Premature Aging Gene Discovered

The gene that causes Werner's syndrome, which causes a rapid acceleration of aging, appears to encode a DNA-unwinding enzyme, and may provide clues to cancer and other diseases of old age

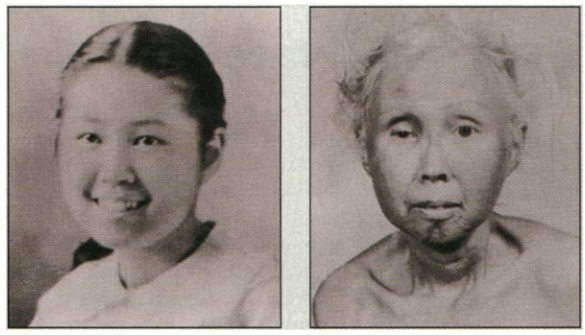
Just about everyone dreads the physical decline so often associated with aging. But people with the rare inherited disease known as Werner's syndrome have to face it far sooner than most. Unexpectedly, while they're still in their twenties, their hair grays, their skin loses its suppleness, and their vision clouds from cataracts. Even worse, they get cancer, heart disease, and a host of other diseases that usually don't strike until later in life. Most die before age 50. Aging experts have long wondered just what kind of molecular defect could cause such a striking acceleration of the aging process—and now they know.

On page 258, an international team of geneticists, led by Gerard Schellenberg of the Veterans Affairs Puget Sound Health Care System in Seattle, reports discovering the gene at fault in Werner's syndrome. Aging experts are already delighted by the finding. "This is really exciting for us because this is the first time that any gene that has been associated with aging has been identified," says David Finkelstein, a molecular biologist at the National Institute on Aging.

One reason for the excitement is that the structure of the protein encoded by the gene indicates that it's a helicase, an enzyme that unwinds the paired DNA strands of the cell's genes—a necessary prelude to such key activities as the repair, replication, or expression of the genetic material. And that suggests that the mutations that cause Werner's syndrome may exert their harmful effects by upsetting one or another of those activities. By teasing out what does happen, researchers hope they will eventually be able to design treatments that slow aging.

The gene may also yield insights into cancer, because Werner's syndrome brings with it an array of rare tumors. As Robert W. Miller, an emeritus epidemiologist at the National Cancer Institute, points out, "It's not only an aging gene; it's a cancer gene." Indeed, Miller compares it to *p53*. Five years ago, researchers found that mutations in *p53* cause Li-Fraumeni syndrome, another rare inherited disorder associated with an extremely high cancer risk, and they are involved in many nonhereditary cancers as well.

Schellenberg says he began looking for the Werner's syndrome gene in 1992. At that point, Makoto Goto from Tokyo Metropolitan Otsuka Hospital and his colleagues had already shown that the gene is located on the short arm of chromosome 8 by genetic linkage studies—comparing the inheritance of the disease with that of markers at known locations on the chromosomes. To continue the hunt, Schellenberg began by doing further genetic studies aimed at narrowing down the gene's location. He then wanted to sequence DNA from the suspect region and scan the sequence to find likely genes. "My philosophy was to bring all the different gene identification technologies to bear [on this problem]," he recalls.



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Taking its toll. As a teenager *(left)*, this Japanese American looked normal, but by age 48, the effects of Werner's syndrome were readily apparent.

Other groups were also searching for the gene, but Schellenberg says the hunt was aided by a remarkable spirit of cooperation between competing groups. For example, his team and that of rival gene-hunter Tetsuro Miki of Osaka University Medical School shared tissue samples from affected families in order to improve each other's chances of pinning down the gene's location. Schellenberg credits the additional families and subjects with helping his team to narrow the search to a section of chromosome encompassing just a million bases—still a lot of DNA, but manageable for the detailed sequencing effort that followed.

This began in early 1995, when Chang-En Yu and Junko Oshima from Schellenberg's lab teamed up with sequencing expert Ying-Hui Fu from Darwin Molecular Corp., also in Seattle. Each time the researchers came across a gene in the DNA they were sequencing, they looked to see whether people with Werner's syndrome, but not unaffected people, had mutations there. Finally, after sequencing 650,000 bases—possibly the most DNA ever sequenced in a gene hunt—and identifying four known genes and six new ones, whose sequences did not appear in the databases, the scientists found the one they were looking for.

