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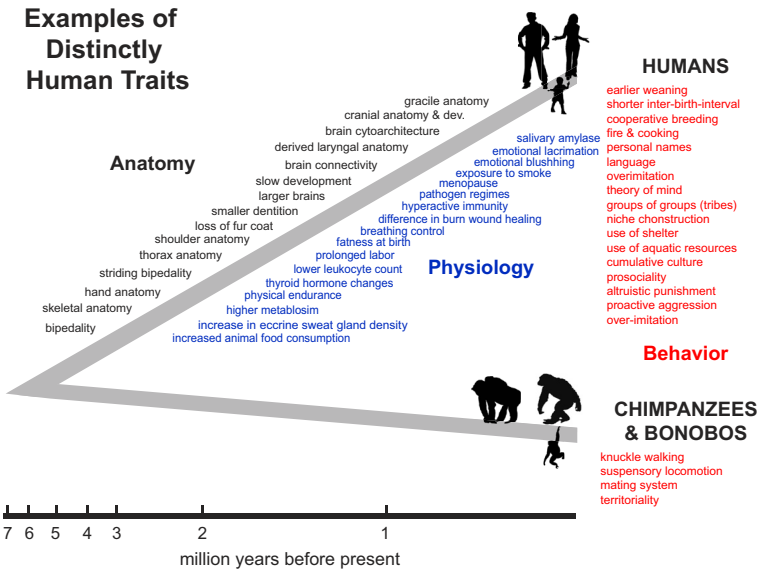
COMPARATIVE PHYSIOLOGICAL ANTHROPOGENY: EXPLORING MOLECULAR UNDERPINNINGS OF DISTINCTLY HUMAN PHENOTYPES



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anthropogeny; comparative physiology; human origins; human-specific disease; pleiotropy

CLINICAL HIGHLIGHTS

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Abstract

Anthropogeny is a classic term encompassing transdisciplinary investigations of the origins of the human species. Comparative anthropogeny is a systematic comparison of humans and other living nonhuman hominids (so-called "great apes"), aiming to identify distinctly human features in health and disease, with the overall goal of explaining human origins. We begin with a historical perspective, briefly describing how the field progressed from the earliest evolutionary insights to the current emphasis on in-depth molecular and genomic investigations of "human-specific" biology and an increased appreciation for cultural impacts on human biology. While many such genetic differences between humans and other hominids have been revealed over the last two decades, this information remains insufficient to explain the most distinctive phenotypic traits distinguishing humans from other living hominids. Here we undertake a complementary approach of "comparative physiological anthropogeny," along the lines of the preclinical medical curriculum, i.e., beginning with anatomy and considering each physiological system and in each case considering genetic and molecular components that are relevant. What is ultimately needed is a systematic comparative approach at all levels from molecular to physiological to sociocultural, building networks of related information, drawing inferences, and generating testable hypotheses. The concluding section will touch on distinctive considerations in the study of human evolution, including the importance of gene-culture interactions.

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Distinctly Human Diseases: It is not surprising to find disease processes that are restricted to certain taxa or even specific to a particular species. A distinctly human disease should be very common in humans but rarely reported in closely related species such as great apes (even in captivity) and/or could not be experimentally reproduced in such species (in the days when such studies were allowed). A caveat is that reliable information is limited to data on a few thousand captive great apes (mostly chimpanzees). However, most were cared for in NIH-funded facilities, with full veterinary care and thorough necropsies. Especially regarding some of the probable and possible differences, it must again be admitted that the absence of evidence is not evidence of absence. However, when considering diseases that are very common in humans, the interpretation is likely to be correct.

1. ANTHROPOGENY: EXPLORING HUMAN ORIGINS

1.1. What is Anthropogeny?

Anthropogeny refers to the transdisciplinary investigation of human origins and the evolutionary processes involved. While the earliest use of this term seems to be almost 200 years old (1), it fell into disuse in the 20th century until revived in the 21st century (2). Comparative anthropogeny is thus a systematic comparison of humans and other living nonhuman hominids (so-called "great apes") (3). We begin this review with a historical perspective, briefly describing how the field progressed from the early evolutionary insights of Darwin, Wallace, and Huxley to the current emphasis on in-depth molecular and genomic investigations of "human-specific" biology. While some genetic and

molecular differences between humans and other hominids have been revealed in the last several decades (most information is available about human-chimpanzee differences), these findings still largely fail to explain most distinctive anatomical and physiological divergences of humans from other living hominids. Further developments in the analysis of genetic data, which are often fragmentary, combined with parallel studies in other -omics fields, are required to fully exploit these approaches (see sects. 1.5–1.7) (4).

We suggest returning to a systematic comparative approach at all levels, from molecular to physiological to behavioral and sociocultural, building networks of related information, drawing inferences, and generating testable hypotheses relating to both normal and pathological states. The next section of this review will proceed systematically through the most distinct, historically interesting, and medically relevant phenotypes and molecular mechanisms that might differentiate human physiology from that of other living hominids. A complementary approach is "physiological anthropogeny," to undertake the comparison along the lines of the typical preclinical medical school curriculum, i.e., beginning with anatomy and considering each physiological system of the body. In the following sections, we will compare humans and other hominids and in each case consider both normal mechanisms and pathological states and individual genetic and molecular components that are relevant. This may help make the information more accessible to physiologists or physicians interested in this perspective. However, the combined expertise of the present authors does not come close to covering all the relevant specialties, and we will therefore focus on aspects with which we are most familiar. The concluding sections will touch on unique considerations in the study of human evolution, including the importance of gene-culture interactions so characteristic of our species. The future of understanding "uniquely human" physiology will depend on developing the proper models, in silico, in vitro (cells, organoids), and in vivo (whole organisms). Recent advances in genome editing may also prove useful for developing organoid and animal models for validated genetic traits. Throughout this review, we will limit the use of the term "uniquely human" and instead use "distinctly human," or "human specific," to refer to human phenotypes that appear to be derived within the hominin lineage and are absent or much less prominent in other hominids.

The currently existing approach is exemplified by the Matrix of Comparative Anthropogeny (MOCA), which addresses such comparative questions from the perspective of broad domains of human knowledge (3, 5) (https://carta.anthropogeny.org/moca).

It is a compilation of over 600 topics, each addressing an allegedly human-specific feature as compared to the living great apes. It represents the only such current collection and aims to provide a key resource to the many researchers interested in understanding the many peculiarities of the human phenomenon.

1.2. *Early Beliefs and Theories About Human Origins*

Questions about human origins have long challenged the world's brightest thinkers. Early religion-centric myths assumed that our species must have a divine origin, because our physiological and behavioral phenotypes appeared so distinct (at least, when viewed from our anthropocentric perspective). Prior to the 1800s, and before the understanding of evolutionary descent by natural selection, humans were also seen from the Western religious perspective as being at the apex of creation, situated at the peak of a scala naturae, the medieval conception of a natural order, in which all living organisms were arranged in a linear order from simple to complex (6). This misconception is also reflected in the zoological term "primates" (7) (meaning "first in rank") and still unconsciously persists in the way we refer to "lower" and "higher" organisms.

What have we learned in the 150 years since Darwin and Huxley theorized the evolutionary relationship of humans with African apes (8, 9)? Early evolutionary thinking depended on comparing easily observed phenotypes, such as anatomy and behavior. The dramatic differences between humans and apes in such phenotypes led these thinkers to propose a long history of distinct evolution between humans and other living ape species.

As the concepts of evolution began to be proposed by biologists, some challenged the notion of humans as another species that descended from ancient ancestors shared with the rest of the living world, especially in the complete absence of fossils indicating any intermediate forms. It was hard to deny, however, that humans shared much anatomical homology with primates, in particular with the African apes. Evolutionary concepts at that time depended entirely on comparing anatomy and behavior (the latter usually in captivity before the first long-term scientific observations in the wild, dating only to the 20th century). Years of taxonomical analyses based on detailed comparative studies erroneously placed the great apes (African and Asian) into a monophyletic group called "pongids." In the decades following Darwin, advances in careful postmortem autopsy were rapidly improving understanding of human anatomy and physiology but also contributing methods for taxonomists and evolutionary thinkers to shape their own understanding of the relationships between species. Anatomical studies seemed to suggest a close relationship between humans and the

African apes. In addition to anatomy, the behavior was also considered an important factor for understanding the closeness of these relationships. In fact, comparing the anatomy and behavior of different species can inform views about the sequence by which different species diverged from their last common ancestors. Living nonhuman hominids exhibit striking contrasts in social organization, mating system, and social dominance patterns, and it is still unclear which of these are ancestral or derived or possibly even independently derived in more than one lineage. Regardless of these limitations, the comparative theories of 19th-century evolutionary biologists, certainly also influenced by the intellectual dogma of the time, suggested that while humans shared common evolutionary ancestors with the African apes, they must also have had a long and distinct history of separate evolution. We now understand that the phenotypic differences between two species are not strictly related to the time since those species diverged. The transition between these two scientific perspectives is better understood in the context of the last 150 years of research in evolution, from Darwin to the revolution of modern molecular biology, genetics, and developmental biology, much aided by numerous fossils from Africa and beyond.

The modern evolutionary synthesis of the 1930–1950s, which merged Darwinian evolutionary theory with breakthroughs in genetics, paved the way for modern evolutionary and genetic sciences (10). Sewall Wright, a key architect of the modern synthesis, built on his insights into gene-environment interactions in evolution to introduce the adaptive landscape model (11, 12). Recalling the evolutionary concept of an adaptive landscape is an invaluable tool for modern scientists and physicians alike when investigating the physiology of their species of interest, in the case of medicine the human species and its natural variation, as well as the pathology of disease. The degree to which the adaptive landscape itself has come under the pervasive impact of human "niche construction" due to human culture and associated technologies cannot be underestimated (13, 14). There is also renewed interest in the Baldwin effect (15) as a mechanism for shaping human biology via human culture. The Baldwin effect suggests that phenotypic changes occurring in an organism as a result of its interaction with its environment become gradually assimilated into its developmental genetic or epigenetic repertoire (16, 17). Waddington's genetic assimilation theory is another way to conceptualize how external factors including culture could become internalized as part of an organism's biology, via genetic accommodation (16, 18).

1.3. *Anatomical and Physiological Differences Between Humans and "Great Apes"*

In *Evidence as to Man's Place in Nature* (8), Huxley refers to the 1598 account of Portuguese sailor Duarte Lopez, illustrated by the brothers DeBry, as the first western report of the great apes. Englishman Andrew Battell described two apes he called *Engeco* and *Pongo* in 1613, deriving the names from native names for the chimpanzee and gorilla. As the 17th-century European exploitation of Africa unfolded, European sailors further documented the African apes, and the first captive chimpanzees were delivered to Western anatomists for scientific study. In 1699, after dissecting the first chimpanzee to arrive in England, anatomist Edward Tyson published *Orang-Outang, sive Homo Sylvestri* (19), which includes detailed illustrations and meticulously described observations (at this time *Orang-Outang* described the red Asiatic and the black African varieties). Tyson compared these animals to both humans and monkeys with lists of gross similarities (48 included) and differences (34 included) between chimpanzees and humans. The differences listed by Tyson included flatness of the nose, cranial brow ridge, curvature of the spine, roundness of the kidney, and hairiness of the body. In this very earliest comparative study of the chimpanzee, and almost two centuries before evolutionary thinking would sweep scientific thought, Tyson reported his specimen was "more resembling a Man, than any other animal."

During the following period, chimpanzees were occasionally captured and transported to Europe. After suffering short periods in captivity, the animals would die and be dissected as zoological specimens. Publications supported Tyson's belief that the larynx and respiratory anatomy of the chimpanzee is not different enough from humans to explain its lack of speech. Traill's 1821 report (20) of a dissection of a captive chimpanzee suggested that this uniquely human trait must be derived from neurological differences. By the end of the 19th century, the popularity of European menageries led to an increase in the number of apes transported to the West. Advances in husbandry for captive chimpanzees increased their life span and enabled reproduction. In 1930, Yale psychologist Robert Yerkes founded the National Primate Research Center, later named after him, and located at Emory University. Throughout the 20th century, studies performed on captive chimpanzees at Yerkes and around the world illuminated distinctly human physiological and anatomical characteristics (see **FIGURE 1**). From the 1950s on, large numbers of chimpanzees were captured across Africa and shipped to facilities in Asia, Europe, and the Americas such as the Delta Regional Primate Research Center at Tulane University (22).

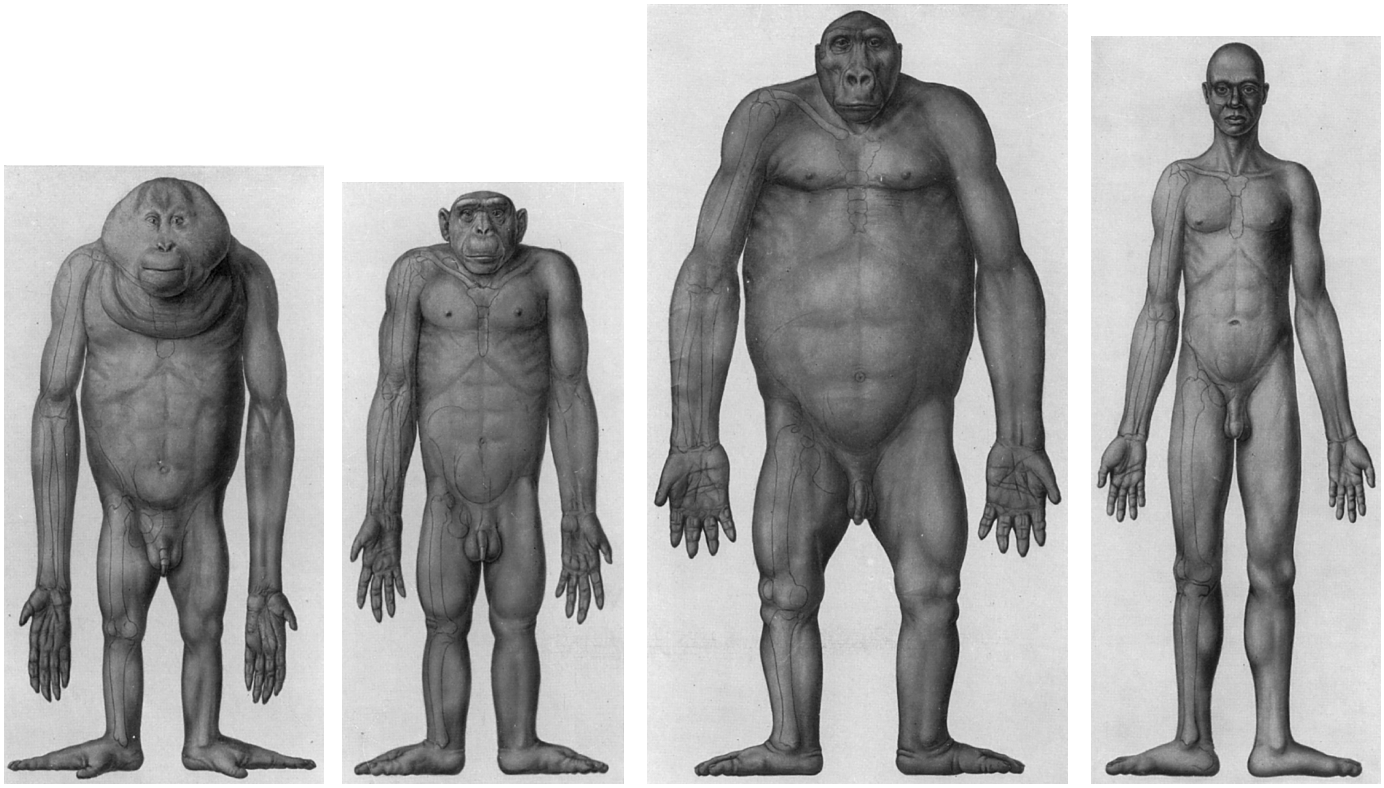

FIGURE 1. Humans and great apes display many differences in gross anatomy and physiology. Image is from Ref. 21 and was used with permission from the publisher (www.schweizerbart.de/journals/anthranz).

Some biomedical research was also conducted in Africa, including on hundreds of chimpanzees in the Belgian Congo (Stanleyville now Kisangani: hepatitis studies and polio vaccine efficacy and safety studies) (23), Liberia (Monrovia, New York Blood Center: HBV vaccine safety studies) (24), and Gabon (Franceville, International Centre for Medical Research: ongoing studies on virology and immunity) (25, 26).

1.4. Immunological and Molecular Comparisons of Human and "Great Ape" Proteins

With the foundations of modern understanding of evolution in place, mid-20th-century evolutionary biologists gained access to a new toolbox: molecular biology. Nuttall published perhaps the first molecular examination of the relationship between humans and nonhuman primates, observing that serum from rabbits immunized with human serum weakly cross reacted with that of nonhuman primates. Collecting blood samples from as many animals as possible, Nuttall and Inchley (27) tested and measured the amount of precipitated protein in each reciprocal reaction.

Allan Wilson at the University of California Berkeley and his student Vincent Sarich (28, 29) used an immunological dissimilarity index in groundbreaking papers that would begin to change the public view on how distant or closely related humans are from our living relatives. Because relatively conserved regions of the genome are slowly but steadily undergoing changes over time, these regions serve as good representations of how long two species independently evolved since diverging from their last common ancestor. Today this type of calculation is trivial, with the ability to rapidly compare sequence conservation.

Sarich and Wilson's immunological index allowed them to read this evolutionary record without having tools to sequence genetic material. The immunological dissimilarity was determined by reading microcomplement fixation, which only required a microscope. The microcomplement fixation method measured the cross-reactivity of an antibody raised in rabbits against the serum albumin of one species with its reactivity with the serum albumin of another species. The closer two proteins are in the primary sequence, the more reactive an antibody raised against one will be against the other. Over evolutionary time, mutations in the primary protein sequence accumulate and can be read as a molecular clock by calibrating the rate of these mutations in years using a divergence time found in the paleontological record. Applying this molecular clock approach provided an estimated time since divergence of chimpanzees and humans of only ~3–5 million years ago, while the estimate for divergence from gorillas was ~16 million

years ago and ~30 million years ago from old-world monkeys (30).

This molecular calculation directly falsified the contemporary theories that humans had a long, separate evolutionary history from other living apes by suggesting that humans and chimpanzees are instead very similar. The genetic similarity between *Homo* and *Pan* even led to serious suggestions that the three living species be classified within a single genus (31, 32). Mary-Claire King, working with Allan Wilson, demonstrated that the DNA and amino acid sequences of most human and chimpanzee serum proteins were in fact at least 99% identical and that the other primates also shared highly similar sequences. This suggested that many of the phenotypic differences observed between humans and chimpanzees might be explained by gene expression changes, not just accumulations of coding DNA changes. Even at this stage, with limited knowledge about mammalian genetics and molecular biology, King and Wilson's classic paper "Evolution at two levels in humans and chimpanzees" (33) suggested that to produce the set of phenotypic differences between species, small evolutionary changes must affect the regulation of timing, location, and levels of gene expression, rather than only the changes in the proteins encoded by the gene.

The earliest molecular studies on the relationship between humans and chimpanzees were limited to the study of proteins and cytological karyotyping. In 1973, Dorothy Warburton and others (34) used trypsin-Giemsa G-banding to karyotype the chimpanzee and proposed a standard nomenclature for chimpanzee chromosomes. They observed that while some chromosome banding patterns were indistinguishable between humans and chimpanzees, other chromosomes appear more prone to undergo rearrangement, particularly certain regions that she called "hot-spots." These astute observations foreshadowed the structural pliability that remains one of the great challenges in understanding mammalian genomes. Mitchell and Gosden (35) revealed that human chromosome 2 represents the result of a fusion event between two ancestral chromosomes that remain separate in all the great apes. During the process of sequencing the chimpanzee genome, a proposal to modify chromosome nomenclature to reflect the true homology across hominid karyotypes became widely accepted and is now standard (36).

By the 1980s, Charles Sibley and Jon Ahlquist developed a method that used techniques in nucleic acid hybridization to determine the relative similarity of DNA sequences and infer taxonomic relationships, providing DNA evidence to parallel prior studies of proteins. The Sibley-Ahlquist method of taxonomy was accomplished by hybridizing DNA from two species and measuring the differences in melting temperature to determine relative sequence similarity. During these years, the phylogeny of humans and our living hominoid relatives remained a topic of debate. In 1984, Sibley and Ahlquist (37) applied their method to resolve the phylogeny of humans and the great apes. Their methods yielded the frequently quoted >98% sequence identity figure for human and chimpanzee DNA, which is however based on the exclusion of highly repetitive DNA (or approximately half the entire genome).

