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Abstract

Infections have imposed strong selection pressures throughout human evolution, making the study of natural selection's effects on immunity genes highly complementary to disease-focused research. This review discusses how ancient DNA studies, which have revolutionized evolutionary genetics, increase our understanding of the evolution of human immunity. These studies have shown that interbreeding between modern humans and Neanderthals or Denisovans has influenced present-day immune responses, particularly to viruses. Additionally, ancient genomics enables the tracking of how human immunity has evolved across cultural transitions, highlighting strong selection since the Bronze Age in Europe (<4,500 years) and potential genetic adaptations to epidemics raging during the Middle Ages and the European colonization of the Americas. Furthermore, ancient genomic studies suggest that the genetic risk for noninfectious immune disorders has gradually increased over millennia because alleles associated with increased risk for autoimmunity and inflammation once conferred resistance to infections. The challenge now is to extend these findings to diverse, non-European populations and to provide a more global understanding of the evolution of human immunity.

1. EXPLORING IMMUNITY THROUGH EVOLUTIONARY GENOMICS

Since humans appeared in Africa around 300,000 years ago, they have coexisted with pathogens, and infectious diseases have imposed strong selection pressures on the evolution of the human genome (1–4). Clinical and epidemiological genetic studies have identified variations in specific human genes and pathways that account for differences in susceptibility to, or severity of, both rare immune disorders and common infectious diseases (5–8). It has become clear that evolutionary genetic approaches, fueled by the increasing availability of genomic data sets from populations worldwide (9–12), are a valuable complement to disease-focused immunological and genetic research (3, 4, 13, 14). These approaches aim to delineate human genes that are evolving under natural selection by detecting the signatures selection has left on patterns of genomic diversity (2, 15). Unsurprisingly, evolutionary studies have revealed a strong impact of selection on genes involved in immunity (3, 4), consistent with the mortality burden imposed by infections throughout human evolution (1, 16).

The dissection of the various forms of selection has proven useful in informing us about the biological relevance of immunity genes. Negative selection (or purifying selection), which eliminates deleterious alleles from the population, primarily affects genes with essential, nonredundant functions (17–20). In contrast, relaxed selective constraints on nonessential genes allow loss-of-function variants to change randomly in frequency, reflecting greater immunological redundancy (13, 21). Additionally, positive selection increases the frequency of beneficial alleles, eventually leading to fixation (100% frequency) within the population. Notable cases of ongoing positive selection include genes associated with resistance to malaria, hepatitis C virus infection, and other infectious or immune traits (1, 13, 22, 23). Conversely, balancing selection maintains functional diversity (2, 24) and can operate over various timescales (25)—from millions of years for MHC (26) to approximately 20,000 years for the sickle-cell mutation (HbS) (27). Finally, polygenic selection, which acts on weak-effect alleles at multiple loci, is believed to have been pervasive (28), yet its effects on human immunity remain poorly understood (29).

Population admixture, which is very common among modern humans (30), can also facilitate genetic adaptation by enabling the exchange of advantageous alleles between populations (31)—a phenomenon known as adaptive admixture. Malaria resistance offers a prime example of the beneficial role of admixture: The African-specific Duffy-null allele at *ACKR1* (or *DARC*) was introduced in multiple admixed groups within and outside Africa, presumably because of the allele's protective role against *Plasmodium vivax* malaria (32–37) (**Table 1**). Similarly, African rainforest hunter-gatherers have acquired the HbS allele, which confers protection against *Plasmodium falciparum* malaria, through adaptive admixture from neighboring farmers (27). Furthermore, in southern Africa, Sān hunter-gatherers who admixed with farmers present stronger selection signals at immune genes compared with nonadmixed groups, suggesting that incoming populations can bring new pathogens to which local populations can rapidly adapt (38).

Population genetics has uncovered the molecular footprints of selection within or near immunity genes, but the answer to how the selected mutations affect immune phenotypes remains largely elusive. To address this question, the combination of population genetics with functional genomics approaches has proven informative in defining the nature of the selected phenotypes (4, 39). Studies of expression quantitative trait loci (eQTL), which map genetic variants that control gene expression, have defined the extent and genetic basis of individual and population differences in the responses of immune cells to pathogen-associated stimuli (40–51). Interestingly, eQTL associated with the immune response are strongly enriched for positive selection signals and often colocalize with disease-causing variants (4, 42, 44, 48–50), suggesting that differences in disease

Table 1 The human genes under natural selection discussed in this review[a]

Gene(s)	Type(s) of selection[b]	Continent(s)	Phenotype(s)	Reference(s)
EPAS1	Adaptive introgression	East Asia	Hypoxia at high altitude	103
HLA genes	Adaptive introgression, adaptive admixture, positive selection	Europe, East Asia, Americas	Immune responses to pathogens	32, 105, 139–145, 152, 153, 170, 187–191, 193
OAS1/2/3	Adaptive introgression	Europe, East Asia	Immune responses to pathogens	20, 85, 108, 109
TLR1/6/10	Adaptive introgression, positive selection	Europe, East Asia	Immune responses to pathogens	17, 20, 106, 139, 146, 152, 153
STAT2	Adaptive introgression	Oceania	Immune responses to pathogens	85, 107
IFITM1/2/3	Adaptive introgression	Europe	Immune responses to pathogens	20
IL17A, IL17F	Adaptive introgression	Europe	Immune responses to pathogens	20, 85
TNFAIP3	Adaptive introgression	Oceania	Immune responses to pathogens	94, 96, 98, 121
IRF4	Adaptive introgression	Oceania	Immune responses to pathogens	94
TRIM genes	Adaptive introgression	South Asia	Immune responses to pathogens	123
LZTFL1	Adaptive introgression	South Asia	Immune responses to pathogens	126, 128, 129, 131, 132
ACKR1 (*DARC*)	Adaptive admixture	Africa, South Asia	Resistance to *Plasmodium vivax* malaria	32–37
HBB	Adaptive admixture	Africa, South Asia	Resistance to *Plasmodium falciparum* malaria	27
IRF1	Positive selection	Europe	Immune responses to pathogens	152, 153
SH2B3	Positive selection	Europe	Immune responses to pathogens	14, 23, 152, 153, 204, 205
FUT2	Positive selection	Europe	Resistance to norovirus	14, 23, 152, 199, 200, 205
TYK2	Negative selection	Europe	Susceptibility to tuberculosis	154, 155
ERAP2	Positive selection	Europe	Resistance to plague	178–181
CD83	Positive selection	Americas	Immune responses to pathogens	194

[a]The gene name; the type of selection signal detected; the continent where selection occurred; the phenotype proposed to be under selection; and the corresponding, most representative references are shown.
[b]Positive selection refers in these cases to the classic sweep model, wherein positive selection acts immediately on a de novo mutation.

risk can result from past selection processes that targeted regulatory variants. For example, a recent single-cell-based study has shown that a substantial fraction of eQTL detected upon exposure to SARS-CoV-2 colocalize with COVID-19 risk variants (50), supporting the notion that regulatory variants contribute to disease risk. Interestingly, SARS-CoV-2-specific eQTL and coronavirus-interacting human proteins present enrichment in positive selection signals in East Asians only (50, 52), suggesting long-term selection exerted by coronavirus-like viruses on East Asian populations.

