Marie: Hello and welcome to *The Parkinson's Research Podcast: New Discoveries in Neuroscience*. I'm your host Dr. Marie McNeely, and I've partnered with The Michael J. Fox Foundation for Parkinson's Research to bring you to the forefront of the field of neuroscience to discuss the latest advances and discoveries with leading experts.

The Michael J. Fox Foundation created this podcast for researchers, clinicians, and industry professionals with the hope that these conversations and the resources we share will advance your efforts and partnerships to improve brain health. We are welcoming guests with a range of experiences and viewpoints; the views expressed belong to the guests themselves. And today we are thrilled to be welcoming our guest, Dr. Huw Morris

Listeners, Huw is Professor of Clinical Neuroscience at University College London Institute of Neurology, as well as an Honorary Consultant Neurologist at the Royal Free Hospital and the National Hospital for Neurology and Neurosurgery Queen Square. Today, we are excited to talk more about Huw's research, including his work on the genetics and pathogenesis of Parkinson's disease and other Parkinsonian syndromes. So Huw, welcome to our show today. How are you?

Huw: Thanks, Marie. Well, it's a real pleasure to join you on the show. Things are warming up now for the spring in London. So, that's good.

Marie: Fantastic. We're excited to learn more about you today, but let's start with your background. So Huw, can you tell us a little bit more about your background and how you found your way to your current positions?

Huw: Well, my research career in neurology started here at Queen Square about 25 years ago, I guess now. So, I was working at that time with Andrew Lees, who ran the Brain Bank here at Queen Square and led a huge amount of research in diagnosis of Parkinson's and Parkinson's plus conditions. And I was looking for a research position, and he asked me whether I wanted to do some research on the genetics of PSP, progressive supranuclear palsy. My response to that was that I didn't think that it was very genetic at that time. I was totally wrong, actually, but that was my initial response.

And then he said, well, as part of the project, you can go to the Western Pacific Island of Guam and research a condition that occurs there in Guam, this Guam, Parkinsonism dementia complex. And when he said that, my response really was, where do I sign and when can I start? So, that was the hook that kind of got me in originally.

So, what happened then when we started studying patients with PSP, this Parkinson's plus atypical Parkinsonian condition here in London. So, that's a tau-related neurodegenerative condition. Often misdiagnosed as Parkinson's disease, but with a much more malignant disease course. So, that was half of the study that I did. And then the other half was to go to Guam and to work with John Steele, who actually had originally described PSP, but to study another tau-related condition on Guam, this Parkinson's dementia complex.

Actually, sometimes overlapping with ALS in patients with Guam. And actually at one time, the rate of ALS on Guam was about 100 times the rate of ALS in patients in North America and in Europe. So, it was really a very common condition. No one really understood why there was this epidemic of this neurological condition on Guam. Many of the patients have a tau pathology, which is similar to the pathology seen in PSP, although there are differences. It is a different pathology, but it's similar to PSP pathology. So, we launched some genetic investigations that we did on patients in Guam in conjunction with John Hardy, who is then in Mayo Clinic of Florida and my supervisor, Nick Wood and Andrew Lees and Jordi Perez-Tur. So, we started looking into genetic of this.

We did not find anything very conclusive. We found that the background variation of tau gene is different in people in different parts of the world, which is probably an important part of the explanation of risk for some of these conditions. But we didn't really find a definitive underlying cause for the condition. I think now looking back on that, many different hypotheses were put forward as to why people got that condition on Guam. So, whether it could be to do with eating cycad plants, whether it could be exposure to toxins like aluminum in the water, various other hypotheses put forward, none of which really have been conclusively proven. I think the most likely thing is that there had been, at one stage, an infection in Guam and that there was some response to the infection that had led to the neurodegenerative condition.

And actually there is this kind of precedent for this because we know that people can get a tau-related neurodegeneration after measles infection. That's SSPE. We know that in the 1920s and 1930s in London, this condition of post-encephalitic Parkinsonism was actually more common than Parkinson's disease in London at that time. So, there was an infection, which was initially thought to be influenza, but probably was not influenza, that triggered a Parkinsonian condition. So, I think that's the most likely explanation. But this is unproven. We don't have any firm evidence for an infection triggering the disease on Guam.

But we know that this can happen. And I think that seems the most likely thing because that disease now has become very uncommon. So, now very few people on Guam have that condition, which obviously is good that that

degenerative condition is sort of fading away. But it leaves a bit of an enigma, a bit of a mystery as to why that happens. So, I developed, obviously, an interest in conditions affecting people in different parts of the world at that time.

