BrJP
Brazilian Journal of Pain

CASE REPORT

4G/5G polymorphism of the PAI-1 gene in a patient with chronic pain. Case report with expanded management following genetic diagnosis

Polimorfismo 4G/5G do gene PAI-1 em paciente com dor crônica. Relato de caso com conduta ampliada a partir do diagnóstico genético

Ana Carolina Silva Rocha[1], João Batista Santos Garcia[2]

[1.] Universidade Federal do Maranhão (UFMA), Faculdade de Medicina, São Luís, MA, Brasil.
[2.] Universidade Federal do Maranhão (UFMA), Departamento de Medicina II, São Luís, MA, Brasil.

Correspondence to:
Ana Carolina Silva Rocha
acs.rocha@discente.ufma.br

Submitted on:
May 28, 2025.
Accepted for publication on:
February 3, 2026.
Conflict of interests:
none
Sponsoring sources:
none.
Data availability
The data that support the findings of this study are available from the corresponding author upon reasonable request.

Associate editor in charge:
Renato Leonardo de Freitas

Editor in charge:
Juliana Barcellos de Souza

ABSTRACT

BACKGROUND AND OBJECTIVES: Vascular and bone disorders may underlie chronic pain syndromes that are difficult to manage and may be associated with predisposing genetic alterations. The PAI-1 gene polymorphism promotes a prothrombotic state that favors the development of local vascular thrombosis, such as osteonecrosis. Thus, this study aims to report a case of chronic pain associated with the 4G/5G polymorphism of the PAI-1 gene.

CASE REPORT: A 29-year-old male patient with complaints of difficult-to-control bone pain for over 10 years and osteonecrosis of the femur and tibia, with no defined etiology. He had a history of five episodes of acute myocardial infarction and episodes of sudden-onset dyspnea, initially attributed to possible pulmonary embolism, without a confirmed cause. Extensive investigations were conducted until his referral to the Chronic Pain Clinic, where a genetic disorder was suspected, and specific testing was requested. The results confirmed the presence of the 4G/5G polymorphism in the PAI-1 gene, clarifying the predisposition to thrombotic events throughout his life and the intense pain in the knee and hip regions. The patient continued anticoagulant therapy under the care of the hematology team and remained under ongoing treatment for pain management at the Chronic Pain Clinic of HUUFMA.

CONCLUSION: Prolonged and difficult-to-control pain may manifest as a consequence of the 4G/5G polymorphism in the PAI-1 gene, which is associated with a predisposition to thrombotic events such as osteonecrosis. This association highlights the relevance of genetic factors in the management of chronic pain.

KEYWORDS: Case report, Chronic pain, Osteonecrosis, Plasminogen activator inhibitor-1, Thrombosis.

RESUMO

JUSTIFICATIVA E OBJETIVOS: Distúrbios vasculares e ósseos podem ser responsáveis por quadros de dor crônica de difícil controle e estar associados a alterações genéticas predisponentes. No polimorfismo do gene do PAI-1 há a formação de um estado protrombótico que favorece o desenvolvimento de trombose vascular local, como a osteonecrose. Assim, este estudo tem como objetivo relatar um caso de dor crônica associada ao polimorfismo 4G/5G do gene PAI-1.

RELATO DO CASO: Paciente do sexo masculino, 29 anos, apresentando queixas de dores ósseas de difícil controle há mais de 10 anos e osteonecrose no fêmur e na tíbia, sem etiologia definida. Possuía histórico de cinco episódios de infarto agudo do miocárdio e de dispneia súbita, inicialmente atribuída a uma possível embolia pulmonar, sem causa definida. Realizou-se uma intensa investigação até a chegada ao ambulatório de Dor Crônica, onde surgiu a suspeita de doença genética e solicitou-se a realização de exame específico. Após o resultado, confirmou-se o polimorfismo 4G/5G do gene PAI-1, esclarecendo a predisposição a episódios trombóticos ao longo de sua vida e a dor intensa na região de joelhos e quadril. O paciente seguiu em tratamento com anticoagulantes pela equipe de hematologia e foi mantido em tratamento contínuo do quadro álgico no Ambulatório de Dor Crônica do HUUFMA.

CONCLUSÃO: A dor prolongada de difícil controle surge como uma manifestação do polimorfismo 4G/5G do gene PAI-1, associada à predisposição a eventos trombóticos, como a osteonecrose. Assim, essa associação ressalta a relevância de fatores genéticos no manejo da dor crônica.

DESCRITORES: Dor crônica, Inibidor 1 de ativador de plasminogênio, Osteonecrose, Relato de caso, Trombose.

