Modern humans inhabit a variety of environments and are exposed to a plethora of selective pressures, leading to multiple genetic adaptations to local environmental conditions. These include adaptations to climate, UV exposure, disease, diet, altitude, or cultural practice and have generated important genetic and phenotypic differences amongst populations. In recent years, new methods to identify the genomic signatures of natural selection underlying these adaptations, combined with novel types of genetic data (e.g., ancient DNA), have provided unprecedented insights into the origin of adaptive alleles and the modes of adaptation. As a result, numerous instances of local adaptation have been identified in humans. Here, we review the most exciting recent developments and discuss, in our view, the future of this field.

Local Adaptation in Human Evolution

Local adaptation occurs when, due to genetic change, individuals from a population have higher average fitness in their local environment than those from other populations of the same species [1]. It is driven by natural selection that differs among populations and, over time, leads to genetic and phenotypic population differentiation [1]. The selected alleles underlying these adaptations may be more beneficial in one environment than others, or may be beneficial in one environment while being neutral in others [2].

Local adaptation is particularly important in human evolution because modern humans have rapidly colonised a wide variety of novel environments, both within Africa and in other territories after the ‘Out of Africa’ migration (50 000–70 000 years ago) [3,4]. The settlement in each territory, and the development of local cultural practices, drove local adaptations. In fact, we know that local adaptation contributed significantly to genic population differentiation [5] and that humans have locally adapted to diverse diets [6–8], pathogens [9,10], altitudes [11,12], and ambient temperatures [13]. Many of these adaptations result in average phenotypic differences amongst people of different ancestries, leading to population differences in important phenotypes, including health-related traits (see Glossary), disease prevalence, and drug response. Thus, investigating local adaptation can reveal the origin of critical population phenotypic differences. Because the recent split among populations means that most genetic and phenotypic variation is found within (rather than between) populations, identifying the cases where population differences have an adaptive origin is particularly important; these are the cases where genetic changes affect function, phenotype, and fitness. In fact, local adaptation is responsible for some of the most striking differences among human groups (Table 1, Key Table).

More generally, a deep understanding of local adaptation (and conversely, of neutral population differentiation) is vital in our understanding of how modern patterns of genetic variation in humans arose. Finally, unravelling the evolution and function of locally adapted alleles has the potential to help us determine the functional consequences of phenotypically relevant alleles and reveal the genetic basis of the biological response to critical environmental pressures (e.g., how changes in certain genes mediate tolerance to low temperature or hypoxia), contributing directly to our understanding of the biological basis of important phenotypes, including disease (Box 1).

Highlights

Local adaptation has critically contributed to the (modest) genetic and phenotypic differentiation that exists among human groups, including in health-related traits that contribute to population health disparities.

Local adaptation has happened on alleles of diverse origin (on new, pre-existing, and introgressed alleles) and through diverse mechanisms (monogenic and polygenic adaptation).

Ancient DNA will play a key role in our understanding of local adaptation by improving inferences of past events. Further, it has revealed the importance of adaptive introgression, by which modern humans acquired adaptative alleles from archaic humans.

Novel analysis methods will improve our power to identify targets of local adaptation, especially those with weak signatures. Combining genetic and environmental information promises to improve the identification of genomic targets and the corresponding selective force.
Here, we provide a global perspective of, in our view, the main developments in human local adaptation over the last few years. Several aspects of this field have been recently covered in excellent reviews (e.g., phenotypes under selection [14], adaptive archaic introgression [15], and extreme environmental adaptation [16]) and local adaptation is a large research field. We have thus focused on the most recent advancements in our understanding of the origin of adaptive alleles and modes of local adaptation, as well as new types of data and strategies to identify the targets of adaptation that can help circumvent the main challenges in the field. Some of the most striking known adaptations are presented in Table 1 and discussed in Boxes 1–3.

**Origin of Selected Alleles**

A beneficial allele can arise from a de novo mutation, be previously polymorphic (standing variation) or be introduced by admixture with other populations [17,18] (Figure 1A). Understanding the origin of alleles is important, not only because it informs on how adaptations originate, but also because each mode generates different signatures and requires different identification methods.

