in vertebrates," says Fazeli.

And that's not all. Culotti's group had previously found another netrin receptor in worms, called UNC-5, that apparently switches an axon's response, turning UNC-6 into a repellent rather than an attractant. Now, proteins homologous to this netrin receptor are turning up in vertebrates. The two other *Nature* papers report such homologs in rats and mice, and both are active in the brain and spinal-cord regions.

All this suggests that netrins and their receptors make up a genetic module so powerful that it is conserved across worms, rats, mice, and even humans—and that DCC itself is a netrin receptor, expressed at the tips of growing axons and given the job of guiding them to the right position, says Culotti. The accumulating evidence makes it more and more difficult to see how *DCC*'s absence in colorectal tumor cells could be the crucial factor permitting cancerous growth, says Ray White, a human geneticist at the University of Utah.

Another gene in the 18q21 region could be the real culprit, with DCC as an innocent neighbor, says White. At least two other candidate tumor suppressors, called *Smad2* and *Smad4*, have already been traced to the area; *Smad4* loss is suspected as a leading cause of pancreatic cancer (*Science*, 19 January 1996, pp. 294 and 350). Both genes seem to modulate signals carried by a protein called TGF-β and its relatives, which among other functions are thought to direct the development of colon cells. All three genes, however, could merely be carried along for the ride when the entire 18q21 region is deleted. So, although all the candidate genes appear to have links to the colon, "somebody could find a [tumor-suppressor] gene that's an even better target than these," explains Vogelstein.

But Fearon notes that *DCC* might be more than just a receptor for netrins, perhaps interacting with other signaling molecules in some other pathway regulating cell movement or cell fate. *DCC* appears to be expressed at low levels in many cells that might need directional cues, Fearon says, including the colonocytes that slowly migrate up the lining of the colon, then slough off. "I think most of the data still weigh in for *DCC* as the most likely candidate," he says.

And the new data on *DCC* don't diminish its diagnostic usefulness as a marker for aggressive colorectal tumors, adds Beth Israel Deaconess's Summerhayes, because it seems clear that DCC is at least close to the actual tumor suppressor. Whichever gene proves to be the crucial target of deletion, *DCC*'s story illustrates that developmental biology has a role to play in cancer research, says Johns Hopkins cancer researcher Scott Kern: "There's no better place to apply [the growing knowledge of development] than in human cancer biology."

–Wade Roush

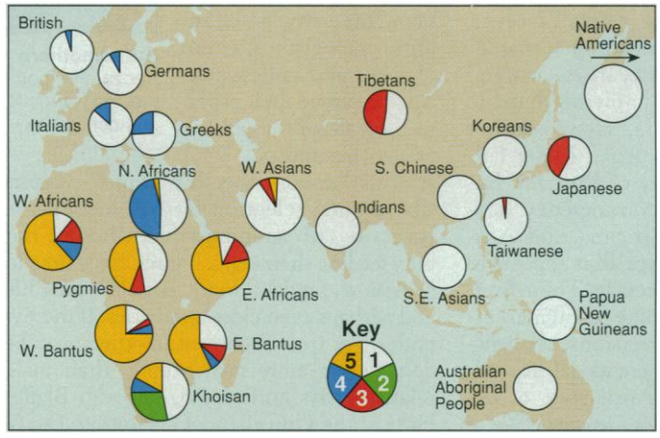
MEETING BRIEFS

Ideas on Human Origins Evolve At Anthropology Gathering

ST. LOUIS More than 1000 anthropologists gathered here from 1 to 5 April for the 66th annual meeting of the American Association of Physical Anthropologists and associated groups. Researchers presented new genetic and fossil findings marking key milestones in long-running debates on such topics as the ancestors of apes (*Science*, 18 April, p. 355), the origins of modern humans, and the evolution of menopause.

