

Foreseeing the future?
GENES AND RISK





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Introduction

Genes are in the news. Whether it's because scientists have sequenced the human genome or uncovered a gene fault involved in cancer or the police have caught a criminal thanks to DNA evidence – genetics is all around us. Fifty years on from the discovery of the structure of DNA, the double helix has become part of our visual landscape – even appearing in adverts for cars!

As a result of this increased public profile of genetics, we have become more aware of the role that this burgeoning area of science and medicine has – and will in the future have – upon all our lives. Nowadays, it is not uncommon for an illness or death in the family to prompt us to think 'Is it genetic and could it affect me?' For instance, when a mother is diagnosed with breast cancer, her adult daughters might start wondering whether they might also be at risk of developing breast cancer. It's sometimes easy to feel that we are surrounded by genetic risks like these. However, a greater awareness of the contribution that genes make to both rare and common diseases shouldn't make us feel more at risk. Instead, it should help to understand risk properly and, quite often, to be reassured that our risk is no higher than average.

And so, the aim of this booklet is to help understand genetic risk and to put it into perspective. It's all about putting genes in their place.



Understanding genetic risk

There are two main ways in which genes are involved in disease: common genetic variation giving a susceptibility to common diseases; and rare genetic faults causing a rare genetic condition.

Genes and common diseases

We only need look at our friends and family to see that human beings are very different from one another: in their appearance, their personality and their abilities. Because there are so many factors which shape us as human beings, it is difficult to point to the origin of our straight As or our good looks. But some of these differences are due to subtle variations in our genes. Most of the time, genetic variation between us is completely benign. But it only takes a sick family member to make you wonder whether you've inherited a potentially more damaging variation. A son whose father has had his third heart attack may be concerned he has a raised risk himself.

Each of us carries a number of gene variants that may contribute to differences in susceptibility to specific common diseases. Those diseases include diabetes, high blood pressure, stroke, coronary artery disease, many cancers and conditions such as Alzheimer's disease and schizophrenia. It's important to remember that genes alone do not cause these diseases. One or more genes can influence the development of a disease later in life, but they are not the only contributory factor. Common conditions like heart disease may have as much to do with the diet of the sufferer and how often (or how little!) they exercise than with their genes. And so, it can be said that some people might have a genetic *susceptibility* to a particular disease: their risk of developing the disease is higher than average, though it is often difficult to say how much higher than average it is.

Rare genetic conditions

Genetic faults that are the sole cause of a serious condition are individually very rare: the most common of these conditions affects 1 in 2500 people. But there are about 4000 of these so-called 'single gene' conditions (caused by a fault in one gene), so in total an estimated one percent of the population are affected and because they are often severe, they can wreak havoc in the family. In many of these families, though by no means all, the genetic fault

responsible has been passed on from one generation to the next. There are three main ways in which a genetic condition can be passed down through families. Understanding these patterns of inheritance, helps us to quantify genetic risk.



Autosomal recessive inheritance

Autosomal recessive conditions require two copies of a faulty or missing gene – one from each parent – to be passed down for it to have an effect upon the recipient. A child can be born with an autosomal recessive condition if each of its parents is a ‘carrier’ of the same faulty gene. Carriers have one copy of a particular gene fault, but because they have another working copy of the gene, the effect is not noticed because the other gene is working fine. If someone inherits two copies of a faulty or missing gene they do not have a working copy and are therefore affected by the disease.

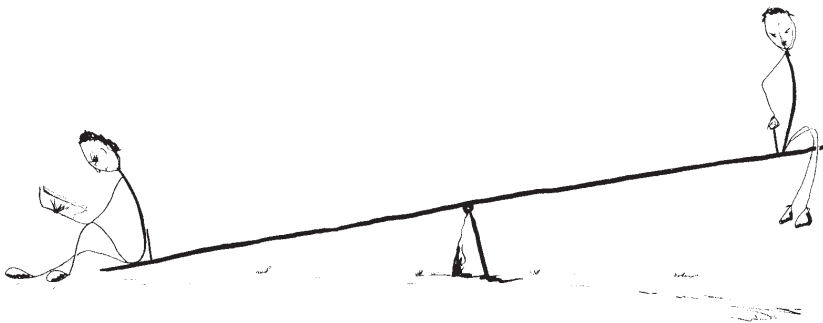
When both parents are carriers of an autosomal recessive condition, there is a one in four chance (25%) with each pregnancy that the child will be affected by that condition. As indicated in the diagram, a child born to such parents has a three in four chance (75%) of being unaffected: a one in four chance of inheriting two normal genes and a two in four chance (50%) of the child being a healthy carrier, like its parents, with one faulty gene and one normal gene.

