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ORIGINAL ARTICLE

Genetic polymorphism between the Sorani and Hawrami kurdish populations and COVID-19 outcome

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Abstract

Background Coronavirus Disease 2019 (COVID-19) is a global pandemic, and mortality and clinical consequences vary across countries. One of the factors influencing COVID-19 outcomes is genetic polymorphism. Two Kurdish populations, Sorani and Hawrami, live in the Sulaimani province of the Kurdistan Region of Iraq. It seems Hawrami had a milder COVID-19 outcome. According to previous research conducted on various ethnic groups across the globe, single nucleotide polymorphisms (SNPs) in the interferon-induced transmembrane protein 3 (IFITM3) and interluken-6 (IL6) genes were associated with the severity of COVID-19 in those populations.

Methods and results We hypothesized that Hawrami may have protective SNPs. So, in this study, we used DNA sequencing to genotype three IFITM3 SNPs and nine IL6 SNPs by DNA sequencing to investigate the association of Sorani and Hawrami population polymorphisms. Genotype AA for the rs12252 SNP in IFITM3 was insignificantly more common in the Sorani group (54% vs. 44%). The Hawrami population showed a higher percentage of the CC genotype of the rs34481144 SNP in the IFITM3 gene (62% vs. 44.3%) and a higher proportion of the non-risky GG genotype of the rs1800795 SNP in the IL6 gene (53.4 vs. 43.3); however, the SNPs were insignificantly associated between the two populations.

Conclusions IFITM3 and IL6 SNPs have no statistically significant association between the two Kurdish populations. The decreased proportion of non-risk alleles at rs34481144 and rs1800795 in the Hawrami population may partially support the research hypothesis. However, contrary to our hypothesis, the Sorani group had an insignificantly higher protective variant of the rs12252 SNP.

Keywords IL6 · IFITM3 · SNP · COVID-19 · Kurd

Introduction

Coronavirus Disease 2019 (COVID-19) is a worldwide pandemic with a high mortality rate. It is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1, 2]. Patients infected with SARS-CoV-2 exhibit a broad variety of symptoms and disease progressions that are not solely due to their age or other health issues. Because of the wide spectrum of intensity in clinical manifestations, host genetics are likely to have a significant effect on COVID-19 vulnerability and severity [3–6].

Extensive research has been conducted on the role of host genetic factors in COVID-19 development, and these investigations have identified several gene susceptibility variations, although with various degrees of evidence [7]. The most studied candidate gene polymorphisms for the impact of COVID-19 are interferon-induced transmembrane 3 (IFITM3) and interleukin-6 (IL6) [8–10].The IFITM3 protein is essential for adaptive and innate immunity [10]. IFITM3 is expressed in the membranes of the lysosome and endosome and inhibits the enveloped virus from fusing with the membranes of the host. Prior studies on IFITM3 single nucleotide polymorphisms (SNPs) have shown that some alleles may be risk factors that affect the severity of viral infections, such as SARS-CoV-2 [11, 12].

Interleukin 6 (IL6) is a multifaceted cytokine, with both pro-inflammatory and anti-inflammatory properties.

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It is highly involved in the immune system's cytokine cascade, and plays a vital role in mounting an immunological response [13]. The IL6 gene is located on chromosome 7 in the 7p21 region. The expression of IL6 is regulated mainly by the 5-prime region of the gene. This region is known to contain multiple single nucleotide polymorphisms (SNPs) that affect the promoter and transcription regions of the IL6 [14]. The most extensively studied SNP was rs1800795 (-147 G/C), which affects IL6 protein levels. The candidate SNP may influence the intensity of inflammatory, autoimmune, and infectious illnesses [15, 16]. Several studies tried to investigate the effect of these SNPs on the IL6 and IFITM3 genes, but the findings were inconclusive [10, 17, 18]. This inconsistency is attributable to ethnic variations and group genetic diversity [19].

