How culture shaped the human genome: bringing genetics and the human sciences together

Kevin N. Laland, John Odling-Smee‡ and Sean Myles§ ||*

Abstract | Researchers from diverse backgrounds are converging on the view that human evolution has been shaped by gene–culture interactions. Theoretical biologists have used population genetic models to demonstrate that cultural processes can have a profound effect on human evolution, and anthropologists are investigating cultural practices that modify current selection. These findings are supported by recent analyses of human genetic variation, which reveal that hundreds of genes have been subject to recent positive selection, often in response to human activities. Here, we collate these data, highlighting the considerable potential for cross-disciplinary exchange to provide novel insights into how culture has shaped the human genome.

Accounts of human evolution frequently assume that the selective events that shaped us were changes in the external environment, stemming from events beyond human control. For instance, theories of the inception of *Homo* species emphasize a global trend towards cooler, drier climates, which pushed an arboreal ape out of contracting forests into savannah[1]. Likewise, heat stress in the open is a plausible hypothesis for the evolution of bipedality, hairless skin and sweating[2–4]. By contrast, little consideration has been given to the possibility that cultural practices might have transformed the selection pressures acting on humans. This may be because it has only recently been shown that natural selection can bring about substantial changes in genomes that are detectable over thousands of years, as revealed by measurements of the typical rates of response to natural selection among animals in the wild[5] and statistical analyses that detected recent rapid adaptation in the human genome[6–11].

This traditional conception of human evolution is now being challenged by recent anthropological studies that show that human cultural practices have modified environmental conditions, triggering changes in allele frequencies[12,13]. In addition, analyses of data from the human genome have revealed numerous genes that have experienced recent positive selection, many of which exhibit functions that imply that they are responses to human cultural practices[6–11,14]. For instance, several lines of evidence show that dairy farming created the selective environment that favoured the spread of alleles for adult lactose tolerance[12,13,15,16]. Estimates for the number of human genes that have been subject to recent rapid evolution range from a few hundred to two thousand: Williamson *et al.*[14] conclude that up to 10% of the human genome may be affected by linkage to targets of positive selection. Although in the majority of cases it is not known what phenotype was the target of the inferred selection, nor which environmental conditions favoured such phenotypes, human cultural practices remain strong candidates, and geneticists are increasingly considering culture as a source of selection on humans[17,18].

Such data are consistent with two branches of mathematical evolutionary analysis: gene–culture co-evolutionary theory, which explores how genetic and cultural processes interact over evolutionary time[19–23], and niche-construction theory[24–30], which investigates the evolutionary impact of the modification of environments by organisms. The models provide hypotheses for, or novel insights into, the evolution of learning, culture, language, intelligence, cooperation, sex differences and mating systems. Analyses of these models have confirmed that genes and culture could plausibly co-evolve, often revealing patterns and rates of change that are uncharacteristic of more traditional population genetic theory[22,31–34]. Gene–culture dynamics are typically faster, stronger and operate over a broader range of conditions than conventional evolutionary dynamics, leading some practitioners to argue that gene–culture co-evolution could be the dominant mode of human evolution[32–34].

**School of Biology, University of St Andrews, Bute Building, Westburn Lane, St Andrews, Fife KY16 9TS, UK.*
‡School of Anthropology, University of Oxford, 51/53 Banbury Road, Oxford OX2 6PE, UK.
§Institute for Genomic Diversity, Cornell University, Ithaca, New York 14853-2703, USA.
||Biology Department, Acadia University, Wolfville, Nova Scotia B4P 2R6, Canada.
Correspondence to K.N.L.
e-mail:
knl1@st-andrews.ac.uk
doi:10.1038/nrg2734

Box 1 | **What is culture?**

To the layperson, the term 'culture' typically evokes images of fine art and fashion, but historically anthropologists have characterized culture as the complex of beliefs, values, behaviour and traditions associated with a particular population. Neither notion is particularly conducive to scientific analysis. Human culture has proven a difficult concept to pin down, and there exists little definitional consensus within the social sciences[12]. In this vacuum, geneticists and biological anthropologists, eager to explore how cultural phenomena interact with genes, have taken a pragmatic line to studying culture. For these researchers, culture is information that is capable of affecting individuals' behaviour, which they acquire from other individuals through teaching, imitation and other forms of social learning[33]. Here, 'information' includes knowledge, beliefs, values and skills. Cultural change can then be modelled as a Darwinian process comprising the selective retention of favourable culturally transmitted variants, as well as various non-selective processes, such as drift[20,21]. Rather than attempting to describe the entire culture of a society, culture is broken down into specific traits (for instance, milk users or non-users, or consumption of a starch-rich or starch-poor diet), which allows their frequencies to be tracked mathematically.

This broad characterization opens up the possibility of culture in other animals, and indeed traditions for exploiting prey or food sites, tool-use and vocalizations have been reported in a variety of animals, including fish, birds, cetaceans and non-human primates[93]. These traditions exhibit several properties of interest to biologists[93]. Perhaps the most obvious is that culture is a source of adaptive behaviour; individuals can efficiently acquire solutions to problems, such as 'what to eat?' and 'with whom to mate?', by copying others. But a variety of studies, ranging from investigations of fish mating sites to human foraging traditions, have established a capability of culture to propagate behaviour in a manner that is to some degree independent of the ecological environment. Culture can also generate patterns of phenotypic variation in space: clines in behavioural characteristics have been reported for orang-utan behaviour, birdsong and whale vocalizations. Moreover, these traditions modify the action of selection. For instance, models suggest that song learning in birds affects the selection of alleles influencing song acquisition and preference, can facilitate speciation and can lead to the evolution of brood parasitism[94–96].

The premise of this article is that cultural practices have shaped the human genome. We further suggest that a gene–culture co-evolutionary perspective provides opportunities to integrate findings from human genetics and evolutionary theory with anthropological and archaeological data, generating novel hypotheses and ultimately resulting in a more comprehensive understanding of human evolution. Prominent researchers have called for an interdisciplinary project along these lines[17,18]. This perspective also offers novel hypotheses, methods and explanatory mechanisms with which to understand human genetic variation and aspects of human uniqueness, and helps to explain some conflicting findings.

We begin by describing theoretical models of gene–culture co-evolution, outlining the insights that these have generated. This is followed by a description of the anthropological evidence for gene–culture co-evolution. We then discuss genetic studies that have identified loci that have been subject to recent selection, and describe how the conclusion reached by geneticists, that many of these selective sweeps may be in response to human activities, fits with both the formal theory and anthropological evidence. Finally, we consider how these diverse approaches can be better integrated, and explore the implications for researchers investigating the human genome.

Models of gene–culture co-evolution

The argument that genes and culture co-evolve was championed over 30 years ago by pioneers of the field of 'gene–culture co-evolution', a branch of theoretical population genetics[19–23,31,33–35]. These researchers view genes and culture as two interacting forms of inheritance, with offspring acquiring both a genetic and a cultural legacy from their ancestors. Genetic propensities, expressed throughout development, influence what cultural organisms learn. Culturally transmitted information, expressed in behaviour and artefacts, spreads through populations, modifying selection pressures that act back on populations (see BOX 1 for a definition of culture).

Gene–culture co-evolutionary analyses typically build on conventional population genetic theory. In addition to tracking how allele or genotype frequencies change in response to evolutionary processes, such as selection and drift, the analyses incorporate cultural transmission. A worked example of the modelling approach is shown in BOX 2, which addresses the rapid spread in East Asia of an amino-acid-altering variant in ectodysplasin A receptor (*EDAR*), a gene involved in hair morphology. Gene–culture analyses explore how learned behaviour co-evolves with alleles that affect the expression and/or acquisition of the behaviour or whose fitness is affected by the cultural environment. The approach has been deployed to explore the adaptive advantages of reliance on learning and culture[21–23,33,36], to investigate the inheritance of behavioural and personality traits[37–39], and to investigate specific topics in human evolution, such as language or cooperation (TABLE 1).

These analyses have been mainly conducted without any specific knowledge of the human genes involved; rather, hypothetical genes have been proposed with assumed functions, and the dynamics of their co-evolution with cultural traits have been explored. In spite of this, there exists a surprising correlation between the topics addressed in these analyses and the genes that are now known to have been subject to recent selection (discussed below). In BOX 3, we show that gene–culture co-evolutionary theory provides possible explanations for why genes expressed in the externally visible phenotype (for example, hair and eye colour) might be likely targets for selection. These examples provide attractive hypotheses for further investigation because the relationship between gene and phenotype is comparatively well established.

Effects of culture on selection. Gene–culture co-evolutionists view culture as a dynamic process that can shape the material world[21,22,33,34]. Their models have established that cultural processes can dramatically affect the rate of change of allele frequencies in response to selection, sometimes speeding it up and sometimes slowing it down. Recent estimates of the coefficient of selection associated with selected human genes exposed to culturally modified selection pressures reveal extraordinarily strong selection. The lactose-tolerance allele has spread from low to high frequencies in less than 9,000 years since the inception of farming, with an estimated selection coefficient of 0.09–0.19 for a Scandinavian population[40]. Such

observations, combined with the shallow time-depth associated with many recently selected human genes[6], raises the question: could culturally derived selection pressures be stronger than non-cultural ones?

The answer is yes, for two reasons. First, cultural processes occur by virtue of acquired knowledge carried in human brains that is often reliably transmitted between individuals. Although their constancy varies from trait to trait, there is evidence that culturally modified selective environments are capable of producing unusually strong natural selection that is highly consistent in directionality over time[40]. Second, many genes are favoured as a result of co-evolutionary events triggered by phenotypic changes in other species, or in response to other gene-frequency changes in their genomes. When changes in one genetic trait drive changes in a second, the rate of response in the latter depends in part on the rate of change in the former, which, as a rule, is not fast. In comparison, new cultural practices typically spread more quickly than a genetic mutation, simply because cultural learning operates at faster rates than biological evolution[22]. If a cultural practice modifies selection on human genes, the larger the number of individuals exhibiting the cultural trait, the greater is the intensity of selection on the gene. A rapid spread of the cultural practice leads very quickly to maximal intensity of selection on the advantageous genetic variant(s). The effect of these factors has been repeatedly demonstrated by gene–culture co-evolutionary models, which consistently report more rapid responses to selection than conventional population genetic models[21,22,31,41,42]. This may help to explain the argument that culture has 'ramped up' human evolution[17], although other factors are also likely to have a role, such as the increased number of new mutations in the larger populations that have been facilitated by agriculture[17,43].

However, equally important is the observation that cultural selection pressures may frequently arise and cease to exist faster than the time required for the fixation of the associated beneficial allele(s). In this case, culture may drive alleles only to intermediate frequency, generating an abundance of partial selective sweeps[44]. Coop *et al.*[44] suggest that complete selective sweeps at single loci in humans may be uncommon and that adaptations over the past 70,000 years may be primarily the result of partial selective sweeps at many loci.

