CASE REPORT

SLCO2A1 Gene Variant in a Portuguese Patient with Primary Hypertrophic Osteoarthropathy

Ivana Cardoso[1], Mariana Rodrigues[2], Francisca Aguiar[2], Ana Grangeia[5], Iva Brito[2]

Port J Pediatr 2022;53:604-9
DOI: https://doi.org/10.25754/pjp.2022.25476

Abstract

Primary hypertrophic osteoarthropathy is a rare disease characterized by three major clinical symptoms: pachydermia, periostosis, and digital clubbing. Diagnosis of primary hypertrophic osteoarthropathy is based on clinical and radiographic characteristics confirmed by genetic studies. A complete form of the syndrome is reported in a male patient, with disease onset in adolescence. There were compatible clinical and radiological findings, presenting the three cardinal findings as well as other associated manifestations, such as hyperhidrosis and acne. A genetic study revealed an apparently homozygous variant in the *SLCO2A1* gene, c.644C>T, in the exon 12, which causes the exchange of the highly conserved amino acid serine by a phenylalanine in 215 position in the protein. To the best of our knowledge, the homozygosity of this variant has not yet been described in disease databases, such as ClinVar, and it constitutes the first genetically confirmed case of primary hypertrophic osteoarthropathy in a Portuguese patient.

Keywords: Adolescent; Anti-Inflammatory Agents, Non-Steroidal/therapeutic use; Genetic Variation; Osteoarthropathy, Primary Hypertrophic/diagnosis; Organic Anion Transporters/genetics; Osteoarthropathy, Primary Hypertrophic/genetics; Osteoarthropathy, Primary Hypertrophic/drug therapy; Portugal

Keypoints

What is known:
- Primary hypertrophic osteoarthropathy is a very rare disease with gradual onset.
- Diagnosis of primary hypertrophic osteoarthropathy is based on clinical and radiographic characteristics confirmed by genetic studies.

What is added:
- For the first time, homozygosity of the *SLCO2A1* gene variant, c.644C>T, is described in disease databases.
- This study reported the first genetically confirmed case of hypertrophic osteoarthropathy (PHOAR2) in a Portuguese patient.

Introduction

Primary hypertrophic osteoarthropathy (PHOA), also known as pachydermoperiostosis and Touraine-Solente-Gole syndrome, is a very rare disease with gradual onset and accounts for 3%-5% of all cases of hypertrophic osteoarthropathy.[1,2] Secondary hypertrophic osteoarthropathy, also called pulmonary hypertrophic osteoarthropathy, is associated with underlying cardiopulmonary diseases and malignancies.[1]

Primary hypertrophic osteoarthropathy is a congenital multisystemic entity characterized by three major clinical symptoms: pachydermia (thickening of the skin), periostosis, and digital clubbing.[1,3,4]

In 1935, three dermatologists, Touraine, Solente, and Gole individualized primary hypertrophic osteoarthropathy as a hereditary disease and categorized it into three clinical forms: the complete form, involving all three major symptoms, the incomplete form, with periostosis without pachydermia, and the fruste form with pachydermia and minimal or no skeletal anomalies.[5-7]

Hypertrophic osteoarthropathy is characterized by a symmetric periosteal reaction on radiographic examination. This periosteal reaction typically occurs in the long bones and in the phalanges. In the long bones, the diaphysis is typically affected first, with involvement of the metaphysis and epiphysis, indicating progression of the disease. In secondary hypertrophic

1. Pediatrics Department, Vila Nova de Gaia Hospital Center, Vila Nova de Gaia, Portugal
2. Pediatric and Young Adult Rheumatology Unity, Centro Hospitalar Universitário São João, Porto, Portugal
3. Pediatrics Department, Hospital de Braga, Braga, Portugal
4. Rheumatology Unity, Centro Hospitalar do Baixo Vouga, Aveiro, Portugal
5. Human Genetics Department, Centro Hospitalar Universitário São João, Porto, Portugal
Corresponding Author
Ivana Cardoso | E-mail: ivana.cardoso@chvng.min-saude.pt
Address: Centro Hospitalar Vila Nova de Gaia / Espinho, Unidade II, Rua Dr. Francisco Sá Carneiro, 440-129 Vila Nova de Gaia, Portugal
Received: 16/09/2021 | Accepted: 14/04/2022 | Published online: 01/07/2022 | Published: 01/07/2022

osteoarthropathy, the epiphyseal region is usually spared. Radiographs may also show acro-osteolysis or tuft hypertrophy of the phalanges.[8]