Kurds are the world's largest nation without an independent state, and they inhabit the region of Kurdistan, which is partitioned among four countries [14]. Sulaimani Province in Kurdistan Region of Iraq is home to a large Kurdish Sorani population and a smaller Kurdish Hawrami population. During the COVID-19 pandemic, there were some non-official indications and beliefs among medical staff that the proportion of mortality and COVID-19 severity were lower among the Hawrami population. Therefore, we hypothesised that the Hawrami population might have a different polymorphism in the IFITM3 and IL6 genes compared to the Kurdish Sorani population; thus, this study was conducted on a group from both populations to determine the potential cause of the mild outcome of COVID-19 in the Hawrami Kurdish population.

Materials and methods

Study participants and sampling

In this research, nasopharyngeal swab samples were taken from 98 Kurdish Sorani population members in Sulaimani province, KRG, Iraq. Another 48 samples were taken from the Kurdish Hawrami population. The donors were all unvaccinated, and their ages ranged from 20 to 60. The nasopharyngeal swabs were stored in viral transport medium (VTM) at -70 °C in the COVID-19 molecular diagnostic laboratory of Shahid Tahir.

Amplification of IFITM3 and IL6 gene

The VTM samples were subjected to DNA extraction using an addbio genomic DNA extraction kit according to the manufacturer's instructions (addbio, South Korea). The PCR amplification reaction was done according to the manufacturer's instructions using the Add Star Taq master mix PCR kit (addbio, Korea). In brief, the PCR reaction was done by mixing 10 µL of master mix, 5.0 µL of DNA sample, 3 µL of DEPC-H2O, and 1 µL of 10 pmol from each of the forward primer and reverse primer (Table S1). The thermocycler (Bio-Rad, USA) was set up for an initial denaturation phase of 5 min at 95 °C, followed by 40 cycles of denaturation at 94 °C for 30 s, annealing at 59 °C for 30 s, extension at 72 °C for 45 s, and a final extension phase of 3 min at 72 °C. Loading 4.0 L of PCR product on a 1% agarose gel in 1 TBE buffer was used to examine the PCR products. The gel was stained with 7 µL safe gel dye (addbio, Korea). Electrophoresis was run at 120 volts for an hour on the electrophoresis system. The 100 bp DNA ladder is used to show the migration pattern of the PCR amplicons.

Sequencing and genotyping

The PCR products were purified according to the manufacturer's instructions using the addPrep PCR Purification Kit (addbio, South Korea). The samples were subsequently sequenced using the Sanger technique at a South Korean Macrogen sequencing facility. Using forward and reverse primers, the identification of each nucleotide sequence was validated (Table S1). FinchTV was used to evaluate and analyze the DNA sequence quality. High single-base peaks with high Phred quality scores were identified as homozygote SNPs, whereas overlapping peaks of two nucleotide bases with lower Phred quality scores were identified as heterozygote SNPs. The DNA plus strand was used to identify all SNPs in this investigation (cDNA strands). For the rs1800795 SNP, for instance, guanine (G) is the major frequency allele and cytosine (C) is the minor frequency allele, and so on for other SNPs.

Statistical examination

Hardy-Weinberg equilibrium was computed using the database at wpcalc.com (https://wpcalc.com/en/equilibrium-hardy-weinberg/). Allele frequency, genotype distribution, and haplotype analyses were performed using the SHEsis online database (http://analysis.bio-x.cn/myAnalysis.php) [20]. Version 25.0 of the Statistical Package for the Social Sciences was used for statistical analysis (SPSS, Chicago, IL). The chi-square test was performed to analyze the association between SNP, genotype, and allele in the Sorani and Hawrami groups. The odds ratios (OR) and 95% confidence intervals (CI) were analyzed using logistic regression to assess the role, degree of relationship, and risk of the variations in both groups.

Results

This study was conducted to compare the IFITM3 and IL6 polymorphisms of the Sorani and Hawrami Kurdish groups. Twelve SNPs were genotyped, including two synonymous SNPs (rs12252 c.42 A>G (S14S) and rs11553885, c.165G>A (P55P) and one SNP from the IFITM3 core promoter region near the transcription start point, c. -23 C>T (rs34481144). (Fig. 1A). As well as two missense SNPs in IL6, rs2069830 c.94 C>T (P32S), and rs142759801, c.91 C>A (P30T). These two SNPs also overlapped with the intron of IL6-AS1, an antisense long non-coding RNA (lncRNA) (Fig. 1B). The rs2069857 c.-48 variant is also found in the intron of the IL6-AS1 overlap sequence and the prime untranslated region of IL6. The remaining six SNPs were in the IL6 promoter region near the transcription start point and overlapped with the intron of IL6-AS1. These include the following variants: -190 C>T (rs2069829), -176 G>C (rs2234683), -174 G>C (rs1800795), -111 G>T (rs13447446), and c. -85 T>C (rs527770772), -63 C>G (rs13447445). All SNPs were found to be in Hardy-Weinberg equilibrium. (Table 1) provides a summary of the SNP genotyping results.