Niche-construction theory

Niche-construction theory is a branch of evolutionary biology that emphasizes the capacity of organisms to modify natural selection in their environment and thereby act as co-directors of their own and other species' evolution[24,45]. Examples include animals manufacturing nests, burrows and webs and plants modifying

Box 2 | Constructing a mathematical model of gene–culture co-evolution

To illustrate gene–culture co-evolutionary theory, we present a worked example inspired by the observation that a functional non-synonymous substitution in the ectodysplasin A receptor (*EDAR*) gene that is associated with thicker hair (as well as with changes in the skin, teeth and sweat glands) has experienced strong recent positive selection in East Asia[9,97]. How could cultural practices explain this selection? One possibility is a gene–culture co-evolutionary version of sexual selection (BOX 3). Here, we show how it is possible to quantify the changes in frequencies and interactions between culturally transmitted mating preferences and genetic variants of *EDAR* using gene–culture co-evolutionary theory.

For simplicity, we consider two culturally learned preferences, labelled *h* and *H*: *h* individuals mate at random with respect to hair thickness (and other phenotypic effects of *EDAR*), whereas *H* individuals preferentially choose as mates partners with thicker hair. We also consider a single diallelic locus that has alleles A_1 and A_2: A_1A_1 individuals possess thin hair, A_2A_2 individuals possess thicker hair and the hair of A_1A_2 individuals is a function of the dominance parameter d ($0 < d < 1$). That means there are six possible combinations of genotype and mating preference, known as phenogenotypes: A_1A_1h individuals (who have thin hair and no preference for hair thickness in their partners), and similarly A_1A_1H, A_1A_2h, A_1A_2H, A_2A_2h and A_2A_2H individuals, to which we allocate frequencies x_1–x_6. We assume that *H* individuals choose A_1A_1, A_1A_2 and A_2A_2 mates with frequencies $(x_1 + x_2)/z$, $(1 + \alpha h)(x_3 + x_4)/z$ and $(1 + \alpha)(x_5 + x_6)/z$, in which $z = 1 + \alpha h(x_3 + x_4) + \alpha(x_5 + x_6)$. If mating preferences are handed down from parent to offspring, we can specify four classes of matings, namely *h* mothers with *h* fathers (or *h*×*h*), and likewise *h*×*H*, *H*×*h* and *H*×*H* matings, which give rise to proportions b_3, b_2, b_1 and b_0 offspring of type *h* (and $1 - b_3$, $1 - b_2$, $1 - b_1$ and $1 - b_0$ of type *H*). It is apparent that a mating of two A_1A_1h individuals would occur with frequency x_1^2 and give rise to A_1A_1 offspring, proportion b_3 of which would be *h*.

We could similarly calculate the expected proportions of offspring in each phenogenotype category for each of the 36 possible phenogenotype matings. Weighting these proportions by mating frequencies, summing across matings and multiplying by phenogenotype fitness would give us the expected proportion of each phenogenotype in the offspring generation. This leads to a system of six recursive equations, which specify the frequencies of each phenogenotype in the offspring as a function of their frequencies in the parents, as well as the parameters d, $b_3 - b_0$ and α. This system can then be analysed using conventional mathematical methods to investigate whether the appearance of a cultural preference for *H* could explain the rise in frequency of the *EDAR* allele, and to specify the conditions under which this occurs. Methods are available to incorporate assortative mating, learning from non-kin, a variety of cultural transmission biases (for example, conformity) and demographic effects.

Note the above logic applies irrespective of whether it is hair thickness or some other character (for example, REF. 98) that is the focus of sexual selection, and similar models can be devised for naturally selected traits. The important general point here is that, because of its dynamic interactive properties, culture typically cannot adequately be treated as a background condition for selection, and must be incorporated into a dynamic model if the analysis is to be accurate. For a more detailed introduction, see REFS 20,21,41.

Table 1 | **Mathematical models of gene–culture co-evolution**

Topic	Assumed gene function	Refs
The evolution of learning, social transmission and culture; the evolution of social learning strategies (unbiased transmission, direct bias, indirect bias, frequency dependent bias, and so on); the analysis of reliance on social learning; the evolution of teaching	Genes that affect learning; genes predisposing individuals to learn from others and to do so in particular ways or under particular circumstances, or to learn from particular individuals	19–21,23,33, 35,36,119–124
The co-evolution of genes for lactase persistence and milk use	Gene for adult human lactase persistence (*LCT*)	13,31,40
The evolution of language; the co-evolution of sign language and hereditary deafness	Language-facilitating genes (for example, forkhead box P2 (*FOXP2*)); genes for hereditary deafness	125–128
The inheritance of intelligence, behavioural and personality traits	Genes that affect personality and intelligence	38,39,54,129,130
The evolution of handedness and lateralized structures	Genes for lateralization of hand preference	37
The evolution of cooperation; the evolution of ethnic markers and conformity	Genes predisposing individuals to cooperate with in-group members, to not cooperate with or be hostile to out-group members, to punish non-cooperators, to express pro-social emotions, to internalize norms and to conform	21,131–138
The evolution of incest taboos and avoidance of sibling mating	Genes predisposing individuals to an aversion to mating with individuals with whom they are reared	139,140
Sexual behaviour; sexual selection with culturally transmitted mating preferences and genetically transmitted traits; culturally transmitted paternity beliefs and the evolution of human mating systems	Genes for skin, hair and eye colour, body and face shape, and facial and body hair; genes that affect degree of character symmetry, degree of neoteny, level of aggressiveness, emotionality, personality traits, promiscuity, jealousy and faithfulness	42,94,141
The effects of sex-biased infanticide and parental investment; the effects of sex-selective abortion on sex-ratio evolution	Sex-ratio distorter genes	43,142,143
The evolutionary consequences of cultural niche construction	Genes related to metabolism, immunity and pathogen defence and the nervous system	45,46

nutrient cycles[24]. The defining characteristic of niche construction is not modification of the environment *per se,* but rather an organism-induced change in the selective environment[24]; hence the term includes migration, dispersal and habitat selection, in which organisms relocate in space and experience new conditions.

Effects of niche construction on evolution. Genetic and ecological models have demonstrated that niche construction can affect evolutionary outcomes, even without culture[24–30]. For instance, niche construction can modify selection, leading to the fixation of alleles that would otherwise be deleterious[26,27], can allow the persistence of organisms in inhospitable environmental conditions that would otherwise lead to their extinction[25], and be favoured even when costly because of the benefits that will accrue to distant descendants[29]. However, mathematical models reveal that niche construction due to cultural processes can be even more potent than niche construction due to other (gene-based) non-cultural processes, and they show that cultural niche construction can modify selection on human genes, with resulting effects on evolutionary outcomes[24,34,46,47]. Indeed, human niche construction is informed by a uniquely potent and cumulative cultural knowledge base[24,48].

It is highly likely that human cultural niche construction has co-directed human evolution in this manner. Over the past 50,000 years, humans have spread from Africa around the globe, experienced an ice age, begun to exploit agriculture, witnessed rapid increases in densities, domesticated hundreds of species of plants and animals and, by keeping animals, experienced a new proximity to animal pathogens[3,48,49]. Each of these events represents a major transformation in human selection pressures, and all (except the ice age) have been self-imposed. Humans have modified selection, for instance, by dispersing into new environments with different climatic regimes, devising agricultural practices or domesticating livestock. Niche-construction theory leads to the expectation that gene–culture co-evolution has been a general feature of human evolution.

Counteractive niche construction. Organisms can initiate or respond to a change in an environmental factor; the former is categorized as inceptive niche construction and the latter as counteractive niche construction[24]. Inceptive and counteractive niche construction may also act together. For example, inceptive niche construction may allow humans to invade a new environment, but they may only be able to tolerate and exploit it by buffering some of the novel selection pressures they encounter through counteractive niche construction.

Counteractive niche construction is of interest here because it may oppose or nullify the effects of environmental change, and it functions to protect organisms from shifts away from environmental states to which they are adapted. Counteractive niche construction buffers selection, and the more potent the capacity for counteractive niche construction, the more effective this buffering should be.

For example, imagine an ancestral population that has been exposed to changes in temperatures. In the absence of niche construction, this would engender bouts of selection for genes favoured in hot or cold climates. However,

if humans can put on or take off clothes, build fires, find caves and develop means of cooling, they effectively counteract these changed selection pressures. The temperature changes actually experienced by the population are dampened relative to the external environment and as a consequence selection is weak. The logic is identical to counteractive niche construction in animals, such as the habits of bees and wasps of cooling nests with water droplets and warming them through muscular activity[24], but human counteractive niche construction acts faster, and is therefore more potent, because it is reliant on culture. One prediction from this cultural mitigation of selection is that we now expect more (of what would otherwise be) deleterious alleles in the human gene pool than we would in the absence of cultural activities.

Theoretical work on cultural niche construction[46] has generated a number of predictions that apply to geographical variation in allele frequencies, some of which have begun to attract support[24]. For instance, if we compare humans with other animals, or recent species with early species of *Homo*, we would expect those populations that are more capable of buffering selection through culture to exhibit less evolutionary response in morphology to fluctuating climates or latitude, a broader habitat range, more rapid colonization and less robust morphology. Variation in the capacity for counteractive niche construction potentially explains genetic differences between humans and other animals and geographical variation in human allele frequencies. Possible candidates with which to evaluate these predictions include heat-shock genes and genes that affect body shape and temperature regulation.

Box 3 | **Sexual selection with a culturally transmitted mating preference**

Genes that are associated with our externally visible phenotypes show among the strongest signatures of local adaptation. For example, the lighter skin pigmentation in non-African populations is the result of selection on a number of skin pigmentation genes[99–101]. Various genes that are involved in skeletal development have also been shown to show signatures of local adaptation from genome scans[6,102]. Genes that are expressed in hair follicles (such as ectodysplasin A receptor (*EDAR*) and *EDA2R*), in eye and hair colour (such as solute carrier family 24, member 4 (*SLC24A4*), KIT ligand (*KITLG*), tyrosinase (*TYR*) and oculocutaneous albinism II (*OCA2*)) and in freckles (such as 6p25.3 and melanocortin 1 receptor (*MC1R*)) are also well represented in recent selective events[6,7]. Although some variation can be attributed to natural selection, many of these selective events could potentially be explained through a form of sexual selection in which society-specific culturally learned mating preferences favour biological traits in the opposite sex.

K.N.L.[41] developed a mathematical model that combines sexual selection and gene–culture co-evolutionary theory (see also REF. 103). He found that even if human mating preferences are learned, socially transmitted and culture-specific, sexual selection will still result; indeed, culturally generated sexual selection was found to be faster and more potent than its gene-based counterpart. Given the pervasiveness of cultural influences on human mating preferences, social transmission may exert a powerful influence on the selection of secondary sexual characteristics and other physical and personality traits that affect human mate choice[41,103].

