**Behind the Genes Transcript: How can parental insights transform care for rare genetic conditions?**

**Jillian Hastings-Ward, Dr Karen Low, Lindsay Randall**

**Jillian: Welcome to Behind the Genes**

**Lindsay:** Historically, there’s been a significant absence of patient voice in rare disease research and development, and knowing that’s changing, I think that’s really empowering for families and to know that professionals and industry are actually listening to our stories and unmet needs and really trying to understand, and that offers much greater impact on the care and treatments of patients in the future.

**Jillian: My name is Jillian Hastings-Ward. On today’s episode I’m joined by Dr Karen Low, Consultant Clinical Geneticist and Chief Investigator for the General Cohort Study, and Lindsay Randall, Paediatric Practice Development Nurse and founder of Arthur’s Quest, which is a UK registered, non-profit, raising awareness for the ultra-rare condition: SLC6A1, developmental and epileptic encephalopathy. Welcome to you both.**

**Today we’ll be discussing the GenROC study, which is aiming to understand more about the health, development and valuing the experiences of children with neurodevelopmental conditions. If you enjoy today’s episode we’d love your support. Please like, share, and rate us on wherever you listen to your podcasts.**

**Thank you both very much for joining us today, Karen and Lindsay. There’s a lot we want to cover, but first of all it would be great just to put a little bit of context around the Gen-Roc study. Karen, can you tell us a bit about what the study is aiming to do, who is eligible and why do you want them?**

**Karen:** Thank you. And thank you so much for having me today, Jillian. So, the GenROC study, first to just explain to people what ‘GenROC’ stands for. GenROC stands for the Genetic Rare Syndromes Observational Cohort Study. Just to give you some context about the study, I’m a clinical geneticist and most of my clinical work focuses on paediatrics, so I see children in my clinics and the sort of children I see generally are children with rare genetic syndromes. The last five to ten years we’ve got much better at diagnosing children with these rare conditions and that’s because testing has got so much better.

We can now do whole genome sequencing and we can do that on the NHS, which is amazing, children can get their tests as part of their clinical care, so it means that a lot more children are being diagnosed with rare conditions, about 2,000 per year in the UK. And the thing about that is, that I see these children in my clinics and I give their families that diagnosis.

But the problem is for so many of these ultra-rare conditions, like Lindsay’s family has, we sit there and we say to the family, “Well, your child has got ‘X’ condition,” and we give them some information from maybe one or two publications and linked to a leaflet and a Facebook group. And then we say, “But really we don’t know that much about this condition.” And they say, “But what is it going to mean for them when they are growing up or when they are adults? Will they be able to finish school? Will they be able to work? What is it going to mean?” And I have to shrug my shoulders and go, “I’m not really sure.”

And as a geneticist and as a doctor and as a mother really, I just felt that wasn’t good enough, and I found it really frustrating and I know that the families that I work with, that I look after, also find it frustrating and I wanted to do better.

And I also found it frustrating that for many genes, researchers would publish two or maybe three publications about these conditions, and then they would move on to the next novel gene, and actually, the journals are a bit like that as well, they like novel things, they like new conditions, they like the next gene. And so, it means that actually data doesn’t always carry on being gathered in these rare conditions, and there are a lot of them.

That was another thing, I sort of felt that these conditions were being done a disservice and that we needed to do better, so that’s where the whole idea of the GenROC study came from was my drive and desire to improve things for families and actually to work with families to improve that, and that’s where so this is a very highly co-produced study and right from the outset I’ve involved parents in telling me what they wanted to know and I’ve got a very, very active PPI group, full of parents of children who have got rare genetic conditions, and also I’m really lucky to have a young adult who has a genetic neurodevelopmental disorder herself and they all tell me about essentially what I should do and what I shouldn’t do. They tell me when I’m not doing enough or when I need to do something differently, so it’s very highly co-produced, they’re highly involved all along the way.

So, children with a confirmed genetic diagnosis in a list of eligible genes which people can see on our website if they Google GenROC University of Bristol, we’ve got a very easy checker for eligible genes, but they are essentially the most frequently diagnosed genes in rare neurodevelopmental disorders. And if their child is under 16, has a confirmed diagnosis and doesn’t have any other genetic diagnoses then they can go into the GenROC study, that’s essentially the eligibility criteria.