Selection on de novo mutation (SDN) acts on a new allele that is advantageous upon emergence because the selective pressure predates the mutation. The new, advantageous mutation tends to rapidly increase in frequency in the population under selection. However, an adaptive mutation must appear at the right time and in the right population and even then, most new advantageous mutations are lost due to random genetic drift. The likelihood of loss is reduced if selection is strong or the new allele is over-dominant and most beneficial in heterozygosity (since alleles are mostly in heterozygotes while their frequency is very low) [19].

Selection on standing variation (SSV) is when previous polymorphisms (segregating alleles) become advantageous following changes in selective pressure, usually resulting from environmental change [17,18,20,21]. The selected allele is thus older than the selective pressure. SSV was likely important in human local adaptation: the recent and rapid nature of local selection in non-Africans means that there was little time for the emergence of de novo mutations, the small effective population size translates in low effective mutation rate, and population growth allows the maintenance of low-frequency polymorphisms that would otherwise be lost (but that can mediate SSV) [18,20]. Here, selection may favour alleles that were previously slightly advantageous or deleterious (due to a shift in selective pressure), or maintained by balancing selection [20]. Alleles under balancing selection have great potential to mediate quick genetic adaptations when the population encounters new environments, since they necessarily affect phenotype and fitness, and are already at intermediate frequencies at the onset of selection [19,20].

Admixture between genetically distinct populations may also introduce beneficial variants in a population, a process of gene flow that has been pervasive in humans [22–26]. For example, alleles conferring lactase persistence spread from eastern African pastoralists to southern African Khoisan populations [23] and from early European pastoralists into modern European populations [27,28]. Also, a Duffy blood group allele of African origin under strong positive selection has provided widespread malaria resistance in modern Malagasy populations [29].

The extensive admixture between modern and archaic humans such as Neanderthals and Denisovans (called introgression) has been a major recent surprise [30–32]. It is now clear that whilst most non-neutral introgressed alleles were deleterious and removed by purifying selection [33,34], some were then advantageous in modern humans (adaptive introgression). Because only some human populations experienced introgression (from Neanderthals only into non-Africans, from Denisovans only into Melanesians and some other Asians [30–32,35–37]), all adaptive introgression generated population differences. It is perhaps unsurprising that archaic
### Table 1. Overview of Key Known Genes under Local Adaptation in Human Populations