The hypothesis leads to several predictions[34]. First, it suggests that we should expect to see mate-choice copying and the social transmission of mating preferences in humans, predictions that have received recent support[34]. Second, genes that affect such sexually selected traits should show evidence of recent selection, which seems to be the case. Third, and germane to this article, there should be population-wide correlations between specific culturally transmitted preferences and gene-based traits in both sexes.

Counteractive niche construction also helps to explain a lack of correspondence between human allele frequencies and selective environments. When our ancestors migrated to higher latitudes, they probably exhibited only modest physical changes because they primarily responded culturally. If hominids have evolved more in response to self-constructed selection pressures and less in response to independent factors than other mammals, then hominid populations may have become increasingly divorced from local ecological pressures. Support for this comes from a study of behavioural variation in African societies in which most traits examined correlated with cultural history rather than ecology[50]. There is potential here for a research programme that seeks evidence, in human genomes or phenotypes, for genes that have not changed in circumstances in which we know that human environments have changed. For instance, unlike other mammals (and hominins such as *Homo floresiensis*), human island dwellers are probably not any shorter in stature than mainland dwellers[51]. Similarly, whereas many mammals show obvious adaptations to extreme temperatures, we anticipate that humans will exhibit comparatively few physical adaptations to temperature extremes.

Anthropological evidence

Another source of evidence for gene–culture co-evolution comes from anthropological and archaeological studies of contemporary, or recent, human populations, which demonstrate gene–culture co-evolution in action. Anthropology is the study of human beings, and requires understanding of humans' ecological context in addition to social and cultural contexts. Archaeology can be viewed as a sub-branch of anthropology that investigates past human populations, their culture and their relationship with their environment. In the case of archaeology, methods are available to distinguish between functional and stylistic (or neutral) traits, based on frequency patterns through time, which allows the causes and consequences of human activity to be explored. Paleoanthropologists and archaeologists also use a variety of sophisticated techniques to date fossils and artefacts[49]. Researchers frequently develop hypotheses based on theory, or derived from observations of human interactions with environments or artefacts, and test these through exploring the co-occurrence and co-dependence of cultural traits and genetic or phenotypic variation. Recent years have witnessed the emergence of mathematical phylogenetic methods applied to cultural variation, which have provided a new tool for the investigation of gene–culture co-evolution[13,52–53].

The best-known cases of gene–culture co-evolution in anthropology are for adult lactose absorption (discussed below) and the 'sickle-cell' gene in the presence of malaria, a case in which yam cultivation was likely to have contributed to the spread of the disease[12] (BOX 4). Other examples include: anthropological studies of the impact of human aggregation on the spread of genes that confer resistance to crowd diseases; the co-evolution

Box 4 | **Anthropological studies of gene–culture co-evolution**

Populations of Kwa-speaking agriculturalists from West Africa cut clearings in forests to grow crops, often yams[12,104]. The removal of trees had the effect of inadvertently increasing the amount of standing water when it rained, which provided better breeding grounds for malaria-carrying mosquitoes. This intensified natural selection on the haemoglobin S (*HbS*) 'sickle-cell' allele because, in the heterozygous condition, it confers protection against malaria. The fact that adjacent populations whose agricultural practices are different do not show the same increase in allele frequency supports the conclusion that cultural practices can drive genetic evolution[12,104]. It is not just yam cultivation that generates this pattern of selection: modern Asian tyre manufacturing is having the same effect. Mosquitoes infest the pools of rainwater that collect in tyres stored outside, and tyre export is contributing to the spread of malaria and dengue[105]. Malaria became a major health problem only after the invention of farming but, as described in the main text, several genes seem to have been favoured by selection because they provide resistance to it.

Ancestral humans also modified their selective environment through dispersal. During their settlement of the Pacific, the ancestors of present-day Polynesians experienced long open-ocean voyages, which subjected them to cold stress and starvation. There may therefore have been strong selection for energetic efficiency during the Polynesian migrations[106,107]. A type 2 diabetes-associated allele that may lead to a 'thrifty metabolism' shows a signature of strong positive selection in Polynesians[108], as predicted by the thrifty-gene hypothesis[109]. Therefore, present-day Polynesians may have inherited an increased type 2 diabetes susceptibility because their ancestors decided to expand into the Pacific. A second example is the hypothesis that populations vary in their sensitivity to sodium as a result of selection for enhanced salt-retaining capacity in tropical climates[110]. Populations that moved into colder climates required a thermodynamic shift from heat dissipation to heat conservation. Several studies have found that genes underlying salt sensitivity show a highly unusual geographic distribution that is suggestive of differential selective pressures during the out-of-Africa expansion[111]. Potentially, cultural variation in diet mediated this selection. Therefore, differences in susceptibility to salt-sensitive hypertension between human populations may be a consequence of population movements, habitat selection and cultural tradition. Niche-construction theory potentially helps researchers to understand why human populations are sometimes adapted to their environments and sometimes not.

of diet and genes conferring resistance to disease; the co-evolution of cooking with genes that are expressed in the brain and digestive tract and involved in the determination of tooth size; the co-evolution of culturally facilitated dispersal and pigmentation; and the co-evolution of salt sensitivity and body shape[12,32,43,48,54–57].

Another case is dispersal into new environments, which provides an example of inceptive niche construction triggering selection on human genes. Humans expanded rapidly within and out of Africa over the past 100,000 years and came to inhabit radically different physical environments. The 'where-to-go' decisions of our ancestors, and the cultural capabilities that rendered such dispersals possible, may have shaped the global genetic landscape and the worldwide distribution of disease susceptibility. A strong candidate example is provided by Polynesians and type 2 diabetes (BOX 4).

Genetic evidence for gene–culture co-evolution

Researchers' ability to assess the relative importance of gene–culture co-evolution was previously hindered by the use of candidate gene studies. These studies had an ascertainment bias — patterns of nucleotide diversity were studied only at loci that had previously been linked to a putatively adaptive phenotype. Although many successful studies have used a candidate gene approach, currently putatively selected genes are most often identified from genome scans, which involve evaluating genotypes from across the entire genomes of multiple individuals for signatures of selection. Genome scans have provided the first steps in evaluating without bias the relative contribution of gene–culture co-evolution to human adaptation.

Recently, mathematically minded geneticists have developed methods for detecting statistical signatures in the human genome of recent, strong positive selection — genes that have been favoured by natural selection over the past 100,000 years[6–11,14,58,59]. Such signals include high-frequency alleles in linkage disequilibrium, unusually long haplotypes of low diversity and an excess of rare variants. Although relatively sensitive statistical tests for positive selection have been developed, they do not always give consistent results[7,10] and are subject to confounding effects[60,61]. The analyses either specify a likelihood that a specific allele has been subject to a recent selective sweep[14] or produce a list of genes that appear as outliers in the genome-wide distribution of a test statistic[62,63], so it is not completely clear how many genes have been affected by recent selection. Lists of selected genes contain unknown numbers of false positives, and the results of any genome scan should be interpreted with caution[59]. Nonetheless, a reasonable reading of the data suggests that, thus far, somewhere between a few hundred and a couple of thousand regions in the human genome have been shaped by recent selection. Genetic variants showing signs of recent positive selection are not restricted to single-base-pair substitutions, but also include genomic rearrangements[64] and copy-number variants[65]. Nor is positive selection restricted to the protein-coding regions of the human genome, as adaptive regulatory variants have also been identified[66,67].

A large number of the genes that have been identified from the above-mentioned genome scans may have been shaped by culturally modified selection pressures (TABLE 2). However, we stress that in the vast majority of cases it has yet to be proven that the source of selection on the gene is derived from a cultural practice. The task for the human evolutionary sciences now is to complete the connections from genotype to phenotype to selection pressure for the long list of selected genes generated from genome-wide scans.

Overrepresented categories of genes subject to positive selection. There are several categories of human genes that seem to be overrepresented in lists of positively selected genes (TABLE 2). Williamson *et al.*[14] reported that among 56 unlinked heat-shock genes, 28 showed evidence of a recent selective sweep in at least one population, conceivably in response to culture-facilitated dispersal and local adaptation. Wang *et al.*[7] identified pathogen response as an overrepresented category (10% of selective events) and gave numerous examples of genes involved in host–pathogen interactions. These authors suggest that shifts from a hunter-gatherer

nomadic lifestyle to an agrarian lifestyle were likely to have facilitated the spread of infectious agents, leading to the rapid rise in the frequency of alleles that protect against these agents. Genes involved in the human immune response are also well represented[14,63]. Equally prevalent are genetic responses to changes in diet, which are discussed in BOX 5.

Another interesting case concerns the brain growth and development-related genes abnormal spindle, microcephaly associated (*ASPM*) and microcephalin 1 (*MCPH1*), which show signs of natural selection and a marked geographic structure[68,69] and co-vary with linguistic tone (the use of voice pitch to convey lexical or grammatical distinctions)[70]. Dediu and Ladd[70] propose that the relationship between genetic and linguistic diversity may be causal: certain alleles can bias language acquisition or processing and thereby influence the trajectory of language change through cultural transmission.

The results of genetic studies have matched well with theoretical gene–culture co-evolution models in the sense that hypothetical genes with assumed functions in the models have been confirmed to exist and to be subject to recent selection. One prominent example is the co-evolution of dairy farming and lactose tolerance[31,71,72], which is discussed in detail in the next section. Other matches between hypothetical genes that have been investigated in gene–culture models and specific genetic loci that are now known to be subject to recent selection include: the evolution of language with genes that facilitate language (for example, forkhead box P2 (*FOXP2*) and *ASPM*); the co-evolution of sign language and hereditary deafness with the connexin deafness gene (*DFNB1*, also known as *GJB2*); the co-evolution of cultural niche construction (for example, agriculture) with genes related to metabolism, immunity and pathogen defence (for example, *CD58*, apolipoprotein B mRNA-editing enzyme, catalytic polypeptide-like 3F

Table 2 | **Genes identified as having been subject to recent rapid selection and their inferred cultural selection pressures**

