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Commentary

Paleoepidemiology: from Ancient Bones to Live Fossils and Mental Illness

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Introduction

We read with great interest the article by Jennifer Klunk et al. "Evolution of immune genes is associated with the Black Death" published in the Journal Nature on October 19, 2022. This article discusses the 14th century bubonic plague pandemic, believed to have been caused by *Yersinia pestis (Y. pestis)*, which spread throughout Europe, the Middle East, and Northern Africa, decreasing the population in these regions by up to 50%. The authors have examined the DNA of about 200 individuals found in two European burial sites who died before, during, and after the Black Death plague. They concluded that the Great Pestilence had placed selective pressure on the human population, so that the subsequent generations have inherited several genetic variants that increased the prevalence of contemporary disease. For example, Black Death survivors exhibited the full-length, as opposed to the short form, of the gene Endoplasmic reticulum aminopeptidase 2 (ERAP2) which helped them defeat the pathogen. However, the preservation of this gene has escalated the prevalence of several contemporary diseases, including autoimmune disorders, and possibly cancer, and hypertension. For example, today, three quarters of modern humans express ERAP2 and the prevalence of autoimmune disorders, cancer, and hypertension is 15.9%, 20.2%, and 49.64% respectively, suggesting that medieval pathology can influence the outcome of present-day diseases [1-3]. Conversely, the ERAP2 mutation protects against infection with Human Immunodeficiency Virus (HIV) and SARS-CoV-2, the etiologic agent of the COVID-19 pandemic [4-5].

The Y. pestis etiology of the Black Death has been challenged lately as several researchers, such as Scott and Duncan from Liverpool University in UK, believe that the 14th century plague may have been caused by an Ebola-like virus, rather than a bacterium [6]. Others have hypothesized that the Great Pestilence may have been engendered by a combination of two pathogens, such as *Y. pestis* and HIV, the latter is currently believed to be an ancient virus [7]. These paradigms are based on the discovery that the chemokine receptor 5 (CCR5)-delta32 (CCR5Δ32) variant, (expressed by macrophages and T cells), is protective against several pathogens, including *Y. pestis*, Ebola, HIV, and smallpox, suggesting historical exposure to these agents [8-9]. Indeed, this mutation, found primarily in the Caucasian population of Europe, was identified in skeletal remains from Germany dated at 900 BC, suggesting that the 14th century infection, like the previous epidemics, including the plague of Justinian (541–549 AD), could have been caused by any of the above pathogens [10]. In addition, the black rat (*Rattus rattus*), believed to be the dominant reservoir of *Y. pestis*, is absent in some plague-affected countries, such as Iceland and Norway, suggesting that a different etiologic agent may have caused the Black Death [11-12]. Along this line, researchers from the University of Stirling in Scotland and Max Planck Institute in Germany believe that the Black Death started in the area of modern-day Kyrgyzstan and was spread by humans, rather than *Rattus rattus*, a hypothesis that could explain the above discrepancies without excluding other infectious agents [13].

About 30 years prior to the Black Death pandemic, there was the Great Famine of Europe (1315 to 1322) which likely altered populational immunity so that the dissemination of infection could have been carried out by the less symptomatic individuals [14-15]. Indeed, it was recently observed that *Y. pestis* can avert detection by "hiding" inside the host polymorphonuclear (PMN) leukocytes, suggesting that this pathogen may thrive in dormant state in some individuals who could have become "superspreaders" [17]. In addition, the Black Death contemporaries observed that the wealthy men were more likely to die of this disease compared to women and the poor; since pathogens require iron to thrive, anemia may have been a protective factor [16]. This may also mean that the less symptomatic women and the poor could have spread the disease, validating the hypothesis that humans and not rats disseminated this infection.

Although direct molecular evidence has not been obtained from skeletal remains older than 1,500 years, *Y. pestis* is believed to have caused human pandemics as far back as the Bronze Age [18-19]. For example, the Plague of Athens in 430 BC was reported by Thucydides to manifest the following symptoms: "violent heats in the head, and redness and inflammation in the eyes, the inward parts, such as the throat or tongue, becoming bloody and emitting an unnatural and fetid breath". Today, more than 2,000 years later, the etiology of Athenian epidemic remains uncertain, however the causative agents were narrowed down to the bubonic plague, typhoid fever, cholera, measles or Ebola. The later incriminates the African continent as the possible infection source as Thucydides goes on to state that the disease "first began, in the parts of Ethiopia above Egypt, and thence descended into Egypt and Libya and into most of the King's country…" indicating that Ebola or other hemorrhagic fever could have been the likely etiologic factor [20].

The study of ancient diseases requires a multidisciplinary approach that must include among others, archeologists, anthropologists, molecular biologists and zoologists. Along this line, paleoepidemiology can be conceptualized as the study of contemporary genomes and archeological accounts of human remains to elucidate the etiology of historical "plagues" and develop better cures for modern diseases [21-22].

