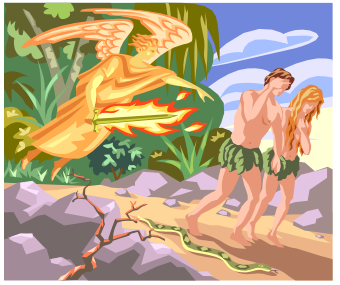
Updating Our Genetic Prehistory

David L. Wilcox



Presuppositions: Setting the Stage

1. The earth and its fullness belongs to the Lord - it is His creation. Expectations (predictions) about it drawn from the Biblical narratives are thus verifiable or falsifiable by valid data from God's creation.

2. This includes theological statements making real world predictions. Creation's data cannot be simply rejected, but requires theological reconciliation.

3. But traditional understandings predict (expect or state) patterns of data far different than those of modern investigation, producing a serious dilemma.

4. All theories are human formulations, but the data they explain are not human creations, but discoveries of God's truth. Theology may reject the theory, but it cannot reject the data – which means giving them rational explanation.

5. My intent is to survey recent genetic data related to the origin, nature and early prehistory of the human species. There are issues. They must be faced and worked out by theologians and scientists in open discussion.

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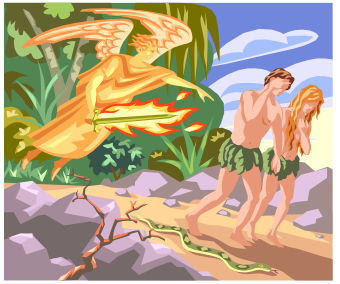
Preliminary Summary of Points



1. mtDNA 'Eve' – recalibration & new data places the human population root at least 180,000 years ago among the Khoisan people of South Africa.

2. New data on autosomal genetic diversity confirms that location and people.

3. New sequences located by genealogy searches place 'Y' chomosome 'Adam' in north-west Africa around 210,000 years ago. .

4. A possible reconciliation of the discrepancy may be people movements due to climate effects of the super-volcanic explosion at Toba (Indonesia) 74,000.

5. The rest of the earth was settled from Africa after 60,000 years ago – probably. The debate, re: time and path, is due to alternate techniques for calculating mutation rates – using living people or ancient ones.

6. Various techniques (linkage disequilibrium, retained diversity) use genetic data to calculate the history of human Ne (effective population size). Estimates average around 10,000 long term until the middle Pleistocene.

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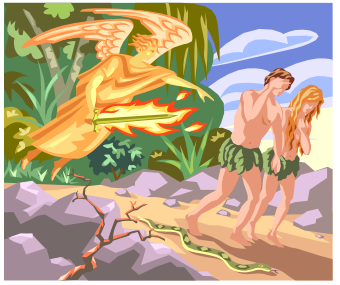


Preliminary Summary of Points

7. Very good, very new data for Neanderthal and Denisovan genomes provide evidence for some non-African interbreeding , and potentially, may allow specific identification of the genes which make us different than they were.

8. Although the data can be consistent with a bottleneck around 150,000 years ago, allele diversity (esp. at HLA loci) requires more than two ancestors.

9. What of the 'chimp connection'? – the idea of common plan is a double-edged sword. Chimp genes 'match' ours – but chimp bodies match 'gorillas' .

10. The ENCODE project – not 95% junk DNA, but the controlling RNA hierarchy – human uniqueness is here, particularly in neural control loci.

11. These genetic neural alterations make a profound difference in the brain's developmental trajectories – & probably our minds and skulls.

12. There is new data about specific 'famous' genes such as FOX-P2 or HAR1.

13. Humanity's genetic uniqueness was and is generated by ALUs - hyper-active retrotransposons cutting and pasting our genome. Random???

Batini 2012 The jigsaw puzzle of our African ancestry - unsolved or unsolvable? Batini and Jobling *Genome Biology 2011,* ***12:118***

The African root of humanity seems undeniable. However, there are differences between the specific origin points for Y chromosomes, mtDNA, autosomal DNA, language and archaeology.

In contrast, Wayne Frair's Separate Creation paradigm assumes (predicts) genetically equidistant continental populations

Frair 2000, Baraminology – Classification of Created Organisms, Creation Research Society Quarterly Journal 37:2, 82-91

Behar has recalculated the mtDNA tree based on a reference specimen from the root of the tree instead of the periphery. The new divergence point ('mitochondrial Eve') is around 185,000 years ago and separates the Khoisan people from the rest of *Homo sapiens*. Neanderthal sequences form a similar tree from around 200,000 years ago, but remain distant from modern humans.

Behar et. al., 2012 A 'Copernican' Reassessment of the Human Mitochondrial DNA Tree from its Root The American Journal of Human Genetics 90, 675–684, April 6, 2012

Schlebusch and Barbieri have further evaluated the amount of divergence present within the Khoisan people, placing the separation of the L0K and L0D halpogroups at around 100,000 years. This both supports the those people as the most ancient divergent human group, and indicates their population has been structured (with significant tribal separation) since that date.

Schlebusch, et. al. 2013 MtDNA control region variation affirms diversity and deep sub-structure in populations from Southern Africa
BMC Evolutionary Biology 2013, 13:56 doi:10.1186/1471-2148-13-56

Barbieri, et. al., 2013 Ancient substructure in early mtDNA lineages of southern Africa
American Journal of Human Genetics, Volume 92, 2013

Schlebusch has similarly shown that autosomal (nuclear) DNA SNP's are most diverse in the Khoisan population, consistent with their status as the earliest independent human group, showing a population divergence point of around 100,000 years ago.

Schlebusch, et. al., 2012 Genomic Variation in Seven Khoe-San Groups Reveals Adaptation and complex African History
Science 338, 374 (2012);

Likewise, Pickrell used SNP's from the nuclear genome to confirm the South African origin of our species. They identified the Khoisan chromosomal component of multiple South African tribal groups and calculated their time of divergence. They showed that the ancient click-speaking people of Tanzania – the Hadza and the Sandawe – are distantly related to the Khoisan, but that no other groups have those SNP's.

Pickrell, et. al., 2012 The genetic prehistory of southern Africa *Nature Communications*, 3:1143 *2012*

In 2008, the accepted root of the human Y chromosome lineage was set at around 60,000 years ago in Northeast Africa. Since then, the discoveries of a series of new deep branches of the entirely African A haplogroup have greatly extended the convergence point, and placed it in Northwestern Africa. The new time for 'Y chromosome Adam' is either 209,000 or 338,000 years depending on the method used to calculate mutation rate – which is under considerable dispute. The location of Y chromosome 'Adam' in the north is not under dispute, but this does raise questions when compared with the mtDNA 'Eve' location in the south.

