

# Rapid, adaptive human evolution facilitated by admixture in the Americas

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## Abstract

Humans have migrated from their ancestral homelands in Africa to nearly every part of the world. Human migration is characterized by a recurrent process of physical isolation and genetic diversification followed by admixture, whereby previously isolated populations come together and exchange genes. Admixture results in the introgression of alleles from ancestral source populations into hybrid admixed populations, and we demonstrate how introgression can facilitate rapid adaptive evolution by introducing beneficial alleles at intermediate frequencies. We provide examples of adaptive introgression between archaic and modern human populations and for admixed populations in the Americas, which were formed relatively recently via admixture among African, European, and Indigenous American ancestral populations. Adaptive introgression has had an outsized effect on the human immune system. In light of the ubiquity of admixture in human evolution, we propose that adaptive introgression is a fundamentally important mechanism for driving rapid adaptive evolution in human populations.

## Human migration, genetic divergence, and admixture

The story of human evolution is one of nearly constant migration. The impulse to leave one's home, explore, and settle new territories is a seemingly universal hominid trait, manifest across multiple species and sub-species of the genus *Homo*, and one that ultimately allowed for humans to populate nearly every corner of the globe. Our hominid ancestors, and their earliest human descendants, have embarked on numerous long distance migrations around the world since their origins on the African continent. Fossil evidence suggests that *Homo erectus* migrated out of Africa to Eurasia just over 2 million years ago (ya), and *H. heidelbergensis*, a putative ancestor to both archaic and modern humans, left Africa ~800,000 ya (Fleagle, et al., 2010; Zhu, et al., 2018). The modern human sub-species – *Homo sapiens sapiens* – is thought to have originated from an African lineage of *H. heidelbergensis* ~300,000 ya (Schlebusch, et al., 2017), and began to migrate out of Africa and around the world starting ~75,000 ya (Henn, et al., 2012; Nielsen, et al., 2017). The phenomenon of migration has had a profound impact on the genetic composition of human populations worldwide, simultaneously driving the joint processes of genetic divergence and admixture. We are particularly interested in how admixture, and the resulting introgression of alleles from ancestral source populations, may have accelerated adaptive evolution in human populations.

*H. sapiens'* long and steady march out of Africa, through Asia, Oceania, and Europe, and finally throughout the Americas, entailed repeated episodes of population divergence followed by admixture, whereby previously separated populations came together and mixed (Figure 1A). Indeed, we can consider human evolution to be characterized by a recurrent pattern of: (1) (e) migration, (2) isolation, (3) divergence, (4) (im)migration, and (5) admixture (Figure 1B). Human populations constantly migrate to new lands, often resulting in physical isolation, which in turns leads to genetic diversification of the isolated populations. Genetic divergence of isolated populations can occur via genetic drift, owing to small population sizes, and/or natural selection based on local adaptations. However, population isolation does not last forever; eventually, additional waves of migration bring previously isolated populations together again. Any time previously isolated human populations encounter one another, even when those populations are from distinct sub-species, as was the case when modern humans encountered Neandertals and Denisovans, they interbreed, exchanging genes and yielding new hybrid lineages with genetic contributions from multiple ancestral source populations. As David Reich has detailed in his recent book-length treatment of the

ancient DNA revolution, this pattern of migration-driven divergence and admixture has been repeated countless times in archaic and modern human populations around the world (Reich, 2018). Admixture is not a bug of human evolution – it is in fact a ubiquitous feature of our species (Hellenthal, et al., 2014).

We posit that the process of genetic admixture has had a major impact on accelerating human adaptive evolution, in particular by stimulating the rapid evolution of introgressed alleles in recently admixed populations (Jordan, 2016). This model of human evolution shares much in common with Sewall Wright’s Shifting Balance Theory, which emphasized the importance of population sub-division and subsequent migration in facilitating adaptive evolution (Wright, 1932). In this chapter, we briefly review studies related to the pace of human adaptive evolution, explaining how admixture can speed up this process, followed by a more detailed treatment of adaptive introgression in both archaic and modern human populations. We emphasize rapid adaptive introgression in the Americas, the region of the world that has experienced perhaps the greatest single admixture event in human history, whereby African, European, and Indigenous American populations that were previously isolated for tens-of-thousands of years were suddenly brought together again following Columbus’ arrival in the New World (Crosby, 2003; Mann, 2011).