Genes	Function or phenotype	Inferred cultural selection pressure	Refs
LCT, *MAN2A1*, *SI*, *SLC27A4*, *PPARD*, *SLC25A20*, *NCOA1*, *LEPR*, *LEPR*, *ADAMTS19*, *ADAMTS20*, *APEH*, *PLAU*, *HDAC8*, *UBR1*, *USP26*, *SCP2*, *NKX2-2*, *AMY1*, *ADH*, *NPY1R*, *NPY5R*	Digestion of milk and dairy products; metabolism of carbohydrates, starch, proteins, lipids and phosphates; alcohol metabolism	Dairy farming and milk usage; dietary preferences; alcohol consumption	6,7,16,41,63, 102,118, 144,145
Cytochrome P450 genes (*CYP3A5*, *CYP2E1*, *CYP1A2* and *CYP2D6*)	Detoxification of plant secondary compounds	Domestication of plants	6,63,146,147
CD58, *APOBEC3F*, *CD72*, *FCRL2*, *TSLP*, *RAG1*, *RAG2*, *CD226*, *IGJ*, *TJP1*, *VPS37C*, *CSF2*, *CCNT2*, *DEFB118*, *STAB1*, *SP1*, *ZAP70*, *BIRC6*, *CUGBP1*, *DLG3*, *HMGCR*, *STS*, *XRN2*, *ATRN*, *G6PD*, *TNFSF5*, *HbC*, *HbE*, *HbS*, *Duffy*, *α-globin*	Immunity, pathogen response; resistance to malaria and other crowd diseases	Dispersal, agriculture, aggregation and subsequent exposure to new pathogens; farming	6–8,14,16,50, 63,148,149
LEPR, *PON1*, *RAPTOR*, *MAPK14*, *CD36*, *DSCR1*, *FABP2*, *SOD1*, *CETP*, *EGFR*, *NPPA*, *EPHX2*, *MAPK1*, *UCP3*, *LPA*, *MMRN1*	Energy metabolism, hot or cold tolerance; heat-shock genes	Dispersal and subsequent exposure to novel climates	14,150
SLC24A5, *SLC25A2*, *EDAR*, *EDA2R*, *SLC24A4*, *KITLG*, *TYR*, 6p25.3, *OCA2*, *MC1R*, *MYO5A*, *DTNBP1*, *TYRP1*, *RAB27A*, *MATP*, *MC2R*, *ATRN*, *TRPM1*, *SILV*, *KRTAPs*, *DCT*	The externally visible phenotype (skin pigmentation, hair thickness, eye and hair colour, and freckles)	Dispersal and local adaptation and/or sexual selection	9,14,63,97, 101,151
CDK5RAP2, *CENPJ*, *GABRA4*, *PSEN1*, *SYT1*, *SLC6A4*, *SNTG1*, *GRM3*, *GRM1*, *GLRA2*, *OR4C13*, *OR2B6*, *RAPSN*, *ASPM*, *RNT1*, *SV2B*, *SKP1A*, *DAB1*, *APPBP2*, *APBA2*, *PCDH15*, *PHACTR1*, *ALG10*, *PREP*, *GPM6A*, *DGKI*, *ASPM*, *MCPH1*, *FOXP2*	Nervous system, brain function and development; language skills and vocal learning	Complex cognition on which culture is reliant; social intelligence; language use and vocal learning	6,7,14,63, 68–70,78,149
BMP3, *BMPR2*, *BMP5*, *GDF5*	Skeletal development	Dispersal and sexual selection	6,63
MYH16, *ENAM*	Jaw muscle fibres; tooth-enamel thickness	Invention of cooking; diet	80,113

ADAMTS, ADAM metalloproteinase with thrombospondin motif; *ADH*, alcohol dehydrogenase; *ALG10*, asparagine-linked glycosylation 10; *AMY1*, salivary amylase 1; *APEH*, *N*-acylaminoacyl-peptide hydrolase; *APOBEC3F*, apolipoprotein B mRNA-editing enzyme, catalytic polypeptide-like 3F; *APBA2*, amyloid β precursor protein-binding, family A, member 2; *APPBP2*, amyloid β precursor protein-binding protein 2; *ASPM*, abnormal spindle, microcephaly associated; *ATRN*, attractin; BMP, bone morphogenetic protein; *CCNT2*, cyclin T2; *CDK5RAP2*, cyclin dependent kinase 5 regulatory subunit-associated protein 2; *CENPJ*, centromere protein J; *CETP*, cholesteryl ester transfer protein; *CSF2*, colony stimulating factor 2; *CUGBP1*, CUG triplet repeat, RNA-binding protein 1 ; CYP, cytochrome P450; *DAB1*, disabled homologue 1; *DCT*, dopachrome tautomerase; *DEFB118*, defensin β118; *DGKI*, diacylglycerol kinase ι; *DLG3*, discs, large homologue 3; *DSCR1*, Down syndrome critical region 1; *DTNBP1*, dystrobrevin-binding protein 1; *EDAR*, ectodysplasin A receptor; *EGFR*, epidermal growth factor receptor; *ENAM*, enamelin; *EPHX2*, epoxide hydrolase 2; *FABP1*, fatty acid-binding protein 1; *FCRL2*, Fc receptor-like 2; *FOXP2*, forkhead box P2; *G6PD*, glucose-6-phosphate dehydrogenase; *GABRA4*, γ-aminobutyric acid A receptor, subunit α4; *GDF5*, growth differentiation factor 5; *GLRA2*, glycine receptor α2; GRM, glutamate receptor, metabotropic; Hb, haemoglobin; *HDAC8*, histone deacetylase 8; *HMGCR*, HMG coenzyme A reductase; *IGJ*, immunoglobulin joining chain; KRTAP, keratin-associated protein; *LCT*, lactose; *LEPR*, leptin receptor; *LPA*, lipoprotein A; *MAN2A1*, mannosidase, alpha, class 2A, member 1; MAPK, mitogen-activated protein kinase; *MATP*, membrane-associated transporter protein; MC, melanocortin; *MCPH1*, microcephalin 1; *MMRN1*, multimerin 1; *MYH16*, myosin, heavy chain 16; *MYO5A*, myosin VA; *NCOA1*, nuclear receptor coactivator 1; *NPPA*, natriuretic peptide precursor A; NPY, neuropeptide Y; *OCA2*, oculocutaneous albinism II ; OR, olfactory receptor; *PCDH15*, protocadherin 15; *PHACTR1*, phosphatase and actin regulator 1; *PLAU*, plasminogen activator, urokinase; *PON1*, paraoxonase 1; *PPARD*, peroxisome proliferator-activated receptor δ; *PREP*, prolyl endopeptidase; *PSEN1*, presenilin 1; RAG, recombination activating gene; *RAPSN*, receptor-associated protein of the synapse; *RAPTOR*, regulatory-associated protein of mTOR; *SCP2*, sterol carrier protein 2; *SI*, sucrase-isomaltase; *SILV*, silver homologue; *SKP1A*, S-phase kinase-associated protein 1; SLC, solute carrier; *SNTG1*, syntrophin γ1; *SOD1*, superoxide dismutase 1; *STAB1*, stabilin 1; *STS*, steroid sulfatase; *SV2B*, synaptic vesicle glycoprotein 2B; *SYT1*, synaptotagmin 1; *TJP1*, tight junction protein 1; *TNFSF5*, tumour necrosis factor superfamily, member 5; *TRPM1*, transient receptor potential cation channel, subfamily M, member 1; *TSLP*, thymic stromal lymphopoietin; TYR, tyrosinase; TYRP1, tyrosinase-related protein 1; *UBR1*, ubiquitin protein ligase E3 component n-recognin 1; *UCP3*, uncoupling protein 3; *USP26*, ubiquitin-specific peptidase 26; *VPS37C*, vacuolar protein sorting 37 homologue C; *XRN2*, 5′–3′ exoribonuclease 2; ZAP, ζ-associated protein kinase.

Box 5 | **Genetic responses to human diet**

Cultural variation in human diet clearly explains some of the adaptive genetic differences between human populations. One compelling example of a human-culture-initiated selective sweep concerns the evolution of the human amylase gene[112]. Starch consumption is a feature of agricultural societies and hunter-gatherers in arid environments, whereas other hunter-gatherers and some pastoralists consume much less starch. This behavioural variation raises the possibility that different selective pressures have acted on amylase, the enzyme responsible for starch hydrolysis. Consistent with this hypothesis, Perry *et al.*[112] found that copy number of the salivary amylase gene (*AMY1*) is positively correlated with salivary amylase protein level and that individuals from populations with high-starch diets have, on average, more *AMY1* copies than those with traditionally low-starch diets. Higher *AMY1* copy numbers and protein levels are thought to improve the digestion of starchy foods and may buffer against the fitness-reducing effects of intestinal disease.

More generally, the transition to novel food sources with the advent of agriculture and the colonization of new habitats seems to have been a major source of selection on human genes[6,113]. Wang *et al.*[7] describe protein metabolism as an overrepresented category (15%) in selective events, and affected genes include ADAM metallopeptidase with thrombospondin motif 19 (*ADAMTS19*), *ADAMTS20*, *N*-acylaminoacyl-peptide hydrolase (*APEH*), plasminogen activator, urokinase (*PLAU*), histone deacetylase 8 (*HDAC8*), ubiquitin protein ligase E3 component n-recognin 1 (*UBR1*) and ubiquitin-specific peptidase 26 (*USP26*). Several genes related to the metabolism of carbohydrates, lipids and phosphates also show signals of recent selection, including genes involved in metabolizing mannose (*MAN2A1* in Yorubans and East Asians), sucrose (*SI* in East Asians) and fatty acids (solute carrier family 27, member 4 (*SLC27A4*) and peroxisome proliferator-activated receptor δ (*PPARD*) in Europeans, *SLC25A20* in East Asians, nuclear receptor coactivator 1 (*NCOA1*) in Yorubans and leptin receptor (*LEPR*) in East Asians)[6]. Williamson *et al.*[14] add sterol carrier protein 2 (*SCP2*), which has a role in the intracellular movement of cholesterol. There is also evidence for diet-related selection on the thickness of human teeth enamel[114] and bitter-taste receptors[115], and the promoter regions of many nutrition-related genes have experienced positive selection during human evolution[116]. In addition, there is a strong signal of selection in the alcohol dehydrogenase (*ADH*) cluster in East Asians, which is thought to be an interaction between the functional polymorphisms of the alcohol-metabolism genes in protection against alcoholism[117]. One argument is that hypersensitivity to alcohol has been adaptive through protecting against alcoholism[118].

(*APOBEC3F*) and *CD72*); and models of the evolution of learning and cognition with nervous system genes (for example, cyclin dependent kinase 5 regulatory subunit-associated protein 2 (*CDK5RAP2*), centromere protein J (*CENPJ*) and γ-aminobutyric acid A receptor, subunit α4 (*GABRA4*)). This correspondence is potentially significant, as it means that the models can potentially shed light on the mechanistic interactions that led to the selective sweep and that potentially explain patterns of genetic variation. A possible example is provided by genes that are associated with our externally visible phenotypes, which could be explained through a form of sexual selection in which society-specific culturally learned mating preferences favour biological traits in the opposite sex, as described in BOX 3.

Cultural boundaries and gene flow. Another way that gene–culture interactions can play a part in human evolution is when linguistic and cultural differences affect patterns of gene flow between human populations. For example, ancestral Caucasian mitochondrial DNA (mtDNA) types seem to have been replaced by Iranian mtDNA types in the Gilaki and Mazandarani in southern regions of Iran, but they retain Caucasian Y chromosomes[73]. Probably due to the patrilocal culture, local Iranian women were incorporated into these populations and thereby replaced their mtDNA types and their language. In Polynesia, mtDNA types come primarily from Asia, whereas Y chromosomes originate mostly from New Guinea. The data suggest that when Polynesian ancestors arrived in New Guinea from their voyages originating in Taiwan, New Guinea Y chromosomes invaded their gene pool but New Guinea mtDNA types were rarely introduced. Therefore, there was a pronounced admixture bias in Polynesians towards more New Guinea men than women, perhaps as a result of the matrilocal culture in ancestral Polynesian society[74]. There are other examples of indirect effects of cultural traits, such as social system, on human genetic variation[75,76]. These examples show that human culture can have an influence on neutral patterns of genetic variation.