**Jillian: That’s really interesting. It’s very helpful to hear the background and I think as a parent of a child with a very rare disorder hearing that the clinicians also recognise this gap and the sort of pause that happens once you have your initial diagnosis, is really helpful and really encouraging.**

**Lindsay, can we turn to you next and can you unpack a little bit about what it meant for you to get a rare diagnosis for your child and what point on your family journey was that compared to where you are now?**

**Lindsay:** I think to get a rare diagnosis for us was difficult and challenging and I think the first kind of challenge that any family has is actually being well-informed by a paediatrician who is also well-informed, and that’s not always the case. That can affect the way we acknowledge or accept a diagnosis and how we also access support and how we understand what more we can do to make more connections.

We did have genetic counselling offered, but I think there are families out there who don’t get genetic counselling offered to help them understand the child’s diagnosis, and then there’s a heavy reliance on the internet, and as you said, there’s a lack of information out of there. A lot of conditions are newly diagnosed or they’re very complicated genes to work with, or as Karen said, they’ve had a couple of papers and people have moved on. And I think that does cause an immense feeling of isolation.

We were diagnosed in 2018, our son, our first child, and exactly as Karen said, it was a fairly quick appointment of, “We don’t really know much about this condition at the moment, there’s a couple of papers. We know of 34 children in the world at the moment with your condition. Here’s a Facebook group,” which we did join. And it is overwhelming to be given a diagnosis that’s delivered with such little hope I guess, finding sources of information that’s valid and robust is challenging, not everyone knows how to do that or has a skillset to conduct searches of academic research and I think that clinicians could definitely do better in also signposting the kind of umbrella charities like Unique and Contact and Swan and patient organisations, because I know that would have been definitely helpful for us as a family to be able to have opportunities to connect with others.

**Jillian: Thank you. Our diagnostic journey has been a bit a similar in that we were diagnosed through the NHS, and that at the time my son was the first person diagnosed with his disorder in the whole of the UK so it was really a big question mark, it was a question of our geneticist saying, “Here’s the three PDF articles that we know exist in the world about this condition. Can you read them and tell us whether you think that sounds like him in order for us to be confirming our diagnosis?” I very much hear what you’re saying there about feeling lost in the wilderness. And we too joined a Facebook group quite shortly after we got our diagnosis, and at the time my son was among the older ones or certainly as time has gone by he has been among the older children, so it can be really hard to know what might happen next.**

**I think that now as Karen was saying we’re getting much better at diagnosing people thanks to all the extra testing that’s happening, that happens much earlier in life than it has done in the past, but I think then it still leaves a gap in parents’ understanding because you don’t necessarily know what the next ten years might look like for example. And so, I think making connections with people who are in that age bracket can be really important, but it’s very hard to do.**

**So Lindsay, I’m conscious that your professional training as a nurse must have stood you in quite good stead when you were faced with a barrage of medical literature shortly after your diagnosis, but I think one thing that every parent shares is the desire to do the best for their child and especially in this world of rare disorders. There’s a huge amount of energy that comes through the community I think, faced with the need to try and self-start and build these networks and connections for themselves. Is that something that you’ve seen in your community as your experience?**

**Lindsay:** Yes, definitely. I think we’re a growing community and over the years of course more and more children and young adults have been diagnosed with a few older adults coming through. It is very much a global networking effort and parent/patient organisations have been set up in many countries now by parents of children with children with SLC6A1. I definitely think that drive to become an expert in your child’s condition is a long journey and one of continual learning and actually a lot of families simply don’t have a capacity to take that on, I think often the medical and scientific jargon is difficult to understand and that makes it challenging to access.

And as you said, as a paediatric nurse, I at least have some existing skills to understand healthcare to read the research and speak with medical and scientific professionals with some confidence, but in some ways, that has increased the burden I’ve placed on myself to become an expert for my children and other children and families who are not in the same position as me.

It does require a lot of dedication and time, and that does have implications on families because it’s time away from our children and from home, and from the remnants of our lives that we desperately try to cling onto, to not lose all sense of ourselves. It’s not often spoken about but I do see the strain it places on the families, as well where there’s a lot of separation and divorce sadly in the rare disease communities, and often that’s as a result of one parent’s drive to be the expert, which seems to cause one parent to fulfil more burden of care and that fosters some level of resentment or sense of loneliness towards the other one.

**Jillian: There are some scary statistics out there around familial breakdown in this context, and it is something which there are so many factors at play, but it definitely seems to be quite widely recognised and definitely a problem.**

**In terms of the time that people have to spend on liaisons with the research community and the clinical community, that could bring us quite nicely back into a question for you, Karen, about what kind of information the GenROC study is looking to collect from families, can you tell us a bit more about that, please?**

**Karen:** Yes, absolutely. As I said before, I’ve been very conscious of the sort of lives that our families are living, and listening to Lindsay, her story is very reminiscent of so many others and yours, Jillian. So I know families have about a gazillion hospital appointments, their children are often also very, very ill intermittently or a lot of the time, then they’ve got school stuff to deal with or they’ve got EHC plans to try and fight for. It’s more than a fulltime job in itself just being a parent of a child with a rare disease and it’s hard work, so me asking them to do anything else is asking a lot.

