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Nutrition and its role in human evolution

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Abstract. James WPT, Johnson RJ, Speakman JR, Wallace DC, Frühbeck G, Iverson PO, Stover PJ (London School of Hygiene and Tropical Medicine, London, UK; Division of Renal Diseases and Hypertension, University of Colorado, Denver, CO, USA; Institute of Genetics and Developmental Biology, Chinese Academy of Sciences, Beijing, China; Mitochondrial and Epigenomic Medicine, Children's Hospital of Philadelphia Research Institute, Philadelphia, PA, USA; Endocrinology and Nutrition, Clinica Universidad de Navarra, Pamplona, Spain; Department of Nutrition, University of Oslo, Oslo, Norway; Vice Chancellor and Dean for Agriculture and Life Sciences, Texas A&M AgriLife, College Station, TX, USA). Nutrition and its role in human evolution (Review). *J Intern Med* 2019; https://doi.org/10.1111/joim.12878

Our understanding of human evolution has improved rapidly over recent decades, facilitated by large-scale cataloguing of genomic variability amongst both modern and archaic humans. It seems clear that the evolution of the ancestors of chimpanzees and hominins separated 7–9 million years ago with some migration out of Africa by the earlier hominins; *Homo sapiens* slowly emerged as climate change resulted in drier, less forested African conditions. The African populations expanded and evolved in many different conditions with slow mutation and selection rates in the human genome, but with much more rapid mutation occurring in mitochondrial DNA. We now have evidence stretching back 300 000 years of humans in their current form, but there are clearly four very different large African language groups that correlate with population DNA differences. Then, about 50 000–100 000 years ago a small subset of modern humans also migrated out of Africa resulting in a persistent signature of more limited genetic diversity amongst non-African populations. Hybridization with archaic hominins occurred around this time such that all non-African modern humans possess some Neanderthal ancestry and Melanesian populations additionally possess some Denisovan ancestry. Human populations both within and outside Africa also adapted to diverse aspects of their local environment including altitude, climate, UV exposure, diet and pathogens, in some cases leaving clear signatures of patterns of genetic variation. Notable examples include haemoglobin changes conferring resistance to malaria, other immune changes and the skin adaptations favouring the synthesis of vitamin D. As humans migrated across Eurasia, further major mitochondrial changes occurred with some interbreeding with ancient hominins and the development of alcohol intolerance. More recently, an ability to retain lactase persistence into adulthood has evolved rapidly under the environmental stimulus of pastoralism with the ability to husband lactating ruminants. Increased amylase copy numbers seem to relate to the availability of starchy foods, whereas the capacity to desaturase and elongate monounsaturated fatty acids in different societies seems to be influenced by whether there is a lack of supply of readily available dietary sources of long-chain polyunsaturated fatty acids. The process of human evolution includes genetic drift and adaptation to local environments, in part through changes in mitochondrial and nuclear DNA. These genetic changes may underlie susceptibilities to some modern human pathologies including folate-responsive neural tube defects, diabetes, other age-related pathologies and mental health disorders.

Keywords: genetics, human evolution, nutrition.

Introduction

Before the development of genetic analyses, there were three approaches to the study of human evolution: analysis of anthropological, archaeological and fossil evidence. Notably, all these approaches accepted that *Homo sapiens* arose in Africa and no human-like species emerged in Africa

until at least 2 million years ago although early primates occupied not only Africa but also Eurasia before retreating to Africa as the globe cooled. Our current understanding of human evolution and nutrition relates to the wet and warm forested lands of Africa where our ancestors relied on a rich supply of fruit and leaves for their nourishment. The chimpanzee and pre-*Homo* lineages diverged from one another about 7–9 million years ago, and several different types of early forms of hominins evolved increased brain sizes which further increased along the *Homo sapiens* lineage resulting in average brain sizes approximately three times that of chimpanzees [1]. These substantial phenotypic differences contrast with the extremely high identity (>99%) of the human and chimpanzee proteomes [2] and in turn highlight the important role of regulatory changes during hominin evolution [3]. Consistent with this hypothesis, mRNA comparisons of human and chimpanzee brains show transcriptional differences [4], for example in genes involved in neuronal communication, ion transport and regulatory processes whilst quantitative comparisons of protein levels indicate differences in perception and cognition, metabolic processes and the organization of the cytoskeleton [5].

Accounting for the environmental factors that drove human adaptation is currently challenging, but we know that 2–3 million years ago there was a marked change in climate with far less rainfall such that our pre-Homo ancestors were faced with more open, drier grasslands inhabited by a variety of small and large animals. To survive in this emerging landscape required the ability to move rapidly and to adapt. The ability to act collectively and to safeguard offspring and the more vulnerable members of a group both during the day and night from large predators emerged. The food environment also changed, as the primates were no longer able to rely on a plentiful supply of fruit, but it was possible to catch and eat a variety of small and large animals as well as eating roots and tubers. This demand for food and the avoidance of capture by predators probably promoted the development of cooperative and social behaviour. This emerging environment then meant a substantial change in dietary practices providing much more protein, fat and minerals. It is also clear that the fatty acid desaturase enzymes (FADS I and II) emerged at this time [6] and allowed the oleic acid found in animals to be elongated, incorporated into triglycerides and desaturated to produce the long-chain essential fatty acids. So there was a marked increase in the availability of fat including more essential fatty acids and protein. This shift in diet also provided the substrates that allowed an expansion of the brain and a whole series of behavioural and social developments to emerge. Highly conserved non-coding regions showing rapid sequence changes accompanied the development of distinctly human cognitive functions with the emergence of a human-accelerated regulatory enhancer (HARE5) of FZD8, a receptor of the Wnt pathway involved in transferring signals across cell membranes which is implicated in brain development and size [7] Anatomically, we know that this was the time when the brain grew rapidly, approximately doubling in size, which demanded far more energy [8] as well as fatty acids for the enormous increase in the mass of cell membranes associated with the highly integrated convolutions of the much larger, more complex brain with its greater nuclear systems and connections in the emerging hominin species. In this new environment, the fatty acids and protein supply were now more plentiful if groups of individuals also worked collectively to trap animals. This social learning passed on to the following generations and the discovery of fire and its transforming effect on the ability to readily eat, digest and absorb food also made an enormous difference.

