

## 9.4 Trinucleotide repeats and Imprinting

### Trinucleotide repeats

Approximately 10% of the human genome is composed of repetitive DNA repeats which are usually inherited in a stable form. Certain trinucleotide repeats become unstable and prone to dramatic expansion affecting the expression of neighbouring genes.

#### Trinucleotide repeat expansion diseases

Interestingly, to date, trinucleotide repeat expansion has been implicated only in conditions with a neurological component, for example:

- Huntington's disease
- Myotonic dystrophy
- Fragile X syndrome
- Friedrich's ataxia
- Spinocerebellar ataxia

#### *Anticipation*

Inherited diseases can occur at an earlier age in successive generations. This is called 'anticipation'. One biological explanation of anticipation is the unstable expansion of DNA trinucleotide repeat sequences. The instability of these repeats means that different members of the same family can show different repeat lengths which positively correlate with clinical severity.

#### *Parent of Origin Effect*

Some trinucleotide repeats can rapidly expand over the course of one generation depending on the parent of origin:

- Juvenile Huntington's disease can occur following paternal inheritance of a trinucleotide repeat
- Congenital myotonic dystrophy can occur following maternal inheritance of a trinucleotide repeat

#### *Premutation carriers*

Fragile X syndrome is an X-linked recessive condition that predominantly manifests as learning difficulties in boys and also some girls. Female carriers of a 'pre-mutation' (small expansion only) are at 25% risk of developing premature ovarian failure. Male 'pre-mutation' carriers are at risk of tremor, ataxia and cognitive impairment in older age.

#### Anticipation without trinucleotide repeat expansion

Many other conditions display an earlier onset of disease in successive generations without any evidence of trinucleotide repeat expansion, for example familial rheumatoid arthritis, inflammatory bowel disease and familial leukaemia. This may in part be due to statistical ascertainment bias, earlier diagnosis through improved care or other, as yet unknown, biological mechanisms.

#### Genetic testing

- Molecular genetic testing is widely available for many trinucleotide disorders

### Imprinting

Genomic imprinting is a genetic mechanism by which genes are selectively expressed from the maternal or paternal homologue of a chromosome. Imprints are erased during the early development of the male and female germ cells and then reset prior to germ cell maturation. The imprint remains throughout life. Imprinting defects are more common following IVF, with Beckwith-Wiedemann syndrome being particularly more common.

Imprinted genes can be altered in different ways to produce a non-functioning copy of a gene with a resultant phenotype:

- Mutated
- Silenced
- Deleted
- Uniparental disomy: each chromosome of a pair has been inherited exclusively from one parent, usually by non-disjunction.

#### Imprinting and human disease

In humans, over 50 genes are known to be imprinted and often have roles in growth and development. Some examples of imprinted genes and their phenotypes are:

- Prader-Willi syndrome (loss of paternal gene expression at chromosome 15q11-q13).
- Angelman syndrome (loss of maternal gene expression at chromosome 15q11-q13)
- Beckwith-Wiedemann syndrome (loss of maternally or paternally expressed genes at chromosome 11p15.5)
- Albright Hereditary Osteodystrophy or pseudohypoparathyroidism (loss of maternally or paternally expressed gene at chromosomes 20q13.32)
- Russell-silver syndrome (loss of paternal gene expression at 7q32.2).

#### Genetic testing for imprinting disorders

- For a microdeletion, FISH studies may be used.
- Analysis may be undertaken using DNA from the affected patient to look for abnormal methylation patterns suggestive of an imprinting defect.
- To look for uniparental disomy, DNA is required from both the affected patient and also the parents.
- Direct molecular genetic analysis to look for a specific gene mutation of an imprinting centre locus.

**Pictures:**

**FRAX**

**DNA result showing expansion**

**PWS**

**Angelman**

**?imprinting diagram**