Evolutionary Adaptations to Dietary Changes

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Abstract

Through cultural innovation and changes in habitat and ecology, there have been a number of major dietary shifts in human evolution, including meat eating, cooking, and those associated with plant and animal domestication. The identification of signatures of adaptations to such dietary changes in the genome of extant primates (including humans) may shed light not only on the evolutionary history of our species, but also on the mechanisms that underlie common metabolic diseases in modern human populations. In this review, we provide a brief overview of the major dietary shifts that occurred during hominin evolution, and we discuss the methods and approaches used to identify signals of natural selection in patterns of sequence variation. We then review the results of studies aimed at detecting the genetic loci that played a major role in dietary adaptations and conclude by outlining the potential of future studies in this area.

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INTRODUCTION

The evolutionary history of hominins has been characterized by significant dietary changes, which include the introduction of meat eating, cooking, and the changes associated with plant and animal domestication. Decades of anthropological research have been devoted to elucidating this dietary history, in part because these shifts were likely associated with major anatomical and cultural changes (e.g., the increase in relative brain size and the advent of modern civilization via agriculture). However, this reconstruction is also crucial for understanding the evolutionary context of our modern diets and the diseases often associated with them.

In parallel with the historical reconstruction of hominin diets, molecular evolutionary analyses have been used to interrogate the genome for signals of genetic adaptations to different dietary regimes. A major advantage of many evolutionary genetic approaches is that they do not necessarily require strong assumptions about the specific genes and alleles that were targets of diet-related selective pressures. For this reason, evolutionary genetic analyses have the potential not only to inform existing adaptive hypotheses of hominin dietary history, but also to help generate new ones.

Here, we bring together these two areas of inquiry, namely anthropology and evolutionary genetics, to highlight their recent findings related to human dietary history and to discuss the limitations of different approaches. We start by providing a brief overview of the major dietary shifts in hominin evolution and discussing the evolutionary genetics methods and approaches used to identify signals of natural selection. We then review the results of genetic studies aimed at detecting the loci that played a major role in dietary adaptations and conclude by outlining the potential of future studies in this area.

Hominins: the lineage up to and including extant humans following divergence from the human-chimpanzee common ancestor ~6 Mya

Natural selection: the process by which beneficial traits that are heritable increase in frequency over time whereas unfavorable heritable traits become less common

DIETARY SHIFTS IN HOMININ EVOLUTION

To make inferences about ancient diets, anthropologists have applied a number of different methodologies and approaches to the fossil and archaeological records (for review, see 158). For example, the specific shapes of molar cusps may suggest adaptations to a leaf- or fruit-based diet, or to a more general one. Microscopic wear patterns on tooth surfaces reflect the fracture-resistance properties of the foods eaten in the weeks before death. Stable isotope ratios (e.g., $^{18}O/^{16}O$) from fossil teeth and bone represent a broad signature of foods consumed at the time when those tissues were formed. The community composition of nonhominin fossil remains at a site may help researchers reconstruct the paleoenvironments in which our ancestors foraged. Here, we provide a summary and a critical appraisal of the available evidence for the most important dietary transitions during hominin

evolution, following an approximately historical order (**Figure 1**).

Early Hominins

Due to the limited number of early hominin fossils (19, 61, 134) and the nearly complete absence of chimpanzee-lineage fossils (102), it is difficult to reconstruct the diet of the earliest hominins. The closest extant evolutionary relatives to humans, i.e., chimpanzees and bonobos, have predominantly frugivorous diets (75), but it is probably an oversimplification to use them as strict models for our common ancestor (130). However, recent descriptions of the fossil remains of the oldest (~4.4 million years old) relatively complete hominin fossil discovered to date, *Ardipithecus ramidus* (168), shed some more light on ancestral diets.

Classically, it had been thought that the earliest hominins moved from a forested habitat to a savanna one (perhaps the openness and tall grasses of which explain the selective advantages of bipedality), accompanied by a shift to the harder and tougher food items more common in the new environment (25, 145). However, a careful reconstruction of the environment of fully bipedal *Ardipithecus ramidus* suggests that this hominin lived in a woodland to patchy forest, not savanna (96, 167, 170). The ~6-million-years-old environment of the hominin *Orrorin tugenensis* was reportedly similar (119). Therefore, alternate scenarios for hominin origins and bipedality should be considered and tested (e.g., see 174). The stable isotope ratios and dental morphology and wear of the *Ar. ramidus* remains were intermediate between chimpanzees and later hominins including *Homo*, suggesting a diet that was fairly general and mixed (150, 167) rather than specialized on one food component such as fruit or tough vegetation.

Subsequent hominins did transition to more open environments (72, 122) and encountered more mechanically challenging foods. The large and thick-enameled teeth of australopithecines [~4.1–1.4 million years ago (Mya)] suggest diets that included hard foods (e.g., 154). However, there is some disagreement over the specific food items for which such dental morphology might have been used. Recent biomechanical modeling studies of craniofacial strain suggested that australopithecines may have used their premolars to open the strong shells (endocarps) of relatively large seeds (149). However, other researchers focus on starch-rich underground storage organs (USOs), such as bulbs and corms, as a major component of australopithecine diets. The hardnesses of some raw USOs are sufficient to explain, potentially, the australopithecine craniodental morphology (37). Consistent with the idea that USOs were an important food source, fossils of mole rats—USO specialists—are found at the same fossil sites with hominins significantly more often than expected by chance (90). Moreover, the stable isotope ratio signatures suggest that the co-occurring mole rat and hominin fossils may have been consuming similar foods (177).

These two hypotheses (large seeds versus USOs as major food sources) to explain the australopithecine craniodental morphology are not necessarily incompatible, as it is unlikely that any hominin species consumed only one type of food. In fact, some surveys of craniodental morphology suggest significant interindividual dietary variability in australopithecines (132, 142) (but see 159). It is important to consider the possibility that even relatively rarely consumed foods may have been critical for survival, when preferred foods were not available (e.g., seasonally). The ability to utilize such "fallback food" sources may have been a strong selective pressure during hominin evolution.

Mya: million years ago

USOs: underground storage organs

Meat: Scavenging and Hunting

Chimpanzees hunt small primates and nonprimate mammals, but only occasionally, and meat is a minor component of their diet (120, 147). In contrast, meat is a critical food resource for modern human hunter-gatherers, along with plant foods (17, 36, 101, 136, 146). The earliest evidence for meat-eating in hominins dates to ~2.5 Mya (35). Some of the fossil findings

are consistent with scavenging activities, but on the whole, there is still considerable uncertainty about the relative importance and timing of scavenging versus hunting in hominin evolution (17, 36, 136, 146). Beyond the high caloric gains from the consumption of animal source foods, meat also provides proteins, iron, zinc, vitamins, and other critical dietary components (99). The adoption of large-scale meat-eating may have necessitated advanced processing techniques, such as cooking (see below), in part because raw meat is difficult and slow to chew, thus limiting consumption in large quantities (173).

