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REVIEW

Reconstructing phylogenies and phenotypes: a molecular view of human evolution

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Abstract

This review broadly summarizes how molecular biology has contributed to our understanding of human evolution. Molecular anthropology began in the 1960s with immunological comparisons indicating that African apes and humans were closely related and, indeed, shared a common ancestor as recently as 5 million years ago. Although initially dismissed, this finding has proven robust and numerous lines of molecular evidence now firmly place the human-ape divergence at 4–8 Ma. Resolving the trichotomy among humans, chimpanzees and gorillas took a few more decades. Despite the readily apparent physical similarities shared by African apes to the exclusion of modern humans (body hair, knuckle-walking, thin tooth enamel), the molecular support for a human–chimpanzee clade is now overwhelming. More recently, whole genome sequencing and gene mapping have shifted the focus of molecular anthropology from phylogenetic analyses to phenotypic reconstruction and functional genomics. We are starting to identify the genetic basis of the morphological, physiological and behavioural traits that distinguish modern humans from apes and apes from other primates. Most notably, recent comparative genomic analyses strongly indicate that the marked differences between modern humans and chimpanzees are likely due more to changes in gene regulation than to modifications of the genes themselves, an idea first proposed over 30 years ago. Almost weekly, press releases describe newly identified genes and regulatory elements that seem to have undergone strong positive selection along the human lineage. Loci involved in speech (e.g. *FOXP2*), brain development (e.g. *ASPM*), and skull musculature (e.g. *MYH16*) have been of particular interest, but some surprising candidate loci (e.g. those involved in auditory capabilities) have emerged as well. Exciting new research avenues, such as the Neanderthal Genome Project, promise that molecular analyses will continue to provide novel insights about our evolution. Ultimately, however, these molecular findings can only be understood in light of data from field sites, morphology labs, and museum collections. Indeed, molecular anthropology depends on these sources for calibrating molecular clocks and placing genetic data within the context of key morphological and ecological transitions in human evolution.

Key words DNA; gene expression; last common ancestor; molecular anthropology; molecular systematics.

Introduction

Clues to understanding our origins have traditionally come from fossil specimens and morphological comparisons of living taxa. But over the last half century, advances in molecular biology have provided new tools for resolving long-standing questions about our evolutionary past. New discoveries in human evolution are now as likely to emerge from a genetics lab as from the East African Rift Valley.

Here I briefly review what molecular biology has and can contribute to our understanding of human evolution. Specifically, I discuss how molecular analyses address the following questions: What are the evolutionary relationships among humans and the other African apes? When did modern humans and extant apes last share a common ancestor? And what important genetic changes have occurred on the human lineage since this divergence?

First, it is worth placing human and ape evolution in a broad context. Although the focus here is on human-ape relationships, molecular biology can also tell us how, evolutionarily, apes are related to other primates and primates are related to other mammals.

Primates are one of 20 orders of placental mammals (Nowak, 1999). The evolutionary relationship among these orders has been difficult to resolve using morphology alone as many shared features have arisen independently in different lineages under similar selective pressures

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(Novacek, 1992). Based on comparative anatomy and paleontology, primates have traditionally been grouped with tree shrews (Scandentia), flying lemurs (Dermoptera), and, briefly, even with bats (Chiroptera or specifically Megachiroptera) (Gregory, 1910; Wible & Covert, 1987). But more recent, large-scale reconstructions of early mammalian phylogeny (see also www.tolweb.org) based on both morphology and molecular data, place primates in the superorder Euarchontoglires (Murphy et al. 2001a,b; Kriegs et al. 2006; Asher, 2007; and on supertrees see Bininda-Emonds et al. 2007). This superorder includes five orders: rodents (Rodentia), rabbits (Lagomorpha), tree shrews, flying lemurs and primates, with flying lemurs and primates being likely sister taxa (Janecka et al. 2007). Euarchontoglires is a robust clade, exclusively sharing a particular type of retroposed element (7SL RNA-derived short interspersed nuclear elements, Nishihara et al. 2002). These elements are small pieces of nuclear DNA that are present in multiple copies and integrate randomly in the genome. The probability that the same element would integrate independently in the same genomic location in multiple lineages is negligible, making these ideal markers for detecting ancient relationships as, unlike with sequence data, molecular homoplasies at these loci should be exceedingly rare.

The identification of this Euarchontoglire clade revealed a primate–rodent relationship that many researchers had overlooked (Murphy et al. 2001b). Moreover, it indicated that the neuro-anatomical similarities previously used by some to link primates and bats (Pettigrew et al. 1989) are misleading convergences, as bats group in a different superorder, Laurasiatheria, containing carnivores, artiodactylids and others (Murphy et al. 2001b).

Molecular analyses have similarly resolved taxonomic misgroupings within the primate order. Most notably, tarsiers are now recognized as more closely related to monkeys and apes, despite their obvious physical similarities to lemurs, lorisis and galagos (Schmitz, 2001, but see Yoder, 2003). Thus, the category 'prosimian', although still commonly used, is paraphyletic.

Other surprising relationships revealed by molecular analyses include a division of mangabeys, with the terrestrial *Cercocebus* being more closely related to drills and mandrills (*Mandrillus*) and the arboreal *Lophocebus* more closely related to baboons (*Papio*) and geladas (*Theropithecus*) (Disotell et al. 1992); as well as the recognition of callimico – whose single births and lack of a third molar seem so unique among the callitrichids – as a sister taxon to the marmosets (*Callithrix*), with tamarins (*Saguinus*) as the outliers (Pastorini, 1998).

Such examples illustrating how molecular data can overthrow seemingly obvious phylogenies based on physical similarities are now common. Although there remains some argument concerning the relative merit of morphology- vs. DNA-based phylogenies, most recognize that the two approaches provide complementary insights into evolutionary history (Donoghue & Benton, 2007). Molecular data can provide more robust phylogenies than anatomical data alone, as they are less subject to homoplasies. Many of the molecular changes used to reconstruct evolutionary relationships are random, rare events (e.g. the 7SL retroposed element mentioned above) that are unlikely to occur repeatedly. Molecular data can, roughly, pinpoint the time and relative order in which lineages diverge, while fossil data describe the gain and loss of characters recognized as lineage specific. Initially, though, the molecular approach to assessing evolutionary relationships was controversial, especially as it was first applied to apes and humans.

Genetic relationships among the apes

That modern humans and extant apes share striking similarities was already much discussed in the 19th century by the likes of Huxley (1863), Darwin (1871) and even Queen Victoria, who described a captive orangutan as 'painfully and disagreeably human' (Ridley, 2004). However, it was not until the 1960s, a full century later, that molecular methods were used to examine this relationship. To fully appreciate how revolutionary this molecular approach was, we must consider the prevailing views of human origins at that time. Gorillas (*Gorilla*) and chimpanzees (*Pan*) were assumed to be recently and closely related to each other, early descriptions even grouped them in the same genus (Groves, 2001), and the lineage leading to modern humans was thought to have diverged from these apes about 15–28 Ma (Pilbeam, 1966, 1970).

It is also worth noting, as an aside, that we now recognize two extant species of *Pan* (*Pan troglodytes*, the common chimpanzee, and *Pan paniscus*, the bonobo) and two extant species of *Gorilla* (*Gorilla gorilla*, the Western Gorilla, and *Gorilla beringei*, the Eastern Gorilla) (Groves, 2001). Throughout this review, 'chimpanzees' refers to both common chimpanzees and bonobos, 'gorillas' refers to both extant species of gorilla, and 'humans' refers to extant modern humans.

