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Genetic association study of the rs10774671 variant of the *OAS1* gene with the severity of COVID-19 in an Ecuadorian population.

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Keywords: complex trait; COVID-19; genetic association study; genetic variant; Hardy-Weinberg equilibrium; innate immune processes.

Abstract. COVID-19 exhibits a wide range of phenotypic manifestations, from asymptomatic to severe phenotypes with fatal complications. The existence of risk factors cannot entirely explain the variance in the phenotypic variability of COVID-19. Genome-wide association analyses have identified target human genes related to virus transmission and the clinical phenotype observed in COVID-19 patients. Genetic variants on the *OAS1* gene have been associated with innate immune processes (entry phase and viral replication in host cells). The A or G alleles of rs10774671 in OAS1 encode isoforms with different antiviral activities. One hundred COVID-19 patients were genotyped for the rs10774671 using RFLP-PCR (severe form, n = 43; asymptomatic-mild, n = 57). The susceptibility of the two groups to the severe phenotype of COVID-19 was compared. The allele frequency for A was 0.8. The genotypic frequencies for AA and GG homozygotes were 0.62 and 0.02, respectively. A Hardy-Weinberg equilibrium deviation was found in both groups. No statistically significant associations were found in genetic models adjusted for sex (for the additive model OR = 1.18, 95% CI = (0.53-2.61), p = 0.69). A relatively recent mix of different ethnic groups and sample size may influence these findings.

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Estudio de asociación genética de la variante rs10774671 del gen *OAS1* con la severidad de COVID-19 en una población ecuatoriana.

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Palabras clave: estudio de asociación genética; equilibrio Hardy-Weinberg; rasgo complejo; variante genética; procesos inmunes innatos.

Resumen. La COVID-19 presenta una amplia gama de manifestaciones clínicas, desde asintomáticas hasta formas graves con complicaciones mortales. La variabilidad fenotípica de la COVID-19 no puede explicarse totalmente por la existencia de factores de riesgo. Se han identificado genes humanos diana relacionados con la transmisión del virus y el fenotipo clínico observado en pacientes con COVID-19 mediante análisis de asociación de genoma completo. Las variantes genéticas del gen *OAS1* se han asociado con procesos inmunitarios innatos (fase de entrada y replicación viral en las células hospedadoras). Los alelos A o G de rs10774671 en *OAS1* codifican isoformas con diferentes actividades antivirales. Cien pacientes con COVID-19 fueron genotipados para el rs10774671 mediante RFLP-PCR (forma grave, n = 43; asintomática-leve, n = 57). Se comparó la susceptibilidad de los dos grupos al fenotipo severo de COVID-19. La frecuencia alélica para A fue de 0,8. Las frecuencias genotípicas para los homocigotos AA y GG fueron 0,62 y 0,02, respectivamente. Se observó una desviación del equilibrio de Hardy-Weinberg en ambos grupos. No se encontraron asociaciones estadísticamente significativas en los modelos genéticos ajustados por sexo (para el modelo aditivo OR = 1,18, IC 95% = (0,53-2,61), p = 0,69). La mezcla relativamente reciente de diferentes grupos étnicos y el tamaño de la muestra pueden influir en estos resultados.

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INTRODUCTION

COVID-19 is a human-to-human transmissible viral infectious disease [1]. Until the beginning of 2023, it had been responsible for about 7 million deaths worldwide [2]. Subjects infected with SARS-CoV-2, the etiological agent of COVID-19, have a wide range of phenotypic variability, from asymptomatic to severe forms of the disease [3]. This broad clinical variability is partially explained by risk factors that include age (> 65 years), male sex, and the presence of comorbidities such as obesity, cardiovascular diseases, diabetes mellitus, and respiratory disorders, among others [4]. Therefore, the variance in the clinical phenotype of COVID-19 may be caused by additional host-specific factors [5].

