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Phenotype and outcome of pulmonary arterial hypertension patients carrying a *TBX4* mutation

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PAH due to *TBX4* mutations may occur with or without skeletal abnormalities across a broad age range from birth to late adulthood. PAH is usually severe and associated with parenchymal abnormalities, alveolar and pulmonary vascular remodelling, and low D_{LCO} . <http://bit.ly/38jM37U>

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ABSTRACT

Introduction: *TBX4* mutation causes small patella syndrome (SPS) and/or pulmonary arterial hypertension (PAH). The characteristics and outcomes of PAH associated with *TBX4* mutations are largely unknown.

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Methods: We report the clinical, functional, radiologic, histologic and haemodynamic characteristics and outcomes of heritable PAH patients carrying a *TBX4* mutation from the French pulmonary hypertension (PH) network.

Results: 20 patients were identified in 17 families. They were characterised by a median age at diagnosis of 29 years (0–76 years) and a female to male ratio of three. Most of the patients (70%) were in New York Heart Association (NYHA) functional class III or IV with a severe haemodynamic impairment (median pulmonary vascular resistance (PVR) of 13.6 (6.2–41.8) Wood units). Skeletal signs of SPS were present in 80% of cases. Half of the patients had mild restrictive or obstructive limitation and diffusing capacity of the lung for carbon monoxide (D_{LCO}) was decreased in all patients. High-resolution computed tomography (HRCT) showed bronchial abnormalities, peri-bronchial cysts, mosaic distribution and mediastinal lymphadenopathies. PAH therapy was associated with significant clinical improvement. At follow-up (median 76 months), two patients had died and two had undergone lung transplantation. One-year, three-year and five-year event-free survival rates were 100%, 94% and 83%, respectively. Histologic examination of explanted lungs revealed alveolar growth abnormalities, major pulmonary vascular remodelling similar to that observed in idiopathic pulmonary arterial hypertension (IPAH) and accumulation of cholesterol crystals within the lung parenchyma.

Conclusion: PAH due to *TBX4* mutations may occur with or without skeletal abnormalities across a broad age range from birth to late adulthood. PAH is usually severe and associated with bronchial and parenchymal abnormalities.