DNA GENETIC TESTING – screening for genetic conditions and genetic susceptibility

FACT SHEET 21

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Important points

- DNA genetic testing and genetic screening involve the same testing processes to confirm or refute a suspected DNA change
- Tissues tested include blood, skin, saliva and hair follicles and, prenatally, embryo, placental tissue and amniotic fluid; DNA can be tested using blood
- ***Genetic screening*** is done for a particular condition in individuals, groups or populations *without* family history of the condition
- ***Genetic testing*** is done for a particular condition where an individual is suspected of being at increased risk due to their family history or the result of a genetic screening test
- **Direct gene testing** looks at the presence or absence of a known gene mutation by examining the sequence of letters in the information in the gene
- The test is very accurate and used for diagnosis and screening including prenatal, genetic carrier testing and screening, presymptomatic and predictive testing
- Limitations include:
  - Interpretation of the test result eg. finding that a person has a faulty gene does not always relate to how a person is, or will be, affected by that condition
  - The testing may be time-consuming and expensive for the health service if not for the patient
  - For some complex conditions eg. cancer, the testing may have to be done on a family member with the condition to identify a family-specific mutation in the gene (mutation searching) before unaffected family members can be offered predictive testing
- **Indirect gene tracking (linkage)** relies on comparing DNA markers from family members with the condition to markers in unaffected relatives
- Used in situations where the gene itself has not been precisely located or where mutation(s) in a gene have not yet been defined; the test is not as accurate as direct gene testing but can be used in diagnosis including prenatal and presymptomatic and predictive testing
- It may not always be possible to find DNA markers that enable the scientists to tell the difference between the faulty gene copy and the working gene copy

Both genetic testing and genetic screening involve the same testing processes to examine an individual's chromosomes, DNA or the biochemical product of a gene, typically a protein to confirm or refute a suspected chromosomal, DNA or gene product change. See Genetics Fact Sheets 1, 4, 5 & 6 for an explanation of genes, chromosomes, mutations and chromosomal changes.

The difference between genetic testing and genetic screening is the target group for the testing.

- ***Genetic screening*** is done for a particular condition in individuals, groups or populations *without* family history of the condition
- ***Genetic testing*** is done for a particular condition where an individual is suspected of being at increased risk due to their family history or the result of a genetic screening test

How is the testing done?

Different types of genetic tests are used depending on whether an individual's chromosomes, the protein-product of a gene, or the DNA itself are examined.

Body tissues used in testing depend on the particular test:

- The examination of chromosomes (called cytogenetic testing) is usually carried out on blood or, in the case of testing in pre-pregnancy or pregnancy, on the embryo, amniotic fluid or chorionic villus material (see Genetics Fact Sheets 17C and 18)
- Blood is usually also the source for determining if a protein is either absent, present in abnormal amounts or has a changed structure. Occasionally other body fluids or tissues need to be examined
- DNA to be tested can be extracted from the cells of a variety of body fluids or tissues. While the majority of tests are carried out using DNA from blood cells, cells obtained from the lining of the cheek using a mouth-wash or the cells in the roots of an individual's hair may also be sources of DNA

Testing the DNA

Figures 21.1 and 21.2 show how DNA testing is done.

Step 1:

In the laboratory, using enzymes that are chemical 'scissors', the DNA is cut into hundreds of small pieces (*Figure 21.1*) at sites where there are specific sequences of the DNA letters (usually 4-6 letters in length).

As everyone's DNA has some small differences, the sites may be at different places in people's non-coding DNA and so the enzymes will cut the DNA into different sizes in different people.

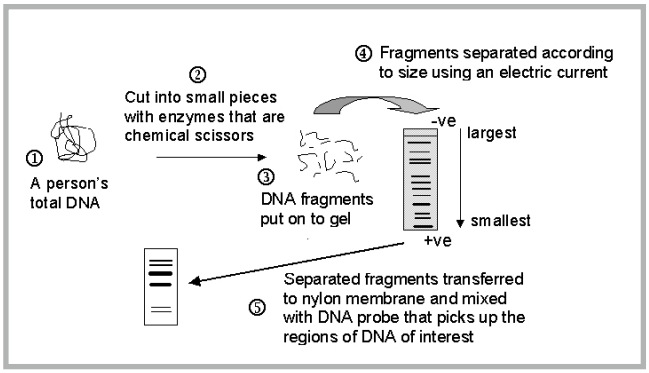

Figure 21.1: *When testing the DNA, it is extracted from the tissue, cut into pieces by chemical 'scissors' and then the pieces are separated on a gel. The piece of DNA of interest that contains a particular gene can be selected from the 20,000 or so genes in an individual's DNA using a special chemical 'probe'.*

