1 **The Out of East Asia model versus the African Eve model of modern human**
2 **origins in light of ancient mtDNA findings**

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12 Africa model, MGD theory, neutral theory, molecular clock

13

14 **Abstract**

15 The first molecular model of modern human origins published in 1983 had the
16 mtDNA phylogenetic tree rooted in Asia. This model was subsequently overlooked
17 and superseded by the African Eve model in 1987 that was premised on the
18 unrealistic infinite site assumption and the now failed molecular clock hypothesis. We
19 have recently developed a new framework of molecular evolution, the maximum
20 genetic diversity (MGD) hypothesis, which has in turn led us to discover a new model
21 of modern human origins with the roots of uniparental DNAs placed in East Asia.
22 While the African mtDNA Eve model has haplotype N as ancestral to R, our Asia
23 model places R as the ancestor of all. We here examined ancient mtDNAs from the
24 literature focusing on the relationship between N and R. The data showed that all
25 three oldest mtDNAs were R with the 45000 year old Ust'-Ishim a basal type and the
26 two ~40000 year old samples sub-branch of R. Among the numerous mtDNAs of
27 39500-30000 year old, most were R subtype U and only two were N samples, the
28 39500 year old Oase1 and the 34425 year old Salkhit. These N types are basal and
29 hence likely close to the root of N. These ancient DNA findings suggest that basal R is
30 ~5000 years older than basal N, thereby confirming the East Asia model and
31 invalidating the African Eve model.

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34 Introduction

35 Investigation into the question of human origins has a long history and two
36 competing models termed “Multiregional” and the “Recent Out-of-Africa” hypothesis
37 have been proposed ¹. In the Multiregional model ²⁻⁴, recent human evolution is seen
38 as the product of the early and middle Pleistocene radiation of *Homo erectus* from
39 Africa. Thereafter, local differentiation led to the establishment of regional populations
40 which evolved to produce anatomically modern humans (AMH) in different regions of
41 the world. *Homo* has been a single species since the genus first appeared in the fossil
42 record ~2.3-2.8 million years ago. The model has ample evidence from fossils and
43 Paleolithic cultural remains but consistent molecular evidence has been lacking until
44 very recently ⁵.

45 The single origin Recent Out of Africa model assumes that there was a relatively
46 recent common ancestral population for *Homo sapiens* which already showed most if
47 not all of the anatomical features shared by present day people. This population
48 originated in Africa ~200 ky ago, followed by an initiation of African regional
49 differentiation, subsequent radiation from Africa, and final establishment of modern
50 regional characteristics outside Africa ^{1,6}. These modern Africans replaced the archaic
51 *Homo* in Eurasia with limited genetic mixing ⁷⁻¹¹. Support for this model comes from
52 the African location of the earliest fossils of some AMH features ^{12,13} and the molecular
53 clock and neutral theory interpretation of the greater genetic diversity in Africans ⁶.
54 However, completely modern humans older than 20000 years have yet to be found in
55 Africa but did exist in Daoxian South China, although the Daoxian site has no

56 skeletons other than teeth, leaving it uncertain whether features other than teeth are
57 also completely modern ^{14,15}.

58 While long overlooked, there is in fact a third model based on mtDNA analyses. In
59 1983, researchers derived the first mtDNA phylogenetic tree and rooted the tree in
60 Asia ¹⁶. Unfortunately, this Asia model was superseded 4 years later by the African
61 Eve model without any valid reasons ⁶. The African Eve model assumes the molecular
62 clock while the Asia model not. Given that the universal molecular clock is widely
63 acknowledged to be unreal ¹⁷⁻²², a reexamination of these models is clearly warranted.
64 Furthermore, the Africa model requires the neutral theory and the infinite site
65 assumption, which, while largely sound as a null model and a framework for
66 pre-saturation evolutionary processes, are not *a priori* valid and have met with great
67 difficulties as an explanatory framework for most molecular evolutionary phenomena
68 ²³⁻²⁷. Obviously, inferring human origins by using genetic diversity data must wait until
69 one has a complete understanding of what genetic diversity means.

70 We have in recent years examined the longstanding genetic diversity riddle and
71 developed a more complete evolutionary account, the maximum genetic diversity
72 (MGD) hypothesis, that has been productive in addressing both evolutionary and
73 biomedical problems ^{21,28-36}. The MGD theory has solved the two major puzzles of
74 genetic diversity, the genetic equidistance phenomenon and the much narrower range
75 of genetic diversity relative to the large variation in population size ^{27,28}. The genetic
76 equidistance result of Margoliash in 1963 is in fact the first and best evidence for MGD
77 rather than linear distance as mis-interpreted by the molecular clock and in turn the

78 neutral theory^{19-21,28,34,37,38}. The MGD regards the genome to be mostly functional and
79 under stabilizing selection. We have shown that genetic distances or diversities today
80 are mostly at optimum saturation no longer related to time of evolution. However, the
81 molecular clock and neutral theory misread reality of genetic diversity as still related to
82 time of evolution.

