COVID

MDPI

Article

MMS19 and IFIH1 Host Genetic Variants Associate with SARS-CoV-2 Infection in Elderly Residents of Long-Term Care Facilities

Sandra Franco [1,*], Macedonia Trigueros [1], Dolors Palacín [2], Josep Maria Bonet-Simó [2], Maria del Mar Isnard [2], Nemesio Moreno [2], Lourdes Mateu [3,4], Nuria Prat [2], Marta Massanella [1,5] and Miguel Angel Martinez [1] on behalf of the CoronAVI@S [M1] Study

[1] IrsiCaixa Infectious Research Institute, Campus can Ruti, 08916 Badalona, Spain; mtrigueros@irsicaixa.es (M.T.); mmassanella@irsicaixa.es (M.M.); mmartinez@irsicaixa.es (M.A.M.)
[2] Direcció d'Atenció Primària—Metropolitana Nord, 08023 Sabadell, Spain; mpalacin.centre.ics@gencat.cat (D.P.); jmbonets@gencat.cat (J.M.B.-S.); misnard.bnm.ics@gencat.cat (M.d.M.I.); nmorenom.bnm.ics@gencat.cat (N.M.); nprat@gencat.cat (N.P.)
[3] Infectious Disease Department, Hospital Universitari Germans Trias i Pujol, 08916 Badalona, Spain; lmateu.germanstrias@gencat.cat
[4] Fundació Lluita contra les Infeccions, Campus Can Ruti, 08916 Badalona, Spain
[5] Centro de Investigación Biomédica en Red de Enfermedades Infecciosas, CIBERINFEC, 28029 Madrid, Spain
* Correspondence: sfranco@irsicaixa.es; Tel.: +34-934656374

Abstract: The coronavirus disease 2019 (COVID-19) pandemic has significantly affected older adults. Identifying host COVID-19 susceptibility genes in elderly populations remains a challenge. Here, we aimed to identify host genetic factors influencing the susceptibility to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. We genotyped 12 single-nucleotide polymorphisms (SNPs) previously associated with the innate immune response in a total of 97 elderly (age > 65 years) residents of three long-term care facilities located in Barcelona, Spain. Individuals were PCR-tested during the SARS-CoV-2 outbreaks between September and November 2020. SARS-CoV-2 PCR tests revealed infections in 81 residents. Importantly, the 16 uninfected residents remained SARS-CoV-2 seronegative until vaccination (January and February 2021). After adjusting for sex and age, we found that two SNPs were significantly associated with SARS-CoV-2 infection susceptibility—*MMS19* nucleotide excision repair protein homolog (MMS19)/rs2236575 ($p = 0.029$) and interferon-induced helicase C domain-containing 1 (IFIH1)/rs1990760 ($p = 0.034$). No association with SARS-CoV-2 infection was found for 10 additional genotyped SNPs, which included 4 SNPs on chromosome 12 in the gene encoding oligoadenylate synthetase (OAS). Our results indicate that MMS19/rs2236575_A and IFIH1/rs1990760_TC genetic variants were associated with a resistance to SARS-CoV-2 infection in a cohort of institutionalized seniors.

Keywords: SARS-CoV-2; infection susceptibility; host genetics; elderly; COVID-19

Citation: Franco, S.; Trigueros, M.; Palacín, D.; Bonet-Simó, J.M.; Isnard, M.d.M.; Moreno, N.; Mateu, L.; Prat, N.; Massanella, M.; Martinez, M.A., on behalf of the CoronAVI@S [M1] Study. MMS19 and IFIH1 Host Genetic Variants Associate with SARS-CoV-2 Infection in Elderly Residents of Long-Term Care Facilities. *COVID* **2024**, *4*, 1245–1252. https://doi.org/10.3390/covid4080089

Academic Editor: Bruno Mégarbané

Received: 3 July 2024
Revised: 31 July 2024
Accepted: 6 August 2024
Published: 7 August 2024

1. Introduction

The elderly population is particularly vulnerable to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and severe coronavirus disease 2019 (COVID-19) [1]. Specifically, residents of long-term care facilities (LTCFs) are at a higher risk of SARS-CoV-2 transmission and infection [2,3]. LTCF population density may account for this increased risk of transmission. Described risk factors for infection and disease severity are sex, age, ethnicity, obesity, and cardiovascular and respiratory diseases. Current vaccines have successfully reduced both SARS-CoV-2 transmission and COVID-19 severity [4,5]; however, the development of new tools to predict virus transmission and disease burden may improve current and future treatments as well as disease prevention strategies. Several

large-scale genetic association studies have consistently identified human host single-nucleotide polymorphisms (SNPs) that are implicated in the biology and epidemiology of COVID-19 [6–11]. These studies suggest different mechanisms to explain why some individuals are more prone to infection by SARS-CoV-2 or being more severely affected by the disease upon infection [12,13]. Host genetics can inform us about disease etiology and provide new means for patient management. Population-specific risk variants have also been reported [8,14,15].

