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Short communication

The influence of *IFITM3* polymorphisms on susceptibility to SARS-CoV-2 infection and severity of COVID-19

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ABSTRACT

Background and aims: The interferon-induced transmembrane protein 3 (IFITM3) plays an important role in the adaptive and innate immune response by inhibiting viral membrane hemifusion between the host and viral cell cytoplasm. Single nucleotide polymorphisms (SNPs) in the gene *IFITM3* have been associated with susceptibility and severity of influenza or other viral infections. We aimed to analyze the role of SNPs in the gene *IFITM3* in SARS-CoV-2 infection.

Methods: We performed genotyping of the SNPs rs12252 and rs34481144 in the gene *IFITM3* in 239 SARS-CoV-2-positive and 253 SARS-CoV-2-negative patients. We analyzed the association of the SNPs with susceptibility to SARS-CoV-2 infection and severity of COVID-19.

Results: SARS-CoV-2-positive and SARS-CoV-2-negative patients did not differ regarding demographics. Neither *IFITM3* rs12252 nor rs34481144 polymorphisms were related to SARS-CoV-2 infection risk or severity of COVID-19. Interestingly, we observed the putative deleterious rs12252 CC genotype only in SARS-CoV-2-positive patients (N = 2). Also, we found a non-significant higher frequency of rs34481144 A-allele carriers in the patients with 'serious' COVID-19.

Conclusions: In summary, we could not confirm the recently reported influence of polymorphisms in the gene *IFITM3* on SARS-CoV-2 infection risk or severity of COVID-19 in a German cohort. Additional studies are needed to clarify the influence of the rs12252 CC genotype on SARS-CoV-2 infection risk and the rs34481144 A-allele on course of COVID-19.

1. Introduction

The interferon-induced transmembrane (IFITM) proteins play a critical role in the antiviral defense in the adaptive and innate immune response. The human *IFITM* locus is located on chromosome 11p15.5 and comprises five genes, including *IFITM3*. The gene *IFITM3* is an IFN-stimulated gene (ISG) and the protein IFITM3 is mainly expressed on endosomes and lysosomes. It prevents hemifusion of the viral membrane and host cellular membrane in a broad spectrum of enveloped viruses, e. g. influenza A, Ebola, Marburg or SARS-CoV [1].

Previous studies have reported that single nucleotide polymorphisms (SNPs) in the gene *IFITM3* may diminish the antiviral effects of IFITM3 causing a higher infection susceptibility and disease severity [2]. The C-allele of the SNP rs12252 (c.-22T>C) was found to be significantly associated with severity of H1N1 and H7N9 influenza A virus infections in Asians and Caucasians [3,4]. The C-allele of rs12252 is more common in East Asians with a minor allele frequency (MAF) of 0.47 compared to a lower MAF of 0.04 in the European population. Mechanistically, it is

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predicted that the SNP rs12252 alters a splice acceptor site, resulting in a truncated and mislocalized IFITM3 protein, which lacks the first 21 N-terminal amino acids (Δ21IFITM3). The functional consequences of the truncation are still discussed controversially and need to be conclusively demonstrated [2,5]. In a first preliminary study, Zhang *et al.* observed a significantly higher frequency of rs12252 C-allele carriers in patients with severe COVID-19 (N = 24) compared to patients with mild COVID-19 (N = 56) [6]. Recently, it was shown in a Spanish cohort, that C-allele carriers of the SNP rs12252 have a 2-fold increased risk for SARS-CoV-2 infection (N = 311) compared to a reference group (N = 440) collected before the pandemic [7].

The A-allele of a second SNP (rs34481144, c.-22-64G>A), which has the highest MAF in Europeans (0.46) and a very low MAF in East Asians (0.01), was also reported to be a risk factor for severe influenza A virus infections [4,8]. In an European study Allen *et al.* showed that the A-allele of this promoter SNP causes decreased *IFITM3* mRNA and protein levels, diminishing the antiviral defense capacities of IFITM3 [9]. Up to now, no case-control studies have been performed analyzing the role of rs34481144 in COVID-19.

For SARS-CoV the restriction of S protein-mediated entry by IFITM1, IFITM2 and IFITM3 could be demonstrated in a functional *in vitro* study [10]. The sequence similarity between SARS-CoV-2 and SARS-CoV is 82% [11]. Because SARS-CoV-2 also enters the cells using the S protein, which binds to angiotensin-converting enzyme 2 (ACE2), it is hypothesized that IFITM3 may as well play an important role in SARS-CoV-2 infection.

