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Identification of Novel Genetic Variants in Pulmonary Arterial Hypertension through Whole Exome Sequencing in a Korean Population

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Pulmonary arterial hypertension (PAH) is a rare disease that affects 15 to 50 people per million and is characterized by narrowing, thickening, or hardening of the pulmonary arteries. These pathological changes disrupt blood flow to the lungs and increase pressure within the pulmonary arteries. Advances in research have led to the development of new drug treatments, such as those targeting the BMPR2 gene, but these treatments neither provide definitive cures nor are they tailored to non-Caucasian populations. Therefore, we cannot completely explain PAH patients in Korea. Known genetic variants, such as BMPR2 and EIF2AK4, do not explain the cause in many patients, leading to the search for new pathogenic variants that contribute to PAH.

In this study, we analyzed whole exome sequencing (WES) data from 89 Korean PAH patients using gene burden analysis. To focus on novel variant discovery, we excluded 13 samples with known pathogenic variants and another 10 samples from 18 related pairs to ensure accurate gene burden calculations. Subsequent downstream analyzes utilized 66 samples.

We identified GeneA and GeneB as significant genes using two distinct approaches: control-free methodology and case-control comparison. These genes demonstrated significance in no-control tests and had the lowest p-values in case-control comparisons. Variants detected within these genes showed high expression in arteries, endothelium, and lung, representing potential novel causative genes for PAH. Additionally, we will use MetaSVM and alphamissesne and primateAI-3D scores. So we will compare the new deleteriousness scores and describe the deleteriousness of novel pathogenic variants.