Journal of Infection 86 (2023) e67–e69

Contents lists available at ScienceDirect

Journal of Infection

journal homepage: www.elsevier.com/locate/jinf

Letter to the Editor

ACE1 *rs1799752* polymorphism is not associated with long-COVID symptomatology in previously hospitalized COVID-19 survivors

Dear Editor

Viral mechanisms of infection of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the agent responsible of the coronavirus disease, 2019 (COVID-19), suggest the involvement of surface receptor for S1 of the angiotensin-converting enzyme 2 (ACE2) and transmembrane protease serine-2 (TMPRSS2) receptors.[1] Single studies have found that single nucleotide polymorphisms (SNP), e.g., ACE2 *rs2285666*, ACE2 *rs2074192,* or TMPRSS2 *rs12329760,* seem to be potentially associated with severity of COVID-19; however, current evidence is still not conclusive.[2] Another potential SNP that could be implicated in various clinical diseases (e.g., renal damage, pneumonia, ischemic stroke) and also immunological reaction (i.e., cytokine storm) induced by SARS-CoV-2 is ACE1 *rs1799752*.[3] In fact, evidence suggests that the D allele of this SNP is associated with higher severity of SARS-CoV-2.[4]

Although ACE2, TMPRSS2 and ACE1 receptors are highly expressed in the lungs and respiratory tract, these receptors are also present in several other tissues explaining the heterogeneity clinical presentation of COVID-19. Accordingly, it could be proposed that these receptors are potentially also associated with the presence of symptoms after the acute phase of the infection, i.e., long-COVID. Mariani et al. have recently observed that post-COVID symptoms are present for up to one year in a heterogeneous population.[5] Additionally, a recent meta-analysis reported that post-COVID fatigue can be present in up to 51% of COVID-19 survivors.[6] Our group has recently identified that ACE2 *rs2285666*, ACE2 *rs2074192,* TMPRSS2 *rs12329760* and TMPRSS2 *rs2070788* polymorphisms do not predispose for long-COVID symptoms in previously hospitalized COVID-19 survivors.[7]

We present here a secondary analysis, genetic part of THE LONG COVID EXPERIENCE STUDY,[7] of the potential association between ACE1 *rs1799752* polymorphism and the presence of long-COVID symptomatology.

Briefly, unstimulated whole saliva samples were collected from 288 COVID-19 survivors who were hospitalized at three urban hospitals in Madrid (Spain) during the first wave of the pandemic (March-May 2020). All participants provided written informed consent. The study was approved by the Institutional Ethics Committees of all involved institutions (HSO25112020; URJC0907202015920; HUFA20/126; HUIL/092-20). Genotyping collection and procedures have been previously published.[7] Identification of each possible genotype of ACE1 *rs1799752* polymorphism was conducted by using specific fluorescent dyes. The ACE1 *rs1799752* is an insertion/deletion of an Alu repeat sequence that is interrogated using a pair of assays. The possible variants of the ACE1 *rs1799752* (the mutant Alu insertion allele -I allele- and the wild type of deletion allele -D allele-) SNP lead to the following genotypes (D/D, D/I, I/I) derived from the sequence:

CCCATTTCTCTAGACCTGCTGCCT [**-/ALU**] ATACAGTCACTTTTAT-GTGGTTTC

Demographic, medical comorbidities, and hospitalization data were collected from hospital medical records. Post-COVID symptomatology was collected during a face-to-face appointment conducted by experienced healthcare professionals at 17.8 (SD 5.2) months after hospitalization.[7] Dyspnea at exertion (n = 196, 68%) and fatigue (n = 181, 63%) were the most prevalent post-COVID symptoms in the total sample. Other post-COVID symptoms included pain (n = 117, 40.6%), memory loss (n = 92, 32%) or hair loss (n = 77, 26.7%). The genotype distribution (D/D genotype n = 109, 37%; D/I genotype n = 173, 60%; I/I genotype n = 6, 3%) deviated from that expected based on the Hardy-Weinberg equilibrium, a result also extensively found in published COVID-19 studies. Overall, no significant differences in long-COVID symptoms were observed depending on the genotypes of ACE1 *rs1799752* SNP (Table). No sex differences in the genotype distribution (P = 0.723) were either found.

The results of this secondary analysis reveal that ACE1 *rs1799752* polymorphism does not predispose to developing long-COVID symptoms when evaluated in previously hospitalized COVID-19 survivors. Current results would agree with our previous report on ACE2 and TMPRSS2 polymorphisms.[7] The lack of association between these SNPs and long-COVID could be explained by the significant gene variability existing (i.e., ethnic differences) across populations.[8] Further, the lack of relationship among SNPs associated with COVID-19 severity and the presence of long-COVID reinforce the idea that the severity of the disease is not associated with the development of post-COVID symptoms since the presence of these symptoms is similar between hospitalized and non-hospitalized patients.[9] Similarly, the D allele of the ACE1 *rs1799752* polymorphism has been associated with a higher risk of hospitalization in patients with co-morbidities at the acute phase of the infection since these individuals are at a higher risk for developing acute respiratory distress syndrome (ARDS).[10] In our study, no differences in previous medical co-morbidities depending on the ACE1 *rs1799752* genotype were observed.

