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# New insights into human immunity from ancient genomics

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## Abstract

Population genetic studies have clearly indicated that immunity and host defense are among the functions most frequently subject to natural selection, and increased our understanding of the biological relevance of the corresponding genes and their contribution to variable immune traits and diseases. Herein, we will focus on some recently studied forms of human adaptation to infectious agents, including hybridization with now-extinct hominins, such as Neanderthals and Denisovans, and admixture between modern human populations. These studies, which are partly enabled by the technological advances in the sequencing of DNA from ancient remains, provide new insight into the sources of immune response variation in contemporary humans, such as the recently reported link between Neanderthal heritage and susceptibility to severe COVID-19 disease. Furthermore, ancient DNA analyses, in both humans and pathogens, allow to measure the action of natural selection on immune genes across time and to reconstruct the impact of past epidemics on the evolution of human immunity.

## **Introduction**

The relationship between humans and microbes is double-edged; they can complement each other to maintain homeostasis, like in the case of microbiota, or risk fatal conflict, like when microbes cause infectious disease. Microbes have accompanied humans since their origins in Africa ~200,000-300,000 years ago and through their subsequent dispersals around the world over the last ~60,000 years [1]. During their spread, humans have also encountered a highly diverse set of new climatic, nutritional, and pathogenic conditions, to which they had to adapt [2]. Given the strong mortality burden imposed by pathogens, it is not surprising that human genes involved in immune functions have evolved under the strongest selection pressures, whether purifying, positive or balancing [3,4]. By exploring how natural selection has shaped the variability of immune genes, population genetic studies have informed their biological relevance—essentiality, redundancy or adaptability—and provided a valuable complement to clinical, epidemiological and immunological approaches [5]. Furthermore, there is increasing evidence to suggest that natural selection has contributed to the observed population differences in immune responses and susceptibility to infectious, inflammatory and autoimmune diseases [6,7].

In this review, we will not focus on the insights provided by population genetic studies of the immune system, as they have been extensively reviewed elsewhere [1,3-9]. Instead, we will discuss how hybridization with archaic hominins and modern admixture between populations (**Figure 1**) can facilitate human adaptation to pathogens and how such events have affected present-day individual and population differences in immune responses. Finally, we will highlight how the use of ancient DNA, from humans and pathogens, can inform the dynamics of past epidemics and pinpoint genes and functions of key importance in immunity to infection.

## **The legacy of archaic hominins on human immunity**

When modern humans left Africa to settle the rest of the world, they encountered 'archaic' hominins such as Neanderthals in Eurasia and Denisovans in the Asia-Pacific region [10]. The sequencing of the genomes of archaic hominins, including high-coverage genomes from three Neanderthals [11-13] and one Denisovan [14], as well as several low-coverage Neanderthal genomes [15], has generated unprecedented knowledge on the extent of admixture between modern and archaic humans. We have learned that most of the Neanderthal ancestry present in the genomes of modern humans results from a single admixture event occurred after the out-of-Africa, while there is increasing evidence suggesting that several admixture events with Denisovans took place in different regions, and at different times [16-18]. This has resulted in ~2% Neanderthal ancestry in the genomes

of all non-Africans, <1% Denisovan ancestry in East and South East Asians, and up to 5% Denisovan ancestry in some Pacific groups [18-21].

Recent studies have shown that hybridization with closely related species can be a source of advantageous variants facilitating the acquisition of beneficial traits (i.e., adaptive introgression) [22]. Although the introgression of archaic material was generally selected against in humans [23], high levels of Neanderthal or Denisovan ancestry at specific loci can be indicative of adaptive introgression [10]. Over the past few years, several studies have shown that archaic introgression has affected human immune functions, supporting the notion that ancient admixture facilitated genetic adaptation of modern humans to the new pathogens they encountered around the world. An influential study showed that innate immunity genes are enriched in Neanderthal ancestry, highlighting the beneficial nature of Neanderthal introgression [24]. Since then, other reports have detected high levels of Neanderthal or Denisovan ancestry at some specific genes, including the antiviral *OAS* genes, the *TLR1-6-10* gene cluster or the inflammation-related *TNFAIP3* gene [24-29]. More recently, a genomic study of Pacific populations, who present the highest levels of archaic ancestry worldwide [19-21], has shown that while Neanderthals facilitated human adaptation related to phenotypes as diverse as immunity, neuronal development, metabolism and dermatological/pigmentation phenotypes, the beneficial nature of Denisovan introgression is primarily restricted to immune functions [18].

