

The Genetics Behind Alzheimer's Disease:

An Interview With Alison Goate, PhD



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BY MICHAEL DREGNI

In 1991, Alison Goate, PhD, and her colleagues made a pioneering discovery in the field of genetics related to Alzheimer's disease: They found a gene mutation in a family that had inherited dementia over three generations.

Examining what became known as the amyloid precursor protein (APP) gene variation, Goate remembers thinking, "I am the first person to see a cause of Alzheimer's disease. . . . It was a eureka moment . . . but it was also spooky and scary."

Since then, several other gene variations that increase people's

risk factor for Alzheimer's have been discovered. (For more on these gene variations, see "Untangling Alzheimer's" at ELmag.com/alzheimers.)

Goate is now one of the world's leading dementia researchers and a professor of neuroscience and director of the Ronald M. Loeb Center for Alzheimer's Disease at the Icahn School of Medicine at Mount Sinai in New York City.

She discussed genetics and Alzheimer's, concerns about genetic testing, and other issues around the disease in this exclusive interview.

Q&A

Experience Life | Can you tell us about the discovery of the first Alzheimer's-related gene variation in 1991?

Alison Goate | There was this real eureka moment when we found this mutation which was in a strong candidate unit: A gene (amyloid precursor protein, or APP) that encodes one of the proteins that accumulates in the brain called beta-amyloid, and we found this totally novel variant in a family that had an inherited form of the disease. All of the affected individuals in the family carried this mutation and none of their well siblings

or relatives did. And we were able to show that basically this variant didn't exist in healthy people who weren't part of a family that had an inherited form of Alzheimer's. It was very clear-cut that this was likely to be the cause of the disease in the family, and since then obviously this mutation turned out to be one of the more frequent mutations in families where there's an inherited form of Alzheimer's disease. There have been multiple other families found now with exactly the same mutation, but also other mutations within that APP gene in other families, and since then

several other mutations [as well].

It was an amazing moment. There are not many moments like that in science — and certainly in the kind of genetics we do now. It's never quite the same [now] because the genetics we do is really a slow process of cumulative information. It's one of the few times in 25 to 30 years where you were able to look at a single piece of data and say this is it: I know that this is the cause of the disease in this family.

But it was also spooky and scary. When you do these genetic studies on families with an inherited form of the disease, you inevitably develop

a relationship with the family. They are devoting their time and effort to helping you do this research because obviously they have a vested interest in it, but also an altruistic one for other family members.

The spooky part of this was that now you have in front of you information about people who will likely develop the disease but haven't yet shown any symptoms. And that's a really heavy load for anyone to have in front of them. To look in a room of people whom you've met and interacted with over a period of time and think, "I know some of you are going to develop the disease in the future."

EL | Once these various gene variations were found, did people want to go through genetic testing to see if they had them?

AGI There are relatively few people in these families who want to know whether or not they carry the genes because there's no treatment. So knowing whether you carry the mutation or not has had some practical benefits in that you can organize your life and finances so the people you care about are secure afterwards, or if you haven't had children you may decide you don't want to have children or you want to adopt children or use assisted reproduction, so that you know that you're implanting an embryo that doesn't carry the mutation, so you don't pass it on. But other than those organizational things, there is no treatment. That was really the bottom line.

Most people would go through the process of finding out whether or not they carried the gene that causes the disease if they knew something could be done about it — that if they

found that out, they could go on a drug to prevent disease before they showed any clinical symptoms. Then most people would say, "Yes, I'd like to take the test."

In the absence of a drug like that, most people have said, "Well, what's the point in knowing? I'm going to find out eventually anyway. And I don't want to live with the burden of that for 15 or 20 years until it happens — I'll just wait and see what cards I've been dealt." But now that there are more clinical trials ongoing, and indeed there are several clinical trials that are focused on families with mutations like this, then people want to get involved.

Twenty years ago, honestly we had nothing to offer them. We were able to say, "We know what the cause of the disease in your family is, and we'll be studying this and hopefully we'll be able to develop a drug as a result of this." But we weren't able to offer them anything concrete in the short term. Now there is the possibility to participate in these drug trials.

EL | How prevalent is the APP gene variation that can lead to early-onset Mendelian Alzheimer's?

AGI Less than 1 percent of people with Alzheimer's carry these mutations, but because they happen to people in the prime of life, it's even more shocking — that someone in their 30s or 40s or 50s with an active life and job and family should suddenly come down with a disease that we think of as a disease that only affects old people.