To date, Schellenberg's group has found four different mutations disrupting this gene in Werner's syndrome patients. One of the 144 healthy people who served as controls also had one of these mutations, but in only one of the two copies of the gene. (Because Werner's syndrome is a recessive disease, symptoms don't develop unless both gene copies are mutated.) "We had started wondering where it was, but then it showed up and it was absolutely clear [what it was]," says molecular biologist David Galas of Darwin Corp. "I think it's the first human gene that's been identified by large-scale sequencing like this, but I think this [approach] is going to become more and more commonplace." Meanwhile, Miki had also been closing in on the gene, but was still not there when Schellenberg let him know the hunt was over.

The sequence of the Werner's syndrome gene, which encodes a protein containing 1432 amino acids, does not exactly match anything else in the databases. But because part of it closely resembles the sequences of genes that code for known helicases, Schellenberg and his colleagues assume this gene, too, codes for one, although they have not proven that directly.

Assuming that it does, however, that "tells you straight away that there are DNA transactions that are important [for Werner's syndrome]," says S. Michal Jazwinski, a molecular geneticist at Louisiana State University Medical Center in New Orleans. Exactly what kind of transaction is still unclear, however.

Although the half-dozen or so known helicases all unwind the DNA, they prepare the way for different activities, whether DNA replication or repair, or gene expression, or chromosome recombination, the shuffling of chromosomal segments that takes place during formation of the germ cells. Derangements in any of these processes have the potential to damage the genetic material, and thus the cell. And that

in turn could cause cells to function poorly, causing premature aging.

If the DNA damage happened to inactivate tumor suppressor genes or activate oncogenes, it might also cause cells to grow out of control and produce cancerous tumors. In fact, there's already evidence that a faulty helicase can cause cancers. Just 5 months ago, a team led by geneticist James German of the New York Blood Center in New York City pinpointed the gene for Bloom's syndrome, another rare disease associated with several cancers and numerous chromosome abnormalities, and it, too, specifies a helicase, German reported in the 17 November 1995 issue of *Cell*.

Still unclear, however, is why a helicase mutation would cause the unusual cancers seen in Werner's syndrome patients. Most cancers arise in epithelial tissue—the skin or the linings of the colon and lungs and of the mammary ducts. But in the April issue of *Cancer Epidemiology, Biomarkers and Prevention*, Japanese and U.S. researchers, including Miller, report that the cancers associated with Werner's syndrome are just as likely to develop in nonepithelial tissue, such as muscles and connective tissue.

But before researchers can explore this issue or pursue analogies between the Werner's syndrome gene and known helicase genes, they will need to test the hypothesis that it really does code for a helicase. Then they will want to explore what effects, if any, mutations in the gene have on DNA repair or other aspects of DNA metabolism. Another promising avenue of investigation concerns whether even "normal" people carry different versions of the gene that might affect their life-spans.

Still, as Schellenberg cautions, answering these questions won't explain everything about aging. "I don't want to sell Werner's syndrome as a total mimic of aging," he emphasizes. He notes that there are some key differences between how people with Werner's syndrome age and the way everyone else ages—and not just in the kinds of cancer they suffer from. Although prematurely old, the patients do not develop Alzheimer's disease or high blood pressure, for example.

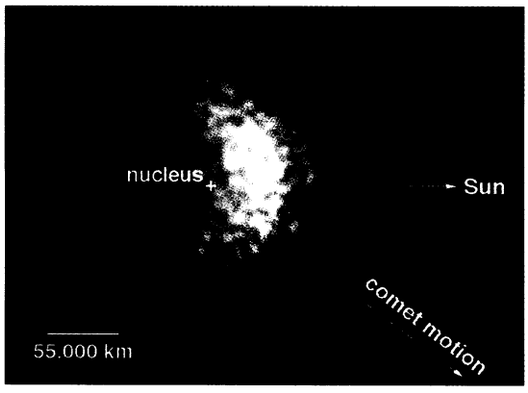
And even if the gene does play a role in normal aging, it can't be acting alone. Researchers estimate that some 70% of human genes are involved in some way in determining how long people live. "There's no one switch that you flip and the organism ages," Jazwinski says.

