

# Human Genetic Adaptations to Environmental Pressures: The Role of Migration in Evolutionary Success

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## ABSTRACT

Human evolution has been shaped by complex interactions between genetic variation, environmental pressures, and human migration. This review explores the mechanisms by which genetic adaptations have enabled humans to survive and thrive across diverse ecological contexts. The focus is on how migration has contributed to the spread and maintenance of beneficial alleles, influencing contemporary patterns of genetic diversity. We critically examine genetic adaptations associated with resistance to infectious diseases such as malaria, leprosy, and human immunodeficiency virus (HIV), as well as the evolution of immune responses shaped by transitions between tropical and temperate climates. Adaptations to high-altitude environments, including changes in oxygen regulation through genes like *EPAS1* and *EGLN1*, are discussed alongside dietary shifts such as lactase persistence and their connection to cultural practices like dairy consumption. Other examples include genetic variants that promote vitamin D synthesis in northern latitudes and variants linked to energy conservation in historically food-scarce environments. To ensure scientific rigor, we applied strict inclusion criteria focused on relevance, statistical significance, replication across populations, and biological plausibility. Studies were selected independently of authorship and drawn from large-scale genomic datasets representing diverse populations. The review also considers microbial and molecular markers, such as those derived from *Helicobacter pylori* phylogeography, which offer additional insights into human migration histories. Rather than presenting a summary of isolated findings, this review integrates results across evolutionary domains to clarify how environmental challenges and human movement have jointly shaped the human genome. By adopting an interdisciplinary approach, combining insights from genomics, anthropology, and population biology, the study highlights how adaptation and migration have contributed to present-day genetic diversity. This perspective supports a broader understanding of human resilience and the evolutionary processes underlying global genetic variation.

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## Introduction

Genetic variations are inherited across generations through both deterministic and random processes, with genetic drift playing a pivotal role in shaping allele frequencies. Conversely, beneficial genetic variants exhibit a higher probability of transmission due to

selective advantages. Key factors influencing human evolution include mutations, selective environmental pressures, migration, and genetic drift (Domínguez-Andrés and Netea, 2019).

However, despite extensive research on these mechanisms, critical gaps remain in understanding how interdisciplinary approaches (e.g., genomics, anthropology, and



bioengineering) can collectively explain human adaptation. Specifically, few studies have integrated molecular markers (*e.g.*, *Helicobacter pylori* strains) with anthropological evidence to trace migration-driven genetic changes or systematically compared the roles of mutation versus recurrent migration in allele dissemination. Given this context, this review aims to advance our understanding of how migration has influenced human genomic evolution in ways not fully captured by existing models. Migration refers to the transfer of genetic material between different populations. While it can reduce genetic differentiation between populations, it often increases within-population genetic diversity by introducing new alleles into the gene pool (Parsons, 1963).

Mark Stoneking, a prominent evolutionary geneticist, put forth the African Eve hypothesis, which posits that modern humans originated in eastern Africa (Wolinsky, 2008). The African continent is widely recognized as the origin of humanity, with its genomes exhibiting greater genetic variation than those found in any other region. However, it is crucial to acknowledge that only a limited portion of the genetic diversity present between African individuals has been extensively explored (Choudhury *et al.*, 2021). Researchers identified over 3 million uncharacterized genetic variants, mostly in newly sampled ethnolinguistic groups. They also found previously unreported loci under strong selection, primarily associated with genes related to metabolism, DNA repair, and viral immunity (Choudhury *et al.*, 2021). After the release of the human genome, continuous improvements in genomic sequencing have provided new understandings of how ancient human migrations relate to today's genetic variations that affect the capacity to digest or metabolize various nutrients, skin pigmentation, cold tolerance, and disease resistance (Hunter, 2014). Here, we critically evaluate these advances and highlight unresolved questions, such as why certain adaptive alleles (*e.g.*, for cold tolerance) show geographic clustering despite recurrent migration events. As our human ancestors migrated from the African savannahs, crossing the Alps into Northern Europe and Asia around 200,000 to 60,000 years ago, they adapted to new environments (Hunter, 2014).

The traditional model of molecular adaptation suggests that a favored allele originates from a single mutational event. However, this view fails to consider that beneficial alleles may enter a population multiple times, either through mutation or migration, throughout the process of natural selection (Pennings and Hermisson, 2006). A key objective of this review is to reconcile these competing perspectives by analyzing case studies where allele distribution patterns challenge the "single origin" assumption.

As humans migrated across the globe, natural selection favored alleles advantageous in the new ecosystems for both hosts and pathogens (Karlsson *et al.*, 2014). Earlier studies introduced a simple model to estimate the variation in the time it takes for advantageous alleles to become fixed in different areas of a population's range. The researchers suggested that sporadic long-distance migrants might be considerably more effective than short-distance migrants at disseminating these beneficial alleles (Rogers and Harpending, 1986). These beneficial adaptations then proliferated within populations, resulting in distinct ancestral origins and geographical distributions of advantageous alleles in the genomes of present-day humans (Domínguez-Andrés and Netea, 2019).

To address the identified gaps and advance our objectives, this review is structured as follows: First, we analyze methodological challenges in tracing migration-driven genetic changes. Next, we present case studies of gene-environment interactions, and finally, we propose a revised model of human adaptation that accounts for recurrent migration and interdisciplinary evidence.

### **Methodology of literature selection**

To ensure the comprehensiveness and accuracy of this review, a systematic literature search was conducted using multiple scientific databases, including PubMed, Scopus, Web of Science, and Google Scholar. Keywords such as genetic adaptation, human migration, positive selection, dietary adaptation, pathogen pressure, and high-altitude adaptation were employed in various Boolean combinations.

Inclusion criteria encompassed peer-reviewed articles published in English from 2000 onward

that provided original data or meta-analyses related to human genetic adaptation or migration patterns. Exclusion criteria included non-peer-reviewed sources, articles focusing solely on animal models, or studies with inconclusive findings.

To prioritize the findings discussed in this review, we applied several explicit criteria: (i) empirical support from genome-wide association studies (GWAS) with genome-wide significance thresholds ( $p < 5 \times 10^{-8}$ ), (ii) consistent replication across diverse populations, (iii) biological plausibility based on known gene functions, and (iv) relevance to human migratory events or environmental transitions (*e.g.*, diet, climate). Studies lacking statistical robustness or population-level replication were excluded from core discussions to enhance the interpretive validity of the review. Studies utilizing large-scale genomic datasets, such as the 1000 Genomes Project, Human Genome Diversity Project, and Simons Genome Diversity Project, were prioritized to ensure robustness of the findings. Efforts were also made to minimize selection bias by cross-validating findings across multiple populations and geographic regions (Bycroft *et al.*, 2018). Furthermore, when synthesizing findings across studies, we carefully considered the statistical robustness of each source. Particular attention was paid to sample sizes, effect sizes, population stratification controls, and replication consistency. Studies that reported genome-wide significance and corrected for multiple testing (*e.g.*, Bonferroni or FDR correction) were prioritized to reduce the risk of false positives (Ioannidis *et al.*, 2001). This methodological approach strengthens the reviews' transparency and scientific credibility by ensuring not only broad coverage but also the inclusion of statistically robust and well-replicated findings.

