The genetics of alcoholism & anxiety

Voiceover: [00:00:02]
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[00:00:50] European Researchers Night is a Europe wide public festival, which brings researchers closer to the public. All events run as part Explorathon 2021 can be found on the website atwww.explorathon.co.uk and the programme is funded by the European Union's Horizon 2020 Research and Innovation Programme under grant agreement 101036101. After listening today, please let us know any comments or feedback by tagging us on Twitter using the hashtag Explorathon21

[00:01:28] Now, over the years, a range of studies have indicated that some people may be more predisposed to certain conditions such as alcoholism, drug addiction, obesity or depression. But where does that susceptibility come from? Research from the University of Aberdeen is investigating whether switches within our own genes can influence our likelihood of being affected by these complex conditions.

[00:01:52] Today, I'm joined by Dr. Alister Mackenzie, we did at the University of Aberdeen Institute of Medical Sciences, who is leading work into this area. Thank you for joining me.

Alasdair MacKenzie: Thank you. Nice to be here.

Voiceover: [00:02:06] So tell me a bit about your research.

Alasdair MacKenzie: [00:02:09] My research is about the genetic switches, which turn genes on and off and keep us healthy and how they might go wrong in disease. So that's essentially, in a nutshell what I do. Just to expand on that a little bit. We all know that DNA and our genomes control who we are on what we are, but also control our susceptibility to diseases such as alcohol abuse or alcohol addiction, alcoholism or drug addiction or depression, which affects huge numbers of people in the UK every year. And so in order to try and address these problems, because they do cause quite major societal problems as well as health problems, there's been major investment into finding out what causes these mental health problems, which addiction is a major cause. Addiction and anxiety and depression.

[00:03:06] But these are the major things. So research into these problems have primarily looked at genes and in order to really make sense of what I do, I may have to,

first of all, tell you what a gene is. So if you look at the genome, each cell in our body has two metres of DNA and that's all the information required to build a human body. The genes only make up one point seven percent over the next two metres.

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So the genes actually make only a tiny proportion of the amount of information required to make a human. And so essentially, in a nutshell, genes make proteins that make your body. As I said, they only make up one point seven percent of the genome. However, they're distributed along that genome like tiny little pearls along an enormous necklace. But what falls between these beads on the necklace is what we have dismissed previously in the past as junk DNA.

[00:04:07] And it's only very recently in the last 5 to 10 years, we are starting to ask questions about what exactly is in that it essentially the bits of string between the beads, the pieces of DNA between the genes. What does that do? And the reason we're asking that question and that question is much more important nowadays. This is because the big genetic studies that we're able to do nowadays on the causes of disease, where they look at differences, genetic changes between people. They try to associate these genetic changes to susceptibility to disease.

[00:04:43] And in about 99% of cases, and this came as a massive disappointment for the majority of geneticists, in the vast majority of cases, changes that cause disease are not in the beads. They're not in the genes themselves. But they are in the little bits of string between the beads of DNA from the 97% 98% of your genome, which has been previously dismissed as junk DNA.

[00:05:07] And even more recent research now suggests that these changes are associated with the disease, don't actually affect genes at all, it affects switches which tell the genes where to be switched on particular times and in particular places, and it's these gene switches or enhancers, as they're called we're interested in studying.

[00:05:30] Why is it an important issue to research? Well mental health problems will affect more than a quarter of us at any time during our lives? And it causes huge economic, social, economic and health problems. And so, as I said, enormous amounts of money have been invested into understanding mental health conditions. But we've made very little progress in understanding the actual mechanisms. How we can understand why some people are more susceptible to mental health disorders and how we can predict whether someone will eventually develop a mental health disorder or whether we can start finding ways to treat these mental health disorders.

[00:06:11] And so it's really essential we understand how they come about. And once we get an understanding of what causes, what is the molecular basis of the genetic basis of these mental health disorders, then and only then can we start to develop drugs and start to develop therapies or treatments to address these problems and maybe try to improve people's lives by mitigating the worst mental health problems.

Voiceover: [00:06:38] What is it that you're really investigating with those switches?

Alasdair MacKenzie: [00:06:43] Yeah, so what we're interested in finding out, first of all, is where are the switches and what do they do? You have to know that. It's like trying to find out what was wrong with a car engine. You can't really understand how a car breaks down and fix it unless you know what the engine looks like and how the engines put together.