Luckily, I find, with the families I work with, who are universally wonderful I should add, that they are actually just really enthusiastic anyway about research for their child’s condition, and that’s because there isn’t enough information out there, so it’s relevant and important to them. But because they have no time at all, and any time they do give is their own personal time when they could be finally putting their feet up and watching something on TV, I have to make it as low effort as possible.

The questionnaire is all online, using a user-friendly and interface as we’ve been able to develop. It’s very user-friendly, it takes 10-15 minutes to complete; they can come and go from the questionnaire as well. We only ask for one time point at the beginning, which is all the sort of stuff that most parents will be able to tell you off the top of their head as well, so they don’t have to go looking for loads of information, apart from a height and a weight. Then later down the line we’re going to ask for a second questionnaire, it’s in the process of being finalised and again that will be the same amount of time, very easy to do, online, at their convenience. It was co-produced with the PPI group, they’ve tested it for me, I’ve had really good feedback and I’ve asked parents who are in the study as well for feedback. Everyone tells me it’s not too difficult or burdensome for them to do.

The secondary questionnaire has been very much informed by conversations with the parents that I had as part of a nest of qualitative interview study in GenROC, and that has driven that secondary questionnaire quite differently to what I thought it might be when we first set up the GenROC study. At the beginning I thought it might just be: have things changed for your child? Can you give us a bit more clinical data? But actually I realised that probably I will still gather that information, but they probably won’t have changed that much within the timespan in the study because it will only be a year or two after they completed the first questionnaire, and actually I realised that it would be much more useful to look at the impact of the genetic diagnosis, look at how they’re accessing services within the NHS, what sorts of services they are accessing, Impact on the family and also looking at priorities for families.

So families have talked to me about what their priorities are in rare disease, both in service provision but also in research, and I really am a very strong believer that we need to be given the limited funding, we need to be doing the research that matters the most to the families, not to the researchers. What do families actually want us to look into? Actually, do they want us to be looking into behaviour and what strategies work best for example, rather than something else very medical – what matters the most? And so that’s going to be a specific question in that secondary questionnaire, really trying to identify what matters to families the most and then how that can be translated into clinical research in the future. So I’m really interested to see what’s going to come out of that.

**Lindsay:** I think that sounds brilliant, Karen because I think historically there’s been a significant kind of absence of patient voice in rare disease research and development, and knowing that that’s changing, I think that’s really empowering for families and to know that professionals and industry are actually listening to our stories and unmet needs, and really trying to understand, and that offers a much greater impact on the care and treatments for patients in the future and certainly it makes endpoints more relevant to families as well.

**Jillian: What kind of outputs are you going to be looking at?**

**Karen:** The height and weight, the reason I’m asking for that is really because we are trying to work on growth charts for children and that’s because growth charts for children with rare conditions don’t exist by enlarge, there are a very, very tiny number of rare syndromes or conditions that have their own growth chart. The problem is that most children with these sort of rare conditions that we’re talking about are either quite small or quite big, and the problem is that the paediatricians look at their growth and they go, “Oh well, you’re much bigger or much smaller than other children your own age, what shall we do about that?” and particularly the little tiny ones it causes lots and lots of concern, so quite often these sort of growth parameters mean that the paediatricians do lots and lots of tests or put feeding tubes down, or add lots of calories, so it can be quite invasive and interventional actually that sort of growth parameter.

But actually, sometimes that’s because of the genetic condition and no matter how much feeding you do it’s not going to change anything. The difficulty is we don’t know that for certain, and actually we need good growth charts where paediatricians can make that call, and conversely sometimes a child actually does need investigating and the paediatrician puts it all down to their genetic condition, and that’s why we need these growth charts. So GenROC is aiming to gather growth data from all these children and then we’re going to work closely with Decipher, which is a website that was developed through the DDD study, which already holds lots of data from that study, so we’re building on the power of that study and we’re going to be generating growth charts for all of these genes.

We’ve developed a new method for producing growth charts for rare conditions where you’ve got small numbers of patients – that was never possible before, so we’ve already proven now for four conditions we can, so the next stage is using all the GenROC data, putting it into Decipher and coding it in. So, if you join GenROC, that data will be used to develop a growth chart for your child essentially and their genetic condition, so I’m really excited about it because I feel like that’s a very concrete definite given now for all the families in GenROC, which is just brilliant.

