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Speaker 2: Navigating Parkinson's disease can be challenging, but we are here to help. Welcome to The Michael J. Fox Foundation podcast. Tune in as we discuss what you should know today about Parkinson's research, living well with the disease, and the Foundation's mission to speed a cure. Free resources like this podcast are always available at michaeljfox.org.

David Kumbroch: Welcome to the Parkinson's Science POV podcast. This podcast is a resource for people with Parkinson's, their loved ones, as well as researchers studying neurodegenerative diseases. I'm David Kumbroch. I'm a senior science writer here at The Michael J. Fox Foundation, and this episode is brought to you with support from Prevail Therapeutics.

Today, we're joined by Dr. Brian Fiske and Dr. Thomas Gasser. Dr. Fisk is a chief scientist here at The Michael J. Fox Foundation and a Parkinson's Science POV series regular guest, so you may recognize him, and Dr. Gasser is a clinician and neuroscientist working in a university hospital in Germany. Today, we're going to dive into the links between Parkinson's and genetics in an almost literal way, starting at the surface of what these links mean and then getting deeper into the science of what genetic research is teaching us about Parkinson's.

Genetics is the study of the human genome, which is essentially the code that people are built out of. The human genome boils down to just four letters, and a single person's genome contains roughly 3 billion pairs of these letters. Genetically, you can take any two people on Earth, and their quote unquote, "genetic code" is roughly 99% the same, but the small differences in code can lead to different experiences and outcomes. Researchers have found that some forms of Parkinson's disease can be linked to what we call variants or mutations of important genes, and that's where I want to start the conversation today. So first off, Thomas, thank you so much for joining us, and I was hoping you would start by talking a little bit about how genetic mutations are linked to Parkinson's disease.

Dr. Thomas Gasser: Thanks for the introduction and thanks for having me in this conversation. So it's very interesting that about 25 years ago or so, most people would have said, "Well, Parkinson's is a purely environmental disease. It's caused by some toxins and it doesn't have to do anything with the genetic makeup of the patient or the person with Parkinson's." And this has greatly changed, and today, I think most people would be convinced that some form of genetic composition is important for each and every single Parkinson patient, but the composition of this genetic contribution differs from person to person. Some have a very strong genetic component to their disease, some have a weaker genetic component to their disease, but I don't think that there's anybody who doesn't have any component of genes that influence disease onset, disease risk and disease course.

And I think that has been a major change in our perception over the past 20 or 25 years, and it's very important because it leads the way to a more causal

understanding of the disease, which in turn leads the way to a more profound treatment, because it's not just about treating the symptoms and ameliorating the symptoms of the disease, but it's really at going down to the causes and changing the course of the disease, stopping the progression of the disease, maybe preventing the disease altogether. So that's why this change of attitude and perspective is so important.

David Kumbroch: That's interesting. Brian, do you want to add on to that?

Dr. Brian Fiske: Yeah. No, I think it's such a great powerful way to think about genetics, that again, it's really a spectrum, that you do have these see no single gene forms of Parkinson's where a mutation maybe in a particular gene can have a powerful effect, like you said, Thomas, in driving risk for Parkinson's disease. But then there are also people, maybe as you said, maybe everybody with Parkinson's exhibits smaller sets of gene changes that might in combination work to drive risk for Parkinson's. And so I think that concept, I think people tend to think in the community that, oh, I have this one genetic change and that's related to my Parkinson's. But I think this concept that it's more complex than that I think is really important to understand and why I think studying genetics of Parkinson's has been so important and powerful in driving our understanding of the disease. That it's those multiple genes maybe working together that might actually contribute to a larger percentage of the cases of the disease.

David Kumbroch: It's interesting, I think to further explore that, Thomas, I was hoping you would be able to clarify a little bit about the difference between association and cause in genetics, because I think that that difference is a really important nuance that maybe not everybody who's just getting into genetics understand.

Dr. Thomas Gasser: Okay. So now generally in medicine, it's of course very important to understand the difference between association and cause, and in most cases, this is actually very difficult. Now, in the case of genetics, there is at least one fixed point that we can be sure that it's true, that there is always one line of causation that goes from a genetic variant or the genetic code to the gene product and never the other way around. So it's not that the environment or the cellular composition changes the code of our genome. It's always that the code of our genome is determining what's happening downstream in terms of protein production, protein distribution in the cells, it's all basically masterminded by the genetic code. So that is important, and that's why when we say a genetic association, we do imply that this is a causative connection.