Cooking

The oldest incontrovertible evidence for human-controlled fire dates to 800,000 years ago (800 kya) in Israel (59). There are other, less certain, sites dating to as early as ~1.5 Mya (18, 165). Wrangham and colleagues (175) suggest that cooking food may have been part of hominin culture as early as ~1.9 Mya, based on the tooth size reduction observed in *Homo erectus* that suggests a shift to the processing of softer foods. Regardless of when cooking originated, this technology likely represented a major dietary shift because it increased the digestibility of both meat and plant foods (37, 144, 173–175). In fact, without roasting, some otherwise edible tubers are too tough for human consumption (37).

We lack direct evidence for fire and cooking as early as Wrangham et al. (175) suggested. However, if the early date they suggest is correct, the ensuing dietary shift may have facilitated the increase in relative brain size observed at the same time in hominin evolution. The brain size increase, coincident with a decrease in gut size, suggests an improvement in dietary quality (3, 175). Whether such a diet quality change was accomplished with the aid of cooking or simply by advancements in stone tool technology, and whether meat or starch-rich USOs were the most critical high-energy food source in this scenario, is the subject of vigorous debates (45, 88, 108, 175 and comments therein). This debate may not be resolved soon because evidence of human-controlled fire and the sticks presumably used to dig up tubers do not preserve well in the archaeological and fossil records. However, some insights may be gained from the study of feeding behavior of contemporary primates; for examples, chimpanzees in a savanna habitat were observed to use sticks and pieces of bark and tree trunk to harvest USOs (71); thus, similar behavior for early hominins is not inconceivable. Whether meat or USOs were the major dietary components, numerous toxins are generated as by-products of cooking, the metabolism of which would have presented novel challenges to the hominin digestive system. For example, acrylamide can be produced by the Maillard reaction (109, 143), a condensing of amino acids and sugars accelerated by cooking, the components of which have been associated with human cancers (24).

Plant and Animal Domestication

The origin and spread of agriculture and animal husbandry over the past ~12,000 years, with centers of domestication in Asia, Europe, South America, and Africa, represent the most recent major shift in human diets. The food production and storage technologies associated with this dietary shift led to population densities that are orders of magnitude greater than what is possible under hunter-gatherer subsistence economies. However, on the whole, the spread of agriculture was associated with an astounding relative reduction in the nutritional intake diversity. For example, 50%–70% of the calories in the agricultural diet are from starch alone (32). In addition to a reduction in nutritional diversity, agricultural diets may also have been associated with a caloric availability that exceeds growth and energetic requirements, as observed among the most developed contemporary agricultural economies.

What are the possible consequences of the narrowed focus on domesticated plant and animal products, as well as excess caloric availability, relative to the likely diets of our human ancestors? Neel's "thrifty genotype" hypothesis

(110) suggests that type 2 diabetes (T2D) may be one modern consequence of an older history of natural selection for metabolic efficiency in the face of limited or unpredictable food availability in a hunter-gatherer economy.

In the "carnivore connection" hypothesis, Brand Miller and Colagiuri (28, 107) propose that under a past meat-rich and carbohydrate-poor diet, insulin resistance would have been favored, but that it is now detrimental following the shift back to high-carbohydrate diets associated with agriculture. Based on data from ethnographic observations of modern hunter-gatherer societies, Eaton & Konner (41) and Cordain et al. (33) estimate that ~65% of the diets of preagricultural paleolithic humans may still have come from plant food products. Therefore, although it may be an oversimplification to characterize preagricultural hunter-gatherers as "primarily carnivorous" (107), a contribution of 35% or higher to the diet from animal source foods would likely have resulted in substantially higher levels of protein and lower levels of dietary carbohydrates compared to their agricultural descendents (33). Therefore, it is still possible that the change in meat content during the transition from hunting-gathering to agriculture represented a significant selective pressure on insulin signaling and human metabolism, as predicted in the carnivore connection framework. Despite the uncertainties about dietary inferences, it remains important to consider carefully the context of ancestral human diets when trying to understand the potential adaptations to and medical consequences of our current ones.

Erratum

APPROACHES FOR DETECTING SIGNALS OF GENETIC ADAPTATIONS

A critical appraisal of the evidence for genetic adaptations to dietary changes requires an understanding of the basic principles of the evolutionary analyses aimed at detecting signals of natural selection. In this section, we review the main models of natural selection, with a particular focus on those that are more likely to apply to adaptations to dietary changes. We also provide a summary of the most widely used approaches and statistical tests of selection and conclude by discussing the statistical issues related to the interpretation of selection signals.

Models of Natural Selection

Natural selection is the process by which beneficial traits that are heritable increase in frequency over time whereas unfavorable heritable traits become less common. This process can take place according to a variety of models, which generate different signatures in patterns of genetic variation. Directional selection occurs when one of the two alleles at a polymorphic site is favored over the other so that it will rapidly increase in frequency; if selection is steady for a sufficiently long period of time, the favored allele will reach fixation. Under balancing selection, two or more alleles are maintained in the population at a stable equilibrium frequency for as long as the selective pressure is present; under a particular model of balancing selection, heterozygous individuals have fitness greater than that of both homozygotes, and a new allele is expected to quickly rise in frequency until it reaches equilibrium. Several additional models with spatially and temporally varying selection (54) may be relevant to adaptations to changes in human diet. Humans inhabit a vast range of habitats that differ in terms of nutrients and resources and that limit the range of possible dietary regimes in any given location; this implies that selective pressures related to diet have varied over geographic space as populations spread to different regions of the world and adapted to use the dietary components available in those environments. In addition, as discussed in the previous section, hominin diets have changed dramatically over time, including the recent past (i.e., the last 10,000 years), leading to new selective pressures at different junctures during evolutionary time. The adaptive responses to new selective pressures may have involved new alleles generated by mutation or introduced from a nearby population or they may have used

EHH: extended haplotype homozygosity

TD: Tajima's D

Nonsynonymous: refers to a nucleotide change in the coding region of a gene that alters the amino acid sequence of the resulting protein

Synonymous: refers to a nucleotide change in the coding region of a gene that does not alter the amino acid sequence of the resulting protein

existing alleles that were not advantageous (either neutral or slightly deleterious) prior to the environmental shift. The latter scenario affords a faster adaptive response and, therefore, may be common in species, such as humans, that have undergone dramatic environmental and dietary changes.

The Signatures of Natural Selection

Most population genetic approaches to detecting advantageous variants rely on the property of positive natural selection to drive the beneficial allele to high frequency at a rate that is much faster than that for a neutrally evolving allele. As shown in **Figure 2**, if a new advantageous allele is introduced into a population by the mutation process, it is necessarily associated with a particular haplotype background. As this allele is driven quickly to intermediate or high frequency, only few recombination events will take place and, as a consequence, the neutral alleles that are tightly linked to the selected site will tend to increase in frequency along with the advantageous allele. This process generates a local pattern of extended identical haplotypes [referred to as extended haplotype homozygosity (EHH)]. This process is often referred to as a partial or incomplete selective sweep, and a number of statistical tests have been developed to detect the resulting pattern (64, 80, 83, 124, 162). If selection is directional and steady over a long enough period of time, then the advantageous allele will go to fixation. In this case, which is referred to as a complete selective sweep, all variation near the selected site will also be fixed while new mutations arising during the sweep will occur at low frequencies. Therefore, the expected pattern near a fixed advantageous allele consists of a reduction in polymorphism levels and a relative abundance of rare variants in the spectrum of allele frequencies. A skew toward rare variants can be assessed by means of summary statistics of the frequency spectrum; the most widely used of these statistics is Tajima's D (TD) (152), but others are also common (43, 49). Conversely, an excess of intermediate frequency variants, as expected under some models of balancing selection, will generate a positive TD value. A number of statistical tests have been developed to capture the impact of positive natural selection under these models; we refer the readers to several recent reviews for details (14, 111, 113, 125).

