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First Bardet-Biedl Syndrome Gene Identified

Researchers have pinpointed a gene mutation that causes Bardet-Biedl syndrome (BBS), a rare genetic disorder that can lead to mental retardation.

"BBS is a relatively rare disorder, but it has an interesting constellation of features, including obesity, mental retardation, polydactyly [additional digits], genital abnormalities and retinitis pigmentosa, which can lead to blindness," said Val C. Sheffield of the Howard Hughes Medical Institute at the University of Iowa. "One reason we are studying BBS is that it might give insight into obesity and other common disorders."

"It will be interesting to see if this gene is involved in more common disorders, such as diabetes."

— Val C. Sheffield

The discovery by Anne M. Slavotinek and Leslie G. Biesecker at the National Human Genome Research Institutes, Sheffield and colleagues at the University of Iowa and a number of other institutions is reported in the September 2000 issue of the journal *Nature Genetics*.

Particularly interesting about BBS, said Sheffield, is that it arises from defects in at least six different genetic loci (regions of chromosomes). "When we first began to study BBS, our hypothesis was that it was an autosomal recessive, single locus disorder," said Sheffield. "We had found an inbred population of Bedouins in Israel with BBS and mapped the gene to a locus on human chromosome sixteen. We then identified a second Bedouin population with the disease, and found that their affected gene didn't map to same location. This gave us the first clue that there was genetic heterogeneity in people with BBS."

Sheffield and his colleagues first zeroed in on the newly discovered BBS gene, called *MKKS*, because Biesecker and his colleagues had established that it caused McKusick-Kaufman syndrome (MKS) in a large Amish population. "The one phenotypic feature shared by people with BBS and MKS is extra digits," said Sheffield. There was also evidence that there may be a BBS locus on chromosome twenty, where the *MKKS* gene resides. "So,

we screened the *MKKS* gene for mutation in BBS families whose disease showed no evidence of linking to any of the other known loci," he said.

The screening revealed that four of the 34 people with BBS had mutations in the *MKKS* gene. Importantly, said Sheffield, the mutations in *MKKS* were of the type that completely knocked out the gene's function, leading the scientists to hypothesize that MKS might be due to a crippled form of the *MKKS* gene, whereas BBS is caused by a complete knockout of the gene.

According to Sheffield, the finding of the nonfunctional *MKKS* gene in a relatively small group of people with BBS hints that the gene is, indeed, a cause of the disorder. "It's pretty much what we expected," he said. "You would expect that the majority of the disease in those families would be caused by defects at one of the other five loci. We expected only about ten percent of families to be accounted for by the *MKKS* gene."

According to Sheffield, the discovery of the role of *MKKS* in BBS will likely help pry open other secrets of the disease. "We're interested in using this as a clue, hopefully, to finding the other BBS genes," he said. According to Sheffield, the protein produced by the *MKKS* gene is likely to be a common part of a metabolic pathway that is altered to produce the constellation of abnormalities seen in BBS patients.

While the protein product of the *MKKS* gene is still unknown, he said, the gene has a similar sequence to other genes that produce chaperonins, proteins that aid in the proper folding of newly synthesized proteins.

Discovering the role of *MKKS* in BBS might also lead to insights into other more common diseases, said Sheffield. "We are intrigued that these BBS families have a high incidence of diabetes," he said. "So, it will be interesting to see if this gene is involved in some of these more common disorders. While that is unlikely, I think that studying the *MKKS* protein, and the protein it interacts with, may lead us to pathways or to complex structures that may play a role in more common diseases such as diabetes."