The introgression of archaic material in humans has been also found to affect molecular phenotypes, such as gene expression [30,31]. For example, two studies found that mutations associated with gene expression variation (expression quantitative trait loci, or eQTLs) in monocytes and macrophages are enriched in Neanderthal ancestry in Europeans, particularly eQTLs associated with antiviral responses [32,33]. Supporting further the notion that Neanderthals facilitated genetic adaptation of early Eurasians to viral challenges, viral-interacting proteins (VIPs) also are enriched in Neanderthal ancestry in modern humans, specially proteins interacting with RNA viruses [34]. A recent study has explored how Neanderthal ancestry has affected other layers of gene regulation, including promoters, enhancers and miRNA-mediated regulation, and found that Neanderthal ancestry has mostly affected enhancers that are active in adipose-related tissues and various types of primary T cells [35]. Collectively, these studies highlight the importance of archaic introgression as a vehicle for modern human adaptation, by serving as a possible reservoir of resistance alleles against newly-encountered pathogens.

### **Neanderthal heritage and the recent COVID-19 pandemic**

Recent works have explored the links between admixture with archaic hominins and human immunity against SARS-CoV-2 infection [36,37]. Several genomic regions have been

associated with increased susceptibility of developing severe forms of COVID-19, including a region in chromosome 3 that spans 50 kb and contains 6 genes [38]. The risk haplotype, which increases by 60% the odds of being hospitalized because of COVID-19, is of Neanderthal origin and is present in 16% of individuals from Europe, 50% of people from India and up to 63% of individuals from Bangladesh (**Figure 2**) [36]. Interestingly, an independent study has shown that individuals of Bangladeshi origin living in the UK has twice more chances to die from COVID-19 than the general population, supporting the deleterious nature of the genetic risk factor [39]. Yet, the high frequency of the risk haplotype among some contemporary populations suggests a different, even opposite adaptive value for it in past populations, when challenged by other pathogens.

Of note, the Neanderthal risk haplotype on chromosome 3 is absent among East and South-East Asian populations, an observation that well fits the extraordinarily low mortality observed in this region with respect to the number of cases. Although other factors may explain such low mortality rates, including socio-cultural and lifestyle factors, and a different management of the pandemic, a recent study argues that East Asians present some form of biological adaptation to coronaviruses. By analyzing selection signals in 420 genes encoding proteins that interact with coronaviruses in 26 worldwide populations, researchers have shown that the signals of positive selection, dating back to 20 000 years ago, are only present in populations of East-Asian ancestry [40]. This suggests that an ancient coronavirus-like epidemic occurred in the ancestors of East Asians, the genetic legacy of which might confer, at least to some extent, higher levels of protection against severe COVID-19 among contemporary populations living in this region.

Finally, another report shows that the legacy of Neanderthals has not only been detrimental for modern humans in the context of the COVID-19 pandemic. A Neanderthal haplotype on chromosome 12, overlapping the antiviral *OAS1*, *OAS2*, and *OAS3* and present at frequencies of ~30% in all non-African groups (**Figure 2**), has been found to reduce the odds to develop severe COVID-19 by 22% [37]. This observation, together with previously-reported signals of positive selection targeting the Neanderthal *OAS* haplotype in humans [27], lend support to the notion that Neanderthal introgression has been mostly beneficial for human adaptation to viral challenges [33,34].

### **Modern human admixture as a source of beneficial immune variation**

Population genetic studies have distinguished two important periods in human evolution: the Late Pleistocene, when populations of hunter-gatherers dispersed over the globe, encountered archaic hominins and diversified, and the Holocene, a more recent period when large-scale population dispersals, facilitated by technological and/or demographic changes, resulted in admixture between differentiated populations. Ancient DNA studies have shown,

for example, that admixture has occurred from ~7,500 years ago onward in Western Europe, between autochthonous hunter-gatherers and farmers originating from Anatolia [41,42]. Likewise, following their dispersals from western Central Africa ~5,000–3,000 years ago, Bantu-speaking populations admixed with hunter-gatherer and pastoralist groups from the rainforest, the East African highlands and the Kalahari Desert [43,44]. In the Pacific, population dispersals starting from Taiwan, known as the Austronesian expansion, resulted in extensive admixture with populations from Indonesia, the Philippines and Near Oceania within the last ~3,000 years [18,45,46]. Together, these studies indicate that recent admixture has been pervasive and has repeatedly shaped the genetic diversity of modern humans [47].