Autosomal dominant inheritance

When there is an autosomal dominant disease in the family, parents may know that they are at risk of having a child with that disease. Autosomal dominant diseases are individually rare conditions which require just a single faulty gene to be passed down from one parent (or arising anew in the sperm or egg) for it to have an effect. There is a one in two chance (50%) that each child born to a person with a dominant genetic condition will be affected by that condition.

X-linked inheritance

Sometimes genetic conditions are passed down through the X chromosome of which boys have one (they also have a Y chromosome) and girls have two. These conditions are called X-linked. Like autosomal recessive conditions, X-linked ones can be passed on by healthy carriers (or may arise anew in the egg). But here, carriers are usually female and sufferers are usually male. Because females have two X chromosomes, a faulty gene on one has no noticeable effect. But because males have only one X chromosome, there is no working copy of the gene to compensate for its effect. Thus, in the case of X-linked diseases, males are affected by a single dose of a faulty gene. Any boys born to a female carrier have a one in two (50%) chance of being affected by an X-linked condition, whilst the chance of having a baby girl who is a carrier is also one in two (50%).



Responding to risk

It's one thing having someone tell you that you have a one in four or a one in 4000 risk of developing a medical condition. But how do you respond to that information? People often say that, as human beings, we are very bad at understanding risk – after all, we play the National Lottery with a one in 13 million chance of winning! But what this assumption fails to take into account is our ability to weigh up two different things: how likely a particular outcome is *and* how good or bad that outcome would be. And so, risk can be understood as having two components: chance and burden.

Chance

Chance is the first component of risk and it is something that professionals usually provide. It is about making an empirical judgement about how likely a particular outcome is. Sometimes, working out a genetic risk is fairly straight forward. For instance, if a couple has already had a child with a recessive genetic condition, such as cystic fibrosis, their chance of having another child with the same condition is one in four (25%). However, working out the chance of a condition cropping up is not always so simple. The likelihood of developing a more common disease, like coronary heart disease, depends not just upon genetics, but upon many non-



genetic factors such as diet, exercise and whether or not one smokes. In such circumstances, it might be possible to tell someone that they are at higher than average risk of a particular disease. But it may not be possible to be more precise than that.

Burden

The second component of risk is assessed by the patient or prospective parents, who have to make a decision about how to proceed. This decision can be made with the support of professionals (such as doctors, nurses and counsellors), community advisors and friends and family. And so, arriving at a meaningful risk assessment is a process of consultation and personal reflection – even soul searching. It cannot be downloaded from the internet! For some people, a very low risk of a genetic condition will be unacceptable, whereas, for others, it will be a risk worth taking.

Some of the issues which people consider when they are assessing the seriousness of a risk are:

- Treatment availability: its likely success and its impact (such as repeated hospitalisation)
- Psychological ability to cope: either with the test result or the birth of an affected child
- Resources: special needs resource availability, the income of the parents
- What needs to be done to avoid the risk (such as termination of pregnancy)

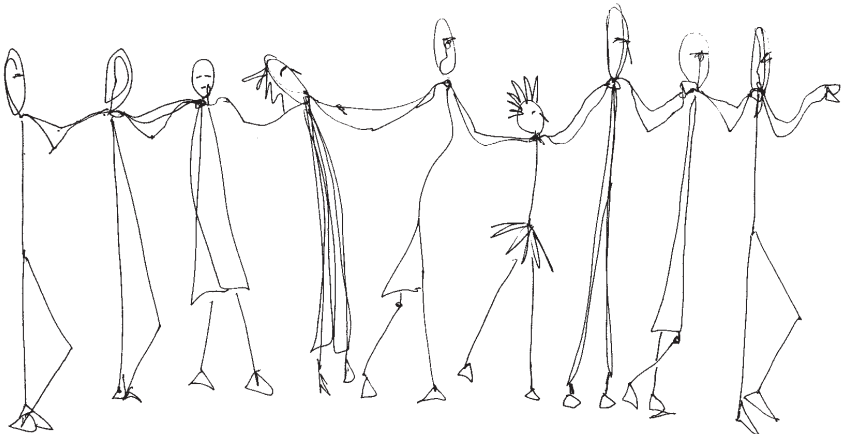
Considering these and other factors helps people to come to a personal judgement as to how to respond to genetic risk. But sometimes there is one further thing to take into account: whether or not to take a genetic test.