Cultural selection and human uniqueness. Thus far we have dwelt on variants that are under local, geographically restricted selection and that differ between human populations. However, genetic variants under selection in humans also include variants that experienced selection along the human lineage and became fixed. The best-known example here is the *FOXP2* gene, mutations in which cause deficiencies in language skills[77]. Only four *FOXP2* mutations occur in the evolutionary tree of mice, macaques, orangutans, gorillas, chimpanzees and humans, two of which occur in the evolutionary lineage leading to humans, which is suggestive of positive selection[78]. One interpretation is that this selection introduced a change in the *FOXP2* gene that was a necessary step to the development of speech. However, the gene may also have been favoured for other reasons, such as vocal learning or lung development[79]. Another interesting case here is the sarcomeric myosin gene *MYH16*, which underwent a deletion in the hominin lineage[80]. This gene is expressed primarily in the hominid mandible, and its loss is thought to result in a massive reduction in jaw muscle, with a timing that may coincide with the appearance of cooking. If confirmed, here a cultural process has removed a constraint, allowing genetic

change to occur that would be deleterious in its absence. Several other gene deletions may have occurred in conjunction with changes in diet[18].

Cultural processes are likely to have had other effects on our genes — for instance, rendering some housekeeping genes essential (that is, lethal if they mutate). In these cases, it is purifying selection, rather than positive selection, that acts in conjunction with cultural processes. Liao and Zhang[81] found that vacuole-protein genes are essential in humans because they remove toxins in cells, but homologous genes are not essential in mice. They suggest that recent increases in the longevity of humans render these genes crucial, as toxins can now build up for longer, to the point at which they are lethal if not removed. Human longevity has, of course, been extended largely through cultural practices[55,82].

Dairy farming and lactose tolerance

The co-evolution of dairy farming and adult lactose tolerance is the most extensively investigated example of gene–culture co-evolution to date. It illustrates the range of methods that can be used to investigate gene–culture co-evolution, including: anthropological and demographic studies of the covariation between cultural practices and human phenotypes; detection of a variety of statistical signatures of recent selection by geneticists; analysis of ancient DNA to determine whether ancestral populations possessed putatively adaptive alleles; statistical estimation from genetic data of the magnitude of selection pressures; biochemical analyses; analyses of genetic variation in animals (and plants) that have co-evolved with humans; and mathematical models of gene–culture co-evolutionary processes using population genetic and phylogenetic methods.

In most humans, the ability to digest lactose disappears in childhood, but in some populations lactase activity persists into adulthood: this is known as lactose tolerance[12,83]. Lactose tolerance is frequent in northern Europeans and in pastoralist populations from Africa and the Middle East, but is almost completely absent elsewhere; these differences relate to genetic variation near the lactase (*LCT*) gene[12,84,85]. A SNP located 14 kb upstream of *LCT* has been shown to be responsible for lactose tolerance in Europeans[86,87], and several nearby SNPs associate with lactose tolerance in African and Middle Eastern dairying populations[16,88]. A strong correlation exists across cultures between the frequency of lactose tolerance and a history of dairy farming and milk drinking[12,89,90]. This observation led to the 'culture historical hypothesis': dairying created the selection pressures that drove alleles for lactose tolerance to high frequency[12,91]. Other human populations have traditions for consuming fermented milk products, such as cheese and yogurt, that have lower levels of lactose, and it may be no coincidence that these populations exhibit intermediary frequencies of lactose tolerance[12].

Various studies now support the culture historical hypothesis, as opposed to the counter-hypothesis that the presence of the lactose-tolerance allele allowed dairying to spread, or that the allele spread for some reason unconnected to dairying. The signature of selection around the lactase gene is one of the strongest in the human genome[6], and the onset of the selection has been dated to 5,000–10,000 years ago[40]. The lactose-tolerance allele was absent in ancient DNA extracted from early Neolithic Europeans[15], which suggests that the allele was absent or at low frequency 7,000–8,000 years ago. The increasing frequency of lactose tolerance and the spread of dairying also affected geographical variation in milk-protein genes in European cattle breeds, which co-vary with present-day patterns of lactose tolerance in human populations[92]. These various lines of evidence support a scenario in which early Neolithic humans exposed themselves to a strong selection pressure for lactose tolerance by drinking fresh milk.

Theoretical backing for this scenario comes from gene–culture co-evolutionary models that have investigated the evolution of lactose tolerance[31,71,72]. Feldman and Cavalli-Sforza[31] constructed a model in which lactose tolerance was controlled by a single gene, with one allele resulting in lactose tolerance and the other resulting in lactose intolerance, and in which milk drinking was a learned tradition. Their model showed that whether or not the tolerance allele achieved a high frequency depended crucially on the probability that the children of milk drinkers themselves became milk drinkers. If this probability was high, then a significant fitness advantage to lactose-tolerant individuals resulted in a high frequency of lactose tolerance within a few hundred generations. However, if a significant proportion of the offspring of milk drinkers did not exploit dairy products, then unrealistically strong selection favouring lactose tolerance was required for the allele to spread. Holden and Mace[13] applied comparative phylogenetic methods to human cultural groups and found strong support for the dairy-farming hypothesis. Their analysis also revealed that dairy farming evolved first, which then favoured lactose tolerance, and not the other way around.

The key point emerging from this case study is that multiple disciplines seem to be necessary but that no discipline on its own is sufficient to establish cause and effect in putative gene–culture interactions. This reinforces the argument for an interdisciplinary research programme[18].

Implications for future research

The aforementioned data raises the possibility that gene–culture co-evolution may have been widespread, and acted on many human traits, throughout the history of our species. However, this conclusion would be premature. Of the regions of the genome that have been identified as being subject to recent selection, few causal variants have been confirmed or linked to an adaptive phenotype. Of the recognized adaptive phenotypes, few can definitively be associated with selection pressures, let alone unequivocally linked to culture. This is the great challenge for the field of gene–culture co-evolution, and it is a formidable challenge. Nonetheless, the best-researched examples, such as the lactose-tolerance case, not only show that gene–culture co-evolution occurs but also illustrate the

means to establish this. It is now an empirical issue to determine its extent.

We also emphasize that there are still serious analytical challenges in scanning for selection, and it is difficult for researchers to be confident about which loci, or how many, are genuine targets of selection. A fraction of the examples discussed above are probably false positives. However, the case for gene–culture co-evolution does not rest exclusively on genetic data, but is reinforced by theoretical analyses. Such theory demonstrates the mechanisms by which gene–culture interactions can affect evolutionary rates and dynamics, can help to explain geographical variation in gene frequencies, and both speed up and buffer selection on genes. The models, together with the anthropological data, also generate a large number of testable hypotheses and predictions, some of which have already been confirmed. One might also argue, given the shallow time depth for selection on many human genes, that the case for gene–culture co-evolution is reinforced by the sheer ubiquity of culture in modern human lives — it becomes hard to think of selection acting on humans that would not be modified by culture!

There are reasons to anticipate that gene–culture interactions may have had a prominent role in local, geographically restricted adaptation over the past 50,000 years. Not only did humans recently come to occupy nearly every habitable corner of the earth, but cultures rapidly diversified during the out-of-Africa expansion. Moreover, human culture is cumulative, with tools and technology building on earlier forms, which implies that humans must possess more culture, and more potent culture, now than earlier in history. For comparison, the lithic technology of early *Homo* species remained largely unchanged for a million years. These considerations imply an increasing significance of gene–culture co-evolution with time. A gene–culture co-evolutionary perspective predicts that the genetic signatures of recent positive selection (for example, since the out-of-Africa expansion) will more often have been generated by culture than signatures of selection from earlier time periods in human evolution (for example, before the out-of-Africa expansion). As previously mentioned, however, linking a selected locus to a cultural trait is challenging and has only been accomplished for a small number of loci. Nevertheless, our prediction of an increasing significance to gene–culture co-evolution over time can be evaluated with increasing precision as researchers reveal the selection pressures responsible for these signatures of selection. It is not inconceivable that we will someday be able to state with confidence that the temporal pattern of signatures of selection in the human genome is consistent with the temporal changes in the potency of human culture as a selective agent.

This leaves us to ask: how can researchers differentiate the molecular signatures of selection generated by culture from non-cultural selective factors? This would be difficult by looking at molecular data alone, but other methods can be deployed to address this question. For instance, comparative statistical tools can be used to evaluate the dependency of one trait (for example, an allele frequency) on another (for example, a cultural trait) using phylogenetic methods[24], with the prediction that allele frequencies will co-vary with the cultural trait and not other ecological variables. A good example is Holden and Mace's[13] analysis of the predictors of lactose-tolerance frequency; they showed that these predictors co-varied with dairy farming and are not explained by latitude. Gene-frequency changes can be evaluated in contemporary human populations by again investigating the dependency of allele frequencies on cultural traits. A good example is Durham's[12] analysis of the relationship between the haemoglobin S (*HbS*) allele and yam cultivation. The relative merits of hypotheses in which genetic change comes first and triggers a cultural response, or vice versa, can be evaluated by extracting ancient DNA from ancestral populations, as Burger *et al.*[15] did for lactose tolerance.

Gene–culture co-evolution also has some practical implications. Models of human evolution that fail to consider the role of culture may need to be replaced by models that acknowledge gene–culture associations. Gene–culture co-evolutionary methods too will change, as theoreticians will be able to construct models that explore the evolution of specific identified genes of known frequency. Moreover, it is clear that culture can generate non-trivial demographic effects[72], and researchers would be wise to take account of these. The requisite tools are largely in place to produce these improved models[20,21], and it is merely a case of integrating findings from different disciplines. This will allow researchers to make quantitative and qualitative predictions about genetic and phenotypic variation across populations, or to draw inferences about the processes that have led to patterns of gene frequencies. Unbiased genome-wide scans will potentially provide theoreticians with a suite of new cases of gene–culture co-evolution to explore. On the negative side, knowledge of actual genes may invalidate some theoretical analyses by revealing their assumptions to be unrealistic, and new kinds of models may need to be developed, but this too will lead to progress in the longer term. Empiricists seeking to understand temporal and spatial variation in human allele frequencies, or human uniqueness, will need to consider the role of cultural variables, and may need to work side-by-side with anthropologists, archaeologists or theoreticians to establish whether the molecular signatures of selection they observe are indeed the result of gene–culture interactions. More generally, researchers will soon be able to integrate theory and empirical data in sophisticated ways, building on the theoretical framework provided by gene–culture co-evolution and niche-construction theory. This should support a deeper understanding of the processes of human evolution and the causes of patterns of genetic variation than was possible until recently. To quote Varki *et al.* (p759)[18]: "Such attempts will only yield true success if experts from multiple disciplines coalesce into transdisciplinary teams … avoiding preconceived notions based on the understanding of the evolution of other species."

