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Surviving Males With *PORCN* Variants: Expanding the Clinical, Molecular, and Mechanistic Spectrum

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ABSTRACT

Pathogenic variants in *PORCN* cause focal dermal hypoplasia (FDH/Goltz syndrome), an X-linked dominant disorder historically considered lethal in males, with milder presentations now recognized as PORCN non-Goltz spectrum (PONGOS). We report three male patients identified by exome sequencing: one with a mosaic de novo variant (c.727C>T; p.Arg243*) showing FDH features, and two siblings with an inherited non-mosaic variant (c.1315T>G; p.Trp439Gly) from their unaffected carrier mother with a PONGOS phenotype. These cases confirm that male survival is possible with both mosaic and non-mosaic *PORCN* variants and expand the clinical and molecular spectrum of the disease. Our findings highlight the role of residual protein function in clinical variability and have important implications for diagnosis, genetic counseling, and management in families with apparently unaffected carrier mothers.

1 | Introduction

PORCN (Porcupine *O*-acyltransferase) encodes an endoplasmic reticulum *O*-acyltransferase which is required for the palmitoylation of Wnt ligands [1]. This is a key step for their secretion and activity in the Wnt/β-catenin signaling pathway [1]. This pathway plays a central role in embryonic development and tissue homeostasis [2]. Loss-of-function variants in *PORCN* disrupt Wnt signaling, leading to the abnormal development of ectodermal and mesodermal derivatives, including the skin,

skeleton, teeth, and eyes [2]. Cutaneous manifestations typically follow Blaschko's lines due to X-chromosome inactivation mosaicism [3].

Focal dermal hypoplasia (FDH; Goltz syndrome, OMIM #305600) is an X-linked dominant disorder caused by pathogenic variants in *PORCN* [4]. It is generally considered to be lethal in non-mosaic males [5]. FDH is characterized by significant clinical variability affecting multiple systems, including linear dermal atrophy, papillomas, pigmentary changes, and skeletal, ocular, dental, and visceral anomalies [4, 5].

Although around 400 cases have been reported, the majority of these are in females. Affected males who survive are rare and usually present mosaic variants [5]; only a limited number of non-mosaic male cases have been described [6–10]. More recently, non-mosaic male patients presenting with atypical or attenuated phenotypes have been suggested to constitute a PORCN non-Goltz spectrum (PONGOS), thereby extending the phenotypic and genotypic boundaries of the disorder [11].

Here, we present three additional male patients with *PORCN* variants identified by exome sequencing: one mosaic case consistent with FDH, and two non-mosaic cases compatible with the PONGOS spectrum. These cases further delineate the clinical spectrum associated with PORCN dysfunction.

2 | Materials and Methods

2.1 | Patients and Clinical Characterization

Three patients from two unrelated families were included. Clinical characterization was performed using Human Phenotype Ontology (HPO) terms and was compared with the previous clinical features reported in the published cases (Table 1).

Family 1 comprises a 3-year-old Italian male (Patient I) with multisystem involvement, including neonatal jaundice, cryptorchidism, and torsional malalignment of the right foot. Craniofacial findings included mild right facial cleft (Tessier type II), accessory labial frenulum, and left hemifacial hypertrophy. Cutaneous manifestations were prominent: desquamative and hypotrophic skin lesions on face, trunk, and limbs, with erythema, telangiectasias, skin atrophy, sparse hair, nail pterygium, and mild koilonychia (Figure 1A,B).

Family 2 includes two Spanish male siblings (Patients II and III; Figure 1D), both diagnosed with idiopathic pulmonary arterial hypertension (IPAH) confirmed by right heart catheterization. The older brother (12 years), diagnosed at 9 years of age, presented with exertional syncope, a mean pulmonary arterial pressure (mPAP) of 46 mmHg, pulmonary vascular resistance (PVR) of 11.49 WU m^2, right ventricular hypertrophy, and moderate-to-severe exercise limitation. He is currently in WHO functional class II on dual therapy (Ambrisentan/Tadalafil). Additional findings included strabismus and mild right renal pelvic ectasia. The younger brother (6 years), diagnosed at 3 years of age through familial screening (mPAP 40 mmHg), additionally showed left iris coloboma, congenital pseudoarthrosis of the right clavicle, high-grade bilateral vesicoureteral reflux (Grade IV–V) with hydronephrosis, and thyroid disease. He is also managed with dual PAH therapy.