Karafet, et. al., 2008 New binary polymorphisms reshape and increase resolution of the human Y chromosome haplogroup tree - *Genome Research* 23 388-395

Cruciani, et. al., 2011 A revised root for the human Y chromosome phylogenetic tree - the origin of patrilineal diversity in Africa - *The American Journal of Human Genetics*, 88, 814-818.

Scozzari , et. al., 2012 Molecular Dissection of the Basal Clades in the Human Y Chromosome Phylogenetic Tree journal. *PLOS One*, 7:11, e49170

Mendez 2013 An African American Paternal Lineage Adds an Extremely Ancient Root to the Human Y Chromosome Phylogenetic Tree. *The American Journal of Human Genetics* 92, 454–459, March 7, 2013

A considerable debate was generated by a study that measured mutation rates in living populations over one generation, using them to calibrate the timing of genetic genealogies rather than using the accepted times since common ancestors. The rates were about ½ those previously assumed, potentially pushing all dates much further back. This would imply among other things, much earlier divergence roots, a larger initial population, and an earlier dispersal from Africa (around 100,000 years ago through the Sinai rather than 60,000 years ago through Yemen). Several different studies have replied to this. For instance, Qiaomei used 10 ancient anatomically-modern human mtDNA genomes to calculate the mutation rate directly – giving a later timing. Mele evaluated the level of linkage disequilibrium in local populations world wide to determine which route was most likely, supporting the southern route. Soares evaluated the timing of the origin and expansion of the mtDNA L3 haplogroup which very early gave rise to the M & N haplogroups which settled the world, and showed L3 could not have arisen before 70,000 years ago. I conclude the later dates remain valid.

Scally & Durbin, 2012 Revising the human mutation rate - implications for understanding human evolution. *NATURE REVIEWS : GENETICS 13, 745-753*

Qiaomei, et. al., 2013 A Revised Timescale for Human Evolution Based on Ancient Mitochondrial Genomes *Current Biology*, 23:7, 553-559

Mele, et. al., 2011 Recombination Gives a New Insight in the Effective Population Size and the History of the Old World Human Populations. *Molecular Biology and Evolution 29:1, 25-30*

Soares, et. al., 2012 The Expansion of mtDNA Haplogroup L3 within and out of Africa. *Molecular Biology & Evolution.*29:3, 915-27

Which leaves the question of why 'Adam' and 'Eve' were living so far apart. Of course, these are not the Biblical individuals, but one would still expect the location of the earliest populations of males and females to be the same. The explanation, I would propose, lies in the African 'glacial' climate cycle. Basically, during glacial maxima and minima (now) North Africa is extreme desert. But, during the periods between, patterns of rainfall shift and the Sahara becomes Savannah and / or grassland for thousands of years. Thus, humans would have spread north across the Sahara and multiplied following the pent-ultimate glacial maximum (150,000 years ago), and the pent-ultimate glacial minimum (110,000 years ago), but would have been driven out as the climate worsened around 73,000 years ago. In fact, this exodus would probably have been quite abrupt since this is when the super volcano Toba exploded and cooled the earth. Thus, the northern tribes could likely have swept across the south and replaced the local males in a 'surfing' process of progressive displacement. That would replace the southern Y chromosomes, but the incoming northern autosomes & mtDNA's would be diluted out.

Tjallingii, et. al., 2008 Coherent high- and low-latitude control of the northwest African hydrological balance. *Nature: Geoscience 1, 670-675*

D'Errico,, et. al., 2009 Additional evidence on the use of personal ornaments in the Middle Paleolithic of North Africa. *PNAS 106:38, 16051-16056*

Trauth, et. al., 2008 Trends, rhythms and events in Plio-Pleistocene African climate. *Quaternary Science Reviews 11*, 399-411

Robock et al. 2009 Did the Toba volcanic eruption of ~74k BP produce widespread glaciation? *Journal of Geophysical Research 114,*

When did we start wearing clothes? Well, apparently lice started living in them between 170,000 and 80,000 years ago. This corresponds well with the pent-ultimate glacial maximum and a possible bottleneck. Certainly modern behavior….

Toups, et. al., 2010 Origin of Clothing Lice Indicates Early Clothing Use by Anatomically Modern Humans In Africa.
Molecular Biology and Evolution 28(1):29–32

The rest of the earth was settled by African emigrants leaving Africa about 65,000 years ago via the southern end of the Red Sea into Yemen. Apparently, the first wave moved eastward along the coast of the Indian Ocean, settling East & South Asia, arriving in Australia around 50,000 years ago. A population apparently remained in residence in refuges along the Arabian coast and the area of the Persian Gulf. A second wave apparently moved out from these Middle East refuges around 45,000 years ago – moving east through Asia & north-west across Europe. These migration events are easiest to trace via the progressive splitting of M and N haplogroups of mtDNA (females) & the F, C, and D haplogroups of the male Y chromosome.

As previously discussed, the timing debate centers around mutation rate calculations. But it also involves the nature of the archeological record in and along the Asian route of expansion – pre & post Toba. See Petraglia (2007) versus Mellars (2013). I think the later date fits the data.

Petraglia, et. al., 2007 Paleolithic Assemblages from the Indian Sub-continent Before and After the Toba Super-Eruption. *Science*; 317 ,5834

Mellars, 2013. Genetic and archaeological perspectives on the initial modern human colonization of southern Asia.
PNAS 10, 1073

RE: Linkage disequilibrium:

The average length of Haplogroup blocks is inversely proportional to the time a population has lived in its present location, and to Ne – its effective size. Linkage disequilibrium can also can indicate the time of admixture (if some sections of the genome have longer blocks). For individual genes – the length of flanking haplogroups is inversely proportional to the how long ago a beneficial gene was introduced into the population and indicates selection.

Such studies (Campbell and Tishkoff, 2008; Mele, et. al., 2011) show that all African populations have far shorter linkage groups than any population outside of Africa. This indicates that African populations are older, and hence the original source of the world's various local populations.