So if we have a gene variant that's associated with Parkinson's disease, it means that it increases the risk for Parkinson's disease. Or let's say initially, we say we look at two groups - a group of patient with Parkinson's and a group of healthy controls - and the variant is more common in the patient group than in the controls. Now, in many other associations, you would say, "Well, you don't really know if there is a causative connection," but in genetics, it means that the variant that you have inherited from your father or your mother is in your cells, and this determines the product of the gene in the cell and how it is metabolized and how it is produced, and this again is associated with the frequency and the course of the disease, but that's a causal connection. There is a difference between

causation and association, but in the terms of genetics, it always goes one way. It always goes from the gene to the gene product, and then to the phenotype to the disease.

Dr. Brian Fiske: It's an interesting geneticist definition I think of cause and association being in some ways more of an exact definition. I think as a biologist, I tend to think of cause and an association in more of a biological context, and it's a little bit different because for me, if you mess with X, you get Y, and so you can follow that usually in biology experiments, at least in the context of the laboratory types of experiments we can do today. You can actually see that cause and effect. I think in genetics, I think there's a more defined way of thinking about it. Again, you're looking, as you said, at families or a population of people and you're not necessarily... We're getting better at it of course, being able to follow people over time with genetic changes to see if they eventually get Parkinson's, and of course that is the ultimate cause-effect type of study.

But in many cases, you're doing, as you said, an association, looking at people with Parkinson's and people without, seeing what the genetic changes are in the people with Parkinson's, and using statistics basically to create that cause and association type of concept. But it's an important part of how we think about the role that these genes really play.

David Kumbroch: I want to make sure we capture that complication there of how many different factors are at play, both genetically and non-genetically. So Brian, could you elaborate a little bit about what we know about the mix of factors that contribute to PD, both genetically and outside?

Dr. Brian Fiske: Yeah, and there's a concept that I've always heard that people use, this idea of heritability, which is in many ways more of a statistical, I think, concept so it's hard to get into the specifics here perhaps. But this idea that estimates of Parkinson's being about having about 30% heritability, and that being driven by a variety of different ways and people can calculate that number. But that concept that not all of Parkinson's, if it was purely totally, fully a hundred percent genetics, obviously then heritability would be a hundred percent, but it's not, so what does that actually mean? And I think this gets a little bit at some of the things we talked about where there are a lot of smaller effect genes simmering in the genome perhaps that are working in combination to increase risk, and some of those we maybe can't see yet and so maybe that 30% is a lower and a lower limit of the number.

But it also, I think rightfully, implies that there may be other factors out there in environment, lifestyle, simple aging, the randomness of biology that could be driving risk for Parkinson's as well. So I think it is definitely a combination probably of factors with one end being particularly robustly genetic, where you definitely can see fairly strong association of having a certain mutation and you having Parkinson's disease or eventually getting Parkinson's, and then there's the other extreme which is I think a little bit harder to define.

Dr. Thomas Gasser: There may be one thing that is important. So if you're talking about a 30% heritability, we are basically describing a group phenomenon, that maybe that

doesn't really imply necessarily to each individual patient but to a group of patients. And each individual has both components, has inherited genetic components and has non-genetic components, and as you say, Brian, actually there is a lot more now popping up in terms of specific environmental aspects. So Parkinson's disease has just recently in Germany been accepted as a disease that is at least in part caused by environmental toxins used in agriculture, and in France, it has been thought for a longer time already. And so for each individual, that the specific composition changes, but on average, I think we can say, and we are pretty far and pretty sure about that, it's about a 30% total heritability.

David Kumbroch: Thomas, would you mind just defining heritability for us?

Dr. Thomas Gasser: It is just another word for the genetic component. So you inherit a wide variety of genetic variants from a hypothetical standard human genome sequence, and the contribution to the disease risk by that total mixture of stronger and weaker effects from the genome, that would be called heritability.

David Kumbroch: Thank you. I'd like to drill down on that a little bit. Let's say you've got someone in your family with Parkinson's, a parent, a grandparent or maybe even both. How do you think about your personal risk from that perspective of, well, this runs in my family and so genetically it's being passed down, but then what does that mean for me specifically?

