Finding Charcot-Marie-Tooth gene ends a quest and begins new era of personalized genomic medicine

March 10 2010

Baylor College of Medicine's Dr. James Lupski came to the end of a personal quest earlier this year when the Baylor Human Genome Sequencing Center sequenced his complete genome and identified the gene involved in his own form of Charcot-Marie-Tooth syndrome, which affects the function of nerves in the body's limbs, hands and feet. At the same time, the finding opened a new door showing that genome information has clinical importance.

"This is the first time we have tried to identify a disease gene this way," said Lupski, vice chair of molecular and human genetics at BCM. "It demonstrates that the technology is robust enough that we can find disease genes by determining the whole genome sequence. We can start to use this technology to interpret the clinical information in the context of the sequence - of the hand of cards you have been dealt. Isn't that the goal or dream of personalized genomic medicine?"

In a report that went online in the *New England Journal of Medicine* today, Lupski, Dr. Richard Gibbs, director of the Human Genome Sequencing Center, and other experts describe the process of the whole genome shotgun study that led to the discovery of different mutations in the copies of the gene SH3TC2 that Lupski inherited from his parents. While neither parent has the disease, which affects the peripheral nerves, four of their children inherited both mutations and had the disease.

"I have the disease and I have two mutant genes," said Lupski. "I know I have a genetically-recessive disease and I've known that for 40 years."

Now he knows the gene at fault. In taking the research further, he and his colleagues also found that a person who carries only one of the recessive mutations is susceptible to carpal tunnel syndrome. This disorder usually affects people who perform repetitive motions that compress the median nerve where it crosses the wrist.

"I wonder how often this occurs," he said. "People who carry one gene for a recessive disease may have susceptibility for complex traits. Will we be able to look at some alleles (gene copies) like this to see what you might be susceptible to?"

To date, fewer than 10 personal genomes have been completed - most of them an intellectual exercise. On May 31, 2007, Gibbs and representatives of what was then 454 Life Sciences Inc., presented Nobel Laureate Dr. James Watson, co-discoverer of the DNA double helix and developer of the Human Genome Project, his full genome in ceremonies at BCM.

Reporting the information in a genome is an awful lot of work, said Lupski.

"When evaluating personal genomes like those of Watson and others one is struck with awe at the inability to interpret a lot of what we see. Currently, we only know the function of 5 percent to 10 percent of the approximately 25,000 genes in our genome that it takes to make a human being. I think at least what this paper (in the New England Journal of Medicine) tells us is that the data are robust enough that we can start to use it to interpret clinical information in the context of the genome sequence," Lupski said.

When looking for a specific disease-causing mutation in a gene, one must understand both the sequence of the specific genes, as well as the different changes in them - nucleotide switches, deleted or duplicated genetic material - that can cause the disease and affect the degree to which a person experiences it. Then mutations in different genes can cause similar genetic diseases.

Lupski and his team identified the first duplication on a chromosome that gave rise to Charcot-Marie-Tooth disease and published those data in 1991. Since that time, mutations or changes in as many as 40 genes have been shown to cause diseases like Charcot-Marie-Tooth. None accounted for the disorder that affects Lupski himself and some of his siblings.

After Watson's genome was sequenced, Gibbs offered to sequence all of Lupski's genome. That would enable the pioneering geneticist to find the answer that he had sought since he decided to become a physician-researcher early in life. They used the whole genome shotgun approach. In this approach, the scientists break up a person's genome into different small fragments that they then clone. They then isolate and sequence the clones, using a computer algorithm to reassemble the genome into its proper form.

In this case, Gibbs and his colleagues sequenced Lupski's entire genome and identified all the functional variants in genes that were likely to be related to Charcot-Marie-Tooth.

In one allele or member of the gene SH3TC2 pair, these researchers identified a "nonsense" mutation, which means there is a premature stop to the message that results in a protein. This mutation had been reported previously in Charcot-Marie Tooth in particular ethnic groups. They also identified a new missense mutation in the second gene. (Missense mutations are those in which a single letter in the genetic code [A-T-C-

G] is different, resulting in the production of a different amino acid. This difference can result in a protein that cannot carry out its appointed task in the cell.)

The nonsense mutation was found in one parent and two siblings who did not have the disease. The missense mutation was found in another parent and one grandparent, neither of whom had the disorder. Only siblings who inherited both mutated genes had the Charcot-Marie-Tooth 1 disorder.

The whole shotgun sequencing approach contrasts to other diagnostic approaches. Other tests can look at known variations, but the fact that different kinds of changes in different genes that are inherited recessively or dominantly can cause the disease complicates diagnosis.

"Clinical and genetics experts struggling with poorly understood high-penetrance genetic diseases must now seriously consider this approach for illuminating the molecular etiology of these cases, and ultimately providing better patient management for families living with such diseases," the authors wrote.

"We hope we can use the information about you and your genome in your care," said Lupski, who is both an M.D. and a Ph.D. "If you have hypertension, can we use your genome to figure out a better treatment for you? It will take a lot of time. We don't know what 90 percent of the genes in the genome do."

Because they anticipate that this information will be valuable to physicians in practice, they included a glossary of terms relating to DNA sequencing to enhance comprehension of their report. Lupski and Gibbs both hope that this begins a new era of clinical sequencing.

On a more philosophical note, the whole genome sequencing provided

Lupski clues to what makes an individual.

"My genome has 3.5 million differences from the reference genome (sequenced in the original human genome project)," he said. "I have hundreds of thousands of differences from all the other genomes that have been sequenced. I expect that to hold true for others. Everyone is truly unique."

More information: www.nejm.org

Provided by Baylor College of Medicine