Hominin migration

About 2 million years ago, some hominins migrated from Africa. Various names have been assigned to these early hominins, for example Homo heidelbergensis to reflect the original site of their discovery in Germany. They were short and stocky and built shelters and used fire to keep warm in the colder climates and used wooden spears to hunt large animals. One of these hominin species, the Neanderthals, spread quickly throughout Europe and thrived for hundreds of thousands of years. The anthropological and fossil evidence can be interpreted to favour a series of different options for the migratory process with interbreeding of different branches. For example, the archaic hominins who migrated to Asia and whose artefacts were recently found in Siberia are called Denisovans and were related to but clearly different genetically from the Neanderthals [9]. Human interbreeding also occurred with the Neanderthals such that modern human genomes have about 1.2% Neanderthal ancestry, but these sequences are very rarely observed in Africans and show

heterogeneity across the genome with the X chromosome having only about a fifth of the Neanderthal ancestry of the autosomes [10]. The Denisovans meanwhile interbred with the ancestors of the Oceanic groups of modern humans. Currently, New Guineans and Australians have over 3% Denisovan ancestry with the other Oceanic groups beyond the Makassar Strait in Asia having from 0.9% to 3% Denisovan ancestry. The Native North Americans have similar amounts to the Siberians and East Asians—this is consistent with the current models of human dispersal [11]. Thus, different ethnic groups have different amounts of archaic hominin DNA sequence.

African data also suggest that there was some interbreeding with ancient hominins who continued to exist in Africa until about 35 000 years ago with 2–5% of current African DNA being derived from these archaic hominins with whom there is a common ancestry 1.2–1.3 million years ago.

Recent discoveries and modern genetics emphasize that *Homo sapiens* arose as a discrete entity in Africa over 300 000 years ago. This observation is primarily based on new findings in a Moroccan cave [12, 13]. The dominant groups of *Homo sapiens* were developing in Africa, and more recent genetic studies by Tishkoff et al. [14] emphasize how different groups increased markedly with further migrations and adaptations to the remarkably different ecosystems of Africa. The current anthropological division of the multiple African groups or tribes into four major groups is based on their use of different types of language which are consistent with genetic analyses, emphasizing the diversity of form of Homo sapiens in different environments [15] (Fig. 1). Studies suggest that over 2000 languages are still in use in Africa. The evolution, migration and specialization of different populations continued for 2–3 million years as African populations were exposed to remarkably different environments in terms of diet, different pathogen burdens in varied environments and differences in altitude. Indeed, the striking differences in the environment and food availability have continued for millennia and persist to this day as illustrated by an overall picture of the current terrestrial systems in Africa [16] (Fig. 2). There are very different African landscapes, and only a small part of the land mass has major rivers or a coastal area allowing access to fish. Outside Africa, the terrestrial, food and pathogen environment are also very different. Major trade in food stocks is only a comparatively recent feature in most parts of the world. So many populations still live in an environment where they are very dependent on local crops and many are also subject to major seasonal changes in the types of food available.

Fig. 1 *The language groups of Africa which encompass over 200 diverse genetic groups that have evolved in Africa over at least the last 3000 years. The geographic distribution of the major linguistic groups in Africa. The map was drawn using information with geographic locations of ethnic speakers in Africa based on published sources as listed by Gomez* et al. *[15]. The geographic range occupied by Bantu speakers, the major linguistic subfamily within the Niger-Kordofanian phylum is shown as the darker green area. The putative centers of origin and estimated time of initial expansion shown by the different arrows are based on linguistic studies for three of the four language families. Afroasiatic-speaking pastoralists were the first food-producing populations to migrate into East Africa (marked X on the map) about 5000 YBP (Years Before Present) followed by Nilo-Saharan-speaking pastoralists circa 3000 YBP (marked as Y) and later Bantu-speaking agriculturalists after circa 2500 YBP (Z). P and q represent the initial expansion of pastoralists (2500 YBP) and later Bantu speaking agriculturalists (after 2000 YBP) to southern Africa from East Africa, respectively.*

As the different African groups evolved in response to these external pressures, they migrated across Africa so a substantial admixture of the different African populations emerged, particularly influenced by the more recent Bantu migration from