When selection acts on a variant that is advantageous in only a subset of populations, the frequency of that variant may differ across populations to a greater extent than predicted based on random drift. Several approaches have been devised to detect such adaptations to local environments. Historically, the most widely used approach is based on the statistic F_{ST}, and its modifications (11, 29), which summarizes allele frequency differences between pairs of populations or over multiple populations (166). Variants with unusually large F_{ST} values are typically interpreted as being the targets of selective pressures that are restricted to specific environments, as might be expected for populations that specialize on certain dietary components (92). Another strategy consists of setting up multiple independent contrasts between closely related populations that have different diets; this approach, as applied to the gene coding for salivary amylase, is exemplified in **Figure 3*A***. By comparing populations that are genetically similar, there is power to detect small to moderate differences in allele frequencies due to the specific selective pressures acting in one population but not in the other. A recently developed method puts this approach on a firmer statistical ground, as it compares allele frequencies between populations classified based on an environmental variable, e.g., main dietary component or subsistence, while controlling for the correlation between human populations due to population history and for differences in sample size across populations (31) (**Figure 3*B***).

Additional information regarding the action of natural selection on genetic variation may be extracted by comparing the pattern of nonsynonymous variants within a coding region to that of synonymous variants (which are assumed to be mostly neutral). For example, if

natural selection drives multiple advantageous mutations within the same gene to fixation, this may generate an excess of nonsynonymous relative to synonymous changes between species compared to the ratio observed within species (104). Alternatively, an excess of nonsynonymous relative to synonymous mutations may be observed in the variation within species compared to that between species. One possible interpretation for this pattern is that weak purifying (rather than positive) selection acts on nonsynonymous polymorphisms. Under this scenario, the nonsynonymous variants in excess are slightly deleterious mutations that are not immediately eliminated from the population but are unlikely to become fixed or even reach intermediate frequencies. Several genome-wide surveys suggest that this model may apply to many human genes (22, 23, 63). An alternative scenario is that positive selection favored multiple nonsynonymous variants at the same time in the same population; this may be the case if the adaptive response to a change in environmental pressures involves nonsynonymous variants that existed prior to the onset of new selective pressures (see below). Under the first scenario, nonsynonymous variants are expected to be rare, while the second scenario may lead to nonsynonymous variants at intermediate frequencies. In addition to the comparison of nonsynonymous and synonymous variants, this general approach can be applied to other functional categories of sites, e.g., promoter versus intron sites (68); however, classifying noncoding sequences based on their functional properties is more ambiguous than it is for coding sequences. As a consequence, the results of these analyses must be interpreted with caution.

Interpreting the Results of Genome Scans for Selection Signals

Assessing the statistical significance of the results of the tests described above is not trivial. This is because current patterns of human genetic variation result not only from selective processes, but also from population history, and disentangling the effects of these processes is challenging. To circumvent this problem, many investigators have taken an empirical route that does not make assumptions about the history of populations and aims at identifying the loci with the most unusual patterns compared to large-scale datasets of genetic variation. For example, genome-wide patterns of variation may be summarized by means of one or more test statistics, which are used to rank loci in the genome; those loci falling above an arbitrary cut-off (typically the top 5%) are identified as unusual and are often referred to as outliers. Under the assumption that most loci in the human genome evolve neutrally, these outliers represent candidate targets of strong selective pressures. However, if selection is weak, advantageous alleles may have patterns of variation that are distinct but not necessarily extreme relative to genome-wide patterns. In an attempt to identify loci with more subtle selection signals, investigators have compared the strength of the evidence for adaptations across groups of genes in different biological processes (e.g., genes involved in metabolic processes versus all other genes); a significant excess of signals in one group of genes suggests that the biological process as a whole was a target of selection, even though the signals at individual genes may not reach genome-wide significance (4, 153, 162, 163).

Regardless of the approach used for assessing the statistical significance, the power of neutrality tests varies greatly as a function of a number of factors, among which are the strength and the timing of selection and whether selection acts on standing variants or new mutations. These differences in power pose a serious challenge for reconstructing the history of adaptations to dietary components because human diet has changed significantly at multiple points in time. In general, all methods have the least power when the onset of selection was recent, as in the case of the spread of agriculture starting approximately 12,000 years ago; however, methods based on haplotype structure (e.g., EHH) or differences in allele frequencies (e.g., F_{ST}) may have adequate power if the intensity of selection was sufficiently strong. Because few weakly to moderately advantageous

alleles are expected to go to fixation in as little as 10,000 years, signals of completed selective sweeps (i.e., reduction in polymorphism levels and a skew toward rare variants—negative TD) are unlikely to be powerful enough to detect the impact of dietary changes associated with agriculture, but are suitable for studying older selective pressures such as those that might have been associated with the introduction of cooking. Although relatively powerful, these tests yield results that may be difficult to interpret because controlling for the effect of population history remains a challenge. Conversely, tests based on the comparisons between species, and especially those that consider the ratio of nonsynonymous to synonymous mutations in a lineage-specific framework (105, 176), have power to detect older selective events, such as those associated with the transition to savannah environments of early hominins starting approximately 4 Mya. A further advantage of these tests is that the effect of population history on patterns of variation is not a serious confounder as it is for tests based on comparisons at the population level; therefore, assessing the statistical significance of these tests is more straightforward. However, a major limitation of methods based on the comparison between nonsynonymous and synonymous variants is that they are powerful only in the case of repeated selective events at the same gene; in other words, if adaptation at a given gene is given by a single beneficial nonsynonymous mutation that goes to fixation, a significant excess of nonsynonymous to synonymous variants is not expected.

Another important factor in assessing the evidence for adaptations to dietary changes is whether selection is likely to have involved standing rather than new variants. Because standing variants that become advantageous under new environmental conditions allow populations to respond more quickly to the new selective pressures, this selection model may be particularly appropriate for understanding how humans adapted to their ever-changing diets. Theoretical studies have shown that the pattern of variation expected under this scenario may not be distinguishable from that typical of neutrally evolving regions of the genome, leading to a marked reduction in power (70, 116, 117, 121). This is because the frequency trajectory of such mutations is characterized by a longer initial phase, prior to the rapid rise in frequency, during which mutation and recombination events can generate substantial diversity in the chromosomal background of the mutation. As a result, a partial selective sweep will rarely generate a pattern of long-range EHH, and a completed selective sweep is unlikely to result in a reduction of diversity levels (121). In contrast, methods based on the differentiation of allele frequencies should remain powerful as long as the actual target of selection is included in the analysis. Likewise, the power of methods based on the comparison of nonsynonymous to synonymous variants does not depend on whether the selected alleles were standing variants or new mutations.

