

Revisiting neanderthal ancestry: Evolutionary insights and biomedical relevance

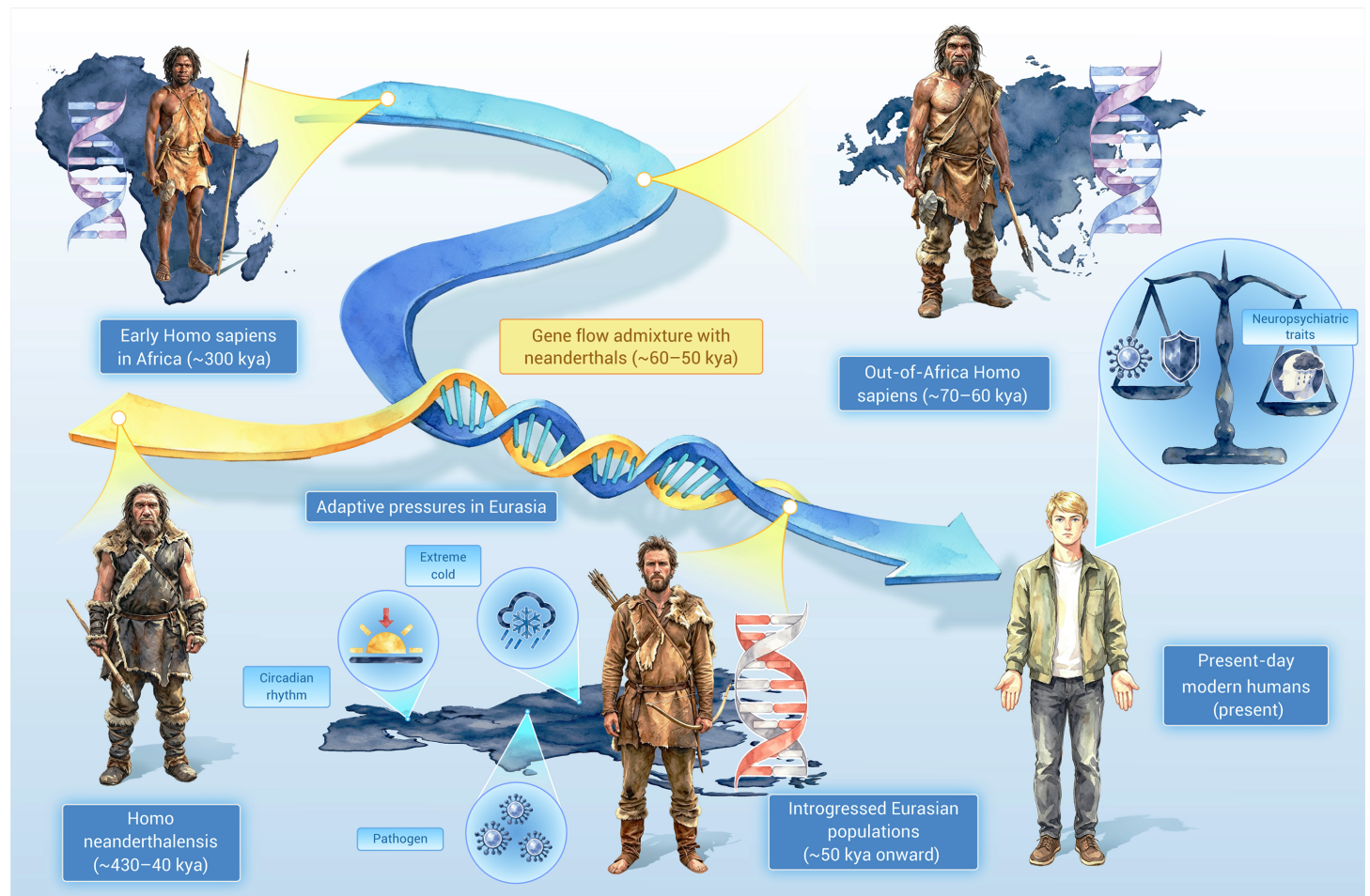
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GRAPHICAL ABSTRACT



PUBLIC SUMMARY

- Ancient interbreeding with Neanderthals left a lasting genetic legacy in present-day human genomes.
- We identify genomic regions where this archaic DNA continues to influence modern human biology.
- Archaic variants contribute to the regulation of immune defense and neurobiological processes in modern humans.
- Understanding this legacy provides important insights into the evolutionary origins of human disease risk.

Revisiting neanderthal ancestry: Evolutionary insights and biomedical relevance

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The sequencing of the Neanderthal genome revealed that interbreeding with early modern humans left a genetic legacy of approximately 1–2% in non-African populations. This introgression provides a natural experimental pathway for exploring the complex functional consequences of archaic ancestry and the evolutionary forces shaping the modern human genome. This review outlines the spatiotemporal dynamics of admixture, suggesting multiple waves of gene flow, and examines the evolutionary fates of introgressed sequences—from purifying selection removing deleterious alleles to adaptive introgression aiding human adaptation to Eurasian environments. Neanderthal-derived alleles have been linked to variation in immune responses, skin barrier, metabolism, and susceptibility to neurological and psychiatric disorders. These effects are complex and context-dependent, including potential antagonistic pleiotropy, where alleles that were once adaptive may now increase disease risk. We highlight future directions, including integrating ancient DNA with multi-omics data, expanding studies to diverse populations, and using functional genomics to identify causal mechanisms.

INTRODUCTION

The genetic legacy of our closest evolutionary relatives, the Neanderthals (*Homo neanderthalensis*), continues to influence human biology today. *Homo neanderthalensis* occupied Europe and western Asia from ~ 400 kya, before disappearing from the fossil record.¹ During the major dispersal of modern humans out of Africa ~ 60 kya, contact with Neanderthals resulted in introgression, which left approximately ~ 1–2% of Neanderthal ancestry in the genomes of present-day non-African populations.^{2,3}

The publication of the first draft Neanderthal genome in 2010 represented a turning point in human evolutionary studies.³ This landmark work shifted the field from asking whether interbreeding occurred to investigating the mechanisms, timing, and consequences of such admixture. Since then, population genomic studies have revealed that introgressed Neanderthal alleles have been subject to diverse evolutionary fates, including both positive⁴ and negative selection,^{5,6} and continue to influence phenotypic variation and disease susceptibility in modern humans.^{7–9}

This review synthesizes key advances in Neanderthal introgression research over the past fifteen years. We first delineate the spatiotemporal landscape of admixture events. We then examine the selective pressures acting on introgressed loci and their evolutionary consequences. Subsequently, we summarize evidence on the association between Neanderthal-derived variants and phenotypes in immunity, metabolism, and neurobiology. We further discuss the complexity of these effects, including context dependence and the potential for antagonistic pleiotropy. Finally, we highlight current methodological limitations and propose future directions for integrating multi-omics approaches and expanding research beyond Eurasian populations.