This review does not aim to provide an overview of how the various selection types have targeted immunity genes, nor does it delve into how functional genomics has increased our understanding of the genetic and evolutionary bases of immune response variation, as these topics have been extensively reviewed elsewhere (3, 4, 13, 14, 39, 53, 54). Instead, our focus will be on how the study of ancient DNA (aDNA), which has made spectacular progress over the last decade, has enabled us to appreciate new aspects of the evolution of human immunity (**Figure 1**). These new aspects include the exchange of beneficial immune variations between humans and archaic

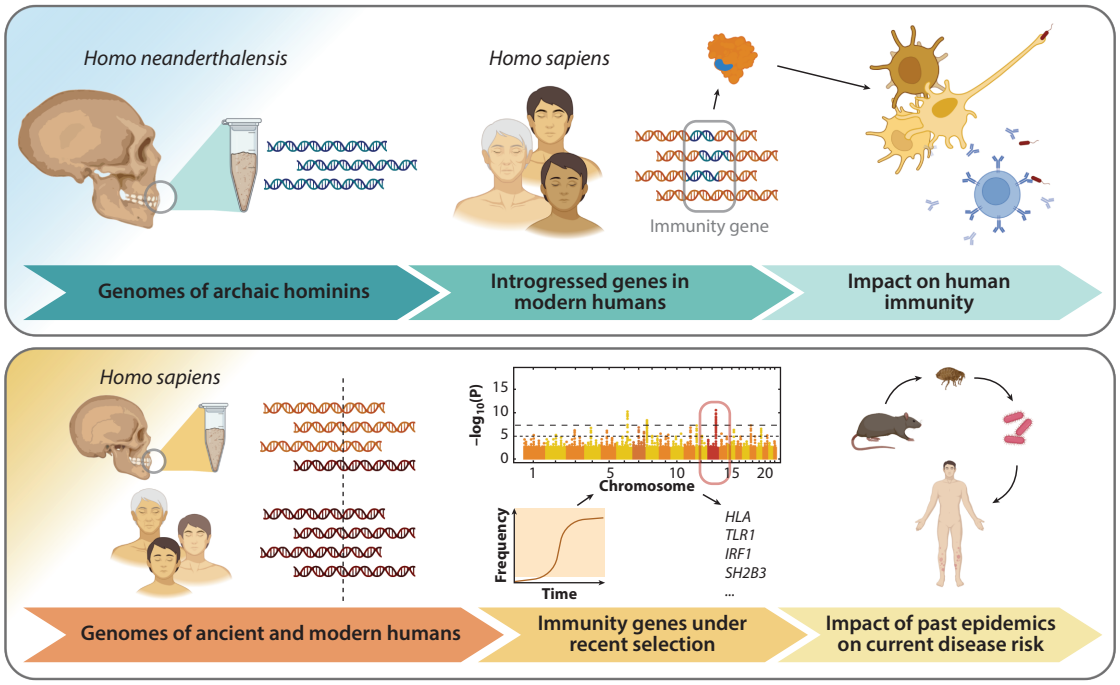

Figure 1

Insights into human immunity from ancient DNA studies. (*Top*) Genome sequencing of archaic hominins, i.e., Neanderthals and Denisovans, enables the identification of DNA segments in modern human genomes that are inherited from these archaic lineages (i.e., introgressed DNA). Several human genes, particularly those involved in immunity, show high proportions of introgressed DNA, which can affect present-day human immunity and immune-related disease risk. (*Bottom*) Genome sequencing of multiple ancient and modern humans enables the detection of immunity genes that evolved under natural selection over a given time period. The study of the effects of beneficial variants on present-day disease risk can shed light on the evolutionary origins of immunity-related diseases. Figure adapted from images created with BioRender.com.

hominins, namely Neanderthals and Denisovans; the evolution of human immunity across different epochs, from the Neolithic period to the present day; and the impact of past selection on the present-day susceptibility to infectious, autoimmune, and inflammatory disorders.

2. THE RISE OF ANCIENT GENOMICS

The era of ancient genomics—the study of DNA from ancient remains—began in 1984 with the publication of a short sequence of mitochondrial DNA from the quagga, a zebra subspecies that became extinct in the nineteenth century (55). Sequencing aDNA poses several methodological challenges: aDNA is heavily degraded (DNA segments rarely exceed 100 nucleotides), chemically altered (cytosine is converted to uracil by hydrolytic deamination), and often contaminated (mostly by environmental DNA but also by modern human DNA) (56). However, advancements in DNA sequencing techniques and the development of computational tools for aDNA data analysis have substantially reduced the constraints imposed by these challenges. Forty years after the publication of the first aDNA sequence, we now have access to genomes of extinct hominins, including 430,000-year-old early Neanderthals (57) and the more recently discovered Denisovans (58, 59); of ancient horses from more than 500,000 years ago (60); and of mammoths from more than a million years ago (61). We even have ancient environmental DNA documenting plant and animal assemblages from around two million years ago (62).

2.1. Tracing Human History Through Ancient Genomics

The first genome from an ancient "modern human" was obtained in 2010 from a hair sample of a Paleo-Eskimo dating back around 4,000 years from Greenland (63). Since then, aDNA data for thousands of ancient humans have been generated. Although some genomes go back around 40,000–45,000 years, such as those of the Ust'-Ishim individual from Siberia (64), the Tianyuan individual from China (65), or the Zlatý kůň individual from Czechia (66), most of the genomes date back no more than 10,000 years (67, 68). aDNA studies have greatly improved our understanding of the genetic history of our species, including the discovery of ancient lineages that vanished and did not contribute to the genetic diversity of contemporary humans, as well as ancient lineages that have persisted until the present (67, 68). These studies have also uncovered important and previously unknown demographic events, such as ancient population splits in Africa that can date back as deep as 350,000 years ago (i.e., the split between Khoe-Sān hunter-gatherers and other groups) (69), the complex formation of present-day European populations (70), and events of population admixture and replacements underlying the peopling history of Eurasia, the Pacific, and the Americas (67, 68, 71, 72).