BIOLOGICAL PROCESSES AFFECTED BY DIETARY CHANGES

Changes in food availability and diet composition during hominin evolution likely created strong selective pressures on multiple biological processes. Identifying the genetic loci that were targeted by these diet-related selective pressures may provide insights into the evolutionary history of our species as well as into the biological pathways that mediate the effect of dietary risk factors for common diseases, such as diabetes, hypertension, and cancer. This exciting prospect has attracted the attention of many investigators who have used approaches based on evolutionary principles to learn about the impact of selection on specific loci. In order to overcome some of the limitations discussed above, several evolutionary studies have focused on genes and variants with known functional significance; by combining different sources of evidence (i.e., functional and evolutionary), this strategy attempts to provide more interpretable results and to increase the confidence that true signals of adaptation are detected.

Below, we focus on studies that fall into one or more of the following categories: (*a*) studies of candidate genes for which strong prior hypotheses were formulated based on their biological function; (*b*) studies of genetic variants that are strong candidate targets of natural selection based on their effects on relevant phenotypes; and (*c*) studies reporting robust signals of selection. In this section, we examine the evidence for genetic adaptations in response to dietary changes and the adoptions of dietary specializations. For each biological process, single gene studies are discussed first, followed by a review of the results obtained in genome-wide scans for selection.

Metabolism

Metabolism is the process of building molecular structures from nutrients and breaking them down for energy production. Although many metabolic pathways play an important role under all dietary regimes, specific pathways and reactions may become critical when populations specialize on particular dietary components. For this reason, initial efforts to identify genetic adaptations to dietary specializations have focused on enzymes that have a well-characterized and highly specific functional role in nutrient metabolism. To date, patterns of genetic variation at the genes coding for the lactase (*LCT*) and the amylase (*AMY1*) enzymes provide two of the most interpretable examples of genetic adaptations to dietary specializations in human metabolism.

All nonhuman mammals lose their ability to digest lactose, i.e., the main carbohydrate present in milk, rapidly after weaning (21, 89, 133). This is a consequence of decreased levels of the enzyme lactase-phlorizin hydrolase, which is expressed in the gut. In humans, some individuals can digest lactose during adult life. By the early 1970s, it was established that the lactase persistence (LP) phenotype has a genetic basis and is inherited as a dominant trait (44, 106, 127). LP is a common phenotype only in populations with a long history of pastoralism and milk production (82, 151 and references therein).

LP: lactase persistence

Before any evidence of positive selection at the lactase locus had been discovered, several researchers suggested the *LCT* gene as a target of selection in European populations due to the high milk and dairy content in adult diets (7, 76, 103, 138). The first evidence of positive selection at the *LCT* gene was based on elevated F_{ST} values between European Americans and both African Americans and East Asians, and on significant EHH for the haplotype carrying a LP variant (13). However, although this variant explains LP in European populations, it is present only at low frequencies in African populations in which the LP phenotype is common. In fact, a later study identified additional variants that are associated with LP in African pastoralist populations (156). Tishkoff et al. (156) provided strong evidence that at least one of these African variants experienced recent positive selection, as indicated by a significant EHH score. More recently, two additional variants in the regulatory region of the *LCT* gene were identified in Middle Eastern populations from Saudi Arabia (42). In vitro studies showed that these variants affect *LCT* gene transcriptional regulation and that they are associated with a strong signature of natural selection based on EHH (42). These results altogether indicate that the LP phenotype is characterized by genetic heterogeneity and represents a striking example of convergent evolution in human populations. It is to be noted, however, that the LP variants identified so far do not account for all the phenotypic variation observed; thus, it is likely that additional variants will be identified in the future.

In an attempt to elucidate the history of the selective pressures acting on the LP phenotype, different authors have estimated the age of the most recent common ancestors of each LP mutation. All estimates point to relatively recent dates: 8000–9000 years ago for the European mutation, 2700–6000 years ago for the African mutations, and 4000 years ago for the Middle Eastern mutations (13, 42, 156, 162). Taken at face value, these dates are consistent with the

time frame for animal domestication (5, 50). However, the true ages of these alleles are likely to be older (see Open Questions and Future Directions section).

Consistent with the studies cited above, signals of a recent selective sweep in European populations have been identified at the *LCT* locus in virtually all genome-wide scans for selection performed so far (125, 126, 162, 169); in most studies, the *LCT* gene carries one of the strongest signals in the entire genome, with haplotype homogeneity extending up to 2 Mb (**Figure 2*B***). This pattern suggests that the selective pressure associated with adult milk consumption was very strong.

Digestion begins in the mouth. The enzyme amylase, expressed in both the saliva and pancreas, is responsible for starch hydrolysis. Salivary amylase, after initiating starch digestion in the mouth, can persist in the stomach and intestine after swallowing, thus augmenting the enzymatic activity of pancreatic amylase in the small intestine (48, 91). The salivary amylase gene *AMY1* is present in multiple copies in the human reference genome. The gene copy number varies greatly across individuals and across populations (60, 81), and it is correlated with the amount of protein product in saliva (118). Based on the hypothesis that changes in the amount of starch in the diet exerted a selective pressure on the amount of amylase present in saliva, Perry and coworkers (118) compared *AMY1* copy number between populations with high- and low-starch diets. Individuals from populations with starch-rich diets were found to harbor a higher number of copies of the amylase gene as compared to those from low-starch populations (**Figure 3*A***). As discussed above, adaptations to a starch-rich diet may have played important roles during the migration of early hominins from rainforest and wooded habitats to the savannah, where carbohydrate-rich food sources such as roots and tubers probably became an important dietary component, thus changing evolutionary pressures on salivary amylase gene copy number. However, more recent specializations to starch-rich diets, as in agricultural populations, could also explain the signal of natural selection at the *AMY1* gene locus.

In addition to the *LCT* and *AMY1* genes, other enzymes may be important in dietary adaptations. For example, the *NAT2* gene is a possible target of selective pressures associated with the agricultural transition (97, 98, 115). This gene encodes the drug metabolizing enzyme N-acetyltransferase 2, which is involved in activation/deactivation of toxic compounds that are commonly found in native food or are generated by cooking or other treatments. Several nonsynonymous polymorphisms associated with altered acetylation activity occur at low to intermediate frequencies in humans with a markedly broad geographic distribution. By comparing populations with different modes of subsistence, Luca et al. (97) found that the fast acetylator alleles are significantly more common in hunter-gatherer populations compared to pastoralists and agriculturalists. This finding was interpreted as the result of the reduced dietary availability of folates in the transition to an agricultural diet. Because the slow acetylator alleles have a broad geographic distribution, they are likely to predate the differentiation of human populations and the onset of agriculture; therefore, the *NAT2* slow acetylator alleles may represent a case of selection on standing variation. The *NAT2* gene and drug metabolizing enzyme genes as a group have not been associated with strong signals of selection in genome-wide scans. Given the limited power of detecting selection on standing variation, the lack of signals in genome-wide studies is not necessarily surprising.

Other genes involved in metabolism have been shown to carry signals of selection in genome-wide studies. These studies have used approaches that differ with regard to the time period that they interrogate.