Dr. Thomas Gasser: So there are actually studies, and this is a method where epidemiology gives the answer. So if you look at a thousand individuals with Parkinson's and then you look at the next generation and count the numbers of individuals who also develop Parkinson's disease and compare it to a group of individuals that have no family history and there's nobody else in the family who has a disease, that will result in an increase of risk, no matter of not regarding any specific genes, an increase of risk of about twofold or two and a half fold or so. Now that is significant if you look at a large number of individuals. For an individual person, that's actually not that important because the overall lifetime risk to develop Parkinson's disease is one or 2%, so an increase by a factor of two would mean it's about two to 4% the overall increase.

Now, if I look at my own history that's in front of me when I get older and older, that's nothing that really worries me too much, if I have one or a 2% risk to develop Parkinson's disease. I can have a risk to develop a stroke, to develop tumors. All kinds of things can happen to me when I age, and so that doesn't really give me such a headache. On the other hand, if you have a stronger family history that really suggests let's say an autosomal dominant or an autosomal recessive Mendelian format. Now, there are a lot of technical terms. So dominant means it's caused by a variant, a genetic variant that is passed on from generation to generation, and only one variant, because you have a mixture of information coming from both parents and only one variant will determine the disease risk, so that's dominant.

A recessive inheritance means that information or gene variants from both parents have to meet together and come together in the individual at risk to define the disease risk. Now, if you have that situation, so you have two or three or four

individuals with Parkinson's disease in the family, then you can calculate depending on the strength of the variant that your disease risk is maybe 20, 30, 40%, or even up to 50% if it's a fully penetrant, so a very, very strong variant. So that would be something that you start considering a realistic risk that comes from genetics. If you don't have that type of family history, I think it's almost negligible compared to all the other risks that you develop during your life when you age.

David Kumbroch: Thank you. Brian, I wanted to dig a little bit deeper on if you find yourself in that position where you feel like you've identified a risk, there are limits to what you can do proactively, but there are some steps you could take to engage your healthcare providers, make sure that you're all looking at the same things and that you understand your risk collectively. Could you speak a little bit about that?

Dr. Brian Fiske: Sure. So it's important I think, again, also give everything Thomas just said about appreciating what risk means in the context of your family in your life, and appreciating that in many of the really strong genetic forms of Parkinson's are still fairly rare in the population, so you would know if there's a really strong family history. So for many people, the risk is probably not as critical, but it's also important to know that today, we don't really have anything available as a treatment that you would give to someone based on their genetic makeup or their genetic risk. So there's nothing really we could do specifically that if you came and said, "I had genetic factor X. What do I do?" We can't say, "Oh, here, take this drug. This is the thing for you."

Now, saying that, there are certainly a lot of treatments that are currently in development, including some that are actually in clinical testing now, that eventually if those show any potential promise could be offered to people in the future perhaps based on their genetic makeup, and so that's obviously something that we're continuing to monitor and look at. But today, I think it really just is about for people who do pursue and want to identify and find out their genetic risk for diseases like Parkinson's, it's a lot about just healthcare ownership and engagement, being aware of your own health in the same way you might monitor your blood pressure or your cholesterol levels, a lot of things. Genetics is another biological component of just our natural lives that can be sometimes informative for us.

But it's understanding, like Thomas was saying, really understanding the context of those genetic drivers. Speaking with the genetic counselor if you do want to pursue that I think can be a good first step, just to make sure you appreciate what the risk really means, but then thinking about are you someone who regularly engages in your health and is aware of exercise and the role of exercise and good diet and all the things that we know we should all be doing as we get older anyway? That these are things that probably can help, if not prevent these diseases from happening, certainly can maybe delay the onset or counter some of the effects that these disease processes may have.

So I think if you're someone who does pursue that sort of genetic awareness of the potential risks for these diseases, educating yourself, making sure you understand, again, the context of that risk, and then just being aware of your own

health and the things that you can do to just generally stay healthy are probably the kinds of things that could be important. And Thomas, I know you probably have ways that you talk to patients as well about these kinds of issues.