2.2. Leveraging Ancient Genomes to Study Human Adaptation

Ancient genomic studies also provide a unique opportunity to trace genetic adaptations of human populations in response to changing climates, nutritional resources, and pathogens (73). While the study of genetic diversity in present-day populations offers indirect evidence of past biological adaptations, these genomic footprints provide limited insights into the causes, timing, and intensity of selection, as well as into the origins of beneficial variation (2, 15, 74). In contrast, aDNA allows for the direct observation of events of genetic adaptation, including those facilitated by genetic exchanges with archaic humans, and greatly improves the assessment of the timing of selection and its strength (i.e., the selection coefficient) (68, 74). By enabling the detection of genetic variants inherited from archaic humans (**Figure 2**) and charting changes in allele frequencies across different epochs (see the sidebar titled Ancient and Modern DNA Time Transects), ancient genomics can tackle these important questions in human physiology: What are the biological processes most affected by genetic exchanges between modern humans and other hominins such as Neanderthals or Denisovans? Which genes harbor variants that have decreased the most, through negative selection, or increased the most, through positive selection, over time? As discussed in Sections 3 and 4, aDNA studies have proven powerful in elucidating immune functions critical for human survival against infection, underscoring the value of ancient genomics in immunology.

3. THE HERITAGE OF ARCHAIC HUMANS ON MODERN HUMAN IMMUNITY

Sequencing the genome of extinct hominins stands as one of the most remarkable achievements in the field of ancient genomics (75). While *Homo sapiens*, or anatomically modern humans (referred to as "humans" for convenience in this review), are today the sole representatives of the human lineage, at least three human lineages coexisted until about 40,000 years ago: humans, Neanderthals, and Denisovans. Humans originated in Africa about 200,000–300,000 years ago and spread around the world over the last 60,000 years, while Neanderthals and Denisovans had lived in western and eastern Eurasia, respectively, for hundreds of thousands of years before the arrival of *H. sapiens* (71, 75, 76). Three high-coverage genomes from Neanderthals (77–79), along with several moderate- to low-quality Neanderthal genomes (80, 81), have been sequenced so far. At present, only one high-coverage Denisovan genome is available (58, 59). Interestingly, this

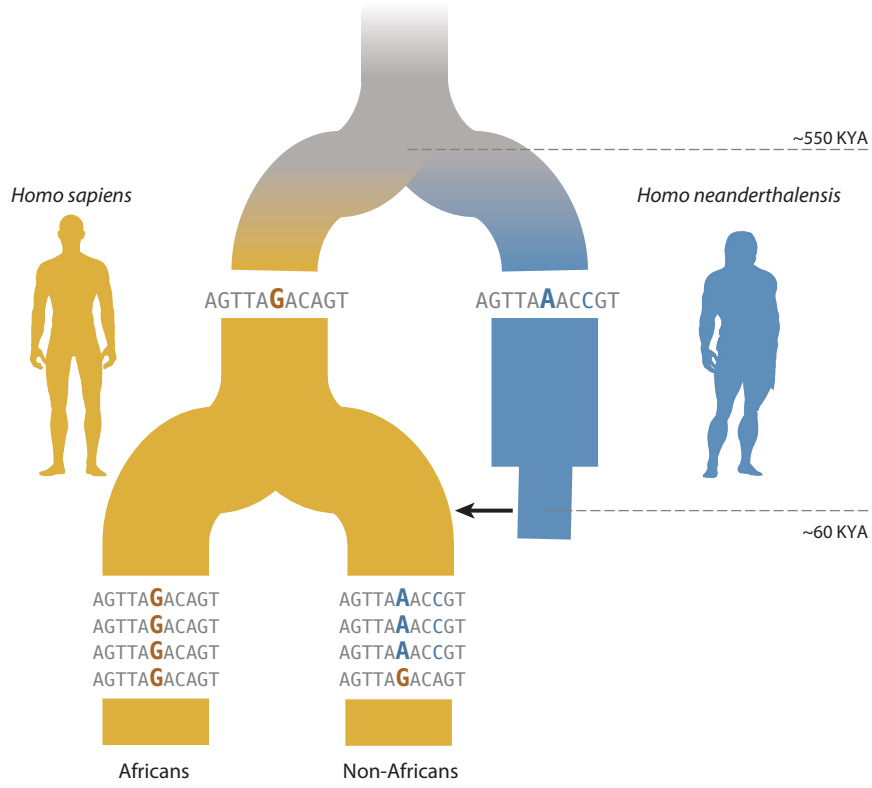

Figure 2

Neanderthal introgression into modern humans. After their split approximately 550 thousand years ago (KYA), the ancestors of modern humans and Neanderthals evolved separately on different continents until they met in Eurasia and admixed approximately 60 KYA. This interbreeding resulted in the transfer of genetic variation from archaic hominins into non-Africans, a process referred as to introgression. In this example, non-Africans carry the A mutation (*blue*) inherited from Neanderthals because of introgression, whereas Africans do not.

archaic human lineage was identified solely through its genome sequence divergence from that of Neanderthals and was named after the Denisova Cave in Altai, Siberia, where it was discovered. Based on genome comparisons, we know that the ancestors of the three lineages started to diverge about 550,000 years ago, with Neanderthals and Denisovans splitting later, about 400,000 years ago, and that they all interbred to different extents (75). For example, the discovery of a bone from a young female in the Denisova Cave, whose genome shows that she had a Neanderthal mother and a Denisovan father, attests to interbreeding between the two ancient groups (82).

3.1. Introgression from Neanderthals and Denisovans

The debate over whether *H. sapiens* interbred with archaic lineages dates back to the discovery of the first Neanderthal in 1856 in the Neander Valley, Germany. A fundamental insight into this controversy came with the sequencing of the first Neanderthal genome, revealing that approximately 2% of the genomes of all contemporary non-Africans are of Neanderthal origin and providing initial evidence of genetic exchanges between the two lineages—a process referred to as introgression (**Figure 2**)—around 60,000 years ago (83, 84). Subsequent sequencing of additional Neanderthal

ANCIENT AND MODERN DNA TIME TRANSECTS

The detection of natural selection on modern genetic diversity makes simplifying assumptions (74, 211): Selection pressure is constant over time—which is unrealistic in the context of infectious diseases—and the selected mutation originated in the study population, despite evidence that human populations have acquired adaptive variants from other populations and archaic humans. Ancient genomics provides direct access to allele frequency changes over time, circumventing these assumptions.

Time series DNA data enable the estimation of the temporal frequency trajectory of mutations, revealing when and in which population the mutation originated and how rapidly it changed in frequency (**Figure 3**). A rapid increase (or decrease) in frequency may indicate positive (or negative) selection, unlike the trajectory observed for alleles evolving under neutrality (**Figure 3*a*,*b***). However, migration can also increase allele frequencies if a population carrying the allele moves into the studied region during the time transect (**Figure 3*c***). This process, known as population discontinuity, can mimic selection signals. Methods have been developed to estimate the time of onset and strength of selection from time series data (212–214). Some of these methods explicitly account for population discontinuity, enabling more accurate detection of selection signals (139, 152, 153, 215).

genomes, along with the Denisovan genome, has provided more refined insights into the extent of archaic gene flow into humans, as well as the timing and number of independent admixture events (known as pulses) (59, 77, 78, 80, 81).