Genome-wide association studies have reported associations between the severe form of COVID-19 and chromosomal regions, including 12q24.13, which harbors a gene cluster encoding antiviral restriction enzyme activators (*OAS1*, *OAS2*, and *OAS3*). These activators are involved in viral RNA degradation and viral replication inhibition [6,7]. The *OAS1* gene encodes the enzyme 2′-5′ oligoadenylate synthetase 1

(2-5A), an activator of the ribonuclease L (RNaseL), which degrades viral RNA within the host cell, blocks viral replication and inhibits viral protein synthesis. The genetic variant rs10774671 is a G→A transition in the last nucleotide of intron 5 of the *OAS1* gene, which affects the nonsense-mediated decay and the splicing site and controls the differential expression of isoforms with lesser enzymatic activity [7,8]. Different allele and genotype frequencies have been reported in studies, including those of European, African, and Latin American Afro-Caribbean populations, likely due to the influence of the ancestral factor [9,10]. Despite being a multiethnic society composed of different communities with South American, West Eurasian, and Sub-Saharan ancestries, the Ecuadorian population has a strong Native South American ancestral influence, which is considered the second highest for this region's population [11].

The percentage of severe cases and deaths among individuals of Hispanic ancestry was higher than that reported for the general population. For instance, in New York City, one of the communities hardest hit by the SARS-CoV-2 virus globally, more Hispanics per capita have died from COVID-19 than any other ethnic group. Infection rates on the Navajo Nation Indian Reservation have also been reported to be particularly high[12]. Native Americans represent more than a third of the COVID-19 cases in the state of New Mexico, despite making up only 9% of the population [13]. These ethnic differences do not appear to be caused by socioeconomic conditions or access to health services since Latin American non-Sub-Saharan ancestry was reported as a factor associated with morbidity and mortality from COVID-19 in a study that included health professionals with similar economic and educational status [14].

Latin America is one of the regions where the impact of COVID-19 has been most severe. Poor sanitary conditions of infrastructure, health personnel, and an immunologically vulnerable population are two factors that influenced this impact. Ecuador was one of the countries that was dramatically impacted at the beginning of the pandemic. However, sustained vaccination campaigns were able to mitigate this impact partially. Fifteen million people, or 86% of the population, have received at least one dose [15], with 14 million (or 79%) receiving two or more doses [16]. Few genetic association studies between COVID-19 and susceptibility genes have been reported for the Latin American populations. For this reason, we examined the association between the rs10774671 variant of the *OAS1* gene and the severe form of COVID-19 among Ecuadorian individuals.

METHODS

Design and Study Subjects

In this observational, analytical, and case-control study, a total of 100 Ecuadorian individuals with COVID-19 were analyzed. The individuals were divided into two groups: 43 patients with the severe clinical picture (group A) enrolled from October 2021 to March 2022 and 57 subjects with the asymptomatic-mild form (group B) enrolled in January 2021 at the Quito Sur Hospital of the Ecuadorian Institute of Social Security, Quito, Ecuador. Group A consisted of individuals without regard to sex who had a diagnosis of COVID-19 severe form confirmed by a positive RT-PCR test specific for SARS-CoV-2; a chest computed tomography image showing a pattern of viral pneumonia due to diffuse infiltration of both lungs greater than 50% (CORADS 6); and the presence of respiratory failure and the need for mechanical ventilation (PaO2/FiO2 ≤ 100mmHg (with PEEP ≥ 5cm H2O) and SpO2/FiO2 ratio <315). This group had received at least two doses of SARS-CoV-2 vaccines. Group B subjects presented the disease's asymptomatic or mild clinical form, validated by a positive RT-PCR test for SARS-CoV-2. Group B was made up of health workers from the same hospital who provided care for patients with the severe

form of COVID-19 admitted to the intensive care unit. When the subjects from Group B were diagnosed with COVID-19, they had not received any vaccination against COVID-19. This method of subject selection was carried out to identify COVID-19 protective alleles. The exclusion criteria for both groups included consanguineous individuals, minors, pregnant or nursing women, and refugees or displaced with little or no knowledge of the Spanish language.

