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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

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Abstract

Evidence was recently brought forward in England and the USA that Black, Asian, Latinos and Minority Ethnic people present higher mortality risk from COVID-19 than White people. While socioeconomic factors were suggested to contribute to this trend, they arguably do not explain the range of the differences observed, allowing for possible genetic implications. Almost concurrently, the analysis of a cohort in Chinese COVID-19 patients proposed an association between the severity of the disease and the presence of the minor allele of rs12252 of the IFITM3 gene. This SNP, together with rs34481144, are the two most studied polymorphisms of IFITM3 and have been associated in the past with increased severity in Influenza, Dengue, Ebola, and HIV viruses. Interferon-induced transmembrane protein 3 is an immune effector protein that is pivotal for the restriction of viral replication, but also for the regulation of cytokine production. Following up to these two developments in the SARS-CoV-2 pandemic, the present study investigates a possible connection between differences in mortality of ethnic groups in England and the haplotypes of rs12252 and rs34481144. The respective allele frequencies were collected for all 1000 Genomes Project's populations and subgroups were pooled wherever possible to create correspondences with ethnic groups in England. A strong correlation was observed between the reported Standardized Mortality Ratios and the frequency of the combined haplotype of both reference alleles. If confirmed clinically, this finding could be pointing at possible hijacking of IFITM3 by SARS-CoV-2 virus and is expected to impact our understanding of the disease mechanisms behind COVID-19.

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Introduction

Very recent, emerging scientific evidence from international (Kirby, 2020) and UK (Aldridge et al., 2020) COVID -19 patient reports and death records, indicate a disproportionate effect of the novel coronavirus on ethnic minorities. According to CDC (CDC, 2020), Black, Asian and Minority Ethnic (BAME) people are at higher risk of death from COVID-19. Importantly, an Indirect Standarization of NHS mortality data in England (Aldridge et al., 2020), revealed that the adjusted for age and region Standardized Mortality Ratios (SMRs), were highest in Black African, Black Caribbean, Pakistani, Bangladeshi, and Indian minority ethnic groups. On the contrary, White Irish and White British ethnic groups exhibited a significantly lower risk of death. Similarly, in the USA (Garg et al., 2020), preliminary data compiled from hospitals in 14 US states, confirmed the UK study outcomes, showing that African Americans are also disproportionately affected by COVID-19. Specifically, African Americans represented 33% of COVID-19 hospitalizations, despite only making up 18% of the total population studied. In a subsequent analysis, among COVID-19 deaths in New York City, for which race and ethnicity data were available, death rates from COVID-19 among black or African Americans and Hispanic or Latinos were substantially higher than that of white or Asian people (Garg et al., 2020).

Several reasons have been proposed to explain these ethnic discrepancies in COVID-19 mortality risk arising from these preliminary studies. Chronic pre-existing conditions, such as CVD, diabetes, hypertension, obesity, etc. are more common in minorities compared to Caucasian populations and have all been associated with adverse outcomes in COVID-19 (Centers for Disease Control and Prevention, 2020; Kirby, 2020). However, race disparities in those diseases are not large enough to fully explain the COVID-19 death disparity (Aldridge et al., 2020). Factors such as housing and living conditions, use of public transportation, occupation-related differences that prohibit the work from home, or the lack of regular access to primary health, may have all played an important role in producing disproportionate death rates among BAME groups (Aldridge et al., 2020; Kirby, 2020; Niedzwiedz et al., 2020; Khunti et al., 2020). Nevertheless, it is evident that inequalities in socioeconomic status parameters do not seem to adequately explain the range

of differences, and in some instances, the extreme variations observed among ethnic minorities in mortality rates from COVID-19 infection (Kirby, 2020).

As the importance of genetic imprinting and the role of genetic variants (SNPs) in the modulation of individual susceptibility to, and severity of infectious diseases has been well established (Chapman et al., 2012; Zhao et al, 2018), we turned our focus into two very highly studied polymorphisms of the interferon-induced transmembrane protein 3 (IFITM3) gene: rs12252 and rs34481144. IFITM3 encodes an immune effector protein that is pivotal for restriction of viral replication (Brass et al., 2009) of many enveloped RNA viruses including HIV-1, influenza A virus (IAV), Ebola and Dengue virus (Brass et al., 2009; Feeley et al., 2011; Huang et al., 2011; Everitt et al., 2012; Compton et al., 2014). IFITM3 has been demonstrated to affect severity of infection and improve the host cellular defenses against viruses (Brass et al., 2009; Everitt et al., 2012; Compton et al., 2014). Interestingly, IFITM3 has also been shown to act as a regulator of antiviral immunity that controls cytokine production to restrict viral pathogenesis, in CMV (Stacey et al., 2017) and Sendai virus (Jiang et al., 2017). This finding is particularly important since cytokine storm in influenza can lead to a rapid progression of the infection in humans (Wang et al., 2014) and the same observation is apparent in COVID-19 severe and deadly cases as well (Giamarellos-Bourboulis et al., 2020; Blanco-Melo et al., 2020).

The minor allele of rs12252 (C in minus, or G in plus strand orientation) has been associated with rapid progression of acute HIV infection (Zhang et al., 2015), with the severity of influenza (Zhang et al., 2013) and very recently with COVID-19 severity (Zhang et al, 2020). The minor allele of rs34481144 (A in minus, or T in plus strand orientation) was previously found to be correlated with increased severity of IAV infection (Allen et al., 2017). Moreover, the minor allele of rs34481144 is also associated with enhanced methylation on the IFITM3 promoter of CD8+ T cells, and general transcriptional repression of the broader locus surrounding IFITM3, which includes several genes known to be involved in host responses to viral infection (Wellington et al., 2019).