Step 2:

The cut DNA is placed into a slab of 'jelly' (a gel matrix) and an electrical current is applied so that the 'jelly' becomes electrified and has a 'positive' (+) end at the top and a negative (-) end at the bottom - just like the positive and negative ends of a battery. As the DNA is a chemical which has a negative charge, the DNA moves towards the positive end of the gel or from the top to the bottom.

The pieces of DNA separate on the gel according to size: the biggest pieces move the slowest and so will be closest to the top of the gel. The gel now contains all of the individual's DNA spread from the top to the bottom of the gel.

Step 3:

To select out the pieces of DNA that need to be analysed, the pieces of DNA that have spread through the gel are covered with special DNA 'probes'. The probes have been made in the laboratory and contain a match for the DNA sequence that the test is designed to identify. The probes in fact have the opposite letters in the genetic code sequence to the sequence in the gene or DNA segment that needs to be isolated. The two sequences match up because of the ability of the letters A and T, and C and G to pair with each other as shown in *Figure 21.2*.

The development of the probes used is critical. They can be expensive to develop and the process may take some time.

- Recent developments have enabled faster testing to see if a genetic condition is due to having the loss of copies of particular gene(s) (*deletion*) or too many copies (*duplication*). The probes are produced in the form of ***microarrays***
- The same principles described above are used in microarray testing except that the DNA from the person being tested is applied to a very small unit on which thousands of different 'probes' representing thousands of regions of DNA or genes have been placed. Microarrays can be built that are specific for one particular chromosome or include all of the DNA in a human cell (the genome)

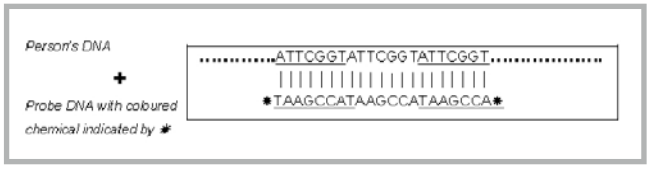

Figure 21.2: *The sequence of 'letters' in the DNA probe is opposite to that in the genetic code in the gene so that the probe hybridises with the gene.*

An example of the result of a DNA genetic test as seen in the laboratory is shown in *Figure 21.3*. There are two copies of each gene. In this case

- Person A has two faulty copies of a gene and may have the genetic condition
- Person B has one copy that is faulty and the other is working. Therefore this person is a carrier of the faulty gene
- Person C has both copies of this gene containing the right information and has normal gene function

The DNA examination may involve the analysis of the gene itself (**direct gene testing**) or of short segments of the DNA close to or within a gene (**indirect gene tracking or linkage**).

Direct gene testing

Once a gene has been located precisely on a chromosome, the next steps are for scientists to determine the normal chemical structure of the gene and the changes that alter the coded message.

Where the change(s) in the gene are known, the gene can be examined directly for their presence or absence. In this case, the test is very accurate.

Direct gene testing is now possible for many genes following the completion of the mapping of the human genome and continuing work in the field (see Genetics Fact Sheet 24).

Uses of direct gene testing in genetic testing and genetic screening

a) Diagnosis

A direct gene test can be used to diagnose a genetic condition.

This can be very useful when the clinical picture is not clear.

