Correspondence regarding "T-box protein 4 mutation causing pulmonary arterial hypertension and lung disease": a single-centre case series

To the Editor:

With great interest we read the article "T-box protein 4 mutation causing pulmonary arterial hypertension and lung disease" by Maurac *et al.* [1]. The authors elegantly demonstrated a case of a female *TBX4* mutation carrier presenting with adult-onset pulmonary arterial hypertension (PAH) in combination with bronchial and pulmonary parenchymal abnormalities which could be related to this mutation [1].

This case fits well together with the recent observation made in the French registry of heritable pulmonary hypertension (HPAH) that *TBX4* mutations are frequently found in both adult and paediatric PAH cases [2, 3].

Here, we present data on the currently known *TBX4* mutation carriers in our institute. The cohort consists of three mutation carriers without PAH, one patient with early PAH and four patients with HPAH. In all but one patient, a diagnosis of PAH was made in adulthood. Four different heterozygous variants in *TBX4* were identified in the eight subjects (two families were included in the cohort). All variants were classified as "likely pathogenic" or "pathogenic", including missense mutations (subject 1, 5 and 8) and frameshift mutations (subject 2, 3, 4, 6 and 7). A targeted gene panel was analysed in our cohort using next generation sequencing. Using this technique only small deletions or insertions were detected. To date, it has not been possible to determine the disease penetrance of TBX4 mutations, due to the low number of known carriers of such mutations [4].

The median age at diagnosis of PAH in our cohort was 31 (interquartile range (IQR) 39) years, while carriers without PAH had a median age of 39 (IQR 20) years. Remarkably, all patients were female and all carriers without PAH were male. All subjects, including the carriers without PAH, had skeletal anomalies on clinical examination, including a sandal gap in all and a small patella in one carrier without PAH and two HPAH patients. Subject demographic and clinical characteristics are shown in table 1. Two carriers without PAH were assessed by echocardiography alone, while six subjects underwent at least one right heart catheterisation (RHC) for diagnostic or research purposes (one carrier without PAH). The systolic pulmonary artery pressure on echocardiography was not measurable in two carriers without PAH because no tricuspid insufficiency could be measured. No other signs of PAH were noticed on echocardiography. In the six subjects in whom RHC was performed, elevated mean pulmonary artery pressures (mPAP) (median 44 mmHg, IQR 66.5 mmHg) and pulmonary vascular resistance indices (median 6.2 WU, IQR 15.1 WU) were demonstrated. However, only four out of six subjects met all criteria for a strict diagnosis of PAH based on the current guidelines [5]. One subject had early signs of PAH including a mPAP of 28 mmHg, but PVR did not exceed the threshold of 3 WU (2.4 WU). All four HPAH patients and the early PAH patient were treated with pulmonary hypertension-targeted therapy, predominantly double combination therapy (table 1).

Noticeably, all subjects with HPAH had a medical history of asthma with a mildly reduced forced expiratory volume in 1 s (median 74% of predicted value, IQR 11%). In addition, median diffusing capacity of the lung for carbon monoxide (D_{LCO}) was mildly reduced (65% of the predicted value, IQR

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A single-centre case series of adult subjects with a TBX4 mutation, in whom two distinctive findings on HRCT (*i.e.* tracheal and bronchial diverticulosis; irregular bronchial walls) were observed http://bit.ly/2v3s7HE

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TABLE 1 Patient characteristics and demographics

	Subject 1	Subject 2	Subject 3	Subject 4	Subject 5	Subject 6	Subject 7	Subject 8
Diagnosis	Carrier without PAH	Carrier without PAH	Carrier without PAH	Early PAH	HPAH	HPAH	HPAH	HPAH
Family number	2 : I-2	1 : II-2	1 : II-3	1 : II-1	2: I-1	3 : I-1	1 : I-1	4 : I-1
TBX4 mutation	c.1164dup p.(Arg389fs)	c.1112del p.(Pro371Leufs*8)	c.1112del p.(Pro371Leufs*8)	c.1112del p.(Pro371Leufs*8)	c.1164dup p.(Arg389fs)	c.40_49del p.(Phe14Argfs*28)	c.1112del p.(Pro371Leufs*8)	c.916G>T p.(Glu306*)
Characteristics								
Age at diagnosis years	27	47	39	50	16	31	63	19
Gender	Male	Male	Male	Female	Female[#]	Female	Female	Female
NT-proBNP ng·L^{-1}		24	18	91	109	226	451	1627
Medical history	No	No	No	Asthma	Asthma, colitis ulcerosa	Asthma	Asthma	Asthma
Smoking >1 pack-year	No	No	No	No	No	No	No	No
Sandal Gap	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Small patella	No	Yes	No	No	Yes	No	No	Yes
Pulmonary function test								
FEV_1 %	96	91	100	97	73	75	84	70
FVC %	97	111	107	107	88	84	102	71
FEV_1/VC %	80	67	75	72	72	77	70	87
D_{LCO} %	120	-	99	98	73	58	65	65
Echocardiography								
PASP mmHg	No TI	No TI	24	No TI	51	122	60	130
Signs of PH on echo	None	None	None	Mid-systolic notch PA flow	RV dilation	Mild PE, RV hypertrophy and dilation	RV hypertrophy	RV dilation
Right heart catheterisation								
mPAP mmHg			20	28	45	91	43	97
Cardiac output L·min^{-1}			8.5	6.3	5.5	2.8	5.5	5.3
PVR WU			0.9	2.4	6.9	17.9	5.5	16.9
Wedge pressure mmHg			12	13	7	14	13	7
HRCT	Sporadic tracheal and bronchial diverticulosis, irregular bronchial walls		Sporadic tracheal and bronchial diverticulosis, irregular bronchial walls	Multiple tracheal and bronchial diverticulosis, irregular bronchial walls, air trapping, perifissural nodules	Multiple tracheal and bronchial diverticulosis, irregular bronchial walls, interlobular septal thickening	Multiple tracheal and bronchial diverticulosis, irregular bronchial walls, air trapping, centrilobular ground-glass opacities	Sporadic tracheal and bronchial diverticulosis, irregular bronchial walls, air trapping, small subpleural nodules	Multiple tracheal and bronchial diverticulosis, irregular bronchial walls, air trapping, centrilobular ground-glass opacities
PAH specific treatment				ERA	ERA, PDE5-i	ERA, PDE5-i	ERA, PDE5-i	ERA, PDE5-i, prostacyclin analogue