Similar to the amylase study, Hancock and colleagues (65) compared allele frequencies across populations with different subsistence and using different main dietary components while controlling for the correlation between human populations due to population history. These authors analyzed a genome-wide dataset

of approximately 650,000 single nucleotide polymorphisms (SNPs) in worldwide human population samples (94) and classified each population depending on whether they used cereals, roots and tubers, or fat, meat and milk as their main dietary component. Significant evidence for adaptations to a diet rich in roots and tubers (**Figure 3*B***) was observed particularly in genes involved in starch/sucrose and folate metabolism. These findings are consistent with the high carbohydrate and low folate content of roots and tubers. Roots and tubers remain an important dietary component in many contemporary human populations, including those living in harsh environments that do not support other types of crops. Several interesting individual signals were observed also for other dietary components. For example, a stop codon in the pancreatic lipase–related protein 2 gene (*PLRP2*) was found to occur at higher frequency in populations that specialize on cereals. This gene codes for an enzyme that hydrolyzes galactolipids (6, 137), which are main triglyceride components in plants. Interestingly, PLRP2 is present in the pancreas of nonruminant herbivores and omnivores but is absent in carnivore or ruminant pancreas (34).

Additional scans for selection based on genome-scale variation data in human populations have pointed to other sets of metabolism genes. Voight et al. (162) identified an enrichment for signals of EHH in genes involved in metabolism of carbohydrates, lipids, and phosphates and in vitamin transport. Similarly, using information about population differentiation (F_{ST}), Barreiro et al. (10) found an enrichment of highly differentiated variants in genes involved in metabolic pathways, such as ethanol and intestinal zinc pathways. As for other genome-wide studies, there is no functional evidence associated with the evolutionary signals. Future analyses will determine whether these signals coincide with variants with detectable effects on function and fitness.

These studies as well as the analysis of Hancock et al. (65) have reasonable power to detect relatively recent adaptations; therefore, it is plausible that most of the signals identified in these studies coincide with the transition to agriculture and animal farming. In contrast, molecular comparisons between human and chimpanzee interrogate deeper time periods and have the potential to identify older selective events, such as those associated with increased meat consumption or the use of the plant compounds encountered in savanna environments. One of the molecular phenotypes that natural selection may act on is the regulation of gene expression, thus raising the possibility that variants in promoters and other regulatory elements (e.g., enhancers) are targets of selection. Consistent with this prediction, Haygood et al. (68) compared the rates of nucleotide substitutions in promoters to those in intronic regions (as proxies for neutrality) between human and chimpanzee and found that *cis*-regulatory regions of genes involved in metabolism and nutrition evolved at a faster rate compared to introns. These results are consistent with the repeated fixation of advantageous promoter alleles some time since the split between human and chimpanzee.

Blekhman and coworkers (16) performed a genome-wide between-species comparison of steady-state mRNA transcript levels to identify targets of selection. They analyzed expression profiles in liver, kidney, and heart tissue samples from human, chimpanzee, and rhesus macaque to search for candidate genes under directional selection as those showing significantly elevated or reduced expression levels exclusively in the human lineage compared to the other two primate species. The set of top candidate genes in this analysis was enriched for genes involved in carbohydrate metabolism, lipid metabolism, and calcium signaling. Genes involved in the metabolism of riboflavin, glycerolipids, and fatty acids were also enriched for signals of directional selection. Although these patterns may be attributed to a variety of dietary changes, they are consistent with the hypothesis by Finch & Stanford (45) that the ancient shift to a diet including substantial quantities of meat was probably accompanied by genetic adaptations against the detrimental effects of fats, toxins, and pathogens.

SNPs: single nucleotide polymorphisms

Sensory Perception

Derived allele: the allele that appeared in the human lineage; usually inferred as the allele that is different from the one present in an outgroup species (in most cases chimpanzee)

Feeding is a multisensorial experience; before being tasted, food is seen, touched, and smelled. Processing of food in the mouth leads to the release of additional molecules that stimulate taste and olfaction, as well as to the production of sounds that stimulate audition. The five senses are developed to different degrees across species reflecting their feeding habits and needs as well as to the whole complex of interactions with the surrounding environment. As a consequence, many studies have sought to understand the evolution of olfaction, vision, and taste in human and nonhuman primates, with important implications for understanding adaptations to dietary changes (46, 51–53, 55, 58, 141, 160, 161, 164, 171).

Taste perception occurs when chemical molecules from food stimulate taste receptor cells. Humans and most mammals can perceive and discriminate five different tastes: sweet, sour, bitter, salty, and umami (8, 87, 95). Perception of these different taste modalities is mediated by different receptors. A special focus of evolutionary analyses has been on the bitter taste because of its role in preventing the ingestion of poisonous food (39, 56).

Bitter-taste receptors are G protein–coupled receptors encoded by the TAS2R gene family (2, 26, 135). Bitter-taste perception is a variable trait in humans, and its genetic basis was first identified in the 1930s by studying individual responses to phenylthiocarbamide (PTC) (15). Although PTC is a synthetic compound, the ability to taste it strongly correlates with the ability to taste natural bitter compounds present in food (9, 40, 62, 128).

The first bitter-taste receptor gene to be identified was *TAS2R38* (38, 86). Based on a resequencing survey of this gene, Wooding et al. (172) identified two major haplotypes (taster and nontaster) present at intermediate frequency in all continents, resulting in a departure from neutrality in the allele frequency spectrum. In addition, the haplotype frequencies are remarkably similar across populations. The authors concluded that balancing selection maintained the two *TAS2R38* haplotypes at similar frequencies in ethnically diverse populations. They further speculated that the heterozygote for the taster and nontaster haplotypes has a selective advantage over the two homozygotes due to the ability to identify a larger number of toxins; however, no functional or phenotypic data in support of this hypothesis have yet been provided. Variation in bitter-taste sensitivity also occurs within chimpanzees. However, the genetic variant identified in the chimpanzee ortholog of *TAS2R38* is different from any of those identified in humans; therefore, the nontaster phenotype evolved independently in the two species (171).

Evidence for natural selection was reported also for a different bitter-taste receptor gene: *TAS2R16*. Three nonsynonymous nucleotide changes were proposed as putative targets of selection because of the high frequency of the derived alleles (i.e., the allele that appeared for the first time in the human lineage and is different from the one present in chimpanzee) (141). The derived allele at one of these sites, located in the region implicated in the receptor-ligand interaction, confers increased sensitivity for a range of structurally different glycosides, of which some have beneficial and others have toxic effects. The allele age estimate for this polymorphism (between 77,700 and 791,000 years ago) and its worldwide geographic distribution suggest that it originated before the introduction of agriculture and the migration of modern humans out of Africa; therefore, the authors speculated that this mutation conferred increased protection against cyanogenic toxins in plant foods in ancestral hunter-gatherer populations (141).