Molecular Analysis

Ten milliliters of peripheral blood were drawn from each subject in an EDTA tube. In order to reduce bias in the laboratory phase, each tube was assigned a unique code without discriminating to which clinical group it belonged. The Column-Pure Blood Genomic DNA (ABM, Vancouver, Canada) kit was used to extract DNA according to the manufacturer´s instructions. The Qubit ds-DNA BR ASSAY Kit (21000 ng 100RX (Invitrogen, Massachusetts, USA) was then used to quantify the DNA using the Qubit fluorometer (Invitrogen, Massachusetts, USA). The DNA quality was determined by electrophoresis in 1.5% agarose gels at 80V for an hour, with the bands visualized using the Microtek Bio-1000F program scanner (Microtek International Inc., Hsinchu City, Taiwan). The forward primer 5'-TCC-AGA-TGG-CAT-GTC-ACA-GT-3' and the reverse primer 5'-TAG-AAG-GCC-AGG-AGT-CAG-GA-3´ were used to carry out the PCR, based on earlier research [17]. The master mix and thermocycler settings (Applied Biosystems MiniAmp, Thermo Fisher Scientific Inc., Massachusetts, USA) for PCR were performed based on a previously published [18] method with modifications. PCR products were examined by electrophoresis on 1.5% agarose gels in the blueGelTM system (48V, 45 minutes) (MiniPCR Bio, Massachusetts, USA). Subsequently, these products were digested with 10 U of *Alu*I at 37°C for 16 hours, in a total volume of 20 μl, following the manufacturer's instructions. They were electrophoresed in 3% agarose gels in the Thermo ScientificTM equipment (120V, 2 hours) (Thermo Fisher Scientific Inc., Massachusetts, USA). Ten percent of all samples were randomly sequenced to control the reproducibility and quality of genotyping of PCR-RFLP, which showed complete matching of results.

Statistical Analysis

Used software included InfoStat, Microsoft Excel 2019, SNPStats [19] (https://www.snpstats.net/), and the Hardy-Weinberg statistical package for R Studio [20]. Allelic and genotypic frequencies were calculated by direct counting and expressed in proportions and percentages. The exact test examined genotypic and allelic frequencies to determine whether the groups were in Hardy-Weinberg equilibrium (HWE) [21]. The Fisher's exact test was then used to compare allele frequencies between group A (severe COVID-19 phenotype) and group B (mild and moderate COVID-19 phenotype). The association between the rs10774671 alleles and the severe phenotype of COVID-19 was estimated considering different inheritance models (codominant, dominant, recessive, overdominant, and additive) [22], expressed in frequencies and percentages. For each analysis, the odds ratios (OR), 95% confidence intervals (95% CI), and corresponding p values were calculated. An association was considered significant when the p-value was < 0.05 in all two-tailed statistical tests.

Ethical Considerations

Participants gave their written consent to sample extraction, the use of clinical histories, and the processing of biological samples. Hospital staff members collected the samples and data; they had no interaction with the researchers who conducted the molecular tests. The data were collected according to the WHO "COVID-19 Case Registration Form", and the information was handled confidentially. This study had the ethical, legal, and methodological endorse-

ment of the Ethics Committee for the Expedited Review of COVID-19 Investigations of the Ministry of Public Health of Ecuador (MSP-CGDES-2020-0244-O1).

RESULTS

Table 1 shows the allelic and genotypic frequencies discriminated by groups (whole group, groups A and B). Alleles and genotypes were not found in HWE in the analyzed groups. Likewise, no allele or genotype was significantly associated with the severe phenotype of COVID-19 enough to be considered an associated factor (risk or protective) (OR (95% CI) = 1.17 (0.43-1.72), 1.04 (0.46-2.35), respectively). Although it was not statistically significant, this estimation revealed that the additive model had the best fit (OR (95% CI) = 1.18 (0.53-2.61); p = 0.69; Table 2).

DISCUSSION

In the current study, a higher frequency of the A allele was found in the three groups analyzed, with a value around 0.8 for the rs10774671 variant of the *OAS1* gene in a mestizo population with a high Native South American influence. The contrast between these values and those observed in other research conducted in various ethnic settings is striking. In a sample of 301,842 individuals from all continents, a higher frequency of the A allele of 0.6346 was reported [10]. In this same database, for Latin American individuals of Afro-Caribbean ancestry (n = 1,394) and subjects with primarily European and Native American ancestry (n = 6,656), the frequencies of the A allele were reported at 0.5703 and 0.7763, respectively [10]. A frequency similar to that of the present study for the A allele (0.796) was reported by a Mexican study with similar methodological features[23]. The allele A determines the differential expression of isoforms depending on the virus type. This allele has been the subject of study for other viral diseases, finding significant associations as a risk factor for initial infection with West Nile virus (WNV)[24] as well as hepatitis C virus (HCV) [25].