SPATIOTEMPORAL DYNAMICS OF *HOMO SAPIENS*–NEANDERTHAL ADMIXTURE

With the recovery of hominin fossils and advances in ancient DNA analysis, researchers have begun to reconstruct the complex spatiotemporal dynamics of interactions between *Homo sapiens* and Neanderthals. The timing of the earliest genetic exchanges remains unresolved. Some studies suggest that as early as ~ 250 kya, small-scale introgression from the modern human lineage into Neanderthal populations may have occurred,¹⁰ leaving little

detectable legacy in present-day genomes.¹¹ Fossil evidence consistent with this scenario includes the Apidima 1 specimen from southern Greece (~ 210 kya), whose mosaic of modern and archaic features indicates that early dispersals of modern humans beyond Africa were not confined to the Levant.¹²

High-coverage ancient genomes provide more consistent evidence for modern human–derived segments in Neanderthals from the Altai region dated to ~ 100–150 kya.^{2,13} Archaeological and fossil finds from the same interval, such as the Skhul/Qafzeh sites in Israel,¹⁴ and the Nesher Ramla individual,¹⁵ further indicate the presence of modern human populations across the Levant and the Arabian Peninsula, providing a geographic setting for gene flow.

More recent large-scale population genomic analyses and modeling suggest that, following the attenuation of early gene flow from *Homo sapiens* into Neanderthals, Neanderthals into *Homo sapiens* gene flow became the predominant pattern.¹¹ The Neanderthal ancestry component shared by all present-day non-African populations largely derives from a single major admixture event ~ 45–50 kya in western Asia.¹⁶ This encounter introduced ~ 1–2% Neanderthal ancestry into all non-Africans, a contribution that has persisted as a stable component of the modern human genome.^{3,5,6} East Asian populations generally carry higher levels of Neanderthal-derived segments, which is consistent with genetic evidence of multiple independent admixture events in eastern Eurasia.^{5,17–19} Later sporadic contacts are also evident. The Oase 1 individual from Romania (~ 40 kya) retains Neanderthal ancestry from only 4–6 generations back, attesting to continued, localized interactions into the Late Pleistocene.²⁰

Together, these lines of evidence indicate that interactions between modern humans and Neanderthals were not isolated encounters, but instead represented prolonged, multi-regional, and asymmetric episodes of gene flow extending over tens of thousands of years.

THE EVOLUTIONARY FATE OF INTROGRESSED ANCESTRY

The evolutionary fate of Neanderthal alleles in the modern human genome is highly heterogeneous. Under natural selection, most introgressed segments were eliminated by extensive purifying selection due to incompatibility with the modern genomic background or the presence of mildly deleterious effects,^{21–23} while only a minority persisted through genetic drift or positive selection (Figure 1).

Purifying selection and genetic purging

The proportion of Neanderthal DNA in modern humans declined from an initial 3–6% to ~ 1–2%,^{21,24} a direct reflection of the continual elimination of introgressed variants by natural selection.⁶ The underlying cause lies in the long-term small effective population size of Neanderthals, which allowed mildly deleterious mutations to accumulate in their gene pool.²⁵ Following admixture, these deleterious variants were efficiently purged within the large effective population size of modern humans.^{6,22,26–28} This process of removal was particularly intense during the early generations after admixture.¹⁶

Purifying selection was particularly pronounced in functionally important and low-recombination regions. Neanderthal ancestry is markedly depleted on the X chromosome,²⁹ with extensive “Neanderthal deserts” surrounding genes such as *FOXP2* involved in brain^{30,31} and reproduction,^{25,32} and meiotic gene regions being almost entirely devoid of archaic ancestry.^{33,34} The virtual absence of Neanderthal ancestry in the mitochondrial genome suggests either a maternal inheritance bottleneck or intense purifying selection during

