2024 Pulmonary Vascular Disease Award, funded in part by Johnson & Johnson

Providers Involved: Kali Hopkins, MD (graduated ACHD fellowship in 2024) and Maria Trivieri, MD (Medical director of the Pulmonary Hypertension Program at Mount Sinai)

Title: ***Investigating the Genes Involved in Pulmonary Arterial Hypertension in Congenital Heart Disease, Continued***

Heart defects are the most common type of birth defect, affecting up to 1% of the population worldwide. Congenital heart disease (CHD) can manifest in a variety of ways, ranging from simple lesions to complex defects that require major surgeries. Advances in pediatric cardiology and cardiac surgery have provided extraordinary opportunities for children with severe CHD, with the majority now surviving into adulthood. However, a major long-term complication of CHD that is still prevalent today is pulmonary arterial hypertension (PAH).

PAH is a progressive disease characterized by chronically elevated blood pressure in the pulmonary vasculature leading to right ventricular hypertrophy, heart failure, and premature death. PAH can occur in patients with repaired or unrepaired CHD, and studies have shown that as much as 10% of adult CHD patients are at risk. PAH usually results from increased blood volume or high-pressure blood flow in the lungs most commonly due to ventricular septal defects (VSD), atrial septal defects (ASD), or patent ductus arteriosus (PDA). Over time, this leads to changes in the vessel walls that result in PAH. PAH is a significant burden for patients, with common symptoms being shortness of breath, chest pain, and exercise intolerance. PAH can be a debilitating and life-shortening condition, which highlights the importance of further research to improve patient outcomes.

In recent years, there have been great strides in the understanding of the genetic basis of PAH. However, the genetic basis of PAH in patients with CHD is not well understood. Our research project aims to identify and characterize genetic mutations in patients with CHD and PAH, which could have a significant impact on predicting the long-term prognosis of patients with CHD by guiding diagnostic testing and treatment. This could improve the quality of life of patients with CHD and potentially extend their lifespan.

PAH is a severe complication associated with CHD that is a significant source of morbidity and mortality. The genetic basis of PAH in patients with CHD has not been comprehensively studied to date, and it remains unclear if specific genetic mutations contribute to the pathogenesis of this disease.

Note: This is an extension of last year's research. More background and results:

The continuation of this project focuses on continuing to better understand the genetics of PAH in patients with CHD. Our first step was to conduct a genome-wide association study using the PAHBiobank housed in Cincinnati. The Biobank is a rich repository of genotypic and phenotypic data for patients with Group 1 pulmonary hypertension consisting of approximately 2,400 subjects. We identified 87 subjects with PAH and atrial septal defects and PAH and 2,193 control subjects. The genome-wide association study yielded a handful of rare variants with statistical significance for potential association with the two disorders but could not be confirmed using additional biobanks. The biggest roadblock with this methodology is the small number of subjects and controls due to the rarity of the disorder.

Our next step was to conduct a polygenic risk score (PRS) using data from a pooled genome-wide association study of participants with PAH. We created the PRS and tested it using the UK Biobank to see if we could predict which participant with an atrial septal defect would develop PAH. Similar to our first methodology, the predictive power has been limited by the small number of subjects with the disease, even in a 500,000-participant biobank like the UK Biobank. We are now identifying continuous variables of participants in the UK Biobank to enhance the predictive power of the PRS.

Due to the rarity of PAH in general and even more so for those with CHD, these typical genetic methodologies are limited. We would therefore like to pivot our project to do a deeper dive into fewer cases. With this additional funding, we plan to start a biobank with patients at Mount Sinai Hospital with CHD and associated PAH. We plan to also include family members with or without similar disease states up to two generations away. We would perform genomic sequencing, including DNA, RNA, miRNA, and proteins, along with deep phenotypic data analysis. This would allow for a more Mendelian genetics analysis and potentially identify genes in specific families. While further down the line, our eventual goal would be to include participants from other institutions as a first of its kind familial biobank for PAH and CHD.