Host genetic markers associated with severe COVID-19: A systematic review

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ABSTRACT

Background: Severity of COVID-19 has been linked to several factors. As any other polygenic-multifactorial phenotype, genotype is not determinant in this prediction but may add actionable information. There is no consensus yet as to which genetic markers are useful, but several studies have been published that postulate different hypotheses acknowledging the relevance of including host genetics among the variables that predict the risk for severe forms of the disease. **Objective**: The objective of this study is to perform a systematic review that summarizes the projects, studies and postulated markers in order to establish if their application in clinical practice is currently feasible. **Materials and methods**: A comprehensive search was conducted in Pubmed. The inclusion criterion was studies of patients with COVID-19 who had germinal genetic markers of interest sequenced. The selected studies had to include at least a group of patients with the severe form of the disease. **Results**: 7 studies that met the criteria were included, which involved 6347 individuals. Markers for 19 genes have been postulated as relevant. **Conclusion**: The performed analysis indicates that multiple markers may be correlated with worse evolution of COVID-19; however, great heterogeneity has been found among the studies, which still precludes their translation into clinical practice.

KEYWORDS

Genetic predisposition, COVID-19, Computational biology, Genomics, Genome-Wide association study

Marcadores genéticos del huésped asociados con COVID-19 grave: una revisión sistemática

RESUMEN

Antecedentes: La severidad de COVID-19 depende de múltiples factores. Del mismo modo que en cualquier fenotipo multigénico-multifactorial, la genética no es determinante en esta predicción pero sí puede brindar información accionable. No hay un consenso aún sobre cuáles son los marcadores genéticos de utilidad pero sí hay varios estudios que postulan diferentes hipótesis, reconociendo la importancia de incluir la genética entre las variables que predicen riesgo de cuadros graves. Objetivo: El objetivo del estudio es realizar una revisión sistemática que resuma los proyectos/estudios realizados y los marcadores postulados con el fin de establecer si actualmente es posible su uso en la práctica clínica. Materiales y métodos: Se realizó una búsqueda exhaustiva en Pubmed. El criterio de inclusión fue estudios de pacientes COVID-19 con secuenciación de marcadores genéticos germinales de interés. Los estudios seleccionados debían incluir un grupo de pacientes que desarrollaron formas graves de la enfermedad. Resultados: 7 estudios cumplieron los criterios, los cuales involucran a 4604 individuos. Se postularon como relevantes marcadores en 19 genes. Conclusión: El análisis realizado evidencia múltiples marcadores que podrían estar correlacionados con peor evolución de COVID-19; sin embargo se detectó gran heterogeneidad en los resultados lo cual no permite aún la traslación a la clínica.

PALABRAS CLAVE

Predisposición genética, COVID-19, Biología computacional, Genómica, Estudio de asociación del genoma completo

INTRODUCTION

In December 2019, a large number of individuals developed pneumonia in the city of Wuhan, which attracted the interest of China, and the whole world [1]. After the identification of a coronavirus as the source of this outbreak, and the realization that it had the ability to provoke a severe acute respiratory syndrome [2], the Coronavirus Study Group taxonomically recognized it as being related to SARS-CoV, so they named it SARS-CoV-2 [3]. On February 11th 2020, World Health Organization (WHO) defined the name for the disease caused by this virus as COVID-19 [4], and on March 11th they characterized it as a pandemic [5]. On January 10th 2019, the first whole sequence of SARS-CoV-2 was published, and by April 7th 2020 more than 500 sequences had been deposited in GenBank [6].

Even though in most cases COVID-19 is associated with mild symptoms, or SARS-CoV-2 infected individuals may even be asymptomatic, the mortality risk for severe forms of the disease is high. In patients with mild and moderate symptoms, currently available treatments include oxygen administration, antiretrovirals, immunomodulators and antithrombotics. New treatments for COVID-19 are constantly being tested, but no consensus or a definite solution for severe forms of the disease has yet been found.

The pandemic has affected, by June 8th 2021, 173,609,772 people worldwide [7] and has caused 3,742,653 deaths [7]. According to WHO, by June 8th, there are 102 vaccines in clinical development, 185 in pre-clinical development and 2,092,863,229 people have been vaccinated [7]. At least 60% of the population is currently considered to need to be vaccinated in order for the region to achieve herd immunity, but this percentage is under revision and depends on several variables [8].

