Journal of the Hong Kong College of Cardiology

Volume 29 | Issue 3 Article 1

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Recommended Citation

Kin Shing Lun, Understanding the Genotypes and Phenotypes Relationship: Progress toward a Precision Medicine Approach in Pediatric Pulmonary Hypertension *Journal of the Hong Kong College of Cardiology* 2022;29(3):100-101 https://doi.org/10.55503/2790-6744.1474

EDITORIAL

Understanding the Genotypes and Phenotypes Relationship: Progress toward a Precision Medicine Approach in Pediatric Pulmonary Hypertension

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Advances in DNA sequencing technology have facilitated genomic studies in families and large cohorts of patients. Insights from human genetics are increasing our knowledge of the pathobiology of pulmonary arterial hypertension and significantly impacting our therapeutic approach to patients with different genetic subtypes [1]. The article authored by Dr Zhuoyuan Xu et al. [2] in this issue suggested that there is a need for early genetic diagnosis and individualized pulmonary hypertension targeted management in childhood-onset pulmonary arterial hypertension. Dr Xu's hospital is a nationwide tertiary referral centre for the management of pediatric pulmonary hypertension. Their study is probably one of the largest genetic studies of childhood-onset idiopathic pulmonary arterial hypertension in China. It is impressive to note that they recruited 114 patients within a study period of twelve years. Pediatric pulmonary hypertension has been vastly understudied relative to adult-onset pulmonary arterial hypertension, and there is inadequate information on the natural history of diseases with different genetic mutations. We anticipate that more studies will be performed on pediatric pulmonary arterial hypertension to improve our knowledge. In their cohort, Dr Xu's group had shown the worst outcome of patients with ACVRL1 mutation. If further studies have also demonstrated poor prognosis in these patients, then aggressive early combination targeted pulmonary vascular medical therapy is indicated to slow down or halt the disease. Early intervention such as reversed Pott shunt or lung transplantation is required for those not responsive to aggressive medical therapy [3]. Understanding the genotypes and phenotypes is the step toward individualized and precision approaches to managing pediatric pulmonary arterial hypertension. This approach is essential because the prognosis of pediatric idiopathic pulmonary arterial hypertension is even worse than that of adults. Dr Xu commented that the mortality remained significant despite significant advances in management in their cohort.

Emerging data from genetic studies indicate that the genetic basis in children differs from that of adults. All the data suggest that the diagnostic yield of genetic testing is incredibly high for pediatric pulmonary arterial hypertension, approaching 50% [4]. Xu et al. [2] reported an even higher diagnostic yield of 64%. The frequency of ACVRL1 and ENG mutation of 8% in their study is higher than the frequency of 1% among pediatric idiopathic pulmonary arterial hypertension cases of European ancestry [5]. Further studies are needed to determine whether these differences are true genetic ancestry effects or random differences due to relative small sample size.

Knowledge of genetic diagnoses can promptly influence clinical management of pediatric pulmonary arterial hypertension, including screening of associated conditions, multimodal medical treatment, and early surgical intervention decisions. For instance, ACVRL1/ENG variant carriers with hereditary hemorrhagic telangiectasia are at risk of arteriovenous malformations in the brain, liver and lung. Periodic MRI surveillance is required for these patients. Biallelic mutations in

Received 29 July 2022; accepted 5 August 2022.
Available online 23 September 2022
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https://doi.org/10.55503/2790-6744.1474

EIF2AK4 are diagnostic for pulmonary veno-occlusive disease/pulmonary capillary hemangiomatosis without requiring a highly risky lung biopsy. Early listing for lung transplantation might improve outcomes. A genetic diagnosis can lead to cascade genetic testing of family members to identify those at risk for developing pulmonary arterial hypertension. Therefore, genetic testing of childhood-onset idiopathic pulmonary arterial hypertension is becoming more routine, and Dr Xu's article also highlighted the need for early genetic diagnosis. Many centres now perform analysis of child-parent trio to increase the diagnostic yield of exome sequencing.

Although there are significant advances in DNA sequencing technology, what we know is really the tip of the iceberg. Apart from genetic variants, epigenetic and environmental factors also modify the clinical presentation. There is a need for large international consortia to identify additional genetic variants, evaluate penetrance, and understand the clinical course, prognosis, and response to various therapies in patients with different genetic mutations.

Ethics information

Not applicable.

Funding

None.

Conflict of interest

None.

Acknowledgement

None.

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