The relatively homogeneous nature of Neanderthal segments in humans, along with the consistent fraction of Neanderthal introgression of around 2% across all non-Africans (85), supports the occurrence of a single, major admixture event coinciding with the time when humans left Africa and before their split into European, Asian, and Oceanian lineages (67, 71, 75, 86). Although the slightly higher Neanderthal ancestry detected in East Asians compared with Europeans suggests an additional pulse of admixture between Neanderthals and humans (87, 88), this difference could stem from subsequent admixture of Europeans with a human group carrying little to no Neanderthal ancestry, from different generation intervals, or from methodological issues (70, 89, 90). In contrast, comparisons of Denisovan and modern human genomes worldwide have revealed multiple geographically localized admixture pulses. Denisovan-related ancestry is detected in up to 5% of the genomes of some contemporary Oceanians and in small amounts (<0.2%) in East Asians, South Asians, and Native Americans (91). Unlike Neanderthal segments in humans, which are closely related to the Neanderthal genomes sequenced so far, the Denisovan DNA present in humans diverges more from the Denisovan genome, suggesting greater genetic diversity among Denisovans than among Neanderthals (92). Furthermore, the Denisovan contributions to humans appear to have originated from at least two different Denisovan groups and occurred through up to four independent pulses (92–95).

A fascinating question concerns the human genes that have retained archaic DNA fragments and the fragments' effect on present human physiology. In most cases, negative selection acted upon archaic material, resulting in a global depletion of Neanderthal and Denisovan ancestry within genes and in specific regions of the human genome, termed deserts (85, 91, 96, 97). These deserts are particularly observed on the X chromosome and in testis-specific genes, supporting the notion of reduced fitness in male hybrid offspring (85). However, some human genomic regions contain archaic DNA fragments at high population frequencies, suggesting a selective advantage of archaic material—a phenomenon known as adaptive introgression (75, 98–100). Having inhabited Eurasia for at least 300,000 years before the arrival of modern humans, Neanderthals and Denisovans were likely more adapted to the environmental conditions that humans faced

during their dispersal across the globe. Numerous studies have identified high-frequency archaic fragments in the human genome, particularly near genes associated with body morphology; skin pigmentation; metabolism; and responses to temperature, altitude, and sunlight (reviewed in 75, 101, and 102). These findings provide strong evidence for the beneficial effects of archaic introgression on human adaptation. An emblematic case involves the genetic adaptation of Tibetans to the extreme hypoxic conditions associated with high altitude. This adaptation appears to have been facilitated by the introgression of a 33-kb Denisovan DNA segment encompassing *EPAS1* (**Table 1**), a gene encoding a hypoxia-induced transcription factor; the frequency of this segment exceeds 80% in Tibetans, but the segment is rare or absent in other populations (103).

3.2. The Influence of Neanderthal Heritage on Present-Day Human Immunity

Not only do genes associated with immunity emerge as frequent targets of selection within human populations (3, 4), but studies also have shown that archaic introgression has particularly affected the immune system, supporting the notion that archaic admixture facilitated human genetic adaptation to new pathogens encountered (**Table 1**) (3, 75, 104). The first link between archaic admixture and immunity came from the *HLA* locus, where several haplotypes appear to have been introduced into humans through admixture with Neanderthals and Denisovans (105). Since this initial study, numerous immunity genes have been shown to be affected by archaic introgression. High levels of Neanderthal ancestry have been detected in the antiviral *OAS* genes; the *TLR1/6/10* gene cluster; and genes encoding the transcription factor STAT2, the restriction factors IFITM1/2/3, and cytokines such as IL-17A and IL-17F (20, 85, 98, 99, 106–109). Particularly noteworthy is a study that took a broader approach by examining the degree of Neanderthal ancestry in more than 1,500 genes encoding various components of the human innate immunity system (20). The researchers found that these genes exhibit higher levels of Neanderthal ancestry compared with the rest of the coding genome, suggesting an overall retention among Eurasians of Neanderthal alleles that affect innate immunity.

Studies of eQTL have revealed that the introgression of Neanderthal variants in humans can affect molecular phenotypes (109–111). For example, Neanderthal-inherited variants both reduce *OAS3* expression in response to influenza virus and to the synthetic ligand gardiquimod, which mimics infections with single-stranded RNA viruses, and encode alternate isoforms of *OAS1* and *OAS2* (109). Similarly, eQTL studies in monocytes and macrophages exposed to ligands activating the Toll-like receptor (TLR)1/2, TLR4, and TLR7/8 pathways, as well as to pathogens such as the influenza virus or the bacteria *Listeria monocytogenes* and *Salmonella enterica* serovar Typhimurium, have shown that eQTL are enriched in Neanderthal ancestry in Europeans, particularly eQTL associated with responses to viral challenges (17, 44, 48). The connection between Neanderthal introgression and human antiviral responses is further supported by the observation that human genes encoding viral-interacting proteins are also enriched in Neanderthal ancestry, especially those proteins that interact with RNA viruses (112). Notably, Neanderthal-derived variants in humans are particularly present within active enhancers in various types of primary T cells (113) and have contributed large-scale variation in T cell receptor genes (114). Furthermore, Neanderthal introgression appears to have played a role in shaping ultimate organismal phenotypes, as suggested by reported overlaps between Neanderthal variants and associations with certain autoimmune and inflammatory conditions (85, 115, 116).

The identification of the causal mutations within Neanderthal haplotypes that are associated with human phenotype variation remains, however, somewhat limited. To address this gap, large-scale functional screens can enhance our understanding of the effects of archaic variants on human molecular phenotypes, such as gene expression and splicing (117, 118). For example, a functional

study utilized a massively parallel reporter assay (MPRA) to directly assess the regulatory activity of more than 5,000 variants within Neanderthal haplotypes in K562 cells (117). The MPRA revealed that approximately 2,500 of these variants are located within active *cis*-regulatory elements, with 292 significantly modulating gene expression by, for example, altering binding to transcription factors crucial in immunity, such as TFEB, E2F3, SNAI1, CTCFL, NFIC, and SP1. Furthermore, these 292 variants are enriched for associations with neutrophil and white blood cell counts and are associated with altered expression of genes implicated in the type I interferon signaling pathways, innate immunity, the inflammatory response, and antiviral defense (117). Collectively, these studies highlight the impact of Neanderthal introgression on human immunity and propose mechanistic explanations for how archaic genetic variants have shaped present-day immune response variation.

