

# Genetics Demystified: Understand Your Risk for Dementia

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## Transcript

### [0:00 Introduction]

*Dr. Anthony Levinson:* It's a wonderful opportunity to talk to you a little bit about a fairly complex topic that we're going to try to do our best to cover some of the basics tonight. So let's dive right in with a couple of potential scenarios.

So Linda, who's 35, has always been interested in her background and her family. She sends a DNA kit to a popular genetic company in order to learn more about her background. And a few weeks later, sitting at her computer looking at her email, she gets her results back and is a bit surprised and shocked to find out in the section on the APOE gene that she carries an APOE e4 gene variant. And it says in the report that this is potentially going to be increasing her risk of Alzheimer disease. So now she's not sure what to do.

On the right hand side is David, who's a 48-year-old architect. He is very close with his family. He prides himself and his family prides themselves on their longevity. He has many relatives who have lived well into their 90s. Unfortunately, there's one common thread that he's also aware of, is that many of his relatives in their 90s have developed dementia. And so he's wondering as well about whether he is at increased risk given his family history.

I think these are some of the common scenarios that we see people sometimes reflecting on with respect to genetics. So today we're going to talk a little bit about a broad overview and some of the other non-modifiable risk factors, things you can't change. Tricia is going to give an overview of some of the genetic factors, and then we'll talk about some of the things that you can do with respect to modifiable risk factors that may actually help to reduce your risk of dementia or slow progression, no matter what the genetics say. Then we'll briefly touch on some additional resources.

### [2:17 What is dementia?]

*Dr. Anthony Levinson:* So, I think many of you are probably familiar with it, but it's good that we start on common ground. So, when we say somebody has a dementia, it implies that there are cognitive or brain issues, often memory impairment, but also other ones, as we'll see. It's typically something that can be assessed by a physician in an office setting, and some form of objective cognitive testing will typically show the memory deficit. And in order to be called dementia, it has to be severe enough that it interferes with day-to-day function.

And some of the various brain functions or cognitive domains that may be affected include learning and memory. So, forgetting names or appointments, repeating oneself. Language issues, like problems word finding. Visual-spatial challenges, so possibly getting lost or no

longer being able to drive safely. Executive functioning refers to more complex tasks like planning, decision making, sequencing, things like cooking a complex meal. And then there may also be changes to the brain that impact social aspects or personality.

### **[3:41 What causes dementia?]**

*Dr. Anthony Levinson:* When we think about the different causes of dementia, broadly speaking, for most of the types of dementia that occur in older adults that are what we call progressive or neurodegenerative or degenerative, that affect the brain and progress, they can sort of be simplified into two main families of diseases that involve some form of a toxic protein and then blood vessel health, so vascular dementia.

### **[4:16 What are the different types?]**

*Dr. Anthony Levinson:* And dementia, it's important to remember, is an umbrella term from that standpoint. There are many, many causes, over 50 types of dementia, but some of them are quite rare. So, normally we talk about the most common ones, like Alzheimer disease, which probably accounts for about 50 or 60% of all dementias. Vascular dementia, which is thought to be the second most common. There are sometimes a mix of different types of dementias. So, often somebody might have some Alzheimer's and some vascular dementia. And then other ones that many of you may have heard of include frontotemporal dementia, Lewy body dementia, and other more rare causes like Huntington disease. But I mention these different types because it adds complexity when we talk about genetic factors, because these different disorders may have different genetic factors, which we'll talk about.

The scope here, even since the time I made this slide, some of the data is already out of date. So, if you were here for the pre-webinar slideshow, there's now thought to be over 650,000 people living with dementia, about 25,000 new cases per year, probably almost a million by 2032. And of course, this impacts many of you, because I saw from the poll, many of you are care partners of people living with dementia. So, this is a very important disorder. The more we can understand about the different factors related to dementia, hopefully the more we can do to lessen the impact.

### **[6:00 What are the risk factors?]**

*Dr. Anthony Levinson:* In terms of thinking about all dementias, including Alzheimer's and others, when we look at one of the most important factors that we can't modify, it's age. And so why is the prevalence increasing in Canada? In part, it has to do with our aging population. If you look at the age on the left, when somebody's 65 to 69, the prevalence of dementia is not that high, it's maybe around 1%. But essentially the prevalence doubles every five years after that. Now, not everybody is going to get dementia as they age. And as we'll talk about, it's a constellation or combination of different factors that contributes to the risk of developing dementia, including genetics. But age is a major non-modifiable risk factor. And you can see in people's 90s, probably about 30% of people in their 90s will develop dementia.

