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Could the Denisovan Genes have conferred enhanced Immunity against the G614 Mutation of SARS-CoV-2?

It is striking that East Asian, South East Asian and South Pacific Populations appear relatively unscathed by the second and subsequent waves of the SARS-CoV-2 pandemic compared to the rest of the world. This is more so with the more infectious G614 mutation of COVID-19. Adherence to social distancing measures and face protection do not explain the almost 30-fold difference in infection incidence between Asian and European/American populations. The populations in the Indian Subcontinent are an exception, as infections rates were elevated compared to other Asian countries.

Differences in immune responses between European and African populations have been alluded to because of archaic introgression of immune-related Neanderthal genes in the European genome. As opposed to the European genome, the Asian genome has a higher introgression of the Neanderthal's sister species' genes, the Denisovan genes, which are more commonly found in East and South East Asia and the South Pacific populations. Contrastingly the Denisovan genes are scantily found in the populations of the Indian Subcontinent.

Lockdown in China and bordering nations, led to significant reductions in atmospheric pollution, which itself significantly attenuates pulmonary immunity. Following lockdown in January the G614 variant emerged in China. With improved immunity following lockdown, the Denisovan immunity-related gene may have been allowed to be expressed more effectively, protecting Asian populations against the more infectious G614 variant of SARS-CoV-2 during the subsequent waves of the pandemic.

KEY WORDS: *SARS-CoV-2/ COVID-19; G614 variant; infection incidence; Denisovan genes; Immunity; Asian Populations*

Background

The populations in Europe and the Americas continue to sustain significantly higher infection rates compared to Asian and South Pacific populations (Table 1).¹ This became more apparent with the emergence of the more contagious D614G variant of the SARS-CoV-2 following the pollution reducing-lockdown in China. Exceptions to this pattern of infection incidence were the populations of the Indian Subcontinent.

Besides the reduction in pollution, including the PM2.5 component, the decrease in infections in the East, South-east of Asia and South Pacific populations may be partially attributed to the more stringent adherence to social distancing and face

protection. However social distancing measures reducing human to human transmission¹ cannot explain the almost 30-fold difference in infections rates between East, South-east of Asia and South Pacific and the rest of the world. There may be a deep-seated evolutionary immunological reason providing these Asian populations protection from the 2nd wave of the COVID-19 pandemic.

TABLE 1. Comparison of Asian and European/American Incidences of SARS-CoV-2 infection incidence per 100,000 population (p-value is < .00001) (John Hopkins Coronavirus Resource Centre (26/1/21)).²

Asian Populations	Infection Incidence /100,000	European/American Populations	Infection Incidence /100,000
Tokyo	686	England	5730
Beijing	4.78	France	4774
Thailand	21	Madrid Spain	7425
Taiwan	3.7	Czechia	8843
Indonesia	370	Austria	4521
Philippines	471	Quebec	2998.5
South Korea	148	New York	6928
Papua New Guinea	9.5	Mexico City	4996

Discussion

Differences between Europeans and Africans immunity have been explained by the introgression of Neanderthal immunity-related genes in European Homo sapiens. Individuals of Homo sapiens African descent have a stronger response to infections such as *Listeria monocytogenes* and *Salmonella typhimurium* limiting bacterial growth.³ Human leukocyte antigen (HLA) genes critical to pathogen recognition have shown archaic ancestry from both Neanderthals, and the sister subspecies the Denisovans,⁴ the name derived from the Denisova Cave (located in South Siberia off the northern border of Mongolia), where the first Denisovan fossils were first found.⁵

While the Neanderthal species occupied Europe, the Denisovan species dominated Asia during the Lower and Middle Paleolithic periods. Similar to the differences in archaic immunity between Europeans and Africans, there may be similar differences between Asian and European/American populations in the immunological reaction to SARS-CoV-2.

Introgression of Denisovan genes in the *Homo sapiens* genome may offer more protection against SARS-CoV-2 than genomic insertion with Neanderthal genes. *Homo sapiens* appears to have obtained I207L, a gene variant from Denisovans, which increases the immune and inflammatory response to infections. The I207L gene variant was found from the Denisovan fossil found in the Denisovan Cave, but absent from Neanderthal remains found in the same cave. These findings suggest that the gene mutation enhancing immunity appeared after the divergence of the Denisovan and Neanderthal origins, about 400,000 years ago.⁶