With each decade's advances in technology, scientific evidence of the relationship between humans and the great apes compounded, and the public view of human origins began to shift. In 1982 a meeting of scientists from around the world was held at the Pontifical Academy of Sciences in the Vatican to advise the official position of the Catholic Church regarding the evolutionary relationship of humans, our living relatives, and our extinct paleoanthropological relatives and ancestors (38). The published proceedings represent one of the first to suggest a much younger divergence time between humans and chimpanzees (5–7 million years ago) than previously assumed (20 million years ago).

Increased insights into mutational patterns also confirmed the theory of neutral evolution (39) in as much that most DNA changes occur without causing direct phenotypic effects. This realization creates an important challenge for identifying differences with adaptive consequences. It put a brake on pan-adaptationist interpretation but also provided a background "neutral" mutation rate that allows one to detect outcomes of natural selection when deviations from such a background rate are detected.

Work throughout the 20th century suggested that human and chimpanzee proteins bear striking similarities and that subtle genetic changes orchestrate the differences observed between humans and great apes. The latest whole genome data have revealed that human genomes actually differ by ~5% from those of chimpanzees and bonobos, due to the existence of large numbers of differentially duplicated or deleted noncoding genomic elements in each lineage. However, the sequence similarity of ~99% for most expressed proteins has also been confirmed. Whole genome comparisons have also led to the appreciation of structural variation, involving complex and nested duplication and deletion events of much larger genomic segments as an important source of both evolutionary innovation and molecular pathogenesis (40, 41).

1.5. Candidate Gene Differences and Comparative Genomics

Until two decades ago, there were no defined specific genetic or molecular differences between humans and

other hominids with clear-cut biological, biochemical, or physiological consequences. The first specific mechanistic difference identified was a fixed pseudogenization (loss of function) of the *CMAH* gene encoding a sialic acid modifying enzyme, which caused the lack of one of the two major types of sialic acids that typically cover mammalian cell surfaces (42–44). Human *CMAH* inactivation was a distinct genetic difference between humans and chimpanzees that has since been determined to be involved in many human-specific phenotypes (see below and **TABLE 1**).

With the availability of high-quality whole genome data, we can now make a list of genetic loci with differences and select candidates of interest to investigate. Many of these changes are found within regions undergoing positive selection, and many fall into one of the following categories: changes in gene copy numbers, novel genes, pseudogenes, and genes with significant human-specific changes in expression. Other changes are related to structural differences, and some have consequences for posttranslational modifications (e.g., the pseudogenization of *CMAH* eliminating Neu5Gc in humans as discussed above and below). What can we learn from investigating these rare differences between human and chimpanzee genomes? As we wrote in response to the first chimpanzee genome draft, this task is much like hunting for needles in a haystack (67). Besides the small fraction made up of coding genes, the vast majority of the mammalian genome consists of regulatory elements, large regions of repeat sequences and duplications, and transposable elements. Pointing to specific genetic changes that contribute to the human phenomenon is a daunting task as it must include countless regions that are not directly encoding proteins. The detailed functions of the genome, already complex in its diverse types of genetic elements and sequences, are further obscured by chromatin organization and epigenetic modification of DNA and histone tails. Furthermore, many genomic differences could represent the result of genetic drift or neutral evolution, rather than the outcome of natural selection. Ongoing developments in methods and -omics approaches [epigenomics (68), genomics, transcriptomics, proteomics, lipidomics, metabolomics, and glycomics] provide opportunities for advances in comparative anthropogeny in the coming decade (69). We also look forward to models that take advantage of pluripotent stem cells (70) and CRISPR-Cas9 genome editing. For example, the reintroduction of an archaic *NOVA1* splicing factor variant in human-induced pluripotent stem cells (hiPSCs) and production of cortical organoids (71), or knockout of the human-specific gene *ARHGAP11B* in hiPSCs (72) (for more about these examples, see sect. 3.13). Another example is a comparison of human-specific, versus Neanderthal variants of the gene encoding transketolase-like 1 (TKTL1) and their effects on the abundance of basal radial ganglia during corticogenesis in mouse and ferret brains in vivo, as well as in human embryonal stem cells (73). These studies are in their infancy and genome editing requires stringent controls for unintended and off-target effects (74).

For these human-specific genetic changes, a process of logical analysis must be applied to select changes that may contribute to distinctly human biology and disease. After this selection, in-depth investigations can take advantage of robust biological models available today, including laboratory animals and human and nonhuman cell lines, to determine the consequences. Several elements can be taken into consideration in the primary selection process. Chief among them are known links to distinctly human phenotypes. Humans display many traits that differ radically from those observed in the chimpanzee and other nonhuman hominids, such as obligate bipedality, loss of body hair (actually, miniaturization of body hair), and large brain size relative to body size. Changes in genes that are known to be involved in these human-specific phenotypes are obvious prospective candidates. Many common diseases also appear to be human specific, including certain types of carcinomas (cancers of epithelial origin) and many infectious diseases, suggesting human-specific biological mechanisms are associated with these pathologies. In rare cases, genetic mutations identified in individuals with hereditary or congenital disorders offer insight into human phenotypes (75–78). By taking advantage of these "clues," it is possible to predict which of the many changes found in highly conserved genetic regions may contribute to distinctly human biology and disease. These types of clues were implicated in *FOXP2*, a gene encoding a transcription factor associated with a heritable speech disorder and later found to contain human-specific evolutionary changes that appear to be involved with our unusual linguistic abilities (79–81).

With the advent of improved DNA sequencing methods, it became possible to produce a draft of entire genomes, and in 2005 the chimpanzee became the fourth mammalian genome published (82). Across all genomic regions, humans and chimpanzees share ~96% sequence similarity. In accordance with King and Wilson's 20th-century discovery, we share ~99% of sequences that are directly responsible for encoding proteins. Out of the more than 20,000 protein-coding genes found in the human and chimpanzee genomes, ~3,000 code for completely identical amino-acid sequences, and across the proteome there is an average of only 1 amino acid difference per protein. Minor changes in amino acid sequence can of course completely alter a protein's function, including abolishing an enzyme's activity.

Table 1. ***Diverse (pleiotropic) human-like phenotypes of mice with human-like CMAH/Neu5Gc deficiency in mice***

Human-Like Phenotype	Mechanisms	References
Delayed wound-healing	Unknown	45
Age-dependent hearing loss	Unknown	45
Enhanced cancer progression	Tumor inflammation with incorporated dietary Neu5Gc by anti-Neu5Gc antibodies ("xenosialitis")	46, 47
Partial resistance to *E. coli* SubAB toxin	Markedly reduced density of Neu5Gc	48
B cell overreactivity	Reduced CD22/Siglec-G ligands	49
Human-like insulin resistance	Variable: affected by diet and/or microbiome?	50
Reduced fertility with wild-type mice	Relationship to origins of genus *Homo*, via cryptic female choice?	51
Induction of anti-Neu5Gc antibodies	Novel mechanism involving dietary Neu5Gc and *H. influenzae*	52
Enhanced clearance of Neu5Gc-bearing human biotherapeutics	Complexes with anti-Neu5Gc antibodies	53
Overreactivity of T cells	Unclear	54
Macrophage overactivity	Loss of optimal ligands for laminins/agrins? Anti-Neu5Gc antibodies?	55, 56
Sensitivity to typhoid toxin	Typhoid toxins strong preference for Neu5Ac	57, 58
Sensitivity to Pneumococcus	Free Neu5Ac preferentially recognized over free Neu5Gc	59
LPS overreactivity and enhanced phagocytosis by macrophages	Uncertain mechanism	60
Human-like sensitivity to *Vibrio cholerae* neuraminidase and cholera toxin	Neuraminidase prefers Neu5Ac	61
Human-like endurance running phenotype	Multiple	62
Human-like enhancement of endothelial activation in vitro by Neu5Gc and anti-Neu5Gc antibodies		63
Human-like enhancement of atherosclerosis progression	Multiple intrinsic mechanisms and "xenosialitis" by dietary Neu5Gc and anti-Neu5Gc antibodies	64
Human-like microbiota expressing Neu5Gc-preferring sialidases	Induced by Neu5Gc-rich diet	65
Human-like aggravation of muscular dystrophy phenotype in mice	Multiple intrinsic mechanisms and "xenosialitis" by dietary Neu5Gc and anti-Neu5Gc antibodies	66

Multiple (mutually nonexclusive) mechanisms potentially contribute to biological impact of Neu5Gc loss in *cmah* null mice (and likely in humans) and examples are as follows. Biophysics: *1*) loss of millions of hydrophilic cell surface Neu5Gc hydroxyl groups (replaced by hydrophobic acetyl groups on Neu5Ac) are cell surfaces of humans and cmah null mice more hydrophobic than chimpanzee or wild-type counterparts? *2*) Likely global changes in cell surface biophysics, which could have ramifications on cell surface receptor localization, clustering, and signaling. Receptor biology: *3*) Neu5Gc loss could potentially reduce cell surface (Neu1) neuraminidase activity. Reports implicate NEU1 as a regulator of signaling responses, and Neu1 prefers Neu5Ac to Neu5Gc, in some linkages. Metabolism: cytosolic degradation of excess Neu5Gc generates glycolate (instead of acetate from Neu5Ac breakdown), possibility of altered cell metabolome. Transcription: RNA sequencing data implicated CREB1, C/EBPa, and C/EBPb as candidate transcription factors affected by cmah loss. Target genes include IL-6. Immunology: *1*) altered recognition by immunoregulatory siglecs with Neu5Ac versus Neu5Gc binding preference. *2*) Anti-Neu5Gc antibodies interact with metabolically incorporated Neu5Gc principally derived from dietary red meats, to cause inflammation ("xenosialitis").

This extremely high similarity is a result of strong selection pressures that act on peptide-coding sequences and only about ~6 million years of independent evolution since the divergence of the human-chimp lineages. Ranking of regions in the human genome manifesting significant evolutionary acceleration showed that most of these "human-accelerated" regions (HARs) do not code for proteins. The most dramatic change is seen in *HAR1*, which is part of a novel RNA gene (*HAR1F*) that is expressed specifically in the developing human neocortex (83). Similarly, there have also been numerous human-gained enhancers (HGEs), regulatory sequences, that are derived and distinct to humans, several of them involved in neurodevelopment (84–86). Small changes in regulatory DNA can produce dramatic consequences for phenotypes, a key example being the massive cortical expansion during recent human evolutionary history, which seems to be driven in part by regulatory elements found in HARs (87). In addition to HARs, there are also many large segmental duplications and deletions that produced functional consequences through human-specific losses and gains of paralogs, pseudogenization, and gene conversion. A 2011 study identified 510 sites that are conserved throughout primate evolution including in chimpanzees but have undergone complete deletion in the human lineage and coined these changes as hCONDELs (88).

Recently, high-resolution assemblies of the genomes of our closest living ape relatives were constructed and annotated using long-read sequence assembly together with full-length RNA sequencing to allow for the identification of transcripts in each species without depending on the human reference for mapping and exon identification (89). Prior to this, studies of great ape genomes were dependent on the human reference genome to map sequencing reads. This new analysis allowed a high-quality snapshot of the genomic differences between the great apes and humans. For example, chimpanzee and gorilla genomes are slightly larger than those of humans, due to ape-specific parallel expansions of segmental duplications. De novo genome assemblies, such as the latest bonobo genome (90), enable unbiased interpretation of genomic differences between species. It is important to remember that a mutation that causes a phenotype or disease in humans may be inert in another species due to differences in genomic background. Interpretation is further complicated because one gene can have pleiotropic effects in different systems (**FIGURE 2** and **TABLE 1**).

High-resolution sequence assemblies specifically enabled the discovery of lineage-specific structural variants including segmental duplications, inversions, short tandem repeats, and changes in retrotransposons. In addition to these novel structural variants, the de novo assembly of ape genomes allows for a higher resolution picture of human-specific protein coding features. A comparison of the human genome annotation with cDNA construction from ape-induced pluripotent stem cells (iPSCs) identified 57 exons uniquely gained and 13 exons lost in the human genome. These variants are prime candidates for functional validation in experimental systems (89). Massively parallel reporter assays for cis-regulatory enhancers in different human cell lines are providing treasure troves of human-specific regulatory sequences that differ even between humans and our archaic cousins the Neanderthals (85, 91).

Our discussion of genetic and genomic approaches is intended to provide background and context for physiological and comparative anthropogeny. In this review, we cannot give comprehensive treatment to these topics and refer the reader to other reviews that cover important developing fields such as comparative structural genomics associated with gene expression (92), archaic hominid genomics (93), and functional genomics (69).

1.6. Ancient DNA and Archaic Genomes and Their Impacts on Physiology

Advances in DNA extraction, enrichment, purification, and sequencing have developed over the last four decades (94), leading to the construction of draft genomes for the extinct *Homo* species Neanderthal (95) and Denisovan (96). In the last decade, many more individuals of extinct archaic hominids and ancient modern *Homo sapiens* of varying ages dating back to over 40,000 years ago have been sequenced (97, 98).

Comparison of modern human genomes to those of our extinct relatives reveals archaic admixture, indicating interbreeding, particularly between Neanderthals and their contemporary humans in Eurasia (99). Denisovan admixture is also apparent outside Africa and is particularly extensive in some Southeast Asian and Australasian populations (100, 101). Some biological consequences appear to be directly related to certain alleles derived from these admixture events including susceptibility to infection by SARS-Cov2 virus and severity of COVID-19 (102, 103).

Recent advances in DNA purification and sequencing have also enabled the reconstruction of DNA methylation patterns in ancient samples, enabling comparative epigenomic studies (68). Comparison of methylation patterns has revealed changes in epigenetic regulation of gene networks involved in important morphological features of modern *Homo sapiens*, including the vocal tract and the face (104, 105). The available archaic hominin genomes have led to the paradoxical situation where we have genomic information about Denisovans but

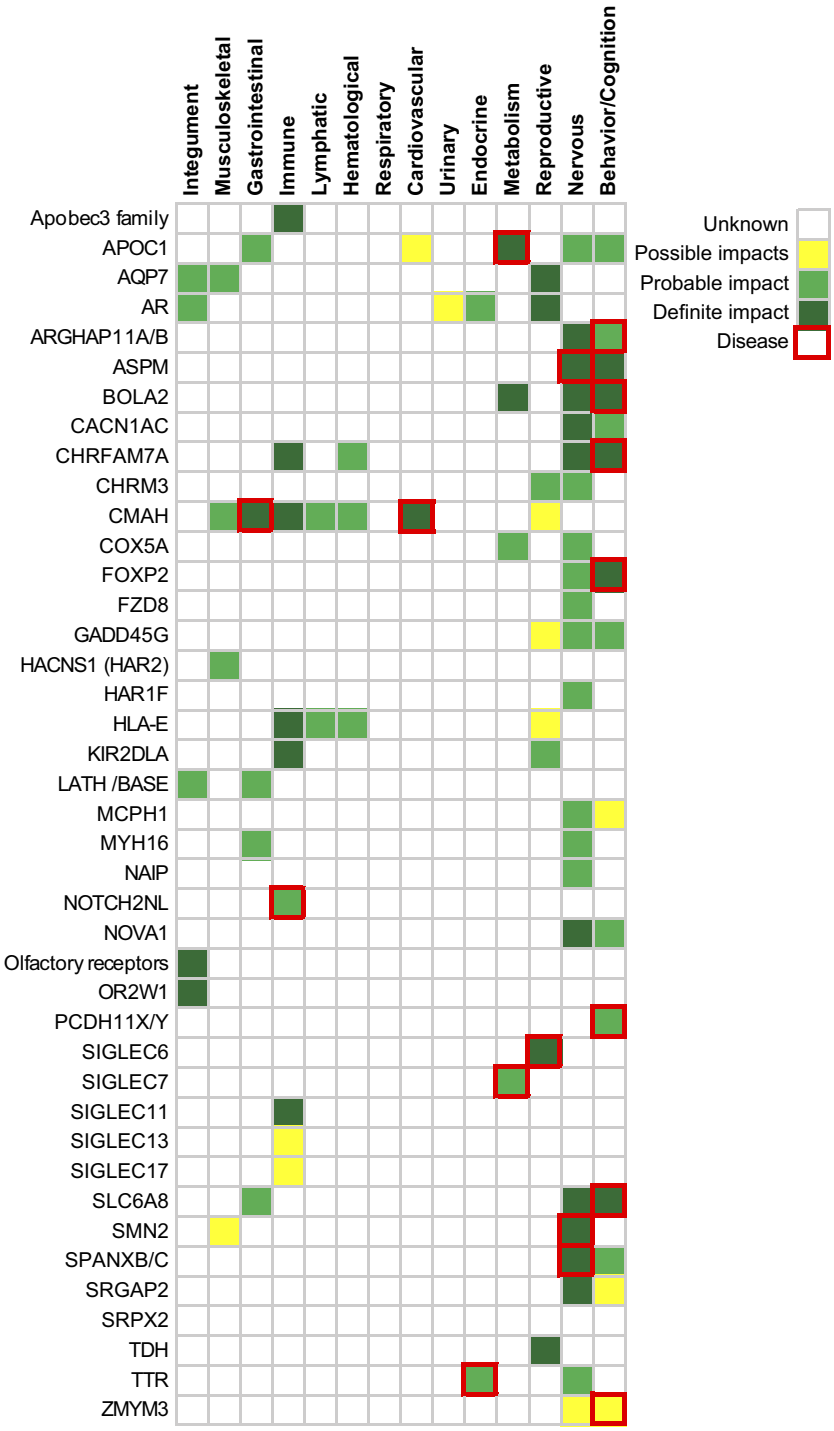

FIGURE 2. Many human-specific genetic changes have effects throughout human physiology. While utterly incomplete, this graphical representation illustrates the potential impact that select human-specific genetic changes found in **TABLE 2** may have in human-specific physiology and highlights systems where these genes are known to be associated with diseases.

mostly lack morphological data due to the lack of confirmed Denisovan fossils, a situation that might be changing in the near future. Deep learning algorithms such as convolutional neural networks (106) have allowed the detection of adaptive introgression from Neanderthal and Denisovan genomes into the genomes of living Europeans and Melanesians, respectively. A combination of approaches is contributing to the ability to predict phenotypes of archaic hominins (105, 107–109). Characterizing phenotypic differences between archaic hominins and modern humans highlights uniquely derived traits of *Homo sapiens*. It is important to emphasize, however, that Neanderthal and Denisovan introgression occurred after the emergence of behaviorally modern humans, effectively ruling out contributions from these archaic cousins as key ingredients for explaining the origin of our species in Africa over ~200,000 years ago. Modern populations in sub-Saharan Africa have significantly less Neanderthal DNA when compared with Eurasian populations (0.6% vs. 2%). This ancestry appears to be explained by Eurasian "back-migration"

into Africa in the last 50,000 years, as well as pre-OOA (out of Africa) human-to-neanderthal introgression around 100,000–150,000 years ago resulting in shared haplotypes between modern Africans and Neanderthals (110).

1.7. Comparative Studies of Gene Expression and Networks

Identification of lineage-specific changes affecting genes with known functions facilitates a candidate gene approach to the systematic investigation of specific mechanisms involved in distinctly human phenotypes (this approach is highlighted above and in **TABLE 2** and **FIGURE 2**). However, comparative genomic studies reveal that the most rapidly evolving sequences within the genome consists of regulatory elements (regions of the genome involved in the regulation of gene expression including the timing, location/cell type, and level of expression). While the biological consequences of these changes can be more elusive to investigate than amino acid coding changes, gene expression studies have become an important tool in understanding human-specific gene regulation. A massively parallel enhancer assay found that more than 30% of 36,656 putative human-specific enhancer sequences had differential activity in human neural stem cells when compared with chimpanzee orthologues (163). Future in vivo studies of the elements identified in this study may reveal links between specific enhancers and traits.

With a particular interest in the distinctive aspects of human cognition, analysis of gene coexpression networks has been employed to study human-specific patterns of regional and developmental gene expression in the brain. In 2004, Khaitovich et al. (164) used gene expression microarrays to compare gene expression across brain regions in a collection of tissues from humans and chimpanzees. The following year, with the completion of the chimpanzee genome draft, it became apparent that changes in protein sequences and gene expression seem to show similar patterns between tissues (165). Analysis of this expression microarray data found that a small number of changes between human and chimpanzee transcription factors can produce coordinated changes in transcriptional networks in the brain (166). A later study used next-generation sequencing and gene expression microarrays to produce higher resolution data for weighted gene coexpression network analysis (WGCNA) comparing brain regions of humans, chimpanzees, and rhesus macaque (167). Besides detecting elevated levels of differential expression in the human frontal lobe, this study discovered that humans have more complex transcriptional programs. Networks of human brain transcriptomes contained the greatest number of modules in their systems-level analysis. Human-specific changes in transcription factor-associated expression modules, particularly in glial cells (168), are directly related to the human-specific developmental neoteny: the concept involving changes (usually delays) in developmental timing that result in biological novelty (169, 170). Most recently, single-cell RNA sequencing of cerebral organoids produced from human- and chimpanzee-induced pluripotent stem cells were used to further discriminate the significance of human-specific expression patterns in glia (171) and differences in the control of neurogenesis-associated retrotransposon activity (112). Brain transcriptomic studies contrasting bulk RNA sequencing with single nuclei transcriptomes from brain samples of humans, apes, and monkeys representing 33 brain regions have not only provided a large number of novel candidate genes that have undergone acceleration in expression changes along the human lineage but have also revealed that nonneuronal cells, such as astrocyte and oligodendrocyte progenitors, display more differences in the human lineage than neuronal cells (172).

