

Global impact of micronutrients in modern human evolution

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In this study, Rees et al. evaluate the role of dietary micronutrients in driving local genetic adaptation and population differentiation in humans. The authors find evidence that micronutrient-associated positive selection has shaped human genetic diversity and highlight the potential health risks of changing levels of dietary micronutrients across the globe.



Global impact of micronutrients in modern human evolution

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Summary

Micronutrients are essential components of the human diet, but dietary levels above or below their narrow, recommended range are harmful. Deficiencies increase the risk of stunted growth and metabolic, infectious, and respiratory disorders, and have likely been pervasive in human history, as local soils poor in micronutrients are widespread. Deficiencies are also common today, affecting approximately 2 billion people. Limited evidence exists for selenium, zinc, iodine, and iron deficiencies driving local adaptation in a few human populations, but the broader potential role of micronutrients in shaping modern human evolution remains unclear. Here, we investigate signatures of positive selection in 276 genes associated with 13 micronutrients and evaluate whether human adaptation across global populations has been driven by micronutrients. We identify known and previously undescribed instances of rapid local adaptation in micronutrient-associated genes in particular populations, including previously undescribed individual signatures of adaptation across most of the world. Further, we identify signatures of oligogenic-positive selection in multiple populations at different geographic and temporal scales, with some recapitulating known associations of geology and micronutrient deficiencies. We conclude that micronutrient deficiencies have likely shaped worldwide human evolution more directly than previously appreciated and, given the ongoing depletion of soil quality from over-farming and climate change, caution that some populations may be at higher risk of suffering from micronutrient-driven disorders going forward.

Introduction

The composition of the human diet varies widely across populations, due to both environmentally induced factors and recently introduced cultural practices, most notably the Neolithic revolution.^{1–4} In some cases, components of the diet can act as selective pressures, driving local genetic adaptations to mitigate novel dietary stressors. Selective pressures include culturally introduced practices, such as milk drinking in adulthood,^{5–8} but also challenges posed by local environments, such as nutritionally poor diets,⁹ high fatty acid content of local foods,^{10,11} or the presence of toxic^{12–14} or deficient^{13–19} levels of chemicals in the diet via their accumulation in local plants and animals. Micronutrients are particularly important chemical elements of the human diet and directly dependent on local geology, and they play a central role in a multitude of physiological processes (e.g., metabolism, the maintenance of tissue function, immunity, and healthy growth or development^{20–26}).

Micronutrient is a broad term that includes vitamins and minerals that are essential in very small and specific amounts. They cannot be synthesized within the body (with the exception of vitamin D²⁴) and must instead be absorbed from the diet. However, global soils are highly variable in their levels or bioavailability of micronutrients, even among proximal locations.^{27–29} Soil geology has therefore likely had a tremendous effect on the micronutrient composition of local human diets throughout

much of our species' evolution. In more recent history, human cultural practices, such as agriculture, over-farming, or food practices, may have also disturbed the levels of dietary micronutrients.^{4,27} Potential differences in dietary micronutrients across human populations are of great importance because even slight deviations from their narrow, required range in the diet can result in micronutrient deficiency or toxicity.^{20,21,23,24,26,30}

Micronutrient deficiencies impair mental and physical development and are particularly dangerous in early development.^{20,21,26} The most common deficiencies, those in zinc, iron, iodine, folate, and vitamin A, are associated with increases in birth defects, vision loss, and poor cognitive function and development.^{31–35} Micronutrient deficiency is also pernicious outside key periods of development, increasing the risk of various metabolic, infectious, and respiratory diseases, as well as directly causing anemia, goiter, Kashin-Beck disease, and Keshan disease.^{29,36,37} Diseases induced or exacerbated by micronutrient deficiencies have been insidious across recorded history and likely throughout human evolutionary history, and they also remain a dominant public health concern today.^{20,23,26,38,39} Across the globe, 178 million children under the age of 5 years are estimated to have stunted growth due to micronutrient deficiency.²¹ Excess levels of dietary micronutrients are relatively rare, and typically result in gastrointestinal stress, nausea, vomiting, and diarrhea.³⁰ Most cases of toxicity stem from poor industrial practices poisoning local soils or as a result of excess

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supplementation^{30,40–44} and were likely uncommon throughout most of human history.

Indeed, the limited existing evidence only supports a role of soil-induced micronutrient deficiency as a selective pressure in humans. Selenium-deficient soil in East Asia has been linked to signatures of positive selection in selenium-associated genes such *DIO2* (MIM:601413), *SELENOS* (MIM: 607918), *GPX1* (MIM: 138320), *CELF1* (MIM: 601074), and *SEPHS2* (MIM: 606218).¹⁵ Iodine-deficient rainforest soil has been suggested to drive signatures of positive selection in iodine-associated *TRIP4* (MIM: 604501) and *IYD* (MIM: 612025) in the African rainforest hunter-gatherer Biaka population.¹⁶ Additionally, the rainforest hunter-gatherer Efe populations in Central Africa have lower incidence of goiter, an enlargement of the thyroid gland caused by iodine deficiency, than the neighboring Bantu-speaking populations occupying the same iodine-deficient soil of the Ituri forest (42.9% vs. 9.1%⁴⁵), suggesting the presence of an adaptive response to iodine deficiency in the rainforest hunter-gatherer populations. Finally, low levels of zinc in soil and crops in East Asia are correlated with the frequency of a haplotype of the zinc-transporter *SLC30A9* (MIM: 604604) that has signatures of positive selection in some East Asian populations.¹⁹

However, the overall relevance of micronutrients as selective forces in human evolution remains unknown. First, it is unclear if only micronutrient deficiencies have acted as effective selective pressures in human evolutionary history or if toxic levels of micronutrients, induced by geology or human cultural practices, has also driven genetic adaptation. Second, it is unknown if all micronutrients have acted as effective selective pressures in human evolutionary history or if this is the case for only a few key minerals or trace metals. Finally, it is unclear whether putative genetic adaptation is geographically and temporally widespread or restricted to a few populations under extreme dietary levels of a particular micronutrient. Given the critical role of micronutrients in human health and their variation in dietary levels across human populations, understanding their influence in genetic variation and population differentiation is important to understand not only human evolution but also contemporary health disparities.

Here, we evaluate the role of dietary micronutrients as a selective force in modern human evolution by studying the patterns of genetic variation in gene sets associated with the uptake, metabolism, or regulation of 13 micronutrients in 40 geographically diverse modern human populations. By analyzing about ~300 genes known to play a functional role in the metabolism and function of these micronutrients, with measures of allele-frequency differentiation and genealogical inferences, we identify genomic signatures of positive selection both at the level of individual genes and of the set of genes related to each micronutrient. We find widespread individual signatures of positive selection in multiple genes associated

with different micronutrients at different time points in human evolutionary history, suggesting that micronutrients have been a powerful selective force in modern humans.

Material and methods

Simulation design

We first aim to assess, using simulations, which methods are able to identify even subtle signatures of positive selection in the genome. The forward-simulator SLiM⁴⁶ was used to simulate 100-kbp gene regions undergoing positive selection on standing genetic variation in one of four focal populations: African, European, East Asian, and American (see [Note S1](#)). These simulations feature a simplified demographic model, for example by not including deep structure in Africa^{47–50} (see [Note S1](#)), and are therefore most informative for power in populations with demographic histories similar to those modeled here.

To approximate selection on standing variation, at one of four time points (1, 5, 10, and 40 kya), a single polymorphic allele segregating in the focal population (at frequency between 0.1 and 0.15) was tagged and given a selection coefficient drawn from $U(0, 1)$. A burn-in period was first simulated between 1.66 mya and 70 kya (where population-genetic parameters were scaled to reduce CPU time⁴⁶) before the forward simulation from 70 kya-present covering all population splits, expansions, and migrations as described in [Figure 1A](#), as well as the onset of selection in one time point in one population ([Note S1](#)). For each scenario of positive selection (16 combinations of one selection time point in one metapopulation), ~10,000 simulations where the selected allele remained polymorphic in the focal population were completed. A matched number of simulations were run under neutrality ([Note S1](#)). For each successful simulation (those where the selected allele was not lost), VCF files of 50 individuals for each metapopulation were generated.

Assessing accuracy of methods

We tested the accuracy of seven methods to identify signatures of weak positive selection in the simulated genetic data: iHS, nSL, XPEHH, XPnSL, F_{ST} , tSDS, and Relate (see [Note S2](#)^{53–59}). For each method, we identified SNPs that fall in the extreme 5% tail of neutral distributions as those with signatures of positive selection (where neutral distributions are built from neutral simulations; [Note S2](#); [Figures S2–S9](#)). To evaluate accuracy, we calculated true-positive rate (TPR; percentage of truly selected SNPs that fall in the extreme 5% tails of the neutral distribution), false-negative rate (FNR; percentage of truly selected SNPs that fall outside the extreme 5% tails of the neutral distribution, or 1-TPR), and false-positive rate (FPR; the percentage of non-selected SNPs that fall in the extreme 5% tails of the neutral distribution; discussed in [Note S2](#)). As an additional exploration of the recent Relate method,⁵⁶ we also compared the accuracy of using the raw output ($-\log_{10} p$ value) to using the tails of the neutral distribution to identify SNPs with signatures of positive selection ([Note S2](#), [Figures S10 and S11](#)).