Additional symptoms of primary hypertrophic osteoarthropathy include arthropathy, coarsening of facial features, hyperhidrosis, acne lesions, seborrhea, folliculitis, *cutis verticis gyrata*, palpebral ptosis, and acro-osteolysis of the long bones, among others.[4,9,10,11]

Cases have been reported with an autosomal recessive inheritance pattern with pathogenic variants in *HPGD* and *SCLCO2A1* genes causing primary hypertrophic osteoarthropathy type 1 and 2, respectively (PHOAR1, MIM259100, and PHOAR2, MIM614441). *HPGD* gene has been mapped to chromosome 4q34.1 (MIM601688), which encodes 15-hydroxyprostaglandin dehydrogenase, and the *SLCO2A1* gene has been mapped to chromosome 3q22.1-3q22.2 (MIM601460), which encodes a prostaglandin transporter protein responsible for the degradation of prostaglandin E2.

Pathogenic variants in the *SLCO2A1* gene can also be associated with a form with autosomal dominant inheritance.[12,13] Several different pathogenic variants in the *HPGD* and *SLCO2A1* genes have been reported in different ethnic groups.[3,11]

Primary hypertrophic osteoarthropathy usually affects males, with a male to female ratio of 7:1.[8] It begins during childhood or adolescence and progresses gradually over the next five to 20 years before stabilization.[1,14] Moreover, PHOAR1 onset occurs during infancy or childhood, whereas PHOAR2 usually presents during puberty.[5]

The differential diagnosis depends on the presenting phenotype and age of onset and includes secondary hypertrophic osteoarthropathy, juvenile idiopathic arthritis and other inflammatory juvenile arthritis, synovitis-acne-pustulosis-hyperostosis-osteitis syndrome, thyroid acropachy, and acromegaly.[2,7,8] Secondary causes of hypertrophic osteoarthropathy should be excluded, especially when dermatological signs are not prominent.[7]

The diagnosis of pachydermoperiostosis is based on clinical and radiographic characteristics and confirmed by genetic studies.[10,15]

Since primary hypertrophic osteoarthropathy seems to result from prostaglandin metabolism impairment, treatment with non-steroidal anti-inflammatory drugs as well as prostaglandin E2 synthesis blockers seem to be plausible. A systematic review found that non-steroidal anti-inflammatory drugs are effective in improving musculoskeletal symptoms, but not other manifestations.[4] In most cases, the therapy will be palliative and directed toward amelioration of the patient complaints.

Case Report

We report the case of an otherwise healthy 15-year-old Caucasian male patient, born to non-consanguineous Portuguese parents. He was an only child and neither his parents nor grandparents had a history of any relevant known diseases. He was referred to our pediatric rheumatology clinic for suspected juvenile idiopathic arthritis, due to painful and swollen knees, ankles, and hands, slowly worsening over 1.5 years. The pain had a mechanical pattern, and the patient experienced no morning stiffness, loss of function, or interference with daily activities. Prompt relief with non-steroidal anti-inflammatory drugs was reported.

There were no constitutional symptoms, rashes, ulcers, ocular, gastrointestinal, cardiac, or respiratory complaints.

On examination, the patient presented with coarse facial features, including thickening of facial skin and prominent folds on the forehead and cheeks, facial and truncal acne (Fig. 1), palmoplantar hyperhidrosis, and seborrhea.

Painless digital clubbing of the hands and toes was also evident (Fig. 2). The knees and ankles were diffusely swollen and non-tender, with thickened and rough-textured skin and bilateral knee effusions (Fig. 2).