The early assumptions, that gorillas and chimpanzees were sister taxa and that the divergence of the human clade was old, are readily understandable – extant apes look very similar and modern humans seem so unique. The African apes share seemingly-derived traits, such as knuckle walking and thin tooth enamel (Kluge, 1983; Schwartz, 1984; but see Richmond & Strait, 2000), while humans have tools, culture and language. In the 1960s, Jane Goodall (1998) was only just beginning her work on the chimpanzees at Gombe, and so it was not yet recognized that chimps also use tools (McGrew, 1992), and have a form of culture (Whiten et al. 1999) and complex communication (Crockford & Boesch, 2003).

In addition, at that time, paleontologists thought the fossil 'hominid' *Ramapithecus* provided evidence that the

human lineage must be very old. The fossil teeth of *Ramapithecus* were thought to show a human-like dental arcade and it was classified as a hominid (equivalent to the term hominin used today), an early human ancestor preceding *Australopithecus* on the human lineage (Simons, 1964; Pilbeam, 1969). The *Ramapithecus* specimens dated to ~14 Ma and the human–ape split was assumed to predate that (Pilbeam, 1966). Later, new fossil evidence and new interpretations of the existing fossils clearly indicated that *Ramapithecus* was not a hominin, but rather belonged on the orangutan lineage (Andrews & Cronin, 1982). Nonetheless, the hominid status of *Ramapithecus* and the consequentially early date for the ape–human divergence had wide acceptance in the 1960s.

So when biochemists Allan Wilson and Vince Sarich were bold enough to claim in a 1967 *Nature* article (Sarich & Wilson, 1967) that humans and apes shared a common ancestor as recently as 5 Ma, their claims were largely dismissed by contemporary anthropologists (see Lewin, 1988 for an entertaining account of this 15-year debate). This study, along with Emil Zuckerkandl's and Morris Goodman's protein comparisons demonstrating that humans may be more similar to African apes than African apes are to orangutans (Zuckerkandl et al. 1960; Goodman, 1962; Goodman et al. 1983), arguably mark the beginning of molecular anthropology.

Sarich & Wilson (1967) measured the immunoprecipitation reaction between primate blood proteins and an antiserum for human blood proteins. The more dissimilar the primate protein is from human protein, the weaker the immunoprecipitation reaction, so these immunological tests provided a novel way to quantitatively measure similarities among the blood proteins of various species. Following Zuckerkandl & Pauling's (1965) suggestion that molecular changes accrue at a consistent, clock-like rate, and assuming that the Old World monkey–ape split occurred about 30 Ma (based on fossil evidence), Sarich and Wilson estimated that the human–ape split had about 1/6th the time depth of the ape–monkey split, which gave a divergence date of about 5 Ma. But this left unanswered questions about the specific relationships among the African apes.

The trichotomy

Molecular biologists, conveniently unhampered by a fossil record and paleontological dogma, found this time frame plausible. For them, the unsettled issue now was the lack of resolution of the gorilla–chimpanzee–human trichotomy. Resolving this trichotomy became a pressing issue driving the next few decades of molecular anthropology. As new methods were developed, various approaches were taken, and attempts to resolve the trichotomy used chromosomal comparisons, DNA-hybridization, protein sequencing and ultimately DNA sequence and gene expression data (Table 1).

Table 1 Lines of molecular and anatomical evidence identifying relationships among African apes and humans

Type of evidence	Relationship
Molecular	
Immunological test Sarish & Wilson 1967	
Protein (globin) sequences Goodman, 1983	
Chromosomes (karyotypes, FISH) Yunis & Prakash, 1982	
DNA-DNA hybridization Sibly & Alquist 1984	
DNA sequences (mtDNA, nuclear) Ruvolo, 1997	
Gene expression profiles Uddin et al. 2004	
Anatomical	
General morphology Kluge, 1983	
Temporal bone Lockwood et al. 2004	
Soft tissue Gibbs et al. 2002	

H = human; C = chimpanzee; G = gorilla.
FISH = fluorescent in situ hybridization.
mtDNA = mitochondrial DNA.

Resolving the trichotomy: chromosomes

Long before the advent of the polymerase chain reaction (PCR), automated sequencing, and comparative genomics, large scale molecular differences were assessed by looking at karyotypes – microscopic views of stained chromosomes. Major chromosomal rearrangements, such as inversions or fusions, could be identified by comparing the number and appearance of G-bands on karyotypes or, later, by pin-pointing analogous chromosomal regions with chromosome painting and fluorescent *in situ* hybridization (FISH). These chromosomal changes can be compared among taxa and used to identify evolutionary relationships.

The most striking aspect of hominoid karyotypes is that humans have 46 chromosomes whereas gorillas and chimpanzees have 48 (Yunis & Prakash, 1982). Human chromosome 2 seems to be a fusion of ape chromosomes 12 and 13. As orangutans have 48 chromosomes, this is clearly a derived feature of the modern human karyotype, rather than a shared synapomorphy of the African apes. Provocatively, Disotell (2006) speculates that this fusion may be very recent and perhaps even accounts for the

supposed lack of interbreeding between modern humans and Neanderthals (see below; Currat & Excoffier, 2004).

Although initial cytogenetic analyses suggested that chimpanzees and gorillas might share some unique chromosomal inversions (Stanyon & Chiarelli, 1982), these are now confirmed to be independent and non-identical mutations (Goidts et al. 2005). Humans and chimpanzees, however, do share identical inversions on chromosomes 7 and 9 that are not evident in the gorilla karyotype (Wimmer et al. 2002). Thus, the general phylogeny obtained from chromosomal comparisons suggests humans and chimpanzees are sister taxa (see also Dennehey et al. 2004).

Resolving the trichotomy: DNA–DNA hybridization

An intuitively more attractive approach to resolving the trichotomy would be to compare the DNA molecules themselves, and in the days before automated sequencing this was done by an ingenious technique of DNA–DNA hybridization (King & Wilson, 1975). A normal double-stranded piece of DNA will 'melt' – the two strands will separate – at a given temperature. But if the two strands are not perfectly complementary (i.e. if there are mismatches between them) the DNA will melt at a lower temperature. The more dissimilar the strands, the lower the melting temperature will be. Applying this principle, King & Wilson (1975) compared sequence similarity between chimpanzees and humans simply by hybridizing their DNA and determining the temperature at which that DNA hybrid melts. Based on the high melting temperature of the hybrid, it seemed human–chimpanzee sequence similarity was an astonishing 99%. This elegant experiment provided an accurate measure of human–chimpanzee sequence similarity three decades before the actual genomic sequences of these species could be compared. Moreover, King & Wilson (1975) proposed an explanation to account for how chimpanzees and humans could be so similar on the genetic level yet so different in terms of behaviour, cognition, and morphology. Most of the truly important genetic changes, they posited, were small changes to the regulatory regions effecting gene expression – turning genes on and off. A small genetic change (e.g. via gene arrangement) could have a dramatic phenotypic impact if it modified the expression patterns (timing, anatomical location) of other genes. This, like most of Allan Wilson's theories, showed remarkable foresight and such regulatory changes are now being identified, including some likely to underlie cognitive differences between chimpanzees and humans (Donaldson & Gottgens, 2006; Pollard et al. 2006a; see below).

