Genetics in the NHS: Looking towards the Next Generation

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Good afternoon everybody thanks for coming along to our talks today. My name is Jon Williams and I am currently working as a Pre-registration Clinical Scientist in the Oxford Medical Genetics Laboratories. I thought I would give you a bit of an introduction to my background and how I got into this job. I did my undergraduate in Leicester in Medical Genetics and I graduated in 2007. I then stayed in Leicester to do a PhD with Nicola Royle and, as I already said, I am currently working as a Pre-Reg Scientist whilst completing the final year of my training scheme to become a Clinical Scientist.

Clinical Science in the NHS can be broadly split into two main categories in terms of life sciences. On one side of things we have the cellular sciences, so these cover the disciplines of reproductive medicines, cytology - which is looking at isolated cells in things like the cervix - and histology - which is when you are looking at tissues samples that pathologists take from patients. Then on the other side of things, we have the blood scientists, where generally they are looking at blood samples, as the name suggests, and these cover disciplines like biochemistry, immunology and haematology, and genetics falls somewhere in the middle of those disciplines. All of these disciplines actually train Clinical Scientists now. There is also a set of related disciplines called the physical sciences, which cover things like respiratory sciences and cardiovascular sciences, but I don't know too much about those so I can't really take any questions on those sides of things, but some of these other disciplines I know bits and pieces about.

Not everybody has actually heard of Clinical Scientists and aren't really aware of the work we do, but we actually have a key role in a number of patient diagnosis. There is some sort of statistic in the NHS that something like two thirds of all patient diagnoses come through scientists at some point. So the role of the Clinical Scientist is to assist and advise the clinical team, so the doctors in particular, on individual patients diagnosis. We perform, analyse and report on a variety of laboratory tests, we do a large amount of research and development and we also have an

educational role. So in terms of genetics it often involves SpRs coming in and learning about the lab work that helps them make their clinical diagnosis.

In terms of genetics in the NHS, traditionally genetic testing has been divided into regional centres spread out across the country. The main regional genetics centres incorporate cytogenetics, molecular genetics and they tend to be linked to a Clinical Genetics department as well, so coming to a one stop shop for everything. The types of testing we do falls into two main categories and we carry out familial testing, so these are the individuals with a family history of a condition when a mutation causing it is known and they want to know if they are a carrier for a given disease such as cystic fibrosis. We do diagnostic testing, so this will be in patients presenting with symptoms and they will send a sample and will say we think this patient has genetic diagnosis X and then we go away and look for the mutations causing that disease. We also do a small amount of pre-symptomatic testing, so this is in conditions like Huntington's disease where a patient will come in whose parent may have developed the disease later in life and they want to know whether they are going to go on an develop that condition, so we do the testing for those things as well.

Outside of the classical clinical genetics disciplines genetic techniques are becoming widespread among lots of different pathology disciplines, in particular disciplines like microbiology and virology that now do things like next generation sequencing to look for various pathogens. There was a big paper from Addenbrooke's a couple of years ago looking at MRSA by sequencing technology, so there are lots of developments in genetic techniques. This map summarises where the regional genetic centres are in the UK. The Scottish centres are a little bit different and my talk doesn't really cover them today. They have a different Clinical Scientist Training Programme to the rest of us but, in general, the labs shown in blue will offer training to X number of scientists a year and they will employ Clinical Scientists once they have finished their training. There are also some specialist centres that are dotted in black, so these will be reference laboratories that handle one particular type of disease, so the one located at Oxford looks at all the haemoglobinopathies, the one in Cardiff looks at some of the muscular dystrophies, and then there are a couple dotted around in London as well but again these are a bit different to the regional centres.