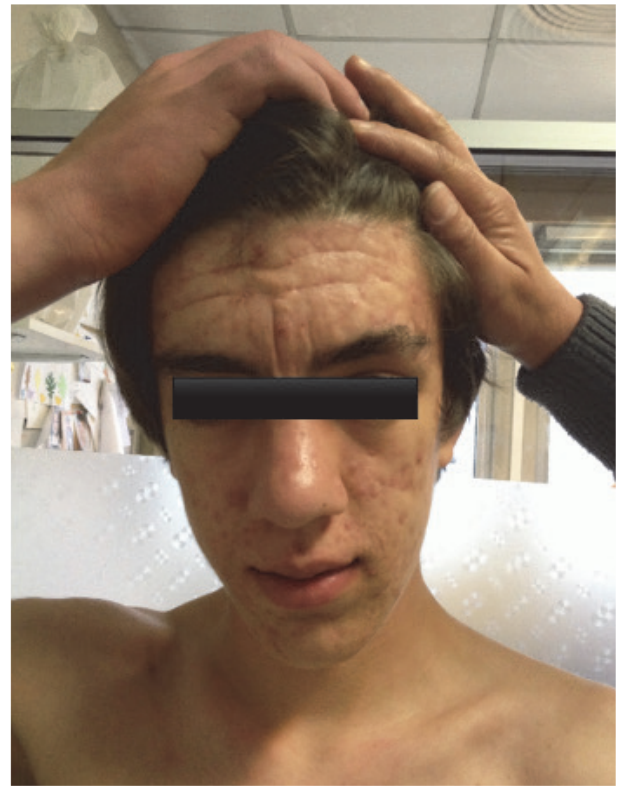

Figure 1. Face with coarse facial features, thickening of the skin, and prominent skin folds on the forehead and cheeks. Facial and truncal acne.

Plain films showed soft tissue swelling and periosteal ossification with cortical thickening of long bones, metaphyseal diaphyseal enlargement of the femur, tibia, fibula, metacarpals, humerus (Fig. 3), and radius with preservation of articular surfaces and no acroosteolysis. The right clavicle was also enlarged (Fig. 3).

Isotope bone scan with technetium-99m revealed mildly increased symmetrical uptake in the tubular bones along the cortical margins of the diaphysis and metaphysis (the double-stripe or parallel-track sign) (Fig. 4).

Clinical and imagiological findings were compatible with a diagnosis of hypertrophic osteoarthropathy. Laboratorial studies showed an elevated erythrocyte sedimentation rate (25 mm in the first hour, normal range 0-15 mm in the first hour) and C-reactive protein (22 mg/L, normal range < 3 mg/L). Full blood count with film, renal, and hepatic function, lactate dehydrogenase and electrolytes had no changes. Bone biochemistry, including serum calcium, phosphorus, serum total alkaline phosphatase, and parathyroid hormone was within the normal range. Endocrine workup excluded growth hormone excess and thyroid changes. The immunological panel was unremarkable, including negative antinuclear antibodies, rheumatoid factor, and anti-citrullinated protein antibodies.

To exclude secondary causes, an electrocardiogram, echocardiogram, plain chest film, and tuberculin skin test were also performed, which were unremarkable. It was not possible to obtain prostaglandin E2 levels in our patient.

The genetic study included an analysis of the *SLCO2A1* gene, which was conducted after obtaining the written informed consent. Exons 1-14 and the respective exon-intron boundaries of the *SLCO2A1* gene were amplified by a polymerase chain reaction and analyzed by direct sequencing. The patient was found to carry, apparently, a homozygous variant, c.644C>T, in the exon 12 of the gene, which causes the exchange of the highly conserved amino acid serine by a phenylalanine in 215 position in the protein. To the best of our knowledge, homozygosity of this variant has not yet been described in the disease databases, such as ClinVar, and it constitutes the first genetically confirmed case of hypertrophic osteoarthropathy (PHOAR2) in a Portuguese patient.

The patient received oral naproxen with significant improvement of musculoskeletal symptoms. Intra-articular steroid (triamcinolone hexacetonide) joint injections of the knees provided only short-term relief (2-3 months). He was referred to dermatology and received topical and systemic acne treatment.

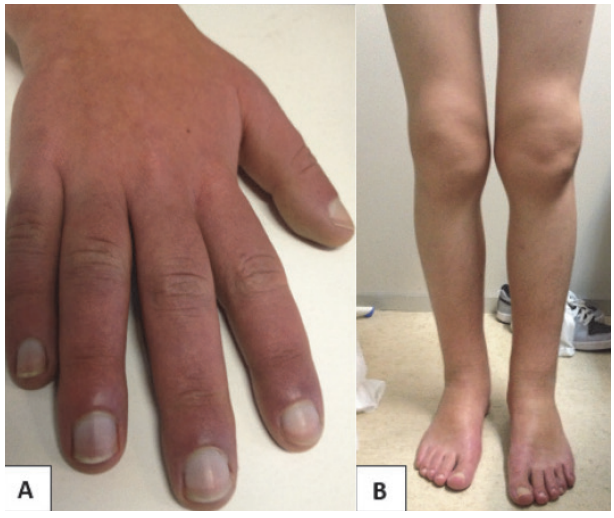

Figure 2. A. Digital clubbing of the hands and toes. B. Diffuse edema of the knees and ankles, with thickened rough-textured skin and bilateral knee effusions.