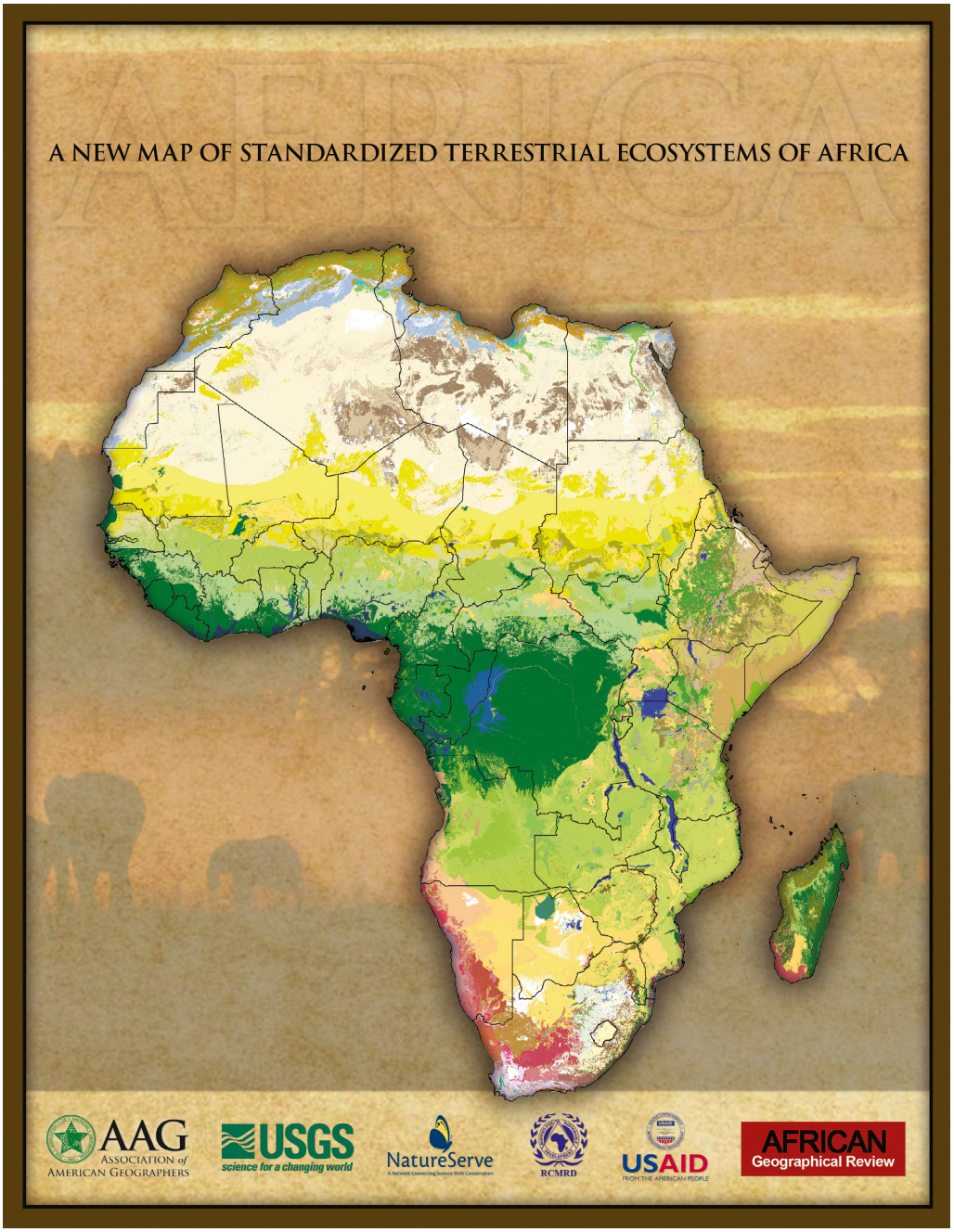

Fig. 2 *The current different terrestrial ecosystems with varying capacities to produce food in Africa. Taken from Sayre R., Comer P, Hak J* et al. *[16] where each of the seven ecosystems is a conglomerate of fairly similar ecosystems. These seven overall groups include (i) tropical forests, (ii) temperate forests, (iii) tropical grassland, savannas & shrubland, (iv) temperate grassland and shrubland, (v) warm desert & semi-desert woodland, scrub & grassland, (vi) tropical rock vegetation and finally, (vii) Mediterranean temperate rock vegetation. The detailed areas within each of these groups is set out in detail in figure 9 in http://www.aag.org/galleries/publications-files/Africa_Ecosystems_Booklet.pdf.*

West Africa to sub-Saharan Africa over the last 4000 years. So it is not surprising that within the very large African populations there is great genetic diversity.

The availability of different foods seems to have contributed to some local adaptations, for example in amylase copy number variation, lactase persistence, bitter taste perception and indeed the propensity to some haemoglobinopathies [17]. There is also evidence of local amplification of the FADS genes [6], which increase long-chain polyunsaturated fatty acid (LC PUFA) synthesis from plant-based medium-chain fatty acids. These may have played an important role in allowing African populations in a predominantly plant-based environment to rapidly expand throughout the African continent 60 000–80 000 years ago. Adaptation in the FADS gene has involved different alleles in different environments, for example in Europe where again it seems to reflect changing environmental circumstances, for example the development of agriculture [18]. The prevailing risk of infections also means that immune-related genes have also been major targets for selection. Pygmies evolved in the forests of West Africa where meat sources were more meagre whereas the tall, thin Masai emerged in East Africa sustained by their high protein diet of milk, blood and meat [19]. Attempts are now being made to link the wide variation in the human form and appearance, that is the phenotype of *Homo sapiens*, with our genetic understanding of the role and interactions of different genes, but this is currently far from straightforward.

Genetic mutation rates and evolution

The nuclear DNA is subject to seemingly random mutations that alter DNA primary sequence, including coding mutations that affect proteins' amino acid sequences and noncoding mutations that affect the regulation of gene expression. Likewise, single or multiple base deletions or duplications also occur in the germ line during human development. Early work focused on evaluating the contribution of different single nucleotide polymorphisms (SNPs) to human phenotypes, but these associations are not as informative as the more expensive but comprehensive whole-genome sequencing being applied to reveal the genotype–phenotype linkages [20]. This has shown that duplications rather than deletions of genes have had a much greater impact on accelerating human genetic diversity as seen by the differences in the genetic make-up and functional capacities of different populations. These duplications are much more evident in non-African populations than in Africa.

Copy number changes and their effects

DNA copy number expansions occur at increased frequency during periods of rapid evolutionary change and can take many forms; some of these are deleterious and lead to metabolic abnormalities. One example is the trisomy of a whole chromosome. For example, trisomy of chromosome 21 leads to Down's syndrome and other examples are associated with heart defects, psychiatric disorders and kidney defects [21]. Later in life, cancer development involves gene duplication and these may amplify the risk of cancer proliferation [22]. The early analyses suggested that increased copy numbers are advantageous, but with more modern techniques of analysis, there seem to be more disadvantages than advantages in the consequences of copy number increases [23].

One example, however, of a benefit of increased gene copy numbers comes from considering the amylase gene responsible for the digestion of starches. Individuals from populations with high-starch diets, that is agricultural societies and hunter gatherers, have on average more amylase 1(*AMY1*) copies than individuals with traditionally low-starch diets as in rain forest dwellers or some pastoralists. Copy numbers of all three amylase genes seem prone to changes in copy numbers, but *AMY 1* shows the greatest variation. Though unusually prone to copy number variation, the extreme copy number differentiation observed at *AMY1* is consistent with local adaptation. It has been suggested that the extra *AMY1 gene* copies with their resulting increase in amylase protein levels not only improve the digestion of starchy foods, but may also help to overcome the impact of intestinal diseases [24]. This duplication in a modern setting has also been linked to a reduced propensity to obesity but this was not confirmed in a subsequent rigorous analysis [25].

Biased gene conversion

The process of meiosis in reproduction involves first the duplication of chromosomes and then the exchange of genetic information before cell division occurs. This genetic exchange between homologous

chromosomes seems straightforward and provides the benefits of greater genetic diversity with the formation of new haplotypes, but can also be considered a driver of sequence evolution. Indeed, gene conversion provides a basis for evolution and is considered to be 100 times more frequent than nucleotide point mutations. It is also now known that gene transfer can occur without the reciprocal receipt of genes so there is a unidirectional flow of genes which occurs typically close to the point in meiosis where the double-strand break occurs. This gene conversion process is biased in favour of guanine–cytosine (GC) base pairs rather than adenine–thymidine (AT) base pairs. So AT/GC heterozygotes produce more GC than AT gametes, thus conferring a population advantage to GC alleles in high-recombining regions. This apparently unimportant feature of molecular machinery is considered to have major evolutionary consequences. 1%–2% of the human genome is subject to a strong genetic bias in favour of GC selection. This evidence of bias is stronger in African than in non-African populations, reflecting the early differences in effective population sizes. However, due to the more heterogeneous patterns of recombination genetics amongst African genomes, the fraction of the genome affected by this bias is greater in non-African populations. The location of recombination hotspots also evolves very rapidly, so it is now predicted that a large fraction of the genome will become affected by short sections of GC bias [26]. In Africa, these gene conversion events seem to have generated variation that was adaptive and conferred greater resistance to malaria by altering sequences of glycophorin A and B, which determine MN and Ss blood types. These adaptive mutations alter the form of two major receptors that are expressed on erythrocyte surfaces and interact with parasite ligands [27].