To approximate polygenic selection, we combined simulated gene regions into gene sets. We then evaluated the accuracy of the gene set enrichment method SUMSTAT⁶⁰ to identify polygenic selection. The SUMSTAT method is as follows: for each gene set, the p value of the SNP with the strongest evidence of

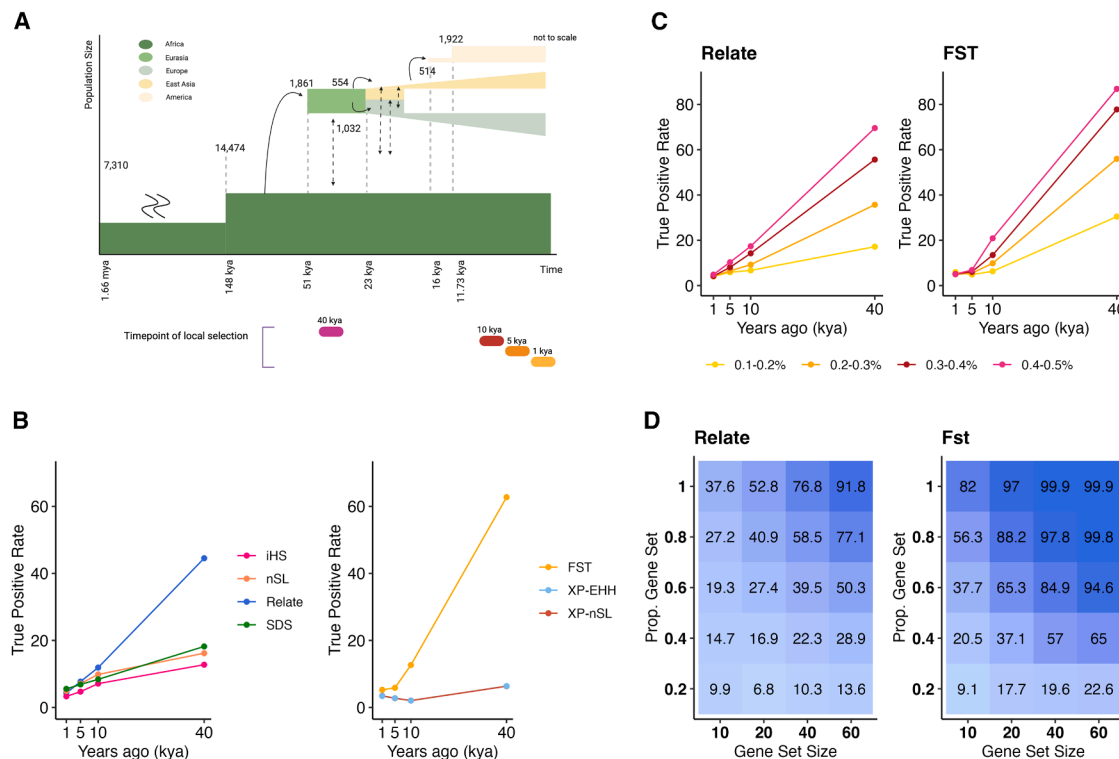


Figure 1. Overview of simulation framework and power analysis

(A) Schematic overview of the simulation design, including demographic model (top; where dashed lines correspond to time points of population splits and changes of effective population size, based on models from the literature^{51,52}) and the variable time points of positive selection (bottom).

(B) Percentage of selected SNPs identified as under positive selection (according to the tail of the neutral distribution; y axis) at four different time points (x axis) for different methods tested on individual populations (left) and between population pairs (right). Both plots represent the simulated African population (other simulated populations for methods tested on individual populations and between population pairs are given in Figures S2 and S3, respectively).

(C) Percentage of selected SNPs identified as under positive selection (according to the tail of the neutral distribution; y axis) at four time points (x axis) for Relate (left) and F_{ST} (right) by simulated selection coefficient (see legend), for the African population (other populations shown in Figures S4 and S5).

(D) Percentage of selected gene sets identified as under positive selection (according to the tail of the neutral distribution; numbers inside matrix) for gene sets of different size (x axis) and different proportion of gene regions under positive selection (y axis) for Relate (left) and F_{ST} (right). Shown for positive selection at 40 kya in the African population; all other time points of selection and simulated populations shown in Figures S12 and S13. Created in BioRender. Rees, J. (2025) <https://BioRender.com/o76t447>.

positive selection (as calculated from the neutral distribution) in each gene region is extracted and summed to give a final score (or SUMSTAT value). SUMSTAT values are compared to the neutral distribution (as generated from applying the SUMSTAT method to 1,000 random gene sets simulated under neutrality), and the gene sets with SUMSTAT values in the extreme 5% tail are identified as those with signatures of positive selection. For our two most powerful methods (F_{ST} and Relate), we evaluated the accuracy of the SUMSTAT method on gene sets of various sizes (10, 20, 40, and 60) and gene sets with varying proportions of true selected gene regions (20%, 40%, 60%, 80%, and 100% gene regions within a gene set under a selection) to consider a range of selection scenarios (Figures S12 and S13).

Micronutrient-associated gene sets

Micronutrient-associated (MA) gene sets were generated from relevant datasets (e.g., Human Metabolome Database⁶¹) and literature searches for each of the 13 micronutrients. The literature used includes clinical studies, functional biochemical studies,

and studies identifying signatures of natural selection (see Data S1). Signatures of natural selection have only been identified in genes associated with selenium, zinc, iron, calcium, and iodine as identified from either genome-wide selection scans or studies of positive selection on gene sets functionally associated with their respective micronutrient.^{15,16,18,19,62–64} All such genes are considered because of their functional associations and make up only a small proportion of the total MA genes (17 of the 276 MA genes, 6.2%). Hence, the ascertainment bias from the literature search in this regard is minor.

In total, we identified 276 genes associated with 13 micronutrients, of which 269 remained after filtering out segments of the genome according to an accessibility mask⁶⁵; see below). The resulting MA genes are largely randomly distributed along the human genome; there are only 11 pairs of MA genes within 10 kbp of each other (Table S11), and, in these few cases, signatures of positive selection cannot be strictly assigned to either of the genes in the pair. Further, some genes are associated with multiple micronutrients; for analyses where this is undesirable (see results), we generated non-overlapping gene sets, where no

overlap exists among sets and each gene is assigned to only the micronutrient for which we consider its most important functional association (Data S1).

We also generated a database of background genomic regions matched to each MA gene. For each MA gene, we sampled 1,500 regions from the human genome, each beginning at the starting genomic coordinate of a random human gene and then matched in exact length to the respective MA gene. Here, we are agnostic to the function of candidate SNPs and match the background-gene regions to the full length of the MA gene. To account for the SNP density of genes within each set, only the 1,000 gene regions with the SNP densities closest to each associated MA gene were retained. The SNP densities were from Yoruba individuals⁶⁵ because matching SNP densities to those of the target populations could result in background genes with unusual evolutionary histories if MA genes are under selection. This results in a random set of gene regions (referred to as background-gene regions) that were used to represent the random genomic background. Seven MA genes have SNP densities significantly above those of their respective background-gene regions, but these do not cluster by micronutrient (Table S12). Background-gene regions were then grouped into gene sets of sizes matched to those of their respective MA-gene sets. These are referred to as background-gene sets.

The population-genetic dataset

Whole-genome sequence data were collected from the HGDP dataset.⁶⁵ Here, we use the assigned populations as proxies for genetic ancestry groups. Small population sample sizes can generate noisy allele frequencies, so 22 populations with small sample sizes (sample size 12 or below) were merged with populations that were genetically very similar and either geographically close or separated by very recent migrations (see principal-component analysis [PCA] and admixture analyses; Figures S14–S20 and Note S3). Three populations had sample sizes below 12 but did not group naturally by geography or genetics. Of these, only the African Ju/'hoan (previously referred to as San by the HGDP; $n = 6$ ⁶⁵) were retained in our dataset given their unique genetic history (Note S3). The final dataset comprises 913 individuals from 40 populations, over eight major geographic areas (Africa, the Middle East, Europe, East Asia, Central-South Asia, Oceania, and the Americas) and represents a significant proportion of human geographic and cultural diversity (Table S13).

Identifying the genomic signatures of positive selection

We used two methods to identify the genetic signatures of positive selection in single loci (F_{ST} and Relate^{56,59}). These methods have high power to identify strong positive selection or selection on *de novo* mutation but also perform considerably better than additional considered methods (see “accessing accuracy of methods”) when considering weaker selection and/or selection on standing variation. Importantly, the signatures of positive selection identified by F_{ST} and Relate are related but subtly different. SNPs with extreme F_{ST} values are the most highly differentiated between populations; a key property of F_{ST} , therefore, is that it can only identify signatures of positive selection that have arisen following the split of the two populations used in each pairwise calculation. Relate, on the other hand, identifies sites that have risen to an unusual frequency, given their age and the number of lineages present when they first arose, over the

entire inferred history of the locus in each population. In reality, this is up to the time of the common ancestor of all populations used in the genealogical inference. Therefore, it is not expected that these statistics will necessarily identify the same SNPs as having signatures of positive selection and, in theory, using both allows us to identify adaptation that has occurred differentially between populations and within the specific inferred history of an individual population.

Before calculating per-SNP F_{ST} , we filtered the VCF files to remove indels, retain only biallelic sites, and retain only the regions given in the accessibility mask.⁶⁵ This mask is based upon the 1000 Genomes Project's strict mask (which removes regions of low coverage and mapping quality⁶⁶) while also removing regions of excess heterozygosity and regions of the GRCh38 genome build that have patch scaffolds or alternative loci. Over our entire dataset, this conservative filtering results in 45,819,591 SNPs. Per-SNP F_{ST} was then calculated for all autosomal SNPs with the Weir and Cockerham method in VCFTOOLS.^{59,67} We calculated pairwise F_{ST} for all populations vs. the African Yoruba to capture allelic differences (1) of all populations against the same population and (2) between African and non-African populations. The analysis with F_{ST} thus most explicitly focuses on adaptation following the out-of-Africa migration,⁶⁸ but we note that elevated F_{ST} shared over many non-African populations can also indicate adaptation in the Yoruba population. To recognize that diverse environments^{69–74} may also drive adaptations within Africa, we also calculated F_{ST} for all African population pairs, which are presented in Figure S32.

To leverage as much information as possible, we used all 929 individuals in the HGDP dataset⁶⁵ to infer the genealogical trees with Relate.⁵⁶ We filtered the VCF dataset to retain only biallelic sites and those regions retained in the accessibility mask.⁶⁵ We also removed SNPs with more than 10% missing data, as recommended for phasing.⁷⁵ Phasing was performed with SHAPEIT 2 (0.3-Mb window size and 200 conditioning states⁷⁵), resulting in 47,299,072 SNPs that were used for tree inference. Before running Relate, we followed the advised pre-processing step⁵⁶ that determines the ancestral state of variants (using the ancestral human genome from Ensembl⁷⁶), adjusts the distances between SNPs (necessary when using a mask to remove regions), and generates an additional annotation file (detailing the upstream and downstream alleles and the number of carriers of the derived allele in each population). Genealogical trees were then inferred along the genome with Relate. We then restricted our analysis to the 913 individuals representing our 40 populations. For each of the 40 populations in our dataset, we extracted and re-inferred their genealogical trees, simultaneously estimating population size changes, branch lengths, and average mutation rate. We used the DetectSelection module in Relate to calculate the probability under neutrality of each autosomal SNP reaching its observed frequency today, given its inferred genealogical history. This latter step was also done for each of the 40 populations individually.