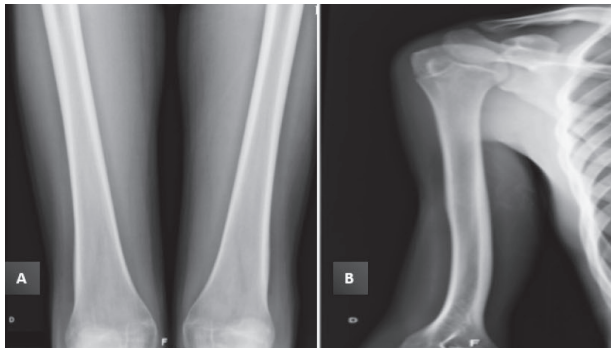

Figure 3. A. Plain film of the femurs: soft tissue swelling and periosteal ossification with cortical thickening, metaphyseal diaphyseal enlargement with preservation of articular surfaces and no acroosteolysis. B. Plain film of the right upper limb: soft tissue swelling and periosteal ossification with cortical thickening, metaphyseal diaphyseal enlargement of the humerus with preservation of articular surfaces and no acroosteolysis. The right clavicle was also enlargened.

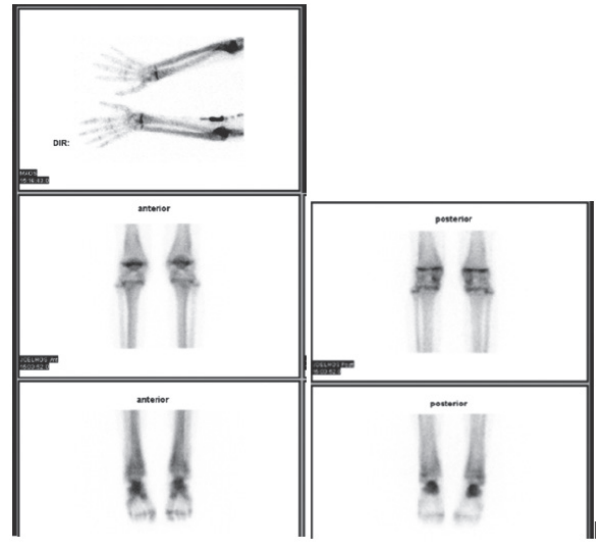

Figure 4. Isotope bone scan with technetium-99m showing a mildly increased symmetrical uptake in the tubular bones along the cortical margins of the diaphysis and metaphysis (the double-stripe or parallel-track sign).

After six years, the patient maintains regular follow-up, and the treatment with non-steroidal anti-inflammatory drugs has been successful in managing the pain and decreasing joint swelling. However, the patient continues to have the same features, and only skin thickening findings have been slowly evolving. There were no new complaints and genetic confirmation of hypertrophic osteoarthropathy allowed the team to stop the investigation of a secondary cause.

Regular laboratory examinations show no signs of anemia or pancytopenia, and erythrocyte sedimentation rate and C-reactive protein remain mildly elevated. Furthermore, the patient and his family have received genetic counselling.

Discussion

The authors present a PHOA2 patient with a *SLCO2A1* variant, apparently homozygous, given that the genetic study only included sequencing analysis and no gene deletions were studied. Furthermore, it was not possible to perform segregation studies on parents.

Our patient presented phenotypic characteristics similar to other cases with homozygous or compound heterozygous *SLCO2A1* variants, presenting a complete form of primary hypertrophic osteoarthropathy with some usual additional findings, such as *cutis verticis gyrata* and acne.

Clinical history, thorough physical examination, and simple radiologic images were very suggestive of primary hypertrophic osteoarthropathy. Periostosis is the hallmark feature of hypertrophic osteoarthropathy, with the radius, ulna, tibia and fibula most commonly affected.[15]

Following the exclusion of secondary hypertrophic osteoarthropathy and other differential diagnoses, genetic studies may be useful to confirm the diagnosis and classify the primary hypertrophic osteoarthropathy type. This provides not only genetic diagnostic confirmation that allows for future genetic counseling but also provides clues regarding the lifelong need for regular screening for myelofibrosis. In fact, myelofibrosis, which can significantly reduce life expectancy, has only been described in some PHOA2 cases. This supports the hypothesis that the pathogenesis of myelofibrosis may be related to prostaglandin transporter *SLCO2A*.[5,10] It is not yet clear which PHOA2 patients are at higher risk of developing this condition, or whether PHOA2 patients require monitoring, given the rarity of the condition.

