Fanfare over Finding First Fat Gene

Eight years of genetic sleuthing finally paid off this week for scientists seeking to understand the much studied, much lamented problem of obesity.

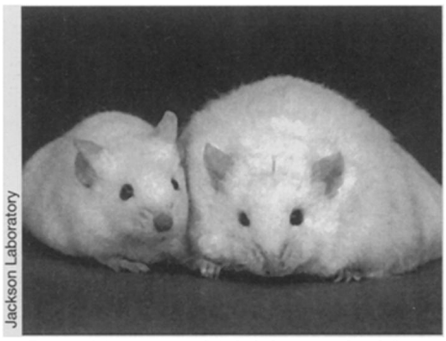
For the first time, molecular geneticists have identified and made copies of a gene essential for keeping the body's weight stable. They first tracked the gene down in mice and then used the mouse gene to locate the human equivalent. The genes are an 84 percent match, says Jeffrey M. Friedman of the Howard Hughes Medical Institute at Rockefeller University in New York.

"What you have is a discovery that forms the basis for a new and rational approach to the treatment of obesity," comments Timothy J. Rink, a physiologist at Amylin Pharmaceuticals in San Diego.

Many obesity experts say they know how to get people to diet, lose weight, and want to stay slim, but the body regains those pounds, frustrating everyone involved. With the new gene in hand, scientists can examine why this happens.

"This is a pivotal step in the understanding of body weight," Rink says.

For a century, physiologists have argued about how the body balances food intake against energy use, controlling weight gain and loss. In recent years, some indirect evidence has suggested that fat-laden cells produce a blood-borne messenger that tells the brain to suppress the appetite. But until now, no one could pin down the identity of any satiety hormone.



Does this mouse (right) have a bad fat-regulating gene?

Then, inspired by the way geneticists had tracked down the mutant gene in muscular dystrophy (SN: 9/7/85, p.151), Friedman tried the same approach with a strain of mouse called obese. These mice gain up to three times their normal body weight and often develop insulin-independent diabetes.

In this strain, the altered gene probably results in the production of a faulty signaling hormone, Friedman and his colleagues report in the Dec. 1 NATURE. The gene is also defective in another excessively plump mouse strain, but in these mice the gene seems inactive, they note.

Friedman plans to make the gene's protein product next. If it is the satiety signal, it should make obese mice lose weight. Because of similarities between the mouse and human versions of this so-called obese gene, such positive results could bode well for humans seeking help in shedding pounds.

"But it's a long way from cloning a gene to [having] a therapeutic," Rink warns. He and Friedman both emphasize that many other genes — and proteins — probably help keep weight stable.

Yet even if these obese mice don't slim down, the discovery should have far-reaching effects. "I think it will change the way we think about obesity and the way we do obesity research," says Beverly J. Paigen, a geneticist at the Jackson Laboratory in Bar Harbor, Maine.

— E. Pennisi

Breast cancer gene hides many mutants

On Oct. 7, a team of 45 researchers published a paper describing a gene responsible for some cases of inherited breast cancer. Immediately, thereafter, gene hunters all over North America began the race to confirm the finding.

Now, three scientific teams have done just that. Their results verify the link between the gene BRCA1 and breast or ovarian cancer, or both, in some families. Taken together, the data on 100 families provide a sobering view of the complexity of these cancers.

Collectively, the groups found not one, not two, but 22 distinct defects in the genetic coding that makes up BRCA1. "There's a lot of heterogeneity of mutations in this gene," says Francis S. Collins, director of the National Center for Human Genome Research in Bethesda, Md., and leader of one of the research teams.

In the short run, those results dash the hope of devising a simple blood test to identify people who have inherited a mutant BRCA1. The three scientific reports, as well as an editorial, appear in the December NATURE GENETICS.

In one report, Collins and his colleagues studied 50 families with a history of breast and ovarian cancer. The researchers obtained sample DNA from each individual in the study, homed in on BRCA1, and scoured the gene for flaws in the genetic code. They found a number of mutations, one of which contains a clue to BRCA1's function. In some cases, BRCA1 has a flaw that can lead to the production of a defective protein, one with an altered zinc-finger region.

Researchers believe that BRCA1, when healthy, may act as a tumor-suppressor gene. The triad of reports suggests that a mutant BRCA1 produces a flawed protein or no protein at all. Researchers suspect that the BRCA1 protein product helps regulate other genes in a cell. When it's absent or malfunctioning, a cell may turn malignant.

The team led by Mary-Claire King of the University of California, Berkeley, found a mutation that causes a similar mistake in the zinc-finger region of the BRCA1 protein. This study of 20 families also describes a handful of BRCA1 mutations. One notable one: a defect in BRCA1 that seems to predispose women to develop breast cancer at a very early age.

Finally, Steven A. Narod of McGill University in Montreal and his coworkers analyzed BRCA1 in 30 Canadian families. This team also found a number of flaws in the gene.

When considered together, the results from the three studies show that just 31 of the 100 families showed a BRCA1 mutation. What about the remaining 69 families, all of which had a history of breast and ovarian cancer? The DNA probe could have missed some BRCA1 defects.

"It's still possible there are unaccounted-for mutations," says Lawrence C. Brody of the National Center for Human Genome Research. Then again, some families' tumors may be sporadic and thus have no common genetic basis, points out Brody, coauthor of one report.

These papers indicate that no predominant BRCA1 mutation exists, and they suggest that the "prospects for wide-scale screening of BRCA1 look dim," says NATURE GENETICS Editor Kevin Davies. If further study bears that suspicion out, a blood test for mutations in BRCA1 would have to look for a great number of flaws in the genetic code, he adds.

— K.A. Fackelmann