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Clinical Research Article

Endocrine Alterations in Patients With Pachydermoperiostosis

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Abstract

Context: Pachydermoperiostosis (primary hypertrophic osteoarthropathy, PHO), usually due to biallelic loss of function variants in *HPGD* and *SLCO2A1*, has some features overlapping with acromegaly and is often referred to endocrinologists. A detailed endocrine assessment is not available for these patients.

Objective: To assess the genetic and endocrine characteristics of patients with PHO referred to endocrine centers with a possible diagnosis of acromegaly.

Methods: Seventeen patients from 14 families in which acromegaly was excluded based on lack of elevated insulin-like growth factor (IGF)-1 levels and/or growth hormone suppression on an oral glucose tolerance test were assessed for *HPGD* and *SLCO2A1* variants.

Results: Age at diagnosis was 26.2 ± 9.0 years (mean ± SD, range 9-43). Digital clubbing was present in all patients. Periostosis (94%), arthralgia (88%), periarticular edema (77%), pachydermia (82%), and coarsened facial features resembling acromegaly (71%) were present in the vast majority of the patients, while eyelash trichomegaly, blepharoptosis, high-arched palate, gingival hypertrophy, gastrointestinal symptoms, and marfanoid habitus were seen in some. Nine patients (53%) had low IGF-1 levels; the rest of the patients had IGF-1 levels in the lowest quartile of the reference range. Estradiol concentration was increased above the normal range in 8 male patients (62%) with normal testosterone and prolactin levels. Biallelic *HPGD* (2/14 kindreds) or *SLCO2A1* (8 novel) variants (12/14 kindreds) were found. Two patients had no identifiable pathogenic/likely pathogenic variant in *HPGD* or *SLCO2A1*. Their phenotype was not different from the other patients.

Conclusion: We establish that low IGF-1 and elevated estradiol levels are frequent features of PHO. Nine novel and 5 known pathogenic/likely pathogenic genetic variants were identified.

Key Words: pachydermoperiostosis, primary hypertrophic osteoarthropathy, *HPGD*, *SLCO2A1*, pseudoacromegaly

Abbreviations: ^{99m}Tc-MDP technetium, 99^{m} methylene diphosphonate; BMI, body mass index; CEAS, chronic enteropathy associated with the *SLCO2A1* gene; COX, cyclooxygenase; DHEAS, dehydroepiandrosterone sulfate; FGF, fibroblast growth factor; GH, growth hormone; GHR, GH receptor; HPGD, hydroxyprostaglandin dehydrogenase; IGF, insulin-like growth factor; LLN, lower limit of the reference range; NSAID, nonsteroidal anti-inflammatory drug; OGTT, oral glucose tolerance test; PCR, polymerase chain reaction; PGE2, prostaglandin E2; PHO, primary hypertrophic osteoarthropathy; SHO, secondary hypertrophic osteoarthropathy; SIRT1, sirtuin 1.

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Primary hypertrophic osteoarthropathy (PHO), also known as pachydermoperiostosis, is a rare hereditary disease characterized by thickened skin and excessive skinfolds (pachydermia), hyperhidrosis, seborrhea, synovial joint effusions, digital clubbing (also termed Hippocratic fingers), enlargement of hands and feet, and thickened periosteal tissue involving the long tubular bones (periostosis) resulting in cylindrical thickening of limbs (in severe cases referred to as elephant leg) (1). PHO can be categorized into 3 clinical forms depending on the varying degree of skeletal and cutaneous involvement: a complete form characterized by periostosis and pachydermia, an incomplete form with bone changes, but without pachydermia, and a form fruste with pachydermia and minimal skeletal changes (1). However, severity of these major manifestations can be variable based on genotype (see below) and based on sex, as the complete form is almost exclusively characteristic of males, whereas females are asymptomatic or have only mild symptoms. As the clinical and radiologic signs are variable and often nonspecific, these patients may present a diagnostic challenge for physicians and radiologists.

In the majority of the cases, the disease is due to loss of function variants in either of 2 genes. 15-Hydroxyprostaglandin dehydrogenase (*HPGD*) is the main enzyme of prostaglandin degradation with biallelic loss of function variants causing autosomal recessive primary hypertrophic osteoarthropathy type 1 (PHOAR1, OMIM 259100) (2). The second gene, solute carrier organic anion transporter family member 2A1 (*SLCO2A1)*, encodes a prostaglandin transporter and its activity is crucial for the appropriate degradation of prostaglandins (3, 4). Both autosomal recessive (PHOAR2, OMIM 614441) and dominant (PHOAD, OMIM 167100) inheritance patterns have been reported in patients with *SLCO2A1* gene variants (5-8). Elevated circulating prostaglandin E2 (PGE2) was found in patients with both *SLCO2A1* and *HPGD* variants. These data suggest that PGE2 and its metabolism play an important role in the disease mechanism (2, 5, 9, 10). PGE2 is synthetized by cyclooxygenase (COX) enzymes. Prior to degradation, which mainly occurs in the lungs, PGE2 must first be transported across the plasma membrane into the cytoplasm by prostaglandin transporters such as SLCO2A1, SLCO3A1, and SLCO4A1. Inside the cell, HPGD degrades PGE2 to its metabolite 13,14-dihydro-15-ketoprostaglandin E2 (9).

PHO needs to be distinguished from the more common secondary hypertrophic osteoarthropathy (SHO) usually associated with chronic hypoxia in pulmonary (eg, cystic fibrosis, pulmonary fibrosis, emphysema), cardiovascular (eg, congenital cyanotic heart disease), systemic inflammatory (eg, sarcoidosis, inflammatory bowel disease, polyarteritis nodosa), and neoplastic processes (non–small cell lung cancer, solitary fibrous tumor of the pleura, and pleural mesothelioma) (11). SHO may also manifest as a paraneoplastic syndrome due to other nonpleural or pulmonary tumors such as esophageal cancer, gastric cancer, colon cancer, osteosarcoma, nasopharyngeal cancer, breast cancer, and Hodgkin lymphoma, potentially due to increased COX2 activity in tumor cells (12-19). The mechanism of PHO and SHO is often similar, as elevated circulating PGE2 can be seen in both (20).

Patients with PHO with enlarged hands and feet, coarsened facial features, and excessive sweating are often referred to endocrinologists with suspicion of acromegaly; indeed, PHO belongs to the group of conditions called pseudoacromegaly (21, 22). However, detailed hormonal analysis, including the growth hormone (GH)–insulin-like growth factor (IGF)-1 axis, of patients with PHO is not available. Therefore, in this study we aimed to characterize a group of patients with PHO who were referred to endocrinology centers for investigation for a possible diagnosis of acromegaly.

Materials and Methods

Seventeen patients from 14 families diagnosed with PHO were included in this study (Table 1) (23, 24). One additional patient, father of 1 of the affected patients (Patient 12), was also assessed but not included in the clinical descriptions of the cohort. In 11 families only 1 person was affected, while in 2 families 2 brothers were affected and in 1 family the brother and sister were affected. Biochemical and hormonal measurements were performed in the morning after 12 hours of fasting. Acromegaly was excluded on the basis of lack of elevated serum IGF-1 levels for age and/or GH suppression below 0.4 µg/L during a 75-g oral glucose tolerance test (OGTT), and (if performed) negative pituitary magnetic resonance imaging findings. Serum GH, IGF-1, morning cortisol, dehydroepiandrosterone sulfate (DHEAS), total testosterone, estradiol, prolactin, and insulin from blood samples from South Asian patients were analyzed with electrochemiluminescence immunoassay using the eCOBAS 8000 analyzer (Roche) except for 2 cases (Patient 5 and Patient 8) where a chemiluminescence immunoassay using both ADVIA Centaur XP analyzer (Siemens) and IMMULITE 1000 (Siemens) was applied. European patients' samples were analyzed with a chemiluminescence immunoassay using the LIAISON XL analyzer (DiaSorin) for GH, IGF-1, morning cortisol, DHEAS, total testosterone, estradiol, prolactin, and insulin. Bone mineral densities of the lumbar spine and proximal femur and body composition were measured with dual-energy X-ray absorptiometry (Prodigy Advance, GE Lunar or Horizon A Hologic). For bone scintigraphy a technetium 99^{m} methylene diphosphonate (^{99m}Tc-MDP) bone scan was used. The study was approved by the ethics committees of the respective institutes (Centre of Postgraduate Medical Education, Warsaw, Barts and the London School of Medicine, London and Postgraduate Institute of Medical Education and Research, Chandigarh) and written informed consent was obtained from all patients.

