

Walker A motif of the second nucleotide-binding domain, creating an open dimer interface. This conformation is not consistent with biochemical characterization of the catalytic transition state. Vanadate-induced cleavage of both the Walker A and family signature of the maltose transporter demonstrates the close proximity of both motifs in the vanadate-trapped species (10), and mutagenesis experiments highlight the importance of the family signature in catalysis (12, 13). The MsbA structure is characterized as a “post-hydrolysis” ADP-vanadate state rather than the catalytic transition state specifically because of this open nucleotide-binding site dimer configuration. These results raise the question of why ADP and vanadate are asymmetrically “trapped” in just one of the two

sites if the dimer has opened. Low resolution prevents an answer here. Perhaps, at 4.2 Å, there are not enough data to reveal differences between the two monomers within the dimer. The authors forced the monomers to be identical by imposing strict noncrystallographic symmetry. In the end, we are presented with a less than satisfying symmetric solution to the structure of what may be an asymmetric dimer in the crystal. This data set does not allow us to draw specific conclusions about side-chain interactions and, more important, protein-nucleotide interactions. That awaits atomic resolution.

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10.1126/science.1113414

## EVOLUTION

# Did Early Humans Go North or South?

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**B**y analyzing the DNA of living humans from different locations, geneticists are able to assemble a detailed reconstruction of prehistoric human colonization of the world. This research endeavor was championed by the late Allan Wilson and his colleagues (1, 2), who led the way with their studies of maternally inherited mitochondrial DNA (mtDNA). Their work led to the proposal of a recent African origin for modern humans, some 5000 generations ago. Anthropologists and geneticists have since joined forces to create a broad framework of possible prehistoric human migration routes and time scales (3–6). The two latest additions to this framework are described by Thangaraj *et al.* (7) on page 996 and Macaulay *et al.* (8) on page 1034 of this issue.

Our current understanding is that modern humans arose ~150,000 years ago, possibly in East Africa, where human genetic diversity is particularly high. Subsequent early colonization within Africa is supported by old genetic mtDNA and Y chromosome branches (often called “haplogroups”) in the Bushmen or Khoisan of the Kalahari Desert, and in certain pygmy tribes in the central African rainforest. Early

humans even ventured out of Africa briefly, as indicated by the 90,000-year-old Skhul and Qafzeh fossils found in Israel. The next event clearly visible in the mitochondrial evolutionary tree is an expansion signature of so-called L2 and L3 mtDNA types in Africa about 85,000 years ago, which now represent more than two-thirds of female lineages throughout most of Africa. The reason for this remarkable expansion is unclear, but it led directly to the only suc-

cessful migration out of Africa, and is genetically dated by mtDNA to have occurred some time between 55,000 and 85,000 years ago. Studies of the paternally inherited Y chromosome yield time estimates for the African exodus that are in broad agreement with those derived from mtDNA.

It is at this point in the narrative that the studies by Thangaraj *et al.* (7) and Macaulay *et al.* (8) come into the picture. Which route did the first Eurasians take out of Africa? Most obvious, perhaps, is the route along the Nile and across the Sinai Peninsula leading into the rest of the world (see the figure). But if that were so, why was adjacent Europe settled thousands of years later than distant Australia? In Europe, Neanderthals were replaced by modern humans only about 30,000 to 40,000 years ago, whereas southern Australia was definitely inhabited



**How did they get there?** Hypothetical routes along the Indian Ocean coastline that could have been taken by early humans emigrating out of Africa. The oldest human traces outside of Africa and the Levant are at Lake Mungo in Australia (>46,000 years old) and in the Niah Cave of Borneo (>45,000 years ago). New mtDNA data, from Malaysians and aboriginal Andaman islanders, suggest that human settlements appeared along the Indian Ocean coastline 60,000 years ago (7, 8).

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46,000 years ago and northern Australia and Southeast Asia necessarily even earlier (9, 10). Or did our ancestors instead depart from East Africa, crossing the Red Sea and then following the coast of the Indian Ocean (11)? A purely coastal “express train” would conveniently explain the early dates for human presence in Australia, but would require that humans were capable of crossing the mouth of the Red Sea some 60,000 years ago. Why, then, was this feat not repeated by any later African emigrants, particularly when the Red Sea level dropped to a minimum about 20,000 years ago?

