Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Short Communication

Loss-of-function mutations in *IFNAR2* in COVID-19 severe infection susceptibility

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ABSTRACT

Recent COVID-19 (coronavirus disease 2019) host genetics studies suggest enrichment of mutations in genes involved in the regulation of type I and type III interferon (IFN) immunity in patients with severe COVID-19 infection. We performed whole-genome sequencing analysis of samples obtained from patients participating in the ongoing ODYSSEY phase 3 study of hospitalised patients with severe COVID-19 infection receiving supplemental oxygen support. We focused on burden testing of categories of rare and common loss-of-function (LOF) variants in all of the IFN pathway genes, specifically with MAF < 0.1% and MAF < 1%. In a model including LOF and missense variants (MAF < 1%), we report a significant signal in both *INFAR1* and *IFNAR2*. We report carriers of rare variants in our COVID-19 cohort, including a stop-gain *IFNAR2* (NM_000874:exon9:c.C966A:p.Y322X) amongst carriers of several other *IFNAR* rare nonsynonymous variants. Furthermore, we report an increased allelic frequency of common *IFNAR2* variants in our data, reported also by the COVID-19 Host Genetics Initiative.

Innate interferons (IFNs α/β and λ) play a major role in the induction and amplification of a crucial antiviral programme in response to viral infections. Specifically, type I IFNs play a crucial role in early-phase antiviral defence, whereas cytokines/chemokines are associated with induction of later inflammatory responses and the cytokine storm [1]. Recently, Zhang et al. reported enrichment of mutations in genes involved in the regulation of type I and type III IFN immunity in patients with severe COVID-19 (coronavirus disease 2019) [2]. Furthermore, van der Made et al. reported four young male patients with severe COVID-19 with predicted loss-of-function (pLOF) and missense variants in Toll-like receptor 7 (*TLR7*) associated with impaired IFN responses [3]. The high-affinity interferon α/β receptor *IFNAR2* –/– genotype is associated with higher rates of influenza A virus (IAV) infection but decreased susceptibility to bacterial superinfection post IAV infection [4]. A recent study reported 50 COVID-19 patients with significantly impaired type I IFN activity, suggesting that type I IFN deficiency in the blood may be a hallmark in severe COVID-19 patients [1].

We have performed whole-genome sequencing (WGS) analysis on samples obtained from patients participating in the ongoing ODYSSEY - phase 3 randomised study of tradipitant in hospitalised patients with severe COVID-19 who are receiving supplemental oxygen support. The cohort of severe hospitalised COVID-19 cases was multi-ethnic, with an age range of 35–87 years (68% male, 32% female). We first focused on loss-of-function variants (rare pLOF) in all of the IFN genes as described in Zhang et al. [2]. We performed burden testing of categories of rare LOF variants in all the IFN pathway genes, specifically MAF < 0.1% and MAF < 1%. Whereas we did not detect pLOFs in the MAF < 0.1% category, in MAF < 1% in a model including LOF and missense variants, we see a significant signal in *INFAR1* and *IFNAR2* (Table 1).

A detailed description of the methods is provided in the Supplementary Material.

We report carriers of these variants in *IFNAR2* (NM_000874:exon9:c.C966A:p.Y322X) and *IFNAR1* (NM_000629:exon9:c.A1264C:p.S422R) in our COVID-19 cohort (amongst other rare nonsynonymous variants not tested functionally). *IFNAR2* Tyr322Ter is rare in general population, with 11 homozygous individuals reported among approximately 125 000 reference genomes in The Genome Aggregation Database (gnomAD). All 11 homozygous individuals were of East Asian descent with minor allele frequency of 0.03787

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Table 1
Burden testing of categories of rare and common predicted loss-of-function (pLOF) variants with MAF threshold categories of MAF < 0.1% and MAF < 1%

