GENE MUTATION

Objectives

1. Define mutation and contrast somatic vs. germline mutations.
2. Classify the types of mutations and their severity.
3. Recognize how mutations occur.
4. Describe three mechanisms by which DNA is repaired.

Outline

A. Mutations
   1. Types of Mutations
      a. Effects
   2. Mechanisms of Mutation
      a. Spontaneous
      b. Mutagens

B. DNA Repair
   1. p53

A. Mutations

- Changes in genetic material (DNA)
    - i.e., Nucleotide sequence changed
    - change in the genotype
- Effects on phenotype (mutant)
    - No effect
    - Reduce/Increase amount of protein
    - Prevent production of protein
    - Loss of gene function
    - Hamper control of genes

Table 12.3

How Mutations Cause Disease

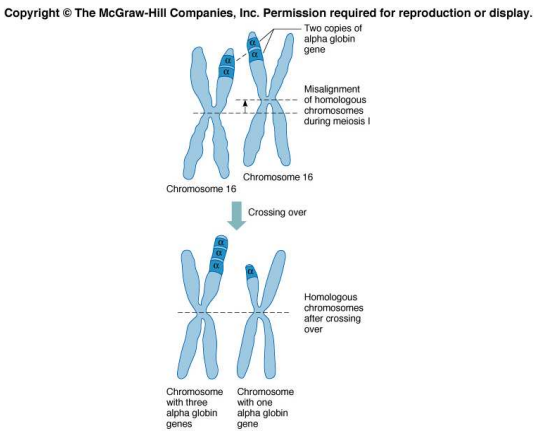
Disease	Signs and Symptoms (Phenotype)	OMIM Number	Protein	Genetic Defect (Genotype)
Cystic fibrosis	Frequent lung infection, pancreatic insufficiency	602421	Cystic fibrosis transmembrane regulator (CFTR)	Missing single amino acid or other defect alters conformation of chloride channels in certain epithelial cell plasma membranes. Water enters cells, drying out secretions.
Duchenne muscular dystrophy	Gradual loss of muscle function	310200	Dystrophin	Deletion in dystrophin gene eliminates this protein, which normally binds to inner face of muscle cell plasma membranes, maintaining cellular integrity. Cells and muscles weaken.
Familial hypercholesterolemia	High blood cholesterol, early heart disease	143890	LDL receptor	Deficient LDL receptors cause cholesterol to accumulate in blood.
Hemophilia A	Slow or absent blood clotting	306700	Factor VIII	Absent or deficient clotting factor causes hard-to-control bleeding.
Huntington disease	Uncontrollable movements, personality changes	143100	Huntingtin	Extra bases in the gene add amino acids to the protein product, which impairs certain transcription factors and proteasomes.
Marfan syndrome	Long limbs, weakened aorta, spindly fingers, sunken chest, lens dislocation	154700	Fibrillin	Too little elastic connective tissue protein in lens and aorta.
Neurofibromatosis type 1	Benign tumors of nervous tissue beneath skin	162200	Neurofibromin	Defect in protein that normally suppresses activity of a gene that causes cell division.

- somatic mutation
    - can be cancerous
- germline mutation (constitutional)
    - heritable

1. Types of Mutations

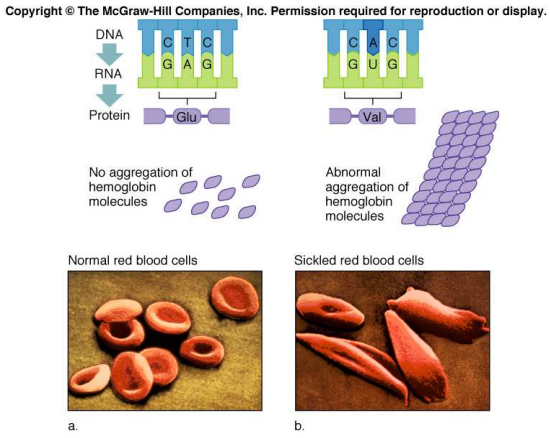
- Point mutation
    - Transition
    - Transversion

