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The ever-expanding phenotypical spectrum of human TBX4 mutations: from toe to lung

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Since the discovery of the TBX4 gene, the phenotypical spectrum of human TBX4 mutations is rapidly expanding from syndromes with skeletal dysplasia, to pulmonary hypertension to developmental lung diseases, all associated with disrupted organ development http://bit.ly/2MvYful

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Transcription factors of the T-box family are known to be involved in the regulation of embryonic developmental processes. T-box factor 4 (TBX4), one of its members first discovered in 1996, is expressed in a wide variety of tissues during organogenesis [1, 2]. The TBX4 gene is located on chromosome 17, region q23.2 [3]. Most information on TBX4 defects have been obtained from animal models that have revealed that TBX4 plays a critical role, governing multiple processes during early limb and respiratory tract development. Loss of Tbx4 has been shown to block hindlimb and pelvic development, disrupts the development of the respiratory system and affects early embryonic vascularisation [4]. In mice, TBX4 (in concert with TBX5) regulates the process of lung branching by controlling the expression of the secreted fibroblast growth factor (FGF) 10 and activation of FGF10 signalling. Also, in the trachea, TBX4 and TBX5 are important for the formation of cartilage rings, although a distinct pathway that does not involve FGF10 regulates this [5]. The clinical phenotype of TBX4 defects in humans however, has begun only very recently to reveal itself (figure 1).