Thus, we analyzed whether the above described associations of the variants rs12252 and rs34481144 in the gene *IFITM3* could be observed in a German cohort with SARS-CoV-2 infection as well.

2. Methods

2.1. Study participants, recruitment and outcome of the patients

The study was conducted following approval of the Ethics Committee of the Medical Faculty of the University of Duisburg-Essen (20-9230-BO) and in cooperation with the West German Biobank (WBE; 20-WBE-088). Written informed consent was obtained from study patients.

Enrolment started on March 11, 2020, and ended on September 30, 2020. Patients were initially recruited upon presentation with COVID-19 typical symptoms, i.e. fever, cough, and dyspnea or who were admitted to the hospital with already confirmed SARS-CoV-2 infection. We included 239 SARS-CoV-2-positive patients. Patients were classified as SARS-CoV-2-positive with at least one positive real-time reverse transcription polymerase chain reaction (RT-PCR) test result. Follow-up was completed on October 31, 2020, at which time all patients either were discharged from the hospital as “cured” or had a fatal outcome of the disease. We also studied 253 SARS-CoV-2-negative patients, who presented with COVID-19 typical symptoms, but were tested exclusively negative for SARS-CoV-2 by RT-PCR. These patients were hospitalized at the University Hospital Essen or treated as outpatients, due to other medical conditions. Clinical outcome was defined as follows according to the criteria of the ECDC [12] - ’moderate’: outpatients and hospitalized patients; ’serious’: hospitalized patients admitted to an intensive care unit and/or became dependent on mechanical ventilation and all cases of COVID-19-related deaths during the hospital stay. In contrast to the ECDC classification, where patients are counted up to three times, every patient only counted once according to the worst clinical outcome observed during the hospital stay in our study. The patients included in this study were of Caucasian origin.

2.2. Genotyping of IFITM3

Genomic DNA was extracted from 200 μl EDTA-blood using the QIAamp® DNA Blood Mini Kit (Qiagen, Hilden, Germany). In cases where EDTA-blood was not available (N = 20), genomic DNA was extracted from liquid nitrogen-frozen viral transport medium of the nasopharyngeal swabs containing swabbed human cells with the QuickDNA™ Microprep Kit (Zymo Research GmbH, Freiburg, Germany). All DNA extractions were performed under biosafety level 2 precautions. To prevent spreading of infectious aerosols, DNA from nasopharyngeal swabs was extracted within a biological safety cabinet wearing protective clothing. Polymerase chain reaction was performed with 2 μl genomic DNA and 30 μl *Taq* DNA-Polymerase 2x Master Mix Red (Ampliqon, Odense, Denmark) with the following conditions: initial denaturation 95 °C for 5 min; 38 cycles with denaturation 95 °C for 30 sec, annealing at 60 °C for 30 sec and elongation 72 °C for 30 sec each; final elongation 72 °C for 10 min (biotinylated forward primer: 5′ [BIO] ATGTGGATCACGGTGGACG 3′; reverse primer 3′ AGGAATTTGTTCCGCCCTCA 5′). Genotyping of all samples was performed by Pyrosequencing according to the manufacturers’ instructions (Qiagen, Hilden, Germany). In brief, biotinylated PCR amplicons were immobilized on streptavidin-coated sepharose beads (GE Healthcare, Solingen, Germany) with the vacuum tool of the workstation (Qiagen, Hilden, Germany). In the next step, PyroMark denaturation solution (Qiagen, Hilden, Germany) was used to separate the complementary strand from the biotinylated strand. The biotinylated, single-stranded DNA remains immobilized on the vacuum tool. Finally, the single-stranded DNA was released into the sequencing plate containing 0.3 μM sequencing primer (5′ CCTTCTTCTCTCCTGTCAA 3′ for rs12252 and 5′ CCATCCCAGTAACCCGACC 3′ for rs34481144, respectively). After incubation at 80 °C for 2 min, the hybridized primer and single-stranded template were incubated with the enzymes DNA polymerase, adenosine triphosphate (ATP) sulfurylase, luciferase and apyrase, as well as the substrates adenosine 5′ phosphosulfate (APS) and luciferin. Addition of dideoxyribonucleotide triphosphates (ddNTPs) was performed sequentially. Each incorporation event is accompanied by the release of pyrophosphate (PPi) in a quantity equimolar to the amount of the incorporated nucleotide. ATP sulfurylase converts PPi to ATP, which drives luciferase-mediated conversion of luciferin to oxyluciferin that generates visible light. The height of each light signal is proportional to the number of nucleotides incorporated and can be visualized in the Pyrogram. Apyrase continuously degrades unincorporated nucleotides and ATP and when degradation is complete another nucleotide is added. Analyses were performed on the PyroMark Q96 MD instrument (Qiagen, Hilden, Germany). Assay design was validated by Sanger sequencing of five samples with various genotypes for the respective SNPs.