Following up to the very recent study on COVID-19 NHS mortality data in BAME groups, and the suggested implication of an IFITM3 variant in the severity of COVID-19 in Chinese patients, the purpose of the present study was to investigate a possible association between the stand-alone and combined frequencies of the alleles of the IFITM3 gene variants rs12252 and rs34481144, on COVID-19 standardized mortality ratio of ethnic groups in England.

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Results

The rs12252 and rs34481144 allele and haplotype frequencies were collected for all available ancestral populations from LDlink (Machiela et al., 2015) (Table 1). The plus orientation for the reference and minor alleles was retained throughout this analysis, for better data handling and in compliance with dbSNP. Rankings were produced by sorting all populations by individual allele (rs12252:A, rs12252:G, rs34481144:C, rs34481144:T) and by haplotype frequency ratios (rs12252_rs34481144: h1_ratio=A_C/(A_T+G_C), h2_ratio=G_C/(A_C+A_T), h3_ratio=A_T/(G_C+A_C), G_T haplotype not represented) and subsequently compared to the reported Standardized Mortality Ratios (SMR) of ethnic groups in England (Figure 1b). The one ranking that visually appeared in line with the reported SMR was produced by the A_C/(A_T+G_C) ratio (h1 ratio), specifically African groups, followed by South Asian, followed by interchanging East Asian and White groups (Figure 1a). While this finding was already interesting enough to warrant further discussion, an attempt was made to correlate directly the two rankings. UK demographics sources were therefore consulted (Office for National Statistics, UK, 2011; Chanda & Ghosh, 2012) in order to pool, wherever possible, the ancestral subgroups to the reported ethnic groups in England. In these terms, and with all reservations tied to the inevitable discrepancies of simplified socio-genetic correspondences, the following pools were formed: [AFR-YRI, AFR-LWK, AFR-GWD, AFR-MSL, AFR-ESN]>"African", [SAS-STU, SAS-GIH, SAS-PJL]>"Indian", [EAS-CDX, EAS-CHS, EAS-CHB]>"Chinese", [EUR-CEU, EUR-IBS, EUR-TSI, EUR-FIN]>"White Other". A pool for the reported Pakistani group failed to form from ancestral populations, as the Punjabi (SAS-PJL), being the only related subgroup, account roughly for just 45% of Pakistan's demographics, while in London the community includes comparable numbers of Punjabis, Pathans and Kashmiris, with small communities of Sindhis and Balochis (Department for Communities and Local Government, UK, 2009). Moreover, the Punjabi form also a considerable part of India's pool (at least 40% of Delhi's total population), therefore a single-ended direct correspondence between Punjabi and British Pakistani was not warranted in this case. The haplotype frequencies were simply averaged within pooled groups, and both the h1 ratios and SMR were normalized to the White British result (represented uniquely by EUR-GBR subgroup) (Table 2). The two rankings were finally traced one versus the other (Figure 2) with Pearson correlation $r=0.9687$, $p=3*10^{-4}$ (Figure 3).

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Discussion

This level of correlation appears to be remarkable, considering the required approximations made in ancestral groups pooling, as well as the theorized multi-parametric causes of the observed COVID-19 SMR in England's ethnic groups (potentially involving prior health status, income level, household density, behavioral biases, questionable attribution of death to COVID-19, etc.). Nonetheless, as far as possible discrepancies in group pooling approximations are concerned, this result merely confirmed what has already been implied by the ranking of all ancestral subgroups by the h1 ratio, specifically the visually striking sequence of Africans followed by South Asians, then by White Non-British, Chinese, and finally White British, with a random permutation (5 items) chance of 0.8%, or 1/120. Moreover, regarding the theorized multi-parametric background underlying any observed ethnic SMR pattern in COVID-19, it has been argued e.g. that race disparities in pre-existing health conditions are not large enough to fully explain the observed disparity in mortality, or that ethnic minorities in England are younger on average than white British population and therefore, less susceptible at least in theory (Kirby, 2020), implying the existence of other influencing factors, possibly genetic. However, it remains possible that, given the inherent uncertainty on the actual number of total COVID-19 cases worldwide, ethnic minorities may in fact be facing a bigger risk of infection in the first place, e.g. by working in jobs that require more frequent and/or close social contact.

Regardless of the observed correlation's strength between mortality ratios in ethnic minorities in England and a specific haplotype involving just 2 SNPs of IFITM3, the fact that the proposed risk haplotype (A_C) involves the Reference alleles of both studied SNPs, appears as counterintuitive. Especially so, since it has been suggested after analysis of a Chinese cohort, that the minor allele rs12252:G was linked to increased COVID-19 severity (Zhang et al., 2020). In fact the minor allele rs12252:G was linked to worse outcome in almost every instance, such as increased influenza severity (Zhang et al., 2013), or more rapid HIV progression (Zhang et al., 2015), albeit always observed on Chinese patients and not in European or American cohorts. This is noteworthy, as minor allele rs12252:G is found in large numbers in Chinese populations (roughly 50%), but is on the contrary very rare in European populations (1-8%), or infrequent in South Asian (10-18%), or African groups (21%-33%). Interestingly, an inversed trend is observed in the other half of the discussed A_C haplotype, with namely rs34481144:T being very rare in Chinese populations (1-2%), rare or infrequent in African groups (2-14%), but quite frequent in