Mele, et. al., 2011 Recombination Gives a New Insight in the Effective Population Size and the History of the Old World Human Populations.
Molecular Biology and Evolution 29:1, 25-30

Campbell and Tishkoff, 2008 African genetic diversity: implications for human demographic history, modern human origins, and complex disease mapping. *Annual Review of Genomics and Human Genetics 9, 403-433*

Estimates of Human Ne – effective population size

Based on population logic – small populations lose diversity (INDELS, SNPs, Microsatellites, alleles, TEs, etc) & have low levels of linkage disequilibrium, etc. Ne also can be estimated for various time points in the past based on the amounts of remaining genetic diversity generated at those time points. Ne can be calculated for mtDNA, Y chromosomes, X chromosomes and autosomes – with sometimes differing results. The math gets complex --

But in summary: African Ne's are about 4 fold greater than Non-African Ne's. There is a general consensus for our (human) ancestral Ne of about 10,000 – see the estimates below.

Recent estimates of human Ne:

Tenesa	2008	Ne = 7500
Campbell	2010	Ne = 15,000
Mele	2011	Ne = 4000
Gronau	2011	Ne = 9000
Blum	2011	Ne = 14,000
Huff	2010	Ne = 9244
Hawks	2011	Ne = 10,000

Huff gives additional interesting values based on haplotypes linked to ancient Alu's (jumping genes). The value of 9300 applies to the last million years – before that, our ancestral Ne was 18,500 (and no more than 26,000). Compare that to the Chimp Ne of 21,000 and the Gorilla Ne of 25,000.

Also – different scenarios of population history can predict different – or the same – results

Estimates of Human Ne – effective population size

Tenesa, et. al., 2007 Recent human effective population size estimated from linkage disequilibrium. *Genome Research 17: 520-526*

Campbell & Tishkoff 2011 The evolution of human genetic and phenotypic variation in Africa *Current Biology* 20, R166–R173

Mele, et. al., 2011 Recombination Gives a New Insight in the Effective Population Size and the History of the Old World Human Populations. *Molecular Biology and Evolution 29:1, 25-30*

Gronau, et. al., 2011 Bayesian inference of ancient human demography from individual human sequences. *Nature Genetics* 43, 1031-1034

Blum and Jacobssen, 2011 Deep Divergences of Human Gene Trees and Models of Human Origins. *Molecular Biology and Evolution 28:2, 889-98*

Huff , et. al., 2010 Mobile elements reveal small population size in the ancient ancestors of *Homo sapiens* PNAS early edition

Hawks *2011 From genes to numbers - effective population sizes in human evolution.* Chapter in Recent Advances in Paleodemography, J-P Bocquet-Appel, ed., Springer

Li and Durbin 2011 Inference of human population history from individual whole-genome sequences. *Nature* 475(7357):493-6

Blum and Jakobsson (2012) raise the interesting discrepancy between the calculations for the common ancestors (TMRCAs) of different parts of the genome. Autosomal and X-linked genes have TMRCAs of on average, respectively, 1,500,000 and 1,000,000 years. Y chromosome and mtDNA TMRCAs are as we have seen around 200,000 years. They calculate the deep gene genealogies are consistent with the Out-of-Africa scenario if the ancestral Ne was around 14,000. They propose a bottleneck in the Middle Pleistocene (around 150,000 years ago) possibly arising from an ancestral structured population, as a possible scenario which can reconcile the contradictory findings. Both a "multiple archaic populations" model and a sudden bottleneck, can account for the 8-fold discrepancy between TMRCAs. Both scenarios of human evolution are different versions of a bottleneck in the human lineage before the succeeding migration out of Africa. Neither recent admixture (from Neanderthal) nor long-standing admixture (structured population) will do so.

Blum and Jakobsson 2012 - Deep Divergences of Human Gene Trees and Models of Human Origins *Molecular Biology and Evolution* 28(2):889–898

A similar pattern of historic changes in the Ne of the human population have been reported by other researchers – for instant Meyer, et. al. 2012 - based on comparisons between modern and Denisovan (archiac) genome sequences. Their calculations show low human Ne's around both of the last two glacial maxima, and higher Ne's during the last glacial minina.

Meyer, et. al. 2012 A High-Coverage Genome Sequence from an Archaic Denisovan Individual. *Science 338, 222-226*

Most people are aware that we have surprisingly complete data (Meyer, et. al. in 2012) from the genome sequences of our extinct closest relatives, the Neanderthals and the Denisovans, providing us important clues to human origins. They are less likely to know that Sven Paabo reported in May 2013 that they have obtained several new very good DNA samples from the Denisovan cave – from both more Denisovans and Neanderthals. Preliminary reports indicate that the Denisovans were members of a large population (diverse mtDNA) which showed some interbreeding (17%) with both Neanderthals and a more ancient hominine lineage (4%). Neanderthals, on the other hand, were inbred – a reduced population. The two lineages had mostly separated by 300,000 years ago, and their source population had separated from that leading to modern (African) humans about 450,000 years ago. But, it is clear that modern humans outside of Africa have a few (3%) 'Neanderthal' alleles, and that these are closest to the Caucasus group of Neanderthals. Also, some modern Melanesian populations have a few (5%) Denisovan alleles. The comparison of these archaic genomes allows the identification of thousands of genetic sequences unique to *Homo sapiens,* some of which I will discuss later. *But clearly a lot more is to come.*

Meyer, et. al. 2012 A High-Coverage Genome Sequence from an Archaic Denisovan Individual. *Science 338, 222-226*

Pennisi 2013 More Genomes From Denisova Cave Show Mixing of Early Human Groups. *Science 340, 799*

Lalueza-Fox, et. al., 2011 Genetic evidence for patrilocal mating behavior among Neandertal groups. *PNAS* 108:1, 250–253

Although clearly different species, a detectable amount of interbreeding occurred between some modern human (*Homo sapiens*) populations and the survivors of archaic lineages such as the Neanderthals, as shown by the presence of archaic gene sequences in some modern populations. Although it appears that level of interbreeding was very slight, some of the archaic genes – notably immune alleles – are very common in non-African populations. Parham's team predicted that 50 percent of the HLA-A alleles found in Europeans, up to 80 percent in Asians, and up to 95 percent in Papua New Guineans have an archaic origin. For instance, 50 to 60 percent of the HLA-A alleles found in certain populations in China and Papua New Guinea are HLA-A*11, one of the Neanderthal alleles. This may be due to selection for unique immune alleles more suitable for the antigens in a new environment – which could have produced some background selection / genetic hitchhiking.

