Recent advances in understanding the adaptive evolution of metabolic genes and traits

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Purpose of review
This review summarizes the recent advances in understanding the adaptive evolution of metabolic genes and traits, providing insights into gene-diet interactions in human evolution and health.

Recent findings
The rapid accumulation of ancient DNA across time and geography illuminates unprecedented details of some well-established examples of genetic adaptation to diet, such as the *LCT* and *FADS* genes. Novel cases of thrifty genes were identified, especially a microRNA at the *LCT* locus that controls energy expenditure and glucose homeostasis, connecting the historical adaptation to present-day metabolic disorders. A new example of gene–diet–microbiota interactions was established among the *AMY1* copy number, starchy diets, and resistant-starch-digesting *Ruminococcus*. The explosion of genome-wide association studies in large cohorts unravels the present-day health implications of historically adaptive genetic variants. It also enables studies into the polygenic adaptation of metabolic traits, revealing intriguing adaptive signals for increased bone mineral density, blood pressure, and risk of type 2 diabetes, but decreased body mass index and HbA1c.

Summary
The rapid accumulation of ancient and modern DNA has fueled the characterization of novel and existing cases of genetic adaptation. However, transferring these evolutionary insights into genome-informed precision nutrition requires extensive mechanistic studies and genotype-aware clinical trials.

Keywords
gene–diet interactions, gene–diet–microbiota interactions, genetic adaptation, polygenic adaptation

INTRODUCTION

Elucidating gene-diet interactions and the health consequences of gene–diet mismatches will guide the future practice of precision nutrition in combating the current epidemics of chronic diseases. Genetic adaptation to diet during human evolution has shaped our genome, the patterns of genetic variations across populations, and their relationships with diets. Well-known examples of genetic dietary adaptation have been established [1,2▪]. For instance, a regulatory variant of the lactase-encoding gene (*LCT*) enables the continuous expression of the enzyme into adulthood and maintains the ability to digest lactose. This variant and its enabled phenotype, called lactase persistence (LP), have become more common over time in human populations that have a long history of drinking milk. Individuals without the LP variant suffer from adverse intestinal symptoms if they drink milk, a digestive disorder known as lactose intolerance. Another more recently established example is related to a cluster of three genes encoding fatty acid desaturases (*FADS*). Two of them, *FADS1* and *FADS2*, are known to encode the rate-limiting enzymes in the biosynthesis of omega-6 and omega-3 long-chain polyunsaturated fatty acids, which are scarce in plant-based diets but enriched in seafood. Genetic variants upregulating *FADS1* expression and thus enhancing biosynthesis have been subject to positive selection in farming populations, which traditionally relied heavily on plant-based diets. On the other hand, the same genetic variants are rare in Greenlandic Inuit, who have traditionally subsisted on seafood. These *FADS* genetic variants have been associated with a wide

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KEY POINTS

- Ancient DNA reveals that the onset of rapid frequency increase of adaptive *LCT* and *FADS* variants were in the Bronze Age, much later than the initiation of the Agricultural Revolution.
- A microRNA, miR-128-1, locating at the *LCT* locus and carrying the same adaptive signal, controls energy expenditure and contributes to obesity and type 2 diabetes.
- Historically adaptive variants at *LCT* and *FADS* are associated with a large number of metabolic diseases in large epidemiological cohorts.
- The copy number of *AMY1* modifies one's ability to digest high-starch diets and thus impacts the composition of the oral and gut microbiome.
- In recent European history, there was positive selection for increased bone mineral density, blood pressure, and risk of type 2 diabetes, but decreased body mass index and HbA1c.

range of metabolic and inflammatory conditions, supporting the possibility of genome-based dietary matching to reduce disease risks. These examples of genetic adaptation to diet illustrate the needs and the promising opportunities of identifying historically forged gene-diet interactions and matching our current dietary practices to individual genetic backgrounds (Fig. 1).