Dr. Thomas Gasser: Yeah. This is obviously an important topic that a lot of patients and family members and at risk individuals raise. I think that the best evidence is actually at the moment physical activity that you can stress, and that is of course also easily transported advice because everybody knows that there could be more that I could do and it's helpful for so many things. And there are some estimations that all those modifiable risk factors for neurodegeneration in total could reduce the overall prevalence of neurodegenerative diseases by 40%. Now we would have 40% less Parkinson's, Alzheimer's and other neurodegenerative diseases if we would really take care of all the modifiable risk factors that there are.

David Kumbroch: That's a really interesting explanation of the links between genetics and health, but I also want to make sure that we dive into the links between genetics and research. People with PD linked mutations are a critical resource for scientists who want to learn more about the disease. So Thomas, could you tell us a little bit about why are people with these mutations, both those who do and don't have Parkinson's, such a valuable resource for researchers?

Dr. Thomas Gasser: Absolutely. That's a very good question, and I think there are a number of reasons why we really need to study those cohorts of individuals and their family members, asymptomatic mutation carriers with specific genetic mutations. One reason is of course that this opens up a window in the pre-symptomatic phase of the disease. So if you go out on the street and collect a hundred individuals, you're sure that one or two of them will develop Parkinson's disease in the next 20, 30 years, depending on how old your cohort is, but 98% will not. If you select for patients who carry a certain risk variance, that risk of course is much higher. It's not a hundred percent. All of those variants have what is called a reduced penetrance, so there are individuals who seem to be able to balance the lateris effect of those variants, either with some other genetic variants or with lifestyle factors, but of course that is a very strong enrichment of those individuals who will eventually develop Parkinson's.

And then this group is very homogeneous in the molecular path to Parkinson's disease, and there are different paths that already we know. The genes that we know that increase the risk for Parkinson's disease influence different pathways, different mechanisms that are partially overlapping and that play a role, for example, in the degradation and elimination of certain protein products. That's the so-called lysosomal pathway. They play a role in the energy production of neural cells. That's the mitochondrial pathway. And those pathways can be studied basically in isolation in those individuals that have certain risk variants.

In those individuals who do not have those risk variants, probably the same pathways play a role. We know that from the so-called genome-wide association studies. The same pathways play a role, but in a mixture.

So the ones with the strong genetic causative variants are a prototype for certain pathways to Parkinson's disease, and in all the others, it's more of a mixture of all

those different pathways. And that's why it's very important. It's the window that you look at, so the pre-symptomatic window, and the other one is the pathway that is defined that leads to the neurodegeneration and the disease.

Dr. Brian Fiske: Yeah, this point I think is such a powerful one because I think people sometimes don't fully appreciate, oh, if I don't have that genetic form, that means my Parkinson's must be different. But I think as you said earlier, our genes really just are the instructions for the biology going on in our cells, and if you mess up with something in your genes and alter it or mutate it or have a different variant, that can obviously potentially alter the biology in the cell. And it's really that biology that the genetics is pointing to. It's not so much just the fact that you have an A versus a T versus a G versus a C, the letters of our DNA.

It's something about the biology that the genetics is pointing to, and that's really powerful because then once you know that, okay, this biological pathway, if I mess with it from a genetic standpoint, I can still look in other people who don't carry that same genetic change just to see if that biology is also messed up in those individuals and maybe from another factor, like you said, because of an environmental factor or some other combination of factors, but maybe it's converging on the same biology.

And so that insight that's the flag in the ground that genetics provides as an initial hint of what might be going on is such a powerful one and has fueled essentially the therapeutic pipeline for Parkinson's disease in the last 20 years, I think, with many of the biologies now being looked at therapeutically driven by that genetic insight that we have obtained from those early studies.

David Kumbroch: So we've touched on a lot of the different factors that play a role here in Parkinson's and that are being studied, which range from environmental factors to genetic factors, et cetera, et cetera. So Thomas, what do we expect specifically from genetics research in Parkinson's going forward? What are the next big questions that we hope genetics can answer when it comes to PD?

Dr. Thomas Gasser: Well, again, I guess there are a lot of things that I would expect to develop over the next years or so. One very interesting aspect that I think that became clear in the past let's say four or five years is that the genetics of Parkinson's disease has shown us and will show us even more that the diversity of Parkinson patients that we can examine and that we have is much larger than we had thought. So most of our studies so far were focused on a very small percentage of individuals in the world, namely people from Western Europe and the US, so basically, genetically, only a very small group of entire humanity. And now the big ASAP and GP2 project, which is specifically trying to widen the scope here to look at Parkinson's genetics in all of humanity as far as it can be reached, and I think there we are making big progress but we're not going to reach every part of the world to the same extent.

