Developmental biology and human evolution

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Abstract

The Evolutionary or Modern Evolutionary Synthesis (here identified as the Synthesis) has been portrayed as providing the foundation for uniting a supposed disarray of biological disciplines through the lens of Darwinism fused with population genetics. Rarely acknowledged is that the Synthesis’s success was also largely due to its architects’ effectiveness in submerging British and German attempts at a synthesis by uniting the biological sciences through shared evolutionary concerns. Dobzhansky and Mayr imposed their bias toward population genetics, population (as supposedly opposed to typological) thinking, and Morgan’s conception of specific genes for specific features (here abbreviated as genes for) on human evolutionary studies. Dobzhansky declared that culture buffered humans from the whims of selection. Mayr argued that as variable as humans are now, their extinct relatives were even more variable; thus the human fossil record did not present taxic diversity and all known fossils could be assembled into a gradually changing lineage of time-successive species. When Washburn centralized these biases in the new physical anthropology the fate of paleoanthropology as a non-contributor to evolutionary theory was sealed. Molecular anthropology followed suit in embracing Zuckerkandl and Pauling’s assumption that molecular change was gradual and perhaps more importantly continual. Lost in translation was and still is an appreciation of organismal development. Here I will summarize the history of these ideas and their alternatives in order to demonstrate assumptions that still need to be addressed before human evolutionary studies can more fully participate in what is a paradigm shift-in-the-making in evolutionary biology.

Introduction

The history of evolutionary thought is interesting especially because it is continually being rewritten. Consider Charles Darwin. It is commonplace to read in textbooks and popular works that had he slit the pages of the reprint of Mendel’s publication of his sweet-pea experiments rumored to have been in his library he would have discovered the missing element in his theory of evolution by natural selection: namely, the role of population genetics in explicating evolution as the result of long-term adaptation. But he did not. The world thus had to wait for nearly a century for the population geneticist of the Synthesis, Theodosius Dobzhansky, to fill this lacuna. And he did with the assumption that the evolution of species and their clades (macroevolution, which no one can observe in a lifetime) could be understood by studying generational changes in gene/allelic frequencies as reflected in morphology (microevolution, which one can observe in a lifetime) (see historical review7). But Darwin could never have embraced Mendel’s conception of particulate inheritance. Like many of his contemporaries, Darwin believed in blending inheritance, which he incorporated into his theory of heredity, pangenesis.2 When Bateson and Saunders3 at the request of Galton on behalf of the Royal Society applied Mendel’s principles to animals, an intellectual rift emerged between Darwinians and their critics, Mendelians.1,4,8

Darwin’s5 emphasis on gradual evolutionary change and continuous variation led him to believe that had extinction or loss of geological deposits not eliminated morphologically intermediate forms, we would behold a continuum at any point in time between individuals, sexes, and species. Unfortunately, extinction and geological events created an artificial picture of discontinuity in a world that in reality is and was seamlessly continuous. Mendelism, however, with its emphasis on discrete, non-blending units of heredity, lent itself to believing that the morphological features they produced were also discrete and discontinuous. By insisting that gradual change through the accumulation of infinitesimally small variations over long periods of time constituted evolution, Darwin rejected a fact well-known to animal and plant breeders: namely, the plant or animal a breeder selected to serve as the progenitor of a new breed or variety often appeared in one generation not only without warning, but replete with its unique attributes. Further, this monstrosity (to use 19th century language9,10,12) was capable of breeding with parental-type stock. Darwin’s argument for rejecting monsters as evidence of evolution was that these individuals would not be able to survive in the wild. Yet for the saltationists Huxley13 and especially Mivart14, monsters did furnish material for the study of evolution.1,4 Huxley criticized Darwin for dismissing natura facit saltum and invoked many of the examples Darwin rejected — such as the case of the emergence of the Ancon sheep — to argue that novel morphology, and thus also species, arose abruptly. Mivart argued further that changes important to the survival of an organism must emerge in or nearly in final form, most likely from major alterations of development.

