haps living in tents," Roberts says.

Hodder is more circumspect. "I can accept that sections of the community, perhaps unmarried young men, were living away in shelters and looking after crops," he says. "But I could not accept a model in which there were whole chunks of the community living away. There is no evidence for that, and it would not fit with the type of social system we see here. It is highly structured, integrated, and cohesive."

As for what made the community so cohesive, Hodder believes the answer lies in the lime-rich marl clays used to make plaster—the "canvas" on which Çatalhöyük's artists created their imaginative works. It was this shared symbolic expression, Hodder believes, that held the community together.

The most accessible supply of this clay, Hodder notes, would have been in the marshy floodplain, where the alluvial deposits above the marl were thinnest and "getting to the marl [would be] easier." Roberts's team has found a number of pits, dating from the Neolithic period, dug into this marl just off-site—an indication that the villagers were quarrying. And there is considerable evidence that plaster was essential to life at Çatalhöyük. Inside the mud-brick houses, almost every surface was carefully plastered with annual coats, with special care taken on the walls and on long platforms under which the bones of the settlers' ancestors were buried. On many of the walls, fantastic paintings of hunting scenes, vultures, and leopards have been found over the years of excavation, as well as plaster sculptures of bulls' heads and what some have interpreted as depictions of goddesses. "They were plaster freaks," Hodder says.

This explanation does not appeal to everyone, however. "While economic factors always seem a little inadequate to explain ... a site as interesting as Çatalhöyük," comments Runnels, "Neolithic peoples first had to secure a dependable supply of food before they could concentrate on ritual practices." Runnels adds that the Greek early Neolithic sites he has studied "made little or no use of decorative plaster, so I cannot accept the idea that plaster sources for ritual were an important component for determining early Neolithic settlement patterns."

More excavations—which are expected to continue for many years—could explain just why the founders of Çatalhöyük chose to build their village in the midst of rising waters. But if past experience is any guide, they might also turn up a whole host of new and fascinating enigmas. **–MICHAEL BALTER**

EVOLUTIONARY GENOMICS

The Ups and Downs of Evolution

ATAMI, JAPAN—Some 200 geneticists came together last month in this hot springs resort in the foothills of Mount Fuji to celebrate the 70th birthday of renowned evolutionary geneticist Masatoshi Nei. Born and educated in Japan, Nei has spent more than 30 years at U.S. universities, most recently Pennsylvania State University, University Park, and has trained many of the scientists making presentations here. In addition to conveying their appreciation, participants discussed cancer genes, speciation, and the impact of replication timing on genetic fidelity.

BRCA1's Role as Cancer Agent

Mutations in the *BRCA1* are thought to be the most common predisposing factor in familial breast and ovarian cancer. Now geneticist Simon Easteal and Gavin Huttley of Australian National University (ANU) in Canberra, John Hopper of the University of Melbourne, and Deon Venter of the Murdoch Children's Research Institute in Melbourne report that *BRCA1* mutations may also be involved in nonfamilial forms of breast and ovarian cancer, which are much more common. The results may eventually help screen for women who have an increased risk of developing breast cancer, and they could also have implications for future therapies.

The finding grew out of work on the evolutionary characteristics of *BRCA1*, a large gene known to be involved in DNA-repair and cell-cycle regulation and other processes. The ANU group had previously reported that in several primate species, the gene is frequently altered by mutations that cause one amino acid to be replaced by another. Because such amino acid substitutions indicate that natural selection has acted on a gene, the finding suggested that the cancer susceptibility associated with mutations of *BRCA1* may be a byproduct of human adaptive evolution.