For the most part, if you carry a mutation in the Presenilin genes [PSEN1 and PSEN2, two other gene variations that may also lead to early-onset

Alzheimer's] and APP genes, then you will develop the disease before the age of 60. And it's highly penetrant, which means that if you carry one of these gene variants, 95 to 100 percent of the time you're going to develop Alzheimer's disease at some point in your life.

EL | What's the most common gene variation connected with Alzheimer's?

AGI The most common risk factor for Alzheimer's disease, apart from age, is APO E4 [Apolipoprotein E4]. This is a protein that is involved in cholesterol transport in the body, and it exists in three forms — E2, E3, and E4. They're all reasonably common: The least common of these is the E2, which has a frequency of about 7 percent in the population; E4 is about 15 percent in most populations; and everyone else will then carry an E3. These increase your risk but don't mean that you will definitely get the disease.

So people carrying an APO E4 allele [any of two or more variants of a gene that arise by mutation and are found at the same place on a chromosome], if they have one copy of the E4 allele, they're at about a threefold increase risk for the disease compared with someone who doesn't have an E4 allele. If you have two E4 alleles, you have about a tenfold increase in risk, which is obviously a pretty substantial increase in risk. A fairly large number of people with two E4 alleles will develop Alzheimer's.

But on the positive side there are some people who carry two APO E4 alleles and don't develop Alzheimer's disease. And so one of the things we're interested in right now genetically is what protects those people? Why

don't they develop disease? Do they have other compensatory DNA variants that protect them, or are there epigenetic changes that protect them? Why do these people not develop disease in the face of a strong risk factor?

EL | Are there other gene variations connected with Alzheimer's?

AGI From very large studies of common variation in the genomes, we have identified between 20 and 30 new loci, points in the genome, that are associated with modest increases in risk. This is in studying over 70,000 individuals [in the Genome-Wide Association Studies, or GWAS]. They have identified evidence that these other genes generally increase your risk by 10 or 20 percent.

They're common, so lots of people carry them. But they have a small impact on risk.

But honestly, if you have two APO E4 alleles, then the rest of the genes probably don't have a huge impact. E4 is definitely the big fish in all of this. These other genes are definitely important in helping us understand what the biological mechanisms are behind risk or protection against disease. (For more on the science behind gene variations, see ELmag.com/snps.)

EL | How do epigenetics — a process where genes are turned on, or conversely, left dormant — affect our genes' role in our risk for Alzheimer's?

AGI I think it's also important to think about why some people age healthily in the face of carrying these variants: What is it about these people that protects them from the disease?

It's certainly possible that people with APO E4 alleles may not develop Alzheimer's

disease — that there's some epigenetic changes that have prevented them from developing the disease. That's certainly a possibility. And the fact remains that aging is actually the most important risk factor for Alzheimer's disease. I think all of this suggests that epigenetic changes to our genomes over a lifetime can have cumulative consequences that either increase the risk of developing Alzheimer's disease or protect you from getting the disease.

EL | What are some of the other little-known health factors that put us at risk for Alzheimer's?

AGI Most people who have Alzheimer's disease probably have it because they have a combination of genetic risk factors and other health factors that influence their risk for the disease.

People who have had a head injury with loss of consciousness are at greater risk. This could potentially be an epigenetic response in the sense that one of the things we know is that two of the genes that are important in Alzheimer's disease, APP and APO E4, are proteins that are regulated in response to brain injury. So if both proteins are up-regulated in response to a head injury, there could be downstream consequences that are never properly resolved. So if you have a genetic risk that predisposes you to Alzheimer's disease and you have a head injury like that, those two things combine together to increase your risk substantially.

It's not clear right now how much influence head injury with loss of consciousness has in absence of that genetic factor. There's been a lot of publicity in the last few years about concussions and head

injuries in sports and how that leads to a degenerative disease sometimes called CTE or chronic traumatic encephalopathy that people have reported in football and hockey players; that's a slightly different disease in that you generally don't have that amyloid accumulation. You have the other protein that you find in Alzheimer's brains, the tau tangles — you find a lot of those in people with CTE. So there are some similarities between these diseases and some differences.