Genetic Testing

Genomic DNA was extracted from peripheral blood using the Qiagen DNA Extraction Kit (Qiagen, Germany) according to the manufacturer's instructions. *HPGD* (NM_000860.6) and *SLCO2A1* (NM_005630.3) underwent polymerase chain reaction (PCR) amplification. Primer sequences are listed in Table S1 (25). PCR conditions are as follow: for all *HPGD* exons and for *SLCO2A1* exon 2-6 and 8-14 Taq DNA Polymerase (NEB #M0273) was used with the denaturing step at 95°C for 2 minutes followed by 40 cycles of denaturation at 95°C for 30 seconds, annealing at (58-61.1°C) for 30 seconds, extension at 6°C for 20 seconds, and a final extension at 68°C for 5 minutes. For *SLCO2A1* exon 3 and 7 Platinum SuperFi II DNA Polymerase (Thermofisher #12361010) was used with denaturation step at 98°C for 30 seconds, followed by 40 cycles of denaturation at 98°C for 10 seconds, annealing at 60°C for 30 seconds, extension at 72°C for 30 seconds, and a final extension at 72°C for 5 minutes. The PCR products were purified by column

Table 1. Clinical characteristics of patients with primary hypertrophic osteoarthropathy

	Patient ID	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	P11	P12	P13	P14	P15	P16	P17
	Corresponding figure	**Fig. S1**	**Fig. S2**	**Fig. S3**	**Fig. S4**	**Fig. S5**	**Fig. S6**	**Fig. S7**	**Fig. S8**	**Fig. S9**	**Fig. S10**	**Fig. S11**	**Fig. S12**	**Fig. S13**	**Fig. S14**	**Fig. S15**	**Fig. S16**	**Fig. S17**
Demographics	Gender	Male	Male	Male	Male	Male	Male	Male	Male	Male	Male	Male	Male	Male	Female	Male	Male	Male
	Ethnicity	Poland	Poland	Zimbabwe	India	India	India	India	India	India	India	India	India	India	India	Poland	India	Romania
Chronology	Current age	30	15	33	21	50	39	22	28	55	46	27	24	20	23	27	36	54
	Age at diagnosis	24	9	28	20	42	30	21	24	43	43	26	20	20	23	22	30	19
	Onset of symptoms	3	3	5	15	32	17	18	20	25	26	18	12	13	3	7	28	14
Skin and soft tissue	Digital clubbing	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
	Cutis verticis gyrata	—	—	+	+	+	+	+	+	+	+	—	+	—	—	+	—	+
	Dermal hypertrophy	+	+	+	+	+	+	+	+	+	+	+	+	—	—	+	—	+
	Hyperhidrosis	+	+	+	—	—	+	+	+	—	—	—	+	—	—	—	+	+
	Seborrhea	+	—	+	+	—	+	+	+	+	+	+	+	—	—	+	+	+
	Acne	—	—	—	+	—	+	—	+	—	—	+	+	—	—	+	—	—
	High-arched palate	+	+	—	—	+	+	—	+	+	+	—	NA	—	—	+	—	+
	Gynecomastia	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	Blepharoptosis	+	—	—	+	+	+	—	—	+	—	+	+	—	—	+	—	+
	Long eyelashes	+	+	+	+	—	+	+	—	+	—	—	+	+	—	+	—	—
Musculoskeletal	Arthralgia of large joints	+	+	+	+	+	+	+	+	+	+	+	+	+	—	—	+	+
	Synovial effusions	+	+	—	—	—	+	+	—	+	+	+	+	—	—	+	—	—
	Periarticular edema	+	+	+	+	—	+	+	+	—	—	+	+	+	—	+	+	+
	Widened cranial sutures	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	Wormian bones	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	
	Acromegalic facies	+	—	+	+	+	+	+	+	+	+	+	+	—	—	—	—	+
	Pectus excavatum	—	—	—	—	—	+	—	—	—	—	—	+	—	—	—	—	—
Other systems	Anemia/other cytopenia	—	—	+	+	—	—	+	+	+	+	+	+	+	—	+	—	—
	Myelofibrosis	—	—	—	+	—	—	—	—	+	+	—	+	—	—	—	—	—
	Gastrointestinal symptoms	+	+	—	+	—	—	—	—	+	+	+	+	—	—	+	—	—
	Gastrointestinal disorders	—	—	—	+	—	+	—	+	+	+	+	+	—	—	+	—	—
	Gastrointestinal details	Diarrhea, occasional blood on stool	Diarrhea		Dyspepsia, gastric folds hypertrophy, acute prepyloric gastritis		Esophageal nodule with nodular mucosa of the first portion of duodenum (D1)		Gastric folds hypertrophy	Dyspepsia, gastric folds hypertrophy	Constipation, abdominal pain, hepatosplenomegaly, gastric folds hypertrophy	Diarrhea, antral hyperemia, decreased height of duodenal folds in the second portion of duodenum (D2)	Diarrhea, gastric folds hypertrophy, decreased height of duodenal folds in the second portion of duodenum (D2) later developing to edematous mucosa, terminal ileal ulcer, hiatus hernia		None Currently suffering from left empyema thoracis	Nausea, vomiting, heartburn, diarrhea, erosions in UGIE		
	Patent ductus arteriosus	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Familial aspects	Family history	+	+	—	—	—	—	—	—	+	+	—	+	—	+	—	—	+
	Consanguinity	—	—	—	—	Second degree	—	—	Second degree	—	—	—	—	—	—	—	—	—
Anthropometry	Height (cm)	202	133	172	165	175	171	166	166	170	170	166	157	166	153	166	176	176
	Body mass (kg)	83	26	78	50	65	52.4	53	55	65	70	56	50	50	30	57	85	75
	Body mass index (kg/m^2)	17.3	14.7	26.4	18.4	21	17.9	19.2	19.9	22.5	24.2	20.3	20	18.1	12.8	20.7	27.4	24.2
	Maternal height (cm)	167	167	NA	157	160	NA	163	150	158	158	154	150	148	148	164	146	170
	Paternal height (cm)	182	182	NA	180	170	NA	175	170	174	174	162	158	167	167	178	167	176
	Midparental height (cm)	181.5	181.5	NA	175	172	NA	176	167	173	173	164.5	160.5	164	157.5	178	163.5	180
	Difference from midparental height (cm)	20.5	−48.5[a]	NA	−10	3	NA	−10	−1	−3	−3	1.5	−3.5	2	−4.5	−12	12.5	−4
DEXA	L1-L4 Z score	1.9	NA	NA	−0.6	0.5	NA	−0.7	0.6	0.6	1.5	−1.6	−1.3	−1.5	−3.4	1.3	NA	−1.0
	Neck Z score	3.2	NA	NA	0.8	−0.4	NA	−0.7	−0.2	−0.2	2.1	−0.4	0.3	−0.3	−2.6	0.2	−0.2	−0.3
Treatments	NSAID	+	+	+	+	—	—	+	+	+	+	+	+	+	—	—	+	+
	Paracetamol + tramadol	—	—	—	—	+	—	—	—	—	—	—	—	—	—	—	—	—
	Bisphosphonate	+	—	—	—	—	+	—	+	+	—	—	+	+	—	—	—	—
	Corticosteroids	—	—	—	+	—	—	—	+	—	—	+	+	—	—	—	—	—