Some limitations of the current data should be recognized. First, only previously hospitalized COVID-19 survivors were included, therefore, the role of these SNPs in non-hospitalized patients is yet to be invetigated. Second, it could be possible that larger samples could identify genotype differences, accordingly, our data should be considered exploratory. Population-based cohort studies and a whole genome SNPs analysis might help to validate current results and identify other genes potentially related to long-COVID symptoms.

https://doi.org/10.1016/j.jinf.2022.12.026

Table
Pre-Infection data and post-COVID symptoms according to the ACE1 *rs1799752* Polymorphism Genotype (n = 288).

	D/D (n = 109)	D/I (n = 173)	I/I (n = 6)	P value
Age, mean (SD), years	58.0 (12.0)	55.5 (13.5)	55.0 (12.0)	0.372
Gender, female n (%)*	58 (53.2%)	84 (48.5%)	2 (33.3%)	0.723
Weight, mean (SD), kg.	80.5 (17.0)	81.2 (17.0)	80.5 (4.0)	0.934
Height, mean (SD), cm.*	167 (8.5)	167 (10.0)	170 (6.5)	0.226
Number co-morbidities, mean (SD)	1.3 (1.0)	1.3 (1.0)	1.3 (1.0)	0.932
Medical co-morbidities, n (%)				
Hypertension	37 (34.0%)	59 (34.1%)	4 (66.6%)	0.406
Diabetes	15 (13.8%)	14 (8.1%)	1 (16.7%)	0.318
Cardiovascular Diseases	10 (9.2%)	11 (6.4%)	0 (0.0%)	0.556
Asthma	11 (10.1%)	21 (12.1%)	0 (0.0%)	0.6237
Obesity	30 (27.5%)	59 (34.1%)	1 (16.7%)	0.511
Chronic Obstructive Pulmonary Disease	2 (1.8%)	4 (2.3%)	0 (0%)	0.901
Number post-COVID symptoms, mean (SD)	3.0 (2.0)	2.9 (1.8)	3.5 (2.8)	0.366
Post-COVID symptoms, n (%)				
Fatigue	66 (60.5%)	110 (63.6%)	5 (83.3%)	0.776
dyspnea at exertion	71 (65.1%)	121 (70.0%)	4 (66.7%)	0.892
Memory Loss	41 (37.6%)	47 (27.2%)	4 (66.7%)	0.100
Hair Loss	28 (25.7%)	47 (27.2%)	2 (33.3%)	0.925
Concentration Loss	17 (15.6%)	25 (14.5%)	2 (33.3%)	0.505
cognitive blunting - brain fog	18 (16.5%)	23 (13.3%)	0 (0.0%)	0.507
dyspnea at rest	12 (11.0%)	25 (14.5%)	3 (50.0%)	0.051
Ocular Disorders	14 (12.9%)	26 (15.0%)	1 (16.7%)	0.882
Anosmia/Hyposmia	8 (7.5%)	21 (12.1%)	0 (0.0%)	0.342
Skin Rashes	12 (11.0%)	24 (13.9%)	1 (16.7%)	0.782
Gastrointestinal Disorders	11 (10.1%)	16 (9.25%)	0 (0.0%)	0.731
Ageusia/Hypogeusia	9 (8.25%)	9 (5.2%)	2 (33.3%)	0.797
Days at hospital, mean (SD)	7.3 (7.4)	8.7 (9.8)	8.5 (7.7)	0.415

Role of the funding source

The project was supported by a grant from Novo Nordisk Foundation NNF21OC0067235 (Denmark) and by a grant associated to the Fondo Europeo De Desarrollo Regional - Recursos REACT-UE del Programa Operativo de Madrid 2014–2020, en la línea de actuación de proyectos de I+D+i en materia de respuesta a COVID 19 (LONG-COVID-EXP-CM). Both sponsors had no role in the design, collection, management, analysis, or interpretation of the data, draft, review, or approval of the manuscript or its content. The authors were responsible for the decision to submit the manuscript for publication, and the sponsor did not participate in this decision.