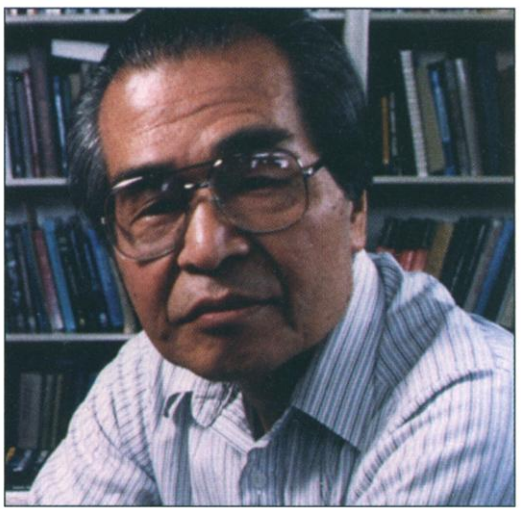
With the link between familial cancer and mutations at single locations well established, Easteal and his colleagues went looking for interactions between DNA sequence variations (polymorphisms) at several different sites. They zeroed in on two *BRCA1* sites that showed strong indications of being the target of natural selection. By comparing these regions of the gene with their counterparts in other primate species, they determined that one of the polymorphisms, which they dubbed the ancestral state, had been conserved and that one, which they called the derived state, had changed significantly.

Using the health histories and genetic profiles of participants in the Australian Breast Cancer Family Study (*Science*, 19 June 1998, p. 1831), the researchers went on to show that women with nonfamilial breast cancer had a higher incidence of the ancestral state at one locus and the derived state at the other. Conversely, members of the control population, who did not have breast cancer, were more likely to have either derived states at both loci or ancestral states at both.

"We conclude that interaction between haplotype variants contributes to breast cancer risk," Easteal says. "I think that this is the first time interactions between such variations have been identified as contributing to a disease state," he adds, noting that it's not clear how the interactions increase susceptibility to breast cancer.

Audience members were hungry for more details, in particular the sizes of Easteal's control and case samples and the degree of increased risk to women carrying mixes of the haplotypes. There were 86 cases and 89 controls, Easteal explained later. And the effect "is small but significant. The full picture will be revealed when the study is published," he promised.

Despite having only part of the picture, "it was exciting stuff," says



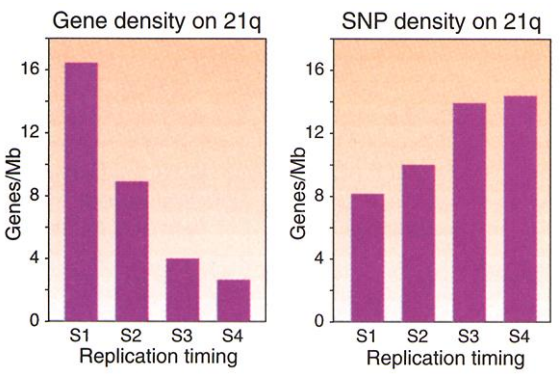
CREDIT: PENNSYLVANIA STATE UNIVERSITY

Birthday boy. Masatoshi Nei is still going strong at 70.

Andrew Clark, a population geneticist at Pennsylvania State University, University Park. He says the report helps point up the increasing complexity involved in unraveling genetic disorders.

Early Zones Get the Good Gene

DNA replication is not smooth and continuous. It proceeds in spurts, starting at different times at various points along a chromosome and pausing occasionally as the replication on one chain of the double-helical DNA waits for the replication coming the other way on the second chain. Those irregularities have led some scientists to speculate that the regions at the edges of replication zones might be more prone to genetic mutations than the DNA in the middle of the zones. Toshimichi Ikemura, a geneticist at the National Institute of Genetics in Mishima, Japan, and colleagues there and at the RIKEN Genomic Sciences Center in Yokohama have now confirmed those suspicions by correlating early and late replicating regions with the locations of known disease genes.



A matter of timing. More genes were found in the earlier DNA replication zones, where replication fidelity tends to be highest, whereas single-nucleotide polymorphisms (SNPs) were clustered in the later zones, where errors are more likely.

Ikemura and his colleagues used a cell-sorting technique to determine the replication timing of 450 sites identified by unique sequence strings on the long arms of human chromosomes 11 and 21. The technique allowed them to determine if a gene fell within the very early, early, late, or very late periods of DNA synthesis, which in cell-cycle shorthand are designated as S1, S2, S3, and S4, respectively. "You can determine the replication time of any genome locus with a unique sequence," Ikemura says.

