Letter to the Editor

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COVID-19: Possible Impact of the Genetic Background in *IFNL* Genes on Disease Outcomes

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Dear Editor,

The causative agent of the pandemic COVID-19 outbreak, SARS-CoV-2, is a member of the Coronaviridae family of enveloped viruses with a positive-sense single-stranded (ss) RNA genome [1]. Generally, ssRNA viruses are recognized by the host immune system in first-line defense via innate pattern recognition receptors (PRR), such as Toll-like receptor 7 (TLR7), which is a primary sensor for extracellular or endosomal nucleic acid patterns of viral origin.

Mouse hepatitis corona virus (MHV) is a prototypic β-genus coronavirus and a well-studied model for SARS-CoV. Host control of MHV infection is completely dependent on TLR7 triggering by viral RNA causing an immediate interferon (IFN) response [2]. Similarly, in MERS-CoV infection, a timely IFN signaling has been shown to protect mice from a lethal outcome, i.e., fatal pneumonia [3]. *TLR7* is a gonosomal-encoded, X-linked gene. Sex differences in TLR7 responses have been reported for humans – with female sex better coping with viral infection [4–6] – which is also a feature of COVID-19.

Upon binding viral nucleic acid motifs, TLR7 induces the expression of type I IFNs (IFN-α and IFN-β) and the expression of the more recently described family of type III IFNs (IFN-λ_{1-4}). During viral infection of lung and liver epithelium, for example, notably, type III IFNs, rather than type I IFNs, are found to be activated [7]. Type III IFNs seem to be the major IFNs induced in airway epithelial cells during infection [7]. Moreover, while type I IFNs act on ubiquitously expressed receptors, type III IFN action is restricted as receptors are particularly expressed on epithelia, e.g., of the lung. Type III IFN induction and its effectors might naturally combat respiratory infections and might constitute a promising therapeutic target pathway.

A common germ line genetic variation within the type III IFN gene locus has been most convincingly shown to determine the host's capacity to cope with an infection induced by hepatitis C virus (HCV), an enveloped ssRNA virus of positive orientation, too, featuring tropism for liver epithelial cells. One candidate variation is suggested to be a dinucleotide polymorphism within the *IFNL4* gene (rs368234815/rs11322783 [TT/ΔG]) determining

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the host's capability to encode a functional IFN-λ_4 protein [8]. Paradoxically, the *IFNL4* knockout variant TT is favorable for virus eradication and resolution of infection, presumably by the deactivation of an IFN-α-desensitizing control mechanism, antagonizing IFN-α efficacy [9].

Globally, the frequency of the favorable knockout variant TT amounts up to 0.841 among Asian populations, which lessens down to 0.689 and 0.293 for individuals of European or African ancestry, respectively. Apart from national measures that unambiguously successfully control viral spread, populations might differ in susceptibility. Moreover, within a given population, individuals might be at different risk, not only due to gender or age [1]. This is to encourage personalizing approaches considering the genetic background in *IFNL* genes as a host-specific indicator for the outcome of the prevalent RNA viral infections outside of HCV.

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Author Contributions

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