Sibley & Ahlquist (1984; also see Caccone, 1989) applied DNA–DNA hybridization experiments to further resolve the relationships among the apes, specifically the human–chimpanzee–gorilla trichotomy, and found that the chimpanzee–human heteroduplex (hybrid, double-stranded DNA) was more thermostable than either the chimpanzee–gorilla or the gorilla–human hybrid, therefore also supporting a chimp–human clade. However, critics remained skeptical of this conclusion (Marks, 1988), claiming, among other things, that this approach is generally best for comparing much older divergences (> 10 Ma), and the chimpanzee–human clade was not yet universally accepted.

Resolving the trichotomy: DNA sequence data

Early comparative analyses of protein, especially globin, sequences confirmed that African apes group with humans, to the exclusion of orangutans (Goodman, 1983), but among the hominoids, protein sequences generally showed too few differences to allow for fine-scale phylogenetic reconstruction (Romero-Herrera, 1978; Goodman, 1983). Thus, breakthroughs in DNA sequencing methodology (Maxam, 1977; Sanger, 1977) were quickly seized upon in the hope that sequence comparisons might provide a more precise resolution of the trichotomy. Anderson et al. (1981) reported the first complete sequence of the human mitochondrial genome, and Brown et al. (1982) provided comparative mitochondrial DNA sequence data (~900 bp of coding mtDNA) for the apes.

But reconstructing phylogenies from small segments of sequence data can be misleading, as gene trees do not necessarily reflect species trees. When comparing multiple species at a single genetic locus, the most similar sequences might not be from the most closely related species. This is in part because polymorphic alleles that persist after speciation events might sort themselves in a way that is discordant with the species tree (Fig. 1). When sequential species splits happen over a short time period, or when the effective population size of the common ancestor is large, there is a greater risk of gene tree–species tree discordance (Edwards & Beerli 2000; Chen & Li, 2001). Consequently, phylogenetic trees based on single loci should be viewed with caution and the best approach is to examine numerous loci across the genome.

So it is not surprising that phylogenetic analyses of single loci have yielded contradictory trees, with some supporting a chimpanzee–gorilla clade, some supporting a chimpanzee–human clade, and some even supporting a gorilla–human clade (review in Ruvolo, 1997; Ebersberger et al. 2007). But when DNA sequence data are compiled across multiple loci, either by concatenating it as a single sequence and constructing a single phylogeny or by conducting multilocus significance tests on independent phylogenies, the support for a chimpanzee–human clade is overwhelming (Ruvolo, 1997; Chen & Li, 2001). Yet the proportion of single-locus phylogenies that are incongruent with the species tree is high (about 40%, Chen & Li, 2001), suggesting that the two splits happened in quick succession and that the last common ancestor of apes and humans had a relatively large effective population size, on the order of 50–100 000 (Chen & Li, 2001; see also Hobolth et al. 2007).

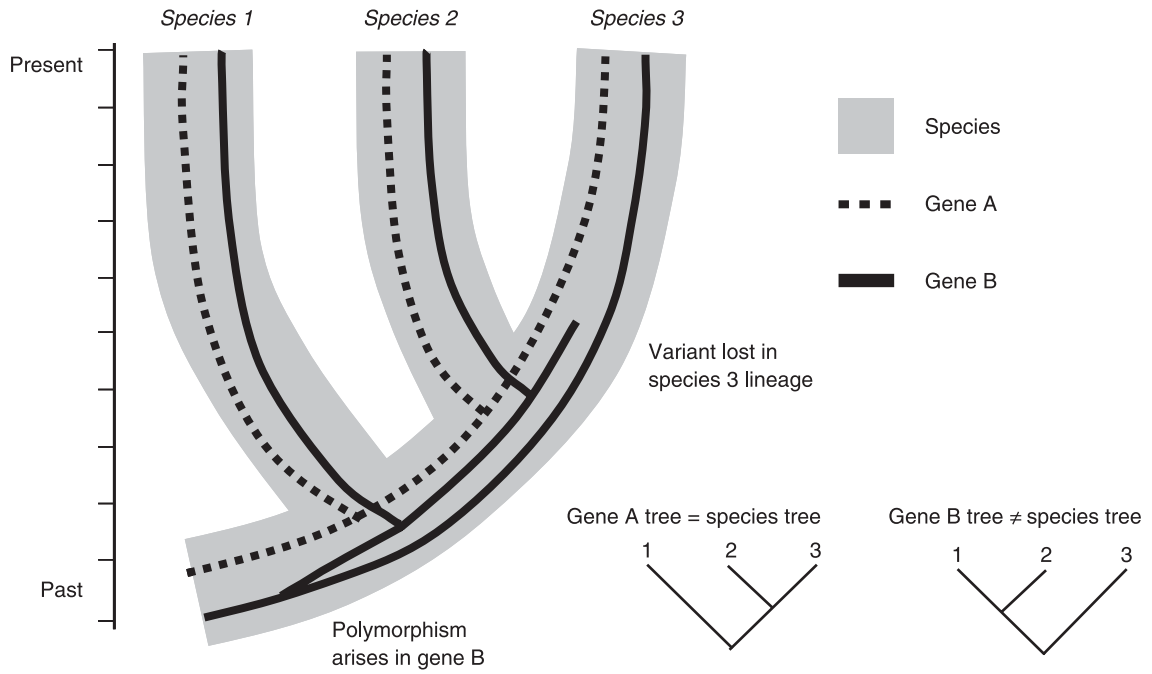

Fig. 1 Schematic scenario for discordant gene trees and species trees. Ancestral polymorphisms (e.g. at Gene B here) lost in one lineage (Species 3) but maintained in other lineages (Species 1 and 2) can produce gene trees that do not accurately reflect species relationships. Thus, phylogenetic reconstructions should include sequence data from multiple loci trees (see also Edwards & Beerli, 2000).

Thus, after decades of debate, a consensus was emerging (Table 1; Bishop & Friday, 1986; Ruvolo, 1997) and the problem of ape phylogeny was considered solved; despite our apparent uniqueness, humans and chimpanzees are in fact sister taxa. Gorillas, not humans, are the odd ape out. This resolution of the trichotomy (*Homo-Pan* clade) has more recently been supported by comparisons of soft tissue anatomy (Gibbs et al. 2002), temporal bone morphology (Lockwood et al. 2004) and even gene expression patterns in the brain (Uddin et al. 2004). Indeed the close genetic similarity between chimpanzees and humans has led some to argue that we should enlarge the genus *Homo* to include *Homo troglodytes* (chimpanzees) and *Homo paniscus* (bonobos) (Goodman et al. 1998; Wildman et al. 2003).

Dating the chimpanzee–human split

Clearly, then, the African ape clade should include humans. But what of Sarich & Wilson's (1967) claim that our shared ancestry is very recent? This too, has now gained wide acceptance. Estimated ape divergence dates are in general agreement across studies and loci: chimpanzees and humans likely diverged 4–8 Ma, about 2 million years after the divergence of gorillas (6–10 Ma; (Fig. 2 and references within).

These divergence dates are summarized here with a rather broad 4-million-year spread, and the individual estimates vary in the degree of precision and overlap (Fig. 2). This variation reflects the fact that independent molecular markers can have evolutionary histories that differ from each other and from the species tree (see above, Fig. 1) and that researchers often make different assumptions about the data and mode of evolution. Chosen models of evolutionary change and fossil-based calibration points, in particular, influence estimated divergence dates.