Studies of regulatory changes in specific genes have identified important links to distinctly human traits. Epigenomic profiling of cranial neural crest cells derived from human and chimpanzee iPSCs identified over 1,000 species of divergent enhancer regions, as well as differential expression of PAX3, which is known to be involved in craniofacial development in rodents and humans (173). A later study of cranial neural crest cells produced from tetraploid hybrid human-chimpanzee iPSCs found human-specific selection on hedgehog signaling, including genes known to be involved in craniofacial development (78). Maps of DNA methylation in Neanderthal and Denisovan genomes were reconstructed and compared to methylation patterns in humans and chimpanzees, identifying changes in methylation of genes associated with face and voice traits in mice and humans (105).

2. COMPARATIVE ANTHROPOGENY: DISTINCTLY HUMAN PHENOTYPES AND DISEASE

2.1. The Genome Is Not a "Blueprint"

The genome is often described as a "blueprint" for a living organism (174), but this analogy fails to reveal or incorporate the complexity of the regulatory mechanisms described above. It is inadequate to think of the genome as independently capable of encoding a phenotype. Whereas a blueprint contains strict directions that are precisely followed by engineers to produce a specific result, the information in the genome produces

Table 2. ***Functionally validated human-specific human-universal genetic changes***

Genetic Locus	Changes	Biological Impact	Disease	References
APOC1	Pseudogenization of APOC-1B	Apolipoprotein metabolism, associated disease		111
Apobec3 family	Human-specific expression changes	Viral susceptibility; line-1 activity	HIV and SIV infection	112, 113
AQP7	Duplication	Sweating?		114
AR	Deletion of regulatory sequence affected	Androgen hair		88
ARGHAP11A/BARGHAP11B	Human-specific partial gene duplication of ARHGAP11A	bRG/oRG proliferation and neocortical expansion		115, 116
ASPM	Fixed amino acid changes in human lineage and recent positive selection	Cerebral cortical brain enlargement	Microcephaly	117, 118
BOLA2	Duplication (since Neanderthal divergence)	Iron metabolism in brain	Psychiatric disorders	119
CACN1AC	Expansion of a single copy of a 30mer sequence to a large polymorphic VNTR array. Increased expression in humans	Subunit of L-type voltage dependent calcium channel common in neurons	GWAS has suggested involvement of variation at the locus in bipolar disorder and schizophrenia	120
CHRFAM7A	Fusion of two partially duplicated genes	Wound, healing, immune function and neurodevelopment		121–123
CHRM3	Human-specific line element insertion, exon gain, signatures of selection			124
CMAH	Human-specific pseudogenization	Human loss of Neu5Gc: many effects (see **Table 1**)		125
COX5A	Human-specific coding changes	Mitochondrial energy in brain	Mitochondrial deficiency, ophthalmoplegia	126, 127
FOXP2	Fixed amino acid changes	Speech and brain region	Speech and language disorder	128
FZD8	Human accelerated enhancer	Increased brain size, neural progenitor cell proliferation		129
GADD45G	SVZ transcription affects pituitary expansion	SVZ transcription affects pituitary expansion		130, 131
HACNS1 HAR2	Human accelerated enhancer			84
HAR1F	Nucleotide substitutions	Regulatory RNA affects brain development		132
HLA-E	Human mutation in signal peptide	Human mutation in signal peptide		133
KIR2DLA	AA changes deleterious in humans	AA changes deleterious in humans		133
LATH /BASE	Frame shift, stop codon	Loss of protein in saliva		134

Continued

Table 2.—*Continued*

Genetic Locus	Changes	Biological Impact	Disease	References
MCPH1	Fixed amino acid changes in human, and polymorphic changes under selection	Brain-developmental delay and improved memory	Primary microcephaly	135, 136
MYH16	Human-specific gene loss	Skeletal jaw muscle		137
NAIP	Higher copy number in humans	Brain expansion (polymorphisms affect disease risk)		138
NOTCH2NL	Higher copy number in humans	Promotes Notch signaling in cortical progenitors through cis-inhibition of Delta-Notch interactions; promotes proliferation of basal progenitors	Protein levels of Notch2NL associated with severe neurological disorders	76, 139–142
NOVA1	Human-specific (and Neanderthal-divergent) splice factor, dimeric RNA-binding protein	Affects isoform levels of hundreds of target genes. Neuronal cell migration and organoid development		143
Olfactory receptors	Pseudogenization	Many pseudogenes in humans, affecting olfaction		144
OR2W1	Human-specific coding changes affect protein activation in response to specific olfactory ligands	Human-specific coding changes affect protein activation in response to specific olfactory ligands		145
PCDH11X and PCDH11Y	Human-specific duplication (amino acid change from Neanderthal Y)		Speech and language disorders	146, 147
SIGLEC6	Uniquely human placenta expression		Preeclampsia	148
SIGLEC7		Pancreatic islet cell expression	Diabetes risk?	149
SIGLEC11	Human-specific expression pattern	Human-specific microglial expression. Human-specific ligands?		150,151
SIGLEC13	Human deletion	Immune regulation?		152
SIGLEC17	Human-specific pseudogenization	NK cell activation?		152
SLC6A8	Human brain expression increase	(Hypothesized) tolerance for increased meat consumption	Intellectual, language, epilepsy, microcephaly	153
SMN2	Human-specific gene duplication	Motor neuron maintenance	Spinal muscular atrophy	138, 154
SPANXB and SPANXC	Chimpanzee-derived amino acid changes	Spermatogenesis		155
SRGAP2	Human-specific gene duplication	Human-specific paralogue affects dendrite formation and neural cell network activity		156, 157

Continued

Table 2.—*Continued*

Genetic Locus	Changes	Biological Impact	Disease	References
SRPX2	Fixed amino acid substitution	Human-specific R75K mutation in congenital disease-impacted protein sequon but no experimental validation		158
TDH	Pseudogenization	Altered L-threonine catabolic pathway in humans		159
TTR	Fixed amino acid substitutions in regulatory region and coding sequence	Altered thyroid hormone binding	Thyroid disorders	160, 161
ZMYM3	"GA" simple sequence repeat length in 5'-UTR of X-linked zinc finger protein	Exceptional length in humans component of histone deacetylase-containing multiprotein complexes that function through modifying chromatin structure to keep genes silent	Among top 3 genes involved in progression to LOAD	162

This table summarizes known functional genetic differences and the physiological systems implicated. AA, amino acid; GWAS, genome-wide association study; SIV, simian immunodeficiency virus; SVZ, subventricular zone; UTR, untranslated region.

highly variable results depending on many environmental factors. The genome may better be thought of as a "recipe book," because it contains many instructions for different biological components and pathways, but depending on how those recipes are used and what ingredients are available, even the same recipes may produce dramatically different products. The genetic "recipes" contained within the genome are directed by evolutionary pressures and/or biological developmental pathways and, in the unusual case of humans, are also subject to strong cultural influences. These cultural inputs range from a diet of cooked food to symbolic behavior, including personal names and language, belief systems, and many other socioculturally defined aspects of human life. The recipe book analogy, like any analogy, is also incomplete, but it serves to illustrate the many complicating facets by which environment influences phenotype. Human and primate development, existing in the context of sexually reproducing populations of multicellular organisms, depends on interactions between genomes and their environments, including rich microbiota (175). Such development is also subject to a range of constraints resulting from each lineage's contingent evolutionary history (176).

2.2. Life History Differences

Life history features play a critical role in the evolution of all organisms. The timing of embryonic and postnatal development, age at sexual maturity, rate of reproduction, parenting, and longevity, all can dictate how an organism's resources are allocated across the many factors that affect Darwinian fitness (177). In 1949, Adolph Shultz (178) called for the investigation of distinctly human ontogeny to better understand the many distinctly human physical characteristics found in adults. Among living apes, human life history is unusual with several distinctive differences including first, a prolonged developmental period, including assisted birth and caring of helpless infants; second, earlier weaning of the young; third, delays in development giving rise to the human distinct period of childhood characterized by slow somatic growth and steady brain development; and, fourth, a long life span, marked by postreproductive survival, which enables older individuals to assist in the caretaking of multiple generations of offspring (**FIGURE 3**) (179). The prolonged developmental period that is characteristic of humans has been highlighted many times throughout the course of research on human life history. The earliest molecular studies suggested that the most dramatic changes in the human genome lie in regulatory regions, a finding that has been confirmed by the most recent generation of genomic and postgenomic data, and indeed these regulatory elements changed in the human lineage are primarily involved in developmental processes (87, 91, 180). The goal of this section is to review the major characteristics of human life history. For excellent discussions on the evolutionary dynamics involved, please see Refs. 177 and 179.

It remains to be determined how many of these life history changes in the human lineage came about as a biological response to the pervasive cultural nature of humans, including language acquisition and knowledge

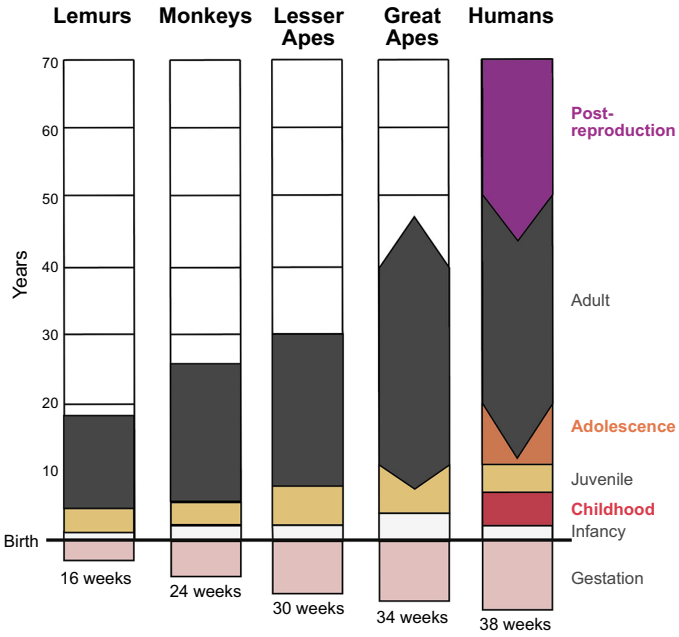

FIGURE 3. Human life history is distinctive among the apes.

transfer, especially between generations (see sects. 2.5 and 3.7 for further discussion on these topics). Many life history changes likely occurred in response to gene-culture interactions. Compared with chimpanzees, humans begin reproduction at a relatively old age due to a prolonged period of life that we call "childhood" (181, 182). Bogin and Smith (183) suggests that the human life cycle has three new stages when compared with that of nonhuman primates: the life cycle of other living species of apes is characterized by the "infant, juvenile, and adult" stages, whereas humans proceed through "infant, child, juvenile, adolescent, adult, and postreproductive woman" (**FIGURE 4**). While differences in specific biological factors involved with life history have been identified, such as the timing of gonadotropin expression (186–188) or metabolic activity during development (189, 190), the distinctively human life history stages of childhood, adolescence, and postreproductive life may be understood in the light of biocultural evolution. Because human social structures largely revolve around core ties between kin, cooperative breeding strategies in humans not only act on the frequency of genetic variants (alleles) but also on the spread of cultural ideas (191). Bogin et al. (192) call this coordinated proliferation of genetic and cultural elements "biocultural evolution."

2.3. Gene-Culture Coevolution (Biological Enculturation, Biocultural Evolution)

Human biology is inextricably codependent with human culture. The origins of one cannot be understood without considering the other. A critical factor in human evolution is the effect that the emergence and transmission of culture have on gene selection (193, 194). In many animal species, sexual selection produces pronounced phenotypes that may not dictate fitness outside of the species' particular mating behaviors. In humans, however, biological enculturation affects almost every gene and phenotype in both sexes. The notion that cultural forces may shape biology has been much discussed, but clear examples such as the ones listed below (**FIGURE 5**; Refs. 149, 179, 195–221) remain relatively rare. We believe that the examples discussed below provide convincing evidence for how profoundly human biology has been shaped by cumulative culture, essentially the human adaptive landscape being defined in part by human culture. However, some may interpret the rarity of such examples as suggestive that many biological traits in humans evolved independently of the influence of culture (222).

Theodosius Dobzhansky famously wrote "Human evolution cannot be understood as a purely biological process, nor can it be adequately described as a history of culture. It is the interaction of biology and culture. There exists a feedback between biological and cultural processes" (223). Most strikingly, the development of human brains appears to "anticipate" cultural input in the form of language (spoken or signed) (207, 224). The absence of such linguistic input has major negative effects on individual brain and cognitive development (224). Human hand morphology (wrist, fingers, thumb, and musculature) reflects the internalization of manipulative skill and production of stone tools, for which there is now over 2 million years of archeological records, as well as cordage, baby slings, mats, baskets, and other organic tools that do not leave a deep archeological record (195, 225). Similarly, running and the use of projectile spears seem to have left clear biological imprints on human skeletal anatomy (shoulder, neck, torso, chest, and waist) (226–228). The precise age of regular controlled fire use by humans is a subject of controversy but is at least several hundreds of thousand years old (229), thus predating the origin of modern *H. sapiens*. Data from contemporary raw food eaters in Germany and experiments in laboratory mice suggest that human biology evolved to require cooked food (203, 230, 231). No traditional culture is known where cooking is not a norm (232), and cooking is included among Brown's cultural universals (233). The liabilities of fire use include the risk of burn wounds and damage to the lungs from fire smoke, especially when exposure occurs in caves or shelters and even possibly susceptibility to tuberculosis (234). These liabilities seem to have led to certain biological adaptations in modern humans. (201, 202).

The culture-bearing capacity of our species is thought to be strongly dependent on our large brains, which also

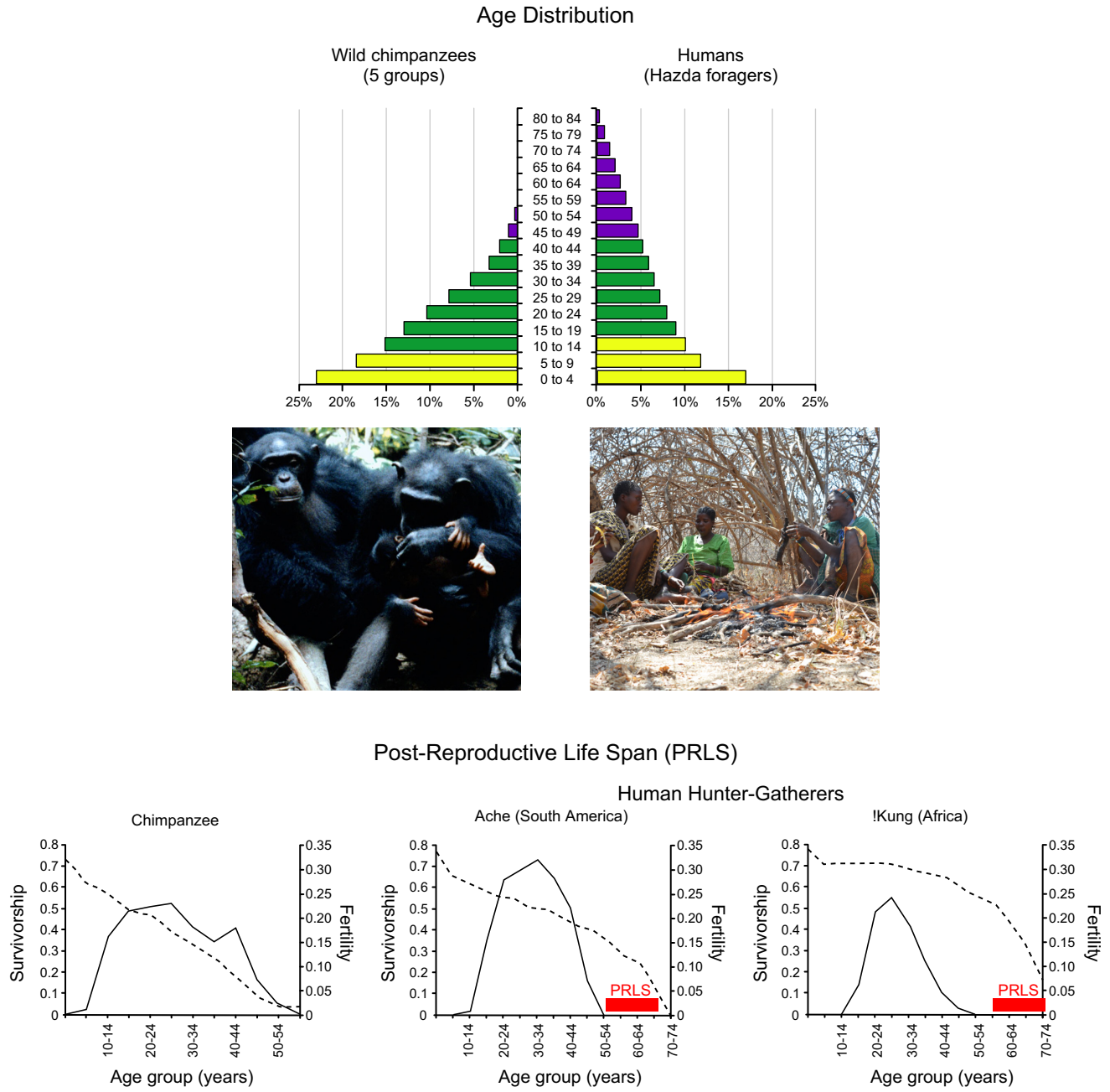

FIGURE 4. *Left*: human-specific postreproductive life span illustrated in the Hadza and contrasted to 5 different chimpanzee groups. Population pyramids in wild chimpanzees and Hadza Foragers, color coded by fertility (yellow: juvenile; green: adult; purple: postreproductive adult). *Below*: survivorship (solid line) and fertility (dashed line) in chimpanzees and the Ache and! Kung Foragers. Bar graphs at *left* are from Ref. 184 and were used with permission from *Proceedings of the National Academy of Sciences U S A*. Graphs at *right* are from Ref. 185 and were used per terms of CC-BY license.

provide the biological substrate for language (235). The human brain is much larger than expected for a mammal of our body size and consumes >20% of daily energy requirements in adults and even more during childhood and adolescence (236). In that context, the proposal that human metabolism runs much higher than in our close relatives may not be too surprising (237). In contrast, other studies have found a highly variable range of physical activity and energy expenditure among humans and wild terrestrial mammals (238) leading to the ongoing discussion over the relatively high demand of big brains and the comparative energy expenditure of humans and great apes.

Regardless, there are several puzzling discrepancies that suggest the importance of big brains may be overrated. First, the expansion of the human brain occurred mostly starting 2 to ~0.5 million years ago, a period during which there was no archaeological evidence of major advances in brain functions (although the manufacture of biface stone tools and increased carnivory

Biology	Culture	References
Hand anatomy	Complex tool manufacture and use	(195,613)
Shoulder anatomy	Projectile weapons	(196, 197)
Pro-social psychology	Complex social structure and networks	(198, 199)
Post-reproductive survival	Cultural transmission/grandmothers	(197, 200)
ARH (aryl hydrocarbons receptor) gene mutation	Use of fire	(201)
wound healing	Use of fire	(202)
Gene expression levels & gene evolution in liver	Cooking	(203)
Jaw/tooth morphology & anatomy	Cooking	(204)
Hyperactive Immune Responses	Home Bases	(205, 149)
Liquid saliva	Spoken language	(206)
Brain anatomy, arcuate fasciculus	Language	(207)
Social blushing	Cultural norms	(208)
Delayed development and brain maturation	Cultural transmission	(209)
Genomic architecture of populations	Cultural mating patterns	(210)
Body lice	Clothing	(211, 212)
Lactase persistence	Animal milk use	(213)
Salivary amylase gene number	Grain agriculture	(214, 215)
PDE10A expression levels & large spleen	Submarine hunting	(216)
Malaria resistances	Agriculture created novel niches for mosquitoes	(217)
Sucrase/isomaltase gene function loss in some inuit	Culture mediated colonization of the arctic	(218, 219)
Thrifty genes (e.g. PPARGC1A) in Polynesians	Long distance marine expeditions	(220)
Germ line mutation rate	Older parental age	(221)

FIGURE 5. Examples of biological enculturation, biological traits directly shaped by cultural practices, from oldest to most recent.

may represent some evidence; Ref. 239). Second, the maximum brain size was reached ~0.5 million years ago (240), well before the archaeological evidence for modern humans appeared in Africa. Third, there is a poor correlation between brain size and IQ in modern humans (241). Fourth, infants who have had half their brains removed (hemispherectomy) early in life for intractable epilepsy can end up with near-normal cognitive functions as adults (242). Fifth, there are rare cases where otherwise normal humans are incidentally found to have gross hydrocephalus with only a thin rim of cerebral cortex remaining (243). Finally, there are rare otherwise normal individuals with highly superior autobiographical memory (HSAM) (244–246) who are able to recall with considerable accuracy, fine details of daily experiences that occurred over many previous decades, suggesting that the capacity of the brain is not fully utilized in normal humans. These individual cases are rare examples existing within modern human populations. Taken together, it seems that the big brains of humans were necessary but not sufficient to achieve modern cognitive abilities and that relative brain size alone is no longer such a key factor. If this is true, there remains a question of what other selective factors drove the continued expansion of the brain from ~2 to about ~0.5 million years ago.