83 Based on the MGD theory, we have developed the “slow clock” method that only
84 uses slow evolving DNAs for demographic inferences because they are more likely to
85 be neutral and away from the saturation phase of evolution^{5,34,39,40}. Our analyses
86 have led to a new scheme of modern human origins largely consistent with the
87 multiregional model in terms of autosomes where the first split among major human
88 groups is placed at ~1.9 million years ago⁵. Different from the multiregional model,
89 however, our new scheme has solved the origin problem of the modern uniparental
90 DNAs that obviously can only have originated from a single region as the coalescence
91 time of the modern mtDNA lineages is much shorter than 1.9 million years and as
92 archaic humans, such as Neanderthals, Denisovans, and Heidelbergensis, clearly
93 carried distinct lineages⁴¹. Our model placed the roots of both mtDNA and Y
94 chromosome in East Asia⁵, which independently confirms the 1983 finding on the
95 Asia origin of mtDNA¹⁶. Our model furthermore specifically places the least
96 differentiated haplotype R0 or R* as the ancestor of all mtDNA haplotypes, which is in
97 contrast to the African Eve model that puts R downstream of haplotype N (Figure 1).
98 The R0 haplotype is most common today in the Southern Chinese group in the 1000
99 genomes project, implicating the origin of the modern mtDNA lineage in Southern

100 China⁵. Our mtDNA tree was derived from analyzing present day haplotypes without
101 needing to use ancient samples. Therefore, its validity can be independently tested by
102 using ancient DNAs.

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105 **Figure 1. mtDNA phylogenetic tree of the Out of East Asia model.** Only major
106 braches and representative mutations are shown. Slow evolving sites (altering protein
107 and RNA sequences) in black and fast sites in red. Also shown are several
108 representative ancient DNAs that were placed based on their variant types. It should
109 be noted that tree topology was built without making use of any ancient DNAs.

110
111 The Africa model assumes the infinite site assumption to classify haplotype
112 relationships based on inference of ancestral and derived alleles with the allele
113 identical to that of chimpanzees as the ancestral. However, the infinite site model is in
114 fact unrealistic because there is overwhelming evidence of mutation saturation as
115 explained by the MGD theory, which makes the inference of ancestral alleles

116 meaningless. Actually, the Africa Eve phylogenetic tree cannot even meet the
117 minimum standard of a scientific model, i.e., self-consistency, as it contains huge
118 number of back mutations (reversions to an ancestral allele) that violate the infinite
119 site assumption required to build the Africa model in the first place. These mutations
120 can be found in the official mtDNA tree, phylotree (<http://www.phylotree.org/>), and are
121 designated by an exclamation mark (!) following the position numbers in phylotree.
122 The total number of these back mutations in phylotree is 1180 per our manual
123 counting. For example, of the 5 defining mutations for haplotype N, one at site 15301
124 is a back mutation.

125 Another premise (inferred from the molecular clock) for the Africa model is that
126 the original ancestor group should today show highest genetic diversity. However, as
127 the MGD theory explains, reality is that different groups may show different maximum
128 genetic diversity and human groups today are at saturation level of genetic diversity
129 for the fast evolving DNAs⁵. Africans do have the highest genetic diversity but only in
130 fast changing variants and deleterious variants such as stopcodon gain/loss variants⁵.
131 They in fact do have the highest genetic diversity in slow evolving neutral variants⁵.

132 Unlike the Africa model, our Asia model, as well as that of Johnson et al¹⁶,
133 however, is based on the common sense that the original type should be the least
134 differentiated. The original ancestor should mostly carry major alleles at SNP sites
135 because as the ancestor population grew in size only a small fraction of the group
136 should carry alternative mutant alleles (mutations are rare events). Indeed, the 45000
137 year old Ust'-Ishim's mtDNA had fewer SNPs to begin with and the one he did have

are all common alleles in today's population (>67%) except one site 16150¹⁰. The Asia model also regards mutations in mtDNA to be functional, which has ample evidential support^{26,33,42,43}, and classifies haplotypes based on sharing of alleles with more weight on the slow evolving sites (altering protein or RNA sequences)⁵. Hence, the Asia model is inherently more sound and self-consistent than the Africa model due to stronger theoretical foundations and far more realistic assumptions. Nonetheless, direct experimental test of these models is required to be absolutely certain. As our mtDNA tree was not derived by making use of ancient DNAs, it can be independently tested by using ancient samples. Recent discoveries in ancient DNAs have made such test possible and we here found the Asia model strongly supported by the ancient mtDNAs findings from the recent literature.