1. Klein, R. G. *The Human Career: Human Biological and Cultural Origins* (Univ. of Chicago Press, 1999).
2. Wheeler, P. E. The thermoregulatory advantages of hominid bipedalism in open equatorial environments: the contribution of increased convective heat loss and cutaneous evaporative cooling. *J. Hum. Evol.* **21**, 107–115 (1991).
3. Boyd, R. & Silk, J. *How Humans Evolved* 3rd edn (Norton & Co., New York, 2003).
4. Kingdon, J. *Lowly Origins* (Princeton Univ. Press, 2003).
5. Kingsolver, J. G. *et al.* The strength of phenotypic selection in natural populations. *Am. Nat.* **157**, 245–261 (2001).
6. Voight, B. F., Kudaravalli, S., Wen, X. & Pritchard, J. K. A map of recent positive selection in the human genome. *PLoS. Biol.* **4**, e72 (2006).
7. Wang, E. T., Kodama, G., Baldi, P. & Moyzis, R. K. Global landscape of recent inferred Darwinian selection for *Homo sapiens*. *Proc. Natl Acad. Sci. USA* **103**, 135–140 (2006).
References 6 and 7 describe alleles that have been subject to recent rapid selection and posit a role for cultural practices.
8. Sabeti, P. C. *et al.* Positive natural selection in the human lineage. *Science* **312**, 1614–1620 (2006).
9. Sabeti, P. C. *et al.* Genome-wide detection and characterization of positive selection in human populations. *Nature* **449**, 913–918 (2007).
10. Nielsen, R., Hellmann, I., Hubisz, M., Bustamante, C. & Clark, A. G. Recent and ongoing selection in the human genome. *Nature Rev. Genet.* **8**, 857–868 (2007).
11. Tang, K., Thornton, K. R. & Stoneking, M. A new approach for using genome scans to detect recent positive selection in the human genome. *PLoS. Biol.* **5**, e171 (2007).
12. Durham, W. H. *Co-evolution: Genes, Culture and Human Diversity* (Stanford Univ. Press, 1991).
A classic anthropological text that investigates the relationship between genes and culture.
13. Holden, C. & Mace, R. Phylogenetic analysis of the evolution of lactose digestion in adults. *Hum. Biol.* **69**, 605–628 (1997).
A comparative statistical model that was used to test hypotheses about the evolution of lactose absorption in humans.
14. Williamson, S. H. *et al.* Localizing recent adaptive evolution in the human genome. *PLoS. Genet.* **3**, e90 (2007).
15. Burger, J., Kirchner, M., Bramanti, B., Haak, W. & Thomas, M. G. Absence of the lactase-persistence-associated allele in early Neolithic Europeans. *Proc. Natl Acad. Sci. USA* **104**, 3736–3741 (2007).
16. Tishkoff, S. A. *et al.* Convergent adaptation of human lactase persistence in Africa and Europe. *Nature Genet.* **39**, 31–40 (2007).
17. Hawks, J., Wang, E. T., Cochran, G. M., Harpending, H. C. & Moyzis, R. K. Recent acceleration of human adaptive evolution. *Proc. Natl Acad. Sci. USA* **104**, 20753–20758 (2007).
18. Varki, A., Geschwind, D. H. & Eichler, E. E. Explaining human uniqueness: genome interactions with environment, behaviour and culture. *Nature Rev. Genet.* **9**, 749–763 (2008).
19. Feldman, M. W. & Cavalli-Sforza, L. L. Cultural and biological evolutionary processes, selection for a trait under complex transmission. *Theor. Popul. Biol.* **9**, 238–259 (1976).
20. Cavalli-Sforza, L.L. & Feldman, M. W. *Cultural Transmission and Evolution: A Quantitative Approach* (Princeton Univ. Press, 1981).
A classic book that describes the mathematical modelling of human culture and its co-evolution with genes using theoretical population genetics.
21. Boyd, R. & Richerson, P. J. *Culture and the Evolutionary Process* (Univ. of Chicago Press, 1985).
Another classic book on the mathematical modelling of human culture and its co-evolution with genes, but with a more anthropological perspective.
22. Feldman, M. W. & Laland, K. N. Gene–culture co-evolutionary theory. *Trends Ecol. Evol.* **11**, 453–457 (1996).
23. Enquist, M., Eriksson, K. & Ghirlanda, S. Critical social learning: a solution to Roger's paradox of nonadaptive culture. *Am. Anthropol.* **109**, 727–734 (2007).
24. Odling-Smee, F. J., Laland, K. N. & Feldman, M. W. *Niche Construction: The Neglected Process in Evolution. Monographs in Population Biology 37* (Princeton Univ. Press, 2003).
The major book on niche-construction theory.
25. Kylafis, G. & Loreau, M. Ecological and evolutionary consequences of niche construction for its agent. *Ecol. Lett.* **11**, 1072–1081 (2008).
26. Laland, K. N., Odling-Smee, F. J. & Feldman, M. W. On the evolutionary consequences of niche construction. *J. Evol. Biol.* **9**, 293–316 (1996).
27. Laland, K. N., Odling-Smee, F. J. & Feldman, M. W. Evolutionary consequences of niche construction and their implications for ecology. *Proc. Natl Acad. Sci. USA* **96**, 10242–10247 (1999).
A key paper on niche-construction theory.
28. Boni, M. F. & Feldman, M. W. Evolution of antibiotic resistance by human and bacterial niche construction. *Evolution* **59**, 477–491 (2005).
29. Lehmann, L. The adaptive dynamics of niche constructing traits in spatially subdivided populations: evolving posthumous extended phenotypes. *Evolution* **62**, 549–566 (2008).
30. Silver, M. & Di Paolo, E. Spatial effects favour the evolution of niche construction. *Theor. Popul. Biol.* **20**, 387–400 (2006).
31. Feldman, M. W. & Cavalli-Sforza, L. L. in *Mathematical Evolutionary Theory* (ed. Feldman, M. W.) 145–173 (Princeton Univ. Press, 1989).
32. Ehrlich, P. R. *Human Natures: Genes, Cultures, and the Human Prospect* (Island Press, Washington DC, 2000).
33. Richerson, P. J. & Boyd, R. *Not By Genes Alone: How Culture Transformed Human Evolution* (Univ. of Chicago Press, 2005).
34. Laland, K. N. Exploring gene–culture interactions: insights from handedness, sexual selection and niche-construction case studies. *Phil. Trans. R. Soc. Lond. B* **363**, 3577–3589 (2008).
35. Laland, K. N. & Brown, G. R. *Sense and Nonsense: Evolutionary Perspectives on Human Behaviour* (Oxford Univ. Press, 2002).
36. Rogers, A. Does biology constrain culture? *Am. Anthropol.* **90**, 819–813 (1988).
37. Laland, K. N., Kumm, J., Van Horn, J. D. & Feldman, M. W. A gene–culture model of handedness. *Behav. Genet.* **25**, 433–445 (1995).
38. Cavalli-Sforza, L. L. & Feldman, M. W. Models for cultural inheritance I: group mean and within-group variation. *Theor. Popul. Biol.* **4**, 42–55 (1973).
39. Otto, S. P., Christiansen, F. B. & Feldman, M. W. *Genetic and Cultural Inheritance of Continuous Traits. Morrison Institute for Population and Resource Studies Paper Number 0064* (Stanford Univ. Press, 1995).
40. Bersaglieri, T. *et al.* Genetic signatures of strong recent positive selection at the lactase gene. *Am. J. Hum. Genet.* **74**, 1111–1120 (2004).
41. Laland, K. N. Sexual selection with a culturally transmitted mating preference. *Theor. Popul. Biol.* **45**, 1–15 (1994).
42. Laland, K. N., Kumm, J. & Feldman, M. W. Gene–culture co-evolutionary theory: a test case. *Curr. Anthropol.* **36**, 131–156 (1995).
43. Cochran, G. & Harpending, H. *The 10,000 Year Explosion. How Civilization Accelerated Human Evolution* (Basic Books, New York, 2009).
44. Coop, G. *et al.* 2009. The role of geography in human adaptation. *PLoS Genet.* **5**, e1000500 (2009).
This group studied the geographical distribution of recently selected genes and found that strong sustained selection is rare and partial sweeps are common.
45. Lewontin, R. C. in *Evolution From Molecules to Men* (ed. Bendall, D. S.) 273–285 (Cambridge Univ. Press, 1983).
46. Laland, K. N., Odling-Smee, F. J. & Feldman, M. W. Cultural niche construction and human evolution. *J. Evol. Biol.* **14**, 22–33 (2001).
A theoretical analysis of human niche construction and its effects on human evolution.
47. Borenstein, E., Kendal, J. & Feldman, M. W. Cultural niche construction in a metapopulation. *Theor. Popul. Biol.* **70**, 92–104 (2006).
48. Smith, B. Niche construction and the behavioral context of plant and animal domestication. *Evol. Anthropol.* **16**, 188–199 (2007).
49. Stringer, C. & Andrews, P. *The Complete World of Human Evolution* (Thames & Hudson, London, 2005).
50. Guglielmino, C. R., Viganotti, C., Hewlett, B. & Cavalli-Sforza, L. L. Cultural variation in Africa: role of mechanism of transmission and adaptation. *Proc. Natl Acad. Sci. USA* **92**, 7585–7589 (1995).
51. Perry, G. H. & Dominy, N. J. Evolution of the human pygmy phenotype. *Trends Ecol. Evol.* **24**, 218–225 (2009).
52. Fortunato, L. in *Early Human Kinship: From Sex To Social Reproduction* (eds Allen, N. J., Callan, H., Dunbar, R. & James, W.) 189–199 (Blackwell Publishing, Oxford, 2008).
53. Mace, R., Holden, C. J. & Shennan, S. (eds) *The Evolution Of Cultural Diversity. A Phylogenetic Approach* (Left Coast, Walnut Creek, California, 2005).
54. Balter, M. Are humans still evolving? *Science* **309**, 234–237 (2005).
55. Hawkes, K., O'Connell, J. F., Blurton-Jones, N. G., Alvarez, H. & Charnov, E. L. Grandmothering, menopause, and the evolution of human life histories. *Proc. Natl Acad. Sci. USA* **95**, 1336–1339 (1998).
56. Aiello, L. C. & Wheeler, P. The expensive-tissue hypothesis. *Curr. Anthropol.* **36**, 199–221 (1995).
57. Wrangham, R. W., Jones, J. H., Laden, G., Pilbeam, D. & Conklin-Brittain, N. The raw and the stolen: cooking and the ecology of human origins. *Curr. Anthropol.* **40**, 567–594 (1999).
58. Sabeti, P. C. *et al.* Detecting recent positive selection in the human genome from haplotype structure. *Nature* **419**, 832–837 (2002).
59. Akey, J. M. Constructing genomic maps of positive selection in humans: where do we go from here? *Genome Res.* **19**, 711–722 (2009).
60. Berglund, J., Pollard, K. S. & Webster, M. T. Hotspots of biased nucleotide substitutions in human genes. *PLoS. Biol.* **7**, e1000026 (2009).
61. Galtier, N., Duret, L., Glémin, S. & Ranwez, V. GC-biased gene conversion promotes the fixation of deleterious amino acid changes in primates. *Trends Genet.* **25**, 1–5 (2009).
62. Pickrell, J. K. *et al.* Signals of recent positive selection in a worldwide sample of human populations. *Genome Res.* **19**, 826–837 (2009).
63. López Herráez, D. *et al.* Genetic variation and recent positive selection in worldwide human populations: evidence from nearly 1 million SNPs. *PLoS ONE* **4**, e7888 (2009).
64. Stefansson, H. *et al.* A common inversion under selection in Europeans. *Nature Genet.* **37**, 129–137 (2005).
65. Nguyen, D-Q., Webber, C. & Ponting, C. P. Bias of selection on human copy-number variants. *PLoS Genet.* **2**, e20 (2006).
66. Prabhakar, S. *et al.* Human-specific gain of function in a developmental enhancer. *Science* **321**, 1346–1350 (2008).
67. Quach, H. *et al.* Signatures of purifying and local positive selection in human miRNAs. *Am. J. Hum. Genet.* **84**, 316–327 (2009).
68. Evans, P. D. *et al.* Microcephalin, a gene regulating brain size, continues to evolve adaptively in humans. *Science* **309**, 1717–1720 (2005).
69. Mekel-Bobrov, *et al.* Ongoing adaptive evolution of *ASPM*, a brain size determinant in *Homo sapiens*. *Science* **309**, 1720–1722 (2005).
70. Dediu, D. & Ladd, D. R. Linguistic tone is related to the population frequency of the adaptive haplogroups of two brain size genes, *ASPM* and *Microcephalin*. *Proc. Natl Acad. Sci. USA* **104**, 10944–10949 (2007).
71. Aoki, K. A stochastic model of gene–culture co-evolution suggested by the 'culture historical hypothesis' for the evolution of adult lactose absorption in humans. *Proc. Natl Acad. Sci. USA* **83**, 2929–2933 (1986).
72. Itan, Y., Powell, A., Beaumont, M. A., Burger, J. & Thomas, M. G. The origins of lactase persistence in Europe. *PLoS Comput. Biol.* **5**, e1000491 (2009).
73. Nasidze, I., Quinque, D., Rahmani, M., Alemohamad, S. A. & Stoneking, M. Concomitant replacement of language and mtDNA in South Caspian populations of Iran. *Curr. Biol.* **16**, 668–673 (2006).
74. Kayser, M. *et al.* Melanesian and Asian origins of Polynesians: mtDNA and Y chromosome gradients across the Pacific. *Mol. Biol. Evol.* **23**, 2234–2244 (2006).
75. Oota, H., Settheetham-Ishida, W., Tiwawech, D., Ishida, T. & Stoneking, M. Human mtDNA and Y-chromosome variation is correlated with matrilocal versus patrilocal residence. *Nature Genet.* **29**, 20–21 (2001).
This article shows how cultural boundaries can shape gene flow.
76. Cordaux, R. *et al.* Independent origins of Indian caste and tribal paternal lineages. *Curr. Biol.* **14**, 231–235 (2004).

