The Influence of Hemochromatosis Gene (HFE) Mutations on SARS-CoV-2 Susceptibility and COVID-19 Severity

Ristić, Smiljana; Milić, Sandra; Tatalović, Tanja; Bilobrk, Matea; Rončević, Dobrica; Ćurko-Cofek, Božena; Barac-Latas, Vesna; Starčević Čizmarević, Nada

Source / Izvornik: **Balkan medical journal, 2023, 39, 1 - 3**

Journal article, Published version
Rad u časopisu, Objavljena verzija rada (izdavačev PDF)

https://doi.org/10.4274/balkanmedj.galenos.2023.2023-1-39

Permanent link / Trajna poveznica: https://urn.nsk.hr/urn:nbn:hr:184:932823

Balkan Med J 2022;39:1-3

The Influence of Hemochromatosis Gene *(HFE)* Mutations on SARS-CoV-2 Susceptibility and COVID-19 Severity

Smiljana Ristić[1]*#, Sandra Milić[2]#, Tanja Tatalović[3], Matea Bilobrk[4], Dobrica Rončević[4], Božena Ćurko-Cofek[5], Vesna Barac-Latas[5], Nada Starčević Čizmarević[1]

[1]Department of Medical Biology and Genetics, Faculty of Medicine, University of Rijeka, Rijeka, Croatia

[2]Department of Gastroenterology, Clinical Hospital Centre Rijeka, Faculty of Medicine, University of Rijeka, Rijeka, Croatia

[3]Department of Rheumatology and Clinical Immunology, Clinical Hospital Centre Rijeka, Faculty of Medicine, University of Rijeka, Rijeka, Croatia

[4]Department of Epidemiology, Teaching Institute of Public Health of Primorje-Gorski Kotar County, Faculty of Health Studies, University of Rijeka, Rijeka, Croatia

[5]Department of Physiology, Immunology and Pathophysiology, Faculty of Medicine, University of Rijeka, Rijeka, Croatia

#Contributed equally

To the Editor,

Coronavirus disease-2019 (COVID-19) is an extremely complex disease wherein numerous genetic and epigenetic factors determine the variable phenotypic manifestations.

Owing to the wide range of symptoms, ranging from an asymptomatic condition to a mild, severe, or critical disease state, host genetics have been hypothesized to influence susceptibility to COVID-19, as in other infections. Until date, several genetic studies have been conducted using a variety of approaches and have identified genetic variants that may affect the susceptibility to and severity of COVID-19.[1]

Recent studies have reported that the serum level of ferritin progressively increases with disease severity in patients with COVID-19 and is correlated with poor prognosis.[2] In addition, a meta-analysis evaluated the discriminatory biomarkers in patients with COVID-19 and found serum ferritin as one of the strong biomarkers indicating the severe form of the disease.[3]

High ferritin levels are present in iron overload, which induces oxidative stress, and impairs the immune response. Viruses depend on iron to replicate efficiently in host cells. Therefore, iron overload can affect the severity and increase mortality from viral infections.[4] A similar negative effect of iron overload on the immune response has been demonstrated in cases of hereditary hemochromatosis (HH).[5] Recently, the case of a 51-year-old man who developed severe COVID-19 and was found to have HH on post-mortem was reported, which suggests a possible link between iron overload and the development of severe COVID-19.[6] HH is caused by hemochromatosis gene (*HFE*) mutations, with patients being homozygous, or compound heterozygous for the p.C282Y and p.H63D mutations.

Based on these data, we hypothesized that *HFE* mutations may be a risk factor for severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) infection and affect the outcomes of COVID-19 in patients with suspected HH.

To investigate the association between the *HFE* mutations and COVID-19, we retrieved high-quality data on demographic characteristics, laboratory tests for severe acute respiratory syndrome-coronavirus (SARS-CoV-2) (PCR-based), clinical symptoms and outcomes, and vaccinations from the records of 240 patients admitted to the Department of Gastroenterology, Clinical Hospital Center, between 2010 and 2020. All these patients had high serum iron parameters (such as serum iron and/or ferritin and/or transferrin saturation > 45%) and some of them presented with HH-related symptoms. Genotyping of p.C282Y and p.H63D mutations were also performed in all patients.

