Double the value: How researching twins benefits everyone

SHANE HUNTINGTON

I'm Shane Huntington. Thanks for joining us. In the current era of genome research we might imagine that solutions to many of the medical problems faced by society can be found in our genes. Although a nice idea it fails to consider the effect that our environment has on our health. In many cases health problems are caused by a combination of genetic susceptibility and environmental conditions and it can be difficult to separate the relative importance of the two. Ideally we need to examine how a person's genes react in multiple environments. One important approach to doing this is through the study of twins. Today on Up Close we speak to an epidemiologist about how genetic studies of twins help us tease out important information on environment contributions to matters of health. Professor John Hopper is Director of Research at the Centre for Molecular Environmental Genetic and Analytic Epidemiology in the Melbourne School of Population Health at the University of Melbourne. He is also the Director of the Australian Twin Registry. Welcome to Up Close, John.

JOHN HOPPER

Thanks, Shane.

SHANE HUNTINGTON

Now you work in this field of epidemiology what exactly does that involve?

JOHN HOPPER

Epidemiology is a word that people either confuse with ?epi-der-mi- ology? and ask me about their skin condition at a party or confused with epidemics. But actually it's a general term that's used to mean studying how the environment in its broader sense, including lifestyle factors, influence outcomes especially in terms of disease
outcomes and health related outcomes.

SHANE HUNTINGTON

Now how has this field changed over the last few decades as we've had this explosion of genetic knowledge coming forward?

JOHN HOPPER

Well, in the last century much epidemiology treated everybody as created equal and of course we hope we are all equal under the law, but the reality is that we all differ enormously in terms of underlying genetic susceptibility. So for example take breast cancer or colorectal cancer, having a first degree relative who's got the disease doubles your risk of getting that disease. Then we ask, well, okay, if that was genetic how strong would the genetic factors have to be to explain that? The answer is that people at the top quarter of risk in terms of their genetics would be 20 times the risk of people in the lower quarter of that risk. So bubbling away underneath us there's this incredibly strong difference in genetic risk for particular diseases. For example, in the past it has been in a sense ignored, but now with the new genetics coming through the Human Genome Project we're at last able to think about prevention in terms of individual factors; does it matter if you smoke if you're down one end of that genetic scale, or does it matter incredibly much whether or not you take oral contraceptives if you're at the other end of the scale? These are the sorts of issues that we're now able to address in modern epidemiology.

SHANE HUNTINGTON

When you consider a particular disease how do you go about determining the role that the genetic components have versus the role that the environmental components have?

JOHN HOPPER

Well, without actually measuring the genes - and this goes back to the twins studies that the biggest insight into your genetic risk, or likely genetic risk, of disease is to look at your relatives. I talked about first degree relatives; siblings, parents. But the twins are an exquisite example of relatives, especially monozygotic pairs, that's twins where they're genetically identical, they're developed from the one egg; monozygous. So they give a wonderful control for genetic factors, but also dizygotic pairs, those are pairs that develop at the same time from two different distinct eggs and are as alike as siblings in general, they give a contrast. So monozygotic pairs share all the genes and they share the same age, sex, the same upbringing and so, dizygotic pairs to a large extent share the same environment but they differ in the
sense that they only share half their genes. So immediately we've got a scientific
design to ask the question, are genetic factors important? We do that by asking, are
monozygotic pairs more similar for the particular issue that you're interested in than
dizygotic pairs? If they're no more similar genetics cannot be important. If they are
more similar then it opens up that whole realm that genetics might be the reason why
monozygotic pairs are more similar.

SHANE HUNTINGTON

Do you require a scenario where the twins have to be separated environmentally for
you to be able to tease out this information, or if they're brought up in the same
house, the same food, the same schools, the same environments, how does that
affect the sort of studies you do?