| Category         | Adaptation                      | Gene target(s)       | Population with adaptations | Refs* |
|------------------|---------------------------------|----------------------|-----------------------------|-------|
| Diet             | Lactase persistence             | LCT                  | Eurasians and Africans      | [S1–S4] |
|                  | Fatty diets                     | FADS                 | Greenland Inuit             | [S5]  |
|                  | High arsenic levels             | AS3MT                | Argentinians                | [S6]  |
|                  | Low selenium levels             | D2, S2S, GXP1, GXP3, CELF1, SPS2, SEPSECS | Chinese | [S7–S9] |
|                  | Low iron levels                 | HFE                  | Europeans                   | [S10,S11] |
|                  | Low iodine levels               | TRPV4                | Central African Pygmies     | [S12] |
|                  | Low calcium levels              | TRPV6                | Non-Africans                | [S13,S14] |
|                  | Zinc levels                     | SLC30A9, SLC39A8     | East Asians and Africans    | [S9,S15] |
|                  | Ergothioneine deficiency        | IBD5 (SLC22A4, SLC22A5) | Europeans                  | [S16,S17] |
|                  | Frequent starvation             | CREBRF               | Samoans                     | [S18] |
|                  | Alcohol consumption             | ADH1B                | Asians                      | [S19–S21] |
| Pathogens        | Malaria resistance              | HBB, HBA, HPA, GYPA, GYPB, GYPD, FY | Sub-Saharan Africans | [S22–S24] |
|                  | ‘African sleeping sickness’     | APOL1                | Western Africans            | [S25] |
|                  | Hepatitis C                     | IFNL4, IL28B         | Eurasians                   | [S26–S28] |
|                  | HIV                             | CUL5, TRIM5, APOBEC3G | Beika                      | [S28–S29] |
|                  | General immune function         | ADAM17, ITGA1, LAG3, IL6, LRLC19, PON2, OAS1, OAS group, HLA group, STAT2, STAT2, TLR1-TLR6-TLR10 | Across populations | [S16,S30–S35] |
| Oxidative stress | High altitude                   | EGLN1, EPAS1, PPARA  | Tibetans (EPAS1 in Han Chinese) | [S36–S38] |
|                  |                                 | EGLN1, EDNRA, PRKAA1, NOS2A, BRINP3 | Andeans | [S39–S41] |
|                  |                                 | VAV3, CABARA1, ARNT2, THR5, BHILHE41 | Ethiopians | [S42,S43] |
|                  | Breath-hold diving              | PDE10A, BOKR2        | Bajau (Indonesia)           | [S44] |
| Cold resistance  | Cold perception                 | TRPM8                | Eurasians                   | [S45] |
|                  | Energy regulation and metabolism| OPT1A, LRP5, THADA   | Siberians                   | [S46] |
|                  | Cardiovascular function         | PRKG1                | Siberians                   | [S46] |
|                  | Differentiation of brown and brite adipocytes | TBX15 | Greenlandic Inuit | [S5] |
| UV exposure      | Pigmentation changes            | SLC24A5, SLC45A2, OCA1-4, TYRP1, DCT, TYR, MC1R, HYAL2 | Across populations | [S47–S53] |
|                  | Low vitamin D levels            | DHR7, NADSYN1       | Northern European populations | [S16] |
| Height           | Undetermined function           | DOCK3, CISH, HESX1, POU1F1 | Central African rainforest hunter-gatherers | [S54–S56] |
|                  | Undetermined function           | Highly polygenic     | Europeans                   | [S16,S67–S62] |
| Hair thickness   | Undetermined function           | EDAR                 | East Asians                 | [S1,S63] |
| Diet             | Starchy foods                   | AMY1                | Across populations          | [S64] |
| Unknown          | Undetermined function           | 17q21.31 gene region | Icelandic | [S65] |
alleles were beneficial in Eurasia because Neanderthals and Denisovans inhabited these territories since shortly after their divergence from modern humans (estimated over 800,000 years ago) and in theory had time to locally adapt; humans could rapidly acquire these adaptations through introgression, easing their transition into these novel environments [30,36,38].

In other cases, advantageous alleles may have deleterious pleiotropic effects. Adaptations to low amino acid levels, likely due to agricultural diets, may lead to higher risk of celiac disease and inflammatory bowel disease today [27,110]. Alleles mediating adaptations to malaria, African sleeping sickness, and cold ambient temperature are also associated with increased prevalence of sickle cell anaemia, chronic kidney disease, and migraine in various populations [13,111,112].

Modern populations may also be exposed to novel conditions due to recent migration or ecological change. Micronutrient levels in soils are highly variable and have resulted in genetic adaptations to at least toxic arsenic levels and low selenium levels [7,70]. Individuals from other populations that migrate to these environments (and that lack such local adaptations) face numerous complications if micronutrient levels are not managed or supplemented via other means.

Population-specific adaptation can result in differences in the outcome of treatment. The pseudogenising allele of IFNL4, adaptive in Eurasian populations, results in more rapid clearing of hepatitis C virus infection in these populations and a better health outcome following treatment [54]. There are also multiple alleles associated with protection against HIV that are fixed (CUL5) or at high frequency (TRIM5, APOBEC3G) in the Biaka, suggesting population differences in resistance to HIV [113].

These local differences ultimately contribute to population differences in the genetic basis of common disease and the response to treatment, reducing the transferability of GWAS and contributing to an ongoing bias where highly studied populations benefit most from genomic and personalised medicine. An improved understanding of the adaptations that populations have historically undergone will thus help develop targeted healthcare strategies and identify the populations most at risk.

