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Association of IFNAR2 and TYK2 with COVID-19 pathology: current and future

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1 Introduction

Determining prognostic factors in COVID-19 is important in triaging patients in critical situations (1, 2). In COVID-19, expression of interferon α/β receptor subunit (*IFNAR*) 2 and tyrosine kinase 2 (*TYK2*) has been suggested to be associated with COVID-19 outcomes. To offer potential therapeutic strategies and contribute to better patient care and treatment decisions, we would like to summarize the current findings on the association of *IFNAR2* and *TYK2* genes with COVID-19 pathology and propose future challenges.

2 Blockage of IFNAR signaling

Recent genome-wide association studies have shed significant light on the potential involvement of *IFNAR2* and *TYK2* in the dynamics of SARS-CoV-2 infection (3–5). Increased expression of *IFNAR2* has been correlated with a decreased probability of developing critical COVID-19 (3, 6). When type I interferons (IFN-α/β) bind to IFNAR2, it triggers the JAK-STAT signaling pathway, leading to the activation of IFN-stimulated genes (ISGs) that produce antiviral proteins. The activation of ISGs results in the production of proteins that inhibit viral replication and enhance the immune response. This response helps to control the spread of the virus within the host, providing a crucial defense mechanism against COVID-19 (7). Therefore, genetic variations in the *IFNAR2* gene, such as rs2236757 and rs3153, can alter the structure and function of the IFNAR2 protein. These polymorphisms may lead to reduced expression of the receptor or changes in its binding affinity for IFNs. Individuals with certain *IFNAR2* polymorphisms have a higher risk of severe COVID-19 and increased mortality due to impaired antiviral response (8). Furthermore, TYK2 expression is involved in the regulation of IFNAR signaling, indicating its potential significance in disease management (6). Our published work

reveals a substantial decrease in the mRNA expression levels of *IFNAR2* and *TYK2* in peripheral blood leukocytes among individuals with COVID-19 (1). Despite the established role of IFNs being induced during viral infections and limiting viral replication through IFN receptor signaling, it is noteworthy that severe cases of COVID-19 display significantly reduced IFN levels compared to other viral infections (9). Lower levels of IFNAR2 can impair the body's ability to respond to viral infections, leading to more severe disease outcomes. IFNAR2 exists in three isoforms, two of which are soluble but lack the ability to activate signaling upon interaction with type I IFN. Consequently, the efficacy of type I IFN action may be influenced by the relative abundances of these IFNAR2 isoforms, as proposed by Aliaga-Gaspar and colleagues in 2021 (10). In severe COVID-19 cases, higher levels of soluble IFNAR2 (sIFNAR2) have been observed, which can bind to IFNs and prevent them from interacting with cell surface receptors, thus impairing the signaling pathway (11). Coronaviruses, skilled at hiding viral RNA from pattern recognition receptors, may employ these strategies to enable covert replication. The virus interacts with specific proteins to impede IFN responses, avoid detection, or directly block IFNAR signaling. Hence, additional research on *IFNAR2* and *TYK2* expression in COVID-19 can significantly contribute to finding a conclusive treatment for this worldwide crisis.

3 Discussion

Our study did not establish that the expressions of *IFNAR2* and *TYK2* genes serve as a predictor of severity of COVID-19, likely due to limitations such as small sample size (1). However, prior evidence suggests that *IFNAR2* and *TYK2* variants could be linked to disease severity due to their high affinity to type I IFNs (3, 12–14). Additionally, measuring soluble IFNAR levels may offer insights into predicting disease severity or mortality risk (12). The most intriguing study conducted by Pairo-Castineira et al. involved a prospective multicenter investigation. They analyzed 2,244 critically ill cases across 208 UK intensive care units, encompassing patients of European, South Asian, African, and East Asian descent. The study focused on the *IFNAR2* gene located on chromosome 21q22.1 and a gene proximal to *TYK2* on chromosome 19p13.2. Their findings indicated that low *IFNAR2* gene expression (OR = 1.28, $P = 4.99 \times 10^{-8}$) or high *TYK2* gene expression (OR = 1.6, $P = 2.3 \times 10^{-8}$) correlates with life-threatening conditions (3). A study conducted in a Mexican cohort investigated *IFNAR2* variants (rs2236757, rs1051393, rs3153, rs2834158, and rs2229207) using Taqman® assays in 1,202 patients with severe COVID-19. The findings revealed an association between four of these five variants (rs2236757, rs1051393, rs3153, and rs2834158) and mortality risk among severe COVID-19 patients (15). Consequently, it can be inferred that some *IFNAR2* variants may negatively impact the antiviral effects of IFN α/β (16). Our study revealed that *IFNAR2* and *TYK2* mRNA expressions were significantly downregulated in COVID-19 patients compared to healthy subjects. The discrepancy that our results did not support upregulation of *TYK2* expression may be due to differences in sample size and ethnicity among populations (1). However, at least, impaired IFNAR signaling due to decreased *IFNAR2* expression appears to be associated with COVID-19 severity, as supported by various studies. Specifically, we observed a negative correlation between the expression levels of *IFNAR2* and *TYK2* transcripts in COVID-19 patients (1). This suggests that altered *TYK2* expression may impact immune responses during infection. Further investigation of this issue can be considered as a therapeutic goal.