The frequency of the AA genotype for the rs12252 SNP of IFITM3 was greater in the Sorani group than in the Hawrami group. Nevertheless, the chi-square test revealed no statistically significant association between the Sorani and Hawrami groups ($chi^2 = 1.346$, P = 0.245). The statistical analysis of logistic regression was used to figure out the role and strength of the association between the variants. It showed that there was no significant difference between the Sorani and Hawrami groups for rs12252, with P = 0.310 and odds ratios of 0.671. (Fig. 2A). The genotype combinations of the (AG + GG vs. AA) dominant model were also evaluated using MedCalc biostatistical analysis, which demonstrated a statistically non-significant difference (P = 0.000, OR = 5.212) between the two groups. In this research, the frequency of alleles was also analyzed, and the miner (G) allele was shown to be non-significantly more abundant in the Sorani group (P = 0.341, OR = 1.304). (Table 1). In IFITM3 rs34481144, the Hawrami group had a greater frequency of the CC genotype, while the Sorani group had a higher frequency of the TT genotype, but there was no statistical significance (Fig. 2B).

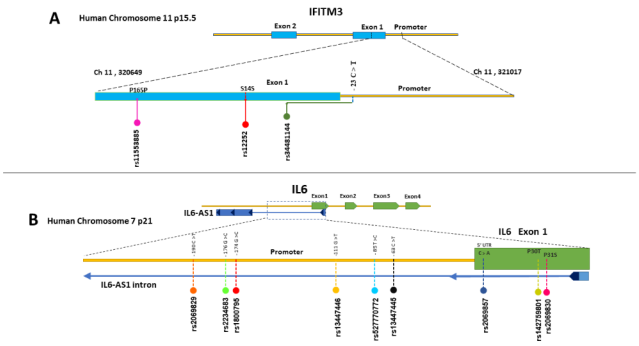

Fig. 1 SNPs representation of the IFTIM3 and IL6 gene (**A**) A cartoon representation of the seven SNPs in the IFTIM3 gene (**B**) A cartoon representation of the seven SNPs in the IL6 gene

The Hawrami group exhibited a greater proportion of GG genotypes for the rs1800795 SNP on the IL6 gene, while the Sorani group had a higher proportion of CC genotypes (Fig. 1C). Chi-square analysis showed that rs1800795 didn't have a statistically significant link to either group (Table 1). To investigate the role and degree of association between the variants, a logistic regression analysis was done. According to the data, the odds ratios were not significant. MedCalc biostatistical analysis was also performed on the genotype combinations of the dominant model (CG + CC vs. GG); the findings were (P = 0.25, OR = 0.718). This indicates that, compared to the GC and CC genotypes, the dominant model of the GG genotype was 0.718 times more common in the Hawrami population. Statistically, this increase in frequency is insignificant.

All patients in both groups were homozygous for the following main alleles: rs11553885 (G), rs2069830 (C), rs142759801 (C), rs2069857 (C), rs2069829 (G), rs2234683 (G), rs13447446 (T), rs527770772 (C), and rs13447445 (C). Because there was no polymorphism in these nucleotides in both groups of the Kurdish population, statistical analysis was not applicable (Table 1).

In this study, haplotype analyses were conducted for all SNPs to identify possible significant haplotypes. As a result, the SHEsis database demonstrated five haplotypes (Table 2S2). No haplotypes had a statistically significant prevalence in either group.