Chronic inflammatory diseases are more prevalent in older people. Ageing is associated with an immunosenescent phenotype characterized by a progressively proinflammatory state and a reduced immune response against pathogens [16]. Accumulation of damaged DNA as a consequence of ageing is the principal cause of age-related diseases. MMS19 is a component of the iron–sulfur protein assembly machinery involved in DNA metabolism and DNA repair, and its de-regulation has been associated with some particular cancers [17]. Adenosine deaminase acting on RNA 1 (ADAR1) has RNA editing functions and is responsible for activating the intracellular sensors, RIG-I and IFIH1 (MDA5), that sense viral replication, leading to the activation of several genes involved in the innate immune response (IFNAR2, IFNL, OAS) and inflammation [18]. SNP polymorphisms in ADAR-1, IFIH1, and PNPLA3 are involved in liver inflammation [19]. Furthermore, several host proteins involved in immune innate signaling pathways, such as MDA-5/IFIH1, TRIF, IFNAR2, IFITM3, IFN L3/4, are associated with severe COVID-19 [20]. Recently, a haplotype inherited from Neanderthals comprising SNPs in three isoforms of the OAS gene (OAS-1, OAS-2, OAS-3) were found to protect against SARS-CoV-2 infection [9]. Overall, these studies highlight the relevance of SNPs associated with innate signaling with susceptibility to viral infections, but do not address the effect of age. In this study, we aimed to identify host genetic factors influencing susceptibility to SARS-CoV-2 infection in LTCF residents. Due to the extreme importance of age as a risk factor for severe COVID-19, we considered it in our genetic analyses [12]. Our study included uninfected and infected individuals with SARS-CoV-2 that were recruited early in the pandemic before the initiation of vaccination.

2. Materials and Methods

2.1. Study Participants

A total of 97 residents of three LTCFs located in Barcelona, Spain, were randomly included in this prospective observational study (CoronAVI@S study). Plasma samples were collected before vaccination from September to November 2020 [12]. SARS-CoV-2 serology was performed to sub-classify participants into infected and uninfected individuals depending on their PCR and serology status.

2.2. Ethics

The CoronAVI@S study was approved by the Ethics Board of the Institut Universitari d'Investigació en Atenció Primària Jordi Gol (20-116P). All participants provided written informed consent before inclusion.

2.3. Single-Nucleotide Polymorphism Genotyping

Genomic DNA was extracted from peripheral blood mononuclear cells using Quick Extract DNA Extraction 1.0 solution (Epicentre/Lucigen) as previously described [19]. Two microliters of extracted DNA were used for SNP genotyping (Applied Biosystems, Waltham, MA, USA). The reference numbers of the TaqMan assays used for genotyping on a Quantstudio 5.0 from Applied Biosystems were ADAR1/rs1127313, (C_8724398_10); IFIH1/rs1990760, (C_2780299_30); MMS19/rs2236575 (C_1797584_30); OAS-1/rs4767027 (C_28015278_10); OAS-1/rs10774671 (C_2567433_10); OAS-2/rs1293767 (C_8920276_10); OAS-3/rs10735079 (C_31831768_10); IFNL3/rs12979860 (C_7820464_10); IFNAR2/rs2236757 (C_11354003_30); and PNPLA3/rs738409 (C_7241_10). The SNPs, IFNL3/rs4803217 and

TNFAIP8L1/rs1060555, were determined using IDT DNA assay Hs.GT.rs4803217.A.1 and Hs.GT.rs1060555.G.1, respectively, and also assayed by Quantstudio 5.0 (Applied Biosystems).

2.4. Statistical Analysis

Haplotype estimation and association with patient susceptibility to SARS-CoV-2 infection were achieved using Haploview 4.2 (Broad Institute of Harvard and MIT, Cambridge, MA, USA) and SNPSTATS [21]. Dominant, overdominant, recessive, and log-additive inheritance models were fitted using the SNPSTATS online program [21], reporting *p* values for the SNP association of the inheritance model with the smallest AIC. To enhance the robustness of our findings, we performed a bootstrap resampling with 100 interactions and calculated empirical *p*-values as the proportion of times the observed *p*-value was greater than the *p*-value derived from the bootstrap resampling. Risk factors (sex and age) were included in the genetic analysis to adjust the association of each SNP to infection susceptibility. Hardy–Weinberg equilibrium, minor allele frequency (MAF), and SNP linkage disequilibrium (LD) were also determined by Haploview 4.2. Correlation between the variables was assessed using nonparametric Spearman's correlation. Mann– Whitney U and chi-squared tests to compare the infected and uninfected individuals were performed using GraphPad Prism 9.0 (GraphPad Software, San Diego, CA, USA).

