Looking for the Father of Us All

After finding the controversial "mitochondrial Eve," molecular biologists are hoping that the Y chromosome will lead them to the genetic Adam

IN THE BEGINNING THERE WAS EVE. OR, TO put it another way, in 1987 Allan Wilson of the University of California at Berkeley and his colleagues announced that, on the basis of genetic evidence from mitochondria (energy-producing organelles in the cell) they had traced humanity's maternal descent to one woman who lived in Africa between 100,000 and 200,000 years ago. After that, of course, the mitochondrial Eve, whom Wilson dubbed "the mother of us all," was in need of a genetic consort. Finding Adam is—for technical reasons—more complex than identifying Eve, but now a small band of researchers is hot on the genetic trail of "the father of us all."

Using variations in the Y chromosome (which only males have), they are trying to trace the human lineage to its paternal source. "Theoretically, the Y should serve as a mirror image" of the genetic variations in mitochondria that led to Eve, according to David Page, a geneticist at MIT's Whitehead Institute. And indeed, the most daring of the Y chromosome researchers—Gérard Lucotte in Paris—claims he has already found the genetic Adam: an African whose closest modern counterpart is an Aka pygmy in the Central African Republic (see box on next page).

But most researchers say it's still too early to pinpoint the founding father. Aside from the technical problems in dealing with the Y chromosome, the field is still so young "we haven't even had a meeting yet," says Michael Hammer, a postdoc in the lab of Richard Lewontin at Harvard. Only a half-dozen international teams are involved, and the hunt for Adam is just now shifting from DNA hybridization studies—on which Lucotte relied—to a more precise analysis of actual nucleotide sequences. In fact, some researchers doubt whether science will ever be able to identify Adam as precisely as Wilson and his coworkers claim to have identified mitochondrial Eve. Still, there is little doubt that as this new field burgeons, it will provide fresh insights into the evolution of the human species and the ancestry of specific populations.

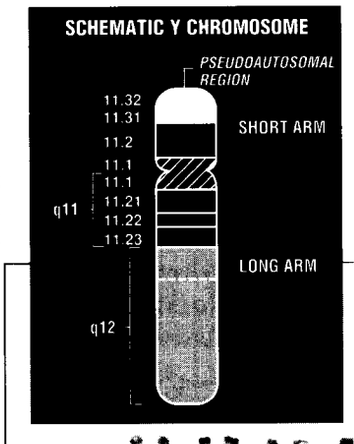
Most workers now studying the Y for its evolutionary significance were drawn into the field by Wilson's startling 1987 announcement. Wilson and his colleagues relied on mitochondrial DNA, because, unlike nuclear DNA, the genetic material in the mitochondria comes only from the mother (by way of the egg's cytoplasm). The Berkeley team collected samples of mitochondrial DNA from women of African, Asian, European, and Middle Eastern ancestry. They then examined the DNA for the variations in nucleotide sequence known as polymorphisms. The pattern of variations suggested to Wilson and his co-workers that our common ancestor was a sub-Saharan woman. Not only that, they claimed that the steady rate of mutations in the mitochondrial DNA functioned as a "molecular clock" that enabled them to say when Eve lived.

Those conclusions, particularly the positing of a steady molecular clock, aroused a thunderstorm of controversy. But they also suggested additional lines of research—on the molecular ancestry of men. "The quest is about the history of *Homo sapiens*, not about the history of the mitochondria," says Robert Dorit, an evolutionary geneticist working on the Y in geneticist Walter Gilbert's lab at Harvard. "So the obvious attack on the problem is to see if work on other molecules would give you the same picture."

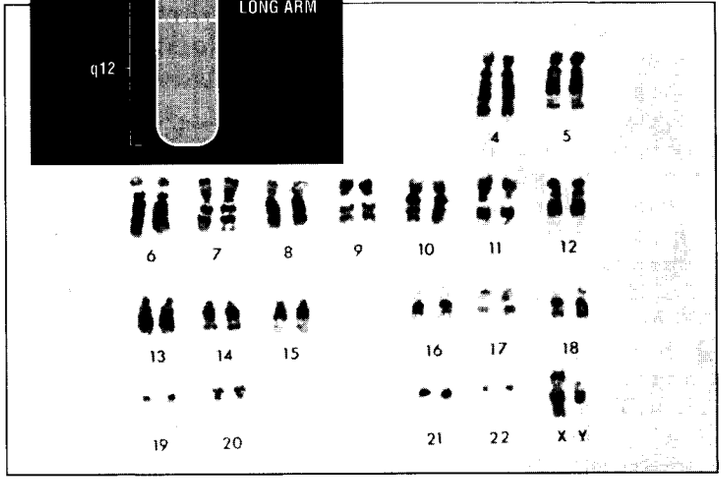
An obvious place to go was the Y chromosome, which is unusual because it is limited to men. Since only a small portion of the Y (the "psuedoautosomal" region on the short arm) is subject to recombination with the X chromosome, the bulk of the Y chromosome remains unchanged through generations—except for rare mutations. Hence, it should be an accurate tracer of an ancient paterfamilias.