It has been reported that pachydermia severity and the associated histological changes correlate with serum prostaglandin E2 levels.[16] Prostaglandin E2 can mimic the activity of osteoblasts and osteoclasts, which may be responsible for acro-osteolysis and periosteal bone formation. Moreover, the prolonged local vasodilatory effects of prostaglandin E2 may explain digital clubbing. Increased levels of prostaglandin E2 on the skin promote the development of the epidermis, epidermal hyperplasia, and sebaceous gland hyperplasia in animal models. It was found that peptic ulcers and myelofibrosis occurred only in PHOAR2 patients, and that the urinary levels of prostaglandin E2 metabolites are significantly higher than that in PHOAR1 patients.[5] The urinary prostaglandin E2 showed a positive correlation with erythrocyte sedimentation rate and hypersensitive C reactive protein and a negative correlation with hemoglobin. However, the level of serum prostaglandin E2 and prostaglandin E2 metabolite showed no significant correlation with erythrocyte sedimentation rate, hypersensitive C reactive protein, or hemoglobin. In the future, the urinary level of prostaglandin E2 or prostaglandin E2 metabolite could be useful in diagnosing primary hypertrophic osteoarthropathy.[1,10]

The incidence of this disease is probably underestimated, and clinical awareness is warranted. Although this disease usually stabilizes spontaneously in young adulthood, there is no curative treatment for the skeletal, soft tissue, or skin abnormalities, and continued monitoring for signs of myelofibrosis is advisable.

Most patients, such as ours, show significant improvement with non-steroidal anti-inflammatory drugs. This is consistent with the idea that reducing the production of implicated prostaglandins would limit disease activity.[10]

According to the most evident phenotypic characteristics, other medical therapies have been tried, such as intravenous bisphosphonates, corticosteroids, and infliximab for bone and joint symptoms.[15,17] Beta-blockers and glycopyrrolate have been proposed as potential treatments for hyperhidrosis, and surgical interventions might be required for the correction of clubbing or management of bony growths.[15] Plastic surgery could be necessary to remove excess facial skin.[15,18]

Author Contribuitions

IC participated in the study conception or design. IC and AG participated in acquisition of data. IC, MR, FA, AG and IB participated in the analysis or interpretation of data. IC participated in the drafting of the manuscript. AG and IB participated in the critical revision of the manuscript. All authors approved the final manuscript and are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflicts of Interest

The authors declare that there were no conflicts of interest in conducting this work.

Funding Sources

There were no external funding sources for the realization of this paper.

Protection of human and animal subjects

The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki 2013).

Provenance and peer review

Not commissioned; externally peer reviewed

Confidentiality of data

The authors declare that they have followed the protocols of their work centre on the publication of patient data.