3. Results

Study participants were tested by PCR during the SARS-CoV-2 outbreaks at their respective LTCFs between September and November 2020. During this period, 81 of the participants tested positive for SARS-CoV-2 (80% female, mean age 87 years) and 16 tested negative (Table 1). The number of females was significantly higher in the infected group than the uninfected group ($p = 0.0104$). Only three infected individuals required hospitalization after an acute infection. Interestingly, 16 uninfected individuals remained seronegative for antibodies against the virus nucleoprotein until vaccination (January and February 2021) [18]. Table 1 shows the clinical and biochemical characteristics of the study patients. Compared with SARS-CoV-2-infected individuals, uninfected individuals had significantly higher glucose levels (Table 1). The higher glucose level in the uninfected group may be due to the higher number of diabetic individuals in this group (n = 8/16) compared with the infected group (n = 17/81; $p = 0.0153$, chi-squared). No other differences were found between the infected and uninfected individuals.

Table 1. Clinical and biochemical characteristics of participants.

	SARS-CoV-2 Infected	**SARS-CoV-2 Uninfected**	***p*-Value**
N (%)	81 (83.5)	16 (16.5)	
Age, years	87 (81–90)	80 (74–91)	0.1668
Female	65 (80.2)	8 (50)	**0.0104** [2]
AGM level [1]			0.1460 [2]
1	0	0	
2	4	3	
3	38	6	
4	39	7	
Albumin (g/L)	37.55 (35.9–39.75)	38.2 (36.93–39.5)	0.2725
Alanine aminotransferase (U/L)	11 (8.5–14)	12.5 (9.25–17.75)	0.3694
Aspartate aminotransferase (U/L)	17 (14–20)	18 (15.25–21.25)	0.3431
Creatine kinase (U/L)	42.5 (33.25–71)	47 (34.5–73.25)	0.7907
High-density lipoprotein (mg/dL)	46.2 (40.73–56.53)	42.4 (36–47.8)	0.1135
Total cholesterol (mg/dL)	193 (162–228)	198.5 (131.8–230.8)	0.6147
Creatinine mg/dL	0.81 (0.675–1.035)	0.82 (0.6925–1.25)	0.8186

Table 1. *Cont.*

	SARS-CoV-2 Infected	SARS-CoV-2 Uninfected	*p*-Value
Alkaline phosphatase (U/L)	78 (66.25–104)	89 (72.25–112.8)	0.2704
Ferritin (ng/mL)	66.5 (34–144.3)	108 (50–195.8)	0.1604
Fibrinogen (mg/L)	484 (415–539.5)	471.5 (386.3–535.5)	0.8820
Phosphate (mmol/L)	3.4 (3.1–3.8)	3.4 (3.225–3.6)	0.9087
Gamma-glutamyltransferase (U/L)	17 (13–26)	25.5 (15–32)	0.1615
Glucose (mg/dL)	92 (83–106)	111 (90–136)	**0.0329**
Hematocrit (%)	38.2 (35.55–40.35)	37.25 (32.88–40.3)	0.5044
Hemoglobin (g/dL)	33.5 (33–34.1)	33.95 (33.33–34.45)	0.0891
Lactate dehydrogenase (U/L)	171 (143.8–187.8)	172.5 (156.5–192.5)	0.7683
Leucocyte count ($\times 10^9$/L)	6.2 (5–7)	6.3 (4.97–7.8)	0.8605
Lymphocyte count ($\times 10^9$/L)	1.7 (1.35–2.05)	1.75 (1.225–2.35)	0.8263
Magnesium (mg/dL)	2.06 (1.898–2.188)	2.03 (1.893–2.115)	0.2356
Platelet ($\times 10^9$/L)	205 (168–249.5)	180 (145.8–221.5)	0.1236
Potassium (mmol/L)	4.32 (4.153–4.53)	4.39 (4.073–4.588)	0.6842
Serum protein (g/L)	65.95 (63.15–68.78)	65.35 (61.18–68.98)	0.7870
Sodium (mmol/L)	140.9 (139.1–142)	140 (138.6–141.6)	0.2790
Prothrombin time (s)	11.75 (11.2–12.4)	11.8 (11.1–13.2)	0.6207
Triglycerides (mg/dL)	115.5 (81.5–148.8)	111 (88.25–165.5)	0.8935
Partial thromboplastin Time (s)	30.05 (28.53–33.15)	30.55 (28.8–35.68)	0.3548
Urea (mg/dL)	40 (34–51)	43.5 (32–53)	0.7094

Values are given as n (%) or median (interquartile range, 25–75% percentiles). [1] AGM level: Stratum of Adjusted Morbidity ranging from 1 to 4 according to the number of comorbidities and their need for health care. [2] Chi-squared test, whereas all other *p*-values were determined by the Mann–Whitney U test, both tests were performed using GraphPad Prism 9.0 (GraphPad Software).

