Dementia Dialogue; Season 4, Episode 52

Young Onset Dementia: Genetic Testing – To test or not to test?
Transcript of interview with Jillian McConnell and Dr. Mario Masellis

David - Welcome to Dementia Dialogue and today's episode on genetics and dementia.

This is the sixth episode in our series on young onset dementia.

Jillian McConnell discusses his complex topic with Dr. Mario Masellis, a research physician at Sunnybrook Hospital in Toronto. Dr. Maselli reviews some very complex issues.

To assist our listeners, we have prepared a transcript that can be found with the show note on our website. You can download it from there.

Let's listen in.

Jillian - Welcome Dr. Masellis. Thanks for joining us today. It's such a pleasure to have you.

For our listeners who might be hearing about this for the first time, can you give an overview of the role that genes play in Alzheimer's disease?

Dr. Masellis – Yes. Just in terms of the genetics of Alzheimer's disease, I think that first of all, we need to start by talking a little bit about the most common form of Alzheimer's disease, which is what we called late onset, sporadic Alzheimer's disease and what that means is that there is not a strong genetic tendency in that group of disorders. Except there is a gene called the apolipoprotein e gene or APOE which is a very strong genetic risk factor for late onset of sporadic Alzheimer's disease. If you have this particular genetic variation that it increases the risk for developing Alzheimer's disease in combination with the other strong risk factors such as increasing age, cardiovascular, risk factors and lack of exercise and lack of a healthy diet.

So that's the genetics of the most common form of Alzheimer's disease, which is called, what we call a kind of a complex genetic risk. That is the combination of both environmental risk factors, other health factors, such as cardiovascular risk factors, lifestyle choices, together with APOE gene genetic variant called the a APOE epsilon 4 allele that increases risk for late-onset forms of dementia.

However, there are three other genes that are passed down, that can be passed down from your mother's side or your father's side and inherited in what we call an autosomal dominant fashion. There are rare variations with which are called mutations, genetic mutations within a one of three genes that are causative for Alzheimer's disease and often what we call early onset or young onset Alzheimer's disease. This is different from APOE. APOE as a risk factor, meaning if you have it, it doesn't guarantee you will get Alzheimer's disease.

Whereas if you have a mutation in one of these three genes, then there's pretty much 100% likelihood you will develop it at some point in your life. So very high, what we call highly penetrant genetic mutations that cause younger-onset forms, or early onset forms of Alzheimer's disease. And these three genes include:

- The amyloid precursor protein, also know as APP as a short form for it.

- The presenilin 1 gene, which is PSEN 1
  and
- the presenilin 2 gene PSEN 2

and what we know about all three of these genes is that the majority of mutations that occur in these genes, what happens is they increase the level of amyloid in your brain and amyloid is one of the proteins that go awry in Alzheimer's Disease and we think that's a major contributing factor to the development of Alzheimer's Disease, particularly familial forms of Alzheimer's Disease and that typically occur at a younger age with these mutations.

Jillian – So if you're interested in genetic testing, or actually better yet, can you explain what genetic testing is? And then how it would work for someone who is diagnosed with Alzheimer's Disease and perhaps someone who isn't, but might be concerned that they might be in the future?

Dr. **Masellis –** Yeah so first of all genetic testing has become more widely available for genetic disorders, all types of genetic disorders including genetic forms of Alzheimer's Disease, that are strongly imperative in families.

What genetic testing entails is you would give a blood sample. So they take blood from a vein in your arm most commonly and sometimes they can even do it from saliva in your mouth or by scraping the cheek cells, the cells on the inside of your cheek. And from that, they can extract your genetic code or your DNA.

So from a genetic standpoint, we're able to use a technology in the lab called PCR to amplify our DNA sequence and specifically for genetic testing of Alzheimer's Disease, we amplify the genes implicated in Alzheimer's Disease. So we amplify up the gene region for APP, or for presenilin 1 or presenilin 2 and for early onset genetic cases, we typically screen for these mutations in these genes by amplifying it up and then by looking at the DNA sequence we can see if someone has inherited an aberrant version of the gene, which is called the mutation.

