Palmoplantar keratoderma and digital clubbing in 2 sisters with hypertrophic osteoarthropathy

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INTRODUCTION

Several hereditary syndromes manifest with a distinct thickening of the palmar skin referred to as keratoderma. However, historically, the genetic cause of the condition has not always been resolved. We report 2 sisters who presented with palmoplantar keratoderma, digital clubbing, and hyperhidrosis, who were subject to a clinical case report in 1972.[1] At a revisit, 50 years after the initial case presentation, the family was molecularly diagnosed with a deleterious variant in the gene 15-hydroxyprostaglandin dehydrogenase (*HPGD*), found in both sisters (OMIM #259100). This case report illustrates the natural course of hypertrophic osteoarthropathy over 50 years.

Abbreviation used:

HPGD: 15-hydroxyprostaglandin dehydrogenase
PHO: primary hypertrophic osteoarthropathy
PPK: palmoplantar keratoderma

CASE REPORT

Our index case (IV-1) was a woman with keratosis on her palms and soles that started in early childhood. In her 20s, she was clinically diagnosed with *keratodermia palmaris et plantaris*, accompanied by digital clubbing and a skeletal deformity of the distal aspect of the phalanges of her fingers and toes. Because of pronounced hyperhidrosis, she underwent bilateral cervical sympathectomy at the age of 20. At 30 years of age, she again received medical attention for the clubbing of her fingers and toes. An X-ray investigation of her hands revealed an atrophic deformity of the apical tuft of the distal phalanges, which appeared spatulated. Her ankles had coarse cortex structures but no cortical thickening. Extended investigations did not find any aberrations indicative of respiratory, cardiac, or endocrine disease. Besides descriptive diagnoses, no explanation could be given regarding the cause of the triad at that time.[1]

IV-1 was the oldest of 3 sisters in a family with 4 children (Fig 1). Her younger sister by 2 years (IV-3) was equally affected by hyperkeratosis, hyperhidrosis, and clubbing of the fingers and toes. Additionally, IV-3 had similar deformities of her terminal phalanges, evident from an early age. Consecutive X-ray investigations during her 20s showed no progress of the skeletal abnormalities. The parents and the 2 other siblings did not display any of the disease manifestations. However, the parents were first cousins, making a recessive mode of inheritance likely (Fig 1). No other relatives

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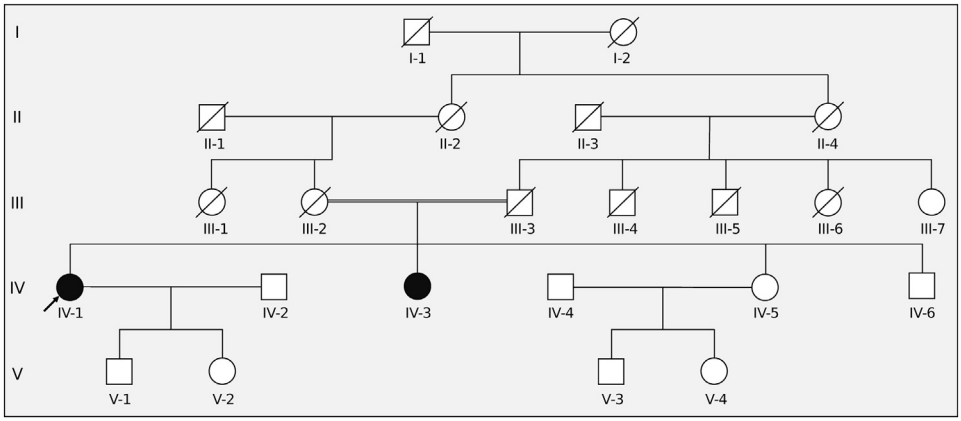

Fig 1. Pedigree of the affected family. Black color marks subjects affected by palmoplantar keratoderma, digital clubbing, and hyperhidrosis.

were known to suffer from similar symptoms, and the son and daughter of IV-1 and her 5 grandchildren were healthy in this regard.

At 82 years of age, IV-1 presented again to our clinic with onychosis and her >70-year history of palmoplantar keratoderma (PPK). She displayed brittle hypertrophic nails with severe onycholysis and a nearly complete detachment of her left thumbnail (Fig 2). A symmetrical focal keratosis still affected the palms of her hands and took on a wavy pattern as it stretched out to the tips of her fingers. The keratosis on the soles of her feet was predominantly localized to the forefeet and heels. The wavy pattern was not as noticeable as on the phalanx of her fingers, which all displayed signs of clubbing. Residual signs of hyperhidrosis were apparent on her shins and feet. Besides PPK, presbycusis, osteoarthritis in her knees, and cataract surgery, IV-1 was healthy and not receiving any medical treatment. A technetium-99m bone scintigraphy scan, initiated after a suspected abnormal tomography of a knee joint, only demonstrated increased but irregular absorption in the calvarium, which is not unusual in older women.[2] *Trichophyton rubrum* DNA was isolated from her toenail and her nails improved with oral terbinafine 250 mg once daily for 6 weeks.

To screen for a potential genetic cause, we performed whole exome sequencing on a blood sample from IV-1. Genomic DNA was extracted from EDTA blood. Genetic variation in *HPGD* was identified by aligning the TWIST comprehensive exome (Twist Bioscience) sequencing reads to the hg19 reference sequence followed by variant calling and annotation. We used the bioinformatic pipeline bcbio-nextgen version 1.1.5 (pypi.org/project/bcbio-nextgen), including bwa 0.7.17, picard 1.96, SAMtools 1.9, and GATK 4.1.3.0. Variant annotation was performed using Ensembl Variant Effect Predictor. Directed Sanger sequencing of *HPGD* exon 2 was performed using forward primer TGCCAAATTTCAGGTCCAGG and reverse primer TCAAGGTAGCTGCTCTCGAG.