(*continued*)

Table 1. Continued

Patient ID	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	P11	P12	P13	P14	P15	P16	P17
Corresponding figure	Fig. S1	Fig. S2	Fig. S3	Fig. S4	Fig. S5	Fig. S6	Fig. S7	Fig. S8	Fig. S9	Fig. S10	Fig. S11	Fig. S12	Fig. S13	Fig. S14	Fig. S15	Fig. S16	Fig. S17
Danazol	−	−	−	+	−	−	−	−	−	−	−	+	−	−	−	−	−
Surgery	−	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Ruxolitinib	−	−	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−
Hydroxychloroquine	−	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−
PPI	−	−	−	−	−	−	−	−	−	−	−	−	−	−	+	−	−
Rifaximin	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Trimebutine	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Oral/IV iron	−	−	−	−	−	−	−	−	−	−	−	+	−	−	+	−	−
Oral potassium	−	−	−	−	−	−	−	−	−	−	−	−	−	−	+	−	−
Propantheline bromide	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−

Abbreviations: NA, not available; DEXA, dual-energy X-ray absorptiometry; NSAID, nonsteroidal anti-inflammatory drugs; PPI, proton pump inhibitor; IV, intravenous.
*Yet to reach final height.

purification using the QIAquick PCR Purification kit (Qiagen, Hilden, Germany; 28106). Sanger sequencing was performed under standard conditions by (GATC Biotech company, Germany). Results were analyzed with SnapGene (https://www.snapgene.com/).

In Silico Classification of the Identified Variants

All *HPGD* and *SLCO2A1* variants were annotated using the American College of Medical Genetics and Genomics classification (benign, likely benign, variant of uncertain significance, likely pathogenic, and pathogenic) (26). The databases and prediction programs used are listed in Table S2 (25).

Statistics

Data are expressed as mean and SD or median and range. Distribution was assessed by the Shapiro–Wilk test, and the Mann–Whitney U test and the Wilcoxon test were used as appropriate. A P value less than .05 was considered to be statistically significant. Missing data were omitted in the statistical analyses. The data were analyzed using STATISTICA 13 software.

Results

Genetic Results

Twelve kindreds out of the 14 families were identified with pathogenic/likely pathogenic variants in the 2 known genes causing PHO (Table S3 (25)). In 2 families, homozygote *HPGD* changes were found. One of these variants has been previously described (p.Leu59Valfs*8) and the other (c.699+5_8delgtaa) is a novel variant (Fig. 1) (27, 28). One patient's photograph was previously published (29). Ten families were identified with 12 different pathogenic/likely pathogenic variants in *SLCO2A1* (Figs. 2 and 3). Eight kindreds had homozygous change while 2 kindreds had compound heterozygote variants (Table S3 (25)). Eight of the 12 *SLCO2A1* variants have not been previously described. Two patients from 2 different kindreds, 1 with a clinically incomplete form (Patient 16) and 1 patient with a complete form (Patient 17) of PHO had no identifiable pathogenic/likely pathogenic variant in *HPGD* or *SLCO2A1*. The identified 9 novel variants (1 in *HPGD* and 8 in *SLCO2A1*) were deposited to the dbSNP (batch ID:1063650). We also identified 8 variants (2 in *HPGD* and 6 in *SLCO2A1)* that have previously been described as polymorphisms (Table S4 (25)).

Clinical Characteristics

All our patients with PHO except 1 were males, 14 with the complete form of the disease and 3 with the incomplete form (Patient 13, Patient 14, and Patient 16). In 3 kindreds 2 siblings were affected (Patients 1-2, 9-10, and 13-14). The only female we identified with the homozygous *SLCO2A1* variant (Patient 14) presented with digital clubbing and no other manifestation, in contrast to her brother (Patient 13) who presented with the incomplete form of PHO. In 1 kindred, a homozygote patient (Patient 12) had the full clinical picture, while his heterozygote father had mild symptoms. The other 10 patients had no known clinically affected male or female siblings or parents. Out of the kindreds with homozygote variants (n = 10), 2 had known second-degree consanguinity in the family (Patients 5 and 8).

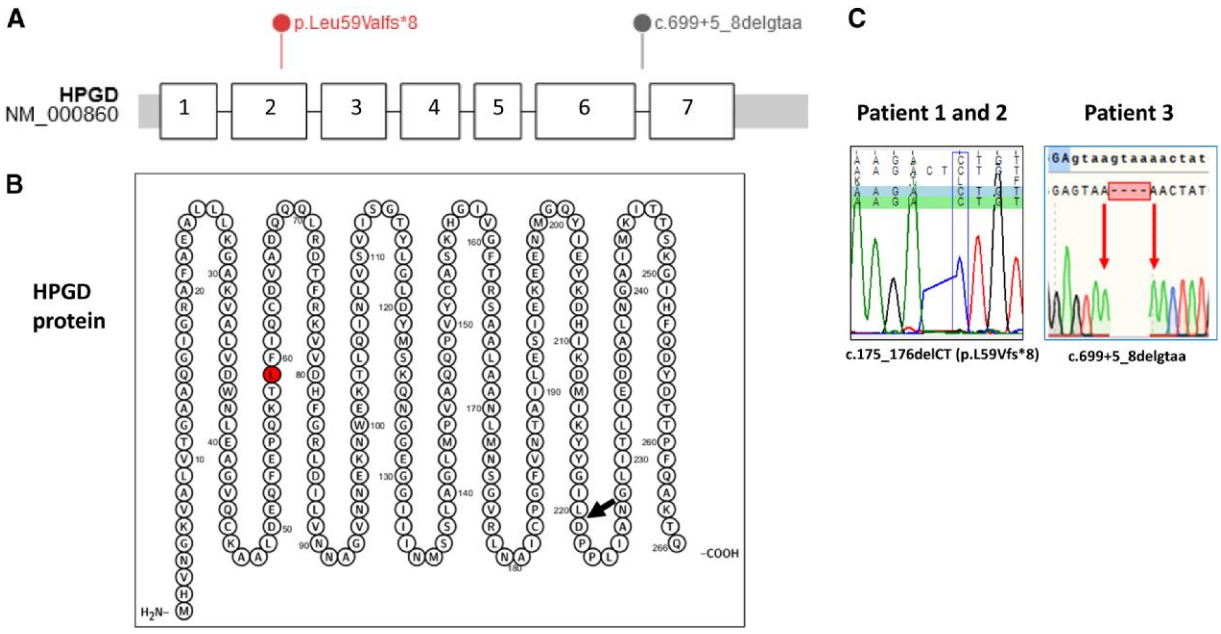

Figure 1. (A) Location of identified variants in the *HPGD* gene. Frameshift variant (previously described) is indicated by in red and the splice variant (novel) is shown in black. (B) The location of the identified mutated amino acid in HPGD protein. The red amino acid marks the site of the c.175_176delCT (p.L59Vfs*8) change. The black arrow shows the exon–intron junction around the c.699+5_8delgtaa variant. The figure was generated by the PROTTER tool (https://wlab.ethz.ch/protter). (C) The electropherograms showing the identified variants in *HPGD* gene. On the left, the first, fourth and fifth row represent the patient's DNA sequence. The second row is the reference sequence and third row is the protein sequence. On the right, the top row represents the reference sequence while the bottom row represents the patient's sequence.