JOHN HOPPER

Well, exactly. I was very careful in that last explanation to say it might say that
 genetic factors are important because it could be that monozygotic pairs are more
important because they share their environment more similarly. We have to be very
careful of that. In the case of twins who are separated at or soon after birth are
wonderful examples to try and get around that problem, but they're very very rare.
There's been some fascinating research done by Tom Bouchard in the United States
over many year of inviting such twins to come and be measured for a whole range of
factors and some wonderfully spooky instances of having the same name given to
their children and all the rest of it come out. Fascinating stuff but unfortunately that is
not available in large scale for most people. So we have to go back to comparing
monozygotic and dizygotic pairs but understanding that they have generally been
brought up together. They tend to move apart around the age of 18 so that starts to
bring into play of different environmental factors operating later in life but certainly in
early life we don't separate twins for scientific research. Not yet. [chuckles].

SHANE HUNTINGTON

Hopefully not ever. Now, we have this scenario here where you have two separate
sorts of twins occurring. Why are they occurring in pregnancy over single births?
What's actually happening in the pregnancy that says all of a sudden you have two
babies instead of one?

JOHN HOPPER

Well, I should point out at this stage I'm not a biologist, I'm a statistician so you're
getting a very lay understanding. But most women produce one egg per cycle. But
sometimes we have what is called multiple ovulation and women produce more than
one egg. Then during that cycle there's the chance that more than one of those eggs will be impregnated and that leads to dizygotic twinning. As for monozygotic twinning I don't think people really understand from what I've talked to people - there's not a consensus about what is the process that leads to a cell very early on that's developing as a human being to divide into two separate cells. One theory I've heard people talk about comes back to this issue of what we call epigenetics. This is where the actual germline genes don't change but they become influenced - technical words like methylated, so there's some subtle things that happen to the way the genome is operating that the cells might recognise that suddenly this cell which was part of them is different. That may lead to the separation of the cells at this early stage in life that then go on to develop as a monozygotic pair. So genetically identical but something has happened to cause that division at an early stage.

SHANE HUNTINGTON

Now, you mentioned germlines. What exactly are they?

JOHN HOPPER

Well, the germline is the set of genes you get from your parents. That's in every cell of your body has the same - in principle the same genes. Now, as cells divide mistakes can occur and that can lead to what we call somatic mutations that can lead to disease. But the underlying blueprint that you're given is your germline DNA.

SHANE HUNTINGTON

This is Up Close coming to you from the University of Melbourne, Australia. I am Shane Huntington and in this episode we're talking about the importance of twin research with Professor John Hopper. John, when we look at the two different types of twins, identical and non-identical, what are the percentages that you get on average from the different types?

JOHN HOPPER

Well, it varies from country to country, time to time, but approximately one in 80 births are twin births, so one in 40 people in the population are twins, a couple of per cent. Of those roughly 20 or 30 per cent are monozygotic pairs. The dizygotic pairs, of course, could be boy/girl pairs and there's as many boy/girl pairs as there are boy/boy and girl/girl pairs.

SHANE HUNTINGTON
John, I'm guessing it's also possible for a woman to be impregnated multiple times within a short period, say, a few days, where essentially you have that scenario where two eggs have been fertilised, potentially by the same male or potentially even by different males. How does that play out in terms of twins?

JOHN HOPPER

So what we think are dizygotic pairs are actually still from two eggs but they are now only sharing the mother because there are two fathers. So they're a degree of separation from the normal dizygotic pair. If we were to do a genome wide scan of those people we would have quickly identified those pairs and we can take that into account. That's another reason why zygosity testing could be very important, but it also does raise the questions that whenever you get genetic information you're opening up sometimes a Pandora's box you maybe didn't want to know about. That's why giving genetic information back - that's why it has to be done by, in a sense, a properly thought through professional service so that people understand the implications of having that information.

SHANE HUNTINGTON

Are all the twins that look very similar actually identical twins?