Twenty five years later now, we have the opportunity to take that forward within the Global Parkinson's Genetics Program, within the GP2 Program, funded by ASAP and in conjunction with The Michael J. Fox Foundation. So, we have this amazing opportunity to work with investigators, neurologists, researchers, patients from different parts of the world and try to understand how Parkinson's disease and Parkinsonism affects people in different parts of the world. But I have a particular interest in these tau-related conditions. And my guess is that we will find other — well, we know that there are other clusters of tau-related Parkinsonism in other parts of the world. And I think that the GP2 project is going to give us incredible tools to understand this, to build collaborations with investigators in other parts of the world. So, that's a longstanding interest that I have in PSP and tau conditions, which is now being re-activated, re-energized within the GP2 project.

Marie: Absolutely. And bringing things from Guam back to the UK. I know you are also leading a longitudinal UK-wide study of PSP, as well as corticobasal degeneration and MSA (multiple system atrophy). Can you tell us a little bit more about this initiative?

Huw: So, this was funded by the PSP Association initially in the UK then with support from the MSA Trust. So, these conditions are much less well-known, less well-studied than Parkinson's disease is, but essentially around 2010-2011, really inspired by PPMI. We wanted to set up a study where we would essentially run a drug study, except without a drug treatment. So, we would follow up patients over time, we would collect biosamples, we would see what happened to the progression of the condition over time and try to understand how the disease affected people differently, how it progressed, why it progressed, why some people progress slowly, some people progress quickly. That's a major driver of our research and to develop a fuller picture of the disease.

So, that eventually started in 2014-2015. To date, we've recruited about 1,500 patients with atypical Parkinsonism in the UK. So, we've grown from seven study sites to 28 study sites in the UK that are recruiting patients. We've been incredibly well-supported by the PSP Association, by MSA Trust, and also CBD Solutions. But also patients volunteering to be involved in these studies, which involved donating biosamples, having clinical assessments and brain imaging. And patients with these conditions, they tend to progress much more quickly than Parkinson's disease. So, unfortunately, the sort of median survival is six to eight years after disease onset.

So, they progress really very quickly. And patients are very willing, by in large very willing, to be involved in research, even though they know this research may not benefit them directly, but may be helpful in developing treatments for people to come later on as trials get developed that are based on hopefully the biology that we can kind of uncover through this research, but also developing the tools, in terms of ways of monitoring disease progression, that can be deployed in clinical trials.

One of the interesting things that we did actually that I think in a way has been particularly telling and hopefully may help to lead to new trials for patients with these conditions, because we just asked a very simple question about patients with PSP, progressive supranuclear palsy. Why some people progress slowly and some progress quickly.

And we did a genome-wide association study to look across the genome for genetic variants that might provide some explanation as to why some PSP patients progress extremely quickly. And some had a much more slow and indolent disease course. To our amazement, when we did that study, in work that was done by our clinical fellow at that time Ed Jabbari, was that we found, as we looked across the genome, there was variation adjacent to the LRRK2 locus in chromosome 12, but actually was a major determinant of survival in patients with PSP.

So, obviously, this gene is a really important gene for Parkinson's. We know that there's both a rare variation and common variation at that locus that is a risk factor for Parkinson's. But it turns out the same locus seems to be important for a completely separate neurological Parkinsonian condition — PSP.

And obviously that instantly suggests that potentially those types of therapies might also be helpful for PSP patients. That's something that we kind of have discovered, if you like, through analyzing progression, we've continued to build the cohort, collect more bio samples. And I'm sure there's a lot more work to do, again, through GP2 with our data and samples, but collaborating with investigators from other parts of the world, who can help with analyzing this data and understanding disease progression.

One of the things that we're kind of turning to looking at now is actually getting the diagnosis right early on in the disease course. So, patients with PSP are often misdiagnosed as having Parkinson's disease. So, they're often initially thought to have Parkinson's disease, or some other problem with their gait, walking, or balance. And the average time in our study for patients having their first symptom to coming through to being diagnosed with PSP is three and a half years. So, there's a very long duration when people are progressing, getting worse, being given levodopa treatment, which is not working very well. It’s

obviously very frustrating for patients and their families. And it's a long delay until a diagnosis is made.

I think there are a few different reasons for that. I think it's partly because some neurologists may not be very familiar with the clinical features of these conditions. It may also be because there is reticence in giving a diagnosis, which has got a much worse prognosis to patients until people are completely sure of the diagnosis.

And I undoubtedly it relates in part to the fact that we haven't really got a test for this condition, that we can say, we think you have this condition because you've had this test, which has shown that you are likely to have PSP. So, we're setting up a new study now, which is called the ExPRESS Study, in which we're aiming to recruit people when they're first referred in from their primary caregiver to a neurology clinic or to a movement disorders clinic.

So, the very first time they come, we're aiming to recruit people and to monitor what happens to people in the first few months when they're being seen and given treatment. For a subset of patients we hope to collect bio samples, so we'll have blood samples, spinal fluid samples, to try to develop markers that may enable this diagnosis very early on the disease course. And we think by extrapolation from Alzheimer's therapies, that for a therapy to be effective, it probably has to be used quite early in the disease course.