In a monographic embrace of Mendelism and criticism of Darwin’s insistence on gradual change, Morgan15 also cited as evidence of the abruptness with which evolutionary novelty could arise the same exam-
examples of the sudden origin of monsters that Darwin dismissed as providing insight onto evolutionary change. It therefore is remarkable that it was Morgan who ultimately devised the argument for melding Darwinism and Mendelism.2,17 And, also ironically, Morgan paralleled Darwine in accepting part of biological observation as necessary for evolution and rejecting the rest. Upon establishing the first fruit-fly population genetics laboratory Morgan and colleagues18 carried out numerous experiments in an attempt to map the location on chromosomes of hereditary units. Although Johanssen19 had earlier introduced the term gene, Morgan referred to units of heredity as hereditary factors perhaps because, like Bateson,2,20 Johanssen believed that genes existed in the cytoplasm, not on chromosomes. Morgan’s5,17 initial argument was the following: i) mutations that occur in laboratory animals do not differ from those that occur in wild animals; ii) the same mechanisms/processes that produce small-scale mutations (and concomitantly small-scale phenotypic changes) also underlie large-scale mutations (and concomitantly large-scale phenotypic changes), both kinds of which he observed in his fruit-flies; iii) mutation is random relative to selection, which can only act on features once they have appeared; and iv) as with the odds in a sequence of coin tosses yielding heads versus tails, a mutation affecting one feature does not ensure that the next mutation would follow suit.

Curiously, though, after presenting this logical thought experiment Morgan2,16,17 then rejected much of it. First, as Darwin had earlier denied to monsters the wherewithal to survive in nature, Morgan invoked the same fate for individuals bearing the phenotypic results of large-scale mutations. Consequently, he asserted, the only mutations and their phenotypic expressions that would be viable in nature were small-scale mutations, which would produce minor phenotypic change or variation. Second, Morgan declared, a mutation in one direction would bias subsequent mutations to follow suit. Over time, selection opting for these micromutations via their products would gradually change the population or species both phenotypically and genetically.

As for Mendelian factors and the features they produced being discrete and discontinuous, Morgan proclaimed that since the mutations and thus their phenotypic expressions must be so incredibly minuscule for an organism to survive, variation was essentially continuous. Thus, in one fell swoop Morgan melded Darwinian notions of selection and gradualism with Mendelian inheritance, with the proviso that micromutation, not selection or blending inheritance,2,22 produced the variation upon which selection then acted. Also with Morgan, the notion of their being specific genes for specific morphological features (abbreviated here as genes for) became an integral part of Darwinian evolutionary theory.

The evolutionary synthesis3 and the stultification of intellectual heterodoxy

The Synthesis that Dobzhansky24, Mayr25, and Simpson26 contrived promoted population genetics over all other biological disciplines and its reliance on the notion of specific genes for specific features. Unfortunately, as the embryologist de Beer27 bemoaned, this emphasis bypassed entirely the developmental processes that give rise to a functionally integrated adult organism because, in a genes for conception of biology, one need focus only on parental transmission of alleles to the zygote and the adult progeny.

Absent from the Synthesis’ version of evolution was consideration of, or even a perceived need to consider development broadly, much less in its details: e.g. in the timing of induction, threshold effects, regulation of development, protein/enzyme-gene interactions, epigenetic interactions etc that are intricately intertwined in the development of an organism from its undifferentiated to fully adult state. But this is not to say that all evolutionary biologists were as narrow-minded.

For example, in his Vibratory or Undulatory theory of evolution, Bateson (e.g. Refs. 10,20) sensed correctly19 that the origination of organismal novelty – especially differences between taxa in repeated or meristic features – resulted from internal alterations of developmental oscillations. Beginning with his early work on amphibian morphogenesis (e.g.Refs. 28,29), J. Huxley was keenly aware of the importance of incorporating development into a viable theory of evolution (e.g. Refs. 23,30). In the preface to his 1942 monograph, Evolution: The Modern Synthesis, in addition to Dobzhansky, Huxley acknowledged the contributions of Goldschmidt ([in developmental genetics21 and evolution32] and Waddington [in developmental genetics and epigenetics33]). He then commented: ‘Equally obvious is my debt to the Morgan school and to Goldschmidt, but clearly this would apply to any modern book dealing with evolution (p. 8).’ How mistaken Huxley was given the hostility with which Dobzhansky24, Mayr25, and even Simpson26, who studied extinct mammals, attacked Goldschmidt.