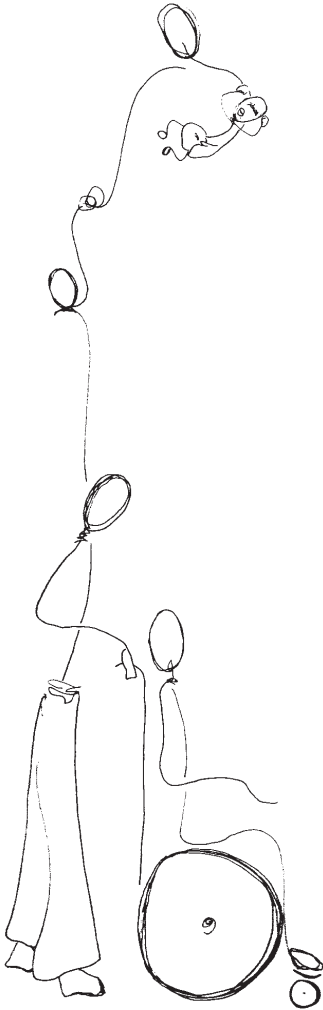
Genetic testing: what it can and can't tell you

Most people have had medical test to help diagnose something that's wrong with them (a blood test for instance) and, in some respects, genetics is no different from that. Quite often, people have a genetic test to help their doctor diagnose an illness or a genetic condition they are suffering from. But there are two other reasons for which people may have a genetic test: because their family history suggests that they are at high risk or because a hidden genetic risk is uncovered through routine screening.

Aiding diagnosis

When someone has serious symptoms – a sick new-born baby for instance – a precise diagnosis is required. This can be done either by taking a detailed family history – looking at how a particular condition or symptoms appear in close relatives, or by performing a genetic test. Usually, the geneticist uses both approaches. A diagnosis of this nature needs to be done at a specialist genetics centre because it is usually more complicated than it first appears and because such centres are able to provide the scientific, medical and emotional support that families often need.





High risk family history

When someone already knows, because of their family history, that they are at risk either of developing a condition themselves or of having a baby with that condition, a genetic test can sometimes provide the answer. If the condition in question is one for which a genetic test has been developed, testing can reveal in advance whether the condition is going to crop up, either by testing during pregnancy or testing a child or adult. A couple who have a child with sickle cell anaemia, for example, know that they have a one in four risk of having a second child with the condition. They may wish to have a genetic test during the second pregnancy to see whether the baby will be affected.

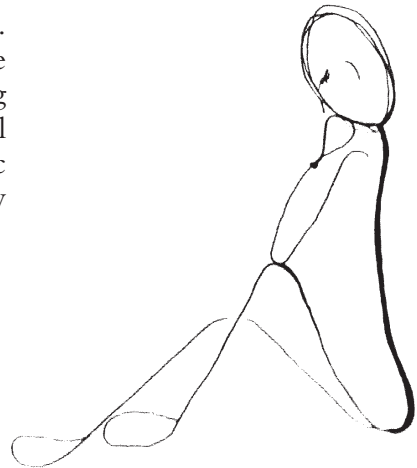
When someone already knows they are at risk of a genetic condition which develops later in life, testing can help to quantify that risk, giving a clear yes or no answer to whether they will develop the condition in question. In this instance, genetic testing can turn a chance into a certainty - either that they will nor

will not develop the disease. A small proportion of breast cancer cases, for example, are caused by a faulty gene passed down through the generations. A young woman who knows the faulty gene is present in her family may wish to have a genetic test to tell her whether she also has it. If she does not have the faulty gene, she knows that her risk of getting breast cancer is no higher than the rest of the population.

Hidden genetic risk

Not everyone at high risk of a genetic condition, either in themselves or their future children, knows that they are. Genetic conditions sometimes crop up in a family without any prior warning and the birth of a affected child, for instance, comes as a complete shock to the parents. This may be because the genetic fault has arisen anew during the formation of egg or sperm, or at conception, as in the case of Down's syndrome. Alternatively, a disease could come out of the blue because both the parents are unwitting carriers of the faulty gene and pass it down to their children. These are autosomal recessive conditions (see page 5).