In the last two years, significant advances have been made in understanding the adaptive evolution of metabolic genes and traits. Arguably, the most impressive progress was the use of genetic data from ancient human remains (i.e., ancient DNA, or aDNA) across various historical periods to directly depict the frequency trajectory of a genetic variant, enabling a novel set of methods to identify adaptive genetic variants and revealing unprecedented details about the timing of mutation, the onset of selection, and the selection strength [3]. Another major progress lies in the explosion of genome-wide association studies (GWAS) in large cohorts. It unravels the present-day health implications of historically adaptive genetic variants and enables studies into the polygenic adaptation of complex

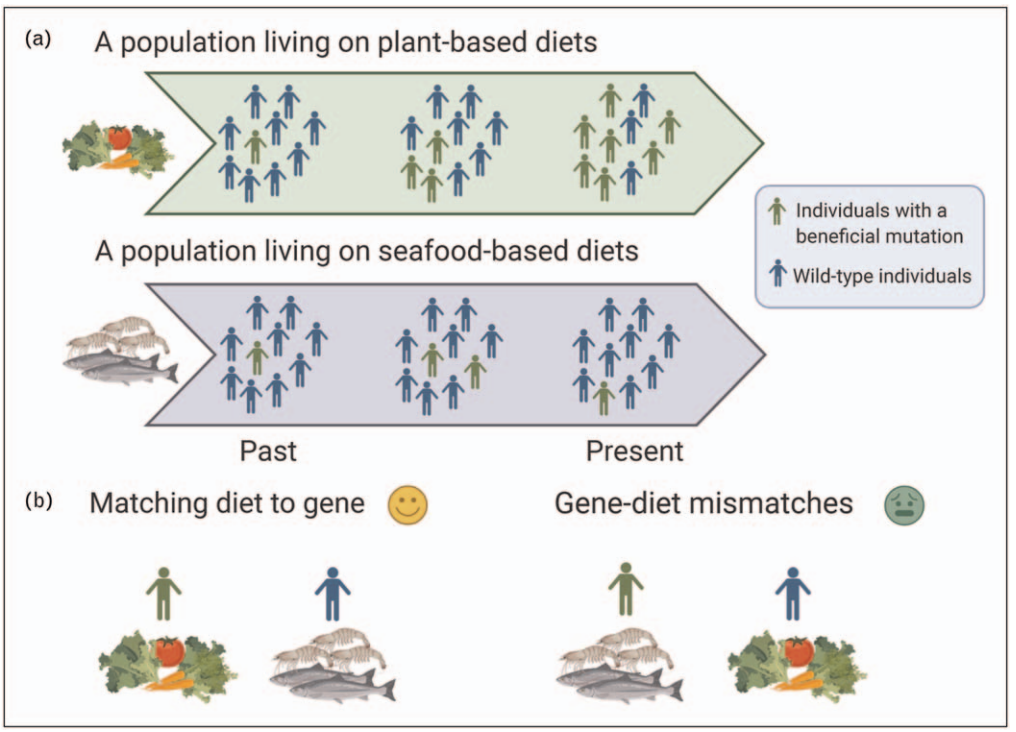

FIGURE 1. A simplified schematic of gene-diet interactions in human evolution and health. The schematic is based on the evolutionary history of *FADS* genes. (a) Beneficial mutations enhancing the biosynthesis of long-chain fatty acids from plant-derived precursors were adaptive to plant-based diets and increased in frequency. In populations living on seafood-based diets, the wild-type allele was maintained at a high frequency. (b) In present-day individuals, matching diet to one's genetic background ensures optimum nutrition and health, whereas gene–diet mismatches may result in nutritional deficiencies and metabolic diseases.

metabolic traits. Additionally, novel cases of thrifty genes and gene–diet–microbiota interactions were established.

