# A guide to genetic tests that are used to examine many genes at the same time

This leaflet gives you information about genetic tests that target many different genes at once. The information may help you to decide whether or not to have the test and help you to understand the results.

## Why are these tests ordered?

For many people with a genetic condition, finding out the cause of the condition can be important. Understanding the genetic basis of the condition might help health professionals to give you information about the progress of the condition, possible preventive actions or treatment. Individuals with a genetic condition may just find it helpful to know why their signs and symptoms occur.

Traditionally, genetic tests were targeted at just one gene. This meant that the health professional providing your care needed to have a strong idea of what was causing the condition in order to choose the correct test. This is not always possible with conditions that may not fit an obvious pattern or when the condition could be caused by changes in one of a large number of genes. In many instances that meant multiple tests of several genes over a period of time, and more laboratory time and effort was needed to obtain a result.

With new technologies it is possible to examine many different genes at the same time. These tests are usually ordered by health professionals with special expertise in genetics and/or genetic counselling.

## What are genes?

Our bodies are made up of millions of cells. Most of those cells contain a complete set of genes.

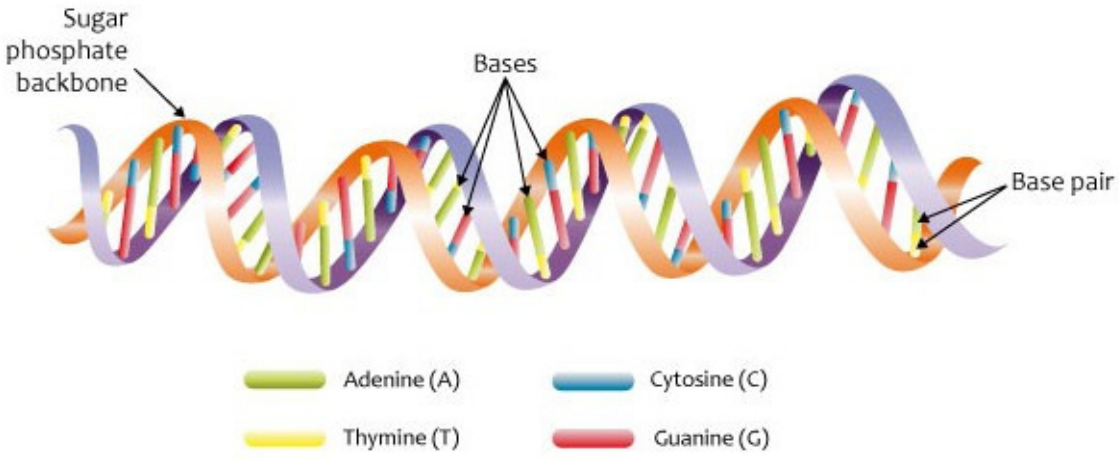
Genes act like a set of instructions, controlling our growth and how our bodies work. They are also responsible for many of our characteristics, such as our eye colour, blood type or height. We have thousands of genes. We each inherit two copies of most genes, one copy from our mother and one copy from our father. That is why we often have similar characteristics to both of our parents. The genes are composed of specific sections of DNA[1] which are a bit like the instruction manual inside the gene. It is made up of four different biochemical building blocks, the bases, represented by four letters, A, C, G and T[2]. The sequence of these letters determines what instructions are stored in the gene. For example, AAGGTC might give the instruction for brown hair whereas AAGGCT might give the instruction for blonde. Sometimes,

[1] DNA is the abbreviation of the name of the biochemical compound within the chromosomes that contains the genes: deoxyribonucleic acid

[2] The four bases that in a specific order form a DNA strand are Adenosine, Cytosine, Thymine and Guanine.

there is a change in the sequence of the letters, which stops the gene from working properly: this is like a spelling mistake. This change can cause a genetic condition because the gene is not communicating the correct instructions to the body. Changes in the usual sequence of letters can be called variants or mutations.

Figure 1.