Similarly to adaptive archaic introgression, theoretical and empirical evidence suggests that modern admixture has also facilitated human genetic adaptation [48-50] (**Figure 1**). Although the role of this process, known as 'adaptive admixture' (or adaptive gene flow), in human evolution is yet to be fully determined, there is a growing number of cases of adaptive traits that have been acquired via intraspecies admixture, including resistance to pathogens. The most striking example is the Duffy-null *FY\*O* allele, which is thought to confer protection against *Plasmodium vivax* malaria (**Figure 3**). Indeed *FY\*O* carriers do not express the Duffy antigen/chemokine receptor, which is required for the invasion of human erythrocytes by *vivax* merozoites [51,52]. *FY\*O* occurred ~42,000 years ago in sub-Saharan Africa, where it has reached near fixation, possibly because *vivax* malaria was once endemic in the region [53]. Interestingly, *FY\*O* has been shown to be under strong, recent positive selection in African-descent admixed populations from various regions where *vivax* malaria is nowadays endemic, including Madagascar [54,55], Cabo Verde [56], Sudan [57] and Pakistan [58]. In the context of malaria, a recent study has shown that the hemoglobin  $\beta^S$  sickle mutation, a well-known resistance factor against *falciparum* malaria, occurred ~22,000 years ago in the ancestors of present-day Bantu-speaking farmers from Central Africa, and was acquired by rainforest hunter-gatherers through adaptive admixture over the last 6,000 years [59]. These findings collectively reinforce the view that *Plasmodium* parasites have imposed a strong burden on human populations for more than 20,000 years [53,59].

One of the earliest accounts of adaptive admixture in humans was described for the human leukocyte antigen (HLA) loci, which show an excess of African ancestry in admixed Puerto Ricans [60]. Although it has been advocated that different methodological artifacts can confound the analyses [61], the signal has been consistently detected in populations from Mexico, Colombia, Costa Rica and Argentina [62-64]. Given the role of HLA in resistance to infections [65,66], it has been suggested that *HLA* alleles of African-descent have been selected to protect Native Americans from diseases introduced during the European colonization, such as smallpox, measles, and typhus. However, it is unclear which

pathogen(s) was (were) responsible for the demographic collapse of Native Americans, a question that ancient DNA studies may soon resolve [67]. Adaptive admixture at *HLA* genes has also been described in Central Africa [44] and Near Oceania [68], highlighting *HLA* as a hotspot of recent selection. Overall, these findings suggest that, in addition to adaptive introgression, intraspecies admixture has facilitated genetic adaptation to the ever-changing world of pathogens that threatens our species.

### **Understanding recent immune evolution using ancient DNA data**

Our understanding of the evolution of immune response genes has long been limited to statistical inferences from patterns of genetic variation in contemporary populations, including those harboring genetic material from archaic hominins. However, ancient DNA techniques have facilitated studies of human adaptation to pathogen exposure; by analyzing the genomes of populations from different epochs, one can directly measure the effects of natural selection (**Figure 4**). In doing so, recent studies have increased our understanding of the last 10,000 years of human evolution, a time transect that benefits from more than 5,000 available ancient human genomes, covering mainly Europe but also other regions of the world.

A pioneering study, based on 230 Eurasian samples across the Holocene period, revealed 12 loci under strong positive selection, including three that are directly linked to immune functions: the *TLR10-TLR1-TLR6* gene cluster, genes regulating autophagy and the *HLA* region [69]. Another study sought to explore how the arrival of Europeans to the Americas may have altered the exposure of Native Americans to new pathogen cues. Based on exome sequences from a population of First Nations of the northwest coast of Canada, dating from before and after the first contact with Europeans, the authors observed a recent decrease in frequency of formerly beneficial *HLA-DQA1* alleles in the indigenous population, which they attribute to the environmental changes triggered by the European arrival [70]. However, which precise *HLA* alleles or haplotypes have played a major role in human biological adaptation remains an open question [71]. In this context, the reconstruction of *HLA* class I and II alleles for a large number of Europeans belonging to the Wartberg culture (5,500-4,800 years ago) indicates that immune response was probably more adapted to viral than bacterial infections during the Neolithic [72].