The importance of adaptive introgression has been one of the main recent realisations in the field and it has already been shown to contribute to immune function, oxidative stress, and pigmentation (Figure 2) [39–43]. Introgressed alleles have been suggested to be particularly important in resistance against viruses, especially against RNA viruses in Europeans [44]. In rare instances, multiple archaic alleles are maintained, perhaps because genetic diversity itself was advantageous [43,45].

### Signatures of Local Adaptation

Positive selection leaves characteristic signatures in genomes, which differ depending on the genetic basis of the selected phenotype(s), the origin of the allele, and the tempo and strength of selection.

Monogenic adaptation shows strong selection signatures in a single adaptive allele. These signatures have been studied for decades, so most known adaptations are monogenic (Table 1 and

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**Notes to Table 1:**

*Selection noted as across populations indicates that selection is seen differentially across multiple populations according to the strength of the selective pressure. Table references are listed in the supplemental information online.

Indicates gene variants that are a result of adaptive introgression with Denisovan populations (in OAS1 it may be the result of an introgression event with an older archaic human or be the result of a double introgression event [S31,S66]).

Indicates gene variants that are a result of adaptive introgression with Neanderthal populations.

For a more comprehensive list of the genes identified as targets of selection under high altitude, see [S67].

Selection acting on structural variations (deletions, insertions, inversions, duplicates, and copy number variations [S68]).
Selection signatures were historically categorised into those from ‘hard’ or ‘soft’ sweeps [18,21,46,47], where hard sweeps are a result of strong SDN [18,21,46,47] and soft sweeps result from weak selection, SSV, or recurrent mutations [18,21,46,47] (although recurrent mutations are not particularly likely in humans, owing to our low effective mutation rate [18]).

The frequency of the selected allele, and hence the differentiation between populations, depends on the strength of selection and is largely independent of the allele origin. Thus, unusually large allele frequency differentiation in a SNP can be considered a nearly universal signature of strong local adaptation. The mode of adaptation impacts mostly the signatures of linked variation (Figure 1B), with alleles that rapidly increase in frequency having linked haplotypes of low diversity and many low-frequency variants, and their genealogies having a star-like shape (a long internal branch, short terminal tips) [48]. With SDN, classical signatures in the genomic region neighbouring the selected site include extended high population differentiation, skews in the site frequency spectrum, and extended haplotype homozygosity in long genomic regions (a selective sweep), with the strength of signatures largely dependent on the timing and strength of the selective sweep [12,48–51]. Under SSV the signatures of linked variation are usually highly reduced, largely due to the presence of the selected allele on multiple haplotype backgrounds and populations. Thus, linked signatures of SSV can be highly variable depending on the age and frequency of the segregating allele [17]. Nevertheless, signatures of SSV may resemble those of SDN if the beneficial allele only slightly precedes the onset of selection [18].

Determining the relative importance of SSV versus SDN in human evolution has been a recent focus of investigation and debate [52,53]. Whilst distinguishing between the two modes of

**Box 2. Locally Adapted Genes and Traits in Humans**

A selection of genes identified as playing a role in human local adaptation are presented in Table 1. Key observations are:

- Genetic changes mediate adaptations to local cultural pressures. These can allow unique cultural practices, such as breath-hold diving in the Bajau [114].

- Adaptive responses to agricultural practices are widespread. Lactase persistence is easily the best-known example of local adaptation (reviewed by [115]) and emerged with agriculture [22,23,115]. Additional agricultural adaptations to diet (micronutrient or amino acid levels) and to pathogens (facilitated by densely packed living conditions and exposure to zoonotic diseases [22,23,116]) accompanied the switch to an agricultural lifestyle.

- Micronutrients are typical targets of dietary local adaptation. Micronutrients are necessary and irreplaceable in the diet, but toxic in excessive amounts. Local adaptation has been identified in multiple micronutrients [7,70], particularly in the regulatory variants maintaining micronutrient homeostasis [117].

- There is strong and diverse evidence for selection in response to pathogen pressure. This highlights disease as a major driver of adaptation [10,27,44]. There is also evidence for the role of adaptive introgression in pathogen resistance [30,41,44].

