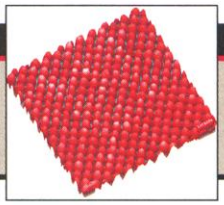


HUMAN GENOME RESEARCH

SNP Mappers Confront Reality And Find It Daunting

A year ago, a consortium of pharmaceutical giants and Britain's Wellcome Trust launched a novel venture: They would put together a database of 300,000 genetic markers called SNPs and give them away. They wanted to be sure that all researchers had access, because SNPs promised to pinpoint the genes involved in common diseases such as hypertension, cancer, and diabetes—a heretofore impossible feat. Enthusiasm grew, and SNPs became widely touted as the key to a brave new world of personalized medicine—with drugs tailored to an individual's genotype and simple tests to determine one's risk of specific diseases. But a closed meeting held last week, sponsored by the SNP Consortium and the U.S. National Human Genome Research Institute (NHGRI), concluded that those promises may be harder to achieve than expected.

THE SNP CONSORTIUM

- AstraZeneca PLC
- Aventis
- Amersham Pharmacia Biotech
- Bayer AG
- Bristol-Myers Squibb Co.
- Hoffmann-La Roche
- Glaxo Wellcome PLC
- IBM
- Motorola
- Novartis
- Pfizer Inc.
- Searle
- SmithKline Beecham PLC
- Wellcome Trust

The meeting was called to answer a deceptively simple question: How many SNPs are needed to find genes that confer susceptibility to common diseases? The question is not purely academic. When genomics companies like Genset, Incyte, and Celera began building private SNP databases in the late 1990s, National Institutes of Health (NIH) officials, worried that academic researchers would be shut out of the field, started a crash program in 1998 to find 100,000 SNPs. Like the 300,000 of the SNP Consortium, these would be made freely available.

Since then, investigators have been finding SNPs by the barrelful. The consortium, which has since been joined by Motorola, IBM, and Amersham Pharmacia Biotech, is about to release 27,000 more SNPs, which will bring the total in NIH's SNP database to more than 50,000. But whether those efforts will yield enough SNPs to track down disease genes reliably is anyone's guess, according to participants at last week's workshop. "What emerged from the meeting is a more realistic appraisal of how complicated it is to even make those estimates," says Nancy Cox of the University of Chicago.

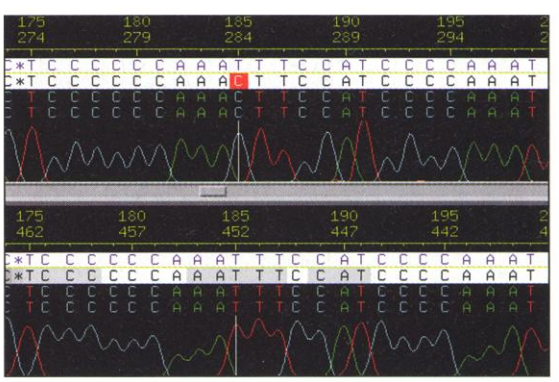
SNPs, short for single nucleotide polymorphisms, are places along the chromosomes where the genetic code tends to vary from one person to another by just a single base. They are estimated to occur about once every 1000 bases along the 3-billion-base human genome. SNPs in genes or control regions may influence susceptibility to common diseases. Others probably have no function but could provide valuable markers for gene hunters: If they lie close to a susceptibility gene, they are likely to be inherited along with it. Indeed, what galvanized researchers a few years ago was the possibility of building a map with SNPs peppered along the genome as landmarks. With such a map, investigators could compare individuals with a disease to a control group to see whether their SNP patterns varied. If so, the SNPs might lead to the genes involved in that disease.

In general, the more markers on a map, the easier it is to find genes. But with the cost of identifying each SNP hovering at about $100, according to Collins, there's a big incentive to use the fewest possible. When the NIH effort began, NHGRI chief Francis Collins, Aravinda Chakravarti of Case Western Reserve University in Cleveland, and others pegged that number at 100,000, or about one SNP every 30 kilobases. So they were "rather rattled," admits Collins, when Leonid Kruglyak of the University of Washington, Seattle, published a paper in *Nature Genetics* last summer asserting that 500,000 or even 1 million SNPs, spaced every 3 kilobases or less, would be needed to track down susceptibility genes. (Earlier studies had, in fact, pointed in that direction—see *Science*, 18 September 1998, p. 1787.)

