This changes the amino acid used to valine, and this simple change in the amino acid sequence leads to a significant change in the structure of the haemoglobin molecule synthesised, with devastating effects on health.

The consequences of other mutations such as small-scale deletions or insertions of one or more nucleotides depend on how the reading frame is altered. If any number of nucleotides other than exact multiples of three are inserted or deleted, the reading frame downstream of that segment is disrupted (frameshift mutation). Where exact multiples of three nucleotides are involved, there is less disruption and the outcome can result in milder disease (in-frame mutation). Duchenne muscular dystrophy results from a frameshift mutation (deletion) within the dystrophin gene. The milder Becker muscular dystrophy results from an in-frame deletion in the same gene.

Mis-sense, nonsense, frameshift and in-frame mutations can all occur in the same gene. The cystic fibrosis transmembrane regulator (CFTR) gene on chromosome 7 is an example of this (Collins, 2009). Where both chromosomes of a pair carry a mutation in the CFTR gene, the individual will have cystic fibrosis, although the severity and clinical outcome will vary according to the type of mutation.

Another mutation that can be associated with disease is where a short sequence of nucleotides (typically three) is repeated within the gene, and the number of repeats increases above a specific threshold. Huntington’s disease is caused by repeating units of CAG within the HD gene on chromosome 4. The normal range of such repeats is 5-35, but anything above 37 is pathogenic, leading to the disease. The size of the expanding repeat can vary substantially in other genes too, up to many thousands, and repeat length is often correlated with the severity and/or age of onset of the condition. Conditions caused by expanding repeats include Fragile X syndrome and myotonic dystrophy.

Deletions, insertions and inversions of genetic material are all alterations to the chromosomal structure. These changes can involve much larger segments of DNA, sometimes spanning one or more genes, where there have been breaks in the DNA molecule that have not been repaired correctly. Alterations to chromosome number as a result of faults during meiosis also lead to duplication or deletion of genetic material, such as with Down’s syndrome.

The diseases that can result from mutations within a single gene show characteristic patterns of inheritance, as first described by Mendel. The type of pattern depends on the outcome of the mutation, that is, whether there is a loss or gain of function. If the outcome is sufficiently marked for it to be shown when only one gene of a pair is mutated, the inheritance pattern is said to be dominant. There is a

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**Box 2. Pace of discovery**

At its outset, many felt the Human Genome Project was hugely ambitious, but it was completed in 2003 under budget and ahead of time. The pace of studies continues to increase because:

- Breakthrough technological developments lead to quicker and cheaper genome sequencing. The costs of genome sequencing are halved approximately every 22 months (Guttmacher and Collins, 2005);
- Large cohorts of people are being used, often in multinational studies. Large sample sizes are important in detecting relatively modest effect sizes associated with genetic variants. For example, the UK BioBank provides a sample of around 500,000 volunteers;
- Bioinformatics has also advanced to deal more efficiently with massive datasets.

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**Fig 2. Genetic and environmental contributions to single-gene and complex disorders**

A – single-gene disorders. A variant in a single gene is the primary determinant of a disease and is responsible for most of the disease risk or trait variation (dark grey sector), with possible minor contributions from modifier genes (light grey sectors) or environment (blue sector)

B – complex disease. Many variants of small effect (light grey sectors) contribute to disease risk, along with many environmental factors (blue sector)


**Fig 3. The interplay between genome and environment**

<table>
<thead>
<tr>
<th>GENETIC</th>
<th>ENVIRONMENTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duchenne muscular dystrophy</td>
<td>Skin cancer</td>
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<tr>
<td>Haemophilia</td>
<td>Infectious diseases</td>
</tr>
<tr>
<td>Crohn’s disease</td>
<td>Asthma</td>
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<tr>
<td>Pyloric stenosis</td>
<td>Diabetes</td>
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<tr>
<td>Huntington’s disease</td>
<td>Road traffic accidents</td>
</tr>
</tbody>
</table>

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**Fig 3. The interplay between genome and environment**

- Duchenne muscular dystrophy
- Haemophilia
- Crohn’s disease
- Pyloric stenosis
- Asthma
- Diabetes
- Skin cancer
- Infectious diseases
- Road traffic accidents