The G word transcript

Why is Diversity in Parkinson’s Research so important?

**Candice:** Hello and welcome to the G Word podcast. My name is Candice King and I'm Patient and Public Engagement Manager at Genomics England, working in the Diverse Data Initiative.

**Will:** And I'm Will Townley, Cohorts Manager at Genomics England, and we both work in the Diverse Data Initiative. The initiative aims to reduce health inequalities and improve patient outcomes in genomic medicine for underrepresented communities.

**Candice:** On today's episode, we'll be joined by Dr. Mie Rizig and Sir John Hardy, who have recently authored a paper in The Lancet Neurology. The paper describes a novel African ancestry Parkinson's disease genetic risk factor. We will be discussing the need for diversity in genetic research, the key findings from their study, and opportunities for future research in Parkinson's disease. If you enjoy today's episode, we'd love your support. Please like, share and rate us on wherever you listen to your podcasts.

**Will:** Welcome Mie and John. It's a pleasure to have you with us today. I'd like to start by just asking you to let us know a bit more around your background and how you became interested in Parkinson's disease. Mie, would you like to start?

**Mie:** Yeah, thank you very much Will and Candice for inviting us. So my name is Mie Rizig. I'm a neurologist and a neurogeneticist. I work in UCL Queen's Square Institute of Neurology and in Imperial at Charing Cross in West London. My passion is studying the genetic and the clinical diversity of neurodegenerative conditions, particularly Parkinson's disease. I focus in underrepresented populations, and I mean by underrepresented population, those people have been Historically not being studied in genetic studies, in particular Africans and people from an African admixed background, those including people from the Afro Caribbean's origin.

And my journey in my research started after my PhD, so I trained as a molecular geneticist and I completed my PhD in UCL. And after that I started a postdoc fellowship in Queen Square. And at that time I was supervised by Professor Nick Wood and I was given a task to recruit and clinically characterized a cohort of patients in the UK with a particular genetic mutation called the Lark2. And it was predisposing people to Parkinson's disease and the majority of those people either from a European or a Jewish background. Through my time in my postdoc fellowship, I realised that little or no research was done in people from an African or an African admixed background. And that led me to seeking to do more to resolve that situation.

And out of frustration, I took about four years out of my clinical training after my Bostock Fellowship. And I worked with my colleagues in different African continents. And I reached to Several teams in UCL, including John, who is with us today, and teams in the NIH in America, to try and establish a group of people who are dedicated to understand the genetic of Parkinson's disease.

And this resulted in building up a pan African collaborative effort. The consortium itself is called the International Parkinson's Disease Genomic Consortium Africa. It includes about a hundred and ten neurologists from about twelve. [00:04:00] African countries, and it's been funded by the Michael J. Fox Foundation, and I guess we'll talk more about the success story in the next hour.

**Will:** Thank you very much. John will you give us a little bit about your background too?

**John:** Sure. So I actually started off by being a pharmacologist interested in brain diseases, but in 1983, there was a paper studying the genetics of Huntington's disease. by Jim Gusella at Harvard, showing that the gene for Huntington's disease is on chromosome 4. And for me, that was a really important paper to read, because it suddenly made me realize that you could use genetics to find out how diseases start.

And I was lucky to be hired by the department at St. Mary's Hospital Medical School, now part of Imperial College, where I was able to, the department was full of molecular geneticists, and they really taught me and supported me as I switched the focus of my lab from being pharmacology and pathology to being genetics.

And so I've been studying genetics of Alzheimer's disease, Parkinson's disease, and frontotemporal dementia ever since. And, you know, most of the work we've done, Was in white people and of course we made a lot of findings in white people, but it's clearly time that we understood the disease across the world and for the benefit of everybody and not just the populations who have been studied before so that's why You know, when me came along, you know, I was very glad and honoured to help her to set up her program of work looking at Parkinson's disease and dementia in Africa.

**Candice:** Thanks so much, John. And again, a welcome from me to both of you to the podcast. Mie I wonder whether as we're talking about Parkinson's in this episode, if you could give us a brief overview of what Parkinson's is and how it affects people living with the disease.

**Mie:** Parkinson's disease is a progressive neurodegenerative condition. It has what we call motor symptoms, which people can see. These are the stiffness, the slowness of movement. But it has a hidden aspect of it, which we call it non motor symptoms. These are related to people mood, cognition, bowel functions, swallowing functions. So main... Aspects of their daily life can get affected and disrupted by Parkinson's disease.