But reality isn't quite as neat as theory: The genetic material on the Y yields a somewhat blurrier image of the past than mitochondrial DNA does. That's partly because the Y chromosome is thought to be a genetic junk pile. "There is a long-standing presumption that the Y chromosome is a dud that contains only junk DNA with the sole exception of that trivial bit of DNA that turns on male sex development," jokes Yale University geneticist Kenneth K. Kidd. "What has been learned though, is that there are only three genes found in the Y-specific region."

Those few genes and other bits of variation hidden in the noncoding regions of the Y junk pile are the geneticists' buried treasure—that's why they lament the fact that they have found so few of them on the Y so far. They hope those few polymorphisms could give them a handle on the descent of men. In their search, most groups have used DNA hybridization methods like those employed by Lucotte. He takes blood samples from the male populations he wants to study, and then uses special probes called p49a and p49f, which detect restriction fragment length polymorphisms—RFLPs—in the q11 region. Those probes are used to find variations at the same site in



Genetic "junk pile"
The pseudoautosomal region of the Y is the only site of many functional genes. The rest of the long arm is made up mostly of "junk" DNA.



Joe Leigh Simpson, University of Tennessee

different people's DNA. The DNA is first cut up in fragments using enzymes, then separated by size on a gel. The radioactively labeled Y chromosome probes are then hybridized, or bound to the fragments, marking various haplotypes—unique sections of DNA that are like genetic fingerprints of an individual or population.

In contrast to Lucotte, none of the other researchers now using DNA hybridization methods claims to be able to narrow Adam's heritage down to a single population. For example, Nathan Ellis and Peter Goodfellow at the Imperial Cancer Research Fund in London, using a systematic approach, surveyed one polymorphism on the Y chromosome of men from around the world. They found the same polymorphism among the !Kung bushmen of the Kalahari Desert, two different groups of pygmies, and Ethiopian Africans—but not in non-Africans or Bantu-speaking South Africans. From this data they tentatively concluded that the first father did live in Africa.

Although the DNA hybridization methods have gotten the field of Y chromosome work off to a running start, even the researchers who are using it admit there are drawbacks to using polymorphisms alone. "We don't know the molecular basis of these polymorphisms," admits University of Calabra geneticist Silvana Santachiara, who is part of an Italian team studying the Y with Lucotte's probes. "We know they concern a certain part of the Y chromosome, but it's impossible to use these polymorphisms to make an [evolutionary] tree of populations."

And an evolutionary tree of the male Y chromosomes is clearly what is needed. Yet there are problems: mainly, that no one knows where on the Y these polymorphisms occur when they use Lucotte's probes to find them, or whether they were even caused by the same mutation. The bands in the gels are a relatively crude measure of the DNA, because they don't give researchers the nucleotide sequence of the polymorphism or a specific site. And there's no guarantee that his probes are always pulling out sections of DNA from precisely the same site. The Y chromosome is not well characterized geneti-

Was Adam Very, Very Short?

Paris—Although the study of the Y chromosome as an evolutionary tool is still in its infancy, that hasn't deterred one researcher—Gérard Lucotte of the Collège de France in Paris—from using it to pinpoint "Adam," the genetic father of us all. According to Lucotte's formulation (which some other researchers think is a bit premature), Adam was a pygmy who lived 200,000 years ago in what is now the Central African Republic. His Garden of Eden, Lucotte argues, was a triangle situated between the Oubangui, the Sanga, and the Lobaye rivers in that country.

Lucotte took advantage of the world's first Y chromosome bank, created at the Pasteur Institute in Paris by molecular biologist Jean Weissenbach to examine DNA from populations around the world and to look for polymorphic markers: short regions of DNA that may differ by one or more nucleotides. Most of the regions, he found, did not vary much from one individual to another, probably because the Y chromosome has no homologous chromosome to recombine with—and therefore doesn't undergo much exchange of genetic material.

