

Into the Headlines_ Episode 5: The Orkney Gene Variant

Speaker 1: (00.01) Genetic science has changed the way we live our lives. For some people, having their genes tested for potential hereditary conditions can be the very literal definition of knowledge being power. Recent research conducted by leading geneticists from the Universities of Aberdeen and Edinburgh has found that one in 100 people who have grandparents from Orkney have a gene variant that causes a higher risk of developing breast and ovarian cancer. Testing is currently available in Scotland to those who know of a direct family connection to the gene or have a history of ovarian or breast cancer in their family. Now planning is underway for a small pilot trial that will offer testing for the gene variant to anyone living in Westray with a Westray-born grandparent, regardless of family history. From the University of Aberdeen I'm Laura Grant, join me, as we go Into the Headlines.

Intro music: (00.52)

Speaker 1: (01.08) Episode 5 – The Orkney Gene Variant. So I'm joined today by Zosia Miedzybrodzka, professor of medical genetics at the University of Aberdeen and director of the NHS North of Scotland Genetic Service based within NHS Grampian; Jim Wilson, professor of human genetics at the University of Edinburgh, and Bethan Davies, who lives in Orkney who has been tested for the BRCA1 gene variant. Welcome all.

Speaker 2: (01.36) Hello

Speaker 3: (01.37) Hello

Speaker 1: (01.38) Zosia, can you start by giving us an overview of the research?

Speaker 3: (01.41) So, more than 20 years ago I was asked by the breast screening unit that had gone up to Orkney to start doing breast screening on the spot up there, to come up and evaluate women with a family history of breast cancer because there just seemed to be quite a lot that needed an assessment and it was easier for the doctors to come to Orkney than all of the patients to come south. So we started doing a familial cancer clinic and that became the Orkney Genetic Clinic which sees any genetic condition. And over time we started to identify a number of family groups that initially didn't seem to link up but then genetic testing for the genes BRCA1 – sometimes we call it 'BRACA' 1 and BRCA 2 and then now we do more, but those were the main two genes to start with. We started to be able to offer that test and we started to see the same gene alteration crop up in different families that were coming to see us. And we realised that actually that suggested they had a common origin and we were able to at least link some of them together using what I call genealogy, so that's births, marriages and deaths registers, and so on. And we were also then able to show that they originated back in Westray in the 1800s but that was a long process and it was only 2016 when the gene difference was clearly recognised as disease causing and that was when we started to offer the test widely through the family that has become extended and extended more so that we now have hundreds of individuals drawn in to a family tree although only some of them have the gene variant. But I wanted to know how common that variant was and that was where I came to speak to Jim.

Speaker 2: (03.54) Exactly, so my side of the story also starts a while ago, nearly 20 years ago because we were interested in isolated populations such as Orkney and Shetland and there are many such populations around the world such as Iceland and Finland and Sardinia

and it was popular to study them because they have a subtly different gene pool. So we set up the Orcades study, the Orkney Complex Disease Study and over time recruited a little over 2,000 volunteers who were able to give consent and had three or four grandparents from Orkney, in the vast majority of cases. So they were recruited through a clinic with research nurses who took their blood for DNA samples and also gave them a number of measurements of risk factors for disease, ranging from blood pressure through to cholesterol and lung function and various other assessments. And we were able, in time, to take advantage of a new technology called Exome Sequencing. So it reads every gene in the genome, looking at different variants, whether they be common or rare and this is when we were able suddenly to notice that in the BRCA1 gene there was really an astonishing number of people in our cohort in the Orcade study who carried a variant that looked to be a nasty variant, a disease-causing, a pathogenic variant in this gene and so we came together around about that time with Zosia to put these findings together and try to make sense of them and see what they meant for the people of Orkney and to write a paper and then work out what we would do next. So that's where I fit into the picture, bringing the sort of population-based view rather than a clinic-based view where we are looking at people who are generally well rather than those who have appeared because they are ill or closely related to someone who is ill.

Speaker 1: (05.56) So there's been a huge amount of coverage in the media about this, but who needs to be aware of it in terms of their family history and should they be concerned?

Speaker 2: (06.05) Well I'll hand over to Zosia in two seconds because I think that's in her domain but I first wanted to point out that people who were in the Orcades study, we have been one of the first studies in the whole of the UK to get permission that we are able to return these so-called actionable findings to these variants like this BRCA1 variant, that we can do something about these variants, increase the risk of serious disease, but there are treatments or enhanced screening or other interventions available from the NHS which can improve ameliorate or even perhaps cure and prevent the outcome so we have fed back to the consenting members of our cohort now and they will have heard of this directly from us, so they then can follow up their usual pathway of care, via Zosia's clinic, if they wish to do so. So the people who have been in our studies and have not heard from us, if they consented to receive that information, then they do not carry this particular BRCA1 variant. That's not to say they may not carry some other variants that we will look at in the future but these people don't need to worry. In terms of the general public, I'll let Zosia speak to that.

