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Adaptations to local environments in modern human populations

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Abstract

After leaving sub-Saharan Africa around 50,000–100,000 years ago, anatomically modern humans have quickly occupied extremely diverse environments. Human populations were exposed to further environmental changes resulting from cultural innovations, such as the spread of farming, which gave rise to new selective pressures related to pathogen exposures and dietary shifts. In addition to changing the frequency of individual adaptive alleles, natural selection may also shape the overall genetic architecture of adaptive traits. Here, we review recent advances in understanding the genetic architecture of adaptive human phenotypes based on insights from the studies of lactase persistence, skin pigmentation and high-altitude adaptation. These adaptations evolved in parallel in multiple human populations, providing a chance to investigate independent realizations of the evolutionary process. We suggest that the outcome of adaptive evolution is often highly variable even under similar selective pressures. Finally, we highlight a growing need for detecting adaptations that did not follow the classical sweep model and for incorporating new sources of genetic evidence such as information from ancient DNA.

Introduction

Since their migration out of Africa 50–100 thousand years ago (kya) [1,2], anatomically modern humans have colonized a wide range of environments in a relatively short time period. For example, archaeological studies provide evidence of human habitation in environments extremely divergent from those of sub-Saharan Africa, such as cold climates in arctic Siberia or high-altitude environments in the Tibetan plateau, as early as 27 and 30 kya, respectively [3,4]. In addition to differences in the physical environment, cultural transitions such as the introduction of agriculture and pastoralism also contributed to divergence of human environments [5,6]. Therefore, it is likely that human populations accumulated locally adaptive features, through genetic and non-genetic mechanisms. Understanding the genetic basis of heritable beneficial traits is a major goal of human genetics [7–10]. Morphological and physiological traits showing unusually large inter-

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population variation, such as skin pigmentation [11–21] and lactase persistence [22–30], have been prioritized as candidates for adaptation to local environments.

Genomic tools allow the detection of loci involved in population-specific adaptations using both phenotype-dependent and -independent approaches. Using phenotype information, genome-wide association studies (GWAS) have successfully identified over 13,000 single nucleotide polymorphisms (SNP) associated with a wide range of traits, a portion of which are likely to be adaptive [31]. However, GWAS frequently require a large number of samples, especially if the trait of interest is highly polygenic [32,33]. Population genetics approaches, not bound by a specific phenotype, scan the genome for signatures of recent positive selection, such as unusually large divergence in allele frequency between populations [34–36] or extended haplotype homozygosity around selected variants [7,8,37]. The power of these phenotype-independent approaches is adequate with relatively small sample sizes, but – unlike GWAS – it does not increase substantially with much larger numbers of individuals per population [7–9]. Given that whole genome genotyping and sequencing is becoming increasingly inexpensive and a large number of population samples are available, the feasibility of these studies is no longer a challenge. However, connecting genetic loci found through these approaches to relevant phenotypes remains problematic.

In this review, we summarize recent advances in understanding genetic adaptations to local environments in human populations, focusing on their genetic architecture and using lactase persistence (LP), skin pigmentation, and high-altitude adaptation as case studies (Figure 1).

To what extent is natural selection repeatable?

There are many known cases of populations sharing similar selective pressures. Consumption of fresh milk in Europe, Middle East and East Africa and high-altitude environments of the Tibetan, Andean and Ethiopian highlands are good examples. This sharing of selective pressures provides an opportunity to observe multiple independent realizations of the adaptive evolutionary process. A growing body of evidence suggests that the outcomes of this process are highly variable, both in terms of phenotypes and of their genetic bases. At the same time, some sharing of adaptive changes at the level of biological pathways is also emerging from inter-population and inter-species comparisons.

LP refers to a continued expression of the lactase-phlorizin hydrolase (LPH), encoded by the *LCT* (lactase) gene [38]. LP is found at high frequency in people of Northern European ancestry and populations in East Africa, Middle East, and South/Central Asia who traditionally practice pastoralism and regularly consume milk and other dairy products as adults [39,40]. Based on this association, LP was hypothesized to confer a selective advantage because consumption of fresh milk and other dairy products allowed for efficient caloric intake [41], calcium assimilation in high latitude [42], or increased water absorption from milk in arid environments [43].