77. Fisher, S. E., Vargha-Khadem, F., Watkins, K. E., Monaco, A. P. & Pembrey, M. E. Localisation of a gene implicated in a severe speech and language disorder. *Nature Genet.* **18**, 168–170 (1998).
78. Enard, W. *et al.* Molecular evolution of *FOXP2*, a gene involved in speech and language. *Nature* **418**, 869–872 (2002).
79. Enard, W. *et al.* A humanized version of Foxp2 affects cortico-basal ganglia circuits in mice. *Cell* **137**, 961–971 (2009).
80. Stedman, H. H. *et al.* Myosin gene mutation correlates with anatomical changes in the human lineage. *Nature* **428**, 415–418 (2004).
81. Liao, B. Y. & Zhang, J. Null mutations in human and mouse orthologs frequently result in different phenotypes. *Proc. Natl Acad. Sci. USA* **105**, 6987–6992 (2008).
82. Caspari, R. & Lee, S. H. Older age becomes common late in human evolution. *Proc. Natl Acad. Sci. USA* **101**, 10895–10900 (2004).
83. Scrimshaw, N. & Murray, E. The acceptability of milk and milk products in populations with a high prevalence of lactose intolerance. *Am. J. Clin. Nutr.* **48**, 1079–1159 (1998).
84. Hollox, E. J. *et al.* Lactase haplotype diversity in the old world. *Am. J. Hum. Genet.* **68**, 160–172 (2001).
85. Swallow, D. M. Genetics of lactase persistence and lactose intolerance. *Annu. Rev. Genet.* **37**, 197–219 (2003).
86. Enattah, N. S. *et al.* Identification of a variant associated with adult-type hypolactasia. *Nature Genet.* **30**, 233–237 (2002).
87. Lewinsky, R. H. *et al.* T-13910 DNA variant associated with lactase persistence interacts with Oct-1 and stimulates lactase promoter activity *in vitro*. *Hum. Mol. Genet.* **14**, 3945–3953 (2005).
88. Enattah, N. S. *et al.* Independent introduction of two lactase-persistence alleles into human populations reflects different history of adaptation to milk culture. *Am. J. Hum. Genet.* **82**, 57–72 (2008).
89. Ulijaszek, S. J. & Strickland, S. S. *Nutritional Anthropology: Prospects and Perspectives* (Smith-Gordon, London, 1993).
90. Myles, S. *et al.* Genetic evidence in support of a shared Eurasian–North African dairying origin. *Hum. Genet.* **117**, 34–42 (2005).
91. Simoons, F. Primary adult lactose intolerance and the milking habit: a problem in biological and cultural interrelations. II. A culture historical hypothesis. *Dig. Dis. Sci.* **15**, 695–710 (1970).
92. Beja-Pereira, A. *et al.* Gene–culture co-evolution between cattle milk protein genes and human lactase genes. *Nature Genet.* **35**, 311–313 (2003).
93. Laland, K. N. & Galef B. G. Jr (eds) *The Question of Animal Culture* (Harvard Univ. Press, 2009).
94. Lachlan, R. F. & Slater, P. J. B. The maintenance of vocal learning by gene–culture interaction: the cultural trap hypothesis. *Proc. R. Soc. Lond. B* **266**, 701–706 (1999).
95. Beltman, J.B., Haccou, P. & ten Cate, C. The impact of learning foster species' song on the evolution of specialist avian brood parasitism. *Behav. Ecol.* **14**, 917–923 (2003).
96. Beltman, J. B., Haccou, P. & ten Cate, C. Learning and colonization of new niches: a first step towards speciation. *Evolution* **58**, 35–46 (2004).
97. Bryk, J. *et al.* Positive selection in East Asians for an *EDAR* allele that enhances NF-κB activation. *PLoS ONE* **3**, e2209 (2008).
98. Chang, S. H. *et al.* Enhanced Edar signalling has pleiotropic effects on craniofacial and cutaneous glands. *PLoS ONE* **4**, e7591 (2009).
99. Izagirre, N., Garcia, I., Junquera, C., de la Rua, C. & Alonso, S. A scan for signatures of positive selection in candidate loci for skin pigmentation in humans. *Mol. Biol. Evol.* **23**, 1697–1706 (2006).
100. Lao, O., de Gruijter, J. M., van Duijn, K., Navarro, A. & Kayser, M. Signatures of positive selection in genes associated with human skin pigmentation as revealed from analyses of single nucleotide polymorphisms. *Ann. Hum. Genet.* **71**, 354–369 (2007).
101. Myles, S., Somel, M., Tang, K., Kelso, J. & Stoneking, M. Identifying genes underlying skin pigmentation differences among human populations. *Hum. Genet.* **120**, 613–621 (2007).
102. Myles, S. *et al.* Identification and analysis of high Fst regions from genome-wide SNP data from three human populations. *Ann. Hum. Genet.* **72**, 99–110 (2008).
103. Ihara, Y., Aoki, K. & Feldman, M. W. Runaway sexual selection with paternal transmission of the male trait and gene–culture determination of the female preference. *Theor. Popul. Biol.* **63**, 53–62 (2003).
104. Livingstone, F. B. Anthropological implications of sickle-cell distribution in West Africa. *Am. Anthropol.* **60**, 533–562 (1958).
105. Hawley, W. A., Reiter, P., Copeland, R. S., Pumpuni, C. B. & Craig, G. B. *Aedes albopictus* in North America: probable introduction in used tires from Northern Asia. *Science* **236**, 1114–1116 (1987).
106. Bindon, J. R. & Baker, P. T. Bergmann's rule and the thrifty genotype. *Am. J. Phys. Anthropol.* **104**, 201–210 (1997).
107. Houghton, P. The adaptive significance of Polynesian body form. *Ann. Hum. Biol.* **17**, 19–32 (1990).
108. Myles, S. *et al.* Identification of a candidate genetic variant for the high prevalence of type II diabetes in Polynesians. *Eur. J. Hum. Genet.* **15**, 584–589 (2007).
109. Neel, J. V. Diabetes mellitus: a 'thrifty' genotype rendered detrimental by 'progress'? *Bull. World Health Organ.* **77**, 694–703 (1962).
110. Gleibermann, L. Blood pressure and dietary salt in human populations. *Ecol. Food Nutr.* **2**, 143–156 (1973).
111. Young, J. H. *et al.* Differential susceptibility to hypertension is due to selection during the out-of-Africa expansion. *PLoS Genet.* **1**, e82 (2005).
112. Perry, G. H. *et al.* Diet and the evolution of human amylase gene copy number variation *Nature Genet.* **39**, 1256–1260 (2007).
A good example of gene–culture co-evolution in which changes in human diet favour copies of a gene.
113. Richards, M. P., Schulting, R. J. & Hedges, R. E. M. Archaeology: sharp shift in diet at onset of Neolithic. *Nature* **425**, 366 (2003).
114. Kelley, J. L. & Swanson, W. J. Dietary change and adaptive evolution of enamelin in humans and among primates. *Genetics* **178**, 1595–1603 (2008).
115. Soranzo, N. *et al.* Positive selection on a high-sensitivity allele of the human bitter-taste receptor TAS2R16. *Curr. Biol.* **15**, 1257–1265 (2005).
116. Haygood, R., Fedrigo, O., Hanson, B., Yokoyama, K. D. & Wray, G. A. Promoter regions of many neural- and nutrition-related genes have experienced positive selection during human evolution. *Nature Genet.* **39**, 1140–1144 (2007).
117. Chen, C. *et al.* Interaction between the functional polymorphisms of the alcohol-metabolism genes in protection against alcoholism. *Am. J. Hum. Genet.* **65**, 795–807 (1999).
118. Han, Y. *et al.* Evidence of positive selection on a class I *ADH* locus. *Am. J. Hum. Genet.* **80**, 441–456 (2007).
119. Boyd, R. & Richerson, P. Why does culture increase human adaptability? *Ethol. Sociobiol.* **16**, 125–143 (1995).
120. Feldman, M. W. & Zhivotovsky, L. A. Gene–culture co-evolution: towards a general theory of vertical transmission. *Proc. Natl Acad. Sci. USA* **89**, 11935–11938 (1992).
121. Feldman, M., Aoki, K. & Kumm, J. Individual versus social learning: evolutionary analysis in a fluctuating environment. *Anthropol. Sci.* **104**, 209–231 (1996).
122. Henrich, J. & Boyd, R. The evolution of conformist transmission and the emergence of between-group differences. *Evol. Hum. Behav.* **19**, 215–241 (1998).
123. Henrich, J. & McElreath, R. The evolution of cultural evolution. *Evol. Anthropol.* **12**, 123–135 (2003).
124. Efferson, C., Lalive, R., Richerson, P., McElreath, R. & Lubell, M. Conformists and mavericks: the empirics of frequency-dependent cultural transmission. *Evol. Hum. Behav.* **29**, 56–64 (2008).
125. Aoki, K. & Feldman, M. W. Toward a theory for the evolution of cultural communication: co-evolution of signal transmission and reception. *Proc. Natl Acad. Sci. USA* **84**, 7164–7168 (1987).
126. Aoki, K. & Feldman, M. W. Pleiotrophy and preadaptation in the evolution of human language capacity. *Theor. Popul. Biol.* **35**, 181–194 (1989).
127. Aoki, K. & Feldman, M. W. Recessive hereditary deafness, assortative mating, and persistence of a sign language. *Theor. Popul. Biol.* **39**, 358–372 (1991).
128. Lachlan, R. F. & Feldman, M. W. Evolution of cultural communication systems: the co-evolution of cultural signals and genes encoding learning preferences *J. Evol. Biol.* **16**, 1084–1095 (2003).
129. Feldman, M. W. & Otto, S. P. Twin studies, heritability, and intelligence. *Science* **278**, 1383–1384 (1997).
130. Cochran, G., Hardy, J. & Harpending, H. Natural history of Ashkenazi intelligence. *J. Biosoc. Sci.* **38**, 659–693 (2005).
131. Boyd, R. & Richerson, P. J. Cultural transmission and the evolution of cooperative behavior. *Hum. Ecol.* **10**, 325–351 (1982).
132. Boyd, R. & Richerson, P. J. The evolution of reciprocity in sizeable groups. *J. Theor. Biol.* **132**, 337–356 (1988).
133. Boyd, R., Gintis, H., Bowles, S. & Richerson, P. J. The evolution of altruistic punishment. *Proc. Natl Acad. Sci. USA* **100**, 3531–3535 (2003).
134. Henrich, J. *et al.* Costly punishment across human societies. *Science* **312**, 1767–1770 (2006).
135. Gintis, H. The hitchhiker's guide to altruism: gene–culture co-evolution, and the internalization of norms. *J. Theor. Biol.* **220**, 407–418 (2003).
136. Gintis, H. The genetic side of gene–culture co-evolution: internalization of norms and prosocial emotions. *J. Econ. Behav. Organ.* **53**, 57–67 (2004).
137. Fehr, E. & Fischbacher, U. The nature of human altruism. *Nature* **425**, 785–791 (2003).
138. McElreath, R., Boyd, R. & Richerson, P. J. Shared norms and the evolution of ethnic markers. *Curr. Anthropol.* **44**, 122–129 (2003).
139. Lumsden, C. J. & Wilson, E. O. *Genes, Mind and Culture* (Harvard Univ. Press, 1981).
140. Aoki, K. & Feldman, M. W. A gene–culture co-evolutionary model for brother–sister mating. *Proc. Natl Acad. Sci. USA* **94**, 13046–13050 (1997).
141. Mesoudi, A. & Laland, K. N. Culturally transmitted paternity beliefs and the evolution of human mating behaviour. *Proc. R. Soc. Lond. B* **274**, 1273–1278 (2007).
142. Kumm, J., Laland, K. N. & Feldman, M. W. Gene–culture co-evolution and sex ratios: the effects of infanticide, sex-selective abortion, and sex-biased parental investment on the evolution of sex ratios. *Theor. Popul. Biol.* **46**, 249–278 (1994).
143. Kumm, J. & Feldman, M. W. Gene–culture co-evolution and sex ratios: II. Sex-chromosomal distorters and cultural preferences for offspring sex. *Theor. Popul. Biol.* **52**, 1–15 (1997).
144. Osier, M. V. *et al.* A global perspective on genetic variation at the *ADH* genes reveals unusual patterns of linkage disequilibrium and diversity. *Am. J. Hum. Genet.* **71**, 84–99 (2002).
145. Elbers, C. C. *et al.* Variants in neuropeptide Y receptor 1 and 5 are associated with nutrient-specific food intake and are under recent selection in Europeans. *PLoS ONE* **4**, e7070 (2009).
146. Thompson, E. E. *et al. CYP3A* variation and the evolution of salt-sensitivity variants. *Am. J. Hum. Genet.* **75**, 1059–1069 (2004).
147. Wooding, S. P. *et al.* DNA sequence variation in a 3.7-kb noncoding sequence 5′ of the *CYP1A2* gene: implications for human population history and natural selection. *Am. J. Hum. Genet.* **71**, 528–542 (2002).
148. Saunders, M. A., Hammer, M. F. & Nachman, M. W. Nucleotide variability at *G6pd* and the signature of malarial selection in humans. *Genetics* **162**, 1849–1861 (2002).
149. Nielsen, R., Hellmann, I., Hubisz, M., Bustamante, C. & Clark, A. G. Recent and ongoing selection in the human genome. *Nature Rev. Genet.* **8**, 857–868 (2007).
150. Hancock, A. M. *et al.* Adaptations to climate in candidate genes for common metabolic disorders. *PLoS Genet.* **4**, e32 (2008).
151. Sulem, P. *et al.* Genetic determinants of hair, eye and skin pigmentation in Europeans. *Nature Genet.* **39**, 1443–1452 (2007).