The researchers then correlated the different stages of replication with genomic characteristics, such as the locations of genes and of the DNA variations known as single-nucleotide polymorphisms (SNPs), that had been compiled by other groups. They found that regions of high gene density coincide with early replication zones, whereas late-replicating zones tend to be gene -poor.

The researchers were particularly interested in what was happening in the transition zones, where replication pauses. "We expected this zone to be rather dangerous, because we know that a pause in replication enhances the possibility of DNA damage," Ikemura says. The data support that assumption. Ikemura and his colleagues found that SNP density was generally higher in the late-replicating zones, with peaks in the transition period between the two late replication stages.

The possibility that those variations might contribute to disease was buttressed by the researchers' finding that 10 of the 15 known oncogenes and tumor suppressor genes on chromosomes 11 and 21—genes that, when mutated, can contribute to cancer development—are located in or close to replication transition regions. The transition regions also host an additional 21 genes related to hereditary diseases, including familial Alzheimer's and amyotrophic lateral sclerosis. This high mutability makes these "high-risk, high-return regions," Ikemura says. "The risk of disease is high for individuals, but for populations the accelerated mutation [rate] in these regions may be good from an evolutionary viewpoint."

Andrew Clark, a population geneticist at Pennsylvania State University, University Park, sees Ikemura's findings as supporting the idea that the time of replication "has a huge impact on things like gene density and mutation rates and patterns of mutation." This knowledge, he says, will help in understanding the mechanics of evolution at the genetic level.

Vision Gene Aids Speciation

Evolutionary biologists have long been fascinated by the cichlid fish in lakes Tanganyika, Victoria, and Malawi in East Africa's Rift Valley because they provide a striking example of explosive adaptive speciation. Victoria, at 12,000 years the youngest of the three lakes, is home to more than 300 cichlid species that presumably derived from a few common ancestral populations. Norihiro Okada and Yohei Terai, geneticists at the Tokyo Institute of Technology, in collaboration with Jan Klein, a geneticist at the Max Planck Institute for Biology in Tübingen, Germany, report finding a gene that may have contributed to this speciation by influencing the mating choices of female cichlids and thus possibly leading to the reproductive isolation of the various species.

The team was looking for the genes behind several traits that distinguish cichlid species. The researchers included genes involved in color vision in their survey because previous experimental work by other groups had shown that females choose their mates by responding to body coloring. They hit pay dirt with one that codes for long wavelength sensitive (LWS) opsin, a protein that determines the eye's sensitivity to red light.

In screening 15 species of Lake Victoria cichlids, the researchers came up with 14 different variants (alleles) of the gene for LWS opsin. "This amount of variation in the [gene] is probably the result of natural selection," Okada suggests. The various alleles produce proteins with slightly different amino acid sequences, and this in turn affects the spectrum of light those proteins detect. That could make them the source of the color preferences shown by female cichlids.

Okada says that other genes are undoubtedly also involved in the speciation. But of the 100 or so analyzed, this gene was the only one in which variations could plausibly affect species formation. "As far as we know, this is the first gene with an adaptive role in speciation that has been characterized in vertebrates," he says.

Not everyone is convinced that the Okada team has identified a speciation gene. Masatoshi Nei of Pennsylvania State University, University Park, says a true speciation gene has to somehow result in "the reproductive inviability of offspring of closely related species." However, different cichlid species can produce fertile offspring, at least in the laboratory.

Chung-I Wu, a geneticist at the University of Chicago who has worked extensively with speciation in fruit flies, agrees that what they've found does not meet the classic definition of a speciation gene. "But speciation is very complex," he says, and this work should help researchers "start moving in the direction of understanding the speciation phenomenon."

–DENNIS NORMILE

Color coded. A vision gene may help female cichlid fish choose their mates.

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