I thought it would be useful to go over the testing we do and talk a little bit to you about the techniques we do and the types of diagnoses we make. These are all live cases I have actually been involved in as I have gone through my training. Hopefully those that have done the genetics degree streams will know that this is a human karyotype. So this is when we take cells and fix them in metaphase and do staining techniques to look at the banding pattern across distinct individual chromosomes. One of the main reasons we do this sort of test is for children that present with developmental delay, because this can often be associated with chromosomal abnormalities. Generally, what the Clinical Scientists job is, is to look at each one of these chromosomes in turn, work out which chromosome it is for starters, compare it to its homologous partner and try and work out whether there is something unique going on. So, as I am sure all of you are aware, humans should all have 46 chromosomes but what is important in this patient is that if we look at the chromosome 21 this patient actually has a chromosome 21 that is attached to an extra bit of chromosome 9. So effectively, this patient has got an extra bit of chromosome 9 attached to one of their 21s and that is the cause of their developmental delay. What happens then is that we will then get the parents of this patient in and have a look at their chromosomes and often what we will find is that the parents will carry a balanced translocation and then that kind of thing we can then roll out around the rest of the family to offer more testing to the family. So this is the work of Cytogeneticists.

Something else that the Cytogeneticists do is something called fluorescence in situ hybridisation. So again this involves either metaphase cells or cells in interface and we use specific fluorescent label probes to look at unique parts of the genome. So in this case we are using a probe to the elastase gene on chromosome 7 which is shown in red and a control probe that combines the chromosome 7 centrally. What this patient has is a disease called William's syndrome which is associated with a specific deletion across chromosome 7 of which this red probe binds to in the patient cells you can see have got two of the control probes so we know we have two chromosome 7s but only one of them has got this elastase gene which is deleted in William's syndrome. So that's another example of the type of thing we do.

More frequently, in cytogenetics, we do something called Comparative Genome Hybridisation, CGH. In this technique what we end up with is a glass slide covered in hundreds of thousands of little pieces of DNA. We then label patients DNA and a control samples DNA in two different fluorescent colours and hybridise the walls of the glass slide. We then use computer software to look for each individual probe, shown here with these little dots, and look at the amount of each colour each probe shows and we can decide if a patient has a deletion or duplication of specific regions of the genome. What this patient here has, is a small duplication on chromosome 17, which again appears to be causing some developmental delays. So this is another big set of testing that we now do as Cytogeneticists.

So that's what the guys who work in cytogenetics do whereas in molecular genetics we actually look at DNA right at the smallest level. These are typically tests using the polymerase chain reaction. This is a patient who came in with a family history of fragile X syndrome, so this is associated with an expansion in the untranslated region of the FMR1 gene on the X chromosome. What happens is when you get this expansion it becomes methylated and shuts off the expression of the gene next to it. At the same time, it creates something called the fragile site which when you are looking at cells in metaphase appears like a little tiny break on the X chromosome. Previously the only way to diagnose this was to look at the chromosomes and count loads of X chromosomes. We now use a fluorescent PCR assay which amplifies across the repeated itself and we then use a type of electrophoresis, a bit like capillary sequencing, and you will see that in the normal female you get two smaller alleles whereas in a female who carries the condition you would get one small one and one much bigger one. So that's another type of testing we do.

The other thing that is a real development area in molecular genetics on the NHS is using a technique called MLPA which is Multiplex Ligation Dependent Probe amplification, or something equally catching. So this is a technique to detect deletions or duplications of individual genes in the genome. What we do is we take a probe that comes in two distinct parts, one of which is fluorescently labelled. So the probe itself has a region that binds to a specific region in the middle, it then has a non-complimentary bit at each end which are shared between lots of different probe sets and these are when we have a single set of PCR primers that can provide all of the probe products at once.

We ligate them onto the pieces of the human genome and we then carry out a ligation reaction so that when we denature these probe and target region complexes the only way we can get a PCR product is if the probe is actually ligated properly. So what you find is regions that have been deleted and you can't the bits of the probe ligated together so you can't amplify them so you don't get a signal from them later on. So again we use lots of computer software to show us that these exons in the survival of motor neuron 2 gene have been deleted in this patient and this was a patient that came in for testing for a condition called spinal muscular atrophy. This is associated with deletion of a particular one of these SMN genes that causes the disease.

