Dr. Brian Fiske: Hello everybody, and welcome to our Third Thursdays webinar. I am Dr. Brian Fiske, I'm senior vice president of research programs at The Michael J. Fox Foundation, and I'm going to be your moderator today. Is Parkinson's Disease inherited? So really until the late 1990s, if you asked that question, many scientists and doctors would have actually said no. But in 1997, scientists reported some of the first gene mutations in a number of Italian and Greek families with Parkinson's Disease, and after this point, this really led to a massive effort among researchers to find more of these genetic changes that could explain Parkinson's Disease around the world. That information is now a key driver of not really only our understanding of Parkinson's Disease, but it's actually the basis of probably what are some of the most promising new treatments in development for Parkinson's today. So today we're going to be talking about Parkinson's genetics.

So I'm going to start here first with a little bit of primer, because I think it's important for all of us to kind of get oriented again about what we're going to do. So I'll talk a little bit about what is a gene mutation in a moment. We're going to talk a little bit about what the risk of Parkinson's actually is when you carry one of these gene mutations. We're also going to talk a little bit about, and actually hear from a few individuals on our panel, who I'll introduce in a moment, hear a little bit about what it means to get tested for some of these genetic changes linked to Parkinson's Disease. And then importantly, here at the end, we're going to talk really about what I think is most exciting here is how this genetic information is actually leading to new therapy development for Parkinson's Disease. And finally, we're going to wrap up, we're going to talk a little bit about what's sort of the future of Parkinson's Disease genetics and some of the ways that even you can get involved as well. And then at the end, we'll actually have time for a Q&A, so we'll talk a little bit more about how you can submit your questions in a second.

Let me introduce our panelists. I'm thrilled to have you sitting here virtually with a number of really great people. We'll start over there on the left, and I'd like to introduce Ofer Nemirovsky. Ofer is a senior advisor actually at an investment firm in Boston. But importantly for me, and for others at the Michael J. Fox Foundation, he's actually a member of our board of directors. Ofer carries actually a mutation in a particular gene called GBA. And he's going to help us talk a little bit today about the impact that has had on his life as someone with Parkinson's Disease. Thanks for joining us Ofer.

Ofer Nemirovsky: Pleasure to be here. Thank you.

Dr. Brian Fiske: Next we have Reni Winter-Evans. Reni lives in Indiana. She's actually a social worker and timely for 2020 she's actually a COVID-19 contact tracer. Reni has an interesting story where she's learned about her sort of link to Parkinson's Disease through a particular mutation in a gene called LRRK2, and we'll get to talk a little bit more about her journey later on in the presentation today. But she's also a research ambassador for the foundation. She participates in a lot of

research studies and so she can talk a little bit more about that as well. Thanks for joining us today and sharing your story Reni.

Reni Winter-Evans: Thank you very much. It's great to be here.

Dr. Brian Fiske: And finally, I'm thrilled to also have Dr. Dr. Ignacio Mata, or Nacho as he likes to go by among his colleagues. Nacho's a geneticists at the Cleveland Clinic, and actually leads a really important effort called the Latin American Research Consortium on the Genetics of Parkinson's Disease. And he's going to actually be helping me talk through some of the complex aspects of genetics and sort of the genetics of Parkinson's Disease. Thanks for joining us today, Nacho.

Dr. Dr. Ignacio Mata: Thank you, Brian. Very excited to be here.

Dr. Brian Fiske: All right, so let's dive right in. So I think before we can really talk about the genetics of Parkinson's it's important that we sort of get everybody oriented and sort of what do we mean by genetics and genes and sort of this whole concept. And so some of you who maybe have joined past webinars have a little bit of knowledge of genetics, but there may be a few of you who've joined for the first time today, or maybe haven't taken a biology class in a number of years.

So let's start with a few basics right here. And when we talk about genetics, we're talking about genes and ultimately really we're talking about DNA. Now you've probably heard those letters before, DNA. DNA is really the chemical basis of heredity for life on earth. You can kind of think of it as the master cookbook that lives deep within the cells of our body. Actually, each of us carries a mixture of DNA inherited from our parents and our parents who inherited their DNA from their parents and so on and so forth, really all the way back to the beginnings of DNA based life on earth. Now, within those stretches of DNA are things we called genes and you can think of these genes, if DNA is sort of the cookbook, think of genes as really the recipes within the cookbook. And each gene provides the instructions that tell a cell in our body how to make a particular type of protein.

We'll talk a little bit more about why proteins matter later in the presentation today, but proteins really are the real labor force in our cells. They are the enzymes that break down our food, make energy to keep our cells working. They are the structures and sort of little engines that maintain the shape of our cells and help move cellular machinery around to where they need to be. They're the molecular telephone operators that communicate information within and between cells of the body. So they kind of do everything really. Now our cells read different genetic recipes within the DNA cookbook, therefore making specific proteins, this in turn gives each cell their particular role. So, some cells are heart cells, muscle cells, brain set cells, for example. Now in humans, believe it or not, we are about 99.9 percent genetically identical to each other, meaning that most of the proteins we make in our bodies, that most of the recipes our cells read are the same.

