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Speaker 1: 00:00:17  You're listening to audio from one of our Third Thursday Webinars on Parkinson's research. In these webinars, expert panelists and people with Parkinson's discuss aspects of the disease and the Foundation's work to speed medical breakthroughs. Learn more about the Third Thursday Webinars at michaeljfox.org/webinars. Thanks for listening.

Dave Iverson: 00:00:37  Hello everyone and welcome to today's Third Thursday Webinar from The Michael J. Fox Foundation. This is part of our continuing series of webinars where we explore different topics that are important to all of us in the Parkinson's community. Our topic today is genetic discoveries and how they lead to Parkinson's therapies, so we know that there will be important questions that you'll want to pose and again, we'll do our best to get to those.

All right, let's review what we're going to be focusing on today. We're going to talk about genetic discoveries and their role in leading to Parkinson's therapies. There's been a tremendous breakthrough in the past decade in what we've learned about genetics and Parkinson's disease, an explosion of new research. We're going to talk some about why that's so important both to our understanding of the disease and the way in which genes influence proteins that we think are also involved in Parkinson's disease. We'll talk about that relationship, how we get from genes to proteins to therapies and the significance of those potential therapies in Parkinson's disease.

We'll also spend some time talking about how you can participate in genetic research, whether or not you carry a Parkinson's disease mutation or a mutation that's been linked at least to Parkinson's disease. It's the only way we'll make progress is with that kind of research participation.

Here's who's joining us as part of our panel webinar today. First, my friend and colleague Anna Cohn Donnelly. Anna has been a member of The Michael J. Fox Foundation's patient council for a number of years now. She was first diagnosed with Parkinson's disease eight years ago and Anna carries the LRRK2 mutation, which is one of the genetically linked causes of Parkinson's disease that we'll be talking about today. Anna, thanks so much for being part of our webinar today.

Anna Cohn Donnelly: 00:02:41  Welcome. Glad to be here.
Dave Iverson: 00:02:43 Happy to have you join us. Joining us as well is Dr. Roy Alcalay. Dr. Alcalay is an assistant professor of neurology at Columbia University and one of the leading researchers exploring this relationship between genetics and Parkinson's disease. Roy Alcalay, thanks for being with us as well.

Roy Alcalay: 00:03:03 Thank you for having me.

Dave Iverson: 00:03:04 And joining us too is Dr. Andy Singleton. Dr. Singleton is the chief of the laboratory of neurogenetics at the National Institute on Aging within the National Institutes of Health. Andy has been working in the vineyards of genetic research and Parkinson's disease for a good while now and has helped further many of the advances that we're going to be talking about. Andy, thanks again for being part of our program.

Andy Singleton: 00:03:29 It's a pleasure, I'm looking forward to it.

Dave Iverson: 00:03:31 All right. Let's get started. We're going to talk a little bit first about genetics and Parkinson's and just a little bit of genetics 101. Dr. Alcalay, first, we see that first point at the top that our genetic differences are instrumental in who we are and different distinctions within us. We use the example there from eye color to risks for disease. Sometimes that's not quite well understood, we sometimes think that there might be a red-haired gene versus a brown-haired gene, and that's not really the way it goes.

So, can you give us just a little bit of a deeper understand I guess, about the role genetics play in our differences, for us particularly, in the way in which it might lead to propensity for a particular disease condition?

Roy Alcalay: 00:04:28 Sure, thank you. I think that there are typical conditions that everybody knows are what you consider very genetic, where the genetic risk factor is known and if you have it, one would have the disease, like Tay-Sachs or cystic fibrosis or thalassemia. But the fact is that most of the medical conditions that people have and that makes people go to the doctor are a bit more complex. We call them genetically complex conditions or disorders, where there isn't a single gene if you have a mutation in it, you'll have the disease and if you don't have a mutation in it, you won't have the disease. But rather, multiple risk factors may lead to the development of the condition and there's genetic risk factors, there are environmental risk factors and there's interaction among all these risk factors that we don't quite know in many cases how exactly they interact but that's where a lot of the research focuses on.
Just to give it a specific example, LRRK2 is considered the most common genetic dominant risk factor for Parkinson's, so if you have the gene, you have mutation in the gene, you have a significantly increased risk for Parkinson's. But still, many studies show that only one third of those with a mutation will develop Parkinson's, which means that there's contribution from a lot of other genes and environmental factors that would modify this risk and may change whether you have the disease or not or if you have it when you're younger or older.

Dave Iverson: 00:06:16 And so really, all of this exists on a kind of continuum that increases one's odds perhaps one way or the other. And Andy Singleton, you've been such a pioneer in this field. I want to come to you next. We see these next two points that relay how much now we think genetics plays a role in Parkinson's. If we had been doing this in some version, there weren't webinars 20 years ago, but if we had been doing some kind of panel discussion about this topic, the general view would have been that genetics doesn't play any role in Parkinson's at all. Ten years ago, as it says on the slide here, we realized that there were maybe ten genetic regions that might affect Parkinson's. Now, we see that's grown by eight-fold all the way up to 80.