Other studies aimed more broadly at characterizing the evolutionary trajectory of the entire bitter-taste receptor family (46, 164). These studies concluded that relaxation of selective constraints is the main evolutionary mechanism acting on this gene family in primates and in human populations. However, in the comparison of seven primate species (including humans), Fischer et al. (46) found that the average ratio between the rates of nonsynonymous and

synonymous substitutions for 25 bitter-taste receptor genes varies across protein domains. Specifically, the extracellular domains (possibly involved in ligand binding) show an excess of fixed nonsynonymous relative to synonymous substitutions. Based on this observation, the authors speculated that positive selection drove different nonsynonymous mutations to fixation in different species. Caution needs to be taken in interpreting this result because the excess of nonsynonymous substitutions is not statistically significant. Despite this caveat, because nonsynonymous substitutions in the ligand binding domain may change the ligand specificity of the receptor, it is possible that the introduction of new components in the diet exerted a selective pressure in diversifying the ligand specificity of bitter-taste receptors.

Olfactory receptor (OR) genes constitute the largest gene family in mammals (20). In humans, functional genes and pseudogenes are interspersed in clusters located on most chromosomes (12, 57, 157). Humans, compared to other apes, have experienced relaxation of evolutionary constraints on OR genes as suggested by the larger number of OR pseudogenes accumulated in the human lineage compared to other apes (53). However, when the focus is on patterns of variation in human populations, some OR genes present evidence of completed selective sweeps as indicated by a significant skew toward rare variants and low levels of polymorphism (51, 53).

Additional evidence for adaptations in OR genes was provided by genome-wide scans for signals of selection based on signals of complete selective sweeps in human populations (169), on the ratio of nonsynonymous to synonymous substitutions in humans compared to chimpanzee (27, 112), and on EHH in genes involved in olfaction (162). Because the methods used in these studies interrogate different time depths, these findings suggest that OR genes have undergone multiple adaptive events, possibly reflecting the numerous dietary shifts that occurred throughout hominin evolution.

In addition to taste and olfactory receptor genes, the broader category of genes involved in chemosensory perception was also reported to be enriched for signals of selection based on the EHH approach (162), nonsynonymous to synonymous substitutions ratio in the comparison between human and chimpanzee species (27, 111), and population differentiation (F_{ST}) (10).

OR: olfactory receptor

Appetite Control

Appetite includes various aspects of eating patterns such as frequency and size of eating episodes, choice of high-fat or low-fat foods, energy content and diversity of foods consumed. The regulation of appetite is a biological process tightly connected to the environmental availability of food and to lifestyle. Therefore, genes involved in appetite control are potential candidates as targets of selective pressure as humans faced different dietary challenges.

Feeding behavior is controlled by hormonal as well as psychological and neural signals. Genes encoding hormones responsible for long-term energy stores and hunger-satiety hormones have been studied in the context of understanding the genetic basis of metabolic diseases such as T2D. As energy deficit is most likely to compromise survival, it is not surprising that the strongest signals of selection are observed in pathways that increase food intake and decrease energy expenditure when stores are depleted.

A genome-wide scan for selection signals showed that there is extended haplotype homozygosity around the leptin receptor gene (*LEPR*) (162). In addition, strong correlations between allele frequencies and climate variables were observed for this gene following a pattern similar to variants in candidate genes for the metabolic syndrome (66).

One of such genes is *TCF7L2*, which was identified as the gene with the strongest signal in whole-genome association studies for T2D (1, 129, 131, 140, 178). Two SNPs in this gene also showed evidence of spatially varying selection. Specifically, the frequency of the derived allele for the SNP that protects against T2D is higher in non-African compared to African

populations and is strongly correlated with climate variables. The protective allele at this same SNP also shows a signature of positive selection based on EHH in Africa, Asia, and Europe (69). Crude estimates of the age of the haplotype tagged by the protective allele point to relatively recent dates (i.e., 11,933, 8401, and 4051 years for the European, East Asian, and Yoruba populations, respectively), roughly coincident with the introduction of agriculture in each population. Furthermore, a significant association was detected in male individuals between fasting plasma concentrations of the hormones ghrelin and leptin and the number of copies of the haplotype tagged by the protective allele. These two hormones are involved in the short-term neuroendocrine regulation of appetite and the long-term regulation of fat storage and energy metabolism. It was hypothesized that the protective allele conferred a selective advantage relative to the dietary shift and the change in food availability associated with the agricultural transition.

Based on the evidence available so far, it is not possible to determine whether the signals observed at *LEPR* and *TCF7L2* are the results of adaptations to cold climate or to changes in diet and lifestyle. Nonetheless, these genes represent interesting candidates for how the short-term neuroendocrine regulation of appetite and long-term regulation of fat storage and energy metabolism may have evolved under positive natural selection during human evolution.

Morphological Development of the Digestive System

Although morphology of the digestive system is likely to have adapted to dietary shifts, few unambiguous signals of positive natural selection have been observed in this category of genes.

Dental enamel thickness is a phenotypic trait of particular interest, as it may reflect adaptation to variable fracture-resistance properties of food items (157–159). Enamelin peptides are thought to be involved in the formation and elongation of enamel during tooth development (78, 79, 100). Mutations in the gene coding for enamelin (*ENAM*) have been observed in patients with amelogenesis imperfecta, i.e., an inherited defect of dental enamel formation. Moreover, enamel thickness is a polymorphic phenotype in human populations, with African Americans having thicker enamel compared to European Americans (67). The *ENAM* gene was identified as a possible target of recent positive selection in humans in genome-wide scans for selection (73, 84). In a follow-up study, Kelley & Swanson (85) resequenced the *ENAM* gene in 10 human populations and 12 primate species with different diets. Patterns of genetic variation showed a deficit of diversity levels and a skew toward rare variants in the non-African population samples consistent with a complete selective sweep in these populations. Nine nonsynonymous SNPs were observed; one of these SNPs is a particularly good candidate as a selection target because the derived allele is nearly fixed in non-Africans, it occurs at a conserved position across mammalian species, and it results in a change from a polar to a nonpolar residue. Despite these clues, the phenotypic effect of this nonsynonymous polymorphism is unknown. Likewise, the possible selective advantages of lower enamel thickness in non-African populations are unclear. At the interspecific level, sequence comparisons of the *ENAM* gene across primates detected a significant excess in the rate of nonsynonymous relative to synonymous substitutions in primate lineages that experienced dietary shifts (i.e., changes between folivorous, frugivorous, or omnivorous diets) (85).

A fixed frameshift deletion specific to the human lineage has been identified in the gene *MYH16* (148), which encodes the predominant myosin heavy chain expressed in the masticatory muscles of nonhuman primates. This deletion may have been associated with the gracilization of the masticatory apparatus in humans, as observed in the genus *Homo*.

OPEN QUESTIONS AND FUTURE DIRECTIONS

As discussed above, there is now a rich database of interesting observations that may reflect adaptations to dietary changes during hominin

evolution and allow formulating new hypotheses to be tested in follow-up studies. However, the molecular genetic evidence for these adaptations often comes without a full understanding of the functional and phenotypic consequences of the implicated genetic variants or changes. Other than a few digestive enzymes (e.g., lactase, amylase), which have very specific functions, most genes involved in the processing and digestion of food have multiple functions and are expressed in more than one tissue. Therefore, it is often difficult to reject the possibility that signals of selection result from adaptations unrelated to diet. Moreover, due to the complexities of molecular mechanisms involved in the regulation of gene expression, extensive functional work is required to elucidate the functional and evolutionary significance of gene regulatory changes that affect the digestive system. Despite these challenges, this work, especially if based on systems biology approaches, has great potential to add significantly to our understanding of hominin dietary evolution.

