

The RBCT was a unique and ambitious undertaking, and the report of the ISG, supported by unprecedented contemporary publication of a suite of peer-reviewed papers (including [5–7,11], see [4] for a full list), provides compelling evidence for the profound influence of wildlife ecology and sociobiology on disease dynamics, and, ultimately, on the efficacy of management interventions. The challenge now facing epidemiologists and ecologists is to further our understanding of not only how transmission rates change with density and social structure, but also how they might be positively influenced by management interventions.

Disclosure statement

C.L.C. served as an ecological advisor to the ISG and R.J.D. also advised on some aspects of the Group's work. Both are authors of some of the resulting papers, but not of the main report. G.C.S. analysed some of the trapping data during the trial.

Acknowledgements

We acknowledge financial support from Defra for the long-term investigation of bovine TB at Woodchester Park.

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0169-5347/\$ – see front matter.

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doi:10.1016/j.tree.2007.10.011 Available online 11 January 2008

Research Focus

Demeter's legacy: rapid changes to our genome imposed by diet

Etienne Patin and Lluís Quintana-Murci

Human Evolutionary Genetics, Centre National de la Recherche Scientifique (CNRS) URA3012, Institut Pasteur, 25 rue Docteur Roux, 75724 Paris Cedex 15, France

The transition from foraging to farming allowed humans to produce several foods in abundance that were previously scarce. However, early farmers had to adapt to benefit fully from this energy-rich but initially detrimental food supply. Perry *et al.* recently showed that natural selection has increased the copy number of a gene encoding a starch-digesting enzyme in farming populations. This study illustrates that genetic adaptation to new diets has occurred in humans since the agricultural revolution.

Agriculture: a poisoned chalice

In most food-producing societies, the concepts of abundance and fertility are tightly linked to agriculture. For

instance, Demeter, the Greek goddess of crops, was thought to bring springtime and to nourish youth. This protective role illustrates the common representation of farming as a source of health and abundance. However, archaeological records, including clear signs of anaemia in early farmers' bones [1], clearly contradict this mythological image. The transition from hunter-gathering to farming was initially associated with a heavy disease-burden, because early farmers had not yet adapted to their new diet and this caused deleterious digestive disorders [1].

A key question in nutritional ecology concerns how our ancestors adapted to new food supplies, particularly those associated with the emergence of farming (Box 1). Cultural adaptation can provide a partial answer, because humans can process foods (e.g. by cooking or fermentation) to increase digestibility. However, changes in the genetic

Corresponding author: Quintana-Murci, L. (quintana@pasteur.fr).

Box 1. The 'Neo-diet' of farming communities

Until the end of the Pleistocene, human populations subsisted by fishing, hunting wild animals and gathering wild plants, with no direct control over the reproduction of the species exploited. At various times between 10 500 and 4000 years ago, food production based on plant and animal domestication appeared independently in several regions of the world [12]. In most cases, this transition was associated with a shift from a nomadic to a sedentary lifestyle. Archaeological evidence indicates that farming societies consuming domesticated species had a much less diverse diet than hunter-gatherer societies, probably because only a few plants and animals were amenable to selective breeding for desirable traits. Farming populations adopted a less diverse, energy-rich, carbohydrate-dense diet composed principally of cereals (e.g. maize, rice, wheat and barley, etc.), fatty meats, dairy products, starchy root vegetables (e.g. potatoes and yams), alcoholic beverages and salt [1]. The human digestive system was not accustomed to several of these newly introduced nutrients (e.g. maltose from starch, lactose from milk, gluten from wheat, alcohol, etc.) or at least, to high concentrations of these nutrients in the gut. Our ancestors, as with all other great apes, possessed the enzymatic machinery necessary to metabolise these substances, but the basal expression of such enzymes was not yet adapted to an increase in the amount of these nutrients passing through the gut.

regulation of food metabolism might also have contributed to human adaptation to a changing diet (Figure 1). This hypothesis remained speculative until recently. Perry *et al.* [2] have now demonstrated that expression of the gene encoding the enzyme responsible for starch hydrolysis has adapted to increases in starchy food intake due to the introduction of farming.

