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Response: HLA Sequence Polymorphism and the Origin of Humans

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REFERENCES AND NOTES

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Response: Rampino (in his letter) and Knoll et al. (in their response) attempt to refute our proposition (1) that Late Permian marine invertebrate mass extinctions coincide with the widespread development of marine anoxia and dysoxia. Their arguments are based on diametrically opposed interpretations of the Permian-Triassic deep sea record of Japan, and both rely heavily on the data from the same paper (2). Thus, neither letter challenges the well-established fact that most Late Permian marine invertebrates disappeared in shallow marine settings at levels marked by the appearance of dysaerobic or anaerobic biofacies (3). Rampino notes that the decline of radiolarians in Japanese sections occurs within a thin, siliceous claystone of latest Permian age immediately beneath a thin, basal Triassic organic-rich mudstone—a dysaerobic facies (2). He therefore argues that the extinction (of radiolaria at least) occurred before the development of oxygen-poor conditions. However, he does not mention the evidence of dysoxic conditions in the claystone, namely, common microchannels of pyrite and discontinuous lamination (2).

Conversely, Knoll et al. acknowledge the oxygen-poor conditions recorded by the claystone (and the several meters of bedded, grey chert developed beneath this level) and argue that the organic-rich mudstone records improved oxygenation. This is counter to Kakuwa’s (and our) interpretation that this layer was a dysaerobic facies (2) and is primarily based on the presence of burrows in the mudstone and the interpretation of pyrite sulphur isotope variations (4). Kakuwa only illustrated millimeter-sized burrows from the claystone and mudstone, but did not document trace fossils from the underlying grey cherts.

Our observations of the chert ichnofabrics reveal them to be pervasively bioturbed by centimeter-sized burrows, testimony to substantially better benthic oxygen values than those of the organic-rich mudstone. The ichnofabrics, therefore, reveal a story of gradually declining benthic concentrations of O in the Late Permian record of Japan, culminating in low dysoxic conditions at the Permian-Triassic boundary. Identical changes are seen in contemporaneous shelf sections (5). Pyrite δ34S variations show a sharp negative swing in the organic-rich mudstone (4), which Knoll et al. interpret as a signature of a fully oxygenated water column. However, strongly negative values of pyrite sulphur (S) can also indicate intensely anoxic conditions such as those pertaining in the present-day Black Sea, where sulphide disproportionate bacteria repeatedly process and lighten elemental S (6). Sulfur isotypes of evaporites provide more conclusive, less equivocal evidence of global changes in the S cycle. These reveal a rapid positive swing beginning in the latest Permian and continuing into the Early Triassic (7), which indicates a major phase of pyrite burial and oceanic anoxia. This evidence alone seems sufficient to rule out the scenario of oceanic overturn and ventilation proposed by Knoll et al. (8).

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REFERENCES

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HLA Sequence Polymorphism and the Origin of Humans

In the paper, “The myth of Eve: Molecular biology and human origins” (1), Francisco J. Ayala has made some questionable inferences about the origin of the human species based on analyses of mitochondrial DNA (mtDNA) and human lymphocyte antigen (HLA) sequence polymorphism. Ayala (i) argues that the data on primate HLA class II sequence diversity contradicts the “Mitochondrial Eve” hypothesis (2) about modern human origins, and (ii) estimates that the size of the founding human population was at least 100,000, primarily on the basis of assumptions about the number of DRB1 alleles transmitted to humans from the ancestral species.

It is inherent in the nature of maternal inheritance that all contemporary mtDNA lineages are derived from (or coalesce to) a single founding lineage. The hypothesis as stated by Cann et al. (3) simply postulated that this founding lineage was African and that the coalescence time was on the order of 100,000 to 200,000 years. The identification of a particular founding African mtDNA lineage says nothing about the size of the human population at that time. An estimate of the effective human population size (Ne), based on the diversity of mtDNA sequences among contemporary humans, was reported by Wilson and colleagues over a decade ago (4); Ne = 6000 females. Other recent estimates, based on classical polymorphisms (5) and Y chromosome–DNA markers (6), are also on the order of 10,000 individuals. Ayala argues that, when one considers various sources of error, these estimates are not inconsistent with his estimate of more than 100,000 individuals from the HLA data. In our view, however, a more realistic appraisal of the HLA class II sequence polymorphism also leads to an Ne of about 10,000, in line with Ne estimates from other molecular genetic data.

The extensive polymorphism at the HLA class II loci (for example, DRB1) is localized to the second exon, which encodes the peptide binding groove, and, in particular, to those codons encoding amino acids involved in interaction with the peptide and T cell receptor. The crust of the argument relating the contemporary HLA polymorphism to the size of the founding human population is the estimated number of alleles that were transmitted to the human lineage from the ancestral species. Obtain-
ing this estimate involves critical assumptions about the "age" of contemporary alleles and the rate of allelic diversification. Many DRB1 polymorphic sequence motifs are shared among different contemporary primate species, suggesting either conservation over millions of years of evolution, or convergent evolution. Many of the DRB1 "allelic lineages" (that is, a cluster of closely related alleles that may have a single serotype, such as DR1) may predate the separation of the hominoid species (5 to 7 million years ago). However, given the significant amount of postspeciation sequence diversification within these lineages inferred from phylogenetic tree analysis (7, 8), the number of DRB1 alleles transmitted from the ancestral species to modern humans may be substantially less than that estimated by Ayala.

