HIGHER LEVELS OF GENETIC VARIATIONS OF SPIKE FOR SOME SARS-COV-2 LINEAGES AMONG IMMUNOCOMPROMISED PATIENTS

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BACKGROUND

State of the Art

While the **median duration of SARS-CoV-2** viral RNA detection in nasopharyngeal swabs collected from immunocompetent population is approximately **18 days**, SARS-CoV-2 carriage **lasted longer in immunocompromised hosts**. With such a prolonged infection, this population has been associated with **a higher probability to select novel SARS-CoV-2 mutations**, especially in the Spike protein, a key target for vaccines and therapeutics.

Objective

In this study, we conducted a **case-control study** to measure the **genetic diversity of SARS-CoV-2** and to search for **specific minority variants within the immunocompromised population**.

MATERIALS AND METHODS

Materials

478 immunocompromised patients and **234 health care worker controls** (HCW) from two large hospitals in Paris (France) diagnosed with SARS-CoV-2 infection by **RT-qPCR** were enrolled.

Methods

1. Whole-Genome sequencing was performed according to the ARTIC protocol on the **Oxford Nanopore** platform.
2. Raw sequence data were mapped to the **Wuhan-Hu-1 reference genome**, and consensus sequences were produced to determine the lineage.
3. Only sequences covering at **least 95% at ≥50X** depth of a viral gene were investigated.
4. We defined a **minority variant** when it was present in **≥5% and <50% of the reads**; and a majority variant when it was present in >50%.

RESULTS

"A Game of Variation"

A principal component analysis (PCA) revealed that each SARS-CoV-2 lineage clustered together based on majority and minority SARS-CoV-2 mutations.
Similar results were observed for immunocompromised hosts but with **some outliers**, suggesting **a higher SARS-CoV-2 genetic diversity** in this population (**Figure 1**).

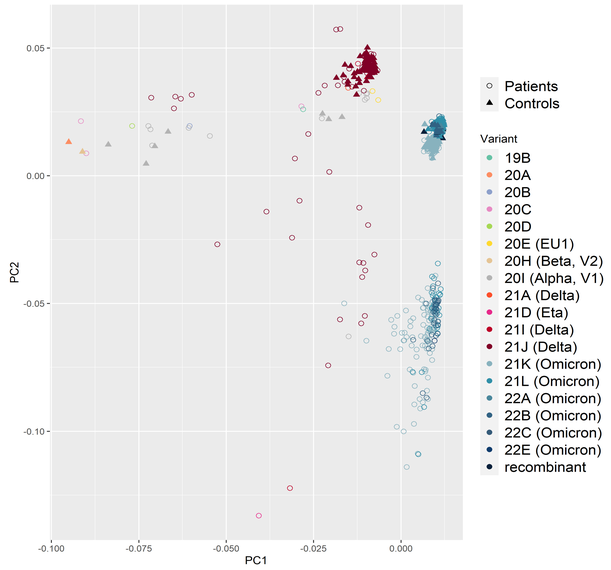

Figure 1. Principal component analysis of SARS-CoV-2 genetic diversity according to major and minor mutations. Each lineage is associated with a specific color. The shape indicates the patient category.

More minority non-synonymous mutations were detected in most of the genes ($p < 0.01$, Wilcoxon test) for the different lineages, except for the Alpha variant, in immunocompromised hosts compared to the controls (Figure 2).

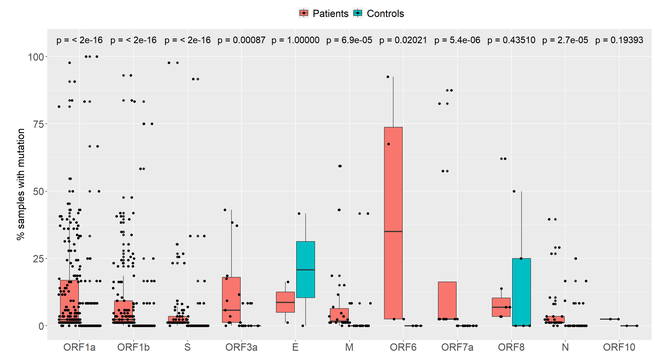

Figure 2. Percentage of samples (here infected with Omicron BA.5) with a specific mutation according to each viral gene and patient category. Comparisons between categories was done using the Wilcoxon test. Box boundaries represent the first and third quartiles and the length of whiskers correspond to 1.5 times the interquartile range.

From minority to fixed mutations

In **3/52** patients infected with the **Delta variant**, we concomitantly detected at low frequencies the Spike mutations **H655Y, N679K, N764K, D796Y** that are **Omicron variants** signature mutations.
Seven patients infected by **Omicron BA.1** lineage had Spike **R346T** at low-frequency, later **fixed in Omicron BA.4.6 and BQ.1.1**.
Eight patients infected by **Omicron BA.2** lineage had **D3N** in the **M gene** at low-frequency, later **fixed in Omicron BA.5**
None of these mutations were observed in the genomes from **controls**.

CONCLUSION

Higher genetic diversity in among sequences issued from immunocompromised hosts for some lineages.
Immunocompromised patients associated with a risk of emergence of novel, possibly immune escape / more virulent, SARS-CoV-2 variants.

ADDITIONAL KEY INFORMATION: Funded by ANRS | MIE EMERGEN consortium. Author Contact Information : valentinemarie.ferre@aphp.fr