But it's that 0.1 percent difference, that is really enough to create the whole of a wide variety of traits and differences that make each of us so unique. Now, when it comes to disease, of course, sometimes those differences we see in the genes and the recipes, again for making proteins, we like to call them variants, gene variants, or sometimes we might call them mutations. These changes can actually create changes in the protein recipe itself, and that can ultimately alter how our cells function. And in some case, depending on how severe that change is, cause or increase risks for diseases like Parkinson's Disease. Now for Parkinson's, we've actually identified a fair number of genetic changes that we think are linked to either leading sort of causing Parkinson's in some cases, or at least increasing the risk for Parkinson's in others. And so we're going to be talking about that more here in a moment.

Let's actually dive into that. And for this, I'm actually going to have our panelist, Dr. Mata actually help us walk through this. Nacho, so you and I have talked about this before about kind of how complex the genetics of Parkinson's can be and especially when trying to explain it to the community, the Parkinson's community. I mean, one of the big questions I think we often get is kind of how genetic is Parkinson's Disease. For example, we know there are families that have this sort of clear evidence of a genetic cause, but then there's also genetic changes that may by themselves not contribute a whole lot of push towards disease, but maybe in aggregate can increase risk. So this gets really complicated I think, for a lot of people. So could you just walk us through a little bit more specifically what do we mean when we talk about how genetic Parkinson's Disease? And really what does that mean?

Dr. Ignacio Mata: Right. Well, I think as a geneticist, we always think about genetic diseases are something that is always inherited from parents to their kids and their kids to their own kids. So I think in that such a term, Parkinson's Disease would not be considered really a genetic disease per se, because there's very few cases where it is actually a genetic variant that you introduced very well, that actually causes the disease, and if you inherit it, you will develop the disease 100 percent of the times. In most cases, everything really genetic, genetic is really what defines us, it tells us what your color of your hair is, or your color of your eyes, and some even behavioral traits. So obviously genetics plays a very important role on any disease risk and in Parkinson's Disease, it's no much different. And being that it's such a complex disease and the brain being so complicated, I think, it shows you how many genes are involved and how again, how complex this disease is from a biology standpoint. On how many different players, and that's only the genetic part, but there's also an environmental part, right? So there's a huge combination of things that really have to happen in most cases for somebody to develop the disease.

Dr. Brian Fiske: Yeah. Thanks for that. And so I think one of the ways we like to think about it and the slide sort of prevents, or provides a little bit of that sort of concept is this sort of range of genetics again. And so we can think about those genes that are pretty rare, but carry a high risk if you have those particular changes versus those that are sort of lower risk but maybe an aggregate, and more frequent in

people, but maybe an aggregate can increase your risk. And could you talk a little bit more about that concept again? Because I think, again, that's such a powerful thing when we think about Parkinson's Disease genetics.

Dr. Ignacio Mata: Right. So exactly. So I think we need to differentiate those two things that I was trying to explain before. The ones that will be associated to familiar forums, which is very few and maybe even less than 5 percent of the patients are caused by one of these rare variants. Right? So you have to explain it maybe in lay terms. I always like to think about the genome as all these different buttons that the plane cockpit has, right? So if you run into, if you walk into a cockpit you see all these buttons. So our cells are kind of like that. It has all these different genes that needs to be turned on and turned off and really there are kind of two types of buttons. So there's buttons that are completely necessary for the plane to function well, right?

So for example, you can think about the button that turns on and off the engines. And if something goes wrong with that button, the plane won't fly or if it's flying, it might stop flying, which is it has a big effect. That's what we usually call in genetics, having a big effect or a huge impact on, in this case, a disease risk or, yeah, a disease risk. But there are other variants or other buttons on the plane where if something goes wrong it might get uncomfortable, but it's not enough to become a problem. Right? So you can think of, for example, the AC going off. And I think we all have been on a plane where the AC wasn't working or the heat was too hot. And I mean, it makes it uncomfortable, but in terms of genetics, those variants don't really cause the disease per se.

But if you start accumulating some of those, imagine that the AC is not working, but then they ran out of water and you're stuck in a flight from, I don't know, New York to Sydney so it's 13, 14 hours, now it becomes a problem. Right? So now people are dehydrating. So, I like to think about those sort of things as a different event that can have potentially some very low effects, but combined it can reach a much larger effect. So in this figure, I think we can see the same thing. So in the bottom, from left to right, we see how common these variants, these genetic changes are in the population. And when we say they're common, it could be more than 10 percent in the normal population. So we all carry some of these variants.

And on the left you have things that are really rare. So usually less than five or 1 percent in the normal, in the healthy population. And then on the left, we have the PD risk. So being on the bottom, very low risk and on the top, really high risk. So we can have three groups of variants. And you can see that some of the genes repeat themselves. So you see the LRRK2, which we're going to talk about later, this gene shows up in two categories. And that means that a different variant in the same gene can also have different effects. So in here we see that synuclein, which is a gene that I think everybody's familiar with, the SNCA gene that you can see in here. So variants in that gene are very rare in the normal population, but the effect is quite big.