## Results

### Distribution of advantageous alleles

The 1,000 Genomes Project populations exhibit significant variations in susceptibility and resilience to specific diseases, reflecting their migratory histories (Hunter, 2014). A key area of research focuses on genetic adaptations associated with the prevalence of autoimmune

and inflammatory conditions. Growing evidence suggests that risk factors for certain disorders are correlated with resistance to infectious diseases. From a pathogen-pressure perspective, migrants encounter diverse environments containing potential pathogens during migration, necessitating robust defense mechanisms (Møller and Erritzøe, 1998).

### Positive selection to increase the frequency of favored alleles

A beneficial allele can enter a population through mutation or migration during a selective phase (Pennings and Hermisson, 2006). Natural selection drives changes in trait frequencies within populations based on reproductive success. Specifically, positive selection increases the prevalence of advantageous alleles, negative selection removes deleterious alleles, and balancing selection maintains diversity (Karlsson *et al.*, 2014). Some studies suggest that repeated selection for highly advantageous alleles may account for observed diversity patterns (Payseur and Nachman, 2002).

### Resistance to certain diseases

#### Immune adaptation

Le Souef *et al.* (2000) proposed that populations from tropical environments develop more proinflammatory immune responses compared to those migrating to temperate regions. The strongest evidence for this lies in polarized type 2 T-helper (Th2) lymphocyte responses against helminthic infections, as well as atopic conditions associated with filaggrin (FLG) deficiency (Le Souëf *et al.*, 2000; Lynch *et al.*, 1998).

When human ancestors emigrated from East Africa, they likely had immune functions adapted to tropical conditions. In these environments, infectious diseases were prevalent, with parasitic infections, particularly helminths, being endemic due to favorable heat and humidity. As a result, parasitic diseases were less common in cooler climates (Stromberg, 1997). For helminth infections, strong Th2 responses were essential, as they provide resistance to such infections (Lynch *et al.*, 1998). Lynch *et al.* (1998) demonstrated that children with elevated IgE responses, which indicate a strengthened protective response against

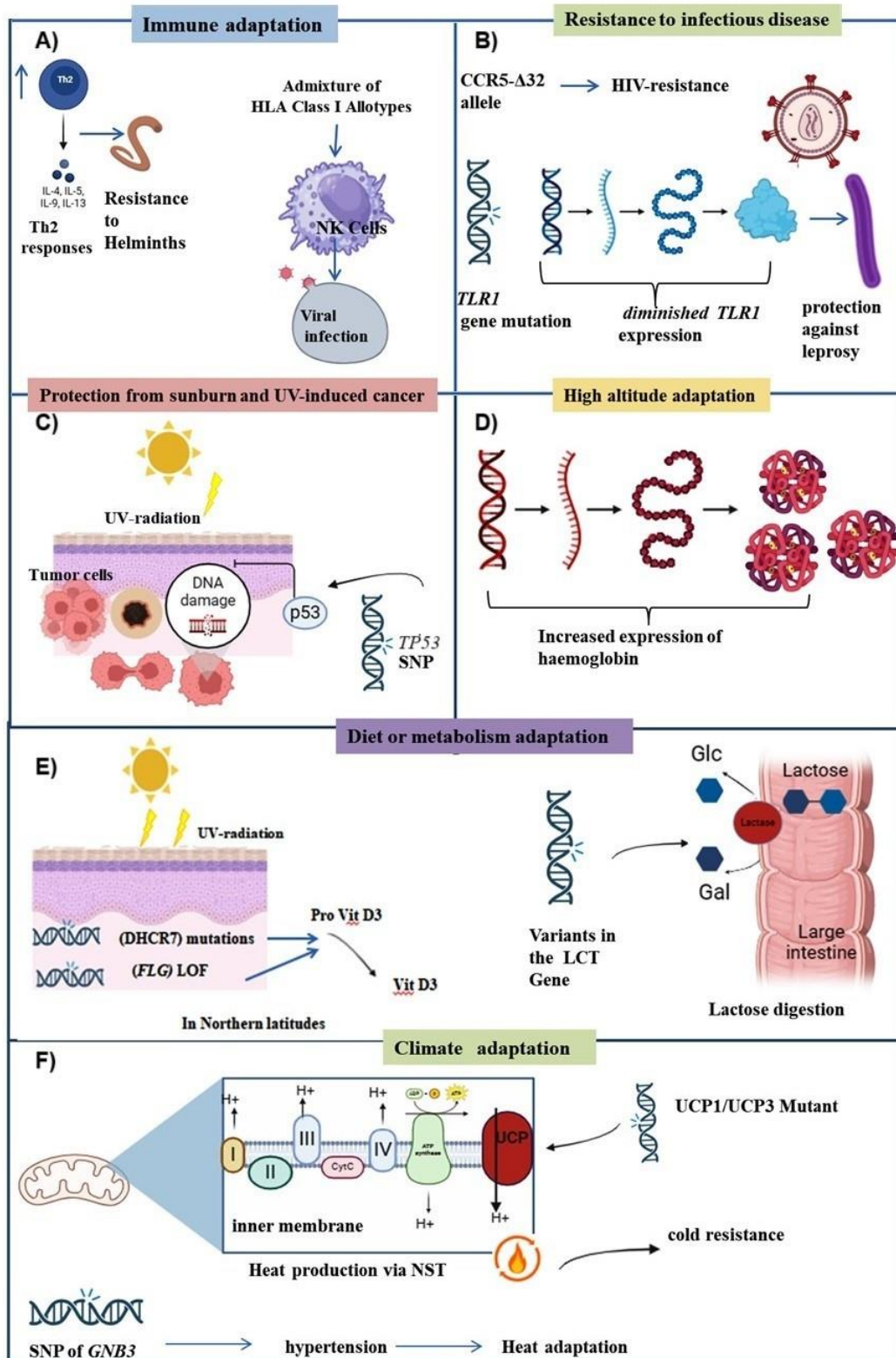
helminthic parasites, had significantly lower infection intensities compared to non-atopic peers. These findings support the idea that enhanced Th2 responses offer a selective evolutionary advantage.

The advancement of transportation and communication significantly contributes to the global spread of microorganisms. The mass movement of people creates new pathways for the transmission and establishment of both familiar and emerging infectious diseases (Soto, 2009). Natural killer (NK) cells play a crucial role in fetal development, as well as in the regulation of infections and cancer. Their activity is influenced by the interactions between variations of inhibitory killer cell immunoglobulin-like receptors (KIR) and the diverse HLA-A, -B, and -C ligands found on tissue cells. Certain HLA-A and -B alleles serve as KIR ligands, playing a role in immune modulation. Deng *et al.* (2021) showed that the Chinese Southern Han (CHS) population possesses enhanced NK cell repertoires in terms of diversity, quantity, and effector strength, which may improve immunity to local viral infections. This enhancement is partly attributed to admixture with neighboring populations (Fig. 1A). Previous studies have documented migratory patterns from North to South, highlighting admixture events among Han and Southeast Asian populations, along with genetic divergence between Northern and Southern Han groups (Hellenthal *et al.*, 2014). Building on these findings, Deng *et al.* revealed that specific *HLA-B* alleles, notably *HLA-B46:01* and *HLA-B58:01*, are significantly more frequent in the Southern Han population (Deng *et al.*, 2021). The emergence of *HLA-B58:01* is likely attributed to admixture processes (Chen *et al.*, 2016), a hypothesis supported by its high frequency in Northern Asia (Machulla *et al.*, 2003), indicating a probable Northern Han origin. Numerous investigations have revealed strong indications of last combination in Amerindian and Hispanic populations, particularly within the major histocompatibility complex (MHC). A consistent observation in these studies is the acquisition of HLA allotypes that provide advantages to populations facing

previously unknown pathogens (Norris *et al.*, 2020). The *B46:01* allele is more prevalent among Southeast Asians than East Asians, suggesting that it may have conferred advantages to the Southern Han during their southward migration. The increased frequency of the *B46:01* and *B58:01* alleles in the Southern Han population is likely the result of historical admixture events with neighboring Southeast Asian groups, reflecting southward migration and subsequent genetic exchange (Abi-Rached *et al.*, 2018). These findings align with our interdisciplinary objective stated in the introduction, demonstrating how the integration of genomic data (*e.g.*, HLA alleles) with anthropological evidence (*e.g.*, migration routes of the Southern Han) can resolve gaps in understanding gene-culture coevolution. Specifically, the admixture-driven distribution of *HLA-B* alleles highlights the interplay between migration, pathogen pressure, and population-specific genetic adaptations.