From bones to viral fossils

Human endogenous retroviruses (HERVs), comprising about 8% of the genome, are viral fossils that have originated with ancient infections and have been incorporated into the human DNA where they continued to dwell until the present time [23]. As HERVs have coexisted with their hosts for thousands of years, some of these relics have assumed physiological functions that include placentation and neuronal signaling in the Central Nervous System (CNS) [24-25]. HERV "domestication" has also contributed to pathology, including the generation of "jumping genes" or transposable elements (TE), such as long terminal repeats (LTRs) and long interspersed nucleotide elements (LINEs). These double stranded segments are capable of exiting the genome and reentering at another DNA site, causing genomic instability [26-27]. As genome destabilization is a hallmark of cancer and neuropsychiatric pathology, including schizophrenia and bipolar disorder, HERVs may promote these diseases [28-29]. In contrast, inhibiting the "cut and paste" property of jumping genes may comprise a new druggable target Mental illness [30]. On the other hand, substances of abuse, such as cocaine and methamphetamine, were shown to also destabilize the genome, probably explaining the association of these agents with psychosis [31-32].

Neuronal Arc is an ancient viral gene and TE which encodes for Gag, a LTR element, essential for the CNS synaptic plasticity and long-term potentiation, highlighting the role of this paleovirus in human neurophysiology [33-34]. Dysfunctional Arc has been implicated in pathology, including schizophrenia, autism spectrum disorder (ASD), and multiple sclerosis (MS), suggesting that ancient viruses can cause contemporary disease [35].

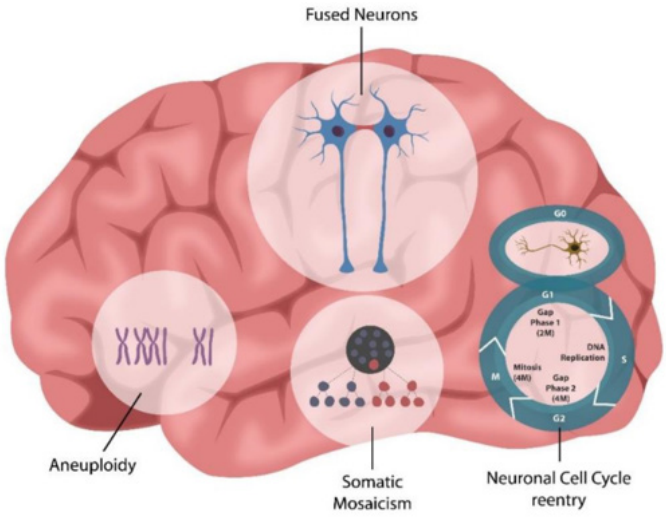

Figure 1: Viruses, including COVID-19 and HIV activate HERV ENV, inducing pathology mediated by abnormal neuronal fusion, aneuploidy, somatic mosaicism, and cell cycle reentry that can trigger neuronal loss.

Among HERV products, the envelope protein (HERV ENV) encodes for Syncytin-1, a physiological fusogen implicated in cell-cell fusion and placentation [36]. Several viruses, including SARS-CoV-2 and HIV are known to hijack HERV ENV, triggering aberrant cell-cell fusion or syncytia formation, a pathology documented in cancer, multiple sclerosis (MS), and schizophrenia [37-39]. Indeed, neuronal fusion, aneuploidy (abnormal number of chromosomes), somatic mosaicism (mutations in DNA sequence), and cell cycle re-entry of postmitotic neurons are hallmarks of aging and neuropathology, including schizophrenia and Alzheimer's disease (Figure 1) [40].

Conclusion

Historical plagues, including the Black Death, are not restricted to the past as their modern sequelae are living proofs of a time continuum, associated with both detrimental and beneficial effects. For example, the overall human life expectancy has increased after the 14th century bubonic plague, suggesting that the selective pressure the pandemic placed on the population, led to optimization of cellular processes involved in the prompt elimination of infected cells. Indeed, ERAP2 gave people a 40% survival advantage against the plague, but at the same time elevated the risk of present-day autoimmune diseases, and possibly cancer and hypertension.

HERVs are viral fossils which reside in the DNA of people living. Today some of these relics have been "domesticated" and "work "for the host. However, excessive TE mobilization, or their hijacking by exogenous viruses can trigger pathology, including cancer, neurodegeneration, and mental illness. HERVs are contemporary witnesses of historical infections buried deep in human genomes as opposed to Burial Sites. However, both archeological and live molecular fossils are sources of ancient pathology which contribute to a better understanding of present diseases and the development of novel treatments.

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Conflict of Interest

No conflict of interest.

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