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Does Chromosome 4 Hold the Secret to Human Longevity?

By comparing the DNA of siblings who are extremely long-lived, researchers believe they have found a region on chromosome 4 that may hold an important clue to understanding human longevity. According to the researchers, their finding is "highly suggestive" that somewhere in the hundreds of genes in that region of chromosome 4 is a gene or genes whose subtle modifications can give a person a better chance of living well beyond the average life expectancy.

The researchers believe that additional genetic analyses of nonagenarians and centenarians will lead to the identification of a few genes that confer longevity in humans. They also believe that their studies may turn up "good" versions of a multitude of genes that enable people to avoid age-associated diseases such as heart disease, stroke, diabetes, cancer and Alzheimer's disease.

"We believe that we can find the genes that allow humans to live to be much older than average, as well as the metabolic pathways they influence. And it may turn out that there are similar pathways in lower organisms."

— **Louis M. Kunkel**

In an article published in the August 28, 2001, issue of *Proceedings of the National Academy of Sciences*, a scientific team led by Howard Hughes Medical Institute investigator Louis M. Kunkel and Thomas Perls at Beth Israel Deaconess Medical Center reported the results of a genome-wide study of 308 long-lived people. The study group included 137 siblings. The research team included scientists from Children's Hospital in Boston, Harvard Medical School, Whitehead Institute for Biomedical Research, Rutgers University, and Beth Israel Deaconess Medical Center.

"It is clear to us that longevity has a genetic component," said Kunkel. "Frequently, if there is one sibling who has lived to be a hundred, there will be a second or third sibling who also will live to be a hundred. And while these people were fortunate enough not to have 'bad' gene alleles at the loci

involved in age-related diseases, they also had alleles that enabled them to live often twenty years beyond their life expectancy, and remain active and in reasonably good health." An allele is an alternate form of a gene.

According to Kunkel, the research team launched its search for longevity genes based on an educated scientific hunch. "Most investigators would say that longevity is just too complicated a trait to be influenced by only a few genes," he said. "But we took a chance that this was the case, because in lower organisms such as nematodes, fruit flies and yeast there are only a few genes that need to be altered to give a longer life span. So, my feeling was that there were only a few genes, perhaps four to six in humans, that would do the same."

Thus, Kunkel and his colleagues did a genome-wide comparative analysis of 137 sets of two or three siblings who were at least 90, where one member of each sibship was 98 or older. Their mapping studies used 400 known genomic markers to determine whether the sibling sets shared specific chromosomal regions in significantly greater excess than predicted by chance inheritance from their parents alone.

"We found that on chromosome four there was a little blip of allele sharing that was greater than would be predicted by chance," said Kunkel. "We term this finding as 'highly suggestive,' because it is ninety-five percent certain that it is not by chance — thus with a five percent likelihood that we just happened to get this blip," he said.

Kunkel cautions that finding allele sharing on chromosome 4 represents only the beginning of the arduous process of pinpointing the gene or genes that influence longevity. "We have two major challenges," he said. "First, we will have to replicate these findings in another hundred or so sibships to confirm them, and perhaps to determine whether there may be another shared locus." Some of the subjects studied did not share a locus on chromosome 4, so Kunkel and his colleagues suspect that other shared loci might exist.

"Second, we must try to find the gene in this region of chromosome 4 that confers the longevity phenotype," said Kunkel. "This is an extremely complicated process because there are perhaps as many as five hundred genes in this region, and one of them has a single sequence variation that confers this phenotype. This variation is not a mutation as in genetic disease. Rather it is a very subtle genetic difference that produces a protein that may either work slightly better or be less active than in the normal population."

According to Kunkel, a thorough search for such a subtle genetic variation — called a single nucleotide polymorphism — in one gene will require performing 200,000-400,000 genetic analyses on some 200 long-lived subjects. The researchers must then compare those results to genetic analyses performed on a similar number of people with normal longevity.

"We are extremely excited about the prospects for this work," he said. "We believe that we can find the genes that allow humans to live to be much older than average, as well as the metabolic pathways they influence. And it may

turn out that there are similar pathways in lower organisms."