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European groups (38-56%). In turn, rs34481144:T was found to correlate strongly with increased influenza severity in 3 independent cohorts (Allen et al., 2017). These 3 independent cohorts, however, did not confirm the link between rs12252:G and increased influenza severity, as was suggested in Chinese cohorts. To add to the controversy of the possible antiviral effects linked to rs12252, a detailed study on 293T cells of the putative truncated variant Δ1-21 that was expected to result from the rs12252:G mutant, showed increased potential to restrict HIV replication and therefore an advantage compared to the complete IFITM3 protein carrying the Reference allele (Compton et al., 2016). However, this truncated version was not observed later in the blood of IAV or HIV patients (Randolph et al., 2017; Makvandi-Nejad et al., 2018). The actual role and consequences of rs12252 is therefore still not fully elucidated, while rs34481144 is currently believed to disrupt the binding of CTCF, a transcription factor, also known as CCCTC-binding factor, at IFITM3 promoter (Allen et al., 2017).

As part of the IFITM family of proteins, one of the evolutionary ancient first lines of antiviral cellular defenses, the localization in endosomal or lysosomal membrane, or even at the surface, e.g. of $CD4^+$ T cells and the exact antiviral mechanism of IFITM3 is regulated by many different post translational modifications, mainly palmitoylation, ubiquitination and phosphorylation. It is shown that genotypic variants of IFITM3 play a role in diversifying a host's potential antiviral repertoire, in conjunction with selective post translation modifications, and therefore should not be considered *de facto* as risk factors but rather as trade-offs in antiviral specificity (Compton et al., 2016). Similarly, in the case of SARS-CoV-2, the observed strong correlation of haplotype h1 (A_C), which involves both rs12252 and rs34481144 reference alleles, with increased morbidity in ethnic groups in England, could be pointing at a specific antiviral advantage conferred by the presence of each minor allele. However, since both minor alleles are not observed together (haplotype G_T is not represented), it is harder to conceive an independently equivalent beneficial effect by each distinct minor allele in haplotypes A_T (here, minor> rs34481144:T) or G_C (here, minor> rs12252:G). Instead, it is more tempting to consider the possibility of the effective hijacking of IFITM3 by SARS-CoV-2 in order to infect the cell, or to replicate, or to propagate, or involving more than one of these phases. Indeed, there are known examples of similar hijacking, for example by the coronavirus that causes the common cold, HCoV-OC43 (Zhao et al., 2014), or by human cytomegalovirus (HCMV) (Xie et al., 2015). More specifically for HCoV-OC43, it was shown that all three types of interferons, IFN-α, IFN-γ, and

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IFN-λ, actually enhance HCoV-OC43 infection, while IFITM3 possibly promotes the low-pH–activated membrane fusion between the viral envelope and endosomal membranes. In contrast, human cytomegalovirus hijacks BST-2/tetherin to promote its entry into host cells and co-opts viperin to facilitate its replication, with IFITM3 facilitating the formation of the virion assembly compartment, but the virus is otherwise less sensitive to IFNs. In the case of SARS-CoV-2, it is therefore not inconceivable that if there is in fact a pro-infection role of IFITM3, that the virus could have evolved to hijack the most abundant haplotype A_C (59% abundance across all populations).

The recent suggestion that rs12252:G is the risk allele in a n=80 COVID-19 cohort with Chinese patients is nonetheless challenging the above conclusion (Zhang et al., 2020). However, given that the cohort took place at Beijing You'an Hospital, if it is safe to assume that patients belonged to EAS-CHB group (Han Chinese in Beijing), the subgroup with the highest frequency in rs12252:G (55%), then an alternative reading of the result may be possible. With 28/80 patients hospitalized with pneumonia being homozygotes rs12252:GG, 37/80 being heterozygotes rs12252:AG and 15/80 being homozygous rs12252:AA, this results to 58% (93/160) abundance for the G allele and 42% (67/160) abundance for the C allele. As the prior probability for the G allele was as high as 55%, the previous results seem inconclusive, at best, and therefore do not challenge the current suggestion that the all-reference-alleles A_C appears to be the risk haplotype.

Further corroborating the present observation are data from the USA, from a preliminary analysis of death rates from COVID-19 in New York City that shows 92.3 deaths per 100,000 population among black or African American people, followed by Hispanic or Latino people (74.3), then by white (45.2) or Asian (34.5) people (Kirby, 2020). The same trend was clearly displayed in the initial ranking by h1 ratio (Figure 1a), with American populations (AMR) occupying the middle of the chart, between African and European / Asian populations. Moreover, in the context of the A_C haplotype, the lower death rate of Asian people compared to white people in the above New York data, could be in line with fewer White British in the reported “white phenotype” in the USA (1.5M in USA & Canada) but higher Japanese proportion (>1.5M in the USA) in the reported “Asian phenotype”, while White British (EUR-GBR) and Japanese (EAS-JPT) ethnic subgroups share (together with EUR-FIN) the lowest h1 ratio among all subgroups. It is also noteworthy, that EUR-IBS (Iberian Population in Spain) and EUR-TSI (Toscani in Italia),

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representative of two countries that suffered higher death rates than other European countries, share the highest h1 ratio between all European subgroups.