- The same adaptive phenotype may be achieved by different genes in different populations. This is particularly clear for altitude adaptation in Ethiopian, Andean, and Tibetan populations (the latter population acquiring an adaptive gene variant from archaic humans) [12,82,100]. Further, multiple different variants upstream of the LCT gene region evolved independently in African and European populations to allow people to consume milk past weaning [22].

- Adaptive introgression from archaic humans has played a fundamental role in adaptation to multiple environmental factors. This includes resistance to pathogens, UV exposure, and high altitude [29,39,41–43,82].

- The adaptive function of some population-specific phenotypes remains unclear. For example, the short stature of multiple rainforest hunter-gatherers (found in Central Africa, South America, and Southeast Asia) appears to be selected by a shared environmental pressure that is currently unknown [118]. A selective origin of the cline in height in Europeans has also been suggested, although the statistical validity of this result is currently under debate [46,96,97].
Figure 1. Characterisation of Selection on Standing Variation, Selection on de Novo Mutation and Adaptive Introgression. (A) Cartoon showing the rise in frequency of an allele through a population according to its origin. The stars represent mutations (blue: mutation present in the population prior to selection; yellow: mutation occurring after the onset of selection; and red: mutation present in an archaic population which spreads through a receiving population following an admixture event). The frequency of each mutation in a population following a selection event is represented by the number of people icons of their respective colours under each panel. The red walking person icon in the top right represents an archaic human. (B) Cartoon depicting the haplotypes arising from selection on standing variation (SSV), selection on de novo mutation (SDN), and adaptive introgression. Stars represent the beneficial allele and grey circles represent neutral linked polymorphic alleles. (C) Some of the most common statistics used to identify local adaptation (not a comprehensive list) [12,48,49,51,121–124]. Figure created using Biorender.com. Abbreviations: iHS, integrated haplotype score; LRH, long range haplotype; PBS, population branch statistic; SDS, Singleton density score; XP-EHH, cross-population extended haplotype homozygosity.
adaptation is challenging, approaches that integrate multiple aspects of the signature, for example, Approximate Bayesian Computation (ABC) or Supervised Machine Learning (SML) [17,47], allow us to start addressing this question. ABC has been used to determine the mode of selection in multiple studies [13,54–57], but only very recently has it been applied genome-wide, due to computational requirements [58]. Applications of SML have suggested that these methods perform relatively well when demographic history is unknown and that SSV and polygenic selection are dominant in human adaptation [46,47,59], although this has been contested [60]. Because selection signatures depend on the age, strength, and frequency of the selected allele, none of which follow discrete distributions, a binary categorisation (hard versus soft) does not necessarily represent selection signatures [59] and more work is needed to integrate all different models of selection.

Figure 2. Visualisation of the Events of Adaptive Introgression from Archaic Human Populations into Modern Humans. The red and purple persons indicate human populations having undergone adaptive introgression with Neanderthals and Denisovans, respectively [9,31,38,39,41–43,63,125–131]. Strongly or moderately supported examples of adaptive introgression from archaic populations are shown across a simplified modern human lineage (phylogeny edited from [132]). Adaptive introgression events are shown on the lineages on which they happened. The gene(s) believed to be under selection in each case is noted in the linked boxes. STAT2 shows two haplotypes arising from introgression, haplotype N from Neanderthals in non-Africans and haplotype D from Denisovans in Melanesians [38,130]. OAS1 is highlighted as, whilst it shares much variance with the Denisovan gene region, the direct source is suggested as an unknown archaic population [40]; its presence in Melanesians could possibly be the result of a double introgression event [133]. Figure created using Biorender.com.
Adaptive admixture and introgression pose a double challenge: distinguishing genome segments shared among populations due to admixture/introgression from those shared due to shared ancestry or incomplete lineage sorting [39] and distinguishing admixed/introgressed segments that are adaptive from those that are neutral. Introgressed segments are long, accompanied by a high level of observed linkage disequilibrium (LD), young, present only in some human populations, and unusually similar to the archaic genomes [61,62]. These characteristics allow us to identify introgressed segments [38,39,43,63] but they mean that classical selection signatures cannot be used to identify adaptive introgression as we expect, for example, long-range LD under neutral introgression. Given the challenges associated with using signatures of linked variation, unusually high frequency of an introgressed segment, when compared with the empirical distribution of other introgressed segments, is probably the strongest evidence for adaptive introgression [41–43].

