

MAY 14, 2004

## Researchers Snare New Cilia Genes

Howard Hughes Medical Institute researchers have used a combination of brainpower and computer power to identify a multitude of new genes that control the formation of tiny, hair-like cilia that stipple the surfaces of many organs in a wide variety of creatures.

The genes are considered important because of the ubiquity of cilia, which are critical for transport and sensory structures located throughout the human body—including the brain, nose, ears, eyes, lung, kidneys and sperm.

---

**"We used two months of computer analysis to discover genes that would have taken seven or eight years of genetic screening to isolate."**

— **Charles S. Zuker**

---

Led by Howard Hughes Medical Institute investigator Charles S. Zuker, the researchers reported their findings in the May 14, 2004, issue of the journal *Cell*. Zuker and his colleagues at the University of California, San Diego, collaborated on the studies with a co-author from the Max Planck Institute of Biochemistry in Germany.

According to Zuker, the cilia genes they identified may prove important in understanding the causes of genetic diseases involving cilia. "There have been a number of genetic disorders that produce very complex syndromes, affecting tissues that appear to be completely unrelated to each other," said Zuker. "For example, there are disorders that affect a person's retinas, kidneys and lungs. Clinicians have begun to realize that what's common among these organs is that they all have ciliated cells.

"Now that we have massively expanded the number of candidate genes that can be examined for mutations in these disorders, it is far more likely that the culprit gene defects will be identified," he said.

The scientists' broad genomic comparison of species was sparked by a discovery by the paper's first author, Tomer Avidor-Reiss, said Zuker. "He found that genes he had laboriously isolated in fruit flies that were responsible for cilia needed for the senses of hearing and balance were highly conserved in nearly all of the ciliated organisms for which genomes had been sequenced. But they were absent in every one that had no cilia. It was a

stroke of genius on Tomer's part to propose that we could perform large-scale comparisons of entire genomes of such organisms to quickly identify new genes involved in cilia formation.”

Seeing an opportunity, the researchers chose to compare the genomes of eight organisms, including those that had retained cilia in their anatomy and those that had lost the structures during evolution. The ciliated organisms included human, fruit fly, roundworm, an algae and the organisms that cause malaria and sleeping sickness. The non-ciliated organisms were the mustard plant, yeast and an amoeba.

“It was a process that could be called ‘in silico subtraction,’” said Zuker of the computer analysis they performed. “In essence, we screened the genomes in such a way that those of the non-ciliated organisms could be subtracted from those of the ciliated ones.” The result, said Zuker, was an array of genes that included the genes associated with cilia formation.

Using various forms of their computational genomic subtraction strategy, the researchers identified genes common to all ciliated organisms, as well as those that are restricted to particular subtypes of cilia. These subtypes include those that are motile—such as those found in sperm and lungs—and those of a type called “compartmentalized” that are key structures in sensory organs—including the senses of vision, hearing and olfaction. In all, the researchers identified 187 cilia-related conserved genes from the over 150,000 genes analyzed.

To confirm that the genes their studies revealed were, indeed, important to cilia formation, they screened the collection for the presence of known cilia formation genes. They found that the vast majority of known genes were contained in those uncovered in their study.

To demonstrate that new genes discovered by their computational method actually functioned biologically to construct cilia, the researchers then concentrated on a set of six compartmentalized genes known as “outer segment genes,” or OSEGs. Specifically, they did experiments to prove that these genes were expressed in sensory neurons in the fruit fly, and that they were necessary for normal cilia formation in those cells. Zuker and his colleagues also showed that the proteins produced by the genes function as critical “cargo carriers” that transport molecules necessary for cilia formation and function.

Zuker noted that this comparative genomic strategy could significantly speed gene discovery. “We believe that this analysis saved us several years of work,” he said. “We used two months of computer analysis to discover genes that would have taken seven or eight years of genetic screening to isolate.

“The technique is also quite generalizable,” said Avidor-Reiss. “All you need is a biological process that is conserved in the genomes of enough species to be compared, and selectively lost in others.”