

VNTR of the *ATXN2* gene as a biomarker of thrombophlebitis in patients with type 2 diabetes and COVID-19

El VNTR del gen ATXN2 como biomarcador de tromboflebitis en pacientes con diabetes tipo 2 y COVID-19

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To the editors,

We would like to highlight the articles published by Carrillo-Esper et al.¹ regarding coagulopathy by COVID-19, and by Ramírez et al.² regarding thrombophilia in diabetes. In this sense, we also analyzed patients with type 2 diabetes mellitus (DM2) as a marker for (CAG)_n expansion in the *ATXN2* gene, as it is associated with diabetes, and metabolic hematological and inflammatory parameter, such as hemoglobin levels, hematocrit increase, the average hemoglobin concentration, mean corpuscular volume, and platelet count³⁻⁵. Considering that DM2 is a sensitivity factor for SARS-CoV-2, we explore the risk for superficial thrombophlebitis in 184 diabetic patients previously genotyped for (CAG)_n expansion in *ATXN2* (Fig. 1) with COVID-19 and carriers of chronic peripheral vascular disease. Thus, 38 diabetic patients had superficial thrombophlebitis exacerbated during the infection, with a relative risk increase of 2.6 for those who were genotype carriers with repeated alleles over 23 (Table 1). On the other hand, an allele of 23 or a lower number of repeats decreases the risk. In addition, in our gene bank of 42 patients with dominant autosomal spinocerebellar ataxia type 2 (SCA2), we detected a case with thrombophilia in a patient who was

a carrier of genotype 22/52. Finally, the SCA2 is a pathology with high risk for DM2, COVID-19, and development of acute thrombotic microangiopathy. Therefore, our study suggest that long expansions within the normal and mutant range of the VNTR of the *ATXN2* are a risk factor for coagulopathy due to COVID-19 and thrombophilia in patients with SCA2. Thus, VNTR could be used as a predictive biomarker to begin early thromboprophylaxis in these sensitive groups. Due to the genetic diversity of the population and the frequency of COVID-19, verification in epidemiology replica studies is required.

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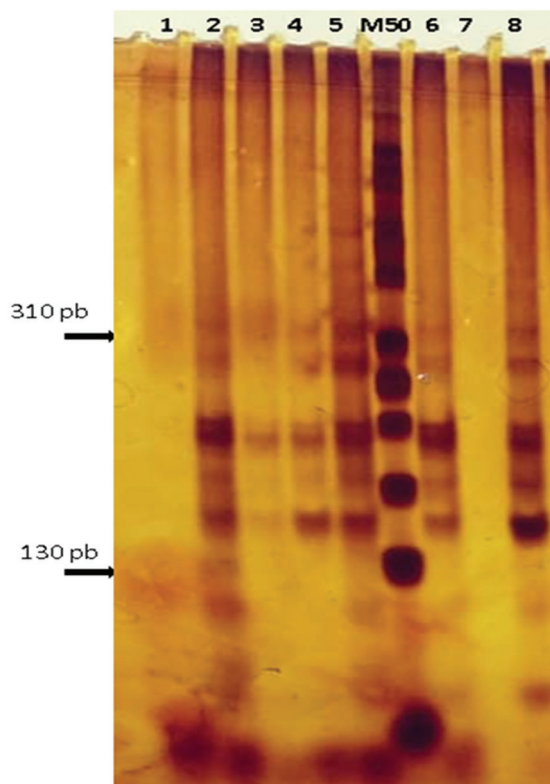


Figure 1. Polyacrylamide electrophoresis 6% (19:1), VNTR (CAG)*n* standardization of gene ATXN2 by final PCR-point. 28-cycle amplification program, initial denaturalization at 96 °C for 5 minutes, denaturalization for 1 minutes at 96 °C, alignment for 1 minute at 59 °C, elongation for 30 seconds at 72 °C, and final elongation for 1 minute at 72 °C^{4,5}. Track 1: blank sample. Track 2: DNA sample at 4 Mm (MgCl₂). Track 3: sample at 1.5 mM (MgCl₂). Track 4: DNA sample 2 mM (MgCl₂). Track 5: DNA sample 2.5 mM (MgCl₂). Track 6: SCA2 patient sample 2 mM (MgCl₂). Track 7: blank sample. Track 8: DNA sample 3 Mm (MgCl₂). Track 9: DNA sample 3 Mm (MgCl₂). Track 11: DNA sample 3 Mm (MgCl₂). The band of 130 pairs of bases corresponds to the 22 repeated CAG allele, while the band of 310 pairs corresponds to the allele of 52 repetitions; therefore, the analyzed sample belongs to a heterozygous patient with genotype 22/52 repeated CAG^{4,5}.

Table 1. Association of VNTR of ATXN2 with thromboflebitis in type 2 diabetes patients

Genotypes (No. repetitions)	Group A: diabetics with thromboflebitis and COVID-19	Group B: diabetics without thromboflebitis and without COVID-19	Group C: asymptomatic COVID-19 carriers
18/22	0	0	5
22/22	0	125	87
22/23	0	21	0
22/24	10	0	0
22/25	8	0	0
22/27	5	0	0
22/29	10	0	0
22/30	5	0	0
Alleles (No. repetitions)	No. chromosomes	No. chromosomes	No. chromosomes
18	0	0	5
22	48	271	179
23	0	21	0
24	10	0	0
25	8	0	0
27	5	0	0
29	10	0	0
30	5	0	0

In the analysis of genotypes starting from the cut-off point of more than 23 repetitions, an association with thromboflebitis is found, with a corrected Yates' χ^2 of 17.99 ($p = 0.00002$) and a relative risk of 19.21 with a confidence interval of 95% of 2.679-137.7, explaining a etiological fraction in the population of 92.36% and an etiological fraction in exposed of 94.79%. When comparing an allele distribution from the cut-off point of 23 or less repetitions between groups A and B, an association is observed as a protective factor with a corrected Yates' χ^2 of 124.8 ($p < 0.0000001$), a relative risk of 0.1544 with a confidence interval of 95% of 0.1184-0.2014, a preventable fraction in the population of 75.35% and a preventable fraction in exposed of 84.56%.

Conflicts of interest

The authors declare no conflicts of interest.

Ethical disclosures

Protection of people and animals. The authors declare that no experiments have been made on human beings or animals for this research.

Data confidentiality. The authors declare that no patient data appears in this article.

Right to privacy and informed consent. The authors declare that no patient data appears in this article.

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