So again, when we're talking about risk factors, we want to situate genetics within the category of non-modifiable things that you really can't change. So, age is very important. Gender, family history, and genetics are considered the non-modifiable risk factors. And it is also really important to remember that most cases of most dementias are not thought to be strongly caused by genetics or inherited. It isn't to say that there aren't susceptibility or risks related to the genetic factors, but they're not strongly causal. So often, if we think about what types of dementias are really strongly familial or related to genetics, it's thought to be really only about 1% that are strongly determined by genetics. So those modifiable risk factors, which we'll come back to later, turn out to be very important.

## **[8:08 How does genetics influence the risk for dementia?]**

*Dr. Tricia Woo:* So, genetics and dementia, what's the connection? Well, in order to get there, we need to start at the basics. We need to start at understanding the principles or the simplistic ideas behind genetics and inheritability. If you remember back in your Biology 101 days, the body is made up of millions and millions of cells. Brain cells, liver cells, heart cells, all with its own job and its mandate. But how does it know? How does it know what kind of cell it should be and what its job should be? Well, it's written in the DNA.

In each cell, there are 23 pairs of chromosomes, half the genetic material from your Mom, half from your Dad. On each chromosome, there are strands of DNA, that double helix that you remember learning about in middle school. In the DNA are sequences. AGTC are the basic building blocks, and they build into genes, which are signals, signals to the cell as to what kind of cell it should be and what its job should be. Genes are what cause your eye color to be a certain color. Genes can also be variants. There can be variations of them. Genes sometimes can mutate, and sometimes genes can also cause susceptibilities or trouble with disease.

A few statements about genetics and dementias that are true across all types of dementia. First, as you've already heard, most of the cases of dementia are not strongly caused by genetics, i.e., having gene X does not give you dementia Y. Most cases, the vast majority of cases are what we call sporadic. Sporadic can mean unpredictable, but really what it means is it's a combination. Think of it like a stew. A stew of age, some genetic susceptibility, environment, medical and lifestyle factors.

As you've already heard, age is the number one non-modifiable risk factor. Now, as I said, within this stew, there are genes. Genes do have a role to play. And many of the genes that have been found in the dementias are what we call susceptibility genes. So what that means is it changes your risk. Doesn't cause it, but it changes your risk. And because Alzheimer's disease, or Alzheimer's dementia is the most common form, it is the most popular. It is also very, very well studied. So, we're really going to focus in on Alzheimer's disease and its genetics.

So, the vast, vast majority of cases, over 95% of the cases, are what we call sporadic Alzheimer's disease. Classic presentation is age over age 65. So older presentation, what we call late life presentation. And as I said, it is a combination of some susceptibility genes, but also lifestyle and environment to create the perfect storm.

As I mentioned before, susceptibility genes do not cause Alzheimer's disease. Multiple genes have been identified and only some of them have been fully studied. The most popular one, or the most famous one, if you will, is the APOE gene. The APOE gene has a day job. Its day job is to make a protein to help cholesterol, carry your cholesterol into the bloodstream. And scientists, when looking at a population level, have noticed that APOE has a number of alleles or variations. There's e2, e3 and e4. All slightly different, but all doing the same, similar job. At the population level, what they noticed is persons that had e2 seemed to have a slightly lower risk of developing Alzheimer's disease. Those with e3 had the usual or standard amount of risk, and those with e4 seemed to have a higher risk.

Now, this is at a population level. And so one of the things you need to think about is, well, what's the natural prevalence of all these different variations within that particular population? And in the population that was studied initially, which was primarily European background, 5 to 10% of that population had e2, maybe 15% to 25% had e4, but really most people had three. And so what this brings up is that the population that's being studied will also have an impact on how many or your risk at an individual level. And this is known as genetic ancestry.

So, as I mentioned, the initial study was done on a European background population. If this was at a different population that was studied, for example, a population that came from Africa or from Asia, or from the Middle East or from Latin America, would have a different prevalence or different makeup or occurrence of these different variants or alleles.

But what does this mean at a personal level? So, as I mentioned before, you get half your genetic material from Mom and half from Dad. So, on the right-hand side, you can see a table of different combinations of genes that you can inherit from your parents. Of course, the ones that you're most interested in are with the one that is slightly unhelpful, that APOE e4. And you can see there are a few combos, two combos where there is a single allele of APOE e4 and one combination that has two copies of APOE e4. What does this mean for your lifetime risk of Alzheimer's? Well, again, studied in large populations, the estimate is the average lifetime risk of Alzheimer's disease is about 15%. Most of that risk does come later in life. As you've already heard. Persons that have no APOE e4 alleles may have a slight reduction, maybe 9%. Those with one APOE allele may have a slight increase in risk at 29%. Two copies, even higher risk.

