The Cellular and Molecular Basis of Inheritance

Components of Inheritance
- Cell
  - Nucleus
  - Cytoplasm
- DNA
  - Composition
  - Structure
  - Replication
  - Transcription
- Chromosomes

Cell Cycle / Mitosis

The Human Genome

The nuclear genome

- Approximately 3,200,000,000 nucleotides of DNA
- Either 23 or 24 different types of chromosomal DNA molecules
- About 20,000 to 25,000 genes, or maybe less!

The mitochondrial genome

- 16,569 nucleotides
- A small circular DNA
- 37 genes

Mitochondrial DNA

- The mtDNA genome is very compact, containing little repetitive DNA

- Codes for 37 genes, which include
  - Two types of ribosomal RNA
  - 22 transfer RNAs
  - 13 proteins

- Inherited almost exclusively from the oocyte leading to the maternal pattern of inheritance
**What is a "GENE"?**

Unit of DNA that contains the information to specify synthesis of a single polypeptide chain or functional RNA.

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**The Human Genome**

- **Nuclear genome**
  - Highly conserved sequences
  - Poorly conserved sequences
- **Mitochondrial genome**
  - Protein-coding genes
  - rRNA genes, regulatory sequences
  - Transposon-based repeats
  - Heterochromatin
  - Other sequences

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**Types of DNA Sequence**

- **Nuclear Genes**
  - Unique single copy
  - Multigene families
  - Classic gene families
  - Gene superfamilies
  - Pseudogenes
- **Extragenic DNA**
  - Tandem repeat
  - Satellite
  - Minisatellite
  - Telomere
  - Hypervariable
  - Microsatellite
  - Interspersed
  - Short interspersed nuclear elements
  - Long interspersed nuclear elements
Most human genes are unique single-copy genes coding for polypeptides.

Include enzymes, hormones, receptors, and structural and regulatory proteins.

Have similar functions, arisen through gene duplication events.

Some are found physically close together in clusters; for example, the α and β globin gene clusters on chromosomes 16 and 11.

Others are widely dispersed throughout the genome occurring on different chromosomes, such as the HOX home box gene family.
Pseudogenes

Closely resemble known structural genes but, in general, are not functionally expressed.

Regulation of Gene Expression

- Housekeeping genes
- Many other genes only express in specific cells or stage of cell development
- Control of gene expression
  - Control of Transcription
  - Post-Transcriptional Control

Mutations

- Heritable alteration or change in the genetic material
- Can arise through exposure to mutagenic agents, but the vast majority occur spontaneously through errors in DNA replication and repair.
- Somatic mutations & Germ line mutation
- It is estimated that each individual carries up to six lethal or semilethal recessive mutant alleles
Types of Mutation

- Substitution
- Deletion
- Insertion

Substitution

<table>
<thead>
<tr>
<th>Group</th>
<th>Type</th>
<th>Effect on Protein Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>Synonymous</td>
<td>Silent</td>
<td>Same amino acid</td>
</tr>
<tr>
<td>Non-synonymous</td>
<td>Missense</td>
<td>Altered amino acid—may affect protein function or stability</td>
</tr>
<tr>
<td></td>
<td>Nonsense</td>
<td>Stop codon—loss of function or expression due to degradation of mRNA</td>
</tr>
<tr>
<td></td>
<td>Splice site</td>
<td>Aberrant splicing—on skipping or intron retention</td>
</tr>
<tr>
<td></td>
<td>Promoter</td>
<td>Altered gene expression</td>
</tr>
</tbody>
</table>

Substitution/Missense

**normal HBB gene**

<table>
<thead>
<tr>
<th>V</th>
<th>H</th>
<th>L</th>
<th>T</th>
<th>P</th>
<th>E</th>
<th>K</th>
<th>S</th>
</tr>
</thead>
<tbody>
<tr>
<td>GTG</td>
<td>CAT</td>
<td>CTG</td>
<td>ACT</td>
<td>CCT</td>
<td>GAG</td>
<td>GAG</td>
<td>AAG</td>
</tr>
</tbody>
</table>

**sickle-cell mutation**

<table>
<thead>
<tr>
<th>V</th>
<th>H</th>
<th>L</th>
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<td>GAG</td>
<td>AAG</td>
<td>TCT</td>
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</table>
### Deletion

<table>
<thead>
<tr>
<th>Group Type</th>
<th>Effect on Protein Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-frame deletion</td>
<td>In-frame deletion of one or more amino acid(s)—may affect protein function or stability</td>
</tr>
<tr>
<td>Likely to result in premature termination with loss of function or expression</td>
<td></td>
</tr>
<tr>
<td>Partial gene deletion</td>
<td>May result in premature termination with loss of function or expression</td>
</tr>
<tr>
<td>Whole gene deletion</td>
<td>Loss of expression</td>
</tr>
</tbody>
</table>

### Insertion

<table>
<thead>
<tr>
<th>Group Type</th>
<th>Effect on Protein Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-frame insertion</td>
<td>In-frame insertion of one or more amino acid(s)—may affect protein function or stability</td>
</tr>
<tr>
<td>Likely to result in premature termination with loss of function or expression</td>
<td></td>
</tr>
<tr>
<td>Partial gene duplication</td>
<td>May result in premature termination with loss of function or expression</td>
</tr>
<tr>
<td>Whole gene duplication</td>
<td>May have an effect because of increased gene dosage</td>
</tr>
<tr>
<td>Dynamic mutation</td>
<td>Altered gene expression or altered protein stability or function</td>
</tr>
</tbody>
</table>

### Frameshift Mutation

(A) ACAUUGUAUGNOWTOUCANSEEWONTHERNAANGETHIT
(B) ACAUUGUAUG NOW YOU CAN SEE HOW THE RNA CAN GET HIT
(C) ACAUUGUAUG NOW YOU CAN TSEE ENO WTH ERN ACA NGE THI T

*Figure 12.1: Frameshift Mutation.*
## Mutation Nomenclature

<table>
<thead>
<tr>
<th>Type of Mutation</th>
<th>Nucleotide</th>
<th>Protein Designation</th>
<th>Consequence Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Missense</td>
<td>c.482G&gt;A</td>
<td>p.Arg161His</td>
<td>Arginine to histidine</td>
</tr>
<tr>
<td>Nonsense</td>
<td>c.1756G&gt;T</td>
<td>p.Gly582X</td>
<td>Glycine to stop</td>
</tr>
<tr>
<td>Splicing</td>
<td>c.421 + 1G&gt;T</td>
<td></td>
<td>Splice donor site mutation</td>
</tr>
<tr>
<td>Deletion (3 bp)</td>
<td>c.1078T</td>
<td>p.Val359TerX11</td>
<td>Frameshift mutation</td>
</tr>
<tr>
<td>Deletion (3 bp)</td>
<td>c.1652_1654delCTT</td>
<td>p.Phe551del</td>
<td>In-frame deletion of phenylalanine</td>
</tr>
<tr>
<td>Insertion</td>
<td>c.3805_3806insT</td>
<td>p.Leu1258PheX87</td>
<td>Frameshift mutation</td>
</tr>
</tbody>
</table>

## Functional Effects of Mutations on the Protein

**Loss-of-Function Mutations.**
- Either reduced activity or complete loss of the gene product
- Usually inherited in an recessive manner

**Gain-of-Function Mutations.**
- Either increased levels of gene expression or the development of a new function(s) of the gene product.

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In the cell
DNA is monitored and being repaired Constantly