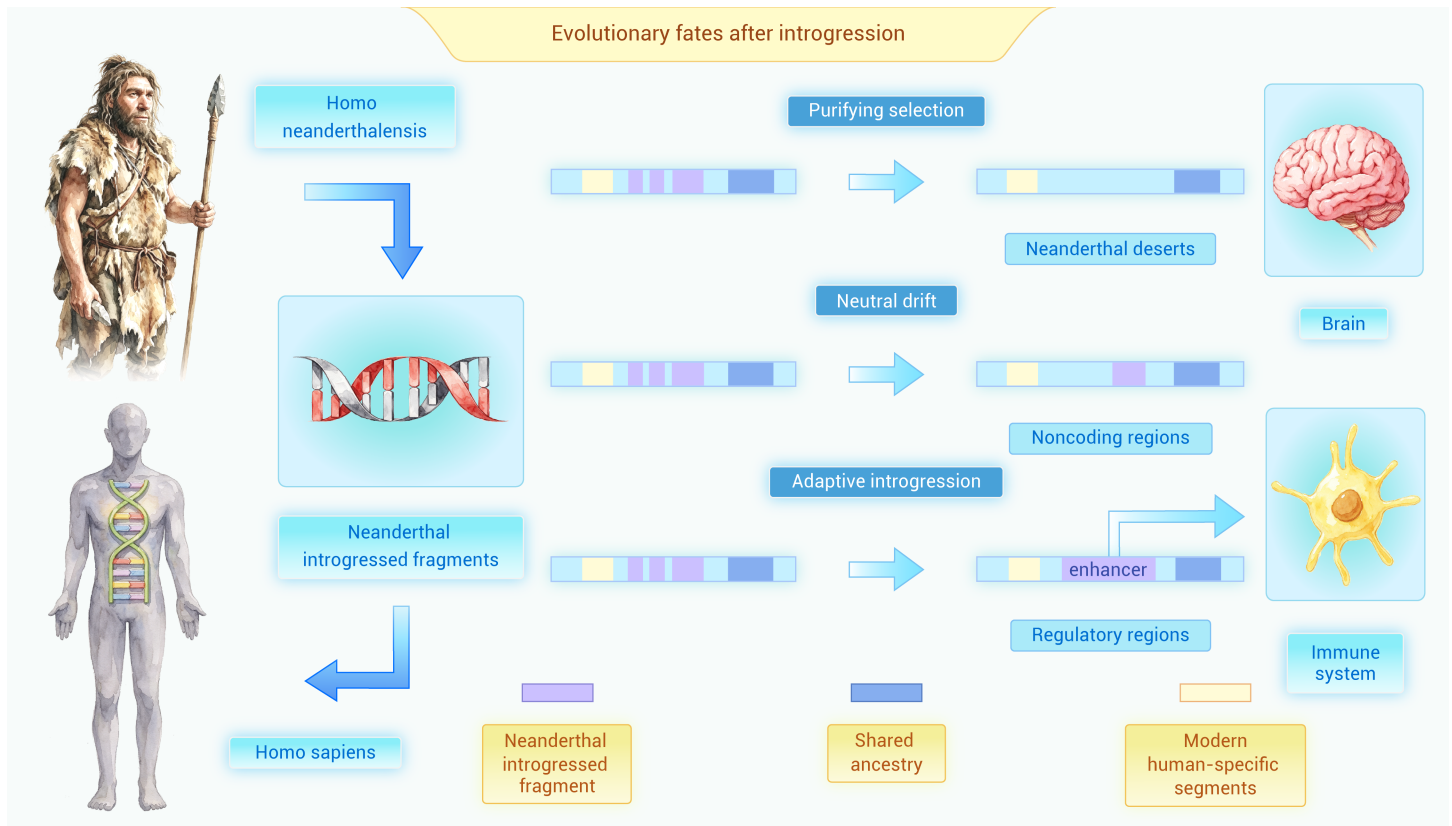


Figure 1. Diverse evolutionary trajectories of Neanderthal introgressed fragments in modern humans Following interbreeding between Neanderthals and early modern humans, introgressed DNA fragments underwent heterogeneous evolutionary trajectories. Most were purged by purifying selection, forming Neanderthal gene deserts especially around brain-associated genes; others persisted neutrally within noncoding regions through genetic drift. In contrast, introgressed alleles conferring adaptive advantages were maintained through adaptive introgression, particularly enriched in regulatory regions such as enhancers, linked to immune function.

hybridization.³⁵ In the brain, Neanderthal variants contribute minimally to heritability, while traits linked to cognition and emotional regulation, such as schizophrenia, show evidence of strong selective removal.^{30,36,37} Collectively, these observations reinforce the notion that introgressed alleles affecting reproductive isolation, development, or neural function were progressively purged across generations.³⁸

Neutral drift and adaptive introgression

Although purifying selection has been the dominant force,³⁶ many Neanderthal alleles persisted because they were either neutral and drifted to fixation, or beneficial—with some rising rapidly in frequency upon introgression and others remaining latent before being favored by later environmental or genomic changes.^{21,39,40} Functionally, adaptive benefits were particularly evident in genes related to skin,³⁶ hair,⁴¹ immunity⁴² and metabolism.^{43,44} Introgressed variants enhanced resistance to novel Eurasian pathogens, involving loci such as *HLA*, *TLR*, *OAS1/2/3*, and *TNFAIP3*.^{44,45} Positively selected archaic haplotypes frequently acted through regulatory mechanisms, including expression quantitative trait loci (eQTLs),⁴⁸ enhancers,⁴³ and splicing regulation,⁴⁶ with enhancer modulation emerging as a particularly widespread consequence of introgression.⁴³ Many Neanderthal-introgressed alleles exhibit antagonistic pleiotropy, conferring adaptive advantages in certain contexts while predisposing to deleterious outcomes in others.⁴⁷ The following section will present an in-depth examination of this phenomenon using COVID-19 as a paradigmatic case study.

NEANDERTHAL LEGACY AND PHENOTYPIC ASSOCIATIONS

Building on the evolutionary dynamics discussed above, recent research has increasingly focused on linking adaptive introgressed fragments to phenotypic variation in present-day humans. Advances in the integration of paleogenomics with modern genetic technologies are enabling researchers to establish a systematic, multi-layered analytical framework to identify, characterize, and functionally evaluate Neanderthal adaptive introgressed regions and their functional effects.³ This framework typically integrates

archaic genome comparisons, population genetic inference, phenotype association analyses, and experimental validation, thereby enabling a comprehensive understanding of the evolutionary and biomedical significance of archaic introgression (Figure 2). See the following section for a tiered framework clarifying the clinical relevance of archaic introgression.

A tiered framework for interpreting the biomedical relevance of archaic introgression

Level 1—Statistical Association (Candidates)

- Population-scale studies (e.g., GWAS, genome-wide association studies) identify archaic haplotypes correlated with modern phenotypes.
- Constraint: these associations indicate potential relevance but do not establish causality. Extensive linkage disequilibrium (LD) within large introgressed blocks often makes it difficult to distinguish the true causal variant from nearby “passenger” alleles.

Level 2—Molecular Mechanism (Prioritization)

- Functional genomics including eQTL/sQTL mapping, Massively Parallel Reporter Assays (MPRAs), and CRISPR-based screens—reveal how specific archaic alleles modulate gene expression or splicing.
- Significance: these methods establish a molecular link, providing a plausible path from genotype to phenotype, but they do not necessarily prove physiological impact.

Level 3—Biological Causality & Actionability (Validation)

- Validation in physiologically relevant models (iPSC-derived cells, organoids, or in vivo systems) confirms that archaic variants drive complex cellular or systemic phenotypes.
- Conclusion: only at this stage can clinical actionability be inferred with high confidence.