By centralizing population genetics as the key to understanding evolutionary processes, Dobzhansky24,25,26 shifted focus in evolutionary biology from systematic considerations of species to a more ambiguous notion of variation within populations and their change over time (see review in Ref. 35), which consequently denied paleontology input into the formulation of theories of evolution, especially the origin of species. This is obvious in Simpson’s25 contribution to the synthesis, Tempo and Mode in Evolution, in contrast to Dobzhansky and Mayr’s volumes, whose titles proclaimed relevance to the essential issue in evolutionary biology, the origin of species. Excluded from discussion of species’ origins, a paleontologist was left to rail against neo- and paleontologists who he perceived as upholding outdated typological thinking or essentialism rather than adopting the tenets of the Synthesis (e.g. Refs. 36,37,38). It was only in the late 1950s that Mayr took up this baton in earnest and through a biased reporting of history seduced most, especially English-speaking, evolutionists with a false dichotomy between typological with population thinking.29 As Winsor has detailed, Mayr’s assault was actually against saltationists, whom he painted with the brush of anti-Darwinism. From the perspective of an ill-defined notion of population thinking the Synthesis’ embrace of Darwinian gradual evolution by natural selection blurred distinction between races, species, and higher taxa.39 From a saltational perspective, the origin of species, including those that were ancestors of higher taxa, did not lie in natural selection but in other processes. And this was anathema to Mayr and fellow neo-Darwinians (see also Refs. 1,14).

Was the evolutionary synthesis a synthesis?

By excluding or minimizing all biological pursuits except for population genetics and population thinking it is difficult to embrace the Synthesis as having been synthetic in the sense of it integrating diverse biological fields. Indeed, as Jepsen40 recounted, the goal of the Synthesis was to unite supposedly disparate biological disciplines under the same umbrella: Darwinism infused with population genetics. In contrast, efforts from the German school by Schindewolf41 and Goldschmidt42 to encompass development, genetics beyond the populational and its underlying genes for concept, and comparative morphology (including paleontology) in evolutionary models were more credible.
attempts at a synthesis. In further contrast to the Synthesis, intellectual openness characterized the British school, as witnessed in J. Huxley’s convening scholars representing the breadth of biology not only to discuss problems specific to each discipline, but also to acknowledge their shared concerns about the relevance, meaning, and delineation of species. Consequently, the title of Huxley’s monograph, *Evolution: The Modern Synthesis* was not meant to reflect the triumph of the Synthesis. Rather, as he expressed in the quote above regarding the relevance of Goldschmidt and others’ work to evolutionary thought, Huxley’s title reflects his appreciation of the topical breadth and degree of transdisciplinarity necessary to begin a true evolutionary synthesis.

The question then is not solely directed to understanding how or why the Synthesis survived, but that it so successfully submerged other, more pluralistic attempts to forge a biological synthesis. For indeed, the *ad hominem* assaults Dobzhansky et al. (e.g. Refs. 24-26,36,37) levied against the proponents of the German school hardly constitute scientific refutation or falsification. But the underlying message was sufficient for the Synthesis to triumph over other endeavors. Namely, as Simpson bluntly put it, after World War II those in the East (Germany), who had become isolated from those in the West, suffered intellectual stagnation while he and fellow Western evolutionists proceeded down the correct intellectual path.

As for the fate of the British school, World War II certainly had an impact on Britain’s economy and thus on higher education and research. But this may not be the entire explanation. Rather, as a review of the evolutionary literature coming out of the United States for the next two decades or so reveals, there was little or no reference to Huxley or his colleagues’ work. In other words, the British school suffered the fate of being ignored.

When Simpson eventually discussed the edited volume that emerged from Huxley’s workshop, *The New Systematics*, he brought an attack similar to his reviews of Schindewolf and others of the German school. He condemned Huxley’s effort as insignificant and of no value to field. As Simpson (p. 64) wrote: …from that book alone it is hardly possible to determine exactly what was new about its systematics or to draw up a formal statement of its principles, but it did make it clear that there was a ferment working in the field. Simpson further demonstrated his disregard for Huxley’s effort by summarizing his approach to systematics and taxonomy, which, he declared represented the new, new systematics (p. 64).