Adjusting the spit to the pot

Recent studies have demonstrated a clear role for positive selection in the evolution of *Homo sapiens*, despite the fact

that these changes in selective pressure have occurred very recently [3]. The dietary revolution associated with farming societies might have thus imposed a selective pressure sufficiently intense to modify the expression profiles of digestive enzymes. Perry *et al.* [2] provide support for this idea in their recent study. They assessed the extent to which the consumption of starch, a prominent component of the diet of farmers, has exerted selective pressures detectable in our genome. They characterised patterns of genetic variation for salivary amylase, the enzyme responsible for starch digestion in humans. The amylase-encoding *AMY1* gene is present in multiple copies on chromosome 1p21.1. The number of copies varies between individuals. Perry *et al.* found a significant correlation between *AMY1* genotype (copy number polymorphism) and phenotype (amylase concentration in saliva). They also observed that populations with traditional starch-dense diets had a higher *AMY1* copy number than populations with low-starch diets, such as rainforest and arctic hunter-gatherers. Indeed, population differentiation between the high-starch Japanese and the low-starch Siberian Yakut was significantly higher at the *AMY1* locus than at most other loci with variable copy numbers. Finally, the lower *AMY1* copy number observed in chimpanzees than in humans (about one-third lower in chimpanzees) is consistent with the lower salivary amylase concentrations in these primates (one-sixth to one-eighth of concentrations in humans) and their predominantly starch-poor diet. These observations indicate that low *AMY1* copy number is the ancestral state in humans. Thus, amylase concentration was probably initially low in the saliva of ancestral hunter-gatherers, and then gradually increased in populations with high-starch diets (including farmers), facilitating digestion of the new food supply.

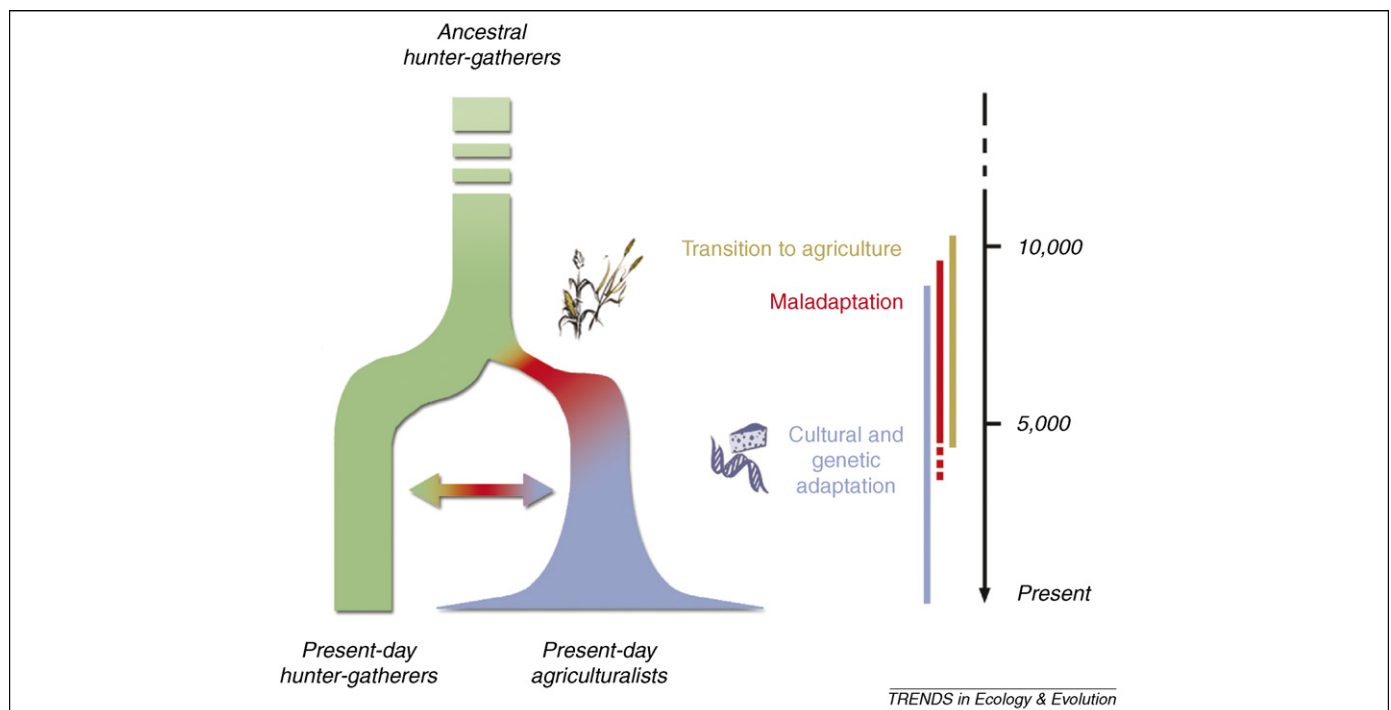


Figure 1. Schematic diagram of human evolutionary history in terms of lifestyle, population size and diet. The middle arrow illustrates the continuously open option for hunter-gatherers to become farmers and vice versa (for an example of lifestyle reversion, see [11]). Note that this diagram does not imply that hunter-gatherers have not continued to evolve until the present day. We simply know much less about the environmental changes to which they have had to adapt.