By far and wide the largest amount of our work now actually focuses on DNA sequencing of particular genes. The vast majority of the genetics labs in the country now offer a medium to high throughput Sanger sequencing based system. So in these techniques, you all know about Sanger sequencing so I won't go into it in any kind of depth, but we use PCR to amplify individual exons and then Sanger sequence them one by one per patient. So it is a long-winded process but we actually use robotics to sequence lots and lots of patients and lots of regions in one go. Increasingly now we are using Next Generation techniques, so this is where the next generation part of my talk comes in, and these are these massively parallel sequencing technologies that have come into place really quite routinely in the last few years and now, for the same price that we used to offer to Sanger sequence one or two genes, we can sequence up to two hundred genes in one go with fairly quick turnaround times. In the definitely not too distant future we are going to start offering things like whole genome and whole exome sequencing and whole exome sequencing is something that we are actually doing in Oxford already so these are techniques that are actually coming into the NHS quite rapidly and are a really exciting development areas.

I don't know how much you guys do about Next Generation sequencing in your lectures, so I thought I would quickly kind of touch on the sort to technology we use. The most popular technology in the NHS is based on Illumina sequencing. This uses glass slides called flow cells and on these flow cells you have lots and lots of little probes that are specific to adapters that you stick on to the ends of bits of DNA you want to sequence, you wash those through the flow cells and individual molecules stick to kind of each little spikey bit on the glass slide and then, by a technique called bridge amplification, you develop these little clonal populations of sequenced bits of DNA that you want

to sequence. You then use a technique like Sanger sequencing to stick terminators on your little fluorescent dyes and then essentially you just use a really expensive camera to take a picture of the glass slide and look where the fluorescent is all across it. You do that lots and lots of times and what you end up with is a picture of each cluster after each cycle of amplification and you just use these to build up the read for each cluster. So this would be G-G-T-G-C-C-A for that individual piece of DNA. Using this technique we can do up to fourteen patients on one run, and two hundred complete genes at a time, so it is really high throughput and a lot cheaper than Sanger sequencing used to be for equivalent amounts of data. The big problem that we have, and where the Clinical Scientists come into play, is that when we actually detect a sequence variant, so in this instance the patient has a G where the reference sequence has a T, we need to be able to interpret whether those are polymorphisms, so just benign changes in the gene end that we all have lots of, or whether they are actually a variant that are causing the disease, and this has become a big part of our workload.

We have various ways in which we can investigate these variants of uncertain clinical significance, so we use public databases such as dbSNP or the Genome Projects to see if they have been seen in normal populations. We look at things like amino acid conservation, so we do multiple line ups of the protein products to see how well that amino acid is conserved. We can also look at specific domains of the protein, so this is a patient who I sequenced a couple of weeks ago who had a variant at this particular position which changed the glutamate residue for a glutamine residue at this position so what I did, this variant wasn't in any of the public databases, it is in a really well conserved amino acid in the related protein in different species and when we look at related protein in lots of different species we can still see it is really quite well conserved. This still didn't give me enough information about this variant, so we can then do things like pull out the crystal structures of given proteins. So what we find is that when we look at the glutamate that has changed it sticks out quite nicely into another bit of the protein that is involved in dimerization. So in this particular variant we can say if we change the charge on this so it is going from an acidic residue to a basic residue we can say that that is going to cause a charge disruption that will stop this protein dimerising and that is probably what is causing this patients dominant disease. So by a lot of bioinformatics tools we can really get to the root of what might be causing the patient problems.

So that is all the work we do, and it's been a whistle stop tour through all the work of a Clinical Scientist. I will talk to you a bit about our actual training programme now.