2.4. *Polymorphic Genetic Changes Potentially Reflect Ongoing Selection*

Genetic changes that are not universal to all human populations can contribute to phenotypic variation within different populations and the human species. These are very interesting, and we list some extensively investigated examples in **TABLE 3**. While interesting in the level of human populations, these are not particularly helpful in considering human ape differences at the species level. Examples include human leukocyte antigen (HLA) haplotypes (263); genetic variants underlying variation in skin, eye, and hair pigmentation (264); and metabolic adaptations to certain diets (high in starch, lactose, or saturated fats) (214). Some dietary adaptations are closely linked to cultural dimensions, such as the multiple independent evolutions of lactase persistence in Europe and Africa linked to the consumption of animal milk (213, 265); the independent increase in salivary amylase in human populations with long histories of grain agriculture and/or consumption of starch-rich tubers (214); the loss of function of sucrase/isomaltase in arctic populations after millennia with very little carbohydrates in local diets (218, 219); and digestion of galactans in nori (red algae of genus *Pyropia*) in East Asian populations (266). Some dietary polymorphisms selected in particular populations have been linked to secondary negative consequences; for example, adaptions of certain fatty acid dehydrogenases in response to the traditional diet of Greenlandic Inuit people also affect membrane fatty acid composition, growth hormone regulation, and height and weight (267). In the context of social complexity, humans are distinctly characterized by large social networks and division of labor and the question arises as to the critical importance of social tolerance of strangers who culturally signal group identity and psychosocial diversity, whereby each group can greatly benefit from diverse minds, temperaments, and personality types (268–270). The ancient fossil evidence for human care of individuals who are sick, injured, or disabled is a testament to a kind of social and

Table 3. ***Examples of genetic loci with human-specific polymorphisms present in all human populations***

Genetic Locus	Changes	Biological impact	Disease	References
APOE	Mutations from ancestral isoform	Cardiovascular disease and Alzheimers		247
CD33	Alternate splicing	Alzheimers		248–255
CCL3L1	Immune function		HIV/AIDS	256
Olduvai domain	Selection across hominins and polymorphic in humans	Brain expansion	Microcephaly	257, 258
OCLN	Human specific pseudogene polymorphism	Transforming growth factor-β regulation and cell migration	Hepatitis C viral entry	138
SIGLEC5	Polymorphic pseudogenization	Human-specific pseudogenization		149, 152
SIGLEC12	Human-specific functional inactivation	Human loss of Sia binding	Increased cancer risk?	259, 260
SIGLEC14	Polymorphic pseudogenization	Innate immune response		261
SIGLEC16	Polymorphic pseudogenization	Innate immune response Microglial expression		262

cultural buffer of natural selection and is possibly as old as the genus *Homo* (271). If an individual with novel genetic variants survived because of this buffering and was capable of reproduction, it could result in the persistence of alleles that would not persist in the genetic pool of any other species.

2.5. The Human Brain: an Organ with Open-Ended and Prolonged Postnatal Potential?

The human species evolved a highly species-specific mode of communication known as language (spoken or signed). Language is a diagnostic feature of our species and a key human cultural specialization with profound biological correlates. In contrast to all the other known forms of animal communication, languages use combinatorial systems of sounds or gestures, allowing the creation of infinite meaning and effectively making it possible for individuals to share their brains. The only other evolved system known to have generated near-infinite possibilities is the adaptive immune system of vertebrates, where somatic recombination and hypermutation generate different antibodies with virtually infinite specificity for antigen (272). Language has been convincingly argued to represent a human-specific "organ" (273). The human brain has derived and has prominent anatomical features that are strongly lateralized and linked to language functions such as the arcuate fasciculus (207). Each of the 6,000 plus existing human languages persists solely as the product of living human minds perpetuating and further evolving ancient linguistic traditions, and it was not until the very recent invention of writing 5,000 years ago (274) that languages could be preserved outside human minds. Underlying languages are the capacities for symbolic thinking and the use of personal names. Understanding of symbols is a capacity that has been experimentally demonstrated for trained captive apes, but personal names have not been demonstrated to exist in nonhumans [with the possible exception of signature whistles in the bottlenose dolphin (*Tursiops truncatus*) (275), but these are apparently used as self-identifiers, and vertically transmitted, learned call signatures in Green-rumped Parrotlets (*Forpus passerinus*) are the closest to names in animals (276)]. The human symbolic capacity is powerfully illustrated by the capacity of humans to understand and interpret footprints, an ability not demonstrated for any other species and a capacity to provide important advantages to hunters using sophisticated, complex, poisoned projectile weapons (277).

Another puzzling feature of the human mind was pointed out by Alfred Russel Wallace. The first formal presentation of the theory of evolution via descent by natural selection consisted of two abstracts simultaneously proffered by Darwin and Wallace (in their absence) at the Linnean Society on July 1st of 1858 (278). Later, Wallace was widely criticized by the scientific community

for questioning whether the human mind could possibly be the product of natural selection. Despite his apparently spiritual explanations, Wallace's key point remains valid: how could natural selection, acting in ancient times, have selected for so many abilities of the human mind, which we continuously find new ways to exploit? For example, writing was invented very long after the modern human mind evolved, but writing changes constantly and in the future will be utilized in ways that we cannot predict. The standard explanation of exaptation (a useful feature arising during evolution for a different reason being subsequently coopted for new function) seems inadequate, as the human mind routinely handles many complex situations today that did not exist during its evolution. "Wallace's Conundrum" remains unresolved "–that the same law which appears to have sufficed for the development of animals, has been alone the cause of man's superior... mental nature, –will, I have no doubt, be over-ruled and explained away. However, I venture to think they will nevertheless maintain their ground, and that they can only be met by the discovery of new facts or new laws, of a nature very different from any yet known to us" (279).

Perhaps aspects of distinctly human features arose because there was a relaxation of selection for the maintenance of genome integrity, thus allowing humans to become much more dependent on intergenerational cultural transfer (2). Comparative genomics does not show strong evidence for this notion (280). On the other hand, humans currently migrating from the gamut of genetically disparate populations around the world achieve similar intellectual and technical performance in places such as the diverse student bodies and faculties of large universities. These immigration stories illustrate that the human brain already achieved its full potential at the origin of our species ~200,000 years before the prolonged genetic isolation of populations after leaving Africa (281). Alternatively, it may be that we are still underestimating the cognitive demands exerted by the lifestyle of a periplanetary cultural species such as that of our hunter-gathering ancestors who, despite their comparatively simpler societies and technologies, lived in a rich sociocultural world of complex social connections, embedded in age-old oral histories, vivid imagination, and the creation and maintenance of shared meaning through norms and rituals (i.e., cumulative culture!). The biological capacity to carry culture, and the profound biological enculturation of humans long before the advent of writing and counting, could well have selected for the human mind as a highly responsive and flexible organ of imagination with surprisingly few limits on what it can invent, imitate, pass on to others, or worry about. Irrespective of why or how this came to pass, the question remains as to why it only happened once in the human lineage, and we are left without any evidence for a similar capacity in any other living species.

Kahneman (282) suggested that the human mind has two distinct modes of operation: a rapid instinctive and emotional response to problems and a slow more considered deliberate and logical way of operating. It seems likely that the great apes also have the fast emotional response but not the slow analytical capacity. According to the "fast and slow" theory, this could be what distinguishes the human mind. Analytical capacity may be the origin of imagination because analytical capacity involves thinking through imaginary options and consequences before acting. Language may have been a key ingredient for this type of thinking (283).

2.6. The Distinctly Human Capacity for Language

Human language, spoken or signed, appears to be an evolutionary singularity as there remains an almost complete absence of evidence for generative grammar in nonhuman species. The most complex "syntax" in nonhuman primates is the combination of two different alarm calls into a signal with a new meaning in some species of guenon monkeys (*Cercopithecus campbelli* and *C. nictitans*) and birds (e.g., *Parus minor* and *Turdoides bicolor*) (284). This diagnostic feature of our species allows individuals within and between social groups to "share their minds" over space and time, to tell stories about individuals who lived in the past, might live in the future, or are entirely fictitious. Language allows for the creation of infinite meaning and for the construction of alternate realities and shared imaginations, with powerful effects within all known human societies. The combination of personal names with the widespread human practice of gossip (285) allows for the establishment of reputation, and this again has profound effects on individual behavior, via individual concern for reputational management as a means for heightened social success (286). Clearly, the capacity for speech and language must have evolved in our lineage, but there is currently no agreement about how this evolution took place and which preexisting features of communication (gestural or vocal), (287, 288) ritual behavior, coordinated actions, recursive behavior patterns and embedded action patterns required for complex tool manufacture (289) or the teaching of such manufacture (290), and alterations of neuronal control of breathing potentially linked to bipedalism (291) may have provided the needed combinations of exaptation for the evolution of human language (292, 293). There is currently no hard evidence for the precise age of human language, but with estimates that *H. sapiens* originated over 200,000 years ago and diverged from Neanderthals over 800,000 years ago, there is a high likelihood that

language is much older than the ~100,000 years often mentioned. The importance of fire in providing daily opportunities to communicate is another example of how cultural behavior (fire making) can create novel opportunities for biology (the capacity for language) (294).

2.7. Human Exceptionalism

Human exceptionalism refers to the view that humans are categorically or distinctly different from all other animals, an opinion that has gone from being commonly held to becoming a subject of widespread criticism and even ridicule. One reason is the secondary danger of anthropocentrism, a worldview that sees humans as the teleological outcome of evolution and the source of all value and of nature as merely being of value primarily as a means to the ends of humans. The previous section on Wallace's conundrum can be seen as an example of human exceptionalism.

While each living species has defining features, the value that one places on any particular feature is a matter of opinion and choice. Thus it is cogently argued by some that humans are just another species of ape. However, the very existence of this review, created to communicate our views to many other humans on every continent, and disseminated by multiple mechanisms, highlights some of what is unusual (and unexplained) about humans. While each species of great ape has unique traits, the trajectory of the human species from our common ancestor with chimpanzees and bonobos to our current status as the primary driver of ecological, geological, and atmospheric change planet-wide is perhaps exceptional (**FIGURE 6**). Would you the reader not agree that humans are the most Destructive, Devious, Dangerous, Deadly, Diabolical, and ecologically Damaging species on earth today? However, simultaneously, we will likely agree that humans can also be the most Caring, Compassionate, Considerate, Cooperative, and Conservationist species on earth today. Perhaps we should talk about "Human Evolutionary Exceptionality?"

A study of brain morphology in humans and chimpanzees identified a strong correlation between heritable genetic markers and certain measurements of brain shape and organization in chimpanzees but less so in humans (295). This finding reveals that the human

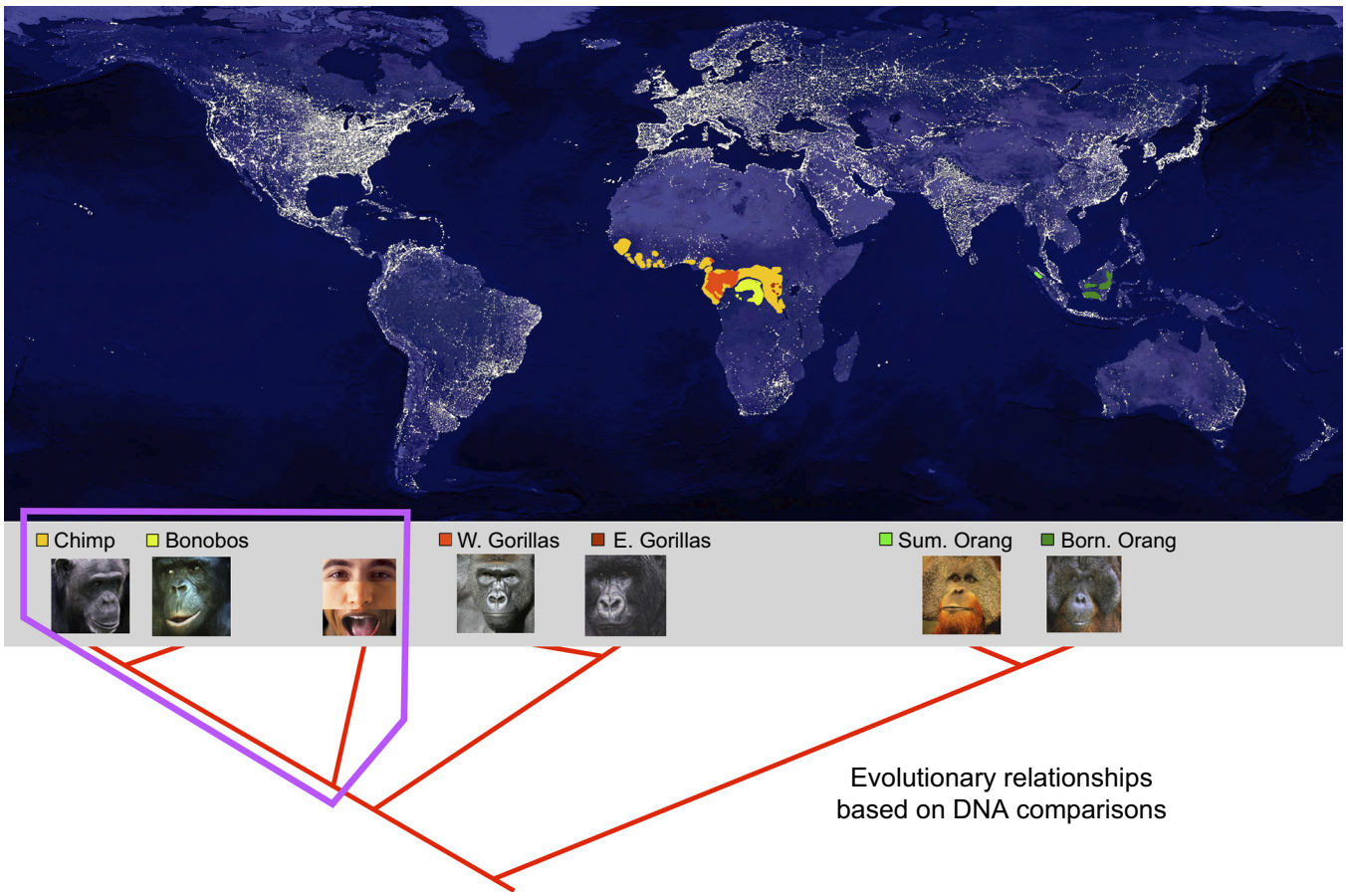

FIGURE 6. Human exceptionalism: we are the only primate to have settled the entire planet and to have satellites take images of our distribution, despite our close genetic relatedness to 2 species of great apes. Global distribution of each great ape species is plotted according to color (see legend in figure).

Table 4. ***Distinctly human diseases: human-specific pathologies as compared to the great apes***

Difference	References
Definite difference	
Myocardial infarction (coronary thrombosis)	64, 303, 304
Malignant malaria (*P. falciparum*)	305–307
Typhoid fever (*Salmonella typhi*)	57, 58
Cholera (*Vibrio cholerae*)	61, 308
Mumps (epidemic parotitis)	309
Whooping cough (pertussis/diphtheria)	310
Smallpox (variola)	311
Gonorrhea (*Neisseria gonorrhoea)*	312–315
Group B streptococcal infections	316
Meningococcal meningitis	317
Hemophilus influenzae infections	318
Missing endemic transmissible retroviral infections, e.g., spumaviruses	319, 320
Probable difference	
Human-influenza A infections	321, 322
Alzheimer's disease	323–326
Carcinoma (cancers of epithelial origin)	260, 303, 327–330
Rapid Progression of HIV infection to AIDS	331–333
Hepatitis B/C complications (cirrhosis, cancer)	334–336
Muscular dystrophy severity	55, 66
Preeclampsia (pregnancy-induced hypertension)	337, 338
Possible difference	
Frequency of early fetal wastage?	339
Frequency of premature labor and birth	340
Frequency of chronic female iron deficiency	341
Bronchial asthma	342
Hydatidform molar pregnancy	343, 344
Schizophrenia	345
Bipolar disorders	345
Polycystic ovarian syndrome (PCOS)	150

We previously described many human-specific pathologies as compared to the great apes (302). A listing is provided and details can be found in prior publications (302, 346). See Ref. 302 for criteria for a "distinctly human" disease.

brain is not only highly unusual for being more than three times as large as an ape brain (relative to body size) but also unusual in its ability for gene-independent development; monozygotic twins show no more similarity in brain morphology than any other pair of siblings (296). In monozygotic twins, psychiatric disorders are only 30–70% hereditary (297–300). This relaxed genetic control of brain organization, along with delayed brain development and high levels of synaptic plasticity (301), may contribute to the neurological mechanisms enabling cultural influence and learning during childhood to shape the development of the human brain. As discussed earlier, language is another trait that appears to be human-specific, although the absence of evidence of language in other species is not evidence of absence.

We previously described many human-specific pathologies as compared to the great apes (302). **TABLE 4** provides a listing, and details can be found in prior publications (302, 346). The review by Lowenstein et al. (346) is very comprehensive with anatomic descriptions and diseases, which are common in humans but more rarely seen in the great apes.

3. COMPARATIVE PHYSIOLOGICAL ANTHROPOGENY: A SYSTEMIC PERSPECTIVE ON DISTINCTLY HUMAN PHENOTYPES

This section will highlight interesting examples of distinctly human phenotypes. It is important to note that there are many examples that we will not cover because of space limitations. Because we also choose to highlight examples that we are most familiar with, certain subjects will be covered in more detail than others.

3.1 The Integument

Perhaps the most obvious difference in the physical appearance of humans and great apes is the human-

specific lack of a fur coat. It is more precisely described as a strong reduction or miniaturization of the fur coat, given that humans and apes are estimated to have comparable numbers of hair follicles (347). Differences include the density, length, and distribution of body hair, as well as male pattern baldness, androgenic hair, and pubic hair. The evolution of pubic lice has been used to estimate the time depth of body hair reduction and pubic hair gain in humans (348). It is also worthwhile to mention the human-specific remodeling of the skin microbiome (349) and the body lice that have evolved to specifically take residence in the ecology of the presumably clothed "naked" ape (211, 212).

Hair and eccrine glands of the skin play important roles in maintaining thermoregulation (350). In chimpanzees, piloerection is a visually obvious display of arousal (350). Although there are visible differences in the amount of hair between humans and great apes, the human skin has an abundance of fine (vellus) hair that is not readily visible. Analysis of postmortem full-thickness skin biopsies revealed that although hair density is similar in humans and chimpanzees (but different from macaques), humans have a 10-fold higher number of eccrine glands as compared to chimpanzees and macaques (347).

Variation in human skin coloration is mainly a product of natural selection throughout the history of human migrations (351). Humans also exhibit far greater variation in hair color and pigmentation patterns than great apes (352). In addition, humans differ in the continuous growth of scalp hair and facial hair in many males (353). Populations inhabiting nonequatorial regions responded to low levels of ultraviolet B light by decreasing pigmentation, which protects from potentially harmful levels near the equator. In European populations, genetic signatures around melanocortin 1 receptor (*MC1R*) and solute carrier family 24 member 5 (*SLC24A5*) genes imply that both natural selection and genetic drift contributed to the evolution of depigmented skin, while in Asian populations a similar depigmentation occurred via a different unknown genetic mechanism (264). Some dermatological pathologies appear to be quite rare in nonhuman primates, including cases of allergy, psoriasis, and benign and malignant tumors of the skin (354). In humans, graying of facial and scalp hair begins at some point in midlife and gradually progresses with age (355). In chimpanzees, graying of facial hair reaches a plateau in each individual and does not follow a progressive pattern into late life as in humans (356).