3.3. The Impact of Denisovan Heritage on Present-Day Human Immunity

The most intriguing observation from studies of Denisovan introgression is the overall enrichment of Denisovan genetic material in human genes involved in molecular and cellular processes related to immunity (e.g., *TNFAIP3*, *PELI2*, *BANK1*, *CCR10*, *CD33*, *DDX60*, *IRF4*, *JAK1*, *VSIG10L*, *OAS2*, and *OAS3*) (94, 95, 98, 119). Among them, *TNFAIP3* stands out as a prototypical immunity-related gene wherein Denisovan introgression has been consistently detected (**Table 1**) (94, 96, 98) This gene encodes the A20 protein, which inhibits NF-κB activation and TNF-mediated apoptosis. A20 plays an important role in cytokine-mediated immune and inflammatory responses, and genetic variation at *TNFAIP3* has been associated with autoimmune disease risk (120). The Denisovan *TNFAIP3* haplotype is present at a frequency of more than 50% in southwest Pacific populations but is absent elsewhere (94, 121). Functional studies have shown that the beneficial effects of the Denisovan haplotype may arise from a partial phosphorylation deficit of the resulting A20 protein, coupled with heightened immunity without the induction of spontaneous inflammation (121). Another example is *IRF4*, whose product regulates TLR signaling and interferon responses to viral infections; *IRF4* is encompassed by an approximately 29-kb-long Denisovan haplotype, found at a frequency of more than 60% among hunter-gatherers from the Philippines (94).

3.4. Differing Functional Contributions of Neanderthals and Denisovans to Modern Humans

In Oceanians, who exhibit the highest levels of combined Neanderthal and Denisovan ancestry worldwide (58, 91, 96, 122), the comparison of the extent of archaic introgression shows that while Neanderthal ancestry is evenly distributed (∼2.5%), Denisovan ancestry varies considerably across populations (∼0–3.2%) (94). Importantly, whereas Neanderthal introgression has affected diverse phenotypes such as immunity, neuronal development, metabolism, and pigmentation, the beneficial effects of Denisovan introgression are primarily restricted to the regulation of innate and adaptive immunity (94). Additionally, a functional study conducted with Papuan individuals reported an enrichment of Denisovan variants compared with Neanderthal variants within *cis*-regulatory elements active in immune cell types such as hematopoietic stem cells and B cells, suggesting a more pervasive contribution of Denisovans to immunity-related regulatory processes (119). Moreover, a recent study of more than 2,000 Indians revealed that high-frequency Denisovan segments in South Asians are also enriched for genes associated with immunity (123), including several members of the *TRIM* gene family, which play key roles in pathogen resistance, notably against viruses (124).

The observed differences between Neanderthal and Denisovan contributions to modern humans make it tempting to speculate that humans inherited from Neanderthals a set of adaptive

genetic variants spanning multiple phenotypes, likely facilitating adaptation to the new environments encountered by humans after their departure from Africa. Conversely, the admixture with Denisovans—which occurred later, as humans reached the Asia-Pacific region—primarily facilitated adaptation related to resistance against local pathogens.

3.5. Archaic Introgression and the COVID-19 Pandemic

The COVID-19 pandemic has brought devastating consequences worldwide, affecting mortality, health, and the economy. Yet it has also presented an unprecedented opportunity to delve, on a large scale, into the factors influencing infectious disease risk. Human genetic factors driving clinical variability of SARS-CoV-2 infection have been dissected to a degree never before seen in the field of infectious disease research (reviewed in 125). Focusing on the impact of archaic introgression on COVID-19, two initial studies reported associations between Neanderthal-introgressed variants and COVID-19 risk (126, 127). One such association involves an approximately 75-kb Neanderthal haplotype on chromosome 12 that is found at a frequency of about 30% in Eurasians and is associated with a 22% lower relative risk of hospitalization for COVID-19 (127–129). This haplotype encompasses the *OAS* gene cluster and leads to a splice variant of *OAS1*, encoding a more active protein likely to be more efficient in eliminating cells infected with RNA viruses (109, 130). This finding once again highlights the potential benefits of Neanderthal introgression for human survival against RNA viruses.

However, not all Neanderthal-introgressed material confers beneficial effects on disease risk. Neanderthal segments introduced into the human genome around 60,000 years ago and subsequently selected for their advantageous effects can, because of changes in environment, lifestyle, and the emergence of new infectious agents, become deleterious for present-day human health. This situation is attested by another association linking Neanderthal-introgressed variants to COVID-19 risk (126). This region spans a 49-kb Neanderthal haplotype on chromosome 3 that contains six genes (*SLC6A20*, *LZTFL1*, *CCR9*, *FYCO1*, *CXCR6*, and *XCR1*). Carriers of this haplotype, which is present at frequencies of around 16% in Europeans and up to 60% in South Asians but is absent in East Asians, have 60% higher odds of hospitalization for COVID-19 (126, 128, 129, 131). Functional data suggest the involvement of *LZTFL1*, as well as other nearby genes whose expression is affected by the Neanderthal haplotype, such as *CCR1* and *CCR5*, in the modulation of COVID-19 severity (132, 133).

Besides the impact of Neanderthal introgression on COVID-19 risk, Neanderthal variants that alter leukocyte responses to SARS-CoV-2 notably affect myeloid cells, a single-cell-based study has revealed (50). This study has also delineated the regulatory effects through which archaic introgression influences immune responses to influenza A virus and SARS-CoV-2. These effects involve the cell type–specific regulation of genes such as *OAS1*, *OAS3*, *PNMA1*, *TLR1*, *FANCA*, *IL10RA*, *TRAF3IP3*, or *TNFSF13B* (50). Taken together, these findings further support the notion that Neanderthal introgression can affect the present-day risk of immunity-related diseases, including COVID-19, by altering specific cellular and molecular mechanisms of immune function.

4. THE EVOLUTION OF HUMAN IMMUNITY OVER THE LAST 10,000 YEARS

Human history is characterized by two broad periods: the late Pleistocene (130,000–11,000 years ago)—during which humans settled the entire planet, formed isolated populations of hunter-gatherers, and admixed with archaic lineages—and the Holocene (from 11,000 years ago onward), which was marked by a relatively stable, warmer climate and major technological advancements that fueled population growth, large-scale spatial expansions, and widespread admixture between

human populations. A third, more debated, period is the Anthropocene, starting in the mid-twentieth century with the first geological and ecological signs of the impact of human activities on the planet. Each of these periods has arguably been characterized by profound transformations in demography, subsistence strategies, and health-related practices, which may in turn have affected infectious disease risk (16, 134). However, although periods of rapid changes in disease prevalence have long been suspected, direct evidence remains elusive. Only recently has ancient genomics enabled the lifting of the veil on human adaptive changes over these periods and addressed, for the first time, central questions in immunology such as the following: Have major epidemiological transitions exposed humans to new infectious diseases? What pathogens have exerted the strongest selection pressures on human populations since the Neolithic period? Has the human immune system evolved to be more reactive, potentially making present-day people more susceptible to inflammation?

4.1. From the Neolithic Period to the Bronze Age

The impact of the emergence of agriculture on human health is a long-standing question in archaeology, genetics, and evolutionary medicine. Based on present-day epidemiological data, researchers have argued that the Neolithic transition, which started around 11,000 years ago, heightened the exposure of early farmers to zoonoses, anthroponoses, and sapronoses, with exposure fostered by proximity to domesticated animals, increased human density and mobility, and sedentism, respectively (135–137). While archaeological records suggest that early agriculturalists suffered from infections, osteo-pathological evidence has remained largely inconclusive (138). In contrast, the comparison of hunter-gatherers' ancient genomes with those of farmers, along with the sequencing of ancient pathogens (see the sidebar titled Ancient Pathogens and Ancient Epidemics), enables us to address whether the Neolithic transition resulted in the spread of new pathogens and to identify human genes that have been key to surviving these infections.