But what does this mean? If I have no copies of APOE e4, am I off the hook? No, not really, because there are other lifestyle modifications and environmental factors that may come into play. If, for example, I'm also a professional boxer and I refuse to wear a headgear, well, that's going to increase my risk and all of that good that came with that probably would kind of get negated. On the other hand, if I happen to have two copies of APOE e4, is it written in the stars or written in the genes that I will get Alzheimer's? No, not necessarily. There are a number of other factors that will come into play that could reduce your risk, such as becoming bilingual, such as having a vigorous exercise program, et cetera. So, simply having APOE e4 does not confer a causality of getting Alzheimer's disease, but it does change the risk a little bit and is a susceptibility gene.

What about other forms? Well, there are a few forms of Alzheimer's disease dementia that might be more strongly genetically linked, and there's a few listed here, for persons with

Trisomy 21 or Down syndrome, persons with Huntington's disease, which is a neurological condition, or some rare forms of familial Alzheimer's disease, which are often young onset.

Let's talk about this familial Alzheimer's disease. First, it's pretty rare. As you've heard, most of the cases are sporadic. These cases less than 5%, some as low as 1%, or even less than 1%, depending on the region and the patient population in question. These persons present very early, so, unlike the classic older adult, these people present in their 30s, 40s or 50s. If you look at the chart on the right, that's a family tree. Everybody with gray is an affected person. So you can see it is very strongly expressed. It's what we call an autosomal dominant pattern. And the genetics for this have been studied. There are three genes, presenilin 1 and 2, and APP. And mutations in any one of these can be a factor in having this type of familial Alzheimer's disease. But as I said, this is very rare.

Another special population are persons with Down syndrome. These people have three copies of chromosome 21, and as luck would have it, they have an extra copy of the APP gene, which I just talked about in the previous slide, and that increases their risk of Alzheimer's disease. In looking at large populations of persons with Down syndrome, up to half of them will develop Alzheimer's disease in relatively early age in their 50s and 60s.

Huntington's, similarly, can also be very genetically heavily linked. Now, this diagram is a very nice schema to kind of show you how the genetic factors and environmental factors intermingle and change. If you look at the bottom line, green means more genetic, blue to red means more environment. So, you can see the relative proportion of mix in different types of disease.

So, let's start at the top. The first is chronic traumatic encephalopathy, or CTE. This primarily occurs in young people with repeated head trauma, most notably in professional athletes that are boxers, play American football, or are professional wrestlers. So, for these people, repeated head trauma or environmental problems are the main cause as opposed to genetics. So, you can see it's mostly blue and red. Mostly red, actually, and a tiny bit of green.

Then moving down to the second line, we have Alzheimer's disease. And you can see on the left, there is a little bit of green, there is a little bit of genetic input that would account for some of the young familial cases, as well as possibly some susceptibility. But the vast bulk of it really is environmental. A lot of blue, lot of red.

Even more so if you look down below is vascular dementia, also known as stroke-related dementia. Again, genetics does play a small part, primarily in susceptibility. But again, lifestyle choices, environmental factors weigh heavily in the creation of this particular disease condition.

Then, looking down at the last example, we have Huntington's disease, and this is a very genetic, very strongly genetic neurological condition that affects your movement, but also your thinking. And for this one, it is mostly genetic as an impact with very, very little environmental input.

## **[19:20 Should you get a genetic test?]**

*Dr. Tricia Woo:* So, the big question should you get a genetic test? What does it mean? Well, before we answer that question, you have to think, well, why are you getting this test? You want to think about whether you're using it for research purposes versus clinical care or personal care, as the case may be. If you are participating in research studies, as I've alluded to, there are many, many research studies on different populations of people looking at their susceptibility and following them over time. So, there will be some people that are doing it as part of a research project, and we're not going to delve into that too deeply. Most of the people that are thinking about genetic testing are thinking about it in clinical care context, in the two cases that you heard at the beginning.

And just to kind of give you some context for clinical care, genetic testing is formally ordered by a physician. It's a referral process. Usually there's a genetic counsellor involved. At the local place where I work, it is a specialty clinic, a specialty genetics clinic, and it involves multiple visits. You meet with a genetic counsellor to go through your family tree, go through your symptoms, go through any imaging you might have, then you get the testing, and then finally you have another session with the genetic counsellor to actually explain what it all means to you personally. As you can imagine, this is a very emotionally stressful process, and you want to make sure that you have the proper support.

For the vast bulk of cases, as I've mentioned, they are mostly sporadic Alzheimer's disease cases, 95% and plus. And for that patient population and that family population, genetic testing is generally not recommended. Genetic testing may be indicated in very select cases. So, if you find yourself with a family history of very young onset, of 30-year-olds and 40-year-olds getting Alzheimer's, that may be a discussion for you to have with your own professional healthcare team, or if you're worried, or have Huntington's disease or any other strongly neurological condition, that may be a condition for having a test done.