Models of evolutionary change, that is, assumptions about the rate and pattern by which mutations accrue, obviously influence divergence estimates. Rates of evolution (the settings of molecular clocks) often vary among lineages and a 'global molecular clock' cannot be applied (Thorne et al. 1998; Ho & Larson, 2006). The patterns of variation in evolutionary rates differ between mitochondrial and nuclear DNA and among nuclear DNA segments (reviewed in (Hasegawa et al. 2003). This is an important issue for understanding ape evolution, as the African ape lineage, and *Homo* lineage in particular, seems to have undergone an evolutionary slowdown, probably associated with longer generation times (Goodman, 1971; Li & Tanimura, 1987; Yi et al. 2002; Elango et al. 2006).

Current analytical methods usually employ either a maximum likelihood approach using local clocks (rates can vary across the tree, but are constant along smaller-scale lineages and branches; e.g. Yoder & Yang, 2000) or Bayesian methods (but also see Hobolth et al. 2007). Bayesian analyses use fixed divergence dates at multiple nodes, based on the fossil record, and assume that along lineages, evolutionary rates change either continuously over time or in discreet jumps (e.g. Thorne et al. 1998; Huelsenbeck et al. 2000).

Several calibration points based on paleontological data are routinely used in primate tree reconstruction: the

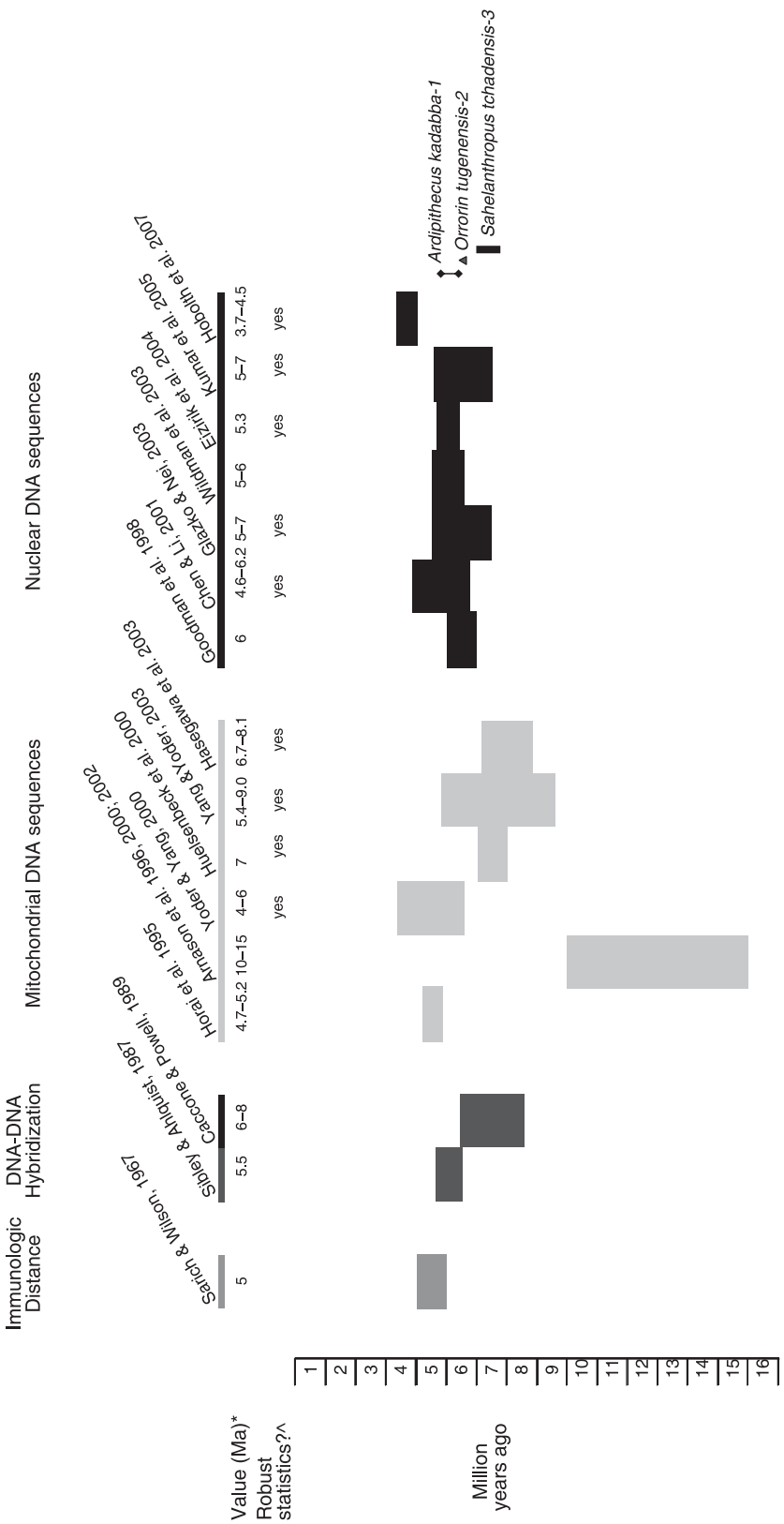

Fig. 2 Estimated dates for the human–chimpanzee divergence and early fossil hominins. Divergence dates are generally consistent across studies and loci. Most studies date the split within 4–8 million years ago. Purported early fossil hominins fall at the early end of this range. Given here are recent and oft-cited estimates. For a review of the 20+ studies reporting hominoid divergence dates see Steiper & Young (2006). [1] Haile Selassie et al. (2004); [2] Senut et al. (2001); [3] Brunet et al. (2002, 2005). *Given to level of precision reported in original publication, rounded to nearest 0.1 million years. ^Robust statistics – modelled using variable rates of evolution, multiple calibration points, likelihood and/or Bayesian analyses.

African ape–orangutan split at 12–16 Ma; the ape–Old World monkey split at 20–25 Ma; and the cetacean–artiodactyl (whale–cow) split at 53–60 Ma (e.g. Arnason et al. 1998; Yoder & Yang, 2000; Raaum et al. 2005; Steiper & Young, 2006).

Arnason and colleagues (2002, 2000, 1996) argue that primate fossil calibrations are too recent and yield underestimated divergence times. Using older calibration points (e.g. cetacean–artiodactyl at 60 Ma) they argue that humans and chimpanzees diverged 10–15 Ma, twice as early as other estimates (Fig. 2, although current work by the same group suggests a slightly more recent human–chimpanzee split at about 8 Ma; Arnason, pers. com). However, when robust methods of analyses allowing for variable evolutionary rates and multiple, including non-primate, calibration points are employed, there is little support for these older divergence dates (Yoder & Yang, 2000).

At the other extreme, recent application of new statistical models to analyze almost 2 million base pairs of ape nuclear DNA, conclude that the human–chimpanzee split is more *recent* (3.7–4.5 Ma) than is generally assumed (Hobolth et al. 2007). Interestingly, these variable divergence estimates might support a recent claim that humans and chimpanzees likely diverged early (perhaps ~6 Ma), then continued to exchange genes for several million years before splitting permanently (Disotell, 2006; Patterson et al. 2006).