Mitochondrial DNA and its high mutation rates

The mitochondria have their own DNA which is exclusively derived from the maternal line, the sperm mitochondrial DNA being eliminated at fertilization. Mitochondrial DNA is about 20 times more vulnerable to mutation during the lifetime of an organism than nuclear DNA and can occur in any of the mitochondria within any one cell. The number of mitochondria can vary from none in an erythrocyte to over 2000 in a liver cell to a quarter to half a million in the oocyte. The high mitochondrial DNA mutation rate regularly introduces mitochondrial DNA mutations into cells and the maternal germ line. Since a new mutation arises in a population of normal mtDNAs, the initial state is a cell with a mixture of mutant and normal mitochondrial DNAs, that is a state of heteroplasmy. The consequence is that as long as the mutant mitochondrial DNA is at a low cellular percentage, its deleterious effects will be masked by the more abundant normal mtDNAs. Since the majority of functional mitochondrial DNA mutations are deleterious, it is essential that heteroplasmic mitochondrial mutations rapidly segregate out in the maternal germ line so that the deleterious mitochondrial DNA mutations can be eliminated by natural selection. This system in mammals is based on generating a severe constriction of the number of mtDNAs within the maternal germ line followed by the elimination of germ cells with high percentages of deleterious mutant mitochondrial DNAs. After fertilization, the mitochondrial DNAs from the oocyte do not replicate until the blastocyst stage. This results in the apportioning of the mitochondrial DNAs into individual female primordial gene cells. Various estimates have been made of the number of functional mitochondrial DNAs that are introduced into each primordial gene cell, with the lowest estimate being about 8 mitochondrial genetic units. Subsequent amplification of these mitochondrial DNAs generates half a million oocyte mitochondrial DNAs. Then at ovulation or soon after fertilization, the oocytes/embryos with high levels of mutant mitochondrial DNAs and consequently severely affected mitochondria and energetic impairment are eliminated by selection. Hence, only the most energetically robust oocytes give rise to functional embryos and offspring. Since selection is based on the degree of energetic dysfunction, oocytes with mild mitochondrial DNA mutations or low heteroplasmy can survive and be fertilized. This permits the introduction of extensive mitochondrial DNA diversity into the population, some of which permits adaptation to changing energetic environments. Those embryos with low levels of deleterious heteroplasmic mutations that do survive can give rise to variable heteroplasmic tissues. This is because as the embryo develops it is a matter of chance what proportion of mutant and normal mitochondrial DNAs are introduced into each daughter cell. As a result, a heteroplasmic oocyte can give rise to an individual whose tissues have different percentages of mutant and normal mitochondrial DNAs and differential organ energetic dysfunctions. Differential organ energetics also changes mitochondrial metabolism and

mitochondrial metabolites which are the key co-factors for regulation of the signal transduction system and the epigenome. Hence, variable energetics results in variable nuclear DNA gene expression and variable clinical manifestations [28].

As *Homo sapiens* expanded in Africa, mitochondrial DNA mutations arose along different maternal lineages. Some of the functional variants proved to be beneficial in particular environments, resulting in the regional expansion of descendant mitochondrial DNAs from that founder. This generated regional groups of related haplotypes, termed haplogroups. African populations have numerous mitochondrial DNA haplogroups encompassed within the greater African macrohaplogroup 'L'. About 65 000 years ago, two mitochondrial DNAs arose in north-western Africa and only these two mitochondrial DNA lineages, designated 'M' and 'N', successfully left Africa to colonize the rest of the world (see Fig. 3). Macrohaplogroup N mitochondrial DNAs moved directly into the temperate zone and became distributed throughout temperate Eurasia, giving rise in Europe to haplogroups H, I, J, Uk, T, U, V, W and X. Macrohaplogroup M mtDNAs migrated along the southern subtropical Asia coast ultimately reaching Australia. Later, variants arose in the M lineages that generated haplogroups that could move into temperate Asia. Finally, only three mitochondrial DNA haplogroups became enriched in Siberia and crossed the Bering land bridge to found the paleo-Native Americans. Hence, the regionality of mitochondrial DNA population variation is the result of adaptive selection to environmental factors such as thermal stress and immune responses to infection.

Whilst the founding haplogroup mitochondrial DNA variants were probably mostly beneficial in the environment in which they originated, these same variants can be maladaptive in other environments. This can result in the differential predisposition to a range of metabolic and degenerative disease [29].

Evolution of the immune system

The genetic control of the immune system is another example of rapid evolution. The innate system of immunity involves a series of barriers and nonspecific responses to pathogens and is a component of the immune system common to all organisms. However, the adaptive mechanisms of immunity are fundamental to the ability of vertebrates to cope with new environments and have shown marked evolutionary changes [30]. However, it is now recognized that the innate and adaptive immune mechanisms interact in a variety of complex ways and continue to show the impact of different environments [31]. The adaptive system involves a variety of lymphocytic responses to 'nonself' antigens, which have responded dramatically as the environments of hominins have changed. Several components of the type 2 lymphocytic immune response pathway have been subject to recurrent positive selection in the primate lineage [32] and *Homo sapiens* have human-specific immune responses enriched for genes involved in apoptosis. However, these multiple adaptive systems seem to have made humans more susceptible to cancers, with also a greater susceptibility to some infectious diseases and to immune-related disorders, for example allergies and autoimmune diseases [33]. Variability of the human genes relating to immunity is less than in apes perhaps reflecting the fact that the non-African populations are derived from a relatively small group migrating out of Africa with subsequent population expansion. Several immune genetic signatures show positive selection in populations exposed to malaria; several MHC alleles common in West Africans are rare in other ethnic groups and have long been associated with protection from severe malaria [34]. In different climates, some pathogens such as malaria, trypanosomiasis and schistosomiasis do not thrive but other infections prevail so different societies have been repeatedly challenged by very different pathogens which in turn have entrained very different immunological responses.