Unfortunately, by the time Simpson wrote these words, the evolutionary die had been cast. The only credible way in which one should think about evolution was through the lens of the Synthesis. This is historically interesting because, in the end, no one actually knew what the Synthesis was. Rather, because of the Synthesis’s architects attacks or dismissal by other means of potentially viable syntheses, one really only knew what the Synthesis was not.

### Whither human evolutionary studies?

Given the intellectual battles waged on the evolutionary front during the first half of the 20th century, it is noteworthy that human paleontologists were silent. One can point to Henry Fairfield Osborn’s theory of *aristogenesis*, which was a version of orthogenesis or *purpose-driven* evolution. But Osborn was a vertebrate paleontologist first and turned his attention to human evolution only later in his career (e.g. Ref. 46).

This was, however, not unusual. Either one was a human anatomist who, as a student of human morphology, was deemed or thought himself qualified to issue declarations on the taxonomy and phylogenetic relationships of human-like fossils. Or one was a vertebrate paleontologist who gained authority from having tackled the systematics and phylogenetic relationships of other groups and then decided to wade into the arena of human fossils. Odd as it may seem, these activities did not also demand embracing the Synthesis or even contributing to evolutionary theory. To the contrary, by accepting evolution simply as descent with modification one could turn to what most paleontologists thought they should be doing: namely arguing that a particular fossil could plausibly be interposed chronologically and morphologically between others as a means to elaborating a picture of evolution through putative ancestor-descendant sequences. But the individuals who defined the future of human evolutionary studies were neither human anatomists nor paleontologists: Theodosius Dobzhansky beginning with Ref. 47 and Ernst Mayr.

Dobzhansky focused on human variability, both morphological and genetic, such as blood groups. His belief in the role of selection affecting gradual genetic and consequently morphological change after geographic isolation separated incipient daughter species from the parental lineage led him to this conclusion: *Since at some point in time humans developed culture, which removed them from the whims of selection, they “controlled” their own evolutionary destiny. Specifically, protected by the barrier of culture, humans would not speciate.*

Mayr’s interpretation of the human fossil record, of which like Dobzhansky he lacked first-hand knowledge, reflected a different bias. Mayr proclaimed that while human variability is great now, it was even greater in the past. From this assumption Mayr asserted that since a comparative morphologist would err and not allocate Congo pygmies and Watusi to the same species, *Homo sapiens*, it was unreasonable to interpret the human fossil record as providing evidence of taxic diversity. Mayr (p. 109) then collapsed what he described as a *simply bewildering diversity* of [taxonomic] names into one genus, *Homo*, which he defined on the basis of bipedality. Within this genus, which he envisioned as a seamlessly transforming, non-diversifying lineage, Mayr lumped the known early hominids into the species *transvaalensis*, which was succeeded by a species *erectus* that morphed into the species *sapiens*.

One could suggest that Dobzhansky’s and especially Mayr’s constraining to one continually changing lineage a human fossil record that even then demonstrated taxic diversity was guided by their reaction to the ethnic cleansing enacted during World War II. But it is odd not only that this scheme was accepted so readily, but also that so many who study human evolution still embrace it.

Why? Historically, it would seem, someone representing human evolution had to jump onto the Synthesis’ wagon, and it was Sherwood Washburn.

Echoing Simpson’s denigration of the German school for engaging in *typological thinking or essentialism*, Washburn berated physical anthropologists for remaining in this outmoded mindset of thinking in terms of fixed types rather than adopting the *population thinking* of the Synthesis (e.g. Refs. 25,26,37,48,51). Washburn thus became a convert of the central dogma of the Synthesis six years before Mayr’s lecture to the Anthropological Society of Washington, which was the beginning of his unashamed campaign to demolish non- or anti-Darwinian alternatives to the Synthesis’ version of Darwinism by pitting population against typological thinking (see review of Mayr in Ref. 39).