Signatures of positive selection in MA genes

F_{ST} values and Relate probabilities were extracted for all SNPs spanning 10 kbp up- and downstream of each MA-gene coordinates. For each population (or population pair), SNPs that fall in the tails of the F_{ST} and Relate empirical distributions (built from all SNPs along the genome) were identified as those with signatures of positive selection. This empirical approach frees us from requiring inferred demographic models that do not exist

for these populations, and the SNPs identified will be enriched for true targets of positive selection—even if not every SNP is a true target. Further, while the raw output of Relate can be used to identify candidate SNPs, using the tails of the empirical distribution increases accuracy in populations of smaller sample sizes (similar in size to those used here; [Figure S10](#)). For this case, the tail of the empirical distribution of Relate identifies SNPs that have an unusually fast spread compared to all other SNPs within this population's inferred history.

When considering signatures at the SNP level, we label the SNPs in the 0.1% tail of either the F_{ST} or Relate empirical distribution as having individual signatures of positive selection. We refer to these as candidate SNPs. When considering signatures across entire MA-gene sets, we label the SNPs in the 5% tail of the empirical distribution as significant SNPs, potentially contributing to polygenic adaptation in that gene set.

For all MA-gene SNPs, the empirical p values of F_{ST} and Relate have a weak correlation (r varies between 0.02 and 0.032) that is nevertheless significant ($p\text{-value} < 2 \times 10^{-16}$), likely due to the very large number of datapoints ([Table S14](#)). When only considering significant SNPs identified by F_{ST} and with a lower frequency in the Yoruba population, this weak, positive correlation becomes insignificant in the African Mandenka and Jul'hoan populations ([Table S15](#)). These two methods thus identify slightly related, but not fully overlapping, sets of significant and candidate SNPs.

We first evaluated whether there is an excess of SNPs with signatures of positive selection across each micronutrient by comparing, using a chi-squared test, the observed number of candidate and significant SNPs across entire MA-gene sets to the expected number of SNPs above each significance threshold (5% or 0.1% of the total number of SNPs, respectively). This was repeated for each MA-gene set separately, testing for an enrichment of SNPs at the 5% significance level only.

To explicitly investigate the signatures of polygenic adaptation in individual micronutrients, we used the gene set enrichment method SUMSTAT.^{60,77} For each population and MA-gene set combination, and separately for F_{ST} and Relate, the p value of the top-ranking SNP of each gene in the set (as calculated from the empirical background distribution) was extracted. In the case of SUMSTAT values calculated from F_{ST} , we only consider F_{ST} calculated between Yoruba and each test population. These p values were summed across each MA-gene set to generate a summed MA-gene set value, or SUMSTAT value, for each micronutrient. The SUMSTAT values for each micronutrient were then compared to summed values calculated for each population from 1,000 background-gene sets (see section “[micronutrient-associated gene sets](#)”). Micronutrients with SUMSTAT values that fall in the 5% tail of this background distribution were identified as candidates for polygenic adaptation.

We isolate the MA genes with the most extreme evidence of positive selection (passing our stringent Bonferroni threshold; $p \leq 4.65 \times 10^{-6}$) as candidates for driving monogenic adaptation (see section “[positive selection on individual MA genes](#)”). To explore whether top-ranking SNPs may be adaptively introgressed from archaic humans, we determined which SNPs fall in regions previously inferred as introgressed from Neanderthal and Denisovan (see [Note S4](#)^{78,79}).

Inferring time of positive selection

We use CLUES2⁸⁰ to estimate the strength and likelihood of selection from generations 500, 1,000, 1,500, and 2,000 (correspond-

ing to time points beginning at 14, 28, 42, and 56 kya; [Data S4](#)). This method leverages inferred local trees to jointly estimate the timing and strength of selection, using a hidden Markov model that treats inferred local trees as the observed state and the allele-frequency trajectory as the hidden state.^{80,81} Signatures of positive selection were identified in SNPs with $p \leq 0.001$; a cutoff of $p \leq 1 \times 10^{-10}$ was used to identify the SNPs with the strongest evidence of positive selection ([Figures S22–S30](#)).

Building haplotype networks

Haplotype networks were built for 10-kbp regions surrounding candidate SNPs (see [Table S8](#)) in three zinc-associated genes with geographically widespread signatures of positive selection (identified in more than 10 populations) at the more stringent threshold of $p < 0.0001$. The candidate SNPs chosen for this analysis were those with signatures of positive selection identified in the highest number of populations ([Table S8](#)). These regions were extracted from the phased data (see section “[identifying the genomic signatures of positive selection](#)”) and used to build a median joining tree network in POPART.⁸²

Results

Simulating positive selection in human populations and power results

We first evaluate the power of different methods to identify diverse signatures of positive selection ([Figure 1](#)). Many current methods to identify the genomic signatures of positive selection have good power for strong selection on *de novo* mutations^{53,83–86} but have considerably lower power when selection is weak, on standing variation or polygenic. Identifying the subtler signatures of positive selection is important, however, given that selection on standing variation likely plays a significant role in local adaptation in modern humans^{83,87–89} and that many complex traits, such as micronutrient uptake or metabolism, are polygenic in nature.^{15,60,90–92}

For this reason, we designed simulations to test the power of commonly used methods to identify the signatures of positive selection on standing genetic variation at both the monogenic and polygenic level at four time points (1, 5, 10, and 40 kya) in four simulated populations (African, European, East Asian, and American) and two strengths of selection (0.001 and 0.005) ([Figure 1](#), section “[material and methods](#)”; [Note S1](#)), as well as neutral simulations under the same demographic model. To assess power, we simulated the process of identifying SNPs with signatures of positive selection by identifying selected SNPs that fall in the extreme 5% tail of the neutral distribution ([Note S2](#)). This allows us to calculate the TPR (the percentage of selected SNPs with evidence of positive selection).

We evaluated methods that identify candidate SNPs as those with unusual allele-frequency differentiation between populations (F_{ST} ⁵⁹), extended haplotype homozygosity (iHS, nSL, XPEHH, and XPnSL^{53–55,58}), and unusual local inferred genealogies, such as those with short terminal tips (SDS⁵⁷) or indicative of unusually rapid allele-frequency increase (Relate⁵⁶) ([Note S2](#)).

For all methods, and as expected, the TPR is highest for the oldest simulated selection (positive selection initiated 40 kya; [Figures S2 and S3](#)). The haplotype-based methods and SDS have relatively low power in our simulations at all time points ($\text{TPR} \leq 19$; see [Note S2](#); [Figures S2 and S3](#)), likely because we model selection on standing variation. In contrast, the allele-differentiation method (F_{ST} ⁵⁹) and the tree-recording method (Relate⁵⁶) have appreciable power when selection starts 40 kya ($\text{TPR} \geq 51.6\%$ and $\geq 27.4\%$ for F_{ST} and Relate, respectively; [Figures 1B, S2, and S3](#)), and they retain power higher than or equal to the other methods for younger selection ([Figure 1C](#)). Also as expected, TRP improves with stronger selection: TPR is as high as 69.6% and 86.9% for Relate and F_{ST} , respectively, when selection in the simulated African population has selection coefficients between 0.04% and 0.05% ([Figure 1C](#); all other simulated populations and time points shown in [Figures S4 and S5](#)).

Finally, we simulated polygenic selection by grouping simulated gene regions into gene sets of variable size ([Figures 1A and 1E](#)) and using the gene-set method SUMSTAT,^{60,77} which sums the strongest evidence of positive selection for each gene within a gene set and compares this sum to that of a comparable neutral distribution (see section “[material and methods](#)”). We run SUMSTAT with the two best-powered methods: F_{ST} and Relate. SUMSTAT performs notably better when based on F_{ST} than Relate for positive selection initiated at 40 kya ([Figures 1D, S12, and S13](#)), but both perform well when gene sets are large and all genes in the set are selected (where F_{ST} and Relate have TPR of $\geq 99.9\%$ and $\geq 76.8\%$, respectively, for gene sets of size 40 or larger). Power drops for gene sets that are smaller or contain neutral genes ([Figure 1D](#)) and, naturally, for more recent selection (e.g., $\text{TPR} \leq 53.9\%$ for large gene sets containing only selected genes with selection at 10 kya or earlier; [Figures S12 and S13](#)). Still, power remains appreciable even when many genes in a set evolve neutrally; for example, for selection starting 40 kya, F_{ST} maintains a TPR of ≥ 84.9 when gene sets contain 40 genes or more and only 60% of genes are under selection ([Figure 1D](#)).

While these power estimates are specific to our particular model and should not be considered universally accurate, they allow us to select the best methods for this study. Following this analysis, we selected Relate⁵⁶ and F_{ST} ⁵⁹ to identify signatures of positive selection in MA genes in genomic data. These methods have the highest power to identify selection on standing variation and are, in our view, most suited to identifying the varied signatures that accompany positive selection. The combination of these two methods can also be informative; Relate calculates the probability of selection since the onset of mutation, which typically predates the split of populations, and as a consequence is more likely to detect selection on *de novo* mutations that are typically old enough to be shared among populations. In contrast to Relate, F_{ST} identifies only local adaptation post-dating the split of

the population pair and has equal power for selection on standing variation. Using both methods not only maximizes power to identify local adaptation but can also allow us to make a finer-scale inference of the evolutionary history of the alleles.^{89,90}

Gene and population datasets

We investigate the evolutionary history of gene sets associated with 13 micronutrients, selected based on their importance in public health and our knowledge of the genetic basis of their biology^{15,20–26,63,93–104}: calcium, chloride, copper, iodine, iron, magnesium, manganese, molybdenum, phosphorus, potassium, selenium, sodium, and zinc. This includes all trace metals and macrominerals ([Table S1](#)), with the exception of fluoride and sulfur, which were omitted due to limited knowledge of their functionally associated genes in humans. For similar reasons, this study does not investigate the role of the 13 essential vitamins in human adaptation.

We manually curated gene sets associated with the uptake, regulation, and metabolism of these micronutrients ([Table S1](#), section “[material and methods](#)”). After filtering for genome accessibility⁶⁵ (“[material and methods](#)”), a total of 269 MA genes (henceforth referred to as MA genes; [Data S1](#)) are included across the 13 MA-gene sets. Random sets of gene-containing genomic regions approximately matched in length and SNP density to the genes in each MA-gene set, and therefore representative of comparable genomic regions, were generated to serve as proxies of random genomic backgrounds. These are henceforth referred to as background-gene sets.