**Jillian: And is that something which will be shared with the families individually?**

**Karen:** Really great question. I hadn’t planned on sharing the growth charts individually with the families, but that’s something I can also go back to my PPI group and discuss with them about whether that’s something people would want, and also I have a newsletter which goes out every three months to the families, so I can certainly ask that question actually directly. It’s going to be widely available, the growth charts, we’re going to make sure that they’re accessible to paediatricians and clinicians etc. but in terms of output to the study, definitely the growth charts, we’re also hoping to have other clinically useful outcomes depending on the different genes that come into the study. We essentially have a cohort of children with rare conditions, everyone puts everything down to a specific genetic condition but we know that there must be other factors at play that influence how children do.

And this is a really unique thing we’re trying to do with GenROC actually, looking at aside from that genetic variant, that alteration, what other factors are influencing how children are doing? Because some of those might be modifiable, you know, or some of them there could be things that could be put in place to help improve outcomes. So I’m quite excited about that as well, because that’s quite new and novel and not really been thought about in this context before, so that will be an output.

And the other output is something that I’m working on with Unique, which is the rare disease charity who has worked with us on GenROC from the start, and they are involved in our PPI as well and that is going to be looking at a template, calling it a report at the moment, it’s in very early days, but something that parents will be able to hold, it’s going to have lots of drop-down boxes that can be tailored and modified for individual patients and children, which will be a bit of a guide that they can give to clinicians, professionals, education, telling them about their condition but also telling them on an individualised basis about what needs to be looked for in the future. Because parents tell me they are fed up of having to tell everybody about their child’s condition constantly, all the time, over and over again. So what the point of this output would be is to try and ease that burden a little bit. This is very early stages but we’re going to involved parents all along the way.

**Jillian: And is that something which builds on the hospital passport idea that we’ve seen emerging around the world over the last few years where parents can start off telling their child’s story on their own behalf?**

**Karen:** So, it’s come from my own lived personal experience of being a mother of a child with autism and I haven’t really spoken about that publicly before, so it’s something I’m saying for the first time. I have a child who has autism and I have had to navigate things like a DLA application form.

**Jillian: That’s Disability Living Allowance.**

**Karen:** Yes, exactly, which is a horrendous form, it’s the most horrible form to complete, probably apart from an EHCP plan form but it’s a horrible form to complete, it’s quite upsetting as a parent and it’s also got millions of boxes that you have to fill in. But one of the things that really, really helped me when I was completing that was a charity who had come up with lots of dropdowns that you could select from that might be applicable to your child to help you complete this form. And so it made me really think, “Well, could we do something similar for our children with genetic conditions but come up with lots of dropdown options that might apply to their child in all sorts of different areas?” And that was the inspiration, it was that, and doing the qualitative study that I’ve already done with parents of children in GenROC who were telling me about how fed up they were of having to constantly tell everybody about their child’s condition over and over again.

**Jillian:** **Yes, that’s probably very helpful to empower families to use standard terminology across the different families because my own son has epilepsy as part of his condition but actually trying to describe what his seizures look like I’m not sure I’m using the right words to fit the right boxes to fit them into the right categories with the neurologist. So that level of standardisation is something that we definitely need embedded into the system in order for more people to be able to use this data more effectively, so that sounds very helpful.**

**Lindsay, coming back to you, what are you hoping to get out of this study, or what are you hoping this study will do on your behalf for the world? What motivated you to take part?**

**Lindsay:** I think I would like to see all of the aims of the study realised and for the study data to be used to inform the development of standards of care for a wide range of conditions, those included in the study. I think it would be great if that information, as Karen said, is available not only to the participants but also to children diagnosed with those conditions in the future and also it’s an opportunity to consider themes that are identified across the disease groups as that can also help inform future research and look at investigations into the mechanisms of disease and where actually therapeutics could treat maybe more than one disease at a time and increase potential for basket trials and early access programmes – thank you to Dr Karen Low and her team for conducting the project because it included a comprehensive list of rare diseases, it really does give parents and patients an opportunity to have a voice and to contribute, which is empowering, and it gives them a little bit of autonomy as well over their direction that science and research goes to.