Physiological and pathophysiological differences between populations

Altitude adaptation

Given the diversity in nuclear and mitochondrial DNA patterns amongst different populations, one might expect to find physiological differences of both nutritional and metabolic importance, particularly given the differences in stature and body weight. Populations that evolved at high altitudes possess adaptations that allow them to cope far better with lower oxygen partial pressures. Currently, over 140 million people live above 2500 m and analyses in Tibet, Ethiopia and the Andes reveal distinct genetic adaptations to the altitude-related hypoxia in each region [35]. In Tibet, the adaptation does not involve polycythaemia but a change so that erythropoiesis is not triggered and the hypoxia-inducing changes that are normally

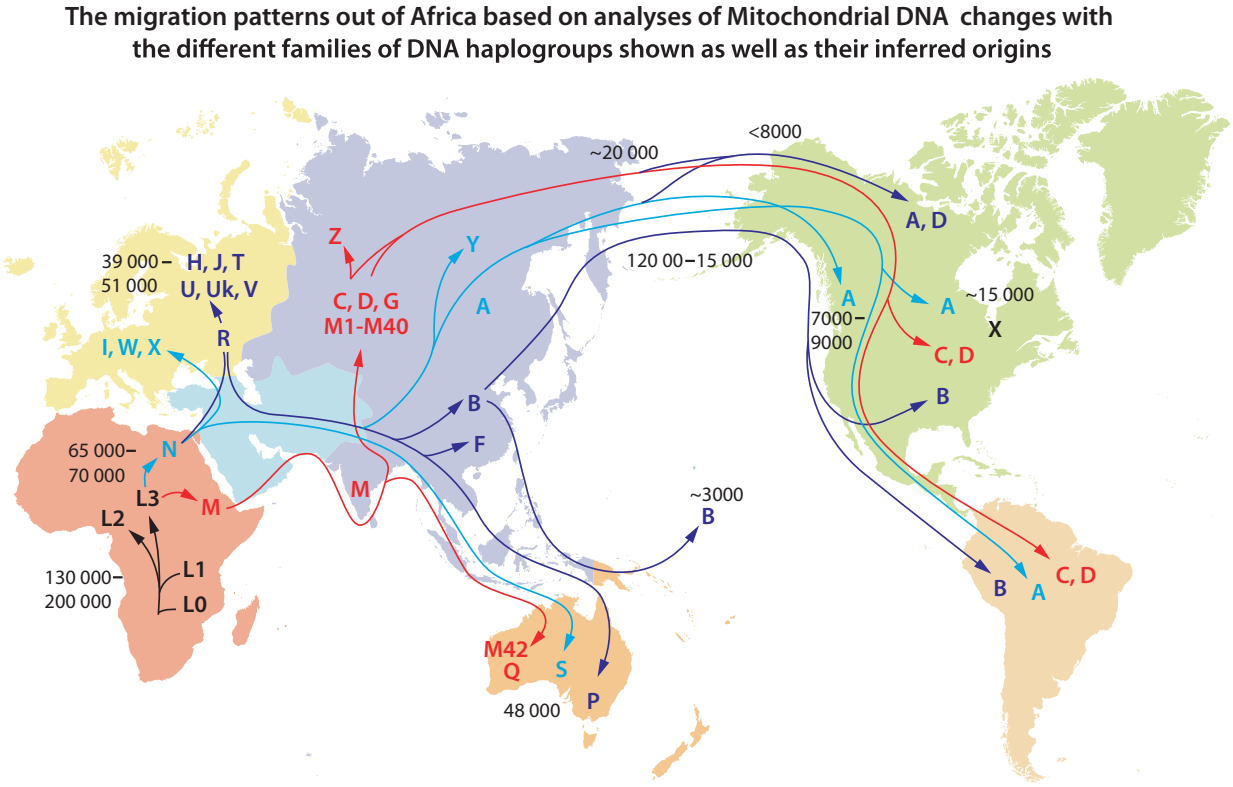

Fig. 3 *The migration patterns out of Africa based on analyses of Mitochondrial DNA changes with the different families of DNA haplogroups shown as well as their inferred origins. 'Taken from Wallace [28] but reaffirmed in reference 29. The migration of female homo sapiens, as assessed in different regions' indigenous peoples' different mitochondrial DNA (mtDNA) haplotypes with their intrinsic historic imprints, suggests the sequence of movement of women from Africa and the migration of peoples across Eurasia, Australia, and the Americas as shown in the figure. The numbers within the figure denote Years Before the Present (YBP). The uniparentally inherited mtDNA can only change by sequential accumulation of mutations along radiating female lineages. Therefore, the mtDNA mutational tree and ancient migrations of women were reconstructed by sequencing mtDNAs from indigenous populations and correlating their regional clusters of related haplotypes (haplogroups) with the population's geographic location. The haplogroups are regional because they were founded by regionally adaptive functional variants. African haplogroup L0 is the most ancient mtDNA lineage found in the Koi-San peoples, L1 and L2 in Pygmy populations. From haplogroup L3, two mtDNA lineages, M and N, arose in Ethiopia and successfully left Africa to colonize the rest of the world about 65 000–70 000 YBP. The founder mtDNA of macrohaplogroup N harboured two mtDNA missense mutations,* ND3 *G10398A (A114T) and* ATP6 *G8701A (A59T), whereas the founder of macrohaplogroup M did not harbour major functional mutations. Early M and N emigrants from Africa moved through Southeast Asia, ending in Australia. N mtDNAs also moved north from Africa into the Middle East to generate submacrohaplogroup R and European-specific haplogroups H, J, T, U, Uk, and V (from R) and I, W, and X (from N). N and R gave rise to Asian haplogroups A+Y and B+F, respectively. The group with haplogroup M moved north out of Southeast Asia to colonize Asia, generating haplogroups C and D and multiple M haplogroups. Haplogroups A, B, C, D, and X subsequently migrated to the Americas. The mtDNA mutation rate is 2.2–2.9% per million years and far higher than the mutation rate in nuclear DNA'.*

observed in a cell are suppressed [36]. Surprisingly, two generic mechanisms for Tibetan adaptation to high altitude involve the acquisition of a Denisovan chromosomal segment that regulates the hypoxia initiation factor (HIF) pathway and a missense mutation in a mitochondrial DNA gene.

Malaria resistance

Another example of human adaptation involves the evolution of a variety of traits which help prevent malaria. These include several changes in red cell function such as glucose 6 phosphate deficiency, but

this condition has the disadvantage of anaemia precipitated by infections or by eating fava beans [37]. Pyruvate kinase deficiency, haemoglobin C, E, alpha and beta thalassaemia and sickle cell disease are additional genetic disorders of the erythrocyte which also impair malarial parasites [38] although the sickle cell trait and the thalassaemias have far better documented malaria resistance than the Hb C trait. The global distributions of the sickle cell and thalassaemic traits are shown in Fig. 4. Alpha thalassaemia in the people of the high Himalayan valleys of Nepal and India confers particularly high malarial resistance [39]. Although sickle cell haemoglobin in its homozygous form is disadvantageous in precipitating major illness after infections and in poor countries leads to high death rates in childhood, that is before the age of reproduction, the mutation is maintained because individuals with the more abundant heterozygous sickle cell trait, HbAS, are also far more resistant to malaria [40]. This resistance relates to gene changes in the haemoglobin protein sequence which causes the haemoglobin to aggregate under the low oxygen tension generated by the malarial parasite metabolism within the erythrocytes. Other gene variants that affect malarial infection of erythrocytes alter genes encoding the glycophorins on the surface of the erythrocytes. These same proteins are used as receptors by the malarial parasite to invade the erythrocyte. For example, individuals with blood group O are more resistant to malaria. These glycophorin changes are also apparent in the genes of chimpanzees possibly signifying independent gene selection effects. There is also a host cell microRNA in sickle cells that is translocated into the malarial parasite and inhibits its replication. Thus, malaria exerts a powerful selective pressure on erythrocyte proteins and human evolution.