Corresponding author: Smiljana Ristić, Department of Medical Biology and Genetics, Faculty of Medicine, University of Rijeka, Rijeka, Croatia
e-mail: smiljana.ristic@uniri.hr

Received: January 16, 2023 Accepted: March 11, 2023 Available Online Date: • *DOI: 10.4274/balkanmedj.galenos.2023.2023-1-39*

Available at www.balkanmedicaljournal.org

ORCID iDs of the authors: S.R. 0000-0002-5484-6445; S.M. 0000-0002-6635-5360; T.T. 0000-0001-9320-7171; M.B. 0000-0002-3813-0711; D.R. 0000-0002-8599-8951; B.Ć-C. ORCID ID: 0000-0002-2591-7267; V.B-L. 0000-0001-5751-6217; N.S.Č. 0000-0002-7779-0237.

Cite this article as:
Ristić S, Milić S, Tatalović T, Bilobrk M, Rončević D, Ćurko-Cofek B, Barac-Latas V, Čizmarević NS. The Influence of Hemochromatosis Gene *(HFE)* Mutations on SARS-CoV-2 Susceptibility and COVID-19 Severity. . *Balkan Med J.*;

TABLE 1. Epidemiological and Genetic Characteristics of Patients Enrolled in the Present Study.

	SARS-CoV-2 positive n = 100	SARS-CoV-2 negative n = 140	P-value
Male/female (%)	59/41	70/30	0.077
Age (x ± SD), years	54.8 ± 16.7	58.9 ± 15.8	0.561
Vaccination +/- (%)	65/35	76/24	0.065
***HFE* genotypes/alleles*, n (%)**			
p.C282Y/p.C282Y	2 (2.0)	9 (6.4)	0.093
p.C282Y/p.H63D	7 (7.0)	9 (6.4)	0.861
p.H63D/p.H63D	8 (8.0)	8 (5.7)	0.484
wt/p.C282Y	9 (9.0)	17 (12.1)	0.440
wt/p.H63D	24 (24.0)	34 (24.4)	0.817
wt/wt	50 (50.0)	63 (45.0)	0.444
p.C282Y allele	20 (10.0)	44 (15.7)	0.069
p.H63D allele	44 (22.0)	59 (21.0)	0.807
HFE* polymorphism*			
p.C282Y (partial r = 0.0917)			0.159
p.H63D (partial r = -0.0396)			0.544

*Fisher's exact test and the $\chi 2$ test were performed to compare the frequency of *HFE* genotypes/alleles between the SARS-CoV-2 positive and SARS-CoV-2 negative groups.
**Partial correlation coefficients (r) were calculated to test the correlation between *HFE* genotypes and susceptibility to SARS-CoV-2 infection, after adjusting for age, sex, and vaccination.
SARS-CoV-2, severe acute respiratory syndrome-coronavirus

Table 1 presents the study patients' characteristics. Of the 240 patients, 100 (41.7%) were SARS-CoV-2 positive and 140 (58.3%) were SARS-CoV-2 negative. Both the study groups were similar in age, with a slightly higher proportion of males and a higher proportion of vaccinated individuals in the SARS-CoV-2-negative group.

We found no difference in the *HFE* genotype distribution or allele frequency between the infected and uninfected individuals in the entire cohort (Table 1). Moreover, there was no significant association between susceptibility to SARS-CoV-2 infection and the p.C282Y polymorphism (partial $r = 0.0917$, $P = 0.159$) or p.H63D polymorphism (partial $r = -0.0396$, $P = 0.544$) after considering age, sex, and vaccination as possible confounders.

In addition, carriers of *HFE* mutations do not have a more severe clinical form of COVID-19. According to the medical records, all patients had a mild/moderate form of the disease and recovered without hospitalization, with no severe/critical cases recorded. This finding may be attributed to the fact that half of the patients (52%) were infected after the spread of the Omicron variant of SARS-CoV-2 in our study population, which is known to cause a milder form of the disease.