Evidence Hierarchy for Increasing Confidence:

Association (GWAS) → Regulatory Link (eQTL) → Molecular Proof (MPRA/CRISPR) → Physiological Impact (Cell/Organoid/In Vivo)

Summary:

- Where to look: association studies highlight candidate loci.

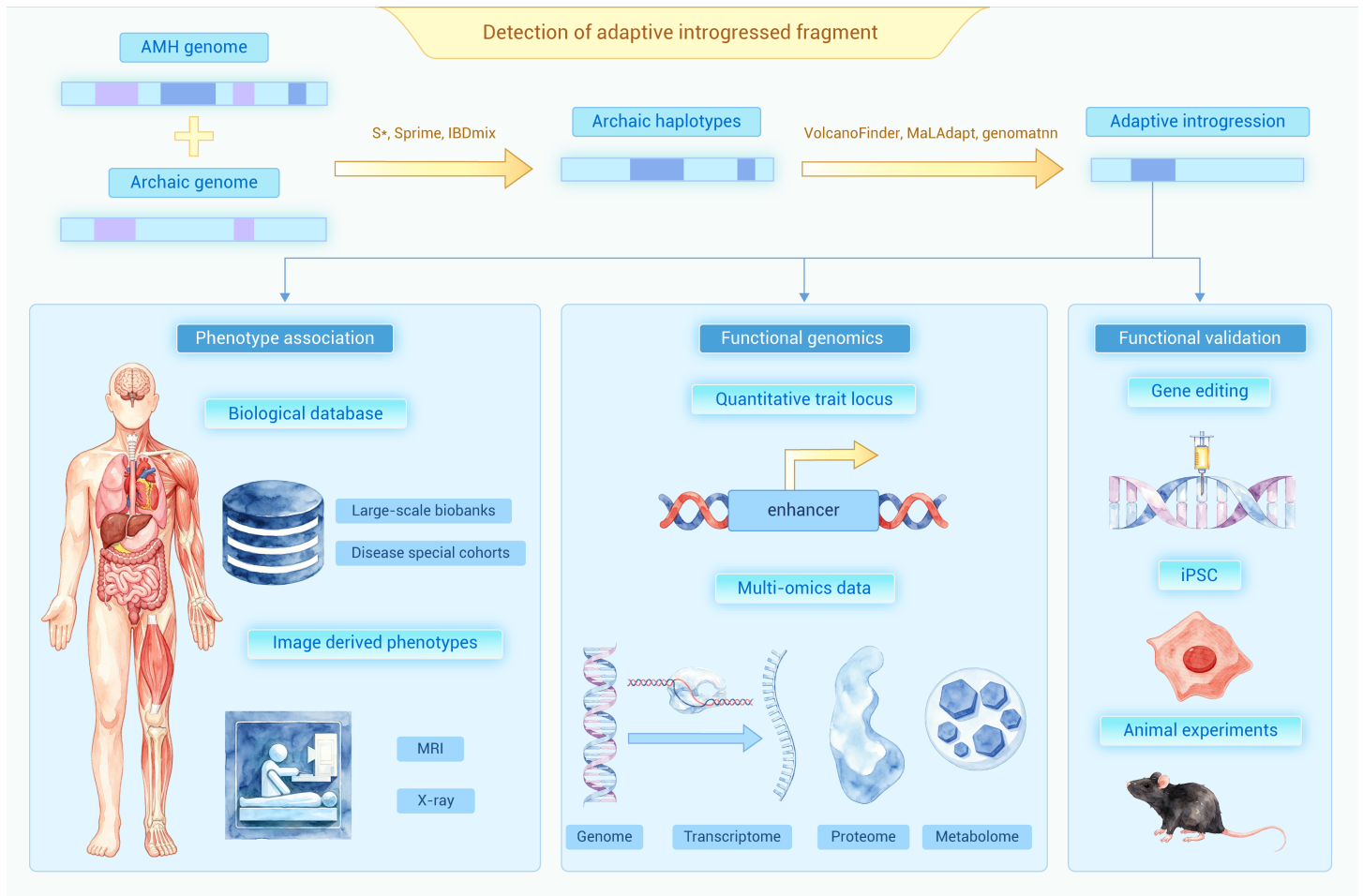


Figure 2. Framework for detecting adaptive Neanderthal introgression and elucidating functional consequences Introgressed haplotypes are identified through comparative genomic scans (S*, Sprime, IBDmix) and tested for adaptive signals (VolcanoFinder, MaAdapt, genomatnn). Phenotype-level associations are explored using biobank and imaging data; functional genomics analyses investigate the interplay between genetic variation and molecular regulation across multiple omics layers; experimental validations employing gene editing, iPSCs, and animal models are used to explore causal mechanisms. The specific evidentiary hierarchy of this framework is detailed in the following section.

- How it works: molecular assays clarify underlying mechanisms.
- Why it matters: high-level functional validation establishes physiological relevance.
- Goal: this framework prevents overinterpreting statistical correlations as proven biological mechanisms.

Methodological framework for detecting archaic introgression

At the initial stage, introgressed fragments are typically detected and quantified through comparisons of modern and archaic genomes. A variety of computational approaches have been developed for this purpose, including algorithms such as S*,⁴⁸ Sprime,⁴⁴ and IBDmix,⁴⁹ as well as hidden Markov model (HMM)-based frameworks that can detect archaic segments without a reference genome.⁵⁰ Once candidate regions are identified, signals of positive selection can be evaluated using haplotype-based statistics such as XP-EHH,^{51,52} iHS^{53,54} or allele frequency spectrum-based approaches such as the composite likelihood ratio (CLR) test.^{55–58} However, most current detection frameworks primarily focus on single nucleotide variants and short insertions or deletions, whereas structural variants within introgressed haplotypes remain comparatively understudied. Nevertheless, recent work has begun to highlight the evolutionary importance of such variation. For instance, a large Neanderthal-derived copy number variant on chromosome 8p21.3 was reported to occur at high frequency in Melanesian populations, representing one of the clearest cases of adaptive introgression involving structural variation.⁵⁹

