Chapter 9

A Phylogenetic Approach to the Uneven Global Distribution of the COVID-19 Pandemic:

Y-Chromosomal Haplogroups and COVID-19 Mortality

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ABSTRACT

A possible role of Y chromosomal haplogroups in COVID-19 mortality is discussed without claiming causality. The mortality of COVID-19 seems unequally distributed in different populations and statistically significant regional covariation is presented between COVID-19 mortality and the haplogroup Y-R1b. Y-R1b is suggested as a possible marker for mortality in the first wave of the pandemic affecting the Western Europe. September 2020 the pandemic involved also Eastern Europe severely in a second wave, while South East Asia, with a very high frequency of Y-0, had strikingly low COVID-19 mortality rate. Eastern Europe is dominated by Y-haplogroups (i.e., Y-R1a), with close ancestry to Y-R1b. Molecular mechanisms mediated by the Y chromosome involved in COVID-19 mortality are discussed, presenting a possible role of KDM5D in androgen receptor modulation and regulation of TMPRSS2 known to enable SARS-CoV-2 binding to ACE2 and facilitating virus entrance into the cell and virus replication. Sex bias and comorbidities point at the role of variations in the Y-chromosomal phylogeny.

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The coronavirus SARS-CoV-2 emerged in 2019 and spread rapidly to become a global pandemic in 2020. Extending beyond the governments' differences in use of quarantine and isolation, the morbidity and mortality of COVID-19 appeared to be unequally distributed in different populations. Differences related to age and sex were early observed. In addition, some peculiar geographical differences emerged. The uneven pattern of the pandemic outspread is difficult to fully explain by temporal, contextual and environmental parameters. In this chapter, we will elaborate further on these differences. It is important to investigate all possible reasons for this inequality trying to understand how the virus, and evolving virus mutations, might affect different populations differently.

A statistical significant regional covariation between COVID-19 and the Y-chromosome-related haplogroup R1b, was early identified. In this chapter, after presenting a brief history of the Y-chromosomal phylogenecy, we draw the attention to observed covariations between the Y-chromosomal related characteristics and certain clinical phenomena, before suggesting a hypothesis on the possible relation between genetic variations of the Y-chromosome and susceptibility to death related to COVID-19.

It is too early to conclude on a possible causal relationship. The statistical covariation in itself is not sufficient to claim causality. A possible support to the hypothesis, we may find in the fact that there are other clinical conditions showing such a relationship. We still lack strong evidence related to specificity and biological plausibility. Further data is needed to analyse a possible gradient between Y-chromosome-related characteristics and mortality of COVID-19 in different populations.

THE UNEVEN GLOBAL PATTERN OF THE COVID-19 PANDEMIC

When the COVID-19 epidemic was crossing international boundaries and affecting an increasing number of people worldwide, it was at a long awaited timing when it was declared a pandemic on March 11, 2020(WHO announces COVID-19 outbreak a pandemic, n.d.). A reason for this was that at the time a pandemic was declared according to the definition used by The World Health Organization (WHO,) it was obvious that COVID-19 affected regions unevenly and that some regions were extraordinarily affected(Singer et al., 2021).

The pandemic affected Europe strongly already in February and March 2020 during the first outbreak or pandemic wave lasting until September 2020 (Covid 19 - Epidemic 'Waves', n.d.; Yang et al., 2020). During the emergence and first wave of the pandemic an underlying pattern seemed to emerge.

From the early onset it was clear that some countries were hit harder than others. Mortality rates in countries like Italy, Belgium, France, and Spain were high, whereas eastern Europe, like Russia, Hungary and Poland had hardly any diseased at this point. Countries with common borders like Slovenia and Italy had strikingly different mortality rates with thousands of diseased in Italy and almost none in Slovenia at the same time during the first wave of the pandemic.

In Wuhan in China, where the initial cases were registered late 2019, 2-3000 deaths were reported until March 2020. The total reported mortality in China today (as of May 2021) is approximately 5000, which is close to zero percent in a population of 1,4 billion people. Still, in March 2021, the mortality rates in Japan and South East Asia are surprisingly low.

One also noticed consistent regional differences within countries such as Italy, with a high mortality in specific regions, like Lombardy in northern Italy and low mortality rates in the southern parts of the country.

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