

Is 100 the New 80?: Centenarians Studied to Find the Secret of Longevity

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Centenarians—those who live past age 100—may help researchers find the key to living longer, healthier lives. The reason, say scientists who study this elite group: centenarians may possess genes that protect them from disease into old age.

One in every 10,000 individuals in the U.S. reaches the age of 100. There are currently an estimated 60,000 centenarians in the U.S. with up to 70 beyond the age of 110. For the past decade, researchers have marveled at these folks who often live independently—and free of major disabilities—well into their 90s, if not longer.

To better understand their exceptional longevity, scientists have recruited centenarians for extensive physical and genetic screening. Of particular interest to researchers is that some of the oldsters have a history of obesity and heavy smoking. But despite these risk factors, most centenarians remain healthy up to the last few months of their lives and, in some cases, up until their dying breaths.

Although sheer luck no doubt plays a role, "there is also a striking family history that supports a genetic component," says Nir Barzilai, a geneticist at the Albert Einstein College of Medicine in New York City. In fact, he adds, the odds of centenarians having a relative who lived into old age is 20 times that of the average person.

The goal now is "to find the subtle genetic differences between

individuals in the genes or families of genes associated with longevity," says Judith Campisi, a senior scientist at the Lawrence Berkeley National Laboratory in California. By understanding the underlying biology of aging, she notes, it may be possible to develop drugs in the future that will promote healthy aging and delay age-related diseases such as some cancers, arthritis, diabetes, high blood pressure and heart disease.

The first genetic clues for slowing aging emerged from animal models in which the effect of individual genes on average life spans could be tested. From these early studies, it became clear that insulin (a hormone secreted by the pancreas that signals cells to absorb sugar) and its receptors are critical for longevity in species from yeast or fungi to humans.

Insulin lies at the heart of the "biological pathway whose main function is to affect how efficiently we process food into energy," says Bradley Willcox, a geriatrics specialist at the University of Hawaii. His team recently found that a variant in the insulin-pathway gene, FOXO3A, in Japanese men over age 95 was associated with improved energy usage and greater sensitivity to insulin. (Type 2 diabetes, marked by resistance to insulin, now affects 24 million people in the U.S. alone.)

Examining the blood profiles of centenarians has also yielded tantalizing targets for further study. Barzilai observed that centenarians had higher levels and larger particles of HDL—high-density lipoprotein, or the so-called good cholesterol. Genetic screening later revealed that 24 percent of centenarians from Ashkenazi Jewish populations carry a variant in the CETP gene—an enzyme important for cholesterol metabolism—that reduces the level of the protein CETP in the blood and is linked to a lower prevalence of hypertension, cardiovascular disease and memory loss.

CETP inhibitors have been sought by the pharmaceutical industry as a method for increasing HDL levels and protecting patients against heart disease. But clinical trials of such a drug, Pfizer's Torcetrapib, were halted in 2006 when investigators discovered that it was associated with an increased risk of death from heart attack and other complications, including cancers and infections.

Daniel Rader, a cardiologist at the University of Pennsylvania School of Medicine in Philadelphia, remains optimistic, however, that other CETP inhibitors could work, because the failure of Torcetrapib was likely due to "effects on blood pressure that were unrelated to CETP inhibition." Pharmaceutical giant Merck is currently testing a new CETP inhibitor, Anacetrapib, but Rader cautions that any potential longevity benefits could simply stem from the drug's ability to decrease the risk of heart disease—the number one killer in the U.S.

More expansive genetic studies are now underway as researchers "look at the rate of genetic variation across the entire genome" of centenarians, says Thomas Perls, director of the New England Centenarian Study at Boston University. By examining over one million gene variations, scientists hope to find additional target genes for longevity studies that may not be obvious from blood screening and animal testing.

Perls acknowledges that the research is controversial as critics insist that centenarians may be too genetically diverse to pinpoint any common factors that promote healthy aging. But he points out that supercentenarians (those living past age 110) share even more genetic factors than centenarians, possibly improving the chances of finding protective gene variants.

"We already know what it takes for the vast majority of us to reach our late 80s in good health," Perls says. That is, stop smoking, exercise, eat a balanced diet and manage stress. "The trick will be

to get people from 88 to 100," Perls adds, "but there will never be a magic bullet."