Walking the Jungles and Deserts of Chromosome 7

Searching for meaning among the genes.

Clinical geneticists lately have been making their way to Stephen W. Scherer's small office at The Centre for Applied Genomics, located in the research area of Toronto's Hospital for Sick Children (affectionately known as "Sick Kids"). They know that Scherer, an HHMI international research scholar and director of the center, plays an important role in the Human Genome Project—particularly regarding the detailed mapping of chromosome 7, which figures in numerous genetic diseases—and they need his help in using the project's results to counsel parents and would-be parents.

President Bill Clinton said that the Human Genome Project created "the most important, most wondrous map ever produced by humankind." But the clinicians seeking out Scherer had difficulty reading the map—its databases were designed by molecular biologists for other molecular biologists. Scherer believed there had to be a way to make the project more accessible.

Scherer took what he says was his first "walk along chromosome 7" in the late 1980s when, as a graduate student, he worked in the laboratory of the Sick Kids' team that identified the *CFTR* gene, mutations of which cause cystic fibrosis. Over the years, Scherer has identified other disease genes on chromosome 7, including the Sonic Hedgehog gene, which causes holoprosencephaly, a disorder marked by developmental defects in the face and brain, and those involved in Williams syndrome, which results in a range of medical and developmental problems. In a paper first published online in *Science* in April 2003, Scherer and colleagues presented the sequence of chromosome 7 in conjunction with a database that linked no fewer than 440 places on the chromosome to specific diseases. (A map of the chromosome—well, 99.4% of it—was also published in the July 10, 2003, issue of *Nature* by a team that includes HHMI investigator Sean R. Eddy of the Washington University School of Medicine.)

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Figuring out how the chromosome was put together was like solving a jigsaw puzzle with 158 million pieces, says Scherer, and it had other features that also confounded researchers' efforts. The chromosome has gene jungles, for example—gene-rich regions where some genes overlap—and like all chromosomes, it has gene deserts, vast stretches where there are no apparent genes. "What was evolution thinking about when it was designing this real estate?" he wonders.

Fortunately, the Chromosome 7 Project team had an advantage unique among participants in the publicly funded Human Genome Project—a deal with Celera Corporation, the project's private-sector competitor, to use its chromosome 7 databases. As Scherer explains it, the Celera data had more jigsaw-puzzle pieces, while the public consortium put together the pieces it had in a more complete way. "So in fact the two projects were very complementary," says Scherer, and by combining the data from the public and private sectors, "we had essentially all the jigsaw pieces."

Simply fitting the pieces together was just the first part of the Chromosome 7 Project, however. The challenge now is to figure out just what these pieces mean—what the genes do. Back in the 1980s, when grad-student Scherer first "walked" along the chromosome, the only way to identify the cystic fibrosis gene, for example, was to first study the genetic makeup of cystic fibrosis patients and then hunt along the chromosome's hundreds of millions of nucleotides to see whether there was a small difference between a cystic fibrosis patient's genome and that of an illness-free child. To do that, one had to walk carefully and slowly indeed.

Breakpoints

These days, the process has been reversed. The Chromosome 7 Project has identified regions of the chromosome sequence, called breakpoints, that are especially fragile and can be interrupted. Other genes have their chemical orders reversed, as if they were chemical dyslexics. Still others have genes on different parts of the chromosome than might normally be expected. Thus, now researchers first identify the breakpoint or other mutation, and then put the call out to the medical and research communities to report diseases and symptoms of people who possess these genetic markers.

More than 90 scientists in 10 countries have responded by sending this kind of information to the project. "We collected, worldwide, [data on] as many patients as we could with chromosome 7 rearrangements. They could be deletions or translocations or inversions that had defined clinical conditions," says Scherer.

The result can be seen on the Internet at *www.chr7.org*. The site is organized so that a user can click on any point or gene on the chromosome. It then lists the diseases and conditions associated with mutations of that gene.

During the first week the site was up, it received 14,000 hits. "So a lot of people are looking for this information," says Scherer. The site has also already added a hundred rearrangements and breakpoints to the 440 listed in April. "People keep sending us e-mails saying 'you missed this gene' or 'we found a new gene,' " says Scherer. "This [effort] is going through the roof."

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Rapid Response to SARS

Just as Scherer's team was working to publish results of the Chromosome 7 Project in the journal *Science* and on the project's Web site, severe acute respiratory syndrome (SARS) struck Toronto's hospital system. Scherer had to move the staff of his applied genomics center and draw up contingency plans to relocate its facilities. Because the center is situated in the hospital's research wing, some distance away from patient areas, its researchers were allowed to return relatively soon. This proved fortuitous, because the genome center staff was able to work around the clock to quickly sequence and share with their colleagues the first piece of the Toronto form of the virus suspected of causing SARS.

Toronto shared with Hong Kong the dubious distinction of being an epicenter of a SARS outbreak. But there was also a silver lining—Scherer's colleague and mentor, the chief investigator of the cystic fibrosis gene project at Sick Kids, is Lap-Chee Tsui, now head of the University of Hong Kong. (At the time of the cystic fibrosis project, Tsui too was an HHMI international research scholar.) Scherer's team sent essential scientific reagents and information not available in Hong Kong to the university by courier and e-mail. "So what would have otherwise taken weeks for them to get, they were getting in less than 36 hours," says Scherer. "We also helped them analyze the sequence of the Hong Kong variant, so it was kind of important that we were actually here."

LUIS ENRIQUE ASCUI/GETTY IMAGES

Wearing masks to help contain the spread of SARS, passengers from Hong Kong arrive at Singapore's Changi Airport this past April.