

Capture the Exon, Narrow the Hunt

TODAY'S GENETIC TECHNIQUES MAKE IT POSSIBLE
TO TRACK DOWN DISEASE MUTATIONS FASTER THAN EVER.

Scanning the human genome for a single disease-causing mutation is like taking a copy of *War and Peace* in a foreign language and searching for one misspelled word—a daunting and time-consuming task. But by narrowing the search in the right way, says one HHMI scientist, finding a mutation for even the rarest of diseases doesn't have to be difficult.

HHMI investigator Friedhelm Hildebrandt, of the University of Michigan, used an innovative combination of genetic techniques to find a mutation that causes kidney failure and blindness in affected children. The mutation is known to exist in only 10 families worldwide.

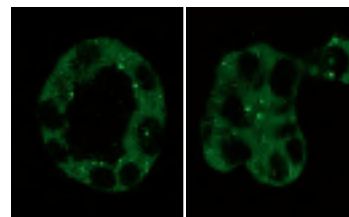
For years Hildebrandt's team has been collecting genetic samples from families with Senior-Loken syndrome, for which no treatment is available. They have more than 600 families in their database and have linked nine different genes to the disease. But there were still unexplained cases.

Rather than scrutinizing the entire genomes of affected individuals for mutations, the researchers narrowed their search. First, they sequenced only exons—stretches of DNA that code for proteins—which make up only 1 percent of the genome. Then, the team focused on 828 genes known to contribute to the function of cilia, cellular structures affected by the nine previously identified genes. Finally, they searched their database for matching DNA regions

in two siblings affected by Senior-Loken syndrome.

The techniques made the search much more efficient than traditional methods, and it paid off: the team found mutations in a gene called *SDCCAG8* in 10 families affected by the syndrome. The group had been unable to find this gene despite a 6-year search, because of the syndrome's rarity. So-called "exon capture" allowed its identification in a single family within 6 months.

The exact role of the *SDCCAG8* protein in the syndrome isn't known, but it is involved in the function of cilia—sensory extensions of a cell—in the kidneys and eyes, the scientists reported online September 12, 2010, in *Nature Genetics*. Furthermore, normal kidney cells form hollow, symmetrical spheroid structures when grown in a gel, but cells lacking *SDCCAG8* form irregularly shaped spheres. Hildebrandt hopes they can use this trait to test compounds that might restore *SDCCAG8*'s function. ■ —SARAH C.P. WILLIAMS



Grown in a gel, kidney cells lacking *SDCCAG8* (right) don't form the perfect spheroids shown by normal kidney cells (left).

IN BRIEF

research scholar Vilma Martins, have added evidence to that case.

Martins and her colleagues showed that PrPC stimulates protein synthesis in neurons, possibly at their synapses—the junctions where electrical and chemical signals pass between neurons. By binding to a protein called stress-inducible protein 1 (STI1), PrPC turns on two signaling pathways known to be involved in neuroprotection, learning, and memory consolidation.

The scientists found that infecting cells with the abnormal prion protein blocked the ability of PrPC to turn on the STI1-dependent signaling pathways. This explains, in part, the detrimental effects of misfolded prion proteins in diseases. Not only are the abnormal proteins toxic, they also prevent the cell from responding to STI1. This could lead to neurodegeneration, the researchers hypothesize in the July 20, 2010, issue of *Proceedings of the National Academy of Sciences*.

PROTEIN LINKED TO MEMORY AND LEARNING

A protein that's been implicated in extending the lives of laboratory animals by preventing obesity and maintaining a healthy metabolism is now shown to be involved in keeping the brain healthy too.

Drugs that boost the protein, called SIRT1, are already in human trials related to extending life spans.

In 2007, a team led by HHMI investigator Li-Huei Tsai first investigated SIRT1's role in the brain. Tsai's group at the Massachusetts Institute of Technology showed that it helped protect neurons in a mouse model of Alzheimer's disease.

To understand more about the protein, the researchers developed mice that could not make functioning SIRT1. The mice had severe learning and memory impairments, and also fewer neurons and neuronal connections in their brains, compared with normal mice. Because of the gene's widespread effects on the body, Tsai suspected that SIRT1 wasn't acting directly in the brain but was controlling other genes important for neuronal health. As she studied the expression of various genes in the brain, she found that mice lacking SIRT1 had a low level of CREB, a protein known to be important in synapse function.

Tsai and her colleagues revealed that SIRT1 affects CREB through the regulation of a microRNA molecule called mir134. Mice with too much mir134 in their brains had the same learning and memory deficits as mice lacking SIRT1. Furthermore, removing mir134 from the SIRT1-deficient mice

reversed the cognitive effects. The study, published August 26, 2010, in *Nature*, suggests that SIRT1-boosting drugs may work to treat neuronal diseases.

STEM CELLS RECALL THEIR ORIGINS

Four years ago, researchers discovered how to reprogram adult cells—including skin, muscle, and blood cells—into seemingly blank slates that could develop into any cell type. The so-called induced pluripotent stem cells (iPS cells) were hailed as an alternative to embryonic stem cells. Now, two groups of HHMI researchers have shown that iPS cells don't have such a blank slate after all. But all is not lost—they've also discovered new ways to erase the cells' memories of their origins.

HHMI investigator George Q. Daley, of Children's Hospital Boston, was working to coax iPS cells into becoming blood cells to treat thalassemia, a blood disease. His team found that iPS cells originally derived from blood cells did a much better job than those that started out as skin cells. To figure out why, the scientists analyzed the patterns of methylation—a chemical signature of gene silencing—in each type of iPS cell. A similar analysis was done independently by HHMI early career scientist Konrad Hochedlinger, at Harvard University.