Genetic basis of addiction

My name's Dr Gursharan Kalsi, and today I'm going to be talking about the genetics of addiction. I've been working in the field of molecular genetics for the past 25 years. I started with schizophrenia and moved to bipolar, and then I realised I needed to actually understand the brain more.

And addiction genetics seemed to be the natural transition. In fact, it's a fascinating field because you understand behaviour. And what I'm going to talk about today is really, "What is it that makes a person become addicted?"

Researchers asked themselves in the 1940s and '50s, and they decided that the way to answer this question was to set up large twin and family studies. It was already known that if a family had an addicted parent or relatives that the children of the addicts were eight times more likely to develop addiction. Well, that could be just the environment. Was there more to this question? In the '50s, there were two main groups. There was a large twin sample that was set up in Virginia and another that was set up in the West Coast.

If you grow up in a really lousy, very dysfunctional environment, then you might end up becoming addicted. Was there more to this question? In the '50s, there were two main groups. There was a large twin sample that was set up in Virginia and another that was set up in the West Coast.

And they asked themselves the question, if we use identical twins and non-identical twins, perhaps we could tease out: "Were the genes playing a role, or was it the environment, or was it a mixture of the two?" In one of the studies, which was the Virginia twin sample, they looked at 861 pairs of identical twins and 653 non-identical or fraternal twins.

And the idea is that the identical twins must share almost all their genes. So if you saw an effect that was stronger in the identical twins, then that suggested that genetic factors were playing a big role. But if you saw the same effect in non-identical twins, then really the environment must be playing a role.

And in this particular study, they found that almost 50 to 60% of the risk of becoming alcoholic--and this was an alcohol sample--was really due to genetic factors. Yes, the environment was playing a role, but not such a big role as the genetics were. And in fact, we call this phenomenon heritability.

This is where you have a characteristic that you inherit - can be due to genetic factors - is termed as a heritable factor. And we give this, almost a jargonistic term, called heritability. And if you look at other disorders, common disorders like schizophrenia and bipolar, they have a high heritability. And substance abuse and alcoholism is up there almost to about 60%. So this is highly heritable.
The same group then went on to look at how genes’ environment alter over time. And they looked at four different substances, one that's fairly common and a lot of us consume, which is caffeine. Another one was cigarettes smoked. And then the third one was the alcohol drinks that people had consumed. And the fourth one was cannabis.

And so they measured the rates of the genetic factors and environmental factors and, not the family environment, but also their personal environment: things like what mates they have, do they have school friends? Are their neighbours actually affecting them? And they found something really surprising: that in fact the family environment stayed stable over ages.

In one case in cannabis, there was a dip in consumption over about the age of about 20 to 30, because obviously the people kind of settled down. And then they cut back. And then it went up again. Their personal environment didn't change over time. What did change was the genetic aspect.

At a younger age, say up to about teens, it's the environment that makes a difference. So your peer group is really important. But as you get to, say, an adult and older, the family environment doesn't play a role. Your personal environment stays stable. But the genetic aspect actually causes some individuals to become dependent and consume more than they should, which, in clinical terms is known as risky consumption.

So our next key question today is, we've seen that genetic factors are important, so what are these genes? And more importantly, how do they affect addiction? And addiction meaning, in this case, a compulsive use of a drug, and we will look at some of these genes. But before I get to that, we want to look at what kind of genes.

Are there certain factors that make certain genes more relevant? Well, certainly the way the drug is going to be metabolised is going to be important. In some individuals, this may be the rate - might actually affect whether they consume the drug more, also the way the drug makes them feel. If the drug makes a person feel good, then they will want to go on to take more and more.

You've had lectures on the neurochemistry a little bit. And you'll have heard that dopamine is raised by most drugs. Dopamine is that chemical in the brain that makes us feel good. For some of us, we don't need to consume drugs to feel good. Maybe a shopping expedition is all we need. But for some individuals, they need to take more and more drugs in order to feel good.

In an interesting study on smoking, one study looked at over 30,000 smokers. And they looked at the genes that code for two enzymes that actually break down nicotine. These are cytochrome A6 and B6. And they look to see if you see a change in the sequence of these enzymes, would that make a difference to smoking?

And for one of the genes, cytochrome six, there's a variant, ie, a change in that gene which has a reduced function of the enzyme. And guess what? Those people actually smoked less. There was reduced smoking. So this in a way is interesting, because perhaps we could design drugs that actually would help people reduce smoking.

Alcohol, a lot of work has been done on the metabolism in alcohol. And partly because alcohol is a very common drug. In most societies on Earth, this is a socially acceptable drug. But it's the
third leading cause of death, so we need to understand what is it that makes people want to drink so much?

Two enzymes that break alcohol down are alcohol dehydrogenase and acetaldehyde dehydrogenase. And people then started asking, would the genes that code for these enzymes, if we looked at the variants, would that make a difference to drinking behaviour? And indeed it does.

But what is interesting is that some of the variants actually produce— they are protective factors. There's one particular variant called ADH1B. The variant is the '2' of this particular gene. It occurs at a higher frequency in East Asians. And it makes them feel very sick.

What happens is that this particular variant produces - metabolises - alcohol to a greater extent. And this leads to an accumulation of an intermediate chemical called acetaldehyde. Acetaldehyde is very toxic. It makes people feel sick, and therefore they actually don't want to drink.

But that doesn't explain why people become dependent. So there must be other factors and other genes. And more recently there's been a study that was done in an ageing population. And they found that the gene ADH1A actually leads to increased drinking. But it isn't associated with alcohol dependence.

What it is associated with is the number of drinks. So it's actually somehow leading to people drinking more. There was another study done in Australia, and that found a similar result where this gene was associated with increased drinking. So here we have genetic factors that actually lead to either more drinking or some sort of behaviour.

Genetics research in addiction is a very young field. People have only seriously asked themselves questions for the last 10 or 20 years. We have published, we have researched and found certain genes that are playing a key role. This is now very encouraging, and we want to actually look for new genes and have already talked about trying to find new genes.

What is going to be very important going forward is finding additional genes and then putting them together. And in fact, at the moment there are some very interesting research programmes that are going on. They have devised computer algorithms that can put together the information about all the different genes and say, well, what do they tell us about the mechanism of addiction?

Because just identifying a few genes doesn't tell us really why people become addicted. But if we can understand the mechanism, then what we can do is actually understand the kind of person who is likely to become addicted. If we can identify addiction early, if we can identify the marker, say the personality traits, at a much earlier age, then we can help these individuals at an earlier age.

And that way, we can actually prevent them from getting into the cycle of addiction. And I think that's where we want to go, where we can actually offer these individuals a better quality of life at a much earlier age. It's no point bringing in policies when the person is 30 years old or 20 years old and they're dependent on heroin, and really they cannot get out of that cycle.
The key thing is helping them at a much earlier age when they can manage the disease. And I think this is what we want to aim for with genetics research.