As a group, the mean age of the onset of the first symptoms was 15.8 ± 8.9 years (mean ± SD and range 3-32 years) and age at diagnosis was 26.2 ± 9.0 years (range 9-43 years). One patient with a *HPGD* mutation was diagnosed in childhood (9 years). The mean age of the first symptoms in the patients with *SLCO2A1* mutation was higher than in patients with *HPGD* mutation (17.7 ± 7.8 years vs 3.7 ± 0.9 years, $P = .02$). All patients underwent hormonal investigation to exclude acromegaly due to enlarged hands and feet. Digital clubbing was present in all patients and periostosis was present in all male patients. Arthralgia of large joints was present at diagnosis in 15/17 of the patients (88%) and was accompanied by the presence of periarticular edema in 13 patients (77%). One of the patients (Patient 15) with *SLCO2A1* mutation denied arthralgia at diagnosis despite having "elephant legs." Synovial effusions were found in 9/17 patients (53%) (in 2 patients with *HPGD* mutation and in 7 with *SLCO2A1* mutation). Fourteen patients had pachydermia (82%) (3 patients with *HPGD* mutation, 10 with *SLCO2A1* mutation, and 1 patient without detected pathogenic variant) and 11 (65%) (1 patient with *HPGD* mutation, 9 patients with *SLCO2A1A* mutation, and 1 patient without detected pathogenic variant) presented a severe degree of dermal hypertrophy as cutis verticis gyrata. Coarsened facial features suggesting acromegaly were present in 12/17 patients (71%), in 2 patients with *HPGD* mutation, in 9 with *SLCO2A1A* mutation, and in 1 patient without detected pathogenic variant (Figs. S1-S17 (25)). Ten patients (59%) presented with long eyelashes and in 9 patients (53%) blepharoptosis was also found.

Nine patients complained of excessive sweating (53%) and 13 patients (77%) had seborrhea, which was accompanied by acne in 6 patients (35%). Eight patients (47%), harboring *HPGD* or *SLCO2A1* variants, complained of gastrointestinal symptoms such as diarrhea, nausea, dyspepsia, and blood on stools. In 8 patients (47%) upper gastrointestinal endoscopy was performed which identified gastric fold hypertrophy (n = 5), gastritis (n = 3), decreased height of duodenal folds (n = 2), and gastric and intestinal ulcerations (n = 2). None of the patients had a history of delayed cranial sutures closure or patent ductus arteriosus at birth.

The mean height of adult patients with PHO was 169.8 ± 10.3 cm and was not different than the mean midparental height. The height of the adult patients was higher than the midparental height in 6 patients: 1 of them was suspected of pituitary gigantism before PHO diagnosis (Patient 1 with *HPGD* mutation). Height was shorter than the midparental height in 11 patients. The mean body mass of adult male patients was 63.0 ± 12.1 kg and the mean body mass index (BMI) of all patients was 20.7 ± 3.2 kg/m^2. Only 2 patients (12%) had a BMI above 25 kg/m^2 (26.4 and 27.4 kg/m^2), and 5 patients (29%) had a low BMI <18.5 kg/m^2 (18.1, 18.4, 17.3, 14.7, and 17.9 kg/m^2). The mean percentage of fat mass was 25 ± 5% in patients where this was available (n = 11). Table 1 summarizes the patients' clinical characteristics.

Clinical Chemistry and Hematology

Six patients (35%) with a *SLCO2A1* mutation had hypoalbuminemia (albumin concentration <35 g/L; 532 µmol/L). No patient with *HGPD* mutation had hypoalbuminemia. One patient had impaired fasting glucose (fasting glucose 111 mg/dL; 6.17 mmol/L) and another patient had type 2 diabetes mellitus (anti-GAD65 negative, C-peptide 1.55 ng/mL at diagnosis) requiring insulin treatment. The rest of the patients had normal fasting glucose levels (83.4 ± 9.4 mg/dL; 4.63 ± 0.52 mmol/L). The mean serum creatinine concentration was 0.60 ± 0.10 mg/dL; 53.0 ± 8.84.5 µmol/L (normal range 0.63-1.16 mg/dL; 55.7-102.5 µmol/L). The patient

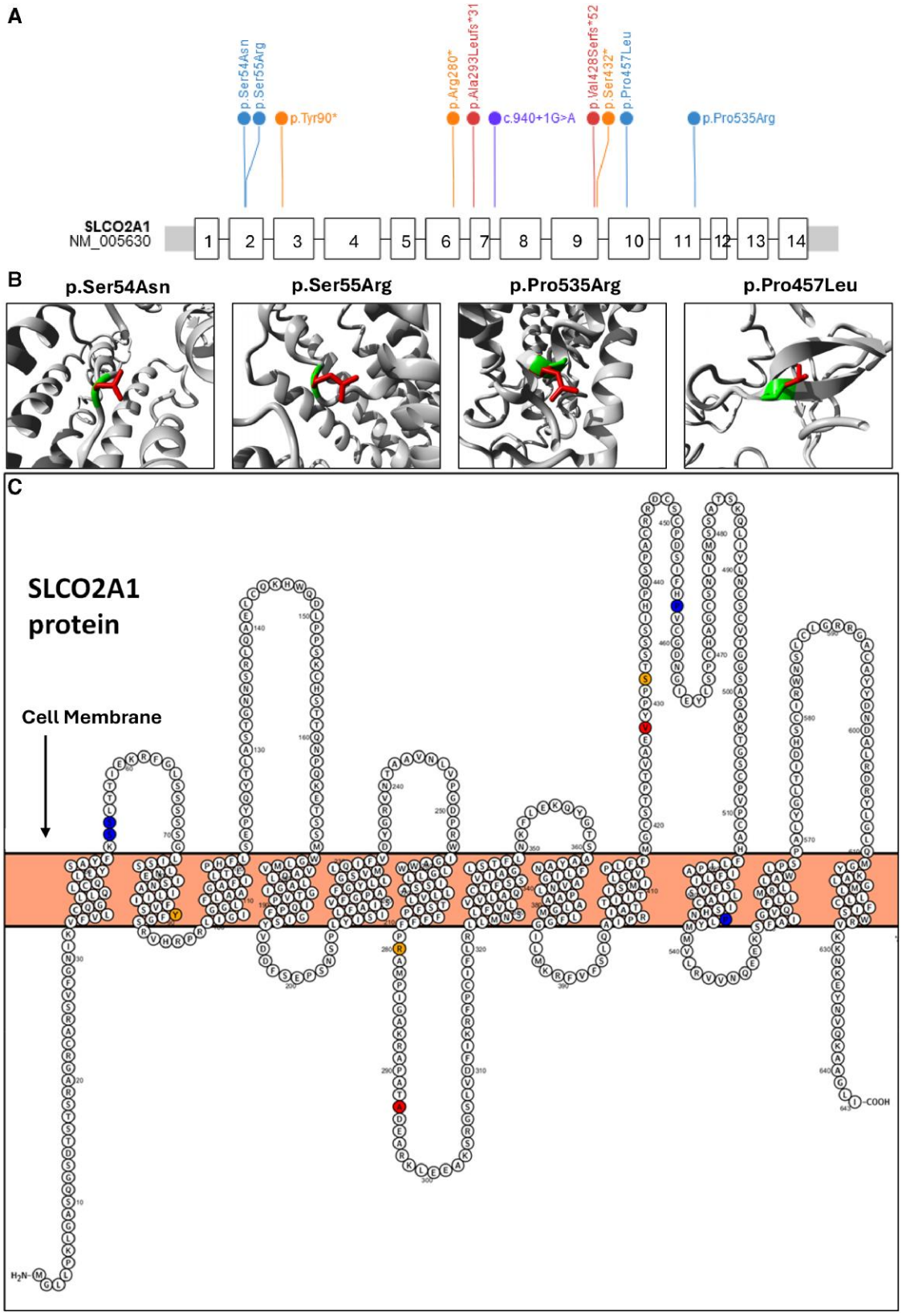

Figure 2. (A) Location of identified variants in the *SLCO2A1* throughout the gene. Blue numbers represent missense changes, orange nonsense, red frameshift, and purple splice site changes. (B) Three-dimensional model of the missense *SLCO2A1* variants with green representing the wild-type and red representing the mutant residue. Figures were prepared with HOPE protein structure analysis tool. (C) Location of the identified mutated amino acids in SLCO2A1 protein. Missense variants are in blue, nonsense in orange, and frameshift variants are in red. Figure was generated by PROTTER tool.

