Immunogenetics (2023) 75:91–98
https://doi.org/10.1007/s00251-022-01281-6

ORIGINAL ARTICLE

Age-dependent effect of the *IFIH1/MDA5* gene variants on the risk of critical COVID-19

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Received: 29 August 2022 / Accepted: 20 October 2022 / Published online: 25 November 2022

Abstract

MDA5, encoded by the *IFIH1*gene, is a cytoplasmic sensor of viral RNAs that triggers interferon (IFN) antiviral responses. Common and rare *IFIH1* variants have been associated with the risk of type 1 diabetes and other immune-mediated disorders, and with the outcome of viral diseases. Variants associated with reduced IFN expression would increase the risk for severe viral disease. The MDA5/IFN pathway would play a critical role in the response to SARS-CoV-2 infection mediating the extent and severity of COVID-19. Here, we genotyped a cohort of 477 patients with critical ICU COVID-19 (109 death) for three *IFIH1* functional variants: rs1990760 (p.Ala946Thr), rs35337543 (splicing variant, intron 8 + 1G > C), and rs35744605 (p.Glu627Stop). The main finding of our study was a significant increased frequency of rs1990760 C-carriers in early-onset patients (< 65 years) ($p = 0.01$; OR = 1.64, 95%CI = 1.18–2.43). This variant was also increased in critical vs. no-ICU patients and in critical vs. asymptomatic controls. The rs35744605 C variant was associated with increased blood IL6 levels at ICU admission. The rare rs35337543 splicing variant showed a trend toward protection from early-onset critical COVID-19. In conclusion, *IFIH1* variants associated with reduced gene expression and lower IFN response might contribute to develop critical COVID-19 with an age-dependent effect.

Keywords IFIH1/MDA5 · COVID-19 · SARS-CoV-2 · Genetic association

Introduction

The coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 exhibits a wide range of manifestations, from asymptomatic to mild–moderate symptoms and severe pneumonia with hospitalization (Luo et al. 2022). Critical patients require life support in the ICU and are at high risk of death, with several well recognized life-threatening risk factors such as advanced age, male sex, and pre-existing cardiovascular diseases (hypertension, diabetes, dyslipaemia) (Portuondo-Jimenez et al. 2022). In addition to these, the genetic background of each individual would contribute to the susceptibility to develop a severe manifestation of COVID-19 (Ellinghaus et al. 2020; COVID-19 Host Genetics Initiative 2021; Kousathanas et al. 2022; Coto et al. 2021; Nakanishi et al. 2021; David et al. 2022).

The pathological hallmark of COVID-19 is an exacerbated inflammatory host response known as cytokine storm (Nile et al. 2020). This drives the recruitment and accumulation of leukocytes in tissues, causing acute respiratory

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distress syndrome (Hadjadj et al. 2020). Critically ill patients showed lower antiviral and a greater inflammatory responses, which exacerbates the damage to the lung tissue (Wang et al. 2020; Alon et al. 2021).

MDA5 (melanoma differentiation-associated protein 5) is a receptor dsRNA helicase encoded by the *IFIH1* gene. MDA5 is a cytoplasmic sensor of viral RNAs that triggers interferon (IFN) innate immune antiviral responses (Dias Junior et al. 2019; Sampaio et al. 2021; Thorne et al. 2021; Yin et al. 2021). Thus, the loss of MDA5 might impairs the antiviral response increasing the risk of severe infection (Kim et al. 2014; Asgari et al. 2017; Lamborn et al. 2017). Moreover, anti-MDA5 antibodies have been reported in COVID-19 patients and high levels correlated with severe disease and unfavorable outcomes (Wang et al. 2021). In opposition to the increased risk of viral disease associated with the loss of MDA5, *IFIH1* gain of function variants would result in the over activation of inflammatory pathways and increased risk of several autoimmune and inflammatory diseases (Rice et al. 2014, 2020; Tonutti et al. 2022).

In reference to the COVID-19, MDA5 is the main sensor of SARS-CoV-2 in lung epithelial cells and would regulate the early IFN response to inhibit viral replication. MDA5 has been associated with the extent of SARS-CoV-2 infection and the risk of developing severe-critical COVID -19 (Sampaio et al. 2021; Thorne et al. 2021; Yin et al. 2021; Rebendenne et al. 2021; Amado-Rodriguez et al. 2022).