The Scientist Training Programme is a pretty new scheme. The year I started, three years ago, was the first year this version of the scheme was offered. Essentially it is a graduate scheme, so you apply to it with your undergraduate degree, when you are in the final year of your undergraduate degree. The only requirement is that your degree is related to the discipline you want to apply for. So if you want to do genetics and you have a Biochemistry degree that will probably be ok, but if you have got a Zoology degree it might be a bit more ropey. They demand that you have a 2:1. In reality all of these schemes are massively over-subscribed and the vast majority of people will have some sort of postgraduate qualification. So if you apply from your undergrad and you don't get in, don't be dismayed go away and get a Masters and have another go and it will be worthwhile. So it is very very competitive and there is a very competitive application process for it.

The actual training programme has a work based component and an academic Masters component. It is also tied in with gaining some clinical experience. So Clinical Scientists generally don't see patients but, as part of our training, we are encouraged to go into the clinic with the Geneticists and actually sit down with the patient and find out what goes on with that side of things. This is the standard slide they throw at you to summarise the scheme to you. In your first year you do four different rotations, one of which is in your specialism, and then you do another three in one of the related disciplines. So, if you were doing biochemistry you would do rotations in genetics, haematology and immunology. You then have an elective period of 4-6 weeks and this is all sounding a bit like medical school training now I guess, so we have an elective period and then you do your single specialism after that and in the background all the way through you have got your Masters degree which includes a big project R&D component.

A little bit about the Masters component, essentially what it seeks to do is back up the clinical training you are doing in the lab with kind of the academic things about the disease. So if you are doing Prader-Willi / Angelman syndromes testing you will be doing a bit in your Masters on Prader-

Willi / Angelman syndromes. It's three years part time and it is all distance learning, so it is actually run by the University of Nottingham for genetics, but they deliver all your things through an iPad. So you get given an iPad at the start of your course and they deliver your lectures as little iBooks that you view. There is barely any coursework which is the good news, but there is exams for every module, which is the bad news. There is also a large project component which is a dissertation and a viva as you would expect for most other Masters degrees. What is really nice about it, certainly if you don't really have a postgraduate qualification, is it is the few ways to get one that you are not going to have to pay for. You get paid while you are training and your Masters is all paid for at the same time. So it is a nice way of getting a Masters.

Onto the important bit for you guys, how much do we get paid? Pretty well as life scientists go to be honest, you are paid according to the NHS Agenda for Change pay scales which are set by central government. Everybody that does the same job theoretically gets paid the same amount of money in the NHS, it's how it is meant to work, and you get yearly increments so you work for a year then they give you a bit more the next year. Trainees begin at band 6 which starts at about £25,500, which for coming out of your undergrad would be a nice salary to start on. Clinical Scientists are generally either on band 6 or 7 and this rises to about £40,000, so there are plenty of people who get the Clinical Scientists qualification, just sit all the way through and finish their career on £40,000, which isn't too bad really. Career progression past the Clinical Scientist level is dependent on taking more exams I am afraid. As Clinical Scientists we are encouraged to take the FRCPATH exams so these are equivalent to medical consultant examinations, it's a very similar exam and as you would expect because of that it has got a really low pass rate, but it is the only way into the more senior positions and supposedly as a Consultant Clinical Scientist in charge of your lab you can earn up to a £100,000. I know one person that gets anywhere near that, so it's a bit of a pyramid scheme, but the jobs are there.

Why should you all come and work in the NHS? What I really like about it is that I get to use the expert knowledge I gained to directly help people. It is one of the few science jobs, as I said I came out of research, and you constantly get asked in research "What do you do?"? "Why is that useful for me?" And a lot of the time you can't answer that. What is really nice about this sort of job is you