Back to Africa

Since the mid-1980s, two diametrically opposed hypotheses for the origin of modern humans have been battling for primacy. One, called Regional Continuity, holds that our earliest ancestors arose in Africa and spread around the world more than 1 million years ago. Modern humans then arose in many different regions through separate evolution and interbreeding. The other—the favored contender—is the theory known as Out of Africa, which suggests that our ancestors arose in Africa and swept around the globe 100,000 years ago, completely replacing existing human populations on other continents. This model hasn't been proven,



SOURCE: M. F. HAMMER *ET AL.*, *GENETICS* **145**, 787 (1997)

Male routes. A marker on the Y chromosome comes in five types (pie charts). One version (red) is found chiefly in Asians but also in a few Africans, suggesting that it arose in Asia and was later carried back to Africa by migrating (male) human ancestors. This marker then gave rise to others in Africa (blue, yellow).

but a series of genetic and fossil studies have suggested to many researchers that, as Stanford University geneticist Neil Risch put it last year, "the rest of the world emerged from the northeast corner of Africa" (*Science*, 8 March 1996, pp. 1364 and 1380).

Now, a middle ground may be emerging, as new data from two international teams of geneticists challenge the most extreme version of Out of Africa. That theory predicts that all genes in modern humans were inherited from a small number of Africans, but the new data suggest that some modern human genes come from ancestors in Asia, not Africa. The new evidence falls far short, however, of proving Regional Continuity; rather, it shows that both of these leading models of how modern humans emerged have been overly simplistic. "There's more than one migration out of Africa," says Michael Hammer, a geneticist at the University of Arizona, Tucson. "And the direction is not just one way. Some are moving back to Africa."

Hammer came to that conclusion after studying DNA in 1500 males from 60 populations around the world. One region he focused on was a 2600-base-pair segment of the Y chromosome: the YAP region, which is passed from fathers to sons. This segment varies among individuals, but the sequences cluster in five major groups, known as haplotypes (shown in five colors; see map). The haplotypes occur in different frequencies in different populations, and Hammer's team found that one—YAP haplotype 3 (shown in red)—shows up far more often in Asians than Africans. Its sequence shows more diversity in Asians, implying that the haplotype had more time to acquire mutations in Asia than in Africa—and, therefore, that it arose in Asia. Its presence in some Africans hints that human ancestors migrated back from Asia into Africa at some point, says Hammer.

What's more, Hammer's team thinks that

this haplotype is ancestral to two of the most common ones found in Africa—haplotypes 4 and 5 (shown in blue and yellow)—because all three share a common sequence missing in other African haplotypes. In a paper in the March issue of the journal *Genetics*, Hammer and colleague Stephen Zegura conclude that "a major component of [modern] African diversity is derived from Asia."

But these findings come from just one gene in males, which may reflect the movements of a few men rather than entire populations. So, Hammer was pleased to hear similar findings at the meeting from another piece of nuclear DNA, the beta-globin gene on chromosome 11, which is inherited from both parents. Geneticist John Clegg of the Institute of Molecular Medicine in Oxford, England, along with population geneticist Rosalind Harding, and their colleagues, sequenced a 3000-base-pair region that included the beta-globin gene in 349 individuals from nine populations in Africa, Asia, and Europe. Using new computational methods, they built a genetic family tree to sort out the sequences, which fell into four major groups of haplotypes.

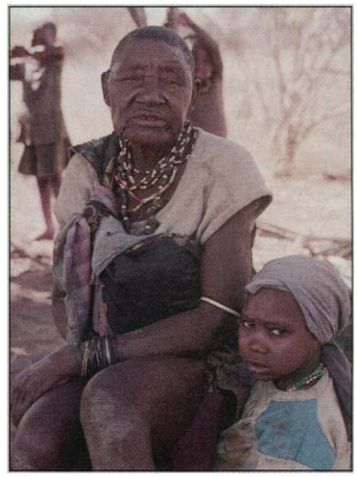
The team then used mutation rates for human nuclear genes to calculate how long ago the sequences split from one ancestral haplotype. They found that the oldest version of the gene, haplotype B2, arose more than 800,000 years ago in Africa. Some time before 200,000 years ago, however, B2 gave rise to a set known as C haplotypes. These are common in Asians and very rare in Africans—implying that the haplotypes arose in Asia, says co-author and molecular anthropologist Malia Fullerton, of the University of Durham, England. Asians also have two ancient C haplotypes not found in Africans, and Africans have one C haplotype that appears to have been brought in recently. These findings again suggest that some Asian markers are older than African versions, challenging the complete replacement model, according to a paper in the April issue of the *American Journal of Human Genetics*. "We're seeing evidence of a widely dispersed human population about 200,000 years [ago], both in Africa and Asia. And both contributed to the gene pool" of modern humans, Fullerton says.