### **Admixture and the pace of adaptive evolution in human populations**

In their book *The 10,000 Year Explosion*, authors Cochran and Harpending take aim at the anthropological doctrine which holds that human biological evolution came to a halt around 50,000 ya, thereafter being superseded by a far more dynamic cultural evolution (Cochran and Harpending, 2009). In distilling this so-called ‘conventional wisdom’ regarding human evolution, they quote Stephen Jay Gould as saying “There’s been no biological change in humans in 40,000 or 50,000 years. Everything we call culture and civilization we’ve built with the same body and brain”. The basic idea underlying this assertion is that the explosion of human culture and behavioral modernity that marked the Upper Paleolithic essentially liberated humans from the strictures of biological evolution. This happened because rapid cultural evolution, in the form of tool and technology development, obviated the need to respond to environmental pressures by the slower process of natural selection. The authors convincingly dismiss with this (perhaps slightly straw man) argument and stress instead that technological developments, the invention of agriculture in particular, actually accelerated human adaptive evolution by allowing for larger population sizes and consequently more adaptive mutations (Hawks, et al., 2007).

The recent acceleration of human adaptive evolution covered in *The 10,000 Year Explosion* was based on the authors’ own research along with the work of many other scientists who have taken advantage of the accumulation of human genome sequence variation data to detect signals of adaptive evolution genome-wide in multiple populations around the world (Fan, et al., 2016; Oleksyk, et al., 2010; Sabeti, et al., 2006; Vitti, et al., 2013). This impressive body of research has leveraged the ongoing growth of human population genomic datasets, along with the development of increasingly sensitive methods for detecting adaptive evolution, to steadily decrease the amount of elapsed time needed to observe adaptation events. For instance, the agricultural revolution 10,000 ya led to adaptive evolution for calcium absorption in European populations (Akey, et al., 2004). Adaptive mutations that conferred lactose tolerance in Europeans (Bersaglieri, et al., 2004) and increased energy metabolism in East Asia (Helgason, et al., 2007) emerged independently 8,000 ya. Lighter skin pigmentation and increased height were selected for in Europeans 6,000 ya and 5,000 ya, respectively (Field, et al., 2016; Gibbons, 2007). Sickle cell mutations for protection

against malaria were initially proposed to have arisen multiple times in African populations, with estimates around 3,000 ya (Currat, et al., 2002; Ohashi, et al., 2004), but a recent study has proposed that these haplotypes are derived from a common ancestral haplotype that emerged 7,300 ya (Shriner and Rotimi, 2018). Perhaps the most recent sequence-based evidence for human adaptive evolution, at the lactase and major histocompatibility loci, dates to 2,000 ya (Field, et al., 2016). Here, we present evidence in support of our thesis that adaptive human evolution has occurred in the Americas within the last 500 years, an exceedingly short amount of time with respect to human evolution, via introgression of beneficial haplotypes from ancestral source populations.

Despite the findings on selection outlined in the previous paragraph, human adaptive evolution is still largely regarded as a slow process, which is constrained by the introduction of new adaptive alleles via mutation. This can be illustrated by the classic population genetic model showing the rate at which the frequency of an adaptive allele will increase in a population (Figure 2). A new mutant allele will be introduced at the low population frequency of  $1/(2 \times N_e)$ , where  $N_e$  is the effective population size. For example, a relatively small effective population size of 5,000 will yield an initial mutant allele frequency of 0.01%. If the new allele is adaptive, selection will act to increase its population frequency ( $p$ ) over time proportional to the selection ( $s$ ) and dominance ( $h$ ) coefficients, according to the recursion equation  $p_{i,t+1} = p_{i,t}w_i/\bar{w}$ , where  $i$  is the allele,  $t$  is the current generation,  $p$  is the allele frequency,  $w_i$  is the marginal fitness of the allele  $i$ , and  $\bar{w}$  is the population mean fitness. The increase in adaptive allele frequency happens extremely slowly at the end of the low end of the allele frequency spectrum. Under an additive dominance model ( $h = 0.75$ ) with a strong selection coefficient of  $s = 0.1$ , it will take more than 100 generations to see a 20% increase in the initial frequency of the adaptive allele. However, as can be seen in Figure 2, the rate of adaptive allele frequency increase speeds up tremendously at intermediate allele frequencies. Under the same dominance and selection parameters, but starting from an intermediate allele frequency of 35%, a doubling of the adaptive allele frequency can occur in less than 20 generations. This feature of adaptive evolution is what leads us to believe that admixture can facilitate extremely rapid human adaptation. When two or more previously isolated populations converge and mix, they introduce alleles to the newly formed admixed population at intermediate frequencies proportional to the percent contributions of each ancestral population. Since admixture introduces new alleles at intermediate frequencies via introgression in this way, it has the potential to allow for substantial increases in the frequency of adaptive alleles over a relatively small number of generations.