Obviously, the development of the synuclein amplification assay for Parkinson's or for other for synuclein pathology is extremely important, I think, and there's work being carried out on developing that type of assay for tau disorders. But you can imagine what may happen is when patients are first referred in, particularly if they're going to be involved in a biologic trial for tau or synuclein, they may have this type of either CSF assay or developed skin biopsy and blood assays that will look at this fundamental protein that's involved in the disease process and will direct people towards the right therapeutic trial. And hopefully ultimately the right treatment which will prevent their disease from progressing.

So, we're trying to focus now on people very early in the disease course to enable early diagnosis. I think there's going to be development as well in imaging, in MRI imaging, and in protein-based imaging, so imaging synuclein and tau in the brain of patients with these conditions, which I think is going to be helpful early on in the disease course. And there's undoubtedly also going to be progress with digital markers, so watches and smartphones that can monitor activity and other parameters that may help with this early diagnosis.

So, I think this is the way ahead. And in a way we're kind of guided a bit by what's happened with Alzheimer's disease and which biomarkers have been very

helpful in diagnosing people with the Alzheimer's process. The proteins involved in Alzheimer's early in the disease process, and that's already helped drive clinical trials. And I hope the same thing is going happen for patients with PSP and Parkinson's and help us to get a better diagnosis early on in the disease course.

Marie: Absolutely. I think you brought up some really important points there, and just the importance of being able to get this differential correct diagnosis early in the disease course for Parkinson's disease and some of these atypical Parkinsonian syndromes. And you mentioned that your career started in this area of the latter, the atypical Parkinsonian syndromes, but you've also done quite a bit of work in Parkinson's disease, and I'd love to dive into some of that research. So, can you talk a little bit about the work that you've done kind of looking at the genetics of Parkinson's disease and some of the different drivers of specific features?

Huw: So, actually, when I finished doing my neurology training, my PhD, I moved then to work in Cardiff in Wales. And what I'd started to study then was early-onset Parkinson's. So, I was particularly interested in what happens when people get Parkinson's in their 20s or 30s. Obviously, that's a very unusual thing to happen. And I thought that this would be a good group of patients to study. So, we set up a study in Cardiff called the Calypso study, where we started to recruit patients with early-onset Parkinson's. We know that the average age of onset for Parkinson's in the UK is 68. So, that's the average age of developing Parkinson's.

But if you develop Parkinson’s when you're 35 or 40. That's a very unusual thing to happen. And there's got to be a good reason for that. So, whether that's an environmental exposure that's led to Parkinson's or it's a genetic factor, there must be something major that's happened to lead someone to develop Parkinson's very early on in life. And that's a sort of driving scientific question to understand that that lead us to set up this cohort to recruit patients and to explore the genetics and the genetic technology as they've developed to try to look into that question. The work that we did in Cardiff was with Nigel Williams in Cardiff and Mirdhu Wickremaratchi, actually who is a clinical fellow who worked really, really hard assessing lots of patients and collecting biosamples from early-onset Parkinson's patients.

At the time we started this, parkin had been identified as a common cause, or relatively common cause, of very early onset Parkinson's. We thought that we would discover lots of new genes for this. I think it's probably fair to say that we have not discovered a major new gene that accounts for another 20%, shall we say, of early-onset Parkinson's patients.

There have been so much rarer genes that have been identified. We've contributed samples to those sort of discovery efforts, but so far we haven't identified a single new gene that accounts for someone getting Parkinson's at the age of 35, shall we say? What we have kind of discovered as a contributor is we went on, of course, to do genome-wide association studies to look at common variation across the genome.

So, we collaborated and that was really — the starting on those studies — was the sort of birth of large-scale collaboration. So, essentially in this research, we look at genetic variation across the genome. We look at the difference between cases and controls (people with Parkinson's and without Parkinson's). And look at common variation that all of us carry, but look at if any of these common variants are more common in Parkinson's cases than controls.

And as you probably know, we're now at kind of 90 variants across the genome that increase the risk of Parkinson's. They're not sufficient to cause Parkinson's, and they happen in lots of people who don't have Parkinson's, but we can see they're more common, and they must be contributing to the biology of Parkinson's and development of Parkinson's in some way because we can see that consistently there's a difference between cases and controls.

What we found when we looked at patients with early-onset Parkinson's was that they had more of these common variants. So, someone who's 60 might, for argument’s sake, have like 10 of these variants. So, these are common variants that slightly increase your risk of Parkinson's, but if you get Parkinson's at 40, you might have 20 or 30 of these variants. So, in fact, you have more and more of these variants combining together to increase risk and to make the disease happen earlier in your life course.