Interestingly, no biological or archeological evidence for diseases of epidemic proportions have been noted earlier than the Bronze Age in Europe [73]. The notion that the Bronze Age has been an important period of biological adaptation to pathogens, and particularly to bacteria, has been recently reinforced by a study that focused on human genetic susceptibility to *Mycobacterium tuberculosis* (*M. tuberculosis*) [74]. Using a database composed of more than 1,000 ancient European genomes, dating from the Mesolithic to the

Middle Ages, we have analyzed the frequency trajectory of the only mutation so far identified as underlying, in homozygosity, a common monogenic form of human tuberculosis (TB), the *TYK2 P1104A* variant, which is present in 2-4% of contemporary individuals of European ancestry [75,76]. The study has shown that the TB-risk mutation appeared in western Eurasians ~30,000 years ago, but has evolved under strong purifying selection only for the last 2,000 years [74]. These analyses indicate that TB has imposed a heavy burden on European health over the last two millennia, a date that coincides with the emergence of some specific *M. tuberculosis* strains in the region [77-79].

### **Reconstructing past epidemics through ancient pathogen genomics**

To understand how past epidemics have forged the evolution of the immune system, one can also leverage the field of ancient pathogen genomics, which has proven to be informative for identifying causative agents of past pandemics and reconstructing the history of human exposure to pathogens [80,81]. The most remarkable example relates to *Yersinia pestis* (*Y. pestis*), the causative agent of plague. By reconstructing the genome of *Y. pestis* preserved in Neolithic farmers of ancient Sweden, found to be basal to all modern and ancient known strains, a recent study envisioned the possibility of a prehistoric plague pandemic predating all other known human pandemics [82]. Yet, flea adaptation, known to enhance plague dispersal, was not acquired by *Y. pestis* until the end of the Neolithic, suggesting the rise of plague epidemics during the Bronze Age [83].

The field of ancient pathogen genomics can also inform the history of infectious agents that remain highly relevant to public health today, as is the case of *M. tuberculosis*. Whereas modern genetic data had suggested an African origin and out-of-Africa dispersal 70,000 years ago for the causative agent of TB [84], studies based on a 1,000-year-old mycobacterial genome from Peru had re-estimated its emergence to a maximum of 6,000 years ago [85]. Other works, based on high-quality ancient mycobacteria of the 18<sup>th</sup> and 17<sup>th</sup> centuries, have also supported a recent origin of TB, and the appearance of one of the most prevalent lineages of *M. tuberculosis* less than 2,500 years ago [78,79]. Altogether, the integration of both ancient human and pathogen genomes into disease modelling, combined with appropriate immune functional validation, will help delineate the most significant host–pathogen interactions during human evolution.

### **Conclusions**

Understanding how immune gene variation has contributed to our species' survival and success through archaic or modern admixture has been a topic of active research over the past few years. The sequencing of the genomes of archaic hominins and their contribution to



modern non-African ancestry [10] has allowed to unravel some key immune players that facilitated the adaptation of early non-Africans to the newly encountered environments. Likewise, admixture between modern human groups during the Holocene has enabled genetic adaptation to pre-existing pathogens, supporting the *poison/antidote model* whereby a population transmits a new disease to another population (the poison) but also the means to fight it (the antidote) [34]. Possible cases include that of rainforest hunter-gatherers from Central Africa who recently acquired the sickle-cell mutation from neighboring farmers to prevent malaria [59], and that of Latin Americans who have most likely acquired beneficial *HLA* alleles through admixture with Africans, following the European colonization and the respective introduction of new pathogens [60,62-64]. Despite these new findings, the study of how humans from different regions of the world have historically adapted to the diverse set of pathogens they have encountered remains in its infancy. Yet, the study of human genetic diversity is at the basis of understanding the observed population differences in immune responses, which is essential for the development of therapeutic treatments at a worldwide scale. Exploring, for example, immune gene diversity in Pacific populations, with the highest amount of combined archaic ancestry, and in African populations, with the lowest, might reveal key genetic components underlying population disparities in susceptibility to infectious, inflammatory, and autoimmune disorders.