[00:07:02] So the first stage is always looking to see what the engine looks like. What the structure or the function of these switches are. In the past, finding them has been the problem. But what we've been able to do, what we've been able to demonstrate is that many of these gene switches remain unchanged for hundreds of millions of years of evolution. So we can detect them between different species by virtue of the fact that they've not changed in millions and millions of years.

[00:07:30] So some of the switches that we're working on, that control, anxiety, alcohol intake or fat intake have actually been conserved all the way back to reptiles. So that allows us to find the second thing that we would able to do is we're able to recover these gene switches from the human genome and to test their activity using different tests. One of the things we've done, for example, is to use cell lines where we knock out a gene switch and we're able to show that the genes surrounding that gene switch turned off.

[00:08:03] So that genes is just as important in controlling both genes, are turned on and off. Another thing we've done, just, we only managed to do it five years ago thanks to crisper genome editing. We were able to knock these switches out in mice. And when we gave the mice, these mice that lack the switches, the choice of either 10% ethanol or water, the mice that had the switch, the mice which were normal mice when exposed 10%, they guzzled it and the mice that lacked the gene switch didn't like the ethanol as much.

[00:08:36] So they were given the free choice and they chose water over ethanol in about 90 percent of the time, that was quite a significant result. The second result we found was that when we allowed, when we put the animal in a test for anxiety, the test is essentially just called the elevated zero maze and you put the animal in this loop on where two of the three quarters of the loop are enclosed, on animals with higher anxiety tend to sit in the cupboard regions of the maze, whereas animals which have little anxiety explore far more. And we're able to show that if you knocked out the switch, the animals explored much more.

[00:09:17] In a similar fashion, we were able to show that animals have given the choice of low fat or high fat foods, well they didn't like the high fat food as much. That wasn't as certain in our results as what we showed with the alcohol, but it was significant. And it could be that this gene switch controls these behaviours in humans as well. In fact, we had a collaboration with Andrew McIntosh at the University of

Edinburgh. We were able to show that that there was existing data showing that DNA changes within the switch in the human population are linked to increased alcohol intake and anxiety in men.

[00:09:56] So in human males. So that quite nicely linked in with some of our own data showing that the anxiety phenotype that we saw in our knockout mice was more pronounced in male mice. So there's quite a lot of sexual selection here, or sex specificity, I should say.

[00:10:13] So the next important stage is to determine whether we can use this gene switch as a possible drug target because we've identified several molecular mechanisms which control the activity of the gene switch. And we've been using drugs to show that not only can we switch the switch on and off, but can also show that depending on what genetic variant you have depends on the ability of the switch to respond to the drug. So one of the versions responds very well to the drug and the other one doesn't. And this raises the possibility of a personalised approach to therapeutics centred around these genes.

Voiceover: [00:10:52] So you've touched on some of the findings of your work can do in terms of the next stage, is that any other next stages to that work, how you can use those research findings?

Alasdair MacKenzie: [00:11:03] Well clearly, the fact is that we have pushed the boundaries here without the cutting edge of gene switches and enhancer research. And the question is, can we start looking at lots of other switches? So it's just a matter of scaling things up to see if we can find other switches, which might also contribute to these disorders.

[00:11:23] Although I did say that the genes which control the anxiety and alcohol intake content, it's important to point out that this is not the only gene switch which controls these behaviours. The human genome is very much like a computer where just hundreds, thousands, upon millions of these gene switches. And so the eventual PVA that someone exhibits through life not depend on one gene switch, but may depend on the coordinated activity of hundreds or thousands of genes. Some of which are turned on, some of which are turned off, and others which may contain changes which make an individual more susceptible to either addiction or anxiety or depression.

[00:12:05] The eventual goal is to hopefully scale this up. Now we have a proof of concept of being able to identify them, to be able to knock, knock them out in mice, be able to show that they're relevant to humans, we hope to be able to scale it up and start to look at other genes

Voiceover: [00:12:22] And you've touched a depression, fat intake. Do you think these gene switches could influence on other conditions and diseases that humans suffer from?

Alasdair MacKenzie: [00:12:32] Absolutely. I think that what we've been able to gather from lots and lots of these big association studies over the last 10 to 20 years since we've had access to the human genome sequence, we've been able to run these genome wide association studies, or GWAS, which are just enormous undertakings involving hundreds of thousands of patients, they call patient cohorts, hundreds of thousands. And we've also been able to look at hundreds of thousands of different changes within the genomes of these individuals in order to allow us to then link individual changes to the disease susceptibility.