So that's the process of genetic testing, is taking but set your blood sample, extracting DNA from the blood sample, looking at the DNA sequence of these three genes that can cause Alzheimer's disease if a mutation is found in it in one of these three genes and then we get a readout that tells us if someone has a mutation or now.

Now generally speaking, we start the process in someone who we suspect has an early onset form of Alzheimer's Disease. Or a familial onset form of Alzheimer's Disease based on having two or more first-degree, family members or relatives like a brother or sister or a parent who also had Alzheimer's Disease.

So we offer, for example, genetic testing for these mutations in these three genes if someone has a very strong family history of Alzheimer's Disease, meaning at least two first-degree relatives with the disease or alternatively if they have an atypical form of Alzheimer's Disease or an early onset form of Alzheimer's Disease. Because early-onset forms, we tend to find aberrant genes more frequently than in late onset forms of Alzheimer's.

Jillian - So given that, is there genetic testing there available for all types of dementia or we really focusing on early onset Alzheimer's Disease? Are we looking at the

possibility of frontotemporal dementia being included in that or vascular dementia or they are other varieties of dementias and A.D. that we know exists out there for people.

Dr. **Masellis –** So all forms of dementia can have what we call, can be sporadic in nature and they tend to be later in onset, meaning that there's not a strong family history or they can be kind of earlier onset or they can be strongly inherited in families based on the criteria I gave you.

So when we are going to test for any type of dementia, we want to make sure that, it's an early onset form or if it's in atypical form of dementia, that's where we would want to do testing, genetic testing or alternatively, if there's a strong family history as described, with more than two first-degree relatives.

So all forms of dementia, whether it's Alzheimer's Disease and I've presented you the case of the complex late-onset form with the genetic risk factor APOE, combined with other environmental, lifestyle risk factors and medical risk factors for late-onset form. And then I give you the circumstance of genes associated or genes causative of familial Alzheimer Disease, which are often strongly inherited and often occur at a younger age.

The same thing applies to frontotemporal dementia. So frontotemporal dementia, up to about 40% of people with frontotemporal dementia, so it tends to be more strongly genetic than Alzheimer's Disease. Up to about 40% of individuals with frontotemporal dementia have a very strong family history and we have genetic causes for of that 40% about half of them there are mutations in three major genes that can cause it; the C9 or ORF72 gene the granulin gene or the MAPT gene (which is called microtubule-associated protein tau).

There are some other, rarer causes of frontotemporal dementia but I won't mention that, that runs and families.

For Lewy Body dementia, it's even less strongly genetic then frontotemporal dementia is and even less than Alzheimer's Disease, but they're having mutations discovered in the alpha synuclein gene which encodes for alpha synuclein, the main protein that goes awry in Lewy Body dementia.

For vascular dementia, less is known about genetic forms of vascular dementia, but probably one of the more common types is a disease known as CADASIL, it’s a very long name, I won’t summarize what that stands for, but this causes young onset strokes in the brain, small vessel strokes that eventually culminates in dementia and the gene that we can test for in that group of disorders is called the NOTCH3 gene.

You know, there are other rarer forms of dementia that also have genetic causes. So when we're trying to characterize a patient as having, whether or not we should get genetic testing for a patient, what we need to start with is a very good family history. If there's a strong family history of more than two first-degree relatives, once again brother, sister or parent, then we should pursue genetic testing.

If the case of dementia is atypical, and what I mean by that is it’s not classical for Alzheimer's Disease, we suspect it’s Alzheimer's disease, but it presents in a different way and in the case of it being younger-onset, then genetic testing should also be considered as well.

And sometimes we have cases of dementia that don't fit nicely into one specific category. It doesn't look like Alzheimer's Disease. It doesn't look like Parkinson's or Lewy Body dementia. It doesn't look like frontotemporal dementia and it's younger-onset and there's a family history, we can now order genetic panels that look at mutations in twenty or thirty genes known to be associated with a bunch of different types of dementia and that allows us sometimes to find a cause for their dementia syndrome.