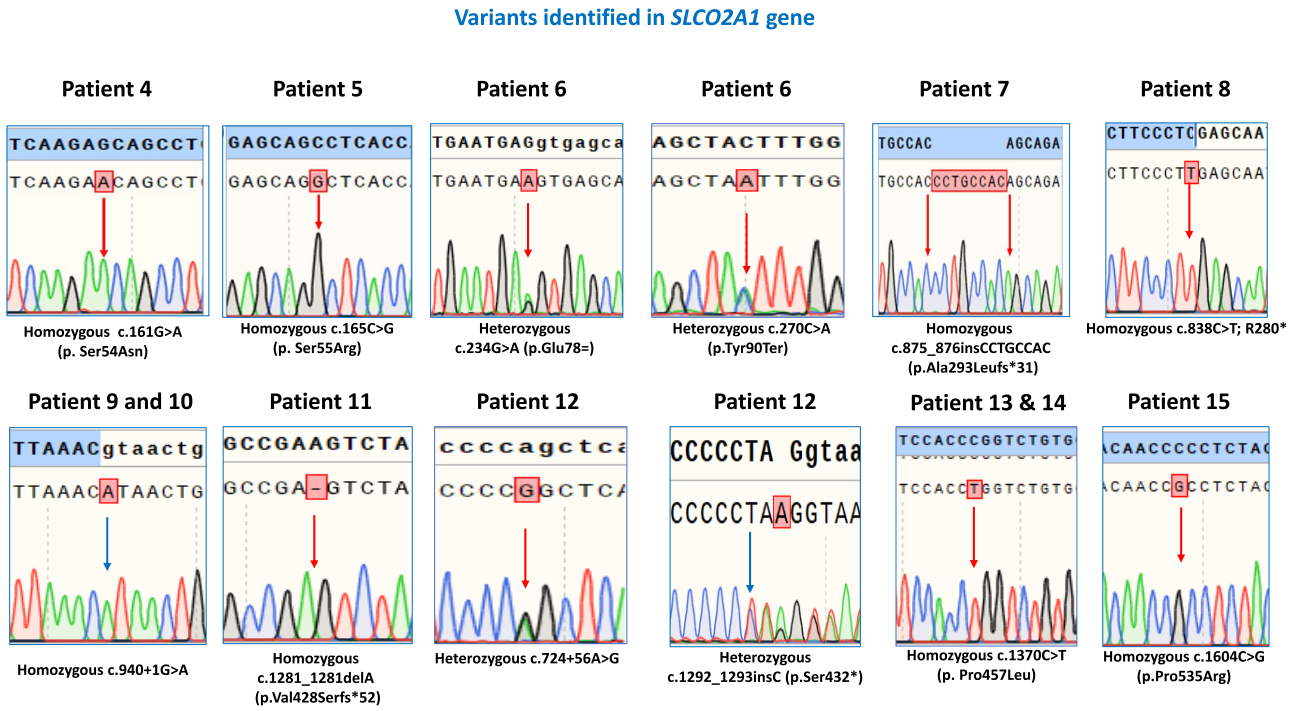

Figure 3. The electropherograms show the identified variants in *SLCO2A1* gene. The top row represents the reference sequence while the bottom row represents the patient's sequence.

with type 2 diabetes mellitus had chronic kidney disease with an elevated creatinine level; his data were excluded from this calculation. Ten patients, 9 with *SLCO2A1* mutation and 1 with *HPGD* mutation, had anemia (59%). Four patients, all with *SLCO2A1* mutation (24%), had confirmed myelofibrosis and 3 of them required red blood cell transfusions. The majority of patients had an increased C-reactive protein level with the median value of 8.2 mg/L (normal range 0-5 mg/L), although some of these patients were using nonsteroidal anti-inflammatory drugs (NSAIDs) when C-reactive protein was measured (Table 2).

Hormonal Assessment

None of the patients had elevated fasting GH or IGF-1 levels above the reference range for age. The median fasting GH concentration was 0.93 µg/L (range 0.04-3.4). Nine patients had fasting GH level ≤1 µg/L, and 8 patients had GH concentration exceeding 1 µg/L. Out of 14 patients who had an OGTT performed, all suppressed GH <1 µg/L, but 4 of them (28%) did not suppress GH <0.4 µg/L. The median GH nadir on OGTT was 0.27 µg/L (range: 0.02-0.74). The BMI of the patients who did not suppress <0.4 µg/L did not differ significantly from those who did suppress GH <0.4 µg/L. Nine patients (53%) had IGF-1 concentration below the lower limit of the reference range (LLN) and the other 4 patients (24%) had IGF-1 levels in the lowest quartile of the reference range for age. We found lower median IGF-1 levels in patients with a complete form of PHO than in those with an incomplete form of PHO (0.87 × LLN vs 3.44 × LLN; $P = 0.038$). There was no difference between patients harboring *SLCO2A1* or *HPGD* variants in terms of IGF-1 levels. The BMI of the patients with low IGF-1 did not differ significantly from BMI of the patients with IGF-1 concentrations within the normal range for age.

The median fasting insulin level was 2.6 µIU/mL (range 0.4-7.83). The mean HOMA-IR index was 0.7 ± 0.4 and was below 2.5 in all patients where data were available. One patient had subclinical primary hypothyroidism with negative antithyroid antibodies, normal thyroid ultrasound, and no family history of thyroid disease. The mean morning serum cortisol was 9.8 ± 2.4 µg/dL (270.5 ± 66.2 nmol/L); however, 6 patients (35%) had morning cortisol level <10 µg/dL (276 nmol/L) and all of the patients had morning serum cortisol concentration <15 µg/dL (414 nmol/L). None of them had symptoms of adrenal failure. Nine of the 15 patients (60%) for whom result was available had DHEAS levels below the normal range for sex and age, while only 1 patient (Patient 4) was taking glucocorticoids at the time of evaluation. The decreased level of DHEAS was found only in patients with *SLCO2A1* mutations.

While testosterone and prolactin levels were normal, estradiol concentration was increased above the normal range in 8 male patients (62%) and the mean concentration was 56.3 ± 24.7 pg/mL (207 ± 91 pmol/L); however, none of them had clinical evidence of gynecomastia. The increased levels of estradiol were found only in patients with *SLCO2A1* mutations and in 1 patient without a pathogenic variant in either of the 2 genes. A female patient had normal estradiol concentration and regular menstrual cycles. Table 2 summarizes the patients' biochemical and hormonal results.

Skeletal Changes

Radiography of the appendicular skeleton showed subperiosteal reactions in all assessed subjects (6 patients with extensive, 4 with moderate, and 3 with mild changes, based on visual assessment by an expert radiologist) and acro-osteolysis in 1 adult patient with *HPGD* mutation. ^{99m}Tc-MDP scan showed increased flow and soft tissue pooling in the early

Table 2. Biochemical and hormonal characteristics of patients with primary hypertrophic osteoarthropathy