The *IFIH1* gene has several common polymorphisms that have been associated with the risk of immune-mediated diseases. Among others, rs1990760 is a missense change (p.Ala946Thr) associated with type 1 diabetes and other autoimmune diseases (Liu et al. 2009; Cen et al. 2013; Gorman et al. 2017; Borysewicz-Sańczyk et al. 2020; Shapiro et al. 2021).This change would result in differences in the ATPase activity due to conformational alteration of the protein (Funabiki et al. 2014). Mutations that inhibit ATPase activity are capable of enhancing the IFN-I (IFNβ) response (Bamming and Horvath 2009). In addition to the structural change caused by the p.Ala946Thr that could affect the MDA5 function, this SNP might also impact the *IFIH1* expression. Most of the reported studies described increased basal MDA5 levels for the p.946Thr autoimmune-risk allele, with higher expression of IFN (Downes et al. 2010). While this allele might be detrimental for autoimmune disorders, it could be also protective against viral disease by enhancing the early innate immune response (Gorman et al. 2017). In this context, allele rs1990760 T was found at reduced frequency in patients with chronic hepatitis C compared to uninfected controls and was also associated with spontaneous clearance of HCV infection (Hoffmann et al. 2015).

In addition to common gene polymorphisms, *IFIH1* has several rare deleterious variants present at frequencies > 1% in Europeans. The rs35337543 is a putative splicing variant (c.1641 + 1G > C) that would result in the skipping of exon 8 removing 39 amino acids of the helicase domain (Asgari et al. 2017; Forbester and Humphreys 2021). This variant would be protective for T1D, but as a risk factor for recurrent viral infection (Asgari et al. 2017; Nejentsev et al. 2009; Mine et al. 2020). The rs35744605 (c.1879 G > T) introduces a premature stop codon (p.Glu627Stop) and would result in the loss of the 399 C-terminal amino acids of MDA5. This variant is present in approximately 1% of the individuals of European ancestry, and was associated with decreased risk of T1D and increased risk for recurrent viral infection (Asgari et al. 2017; Downes et al. 2010; Chistiakov et al. 2010).

Our aim was to determine the impact of the *IFIH1* variants in the risk of critical COVID-19 and death. For this purpose, we studied critical (ICU), less severe patients and asymptomatic individuals from a Spanish population.

Methods

Patients

This study was approved by the Ethical Research Committee of Asturias and the participants (patients and controls) or their next of kin gave their informed consent. All the participants were from the region of Asturias (Northern Spain, total population one million, 25% > 65 years). Individuals from non-European ancestry were not included, and none of the patients had been vaccinated against SARS-CoV-2. We studied 477 COVID-19 critical patients who required admission to the Intensive Care Unit (ICU) of Hospital Universitario Central Asturias during the period March 2020 to July 2021. During the study period, dexamethasone was added to critical COVID-19 treatment based on published trials (WHO Rapid Evidence Appraisal for COVID-19 Therapies REACT Working Groupet al. 2020). For this reason, most of the ICU patients who did not receive this treatment ($N = 58$) were hospitalized during the first pandemic weeks.

The less severe group consisted of patients ($N = 431$) with COVID-19 symptoms who required hospital admission with no need for ICU. We also studied 195 individuals from the general population with the same age distribution as the patients. These controls were followed during the study period and did not have COVID-19 symptoms, although the absence of SARS-CoV-2 infection was not confirmed by serological tests.

Genotyping

The DNA was obtained from whole blood leukocytes and all the individuals were genotyped for the IFIH1 polymorphisms with real-time PCR Taqman assays (Fisher scientific): rs35337543, assay id C_25985625_10; rs35744605,

assay id C_25982959_10; rs1990760, C_2780299_30 (suppl. Fig. 1). The quality of the genotyping method was determined by sequencing PCR fragments with different genotypes (suppl. Figs. 2–4).

Statistical analysis

The statistical analysis was performed to determine the association between the study variants and the disease onset age and the risk of death among the critical ICU COVID-19 patients. Patients aged < 65 or ≥ 65 years were classified as early and late onset, respectively. We also compared the critical ICU with non-critical patients and healthy controls. All the patients´ values (age, sex, cardiovascular comorbidities, IL-6, corticosteroid treatment) were obtained from the clinical history at ICU admission. For the blood IL-6 levels, the ICU patients were categorized as > 70 and ≤ 70 pg/mL based on previous reports that considered this cut-off value as significant predictor of COVID-19 mortality (Del Valle et al. 2020).

All the data (including the genotypes) were annotated in an excel file and the statistical analysis was performed by logistic regression with the linear generalized model in the R-free software (www.r-project.org). The post hoc power was calculated based on the observed SNP frequencies in the groups.