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150 **Results and discussion**

The relationship between N and R is the most obvious difference between the Africa and the Asia model. Of the three oldest mtDNAs, all turned out to be R, the 45000 year old Ust'-Ishim from Siberia¹⁰, the 40328 year old Tianyuan from Northern China⁴⁴, and the 39805 year old Fumane2 from Riparo Bombrini Italy⁴⁵. Tianyuan was haplotype R subtype B as reported. Fumane2 was closest to extant HV or H haplotype (KP34013 and KF523402) per our analyses of the NCBI database. Only the oldest R sample Ust'-Ishim was found to be basal, consistent with expectations. All three had the expected mutations within R haplogroup (73G, 263G, 750G, 1438G, 2706G, 4769G, 7028T, 8860G, 11719A, 14766T and 15326G). But Ust'-Ishim had

160 only 1 extra mutation (16150T), Tianyuan had 6 extra mutations (a 9 bp deletion, 5348,
161 5836, 11257, 16189, 16293), and Fumane2 had 3 (5585A, 16129A and 16304C).
162 These extra mutations are mostly minor or rare alleles in present day people,
163 indicating that Ust'-Ishim is more basal and less differentiated than the other two
164 younger samples.

165 Among relatively younger samples of 39500-30000 years old, two N samples
166 were found, the 39500 year old Oase1 from Romania⁹ and the 34425 year old Salkhit
167 from Mongolia⁴⁶. In contrast to the rarity of N, numerous samples of R subtype U
168 were found in Europe as recently summarized by Deviese et al⁴⁶, indicating that R*
169 basal samples may only be expected near the time when the root of R lived, which
170 should be close to 45000 years ago as marked by the R* sample Ust'-Ishim. If R is
171 indeed the root of modern mtDNA, then the modern lineage should not be much older
172 than 45000 years old. In fact, while partially modern skeletons can be found in many
173 sites in Africa and Asia at 310000-80000 years ago^{14,15,47-53}, no human skeletons that
174 were fully modern for all key skeletal features have been found prior to 50000 years
175 ago⁵⁴. As the demise of Neanderthals is thought to be associated with the arrival of
176 modern humans and occurred at ~40000 years ago⁴⁵, one can infer that the
177 appearance of fully modern humans may not be much earlier than 40000 years ago. If
178 it is much earlier, one would have the difficulty to explain the long lag before the
179 demise of Neanderthals.

180 Both the N samples were found to be basal N* and not directly ancestral to any
181 present day haplogroups⁴⁶. Oase1 had all N defining mutations except 8701G and

182 9540C and 6 extra mutations (3205A, 3462T, 4232C, 7158G, 8749C, 11016A). Salkhit
183 had all N defining mutations and 10 extra mutations (4113A, 5492C, 8155A, 9456G
184 slow, 9509C, 10364A, 14578T, 15077A slow, 16169T, 16092Gap). These extra
185 mutations are also mostly minor or rare alleles in present day people. So, both of
186 these N* samples appear to be far more differentiated than the R* type of Ust'-Ishim.
187 As these two N* samples had ages of 39500-34425 years and no N subtypes were
188 found in the numerous mtDNA samples from 40000-30000 years ago, which is in
189 contrast to the abundantly found R subtype U, one can infer that the basal N*
190 ancestor probably lived at 39500-34425 years ago and cannot be much earlier than
191 39500 years ago or older than R*. It is therefore highly unlikely to detect the presence
192 of N in future samples older than 45000 years or the oldest R.

193 These two samples all have private mutations that are rarely found in today's
194 samples, indicating that those rare private mutations may represent adaptive changes
195 related to adaptation to ancient environments and may not be used to classify these
196 two samples as non-basal N. We note that Deviese et al ⁴⁶ used the molecular clock
197 method to calculate a split time between Salkhit and basal N* to be 19000 years and
198 thus considered the appearance of N* basal type to be at ~50000 years ago. However,
199 such calculation may not be realistic as it did not consider the adaptive non-neutral
200 roles of the ancient variants. Variations in mtDNA are mostly adaptive or under natural
201 selection. Although distance among haplotypes may show some meaningful
202 correlation with time of separation, such correlation are all derived by using present
203 day haplotypes where the effects of variations due to adaption to environments from

different eras are minimized. But comparing ancient DNA with present day haplotypes would represent a very different picture, because some variants in ancient DNAs may represent adaptive changes specific to the ancient environment. Those variants could be changed by today's environments rather than by neutral drift. Therefore, one cannot use the molecular clock derived from present day samples to calculate the split time between an ancient sample such as Salkhit and other haplotypes of either today's or ancient. In addition, if basal N* is indeed 50000 years old, it would contradict other findings. For example, one should find within the time window of 40000-30000 years ago differentiated N subtypes. And yet, only non-differentiated N were in fact found (Oase1 and Salkhit) that do not belong to any known present day haplotypes under N. In contrast, for a basal haplotype of truly 45000 years old such as R* , nearly all R samples found for the time window of 40000-30000 years ago were differentiated R subtypes such as U and B. Taken together, the combined data do not support placing basal N* at >40000 years ago.