Discussions

IFITM3 has been shown to inhibit many pathogenic viruses from the orthomyxovirus, flavivirus, filovirus, and coronavirus families [21–23]. Spike proteins from various coronaviruses, including SARS-Co-2, use distinct methods to infiltrate cells. Polymorphisms in the IFITM3 genes are thought to affect the positioning of IFTIMs in the plasma membrane, which impacts vulnerability to viral infection [19, 21, 22].

The IL6 gene encodes interleukin-6, a protein with both anti- and pro-inflammatory characteristics. According to epidemiological and DNA polymorphism studies, chronic obstructive pulmonary disease and asthma have different degrees of symptoms across individuals [24]. Certain viral diseases have been related to IL6 polymorphisms, including hepatitis B and hepatitis C virus (HCV), as well as

Table 1 The genotyping results of IFITM3 and IL6 SNPs between Sorani and Hawrami populations

SNP	Hawrami Numb (%)	Sorani Number (%)	Ch^2	P value	OR	P value	(95% CI)
AA	22 (44%)	53 (54%)	1.346	0.245	Reference		
AG	28 (56 %)	45 (56%)			0.671	0.310	0.311–1.448
GG	0 (0%)	0 (0%)			0	0	0
A Frequency	72 (0.72)	151 (0.72)					
G Frequency	28 (0.28)	45 (0.29)					
AG + GG vs AA Dominant					1.2273	0.46	0.7125–2.1139
G vs A			0.905	0.341	1.304		0.753–2.259
rs34481144							
CC	31 (62%)	43 (44.3%)	4.6	0.1	Reference		
CT	16 (32%)	41 (42.2%)			0.059	7.965	0.959–66.138
TT	3 (6%)	13 (13.4%)			0.249	1.602	0.719–3.569
C Frequency	78 (0.78)	127 (0.654)					
T Frequency	22 (0.22)	67 (0.345)					
AG + GG vs AA Dominant					0.6909	0.217	0.3838–1.2437
G vs A			4.912	0.06	0.534		0.305–0.934
Rs1800795							
GG	23 (53.4%)	39 (43.3%)	3.156	0.206	Reference		
GC	20 (46.5%)	64 (51%)			0.999	0	0
CC	0 (0%)	5 (5%)			0.338	1.453	0.677–3.121
G Frequency	0.642	0.734					
C Frequency	0.357	0.265					
GC + CC vs GG Dominant					0.7182	0.25	0.4082–1.2638
G vs C			1.759	0.184	1.538	0.67	0.37–1.212
rs2069829							
CC	%100	%100			Reference		
rs2234683							
GG	%100	%100			Reference		
rs13447446							
GG	%100	%100					
rs13447445							
CC	%100	%100			Reference		
rs527770772							
TT	%100	%100			Reference		
rs2069857							
CC	%100	%100			Reference		
rs142759801							
CC	%100	%100			Reference		
rs2069830							
CC	%100	%100			Reference		
Rs11553885							
GG	%100	%100			Reference		

influenza and coronaviruses [25–29]. Several investigations have linked polymorphisms in the IL6 gene promoter area to inflammation [15, 30]. Because IL6 is important in the regulation of CD4-T cells, studying SNPs in IL6 may provide insight into the genesis and development of COVID-19 [31].

This study looked at three SNPs in the IFITM3 gene and nine SNPs in the IL6 gene to see if there was a link between these genetic differences and the Sorani and Hawrami groups of Kurds. The goal was to find out why the Hawrami Kurds have a milder reaction to COVID-19.

We hypothesized that the Hawrami population would have a distinct allele as compared to the Kurdish Sorani population in the IFITM3 and IL6 gene because of the reduction in mortality and intensive care unit admissions that we observed in the Hawrami population in relation to COVID-19.