Jillian - You've explain it really well in terms of how it looks and who's a good candidate. Does the person who is living with a diagnosis, have to be tested in order for the family members to be diagnosed or go to genetic testing, rather? Or they able to do that on their own? So if my mom or dad has a dementia, do they have to be tested genetically as well in order for me to get tested?

Dr. **Masellis –** That's an exellent question and you've probably heard of direct-to-consumer genetic testing via 23 and Me and other companies have come to the market now. So if an individual wanted to get all of their genes screened for mutations, they can send blood to 23 and Me. This is not recommended for many different reasons. First of all, if we suspect someone has a genetic form of Alzheimer's Disease and if someone's father, for example was diagnosed with genetic Alzheimer's Disease and a genetic mutation was confirmed, the best route for someone who is unaffected like a child or a sibling who is unaffected to get screened, would be for their family doctor or one of their physicians to refer them to see a clinical geneticist.

The clinical geneticist will then have a very detailed discussion with them about what are the implications of finding out a genetic mutation result for a disease we currently do not have a treatment for. What are the implications should that information be inadvertently shared with your employer or with insurance companies. Thankfully in Canada, we have a Genetic Non-Disclosure Act which means that what genetic mutation finding is not to be shared beyond the patient and the doctor but you know there's always a possibility it could get disclosed so what are the implications of finding out a genetic result?

What are the implications for example, if your parent had young onset Alzheimer's Disease and a mutation in the APP gene was discovered for example or let's say the presenilin1 gene. That has implications for you deciding whether or not you want to have children. It also has implications for making decisions regarding your job. If you have a very high-powered job and have a lot of responsibility at that job and you worry that at some point, you may display signs or symptoms of the disease based on having inherited a genetic mutation for it, then you may consider changing your job or changing our role.

So lots of personal decisions can come from this. It's also very stressful for a patient, for a person who doesn't have a disease to find out they're at extremely high risk, nearly a 100% chance of getting the disease if they have a mutation causing autosomal dominant Alzheimer's Disease, that can cause you no symptoms like depression to emerge and even suicide in some circumstances. So it can be a very stressful process and I would never advise someone who is asymptomatic to find out their genetic results without having the support of a clinical geneticist or genetics counselor, to provide a discussion about the implications of finding a genetic results.

Why do some people want to find out a genetic result, why do some people don't want to find out the results? Well, one reason for finding other genetic result is that if you want to have children with your partner, then you can now go through a process of getting yourself screened for a mutation without you even finding out the results of the of the mutation for the purposes of selecting an embryo to be given to your partner, to have a child that would be guaranteed to be mutation free, if indeed you had that mutation. And you can do this knowing you have the mutation, you can also do this without knowing you have the mutation. That could be done all blindly. But this is a costly expense. You have to go through in vitro fertilization and implantation of embryo, once it's been selected, the embryos have to be genetically tested as well.

But this is something that was not available ten years ago or twenty years ago. And as an option for young couples who find out that they may have a genetic disorder running in their family, such as genetic Alzheimer's Disease, to help prevent a mutation from being passed on to their offspring.

Another reason why people now are pursuing genetic testing for genetic forms of Alzheimer's Diseases is we now have clinical trials of new therapies that are targeted specifically for people at risk of developing Alzheimer's Disease based on inheritance of one of these mutations.

Some of the studies, you don't need to know your genetic results and they can randomize you to placebo or drug without knowledge, but some studies from pharmaceutical companies do require you to know your genetic result and the only way you can get into the trial is to know your genetic result.
So that may be another reason why people want to find out there genetic result.

My recommendation would be that if there's a strong family history of a genetic disorder and your family member has tested positive for one of the mutations causing genetic forms of Alzheimer's Disease, then if you are considering finding out your genetic result, it would probably be best to get your family physician or your care provider to refer you to see a clinical geneticist or genetics counselor and organize, and/or because they often work together to have a frank discussion about what the implications of finding a genetic results are before you go and get tested.
And then the genetics counselor or the clinical geneticist can order the genetic testing for you, on your behalf.