In humans, the keratin filament gene *KRT41P* is a nonfunctional pseudogene. While great apes have a functional ortholog, a single base-pair substitution introducing a premature stop codon is fixed in the human lineage (357). Population-level sequence analysis suggests that the human mutation may have occurred ~240,000 years ago. While none have yet been noted, this change could be involved in some human-specific phenotypes of hair. We have included this as one example of a genetic change of interest that warrants further experimental investigation.

Continuously growing scalp hair, pubic hair, and motile eyebrows are all further characteristic features of the human integument not observed in any of the great ape species (352). The importance of scalp hair for the expression of cultural identity and the powerful communicative power of eyebrow movement (358) may both represent examples of culture biology coevolution. Facial expressions recruiting many aspects of the human face appear to be universal and globally comparable (359).

Humans across populations also experience emotional blushing, a phenomenon that fascinated Darwin, who called this physiological reaction to self-attention, shame, and modesty the "most peculiar of all human emotions" (208). This subconscious reaction, triggered by the realization of transgression of social norms, occurs only in the presence of a human audience and is more visible in humans who have low melanin levels and paler skin (360). In all humans, this reaction is often accompanied by sweating. Blushing is a common phenomenon in all human populations, but its association with color change is only prominent in paler populations; in darker skinned populations, it can be known as "dying of shame or feeling shame" (360). A similar emotional reaction to the public violation of social norms has not been reported for any nonhuman species. This potentially overwhelming reaction, regulated by the sympathetic nervous system and involving the largest human organ (the total surface of human skin is estimated to be over 20 square meters if all folds are included (361), is very much dependent on a theory of mind, i.e., the capacity of individual humans' minds to imagine what other minds are thinking, the ability to ascribe mental states to others. It provides yet another example of biological inculturation. There is evidence for a theory of mind in great apes, but there is an ongoing debate as to potential limitations in apes such as their struggle to understand the false beliefs of others and the best ways of experimentally exploring this (362, 363).

Fully formed breasts in virgin females (364) do not exist in any other mammalian species. A definite explanation of this derived human organ is still missing but likely includes sexual selection via male mate choice in our species that lacks any overtly advertised ovulation (365). Proposed mechanisms include honest signaling of residual reproductive value (366).

3.2. The Musculoskeletal System

The gross study of the musculoskeletal system allowed the earliest anatomists to characterize many of the similarities and differences between humans and other hominins. Reports of human-chimpanzee differences in musculature and skeletal structures began with Tyson's 1699 publication (19). Of course, bones are privileged in the study of mammalian species' evolutionary history because they are the only part of the mammalian body that reliably forms fossils (together with teeth). We must deduce the evolutionary history of almost all other tissues from living species; however, paleontology offers a direct glimpse into the evolutionary history of the skeletal system. Bones can fossilize under ideal geological and climatic conditions. In contrast, soft tissue will decay over time and only leave traces where it was attached to bones. Fossils result from a process of mineralization, whereby infiltrating minerals effectively turn the bone to stone, while maintaining the original morphology in fine detail. While fossilized remains are the only available options for many ancient and extinct species, they offer limited information.

Cranial morphology differs in humans and great apes mainly with regard to size, globularity, basicranial flexion (367), and position of the foramen magnum (368, 369). The human face is retracted under the globular cranium, and both the maxilla and mandible are smaller (370). The cranial bone is much thinner in humans, who also lack a large supraorbital torus (brow ridge) and a sagittal crest found in some male apes and much reduced muscle attachment in the nuchal area (371). In the facial musculature, humans seem to exhibit a difference in the presence of true risorius muscle (226). A reduction in chewing muscles occurred in the lineage leading to humans, which included the loss of myosin heavy chain 16 protein (*MYH16* is a pseudogene in humans) (137); however, that change merely accompanied the evolution of a larger cranium and was likely not causally related to it (372). Whereas other apes have a superficial head of the temporalis muscle, humans retain the complex system of temporal fascia but have lost the superficial muscle (373). Humans have evolved a characteristic external nose in both sexes, and the selective pressures for this feature remain poorly investigated but include adaptation to climate, respiration during running, or even better capacity for directional olfaction and pronounced sexual dimorphism (374–376). Human teeth are much smaller than chimpanzee teeth but have much thicker enamel. The sexual dimorphism in canine teeth is much reduced in humans, and humans have lost the canine diaphysis and the sharpening by friction seen in male great apes (377). Delayed development is evident in human dental maturation as well. (378, 379). The os penis (baculum) is vestigial in male chimpanzees but completely absent in humans (380).

Upright bipedal walking, an ancient hominin behavior predating *Homo* by several million years (381), is another major feature reflected in distinctively human skeletal features (**FIGURE 7**). Skeletal adaptions to accommodate bipedal locomotion include feet, knees, pelvis, torso, neck, and cranium (382). The number of lumbar, thoracic vertebrae varies among humans and the great apes, and in addition there are variations in the morphology of the spinous processes of the vertebrae as well (383). Human lumbar vertebrae have evolved a bearing function, reflected in their size and in the curving column associated with bipedalism. The anterior inferior iliac spine is distinctly human in that it assists with the

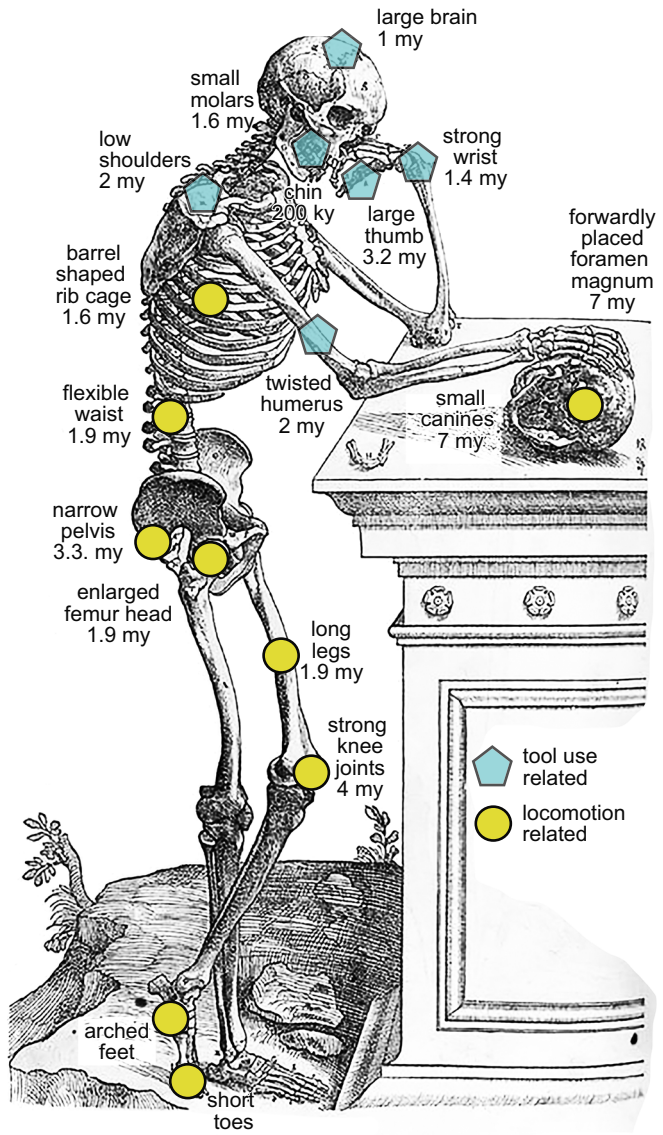

FIGURE 7. Anatomical specialization of the human skeletal system to bipedal locomotion and tool use. Image is by Andreas Vesalius, *De Humani Corporis Fabrica*, 1543 (public domain).

repositioning of the gluteal muscle to control the pelvis and pelvic floor while walking upright and running (384).

The human iliotibial band (ITB) stores greater elastic energy than in chimpanzees, another potential adaptation to bipedal locomotion and especially endurance running (226). Among hominids, endurance running is a uniquely human behavior and partly depends on derived skeletal traits including body proportions that facilitate the running stride, trunk musculature that increases stability and balance, and tendinous structures that act as springs to conserve energy (227). Human hindlimb muscles operate joints in a narrow range of activities, whereas limb muscles of the chimpanzee and other great apes are optimized for the movement of joints over a wide range of activities, from arboreal to traversing different environments on the grounds (385). These uniquely bipedal loading forces are likely responsible for the increased trabecular anisotropy at the proximal femur in humans compared with any other ape (386).

The human foot has evolved to be much stiffer than that of the great apes (228) and features a longitudinal arch capable of storing elastic energy in the Achilles and plantar structures (387). Compared with apes, the human foot has much larger heel bones and much smaller toes that, not capable of grasping, are adapted to a bipedal gait and pushing off the entire body weight with each step (387).

The human hand has enormous dexterity, and analysis of medical imaging of chimpanzees, bonobos, and human cadavers, along with dissection, revealed differences as well as similarities in the hand muscles (225, 388–390). The production of stone tools is a behavior that predates the genus *Homo* (391); in contrast, we do not know the true age of fiber technology (twines, ropes, nets, infant-carrying slings, etc.) as such technology does not survive in the archeological record. Compared with chimpanzees, humans have an increased ability to precisely grip and handle objects (195). Several morphological features involved in precision gripping were found in *Australopethicus afarensis*, but the complete set of skeletal adaptions that enable human-like movement do not appear in the fossil record until *Homo* (**FIGURE 7**) (195). Flintknapping depends on the strength and dexterity of the human fingers, in particular the thumb, to absorb the high normal forces produced during striking and involves highly asymmetrical sets of motion (389, 390). Humans and other apes share the same collection of finger and forearm muscles, but in humans a greater number of these muscles are attached to the thumb (392). Virtual modeling of thumb musculature based on fossils of several species of ancient hominins suggests that the enhanced force-generating capacity seen in modern humans was shared by other species of *Homo* since the origin of the genus (393). The human hand may also have evolved for combat given the derived buttressing capacity of the hand in fist formation (394). The human shoulder can store elastic energy and allows human to single handedly throw items, rocks, or spears at much higher speeds than chimpanzees (196, 197). Studies of fossil *H. erectus* have found that this capacity dates back to over 2 million years ago (395).

Speech production involves a complex coordination of air pressure release, produced in the lungs, combined with the modulation of the larynx, tongue, jaw, and lips. This coordination heavily depends on the musculature of the abdomen and the system of nerves that extend from the spinal cord and control these muscles and the control of the larynx, tongue, jaw, and lips. The human spinal cord differs from that of great apes at the thoracic vertebrae, with larger vertebral canals relative to body mass than other primates, and a greater cross-sectional area of the spinal cord in this thoracic region (396). These changes accommodate precise motor control of the chest muscles and may be involved in the regulation of air pressure during the production of speech. Based on a single specimen with intact thoracic vertebrae (Turkana boy), it appears that *H. erectus* did not have human-like enlarged canals in this region suggesting that this is a recent evolutionary change (397).

Chimpanzee muscle is similar to human muscle in its single-fiber contractile properties but exhibits a much higher fraction of myosin heavy chain (MHC II) isoforms. Unlike humans, chimpanzee muscle is composed of ~67% fast-twitch fibers (MHC IIa + IId) (398). There are potential differences in muscle fatiguability between humans and apes, as the loss of function of the sialic acid modifying *CMAH* gene leads to a decrease in fatiguability in model *Cmah* knockout mice (62). There are at least 14 atavistic muscles that are present in the adult chimpanzee but completely disappear in humans during early development (399).

3.3. The Gastrointestinal System and Nutrition

Wild apes spend several hours each day chewing their food. Humans in all known societies prefer cooked food and spend much less time chewing (203). Food processing and cooking make nutrients more accessible, detoxify many plant compounds (especially lectin proteins in large, protein-rich legume seeds), and improve the digestibility of many animal and plant foods (203). Other food processing including leaching of toxins (alkaloids) or antinutrients (tannins and phytates) from plants or seeds, and the pounding of food items provides similar advantages (400). Given the preference of all documented human cultures for cooked food, and evidence for negative consequences on female fertility of raw

food diets (230), it is safe to consider cooking a biological human trait and to see humans as cucinivores (204, 401). Unlike the closely related great apes, humans consume much larger quantities of starch-rich foods including tubers, corms, sago palm starch, and grains. This behavior is reflected in the human genome's increased copy numbers of salivary amylase genes (214, 215). Human saliva appears more diluted and less viscous than chimpanzee saliva, has lower protein content, and has distinct protein profiles, lacking latherin for example (206). Humans have long small intestines compared to the great apes but shorter colons, likely reflecting differences in diet (402, 403). Most primates, especially leaf-eating primates, have to digest the cellulose cell walls and chloroplasts of their plant diet in the foregut, cecum, or large intestine with help of cellulases, pectinases, and other polysaccharide hydrolyzing enzymes produced by their microbiota (404). The digestion and passage kinetics of food are comparable in chimpanzees and humans (403), and mean transit time is similarly affected by fiber content.

Carnivory was a key component of the diet of preagricultural humans and involved scavenging for meat (inside bones with the use of stone tools) and hunting with projectile weapons, nets, and traps (cliffs, pit traps, hunting traps/desert kites, and snares). Unlike other primates, humans scavenge and hunt animals much larger than themselves (405). In rare cases, human populations have adapted to extreme carnivory, such as in the high arctic, where diets extremely rich in animal protein and fat, and very poor in carbohydrates, produced selection for specific alleles of metabolic genes (214, 406). There are no examples of purely vegetarian diets before the development of agriculture (203). As omnivores, humans have relied heavily on large numbers of plant foods from above and below ground, but also to a much larger extent than the omnivorous chimpanzees, humans rely on animal foods. Among the great apes, chimpanzees are the only nonhuman species known to regularly consume vertebrate prey, but they do so in much lower quantities than ancestral human populations and always consume their prey fresh and raw (407). Honey, which can represent a substantial fraction of seasonal food is prized by all human populations with access to it, and the ability to collect large amounts of honey and protein- and fat-rich bee larvae depends critically on the capacity to make fire and generate smoke (408).

A key difference in food acquisition between humans and other hominids is that food sharing is a central feature of human eating, whereas food transfer in most apes is more akin to "tolerated theft" (409). The earlier weaning in humans requires the transfer of food from older individuals to the newly weaned young to provide sufficient calories (410). Consumption of ruminant prey, among the most common large prey on grassland, likely led to the evolution of human-specific detoxification of phytanic acid of chloroplast lipid origin in humans (404). There is the distinct possibility that humans have undergone adaptations for carnivory including selection at the APOE gene cluster; human ApoE4, which is similar to chimpanzee ApoE, may have been involved in tolerating the inflammatory stress involved in red meat consumption (411).

The appendix, located at the beginning of the cecum, is much longer in chimpanzees than in humans. In the young of both humans and chimpanzees, the appendix contains lymphoid aggregates. Appendix lymphoid collections decrease in size in aging humans but persist in aged chimpanzees (412).

Diet as well as host morphology and phylogeny can influence the bacterial composition of the gut microbiota in humans and captive apes, and captivity influences the gut microbiome of captive great apes (413, 414). Comparisons of human microbiota to that of chimpanzees, bonobos, and gorillas have revealed that there must have been a relative loss of microbial diversity along the human lineage (413). Since the onset of the Neolithic and the development of pastoralism and agriculture, some human societies have produced surplus food that can be stored, traded, taxed, and stolen. A surplus of food also carries the risk of overabundance, as currently observed in most industrial nations, where easy access to calorically dense foods is contributing to an epidemic of obesity and metabolic syndrome (415). Among captive great apes, especially chimpanzees, obesity is frequently an important health issue, especially for females (416). Inactivation of the Uricase gene in apes occurred in a common ancestor of modern humans and great apes living around 15 million years ago in Europe (417). It has been suggested that the loss of Uricase and increase in uric acid enabled increased fat stores in these Miocene apes, a trait that could be related to the obesity epidemic in modern humans (418, 419). This loss of function is shared between humans and their ape relatives.

3.4. The Immune System

Different mammalian species exhibit vast amounts of variation with regard to their immune defenses in both function and anatomy (420). Three correlates of immune defense levels include the ease of white cell activation, the number of circulating white cells, and the relative size of the spleen. Among living hominids, the spleen varies in size and shape, with the human spleen being larger than that of the chimpanzee (421).

Maintaining immune defenses comes with a high cost, including the frequent generation of inflammation-related oxidative damage to self-tissues, which may be associated with increased disease risks. Several features of an organism and its environment contribute to the pathogen regime it will be exposed to during its lifetime. These include the number and different types of pathogens encountered but also changes in body size and longevity, social behavior (group size and intergroup exchanges), ecological parameters, and diet. Within primates, there exist large differences in apparent pathogen and parasite load. Old-world monkeys appear to harbor higher viral diversity than prosimians. Species-specific mating systems also appear to influence immune defenses, as species with more promiscuous mating systems (multimale, multi-emale) have higher white blood cell counts. This has been interpreted as a response to the higher occurrence of sexually transmitted infections. (422).

Effective recognition of infection by the adaptive immune system is mediated by the recognition of pathogen antigens presented by MHC molecules, both MHC type 1 expressed in most body cells and MHV type II of antigen-presenting cells (dendritic cells and macrophages). Genes of the MHC system (called the HLA system in humans) exhibit much sequence and structural overlap between humans and apes. (423, 424). MHC proteins simultaneously provide "self" recognition and nonself antigen detection for T cells and natural killer cells as these highly variable immune presentation (MHC) molecules present intracellular content (MHC class 1) by most cells or absorbed extracellular content (MHC class II) by dendritic cells and macrophages.

Despite the generally much higher levels of genetic diversity found in chimpanzees, their MHC type I diversity appears reduced, suggesting past selection, possibly by retroviruses (425). Comparative genomics provide clear evidence for million-year-old, past episodes of retroviral invasion restricted to both gorillas and chimpanzees (426).

NK cells and T-cells express killer cell immunoglobulin-like receptors (KIRs) that are crucial for the detection of MHC manipulating intracellular pathogens. KIR genes rapidly evolve and are subject to copy number variation in both pes and humans. KIR proteins recognize MHC molecules on cells presenting antigens via MHC molecules and inhibit NK cell activation. The human genome contains at least 15 different KIR genes encoding receptor proteins specific for MHC class I molecules (also known as HLA-A, B, and C). Chimpanzees have orthologous Patr-A, B, and C genes. Four shared, derived lineages of KIR genes exist in living hominids, and these evolved from a common ancestral KIR ~135 million years ago (427–429). Each hominid species has independently evolved different numbers of KIR genes within these lineages. Each of these genes can encode either inhibiting or activating receptors. Only seven lineage III KIR genes exist in humans while nine exist in chimpanzees. Among these, just two are true orthologous (identical by descent). The vast majority of KIR genes evolved independently after the divergence from their last common ancestor (427). There are more genes encoding activating KIRs in humans and twice as many genes encoding inhibitory than activating KIR proteins in chimpanzees (428). Humans show polymorphism with haplotypes with varying numbers of active KIR genes, and haplotype frequencies vary between populations (429). The combined effects of the ability of human ancestors to populate new and variable ecosystems and the repeated occurrence of demographic bottlenecks during global expansion likely impacted the extensive variation in human KIR genes.

The lymphocytes of humans appear to be more readily activated than those of chimpanzees as measured by cytokine activation and resulting expression of activation markers upon exposure to several stimuli. This became evident when a therapeutic based on the activation of CD28 T cells led to extreme cytokine storms in human subjects (205). Similarly, the traditional test for exposure to tuberculosis, the "tuberculin test," consisting of antigen challenge to the skin, requires up to 10 times the dose of the antigen in chimpanzees for a positive reaction compared to humans (430, 431). This contrast is indicative of differences in "delayed-type hypersensitivity," a process involving several types of lymphocytes but particularly T cells.

Differences in the risk and severity of certain infectious diseases between humans and chimpanzees may be related to differences in lymphocyte activation. Several human-specific diseases including human immunodeficiency virus (HIV) infection progressing to AIDS, hepatitis C infection progressing to cirrhosis and hepatocellular carcinoma, and autoimmune disorders may be exaggerated by the overactivation of adaptive immune responses. A key difference in the immune reactivity of chimpanzee and human lymphocytes appears to be partly related to the differential expression of innate immune receptors, in particular the *SIGLEC* family (Sialic acid binding Ig-like lectins) (149, 205, 432). For example, the expression of Siglec-5 appears to moderate T- and B-cell immune responses in chimpanzees, while Siglec-5 is not upregulated in humans during lymphocyte activation, allowing increased lymphocyte activity (205). Humans and chimpanzees also express paired Siglecs, which, although they recognize similar ligands, have opposite signaling properties. One possible explanation is that microbial pathogens evolve the capacity to exploit inhibitory Siglecs

during infection, and as a response activating Siglecs evolve as a host response. Thus receptor pairs such Siglec-5/-14 and Siglec-11/-16 are the consequences of a host/pathogen "arms race." In contrast to chimpanzees, the activating members of both pairs undergo polymorphic pseudogenization in human populations (152, 262, 433, 434). There are several other distinctly human changes in the CD33-related Siglecs (435).

