Case Letters

Primary hypertrophic osteoarthropathy: Report of two novel genetic variants in the *SLCO2A1* gene in two Mexican patients

Sir,

Primary hypertrophic osteoarthropathy (OMIM #259100, #614441), also known as pachydermoperiostosis and Touraine–Solente–Golé syndrome, is a very rare disease characterized by the presence of pachydermia, digital clubbing and periostosis.[1]

Its pathogenesis involves genes related with prostaglandin E2 metabolism. Cases have been reported with an autosomal recessive inheritance pattern with pathogenic variants in *HPGD* and *SCLCO2A1* genes responsible for pachydermoperiostosis type 1 and 2, respectively. In addition, some cases with an autosomal dominant pattern have been reported in which the responsible genes are unknown.[1,2]

Here, we report two patients with novel mutations in the *SLCO2A1* gene. Patient 1 was a 23-year-old male patient who attended the dermatology clinic with a 10-year history of severe acne and hyperseborrhea. On physical examination, the presence of deep furrows and thickened skin on his forehead and cheeks, acne scars, digital clubbing of hands and feet and knee swelling were noticed [Figure 1]. An X-ray of the extremities revealed new periosteal bone formation circumferentially along the shaft of the tibia and fibula as well as cortical thickening at the distal ends.

The second patient was a 24-year-old male patient with an 11-year history of bilateral knee pain, swelling and reduced range of movement. On physical examination, we noticed the presence of deep frontal furrows, thickened upper and lower eyelids, Ota nevus on the left side of the face, prognathism, bilateral knee and ankle swelling, clubbing of fingers and toes and watch-glass nails [Figure 2]. The anteroposterior X-ray of the knee revealed a subperiosteal reaction in the lateral condyle of the femur and tibia.

Both patients lacked a family history of similar occuring. Laboratory findings, including complete blood count, thyroid function tests and serum growth hormone levels, were normal. Pachydermoperiostosis was diagnosed based on clinical findings.

Patient 1 was compound heterozygous due to a duplication of the second coding base of the *SLCO2A1* gene, which was detected by Sanger sequencing and confirmed by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). The mutation was found in exon 1 at the start codon, and a severe effect on transcription of the gene is expected. The c.572G>C variant identified is a missense mutation that results in a change of Glycine to Alanine located at the residue position 191 where a transmembrane helix is found and where other pathogenic mutations have previously been reported.[3] The mutation is predicted to be pathogenic by PolyPhen-2 predictions. Another known polymorphism, c.1186G>A (p.A396T), has also been identified.

In the second patient, a homozygous c.96+5>A change in the first intron was identified that is close to the first exon affecting splicing,

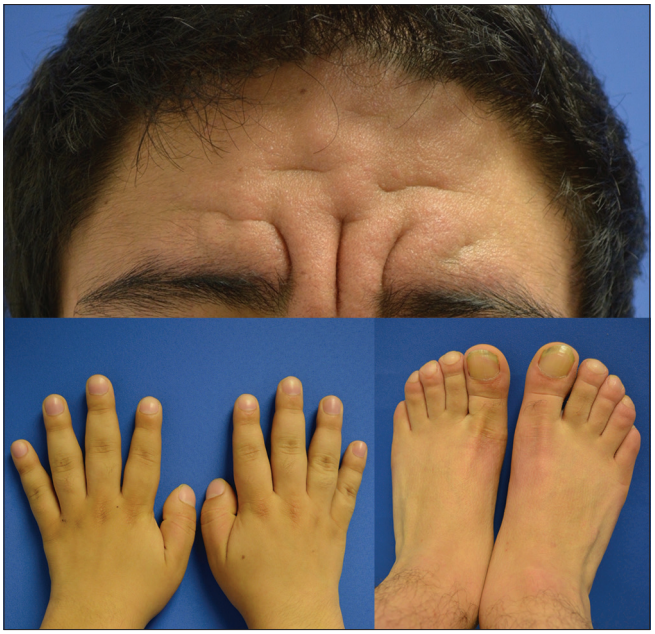

Figure 1: Patient 1: Presence of deep furrows and thickened skin on the forehead and digital clubbing

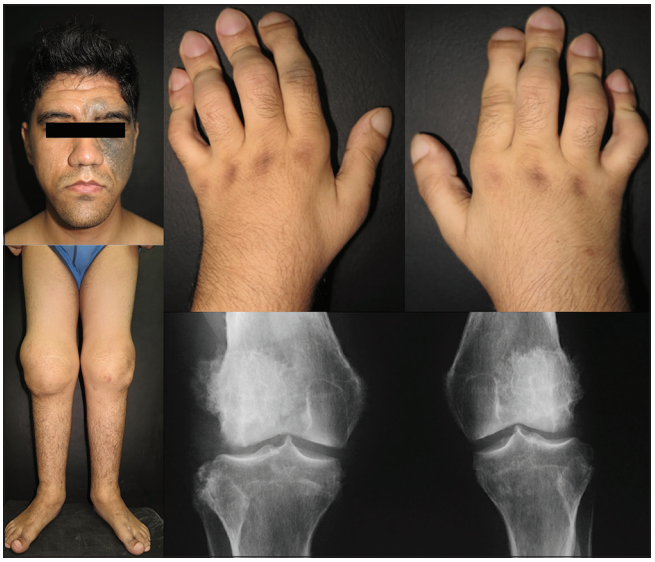

Figure 2: Patient 2: Presence of deep frontal furrows, nevus of Ota on the left side of the face and prognathism, bilateral knee and ankle swelling, digital clubbing and watch-glass nails. The anteroposterior X-ray of the knee reveals a subperiosteal reaction in the lateral condyle of the femur and tibia

which is considered pathogenic. Mutation analysis was only performed in the father, and we found that he is a carrier of the same genetic variant.

More than 40 pathogenic variants have been described for the *SLCO2A1* gene.[3,4] Till date, no clear genotypic/phenotypic correlation exists. However, some authors have reported that in some genetic variants, such as nonsense or splicing mutations, more severe phenotypes can be observed.[5] Clinical manifestations in patients with *SLCO2A1* gene mutations exhibit variable expressivity. However, it is important to highlight that most cases have been described in males and clinical characteristics appear at puberty. In patients with mutations in the *HPGD* gene, earlier disease initiation is noted. There are several hypotheses regarding the association of disease initiation and sex hormones, although these hypotheses have not been confirmed.[4] Although the effects of increased prostaglandin E2 on the skin are not fully understood to date, increased levels of this prostaglandin promote the development of the epidermis, epidermal hyperplasia and sebaceous gland hyperplasia in animal models.[6] In addition, a more severe phenotype is noted in patients with higher urinary prostaglandin E2 levels.[5]

In conclusion, we identified two different *SLCO2A1* mutations. Further testing of mRNA expression in *in-vivo* models is needed to understand the effect of the genetic variants identified in these patients.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that name and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

Alejandra Villarreal-Martínez, Osvaldo T. Vázquez-Martínez, Laura E. Martínez-de-Villarreal[1], Domingo Garay-Mendoza[2], Candelario Rodríguez-Vivian, Jorge Ocampo-Candiani, Edgar De La Rosa-Marbán[1], Marisol Ibarra-Ramírez[1]

Departments of Dermatology, [1]Genetics and [2]Traumatology and Orthopedics, Hospital Universitario "Dr. José Eleuterio González", Monterrey, Nuevo León, México

Correspondence: Dr. Marisol Ibarra-Ramírez, Francisco I. Madero Y Gonzalitos, Mitras Centro, Monterrey, Nuevo León 64460, México.
E-mail: m.ibarrar25@gmail.com

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