A vital daily amount of cereals and milk

Perry *et al.* did not provide classical statistical support for the action of positive selection on *AMY1* copy number, because neutrality tests at the inter-species and within-species level have not yet been adapted to copy number variation. However, the widespread occurrence of high *AMY1* copy number in unrelated populations with starchy diets does support the hypothesis that these human groups independently acquired extra copies by positive selection, rather than through shared ancestry. This, together with growing evidence that convergent evolution favours lactase persistence in humans (Box 2), suggests that a strong selective advantage is conferred by high levels of amylase in saliva or lactase in the small intestine. So why have these two phenotypes been so beneficial to farmers?

First, starch and lactose have detrimental effects on human health unless amylase and lactase are present in sufficient quantities [2,4]. Early farmers were probably weakened by the burden of new infectious diseases, and digestive disorders might have reduced lifespan further under these critical conditions. Second, an energy-dense diet is essential during human pregnancy and early childhood, directly increasing neonatal survival rates [5]. Third, inefficient starch digestion probably prevented early farmers from profiting from the other components of starchy nutrients, such as cereal fibres. Finally, there

were probably so few species both available and suitable for domestication at the time that early farmers had little choice in terms of what they could eat in sufficient quantities to prevent starvation and to sustain the increase in density of settled populations. Farmers naturally able to metabolise starch and lactose would clearly have been at an advantage in terms of both energy intake and fecundity.

Winning the evolutionary race

The observed differences in *AMY1* copy number between populations of recent common ancestry (e.g. Siberian Yakut and Japanese) suggest that populations with starchy diets have obtained extra *AMY1* copies over the past few hundred generations [2]. The observed frequency of the lactase-persistence allele and its associated variation are compatible with positive selection events beginning only 5000 to 12 000 years ago in Northern Europe, 1400 to 3000 years ago in the Urals, and 3000 to 7000 years ago in East Africa [6,7]. These findings for amylase and lactase suggest that humans show rapid genetic adaptation to new nutrients. However, these two genes are unusual in several ways, meriting further examination. *AMY1* is one of the most variable loci in the genome in terms of copy number [8], implying a rapid copy-number response to new selective pressures (due to mutation). The dominant mode of inheritance of the lactase-persistence allele (Box 2) directly affects the time required for this mutation to reach high frequency; dominant alleles can increase in frequency much faster than recessive alleles, because only one copy is required to modify individual fitness. This, together with the much lower probability that new mutations will be dominant rather than recessive [9], indicates that the spread of most potentially selected alleles would probably be much slower than that of the lactase-persistence allele. Thus, the rate of adaptation of amylase and lactase genes should not be seen as being typical of diet-related genes. Human genes have probably adapted rapidly to dietary changes, but additional evolutionary studies of genes involved in the metabolism of farming-derived nutrients (e.g. sucrase-isomaltase, transglutaminases, etc.) are now required. In addition, these studies should be carried out in ethnologically well-defined human populations for which detailed nutritional information is available. Indeed, different lifestyles do not necessarily involve radical changes in diet; for example, the Hadza hunter-gatherers do consume starch-rich tubers [10]. This should make it possible to determine whether our genes are winning the evolutionary race.

What drives human evolution?

Knowledge is more easily transmitted than alleles, so cultural adaptation probably played a key role during the adaptive period accompanying the agricultural revolution. Early farmers processed food to decrease its potential to cause digestive problems (e.g. by adding bacterial lactase to dairy products), thereby using their technical abilities to sustain their demographic explosion. Nonetheless, the work of Perry *et al.* [2] clearly demonstrates that our genes did not lag behind, but instead evolved quite rapidly (Figure 1).