There were two M samples aged 34000-35000 years, Goyet Q116-1 and Goyet Q376-3 from Belgium, found among samples older than 30000 years, and one M sample of 28000 years old from La Rochette France^{55,56}. As M is downstream of R and N in the Asia model but is parallel to N in the Africa model, the rarity of M relative to R and N in samples older than 35000 years is consistent with the Asia model but not the Africa model. Also, if the Africa tree is true where N and M are sister branches, the rarity of M in samples older than 35000 years ago further suggest that basal N* could not be 50000 years old.

226 That R* haplotype was found to be 5000 year older than N* haplotype as
227 discussed above is consistent with the 2 SNP difference between R and N (Figure 1)
228 and the mtDNA mutation rate of 2.67×10^{-8} substitution per site per year (5000 x 16500
229 x $2.67 \times 10^{-8} = 2.2$ substitution) as recently used by others ⁴⁶. This suggests that the
230 ages of the oldest R* and N* samples found so far were likely to be close to the real
231 ages for the R and N ancestors. If the Africa model is true, the age of the original
232 African L0 ancestor of all modern humans would be 120000 years old (35 SNPs
233 separate L0 and N). However, as there are no completely modern humans found in
234 Africa that are more than 20000 years old, the classification of L0 lineage as the
235 original ancestor may be unrealistic. It is however placed as one of the last evolved in
236 the Asia model, where its highly differentiated feature is a result of hybridization of
237 AMH with archaic humans and coevolution of mtDNA with the admixed nuclear
238 genome ⁵. It should be noted that the calculations here using molecular clock were all
239 dealing with present day haplotypes within the same environmental or time period.
240 Thus, effects of variants adaptive to environments of different eras are non-issues.

241 The original mtDNA type should leave more descendants today than the subtypes
242 because mutations are rare events and occur only to rare individuals in a large
243 population. We next asked whether the R haplotype is more popular today than other
244 types by examining the data collected by the mitomap database
245 (<https://www.mitomap.org/MITOMAP>). There are 64531 R samples in the database as
246 inferred by using the R defining SNP 16223C, representing 53.6% of the whole
247 collection. While the database may not be free of sampling bias and not all 16223C

248 carrying samples are R due to independent mutations (again violating the infinite site
249 assumption), one can nonetheless infer that it is highly likely for the R group to be
250 larger than any other haplogroup as it is found larger than all the other haplogroups
251 combined.

252 In contrast to the Asia model, the Africa model requires rare individuals with new
253 mutations to have a reproductive advantage over ancestral populations, hence
254 accounting for why the R group is much larger than any of its ancestor group, or why
255 L0 is smaller than the mutant group L1'2'3'4'5'6, why L1 is smaller than the mutant
256 group L2'3'4'5'6, why L5 is smaller than the mutant group L2'3'4'6, why L2 is smaller
257 than the mutant group L3'4'6, why L6 is smaller than the mutant group L3'4, and why
258 L4 is smaller than the mutant group L3. Such repeated reproductive advantages that
259 must be granted to each round of new mutations leading to a new haplotype are in
260 plain contradiction to the neutral mutation premise required to build the Africa model in
261 the first place.

262 In summary, the Out of East Asia mtDNA model is inherently more sound and
263 self-consistent than the African Eve model due to stronger theoretical foundations and
264 far more realistic assumptions. The original R and N are likely to have ages close to
265 those of the so far found oldest R* and N* samples, which showed that R* is older
266 than N* by 5000 years. These results plainly invalidate the African Eve model and
267 confirm the Out of Asia model. We expect our conclusion here to be further
268 strengthened by future ancient DNA studies.

269

270 **Methods:**

271 Sequence alignment and mismatches were performed using blastn at the NCBI
272 database. The number of back mutations in the mtDNA tree was inferred by counting
273 the exclamation marks (!) that designate the back mutations in the official mtDNA tree
274 phyloree (<http://www.phylotree.org/>). The number of R samples in the mitomap
275 database (<https://www.mitomap.org/MITOMAP>) were calculated by counting the
276 number of haplotypes having the R defining SNP 16223C.

277

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281

282 **Additional Information:**

283 **Competing Interests**

284 The authors declare that they have no competing interests.

285

286 **Author contributions**

287 Y.Z. and S.H. devised the project, analyzed the data and wrote the manuscript.

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