Lipoprotein genetics, trypanosomiasis resistance but sensitivity to renal disease

An example of population differences which may have related to diet during evolution involves resistance to African trypanosomiasis. Trypanosomes take up apolipoproteins from the circulation, and certain genetic polymorphisms in apolipoprotein L1 (APOL1) confer protection and are present in Africans living in endemic areas. Unfortunately, these polymorphisms also increase the risk for the development of kidney disease and largely accounts for why African Americans are at increased risk for end-stage renal disease [41].

Primate uricase deficiency

Inactivating mutations in the uricase gene began to accumulate approximately 20 million years ago in the great ape/human lineage leading to progressive loss of activity followed by a complete silencing of the gene around 15 million years ago. This occurred during the period of progressive extinction of apes in Europe due to climatic change. The loss of the uricase gene it has been suggested provided a survival advantage for European primates by enhancing the effect of dietary fructose in stimulating fat and glycogen synthesis as well as resulting in a modest rise in serum uric acid levels [42]. Tests with the ancestral uricase also show its effect in blunting fructose's metabolic effects [42] and increases in uric acid levels are associated with increasing insulin resistance [43]. Recent studies have also suggested that high salt and high glycaemic diets induce the metabolic syndrome in part by inducing endogenous fructose generation that engages this genetic-dietary interaction [44]. It is uncertain, however, how important this pathway is for the current epidemics of obesity and diabetes.

Population differences in nutritional processing?

Some evident population differences in nutritional processing based on genetic differences are summarized in Table 1 [45, 46], but four examples will be considered here in more detail.

Persistence of lactase in some populations

Although the enzyme lactase normally declines in its expression and activity after weaning, some population groups in Africa, the Middle East and Europe display marked persistence of lactase throughout life [47] – see Fig. 5 [48]. This adaptation for lactase persistence seems to have been provoked by the development of the domestication of cattle, sheep and goats about 7500–9000 years ago [49]. Whilst lactase persistence is seen in many pastoralists, the genetic mechanisms for lactase persistence differ between different African groups and between Africans and Europeans, European lactase persistence having arisen about 2000 years ago. Given that weaning and the loss of immune input from breastmilk are associated with multiple exposures to diarrhoeal diseases and other infections leading to anorexia, the persistence of lactase would be a crucial advantage. Children's mortality rates have been exceptionally

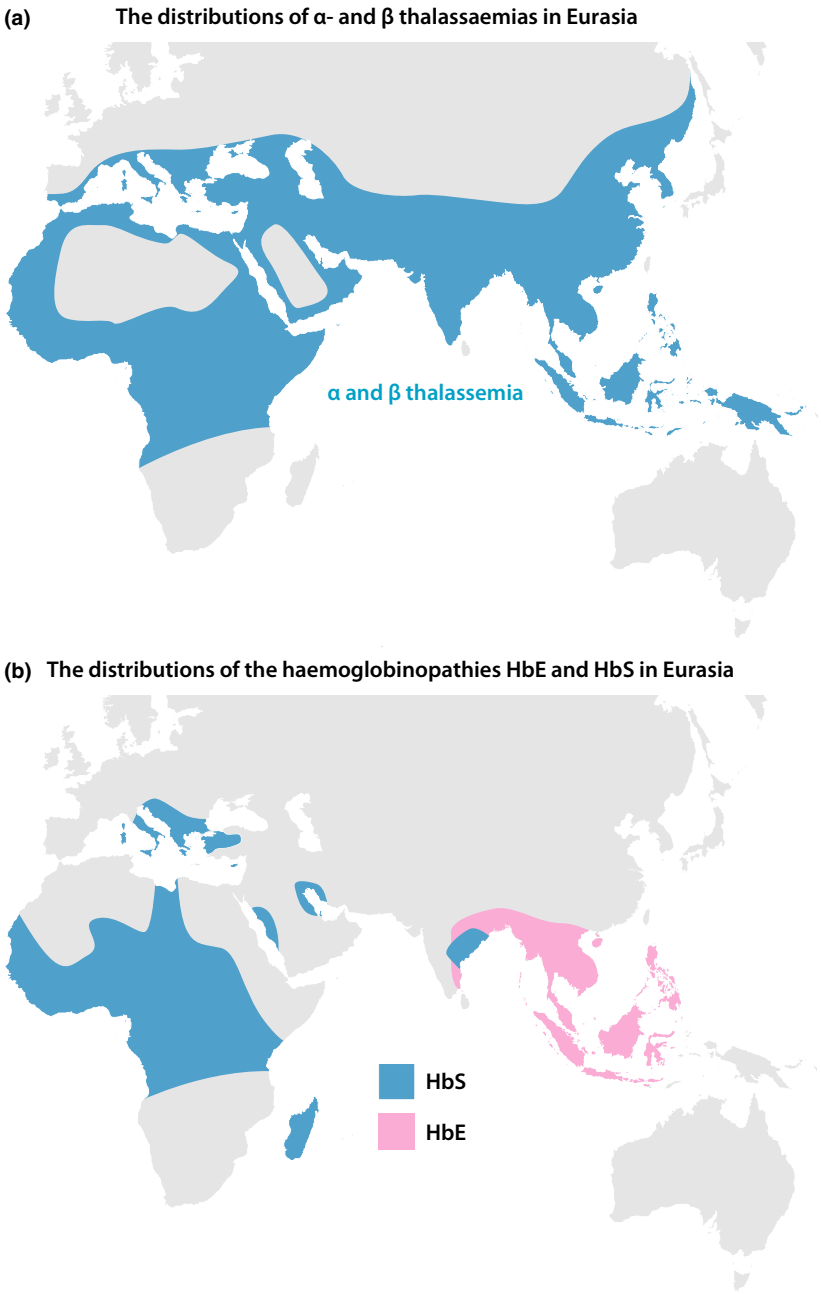

Fig. 4 *(a) The distributions of the thalassaemias in Eurasia. (b) the distribution of the haemoglobinopathies HbE and HbS in Eurasia. Taken from Williams and Weatherall [38].*

high for millennia with up to a 50% mortality for children under 5 years of age. It is therefore not surprising that any genetic change that involved a tendency towards lactase persistence would be rapidly selected as advantageous; indeed, mutations conferring lactase persistence have been estimated to be the most strongly selected mutations of all episodes of positive selection so far examined.