Ancient DNA studies are also expected to shed light on the role of yet unknown immune-related loci, especially on those having undergone purifying selection, that is, the selective removal of deleterious alleles from the population. The use of modern DNA datasets to study negatively-selected variants has been a daunting task because, in light of their deleterious nature, such variants are underrepresented, if not extinct, in contemporary populations. In this context, ancient genomic studies based on allele frequency fluctuations over time, as that on the TB-risk *TYK2* P1104A allele [74], can be used to delineate human genetic variants that have been selected due to microbial pressure. Studies of ancient populations dating from before, during and after massive death episodes, such as past epidemics, might reveal strong signatures of selection owing to specific infectious agents. For example, ancient DNA data should help reconstructing the impact of Black Death in European populations as well as the burden caused by the European arrival (and their pathogens) in Native American populations at the immune level. Furthermore, the reconstruction of how humans have adapted to major pandemics in the past will help understanding the genetic factors involved in our current predisposition to infectious disease. In this context, additional studies with denser ancient DNA datasets across time and space, combined with modern genomes from additional populations and innovative methodological tools to detect more complex patterns of selection, will improve our understanding of the determinants of human immune evolution and its current diversity.

## Conflict of interest statement

Nothing declared

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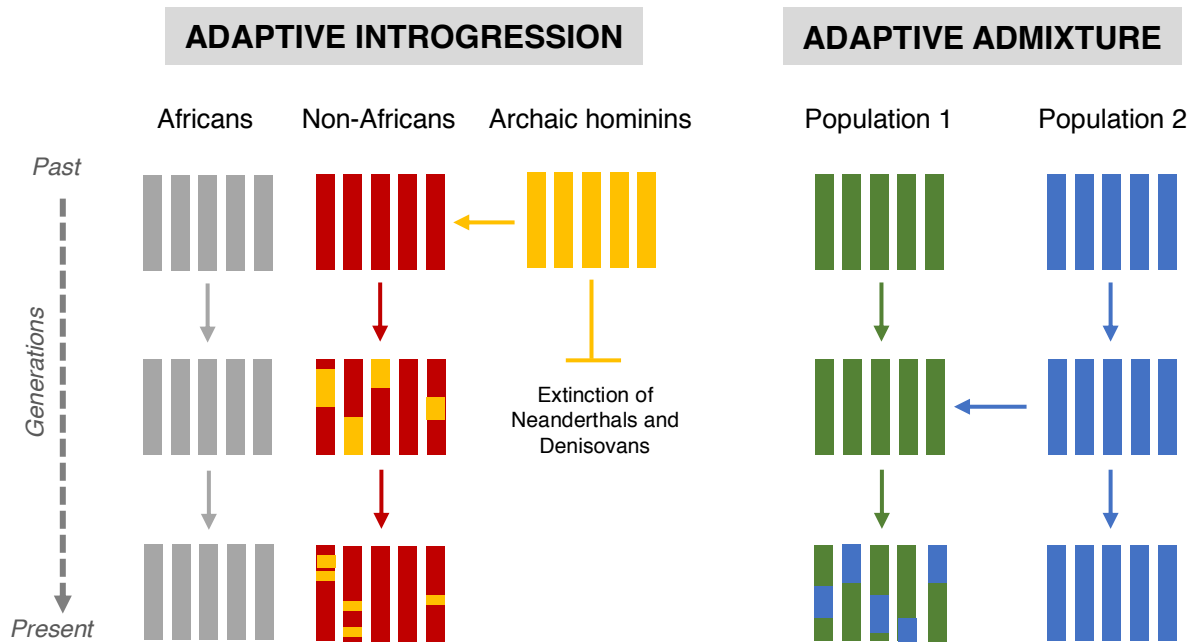
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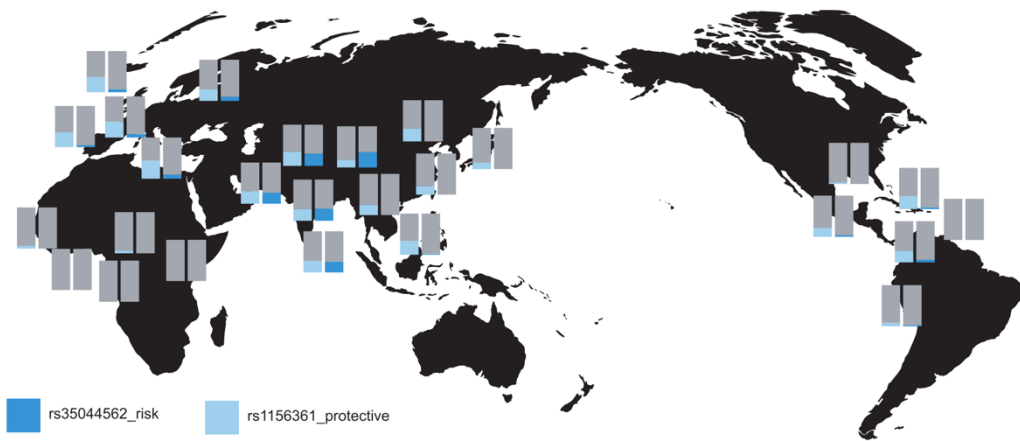
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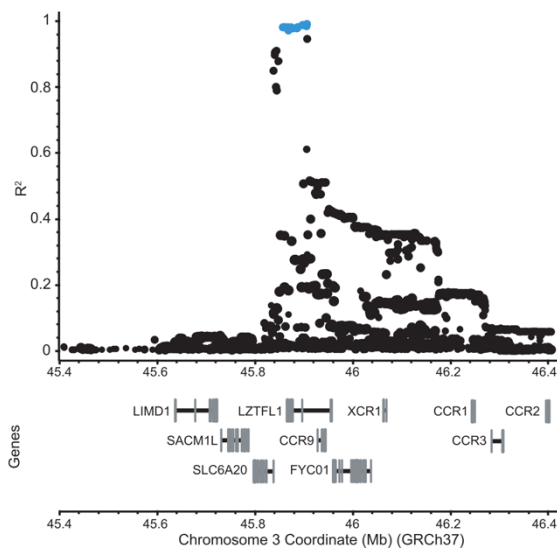