Gene	MAF_gnomAD_GENOME_ALL < 1% (n = 50)	Any missense, splicing, pLOF (n = 1876)	OR	95% CI	Z	P-value	P-value (Fisher)
IFNAR1	4	15	10.7884	3.4466–33.7696	4.09	<0.0001	0.0010845
IFNAR2	4	50	10.5855	3.3817–33.1351	4.05	0.0001	0.037353
IKBKG	1	0	113.727	4.5755–2826.7680	2.89	0.0039	0.025961
IRF3	3	78	1.4714	0.4481–4.8315	0.64	0.5244	0.1961
IRF7	1	23	1.6442	0.2176–12.4211	0.48	0.6298	0.34314
STAT1	1	6	6.3605	0.7514–53.8430	1.7	0.0896	0.15565
STAT2	6	65	3.7993	1.5631–9.2346	2.95	0.0032	0.0069853
TBK1	1	2	19.1224	1.7052–214.4468	2.39	0.0167	0.073966
TICAM1	1	60	0.6177	0.0839–4.5483	0.47	0.6362	0.32894
TLR3	1	76	0.4834	0.0659–3.5472	0.72	0.4747	0.27071
TRAF3	1	6	6.3605	0.7514–53.8430	1.7	0.0896	0.15565

OR, odds ratio; CI, confidence interval.

compared with an overall population frequency of 0.00283 (gnomAD). For this stop-gain, we report (based on our WGS samples) a MAF of 0.009 versus 0.0013 in our controls.

Our findings are consistent with reports where genome-wide association studies have shown associations of *IFNAR2* polymorphisms with severe infections, including COVID-19 infection [2]. For the missense variant in *IFNAR1* (NM_000629:exon9:c.A1264C:p.S422R), Zhang et al. transiently transfected the fibroblast cell line SV40 (with overexpression of the variant) and stimulated with IFN α2 or IFNγ and reported a significant change of phosphorylation status of *STAT1* compared with the wild-type. In our cohort, both carriers (heterozygotes) were female, survivors, aged >75 years (plasma IFN-γ levels of 9.6 pg/mL and below the limit of quantification). The key rare pLOF and missense variants are shown in Fig. 1. Furthermore, we report increased allelic frequency on common *IFNAR2* variants in our data, as also reported by the COVID-19 Host Genetics Initiative. We specifically focused on rs12482556 reported as the second highest significant signal in the latest COVID-19 Initiative results [5]. In our cohort, we report a global MAF of 0.44 versus 0.32 in our 1000 Genomes controls as well as a gnomAD global MAF of 0.31. Variants detected have previously been associated with risk of susceptibility to hepatitis B (rs2229207) and herpes simplex encephalitis (rs151272128). For rs2229207, we show the respective levels of IFNγ across genotypes (Fig. 1) with minor allele showing lower levels of IFNγ.

IFNAR2 LOF mutations including Tyr322Ter may increase susceptibility to severe COVID-19 infection especially among Asian-descent populations where the mutation is more prevalent. We also make the observation that the *IFNAR2* Tyr322Ter homozygous state may explain the increased mortality associated with MMR (meases, mumps and rubella) vaccination in Japan that led to the discontinuation of the triple live-attenuated virus vaccine in that country [6]. Notably, *IFNAR2* LOF mutation was reported in a young child with post-MMR vaccination encephalitis [6]. Given that high-affinity IFNAR2 as well as components of its downstream signalling (TYK2, STAT1 and STAT2) are all implicated in viral resistance, the natural corollary would be potential negative effects of JAK/STAT inhibitors such as some current treatments for atopic dermatitis or rheumatoid arthritis in the presence of LOF or other missense variations. Our findings are consistent with reports where genome-wide association studies have shown associations of *IFNAR2* polymorphisms with severe infections, including COVID-19. Type I IFNs became one of the more promising potential drug candidates for COVID-19, with initial clinical trials showing preliminary results in reducing the severity of the disease [7]. We believe further dissemination of such WGS studies will enable quicker understanding of the nature of this heterogeneous host–virus interaction and especially of the severe manifesation of this infection.

Declaration of Competing Interests

Authors are employees of Vanda Pharmaceuticals.

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Ethical approval

All patients consented to the study. The study was reviewed and approved by Advarra IRB; Pro00043096.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jgar.2021.06.005.

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