Jillian - What would be the time frame of starting the process to getting a result?

Dr. Masellis – So if someone has the disease, so if I've diagnosed the person with young onset Alzheimer's Disease and I suspect they have a genetic form of it, I can order the genetic testing myself.

However, I'm not qualified to do that for a family member who is unaffected. So what typically happens is there's a referral made to a genetics counselor and I can be anywhere from six months to even up to a year-and-a-half to two years of waiting time to get to see a clinical geneticist. And once you see them, they meet with you, they have a discussion and then they can do the paperwork to submit and you typically can find out a genetic results once your blood has been submitted for testing to a laboratory, anywhere between two up to as long as six months afterwards, and sometimes even longer. The process is still not out there and depending on which company is doing it, some companies take a lot longer than others.

Now the other process in Ontario, and probably applies for all of Canada, is that you also have to get approval from the Ministry of Health for funding to do the genetic test. Whether you are a patient with Alzheimer's Disease or whether you're someone who's at risk of it based on coming from a strong family history of Alzheimer's Disease.

So the other alternative is that people may opt to pay for the testing themselves through a geneticist and that sometimes can speed the process up because the approvals and also take up to about a month to get back.

Jillian - And the geneticists or the genetic counselor would be there and in consultation when you received those results, correct?

Dr. Masellis – Si if I received a positive result for a patient with Alzheimer's Disease, then I disclose that to the patient and their family, their immediate family. And then the genetic councillor or clinical geneticist will do that for someone who is asymptomatic, who does not have the disease yet.

Jillian – And just for clarity, if you are an asymtomatic person who is interested in getting a genetic test and the results come back where you are positive for that specific gene, whether it be APP or the psen1 or psen2, does that guarantee that you will develop early-onset Alzheimer's Disease or is that just an indicator of a higher or heightened risk?

Dr. Masellis – That’s a very good question. So the mutations that cause Alzheimer's Disease are what we call highly penetrance. What that means is there's an extremely high chance, if you live long enough, likely 100% chance or close to it, of getting that disease. There may be other modifying genes that we don't know about, that may be somewhat protective against it but we haven't discovered those genes yet. But because these mutations are highly penetrant, then there's a very very high likelihood of developing Alzheimer's Disease, if you inherit one those genes.

And the same thing goes for frontotemporal dementia, although there's more variability with frontotemporal dementia. In contrast the apolipoprotein e epsilon 4 allele is a risk factor, doesn't guarantee you will get it, but there is a higher likelihood of getting it with this gene inheritance.

Now presenilin 1 predominantly causes early onset forms of Alzheimer's Disease, presenilin 2 and APP can cause both early-onset forms and later onset forms, although not typically as late as late onset disease does. So there is even variability in the early onset nature of familiar forms of Alzheimer's Disease.

Jillian - Are there areas in which the accuracy might be questioned?

Dr. Masellis - We're getting much better now at determining if a genetic variant discovered in a gene is likely a causative variant of Alzheimer's Disease, okay?
So sometimes we get back genetic reports and it says something like, “a variant of unknown significance”. So they find a new mutation that they're not sure of whether or not it could cause the disease or not. But now we have sophisticated algorithms where you can input this genetic variation into a program that tells you how damaging the variant is to the gene function. And then if we discover a gene variant or a mutation,

that has already been proven to cause Alzheimer's Disease, then we feel very confident in saying that this is a causative mutation.

And what defines a causative mutation is not only how damaging the mutation is to the gene function, but it also is the inheritance pattern. So if we see that this mutation is occurring in every person in a family that has Alzheimer's Diseaese but every person in the family who does not have Alzheimer's Disease does not have the mutation then that's high evidence that this mutation is causing the disease.

And we also look at the population frequency of the mutation. These mutations are, by definition a genetic mutation occurs in less than 1% of the population, if a whole bunch of the healthy population who does not have Alzheimer's Disease also have this mutation then it's likely a mutation that's not causative.

