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# Environmental variation and genetic diversity contribute to population differences in immune responses to SARS-CoV-2 and COVID-19 risk

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**TITLE: Genetic and environmental drivers of population differences in immune responses to SARS-CoV-2**

**This is a summary of:** Aquino, Y. *et al.* Dissecting human population variation in single-cell responses to SARS-CoV-2. *Nature* <https://doi.org/10.1038/xxxx> (2023)

**STANDFIRST: brief summary**

Single-cell profiling reveals marked differences in immune responses to SARS-CoV-2 across human populations, due to both cytomegalovirus-induced changes in blood cell composition and genetic variations at regulatory loci. Both natural selection and admixture with Neanderthals contributed to population differentiation at these loci, shaping immune responses to SARS-CoV-2 and COVID-19 risk.

**SECTION 1: The question**

The COVID-19 pandemic has unveiled a significant range of clinical variations among individuals infected with SARS-CoV-2, ranging from asymptomatic cases to lethal disease. While advanced age remains a primary risk factor<sup>1</sup>, male sex, comorbidities, and various human genetic and immunological factors also contribute to disease outcomes<sup>2,3</sup>. From an evolutionary standpoint, there is compelling evidence to support the notion that infectious agents have had an overwhelming impact on human survival, exerting selection pressures that have shaped population genetic variation<sup>4</sup>. Interestingly, there is growing evidence linking the genetic legacy of Neanderthals in some human populations and present-day immunity, with reports indicating that the severity of COVID-19 can be influenced by mutations of Neanderthal origin<sup>5</sup>. However, our understanding of the extent to which different human populations exhibit distinct responses to SARS-CoV-2 and the role of environmental, genetic, and evolutionary factors in driving these population differences in immune responses remains limited.

**SECTION 2: The observation**

To investigate potential variations in peripheral immune responses to SARS-CoV-2 across different populations, we exposed peripheral blood mononuclear cells obtained from healthy donors of Central African, West European, and East Asian ancestries to SARS-CoV-2 and, for comparison with another respiratory RNA virus, to influenza A virus (Fig. 1). Through single-cell RNA sequencing, we analyzed the responses of 22 cell types to both viruses in both unstimulated and virus-treated cells. Additionally, we integrated these data with serological and genetic information collected from the same individuals. This approach allowed us to assess the extent of population disparities in immune responses to SARS-CoV-2 and identify contributing factors.

We first observed that the immune responses to SARS-CoV-2 closely resemble those triggered by the influenza virus, except for monocytes, which elicits a specific pro-inflammatory response when exposed to SARS-CoV-2. We identified approximately 900 genes that displayed differential responses to SARS-CoV-2 between populations. Through statistical and population genetic analyses, we show that inherent variations in blood cell composition, influenced by environmental factors like exposure to cytomegalovirus (a mostly harmless, latent human

infection), primary drive population differences in immune responses to SARS-CoV-2. Additionally, we identified hundreds of human genetic loci that contribute to population differences in immune responses, with these regulatory alleles present at varying frequencies among the studied populations. Furthermore, we found that past natural selection has influenced present-day immune responses to SARS-CoV-2, particularly among individuals of East Asian descent, and uncovered alterations in anti-viral mechanisms resulting from ancient interbreeding between Neanderthals and modern humans. Importantly, our study highlights the direct impact of genetic variants influencing immune responses to SARS-CoV-2 on susceptibility to, or severity of, COVID-19 (Fig. 1).

**SECTION 3: The implications**

Our study reveals significant variations in the responses of human populations to SARS-CoV-2. These population differences in immune responses primarily stem from variations in lifestyle and past exposures that have affected blood cell composition. However, genetic variants can also exert a strong influence on the response of specific genes to SARS-CoV-2, these variants not only affecting variation in gene expression but also, in some cases, COVID-19 risk.

While our analyses identify latent cytomegalovirus infection as an important driver of population differences in immune responses, through its effects on blood cell composition, the impact of other environmental or socio-demographic variables in the way individuals and populations respond to SARS-CoV-2 infection remains unknown. Furthermore, studies investigating the effects of age and sex, as well as utilizing other viral strains and different human tissues, on immune responses to SARS-CoV-2 at the single-cell resolution are necessary to obtain a comprehensive understanding of how different populations cope with this virus.

Despite these limitations, this study underscores the importance of expanding human genomics research beyond its predominant focus on individuals of European ancestry. Additionally, it establishes connections between past evolutionary events, such as natural selection or Neanderthal admixture, and present-day population disparities in immune responses and disease risk.

**SIGNING OFF**

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**SECTION 4: Behind the paper**

This research project emerged during the COVID-19 pandemic, when we realized we could apply our expertise on population and functional genomics of immunity to investigate the immunological basis of disparities in COVID-19 risk. The project was quickly funded thanks to COVID-19-dedicated grants by French and European funding agencies, but it took several months of optimization to achieve the target multiplicity of infection for the scRNA-seq experiment.

To our surprise, we immediately uncovered strong differences in cell composition between populations. Yet, annotating each cell population with confidence took careful analysis and validation by immunologists, ultimately allowing us to identify latent cytomegalovirus infection as a primary source of these differences.

The most exciting time of the project to me was the identification of signals of natural selection at genes associated with COVID-19 risk, such as *DR1*, lending supports to the

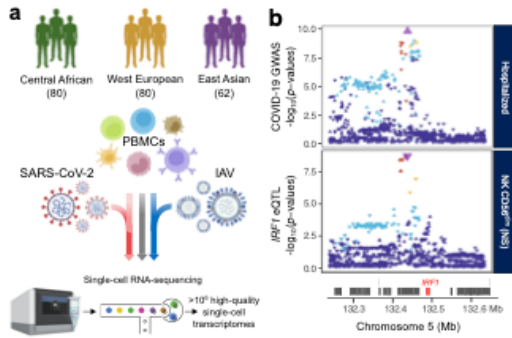
relevance of evolutionary genetics approaches to provide direct insights into disease etiology.

M.R.

## REFERENCES

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## FIGURE



## FIGURE 1 LEGEND

### Population genetic analysis of single-cell responses to SARS-CoV-2 and IAV informs on COVID-19 risk.

**a.** Study design. Created with BioRender.com. **b.**

Colocalization analysis between *IRF1*-associated variants and COVID-19 severity locus. Upper/lower panels show the two-sided Student's *t*-test  $-\log_{10}(p\text{-value})$  profiles for association with COVID-19-related hospitalization, and basal expression of *IRF1* in CD56<sup>dim</sup> NK cells. For each SNP, the direction of the arrow indicates the direction of the effect. The color code reflects the degree of LD ( $r^2$ ) with the consensus SNP identified by colocalization analyses. (purple).