Not all of our DNA gives instructions to the body. In between the genes are large parts of DNA that are not known to have a function: (sometimes known as the 'non-coding DNA'). Within the genes themselves there are sections of DNA that contain the information that is important for the genes to function (the exons), and sections of DNA that are not used directly by the gene (the introns). These coding and non-coding sections alternate along the gene (Figure 2). The size of each gene varies considerably.

| | Exon (coding) | Intron (non-coding) | Exon | Intron | Exon | Intron | Exon | |
|---|---|---|---|---|---|---|---|---|
| Start of gene | | | | | | | | End of gene |

Figure 2. Diagram to show structure of exons and introns within the gene (diagram not to scale).

## What types of tests might be ordered?

In recent years, a number of new tests have become available that enable the geneticist to examine a number of genes at the same time. These tests are also

known as ‘next generation sequencing’ tests, sometimes written as NGS. Sequencing means finding the order of the A, C, T and G bases within the DNA. With these new techniques, thousands of sections of DNA can be sequenced in one test. These sequences are then compared to the usual sequence, or order of the individual bases, of the human DNA and any differences between the two are noted.

## Gene panel testing

There are two main types of panel testing.

### *Targeted Gene Panel Testing*

This is a technique in which a number of specific genes that are linked to a particular genetic condition are examined at the same time. Such a test may read the information coded in the exons (coding parts) of 20 to over 100 genes. Examples of conditions for which targeted gene panels have been developed are hearing impairment, epilepsy and eye disorders, which may be caused by mutations in one of many separate genes. With this test, even though we might be looking at a number of different genes, the analysis is targeted on the specific condition present in the family.

### *Untargeted disease gene panel testing*

This test is a gene panel that covers the exons of all approximately 2600 genes with a known disease-related function. Such an untargeted panel is helpful in those conditions where many genes are involved, like intellectual disability, or where the targeted panel (as above) has not revealed a result for the family. Usually the analysis will in first instance focus on those genes that are known to be related to the condition for which the test was requested. However, if that does not reveal an answer your health provider may discuss with you to analyse all genes that were read – sequenced- as part of the panel.

## Whole exome or genome sequencing

This type of testing may be used when the panel of genes is not available or when the diagnosis is very unclear. Again, there are two main types.

### *Whole exome sequencing*

Because looking at the whole DNA sequence is still very expensive, sometimes it makes more sense to look specifically at that part of the DNA sequence which gives the instructions to the body (the exons). Whole exome sequencing looks specifically at the instruction sections of almost all the known genes (approximately 20,000). The analysis in first instance will focus on those genes that are known to be related

to the condition for which the test was requested. However, if that does not reveal an answer your health provider may discuss with you analysing all genes that were sequenced. This test may therefore reveal variants in genes with yet unknown functions or variants related to another clinical condition.

Because whole exome sequencing reveals a lot of information, including information in yet unknown genes, usually the parents are tested at the same time as the affected child in order to compare the genetic variants in the genes of the child with those in the parents. This is called trio analysis.

***Whole genome sequencing***

This technique enables the laboratory scientist to look at almost your entire DNA sequence in detail: exons, introns and all material in between the genes. Whole genome sequencing is sometimes used in cases of very sick children who do not have a diagnosis and where a result is needed quickly. One of the limitations of this technique is that it is very expensive and vast amounts of genetic information are generated, some of which is difficult to interpret.

## What could the results be?

The results could either show that there is a change to the usual sequence of the genetic material found in your sample (a variant) or there is not. If a variant is found, laboratory scientists and your health professionals will check to see if that specific variant has been found in other people who have a similar condition to you. We all have some variations in our genetic material, no two people have exactly the same DNA sequence. However, many of the variations are completely normal and have no clinical effect, others enable us to have different characteristics and features. At this stage of our understanding of genetics, we do not always know if a rare variant could be harmful or not.

Depending on the answer to this, you may receive one of the following results:

- The variant is thought to be definitely the cause of your condition or contributes to it in some way. Usually we know this because it has been found in many others with the same condition. Professionals call this a pathogenic or disease-causing variant.
- There is a variant but it is not certain if this is connected with your condition. This is sometimes called a variant of unknown significance and you may have to wait until science has advanced further to find out what it means for you.
- The variant is thought to be harmless and not the cause of your condition. This is called a polymorphism or benign variant.
- There is a variant with known disease-causing effect, but it is connected to another disease than the one the test was done for (see unexpected results).

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If a variant is found and we do not know yet what it means, your health professional may be able to give you more information later on as our genetic knowledge improves. If we don't find a variant, it does not necessarily mean there is no genetic cause for your condition. We still do not have enough understanding of genetics to recognise the underlying causes for all conditions.