For the entire cohort of 97 individuals, we analyzed 12 SNPs from seven host genes previously associated with the innate immune response [9–11,18,19] or essential host co-factors involved in SARS-CoV-2 replication [22,23]. The observed allele SNP frequencies were characteristic of Southern European populations. All the variants had a minor allele frequency >0.01 and were in Hardy–Weinberg equilibrium (Table 2). The four SNPs in the OAS gene were in high LD (R2 > 0.81). The SNPs in the IFNL3 gene were also in high LD (R2 = 0.94). No other significant LD was observed among the other study SNPs. For the association analyses for each SNP, we adjusted for sex and age, identifying genetic associations between susceptibility to SARS-CoV-2 infection and two SNPs— MMS19/rs2236575 in the dominant model (odds ratio [OR] 6.57, 95% CI 0.80–53.87, $p = 0.029$) and overdominant model (OR 3.60, 95% CI 0.97–13.30, $p = 0.041$), and IFIH1/rs1990760 in the overdominant model (OR 3.57, 95% CI 1.04–12.29, $p = 0.034$; Table 2). After adjusting for multiple comparisons, by means of bootstrap techniques, MMS19/rs2236575 and IFIH1/rs1990760 remained significantly associated with susceptibility to SARS-CoV-2 infection (Table 2). In the unadjusted analysis, MMS19/rs2236575 was the only variant related to susceptibility to SARS-CoV-2 infection in the dominant ($p = 0.022$) and overdominant ($p = 0.049$) models.

We made a Spearman's correlation between our clinical data (Table 1) and MMS19/rs2236575 and IFIH1/rs1990760 individually in the entire cohort in the infected and uninfected individuals. In the entire cohort, we did not find any significant correlation with any of the clinical parameters described in Table 1. In the infected group, only MMS19_AA genotype was significantly correlated with lower levels of Creatine Kinase (Spearman $r = -0.25$, $p = 0.0231$). In the uninfected group, MMS19_AA genotype was significantly correlated with lower levels of phosphate ($r = -0.66$, $p = 0.0043$). We also found that the IFIH1_CC genotype was significantly correlated with higher levels of albumin ($r = 0.52$, $p = 0.0398$), platelets ($r = 0.51$, $p = 0.0410$), total protein ($r = 0.618$, $p = 0.0112$) and significant lower levels of prothrombin time ($r = -0.5820$, $p = 0.0185$) and phosphate ($r = -0.54$, $p = 0.0297$).

Table 2. Association of 12 single nucleotide polymorphisms from 7 host genes with susceptibility to SARS-CoV-2 infection.

SNP	Gene	Chr: pos	MAF	HW *p*-Value	Alleles	COVID-19 (n = 81)			Uninfected (n = 16)			OR (95% CI)	*p*-Value	*p*-Value Bootstrap	Model
					1/2	1/1	1/2	2/2	1/1	1/2	2/2				
rs1127313	ADAR-1	Chr1: 154583949	0.48	0.11	G/A	18	47	16	4	10	2	0.91 (0.25–3.34)	0.89	0.98	D
rs1990760	IFIH1	Chr2: 162267541	0.43	0.84	T/C	28	35	18	4	11	1	3.57 (1.04–12.29)	**0.034**	**0.031**	OD
rs2236575	MMS19	Chr10: 97465981	0.46	0.55	T/A	25	39	16	1	12	3	6.57 (0.80–53.87)	**0.029**	**0.046**	D
rs4767027	OAS-1	Chr 12: 112921352	0.38	0.40	C/T	30	37	14	9	5	2	0.43 (0.14–1.33)	0.14	0.14	D
rs10774671	OAS-1	Chr 12: 112919388	0.40	0.53	A/G	27	38	15	9	5	2	0.33 (0.10–1.07)	0.061	0.050	D
rs1293767	OAS-2	Chr 12: 112987349	0.37	0.51	G/C	33	35	13	7	7	2	0.81 (0.26–2.49)	0.71	0.65	D
rs10735079	OAS-3	Chr 12: 112942203	0.42	0.84	A/G	26	39	16	7	7	2	0.60 (0.19–1.90)	0.39	0.40	D
rs12979860	IFNL3	Chr 19: 39248147	0.29	0.14	C/T	42	31	8	10	3	3	0.40 (0.10–1.58)	0.17	0.19	OD
rs4803217	IFNL3	Chr 19: 39243580	0.27	0.44	C/A	43	31	7	10	4	2	0.51 (0.14–1.81)	0.28	0.31	OD
rs1060555	TNFAIP8L1	Chr 19: 4652810	0.32	0.17	C/G	36	38	7	5	11	0	1.29 (0.38–4.35)	0.68	0.71	D
rs2236757	IFNAR2	Chr 21: 33252612	0.30	0.09	G/A	41	28	11	10	5	1	0.41 (0.12–1.42)	0.14	0.13	D
rs738409	PNPLA3	Chr 22: 43928847	0.24	1.00	C/G	48	28	5	7	9	0	2.16 (0.69–6.80)	0.18	0.16	D