Adaptive evolution of the *LCT* locus and lactase persistence

The adaptive evolution of the *LCT* locus, the textbook example of genetic adaptation to diet and the strongest adaptive signal in the human genome, still has many missing details, such as the origin of the LP allele, the onset of positive selection, the acting environmental factors, and the absence of positive selection in Central Asian pastoralists. Burger *et al.* set out to pinpoint the timing of the LP allele surge in Europe and to test a previous hypothesis that it was driven by an influx of pastoralists from the Pontic–Caspian Steppe beginning around 5,000 years ago [4,5]. They generated genetic data for 14 warriors from the Tollense Bronze Age battlefield in northern Germany dated ~3,200 years before present (BP), and showed that these samples represent a single unstructured Central and Northern European population. The frequency of the LP allele (rs4988235: G > A, also known as -13,910: C > T) is 7.1% in this sample. Re-analyzing published aDNA, Burger *et al.* estimated a similarly low frequency (4.6%) in an older Bronze Age sample from Mokrin in Serbia dated ~4,100 to ~3,700 BP. Much higher frequencies were observed in more recent samples, and the selection strength since the Bronze Age was estimated to be 6%, much higher than other recent estimates based on modern (1.6%) [6] and ancient DNA (1.8%) [7]. To evaluate the role of Steppe-associated migration in driving the spread of LP allele in Bronze Age Europe, Burger *et al.* genotyped the rs4988235 in 37 Eneolithic and Early Bronze Age samples from Eastern Europe and the Steppe region (~5,980 to ~3,980 BP). They did not find the LP allele in this sample, consistent with the re-analysis of published data that yielded estimates of 0–1.8%. The low LP allele frequency in these Steppe samples does not support the hypothesis that the Steppe-associated influx into Europe drove the LP allele surge [4]. These observations of a low frequency before the Bronze Age, a dramatic frequency increase since then in most of Europe, and a low frequency in the initial Steppe-ancestry samples were confirmed by multiple recent studies based on aDNA in western Russia and East Baltic [8,9], Northern Europe [10], and the Iberian Peninsula [11].

One unsolved mystery is the low LP allele frequency in nomadic pastoralists of the Eastern Eurasian Steppe, who have sustained dairy pastoralism for the last 5,000 years [12,13]. Segurel *et al.* estimated the prevalence of LP in 30 Central Asian populations by genotyping 963 individuals at rs4988235. Categorizing populations by subsistence mode, they found that the LP frequency is 12.2% in pastoralists, 17.5% in farmers, and 10.3% in hunter-gatherers [13]. The temporal dynamics of LP in Eurasia were further examined in 1,434 published ancient individuals. The earliest reliable LP individual in Central Asia was found in Kazakhstan and dated to 3,713 BP. The LP prevalence remained low from Iron Age (5.6%) to the present days [13]. Another aDNA study, by Jeong *et al.*, generated new genome-wide data for 214 individuals from 85 Mongolian and 3 Russian sites, spanning 6,000 years of time from 6,600 to 600 years ago. They did not find the LP allele in any Eastern Steppe individuals from the Bronze Age or the Early Iron Age. Although it was observed in later periods, the frequency has been low (~5%) over time [14]. Multiple hypotheses have been proposed to explain the lack of adaptive evolution of the *LCT* locus in these pastoral populations, including cultural adaptation by processing fresh milk to reduce lactose, and colonic adaptation by acquiring unique lactose-digesting gut microbiota [13,14]. Solving this mystery will enrich or even re-write this textbook example of genetic dietary adaptation.

An alternative target of positive selection at the *LCT* locus

Many metabolic traits, in addition to LP, have been associated with the *LCT* locus. A simple search in PhenoScanner, a database of existing genotype-phenotype associations [15], reveals 20 diseases and traits associated with rs4988235 at the genome-wide significance level ($P < 5 \times 10^{-8}$), ranging from blood lipids, the fat mass of various body parts, body mass index (BMI), hip circumference, to Parkinson's disease and forced vital capacity. Similar associations were found in a phenome-wide association analysis (PheWAS) in UK Biobank [16] (Fig. 2a). What are the genetic and molecular underpinnings for these metabolic associations? Aiming to address this question, Wang *et al.* focused on a microRNA, miR-128-1, which locates about 150 Kb downstream of *LCT*, shares the same strong adaptive signal, and has been previously shown by the same research group to regulate cholesterol and triglyceride homeostasis [17▪▪]. With epigenomic and expression quantitative trait locus analysis, they showed that the long adaptive haplotype is associated with locus-wide increased chromatin accessibility and coordinated elevated expression of multiple genes, including miR-128-1. An impressive set of functional experiments were further carried out in mouse models. It was shown that antagonism and genetic ablation of

