

**DR. RICHARD CASELLI:** My name is Dr. Richard Caselli in the Department of Neurology from the Mayo Clinic in Arizona. My colleagues and I have been involved in a study entitled Normal and Pathological Aging. And we started about 17 years ago.

Since 1994, we have been recruiting people into a longitudinal aging study. Our goal has been to study what changes might occur to our cognitive skills as we age and whether our genetic risk for developing Alzheimer's disease influences that. Our research was made possible by a discovery in the early 1990s that a very common gene called apolipoprotein E4 increases in our risk for Alzheimer's disease.

About 20% to 25% of the US population carries this gene. About 2% of the population carry a double dose of this gene. And that 2% constitutes the group at highest risk for developing Alzheimer's disease.

In our previous research, we've shown that possession of even one copy of the gene accelerates our age-related memory decline beginning in our mid to late 50s, so between age 55 and 60. And for that smaller subgroup to have two copies of the gene, that effect is more pronounced.

In our latest work, we were looking at the influence of other common medical problems that are known to predispose to cardiovascular disease, specifically hypertension, diabetes, cigarette smoking, and people who have high cholesterol levels. So many people have one or more of these problems. And the question is, does this have a disproportionate effect on people who carry this apolipoprotein E4 gene?

What we find is that people who do not have that gene do not seem to suffer any greater loss of memory as they get older, as long as they preserve their general health. That is, they don't have a stroke. If they have a stroke, then that's a whole other story.

In people who have one copy of the gene, interestingly, we also failed to see any significant further effect. But in that small subgroup of about 2% of the population who have a double dose of the gene, possession of any one of those factors or more further accelerated the risk of memory decline. So that if you looked at the performance of one of these individuals in their 40s with these cerebrovascular or cardiovascular risk factors, they looked more like one of their gene mates in their 60s who didn't have those cardiovascular risk factors. So roughly a 20 to 25 year aging effect, if you will, on their memory performance on tests.

I should emphasize that their performance on these tests still appeared normal. It was just that when we compared them to the other groups that we saw that there was a difference. So that normally a younger person will improve if given the same test over repeated times. But these folks who have a double dose of the gene and have these cardiovascular risk factors fail to show that improvement with repeated test administration. And on top of that, as they age, they show further decline in their memory skills.

What we think this implies for the general public, we don't believe everybody needs to go out and get genetic testing for Alzheimer's disease. But we do want to emphasize what our cardiology colleagues have been telling us for years that treatment of hypertension, diabetes, high cholesterol, and smoking cessation are all very important. This is one more reason to consider that.