Multiple genetic variants associated with LP have been found in different populations: C/T₋₁₃₉₁₀ (rs4988235), C/G₋₁₃₉₀₇ (rs41525747), T/G₋₁₃₉₁₅ (rs41380347) and G/C₋₁₄₀₁₀ (rs145946881) are most frequently found in Europeans, Ethiopians, Saudi Arabians and Tanzanians, respectively [22–25,28,30]. These variants harbor signatures of recent positive

selection [24–28,30,44], increase enhancer function [24,25,28,45–47], and are located in binding sites for major transcription factors in intestinal epithelia such as Oct-1, HNF1 α and HNF4 α [23,25,45–47]. Interestingly, all of them are found within 100 bp of each other, suggesting a simple architecture for LP with a small mutational target size. Each of these variants is associated with simple haplotype patterns, consistent with single mutational events [24,30].

Human skin pigmentation shows a strong correlation with latitude and UV radiation level, leading to the hypothesis that skin reflectance is a compromise between UV-induced vitamin D synthesis and protection from damage by strong UV radiation [48,49]. Assuming a darker pigmentation as the ancestral phenotype, genetic studies have focused on the evolution and the genetic basis of lighter skin pigmentation in Europeans and East Asians, who share low exposures to UV radiation. Skin pigmentation is known to be strongly affected by the ratio of brown/black eumelanin and red pheomelanin and by the distribution of melanosomes [50]. Candidate gene studies revealed variants associated with skin pigmentation in many genes involved in melanogenesis, such as *MC1R*, *MATP* (*SLC45A2*), *SLC24A5*, *TYR*, *DCT*, *OCA2* and *KITLG* [11–16,51–54]. Recent genome-wide association studies added new genes, including *SLC24A4* and *IRF4*, and replicated findings from candidate gene studies [55–57]. Many of these pigmentation-associated variants are specific to either Europeans or East Asians, strongly supporting independent evolution of light skin pigmentation in these populations. For example, missense mutation L374F (rs16891982) in the *MATP* gene, which may have a role in tyrosinase trafficking in melanocytes [58], is almost fixed in Europeans but absent in East Asians or Africans [13,59]. In contrast, a derived missense variant H615R (rs1800414) in the *OCA2* gene reaches high frequency in East Asians but is absent in Europeans or Africans [54,60–62]. *OCA2* SNPs associated with blue eye color in Europeans are associated with haplotype backgrounds different from that of rs1800414, consistent with their distinct evolutionary history [18].

Although LP and light skin pigmentation provide examples of adaptive phenotypic convergence in response to a given environment, different phenotypes are observed across populations living at high-altitude (>2,500 m) (Table 1). High-altitude environments are challenging for long term human habitation due to various environmental stressors, such as low barometric O₂ pressure, low temperature and high UV radiation [63,64]. Hypobaric hypoxia, induced by low barometric O₂ pressure, has been hypothesized as a major selective pressure because it greatly affects human physiology in a way that cannot be modified through cultural or behavioral practices [63,65]. Indeed, the study of high-altitude physiology started with descriptions of chronic mountain sickness, characterized by extremely high erythrocyte level and low levels of blood oxygen saturation [66], in Andean highlanders [67,68]. In addition to chronic mountain sickness, the impact of long term residence in high-altitude is evident in several other clinical symptoms, such as high-altitude pulmonary hypertension [69] and pregnancy complications [70].

Interestingly, physiological studies of indigenous high-altitude populations, such as the Aymara and Quechua people from the Andean altiplano, Tibetans from the Tibetan plateau, and Amhara and Oromo from the Ethiopian highlands, revealed distinct patterns of physiological changes in each population (Table 1) [71–77]. For example, Andean

highlanders, as well as acclimatized visitors from lowland, show increased blood hemoglobin concentrations, while Tibetans and Ethiopian Amhara show no such increase up to 4,000 m altitude [73,74,78,79]. Andean highlanders show high prevalence of chronic mountain sickness around 5%, but Tibetans are known to be more resistant to it, with only 1% prevalence [80,81]. Ethiopian highlanders are also hypothesized to be resistant to chronic mountain sickness because there has been no case reported [81].