Another complication in interpreting the results obtained so far is that dietary changes usually occurred within the context of broader transitions in human ecology. As a consequence, changes in diet during hominin evolution may be correlated with other aspects of the environment that are unrelated to diet, e.g., climate, pathogen load, and mode of subsistence. Therefore, it is difficult to dissect the specific impact of dietary changes as a selective pressure. For example, lactase-persistence individuals can take advantage of the nutritional properties of milk, but milk consumption may also have been protective against dehydration and enterobacteric diseases caused by parasites present in water (30, 77, 139). This advantage was particularly important in hot geographic areas, where lactose-intolerant individuals could not use milk to compensate for water loss. It has also been suggested that, in addition to the nutritional advantage, LP provided an advantage at high latitudes, where reduced sunlight and therefore low vitamin D are associated with increased prevalence of rickets and osteomalacia. Lactose promotes the absorption of calcium present in milk, and it has been suggested that calcium might reduce the breakdown of vitamin D in the liver, therefore compensating for the reduced sunlight (47, 155). Climate influenced human lifestyle with consequences not only on diet, but also on other aspects of human physiology, such as energy balance. For example, leptin is involved both in the control of appetite as well as in energy balance; therefore, the signal of selection identified at the *LEPR* may be due to selection on either biological process or on the interaction between the two.

An approach often used to connect signals of selection with specific historical changes in diet is to estimate the ages of the selected alleles. However, most dating methods estimate the age of the most recent common ancestor of the haplotypes carrying the allele examined; such estimates represent only a lower bound for the true age of the selected allele. Moreover, recent simulation analyses have shown that these estimators have a substantial bias downward, thus leading to a significant underestimation of both the age of the most recent common ancestor and an even more severe underestimation of the allele age (J. Kelley and M. Przeworski, personal communication). Finally, it should be noted that the allele age is only loosely related to the onset of the selective pressure, which is the only relevant information for connecting selection signals with specific dietary changes. Therefore, although reconstructing the sequence of events associated with selection signals can potentially provide crucial insights into the history of genetic adaptations to dietary changes, improved methods for allele dating are necessary to make robust inferences.

The insights obtained through studies of genetic variation at the population level are focused on recent time periods because this is where they have the most power to identify potential signatures of natural selection. Signals of such recent selective pressures are typically associated with variants that are still segregating in modern humans; therefore, further information about their role in dietary adaptations

can be gained through genotype-phenotype association studies. Importantly, learning about dietary adaptations in the recent time scale is also facilitated by the relatively rich archeological record from these time periods, which can provide useful information regarding the behavioral ecology and cultures of human populations over the past 30,000 years.

In contrast, the more remote periods of hominin evolution are less amenable to inferences about adaptive dietary shifts, limited principally to information that can be gleaned from the fossil record. The molecular genetics analyses that may ultimately provide the most insight here might not be of humans. For example, Hoberg et al. (74) presented an interesting phylogenetic analysis of *Taenia* tapeworms that may inform our understanding of meat eating in hominin evolution. Humans are parasitized by three *Taenia* tapeworm species: *T. saginata*, *T. asiatica*, and *T. solium*. Cattle and swine are the intermediate hosts for these tapeworms today; humans who consume undercooked tissues from these animals can develop tapeworms. Hoberg et al. (74) used morphological variables to estimate the phylogeny of 35 *Taenia* species including the three human ones: *T. saginata* and *T. asiatica* are sister species and most closely related to a lion (*Panthera leo*) tapeworm, whereas *T. solium* is most closely related to a hyena-infecting tapeworm, suggesting two independent shifts to humans/hominins. Based on an analysis of mitochondrial DNA sequences, *T. saginata* and *T. asiatica* diverged approximately 900 kya, long before animal domestication (74). Presumably, hominins acquired the ancestral parasite of these two extant species when scavenging or hunting intermediate mammal hosts, which are also the prey of lions. Therefore, if accurate, the ~900 kya estimate for *T. saginata* and *T. asiatica* divergence would provide a lower bound estimate for the beginnings of this behavior and of the concomitant dietary change.

Another potentially fruitful line of investigation centers on the evolutionary ecology of the human gut microbiome, or the diversity and densities of bacterial species populating the human gastrointestinal tract. Signals of adaptive evolution may be detected on both sides of this symbiotic relationship and could provide insight not only in terms of evolution of the immune response (123), but also in terms of the evolution of the digestive system itself (93), potentially including our ability (and efficiency thereof) to digest food compounds that have been of particular importance in hominin evolution.

The continued development and extensions of these and similar lines of research will complement insights about hominin dietary evolution that can be made from the fossil and archaeological records. The elucidation of the evolution of human diet and of the history of genetic adaptations to dietary shifts is still in its infancy. Ultimately, a coherent reconstruction of this complex history will require weaving together evidence from different disciplines and different approaches. The work so far has already opened new avenues of investigation and has formulated interesting hypotheses to be tested in future studies.

SUMMARY POINTS

1. Humans inhabit diverse environments and use various subsistence strategies that are associated with selective pressures on human metabolism and homeostasis.
2. Evolutionary genetic approaches can detect episodes of genetic adaptation under some scenarios but have limited power in the case of selection acting on standing variants rather than new advantageous mutations.
3. Genes involved in metabolism carry signatures of selection in single-gene and genome-wide studies.

4. Other categories of genes with potential signals of selection are chemosensory perception, appetite control, and those involved in the development of the digestive system.
5. The molecular genetic evidence for diet-related adaptations in human evolutionary history is often lacking a full functional validation and is biased toward recent time periods.

FUTURE ISSUES

1. By gaining further knowledge on past human diets, it is possible to achieve a better understanding of potential adaptations to and clinical consequences of our current ones.
2. New approaches for detecting signals of selection on standing variation are likely to identify variants that became advantageous during or following dietary shifts.
3. The molecular genetic analyses of gut microbial flora and parasites species are promising alternative approaches to gain insights into the more ancient time periods of hominin evolution.