The new physical anthropology that Washburn imposed on human evolutionary studies, with its emphasis on humans as descendants of an extremely, almost unnaturally variable and gradually transforming lineage species may have seemed reasonable at the time. Nevertheless, as with the tenets of the Synthesis, the intellectual stultification with which Mayr and then Washburn shackled human paleontology, and subsequently Mayr the anthropological community in general, has outlived its usefulness — if as hindsight suggests, they were ever useful. At the very least, alternatives to suggestions that have been so long-lived and even elevated to the level of truth should be considered.
Species, speciation, and genes: the legacy of the synthesis

Although the title of Mayr’s monograph contribution to the Synthesis was Systematics and the Origin of Species, very little in it deals with the practice of systematics. In contrast to J. Huxley and colleagues’ focus on how conceptualizing species depends on the type of organism under study, Mayr provides no insight into the matter whatsoever. Rather, one of his primary objectives is to prove by assertion that the origin of species is a slow, continuous, and smoothly transformational process. For example:

That speciation is not an abrupt, but a gradual and continuous process is proven by the fact that we find in nature every imaginable level of speciation, ranging from an almost uniform species at one extreme to one in which isolated populations have diverged to such a degree that they can be considered equally well as separate, good species at the other extreme... A widespread species is more likely to represent the first stage of speciation than one with a narrowly restricted range. (p. 159)

This quote is representative of Mayr’s belief in his powers of observation being so finely honed that, as he proclaimed elsewhere, he could actually identify species in the making. Mayr’s dogmatism also led him to diminish or even reject the importance of all modes of speciation (e.g. sympatric, allopatric speciation via peripheral isolates, and especially polyploidy in plants) but one. Specifically, complete geographic isolation (= allopatry) of the sort that cleaves a parent species and especially polyploidy in plants) but one. Specifically, complete geographic isolation would presumably impose on daughter populations would guide them toward reproductive isolation. Mayr combined these elements in his biological species definition:

A species consists of a group of population which replace each other geographically or ecologically and of which the neighboring ones intergrade or interbreed wherever they are in contact or which are potentially capable of doing so (with one or more of the populations) in those cases where contact is prevented by geographical or ecological barriers.

Or shorter: Species are groups of actually or potentially interbreeding natural populations, which are reproductively isolated from other such groups (p. 120).

It is not obvious how this definition clarifies anything. Indeed not only is it next to impossible to apply the biological species definition to extant organisms, it is inapplicable to extinct organisms. Yet Mayr was so convinced of the veracity of his definition and so dead-set on demolishing theoretical alternatives to the Synthesis’ emphasis on gradualism that he could declare: …the species concept has been clarified by the taxonomist, and we know now that species differ by so many genes that a simple mutation would, except for some cases in plants, never lead to the establishment of a new species (p. 155).

How Mayr or his contemporaries knew that species differ by so many genes is a mystery except in the context of believing, in the Morganian sense, that there are specific genes for specific morphological features and then extrapolating from the speculation (species differ by many features) to the even more speculative claim that species differ by many genes. Of course, none of this has any connection to the conception of allopatry leading to reproductive isolation. Further, as Mayr knew from his own ornithological work, taxonomists often erect a new species, or even a new genus and species, on the basis of only one or a few features. This inconsistency notwithstanding, a legacy of the Synthesis that remains cemented in paleoanthropology is the unacknowledged inferring of specific genes for specific morphologies from the very morphological features these genes are supposed to underlie. This is obvious in the language of multiregionalists (e.g. Refs. 52-53), as well as of those who embrace a gradual and smoothly continuous transition from archaic to modern humans (e.g. Refs. 56-59). In particular it is commonplace to read in the literature of specimens deemed intermediate or providing evidence of hybridization described as presenting a mix of Neanderthal and modern human features. The implication and sometime overt claim is that there are genes for traits that are specifically Neanderthal and other genes for traits that are specifically modern human, and that the traits these genes supposedly underlie will be reflect in hybrids.

