

Variant ELMO1 rs1345365 is associated with pseudoperniosis in patients with COVID-19

La variante rs1345365 de ELMO1 está asociada a pseudoperniosis en pacientes con COVID-19

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To the Editor,

Pseudoperniosis, known as chilblains on the hands and skin, corresponds to areas of lesions with erythema or purplish discoloration, vesicles, and pustules, typically asymmetrically distributed. It is considered the 5th most common dermatosis in patients infected with SARS-CoV-2 (COVID-19) and is the most characteristic one too. It is often seen in young patients and in the later stages of the disease¹. Due to its clinical nature, various vascular factors, such as endothelial dysfunction and COVID-19-induced microangiopathy have been proposed as possible biological determinants¹. In this regard, the rs1345365 polymorphism of the ELMO1 gene is a candidate marker for describing this condition, as it regulates vasculogenesis, angiogenesis, fibrogenesis, inflammation, apoptosis, and cell migration², which are all dysregulated processes in patients with COVID-19.

With these considerations, 830 men were selected out of a total of 4370 COVID-19 patients treated at CIMETP and ME Piel Centro Dermatológico, 415 of whom presented with unilateral (n = 812) or bilateral pseudoperniosis (n = 18), while the remaining 415 had not develop any type of dermatosis and were age-matched with the cases (range, 18-45 years). The patients were diagnosed with COVID-19 using the real-time polymerase chain reaction (PCR) assay.

DNA was extracted from peripheral blood using the GeneCatcher kit (Invitrogen) to amplify the rs1345365 polymorphism of the ELMO1 gene through an allele-specific PCR assay, with the previously reported primers and reaction mixture conditions, amplification program, and polyacrylamide gel electrophoresis². Thus, the ancestral homozygous G/G genotype was found more frequently in patients with pseudoperniosis, while the reference homozygous A/A genotype was more common in controls. A total of 5 models were analyzed using multiple logistic regression (MLR), and the homozygous G/G genotype was found to be associated with higher risk in different models (Table 1).

This is the first study ever conducted showing a possible relationship between pseudoperniosis in COVID-19 patients and the rs1345365 variant of the ELMO1 gene. There is this possibility of false positives (and negatives) regarding ELMO1 variant genotyping due to the allele-specific PCR; however, the primer design includes the introduction of mutations that increase specificity and decrease the rates of false-positives or false-negatives². There is also this possibility of false negatives with COVID-19 and pseudoperniosis due to mutations in the S gene that escape qRT-PCR, such as the 69-70 deletion; in both

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Table 1. Distribution of the rs1345365 polymorphism of the ELMO1 gene in COVID-19 pseudoperniosis

Genotypes	Cases (n)	Controls (n)			
GG	75	21			
GA	105	126			
AA	235	268			
Alleles A					
G	575	662			
	255	168			
MLR models	X ²	Correlation coefficient	p	Risk ratio (odds)	95%CI
GG genotype vs GA+AA	33.5	0.403	0.0000001	1.67	1.4-1.9
GG+AA genotype vs GA	2.6	0.012	0.1039	1.07	0.9-1.1
GG genotype vs GA	29.25	0.515	0.0000001	1.7	1.4-2.6
GG genotype vs AA	31.84	0.397	0.0000001	1.6	1.4-1.9
GA genotype vs AA	0.1019	0.004	0.749	0.9	0.8-1.1

MLR, multiple logistic regression; 95%CI, 95% confidence interval .

cases, false negatives can be reduced by sequencing PCR products. Certainly, the models presented confirm that pseudoperniosis was better explained by a predominance of the recessive model, in which heterozygotes do not have a greater influence. In light of these findings, the lack of specificity of the variant, is related to the multifactorial nature of this trait, which is why markers in other candidate genes should be looked into. However, the fact that this gene has been frequently explored in melanomas and other dermatological diseases, such as psoriasis^{3,4}, supports its role in the development of pseudoperniosis.

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Conflicts of interest

None declared.

Ethical disclosures

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).

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

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

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