Why is that so significant, Andy, in our understanding of Parkinson's, to get a deeper understanding of the role that genetics play in particular?

Andy Singleton: 00:07:12 Yeah, I think that it really bounces off something that Roy was talking about earlier. This is the notion of moving from an idea where it's one gene, one disease to an idea where multiple genetic variants each contribute small amounts to whether you have a particular trait, and that trait could be disease. So we've moved from a space where we're trying to find single mutations that invariably cause disease to a space where we're trying to find genetic changes that are very, very common in the general population that you or I carry that increase or decrease your odds for disease.

So the notion really with all of this work is that by furthering our genetic understanding, by understanding how variants influence risk and how they control genes and what those genes do, we can use that to understand the underlying processes that really are the disease itself. What are the molecular changes, the cellular changes that represent the disease process? If we can use genetics to understand that process, can we then find viable points to intervene?
So Andy, does that mean in a sense that rather than looking at genetics as this, well it just affects this sort of small percentage. We sometimes hear the phrase that genetics accounts for maybe 10 percent of cases of Parkinson's disease where there's this direct causal link. What you're arguing is that this deeper understanding of all of the interplay between different genes really means that a deeper understanding of genetics furthers our understanding of the disease for everyone. Or put differently, genetics plays a role in Parkinson's disease for everyone. Is that right?

Yeah, I think that's true and I think you can think of this in two ways, and the two ways are complementary. We look at rare gene mutations and we study those in our labs because they're kind of easier to handle. They're easier to conceptualize and they're easier to model, but we still think that everything we find based on those mutations is generalizable to the typical disease. The kind of second part to this is that now we're beginning to understand that every single case of Parkinson's disease has a genetic component and every single case of Parkinson's disease probably has an environmental component. We're not really in this space anymore of is it genetics or is it environment? It's clearly both in everybody.

Well, let's drill a bit deeper then, and explore what we're beginning to learn in this complicated, interrelated interplay between genes and the environment and others. We've listed on this slide here some of the genes that are of the most interest to scientists like you and Roy Alcalay. Among them, the synuclein gene, SNCA, GBA, and LRRK2, which we've already referenced.

I believe so strongly in research and patient participation in research, and have been involved in research studies up until the time I was shown to have the LRRK2 gene mutation. But having found that out, it kind of doubled my commitment to get involved. We were just talking about how our understanding of
Parkinson's has deepened greatly by studying people who have a particular genetic disorder, and if I can help other people and help myself at the same time, I'm committed to doing that. So, finding out was a surprise. I didn't expect to find out I had the gene mutation I do, and I'm going to try and use that to everybody else's advantage.

Dave Iverson: 00:11:35 And we'll talk more about how people could get specifically involved in genetic research as we move forward. Let's take our next step and talk more about how gene mutations and genetics play a role in the development of disease. We'll walk people through in this particular slide, the way in which cells are the kind of recipes that ... Or use the recipes rather, that are in our genes to make proteins and the proteins then do many things. We list the variety of examples in that and then we mention that sometimes there are mutations that may cause a dysfunction in proteins which play a role in disease.

So Roy Alcalay, can you give us an example of what we're learning about that, that there's certain, perhaps, roles that genetics play in causing proteins to not behave the way we want them to behave in essence, and are involved in the disease process? In alpha-synuclein for example, how might that happen? We know that's that sticky protein that gets clumped together in Parkinson's. What's the connection between the genetics of that, the proteins that go bad and disease?

Roy Alcalay: 00:13:00 And you're asking specifically about alpha-synuclein?

Dave Iverson: 00:13:07 Well, by way of an example. You can take that though in whichever way you wish.

Roy Alcalay: 00:13:12 Sure. So, I think that when we look at how much we've learned about Parkinson's over decades of research, the two very important sources of information we have are the genetics, where really there's a huge influx of data in the last one or two decades. The other major source of information that helps us advance Parkinson's research is when people who passed away with Parkinson's donated their brains and we look at the brain under the microscope and the overwhelmingly most common change that you see in people with Parkinson's brains under the microscope is the position of the protein alpha-synuclein within the nerve cells, the neurons, in what we call Lewy bodies.

Now, this association has been known for many decades and we knew that Lewy bodies are the major finding in Parkinson's brains. It took a little bit longer to discover that the protein that is deposited in those Lewy bodies is alpha-synuclein. Then, to
support the notion that alpha-synuclein is important in Parkinson's, people discovered that mutations in alpha-synuclein increased the risk for Parkinson's. Now, even more interesting to help us with research, we found that if you have too much of the genetic information of alpha-synuclein, if you have duplication or triplication of the gene, your risk for Parkinson's is increased and it's probably higher and with a faster progression if you have three copies of the gene compared to two copies of the gene.

So, it's only logical, even though we're still trying to prove it, that maybe reducing the burden of alpha-synuclein or changing the metabolism of alpha-synuclein would either slow down or even prevent Parkinson's. So every time a gene or a mutation is diagnosed that is associated with Parkinson's disease risk, the next question is how can we work on that biological pathway to try to help people with Parkinson's? So with alpha-synuclein, which we hypothesized and it still hasn't been shown in humans in actual clinical trials, is that maybe reducing the alpha-synuclein burden will reduce Parkinson's rate of progression or maybe even in the future Parkinson's risk.