Interestingly, now that it is more feasible to sequence and compare both contemporary and ancient nDNA, a similar language and apparently more biological scenario of the genes for conception has emerged. In this case, specific genes are identified as Neanderthal or Homo sapiens in comparison with Pan from which their transformation to generate features deemed Neanderthal or Homo sapiens are then extrapolated. Of further note is that genes identified as Neanderthal and present in the Eurasians but not in the sub-Saharan Africans in the sample are said to represent a period of interbreeding between Neanderthals and ancestors of modern Eurasians after the later diverged from an African ancestor. This scenario is reminiscent of an interpretation of human and chimpanzee nDNA sequences as reflecting a prolonged period of interbreeding between the forerunners of these two living hominoids. Informing these investigations is the belief that one can identify genes that are specifically chimpanzee, Homo sapiens, and Neanderthal.

As to the interpretation of Neanderthal-Homo sapiens similarities and differences, Green et al. assume a close human-chimpanzee relationship and then use chimpanzee DNA sequences to determine character polarity. In other words sequence data do not generate either a human-chimpanzee or a human-Neanderthal sister relationship. These relationships – to the exclusion of other primates – are first taken as real and then similarities between Neanderthal and chimpanzee sequences are interpreted as primitively retained in the extinct hominid. When Neanderthals and/or modern humans differ from the ape, the differences are interpreted as derived character states.

Yet while this approach to assessing molecular polarity – a single taxonomy is defined a priori as representing in its entirety the primitive state against which to judge the primitiveness or derivedness of two or a few taxa – is commonplace, it is also contradictory. Namely, as articulated by Zuckerkand and Pauling in their molecular assumption (see Ref. 65), and subsequently embraced by other molecular systematists without question (e.g. Refs. 66,67-71), if molecular change is supposed to be an ever-ongoing process (such that taxa acquire molecular difference as a function of time since divergence), how can a taxon also remain totally primitive (= unchanged)? Furthermore, if the endeavor is to generate a theory of relatedness, how can one begin the analysis by assuming first which taxon will be the primitive sister of other taxa?

With regard to hominid evolution, this contradiction is alive and well. For instance, Green et al. analyze only three taxa: Pan, Neanderthal, and Homo sapiens. Pan is presumed primitive in the small portion of the DNA analyzed. When H. sapiens and H. neanderthalensis differ in DNA sequence or gene, the inference is that there are specific Neanderthal and specific human genes. The task is then to identify these genes in order to generate a scenario of how H. neanderthalensis morphology was converted into H. sapiens morphology. And Green et al. do just that. They propose (p. 717) that an evolutionary change in RUNX2 was of importance in the origin of modern humans and that this change affected aspects of the morphology of the upper body [especially rib cage and clavicle shape] and cranium [especially frontal protrusion and bossing] (notes from their text added). But while this makes a nice story, it does not actually reflect the developmental context of RUNX2 (CBGA1) or the affects of altering it.

Mutations affecting the RUNX2 (CBGA1) gene are autosomal dominant and reduce the amount of functional RUNX2 transcription factor...
in cells, thereby systemically impacting chondro- and osteo-genesis as well as tooth formation (e.g. Refs. 73, 74). The disorder caused by this dysregulation is cleidocranial dysplasia and its manifestations include short stature and arms, scoliosis, short tapering fingers, broad thumbs, hypo-/a-plastic clavicles (with concomitant medial approximation of shoulder joints), extreme medial approximation of distal femora, patent fontanelles and metopic/frontal suture, poorly pneumatized mastoid processes, bulging frontals (as also seen in normal third-term fetuses and neonates with unfused frontal sutures), widespread orbits, flat nasal regions, small upper jaws, supernumerary or peg-shape teeth, and developmental inhibition of primary teeth. There are also significant soft-tissue anomalies.75,76

For Green et al.'s scenario to work, Neanderthals must be primitive relative to *H. sapiens*, with alteration of the *RUNX2* signaling pathway transforming features of the former hominin into those of the latter species. If we assume that mutations affecting *RUNX2* in modern humans convert to the primitive state, proper chondro-, osteo-, and odonto-genesis would be impaired. Yet morphologically normal Neanderthals do not present hypoplastic or aplastic bone or tooth formation. To the contrary, *H. neanderthalensis* had robust and oversized long bone epiphyses, medial outgrowths from the lateral walls of the nasal cavity, often thick diaphyseal bone, and relatively tall and in profile anteriorly curved supraorbital margins; some individuals also develop taurodontism, which is characterized by development of an extremely long, molar root with barely differentiated root tips (cf. Refs. 57, 78-81). Further, *H. neanderthalensis* developed noticeably protrusive nasal regions and large maxillae that taper anteriorly (producing a wedge-shape snout), an extremely long thumb, terminal manual phalanges that are distally compressed anteroposteriorly and broad laterally, and widely separated shoulder joints due in part to development of the relatively longest clavicle of any primate (ibid.).

