Gene Mutation and DNA Repair

- Xeroderma Pigmentosum:
  - wo individuals with xeroderma pigmentosum, the boy shows marked skin lesions induced by sunlight. Mottled redness (erythema) and irregular pigment changes in response to cellular injury are apparent. Two nodular cancers are present on his nose.
- Charles Darwin's concept of "descent with modification"
  - As many more individuals of each species are born than can possibly survive and as consequently there is a frequently recurring struggle for existence it follows that any being *if it vary* in any manner profitable to itself under the complex and sometimes varying conditions of life *will have a better chance of survival and thus be naturally selected*. From the strong principle of inheritance any selected variety will tend to propagate its new and modified form"
- Genetic Variation
  - is the diversity of different genomes that give rise to different individuals
  - Genomes can change over time
  - Changes are heritable (through germline)
  - DNA is the hereditary material
    - changes in the DNA at the nucleotide level or at higher level (Mutation) are the 'ultimate' source of genetic variation
    - recombination also gives rise to genetic variation
    - **Spontaneous Mutation**- occur in nature and mainly due to errors in DNA replication
    - **Induced Mutations**- due to chemical or physical damage
      - muller 1927, Stadler 1928 use of x-rays
- Categories of Mutation
  - **Somatic Mutations**- not inherited most likely to be visible if dominant
  - **Gametic changes are heritable**- recessive X-linked
  - **Nutritional/biochemical mutations**- prototrophs/auxotrophs
  - **Behavioral mutations**- hard to discern
  - **Regulatory mutations**- over/under expressed gene
  - **Lethal mutations**- cannot survive to reproduce
  - **Conditional mutations**- ex) temp. sensitive
  - **Neutral mutations**- effect on fitness level of the organism is negligible; no effect on gene product on expression
- Molecular Basis of Mutation: Genetic information read in triplets (codons)
  - **Transition**- pyrimidine replaces pyrimidine or purine replaces purine
  - **Transversion**- pyrimidine replaces purine or purine replaces pyrimidine
  - **Missense**- amino acid changed to a different aa
  - **Nonsense**- amino acid changed to a stop codon
- Spontaneous mutations occur due to replication errors and base modifications
  - **Tautomeric shifts**

        - Purines and pyrimidines exist in alternative forms differing by a single proton shift
        - less frequent forms base pair with non-complementary bases
            - ex) T(enol)-G(keto) or C(imino)-A(amino)
        - If these forms exist transiently during DNA replication then transition mutations can occur (note that pairing is still between a purine and a pyrimidine)
    - **Oxidative damage**
        - damage to bases by oxidative species such as superoxides and hydrogen peroxide modify bases and lead to mispairing
- Figure 14-3
    - Formation of a T-A to C-G transition mutation as a result of a tautomeric shift in adenine
- Apurinic Sites and Deamination
    - "Spontaneous" loss of purine (AP site) leads to inadequate template- another nucleotide can be inserted
        - in deamination an amino group is converted to keto group, this causes an alteration in base pairing efficiencies
- Induced mutations arise from DNA damage caused by chemicals and radiation
    - **Base analogs**: Chemicals that substitute for purines or pyrimidines
        - ex) similarity of 5-bromouracil (5-BU) structure to thymine structure. In the common keto form 5-BU base-pairs normally with adenine behaving with adenine behaving as an analog In the rare enol form it pairs anomalously with guanine
    - **Alkylating Agents**: One of the first chemical mutagens known (WWI)
        - Alkylating agents such as EMS donate an alkyl group to amino or keto groups in nucleotides cause transition mutations
    - **Acridine Dyes and Frameshift Mutations**
        - ex) acridine orange can cause frameshifts, they wedge between bases causing slippage or improper pairing leading to addition or deletion of a base pair
- UV and high energy radiation
    - Shorter wavelength
        - UV radiation is mutagenic- major effect is to induce pyrimidine dimers between adjacent base- pairs along a DNA strand
    - Ionizing radiation
        - X-rays, gamma rays, cosmic rays
        - electrons are ejected from atoms and they become 'free radicals' - leading to several types of reaction that can alter DNA and resulting in point mutations
    - Also chromosome aberrations (breakage of DNA bckbone) "Target Theory" 1924 that x-rays cause damage at single sites (mutation)- also- effect is cumulative
- Dimer formed between adjacent thymidine residues along a DNA strand

    - Induction of a thymine dimer by UV radiation leading to distortion of the DN the covalent crosslinks occur between the atoms of the pyrimidine ring
- Single Gene Mutations cause a wide range of Human Diseases
    - A single base pair (SNP) change can result in a serious genetic disorder
    - OMIM database has over 3000 human genetic diseases cataloged
    - About 30% of SNPs cause stop codons (nonsense mutations) 15% abnormal splicing
- Case studies of mutation in human genes:
    - Trinucleotide repeats:
        - Huntington disease
            - Repeat: CAG
            - Normal number: 6-53
            - affected number: 36-129
        - Myotonic dystrophy
            - Repeat: CTG
            - Normal number: 5-35
            - affected number: >200
        - Fragile X syndrome
            - Repeat: CGG
            - Normal number: 6-50
            - affected number: >200
        - Spinolumbar Musc. Dys
            - Repeat: CAG
            - Normal number: 10-30
            - affected number: 35-60
    - Loss of CAG makes long tracts of glutamine that can cause proteins to aggregate
    - number of repeats increases in each generation
        - genetic anticipation
    - Sometimes mutation is in coding region, other times upstream or downstream
- Single Gene Mutations Cause a wide range of Human diseases
    - ABO blood type alleles:
        - 4 common nucleotide substitutions in I^A and I^B alleles that change amino acid sequence of protein
        - I^o allele (lack glycosyltransferase)- deletion of one nucleotide causing a frameshift and an abnormal and truncated (shorter than normal) protein
    - Muscular Dystrophy
        - Common (severe) duchenne (DMA) and milder becker forms (BMD) gene (2 mill. bp) - 14 kb message - 3685 aa most mutation cause premature termination
        - 65% substantial deletions
        - most DMD changed reading frame but BMD did not
- Organisms use DNA repair systems to counteract mutations
    - necessary for survival of organisms on earth