Ideally, these questions would be answered by investigating ancient fossils and DNA from the Arabian Peninsula. But because this option is currently not available, Thangaraj *et al.* and Macaulay *et al.* have centered their investigation on the other side of the Indian Ocean, in the Andaman Islands and Malaysian Peninsula. Both groups used genetic studies of relict populations known to differ substantially from their Asian neighbors to estimate the arrival time of the first humans in these locations. Thangaraj and colleagues sampled the Andamanese, who were decimated in the 19th century by diseases imported by the British and then suffered displacement by modern Indian immigration (12). Macaulay and co-workers sampled the native tribal people of Malaysia, called the Orang Asli (“original people”).

Fortunately, the two teams arrived at compatible conclusions. In the Andaman Islands, Thangaraj *et al.* identified the M31 and M32 mtDNA types among indigenous Andamanese. These two mtDNA types branched directly from M mtDNA, which arose as a founder 65,000 years ago. This time estimate for the arrival of M founder mtDNA is matched by that of Macaulay and co-workers. These investigators found mtDNA types M21 and M22 in their Malaysian data set. These M types are geographically specific branches of M that branched off from other Asian mtDNA lineages around 60,000 years ago. Thus, the first Eurasians appear to have reached the coast of the Indian Ocean soon after leaving Africa, regardless of whether they took the northern or the southern route. Interestingly, the adjacent Nicobar Islands do not harbor any old mtDNA branches specific to the islands. Instead, their mtDNA has a close and hence recent genetic relationship (on the order of 15,000 years or less) with the mtDNA of other Southeast Asian populations. This is not unexpected given the more Asian appearance of the Nicobar islanders.

Macaulay and colleagues go two steps further and estimate the prehistoric migration speed of early humans along the coast of the Indian Ocean; they also estimate the likely population size of the emigrant population. Comparing genetic dates of founder types

between India and Australia, and assuming a 12,000-km journey along the Indian Ocean coastline, they suggest a migration speed for the first Eurasians of 0.7 to 4 km per year. This value is of the same order of magnitude as genetically dated inland journeys of migrant populations during the last Ice Age, 60,000 to 10,000 years ago (6).

One intriguing question is the number of women who originally emigrated out of Africa. Only one is required, theoretically. Such a single female founder would have had to carry the African L3 mtDNA type, and her descendants would have carried those mtDNA types (M, N, and R) that populate Eurasia today. Macaulay *et al.* use population modeling to obtain a rough upper estimate of the number of women who left Africa 60,000 years ago. From their model, they calculate this number to be about 600. Using published conversion factors, we can translate this estimate into a number between 500 and 2000 actual women. The authors’ preferred estimate is several hundred female founders. All such estimations are influenced by the choice of parameters and by statistical uncertainty; hence, it is understood that the true number could have been considerably larger or smaller. Improved estimates will involve computer simulations based on informed scenarios using additional genetic loci.

Time is short if researchers wish to secure data on dwindling indigenous populations such as the Andamanese and the Orang Asli. The studies by Macaulay *et al.* and Thangaraj *et al.*, which are devoted to the peoples inhabiting the “southern route” along the Indian Ocean, are therefore very welcome. We hope that the new findings will inspire archaeological exploration between the Arabian Peninsula and Southeast Asia in search of the remains of the first Eurasians 50,000 to 100,000 years ago.

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10.1126/science.1113261

#### GEOPHYSICS

## Past and Future Earthquakes on the San Andreas Fault

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**T**he San Andreas fault is one of the most famous and—because of its proximity to large population centers in California—one of the most dangerous earthquake-generating faults on Earth. Concern about the timing, magnitude, and location of future earthquakes, combined with convenient access, have motivated more research on this fault than on any other. In recent years, an increasing number of sites along the fault have provided evidence for prehistoric earthquakes (1, 2).

Damaging earthquakes are generated by rupture that can span hundreds of kilometers on a fault. Data from many sites must therefore be integrated into “rupture scenar-

ios”—possible histories of earthquakes that include the date, location, and size (length of fault rupture) of all earthquakes on a fault during a period of time. Recently, rupture scenarios for the southern San Andreas fault have stimulated interest in how different scenarios affect interpretations of seismic hazard and underlying models of earthquake recurrence behavior.

Large earthquakes occur infrequently on individual faults. Scientists therefore cannot test recurrence models for damaging earthquakes by waiting for a series of large earthquakes to occur or by consulting instrumental records, which span at most 100 years. Records of large earthquakes must be dug out of the geologic record to characterize earthquakes that predate the instrumental record.

Such studies tend to provide samples of the date and ground displacement at isolated sites along the ruptures, hundreds of kilometers long, caused by large paleoearthquakes. Key insights into fault recurrence behavior have been gained from site-specific data on

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