Speaker 3: (07.22) What's been key about us being able to work together is that we now have a view on how common this gene alteration is of people of any Orcadian ancestry, that's 1%, and what I think is also a really important finding is that the vast majority of those people with the alteration have a Westray grandparent, a Westray-born grandparent, and that acts as a way of being able to narrow down how many people from Orkney do appear to be at risk. So we are making the recommendation that if people have a Westray grandparent we would like them to be able to have a test for this gene alteration. Now at this present point in time that recommendation is made on the basis of the science but we need to put a system in place and putting a system in place always need money. So what we are fortunate to have been able to do with a charity called Friends of ANCHOR is to put in place a pilot project so that people who are living at the moment in Westray who have a Westray grandparent have the opportunity for a test. We want to then build that, once we know how many of those people will want a test once we get the system up and turning, we want to be ready to roll that out to the other Orkney isles but also beyond, across mainland Scotland as well, so we are in the process of setting that up but also fundraising at the same time to get a system in place and then the long term aim is that once we've got things up and running is

that we will ask the NHS to take on funding for testing for people who at this point in the short term maybe don't feel ready to be tested just right now but might want it down the line, or as younger people get older and feel that the time in their life has come, it's just that building up towards a long term service that we are in the process of doing. So right now, if somebody has a family history of breast or ovarian cancer in themselves or a close relative and they have Westray grandparents they can seek a test through NHS Care and we broaden that out to wider Orcadian heritage in that specific instance. But if you don't have a close relative with breast or ovarian cancer the service isn't there just yet but it's coming.

Speaker 1: (09.56) I was going to ask, just to be clear, people who are tested and perhaps have the gene variant, that doesn't mean they are definitely going to get breast or ovarian cancer though, does it?

Speaker 3: (10.07) That's correct. It is a high chance for women. So what by high what we mean it's somewhere around 50% will develop breast cancer but it does depend a little bit on what the rest of the family history is; and round about 50% will get ovarian cancer. But on the plus side, if we know that then we can put screening in place. Normally we would start breast screening for women once they are 50 and they only get it every three years and it's done with an x-ray test, whereas what we are able to do is just after 25 or so we are able to start screening with MRI for people who have the gene, so that's a much more powerful test and it's done every year instead of every three years. Women who have that gene can also have the opportunity to have their ovaries removed using laparoscopic surgery, usually round about their 40th birthday or after, once they've completed their family. And a few women choose to have prophylactic mastectomies but we find the majority of our patients don't go down that route.

Speaker 1: (11.19) What does the testing involve for the pilot?

Speaker 3: (11.20) In the pilot we're going to be using a mouthwash sample, people just spit into a tube, and one of the things we're exploring with the local community in Westray is how to make those kits available. It may be in a box that people can collect from somewhere, it may be ordered online by sending an email, or it may be by something more innovative like picking them up at the library. It will depend on how the conversation with the community goes.

Speaker 1: (11.55) And is it just open to women or do you want to hear from men too?

Speaker 3: (11.59) At this stage the testing is open to men because they may have daughters who have a chance of inheriting it. For everyone who has the gene they've got two copies of it. They have a normal copy – and when I say have the gene, the faulty copy of the gene – so a normal and a faulty one, and its only if they pass the faulty one on when the egg or the sperm is made that it goes on to the next generation, so it's a 50-50 or a one in two chance. But men can pass it on just as much as women can, so that's the reason for making the test available to men, because we know for the next generation it'll be important. And one of the things that Jim and I will be exploring in the months to come is that as his next phase of work, the Viking 2 study, starts to bring in results and we scale up the knowledge we have we probably need to drill in a bit closer to the story about whether just checking people with Westray grandparents is enough or we should be looking at maybe great-great grandparents, or there may be a bit more testing but at least we know that people with Westray grandparents have the highest chance, that's where we should focus first of all.

Speaker 1: (13.13) Well I was going to ask if this is something that can be applied to other populations. Is it likely there's other places like Orkney where there may be similar heightened risks?

