Observing Patterns in Inherited Traits

1 Tall, Fit, and Vulnerable

- Ronalda Pierce and Flo Hyman, both young and athletic, died suddenly of aortic aneurysms
  - The rupturing of the aorta, a large artery
- Both suffered from Marfan's syndrome, a dominant genetic disorder
  - Defective version of the *fibrilin* gene
    - A defective version of this gene produces either no fibrilin protein or a protein with reduced function

- Fibrilin is an important structural element of connective tissue
  - Connective tissue connects and supports other body tissues
    - Connective tissue strengthens the aorta, etc.
  - Reduced amounts of functional fibrilin weakens the body's connective tissue
    - Such persons are prone to aortic aneurysms

2 Autosomal Genetic Disorders

- Most genetic traits and disorders are caused by a gene (or genes) on one of the 22 pairs of non-sex chromosomes
  - Most genetic traits and disorders are "autosomal"
  - Most genetic traits and disorders are not X-linked

- Some genetic disorders are dominant
  - One copy is sufficient to cause the disorder
  - e.g., Marfan's syndrome
- A person with a dominant genetic disorder has a 50% chance of passing it on to any given offspring

- How can a person with a dominant genetic disorder live long enough to pass it on?
  - Many of these disorders are not debilitating
    - e.g., Polydactyly

- The debilitating symptoms may not be exhibited until well into adulthood
  - Symptoms begin well into reproductive years
  - e.g., Huntington disease

- Autosomal recessive disorders
  - Homozygous dominant (AA) not affected
  - Heterozygous (Aa) not affected
  - Homozygous recessive (aa) affected
    - Only affects an individual who has 2 recessive copies of the gene

- Two parents heterozygous for an autosomal recessive allele can have children with the disorder and without the disorder
  - There is a 25% chance that any given child will have the disorder
  - There is a 75% chance that any given child will not have the disorder
- Individuals heterozygous for an autosomal recessive allele are termed "carriers" for the disorder

Galactosemia
- Caused by autosomal recessive allele
- Gene specifies a mutant enzyme in the pathway that breaks down lactose
- Causes build-up of galactose-1-phosphate, which results in a spectrum of problems, possibly including death

3 X-Linked Inheritance
- Hemophilia is a genetic disorder in which blood fails to clot properly
  - Multiple proteins interact to make blood clot
  - About 80% of hemophiliacs lack a functional version of one of these proteins
    - Factor VIII
  - Minor cuts can be life threatening to a hemophiliac

- Hemophilia is an X-linked disorder
  - So are red-green colorblindness and Duchenne muscular dystrophy
  - Each of these disorders is caused by a defective gene on the X chromosome
    - This defective allele encodes either no protein or a protein with reduced function
- X-linked disorders are more common in males than in females
  - Why do you think this is true?

The Genetics of Color Vision
- Red-green colorblindness is an X-linked recessive genetic disorder

- The genes for our red and green pigment proteins are on the X chromosome
- A red-green colorblind person has no alleles of pigment genes that encode the proper proteins

- We have two copies of most of our genes
  - One copy on each chromosome in a homologous pair
- Two recessive alleles are required to produce the recessive phenotype
  - One functional allele is sufficient for the dominant phenotype in these cases

- The X chromosome is fairly large
  - Contains ~1,500 genes
- The Y chromosome is very small
  - Contains only 78 genes
- Females possess two X chromosomes
  - Two copies of all X-linked genes
- Males possess a single X chromosome
  - Only one copy of all X-linked genes
  - Their Y chromosome does not contain copies of these genes

- Females require two recessive alleles to have a recessive X-linked phenotype
  - "Backup" if one of their alleles is faulty
- Males require only one recessive allele to have a recessive X-linked disorder
  - No "backup" if their allele is faulty

- Colorblindness affects more males than females
  - ~ 8% of the male population has some degree of colorblindness
  - ~ 0.5% of the female population has some degree of colorblindness

- If a woman passes a recessive X-linked allele to her offspring
  - Her son will be colorblind
    - He will not receive any copy of this gene from his father
      - His father will give him a Y chromosome
  - Her daughter will probably not be colorblind
    - She is likely to receive a functional copy of this allele from her father

4 Tracking Traits with Pedigrees

- Medical pedigrees can be helpful for genetic disorders
  - Provide a family history of the disease

- Help to determine whether a condition is
  - Dominant or recessive
  - X-linked or autosomal
- Help establish probabilities for future inheritance
  - Identification of carriers is an important part of this

- What can we learn from this pedigree?
  - Only two individuals have the disorder
    - Mendelian genetics allows us to deduce that the condition is recessive
  - Numerous carriers (heterozygotes) are identified
  - Genotypes of some individuals cannot be determined
    - The likelihood that specific individuals are carriers can be determined