2.2 | DNA Extraction and Sequencing

Genomic DNA was extracted from peripheral blood. Trio-based exome sequencing was performed in Family 1 (Twist Core Exome kit, NovaSeq6000) and in Family 2 (Agilent SureSelect v6.0, NovaSeq6000). Reads were aligned to GRCh38; variants were called and annotated using GATK/eVai (Family 1) and an in-house pipeline/*VarSeq* (Family 2), and filtered by quality, allele frequency, variant type, and functional impact (Figure S1). All variants were classified according to ACMG/AMP guidelines [12], with application of current ACGS recommendations [13] guidelines and confirmed by Sanger sequencing with familial segregation studies.

3 | Results

3.1 | Family 1

Trio-based exome sequencing identified a mosaic nonsense variant in *PORCN* (NM_203475.3:c.727C>T; p.Arg243*) (Figure 1C), located in exon 9/15, classified as pathogenic per ACMG guidelines [12, 13] (PVS1: very strong; PS4: Moderate; PM2: supporting; with mosaicism disregarded in classification) (Table S1). The aberrant transcript is predicted to undergo nonsense-mediated decay (NMD) [14], and the variant has been previously reported in FDH [15].

3.2 | Family 2

Exome sequencing in both siblings identified a hemizygous missense variant in *PORCN* (NM_203475.3:c.1315T>G; p.Trp439Gly) (Figure 1E), classified as likely pathogenic (PM2: supporting; PP3: strong; PM5: supporting), absent from all population databases (gnomAD, ESP, Kaviar, Bravo). *In silico* tools consistently supported pathogenicity (CADD: 32; REVEL: 0.955; AlphaMissense: 0.97) (Table S1). Notably, a distinct mosaic variant at the same position (p.Trp439Arg) has been reported in a male with typical FDH [16]. Sanger sequencing confirmed maternal inheritance in both siblings (Figure 1F).

4 | Discussion

The classical view of FDH as male-lethal is being reconsidered with the identification of surviving males carrying pathogenic *PORCN* variants [6, 11, 15]. Our three cases reinforce a dosage-sensitive model of Wnt signaling, where complete loss is lethal but partial function (through mosaicism or hypomorphic variants) allows survival [2]. In mosaic males, coexistence of wild-type and mutant cells enables functional complementation, explaining segmental cutaneous lesions along Blaschko's lines [3]. In contrast, non-mosaic survivors likely carry variants retaining partial protein function, consistent with the predominance of missense changes in functional domains.

TABLE 1 | Genetic and clinical features of all reported male patients with PORCN-related FDH/PONGOS.

		Patient (reference)	HGVS					Mosaic	Birth weight (g)	Typical skin/hair findings	Microphthalmia (HP:0000568)
			Gene	Transcript	cDNA	Exon	Protein alteration				
PONGOS	1	This study	*PORCN*	NM_203475.3	c.1315T>G	15	p.Trp439Gly	−	N/A	−	−
	2	This study	*PORCN*	NM_203475.3	c.1315T>G	15	p.Trp439Gly	−	N/A	−	−
	3	Madan et al.	*PORCN*	NM_203475.3	c.749C>T	9	p.Ser250Phe	−	1900	−	+
	4	Madan et al.	*PORCN*	NM_203475.3	c.749C>T	9	p.Ser250Phe	−	N/A	−	+
	5	Brady et al.	*PORCN*	NM_203475.3	c.470G>A	5	p.Gly157Asp	−	3010	−	+
	6	Brady et al.	*PORCN*	NM_203475.3	c.470G>A	5	p.Gly157Asp	−	3040	−	+
	7	Wawrocka et al.	*PORCN*	NM_203475.3	c.734A>G	9	p.Tyr245Cys	−	3800	−	−
	8	Wawrocka et al.	*PORCN*	NM_203475.3	c.734A>G	9	p.Tyr245Cys	−	3250	−	+
	9	Wawrocka et al.	*PORCN*	NM_203475.3	c.734A>G	9	p.Tyr245Cys	−	3550	−	+
	10	Arlt et al.	*PORCN*	NM_203475.3	c.847G>C	10	p.Asp283His	−	3070	−	−
	11	Fukahori et al.	*PORCN*	NM_203475.3	c.368T>G	4	p.Met123Arg	−	2110	−	+
	Frequency									0/11	7/11
	Percentage									0%	64%