A seminal study sought to uncover the genetic variants that have been selected over the last 8,500 years of Eurasian history by generating ancient genomes from 230 west Eurasians (139). The authors identified two immunity-related genomic loci that had experienced strong selection over the past millennia (**Table 1**). The first, *HLA*, is a well-known hotspot of selection;

ANCIENT PATHOGENS AND ANCIENT EPIDEMICS

Archaeological human remains contain not only human aDNA but also appreciable amounts of aDNA from pathogens that infected, and potentially killed, the sampled individuals. Ancient pathogen genomics—the study of genomic data from pathogens retrieved from ancient human, animal, or plant remains—has emerged as a promising field that provides insights into microbiology, evolutionary biology, epidemiology, and medicine (216). Historically, infectious diseases have been retraced from historical records or paleopathological evidence, but neither approach confidently identifies the microbes involved. Since the publication of the first ancient bacterial genome in 2011 (173), ancient pathogen genomics has transformed our views of human-pathogen coevolution. Major findings include the demonstration that *Yersinia pestis* was the causative agent of three historical plague pandemics, including the Black Death and its likely origins in Central Eurasia (173, 217); genomic evidence that Late Neolithic Eurasians were infected by *Y. pestis* strains that lacked flea-borne transmission (162, 164); the discovery that hepatitis B virus diversified around the time when humans reached the Americas (218, 219); and evidence that Pre-Columbian Native Americans were infected by a form of the *Mycobacterium tuberculosis* complex (*Mycobacterium pinnipedii*) related to strains that infect seals and sea lions (220).

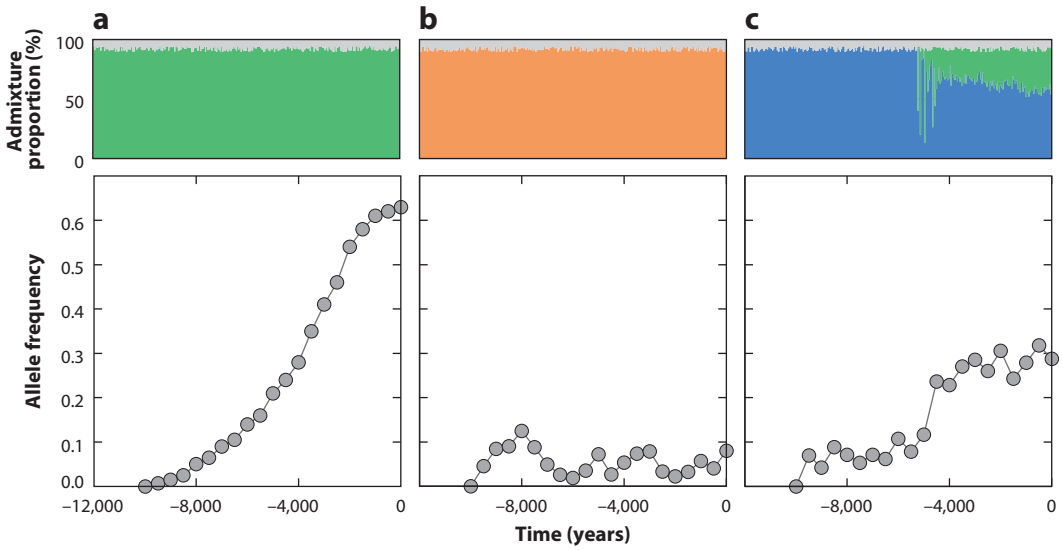

Figure 3

The temporal frequency trajectory of a selected and a neutral mutation under population continuity or discontinuity. (*Top*) Genetic ancestry proportions, depicted in different colors, represent a hypothetical transect of ancient individuals spanning the last 12,000 years of human evolution. Panels *a* and *b* depict population continuity, wherein no changes in genetic ancestry occur over time, whereas panel *c* illustrates population discontinuity, wherein changes in genetic ancestry occur over time. In the last example, migrants introduced genetic ancestry (*green*) into a recipient population approximately 5,000 years ago. (*Bottom*) The expected temporal frequency trajectory of a mutation under (*a*) natural selection (increase in frequency of a beneficial mutation through positive selection), (*b*) absence of selection or neutrality (random variation of allele frequencies of a neutral mutation), and (*c*) neutrality and population discontinuity (the arrival of a new population results in the increased frequency in the recipient population of a neutral allele through admixture).

it is characterized by exceptionally high genetic diversity and strongly affects susceptibility to infectious, inflammatory, and autoimmune diseases (140). Independent selection signals have subsequently been detected at this locus, highlighting both *HLA* class I genes and *HLA* class II genes as candidate targets of selection (141–145). The second locus includes *TLR1*, a key innate immunity sensor shown in prior research to be under selection in Europeans (17, 146). Beneficial *TLR1* alleles, including the I602S missense variant, have been associated with resistance to bacterial infections (147, 148); reduced inflammatory responses to TLR1/2 activation (48); and susceptibility to asthma, eczema, and allergic disorders (149–151). Yet the timing of the detected selection events could not be estimated because of the limited number of ancient genomes studied. Two recent large-scale studies have analyzed more than 2,000 genomes of ancient and present-day Europeans (152, 153). By estimating the temporal trajectory of a million allele frequencies (see the sidebar titled Ancient and Modern DNA Time Transects), these studies have not only identified known and novel immunity-related genes under selection but also revealed the likely time of onset of selection on these genes (**Figure 3**). Variants near the *HLA*, *TLR1*, *IRF1*, and *SH2B3* genes appear to have been under positive selection in early farmers since the Neolithic period (**Table 1**). These findings provide likely examples of human genetic adaptations to pathogens associated with the emergence of farming in Europe.

However, not all selection events began during the Neolithic period. When estimating the time of selection for the 89 loci displaying the most compelling evidence of rapid evolution, researchers found that >70% had experienced selection since the Bronze Age, which began around 5,000 years ago (152). These loci are enriched in immunity genes, suggesting that ancient

Europeans faced increased exposure to infectious agents mainly during the Bronze Age rather than during the Neolithic period. This notion is further supported by a separate aDNA study of a major genetic risk factor for clinical tuberculosis, the *TYK2* P1104A variant (154), which showed that tuberculosis has imposed a heavy burden on Europeans primarily over the past 2–3 millennia (155). The reasons why immunity genes rapidly evolved in Europeans during the early Bronze Age are currently unknown. Nevertheless, two explanations, which are not mutually exclusive, have been put forward: (*a*) The Bronze Age European population underwent explosive growth (156) that resulted in increased selection efficacy (157), and/or (*b*) the fast-paced migrations of pastoralists from the Pontic-Caspian Steppe (158), increased animal husbandry (159), and the emergence of large urban cities (160) during this period may have resulted in changes in exposure to pathogens such as the measles virus, *Mycobacterium tuberculosis*, and *Yersinia pestis* (160–164).

