Information sheet 4: genetic tests

Clinicians use a variety of different genetic tests designed to detect point mutations or dosage mutations in either germ line or somatic DNA (see Information sheets 1,2,3).

Table 1: types of genetic test in routine practice

Test	Technology	Purpose
Single mutation test	Detection of a single specific gene mutation:	Allows testing for either a mutation already to be known in a family or a mutation that commonly occurs in a particular disease.
Multiple mutation test	Detection of a single specific gene mutation:	Used to screen for multiple specific mutations, usually where common mutations are recognised (e.g. cystic fibrosis)
Single gene sequence	Sequencing and analysis of a single gene	Used in situations when a disease is only caused by mutations in one gene.
Panel test	Sequencing and analysis of a set of gene	Used in situations when a disease may be caused by mutations in a number of different genes.
Whole exome sequence	Sequencing of all exons and analysis of a 'virtual gene panel'	Used in situations when a disease may be caused by mutations in a number of different genes. Usually more sensitive than a panel test. Allows future re-analysis of additional genes.
Whole genome sequence	Sequencing of the entire DNA code and analysis of a 'virtual gene panel'	Used in situations when a disease may be caused by mutations in a number of different genes. Can be more sensitive than an exome test. Allows future re-analysis of additional genes.
Array CGH *	Dosage comparison of DNA sequence with a reference DNA sample	Detects deletions and duplications of DNA sequence. Has largely replaced microscopic chromosome analysis.

* comparative genome hybridisation

DNA analysis: single or multiple mutation testing

Such tests are generally fast and focussed on very specific known mutations. For example, in 'predictive genetic testing', an individual's DNA is tested to see if it shares a mutation previously identified in a relative.

Another use of this technology is to screen a gene for mutations known to be common in a given population. A typical indication is cystic fibrosis: in Northern Europeans, 25 specific mutations in the CFTR gene account for the majority of mutations in that population (although over 1900 mutations have been described in this gene across the world). Screening the gene for these common mutations is fast and efficient compared to whole gene sequencing.

DNA analysis: point mutation scanning

When we analyse DNA we need to start by creating a digital copy of the chemical DNA code. That process is called 'sequencing'. There are many different ways of sequencing DNA but they essentially all do the same thing. Sequencing may be restricted to a single gene, a group of genes ('panel testing'), all of the exons ('exome sequencing') or even the entire genome ('genome sequencing').

Once DNA has been sequenced, the code can be analysed. This is a computer-assisted process that involves identifying any changes from the current version of 'normal' and assessing whether they are likely to interrupt the function of the gene or not. Larger datasets clearly require more compute time.

When scientists analyse a gene, or genes, from someone with an inherited condition, we compare that information with the reference normal sequence (see Information sheet 2). When they do so, we are usually able to classify each base as either 'normal' (which means it matches the reference normal sequence) or 'abnormal' (which means that it is different from the reference sequence). At present, scientists quite commonly find a change in the DNA code that could be an acceptable normal variation in the spelling of the gene, but which hasn't been seen before, or which is felt by some computer analysis programmes to potentially have a harmful effect on the gene.

This is the basis of the three types of result that we see from using DNA testing in health care:

1. A normal result: this means that the gene, or genes, that have been sequenced and analysed are no different to the reference normal sequence.

2. A 'mutation' in the gene[1], or one or more of the genes, which means that a change has occurred in the way the gene(s) is written which stops it from working properly.

[1] Technically, scientists now use the terms 'pathogenic variant' instead of 'mutation'.

3. A ‘variant of uncertain significance’ (VUS or VOUS): this means that there is a change from the reference sequence but it is not possible to say whether it is an allowable – but rare – normal variant of the gene sequence or a mutation.

Chromosome analysis

In general, most laboratories have moved on from traditional chromosome analysis – which involved examining chromosomes using a powerful microscope – to ‘array’ technology.

An array CGH test (see Figure 1 below) essentially breaks a patient’s chromosomes and those from a ‘normal control’ (effectively, a normal person) into millions of matching DNA fragments. The fragments from each person are labelled with a different fluorescent dye. The control samples are fixed to a glass plate so their locations are known (this is called an array). An equal amount of DNA from the patient is added; the different fragments find their counterparts in the normal array and stick together.

If the patient and control samples have the same number of copies of each fragment, they emit a ‘mixed’ fluorescent signal (brown in Figure 1). If the patient has a deletion or a duplication of chromosome material, the fluorescent signals from the corresponding fragments emit a different colour. A scanning instrument can assess the fluorescent signals from each of the fragments being tested and a computer reconstructs the entire genome.

This technique has found its major application in the investigation of children with neurodevelopmental delay and physical problems.

Figure 1: array CGH