(Continues)

TABLE 1 | (Continued)

		Patient (reference)	HGVS					Mosaic	Birth weight (g)	Typical skin/hair findings	Microphthalmia (HP:0000568)
			Gene	Transcript	cDNA	Exon	Protein alteration				
Classical FDH	12	Alkindi et al.	*PORCN*	NM_203475.3	c.1093C>T 46,XXY	13	p.Arg365Trp	XXY	N/A	+	+
	13	This study	*PORCN*	NM_203475.3	c.727TC>T	6	p.Arg243*	+	2600	+	−
	14	Durack et al.	*PORCN*	NM_203475.3	c.1039_1046delinsT	12	p.Leu347Trpfs*50	+	N/A	+	−
	15	Rao et al.	*PORCN*	NM_203475.3	c.898G>T	10	p.Glu300*	+	2400	+	−
	16	Yoshihashi et al.	*PORCN*	NM_203475.3	c.129G>A	2	p.Trp43*	+	3290	+	−
	17	Stevenson et al.	*PORCN*	NM_203475.3	c.956dup	11	p.Asn320Glufs*99	+	N/A	+	−
	18	Vreeburg et al.	*PORCN*	NM_203475.3	c.886del	10	p.Arg296Glyfs*18	+	1050	+	−
	19	Bornholdt et al.	*PORCN*	NM_203475.3	c.502G>A	5	p.Gly168Arg	+	N/A	+	−
	20	Bornholdt et al.	*PORCN*	NM_203475.3	c.1110del	13	p.Ile371Serfs*28	+	N/A	+	−
	21	Bornholdt et al.	*PORCN*	NM_203475.3	c.1186C>T	14	p.Arg396*	+	N/A	+	−
	22	Bornholdt et al.	*PORCN*	NM_203475.3	c.1315T>C	15	p.Trp439Arg	+	N/A	+	−
	23	Maas et al.	*PORCN*	NM_203475.3	c.571C>T	6	p.Gln191*	+	N/A	+	−
	24	Wang et al.	*PORCN*	NM_203475.3	c.1059_1071dup	12	pThr358Profs*65	+	N/A	+	−
	25	Wang et al.	*PORCN*	NM_203475.3	c.370C>T	4	p.Arg124*	+	N/A	+	−
	26	Wang et al.	*PORCN*	NM_203475.3	c.1064_1081del	12	p.Ala355_Val360del	+	N/A	+	−
	27	Wang et al.	*PORCN*	NM_203475.3	c.1093C>G	13	p.Arg365Gly	+	N/A	+	+
	28	Bostwick et al.	*PORCN*	NM_203475.3	c.956dup	11	p.Asn320Glufs*99	+	N/A	+	+
	29	Bostwick et al.	*PORCN*	NM_203475.3	c.1059_1071dup	12	pThr358Profs*65	+	N/A	+	−
	30	Peters et al.	*PORCN*	NM_203475.3	c.853_855del	10	p.Thr285del	+	2700	+	−
	31	Young et al.	*PORCN*	NM_203475.3	c.956dup	11	p.Asn320Glufs*99	+	N/A	+	−
	32	Frisk et al.	*PORCN*	NM_203475.3	c.1274_1275del	14	p.Thr425Argfs*45	+	N/A	+	−
	Frequency									21/21	3/21
	Percentage									100%	14%
Total frequency										21/32	10/32
Total percentage										66%	31%

(Continues)

TABLE 1 | (Continued)