DISCLOSURE STATEMENT

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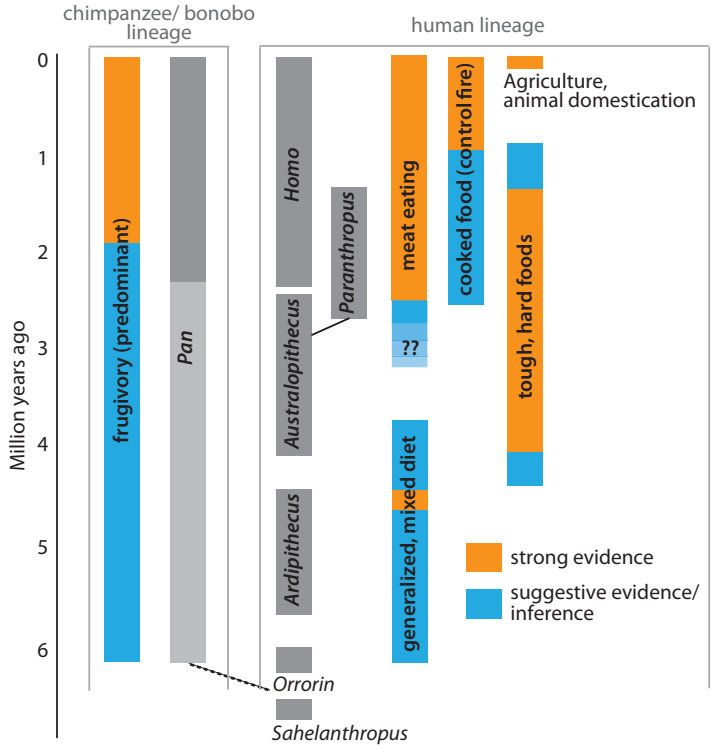

Figure 1

Timeline of the main dietary shifts during hominin evolution. Approximate dates of existence for human- and chimpanzee/bonobo-lineage genera are depicted in gray boxes. Timing of some of the important dietary transitions in hominin evolution is highlighted in orange and blue boxes to indicate whether these transitions are supported strongly or suggestively, respectively.

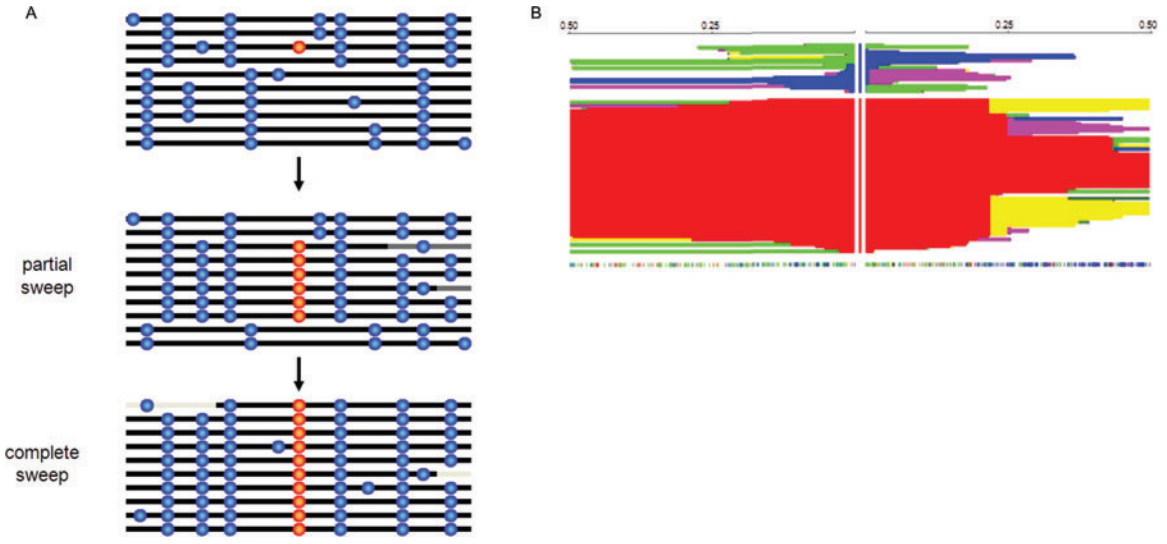

Figure 2

The impact of selective sweeps on patterns of neutral variation tightly linked to an advantageous mutation. (*A*) Neutral mutations and advantageous mutations are shown as blue circles and red circles, respectively. Gray bars indicate the results of recombination events involving a chromosome not carrying the advantageous mutation. (*B*) Extended haplotype homozygosity around the European lactase persistence (LP) mutation (at the center of the display) (162). The ancestral and derived states of the LP variant are represented by the blue and red vertical lines, respectively. The distance (in Mb) spanned by the haplotypes is displayed at the top of the graph. A continuous block of the same color represents a haplotype that is shared among many chromosomes.

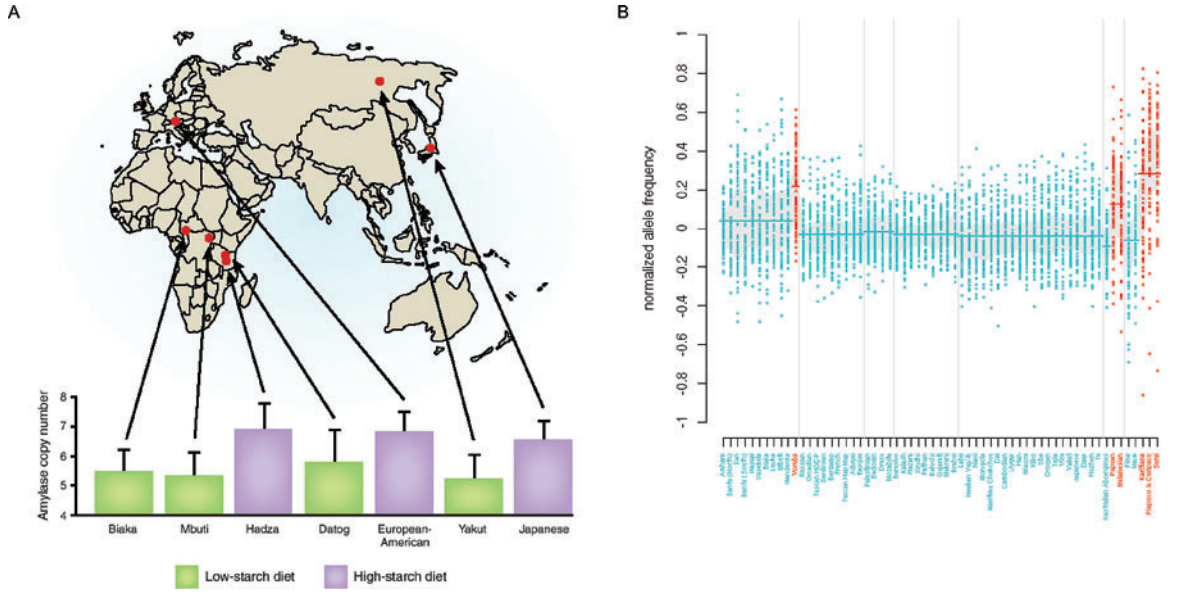

Figure 3

Multiple contrasts between closely related populations that differ in their diet composition. (*A*) The distribution of salivary amylase copy number in the seven population samples analyzed by Perry et al. (118). The bar chart represents the average copy number for each sample (error bars represent two standard errors) (114). From Reference 114. (*B*) Normalized allele frequency plotted against population for the variants that showed the strongest correlation with the main dietary component roots and tubers in the study by Hancock et al. (65). Vertical lines separate populations into seven major geographical regions (from left to right: sub-Saharan Africa, Europe, Middle East, West Asia, East Asia, Oceania, and the Americas). Red denotes populations that specialize on roots and tubers, and all other populations are colored blue. Horizontal lines are drawn through the mean for the set of populations in a given region that are part of the category of interest; gray shading denotes the central 50% interval. Within the same geographic region, populations whose main dietary components are roots and tubers are characterized by a shift in the mean allele frequency compared to populations with different main dietary components.

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Errata

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