### Resistance to Infectious Disease

A prominent example of genetic adaptation in humans is the sickle cell allele of the  $\beta$ -globin gene, which confers resistance to malaria. This allele is particularly interesting as it appears to have undergone multiple mutations at a single base pair (Flint *et al.*, 1993). The prevalence of various hemoglobinopathies - including  $\alpha$ - and  $\beta$ -thalassemias, as well as hemoglobin C (HbC), E (HbE), and S (HbS)- is primarily attributed to their protective effects against malaria. These hemoglobinopathies are characterized by: 1)  $\alpha$ - and  $\beta$ -thalassemias involving reduced globin protein synthesis, and 2) three structural mutations of the  $\beta$ -globin chain: HbC ( $\beta6$  Glu→Lys), HbE ( $\beta26$  Glu→Lys), and HbS ( $\beta6$  Glu→Val). While each structural hemoglobin variant results from a specific single-nucleotide mutation altering a  $\beta$ -chain amino acid, thalassemias arise from a broader range of mutations. The scientific consensus holds that these hemoglobinopathies provide malaria protection, with natural selection having significantly influenced their gene frequencies in malaria-endemic regions.



**Fig. 1.** Overview of genetic adaptations in human populations to environmental pressures: A) *Th2*-related immune genes and *HLA* alleles aid in helminth and viral resistance; B) *CCR5* Δ32 and *TLR1* mutations provide protection against HIV and leprosy; C) *TP53* SNPs reduce UV-induced DNA damage and cancer risk; D) Hypoxia-related genes enhance hemoglobin production at high altitudes; E) *DHCR7*, *FLG*, and *LCT* variants contribute to vitamin D synthesis and lactose tolerance; F) *UCP1/UCP3* and *GNB3* polymorphisms improve cold and heat adaptation.

This concept was first proposed over 40 years ago and has gained support primarily from epidemiological studies (Allison, 1964) and in vitro research (Pasvol *et al.*, 1977), particularly concerning HbS (Friedman, 1979). Additional abnormal hemoglobin that confers malaria protection include the T125C polymorphism in the caspase 12 gene (*CASP12*), polymorphisms in human leukocyte antigen (HLA) loci, variants of hemoglobin B (HBB) and hemoglobin C (HBC), mutations in the Duffy antigen receptor gene (*DARC*), thalassemia (both  $\alpha$  and  $\beta$ ), and sickle cell disease (Domínguez-Andrés and Netea, 2019).

Host responses to *M. leprae* exposure vary significantly, with increasing evidence that genetic factors influence infection severity (Fernando and Britton, 2006). Clinical studies have established associations between infectious diseases and Toll-like receptor (*TLR*) gene single-nucleotide polymorphisms (SNPs), highlighting these receptors' importance in immune responses (Turvey and Hawn, 2006). One notable SNP within *TLR1*, known as the I602S *TLR1* SNP, is linked to abnormal transport of the receptor to the cell membrane and reduced responses of blood monocytes to bacterial stimuli (Fig. 1B). Interestingly, this SNP also confers protection against leprosy (Johnson *et al.*, 2007). The 602S allele is linked to a reduced occurrence of leprosy, indicating that *Mycobacterium leprae* may exploit the TLR system as a means of immune escape. Genotyping data indicate that the 602S allele is most prevalent among individuals of European descent, with a frequency of 75%. In contrast, individuals of Turkish descent exhibit a lower frequency of 43%, while those of African descent have the lowest frequency at 26%. Overall, the findings suggest that more than half of individuals of European descent are homozygous for the 602S allele (Johnson *et al.*, 2007).

HIV originated in simian populations before zoonotic transmission to humans in West Africa during the early 20th century. By around 1960, the virus had disseminated across large regions of the continent and eventually spread globally, partly facilitated by a group of Haitian professors who returned from Africa (Marsh *et al.*, 2019).

CCR5 is a chemokine receptor that plays a crucial role in HIV-1 pathogenesis and is a primary target for limiting infection, as mutations in this receptor confer resistance to individuals (Stephens *et al.*, 1998). The *CCR5*  $\Delta 32$  mutation involves a deletion that removes the HIV-1 co-receptor on lymphocytes (Fig. 1B), offering substantial defense against HIV-1 and, consequently, AIDS (Hütter *et al.*, 2009).

## Distribution of beneficial adaptations

### Protection from sunburn and UV-induced cancer

Melanin pigmentation plays a critical photoprotective role in human skin. The remarkable diversity of skin colors observed globally has emerged through human migration from founder populations combined with environmental influences. Studying the genetic basis of skin and hair color provides insights into human evolution and the selective pressures underlying these adaptations. Recent studies of African populations have revealed a complex genetic architecture involving both skin-lightening and skin-darkening alleles (Huang *et al.*, 2021). Further investigation of pigment variation in Africa will likely identify additional genes. Conversely, East Asian and European populations in high-latitude, low-sunlight environments experience selective pressures favoring lighter skin tones. While UV radiation is necessary for vitamin D synthesis (essential for bone health), protection against UV radiation prevents folate photo-degradation, resulting in evolutionary selection for darker skin (Jones *et al.*, 2018). Clear evidence of diversifying selection has been identified in major pigmentation genes of Asian and European populations (Huang *et al.*, 2021).

The variation in skin, eye, and hair pigmentation intensity can be attributed to single-nucleotide variations (SNVs) in genes responsible for key proteins involved in melanin synthesis within melanosomes (Pavan and Sturm, 2019). For instance, the lighter skin tone observed in European populations is predominantly explained by SNVs associated with genes such as *OCA2* (encoding the *OCA2* melanosomal transmembrane protein), *SLC45A2* (encoding the solute carrier family 45 member A2), and

*SLC24A5* (Skoglund and Mathieson, 2018). These SNVs result in functional impairment in the encoded pH regulator, ion transporter, and potassium-dependent sodium/calcium exchanger, respectively, leading to decreased production of black/brown eumelanin in melanosomes (Pavan and Sturm, 2019; Skoglund and Mathieson, 2018). Lighter skin pigmentation improves UV-B-induced vitamin D3 synthesis, particularly beneficial for high-latitude populations (Jablonski and Chaplin, 2018). Additionally, UV-B absorption by 7-dehydrocholesterol (vitamin D3 precursor) protects cholesterol-producing organisms (including animals and plants) from radiation damage, helping prevent autoimmune diseases, cancers, and cardiovascular disorders (Holick, 2004). Although the G allele of the TP53 gene is associated with an increased risk of testicular cancer, it may also offer adaptive advantages, such as enhanced DNA repair or apoptosis pathways that protect against UV-induced skin damage (Fig. 1C). This dual effect illustrates a possible trade-off shaped by environmental selection pressures (Zeron-Medina *et al.*, 2013). The prevailing theory suggests that the ability to tan in regions with moderate latitudes offers a protective barrier against skin cancer during the intense summer sunlight. Conversely, the lightening of skin tone in winter promotes improved absorption of weaker solar radiation, facilitating the synthesis of vitamin D (Zeron-Medina *et al.*, 2013).

