Genetic Data and the African Origin of Humans

S. A. Tishkoff et al. (1) provide an intriguing analysis of human genetic variation at the CD4 locus. We are concerned, however, that their data do not provide significant support for the estimate that modern humans first emerged from Africa in the last 100,000 years. It appears that a robust estimate of this migration time will require the use of numerous loci.

The estimate, which is predicated on a set of assumptions listed in their paper, depends in part on estimating the relative ages of the Alu deletion [Alu(−)] allele in African and non-African populations. Tishkoff et al. argue that among Africans, the frequency of Alu(−) chromosomes linked to the progenitor [90 base pair (bp) specific tandem repeat polymorphism (STRP)] allele is given by $e^{-N_{A} \mu}$, where $N_{A}$ is the age of the Alu(−) allele and $\mu$ is the STRP mutation rate. (They give an equivalent expression for non-Africans, in which $N_{A}$ represents the time of migration out of Africa.) Under the assumption of no back mutations, this expression does give the expected frequency of the 90-bp allele on Alu(−) chromosomes. Because many of the individuals in the sample will have a shared ancestry, the alleles found in different individuals are highly correlated, and so an estimate based on this procedure may have an extremely high variance.

In estimating the age of the Alu(−) mutation, it is convenient to consider the problem in a coalescent framework (2). In this view, the individuals in a sample are related to one another by some ancestral tree (strictly speaking, this is ancestry at a specified locus). When a mutation occurs at some point on the tree, all the individuals who trace their ancestry through that point on the tree will carry that mutation (recall the assumption of no back mutation). This means that a mutation that occurs near the root of the tree will often be carried out by a large proportion of the sample.

We have investigated the problem of establishing a lower bound on $N_{A} \mu$, given the authors’ observation that 34 out of 85 non-recombinant African Alu(−) chromosomes carry the progenitor allele [some of the Alu(−) chromosomes seemed to be descended from a single recombinant and were excluded from the original analysis]. Their estimate of the migration time out of Africa is crucially dependent on this lower bound. No detailed theory exists for finding such a bound analytically. We can, however, approximate confidence intervals with the use of simulations of the coalescent process. If the entire African sample consisted of non-recombinant Alu(−) chromosomes, it would be reasonable to set bounds on $N_{A} \mu$ by using standard coalescent assumptions to generate random trees with 85 tips (3).

In this case, we also know the Alu(−) frequency in the total sample, and it is possible to use the coalescent approach to get the distribution of mutations in the Alu(−) chromosomes conditioned on that frequency. In order to do this, we have generated trees of 806 chromosomes [the sample size in the article (1)] and selected only those that contain a clade of 132 chromosomes [the total number of Alu(−) chromosomes]. The relative times of the nodes in the tree of 806 are drawn from an exponential distribution [the parameter is $\{2\}^{-1}$ between nodes $n_{i}$ and $n_{j}$ (4)]. Taking the clade of 132 to correspond to the 132 Alu(−) chromosomes, we have now specified the relationships within a simulated data set in which all the relative branch lengths have been drawn from the appropriate conditional distribution.

In the original data set, 47 of the 132 Alu(−) chromosomes were recombinants and were excluded from the analysis. In order to further condition our own analysis on this information, we have selected only those trees in which a clade of 47 lies within the clade of 132 Alu(−) chromosomes.

This procedure has allowed us to generate trees of 85 individuals whose relationships to the larger sample closely mimic those in the original data set. Each simulation specified the relative lengths of all the branches, and so picking a trial value of $N_{A} \mu$ for the top of the Alu(−) clade determined the expected number of mutations along each branch. For each simulated tree, and trial value of $N_{A} \mu$, the number of mutations on each branch was drawn from a Poisson distribution with that expected value.

Our results, based on 10,000 random trees that meet the above criteria, are rather striking. The value of $N_{A} \mu$, estimated using the method of Tishkoff et al., is 0.916; however, we have found the lower bound to be 0.12 at the 5% level of statistical significance (5). This indicates that their estimate of $N_{A} \mu$ could be seriously in error, and even without taking into account the variance in the other estimates in the original calculation, the technique used cannot reject a migration time out of Africa as much as sevenfold greater than the original estimate.