Both estimates may be right, depending on where you are in the genome, explains Nicholas Schork, a geneticist at Case Western Reserve who is on leave at Genset in La Jolla, California. In regions of the genome prone to genetic reshuffling, many more markers may be needed than in relatively stable areas. The trouble, says Schork, is that there's no way to know in advance which type of region you are working in.

Another confounding factor, according to population geneticist Kenneth Kidd of Yale University, is that the usefulness of any one SNP varies enormously from population to population. Just one-third of the SNPs found so far seem to be widely applicable in all populations, says Kidd. That means investigators who want to study a particular ethnic group will have to find more SNPs.

Factoring in all these complexities, Collins left the meeting thinking that 600,000 to 1 million SNPs would be ideal. "We should continue to build the SNP catalog into the millions," especially, he says, as costs will drop once the human genome is sequenced.



Switching bases. SNP, with cytosine (red) substituted for thymine, shows up in top trace.

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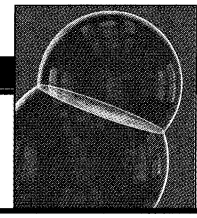
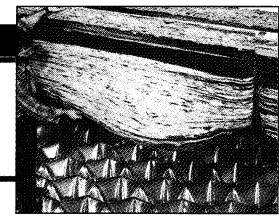
But, Collins added, considerable progress could still be made with a smaller set of markers. For instance, Allen Roses of Glaxo Wellcome presented unpublished data at the meeting showing that SNPs spaced about 30 kilobases apart were sufficient to pinpoint genes involved in four diseases: psoriasis, migraine, Alzheimer's, and diabetes.

To Schork, the bottom line is that "SNP mapping works for some diseases, but it





won't work for all." Adds Pui-Yan Kwok of Washington University in St. Louis: "It is not a surefire approach by any means."

Despite the uncertainties, official enthusiasm for SNPs seems undiminished. NIH and the SNP Consortium are about to embark on a 3-month project to sequence massive amounts of DNA to help finish the genome project. That effort should turn up a half-million or more SNPs, says Collins. The Japanese government, too, is embarking on an effort to find 200,000 SNPs. Within a year or two, there should be enough SNPs around to figure out whether they will live up to their advance billing. **–LESLIE ROBERTS**

SCIENTIFIC COMMUNITY

Oxford Wins a Crown Synchrotron Jewel

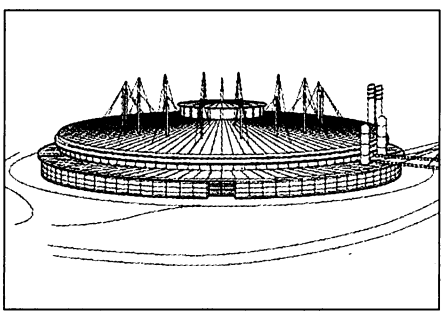
In this tale of two cities, one rejoices while the other pines for what might have been. On 13 March U.K. science minister David Sainsbury announced that DIAMOND, an $880 million synchrotron project that will allow scientists to probe the atomic structure of everything from proteins to ceramics, will be set at the Rutherford Appleton Laboratory (RAL) near Oxford. Losing out was the heir apparent—the Daresbury laboratory near Manchester, the site of the U.K.'s current synchrotron facility. Many scientists are denouncing the selection. "This is a crazy decision," says University of Liverpool physicist Peter Weightman, a longtime synchrotron user. "It's a triumph of finance over scientific arguments."

Soon after the British government proposed DIAMOND in 1993, financing problems put the project on hold. Five years later, a pair of strange bedfellows came to the rescue. The Wellcome Trust, Britain's largest medical charity, offered to put $184 million toward DIAMOND, and the French government pledged $56 million up front and up to $13 million a year in operating costs (*Science*, 6 August 1999, p. 819).