Adjusted by sex and age. Chr, chromosome; Pos, position; MAF, minor allele frequency; HW p-val, *p*-value from the Hardy-Weinberg equilibrium test ($p > 0.05$); OR (odds ratio); CI (confidence interval). D (Dominant; heterozygous and homozygous have the same risk, 1/1 vs. 1/2 + 2/2), and OD (Over Dominant; heterozygous are compared to a pool of both homozygous alleles, 1/1 + 2/2 vs. 1/2) models.

4. Discussion

In this study, we tested the association between host genetic polymorphisms and susceptibility to SARS-CoV-2 infection. After adjusting for sex and age, we found that residents of the LTCFs carrying MMS19/rs2236575_A and IFIH1/rs1990760_TC genetic variants were protected against SARS-CoV-2 infection.

The IFIH1/rs1990760 TT variant was previously reported to confer resistance to SARS-CoV-2 infection and explain the epidemiological features of the pandemic in different countries [24]. Importantly, COVID-19 patients with the IFIH1/rs1990760 TT variant have an attenuated inflammatory response and better outcomes [25]. The human gene IFIH1 encodes a helicase, melanoma differentiation-associated gene-5, which acts as a cytoplasmic virus receptor and triggers the transcription of type-1 interferon genes and the systemic inflammatory response. IFIH1/rs1990760 has been previously linked to bowel disease, type 1 diabetes, vitiligo, and liver disease progression in HIV-1 patients [19,26].

In the overdominant model, the heterozygote gives an advantage to the carrier; in our case, individuals with the IFIH1rs1990760_TC genotype have a lower risk of becoming infected with SARS-CoV-2. This observation is consistent with prior ones where the overdominant model of inheritance of rs73064425 in the LZTFL1 gene was most significant, suggesting C/T as risky genotype with susceptibility to COVID-19 [27].

In contrast to the IFIH1/rs1990760 variant, we are the first to describe a possible implication of MMS19/rs2236575 variants in susceptibility to SARS-CoV-2 infection. MMS19 is a component of the cytosolic iron-sulfur protein assembly machinery that transfers Fe/S clusters to various DNA metabolism-associated Fe/S proteins [28]. In the Turkish Genome Project data (https://tgd.tuseb.gov.tr/en/variant/10-97465981-T-A, accessed on 31 July 2024), we found that the SNP MMS19/rs2236575 is an intronic mutation located in a regulatory region of the MMS19 transcript 14. Whether MMS19/rs2236575 associates with the loss-of-function (LOF) of MMS19 remains to be clarified. This LOF would then likely reduce the ability of the virus to replicate because of its dependence on MMS19 for acquisition of its required iron sulfur cofactors. MMS19 is implicated in DNA replication and repair, and its deregulation has been linked to numerous human diseases, including cancer [17]. MMS19 degradation and its downregulation is a common feature in cancer and genomic stability and is evolutionarily controlled [29]. MMS19/rs2236575 has been explored as a possible marker of advanced epithelial ovarian cancer [30]. Finally, the MMS19 protein has been described as a potential cofactor of the SARS-CoV-2 RNA-dependent RNA polymerase [22]. The virus helicase (nonstructural protein 3) has a Fe/S cluster that modulates its RNA-binding and unwinding activities [23].

Isoforms in the Neanderthal haplotype on chromosome 12 in the gene encoding oligoadenylate synthetase (OAS) play a protective role for individuals of European ancestry against COVID-19 susceptibility and severity [9–11]. An additional finding of our study is that we did not find support for a protective role of OAS after interaction with SARS-CoV-2.

One limitation of our study is the reduced size of our cohort, especially in the uninfected group and, for this reason, our findings require validation in larger cohorts. We identified two host genetic variants associated with susceptibility to SARS-CoV-2 infection in an elderly population. Current SARS-CoV-2 variants tend to cause mild symptoms, with few hospitalizations and deaths [13,31,32]. Nevertheless, our findings can lead to better understanding of SARS-CoV-2 infections.