When this kind of surprise appearance of a genetic condition happens, genetic tests can help diagnose the problem and assist the couple in their future reproductive choices. But is there anything that can be done before such an event takes place? In genetic screening programmes, tests are offered to all or to significant parts of the population, such as pregnant women. It is very different from genetic testing because it is offered to groups or populations of people who may or may not be aware of their increased genetic risk. We already have screening during pregnancy for relatively common conditions like Down's syndrome or spina bifida. But we might want to add to those services by providing screening during pregnancy for autosomal recessive conditions like cystic fibrosis, which affects one in every 2500 babies born.

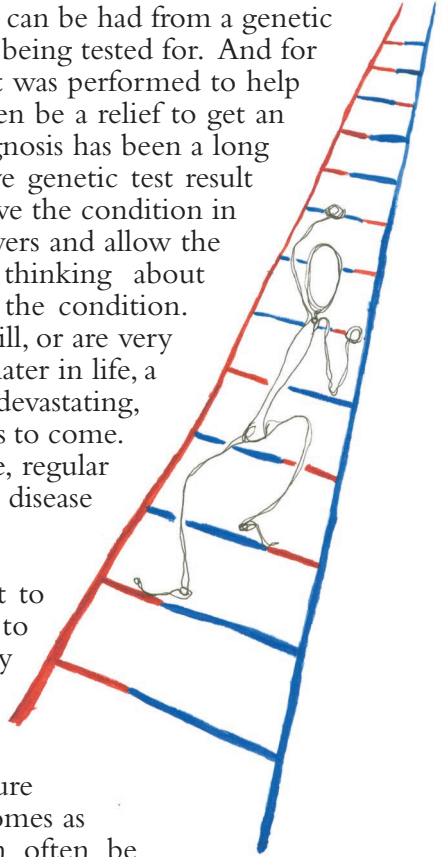


Benefits and limits of genetic tests

You might think that the best result that can be had from a genetic test is that you don't have the condition being tested for. And for many, this is true. But if the genetic test was performed to help diagnose a medical condition, it can often be a relief to get an explanation for it, particularly if the diagnosis has been a long time coming. In this context, a positive genetic test result (one which says that the patient does have the condition in question) can at least provide some answers and allow the person being tested to move onto thinking about treatment options or how to live with the condition. For someone who discovers that they will, or are very likely to, develop a particular condition later in life, a positive result from a genetic test, whilst devastating, can at least prepare the person for what is to come. If, like cancer, the condition is treatable, regular check-ups can be provided to catch the disease in its early stages, should it develop.

When someone is having a genetic test to tell them whether they are likely to develop a condition which affects many family members, a negative test result is often very good news. For instance, if someone has an hereditary form of cancer in their family, discovering for sure that they will not develop the disease comes as an enormous relief. But feelings can often be mixed, particularly if other family members are affected or discover that they *do* have the genetic fault and will develop the condition in future. In such circumstances, relief at their own good fortune can often be mixed with feelings of guilt.

Genetic tests can give people information that enables them to make choices and plan for the future. For instance, a genetic test might give a couple bad news about their sick baby, but it could also help them when they come to think about having another child. Knowing that a test for the condition could be offered during, or even before, pregnancy, could restore their confidence about building a family.



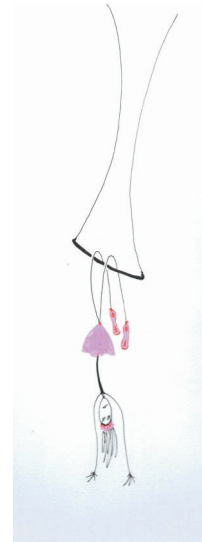
The limits of genetic tests

We've seen that genetic tests can be enormously useful, both to doctors trying to diagnose a mystery condition and to sufferers or unaffected family members who might also be at risk. Tests can give accurate information (whether the news is good or bad), prepare individuals and family members for what is to come and enable them to make choices. But there are limits to what genetic tests can do.

Genetic tests can't always give you a precise answer. For instance, some conditions which develop later in life (known as late onset conditions) don't always appear even when someone has inherited the genetic fault which causes it. Some cancers, for example, have an 85-90% chance of developing in the person with the gene fault. This is because the fault causes the malfunctioning of mechanisms in the body which guard against the proliferation of cancerous cells. Those mechanisms, though impaired, may still work or even if they don't, cancerous cells may not develop in the first place.

