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Letter to the Editor

Variants in *AGTR2* gene in Maya people with COVID-19

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Dear Editor

In February 2020, the first cases of COVID-19 were declared in Mexico, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The statistics increased dramatically as the months wore on, accumulating close to 223,072 deaths (May 2021), bringing the country to the fourth lethality position in the world in early 2021 (<https://covid19.sinave.gob.mx/>). So far, the various environmental causes that lead that point are debatable; however, it is important to consider that genetic causes and high risk for patients with pre-existing comorbidities such as obesity, diabetes, and hypertension, which were already important causes of death in Mexicans, also have an effect on this disease. Concerning these various issues, in 2018, a pilot study was performed in Mexico with the aim of identifying genetic variants that affected type 2 diabetes in people with Maya ethnicity from Yucatan (Domínguez-Cruz et al., 2018). The results obtained showed the variant rs1914711 located in *AGTR2* gene (OR = 6.824; $p = 1.448 \times 10^{-9}$), locus Xq22-q23 (MIM *300034) significantly associated with T2D. Despite the limited sample of the study, it was not found a stratification in the population. This gene encodes the angiotensin II receptor type 2, an interactive part of the protective renin-angiotensin system (RAS; Steckelings and Summers, 2020) promoting vasorelaxation and participates in the regulation of glucose levels (Geng et al., 2013). The *AGTR2* gene also, has been found to be dominant, highly expressed, and highly specific in humans lungs (2.52 [Magic index = $\log_2(1000 \text{ sFPKM}]$; Cui et al., 2020), and in the lungs of the Japanese Macaque (2.70) (<https://www.ncbi.nlm.nih.gov/iebr/research/acemby/av.cgi?db=human&term=AGTR2&submit=Go>). Furthermore, this gene also has been proposed as a novel key gene for the entry of Covid-19 into human cells, although, it needs further confirmation (Cui et al., 2020). The

rs1914711 variant identified in the pilot GWAS study (g.115288474C > A; Domínguez-Cruz et al., 2018) has a relatively high MAF = 0.484 (dbSNP database; <https://www.ncbi.nlm.nih.gov/snp/rs1914711>) compared to the MAF = 0.348743 (43791/125568, TOPMed) of the general reference obtained in this public data-sets. Yucatan is a Mexican state with a dispersed population with a Maya ancestry concentrated in Merida City. Concerning the COVID-19 disease, the lethality in this southern state was 10.10% in May 2021, affecting mainly the male population of the Merida city and Maya communities, with a death rate of 52.70%. In addition, the main comorbidities of the deceased are hypertension (17.57%), diabetes (11.75%), obesity (14.57%), and smoking (3.77%) (<https://datos.covid-19.conacyt.mx/>).

In December 2020, Vicore Pharma (Gothenburg, Sweden, a pharmaceutical company focused on rare lung disorders and related indications) concluded, a randomized, double-blind, placebo-controlled phase 2 trial performed to study the effect of protective agonist C21 drug (Angiotensin II Type II Receptor agonist) in a COVID-19 Trial in a group of 106 volunteers in India who were hospitalized with COVID-19, but they did not receive ventilator management (Vicore Pharma, 2020; Steckelings and Summers, 2020). Recently, preliminary results have been published mentioning a 40% reduction in the need for oxygen supplementation in the group that received C21 compound (Tornling et al., 2021). Previously, the same compound was tested in-vitro, preventing endothelial inflammation and leukocyte adhesion (Rathinasabapathy et al., 2018) and an attenuation in the progression of pulmonary fibrosis and hypertension (Sampson et al., 2016) in in-vitro and in-vivo models.

Given these observations, we suggest that the identification of the high-frequency variant rs1914711 in the *AGTR2* gene associated with

Abbreviations: COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; OR, Odds Ratio; sFPKM, significant fragments per kilobase of transcript per million mapped reads; *AGTR2*, Angiotensin II Receptor Type 2; GWAS, Genome-Wide Association Study; MIM, Mendelian Inheritance in Man; MAF, Minor allele frequency; dbSNP, The Single Nucleotide Polymorphism Database; TOPMed, The Trans-Omics for Precision Medicine; C21 drug, *AGTR2* agonist.

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T2D in a Mayan population, in addition to being a factor for the appearance of T2D, increases the risk of severe Covid-19 disease. In addition, the high mortality in the Maya populations in Yucatan due to COVID-19, also suggests the possibility of using a new therapy with the AGTR2 agonist as a coadjuvant. It is essential to point out the need to support and conduct studies in Mexican populations with COVID-19 virus infection, highlighting the need for genomics approaches to increase pharmacogenetics and pharmacogenomics knowledge to advance in the fields of precision medicine in the context of the COVID-19 Pandemic.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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