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Human adaptation over the past 40,000 years

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Abstract

Over the past few years several methodological and data-driven advances have greatly improved our ability to robustly detect genomic signatures of selective sweeps selection in humans. New methods applied to large samples of present-day genomes provide increased power, while ancient DNA allows precise estimation of timing and tempo. However, despite these advances, we are still limited in our ability to translate these signatures into understanding about which traits were actually under selection, and why. Combining information from different populations and timescales may allow interpretation of selective sweeps. Other modes of selection have proved more difficult to detect. In particular, despite strong evidence of the polygenicity of most human traits, evidence for polygenic selection is weak, and its importance in recent human evolution remains unclear. Balancing selection and archaic introgression seem important for the maintenance of potentially adaptive immune diversity, but perhaps less so for other traits.

Keywords

Natural selection; evolution; Human Evolution

Introduction

The past few decades of human genetics research have emphasized the fundamental similarity of human populations–as demonstrated by the overwhelming support from genetic data for the recent out-of-African model of human origins, extensive gene flow between populations, and low levels of Archaic admixture. Nonetheless, the small number of differences among populations, and the even smaller number that are driven by natural selection, continue to be of great interest partly because of their potential to contribute to the explanation of how humans were able to expand occupy such a diverse range of environments. Despite this interest, and rapidly expanding datasets, there are still relatively few well-understood examples, and our overall picture of the relative importance of different modes of adaptation is limited. While recognizing that non-genetic mechanisms of adaptation such as developmental plasticity and cultural evolution are powerful forces, this review focuses on recent developments related to the detection, classification and interpretation of natural selection in the human genome.

Selective sweeps

The first generation of human genome-wide selection scans produced lists of thousands of putatively selected loci but the limited overlap, number of potential confounding factors, and lack of statistical framework to assess significance led to suspicion that these lists contained high false positive rates (1). This has led to ongoing debate about the extent of positive selection in recent human history, the contribution of “hard” and “soft” selective sweeps, of polygenic adaptation (Figure 1), and whether these features differ between populations (2–6). While these broader questions about the nature of selection remain unresolved, much recent work has focused on the identification, classification and fine-mapping of candidate loci. Many approaches (4, 7–10) combine multiple statistics and use machine learning models trained on simulated data to identify and classify sweeps. While these methods are powerful, they are still limited by our ability to simulate realistic data that incorporate effects such as background selection and heterogeneity in mutation rate.

A more direct way to study natural selection is to use ancient DNA data to directly observe changes in allele frequency over time. Ancient DNA has revolutionized the study of demographic history and is becoming increasingly useful for the study of natural selection and phenotypic evolution (11). While even a single genome can be informative about demographic history, inference of selection requires much larger sample sizes. Ancient DNA based scans can detect strong signals of selection (12) (Figure 2A), but have limited power due to small sample sizes. However, ancient DNA can provide precise estimates of the timing of selection on particular alleles such as those associated with skin pigmentation (12, 13) and lactase persistence (14–16) (Figure 2B). It can help to resolve complex evolutionary histories, for example at the *FADS* locus (17–20) (Figure 2C), and help to separate the effects of selection from those of changes in ancestry. Currently, the vast majority of ancient DNA samples are from Western Eurasia and it is on this region that most ancient DNA studies of selection have focused (with exceptions (21, 22)). Large ancient DNA studies in other parts of the world should allow similar analyses.

The UK Biobank (23) and UK10 (24) projects have enabled particularly deep investigation of recent selection in the British population (25–27). Recently, similar scans have become possible in the Japanese population thanks to BioBank Japan and other cohorts (28, 29). These scans reveal a qualitatively similar landscape of selection between Britain and Japan. Both populations show evidence of selection on dietary, immune and anthropometric phenotypes but carry relatively few strong sweeps. Curiously, in both cases, the strongest signals of selection are at loci associated with a specific agricultural product; ability to consume milk in Britain (the *LCT* locus), and inability to consume alcohol in Japan (the *ADH* locus). On the other hand, the Japanese population does not show the very strong recent signals of selection for pigmentation-associated variation that the British population does (29). More broadly, these data provide the opportunity to assess the extent of parallel adaptation at the level of individual genes, pathways, phenotypes or classes of phenotype in the two populations. It is widely believed that the development of agriculture was one of the strongest forces in recent human evolution and demography, and it represents one of the few repeated experiments in human evolution. The demographic transitions associated with the introduction of agriculture in both the UK and Japan were very similar (30, 31) and the

phenotypic associations available through UK Biobank and BioBank Japan provide an excellent opportunity to test whether the adaptive responses were also similar.