Patterns of genetic variation in MA genes were analyzed in the global HGDP dataset,⁶⁵ which contains 929 individuals sequenced to an average 35× coverage from geographically and culturally diverse populations over seven major continental regions (Africa, Middle East, Europe, Central-South Asia, East Asia, the Americas, and Oceania). Of the populations with the smallest sample size, two were discarded and 22 were merged with populations of very high genetic similarity, generating a final dataset of 913 individuals in 40 populations, with an average sample size of 23 individuals each (see section “[material and methods](#)”; [Note S3](#); [Figures S14–S20](#)). We note that merging populations may reduce sensitivity but will not generate false positives in signatures of local adaptation.

Our 269 MA genes contain 477,029 SNPs (MA-SNPs) across the 40 populations. The distribution of allele frequencies of SNPs across each MA-gene set in Yoruba (which we use as our background population) fits expectations based on chromosome 1 for all micronutrients except for molybdenum ([Table S2](#)). The molybdenum-associated gene set is the smallest MA-gene set in our study ($n = 5$) with its SNPs displaying unusually high allele frequencies (mean allele-frequency difference between these SNPs and chromosome 1 = 0.082; $p = 2.2 \times 10^{-16}$), largely due to the SNPs in the *GPHN* (MIM: 603930) and *MOCS2* (MIM: 603708), indicating possible

selection in these genes in the Yoruba population and otherwise; see section “[positive selection in individual micronutrients](#)”). Still, higher background allele frequencies can bias inferences of local adaptation, so we interpret signatures of positive selection in the molybdenum-associated genes with extreme caution—while confirming that this is not an issue for any of the other MA sets.

MA positive selection

To investigate whether positive selection has shaped the evolution of MA genes in humans, we identify signatures of positive selection in each MA-gene SNP in each population using the tails of the empirical distribution of *Relate*⁵⁶ and *F_{ST}*⁵⁹ (see section “[material and methods](#)”). We calculate *Relate* probabilities for positive selection across the entire genome for each of the 40 populations in our dataset and calculate *F_{ST}* values per SNP between each worldwide population and Yoruba as well as between all population pairs within Africa.^{56,59} SNPs in the extreme 0.1% tail of the empirical distribution (empirical *p* value <0.1%) of each population (*Relate*) or population pair (*F_{ST}*) are considered candidate SNPs and their respective MA genes as candidate MA genes, while those in the 5% empirical tails, the significant SNPs, are considered only for polygenic selection.

First, we consider the evidence that micronutrients, as a group, can be considered an important selective driver in modern humans. For each population, we assess whether MA genes are enriched with signatures of positive selection by evaluating whether the number of SNPs in the 5% and 0.1% tail (significant and candidate SNPs, respectively) across all MA genes is significantly higher than neutral expectations (the same percentage of all SNPs across all MA genes).

When considering the number of significant SNPs identified by *F_{ST}*, the majority of populations (25 out of 40) have significantly more SNPs compared to neutral expectations, with an average enrichment of 8.5% and up to 14.8% more SNPs than expected by chance (chi-squared *p* values <0.05; [Data S2](#)). When only considering candidate SNPs (empirical *p* value <0.1%), 21 populations show an excess of SNPs in MA genes compared to neutral expectations (with an average enrichment of 56.6% and up to 106% more SNPs than expected by chance; chi-squared; all *p* values <0.05; [Data S2](#)). This unusually high genetic differentiation of SNPs in these genes suggests that, as a group, micronutrients may have been an important selective force driving genetic adaptation in modern humans.

Intriguingly, the picture is slightly different for *Relate*, with no populations showing more significant SNPs than expected under neutrality and only nine populations showing more candidate SNPs than expected under neutrality (although with an average enrichment of 45.7% and up to 82.9% more SNPs than expected by chance; chi-squared; *p* value <0.05; [Data S2](#)). As

mentioned above, differences between *F_{ST}* and *Relate* may drive this discrepancy and point to the nature of the selective events. While the results of *Relate* show very strong evidence of positive selection in a small number of genes, the many more SNPs with *F_{ST}* signatures suggest micronutrient-related genetic adaptation may largely be local and/or on previously neutral standing variation.

Positive selection in individual micronutrients

To establish whether the patterns above are due to widespread adaptation across all micronutrients or driven by only a few micronutrients, we repeat the analysis for each individual MA-gene set ([Figure 2](#)). As expected, for the majority of populations, most micronutrients show no excess of significant SNPs in their respective gene sets, indicating that most micronutrients have not driven widespread, global adaptation. On the contrary, and in line with expectations of long-term purifying selection, 137 of the 507 possible micronutrient and population combinations have a statistically significant deficit of significant SNPs (those in the 5% empirical tail) in their respective MA-gene set according to both *Relate* and *F_{ST}*. Nevertheless, all micronutrients show an excess of SNPs in their respective gene set in at least one population, and sometimes in many ([Figure 2](#)). Positive selection may therefore have been driven by several different micronutrients, albeit at local geographic scales and specific time points.

Of the 507 possible micronutrient and population combinations, 45 have a statistically significant excess of significant SNPs (those in the 5% empirical tail) in their respective MA-gene set according to both *Relate* and *F_{ST}* (chi-squared; *p* value <0.05; [Data S2](#)). These represent the most reliable excess of significant SNPs, strongly suggesting the presence of selective pressures associated with the relevant micronutrient in the given population. Notable examples include the excess of significant SNPs identified in genes associated with selenium in three East Asian populations, in agreement the proposed link between low dietary selenium across East Asia¹⁵ and evidence of polygenic or oligogenic adaptation (where oligogenic selection is selection that acts on multiple genes but fewer than considered in classic models of polygenic adaptation). This includes¹⁵ the Yakut, Xibo-Mongolian, and Japanese, which show an excess of 17%, 22%, and 8.6% of significant SNPs when compared with random expectations (see section “[materials and methods](#)”) with *Relate*, and an excess of 40%, 38% and 20% with *F_{ST}* ([Data S2](#)). Further, with *F_{ST}* all East Asian populations have a significant excess of significant SNPs of at least 18%. However, the most striking example is the set of iodine-associated genes of the American Maya, which shows the highest significant excess of significant SNPs over both methods: an excess of 79% and 50% with *Relate* and *F_{ST}*, respectively.

The genes associated with molybdenum show an excess of *Relate* and *F_{ST}* significant SNPs in many

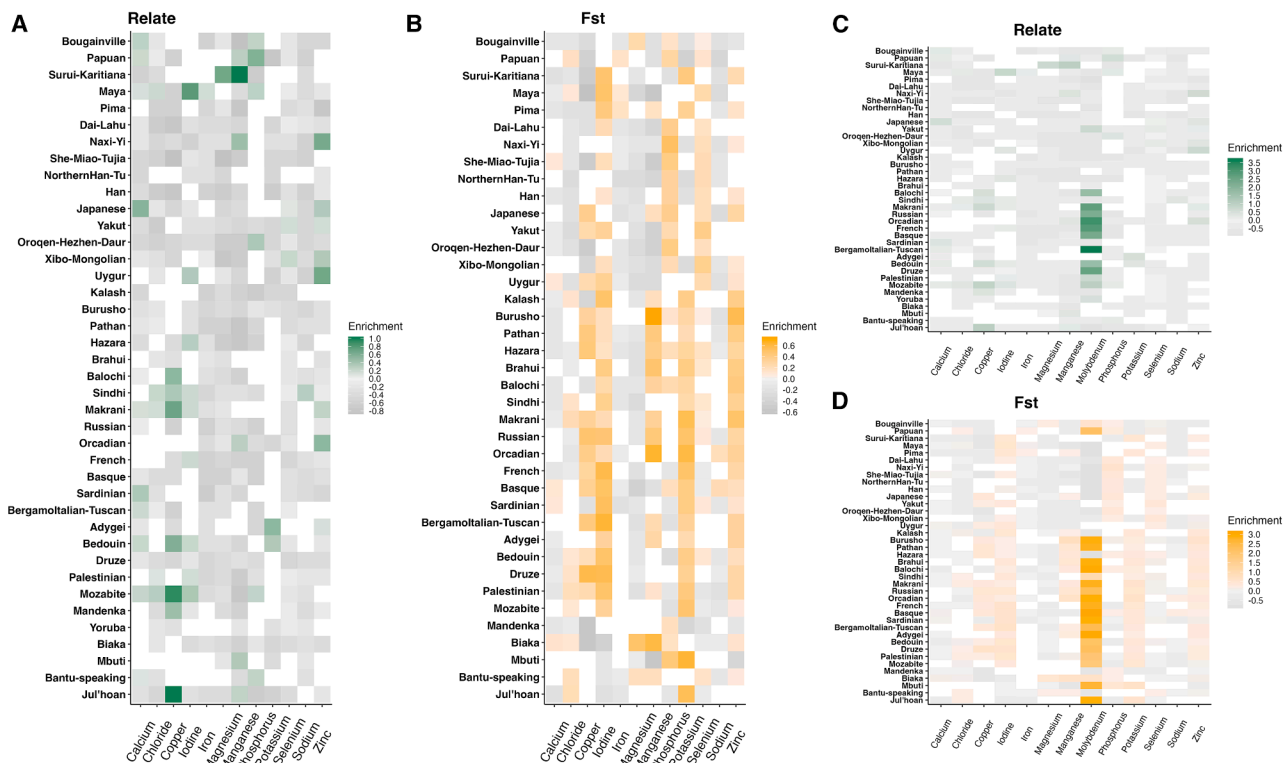


Figure 2. Populations showing a significant excess or deficit of significant SNPs for sets of genes associated with each micronutrient

The excess of significant SNPs for *Relate* and F_{ST} in each population and micronutrient gene set are shown. Significance is calculated by a chi – squared test (comparing the number of SNPs observed in the 5% tail to the expected 5% of total SNPs); gray shows a significant deficit (fewer SNPs in the tail than expected), and green and orange show a significant excess (more SNPs in the tail than expected, for *Relate* and F_{ST} , respectively). (A and B) All MA-gene sets excluding molybdenum for *Relate* and F_{ST} , respectively; (C and D) including the molybdenum gene set for *Relate* and F_{ST} , respectively.

populations (Figure 2), but this appears to be driven by the high number of significant SNPs in two genes, *GPHN* and *MOCS2*, in this very small gene set ($n = 5$). The SNPs in these two genes have high allele frequencies in Yoruba (see section “gene and population datasets”), where elevated F_{ST} may represent selection in this West African population. Still, there is an excess of signatures of positive selection inferred by *Relate* in the molybdenum dataset in many non-African populations, making this a complex but intriguing result worthy of follow-up work.