The most relevant more recently, a couple of clinical trials are starting to initiate, to activate the immune system, one's own immune system against alpha-synuclein exactly for that purpose of making the immune system get rid of the extra alpha-synuclein hoping that that would help slow down Parkinson's.

Dave Iverson: 00:16:06 And we'll talk more about where we are with some of those new exciting clinical trials in just a moment. But Andy Singleton, you were involved in much of that early research and so, I think this is also a time to make a key point perhaps, which is that even though there was the genetic mutation of the alpha-synuclein gene that caused too much alpha-synuclein therefore caused Parkinson's disease, we then subsequently learned as Dr. Alcalay was mentioning, that alpha-synuclein is involved in everyone who has Parkinson's Disease. So this makes this point that as we understand more and figure out maybe a genetic fix to alpha-synuclein, that's also a fix that might be more broadly applicable, right? The potential for these therapies is not just for those who carry the mutation, it's for really, we hope at least, much more broadly applicable to people generally living with Parkinson's disease.

Andy Singleton: 00:17:06 Yeah, I think that's very true. The finding of the synuclein mutation that was back in 1997 and I think that this really elegantly showed that you could look at these very, very rare families and gain genetic insights from them that were broadly
applicable to the typical disease. So we know now that carrying very kind of rare changes in synuclein can cause disease, but that carrying very, very common changes that 40 or 50 percent of the population carry impart risk for Parkinson's disease. So, synuclein by itself is a really nice example of this continuum of genetic risk and how indeed even looking at these rare families and these rare mutations tells us so much about typical Parkinson's disease.

Dave Iverson: 00:18:07 All right. So let's explore next the kind of mapping procedure that allows us to get from gene to protein to therapies, some of those exciting trials Dr. Alcalay was mentioning a moment ago. But before we do that, let me bring in, bring up an audience question because we're getting already a lot of questions about how people find out whether or not they carry a mutation. There are always lots of questions about this, about getting genetically tested, whether one should or should not and a lot of interest in that. So before we dig in to the material on this particular slide, Dr. Alcalay, as someone who's both a scientist and also a physician, what's your general response to people writing in now and saying, "How do I find out if I have a mutation? Should I find out if I have a mutation?"

Roy Alcalay: 00:19:01 I think it's a tricky question. I think that the best answer would be to think what are the implications of me finding out that I have a mutation? So, I would first divide the people who are asking to two major groups and that's the people who have Parkinson's and the people who do not have Parkinson's.

So for the people who have Parkinson's disease, the implications whether they have a mutation or not are not as significant because they have Parkinson's. So finding out if they have a gene that we know a mutation or a change in the gene that is linked to the risk, may help them understand why they developed Parkinson's and also may help them find out whether they're eligible for specific clinical trials. So if one is interested in clinical trials that would be a very actionable thing to do, to say, "Okay. Let's see if I have a gene that is linked to a clinical trial that I could participate in."

If one doesn't have such interests, then it's more of a question of intellectual curiosity and I suggest thinking about the implications before getting tested, where the implications are on one hand, one would get more information about why Parkinson's developed and how to engage in studies that are linked directly in, and that's the pros. And on the cons are what will you tell your family, your kids, your siblings, people that
may choose or not to choose to get tested if they have that information?

With regard to people who do not have Parkinson's disease, I think that it's a tricky question and its very personal. I thought that people who don't have the disease would probably not want to get tested and I found out that I'm wrong based on how many family members of my patients got tested through 23andMe or through The Michael J. Fox PPMI effort.

Roy Alcalay: 00:21:00 So I think it's again a personal question. It's a question whether people want to know or not want to know. Either way I suggest doing it in a system where you can get counseling and information ideally through a Parkinson center that can offer genetic counseling because many of these genes, if you carry them, if you carry a mutation in them, if you carry a certain variant it doesn't mean that one would develop Parkinson's, it just means that the Parkinson's risk is increased and you want to sit with someone that can guide you through it, it's a little bit, like carefully.

Dave Iverson: 00:21:34 I think that's a really important point, Anna, let's get your perspective on that. What motivated you to take a genetic test and what are some of the implications that you think people considering that ought to consider?

Anna Cohn Donnelly: 00:21:50 When I was diagnosed eight years ago I was shocked because I know nobody in my family, my extended family who has had Parkinson's and I almost couldn't even spell the word. And I think in some ways for a number of years I kind of thought maybe I didn't really have it. I had the symptoms and the medications helped but maybe I didn't really have Parkinson's. Just by way of background when The Michael J. Fox Foundation came out with Fox Insight I signed up for it right away and every three months I've been offering information on medication, symptoms, and how my disease is progressing or not progressing. It's been interesting to be involved in that. And one day about a year ago I found out that Fox Insight was now connected to 23andMe and I'd have an opportunity, very easy opportunity to get tested for the LRRK2 gene mutation, so I decided to do that.