–Elizabeth Pennisi

ASTRONOMY

Comet Hyakutake Blazes in X-rays

If you trained a pair of dime-store binoculars on Comet Hyakutake on a clear night 2 weeks ago, it seemed to be sitting in your lap. But when a team of astronomers examined the comet with a far more sophisticated instrument, the German X-ray Roentgen Satellite (ROSAT), they hoped to see a dim smudge at best. X-rays had never been detected from any earlier comet, and theorists had come up with only a few mechanisms by which a comet could muster any x-rays at all. In fact, says Konrad Dennerl of the Max Planck Institute for Extraterrestrial Physics in Garching, "some astronomers wondered why we intended to point an x-ray telescope at a comet" in the first place.



NASA

Making light of theory. Hyakutake's gaseous coma emits unexpected x-rays.

No one is questioning the decision now. A series of snapshots taken between 26 and 28 March had the team as open-mouthed as amateur astronomers in a cornfield: The images revealed a bright, crescent-shaped region of emission on the comet's sunward side, about 30,000 kilometers from its nucleus. The emission flickered on a time scale of hours and reached intensities roughly 100 times higher than even the most optimistic theorists had predicted. "We were prepared to see nothing," says Robert Petre, a team member at the Goddard Space Flight Center in Maryland. "So it was an enormous surprise when this thing was just a boomer."

He and his colleagues—team leader Carey Lisse and Michael Mumma at Goddard and Dennerl, Jacob Englhauser, Joachim Truemper, and Juergen Schmitt at Max Planck—are a long way from explaining their surprising discovery. But they already think it could yield clues to the composition of the comet itself or the behavior of the solar wind, the stream of charged particles from the sun that is washing over the comet.

The team had justified its request for observing time on the off chance that Hyakutake's proximity to Earth—just 10% of the Earth-sun distance at the end of March—and high level of activity would make it possible to see weak x-rays from collisions between dust grains loosed by the comet and those normally present in interplanetary space. Over a 30-hour period, ROSAT took nine exposures of about 2000 seconds each as the comet hurtled across the field of view, capturing the x-ray photons on an instrument called a microchannel plate detector—essentially millions of tiny photomultiplier tubes bundled together. From the raw data, a computer corrected for the comet's motion during the exposures to produce sharp images.

The images reveal what looks like a crescent moon near the sunward edge of Hyakutake's coma—a halo of gas evaporated from the comet's much smaller nucleus of dust and ice. That location, says Mumma, suggests that the emission might result from interactions between the water molecules in the coma and x-rays radiating from the sun. Solar x-rays, he says, could jostle the innermost electrons of, for example, the oxygen atoms in the water; when the electrons returned to their ground states they would reradiate x-rays in all directions—a kind of fluorescence. If so, the detailed spectrum of the emission could yield insights into the elemental composition of the coma. Team members are now thinking of requesting observing time on the Japanese ASCA satellite, which has an x-ray spectrometer, when the comet swings around the sun and passes through ROSAT's field of view again in early July.

But Mumma notes that the fluorescence theory has a serious drawback: The rate of evaporation needed for this mechanism to explain the observed x-ray intensity "strains the imagination." If fluorescence can't do it, he says, perhaps the solar wind is somehow producing x-rays by piling up at the coma's edge and forming a sort of shock wave. Such interactions are known to produce energetic particles that could give off x-rays, but so few of the details have been worked out, says Mumma, that "at this point we're still struggling with the concept."

Other comet researchers, for their part, are applauding the discovery as an example of fortune favoring the bold. "Most people wouldn't even have the guts to ask for the observing time," says Harold Weaver of Applied Research Corp. in Landover, Maryland. "They took a chance and saw something pretty amazing."

–James Glanz