Although lacking the phenotypic information from large biobanks, genetic data from diverse cohorts from Africa (32–35), East Asia (36, 37) and other parts of the world are enabling a broader assessment of human adaptation. These studies confirm that the immune system is a frequent, perhaps the most frequent, target of positive selection and help to identify the genetic basis of putative local adaptations such as short stature in African rainforest hunter-gatherers (33, 34, 38–41).

Polygenic adaptation

Genome-wide association studies (GWAS) indicate that many human traits are highly polygenic-controlled by a large number of variants-many of which have extremely small marginal effects. This observation, coupled with the relatively limited number of selective sweeps, suggested that polygenic adaptation might be an important force in human evolution (42). In this model, complex traits evolve as the result of small shifts in frequency of large number of variants. These shifts are too small to produce classical signals of selection but can be identified in aggregate. Over the past decade, several different studies supported this expectation (12, 26, 43–47). Many of these focused on differential selection for height across Europe, although other traits were also implicated. Recently, with the release and analysis of the UK Biobank dataset, it became clear that the signals of selection of height had been overestimated (48, 49). Specifically, the GWAS on which previous analyses had relied had not fully corrected for the effect of population stratification, leading to overestimation of the effect of selection. If the results for height in Europe–apparently the clearest example of polygenic selection-cannot be trusted, how can we trust evidence for other traits, which surely suffer from similar problems? What about evidence of selection in non-European ancestry populations, which is likely further biased by non-transferability of GWAS effect size estimates (50)?

So, in 2020, the question of the contribution of polygenic adaptation to human evolution is largely back to where it was in 2010. In many cases, patterns of phenotypic variation are highly suggestive of local adaptation (51–53). Many traits are highly polygenic and it seems that we should expect polygenic adaptation to be common. On the other hand, the empirical evidence is relatively weak and polygenic selection tests are highly sensitive to artefacts. Some authors have argued that using GWAS effect sizes estimated in an outgroup population avoids bias associated with population stratification (54, 55). Others have attempted to use effect sizes re-estimated within sibling pairs (56), which should be more resistant to stratification. However, neither of these approaches is totally satisfactory. In any case, even if there is some residual signal of selection, the fact that polygenic selection tests turned out to be unexpectedly vulnerable to population stratification probably warrants additional caution before we accept such claims. Given that we expect polygenic selection to be common, why is it so hard to find?

One possibility is that polygenic adaptation is, in fact, relatively rare. Despite hundreds or thousands of loci with nonzero effects on a trait, widespread pleiotropy might mean that adaptation is driven by shifts in the frequency of a relatively small proportion of loci. That

is, adaptation on polygenic traits may be more oligogenic than polygenic (57, 58). Alternatively, polygenic adaptation could occur without leaving a clearly detectable signature of consistent frequency shifts because effects vary in time due to allelic heterogeneity or interactions (either genetic or environmental), or because selection pressures or effect sizes are fluctuating (58) (Figure 3). Finally, recent theoretical work shows that the details of the response to selection on a polygenic trait are sensitive to the details of the genetic architecture (59–61) so might leave more complex genomic signatures than commonly assumed.

Adaptive archaic introgression

A long-standing hypothesis is that Neanderthals (and Denisovans), who lived in Eurasia for hundreds of thousands of years, carried adaptations to that environment that would have been beneficial to modern humans on their arrival. While, broadly speaking, archaic ancestry was deleterious and selected against in modern humans (62–65), this idea has gained some empirical support from the observation that some specific variants were positively selected (66). Perhaps the best example is of a Denisovan haplotype at *EPAS1* that is associated with altitude adaptation in present-day Tibetans (67). However, even this case is not so simple. The functional variant tagged by the Denisovan haplotype is unclear and not necessarily of Denisovan origin. Even if the functional variant was present in Denisovans, the haplotype was carried by Denisovans living at low altitude (Denisova cave is only 700m above sea level), so did not necessarily represent an altitude adaptation. It may have just been part of Denisovan physiology that happened to later become adaptive in modern humans in the high-altitude environment.