In some cases it's almost guarantee that if you inherit this variant, you will develop the disease. Then in the middle, we have variants that are, they're not that rare. So, 5 percent of us carry one of these variants, but if you carry, you can still not develop the disease. So I think it's very important to keep that in mind. And there are papers where they show people in their 80s and 90s that are carriers of LRRK2 who don't develop the disease. So they're [inaudible 00:13:43]. And we still don't understand how or why some people will develop it or not. And again, I think it's the combination of maybe that variant with other variants, and then also some environmental triggers, which could be pesticides or living a very unhealthy lifestyle. So all those things, they all accumulate.

And then at the end we have the low risk. So you were mentioning there's about 90, at least 90 of these variants that have very little effect. So if you carry one or two or three, you probably won't develop the disease or it won't be the cause of your disease. But when you start accumulating and these are things that are common in the population, so it's very possible that we all carry two, three, four of this. So the more you carry and then also with the environment that triggers, as I mentioned, then that's how you end up developing the disease. I hope that makes it a little bit more clear.

Dr. Brian Fiske: No, I think that's great. And thanks for walking us through that. And I'm just sort of monitoring some of the questions that are coming through already. And as a reminder to folks, if you have a question, feel free to, I think the box in sort of center of your screen, feel free to submit a question. But one thing you mentioned that I think is important is that obviously carrying some of these genetic changes doesn't necessarily always mean you're going to get Parkinson's and there are probably a lot of reasons for that. And you alluded to some of them. Even.

Dr. Brian Fiske: Probably a lot of reasons for that, and you alluded to some of them. Even some of the, "more higher risk genes," don't always necessarily guarantee that you can get Parkinson's, and I think this is interesting, we can talk about this maybe later on when we talk about the future of genetics, but that there probably are a lot of factors, including other genes that in combination might actually protect you from Parkinson's even if you carry some of these genetic changes that are normally linked to having disease. So maybe we can talk about that more near the end of the call today, but I think that's another important point that you raised.

All right, so let's move on for time. So now that we have a grounding, at least, in the genetic basis of Parkinson's as it exists today, let's talk a little bit more with people who actually have gone through this journey of understanding the genetics that linked to Parkinson's and have gone through genetic testing.

So before we go to our panelists and maybe just a couple of quick points here, when you think about getting genetic testing, a lot of ways to think about this, and I think one of the most important things first is to ask yourself why do you want to get genetic testing? Not everybody necessarily wants to go through this

journey. It's important, when you think about these kinds of decisions, to obviously talk to your doctor. It's good to talk to a genetic counselor. Talk to your family members, make sure you understand, again, the reason for why you want to genetic testing.

But, once you do make that decision, there are different ways that you can go about getting genetic testing. You can obviously go directly through your doctor and actually have a genetic test ordered as you would any other medical test. There are also other ways you can both contribute your genetic information and doing so, learn more about your genetics as well, and there a number of different research studies out there. You can find some of these types of studies either through your local universities or we have a Fox Trial Finder effort. We also have actually a study that the Fox Foundation is involved in called Fox Insight that offers genetic testing as well, and you can go direct to consumer companies such as 23andMe, and get tested for firstly, some of the Parkinson's link gene mutations too.

And so there are a lot of different ways you can get involved. Not all of these options necessarily require you to actually know your genetics or learn your genetic status. So all you're interested in is just contributing your DNA to a genetic study, there are many studies out there, including studies led by, by Nacho and his colleagues where all you need to do is supply blood test and they'll do the genetics, and if you don't want to know your gene status, you don't have to learn it, but at least you're contributing also to our understanding of Parkinson's.

So, I'd like to stop here and I'd actually like to hear from two of our panelists, who've actually gone through this journey of getting genetically tested and learn a little bit more about the decisions they made and how it impacted their thoughts about Parkinson's disease. So, Ofer I thought actually would start with you and have you maybe tell us a little bit about your story. How you made the decision to get genetically tested and what that meant for you.

Ofer: Right. Well, in my case, it was an easy decision because my wife was pregnant with our first child, 22 years ago, and she just thought it'd be a good idea, and I agreed for both of us to get genetically tested and just to see what was potentially in store for our kid. And we found out that I had the Gaucher mutation. It was called the Gaucher mutation at that time, it subsequently was called a GBA mutation. And at that time I don't think there was any knowledge as a link to Parkinson's, and I just thought that I had dodged a bullet because if I had received an allele from both parents, then I would have probably had Gaucher disease. But since I only had it from one parent, I thought I dodged the bullet.

It was only later years, later on when I was diagnosed with Parkinson's that I discovered that there are genetic mutations that significantly increase your chances of getting Parkinson's, and one of those is the GBA mutation, which

increases your chances to somewhere between 5X to 10X, what you might be susceptible to in a normal population.

So it was a decision made in, with respect to where we were in our family life, but it came into play and the knowledge was helpful later.

Dr. Brian Fiske: Thanks [crosstalk 00:19:38].

Ofer: But if I had it to do over again, at this point, if I was diagnosed, I would want to get genetically tested, just because, I think more information is better. Some people, when they're about to have a kid don't want to know what gender the kid is. I would want to know, and in my case, I would want to know as much information as I can about my own body, and I think it's just helpful in general because I'm a numbers guy, and I think that if the more information you have in the more numbers you can crunch, the more data you can collect, and potentially the more therapeutics you can come up with down the road.

