Nutrition and its role in human evolution

By

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Abstract

Our understanding of human evolution has developed rapidly over recent decades, facilitated by large scale cataloguing of genomic among both modern and archaic humans.. It seems clear that the evolution of primates incuding the evolution of the ancestors of chimpanzees and the human forms, the hominins, took place 7-9 million years ago with some migration out of Africa by the earlier hominins with *Homo sapiens* slowly emerging as climate change induced 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 occuring 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 with corresponding 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 among non – African popualtions than in Africans. Hybridization with archaic hominins occurred around this time such that all non – African modern humans possess some Neanderthal ancestory and Melanesian populations additionaly possess some Denisovan ancerstory. Human popaultions 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 pattenrs 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. The process of human evolution including genetic drift and an adaptation to local environments, in part through changes in mitochondrial and nuclear DNA. These efects may underlie susceptibilities to some modern human pathologies including folate-responsive neural tube defects, diabetes, other age-related pathologies and mental health disorders.

Introduction

Before the development of genetic analyses there were three approaches to study human evolution, namely analysis of anthropological, archaeological, and fossil evidence. Notably, all these approaches accepted that *Homo sapiens* arose in Africa and no human-like species emerged from 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; further genetic changes occurred during this period. 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 *Homo* lineages diverged from one another about 7-8 million years ago and several different types of early forms of hominins evolved increased brain sizes which further increased along the *Homo sapiens* lneage 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) e.g. in genes involved in neuronal communication, ion transport and regualory processes while quantitative comparisons of protein levels indicate differences in perception and cognition, metabolic processes and the organisation 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 human 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, to adapt and act collectively and to safeguard offspring and the more vulnerable members of a group both during the day and night from large predators. 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 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) 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, e.g. 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 artifacts 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 acros the genome with the X chromosome having only about a fifth of the Neanderthal ancestory of the autosomes (10). The Denisovans meanwhiie interbred with theancestors of the Oceanic groups of modern humans.. Currently New Guineans and Australians have over 3% Denisovan ancestory with the other Oceanic groups beyond the Makassar Strait in Asia ranging from 0.9% - 3% The Native North Americans having similar amounts to the Siberians and East Asians consisten 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 to 1.3 million years ago

Recent discoveries and modern genetics emphasise that *Homo sapiens* arose as a discreet entity in Africa over 300,000 years ago, primarily on the basis of 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 and her colleagues emphasise how different groups increased markedly with further migrations and adaptations to the remarkably different ecosystems of Africa (14). The current anthropological division of the multiple African groups or tribes into 4 major groups is based on their use of different types of language which are consistent with genetic analyses, emphasising the

diversity of form of homo sapiens in different environments(15).(**Figure 1**). Studies suggest that over 2,000 languages are still in use in Africa. The evolution, migration and specialization of different populations have 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. As the different 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 West Africa to Sub-Saharan Africa over the last 4,000 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, e.g. in amylase copy number variation, lactase persistence, bitter taste perception and indeed the propensity to some haemoglobinopathies (16). There is also evidence of local amplification of the FADS genes (17), which increase long chain polyunsaturated fatty acid (LC PUFA) synthesis synthesis from plant-based medium chain PUFAs. 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 invoved different alleles in different environments e.g. in Europe where again it seems to reflect changing environmental circumstances e.g 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, i.e. 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 non – coding mutations that affect 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 dduring periods of rapid evolutionary change and can take many forms and some of these are

in practice deleterious leading to 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, i.e. agricultural societies and hunter gatherers, have on average more amylase 1(*AMY1*) copies than those in 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 ot 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 and resulting increase in protein levels not only improve the digestion of starchy foods, but may also help to overcome the impact of intestinal diseases (24). Although this duplication in a modern setting has also been linked to a reduced propensity to obesity 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 among 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 mitochondrila 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 2,000 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 germline. Since a new mutation arises in a population of normal mtDNAs, the intial state is a cell with a mixture of mutant and normal mitochondrial DNAs i.e. 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 mitrochondrial DNA mutations are deleterious, it is essential that heteroplasmic mitochondrial mutations rapidly segregate out in the maternal germline 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 germline 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 reults 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 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

epxpression and variable clinical manifestions (28)
As *Homo sapiens* expanded in Africa, mitochondrial DNA muttaions arose along different maternal lineages. Some of the functional variants proved to be beneifical 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 macro-haplogroup "L". About 65,000 years ago, two mitochondrial DNAs arose in northwester Africa and only these two mitochondrial DNA lineages, designated "M" and "N", successfully left Africa to colonize the rest of the world. Macro-haplogroup 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. Macro-haplogroup 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 regionaity of mitochondrial DNA population variation is the result of adaptive selection to environmental factors such as thermal stress and immune responses to infection.
While the founding haplogroup mitochondrial DNA variants were 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.(28, 29,) (**Figure 2**). .