## **[21:27 How do you reduce your risk of developing dementia?]**

*Dr. Anthony Levinson:* So, we've talked a little bit about some of the important non-modifiable risk factors, including age, and then some of the genetic factors, including the susceptibility genes, but what can you do if you have some of these genetic factors? And so, increasingly over the last decade or more, people have begun to appreciate that there's quite a bit that individuals can do to reduce their risk of dementia. So, I'm going to talk to you now about what is known in the research field now about things that can promote brain health.

So, when we're talking about risk reduction with respect to dementia, there are a few different things that we're talking about. One is decreasing the lifetime risk of developing dementia. In some cases, it might be delaying the onset. And then finally, some of the risk factors that I'm going to talk about have also got evidence for slowing the progression.

And to some degree, it's around a balance of trying to find things that may reduce damage to the brain, but also some things that might increase capacity. And what I'm going to be talking to you largely derived from what are called systematic reviews or meta-analyses. So, not just sort

of one new study that just popped up in the newspaper, but actually multiple studies that have reinforced that these are sort of the best evidence, risk factors and things that you can do to reduce your risk.

So, I'm going to talk about six ways to promote brain health, and many of these can benefit your brain, whether you already have a diagnosis of mild cognitive impairment or dementia, whether you have susceptibility genes or not.

So, let's start in. First, physical activity and weight management. So, we would recommend something like the 24-Hour Movement Guidelines that Canada has, where you are exercising and getting 150 minutes per week of moderate to vigorous physical activity. You're also doing some balance classes or balance exercises and strength training a couple of days a week, and getting a good night's sleep, and reducing your sedentary activity. These things, healthy and increased physical activity and exercise, have also been shown to benefit people if they have the higher-risk susceptibility genes, like the APOE e4 variant.

In terms of vascular causes or contributors, treating medical conditions and promoting blood vessel health can reduce your risk. One of the only medications that has been shown to reduce the risk of dementia is actually antihypertensives or blood pressure medications. There are non-medication ways of trying to reduce high blood pressure as well. And the same goes for managing diabetes and elevated blood cholesterol. These are all good things to do to help to promote blood vessel health and reduce the vascular damage that might happen to the brain.

Many people are aware that smoking is bad for your lungs and is associated with heart disease. It's also associated with damage to blood vessels in the brain and possibly direct damage to the brain as well. So, if you do smoke, try to stop smoking, and that can help to reduce your risk. Similarly, as we understand more about some of the other health risks of alcohol, we know that people who use a lot of alcohol or are heavy drinkers are at increased risk of various health problems. They're also at increased risk of cognitive problems. So, less alcohol or no alcohol is better.

In terms of diet, there's been increasing evidence to support a sort of brain healthy diet that looks quite a lot like the Mediterranean diet that would be the best-studied one. And what that is is a diet with fresh fruits, vegetables, no real like ultra-processed foods, so healthier whole foods, legumes. As far as protein, there's less red meat and more fish, for example, in the Mediterranean diet. Less salt and more flavouring with herbs, for example. Unfortunately, there's really no compelling evidence to support any sort of magic vitamins or supplements. So, the best supporting evidence for promoting brain health would be around healthy diet.

Cognitive and social activity is also emerged as an important sort of protective factor that can help to build capacity and reduce risk. Patricia was just saying that if you learn a new language or can speak in more than one language, that kind of cognitive activity kind of keeps your brain fresh and active. So, there isn't that much detail on what specific activities, but it's probably things that push you in a bit of a gray zone and keep your brain learning new things. So, learning a musical instrument or a language, pushing yourself, doing harder sudokos than you might normally do.

Social activities as well, it's more like social isolation has been shown to be a bit of a risk factor. So, the more you can get involved in social activities, the healthier for your brain as well. It's probably a bit of a multifactorial thing, right? Because when you're more social, you're probably also getting more cognitive stimulation, and you may also be more physically active if you have to go somewhere, walk somewhere, to meet up with friends.

Finally, I wanted to talk about a few other specific kind of risk factors or conditions. On the one hand, there are certain medications that may interfere with your thinking and memory and processing. So they're not really causing dementia per se, but they may be causing symptoms that can look like dementia because they may interfere with memory or processing speed.

So, these are generally sedating types of medications. But we see people who have been on these medicines for years, and sometimes somebody gets started on a benzodiazepine type of drug for anxiety, and it can accumulate over time. They're older, they may be more vulnerable to side effects. Sleeping pills, same thing. Somebody started a sleeping pill years ago with good intentions, but they haven't stopped them, and they may run into problems with side effects. Certain pain medications like opioids or narcotics may also cause side effects that can look like dementia.