While there is some evidence that classically adaptive traits such as skin pigmentation experienced a contribution from adaptive archaic introgression, by far the strongest evidence for an important role in recent evolution involves the immune system. Specific targets include the toll-like receptor genes *TLR1, 6* and *10* (68, 69), the oligoadenylate synthetases *OAS2* and *3* (70–72), and the interferon pathway (69, 73). However, recent analyses suggest that the effects go beyond these individual loci and apply more broadly over large classes of immune-associated genes (74, 75), largely through regulatory effects (76–78). In some cases, these archaic alleles may have provided protection against pathogens, or classes of pathogen, transmitted directly from archaic to modern humans (75, 79). However, in other cases, for example the *TLR* cluster, positive selection on the archaic allele occurred tens of thousands of years after introgression (69). Like *EPAS1*, much of the adaptive archaic admixture may have contributed to the reservoir of potentially adaptive standing variation, rather than being of immediate advantage, although this remains to be systematically tested.

Balancing selection

One reason why the immune system, in particular, might retain a large reservoir of potential archaic targets of positive selection is that a relatively large proportion of immune-associated variation is under balancing selection. Recently a number of tests specifically designed to detect balancing selection within (80, 81) and between species (82–84) have been developed. These tests broadly confirm enrichment of balancing selection at immune-associated genes, but also highlight a number of intriguing potential new signals. These include loci associated

with reproductive biology or behavior, including the *CADM2* and *ESR1* loci (81, 83, 85, 86). Signatures of balancing selection can be generated by a number of different evolutionary processes-frequency dependent selection, overdominance, and fluctuating selection, for example-and the relative contribution of these processes remains unclear. A key question for future work is to determine whether it is possible, perhaps using ancient DNA, to distinguish the effects of these processes both at specific loci, and more generally across the genome.

Can we do better than just-so stories?

New datasets and statistical approaches have made the detection of genomic signatures of selection much easier. While there is still relatively little overlap between methods, the ability to combine statistics and directly replicate signals with ancient DNA has allowed us to robustly identify parts of the genome under selection. What is less clear, in almost every case, is why those parts of the genome were selected. As has recently been observed (87), even for the clearest and best-known examples of selective sweeps, many of which involve alleles with pleiotropic effects, we almost never know which phenotype is actually under selection. Even when we can make a good guess at the phenotype, we almost never know the mechanism by which it affects fitness. How might we do better?

One approach, as already described, is to borrow information across loci and look for enrichment of selection signals in pathways, or sets of loci associated with a particular trait. But even if we can identify such a trait, it is hard to know whether we should assume that was the specific trait under selection. In parallel, we can try to borrow information across populations (88). Correlating shared environment with shared and parallel adaptation across populations can provide clues to the underlying drivers of that selection. A particularly powerful way to do this is to investigate the few repeated experiments in human evolution. The introduction of agriculture, already discussed, is the most striking example, but others include migration to extreme latitudes or altitudes, urbanization, or response to particular classes of pathogen. Key here is the incorporation of external information, for example archaeological data about subsistence, lifestyle and diet. Finally, we can use the precise temporal information provided by ancient DNA to directly test hypotheses about drivers of selection and we should be ruthless about rejecting or reformulating hypotheses that are contradicted by direct evidence.

Simulations provide an important tool for developing intuition about different demographic and selective scenarios, for evaluating the performance of different methods and for training machine learning models. This has been made much easier by recent developments in population genetic tools including 1) *msprime*, which enables fast coalescent simulations (89) 2) *stdpopsim*, a library of standard demographic models (90) and, in particular 3) *SLiM*, which allows the forward simulations needed to model complex selection (91). Development and maintenance of these tools is critical to enabling future selection studies.