References

1. Honório MLP, Bezerra GH, Costa VL. Complete form of pachydermoperiostosis. An Bras Dermatol 2020;95:98-101. doi: 10.1016/j.abd.2019.04.009.
2. Doshi D. Touraine-Solente-Gole syndrome. Orbit 2018;37:97-101. doi: 10.1080/01676830.2017.1383459.
3. Khan AK, Muhammad N, Khan SA, Ullah W, Nasir A, Afzal S, et al. A novel mutation in the HPGD gene causing primary hypertrophic osteoarthropathy with digital clubbing in a Pakistani family. Ann Hum Genet 2018;82:171-6. doi: 10.1111/ahg.12239.
4. Shakya P, Pokhrel KN, Mlunde LB, Tan S, Ota E, Niizeki H. Effectiveness of non-steroidal anti-inflammatory drugs among patients with primary hypertrophic osteoarthropathy: A systematic review. J Dermatol Sci 2018;90:21-6. doi: 10.1016/j.jdermsci.2017.12.012.
5. Hou Y, Lin Y, Qi X, Yuan L, Liao R, Pang Q, et al. Identification of mutations in the prostaglandin transporter gene SLCO2A1 and phenotypic comparison between two subtypes of primary hypertrophic osteoarthropathy (PHO): A single-center study. Bone 2018;106:96-102. doi: 10.1016/j.bone.2017.09.015.
6. Ma W, Guo S, Li Y, Li Z. Pachydermoperiostosis of the complete type: A novel missense mutation c.101T > C in the SLCO2A1 gene. Eur J Med Genet 2017;60:433-6. doi: 10.1016/j.ejmg.2017.06.001.
7. Mittal A, Gupta N, Soneja M. Touraine-Solente-Gole syndrome. BMJ Case Rep 2019;12:e232238. doi: 10.1136/bcr-2019-232238.
8. Joshi A, Nepal G, Shing YK, Panthi HP, Baral S. Pachydermoperiostosis (Touraine-Solente-Gole syndrome): A case report. J Med Case Rep 2019;13:39. doi: 10.1186/s13256-018-1961-z.
9. Nakazawa S, Mori T, Niizeki H, Nakabayashi K, Tokura Y. Complete type of pachydermoperiostosis with a novel mutation c.510G>A of the SLCO2A1 gene. J Dermatol 2017;44:1411-2. doi: 10.1111/1346-8138.13728.
10. Seta V, Capri Y, Battistella M, Bagot M, Bourrat E. Pachydermoperiostosis: The value of molecular diagnosis. Ann Dermatol Venereol 2017;144:799-803. doi: 10.1016/j.annder.2017.03.027.
11. Xiao J, Zhang DD, Zhang L. A novel mutation in the SLCO2A1 gene in a Chinese family with pachydermoperiostosis. Australas J Dermatol 2019;60:e348-50. doi: 10.1111/ajd.13041.
12. Xu Y, Zhang Z, Yue H, Li S, Zhang Z. Monoallelic mutations in SLCO2A1 cause autosomal dominant primary hypertrophic osteoarthropathy. J Bone Miner Res 2021;36:1459-68. doi: 10.1002/jbmr.4310.
13. Lee S, Park SY, Kwon HJ, Lee CH, Kim OH, Rhee Y. Identification of the mutations in the prostaglandin transporter gene, SLCO2A1 and clinical characterization in Korean patients with pachydermoperiostosis. J Korean Med Sci 2016;31:735-42. doi: 10.3346/jkms.2016.31.5.735.
14. Abdullah NR, Jason WL, Nasruddin AB. Pachydermoperiostosis: A rare mimicker of acromegaly. Endocrinol Diabetes Metab Case Rep 2017;2017:17-29. doi: 10.1530/EDM-17-0029.
15. Rostom H, Javaid MK. A case of primary hypertrophic osteoarthropathy: Management considerations. Int J Rheum Dis 2019;22:2080-1. doi: 10.1111/1756-185X.13736.
16. Sasaki T, Niizeki H, Shimizu A, Shiohama A, Hirakiyama A, Okuyama T, et al. Identification of mutations in the prostaglandin transporter gene SLCO2A1 and its phenotype-genotype correlation in Japanese patients with pachydermoperiostosis. J Dermatol Sci 2012;68:36-44. doi: 10.1016/j.jdermsci.2012.07.008.
17. Sun F, Guo L, Ye S. Primary hypertrophic osteoarthropathy with SLCO2A1 mutation in a chinese patient successfully treated with etoricoxib. J Clin Rheumatol 2018;24:164-7. doi: 10.1097/RHU.0000000000000647.
18. Taichao D, Fuling L, Hengguang Z. Comprehensive surgical strategies for the management of pachydermoperiostosis. Facial Plast Surg 2018;34:330-4. doi: 10.1055/s-0038-1653992.

Variante do Gene *SLCO2A1* em Doente Português com Osteoartropatia Hipertrófica Primária

Resumo:
A osteoartropatia hipertrófica primária é uma doença rara caracterizada por três sintomas clínicos principais: paquidermia, periostose e hipocratismo digital. O diagnóstico de osteoartropatia hipertrófica primária baseia-se em características clínicas e radiográficas confirmadas por estudos genéticos. É relatada uma forma completa da síndrome num doente do sexo masculino, com início da doença na adolescência. Existiam achados clínicos e radiológicos compatíveis, incluindo os três sintomas principais, além de outras manifestações associadas, como hiperidrose e acne. Um estudo genético revelou uma variante aparentemente homozigótica no gene *SLCO2A1*, c.644C>T, no exão 12, que causa a troca do aminoácido serina por fenilalanina na posição 215 da proteína. Tanto quanto é do nosso conhecimento, a homozigotia desta variante ainda não está descrita em bases de dados de doenças, como a ClinVar, e este é o primeiro caso de osteoartropatia hipertrófica primária num doente português com confirmação genética.

Palavras-Chave: Adolescente; Anti-Inflamatórios não Esteroides/uso terapêutico; Osteoartropatia Hipertrófica Primária/diagnóstico; Osteoartropatia Hipertrófica Primária/genética; Osteoartropatia Hipertrófica Primária/tratamento farmacológico; Portugal; Transportadores de Ânions Orgânicos/genética; Variante Genética