**Jillian:** **Fantastic, thank you. Karen, can you tell us a little bit about the timeframe for the study? I realise that we haven’t really touched on that so far.**

**Karen:** Yes absolutely, I’m aiming to recruit 500 children as a total. We’re open at 22 sites across the UK. Coinciding with this podcast actually we’ve opened a second door for recruitment, so the way we’ve recruited so far has been through clinical genetic sites, which is the way we’ve done these sorts of studies in the past, like the DDD study. The problem is that that relies on clinicians identifying eligible patients and clinicians are very, very busy in the NHS. I have worked closely with Unique who have been doing a lot of publicity and the genetic alliance have done publicity as well for the study, so that’s been one way of identifying eligible participants. And also just parent power through social media has been amazing.

The second way we’re going to recruit, and this is going to happen very soon, is through Genomics England. So, we are going to trial a completely novel way of recruiting to research through Genomics England and that is for Genomics England to identify eligible participants for GenROC and this would have been through the 100,000 genome study and then they’re going to send them invite letters, inviting them to take part. So that’s the next phase of recruitment, I think if we have more than 500 then that will be great too, we’ll be able to include those comers too, so that’s not a problem.

But we don’t know whether this will work or not in terms of a way of recruiting to research, this is completely new for Genomics England and I’m a bit of a guinea pig if you like through the GenROC study, but I was quite willing to be that guinea pig because I thought it might increase access. So there will be some parents who have not been told about GenROC who have not heard about it, and who would love to take part, so I feel like this is the way of really widening that net as wide as possible.

**Jillian: I think that is a challenge isn’t it, especially in rare disease – there’s no point doing a public broadcast about an initiative because you’re going to hit so few of the people that you’re interested in, so actually how you access the community is the first challenge and I’m really pleased that Genomics England will be able to help you there because I think that is a very useful route through.**

**I think it will probably be quite reassuring to quite a lot of families who were on the 100,000 Genomes Project who have got a diagnosis of one of the conditions that you’re interested in, and are now perhaps subsequently in the fallow period after you have a diagnosis, wondering what happens next, so I can imagine it might be quite good news for some of them at least that they are now being invited to do something further.**

**And the reason that you’re building forward and you don’t want people who are currently in the deciphering developmental disorders study is because you’re already using their data through another source, is that correct?**

**Karen:** Exactly. So absolutely, I don’t want anyone to feel that I don’t want them, that’s really not the case. I do want them but we have their data already from Decipher, so we’re building on the DDD data already, so they’re already contributing which is just the beauty of it, because that’s what we should be doing in rare disease, we should be building on previous research because you know, you don’t want to be trying to reinvent the wheel.

**Jillian: Agreed. So if someone is listening to this and has a child with a rare developmental disorder and they are interested in finding out more, what are the steps they need to take?**

**Karen:** If they Google Bristol University, GenROC, they’ll come straight to the webpage and everything is on there. There’s a link that they can sign up, the patient information leaflet’s there, the eligible gene list is there, all the information they need, including our email address.

**Jillian: And is there an upper age limit for recruitment?**

**Karen:** Yes, children have to be under 16 and that’s because once they get to 16 many of these conditions have associated learning difficulties, and it’s just very much more complex to try and recruit young adults, young people, with learning difficulties and given it was a cohort study we felt it was going to be too difficult at the moment.

Saying that, I have a huge interest actually in how these conditions present in adulthood, and I’m actually conducting a much smaller study at the moment in KBG syndrome, looking at adults, and so I hope that my future research career will allow me both to follow-up the children in GenROC, so that would be my vision but also to be able to take this forward for other adults with rare conditions, that’s my aim and goal in the medium to long-term, so watch this space for that.

**Jillian: That sounds very exciting, thank you.**

**Lindsay:** I think I would like to say to Karen that I really like the sound of the idea of following patients up into young adulthood and adulthood, as you said, that is definitely a kind of an unknown area in lots of the rare diseases, especially in our condition, SLC6A1, it was mutation and the disease was only really discovered in 2015, so it is fairly new and we have very, very few young people and adults coming through and being diagnosed and connecting with the rest of the community. So, being able to understand the trajectory of conditions better and especially conditions where actually the presentation it’s quite a spectrum, and so the long-term outcomes for people with SLC6A1 can look quite different, so it’s good to collate more information about that I think.

**Karen:** I think it’s really important, so that’s definitely where I’m looking to for the future with GenROC and more widely, I think it’s just something I’m really interested in and has huge relevance for parents and families.

**Jillian: Well, I think we need to wrap up there but thank you both very much Dr Karen Low and Lindsay Randall for joining me today as we’ve been discussing the GenROC study, and how the study aims to improve understanding of how rare genetic syndromes affect the way children grow, their physical health, their development, but also how the patient and parent communities can work more closely with researchers to end up delivering something which is of a huge benefit to everybody.**

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