So, we call that polygenic risk, so in a way we’re kind of calculating polygenic risk scores where you weight all these variants, add them together. And we can see that if you develop Parkinson's at the age of 40, 45, 50 that your polygenic risk — all these variants added together — is much greater than it is in patients in their 60s, 70s, 80s. So, this is kind of a driver of early onset. So, rather than being a single gene that's caused the condition, it may be lots of risk factors acting together.

I mean, technology's changing and improving all the time. We know that actually that there are a lot of people with familial Parkinson's. So, lots of people in the family affected, which obviously is a big clue that people may have a single gene that causes Parkinson's both early-onset and people with later-onset Parkinson's who've got lots of people in their family affected. So, actually currently for all of these individuals who have very early-onset or familial Parkinson's, only about

10% of them at the moment are explained that we know that they have a variation in LRRK2 or synuclein or parkin that causes the condition.

So, about 90% of those individuals that are either in large families or very, very young, do not have an explanation for their condition. And so we think there are more things to discover. Some of it may be polygenic, but we think they're probably are some new genes to discover. And I think that again through collaboration in GP2, particularly the monogenic group in GP2 and sort of new technologies coming through, I still think that it's likely that we will find some new genes that will give us new insights into why Parkinson's occurs in people, but also why the biology behind that that's going to lead to new treatments.

One of the things that was a sort of byproduct, if you like, or the work on early-onset Parkinson's was asking about how the condition is different. If you develop Parkinson's in your 30s, as opposed to developing Parkinson's in your 70s. And I think that what's come out of our research, but also lots of other people doing research in this area, so if you do develop Parkinson's at a younger age, it tends to change much more slowly over time, it tends to progress more slowly, people tend to respond very well to medication, to dopamine medication, they have less risk of getting problems with cognition or falls early on. They do have an increased risk of this dyskinesia, this on-off fluctuations that happen if you develop early-onset Parkinson's. So, there are kind of some clinical differences between people who have early-onset Parkinson's and later-onset Parkinson's. And later-onset Parkinson's, in some ways it's a different type of condition if you develop Parkinson's in your 30s or 40s compared to your 70s or 80s. So, I think that's kind of important in guiding how we talk to patients and what counseling we give them about their treatment and about what to expect in the future based on studying lots of patients with early-onset Parkinson's.

Marie: Very interesting. And setting aside the timing of onset, are you finding evidence for a genetic basis of motor progression in terms of the speed of progression? So, let's say we're looking just at late-onset or just at early-onset, even within those buckets, people progress at different speeds. What are your thoughts, or perhaps hypotheses, about what's happening there?

Huw: So, of course, Parkinson's affects people in different ways. So, some people have very benign forms of Parkinson's. Say after 25 years, they are still working, active, playing sports, walking, doing very well. Some people with Parkinson's have got lots of problems within five years of diagnosis.

So, there's this huge variation in the rate of progression. The question is how we can study that. One way is to study scales that are measured in clinical trials for Parkinson's, like the MDS-UPDRS scale. So, that's kind of like a measure of

motor function that encompasses tremor and rigidity, and gait, and all of these things sort of added together.

One of the things with this is that the data that's been collected on this is largely over quite a short time scale. So, a lot of drug trials for Parkinson's, be they symptomatic drug trials to see if you can kind of improve movement or disease modifying to see if you can alter rate of change, might be over the one to three year time scale. They tend to be quite short. Somwe've started to look at that type of data, but what happens in motor progression? And we've started to do genome-wide association studies to look at that.

So, we've done that, Hirotaka Iwaki, an NIH group, have done that. So far, there are different signals that have come up in the GWAS, and it would be fair to say that there's not really a consistent pattern that's come up in terms of motor progression or early motor progression. One of the loci that we identified in the early motor progression was this gene ACP6 that's involved in mitochondrial function and mitochondrial lipid homeostasis.

I think this type of finding needs to be replicated in other studies, and we need to kind of grow a collaboration, if you like, for this type of study to understand more about early progression in Parkinson's patients. Again, through the GP2 project, we're starting to aggregate clinical data from lots and lots of clinical trials, lots and lots of clinical studies to sort of build up to the type of large numbers that we need to measure these effects.

The other way of doing it is to look at much longer-scale, longer-term outcomes, which are not the sort of things that are collected necessarily, well they may be collected, but may not have many people reaching the outcome in clinical trials. So, that might be in terms of longer-term outcomes for Parkinson's, things that can be measured in people with dementia. When people start to develop significant cognitive impairments, which is a feature of Parkinson's disease and when people start to lose their balance, have problems with their postural reflexes, which is measured with the Hoehn and Yahr Scale, when people die, and we know that those three things are outcomes that can be measured without people having in-depth clinical assessments every three to six months, as might happen in a drug trial. So, those are much longer-term clinical outcomes that clearly mark what can be grouped together as unfavorable progression in Parkinson's patients.