Author Contributions: Conceptualization, S.F. and M.A.M.; methodology, S.F. and M.A.M.; validation S.F. and M.A.M.; formal analysis, S.F., M.T., L.M., M.M. and M.A.M.; investigation, S.F. and M.A.M.; resources, D.P., J.M.B.-S., M.d.M.I., N.M., L.M., N.P. and M.M.; data curation, D.P., J.M.B.-S., M.d.M.I., N.M., L.M., N.P. and M.M.; writing—original draft preparation, M.A.M.; writing—review and editing, S.F., M.T., D.P., J.M.B.-S., M.d.M.I., N.M., L.M., N.P., M.M. and M.A.M.; supervision, D.P., J.M.B.-S., M.d.M.I. and N.M.; funding acquisition, M.M. and M.A.M. All authors have read and agreed to the published version of the manuscript.

Funding: This work was supported by the Ministerio de Ciencia e Innovación (PID2019-103955RB-100), Gloria Soler Foundation and the crowdfunding initiative 'https://www.yomecorono.com'. M.T. was supported by a doctoral fellowship from the Departament de Salut from Generalitat de Catalunya (SLT017/20/000095). M.M. was granted RYC2020-028934-I/AEI/10.13039/501100011033 from the Ministerio de Ciencia e Innovación and State Research Agency, and the European Social Fund "investing in your future".

Institutional Review Board Statement: The CoronAVI@S study was approved by the Ethics Board of the Institut Universitari d'Investigació en Atenció Primària Jordi Gol (20-116P).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data presented in this study are available on request from the corresponding author. The data are not publicly available due to the privacy of the patient.

Acknowledgments: We are deeply grateful to all participants and their families, to the LTCF who participated in this study. We also thank the technical staff of Direcció d'Atenció Primària de la Metropolitana Nord for sample collection in LTCF (S. Reyes Carrión, N. Salarich Solà, A. Vidal, R. Alvarez Viñallonga, J. Tornero, E. Vilamala, C. Suarez, T. Gonzalo, L. Perez, D. Sans, A. Blancas Loras, A. Garcia Archer, J. Borràs, S. Cervelló) and staff of IrsiCaixa for sample processing (L. Ruiz, R. Ayen, L. Gomez, C. Ramirez, M. Martinez, T Puig). We thank D. Ouchi for statistical support and E. Ballana and N. Izquierdo-Useros for their fruitful comments. We thank CERCA Programme/Generalitat de Catalunya for institutional support and Foundation Dormeur for financial support for the acquisition of Quantstudio 5.0 real time.

Conflicts of Interest: The authors declare no conflicts of interest.

References

1. Levin, A.T.; Hanage, W.P.; Owusu-Boaitey, N.; Cochran, K.B.; Walsh, S.P.; Meyerowitz-Katz, G. Assessing the age specificity of infection fatality rates for COVID-19: Systematic review, meta-analysis, and public policy implications. *Eur. J. Epidemiol.* **2020**, *35*, 1123–1138. [CrossRef] [PubMed]
2. Meis-Pinheiro, U.; Lopez-Segui, F.; Walsh, S.; Ussi, A.; Santaeugenia, S.; Garcia-Navarro, J.A.; San-Jose, A.; Andreu, A.L.; Campins, M.; Almirante, B. Clinical characteristics of COVID-19 in older adults. A retrospective study in long-term nursing homes in Catalonia. *PLoS ONE* **2021**, *16*, e0255141. [CrossRef] [PubMed]
3. Prieto-Alhambra, D.; Balló, E.; Coma, E.; Mora, N.; Aragón, M.; Prats-Uribe, A.; Fina, F.; Benítez, M.; Guiriguet, C.; Fàbregas, M.; et al. Filling the gaps in the characterization of the clinical management of COVID-19: 30-day hospital admission and fatality rates in a cohort of 118 150 cases diagnosed in outpatient settings in Spain. *Int. J. Epidemiol.* **2020**, *49*, 1930–1939. [CrossRef] [PubMed]
4. Bar-On, Y.M.; Goldberg, Y.; Mandel, M.; Bodenheimer, O.; Freedman, L.; Kalkstein, N.; Mizrahi, B.; Alroy-Preis, S.; Ash, N.; Milo, R.; et al. Protection of BNT162b2 Vaccine Booster against Covid-19 in Israel. *N. Engl. J. Med.* **2021**, *385*, 1393–1400. [CrossRef] [PubMed]
5. Polack, F.P.; Thomas, S.J.; Kitchin, N.; Absalon, J.; Gurtman, A.; Lockhart, S.; Perez, J.L.; Pérez Marc, G.; Moreira, E.D.; Zerbini, C.; et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. *N. Engl. J. Med.* **2020**, *383*, 2603–2615. [CrossRef] [PubMed]
6. Horowitz, J.E.; Kosmicki, J.A.; Damask, A.; Sharma, D.; Roberts, G.H.L.; Justice, A.E.; Banerjee, N.; Coignet, M.V.; Yadav, A.; Leader, J.B.; et al. Genome-wide analysis provides genetic evidence that ACE2 influences COVID-19 risk and yields risk scores associated with severe disease. *Nat. Genet.* **2022**, *54*, 382–392. [CrossRef]
7. Hu, J.; Li, C.; Wang, S.; Li, T.; Zhang, H. Genetic variants are identified to increase risk of COVID-19 related mortality from UK Biobank data. *Hum. Genom.* **2021**, *15*, 10. [CrossRef]
8. Namkoong, H.; Edahiro, R.; Takano, T.; Nishihara, H.; Shirai, Y.; Sonehara, K.; Tanaka, H.; Azekawa, S.; Mikami, Y.; Lee, H.; et al. DOCK2 is involved in the host genetics and biology of severe COVID-19. *Nature* **2022**, *609*, 754–760. [CrossRef]
9. Zeberg, H.; Pääbo, S. A genomic region associated with protection against severe COVID-19 is inherited from Neandertals. *Proc. Natl. Acad. Sci. USA* **2021**, *118*, e2026309118. [CrossRef]
10. Zeberg, H.; Pääbo, S. The major genetic risk factor for severe COVID-19 is inherited from Neanderthals. *Nature* **2020**, *587*, 610–612. [CrossRef]
11. Zhou, S.; Butler-Laporte, G.; Nakanishi, T.; Morrison, D.R.; Afilalo, J.; Afilalo, M.; Laurent, L.; Pietzner, M.; Kerrison, N.; Zhao, K.; et al. A Neanderthal OAS1 isoform protects individuals of European ancestry against COVID-19 susceptibility and severity. *Nat. Med.* **2021**, *27*, 659–667. [CrossRef]
12. Niemi, M.E.K.; Daly, M.J.; Ganna, A. The human genetic epidemiology of COVID-19. *Nat. Rev. Genet.* **2022**, *23*, 533–546. [CrossRef]