		Coloboma (HP:0000589)	Other ocular defects (HP:0012372)	Any ocular defect	Dental defects (HP:0000164)	Syndactyly (HP:0001159)	Ectrodactyly (HP:0100257)	Nail dysplasia (HP:0002164)	Osteopathia striata (HP:0010740)	Clavicular dysplasia	Costovertebral defect
PONGOS	1	−	+	+	−	−	−	−	−	−	−
	2	+	−	+	−	−	−	−	−	+	−
	3	+	+	+	N/A	+	+	+	+	+	+
	4	−	−	+	N/A	+	−	N/A	N/A	+	−
	5	+	−	+	−	+	−	−	−	−	−
	6	−	+	+	−	+	−	−	−	−	−
	7	−	+	+	−	−	−	−	−	−	−
	8	−	−	+	−	−	−	−	−	−	−
	9	+	+	+	−	−	−	−	−	−	−
	10	−	−	−	+	+	−	−	−	−	−
	11	−	+	+	−	+	+	−	−	−	−
	Frequency	4/11	6/11	10/11	1/9	6/11	2/11	1/10	1/10	3/11	1/11
	Percentage	36%	55%	91%	11%	55%	18%	10%	10%	27%	9%

(Continues)

TABLE 1 | (Continued)

		Coloboma (HP:0000589)	Other ocular defects (HP:0012372)	Any ocular defect	Dental defects (HP:0000164)	Syndactyly (HP:0001159)	Ectrodactyly (HP:0100257)	Nail dysplasia (HP:0002164)	Osteopathia striata (HP:0010740)	Clavicular dysplasia	Costovertebral defect
Classical FDH	12	+	+	+	+	+	+	+	−	−	−
	13	−	−	−	N/A	−	−	+	−	−	−
	14	−	−	−	+	−	−	−	−	−	−
	15	+	−	+	+	+	+	−	−	−	−
	16	−	+	+	−	+	−	+	−	−	−
	17	+	+	+	−	+	+	+	+	−	−
	18	−	−	−	−	+	−	+	−	−	−
	19	+	−	+	+	+	−	−	−	−	−
	20	−	−	−	−	−	−	−	−	−	−
	21	−	+	+	+	+	−	−	−	−	−
	22	−	−	−	−	+	−	−	−	−	−
	23	−	−	−	−	−	−	−	−	−	−
	24	−	−	−	+	−	+	−	−	−	−
	25	−	−	−	−	+	+	−	−	−	−
	26	−	−	−	−	+	−	+	+	−	−
	27	+	−	+	−	+	+	+	−	−	+
	28	+	−	+	+	+	+	+	N/A	N/A	N/A
	29	−	−	−	+	+	+	+	N/A	N/A	N/A
	30	+	+	+	−	+	+	+	−	−	−
	31	+	+	+	−	+	+	+	N/A	−	−
	32	−	+	+	+	+	+	+	+	−	−
	Frequency	8/21	7/21	11/21	9/21	16/21	11/21	12/21	3/18	0/19	1/19
	Percentage	38%	33%	52%	43%	76%	52%	57%	17%	0%	5%
Total frequency		12/32	13/32	21/32	9/29	22/32	13/32	13/31	4/28	3/30	2/30
Total percentage		38%	41%	66%	31%	69%	41%	42%	14%	10%	7%

(Continues)

TABLE 1 | (Continued)

		Diaphragmatic hernia (HP:0000776)	Inguinal hernia (HP:0000023)	Cardiac anomalies	Pulmonary hypertension (HP:0002092)	Brain abnormality (HP:0012443)	Renal anomaly (HP:0000077)	Dysmorphic ears (HP:0031703)	Dysmorphic facial features (HP:0001999)	Age of death	Cause of death
PONGOS	1	−	+	−	+	−	−	−	−	N/A	N/A
	2	−	+	+	+	−	+	+	−	N/A	N/A
	3	−	−	+	+	N/A	+	+	+	42 days	Severe PH and respiratory failure
	4	+	−	+	+	N/A	+	−	+	8 years	N/A
	5	+	−	+	−	N/A	−	−	−	0 days	Respiratory insufficiency
	6	−	−	+	−	+	+	−	−	10 days	Respiratory insufficiency
	7	−	−	−	−	−	−	−	−	N/A	N/A
	8	−	−	−	−	−	−	−	−	N/A	N/A
	9	−	−	−	−	−	−	−	−	N/A	N/A
	10	−	−	−	−	+	−	−	+	N/A	N/A
	11	−	−	−	−	−	−	−	−	N/A	N/A
	Frequency	2/11	2/11	5/11	4/11	2/8	4/11	2/11	3/11		
	Percentage	18%	18%	45%	36%	25%	36%	18%	27%		