While our notion that admixture can dramatically speed up adaptive human evolution is based on a theoretical conjecture, there are numerous empirically observed cases of adaptive introgression in human populations that support this view of evolution. A majority of the studies on adaptive introgression focus on the impacts of admixture between modern humans and archaic hominids, *e.g.* Neandertals and Denisovans. In the sections that follow, we first discuss a few examples of ancient adaptive introgression, as they are by now more widely accepted. Then we review an example of more recent adaptive introgression in Africans. Finally, we discuss adaptive introgression in the Americas, where there are fewer studies and more contention regarding the results. Findings from admixed American populations are particularly provocative in the sense that they point to adaptive evolution occurring over a span of 500 years, or approximately 20-25 generations, an exceptionally short period of time for human evolution.

## Ancient adaptive introgression

Evidence of adaptive introgression acting as a means of rapid human adaptive evolution has been shown via the admixture of modern humans with archaic hominids. Before the modern human out-of-Africa migration, Europe and Asia were populated by other *Homo* species: Neandertals and Denisovans. These archaic populations had isolated and genetically diverged from the ancestors of modern humans hundreds of thousands of years before and were adapted to their respective local environments in Europe and Asia. As modern humans emerged from Africa, they not only encountered new environments, but also these new human-like populations. Admixture of archaic and modern humans created new genomes that combined intermediate frequency adaptive alleles from the archaic populations into the genomic background of the modern humans. This is thought to have helped modern human populations to more quickly adapt to new environments as they settled Europe and Asia, including fighting off novel pathogens. Here we will review a few examples of ancient adaptive introgression; for a more comprehensive review, see (Racimo, et al., 2015).

### *Immune system*

A key factor in the response of the immune system is the *HLA* class I genes of the major histocompatibility complex (MHC). These genes are involved in antigen presentation for immune cell recognition and are very diverse across human populations. Abi-Rached et al. were interested in the evolutionary source of the deeply divergent human *HLA-B* allele, *HLA-B\*73:01* (Abi-Rached, et al., 2011). This allele is found mainly in west Asia and is in linkage with *HLA-C\*15:05*, found in west and southeast Asia. The authors suggested that this allele combination was not present in Africa prior to the out-of-Africa migration. To test this hypothesis, they characterized the archaic *HLA* class I genes from Denisovans and Neandertals, finding that two *HLA-A* and two *HLA-C* alleles in Denisovans were most similar to modern sequences, including the *HLA-C\*15* allele. Geographic locations of these similar modern alleles show a very low presence in Africa, with higher presence in Asia and Oceania. Divergence estimates of these alleles show that they were formed before the out-of-Africa migration, but since the alleles are not present in Africa, they are likely to come from an archaic source populations, namely Denisovans. The authors completed the same analysis with similar Neandertal *HLA-A* and *HLA-C* alleles and found them to be present in Eurasians and absent in Africans. These findings suggest that the immune systems of archaic *Homo* populations were better adapted to local pathogens in the Eurasian environments, and upon migrating out of Africa, modern humans rapidly adapted the immune system through introgression of these sequences.

After the study on *HLA* adaptive introgression, Mendez et al. interrogated *STAT2*, an immune system gene with a role in interferon-mediated responses, for signals of adaptive introgression with Neandertals in Europeans (Mendez, et al., 2012). Initial sequencing of *STAT2* revealed the 'N' haplotype, a deeply divergent haplotype present only in the non-African populations used in this study. When compared with the draft Neandertal reference sequence, the N haplotype most closely matched the Neandertal sequence. In addition to this, the haplotype linkage disequilibrium (LD) including *STAT2* is very long in both West Eurasians (~130 kb) and East Asians and Melanesians (~260 kb), a finding expected if the haplotype was introduced via introgression. The upper divergence estimate between the Neandertal and N haplotype of ~160 kya is more recent than the estimates of divergence between the Neandertal and human reference sequence of ~600 kya. The N haplotype has a 10-fold higher frequency in Melanesians, particularly the

long form of the haplotype, when compared with the rest of the Eurasian populations. This suggests that *STAT2*, or some other gene in the haplotype, was the target of positive selection in Melanesians. In either case, the introgression of *STAT2* into the modern human genome affected interferon signaling in the immune system.