JOHN HOPPER

You're using a value judgement of looking similar. We're all similar and we're all different and that's what twin research is about. We have a series of questions that have been tried out over years to try and differentiate identical twins from non-identical twins and 95 per cent of the time DNA studies show that those questions work. Twins themselves are very attuned, and their parents, to the differences that may not be really due to their germline DNAs, we are told they could be monozygotic. On the other hand we have dizygotic pairs who might, because they're born together and brought up together, they may seem that they're identical but in fact they're not. So it's an open question for a small proportion of twins. One of the issues that the Australian Twin Registry is particularly interested in is the fact that it's quite extraordinary that twins don't know their zygosity, is what we call it; monozygous or dizygous, which would be a simple genetic test now given the technology has moved so far. When you think of all the money that's spent on the twin births just that one final bit that would actually tell the parents the zygosity - and it's an important tissue for twins and the parents. It really can't be underestimated. And as researchers who are involving twins in study we would like to know the zygosity. So counting the number of placentas at birth can give information but that's not the most reliable information. So the bottom line is genetic tests, which basically now are not very expensive, can determine zygosity with very very high accuracy.
You mentioned there that twins want to know their zygosity. Why is that? Is it just general curiosity or are there medical reasons that are beneficial to them down the track potentially?

Yes. Well, there are a whole lot of issues about identity, important issues to twins themselves. But from a medical point of view, remember I mentioned that if a first degree relative has breast cancer or colorectal cancer it doubles your risk. But if that first degree relative is in fact a zero degree relative, in fact a monozygotic pair, then that increase risk is multiplied. So actually knowing the difference between whether your twin is monozygous or dizygous is important in terms of understanding your risks when one of the twins develops a condition.

We know that when we interact with some twins, even actual identical twins, their personalities can be very different. Why is it that when they're brought up in the same environment, similar scenarios, some of them can be so fundamentally different in terms of their personalities?

Well, obviously one explanation is that genes are explaining the full story so it could go back epigenetics when something in the environment has changed the way their genes are being translated into action. But there are also very strong forces within twin pairs to be different. It's within atoms there are forces pulling and pushing in different directions. It is important for twins to have their identities so sometimes they will deliberately go to try and do things to make themselves different. On the other hand a pair of twins that I'm very familiar with, a monozygotic pair, told me that they actually worked out how they're going to deal with life, their personalities, their whole approach to life, they did that together. Now, they've been very successful in life and they've helped each other by help training each other. So it's an intriguing sort of situation that we have to be aware of. It's not just the genes and you said that in your opening remarks, it's the interplaying of genes and the environment and lifestyle that make a human being.

John, could you give us an example of how twin studies have actually been used to determine whether a particular trait or disease is influenced by genetic or
environmental factors?

JOHN HOPPER

Well, the simplest design for looking at environmental factors is to look at twins, mostly monozygotic pairs, who, for whatever reason, differ in the environmental factor that you're interested in. So usually if one twin smokes, the other one does or vice versa. But amongst a lot of twins there will be twin pairs where one smokes and the other doesn't. But we managed to look at a large number of twin pairs and found 20 twin pairs, female twin pairs, where one had smoked for 20 or more years and the other had never smoked. We measure their - what's called their bone density; how strong the bones are essentially. We found that the smoking twin on average had five per cent weaker bones. That translates into a doubling of her risk of having an osteoporotic fracture in later life. So this was a very elegant design. We had this published in the New England Journal of Medicine, quite a few years ago I think. We looked at other possible factors, but really their difference in smoking was so profound and their difference in bone density was so clear that it was, as we said in that paper, compelling evidence and the best sort of evidence you can get rather than doing a randomised trial which, of course, you can't do with individuals. In epidemiology we're relying on observational data. But this observational data with the twin pairs was really, as I say, quite compelling.

SHANE HUNTINGTON

Now, you're a statistician so you must see the fundamental differences between the statistics when you're using twins as opposed to the statistics when you're using these other randomised selections. How different is that? You mentioned there 20 pairs being sufficient to determine this particular scenario. How would that compare to doing it with a normal randomised trial?

