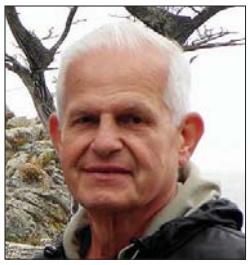

David L. Wilcox

Our Genetic Prehistory: Did Genes Make Us Human?

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Despite our close genetic match with the chimpanzee, the human genome is radically different in its expression and radically different in its outcome. Though we share 98.7% of the same protein-coding sequences,[1] the difference between our species is not in the 1.5% of the genome that codes for proteins, but rather in the 98.5% that controls their production. No other lineage has evolved as fast as ours, at least within the last 1.5 million years. The changes which differentiate us are primarily due to rapid changes in genetic control sequences.[2] These changes involve every known class of control element, with the most profound changes found in the noncoding control elements shaping our neural system, especially the frontal cortex of the cerebrum. Further, the speed of the change is in large part due to the unique action of retrotransposons acting as "genetic engineers," providing the raw genetic material selected in support of our cultural explosion. Although these are "natural" forces which we in part can understand, as Christians we should remember that they reveal what God ordained in eternity and realized through providence.

The discovery that chimpanzees are our closest genetic relatives is one of the most controversial new ideas of the last few decades. What is the source of that counterintuitive idea? How should we react? First, keep in mind that science works by predicting patterns of data based on our understanding of the shape of reality. Thus, let us begin with prediction. Based on known morphological data, what would be the expected (i.e., predicted) pattern of difference in genetic sequences between the various species of primates—assuming common descent versus assuming separate creations?

In the 1960s (before the genetic revolution), the accepted anthropological evaluation of human/ape morphological differences grouped chimpanzees with gorillas, and both with orangutans, as pongids—a separate evolutionary clade from humans. The pongid clade and the hominoid clade were thought to be descended, respectively, from the two extinct ape species *Dryopithecus* and *Ramapithecus*. The anthropological expectation was therefore that molecular distances (immune, protein, or nucleic acid) would be proportional to the perceived physical divergence in lineages. It has been an ongoing and progressive shock to find out how wrong that prediction was.[3]

The logical prediction from separate creations (the baramin paradigm of Wayne Frair and Kurt Wise) paralleled the anthropological expectation. They placed gorillas and chimpanzees within the same "holobaramin," meaning that they shared descent from the same directly created ancestral species. In contrast, humans only resembled apes due to shared common ideas in God's mind—thus humans and apes are within a shared "apobaramin."[4]

In both schools of thought, despite their different background beliefs, the accepted prediction was that the molecular distances would reflect morphological distances.

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They thus shared a common theory, but for different reasons—with different specifying assumptions. However, the predictions of both schools of thought were wrong. Chimpanzee DNA is closer to human DNA than to gorilla DNA. And, gorilla DNA is closer to human DNA than to orangutan DNA. What should be our reaction to this discovery? Should we conclude that human beings are not truly unique image-bearers of God? Of course not, but we should carefully evaluate the data from the creation before we react.

As a heuristic process, science alters its theories as it discovers new patterns in the data—as it should, if the Creator God is the source of those patterns. For the non-Christian who yet believes in a real world, authority is in the data. Likewise, for the Christian, data are authoritative because God created a real world. So, if we truly trust God to be faithful, we should carefully and prayerfully accept corrections to our previous theories. But as Jitse van der Meer has pointed out, that does not mean that we must alter our background beliefs.[5] Rather, we must examine the specifying assumptions by which we have linked those beliefs to our expectations (our theoretical predictions)—and change them when we are mistaken. Genetic anthropology has done so, and we likewise need to evaluate what is legitimate for Christian thought. But first, we should evaluate whether such a change is justified by the data from genetics. That is not easy. The complexity of the discipline has grown exponentially over the last half century.

Starting with the simple Mendelian definition of genes as the determiners of traits (genotype → phenotype), genetics progressed to identifying proteins as agents of traits, and then to DNA as the genetic material which spelled out proteins (through the genetic code, using the mechanisms of replication, transcription, and translation). This was followed by Operon theory, the realization that some DNA sequences are recognized as control elements by proteins, and further, that this recognition allows control proteins to tie the genes into logic circuits. It also became clear that eukaryotic genomes were far more complex than bacterial genomes, both in control structure and in the processing of transcripts (due to the splicing out of introns and the fusing of exons—thus the entire RNA transcript of a locus was not translated). The Human Genome Project which followed showed that there are not enough protein-coding genes (ORFs—open reading frames) to specify known phenotypic complexity. However, alternate transcript splicing increases the transcriptome (effectively, giving more proteins). And now the ENCODE project has suggested that massive amounts of noncoding transcriptions (ncRNAs), including anti-codes, introns, micro-RNAs, long noncoding transcripts (lncRNAs—over two hundred nucleotides), and transposon transcripts act in the control of genetic expression. And of all things, that ultimate genomic parasite, the transposon or jumping gene, looks like an agent of genomic engineering.