Dr. Brian Fiske: Thanks, Ofer. Reni, I know you have an interesting story and your journey, I think was a little different from Ofer's, and I wonder if you could walk us through that.

Reni: Sure, and thank you very much and Ofer, it's nice to finally hear your story. I've seen your picture on Michael J. Fox Foundation brochures and booklets and everything, and it's nice to meet you and hear your story. Yeah, for me, it's a much more recent journey. My father had Parkinson's [inaudible 00:20:51] very mild and he had other things going on, so it wasn't the most prevalent thing in our lives and forgot about it. And then I had started working in hospice, became a medical social worker, went back to school late, graduated in 2017 and started working as a hospice social worker in January of 2018, and one of my first patients had end-stage Parkinson's and most people don't get to that stage necessarily, but there she was. And I was looking for a way to help her be more comfortable. Talk to her sister about the possibility of therapy.

And her sister said, "Well, that won't work because she lost her sense of smell a long time ago." And I thought, "Well, Hmm, I lost my smell sense of smell about five years ago, hmm." And then I was remembering, "Well, let's see my father had Parkinson's disease," and started looking up some of the early symptoms and counted off about five of them that I had myself.

And so in February 23andMe was running a really sweet Valentine's Day, special on their ancestry and health spit kits, and so I suggested to my husband, "Hey, let's go do this." And so we did and got the results in April because mine had to be redone for some reason, and there I was with the LRRK2 mutation, but in the meantime, I had been doing a lot of other research and I saw that there was a mountain of risk factors that with the LRRK2, if you're Ashkenazi Jewish, it raises the risk factor up to 25 percent, and then a little corner of my paternal ancestry is North African Berber, and that raises it up to 41 percent. And then other risk

factors such as living on a farm, drinking well-water being neurochemical. And I thought, "Okay, I early Parkinson's going on, and I diagnosed myself before I went to a movement disorder specialist, and that's how it happened, and I was so glad to know.

Dr. Brian Fiske: Thanks so much. Obviously, a different story from Ofer's, but certainly very compelling, and the fact that you took such charge of your own knowledge about your genetics that really helped you then I think understand what was happening. So I think, again, a really powerful message.

So I'd love to talk to you both a little bit more maybe near the end of the call with some of the questions that we're getting about your experience, but let's move on and talk a little bit about what I think is some of the exciting advances we're making with this genetic information and actually developing new treatments.

So maybe before we dive into where things stand a couple of little points here. First of all, what does it mean, when we understand genetics of Parkinson's, how does that actually lead to our ability to make new therapies? So again, this brings us back to the first slide where I talked a little bit about what genes actually do in the body and how they are really the instructions for proteins in the cell. And again, when we see those changes in the gene recipe, that can actually alter how the protein works and functions in the cell and then cases of disease, if that function is impaired or altered in some significant way, it actually can potentially lead to disease.

And so when we think about the genetics of Parkinson's and, as we look at these various genes that have been linked, some of the ones we've already mentioned, LRRK2, GBA, there are mutations in a gene called alpha-synuclein, which again, is the instructions for making a protein called alpha-synuclein, and by understanding these genetic differences and how they impact those proteins, that's really opened up a whole world of understanding about what goes on in the cells of people with Parkinson's disease and how that ultimately leads to the changes that happen in their body that lead to the symptoms and progression of the disease.

And so when we think then about making drugs and treatments, what we're really thinking about is how can we target that altered biology that was caused by those genetic changes, and use that as a way to then try to fix that problem. So to restore that function of those proteins.

Now, there's an important point here. So we talk a lot about how the genetic changes can lead to these protein changes that then lead to disease, but by knowing that, knowing that these proteins working in the cells can actually lead to Parkinson's disease when they're genetically changed, that plants a flag in the ground for our understanding generally of Parkinson's, because then we could say, "Okay, well, if that genetic change caused that protein to work differently and lead to Parkinson's, maybe there are other factors that can target that same

protein mechanism and also lead to Parkinson's." Maybe it's an environmental toxin that comes in and messes up with that same protein or some other factor that comes in and messes up that same protein machinery.

So even though the genetic change is where we might start, ultimately that information we're learning about, what's happening in the cell can help us maybe Parkinson's disease, generally, even in people who don't carry those particular gene changes. And that really is the most powerful, I think, compelling importance of genetic understanding of Parkinson's is it really potentially paints the picture of what causes Parkinson's disease for everybody. And that's why it's so important to think about, these genetic studies and how they can lead ultimately to treatments that can potentially help everybody with the disease.

So let's actually look at what is happening today. So excitingly, we actually have a large number of clinical trials. So studies that are actually being tested in people with Parkinson's that are developing drugs that target the mechanisms we think underlie some of the genetic changes in Parkinson's and there's three genes in particular that people are most compelled by today.

We've mentioned these again, the LRRK2 gene again, which makes a protein called LRRK2, the GBA gene and the alpha-synuclein gene. And there are companies that are now making drugs that target the altered mechanisms that we think underlie these genetic differences and ultimately how they lead to Parkinson's disease that are in various stages of clinical development. We talk about the different stages of clinical development. You may hear the words phase one, phase two and also phase three. Those are just the different stages of clinical testing. Phase one is usually sort of early safety testing. Phase two is early efficacy testing and seeing if the drug is actually having a benefit. And then phase three is the ultimate test where we're actually looking to see if those drugs are actually having real benefit in a large number of people.