Conclusion

Despite the apparent strength of the observed correlation, it is consented that it doesn't necessarily describe a causal connection, in this case between the prevalence of the described h1 haplotype of IFITM3 and higher mortality from COVID-19, but alternatively capture some secondary process that effectively involves Interferon-induced transmembrane protein 3 or other members of the IFITM family. Therefore, the main incentive of the present study is to turn the spotlight on a potentially exceptionally important role of IFITM proteins during SARS-CoV-2 infections, and specifically of IFITM3 and its two most well studied polymorphisms rs12252 and rs34481144. This may be of importance in the light of upcoming GWAS on severity phenotypes, such as from the COVID-19 Host Genetics Initiative, or from 23andME. However, verification of the reported correlation may warrant cohort designs that address e.g. the efficient representation of varied ethnic subgroups, or examine the importance of host's haplotype zygosity, or the potential connection with a specific SARS-CoV-2 clade (*i.e.*, S, G, V).

Should the relation between the combined rs12252 and rs34481144 haplotype, A_C, be confirmed, then the underlying mechanism of the captured effect is expected to have an impact on our understanding of COVID-19 and boost short- to medium-term research outcomes on antiviral drugs, improved clinical protocols, or potential vaccines. In terms of prognostic clinical testing, it is at present unclear if the detection of the discussed A_C haplotype in one's genome would be a reason for them to be even more cautious towards SARS-CoV-2 infection, than they would have been in the first place, considering that the frequency of this haplotype is close to 59% across all 1000 Genome Projects populations, and that the other 2 haplotypes do not seem to preclude a fatal COVID-19 outcome. However, the personal knowledge of carrying a COVID-19 risk haplotype could result in faster or better targeted/personalized clinical intervention in case of infection, in a way that could mean the difference between life and death. In any case, the complexity and severity of the current pandemic setting, is expected to highlight even further the importance of upcoming COVID-19 related SNP panels, or Polygenic Risk Scores, in the context of both precision and personalized medicine, *i.e.*, better suited drugs and personalized therapeutic protocols.

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Major group	Subgroup	rs12252:A	rs12252:G	rs34481144:C	rs34481144:T	A_T	A_C	G_C
EUR	CEU (Utah residents from north and west Europe)	0.955	0.045	0.505	0.495	0.49	0.46	0.05
EUR	TSI (Toscani in Italia)	0.967	0.033	0.617	0.383	0.38	0.58	0.03
EUR	FIN (Finnish in Finland)	0.919	0.081	0.505	0.495	0.49	0.42	0.08
EUR	GBR (British in England & Scotland)	0.989	0.011	0.440	0.560	0.56	0.43	0.01
EUR	IBS (Iberian Population in Spain)	0.967	0.033	0.603	0.397	0.40	0.57	0.03
EAS	CHB (Han Chinese in Beijing)	0.461	0.539	0.990	0.010	0.00	0.45	0.54
EAS	JPT (Japanese in Tokyo)	0.361	0.639	1.000	0.000	0.00	0.36	0.64
EAS	CHS (Southern Han Chinese)	0.495	0.505	1.000	0.000	0.00	0.50	0.50
EAS	CDX (Chinese Dai in Xishuangbanna	0.521	0.478	0.995	0.005	0.00	0.52	0.48
EAS	KHV (Kinh in Ho Tsi Minh ciry, Vietnam)	0.530	0.470	0.985	0.015	0.02	0.52	0.47
AMR	MXL (Mexican ancestry from Los Angeles)	0.781	0.219	0.820	0.180	0.18	0.60	0.22
AMR	PUR (Puerto Ricans from Puerto Rico)	0.889	0.111	0.702	0.298	0.30	0.59	0.11
AMR	CLM (Colombians from Medelin, Colombia)	0.925	0.074	0.681	0.319	0.32	0.61	0.07
AMR	PEL (Peruvians from Lima Peru)	0.659	0.341	0.900	0.100	0.10	0.56	0.34
SAS	GIH (Gujarati Indian from Houston Texas)	0.835	0.165	0.806	0.194	0.19	0.64	0.17
SAS	PJL (Punjabi from Lahore, Pakistan)	0.823	0.177	0.812	0.188	0.19	0.64	0.18
SAS	BEB (Bengali from Bangladesh)	0.837	0.163	0.831	0.169	0.17	0.67	0.16
SAS	STU (Sri Lankan Tamil from the UK)	0.868	0.132	0.735	0.265	0.26	0.60	0.13
SAS	ITU (Indian Telugu from the UK)	0.897	0.103	0.789	0.211	0.21	0.69	0.10
AFR	ASW (Americans of African Ancestry in SW USA)	0.697	0.303	0.861	0.139	0.14	0.56	0.30
AFR	ACB (African Carribeans in Barbados)	0.776	0.224	0.906	0.094	0.09	0.68	0.22
AFR	ESN (Esan in Nigera)	0.788	0.212	0.990	0.010	0.01	0.78	0.21
AFR	MSL (Mende in Sierra Leone)	0.753	0.247	0.982	0.018	0.02	0.74	0.25
AFR	GWD (Gambian in Western Gambia)	0.783	0.217	0.969	0.031	0.03	0.75	0.22
AFR	LWK (Luhya in Webuye Kenya)	0.702	0.298	0.985	0.015	0.02	0.69	0.30
AFR	YRI (Yoruba in Ibadan, Nigera)	0.667	0.333	0.968	0.032	0.03	0.63	0.33

Table 1. Detailed allele and haplotype frequencies per ethnic subgroup derived from 1000 Genomes Project, for rs12252 and rs34481144.