[00:13:15] And what's come from that is that in every case, the majority, especially in complex diseases like mental health disorders or diseases like arthritis or heart disease, in the vast majority of cases, the changes associated with susceptibility are outside of genes and are probably within these genes switches. So I think we need to completely change our way of looking at the human genome, not in terms of what the genome makes in terms of proteins, but we need to start thinking in terms of what controls these proteins, what turns these proteins on in the right cells at the right time. And we're not just talking about mental health disorders. That's what is the main focus of my research. But we're talking across the spectrum of human disease. And I could include things like type two diabetes, obesity and heart disease and indeed cancer.

Voiceover: [00:14:11] Are you linking your research to other disciplines? And how important is this interdisciplinary approach to this issue of gene switches.

Alasdair MacKenzie: [00:14:18] The bottom line is that not every scientist knows every discipline. So interdisciplinarity is an absolute essential component of top-rated science and our understanding of disease. And so something we've been interested in for a while, for example, like collaborating with a colleague in Manchester, is to understand the effect of environment on these gene switches, on these enhancers.

[00:14:43] On this, we have some surprising results, which we managed to get published last year, where we were able to show that environment can change the activity of these gene switches. So, for example, there's a branch of genetics called epigenetics and this is focussed on changes within the genome, which don't actually change the sequence of the genome it changed the properties of genes or genes switches within the genome without actually changing the sequence, for example, a mutation. So in this case, what we were looking at was a molecular change or a biochemical change called DNA methylation. And this has been understood for many, many years, has played an important role in how genes are turned on and off within the genome.

[00:15:37] But nobody's actually been able to burrow down to determine the actual mechanism of how DNA methylation affects the turning on and off of genes. What we did was we took some of our normal mice. We gave them, well, there were pregnant female, and we gave them the choice of whether to eat high fat diet or normal diet and then allowed the females to give birth to their pups.

[00:16:05] We then analysed levels of the DNA methylation within specific regions of the brains of these pups once they'd grown up. And what we found was that there was a significant change in the methylation pattern within the genes, which we were looking at.

[00:16:22] So this shows that if you change the environment, specifically in this case, the diet of the mother when she's pregnant with these pups, this has an effect on the methylation of the genes that we studied. And when we then took the genes switches in a separate experiment, we did another experiment where we took the genes switch and we actually chemically methylated it and then looked at its activity. We showed that this methylation had a very significant effect on the activity of the gene switch.

[00:16:54] So this shows that we can directly link diet, or maternal diet to anxiety related behaviours and alcohol intake in later life. So this shows that not only the gene switch affected by genetics, but genetic changes. We've been able to show that in human populations we can show that different versions of the same switch causes an increase in alcohol intake or anxiety in certain proportions of the population. Not only demonstrate that, we can demonstrate that the environment affects the methylation and that the methylation affects the activity of the enhancer.

[00:17:30] So we've got a mechanism there which ties genetics with environment to increased susceptibility to conditions such as mental health, mental health disorders.

Voiceover: [00:17:43] And if you were look to 10 years from now, what are your hopes for your research? How do you hope your research has been used?

Alasdair MacKenzie: Well, I hope that people will pay more attention to gene switches and enhancers in gene

[00:17:55] regulation. And the way that we've studied this genes, which is pretty much unique in the majority of people looking at genes switches who tend to look across the whole genome using biochemical markers, and that that's a very useful technique, but it doesn't actually tell you much about the biology of individual enhancers. And so what we've done is we've actually burrowed down and focussed on an example of an individual enhancer which we have shown controls behaviours associated with health and disease. And what I'm hoping our work will persuade other people to start using similar techniques, to start to understand the role of gene regulation and enhancers in gene switches in health and disease. So really, we've been pushing the envelope, if you like, down the direction oftrying to understand the biology of these enhancers and being able to show that they are actually involved in human disease.

[00:18:53] We hope to get more funding to look at more enhancers but otherwise, further down the line, we're hoping to be able to persuade people to use similar methods as we've used to try and understand the biology of these enhancers in the same way.

Voiceover: [00:19:09] OK, thank you very much for your time

Alasdair MacKenzie: [00:19:13] Thank you very much for asking.

Voiceover: [00:19:18] We hope you find today's podcast interesting. But for now, thanks for joining us. And keep an eye out for other experts on podcasts being launched late September. As I said at the beginning, we'd love to get your comments and feedback on today's podcast, so please use the hashtag Explorathon21 to tag us on social media. If you're interested in finding out more about the other events taking place as part of Explorathon 2021, then you can visit the website at www.explorathon.co.uk bye for now.

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