(Continues)

TABLE 1 | (Continued)

		Diaphragmatic hernia (HP:0000776)	Inguinal hernia (HP:0000023)	Cardiac anomalies	Pulmonary hypertension (HP:0002092)	Brain abnormality (HP:0012443)	Renal anomaly (HP:0000077)	Dysmorphic ears (HP:0031703)	Dysmorphic facial features (HP:0001999)	Age of death	Cause of death
Classical FDH	12	−	−	−	−	+	+	+	−	N/A	N/A
	13	−	N/A	−	−	−	−	−	+	N/A	N/A
	14	−	−	−	−	−	−	−	−	N/A	N/A
	15	−	−	−	−	−	−	−	+	N/A	N/A
	16	−	−	−	−	−	+	−	−	N/A	N/A
	17	−	−	+	+	−	−	+	+	N/A	N/A
	18	−	+	−	−	+	−	+	−	N/A	N/A
	19	−	−	−	−	−	−	−	−	N/A	N/A
	20	−	−	−	−	−	−	−	−	N/A	N/A
	21	−	+	−	−	+	−	−	−	N/A	N/A
	22	−	−	−	−	−	−	−	−	N/A	N/A
	23	−	−	−	−	−	−	−	−	N/A	N/A
	24	−	−	−	−	−	−	−	−	N/A	N/A
	25	−	−	−	−	−	−	−	−	N/A	N/A
	26	−	−	−	−	−	−	−	−	N/A	N/A
	27	−	−	−	−	−	−	−	−	N/A	N/A
	28	N/A	N/A	N/A	−	N/A	N/A	+	−	N/A	N/A
	29	N/A	N/A	N/A	−	N/A	N/A	−	+	N/A	N/A
	30	−	−	+	−	+	−	+	−	N/A	N/A
	31	−	−	+	+	−	−	+	−	N/A	N/A
	32	−	+	−	−	−	−	+	+	N/A	N/A
	Frequency	0/19	3/18	3/19	2/21	3/19	2/19	7/21	5/21		
	Percentage	0%	17%	16%	10%	16%	11%	33%	24%		
Total frequency		2/30	5/29	8/30	6/32	6/27	6/30	9/32	8/32		
Total percentage		7%	17%	27%	19%	22%	20%	28%	25%		