### High altitude adaptation

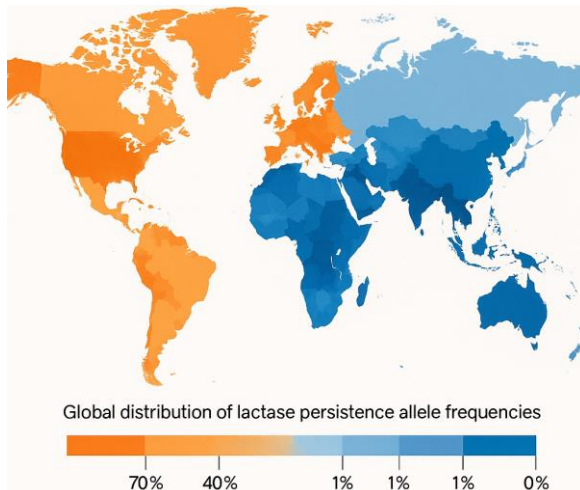
Hemoglobin has undergone selective pressures for additional functionalities throughout human migrations. One notable instance is its adaptation to high altitudes, where the thin atmosphere poses challenges for oxygen intake. Effective oxygen transport becomes crucial at elevated altitudes, leading human evolution to devise diverse mechanisms to achieve this common objective (Hunter, 2014). Matteo Fumagalli emphasized the various adaptations to hypoxia among populations in Tibet, the highlands of Ethiopia, and the Andes in South America. This observation suggests convergent evolution across multiple genes within the hypoxia pathway, which responds to oxygen scarcity, notably through heightened expression of

hemoglobin (Huerta-Sánchez *et al.*, 2013). Yasukochi *et al.* (2020) found evidence of independent positive natural selection on the *EGLN1* gene, part of the Egl-9 family of hypoxia-inducible factors, in high-altitude populations of Tibet and the Andes, with a specific correlation to hemoglobin concentration observed in Tibetans (Yasukochi *et al.*, 2021). Their study involved collecting genotype data from Tibetan (Simonson *et al.*, 2010; Wuren *et al.*, 2014) and Mongolian highlanders who had newly relocated to the Qinghai-Tibetan Plateau (Xing *et al.*, 2013). Despite differences in analytical methodologies and sample origins, multiple studies have consistently identified hypoxia-related genes such as *EPAS1* and *EGLN1* (Wuren *et al.*, 2014). Simonson *et al.* (2010) specifically noted that positively selected haplotypes of *EGLN1* and *PPARA* were significantly associated with the distinct decrease in hemoglobin phenotype observed in highland populations (Simonson *et al.*, 2010). Yasukochi's team further discovered that extended haplotypes containing the "TGCG" motif at key SNP loci underwent rapid population expansion, likely driven by their adaptive advantage against hypobaric hypoxia. Their analysis suggests the combined effects of *EGLN1* SNPs may underlie the unique hemoglobin regulation in Andean highlanders (Fig. 1D), working in concert with other genetic adaptations to hypoxic stress (Yasukochi *et al.*, 2021).

### Diet or metabolic adaptation

The ability to digest lactose into adulthood, mediated by genetic variants in the lactase persistence gene (LCT), represents a classic case of gene-culture coevolution (Ingram *et al.*, 2009; Gerbault *et al.*, 2011). While this trait initially emerged among European populations practicing dairy farming (Young *et al.*, 2005; Ingram *et al.*, 2009), its independent evolution in African and Middle Eastern pastoralist groups demonstrates remarkable convergent evolution (Ranciaro *et al.*, 2014). The global distribution of lactase persistence alleles closely mirrors historical human migrations and the spread of dairy domestication, highlighting how cultural practices can shape genetic adaptation (Fig. 2).





**Fig. 2.** Choropleth map depicting the global distribution of lactase persistence (LP) allele frequencies: The map highlights a distinct north-south gradient of LP prevalence in Europe and the independent emergence of LP-associated alleles in African and Middle Eastern populations with a history of pastoralism. Frequencies are based on aggregated data from the 1000 Genomes Project and published population genetic studies (Ingram *et al.*, 2009).

The ability of adults to digest lactose divides humans into two groups: those with dominant lactase persistence (LP), who can digest lactose, and those lacking this ability, referred to as lactase nonpersistent (LNP), due to a recessive trait (Szilagyi, 2015). Before the evolution of lactose digestion, it was widely believed that all European populations were LNP (Burger *et al.*, 2007). Over 100,000 years ago, ancestors migrated from Africa into Europe and then further eastward into regions including China, India, Siberia, Russia, and the South Pacific. During the last ice age, a landmass known as Beringia connected Siberia to the Americas, facilitating human migration (Malyarchuk *et al.*, 2011). The emergence of lactose digestion occurred approximately 7,500 to 10,000 years ago (Burger *et al.*, 2007). In Europe, the calcium assimilation hypothesis suggests that the geographical distribution of LP and LNP follows a distinct north-south gradient, with LNP prevalence increasing toward the southern regions. Flatz and Rotthauwe (1973) proposed that the ability to digest lactose enhances calcium absorption from dairy products, particularly raw milk, compensating for limited

sunlight exposure and reduced vitamin D synthesis in the skin. This genetic advantage may have contributed to a lower incidence of rickets. During a similar timeframe, lactose digestion began to emerge in Africa and the Middle East. The proposed environmental driver behind this development was the adoption of pastoralism and herding practices, which likely facilitated increased fluid intake, especially in arid regions such as deserts (Simoons, 1970; Holden and Mace, 1997).

In addition to *LCT*, other genes involved in lipid metabolism and insulin sensitivity have shown signs of dietary adaptation. For instance, variants in the *fatty acid desaturase (FADS)* gene cluster, which influences fatty acid metabolism, display strong selection signals in populations with traditional marine or plant-based diets (Mathias *et al.*, 2012). Moreover, the *Alpha-amylase 1 (AMY1)* gene, responsible for amylase production, exhibits copy number variation correlated with high-starch diets in agricultural populations, suggesting a broader genomic adaptation to post-Neolithic dietary practices (Perry *et al.*, 2007). These findings illustrate that dietary adaptation is a polygenic and culturally mediated process, shaped by long-term dietary habits and environmental pressures. A hypothesis known as gene-culture coevolution in Europe posits that the dominance of LP originated in central Europe, with populations subsequently migrating northward and eastward. In later centuries, groups from northern and western Europe migrated to the New World, including the Americas and Australia (Szilagyi, 2015). Gene-culture coevolution applies niche-construction principles to the human species, recognizing that genes and culture undergo similar evolutionary processes. It acknowledges that human society, as a cultural construct, shapes the environment for genetic adaptations that enhance individual fitness (Gintis, 2011).