So for these three genes, we actually have a number of trials that are ongoing for the LRRK2 gene, for example, we have two companies Denali and Biogen that are both making drugs that target this mechanism and are testing those in people with Parkinson's now. We also have a lot of efforts looking at mechanisms, targeting GBA with companies like Sanofi Genzyme, other companies, EastGate Bio, another company called Lysosomal Therapeutics that are developing different approaches to targeting GBA.

Also, a company called Prevail Therapeutics that's developing a particular a unique gene therapy approach, a way of restoring the GBA protein function in people who carry this particular form of Parkinson's disease, and they have an active trial right now called the PROPEL trial that is ongoing and has a potentially promising approach for targeting this particular genetic mechanism.

We also see a lot of companies who are really targeting alpha-synuclein as a potential target for Parkinson's disease. And what's interesting about alpha-synuclein is even though it was originally linked to Parkinson's as a genetic

factor, there were mutations in the alpha-synuclein gene linked into a number of families in Parkinson's back in the late nineties. Again, this was sort of what...

Dr. Brian Fiske: ... Families and Parkinson's back in the late '90s. Again, this was a sort of watershed moment that opened the genetic discovery for Parkinson's disease 20 years ago. But what was found very soon after that genetic discovery was that clumps of the alpha-synuclein protein were found in the brains of pretty much everybody with Parkinson's. So this really opened up I think an important area of investigation to suggest that something about that clumping of that protein, alpha-synuclein, possibly in some cases induced because of this genetic mutation, but in other people who don't carry that mutation caused by some other factor, that that was sort of an underlying, maybe common, feature for pretty much everybody with Parkinson's disease. And so again, that's why you see so many drugs that are being developed already for alpha-synuclein as well.

And so again, we're super excited, certainly from that perspective of The Michael J. Fox Foundation, because we've supported so much work in trying to understand the biology of these genes and then helping to sort of move these therapies forward. And so to see them now in clinical testing in people is really a powerful and exciting sort of milestone for the field.

All right. So what's next for genetic research? Obviously we've uncovered a number of genes. We're learning more about the genetics and ultimately the biology of Parkinson's disease, but there's still a lot more to learn. And I wanted to touch on a few of these points and maybe go back to Nacho and talk a little bit about one I think important part of genetics, which is that a lot of the genetics in Parkinson's done to date has really been just in a subset of the population, sort of in particular European Caucasians. And a lot of the work that we're doing now is making sure that we understand more of the genetics in everybody with Parkinson's disease, and I wonder, Nacho, could you talk a little bit more about some of the work that you're doing in really trying to expand our understanding of Parkinson's really globally and sort of in a more diverse group of people with Parkinson's?

Dr. Ignacio Mata: Sure. And yeah, I just want to clarify that unfortunately it is not a Parkinson's field problem, it's all over across all diseases. There's been a huge underrepresentation of non-European populations. So it is a big issue, not only in Parkinson's disease, but in many other diseases. And the good thing is that we're working towards changing this, hopefully much faster than in other diseases, so we can set the example. But yeah, I think we already talked about some of the variants that have been identified as associated to Parkinson's disease. And the truth is that these studies that have been done with thousands and thousands of patients, I'm talking about almost 38,000 patients and over a million healthy controls, those studies include only individuals that are highly from a European ancestry background.

And there's many reasons why it is this has been done this way. But I think ultimately it's something we need to fix because not only we want to be able to

treat everybody with the best drugs that apply to their ethnic or their genetic makeup, but we also want to understand better the disease. And we believe that these populations that have not been studied could be the key to identifying new genes. And as you said, new genes mean new therapies, more understanding of the disease, so we can provide better care and more opportunities for people to hopefully be able to one day cure this disease. So we've been working on Latino-Americans. So Latinos are one of the populations that are very, very underrepresented, despite the fact that there's a lot of them. In the U.S. it is the fastest growing minority. So there's a lot of them in the U.S., and we need to be able to again provide equally good healthcare to them.

So about in 2006, we started working in Latino-America to try to get enough samples to be able to do these type of studies, right? Because unfortunately, as we mentioned, some of these genetic variants have very low effect. So that means that you need to have thousands and thousands of people to be able to even see them. So we're trying to gather this, and we've been working on this for about 14 years. We're now to the point where we have enough people to be able to do some of the same experiments, some of the same analyses that have been done in European populations, and we're seeing some really interesting things. They have the same amount of Parkinson's in Latinos in general compared to white Europeans. However, a lot of the mutations, for example the LRRK2 variants. They're quite rare in populations in Latin America that have low European ancestry. Those mutations came from we think the Middle East, and they're more common in Europe, North Africa. And in Latin America, not as much, which was surprising.

And in GBA, we see that there are mutations or variants that are specific to different populations. In Colombia there is one that affects about 5 percent of the patients with Parkinson's disease that we've only seen it in Columbia. So it's a very population-specific variance. So all this information really helps us to again provide better care and understand better the disease. And we have many families that we're following that don't have any variants in any of the known genes, so I think this is telling us that there are other things that we can find. So this is obviously very important. And the good thing is that now foundations like the Michael J. Fox Foundation and also the NIH, are very invested on trying to develop this.