Another limit of genetic tests is that they can't tell you much about what a late onset condition will be like (how severe it might be) and at what time it will develop. A final, but fundamental, issue is the availability of the tests. The genetic cause or contribution to many diseases are not well understood and cannot always be identified, meaning that there is no test for them. Even where a test has been developed, it may not be widely available for economic reasons, or it may take a long time for a result to be returned.

Sometimes, a genetic test can give you very precise information but it is information which people feel they can do little with. For instance, a genetic test for Huntington's disease can provide a black and white answer about whether or not the disease will develop at some point. But, with little or no treatment available, many people conclude that it's pointless finding out in the first place.



Who decides?

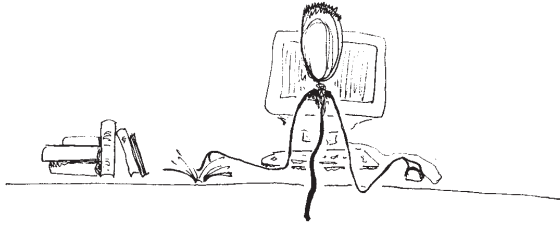
Most people would agree that the decision to have a genetic test is one that only the person involved should take. Genetic tests should never be pushed upon people and they should not be performed without that person's consent. This seems obvious for adults who are able to make up their own mind about whether or not they want a test. But what if the individual being tested is not able to make such a judgement?

Diagnostic testing

Sometimes, when a baby is born with or develops an illness, a genetic test is performed in order to help diagnose the problem. In this context, a genetic test result is relevant to the immediate medical care of that baby and will help to prepare for the future. Although the information gained might be relevant to other family members or future siblings, its immediate usefulness makes the parents' decision for it to go ahead perfectly reasonable. But what if the parents wish doctors to perform a diagnostic genetic test before birth, with a view to ending the pregnancy if the fetus is affected? Some people object to all abortions, but most take the view that when there is a clear indication of a serious genetic condition, the couple concerned should decide how to proceed.

Predictive testing

As we have seen, some genetic tests don't diagnose a current illness, but give a prediction as to whether you will develop it in the future, usually in later adulthood. Adults, who are able to understand the implications of their decision to have a predictive test, should be free to make that decision themselves. But what if the person in question is a teenager wanting to know if they will develop a condition such as Huntington's disease in their forties or fifties? The consensus seems to be that if the test will reveal information which is of medical use now or in the near future, the test can be performed on a child or adolescent. But tests which are predictive of a late onset disease for which there is no treatment should be performed only when the person is old enough to fully understanding the implications of their decision.



Further reading

There's a wealth of information out there about genetics, but where do you start? Here are some suggestions of books and websites to check out if you want to know more.

Books

Matt Ridley *Genome: the autobiography of a species in 23 chapters*
Fourth Estate (2000)

In each of the 23 chapters (one for each chromosome), Matt Ridley takes a particular gene and tells a story, covering everything from genes that we share with animals to those which predispose us to diseases.

Steve Jones *Language of the genes*
Flamingo (revised 2000)

Although originally written in 1994, this book provides a good introduction to genetics, written by a seasoned scientist. Jones considers everything from what our genes can tell us about our evolutionary history to the sex life of a mouse!

Websites

Genetic Science Learning Center

<http://gslc.genetics.utah.edu/>

This American website is a fantastic genetics resource, with information ranging from the genetics of deafness to what a genetic counsellor does. There are hands-on activities, interviews with genetic scientists and downloadable 'primers' on the basics of genetics.

How many like me?

<http://www.techniquet.org/exhibits/hmlm/>

The Techniquet science centre, based in Cardiff, has lots of online science resources but the best for genetics is *How many like me?* Enter your characteristics and see how many other people who have entered their details are just like you!

BBC Gene Stories

<http://www.bbc.co.uk/genes>

An extensive online resource developed to coincide with the *Gene Stories* season of television programmes. There is a wealth of genetics information, plus games, links to other resources and a message board to which you can contribute your views. See the 'Who am I?' section for a well-written introduction to genes and inheritance.

The Human Genome

<http://www.wellcome.ac.uk/en/genome/>

The Wellcome Trust, which funded the British element of the Human Genome Project, has produced a website on how the genome was sequenced, what information has been discovered and how it might affect medicine in the future. The information is fairly difficult, but well explained.

BioNews

<http://www.BioNews.org.uk>

Find it hard to keep up with news stories in genetics? Look no further than BioNews, which provides weekly updates on developments in genetics via its free email newsletter.





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