The detection of antigens belonging to microbial invasions depends on toll-like receptor genes such as TLR1, TLR6, and TLR10 expressed on the cell membranes. Archaic origins of toll-like receptors appear to differentiate between Neanderthal and Denisovan genes. Two of the TLR1, TLR6, and TLR10 gene variants are most similar to the Neanderthal genome, whereas the third is most similar to the Denisovan genome.⁷ Denisovans appear to lack most of the gene mutations linked to coeliac disease suggesting that the variants may actually be in the same genes that are linked to resistance to pandemics.⁸

A genetic variant common in Neanderthal introgression in a particular region of chromosome 3 is associated with greater risk for respiratory failure after SARS-CoV-2 infection.⁹ As a consequence of respiratory failure, lung parenchymal hypoxia ensues, the onset of which initiates an irreversible cascade of inflammatory response resulting in a cytokine storm, a common cause for demise due to COVID-19.¹⁰ Interestingly the presence of Denisovan genes in Tibetans appears to advantage these populations to survive at high altitudes with low oxygen tensions.¹¹ The rate of COVID-19 in Tibet is 0.03/100,000 and similar low incidences were noted in Melanesians who have been noted to have the highest concentrations of the Denisovan genes, with 1.9% and 3.4% of their genome.¹²

Pathogen transmission during pandemics such as COVID-19, are potentially powerful selective forces that can shape surviving species possessing advantageous immunological attributes. This protection may also have occurred in the American Ethnic populations whereby the Asian non-Hispanic population had 40% lower infection rates compared to white non-Hispanic, 60% lower infection incidence than Black non-Hispanics, and 80% lower incidence of COVID-19 infection rates than Hispanic Latino populations.¹³

A clear exception to the low trend in Asian infection rates are the populations in the Indian Subcontinent. In India, Denisovan DNA has been scantily found, mostly amongst isolated, tribal communities. Conversely, significantly less Denisovan genomic ancestry was demonstrated amongst Asians in India and Pakistan of clear Indo-European descent.¹⁴

A similar pattern to the COVID-19 pandemic was seen with the most severe plague of all time, the 1918-19 influenza pandemic (Spanish Flu).¹⁵ Mortality from

the 1918-19 influenza pandemic in Hong Kong and Shanghai, was miniscule compared to the USA and Britain.¹⁶ Whereas the crude death rate from the Spanish Flu in Shanghai was 0.13%, the death rates in the rest of the world were more than 20-fold greater, reporting mortality rates of 2.5% or more.¹⁷ Besides the high mortality rates sustained in European and American populations during the 1918-19 influenza pandemic, the populations who also bore the brunt of death rates were those from the Indian Subcontinent, where an estimated 17 million people succumbed to the Spanish Flu.¹⁸

Emulating the Spanish Flu, the successful dissemination of a COVID-19 pandemic may also depend on the interplay of the viral virulence adapting to the population's innate immunity. This may be the case with the low COVID-19 incidences in the East Asian, South East Asian and South Pacific Populations, as opposed to the 30-fold higher rates in the populations of Europe and the Americas. Similar ominous circumstances may be occurring with the South African B.1.351 and Brazilian B1.1.28 variants of SARS-CoV-2, whereby preliminary data suggests an element of resistance of this variant to some COVID-19 vaccines.¹⁹ The emergence of a variant causing an outbreak in a population with certain innate immunity characteristics, may translate into an epidemic in another population with a different immunity profile.

In the presence of an immunological system that may have diminished efficacy due to archaic genomic origins, an infection such as SARS-CoV-2 may have been able to gain more traction. This is more so in an environment rendered adverse to the respiratory tract, due to high atmospheric pollution levels with particulate matter and other pollutants.²⁰ Similar to pathogen-induced immune responses exposure to atmospheric pollution with particulate matter is mediated by specific Toll-like receptor mechanisms.²¹ Following lockdown in China pollution diminished significantly allowing the more infectious D614G variant to emerge.²⁰ Pollution-reducing lockdown may have allowed the Denisovan gene-conferred immunity to express itself in a more efficacious manner against the D614G variant, protecting the East and South-East populations which possess this gene.

Conclusion

The population distribution of the Denisovan genes closely maps the regions in East and South East Asia and South Pacific which have been relatively unscathed by the 2nd wave of SARS-CoV-2 pandemic mainly driven by the more infectious D614G variant. Archaic genes have been associated with conferring immunity against epidemics. Enhanced immunity by the reduction of atmospheric pollution and the potential protective effect of the Denisovan gene, besides measures of social distancing, may have further protected these populations from the 2nd wave of COVID-19.

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