Genome-wide studies on Neandertal and Denisovan introgression had identified a number of putative Neandertal introgressed regions in modern humans (Sankararaman, et al., 2014; Vernot and Akey, 2014). Dannemann et al. utilized these genomic maps to characterize the adaptive introgression potential of a region containing a haplotype of three Toll-like receptors (TLRs), *TLR6-TLR1-TLR10*, which show some of the highest probabilities of Neandertal introgression (Dannemann, et al., 2016). These genes play an important role in the innate immune system as they are the first line of defense against pathogens and help to activate the adaptive immune response. To characterize this region of chromosome 4 as resulting from an adaptive introgression event, the authors identified evidence of introgression by showing that there are seven main haplotypes for the TLRs and three of these are more similar to archaic sequences than to the rest of modern humans as determined by sequence comparisons. In addition to this, the geographic distribution of the archaic-like sequences provide evidence for introgression as they are mostly found outside of Africa, which is to be expected if introgression occurred when modern humans moved into Neandertal and Denisovan environments. A high differentiation, as determined by  $F_{ST}$ , and previous studies reporting signatures of positive selection on SNPs in *TLR10* provided the authors with evidence that the haplotype was under positive selection. Expression quantitative trait loci analysis showed tissue-specific regulatory effects increasing the expression of these genes in white blood cells. Overall, it was posited that this TLR haplotype could have been adaptively introgressed into the modern human population as a means to affect the innate immune system response with response to potential pathogens, including *H. pylori*. The authors mention that a diversity of haplotypes for TLRs could have increased the adaptation of modern humans in novel environments, such as that encountered after migration out of Africa.

### ***Integumentary system***

Adaptive introgression of Neandertal sequences have also affected the hair and skin phenotypes of Europeans and East Asians, as published by two studies in 2014. Vernot and Akey, as mentioned previously, created a catalog of putative introgressed Neandertal sequences in 379 Europeans and 298 East Asians, part of the Phase 1 data release of the 1000 Genomes Project, using a modified  $S^*$  summary statistic to identify signals of introgression followed by sequence comparison to a Neandertal reference (Vernot and Akey, 2014). The authors then interrogated these sequences to find significantly differentiated introgressed regions between Europe and East Asia as well as shared regions in the two populations with relatively high allele frequency. Using  $F_{ST}$  to identify differentiated variants between the two populations, the authors identified two regions with genes that are part of the integumentary system, in addition to other regions and genes. *BCN2* on chromosome 9 was found to be at ~70% frequency in Europeans while absent in East Asians; this gene has been related to skin pigmentation in Europeans. *POU2F3* on chromosome 11 was found to be at ~66% frequency in East Asians and <1% in Europeans; this gene is expressed in the epidermis and mediates keratinocyte proliferation and differentiation. Both populations shared a total of six regions with >40% allele frequency with signals of adaptive introgression. One of these regions on chromosome 12q13 contains a type II cluster of keratin genes, providing evidence for adaptive variation of skin phenotypes.

A second study to find evidence of adaptive introgression in the integumentary system used a conditional random field approach to identify putative Neandertal introgressed regions in 1,004 modern humans from the Phase I data release of the 1000 Genomes Project (Sankararaman, et al., 2014). They also created a map of Neandertal introgression events in the modern human genome and analyzed the top 5% of genes with the highest inferred Neandertal ancestry. They found that there was a significant enrichment of genes involved in keratin filament formation and posit that Neandertal variants may have helped modern humans adapt to the novel European and Asian environments by affecting their skin and hair.

### ***Altitude adaptation***

A well-studied example of how archaic introgression can provide an adaptive benefit to a modern human population is that of altitude adaptation in Tibetans. Early studies elucidated the molecular underpinnings of adaptation to high altitude living in Tibetans and the high-altitude Sherpa population and noted that *EPAS1* and *EGLN1* are crucial to controlling signals of hemoglobin concentration in Tibetans, compared with other lowland East Asian populations (Beall, et al., 2010; Simonson, et al., 2010; Yi, et al., 2010). Jeong et al. (Jeong, et al., 2014) determined that the Tibetan population was a result of an ancestral “high-altitude” population admixing with a “low-altitude” population. As *EPAS1* had the strongest signal of selection for Tibetans, Huerta-Sanchez et al. (Huerta-Sanchez, et al., 2014) moved forward to identify the source of the adaptive introgression for this gene. After re-sequencing 40 Tibetan individuals (high-altitude) and 40 Han Chinese individuals (low-altitude), the authors found that  $F_{ST}$  for this gene was highly differentiated as expected if there was selection on the high-altitude haplotype in Tibetans. When comparing the Tibetan-specific haplotype to potential donor sequences, it was determined that the haplotype shared more sequence similarity with the Denisovan haplotype than any other extant or archaic population. The authors concluded that introgression from a Denisovan population allowed the modern Tibetan population to rapidly adapt to the high-altitude of the Tibetan plateau.