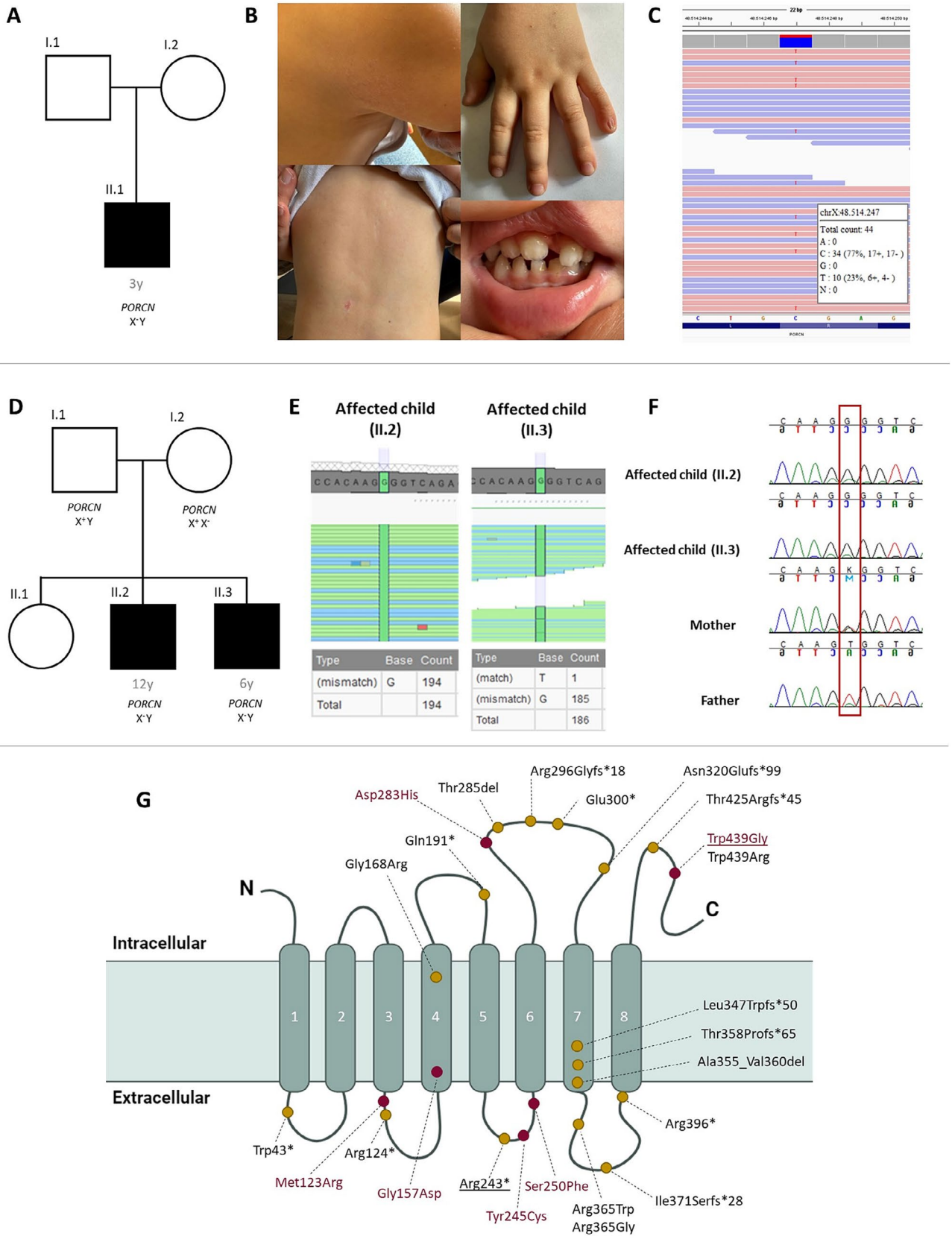

FIGURE 1 | (A) Pedigree of Family 1. (B) Patient I: axillary fold with wrinkles suggesting elastic tissue defect; nail pterygium (fifth finger, left hand); atrophic patch with telangiectasia on shoulder; mild right facial cleft and accessory lateral labial frenulum. (C) Exome sequencing alignment showing the variant in Patient I. (D) Pedigree of Family 2. (E) VarSeq genome viewer showing the variant identified in Patients II.2 and II.3. (F) Sanger sequencing of affected children and parents (DNA unavailable for Individual II.1). (G) PORCN protein model with variants reported in males with PORCN-related disorders (Table 1): constitutional non-mosaic variants in red, mosaic variants in yellow; underlined variants correspond to those described in this article. [Colour figure can be viewed at wileyonlinelibrary.com]

The two siblings with p.Trp439Gly strengthen the emerging PONGOS concept, a phenotype overlapping with FDH but lacking its hallmark cutaneous manifestations [11] (Figure S2) consistent with previously reported non-mosaic male cases [6–8] (Table 1). These data support the hypothesis that distinct molecular mechanisms (complete loss-of-function versus hypomorphic variants) underlie the phenotypic divergence between FDH and PONGOS, rather than representing a simple continuum of severity.