Polygenic adaptation refers to cases when multiple adaptive alleles are under selection in a population, resulting in concerted shifts in allele frequencies that shift the phenotype (even when no single allele experiences strong allele frequency change). Polygenic adaptation is probably common, since most traits are likely polygenic, and it has been proposed to explain adaptations related to diet, metabolism, pathogen resistance, or altitude [64–71]. However, the signatures of polygenic selection are often weak: the multiple small frequency shifts, which may also occur at different time-points, mean that polygenic adaptation is often hard to distinguish from neutral drift [48,72]. Further, the signatures are also highly variable, dependent on the number of loci under polygenic adaptation, their effect sizes, and the origin of these alleles [64,65,67–69,71]. Importantly, polygenic adaptation does not necessarily preclude the presence of strong signatures of selection and, conversely, strong signatures of selection do not negate polygenic adaptation. If many variants controlling a trait have negative pleiotropic effects, a single allele may be selected [73]. Further, the alleles with the largest effect sizes may sweep to fixation, accompanied by additional small increases in frequency of other alleles [73].

**Identifying Local Adaptation**

Identifying instances of local adaptation remains difficult due to the complexity of signatures and the potential misidentification of other processes as positive selection. Alleles can increase in frequency neutrally (due to random genetic drift, often aided by demographic events), sometimes quickly enough that their patterns mimic those of positive selection. Therefore, when there is uncertainty surrounding the demographic model, an unfortunate commonality, it can be difficult to tease apart demographic processes from selection [13,17,46]. Further, purifying selection must be accounted for alongside demography. For example, background selection can increase the effect of random genetic drift and cause strong differentiation between populations, as does local adaptation [74]. Recessive deleterious introgressed alleles can generate heterosis and signatures that can potentially mimic, in some instances, those of adaptive introgression [75,76].

Therefore, any methods to identify positive selection must account for neutral genetic change, demographic factors, and purifying selection. Distinguishing between these processes remains among the greatest challenges in population genetics, but is also one of the topics where recent advances are most exciting. Besides identifying the genetic signatures described earlier, correlations between genetics and the environment represent a promising avenue to identify targets of local adaptation. Naturally, both are limited in the identification of weak signals of selection [64,77].
Identifying Genetic Signatures

A common method to identify signatures of local adaptation is sampling many loci throughout the genome (e.g., all SNPs or genomic windows of a certain length), calculating summary statistics that capture selection signatures at each locus, and comparing these statistics with expectations under neutrality to identify loci with signatures that are unexpected under neutrality. While arguably the best approach, this relies on an accurate neutral expectation based on neutral simulations (which in turn depends on the accuracy of demographic inferences) [78]. The most common approach, thus, is to compare each locus with the empirical genomic distribution to identify outliers, which we cannot categorically state harbour signatures unexpected under neutrality, but that are strong candidate targets of selection [27]. A limitation is that most classic summary statistics were designed to identify strong SDN and are often poorly equipped at detecting weaker signatures of selection (Figure 1C) [12,49,51], with a few notable exceptions [79,80]. For this reason, many new methods focus on the allele frequency change on putatively selected alleles themselves. Including or conceptually rooted in $F_{ST}$, such methods include levels of exclusively shared differences (LSD) [81], population branch statistic (PBS; comparing three pairwise $F_{ST}$ values between three populations [12]), and several derivatives: $PBS_{n1}$ [82], $PBS_{n2}$ [83], and population branch excess (PBE) [84]. To better account for complex population structure (when multiple populations are analysed), methods such as BayEnv can correct for the covariance among populations due to shared ancestry [77,85].