From a broadly comparative, cladistic perspective, in the features cited above Neanderthals are clearly derived relative to other hominids, including *Homo sapiens*.78,80-84 Only by assuming that evolutionary change is essentially orthogenetic can one interpret these and other Neanderthal features as primitive relative to their counterparts in *H. sapiens* (e.g. Refs. 57, 60).

From a developmental perspective, features such as thickened diaphyses, expanded articular regions, lengthening of the thumb, distal broadening of manual terminal phalanges, taurodontism, distinctly mounded supraorbital margin, and extraordinary clavicular elongation are characteristics of hyperostosis, not of hypostosis or hypoplasia, and certainly not of aplasia (cf. Ref. 85). Indeed, since *RUNX2* is critical to normal chondro-, osteo-, and odonto-genesis (e.g.Refs. 73, 74) alterations of it as Green et al. suggest (or more properly, altering expression of the *RUNX2* transcription factor with consequent downstream effects) would not convert skeletal and dental morphology distinctive of Neanderthal into that which is distinctive of *H. sapiens*. Rather, the result would be diagnosable as cleidocranial dysplasia.75,76 Further, since the effects of *RUNX2* are systemically critical for proper skeletal-genesis, it is unlikely that only one or a few features — such as a clavicle, the frontal bone, some ribs — would be affected but the rest of the skeleton and the teeth, not to mention soft-tissue anatomy, would remain unaltered.

As for the uniquely bossed frontal bone of *H. sapiens*, this configuration is not also associated with delayed onset of fontanelle closure, metopism, widely spaced orbits, a flattened nasal region, and a reduced maxilla. But, then, specimens of *H. neanderthalensis* with bossed frontals do not express these features either, e.g. the adults La Ferrassie 1, Amud, Krapina C, or Monte Circeo 1, or the juveniles/adolescents Engis, Roc de Marsal, La Quina 5, or Le Moustier (see descriptions and illustrations in Ref. 79).

On the other hand, in analogy to the correlation between overexpression of the transcription factor ectodysplasin and the development of more complex molar cusp and crest patterns in mice,86 overexpression of the *RUNX2* transcription factor, if part of a signaling pathway that induces hyperostosis and hyperodontogenesis, may have played a role in Neanderthals developing some of their unique cranial, postcranial, and dental morphology. But we will not know if this is the case. As we do not know the signaling pathways that underlie *Homo sapiens*-specific morphology, it is doubtful we are close to understanding signaling pathways that underlie any of the derived features that distinguish extinct species of hominid.

### Biology versus wishful thinking

The notion that one might identify specific genes that make a modern human or a Neanderthal is appealing. Would it not be wonderful to point to a handful of genes as the underlying source of difference between our species and a potential fossil relative? Nevertheless, this is wishful thinking, even if specific genes or gene products implicated in the development of features or biological systems can be identified. For in Metazoa, unlike bacteria, ca. 97-98% of the genome is non-coding and a large proportion of that is comprised of developmentally regulated genes.87

But identifying similar genes or gene products in two or more taxa — even if one can experimentally determine their roles in the development of extant species — does not inform with regard to the recruitment of these molecules in developmental time and cellular space or to their interactions with other molecules.88,89 The complexity and extent of such signaling pathways remain extremely difficult to determine in experimental organisms. It will be impossible in fossils.