13. Pairo-Castineira, E.; Rawlik, K.; Bretherick, A.D.; Qi, T.; Wu, Y.; Nassiri, I.; McConkey, G.A.; Zechner, M.; Klaric, L.; Griffiths, F.; et al. GWAS and meta-analysis identifies 49 genetic variants underlying critical COVID-19. *Nature* **2023**, *617*, 764–768. [CrossRef] [PubMed]
14. Mathur, R.; Rentsch, C.T.; Morton, C.E.; Hulme, W.J.; Schultze, A.; MacKenna, B.; Eggo, R.M.; Bhaskaran, K.; Wong, A.Y.S.; Williamson, E.J.; et al. Ethnic differences in SARS-CoV-2 infection and COVID-19-related hospitalisation, intensive care unit admission, and death in 17 million adults in England: An observational cohort study using the OpenSAFELY platform. *Lancet* **2021**, *397*, 1711–1724. [CrossRef]
15. Wu, P.; Ding, L.; Li, X.; Liu, S.; Cheng, F.; He, Q.; Xiao, M.; Wu, P.; Hou, H.; Jiang, M.; et al. Trans-ethnic genome-wide association study of severe COVID-19. *Commun. Biol.* **2021**, *4*, 1034. [CrossRef]
16. Trigueros, M.; Pradenas, E.; Palacin, D.; Munoz-Lopez, F.; Avila-Nieto, C.; Trinite, B.; Bonet-Simo, J.M.; Isnard, M.; Moreno, N.; Marfil, S.; et al. Reduced humoral response 3 months following BNT162b2 vaccination in SARS-CoV-2 uninfected residents of long-term care facilities. *Age Ageing* **2022**, *51*, afac101. [CrossRef]
17. Torti, S.V.; Torti, F.M. Iron and cancer: More ore to be mined. *Nat. Rev. Cancer* **2013**, *13*, 342–355. [CrossRef]
18. Pujantell, M.; Franco, S.; Galván-Femenía, I.; Badia, R.; Castellví, M.; Garcia-Vidal, E.; Clotet, B.; de Cid, R.; Tural, C.; Martínez, M.A.; et al. ADAR1 affects HCV infection by modulating innate immune response. *Antivir. Res.* **2018**, *156*, 116–127. [CrossRef] [PubMed]
19. Franco, S.; Horneros, J.; Soldevila, L.; Ouchi, D.; Galván-Femenía, I.; de Cid, R.; Tenesa, M.; Bechini, J.; Perez, R.; Llibre, J.M.; et al. Single nucleotide polymorphisms in PNPLA3, ADAR-1, and IFIH1 are associated with advanced liver fibrosis in patients co-infected with HIV-1/HCV. *AIDS* **2021**, *35*, 2497–2502. [CrossRef]
20. Ribero, M.S.; Jouvenet, N.; Dreux, M.; Nisole, S. Interplay between SARS-CoV-2 and the type I interferon response. *PLoS Pathog.* **2020**, *16*, e1008737. [CrossRef]
21. Solé, X.; Guinó, E.; Valls, J.; Iniesta, R.; Moreno, V. SNPStats: A web tool for the analysis of association studies. *Bioinformatics* **2006**, *22*, 1928–1929. [CrossRef] [PubMed]
22. Maio, N.; Lafont, B.A.P.; Sil, D.; Li, Y.; Bollinger, J.M.; Krebs, C.; Pierson, T.C.; Linehan, W.M.; Rouault, T.A. Fe-S cofactors in the SARS-CoV-2 RNA-dependent RNA polymerase are potential antiviral targets. *Science* **2021**, *373*, 236–241. [CrossRef] [PubMed]
