

HbaI genetic variant of *APOE* as an epidemiological factor for post COVID-19 cognitive impairment in the Amerindian population of Oaxaca

Variante genética HbaI de APOE como factor epidemiológico para el deterioro cognitivo post-COVID-19 en población amerindia de Oaxaca

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To the Editor,

Cognitive impairment and the risk of dementia are common in patients who had SARS-CoV-2 (COVID-19) infection, diabetics, and older adults. The number of people with this condition has been projected to reach 115.4 million globally by the year 2050, currently as part of long COVID¹. In the older adult population in Mexico, the *APOE* E4 allele has been reported to be associated with degrees of cognitive impairment. Based on the above, 690 patients with type 2 diabetes mellitus originating from the State of Oaxaca, with Zapotec ancestry and who had COVID-19 corroborated by qRT-PCR (quantitative real-time polymerase chain reaction), with an age range of 30-45 years, were studied, 286 of whom exhibited mild-to-moderate cognitive impairment evaluated using the 3MSE scale. The risk of development was estimated by calculating the odds ratio with a 95% confidence interval according to Wolf's quotient. Using the PCR-RFLP (polymerase chain reaction - restriction fragment length polymorphism) technique, *APOE* genotypes were estimated with the HbaI enzyme^{2,3}. The three alleles that lead to amino acid changes at residues 112 and 158 of apolipoprotein E were detected: the E3 allele (112cis-158arg), the E2 allele (112cis-158cis), and the

E4 allele (112arg-158arg)^{2,3}. Thus, the most frequent genotype in the analyzed population was the E3/E3 and E3/E4 homozygote. A positive association was found as a risk factor for cognitive impairment for the E3-E4 and E2-E3 genotypes, and for carriers of the E4 allele; as a protective factor, for the E3-E3 genotype, the E3 allele, and homozygotes (Table 1).

This is the first report that shows the involvement of the *APOE* gene in long COVID syndrome, particularly post-COVID-19 cognitive impairment. In Mexico, genotypes with the E2 and E4 alleles are involved in diabetes and metabolic alterations^{3,4}. The present results are similar to those reported for the *APOE* E4 and E2 alleles in previous studies^{3,4}, for which reason, in patients with COVID-19 who are diabetic, carrying the E4 allele or the E2-E3 genotype increases the risk of cognitive impairment as a manifestation of long COVID.

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Table 1. APOE Variants in Cognitive Impairment due to Covid-19

Genotype	Type 2 Diabetics with Covid-19 without CI	Type 2 Diabetics with Covid-19 with CI	ORR	p	Chi-square test	95% CI
E2-E2	4	2	1.14	0.6853	0.0001179	0.6452, 2.014
E2-E3	2	14	2.231	0.0001003	13.19 corrected	1.812, 2.746
E2-E4	2	4	1.617	0.2083	1.586	0.9119, 2.867
E3-E3	252	146	0.6699	0.000000932	24.06	0.5699, 0.7873
E3-E4	140	102	0.843	0.05731	3.614	0.7045, 1.009
E4-E4	4	18	6.039	0.0002274	13.59 corrected	1.64, 2.535
Allele						
E2	12	22	0.3769	0.04874	3.884	0.1378, 1.031
E3	646	408	0.7695	0.008624	6.899	0.6385, 0.9273
E4	150	142	1.228	0.04919	3.869	1.009, 1.495

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Conflicts of interests

The author declared no conflicts of interest.

Ethical considerations

Protection of people and animals. The author declares that the procedures followed conformed to the ethical standards of the responsible human experimentation committee and in accordance with the World Medical Association and the Declaration of Helsinki.

Confidentiality of data. The author declares that they have followed the protocols of their work center regarding the publication of patient data.

Right to privacy and informed consent. The author has obtained informed consent from the patients or subjects referred to in the article. This document is in their possession.

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