Mutations

Chapter Twelve
What is a Mutation?

Change in DNA’s nucleotide sequence

1. Specific base changes
   - Molecular level

2. Chromosomal rearrangement
   - Chromosomal level
Affect of Mutations

1. No change in protein
2. Change protein’s
   – Structure
   – Function
   – Location
   – Amount
   – Destroy it completely
3. Provide variation:
   – Neither harmful or helpful
Inherited or Not?

Mutations can occur either in:

• **Germline cells** – sperm or oocyte
  – Then mutation will be inherited in next generation
  – Mutation will occur in every cell in body

• **Somatic cells** – everything not germline
  – Mutation may only occur in specific cells in the body
  – For example – cancer
Types of Mutations

1. Point mutation – alters a single base
   - Missense
   - Nonsense

2. Deletions or insertions
   - Frameshift

3. Duplications

4. Expansions

5. Strand Slippage

6. Chromosomal rearrangement
Point Mutations

• A point mutation is a single nucleotide change (A to G, T or C)

  Transitions – purine to purine
  Or pyrimidine to pyrimidine

  Transversions – purine to pyrimidine
  Or pyrimidine to purine

• Some point mutations encode for exact same amino acid
  – No change in protein
Missense - Point mutation

Point Mutation – a change in a single base

• Missense – when that mutation encodes for a different amino acid
  – Dramatically different amino acid – may have large effect on protein
  – Similar amino acid – may not effect protein’s structure or function

ex

ONE BIG FLY HAD ONE RED EYE
ONE BID FLY HAD ONE RED EYE
Sickle Cell Anemia

- Caused by a **missense** point mutation
- One amino acid in hemoglobin
- Changes from a Glutamate to a Valine:
Nonsense - Point mutation

Point Mutation – a change in a single base
• **Nonsense** – when the amino acid changes to a stop codon
• Therefore making only the beginning of the protein
• Almost always destroys protein’s function

*ex*

ONE BIG FLY HAD ONE RED EYE

ONE BI
Deletions/Insertions

• Deletion:
  – A mutation that removes at least one nucleotide from sequence

• Insertion:
  – A mutation that adds at least one nucleotide to the sequence

• These are usually serious mutations

• Deletions or insertions that affect three bases (or multiples of three) will not cause a frameshift – remove one or more aa
Frameshift Mutation

Frameshift – adding or removing a base that alters the reading frame of translation
• Therefore changing every amino acid that comes after the mutation
• Possibly can alter more than one protein’s function

Example:

ONE BIG FLY HAD ONE RED EYE
ONE BIG FLY HAD ONE RED EYE
Comparison:
Duplications

• Inserting a repeat of the DNA sequence
• Often happens due to:
  – Repetitive DNA sequence
  – Palandromic sequence

Repeat of a nucleotide  A A A A A A A A A
Direct repeat of a dinucleotide G C G C G C G C G C
Direct repeat of a trinucleotide T A C T A C T A C

Complementary base pairing within DNA strand

G T T G G A C T G C G C A G T C C A C A
Inverted repeat

Palindrome

G A A T T C
C T T A A G
Expansions

• When a repeat in the DNA sequence keeps getting duplicated so that the repetitive region actually expands

• Expansions often cause a growing insertion:

<table>
<thead>
<tr>
<th>Pedigree</th>
<th>Age of onset</th>
<th>Phenotype</th>
<th>Number of copies of GAC mRNA repeat</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Older adulthood</td>
<td>Mild forearm weakness, cataracts</td>
<td>50–80</td>
</tr>
<tr>
<td>II</td>
<td>Mid-adulthood</td>
<td>Moderate limb weakness</td>
<td>80–700</td>
</tr>
<tr>
<td>III</td>
<td>Childhood</td>
<td>Severe muscle impairment, respiratory distress, early death</td>
<td>700+</td>
</tr>
</tbody>
</table>
Strand Slippage

This is the mechanism that causes:

1. Deletions
2. Insertions
3. Duplications
4. Expansions

• Caused by the DNA strands:
  – Slipping during replication
  – Misalignment when they reanneal
Strand-slippage

5’ ATGCGGCGGCGGGGGGG
3’ TACGCCGCCGCCGCCCCCCCGCCG

5’ ATGCGGCGGCGGGGGGG
3’ TACGCCGCCGCCGCCCCCCCGCCG

5’ ATGCGGCG
3’ TACGCCGCCGCCGCCCCCCCGCCG

DNA “breathing”

Misalignment

Elongation

# of CGG repeats in a normal gene FMR-1 is < 60
In a Fragile-X patient the # can be >1000
Causes of Mutations

• Spontaneous:
  – Errors in DNA replication
  – Mutational “hot spots”
  – May have predisposing genetics