Although many vaccines are being developed, herd immunity will not be achieved in many countries (especially those with middle and low income that have had greater difficulties in acquiring vaccines) in the short term, so a greater comprehension of the factors that determine the risk for more severe forms of the disease is key to adopt prevention and treatment strategies, not only at population level but also considering personalized/precision medicine paradigms. Even more, new viral strains may emerge in the future, which makes currently available vaccines useless. Many host characteristics have been postulated, and some of them considered proven, as representing risk factors for worse evolution of COVID-19, including age [9,10], gender [9,10] and the presence of certain comorbidities [11], mainly diabetes [9,12,13,14], cardiovascular disease [9,14], hypertension [9] and obesity [14,15,16]. However, the list of risk factors is not yet considered complete [10].

The identification and analysis of the genetic sequence of SARS-CoV-2 have been a central breakthrough for its classification and the development of vaccines in record time. On the other hand, host genetics may play an important role in the prediction of the disease progression, and therefore represent a valuable addition to the list of individual risk factors.

The interest in identifying such markers has been high in the last months of the pandemic. Genomics, bioinformatics and artificial intelligence (particularly the use of Machine learning techniques to infer models based on large volumes of data [17]) have been some of the core scientific disciplines involved in these findings. This applies both to the study of the viral genome and the human one as well. The Host Genetics Initiative [18] has had a central role in these last studies, since it functions as a public data repository for host genetic markers involved with the response to COVID-19. In a similar fashion, GISAID [19,20] has become one of the main databases for viral sequences.

From a molecular point of view, ACE2 -a protein mainly expressed in AT2 alveolar cells- has been found to act as a cellular binding site for the viral spike protein [21,22,23,24]. ACE2 had previously been confirmed as a binding site for other previously known coronaviruses, SARS-CoV and NL63 [25,24]. Another relevant finding was that the product of the human STMP3 gene is used by the virus to perform a cleavage that allows the fusion of the membranes and the following entry of the virus to the cell [23].

In the same cellular types that express ACE2, other key genes for the entry of the virus may be found at high levels: ITGB6, CAV2 [24], as well as genes that allow the newly formed viral particles to leave the cell: CHMP3, CHMP5, CHMP1A and VPS37B [24]. ACE2 levels in lung tissue vary among healthy individuals, in part due to ethnic factors. In people of East Asian origin, higher expression of ACE2 has been seen, which has partially been explained by the differences in allelic frequency in genetic variants in eQTL sites (loci involved in differences in the gene expression) in this population in comparison with others [24,25,26].

Regarding immunity, Human leukocyte antigen (HLA) has a known relevant role in the susceptibility to several viral infections [27] and the severity associated with the disorders these infections may provoke [28]. Even though HLA depends on the genetic characteristics of the individual, the gold standard for HLA testing is currently not genetic sequencing, and correlations between HLA subtypes and their corresponding genotypes is not known in many cases. The same is true for blood ABO groups, which have been associated with severity of COVID-19 by some authors. Variants in the gene IFITM3 have been reported as potentially related to a more severe evolution in patients infected with influenza H749 or H1N1 [29,30]. Patients who harbour certain deleterious variants in the Myxovirus resistance A (MxA) gene appear to have a worse evolution as well, since this gene codes for an antiviral protein stimulated by α and β interferon [31].

Several studies have been performed in order to identify an association between host genetic markers and worse clinical evolution of the SARS-CoV-2 infection, mainly Genome-Wide Association Studies (GWAS).

In this work we had the objective to perform a systematic review in order to evaluate the clinical utility of applying germinal host genetic markers that have been postulated to have predictive value for severe forms of COVID-19.

MATERIALS AND METHODS

This study is a systematic review with qualitative methodology.

SEARCH STRATEGY

A comprehensive search in Pubmed was conducted, using the following expression based on MESH terms: “Genetic Predisposition to Disease”[Mesh] and COVID-19[Mesh].

The search was not restricted by a temporal variable, since the problem is naturally restricted in time, or by the population included.

The search was complemented by articles referenced by the papers originally identified in the search.

ELIGIBILITY CRITERIA

Observational studies which compare severe with non-severe cases on which any kind of genetic test would have been performed to acquire data on the patients' genotype were included.

TABLE 1 SHOWS INCLUSION CRITERIA.

Inclusion criteria
Observational studies which associate genetic markers with severe COVID-19 by: sequencing just one or several single nucleotide polymorphisms (SNP), a full gene, a group of genes of interest, or the individual's whole exome or genome or genotyping through microarray for a group of polymorphic markers (mainly SNP) or using already available molecular information of evaluated COVID-19 patients.
Authors report statistical significance of the results with a P-Value <.05 and odds ratio proving the effect of the variant on susceptibility to severe COVID-19 or bringing the data to allow odds ratio calculation.