It is also possible to analyze the estimate of $N_{A} \mu$ in a similar manner. In this case, however, the coalescent assumption of single origin might break down because there may have been numerous Alu(−) chromosomes in the proposed migration event.

A further problem with the argument presented by Tishkoff et al. (1) is that, in light of other studies of population coalescent times for mitochondrial DNA (6), the Y chromosome (7), and autosomal microsatellite markers (8), it seems unlikely that the Alu polymorphism is as old as 5 million years, as implicitly suggested. However, if it were this old, the absence of the Alu(−) allele in chimpanzees would not rule out an age of more than 5 million years. That is, the Alu(−) allele could have existed in the ancestral population of both humans and chimpanzees and subsequently be lost from the chimpanzee lineage.

This analysis shows that as a result of the shared ancestry of individuals in a population, estimates of mutation times—or population divergences based on a single mutating locus (STRP here)—can be highly unreliable, even when large samples of individuals are used.

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REFERENCES AND NOTES

2. F. Tajima, Genetics 105, 437 (1980).
4. This conditional sampling procedure borrows from an idea introduced for a different problem by R. R. Hudson, in Mechanisms of Molecular Evolution, N. Takahata and A. G. Clark, Eds. (Sinauer, Sunder- lard, MA, 1992), pp. 23-36. There is an implicit assumption of constant population size here; this will lead to a conservative lower bound on $N_{A} \mu$. However, it should be noted that the observation of both the Alu(−) mutation and the Alu(−) recombinant type being in high frequency argues against a model as extreme as exponential population growth [M. Slatkin and R. R. Hudson, Genetics 128, 565 (1991)].

5. This result is based on at least 5% of the simulated sub-trees having a mutant frequency at least as high as that observed by Tishkoff et al. for trial values of $N_{A} \mu \geq 0.12$.


Response: Distinguishing between the “Out-of-Africa” model and the “Multiregional”
model of human evolution depends on the
demonstration of evolutionarily recent time
depths for alleles found in non-African pop-
ulations. Multiregional model enthusiasts
also argue for an African origin, but place
this origin at 1 million years before present
(Y.B.P.), the approximate time at which
Homo erectus remains can be identified out-
side Africa. Thus, for the “Out-of-Africa”
model to be accepted, it is critical that
allelic time depths be more recent than 1
million Y.B.P.

In support of the recent “Out-of-Africa”
model, we (1) attempted to show that a
single chromosomal segment, a CD4 locus
haplotype composed of an Alu(−) allele
and an STRP allele of 90 bp separated by 10
kb, had a recent time depth in non-Africans.
As we emphasized in the article, in the
absence of known recombination be-
tween the sites or mutation rates at the
STRP marker, it is impossible to estimate
an exact time of origin of this haplotype in
non-Africans. However, by making certain
conservative assumptions, it is possible to
place likely upper bounds for this date. We

used several methods of analysis to derive
an upper bound for the coalescent date for
non-Africans. One was based on the vari-
cance observed at the STRP on Alu(−)
chromosomes outside versus inside Africa;
this led to a date of 167,000 Y.B.P. Another
analysis was based on the proportion of
Alu(−) chromosomes with STRP alleles
less than 110 bp outside versus inside Africa
that carry the progenitor (90 bp) STRP
allele. As an upper bound on this propor-
tion, we examined its variability across five
geographically diffuse sub-Saharan African
populations that had more than 10 Alu(−)
chromosomes. The proportion carrying the
90-bp repeat ranged from 0.25 in the
Woloff to 0.53 in the Herero. We used 0.53
as an upper bound for this value across
sub-Saharan Africa. For non-Africans, be-
cause of the small number of Alu(−) chro-
mosomes not carrying the 90-bp allele, we
assumed a Poisson distribution to obtain a
lower 95% confidence bound for this num-
ber. With these two bounds, we obtained a
maximum age of 313,000 Y.B.P. We also
performed other conservative analyses
[notes 40 and 41 in (1)], which gave addi-
tional estimates of maximal dates ranging to
450,000 Y.B.P.