Some other important conditions that are really important to be aware of, hearing loss. So, if you, one, try to prevent your hearing from getting damaged in the first place, so protect your hearing. But it's a good idea to have your hearing checked. And if you do have hearing loss, you are at increased risk of dementia. However, if you use hearing aids, you can mitigate that risk. So, a really important modifiable risk factor. People with hearing loss are about 90% increased risk of developing dementia versus those that don't have hearing loss. And as I said, it is a good news story that with hearing aids, you can reduce that risk, again.

People who have had traumatic brain injury where they have lost consciousness from the force of the blow, or as Tricia was mentioning, if they engage in sort of contact sports or certainly things like boxing, where they're getting hits to the head, that can increase your risk of dementia. So what can you do? Wear a helmet if you are cycling. Be focused on your balance to try to reduce your risk of falls. So, that's where balance exercises and strength training and reducing hazards in your home that might be tripping hazards. So, all of those things can help to reduce your risk of having a head injury.

Major depression is also a risk factor for dementia. So, if your mood is low, get it checked out. And if you need treatment for depression, there are good non-medication and medication treatments available. An emerging risk factor as well is air pollution and secondhand smoke. Now, there may not be that much you can do about air pollution if you're forced to live in the same place, but secondhand smoke is probably something that you can take action on to reduce your exposure.

So, all of those things can help to reduce your risk. And the other thing that has been studied is that the more of these healthy lifestyle behaviours that you can do, the better in terms of reducing your risk of dementia. In an article from 2020, where they studied people over many, many years and looked at their healthy lifestyle behaviours, five different behaviours, physical



activity, light-to-moderate drinking, so not heavy drinking, being cognitively active, not smoking, and having a high quality diet, like the Mediterranean diet. If you engaged in just two to three of those behaviours, you had a 37% lower risk of developing Alzheimer's than somebody who was only doing zero or one of those healthy lifestyle behaviours. If you could do four or five, you had a 60% lower risk of developing Alzheimer's versus those who only did zero or one of those behaviours. So, the more the better.

So, a significant amount of dementia can be delayed or prevented. It's never too early or too late to start. What is good for the brain is good for the body, and vice versa. So, the things that I've talked about in terms of reducing your risk of dementia also turn out to reduce your risk of cancer and heart disease as well. And the more factors you can address, the better. And again, even if you have susceptibility genes, many of these interventions that you do, these healthy lifestyle changes, can still lower that risk.

I just want to mention a couple of other resources. A great resource that was, if you joined it early, the Alzheimer Society has great information on their website, and your local Alzheimer Society also has great programs and opportunities and education sessions like these webinars as well. So, this is a great place to stay up to date. They often post research on genetics or research studies in real-time.

I wanted to talk to you briefly about our McMaster Optimal Aging Portal and a dementia risk initiative as well. So, the Portal is a free website with evidence-based content on various topics related to health and social aspects of aging well. So, beyond just cognitive health and brain health, there's all kinds of topics covered. Our Division of e-Learning team also develops kind of multimedia e-learning lessons on various topics, many of them related to brain health and mental health, including our program on dementia risk reduction. So, that includes an e-learning lesson, about 30 minutes, going in more depth on some of the things that I just spoke to you about. There's also a 12-week free email thing. You can get an email a week about risk factors. There's the voiceover avatar that I've become known for. There's also text content if you prefer to read about the different risk factors and learn a bit more about them.

I saw that many of you joining tonight are identifying as care partners of people living with dementia. Some of you may be familiar with our other site, iGerCare.ca, which is, again, a free website with e-learning lessons on various topics, other resources and we also have recorded videos on various topics such as "What is dementia?", "How to promote brain health", and "Mild cognitive impairment". So, with that, let's just summarize a little bit some of the key points.

*Dr. Tricia Woo:* Sure. So, rounding out the key messages. Number one, most dementias don't run in families or have a very strong genetic cause. Routine genetic testing is therefore not recommended. Most dementias are due to a complex combination of age, genes, environment, and other factors. There are several genes like APOE e4 that may increase the chance of developing dementia, but even with genetics as a risk factor, you can still benefit from a healthy lifestyle.

*Dr. Anthony Levinson:* And if we were to go back to Linda who remember she had was interested in learning about her ancestry, so sent away her DNA sample to one of those genetic testing companies and got back that she had one of the APOEε4 alleles. In her case, she went to the Alzheimer Society website. She learned a little bit more about the risks associated with APOE ε4. She spoke with her doctor, and she also went to the DementiaRisk.ca resource, learned about the various things that she could control to reduce her risk, and engaged in a number of those healthy factors.