Physiological and pathophysiological differences between populations.

Altitude adaptation. Given the diversity in nuclear and mitochondrial DNA patterns among 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 2,500 m and analyses in Tibet, Ethiopia and the Andes reveal distinct genetic adaptations to the altitude related hypoxia in each region(30). 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 observed in a cell are suppressed (31).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 (32). 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(33) 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 **Figure 3**. Alpha thalassemia in the people of the high Himalayan valleys of Nepal and India confers particularly high malarial resistance(34). 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 i.e. before the age for reproduction, the mutation is maintained because individuals with the more abundant heterozygous sickle cell trait, HbAS, are also far more resistant to malaria (35). This resistance relates to gene changes in the hemoglogin protein sequence which cause the haemoglobin to aggregate under the low oxgen 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 propteins are used as receptors by the malarial parasite to invade the erythrocyte. For example, iIndividuals 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

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 of progressive extinction of apes in Europe from 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 (36) Tests with the ancestral uricase also show its effect in blunting fructose's metabolic effects (37) and increases in uric acid levels are associated with increasing insulin resistance (38). Recent analyses have also suggested that high salt and high glycaemic diets induce the metabolic syndrome through a genetic- dietary interaction (39). The uricase mutation cannot, however, explain the range of propensities to weight gain or metabolic disorders observed in contemporary humans.

Population differences in nutritional processing?

Some evident population differences in nutritional processing based on genetic differences are summarised in **Table 1 (**40**,**41**),** but four examples will be considered here in more detail.

Persistence of lactase in some populations.

It is evident that 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 (42) – see **Figure 4** (43). This adaptation for lactase persistence seems to have been provoked by the development of domestication of cattle, sheep and goats about 7,500-9,000 years ago (44).While 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 2,000 years ago. Given that weaning and the loss of immune input from breast milk is 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 high for millennia with about a 50% mortality for children under 5 yrs of age. It is therefore not surprising that any genetic change that involved a tendency toward 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.

Alcohol tolerance.

Alcohol sensitivity is a quantitative trait determined by the cumulative effects of multiple segregating genes and their interactions with the environment (45). 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, uncontaminated sources of liquid, as well as its social and economic attributes. Modern analyses have shown some benefits e.g. in terms of cardiovascular health and the lower prevalence of gallstones in drinkers, but its overall disadvantages are overwhelming. Since 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 populations 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.

Vitamin D.

Changes in population skin pigmentation are generally thought to have occurred 50 -100,000 years ago as some *Homo sapiens* migrated out of Africa (46) 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 UV shielding skin pigment was lost as populaitons moved to higher latitudes with lower incident sun light. 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 poulations has been challenged. Greaves (47) notes that human's closest neigboring 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 suggested that the loss of body hair allowed ready sweating by the early hominin hunter gatherers and 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. However, more recent analyses, indicate a complex picture of identical multiple genes viz *MFSD12*, *DDB1*, *TMEM138*, *OCA2*, and *HERC2* affecting skin pigmentation throughout African populations and these variants are also found in South Asian and Australo- Melanesian popualtions

(48)..

Adaptation in FADS genes and long chain essential fatty acid synthesis
Differences in 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 (17, 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(49) There is therefore the suggestion that populations in different regions of the world have different capacities to synthesise the LCPUFAs but these suggestive studies based in FADS SNP differences, although suggestive, have not been matched yet by analyses of the actual capacity of different human groups to synthesise the longer chain unsaturated fats using either isotopic techniques or actual balance studies with marker or other analyses of end product production(50,51).

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 oalso incur the risk of obesity an ddiabetes (52). To date this theory remans 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 (53). More recent genome wide 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 (54,55) For example, the comparison of active and inactive alleles of the FTO gene 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, with the influence of the FTO alleles been counteracted by a high level of physical activity. A greater propensity to diabetes on weight gain in some populations has been found (56, 57) 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 (58) seems uncertain.

Neel’s hypothesis of evolutionary pressure involving the selection of thrifty genes fimplies that the recurrent famines of the last few muillennia have continued to promote the development of thrifty genes. Yet famine survival still does not necessarily depend on the degree of fat stores (59) 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 known obesity SNPs are no more common than a random selection of SNPs across the genome (60) so the propensity of some individuals to obesity is siuggested to arise from genetic drift in the genes regulating body fatness in individuals i.e. the “drifty gene” hypothesis (61).Such a drift may have started perhaps 2 million years ago when the predation of ancestral humans became less likely.

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 (62).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 (63).

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 (64). 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 (65.66) 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 (67). Thus as with energy metabolism there do not seem to be intrinsic differences in requirements between different ethnic groups that cannot be related to differences in size and body composition.

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 Organisation 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 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 among different groups but the implications of our new understanding of genetic differences is 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 popualtions, 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 (68).

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