	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	P11	P12	P13	P14	P15	P16	P17
Basal GH (μg/L)	0.14	1.09	NA	1.16	1.08	0.2	0.481	0.778	0.036	2.03	1.62	2.98	0.231	1.92	0.17	0.5	3.4
Nadir GH on OGTT (μg/L)	0.46	NA	NA	NA	0.19	0.54	0.21	0.742	0.027	0.347	0.32	0.21	0.024	0.37	0.08	0.48	0.1
IGF-1 (μg/L)	132.1	135.6	88	160	78	90.1	117	99	175.9	168	54.6	87	184	177	102	141	76.3
IGF-1 lower limit of normal	197	63	95	149.1	57	91.4	226	135	53	107	130	123	53	138	197	41	94
IGF-1 upper limit of normal	333	379	537	332.3	241	227	903	328	241	310	295	263	241	533	333	246	252
× Lower limit of normal	0.67	2.15	0.93	1.54	1.37	0.99	0.52	0.73	3.32	1.57	0.42	0.71	3.47	1.28	0.52	3.44	0.81
× Upper limit of normal	0.4	0.36	0.16	0.69	0.32	0.4	0.13	0.3	0.73	0.54	0.19	0.33	0.76	0.33	0.31	0.57	0.3
Lower quartile	231	142	205.5	194.9	103	125.3	395.25	183.25	100	157.75	171.25	158	100	225	231	92.25	133.5
Estradiol (pg/mL)	52.3	NA	NA	50.9	36.6	NA	33.29	41.57	47.16	44	48.8	123	52.8	79.5	97.4	64.2	40.3
Testosterone (nmol/L or ng/mL)	5.36 (ng/mL)	NA	18 (nmol/L)	15.9 (nmol/L)	5.73 (ng/mL)	38.1 (nmol/L)	18.82 (nmol/L)	26.4 (nmol/L)	20.2 (nmol/L)	13.9 (nmol/L)	22.7 (nmol/L)	11.4 (nmol/L)	22.1 (nmol/L)	NA	6.69 (ng/mL)	15.6 (nmol/L)	4.42 (ng/mL)
Prolactin (μg/L)	8.3	4.2	NA	12.8	4.99	16.5	8.77	8.9	10.78	6.85	7.41	7.92	13	13.4	7.3	7.38	14.3
TSH (mIU/mL)	2.421	2.477	3	3.65	2.75	1.79	2.85	5.18	0.924	0.717	1.95	1.88	3.24	4.20	0.749	9.54	1.84
T4 (μg/dL)/FT4 (ng/dL or pmol/L)	14.6 (pmol/L)	14.58 (pmol/L)	8 (μg/dL)	6.92 (μg/dL)	1.59 (ng/dL)	5.67 (μg/dL)	8.64 (μg/dL)	0.98 (ng/dL)	7.09 (μg/dL)	6.89 (μg/dL)	9.62 (μg/dL)	8.77 (μg/dL)	8.28 (μg/dL)	7.09 (μg/dL)	13.68 (pmol/L)	0.99 (pmol/L)	0.92 (ng/dL)
T3 (ng/mL)/FT3 (pg/mL)	3.49 (pg/mL)	4.13 (pg/mL)	4.2 (ng/mL)	1.42 (ng/mL)	2.23 (pg/mL)	1.71 (ng/mL)	1.34 (ng/mL)	2.86 (pg/mL)	1.02 (ng/mL)	1.03 (ng/mL)	1.65 (ng/mL)	1.06 (ng/mL)	1.30 (ng/mL)	1.48 (ng/mL)	3.25 (pg/mL)	9.54 (pg/mL)	NA
Cortisol (μg/dL) 1 μg/dL = 27.6 nmol/L	12.3	7.8	NA	11.1	11.6	13.12	7.1	10.48	6.8	12.9	10.98	5.6	11.2	368 13.3	11	6.3	7.94
DHEAS (μg/dL) 1 μg/dL = 0.0271 μmol/L	206 (124-483)	55 (1.7-62)	NA	64.3 (211-492)	312.4 (136.3-447.6)	49 (124-537)	124 (211-492)	97.2 (168-592)	114 (88-487)	96.4 (88-487)	33.3 (116-479)	57.7 (211-492)	40.2 (211-492)	14.1 (148-407)	96 (161-562)	320 (88.9-427)	NA
Insulin (μIU/mL)	2.6	NA	NA	2.57	Diabetes mellitus	1.86	2.47	2.4	NA	2.73	NA	0.4	4.88	3.84	1.5	7.83	4.28
Glucose (mg/dL) 1 mmol/L = 18 mg/dL	80	82	NA	77	Diabetes mellitus	88	72	80	81	86	NA	NA	85	80	75	84	111
Hypoalbuminemia	—	—	—	+	—	—	—	+	+	+	—	—	+	—	+	—	—
C-reactive protein (mg/L)	5.83	NA	NA	28.35	7.60	15.30	NA	3.98	NA	NA	11.81	33.60	1.52	24	33.60	3.50	8.20

Abbreviations: NA, not available; GH, growth hormone; IGF-1, insulin-like growth factor 1; OGTT, oral glucose tolerance test; TSH, thyroid stimulating hormone; T4, total thyroxin; FT4, free thyroxin; T3, total triiodothyronine; FT3, free triiodothyronine; DHEAS, dehydroepiandrosterone sulfate.

images and increased osteoblastic activity in the distal ends of the both tibiae and the epimetaphyseal region of the long bones in all the delayed images. Additionally, there was abnormally increased osteoblastic activity in the skull in 4 subjects.

Other Clinical Features

In 9/16 (56%) patients a high-arched palate was found (in 6 patients with *SLCO2A1* mutation and in 2 brothers with *HPGD* mutation and in 1 patient without detected pathogenic variant), for the remaining patient this information was not available. In 1 patient with *SLCO2A1* mutation, prominent gingival hypertrophy was observed (Fig. S15 (25)). In 2 patients with *SLCO2A1* mutation pectus excavatum was found. In 2 patients (1 with *HPGD* mutation and 1 with *SLCO2A1* mutation) marfanoid habitus with long arms and thin body was found; 1 of them had also pectus excavatum.

Treatment

All patients except the female patient with mild phenotype received treatment for PHO; 16 patients received pharmacological treatment and 1 patient underwent orthopedic surgery. In the majority of patients (n = 12, 71%) NSAIDs were utilized (among them, the selective COX2 inhibitor etericoxib was the most commonly used). Six patients received bisphosphonates, 4 patients glucocorticoids, and 1 patient hydroxychloroquine. In 2 patients danazol and in 1 patient ruxolitinib were prescribed due to myelofibrosis. Two patients required iron supplementation and 1 patient required potassium supplementation due to hypokalemia while not ingesting glucocorticoids. All patients who were treated with etoricoxib reported improvement in joint symptoms and swelling. The patients who were treated with bisphosphonates experienced improvement in pain. All patients who received steroids or ruxolitinib due to pancytopenia experienced improvement in blood cell morphology; however, 3 patients also required red blood cell transfusions.

Discussion

We show that the majority of our patients with PHO, both with *HPGD* and *SLCO2A1* mutations who were referred for suspected acromegaly, have low fasting GH and IGF-1 levels and low fasting insulin, and male patients have elevated estradiol concentrations. Two families harbored homozygous *HPGD* pathogenic/likely pathogenic changes (1 novel variant) and 10 families had 12 different pathogenic/likely pathogenic variants in *SLCO2A1* (8 novel variants). Eight kindreds had homozygous change while 2 kindreds had compound heterozygous mutation. Two patients from 2 different kindreds had no identifiable pathogenic/likely pathogenic variant in *HPGD* or *SLCO2A1*, but their phenotype was not different from the other patients.

Endocrine Findings

Detailed endocrine assessment has not been previously described for patients with PHO. Enlarged extremities, coarsened facial features, skin changes, and excessive sweating can mimic acromegaly; therefore, endocrinologists need to be aware of the clinical and biochemical picture of pachydermoperiostosis (22). We found subnormal or lower levels of the normal range IGF-1 in all the patients. The lack of complete GH suppression during OGTT could be partly explained by the lean mass of the patients with PHO (mean BMI 20.7 kg/m^2). In a study on healthy subjects, GH nadir concentrations on OGTT were significantly higher in lean and normal weight subjects than in overweight and obese subjects (0.22 vs 0.09 µg/L, $P < .0001$) and 12% of the healthy subjects with a BMI <25 kg/m^2 had GH nadir concentrations above 0.4 µg/L. In our study group, 29% did not suppress GH to <0.4 µg/L on OGTT. The impact of body mass on GH nadir is also true for the healthy males (0.124 vs 0.065 µg/L, $P < .05$) who have generally lower GH nadir than females (30). Low IGF-1 was described before in isolated case reports with (*SLCO2A1* mutation (31)) or without (32) genetic assessment for PHO. We found reduced IGF-1 in patients with both *HPGD* and *SLCO2A1* mutations.