All of these estimates of maximum age
depend on the assumption that the Alu(−)
allele has a maximum age of 5 million years
and originated in Africa. This upper-bound
estimate was used because the allele was not
observed in chimpanzees or gorillas.

Pritchard and Feldman state that the mutation
could technically be even older, but they
also agree that it is far more likely that this
polymorphism is less than 5 million years
old. A younger age seems likely because of
the lifetime survival distribution for neutral
mutations (2). In fact, our data argue for a
more recent origin, albeit still ancient [note
42 in (1)]. Comparing variation in STRP
allele size (calculated by any of several
methods) shows that Alu(−) chromosomes
have less variation than do Alu(+) chro-
mosomes and are therefore likely to have a
more recent coalescent.

Pritchard and Feldman use coalescent
theory and a simulation to calculate a lower
95% confidence bound for N_A.M. The sam-
ple of chromosomes on which their analysis
is based derived from 10 extremely disparate
African populations, spanning the entire
continent, for which there must have been
considerable relative endogamy. Such pop-
ulation structure would make more recent
ages for the Alu(−) allele far less likely
than would appear in Pritchard’s and Feld-
man’s simulation (3). Also, it is implausible
that the population has been constant in
size since the Alu deletion first occurred.

Its rather high frequency in Africa suggests a
rapid increase in the numbers of this chro-
mosome soon after its introduction. Such
growth would lead to a smaller estimate of
variance for N_A.M than that calculated by
Pritchard and Feldman.

Still, even under assumptions implausi-
ibly more conservative than ours, the upper
bound for the estimate of the coalescent
date of the Alu(−) chromosome in non-
Africans is about 700,000 Y.B.P. (using
Pritchard’s and Feldman’s estimate), still
short of the 1 million years speculated by
the “Multiregional” model. Their analysis
thus supports our conclusion that a more

recent date for an exodus of modern hu-
mans from Africa is more likely and that
the CD4 data argue for the “Out-of-Africa”
model rather than the “Multiregional”
model.

We originally stated (1) that the data
we have obtained for the CD4 locus rep-
resent only a single realization of evolu-
tionary history for Africans and non-Africans.
As Pritchard and Feldman point out, it is
tenuous to derive statistical distributions
for coalescent times based simply on
theory because of the arbitrary demog-
graphic assumptions required. The best
way to derive such a distribution is empiri-
cally, combining the results of numerous
different loci. Examination of linkage dis-
equilibrium patterns for other systems in a
fashion similar to what we have presented
for CD4 should provide more definitive
conclusions regarding the coalescence
time for non-Africans.

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Late Permian Extinctions

In their article “Comparative Earth history
and Late Permian mass extinction” (1), A.
H. Knoll et al. suggest that Late Permian
extinctions were caused by the release to the
atmosphere of massive quantities of carbon
dioxide (CO₂) from the deep ocean; that the
CO₂ buildup in the ocean resulted from pri-
mary production in the surface layer; and
that, despite sluggish ocean circulation rates,
the release of phosphorus from decaying or-
ganic matter in deep anoxic waters would
have been sufficient to further stimulate
photosynthesis (2), which would in turn
have led to further organic decay (that is,
positive feedback) before oceanic overturn
and release of CO₂.

Knoll et al. otherwise deemphasize the
role of nutrients in the Permian extinctions,
but if ocean circulation had been sufficient-
ly slow in the Late Permian, phytoplankton
could have largely stripped the surface
mixed layer of nutrients (3) so that a “nut-
rient collapse” could have occurred. Also,
the expansion of gymnosperms during this
time (4) and the greatly increased interior
drainage associated with the formation of
the Pangean supercontinent (5) could have
seeded large amounts of nutrients on
land (4, 6). Greatly decreased nutrient
availability during the Late Permian is con-
sistent with the loss of many suspension-
feeding invertebrates and nekton and the
differential survival of infaunal taxa that fed
on organic-rich sediment (6, 7, 8), as
described by Knoll et al. Moreover, before
Late Permian extinctions, the Perm-Car-
boniferous was a time of increasing nutrient
and food availability in the water column
(6, 7). Thus, just as global marine ecosys-
tems were becoming increasingly depen-
dent on greater food availability in the Late
Paleozoic, the rug, so to speak, could have

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