The presence of PAH in both siblings is noteworthy, as vascular involvement, although previously reported [7], remains insufficiently recognized in *PORCN*-related disorders. In both patients, alternative causes of pulmonary arterial hypertension were systematically excluded, including congenital heart disease, structural abnormalities, and environmental factors, supporting a primary, likely genetic etiology. Notably, PAH has been described in approximately 19% of male individuals harboring *PORCN* variants (Table 1). Given the established role of Wnt/β-catenin signaling in endothelial homeostasis, vascular remodeling, and pulmonary vascular disease [2], PAH may represent an underrecognized manifestation of the FDH/PONGOS phenotype rather than a coincidental finding. Furthermore, PAH has also been reported in other genetically determined ectodermal dysplasias, such as incontinentia pigmenti, a multisystem disorder characterized by involvement of the skin, dentition, ocular anomalies, musculoskeletal abnormalities, and cardiac defects [17]. These observations suggest a potential shared pathogenic mechanism linking ectodermal dysplasia and vascular involvement. These cases underscore that males presenting with precapillary pulmonary hypertension and multisystem anomalies warrant a comprehensive diagnostic approach, including whole-exome sequencing, rather than restricting genetic testing to established PAH-associated genes [18]. Whether vascular involvement constitutes a recurrent feature of *PORCN*-related disorders remains to be determined in larger cohorts.

The maternal inheritance from an apparently unaffected carrier [6] underscores the complexity of *PORCN*-related inheritance, where variant-specific effects determine phenotypic outcome. Skewed X-inactivation or subtle carrier manifestations may be overlooked, with direct implications for genetic counseling, recurrence risk, and prenatal diagnosis.

In summary, our cases support a revised model where male viability depends on residual PORCN function: mosaic loss-of-function variants produce classical FDH, while non-mosaic hypomorphic variants give rise to PONGOS. These findings expand the clinical and molecular spectrum of *PORCN*-related disorders and emphasize the need to reconsider traditional assumptions on inheritance and lethality in X-linked developmental conditions.

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Ethics Statement

This study was approved by the Ethics Committee of La Paz University Hospital (CEIC-HULP: PI-5050). Informed consent was obtained from the family according to local ethical guidelines.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Peer Review

For transparency, the peer review documents associated with this article are available at https://doi.org/10.1111/cge.70228.

References

1. A. Caricasole, T. Ferraro, J. M. Rimland, and G. C. Terstappen, "Molecular Cloning and Initial Characterization of the *MG61/PORC* Gene, the Human Homologue of the *Drosophila* Segment Polarity Gene *Porcupine*," *Gene* 288, no. 1 (2002): 147–157, https://doi.org/10.1016/S0378-1119(02)00467-5.

2. S. E. Clements, "Importance of PORCN and Wnt Signaling Pathways in Embryogenesis," *American Journal of Medical Genetics. Part A* 149A, no. 9 (2009): 2050–2051, https://doi.org/10.1002/ajmg.a.32887.

3. M. B. Harmsen, S. Azzarello-Burri, M. M. García González, et al., "Goltz–Gorlin (Focal Dermal Hypoplasia) and the Microphthalmia With Linear Skin Defects (MLS) Syndrome: No Evidence of Genetic Overlap," *European Journal of Human Genetics* 17, no. 10 (2009): 1207–1215, https://doi.org/10.1038/ejhg.2009.40.

4. P. H. Fernandes, S. Wen, V. R. Sutton, P. A. Ward, I. B. Van den Veyver, and P. Fang, "PORCN Mutations and Variants Identified in Patients With Focal Dermal Hypoplasia Through Diagnostic Gene Sequencing," *Genetic Testing and Molecular Biomarkers* 14, no. 5 (2010): 709–713, https://doi.org/10.1089/gtmb.2010.0089.

5. J. D. Gisseman and H. H. Herce, "Ophthalmologic Manifestations of Focal Dermal Hypoplasia (Goltz Syndrome): A Case Series of 18 Patients," *American Journal of Medical Genetics Part C: Seminars in Medical Genetics* 172, no. 1 (2016): 59–63, https://doi.org/10.1002/ajmg.c.31480.

6. P. D. Brady, H. Van Esch, N. Fieremans, et al., "Expanding the Phenotypic Spectrum of PORCN Variants in Two Males With Syndromic Microphthalmia," *European Journal of Human Genetics* 23, no. 4 (2015): 551–554, https://doi.org/10.1038/ejhg.2014.135.