It's really simple, you just spit into a test tube that they, somebody sends you in the mail and box, and you put it back in the box and send it away and a couple of weeks later you get a diagnosis. So, when it came in, as I mentioned earlier, as an actual LRRK2 gene mutation it was surprising but also assuring
to me that in fact I did have the disease, and maybe there's more I can do about it by helping others through research.

Dave Iverson: 00:22:57 And Anna what about the implications for family? Lori writes in right now, "Well, if you've learned you have the mutation but you have no signs of Parkinson's, what are my odds of getting the disease?" We can ask Dr. Alcalay and Dr. Singleton to answer that part, but I think there's often this concern about, well then what about my kids and all of that. How did you think through those layers of that question? Because as Dr. Alcalay was suggesting it's important to make sure you get good counseling in that process so you don't jump necessarily to wrong conclusions.

Anna Cohn Donnelly: 00:23:31 Yeah, well in my family because this was such a new thing, we talked about it at some length and my siblings, two of my three siblings, living siblings decided to get tested. One found out she carries the gene, one found out she doesn't. But I don't think any of us have an interest in having the next generation tested at this point.

Dave Iverson: 00:23:51 Thank you. And Dr. Alcalay will stay with us one more beat and then we'll return to the content on the slide here but Lori's additional question is, "If you carry the mutation, but you don't have signs of the disease what are your odds of actually getting Parkinson's?" You referenced that kind of 30 percent chance before but give us a little more nuance on that and perhaps even why that's the case? Why doesn't the mutation doesn't necessarily mean that you'll get a disease.

Roy Alcalay: 00:24:20 So, the risk for Parkinson's doesn't only vary between, among the genes that one may carry a variant on, it's also within the same gene. You can have one variant that would increase your risk by two-fold and another variant in the same gene that will increase your risk by ten-fold. So, it is really complicated, I think biologically. Now, on top of the biological complications that not all mutations or variants carry the same risk, we have the problem of the design of, how do we know how to estimate what's the risk of people with mutations to develop Parkinson's? So the only methodology that has been used so far widely, so people could replicate it, would be to ask people with Parkinson's about the Parkinson's in their parents. Assuming that if one, for example, carries the LRRK2 mutation, it means that at least one of their parents carried the LRRK2 mutation and based on the family history extrapolate what is the risk for Parkinson's, the lifetime risk for Parkinson's.
But this methodology is limited because some people may have passed away for other reasons before they reached the time for Parkinson's or maybe Parkinson's was misdiagnosed and it's the best we have, but it's not a great way of estimating. It's not the best idea, the ideal way would have been to have examined all the people and then say yes, the developed Parkinson's at this age or no they didn't. Based on the family history methodology in the Ashkenazi Jewish population we estimate the risk for Parkinson's in LRRK2 carriers is a little bit lower than 30 percent, and in the non-Ashkenazi Jewish population it's a little bit higher, it depends on the study. There were studies that showed 35 percent, but there were studies that showed 80 percent.

So, I don't think that the LRRK2 gene behaves very differently among different populations. I think it's a lot about study design and a lot about how much we know and how much we still do not know. With the GBA gene which is another gene that is relatively common, the gene that is linked to Gaucher, the risk is lower than the risk with LRRK2, but it's also debatable in the literature and the numbers that are given there are anywhere between 10 and 30 percent.

Dave Iverson: 00:26:38 So again a good example I think of why getting appropriate genetic counseling is critical to really get your arms around what these numbers mean, because I think it's sometimes easy to make wrong assumptions. Let's return to the content again on this particular slide and talk a little bit more about how we get from point A to point B and Andy Singleton as you look at this particular slide can you tell us more about the mapping process that you're going through from mutations that lead to proteins and then what goes wrong in that case.

Andy Singleton: 00:27:21 Yes, so in its most simplistic form and the way that most of our understandings come about so far, we're taking a single gene that we know contains mutations that cause disease. And we are attempting to understand, first of all, what the protein that's encoded by that gene does and then secondly, how the mutations change that action. Do they add something new? Do they change the way the protein normally functions? Do they cause it to aggregate? What role do they have? This is done using a whole host of methodologies. Looking at the protein in both its normal form and its mutated form within cells, modeling it in animal systems. Really all with the notion of trying to figure out, what's the problem? Where does this particular mutation exert an effect?
So, I guess a nice example of this, one that really relates to the development of therapeutics is LRRK2. So, mutations in LRRK2 were found back in 2004 and we knew immediately that LRRK2 was essentially a switch, a switch within the cell. LRRK2 stands for Leucine-rich repeat kinase 2 and a kinase is essentially a molecular switch. So the idea was that potentially if we could understand whether this switch was more active or less active than normal when the protein contained a mutation, we could develop therapeutics against that particular switch and indeed that's what's happened. We've shown as a field that the most common mutation in LRRK2, the G2019S mutation seems to increase this switch activity of LRRK2, seems to increase the kinase activity of LRRK2. So, there are a whole host of therapeutics under development which aim to kind of dampen down that activity.