Acknowledgements
The authors' research was supported in part by grants from the Biotechnology and Biological Sciences Research Council (BB/C005430/1) and the European Union (NESTPathfinder, CULTAPTATION) to K.N.L. S.M. is supported by the US Department of Agriculture. We are grateful to M. Feldman, L. Fortunato, P. Sabeti and M. Stoneking for helpful comments on earlier drafts of this manuscript.

Competing interests statement
The authors declare no competing financial interests.

DATABASES
Entrez Gene: http://www.ncbi.nlm.nih.gov/gene
AMY1 | *ASPM* | *EDAR* | *FOXP2* | *LCT* | *MCPH1* | *MYH16*

FURTHER INFORMATION
Kevin N. Laland's homepage:
http://lalandlab.st-andrews.ac.uk
Sean Myles' homepage:
http://www.maizegenetics.net/sean-myles

ALL LINKS ARE ACTIVE IN THE ONLINE PDF

Author Biographies

Kevin N. Laland received his Ph.D. in psychology from University College London, UK, in 1990. After a Human Frontier Science Program postdoctoral fellowship in the Department of Biology at the University of California-Berkeley, USA, and a Biotechnology and Biological Sciences Research Council Fellowship and Royal Society University Research Fellowship in the Department of Zoology at the University of Cambridge, UK, he moved to the University of St Andrews, UK, where he is currently Professor of Biology. He studies behavioural and evolutionary biology, particularly niche construction, social learning and gene–culture co-evolution, using a range of theoretical and empirical methods. He is the author of over 150 scientific articles and 6 books, and is an elected fellow of the Royal Society of Edinburgh.

John Odling-Smee received his Ph.D. in animal learning from University College London, UK, in 1973. He subsequently switched his research interests to evolution and niche construction. That led to a long-term collaboration with Kevin N. Laland at the University of St Andrews, UK, and Marc Feldman at Stanford University, USA, one of the results of which was a co-authored book, *Niche Construction: The Neglected Process in Evolution* (Princeton University Press, 2003). He is currently concerned with the multi-disciplinary applications of niche construction, and was able to pursue that interest at the Santa Fe Institute, USA, in 2009. He is in the School of Anthropology at the University of Oxford, UK, and lectures in human sciences.

Sean Myles completed his Ph.D. in the Department of Evolutionary Genetics at the Max Planck Institute for Evolutionary Anthropology in Leipzig, Germany, in 2007. He is currently a postdoctoral researcher at the Institute for Genomic Diversity at Cornell University, Ithaca, USA, and an adjunct professor in the Biology Department at Acadia University, Wolfville, Canada. He is interested in using modern genomics tools to gain insights into population history, to discover genetic loci underlying locally adaptive phenotypes and to map genes underlying complex traits. His current work focuses on humans and grapes.

Online summary

- A variety of researchers are converging on the view that human evolution has been shaped by gene–culture interactions. Theoretical biologists use models to demonstrate that cultural processes can affect human evolution, anthropologists are investigating cultural practices that modify current selection, and geneticists are uncovering alleles that have been subject to recent selection because of human activities.
- Theoretical population genetics models are used to explore how genes and culture interact over evolutionary time, including how and why culture can affect evolutionary rates.
- Niche-construction theory is a branch of evolutionary biology that emphasizes the capacity of organisms to modify natural selection and thereby act as co-directors of their own, and other species', evolution. Humans are the ultimate niche-constructing species. We specify how variation in buffering through cultural niche construction could explain geographical variation in human genes.
- A further source of evidence for gene–culture co-evolution comes from anthropological studies of contemporary human populations, which demonstrate gene–culture co-evolution in action. Examples include Kwa-speaking yam cultivators in West Africa whose agriculture favoured the haemoglobin S (*HbS*) 'sickle-cell' allele, and Polynesian voyages that led to positive selection for thrifty metabolism, leading to type 2 diabetes susceptibility.
- Geneticists have recently developed methods to identify alleles that have been favoured by recent selection, many of which seem to have been favoured because of cultural activities. Overrepresented categories of genes that have been subject to positive selection include those related to recent changes in human diet and human-induced disease.
- The well-researched example of co-evolution of dairy farming and the lactase gene shows the range of methods used to investigate gene–culture co-evolution.
- We end by asking how prevalent gene–culture co-evolution is, and how researchers can differentiate between a molecular signature of selection generated by gene–culture co-evolution and one generated from a non-cultural aspect of the environment.

ToC Blurb

000

How culture shaped the human genome: bringing genetics and the human sciences together

Kevin N. Laland, John Odling-Smee and Sean Myles

Theoretical, anthropological and genetic studies suggest that human evolution has been shaped by gene–culture interactions. This Review collates data from these diverse fields, and highlights the potential for cross-disciplinary exchange to provide novel insights into how culture has shaped the human genome.