4.2. The Middle Ages

Historical and archaeological records indicate that endemic infectious diseases, including dysentery, tuberculosis, and leprosy, resulted in high mortality rates in medieval Europe (165–167). Genomic screening for ancient pathogens in samples from this period has confirmed that infections by multiple pathogens were common, with hepatitis B virus, variola virus, parvovirus B19, and *Mycobacterium leprae* the most prevalent (e.g., 168). The heavy death toll imposed by these infections has been attributed to two main factors: (*a*) recurrent famines and unsanitary living conditions leading to poor health status and/or (*b*) an immune system that was largely naive to increasingly common infections. The latter scenario implies that genetic factors conferred high susceptibility to infection in medieval times. Accordingly, the *HLA-DRB1**15:01 allele, a strong risk factor for leprosy in present-day individuals, was significantly more frequent in medieval victims of lepromatous leprosy compared with medieval controls (169). In an apparent contradiction to the risk that *HLA-DRB1**15:01 confers for leprosy, the temporal frequency trajectory of this allele supports a history of positive selection for the last five millennia (170), suggesting that the allele has also conferred genetic resistance to other infections, possibly tuberculosis (171), since the Bronze Age.

Beyond endemic diseases, the medieval population endured one of the deadliest epidemics ever recorded. In 1346–1353, the Black Death (BD) or Second Plague Pandemic decimated approximately 30–60% of the population of western Europe (172). aDNA was key to identifying plague as the causative disease; skeletal remains of purported victims bore traces of *Y. pestis* aDNA (173, 174). However, west Eurasians have been exposed to *Y. pestis* for millennia (162–164), raising questions regarding the causes of such an exceptional mortality during medieval times. Virulence factors are unlikely to be the cause, given the high similarity between the genomes of medieval and present-day *Y. pestis* (173). Alternatively, a combination of nongenetic and genetic risk factors may have made the medieval population highly susceptible to plague.

To test the latter scenario and determine the impact of the BD on the evolution of immunity in west Eurasia, aDNA studies have compared the genomes of presumed BD victims with those of medieval or modern controls. An initial study compared 36 BD victims with 50 modern inhabitants of the same region in Germany and reported notable frequency changes at variants located in the *FCN2*, *NLRP14*, *HLA-DRB1*, and *HLA-B* genes between the two epochs (175). However, such changes were found to be compatible with neutral evolution (176). A second study, conducted on 24 ancient individuals from Norway, revealed substantial changes in genetic ancestry between pre- and post-BD periods, hindering the identification of genetic changes caused by the pandemic (177). A third study, which generated genomic data for 67 pre-BD, 42 BD, and 97 post-BD ancient individuals from London and Denmark, provided both genomic and experimental evidence that

variation in the *ERAP2* gene was selected in medieval Europe because it conferred resistance to plague (178, 179). However, subsequent studies have not replicated these findings (180, 181), underscoring the need for larger, multicentric studies involving victims and survivors of the BD.

4.3. The Modern Period

The European arrival in the Americas in 1492 marked the onset of disease epidemics that killed up to approximately 90% of indigenous Americans during the subsequent century (182). Historical records suggest that these outbreaks were primarily caused by viral infections, such as smallpox, measles, influenza, and mumps (183). However, aDNA work has suggested that bacteria could have also contributed; for example, *Salmonella enterica* serovar Paratyphi C was found in human remains from victims of a major epidemic known as cocoliztli, which took place in Mexico from 1545 to 1550 CE (184). The hypothesis that the immune system of Native Americans evolved to resist the pathogens introduced by Europeans has been long-standing (185, 186), yet direct evidence to support the hypothesis has been lacking. By analyzing the genomes of contemporary admixed populations from Latin America, several studies have shown that the *HLA* locus has been under strong selection since admixture, favoring alleles of African origin (**Table 1**) (32, 187–191). These findings suggest that Native Americans acquired genetic resistance to postcontact infections through admixture with enslaved Africans and their descendants following the Transatlantic Slave Trade (192). Yet the exact nature of the infectious agents exerting selection pressures remains an open question.

Ancient genomics has offered direct evidence of selection caused by postcontact epidemics in Indigenous Americans. A pioneering study sequenced the exomes of 50 ancient, precontact First Nations individuals, along with modern representatives of this population from British Columbia, Canada, and searched for extreme allele frequency changes between the two epochs (193). It was found that variants regulating *HLA-DQA1* had reached 100% frequency in ancient First Nations individuals because of local adaptation, but these same mutations have decreased to approximately 40% frequency since contact, owing to negative selection. This rapid decrease in frequency cannot be solely explained by demographic factors such as admixture with Europeans, suggesting that *HLA* alleles that were once advantageous in the North American context became detrimental in the face of European-borne pathogens.

In a separate study, researchers compared the genomes of 5 ancient and 25 modern individuals from the Lake Titicaca region in the Andes (194), which was also affected by European-borne epidemics (195). The strongest differentiation between precontact and postcontact populations was found near the *CD83* gene. CD83 promotes the expression of *HLA* class II genes, and the *CD83* gene is upregulated upon vaccinia vaccination (196), suggesting a role in resistance against smallpox. Collectively, these results provide compelling evidence of natural selection acting on immunity genes in Native Americans since European contact, indicating that genetic susceptibility has played a role in the differential mortality of postcontact epidemics.

5. REPERCUSSIONS OF PAST SELECTION ON IMMUNITY-RELATED DISEASES

While infections have historically been the primary cause of human mortality, their impact has rapidly decreased in the northern hemisphere over the past 150 years, largely because of advancements in hygiene, vaccines, and antibiotics (16). Concomitantly, the prevalence of noninfectious immunity-mediated (NIIM) diseases, such as inflammatory and autoimmune disorders, has increased. Nowadays, up to 10% of Europeans are affected by at least one autoimmune disease (197); this heightened prevalence raises questions about the factors driving it. While age, sex, and

environmental exposures are major contributors, genetic factors—and their interactions with the environment—can also explain a large proportion of interindividual differences in disease risk. Accordingly, genome-wide association studies (GWAS) have identified several hundred variants associated with NIIM diseases, including type 1 diabetes, inflammatory bowel disease, rheumatoid arthritis, and multiple sclerosis (198, 199).

5.1. The Antagonistic Pleiotropy Hypothesis

Genetic studies have revealed that many of the genes associated with autoimmune or inflammatory diseases are also involved in host defense against pathogens (200), suggesting a shared pathophysiology between infectious and NIIM diseases. Additionally, several disease-risk alleles are common and exhibit marked differences in frequency among populations (200). Together, these observations have led to the hypothesis that the increased genetic susceptibility of Europeans to NIIM diseases results from past selection favoring a reactive immune response to infection. According to this hypothesis, beneficial variants that once conferred resistance to infection now predispose individuals to NIIM diseases by promoting inflammation and autoimmunity, a phenomenon referred to as antagonistic pleiotropy (134).