So, I think that's one kind of simplistic way. You take the protein that's encoded by the gene that carries mutations and you try to understand what it does. I think the next kind of generation of understanding is based around trying to not go from one particular gene change to biological understanding, but going from the 40 or 50 or 60 different changes that we know are involved in human disease and trying to map them onto a single network. So that we can understand what those, how those biological processes all interact and trying to find a point to intervene within that biological network. So, really the idea being that the more information that we have, the more we can understand about the underlying biology.

Dave Iverson: 00:30:26 So, and Andy in a sense then, are these genetic changes and this mapping process that you're describing, are these specific windows into the disease? Is this a way, if you think of disease as being this kind of mysterious black box where it's hard to understand what's going on exactly. Is it genetics? Is it environment? What is it? This gives us a particular way of kind of targeting and understanding that process so we can drill down and perhaps find the solution?

Andy Singleton: 00:31:02 Yeah, I really like the analogy of the window. So, when we find a rare mutation it's like looking through the tiny corner of a window in a house and trying to understand the complete layout of that house. Where all the bedrooms are, where all the furniture is, all that kind of stuff. I think that, that has been incredibly beneficial, but the notion of expanding our genetic analysis means that we get to look through more windows and we get to better understand where things are and kind of put things together from multiple angles. So, I think that's a neat analogy.
And Dr. Alcalay does that also mean that those windows are not only a window into a particular house, I may be pushing this analogy too far, but into an entire neighborhood? You know, do you know what I mean? So that, are they this window of someone like Anna who carries the LRRK2 mutation, is that a window not only into her particular path toward disease, but is the supposition here that, that also gives us an understanding more generally of people living with Parkinson's?

Sure, I think the short answer is yes. The longer answer would go back to the point that Andy made earlier that a lot of those genes come up more than once in genetic studies. So the LRRK2 gene, for example, there are mutations in it that clearly increase the risk for Parkinson's to 30, 40, maybe 80 percent, but there's also signals in the LRRK2 gene in genetic studies that include people with non-familial Parkinson's disease or what you call idiopathic Parkinson's disease, which means that LRRK2 probably has a role in the biology of Parkinson's even in people who don't have the, what you call the pathogenic mutations in the gene. I think what a lot of us are trying to do in basic labs is to see whether manipulation of the LRRK2 biological pathway will affect not only people with LRRK2 mutations but may be helpful for the entire Parkinson's community.

And Dr. Alcalay could you just quickly give us a sense of where we are in our, we've mentioned that's there's some ongoing now clinical trials, to test drugs against some of these mutations off the synuclein, LRRK2 and GBA. Again, this is new, none of this would have been going on even just a few years ago. The LRRK2 and GBA trials have just gotten started. How far along are we in that process? Are we getting closer to understanding whether or not we can, as you were describing earlier in our webinar, a way to kind of reduce the impact of some of these proteins that have gone astray?

So I think what's been happening is that, in many cases and that includes alpha-synuclein as well, alpha-synuclein, LRRK2 and GBA two parallel approaches are taken. One is to try to understand better how a mutation in the gene, GBA or LRRK2, causes Parkinson's. And the other approach is a more practical, pragmatic approach that people who have been taking in [inaudible 00:34:36] and say, "Okay, we're not quite sure how LRRK2 is causing Parkinson's. Of course we need to explore that and understand the biological mechanisms. But in the interim we know that if LRRK2 works too much, Parkinson's may develop, so let's slow down the activity of LRRK2 in different ways." And with GBA it's exactly the opposite, we know that mutations that slow down the activity of the enzyme of the GBA
enzyme, increase the risk for Parkinson's, so let's work on this biological pathway to either increase the activity of the enzyme that is not working that well, or decrease the activity of enzymes that work to contrast the activity of GBA and let's see if that would reduce the risk for Parkinson's.

I think that the exciting news is that these studies have reached the point, and they're reaching out to populations of people who carry those mutations to start recruiting them into interventional studies. The LRRK2, I think is going to be starting soon. At least based on the information we receive through The Michael J Fox Foundation. And GBA, which is a little bit more, the GBA mutations if you inherit them from both mom and dad, one would develop the disease Gaucher and Gaucher disease has been studied for many, many decades and there is treatment for Gaucher disease, it just doesn't penetrate the brain. But because of biology of Gaucher, a little bit better because of the experience with Gaucher patients, the pharmaceuticals have been faster in Gaucher than they have been with LRRK2 and they think that actively now around the world there's at least three clinical trials recruiting people with GBA mutations into different drugs that may either enhance the activity of GBA or reduce the activity of competing enzymes.

Dave Iverson: 00:36:33 It's so exciting I think, to think that all of these clinical trials are now in motion and that we may soon learn a great deal more about their potential impact. Let's spend a little time talking about getting involved in research and then we'll start taking more of your questions, there are many that have come in and we'll return to those in a moment. We need people to participate in these trials who have certain genetic mutations, but we also need people who don't. You can participate regardless of whether you have them and these mutations, these studies rather, help us understand the connections that may lead to precision medicine drugs that could work for people regardless of whether you have that mutation. Excuse me again, sorry. Anna, I'll touch again on the last point you mentioned that you're participating in Fox Insight, I think people often wonder, well what's involved? What do I have to do? Describe for us your involvement with that and how complicated or not complicated that involvement actually is.