### **Adaptive introgression in modern humans**

The Bantu-speaking populations (BSPs) of Africa experienced multiple periods of adaptive introgression during their migration throughout Africa over the last 1,500 years (Patin, et al., 2017). As the BSPs migrated, they encountered other African populations, already adapted to their local environments. Genetic ancestry characterization of the BSPs showed admixture with other African populations, including western rainforest hunter-gatherers, eastern African farmers, and San populations. In each of the BSP populations – western, eastern and southeastern – the authors searched for evidence of excess ancestry and compared their findings with signals of positive selection to identify putative adaptively introgressed regions. In western BSPs, there was an overlap of excess western rainforest hunter-gatherer ancestry with a strong signal of positive selection for the *HLA* region and a moderately strong signal for *CD36*. These regions are both related to the immune system response, with *CD36* being associated with susceptibility to malaria caused by *Plasmodium falciparum*. In eastern BSPs, excess eastern African ancestry overlapped a moderately strong signal of positive selection for the lactase gene (*LCT*) providing the lactase persistence phenotype for eastern BSPs. Thus, both the immune system and diet-related phenotypes of BSPs have been influenced by recent admixture and adaptive introgression in these African populations.

## Adaptive introgression in the Americas

We are particularly interested in studying adaptive introgression in admixed American populations (Jordan, 2016). Modern (cosmopolitan) human populations in the Americas were formed primarily by admixture among ancestral source populations from Africa, Europe, and the Americas (Figure 1A). This is considered to be one of the largest and most abrupt admixture events in all of human evolution and one that has had a profound effect on world history (Crosby, 2003; Mann, 2011). Admixed American genomes can be considered as evolutionarily novel in the sense that they contain combinations of ancestry-specific alleles that never previously existed together on the same genomic background. The creation of such novel admixed genome sequences has important implications for health and fitness in modern American populations (Norris, et al., 2018). The possibility of adaptive introgression in the Americas can be considered controversial in light of the fact that the ~20-25 generations that have elapsed since the process of admixture in the Americas began represents a very short amount of time in terms of human evolution, less than 1% of the time that has elapsed since humans migrated out of Africa. In principle, it should be very difficult to observe adaptive human evolution over such a short time scale. Nevertheless, we contend that the Americas represent an ideal laboratory to study adaptive introgression and to explore the possibility of extremely rapid adaptation in human populations.

Our working hypothesis is that numerous alleles were ‘pre-selected’ in ancestral source populations over thousands of years based on their utility in the local environments of Africa, Europe, and the Americas. Subsequently, when the ancestral source populations were suddenly brought back together, some of these pre-selected alleles could have also provided an adaptive benefit in the New World environment. For example, alleles that served to protect their human hosts against infectious disease may have been particularly important in the pathogen-rich environment of the Americas. In addition, neutral alleles that diverged in frequency among ancestral populations based on genetic drift could later become adaptively beneficial in the new environment. In either case, adaptively beneficial alleles introduced at intermediate frequencies via introgression could quickly increase in frequency owing to their utility in the novel admixed populations (see Figure 2 and the previous discussion on how introgression can accelerate adaptive evolution).

The analytical approach used to test this hypothesis is based on the delineation of genome-wide ‘local ancestry’ patterns in admixed populations. Local ancestry refers to the specific ancestral origins – African, European, or Native American – for specific chromosomal regions (*i.e.* haplotypes). Local ancestry is assigned by comparing individual chromosomal segments against the corresponding genomic regions from panels of ancestral population reference genomes (Geza, et al., 2018; Maples, et al., 2013). Once this is done for an admixed American population, the population’s local ancestry fractions for any given region of the genome can be compared to the genome-wide population ancestry averages to search for ‘ancestry-enriched’ regions (Figure 3). Ancestry-enriched regions are genomic segments that show anomalously low or high ancestry fractions, for any given ancestry component, compared to the genome-wide population averages. Statistically significant local ancestry deviations are taken to represent evidence of adaptive introgression. The presence of independent signals of previous positive selection on these same regions in ancestral source populations can be used to provide additional evidence in support of adaptive introgression (Patin, et al., 2017). Below, we review all currently known cases of adaptive evolution in admixed American populations.