Kuan *et al.* (2013) found that mutations in the Dehydrocholesterol Reductase (*DHCR7*) gene, which are linked to increased vitamin D levels, facilitated the early migration of humans to northern latitudes. Their study provided evidence of positive selection on *DHCR7*, a gene that regulates the availability of 7-dehydrocholesterol for conversion to vitamin D3 through sunlight exposure on the skin. The researchers showed



that extended haplotypes associated with vitamin D levels are particularly common in northern regions. Additionally, a prevalent *DHCR7* haplotype underwent a recent selective sweep in Northeast Asia. These findings suggest that genetic variations in *DHCR7* have played a crucial role in recent evolutionary history by affecting vitamin D metabolism. This adaptation likely enabled early humans to prevent severe vitamin D deficiency, facilitating their settlement in regions farther from the equator (Fig. 1E). Researchers have identified an additional genetic mechanism thought to have evolved to enhance UV-B-induced production of cutaneous vitamin D<sub>3</sub>, thus increasing the viability of individuals with lighter pigmentation in northern Europe. Filaggrin (FLG) is an essential epidermal structural protein involved in skin barrier formation and hydration. Consequently, loss-of-function (LoF) mutations in the *FLG* gene, such as R501X, 2282del4, S3247X, and R2447X, have been associated with increased permeability of the stratum corneum and altered UV sensitivity in human skin models (Devos *et al.*, 2012). While some studies have suggested that reduced FLG expression may facilitate greater UV-B penetration and intracutaneous synthesis of vitamin D<sub>3</sub>, attributing this effect solely to FLG degradation may oversimplify a multifactorial process. Other mechanisms, including variations in melanin levels, epidermal thickness, and hormonal regulation, likely play concurrent roles in modulating UV responsiveness and vitamin D production (Eaaswarkhanth *et al.*, 2016). Geographic analyses have demonstrated a latitude-dependent gradient in the prevalence of FLG mutations, with higher frequencies observed in northern European populations. This distribution correlates significantly with variations in circulating 25-OH-vitamin D<sub>3</sub> levels, supporting the notion that FLG LoF variants may have contributed to adaptation in low-UV environments (Thyssen *et al.*, 2014; Li *et al.*, 2016). However, further research is needed to isolate the specific evolutionary advantages conferred by FLG mutations from overlapping traits within linked epidermal gene clusters. The thrifty gene hypothesis remains a pivotal framework for understanding obesity epidemiology, with substantial evidence

supporting its role in shaping metabolic adaptations to historical famine conditions (Prentice *et al.*, 2008; Speakman, 2006). However, contemporary scholarship emphasizes that this model requires nuanced interpretation, as multiple studies demonstrate its limitations in accounting for modern obesogenic environments (Wells, 2011; Speakman, 2008; Sellayah *et al.*, 2014). While the hypothesis effectively explains selective pressures favoring fat storage during periods of food scarcity (Prentice *et al.*, 2008), its application to industrialized societies remains contested due to complex gene-environment interactions.

The central idea of this hypothesis is that during early human evolution, genes promoting efficient fat deposition provided advantages that enabled individuals to survive periods of famine (Speakman, 2008). Amid alternating times of abundance and scarcity, individuals with metabolically thrifty genes effectively utilized food resources, storing fat and gaining weight efficiently. This trait conferred a survival advantage during famines compared to those without these thrifty genes. It is theorized that a famine-like event occurred during human migrations to East Asia and subsequently to the Americas over the last 20,000 years. This event likely intensified the development of metabolically thrifty genes among East Asians relative to Europeans (Prentice *et al.*, 2005).

### **GWAS-identified polymorphisms in Asian populations**

Recent GWAS have revealed several diagnostic genetic polymorphisms specific to Asian populations that reflect unique evolutionary adaptations. These include both SNPs and copy number variations (CNVs) associated with metabolic traits, disease susceptibility, and dietary adaptations.

The rs1229984 polymorphism in the *ADH1B* gene, encoding alcohol dehydrogenase, is highly prevalent among East Asians and results in a His47Arg substitution that increases enzymatic activity. This variant leads to rapid conversion of ethanol to acetaldehyde, often causing facial flushing and alcohol intolerance. It has been positively selected in Han Chinese and Japanese populations, possibly due to its protective effects

against alcoholism and esophageal cancer (Han *et al.*, 2007).

Another key variant is rs671 in the *ALDH2* gene, prevalent in East Asians. This SNP results in the Glu504Lys substitution, severely reducing *ALDH2* activity and further contributing to the alcohol flush reaction. The variant is associated with increased risk of cardiovascular diseases and certain cancers, showing how evolutionary advantages (*e.g.*, pathogen avoidance via aversion to alcohol) may involve trade-offs (Chen *et al.*, 2014).

Copy number variation in the *AMY1* gene, which encodes salivary amylase, correlates with starch-rich diets. Asian agricultural populations, particularly in East and Southeast Asia, tend to have higher *AMY1* copy numbers, reflecting selection pressure from rice-based diets (Perry *et al.*, 2007; Usher *et al.*, 2015).

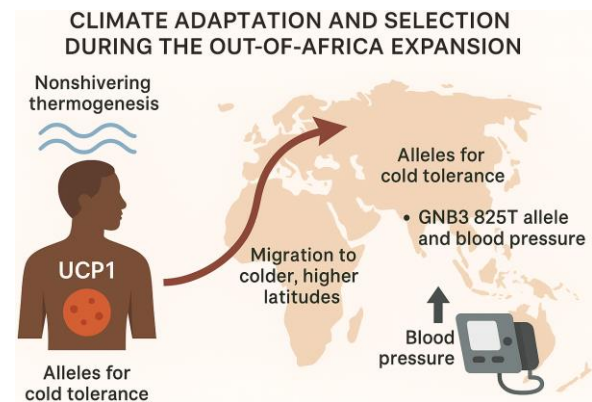
Though originally identified in Europeans, the *FTO* rs9939609 risk allele has been associated with increased body mass index (BMI) in East Asian populations, albeit with smaller effect sizes. Recent meta-analyses suggest that the interaction of *FTO* with traditional high-carbohydrate diets may underlie unique metabolic adaptations (Wen *et al.*, 2012).

A GWAS in East Asians identified rs9277535 in the *HLA-DPB1* region as a significant susceptibility locus for chronic hepatitis B virus infection, particularly in Chinese and Japanese populations. This finding highlights how local pathogen pressures can shape immunogenetic profiles (Kamatani *et al.*, 2009).

### Climate adaptation and selection during the out-of-Africa expansion

The generation of heat through nonshivering thermogenesis (NST) is crucial for maintaining temperature regulation in mammals (Cannon and Nedergaard, 2004). A key component of NST is the uncoupling protein 1 (UCP1), which plays a central role by uncoupling the proton gradients created within the inner mitochondrial membranes to produce heat (Su *et al.*, 2004) (Fig. 1F). Hancock *et al.* (2011) suggested that as certain human populations migrated out of Africa to colder regions at higher latitudes, alleles associated with enhanced thermogenic function became more common due to natural selection. As illustrated in Fig. 3, climate

adaptation during the Out-of-Africa migration shaped the selection of thermogenic and blood pressure-related genes. To test this hypothesis, they conducted genotyping of variants related to thermogenesis and obesity phenotypes in *UCP1*, *UCP2*, and *UCP3* across a global population sample, correlating their findings with climate data. Their study provided evidence of positive selection at *UCP1*, particularly evident in haplotype structure and allele frequency distribution. Furthermore, strong indications of selection associated with cold climates were noted at *UCP3*, adding independent support for its role in cold resistance. Furthermore, Stehmann *et al.* (2002) identified several specific genetic adaptations to cold environments worthy of investigation, including heat shock proteins (often referred to as stress proteins), the *ACP1* locus somatic growth factor, and specialized calcium metabolism.