can directly say that you are helping people, you are giving them a diagnosis. So as an example, one of the services I am working on at the minute is on inherited retinal degeneration. One particular gene that causes this, there has just been a really successful clinical trial in Oxford where they have actually done gene therapy to replace this broken gene, we do the sequencing that tells them that that gene is broken, so there is real direct clinical benefit there. Unlike academic careers, there is also a really well defined career structure as we have already touched upon. There isn't years and years of postdocing trying to get a permanent job, theoretically you can come out of your training and come straight into a permanent job which is nice. There are also lots of opportunities for research in the NHS, so as I have already said there is loads of Next Generation sequencing coming out, array CGH is an expanding area and something that is really interesting is something that is called non-invasive prenatal diagnosis. These are techniques where you actually take a blood sample from a pregnant mother and look at the fetal genome from that blood sample. This is a really nice expanding area. For those of you guys who are interested in bioinformatics they have just started a bioinformatics STP as well. So the NHS is actively trying to train and recruit Bioinformaticians to do all the protein stuff that I like doing, so hopefully they won't take my job any time soon.

In terms of how to go about applying, the positions tend to be advertised in January time, so you guys will have missed this year's intake if you haven't already applied I suspect. They are advertised on jobs.ac.uk and in New Scientist [This is now co-ordinated by the National School of HealthCare Science]. It's a nationwide application process, so you apply to the scheme and you list the geographical regions that you want to work in. That's as far as your choice goes. If you get offered a position it can be in any one of your choices, so it's quite harsh and you won't be able to say I want to stay in Nottingham so I am going to go and work in Nottingham, it will be that Nottingham will be one of your choices but you might end up going to work in Manchester, so that's something to be aware of. You apply to the specialism that you are interested in and you indicate which region you would be interested in. Prior to shortlisting, so this is around the same time as you make your application, you are made to sit aptitude tests which are similar to IQ tests. Luckily I didn't have to do that in my year, it was introduced after my year, probably because I got the job. Essentially I think they were getting so many applications they decided the easiest way to trim down the number of people who they had to short list was by having these arbitrary tests in place. For me it's not the

best way of doing things but it's the only way they have got on such a massively oversubscribed course, but you get a chance to have a go at these tests so they are not sprung on you at the last minute.

The scheme has a very interesting way of doing their interviews as well. I guess if any of you guys have applied for it you might have heard a bit about this. You apply nationally, if you are shortlisted by any of the labs that you are interested in going to everybody goes to Birmingham City Football ground and has a 'speed dating' style interview. So essentially you go into a big room where there are four tables and everybody moves round those four tables. Each station, as they call them, has a particular theme, so a theme might be leadership skills, another them might be technical skills, and from what I can make out they score you from say one to twenty based on your responses at each station. The people that score the highest get offered the jobs, it's as simple as that. So there's not really any room to purvey your personality in those so you really need to make sure that you know your stuff before interview.

In terms of how to go about knowing your stuff, the thing that I can't emphasise enough is experience. They very much want to know what experience you have got that is relevant to the job. This can be things like going to visit one of the local labs, Birmingham is very good at letting people go and have a look round. They also offer an open day once a year I think. If you have done any kind of research projects or you have done a kind of 6 weeks summer project all that counts as relevant experience. You should really go and read up on the work that Clinical Scientists do. There are various websites like NHS networks that describe the type of work we do in more detail and it is worth having a look through those. I really can't emphasise enough, you need to dig out your lecture notes. So one of the mistakes when the postgraduates go in, and where you guys will have an advantage, is that it has been a long time since we have sat our undergrad so we have forgotten an awful lot of the basic stuff that they actually expect you to know. You need to know about inheritance patterns in families and you need to be able to recognise if it is an X link pedigree or a dominant pedigree, all those kind of things. And I would imagine it is similar for the guys who do disciplines like biochemistry and you are going to know about things like the glucose metabolism. Something else that you can do, the genetics labs have whole teams of technical staff and these

guys you don't have to have a training scheme to go and work as a genetic technologist. So these positions get advertised on jobs.nhs.uk and essentially you do the lab work that the Clinical Scientists then analyse the data for. So it is a really interesting position and they do a lot of varying techniques and we couldn't work without them basically. So it is another really good way of getting in.

The NHS careers website is a good place to go and feel free to email me as well.

