**Behind the Genes Transccript**

**Naimah: Welcome to Behind the Genes.**

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**Naimah: My name is Naimah Callachand and I am Head of Product Engagement and Growth at Genomics England. I am also one of the hosts of Behind the Genes. On today’s episode I am joined by Gavin Arno, Associate Director for Research at Greenwood Genetic Centre in South Carolina, Kate Arkell, Research Development Manager at Retina UK, and Bhavini Makwana, patient representative. Today we will be discussing findings from a recently published study in the American Society of Human Genetics Journal which identified two non-coding variants as a cause of retinal dystrophy in people commonly of South Asian and African ancestry. If you enjoy today’s episode, we’d love your support. Please like, share, and rate us on wherever you listen to your podcasts.**

**Okay, so first of all I would like to ask each of the three of you to introduce yourselves. Bhavini, maybe we’ll start with you.**

**Bhavini:** Hi, I’m Bhavini Makwana, patient representative, and also Chair of BAME Vision. I have other roles where I volunteer for Retina UK, and I work for Thomas Pocklington Trust.

**Naimah: Thanks Bhavini. Gavin.**

**Gavin:** Hi, my name is Gavin Arno, I am Associate Director for Research at the Greenwood Genetic Centre in South Carolina, and I am Honorary Associate Professor at the UCL Institute of Ophthalmology in London.

**Naimah: Thanks Gavin. And Kate.**

**Kate:** Hi, I’m Kate Arkell, Research Development Manager at Retina UK.

**Naimah: Lovely to have you all today. So, let’s get into the conversation then. So Gavin, let’s come to you first. First of all, what is retinitis pigmentosa and what does it mean to have an inherited retinal dystrophy?**

**Gavin:** So, retinitis pigmentosa is a disorder that affects the retina at the back of the eye. It is a disease that starts in the rod photoreceptor cells. So, these cells are dysfunctional and then degenerate causing loss of peripheral and night vision initially, and that progresses to include central vision and often patients will go completely blind with this disease. So, retinal dystrophies are diseases that affect the retina. There are over 300 genes known to cause retail dystrophy so far, and these affect different cells at the back of the eye, like retinitis pigmentosa that affects the rods. There are cone rod dystrophies, ones that start in the cone photoreceptors, macular dystrophies that start in the central retina, and other types of retinal dystrophies as well.

**Naimah: Thanks Gavin. And Bhavini, just to come next to you. So, you received a diagnosis of retinitis pigmentosa at the age of 17 after a genetic change was found in the RP26 CERKL gene. At this time only ten other families in the UK had been identified with this type of genetic alteration. Would you mind sharing a bit more about your journey to your diagnosis?**

**Bhavini:** Yeah. So, at the age of 17 is when I got officially diagnosed with retinitis pigmentosa, but leading up to that I was experiencing symptoms such as night blindness. So, I struggled really badly to see in the dark, or just in dim lighting, like this time of the year in winter when it gets dark quite easily, all my friends from college could easily walk across the pavement, but I struggled. I was bumping into a lot of things. Like things that I wouldn’t really see now that I know my peripheral vision, I was losing that, so like lamp posts or trees or bollards, I would completely miss or bump into them. I was missing steps, and had a really, really bad gaze to the sun. Like, everything was really hazy. That continued and I just put it down to stress of exams. You know, just given that age and where I was at the time of my life. But then it kind of continued. So, I went to the see the optician who then referred me, and after months of testing I got diagnosed with retinitis pigmentosa. Back in the late 90s when I was diagnosed there wasn’t really anything about genetic testing, or cures., or treatments. I was basically just told to get on with it, and that was it.

It was only until about 15/16 years later I came across Retina UK, started understanding what retinitis pigmentosa is, and what it means, and then when I was offered genetic testing and counselling at one of my annual Moorfields appointments, they explained to me what it involved, what it could mean, what kind of answers I would get, and I agreed to take part. It was a simple blood test that myself and both my parents took part in.