Anna Cohn Donnelly: 00:37:39 It's not that complicated, sign up for Fox Insight and literally on a monthly basis you'll get a notice that it's time to fill out your forms. And the same questions are asked each time and sometimes there are new questions that may relate to a particular piece of research or at the interest of some clinician working in the field. But basically the questions are to help you
track your symptoms, your medications, how you're living with Parkinson's and some related issues. The nice thing is you get to follow yourself over time, so you can go back and see where was I a year ago, where was I three years ago and see what a dynamic disease it is for each of us. And you can also compare yourself to others with the disease and see how complex and differently Parkinson's affects different people. It's hard not to fill out because you get a lot of reminders from Michael J. Fox if you haven't filled it out on time, so easy to do.

Dave Iverson: 00:38:32 It's true, I sometimes get those. This is your eleventh reminder to fill out a particular thing. But it isn't, as someone who participates in Fox Insight as well, it really isn't that complicated. Dr. Alcalay as a physician and researcher, can you also make the case from your point of view about why it's so crucial for people to participate.

Roy Alcalay: 00:38:54 Sure, so I think I would give you the example of answering also the question that was asked before about whether interventions that work on the LRRK2 pathway or the GBA pathway, will they be helpful for people without mutations? So, for example in studies that we're doing, but others are doing as well measuring the enzymatic activity of both LRRK2 and GBA, we measure that in people with Parkinson's and people without Parkinson's. And this helps us to tell, maybe a LRRK2 intervention or a GBA intervention will not be useful only to carriers, but also in the entire PD population. But it is possible that maybe within the Parkinson's population, even people without mutations are not one group. There are those with low LRRK2 activity that won't benefit from reducing LRRK2 activity, and those with high LRRK2 activity that would benefit from slowing down the activity even though they don't have a LRRK2 mutation.

So, for this we collect, funded by The Michael J. Fox Foundation, we collect urine samples and blood samples and send it to labs, really worldwide. For this specific project that I'm thinking we sent samples to Greece, Australia, Scotland, the United States and Canada. And people are trying to measure the activities or the products of these biological pathways to see whether we can identify who with Parkinson's may benefit from such intervention and who may not. And participating in such study, if you have a center that does that around you, is relatively easy because it's often one time visit or you commit to one time visit and then you decide whether you do more. And often what the researchers would ask for is a blood sample and a urine sample. So, even that one time contribution can go a long way and if you're willing to do more than one time contribution of a blood
sample or a urine sample, I'm sure that there's plenty of Michael J. Fox funded projects that would love to recruit you for them.

Dave Iverson: 00:41:03 And let's touch on one other aspect of participating in research that sometimes get raised as a concern, which is, excuse me again, people worry about whether or not there's privacy issues, worries about will this information get shared? If someone learns I have a mutation will that affect my employment? Will it affect my health insurance? I want to hear from both Anna and Andy Singleton on this, because it's something we've talked about. You and I have before, Anna as members of The Michael J. Fox's Foundations Patient Council. Give me your perspective on this first and then, Andy I know it's a question you're interested in studying and learning about too in terms of patient attitudes. But Anna first, what's your response to those who worry about that?

Anna Cohn Donnelly: 00:41:50 Yeah, you know it's a really interesting question, I have every confidence that in studies such as Fox Insight and even in 23andMe that information is kept confidential,

Anna Cohn Donnelly: 00:42:00 but the Patient Council had a really wonderful conversation about this, and I think almost everyone was in agreement that, let's say someone found out something about myself that I hadn't put into Fox Insight, if it lead to a better, quicker cure, I'm all in favor of it. I believe that everything is kept confidential but if it weren't, it wouldn't concern me. I think it would be helpful to get the information out there.

Dave Iverson: 00:42:27 Yeah, that was the consensus within our group at least. Andy Singleton, I know that you're interested in studying this question further because it's getting people to participate, getting this information is key to furthering our scientific understanding. But that's not to say that people might not have legitimate hesitations.

Andy Singleton: 00:42:46 Yeah, sure. I think that this is where informed consent works pretty well. As you take part in a research study, you have to go through an informed consent process. The idea of this process is to explain any risks associated with taking part in the study. Obviously, we all think about the risks of revealing things through genetic information, the risks for ourselves and the risks for our family members.

I can say that genetic studies are very, very tightly regulated. We have to store the data at a very secure space. There are limitations on what we can do with the data depending on what
we told the patients we would do with it. That is also balanced though, with a desire to want to share the data with other researchers as much as possible.

I think that gone are the days of a slightly eccentric scientist toiling away in a lab by himself making singular discoveries. We’re in a space now where really the great breakthroughs are made through massive international consortia who bring together massive amounts of data all toward the idea of trying to understand and cure disease.

We have to balance the security of the data, which we take very seriously, but also allow ourselves to be able to share data with other researchers who are also of course keeping the data secure within their own research units.