Given that many MA-gene sets are enriched in significant SNPs according to both *Relate* and F_{ST} (Figure 2), positive selection signatures appear to be present in several SNPs in the same gene set. This is consistent with oligogenic adaptation (signatures in some genes in each gene set, perhaps boosted by linkage disequilibrium in individual genes under selection) but can also be due to highly polygenic adaptation (signatures in many genes in each gene set) or strong monogenic adaptation (selective sweeps with strong linkage disequilibrium in individual genes), or every scenario in between. To understand the role of adaptation to micronutrients in shaping human evolution and differentiation, we must turn to deter-

mining which model best explains the observed signatures of positive selection.

Polygenic positive selection

Polygenic positive selection is perhaps the most likely possible mechanism of MA adaptation given (1) the large number of genes associated with micronutrient uptake, metabolism, and regulation^{15,22,23}; and (2) the importance of polygenic adaptation in mediating complex trait adaptation.^{84,91,105} We therefore test the presence of signatures of polygenic adaptation using the gene set method SUMSTAT^{60,77} for each micronutrient and population combination (see section “material and methods”). In brief, this method tests for evidence of polygenic adaptation by combining the strongest evidence of positive selection for each gene within a functional gene set and comparing it with random expectations. We classify micronutrients as having evidence of polygenic selection if the SUMSTAT value falls in the 5% tail of an empirical distribution built from background-gene sets that represent the random genomic background (see section “material and methods”).

All micronutrients, with the exception of molybdenum, have SUMSTAT values within the 5% tail of the

background distribution (built from either Relate or F_{ST} summed values; [Table S3](#)) in one or more populations. Of these, seven micronutrients (phosphorus, sodium, potassium, iodine, calcium, zinc, and selenium) have SUMSTAT values in the 1% tail of the background distribution in one or more populations (see [Table 1](#)). The SUMSTAT values of potassium and phosphorus remain significant even up to the 0.01% tail ([Table 1](#)). Nevertheless, none of them reach the stringent Bonferroni correction threshold $p \leq 9.62e^{-5}$.

If we remove overlapping genes (so that no genes are present in more than one MA-gene set; see [Table S4](#) for details), only the SUMSTAT values of phosphorus, selenium, and iron fall in the 5% tail of the neutral distribution of either Relate or F_{ST} SUMSTAT values in one or more populations. Of these, only the SUMSTAT values of phosphorus in the American Pima population and selenium in the East Asian Xibo-Mongolian population fall in the 1% tail of the background distribution ([Table 1](#)). The limited signatures of polygenic selection inferred from SUMSTAT are thus largely driven by a small number of genes that are functionally associated with multiple micronutrients ([Table 1](#)). Perhaps unsurprisingly, likely targets of positive selection include genes relevant to the biology of multiple micronutrients.

Thus, there is limited evidence of highly polygenic adaptation. In agreement with this, for any individual population, candidate SNPs are found in less than 30% of all genes associated with any micronutrient for Relate and 50% or less for F_{ST} ([Figure S21](#); [Data S3](#)). Still, all MA-gene sets, with the exclusion of those associated with potassium and molybdenum, contain candidate SNPs in three or more genes identified by either Relate or F_{ST} . Six MA-gene sets (those associated with calcium, chloride, iodine, iron, selenium, and zinc) contain candidate SNPs in five or more genes identified by Relate or F_{ST} . In these gene sets, candidate SNPs are identified in as many as seven or 11 genes (as inferred by Relate or F_{ST} , respectively). As such, it does not appear that the observed signatures of positive selection are solely driven by singular genes with strong linkage disequilibrium (LD). Instead, we propose that positive selection acting on multiple genes is common across micronutrient categories, compatible with the oligogenic model of local adaptation.

Positive selection on individual MA genes

Although MA adaptation at the gene set level may be largely mediated by oligogenic adaptation, some adaptations may still be monogenic in nature, as in other cases of dietary adaptation.^{7,9,12,106} To explore such cases, we isolate the MA genes with extreme individual evidence of positive selection as inferred by Relate or F_{ST} ($p \leq 4.65e^{-6}$, falling below the threshold for Bonferroni multiple-testing correction; [Table 2](#)) and present these 15 MA genes as “extreme candidates” for mediating individual

micronutrient adaptation. We do not consider genetic adaptation in these genes exclusive to the populations listed in [Table 2](#) (many of these genes are candidate genes in numerous other populations; see “[a global view of MA adaptation](#)”), but they remain the strongest candidate populations.

Of the 15 extreme candidate MA genes, 10 genes have extreme candidate SNPs in up to three populations, and two genes have extreme candidate SNPs in seven or more populations across the Middle East, Europe, and Central-South Asia (the phosphorus-associated *PDE7B* [MIM: 604645] and the sodium, chloride, and potassium-associated *SLC12A1* [MIM: 600839]; [Table 2](#)). In these latter cases, signatures of selection are therefore both strong and geographically widespread.

Not surprisingly, a good number of extreme candidate MA genes belong to MA-gene sets with limited evidence of adaptation across multiple genes ([Data S3](#)). This includes the magnesium-associated genes of *MECOM* (MIM: 165215) and *MLN* (MIM: 158270) in Central-South Asian populations, which are thus likely mediators of monogenic, rather than oligogenic, adaptation. Conversely, other belong to MA-gene sets with evidence of oligogenic adaptation (e.g., the zinc-associated genes in Eurasian populations; see “[zinc: candidate for widespread adaptation](#)”) and they may not be mediating monogenic adaptation per se, and instead may act as the major drivers of adaptation in that gene set.

Timing of positive selection on iron- and calcium-associated genes

Of the 15 MA genes with extreme candidate SNPs, three are associated with either iron or calcium ([Table 2](#)) and could represent rapid micronutrient adaptation with cultural selective drivers. The dietary changes during the Neolithic revolution, such as the transition from nutrient-rich animal products to cereals and staple crops, resulted in drastic reductions of iron and calcium in the diet,^{1,3,4} which may have driven rapid and recent genetic adaptation in the affected populations.

To establish whether positive selection on iron- and calcium-associated genes co-occurred with the recent dietary changes of the Neolithic revolution, or if selection was older and more likely driven by the migration into novel soil environments, we use CLUES2 to infer the likelihood of selection at different time points across 19 candidate SNPs of iron- and calcium-associated genes (including those extreme candidate SNPs; see [Note S5](#) and [Table S5](#) for criteria in choosing these SNPs). The inference of CLUES2⁸⁰ was run at four informative time points: just after the out-of-Africa migration (2,000 generations; 56 kya), first migrations to Eurasia (1,500 generations; 42 kya), approximate time of major migrations within Eurasia (1,000 generations; 28 kya), and the approximate beginning of the Neolithic transition (500 generations; 14 kya).

CLUES2 identifies signatures of positive selection ($p \leq 0.001$) in three or more populations for each of

Table 1. The SUMSTAT values of all micronutrients and populations within the 1% tail of the empirical distribution of either Relate or F_{ST}

	All genes		Non-overlapping genes		
Population	Relate significance	F _{ST} significance	Relate significance	F _{ST} significance	Genes removed
Phosphorus					
Pima	0.000013	0.556044	0.005012	0.972050	CASR (MIM: 601199; calcium)
Mandenka	0.818281	0.006715	0.984136	0.068766	
Sodium					
Adygei	0.000029	0.028808	0.056801	0.875837	SLC5A5 (MIM: 601843; iodine); HSD11B2 (MIM: 614232] potassium); SLC12A1 (MIM: 600839; potassium, chloride)
Makrani	0.176685	0.000480	0.918623	0.312685	
Brahui	0.001150	0.026743	0.588617	0.867201	
Bougainville	0.003455	0.146640	0.343165	0.949697	
Russian	0.004935	0.017819	0.336204	0.809297	
Pathan	0.004951	0.228682	0.818310	0.981016	
Ju 'hoan	0.005700	0.263232	0.421653	0.989004	
Orcadian	0.005823	0.016658	0.512330	0.859558	
French	0.006133	0.013281	0.619952	0.806131	
Surui-Karitiana	0.620187	0.006800	0.941481	0.766029	
Potassium					
Bantu-speaking	0.222493	0.000043	0.999448	0.163764	SCNN1A (MIM: 600228; sodium); SCNN1B (MIM: 600760; sodium); SCNN1D (MIM: 601328; sodium); SCNN1G (MIM: 600761; sodium) PTH (MIM: 168450; potassium)
French	0.000322	0.008800	0.993678	0.997444	
Orcadian	0.443830	0.001556	1.000000	0.992561	
Surui-Karitiana	0.418921	0.001698	0.999134	0.999696	
Russian	0.017106	0.002343	0.999301	0.990527	
Bergamo Italian-Italian	0.002963	0.029975	0.998941	0.999006	
Bougainville	0.003722	0.079932	0.850007	0.999604	
Palestinian	0.033025	0.005466	0.994873	0.997447	
Mozabite	0.033461	0.008791	0.997262	0.994528	
Kalash	0.038729	0.009572	0.988635	0.992443	
Iodine					
Maya	0.000325	0.101934	0.352666	0.999365	DIO1 (MIM: 147892; selenium); DIO2 (MIM: 601413; selenium); DIO3 (MIM: 601038; selenium)
Mozabite	0.006333	0.717484	0.721672	0.999662	
Russian	0.009037	0.438001	0.738631	0.999544	
Calcium					
Mandenka	0.104698	0.000912	0.945878	0.289385	KCNJ10 (MIM: 602208; potassium); SLC12A1 (MIM: 600839; potassium, chloride); SLC34A1 (MIM: 182309; phosphorus); SLC34A3 (MIM: 609826; phosphorus)
Biaka	0.184204	0.001264	0.991495	0.406607	
Mozabite	0.007348	0.687845	0.613761	0.994571	
Zinc					
Kalash	0.257221	0.004891	0.877790	0.361498	SLC11A1 (MIM: 600266; iron); SLC30A10 (MIM: 611146; manganese, magnesium); SLC39A14 (MIM: 608736; manganese)
Selenium					
Xibo-Mongolian	0.021710	0.009930	0.021710	0.009930	–

Clustering of populations by Relate SUMSTAT p values for each full micronutrient gene set are shown in [Figures S22–S34](#). The p values calculated for the equivalent gene sets with no overlapping genes are given to the right. The “Genes Removed” column lists the genes removed from the non-overlapping gene sets (with their MIM numbers and other micronutrient associations given in brackets). Italics indicate values within the 1% tail of the empirical distribution.