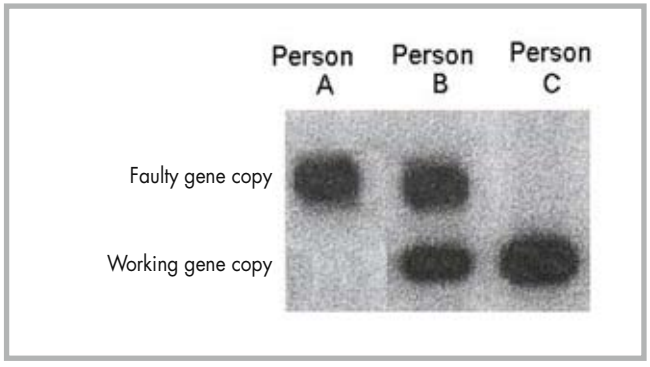

Figure 21.3: *The two fragments of DNA represent the faulty gene copy and the working gene copy. The bands are heavier from persons A and C as there are two copies of the same gene at each band. Person A has two copies of the faulty gene; person B has one faulty copy and one working copy (ie. a carrier of the faulty gene) and person C has two copies of the working form of the gene.*

Genetic testing can be used to diagnose conditions at all stages of life, from conception to the very end of life.

b) Genetic carrier testing

People can also be 'carriers' of changes in genes without showing any signs or symptoms of a genetic condition. Sometimes, this is because these changes make no difference to the gene product. In other cases, the change makes the gene faulty and the gene product is changed, but as we usually have a 'back-up' system that sends the right message to the cell, we can 'carry' faulty genes with no effect on how the body works.

We all carry a number of faulty genes without showing any effects. When, however, both parents are 'carriers' of the same faulty gene, there is a chance that their children will inherit both faulty genes from them and will be affected by a condition. In this case the condition follows a pattern of 'autosomal recessive inheritance' (see Genetics Fact Sheet 8).

Genetic carrier testing may be available for people who have a family history of an inherited condition to determine if they are carriers of the faulty gene involved. This information may be useful in planning pregnancies.

c) Genetic carrier screening

The term 'genetic carrier screening' is used to describe direct gene testing applied to a whole population or to a defined group. For example, genetic carrier screening may be available for people in the population who have no personal or family history of a condition but who have a greater than average chance of carrying a particular faulty gene due to their ancestry.

In Australia, these groups include people with ancestry:

- From Northern Europe and the United Kingdom who have a 1 in 25 chance of being an unaffected carrier of the faulty gene involved in cystic fibrosis (CF) (see Genetics Fact Sheet 33)
- From the Southern European region, the Middle East, the Indian Sub-continent, Africa or Asian countries who have a greater chance of carrying the faulty gene involved in thalassaemia or sickle cell disease (see Genetics Fact Sheet 34)
- Of Ashkenazi Jewish origin who have a 1 in 25 chance of being unaffected carriers of the faulty gene involved in Tay-Sachs disease or several other genetic conditions (see Genetics Fact Sheet 35)

d) Newborn screening

Genetic screening is done on all newborn babies in Australia and New Zealand by a simple blood test to detect a few rare genetic or metabolic conditions.

The blood sample is taken by a heel-prick before the baby leaves hospital, or for home births, on about day 4, and is sent to a special laboratory (see Genetics Fact Sheet 20).

e) Presymptomatic genetic testing

Direct gene testing is now being used to determine if a person will develop certain inherited conditions later in life. This type of genetic testing is referred to as presymptomatic testing where the detection of a faulty gene in a person with a family history of a particular condition, but who currently has no symptoms of that condition, means that that person will certainly develop the condition in later life.

Presymptomatic testing is available for a number of neurodegenerative diseases such as Huntington disease (see Genetics Fact Sheet 44) and some forms of bowel cancer (see Genetics Fact Sheet 49).

f) Predictive Genetic Testing

Sometimes the detection of the faulty gene provides the person with an increased risk estimate, rather than certainty, that they will develop a particular condition later in life. This type of direct gene testing is called predictive testing.

Predictive testing for some families is available for inherited conditions such as an inherited predisposition to haemochromatosis or breast cancer (see Genetics Fact Sheets 36 and 48).