Questions

Q: I was quite interested to hear that Sanger sequencing hasn't yet been phased out entirely, it still has a role to play in all of this?

A: Unfortunately every variation we find by next generation sequencing that we want to report we still have to use Sanger sequencing to report it. Next generation sequencing still has regions of the genome that it's not too good with , so places where you have got strings of nucleotides its still gets a bit rubbish at trying to do those so we can still see artefacts, so we have to Sanger sequence everything that we want to report.

Q: If I understood right from what you were saying, you wouldn't do any karyotyping directly yourself, that's kind of a division of labour there or ….?

A: The way the karyotyping works is it is still a role for a Clinical Scientist but the way the newer generation is being trained we are not going to be expected to do that much of it in the future. So I can karyotype but I don't routinely, it tends to be the Cytogeneticists that have been trained just in that.

Q: Would you say it was better to do a postgraduate first or get the experience, say just from your bachelor's degree get a job in genetic technology for example, or get a postgrad?

A: I would say if you can get a job as something like a Genetic Technologist that is going to be a better option. The fact is that you have to do another postgraduate degree to do this anyway, so doing it for the sake of it, if you don't have to, is probably not worthwhile. They are not that bothered about qualifications except for the core thing of having a 2:1 degree that is relevant. It is experience they really want to hear about. So if you have worked in an NHS lab you can't get better experience for the job than that. I know of people who have come straight from their undergrad just having done a lab based project in genetics or something and that has been fine. What they really want to see is that you have got a commitment to the job and you know what the job involves. So it's that kind of experience as well is what they are really interested in.

Q: One question I get asked probably once or twice a year is from people who are doing the various programmes here and they suddenly discover we are not accredited by the Institute of Biomedical Science and therefore they would need to do additional training for that. How does that compare with what you are talking about here and those kinds of things?

A: Biomedical Scientists are another scientific profession in the NHS so they are different to us. They tend to work in the more traditional pathology disciplines so they will do work in histopathology preparing tissue sections or they might work in biochemistry kind of manning the machines with the blood samples. Their role tends to be more technical than Clinical Scientists and they do an undergraduate degree in Biomedical Science which tends to be at some of the newer universities such as Brookes or DMU they will offer a biomedical science degree that will train you to be a Biomedical Scientist. If someone from a biomedical degree wants to be a Clinical Scientist they have to do the same scheme.

Q: So you are not missing out in that sense by not having done that if you want to get in to the NHS?

A: If you want to get into the NHS as a Clinical Scientist you can do this with any life science degree, that's the way it works, but if biomedical scientists want to take that step up to a Clinical Scientist they are in the same competition as the rest of you guys.

Q: Are there any careers in genetics where you actually have to see patients?

A: There are Consultant Clinical Geneticists, so obviously they have been to medical school and been through SpR training and all that, that's a very long route for you guys. There is also the option to be a Genetic Counsellor. Genetic counselling is probably more oversubscribed than clinical science to be honest. You either have to be a registered nurse and complete specialist modules in genetics and counselling, or alternatively, I think there are still only two Masters degrees in the country for genetic counselling, so I think it used to be Cardiff and Manchester offered a Masters in it. They only take I think about thirty to forty students a year just for the academic bit. After you have done your Masters you then have to try and fight for a trainee genetic counselling position and those are really hard to get. I think even as a big Clinical Genetics department I only know a couple of people who have got on as a trainee counsellor in Oxford. So it is hard but they are a very happy bunch of people they really enjoy their job and I think it can be a really rewarding job if you can get into genetic counselling.

Chris Willmott: We had a talk a couple of years ago by someone who was a Genetic Counsellor, unfortunately I was off ill at the time and it wasn't properly documented so it is not on the website, but I do hope that sometime in the future we will get one of the other graduates or that person back again and we will kind of add to that but it seemed a bit too soon to be asking him again on the basis of the fact that the recording process didn't work properly. We will try and cover that again at some time in the near future.