What we want to find out is whether all the new genetic information shows us to be an upgraded species of chimpanzee or truly a "new" thing. In what sense have these multiple classes of altered genetic controls produced human uniqueness? And how did it occur? Was it gradual or sudden? According to Britten, if any species looks as if it has developed by "punctuated" evolution, it is ours. That, he says, is the implication of the evolution of human cognition within a few million years—a span of time in which typical mammal species remain unchanged.[6]

Cognition is about the brain, and humans do have more neurons than chimps, but not as many as you would think. The real difference is in their neuropil—that is, the white matter connecting the neurons. Humans' neurons have an order of magnitude more neural connections than chimps, longer axons with more branches, increased long connectivity (connections between distant parts of the brain), increased local modularization (local cerebral centers), and dramatically delayed synaptic maturation (increased neural reorganization).[7] There are thousands of unique human genetic changes altering cell proliferation and differentiation, tissue organization, the growth of long axons and dendrites, the amount of axonal branching and connectivity, the timing and degree of synaptic plasticity, and so on.[8] And it is not just the neurons which are different—humans also have a unique class of neuroglial (the astrocytes) which are now known to modulate synaptic activity—the human forms have ten times as many processes and faster calcium waves than the chimpanzee versions.[9]

Direct comparisons of the human nuclear genome with those of the two species of chimpanzees do indeed indicate that we share about 98.7% of our genetic sequence/genome with each of them.[10] But then, if there is such a close genetic match, why are human brains so different from those of chimps?

Both human and chimp genomes have been fully sequenced and placed in the public domain, and powerful comparative algorithms have been developed. But despite truly significant morphological differences,[11] the total sequence difference is only 2% to 4%, and little of that difference (only 1.5%) is between coding sequences. However, 5.5% of the human genome has undergone purifying selection (the removal of alternate sequences), and is therefore composed of significantly different functional sequences. It follows that the most obvious place to look for significant differences are noncoding control sites. Of the long lists of significantly different coding genes and control sequences which have been identified, two-thirds are in noncoding control sequences for the amount, timing, and location of expression of coding genes.[12]

So, human-chimpanzee differences are apparently due to human-specific changes in gene expression rather than changes in protein sequences. In fact, the genes coding for protein sequences expressed in chimpanzee brains may actually have changed their sequences (by mutation) more rapidly than have their human counterparts.[13] But as a general rule, genetic changes of morphology are instead due to modified transcriptional regulators. This makes sense, since morphologies are products of complex genetic programs encoded through a hierarchy of genetic feedback loops. Likewise, alterations in neural complexity are products of complex genetic hierarchies, and occur mainly via noncoding regulatory changes. In contrast, altered physiological traits are due to altered proteins such as channel proteins, transporters, receptors, and enzymes.[14] Tissue-specific changes such as alterations to immunity, olfaction or male reproduction are mostly due to genetic protein-coding changes and show significant pleiotropic inhibition (since proteins can have multiple effects). In contrast, noncoding changes typically do not show pleiotropic constraints.[15] Thus, it makes sense that rodent genomes have higher levels of conservation for regulatory elements than do hominid genomes. This might imply less effective selection, but it more likely indicates higher selection for new adaptive changes such as those in hominid neural systems.[16]

If regulatory mutants are more likely to produce subtle changes than altered proteins, there should be evidence for such noncoding regulators. Apparently most of the transcripts which are copied from DNA do not code for proteins. And a wide variety of these ncRNA (noncoding RNA) transcripts are being recognized as regulators of transcription, particularly through various interactions with transcription proteins. The list of ncRNA effects includes gene silencing, position effect, hybrid dysgenesis, chromosome dosage compensation, imprinting, allelic exclusion, transvection, transduction, paramutation, and altered chromatin modifying complexes. To explain all of these would need a rather large book. However, RNA transcripts are particularly active in tissue differentiation and regulation—and notably, ncRNAs are enriched in specific areas of the central nervous system. Such ncRNAs are sensors of neural stress, influence synaptic plasticity, and are implicated in several neural diseases. Yan et al. identified 82 novel intermediate (50–500b) ncRNA transcripts, many particular to the human fetal brain, with different area-specific expression levels.[17] These ncRNAs regulate protein production and increase the transcriptome (the locally expressed array of proteins). The absence of some of them is correlated to brain tumors.[18] Mattick terms such ncRNAs "environmentally sensitive epigenetic regulators," which allow RNA editing in response to environmental signals—especially in the brain.[19]

