Pulmonary Arterial Hypertension: molecular findings in a group of patients referred for NGS Panel Testing

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Introduction

- Pulmonary arterial hypertension (PAH) leads to increased pulmonary vascular pressures and resistance, as well as right ventricular failure.
- Genetic testing can provide prognostic and management information for patients; it can also identify at risk relatives who need surveillance.
- The yield of this testing is ~10% to 30% in clinical cohorts.[1]
- We describe the findings in a group of PAH patients (defined with heterogeneous inclusion criteria) to provide further support for genetic testing in the PAH patient population.

Methods

- We conducted a retrospective review of patients with a suspected or confirmed diagnosis of PAH tested using a PAH next generation sequencing (NGS) panel at Blueprint Genetics. All patients had a suspected or confirmed PAH diagnosis per the information provided on the test requisition.
- Testing included both sequencing and copy number variant (CNV) analysis for a maximum of 23 genes due to the evolution of panel content (*ABCC8, ACVRL1, AQP1, ATP13A3, BMPR1B, BMPR2, CAV1, EIF2AK4, ENG, FOXF1, GDF2, KCNA5, KCNK3, KLF2, NFU1, NOTCH3, RASA1, SARS2, SMAD4, SMAD9, SOX19, STRA6* and *TBX4),* and up to 28 clinically relevant non-coding variants.
- A diagnostic test result was defined by the identification of pathogenic (P) or likely pathogenic (LP) variant(s), (classified using a modified ACMG/AMP variant classification scheme) consistent with the patient's reported phenotype and known disease inheritance.
- Chi-square analysis was utilized to determine statistical significance where appropriate. A *P*-value <0.05 was considered significant.

One in 5 patients undergoing NGS panel testing for a pulmonary arterial hypertension clinical indication received a **molecular diagnosis.**

23.2% yield in adult patients

18.1% yield in pediatric patients

***P*=0.33**

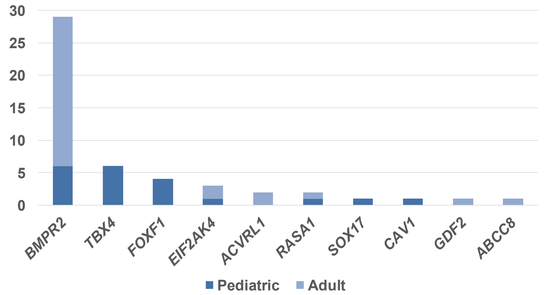
Results

Table: Patient Demographics

Patient Demographics	Number of individuals (n=241)	Proportion of the cohort
Male sex	77	32.0%
Female sex	164	68.0%
Pediatric patients (0-17)	116	48.1%
Adult patients (≥18)	125	51.9%
7-gene panel	3	1.2%
11- or 12-gene panel	72	29.9%
21- or 23-gene panel	166	68.9%

- A diagnostic (sequence or copy number) variant was identified in 20.7% of patients.
- The diagnostic yield was similar in pediatric (<18 years of age) and adult patients: 18.1% (n=21/116) vs 23.2% (29/125) *P*=0.33. However, the distribution of diagnostic variants across genes was different (Figure).
- Diagnostic CNVs were identified in 2.5% of all tested patients and accounted for 11.3% of all diagnostic variants; 50% of diagnostic CNVs were intragenic.

Figure: Distribution of diagnostic variants by gene for pediatric and adult patients



Conclusions

- The genetic findings in this broadly defined cohort are similar to previously reported findings[1] in that:
  - The yield of genetic testing is approximately 20%.
  - The *BMPR2* gene explains the majority of diagnoses.
  - The distribution of causative genes is different in children and adults.
- Unlike other cohorts,[2] the diagnostic yield was similar in children and adults.
- High-resolution CNV capabilities are necessary to maximize the diagnostic yield.

Conflict of interest statement: All authors are employed by Blueprint Genetics.

Blueprint Genetics

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