As mentioned earlier, humans do not synthesize the cell surface sialic acid *N*-glycolylneuraminic acid (Neu5Gc), commonly found in most other mammals. This is due to a loss-of-function mutation in the single copy gene encoding the enzyme CMP-Neu5Ac hydroxylase 2–3 (*CMAH*) million years ago (436). This biochemical change affects most human cell surfaces and could underlie the subsequent adaptation of Siglec-9, members of the family of the CD33-related Siglecs (CD33rSiglecs) (437), and as mentioned earlier CD33-related Siglecs are innate immune lectins found on most immune cells and some other cell types and are thought to mostly dampen immune cell activation via inhibitory motifs (immunoreceptor tyrosine-based) on their cytoplasmic domain. Recombinant chimpanzee and gorilla Siglec-9 proteins strongly prefer binding to Neu5Gc, but recombinant human Siglec-9 binds to both Neu5Ac and Neu5Gc. Studies indicate that this shift in binding preference is representative of the other CD33rSiglecs (438, 439). Chimpanzee Siglec-12 was also found to preferentially bind Neu5Gc (259) but in humans has lost all binding function (260), and ongoing negative selection is currently driving the loss of expression of this nonbinding protein (327,328, 440). Thus the Neu5Ac-binding ability of at least some of the human CD33rSiglecs appears to be a derived state, which was apparently selected for following the loss of Neu5Gc and with it the change in self-associated molecular patterns in the hominid lineage.

Human T lymphocytes express little to none of the CD33rSiglecs receptors, a striking exception among immune cell types (441). T lymphocytes from African and Asian apes display several CD33-related Siglecs. The loss of T-cell Siglec expression specific for humans occurred in the lineage leading to humans, potentially decreasing inhibitory immune signaling. This possibly explains why human T cells react with higher proliferation than chimpanzee T cells when activated by antibodies targeting T-cell receptor complexes. The hyperactivity of human T cells could underlie the observed difference in T-cell-mediated pathology incidence between *Homo* and *Pan* (149).

Mammals express proteins such as Trim5 alpha or APOBEC that inhibit retroviral replication and retrotransposition by LINE-1 elements (long interspersed nuclear elements, the largest class of transposons in the human genome). Trim5 alpha, a splice variant of the Trim5 gene, encodes a protein that inhibits retroviral replication of these retroviruses and other molecular parasites (442). These proteins seem to have species-specific activities, and the human version is strongly restrictive *of Pan troglodytes* endogenous retrovirus (PTERV). This possibly explains the absence of these endogenous retroviruses in the genome of humans. Gorilla Trim5a on the other hand shows better restriction of HIV, but neither orangutan nor gibbon Trim5 alpha shows restriction of either HIV1 or PtERV (443).

These mutually exclusive restrictive activities of Trim5 alpha may indicate the existence of trade-offs between activity against different retroviruses. APOBEC proteins represent another example of innate antiviral defense. APOBEC proteins are cytidine deaminases, mutating minus strand DNA of retroviruses from C to U during reverse transcription, resulting in G to A mutations in the genomic sense strand. The human genome contains 11 different APOBEC genes. These "nucleic acid mutators" induce hypermutation in the genome of viruses, likely reducing the fitness of viral quasispecies. The Vif protein encoded by the HIV genome counteracts this host defense by inducing ubiquitination and subsequent degradation of APOBEC3G (444). Differences in Trim5 alpha and APOBEC between humans and chimpanzees are minimal, but both loci show signs of positive selection, likely due to antagonistic coevolution with past retroviral genes. These differences are unlikely sufficient to explain the apparent difference in susceptibility to HIV1 (445).

Meanwhile, human endogenous retroviruses (HERVs) and the related nonautonomous mammalian apparent LTR- retrotransposon (MaLRs) occupy ~8% of human genomic DNA (446). Most are now replication defective and fixed in the population. Some HERV-K elements however remain polymorphic in our species. HERV-K113, for example, retains intact open reading frames and produces viral particles in vitro (447). Moreover, replication-competent HERV-K elements from in silico-derived consensus sequences have been reanimated experimentally (448). Certain human tumors express HERV-Ks, and it has been suggested that HERV expression may play a role in cancer etiology and certain neurological and autoimmune diseases. Both chimpanzee and gorilla genomes have been bombarded by independent endogenous retrovirus (ERV) infections ~3–4 million years ago (426). Gorillas and chimpanzees may still harbor active ERVs, and their genomes may be relatively more permissive for endogenous retrovirus. Meanwhile, most primate species are frequent hosts to nonpathogenic retroviruses called Foamy viruses (SFV). These appear to be almost commensal and are not associated with any known pathology (319). SFV infection rates >20%

have been documented in wild chimpanzees, but human SFV infections seem to be absent, except for individuals who have regular contact with nonhuman primates (320). There is no explanation for the lack of endemic human SFV infection, given that humans can be asymptomatically infected and can even become asymptomatic long-term carriers of SFV. It is safe to assume that the common ancestor of humans and chimpanzees harbored the virus, which raises the question as to how endemic SFV and other endemic retroviruses were purged from the human population.

Humans infected with human immunodeficiency virus (HIV) tend to succumb to a rapid collapse of their adaptive immune system (AIDS, primarily caused by a loss of CD4+ T cells). Prior to the availability of highly effective antiretroviral drug regimes, an infected person's immune system collapse happened within a few years of infection. The pandemic HIV-1 virus responsible for the AIDS pandemic has its origin in wild chimpanzees of west-central Africa in the 1900s. HIV-2, another, less common virus causing AIDS, originated in sooty mangabey monkeys in west Africa (449). Both chimpanzees and mangabeys show limited detrimental effects due to infection with their respective lentivirus, although some wild East African chimpanzees infected with simian immunodeficiency virus (SIVcpz) have been reported to suffer heightened mortality (450). Some chimpanzee populations exhibit signs of adaptive evolution of CD4 coreceptor glycoprotein (451). Experimental infection of chimpanzees with human HIV isolates, only rarely led to the typical progression to AIDS (331, 332). Some chimpanzee populations in the wild have high rates of SIVcpz infection, with some individuals manifesting AIDS-like syndromes. However, the disease is milder and follows a different time course (450). The different outcome of HIV infection in chimpanzees and humans has not been explained to date. HIV infection in humans appears to result in more T-cell death, possibly associated with differences in T-cell activation described above. The rare humans who are resistant to HIV infection ("long-term nonprogressors") seem protected by other unique mechanisms involving rare, broadly neutralizing antibody production (452).

3.5. The Lymphatic System

The human and chimpanzee spleen look similar on routine histology stains, but when lectin stains are done, one can appreciate differences in architecture (453). This may explain the tendency of the human spleen to be irreparably lacerated in fatal vehicular accidents when traveling on modern highways. (454). The chimpanzee spleen has a lot more supportive trabeculae, and there is evidence of stored heme iron in the splenic macrophages, which is obvious on histopathological examination (455).

The thymus lies under the sternum, just above the heart in the thorax, and is very prominent in young individuals and then becomes smaller with age. In humans, the epithelial component in the thymus is prominent. The chimpanzee and human thymus have similar morphology. There is an outer cortex made up of immature T cells, and the medulla has more mature cells with more cytoplasm thus the medulla appears lighter in color. Lymphomas, which are composed of B cells of a proliferating single clone (more commonly) or of T cells, are not uncommon in aged chimpanzees, unlike carcinomas, which are rare in chimpanzees but common in humans (303).

3.6. The Hematological System

A comparison of human and great ape hematology found several differences of yet-unknown significance. Humans have a significantly lower white blood cell count, including neutrophils (456), Among the great apes, leukocyte counts varied (from highest to lowest: bonobos, chimpanzees, orangutans, and gorillas), but all species tested had a higher count than humans (457). Proteomics of plasma proteins have revealed overall similarities in blood protein composition in two-dimensional gels, but differences in levels of transthyretin (TTR; retinol binding protein) were apparent between humans and the African apes. Unlike other nonhuman primate species, none of the African apes have all four ABO blood types (458, 459).

3.7. The Respiratory System

The nasal passages are lined by respiratory epithelium and have underlying lymphoid collections, which help with immunological defenses. Humans and African apes have sinuses within the cranial bones, which help to lighten the skull and the load on the vertebrae to help with upright walking. The human nose characteristically has its nostrils facing downward, whereas all apes have nostrils oriented upwards (forcing them to hold items above their noses when sniffing them). The apes and larger gibbons also have air sacs, which may allow fast extended call sequences without the risk of hyperventilating because they can rebreathe exhaled air from their air sacs (460). Meanwhile, the formation of the human paranasal sinuses appears unique, not seen in old-world monkeys (461–464). As in humans, the left lung of the chimpanzee is divided into upper and lower lobes, and the right lung is separated into upper, middle, and lower lobes but does not seem to have an azygos lobe (465, 466).

Humans, similar to other primates, have a stiff chest wall compared with other mammals. This feature of primate anatomy gives rise to a relaxed lung volume known as functional residual capacity, which comprises a large percentage of the total lung capacity (467, 468). Dynamic flow parameters, similar to forced expiratory volume commonly used in human patients, have also been measured in nonhuman primates and found to be similar to dogs but larger than that in humans when normalized to lung size (469, 470). Forced oscillometry has been established as a common method of measuring pulmonary resistance and dynamic compliance, and monkeys have been evaluated (468, 471, 472). Other studies in monkeys suggest that peripheral airways contribute about one-third of lung resistance in response to bronchoactive agents (467).

The human vocal tract shares many similarities with that of nonhuman primates (473), and the descent of the human larynx during ontogeny has also been documented in chimpanzees (474). Thus the capacity for speech is unlikely due to anatomical differences in the vocal tract but rather to nervous control of its properties. However, a recent comparative study of primate vocal tract anatomy combined with modeling of sound production revealed uniquely simplified laryngeal anatomy in humans (475).

Interestingly, in humans with congenital central hypoventilation syndrome (also called "Ondine's curse"); autonomic respiratory control is lost due to malfunction of central control of respiration in the brainstem, which is associated with PHOX2B mutation (476). Chronic obstructive lung disease, a human malady involving chronic bronchitis or emphysema, has not been described in chimpanzees (465, 477). Nonhuman primate models of respiratory disease have used chimpanzees for respiratory syncytial virus and influenza A (478, 479). There were recent reports of outbreaks of respiratory tract infections in chimpanzees at two different sites with human respiratory tract viruses (pneumovirus, respiratory syncytial virus combined with *S. pneumoni*ae, and rhinovirus) (480–482).

Infection with the influenza A virus (IAV) is an important zoonotic virus affecting humans globally. IAVs evolve rapidly and alter their antigenic determinants (shifts and drifts) contributing to global human epidemics and pandemics. Chimpanzees have been experimentally infected with IAV to establish transient infection without evidence of severe symptoms. However, the inoculation required an extremely high concentration of viral inoculums, which was directly delivered to the bronchii (483). Many facilities with captive great apes assume that humans can infect the apes with IAV; however, infection with IAV has not been documented in captive or wild apes by antibody screening and viral isolation (484). In contrast, several other respiratory viruses can efficiently infect apes and cause more severe disease including in wild populations (480, 485).

A study of upper airway glycosylation patterns revealed that the cells of the upper airways of chimpanzees lack high densities of α2-6-linked sialic acid, the preferred binding molecule of human-adapted IAV (321). The more modest T -cell reactivity could also underlie the limited symptomatic response to experimental IAV infection in chimpanzees. Finally, exposure to smoke from the environment, indoor fire use, or smoking has a huge impact on human airways and health. It has been hypothesized that regular fire use, group life, and spoken language could have contributed to uniquely human airway disease patterns (234).

3.8. The Cardiovascular System

While the morphology of the heart in different hominoid species is very similar, some important differences have been described. In chimpanzees and gorillas, the left ventricle (LV) is thick walled, spherical, and hypertrabeculated, suggesting an adaptation to counter surges in BP during intense resistance physical activity (486). In contrast, the human LV is comparatively thin walled, elongated, and minimally trabeculated, which could improve ventricular compliance (487), untwisting velocity, and diastolic tissue velocities, so that it can generate prolonged and elevated cardiac outputs to adapt endurance physical activity (487). Torsion of the heart muscle in humans occurs in a counter-clockwise manner (487), unlike the more symmetrical contraction in the chimpanzee heart (486). A comprehensive study about the innervation of the heart [autonomic cardiac nervous system (ACNS)] among the nonhuman primates provided that ACNS morphology is consistent between new-world and old-world monkeys (but significantly different from humans) (488). There are many more capillaries in human hearts as compared to chimpanzee hearts (304). All of these differences may help explain why humans can run for sustained periods for long distances and for prolonged amounts of time.

The histology of the heart in different species is very similar among primates: cardiac muscle myocytes are striated with central nuclei, and skeletal muscle is also striated but has peripherally located nuclei. Recent studies found up to 50% differences in gene expression between cardiomyocytes derived from either human or chimpanzee-induced pluripotent stem cells (iPSCs) (489).

Cardiovascular disease is one of the major causes of mortality in captive great apes (490). Human blood vessels and aortas usually show evidence of atherosclerosis (in humans, "cardiovascular disease" almost always

equals coronary heart disease) whereas in the great apes, atherosclerosis is much less pronounced, and tends to be in the basilar arteries in the brain (491). In captive great apes, idiopathic myocardial fibrosis (IMF) without significant atherosclerosis lesions is much more common, despite their human-like coronary-risk-prone blood lipid profiles (304, 492–496). In humans blood vessels also develop aneurysms, some of which may be congenital, with severe bleeding leading to mortality and morbidity; however, aneurysms are rare in great apes with only a few known cases documented in gorillas (497, 498). It is likely that aneurysms are uncommon in the chimpanzee, but there is insufficient data to be sure (499).

Meanwhile, electrocardiogram and echocardiogram (500–503) as well as biomarkers such as N-terminal pro-brain natriuretic peptide (NT-proBNP) and cardiac troponin T (cTnT) (504, 505) have been applied to measure cardiac function or diagnosis of cardiac disease in nonhuman primates. Cardiac arrhythmias associated with IMF were reported among male chimpanzees (502, 506, 507), and a gorilla case of coronary heart disease (508). High-resolution microcomputed tomography revealed the presence of cartilage and/or bone formation in the cardiac skeleton (termed as "os cordis") in chimpanzees, suggesting the etiology of IMF (509).

3.9. The Urinary System

Anatomically the human and chimpanzee urinary systems are similar, although several human-specific diseases are discussed below. The kidneys are composed of an internal medullary portion and an external cortical region. The medulla is organized into a series of conical structures, which are described as renal pyramids. The number of pyramids in the medulla is one pyramid in most primates (the chimpanzees, lemurs, tarsiers, and the anthropoid apes); however, humans and spider monkeys show multipyramids (510). There is no significant difference in renal histology between humans and other primates: the renal cortex sends tongues down between the pyramids, and blood vessel networks run through the nephrons for filtration and reabsorption, which are composed of glomeruli and tubulus. Neu5Gc sialic acid could associate with hemolytic uremic syndrome (HUS), characterized by progressive kidney injury: red meat-derived Neu5Gc is accumulated in the cell surface of endothelial and epithelial cells of the colon and then subtilase cytotoxin (SubAB), one of Shiga toxin of *Escherichia coli*, attacks the Neu5Gc-positive human cells (511).

The characteristics of salt handling by the kidneys have shown that captive chimpanzees on a high sodium diet developed high blood pressure as in humans (512). The urinary protein-to-creatinine (UPC) ratio in healthy adult captive chimpanzees seems to be similar to that of humans (513). Notably, aging could increase UPC (513) and glomerular sclerosis and tubulointerstitial fibrosis, which is accompanied by heart fibrosis (514), suggesting that disease and dysfunction of the heart could leads to progressive renal dysfunction, known as "cardiorenal syndrome" in humans (515–517).

Pyelonephritis (bacterial infections of the kidney) is relatively common among nonhuman primates, and it could be associated with *Umod* (Uromodulin, also known as Tamm-Horsfall protein) alleles, which are significantly correlated with pathogen diversity and prevalence of antibiotic resistance (518). A gene comparative study in polycystic kidney disease 1 (*PKD1*), whose mutation causes autosomal dominant polycystic kidney disease (ADPKD) in humans, suggested that *PKD1*-pseudogenes evolved in a common ancestor of humans and chimpanzees (519). Gene editing of *PKD1* has produced a human-like APKD model in cynomolgus monkeys/crab-eating macaques *M. fascicularis* (520). A variety of kidney lesion complications in connective tissue disease (CTD), including systemic lupus erythematosus (SLE), systemic scleroderma, Sjögren syndrome, and rheumatoid arthritis, are relatively common in humans (521) but not observed in nonhuman primates. Spontaneous SLE cases in rhesus macaque (522) as well as alfalfa-sprout dietary induced (523, 524) and 2′-oMe phosphorothioate antisense oligonucleotide induced (525) in cynomolgus macaques have been described, suggesting a variety of autoantibodies may cause CTD in primates as in humans (526).

3.10. The Endocrine System

In contrast to humans, chimpanzee females mature earlier (200). Humans also experience menopause, which is distinctly human due to ovarian follicles becoming too depleted to continue cycling. Although ovulatory cycles and hormone profiles of aging chimpanzees do decline with age, reproductive ability in older female chimpanzees is maintained (200). Chimpanzee males develop benign prostatic hyperplasia, similar to humans (527).

A study of cortisol production as an indicator of senescence of the hypothalamic-pituitary-adrenal axis in a population of wild chimpanzees suggests that impairments are intrinsic to the aging process in hominids (528). An analysis of human and great ape blood plasma found an apparent decrease in transthyretin (prealbumin) in humans, and a change in haptoglobin isoforms. Transthyretin (TTR), transporter of thyroxin and retinol, is found both in plasma and cerebrospinal fluid, where it is the major carrier of thyroid hormone. The quantitative analysis found twofold higher levels of TTR in chim-

panzees compared with humans (458). The same study found significant differences between human and chimpanzee thyroid hormone metabolism, which was the first known endocrine difference. Because of the roles that thyroid hormones play in many organ systems, in particular the development of the nervous system, differences may be involved in many distinctly human phenotypes.

A thyroid hormone database was created to examine levels in chimpanzees, bonobos, orangutans, and gorillas. Compared with *Pan* species, gorillas have reduced free T3 and free T4 and elevated TSH levels. In gorillas and orangutans, antibodies to thyroglobulin and thyroid peroxidase were detected in less than 3% of the animals, but with no thyroid dysfunction, compared to 10% in humans. Hypothyroid nonhuman great apes lacked thyroid antibodies. In addition, Graves' disease has not been described in the great apes (529). Male bonobos have a notably less developmental increase in testosterone than male chimpanzees (530).

The development of the adrenal gland varies among primates, and in humans a functional zona reticularis does not develop until 5–8 years of age, and the concentration of the di-hydro-epi-androstenodione sulfate (DHEA-S) hormone is different between males and female humans. In wild chimpanzees, a human-like pattern was observed, with higher urinary cortisol levels in males compared with females by early adulthood (531).

The oxytocin vasopressin system involving these two pituitary neuropeptides and their receptors is of particular interest due to its potential role in mediating pair bonding and reproductive behavior, as well as social bonding (532). A recent neuroanatomical study of receptors for both hormones in postmortem brains of captive chimpanzees has revealed a contrast between their distribution in subcortical areas of humans and chimpanzees. While vasopressin receptors (AVPR1a) are more widely distributed than oxytocin receptors OXTR in chimpanzee brains, human brains exhibit the reverse pattern (533). The observations included the lack of OXTR in reward regions (the ventral pallidum, nucleus accumbens) in chimpanzees, whereas humans have OXTR in these regions.