Limitations of direct genetic testing

- Finding that a person has a change in a gene involved in a particular condition does not always relate to how a person is, or will be, affected by that condition. There may be modifying factors (other genes, environmental factors) that can affect the expression of the message from the gene. This may explain the variability of expression between the affected members of one family
- Despite the recent advances in DNA examination, identifying changes in genes is not always easy.
  - Many of the genes in which changes lead to a condition 'code' for very large messages: changes can occur anywhere along the length of the DNA segment making up the gene
  - A single gene may have many possible changes – some changes make the gene faulty (mutations) and others have no effect on how the gene works. For example, there are over 1000 mutations that have been detected to date, at different places along the length of the gene involved in cystic fibrosis (CF) (see Genetics Fact Sheet 33). It is also likely that there are other mutations that have not yet been identified
  - Laboratories often test for only some of the more commonly known mutations in a gene and not for the presence of all of the mutations that occur much more rarely. In the latter case, laboratories have to rely on a more indirect method to determine whether a mutation is likely to be present or absent in the gene in question (see linkage testing described below)
- For some complex conditions that develop as a result of the interaction between the person's genetic make-up and other environmental or genetic factors, e.g. cancer, the testing may have to be done on a family member with the condition to identify the family-specific mutation in the gene (mutation searching) before unaffected family members can be offered

predictive testing. The testing may be time-consuming and expensive for the health service if not for the patient.

What is indirect gene tracking (linkage)?

Indirect gene tracking is used:

- When a mutation(s) in a gene has not yet been defined
- Where the DNA region containing the gene is known but the gene itself has not been precisely located
- When this method is more straightforward than direct gene testing

In this method of genetic testing, scientists use the fact that there are special segments of DNA that are located very close to the gene on the same chromosome. These segments nearly always travel with the gene when it is passed from parent to child: this is more likely the closer they are to the gene.

These segments of DNA are called 'polymorphic markers': *poly* means many and *morphic* means forms. These markers are different in different families. They are a bit like flashing lights that warn them that either the working copy of the gene, or the faulty copy containing the mutation, is nearby.

The closer the markers are ***linked*** to the gene, the more confident the scientist can be that a marker is travelling with either the working copy or the faulty gene copy. This method of indirect gene tracking is referred to as the ***linkage method.***

The markers that are linked to the faulty or working gene copies are special to each family, so this method of genetic testing can only be done within families. Indirect gene tracking is a 'family test'.

Uses of indirect gene tracking (linkage)

a) Prenatal testing

Indirect gene tracking can be done where the change in the gene causing a genetic condition in a family member is not known but where parents wish to utilise prenatal testing. For example, where parents have a child with cystic fibrosis (CF) in whom the mutation(s) causing the condition cannot be identified.

Scientists examine the DNA markers from the child with CF, who has both copies of the faulty gene, and DNA markers in the parents, who each have a working gene copy and a faulty gene copy.

The markers are then compared to DNA markers from the developing baby to see if the baby has the same markers as his/her brother or sisters with CF. If the markers are the same, the faulty gene copies are likely to be there too.

b) Predictive and presymptomatic testing

Indirect gene tracking is also used in predictive and pre-symptomatic testing for conditions that develop later in life. In this case, the test relies on the examination of DNA markers from the parents (one of whom is or was affected by the condition) and tracking the inheritance of the markers to their children.

Limitations of indirect gene tracking

Indirect gene tracking or linkage testing is often referred to as a 'family test' as it relies on comparing DNA markers from family members who have the condition as well as unaffected relatives.

The larger the number of affected family members, the easier it is to be able to track the linked markers to the faulty gene in the family. Small family size and the availability of DNA from affected family members can limit the applicability of this test for some families. In addition, it will sometimes not be possible to find markers which identify the differences between family members who have two copies of the faulty gene, no faulty gene copy or who are carriers of the faulty gene.

- While markers are most often tracked with the faulty gene copy, sometimes the markers will 'cross over' and travel with the working gene copy instead. If this should happen, the markers that have been travelling with the working gene copy will, in the next generation, be associated with the faulty gene. This potential for 'crossing over' occurs whenever a sperm or an egg is produced
- There is therefore a small risk using this method that the diagnosis of an individual being affected by a particular condition will be incorrect. The more closely the marker is linked to the faulty gene, the more likely it is that the presence of the marker will indicate the presence of the faulty gene

Sometimes it is not possible to find DNA markers that enable the scientists to tell the difference between the faulty gene copy and the working gene copy.

Genetic counselling will provide families considering using indirect gene tracking with an estimated accuracy of the test (see Genetics Fact Sheet 3).