Declaration of interests

No conflict of interest is declared by any of the authors

Acknowledgements

The Center for Neuroplasticity and Pain (CNAP) is supported by the Danish National Research Foundation (DNRF121) and Norvo Nordic Foundation (NNF21OC0067235). We also thank Genomics Unit, Madrid Science Park Foundation, Spain for his valuable support

References

1. Singh HO, Choudhari R, Nema V, Khan AA. ACE2 and TMPRSS2 polymorphisms in various diseases with special reference to its impact on COVID-19 disease. *Microb Pathog* 2021;**150**:104621.
2. Gupta K, Kaur G, Pathak T, Banerjee I. Systematic review and meta-analysis of human genetic variants contributing to COVID-19 susceptibility and severity. *Gene* 2022;**844**:146790.
3. Adli A, Rahimi M, Khodaie R, Hashemzaei N, Hosseini SM. Role of genetic variants and host polymorphisms on COVID-19: from viral entrance mechanisms to immunological reactions. *J Med Virol* 2022;**94**:1846–65.
4. Aziz MA, Islam MS. Association of ACE1 I/D rs1799752 and ACE2 rs2285666 polymorphisms with the infection and severity of COVID-19: a meta-analysis. *Mol Genet Genomic Med* 2022;**10**:e2063.
5. Mariani C, Borgonovo F, Capetti AF, Oreni L, Cossu MV, Pellicciotta M, Armiento L, Bocchio S, Dedivitiis G, Lupo A, Galli M, Rizzardini G. Persistence of Long-COVID symptoms in a heterogenous prospective cohort. *J Infect* 2022;**84**:722–46.
6. Ji G, Chen C, Zhou M, Wen W, Wang C, Tang J, Cheng Y, Wu Q, Zhang X, Wang M, Feng Z. Post-COVID-19 fatigue among COVID-19 in patients discharged from hospital: a meta-analysis. *J Infect* 2022;**84**:722–46.
7. Fernández-de-las-Peñas C, Arendt-Nielsen L, Díaz-Gil G, Gómez-Esquer F, Gil-Crujera A, Gómez-Sánchez SM, Ambite-Quesada S, Palomar-Gallego MA, Pellicer-Valero OJ, Giordano R. Genetic association between ACE2 (rs2285666 and rs2074192) and TMPRSS2 (rs12329760 and rs2070788) polymorphisms with post-COVID symptoms in previously hospitalized COVID-19 survivors. *Genes* 2022;**13**:1935.
8. Smatti MK, Al-Sarraj YA, Albagha O, Yassine HM. Host genetic variants potentially associated with SARS-CoV-2: a multi-population analysis. *Front Genet* 2020;**11**:578523.
9. Fernández-de-las-Peñas C, Rodríguez-Jiménez J, Cancela-Cilleruelo I, Guerrero-Peral A, Martín-Guerrero JD, García-Azorín D, Cornejo-Mazzuchelli A, Hernández-Barrera V, Pellicer-Valero OJ. Post-COVID-19 symptoms 2 years after SARS-CoV-2 infection among hospitalized vs non-hospitalized patients. *JAMA Netw Open* 2022;**5**:e2242106.
10. Sabater Molina M, Nicolás Rocamora E, Bendicho AI, Vázquez EG, Zorio E, Rodriguez FD, Gil Ortuño C, Rodríguez AI, Sánchez-López AJ, Jara Rubio R, Moreno–Docón A, Marcos PJ, García Pavía P, Villa RB, Gimeno Blanes JR. Polymorphisms in ACE, ACE2, AGTR1 genes and severity of COVID-19 disease. *PLoS One* 2022;**17**:e0263140.

César Fernández-de-las-Peñas*
Department of Physical Therapy, Occupational Therapy, Physical Medicine and Rehabilitation, Universidad Rey Juan Carlos (URJC), Madrid, Spain
Center for Neuroplasticity and Pain (CNAP), SMI, Department of Health Science and Technology, School of Medicine, Aalborg University, Aalborg, Denmark

Lars Arendt-Nielsen
Center for Neuroplasticity and Pain (CNAP), SMI, Department of Health Science and Technology, School of Medicine, Aalborg University, Aalborg, Denmark
Department of Medical Gastroenterology, Mech-Sense, Aalborg University Hospital, Aalborg, Denmark

Gema Díaz-Gil, Antonio Gil-Crujera, Stella M. Gómez-Sánchez
Research group GAMDES, Department of Basic Health Sciences, Universidad Rey Juan Carlos (URJC), Madrid, Spain

Silvia Ambite-Quesada
Department of Physical Therapy, Occupational Therapy, Physical Medicine and Rehabilitation, Universidad Rey Juan Carlos (URJC), Madrid, Spain

Maria A. Palomar-Gallego
Research group GAMDES, Department of Basic Health Sciences, Universidad Rey Juan Carlos (URJC), Madrid, Spain

Oscar J. Pellicer-Valero
Intelligent Data Analysis Laboratory, Department of Electronic Engineering, ETSE (Engineering School), Universitat de València (UV), Valencia, Spain

Rocco Giordano
Center for Neuroplasticity and Pain (CNAP), SMI, Department of Health Science and Technology, School of Medicine, Aalborg University, Aalborg, Denmark

*Corresponding author at: Facultad de Ciencias de la Salud, Universidad Rey Juan Carlos, Avenida de Atenas s/n, 28922 Alcorcón, Spain.
E-mail address: cesar.fernandez@urjc.es (C. Fernández-de-las-Peñas)