Both the A and G alleles can be found at the IFITM3 rs12252 locus, but the G allele is a minor variant found with

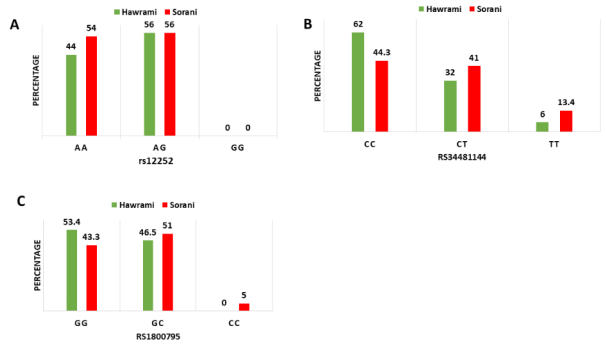

Fig. 2 Overview of genotypes of IFITM3 and IL6 SNPs between the Sorani Kurdish group and Hawrami Kurdish group. (**A**) rs12252 SNP graph shows non-significant association of AA genotype with Hawrami population. (**B**) rs34481144 SNP graph, the percentage of the CC homozygote is more prevalent in Hawrami population. (**C**) Graph of Rs1800795 genotype analysis shows a non-significant association with the Hawrami and Sorani groups, with higher percentage of GG genotype in Hawrami population

much greater frequency among East Asians. This suggests that the consequences of the G allele may be more prominent in the East Asian population (Table S3) [32]. Initial research conducted by Zhang et al. on Chinese patients indicated that those who had the G allele were up to 6.37 times more likely to have severe COVID-19 [33]. A study on Arab ethnicity in Saudi Arabia found that COVID-19 patients with the G allele of rs12252 in IFITM3 had a higher risk of hospitalization and death [11]. However, in our study, there was no discernible difference in the frequency of the G allele in either Kurdish group, and there were also no homozygous GG genotypes. Research on the Iranian population reveals that the AA genotype of rs12252 IFITM3 could aid in the recovery of Iranian patients with COVID-19 [34]. In the current study, the percentage of AA genotype was higher in the Sorani group, which is not consistent with our hypothesis. Despite that, German cohort research could not verify the association between rs12252 IFITM3 polymorphisms and COVID-19 severity [9].

One SNP in the IFITM3 promoter is rs34481144 (Fig. 1A). Reduction of IFITM3 expression, caused by the substitution of the minor T allele for the dominant C allele in rs34481144, which subsequently associates with a decrease in antiviral CD8 + T cells in influenza-infected lung tissue [35]. In this research, a higher rate of risk T alleles was observed in Sorani groups (Table 1). This association, however, was not statistically significant. A meta-analysis of the research demonstrated that there was no statistical association between the rs34481144 gene polymorphism and COVID-19 susceptibility or severity in allele, genotype, and dominant genetic model [36]. However, other research has revealed a link between rs34481144 and a higher likelihood of SARS-CoV-2 hospitalization [10, 18].

Extensive research has been conducted on the rs1800795 SNP of the IL6 promoter gene for a several illnesses across a wide range of ethnic groups and populations in the world; however, the association of the SNP remains contentious due to differences in the pathological condition states and genetic variability among the population. Based on what we found, the GG genotype of the rs1800795 SNP was more common in the Hawrami group, but this was not a statistically significant difference (Fig. 1C). Our results are in line with research in the Kurdish population in Iran, where a correlation between the GG genotype and mild COVID-19 was shown to be statistically insignificant [8]. Furthermore, the GG genotype in the Egyptian community was found to be protective against acute respiratory failure and ICU admittance [37]. Researchers found no statistically significant correlation between the C minor allele of rs1800795 and mortality in the COVID-19 population [38], the later study again support the hypothesis of current research; in which there was no CC genotype identified in the Hawrami population. On the other hand, in the Turkish population, the IL6 rs1800795 polymorphism, GG genotype¸ was found to be significantly linked to the risk of severe COVID-19, which is different from what we found in the Hawrami population [39].

In this investigation, all nine additional SNPs were monomorphic in either Kurdish population; all possessed the dominant allele: rs2069830 (C), rs142759801 (C), rs2069857 (C), rs2069829 (G), rs2234683 (G), rs13447446 (T), rs527770772 (C), and rs13447445 (C). Similar findings were seen in cohort studies on IL6 polymorphism, where alleles for rs13447445, rs2069829, and rs13447446 were monomorphic in Caucasian Americans [40]. One of the limitations of this study is the small sample sizes in both the Hawrami and Sorani Kurdish groups. More research is needed to fully characterize the majority of Iraq's populations and ethnic groups, as well as to look into a broader range of host genetic polymorphisms that may affect the severity of COVID-19.