There are some significant changes in uniquely human proteins, although the majority of identified highly selected human genes do not yet have defined functions. However, more than four hundred are involved with immunity (such as the HLA antigen series), around 130 with sensory perception, one hundred with the brain and another one hundred with gametogenesis.[20] In some cases, significant neural genes have been altered. The most familiar is FOX-P2 which has been implicated in language deficits. FOX-P2 increases axon growth in the striatum of the basal ganglia, resulting in improvements in the learning of motor skills.[21] Likewise, the genes ASPM and MCPH1 are implicated in the size of the brain, as well as PDYN, GLUD2, COX8, and CMAH which may change brain regulation, cerebral metabolism, and so forth.[22] Or, M003-A06, a zinc finger gene with a human-specific allele, controls brain (head) size.[23] And, the highly conserved neuropeptide PACAP which regulates neurogenesis and neuronal signal transduction has eleven amino acid changes, a rate of mutational substitution in humans seven times faster than observed in other mammals—a signal of very strong selection.[24]

A recent scan for newly evolved genes in humans (meaning, genes absent in mice) found 198 genes unique to apes and humans which are specifically upregulated in the fetal prefrontal cortex at a four-fold higher rate than that of other tissues. Fifty-four of these genes are unique to humans. An additional 72 of these genes we share with chimpanzees alone, and the remaining 72 with both chimps and orang-utans. As a general rule, human brain development genes are upregulated and their transcription factors are enriched. Although new genes may arise by different mechanisms, they show the same expression bias. Also, young genes show faster protein sequence evolution than co-expressed older genes. All of this indicates that positive selection for increased brain function acted in their origin and modification.[25]

Alternate exon splicing of the transcripts of human protein-coding genes (open reading frames—ORFs) increases the transcriptome, compensating for the unexpectedly low level of ORFs, and for the lower mutation level in neural loci. The rate of such alternate transcript splicing differs across taxa, but is highest in primates—and among primates, highest in humans, and in human tissues, especially high in the brain. Such widespread human-specific alternative splicing in neural tissues makes clear its importance in the evolution of neuronal gene regulation and function.[26] Further, even the neural somatic genome itself is altered, with 13% of all neurons having copy number variations in their chromosomes.[27]

However, the most significant changes do seem to be regulatory mutations' controlling of the timing and quantity of the gene products, especially in sites close to developmentally active genes.[28] The most rapidly evolving human locus yet identified, HAR-1, is such a control site, producing a lncRNA expressed in the Cajal-Retzius neurons of the neocortex—at the time those neurons are being specified and positioned into the six-layered human cortex.[29] The unique human HAR-1 transcript contains eighteen substitutions (since its divergence from the chimp version) which alter the form of the RNA transcript from a hairpin to a clover-leaf.[30]

In another paper evaluating the recent selection on gene networks contributing to cognitive function, Shulha et al. mapped the genome-wide distribution of histone H3 trimethylated at lysine 4 (H3K4me3), an epigenetic mark sharply regulated at TSS (transcription start sites).[31] They identified 471 sequences with human-specific enrichment or depletion. Thirty-three methylated loci show modern human-specific nucleotide substitutions and regulatory motifs with particularly strong enrichment in prefrontal cortex neurons. One specific locus with strong regulatory selection in neural tissues is prodynorphin, an opioid precursor leading to changes in behavior, perception, and memory.[32]

Nowhere are the chimp/human differences clearer than in the postnatal expression of genes involved with brain development. In a comparison of humans, chimpanzees, and macaques, simple changes in gene expression levels—cis-regulatory changes—accumulated at similar rates. This highlights the striking differences in the timing and shape of human developmental expression patterns which are due to trans-regulatory changes. (cis-regulatory sites are close to specific loci; trans-regulatory sites are distant signaling sites.) Four times as many human-specific genes show altered developmental expression as do chimpanzee-specific genes, again, particularly in the prefrontal cortex.[33] This remarkable developmental remodeling of the human cortex is controlled by the expression of hundreds of genes, but the process is likely driven by alterations in the expression of a few key regulators, such as the microRNAs (which are transcription regulators) preferentially associated with neural activity. Certain specific miRNAs, as well as their target genes, show some of the most rapid rates of human-specific evolutionary change—notably, miR-92a, miR-454, and miR-320b.[34]