EXCLUSION CRITERIA

TABLE 2 SHOWS EXCLUSION CRITERIA.

Exclusion criteria
Studies that did not make use of COVID-19 patients' genotypes obtained by sequencing, but inferred them from hypothesis, bioinformatic analysis only or speculations from population allele frequencies by country or ethnic group.
Studies that did not evaluate genetic predisposition to severe forms of COVID-19 but merely to being infected by SARS-CoV-2.
Studies that only tested for gene expression or other molecular data from the patients but not their germinal DNA.
Studies in which controls are taken from biobanks but are not tested for COVID-19.
Series and report cases
Non peer-reviewed articles

In order to evaluate the eligibility and inclusion/exclusion criteria for the articles that resulted from the search, titles, abstracts and part of the discussion were reviewed.

COLLECTED DATA

The main type of data extracted from each study was the genetic markers deemed to be associated with worse evolution of COVID-19. Other relevant data were extracted as well, such as ethnic group, number of individuals evaluated in each study and technology used for sequencing or genotyping (see Table 3).
The number of papers in which each marker was deemed relevant was evaluated, with the ponderation of the statistical significance of the correlation among the complete set of markers and the severity of COVID-19, using Odds ratios (OR), 95% confidence intervals (CI) and the corresponding p-value. ORs calculations were checked using R language [32] -epitools package [33]- as well as CI and p-value, taking into account the number of severe and non severe cases, with or without each variant of interest. (see Table 4).

BIASES

One of the possible biases in the present analysis is ethnic origin, since the studies mostly include individuals of European ancestry, a phenomenon which may be seen in most studies of multigenic and multifactorial phenotypes [34]. The analysis includes any studies that fulfill inclusion criteria regardless of the ethnic background of the patients evaluated, and if a marker has been postulated by more than one study, a separate analysis by ethnic group would be performed, in order to solve such bias.

EVALUATION OF THE METHODOLOGICAL QUALITY OF THE STUDIES

The Newcastle-Ottawa Scale (NOS) was applied so as to evaluate the methodological quality of the studies included in the present systematic review [35].

RESULTS

The applied search strategy allowed us to identify 207 articles of interest, published until May 2021.

After applying the inclusion and exclusion criteria, 6 papers were considered relevant for the analysis. The review of the references cited by these articles revealed 1 additional paper that was subsequently added to the review (see the flow diagram in Figure 1).

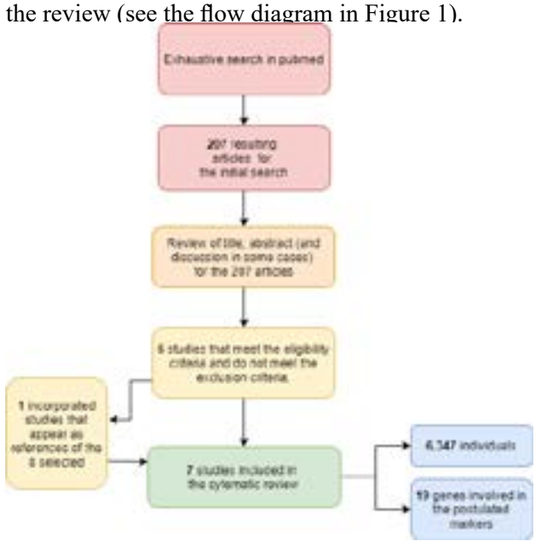

FIGURE 1. FLOW DIAGRAM FOR THE SYSTEMATIC REVIEW

The quality of the included papers was evaluated using the NOS [35]. Table 5 presents the articles included in the review, in a descending order by their score.

TABLE 5. NOS FOR EACH INCLUDED PAPER

Primer Autor	Escala Necastle-Ottawa (NOS)
David Ellinghaus [36]	8
Eleni Gavriilaki [37]	8
Sushma Verma [38]	7
JuanGómez [39]	7
Jianchang Hu [40]	6
Jihad G. Youssef [41]	5
Yonghong Zhang [42]	5

Out of the 7 included papers, the one with the highest number of patients included 3815 individuals, whereas the one with the lowest number evaluated just 13, with a median number of 81 for the whole set of papers. The total number of included patients was 6.347. Several polymorphic markers and genes were identified as possibly associated with severe forms of COVID-19. However, great heterogeneity was seen among the studies. Table 6 compares the postulated markers from each study.
An additional set of papers was identified that did not fully satisfy inclusion criteria, mainly due to the comparison of severe cases with controls taken from biobanks that had not been tested for the disease (nor was there information available regarding severity of the disease, had they been infected). However, some of them have identified potential markers of severity and should therefore be regarded as relevant [43,44,45,46].