This hurdle notwithstanding, what is interesting about the language of gene identification in analyses of ancient DNA is that it not only retains the conception of specific genes for specific morphologies. It also retains the element of population genetics thinking that so troubled de Beer.27 Namely, that by focusing on mutation and hereditary transmis-sion from parent to offspring, the developmental unfolding and differ-entiation of the individual is ignored. Simply identifying the *DLX* (dis-tal-less) gene in butterflies and echinoderm larvae does not reveal that in butterflies this gene is recruited in the signaling pathway that produ-ces wing eyespots,90 while in sea urchins it is expressed simultane-ously with the engrailed and orthodenticle homeobox genes to trans-form larvae from bilateral to radial symmetry.91

In short, simple comparisons of linear sequences of nucleotides do not reveal developmental and morphological differences between eukaryotes, and especially between metazoans. Rather, different and functionally different genes exist as a result of RNA- and transcription factor-mediated alternative intron splicing and exon frame reading, which together construct developmental genes from a stretch of DNA that is identified only by a start and stop codon.92,93 Thus, in terms of organismal development — and not in terms of autosomal genes that may be correlated with, for example, eye color and with which population geneticists have been preoccupied — it is erroneous and certainly abiological to endeavor to identify specific genes for specific structures (e.g. Refs. 94, 95). But since such a gene-morphology relationship had been assumed, how surprising it must have been when, for example, the human genome consortium discovered that rather than >100,000 genes, the human genome comprises ≤23,000 genes, only ca. four times the number of genes in *Saccharomyces* (the budding yeast). How to make >100,000 genes from ca. 23,000? Multiple permutations of alternatively splicing introns and translating (both sense and anti-sense) exon-reading frames!

As Davidson and Erwin96 argued, there is a developmentally integrat-ed hierarchy of instructional information that spans basic gene regulatory networks (GRNs) fundamental to establishing basic body plans to...
differentiation gene batteries (DGBs) involved in the terminal specialization of tissues and structures. In other words, there is a molecule-morphology continuum that cannot be teased apart with molecules and morphology being treated as separate, independent entities. Further, we are barely at the threshold of understanding the role in both plants and animals of non-Mendelian inheritance in developmental and epigenetic processes.

I am not suggesting that morphology is not heritable. For after all, (multicellular) organismal form is ultimately tied to the DNA transmitted from one generation to the next. Also inherited is the hierarchy of integrated signaling pathways that orchestrate the transformation of, for instance, a morula into the adult of its species. But it is not because there are specific genes for specific morphologies that we might hypothesize derived features for subclades and ultimately species of any particular clade. To be redundant, it is the different ways in which introns are alternatively spliced and exon frames read, continuously in different ways from the least differentiated to the most differentiated state of development, with potential input from the developing organism’s surroundings (e.g. cell-cell or organism-environment), that yields the finished product: the organism. Consequently, the quest should be not to identify single genes as smoking guns of species identity. Rather the endeavor should be focused on understanding how inherited DNA, especially developmentally regulated genes, are exploited to create one species rather than another.

Final thoughts

It is a curious historical twist that the underlying presumption in paleoanthropology since Huxley has been to diminish recognition of taxic diversity in the fossil record by referring to a vague notion of extreme variability among living humans and, by unjustified inference, also in their extinct relatives. Although minimizing differences among fossil hominids may have been provoked by a post-World War II backlash to ethnic cleansing and racism, the fact remains that two architects of the Synthesis imposed their non-synthetic view of evolution on human evolutionary studies, and the field succumbed to it. One may well wonder how different evolutionary biology, including paleoanthropology, would have been if the architects of the US-based evolutionist had not submerged the contemporaneous British or German attempts at a true evolutionary synthesis. At the very least, the spirit of alternative thinking that had characterized evolutionary biology for nearly 100 years would likely have made possible the co-existence of competing interpretations of the human fossil record and theories of hominid relationships. Increasing technological sophistication, beginning with the re-emergence of molecular systematics in the 1960s and now the capacity for sequencing large portions of genomes, or the formulation of complex algorithms for managing huge databases, does not necessarily correlate with refinement of phylogenetic theory or methodology. Indeed, any such endeavor is no more sophisticated than the assumptions that underlie it. Hopefully, especially with the current pace of understanding the fundamentals of organismal development, attempts at a true synthesis in evolutionary biology will begin to surface. And as they do, perhaps they not only will spill over into human evolutionary studies, but will have the effect of broadening the scope of the discipline rather than provoking further intellectual retrenchment.

References


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