**Fig. 3.** Schematic representation of climate adaptation and genetic selection during human Out-of-Africa migration: This schematic illustrates how cold climate pressures influenced the selection of thermogenic genes (*e.g.*, *UCP1*, *UCP2*, *UCP3*), stress-related proteins, and metabolic regulators (*e.g.*, *GNB3*, calcium metabolism genes) as humans migrated from Africa to higher latitudes. These genetic adaptations supported cold resistance and influenced traits such as thermogenesis and blood pressure regulation, with modern health implications (*e.g.*, hypertension) linked to ancestral environments. Created with BioRender.com.

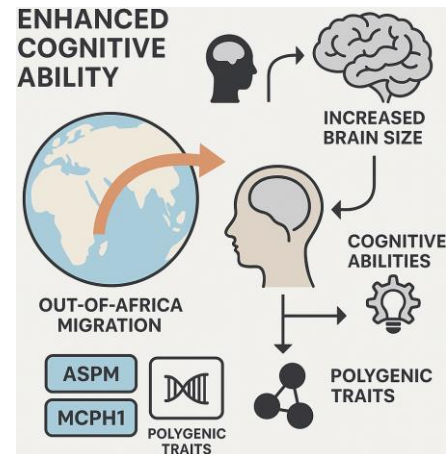
Most individuals in industrialized nations are at risk of developing high blood pressure or hypertension (Vasan *et al.*, 2002). Young *et al.* (2005) demonstrated that susceptibility to hypertension has ancestral origins, with

variations in susceptibility partially arising from differences in exposure to selection pressures during the out-of-Africa expansion. They found that latitude, along with a specific allele known as GNB3 (G protein  $\beta$ 3 subunit) 825T, accounts for a significant portion of global variation in blood pressure levels. As populations migrated northward from Africa, both salt retention and cardiovascular contractility decreased with increasing latitude, which helped to mitigate the rise in average blood pressure associated with latitude. The current epidemic of hypertension within industrialized populations can be linked to the environments in which these individuals reside. Migration studies indicate that average blood pressure levels change as people move into environments that foster hypertension (He *et al.*, 1991). Thus, the increase in blood pressure levels among industrialized populations is more probably due to a higher prevalence of factors such as greater salt intake and obesity, rather than solely an enhanced susceptibility to hypertension. Research suggests that the migration of individuals adapted to warmer climates to colder regions may contribute to the increase in blood pressure levels within populations, particularly among members of the African Diaspora. Furthermore, the evolutionary background of disease susceptibility has important implications for association studies. As noted by Di Rienzo and Hudson (2005), identifying protective alleles may be more achievable than identifying older susceptibility alleles for hypertension. This is because protective alleles have recently reached higher frequencies, resulting in stronger linkage with nearby genetic markers. Table 1 presents the genetic mechanisms of adaptation and protection across human populations, offering insights from key gene variants. While murine models have been instrumental in elucidating the molecular pathways of non-shivering thermogenesis (NST), caution is warranted in extrapolating these results to human populations. For example, the role of UCP1 in brown adipose tissue (BAT) function differs significantly between species, with humans exhibiting less BAT mass and potentially distinct regulatory mechanisms. Thus, findings from mouse models should be contextualized within human-specific

physiological frameworks (Cannon and Nedergaard, 2004).

### Enhanced cognitive ability

Some scholars argue that the out-of-Africa migration presented unique challenges that favored the selection of enhanced cognitive abilities. Figure 4 summarizes key genetic and evolutionary factors potentially involved in cognitive enhancement during human migration.



**Fig. 4.** Cognitive enhancement and human migration: This schematic illustrates the potential evolutionary link between human migration out of Africa and the selection of genes associated with brain development and cognitive function. Key genes such as *ASPM* and *MCPH1*, implicated in microcephaly and cortical growth, show signs of positive selection outside Africa. Genome-wide association studies (GWAS) have also identified numerous loci with small additive effects on intelligence. The figure emphasizes the interplay between genetic, environmental, and cultural factors in shaping human cognitive evolution. Created with BioRender.com

This claim is supported by comparisons of IQ and brain size. However, it remains unclear why the cognitive demands during this gradual migration would be greater than those faced by non-migrant populations living in Africa's diverse and dynamic environments. Genetic studies in this area differ from those related to pigmentation, as interest in a specific gene often arises not from observable phenotypic effects, but rather from its expression in the brain or unexpected patterns of population differentiation. Identifying an underlying selected phenotype may not be straightforward

and is often contentious. It is well established that brain size, and consequently cognitive abilities, have undergone rapid development in the human lineage over the past 3- 4 million

years. While there exists a substantial catalog of potential brain-related genes, relatively few have been thoroughly investigated (Sikela, 2006).

**Table 1.** Genetic mechanisms of adaptation and protection across human populations: insights from key gene variants.

| Genes                                                       | Mechanisms                                                                                  | Adaptations/protections                                                | Populations                                                 | References                          |
|-------------------------------------------------------------|---------------------------------------------------------------------------------------------|------------------------------------------------------------------------|-------------------------------------------------------------|-------------------------------------|
| <i>Th2</i> -related, <i>IgE</i> -related genes              | Strong <i>Th2</i> responses                                                                 | Resistance to helminth infection                                       | Migration from a tropical to a temperate environment        | Le Souëf <i>et al.</i> , 2000       |
| <i>HLA-B*46:01</i> and <i>HLA-B*58:01</i>                   | Enhanced NK cell repertoires                                                                | Augmenting resistance to endemic viral infections                      | Chinese Southern Han (CHS)                                  | Deng <i>et al.</i> , 2021           |
| <i>HBB</i> and <i>G6PD</i> alleles                          | <i>HBB</i> (chr11) and <i>G6PD</i> (chrX) deficiency polymorphisms                          | Protective against severe malaria                                      | Senegalese                                                  | Thiam <i>et al.</i> , 2022          |
| <i>G6PD</i> 202A and <i>G6PD</i> 376G alleles               | <i>G6PD</i> SNPs (e.g. 202A / 376G),                                                        | Protection against severe malaria                                      | Tanzania                                                    | Manjurano <i>et al.</i> , 2015      |
| <i>APOL1</i> (apolipoprotein L1) gene                       | High-risk G1 and G2 alleles killed <i>Trypanosoma brucei rhodesiense</i>                    | Protection against specific <i>Trypanosoma</i> species                 | Common in Uganda and West Africa (UBS), less in Sudan (UNS) | Genovese <i>et al.</i> , 2010       |
| <i>TLR1</i> gene                                            | Knockout mutation in <i>TLR1</i> reduces expression and function, leading to immune evasion | Protection against leprosy                                             | Europeans                                                   | Johnson <i>et al.</i> , 2007        |
| <i>CCR5</i> $\Delta 32$ allele                              | Elimination of the HIV-1 co-receptor on lymphocytes                                         | Protection against HIV-1                                               | Northern European populations                               | Hütter <i>et al.</i> , 2009         |
| SNVs of <i>OCA2</i> (melanosomal transmembrane protein)     | loss of function in the encoded pH regulator                                                | Reduced production of black/brown eumelanin in melanosomes             | Europeans, Africans, and Latin Americans                    | Pavan and Sturm, 2019               |
| SNVs of <i>SLC45A2</i> (solute carrier family 45 member A2) | Loss of function in the <u>ion transporter</u>                                              | Reduced production of black/brown eumelanin in melanosomes             | European                                                    | Skoglund and Mathieson, 2018        |
| SNVs of <i>SLC24A5</i>                                      | Loss of function in potassium-dependent sodium/calcium exchanger                            | Low production of eumelanin in melanosomes                             | Western Europe (Neolithic farming populations)              | Ju and Mathieson, 2021              |
| <i>KITLG</i> / <i>TP53</i> SNP                              | The G allele of <i>TP53</i> rose to a high frequency in Caucasians                          | Increased protection against skin damage from exposure to UV radiation | Europeans                                                   | Zeron-Medina <i>et al.</i> , 2013   |
| Hypoxia pathway genes (e.g., <i>EPAS1</i> , <i>EGLN1</i> )  | Increased hemoglobin expression                                                             | High-altitude adaptation                                               | Tibet, Ethiopian highlands, Andes                           | Huerta-Sánchez <i>et al.</i> , 2013 |
| <i>LCT</i> variant G/A - 22018A                             | Enables lactose digestion and calcium assimilation                                          | Reduces the prevalence of rickets                                      | European                                                    | Flatz and Rothhauwe, 1973           |
| <i>DHCR7</i> mutations                                      | Cause higher vitamin D status                                                               | Prevents severe vitamin D deficiency; aids northern adaptation         | Northern latitudes                                          | Kuan <i>et al.</i> , 2013           |
| <i>FLG</i> LoF (Loss-of-function) mutations                 | Enhances vitamin D3 synthesis via increased UV penetration                                  | UV protection                                                          | Northern European                                           | Thyssen <i>et al.</i> , 2014        |
| <i>UCP1</i> -3826G>A and <i>UCP3</i> -55C>T SNPs            | Increased expression and non-shivering thermogenesis                                        | Adaptation to a cold climate                                           | Migration to higher latitudes                               | Hancock <i>et al.</i> , 2011        |
| <i>GNB3</i> 825 C>T                                         | SNP in <i>GNB3</i> affects blood pressure regulation                                        | Adaptation to heat and salt metabolism                                 | China                                                       | Young <i>et al.</i> , 2005          |