Such miRNAs modulate gene expression post-transcriptionally, again increasing the transcriptome (increasing protein diversity). Iwama et al. evaluated 1433 miRNAs in humans, and identified two major retained peaks of miRNA introduction. Of these, 28% are from the period of the early eutherian radiation and 53% arose during the evolution of the simian lineage into the hominoid lineage. Approximately 28% of the latter group of miRNAs appeared within hominid lineage itself.[35] One example, miRNA-941, expressed in pluripotent cells, acts on human-specific genes involved in neurotransmitter signaling. The deletion of the miR-941 precursor disrupts language/speech. This locus shows a decreasing copy number with the move out of Africa; it (speculatively) has been suggested that it is involved in longer life spans and higher cancer rates.[36] Such significant differences in miRNA expression between human populations probably are involved with local adaptations, for

instance, the "rheostat" control by miR-155 of melanin production gene TYRP1.[37]

Long noncoding RNA transcripts are also involved in the epigenetic regulation of gene expression. A major mechanism of lncRNAs seems to be to tie chromatin (chromosome sections) together into functional locations.[38] On the average, about ten different lncRNA are produced for every coding locus, using alternative reading frames overlapping the locus—including transposons, templating of the noncoding side, and so forth. Long noncoding RNA transcripts are also involved in the epigenetic regulation of gene expression. They are involved in genomic imprinting (and not just the imprinting of alleles). They are activators, regulators—both cis and trans acting—cis-tethers, cis-targeting, trans-targeting, enhancers, decoys, scaffolding, allosteric modifiers, co-activators, and co-repressors (details are beyond the scope of this paper).[39] Ng et al. identified four (of 35) lncRNAs specifically required in neurogenesis and brain development which regulate nuclear proteins and cytoplasmic miRNAs, and induce neural pluripotency in embryonic cells.[40] In addition, lncRNAs sometimes are converted into new protein-coding loci, and the majority of those are expressed in the cerebral cortex.[41]

Of course, there are similar sites in the genome which affect other parts of the body. For instance, a decrease in the rate of apoptosis (programmed cell death) in human brain tissue may have been selected by the pressure to increase brain tissue—but this altered rate is expressed all over the body, which may be the reason humans have more cancer than chimps.[42] Or, the noncoding (control) sequence HACNS1 has evolved very rapidly in humans. In genetically modified mice, the human form of HACNC1 is expressed in the thumb, whereas the chimpanzee form is not. Thus, the modified HACNS1 is probably involved in the altered shape of the human thumb.[43]

Gene expression can also be modified by gene duplication. Genetic loci have been duplicated multiple times in the human lineage (some very recently). Multiple copies of alleles increase the amount of gene product without changing the sequence itself.[44] For instance, AMY1 (an amylase gene) is present in extra copies in populations with high-starch diets,[45] and humans have multiple copies (200+) of the gene DUF1220. The loci produce a protein of unknown function, but it is one highly expressed in neuronal dendrites in those parts of the brain involved with higher cognitive function[46]—and dendrites have just been identified as "micro-processors," significantly increasing the brain's complexity.[47] There is good evidence that such changes in the expression of specific proteins at synaptic junctions are a major cause for advanced neural function.[48]

And it is not just comparisons with the chimpanzee genome which show significant genetic changes—the Neanderthal and Denisovan genomes are also available. But just how different were they? High resolution genome scans of the archaics (the Neanderthals and Denisovans) make it possible to zero in on specific loci which are different in modern humans. Of course, most loci are the same. For instance, the site HAR1 (human accelerated region 1) mentioned above, the most rapidly evolving site on the human genome, is the same in both modern humans and archaic humans.

However, the initial Denisovan study did identify a number of unique "modern" protein loci.[49] These are sites highly conserved in primates, but changed in the modern human lineage *after* separation from the archaics. Of the twenty-three most conserved positions with significant amino acid changes, eight affect nervous system genes in function or development—NOVA1, SLITRK1, KATNA1, LUZP1, ARHGAP32, ADSL, HTR2B, and CNTNAP2. Of these, SLITRK1 and KATNA1 control axonal and dendritic growth, ARHGAP32 and HTR2B are involved in synaptic transmission, and ADSL and CNTNAP2 are implicated in autism. CNTNAP2 is regulated by FOXP2 and is associated with speech problems. NOVA1 is a neuron-specific RNA binding protein, and LUZP1 is a leucine zipper (control) protein active in neural tube development. Both of those loci are subject to alternative splicing. The researchers also located four altered loci affecting the skin and six affecting the eye.