This way, we identified a homozygous deletion of base pairs 175 and 176 (c.175_176del, p.Leu59ValfsTer8, NM_000860.6, rs548208942) in the gene *HPGD*. The variant results in a frameshift that introduces a premature stop codon 7 amino acid residues after the deletion. Therefore, this variant truncates the 266-amino acids long protein after merely 65 residues. Using Sanger sequencing across the deletion, we could validate the variant and confirm its presence in both the index patient and her sister IV-3, who was also found to be homozygous for the pathogenic variant.

DISCUSSION

More than 50 years after their initial presentation, both sisters were diagnosed with the monogenic disease primary hypertrophic osteoarthropathy (PHO; OMIM #259100). Their pathogenic genetic variant has previously been linked to PHO with recessive inheritance.[3,4] PHO often manifests with osteoarthropathy and digital clubbing, pachydermia, delayed closure of the fontanels, coarsening of facial features, thickened calvarium, and congenital heart disease.[5] In line with the phenotypic heterogeneity of the condition, our index case had a delayed closure of her sagittal fontanel, but no coarsening of facial features or signs of heart disease.

Although patients with *HPGD* mutations are not always present with PPK, the clinical presentation in our index patient was dominated by the pronounced keratoderma.[6-9] It displayed the characteristic wavy appearance and coarse structure on palpation. We abstained from taking a palmar biopsy sample and X-ray image since the additional examinations most

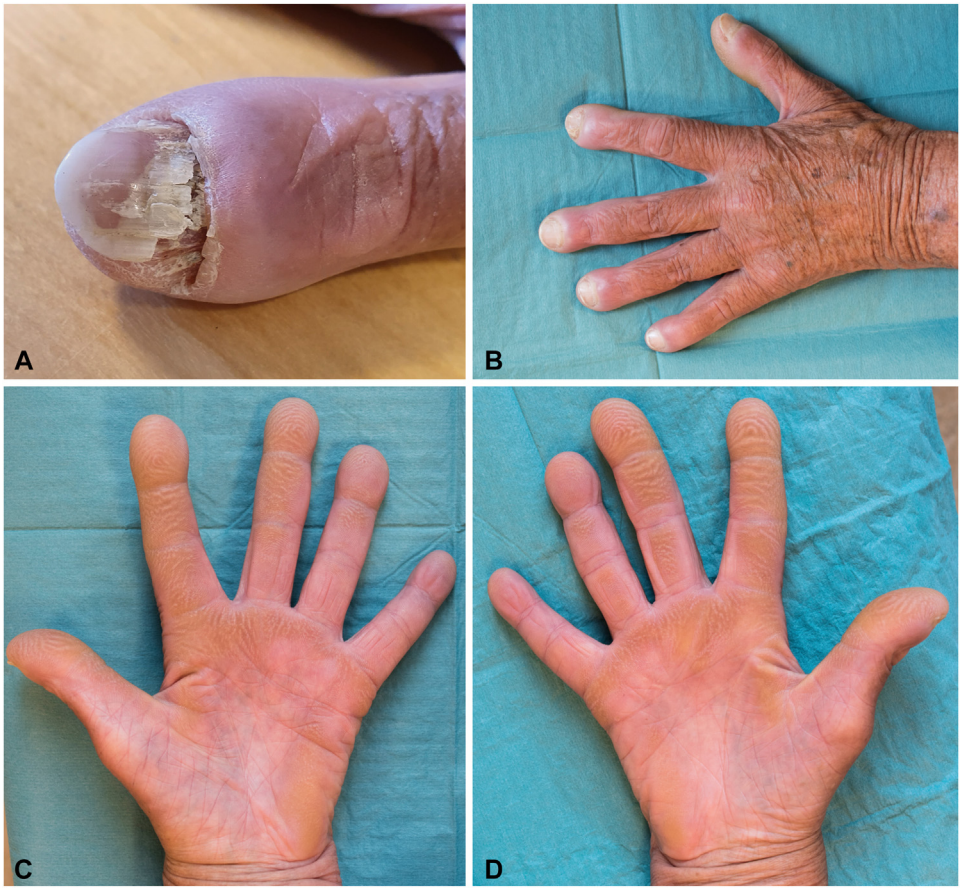

Fig 2. A, Severe onycholysis affecting the subject's right thumb nail. **B,** Notable digital clubbing. Keratoderma affecting the (**C**) left and (**D**) right palms.

likely would have little or no impact on our clinical decision-making. The palmar histology of PPK has previously been described with epidermal hyperplasia and in hyperkeratosis [9].

HPGD is a key enzyme for the biological inactivation of prostaglandins. Hindrance of prostaglandin synthesis by cyclooxygenase inhibitors has been investigated as a means to control disease manifestation in patients with pathogenic variants of *HPGD* [4].

In summary, we report 2 sisters with palmoplantar keratoderma, digital clubbing, and hyperhidrosis, who were diagnosed with PHO using exome sequencing. Their relative longevity and good health, apart from the described disease manifestations, can hopefully bring comfort to younger patients presenting with a similar condition.

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Conflicts of interest

None disclosed.

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