To date, the antagonistic pleiotropy hypothesis has been supported by two lines of evidence. First, several pleiotropic variants confer both protection against infectious diseases and susceptibility to inflammatory or autoimmune conditions. Notable cases include the *HLA-B**27:05 allele, which increases the risk for ankylosing spondylitis and delays HIV disease progression (201); the *FUT2* rs601338 G>A nonsecretor allele, which increases the risk for Crohn's disease, inflammatory bowel disease, and type 1 diabetes while conferring resistance against norovirus and childhood ear infections (199); and the *TYK2* P1104A missense variant, which increases tuberculosis risk (154) while protecting against various autoimmune diseases (202). However, on a genome-wide scale, the genetic effects of variants associated with infectious and NIIM diseases are not systematically antagonistic (128, 203), suggesting that the relationships between these diseases are more complex or that the relevant infections have not been studied yet. The second line of evidence comes from the observation that loci associated with NIIM diseases are enriched in signatures of positive selection in modern Europeans (14, 23, 200, 204, 205). Notably, candidate alleles for selection include risk variants in *HLA*, *FUT2*, and *SH2B3* (**Table 1**), further supporting the view that positive selection has increased genetic susceptibility to autoimmune disorders. Nevertheless, robust estimates of the strength and timing of selection at disease-risk loci, as well as evidence for polygenic selection acting on NIIM disease liability, have been lacking.

5.2. Support from Ancient Genomics for Antagonistic Pleiotropy

Once again, ancient genomics research has been instrumental in addressing these limitations. Data from aDNA have revealed that variants of *IRF1*, *SH2B3*, *IKZF1*, and *FUT2* that are associated with increased risk for inflammatory bowel disease and Crohn's disease have been under positive selection since the Neolithic period (152). Furthermore, a positive correlation between GWAS effect sizes and selection coefficients was observed: The more an allele increases NIIM disease risk, the more positively selected it has been. A polygenic risk score (PRS), calculated as the sum of risk alleles carried by an individual weighted by the alleles' risk effects, was used to estimate ancient Europeans' genetic risk for inflammatory bowel disease and revealed that disease risk has significantly increased since the Neolithic period, suggesting polygenic selection (152). Conversely, the PRS for COVID-19 has decreased, implying that the immune system has evolved to combat a yet-unknown severe infection that triggers an immune response that is shared, at least partially,

with that triggered by SARS-CoV-2. These findings support the role of selection in increasing the risk for gastrointestinal inflammatory diseases over recent millennia, likely because risk variants also conferred resistance to infection through antagonistic pleiotropy.

Another recent study has further supported the antagonistic pleiotropy hypothesis (170). By analyzing 1,509 ancient Eurasian genomes, the authors have traced the origins of risk variants for multiple sclerosis (MS), an autoimmune disease affecting the brain and spinal cord that varies markedly in prevalence worldwide. The authors found that the *HLA-DRB1**15:01 allele, the primary genetic risk factor for MS, started to rapidly increase in frequency around 5,300 years ago among pastoralists from the Pontic-Caspian Steppe. As Steppe-derived populations migrated to Europe by the end of the Neolithic period, around 5,000 years ago, a rapid increase in *HLA-DRB1**15:01 was observed in Bronze Age Europeans. Consistent with this observation, present-day European populations with high genetic ancestry from the Pontic-Caspian Steppe, such as Finnish, Swedish, and Icelandic populations, present the highest frequencies of *HLA-DRB1**15:01. Temporal changes in the PRS for MS indicate that disease risk increased under selection in Europeans between 5,000 and 2,000 years ago. Similar to what has been observed for inflammatory bowel disease, several MS-risk alleles under positive selection are suggestively associated with protection against infections, including tuberculosis, varicella, mumps, and influenza (170). These findings imply that the high prevalence of MS in contemporary Europeans is partly due to positive selection favoring MS-risk alleles during the Bronze Age, as these alleles once conferred protection against infections. However, this pattern is not common to all NIIM diseases. The same study found that the genetic risk for rheumatoid arthritis was highest in local Mesolithic hunter-gatherers and has evolved under continuous negative selection over the past 15 millennia.

These studies collectively support the view that current geographic disparities in risk for immune-mediated diseases, whether infectious or not, result from complex and diverse evolutionary processes and that ancient genomics research is greatly contributing to the elucidation of these processes.

6. FUTURE DIRECTIONS

Research in ancient and modern genomics has revealed how major events in human history, including admixture with extinct hominins, continental migrations, and demographic transitions, have shaped the evolution of human immunity. More recently, studies have shown that natural selection for resistance to past infections may have increased both present-day population differences in infectious disease risk and genetic susceptibility to several NIIM diseases over the last millennia. However, to deepen our understanding of the evolutionary origins of immunity-related diseases globally, these findings need to be consolidated and expanded by addressing several key issues.

First, although population genetics has identified adaptive genetic variations in immunity genes inherited from archaic humans or specific to *H. sapiens*, the phenotypic consequences of most of these variants for immune functions remain unknown. The challenges of uncovering these consequences include mapping candidate alleles to the most relevant tissues, cell populations, or conditions (e.g., exposure to specific immune stimuli, pathogens, or commensal microbes); distinguishing causal mutations among the multiple linked mutations that segregate together; and developing assays to assess the effects of numerous mutations in parallel. Techniques such as MPRA (206), including the treatment of various cell types with external stimuli, will aid in overcoming these challenges and detecting gene-environment interactions in the context of immunity.

Second, there is an urgent need for immunogenomic studies of populations of non-European ancestry, which have likely evolved to survive different infections. Even though thousands of modern and ancient human genomes have been sequenced, the majority of these genomes originate from the northern hemisphere (67, 207, 208). This bias stems from the limited medical infrastructure in the southern hemisphere, preventing the establishment of large cohorts; the historical failure to engage Indigenous and local communities in research in an ethical and inclusive way (209, 210); and poor preservation of archaeological records in hot and humid environments (207). Efforts to build local scientific capacity, raise awareness, and improve aDNA sequencing techniques should contribute to reducing Eurocentrism in genomic research.

Third, the precise historical epidemics that increased genetic susceptibility to NIIM diseases remain unknown. GWAS of infectious diseases are scarce and often underpowered (7, 8) because of challenges in identifying asymptomatic controls exposed to the pathogen of interest, compounded by the fact that most infections historically affecting the northern hemisphere have become rare or extinct. An exception is COVID-19, whose genetic architecture is increasingly well understood (125). Large-scale immunogenomic studies of infections affecting populations that have different genetic ancestries and are exposed to diverse environments are needed, to not only understand the evolutionary origins of infectious and noninfectious immunity-mediated diseases but also reduce disparities in the benefits of genomics research worldwide.

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