- Frameshift
- Deletion/Insertion
- Tandem Duplication

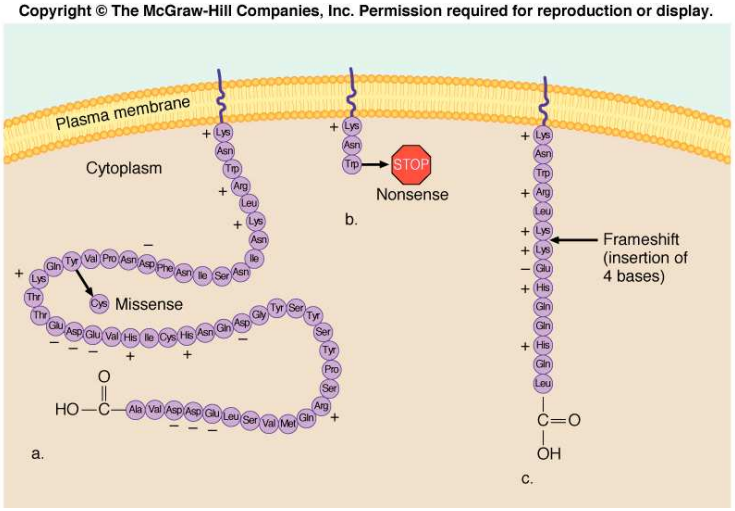


a. Effects

- Point Mutations
  - Silent mutation
    - Redundancy in genetic code
  - Missense
    - Change in single amino acid
      - e.g., β-globin in sickle cell anemia



    - Change in promoter
      - e.g., Becker muscular dystrophy
  - Nonsense
    - Change to stop codon
      - e.g., Factor XI hemophilia



- Deletion/Insertion
  - Frameshifts
    - Triplet codons not read properly
      - One or two nucleotides shift beginning of codon
      - protein sequence after frameshift completely changed

Table 12.7

Types of Mutations

A sentence comprised of three-letter words can provide an analogy to the effect of mutations on a gene's DNA sequence:

Normal	THE ONE BIG FLY HAD ONE RED EYE
Missense	THQ ONE BIG FLY HAD ONE RED EYE
Nonsense	THE ONE BIG
Frameshift	THE ONE QBI GFL YHA DON ERE DEY
Deletion	THE ONE BIG HAD ONE RED EYE
Insertion	THE ONE BIG WET FLY HAD ONE RED EYE
Duplication	THE ONE BIG FLY FLY HAD ONE RED EYE
Expanding mutation	
generation 1	THE ONE BIG FLY HAD ONE RED EYE
generation 2	THE ONE BIG FLY FLY FLY HAD ONE RED EYE
generation 3	THE ONE BIG FLY FLY FLY FLY FLY HAD ONE RED EYE

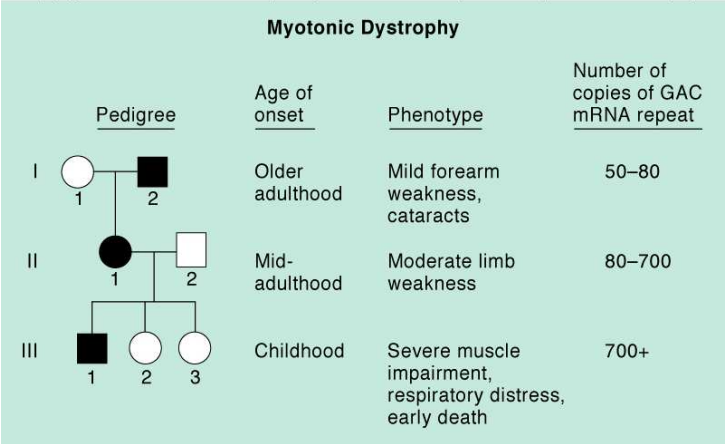
- Deletion/Insertion
  - Removing or adding nucleotides in multiples of three
    - Amino acids added/deleted, but remaining codons unaffected