Results

The rs1990760 (p.Ala946Thr) CC and CT COVID-19 critical patients showed almost identical mean onset ages (63.09 ± 11.57 and 63.44 ± 12.84 years, respectively), and lower than the TT patients (65.80 ± 11.36 years). We thus concluded that allele C (p.Ala946) was associated with a significant lower onset age with a dominant effect (CC + CT) compared to TT (63.39 ± 12.39 vs. 65.8011.36 years; $p = 0.04$). Early-onset critical patients (< 65 years) showed a significantly higher frequency of the C allele compared to late-onset patients, with a dominant effect (CC + CT vs. TT, $p = 0.01$) (Table 1). Moreover, there was a gradient in increased frequency of C-patients according to the age intervals, ranging from 79% in ≤ 50 years to 63% in > 71 years (Fig. 1). The power of the study for the ICU early vs. late onset was 75%. The C-carrier status was associated with early-onset critical COVID-19 after multiple regression analysis ($p = 0.03$) (Table 2).

We determined the association between the rs1990760 and the analytical and clinical variables in the ICU patients (suppl. Table 2). The only significant association was with IL6 at ICU admission: C-carriers had a higher frequency of IL6 > 70 pg/mL ($p = 0.02$).

Table 1 Main characteristics of the early onset (< 65 years vs. ≥ 65) in the critical ICU COVID-19 cases. For the rs1990760, both CC and CT genotypes were increased in the < 65 years old patients, and we considered a C-dominant (CC + CT) effect on the risk of early-onset critical disease

	ICU < 65 ***N* = 235**	**ICU ≥ 65** ***N* = 242**	*p*-value
Male	167 (71%)	178 (69%)	0.12
Corticosteroid, NO	18 (8%)	40 (16%)	
Corticosteroid, YES	217 (92%)	202 (84%)	0.001
BMI ≥ 30	121 (52%)	123 (51%)	0.89
Hypertension*	98 (42%)	164 (68%)	< 0.001
Hypercolesterolemia*	78 (33%)	147 (61%)	< 0.001
Diabetes*	28 (12%)	75 (31%)	< 0.001
Death	25 (10%)	80 (33%)	< 0.001
IL-6 pg/mL** median (IQR)	40 (12–109)	46 (17–125)	-
IL-6 > 70 pg/mL (≤ 70)	106 (50%) (+ 105)	116 (53%) + 102	0.54
rs1990760 C > T# (p.Ala946Thr)			
CC	59 (25%)	49 (20%)	0.01
CT	112 (48%)	102 (42%)	
TT	64 (27%)	91 (37%)	-
Allele C (p.**Ala946**)	0.49	0.41	0.02
Eur: *C* = 0.36–0.40	-	-	-
rs35337543 int8 + 1G > C			
GG	231 (98%)	231 (95%)	0.09
GC	4 (2%)	11 (5%)	-
Allele C	0.01	0.02	0.07
Eur: *C* = 0.02	-	-	-
rs35744605 G > T (p.**Glu627Stop**)			
GG	230 (98%)	238 (98%)	0.70
GT	5 (2%)	4 (2%)	
Allele T	0.01	0.01	0.48
Eur: *T* = 0.01	-	-	-

Eur, allele frequencies among Europeans (www.ensembl.org)

#CC + CT vs. TT

*Data obtained from the electronic clinical history

**Measured in ICU, 211 < 65 years and 218 ≥ 65 years

We determined the association between the study variables and the risk of death in the critical ICU patients (Table 3). We did not find a significant effect of the rs1990760 on the risk of death ($p = 0.23$). However, in the elderly critical patients, the risk of death was significantly increased among rs1990760 C-patients ($p = 0.046$) (suppl. Table 3). Hypertension, dyslipemia, and IL6 > 70 were associated with death in the univariate logistic regression. After correcting by age, only IL6 > 70 remained significantly associated (OR = 1.67, 95%CI = 1.04–2.73).