Obviously, these are quite crude measures, and the reason why these things happen might be quite diverse. Clearly, if you look in groups of Parkinson's patients, mortality, obviously some of that is to do with cardiovascular risk of stroke, heart attack, maybe things that are not related to Parkinson's. So these are, if you like, less precise measures, but we are starting to do genome-wide, or

we are are doing genome-wide studies, looking at genetic variation that affects these long-term outcomes.

I think that, particularly for elderly Parkinson's patients, the cognitive outcomes, developing cognitive impairment, visual hallucinations, dementia, is an extremely important outcome for patients, their family, caregivers. Obviously, it's a very important determinant of people needing more home care support or being admitted to institutional care.

And I think it's interesting that this has perhaps been less-studied as an outcome in Parkinson's trials, particularly what happens over time. Of course, you need to do quite a long-term trial to monitor this. So, you may need to do quite a long-term trial to look at the impact of, say, your synuclein therapy on preventing people developing cognitive impairments in Parkinson's. A dominant hypothesis is that Parkinson's pathology, synuclein, spreads through the brain. It sequentially involves areas through the brain, as people have Parkinson's for a longer time.

And obviously, it kind of makes sense that if you have a therapy that's directed towards synuclein, you may not affect people's tremor that much because the substantia nigra, the brainstem, is already affected, but you may prevent people progressing to develop cognitive impairment (dementia) because that reflects synuclein pathology affecting the cerebral cortex and the limbic areas of the brain. So, in my view, it's interesting that it’s not really been a major kind of outcome measure in clinical trials. I think that's partly because the length of the trial that would need to be done for that type of outcome. But I think this is one of the things that's going to happen in the future is that we're going to see cognitive outcomes being used as trial outcomes for patients with Parkinson's.

Coming back to the genetics. What we found when we looked at time to event, so let's look at big cohorts of Parkinson's patients, 4,000 or 5,000 people, look at time to cognitive impairment, stroke, dementia in Parkinson's. What we found is actually is a major driver genetically is the APOE locus. APOE is the major genetic risk factor for Alzheimer's disease. We know that at autopsy, about 50% of patients with Parkinson's disease dementia have concurrent Alzheimer's pathology.

So, this may be because it's driving, there's some driving of Alzheimer's pathology in patients with Parkinson's that is driving the cognitive impairment dementia. It may also be, and there's some sort of basic science evidence for this, it may also be that APOE drives synuclein pathology as well. There's evidence that it may both drive amyloid tau pathology and Alzheimer's disease, and may also drive Lewey body pathology as well as synuclein pathology in PD dementia.

So, there may be two kind of pathways to this. We know there are actually Alzheimer's biomarkers as well in Parkinson's patients when they're measured at baseline predict the risk of going on to develop dementia. And it does kind of raise the question as to whether there are any therapies that are being developed for Alzheimer's and being licensed for Alzheimer's may also be applicable in preventing cognitive impairment in Parkinson's. I think that's a very important question which needs to be addressed by the community in terms of preventing long-term adverse outcomes for patients with Parkinson's.

One of the really interesting things we discovered in these genome-wide studies looking at progression work that's been led by Raquel Real, doing this work, is that actually the second hit we identified in our genome-wide association study was a locus called LRP1B. So it's an LDL receptor. In fact, this is an APOE receptor.

So, we've actually found through genetic studies that both APOE and APOE receptor are both implicated in the development, in the studies we've done, looking at Parkinson's dementia. And of course, again, as with all of these types of studies, this needs to be replicated in new data, independent data sets to be sure that this is a robust and a reproducible finding. And we're trying to work on trying to understand what this means in terms of the sort of biochemistry and the pathology that's related to this. But again, it sort of highlights this amyloid pathway as being important in Parkinson's patients.

So, I think there's quite a lot that can be understood from trying to understand differences in progression. New work that we're doing, funded by The Michael J. Fox Foundation, is starting to look at RNA expression levels and how that relates to progression. Again, just asking very simple questions, like what's the difference in gene expression when people have slow progression versus fast progression?

And obviously we're going to look at how that links into genetic variation. And then the third thing that is developing now is looking at many, many protein levels in the blood or in the cerebrospinal fluid and how that links or predicts clinical outcomes. In a way, this type of research is becoming quite multimodal, looking at lots of different, like the genetic variation, RNA variation, and protein variation, how that links into progression in Parkinson's patients.

Marie: Absolutely, and I think this research is critical for really breaking down the heterogeneity of this disease and understanding what's happening in individual patients. And then subsequently, how best to treat these individual patients, which I think is a really exciting frontier in the field. And you mentioned some of the genetic drivers for features of Parkinson's disease, but also relatively common is this phenomenon in response to treatment — levodopa-induced

dyskinesia. And I know you've done some work in this area as well. So, what are you seeing in terms of genetic risk or predisposition for the potential for levodopa-induced dyskinesia?