• Exposure to mutagens:
  – Chemical mutagens
  – UV damage
  – Radiation
  – Induced mutation for research purposes
Spontaneous Mutations

- Errors in DNA replication:
  - Wrong base is placed in sequence
  - Strand slippage
- Mutational “hot spots”
  - Some DNA sequences error prone
    - Repetitive, symmetrical, palindromes
- May have predisposing genetics:
  - May carry genes for poorly functioning replication/repair machinery
Chromosomal - Mitosis

- During Mitosis identical chromatids can be misaligned
- This will cause huge chunks of DNA to be:
  - Repeated
  - Deleted
  - Rearranged – translocations
- Chromosomal abnormalities cause many different types of cancers
- Phenotypes are often very severe
Chromosomal - Meiosis

• During Meiosis homologous pairs of chromosomes can be misaligned

• This will cause huge chunks of DNA to be:
  – Repeated
  – Deleted
  – Rearranged

• Chromosomal abnormalities during meiosis almost always lead to early miscarriages – or severe deformities
Exposure to mutagens

• Chemical mutagens
  – Certain chemicals can change DNA
  Heavy metals, organic solvents, nitrates
  
• UV damage
  – Sunlight can mutate DNA
  Skin cancer

• Radiation
  – Ionizing radiation can break DNA backbone

• Induced mutations
  – Research in animals
UV light damage

Thymine (T) dimer formation
DNA Repair Mechanisms

1. DNA Polymerase – proofreading
   • Mutations that arise during replication are immediately repaired

2. Mismatch Repair
   • If mutation is missed by proofreading, then will be repaired (post-replication)

3. Excision repair
   • Remove and replace incorrect bases (can be done at any time in cell cycle)
Polymerase - Proofreading

DNA Polymerase has two jobs:
1. Attaching correct base by complimentary base pairing
2. Proofreading as it goes along; immediately removing any incorrect bases (mismatches)
2- Mismatch Repair

After replication now have four strands:
- Two parental
- Two new copies

• Parental strands are methylated
• There is a mismatch between a parental and newly formed duplex
• Enzymes will remove the base on the newly formed strand and replace by complimentary base pairing once again
3- Excision Repair

- Similar to mismatch repair
- Remove incorrect bases and replace by complimentary base pairing
- However, difference is that more than just incorrect base is removed
- Also excise surrounding bases as well:
  1. Nucleotide excision – up to 30 bases
  2. Base excision – replaces 1 to 5 bases
Excision repair

ATGCUGCATTTGATAG
TACGCGGTAACTATC

AT            AG
TACGCGGTAACTATC

ATGCCGCATTGATAG
TACGCGGTAACTATC

ATGCCGCATTAG
TACGCGGTAACTATC

ATGCCGCATTGATAG
TACGCGGTAACTATC

Nucleotide excision repair – up to 30 bases
Excision repair

Base excision repair – up to 5 bases

ATGCU_UGCATTGA  
TACGGCGTAACT

__ __________
AT GCATTGA
TACGGCGTAACT

ATGCCGCATTGA  
TACGGCGTAACT

ATGCCGCATTGA  
TACGGCGTAACT

Missense

Remove surrounding bases

Fill in with base pairing

Ligate back together
Defects in DNA repair or replication

All are associated with a high frequency of chromosome and gene (base pair) mutations; most are also associated with a predisposition to cancer, particularly leukemia

- Xeroderma pigmentosum (XP)
  - caused by mutations in genes involved in nucleotide excision repair
  - associated with a 2000-fold increase of sunlight-induced skin cancer and with other types of cancer such as melanoma
- Ataxia telangiectasia (AT)
  - caused by gene that detects DNA damage
  - increased risk of X-ray
  - associated with increased breast cancer in carriers
- Fanconi anemia
  - caused by deficient levels of excision repair
  - increased risk of X-ray
  - sensitivity to sunlight
- Bloom syndrome
  - caused by mutations in a DNA ligase gene
  - increased risk of X-ray
  - sensitivity to sunlight
- Cockayne syndrome
  - caused by a defect in transcription-linked DNA repair
  - sensitivity to sunlight
Remember the importance of position of the mutation

- Mutations with no amino acid change
  - Synonymous codons in Genetic Code
- Splice site mutations
  - A point mutation that affects the intron/exon splice site
  - Or frameshift that changes many splice sites
  - Introns become translated
  - Exons are skipped - vital for protein function
Summary:

- Mutation is a change in DNA sequence
- May or may not change protein sequence and function
- Know types of mutations
- Know causes of mutations
- Know DNA repair mechanisms
- Don’t worry about diseases, those are just examples
Next Class:

• Read Chapter Thirteen

• Homework – Chapter Twelve Problems;
  – Review: 1,3,4,6,7,9,13,16
  – Applied: 2,14,15