, Evans et al. [11] reported that BMPR2 mutation carriers were, on average, 6 years younger at diagnosis and had higher mean pulmonary artery pressure, increased pulmonary vascular resistance, and reduced cardiac output.

Over 380 BMPR2 variants have been identified so far, mostly frameshift and nonsense mutations leading to truncated proteins or nonsense-mediated mRNA decay [12, 13]. We identified one novel variant of that kind, a frameshift in the kinase domain in patient 10. Additionally, we found novel frameshift mutations in the cytoplasmic tail of BMPR2 (patients 44 and 608), potentially disrupting SMAD-independent signaling without affecting the canonical pathway [13], and a missense alteration in the kinase domain (patient 3273), impairing membrane trafficking without reducing protein levels.

In conclusion, our findings align with studies in other IPAH populations, confirming the significant role of BMPR2 mutations in PAH and expanding the catalog of novel BMPR2 variants.

Supplementary material

Supplementary material is available at https://journals.viamedica.pl/polish_heart_journal.

Article information

Conflict of interest: None.

Declaration of artificial intelligence use: Nothing to disclose.

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