And it does not just affect the patient, it affects the relatives, it affects It affects the communities, and it affects everyone around the patient. It doesn't have a [00:07:00] curative treatment at the moment. The options which we have to offer the patients are symptomatic, management options, and supportive treatment.

And it affects all ethnic groups. And the global burden of disease data is telling us that the burden of the disease itself is increasing. So people are living longer, they are more affected by neurodegenerative conditions, and the figures of people who will be affected by the condition will double by the year 2050.

A large number of people will come from places like Africa. I must emphasize that despite The situation which we have at the moment is we think we achieve significant advance when it comes into research into Parkinson's disease in the last 20 years. Most of these findings were related to genetic studies.

So the work of John and other colleagues within the field, including some of the people who are collaborating with in this paper in the NIH, made significant advance in the field. So there are about 20 genes or so who has been discovered and predisposing people to what we call monogenic. These are the genetic forms with the familial forms of Parkinson's disease. We understand more about the population risk for Parkinson's disease.

**Will:** And how do these advances translate into something that patients might see a benefit from?

**Mie:** All these advances now has been translated into clinical practice. So now we can test people for certain genetic mutations. provide genetic counselling, give them some advice, and more importantly, they've been involved in clinical trials.

So at least two genes, the ones which have been discovered, they are in phase two or phase three, these basically passing safety stages and they've been tried in patients at the moment. And we think that we are heading towards the right track in term of finding management. If it's not really curative management, it would be something which would be significantly help people.

But as John said, most of these discoveries were done in white populations. So the field is significantly lacking a lot of information or data from diverse populations. And this is not just related to Parkinson's only, but it's related to other areas.

**Candice:** Why might this be an issue to those people from an African or admixed background? Do you think there will be, for example, implications on clinical practice?

**Mie:** Just to give the listener an idea about the deficiency of data in genetic studies. So when we looked at the total number of participants in what we call the whole genome association studies, this is looking at the genetic risk across different variants in the genome, is the number of people from a white background, and this is the Northern Europeans, is about 95%. The number of people from an African background is only 0. 2%. So this is significant. This is a significant disparity. And when you want to translate this into clinical practice, you think about How I will be able to test those people sufficiently enough so I will be able to understand the molecular biology and then offer them treatment.

And the answer is at the moment, people from an African or African ethnics background might not necessarily be able to benefit from these clinical and therapeutic options. which we might be able to offer to other populations. So this is the first point. An example of this, just to simplify it to the people who are interested on the diagnostic and therapeutic options is, for example, testing them for a particular genetic mutation because we know that certain genetic mutation is ancestry specific.

This might not be possible, providing them with genetic counselling if they want to know their family risk. We might not be able to do that is stratifying them for clinical trials and by stratifying is understand how these genetic mutation affect their clinical profile and ultimately we're doing all this to offer people access to therapeutic options and involving them in clinical trials and as we're moving towards more targeted therapeutic trials by not investigating the genetic background in those people, We will not be able to offer them these options because most of these trials will be focused on specific genetic targets.

**Candice:** Thank you so much. It sounds like it's absolutely vital that research is happening with people from African and admixed backgrounds. And I guess that leads us really nicely into talking about your contribution to the area of research and the paper that you've recently published in the Lancet Neurology. So can you tell us a little bit about that paper?

**Mie:** As we discussed, there's Parkinson's disease, is... and neurodegenerative conditions which are affecting people from different ethnic groups. And in fact, at the moment, the figures of Parkinson's disease is increasing massively around the world. Based on the data, which was coming from the global burden of disease, the number of people who will be affected by Parkinson's disease globally will double by the year 2050.

And the number of people who will be affected in Africa is expected to be higher. Then the people from other continents, specifically from Europe and America. So with that in mind, we think that larger people from an [00:13:00] African and African ethnics population, specifically from within Africa, will be contributing to the bulk of people who will need management in the future.

And the genetic discoveries which were made in the past, as I said before, were primarily were in northern Europeans. In fact, all the genome wide association studies. which were done in the past, didn't include any people from an African or African admix. So our paper, the first genome wide association study, looking at the disease risk in an African and African admixed groups.

And what I mean by African admixed group, those people who have an ancestors. from an African origin. In our paper, those people are particularly African American from the southwest coast of America, the Afro Caribbeans. The paper [00:14:00] itself, it's a big collaboration. It involves multiple groups and teams, including neurogeneticists, neurologists, bioinformaticians from different centres. So one of the big achievements on this paper, we showed that through international collaboration, we're able to achieve scientific advance. Otherwise, we would not have been able to achieve it. The second thing for the first one is being the first GWAS in African and African ethnics.