A case study of DNA genetic testing

In the family represented diagrammatically in *Figure 21.4*, neither Jan nor Bill knew that they each carried the faulty gene for cystic fibrosis (CF) until they had Sue who was born with CF ie. there were no other family members with the condition. They now know

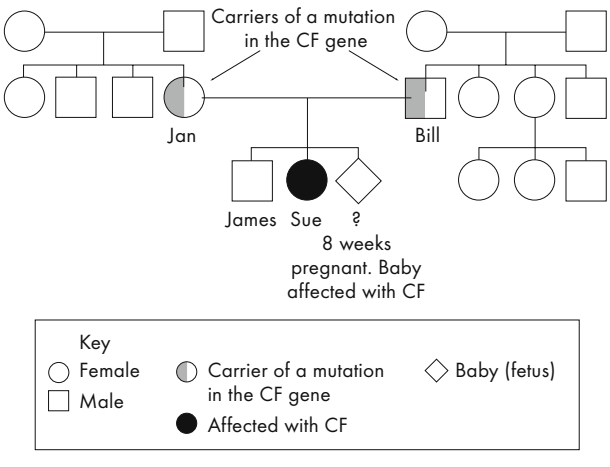

Figure 21.4: *An example of genetic testing when a family member is affected by cystic fibrosis. The family is represented by 'pedigree' symbols.*

that James has 2 chances out of 3 of being a faulty gene carrier for CF (Genetics Fact Sheet 8).

Jan and Bill are concerned about whether any future children will have CF. Jan is currently 8 weeks pregnant and they wish to have testing.

Jan and Bill's brothers and sisters are also concerned and would like to see whether they are carriers of the faulty gene for CF. They each have a 1 in 2 chance of carrying the faulty gene.

- Sue will have two copies of the faulty gene: one inherited from Jan and one from Bill. Sue may have the same mutation in both her gene copies or she may have different mutations in each copy: in either case, both gene copies will be faulty
- The DNA from Sue is examined using direct gene testing to see if the mutation in each copy of the gene involved can be identified
- If the mutations are detected, testing can be offered to Jan and Bill in this or future pregnancies. If the mutations causing the gene to be faulty are relatively common, it will be possible to examine the baby's DNA for these common mutations

If the mutation(s) making the gene faulty in Sue can be identified, Jan's and Bill's brothers and sisters who are planning to have children, can be offered **direct gene testing** to see if they carry a faulty copy of the gene for CF.

- If any of them is a genetic carrier, it may be possible to check their partners to determine if they are also carriers of the faulty gene
- In the future, when James is planning to have children, he will also be able to choose to have carrier testing if he wishes

If however, it is not possible to identify the particular mutation in the two gene copies that Sue inherited, Jan and Bill can be offered **indirect gene tracking (linkage testing)** for prenatal testing during this and further pregnancies.

- DNA markers from Sue, Jan and Bill will be compared to those from the developing baby

Figure 21.5: *The genetic test will show that both Jan and Bill have two bands, as they both have a faulty gene copy and a working gene copy. Sue has two copies of the faulty gene and so has cystic fibrosis (CF). James has inherited both working copies from his parents. The baby's DNA pattern will indicate if she or he has CF, is an unaffected faulty gene carrier for CF or is unaffected with both gene copies having the right information.*

- The test will show if the baby's gene sequence is like Sue's and therefore will have CF (*Figure 21.5*)
- If the pattern is the same as Jan's or Bill's, the baby will be a genetic carrier of CF just like the parents
- Jan and Bill's brothers and sisters may not be able to use this information for prenatal diagnosis in their pregnancies as the markers that are examined are special to Jan and Bill and their children. The markers in the partners of Jan's and Bill's brothers and sisters and in Jan's and Bill's nieces and nephews may also be different

Ethical issues

There are advantages and disadvantages to genetic testing. Genetic testing should only be used after all the benefits, costs and implications have been considered.

Genetic counselling is recommended both before and after testing (see Genetics Fact Sheet 3). Ethical issues arising from genetic testing are discussed further in Genetics Fact Sheet 23.

Other Genetics Fact Sheets referred to in this Fact Sheet: 1, 3, 4, 5, 6, 8, 17C, 18, 20, 23, 24, 33, 34, 35, 36, 44, 48, 49

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