Finally, while most work has focused on ancient selection, very large datasets provide the opportunity to investigate very recent selection-over the past few or even current generations (92–94). Some authors have worried that relaxation of selection due to modern medical care will lead to an overall decrease in fitness (95, 96). On the other hand, much selection

happens *in utero* and large effective population sizes might be expected to increase the efficacy of both negative and positive selection. Modern environmental conditions might promote selection for traits that were previously neutral or deleterious. Despite much speculation about these sorts of effects, there has been relatively little analysis, leaving many opportunities for studies of human adaptation over the past 40, rather than 40,000 years.

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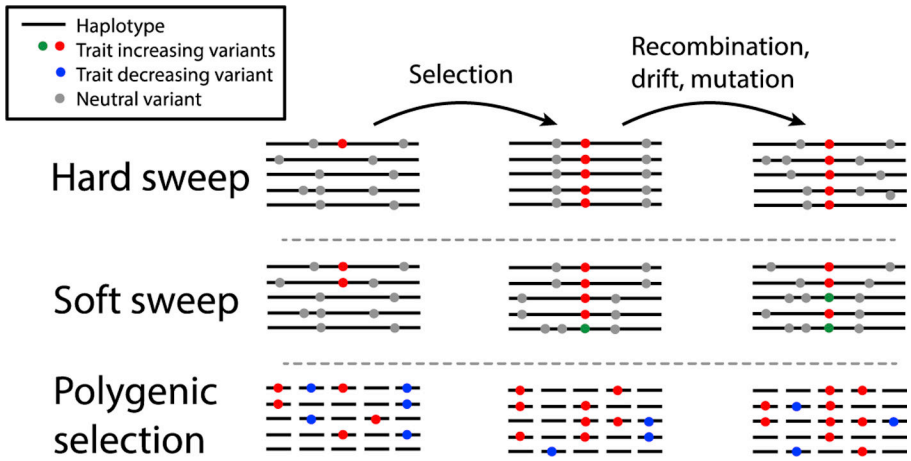

Figure 1: Genomic signatures of adaptation.

Selection on variants affecting a beneficial trait. In a hard sweep, a new (or rare) mutation (red) on a single haplotype increases rapidly in frequency. Variants on the same haplotype (grey) also increase ("hitchhike"), reducing diversity around the selected site (97). Over time, recombination, drift and mutation break down the sweep signature. In a soft sweep (98), the selected variant may already be present on multiple haplotypes (red), or there may be new selected mutations (green) as the sweep is in progress. Diversity is reduced around the sweep but not by as much as a hard sweep. In practice, this signature may be difficult to distinguish from an incomplete hard sweep. In polygenic adaptation (42), variants at many loci genome-wide change frequency; trait-increasing alleles (red) increase in frequency while trait-decreasing alleles (blue) decrease. This process is essentially a large number of weak soft sweeps, but the effects are too small to be detected at any one locus. Variants drift after selection, but mean shifts in frequency are maintained.