The second thing is the value of collaboration. The third most important thing is we showed in the paper that there is a genetic risk in all the loci or a variant, we call it the genetic variants in a locus in chromosome one, which is increasing the risk in people from an African and African admix groups or population and predispose them to Parkinson's disease significantly.

It's been described before in European population, it's called the GBA1. The variant itself, which we described, is unique to the African population. In our paper, we screened about 1, 500 patients, two thirds of them from Nigeria. And one third from different centres across America, and they recruited as part of two consortiums.

**Candice:** What impact does the unique variant have for this cohort of people living with Parkinson's disease?

**Mie:** The variant increases the risk in patients. who they have two copies of this variant by about 300%. And if you have one copy of the variant is increasing the risk by about 50%. So this is significant risk in patients versus control.

The other finding It's not just increasing the risk, but reducing the age of onset. And I mean by this is people who are carrier to this particular variant. They are younger by about two to three years. And the third most important finding is the variant itself is so unique to this population. I mean by so unique is when you screen for the risk variant across other populations, and this will include Europeans, Asians and East Asians, South Asians, it is absent in our internal databases and the external databases. So that will make that variant very exclusive to people from Black and black admixed ancestries. And I would like to draw the attention of, um, the listener to the black admixed groups, because this will encompass very large populations across the world.

**Mie:** In terms of numbers, the number of people in our study who tested positive or carriers for this particular variance is up to 30 to 40%. So, if we can make a projection of this across the number of people who might be carrier to this variance from different populations, based on them being black from a black or black ancestry's background, this will be a significant number of people.

**Candice:** Mie and John, I wanted to ask a question about why you think this research has only been done now? I also wonder if you can speak to some of the barriers you think exist for those people who want to take part in this kind of research.

**John:** As a white guy, I think I can say this, there's been definitely a history of exploitation, and I think that has contributed to, uh, suspicion, understandably suspicion about research and so on.

So, I think that's been part of it. That's gradually changing, I think, but that's definitely been part of it. But it's just also it's economic access. I mean, it's, you know, getting access to health care in poorer countries and in poorer areas of our country is more difficult. And so that's also been a barrier that we have to overcome.

Mie, do you think that's a fair statement?

**Mie:** So there are very big contributors and as a result of this is a lot of people who we see and I can say this as a clinician who practice in the UK and practice abroad as well. You can see there's a lot of patients even in high socioeconomic background in the UK and the US.

They do not have access, even if these clinical trials and, and these, diagnostic, and new studies are, are available. They don't have the right access or the right information to these studies. And I think the community itself, I'm talking about the research community. The clinical community, and the policymakers, they didn't put this item high in the agenda.

So we're not proactively seeking those particular group and try to engage with them. And the most important lesson I learned through the consortium who I work with, is we need to sit with those communities, hear from them. learning from them and devise solutions which are suitable for them. What John described as the exploitation or the lack of understanding as a tool to correct that misunderstanding and make them the drivers or the main drivers to change.

**Candice:** I completely agree with that. I think you make a very valid point that there's a historical mistrust and abuse of trust and that people have such a big role to play in showing us what we need to do to build that trust. I was going to ask you how important do you think it is to engage and involve the people who we're hoping to join studies in the design of the research?

And how important is it to specifically get people from African and admix backgrounds involved in the process of designing research?

**Mie:** It's so vital. I mean, I can't emphasize how vital it is. I keep on telling my patients is researchers and clinicians do not make the change because they wake up in the morning and they've decided, by the way, I want to research Parkinson's.

It doesn't happen that way. It happens because a patient or a family or a community. So the urgency and the need for that change to happen and they love it and they seek and they've asked a lot of questions to make that difference happen. And our role as researchers and clinician is to listen. So I don't think that there is any value of doing any research without making.

The patient, the centre, and I mean by the centre, those are the people who are telling us about their priority. If we do things in a wrong way, they tell us how to do it right. If they prefer certain things to be set in a way where we can't see it or we don't know about it, they need to be the drivers who they tell us how to do things better.

So in answer to your question, I don't think there's any research will exist. or will be successful without having the patients and the communities at the centre of that research.

**Will:** I think that's a really important point and I think as we were just talking [00:22:00] about mistrust earlier, I think that's one way that you can build trust is by listening and adapting and really making sure that research is valuable and addressing the needs of the people it's there to help.