Speaker 2: (13.22) I'd say it's almost certain. When we do what we call population genetics and try to understand the distribution of genetic variants across the populations, and I've been particularly working across Scotland, England, Ireland and Wales actually, we see that Shetland and Orkney are the most distinct gene pools in the whole of Britain and Ireland but the Hebrides are also a distinct gene pool and they can have sub-gene pools, like the Westray gene pool is a sub-gene pool of the Orkney one, and because of that I would predict that we will see other situations like this, it may not be quite as common, it may not reach 1%, one in a hundred, or it could be more common actually, and it may not be a BRCA gene it may be a bowel cancer variant or an inherited arrhythmia, or a tendency to high cholesterol, or any of a number of things and so we've just about completed recruiting 10,000 individuals into the Viking Genes studies, now not only from Orkney and Shetland but including their diaspora, all the people who moved to Aberdeen and Edinburgh and Glasgow and England and to the colonies, to Canada, New Zealand, Australia and so on; but also in the last year people who have grandparents from the Hebrides to extend out this kind of work to the people from the Western Isles and Skye and Islay and so on. So we don't have all of these results yet and it'll keep me busy for a little while but we will certainly be looking to see if we can see any such things. We will be able to return the actionable variants to the volunteers themselves but it will have a much wider impact if we see other communities where we've had this huge uplift in the frequency to the point that we feel that screening would be warranted. I think it's a case of watch this space, we can only do so much at the time and we'll be getting a lot more of this critical sequence data in the autumn of this year (2023) and we'll be able to see much more widely where this kind of thing has happened then.

Speaker 3: (15.29) And from the genetic side of things, the alterations in these genes are particularly well known the known in the Jewish population, it's about one in 40 people with Jewish heritage have a chance of having one of three alterations, two in BRCA1 and one in BRCA2, and in England sort of systematic testing for those gene alterations in people who have just one Jewish grandparent is going to be made available from May and I'm hoping that we may be able to do something similar in Scotland for people of that type of heritage as well. So there are other population groups around the world where these things have happened, I think what's particularly distinct about this one is it's a geographically defined ancestral population within the UK and to me that's why this is a bit of a first.

Speaker 1: (16.30) You've been very good at pre-empting my questions because I was going to ask if the research could be adapted for other diseases but I guess the answer is yes, based on what you've just told me Jim.

Speaker 2: (16.41) Absolutely, the key point is that there's something that we can do about it. There are genetic variants which we will come across that are of a slightly different flavour that there's less can be done, so we're focusing first on the variants where we can take action and the individuals and the community can do something about it.

Speaker 3: (17.01) And at the moment we've been focusing on things that we can treat in adulthood but we may in due course come up against conditions where it has to affect maybe both copies of a gene that can cause a condition earlier in life and it might be about being able to offer parents a chance to see if their child might be affected before they plan a pregnancy. But again, that's probably on our second list isn't it?

Speaker 2: (17.30) Yes. But that's also something that happens in other parts of the world, particularly in Israel where they have a particular genetic history such that they have many of these kinds of gene variants where you need to have two copies, and so I think they are probably world leaders in this kind of testing. I agree, this is a couple of steps down the line, it's quite new I'd say in Scotland and in Britain but that doesn't mean we shouldn't do it. My job is to provide an evidence base for what is out there and work then with Zosia to see how best we can translate that into benefit and impact for individuals and the NHS and communities in Scotland so that's what we're going to do but one step at a time.

Speaker 1: (18.17) You were in Westray to share the findings of your research with the local community. How was it received?

Speaker 2: (18.23) I mean, we were bearers of rather bad tidings, to be honest, but despite that I think it went as well as we could have wished – better. We had a great turnout, people understood what the message was and they were not anything other than stoic, really, in their response. In fact, quite forward-thinking, particularly in terms of the funding that we need, immediately realising the situation in regards to fiscal challenge with the NHS at the moment and while, thankful, that some pilot work could be done in Westray, thinking already about possible opportunities to broaden this out to the rest of Orkney, the rest of Scotland and beyond, in time., So I was really delighted and it went better than I could have hoped.

Speaker 3: (19.14) And I've been astonished really in contrast maybe to other times when we've had similar advances that really it was pretty much universally welcomed as being good to know, not maybe welcomed as good news, but certainly the fact that something could be done. And I think the only frustration was that we were seeking to limit testing to people with Westray grandparents, there was quite an interest in being able to broaden it out further and I think that's where we have to see where the data leads us in terms of whether there would be a benefit for people who don't have clear, known Westray ancestry in being tested, because the evidence we have at the moment is that it's not really needed. But I think as the next generation come through and the generation that maybe took part in Jim's study pass on, it may be relevant to test the next generation.

Speaker 2: (20.16) I agree, people are becoming more and more mixed everywhere, but even within Orkney, and less knowledgeable about exactly where their grandparents or their great-grandparents came from and so this Westray genome, if you like, is going to bleed out into and become mixed in with the Orcadian gene pool in general so definitely the more information we have the better to be able to make the sort of decisions that need to be made about who is eligible and who would benefit.

Speaker 1: (20.47) Now, Bethan, you don't actually have Orcadian ancestry but by coincidence you do happen to live in Orkney, in Kirkwall to be precise, and you also happen to carry the gene variant, is that right?

