Longevity article for website

Random Chance

Josephine Tesauro never thought she would live so long. At 92, she is straight backed, firm jawed and vibrantly healthy, living alone in an immaculate brick ranch house high on a hill in Mount Pleasant, a Pittsburgh suburb. She works part time in a hospital gift shop and drives her 1995 white Oldsmobile Cutlass Ciera to meetings of her four bridge groups, to church and to the grocery store. She has outlived her husband, who died nine years ago, when he was 84. She has outlived her friends, and she has outlived three of her six brothers. Tesauro does, however, have a living sister, an identical twin. But she and her twin are not so identical anymore. Her sister is incontinent, she has had a hip replacement, and she has a degenerative disorder that destroyed most of her vision. She also has dementia. "She just does not comprehend," Tesauro says. Even researchers who study aging are fascinated by such stories. How could it be that two people with the same genes, growing up in the same family, living all their lives in the same place, could age so differently? The scientific view of what determines a life span or how a person ages has swung back and forth. First, a couple of decades ago, the emphasis was on environment, eating right, exercising, getting good medical care. Then the view switched to genes, the idea that you either inherit the right combination of genes that will let you eat fatty steaks and smoke cigars and live to be 100 or you do not. And the notion has stuck, so that these days, many people point to an ancestor or two who lived a long life and assume they have a genetic gift for longevity. But recent studies find that genes may not be so important in determining how long someone will live and whether a person will get some diseases - except, perhaps, in some exceptionally long-lived families. That means it is generally impossible to predict how long a person will live based on how long the person's relatives lived. **Life span not a strong genetic trait** Life spans, says James Vaupel, who directs the Laboratory of Survival and Longevity at the Max Planck Institute for Demographic Research in Rostock, Germany, are nothing like a trait like height, which is strongly inherited. "How tall your parents are compared to the average height explains 80 to 90 percent of how tall you are compared to the average person," Vaupel said. But "only 3 percent of how long you live compared to the average person can be explained by how long your parents lived." "You really learn very little about your own life span from your parents' life spans," Vaupel said. "That's what the evidence shows. Even twins, identical twins, die at different times." On average, he said, more than 10 years apart. The likely reason is that life span is determined by such a complex mix of events that there is no accurate predicting for individuals. The factors include genetic predispositions, disease, nutrition, a woman's health during pregnancy, subtle injuries and accidents and simply chance events, like a randomly occurring mutation in a gene of a cell that ultimately leads to cancer. The result is that old people can appear to be struck down for many reasons, or for what looks like almost no reason at all, just chance. Some may be more vulnerable than others, and overall, it is clear that the most fragile are likely to die first. But there are still those among the fragile who somehow live on and on. And there are seemingly healthy people who die suddenly. **Predisposition a qualified affair** Some diseases, like early onset Alzheimer's and early onset heart disease, are more linked to family histories than others, like most cancers and Parkinson's disease. But predisposition is not a guarantee that an individual will develop the disease. Most, in fact, do not get the disease they are predisposed to. And even getting the disease does not mean a person will die of it. There are, of course, some valid generalizations. On average, for example, obese men who smoke will die sooner than women who are thin and active and never get near a cigarette. But for individuals, there is no telling who will get what when or who will succumb quickly and who will linger. "We are pretty good at predicting on a group level," said Dr. Kaare Christensen, a professor of epidemiology at the University of Southern Denmark. "But we are really bad on the individual level." James Lyons used to think his life would be short. Lyons, a retired executive with the Boy Scouts of America, thought of his father, who died at 55. "He had one heart attack. It was six hours from onset to death, and that was it." Then there were his first cousins on his