They understand the importance of studying other populations, so now we have some funding. So because of this funding, we in Latin America, but also people in Africa, in Southeast Asia, in India. So populations that are very, very big in the world that have not been studied are now being recruited into some of these genetic studies, again to try to understand if there are differences with other populations, and if there are new genes that we can identify and that we can use for again potential therapies. I think this work is very important, and I participate in many global approaches to be able to do this.

And I think that aligning science across Parkinson's is providing the resources that we need to be able to do this. Our goal is to study about 150,000 new

individuals that have not been studied previously, and we want about a third of those to be from underrepresented populations. So we really want to capture people that again have not been represented in genetic studies before, so we can determine what the causes are, what the risk factors. And this will also allow us to understand better I think the environmental factors because different cultures have different lifestyles and they do things differently, so that means that we can learn a lot from studying these populations.

Dr. Brian Fiske: Thanks, Nacho. At the Foundation, one of my hats I get to wear is I lead a number of the funded genetic efforts that we do. And it's been always so fascinating to me as a scientist for sure, but also very sort of thrilling to be able to work with so many really smart people out there doing such great work on the genetics of Parkinson's. So obviously, we continue to need to understand more genetics of Parkinson's. We certainly have made a good start, but there's a lot more we can learn. And really for us to be able to do that, to really be able to understand fully the genetics of Parkinson's, we need people to be able to sort of raise their hand and get involved in research studies and efforts linked to Parkinson's genetics.

And I'd love to have maybe Reni and Ofer kind of step in again and talk a little bit more about the ways they've gotten involved in research specifically and maybe some of the studies that they've participated in, if they're willing to talk more about that. Reni, can you talk a little bit more about some of the research participation you've been a part of?

Reni: Absolutely. It's one of my favorite topics. So as my picture shows, my coping mechanism I guess is to fight back against Parkinson's Disease to try to help prevent it, cure it, treat it in ways that have never happened before. And the research that's going on, that is the whole goal. And having the mutation and seeing that it was very sought after in research studies, I thought, "Okay, this is something I can do to fight back." And so I started that summer that I found out about the variant, I started scouring for research studies that I could participate in. And the first one was the Parkinson's Progression Markers Initiative, which is a multifaceted global effort to track the progression over a period of years.

And so every six months I go to Cleveland Clinic, and one day want to meet Nacho there, and offer basically just various kinds of testing and blood and optional spinal fluids and let them use it for their purposes, and that's every six months. I participate in only observational studies, nothing that involves any kind of medication or treatment, but just observational, but about 15. And I've gone to New York City and other places to be able to participate because it's something I can do to fight this disease, and I'm making a lot of new friends.

Dr. Brian Fiske: Thanks so much. Ofer, I know you've participated in research too, including I think some treatment trials. And I wonder if you would be willing to talk a little bit more about some of the ways you've gotten involved?

Ofer: Sure. When I was first diagnosed, I went on the website at Fox Foundation and looked at Fox Trial Finder, looking to see if there was a clinical trial I could become involved with. But when I realized I had a mutation, I wanted to go on a trial that was specific to that mutation, which I thought might have more of a chance of being effective in my case. And just around that time, Genzyme-Sanofi came up with the first clinical trial related to a specific mutation to GBA. So I've been participating in that trial now for a couple of years, and we'll see how it works out. But I've also been trying to encourage anybody who has Parkinson's to get genetically tested because as I was saying earlier I think the data is very helpful. The more data we have, the better.

If you have 1,000 people who have the GBA mutation and 100 of them develop Parkinson's, then you do an analysis and you find out that the 100 only got five hours of sleep every day and the 900 always ate an avocado every morning. That would be very simple and easy to say, "Okay, you should eat an avocado and get a lot of sleep," but it isn't that clear. But if you get enough people who have the mutation and some of them have the disease and you can analyze the differences between the people who have the mutation and don't get the disease, maybe you can come up with an understanding of what a resilience gene or a protective gene might be. So it's not only important from my perspective to have Parkinson's patients get genetically tested, but also to have their close relatives get tested because chances are some of those close relatives have the same mutation, but don't have the disease. So if you can identify what resilience genes or protective genes the relatives have, those could be good therapeutic targets down the road.

Dr. Brian Fiske: Thanks, Ofer. All right, so we are coming up now I think on the opportunity to talk a little bit more with all of you who are listening in and answering some of your questions. So I've been seeing a sort of a stream of questions coming my way. So I'm going to do my best to-

Reni: I'd like to say at this point that [inaudible 00:42:53].

Dr. Brian Fiske: Sorry? Reni, was that you?

Reni: Yes. I just wanted to jump in and add one thing that a lot of times we forget to mention, I think all of us. And that is the need for healthy controls to participate as well because, like Ofer, I focus on studies that need the mutation that I have, but also people who don't have anything geared towards Parkinson's. So I volunteered, or voluntold, my husband that he needed to participate also as a healthy control. We need family members who maybe aren't connected or friends to also participate as well. So I just wanted to toss that in.