Recent methodological innovations have further improved the sensitivity and resolution of introgression detection. Integrative tools such as VolcanoFinder^{60,61} and machine learning-based frameworks,^{18,27,62} including random forests and neural networks, have been increasingly applied to iden-

tify candidate adaptive introgressed loci. Some studies have further increased accuracy by mapping archaic genomic data onto both GRCh38 and the more recently assembled T2T-CHM13 human reference genome.⁶³ In addition, time-series analyses of ancient genomes, such as those implemented in CLUES2, enable direct reconstruction of the historical allele frequency trajectories, providing empirical insights into the selective dynamics of introgressed variants over evolutionary time.^{64,65}

Despite substantial progress in analytical frameworks, several inherent limitations constrain the detection and functional interpretation of archaic introgression. First, reference and mapping bias remain significant hurdles; reliance on linear reference genomes can lead to the loss of archaic sequences absent from the reference, while inconsistencies in reference genome quality can bias the inferred distribution of introgressed segments. Second, distinguishing true introgression from incomplete lineage sorting (ILS) remains a fundamental challenge, as genealogical discordance generated by ILS can mimic signals of gene flow, leading to the misattribution of ancestral polymorphisms as archaic variation.^{55,66,67} Shared genetic variation can arise from ancestral polymorphisms rather than gene flow, highlighting the need for rigorous evolutionary modeling to minimize spurious signals that may confound conventional selection tests.⁵⁵ Third, within the large, highly linked introgressed haplotypes, extensive LD creates substantial ambiguity in identifying specific causal variants. Pinpointing functional drivers among numerous “passenger” variants that are merely hitchhiking on the same haplotype remains difficult even with high-throughput experimental validation. Fourth, there is a pronounced population ascertainment bias in current datasets; most large-scale analyses have primarily focused on Eurasian populations in major biobanks, leaving the archaic genetic architecture of underrepresented groups (e.g., Oceanian or Southeast Asian populations)

comparatively understudied.^{68,69} Finally, limited concordance among detection algorithms,⁷⁰ exemplified by a systematic comparison of 14 introgression maps that revealed considerable heterogeneity,⁷¹ underscores the necessity of integrating robust molecular evolutionary modeling with cross-method validation to enhance the robustness of archaic genomic inference. Addressing these multifaceted limitations through integrative analytical frameworks, improved demographic modeling, and rigorous functional validation will be essential for the field to move from statistical mapping to a functional understanding of archaic genomic legacies.

Once introgressed regions are identified, researchers often employ integrative strategies to evaluate their phenotypic impact in modern populations. Genome-wide association studies (GWAS),⁷² phenome-wide association studies (PheWAS), and heritability enrichment analyses such as stratified linkage disequilibrium score regression (S-LDSC) are widely used to assess the contribution of archaic variants to complex human traits. These analyses are increasingly supported by large-scale clinical databases and large-scale population resources such as electronic health records (EHR),⁷ to systematically assess the impact of archaic introgressed alleles on complex traits in modern humans.^{28,43} Applications in population-scale resources such as Biobank Japan⁷³ and the UK Biobank⁴¹ have revealed that introgressed segments exert significant and heterogeneous effects on skin pigmentation, immune traits, hair color, sleep, mood regulation, and behavioral features across populations, underscoring their ancestry-specific nature.⁷⁴ However, most large-scale analyses have primarily focused on Eurasian populations, leaving other regions underrepresented. The SEA3K genome dataset has recently addressed this gap by characterizing genetic diversity in mainland Southeast Asians and identifying millions of novel variants.⁵¹ It further revealed population-specific adaptive introgression signals linked to anthropometric, ocular, and immune traits. Importantly, the integration of long-read sequencing (e.g., PacBio HiFi) enabled more accurate validation of introgressed segments, improving structural and haplotypic resolution beyond short-read methods.⁵¹

For functionally prioritized introgressed loci, functional genomics has been increasingly applied to dissect their molecular basis. Quantitative trait locus (QTL) analyses^{8,75} and splicing variation studies²⁸ have systematically highlighted regulatory impacts of archaic alleles at the transcriptomic level. High-throughput functional screening approaches, including massively parallel reporter assays (MPRAs) have enabled the experimental evaluation of thousands of common Neanderthal-derived variants, identifying 292 with demonstrable gene expression-modulating activity.⁷⁶

For introgressed fragments with clear functional and phenotypic associations, multi-level experimental validation systems have been established. At the cellular level, induced pluripotent stem cell differentiation and organoid models are used to probe functional divergence between archaic and modern alleles.^{77–79} Genome editing technologies such as CRISPR–Cas9 enables direct allele replacement or enhancer perturbation experiments to directly compare archaic versus modern variants.^{76,80} At the organismal level, animal models provide *in vivo* evidence of physiological and behavioral consequences with introgressed variants.^{80,81} Although still relatively limited in scope, these experimental approaches represent a critical frontier for elucidating the functional significance of archaic genetic legacies in human health and disease.

Trait and disease associations of neanderthal-derived alleles

By leveraging a systematic methodological framework spanning from genomic detection to functional validation, researchers are able to link Neanderthal-derived genetic fragments with complex traits and diseases in modern humans. Overall, Neanderthal alleles tend to exert modest effect sizes, primarily influencing polygenic complex traits such as immune response,^{47,73} whereas clear evidence for monogenic disorders directly attributable to Neanderthal introgression remains rare. Figure 3 summarizes representative phenotypic associations.

Immune defense and skin physical barriers. As the first line of defense during the out-of-Africa expansion, traits related to immune defense and physical barriers represent the earliest and most intensively studied domains of adaptive archaic introgression^{4,47} in modern humans, providing a crucial genetic foundation for coping with novel pathogens encountered in

Eurasia.^{82,83} Archaic fragments are highly enriched in genes encoding virus-interacting proteins,²¹ and innate immunity genes,⁸⁴ including T cell receptors and Toll-like receptor, forming an important antiviral shield in modern humans.^{19,21}