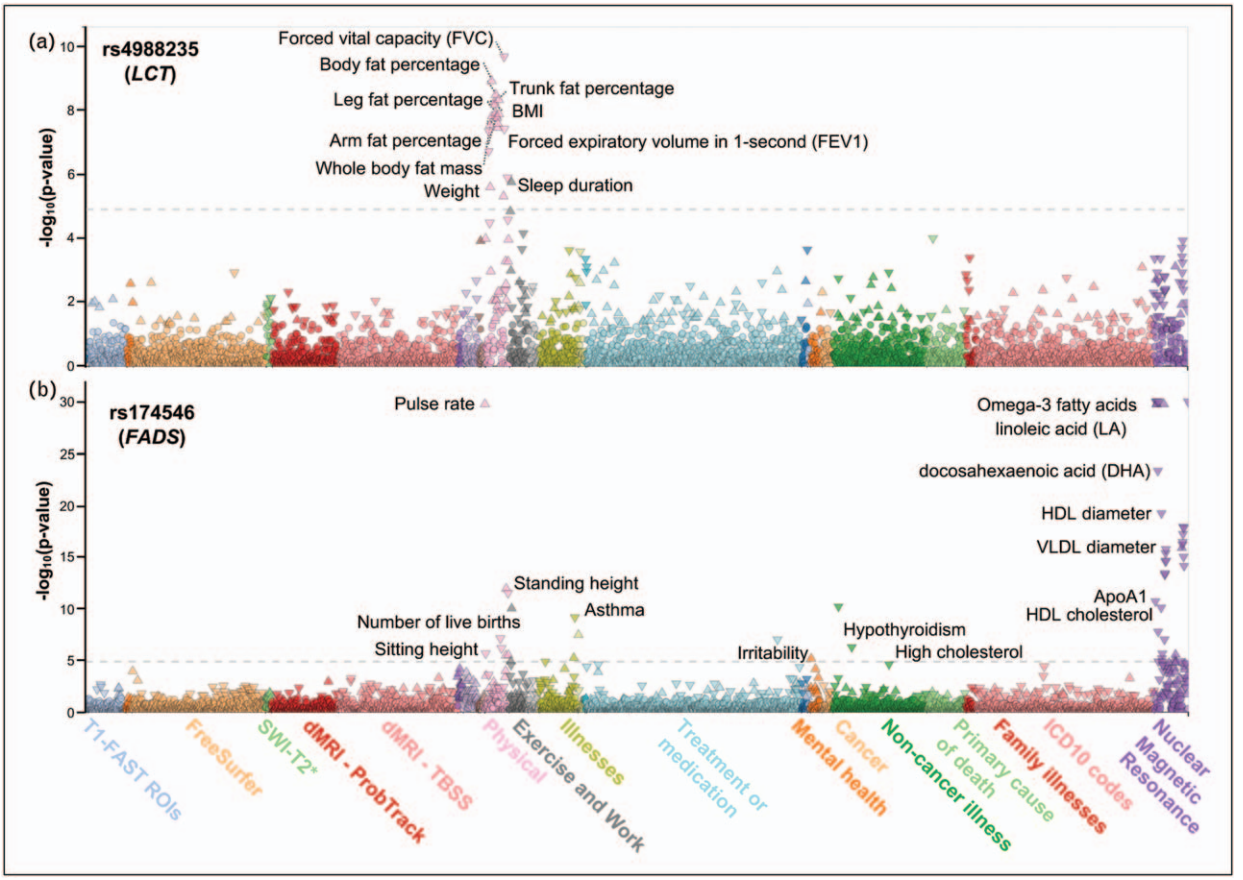

FIGURE 2. Phenome-wide association study of two adaptive genetic variants in UK Biobank. (a) SNP rs4988235 at the *LCT* locus. (b) SNP rs174546 at *FADS* genes. The plots were downloaded from the Oxford BIG Server (http://big.stats.ox.ac.uk/) and modified to enhance resolution.

miR-128-1 result in enhanced energy expenditure, reduced fat mass, and improved insulin sensitivity. This microRNA represents a promising therapeutic target for metabolic diseases, especially obesity and type 2 diabetes (T2D). It also represents an exceptional example of thrifty genes, which were beneficial and adaptive in the ancient times of frequent famine, but are now maladaptive in the modern dietary environment and predispose carriers to metabolic diseases. How much of the adaptive signals at the *LCT* locus could be attributed to miR-128-1 is an interesting topic of future research.