## *Puerto Rico*

One of the first studies on adaptive introgression in the Americas uncovered signals of recent selection and introgression in Puerto Ricans (Tang, et al., 2007). Genetic ancestry characterization of the study population – 192 Puerto Ricans as part of the Genetics of Asthma in Latino Americans study – showed that the population was mainly of European descent with relatively equal fractions of African and Native American ancestries. Local ancestry estimates, when compared with global averages, revealed excess African ancestry on chromosome 6 and excess Native American ancestry on chromosomes 8 and 11. The region of chromosome 6 with African enrichment harbors the major histocompatibility complex (MHC), the first response to invading pathogens for the adaptive immune system. Chromosome 11 shows Native American enrichment of an olfactory gene cluster, which the authors mention, has been shown to be under positive selection and reference other studies (Gilad, et al., 2003; Voight, et al., 2006). The final Native American enrichment on chromosome 8 did not have any clear candidates for adaptive introgression, but the one gene in the region, *CSMD3*, did have some tissue-specific expression. The authors suggest that the enrichment of African alleles of the immune system could be due to them being more advantageous in the new environment as they are genetically more diverse than Europeans or Native Americans and better able to fight off the numerous pathogens imported and endemic to the area. Another reason for the ancestry enrichment could be that these genes played a role in a phenotype that offered a fitness advantage and thus was acted upon by natural selection upon admixture in the New World. For either reason, the immune system of Puerto Rican individuals seems to have been influenced by adaptive introgression of ancestry-specific alleles.

## *Colombia*

A 2015 study to characterize the genetic ancestry of the Colombian population from the 1000 Genomes Project found that similar to Puerto Rico, the Colombian population has mostly European ancestry, followed by Native American and finally African ancestry fractions (Rishishwar, et al., 2015). In addition to understanding the impacts of sex-biased admixture, the authors evaluated local ancestry patterns, looking for locus-specific patterns using a trinomial probability metric to signal areas with excess ancestry. The regions with anomalous ancestry patterns were then interrogated for previously identified signs of positive selection and their phenotypic associations, specifically health-related phenotypes. The authors found signals of African ancestry enrichment for *HLA-B* on chromosome 6, part of the MHC. There was also evidence of enrichment of European ancestry for *SLC24A5* on chromosome 15, a gene that influences skin pigmentation with decreased melanin. In addition to single genes with anomalous ancestry patterns, the authors performed a gene set enrichment analysis to identify pathways containing an abundance of ancestry-enriched genes. They found both the innate and adaptive immune response contained signs of ancestry enrichment. These lines of evidence provide support for the hypothesis that the Colombian genomes retained adaptive ancestry-specific loci that were better suited to combat the wide variety of pathogens in the environment.

As a caveat to the findings, it should be noted that the program used for local ancestry assignment generated very short ancestry tracts, compared with the tract lengths generated from current local ancestry assignment programs such as RFMix (Maples, et al., 2013). It is unlikely that in the ~20-25 generations since the Columbian Exchange that there would be sufficient genomic recombination to

generate the size tracts seen in this analysis and their findings should be validated using contemporary programs.

### *Mexico*

In 2014, a novel two-layer hidden Markov model was proposed for inferring local ancestry of admixed individuals based on the detection of haplotype structure (Guan, 2014). This method was used to characterize the genetic ancestry and highlight regions with excess ancestry-specific loci in Mexican individuals from the HapMap3 Project and 1000 Genomes Project. For both projects, the author found excess African ancestry on chromosome 6 in the MHC region, as well as on chromosome 8p23.1 at a known chromosomal inversion.

A follow-up study on recent selection in Mexican individuals found a significant excess of African ancestry of the MHC on chromosome 6 (Zhou, et al., 2016). The authors analyzed genetic ancestry data from two cohorts of Mexican individuals and found excess ancestry in both cohorts. By being able to replicate the results in a second cohort, there was more confidence in the findings of African ancestry enrichment. In addition to this, the authors developed a technique to infer local ancestry without the concern of inaccurate Native American samples and estimated the amount of selection necessary for this locus to remain significantly enriched with African ancestry. The results suggest that selection was at similar strengths to that of lactase selection in Europeans and the sickle-cell trait in Africans. The authors suggest that the challenging conditions of the New World, with the existing pathogens and those brought over by the Spaniards and Africans could have provided the necessary selection pressure for the African MHC alleles to increase in frequency due to the greater diversity of African MHC. Infectious diseases and epidemics, in addition to harsh living conditions, caused many of the Native American populations to perish, leading to a lack of Native American ancestry at this important immune system locus.

### *African Americans*

A study on ancestry-specific selection in 1,890 African Americans characterized the genetic ancestry of the population to be ~72% African and ~28% European (Jin, et al., 2012). The authors then identified loci with European (or African) ancestry 3 standard deviations above or below the genome-wide average as those potentially under natural selection. Four regions were found to have excess European ancestry and two were found to have excess African ancestry. The excess European ancestry was found to be related to response to influenza infection and the African ancestry was found to be related to general immune system signaling. Using  $F_{ST}$  between African Americans and putative ancestral African populations, the authors identified signals of positive selection and found four regions that carried differentiated SNPs, including those related to malaria response and the MHC, suggesting the immune system of African Americans in the New World was under pressure with response to the novel pathogen environment. It is important to note, however, that the regions with excess African ancestry do not overlap with those putatively under positive selection.