Dr. Brian Fiske: Got it. It's super, super important, I agree. And for many of us who don't have Parkinson's ourselves, but have friends or family who are impacted by the disease, it's a very powerful and an easy way to get involved, is to get involved as a control participant in some of these studies. And there are lots of ways to do that. Again, we have on Fox Insight, a large online study where we also can

as controls participate information to that study. So I 100 percent agree, and thanks for calling that out.

So we're going to move on to some questions from everybody. And as I said, I've been kind of monitoring the question feed, so I'm going to try to answer as many as I can. I may group some questions together that are sort of touching on similar topics. And one sort of set of questions that I see a number of people asking essentially the same question in different ways, and this one I'm going to send to you, Nacho. A lot of questions just kind of about different family patterns I guess is the way I would call it of Parkinson's disease. Both parents have the disease, what does this mean for my risk? Does it skip-

Dr. Brian Fiske: ... Have the disease. What does this mean for my risk? Does it skip generations? An uncle had it, things like that. And I felt maybe, could you talk a little bit more about when you look at a family where there's Parkinson's Disease, as a geneticist, what are you looking for? When you see something, what does that tell you and how do you approach that in thinking about looking for then a potential gene that might be linked to Parkinson's?

Dr. Ignacio Mata: Yeah, so that's a very good question. And actually, because we wanted to keep it short and not very complicated. I didn't really get into the details, but yeah, these genes that we were talking about, some of them are inherited in a different pattern.

So for some of them, having only one variant, either inherited from the mother or from the father, it's enough to either increase the risk in the case of GBA, for example, or cause a disease in the case of synuclein for example. But others, you actually need to inherit two. So you have to come one from the mom and one from the dad. And the first type is called dominance and then the second type is called recessive.

So, when we looked at a family, we always tried to consider both options. Right. So sometimes you will see, for example, that both parents are healthy, but then they have a kid that might have Parkinson's disease. Those usually are recessive. And usually the kid will have the disease early with an early onset. These recessive genes, most of them cause a early onset of Parkinson's Disease. So the younger it is usually the more we think about this recessive or these forms where you have to get two different variants.

So yeah, when we looked at our family, we always tried to look that first, second degree relatives that are affected in the family. They're obviously the more number of people affected in the family usually will be raised as a suspicion of being a genetic cause. But you always have to remember that families also share environments. So for example, if you have a family that lives in a farm, they're all exposed to pesticides.

So, just because there a family history doesn't mean that it's always a genetic, but it also raise a flag. Right. We always want to study those families. But yeah, I think it's very important to remember that these variants are inherited in very different ways and it has different effects. So, it's complicated. That's why we have to go to school for so long to try to understand all this mechanisms and all this biology behind it. Right.

But yeah. In a simple way, again, we look for what we call family aggregation. So many different people in different generations are affected with the disease, with similar symptoms, similar age of onset. I always raise the flag that it could be genetic, but we cannot forget that there are other causes, like the environment, that could have a huge impact as well.

Dr. Brian Fiske: That's actually a really important point too. And goes back to, I think, a conversation we started earlier in the presentation today about this idea that there are other factors that obviously can influence if and when, and whether a gene change might actually lead to Parkinson's.

Or in some cases, and this was one of the questions that popped up in the feed as well, just how that Parkinson's Disease actually looks in response to particular gene change. And the fact that even people who might carry the same genetic change, don't always have the same flavor of Parkinson's Disease.

And I wonder if you could talk a little bit more about this idea of modifying factors. The other kinds of factors that, again, could influence if and how a Parkinson's gene change might actually show up and show itself in an individual.

Dr. Ignacio Mata: Right. Yeah, so that's something, for example, that in the earlier stages of genetic studies, it blew our minds off because when you see a family, you always expect the family to be very similar. Since if it's genetic, you think, well, they all have the same variants. So they would probably suffer a very similar disease.

And not only in the symptoms but sometimes even in their brains, the brains in the LRRK2, in some of their families were very different. They have different things. Most of them have synuclein, but some of them have other proteins that aggregate. And as a researcher, that blows your mind.

And I think it really brought up right from the get go, that there were other things in there that would definitely play a role. Not only in the risks, but also in how developed the disease. And, for example, we know that different genetic forms of the disease have different prognosis. They have different ways that the disease will present, different symptoms that are more common in one versus another.

And I think other, raise a very good point, which is that we need a lot of individuals from all these different categories, from all these different genetic

forms of the disease, to be able to see some of this and understand how that happens. But yeah, I think with the LRRK2, I think is a very good example. Because I think I mentioned before that there are people in their 80s or 90s, they have a mutation that, in most people, will cause the disease. And these people are completely healthy and have no one single symptom of Parkinson's Disease with the same genetic variant.

So there's obviously other genes that play a role, I think. And I'm certain that there's also environmental factors, most of them that we don't really understand yet. And again, I think including these carriers both affected and non-affected from some of these genes will help us determine what do they do different?

Could it be just exercise or could it be in the diet or is it something more fundamental in the biology of these individuals? So, more of a genetic component that is modifying this effect of the same single variant. Because at the end of the day, it's the same single variant. And actually, in Alzheimer's they've shown that the genetic composition, so the ethnicity of the person for the same variant, could actually modify. So that's telling us that there's other genes around the same variant that could be playing a big role.