Acromegaly, with elevated GH and IGF-1 levels and a paradoxical rise of GH on OGTT, has been described in a case report of a patient with typical clinical signs of PHO (33). A 5-mm somatotrophinoma was found on histopathology, while no genetic testing was performed to confirm PHO; therefore, it is unclear if this patient indeed had 2 different diseases. There was no pituitary lesion in our patients where magnetic resonance imaging was performed. Tall stature and marfanoid appearance is not typical of PHO, but has been described (height 180 cm, weight 64 kg, BMI 19.7 kg/m^2) (27) and was seen in 1 of our patients (height 202 cm, weight 83 kg, BMI 20.3 kg/m^2 (29). Both of these families had *HPGD* mutation and patients showed not only enlarged hands, feet, knees, and ankles with digital clubbing, but also exhibited a marfanoid habitus with long extremities compared with trunk, poor skeletal muscle development, scarce subcutaneous tissue, high-arched palate, and pectus excavatum. Marfanoid habitus was also found it in 1 of our patients with *SLCO2A1* deficiency (Patient 6).

As patients with PHO have elevated PGE2 levels, a factor recognized as a GH–IGF-1 axis stimulant, the low circulating IGF-1 levels are somewhat unexpected. In animal studies, PGE2 was considered to be a potent secretagogue of GH (34). Experimental studies both in rodents (35) and humans (36) suggested that prostaglandins can stimulate GH-releasing hormone. However, in another study the response of patients in serum concentrations of GH following PGE2 was variable and a stimulatory effect was seen in some, but not in all, individuals (37). In our cohort of patients with PHO we did not observe increased fasting GH levels. We have found rather low levels of morning fasting GH with the median value of 0.93 µg/L and only in 8 patients was the GH concentration slightly above 1.00 µg/L. Decreased IGF-1 levels in some of patients with PHO may be the result of the resistance to GH in the liver. In addition to regulation by GH, IGF-1 secretion is also responsive to nutritional stimuli. In states of undernutrition, GH levels are normal or elevated in the setting of low IGF-1 levels, suggesting GH resistance. This acquired GH resistance is likely to be an adaptive response to decreased energy intake. Some patients with PHO have hypoalbuminemia that could be related to diarrhea and intestinal ulcerations. In our study, 35% of the patients had hypoalbuminemia, and all of them had *SLCO2A1* gene mutations. Isolated protein deficiency, with otherwise normal energy intake, also results in a state of GH resistance. Unlike in starvation, in which a decrease in GH receptors (GHRs) likely contributes to the GH-resistant state, in protein deficiency, the GH resistance state is likely due to a postreceptor defect. The important fact is that protein deficiency not only results in GH resistance but also

likely results in a state of end-organ resistance to IGF-1 (38). In some patients with PHO and low IGF-1 levels the pathogenic mechanism of GH resistance could be similar to patients with inflammatory bowel disease. Patients with active inflammatory bowel disease generally have normal levels of GH along with a reduced level of IGF-1 and some IGF-1 binding proteins. The cause of GH resistance is likely a combination of impaired nutritional uptake and a direct effect of inflammation on the GH–IGF-1 axis resulting in reduced levels of bioavailable IGF-1 (39, 40). Accordingly, the effects of malnutrition, as observed during severe cases of inflammatory bowel syndrome, results in low insulin levels, which negatively impacts GHR expression in the liver (38, 41). Recently, 2 further proteins have been shown to be important regulators of GH resistance in states of nutritional deprivation: fibroblast growth factor 21 (FGF21) and sirtuin 1 (SIRT1) (42). Both FGF21 and SIRT1 induce GH resistance via STAT5 inhibition (38). In our patients, fasting insulin and mean HOMA insulin resistance index were low and none had fasting insulin concentration above 10 mIU/L. Numerous studies have reported direct effects of inflammatory mediators (tumor necrosis factor-α and interleukin-1β) in inhibiting GHR expression that may also play a role in GH resistance in patients with PHO. PGE2 is regarded as an inflammatory mediator and the majority of our patients presented with raised inflammatory markers such as C-reactive protein. The mechanisms underlying inflammation-induced GH resistance comprise direct impacts on the GHR itself through changes in transcription and translation, but also impacts the downstream signaling intermediates which targets the GHR as well as inflammatory cytokine receptors (41). The mechanism of dysregulation of the GH–IGF-1 axis in pachydermoperiostosis, including assessment of FGF21, SIRT1, and GHR expression and function, requires further research.

We found increased estradiol levels in more than 60% of the male patients, but gynecomastia was not observed. Hyperestrogenism has not been previously described in any studies evaluating patients with PHO. It has been previously seen in patients with SHO and simple clubbing (43, 44). Hyperestrogenism in PHO is probably related to an increased estrogen production due to aromatase activation by PGE2 (43). Estrogens—via stimulating SOCS2 which in turn inhibits GHR signaling (45)—represent a further, fifth, factor inducing GH resistance in PHO, in addition to low insulin, increased cytokines, and elevated FGF21 and SIRT1. The only female in our series was a patient bearing the same pathogenic homozygous variant in *SLCO2A1* as her brother (Patient 13). She had normal estradiol levels and regular menstrual cycles, although a new clinical feature in women carrying *SLCO2A1* mutations, premature amenorrhea, has recently been described (46, 47). Another novel finding was a decreased level of DHEAS in the majority of patients. The mechanism could be similar to other chronic inflammatory diseases such as rheumatoid arthritis (48) or inflammatory bowel disease (49). An elevated C-reactive protein was found despite the fact that the majority of our patients were on NSAIDs at the time of assessment and COX2 inhibitor treatment was proved to decrease inflammation markers in patients with PHO (50).

It is a characteristic finding that the vast majority of our patients had low BMI, low serum creatinine levels, and low fat and muscle mass. Serum creatinine, a parameter dependent on muscle mass, remains constant for the average healthy subject between 20 and 70 years of age, with a mean of 0.90 mg/dL and normal reference interval 0.63 to 1.16 mg/dL for (White) men (51), while slight differences exist depending on ethnicity (52, 53). Low serum creatinine is a better surrogate marker of low muscle mass than a low BMI (54). This phenotype was seen in our patients. Patients with PHO may have low muscle mass due to excess PGE2 (55), as PGE2 causes muscle atrophy by activating the lysosomes, possibly by extrusion of lysosomes from myofibrocytes, as has been observed in the uterine cervix before delivery (56). However, data on the effect of PGE2 on muscles are conflicting in the literature. In older studies it was found that PGE2 increases muscle protein degradation and decreases muscle protein synthesis, and elevated prostaglandins were linked to sarcopenia in aging individuals in animal studies (57, 58). Therefore, it has been postulated that NSAIDs may attenuate the negative effect of prostaglandins on muscles. COX-inhibiting drugs were found to augment muscle mass and strength improvements during resistance exercise based treatment of sarcopenia in older individuals (59). Interestingly, more recent studies show multiple lines of evidence indicating that prostaglandins likely contribute to anabolic signaling events in skeletal muscles (60). For instance, PGE2 stimulates muscle-specific stem cells capable of tissue regeneration throughout life (61) and inhibition of PGE2 production through NSAID administration just after injury hinders regeneration and compromises muscle strength (61). In recent studies a decrease in prostaglandins due to increased 15-HPGD activity was hypothesized to be responsible for muscle atrophy and diminished strength in aged muscles (62).

Gastrointestinal Findings

We found a higher percentage of gastrointestinal abnormalities than reported in the literature: half of our patients complained of gastrointestinal symptoms and 47% of the patients underwent endoscopy, and this identified gastritis, gastrointestinal ulcers, and thickening of the gastric folds. Hypertrophy of gastric mucosa and watery diarrhea occurs in both patients with *HPGD* or *SLCO2A1* mutation, while gastric and intestinal ulcers, chronic gastritis, and gastrointestinal hemorrhage only affects patients with a defective *SLCO2A1* gene (9, 50, 63). Watery diarrhea could typically be triggered by drinking cold drinks or by sexual arousal, which is very disturbing for patients (29, 64). Gastrointestinal ulceration can lead to anemia and hypoalbuminemia, but anemia and hypoalbuminemia can also occur in patients with watery diarrhea (5). As elevated PGE2 could accelerate gastric mucosa cell proliferation, some authors suggest an increased risk of gastric cancer in patients with PHO (63, 65) but this was not observed in our cohort.