Huw: Levodopa-induced dyskinesia affects between 20 and 40% of Parkinson's patients at about five years on treatment. So, as probably many of us know, people about this as fluctuating response, on-off fluctuations, but also dyskinesia — it's these involuntary movements related to levodopa treatment. Clearly, there are clinical determinants of developing levodopa-induced dyskinesias. So, younger age and female increase your risk of developing levodopa-induced dyskinesias. It's pretty clear from clinical studies, like the L-dopa study that the amounts of levodopa you have. When levodopa therapy first came in, people were given very high doses, and clearly being on very high dose levodopa increases your risk of developing dyskinesia. So, there's some kind of clinical determinant.

And I would say actually in the time I've been practicing, I think the rate of dyskinesia has gone down because people use lower doses of levodopa, use amantadine, and they use non-levodopa drugs. We're kind of interested in, of course, as you say, the genetic variation that might relate to this. So actually, a very talented PhD student in our group, Alejandro Martinez Carrasco, has been working on this, looking at data from PPMI, from UK cohorts, putting it together with the genetic data to look at genome-wide, if there are genetic variants that increase your risk of developing dyskinesias.

And we found that there's variation in the expression of a gene that's called DNAJB4 which is a heat-shock protein gene that seems to be linked to the risk of dyskinesias. So, we don't really understand the biology behind that, but there are a number of other loci that have come up from that study, including another LRP gene, LRP8, that is involved in the risk of developing dyskinesias.

We know that some of these genes are expressed at high levels in the striatum in striatal neurons. There seems to be obviously an important area where there is synaptic remodeling that happens, that probably changes levodopa response. But I think that these studies, well, there are two parts. One is that, of course, it may, especially as the power of these studies increases with larger numbers, it may be possible to do a sort of risk profile when someone comes to clinic based on their age, gender, their genetic makeup that will give people a risk, will predict how likely they are to develop dyskinesias. The other side of it is giving some new insights into the biology that might lead to better treatments, that reduce the chance of developing dyskinesias.

So, I think this is very exciting research and that we're starting to drill into the variation that leads to these phenomena. And again, it relies on collaboration

between lots and lots of people who've collected this type of data. I think clearly for this type of thing, the motor progression and the levodopa-induced dyskinesias, one of the richer sources of data is going to be drug trial data. So, a lot of academic-led drug studies have contributed data and are collaborating, pooling their data together with genetic data.

We really like the pharma companies also that are involved with this, where they have data or samples, clearly they're often data-sharing restrictions and confidentiality restrictions that may make that difficult, but obviously it's a very rich set of data. So, even if a trial was unsuccessful, so even if a trial didn't lead to drug X reducing the rate of progression or reducing the rate of dyskinesias, one of the things I think is really important is to be able to go back to the data and to reanalyze it, understand more about the biology of what's happening, and use that to develop better treatments in the future.

So, we'd really like this to be kind of like a standard thing in drug trials that patients donate their time, effort, and biosamples to be involved in these studies. And even if the drug trial itself is unsuccessful in the primary outcome, it may be successful in contributing to the learning more about their condition and developing new treatments in the future. So, we really hope this is the road ahead for Parkinson's genetics, understanding Parkinson's phenotype.

Marie: Absolutely, I think you brought up a lot of really great points and just this idea that it's critical to really be making the most of the data that is being collected. And I think these collaborations and these different tools and resource-sharing initiatives are really important. So, what do you see as some of the most important, or perhaps most impactful, initiatives on this side of the field?

Huw: Just coming back to that point about what happens to data after studies, charitable organizations like The Michael J. Fox Foundation, Cure Parkinson's Trust, Parkinson's UK, I think it's really important that these bodies who are kind of engaged in research, who are supported by patients. I think it's really important that they argue for this and actually try to ensure the maximum use of data and samples that are being used across lots and lots of different studies.

So, there's like a really important advocacy part of that to make sure that the most use is made out of what patients very generously donate when they get involved in a clinical study. In terms of initiatives, we're learning a huge amount from the longitudinal cohort studies. So, in the UK, we've had the Tracking Parkinson's Proband Study, The Oxford Discovery Study, which we've worked on a lot, looking at longitudinal clinical data.

The PPMI study, very similar in the US, with actually much deeper biosample phenotyping in the PPMI study. I think these are extremely informative in what

happens with Parkinson's progression and variation of phenotype between patients. And actually, as these cohorts get older from their initial recruitment, there's more and more information coming through about variation of phenotype. They kind of become more and more informative as time goes on in terms of what happens to patients.

Because we're getting outside of a timescale now of a normal drug study, which goes one year or two years, we give someone a drug and see what happens. And then the study ends and then the patients don't get followed up more. So, I think the PPMI and Tracking Parkinson's/Oxford Discovery, these have now gone much beyond the sort of timescale of a normal drug trial. So, I think that those initiatives funded by The Michael J. Fox Foundation, and Parkinson's UK, and in the UK are extremely important.