Excluding the extreme estimates, analyses of mitochondrial DNA date the human–chimpanzee split somewhere between 4 and 9 Ma, while analyses of nuclear DNA give a tighter range, generally between 5 and 7 Ma (Fig. 2). The molecular estimates are a good, but not perfect, fit with the current fossil record. Many of the purported earliest hominins date to 5–6 Ma (*Orrorin tugenensis*: Pickford & Senut, 2001; Senut et al. 2001; but see Aiello & Collard, 2001; *Ardipithecus kadabba*: Haile-Selassie et al. 2001). However, the earliest purported hominin, *Sahelanthropus tchadensis,* is estimated to have lived 6.5–7.4 Ma (Brunet, 2002; Brunet et al. 2005; Zollikofer et al. 2005; based on faunal correlations), which pre-dates many molecular estimates of the *Homo–Pan* split (Fig. 2). Interestingly, some molecular biologists readily accept the fossil claims and use these slightly earlier split dates to 're-calibrate' primate clocks with a set *Homo–Pan* split at 6–8 Ma (Eizirik et al. 2004; Raaum et al. 2005; Steiper & Young, 2006), while others argue that this disagreement between molecular and paleontological evidence should make us more cautious in our interpretation of the fossil record (Kumar et al. 2005; Hobolth et al. 2007). In any case, it can generally be said that paleontologists and molecular biologists are now, four decades after Sarich and Wilson's contentious proposition, in agreement that humans and chimpanzees are sister taxa who shared a common ancestor ca. 4–8 Ma. Identifying a more precise divergence date may be impossible if, as has been suggested, chimpanzees and humans continued to hybridize after the initial split (Patterson et al. 2006).

Molecular phylogenies and human origins, variation, and adaptation

Molecular phylogenies have similarly aided our understanding of more recent human evolution (see more extensive reviews on this in Jobling et al. 2004; Pakendorf & Stoneking, 2005). Most notably, 'mitochondrial Eve' (Cann et al. 1987; Vigilant et al. 1991) and similar genetic analyses of human population histories (e.g. Underhill et al. 2000; Cavalli-Sforza & Feldman, 2003; Macaulay et al. 2005) have resolved longstanding debates about modern human origins. There is compelling evidence, both genetic and archaeological, for a single recent origin of anatomically modern humans in East Africa, which then expanded and replaced other hominin forms such as Neanderthals (Stringer, 2002).

Large DNA datasets representing a worldwide distribution of over 1000 individuals have provided detailed descriptions of human genetic diversity (Cavalli-Sforza, 2000), and this will soon be expanded with the '1000 Genomes Project' (www.1000genomes.org). The phylogeographic distribution of human diversity suggests a scenario in which modern humans underwent a series of successive bottlenecks while expanding from a small ancestral population (~1–10 000 individuals) about 50 000 years ago (Liu et al. 2006). Although the first fossil evidence of modern humans outside Africa (Israel) dates to 80–100 000 years ago (McDermott et al. 1993), the genetic data suggest these early dispersers probably did not contribute to our current genetic diversity (Liu et al. 2006).

It is also seems unlikely that Neanderthals contributed in any significant way to our modern gene pool. Ten years ago, Svante Pääbo's group retrieved the first Neanderthal DNA (mtDNA) sequence from the type specimen found in 1856 (Krings et al. 1997). Researchers have since sequenced mtDNA segments from numerous Neanderthals and anatomically modern humans (Krings et al. 2000; Serre et al. 2004). Neanderthal sequences, although similar to each other, differ markedly from ancient and contemporary modern humans and sophisticated modeling of potential gene flow scenarios indicate that interbreeding between Neanderthals and modern humans, if it occurred at all, was minimal (rate < 0.1%, Currat & Excoffier, 2004, but see Evans et al. 2006, and more on Neanderthal Genome Project below).

Phylogenetic analyses of modern humans have also yielded evolutionary insights with social, as well as academic, significance. Analyses of human genetic variation and differentiation show that humans world-wide are genetically very similar (Lewontin, 1972, but see Khaja et al. 2006). Indeed, there is more genetic variability in a single chimpanzee community than in a global sampling of humans (Kaessmann et al. 1999a,b), and most variation lies within, rather than between populations (Jorde et al. 2000; Romualdi et al. 2002). Thus, from the perspective of genetics, the concept of race has no biological basis (Lewontin, 1972). In addition, phylogenetic analyses of human populations

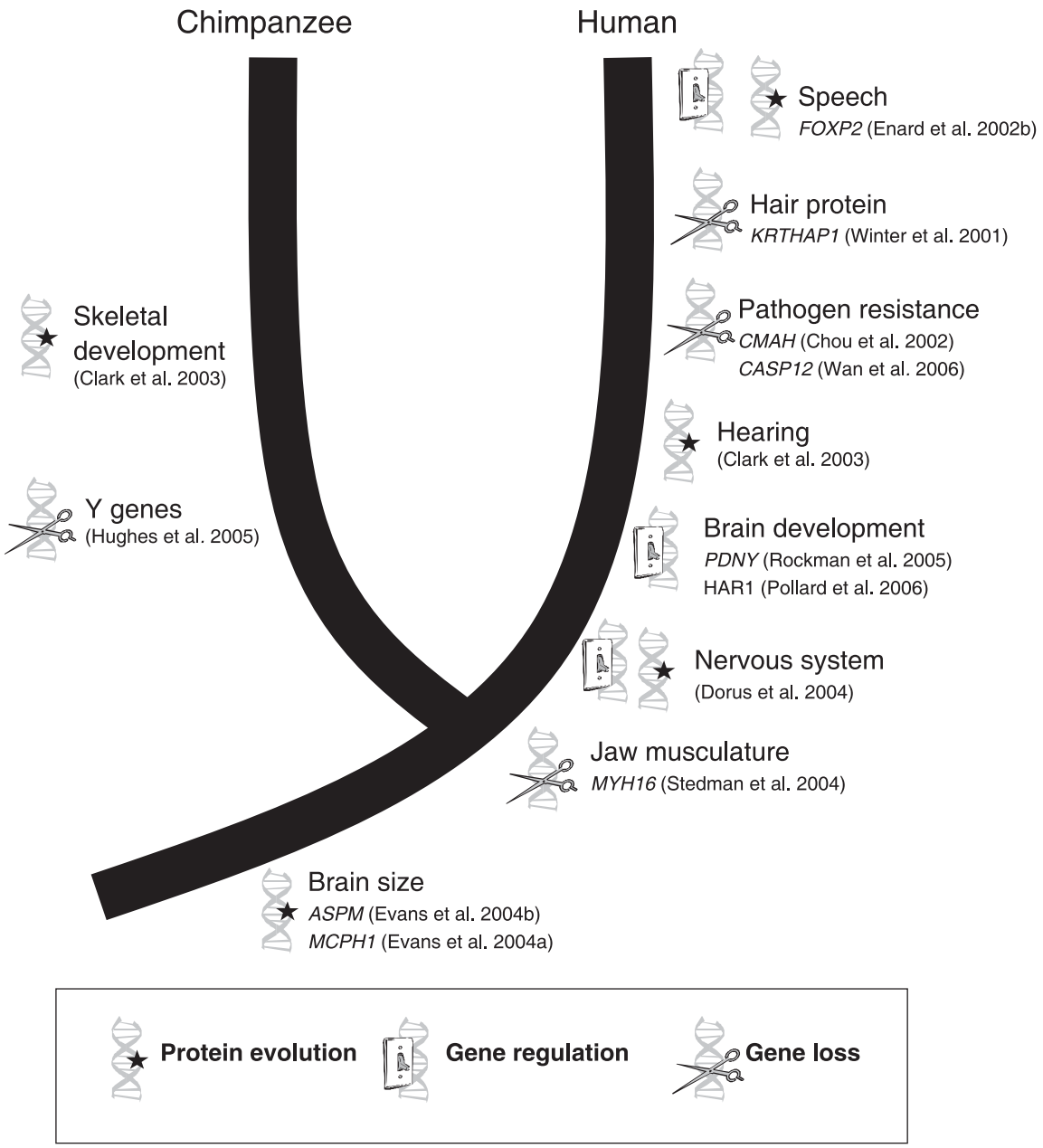

Fig. 3 Some examples of potentially functionally important genetic changes along the human and chimpanzee lineages. Genetic changes of all types (protein evolution, regulatory evolution, gene loss) have been identified. As current research largely focuses on human-, rather than ape-, specific changes, there are fewer known changes along the chimpanzee lineage. Placement does not indicate chronological order.

have unraveled how social and cultural traditions, such as marriage rules and caste systems, can influence human genetic variability and evolution (Bamshad et al. 1998; Oota et al. 2001). Thus, human molecular phylogenies are more than elaborate family trees.

