Researchers discover gene mutations linked to longer lifespans

4 March 2008

Mutations in genes governing an important cell-signaling pathway influence human longevity, scientists at the Albert Einstein College of Medicine of Yeshiva University have found. Their research is described in the March 4 issue of the *Proceedings of the National Academy of Sciences*.

The report is the latest finding in the Einstein researchers' ongoing search for genetic clues to longevity through their study that by now has recruited more than 450 Ashkenazi (Eastern European) Jews between the ages of 95 and 110. Descended from a small founder group, Ashkenazi Jews are more genetically uniform than other groups, making it easier to spot gene differences that are present. In 2003, this study resulted in the first two "longevity genes" ever identified—findings that have since been validated by other research.

The present study focused on genes involved in the action of insulin-like growth factor (IGF-I), a hormone that in humans is regulated by human growth hormone. Affecting virtually every cell type in the body, IGF-I is crucially important for children's growth and continues contributing to tissue synthesis into adulthood. The IGF-I cell-signaling pathway is triggered when IGF-I molecules circulating in blood plasma latch onto receptors on the surface of cells, causing a signal to be sent to the cell's nucleus that may, for example, tell that cell to divide.

Animal research had shown that mutations to genes involved in the IGF-I signaling pathway cause two effects: Affected animals have impaired growth but also longer life spans. So the Einstein scientists reasoned that altered signaling in this pathway might also influence human longevity. To find out, they analyzed IGF-I-related genetic variations in 384 Ashkenazi Jewish centenarians. And since plasma levels of IGF-I do not reflect their levels at a younger age, the researchers also looked at two other groups: the children of these centenarians, and a control group consisting of Ashkenazi Jews the same age as the centenarians' children but with no family history of longevity.

Remarkably, the female children of the centenarians had IGF-I plasma levels that were 35 percent higher than female controls—perhaps a sign that the body was compensating for a glitch in IGF-I signaling by secreting increased amounts of the hormone. That suspicion was strengthened by two other findings: the daughters of centenarians were 2.5 cm shorter than female controls; and when the researchers analyzed the gene coding for the IGF-I cell-surface receptor molecule to which the IGF-I hormone binds, the receptor genes of centenarians and their daughters were much more likely to have a variety of mutations than were the receptor genes of the controls.

"Our findings suggest that, by interfering with IGF-I signaling, these gene mutations somehow play a role in extending the human life span, as they do in many other organisms," says Dr. Nir Barzilai, senior author of the study and director of the Institute for Aging Research at Einstein.

Dr. Barzilai notes that a drug that decreases IGF-I action is currently being tested as a cancer treatment and could be useful in delaying aging. "Since the subjects in our study have been exposed to their mutations since conception, it is not clear whether people would need such a therapy throughout life or if it could help people who received it at a later time."

Source: Albert Einstein College of Medicine