Adaptive evolution of the *FADS* locus

Recent studies, mainly based on aDNA, have illuminated the complex evolutionary history of the *FADS* locus across time and geography. One important study is from Mathieson and Mathieson, who performed an integrative analysis of ancient and modern DNA [18]. Since the causal variants were unknown, their analysis focused on a tag SNP, rs174546 (T > C), whose derived allele C is associated with higher *FADS1* expression and enhanced biosynthesis of long-chain fatty acids. This biosynthesis-enhancing allele is almost fixed (100% frequency) in Africans, ~90% in South Asians, and ~70% in Europeans. Mathieson and Mathieson provided additional evidence and details for three episodes of positive selection on the *FADS* locus in the history of present-day European and African populations. First, using modern DNA of Africans from the 1000 Genomes Project, they confirmed the presence of very ancient positive selection on the biosynthesis-enhancing allele, with an estimated onset of selection between 202,000 and 492,000 BP, which is way before the separation of African and non-African populations. Second, similar analysis with modern European data confirmed strong recent selection on the biosynthesis-enhancing allele, starting between 1,700 and 4,000 BP. These two episodes of positive selection on the same allele would have been counter-intuitive because the ancient episode should have driven this allele to fixation in the ancestors of European populations. Using aDNA of Paleolithic and Mesolithic European hunter-gatherers (~45,000 to ~8,000 BP), the authors

confirmed a previous observation that the biosynthesis-enhancing allele was already close to absence by this historical period, supporting another ancient episode of positive selection on the alternative biosynthesis-reducing allele. Although the study did not have sufficient data to provide an accurate time estimate, the onset of this second ancient selection was estimated to be before or during the out-of-Africa event. The exact driving environmental factors in these three episodes are unknown, although pre-Neolithic hunter-gatherers are thought to rely more on animal-based diets and recent European farmers were more plant-based. Besides defining the three episodes of positive selection, Mathieson and Mathieson analyzed data from 1,055 ancient Europeans (12,000 to 1,000 BP) to investigate the allele frequency trajectory and the onset of recent selection. They found that signals of positive selection were only present in the last 6,000 years, much later than that the initiation of the Agricultural revolution ~10,000 years ago. Notably, similar allele frequency trajectories were observed for another two putative agricultural adaptation variants at *LCT* and *SLC22A4*. The latter has been proposed to be adaptive to the low ergothioneine level of agricultural diets. The presence of strong adaptive evolution only in the last 6,000 years casts doubt on the role of agricultural diets in selecting for these variants [18]. Consistent with the overall picture painted by Mathieson and Mathieson, another study with aDNA from western Russia and Eastern Baltic found that the biosynthesis-enhancing allele increased its frequency from ~10% in Stone Age hunter-gatherers to ~55% in Late Bronze Age farmers [8].

Another major progress lies in clarifying the role of positive selection on the *FADS* locus in Greenlandic Inuit and Native Americans. These populations or their ancestors subsisted on seafood-based diets, which are rich in long-chain omega-3 fatty acids. The absence of biosynthesis-enhancing alleles in these populations has been interpreted as results of positive selection on alternative alleles that downregulate *FADS1* expression and reduce biosynthesis. A very recent study reported similar findings [19]. All these studies compared the allele frequency in the target population with those in Europeans and East Asians, and interpreted extreme frequency differences in the target population as signals of positive selection. However, independent positive selection on the *FADS* locus in Europeans and East Asians could have confounded the selection detection in Native Americans. Mathieson utilized aDNA from 16 individuals from Early Upper Paleolithic Eurasia, dated from 45,000 to 17,000 BP, and showed that the biosynthesis-reducing alleles were already very common (~87.5%) in the ancestral population that migrated into America [7]. The author further demonstrated that using Mesolithic hunter-gatherers to replace either modern Europeans or East Asians in statistical tests obviates the spurious selection signals in Native Americans. This study indicates that Native Americans simply retain the ancestral state of the *FADS* locus in the Paleolithic Eurasians.

Many traits and diseases have been associated with genetic variants at the *FADS* locus [20]. A PheWAS of rs174546 in UK Biobank revealed pulse rate, asthma, hypothyroidism, height, and a long list of lipid and fatty acid-related traits (Fig. 2b) [16]. A simple search in PhenoScanner reveals 85 genome-wide significant associations, highlighting the counts of various blood cells and fasting glucose [15]. The functional impacts of *FADS* genetic variants were also demonstrated in a recent prospective clinical trial of botanical oils containing both linoleic acid (LA) and ɣ-linolenic acid (GLA) [21]. With a randomized, double-blind, crossover intervention, Sergeant *et al.* showed that the supplementation of borage oil, containing 37% LA and 23% GLA, increases the serum concentrations of GLA and dihomo-ɣ-linolenic acid (DGLA) in a genotype-dependent manner. DGLA increased by 57% in homozygotes of the *FADS1*-upregulating allele but by 141% in homozygotes of the *FADS1*-downregulating allele, likely because the *FADS1*-downregulating allele is less efficient in converting DGLA into arachidonic acid (ARA) [21].