Abi-Rached, et. al., 2011 The Shaping of Modern Human Immune Systems by Multiregional Admixture with Archaic Humans. *Science 334, 89-94*

However, the detection of admixture is a matter of probabilities, and different assumptions of just what happened alter the outcomes of calculations. For instance, when and where did admixture occur? Reich, et. al., 2011, assumes single pulses of admixture; Rasmussen, et. al., 2011, propose two waves of modern people entering into Asia, with the Denisovan admixture in first wave, Skoglund & Jakobsson 2011, propose two distinct Denisovan admixture events in Oceanians & East Asians, and Currat and Excoffier, 2011, see a continuous admixture along migration routes which overlapped archaic hominine ranges. Alves, et. al., 2012 point out that assuming higher rates of admixture raises the estimated time of divergence, and also raises the estimated size of the admixed population. In any case, the admixture must have been very limited in either location or in frequency – significant either pre or post reproductive isolation. With only a 5% success rate, the modern 'invasion' would have been swamped.

Reich, et. al. 2011 Denisovia admixture and the first modern human dispersals into southeast asia and oceania. *The American Journal of Human Genetics,* 89:4, 516-28

Rasmussen, et. al. 2011 An Aboriginal Australian Genome Reveals Separate Human Dispersals into Asia. *Science* 334, 94-98

Skoglund and Jacobsson 2011 Archaic human ancestry in East Asia. *PNAS* 108:45, 18301–18306

Currant and Excoffier – 2011 Strong reproductive isolation between human and Neanderthals inferred from observed patterns of introgression *PNAS* 108:37, 15129

Alves, et. al. 2012 Genomic Data Reveal a Complex Making of Humans. *PLOS Genetics* 8:7, e1002837

Obviously the issue of the size of the human population at its origin is important to theology, and the idea of a bottle neck is attractive. However, even if there was a bottleneck around 150,000 years ago, the human population can't be reduced to two people – previous ancestors or not. The problem is that two people can only have four alleles, total, at any specific locus – and if our species was ever that size, all present alleles would have to be descended from those loci. Particularly for the histocompatiblity loci in which high diversity is maintained by selection, there are far too many loci, and the very different existing alleles are homologous to sets of alleles found in other primates. It has been argued that this diversity must have been generated independently in the different species, but this has not been demonstrated as a possibility. The argument runs that since the introns of the *HLA-DRB* loci are more alike within the species, whereas the exons are more alike between species (data from Doxiadis, et.al., 2008), the exons must have been selected to diverge. However, if the specific HLA alleles are under strong selection, and the introns are not, the mutations – and cross-over exchanges – will be tolerated much more easily in introns, allowing a homogenization within the lineage. The initial report on the Chimp Genome Sequence (*Nature* 437, 69-87 (2005) evaluated the amino acid differences between human and chimp genomes for 13,355 protein coding loci out of 21,000. Substitutions in introns were 5.5 times more frequent than in exons. Synonomous exon substitutions were 33% more frequent. Substitutions in intron splicing junctions were 3 times less frequent. This is the sign of how strong the purifying selection is which retains protein sequences – including those of the immune system.

Hughes and Yeager, 1998, Natural Selection at Major Histocompatibility Complex Loci of Vertebrates. *Annual Review of Genetics*. 32, 415-435

Doxiadis, et. al., 2008, Reshuffling of ancient peptide binding motifs between *HLA-DRB* multigene family members: Old wine served in new skins. Molecular Immunology 41:10, 2743

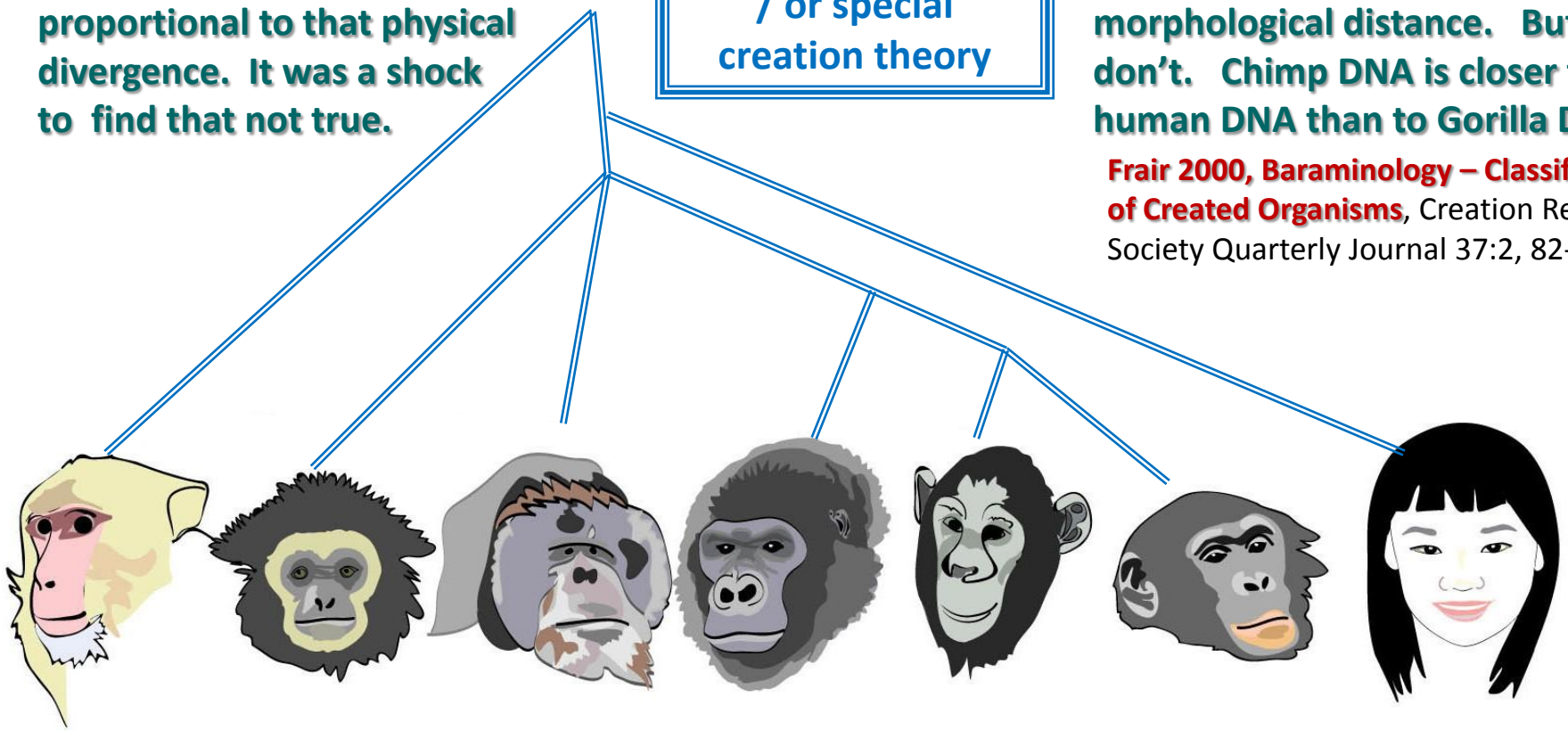
In the 1960's – a pre-genetic evaluation of human / ape differences based on morphology grouped chimps with gorillas, and both with orangutans, as simians – a separate clade from humans. The two clades were thought to be descended, respectively, from Dryopithecus and Ramapithecus. The expectation was that the molecular distances would be proportional to that physical divergence. It was a shock to find that not true.