Dave Iverson: 00:44:33 By the way, I should also mention that we hope to launch within Fox Insight something that I know you've been engaged with, Andy Singleton, which is a survey of patient attitudes, so we get a better sense of what people feel about participating in genetic research in particular and ways in which we can make sure that those concerns are addressed.

Let's turn now to our questions that have been coming in over the course of our hour and take our final 15 minutes to address as many of those as we can. Here's a question from Norman that I'll give to you Andy Singleton which is, "Why the explosion of the disease in recent years? Is this from genetics?" In other words, we've seen some studies recently that project a doubling of the number of people with Parkinson's perhaps in the next 20 years. Does that have to do with genetics? Why is it that we bump into Parkinson's disease more and will be bumping into it more in the future.

Andy Singleton: 00:45:39 Well, I think that there are a couple of things to bear in mind here. First of all, we're doing a much better job diagnosing the disease so we see an apparent increase in the number of cases because we're just better at recognizing it. I think we're seeing it more in the public consciousness because of the great work that the Fox Foundation has done in publicizing this disease. I don't necessarily think that we're seeing an increase in the percentage of folks who will end up with Parkinson's disease. But of course our population is aging incredibly. With aging of the baby boomers, we're seeing a massive shift really in the age distribution of our population. We can expect to see, not necessarily an increase the percentage of folks who get the disease over a certain age, but an increase in the absolute number of folks with the disease.
I think that's worth underlying. We are an aging country and aging in particular in this country, but of course that extends beyond the borders of this country since Parkinson's is largely a disease associated with aging. So if we have more older people we're going to have more Parkinson's just as people continue to live longer.

A question that came in actually before the webinar that I'd like you to address, Dr. Alcalay. Are there examples from other diseases where a genetic discovery led to new therapies? My first thought I guess is cancer, right? We used to focus on cancer by location. You have breast cancer, you have lung cancer. Now there's much more of a precision approach and those are often genetically connected. Is that right? Can you describe examples from other diseases where genetic findings have lead to specific therapy?

There are multiple examples, I think. In Parkinson's we unfortunately are at a disadvantage. We cannot look into the Parkinson's brain under the microscope while people are alive. So we're always a step back behind the researchers that can do that. It's mostly the researchers that do studies of infectious diseases and of cancer. So in infectious diseases, the most common example of using genetics for treatment is HIV where you look at the virus genome to know which medications it would be sensitive to and which medications it will not be sensitive to.

In cancer, they're not genome-typing the person only the way we do. We are taking DNA from the blood to look at what we call the sematic DNA. People with cancer look at the DNA of one's cancer in order to tailor the treatment for the cancer itself.

The examples of using genetics to lead treatment is absolutely there for cancer and for infectious diseases. I think the most recent neurological example boosted the entire field and makes people very hopeful is treating what we call the genetic form of what we call Lou Gehrig's disease, the spinal muscular atrophy. A disease that affects babies and children where we know exactly what the genetic mutations are and intervening specifically on the genes or on the genetic pathway has led to two different competing treatments which were published in 2017 in the *New England Journal of Medicine* back to back of two different approaches. But they're both targeting the genes specifically. And that is very encouraging for us because it's a neurological condition. We are hopeful that we can learn from
their experience and try to implement some of their methodologies in Parkinson's as well.

Dave Iverson: 00:49:56 Dr. Alcalay, perhaps you could describe another example that you mentioned in our phone conversation that we all participated in before this webinar which is that there are also examples of where therapy is developed for a specific genetic version of a disease and then later on we learn that gene-specific therapy actually works on a broader population. I think you were talking particularly about a cholesterol drug. Could you briefly describe that example?

Roy Alcalay: 00:50:29 Sure, so that example even precedes our understanding of ... This happened even before the wealth of knowledge that we have about genetics nowadays. But when statins were first developed with the statin Lipitor, medications like Lipitor Statin, etc. they were first trialed and they were first targeting with a known familial history of high cholesterol. Their cholesterol was really, really high and these were people that were developing heart attacks and cardiovascular complications in their youth or in their 40s at the latest with a genetic disorder that is called Familial Hypercholesterolemia. These were the people that the statins were tried on first, the people that benefited from the beginning.

Now when we look at statins world, the percent of people with this type of genetic disorder who are using statins is really a fraction. It's an example to how a medication or treatment can be developed to treat small population but then once it works and you try it in much larger populations that may benefit from it. Statins are the most common universally prescribed medications. Similarly, it is very possible. We do not know that we will develop interventions or large GBA that initially will be trialed on people who have a higher chance of benefiting from the intervention, but then we'll realize that the entire Parkinson's population may benefit from it.

Dave Iverson: 00:52:14 And that would be a wonderful thing to hope for. And hopefully we'll have more about that soon. [inaudible 00:52:24] raised a very practical question that came in which is, "What should the children of a LRRK2 gene parent be told?" So if you're tested, you learn you have a LRRK2 mutation or one of these others, GBA. When do you talk about that with your children? Anna Cohn Donnelly, let's hear that from a patient perspective first and then Dr. Alcalay to you.