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Ethnic group	SMR-White British Normalized	A_C / (A_T + G_C) - White British Normalized	1000 Genomes Populations	rs12252:A	rs12252:G	rs34481144:C	rs34481144:T	A_T	A_C	G_C	rs12252_rs34481144 : A_C / (A_T + G_C)
African	3.68	3.38	*AFR-YRI, AFR-LWK, AFR-GWD, AFR-MSL, AFR-ESN*	0.74	0.26	0.98	0.02	0.02	0.72	0.26	2.54
Bangladeshi	2.74	2.69	*SAS-BEB*	0.84	0.16	0.83	0.17	0.17	0.67	0.16	2.02
Caribbean	2.51	2.86	*AFR-ACB*	0.78	0.22	0.91	0.09	0.09	0.68	0.22	2.15
Indian	1.93	2.23	*SAS-STU, SAS-GIH, SAS-PJL*	0.84	0.16	0.78	0.22	0.22	0.63	0.16	1.68
White other	1.53	1.38	*EUR-CEU, EUR-IBS, EUR-TSI, EUR-FIN*	0.95	0.05	0.56	0.44	0.44	0.51	0.05	1.04
Chinese	1.30	1.28	*EAS-CDX, EAS-CHS, EAS-CHB*	0.49	0.51	1.00	0.01	0.00	0.49	0.51	0.96
White British	1.00	1.00	*EUR-GBR*	0.99	0.01	0.44	0.56	0.56	0.43	0.01	0.75
Average	2.10	2.12		0.80	0.20	0.78	0.22	0.21	0.59	0.20	1.59

Table 2. Pools of ethnic subgroups were formed to emulate the ethnic populations that are reported in England. Both the h1 ratio (A_C/A_T+G_C) and the SMR were normalized by the corresponding numbers of White British, to allow a direct comparison.

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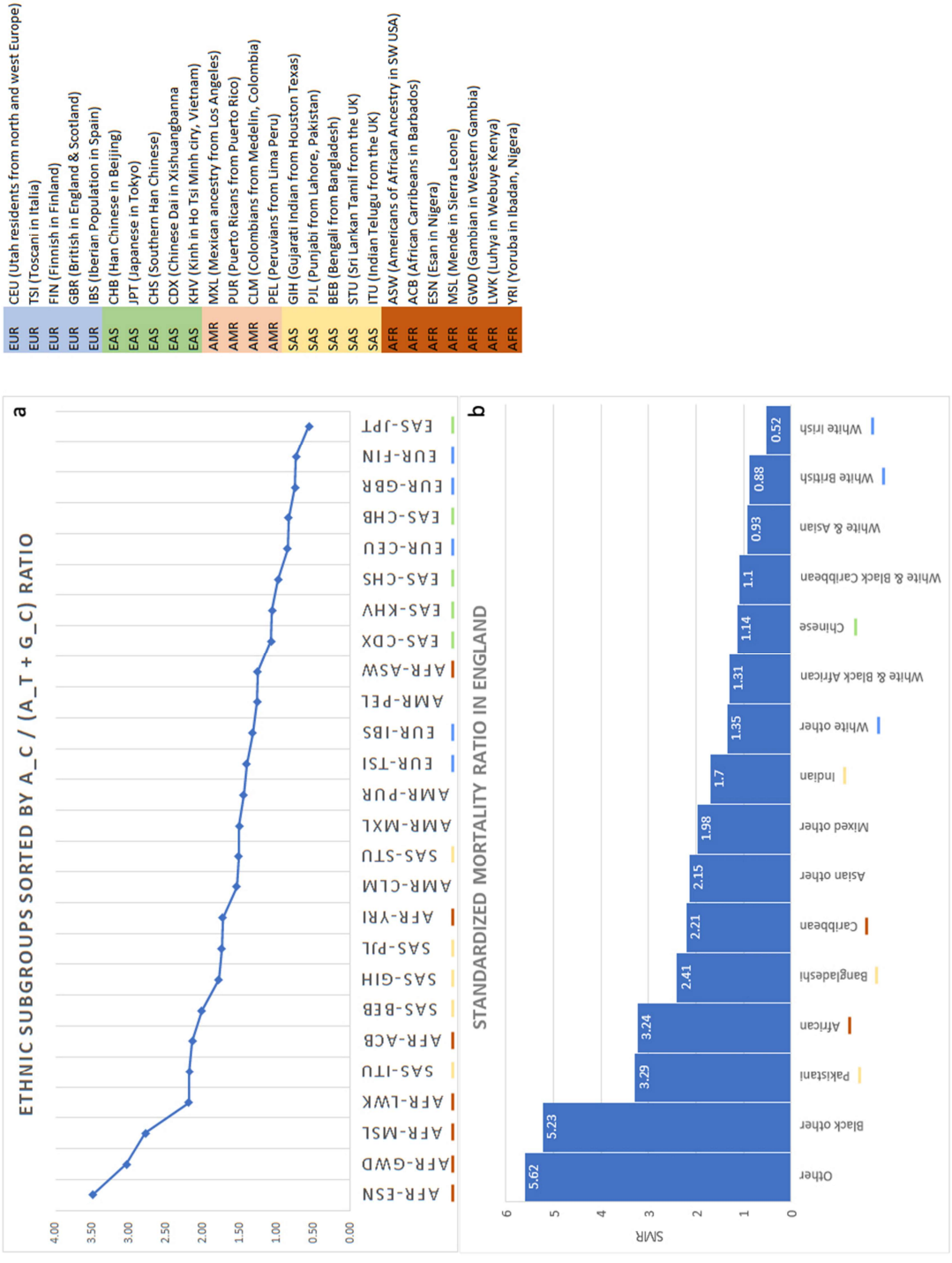

Figure 1. a) Ethnic subgroups from 1000 Genomes Project sorted by h1 ratio. Colored tags are added beneath most subgroups to aid visual identification of major groups and follow the color code on the right. b) Standardized Mortality Ratio of ethnic groups in England, adjusted for Age and NHS Region.