JOHN HOPPER

Well, when you - you can't really do a randomised trial with smoking but you can do observational studies. But when we do the usual epidemiology we sample from the population. We have to think about all the other factors. You may hear the joke that epidemiologists are broken down by age and sex. That's because the first thing you have to consider is adjusting for age and adjusting for sex if you've got different sexed people in the study. With a twin design you control perfectly for those two factors. So here are the major two determinants of an outcome that you have scientifically controlled for simply by design. So trying to get information, for example, on past life. For example, does age at puberty influence breast cancer risk? Now, if you go and ask women in their midlife when one has breast cancer and the other doesn't and you ask them about their age at menarche at best you generally get it to within a year. That's really not terribly discriminatory as a
statistician. If you actually get a pair of twin pairs where one has breast cancer and the other doesn't you can actually ask them who had menarche first. They will know that; who went through puberty first. They will actually know that and they're actually consistent with that. So you've amazingly got an insight on early life environmental exposures by having a design that involves twins.

SHANE HUNTINGTON

Now, I'm curious about the DNA you see in these twins. We often hear discussions about junk DNA and other bits of DNA that we don't use or may be really relevant. How much of the entire genome of an identical twin is actually the same as the other twin? Is it the whole lot or is it just the bit that matters?

JOHN HOPPER

No, well, 100 per cent. Now we can do studies where we measure 500,000 markers across the genome and we can actually look at the twins and we can actually see that monozygotic pairs are identical on those markers. Beautifully we can see that the dizygotic pairs share, on average, half those markers and you can see now, you can determine your genetic relationship by measuring across the whole genome. They do studies, for example, in rural England where they can actually find people who are actually genetically related and are very distant cousins by looking at their genome because they've been brought up in an environment that's been relatively stable over many hundreds of years.

SHANE HUNTINGTON

I'm Shane Huntington and my guest today is Professor John Hopper. We're talking about studies involving twins to research disease here on Up Close coming to you from the University of Melbourne, Australia. John, recently the field of epigenetics has emerged and many of our listeners would be aware of the fact that life forms on this planet evolve depending on the environment they are forced to survive in, but this is very different than that. This is something else. Tell us what is meant by epigenetics?

JOHN HOPPER

Well, again I have to preface this by saying I'm a statistician, but it would appear that the way your genes function changes, and it changes very early in life. There are these processes that go through that sort of tune your genes to how they're going to operate in later life. So most importantly some genes get turned off. I come back to another area of my interest which is colorectal cancer and there are groups of genes which are quite magnificent, these are called DNA mismatch repair genes. When mistakes occur when cells divide these genes operate in pairs to go around and
identify these mistakes and cut out the bit that's wrong and repair it and tie it back together. Now, most of us have operating DNA mismatch repaired genes. Some people unfortunately have inherited a mistake in those genes. They're the people at high risk of colorectal and other cancers. But there's another phenomenon where those genes actually get turned off during life; they get methylated during life by environmental factors we don't know. A very important question is to know what's going on. The result is that that also leads to an increased risk of colorectal cancer. So the intriguing thing is that when you look down the microscope or do what they immunohistochemical tests of these tumours that people develop, you see the same story whether it was due to having what we call a germline mutation or whether it was due to epigenetics. What differentiates that is if you see this tell tale sign for someone who has colorectal cancer at a young it's almost certainly due to a germline mutation. If you see it at a later age it's almost certainly due to this epigenetic phenomenon occurring, or we say somatic mutation, during life. So colorectal cancers before age 45 that have these features are almost certainly due to genetics, colorectal cancers after 55 with this same feature; look the same down the microscope, look the same in the tests, almost certainly due to an environmental effect on the genome, epigenetics.

SHANE HUNTINGTON

When we look at non-identical twins that have shared the very same environment early in their life how useful are they in these studies given the epigenetics and do they tell us something different because of that very early environment that they've shared?

JOHN HOPPER

Well, they are very important because they've shared that so you've controlled for that. But they also now have - the non-identical pairs have the difference in the genome. So now you can apply those same arguments I had about looking at identical pairs, you can start to look also at the genetic differences within the non-identical pairs. So every which way you sort of turn when you think about twins, especially when they're different types of twins, they give different designs that can be used to answer different questions. There's a dozen or so different types of studies that can be done that involve twins that each has their own real strength.