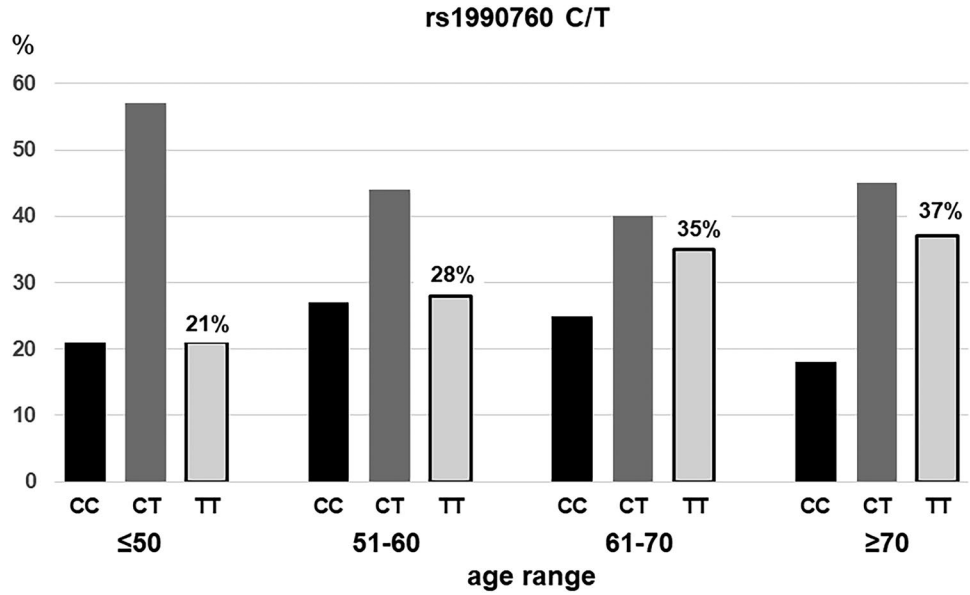

Fig. 1 Frequency of the **rs1990760** T/C genotypes in the ICU patients distributed in age intervals. The frequency of C-carriers (CC + CT) decreased with age

For the no-critical (no-ICU) COVID-19 patients, the C-frequency was also higher among the early-onset cases, without significant difference (suppl. Table 1). In cases < 65 years, the C allele was more frequent in the critical vs. non-ICU patients ($p = 0.05$). In the asymptomatic controls, the frequencies did not differ between the two age groups, with lower frequencies of the C allele (0.36) compared to the two patients groups (suppl. Table 1). Thus, the C allele (p.Ala946) was significantly associated with an increased risk of COVID-19 requiring hospitalization, with a maximum effect for early-onset critical ICU disease (Fig. 2).

In reference to the rare rs35744605 SNP that would introduce a premature stop codon, we did not find significant differences between the age groups (Table 1). The observed allele frequencies were close to the reported among the European populations (MAF = 0.02; www.ensembl.org). One no-ICU patient was a female homozygous for the rs35744605 A, p.627stop (suppl. Figure 4). This genotype has a predicted frequency of 4 in 10,000 in our population and was associated with recurrent viral infections by some authors, likely due to the loss of the MDA5 antiviral function (Asgari et al. 2017). However, the patient was 71 years old with no episodes of recurrent infections. She was SARS-CoV-2 positive during the first pandemic wave (March 2020) and attended the hospital due to bilateral pneumonia with a positive clinical evolution and hospital discharge in 1 week.

The rs35337543-splicing variant would skip exon 8 and the European frequencies were close to the observed in our population. Carriers of the intron-splicing variant were less frequent in the ICU early-onset patients compared to the other groups (Table 1**;** suppl. Table 1). We did not find significant differences between this variant and the study variables. These rare variants had been associated with a reduced risk of type 1 diabetes (Nejentsev et al. 2009; Chistiakov et al. 2010). None of the type 1 diabetes was carrier of the rare alleles, but there were only 4 cases confirmed with this condition.

Table 2 Statistical difference between ICU patients < 65 and ≥ 65 years, univariate and multivariate R-linear generalized models. *OR*, odds ratio; *CI*, confidence interval

	Univariate model		Multivariate model	
	p-value	OR, 95%CI		
Male	0.12	1.13, 0.76–1.69	0.51	1.17, 0.74–1.85
BMI ≥ 30	0.89	0.97, 0.68–1.39	0.44	0.85, 0.56–1.28
Hypertension	< 0.001	2.94, 2.03–4.29	< 0.001	2.03, 1.32–3.12
Hypercolesterolemia	< 0.001	3.11, 2.15–4.55	< 0.001	2.12, 1.27–3.69
Diabetes	< 0.001	3.32, 2.08–5.44	< 0.001	2.14, 1.26–3.69
IL-6 > 70 pg/mL	0.54	1.13, 0.77–1.65	0.53	1.14, 0.75–1.71
rs1990760 CC + CT vs. TT	0.01	1.64, 1.18–2.43	0.03	1.61, 1.03–2.53

