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Adaptations to local environments in modern human populations

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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.

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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 [7,8,9••,10]. Morphological and physiological traits showing unusually large inter-population variation, such as skin pigmentation [11–13,14•,15–19,20•,21•] and lactase persistence [22,23,24••,25–30], have been prioritized as candidates for adaptation to local environments.

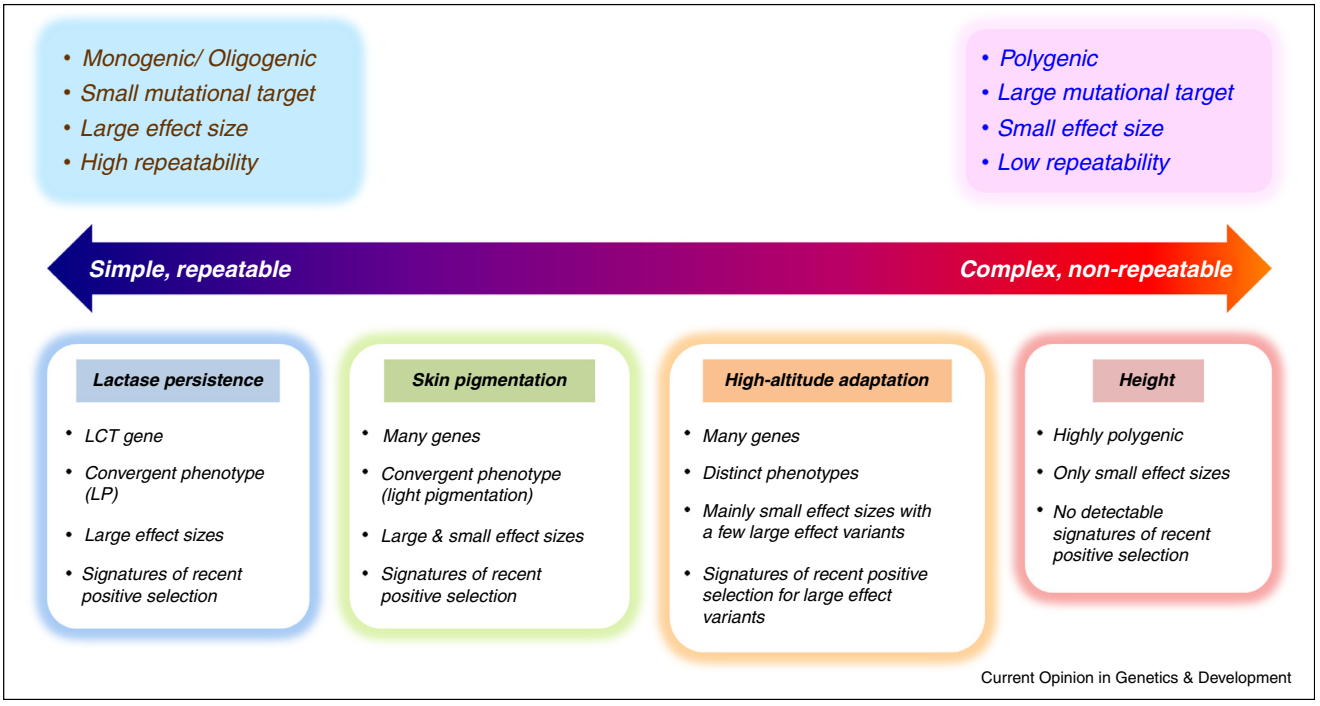
Genomic tools allow the detection of loci involved in population-specific adaptations using both phenotype-dependent and phenotype-independent approaches. Using phenotype information, genome-wide association studies (GWAS) have successfully identified over 13 000 single nucleotide polymorphisms (SNP) 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 [34,35•,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 [7,8,9••]. 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

Figure 1



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

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 [22,23,24••,25,28,30]. These variants harbor signatures of recent positive selection [24••,25–28,30,44], 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, HNF1α and HNF4α [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* [11–13,14•,15,16,51–54]. Recent genome-wide