Content for Midterm 1

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Mendelian Genetics

- Key Terms:
  - Gene - An inherited factor (encoded in DNA) that helps to determine a characteristic
  - Allele - One of two or more alternative forms of a gene
  - Locus - Specific place on a chromosome occupied by an allele
  - Genotype - The set of alleles possessed by an individual organism
  - Phenotype - The trait or the appearance / manifestation of a characteristic
  - Carrier frequency - the proportion of individuals in a population who have a single copy of a specific recessive mutation
  - Conditional probability - additional information based on the situation or the condition
- Gregor Mendel's beans worked excellently as model organisms for the following reasons:
  - The phenotypes of the beans resulted in multiple traits that were easily assayed.
  - The beans grew quickly and easily, allowing for more efficient collection of experimental data
  - The beans grew large amounts of offspring in each generation, allowing for greater quantities of experimental data to be coll ected.
  - Feasible experimental design: i.e. straightforward to set up desired crosses and analyze results
- A model organism is defined as an organism with a high degree of relatedness among organisms that can be readily manipulated to make conclusions that are likely to be relevant to other organisms.
  - Drosophila can be a model organism for other insects
  - Rhesus monkeys and mice may be good model organisms for humans
- Experimental procedure / design for Mendel's pea plant experiment
  - First, isolated "purebred" lines were generated for particular traits. These were then crossed with one another to create hyb rids.
  - Reciprocal crosses were carried out (in which the father and the mother alleles both were tested)
  - Mendel removed the anther from the flowers of the pea plant that would receive the pollen of the other plant, which would pre vent self-fertilization which may interfere with the results of the experiment
  - Then, the flowers were cross-fertilized by brushing the pollen of the other flower onto the stigma of the recipient flower.
  - Large data sets were statistically modeled to explain and predict further experimental results
- Conclusions of Mendel's experiment
  - Blending of genes did not occur
  - Each trait remained discrete: a pea was either yellow or green, never a mix of both.
  - Consisted of a dominant and a recessive trait.
  - Principle of Segregation (Mendel's First Law) - Each individual diploid organism possesses two alleles for any particular characteristic. These two alleles "segregate" when gametes are formed, and one allele goes into each gamete.
    - Sutton formalized the chromosomal theory of inheritance from Mendel's First Law
    - Nondisjunction will violate this law
  - Law of Independent Assortment (Mendel's Second Law) - During gamete formation, different pairs of alleles segregate independently of each other.
    - In the case of crossing over, the alleles no longer segregate independently of each other, and violate this law.
    - Nondisjunction, where both alleles or no alleles go to one gamete, will violate this law.
  - These two laws are the basis of genetics from the view of mendelian inheritance, the most basic understanding of genes.
- Typically, recessive traits are associated with a loss of function of a certain trait.
  - For example, in green pea plants, the green pigment is caused by the presence of chlorophyll. Chlorophyllase, the enzyme whic h is responsible for the breakdown of chlorophyll, functions in yellow pea plants, where the enzyme gets rid of the chlorophyll. However, in green pea plants, the enzyme can't function, and therefore the plant remains green. The loss of function is therefore associated with the recessive gene.
  - Similarly, albino animals carry the loss of function mutation for the production of melanin. The tyrosinase gene in particula r encodes the rate-limiting enzyme.
  - In cystic fibrosis, the CFTR protein is unable to move chlorine to the cell surface, causing thick viscous mucus to build up in the lungs.

Sex-Linkage

- Thomas Hunt Morgan was the first to test the theory of sex-linked genes based on his findings in populations of drosophila, of white and red eyes.
  - In testing his hypothesis, the alleles carrying the white eye trait were found to segregate with the X -chromosome, a strong piece of evidence for the chromosomal theory of inheritance.
  - His tests also proved the importance of reciprocal crosses, which is a pair of crosses between a male of once strain and a fe male of another, and vice versa.
- Sex Determination in Humans
  - A single Y chromosome, even in the presence of several X chromosomes, will still produce a male phenotype.
  - The X chromosome contains genetic information required for both sexes, therefore it is essential
    - Turner's Syndrome: XO
    - Klinefelter's Syndrome: XXY, XXXY, XXXXY, or XXYY
    - Poly X: XXX, XXXX, XXXXX, etc.
    - Down's Syndrome: Trisomy 21
  - X - inactivation
    - Mary Lyon proposed the theory of X-inactivation to explain Barr Bodies
    - All but one X chromosome in humans becomes a Barr body.
    - In early embryonic cells, one X chromosome is chosen to be active and another is chosen to be inactive. This in turn results in that same chromosome to remain inactive or active throughout mitoses.
  - Temperature dependent sex determination (TSD)
    - At high temperatures, turtle eggs will be females, while at low temperatures turtle eggs will be males.
    - Limpet's positions in stack - larvae on top become male, while larvae on bottom become female.
  - Nondisjunction
    - Nondisjunction was first observed by Calvin Bridges in his study of drosophila.
    - Occurs when the chromosomes do not separate during phases of meiosis, leaving one gamete with more or less chromosomes than u sual.

