Correspondence

A novel homozygous mutation in the *SLCO$_2$A1* gene is associated with severe primary hypertrophic osteoarthropathy phenotype in a Saudi patient

Primary hypertrophic osteoarthropathy (PHO), which is a rare autosomal recessive genetic disorder characterized by pachydermia, clubbing, and periosteal reaction, typically begins during childhood or adolescence and progresses gradually over years before the disease stabilizes.

Here, we report a Saudi male patient with a severe form of PHO. Molecular analysis of *HPGD* and *SLCO2A1* genes revealed the presence of heterozygous duplication (c.93+1_93+3dupGTA) and homozygous (c.1016C>T) mutations, respectively. Both mutations in *HPGD* and *SLCO2A1* genes were considered novel mutations. These mutations were not previously described in any of the public domain databases and were not found in our 50 healthy and ethnically matched control individuals.

Heterozygosity of *HPGD* mutation is insufficient to be a pathogenic cause of PHO. However, the presence of homozygosity in the *SLCO2A1* mutation (p.Ser339Phe) confirmed the disease causative mutation.

Primary hypertrophic osteoarthropathy (MIM 614441), also known as pachydermoperiostosis, is a rare disorder characterized by pachydermia, clubbing of fingers, and periostosis.[1,2] The secondary hypertrophic osteoarthropathy is usually associated with an underlying cause of pulmonary, cardiac disease, or hepatic and intestinal disease.[1,3] The disease severity is more common with prominent tendency in males compared to female patients.

Recently, mutations within 15-hydroxyprostaglandin dehydrogenase (*HPGD*)[4,5] and solute carrier organic anion transporter family member 2A1 (*SLCO2A1*)[6,7] genes were found in PHO and contribute to the severity of the disease.

A 23-year-old man was referred to the dermatology clinic to assess facial acne associated with acromegalic features. The patient had grooving in the scalp, greasy skin with acne, and progressive facial furrowing. Palms and soles showed excessive sweating. The progressive enlargement of fingers, toes, hands, and feet with mild pain of large joints were also noticed. There are no other similar complaints in his family.

On examination, the patient was not in distress. Vital signs were stable. Scalp examination revealed cutis verticis gyrata (Fig. 1a). Facial examination revealed a leonine face with indurated thickening of the skin on the forehead with deep rhytides. Mild inflammatory papular acne and seborrheic dermatitis were seen. Hand examination revealed digital clubbing associated with hypertrophy of hands and clear palmoplantar hyperhidrosis (Fig. 1b) with no signs of joint swelling.

Except for a mild decrease of the hemoglobin level with a value of 12.4 g/dl, all of his other laboratory investigations done were within normal limits, including complete blood count, urea, and electrolytes, liver function test, renal profile, thyroid stimulating hormone, growth hormone, and insulin-like growth factor-1.

X-ray examination of the tibia, wrists, and phalanges showed a periosteal reaction with cortical thickening and subperiosteal new bone formation (Fig. 1c). The patient was given botox injections over the palms, clindamycin phosphate 1% topical solution, tretinoin 0.5 mg topical cream over the face, and was referred to rheumatology for arthralgia management.

Peripheral blood samples were obtained after signing a written consent form from the patient and 50 healthy controls. Genomic DNA was extracted from peripheral blood leukocytes using standard techniques. *HPGD* and *SLCO2A1* genes were amplified by polymerase chain reaction and bidirectional sequence using ABI prism Big Dye Terminator v. 3.1 cycle sequencing kit (Applied Biosystems, Foster City, CA, USA) in an ABI 3130 Genetic Analyzer sequencer (Applied Biosystems). Mutations were identified by comparison with the reference sequences of *HPGD* (GenBank accession no NM_000860.5) and *SLCO2A1* (NM_0005630.2), respectively, using CLC Genomics Workbench v 6.0 (CLC bio, Aarhus, Denmark) and checked against an updated single nucleotide polymorphism (SNP) database (dSNPs; http://www.ncbi.nih.gov).

Molecular analysis of the *HPGD* gene identified duplication in exon 1 of the *HPGD* c.93+1_93+3dupGTA mutation in heterozygous state in which this mutation altered the donor splice site of exon1 and not previously described as SNP or mutation in any of the public databases, including dSNPs. Although the presence of such c.93+1_93+3dupGTA heterozygosity mutation is insufficient to cause PHO. Furthermore, molecular analysis of *SLCO2A1* gene revealed the presence of a novel c.1016C>T (p.Ser339Phe) homozygous mutation in exon 8 (Fig. 1d). More analysis on this mutation (c.1016C>T) using different bioinformatics tools, including Mutation