**Naimah: Thanks for sharing that Bhavini. So, I know you were able to receive a diagnosis through whole genome sequencing in the 100,000 Genomes Project after the alteration in the gene was found, and this was found in the coding region of the genome. But in this study that we are talking about in this podcast, we know that the two genetic changes that were found, they were in the non-coding region of the genome. Gavin, could you tell me in simple terms what the difference is between the coding and non-coding region of the genomes and why these findings are significant in this case?**

**Gavin:** Yes, sure. So, the human genome is made up of about 3 billion letters or nucleotides which are the instructions for life essentially. Now, within that human genome there are the instructions for roughly 20,000-25,000 proteins. This is what we call the coding genome. These are the bits of DNA that directly give the instructions to make a protein. Now, we know that that part of the genome is only roughly 2% of the entire genome, and the remaining 98% is called the non-coding genome. Now, we understand that far less well. We have a far poorer understanding of what the function of the non-coding genome is versus the coding genome. So, typically molecular diagnostic testing or genetic testing is focused on the coding genome, and historically that has been the fact. Now with advances in genome technologies like whole genome sequencing and the 100,000 Genomes Project, we are able to start to look at the non-coding genome and tease out the previously poorly understood causes of genetic diseases that may lie within those regions of the genes.

**Naimah: Thanks Gavin, I think you have just really highlighted the possibilities available with looking at the non-coding region of the genome. Kate, coming to you next. I wanted to talk about the importance of uncovering and understanding genetic causes of inherited retinal dystrophies, and how do discoveries like these change the landscape of care for patients with inherited retinal dystrophies?**

**Kate:** So, getting a genetic diagnosis can really help families affected by inherited retinal dystrophy. It helps them and their ophthalmologists to better understand their condition, and in some cases gain some insight into possible prognosis, which helps people feel a lot more in control. It can also potentially inform family planning decisions and even open up options around access to reproductive technologies for example, not only for the individual, but sometimes also for their close relatives. Of course, researchers are making great strides towards therapies, some of which have reached clinical trials. But a lot of these approaches are gene specific, so for people who know their genetic diagnosis, they are more able to recognise research that is most relevant to them and quickly pick out potential opportunities to take part. At the moment it is still the case that around 30% of our community who have a genetic test will not receive a clear result, and that can feel very frustrating. So, the more discoveries like this that are made, the better.

**Naimah: Thanks Kate. So, now we are going to hear a clip from Martin Hills, our Retina UK patient representative who has been diagnosed with autosomal dominant retinitis pigmentosa. Martin has undergone genetic testing and shares more about his experience.**

***Martin:*** *My name is Martin Hills, and I was officially diagnosed with autosomal dominant retinitis pigmentosa in 2001, and because of that I immediately had to stop driving which made a huge impact both on myself and my family. My eyesight has slowly deteriorated over the years. It first started with difficulty seeing at night, and also playing some types of sport, which I think probably was in my 20s. My peripheral vision has been lost slowly and now has completely gone. Fortunately, I still have some reasonable central vision left which is a great help. I am registered as severely sight impaired, and I am also a symbol cane user. My father and aunt were both diagnosed with this condition, and my daughter has been relatively recently, as has altogether eight members of our wider family, and that also includes two younger generations. In 2015 I went for genetic counselling and testing and at that time it was for 176 genes known to be associated with retinal dystrophies. I believe that has now gone up to about 300, but at the time they couldn’t recognise what my faulty gene was, and that has still been the case to my knowledge to date.*

*I have also been part of the 100,000 Genome Project along with several others of my wider family, and I am also a participant in the UK Inherited Retinal Dystrophy Consortium RP Genome Project, which has been sponsored by Retina UK. The impact of not having a positive genetic test result is quite interesting and has really been a rollercoaster. I guess it is all about hope, and to start with when I knew I was going to be genetically tested, I think my first reaction was optimism, and I think if you have a positive test result, that is a real hope for the future. I think that is quite exciting particularly as things seem to be progressing so rapidly. But because I didn’t get a positive result, the next reaction I had really was disappointment because I felt one step behind people with a positive result. Of course the natural reactions are one of frustration, and then I guess followed by realisation of the situation, and heading towards trying to adjust and making coping strategies for the future. I still feel that genetic testing for all forms of medical conditions is so important and has a huge future in understanding and then potential treatments for so many medical issues. I guess it might be a bit too late for me, but if I can contribute to finding a restorative treatment for the younger generations of my family, and for that matter other people, then I think that is good enough for me.*