Right now we don't know very much about the genetics of CTE. It's very unlikely that everyone who does sports and suffers a head injury with loss of consciousness is going to develop CTE, but some people are probably more likely than others to get it, and right now we don't understand who those people are. That's something that's going to be very important for us to figure out: If you have a high genetic risk, you would probably want to know that before you embark on a career as a pro football player.

EL | It's been reported that people with more education are at a lower risk for developing Alzheimer's. Can you explain?

AGI Obviously, "education" is a proxy for a lot of different things, and education is clearly related to socioeconomic status. It's been suggested that it's related to something people call the cognitive reserve hypothesis: As the result of education you have more neuronal connections in your brain and so you can afford to lose more before you show clinical symptoms [of Alzheimer's].

There's work in animal models that show if you keep mice who are genetically at

risk for developing something similar to Alzheimer's disease in an enriched environment so they get to play in cages with lots of toys and things, that those mice will develop the disease at a later stage and are somewhat protected.

Not only educational enrichment but also physical activity — both of those things help. In both the intellectual capacity through education and enrichment of your neuronal connections and also physical activity, which probably does some of the same things — both of those are likely to protect you from developing Alzheimer's disease.

Living a fit and healthy lifestyle is your best protection against getting Alzheimer's.

EL | Can you tell us how cardiovascular disease, type 2 diabetes, and obesity are now understood to all be related to a higher risk for developing Alzheimer's?

AGI Your general cardiovascular health — including diabetes, hypertension, and obesity — is almost certainly important for a healthy brain and the prevention of Alzheimer's disease. So if you carry risk factors for cardiovascular disease, or you have those diseases, then you're at increased risk for Alzheimer's disease.

APO E4 is, in fact, a risk factor for cardiovascular disease. It's actually a bigger risk factor for Alzheimer's than heart disease, but the fact that this protein is so central to both diseases indicates that vascular health and heart health are important components of Alzheimer's disease. If you have blood vessels that are clogged and you have vascular disease and heart disease, you are going to be at higher risk of developing Alzheimer's disease as well.

That's been a long-established link, although not terribly well understood.

Obesity and diabetes are probably all linked together with vascular health. People who have diabetes usually have vascular problems as well. We don't fully understand yet the links between diabetes and obesity and Alzheimer's disease. There does seem to be a connection, but we don't fully understand it at this point, but clearly it's something we really need to get to grips with due to the epidemic of obesity and type 2 diabetes.

Everything we're doing to try and reduce the risk of Alzheimer's could be undone by the large number of people who are now developing what are often age-related diseases at younger ages — we have teenagers with type 2 diabetes, which was really almost unheard of a couple of decades ago. What does that portend for dementia in the future among this group of individuals if they live a lifetime with type 2 diabetes starting in their teens and 20s? What's that going to mean for Alzheimer's disease 20 to 30 years from now? I think that's of great concern to the health community and should be for the government and the general health of our nation.

EL | Are you optimistic about the possibility of finding cures for Alzheimer's?

AGI We now know that there is a very long prodromal [development] period of the disease; we know from imaging studies and biomarker studies that people are accumulating amyloid in their brains probably 20 years before they develop symptoms. In some ways that's a very good thing for us to know because there's a window of opportunity for treating disease

that is huge. If we have early detection and we can pick up these changes 15 or 20 years before someone's actually going to show any clinical symptoms, then we should be able to treat the disease and prevent it from occurring.

I think that that should be a really hopeful message— 20 years ago we didn't know this. We didn't realize that this was a chronic, progressive disease that has this prodromal phase of maybe 15 or 20 years before you see any clinical symptoms — and that's obviously highly analogous to arterial disease.

[With cardiovascular disease] you have an accumulation of plaques in your arteries for a long period of time before you have that heart attack, and this is the same kind of thing where we have this accumulation of amyloid plaques and tangles in our brains for 15 or 20 years before we start to get any memory impairment. So if we can identify those people who are at high risk who are beginning to accumulate these proteins, and we can develop drugs that prevent that accumulation from going any further, then we should be able to stop the disease from occurring.

In some ways, having something that's a "slow leak" that you can plug is a lot better than having something that is immediate and catastrophic — that you have no notion it's going to happen and then you get disease immediately. I think the opportunities for being able to prevent or control Alzheimer's disease once we have some understanding of the disease and we can develop therapeutics that prevent this from occurring are really high. I don't see a reason why we shouldn't be able to accomplish this. The question is how quickly.