2.3. Statistical analyses

Hardy-Weinberg equilibrium (HWE) was calculated using Pearson’s X^2 goodness of fit test and samples were considered as deviant from HWE at a significance level of $P < 0.05$.

For genetic association, we calculated odds ratio (OR) and 95% confidence interval (CI) by Fisher’s exact test using Baptista-Pike method for OR, respectively. Where zero counts caused problems with computation of the OR, Haldane-Anscombe correction was performed by adding 0.5 to all cells. *P*-values are reported two-sided and values of <0.05 were considered significant. Multivariable analysis was performed to estimate independency of the variables age, sex and *IFITM3* rs12252 or *IFITM3* rs34481144 genotypes by logistic regression (likelihood ratio test, backwards).

3. Results

From March 11, 2020, to October 31, 2020, we enrolled and studied 239 SARS-CoV-2-positive and 253 SARS-CoV-2-negative patients to determine the associations of the SNPs rs12252 and rs34481144 in the gene *IFTIM3* with susceptibility to SARS-CoV-2 infection and severity of COVID-19. The characteristics and genotypes of SARS-CoV-2-positive and -negative patients are summarized in Table 1. Distribution of sex ($P = 0.86$) and age ($P = 0.10$) was similar in both groups.

Table 1
Demographics, *IFITM3* genotypes and outcome of the SARS-CoV-2-positive and SARS-CoV-2-negative patients.

	SARS-CoV-2-positive (N = 239)	SARS-CoV-2-negative (N = 253)	Moderate COVID-19 (N = 164)	Serious COVID-19 (N = 75)
Median age (range) – yrs.	59.0 (18–99)	63.0 (22–97)	57.0 (18–94)	64 (26–99)
Male sex – no. (%)	141 (59.0)	147 (58.1)	86 (52.4)	55 (73.3)
***IFITM3* rs12252 T/C**				
TT	215 (90.0)	234 (92.5)	147 (89.6)	68 (90.7)
TC	22 (9.2)	19 (7.5)	15 (9.2)	7 (9.3)
CC	2 (0.8)	0 (0.0)	2 (1.2)	0 (0.0)
Minor allele frequency (C)	0.05	0.04	0.06	0.05
TC + CC vs TT	OR: 1.37, 95% CI [0.73–2.58], $P = 0.34$		OR: 0.89, 95% CI [0.35–2.25], $P = 1.00$	
C vs T	OR: 1.73, 95% CI [0.77–3.89], $P = 0.23$		OR: 0.86, 95 %CI [0.26–2.84], $P = 1.00$	
***IFITM3* rs34481144 G/A**				
GG	73 (30.5)	75 (29.6)	56 (34.2)	17 (22.7)
GA	120 (50.2)	128 (50.6)	74 (45.1)	46 (61.3)
AA	46 (19.3)	50 (19.8)	34 (20.7)	12 (16.0)
Minor allele frequency (A)	0.44	0.45	0.43	0.47
AA + GA vs GG	OR: 0.96, 95% CI [0.65–1.41], $P = 0.84$		OR: 1.77, 95% CI [0.94–3.32], $P = 0.10$	
A vs G	OR: 0.97, 95% CI [0.68–1.39], $P = 0.93$		OR: 1.15, 95% CI [0.66–1.98], $P = 0.67$	

Clinical outcome was defined as follows according to the criteria of the ECDC [12] – 'moderate': outpatients and hospitalized patients; 'serious': hospitalized patients admitted to an intensive care unit and/or became dependent on mechanical ventilation and all cases of COVID-19-related deaths during the hospital stay.
Abbreviations: YRS = Years; OR = Odds ratio; CI = Confidence interval; $P = P$-value as calculated for estimation of significant associations ($P < 0.05$) of *IFITM3* genotypes and SARS-CoV-2 infection risk or COVID-19 severity.

Genotypes for *IFITM3* rs12252 were compatible with HWE ($P = 0.10$ and $P = 0.53$, respectively). The MAF of the C-allele in SARS-CoV-2-positive patients (0.05) was similar to the MAF in SARS-CoV-2-negative patients (0.04). We did not observe an association for an increased SARS-CoV-2 infection risk for C-allele carriers (Table 1). Interestingly, we found CC genotype carriers only within the group of SARS-CoV-2 infected patients (N = 2). Comparing patients with 'moderate' COVID-19 to those with 'serious' COVID-19, we also observed no differences in genotype or allele frequency distribution.