And they've seen that with APOE4, which is a risk factor for Alzheimer's. That if you have that variant in an African ancestry, so somebody that is from a African origin, the risk for the same variant, is actually lower than if you have it in a European background. So, again, they're different factors. A lot of them could be genetic that we don't really understand.

And I have the feeling that for us and for synuclein, it might be the same. And I don't want to blow our results yet, but some of the studies that we're doing in Latin America suggests that it could be true for Parkinson's as well.

So, I think we need to do more studies and I think, yeah, getting people tested and getting people classified in the right type of Parkinson's, either GBA or LRRK2 or synuclein, will really allow us to do these more stratified or grouped analysis that we will understand. And then they'll help us understand what all these factors are. And I think also getting controls and both carriers or non-carriers, are also very important obviously, to be able to answer this question.

Dr. Brian Fiske: Yeah, no. Thanks for that. And really important. I know some of the studies I've been fortunate to be able to fund through The Michael J. Fox Foundation have included some efforts to look at, and particularly for the LRRK2 gene, some of the types of modifying factors, genetic and otherwise, that could potentially be influencing whether someone who carries that mutation, ultimately gets Parkinson's or not.

And it's complex for sure. There's a lot of information we still don't know. And a lot of it comes down to what you said. We need more samples from more

people to really, I think, tease these questions apart. But clearly we think there's something else involved. It's not just a simple single gene leads to Parkinson's and that's the story. There's a lot more to this story as well.

And I'm going to use this maybe as a launching off point, because again, I want to go back to [Offer and Reeny 00:53:31]. And when you think about modifying factors, obviously there are the things that we hope that drug companies will be able to do, new treatments they'll be able to develop to offer people who carry these genetic forms of Parkinson's and ultimately everybody with Parkinson's. But there are things that we can do ourselves as individuals. And we don't necessarily need our doctors to tell us this. Eating better, getting more exercise, things like that.

And I wondered if the two of you could talk a little bit about, when you found out your gene status, was there anything that that caused you to think about doing differently in your lives that maybe helped influence a little bit about how you live your life today? And Reni, maybe I'll start with you.

Reni Winter-Evans: Okay. Thank you. Yes. In doing all of that research, I learned that there had been studies that showed that intense exercise regularly, almost daily basis, if not daily, actually has been shown to slow the progression. And so, I was already doing aquasize and intensified that.

Also, more recent research is being done on inflammation, and Warf-2 specifically. And I had been increasing anti-inflammatory nutrition because of trying to fight osteoporosis, which I've successfully reversed that, and don't have it anymore just through diet and exercise.

But in the meantime, some of my Parkinson's symptoms started to subside in the last six months as I intensified the exercise and the anti-inflammatory nutrition. I didn't know about it scientifically. So I don't know which has more of an effect, but it's working and I have maybe 50 percent of my sense of smell back and some of my arm swing.

And so, I'm thinking, "Okay, I'm going the right direction. And rock steady [inaudible 00:00:55:47]." Yeah. It all is a part of it. It's important to be in control and not expect your doctor or a pill to fix things, but to take charge of your own health. So that's what I've been doing and that's working.

Dr. Brian Fiske: Thanks. Thanks so much for that. Offer, anything you've been doing that altered the way you live your life after learning your status?

Ofer: Reni, I need to talk to you separately. If there's something that regains 50 percent of your smell, that's fantastic. In my case, I mean, I think that we all know what we should be doing in general. Eat well, sleep well, exercise, keep your stress low, but this really just drove home for me that I need to focus on that even more than I've had before. And particularly actually in the variety.

So, I try to confuse my body and do something different every day. So whether it's strength training, or cardio, dancing, boxing, swimming, just to try to keep things different and test every part of my body. That's really what I try to focus on. And if nothing else, it just is good for you in general, even if it doesn't necessarily slow the progression, but I like to think that it does. And there have been many studies that show that it does.

The other thing, for me, and this is, I guess, more of a psychological part of it, is it's motivated me to live more in the present. Instead of thinking or wondering where I'll be in 10 years or 15 years, I really try to focus on where I am now and enjoying it and enjoying my friends and my family.

Dr. Brian Fiske: Thanks so much Ofer. So we are coming to the end of our hour. So I'm going to stop the Q&A now. A couple of things. First of all, thank you everyone for being part of our community and for joining us today. And a big thanks to our panelists for sharing all their information and insight today.

So we'll be sending a link after this call. We'll be sending a link to the webinar so you can watch it on demand if you'd like to rewatch it and re-listen and if you missed a few parts and want to listen to it again. I know there were a few questions in the feed about the role of environmental factors and Parkinson's Disease. We actually have some prior webinars that have touched on that topic. So you can find those in our on demand list as well.

Please do mark your calendar for our next third Thursday webinar, which will be on October 15th. And I'm excited to say our favorite moderator, Dave Iverson, will actually be making a special appearance to bring us an important episode going into the election that's coming up in November.

We'll be discussing Parkinson's policy priorities and the power of the government and making decisions that impact people with Parkinson's and their loved ones. And so we really hope you'll be able to tune into that webinar. So with that, we're going to end the call. And again, thank you everybody for listening.