In Tibetans, multiple studies have found that two candidate genes, *EGLN1* (egl nine homolog 1) and *EPAS1* (endothelial PAS-domain containing protein 1), harbor SNPs with unusually large allele frequency divergence from low-altitude East Asians or associated with extended haplotype homozygosity [35,82–88]. A few studies also reported genetic associations of SNPs in and around these two genes with inter-individual variation in hemoglobin levels, in which the Tibetan major alleles (minor alleles in lowland East Asians) were associated with lower hemoglobin levels [35,82,83,88,89]. The functional relevance of these genes to hypoxia is also striking. *EPAS1* codes for a component of HIF2 (hypoxia inducible factor 2), a major transcription factor induced by hypoxia and regulating erythropoiesis, whereas *EGLN1* is a direct upstream regulator of HIFs and an oxygen sensor [90,91]. These findings led to the hypothesis that long-term high hemoglobin levels are harmful, due to the increased risk of stroke and pregnancy complications; therefore, genetic variants dampening this acclimatizing response were positively selected in Tibetan populations [65].

Interestingly, studies in Andean or Ethiopian highlanders did not find variants discovered in Tibetans [36,84,92,93]. Alkorta-Aranburu et al [36] showed that none of the *EGLN1* or *EPAS1* SNPs found in Tibetans nor tagging SNPs in these genes were significantly associated with hemoglobin concentrations in Ethiopians, even though Ethiopians and Tibetans share the phenotype of unelevated hemoglobin levels [74]. Bigham et al [84] found signatures of recent positive selection at the *EGLN1* gene in both Andeans and Tibetans, but the haplotype background was distinct. Although the Tibetan *EGLN1* haplotype was reported to be associated with hemoglobin levels, the phenotypic effects of the Andean *EGLN1* haplotype have not been investigated. These examples suggest a composite picture in which some populations share an adaptive phenotype (i.e. unelevated hemoglobin levels in Tibetans and Amhara) that is not observed in other high-altitude populations (i.e. Andeans and Oromo). In addition, at the genetic level, different alleles and loci may be involved even when populations share an adaptive phenotype (i.e. Tibetans and Amhara). On the other hand, the same locus (i.e. *EGLN1* and *OCA2*) may be selected in different populations, whether they share the same adaptive phenotype or not.

Although the studies above suggest low repeatability of the adaptive process at the level of individual phenotypes or genes, inter-population and inter-species comparisons suggest sharing of selection targets at the level of biological pathways. A significant enrichment of selection signals around genes involved in the response to hypoxia was found in all three high-altitude populations [36,84,86]. Other biological pathways emerged from human population studies include angiogenesis, embryonic development, DNA damage response and energy metabolism; these pathways are also repeatedly found to be the targets of

adaptive evolution in non-human high-altitude species, as suggested by recently published whole genome sequencing studies [94–98].

What is the relationship between the genetic architecture of a trait and the mode of adaptation?

The genetic architecture of a trait, including the number and effect size of individual variants, the age of a variant at the onset of selection, and the selective advantage or disadvantage of a variant in the ancestral environment, is tightly linked to the mode of adaptation for that particular trait [99,100]. At one end of the spectrum, LP is similar to Mendelian traits. LP variants segregate at frequencies as high as 73% in Northwestern Europeans (C/T₋₁₃₉₁₀) [59] and 57% in Saudi Arabians (T/G₋₁₃₉₁₅) [25]. With their high penetrance, they explain a large proportion of LP phenotype variation, especially in Europe [40]. Although estimates of the selection coefficient are highly variable, ranging from 0.8% to 19% [24–27,44], strong signatures of recent positive selection on young adaptive variants have been detected [24–28,30,44]. Many variants associated with skin pigmentation also show clear signatures of recent positive selection, such as extreme allele frequency divergence between populations and skewed allele frequency spectrum [13–15,18,54,62]. Several of these variants have a relatively large effect size. For example, Beleza et al [57] reported that four loci (*SLC24A5*, *SLC45A2*, *GRM5/TYR* and *APBA2*) explain 35% of the total variation in skin pigmentation in an admixed population of Cape Verde; however, genome-wide ancestry proportions in the same admixed population were estimated to account for additional 22% of the total variation, consistent with a polygenic contribution undetected by genome-wide significant loci.

