A novel mutation in the *HPGD* gene results in the unusual phenotype of palmoplantar keratoderma with digital clubbing and hyperhidrosis

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Key words: digital clubbing; *HPGD* gene; palmoplantar keratoderma; hyperhidrosis.

Palmoplantar keratoderma (PPK) is a disorder of keratinization. Here we present an unusual case of PPK in association with hyperhidrosis and digital clubbing. This patient had a novel homozygous mutation in the *HPGD* gene, a mutation not previously reported in the pathogenesis of this phenotype.

Abbreviation used:
PPK: palmoplantar keratoderma

REPORT

A 24-year-old man with consanguineous parents presented to our clinic with a 10-year history of palmoplantar skin thickening as well as hyperhidrosis (Figs 1 and 2). The patient was examined by more than 5 separate dermatologists. On physical examination, the patient had hyperkeratosis of his palms and soles and hyperhidrosis. The patient also had digital clubbing of all 20 digits, namely, obliteration of the Lovibond angle of all 20 nails (Figs 1 and 2). The rest of the physical examination findings were normal. Family history was negative for any similar condition.

A 4-mm punch biopsy specimen was taken from the patient's left palm, which showed hyperkeratosis, hypergranulosis, mild epidermal hyperplasia, and sparse superficial perivascular lymphocytic infiltrate consistent with keratoderma (Fig 3). Systemic workup for any cardiopulmonary disease and malignancy was nonrevealing.

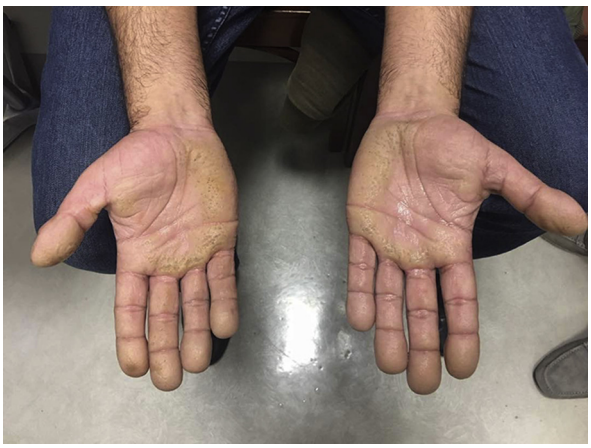

Fig 1. Keratoderma over the palms with hyperhidrosis and notable digital clubbing.

Peripheral blood sample was collected. DNA extraction from the blood was performed using the QIAamp DNA blood midi kit from Qiagen (Cat No./ ID: 51185) using the manufacturer's protocol. Exome sequencing was performed on the patient's DNA to

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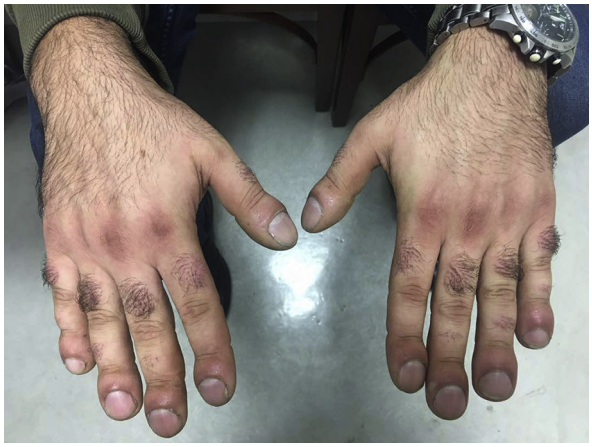

Fig 2. Digital clubbing of all 10 fingertips.

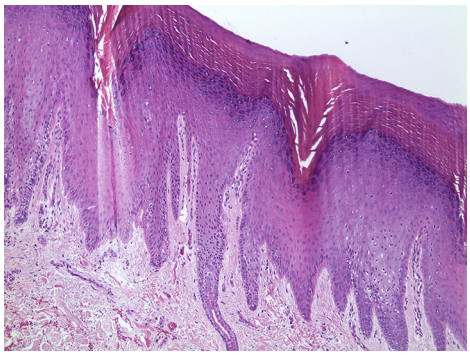

Fig 3. Punch biopsy from patient's left palm consistent with keratoderma.