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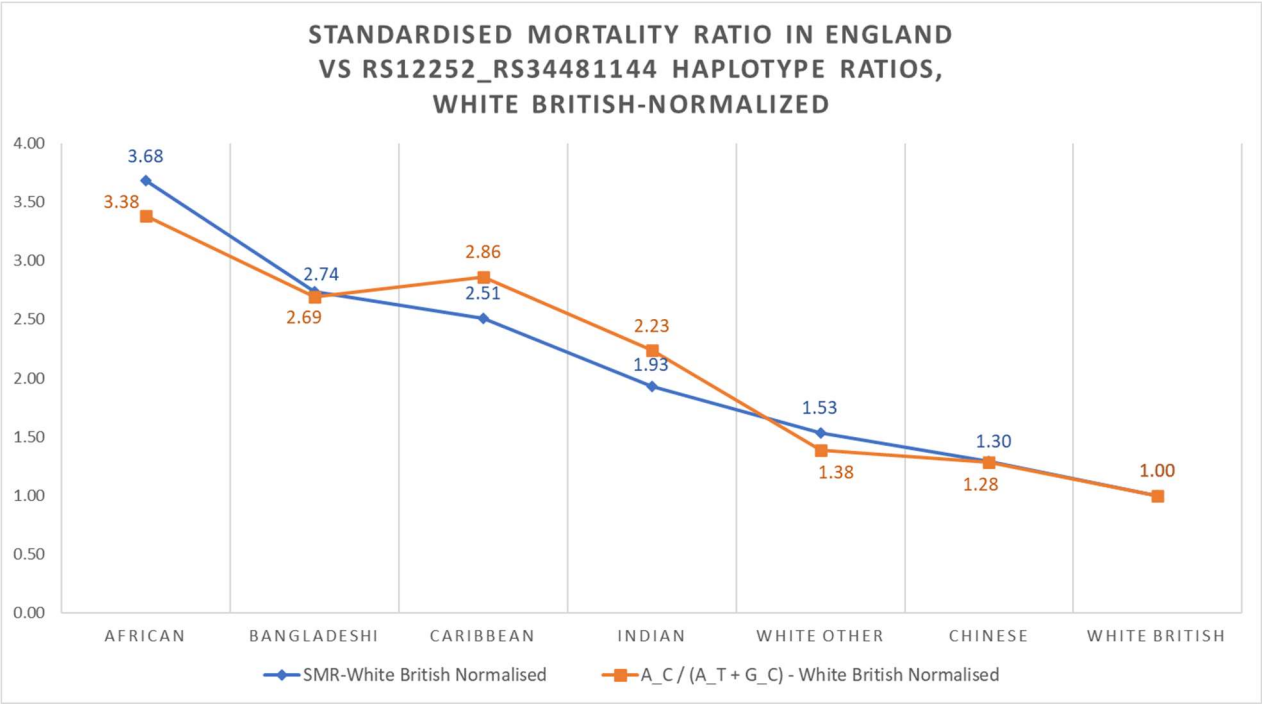

Figure 2. Comparison between Standardized Mortality Ratio of ethnic groups in England, with h1 haplotype ratio of rs12252 and rs34481144 (A_C/(A_T+G_C)) from the best corresponding pools of ethnic subgroups from 1000 Genomes Project. Both ratios are normalized by the corresponding numbers of White British, to allow a direct comparison.

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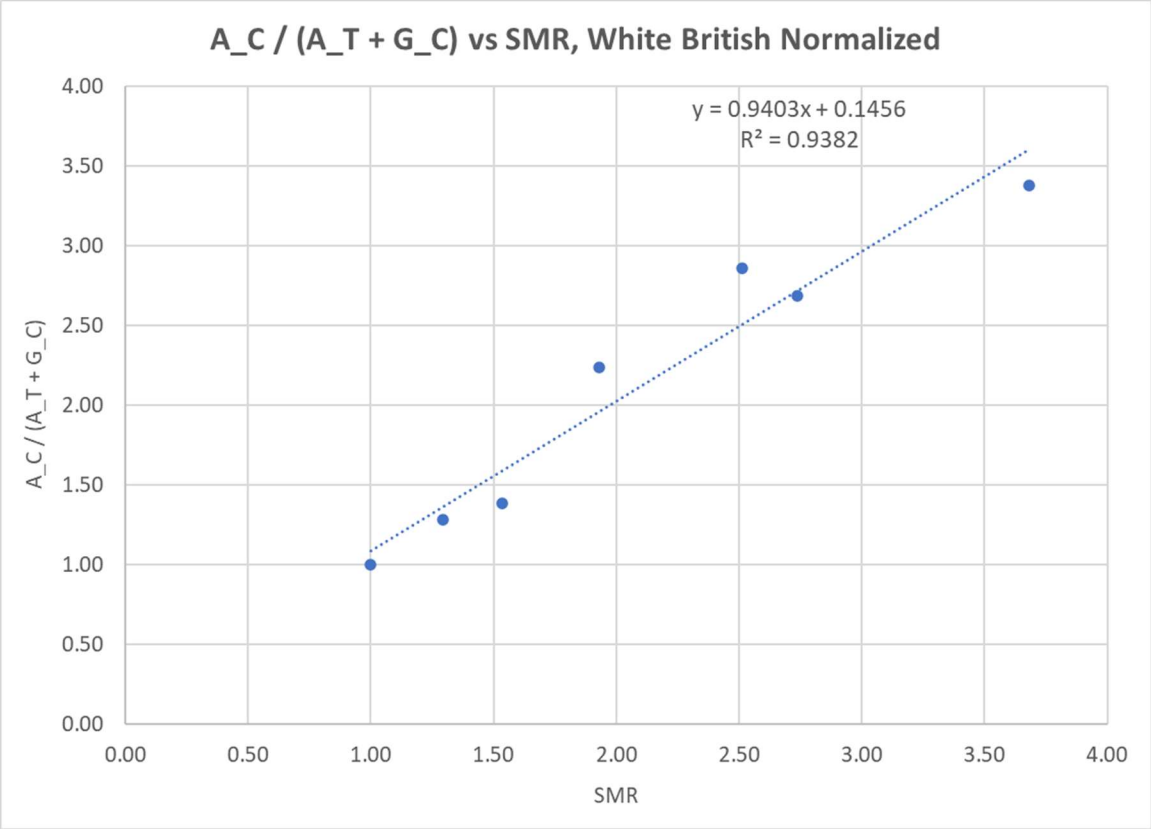