**Figure 1.** Graphical representation of the beneficial nature of ancient or modern admixture. On the left panel, the contribution of genetic material from archaic humans, such as Neanderthals or Denisovans, to non-Africans is represented. Neanderthals contributed genetic material to both Europeans and Asians, while the contribution of Denisovan ancestry is restricted to the Asia-Pacific region. In most cases, the introgression of archaic material was selected against in the genomes of modern humans, yet, in some cases, such archaic segments were beneficial for modern human adaptation a process known as ‘adaptive introgression’. On the right panel, admixture, or gene flow, between two modern human populations is represented. *Population 2* (the donor) has sent gene flow to *Population 1* (the recipient); in some cases, the genetic material of the donor population can be beneficial for the recipient population, and such material can increase in frequency in the latter population by positive Darwinian selection, a phenomenon known as ‘adaptive admixture’ or ‘adaptive gene flow’.

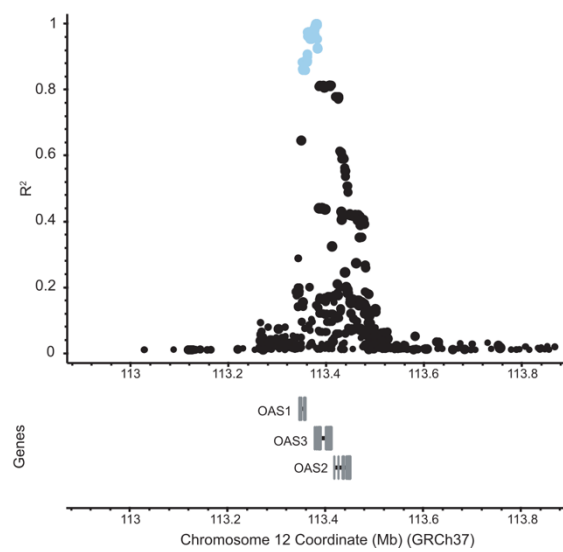