father's side. One died at 57 and another at 50. "He was in a barber chair and had a heart attack," Lyons said of the 50-year-old. "He died on the spot." "He was a big strapping guy, 6-4, healthy and energetic. Then, boom. One day he was there, and the next day he was gone." "I approached my 50s with trepidation," said Lyons, who lives in Lansing, Mich. But his 50s came and went, and now he is 75. He is still healthy, and he has lived longer than most of his ancestors. He is baffled as to why. It seems like common sense. Family members tend to look alike. And many characteristics are strongly inherited - height, weight, a tendency to develop early onset heart disease or to get diabetes. Even personalities run in families. Life span would seem to fit with the rest. Scientists have been trying for decades to find out if there really is a strong genetic link to life spans and, if so, to what extent. They turned to studies of families and of parents and children, but data analysis has been difficult and definitive answers elusive. If a family's members tend to live to ripe old ages, is that because they share some genes or because they share an environment? "Is it good socioeconomic status, good health or good genes?" Christensen asked. "How can you disentangle it?" **Most twins die years apart** His solution, a classic one in science, was to study twins. The idea was to compare identical twins, who share all their genes, with fraternal twins, who share some of them. To do this, Christensen and his colleagues took advantage of detailed registries that included all the twins in Denmark, Finland and Switzerland born from 1870 to 1910. That study followed the twins until 2004 to 2005, when nearly all had died. Now, Christensen and his colleagues have analyzed the data. They restricted themselves to twins of the same sex, which obviated the problem that women tend to live longer than men. That left them with 10,251 pairs of same-sex twins, identical or fraternal. And that was enough for meaningful analyses even at the highest ages. "We were able to disentangle the genetic component," Christensen said. But the genetic influence was much smaller than most people, even most scientists, had assumed. The researchers reported their findings in a recent paper published in Human Genetics. Identical twins were slightly closer in age when they died than were fraternal twins. But, Christensen said, even with identical twins, "the vast majority die years apart." The investigators also asked when the genetic factor kicked in. One hypothesis, favored by Christensen, was that the strongest genetic effect was on deaths early in life. He thought that deaths at young ages would reflect things like inherited predispositions to premature heart disease or to fatal cancers. But there was almost no genetic influence on age of death before 60, suggesting that early death has a large random component - an auto accident, a fall. In fact, the studies of twins found almost no genetic influence on age of death even at older ages, except among people who live to be very old, the late 80s, the 90s or even 100. The average age of death is 68.5 for men in the United States, and 76.1 for women, according to Arialdi Minio of the National Center for Health Statistics. Even though there may be a tendency in some rare families to live extraordinarily long, the genetic influence that emerged from the studies of twins was significantly less than much of the public and many scientists think it is. A woman whose sister lived to be 100 has a 4 percent chance of living that long, Christensen says. That is better than the 1 percent chance for women in general, but still not very great because the absolute numbers, 1 out of 100 or 4 out of 100, are still so small. For men, the odds are much lower. A man whose sister lived to be 100 has just a 0.4 percent chance of living that long. In comparison, men in general have a 0.1 percent chance of reaching 100. Those data fit well with animal studies, says Caleb Finch, a researcher on aging at the University of Southern California. **Random experience, development** Genetically identical animals - from worms to flies to mice - living in the same environments die at different times. The reason is not known, Finch said. "It's random," he said. "Since we can't find any regular pattern, that's the hand wave explanation - randomness." And random can mean more than one thing. "There are two phases of randomness," Finch said. "There's the randomness of life experiences. The unlucky ones, who get an infection, get hit on the head, or get mutations that turn a cell into cancer. And there are random events in development." Random cell growth and division and random differences in which genes get turned on and how active they are during development can cause identical twins to have different numbers of cells in their kidneys and even different patterns of folds in their brains, Finch pointed out. And random differences in development early in life can set the stage for deterioration decades later. But seemingly random events can still come as a shock. That's how Annmarie Bald felt when her identical