Another locus which seems to have been selected after the human lineages diverged is MEF2A, a locus which delays synaptic development, allowing longer plasticity in brain development.[50] In chimps, the expression of this locus peaks before one year, but in humans, it peaks at around five years. Linkage data indicates that the selective sweep for the modern allele of this gene postdates the split from the archaic lineages, a finding which matches physical data from

tooth growth, showing that the Neanderthals matured more rapidly than modern people.[51] There also is skeletal evidence for a different trajectory of cranial growth likewise supporting a difference in genetic expression during brain development. The rounded modern cranium is due to a unique globularization growth phase occurring during the first year, growth which did not occur in Neanderthals.[52] Such changes likely reflect an altered brain and mind—and require alterations in the control sequences of the genome.

But regulatory changes can be quite subtle. A good deal has been made of the fact that FOX-P2, the "speech" gene, is the same in modern humans and the archaics. However, there is a significant difference in the modern FOX-P2 locus. The eighth intron has an altered recognition site for the control protein POU3F2 which decreases the level of expression of FOX-P2, a change in modern people which may lengthen the time available for altering neural hard-wiring.[53]

What is truly mind-boggling is that this explosion of diversity in functional RNA/DNA controls is being driven by jumping genes known as retrotransposons. Retrotransposons, or "short interspersed repeated sequences" (SINEs) are related to retroviruses such as HIV, and they litter the human genome. The most common of these elements in humans, the Alu's, number about 1.1 million copies and compose around 10% of our genome. Alu's have long been considered junk DNA. However, these mobile elements are transcribed, both as distinct RNA polymerase III transcripts and as a part of RNA polymerase II transcripts. (And Pol III transcripts can interact with Pol II to block mRNA transcription.) So, Alu transcripts potentially can have important regulatory functions. And indeed, they have been shown to control mRNA processing at several levels, through complex regulatory functions such as mRNA transcriptional repression or the modulation of alternative splicing, and they are implicated in many genetic diseases. Further, Alu RNAs which are embedded in Pol II transcripts can promote proteome evolution and diversity.[54] By such insertion, transposable elements (TEs) can add, control, or become part of genetic regulatory sequences.

In general, genes with associated Alu's show higher levels of editing in humans, especially if the genes enhance neural complexity. Many specific Alu inserts are of interest—for instance, 57% of the neurally active microcephalin locus is composed of TEs found in the introns. Control areas showing significantly different expression also have a great many differences in INDELs (insertion/deletion mutations) due to retrotransposon activity. Alteration by moving TEs therefore seems likely to have been a major factor in the changes in human gene functions which produced the major morphological and functional changes in the human lineage.[55] That sounds like saying that many derived human characteristics are a matter of "untraceable" genetic "engineering" (mutations) for novel genetic combinations rather than due to the environmental selection of small variants. But of course, selection is also involved in the survival of transposon induced changes. The issue is the high rate of new coding being made available by transposons for selective "evaluation." If selection is the engine of change, new variation is its fuel.

Since Alu's are retroposons, they are transcribed, but only if they are not repressed by methylation, a process controlled by miRNAs. If transcribed, their transcripts can fold into potentially active RNA hairpins, as well as being randomly reverse-transcribed back into the genome, particularly at sites where the DNA is most active. But transposon transcripts do not have a free ride. Piwi interacting RNAs (piRNA 24–30 nt) repress specific TEs by cleaving their transcripts. These small piRNA elements are also under strong selective constraints (based on data from African populations), and there is a strong correlation between the age of the TE family and the number of associated piRNAs. Note, however, that humans have an abnormally low level of those particular piRNAs which specifically deactivate Line 1 reverse transcriptase. (L1—long interspersed repeated sequence 1—codes for those reverse transcriptase enzymes which make DNA copies from specific TE transcripts, the copies which can then be inserted back into the chromosomes.) This human exception suggests that the L1 reverse transcriptase enzyme supports a specific important human function, namely, the continuing insertion of new Alu's.[56]

Of course, such new Alu insertions do cause cancers and other genetic defects—but that is far from the whole story. Alu's are involved in all known classes of regulatory elements, from new exon formation and alternative splicing to gene silencing, from INDEL formation to the regulation of the lncRNAs which organize chromatin loops into functional areas. Jacques et al. published a paper in 2013 titled "The

Majority of Primate-Specific Regulatory Sequences Are Derived from Transposable Elements."[57] They point out that TEs have contributed nearly half of the regulatory elements of the human genome. In mammalian genomes, 44% of the open (active) chromatin is in TE-rich regions, hence with transposon-driven regulatory elements. In primate-specific regions, the figure is 68%. Hundreds of thousands of TE sites in the human genome are highly conserved and enriched with binding sites. Such conserved TEs located within genes frequently act as cis-regulatory elements modulating the expression of their "host" genes.