Table 1 *Ethnic and ancestral differences in nutritional processing and metabolism*

Nutrient	Ethnic differences	Dietary challenge or opportunity	Nutritional significance
Lactose	Asian & most African groups have lactose intolerance but many other societal groups independently evolved capacity to digest lactose	Capacity to domesticate cattle for milk production found in many different parts of the world	Intolerance to high lactose intakes is usual after infancy but several societies relatively recently developed persistent lactase activity.
Starch	Rain forest dwellers in Africa compared with pastoralists	Rainforest dwellers particularly reliant on fruit so lower amylase digestive capacity required but with more sparse forest and open country the availability of tubers and other crops increases starch availability markedly	Amylase 1(*AMY1*) greater copy number improves the digestion in groups on high starch diets vs. pastoralists; higher copy number may also help to overcome the impact of intestinal diseases
Long Chain Fatty Acids	Multiple ethnic group differences across Africa, Europe & Asia depending on traditional diet	Coastal populations have far more dietary long chain fatty acids from fish than in inland communities; animal sources provide some essential fats but otherwise the main unsaturated fat source is from plants so desaturation and elongation to produce essential fatty acids become important.	Ethnic groups with long standing diets low in animal foods have higher FADs* enzymes so able to produce LCPUFAs† more readily
Alcohol	Asia/Oceania societies intolerant	Alcohol tolerance induced about 10 million yrs. ago when capacity to eat fermented fresh fruit became important in tropical forest conditions. Mitochondrial gene mutations relating to acetaldehyde dehydrogenase account for loss of alcohol tolerance in Asians.	Low acetaldehyde dehydrogenase with accumulation of acetaldehyde leading to hot flushing of face + intolerance of alcohol
Folate	Northern Eurasian groups have higher prevalences of the MHTFR C677T polymorphism associated with reduced activity and higher homocysteine levels	Marked differences in the ready availability of dietary folate throughout the year dependant on climate, temperature, rainfall and soil fertility.	Those with low activity of MHTFR C677T enzyme activity have higher needs for dietary folate with greater susceptibility to neural tube defects and possibly other conditions
Vitamin D	Dark skinned populations	Darker skin more protective of skin from intense sun exposure in Africa; lighter skin develops as sun becomes less intense away from the equator.	Darker skinned people need greater exposure to sunlight or more oral Vitamin D2 to avoid bone changes e.g. rickets and to improve immune function

Table 1 (*Continued*)

Nutrient	Ethnic differences	Dietary challenge or opportunity	Nutritional significance
	Ancestral gene change		
Fructose	Humans, Great and Lesser Apes are more sensitive to the effects of fructose in increasing their liver fat and stimulating gluconeogenesis than other mammals due to a loss of uricase that occurred during the Miocene	Tree living primates dependent on fruit as an energy source with the capacity to induce energy reserves important.	May have had a role in protecting ancestral apes from starvation

*FADS, Fatty acid dehydrogenases I and II
†LCPUFAs, Long Chain Polyunsaturated Fatty Acids.

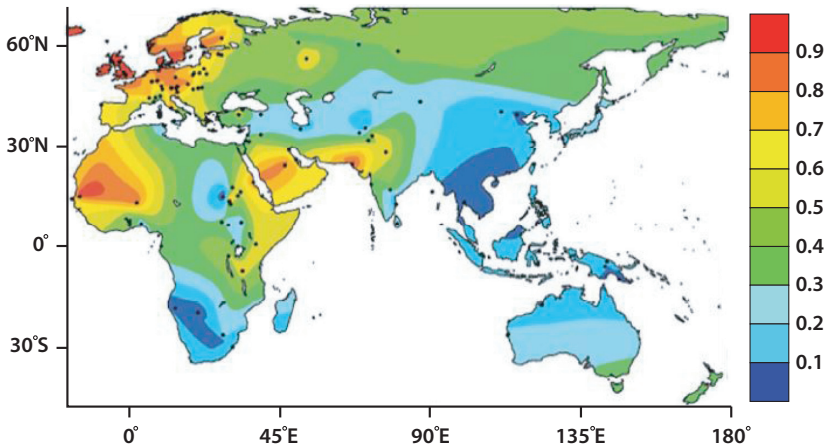

Fig. 5 *The old world distribution of phenotypic lactase persistence. Based on the map in reference 48 with updates available including the correlations of phenotypic lactase persistence with different genotype changes in different populations as shown on http://www.ucl.ac.uk/macelab/resources/glad/LP_maps. The frequencies of lactase persistence are shown with the dots signifying the location of different studies. Genetic changes are associated with these differences but the lactase persistence gene changes vary markedly in different regions suggesting their independent evolution.*

Alcohol tolerance

Alcohol sensitivity is a quantitative trait determined by the cumulative effects of multiple segregating genes and their interactions with the environment [50]. The generation of alcohol by fermenting plants seems to have been an early feature of our evolution and has served a variety of functions including for religious and medicinal purposes and as an uncontaminated source of liquid as well as having social and economic attributes. Modern analyses have shown some benefits, for example in terms of cardiovascular health and the lower prevalence of gallstones in drinkers, but the overall societal disadvantages of heavier drinking are considered overwhelming. Since alcohol sensitivity results from the cumulative effects of multiple different genes, alcohol metabolism varies markedly across populations within Africa, and between Europeans and Asians. In East Asian and Polynesian population, mutations in the aldehyde dehydrogenase genes have a particularly marked effect on alcohol metabolism; in East Asians, acetaldehyde accumulates resulting

in hot flushes and discomfort on drinking alcohol which relates to a mitochondrial genetic mutation in acetaldehyde dehydrogenase activity which is sometimes considered protective of alcoholism and gastrointestinal cancers. Five major haplotypes based on five SNPs across the *ALDH2* gene have been found in East Asian populations with atypical gene activity [51]. The affected Asian populations traditionally have had a major burden of hepatitis B which amplifies markedly the risk of major liver disease, cancers and early death in alcohol drinkers so the atypical gene with lower ADHD activity may have then emerged as a protective response to the burden of endemic hepatitis [52].

Vitamin D

Changes in population skin pigmentation are generally thought to have occurred 50–100 000 years ago as some migrated out of Africa [53] where the intensity of sunlight exposure is less. Since proto-vitamin D requires activation by irradiation with ultraviolet light (UV), it has been assumed that skin pigment shielding the skin from UV was lost as populations moved to higher latitudes with lower incident sunlight. Since deficiency in vitamin D alters calcium metabolism, its deficiency results in bone malformations, the extreme case being rickets. Vitamin D is also important in normal immune function.