Table 12.8

Triplet Repeat Disorders

Disease	OMIM Number	mRNA Repeat	Normal Number of Copies	Disease Number of Copies	Symptoms
Fragile X syndrome	309550	CGG or CCG	6–50	200–2,000	Mental retardation, large testicles, long face
Friedreich ataxia	229300	GAA	6–29	200–900	Loss of coordination and certain reflexes, spine curvature, knee and ankle jerks
Haw River syndrome	140340	CAG	7–25	49–75	Loss of coordination, uncontrollable movements, dementia
Huntington disease	143100	CAG	10–34	40–121	Personality changes, uncontrollable movements
Jacobsen syndrome	147791	CGG	11	100–1,000	Poor growth, abnormal face, slow movement
Myotonic dystrophy type I	160900	CTG	5–37	80–1,000	Progressive muscle weakness; heart, brain, and hormone abnormalities
Myotonic dystrophy type II	602668	CCTG	<10	>100	Progressive muscle weakness; heart, brain, and hormone abnormalities
Spinal and bulbar muscular atrophy	313200	CAG	14–32	40–55	Muscle weakness and wasting in adulthood
Spinocerebellar ataxia (5 types)	271245	CAG	4–44	40–130	Loss of coordination

- Expanding Triplet Repeats
  - Causes protein misfolding
  - Generally dominant
  - Can even affect intron



- Tandem Duplication
    - Complete gene duplicated

- Conditional mutation
    - phenotype expressed only in proper environment.

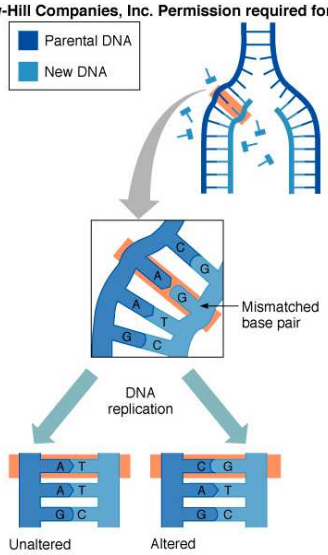
2. Mechanisms of Mutation

a. Spontaneous

- Accident in DNA replication
    - Tautomeric state of nitrogenous base

- Once every 10^5–10^9 bases

- More common in mitochondrial DNA
    - No DNA repair mechanism



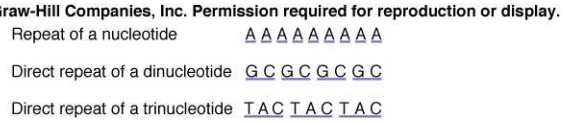
- Extremely common in viral genomes
    - Viral polymerases more mistake prone
- Do not occur evenly throughout genome

Table 12.4

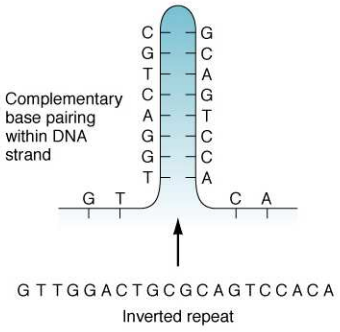
Mutation Rates of Some Genes That Cause Inherited Disease

	OMIM Number	Mutations per Million Gametes	Signs and Symptoms
X-linked			
Duchenne muscular dystrophy	310200	40–105	Muscle atrophy
Hemophilia A	306700	30–60	Severe impairment of blood clotting
Hemophilia B	306900	0.5–10	Mild impairment of blood clotting
Autosomal Dominant			
Achondroplasia	100800	10	Very short stature
Aniridia	106200	2.6	Absence of iris
Huntington disease	143100	<1	Uncontrollable movements, personality changes
Marfan syndrome	154700	4–6	Long limbs, weakened blood vessels
Neurofibromatosis type 1	162200	40–100	Brown skin spots, benign tumors under skin
Osteogenesis imperfecta	166200	10	Easily broken bones
Polycystic kidney disease	600666	60–120	Benign growths in kidneys
Retinoblastoma	180200	5–12	Malignant tumor of retina

