Mutations in pulmonary arterial hypertension genes in children

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Background: Prevalence of germline mutations in the genes associated with pulmonary arterial hypertension (PAH) in childhood-onset PAH is scarcely known.

Objectives: To determine the prevalence of six known genes for heritable PAH gene (BMPR2, ALK-1, ENG, TBX4, KCNQ3 and EIF2AK4) in children with PAH and to describe the clinical characteristics of children harboring mutations.

Methods: Over a period of six years, 71 index cases were included for genetic analysis of PAH genes: idiopathic PAH (n=36); familial PAH defined as one first degree relative with PAH (either one parent or one sibling; 8 families-10 patients- all children were considered index cases as none mutation had been previously identified in the family before inclusion of the case into the study); pulmonary veno-occlusive disease (PVOD; n=2); type 3 PAH associated with congenital heart disease (coincidental CHD) APAH-CHD (n=13); and type 4 (postoperative) APAH-CHD (n=10). All patients with already known or chromosomal anomaly or identified syndrome were excluded from the study.

Results: We found no mutations in children with type 3 and type 4 APAH-CHD. Eight mutations were found in 36 children with iPAH (22%): three in BMPR2, three in ALK1, and two in TBX4. No mutations were identified in ENG, or KCNK3. Four mutations were found in the eight familial PAH families (50%): two in BMPR2, one in ALK1, and one in TBX4. In these four familial forms, only one sibling of an index case with a TBX4 mutation was alive with PAH, and had the same mutation. In the three remaining families, the first-degree relatives who had PAH were all dead at inclusion of the index case into our study with no material available for genetic testing. Finally, we identified mutation in EIF2AK4 in the two patients with clinical, hemodynamic and CT features of PVOD. Outcome of children with mutation and without were similar.

Conclusion: Mutations in the known genes for PAH is either exceptional or absent in children with unusual APAH-CHD. Prevalence of PAH genes mutations is less frequent that in the adult forms of iPAH and familial PAH. Genetic status does not predict outcome in our series.