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TBX4 syndrome: a systemic disease highlighted by pulmonary arterial hypertension in its most severe form

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Thoré and co-workers add to our understanding of TBX4-associated pulmonary vascular disease as a precapillary form of pulmonary hypertension (PH), showing that TBX4 mutations may also cause multisystem anomalies concurrent with, or independent of, PH https://bit.ly/2yIqb9v

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Sometimes we miss the "ah-ha" moment, or, at least require multiple reminders to pay attention. This may have been the case for many of us in the pulmonary vascular field regarding rare variants (mutations) in the gene T-box transcription factor 4 (*TBX4*) and pulmonary hypertension (PH). In 2004, investigators in the Netherlands published the first description of humans with mutations in the T-box transcription factor 4 (*TBX4*) gene. While an interesting manuscript, it undoubtedly created no ripple in the pulmonary vascular disease field, as it described a cohort of individuals with small patella syndrome (SPS) without known cardiopulmonary abnormalities, consistent with prior animal model studies [1, 2]. At that time, SPS was known as a rare autosomal-dominant condition characterised by skeletal dysplasia, including irregular development of the patella and additional anomalies involving the limbs and pelvis. Subsequently, in 2010, geneticists expanded our understanding of the phenotype of subjects with mutations in *TBX4* (and perhaps other loci nearby, including *TBX2*), by describing paediatric cases with a more broadly syndromic condition characterised by variable expression of anomalies, such as skeletal dysplasias (including hand and foot irregularities), developmental delay, hearing loss, congenital heart defects (*e.g.* patent ductus arteriosus, atrial septal defect, aortic valve defects), and PH (no specific PH-related data was provided) [3, 4]. Again, the pulmonary vascular field, current authors included, failed to take notice. Then, in 2013, Kerstjens-Frederikse *et al.* [5], from a paediatric PH specialty centre in the Netherlands, described variations in *TBX4* and surrounding loci in six out of 20 paediatric pulmonary arterial hypertension (PAH) cases associated with syndromic anomalies similar to those previously described in *TBX4* mutants; overall, their data suggested that *TBX4* mutations contribute to the PAH condition in paediatrics. Yet, many in our field retained the impression that *TBX4* mutations were more prominent among children with highly "syndromic" features, and thus associated with a niche subgroup of PH in children.