Recently, the vitamin D scenario for fair skin in northern populations has been challenged. Greaves [54] notes that human's closest neighbouring species, chimpanzee, already has pale skin beneath the dense hair covering. Since the key development of the early hominins was their emergence from the forests of Africa 2–3 million years ago, Greaves suggests that the loss of body hair allowed ready sweating by the early hominin hunter gatherers but exposed fair skin. The development of melanin protection of the skin then emerged through a specific change in the melanin MC1R gene now found in a similar form throughout the many Black African populations. Hence, pale skin may have been the ancestral state that was sustained as people moved into the northern climates. Recent analyses indicate a complex picture of identical multiple genes, viz. SLC24A5, *MFSD12*, *DDB1*, *TMEM138*, *OCA2* and *HERC2* affecting skin pigmentation throughout African populations and these variants are also found in South Asian and Australo-Melanesian populations [55].

Adaptation in FADS genes and long-chain essential fatty acid synthesis

Reference has already made to the evolutionary significance of the capacity to produce long-chain essential fatty acids with different evolutionary polymorphic changes in the FADS genes in different African populations and in Europe [16, 18]. Recently, observations suggesting differential selection of the same FADS genes have been found in Native Americans as observed in Inuits with the suggestion that these arose in Beringia before *Homo sapiens* migrated from Siberia [56]. There is therefore the suggestion that populations in different regions of the world have different capacities to synthesize the LCPUFAs but these suggestive studies based on FADS SNP differences, although suggestive, have not been matched yet by analyses of the actual capacity of different human groups to synthesize the longer chain unsaturated fats using either isotopic techniques or actual balance studies with marker or other analyses of end product production [57, 58].

Thrifty genes

Neel decades ago suggested that *Homo sapiens* had evolved with 'thrifty genes' that would have provided survival advantages during periods of food deprivation but that the changes might also incur the risk of obesity and diabetes in modern societies [59]. To date, this theory remains controversial. The propensity for some individuals within a population to put on weight and become obese in an obesity-inducing environment is, however, markedly influenced by genetic differences with twin and other feeding studies suggesting that inherited traits explain 40–70% of variation in propensity to obesity [60]. More recent genomewide association studies, however, have shown that the genetic architecture of obesity is multifactorial and polygenic with hundreds of common genetic variants that are common exerting only small effects on body weight control [61, 62]. For example, the comparison of active and inactive alleles of the FTO gene, considered the gene with the greatest effect on body weight, reflects a difference of approximately only 1.5 BMI units. Furthermore, the presence of the active alleles does not constitute a biological inevitability for the development of obesity as the influence of the FTO alleles is counteracted by a high level of physical activity, albeit this is also affected by genetics [63]. A greater propensity to diabetes on weight gain in some populations has been found [64, 65] but whether this is an

intrinsic feature of mitochondrial genotype differences in these populations or reflects the early nutritional and other influences of early epigenetic and other programming [66] seems uncertain.

Neel's hypothesis of evolutionary pressure involving the selection of thrifty genes implies that the recurrent famines of the last few millennia have continued to promote the development of thrifty genes. Yet famine survival still does not necessarily depend on the degree of fat stores [67] and the earlier development of social skills and the use of fire in cooking with a continued ability to move rapidly to avoid predators was important. Furthermore, searches for signatures of natural selection at known obesity SNPs are no more common than are found in a random selection of SNPs across the genome [68]. This has led to the hypothesis that the propensity of some individuals to obesity arose from genetic drift in the genes regulating body fatness, that is the 'drifty gene' hypothesis [69].

Protein metabolism and needs

Dietary interventions are complex with interactions between macronutrients, compensatory feeding responses and uncertainty about reference diets influencing the interpretation of outcomes. Nutritional geometry is a state-space modelling approach that explores how animals respond to and balance changes in nutrient availability. In insects and mice, such studies have shown that low protein, high carbohydrate diets are associated with the longest lifespan in *ad libitum* fed animals [70]. Thus, balancing quantity and quality of dietary proteins relative to other nutrients has been considered a key determinant of evolutionary fitness. It has been recently shown in fruit flies that a genome provides a template for defining optimal amino acid proportions. Such exome-matched diets define appropriate amino acid ratios, enhance early life fitness being simultaneously beneficial for growth, appetite, reproduction and lifespan [71].

Higher protein turnover rates are found in chronically undernourished Indian adults but they have a smaller muscle mass and therefore a relatively higher proportion of rapidly turning over tissues [72]. So one might expect that chronic undernutrition would lead to selective adaptation in essential amino acid and therefore total protein requirements, but this does not seem to be true [73, 74]. Between individuals, however, there is substantial variation in requirements which have a log normal distribution reflecting the very different amino acid requirements within a population [75].

Public health implications

Given our new understanding of the genetic variation across populations are we now in a position to specify different food needs for different ethnic groups? Currently, the World Health Organization sets out nutritional needs based on the principle that we are all essentially the same and this was considered very important given the degree of prevailing ethnic prejudice across the globe. The further challenge was that practically all the detailed metabolic and nutrient balance studies leading to an understanding of the nutritional requirements and their variation between individuals have come from studies in North America and Europe and are based for the most part on analyses of metabolism and needs of one ethnic group. It has become accepted that there are differences in lactose and alcohol tolerance and in vitamin D requirements amongst different groups but the implications of our new understanding of genetic differences are only just emerging and we now need detailed metabolic and requirement analysis linked to different genotypes. Already, however, it is clear that the greater propensity of Asians, some Central American populations and some African and the Middle East populations to diabetes on weight gain means that the modest public health measures to prevent weight gain and the development of diabetes have to be far more stringent than those currently promulgated in North America and Europe [76].

Conclusions

Our understanding of the complexity of human evolution is rapidly improving but the analyses of the way dietary factors might have influenced the genetic control of particular metabolic attributes and individuals' susceptibility to disease are only just emerging. Detailed dietary and physiological/metabolic analyses are underway in conjunction with genetic analyses in different African populations but unravelling the basis for the genetic variation in metabolic responses to standardized dietary intake in different populations across the world requires far more detailed and rigorous study.

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Conflicts of interest statement

WPTJ, POI, GF, DCW and PJS have no conflicts of interest. RJJ has equity in Colorado Research Partners that is developing inhibitors of sugar metabolism and also has equity in XORT Therapeutics, which is a start-up company developing novel xanthine oxidase inhibitors.

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