Conclusion

The current study was carried out in response to earlier work that recommended doing host genetic analysis on IFITM3 and IL6 promoter polymorphisms in various countries and ethnicities to investigate the influence of the SNPs on the COVID-19 outcome. This study demonstrated that the studied SNPs of IFITM3 and IL6 were statistically not associated with the Hawrami and Sorani populations at the genotype level. However, a lower frequency of miner-risk alleles in rs34481144 of IFITM3 and rs1800795 of IL6 in

the Hawrami population may support to some extent the hypothesis of the study.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11033-023-08448-8.

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Author contributions PMAR performed the lab work. All authors equally participated in writing, reviewing, and data analysis of the manuscript.

Data availability The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of interest The authors declare no conflict of interest.

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.

Ethic approval In this study, all methods were carried out in accordance with the relevant institutional and national guidelines and regulations. Additionally, we vouch for the Ethics Licensing Committee of the Health Directorate's approval for all experimental protocols (No. 8375 on May 20, 2021). We received verbal consent from an illiterate individual to utilize their samples that had previously been taken from them for diagnostic purposes.

References

1. Zhu N et al (2020) A novel coronavirus from patients with pneumonia in China, 2019. New England journal of medicine
2. Ali AM et al (2022) Disease severity and efficacy of homologous vaccination among patients infected with SARS-CoV-2 Delta or Omicron VOCs, compared to unvaccinated using main biomarkers. J Med Virol 94(12):5867–5876
3. Ovsyannikova IG et al (2020) The role of host genetics in the immune response to SARS-CoV-2 and COVID-19 susceptibility and severity. Immunol Rev 296(1):205–219
4. Rashid P, Salih GF (2022) Molecular and computational analysis of spike protein of newly emerged omicron variant in comparison to the delta variant of SARS-CoV-2 in Iraq. Mol Biol Rep 49(8):7437–7445
5. Abdullah HM et al (2020) Severe refractory COVID-19 patients responding to convalescent plasma; a case series. Annals of medicine and surgery 56:125–127
6. Ali HN et al (2022) Clinical laboratory parameters and comorbidities associated with severity of coronavirus disease 2019 (COVID-19) in Kurdistan Region of Iraq. Practical Lab Med 31:e00294
7. Velavan TP et al (2021) Host genetic factors determining COVID-19 susceptibility and severity. EBioMedicine 72:103629
8. Falahi S et al (2022) Evaluation of the relationship between IL-6 gene single nucleotide polymorphisms and the severity of COVID-19 in an iranian population. Cytokine 154:155889
9. Schönfelder K et al (2021) The influence of IFITM3 polymorphisms on susceptibility to SARS-CoV-2 infection and severity of COVID-19. Cytokine 142:155492
10. Cuesta-Llavona E et al (2021) Association between the interferon-induced transmembrane protein 3 gene (IFITM3) rs34481144/rs12252 haplotypes and COVID-19. Curr Res Virological Sci 2:100016
11. Alghamdi J et al (2021) Interferon-induced transmembrane protein-3 genetic variant rs12252 is associated with COVID-19 mortality. Genomics 113(4):1733–1741
12. Everitt AR et al (2012) IFITM3 restricts the morbidity and mortality associated with influenza. Nature 484(7395):519–523
13. Choy EH et al (2020) Translating IL-6 biology into effective treatments. Nat Rev Rheumatol 16(6):335–345
14. Matsusaka T et al (1993) Transcription factors NF-IL6 and NF-kappa B synergistically activate transcription of the inflammatory cytokines, interleukin 6 and interleukin 8. Proc Natl Acad Sci 90(21):10193–10197
15. Sghaier I et al (2017) Genetic variants in IL-6 and IL-10 genes and susceptibility to hepatocellular carcinoma in HCV infected patients. Cytokine 89:62–67
16. Fujino M et al (2021) The value of Interleukin-6 among several inflammatory markers as a predictor of respiratory failure in COVID-19 patients. Diagnostics 11(8):1327
17. Fife M et al (2005) Novel IL-6 haplotypes and disease association. Genes & Immunity 6(4):367–370
18. Nikoloudis D, Kountouras D, Hiona A (2020) The frequency of combined IFITM3 haplotype involving the reference alleles of both rs12252 and rs34481144 is in line with COVID-19 standardized mortality ratio of ethnic groups in England. PeerJ 8:e10402
19. Zhao X et al (2018) Identification of residues controlling restriction versus enhancing activities of IFITM proteins on entry of human coronaviruses. J Virol 92(6):e01535–e01517
20. Shen J et al (2016) SHEsisPlus, a toolset for genetic studies on polyploid species. Sci Rep 6(1):1–10
21. Brass AL et al (2009) The IFITM proteins mediate cellular resistance to influenza A H1N1 virus, West Nile virus, and dengue virus. Cell 139(7):1243–1254
22. Wrensch F, Winkler M, Pöhlmann S (2014) IFITM proteins inhibit entry driven by the MERS-coronavirus spike protein: evidence for cholesterol-independent mechanisms. Viruses 6(9):3683–3698
23. Perreira JM et al (2013) IFITMs restrict the replication of multiple pathogenic viruses. J Mol Biol 425(24):4937–4955
24. Jin P, Wang E (2003) Polymorphism in clinical immunology–from HLA typing to immunogenetic profiling. J translational Med 1(1):1–11
25. Linnik JE, Egli A (2016) Impact of host genetic polymorphisms on vaccine induced antibody response. Hum vaccines immunotherapeutics 12(4):907–915
26. Riazalhosseini B et al (2018) Interleukin-6 gene variants are associated with reduced risk of chronicity in hepatitis B virus infection in a malaysian population. Biomedical Rep 9(3):213–220
27. Barrett D (2019) *IL-6 blockade in cytokine storm syndromes*, in *Cytokine storm syndrome*. Springer, pp 561–568
28. Gupta KK, Khan MA, Singh SK (2020) Constitutive inflammatory cytokine storm: a major threat to human health. J Interferon Cytokine Res 40(1):19–23
29. Channappanavar R, Perlman S (2017) *Pathogenic human coronavirus infections: causes and consequences of cytokine storm and immunopathology*. In *seminars in immunopathology*. Springer
30. Foster CB et al (2000) An IL6 promoter polymorphism is associated with a lifetime risk of development of Kaposi sarcoma in