Table 2. Genes, their micronutrient associations, and populations with *p* values below the multiple-testing threshold of $4.65e^{-6}$

Gene	MIM numbers	Micronutrient	Population	Relate significance	F _{ST} significance
<i>ATP2B2</i>	108733	calcium	Mandenka	0.000187	<i>7.75e−8</i>
			Sardinian	<i>2.10e−7</i>	0.000969
<i>THRB</i>	190160	iodine	Palestinian	<i>3.23e−6</i>	0.00159
<i>FTMT</i>	608847	iron	Yakut	<i>3.37e−6</i>	0.000827
<i>HIF1A</i>	603348	iron	Basque	<i>2.43e−6</i>	0.000249
<i>MECOM</i>	165215	magnesium	Brahui	<i>1.26e−6</i>	0.000225
<i>FXD2</i>	601814	magnesium	Uygur	<i>2.80e−6</i>	0.00923
<i>GALNT3</i>	601756	phosphorus	Jul'hoan	0.0849	<i>3.5e−6</i>
<i>PDE7B</i>	604645	phosphorus	Druze	0.000586	<i>8.16e−7</i>
			Bergamo Italian-Tuscan	0.000678	<i>2.92e−6</i>
			Sardinian	0.00366	<i>7.02e−7</i>
			Basque	0.00522	<i>2.00e−6</i>
			French	0.000500	<i>4.28e−6</i>
			Orcadian	0.00194	<i>2.24e−6</i>
			Brahui	0.000618	<i>1.53e−6</i>
<i>MLN</i>	158270	phosphorus	She-Miao-Tujia	<i>4.27e−6</i>	0.00460
<i>SCNN1D</i>	601328	sodium, potassium	French	<i>1.87e−6</i>	0.000684
<i>SLC12A1</i>	600839	sodium, chloride, potassium	Palestinian	0.000137	<i>6.37e−7</i>
			Druze	<i>3.61e−05</i>	<i>2.97e−7</i>
			Bedouin	0.00571	<i>1.25e−6</i>
			Adygei	0.00481	<i>2.01e−6</i>
			Bergamo Italian-Tuscan	0.0128	<i>1.58e−6</i>
			Basque	0.000855	<i>2.00e−6</i>
			French	0.000224	<i>7.65e−7</i>
			Russian	0.000519	<i>1.40e−6</i>
			Brahui	0.00106	<i>1.07e−6</i>
			Balochi	0.0129	<i>1.76e−6</i>
			Kalash	0.0504	<i>2.56e−6</i>
<i>SLC4A5</i>	606757	sodium	Russian	<i>3.83e−6</i>	0.000160
<i>SLC30A9</i>	604604	zinc	Han	0.00228	<i>3.55e−6</i>
<i>SLC39A11</i>	616508	zinc	Makrani	<i>1.40e−6</i>	0.0003304
<i>SLC39A4</i>	607059	zinc	Makrani	0.0934	<i>3.95e−6</i>

Given alongside their associated micronutrient and accompanied by the *p* value calculated by the other method to identify selection. Italics indicate values below the multiple-testing threshold of $4.65e^{-6}$.

the 19 candidate SNPs in the calcium- and iron-associated genes (Figures 3 and S22–S30; Data S3). For most calcium- and iron-associated genes, strong evidence for positive selection is identified at time points surrounding major migrations, often in clusters within particular regions in Eurasia (Figure 3), in support of positive selection coinciding with the colonization of novel Eurasian environments. There are a few exceptions where the strongest evidence for positive selection is at the most recent time point in certain popu-

lations, but, overall, SNPs in these genes often have very similar evidence for positive selection across different time points (Figures 3 and S22–S30), so we are largely unable to distinguish among the tested time points when positive selection was most likely. Positive selection on calcium- and iron-associated genes is thus unlikely to have been exclusively driven by the recent dietary changes of the Neolithic, although recent positive selection may have shaped the evolution of a small number of genes in particular



Figure 3. The populations with the strongest evidence for positive selection

The populations with the strongest evidence for positive selection as inferred by CLUES2 ($-\log_{10} p \text{ value} > 3^{80}$) for candidate SNPs (where positions are given according to genome build hg38) in (A) calcium-associated genes *ATP2B2*, *ATP2B4*, *SLC8A1*, *SLC8A2*, and *SLC8A3* and (B) iron-associated genes *FTMT*, *ARHGEF3*, *SLC40A1*, and *FTMT*.

Points colored by the generations for which the evidence of positive selection is observed (see legends on the right); black points indicate that the evidence for selection is equal across all four tested time points.

geographic areas (e.g., Central-South Asia for the calcium-associated *SLC8A1* [MIM: 182305]).

A global view of MA adaptation

Stringent significance thresholds are necessary to robustly identify signatures of monogenic and oligogenic positive selection but allow weaker cases of positive selection to remain hidden. As such, they can result in a limited picture of the geographic distribution of putative adaptations.

To provide a more comprehensive picture of MA-mediated genetic adaptation, we summarize the distribution of signatures of positive selection identified by Relate across all MA genes and populations in Figure 4 (see Figure S31 and S32 for signatures of positive selection identified by F_{ST}). This largely recapitulates previous conclusions; there is high heterogeneity in the evidence of positive selection across micronutrients (both at the level of MA genes and entire MA-gene sets), with some having very strong evidence of having evolved under positive selection. There

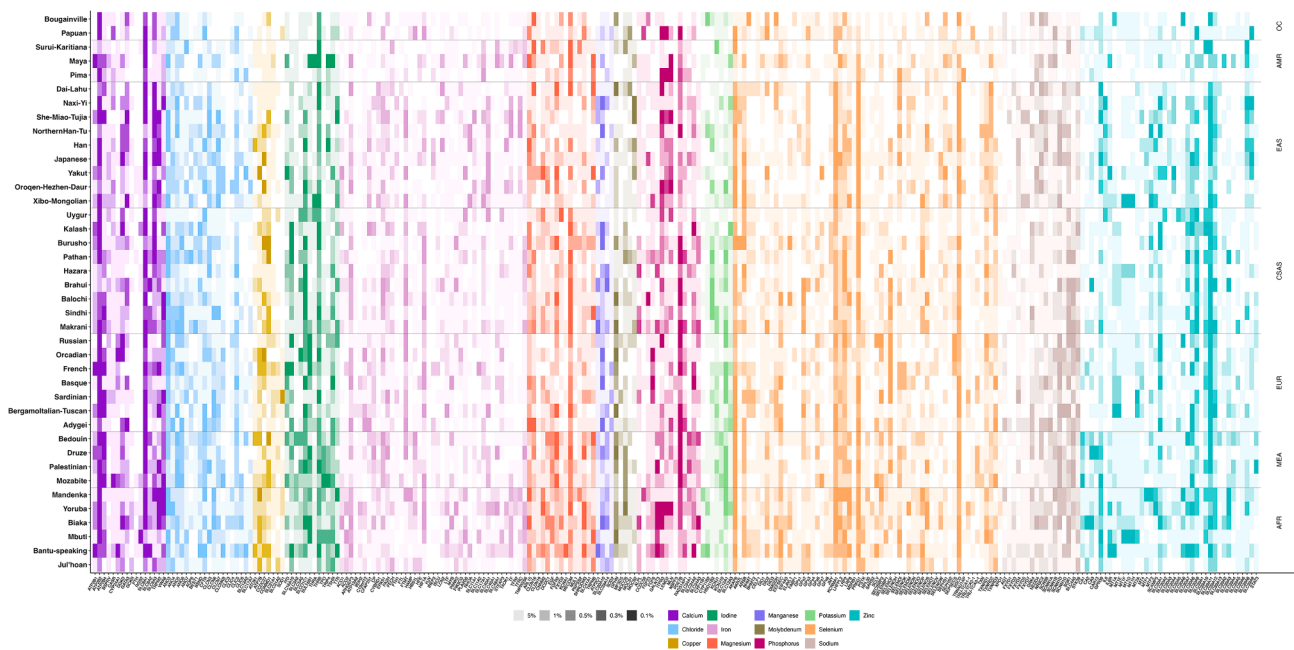


Figure 4. Signatures of positive selection as inferred by Relate across all autosomal MA genes
y axis, colored by micronutrient, and in all populations, x axis is grouped by metapopulation. Darker blocks reflect lower empirical p values (from lightest to darkest: below 5%, 1%, 0.5%, 0.3%, and 0.1%, see left legend).

is also substantial geographic heterogeneity, with some signatures of positive selection clustering in individual populations, while others are present across continental regions or even most non-African populations. Figure 4 suggests that (1) virtually all micronutrients may have acted as selective drivers in particular human populations; (2) many putative instances of adaptation are likely geographically widespread, to a larger extent than previously appreciated; and, most importantly, (3) MA adaptation has likely had a global impact on the patterns of genetic diversity of our species.

However, if we consider each micronutrient as a selective driver, which populations have the strongest evidence of positive selection? This is a challenging question to answer, especially under an oligogenic model, so we develop criteria that consider the number of candidate SNPs, candidate genes, and strength of signatures of positive selection. Here, we focus on criteria across entire gene sets: while genetic drift in populations with extreme demographic histories (e.g., recent bottlenecks or ancient structure^{47,49,65,69,73}) may drive strong allele-frequency change in individual SNPs, such processes are unlikely to result in signatures at the oligogenic level.

While avoiding explicitly comparing populations, we highlight those that, for each micronutrient, have (1) a significant excess of significant SNPs within the associated gene set (Figure 5A, Data S2); (2) a substantial proportion of genes with signatures of positive selection (those with more than 20%; Figure 5B and Data S3) within the associated gene set; or (3) two or more MA genes with the strongest signatures of positive selection (top-ranking MA

genes, defined as those MA genes falling within the five strongest signatures of positive selection when considering all MA genes for that population) within the associated gene set (Figure 5C; Tables S6 and S7). These criteria are *ad hoc*, but they allow us to generate a list of populations with the strongest evidence of oligogenic adaptation associated with particular micronutrients (Figure 5D). Additional populations may have weaker evidence of adaptation for that micronutrient (see Figure 4), but these criteria allow us to highlight and prioritize the most interesting signatures of positive selection among all the populations in this study.