Others have yet to be convinced. Pennsylvania State University postdoc Sarah Tishkoff, a co-author of a recent genetic study supporting Out of Africa, says that more sampling of DNA from Africans is necessary to make sure that these so-called Asian haplotypes aren't descended from an as-yet-unidentified African haplotype. But Tishkoff agrees that both leading models of modern human origins are too simplistic. "This tells us that we have to take into account more complex models," says Tishkoff. "All of us in the field have oversimplified."

Why Life After Menopause?

Why do women live so long after they stop reproducing? Human females are the only ones in the primate family to live well beyond their last pregnancy—often as long as 40 years or more after menopause. Yet, evolutionary theory says that natural selection favors only traits that enhance reproduction—which implies that postreproductive women have no evolutionary reason to live.

Now, a new study of African hunter-gatherers suggests a provocative answer to this riddle: Women live to a ripe old age to make sure their grandchildren eat. By provisioning grandchildren, grandmothers ensure the children's survival, boost their daughters' fertility—and improve the chances that their own genes are passed on. With grandmothers providing food, daughters can breast-feed infants for a shorter period and so bear more babies during their fertile years than primates without helpers do, say University of Utah anthropologist Kristen Hawkes and colleagues, who presented their paper at the Paleoanthropology Society meeting.



JAMES F. O'CONNELL

Grandmotherly love. Among the Hadza, the food that grandmothers provide is crucial to the survival of grandchildren.

This "grandmother hypothesis" suggests that natural selection favored menopause (because only grandmothers who are not busy feeding their own children have time to provision grandchildren), as well as long life and perhaps even close family ties. If the hypothesis is true, then grandmothers may be doing even more provisioning than male relatives, says anthropologist Sarah Blaffer Hrdy of the University of California, Davis. "This is the first serious challenge to the widely accepted view that the human family evolved because males were needed to provision mothers," she says.

Hawkes and colleagues James O'Connell of the University of Utah, and Nicholas Blurton Jones of the University of California, Los Angeles, learned of grandmothers' contributions when they spent a year studying a group of 300 Hadza hunter-gatherers in the rugged hill country southeast of Lake Eyasi in northern Tanzania. The Hadza move from season to season and survive almost entirely on wild resources. Men hunt and collect honey while women dig tubers or collect berries and other fruit.

The researchers found that children's weight gains usually depended on how much time their mothers spent foraging. But when mothers gave birth to new babies, they had less time to find food for older, weaned ones. The "hardworking, incredibly fit" grandmothers, mostly in their 60s, took up the slack, says Hawkes. "What was striking was that these older women were spending more time foraging than younger mothers were," she adds. As a result, the weight gain of children whose mothers were nursing depended on their grandmothers' foraging.

Such provisioning by grandmothers may allow human mothers to have babies closer together than other apes can, and may also explain a suite of other distinctly human traits, says Hawkes, who has worked with University of Utah evolutionary biologist Eric Charnov on this theory. Unlike other primates, humans are weaned early, at a relatively small size, and have extended childhoods and high fertility. The "grandmother hypothesis" provides a "nice story" that could explain why all those features have been selected for, says Hrdy. And it challenges the idea that male hunting is the crucial factor allowing long, dependent childhoods in humans. Hawkes's group found that hunting was a less reliable source of food than the tubers grandmothers dug up.

Unfortunately, the evidence comes only from the Hadza, and Hrdy isn't convinced that this group is a good proxy for the behavior of our ancestors. And although Hawkes's team is studying other hunter-gatherers and other primates, tests of their ideas may be hard to come by. Clues could come from fossils of early humans or the archaeological record, says O'Connell, but several paleoanthropologists at the meeting warned that it will be difficult to identify a unique signature of grandmother provisioning. "I like their paper, but it's going to be really hard to test," says University of New Mexico paleoanthropologist Erik Trinkaus.

For now, however, at least a few anthropologists have shifted their focus away from male hunters to a new group. "If there is a group that we have paid no attention to, it's old women," says Hawkes. The bottom line, at least for the Hadza, she says, is a message worthy of a bumper sticker: "Grandmothers Matter."

–Ann Gibbons