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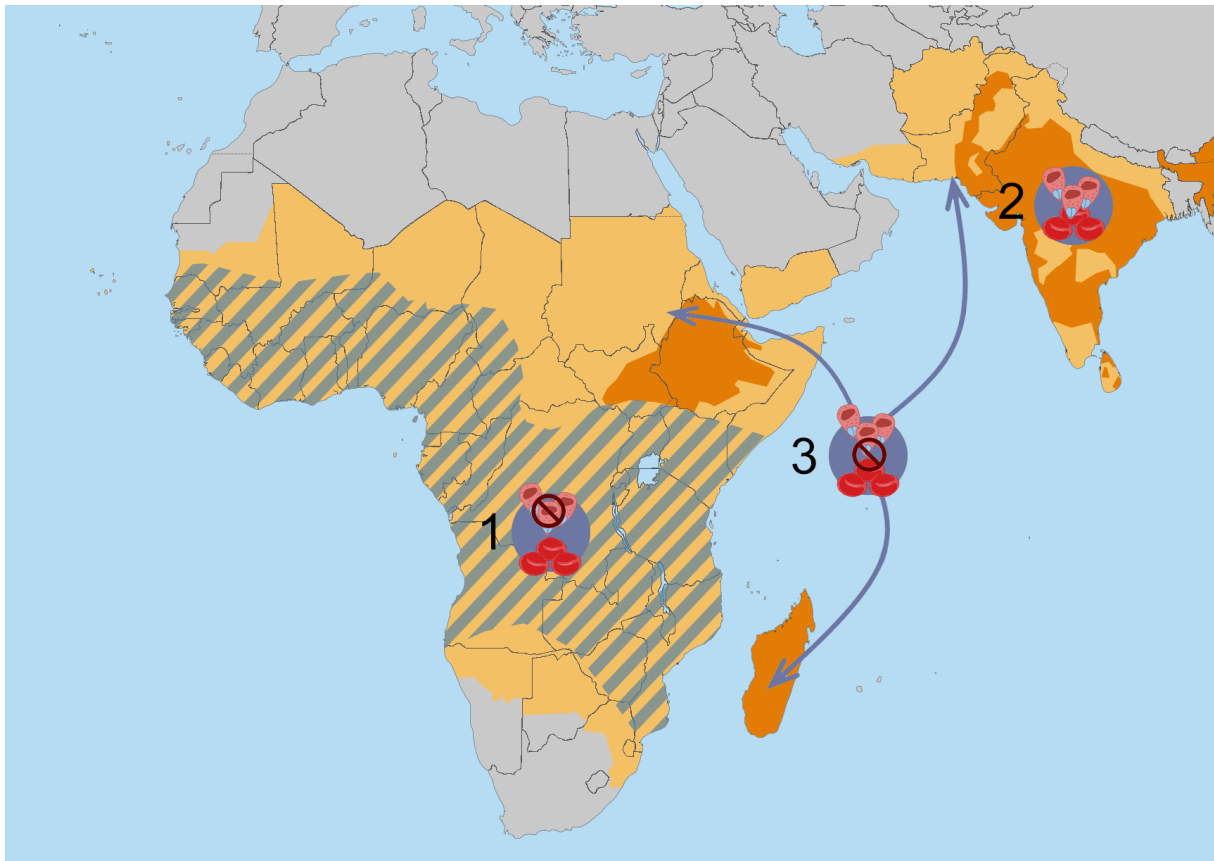
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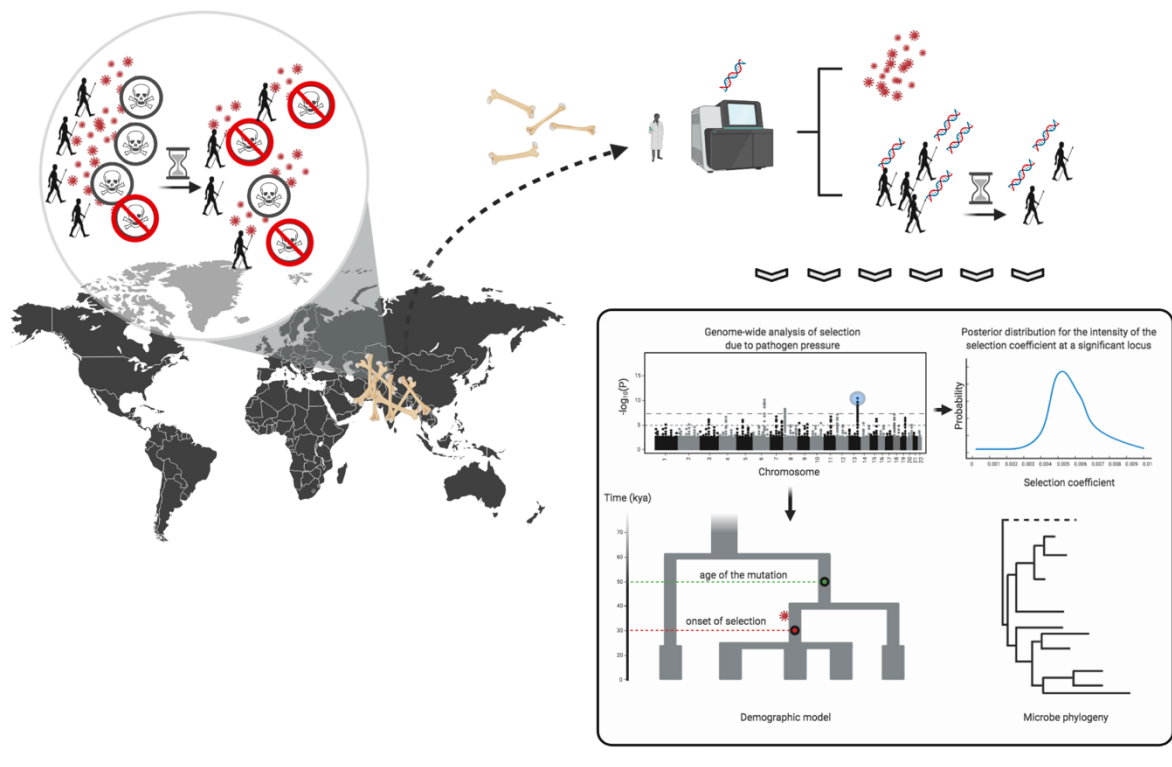
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**Figure 2.** The link between Neanderthal introgression in humans and severity to COVID-19 disease. **(A)** Geographic distribution of the alleles of Neanderthal origin in modern human population that confer risk (rs35044562) or protection (rs1156361) against severe COVID-19. Bar plots indicate allele frequencies for each Neanderthal variant. Frequency data are drawn from the 1000 Genomes Project [86]. Figures on the bottom show linkage disequilibrium between the index **(B)** risk (rs35044562) or **(C)** protective (rs1156361) Neanderthal variants with other genetic variants from the 1000 Genomes Project. Colored circles indicate the core Neanderthal haplotypes ( $r^2 > 0.98$  and  $r^2 > 0.80$ , respectively).