Research has primarily focused on two genes associated with microcephaly; a condition characterized by a small brain size with normal neural structure. Abnormal spindle-like microcephaly associated (ASPM) and Microcephalin (MCPH1) show indications of adaptive selection during human evolution (Evans *et al.*, 2004), as well as in more recent periods (Evans *et al.*, 2005). Both genes exhibit globally distributed young, high-frequency haplotypes that are relatively rare in Africa,

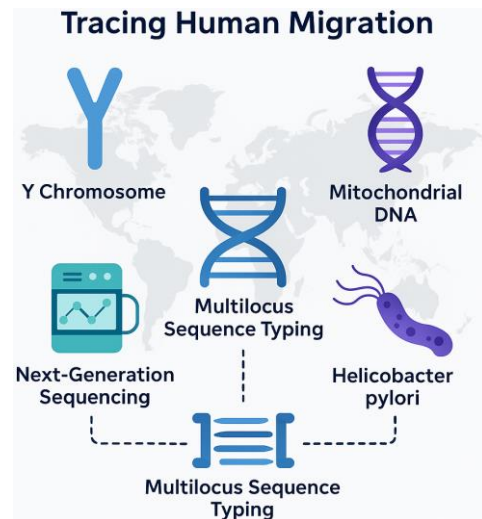
suggesting possible recent regional selection pressures. Selection on these genes is expected to relate to some aspect of intelligence rather than solely to brain size (Woods *et al.*, 2006). However, the prevalent derived alleles for both genes do not correlate with traditional measures of IQ (Mekel-Bobrov *et al.*, 2007), indicating that these gene variants may not have undergone selection, or that the selected phenotype encompasses more than what IQ alone can assess.

Recent GWAS have identified polygenic traits related to cognitive ability, with hundreds of loci showing small but additive effects (Savage *et al.*, 2018). Additionally, neurodevelopmental genes such as human accelerated region 1 (HAR1F) have been implicated in cortical development and may reflect recent human-specific selection (Pollard *et al.*, 2006). Nonetheless, the interpretation of these findings is complicated by gene-environment interactions and the lack of consistent phenotypic markers across populations. Some scholars caution against overinterpreting evolutionary signals in cognitive genes, noting that cultural transmission and environmental complexity can mimic selection patterns. Thus, while the hypothesis of cognitive enhancement through migration is intriguing, current evidence suggests that a multifactorial and culturally contingent model of brain evolution is more appropriate.

### Tracing Human Migration

Over the past two decades, population geneticists have extensively utilized non-recombining DNA from the Y chromosome, mitochondrial DNA, and other markers to investigate, refine, and redefine the prehistoric and historic records of human migratory patterns (Fig. 5). In the near future, or perhaps already, genomic resources such as expressed sequence tags (ESTs)-based microarray analyses, transcriptome libraries, and SNP marker sets will become available for migratory species (Liedvogel *et al.*, 2011). Multilocus sequence typing (MLST) analysis, which employs seven housekeeping genes, has proven valuable in predicting the trajectory of human migrations throughout history (Linz *et al.*, 2007). Introduced in 1998 as a method for conducting epidemiological studies of bacteria (Maiden *et al.*, 1998), MLST analysis reportedly offers more comprehensive insights into human population structure compared to methods that utilize human microsatellite or mitochondrial DNA (Wirth *et al.*, 2004). In terms of technology, Sanger sequencing has traditionally been the primary technique used in most studies. However, the emergence of various cost-effective and user-friendly next-generation sequencing (NGS) platforms has led to a growing preference for NGS over Sanger sequencing in the investigation of human

migration patterns (Kundu and Ghosh, 2015). High-throughput biotechnology facilitates extensive surveys of genomic diversity, GWASs, and NGS (Koboldt *et al.*, 2013).



**Fig. 5.** Schematic overview of molecular and microbial approaches in tracing human migration: Y-chromosome and mitochondrial DNA serve as foundational non-recombining genetic markers. Advances in bioengineering, including multilocus sequence typing (MLST), SNP genotyping, and next-generation sequencing (NGS), have improved the resolution of population structure analyses. Additionally, the genotyping of *Helicobacter pylori* strains (e.g., *cagA*, *vacA*, MLST) provides complementary phylogeographic insights aligned with human movement across continents. Together, these methods represent an integrative approach combining human and microbial genomics in the study of ancient and recent migrations. Created with BioRender.com

As emphasized in the introduction, molecular markers like *H. pylori* strains provide a unique lens to trace human migrations, complementing traditional genomic approaches. This section critically evaluates the utility of *H. pylori* genotyping, particularly MLST, while demonstrating its advantages over conventional human genetic data in reconstructing migratory histories through interdisciplinary lens. *Helicobacter pylori* strains display distinct phylogeographical patterns across various geographic regions, making their genotypes valuable markers for tracing human population

migrations. Currently, two virulence factors of *H. pylori*, *cagA* and *vacA*, along with MLST, are widely used to assess genomic diversity within *H. pylori* populations. There are two primary types of *cagA*: East Asian and Western. Additionally, the right end of the *cag* pathogenicity island is divided into five subtypes, while distinct mosaic structures are present in the signal region and middle region of *vacA*. By analyzing combinations of *cagA*, the *cag* right end junction, and *vacA* genotypes, researchers have identified five major groups (East Asia, South/Central Asia, Iberia/Africa, and Europe) based on geographical associations. MLST studies have revealed seven modern population types and six ancestral population types of *H. pylori*, providing a valuable tool for mapping human migration patterns. Long-term surveillance of extensive *H. pylori* strain collections, including those from indigenous populations, underscores the superior insights offered by MLST analysis compared to human genetic studies in understanding human migration. Although infection rates of *H. pylori* are declining due to improved personal hygiene and living standards, the molecular epidemiology of *H. pylori* infection remains significant and warrants further investigation before it potentially disappears entirely (Yamaoka, 2009).

