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EPAS1 Mutations and Paragangliomas in Cyanotic Congenital Heart Disease

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To the Editor

Pheochromocytomas and paragangliomas are catecholamine-secreting tumors of chromaffin cells with frequent germline, somatic, or postzygotic mutations in genes that are involved in hypoxia-related pathways (including *VHL*, *SDHA*, *SDHB*, *SDHC*, *SDHD*, *SDHAF2*,

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EGLN1, *FH*, *MDH2*, and *EPAS1*).¹ These mutations result in aberrant and constitutive activation of hypoxia-inducible factors (HIFs) even under normal levels of oxygen, a condition known as pseudohypoxia.¹ Beyond genetic causes, prolonged exposure to hypoxia has been reported as an environmental risk factor for pheochromocytomas and paragangliomas that arise in persons living at high altitude.² We previously found that patients who have chronic hypoxemia that is due to cyanotic congenital heart disease were at increased risk for pheochromocytomas and para-gangliomas,³ but the mechanism underlying this association is unclear.

Here we report the identification of gain-of-function somatic mutations of *EPAS1*, which encodes for HIF-2 α , in pheochromocytomas and paragangliomas in four of five patients (80%) who presented with cyanotic congenital heart disease. The clinical and genetic details of the patients are shown in Table 1, and in the Supplementary Appendix (available with the full text of this letter at NEJM.org). The affected residues, 530 and 531, are known to regulate HIF-2 α stability and, when mutant, result in constitutive HIF-2 α activation and tumor growth in vivo.^{4,5}

Given the relatively young age of patients presenting with cyanotic congenital heart disease and pheochromocytomas and paragangliomas, an inherited susceptibility to pheochromocytomas and paragangliomas would be expected to account for most cases.¹ However, no other germline pathogenic mutations or other syndromic tumors that have been associated with pheochromocytomas and paragangliomas were found in these five patients (see the Supplementary Appendix). In contrast, each of the mutations in the present series was somatic. The high frequency of mutations of *EPAS1* in these samples (80%) contrasts with rates of only 5 to 6% in cohorts of unselected patients with pheochromocytomas and paragangliomas,¹ which argues for a causative role for the *EPAS1* mutations in the development of pheochromocytomas and paragangliomas that arise in patients with cyanotic congenital heart disease. These observations, along with the existence of a clear link between pheochromocytomas and paragangliomas with mutations that lead to the activation of HIFs and cellular pseudohypoxia, suggest an exquisite sensitivity of chromaffin cells to HIF-2 α -mediated growth. It is possible that the *EPAS1* mutations endow chromaffin cells that have been exposed to chronic hypoxia with the ability to amplify the oncogenic properties of HIF-2 α .

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Clinical and Biochemical Features of Five Patients Presenting with Cyanotic Congenital Heart Disease and Pheochromocytomas or Paragangliomas (PPGL), with *EPAS1* Mutation Status. *

Patient No. and Age	Description of Cyanotic Congenital Heart Disease and Treatment	Features at PPGL Diagnosis		Catecholamines [†]	PPGL Location and Size	EPAS1 Genotype	
		SaO ₂ [‡] %	Hematocrit %			Tumor	Germline
1, 48 yr	Tricuspid and pulmonary atresia, ASD, and VSD Treatment: Potts shunt at 5 mo of age; right BTS at 5 yr	79	64.4	Paroxysmal atrial fibrillation, diaphoresis, hypertension, anxiety, palpable neck mass	Left adrenal PHEO, 3.0cm×4.0 cm; right carotid body PGL, 1.2 cm×1.7 cm	c.1591C→T, p.Pro531Ser in PHEO; WT in PGL	NA [§]
2, 13 yr	Pulmonary atresia, double-outlet right ventricle, common atrioventricular canal defect, ASD, and VSD Treatment: left BTS at 3 days of age; central shunt at 7 yr; Kawashima, left pulmonary arterioplasty, atrioventricular valvuloplasty, and central shunt closure at 17 yr	85	55.0	Hypertension, diaphoresis, palpitations, dyspnea	Left adrenal PHEO, 6.4cm×5 cm	c.1588G→C, p.Ala530Pro	WT
3, 23 yr	Tricuspid atresia with "normally related greater arteries" and pulmonary stenosis and bilateral SVC Treatment: Left BTS at 4 mo of age; bidirectional Glenn shunt at 2 yr; lateral tunnel fenestrated Fontan procedure at 3 yr; fenestration-device closure at 16 yr; ICD for cardiac arrest at 20 yr	92	47.3	Hypertension, diaphoresis	Abdominal periaortic PGL, 2.9cm×2.7 cm	c.1592C→G, p.Pro531Arg	WT
4, 21 yr	Heterotaxy syndrome with polysplenia, double-outlet right ventricle, right dominant atrioventricular canal defect, hypoplastic left ventricle, interrupted IVC, and AVM in left lung Treatment: pulmonary-artery banding at 2 wk of age; bilateral Glenn shunt and fenestrated intraatrial baffling	77	50.9	Syncope, diaphoresis, dyspnea, chest pain, headaches	Right adrenal PHEO, 4.3cm×4.0cm	c.1591C→T, p.Pro531Ser	WT