Figure 3. Correlation between h1 haplotype ratios and SMR, with Pearson r=0.9687, $p=3*10^{-4}$.

References

Aldridge R.W., Lewer D., Katikireddi S.V. et al. (2020). Black, Asian and Minority Ethnic groups in England are at increased risk of death from COVID-19: indirect standardisation of NHS mortality data [version 1; peer review: awaiting peer review]. Wellcome Open Res, 5:88. https://doi.org/10.12688/wellcomeopenres.15922.1

Allen E.K., Randolph A.G., Bhangale T., Dogra P., Ohlson M., Oshansky C.M., et al. (2017). SNP-mediated disruption of CTCF binding at the IFITM3 promoter is associated with risk of severe influenza in humans. Nature Medicine, 23, 975e83. doi: 10.1038/nm.4370

Blanco-Melo D., Nilsson-Payant B.E., Liu W.C. et al. (2020). Imbalanced host response to SARS-CoV-2 drives development of COVID-19. Cell Press. doi:10.1016/j.cell.2020.04.026

Brass A.L., Huang I.C., Benita Y., John S.P., Krishnan M.N., Feeley E.M., Ryan B.J., Weyer J.L., van der Weyden L., Fikrig E., Adams D.J., Xavier R.J., Farzan M., Elledge S.J. (2009). The IFITM proteins mediate cellular resistance to influenza A H1N1 virus, West Nile virus, and dengue virus. Cell, 139(7), 1243-54. https://doi.org/10.1016/j.cell.2009.12.017

CDC (2020). COVID-19 in Racial and Ethnic Minority Groups. Accessed April 26, 2020. https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/racial-ethnic-minorities.html

Chanda R., Ghosh S. (2012). The Punjabi Diaspora in the UK: An overview of characteristics and contributions to India, Migration Policy Centre, CARIM-India Research Report, /23, Country Reports, 23
Retrieved from Cadmus, European University Institute Research Repository, at: http://hdl.handle.net/1814/24845

Chapman S.J., Hill A.V. (2012) Human genetic susceptibility to infectious disease. Nature Reviews Genetics. 13(3), 175-88. https://doi.org/10.1038/nrg3114

Compton A.A., Bruel T., Porrot F., Mallet A., Sachse M., Euvrard M., et al. (2014). IFITM proteins incorporated into HIV-1 virions impair viral fusion and spread. Cell Host Microbe, 16, 736-747. doi: 10.1016/j.chom.2014.11.001

Compton A.A., Roy N., Porrot F., et al. (2016). Natural mutations in IFITM3 modulate post-translational regulation and toggle antiviral specificity. EMBO Reports, 17(11), 1657-1671. doi:10.15252/embr.201642771

Department for Communities and Local Government, UK. (2009). The Pakistani Muslim Community in England (PDF). Department for Communities and Local Government. 38-39. https://webarchive.nationalarchives.gov.uk/20120920001118/http://www.communities.gov.uk/documents/communities/pdf/1170952.pdf

Everitt A.R., Clare S., Pertel T., John S.P., Wash R.S., Smith S.E., et al. (2012). IFITM3 restricts the morbidity and mortality associated with influenza. Nature, 484, 519-523. doi: 10.1038/nature10921.

Feeley E.M., Sims J.S., John S.P., Chin C.R., Pertel T., Chen L.M., et al. (2011). IFITM3 inhibits influenza A virus infection by preventing cytosolic entry. PLoS Pathogens, 7, e1002337. https://doi.org/10.1371/journal.ppat.1002337

Garg S., Kim L., Whitaker M., et al. (2020). Hospitalization Rates and Characteristics of Patients Hospitalized with Laboratory-Confirmed Coronavirus Disease 2019 — COVID-NET, 14 States, March 1–30, 2020. Morbidity and Mortality Weekly Report, 69, 458–464. http://dx.doi.org/10.15585/mmwr.mm6915e3

Giamarellos-Bourboulis, E.J., Netea M.G., Rovina N. et al. (2020). Complex Immune Dysregulation in COVID-19 Patients with Severe Respiratory Failure. Cell Host & Microbe. In Press. https://doi.org/10.1016/j.chom.2020.04.009

Huang I.C., Bailey C.C., Weyer J.L., Radoshitzky S.R., Becker M.M., Chiang J.J., et al. (2011). Distinct patterns of IFITM-mediated restriction of filoviruses, SARS coronavirus, and influenza A virus. PLoS Pathogens, 7, e1001258. doi: 10.1371/journal.ppat.1001258