It's a really interesting discovery and I was wondering what the next steps might be for research in this area. If money wasn't an issue, which it often can be, what research would you do next?

**Mie:** So the research find a big finding, which I think this is important, but open the avenues of a lot of questions. So we do have, and I think that the reader of the paper will realize that there are a lot of questions which we needed to answer. The first question, which from a clinical point of view, I would like to know, how many people in the world are affected by this variant? So as a what other populations? is affected by it and can benefit with it.

So we wanted to test as many as possible people from an African and African ethnics ancestries to know more about this. The second thing is the clinical presentation of those people. So although the paper identified that variant, But we didn't have sufficient clinical data set from those populations to be able to know how Parkinson affect them if they have this particular mutation.

So for example, how the memory get affected, how the movement get affected, do they progress quicker, do they progress less? And this is really very important from a clinical point of view. We'll be able to cancel them and then we'll be able to advise them and monitor them. The third most important question is how this variant works, but we know that there is about 300 different mutations in that particular gene in the Europeans, and we know that each one of them function in a different way, and we presented in the paper that.

that perhaps this variant have a novel function by which is [00:24:00] modulating what we call a transcription. So in this way, we wanted to dig deeper into this. And definitely a lot of people who are working on cell biology and designing therapeutic trials will go into a different avenues about designing new therapies.

**Will:** Mie, can I jump in here and ask what kind of therapies you mean?

**Mie:** We call them anti ASOs or antisense oligos. So this is a different thing which people might want to progress towards and understand more. So I guess is we do have a lot of things to answer. We do have a lot of opportunities. for research.

And well, I hope one day I will wake up in the morning and money is not an issue. You started by asking, by asking this. So if money is not an issue, I think we do have a lot of things to do and discover.

**Will:** It's really great to hear. And I think it just shows that there is so much exciting research that can happen in the future. And John, what would your next steps be for research in this area if money wasn't a limiting factor?

**John:** I think we just want to recruit more patients and get information and research availability across the continent. Don't you think, me, really?

**Mie:** Yeah, I think resources are a main barrier to research. The research in Parkinson's and other neurodegenerative conditions has been underfunded.

In the African continent itself, communicable diseases and infections were big in the agenda. But now as the continent is aging and there are a higher number of people who are affected by neurodegenerative conditions, big investment Need to go to these areas and certainly Parkinson's disease and other diseases like dementia will benefit from increasing investment and resources.

And one thing to add, which I think Johnny alluded to. is we need to understand Parkinson's disease better. And by understanding Parkinson's disease, and this will reflect into other neurodegenerative conditions, dementias and others, is we don't need only to focus on technology.

**Candice:** Mie I wonder if you could expand on what you mean by technology, and if technology isn't the most important focus to further our understanding of Parkinson's disease. What, in your opinion, do you think the focus should be on?

**Mie:** So in high income settings, we focus on advancing high throughput technologies, imaging technologies, digital technologies, building up big databases. But these things can take us to a limit, so they do have a limit in terms of understanding biology.

So what we needed, we needed to diversify and invest in biology as well. And by diversifying and studying biology, I mean including as many diverse groups as possible. So African is one of those diverse groups. And we can use the biology as a tool for discovery. So if we understand how this particular gene, like the GBA, cause the disease in African population and combine this mutation by the mechanism by which is causing the disease in the European, we advance science in general. So we understand the molecular aspects of Parkinson's disease for all population and the benefit does not go to one. population. It goes to the patients who are affected by the condition worldwide.

And this is a very important and strong message, which we need to consider in our policymaking and funding and thinking about the distribution of resources.

**John:** Actually, I've just thought of one further answer to your question. About what would you do with more money? And that is, me has been involved in this too, and that is more training.

So we train African clinicians, we train and enable African researchers. We've been trying to do a little bit of that by having people from Africa visit the labs and train over here.

**Mie:** I support this, John. The reason for it is when we talk about research as a global endeavour, we think about what we call a capacity building.

And we're not talking just about patients only, we're talking about the diversifying the research for the researchers and the scientific community.

**Candice:** So if we're talking about research as a global endeavour, and as part of that, we are giving and receiving knowledge, what do you think we can learn from our collaborators?

**Mie:** So what we wanted through our consortium is to engage with those researchers so they learn from us and we learn from them. And then what we do well in universities around the UK and institutions in the NIH, we invested in technology and research. Standing genetic medicines better. The Africans colleagues, they know the clinical part of things better, so we learn from them, but they what the clinical part of their patients better.