Table 3 Main characteristics of the ICU death and survivors COVID-19 cases

	Death $N=105$	Survivors $N=372$	p-value
Age < 65	25 (24%)	80 (76%)	**< 0.001**
Male	75 (71%)	270 (73%)	0.82
BMI ≥ 30	54 (51%)	190 (51%)	0.94
Hypertension*	72 (69%)	190 (51%)	**0.001**
Hypercolesterolemia*	62 (58%)	179 (44%)	**0.006**
Diabetes*	26 (25%)	77 (21%)	0.37
Type 1 diabetes	0	4	-
IL-6 > 70 pg/mL	58 (62%)	164 (49%)	**0.003**
Corticosteroid yes	85 (80%)	334 (90%)	0.01
rs1990760C/T ** p.Ala946Thr			
CC	21 (20%)	87 (23%)	0.25
CT	55 (52%)	159 (43%)	
TT	29 (28%)	126 (34%)	-
Allele C (p.**Ala 946**)	0.46	0.45	-
rs35337543 int8 + 1 G > C			
GG	102 (97%)	366 (98%)	-
GC	3 (3%)	6 (2%)	0.09
Allele C	0.01	0.01	-
rs35744605 **G > T p.Glu627Stop**			
GG	99 (94%)	363 (98%)	-
GT	6 (6%)	9 (2%)	0.41
Allele T	0.03	0.01	-

*Data obtained from the electronic clinical history

**For the rs1990760, we compared the C-carriers vs. TT

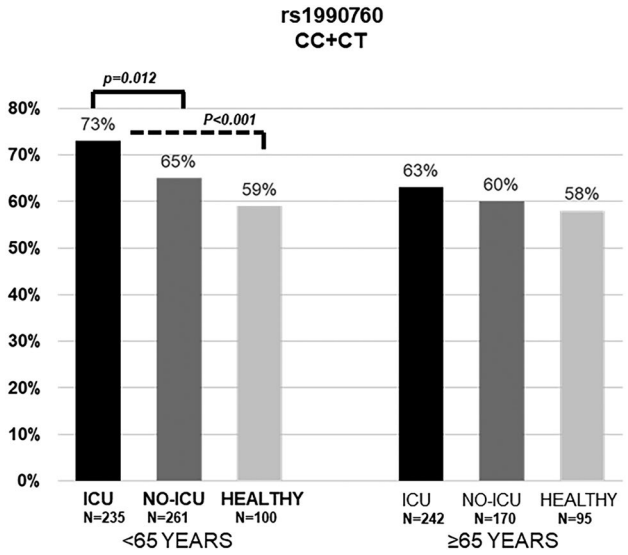

Fig. 2 Frequency of the **rs1990760** C-carriers (p.Ala946) vs TT (Thr946 homozygotes) in the three study groups aged < 65 and ≥ 65 years. Critical ICU, symptomatic no-ICU requiring in hospital treatment, and asymptomatic individuals

Discussion

The main finding of our study was a significant difference of the common *IFIH1* rs1990760 (p.Ala946Thr) frequencies between critical COVID-19 patients aged below/above 65 years. This is the age value used to define early and late-onset COVID-19 by most authors (Nakanishi et al. 2021). Other gene markers have shown differences in the degree of association between the two age groups. For instance, the "top disease" marker in the *LZTFL1* gene showed differences between early and late-onset patients (Ellinghaus et al. 2020; Nakanishi et al. 2021). For the rs1990760, we found a higher frequency of p.Ala946 carriers (CC + CT genotypes) in the critical ICU COVID-19 patients compared to no-ICU cases and healthy population controls. This genotype was also elevated among the elderly deceased patients.

The p.Ala946Thr could be associated with a conformational alteration of the MDA5 that results in different ATPase activities (Funabiki et al. 2014). Mutations that inhibit the ATPase activity would enhance the IFN-I (IFNβ) response (Bamming and Horvarth 2009). In addition to structural changes, this *IFIH1* polymorphism has been associated with gene expression and basal protein levels (Liu et al. 2009; Downes et al. 2010; Zurawek et al. 2015). In reference to COVID-19, MDA5 is the main sensor of SARS-CoV-2 in lung epithelial cells and would thus regulate the early interferon response to inhibit viral replication (Sampaio et al. 2021; Thorne et al. 2021; Yin et al. 2021; Rebendenne et al. 2021; Amado-Rodriguez et al. 2022). Variants that drive a reduced *IFIH1* expression and/or MDA5 function might reduce the IFN antiviral response increasing the risk for viral replication and disease severity (Yin et al. 2021; Rebendenne et al. 2021). In agreement with a protective effect on COVID-19 severity, the rs1990760 T was found at reduced frequency in patients with chronic hepatitis C compared to uninfected controls and was also associated with spontaneous clearance of HCV infection (Hoffmann et al. 2015). While the p.Thr946 allele might be detrimental for autoimmune disorders, it could be protective against viral disease by enhancing the early innate immune response (Gorman et al. 2017). Interestingly, patients with the CT + CC genotypes had higher levels of pro-inflammatory mediators, including IL-6, CXCL10, CXCL16, and CCL7 (Amado-Rodríguez et al. 2022; Zhang et al. 2020). In this study, we confirmed that C-carriers would have increased IL6 levels at ICU admission.