Jiang L.Q., Xia T., Hu Y.H., Sun M.S., Yan S., Lei C.Q., et al. (2017) IFITM3 inhibits virus-triggered induction of type I interferon by mediating autophagosome-dependent degradation of IRF3. Cellular & Molecular Immunology, 15, 858e67. doi: 10.1038/cmi.2017.15

Khunti K., Singh A.K., Pareek M., et al (2020). Is ethnicity linked to incidence or outcomes of covid-19? BMJ, 369, m1548. https://doi.org/10.1136/bmj.m1548

Kirby T. (2020). Evidence mounts on the disproportionate effect of COVID-19 on ethnic minorities. The Lancet Respiratory Medicine, News, Published online May 8, 2020. https://doi.org/10.1016/S2213-2600(20)30228-9

Machiela M.J., Chanock S.J. (2015). LDlink: a web-based application for exploring population-specific haplotype structure and linking correlated alleles of possible functional variants. Bioinformatics, 31(21), 3555-3557. https://doi.org/10.1093/bioinformatics/btv402

Makvandi-Nejad S., Laurenson-Schafer H., Wang L., Wellington D., Zhao Y., Jin B., Qin L., Kite K., Moghadam H.K., Song C., Clark K., Hublitz P., Townsend A.R., Wu H., McMichael A.J., Zhang Y., Dong T. (2018). Lack of Truncated IFITM3 Transcripts in Cells Homozygous for the rs12252-C Variant That is Associated With Severe Influenza Infection, The Journal of Infectious Diseases, 217(2), 257–262, https://doi.org/10.1093/infdis/jix512

Niedzwiedz C.L., O'Donnell C.A., Jani B.D., et al. (2020). Ethnic and socioeconomic differences in SARS-CoV-2 infection: prospective cohort study using UK Biobank. Public and Global Health. https://doi.org/10.1101/2020.04.22.20075663

Office for National Statistics, UK. Ethnicity and National Identity in England and Wales: 2011. Retrieved from Office for National Statistics, at: https://www.ons.gov.uk/peoplepopulationandcommunity/culturalidentity/ethnicity/articles/ethnicityandnationalidentityinenglandandwales/2012-12-11

Randolph A.G., Yip W.K., Allen E.K., et al. (2017). Evaluation of IFITM3 rs12252 Association With Severe Pediatric Influenza Infection. The Journal of Infectious Diseases, 216(1), 14-21. doi:10.1093/infdis/jix242

Stacey M.A., Clare S., Clement M., Marsden M., Abdul-Karim J., Kane L., et al. (2017) The antiviral restriction factor IFN-induced transmembrane protein 3 prevents cytokine-driven CMV pathogenesis. Journal of Clinical Investigation, 127, 1463e74. doi: 10.1172/JCI84889

Wang Z., Zhang A., Wan Y., Liu X., Qiu C., Xi X., et al. (2014) Early hypercytokinemia is associated with interferon-induced transmembrane protein-3 dysfunction and predictive of fatal H7N9 infection.

Proceedings of the National Academy of Sciences of the USA, 111, 769e74. https://doi.org/10.1073/pnas.1321748111

Wellington D., Laurenson-Schafer H., Abdel-Haq A., Dong T. (2019). IFITM3: How genetics influence influenza infection demographically. Biomed Journal, 42(1), 19-26. doi:10.1016/j.bj.2019.01.004

Xie M., Xuan B., Shan J., Pan D., Sun Y., Shan Z., et al. (2015). Human cytomegalovirus exploits interferon-induced transmembrane proteins to facilitate morphogenesis of the virion assembly compartment. Journal of Virology, 89, 3049–3061. doi: 10.1128/JVI.03416-14

Zhang Y.H., Zhao Y., Li N., Peng Y.C., Giannoulatou E., Jin R.H., Yan H.P., Wu H., Liu J.H., Liu N., Wang D.Y., Shu Y.L., Ho L.P., Kellam P., McMichael A., Dong T. (2013). Interferon induced transmembrane protein 3 genetic variant rs12252 C is associated with severe influenza in Chinese individuals. Nature Communications, 4, 1418. doi: 10.1038/ncomms2433

Zhang Y., Makvandi-Nejad S., Qin L., et al. (2015). Interferon-induced transmembrane protein-3 rs12252-C is associated with rapid progression of acute HIV-1 infection in Chinese MSM cohort. AIDS, 29(8), 889-894. doi:10.1097/QAD.0000000000000632

Zhang Y., Qin L., Zhao Y., Zhang P., Xu B., Li K., Liang L., Zhang C., Dai Y., Feng Y., Sun J., Hu Z., Xiang H., Knight C.J., Dong T., Jin R. (2020). Interferon-induced transmembrane protein-3 genetic variant rs12252-C is associated with disease severity in COVID-19, The Journal of Infectious Diseases, 224. https://doi.org/10.1093/infdis/jiaa224

Zhao X., Guo F., Liu F., Cuconati A., Chang J., Block T. M., et al. (2014). Interferon induction of IFITM proteins promotes infection by human coronavirus OC43. Proceedings of the National Academy of Sciences of the U.S.A., 111, 6756–6761. doi: 10.1073/pnas.1320856111

Zhao X., Sehgal M., Hou Z., Cheng J., Shu S., Wu S., Guo F., Le Marchand S.J., Lin H., Chang J., Guo J.T. (2018) Identification of Residues Controlling Restriction versus Enhancing Activities of IFITM Proteins on Entry of Human Coronaviruses. Journal of Virology, 92(6), e01535-17. doi: 10.1128/JVI.01535-17