Box 2. Following the Milky Way

The ability to digest milk rapidly declines after weaning in most humans, owing to a decrease in lactase levels in the small intestine. The ingestion by 'lactose-intolerant' adults of even small quantities of milk causes abdominal pain and diarrhoea [4] (Online Mendelian Inheritance in Man [OMIM] 223100). However, many human populations worldwide, particularly those that have traditionally based their mode of subsistence on pastoralism, can continue to drink milk into adulthood without problems, because lactase expression persists in the gut. Twin studies first indicated a genetic basis for lactase persistence, a trait that seems to be inherited as a single dominant mutation. Genotype-phenotype studies subsequently demonstrated that lactase persistence in Europeans was due to a single mutation in the promoter of *LCT* – the gene encoding lactase – extending *LCT* expression into adulthood. In Europeans, this lactase-persistence allele, T-13910, is part of a haplotype (a combination of alleles) largely exceeding its expected length under neutrality [13]. This genomic feature is a clear signature of recent positive selection, which has allowed the *LCT* allele to reach very high frequencies in European populations, particularly in northern Europe. The geographic distribution of the lactase-persistence allele is strongly correlated with historical milk-consumption. This observation, together with the estimated age of expansion of the T-13910 mutation ~5000–12 000 years ago [6], suggests that lactase persistence emerged in response to the cultural innovation of dairying associated with an agricultural lifestyle.

Intriguingly some East African populations with a high prevalence of lactose tolerance in adulthood do not present the European T-13910 allele. Sarah Tishkoff and colleagues [7] recently solved this conundrum; a different mutation in the *LCT* promoter region – C-14010 – also increases *LCT* expression and has been positively selected in East African pastoralists. This provides a fascinating example of convergent adaptation within our species, and shows that the cultural trait of milk consumption confers such a strong selective advantage in terms of human survival that lactase persistence alleles have emerged independently in several parts of the world.

Future studies of selected human genes will shed light on our ecological past, undoubtedly confirming that our history is shaped by both our culture and our genes.

Acknowledgements

Financial support was provided by Institut Pasteur, by the Centre National de la Recherche Scientifique (CNRS), and by an Agence Nationale de la Recherche (ANR) research grant (ANR-05-JCJC-0124-01). E.P. is supported by the Fondation pour la Recherche Médicale (FRM).

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doi:10.1016/j.tree.2007.11.002 Available online 11 January 2008

Letters

Large fitness benefits from polyandry in the honey bee, *Apis mellifera*

Benjamin P. Oldroyd¹ and Jennifer H. Fewell²

¹ Behaviour and Genetics of Social Insects Laboratory, School of Biological Sciences A12, University of Sydney, NSW 2006, Australia

² School of Life Sciences and Center for Social Dynamics and Complexity, Arizona State University, Tempe, AZ 85287-4501, USA

In the August issue of *TREE*, we argued that multiple mating by social insect queens can enhance colony fitness via an enhanced task allocation system [1]. The essence of the task allocation hypothesis is that in many multiple-mating (polyandrous) eusocial insect species such as honey bees, individual workers are genetically biased to perform specific tasks (genetic task specialization, GTS). Genetic diversity in these colonies provides a worker force that can perform a range of tasks efficiently and can allocate its workers appropriately across tasks as environmental conditions change. Our review showed that there is an accumulating body of evidence for the hypothesis that more genetically diverse colonies can better respond to changing environmental conditions, and indirect evidence that increased genetic diversity positively affects fitness via task allocation. However, we acknowledged that a definitive experimental demonstration linking fitness to genetic diversity remained lacking.

This demonstration is now available. In a new article, Mattila and Seeley [2] provide a compelling demonstration of large fitness benefits of polyandry in the honey bee *Apis mellifera*. These differences occur independently of benefits that can arise from sex allele diversity [3] disease resistance [4] or increased volumes of stored sperm in queens [5] in polyandrous colonies.

Mattila and Seeley created genetically ‘uniform’ colonies by artificially inseminating sister queens, each with semen from a single drone. The performance of these uniform monandrous colonies was compared with that of colonies headed by queens inseminated by a similar volume of semen obtained from 15 unrelated drones – ‘diverse’ polyandrous colonies. By using uniform volumes of semen from unrelated drones, Mattila and Seeley controlled for effects of multiple mating on sperm number (which was made approximately equivalent), and the problem of reduced brood viability – which can occur if a queen mates with a single male carrying the same sex allele as herself [3]. They additionally controlled for disease effects by prophylactically medicating the colonies.

To assess fitness effects of polyandry, Mattila and Seeley constructed artificial swarms containing equal numbers of workers, each with their own polyandrous or monandrous queen mother. They then measured those variables most directly related to colony growth after swarming: the amount of comb built, number of brood reared, weight of food stored and forager activity. Just two weeks after swarms were established, colonies led by polyandrous queens had significantly more comb than monandrous ones, and their lead continued to increase throughout the trial, which extended for nearly 12 months. The polyandrous colonies maintained foraging rates up to 78% higher than uniform colonies, enabling them to store significantly more

Corresponding author: Oldroyd, B.P. (boldroyd@bio.usyd.edu.au).