Information sheet 2: what is a mutation?

Normal

As we saw in Information sheet 1, there are many ways to encode the same information using the 4 letters of DNA code. This suggests that there are many different forms of 'normal'. Normal is not, therefore, a single fixed DNA code but a description of allowable variation.

The current version of the normal genome is called, rather unexcitingly, 'build 38' (https://www.ncbi.nlm.nih.gov/assembly/GCF_000001405.38). This is based on information gathered from the genomes over 1000 people from many different countries around the world. It is in effect an 'average' version of normal. At present it is incomplete, and it is clear that what represents normal to a Northern European may be quite different to someone from Japan or Africa. Future versions of normal will no doubt capture all of this rich variation.

***That* word: 'mutation'**

Although scientists are moving away from this word, 'mutation' quite conveniently captures the idea that, sometime, DNA code changes in such a way that it alters the function of a particular gene.

It is perhaps important to acknowledge that DNA mutation is very common in humans: in fact, *all* of us have dozens of mutations in their germ line DNA (many of which are new to us, developing in either the egg or sperm used to conceive us) and, each day, acquire many thousands of 'new mutations' in our cells, either as random events or caused by external factors such as exposure to radiation or toxins. Much of this mutation has little or no effect, but some mutations *do* have a major effect.

In very general terms, 2 types of mutation are commonly seen in humans:

1. 'point mutation'

This involves the replacement of one base / nucleotide (A, T, C, G) with another. As we saw elsewhere, this is usually perfectly allowable *normal* variation as long at it doesn't change the amino acid code. If it does change the amino acid code, it may stop the protein molecule from working properly, or may even result in the protein being destroyed by the cell. Some amino acids are so similar to each other that substitution of one of another doesn't always result in disease, however.

A particular type of mutation involves changing the normal splice signals at the boundary between an exon and an intron. When this happens, the RNA copy retains a chunk of intron code, resulting in a highly abnormal protein. Such mutations are called 'splice mutations'.

2. 'dosage mutation'

This involves either deletion or duplication of DNA. This may only be as small as a single base or exon, in which case it may result in complete disruption of the normal DNA code; or it may involve a whole gene, block of genes or even a whole chromosome. The effects of such changes are highly varied. For example:

- The familiar condition Down syndrome is caused by duplication of an entire chromosome (chromosome number 21, which has 48 million bases and contains around 600 genes). It is unclear how this leads to the clinical features of Down syndrome.

- A less common condition, Williams syndrome, is caused by deletion of a block of 27 genes from chromosome 7. Again, it is unclear how this leads to clinical problems.

- About 10% of mutations in the *BRCA1* gene are exon deletions and duplications. These result in the same, predictable, increases in cancer risk as we see with point mutations.

The genetic tests used in clinic are specifically designed to detect the above types of mutation.