Controlling transcripts of Alu's are also edited by ADAR (Adenosine Deaminase Acting on RNA) enzymes. Such adenosine to indosine editing forms a significant alternate information mechanism, forming a binary A/I combinatorial code editor expanding the transcriptome and used to refine somatic cellular differentiation. Correlated editing is observed for pairs and triplets of specific adenosines along the Alu sequences. Such A to I editing of Alu transcripts by ADAR1 enzyme is especially high in neural stem cells and is widely involved in the differentiation of human embryonic stem cells, especially in neural cell lines (30 genes).[58] Alu editing modifies the transcriptome at a much higher level in humans than in chimps, particularly in neuronal loci, even where the genomic Alu structure is unmodified.[59]

Transposable elements such as Alu's are common in loci involved with DNA damage and repair, and are notably active in tissue (cell-type) differentiation. TEs play roles in inflammation, immune function, embryogenesis, cellular response to external stimuli, and in hormonal responses.[60] They are activated not only in embryonic cells and cancer cells, but also in some active somatic cells, notably in the brain—as many as 13,692 Alu's and 1,350 SVAs. TEs mobilize protein-coding genes, which are actively expressed in neural cells during development, producing a somatic mosaicism (cells with different nuclear DNA), particularly in the hippocampus and caudate nucleus.[61] This implantation of new TEs continues throughout life in active neural tissue (such as the hippocampus) in which they may be involved in memory formation. Producing further diversity, there are thousands of Alu inserts which vary between populations. Notably, probably due to their longer history, African populations have numerous intermediate frequency inserts which are absent in non-Africans. However, few of these population-specific insertions are in exons, since exonic interruptions are rapidly removed by selection.[62]

Also, most of the extensive INDEL variation (insertion/deletion mutations) between chimps and humans (26,509 sites) is due to Alu insertions in the human lineage, insertions which correlate with significant differences in gene expression and with large INDEL variation close to coding loci. Seventy-seven percent of chimp-human INDEL variants are associated with retrotransposons, and two-thirds of them are in humans. In humans, INDELs are mostly insertions, in chimps they are evenly split between insertions and deletions. There is substantial evidence that INDELs caused by TEs have produced significant adaptive changes in gene regulation in multiple human tissues.[63]

Transposons are also shown to modify and control lncRNAs. As stated, lncRNA transcripts organize chromatin into functional locations, and there are at least five to ten thousand lncRNAs in the genome. TEs specifically signal for the biogenesis of many lncRNAs, including 30,000 unique sites for transcription initiation, splicing, or polyadenylation in humans. Thirty-five thousand of these TEs marked as open chromatin are located within 10 kb upstream of lncRNA genes.[64]

But not all TEs involved in regulation are Alu's. Other ancient DNA transposons, such as the zinc finger ZBED proteins, have also been utilized as regulatory proteins for controlling a variety of "host" functions. ZBEDs originate from hAT transposons, which have contributed modular DNA and protein interacting domains to vertebrate regulatory innovation in lineages from zebra fish to humans.[65]

Further, although genetic stasis is typically maintained by blocking TE mobilization (by DNA methylation and histone modification), physical stress due to climate change, and other things, may disrupt such epigenetic regulation and release the TEs. The epi-transposon hypothesis proposes that TEs can cause a punctuated pattern of evolution due to such alterations in their epigenetic regulation. Methylated (deactivated) Alu sites are frequently reactivated (demethylated) under stress, thus allowing an explosion of new diversification, possibly punctuated change, driving new adaptive evolution. Also note

that the effective epigenetic silencing of retained transposons in eukaryotes not only blocks their activation—it also blocks their selective removal.[66] Such blocking allows further transposon accumulation, which potentiates still higher levels of cleavage and DNA resection, thus increased sequence variation and genome rearrangement. Then, in theory, when some form of shock reactivates blocked TEs by removing their epigenetic constraints, it can allow punctuated bursts of innovation. Such nonadaptive evolution could escape adaptive peaks, disrupt genetic stasis, restructure the genome, and increase genetic innovation and diversification.

Transposable elements move and spread in genomes in a lineage-specific fashion—which is particularly true in humans. Specifically, Alu's are unique to primates and apparently have been involved in their evolution for 55 million years, with new bursts of Alu's appearing at bifurcations of the lineage (for instance, at the time of primate emergence 74K/98K years ago, or at other primate branch points such as 65M, 45M, 30M in old world monkeys, the expansion of ALUY in apes, or the rapid expansion of the ALUYa5 and ALUYb8 families in humans at 2.5–3.5 mya).[67] Britten considers transposing elements to be major actors in the rapid evolutionary alterations which have produced humanity. He ties the uniquely rapid evolution of the human lineage for the last 1.5 million years specifically to Alu activation, showing that TEs continue to actively generate effective genetic alterations at the present.[68] Notably, humans have seven new families of Alu's not present in chimpanzees. In particular, humans have a unique highly active class of Alu's—ALUYa5s—with an Alu insertion rate twice as high as any found in chimpanzees. In further evidence of recent activity, 655 perfect Alu copies have been reported in humans—that is, copies which are so recent that they have not accumulated any mutations.