A recent systematic review summarized that *IFNAR2* variants (specifically rs9976829, rs2834158, and rs3153) are significantly linked to mortality risk (13, 15, 17). Also, variants rs17860118 and rs2229207 in the *IFNAR2* gene have been conclusively linked with susceptibility to SARS-CoV-2 in COVID-19 patients (OR = 1.718, CI 95% = 1.039-2.841, $P = 0.033$, and OR = 1.89, CI 95% = 1.141-3.156, $P = 0.012$, respectively) (13, 18). Based on this recent review, the rs2236757 genetic variant is connected to severe cases of COVID-19 (3, 13, 19, 20). Moreover, the cohort analysis of 694 Brazilian COVID-19 patients reveals a significant link between rs2236757/*IFNAR2* and rs2304256/*TYK2* polymorphisms and worsened COVID-19 outcomes, particularly affecting female and non-white patients (19). Notably, in non-white patients, having both the minor alleles of rs2236757 (*IFNAR2*) and rs12329760 (*TMPRSS2*) leads to an additive increase in the risk of death (19). It appears that this variant interacts with both *TMPRSS2* and *ACE1*. ACE2 acts as the cellular gateway for SARS-CoV-2, while TMPRSS2 facilitates the virus's entry by activating its spike proteins (21). Genetic variations confidently interact differently with factors such as sex and ethnicity to influence the severity of COVID-19 (1). The virus replicates, causing extensive tissue damage and leading to an overwhelming immune response known as cytokine storm (22). This response occurs as the immune system strives to contain viral replication and handle dying and dead cells. This highlights the urgent need for further research and targeted interventions to address these disparities.

Various studies have reported different findings. In a prospective population-based cohort study conducted in the United Kingdom, researchers collected genetic and phenotypic data from individuals aged 40 to 69 years (23). Specifically, ten phenotypes were associated with a genetic variant called rs74956615 (*TYK2*), all showing reduced odds related to the COVID-19 risk allele. These phenotypes included psoriatic arthropathy (OR, 0.31; 95% CI, 0.20–0.47; q=4.5×10−5), rheumatoid arthritis (OR, 0.83; 95% CI, 0.64–0.83; q=0.0003), and thyrotoxicosis (OR, 0.77; 95% CI, 0.68–0.87; q=0.01). Additionally, seven phenotypes were nominally validated in the CATHGEN study, including psoriasis, rheumatoid arthritis, and hypothyroidism (all $P < 0.1$) (23). These COVID-19-related genetic variants underscore the significance of host antiviral defense mechanisms and inflammatory signaling. TYK2's involvement in psoriasis is linked to Th17 responses and IFN-α signaling. Notably, the study clarified previously conflicting associations for autoimmune diseases, revealing a novel

observation: decreased odds of psoriasis associated with rs74956615, suggesting a distinct impact of this allele on *TYK2* gene function compared to prior genome-wide association study analyses of psoriasis.

An in-depth genetic analysis of 109 patients with PCR-confirmed SARS-CoV-2 infection in Morocco has produced compelling results. Logistic regression models have demonstrated that there are no statistically significant differences in the SNPs *IFNAR2* (rs2236757) and *TYK2* (rs74956615) between patients requiring intensive care and those not hospitalized ($P > 0.05$) (24). The observed variances between this study and other findings could potentially stem from ethnic disparities across countries, highlighting noteworthy population-based distinctions (1). Nonetheless, it is crucial to acknowledge that the disparities in our results compared to those of previously cited studies could also be influenced by interactions with other genetic variations or the effects of distinct risk and protective factors within each population (1).