SHANE HUNTINGTON

From a statistician's point of view how small can the sample set be with twins to be able to actually bring out this information? It almost seems as though the answer could be one.
JOHN HOPPER

It could especially in terms of hypothesis generation. On the other hand we've realised that to do that in terms of understanding monozygotic pairs more correlated than dizygotic pairs and so on and so forth, is ironically you need very large samples. You need thousands of pairs. That's what's led to, that realisation about 20 or 30 years ago, has led to the development of these very very large twin registries like the Australian Twin Registry which has over 30,000 pairs of twins. There are similar sized registries especially in Scandinavia, in the United States and other places because that incredible number of twins allows you to answer important questions but also has the possibility, like the smoking discordant pairs study, of within that very large registry there are bits of gold; some twins who are very special because they differ either in a disease or in an environmental exposure.

SHANE HUNTINGTON

Now, you're the Director of the Australian Twin Registry. What does it mean for a pair to be part of that registry?

JOHN HOPPER

Well, the Australian Twin Registry was established 30 years ago by the recognition of needing these large resources and a very special way of doing science. That people from the community coming forward, knowing they're special, participating in science. So for twins on the registry they simply indicate that they're prepared to be in studies. They're not committing themselves to be in studies. But when researchers want to do a particular study they don't have to go out and find their own twins, we can approach twins through the registry and if the twins are interested in a particular study then they can say, yes, and then they can have a one on one relationship with the researchers. It may be just filling out a questionnaire, it may be giving blood, it may be having your bone density measured, it could be anything because this research goes across all of health and actually is more than just health, it's actually scientific issues as well. The twin registries, because they're voluntary registries, we tend to have more monozygotic pairs, more than what you would expect by chance, and more female pairs than we'd expect by chance, because females are more interested in medical research than males. So the hardest pairs to get for the Australian Twin Registry has been the dizygotic male/male pairs.

SHANE HUNTINGTON

Now, Australia is a relatively small country by international standards; just over 20 million people. This is one of the bigger registries in the world. How have we managed to achieve that and does this registry interact with the other ones in some
JOHN HOPPER

Very much it's international research now. There's lots of studies combining twins from many countries to do research and we're looking to form an international network of twin registries to take that forward, especially in terms of epidemiology studies. So coming back to Australia's performance it's a bit like our recent performance in the Olympic Games where we were right up the top there, even though we're a small country. It's because we put a special effort into this and there were some fabulous people 30 years ago that realised the value of having a national twin registry. The National Health and Medical Research Council have supported that as a resource for research for 30 years.

SHANE HUNTINGTON

Finally, as we've seen the growth of IVF as a popular technique to help couples have children, how has that affected these sorts of studies given we sometimes come across scenarios where a mother will have four or even more children?

JOHN HOPPER

Well, we call it the twin registry but in fact we're also of course open for triplets, quadruplets and so on and so forth. When you think about it triplet is actually three pairs of twins. So even within triplet you could have a monozygotic pair and a dizygotic pair. Usually they're all dizygotic. So we do embrace all, as we call, multiples and we have over 100 set of triplets on the Australian Twin Registry.

SHANE HUNTINGTON

John, what is the URL if people are interested in contacting the registry?

JOHN HOPPER

We've just updated our web page and we've made it very interactive. It's www.twins.org.au and we have lots of links there to other organisations, information about twins and twin research. We see this as a way of now talking with our twin membership, providing information, providing a mechanism for twins to talk to each other as well through the fabulous possibilities of the current technologies that are available to us.
SHANE HUNTINGTON

Professor John Hopper, Director of Research at the Centre for Molecular Environmental Genetic and Analytic Epidemiology in the Melbourne School of Population Health at the University of Melbourne, and also the Director of the Australian Twin Registry. Thank you for being our guest on Up Close today and explaining the importance and value of studying twins.

JOHN HOPPER

Thank you very much for having me.

SHANE HUNTINGTON

Information regarding the twin registry can be found on our web site at upclose.unimelb.edu.au. Up Close is a production of the University of Melbourne, Australia. This episode was recorded on 23 February 2012. Our producers for this episode were Kelvin Param and Eric van Bemmel. Audio engineering by Gavin Nebauer. Background research by Dyani Lewis. Up Close is created by Eric van Bemmel and Kelvin Param. I'm Shane Huntington, until next time, goodbye.

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