TABLE 3. DATA EXTRACTED FROM EACH PAPER INCLUDED IN THE REVIEW

TABLE 6 - GENES POSTULATED AS POSSIBLE MARKERS OF COVID-19 SEVERITY. GREEN BOXES SUGGEST A PROTECTIVE EFFECT. RED BOXES SUGGEST A RISK FACTOR FOR SEVERE COVID-19.THE GREY BOX IS A PARTICULAR CASE IN WHICH VARIANTS ON THIS GENE WERE EXPLICITLY TESTED BUT THERE WAS NO SIGNIFICANT DIFFERENCE BETWEEN CASES AND CONTROLS.

DISCUSSION

The existence of intrinsic biological factors that imply differences in the susceptibility, or even immunity, to certain pathogenic agents is a historically known fact. However, only in the last few years the underlying genetic variants that are responsible for such variability in the risk of contagion and the evolution of infection have started to be described. Some clear examples could almost be treated as monogenic characteristics, such as the deletion in the CCR5 gene (and therefore the receptor encoded by it) that confers natural immunity to HIV infection [49], but in most cases susceptibility should be considered a polygenic and multifactorial phenomenon. This implies that no single marker should be held responsible for contagion or immunity to the infection, but rather multiple genetic polymorphisms are probably intervening in the process. These are generally present in the genes that encode proteins that participate in the immune response or different processes of the pathogen's capabilities of entry to the organism and proliferation.

Host genetics should ideally be included in predictive models that include clinical factors such as age, gender, comorbidities or any other variables known to affect the risk of severe forms of COVID-19. This way, in the future it might be possible to predict in an increasingly precise manner the risk of infection and the patient's clínical evolution. Potential benefits of this strategy include intensification of treatment, follow-up and prevention measures for higher risk individuals (including isolation, telecommuting, oxygen saturation monitoring, the frequency of chest imaging and viral load and inflammation testing, besides vaccination prioritization and the adjustment of migratory policies), whereas measures could be relaxed and unnecessary expenses may be cut for lower risk people.

On the other hand, as several authors have already stated [50,51], there are some potential risks for these predictive models. Social and work discrimination, such as limit imposition for transportation, higher costs of insurance or health coverage or unjustified dismissals from jobs. The same way as almost all subdisciplines of human genetics, education for the population and health professionals and regulation or legislation by national or supranational organisms is key to avoid harm in the application of these tests, while maximizing their benefits.

The current analysis revealed that several markers may be related to worse prognosis for COVID-19, but great heterogeneity was seen among the results, which currently precludes their translation into clinical practice.

The identified causes for these discrepancies are many. Since the disease is so new compared to other conditions, data recollection and the search for a consensus between the groups specialized in the subject have had too little time. There was no uniformity in the methods applied to test for genetic markers: most studies were based on SNP microarrays, but used kits from different manufacturers, versions and even number of markers evaluated. Other authors used whole exome or even whole genome sequencing. The number and list of included markers was greatly variable, since some researchers selected SNP based on their scarce biological knowledge of the infection by Sars-CoV-2, others evaluated genes that they had already been working on in their own projects, others performed the analysis based on the technology available for them and others merely tried to replicate previous hypotheses or results. Regarding ethnic origin, some variability was seen but European and Asian populations were predominant. In order to translate the conclusions to other ethnic groups, a higher number of patients and inclusion of individuals of different (currently underrepresented) ethnic background is necessary [34], as well as statistical adjustments. Alternatively, specific studies could be designed to evaluate different ethnic groups, which may reveal other conclusions. The severity criteria was not standardized throughout the whole set of studies (see the variable "Severity criteria" in Table 1).

So as to advance in the homogenization of the relevant genetic markers and the subsequent development of polygenic scores, more time is required for the publication of studies that include higher numbers of individuals from different ethnic backgrounds, and standardization of technologies used and case definitions are essential. Collaboration between the specialized groups working on this subject (including sharing sequencing data) is also key to resolve the biases in a timely manner. At this point, Host Genetics Initiative [18] will probably have a key role as a repository for COVID-19 data and host relevant genetic markers. It will also be of great importance that future research considers the COVID-19 situation and population context in order to avoid a geographic bias due to the differences in the distribution of the Sars-Cov-2 strains (a product of the accumulated mutations and travel tendencies), the differences in health systems response and prevention capabilities for severe cases and the varying advancements in vaccination throughout each region in the world. Studies from Latin American and African population would, for instance, be of great importance.

CONFLICTS OF INTEREST

Authors declare no conflicts of interest

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