In response to these findings, another group performed a genetic ancestry analysis on 29,141 African American individuals and found there to be no evidence of directional selection (Bhatia, et al., 2014). Instead, the authors state that the earlier findings could have been due to chance or systematic biases in

data handling. When directly comparing the 2012 results to the authors' calculations, the authors showed that they get much lower ancestry deviation estimates than previously reported and the 2012 enrichment findings were not replicated. The same results are found when focusing on the positive selection estimates using  $F_{ST}$ ; the previous results were not replicated and there were no overlaps between the two findings.

## Conclusions and future prospects

Adaptive human evolution was postulated to have stopped ~40-50,000 ya, coincident with the emergence of cultural evolution (Gould, 2000; Mayr, 1963). Not only has this anthropological doctrine been shown to be false, but there is abundant evidence that adaptive evolution has actually accelerated over the last 10,000 years (Cochran and Harpending, 2009). Throughout this chapter, we have provided examples of adaptive introgression acting as a means for facilitating rapid human evolution, through admixture with Neandertals and Denisovans thousands of years ago, for admixture in modern Africans 1,500 years ago, and via admixture in the Americas 500 years ago. Admixture and introgression have allowed modern humans to colonize new environments, such as the Tibetan plateau, resist novel pathogens and combinations of pathogens throughout Europe, Africa and the Americas, and generally be better suited to their local environments. The immune system has been shown to be a hotspot of adaptive introgression throughout time as admixture among previously adapted populations allowed modern humans to quickly adapt and thrive in their new environments.

As seen in the contradictory studies of African Americans, signals of adaptive introgression can be due to biases in the data or small sample sizes. To increase confidence in ancestry enrichment acting as signals of adaptive introgression, future studies can ensure that regions with ancestry enrichment also have multiple lines of evidence of positive selection from ancestral populations on the same genomic regions in the admixed populations. In addition, if there are multiple admixed populations with similar ancestral source populations, finding signals of ancestry enrichment and positive selection shared among the multiple populations could provide more confidence that a finding is true as there is likely shared selection pressures in the same area of the world. Selection is also likely to occur on phenotypes which are caused by multiple genes, not just one genomic locus. If the same ancestry enrichment and positive selection signals are seen in multiple genes encoding a polygenic phenotype, then it is likely that adaptive introgression could have led to rapid adaptive human evolution.

Finally, we would like to propose the idea that admixture, now recognized as a ubiquitous feature of human evolution (Hellenthal, et al., 2014; Reich, 2018), has had a far greater impact on human adaptive evolution than formerly recognized. The linked processes of genetic divergence followed by admixture (Figure 1B) have provided abundant raw material for adaptive introgression throughout human evolutionary history, which in turn can provide for extremely rapid adaptive evolution unconstrained by mutation. It may well be the case that, owing to admixture, adaptive evolution of human populations is far more common and much more dynamic than previously imagined.