Neanderthal introgressed alleles exhibit multilayered immunological effects, with the COVID-19 pandemic providing a vivid example of how these archaic genetic components can influence disease outcomes in both protective and deleterious ways (Table 1). Importantly, most current evidence linking Neanderthal introgressed loci to COVID-19 outcomes remains at the level of haplotype-level association, while the underlying causal variants, relevant cell types, and molecular mechanisms are not yet fully resolved. Several Neanderthal-derived haplotypes have been associated with protection against SARS-CoV-2 infection. A Neanderthal haplotype on chromosome 12 spanning the *OAS1–OAS3* gene cluster has been associated with a reduced risk of hospitalization and severe disease.⁸⁵ Its frequency of approximately 25–30% in Eurasian populations suggest positive selection during ancient viral epidemics.^{76,86,87} However, subsequent population genomic analyses revealed that the key splice-site variant rs10774671-G on this haplotype is actually the ancestral allele, reaching 60–70% frequency in sub-Saharan Africans and existing independently of Neanderthal introgression, indicating that this protective variant predated the Neanderthal admixture event.⁸⁷ This nuance highlights the complexity of archaic introgression research: Genomic proximity to Neanderthal fragments does not always imply a Neanderthal origin for the functional effect, necessitating a cautious interpretation of the 'Neanderthal-as-cause' framework. In addition, a ~39-kb Neanderthal haplotype encompassing the *MUC20* locus carries the rs2177336-T allele, an eQTL associated with increased *MUC20* expression in SARS-CoV-2-stimulated cells.⁸⁸ Conversely, introgressed variants have been associated with increased susceptibility. A ~50-kb Neanderthal-derived haplotype on chromosome 3p21.31 represents a prominent genetic association with severe COVID-19,^{9,89} with a frequency of about 50% in South Asians, 16% in Europeans, and near absence in East Asians, indicating strong regional differentiation. While the 3p21.31 haplotype is a robust risk marker, identifying the specific causal variants and their target genes (e.g., *SLC6A20*, *LZTFL1*, or *CCR9*) across different cell types remains an area of active investigation. Functional studies suggest that variants in this region may influence pro-inflammatory responses and worsening disease outcomes.⁹⁰ From an evolutionary standpoint, alleles that may have been advantageous in past pathogenic environments may have become maladaptive in modern environments—a classic example of “evolutionary mismatch”.⁴² Several Neanderthal immune variants that enhanced resistance to viral infections such as SARS-CoV-2, including the *IGHG1* G396R variant, are associated with elevated risks of autoimmune and allergic diseases such as Crohn's disease and systemic lupus erythematosus.^{91–93} Furthermore, adaptive variants illustrate broader principles of genetic balance and epistatic modulation. In the Sardinian population, the risk allele rs35044562 is associated with increased risk of severe COVID-19 but is partly offset by protective HLA haplotypes such as *HLA-A*02:01-B*18:01-DRB1*03:01*,⁹⁴ highlighting the polygenic and interactive nature of immune phenotypes. Collectively, the Neanderthal genetic legacy highlights the complex and context-dependent nature of the dynamic equilibrium between protection and risk, selection and constraint, and ancient adaptation versus modern pathology in the context of COVID-19.

Introgression also contributed to the integrity of physical barriers, notably skin and mucosal protection. To adapt to latitudinal gradients of ultraviolet radiation, Neanderthal alleles at *BNC2*, *OCA2*,⁹⁵ *HYAL2*,⁹⁶ *DPEP1*,⁹⁷ and the 3p21.31 region⁹⁸ modulated skin pigmentation, keratinocyte proliferation and differentiation, and hyaluronic acid metabolism, thereby strengthening epidermal resilience.⁹⁹ Notably, *HYAL2*, a UV-B-responsive gene, underwent positive selection in East Asian populations, likely conferring improved adaptation to solar exposure.⁹⁶ Together, these patterns reveal that natural selection acted in population-specific ways, yielding geographically distinct adaptations, while the bidirectional effects of Neanderthal alleles on skin and hair pigmentation further suggest that Neanderthal groups themselves harbored substantial phenotypic diversity.⁴¹

Metabolism and coagulation. Modern human metabolic and coagulation traits have also been shaped by pathogen-driven selective pressures, with adaptive Neanderthal alleles contributing to population-specific phenotypes.