I'm no kin to the monkey (or the Chimp)?

Expected (predicted) genetic sequence distances based on phenotypic data & / or special creation theory

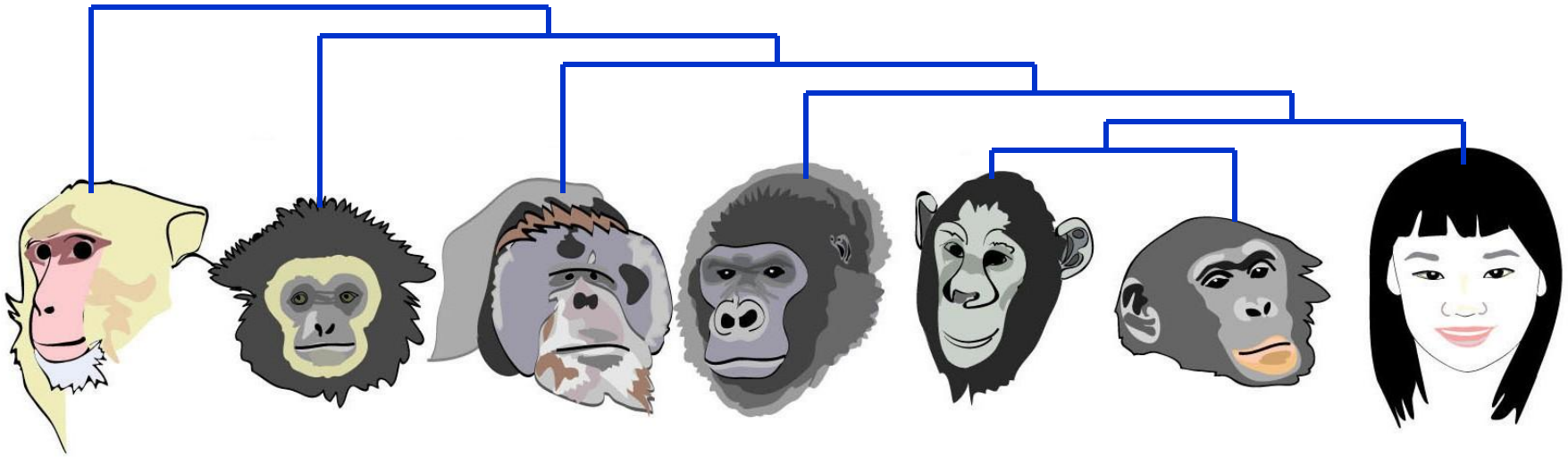
Likewise, in the baramin paradim of Wayne Frair & Kurt Weis, gorilla and chimp are placed in the same 'holobaramin', with common descent. In contrast, humans are only like them due to a common idea in God's mind – an 'apo-baramin'. In both cases, but especially with idea of a common plan, the expectation will be that molecular distances will reflect morphological distance. But they don't. Chimp DNA is closer to human DNA than to Gorilla DNA.

Frair 2000, Baraminology – Classification of Created Organisms, Creation Research Society Quarterly Journal 37:2, 82-91



Hacia, et. al. in 2001 evaluated differences in 29.3 kb of non-coding intergenic sequences, intronic sequences, pseudogenes, non-coding X chromosomes, Y chromosomes and coding sequences – synonymous, nonsynonymous or amino acid divergences. In every case, the distance from human to gorilla was the same as the distance from chimp to gorilla – and the distance from human to chimp was about 20% shorter. In every measure made, the human to chimp distance is the minimum. Yet chimp bodies are more like gorilla bodies. The genetic evidence only makes sense if chimps and humans share a common ancestor, and that ancestor was descended from a more distant common ancestor with the gorilla. This 'falsifies' the predictions of the special creations of kinds following common plans in God's mind. It also 'falsifies' the paradigm of anthropology held in the 1950s & 1960s. It supports a pattern of shared descent - people & chimps descended from common ape ancestors.

Hacia, J.G. 'The ape genome', *Trends in Genetics (2001) 17, 637.*



The Evolution of -> Our Knowledge of Genetic Complexity

Genes → Traits (genotype, phenotype)

Proteins as agents of traits

DNA as genetic material → Spells out protein (code) (Replication, Transcription, Translation)

DNA sequences also recognized as control elements – by proteins

Control proteins tie genes into logic circuits

Eukaryotic genes – Exon / Intron splicing – not all RNA translated

Eukaryotic genetic logic circuits are very complex

Human Genome Project – not enough proteins for the known complexity

Alternate splicing – transcriptome expansion of proteins

ENCODE – Non-coding transcription – anti-code, introns, micro-RNA, long ncRNA, transposons

Transposon movement – ALU expansion, expression – genomic engineering

Inc. exon splicing, control element movement, transcript use, post-conception?

What shall we say about the genes which make us human?

We and chimps share 96% to 99% of our protein coding sequences. Why are we different? Not the 1.5% of our genome that codes for proteins - but the 98.5% that controls their production. Literally, no other primate lineage has evolved as fast as our lineage has during the last 1.5 million years, and it's all due to unique changes in our control genome.

At least 80% - probably more – of our "non-coding" genome is also transcribed, starting from multiple start points, transcribed in both directions, with overlapping reading frames of many sizes and a whole spectrum of alterations, producing a whole zoo of 'new' types of RNA control elements – piRNA, siRNA, miRNA, sdRNA, xiRNA, moRNA, snoRNA, MYS-RNA, crasiRNA, TEL-sRNA, PARs, and lncRNA. Most of these unique RNA transcripts - and there are thousands, if not millions of them - are uniquely active in developing human neural tissue – uniquely active compared to their activity in chimpanzees, much less other primates or mammals. It is the new epigenetic world.