But Lucotte did identify some polymorphisms on the long arm of the Y chromosome, and he utilized them to develop a probe, called p49. With that probe, he was able to locate many polymorphisms and haplotypes (specific combinations of genetic sequences) in a region of the long arm, containing about 100 kilobases, which is designated Yq 11.2. This is probably a noncoding region of DNA: a region that does not carry the code for proteins and therefore is unaffected by evolutionary pressure—but which does accumulate chance mutations.

Lucotte's group used the p49 probe to examine the Y chromosome in a variety of different human populations—beginning with a French population sample. With Serge Hazout of Paris VII University, he then formulated a computer algorithm that retraced the most likely branching pattern for the haplotypes that had been identified in the population survey. The most likely ancestral haplotype, the computer program said, was one known as haplotype XIII.

The group then looked at the distribution of Y chromosome haplotypes in several African populations and found that haplotype XIII was most prevalent among the Aka pygmies. Lucotte was delighted that his genetic findings coincided with some anthropological results. "It seems remarkable," Lucotte told *Science*, "that pygmies, who together with South African bushmen, are believed to be the first inhabitants of the African continent, have a clear-cut dominance of one haplotype that our calculations had pinpointed as the ancestral one."

Other researchers, however, say Lucotte is out on a limb when he begins building evolutionary trees for male populations using his DNA probe data. The main problem is that too little is known about the polymorphisms Lucotte's probes fish out: Their precise location on the Y chromosome and their nucleotide sequences haven't been worked out. Only with that information—or at least some of it—can researchers guarantee that specific DNA sequences aren't, in fact, late intruders in evolution (see accompanying story). Lucotte's polymorphisms, several U.S. researchers say, are useful at this point only for comparing existing populations.

Those investigators are also skeptical about the most specific elements of Lucotte's Adamic history: its timing and precise geographic location. Lucotte acknowledges that his dating of the appearance of Adam at 200,000 years ago is not based on any information specific to the Y chromosome itself or to the rate at which it accumulates mutations—which is not known. Instead, he has simply accepted the date proposed by Allan Wilson and his colleagues at the University of California at Berkeley for the appearance of the mitochondrial Eve, "the mother of us all."

His identification of the southern tip of the Central African Republic, the area wedged between Zaire, Cameroon, and Congo that today is occupied by the Aka pygmies, is also arousing controversy among evolutionary specialists. Classical anthropologists—relying on fossil data rather than genes—have enough data to argue that the original home of humankind was a long way east of Lucotte's "Garden of Eden," somewhere along the Rift Valley of East Africa.

These questions probably won't be settled soon. But in the meantime, Lucotte is pressing on with his work on the Y chromosome. Recently he formed an "international consortium" to study p49 polymorphisms and haplotypes in different populations. His collaborators come from Tunisia, Australia, Japan, and South Africa, among other places. Perhaps, in time, a suitable genetic mate for "the mother of us all" will emerge from this collaboration. ■ ALEX DOROZYNSKI

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cally, and the same sequence could be repeated at different sites—and so the probes might be finding the same sequence at different places in the Y chromosome from different men.

Evolutionary gumshoe. *Michael Hammer is hot on the trail of Adam.*

Researchers in the field say they need the nucleotide sequence—or at the very least a clear location for the polymorphism—to be able to trace when a particular piece of DNA appeared in human males. By having the site or sequence, geneticists can determine if the genetic material also appears in the same location in the DNA of a comparison group—such as chimpanzees. If it's present in both human males and chimps, it seems likely that it was present in a common ancestor and wasn't a later evolutionary addition.

Having established that a particular sequence was, in fact, present at the beginning of the human species, the researchers working on the Y chromosome could then figure out when and how variants on the sequence came into being in different populations—being added or deleted by mutation or by exchange with other chromosomes. "I think if we want an answer about human evolution, we'll have to do it by sequencing," says Lewontin. "Only sequencing will give us unambiguous information. Once that's done, then we can talk about trees." And some groups, such as Goodfellow's in London, are already doing just that.

But, for evolutionary studies, DNA sequencing means rapid analysis of DNA from hundreds of blood samples from around the world. That kind of work was impossible until a few years ago, when the polymerase chain reaction (PCR) came into use. The availability of PCR jump-started studies of the Y chromosome—and the first Y-specific gene was cloned 3 years ago. And geneticists working in the field say that PCR—and the accompanying innovations in gene cloning and automated nucleotide sequencing—offers the best chance of understanding human evolution through the Y chromosome. "I'll put my money on those taking advantage of the new technology," says Page.

