HUMAN GENOME PROJECT

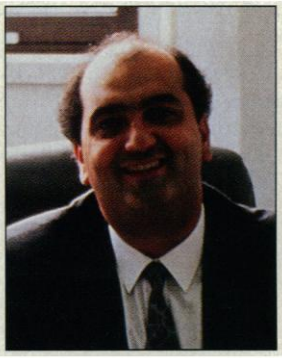
Draft Genome Map Debuts on Internet

When Daniel Cohen of the Centre d'Etude du Polymorphisme Humain (CEPH) in Paris and his colleagues announced completion of the first draft map of the human genome in the 16 December *Nature*, every geneticist's fantasy—a profound understanding of each human gene—may have come one small step closer to reality. But the new map also points to the immensity of the Human Genome Project—the international drive to identify all of the estimated 100,000 human genes by the year 2005—and shows just how essential computers are going to be for handling the mountains of information produced by the endeavor.

Cohen and his colleagues plotted their map with the help of mega-YACs, yeast artificial chromosomes that can carry huge segments of human DNA. Mega-YACs bearing their human genetic cargo can be inserted into yeast cells, where they are copied each time the cells divide. The researchers created copies, or clones, of enough human DNA segments to ensure that almost the whole genome was covered, and that each segment overlapped with its neighbors. Then, by identifying biochemical markers common to two segments, they lined up the cloned segments end-to-end to create a map—albeit still a rough one—of the human genome. That map reportedly includes more than 20,750 overlapping segments of genome from 10 different humans; covers an estimated 87% of the human genome; and bears 2000 markers that serve as signposts for specific regions of the genome.

In their *Nature* paper, Cohen and his colleagues provide only a short "guidebook" to this information, along with an invitation to gene hunters to obtain the full map via Internet, the international electronic network that users access with their computers. "The sheer size of the project made [Internet] the only option" for disseminating the information, says Cohen. Even a condensed version of the data would completely fill several issues of *Nature*. The unabridged version, if printed on paper, "would create a pile several hundred meters high," he says.

But although the new map seems big, just like the first cartographic attempts by any explorer of uncharted territories, it still lacks all but the grossest detail and undoubtedly contains many errors. "The map still needs to be refined, but it is not so bad," says Cohen. "We decided to release the data now, because we believe its good enough to be very useful to the scientific community." Elke Jordan, deputy director of the National Center for Human Genome Research in Bethesda, agrees: "It's a rough map so you have to use it with some caution, but it will be very valuable for making finer maps."



Gene mapper. CEPH's Daniel Cohen.

That effort will be aided, Cohen predicts, by the plans already put into operation for the rapid dissemination of the map coordinates through Internet and of the chromosome segments, which can be ordered from more than 20 labs worldwide. To probe the segments of the new map for disease-causing genes, geneticists must first break the segments into even smaller clones and identify new markers. As they do so, they will spot errors in the map and fill gaps. Eventually, that group effort should help yield detailed maps that geneticists can use to locate new genes rapidly and better understand the structure and function of the genome.

Cohen's map may be rough, but the genome community is anxious to get a look at it. "We received 64 requests for map information [on the first day of publication of the paper]," says Cohen. That's proved to be something of a mixed blessing. "We have a logistics problem that we did not anticipate," Cohen explains "We have only one person at any one time sending out [the files on Internet]." Cohen anticipates that, even by training new people to send out data, it will take weeks to answer all requests.

–**Rachel Nowak**

MATHEMATICS

Fermat Proof Hits a Stumbling Block

For weeks, rumors have been circulating in the mathematics community that Princeton University mathematician Andrew Wiles has run into trouble nailing down parts of his proof of Fermat's Last Theorem, announced last June at a conference in Cambridge, England (*Science*, 2 July, p. 32). On 4 December, Wiles confirmed that the rumors are at least partly true. He sent his colleagues an e-mail notice acknowledging that a problem had cropped up in the manuscript, which he had submitted to *Inventiones Mathematicae*, but expressing confidence he will resolve it. Experts are uncertain how long the problem will take to fix.

"During the review process a number of problems emerged, most of which have been resolved, but one in particular I have not yet settled," Wiles' statement says. The sticking point is a calculation that is "not yet complete as it stands," he says. "I believe that I will be able to finish this in the near future using the ideas explained in my Cambridge lectures." He plans to give "a full account" of the work in a course at Princeton in February.

The procedure of patching up a proof while revising a manuscript is entirely normal, experts say—especially when the proof is as long as this one, which runs approximately 200 pages. But in this case, the stakes are high because proving Fermat's Last Theorem—the assertion that the equation $x^n + y^n = z^n$ has no solutions in positive integers x, y and z for exponents greater than 2—has for centuries been one of the unconquered peaks of mathematics. Wiles' surprise announcement in June was greeted with immediate worldwide acclaim, making any mistake all the more serious.

But even if there is an unfixable flaw, say colleagues, the surviving parts of the proof will stand as a major advance in number theory. "When people finally see this manuscript, they're just going to be bowled over completely," says Ken Ribet of the University of California, Berkeley. Most mathematicians are happy when they write a paper with a single idea in it, he notes, but in Wiles' manuscript, "there are several ideas on every page."

The proof is actually an advance in the theory of elliptic curves, which can be loosely described as the study of rational solutions of cubic equations. In 1986, Ribet proved that Fermat's Last Theorem is true if an assertion known as the Taniyama-Shimura conjecture (until recently known as the Taniyama-Weil conjecture) holds for certain elliptic curves. The heart of Wiles' proof is a mathematical theory that allows him to prove the Taniyama-Shimura conjecture for a large class of elliptic curves, and that part of the proof is independent of the current sticking point.

What's still at issue is whether Wiles has succeeded in proving the Taniyama-Shimura conjecture for the specific curves needed to prove Fermat's Last Theorem. His key result says that one can prove the Taniyama-Shimura conjecture for particular elliptic curves provided one can calculate precise upper bounds for the sizes of algebraic structures known as Selmer groups. This by itself is a "fantastic new result," says Karl Rubin, a number theorist at Ohio State University. That's because the calculation can be carried out easily for a large number of elliptic curves. The calculation is not so