Table I. Reported cases of palmoplantar keratoderma with digital clubbing

Study	History	Family History
Bureau et al[1]	Two brothers with palmoplantar keratoderma, digital clubbing, and hyperhidrosis. Age of onset 7-8 y	Consanguineous parents, with a positive family history
Hedstrand et al[2]	Two sisters with palmoplantar keratoderma, digital clubbing, and hyperhidrosis. Age of onset during childhood (not specified).	Consanguineous parents, with a negative family history
Rauch et al[3]	One patient with palmoplantar keratoderma, digital clubbing, and hyperhidrosis. Age of onset in early childhood (not specified).	Nonconsanguineous parents, with a negative family history.
Barraud-Klenovsek et al[4]	Palmoplantar keratoderma, digital clubbing, and hyperhidrosis. Age of onset not specified.	Nonconsanguineous parents, with a negative family history

determine the molecular signature(s) underlying his condition.

We used the exome capture method of the V6 Sure Select Kit from Agilent (Santa Clara, CA), and ran the libraries on a HiSeq4000 platform from Illumina (Macrogen, Geumcheon-gu, Seoul South Korea). We mapped the generated Fastq files to reference genome using the Burrows-Wheeler Alignment Tool. Using the Genome Analysis Tool Kit, insertions/deletions realignment and variant calling and filtering were conducted. Variant annotation was carried out using SnpEff (Pablo Cingolani, Boston, MA), and results were sent back in Microsoft Excel alongside the BAM and VCF files. The total read bases (bp) was within the 7 to 7.8 $\times$ 10^6 range. The average throughput depth of target regions was 128.5 with more than 70% coverage of >50X. Analysis was then conducted as follows: we first filtered the ~100,000 single nucleotide polymorphisms and short insertions and deletions by eliminating the synonymous variants and variants in the noncoding regions of the genes to reach up around 12,000 single nucleotide polymorphisms and short insertions and deletions. The latter were then filtered out again to keep only the variants with less than a minor allele frequency of 10%.

We identified a novel homozygous mutation in the *HPGD* gene, c.468T>A, leading to a change in the amino acid histidine to glutamine (p.His156Gln). The mutation was not found in 200 chromosomes screened from individuals of the same population. Additionally, in silico analysis using 3 types of software including SIFT (Bioinformatic Institute, Biopolis, Singapore), PolyPhen (Division of Genetics, Brigham & Women's Hospital, Harvard Medical School, Boston, MA), and Varsome (Saphetor, EPFL Innovation Park. Lausanne, Switzerland) predicted the mutation to be deleterious/damaging, and the normal allele frequency across several populations was close to zero.

The triad of PPK, digital clubbing, and hyperhidrosis is rare. PPK and digital clubbing have been reported in few cases, although genetic workup in was not performed (Table I).

HPGD encodes for 15-hydroxyprostaglandin dehydrogenase, an enzyme that catabolizes prostaglandins and is implicated in the pathogenesis of hypertrophic osteoarthropathy (Table II); however,

Table II. Reported mutations of *HPGD* gene with associated phenotypes

Study	Mutation	Phenotype
Bergmann et al[5]	c.175_176del	One patient with the same mutation both with digital clubbing, only 1 with hyperhidrosis.
	c.118G>T c.563C>T	One patient with 2 mutations associated with hyperhidrosis and digital clubbing.
Sinibaldi et al[6]	c.G217+1G>A	One patient with digital clubbing and hyperhidrosis.
Uppal et al[7]	c.175_176delCT	Three siblings with nonconsanguineous parents all with digital clubbing, hyperhidrosis, and pachyderma.
	c.418G>C A140P	Eight family members with digital clubbing and hyperhidrosis. Distant consanguinity.
Tariq et al[8]	c.577T>C	Eleven family members with digital clubbing without hyperhidrosis or other skin manifestations.
Yuan et al[9]	c.310_311delCT	Nine patients (two related, the remaining 7 unrelated) all with digital clubbing and pachyderma.

the role of this gene in the development of palmoplantar keratoderma is not known. It is thought that mutations in the *HPGD* gene lead to elevated levels of prostaglandins, which stimulate tissue remodeling and clubbing of the digits.[5]

Here we identified a novel homozygous mutation in the *HPGD* designated p.His156Gln implicated in the development of hypertrophic osteoarthropathy, hyperhidrosis, and palmoplantar keratoderma.[6,7]

The involvement of the *HPGD* gene in the pathogenesis of this condition offers a novel approach in the treatment of these patients. Prostaglandin inhibitors may play a role in treating such individuals. Targeted gene therapy may play a vital role in both the prevention and treatment of these patients in the future.

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