men infected with human immunodeficiency virus. Blood The Journal of the American Society of Hematology 96(7):2562–2567
31. Kirtipal N, Bharadwaj S (2021) Interleukin 6 polymorphisms as an indicator of COVID-19 severity in humans. J Biomol Struct Dynamics 39(12):4563–4565
32. Phan L et al *ALFA: Allele Frequency Aggregator: National Center for Biotechnology Information, US National Library of Medicine; 2020 [10 Mar]*
33. Zhang Y et al (2020) Interferon-induced transmembrane protein 3 genetic variant rs12252-C associated with disease severity in coronavirus disease 2019. J Infect Dis 222(1):34–37
34. Ahmadi I et al (2022) Impact of interferon-induced transmembrane protein 3 gene rs12252 polymorphism on COVID-19 mortality. Cytokine 157:155957
35. Allen EK et al (2017) SNP-mediated disruption of CTCF binding at the IFITM3 promoter is associated with risk of severe influenza in humans. Nat Med 23(8):975–983
36. Li Y et al (2022) *Interferon-induced transmembrane protein 3 gene polymorphisms are associated with COVID-19 susceptibility and severity: a meta-analysis*.Journal of Infection,
37. Zidan HE, Elbehedy RM, Azab SF (2014) IL6-174 G/C gene polymorphism and its relation to serum IL6 in egyptian children with community-acquired pneumonia. Cytokine 67(2):60–64
38. Smieszek SP et al (2021) Assessing the potential correlation of polymorphisms in the IL6R with relative IL6 elevation in severely ill COVID-19 patients'. Cytokine 148:155662
39. Kerget F, Kerget B (2021) Frequency of interleukin-6 rs1800795 (-174G/C) and rs1800797 (-597G/A) polymorphisms in COVID-19 patients in Turkey who develop macrophage activation syndrome. Jpn J Infect Dis 74:543–548
40. Yee LJ et al (2009) Interleukin-6 haplotypes and the response to therapy of chronic hepatitis C virus infection. Genes & Immunity 10(4):365–372