Researchers use novel approach to uncover genetic components of aging

August 24 2007

People who live to 100 or more are known to have just as many—and sometimes even more—harmful gene variants compared with younger people. Now, scientists at the Albert Einstein College of Medicine of Yeshiva University have discovered the secret behind this paradox: favorable "longevity" genes that protect very old people from the bad genes' harmful effects. The novel method used by the researchers could lead to new drugs to protect against age-related diseases.

"We hypothesized that people living to 100 and beyond must be buffered by genes that interact with disease-causing genes to negate their effects," says Dr. Aviv Bergman, a professor in the departments of pathology and neuroscience at Einstein and senior author of the study, which appears in the August 31 issue of *PLoS Computational Biology*.

To test this hypothesis, Dr. Bergman and his colleagues examined individuals enrolled in Einstein's Longevity Genes Project, initiated in 1998 to investigate longevity genes in a selected population: Ashkenazi (Eastern European) Jews. They are descended from a founder group of just 30,000 or so people. So they are relatively genetically homogenous, which simplifies the challenge of associating traits (in this case, age-related diseases and longevity) with the genes that determine them.

Participating in the study were 305 Ashkenazi Jews more than 95 years old and a control group of 408 unrelated Ashkenazi Jews. (Centenarians are so rare in human populations—only one in 10,000 people live to be 100—that "longevity" genes probably wouldn't turn up in a typical

control group. Longevity runs in families, so 430 children of centenarians were added to the control group to increase the number of favorable genes.)

All participants were grouped into cohorts representing each decade of lifespan from the 50's on up. Using DNA samples, the researchers determined the prevalence in each cohort of 66 genetic markers present in 36 genes associated with aging.

As expected, some disease-related gene variants were as prevalent or even more prevalent in the oldest cohorts of Ashkenazi Jews than in the younger ones. And as Dr. Bergman had predicted, genes associated with longevity also became more common in each succeeding cohort. "These results indicate that the frequency of deleterious genotypes may increase among people who live to extremely old ages because their protective genes allow these disease-related genes to accumulate," says Dr. Bergman.

The Einstein researchers were able to construct a network of gene interactions that contributes to the understanding of longevity. In particular, they found that the favorable variant of the gene CETP acts to buffer the harmful effects of the disease-causing gene Lp(a).

If future research finds that a single longevity gene buffers against several disease-causing genes, then drugs that mimic the action of the longevity gene could help protect against cardiovascular disease and other age-related diseases.

"This study shows that our approach, which was inspired by a theoretical model, can reveal underlying mechanisms that explain seemingly paradoxical observations in a complex trait such as aging," says Dr. Bergman. "So we're hopeful that this method could also help uncover the mechanisms—the gene interactions—responsible for other complex

biological traits such as cancer and diabetes."

Meanwhile, the Einstein researchers are greatly expanding their longevity research: From the 66 genetic markers examined in this study, they are now using a high-throughput technology that allows them to assay one million genetic markers throughout the human genome. The goal is to find additional genetic networks that are involved in the process of aging.

Source: Albert Einstein College of Medicine