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## Figures

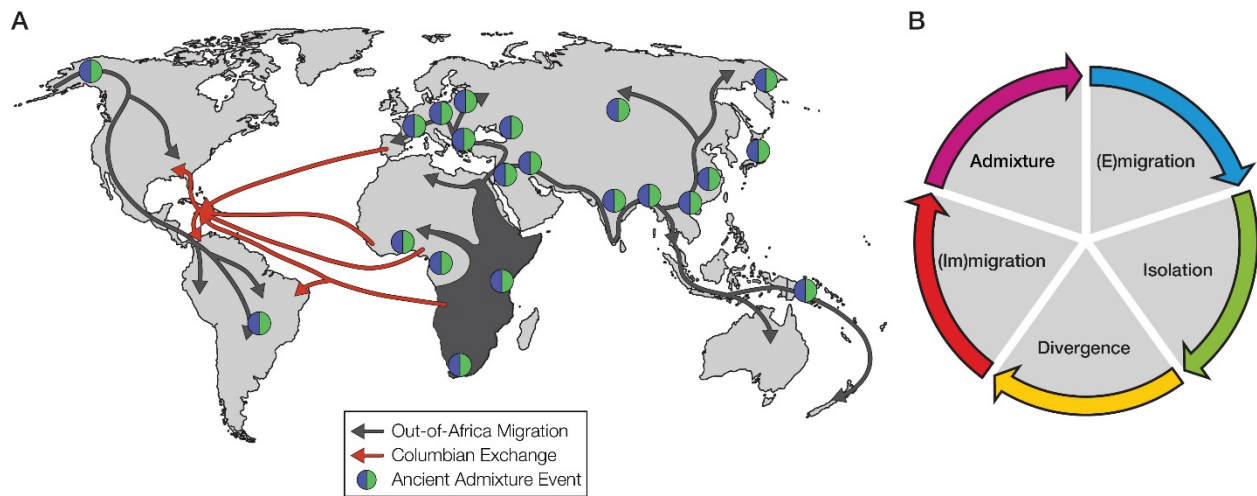


Figure 1. **Human migration, genetic divergence, and admixture.** (A) Out-of-Africa migration routes around the world are indicated with gray lines/arrows. Ancient admixture events are indicated with circles [locations taken from (Reich, 2018)], and the modern admixture event that brought together African, European, and Indigenous American populations, *i.e.* the Columbian Exchange (Crosby, 2003; Mann, 2011), is shown with red lines/arrows. (B) The recurrent and joint processes of migration-driven genetic divergence and admixture are illustrated.

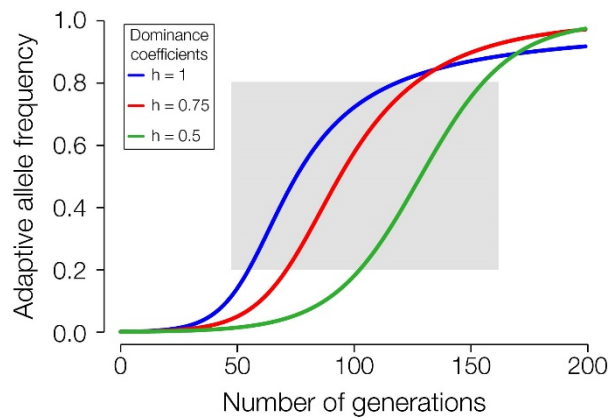


Figure 2. **Population genetic model showing the increase in frequency of an adaptive allele over time.** Adaptive allele frequencies are shown on the y-axis, and time in generations is shown on the x-axis. The model corresponds to a selection coefficient ( $s$ ) of 0.1, and three different allele increase trajectories are shown according to different dominance coefficients ( $h$ ). The gray shading corresponds to the zone at intermediate allele frequencies where the rate of adaptive allele frequency increase is most rapid.

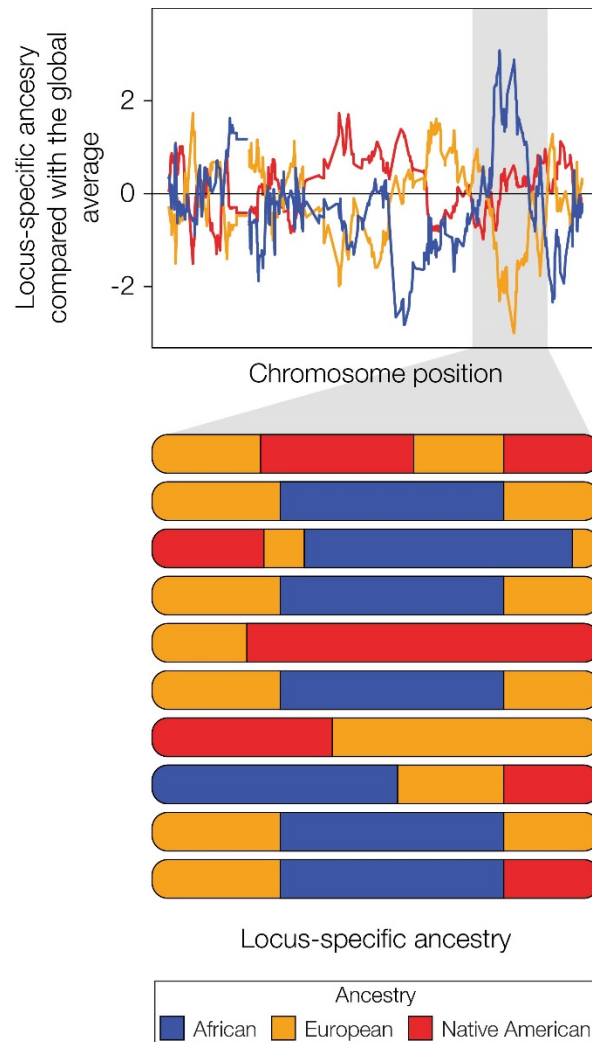


Figure 3. **Ancestry-enrichment analysis for identifying adaptive introgression events.** Locus-specific ancestry patterns – African (blue), European (orange), and Native American (red) – are characterized across all chromosomes in the population. Locus-specific ancestry fractions are compared with the global ancestry fractions along the genome to identify ancestry-enriched (or depleted) segments. An example is shown (gray shading) for a region that is enriched for African ancestry and depleted for European ancestry.