Gene–diet–microbiota interactions during human evolution

The role of microbiota in human genetic adaptation is attracting growing interest [22▪]. The most established example of gene–diet–microbiota interaction is again the *LCT* locus. Individuals without the LP allele have an elevated abundance of *Bifidobacterium* in the gut, which is capable of digesting the unused lactose [22▪]. Another example is established recently for the interaction among the *AMY1* copy number (CN), starchy diets, and resistant-starch-digesting microbes (Fig. 3) [23▪▪]. *AMY1* encodes the salivary amylase that starts the process of starch digestion in the mouth. Its CN ranges from 2 to 15 across individuals. As a genetic adaptation to high-starch diets, high *AMY1* CN is much more common in present-day farming populations than hunter-gatherers [22▪]. To investigate how oral and gut microbiota respond to host *AMY1* CN, Poole *et al.* first performed an association analysis of *AMY1* CN with gut microbiota in 994 subjects and then carried out a month-long diet intervention study in selected subjects of high, medium, and low *AMY1* CN. They found that subjects with high

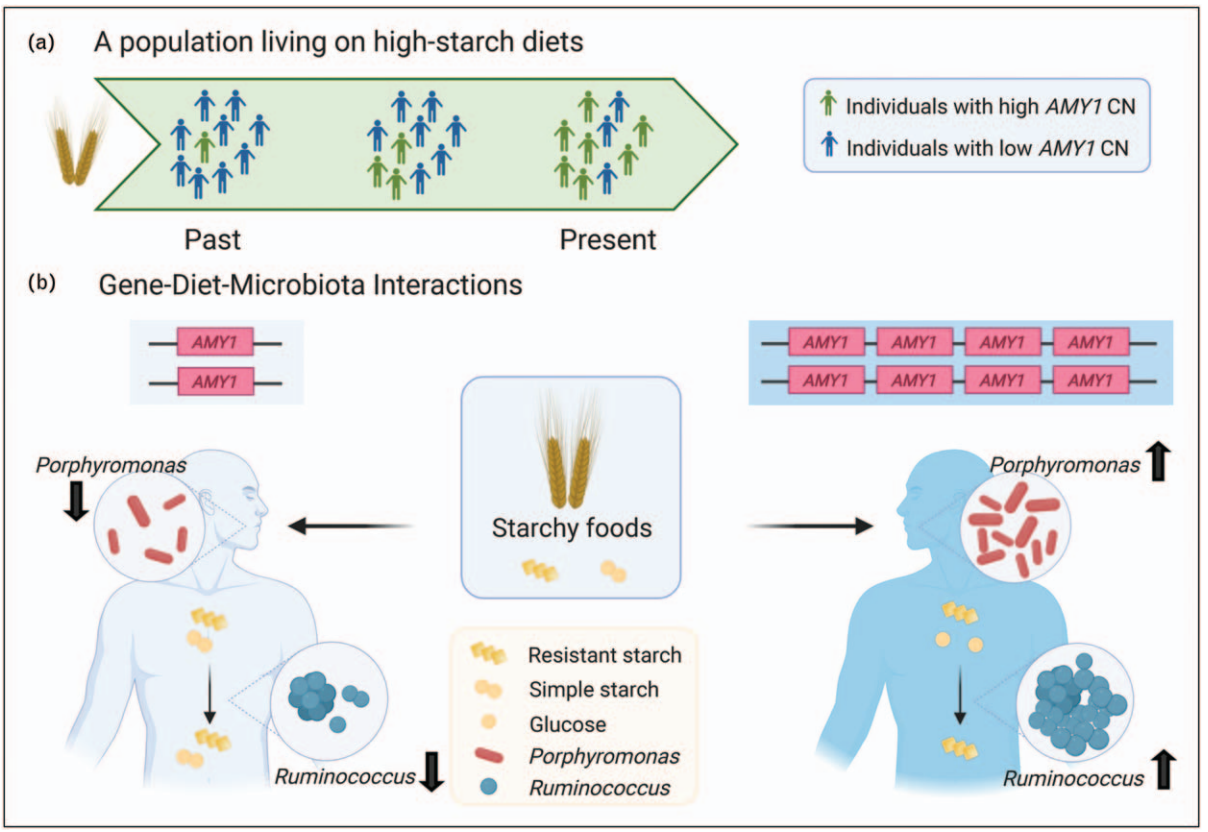

FIGURE 3. The adaptive evolution and gene–diet–microbiota interactions of the *AMY1* CN. (a) High AMY1 CN was adaptive to the high-starch diets of some farming populations and thus became more common over time. (b) High *AMY1* CN leads to rapid digestion of simple starch starting in the mouth and a higher concentration of resistant starch in the gut. These individuals have more *Porphyromonas* and resistant-starch-digesting *Ruminococcus* in oral and gut microbiota, respectively. CN, copy number.

AMY1 CN tend to carry more *Porphyromonas* in their oral microbiota and more *Ruminococcus* in the gut. Oral *Porphyromonas* has been linked to periodontitis, whereas *Ruminococcus* is known to ferment starch that is resistant to host amylase digestion. The authors further showed that the gut microbiota from high *AMY1* CN subjects produce more short-chain fatty acids and, when transferred into germ-free mice, promote adiposity. On the other hand, for individuals with low *AMY1* CN, deep metagenome sequencing reveals that they have enrichment of enzymes involved in the breakdown of complex carbohydrates. Similar associations between host genes and microbiome are reported in recent GWAS [24], calling for evolutionary studies of their historical interactions in human evolution and for functional studies of their roles in human health.

Adaptive evolution of complex metabolic traits