## Discussion

The synthesis of evidence presented in this study reveals fundamental insights about human genetic adaptation, while simultaneously exposing critical gaps in our current understanding. Migration emerges as both a dispersal mechanism for advantageous alleles and a diversifying force in regional genetic architecture, exemplified by the differential distribution of adaptive variants in genes like *ADH1B*, *LCT*, and *EPAS1* across populations. However, these conclusions must be tempered by recognition of persistent methodological constraints that permeate the field. The overwhelming Eurocentric bias in genomic databases - where approximately 78% of GWAS data derive from European-ancestry individuals - creates systematic blind spots in detecting adaptive variants, particularly when combined with inconsistent annotation quality in

underrepresented populations. This representation imbalance becomes especially problematic when studying geographically restricted adaptations, as demonstrated by the stark contrast between well-characterized high-altitude adaptations in Tibetans versus the more fragmentary data available for Andean populations. Beyond population coverage issues, fundamental tensions exist between the statistical requirements of selection detection methods and the ethical imperatives of genomic research. Widely used approaches like iHS and XP-EHH demand large sample sizes, yet such sampling often conflicts with indigenous data sovereignty principles embodied in frameworks like CARE (Collective Benefit, Authority to Control, Responsibility, Ethics). These challenges compound when considering the temporal complexities of adaptation - the estimated 5,000-10,000-year timeframe for lactase persistence evolution, for instance, shows imperfect alignment with archaeological evidence of dairying practices, highlighting how methodological artifacts may distort evolutionary timelines. The interpretive challenges extend to biological plausibility assessments. While strong selection signals for hypoxia-related genes like *EPAS1* in Tibetan populations ( $p < 10^{-15}$ ) suggest clear adaptive stories, the potential confounding effects of epigenetic modulation and population substructure require cautious evaluation. Similarly, the uneven global distribution of *HLA* alleles likely reflects both pathogenic pressures and stochastic founder effects during migrations, illustrating how neutral and selective processes can produce superficially similar genetic patterns. These complexities underscore why claims of genetic adaptation should be treated as working hypotheses rather than definitive conclusions, particularly for polygenic traits where environmental interactions are poorly constrained. Moving forward, the field requires concerted efforts to reconcile scientific rigor with ethical responsibility. Ancient DNA studies from currently underrepresented regions, coupled with functional validation through modern gene-editing techniques, could help bridge existing annotation gaps while respecting cultural sensitivities. Similarly, developing selection detection methods that maintain



statistical power with smaller, ethically-sampled datasets would alleviate current tensions between methodological requirements and community engagement principles. Until such advances mature, researchers must remain vigilant about the provisional nature of adaptation narratives, particularly when extrapolating from limited datasets to broad evolutionary claims. This balanced perspective - acknowledging both the transformative insights and inherent limitations of current approaches - will be essential for building a more inclusive and accurate understanding of human genetic adaptation.

### Future Directions

The study of human migration genetics faces unique challenges that will require innovative approaches to overcome. As highlighted by Liedvogel *et al.* (2011), understanding migratory phenotypes demands precise characterization of behavioral and physiological traits - a principle that remains equally relevant for human migration studies. Moving forward, priority should be given to developing integrated methodologies that combine ancient DNA analysis with functional genomic validation, while addressing the fundamental challenge of distinguishing innate genetic factors from environmentally induced plasticity in migratory populations.

Emerging technologies in single-cell sequencing and gene-editing platforms offer promising avenues for validating adaptive variants, building on the foundational work of Liedvogel and colleagues in establishing migratory genetics as a distinct field. However, these technical advances must be paired with improved phenotypic characterization standards, particularly for complex human traits like altitude adaptation, where the interplay between genetic predisposition and developmental plasticity remains poorly understood.

The field would benefit tremendously from applying Liedvogel *et al.*'s (2011) integrative framework to human studies, particularly through longitudinal research tracking both genomic and cultural evolution in migrating populations. Such approaches could finally achieve their vision of connecting specific genetic variants to fitness consequences across generations. Looking ahead, establishing

international consortia could operationalize these goals while maintaining ethical standards, creating unified protocols that honor both scientific rigor and community engagement principles - the very balance that pioneering work in non-human systems has successfully demonstrated.

### Conclusion

In summary, the complex interplay of genetic variations, migrations, and environmental selective pressures has profoundly influenced human evolution. Advances in genomic sequencing have revealed a wealth of previously unidentified variants, illuminating the ancient migrations of our ancestors and their lasting impact on contemporary genetic landscapes. These migrations have facilitated the acquisition of beneficial adaptations that influence disease resistance, immune responses, and physiological traits such as skin pigmentation and altitude adaptation. Numerous examples illustrate this phenomenon, from the evolution of immune responses to helminth infections in tropical environments to the acquisition of alleles that confer resistance to infectious diseases like malaria, leprosy, and HIV. Additionally, the genetic basis of skin pigmentation reflects the selective pressures exerted by ultraviolet radiation, while adaptations to high-altitude environments highlight the complexity of human physiological responses to environmental challenges. Through the study of genetic adaptations, we gain insights into our shared ancestry, the diverse paths our ancestors traversed, and the remarkable resilience and adaptability of the human species. As genomic research continues to evolve, it holds the promise of uncovering further mysteries of our evolutionary journey and deepening our understanding of what it means to be human. Evolution is intricately linked to migration, environmental adaptation, and genetic variation. For instance, the ability to digest lactose beyond infancy emerged approximately 7,500 to 10,000 years ago, coinciding with the spread of dairy farming practices and the migration of populations across continents. Similarly, genetic adaptations for enhanced vitamin D production, such as mutations in the *DHCR7* and *FLG* genes, enabled human habitation in northern latitudes

with limited sunlight exposure. Moreover, the Thrifty Gene hypothesis posits that historical episodes of famine drove the selection of genes favoring efficient fat storage, providing a survival advantage during periods of food scarcity. As humans migrated to colder regions, adaptations for thermogenesis, such as variations in the *UCP1* gene, became more prevalent, allowing individuals to better withstand colder climates. Molecular markers derived from *Helicobacter pylori* provide valuable insights into human migration. These bacterial strains exhibit clear phylogeographic patterns that often mirror the migratory history of their human hosts. By examining genetic adaptations such as lactase persistence, altitude tolerance, and immune-related polymorphisms, this study highlights how migration has shaped the interplay between human genetics, cultural practices, and environmental pressures across different regions. Overall, investigating genetic adaptations to diet, climate, and other environmental factors offers valuable insights into our species' evolutionary history. As technology continues to advance, interdisciplinary approaches that combine genomics, anthropology, and bioengineering will further enhance our understanding of human migration and adaptation.

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### Conflict of Interest

The authors declare no conflict of interest.

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