Then the political circus began. Wellcome officials lauded the benefits of DIAMOND at RAL, citing the ease of collaborations with an existing neutron source and a huge research community in the "golden triangle" formed by Oxford, Cambridge, and London. Secretary of State Stephen Byers talked up Daresbury, while his own advisers were touting RAL. Whatever tipped the scales toward RAL, the U.K. government isn't telling. "The decision was arrived at behind closed doors rather than through open discussions," contends crystallographer Paul Barnes of Birkbeck College in London. A spokesperson for the U.K.'s Department for Trade and Industry suggests that the preferences of Wellcome and the French were key. "If there hadn't been anyone else involved, [Daresbury] would have been an option," he says.

To soften the blow, Sainsbury also announced a boost for science in England's Northwest, including Manchester, pledging $80 million in new science spending in the region. But the consolation prize may not halt Daresbury's decline. The government has promised to keep Daresbury's synchrotron running until 2 years after DIAMOND comes online, at least another 7 years from now. "I imagine the whole thing will shut down in the long run because the synchrotron really defines Daresbury," says physicist Bob Cernik, Daresbury's trade union representative. Four of Daresbury's 270-strong synchrotron staff have left in the last few months, and Cernik fears the brain drain will accelerate.

–MICHAEL HAGMANN



A synchrotron built for one. Schematic of DIAMOND, a future landmark on Oxford's skyline.

ASTRONOMY

Distorted Galaxies Point to Dark Matter

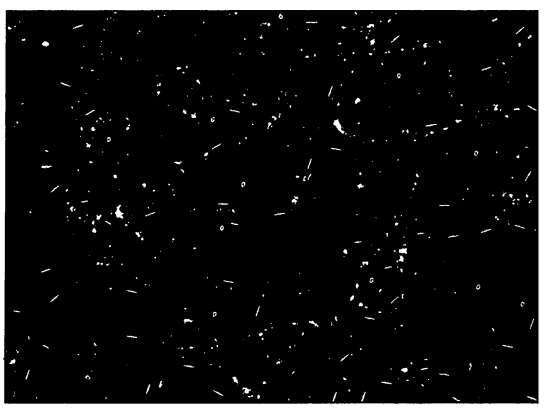
Never have so many astronomers been so eager to claim they can't see straight. Groups working with three different telescopes have detected weak lensing, a distortion of distant galaxies that reveals dark matter strewn across deep space. The results provide a first direct glimpse of the vast tangle of massive, invisible stuff that astronomers and astrophysicists believe makes up most of the mass of the universe.

Almost as interesting as the results themselves is how the researchers chose to make them public: Within days, all three groups rushed their findings into print—or, rather, into preprint—on Astro-Ph, an unrefereed Web server maintained by Los Alamos National Laboratory in New Mexico. Two did so with some misgivings, to avoid being scooped.

Such posting frenzies are becoming common, says Tony Tyson, an astrophysicist with Lucent Technologies' Bell Labs in Murray Hill, New Jersey, and leader of one of the teams. "Various groups have their results in various stages, and then somebody jumps in [with a preprint], and then everybody jumps in." A team working with the Canada-France-Hawaii Telescope (CFHT) in Hawaii made the first splash, followed by a group working with the William Herschel Telescope in the Canary Islands. Tyson's group, working at the Cerro Tololo Inter-American Observatory's Blanco Telescope in Chile, was the third to post its results.

Pricking the three groups' heels was the knowledge that weak lensing may prove the best tool for studying the colossal dark matter infrastructure of the universe. Researchers hope to use the technique to measure the distribution of the ripples and undulations in the intergalactic tangle of dark matter—information that would tell cosmologists precisely how the universe grew up after its birth in the big bang.

To glimpse dark matter, the three teams studied light from galaxies billions of light-years away. Such galaxies appear as faint luminous ellipses in the sky; gravity from intervening dark matter deflects their light, slightly squashing the ellipses in any small patch of sky so that, like schooling fish, neighboring ellipses tend to point in the



Stellar lineup. Dark matter bends light, making distant galaxies appear to be aligned.

CREDITS: (TOP TO BOTTOM) CLRC-DARESBURY LABORATORY; S. COLOMBI/INSTITUT D'ASTROPHYSIQUE DE PARIS