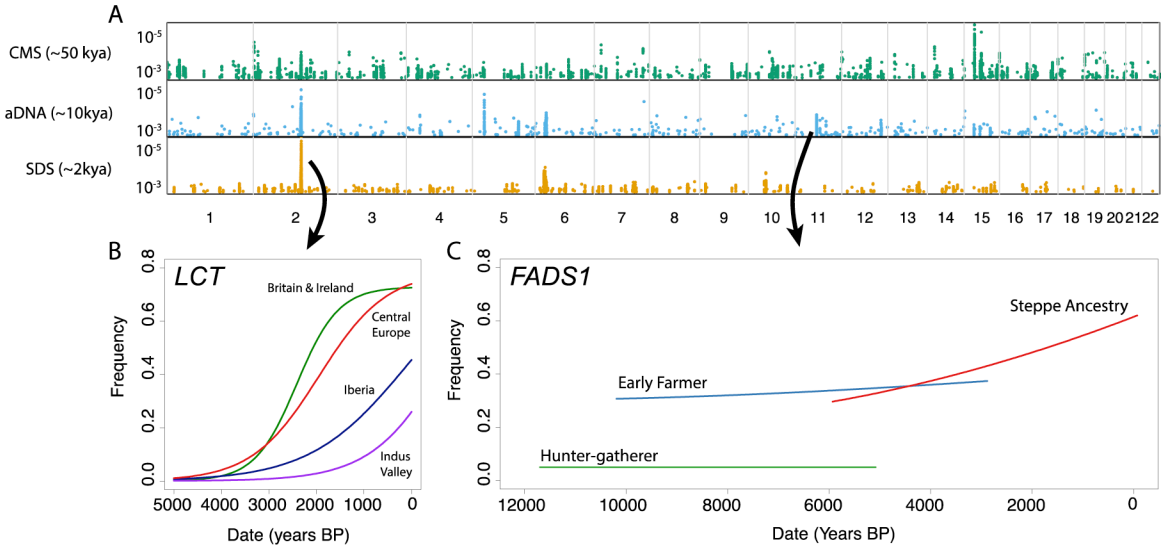

Figure 2: Ancient DNA adds another dimension to selection scans.

A: genome-wide selection scan signals from three different approaches (8, 12, 26) with power to detect selection over different timescales. Y-axis shows $\log_{10}$ quantiles for the top 0.1% of tested markers. **B**: stratified by geographic location, ancient DNA from 668 individuals reveals distinct trajectories of the lactase persistence allele in different parts of Europe. **C**: stratified by ancestry derived from the three main source populations of present-day Europe, ancient DNA reconstructs the evolution of the FADS locus (redrawn from (17)).

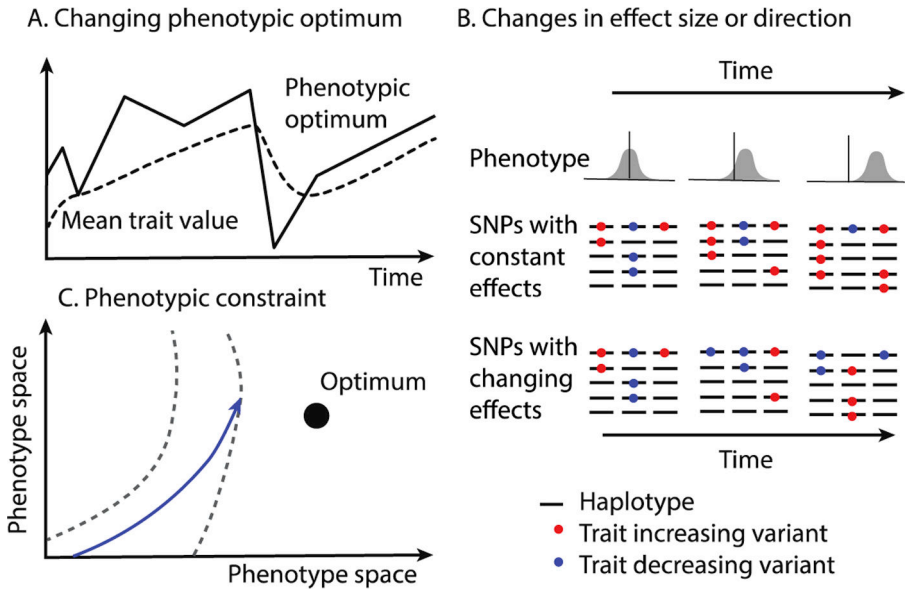

Figure 3: Limits to polygenic adaption. A:
If the phenotypic optimum changes over time, polygenic adaptation will not leave a consistent signal of frequency shift. **B**: Similarly, if effect sizes or direction changes over time due to allelic heterogeneity, or interactions, then polygenic adaption will occur, but will not leave a consistent pattern of frequency shifts. This cartoon shows a population of five haplotypes with three trait-associated SNPs over three time periods, with selection for an increased phenotype. If SNP effects are constant, then trait-increasing SNPs consistently increase in frequency and trait-decreasing SNPs decrease in frequency. On the other hand, if effects change over time, then this signal would be obscured over the long term, even though polygenic adaptation is still occurring. **C**: Finally, polygenic adaptation may be fundamentally limited by pleiotropy, which constrains the range of possible phenotypes that can be reached (between the dashed lines), or the set of variants that can respond to selection.