Keightly, et. al., 2005

St. Laurent, et. al., 2009

Lukic, et. al., 2011

Ng, et. al., 2011

McLean, et. al., 2011

Yan, et. al., 2011

Mattick, 2011

Somel, et. al., 2011

Li, et. al., 2012

Lee, et. al., 2012

Engreitz, et. al., 2013

Barbosa-Morais, et. al., 2012

Shulha, et. al., 2012

Arbiza, et. al., 2013

Iwama, et. al., 2013

ncRNA Human Epigenetics

Keightley, et. al. 2005 Evidence for Widespread Degradation of Gene Control Regions in Hominid Genomes. PLOS Biology 3:2, e32

St Laurent, et. al., 2009 Non-coding RNA transcripts-Sensors of neuronal stress, modulators of synaptic plasticity, and agents of change in the onset of Alzheimer's disease. *Neuroscience Letters. 466(2): 81–88*

Mattack 2009 The Genetic Signatures of Noncoding RNAs journal. PLOS Genetics 5:4, e1000459

Mattick, et. al., 2009 RNA regulation of epigenetic processes. *BioEssays* 31:51–59,

Haywood, et. al., 2010 Adaptive coding in human evolution *PNAS* 107:17, 7853–7857

Mattick 2010 RNA as the substrate for epigenome environment interactions. Bioessays 32, 548–552

Lukic and Chen, 2011 Human piRNAs Are Under Selection in Africans and Repress Transposable Elements. Molecular Biology and Evolution 28(11):3061–3067

Ng, et. al., 2011 Human long non-coding RNAs promote pluripotency and neuronal differentiation by association with chromatin modifiers and transcriptions factors. *The EMBO Journal* 1–12

McLean, et. al., 2011 Human specific loss of regulatory DNA and the evolution of human-specific traits.*Nature* **471**,216–2

Yan, et. al., 2011 Identification and Analysis of Intermediate Size Noncoding RNAs in the Human Fetal Brain. PLOS One 6:7, e21652

Somel, et. al., 2011 MicroRNA-Driven Developmental Remodeling in the Brain Distinguished Humans from Other Primates. PLOS Biology 9:12, e1001214

Lee, et. al., 2012 Epigenetic Regulation by Long Noncoding RNAs. *Science 338, 1435*

Li 2012 Evidence for Positive Selection on a Number of MicroRNA Regulatory Interactions during Recent Human Evolution journal. *PLOS Genetics* 8:3 e1002578

Barbosa-Morais, et. al., 2012 The Evolutionary Landscape of Alternative Splicing in Vertebrate Species. *Science* 338, 1587-93

Shulha, et. al., 2012 Human-Specific Histone Methylation Signatures at Transcription Start Sites in Prefrontal Neurons PLOS Biology 10:11, e1001427

Iwama, et. al., 2013 Human MicroRNAs Originated from Two Periods at accelerated rates in mammalian evolution. *Molecular Biology and Evolution* 30(3):613–626

Arbiza 2013 Genome wide inference of natural selection on human transcription factor binding sites. Nature Genetics 45, 723–729

Engreitz 2013 The Xist lncRNA Exploits Three-Dimensional Genome Architecture to Spread Across the X Chromosome. *Science Express, July*

What effects do these multiple classes of genetic control alterations have on human function? Significant unique human genetic alterations in function include thousands of agents active in cell proliferation and differentiation, tissue organization, long axonal and dendritic growth, axonal branching and connectivity, timing and amount of synaptic plasticity, astrocyte differentiation, and so on. Humans have more neurons than chimps, but not as many as you would think. The real difference is in their neuropril – i.e., the white matter between the neurons. That is because human neurons have an order of magnitude more neural connections, longer axons with more branches, increased long connectivity, increased local modularization and dramatically delayed synaptic maturation. The human neural system retains a unique genetic plasticity which extends throughout the life span. Humans also have unique classes of astrocytes (which are now known to modulate synaptic activity), with ten times more processes and faster calcium waves.

Oberheim, et. al., 2008

Britten, 2010

Haywood, et. al., 2010

Liao, et. al., 2010

Lin, et. al., 2010

Lambert, et. al., 2011

Zang, et. al., 2011

Baillie, et. al., 2011

Zheng, et. al., 2011

Sakai, et. al., 2011

Zeng, et. al., 2012

Liu, et. al., 2012

Hu, et. al., 2012

Chien, et. al., 2013

RE: Human Neural Genetic Change

Oberheim, et. al., 2009 Uniquely Hominid Features of Adult Human Astrocytes. *The Journal of Neuroscience*, 29(10): 3276 –3287

Britten 2010 Transposable element insertions have strongly affected human evolution. PNAS 107:46, 19945–19948

Haywood, et. al., 2010 Adaptive coding in human evolution *PNAS* 107:17, 7853–7857

Liao, et. al., 2010 Contrasting genetic paths to morphological and physiological evolution. *PNAS* 107:16, 7353–7358

Lin, et. al., 2010 Evolution of alternative splicing in primate brain transcriptomes. *Human Molecular Genetics.* 19:15, 2958–2973

Lambert 2011 Genes Expressed in Specific Areas of the Human Fetal Cerebral Cortex Display Distinct Patterns of Evolution. *PLOS One* 6:3, e17753

Zhang, et. al., 2011 Accelerated Recruitment of New Brain Development Genes into the Human Genome. *PLOS Biology* 9;10, e1001179

Baillie, et. al., 2011 Somatic retrotransposition alters the genetic landscape of the human brain. *Nature*. ; 479(7374): 534–537

Zheng, et. al., 2011 MAGUKs, synaptic development, and synaptic plasticity. *Neuroscientist.* 17(5): 493–512.