**Naimah: So, we have just heard from Martin that although he has not been able to have a positive genetic test result, his involvement in various studies may have benefits in helping others find treatment. So, I guess on that point Bhavini, maybe you could comment, or ask you how you felt whenever you were about to get a diagnosis through whole genome sequencing?**

**Bhavini:** Yes. When I got called in almost three and a half years after the testing that took place was a massive, massive relief because not only did I get genetic counselling before the testing period, but I got called in and I spoke to a genetic counsellor who explained what they had been able to find and what kind of RP it was, how it would progress, and just answer so many questions. I am the mother of two daughters and even having two children, I lost a lot of sight after my first daughter, but at that time there wasn’t any evidence or there wasn’t any … you know, there was nothing I even knew about what questions to ask or anything, so I did go on to have a second child and drastically lost more sight. I had always been told, because the lack of awareness and understanding of RP in my family, and I am one of four children, and I am the only one that has it, so there is no other family history. Now I know it could have skipped generations, but I was always told things like it was karma. I must have done something in my past life. I was told to kind of have these herbs or these remedies to cure my sight loss, you know my RP. I was even desperate enough to kind of … all these bogues treatments that you find online. You know, anything. I was so desperate to find anything that would help me.

When I received that testing and the counselling, it explained so much about how my daughters may or may not be affected, how they are carriers, and that was explained to me, how it would progress. So many questions and worries that I had for almost a decade and a half, they were answered. And not only for me, for my family, and all those people that told me all these sorts of things that I used to worry about that could have caused my RP. I was able to explain it to them and they understood that it was nothing to do with me being bad in my past life. It was actually you know, there is something scientific about it. So, it kind of gave me lots and lots of answers, and actually I then created a private Facebook page just with my RP26 CERKL genetic that I have been diagnosed with, just to see if there is anybody else out there, because when I was diagnosed, I think at the time I was told there was only myself and nine other families in the UK diagnosed with this particular gene. Now, I haven’t been that active on it, but you know there are people across the world who found my post and joined the group, and we share experiences about the age that we were kind of diagnosed, the kind of rate the symptoms have developed. It is so fascinating because we have got such similar experiences.

There is parents on there who are there on behalf of their children, and it is just so nice to see … I know it is RP, but the specific gene and the rate of which we have experienced all the symptoms, it is quite similar. So, it has been quite supportive and helpful and reassuring to my family including my daughters.

**Naimah: That’s incredible Bhavini and it’s really nice that you have created that group and created kind of like a support network for all the other families that have been affected by the same genetic condition as well. Yeah, that’s incredible. Gavin, I know the findings in the study show that the genetic changes in this study are more common in people of African and South Asian ancestry. So, so I want to understand why is this an impactful finding in the study?**

**Gavin:** Yes, so Kate mentioned that around 30% of people with inherited retinal dystrophies who have genetic testing don’t get a molecular diagnosis and we are working in my research lab and many other research labs to improve that. Now, that figure is very much higher in patients of for example African ancestry in the UK, and this is partly due to the fact that historically and even now genetic studies have been focused on European individuals and taken place in the US, and the UK, and Europe, and wealthy countries across the world. This means that people of African ancestry are poorly represented in genetic studies, not just genetic studies of genetic disease, but population studies as well. So, we have less of an understanding of the genetic variants found in the genomes of individuals of African ancestry. So, that means we solve less of the genetic cases, particularly at Moorfields we published a paper on this several years ago with the diagnostic rates in European patients versus those of African ancestry, and it was very, very much lower. So, we need to do better for those patients, and this study identified a cause of retinitis pigmentosa in 18 families of African ancestry who were recruited to the 100,000 Genomes Project.