From reconstructing phylogenies to reconstructing phenotypes

Whereas early molecular anthropology focused on reconstructing the African ape tree, today's challenge is to map specific genetic changes onto this tree (Fig. 3). Ultimately, molecular analyses could reveal not just when the last common ancestor of chimpanzees and humans lived, but also how it lived and what it looked like. For now we can begin by asking: What are the changes that occurred on each lineage since humans and chimpanzees last shared a common ancestor? What, genetically, distinguishes us from chimpanzees? In essence, what makes us human?

Aside from changes in testes size and other traits related to sperm competition (Harcourt, 1995), it is difficult to identify unique traits that must have arisen along the

chimpanzee lineage, in part because the fossil record for gorillas and chimpanzees is so poor (McBrearty & Jablonski, 2005). Uniquely-human phenotypic changes, however, are easily identified (but see Wood & Lonergan, 2008). Humans became increasingly bipedal and the post-cranial anatomy changed accordingly (e.g. S-shaped spine, bowl-like pelvis, Lovejoy, 2005; Crompton et al. 2008). Head shape changed and brain size increased (e.g. strong chin, globular brain case, small snout; Cobb, 2008). Body hair was reduced, but the growth-cycle for scalp hair was extended (Neufeld & Conroy, 2004). Human culture expanded to include complex language with syntax (Nowak et al. 2000), elaborate tool production and manipulation, and sophisticated cognitive capabilities (Sherwood et al. 2008). Along with these 'advances' has come an increase in the incidence and severity of many diseases, which makes mapping human–chimpanzee genetic differences of as much interest to medicine as to anthropology (Olson & Varki, 2003).

Looking for nucleotides in a haystack: identifying the important molecular differences

Despite these substantial differences in morphology, cognition and behaviour, we share with chimpanzees almost all of our genes and 98.8% (96% if we include insertions and deletions) of our DNA (Mikkelsen et al. 2005). Interestingly, species of mice that are identical at 98% of their genomes are phenotypically very similar (e.g. *Mus musculus* and *Mus spretus*, Enard et al. 2002a). So a small genetic difference need not correspond to a marked phenotypic difference. There must be something special, then, about this 1.2% genetic difference between humans and chimpanzees.

There are three hypotheses concerning what types of genetic changes are likely to underlie these phenotypic differences (Li & Saunders, 2005). The 'protein evolution' hypothesis proposes that key changes have occurred in coding regions and that these have resulted in important modifications to the encoded proteins. In contrast, King & Wilson's (1975, see above) 'gene regulatory evolution' hypothesis suggests that the striking differences between chimpanzees and human are due not to changes to the genes/proteins themselves, but rather to the pattern and timing of turning genes on and off (gene expression). Finally, the 'less-is-more hypothesis' (Olson, 1999) suggests that gene loss has driven important evolutionary changes in humans. This hypothesis suggests that we have lost many ape-like traits (e.g. body hair, muscle mass) through loss-of-function mutations at key loci (Olson & Varki, 2003).

These three hypotheses are not mutually exclusive and many genetic changes fall into more than one category (Fig. 3). For example, specific amino acid changes that play a role in gene expression (e.g. changes to transcription factors) would support both the protein evolution and gene regulatory evolution hypotheses (see *FOXP2* below). Similarly, the recent report of human-specific deletions of transcription factor binding sites involved in gene expression (Donaldson & Gottgens, 2006), supports both gene regulatory evolution and the less-is-more hypotheses.

But how do we go about identifying these important molecular differences? We could target the 1.2% of bases at which the chimpanzee and human genomes differ, but that is still over 30 million bases, most of which will not be functionally important. Instead, we can either identify regions of the genome that are evolutionarily important – a comparative genomic approach – or examine genes that are likely to be involved in specific traits of interest – a candidate gene approach.

A comparative genomic approach involves scanning genomes for regions that (1) differ between chimpanzees and humans, and (2) seem to have undergone positive selection along one lineage. Thanks largely to strong public promotion by a few key academics (McConkey & Goodman, 1997; McConkey & Varki, 2000; Varki, 2000), the chimpanzee genome was sequenced (Mikkelsen et al. 2005) within a few years of the human genome announcement (Lander et al. 2001), and this has yielded a wealth of information for comparative genomic analyses. Comparisons of the chimpanzee and human genomes generally use the mouse genome to identify which genetic variants are ancestral, but the macaque genome will now provide a more closely-related outgroup (Harris et al. 2007; Gibbs et al. 2007). Comparing the three genomes, one can identify sites of human-specific or chimpanzee-specific deletions, gene duplications, or signatures of rapid evolution (review in Varki & Altheide, 2005; see also Uddin et al. 2008).

Alternatively, we can focus on candidate genes that are likely to be involved in specific traits of interest (e.g. expanded brain, language capabilities). We have clues to the biological function of many genes (see The Gene Ontology database: www.geneontology.org), either from inference based on the structure and cellular location of their proteins, or because we know how mutations at these loci influence the phenotype in humans and other organisms. Indeed, candidate genes underlying important phenotypic variation in humans are often first identified in distantly-related model organisms such as mice, fruit flies or zebra fish (e.g. Lamason et al. 2005).

These two complementary approaches, comparative genomics and the candidate gene approach, have identified important genetic changes identified with all three hypotheses: protein changes, regulatory changes and gene loss.

Protein changes

Perhaps the most intriguing results emerging from genomic comparisons come from bioinformatic scans for genes that have undergone accelerated evolution (i.e. have high ratios of synonymous to nonsynonymous substitutions) on the chimpanzee or human lineage (see also Williamson

et al. 2007; Hawks et al. 2007 regarding recent adaptive evolution in humans). Of the more than 13 000 orthologous genes compared across the two genomes, about 4% show a potential signature of selection (Mikkelsen et al. 2005). Genes showing such a signature include those functionally involved with immune defense, cell signaling, amino acid metabolism, and olfaction (Cargill et al. 2003, Mikkelsen et al. 2005; Nielsen et al. 2005). Interestingly, several genes involved in hearing (e.g. *TECTA*, which encodes a membrane protein of the inner ear) show signatures of accelerated change on the human lineage (Clark et al. 2003; but see Zhang, 2004). It is tempting to speculate that these loci may play a role in understanding spoken language and this finding highlights the need for more detailed assessments of variation in auditory capabilities among African apes, including humans (e.g. Bitterman et al. 2008).