So once again, sometimes we discovered variants of unknown significance and we don't know whether or not it's going to be proven to be causative of the disease and that's how that's getting less and less as we understand more about gene function, and have more tools and techniques at hand to be able to kind of look at them.

Jillian - You mentioned earlier that in your experience, the vast majority of your patients and their families choose not to get tested, correct?

Dr. Masellis - Well I would say that lot of patients who have the disease, their families want to know. So if they have the disease and if I'm advising them to get genetic testing, they will likely do it because once you have the disease, finding out you have a mutation may make you eligible for a very specific clinical trial. So you don't have a lot to lose because you already have the disease.

However, if you don't have the disease, you're asymptomatic but you're related to someone who has a genetic form of Alzheimer's Disease, then it's a different situation altogether because there could be a lot of stress about finding out you have the disease. There could be job implications, other implications, lifestyle implications family planning implications.

So as I've discussed before, a lot of people choose not to find out their genetic result number one because we don't have treatments for the disease. But let's contrast this with cancer. So we now know that there are familial causes of different forms of cancer, but there are treatments for that. So if someone has a familiar form of cancer and there's a mutation that's been discovered in them, that will cause cancer in them, finding out that they have this familial form of cancer mean they can enter into more frequent monitoring or screening programs, surveillance programs for cancer surveillance. And then they could participate even in preventative clinical trials or alternatively get their cancer detected very early on before it has a chance to metastasize to other body parts, to other organs in the body and they can get treated early on for it and thus get cured.

We're not there yet with neurodegenerative diseases, so Alzheimer's Disease, frontotemporal dementia, Parkinson's, Lewy Body dementia spectrum, the vascular dementia spectrum. We don't have any cures for these diseases. We only have clinical trials in a handful of these genetic forms of disease. So those are the implications. This is the reason why people may choose who are asymptomatic, may choose not to find out the results and it's usually a minority do.

Jillian - So then can you speak to some of the reasons why people might choose to get tested as an asymptomatic person? There's obviously, as you mentioned already, we've discussed lots of implications and because of that, a lot of people choose not to go that route. But what if they do go that route? Can you explain why they may just elect to say, despite all that, I'm going to go forward?

Dr. Masellis - Some people want to find out. They want to have as much information about their health status as possible, so that they can make future choices in their life. So future choices, as I mentioned regarding the career, but also future choices down the road.

Like in Canada now, we have medical assistance in dying or the MAID program. So some people may want to find out if they have a genetic mutation so that they can put their paperwork together for that process in the future. Because right now as it currently stands, you're not eligible for MAID if you can't consent to the treatment and dementia is one of these diseases which in moderate to late stages, you may not be able to provide informed consent because you don't understand the implications of making that decision for MAID, right?

So some people may want to have that information for even that aspect of future planning; future planning of death for example. Future planning in terms of their finances. So if I know I'm going to get Alzheimer's Disease by the age of fifty and I'm twenty-five years old, I need to think about my savings and what decisions are going to be made for myself and my family in terms of that.

I talked about Family Planning. That's probably one of the main reasons why young people decide to get genetic testing. Although you don't have to get genetic testing to be eligible for in vitro fertilization and pre-implantation genetic screening of an embryo, right?

And also career decisions and lifestyle decisions. Someone may decide that they don't want to work as hard as they are working if they have the financial resources and they may want to live the last ten years of their life enjoying it as much as possible with as little stress as possible.

They may also want to minimize stress because as you know stress is a risk factor for depression and depression in and of itself can be a risk factor for dementia.

So psychiatric disease, as we learn more about psychiatric disease and psychiatric comorbidities, there may be an increased risk for developing dementia down the road. Not typically someone that has young onset depression but if someone develops depression in their fifties and never had depression before, that's definitely a risk factor for the development of a neurodegenerative disease such as Parkinson's or dementia or Alzheimer's Disease down the road.