Sakai, et. al., 2011 Differential Prefrontal White Matter Development in Chimps and Humans. Current Biology 27, 1397-1402

Zeng, et. al., 2012 Large-Scale Cellular-Resolution Gene profilling in human neocortex reveals species-specific molecular signatures. *Cell* 149, 483–496

Liu, et. al., 2012 Extension of cortical synaptic development distinguishes humans from chimpanzees and macaques. *Genome Research* 22: 611-622

Hu, et. al., 2012 Evolution of the human-specific microRNA miR-941 *Nature Communications* 3, 1145

Chein, et. al., 2013 Targeted Disruption in Mice of a Neural Stem Cell-Maintaining KRAB-Zn Finger-Encoding Gene That Has Rapidly Evolved in the Human Lineage *PLOS One* 7;10, e47481

And it is not just comparisons with the chimpanzee genome which are significant. With high resolution genome scans of the archaic humans, with the Neanderthal and Denisovan people, it becomes possible to zero in on specific loci which are different in modern humans. Of course, most aren't. For instance, HAR1 is the most rapidly evolving site on the human genome. HAR1 produces an RNA control element which is involved in the control of the organization of the layers of the cerebral cortex. The unique human mutations changed the shape of the RNA from a hairpin to a clover-leaf. And HAR1 is the same in both modern humans and archaic humans. But other HAR's were selected after the human lineages diverged, as were other loci. One, for instance, is the MEF2A gene which delays synaptic development. In chimps this peaks before one year, in humans, at around 5 years. The indication is that the selective sweep for this gene postdates the split from the archaic lineages. And indeed, there is supporting evidence of a difference in genetic expression between our species in brain development. For instance, Gunz (2010) evaluation of the trajectory of brain growth in the species indicate our more rounded heads are due to a unique globularization phase in the first year or two of growth not seen in Neanderthals. Thus, the modern skull shape likely reflects an altered brain & mind.

Burbano , et al. (2012) Analysis of Human Accelerated DNA Regions Using Archaic Hominin Genomes. *PLOS ONE* 7(3): e32877

Beniaminov A et al. 2008 Distinctive structures between chimpanzee and human in a brain noncoding RNA. *RNA* ;14:1270-1275

Miller, et. al., 2012 Prolonged myelination in human neocortical evolution. PNAS 109:41, 16480-5

Gunz, et. al., 2012 A uniquely modern human pattern of endocranial development. Insights from a new cranial reconstruction of the Neandertal newborn from Mezmaiskaya. *Journal of Human Evolution 60, 300 – 313.*

Ponce de Leon 2008 Neanderthal brain size at birth provides insights into the evolution of human life history. *PNAS* 105:37, 13764–13768

The evidence of recent change can be subtle. For instance, probably the best known evolved 'neurological' gene is FOX-P2, the so-called 'speech' gene. The FOX-P2 is an ancient highly preserved gene which is needed, for instance, by song birds who must learn a new song. It is not exactly a 'speech' gene – more a gene about learning new muscular tasks. The KE family with speaking difficulties have a mutant form of the gene , not the ancestral allele. Mice engineered with the KE mutation show abnormal striatal activity when faced with learning a new task. True, the normal human form of the gene does have two altered sites compared to the ancestral allele found in chimps and mice. Vernes (2013) reports that the gene has 264 neural targets – it regulates mRNA production in genes involved with axonal and synaptic development. Indeed, the human allele thus altered the brains of mice engineered to express it. So, did those mutations give us speech? If so, the archaic humans made the modern protein. However, the FOX-P2 locus is not exactly the same in modern and archaic genomes. A recent report (Marisis, 2013) identified a number of altered sites in the introns, one of which is a recognition site (in intron 8) for the control protein POU3F2. The modern human haplotype has an altered nucleotide - at a site unchanged (been preserved) since our common ancestor with the zebra fish. This alteration changes the level of expression of FOXP2 - & the modern locus shows signs of a selective sweep. Also, there are unique modern targets for FOX-P2, e.g., the neural gene CNTNAP (Meyer, 2012)

Meyer, et. al. 2012 A High-Coverage Genome Sequence from an Archaic Denisovan Individual. *Science 338, 222-226*

French, et. al., 2012 An aetiological Foxp2 mutation causes aberrant striatal activity and alters plasticity during skill learning. *Molecular Psychiatry (2012) 17, 1077–1085*

Maricic, et. al., 2013 A Recent Evolutionary Change Affects a Regulatory Element in the Human FOXP2 Gene. *Molecular Biology and Evolution 30:4, 844-52*

Vernes, et. al. 2011 Foxp2 Regulates Gene Networks Implicated in Neurite Outgrowth in the Developing Brain. *PLOS Genetics 7:7, e1002145*

Unique modern genes from the initial Denisovan study – Meyer, et. al. 2012

They were examining protein coding sites highly conserved in primates – but changed in the modern human lineage after separation from the Denisovans.

Of the 23 most conserved positions with significant amino acid changes.

8 affect nervous system genes (function or development) (NOVA1, SLITRK1, KATNA1, LUZP1, ARHGAP32, ADSL, HTR2B, and CNTNAP2).

SLITRK1 and KATNA1 – axonal and dendritic growth
ARHGAP32 and HTR2B - synaptic transmission
ADSL and CNTNAP2 are implicated in autism
CNTNAP2 is regulated by FOXP2 and is associated with speech problems

Also, 4 newly changed loci affect the skin, and 6 of them affect the eye.

Meyer, et. al. 2012 A High-Coverage Genome Sequence from an Archaic Denisovan Individual. *Science 338, 222-226*

M Meyer et al. Science 2012;338:222-226

Are we still evolving? It depends on what you mean. There are indications that different human populations have become adapted to changes in their culture or environment by selected genomic changes. Agricultural populations have preserved 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. African population have had a selective sweep of the FAD gene complex which freed them from needing marine omega 3 oils, and allowed the move to the interior from the coastal regions. High latitude populations have conserved mutations which modulated the production of melanin which was blocking the UV they needed for Vit. D / calcium metabolism. But I know of no evidence that the core genes of our neural systems have been selected for different responses in different parts of the world. We still have more genetic similarities, though we come from the ends of the earth, than two chimps living 500 miles apart in the African forest. We remain brothers and sisters, one flesh.

Hollox, 2004 Evolutionary Genetics: Genetics of lactase persistence – fresh lessons in the history of milk drinking. *European Journal of Human Genetics* (2005) **13**, 267–269.

Perry, et. al., 2007 Diet and the evolution of human amylase gene copy number variation. *Nature Genetics 39:10, 1256-1260*

Mathias, et. al., 2012 Adaptive Evolution of the FADS Gene Cluster within Africa. PLOS ONE 7(9): e44926.