The observed genotype frequencies for *IFITM3* rs34481144 were also consistent with HWE ($P = 0.79$ and $P = 0.73$) in SARS-CoV-2-positive and -negative patients. The presence of the A-allele did not correlate with an increased SARS-CoV-2 infection risk or severity of COVID-19 (Table 1). Interestingly, we observed a non-significant higher frequency of the rs34481144 A-allele in the patients with 'serious' COVID-19 (OR: 1.77, 95% CI: 0.94–3.32, $P = 0.10$).

In a multivariable analysis male sex was the only independent predictor for severity of COVID-19 (OR: 2.52, 95% CI: 1.38–4.60, $P = 0.003$). *IFITM3* rs34481144 A-allele showed a trend ($P = 0.07$) for an increased risk of severity of COVID-19 (OR: 1.81, 95% CI: 0.95–3.43).

4. Discussion

Although an association of *IFITM3* rs12252 with SARS-CoV-2 infection risk seems reasonable, C-allele frequency and incidence of the CC genotype was quite low in both SARS-CoV-2-positive and -negative patients of our cohort. Thus, we did not observe a significant effect on infection risk or COVID-19 severity. Nevertheless, we observed the putative deleterious CC genotype only in SARS-CoV-2-positive patients (N = 2). Additional studies are needed to clarify the influence of the rs12252 CC genotype on SARS-CoV-2 infection risk or whether this observation was accidental. Our observed genotype frequencies fit very well to those reported by Gómez and colleagues even though we could not reproduce their significant findings [7]. In the latter study SARS-CoV-2-positive patients were compared to a Spanish control group, from whom samples were collected before the pandemic. In our study we compared samples from patients tested for SARS-CoV-2 as positive or negative by RT-PCR. These two studies do not compare well because of the different composition of the cohorts. Further studies with larger cohorts are needed to clarify the role of *IFITM3* rs12252 in SARS-CoV-2 infection.

The minor allele frequency of the C-allele is considerably higher in East Asians and effects may be more pronounced. Zhang *et al.* observed an up to 6.37-fold increased risk for C-allele carriers to develop severe COVID-19 (MAF 0.30 vs 0.50, $P = 0.0093$) in their preliminary study with Chinese patients [13]. This study included only 80 patients with COVID-19 and the significant observations may, therefore, be fortuitous. Hence the effect of rs12252 on COVID-19 severity needs to be validated in larger cohorts and different ethnicities.

This is the first study analyzing the role of the SNP rs34481144 in the gene *IFITM3* in SARS-CoV-2 infection in a case-control study in Caucasians. An association of this polymorphism with COVID-19 seems plausible based on its association with decreased antiviral defense in other viral diseases [9]. Also some *in silico* studies provided evidence that this polymorphism might be involved in SARS-CoV-2 infection [4,14,15]. Nonetheless, we did not observe a different distribution of rs34481144 alleles or genotypes in SARS-CoV-2-positive compared to SARS-CoV-2-negative patients. The variant was also not associated with course and outcome of COVID-19. It would be interesting to know if rs34481144 might represent a marker for the course of COVID-19 since we observed a non-significant higher A-allele frequency in the patients with 'serious' COVID-19.

In conclusion, we could neither find an association for *IFITIM3* rs12252 nor rs34481144 with SARS-CoV-2 infection susceptibility or COVID-19 severity in a German cohort. Our findings cannot be transferred to populations with different ethnicities. Therefore, the role of variants in the gene *IFITM3* in SARS-CoV-2 infections still needs to be elucidated in larger cohorts encompassing various ethnicities.

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CRediT authorship contribution statement

Kristina Schönfelder: Resources, Methodology, Data curation, Formal analysis, Validation, Writing - review & editing. **Katharina Breuckmann:** Data curation, Investigation. **Carina Elsner:** Resources, Investigation. **Ulf Dittmer:** Investigation. **David Fistera:** Investigation. **Frank Herbstreit:** Investigation. **Joachim Risse:** Investigation. **Karsten Schmidt:** Investigation. **Sivagurunathan Sutharsan:** Investigation. **Christian Taube:** Investigation. **Karl-Heinz Jöckel:** Investigation, Validation. **Winfried Siffert:** Conceptualization, Validation, Supervision, Writing - review & editing. **Andreas Kribben:** Conceptualization, Validation, Supervision, Writing - review & editing. **Birte Möhlendick:** Conceptualization, Resources, Methodology, Formal analysis, Investigation, Supervision, Data curation, Funding acquisition, Project administration, Visualization, Writing - original draft, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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