Ancient DNA (aDNA) provides snap-shots of allele frequencies in the past and as such it is an invaluable resource to identify past rapid allele frequency changes [5], to quantify the genome-wide influence of local adaptation in population differentiation [5], to confirm previous evidence of selection in individual sites [27,56,86], and to identify targets of local adaptation [5,27,56]. Due to the growing availability of historical and prehistorical samples, most studies have been conducted in Europe, showing, for example, low frequency of alleles conferring lactase persistence in Neolithic populations (as well as inferring the age and geographical origin of the selected European allele) [27,86] and questioning the link between selection on $FADS$ and $AMY1$ and the development of agriculture [56]. In cases of admixture, where identification of genetic adaptation is particularly challenging, ancient genomes can help identify the population of origin of alleles, and detect selected sites as those with unusually high contribution of one particular ancestral population (the one carrying the beneficial allele) at a particular locus [27,87]. This has helped identify loci mediating adaptation postadmixture in Europeans [27] and Americans [87] and will definitively improve our understanding in other populations as aDNA becomes available.

aDNA is also integral to identifying the alleles that arise from introgression [39]. As mentioned earlier, identifying adaptive admixture and introgression involves identifying admixture events (often using aDNA) [30,35–37] and then distinguishing neutral from adaptive admixed/introgressed alleles, usually via the higher frequency of the latter. This is typically done still in a series of steps [41–43], rather than using one unified method, with few exceptions [63,88].

Promising new approaches to identify selection are based in SML [46,47,59,89,90] or purely genealogical methods: if gene genealogies can be fully reconstructed, then selection can be more directly inferred from the genealogical tree (reviewed in [91]). This powerful technique to infer selection has been implemented in programmes such as ARGweaver, which is able to detect selection using Ancestral Recombination Graphs [32,93]. While inferring genealogies for large samples is computationally intensive, two recent methods (Relate, tsinfer) are able to efficiently do so. Tsinfer especially boasts computational efficiency (being able to reconstruct relatedness for up to millions of samples) whilst Relate is able to estimate branch lengths and allele ages, allowing its application to identify both monogenic and polygenic adaptation [94,95]. These methods, perhaps as a hybrid
model or in new flavours, promise to have higher power than existing methods to identify genetic adaptation, as well as potentially rewriting how we represent and store genetic data.

Still, identifying polygenic adaptation remains challenging as it involves moderate, concerted allele frequency change of multiple small-effect loci. Approaches to identify such changes include combining genome-wide association studies (GWAS) with population genetic modelling (searching for positive covariance between alleles of similar effects [64,65]). Recent studies suggest that GWAS-based methods can overestimate polygenic adaptation if the trait differs amongst populations and there is hidden population stratification in the GWAS sample [96,97]. Nevertheless, methods to identify polygenic adaptation are not necessarily limited to allele frequency change. Additional statistics include 2DNS, a McDonald-Kreitman-based test designed to consider multiple gene variants [66], and the Singleton Density Score (SDS), a summary statistic that considers the distance between the nearest singletons to a focal SNP [48]. The latter can identify extremely recent selection [48] but may still be influenced by population stratification if GWAS SNPs are used [96]. Nevertheless, methods to identify polygenic adaptation are not limited to GWAS hits: some focus on gene sets [67,98], gene networks [68,69], and admixture graphs [99], which are potentially more robust to these issues.

Environmental Correlations
Correlations between environmental factors and allele frequency, when they are more substantial than expected under population history and gene flow, provide among the strongest evidences of local adaptation [77]. For example, unexpected correlations of allele frequency with latitude and temperature, coupled with independent signatures of positive selection, provide evidence of local adaptation of the cold receptor TRPM8 to cool ambient temperature [13]. BayEnv is probably the most widely used method to investigate such correlations at the genome scale [77]. Further, populations living in extreme environments can help reveal adaptations to harsh selective pressures, such as the arsenic-rich soil in regions of Argentina [7]. When several populations live under similar environmental pressures, comparing them can reveal the same gene(s) conferring shared adaptations across populations or different genes/gene variants mediating independent adaptations (as in the case of high altitude [82,100,101] or lactose in the diet [22]).