twin, Catherine Polk, died in her sleep of a heart attack. It happened seven years ago, when Polk was 43. To this day, Bald, of Forked River, N.J., lives in fear that the same thing will happen to her. She nervously sees her doctor every year for a checkup, and every year her doctor tells her the same thing: her heart is fine. "The question in my mind every day is, 'How did I end up still here and she's gone?'" Bald said. "It's not something you ever get over." Even diseases that are commonly thought to be strongly inherited, like many cancers, are not, researchers found. In a paper in the New England Journal of Medicine in 2000, Dr. Paul Lichtenstein of the Karolinska Institute in Stockholm and his colleagues analyzed cancer rates in 44,788 pairs of Nordic twins. They found that only a few cancers - breast, prostate and colorectal - had a noticeable genetic component. And it was not much. If one identical twin got one of those cancers, the chance that the other twin would also get it was generally less than 15 percent, about five times the risk for the average person but still not a very big risk over all. **Genes a weak predictor of cancer** Looked at one way, the data say that genes can determine cancer risk. But viewed another way, the data say that the risk for an identical twin of a cancer patient is not even close to 100 percent, as it would be if genes completely determined who would get the disease. Dr. Robert Hoover of the National Cancer Institute wrote in an accompanying editorial: "There is a low absolute probability that a cancer will develop in a person whose identical twin - a person with an identical genome and many similar exposures - has the same type of cancer. This should also be instructive to some scientists and others interested in individual risk assessment who believe that, with enough information, it will be possible to predict accurately who will contract a disease and who will not." Alzheimer's disease also has a genetic component, but genes are far from the only factor in determining who gets the disease, said Margaret Gatz of the University of Southern California and Nancy Pedersen of the Karolinska Institute. Gatz and Pedersen analyzed data from a study of identical and fraternal Swedish twins 65 and older. If one of a pair of identical twins developed Alzheimer's disease, the other had a 60 percent chance of getting it. If one of a pair of fraternal twins, who are related like other brothers and sisters, got Alzheimer's, the other had a 30 percent chance of getting it. But, Pedersen noted, Alzheimer's is so common in the elderly that it occurs in 35 percent of people age 80 and older. If genes determine who gets Alzheimer's at older ages, Pedersen says, "those genes must be very common, have small effects and probably interact with the environment." As for other chronic diseases of the elderly, Parkinson's has no detectable heritable component, studies repeatedly find. Heart disease appears to be indiscriminate, striking almost everyone eventually, says Dr. Anne Newman of the University of Pittsburgh, who has studied it systematically in a large group of elderly people. But the general picture is consistent in study after study. A strong family history of even a genetically linked disease does not guarantee a person will get it, and having no family history does not mean a person is protected. Instead, chronic diseases strike almost at random among the elderly, making it perhaps not so surprising that life spans themselves have such a weak genetic link. Matt McGue, a psychology professor at the University of Minnesota who studies twins, contrasts life spans with personality, which, he says, is about 50 percent heritable, or attention-deficit hyperactivity disorder, which is 70 to 80 percent heritable, or body weight, which is 70 percent heritable. "I've been in this business for a long while, and life span is probably one of the most weakly heritable traits I've ever studied," McGue said. **Double chance at 100 years** At the National Institute on Aging, the question still hovers: Is it possible to find genetic determinants of exceptional health and longevity? "If you could identify factors for exceptionally good health, that might allow people to avoid disease," said Evan Hadley, director of the institute's geriatrics and clinical gerontology program. There are two methods to do this, Hadley said. One is to look at how the genes of centenarians differ from those of the rest of the population. But, he said, that requires that if longevity genes exist, they are common among centenarians. And, so far, such studies have not yielded much that has held up - with one well accepted exception: a gene for a cholesterol-carrying protein that affects risk for heart disease as well as Alzheimer's disease. Those who have that gene have double the chances of living to 100. But that chance is not much anyway. Only about 2 percent of people born in 1910 could expect to reach 100. The second approach is to look for rare genes in unusually long-lived families. "If there is something in a family, it may be in only one or a few families," Hadley said. But it

may have a big effect. **Studies continue the search** The National Institute on Aging is starting a research project with investigators at three United States medical centers and at Christensen's center in Denmark. The plan is to find exceptional families, ones in which there is a cluster of very old, closely related members - two sisters in their 90s, for example - whose children, who would typically be in their 70s, and grandchildren, can be studied too. Today, many families have a few members living to advanced ages, but very few families have many of them. And in large families, just by chance, someone may live past 90, but it is unlikely that most of the brothers and sisters will get there. For these families, there does not appear to be a genetic component to life spans. For now, the study is in a pilot phase, testing a scoring system to define the families who seem to fit the criteria. "If you are really, really old in a family, that gets you more points," Hadley said. "You get more points for being 97 than for being 92. But we also are looking at the whole family structure. If there are just two siblings in a family and both live to 98, that's very exceptional. But suppose there are eight kids and they all made it to 87. That's pretty unusual, too." If the researchers find genes in the oldest family members that seem to be associated with protection from a disease like heart disease and with a long life, they will follow the younger members of the family, children in their 60s and 70s, asking if the same genes seem to protect them as they age. Some wonder if the project can succeed, said Newman, who is directing one study center, at the University of Pittsburgh. "The big debate is, is it possible for there to be a few genes that are protective or is it going to be so complicated that we won't be able to figure out the genetic factors? Is it going to be that some people are just lucky?" She is optimistic, reasoning that since some families tend to have early onset of certain diseases, others probably have a genetic predisposition to get diseases like heart disease, cancer and Alzheimer's so late that most members do not get them at all and live very long and healthy lives. "This would be the flip side of early onset," she says.