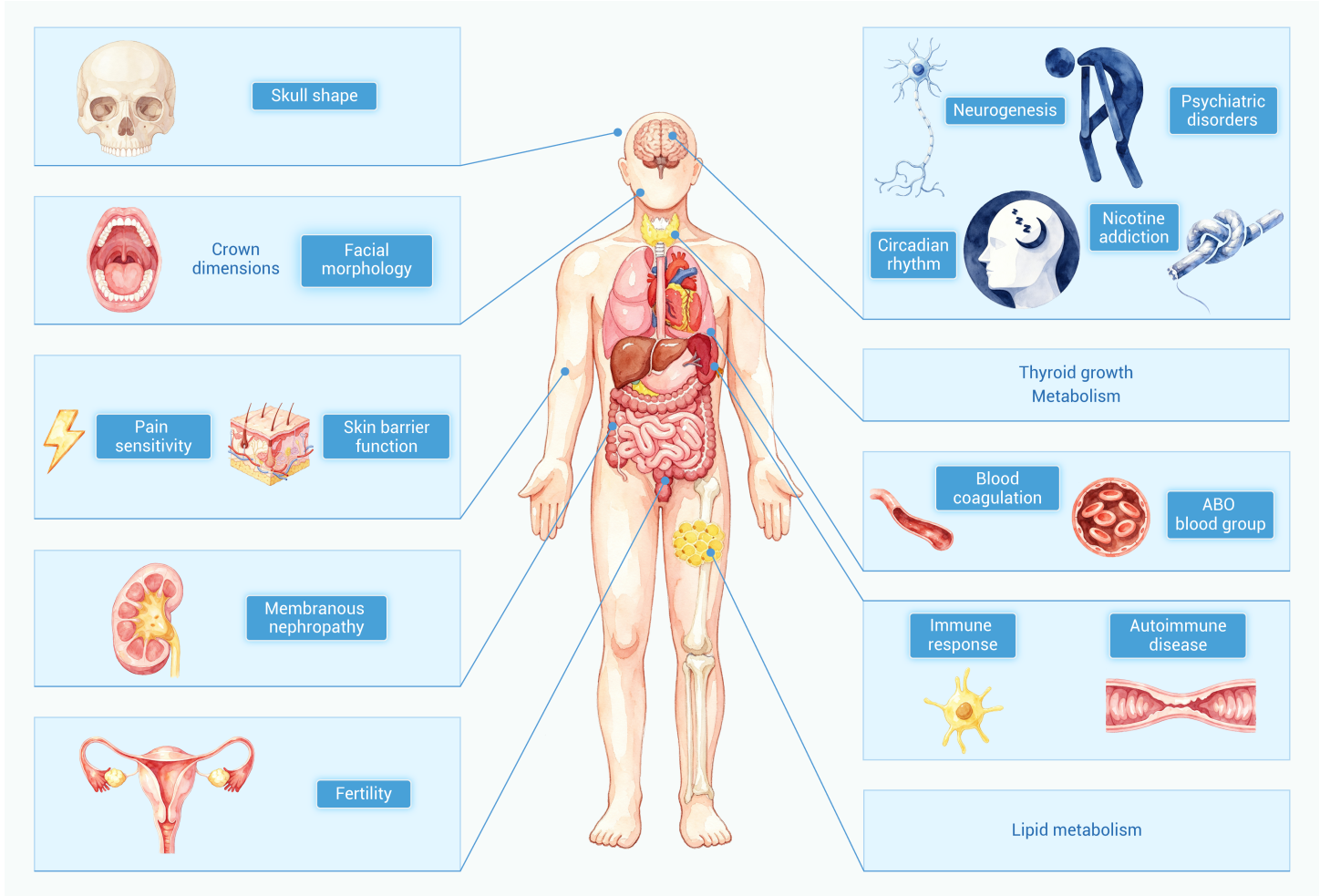


Figure 3. Trait and disease associations linked to Neanderthal introgressed alleles Neanderthal-derived genetic variants contribute to diverse human phenotypes, including craniofacial morphology, skin barrier function, and pain sensitivity; metabolic and thyroid traits, immune and reproductive functions, and neurological or behavioral phenotypes such as psychiatric disorders and circadian regulation.

Table 1. Representative Neanderthal-derived loci associated with differential COVID-19 outcomes.

Category	Chromosomal locus / Gene(s)	Key variant(s) or haplotype	Functional mechanism	Population frequency / distribution	Key references
Protective introgressed loci	chr12: <i>OAS1–OAS3</i> gene cluster	rs10774671-G	Associated with increased production of a more active <i>OAS1</i> isoform, consistent with enhanced RNase L–mediated viral RNA degradation	~25–30% in Eurasians; ~60–70% in sub-Saharan Africans	76,85–87
	chr11: <i>MUC20</i> locus	rs2177336-T	An eQTL associated with increased <i>MUC20</i> expression in SARS-CoV-2-stimulated CD4 ⁺ T cells, strengthening epithelial barrier function	Present in Eurasian populations	88
Risk-associated introgressed loci	chr3p21.31 region	rs35044562	May influence <i>CCR1/CCR5</i> chemokine receptor expression, associated with increased pro-inflammatory signaling	~50% in South Asians; ~16% in Europeans; rare in East Asians	9,89
Epistatic modulation of risk	chr6: HLA extended haplotype	rs35044562 interacting with <i>HLA-A02:01-B18:01-DRB1*03:01</i>	Epistatic interaction between Neanderthal-derived risk allele and modern protective HLA haplotype	Sardinian population specific	94
Broader evolutionary trade-offs	immune loci	/	Ancient immune adaptations enhancing antiviral defense but predisposing to immune dysregulation	Broadly distributed across Eurasia	42,92,93

In East Asian populations, genes involved in vitamin B1 metabolism, such as *SLC35F4* and *SLC35F3*, show strong signatures of positive selection, likely reflecting adaptation to pathogen pressure rather than dietary change.¹⁰⁰ Similarly, variants associated with gluten-sensitive autoimmunity, which is more prevalent in Europeans, may have been positively selected in ancient environments due to their role in enhancing pathogen defense.¹⁰¹ Part of the modern human ABO blood group diversity can also be traced to Neanderthal

or other archaic alleles, which may have been maintained by balancing selection to confer differential resistance to malaria, plague, thereby preserving population-level fitness in variable infectious landscapes.¹⁰² Neanderthal alleles in metabolic and coagulation systems also illustrate classical evolutionary trade-offs. Variants enriched in enhancers active in adipose tissue, including *SLC16A11*¹⁰³ and *PLIN4*, influence lipid metabolism and are linked in modern populations to type 2 diabetes, obesity, and diabetic

nephropathy.¹⁰⁴ Likewise, the *PNPLA3* p.I148M allele promoted fat storage during the Ice Age, enhancing survival, but today represents a risk factor for non-alcoholic fatty liver disease.⁸¹ Adaptive alleles in *FADS1/FADS2*, involved in fatty acid metabolism, similarly reflect ancient metabolic adaptation with implications for cardiovascular and metabolic disease risk in modern humans.¹⁰⁵ Neanderthal-derived *FAME* alleles are consistently associated with higher body mass index and play critical roles in energy metabolism and ferritin regulation,⁸¹ representing molecular relics of energy scarcity and cold-climate adaptation.⁴³ In the coagulation system, Neanderthal-introgressed genes such as *F3* and *VWF* promote hypercoagulability, which may have accelerated wound healing and reduced hemorrhagic mortality in trauma-prone prehistoric environments. In contrast, under modern sedentary lifestyles, these same variants elevate risks for thrombosis and coronary artery disease.^{7,96}

Neurological and behavioral phenotypes. In the domains of neurodevelopment, behavior, and morphology, Neanderthal introgression has been associated with multi-layered and complex effects. On one hand, introgressed alleles have been associated with variation in basic physiological processes and behavioral rhythms;¹⁰⁶ on the other hand, their legacy genetic background may be associated with increased risk for certain neuropsychiatric disorders, while core regions underlying higher cognitive functions exhibit clear signals of modern human-specific evolution.^{107–110} Importantly, most current evidence linking Neanderthal introgression to neuropsychiatric phenotypes is derived from enrichment analyses and PheWAS-style associations, rather than from studies demonstrating causal variants or mechanisms.^{93,111} Studies indicate that Neanderthal-introgressed regions are enriched near genes involved in brain development and function¹¹² and show modest and highly polygenic associations, with individual variants contributing only small effect sizes for phenotypes such as depression, mood disorders, and autism spectrum disorders.¹¹³ These findings, however, typically explain only a small fraction of the total phenotypic variance.³⁶ Interestingly, Neanderthal-introgressed fragments are not enriched for risk loci associated with neurodegenerative diseases such as Alzheimer's or Parkinson's disease.⁵³ An evolutionary-genetic explanation for these psychiatric risk variants is that they lie within functionally constrained genes where strong purifying selection removes deleterious mutations, yet common small-effect variants persist due to weak selective pressure or context-dependent advantages that have allowed their maintenance in modern populations.¹¹⁴ Consistent with this, mechanistic insights into how these variants influence brain function remain limited.