3.11. Metabolism

Comparing populations of sedentary humans with similarly sedentary captive great apes, one study found that humans have much higher total energy expenditure than the great apes and that their basic metabolic rate is higher (237). Another study concluded that human metabolic parameters are predicted based on metadata gathered from various sources reporting the metabolic rates of wild terrestrial mammals (238). Humans have more body fat than other apes (534); infants in particular are born with more body fat, which may be another feature involved with supporting the development of large brains (535). Type 2 diabetes occurs in both humans and aging chimpanzees (536). The presence of Siglec-7 on human pancreatic islets, which is not evident in chimpanzee islets, may play a role in the human disease (432). Downregulation of Siglec-7 expression on human β-cells was found in both type 1 and type 2 diabetes, as well as infiltrating activated immune cells. Overexpression of Siglec-7 in diabetic islets reduced cytokines, prevented β-cell dysfunction and apoptosis, and reduced recruiting of migrating monocytes (537). Restoration of Siglec-7 expression in diabetic islets may represent one therapeutic strategy rising from findings in comparative anthropogeny. Studies of human and nonhuman primate metabolomics have provided evidence for many more differences between humans and nonhuman primates, as compared to chimpanzee macaque differences (538). These studies are still limited to industrialized human populations and restricted to captive ape populations but provide evidence for possibly ancient shifts in metabolic processing of humans, predating the introduction of starch-rich farming diets and industrialized processed foods.

3.12. The Reproductive System

The reproductive biology of humans has become profoundly embedded in cultural norms and technology: from culturally determined marriage patterns, each with different optimal criteria for admissible degrees of consanguinity between marriage partners, to the latest developments in assisted reproduction involving ever more invasive technology and even third parties (sperm and egg donation and surrogate pregnancy).

The existence of arranged marriages in over half of foraging societies studied attests to the strong role of social and third-party control of human reproduction (539) and so does the existence of social norms regulating sexual behavior. Most traditional human societies are mildly polygynous, but (serial) monogamy and pair-bonding seem to be a widespread mode of human mating pattern (540). Like all the great apes, human females spontaneously ovulate, and human females share a lack of overtly advertised ovulation with orangutans and gorillas (541). This contrasts with the two species of the genus *Pan* where multimale, multifemale (polygynandrous) mating systems are accompanied by overt advertising of ovulation by conspicuous perineal swelling as large and as conspicuous as an ape's face. Several reproductive features appear derived in the genus *Pan* ranging from relative testis size, to penile morphology

(coevolved with the large swellings) gamete number and energetics, to the presence of copulatory plugs, all related to the high levels of sperm competition in chimpanzees and bonobos (541).

Placental morphology is remarkably similar between humans and the great apes, but certain genes appear to be uniquely expressed in the human placenta including Siglec-6 (148). The rate of spontaneous loss of pregnancy (early fetal wastage) appears to be higher in humans than in chimpanzees, with little comparative data on the other apes (542). Gestation time is slightly longer in humans, and birth is much less predictable and much more complicated involving prolonged labor. The large size of the human neonate head makes for a very precarious passage through the birth canal, unlike seen in any of the great apes, and makes for obstructed labor in 3 to 6% of births globally (543). The human brain's relatively large size produces an obstetric challenge and causes a fraction of all human births to be traumatic with 3–6% of all global births involving traumatic labor (544, 545). The distinctly human rotation of the fetus during gestation is also related to a large head size at birth (546). The skeletal system evolved several distinctly human adaptations, in both infant and mother, to overcome this challenge. At birth the five skull plates of infants remain unfused, to allow easier passage through the vaginal vault. The skull bones are separated by membranous partitions (fontanelles) which allow the plates to move against each other during passage through the narrow pelvis (547, 548). The human fontanelles fuse between the ages of 2–3; however, the chimpanzee fontanelles fuse within the first few months of life (549). Premature fusion of the human fontanelles leads to craniosynostosis, microcephaly, and subsequent neurological deficits (550). As compared with chimpanzees, the human pelvis has a large circular birth canal (551). This trait begins to appear in the fossil record in the middle Pleistocene era *Homo* (552) and is divergent from reconstructions of a female Neanderthal pelvis indicating that modern human childbirth appeared in the last several hundred thousand years (553). Sherwood Washburn called these competing phenotypes the "obstetric dilemma" (554). Recently, a comparison of prenatal growth rates between human and ape shoulders revealed that human fetuses exhibit a slowing in the growth rate of the shoulder, possibly adapted to obstetric constraints (475).

Because of human babies' rotation in the birth canal, they are born facing away from the mother and help from others is needed during human birth (545, 546). Among other living primates, which can give birth without assistance, obligate midwifery appears to be specific to the human lineage and an example of gene-culture interaction (555). Singleton birth is the norm in humans as in the great apes, but fraternal twinning can be common depending on the population. Human fecundity appears relatively low, and it has been hypothesized that this could be an adaptation to pair bonding (556). Unlike other primate species, humans form lasting pair bonds within large multimale, multifemale social groups and engage in reciprocal exogamy between social groups (557).

Menopause is survived by the majority of human females, whereas great ape females die around the time or shortly after running out of oocytes (200). Menopause in humans was first suggested as an adaptation by Williams (558) and Hamilton (559) proposed kin-selection advantages for grandmothers. Humans have also been characterized as cooperative breeders, which puts our species apart from all the great apes, but there are other primates who evolved cooperative breeding (191). The striking features of human reproduction are thus later onset of sexual maturity, complicated birth, shorter duration of lactation and shorter interbirth intervals, and the fact that human infants are much more altricial and helpless than great ape infants. The existence of infertile grandmothers seems contrary to the concept of "antagonistic pleiotropy," which posits that natural selection cannot operate in late life (559) to prevent aging. However, in keeping with the grandmother hypothesis (560), we have recently noted that humans harbor many uniquely human-specific alleles that directly or indirectly protect the functionality and cognition of such elderly caregivers. Most of these alleles are not present even in Neanderthals, and other archaic hominin lineages, suggesting that grandmothers are unique to modern humans and may have played a key role in the dominance of our species (439). The existence of long, postreproductive survival for females also brings with it strongly altered operational sex ratios, as surviving and still fertile older males compete with younger rivals, and this might have contributed to the evolution of human pair bonding as a form of mate guarding (561).

Upon analysis of gene microarray data, an unusually high level of the *SIGLEC11* transcript in human ovaries and adrenals was observed. This finding was explored further by examining specimens of ovaries and adrenals from multiple humans and chimpanzees. Siglec-11 protein expression in the adrenal gland was variable and seemed to be confined to infiltrating macrophages in capillaries. Western blot and immunohistochemistry analyses confirmed Siglec-11 protein expression in both human and chimpanzee ovaries. However, expression was not primarily on hematopoietic or immune cells but was rather located on ovarian stromal cells in humans and on ovarian tunica fibroblasts in chimpanzees and in ovarian stromal fibroblasts in ovaries from patients with polycystic ovarian syndrome, which appears to be a uniquely human condition (434).

Neisseria gonorrhea is an obligate human pathogen that causes mucosal surface infections of male and female reproductive tracts. Infections commonly begin at the cervix and ascending infections cause fallopian tube pathology leading to inflammation and pelvic inflammatory disease. Asymptomatic infections in women can lead to long-term consequences, which are catastrophic to the reproductive health of certain populations. Through the evolution of interactions with human but not chimpanzee Siglecs, *N. gonorrhea* modulates the human inflammatory response in a species-specific manner (312, 439).

3.13. The Nervous System

Our earlier discussions of life history, gene-culture coevolution, focused on the human brain as an organ of unusually plastic function, illustrating some of the paradigms in which behavioral and psychological features are critical in the complex interplay of the biological, cultural, and psychological in the human phenomenon (see **FIGURES 5 and 8**). Because of this central role of the brain within the human phenomenon, it is particularly interesting to investigate the neurophysiology of humans compared with that of other primate species.

Because of the massive metabolic expenditure of brain tissue, large brains come at a high cost (237), which must be justified by the many critical roles the brain plays in the evolutionary specializations of *Homo*. The human brain is three to four times in volume compared with the chimpanzee, and many open questions in anthropogeny are directly related to cognitive capacities ranging from symbols to language and fire use (**FIGURE 9**) (562). Encephalization quotient (EQ) is a measure that represents the ratio of a species' brain size to body size relative to other mammals. By Jerison's 1973 EQ calculation, the human brain is approximately seven to eight times the expected size relative to other mammals (563).

The fossil record has revealed some information about the timing of human brain expansion, which was largely accelerated between the origin of the genus *Homo* (~2.5 million years ago) and the species *H. sapiens* (~0.5 million years ago) (**FIGURE 10**) (240). *H. heidelbergensis*, *H. neandertal*, and *H. sapiens* have a similar brain volume, but the brain of the anatomically modern human is morphologically distinguished by its increased globularity (565). Cranial fossils can reveal information about brain size and shape, but like other soft tissues we must depend on comparative studies in living organisms to learn more about the evolution of the human nervous system. More recently, the application of modern functional neuroscience to a comparative anthropogeny approach has offered insight into functional comparative neurology (566).

The mammalian brain is composed of the cerebrum, cerebellum, and brainstem. The two cerebral hemispheres are divided into lobes, each of which contains

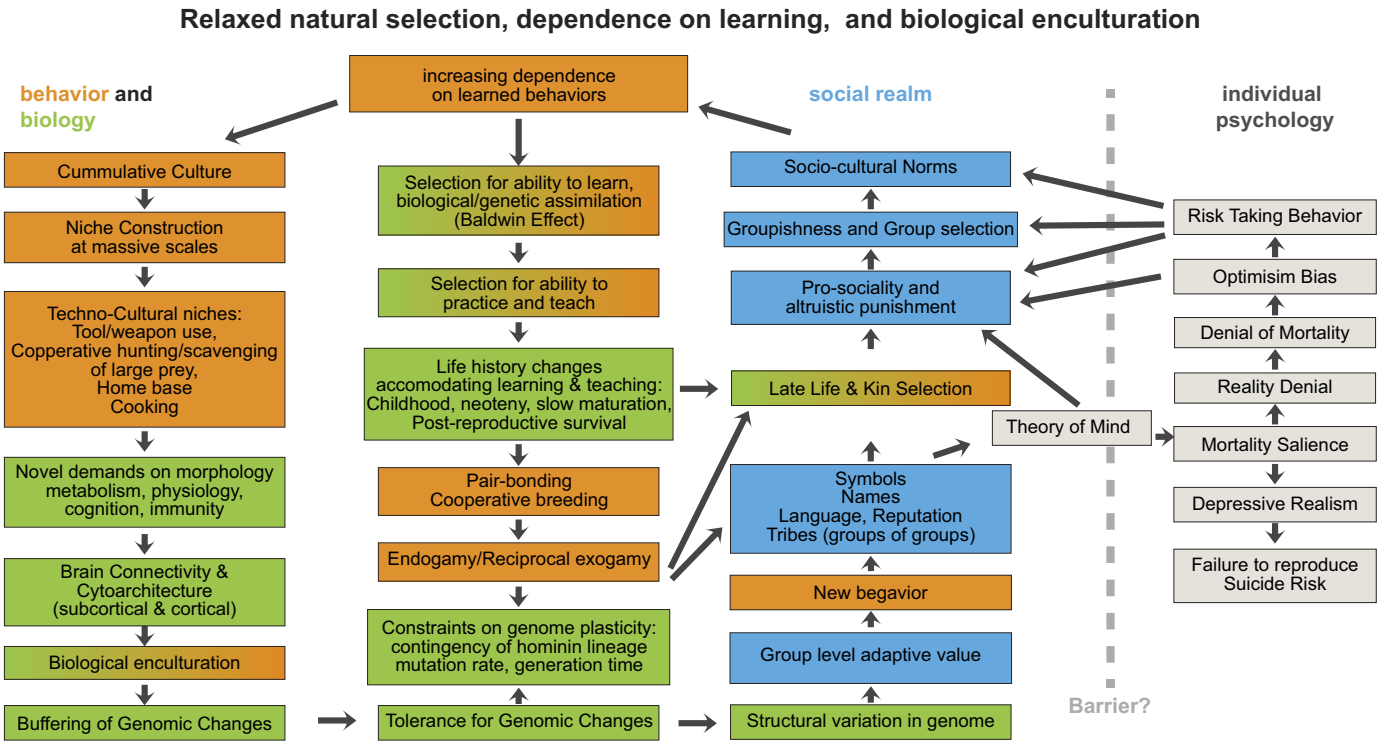

FIGURE 8. Many elements are at play in the evolution of uniquely human traits, including gene-culture interactions and behavior feedback.

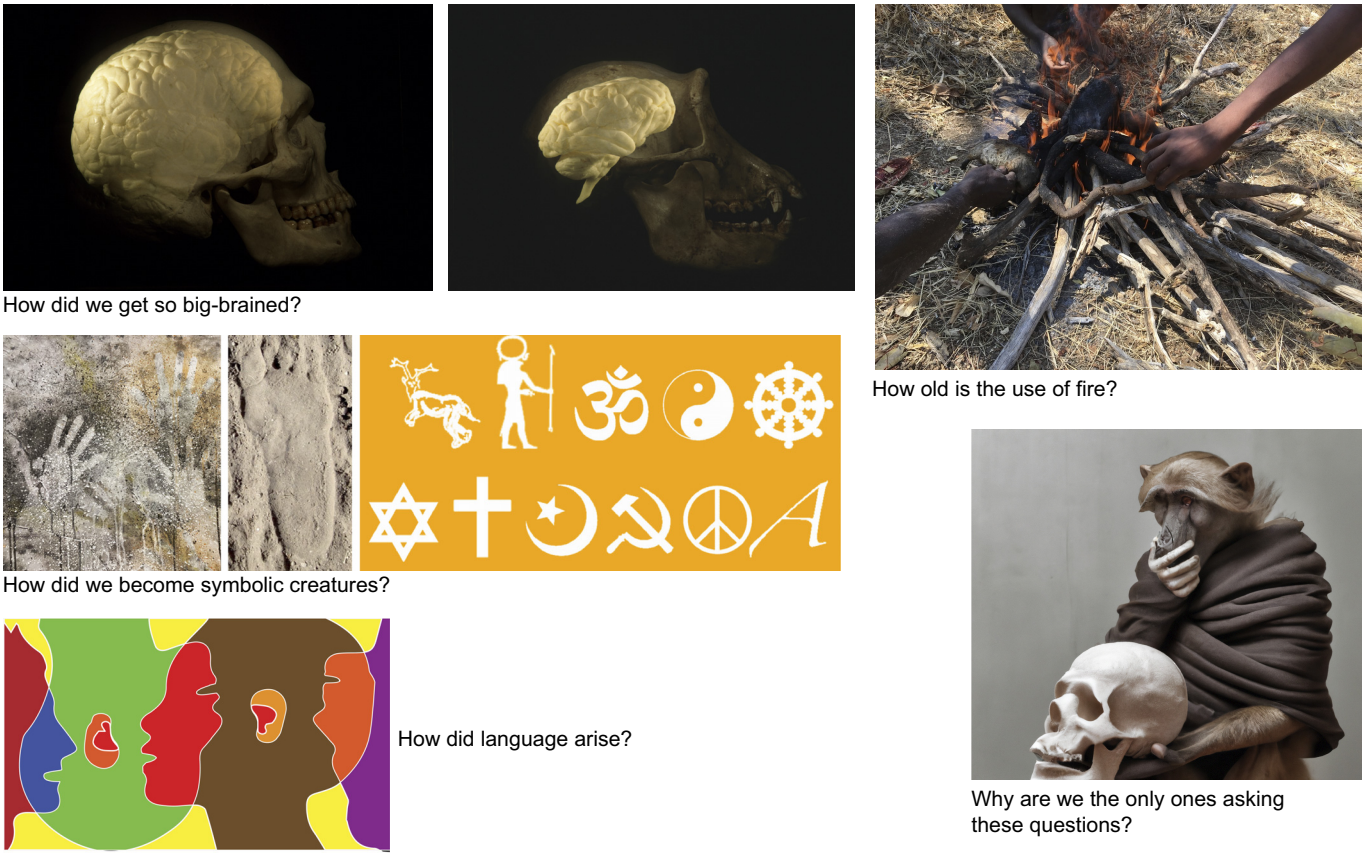

FIGURE 9. There are many unanswered questions about human minds. Human ape skull/brain image copyright Kenneth Garret, used with permission. Baboon with skull was generated by Dalle2.

areas serving specific functions. Korbinian Brodmann's (567) early histological studies compared the brains of humans and other mammalian species, revealing differences in the apparent cortical structures . Brodmann (568), and later others (569, 570), suggested that the large human prefrontal cortex evolved since the human-chimpanzee divergence, and contains novel areas in the human lineage. Alternatively, Ralph L. Holloway (571) proposed that cortical areas are in fact conserved throughout primates and that human brain evolution involved a dramatic reorganization of cells and molecules within and between these conserved areas. This theory was foretelling of findings that would come over the following decades with the development of methods for cellular, molecular, and imaging studies of human and ape brains. Notably, Semendeferi et al. (572–574) used magnetic resonance imaging to compare the relative proportions of brain sectors between groups of living humans, chimpanzees, bonobos, gorillas, orangutans, and gibbons. By including many species of great apes instead of one species or none, imaging live brains instead of postmortem (which experience shrinkage during preservation), and using larger groups instead of one or two individuals, these studies provide reliable data contradicting the conclusion that humans have a distinctively large prefrontal cortex. The human prefrontal cortex is not statistically larger than expected among apes, as apes have a large prefrontal cortex compared with primates, as well as primates compared with other mammals. This finding evokes Holloway's 1966 proposal that distinctively human traits involve reorganization within the brain, somewhat analogous to King and Wilson's theory that the human genome depends upon reorchestrating the expression of existing genes to produce distinctive phenotypes. Indeed, humans show increased levels of differential gene expression in the frontal lobe (167).

Many of the most striking findings of comparative genomics and transcriptomics are changes in regulatory elements and gene expression modules associated with neurodevelopment (575). We discussed some of these findings in previous sections on comparative genomics and genetics and comparative studies of gene expression and networks. Human accelerated regions, which are primarily associated with regulatory elements, are most likely to be neurodevelopmental enhancers (180). The timing of gene expression patterns is largely slowed down during postnatal development in humans (170), in particular genes associated with synaptic maturation (576). The neurological neoteny that these gene expression changes produce may be largely responsible for

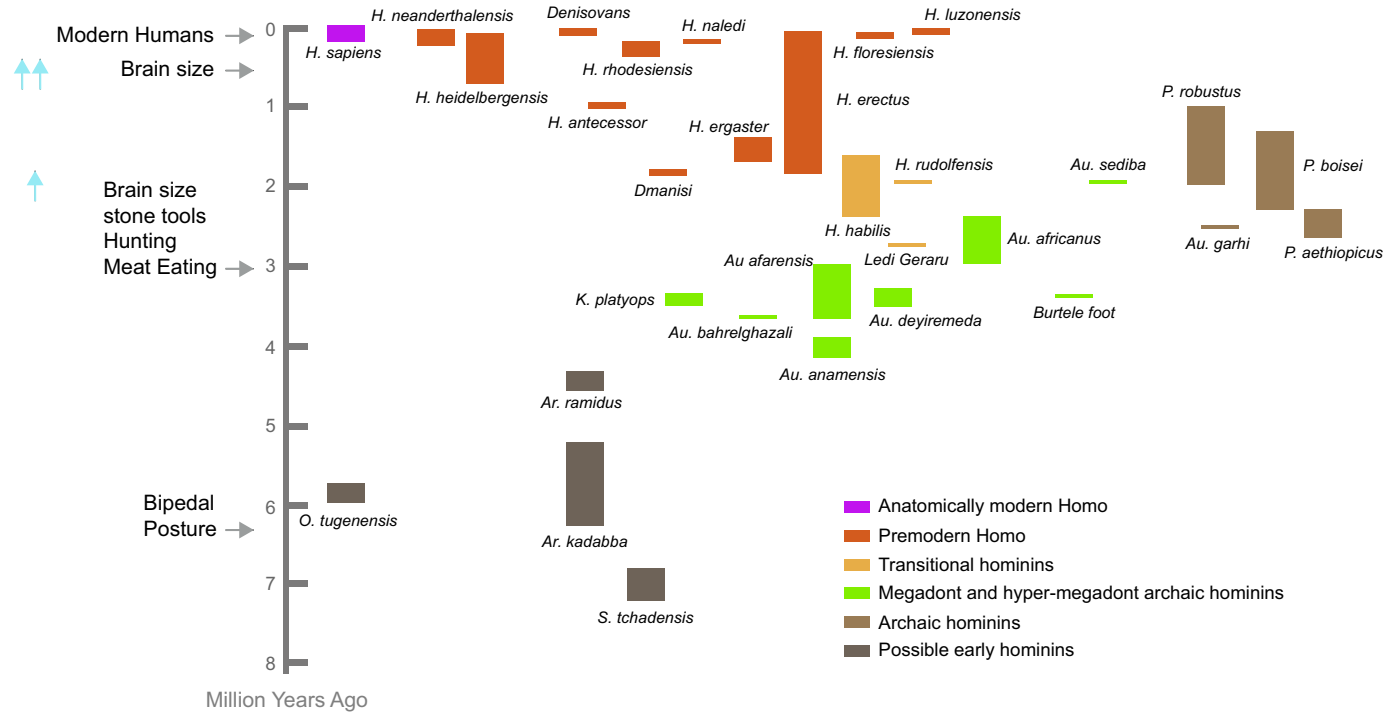

FIGURE 10. Overview of hominin fossils, visualized as a timeline of proposed taxa (image inspired by Ref. 564).

the reorganization that Holloway predicted. A comparison of chimpanzee and human myelination highlights the slowness of human brain development: myelin levels continue to increase in humans through the third decade of life, while chimpanzee brains reach final adult-like levels of myelin around the time of sexual maturity (209). Comparisons of lipid composition of the brain have revealed key differences in lipid profiles (lipidomes) and in rates of change in lipid profiles between humans, chimpanzees, and macaques, reflecting the long delay in retention of similar lipidome in humans possibly associated with prolonged myelination mentioned above (577).