But what a paradox—a uniquely high level of essentially unpredictable inputs from a genetic cut-and-paste mechanism has apparently produced the most remarkable species on the planet! This, of course, does not deny the action of natural selection in vetting these new variants. What is remarkable is not their survival, but their mode of arrival. One hint may be that TE insertions tend to target active genes; thus, higher levels of activity in neural genes might potentiate the production of higher diversity at those loci—at exactly that time when the demand for more neural processing power and plasticity was heating up, producing a snowballing increase in neural capacity.

So, what insights might the knowledge of the unique nature of human genetics yield to a Christian view of humanity? We must not change our background principles—God has made us in God's image. But how should we alter our "specifying assumptions" to connect these data with those background principles? The long discussion of the *imago dei* has centered on several concepts—notably, reason, righteousness, relationship, and rule—or culture, character, community, and commission.[69] And scientific descriptions of human origins do indeed have some relationship to these foci. The rational capability of the human mind is a product of a myriad of genetic alterations to neural loci. Questions of morality and community—as in "theory of mind" studies—are considered key elements of the functional purpose human rationality has played in survival (selective regime). The extended plasticity of human neural development and the recursive nature of human language make possible the growth and retention of culture. And all of these unique human features give us the power, for better or worse, to shape our environment toward our goals. Of course, this no more means that the image of God is "nothing but" a product of our biology, than that a Beethoven concerto is "nothing but" the product of microscopic pits on a plastic disk.

There are really two questions to ask in relating the genetic evidence to the nature of humanity: what has been done, and how was it done? One thing that the data make clear is that the unique character of the human mind is not due to a "magic bullet"; it is not a matter of just a few major alterations to an existing pattern, that is, it is not the injection of a "new" set of control genes. Rather, it involves the wholesale alteration of the entire hominine genetic package. Every known type of regulatory component which acts to shape the brain has been altered. It seems a selecting regime has indeed been at work, drawing the entire genetic system toward the human state. But, speaking of a selective regime is not an explanation—it is simply a description of the exterior pressures implied by the interior change.

Whether or not one wishes to invoke only "natural" causes, the acceptance of providence as a specifying assumption demands that what we see in nature be viewed as the action of the creative hand of God.

That alters the meaning of "natural cause," of course, making it different from the assumptions of a materialist. But "providence" does not necessarily mean that God acted by altering the direction of causation—not if the entire creation has been directed toward this end from its beginning (not that we have arrived yet). The creation is the product of the command of God spoken in eternity; it is shaped by the Word of his power, that Word that has echoed down through all of space and time from its end to its beginning, drawing all things toward the parousia, the final goal—a "holo-teleology." If God ordains the effects (the end point), then that necessitates their causes, and that ordaining occurs in eternity. But for observers within time, those effects simply flow from their causes "naturally."

In terms of the question of how this change was brought about, clearly transposons were a central factor. Alu's in particular have been particularly active in altering the human genome. Does the use of such a uniquely high level of transposon activity in the production of the modern human genome militate against viewing human evolution as a providentially guided process? After all, transposon movement/insertion appears to be a matter of pure "chance," unaffected by the "needs" of an organism. Does this make humanity a happenstance, the product of the biggest engine of chance in the animal kingdom? Or are we seeing the providential hand of God who is the Lord of "chance"? Or both? The evidence of "random" events does not exclude providence—in fact, the meaning can be viewed as quite the opposite. Our origin does not look like "business as usual" in the ecosystem, even if we can explain what happened. This judgment, I would suggest, can be viewed as a valid perception of "design" if one wishes to, but what can be seen is the design of the whole, not the designing of its parts. However, such perception requires the acceptance of the specifying assumption that God governs natural events (the doctrine of providence). Thus, it is rational to hold this view, but it is not necessarily statistically demonstrable to those who cannot perceive it. I do not know what new data will turn up in the next few years, but in my opinion, I do not think that we are irrational in holding that there was a highly directed process involved in the making of humanity.

Return for a moment to the question of how we should react to our kinship with the chimpanzees. Yes, our genetic likeness indicates that we are their closest relatives. But the data surveyed in this paper show that the human race has been made truly different. We are not simply the third chimpanzee species. Our reaction as Christians to all of this should simply be to stand in awe and wonderment at the complex methods which God used to mold us into his image—and to be thankful that he has allowed us to discover so much, to be allowed to look over his shoulder as he created us.