But that shows that Parkinson's disease genetically is different in sub-Saharan Africa from Europe and different in Southeast Asia. There are some variants that are found in African Parkinson's patients that are not found in Europeans and vice versa. There are some mutations that are extremely common, let's say in

North African populations, Arab-Berber populations where Parkinson's basically is a monogenic disease. So in the majority of patients, you will find certain mutations. In other populations, it's far from that and those variants only account for one or two or 3% of populations. And this whole variability will be very important to tailor specific disease modifying treatments, which will be different in different parts of the world, because the disease is different, because there's different genetic causes.

David Kumbroch: Brian?

Dr. Brian Fiske: This idea of the diversity I think is such an important one too. As you said, so much of genetics research was done in a small part of the population for so many years, and as we've expanded the diversity of our genetic understanding, we're learning a lot, both in the context of potentially new biologies that gene discovery in other populations can tell us about other types of ways that biology might be manipulated and different in people with Parkinson's. But also, I think as you were alluding to which I think is also equally powerful, the greater prevalence of certain genetic biology in certain populations that I think is important to appreciate.

Because for example, you mentioned the African variant that was recently discovered in the last couple of years is an example of a new variant, as you said. So it's not as frequent in other populations as it is in people of African descent, but it touches a biology that we actually have been exploring for many years now, particularly around the gene GBA1. And so there actually are therapies that are being tested and developed for people with biology related to GBA1, an impairment that could be then applied to these populations. So it's not I think the value of understanding of diverse range of biology that might lead to Parkinson's, but also the fact that there are populations of people out there who might, as you said, predominantly be driven by a certain biology and would be ripe for the type of therapies that are being developed today, and that we should be importantly looking at those populations and making sure that they're getting access to those treatments as well.

David Kumbroch: We touched briefly there on some really powerful programs that are working to decode some of this global difference between the different types of Parkinson's that we see genetically. I don't want to past that too quickly. Specifically, Thomas, you work on GP2, the Global Parkinson's Genetics Program. You referenced it briefly there and Aligning Science Across Parkinson's, ASAP. Would you mind just briefly talking about the value that those programs provide and what they're doing for genetics research in Parkinson's?

Dr. Thomas Gasser: Yeah. So one thing of course, as I just said, was that they are really widening the scope of the so far vastly underrepresented populations. I think there's another thing that I really love about it, and that is that it really creates a scientific community that is much wider than we had so far. So the GP2 program has a great program, a training program for young individuals from let's say sub-Saharan Africa or Southeast Asia who start to connect via the internet, and they form networks and groups. They discuss research projects, they're very open

about data sharing, and this is one of the big things about the whole GP2 network.

When I started in genetic research, it was a time when you basically didn't know when you were on a bench in a laboratory, you didn't know what happened in the next bench because people were so secretive about it. This has completely changed. Now, it's very much open science, it's a very collaborative atmosphere, and I think that's so much more fun than just to be afraid that somebody might steal your big discovery. So much more fun and also so much more productive to be in an open science environment, and it accelerates progress greatly.

Dr. Brian Fiske: Yeah, I've had a chance to sit in some of the trainee meetings over the last few years as the GP2 program has evolved, and you can just feel the passion and just the powerful appreciation that I think a lot of the trainees have for just having access to something like this. As someone who in my graduate career, I was in my lab doing my one thing, collaborating with the people around me physically maybe in the building around me, but the idea of having this global network of experts that you can connect with and work with I think is such a powerful thing that GP2 has been able to provide. So I a hundred percent agree with your description of that.

David Kumbroch: Both of these programs, ASAP and GP2, are important parts of the Michael J. Fox Foundation's broader research strategy. Brian, I was hoping you would elaborate a little bit about how they fit into the vision of what Fox sees for genetics research going forward and how that fits into the strategic approach that we take to research.