NT-proBNP: N-terminal pro-brain natriuretic peptide; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; VC: vital capacity; D_{LCO}: diffusing capacity of the lungs for carbon monoxide; PASP: pulmonary artery systolic pressure; PH: pulmonary hypertension; mPAP: mean pulmonary artery pressure; PVR: pulmonary vascular resistance; HRCT: high-resolution computed tomography; PAH: pulmonary arterial hypertension; HPAH: heritable pulmonary hypertension; PA: pulmonary artery; RV: right ventricle; PE: pulmonary effusion; ERA: endothelin receptor antagonist; PDE5-i: phosphodiesterase type 5 inhibitor. [#]: at age of 25 years old start of female-to-male transition. Sporadic diverticulosis is defined as less than five protrusions, multiple diverticulosis is defined as more than five protrusions.

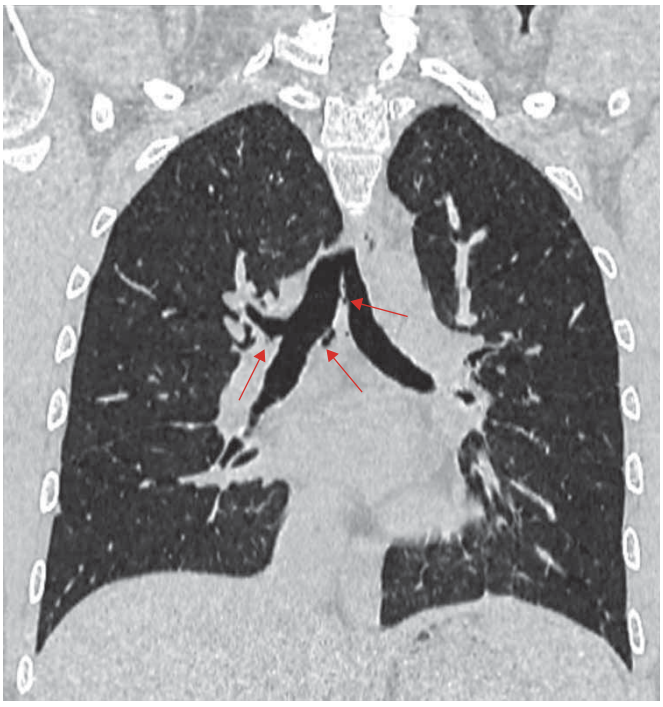

FIGURE 1 Bronchial diverticulosis in a pulmonary arterial hypertension patient carrying a *TBX4* mutation. Coronal image from high-resolution computed tomography with a maximal intensity projection of 2 mm.

11.2%); three out of four HPAH patients had an abnormal D_{LCO} <70%. High-resolution computed tomography was performed in all subjects except one carrier without PAH and showed a spectrum of findings, including air trapping, interlobular septal thickening, centrilobular ground-glass opacities and small nodules. Tracheal and bronchial diverticulosis was found in all subjects, including the carriers without PAH (figure 1). In addition, all subjects showed irregular bronchial walls with changes in calibres predominantly in the (sub)segmental bronchi. Airway abnormalities were milder in carriers without PAH, but there was no relation between extent of airway abnormalities and severity of haemodynamic compromise in patients.

Overall, this small cohort of carriers without PAH and PAH patients carrying a *TBX4* mutation may help to get a better understanding of HPAH. Animal studies have shown that *TBX4* (in concert with TBX5) is important for lung branching and the formation of cartilage rings in the trachea. This may explain the observation that all *TBX4* mutation carriers displayed tracheal diverticulosis and irregularity of the bronchial walls [6]. The lung abnormalities previously observed in *TBX4* mutation carriers form a broad clinical spectrum. Neonatal patients have predominantly severe and diffuse features of growth arrest, including acinar dysplasia, while milder features of bronchial abnormalities, including interstitial remodelling, are more common in patients diagnosed post-neonatally, in childhood or as adults [1, 7–9]. Because airway abnormalities were observed in subjects with no signs of pulmonary hypertension and also because the degree of abnormalities on computed tomography was not correlated to the degree of haemodynamic compromise, it remains to be determined whether pulmonary hypertension in *TBX4* mutation carriers develops as a consequence of airway abnormalities (placing this form of pulmonary hypertension in group 3 of the diagnostic classification). Alternatively, airway and vascular abnormalities in *TBX4* mutation carriers may develop entirely independently.

Further studies are required to better understand phenotypic expression, penetrance (including an apparently much higher penetrance in females) and the optimal treatment approach of *TBX4* associated PAH.

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