This is a fairly large proportion of the patients with RP of African ancestry seen at Moorfields Eye Hospital, and when we contacted collaborators around the world many more families were identified, and I think we ended up publishing around about 40 families who were affected by this particular mutation. So, we can look at that variant, we can look at the DNA sequence around that variant, and we found there is a chunk of DNA around the mutation in the gene that was coinherited by all of those different individuals. So, this is what we call an ancestral haplotype. It’s an ancient variant that goes back many, many generations and it has a fairly high carrier frequency in genomes of African ancestry. So, we think this will be a fairly significant cause of retinitis pigmentosa across the continent of Africa. And so, identifying it will enable us to provide a molecular diagnosis for those families. Potentially there will be many more families out there who don’t know they have this cause of disease yet. They may be affected but they haven’t yet received genetic testing.

But discoveries like this lead to better clinical management. We understand better the progression of the disease when we can study this in many individuals from a wide spectrum of ages and different backgrounds. We can provide counselling as Bhavini was talking about. We can provide patients with a better idea of what the future may hold for their eye disease, and potentially you know we are all aiming towards being able to develop therapies for particular genes and particular diseases. As Kate mentioned many of the gene therapies are gene specific, so if we identify a cause of disease that is predominant like this and affects many, many people, then of course there is more interest from the pharmaceutical industry to develop a therapy for that specific gene.

**Naimah: Thanks Gavin. I think that really does showcase how impactful these findings really are. Kate, can I come to you. So, Gavin touched on it there that people with African and Asian ancestry are significantly less likely to get diagnosed, but why is it important to ensure that these groups are represented in the genomic datasets?**

**Kate:** So, we need to ensure that genetic testing and diagnostic accuracy works for everyone, and not just those of European ancestry. So, as Gavin said if the datasets don’t reflect the genetic variations seen in African or Asian populations, then the tests based on those data are more likely to give incomplete results for those groups of people. We really need a diverse range of genetic information for researchers to work on. As it is clear from this study’s results, populations from African backgrounds for example may have unique genetic mutations linked to retinal dystrophy. So, if those are really underrepresented in datasets based on European populations, that is obviously going to present a problem. Gavin mentioned access to treatment. We need to overcome some of these disparities in healthcare access, and inclusion of broad spectrum of genetic data is actually a foundation for that.

**Naimah: Thanks Kate. So underrepresented groups are often less likely to know about genetic testing due to a combination of social economic and systemic factors that create barriers to access information. Cultural taboos can also play a significant role in shaping attitudes towards genetic testing, and I think Bhavini you kind of touched on this slightly with some of your experiences. I wonder, did you experience any of these cultural taboos?**

**Bhavini:** Yes, some of them, but I think by the time I was informed about what genetic testing and counselling is I had come across Retina UK and I had already started having that background knowledge, so when that was offered to me, I actually had a basic understanding. But as Chair of BAME Vision I work with a lot of ethnic communities, and when I speak about my own personal experience about receiving genetic testing and counselling, I kind of break it down into my own language, and the few common themes that always come out is people don’t really understand what genetic testing and counselling is. They hear the word counselling, and they think it is the therapy that you receive counselling for your mental health or wellbeing. So, again there is already a taboo around the terminology. Then it is lack of understanding and awareness, or where to get that information from. Also sometimes in different cultures, if you have been diagnosed with sight loss, you know blindness is one of the worst sensory things that people can be diagnosed with, so they try and hide it. They try and keep that individual at home, because they think they are going to have an outcaste in the community and the wider family, and you will be frowned upon, people will talk really bad.

So, it is not really common knowledge, so they don’t even talk about it. So, there is a lot of layers to unpick there. That is one of the priority areas in 2025 that we at BAME Vision are going to be working on to try and raise that awareness in different communities about what genetic testing is, what it could mean, how to get genetic testing if it is not offered to you at your own clinic. There is a lot of work I know Retina UK have done, so working with them, and how we can reach different communities to raise that awareness.

**Naimah: That’s great. You have touched on how important the education piece is. I wonder, do you have any other examples of how healthcare providers and genetic counsellors might better engage communities to ensure that they are receiving the care that they need?**

**Bhavini:** Yeah, absolutely. So, I think having information in different languages is essential, and I don’t expect to have lots and lots of leaflets in different languages. Whether it is audio form or whether there is different professionals within that setting that speak different languages that can communicate to those patients, or even their family or friends that could translate. I think language is definitely something. And having representation, so like different people who have accessed this and sharing their story and going out into community groups and sort of sharing those messages, is definitely what has been working for us, and we have been doing that on other topics that we have used.