Sometimes the geneticist will ask other close relatives to provide a blood sample for genetic testing, because this increases the chances for reaching a reliable conclusion of what the variant means in association with your condition or the condition of your child.

While having a genetic diagnosis can be hard to accept, many people feel that having an answer to the questions as to what caused the condition is useful. For some, the worst outcome is to have the test and have no definite results. If this happens to you, it is natural to feel frustrated.

## Could there be unexpected results?

Yes. Because these tests look at a wide range of genes, it is possible that a gene variant that could cause an entirely different condition is found. Your doctor will discuss this with you before the test is done. In general, your doctor may think it is helpful to tell you about anything that is found that might affect your own health in the future, or the health of your children. However, you should discuss whether you would want this information or not before you agree to the test.

The chance of finding an unexpected result differs between the different tests and is lowest in targeted gene panels. In the other tests it is also very low as long as the analyses is focused on the condition for which the test was requested (condition targeted filtering of the results). In whole exome sequencing the chance of finding an unexpected variant has been estimated to be once in every 100[1] tests performed if the analysis is targeted, but around 3 in every 100 tests[2] if the whole exome is searched. One example of an unexpected finding would be if an individual being tested for a mutation that causes familial colon cancer was found to be a carrier of cystic fibrosis.

Having unexpected results can be upsetting, but may allow you to prevent or reduce the effect of a health problem in the future for yourself or your family.

### What types of unexpected results can be found?

A genetic variant may be found that is known to cause a disease later in life. This for instance can be an increased risk for a heart disease or cancer. Professionals usually make a distinction between "actionable" and "non-actionable" findings.

Actionable means that there is known to be a risk to your health, but your doctor can advise you about screening or treatment that could be helpful to prevent or treat the condition. If the result in non-actionable, this means there is an increased risk to your health, but there is no screening or treatment available to prevent or treat the condition. In general, the laboratory tries to avoid finding non-actionable results and these will usually not be mentioned in the laboratory report.

Another type of unexpected result could be finding a variant that does not affect your own health but may result in an increased risk of having an affected child. For example, some genetic conditions (called autosomal recessive conditions) arise when a child inherits a disease-causing gene variant from both parents and has no normal copy of that gene. Healthy carrier parents have one normal and one faulty copy of the gene and do not usually have any problems associated with the condition. A genetic test may indicate you are a healthy carrier of a condition, and if so you will be given information about what this means for your family and future children. There is more information about these situations in the leaflets on autosomal recessive inheritance and X-linked inheritance patterns listed in the resources at the end of this information sheet.

## Could there be results that affect others in my family?

With any genetic test, there could be results that affect your blood relatives. For example, your condition may be one that could be inherited, and this might then be of importance to your children, brothers and sisters or parents. If this is the case, your health professional will explain this.

In some families, sharing information like this can be hard, and naturally most people dislike giving others bad news. Your health professional may be able to offer support to help you explain it to others in your family, for example by providing you with written information to share with them. Patient support groups can also be useful in guiding you and giving you accurate information to share.

## Future use of the sample

In some cases you may be asked if the genetic sample (from you or your child) can be stored and/or possibly used in future for research purposes. If you are asked about this you must be given all the information you need to make a decision and you can ask questions. You should make up your own mind about whether you are willing to agree to this.

## Resources

1. Other leaflets on genetic testing and genetic conditions, in your own language from:

http://www.eurogentest.org/index.php?id=226

Some relevant leaflets are:

What is a genetic test?

What happens in a genetic laboratory?

Autosomal recessive inheritance patterns

X-linked recessive inheritance patterns

2. Educational Websites:
DNA from the beginning
http://www.dnaftb.org/

Understanding Gene Testing
http://www.accessexcellence.org/AE/AEPC/NIH/

**References**

1. Rehm HL, Bale SJ, Bayrak-Toydemir P *et al*: ACMG clinical laboratory standards for next-generation sequencing. *Genet Med* 2013; **15:** 733-747.

2. Dorschner MO, Amendola LM, Turner EH *et al*: Actionable, pathogenic incidental findings in 1,000 participants' exomes. *American journal of human genetics* 2013; **93:** 631-640.