For David, when he was worried about his family history, he did go to talk to his family doctor who did recommend, given the number of people in his family, recommend that he see a genetic counsellor. When the genetic counsellor went over his family history in more detail, though, there weren't actually that many relatives that had developed dementia and those that did were all in their 90s at the time, and it didn't seem to follow a pattern where there was everybody or anybody getting dementia at a much younger age. So, it seemed to fit in line with a sporadic pattern of dementia with only the oldest adults getting it. So, after going over that with the genetic counsellor, it was decided that genetic testing was not warranted in his case. But, he was also interested in doing what he could to live to a ripe old age like many of his ancestors, and also engaged in several of the healthy lifestyle behaviours as well.

So with that, why don't we go to the Q&A?

*Sandra Mallet (Alzheimer Society Brant, Haldimand, Norfolk, Hamilton and Halton):* Wonderful. Thank you both for an absolutely excellent presentation. Great to have all of that information formalized. And thank you so much for sharing the resources, including the Alzheimer Society of Canada.

Many of our viewers may not yet know that Landmark Study part two was released just last week. So, if anyone is interested in that, Alzheimer Society of Canada has that. That's part two of a three part study. So, thank you so much for that. And I know I've already shared this with Dr. Levinson before, but I look forward to getting up on Thursday morning and having my Optimal Aging newsletter sitting there in my email box. So, I really do encourage people that are thinking about how to age optimally to sign up for that newsletter.

So, we do have a Q&A. There is a little box at the bottom of your screen, and I see we are getting a couple questions there. You will also see that in our chat. My coworker, Jake, has just put in a short survey. So, we always really appreciate people taking a moment to go through and answer a survey. And before we finish tonight, we will share a screen with a QR code. We won't do that quite yet because we do want to get to some questions.

So I'm really excited about this one question. So, thank you to our anonymous attendee.

### **[39:45 Is there a link between adult ADHD and Alzheimer disease?]**

*Sandra Mallet (Alzheimer Society Brant, Haldimand, Norfolk, Hamilton and Halton):* Is there a link to ADHD? There is some similarity in the cognitive symptoms, especially in executive

functioning. I've actually been asked that a lot lately, so I look forward to hearing your thoughts on that one.

*Dr. Anthony Levinson:* I can start and then maybe Tricia can join in. I know it's kind of an active area of research at the moment, and there is a group out west that does, I think they're in Alberta, that has been looking more and more into sort of either people who might be diagnosed with both ADHD and mild cognitive impairment, or perhaps they've been diagnosed with mild cognitive impairment or dementia, but it's actually felt that they've been misdiagnosed and they may actually have ADHD that has not yet been accurately diagnosed.

So, I will say that I think this is an emerging area still. There is not a very strong association. I think up until a few years ago, people were tended to be a bit more focused on the diagnosis of ADHD in children. And it's really only in the last decade or so that people have become more attentive to people who may have ADHD that's perhaps gone undiagnosed into their adult life and maybe even into older age. So, you're right that some of the executive function issues and attention issues and working memory issues can be seen in ADHD and in dementia as well. But you can also find executive dysfunction in other conditions as well. So, Tricia, I don't know if you have anything.

*Dr. Tricia Woo:* Yeah, no, absolutely. This is a very hot topic and still emerging and evolving. So, as Dr. Levinson said, that the evidence is changing day by day. And adult diagnoses with ADHD, there are some smaller studies that do show, even with adjusting for confounding factors, there may be a small increased risk of getting dementia. But that is still to be confirmed and elaborated on. But very promising, interesting research that's happening right now on this topic.

*Sandra Mallet (Alzheimer Society Brant, Haldimand, Norfolk, Hamilton and Halton):* Perfect. Thank you so much for that.

### **[42:13 What gene is involved in dementia for those with Down syndrome, and can lifestyle factors help to reduce their risk?]**

*Sandra Mallet (Alzheimer Society Brant, Haldimand, Norfolk, Hamilton and Halton):* I apologize because I might butcher how to pronounce a few of these things, but I'm going to try. Is it also the APOE e4 gene in people with Trisomy 21, or was that APO?

*Dr. Anthony Levinson:* Yeah, that one is APP, which stands for amyloid precursor protein. So, it's different from the APOE e4 gene. And as Tricia said, the APP gene, the amyloid precursor protein, sits on chromosome 21. So, with the extra copy of it, it's thought that the predisposition for dementia in people with Down syndrome, in most cases is that extra copy of the APP or the amyloid precursor protein that is generating more amyloid, that sort of becomes some of the plaques that are sometimes seen in Alzheimer disease. So, yeah, it's the APP gene in the case of Trisomy 21.

*Dr. Tricia Woo:* Agreed.