**Naimah: Yes, they all sound like really important ways to try and engage with different communities. You have already mentioned how amazing that Retina UK have been and the support that you have received from them. So, I wonder Kate, if you could tell us a bit more about the support that is available for those with inherited sight loss, and how these resources can support people from underrepresented groups as well.**

**Kate:** So, we have a range of support services at Retina UK most of which involve our fantastic team of volunteers, one of whom is Bhavini, who are all personally affected by inherited retinal dystrophy themselves. So, they are all experts by experience so to speak. The team also does include members of the Asian community as well. So, if somebody makes a call to our helpline, they will be able to speak to somebody who genuinely understands what they are going through, which can be a lifeline for those who are feeling isolated and especially I think as Bhavini mentioned, if they feel unable to talk openly with their own family and certainly within their community. We have a talk and support service that offers ongoing more regular telephone support as well as in-person and online peer support groups where people can make social connections with others in similar situations. I think Bhavini has mentioned that she herself runs our London and Southeast local group. We also have an information resource called Unlock Genetics. That explains genetics in understandable language and clearly explains how people can access testing and what that will involve. So, we have stories on there from people who have gone through the process and talk about that. So, that is available on our website, and we can provide it in audio format as well.

**Naimah: So Gavin, looking to the future, what does this research mean for patients with sight loss and their families? What does this mean in the future?**

**Gavin:** So, I think now that we have access to whole genome sequencing through projects like the 100,000 Genomes Project, we are able to start the process of understanding new causes of disease that are found outside of the coded region. So, we can now look for non-coding variants that cause disease which was previously not possible because genetic testing was focused on 2% of the genome. As we make discoveries like this these will inform future studies. So, the more we identify this type of variant and are able to functionally test the effect on the gene or the protein, we are able to use that information to lead future tests. What this needs is large population datasets to be able to analyse these sorts of variants at scale. The more genomes we have the better our understanding will be of our population frequencies, and the key thing is here for inherited retinal dystrophies, all of these variants that we are identifying are very, very rare. So, we only find them in a very small number of individuals affected with disease, and an infinitely smaller number of individuals in the unaffected general population. So, the larger that population dataset is that we can study, the better we can understand the rarity of these variants and pick those out from the many, many millions of non-pathogenic or harmless variants that we find in the genomes of all the individuals.

**Naimah: Do you think the paper will help lead the way for diagnosis of other conditions in African and South Asian communities?**

**Gavin:** Yes. The better we understand causes like this, and we are now at the point where most of the genes that cause retinal dystrophy have been identified already, so the remaining causes to be identified will be these more difficult to find cases, non-coding variants, structural variants, which we haven’t touched on today which are larger rearrangements of the genome. These things are harder to find, harder to interpret, so the more that we find like this, the better our ability will be to interpret those sorts of variants. There are many similar findings coming out of genome studies like 100,000 Genomes Project. For example, there was a significant finding recently published on a non-coding RNU gene which causes a significant proportion of neurological disorder in the 100,000 Genomes Project. You need these studies to be able to drive forward the research in areas like this.

**Naimah: Thanks Gavin, and the discovery that you are mentioning is the RNU4-2 gene that was discovered earlier this year. You can hear more about that on our other podcast on our website which is ‘How has groundbreaking genome work discovery impacted thousands far and wide’ to learn more about that as well. But yeah, I agree it is another really great example of how impactful these findings can be.**

**Okay, we’ll wrap up there. Thank you to our guests Gavin Arno, Kate Arkell, and Bhavini Makwana for joining me today as we discussed the findings from a recent study which has identified genetic changes responsible for retinal dystrophy, and people commonly of South Asian and African ancestry. If you’d like to hear more like this, please subscribe to Behind the Genes on your favourite podcast app. Thank you for listening. I have been your host and producer, Naimah Callachand, and this podcast was edited by Bill Griffin of Ventoux Digital.**