So these are just some reasons why people decide to get genetic testing. The reasons why people decide not to get genetic testing are we can't do anything about it but there are no treatments so why should I find out? I don't want to find out because I'm scared. I don't want to find out because I know I will get depressed and down, finding out that I have this mutation and therefore for me not knowing is better than knowing.

Some people want to do the genetic testing and we have to look at the circumstance that they find out that they don't have the mutation. Well that can be a huge relief for them, right? However, if they find out that their sibling does have the mutation that their dad had, then that can also make them feel guilty. So there's lots of different experiences that each individual person will have in terms of finding out if they have a mutation or not.

So it's very complicated. And these are all examples from patients in my clinic or family members of patients in my clinic have discussed with me.

Jillian - And just to reiterate, so all of these really important considerations would be discussed with the geneticist and/or the genetic counselor, correct? So that they really emphasize the valuable role they play throughout this whole genetic testing process.

Dr. Masellis - Yeah, absolutely. I would not advise you to do it on your own through these direct to consumer testing, mainly because you won't even understand what the report is. It's just not that easy to understand the report. And so it's best to do it through a clinical geneticist. They send your blood to a certified genetics laboratory that are able to tell you the likelihood that the mutation is a causative one or not. And therefore, when you find out your genetic results, you'll be most reassured that it's as accurate as possible, whether it's positive or negative,

Jillian - Do you have any final words of advice or insight for those listeners that are considering genetic testing be it for themselves or perhaps a family member?

Dr. Masellis - I would advise them to discuss it with their family, with their partner and before you go the route of speaking to a clinical geneticist, have your advice from your loved ones, your partner, or your family.

And then I think that for patients with the disease, what we are learning from genetic studies, is we're gaining a wealth of information about novel genetic causes for Alzheimer's Disease but also risk factors for Alzheimer's Disease. Eventually we may be at the point where we can generate what's all the polygenic risk score. So if you take into consideration the APOE gene and a bunch of other genes that increase your risk but none on their own are fully causative agent of the disease. If you find out you have a polygenic risk score for late onset forms of Alzheimer's Disease, then that information could push you to do all the right things; get into an exercise routine, change your diet, change your lifestyle, reduce stress, interact more with your family and friends and loved ones, drink less alcohol, do mentally stimulating activities, exercise. These are all preventative for dementia.

So we're not there yet, but it's hoped that as we become more confident in our ability to predict someone's risk for developing Alzheimer's Disease, that this information can be put back to an individual who is at risk to allow them to make lifestyle decisions and and health decisions that can reduce the risk. Because remember late-onset sporadic forms of dementia it’s kind of that genetic loading combined with your environmental risk factor, which is not often the case in the early onset genetic forms of Alzheimer's Disease, where the genetic mutation is so strongly causitive of the disease that it occurs at a very young age when you're still healthy and don't have all these other problems.

Jillian - So it sounds to me that there still might be lots to learn and certainly the future I think is looking brighter when it comes to the information that we're learning about Alzheimer's Disease in general and the role that genetics play with it as the disease progresses.

Well, thank you so much for sharing your time and expertise with us today. It's really a fascinating topic and I have no doubt that the information that you shared will be so helpful to so many of our listeners.

So, once again, thanks for your time.

Dr. Masellis –Thank you very much for having me. It was my pleasure. Thanks.

David - This episode is the final episode in our series on young onset dementia. The series is the most listened to of all of our work thus far.

Our guests have been courageous in sharing how this condition has affected them personally. And we thank them for that courage.

Thanks to Jillian McConnell and Kathy Hickman of the brainXchange who curated and co-produced this series.

Our next episode will be the second of two produced in collaboration with the Partners Project team at UBC. You can receive each of these episodes in your inbox when they are released by subscribing at dementia.dialogue@lakeheadu.ca and putting "Inbox" in the subject line.

Thanks to the Center for Education and Research on Aging and Health at Lakehead University, our institutional partner, and the Public Health Agency of Canada for it's financial support.

Thanks for listening, my name is David Harvey.