7. S. Madan, W. Liu, J. T. Lu, et al., "A Non-Mosaic *PORCN* Mutation in a Male With Severe Congenital Anomalies Overlapping Focal Dermal Hypoplasia," *Molecular Genetics and Metabolism Reports* 12 (2017): 57–61, https://doi.org/10.1016/j.ymgmr.2017.06.002.

8. A. Wawrocka, J. Walczak-Sztulpa, M. Pawlak, A. Gotz-Wieckowska, and M. R. Krawczynski, "Non-Syndromic Anophthalmia/Microphthalmia Can Be Caused by a *PORCN* Variant Inherited in X-Linked Recessive Manner," *American Journal of Medical Genetics Part A* 185, no. 1 (2021): 250–255, https://doi.org/10.1002/ajmg.a.61938.

9. A. Arlt, N. Kohlschmidt, A. Hentschel, et al., "Novel Insights Into PORCN Mutations, Associated Phenotypes and Pathophysiological Aspects," *Orphanet Journal of Rare Diseases* 17 (2022): 29, https://doi.org/10.1186/s13023-021-02068-w.

10. K. Fukahori, K. Yamoto, H. Saitsu, T. Ogata, and K. Nagasaki, "*PORCN* -Related Microphthalmia With Limb Anomalies: Case Report and Literature Review," *American Journal of Medical Genetics Part A* 191, no. 2 (2023): 636–639, https://doi.org/10.1002/ajmg.a.63048.

11. R. Happle, "The PORCN Non-Goltz Spectrum (PONGOS): A New Group of Genetic Disorders," *American Journal of Medical Genetics Part A* 185, no. 1 (2021): 13–14, https://doi.org/10.1002/ajmg.a.61984.

12. S. Richards, N. Aziz, S. Bale, et al., "Standards and Guidelines for the Interpretation of Sequence Variants: A Joint Consensus Recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology," *Genetics in Medicine* 17, no. 5 (2015): 405–424, https://doi.org/10.1038/gim.2015.30.

13. M. Durkie, E. J. Cassidy, I. Berry, et al., "ACGS Best Practice Guidelines for Variant Classification in Rare Disease," 2024.

14. A. N. Abou Tayoun, T. Pesaran, M. T. DiStefano, et al., "Recommendations for Interpreting the Loss of Function PVS1 ACMG/AMP Variant Criterion," *Human Mutation* 39, no. 11 (2018): 1517–1524, https://doi.org/10.1002/humu.23626.

15. K. H. Grzeschik, D. Bornholdt, F. Oeffner, et al., "Deficiency of PORCN, a Regulator of Wnt Signaling, Is Associated With Focal Dermal Hypoplasia," *Nature Genetics* 39, no. 7 (2007): 833–835, https://doi.org/10.1038/ng2052.

16. S. Frisk, C. Grandpeix-Guyodo, K. P. Silwerfeldt, et al., "Goltz Syndrome in Males: A Clinical Report of a Male Patient Carrying a Novel PORCN Variant and a Review of the Literature," *Clinical Case Reports* 6 (2018): 2103–2110, https://doi.org/10.1002/ccr3.1783.

17. TCRM, *Pulmonary Hypertension and Vasculopathy in Incontinentia Pigmenti: A Case Report* (Dove Medical Press, 2017), https://www.dovepress.com/pulmonary-hypertension-and-vasculopathy-in-incontinentia-pigmenti-a-ca-peer-reviewed-fulltext-article-TCRM.

18. C. L. Welch, M. A. Aldred, S. Balachandar, et al., "Defining the Clinical Validity of Genes Reported to Cause Pulmonary Arterial Hypertension," *Genetics in Medicine* 25, no. 11 (2023): 100925, https://doi.org/10.1016/j.gim.2023.100925.

Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Figure S1:** (A) Filtering pipeline for SNV (single nucleotide variant) and InDel variant prioritization. BAM review was performed with VarSeq (Golden Helix, Montana, USA) and IGV browser (26). Variant classification was performed according to the American College of Medical Genetics (ACMG) guidelines (21). (B) Filtering pipeline for copy number variant (CNVs) prioritization. **Figure S2:** Venn diagram showing the characteristic phenotype of FDH and PONGOS. **Table S1:** Molecular characteristics of variants described in all reported FDH and PONGOS male patients.