The genetic basis of height is at the opposite end of the spectrum. Although over 180 loci associated with adult height have been found through GWAS, the amount of genetic variation explained by each individual variant is minimal: these loci together explain only about 10% of the total phenotype variation in height [33]. Turchin et al [101] reported a systematic increase in frequency of alleles positively associated with height in Northern Europeans in comparison to Southern Europeans and suggested that this pattern is unlikely to be a result of genetic drift, supporting a role of consistent weak selection on standing variants associated with taller height in Northern Europe.

Recent positive selection on new mutations and selection on standing variation are not the only modes of adaptation observed in human populations. For example, unlike many other variants associated with skin pigmentation, variation in the *MC1R* gene shows a pattern consistent with relaxation of purifying selection at high latitude [11]. Another interesting case is found in high-altitude adaptations in Tibetans, in which admixture may have induced a second round of selection on adaptive variants. Our recent study suggested a model in which Tibetans originated from the admixture between a population adapted to high-altitude and low-altitude immigrants [89], which allowed us to apply case-only admixture mapping technique [102] to find adaptive loci enriched in high-altitude ancestry in Tibetans. A similar scenario in which one population contributes locally adaptive alleles to another population has been proposed for the introduction of pastoralism and LP from East Africans to hunter-gatherers in Southern Africa [103,104].

Conclusions and future directions

Rapid development in genomics technology has opened up unprecedented opportunities to study the genetic architecture of adaptive phenotypes. With a large amount of genetic variation data densely covering the entire human genome, many variants of large effect have been found for both disease and normal phenotypes. However, a large proportion of phenotypes are affected by numerous variants with small individual effect size [105]. The highly polygenic nature of human phenotypes substantially reduces the power to identify adaptive variants relative to beneficial monogenic or oligogenic traits. For polygenic traits, signals of genetic association and of positive selection, even if individually weak, may jointly provide robust support for adaptation. In addition, the relevance of the signals – in terms of functional biology – to the specific selective pressure can further increase the support for adaptive evolution.

Another interesting approach is to use genetic information of ancient samples to better characterize the frequency change of adaptive variants in a population across time. Several studies already showed its feasibility and value. For example, Sverrisdóttir et al [29] showed that the calcium assimilation hypothesis cannot explain selection on LP variant T₋₁₃₉₁₀ in Europe based on its low allele frequency in Neolithic Iberian samples. Wilde et al [21] also adopted a similar approach to test for positive selection on pigmentation variants and estimate the selection coefficient. As massively parallel sequencing technology becomes more powerful and affordable, ancient DNA studies of autosomal loci will undoubtedly illuminate the evolutionary history of adaptive human phenotypes.

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Figure 1.

A schematic view of the genetic architecture of adaptive traits across its complexity spectrum.

Table 1

A summary of distinct phenotypes in indigenous high-altitude populations

Trait	Andeans	Tibetans	Ethiopian Amhara
Hemoglobin levels	Increased	No increase up to 4,000 m	No increase at 3,530 m
Arterial O ₂ saturation	Decreased	Decreased (lower than Andeans)	No decrease at 3,530 m
Pulmonary arterial pressure	Increased	No increase	Increased
Hypoxic vasoconstriction	Present	Absent	Absent
Resting ventilation	Increased	No increase	Not known
Chronic mountain sickness prevalence	5%	1%	Not reported