With the exception of selenium-associated adaptation in East Asians,¹⁵ zinc-associated adaptation across non-African populations,^{18,19} and putative iron-associated adaptation in Europeans,⁶² the cases presented in Figure 5D represent previously undescribed cases of MA adaptation. This includes the iodine-associated gene set in the American Maya, which fulfills all three of the selection criteria outlined in Figure 5. Importantly, evidence for oligogenic adaptation is identified in all MA-gene sets (bar molybdenum, our smallest gene set of $n = 5$) and across all major global regions (excluding Oceania, of which only two populations are included; Figure 5D). Both Figures 4 and 5 suggest not only that the diversity and prevalence of MA adaptation among human populations is much higher than previously appreciated but also that it may underlie many cases of human local adaptation.

Zinc: Candidate for widespread adaptation

Among the micronutrients referenced in Figure 5, zinc is particularly interesting because of the geographically

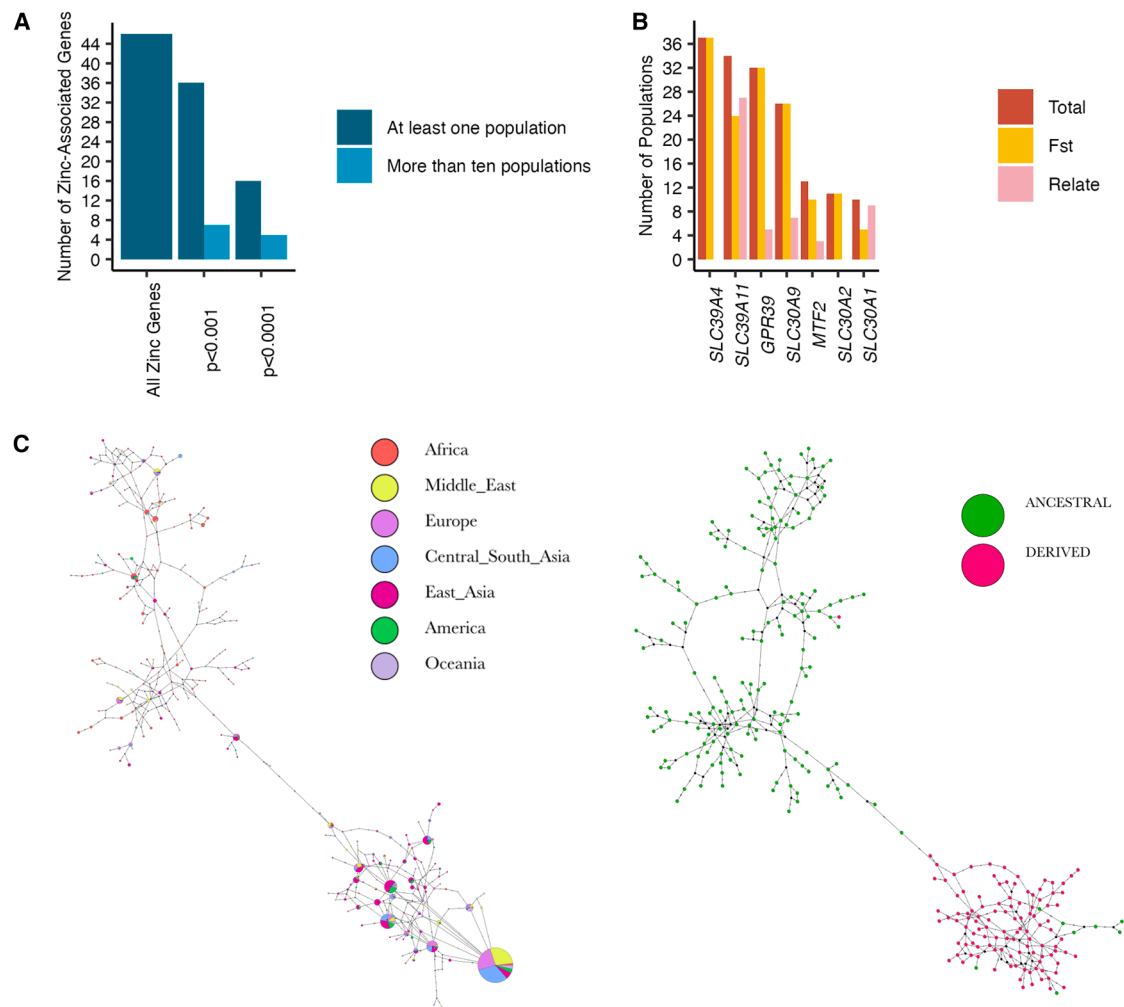


Figure 6. Signatures of positive selection across zinc-associated genes

(A) Number of zinc-associated genes with significant SNPs at the $p < 0.001$ and $p < 0.0001$ thresholds for at least one population (dark blue) or at least 10 populations (light blue).

(B) Number of populations with candidate SNPs identified in the seven genes with geographically widespread signatures ($p < 0.0001$) by Fst and Relate.

(C) Haplotype networks of *SLC39A11* built from the 10-kb locus around the SNP with the strongest evidence of positive selection (in the Central-South Asian Makrani; $p = 1.40 \times 10^{-6}$; hg38 position: 73010373) colored by an individual's population (left) and whether the focal allele is ancestral or derived (right).

non-African individuals (some of which are at high frequency within continental groups; Figure 6C; see section “materials and methods”); conversely, the candidate SNPs in *SLC30A9* and *GPR39* are found on multiple, divergent haplotypes in non-African individuals (Table S8; Figures S33–S38). This suggests that positive selection on both new mutations and standing genetic variation may have mediated zinc-associated adaptation in an ancestral non-African population.

Discussion

For the majority of our history as a species, the diet of populations has been dictated by local food availability, soil quality, and cultural practices.^{7,9,27,38,107,108} Variation among these factors has driven genetic adaptation among

populations across the world,^{7,12,15,18,19,106,109–111} with some adaptations as key considerations in modern public healthcare.^{5,9,12,15} Here, we go beyond such individual cases to investigate the global impact of micronutrients in human evolution, considering their essentiality in human health and variability across the diets of populations. We identify evidence of positive selection across all MA gene sets, including evidence for one or more gene sets in over half of the tested populations, suggesting that, as a group, micronutrients are a more important selective force in recent human evolution. This global signature is driven by particular MA-gene sets, suggesting that some micronutrients played a particularly important role in human local adaptation. It is these adaptations that have the most important implications when considering the role of evolutionary history in the population-level risk of MA disorders today.^{85,112}

Oligogenic local adaptation

A model of oligogenic adaptation is best suited to explain the signatures of adaptation identified in MA gene sets. It remains possible that adaptation was highly polygenic, because, if the signatures of positive selection in individual genes are very weak, the power of even the most powerful methods will remain limited. As shown here, F_{ST} and Relate have higher power than haplotype-based methods to identify weak positive selection and selection on standing variation, but power is still low for recent selection and for the lowest tested selection coefficients. Nevertheless, and in consideration of methodological limitations, our results suggest that only a few genes mediate adaptation for most micronutrients, while purifying selection has likely driven the evolution of the rest of MA genes. Our gene sets include genes involved in uptake, metabolism, and function of the micronutrient, and it is likely that only some of these aspects would evolve upon a particular dietary pressure. A clear example of this is the zinc-associated set, where evidence of positive selection clusters heavily on zinc transporters.

Importantly, we observe evidence of MA adaptation across populations in all major regions of the globe. By extension, human populations may, on average, differ in their micronutrient metabolism, uptake, or regulation, and those with strongest evidence of MA adaptation should be prioritized in future genomic medicine studies. Due to space limitations we are only able to discuss only the most interesting cases: iodine, which has particularly strong evidence of positive selection and potential phenotypic consequence in the American Maya population; selenium, where adaptation coincides with both soil geology and public health across East Asia; and zinc, where adaptation appears to be widely shared outside of Africa and thus contributes to genetic differences between people of African and out-of-African descent.

Iodine

In the Maya population of Central America, the iodine-associated gene set has both a significant excess of signatures of positive selection (Figure 2; Table 1) and a high proportion of iodine-associated genes identified as candidate genes (>20%; Figure 5). High rates of goiter, a swelling of the thyroid gland caused by extreme iodine deficiency, is common among contemporary populations across Central America,^{113,114} indicating iodine deficiency as a pervasive environmental pressure in this region (albeit perhaps exacerbated by socioeconomic inequalities). Given that contemporary populations in this locality likely have substantial recent European and African ancestry, this is not an evaluation of the response to iodine deficiency in the Maya, and it remains possible that this population has evolved genetic adaptations to mediate the risks of dietary iodine deficiency.

Interestingly, four iodine-associated candidate genes in the Maya are also candidates in the Mbuti population of Central Africa, three of which are part of the thyroid hormone pathway: *THRA* (MIM: 190120), *THRB* (MIM:

190160), and *TRIP4*¹¹⁵ (the latter identified as a target of positive selection¹⁶). Rainforest environments, such as those where the Mbuti live, often have iodine-deficient soils,^{35,45,116} and it has been previously suggested that this may drive adaptations in local populations.¹⁶ Thyroid receptors also play an important role in regulating growth, development, and metabolism,^{25,117,118} and it is feasible that adaptations in these genes, driven by low dietary iodine, underlie the distinctive short stature of Maya and Mbuti (height < 160 cm^{113,119}).

Signatures of positive selection in an additional iodine-dependent thyroid receptor (*IYD*) have previously been identified in the Biaka (and recovered here, with SNPs within the 0.3% and 0.5% empirical tail of F_{ST} and Relate, respectively), another short-statured (height < 160 cm¹¹³) population living on the iodine-deficient soils of an African rainforest environment.¹⁶ Incidentally, the short-statured Efe population (another rainforest hunter-gatherer population living in similar rainforest environments in Africa, like the Biaka and Mbuti populations) exhibit a much lower rate of goiter than their neighboring, and much taller, Bantu-speaking populations.⁴⁵ Our results provide additional support for a link between genetic variation of iodine-associated genes and short stature. While there is still significant debate about the adaptive significance of short stature in rainforest hunter-gatherers (with hypothesized advantages including thermoregulation, mobility, and earlier reproduction^{69,113,120,121}), we suggest that, in some populations, short stature may be an evolutionary consequence to adaptations mediating the risks of low dietary iodine.