Single Gene Effects: Dosage and Multiple Alleles

- Dosage Effect: The difference in phenotype from one copy of a dominant allele (or recessive allele) vs. the phenotype for two copies of a dominant (or recessive) allele.
  - This is also known as incomplete dominance.
- Hypomorphic allele
  - Describes an allele with a mutation that causes a partial loss of gene function.

- Complementation: determine whether mutations are at the same locus or at different loci
  - Tests whether phenotypes are caused by mutations in the same or different genes
- Codominance
  - Example of which includes human red blood cells. The transmembrane molecules of the red blood cells are used to identify the type of blood.
  - I^A and I^B are two codominant blood types: if someone had both I^A and I^B genes, then both would show, resulting in the blood type AB.
- Pleiotropy
  - Pleiotropy occurs when one gene encodes for multiple different phenotypes.
- Epistasis : One gene masks the effect of the other gene.
  - Baldness is epistatic to hair color (baldness masks the trait of hair color - if there is no hair, then there is no color phenotype.)

Single gene traits with variable penetrance vs expressivity

- Penetrance: percentage of the population with a particular genotype that shows the expected phenotype -
  - For mendelian inheritance, 100% penetrance is expected.
- Expressivity: the degree or intensity with which a particular genotype is expressed in a phenotype.

Linkage, Recombination, and Genetic Maps

- Genes that are closer together separate more frequently than genes that are further apart.
- Linkage groups - genes segregating together
  - Linkage groups are defined by comparing the frequencies of co-separation.
  - The greater distance between the two genes, the greater chance of recombination.
- Complementation groups - determined by complementation tests
  - A complementation test is used to generate recombinant progeny
  - A simple complementation test is shown on the diagram to the right
- Map distance:
  - RF (recombinant frequency) = (#recombinant progeny / total progeny) * 100
  - 1 % RF = 1 map unit = 1 centiMorgan
  - Map distance allows us to predict cross outcomes.
  - The # recombinant progeny is just the 2 rarest progenies..
  - Most common two is nonrecombinant
  - In order to adjust for total length, the double crossovers must each be added twice.
    - For example, in a cross of AaBb and aabb, the progeny results in 10 AaBb, 40 Aabb, 40 aaBb, and 10 aabb. The # recombinant progeny must be AaBb and aabb, as these two are the rarest among the progeny.
- Crossing over
  - The exchange of different sections of genes (gene loci) with each other on a pair of homologous chromosomes is the definition of crossing over.
  - Double crossover can occur, which will reverse the single crossover:
  - Recombinant chromosomes resulting from the double crossover will only have the middle gene altered.

Coupling vs. Repulsion

- Coupling refers to the linkage of two dominant or two recessive alleles
- Repulsion refers to the linkage of dominant alleles to recessive alleles.

Applications of Gene Mapping

- Classic mutant screens in model organisms
  - Makes use of visible markers
- Mapping quantitative traits (QTLs)
- Mapping of human genes based on existing populations

Gene Mutations

- Categories of mutations
  - Somatic mutations - occur in non-reproductive cells
    - Generates "mosaic organisms" A genetic *mosaic* is an *organism* composed of two or more genetically different populations of cells that originate from one zygote.
    - Somatic mutations may result in malignant tumor oncogenesis.
      - Ex. Retinoblastoma is caused by mutations in the RB gene. Individuals who inherit one copy of the RB - allele are prone to cancer of the retina.
    - Mitotic recombination can also cause somatic mosaicism, which may also contribute to disease.
  - Germline mutations - occur in cells that give rise to gametes
  - Loss-of-function mutation
    - Amorphic alleles - most severe loss of function, recessive
    - Hypomorphic alleles - partial loss of function (recessive or incompletely dominant)
  - Dominant mutations
    - Gain-of-function
    - Protein has new or extra activity
    - Active role in the cell would "override" the wild type allele.
    - Antimorphic - dominant negative mutations
      - Generally found for dimers or multimers
    - Neomorphic - mutation confers new function on the gene
      - Ex. antennapedia in drosophila
    - Hypermorphic mutation - increased activity or expression of a gene.
      - Ex. cancer - increased activity of an oncogene

Central Dogma

- Point mutations - change in a single base.
  - Transitions are purine → purine, pyrimidine → pyrimidine.
  - Transversions are purine → pyrimidine and vice versa.
  - Deletions and insertions are also point mutations.
  - Many mutations have no effect on gene expression, but rather, exist as neutral polymorphisms or variants in DNA.
  - May result in frameshift, nonsense, missense, or silent mutations.
- Nonsense mutations result in truncated proteins
- Large deletions / insertions in coding regions
  - In frame fusions of large or small regions
- Missense mutations may be more or less deleterious
  - Conservative mutations
  - Nonconservative mutations

- Insertions and deletions (INDELs)
- Expanding nucleotide repeats
    - Genetic anticipation - the phenotypes appear earlier and stronger in the offspring of affected parents than in the parents.
    - Increase in the number of copies of a set of nucleotides.
        - ex.) Huntington's disease (refer to page 32 of slides 5)
- Intragenic suppressor mutations