Patient No. and Age	Description of Cyanotic Congenital Heart Disease and Treatment	Features at PPGL Diagnosis			Catecholamines [†]	PPGL Location and Size	EPAS1 Genotype	
		Sao ₂ [‡] %	Hematocrit %	Symptoms			Tumor	Germline
5, 54 yr	of hepatic veins to right pulmonary artery at 2 yr; pulmonary valvectomy and closure of baffle fenestration at 4yr	92	39.7	Hypertension, diaphoresis, palpitations	P-NMN, 23×; P-MN, <2×	Abdominal periaortic PGL, 6.3cm×5.8 cm	WT	WT
	Tetralogy of Fallot with pulmonary stenosis Treatment: Potts shunt at 8 mo of age; intracardiac repair at 9 yr; aortobifemoral bypass for PAD at 38 yr; PVR, tricuspid-valve repair, and left pulmonary arterioplasty at 48 yr; ICD for NSVT at 52 yr							

* Patients 1 and 5 were white women, Patient 2 a Hispanic girl, Patient 3 an Asian man, and Patient 4 a Hispanic woman; race was reported by the patients (Patients 1, 3, 4, and 5) or determined by the investigators (Patient 2). All five patients had had hypoxemia for the duration of their lives. Immunohistochemical testing for succinate dehydrogenase complex subunit A and subunit B was positive in all patients, except that the test for succinate dehydrogenase complex subunit B was only weakly positive in Patient 5. Full details regarding the clinical and biochemical features of these patients are provided in Table S1 in the Supplementary Appendix. ASD denotes atrial septal defect, AVN arteriovenous malformations, BTS Blalock-Taussig shunt, ICD implantable cardioverter-defibrillator, IVC inferior vena cava, NA not available, NSVT nonsustained ventricular tachycardia, PAD peripheral-artery disease, PGL paraganglioma, PHEO pheochromocytoma, PVR pulmonary-valve replacement, SVC superior vena cava, VSD ventricular septal defect, and WT wild type.

[†] Plasma catecholamine levels of normetanephrines (P-NMN) and metanephrines (P-MN) were assessed before PHEO or PGL surgery. Data show the value as a factor above the upper boundary of the normal range (112 pg per milliliter for normetanephrines and 61 pg per milliliter for metanephrines).

[‡] Shown is the arterial oxygen saturation (Sao₂) level at diagnosis. Historical data were available for three patients: Patient 3 had had an Sao₂ of approximately 70% at younger than 4 months of age, 85% at 4 months to 3 years of age, and 92 to 94% at 3 to 23 years of age; Patient 4, a history of Sao₂ values ranging from 70 to 77% throughout follow-up; and Patient 5, an Sao₂ of approximately 80% at younger than 9 years of age and 92% at 9 to 54 years of age.

[§] The existence of two separate tumors with distinct *EPAS1* genotypes in this patient served as evidence of the somatic status of the *EPAS1* mutation in PHEO.