23. Maio, N.; Raza, K.; Li, Y.; Zhang, D.-L.; Bollinger, J.M.; Krebs, C.; Rouault, T.A. An iron–sulfur cluster in the zinc-binding domain of the SARS-CoV-2 helicase modulates its RNA-binding and -unwinding activities. *Proc. Natl. Acad. Sci. USA* **2023**, *120*, e2303860120. [CrossRef] [PubMed]
24. Maiti, A.K. The African-American population with a low allele frequency of SNP rs1990760 (T allele) in IFIH1 predicts less IFN-beta expression and potential vulnerability to COVID-19 infection. *Immunogenetics* **2020**, *72*, 387–391. [CrossRef] [PubMed]
25. Amado-Rodríguez, L.; del Riego, E.S.; de Ona, J.G.; Alonso, I.L.; Gil-Pena, H.; López-Martínez, C.; Martín-Vicente, P.; Lopez-Vazquez, A.; Lopez, A.G.; Cuesta-Llavona, E.; et al. Effects of IFIH1 rs1990760 variants on systemic inflammation and outcome in critically ill COVID-19 patients in an observational translational study. *eLife* **2022**, *11*, e73012. [CrossRef]
26. Della Mina, E.; Rodero, M.P.; Crow, Y.J. Polymorphisms in IFIH1: The good and the bad. *Nat. Immunol.* **2017**, *18*, 708–709. [CrossRef] [PubMed]
27. Rüter, J.; Pallerla, S.R.; Meyer, C.G.; Casadei, N.; Sonnabend, M.; Peter, S.; Nurjadi, D.; Linh, L.T.K.; Fendel, R.; Göpel, S.; et al. Host genetic loci LZTFL1 and CCL2 associated with SARS-CoV-2 infection and severity of COVID-19. *Int. J. Infect. Dis.* **2022**, *122*, 427–436. [CrossRef] [PubMed]
28. Stehling, O.; Vashisht, A.A.; Mascarenhas, J.; Jonsson, Z.O.; Sharma, T.; Netz, D.J.A.; Pierik, A.J.; Wohlschlegel, J.A.; Lill, R. MMS19 assembles iron-sulfur proteins required for DNA metabolism and genomic integrity. *Science* **2012**, *337*, 195–199. [CrossRef] [PubMed]
29. Weon, J.L.; Yang, S.W.; Potts, P.R. Cytosolic Iron-Sulfur Assembly Is Evolutionarily Tuned by a Cancer-Amplified Ubiquitin Ligase. *Mol. Cell* **2018**, *69*, 113–125.e6. [CrossRef]
30. Moxley, K.; Benbrook, D.; Queimado, L.; Zuna, R.; Thompson, D.; McCumber, M.; Premkumar, P.; Thavathiru, E.; Hines, L.; Moore, K. The role of single nucleotide polymorphisms of the ERCC1 and MMS19 genes in predicting platinum-sensitivity, progression-free and overall survival in advanced epithelial ovarian cancer. *Gynecol. Oncol.* **2013**, *130*, 377–382. [CrossRef] [PubMed]
31. Karyakarte, R.P.; Das, R.; Rajmane, M.V.; Dudhate, S.; Agarasen, J.; Pillai, P.; Chandankhede, P.M.; Labhshetwar, R.S.; Gadiyal, Y.; Kulkarni, P.P.; et al. Chasing SARS-CoV-2 XBB.1.16 Recombinant Lineage in India and the Clinical Profile of XBB.1.16 Cases in Maharashtra, India. *Cureus* **2023**, *15*, e39816. [CrossRef] [PubMed]
32. Callaway, E. COVID's future: Mini-waves rather than seasonal surges. *Nature* **2023**, *617*, 229–230. [CrossRef] [PubMed]