**Figure 3.** Adaptive admixture at the Duffy-null  $FY^*O$  allele in modern humans. Gray, light and dark orange areas indicate *P. vivax*-free regions and regions of unstable and stable *P. vivax* transmission, respectively (adapted from ref. [87]). The dashed areas indicate regions where the Duffy-null  $FY^*O$  allele is higher than 90%. In case 1, the region is free from *P. vivax* and most resident populations are resistant to *vivax* malaria. In case 2, *P. vivax* transmission is stable, and most resident populations are susceptible to *vivax* malaria. In case 3, populations have recently acquired *P. vivax* resistance through admixture with sub-Saharan Africans, and resistance is rapidly increasing in frequency under strong positive selection.



**Figure 4.** A general sketch for the rationale of studying past epidemics using aDNA data. Human remains of individuals that have been exposed to ancient pathogens at different epochs, sharing some degree of genetic homogeneity (genetic continuity), are collected for DNA extraction. Human DNA but also microbe DNA can be obtained from the collected bones. Genomics of ancient individuals are then compared, on the basis of prior hypothesis, using statistical tools. Genome-wide assessment of selection at the variant level (Manhattan plot), intensity for the selection coefficient of a significantly selected variant (blue distribution), age of the mutation and onset of selection for the selected variant (demographic model) and a phylogeny for the involved pathogen can all be investigated with the extracted aDNA data.