Dr. Brian Fiske: Yeah. So our research agenda really is focused on, obviously centers on the idea of what can we do to enable and deliver better treatments for people living with Parkinson's, and increasingly now, potentially for those at risk for Parkinson's as well as we think about what prevention and delaying the onset of disease might look like in the future. And so for us, we really focus our work in a few key areas, and particularly I think for genetics, one of the most important areas that we focus on is how do we recenter, if you will, the definition almost, the diagnosis of Parkinson's around biology?

So obviously for, and as Thomas can well attest to, for decades, it's really been driven by the idea of clinical symptoms. You come in and present with a certain set of clinical symptoms, and over time, they give you some medication to see if it's responsive and that eventually you're diagnosed with this thing called Parkinson's disease. And really, not until you pass away and someone can look at your brain would anybody really have any hint of a biological sense of whether you actually had Parkinson's disease defined at a pathological level.

With emerging tools that we have now, we're starting to get to a point where we think we can maybe start to recenter that definition and think about it more in a biologically defined way, and you can do that through a variety of ways. You can do it through genetics, so obviously you can screen individuals and understand their genetics and be able to define potentially their Parkinson's from a genetic standpoint, but also as we develop and we're gaining some ability with some

newer diagnostic tools to link those even genetics to some of the biology so that you can actually get a better picture of what someone's biological definition of Parkinson's is. So a lot of our work, and especially with the work with the GP2 effort, really is I think focused on that idea of a biology centered definition of Parkinson's.

But I think it feeds into a lot of the other work that we have as well. So obviously much of the attention of the foundation for the last 25 years has been on this idea of translation, so how do we translate that biology into the therapeutic ideas that people can take forward and actually develop drugs against to test, ultimately testing people and hopefully if they show benefit, get approved for use in patients? And so a lot of our work is feeding off of the genetic insight coming from studies like GP2 and others to translate that biology, understand what we call the targets that the genetics points to, the biological targets in our cells the genes point to. How can we translate those targets into actual therapeutic development efforts that are needed? So that's another big part of the work we do.

And then ultimately, how do we take all this information and bring it into the clinical trial process? So obviously you can have great therapeutic ideas, you can have great biological insight, but if you can't really do those trials effectively, you're dead in the water. So how do we bring that insight into the actual clinical trial process, speed that clinical trial process up? And that's where a lot of our work, again, defined by genetics, defined by biology, translating it into the measurement tools that we can then use in clinical trials to try to speed those up. So biomarkers, imaging approaches, again, integrating genetic screening into the process so that we can, one, identify the right biology defined Parkinson's individuals to match them with the right biology-directed therapeutic approaches in a clinical trial process. That can hopefully happen maybe faster, certainly in a more informative way if we have that biological insight. So really, genetics I think fuels so much of the work that we do in driving us to that insight.

And then even in the context of connecting our communities, the patient communities. Being more genetically aware, biologically aware of their disease and understanding what they have, being more engaged in their healthcare based on that understanding I think being also a critical piece of that. And also the research and drug development communities. So we've spent a lot of years building consortia, if you will, networks of experts in both academics and drug developers together around core targets and core biology, core genetically defined biology. So we have efforts, for example, around some of the big genetic forms of Parkinson's that are working together to try to understand that biology, and again, translate it into therapy. So it really, I think, touches so much of the work that we do.

David Kumbroch: Thank you so much. I think we've covered a lot of ground here today. Hopefully one of the takeaways from today's episode is the value of participating in research, especially if you have some sort of genetic predisposition, but really, everyone can play a role in finding those next truths that really build up the science of Parkinson's disease. And so whatever you feel like you might be willing to participate or able to participate, you could visit MichaelJFox.org. We

have a trial finder that would help cool you into clinical trials that you might be eligible for. Our flagship study, the Parkinson's Progression Markers Initiative is always recruiting, and we have a number of additional opportunities, for example, GP2, all represented on the website there, MichaelJFox.org.

So I want to thank Dr. Brian Fisk and Dr. Thomas Gasser for joining us here today. We really appreciate your expertise.

Dr. Thomas Gasser: Thank you very much for having me. It was a lot of fun to have this conversation.

Dr. Brian Fiske: Thanks, David. Yes, always fun to be a part of this.

David Kumbroch: Thank you for joining us and listening along and enjoying our deep dive into genetics and Parkinson's disease. For The Michael J. Fox Foundation, I'm David Kumbroch.

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