*Dr. Anthony Levinson:* I did see another question around that, which is, "Is there any evidence-based research indicating that the lifestyle factors also minimize the risk for people with Trisomy 21?". And again, this is kind of an interesting area, there's been a bit of a renaissance lately in studying people with Trisomy 21 and trying to both learn more about Alzheimer disease from that population, but also give something more back to that community, because the age that people with Down syndrome are living is also longer. So, people with Trisomy 21 tend to have other medical issues as well. So, they wouldn't always have lived into their 50s and 60s before, but the longevity now of people with Down syndrome, because of good, improved medical care and other factors, is longer. So, more people with Down syndrome are developing dementia. And as far as I understand, while there's part of that roundabout was saying there hasn't been a ton of research done, my understanding is that these lifestyle factors do also provide benefit. But again, it seems like there's been more interest in more studies involving people with Trisomy 21.

#### **[44:50 How do concussions in early life increase the risk of dementia?]**

*Sandra Mallet (Alzheimer Society Brant, Haldimand, Norfolk, Hamilton and Halton):* The next question is asking around, you mentioned the boxing, American football, wrestling, what are your thoughts on soccer in terms of a sport being where you might head the ball?

*Dr. Tricia Woo:* I think the area of chronic traumatic encephalopathy is also evolving. There's actually an entire institute in Boston just looking at this and its impact, particularly on not only professional athletes, but even at the amateur and junior levels.

And they have found that if you're using a lot of headers in soccer, that can be a smaller risk factor. Certainly, it's not as common as contact sports, where you're actually butting heads, literally. But there is some thought, and this is primarily looking at people that were young athletes that died for other reasons, and then looking at the brain and looking at the amount of trauma and stress that was on their brain and the number of concussive injuries they had in their youth. Again, this is a very hot topic and one of increasing research.

*Dr. Anthony Levinson:* Yeah. And I think there have been some efforts to have heading introduced later in the sport just because of concerns that there may be an increased vulnerability to concussion if people start with heading younger.

*Dr. Tricia Woo:* The sporting associations have been very good and very proactive. If players, particularly young players, are having concussive injuries, there are timeouts. There are, particularly in American football, the American Football association, the NFL have looked at trying to reduce tackling and things to minimize that risk or mitigate that risk as much as they can.

*Sandra Mallet (Alzheimer Society Brant, Haldimand, Norfolk, Hamilton and Halton):* Yes. Wonderful. I know with my own children's sports, that was definitely something that was being paid attention to. So it's good to see that.

## **[46:39 Can tinnitus increase your risk of dementia? What is the role of hearing loss?]**

*Sandra Mallet (Alzheimer Society Brant, Haldimand, Norfolk, Hamilton and Halton):* I have a question here. "Is there any research on tinnitus being associated with increased risk?"

*Dr. Anthony Levinson:* I'm going to let Tricia take that one.

*Dr. Tricia Woo:* I'm not an expert on that particular field of literature, but as far as I know, not really because it is very bothersome, it's a very bothersome symptom, but it depends on how troubling it is.

The reason why hearing impairment is a problem is because that tends to reduce your social interactions. And when you are listening to people, you tend to use all of your brain power just to focus on, just trying to figure out the words, let alone the content. So, if you do have ringing in your ears and chronic tinnitus, my limited understanding is that the impact on later life cognition is not an obvious link.

*Dr. Anthony Levinson:* I think it's a very common symptom. In some cases, it can be associated with hearing loss, and so the hearing loss aspect does function as a risk factor. But it's unclear whether tinnitus or tinnitus is an independent risk factor. But if it is associated with hearing loss, then hearing loss turns out to be a really complex and important risk factor. It's probably, as Tricia's just saying, both things we don't understand that may be more primary, but also the cascading aspect of more social isolation. It also increases your risk for falls quite dramatically. So, you may also predispose yourself to falls and then a traumatic brain injury, which would also increase your risk. So, there could be a few factors, but I'm not aware that tinnitus is sort of an independent one.

*Sandra Mallet (Alzheimer Society Brant, Haldimand, Norfolk, Hamilton and Halton):* Yes. No, that's great. Thank you for those answers.

## **[48:35 I have a strong familial history of Alzheimer disease. Should I get genetic testing?]**

*Sandra Mallet (Alzheimer Society Brant, Haldimand, Norfolk, Hamilton and Halton):* We have someone saying that their maternal grandmother, mother, and uncle have had dementia. And now uncle, who is mother's brother, was confirmed diagnosed with young onset Alzheimer's. Would I be able to get genetic testing, is the question.