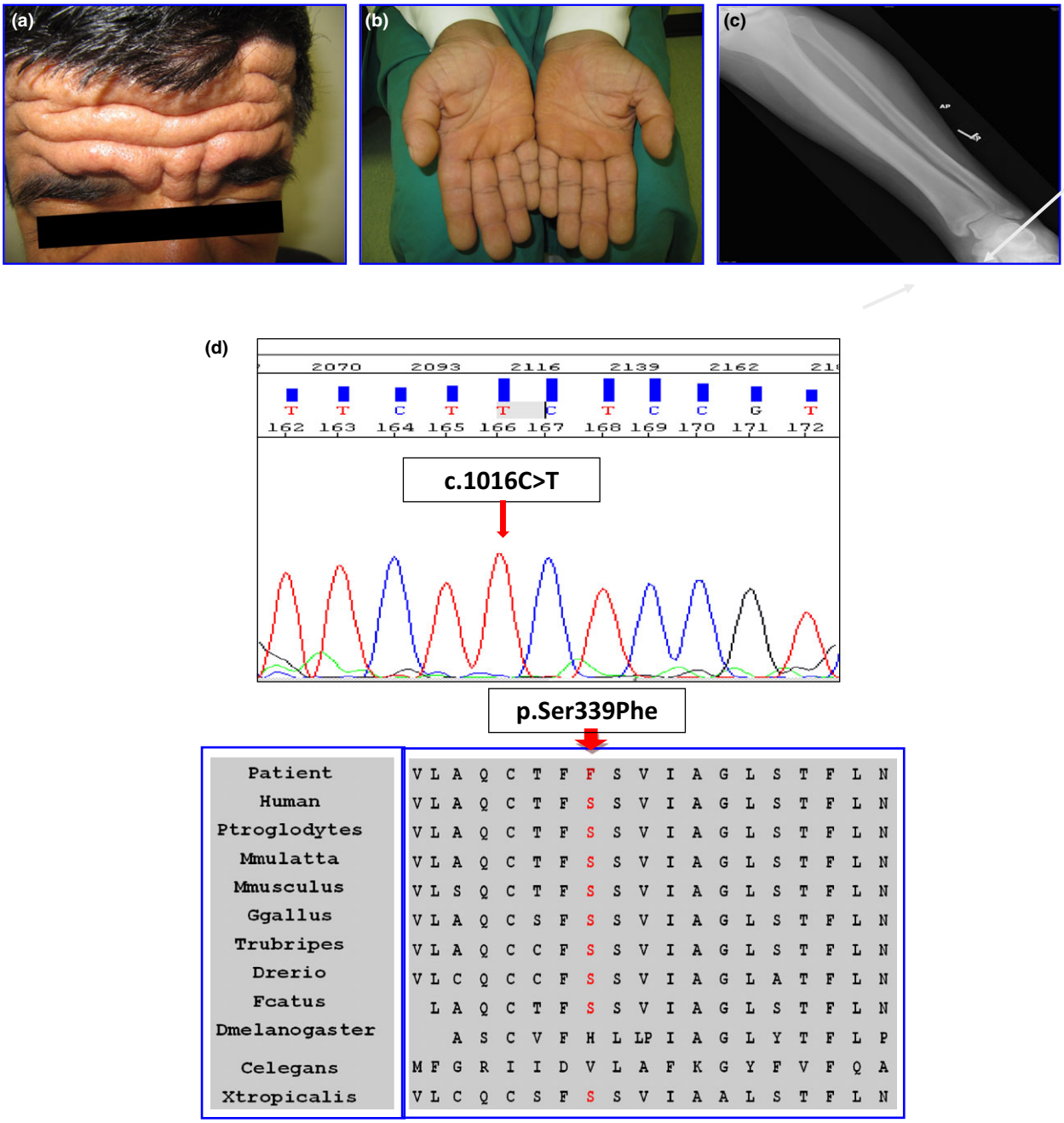

Figure 1 (a) Photograph showing the forehead of the patient with deep skin folds and seborrheic skin with wide pores. (b) Photograph of the palms showing hypertrophy of palmar skin. (c) X-ray of tibia and fibula shows periosteal reaction with cortical thickening (arrows) and subperiosteal new bone formation. (d) Schematic representation of *slco₂a1* gene mutation. Sequence chromatogram of c.1016C>T mutation within exon 8 (upper). Protein sequence alignment of p.Ser339Phe (S339F) across different species showed conserved amino acid sequence at the 339 position (below)

Taster (http://www.mutationtaster.org), predict confirmation of disease causing mutation. This alteration was not previously described as SNPs or mutation in any of the public databases, including dSNPs, and was not found in 50 healthy and ethnically matched control individuals. The c.1016C>T mutations was predicted to result in a p.Ser339Phe (S339F) substitution. Protein sequence alignment of the *SLCO2A1* protein from different species showed conserved amino acid sequence at the 339 position (Fig. 1d).

Defects of both *HPGD* and *SLCO2A1* genes were considered the major cause of PHO due to increased levels of prostaglandin E_2 contributing involvement in the PHO pathogenicity. In our case, heterozygosity of *HPGD* mutation alone was insufficient to be a pathogenic cause of PHO. However, the presence of the novel *SLCO2A1* mutation (p.Ser339Phe) was confirmed to be the causative mutation of this disease.

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