HIGHLIGHTS

- The 4G/5G polymorphism of the PAI-1 gene may contribute to chronic pain through thrombotic and osteonecrosis events
- Genetic factors should be considered in refractory pain of undefined etiology
- Management of osteonecrosis can be improved with PAI-1 assessment

INTRODUCTION

Chronic pain affects more than 30% of the world's population. This condition can lead to development of comorbidities such as anxiety and depression, and is therefore a therapeutic challenge[1,2]. Among the numerous underlying causes of this problem are vascular and bone disorders, such as osteonecrosis, which may be associated with predisposing genetic alterations[3,4].

Plasminogen activator inhibitor (PAI-1) is a glycoprotein of the serpin family that acts by inhibiting enzymes of the fibrinolytic system, mainly by neutralizing t-PA and preventing the conversion of plasminogen to plasmin, thereby favoring the maintenance of the clot[5]. Although it is normally present in low concentrations, under certain conditions, such as PAI-1 gene polymorphism, its levels rise, compromising fibrinolytic activity and increasing the risk of thrombotic events, such as arteriopathy, venous thrombosis, and osteonecrosis[6,7].

Osteonecrosis is a disabling bone disease that compromises patient functionality due to intense pain and mainly affects weight-bearing joints, such as the hip and knee[8]. The onset is usually slow and progressive and may or may not be related to physical exertion. During the advanced stages, the condition can suddenly worsen due to severe ischemia and edema[9,10].

The present study's objective was to report a case of chronic hip and knee pain secondary to osteonecrosis associated with the 4G/5G polymorphism of plasminogen activator inhibitor (PAI-1), in order to highlight the importance of genetic diagnosis in managing the condition. Based on this, it was possible to direct specific and appropriate treatment to the patient's condition, contributing to the improvement of the clinical condition observed. Therefore, the report highlights the relationship between fibrinolytic dysfunction and persistent pain.

CASE REPORT

A 29-year-old male patient, resident of São Luís, Maranhão, was referred to the chronic pain clinic at the University Hospital of the Federal University of Maranhão (HUUFMA) complaining of severe and chronic bone pain for over 10 years, with no defined etiology. The problem was described as stabbing-like pain in the knees and hips, with a feeling of "brittle bones", which worsened at night. He also reported frequent epistaxis since childhood, as well as holocranial and temporal pulsating headache, associated with nausea and emetic episodes, with loss of strength in the upper and lower limbs. The pain condition was refractory to most analgesics, making clinical management difficult. At the time, the patient was taking dipyrone 2 g every 6 hours, amitriptyline 50 mg (2 tablets at night), duloxetine 30 mg once a day, and pregabalin 150 mg every 12 hours.

The patient reported the history of five episodes of acute myocardial infarction. He had undergone two surgeries for hip and knee decompression (corticotomy and medullary evacuation), as well as genicular nerve blocks, and had no significant improvement.

At the age of 21, the patient presented sudden dyspnea, initially investigated as possible septic embolism or lymphatic carcinomatosis, as indicated by chest tomography. However, the final diagnosis was tuberculosis, despite multiple negative BAAR results, with a positive PPD test (20 mm). The patient then underwent treatment with a RIPE regimen for seven months, but during this period he reported a significant worsening of bone pain. During the course of treatment, he developed heart failure with reduced ejection fraction (EF 42%) and mitral insufficiency. He was treated with metoprolol, enalapril, carvedilol, spironolactone, and losartan, with improvement in cardiac function over time.

In 2022, an MRI of the knees revealed areas of bone infarction and osteonecrosis in the proximal metaphysis of the tibia and distal metaphysis of the femur, without signs of collapse. At the same time, an MRI of the pelvis showed areas of osteonecrosis in the femoral heads, affecting the anterosuperior, superior, and posterosuperior areas. A bone densitometry showed osteopenia in the lumbar spine.

The patient was admitted to the HUUFMA for a left knee biopsy and remained hospitalized for one month, during which time he reported severe pain, even during the use of morphine. The bone biopsy of the left tibia showed fragments of bone tissue with areas of necrosis and blood clots. Next, a biopsy of the lesion in the left femoral head was performed, and the histopathological result was consistent with osteonecrosis, confirming the clinical and radiological diagnosis.

During the follow-up, the patient showed symptoms of anxiety and depression, suicidal ideation and sleep disturbances, which were attributed to persistent pain. The lack of response to previous surgical interventions, including two hip and knee decompression surgeries, indicated the severity and complexity of the scenario, in addition to the lack of a pathophysiological factor for diagnosis and constant symptomatology.