*Dr. Anthony Levinson:* I would suggest a referral to a genetic counsellor. I think given a strong family history that seems to follow that pattern. And again, we're providing education, not sort of medical advice. So, it's always a good disclaimer around that. So, I think if we were to look at it from an educational standpoint, in terms of the example that Tricia showed previously, that is the type of family history, especially if there's a known relative who has been diagnosed with kind of a young onset or a familial Alzheimer disease. So, it would be worthwhile talking to

your family doctor and getting a referral for genetic counselling and then following their advice, is what I would say.

### **[49:45 Will genetic testing determine the exact type of dementia a person has?]**

*Sandra Mallet (Alzheimer Society Brant, Haldimand, Norfolk, Hamilton and Halton):* So, our next question, someone says their husband is 55 and diagnosed with young-onset Alzheimer's dementia or frontal lobe dementia. They're supposed to be getting the testing back this week. Will there be something on that that may give a hint to what type he actually has? This is actually something I get asked a lot. People will say to me, the doctor said Alzheimer's, or they said dementia, then they changed it up. Very often it lands on Lewy body or something completely different than the person was thinking. So, I'd love to hear both of your thoughts on that.

*Dr. Tricia Woo:* You want to start, and then I'll add in.

*Dr. Anthony Levinson:* Sure. I think there are a couple of genes that are more strongly associated with particular types of dementia. So, if the genetic testing in this case came back with a few of the well-described genes Tricia mentioned, the presenilin 1 and presenilin 2, and that APP, the amyloid precursor protein, if it came back with one of those, then it's more likely to be an familial Alzheimer dementia. And then there are a few other genes that are more likely to be associated with frontotemporal. So, I would say it's most likely going to be helpful, but there is some overlap in some of the other risk genes. But what would you say?

*Dr. Tricia Woo:* Yeah, absolutely. So, oftentimes when they do do genetic testing, they may do a panel. So, there may be more than one. In this case, it certainly sounds that more than one type of genes or genetic profile has been looked at, and it is one piece of information, often very strongly useful piece of information, but it's also taken in the context of what the person is like in person. If they've had neuroimaging or fancy neuroimaging, spec scanning and pet scanning, that may be another piece of evidence.

So, you put all the different pieces together. It's sort of like looking at a jigsaw puzzle and putting all the pieces together to arrive at a diagnosis. And sometimes it can be a little bit tricky initially, because the symptoms, they may not be reading the textbook, and their symptoms might be slightly different than the classical presentation of one type of dementia or another, or they may have early symptoms of one out of sequence. So, there's some variability in that. But I think if you get all the different pieces of the puzzle, you sit down with your team, your healthcare team, you should be able to piece it together and see what type of dementia they actually do have.

*Dr. Anthony Levinson:* I think this is a very challenging thing sometimes for families and also for clinicians, though, because most people don't have a confirmed diagnosis, it is still clinically, what are the symptoms? And as I explained at the beginning, yes, it's an umbrella term, but sometimes people have a mix. So, I think it is appreciated now, with sort of slightly better neuroimaging, that people may well have a mix of different dementia. So, the pattern

may resemble both, or you have people who have Alzheimer, but just because it's relatively common, it may target, say, the frontal lobes in one person, so they may have more prominent frontal lobe features. So, it looks like a frontotemporal dementia, but it may still be Alzheimer's or a mix.

### **[53:25 Is there research related to different populations, such as Asians, Black and Indigenous, and their genetic risk for dementia?]**

*Sandra Mallet (Alzheimer Society Brant, Haldimand, Norfolk, Hamilton and Halton):* So, we're just coming up to the end of our time, and I really like this question, and if we could just take a moment to address this. Have there been any studies around different populations, such as Asians, Black, Indigenous in relation to genetics and risks? And if so, what are the findings? I know the Landmark Study, Part 2, did address some of these issues, but definitely to see your understanding.

*Dr. Tricia Woo:* Want to go first?

*Dr. Anthony Levinson:* No. I don't.

*Dr. Tricia Woo:* Yes, there are differences. There are differences at many different levels. And this is the wonderful thing about research and diversifying the research and looking at different populations of people. And there's differences at every stage.

So, we mentioned earlier on in the talk about difference in genetics, difference in prevalence of different variants of this APOE gene, and there have been a number of studies looking at different populations from around the world, and they have different prevalences. Some have more of one type of allele versus another, and others do not.

Lifestyle certainly is different. Eating habits are different. Exercising habits are very different. And so, it's a wonderful tapestry of different cultures.

Education level is also something, and level of literacy has also been studied across different cultures. Whether or not you're bilingual. That has also been shown to be very, very protective.

So, lots of different factors have been looked at across cultures. Also, even just looking at people's relationship to the word dementia, how they manage, how they perceive their symptoms, how the caregivers interact with the family members, is also very different.

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