The COVID-19 pandemic has exerted a widespread global impact, prompting numerous nations to investigate the expression of *IFNAR2* and *TYK2* genes. Notably, the available data primarily encompasses individuals of European ancestry, thereby presenting a limitation in the scope of research. The research findings, including our study as well as other research, underscore the notable impact of small sample sizes. Studies with insufficient sample sizes carry the risk of yielding false-negative results, as researchers may overlook existing effects. The dissemination of false negatives not only distorts theoretical comprehension but also impedes scientific advancement. Furthermore, underpowered studies pose a threat to the reliability of research outcomes, emphasizing the critical importance of meticulously considering sample size during study design. Also, control of confounding factors is crucial for obtaining reliable results.

The Omicron variant (B.1.1.159) of SARS-CoV-2 has raised concerns due to its extensive spike protein mutations, particularly in the receptor-binding domain (RBD) and the N-terminal domain (NTD), which are primary targets of neutralizing antibodies (25). Studies have revealed that SARS-CoV-2 variants of concern, including the Omicron variant, can reduce the expression of major histocompatibility complex class I (MHC-I) molecules (26). These MHC-I molecules are vital for presenting viral antigens to CD8+ T cells, which play a crucial role in immune surveillance and defense against infections (26). SARS-CoV-2 variants can potentially modulate angiotensin-converting enzyme 2 (ACE2) expression levels, which are crucial in viral entry. Any changes in ACE2 expression could significantly impact the severity of infection (27). In fact, ACE2 serves as the primary receptor for SARS-CoV-2, binding of the virus to ACE2 facilitates cell entry. So Increased ACE2 expression can enhance viral entry (28, 29). Consequently, infected cells may face challenges in effectively presenting viral antigens to the immune system due to factors such as the downregulation of MHC-I, which impairs antigen presentation and allows the virus to evade immune surveillance (26).

Some research groups, including us (30), have experimentally demonstrated *in vitro* and *in vivo* that spike proteins have pro-inflammatory properties. Among them, an intriguing study by Li et al. (31) compared the strength of action of wild-type and Omicron spike protein on several immunological parameters. It showed that the ability of the Omicron spike protein to increase the transcriptional activity of nuclear factor-κB and the concomitant production of tumor necrosis factor-α, interleukin-6, and monocyte chemoattractant protein-1 in macrophages was lower than that of wild-type spike protein, which may be one factor contributing to the milder virulence of the Omicron strain. However, we have yet to see studies assessing the impact of SARS-CoV-2 variants on the expression of *IFNAR2* and *TYK2* genes, and this limitation is also present in our research. Further, it is reasonable to assume that unique mutations in non-structural protein (NSP) such as NSP3, NSP6, and NSP13, other main structural protein such as M protein, and accessary protein such as open reading flame 7b (ORF7b) and ORF9b may disrupt the expression of *IFNAR2* and *TYK2* by affecting viral pathogenesis and evading the host's immune response (32).

Our study was conducted during the Omicron outbreak, but facility limitations prevented us from identifying the specific variant of SARS-CoV-2 responsible for COVID-19 development in patients during that time (1). Given the lack of literature on the impact of the Omicron variant on the expression of *IFNAR2* and *TYK2*, it is crucial to initiate focused projects for further understanding. Additionally, investigating the association between the temporal course of expression changes of these genes and COVID-19 prognosis after infection with wild-type and mutant strains of SARS-CoV-2 would provide valuable insights. Furthermore, analysis using human ACE2-transgenic rodent experimental models in which *IFNAR2* and *TYK2* genes are deleted or overexpressed in a cell-selective manner may also be useful for better understanding the functional mechanisms of these genes in the pathogenesis of COVID-19 caused by wild-type and mutant strains of SARS-CoV-2. It will be necessary to constantly update the above knowledge whenever major mutations that change the properties of the virus occur in the future.

Author contributions

AR: Conceptualization, Investigation, Methodology, Validation, Visualization, Writing – original draft, Writing – review & editing. MR: Investigation, Writing – original draft, Writing – review & editing. KS: Conceptualization, Investigation, Methodology, Validation, Visualization, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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