The patient sought treatment at the Chronic Pain Outpatient Clinic at the HUUFMA with the mentioned pain and medical history. Given the history of thrombotic events and the progression of osteonecrosis, testing for the 4G/5G polymorphism of the PAI-1 gene was requested. At this consultation, pregabalin was replaced by gabapentin 300 mg (two tablets every 8 hours), tapentadol 100 mg was introduced every 12 hours, duloxetine was increased to 60 mg/day, and the dose of amitriptyline was maintained.

The genetic test results confirmed the presence of the 4G/5G polymorphism in the PAI-1 gene. The patient was referred back to the hematology service. Initially, rivaroxaban 20 mg was prescribed; later, warfarin sodium 20 mg was introduced and rivaroxaban was withdrawn. However, warfarin was suspended due to a suspicion of a new episode of pulmonary embolism. Anticoagulation with enoxaparin sodium 80 mg every 12 hours was then initiated, which did indeed improve the patient's clinical condition, and has been maintained to date.

The patient continued to be monitored by the cardiology and pulmonology teams, regularly using budesonide/formoterol 200 µg and salbutamol as a rescue drugs. Finally, the patient continued to be monitored at the Chronic Pain Clinic at HUUFMA, where pharmacological treatment has provided satisfactory control to date. The current treatment includes topiramate 50 mg, venlafaxine 75 mg, clonazepam 1 mg, mirtazapine 15 mg (half a tablet), dipyrone 1 g every 6 hours, and rescue methadone in case of more intense pain.

DISCUSSION

There are several polymorphisms associated with the PAI-1 gene, which is located on chromosome 7q21.3-q22. One of the main of these polymorphisms is -675 (5G/4G), which is related to the insertion or deletion of a guanosine. The 4G allele is responsible for increased plasma PAI-1 activity, with higher levels in 4G/4G individuals, intermediate levels in 4G/5G individuals, and lower levels in 5G/5G individuals[11]. In a study with 123 individuals undergoing coronary angiography, the 4G/4G genotype was more frequent in the group with severe atheromatosis compared to the other samples, suggesting an association between this polymorphism and a prothrombotic state[12].

Polymorphism of the PAI-1 gene, mainly the 4G/5G variant, alters the production of plasminogen activator inhibitor, which affects the coagulation system. This increases the risk of thrombosis[13] due to reduced fibrinolysis, which compromises blood flow[14] and promotes osteonecrosis due to tissue hypoxia[6,15]. This correlation has also been described in pediatric populations with a genetic predisposition to thrombophilia, suggesting a role for PAI-1 in the pathophysiology of bone necrosis[16].

Osteonecrosis is a common cause of musculoskeletal disability and pain[17]. It is a multifactorial condition related to trauma, corticosteroid treatment, alcoholism, or genetic disorders[8].

The femoral head is the area most susceptible to the development of this ischemic lesion[18], which presents terminally due to bone cell death, compromising the normal regenerative process along bone microfractures. Osteonecrosis is a type of lesion that causes necrosis of the hip joint cartilage and degeneration of the femoral head and is a known consequence of the PAI-1[19] gene alteration. It can also influence the risk of femoral head fracture (FHON), especially in patients exposed to steroids[20].

The patient in the present report has a history of severe and persistent bone pain, as well as osteonecrosis and thromboembolic events prior to the diagnosis of 4G/5G polymorphism of the PAI-1 gene. Studies show that the 4G variant of PAI-1 is associated with an increased risk of acute thrombotic events, such as acute myocardial infarction[16], venous thromboembolism (VTE), and deep vein thrombosis (DVT).

A meta-analysis of 27 case-control studies showed that the PAI-1 4G/5G polymorphism significantly increases the risk of VTE, especially in high-risk and specific ethnic groups, such as Asians[21]. Another study of 544 patients with DVT highlighted PAI-1 as the most common polymorphism among the hypercoagulability tests performed, reinforcing its association with thrombotic conditions[22].

PAI-1 has an effect on bone remodeling and skeletal health. In women with postmenopausal osteoporosis, abnormal regulation of PAI-1 due to polymorphism may be associated with a mechanism of bone loss or inadequate bone repair, which increases the prevalence of osteoporotic fractures due to vertebral deficiency[23]. This finding is relevant to the case in question, given that the patient has osteopenia in the lumbar spine, which could be associated with abnormal PAI-1 regulation influenced by the 4G/5G polymorphism.

There is an association between anxiety and depression and the intensification of pain perception, contributing to a cycle in which physical suffering aggravates emotional discomfort and vice versa[24]. In this case, the patient has anxiety and depressive symptoms associated with chronic pain, reinforcing the direct relationship between these conditions.