Most metabolic traits have a polygenic genetic basis, with many trait-associated genetic variants and each conferring a small effect. Positive selection is unlikely to dramatically increase the frequency of these small-effect variants. However, polygenic adaptation, the coordinated subtle allele frequency shift across many variants, could rapidly change the trait values [25]. Stern *et al.* developed a full-likelihood method that uses genetic variation data and GWAS summary statistics to infer directional selection on polygenic traits in recent human history [26]. It has substantially improved power and is robust to various sources of bias, such as insufficiently corrected population stratification and low sample sizes in GWAS. It was further extended to simultaneously infer selection pressure for multiple polygenic traits, distinguishing direct selection from correlated response. Analyzing 56 human traits with genetic data and GWAS from the British population, the authors found evidence of positive selection for increased bone mineral density and decreased glycated hemoglobin levels (HbA1c). Joint analysis of trait pairs revealed that the signal for HbA1c was likely correlated response to direct selection on blood pressure. It also revealed that there is positive selection for an increased risk of T2D and decreased HbA1c levels, when conditioning on each other.

This opposing selection may seem counterintuitive since HbA1c is a diagnostic criterion for T2D. The authors proposed that since T2D and HbA1c are not perfectly correlated (genetic correlation = 69%), natural selection might have favored T2D-related effects that is not associated with HbA1c, but acted against HbA1c-related traits that are not associated with T2D. The latter might include hypertension and other cardiovascular diseases [26]. Signals of polygenic adaptation for lower BMI and higher blood pressure were also reported by recent studies [27,28]. With the advent of novel methods and less-confounded estimation of genetic effects, more metabolic traits with polygenic adaptation signals are expected to be found.

CONCLUSION

The rapid accumulation of ancient and modern DNA has fueled the characterization of novel and existing cases of adaptive metabolic genes and complex traits. The explosion of GWAS has connected adaptive variants to a wide range of health traits. However, transferring these evolutionary insights into genome-informed precision nutrition requires many more studies. Since most existing GWAS do not explicitly consider dietary habits, future studies need to explicitly evaluate the effects of gene-diet interactions and quantify genetic effects across dietary subgroups. Extensive functional experiments in animal models and human subjects are required to elucidate the mechanistic basis. Eventually, clinical trials have to take into account genotypes when evaluating the effect of specific dietary interventions.

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Conflicts of interest

There are no conflicts of interest.

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