Obviously, the initiative that I'm very involved with now, and which I think is really important, is GP2. So, the Global Parkinson's Genetics Program, funded by ASAP and working closely with The Michael J. Fox Foundation for taking this forward. I mean, the exciting thing about this is that as I kind of alluded to already with the talk about GWAS and what's happened with GWAS. We've done, as times went on from, should we say, 2006 was when we started to plan the first genome-wide association study in the UK, through to kind of when GP2 started.

So, it was kind of planning phases, by 2018, 2019. Over that period, of course, we did more and more collaboration. So, we realized that we had to work together to get to large sort of sample numbers. So, there was more and more collaboration that was happening in the International PD and Genetics Consortium, led by Andy Singleton. We decided to kind of collaborate more and more. And that was kind of happening anyway, but the GP2 Program has just kind of taken that to another level because that's provided the resources, the community to enable this to happen at a kind of order of magnitude greater.

So, we're currently aiming to link together investigators around the world to enable genotyping 200,000 Parkinson's patients. So, I'm involved in helping to coordinate some of the effort. Currently, we've been in touch with 380 cohorts and investigators worldwide who are interested in participating. About 225 now are kind of going through the process of being involved in the GP2 project.

And we actually have kind of legal agreements in place for what we anticipate is approaching 150,000 samples from patients that have been organized, collected by investigators around the world who are part of the GP2 Consortium. So, it's kind of like an order of magnitude.

And some of these questions that we've touched on earlier, like why does someone progress slowly or quickly? Why do people get dyskinesias? I think

we'll get much better answers to those as the numbers of this study increase. The other really important thing, obviously in the name, is that this is a global study. Actually, European ancestry people in the world comprise about three-quarter of a billion, 750 million people are of European ancestry. Of course, the vast majority of people in the world are not of European ancestry.

They're of African ancestry, South Asian, East Asian ancestry. And yet they've been relatively understudied in terms of understanding what goes on in Parkinson's genetics. So, that's really important for kind of equity and for science. So, for equity, of course, if we're right, that we can develop new treatments based on genetics. Obviously, we have to have treatments that are relevant to people who might be of African ancestry or might be of South Asian or East Asian ancestry. So, we think it's important that people from those ancestry groups are studied as well. And that's being very much enabled in the GP2 project.

We hope that at least a third, and I think it's going to end up more than a third, of samples analyzed come from non-European ancestry patients. That's kind of important for equity. It's also important for biology because the background variation is different in different parts of the world. And that gives us completely new insights into what's going on, which is going to be applicable to all Parkinson's patients. Of course, human biology is the same everywhere, but the background genetics is different. So, I think as you touched on in a previous podcast, the Nigerian African-American GWAS showed a variation in the GBA gene that is a really important risk factor for patients in Nigeria with Parkinson's. So, that variant doesn't exist in European patients.

So, we can never detect that in European patients. That study has to be done in patients of African ancestry, but it gives us completely new insights into what's happening with the GBA gene and how that impacts on Parkinson's biology, which hopefully will help all Parkinson's patients. So, there's kind of a scientific aspect to studying people from other parts of the world. The other thing which we're enabling in GP2, which is really important, is actually supporting investigators in other parts of the world to do their own research.

So, to enable African investigators to do research on PD in Africa, South American, India, South Asia, East Asia. So, the idea really is we can offer some core support with generated genetic data and how to do analysis, but we hope that this will be kind of democratic and will be done by people around the world taking forward research as part of the sort of GP2 family of investigators. So, we just, last week, had a very successful meeting in Cartagena in Columbia. That meeting was with a lot of the collaborators in the GP2 project who are working in Central and South America.

The meeting was done with translation in Spanish and with bilingual slides. And it's amazing to see, of course, how much expertise there is in studying Parkinson's patients, but how much enthusiasm there is to be involved in research. And hopefully by enabling that research in South America, but all these other parts of the world, we can really push forward with Parkinson's genetics and develop new insights, which are going to help our patients.

Marie: Definitely, and Huw, I think, as you mentioned in your responses just now and earlier in our conversation as well, there are still many mysteries to be unraveled in the biology of Parkinson's disease, as well as these Parkinsonian syndromes. So, looking forward to the future, what are some of your future directions or what do you see as these key areas of opportunity in Parkinson's disease research?

Huw: I think that one of the important things is that we try to take what we've done back to patients. We try to be as certain as possible, that what we're discovering is translated into trials of new therapies that are going to help patients in the future. So, the trials of drugs that are related to LRRK2, the trials of drugs related to GBA, I hope that they're going to be new targets, new trials that are developed based on the genetic research that's been done in GP2.