PHO can cause chronic enteropathy which may mimic Crohn disease (66-69). There is an entity, chronic enteropathy associated with the *SLCO2A1* gene (CEAS), which is characterized by multiple small intestinal ulcers of nonspecific histology (70) and symptoms including abdominal pain, diarrhea, hypoalbuminemia, and anemia. These manifestations typically appear during adolescence and the clinical course is chronic and intractable. While the majority of the 75 previously reported patients with CEAS were of South Asian origin (Japanese, Chinese, and Korean) (68, 69, 71), 2 female siblings of European origin have been recently reported (72). Among *SLCO2A1* mutations, a splice-site mutation at intron 7 (c.940+1 G>A; rs765249238), was the most frequently observed in patients with CEAS (68, 69). This mutant allele frequency is 0.091% in the Japanese population (68), but it is rarely found in White ethnicity (68, 70). To date, the diagnosis of CEAS has been based on clinical

symptoms and confirmation of small bowel lesions compatible with the disease. Because CEAS mimics ileal Crohn disease with respect to ileal ulcers and stenosis, it is often difficult to distinguish CEAS from Crohn disease by clinical features alone. In a study of 65 patients with suspected CEAS, 46 patients were identified with homozygous or compound heterozygous *SLCO2A1* mutations. In these patients, ileum was the most frequently involved small intestine (98%) (68). One or more clinical manifestations of PHO, such as digital clubbing, periostosis, and pachydermia, are present in 20% to 35% of patients with CEAS with approximately 10% fulfilling the major diagnostic criteria of PHO (the complete form of PHO) (68, 69, 72). It is noteworthy that all of the patients with PHO-like symptoms were males, even though CEAS predominantly affects females (70%). Male patients generally show more severe manifestations because PGE2 production is greater in males than in females (2). Considering that CEAS and PHO are autosomal recessive inherited disorders with shared causative gene mutations, the possible influence of sex-related modifier genes or hormones should be considered for differences in clinical manifestations in males and females (68). However, the only female patient from our group did not have any gastrointestinal symptoms, anemia, or hypoalbuminemia, suggesting that she does not have CEAS. In our study, 2 brothers (Patient 9 and Patient 10) harbored the splice-site mutation at intron 7 (c.940+1G>A), which is the most frequently observed variant in patients with CEAS. This variant has been shown in in vitro functional assay to reduce PGE2 uptake into cells (73). Patient 9 and Patient 10 had the full picture of PHO as well as gastrointestinal symptoms, giant gastric folds on endocopy, hypoalbuminemia, and anemia in lab tests; however, no gastrointestinal ulcers, typical for CEAS, were found on endoscopy. In 2 other patients (Patient 12 and Patient 15) with different *SLCO2A1* variants (Table S3 (25)) intestinal ulcers on endoscopy were detected and these patients suffered from diarrhea, anemia, and hypoalbuminemia. Thus, these 2 patients fit the characteristics of CEAS.

Anemia

Anemia associated with PHO could be due to several causes: chronic, insidious bleeding, malabsorption related to bowel inflammation, chronic inflammation itself, and—in *SLCO2A1* patients—due to myelofibrosis. In our group of patients with PHO, anemia was present in 69% of patients with both *SLCO2A1* and *HPGD* variants. Severe anemia due to biopsy-proven myelofibrosis requiring blood transfusions was present in 4 patients, all with *SLCO2A1* mutations. Similarly to CEAS, the pathogenesis of hypocellular myelofibrosis may be related to SLCO2A1, although anemia has been described in CEAS patients without myelofibrosis (68).

Skeletal Changes

In our series, bone alterations ranged from mild to severe grade at the distal end of long and small tubular bones and this variability phenotypic variability is well-described (74). Plain radiograph usually shows bilateral symmetric involvement of tubular bones (both long bones and phalanges) and calcification at the end of tendons can also be seen. ^{99m}Tc-MDP bone scan is more sensitive than plain radiographs and can detect bony changes earlier, best appreciated on delayed images on a triphasic study. This is attributed to vasodilation and subperiosteal reaction at the distal end of long bones and phalanges (75). Though the subperiosteal bone mass is increased, the bone mineral density values are usually normal. This is due to cortical porosity and loss of trabecular volume (76). These types of changes are mediated by PGE2 which is a key to local osteolytic hypercalcemia as also seen in metastatic breast cancer (77). Although phenotypically PHO could be mimicked by other conditions, the full scale of typical skeletal changes are not found in acromegaly or thyroid acropachy (78). Uncommon conditions like fluorosis, hypervitaminosis (78) and Caffey disease (79) are differentiated from PHO by endemicity, dental involvement and other associated clinical features.

Genetic Changes

We identified 9 novel variants in our cohort. Both clinical phenotype and in silico predictions support the pathogenicity of these variants. While there are a number of overlapping features, some differences can be found in clinical phenotype between patients with *HPGD* and *SLCO2A1*: age of presentation, male gender preponderance, prominence of forehead furrowing, acro-osteolysis, presence of gastrointestinal ulcers and development of myelofibrosis. Within the group of patients with *SLCO2A1*, genotype–phenotype correlation has been seen for the *SLCO2A1* splice-site mutation and our data correspond with this, although gastrointestinal problems can occur with other variants as well. We have not seen other correlations. For instance, patients phenotypes are similar between patients with truncating or nontruncating variants, but comprehensive assessment from multiple cohorts will be needed to identify such differences. We have assessed all pathogenic and likely pathogenic variants found in ClinVar to see if there is an overall pattern of the location of the variants (Fig. S18 (25)). This shows that variants are scattered all over the protein and do not show specific domains more often affected than others. These data suggest that full length of all the exons of the 2 genes need to be assessed, as no obvious hotspot regions can be identified. Our results will be useful for clinicians and researchers to assess genetic variants and to understand the phenotypic variation of this disease.

Our genetic screening could not identify the disease-causing variants in 2 kindreds (Patient 16 and Patient 17) despite both patients having a full clinical phenotype. Patient 17 harbors a homozygous missense c.1186G>A (p.Ala396Thr) and heterozygous synonymous c.840A>G (p.Arg280=) variants in *SLCO2A1* (Table S4 (25)). Although in silico predictions assign some features to these 2 variants (protein stability tests predicted that p.Ala396Thr has decreased protein stability and Human Splice Finder, Mutation Taster and MaxEnt predicted that c.840A>G results in activation of a new cryptic acceptor site and potential alteration of splicing), there is a high heterozygote and homozygote allele frequency (Table S4 (25)) supporting that these are unlikely to contribute to the phenotype. Three benign variants were identified in Patient 16, 2 in the *SLCO2A1* gene and 1 in the *HPGD* gene (Table S4 (25)). All 3 are common in general population, although MutationTaster prediction the homozygous c.234+45G>C change may cause splice site changes.

Limitations of the Study

Some of the clinical parameters are not available for all the patients in the study. We did not have detailed clinical and genetic assessment on all of the first degree relatives, to fully describe the heterozygote patient phenotype. No functional studies were performed on the novel variants.

Conclusions

In summary, we established that low IGF-1, elevated estradiol levels and low BMI are frequent features in both PHOAR1 and PHOAR2 while analyzing data from 14 kindreds with PHO carrying 9 novel and 5 known pathogenic/likely pathogenic genetic variants.

Acknowledgments

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Disclosures

The authors have nothing to disclose.

Data Availability

Original data generated and analyzed during this study are included in this published article or in the data repositories listed in References.

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