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Mastering the genetic epidemiology of children with pulmonary arterial hypertension

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Introduction:
Pulmonary arterial hypertension (PAH) is called hereditary PAH (HPAH) when the disease is familial or caused by mutations in genes, known to be associated with PAH. In the majority of adult HPAH patients, the mutated gene is bone morphogenetic protein receptor type 2 (BMPR2). In childhood PAH, T-BOX4 (TBX4) and activin-A-receptor-like-type-1 (ACVRL1) mutations seem to be enriched, suggesting a different genetic architecture in children with PAH compared to adults. In addition, children with PAH have been reported to present frequently with associated syndromes or dysmorphic features. The aim of this study is to describe the genetic epidemiology in a national cohort of children with PAH.

Methods:
From the Dutch National Network for Pediatric Pulmonary Hypertension (1994-2018) we included 84 children diagnosed with idiopathic PAH, HPAH, PAH associated with congenital heart disease group 3 or 4, or PAH associated with other conditions. Patients were tested on gene mutations in BMPR2, ACVRL1, eukaryotic translation initiation factor 2-alpha kinase 4 (EIF2AK4), Caveolin-1 (CAV1), endoglin (ENG), potassium channel subfamily K member 3 (KCNK3), SMAD9 and TBX4 (with targeted next generation sequencing). Single Nucleotide Polymorphisms (SNP)array for detection of chromosomal numerical variations (trisomies, deletions, duplications) was also performed.

Results:
84 children were enrolled in this study. In 66 children (79%) genetic testing was performed. Absence of genetic testing in 18 children (21%) was mainly due to premature death.
22/66 children had a mutation in a known PAH-associated gene: BMPR2=6, TBX4=7, KCNK3=1, EIF2AK4=1; 2 brothers had PAH associated with a Von Hippel Lindau gene mutation; 5 children had a MMACHC-gene mutation associated with Cobalamin C deficiency and pulmonary veno-occlusive disease. 6/66 children had Down’s syndrome. In addition, 20/66 children had genetic variations not known to be associated with PAH. In 18/66 children no genetic variations were found.

Conclusions:
Our results show that in 33% and 30% of the study population a PAH-associated gene mutation and additional genetic variations not known to be associated with PAH were present, respectively. The majority of children with PAH (48/66, 73%) have genetic variations.
These pediatric-specific genetic associations might provide clues for the identification of etiologic mechanisms leading to PAH.