Moreover, archaic alleles contribute to the regulation of fundamental behavioral traits, including sleep-wake rhythms,⁴¹ nicotine addiction,¹¹⁵ and pain sensitivity.¹¹⁶ At the neurodevelopmental level, introgressed Neanderthal genes such as *UBR4* and *PHLPP1* have been suggested to influence neurogenesis and myelination, correlating with reduced cranial globularity in modern humans.¹¹⁷ Neuroimaging studies further suggest that modern individuals carrying higher Neanderthal allele loads exhibit variations in cranial and brain morphology, particularly in regions such as the visual cortex and intraparietal sulcus.¹⁰⁶ More strikingly, core reading ability loci are significantly enriched in regions lacking Neanderthal variation, and disease-associated alleles in families with reading disabilities represent the ancestral Neanderthal-to-primate versions, whereas non-risk alleles are derived, modern human-specific variants.^{53,118} Collectively, these findings suggest that language and higher cognitive abilities may largely stem from independent evolutionary innovations in the modern human lineage.

Morphological traits and reproductive fitness. Neanderthal introgression exerts detectable effects on human anatomy. Genome-wide analyses reveal that Neanderthal fragments in the 1q32.3 region are associated with increased nasal height,¹¹⁹ consistent with Neanderthal fossil morphology, whereas ancestral alleles at the *HS3ST3A1* locus influence tooth crown size.¹²⁰ These findings confirm that ancient alleles can leave direct evolutionary imprints on facial and dental morphology by modulating developmental processes. Among 61 genome-wide significant variants linked to Dupuytren's contraction, three harbor Neanderthal-derived alleles, with the strongest association mapping to *EPDR1*.¹²¹

A 56-kb Neanderthal-derived haplotype on chromosome 11 encodes the progesterone receptor,¹²² potentially influencing susceptibility to progesterone-

related conditions, including preterm birth. Carriers of this haplotype exhibit higher receptor expression, reduced miscarriage rates, and less early pregnancy bleeding, suggesting a positive effect of Neanderthal-derived progesterone receptor alleles on reproductive fitness.¹²³ Therefore, when evaluating Neanderthal introgressed alleles, it is insufficient to categorize it simply as "beneficial" or "deleterious". Instead, it should be understood within a dynamic framework of evolutionary and environmental interactions, integrating ancient DNA analyses, functional validation, and modern environmental factors.

FUTURE PERSPECTIVES

Investigating the distribution and functional impact of Neanderthal introgressed fragments in modern human populations offers unique insights into the genetic basis of human disease. First, population-specific frequency differences of these introgressed alleles constitute a natural "experiment," providing an ideal model to assess the phenotypic effects of the same allele across diverse genetic backgrounds.¹⁶ Second, the persistence of these alleles records tens of thousands of years of selection: Some alleles were retained due to adaptive advantages, while others were purged due to deleterious effects, offering clues to the evolutionary origins of modern disease susceptibility.^{39,40} Finally, these alleles highlight the dynamic nature of gene-environment interactions: Variants that were advantageous for infection resistance in ancient environments may increase the risk of autoimmune or allergic diseases under modern lifestyles.^{92,93}

Nevertheless, the field faces multiple challenges. Ancient DNA samples remain scarce and vary in quality, with only a limited number of high-quality genomes available for in-depth analysis,^{124,125} limiting our ability to fully capture Neanderthal genetic diversity. Skeletal degradation, microbial contamination, and DNA fragmentation further complicate functional reconstruction.^{124,126} In addition, ancient DNA does not directly retain epigenetic information, requiring researchers to rely on modern human QTL and expression data for indirect inference.^{8,28} At the population level, GWAS remain heavily biased toward European ancestries,³⁶ leaving introgression effects in African, South Asian, and Indigenous American populations underexplored; some disease associations are evident only in specific populations—for example, Icelandic cohort studies show limited effects of Neanderthal introgression on most traits, highlighting clear population- and environment-dependent effects.¹²⁷ Functionally, most findings remain at the level of statistical association, with molecular and system-level validation still limited. Although multi-layered experimental systems exist, challenges remain in modeling human-specific phenotypes.

Encouragingly, technological advances and interdisciplinary collaboration are opening new research avenues. High-quality ancient genomes from diverse temporal and geographic contexts are continuously being discovered;¹²⁸ while emerging paleoproteome¹²⁹ expand the dimensions of analysis. Future research will benefit from more comprehensive ancient genome sampling, more precise functional prediction and validation approaches, and deeper cross-disciplinary integration to systematically reveal the role of ancient gene introgression in contemporary human health and disease. Ultimately, addressing the current Eurasian bias and integrating long-read sequencing technologies to resolve structural variations will be pivotal in decoding the complex genomic legacy derived from archaic hominins.

CONCLUSION

Research on Neanderthal introgression reveals that these archaic genetic fragments have undergone dual evolutionary trajectories in modern humans: Some were eliminated due to deleterious effects, while others were retained for their adaptive advantages, particularly in genes related to immunity and environmental adaptation. These adaptive variants are thought to influence disease susceptibility and phenotypic diversity in modern humans through complex mechanisms. Future investigations should integrate multi-omics data, expand to globally diverse populations, and leverage functional experiments to fully elucidate how this ancient legacy continues to shape contemporary human biology. This paper mainly offers novel perspectives from deep evolutionary history for precision medicine and disease prevention.

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DECLARATION OF INTERESTS

The authors declare no competing interests.

DATA AND CODE AVAILABILITY

Not applicable.