One final question: if God made us through evolution, are we still evolving? It depends on what you mean. There are indications that different human populations have become adapted to changes in their environment or culture through selected genomic changes. For instance, African populations have had an almost complete selective sweep of the FAD gene complex. Their allele freed them from dependence on marine omega 3 oils, and allowed them to move into the interior from the coastal regions. The FAD complex allows us to convert small fatty acids to the long chain versions necessary for brain development.[70] The less efficient, but original, allele is found in the chimp and in both Neanderthals and Denisovians.[71] The more efficient allele is specific to modern humans and arose after the lineages split, with a level of haplotypic diversity which indicates an origin at about 300,000 years. (The haplotypic diversity surrounding the original allele reflects an origin at around 600,000 years.)

This is interesting in light of one proposal, that modern humans evolved from an archaic population in the Levant around 300,000 years ago due to dietary pressures for the high fat intake needed to support their large brains.[72] Individuals with the less efficient allele need high levels of dietary omega 3 and omega 6 oils, which probably tied early members of the species either to marine habitats or to large animal predation. Individuals homozygous for that older allele must take care to breast-feed to support brain development. Individuals homozygous for the efficient allele should avoid overloading with long chain fatty acids to avoid inflammatory diseases.[73] Non-African populations have diversity at the locus; European, about three-quarters the efficient allele; far Asian, about one-half efficient; and Native American, almost entirely nonefficient.[74] Assuming that the African population of 60,000 years ago was mixed, the emigrants apparently took with them both alleles. Either drift or selection seems to have eliminated the efficient allele on the way to America, perhaps due

to a primarily marine diet of the migrants moving through arctic Beringia.

There are plenty of other examples. Agricultural populations have accumulated multiple copies of the amylase gene to digest their bread. Dairying populations have preserved regulatory changes (lactase persistence) which allow them to digest the milk of their cows. High latitude populations have conserved mutations that modulated the production of melanin which was blocking the ultraviolet rays that they needed for vitamin D/calcium metabolism. High altitude populations have adaptive changes to their respiratory and circulatory systems.[75] So yes, local populations are still changing under local selective regimes. But I know of no evidence that the core genes of our neural systems are being selected for different responses in different parts of the world. We would not expect that to be the case, if they have been shaped to allow us the neural flexibility to produce culture. And we are a young species, for all of that. We still have more genetic similarities, though we come from the ends of the earth, than two chimpanzees living 500 miles apart in the African forest. So no, we show no signs of splitting into multiple species. We remain brothers and sisters, one flesh.

Notes

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ASA/CSCA/CiS 2014 Annual Meeting

Pre-Meeting Workshops

McMaster University, Hamilton, Ontario
July 25, 2014
8:30am–4:30pm

Origins Today: Genesis through Ancient Eyes

Leader: *John Walton, Wheaton College*

The rift between faith and science in Christian circles today often results in the marginalization of Christians engaged in the sciences, impediments to evangelism, and the attrition of young believers who are told that Christianity is incompatible with the acceptance of evolution or an old earth. This presentation on Genesis 1–3 offers a fresh perspective on this complex issue by seeking to understand the message of scripture within its ancient context. Attendees will receive a free copy of John Walton's DVD on the same topic.

John H. Walton, professor of Old Testament at Wheaton College, specializes in the ancient Near Eastern backgrounds of the Old Testament, and specifically in Genesis. In recent years, he has focused attention on the issue of origins in books such as Lost World of Genesis One *(IVP) and* Genesis 1 as Ancient Cosmology *(Eisenbrauns). He has also contributed to two recent discussion books,* Reading Genesis 1–2: An Evangelical Conversation *(Hendrickson) and* Four Views of Historical Adam *(Zondervan).*

Progress and Challenges in Understanding Life's Origins

Leader: *Stephen Freeland, U Maryland Baltimore County*

The origin of life on Earth remains one of science's biggest mysteries. On the one hand, there is little agreement about exactly how, when, and where this took place. On the other, there have been remarkable advances on related fronts—from evolutionary biologists using DNA to look back ever further in time to geophysicists detecting life's presence in Earth's oldest rocks; from astronomers discovering ever more-habitable environments within our own solar system and countless solar systems separate from our own to chemists understanding how crucial building blocks may have arisen. This workshop will present an overview of these topics.

Stephen Freeland is an evolutionary biologist who studies how and why life on our planet evolved a system of genetic encoding. He is director of Interdisciplinary Studies at the University of Maryland Baltimore County (UMBC). He received a PhD from Cambridge University's Department of Genetics before crossing the Atlantic to pursue a scientific career in the USA.

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