Ayala estimates that, of the 61 human DRB1 alleles included in the phylogenetic analysis (figure 3 of [1]), 31 are over 6 million years old; this number is arrived at by applying an estimate of the substitution rate ("molecular clock") to the phylogenetic tree. By now, there have been over 100 DRB1 alleles identified in all human populations, but most populations have fewer than 25 alleles. In general, HLA class II second exon sequences are not well suited to phylogenetic analysis and the construction of gene genealogies. Given the evidence for positive selection at sites encoding the antigen binding amino acid residues (9), as well as the patchwork pattern of polymorphism indicative of gene conversion-like events (10), the application of phylogenetic tree-building analyses to the polymorphic second exon DRB1 sequences is problematic, and interpretations based on the topology should be somewhat guarded.

In 1991, two of us showed that the phylogenetic tree for the first part of the second exon (encoding the β-sheet floor of the peptide binding groove) had a different topology from that of the second part, encoding the α-helical wall of the groove (8). Thus, different parts of the second exon of DRB1 have different evolutionary histories, and, hence, the length of the branches separating DRB1 alleles may not be proportional to time. Also, the use of molecular clock analyses, with the assumption of selective neutrality and a constant mutation rate, may be inappropriate for DRB1 second exon sequences and result in an inflated estimate of the divergence times and age.

The problem with applying a molecular clock to HLA polymorphism can be revealed by comparing intron and exon sequences of the DRB1 alleles (11). The sequence differences between alleles in different lineages are only slightly higher (about 1.5-fold) for the exon sequences than for the intron sequences. By contrast, the genetic distance among alleles within an allelic lineage is about 30-fold higher for the exon sequences than for the intron sequences, presumably due to selection. Applying an intron substitution rate for primate sequences (1.4 × 10^−9 per site per year) (12) to these data indicates that the mean age of alleles within a lineage may be about 230,000 years, rather than the millions of years assumed in Ayala's calculation. Thus, these data suggest that only the allelic lineages predate the hominoid divergence, yielding an estimate of 8 to 9 rather than 31 DRB1 sequences that were transmitted to humans from the ancestral species.

With the use of a simulation model following populations containing 60 alleles over evolutionary time periods, Ayala concluded that, even with overdominant selection and selection coefficients (s) of 0.01 to 0.03, N_e must be greater than 100,000 to maintain the more than 30 presumed ancestral alleles. In general, how realistic are the assumptions in Ayala's model and how reliable is his estimate of N_e? On the basis of the data in our study (11) and on the considerations discussed above, the number of ancestral DRB1 sequences is likely to be less than 10 rather than over 30. Furthermore, this model assumes a selected mutation rate of 5 × 10^−7 per gene per generation as the only mechanism for generating new alleles. Recent experimental evidence analyzing HLA class II germline variation in human sperm, potentially generated by interallelic gene conversion-like events, suggests a frequency of around 1/12,000 (13). Thus, even if only 10% of these new variants are selected for, the selected mutation rate would be more than an order of magnitude higher than the number assumed by Ayala. In isolated Native South American populations, previously unreported (and presumably newly arisen) class I and class II alleles have been identified (14), suggesting the generation of several new alleles within the last 10,000 to 20,000 years. In general, selective pressures other than heterozygote advantage may be operating, selecting rare newly arisen variants in different populations. Ayala cites the HLA-related resistance to malaria and plasmodium falciparum (15) as an example of heterozygote advantage; however, what was demonstrated in this study was protection conferred by particular DRB1 and HLA-B alleles, not the operation of heterozygote advantage in the Gambian population.

The Ayala paper (figure 7 in [1]) shows that, even without considering a more realistic mutation rate, an N_e of only 10,000 is required to maintain 10 DRB1 alleles, the approximate number of ancestral DRB1 lineages inferred from the intron data (11). Contrary to Ayala's interpretation, the HLA DRB1 data are, in fact, consistent with the population sizes estimated by mtDNA sequence diversity and with the inference, based on mtDNA and recent CD4 haplotype data (16), of a population bottleneck associated with the "Out of Africa" migration. Thus, it is our view that the N_e of the early human population that can be estimated from the HLA polymorphism data is consistent with the estimates derived from the mtDNA sequence data that formed the basis for the "Mitochondrial Eve" hypothesis.

The distinction between N_e >100,000 as opposed to N_e = 10,000 is not trivial. It has been argued that the "Multiregional" evolution theory of human origins (17), which suggests that the transition from Homo erectus to H. sapiens involved population spread across the Old World from South Africa to Northern Europe and Asia, would require that N_e be much bigger than 10,000 (18). The fact that all the genetic data—including mtDNA, Y chromosome–DNA markers, classical polymorphisms, and (as we argue here) HLA class II sequences—suggest that N_e is on the order of 10,000 provides one of the most compelling arguments against Multiregional evolution and in favor of a recent (African) origin of modern humans.

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The divergence between the lineages that go one to humans and apes and the other to the Old World monkeys occurred 35 million years ago. It follows "that several human gene lineages already existed at that time" (1, p. 1931). The inference of a long-term population no smaller than 100,000 individuals is thus puzzling. That the size of the founding human population on the order of 10,000" if by \(N_e\) they mean the long-term effective size of human populations, this is not correct (1). If they rather refer to the size of the founding population of modern humans, then the genetic data are consistent with such a statement. Second, Erlich et al. state that a founding population on the order of 10,000 individuals "provides one of the most compelling arguments against Multiregional evolution and in favor of a recent (African) origin of modern humans." Erlich et al. find the arguments in favor of a recent African origin to be compelling, but Templeton has recently stated that there is "no evidence that supports the hypothesis of an African–non-African population split either in the mtDNA or the nuclear DNA data" (6). It seems to me that Erlich et al.'s contention should be with Templeton, not with me. I responded to Templeton that "there is plenty of evidence" for the split, and stated my conviction that the weight of the evidence "favors a recent African origin for modern humans" (7). Nevertheless, I am not persuaded that the evidence currently available is compelling.

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