The association between the rs1990760 C and COVID-19 might also explain the heterogeneous impact of the disease in different populations. In this regard, populations with a higher allele frequency of SNP rs1990760 C allele could

be predisposed to reduced *IFIH1* expression and increased vulnerability to COVID-19 infection (Maiti 2020). The association between this allele and critical COVID-19 suggested a decreased protection for severe disease among Europeans that have the highest frequency of rs1990760 C.

In addition to common polymorphisms, *IFIH1* has rare deleterious variants such as rs35337543 (a splicing variant that would result in the skipping of exon 8) and rs35744605 (that introduces a premature stop codon). The splicing variant has been reported as protective for T1D (Shapiro et al. 2021; Mine et al. 2020; Nejentsev et al. 2009). The rs35744605 (p.Glu627Stop) was present in approximately 1% of the individuals of European ancestry, and has been associated with decreased risk of T1D by some authors (Chistiakov et al. 2010). Carriers of the splicing variant would exhibit reduced expression while heterozygosity for the premature stop codon would have no effect on the level of *IFIH1* mRNA (Downes et al. 2010). These loss-of-function variants might increase the risk for viral disease, but our results did not support a significant association with COVID-19 severity. However, the reduced sample size limited the statistical power of the study.

Finally, our study has several limitations. Mainly the limited sample size that would reduce the statistical power. In particular, the number of cases with the rare splicing and premature stop variants was too low and conclusions about the effect on COVID-19 require the study of large cohorts from different populations. The *IFIH1* variants linked to reduced expression have been associated with protection for type 1 diabetes while they could also increase the risk of severe COVID-19. Because type 1 diabetes was rare among our patients, a study including a large cohort of patients with this condition is necessary. The effect of the genotypes on corticosteroid response was limited by the reduced number of critical patients without this immunosuppressive treatment. An increased IL6 blood level at ICU admission was associated with mortality, but we did not measure the IL6 values subsequently. Thus, the effect of corticosteroids on IL6 and a putative modifying effect of the *IFIH1* variants was not evaluated in our study.

In conclusion, we report a significant effect of the common rs1990760 p.Ala946 variant on the risk of critical COVID-19 requiring ICU. The risk was higher among the early-onset (< 65 years) patients. The risk allele was also associated with higher IL6 blood levels at admission. Our results were in agreement with an increased risk for severe COVID-19 among carriers of *IFIH1* variants linked to reduced MDA5 expression and lower interferon production.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00251-022-01281-6.

Author contributions Lead researchers: EC, GMA, LAR, JG. Study design: EC, GMA, LAR, JG. Patient assessment: GMA, LAR, ESR, ILA, CLM, PMV, ECLL, MGC, THV, AIER, CHG. Genetic study: MGMB, EC, ECL, VA, JG. Database: EC, GMA, LAR, ECL, JG. Data filtering and analysis: MGMB,EC, GMA. Statistical analysis: MGMB, EC. Analysis of results: MGMB, EC, GMA, LAR, MGC. Drafting of the manuscript: EC. Revision of the manuscript: all authors. All the authors contributed to this work by recruiting the patients and performing the genetic and statistical analyses. EC takes full responsibility for the accuracy of the data. All the authors approved the submission of this manuscript.

Funding This work was supported by grants from the Spanish Instituto de Salud Carlos III (ISCIII)-European Union Next Generation MRR founds. Grants ISCIII PI-21/00971 (EC) and RICORS2040 (EC).

Data availability The materials and raw data described in the manuscript will be freely available to any researcher without breaching participant's confidentiality. To facilitate the revision of the results by other researchers, a file with the patient's data is available as an Excel file upon request to the corresponding author.

Declarations

Competing interests The authors declare no competing interests.

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