Our results suggest that *HFE* polymorphisms do not affect susceptibility/resistance to SARS-CoV-2 infection or the clinical course of COVID-19 in patients with altered iron parameters. A recent study of COVID-19 patients also revealed that both *HFE* mutations had no effect on disease severity, but the p.C282Y mutation increased the risk of SARS-COV-2 infection in a Czech population.[7]

The present study has several limitations. First, although our study had 80% power ($\alpha = 0.05$, one-tailed) to detect a 1.7-fold increase in the frequency of the p.C282Y allele and a 1.5-fold increase in the frequency of the p.H63D allele, the relatively small number of participants and the lower frequency of the p.C282Y mutation in the population (3%)[8] limit our conclusions about the influence of *HFE* polymorphisms on the susceptibility to SARS-CoV-2 infection and disease progression. Second, for the reasons mentioned above, we did not make a comparison between men and women in our study, although a severe clinical course of COVID-19 was associated with the male sex, and iron metabolism is strongly influenced by sex, with iron, and hepcidin levels usually being lower in women than in men. Third, we could not perform biochemical tests, including that for serum ferritin level, at the time of admission for COVID-19 because we had collected the data retrospectively and none of the patients were hospitalized. Thus, the strength of our study is that it fits into the currently hypothesized role of *HFE* polymorphisms and other genetic variants associated with iron regulation in COVID-19 disease and encourages future research on this topic. Further studies on a larger series of patients from different populations are needed to evaluate the present preliminary results.

Ethics Committee Approval: The study was approved by the Ethics Committees of the Teaching Institute of Public Health and the Clinical Hospital Centre Rijeka (number: 08-820-40/129-22, date: 24.10.2022).

Authorship Contributions: Concept- S.R., S.M., D.R., B.Ć-C., V.B-L., N.S.Č.; Design- S.R., S.M., D.R., B.Ć-C., V.B-L., N.S.Č.; Data Collection and Processing- S.R., S.M., T.T., D.R.; Analysis or Interpretation- S.R., S.M., T.T., D.R.; Literature Search- T.T., M.B., D.R.; Writing- S.R., S.M.

Conflict of Interest: No conflict of interest was declared by the authors.

Funding: This work was supported by the University of Rijeka, Croatia (uniri-biomed-18-137).

REFERENCES

1. Delanghe JR, Speeckaert MM. Host polymorphisms and COVID-19 infection. *Adv Clin Chem.* 2022;107:41-77. **[CrossRef]**
2. Mahroum N, Alghory A, Kiyak Z, et al. Ferritin - from iron, through inflammation and autoimmunity, to COVID-19. *J Autoimmun.* 2022;126:102778. **[CrossRef]**
3. Henry BM, de Oliveira MHS, Benoit S, Plebani M, Lippi G. Hematologic, biochemical and immune biomarker abnormalities associated with severe illness and mortality in coronavirus disease 2019 (COVID-19): a meta-analysis. *Clin Chem Lab Med.* 2020;58:1021-1028. **[CrossRef]**
4. Schmidt SM. The role of iron in viral infections. *Front Biosci (Landmark Ed).* 2020;25:893-911. **[CrossRef]**
5. Reuben A, Chung JW, Lapointe R, Santos MM. The hemochromatosis protein HFE 20 years later: An emerging role in antigen presentation and in the immune system. *Immun Inflamm Dis.* 2017;5:218-232. **[CrossRef]**
6. Riley MJ, Hicks SR, Irvine S, et al. Hereditary haemochromatosis, haemophagocytic lymphohistiocytosis and COVID-19. *Clin Infect Pract.* 2020;7:100052. **[CrossRef]**
7. Hubacek JA, Philipp T, Adamkova V, Majek O, Dusek L. A haemochromatosis-causing HFE mutation is associated with SARS-CoV-2 susceptibility in the Czech population. *Clin Chim Acta*. 2023;538:211-215. **[CrossRef]**
8. Ristić S, Makuc J, Starčević N, et al. Hemochromatosis gene mutations in the Croatian and Slovenian populations. *Clin Genet.* 2003;64:444-446. **[CrossRef]**