Counter to our anthropocentric emphasis on changes along the human lineage, the number of positively selected genes seems substantially smaller in humans than in chimpanzees (Bakewell et al. 2007). It is difficult, however, to interpret the finding that genes involved in traits such as skeletal development have undergone accelerated evolution along the chimpanzee lineage (Clark et al. 2003). Unfortunately, though understandably, these chimpanzee-specific genetic changes have so far received much less research attention than human-specific changes. This will likely be remedied as additional primate genomes become available (Dennis, 2005; Pennisi, 2007).

Taking a more systems-based approach, Dorus et al. (2004) focused on an extensive set of genes (> 200) specifically involved in nervous system biology. These genes showed extensively higher rates of protein evolution in primates compared to rodents and this was especially true for genes involved in nervous system development.

Studies of specific candidate genes involved in controlling brain size have yielded similarly interesting results. Mutations at the genes *ASPM* and *MCPH1* (or *microcephalin*) are known to cause microcephaly, an extreme reduction in the cerebral cortex (Evans et al. 2004a,b) and so it is tempting to speculate that these loci might have played a role in the brain expansion that occurred in the later stages of hominin evolution (Mochida et al. 2004). Sequence comparisons show that *ASPM* has indeed undergone strong positive selection along the great ape lineage and especially along the human lineage (Zhang, 2003; Kouprina et al. 2004; Evans et al. 2004b). One variant of the gene seems to have undergone a recent selective sweep (sharp reduction in variation as the favored variant quickly spreads), around 14 000 ya (Evans et al. 2004b). *MCPH1* has also been the target of strong positive selection along the Catarrhine – Old World monkey and ape – lineage (perhaps associated with the general enlargement of the Catarrhine brain; Evans et al. 2004a) and, interestingly, some argue that one common variant of the allele entered the modern human gene pool via admixture between modern humans and archaic, perhaps even Neanderthal, populations about 37 000 ya (Evans et al. 2006). This result has renewed interest in whether Neanderthals contributed to the modern gene pool (Jones, 2007).

Among the most notable examples of loci showing evidence of human-specific protein evolution is *FOXP2*, the oft-dubbed 'language gene'. Mutations at *FOXP2* are associated with an inherited speech disorder (Lai et al. 2001), making it a strong candidate gene for studying the molecular evolution of human language. Comparisons of *FOXP2* sequences show it is highly conserved and nearly identical across mammals but, intriguingly, humans show a couple of unique *FOXP2* amino acid changes. Initial reports suggested that this genomic region had undergone a positive selective sweep and was fixed in humans within the last 200 000 years (Enard et al. 2002b). But the recent finding that Neanderthals have this same *FOXP2* variant indicates the selective sweep must have happened much earlier, at least 300 000–400 000 years ago (Krause et al. 2007). Although this is a potentially interesting example of *Homo* specific protein evolution, since *FOXP2* is a transcription factor, changes at this locus probably influence regulation of several other genes, thus also providing support for the gene regulatory evolution hypothesis.

Regulatory changes

Studies of gene expression differences among species often employ micro-arrays to analyze gene regulatory changes in various tissues (e.g. blood, liver, brain) across various primates (Enard et al. 2002a). Differences in gene expression patterns between species – like differences in gene sequences – might accrue in a clock-like fashion and therefore many expression differences are likely to be neutral and have no functional importance (Khaitovich et al. 2004). It is nevertheless worth identifying genes that show regulatory differences, and such comparative transcriptomic studies suggest that there has been a general up regulation of genes expressed in the brain along the human lineage (Enard et al. 2002a; Caceres et al. 2003; Uddin et al. 2004), although humans and chimpanzees might differ in gene expression profiles as much, if not more, in the liver than in the brain (Hsieh et al. 2003).

An alternative approach to studying gene regulatory evolution is to identify human or primate specific regulatory elements via 'phylogenetic shadowing' (Boffelli et al. 2003). The idea here is to compare several genomes and look for regions that are highly conserved. These loci have been assumed to have undergone purifying selection, indicating they are functionally important. By comparing mouse, rat and chimpanzee genomes, Pollard et al. (2006a) found 35 000 conserved regions that had changed very little in the 80 or so million years since primates and rodents last shared a common ancestor. They then examined these same regions in the human genome specifically looking for cases

where the regions had changed markedly, that is, had undergone positive selection along the human lineage. They found 49 significant 'human accelerated regions', or HARs, only two of which code for proteins. The other 47 likely correspond to regulatory regions, providing strong support for the regulatory evolution hypotheses of human molecular evolution. One of these regions, HAR1, is highly expressed in the brain, particularly during development of the neocortex, and thus may play an important role in the development of important neurological pathways (Pollard et al. 2006b).

More evidence that gene regulatory evolution has been important in structuring the human brain comes from studies of a gene involved in perception and memory: *PDNY*, a precursor molecular for many neuropeptides (Rockman et al. 2005). Although the coding sequence of *PDNY* does not vary across primates, its promoter region, which determines the activity of the gene, shows human-specific mutations and a signature of strong positive selection (Rockman et al. 2005).

Some differences in gene expression among species are likely due not to differences in regulatory mechanisms, but to differences in gene copy number – a 'more-is-more hypothesis' of sorts. It is worth noting that a third of the gene duplications seen in the human genome seem to be human-specific (i.e. chimpanzees have fewer copies) and probably result in gene expression differences between the species (Cheng et al. 2005). For example, humans carry 212 copies of the gene encoding DUF1220, a protein expressed at high levels in brain regions associated with higher cognitive function (the neocortex; Popesco et al. 2006). By comparison, chimpanzees have only 37 copies of the gene, macaques have 30 copies, and mice have only a single copy (Popesco et al. 2006).

Non-coding DNA duplications are also important. Humans have a large number of unique *Alu* elements (small repetitive pieces of DNA that duplicate and integrate seemingly randomly throughout the genome) that have likely altered functional genes and their regulatory elements (Carroll et al. 2001; Lander et al. 2001; Mikkelsen et al. 2005; see *CMAH* below).

Gene loss

Compared to small nucleotide and/or amino acid substitutions, gene losses (i.e. loss-of-function mutations or gene deletions) and duplications are much more dramatic genetic changes that likely have a great effect on phenotypes and fitness. Scores of genes have been lost in the human lineage since the chimpanzee–human split (reviewed in Hamann et al. 2003; Hahn & Lee, 2005; Wang et al. 2006), including genes involved in taste perception (Wang et al. 2004; Fischer et al. 2005) and sense of smell (Gilad et al. 2003).

Several interesting human-specific loss-of-function mutations are at genes involved in pathogen resistance (Hamann et al. 2003; Wang et al. 2006). Notably, the gene *CMAH,* which produces a certain type of sialic acid (Neu5Gc; sialic acids are cell surface molecule involved in cell–cell interactions and pathogen binding) seems to have been inactivated (*Alu*-mediated inactivation; see above) in humans ~2.8 Ma, just before the expansion of the brain in *Homo* (Hayakawa et al. 2001; Chou et al. 2002). Consistent with this, fossil protein analyses suggest that Neanderthals, like modern humans, lacked a functional copy of *CMAH* (Chou et al. 2002).

In contrast, the gene *CASP12*, whose null version might confer resistance to infection in certain environments, has become inactive more recently and the null version of the gene likely underwent a selective sweep chronologically corresponding to the out-of-Africa migration of modern humans (~50 000 ya; Wang et al. 2006). Thus there is already evidence that human-specific gene losses associated with pathogen resistance have arisen at various times in human evolution.