The Causes and Consequences of Local Adaptation
Ultimately, we aim to identify both the selective force responsible for local adaptation and the consequences that these events have in current population differences. Both are challenging but possible. To identify the selective force, two main avenues are promising. First, determining the timing of the adaptations. Here aDNA is highly valuable, as it can show the frequency of the selected allele through time and estimate when the selective pressure was first exerted [27,56,86]. Second, establishing the function of the genes or genomic elements under selection may help identify the selective force. As usual in genetics, model organisms can be useful [102,103]. For example, the signature of positive selection on SLC24A5 in European populations could be ascribed to pigmentation because the gene affects pigmentation in zebrafish [102]. Also, the insertion of the human form of the EDAR gene (under strong selection in Asian populations and associated with hair thickness and dental morphology) in mice revealed a role of the gene in the mammary and eccrine glands [103], suggesting a plausible selective force.

Still, experiments in model organisms can hardly inform on the consequences of human-specific genetic variants. Doing so is challenging because determining the consequences of human variants on the phenotype often relies on large association studies, while determining their consequences at the molecular level often relies on analyses of transcriptomics, metabolomics, and epigenomics datasets, at least outside of protein-coding regions (Box 3). High-throughput assays can categorise SNP function, including, but not limited to, exploring the effect of individual
Box 3. Epigenetics and Local Adaptation

Due to the links between epigenetic response and environmental change, recent studies have begun to question the importance of epigenetics in local adaptation. Epigenetic response, the somatically heritable change of chemical modification without changes in the DNA sequence, can occur under local changes in environment, especially during development [119]. Such chemical modifications, the most well-studied being DNA methylation, can take place over a much smaller time scale than genetic adaptation and may allow populations to adapt over a few generations, or even within a lifetime [119].

However, it is difficult to show that epigenetic changes are adaptive, rather than a response to change/stress. Unless there are convergent epigenetic changes over populations experiencing the same selective pressures (where an adaptive value may be easier to infer), it is difficult to determine the nature of epigenetic change. Nonetheless, a recent study has suggested a link between positive selection and epigenetic change [120]. The genetic variants associated with the methylation variation between populations of Central Africa, particularly between those with historically different lifestyles, show signatures of positive selection [118,120]. Variants highlighted as under selection for pygmy height (DOCK3, MAPKAPK3, and CSHL) are also differentially methylated across populations according to their lifestyle [118,120]. Even if today the role of epigenetic change in local adaptation remains unclear, epigenetic change has great potential to mediate quick, plastic adaptations to the environment and will undoubtedly become a focus in studies of local adaptation.

Concluding Remarks

Investigations into human local adaptation have benefited enormously from recent developments both in datasets and methods, integrating exciting developments in aDNA, bioinformatics, and our conceptual understanding of how selection may be etched in the genome.

Still, important challenges remain in identifying weaker signatures of selection. This is especially relevant when considering polygenic adaptation and its likely prevalence throughout human adaptation. There has been much progress in identifying these selection signatures in recent years and we predict that continued fervour in tackling this topic will result in many more refined and even novel techniques that will be able to identify previously elusive signatures.

It is also clear that some populations are relatively understudied, limiting our understanding of the effects of local adaptation and biasing our evolutionary knowledge (e.g., in terms of the origin of population differences for health-relevant traits) to well-studied populations. In addition, data limitations can bias our understanding of local adaptation towards previously identified loci and well-known selective pressures. Future studies should be prioritised to populations that have been previously neglected, especially if these populations have complex demographic histories that are at present unresolved. The increasing availability of aDNA will undoubtedly continue to improve our inferences on demographic histories, including classifying complex admixture events, and selective histories of populations.

Advances in studying the genomics of human local adaptation will ultimately improve our insight into how multiple factors have influenced the evolutionary dynamics of different populations, as well as highlighting the complexity of adaptation in human history (including the influence of archaic populations into modern human genetic variance). Further, studies in this field inform on the phenotypically relevant genetic differences among populations, the origin of these differences, and how they can help address health inequalities among human groups (see Outstanding Questions).
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Supplemental Information

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