Selenium

A selenium-deficient soil belt stretches across China,^{108,122} generating selenium deficiency in the diets of local populations. In the regions with the most severe selenium deficiency, there are endemic levels of the cardiomyopathy Keshan disease and the bone disease Kashin-Beck.^{36,37} We identify evidence of oligogenic adaptation in multiple selenium-associated genes in many East Asian populations (Figures 2 and 4; Table 1), in agreement with previous evidence of polygenic or oligogenic adaptation in selenium metabolism genes in East Asian populations.¹⁵ We also find evidence of selenium-associated oligogenic adaptation in several African populations. While there lacks a comprehensive understanding of geospatial variation in soil levels of selenium across Africa, there is evidence for considerable variation in selenium status within and between African countries,^{28,29} which may have driven local adaptation.

Focusing on Asia, where the strongest link between soil and adaptation exists, four selenium-associated genes have frequently co-occurring signatures of positive selection in the same populations: *SGCD* (MIM: 601411), *AKAP6* (MIM: 604691), *PRKG1* (MIM: 176894), and *KCNMA1* (MIM: 600150; Figures 4, S32, and S33; Table S9). While this is simply a qualitative observation, all these genes have intron SNPs associated with selenium

regulation, and epistatic interactions exist between SNPs of *AKAP6* and *SGCD* and between SNPs of *AKAP6* and *KCNMA1*.¹²³ It is thus likely that mutations in these genes interact to regulate selenium levels and that this is the driver of their evolution in humans. In African populations, the strongest signatures of selection in selenium-associated genes are in *LRP8* (MIM: 602600) and *LHFPL2* (MIM: 609718). Most interestingly, *LRP8*, a receptor of the selenoprotein P (*SELENOP* [MIM: 601484]), determines the hierarchy of selenium supply to various organs under deficiency¹²⁴ and increases mRNA concentrations following deficiency induced by *SELENOP* knockout.¹²⁵ Given that both African and East Asian populations exhibit evidence of selenium-associated oligogenic selection but the genes with the strongest signatures differ (Table S10), it is possible that such populations have adapted to changes in dietary selenium, possibly its deficiency, through changes in different genes. Still, without a more comprehensive understanding of the levels of selenium in soil across Africa, this remains speculative.

Zinc

For zinc, the evidence of genetic adaptation is both remarkably strong and geographically widespread (Figures 2, 4, and 5; Table 2). Signatures of positive selection have been previously identified in multiple zinc-transporter genes,^{18,19,64} with much of the literature highlighting *SLC30A9* and *SLC39A4* as those with the strongest evidence of selection.¹²⁶ We provide additional support for these hypotheses here, identifying signatures of positive selection at our most stringent threshold in the Makrani of Central-South Asia (*SLC39A4*) and the Han of East Asia (*SLC30A9*). Further, seven zinc-associated genes (five of them zinc transporters) have strong signatures of positive selection ($p < 0.001$) in at least 10 populations: *SLC30A1* (MIM: 609521), *SLC30A2* (MIM: 609617), *SLC30A9*, *SLC39A4*, *SLC39A11*, *MTF2* (MIM: 609882), and *GPR39*. However, we note that candidate SNPs of *SLC39A4* are identified only by F_{ST} and may be a West African-specific signal of natural selection. It has been previously proposed that the near fixation of the Val372 allele of *SLC39A4* in West Africa is due to increased pathogen stress driving lower zinc uptake in this region,⁶⁴ and it appears to be an interesting exception to the global pattern.

Still, by and large, zinc adaptation appears to be mediated by a network of genes (such as *SLC39A11*, *SLC30A8* [MIM: 611145], *SLC30A10* [MIM: 611146], and *SLC30A1*; Figure 6) across many non-African populations, likely as a result of positive selection on an ancestral population. The haplotypes containing top candidate SNPs of *SLC39A11* provide particularly strong support of this hypothesis; they are identical or near identical in nearly all non-African individuals and support a selection event on an allele segregating at low frequency in an ancestral non-African population. A likely candidate is the ancestral population that migrated out of Africa to the Arabian Peninsula. Given the severely iron- and zinc-deficient soils of the Middle East, espe-

cially Iran,¹²⁷ and detailed history of zinc-deficiency disorders in this region,^{39,128} we propose that significant selective pressure may have driven adaptations to regulate zinc levels in an ancestral population inhabiting these zinc-deficient environments. Zinc-deficient soils exist elsewhere outside of Africa, such as South Asia, where populations exhibiting the strongest signatures of positive selection on zinc-transporter genes live; e.g., the Makrani in modern-day Pakistan, where zinc deficiency is prevalent (22.1%) and up to 96.1% of grain samples are zinc-deficient.^{129,130} We consider it unlikely that selection events were entirely independent from those observed elsewhere, and instead suggest that either (1) additional adaptations in zinc-transporter genes may subsequently have occurred in populations living on similarly zinc-deficient soil, or (2) differences in power across populations of our tests may result in missed signatures in some populations.

Monogenic local adaptation

We identify 15 MA genes with evidence of having undergone particularly rapid increases in allele frequency, consistent with the action of positive selection. This adds to other cases of adaptation to diet previously reported in humans.^{7,9,11,12} These genes represent the strongest candidates of monogenic adaptation in our study, but other candidates for monogenic adaptation may be identified at less stringent thresholds or in currently unsampled populations.

The functions of these 15 genes are diverse and not always exclusively related to their assigned micronutrient.^{23,24} Nevertheless, two magnesium-associated genes have strong signatures of positive selection coinciding with soil geology and biological function. The top candidate SNPs in *FXYD2* (MIM: 601814) and *MECOM* are both identified in Central-South Asian populations (Uyur and Brahui, respectively). Adaptation in these genes may not be exclusive to these populations, but soils across Central-South Asian have particularly high levels of magnesium^{131,132} and both genes have been linked to hypomagnesemia (HOMG2 [MIM:154020]), either directly (*FXYD2*¹³²) or indirectly (*MECOM*, associated with osteoporotic fractures that can be caused by hypomagnesemia^{133,134}). We speculate that selection in these populations might reduce magnesium intake, which would represent an entirely undescribed case of adaptation to mediate micronutrient toxicity. Interestingly, top-ranking SNPs in *MECOM* fall within a region of the genome likely introgressed from an archaic human closely related to the Vindija Neanderthal^{79,135} (see Note S4). This is thus another example of potential adaptive archaic introgression mediating adaptation to local environment.^{10,126,135–137}

Genes associated with nine other micronutrients also have strong signatures of monogenic positive selection. This includes the calcium-associated gene *ATP2B2* (MIM: 108733) and the iron-associated genes *FTMT*

(MIM: 608847) and *HIF1A* (MIM: 603348), which might have mediated adaptation to drastic dietary changes surrounding the Neolithic transition (Figure 3). However, the evidence of positive selection in other iron- and calcium-associated genes (with the exception of calcium-associated *ATP2B4*) does not appear to be strongest at similarly recent time points (Figure 3), and, instead, it appears that the onset of positive selection may largely coincide with the colonization of Eurasian environments, supporting the role of geology in driving MA adaptation.

The way ahead

Here, we show that, beyond the few previously known cases, micronutrients have likely had a significant role in shaping the evolution of genetic variation in humans. For some micronutrients, there is strong evidence that genetic adaptations may have resulted in population-level differences in their metabolism, uptake, or regulation. Given that dietary levels of micronutrients outside a very narrow range has a range of important health consequences,^{20,26,34,36,37,116} these adaptations have the potential to cause or exacerbate health disparities across populations. Indeed, micronutrient deficiencies are already considered a global health issue, affecting an estimated 2 billion people worldwide, with the majority of these individuals in sub-Saharan Africa and South-Central Asia.^{20,21} We see it as a matter of global health to understand how varying micronutrient levels, especially common deficiencies, may affect people of different genetic backgrounds.

Further, global soil micronutrient levels are rapidly changing as a result of climate change, rising CO₂ levels, and over-farming.^{13,27,138} This, alongside increased migration and mobility of global populations, means that many populations will likely encounter micronutrient levels for which they lack adaptations or even have adaptations to regulate in the opposite and now deleterious direction (the “evolutionary mismatch” scenario¹¹²). For many micronutrients and populations, this study represents a first step in understanding the relationship between genetic variation and MA pressures (such as dietary micronutrient levels), but additional work, including individuals of genetic ancestry groups not represented by populations used here, is required to address this accelerating issue and health connotations in contemporary populations.

First, comprehensive characterization of soil environments across the globe may strengthen or dispute associations between genetic signatures and proposed environmental drivers. High-resolution environmental data are needed for phylogenetic regression models,^{139–142} such as phylogenetic generalized least-squares analysis,¹⁴² that can further aid the identification of targets of positive selection driven by soil geology. Currently available variables (e.g., geographic coordinates) are not informative enough of soil geology, which can show large differences

even among neighboring locations.^{14,27–29,38,107,122,132,134} Generating maps of soil micronutrient levels to co-analyze with genomes remains a promising avenue of future work. Inferences of ancestral soil environments should also be considered, given that over-farming depletes soils of their natural nutrients²⁷ and may lead to false associations. This is especially true for phosphorus and chloride-associated adaptation; recent agricultural practices heavily shape phosphorus and salinity levels of soils,^{13,143} and contemporary soil environments are therefore relatively uninformative in identifying ancestral selective pressures.

Second, functional analysis of candidate genes will more clearly elucidate their role, if any, in their associated micronutrient uptake, regulation, or metabolism. This may inform on the adaptive direction of MA genes (i.e., if adaptive variants have likely responded to deficient or toxic levels of micronutrients). Further studies should be done to identify candidate genes in micronutrients unexplored in this study; vitamin deficiency is also an important health concern,^{20,32,144} and there remains a gap in our understanding of genetic adaptation to mediate vitamin uptake or regulation.

Finally, analysis of large biobank datasets and public-health data may reveal relative differences in risk of MA pathologies according to genetic variation, linking local adaptation in response to dietary micronutrients to contemporary health consequences. We highlight the importance of the latter; subtly different genetically encoded responses to dietary micronutrients may contribute to already-existing health inequalities between populations, which may be exacerbated by present and future decreases in soil or diet quality.

Data and code availability

- All data generated for this article are available in the [supplemental information](#) or from the corresponding author on request.
- Scripts are available at <https://github.com/jas-rees/micronutrients-2025/>.

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Declaration of interests

The authors declare no competing interests.

Supplemental information

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