Of particular interest to palaeontologists – as this genetic change might have a tangible link to the fossil record – is the inactivation of a gene (*MYH16*) most prominently expressed in the masticatory muscles of mammals (Stedman et al. 2004). It has been argued that loss of this gene in humans may have resulted in smaller masticatory muscles and consequential changes to cranio-facial morphology and expansion of the human brain case (Stedman et al. 2004). This loss of function mutation was originally dated to ~2.4 Ma, which nicely corresponds with the appearance of *Homo* (Stedman et al. 2004), but results of a broader analyses (30 kb including regions flanking the gene) date the gene loss much earlier, closer to the timing of the chimpanzee–human split, at 5.3 Ma (Perry et al. 2005). Furthermore, it was pointed out that protein expression in muscle fibers is highly plastic and it is unlikely that the inactivation of *MYH16* would have been associated with dramatic changes in hominin masticatory mechanics (McCollum et al. 2006).

It is also tempting to speculate about the functional significance of the human-specific loss of a hair keratin protein gene (*KRTHAP1*). This gene is functional in chimpanzees and gorillas, but was apparently inactivated in humans within the past 240 000 years (Winter et al. 2001). Although the degree to which this gene influences hair phenotype is still speculative, this suggests that changes in human body hair (reduction) and/or scalp hair (longer growing cycle) might be relatively recent.

Although proponents of the less-is-more hypothesis focus on human-specific gene losses (Wang et al. 2006), it is worth noting that many known human genes are fully, or partially, missing from the chimpanzee genome (Mikkelsen et al. 2005). This might be due to incomplete coverage of the chimpanzee genome, or, as both chimpanzees and humans show *intra*-specific variation in the copy numbers of many genes (Perry et al. 2006), these might simply be missing in the one chimpanzee whose genome was sequenced. More information on variation among chimpanzees is needed. Indeed, this caveat applies

to all conclusions based on genomic comparisons, which generally fail to consider possible intra-specific variation. Nevertheless, there is strong evidence that several genes have been inactivated or are degenerate on the chimpanzee Y chromosome (e.g. *USP9Y, TMSB4Y*) but remain conserved and functional on the human Y (Hughes et al. 2005). Although the exact function of these genes is unknown, at least some play a role in spermatogenesis (Sun et al. 1999) and this chimp-specific gene 'decay' is perhaps driven by sperm competition (Hughes et al. 2005).

Of course the evolution of the traits that distinguish and define us is unlikely to have been driven by just a few genes. The constant beat of press releases describing newly-identified 'genes for humanity' (Smith, 2006) suggests that these examples are only the first few pieces of the puzzle. And there is much debate among evolutionary geneticists about the validity of methods used to identify signatures of selection and how best to interpret genomic comparisons (Bakewell et al. 2007). Much of the work reviewed here remains contentious.

New prospects in molecular analyses of human evolution

With the completion of more primate genomes, new insights on gene function, and improved means of detecting signatures of selection (Sabeti et al. 2006), we have much to look forward to in the next few years. In particular, the search for genes involved in conditions like autism (Szatmari et al. 2007) and dyslexia will likely aid evolutionary analysis of human social cognition and complex language.

As we pinpoint specific genetic changes associated with particular phenotypes, we can take advantage of advances in ancient DNA technology (Pääbo et al. 2004) and target those key sites using DNA from fossil specimens. This would allow the reconstruction of characters not preserved in the fossil record, such as hair and skin color. Such reconstruction of paleo-phenotypes has already been demonstrated using ancient DNA from 40 000-year-old woolly mammoth bones (Rompler et al. 2006). By sequencing and functionally testing the mammoth pigmentation gene *MC1R,* Rompler et al. (2006) identified two versions of the gene – one producing light hair and one producing dark hair. Although this pelage variation was already known from preserved mammoth skin, this study successfully demonstrates the potential for reconstructing phenotypes from ancient specimens. Likewise, phenotypic reconstructions targeting a lactase gene in ancient human DNA indicate that Neolithic Europeans were unlikely to have been milk drinkers with dairy-based subsistence (Burger et al. 2007).

Similar phenotypic reconstructions are now in progress for Neanderthals. For example, *MC1R* sequences retrieved from two Neanderthal fossils suggest that at least some Neanderthals had red hair and light skin (Lalueza-Fox et al. 2007). Interestingly, though, the *FOXP2* sequence recovered from Neanderthals is similar to that of anatomically modern humans, thereby indicating that the selective sweep of this variant of the gene predates their divergence (Krause et al. 2007).

Moreover, the Neanderthal Genome Project, aptly described, both figuratively and literally, as 'a study with a lot of balls' (*The Economist*, 27 July 2006) is well underway (Green et al. 2006; Noonan et al. 2006). The project takes advantage of new sequencing technology especially well suited for small fragments of DNA such us those retrieved from fossils. These pieces are attached to tiny beads in a mixture of water and oil, and as copies of the fragments are made on the beads, the incorporation of each nucleotide is detected using fiber-optics and a microchip (Goldberg et al. 2006). The method is fast and cheap and has already proven successful – over 1 million base pairs of likely Neanderthal DNA have been retrieved from a 45 000-year-old bone from Croatia and the project expects to complete the genome by late 2008 (Green et al. 2006).

The completion of the Neanderthal Genome Project will not only address the renewed debate on the genetic relationships between Neanderthals and modern humans (Evans et al. 2006), it will also identify genetic changes associated with very recent human evolution and modern humanity. Both whole-genome comparisons (Rubin & Noonan, 2007) and targeted analysis of candidate genes (Erren et al. 2007) are yielding findings invaluable for reconstructing important events in recent human evolution.

As genetic and genomic data accumulate, molecular anthropology becomes less about molecular bench work and more about bioinformatics. Scanning for world-wide variation in the human genome (e.g. www.1000genomes.org and www.hapmap.org) will help identify regions that have undergone very recent and/or local adaptation (Sabeti et al. 2006; Voight et al. 2006; Kaiser, 2008). An intriguing application of a population-genetic approach found evidence of balancing selection at the prion protein gene in human populations. This suggests that prion diseases, and by inference cannibalism as the mode of transmission, may have been widespread in prehistoric humans (Mead et al. 2003).

Other exciting avenues for future research in anthropology are those involving creative, indirect molecular analysis. For example, phylogenetic analysis of lice have suggested that human clothing is a surprisingly recent innovation in human evolution as human head lice, which live and feed on scalps, and human body lice, which feed on skin but live in clothing, diverged only ~70 000 years ago (Kittler et al. 2003; see also Reed et al. 2007).

Finally, it is worth highlighting that many of the examples given here – genetic analysis relevant to traits like dairy farming, cannibalism and the origins of clothing – illustrate how molecular analyses contribute not only to understanding

human origins, but to ongoing debates in archaeology and social cultural anthropology as well. This is an important point, as ultimately molecular anthropology is a field defined by methodology but addressing a wide range of anthropological issues. As such, it is highly dependent on collaborations across the discipline. Input from paleontologists and functional morphologists are vital for calibrating molecular clocks and placing molecular data within the framework of ecological and morphological transitions in human evolution. Rapid advances in genetic technology and bioinformatics necessitate, now more than ever, a concerted effort among molecular biologists, paleontologists and functional morphologists. Only by jointly examining the entire range of data will we develop the scenarios that best explain and elucidate our evolutionary history.

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