Conversely, the worldwide genotype frequencies for AA and GG homozygotes and heterozygotes were 41%, 18.1%, and 40.9%, respectively [26]. These genotype frequencies are very different from those found in the present study and in the data from the Mexican population, whose respective genotype frequencies were 61.2%, 2%, and 36.7% [23]. Both studies analyzed populations (Mexican

Table 1
Allele and genotypic frequencies for the rs10774671 genetic variant in the *OAS1* gene in the groups analyzed.

Variable	General sample n=100	Group A n=43	Group B n=57	p	OR (CI 95%)
Alelle§					
A	0.8	0.81	0.79	0.723	1.17 (0.43-1.72)
G	0.2	0.19	0.21		
Genotype§§					
A/A	62 (62)	27 (62.8)	35 (61.4)	1	-
A/G	36 (36)	16 (37.2)	20 (35.1)	0.347	1.04 (0.46-2.35)
G/G	2 (2)	0 (0)	2 (3.5)	0.312	0

Group A: individuals with a diagnosis of COVID-19 severe form. Group B: individuals with a diagnosis of COVID-19 asymptomatic or mild clinical severe form. Allelic frequencies are expressed in proportions. Genotypic frequencies are expressed in number of cases and percentages. § p-value of Fisher's exact test (2x2 contingency table). §§ p-value of the Exact test (R Studio).

Table 2
Genetic Models for the Estimation of the Association of the rs10774671 genetic variant of the *OAS1* gene and the severe phenotype of COVID-19.

Genetic Models†		Group A (n=43)	Group B (n=57)	*p*§	OR (CI 95%)
Co	A/A G/G A/G	27 (62.8) 0 (0) 16 (37.2)	35 (61.4) 2 (3.5) 20 (35.1)	0.34	NC‡
Do	A/A+A/G G/G	43 (100) 0 (0)	55 (96.5) 2 (3.5)	0.14	NC
Re	A/A+G/G A/G	27 (62.8) 16 (37.2)	37 (64.9) 20 (35.1)	0.94	1.04 (0.44-2.42)
Overdo	A/G+G/G A/A	16 (37.2) 27 (62.8)	22 (38.6) 35 (61.4)	0.79	1.12 (0.48-2.60)
Ad	-	-	-	0.69	1.18 (0.53-2.61)

Group A refers to individuals with a diagnosis of COVID-19 severe form and Group B refers to subjects who presented the asymptomatic or mild clinical form of the disease, § p-value of Fisher's exact test (2x2 contingency table). † Genetic Models: codominant (Co), dominant (Do), recessive (Re), overdominant (Over-do) and additive (Ad). ‡ NC: Not calculated.

and Ecuadorian) composed of several ethnic groups that underwent a complex process of biological mixing but with a solid Native South American component in their population structure [27,28]. However, despite their close geographic and evolutionary proximity, the genotype frequencies reported for a Peruvian population (78.8%, 1.2%, and 20%, respectively) were very different from those of the present study. This difference could be explained by the fact that the data collected for the Peruvian population belongs to the results published by the 1000 Genomes Project (1 KGP) with a study design different from the one used in our study [26]. Similarly, the effect of the study's sample size cannot be ignored. Despite this, the results for the Mexican and Peruvian populations and the current study show a similar frequency of homozygotes for the minor allele (GG). The high Native South American component of these mixed populations could explain this observation.

No statistically significant differences were found for allele and genotypic frequencies between groups A and B. Genetic models developed from the sex-adjusted frequencies did not support a possible association with the severe form of COVID-19 in Ecuadorian patients. Significant associations were reported between the rs10774671 allele of the *OAS1* gene and the severe phenotype of COVID-19 for European populations (OR = 1.33 (1.13-1.56), $p = 6.45x10^{-4}$) [9]. By contrast, for individuals with Sub-Saharan ancestry, no significant association was found (OR = 1.23 (0.98-1.55), $p = 0.079$) for the allele A. These findings suggest the possibility that ethnic differences in genotype and allele frequencies may account for the inconsistent results when examining the association between genotype and phenotype for this locus and COVID-19.

The evolutionary history of South American ethnic groups may help clarify the epidemiological findings that suggest these populations are more susceptible to developing the severe form of COVID-19. In this context, the G allele of rs10774671 of the *OAS1* gene has been associated with a protective effect against the severe form of COVID-19 for this haplotype in patients of European ancestry [9]. The G allele probably has a Neanderthal origin, whereas the A allele (which confers risk in the European population) is predominantly of Denisovan ancestry[9].