Anna Cohn Donnelly: 00:52:46 I think children need to know that their parents carry the LRRK2 gene mutation or any other mutation. I think when people are
old enough to absorb the information and especially request it, old enough to think through how they’re going to deal with it, then you might want to tell them. I don't know what specific age that would be. Older is better. An ability to decide that the information is important and an ability to understand how to use the information is also important.

Dave Iverson: 00:53:14 Dr. Alcalay, do you concur? Wait until someone's old enough, an adult to really talk about ...

Roy Alcalay: 00:53:20 When you say “children,” it's very wide ... we're all children. So there are a few of my Parkinson's patients in their 70s and 80s who discovered that they're LRRK2 carriers because their children got tested through 23andMe or clinical trials and the kids were in their 50s. I have had experience with both directions. What I advise people with Parkinson's who want to do genetic testing is, think what you'll do with your kids before you get the genetic results. If you choose not to tell them, that's completely fine. It's your genetic data. It's yours to share or not share. But just think about it before you get the results back. Because, on one hand we are talking about older kids. I don't think that people in their ... Kids that are considered kids, it's really not useful to share that information.

But when you get the genetic testing, you need to think okay, if I'm a carrier, will I tell or will I not tell. Don't wait for a positive result to start thinking about that question because some of my patients when they started thinking about that question they said, you know I'd rather not know because I don't want this elephant in the room.

On the other hand there are families again that found out that they are carriers through the children that got tested. In the case of Gaucher it's even more complicated. Gaucher testing is available through prenatal genetic testing. So everyone of us can have a Jewish ancestry but in many centers everyone almost gets prenatal genetic testing that includes the Gaucher gene. They may find out that they are at risk for Parkinson's in a completely random way that is unrelated to Parkinson’s research or to having Parkinson's in the family.

Dave Iverson: 00:55:06 I think everything you have both said underlines the earlier point, which is that it is important, if you are going to get tested, to make sure you get adequate genetic counseling. There's a lot of layers to this, a lot of important things to think through before you make the decision to get tested and/or share that information.
Related to that, here's a question from an individual. Andy, maybe you could take this. This individual says that he was tested genetically nine years ago when he was diagnosed with Parkinson's and didn't learn that he didn't have any mutations, probably LRRK2 or GBA, the ones that are most commonly tested. But he's wondering if he should get retested. In this explosion of genetic information that we were describing earlier. We used to think that there was just 10 now there are 80 different regions. Should you not think of a genetic test, Andy Singleton, as one-time only thing that you should do that again and again as our knowledge increases?

Andy Singleton: 00:56:13 So certainly our knowledge is increasing. I would say that nine years ago the LRRK2 and GBA variants were available for testing and those were probably tested. And those kind of are at the sweet spot of the most common and also confer a considerable amount of risk. All of the things that we've found since then essentially are extremely rare or confer only small amounts of risk individually. So there's not a lot that you can do usefully with that information from a patient perspective from kind of deciding about what you'd like to do.

From a research perspective, they're incredibly useful. So taking part in research, absolutely. I don't think I would recommend retesting though.

Dave Iverson: 00:57:10 And very briefly because we're reaching the end of our hour and I want to give Anna a last chance to comment on the importance of research, but clarify one other thing if you could, Andy, which is a question from Bruce which is, "Can you say a little bit more about the risk within the Jewish population or Parkinson's compared to the general population?" I assume this is a reference to the LRRK2 mutation, which is more common within the Ashkenazi Jewish population. Can you just review those numbers again one more time please?

Andy Singleton: 00:57:39 Yeah, you can put this in the context of how common mutations are in disease carriers. There are two mutations that are particularly common within the Ashkenazi Jewish population. One is in LRRK2 and the other is in GBA. Typically, when you look at a North American population, so not selected based on Ashkenazi Jewish ancestry, we see about 5 percent of Parkinson's disease cases are caused by a variance in those genes. When we look in an Ashkenazi Jewish population, it's much higher. It's close to 20 percent for both of the mutations. There is a more simple genetic component to Parkinson's disease in Ashkenazi Jewish cases than in non-Ashkenazi Jewish cases.
Okay, thank you. We have reached the end of hour. Before we conclude though, I'm going to ask my colleague and friend Anna Cohn Donnelly to make one more comment if you would, Anna, about participation in research and why you found that meaningful in your own experience and what you might encourage others to do.

In short, it's impossible to think about major discoveries in the ways of stopping, reversing, preventing Parkinson's without the participation of people with Parkinson's. We with Parkinson's are critical to advances in research. I would just encourage everybody to see if there's a way they can get engaged. And many of these studies really need people without Parkinson's as well. So I would encourage people who are concerned about the disease and don't even carry it to get engaged in research. And how? Go to Fox Trial Finder. That's one way to find a study going on in your neighborhood that you can maybe be eligible for.

Anna, thank you. Thanks for your participation in this webinar. I also want to thank Dr. Roy Alcalay and Dr. Andy Singleton for their participation in the webinar and of course for their work and the research that they're doing on behalf of all of us living with Parkinson's disease. So thanks. Thanks all three. I'm Dave Iverson. Thanks for joining us on today's webinar.

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