- nucleotide repeats



- palindromes



Palindrome G A A T T C
C T T A A G

b. Mutagens

- Increase mutation rate 10-1000x

- Chemical
  - Alkylating agents
    - Randomly replace DNA base
  - Intercalating agents
    - Slip between bases
    - Cause insertion/deletion of bases
      - e.g., acridine dyes, aflatoxin

Table 12.5

Commonly Encountered Mutagens

Mutagen	Source
Aflatoxin B	F ungi growing on peanuts and other foods
2-amino 5-nitrophenol	Hair dye components
2,4-diaminoanisole	"
2,5-diaminoanisole	"
2,4-diaminotoluene	"
p-phenylenediamine	"
Furylfuramide	F ood additive
Nitrosamines	Pesticides, herbicides, cigarette smoke
Proflavine	Antiseptic in veterinary medicine
Sodium nitrite	S moked meats
Tris (2,3-dibromopropyl phosphate)	Flame retardant in children's sleepwear

- Base analogs
    - Less precise pairing properties
        - e.g., 5-bromouracil pairs A, C
    - Nitrous acid
        - Causes A to pair with C

- Physical
    - Ionizing Radiation
        - Ionize DNA
            - Results in replication errors
        - Break covalent bonds
            - Cause chromosome breaks
        - e.g., X-rays, alpha, beta, gamma rays
    - UV radiation
        - Produce thymine dimers
            - Prevent transcription, replication

B. DNA Repair

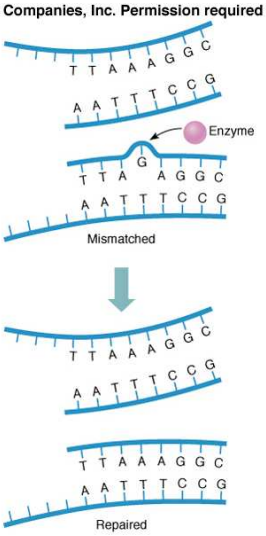
- DNA polymerase very accurate
    - 1 mistake in 10^8 bases

Table 12.11

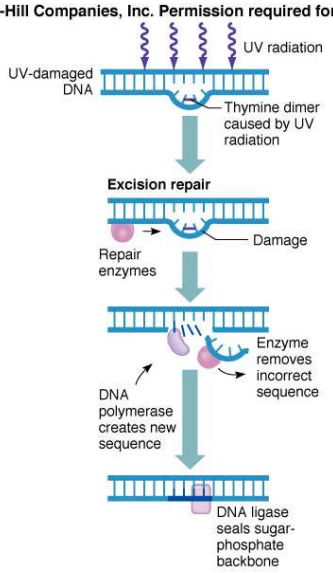
Some DNA Replication and Repair Disorders

Disorder	OMIM Number	Frequency	Defect
Ataxia telangiectasis	208900	1/40,000	Deficiency in kinase that controls the cell cycle
Bloom syndrome	278700	100 cases since 1950	DNA ligase is inactive or heat sensitive, slowing replication
Fanconi anemia	227650	As high as 1/22,000 in some populations	Deficient excision repair
Hereditary nonpolyposis colon cancer	120435	1/200	Deficient mismatch repair
Werner syndrome	277700	3/1,000,000	Deficient helicase
Xeroderma pigmentosum	278700	1/250,000	Deficient excision repair
Trichothiodystrophy	601675	Fewer than 100 cases	Deficient excision repair

- Mismatch Repair
    - New DNA strand proofread and repaired



- Photoreactivation
    - Photolyase uses visible light to break thymine dimers
- Excision Repair
    - Excision enzyme removes thymine dimer and adjacent bases
    - DNA polymerase adds new bases
    - Ligase covalently bonds the sugar-phosphate backbone



- Two types
    - Nucleotide Excision Repair
        - Repairs a variety of mistakes
    - Base Excision Repair
        - Repairs damage from free radical oxygen

1. p53

- Protein that controls cell cycle
- Examines DNA for damage
- If too much damage:
    - Induces apoptosis genes
    - Shuts off p53 production