Although this report does not allow to establish a direct causal association between the 4G/5G polymorphism of the PAI-1 gene and chronic pain, clinical findings and the literature point to a consistent association. The hypothesis that the fibrinolytic disorder contributes to pain is plausible but requires confirmation by more robust studies. Nevertheless, the case highlights the importance of considering genetic factors in patients with refractory pain and undefined etiology.

As for limitations, this is a single case report, which may restrict the generalization of results. However, the study highlights the clinical relevance of including genetic factors in the approach to thrombotic conditions and bone diseases, such as osteonecrosis.

The main contribution of the present study is to illustrate how specific genetic variants may be involved in complex clinical conditions, such as chronic pain. Future studies with larger samples and prospective designs are needed in order to investigate the interaction between the PAI-1 gene, environmental factors, and other genes, deepening the knowledge of the involved mechanisms and therapeutic responses.

CONCLUSION

The results presented herein reinforce the importance of genetic research in the management of chronic pain, given the association between the 4G/5G polymorphism of the PAI-1 gene and the predisposition to thrombotic conditions, which may contribute to the development of circumstances that result in persistent and disabling pain.

REFERENCES

1. Cohen SP, Vase L, Hooten WM. Chronic pain: an update on burden, best practices, and new advances. Lancet. 2021;397(10289):2082-97. http://doi.org/10.1016/S0140-6736(21)00393-7. PMid:34062143.
2. Patel R. The circuit basis for chronic pain and its comorbidities. Curr Opin Support Palliat Care. 2023;17(3):156-60. http://doi.org/10.1097/SPC.0000000000000650. PMid:37096597.
3. Fagundes RBC, Amaro ACD, Reis LVD, Souza ACC, Júnior FAAES. Osteonecrosis of the femoral head secondary to sickle cell disease: literature review. Hematol Transfus Cell Ther. 2020;42(Suppl. 2):S49-50. http://doi.org/10.1016/j.htct.2020.10.081.
4. Garcia FL, Ramalli EL Jr, Picado CHF. Distúrbios de coagulação em pacientes com osteonecrose da cabeça femoral. Acta Ortop Bras. 2013;21(1):43-5. http://doi.org/10.1590/S1413-78522013000100009. PMid:24453643.
5. Daldegan IR, Maciel RAB, Batalha SH, Reis MFR, Camargos MV, Salgado HC, Rangel JMC, Mello TT, Panconi CR, Zimmermmann JB. O papel do inibidor do ativador do plasminogênio (PAI-1) no mau estágio obstétrico. Rev Eletr Acervo Saúde. 2022;15(4):1-8. http://doi.org/10.25248/reas.e10100.2022.
6. Duque FLV, Mello NA. Trombogênese - trombofilia. J Vasc Bras. 2003;2(2):105-18.
7. Evangelista FCG, Rios DRA, Ribeiro DD, Carvalho MG, Dusse LMS, Mota APL, Fernandes APSM, Sabino AP. Apolipoprotein E and PAI-1 gene polymorphisms and no association with arterial ischemic stroke and peripheral arterial disease manifestations. J Bras Patol Med Lab. 2018;54(3):138-45. http://doi.org/10.5935/1676-2444.20180026.

8. Caldas R. Osteonecrosis: a comprehensive review. Int J Clin Rheumatol. 2023;18(9):274-6.

9. Miyahara HS, Ranzoni LV, Ejnisman L, Vicente JRN, Croci AT, Gurgel HMC. Osteonecrosis of the Femoral Head: update Article. Rev Bras Ortop. 2022;57(3):351-9. http://doi.org/10.1055/s-0041-1736308. PMid:35785123.

10. Mont MA, Zywiel MG, Marker DR, McGrath MS, Delanois RE. The natural history of untreated asymptomatic osteonecrosis of the femoral head: a systematic literature review. J Bone Joint Surg Am. 2010;92(12):2165-70. http://doi.org/10.2106/JBJS.I.00575. PMid:20844158.

11. Eccard B, Gonçalves G, Silva S, Rosa M, Francischetti E, Freitas R. Avaliação do polimorfismo 4G/5G do PAI-1 em pacientes com acidente vascular encefálico isquêmico e seus subtipos. Conhecendo Online. 2019;5(1):66-85.

12. Lima LM, Carvalho MG, Fonseca CP No, Garcia JCF, Sousa MO. Associação de níveis plasmáticos de PAI-1 e polimorfismo 4G/5G em pacientes com doença arterial coronariana. Arq Bras Cardiol. 2011;97(6):462-389. http://doi.org/10.1590/S0066-782X2011005000110. PMid:22011808.