Strum, 2009 Molecular genetics of human pigmentation diversity. *Human Molecular Genetics 18, R9-R17*

What is truly mind-boggling is that this explosion of functional RNA control diversity is being driven by jumping genes – transposons. 44% of the regulatory elements in mammalian genomes are transposon driven, & as are 68% of those which are primate specific. In particular, the retroposon class of ALUs make up 10% of our genome – 1.1 million copies. ALU's are unique to primates, & apparently have been involved in their evolution for 55 million years, with a new burst of ALUs at each bifurcation of the lineage. The human lineage in particular has a unique highly active class of ALUs – Ya5's - withan ALU insertion rate twice as high as in chimpanzees. Of course, ALU insertion causes a lot of genetic defectives and cancers – but, that is far from the whole story. ALUs are retroposons, thus transcribed – if they are not repressed by methylation by miRNAs – & their transcripts fold into potentially active hairpins, as well as being reverse-transcribed back into the genome at random sites (where the DNA is most active). Humans have 655 perfect ALU copies, insertions so recent there's been no time for neutral mutations. ALUs add, control, & become part of regulatory sites. They are involved in all known classes of regulatory elements, from new exon formation & alternative splicing to gene silencing, from INDEL formation to the regulation of the long ncRNAs which organize chromatin loops into functional areas. Control ALUs are edited in their own binary code by ADAR enzymes & are involved in somatic cellular differentiation, notably in neural tissue. The implantation of new TEs continues throughout life in active neural tissue such as the hippocampus. It may be involved in memory formation. Last, deactivated ALU sites are frequently demethylated under stress, allowing an explosion of new diversification and possibly punctuated change, driving new adaptive evolution.

Zen, et. al., 2009

Paz-Yaacov, et. al., 2010

Osenberg, et. al., 2010

Polavarapa, et. al., 2011

Baillie, et. al., 2011

Wanichnopparat, et. al., 2012

Fedoroff, et. al., 2012

Dridi, et. al. 2012

Witherspoon, 2013

Jacques, et. al., 2013

Kapusta, et. al., 2013

Hayward, et. al., 2013

RE: The Roles of ALUs in Human Evolution

Zeh, et. al., 2009 Transposable elements and an epigenetic basis for punctuated equilibria. *BioEssays* 31:715–726

Britten 2010 Transposable element insertions have strongly affected human evolution. PNAS 107:46, 19945–19948

Paz-Yaacov-, et. al., 2010 Adenosine-to-inosine RNA editing shapes transcriptome diversity in primates. *PNAS* 107:27, 12174-12179

Osenberg, et. al., 2011 Alu Sequences in Undifferentiated Human Embryonic Stem Cells Display High Levels of A-to-I RNA Editing. *PLOS One* 5:5, e11173

Baillie, et. al., 2011 Somatic retrotransposition alters the genetic landscape of the human brain. *Nature*. ; 479(7374): 534–537

Polavarapu, et. al., 2011 Characterization and potential functional significance of human-chimpanzee large INDEL variation. *Mobile DNA* 2:13

Fedoroff, 2012 Transposable Elements, epigenetics and genome evolution. Science 388, 758-767

Dridi 2012 Alu Mobile Elements- From Junk DNA to Genomic Gems. Hindawi Publishing Corporation. Scientifica. V.2012, Article ID 545328.

Wanichnopparat , et. al., 2013 Genes associated with the cis-regulatory functions of intragenic LINE-1 elements. *BMC Genomics 14:205*

Kapusta, et. al., 2013 Transposable Elements Are Major Contributors to the Origin, Diversification, and Regulation of Vertebrate Long Noncoding RNAs. *PLOS Genetics* 9:4, e1003470

Hayward, et. al., 2013 ZBED Evolution - Repeated Utilization of DNA Transposons as Regulators of Diverse Host Functions. PLOS One 8:3, e59940

Jacques, et. al., 2013 The Majority of Primate-Specific Regulatory Sequences Are Derived from Transposable Elements. *PLOS Genetics* 9:5, e1003504

Witherspoon, et. al. 2013 Mobile Element Scanning (ME-Scan) identifies thousands of novel Alu insertions in diverse human populations. Genome Research, early pub.

Adam and the Sin Problem

Generic Head – Sin originated with Adam, and has been passed along to all his descendents (which is everybody) like a genetic inheritance. (? Does this mean Adam was the only ancestor for the race – or just a particular man who is in all our genealogies? – AKA, Y chromosome Adam)).

Federal Head – Sin originated with Adam. He was not the only man living, but God appointed him as representative and put him to the test. When he sinned, sin passed on to all men everywhere (and when) by divine fiat. I.E., there was a sudden transformation of human life.

Tribal Head – Adam was the "head man" of a small tribe put in the garden. The tribe was put to the test, and they all followed Adam's lead into sin. We are all descended from that tribe (alone?) and have inherited their sinful nature.

Cultural Head – Adam was the appointed race representative in the garden. He sinned. Sin passed on from Adam to all other people then (and now) alive by communication between people – especially in families. Human society suffered a gradual transformation as sin spread like an infectious disease.

Experimental Head – Sin was already there, but we don't know how – that's why the garden was needed, the perfect environment. Adam was the experimental proof of the human condition – he showed we humans are all sinners by nature – that it is not environmental.

Symbolic Head – Adam was a character in a story told to illustrate the human dilemma – we are sinners for some reason or other. But the story does not represent the origin of that state, only it's nature as rebellion against God.

Case Study - B. B. Warfield (1851-1921)

Systematic Theologian at "old" Princeton Seminary -- Formulated concursus argument for inspiration of Scripture, wrote for Fundamentalist involved in founding Fundamentalism (not dispensational).

from:"On The Antiquity and Unity of the Human Race" (1911)

"The fundamental assertion of the Biblical doctrine of the origin of man is that he owes his being to a creative act of God. Subsidiary questions growing out of this fundamental assertion, however, have been thrown from time to time into great prominence, as the changing forms of current anthropological speculation have seemed to press on this or that element in, or corollary from, the Biblical teaching. The most important of these subsidiary questions has concerned the method of the divine procedure in creating man. Discussion of this question became acute on the publication of Charles Darwin's treatise on the "Origin of Species" in 1859, and can never sink again into rest until it's thoroughly understood in all quarters that "evolution" cannot act as a substitute for creation, but at best can supply only a theory of the method of the divine providence...It is to theology...a matter of entire indifference how long man has existed on earth

WHO SHALL TELL THE ANCIENT OF DAYS HOW HE HAD TO ACT IN CREATION? HE IS NOT A TAME LION!