I mean, in a way, this translational part of it, there are sort of two elements to that. So, one is like developing new targets and new things that are going to be of interest to either academic investigators or pharma companies that might be targets for Parkinson's treatments. The other aspect, of course, is having a network of sites that are actually active, collecting Parkinson's patients who could then participate in clinical trials. I think kind of linking together the biology, the drug trials, the clinical sites. So, one of the things we're trying to do now within GP2 is in a kind of working group led by Mike Nalls is to look at patients who might be eligible for clinical trials based on the genetic makeup data that are coming through the GP2 project.

Because drug trials usually want people fairly early in the disease course, this for some cohorts that maybe closed a long time ago, this won't be relevant, but for some cohorts where people might have been recruited, someone might have been recruited two or three months ago, and their genetic exam comes through, they get genotyped. It may instantly or rapidly suggest that they're eligible to be involved in a trial that then targets their particular form, the Parkinson's based on their genetic makeup. So, I think the translational part of it is really important. I think that also kind of decoding what all of this variation means. So, we are getting quite good and increasingly rapid in just like mapping out genetic variation, seeing what's different between patients and controls, and like saying, well, this is associated or causal for the disease.

Of course, the gap is understanding what all that variation means and decoding that in terms of biology. So, if you see a variation in a heat shock protein gene or adjacent to a heat shock protein gene, how does that affect neuronal activity? What pathway is activated? What's the biology of that? What are the targets for new therapies? GWAS — decoding genome-wide association studies, sort of decoding major risk genes for Parkinson's can be quite complex. We need to have resources that enable that to things like cell models where you can explore the variation on cell biology of genetic variants.

So, brain banks where you can look at what's happened to that pathology in the brain, related to that variant, but also to levels of gene expression, to like the total level expression of a gene or the alternative splicing of the gene. And the only way really to do that in a relevant tissue is to be able to study brains from donors who may or may not have Parkinson's where you can link together the variation with the gene expression. So, that's a really important part of what's going to happen over the next five years in decoding genetic variation. Some patients' families very generously donate their brain after they've died to be studied to enable Parkinson's research. I think that's going to become increasingly important over the next five years as you get more and more genetic data to decode what's going on.

There's work that is being done with that within the CRN (collaborative research network) in terms of just collating RNA sequencing data from patients who are involved in these types of studies to help with decoding GWAS. I think that's going to be really important where the science is. There's going to be a lot more done with Parkinson's plus conditions. So, we'll learn a lot more about PSP, MSA, a lot more about how they relate to Parkinson's disease and how they're different. And there's probably going to be, of course, a lot more with biomarkers to actually diagnose these conditions earlier on in the disease course.

And finally, as I kind of alluded to, I think in a way, if you were setting up cohorts, you would be really targeting non-European populations now because of the opportunity to learn new things in non-European populations. That's what's happening in the GP2 project.

Marie: Definitely. And I think Huw, as you pointed out, there's just so much to be hopeful about coming up in the field of Parkinson's research. And perhaps to wrap up our conversation today, if you could share just how you feel like your work is really bringing us closer to finding a cure for Parkinson's or contributing to some of the improved therapies for people with these conditions.

Huw: I think that it is collaborative, of course, what we're doing. Working together with other investigators is very important. I think this switch to progression genetics is important. So, that's something that we've been very keen on. I mean, other

investigators have been doing this as well. So, it's not just our group who has been doing this. So Mike Nalls, Clemens Scherzer, other groups have been looking at progression.

It's quite interesting because of course, what we've done up to this point is case-control. So, looking at what's the difference between someone with Parkinson's and someone who doesn't have Parkinson's. But in a way, that's not the problem that we've got in the clinic. Because what happens in the clinic is you've got someone who comes to the clinic who's got Parkinson's disease. And the question is what can we do to make sure that they're the patient who in 25 years time is playing golf and still working, as opposed to the patients who've got quite a lot of disabilities. That rate of change. I don't know how we can do that related to understanding the rate of progression.

So, rather than why did this patient get Parkinson's first place, why are they in a group that's very benign? Why are they in a group that's progressing very rapidly? And so that switch to studying progression, I think is really, I think what we are contributing in part to taking forward. And I hope that's going to lead to new insights into the biology of Parkinson's and developing new treatments.

Marie: Wonderful. Well, Huw, we appreciate you sharing your research and your insights with all of us today. It's been a pleasure to chat with you on the show.

Huw: It's been a real pleasure, and thanks for asking me to do this.

Marie: Well, Huw, thank you again. And listeners, it's been great to have you here with us as well. If you want to know how The Michael J. Fox Foundation can help your research, please visit michaeljfox.org/researchresources. And you can find new episodes of this show each month on the MJFF website or on your favorite podcast platform. And when you have a moment, please subscribe to our show to make sure you don't miss out on our outstanding lineup of upcoming episodes. We look forward to connecting with you again in our next episode of *The Parkinson's Research Podcast.*