13. Rabieian R, Boshtam M, Zareei M, Kouhpayeh S, Masoudifar A, Mirzaei H. Plasminogen activator inhibitor type-1 as a regulator of fibrosis. J Cell Biochem. 2018;119(1):17-27. http://doi.org/10.1002/jcb.26146. PMid:28520219.

14. Yasar Yildiz S, Kuru P, Toksoy Oner E, Agirbasli M. Functional stability of plasminogen activator inhibitor-1. ScientificWorldJournal. 2014;2014:858293. http://doi.org/10.1155/2014/858293. PMid:25386620.

15. Li L, Wang Y, Yu X, Bao Y, An L, Wei X, Yu W, Liu B, Li J, Yang J, Xia Y, Liu G, Cao F, Zhang X, Zhao D. Bone marrow mesenchymal stem cell-derived exosomes promote plasminogen activator inhibitor 1 expression in vascular cells in the local microenvironment during rabbit osteonecrosis of the femoral head. Stem Cell Res Ther. 2020;11(1):480. http://doi.org/10.1186/s13287-020-01991-2. PMid:33176873.

16. Sherief LM, Beshir M, Raafat N, Abdelkhalek ER, Mokhtar WA, Elgerby KM, Soliman BK, Salah HE, Mokhtar GA, Kamal NM, ElSayed H, Zakaria M. Genetic polymorphism of vitamin D receptors and plasminogen activator inhibitor-1 and osteonecrosis risk in childhood acute lymphoblastic leukemia. Mol Genet Genomic Med. 2021;9(7):e1700. http://doi.org/10.1002/mgg3.1700. PMid:34042331.

17. Yue C, Xue Z, Cheng Y, Sun C, Liu Y, Xu B, Guo J. Multidimensional characteristics are associated with pain severity in osteonecrosis of the femoral head. Bone Joint Res. 2024;13(11):673-81. http://doi.org/10.1302/2046-3758.1311.BJR-2024-0105.R2. PMid:39571603.

18. Petek D, Hannouche D, Suva D. Osteonecrosis of the femoral head: pathophysiology and current concepts of treatment. EFORT Open Rev. 2019;4(3):85-97. http://doi.org/10.1302/2058-5241.4.180036. PMid:30993010.

19. Sobhan MR, Mahdinezhad-Yazdi M, Moghimi M, Aghili K, Jafari M, Zare-Shehneh M, Neamatzadeh H. Plasminogen activator inhibitor-1 4G/5G polymorphism contributes to osteonecrosis of the femoral head susceptibility: evidence from a systematic review and meta-analysis. Arch Bone Jt Surg. 2018;6(6):468-77. PMid:30637301.

20. Lee S, Yoo JI, Kang YJ. Integrative analyses of genes related to femoral head osteonecrosis: an umbrella review of systematic reviews and meta-analyses of observational studies. J Orthop Surg Res. 2022;17(1):182. http://doi.org/10.1186/s13018-022-03079-4. PMid:35346283.

21. Zhang Q, Jin Y, Li X, Peng X, Peng N, Song J, Xu M. Plasminogen activator inhibitor-1 (PAI-1) 4G/5G promoter polymorphisms and risk of venous thromboembolism – a meta-analysis and systematic review. Vasa. 2020;49(2):141-6. http://doi.org/10.1024/0301-1526/a000839. PMid:31920171.

22. Tremblay D, Naymagon L, Troy K, Cromwell C, Edwards C, Schiano T, Kremyanskaya M, Mascarenhas J. The utility of thrombophilia testing in patients with newly diagnosed portal vein thrombosis. Blood Coagul Fibrinolysis. 2020;31(3):213-8. http://doi.org/10.1097/MBC.0000000000000901. PMid:32101880.

23. Kim JO, Han SH, Lee YH, Ahn TK, Lim JJ, Chung YS, Shin DE, Lee WS, Han IB, Kim NK. Association of Plasminogen Activator Inhibitor-1 (PAI-1) Gene Polymorphisms with Osteoporotic Vertebral Compression Fractures (OVCFs) in postmenopausal women. Int J Mol Sci. 2016;17(12):2062. http://doi.org/10.3390/ijms17122062. PMid:27941685.

24. Silva MO, Rodrigues MAF, Oliveira EA, Batista RO, Almeida RLP, Alves RMM. Prevalência de ansiedade e depressão em pacientes com dores crônicas: uma revisão integrativa. Rev UNINGÁ. 2024;69(1):eUJ462.

AUTHORS' CONTRIBUTIONS

Ana Carolina Silva Rocha: Data Collection, Writing - Preparation of the original
João Batista Santos Garcia: Project Management, Writing - Review and Editing, Supervision