It is proposed that Sapiens, Neanderthals, and Denisovans cohabited 100,000 years ago based on evolutionary history and gene flow[29]. Data from genetic analyses of human fossils indicate that hybridization events occurred between modern humans and Neanderthals between 37,000 and 86,000 years ago[30]. This hybridization led to the recombination of adaptive alleles that provided resistance against viruses. However, these genomic segments of Neanderthal origin were rapidly eliminated by selective environmental pressure among modern humans[31]. These haplotypes of Neanderthal ancestry in the *Homo sapiens* genomes of European and Asian populations dropped considerably from 10% to 4% and 2%, respectively[29]. Hence, the decline in the frequency of the GG homozygotes with a protective effect for the severe form of COVID-19 reported in Latin American populations could be attributable to the selective environmental pressure when modern humans migrated to the Americas from Asia. However, the fixation of alleles in populations with recent admixture, such as the Ecuadorian population, may be influenced by other factors, such as genetic drift, including bottle-neck and founder effects. Our investigation's design study and statistical power were inadequate to assess this hypothesis.

The present study has several limitations. None of the analyzed groups presented HWE for the alleles and genotypes evaluated. Precautions were taken to avoid genotyping errors, as different researchers tested molecular analyses to confirm the results separately. In addition, we have randomly sequenced 10% of the samples to verify the results of the PCR-RFLP analysis, which showed complete matching of results. Sample size and stratification might be two more potential sources of this HWE deviation. We wanted to take advantage of the outbreak produced by the *Omicron* variant of SARS-CoV-2, which increased the number of patients hospitalized in our intensive care unit, selecting those who had received at least two doses of the COVID-19 vaccine and contrasting them with subjects who presented COVID-19 in the asymptomatic and mild forms. This would make it possible to find protective alleles. However, this selection method introduces a selection bias that may distort the genetic composition of the groups studied. Such selection bias could explain the lack of homozygous genotypes for the minor allele (GG). The sample size was small, resulting in even smaller sample sizes when broken down into two groups for analysis. Thus, the main limitations of our study were the small sample size and the lack of a replication-independent cohort to verify our findings. The statistical interpretation of the associations is limited by the reduced sample size in our study. We know our results may have a type II error (false negative). Thus, although we did not find a significant association between the rs10774671 variant of the *OAS1* and the severe phenotype of COVID-19 in the Ecuadorian population, we cannot rule out such an association. Therefore, we suggest these associations be further investigated and replicated in other Latin American cohorts with a more significant number of individuals.

To the best of our knowledge, this study is the first effort to identify an association between the rs10774671 of the *OAS1* gene and COVID-19 in mestizo Latin American groups, as previous studies that involved the genotyping of this genetic variant did not assess this relationship. Due to the existing ethnic heterogeneity, new strategies will be needed to assess the genetic components implicated in emerging viral infections in the Latin American population.

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Statement of ethics

The Ethics Committee reviewed and approved the study protocol for the Expe-

dited Review of COVID-19 Investigations of the Ministry of Public Health of Ecuador (MSP-CGDES-2020-0244-O1). The ethical principles of the 1964 Declaration of Helsinki for medical research were adhered to throughout this research. Before beginning the study, the procedures and possible discomfort/risks were fully explained to all participating subjects. Each then voluntarily decided to participate in the study, approved their participation, and signed an informed written consent form in front of a witness. Subjects were allowed to withdraw their participation in the study at any time without consequence.

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Author Contributions

The authors' contributions to the paper are as follows: KP: study concepts and design, data analysis and interpretation, statistical analysis, critical revision of the manuscript for important intellectual content and manuscript preparation; TB: molecular studies and data analysis; CA: biochemical studies and data analysis; IZP: acquisition of data and data analysis; KN: acquisition of data and data analysis; and FAN: study concepts and design, data analysis and interpretation, statistical analysis, obtaining funding, critical revision of the manuscript for important intellectual content and manuscript preparation. All authors read and approved the final manuscript.

Conflict of interest

The authors declare that the research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

Data Availability Statement

The data supporting this study's findings are openly available in DOI: 10.5281/zenodo.7672228 at https://zenodo.org. The data are publicly available privacy and ethical restrictions, as stipulated by the Central University of Ecuador Institutional Review Board.

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