So we learn from them from that point of view. And. We exchange with them our genetic knowledge and our ability to do sophisticated analytical or analysis like bioinformatics, and this is paid dividends because we become partners, and then when they went back to their institutions, they were able to establish departments, which I think this will result in significant collaboration with us and other institutions in the future.

question can raise is perhaps in high socioeconomic setting or maybe in the UK or in the US, maybe we are not as successful in recruiting patients, our people in African countries. So people in Nigeria, for example, managed to [00:30:00] recruit about 2000 patients within three, four years through the network. Maybe we will not be able to do this in high socioeconomic setting or in the UK in a way that's for the barriers that we said because we don't have enough clinicians who may be relating to these communities or may be from those communities so they will be able to reach to them. And how important

**Candice:** do you think it is for researchers to be diverse and also representative of the communities they're trying to recruit?

**Mie:** This is quite important. When a patient's come to the hospital, perhaps They want or they feel more comfortable talking to someone who understand their backgrounds, understand their concern, understand their cultural references. And then we might need actually to start thinking and considering this. So diversifying the workforce within the health systems is really important. Trying to shape our clinical practice and our research, recruitment skills. So be able to tackle things where patients do not talk to us about. So if making them more comfortable talking to someone who looks like them or understand their cultural background will make them more comfortable.

Perhaps we might need to invest more on this and I think you're doing great work on the diverse data trying to tackle this and try to understand the barriers why people from certain backgrounds are not engaging with genetic research in the UK and I guess we will be learning from your effort moving forward.

**Candice:** No pressure then. I do think what you said there is really interesting. In terms of future Parkinson's research in the UK, what do you think people who are living with the condition could expect to see next? And also, how would they find out more if they wanted to?

**John:** I would say contact us. I mean, there's many populations here in the UK who are still not properly served.

Here I'm thinking of, particularly, of the South Asian community. But you know, I think contact us we really want to get out there.

**Mie:** Yeah, I agree with John completely. So in my clinical practice is I work in West London So I see patients regularly from different backgrounds and I spend a little bit of time trying to understand What do they know about research in the UK and we do have fantastic opportunities for research in the UK Genomic England is one of them the diverse data is one of them, but those communities that they do not have access to these information.

So as a clinician, my job is to work hard, and this is what I'm passionate about, and this is what I'm investing all my time and my career in doing, is engaging with these population and try to make them. understand more about the opportunities which are available through the fantastic national health system that we have, the opportunities of research that we have.

And I'm hoping that we will have, we'll get this message across. I'm hoping that populations within the UK from African or African admixed or South Asians or even Middle East populations can contact us. can ask about these opportunities, they will reach out to know more, and hopefully they can get engaged and get the benefit back.

Because by only doing this, and I will emphasize on this, is by only them taking charge of this, we will be able as a clinician and scientist to find Things which are beneficial to them and I hope this message will come across to them and hopefully they will listen.

**Will:** Thank you, Mie. Your passion really comes across. Hopefully, people listening have learned more about research in this area. And if they see similar projects in the future, will know a bit more about the impact that this research can have.

**Candice:** Yeah, absolutely. And I'm hoping as well from our conversation that people understand the value and impact they can have on designing the research that then works for them and that they are able to take part in and understand what that looks like for them and how they can further the area of research.

**John:** Yeah, I think contact us is something to push a little bit. I mean, we, we're always, we always want to, you know, work with communities here in the UK who are not properly served with research opportunities. And I think that this is an important message to get out.

**Mie:** Yeah, and I just want to highlight, we are about to start research studies in the UK, doing exactly the same of what we've done in Africa.

So hopefully people will be able to hear from us about well-established genetic studies for people from an African and African admixed and South Asian and hopefully Middle East communities in the UK. And we will try to replicate what we've done in the African continent, but at the same time finding new findings which might be related to these populations.

**Candice:** And we might have to have you both back on in the future to tell us about your findings in the UK. So how exciting to know that that will be coming up and going ahead.

**Will:** Thank you so much to our guests, Dr. Mie Rizig and Sir John Hardy for joining us today. It's been great to discuss genetic research in Parkinson's disease and the need for diversity in this area. It's exciting to think about what might be possible with genetics research for people living with Parkinson's disease in the future.

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**Candice:** And if you'd like to contact either Mae or John about anything you've heard here today, they are contactable via their email addresses in the episode bio. We've been your hosts Candice King and Will Townley.

This podcast was edited by Mark Kendrick at Ventoux Digital and produced by Naimah Callachand. Thank you for listening.