One leader in using sequencing to study the Y is Hammer, who has been analyzing a 3000-base sequence of Y chromosome DNA in populations from Japan, Asia, Europe, the United States, and Africa. Early results identified nucleotide polymorphisms distinguishing Africans and Europeans. Hammer, however, is reluctant to draw any conclusions about a common ancestor until he has sequenced the region in other populations.

Dorit's group at Harvard is also sequencing Y chromosome DNA, and their early results are surprising—but largely for what they did *not* find. In an analysis of an 800-base region of DNA, Dorit complains that he found "no variation at all, zip, nada" between 16 males who were Nigerian, Japanese, Latin American, African, American, and of other ancestry. That has raised a number of questions, which Dorit is trying to answer with hypotheses such as the "Genghis Khan" approach, in which a few warriors swept across wide geographic regions, raping and pillaging and fathering far more than their share of children.

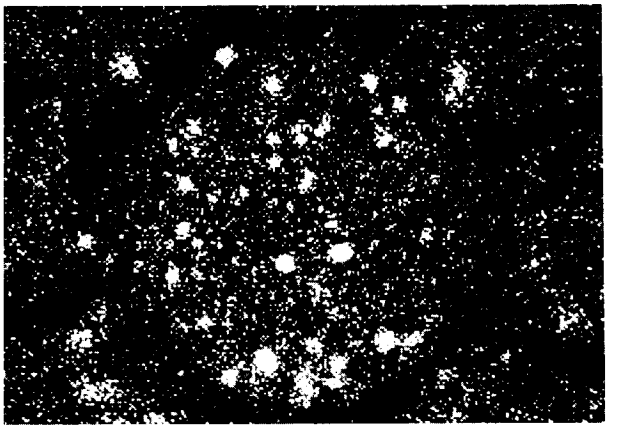
It's just this kind of conflicting data—along with the paucity of known and specifically located polymorphisms—that makes work on the Y chromosome challenging. "Ten thousand scientists working 24 hours a day aren't going to make more variation appear on the Y chromosome," sighs Dorit. And to build a really convincing case, it will require sequencing many polymorphisms, not just one or two.

Finding those variants—which are like needles hidden in a genetic haystack—will require sampling an array of populations. Several researchers are calling for a cell line repository so that all researchers in the field can work with DNA samples from the Y chromosome, mitochondria, and nuclei of cells from defined populations. Kidd at Yale, along with Luca Cavalli-Sforza at Stanford University, has assembled 800 cell lines. But despite his efforts, Kidd has been unable to secure funding that would enable him to share the cell lines more widely.

Ultimately, researchers say they will have to share samples and analyze them with a variety of methods to build a convincing case that their data really are giving them a glimpse into the past. "I think all the systems being studied—mitochondrial, nuclear genes, and the Y chromosome—will be important for finding the answer," says Hammer. "It won't be just one person saying, "Aha! I found the answer. It's a large task for lots of labs to be involved in." And the way the field is growing, it probably won't be too long before more labs are involved. ■ ANN GIBBONS

The Cosmic Eye of Rosat

Philadelphia—For half a decade now, cosmologists have been increasingly confounded by their discovery that galaxies are clustering on scales much larger than the current theories of galaxy formation can explain. But now the researchers may be getting some help from a new eye in the sky, the German–British–U.S. Roentgen satellite (Rosat).



University of Leicester

The glow of cosmic x-rays. *Made by a British team, this Rosat image is much like the one discussed by Hasinger; it shows dozens of quasars amidst the x-ray background.*

The first inkling of this came at the American Astronomical Society meeting here, where Rosat team member Günther Hasinger of the Max Planck Institute for Extraterrestrial Physics in Garching bei München, Germany, presented a long exposure x-ray image showing what may be evidence for the earliest galactic clustering ever seen. Since this is a phenomenon that nobody understands very well yet (*Science*, 18 January, p. 272), astronomers such as George Blumenthal, a leading theorist on galaxy formation at the University of California, Santa Cruz, see it as "potentially a very exciting result." In principle, he added, "This could give us a direct measure of when galaxy clustering begins."

The image in question was something of a target of opportunity, Hasinger told meeting attendees. In the months since Rosat was launched in June 1990, it has spent the bulk of its time systematically scanning the sky to complete its initial objective: an all-sky survey of x-ray sources that will have better angular resolution and more than 100 times better sensitivity than the landmark examination of x-ray sources carried out in the late 1970s by