Cultured neural progenitor cells produced from human- or chimpanzee-induced pluripotent stem cells also reflect human brain neoteny. Human cells have altered cell cycle dynamics with a prolonged metaphase (578). Human cells migrate more slowly and take longer to differentiate into mature neurons than those of chimpanzees or bonobos both in vitro and when transplanted into mice (579).

Outer radial glia cells (oRGCs), the stem cells that give rise to cortical neurons, are increased in number in humans and in primates compared with mammals (580). In humans, clonal expansion of oRGCs in the subventricular zone increases the final number of mature neurons (581). Human astrocytes are also distinctive in their complexity (582).

Differences in cytoarchitecture include density of minicolumns, neuropil space, dendritic arborization, and synaptic density (566). The motility of nascent neurons is higher in chimpanzees than in humans, but human neurons reach further (578).

Studies using methods in functional neuroscience to study connectivity have found interhemispheric connectivity, versus intrahemispheric and more local connectivity in humans (583). The human arcuate fasciculus, which connects areas Broca's and Wernicke's areas and is important for language and speech, is strongly expanded in humans compared with chimpanzees and also contains projections to the middle and inferior temporal cortex as visualized by diffusor tension imaging (207). Studies using magnetic resonance imaging have shown human-like asymmetries in the amygdala and hippocampus "social brain" in chimpanzees, and recent study showed a decrease in grey matter volume in aging chimpanzee brains, similar to that observed in humans (584, 585). Studies of aged chimpanzees have revealed plaques and tangles in the hippocampus and neocortex in the brains of aged chimpanzees, similar to what is seen in humans with Alzheimer's disease; however, the memory impairment seen in humans has not been documented in chimpanzees (586). Cerebrovascular accidents leading to a stroke and disability seen in many humans are rare in chimpanzees (587).

NOVA1, a gene coding for a splicing factor, is an example of a single nucleotide change resulting in an amino acid change in the protein NOVA1. Experiments in iPS-derived brain organoids have revealed that this

small change in DNA sequence, distinguishing modern humans from apes and archaic hominins alike, has major effects on the expression pattern of >100 genes during in vitro neurogenesis, affecting brain organoid shape and neuronal activity patterns (including levels of synchronicity) in this model system (71). The NOVA1 work faces the major limitation that an archaic variant was introduced into a fully modern human genome, similar to the limitations of introducing human sequences into a laboratory animal. One important consideration with CRISPR-Cas9 editing is the potential for deletions rather than the intended substitution, which may have played a role in the dramatic phenotypes identified by Trujillo et al. (74).

Recent work in transgenic marmosets, genetically modified to express a human variant of the gene *ARHGAP11B* under the control of the human promotor, increased the numbers of basal radial glia progenitors in this new world primate's outer subventricular zone (115, 588). The transgenic animals had several notable phenotypes including increased upper layer neuron numbers and neocortex volume, leading to folding of their cortexes, unlike wild-type marmosets, which are lyssencephalic. Thus the human-specific ARHGAP11B gene appears to drive changes in development in marmoset that reflect changes in evolution that characterize human neocortical development (589).

Examples of other human-specific genetic changes that have been studied include a uniquely human splice variant of KLK8 that affects learning and memory (590), FOXP2 in language and speech, SRGAP2C in dendritic cell morphogenesis (591, 592), and microcephalin involved in brain development (116, 593,594). Recent work has provided evidence for a strong effect of uniquely derived variants of two proteins (KIF18a and KNL1) in modern humans, as the transgenic expression of these modified proteins in neuronal cells results in longer metaphase and fewer chromosomal segregation errors (594).

3.14. Behavior and Cognition

Theory of mind refers to the capacity to interpret and understand the psychological state of another individual. In humans this behavior is instrumental to communication and social organization; however, decades of research have not conclusively identified human-like theory of mind in nonhuman hominin species. Premack and Woodruff's classic 1978 paper "does the chimpanzee have a theory of mind" suggested that chimpanzees are able to predict a human actor's goal (362), a finding that was quickly debated (595), and in 1996, Povinelli et al. (596) designed the "begging paradigm" and found while chimpanzees chose to beg from individuals facing them and not turning their back, they could not discriminate when the experimenter placed a bucket over their head or closed their eyes suggesting that they were not aware of the experimenter's sate of "seeing." This series of experiments is inconclusive as to whether chimpanzees or other nonhuman animals are able to prescribe a state of mind to others. Experimental work with captive great apes clearly demonstrates that these species are capable of symbolic perception (597). Tellingly, however, all symbols used are created by humans and the individual apes require much operant conditioning to acquire their symbolic capacities. There is a complete absence of evidence for symbolic behavior in the wild, whereas all known human groups are profoundly symbolic and linguistic. Human hunter-gatherers rely on the capacity to track injured prey by reading tracks, a capacity never documented in a nonhuman species. The importance of hunting with projectile weapons and tracking prey tracks for symbolic thinking and hypothesis testing has been suggested by Liebenberg (277). There is strong evidence for increased pro-sociality in humans reflected in altruistic helping in human infants (198, 598, 599) and children (199), and the fact that while great ape and human infants are very similar in their acquisition of cognitive skills for dealing with the physical world, human infants exhibit much more sophisticated social skills (600). The combination of full theory of mind, pronounced prosociality, and symbolic combinatorial thinking has given our species a range of novel possibilities and limitations. Another unusual aspect of human cognition is a surprising degree of reality denial in the face of factual or experiential knowledge of realities. It is suggested that this peculiar quirk of the human mind was a necessary mechanism to breach the "Evolutionary Psychological Barrier" of mortality salience (knowledge of one's own eventual death) (see the section on individual psychology in **FIGURE 8**). This Mind Over Reality Theory (MORT) can also help explain many unusual features of the origin and potential fate of our species (601).

4. SUMMARY, CONCLUSIONS, AND PERSPECTIVES

4.1. Molecular Underpinnings of Most Distinctly Human Phenotypes Remain Unexplained

Despite the huge increase in the knowledge regarding genetic differences from our closest evolutionary cousins, the molecular underpinnings of most distinctly human phenotypes remain unexplained. One likely reason is that most genetic changes have pleiotropic

effects (a single gene having two or more apparently unrelated effects (see **TABLE 1** legend).

Many characteristic human features may also not have a direct physiological explanation, as humans also carry important characteristics in cultural and social systems. Medicine, for example, is a strictly cultural invention with deep prehistoric roots, and the results of medical practices in populations around the world now have profound biological implications for humans. The practice of medicine depends on sociocultural values and resources surrounding empathy and compassion as well as trade and commerce. It also depends on the derived cognitive capacity to learn and carefully practice complicated skills, such as interventions of modern medicine that directly affect our biology. The field of medicine itself represents a recent merger of social and natural sciences [a "shotgun marriage" of Snow's "two cultures" (602)]. The global economic value of medicine has also reached astronomical scales with the global cost of the healthcare industry's worth around 10 trillion U.S. dollars.

There are also problems with "humanized" mouse or other model animal phenotypes. The genetic manipulation of model organisms is a powerful approach to discovering biological mechanisms. Laboratory rodents, mostly mice, are by far the most commonly used animal model, as these small mammals share much of the basic mammalian biology with humans, despite their small size and short generation times. Importantly, the lineages leading to mice and humans, respectively, diverged over 100 million years ago and each species has since evolved many important differences in their genomes and overall biology. Evolved traits exist as parts of vast, coadapted gene complexes, and thus the simple introduction of a human sequence into a mouse genome can have strong limitations for relevant interpretation. The independent evolution of gene copy numbers across many gene families and gene regulatory networks, including chromatin structures, means that genomic contexts have changed massively in these two distantly related species.

Biomedical research on chimpanzees is now completely prohibited in the United States and Europe. Humans have become their own best models (603). While numerous field research programs continue to provide new data on the genetics, ecology, and

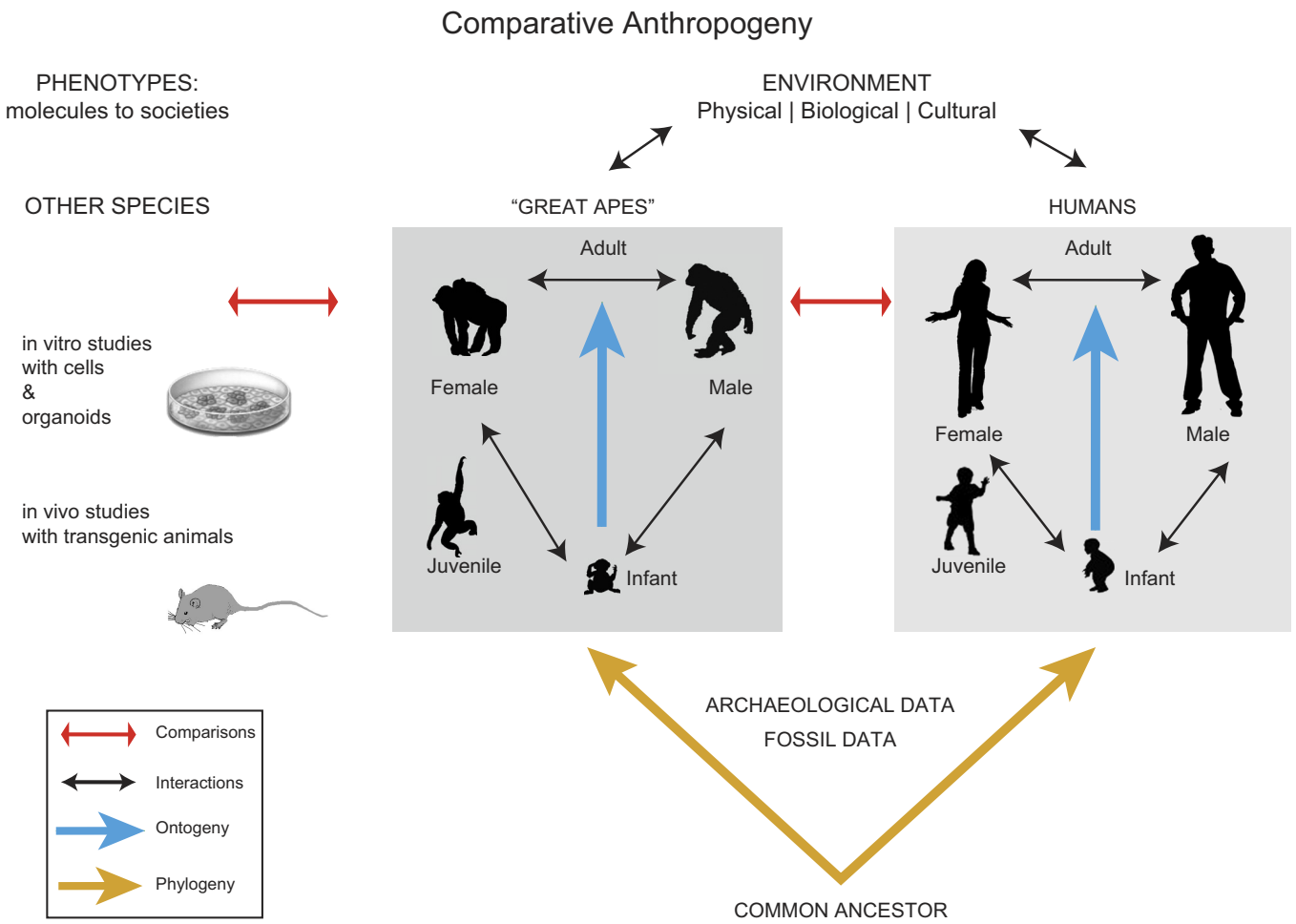

FIGURE 11. Comparative anthropogeny involves ongoing findings in genetics and the use of biological research models.

behavior of living wild great apes, it is practically impossible to study the physiology of these species in the field.

4.2. Most Genetic Changes Have Pleiotropic Effects: Human Loss of CMAH as an Example

If we consider the human loss of CMAH, studies of mice with a human-like disruption of this gene manifest many human-like phenotypes, but the possible mechanisms are diverse and pleiotropic and no single one is usually dominant over the others (see examples in **TABLE 1** legend, likely global changes in cell surface biophysics; ramifications on cell surface receptor localization, clustering, and signaling; and potential reduction cell surface (Neu1) neuraminidase activity. Cytosolic degradation of excess Neu5Gc would generate glycolate (instead of acetate from Neu5Ac breakdown), candidate transcription factors affected by Cmah loss (such as CREB1, C/EBPa and C/EBPb with target genes including IL-6); altered recognition by immunoregulatory Siglecs with Neu5Ac versus Neu5Gc binding preference; and the potential effects of anti-Neu5Gc antibodies interacting with Neu5Gc glycans derived from dietary intake of Neu5Gc ("xenosialitis"). The loss of *CMAH* is a well-studied example of the biological consequences of one genetic change. This example highlights that similar pleiotropic effects must be expected from even minor genetic changes in individual genes or in regulatory sequences. The magnitude of the biological effect may not be clearly predicted from the magnitude of the genetic change.

4.3. The Future of Comparative Anthropogeny

Besides the investigation of human-specific genetic changes, as we discussed in sect. 1.5., several avenues exist for comparative anthropogeny in the coming decades. The advent of ancient DNA studies has added powerful new approaches: the comparison of modern human genomes with the genomes of extinct hominids, such as Neanderthals and Denisovans, which allows the detection of genetic and genomic features clearly derived in modern humans as compared to both the living apes and the archaic hominids who went extinct around 40 thousand years ago (93, 95, 96, 107). The application of machine learning methods to genomic and other data sets promises to reveal new findings (101).

The careful dissection of distinctly human physiology will depend on the comparative approach including genomic, genetic, cell, and organoid-based studies as well as studies in genetically altered model organisms (**FIGURE 11**). Current methods used to capture transcription factor-DNA complexes (ChIP-Seq) and to characterize large-scale interactions between cis-regulatory elements and distant promoter-transcription factor complexes (Hi-C) or other chromatin modifications (ATAC-Seq) promise much

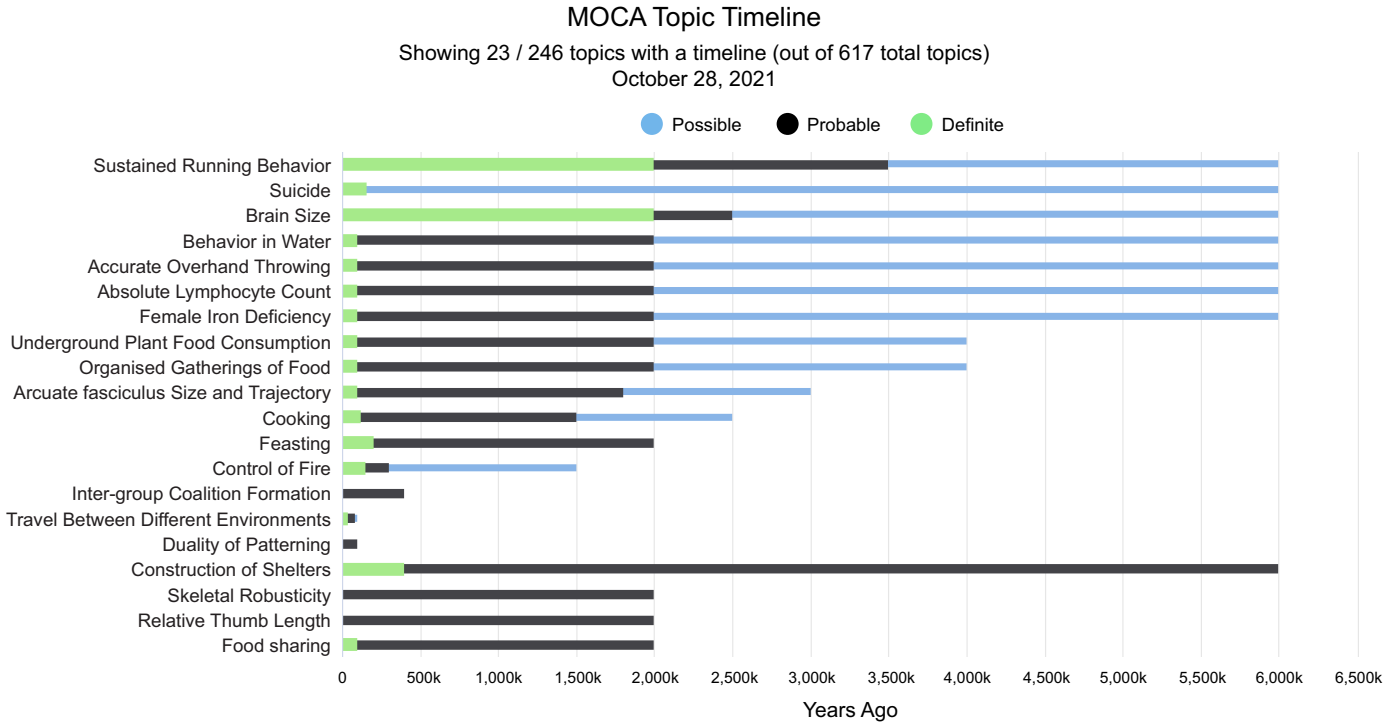

FIGURE 12. Time line of possible, probable, and definite appearance of distinctly human traits. MOCA, Matrix of Comparative Anthropogeny.

needed insights into gene regulation by the 1 million plus enhancer elements in the genome and are bound to reveal many differences between humans and great ape cells, but such studies have yet to be performed (604, 605).

The 2011 Institute of Medicine report on the ethics of chimpanzee research urges against any culling and invasive research of chimpanzees (606, 607). However, this report did not provide NIH support for noninvasive biomedical research in these captive populations, which largely are aging in NIH-funded facilities. With the cessation of any research on captive chimpanzees, with the possible exception of noninvasive work in chimpanzee sanctuaries across Africa (608), nonhuman primate models include several species of macaques and marmosets, which are rapidly becoming the model primate in neuroscience (609–611).

With the advent of global dispersal and ecological dominance of the human species, including the settling of most land masses, alterations to fauna and vegetation on land and in the oceans, and far-reaching effects on most ecosystems and the global climate, it is clear that we have entered a new epoch for which the name Anthropocene has been proposed (612). Many approaches to understanding modern human nature, including questions about human health and disease, overly focus on the very recent past, the Holocene, an epoch that includes the beginning of widespread agriculture during the neolithic, and in the last few thousand years, the invention of written history. The focus of anthropogeny is far beyond these recent periods, on a much deeper time depth, for which data are unfortunately much sparser (**FIGURE 12**). The importance of anthropogeny however lies in the key insights into human nature, as shaped by hundreds of thousands of years of life in small-scale societies, each adapting biologically and culturally to a vast array of dynamic ecological and socio-cultural environments. A better understanding of our origins as the "planet-altering ape" and an appreciation for how our story-telling species came to form a dominant life form on planet earth will contribute greatly to many urgent issues of today. These include human health and disease (e.g., the Hygiene hypothesis), social problems (parochialism/racism and other forms of in-group versus out-group behavior), uneven distribution of wealth and opportunities, and the resulting suffering and social destabilization, care for our children and the elderly, conservation of natural resources and biodiversity.

Major philosophical and political approaches to "Human Nature" rely on a poorly informed understanding of what represents "human nature" and would thus greatly benefit from a more nuanced understanding of the many ways our species has shaped its own destiny starting long before *Homo sapiens* spread from Africa to the rest of the globe. Humans are very much beings of their own making, which is reflected even in our physiology.

DATA AVAILABILITY

Data will be made available upon reasonable request.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

P.G. A.V., and M.V. prepared figures; M.V., K.K., N.V., P.G., and A.V. drafted manuscript; M.V., K.K., N.V., P.G., and A.V. edited and revised manuscript; M.V., K.K., N.V., P.G., and A.V. approved final version of manuscript.

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