Speaker 4: (20.58) Yes. So I tested positive for the BRCA1 mutation back in 2015 and I was tested due to family history. I literally came across the research when I was scrolling through Facebook and I saw it on BBC Radio Orkney and I just shared it on my news feed to say to people, I have actually have this, if you are concerned about carrying it, I think you should go and get tested.

Speaker 1: (21.30) So you have a history of cancer in your family?

Speaker 4: (21.32) Yes, yes so all females in my direct lineage in somewhat wider scope have had breast cancer.

Speaker 1: (21.42) That has to be quite a worry for you.

Speaker 4: (21.44) Well the majority of their first cancers were in their mid to late thirties so obviously that in itself is a bit of a red flag because generally people don't expect to get it until they are a bit older. So that was I think what had encouraged other family members to get tested.

Speaker 1: (22.06) We've heard that people taking part in the pilot will be using a mouthwash sample. The process for you was a bit different, though, wasn't it? It was a blood test.

Speaker 4: (22.14) They don't just go and give you a blood test, before you get to that stage you have an initial consultation where they sort of explain a lot of things to you like, how genetics works cause the vast majority of people don't really know much beyond what you learn in Standard Grade science and that soon disappears as you get into adulthood. So they give you a bit of an explanation of how it works and what the sort of impacts of knowing are, just so you can make an informed decision about the implications of knowing. And then once they are satisfied that you understand what the question is that you are asking then it's just a case of getting a blood test done at the GP and then that gets sent off to the genetics clinic and about three months later you get your result.

Speaker 1: (23.00) So what does testing do for you in terms of how you think about or lead your life going forward. What does having this information mean for you?

Speaker 4: (23.09) For one thing it gives me access to regular screening significantly earlier than the majority of people get, so I have had annual screenings since the age of 25. Up to the age of 30 that's just meeting with a nurse who does a sort of manual check-up, from the age of 30 that is an MRI and a manual check-up; and then from the age of 35 I believe I will receive annual mammograms.

Speaker 1: (23.38) How old are you, if you don't mind me asking?

Speaker 4: (23.40) I'm 32. Outside of that sort of side of things it's just a bit more awareness so I probably check myself a bit more regularly than I would have otherwise and also just a little bit more mindful about my lifestyle. I don't pretend that my body is a temple, I don't live that lifestyle but I have been more active and have been included to eat more healthily more regularly. Just doing what I can but also not cutting out completely the things that I enjoy in my life.

Speaker 1: (24.10) We've got to live, haven't we?

Speaker 4: (24.11) Yes <laughs>

Speaker 1: (24.12) What advice would you give to someone who qualifies for this new pilot testing programme?

Speaker 4: (24.17) I think if you qualify you have got nothing to lose by doing it. It might seem a little bit scary but at the end of the day genetics are in you. Doing the test will not give you the gene, it will not increase your risk, it will only inform you if you have that. To me, it never felt like a life sentence, or a death sentence or anything, it's more like an extra opportunity to prolong your life, you know. It could save your life knowing that, rather than, you know, many people might wait until they are in their 50s before they start doing regular checks by which point it could potentially be too late.

Speaker 4: (24.57) So having this knowledge is a little bit of control and power, in some respects?

Speaker 4: (25.03) Yes, yes. And I think in a lot of ways once you get over the initial shock there is a comfort in knowing, just because you know you will be looked after and you know you get that support. If you are concerned about it, do it, you know, there's a 50% chance that you will learn that you don't have that risk and that's fantastic. The other 50% chance is okay, you do have it, but these are the strategies that are going to be put in place to absolutely minimise your risk and both of those are far better outcomes than having it, not knowing and not getting regular checks.

Speaker 4: (25.40) Wise words for us to end on but end we must I'm afraid as we've come to the end of our time together. Thank you all for joining me, it's been really interesting hearing about the research, and hearing your perspective Bethan, so thank you all.

Speaker 3: (25.54) That was great, thank you.

Speaker 4: (25.55) Thank you very much.

Speaker 1: (25.57) And thanks to you for listening. More information on BRCA1 and breast and ovarian cancer in families is available from the NHS and MacMillan Cancer Support. If you have grandparents from Orkney and have questions about the testing pilot, you can contact the NHS Grampian Genetics Clinic Helpline on 01224 553940. Email enquiries can be directed to gram.orkBRCAgene@nhs.scot. Please be aware that GPs will not be able to assist with gene testing and any questions about this research or the next steps should be directed to the helpline. A series of FAQs and a short video outlining the findings of the research are also available on NHS Grampian's website at nhsgrampian.org/BRCA1. I'll be back soon with another dip into the headlines from the University of Aberdeen. But if you just can't wait, visit abdn.ac.uk/slash/news to catch up on all the latest announcements.

Outro music