5 Changes in Chromosome Structure

6 Aberrations in Chromosomal Sets: Polyploidy

7 Incorrect Chromosome Number: Aneuploidy

- Chromosome structure can be changed
  - Randomly
  - Due to environmental influences
- Main changes that occur
  - Duplication
  - Inversion
  - Deletion
  - Translocation

Polyploidy & Aneuploidy

- Other genetic conditions can be caused by an aberrant number of chromosomes
  - One or more additional full sets of chromosomes can be inherited
    - "Polyploidy"
  - A small number (generally 1) of extra or missing chromosomes can be inherited
    - "Aneuploidy"

- Polyploidy is the condition in which one or more entire sets of chromosomes has been added to an organism's genome
  - e.g., A sperm or egg contains two sets of chromosomes
    - Meiosis failed to separate these sets

- e.g., An egg is fertilized by two sperm

- Polyploidy is a disaster for humans and many other species
  - Polyploidy = death
- Polyploidy is tolerated well by many species
  - Particularly plants
  - Cotton, soybeans, peanuts, bananas, and durum wheat are all polyploid

- Aneuploidy is a condition in which an organism has either more or fewer chromosomes than normally exist
  - Generally one chromosome too many or too few
  - Usually caused by nondisjunction during meiosis

- Nondisjunction is the failure of homologous chromosomes or sister chromatids to separate during meiosis
  - Homologous chromosomes separate in meiosis I
  - Sister chromatids separate in meiosis II
  - If either event is imperfect, all or some of the gametes produced will have an aberrant number of chromosomes

- Nondisjunction occurs during meiosis
  - Gametes with an extra or missing chromosome are produced
  - A fertilization involving this gamete will produce a zygote with an extra or missing chromosome
    - All cells in the resulting embryo will have this same aberrant chromosome number (an improper chromosome number creates a genetic imbalance within the embryo)

- Aneuploidy in humans in surprisingly common, yet goes largely unrecognized
  - Most aneuploid embryos will not survive
    - Generally miscarried during the pregnancy
    - This miscarriage is often so early in the pregnancy that the would-be-mother doesn't even know that she was pregnant
      - She may only think that she is having a hard time getting pregnant

- Some aneuploid embryos will survive
  - Only those with an extra copy of automosome 13, 18, or 21 have a greater chance of survival
    - These are relatively small chromosomes

– Smaller genetic imbalance less likely to result in a miscarriage

- Trisomy 21 results in a condition known as Down syndrome
  - Three copies of chromosome 21
  - Seen in 0.1% of all live births
  - Array of effects
    - Smallish, oval heads
    - IQs well below normal
    - Short stature
    - Reduced life span
    - Infertility in males

- Ten percent of the cases of trisomy 21 are due to nondisjunction in sperm formation
- Ninety percent of the cases of trisomy 21 are due to nondisjunction in egg formation
  - The likelihood of producing an egg with an extra copy of chromosome 21 increases with age
    - The reason is unclear
    - Related to how meiosis produces eggs

- A given "oocyte" (~egg) begins meiosis before the female fetus is born
- These oocytes then remain "paused" in the cell cycle for years or decades
  - The egg's cellular machinery ages during this pause
    - The inability to properly segregate chromosomes is a likely consequence of this aging

- Meiosis I is completed only upon being ovulated
  - The release from the ovary during each monthly ovarian cycle
- Meiosis II is completed only upon being fertilized by a sperm

- Aneuploidy can also affect sex chromosomes
  - Embryos often survive sex chromosome aneuploidies
  - Effects are usually debilitating

- Females with Turner syndrome possess only a single X chromosome
  - Denoted XO
  - Various effects
    - Sterility due to the improper development of the ovaries
    - Generally short

- Often have brown spots ("nevi") on the skin

- Males with Kleinfelter syndrome possess an extra X chromosome
  - Denoted XXY
  - Phenotypically male in most respects
  - Various effects
    - Sterile
    - Tall stature, overweight
    - Possess a more feminine feature (some breast development, a more feminine figure, lack of facial hair)

- Aneuploidy can also take place during mitosis
  - Also a result of nondisjunction
  - Can happen in a cell at any time during an individual's life
    - All cells derived from this aneuploid cell would also be aneuploid
    - Other cells in the individual's body would not be affected

- Most aneuploid cells will die
  - A few can survive
- Aneuploidy is often seen in cancer cells
  - Aneuploidy was initially considered to be a result of cancer
  - It now appears that aneuploidy may be a cause of cancer
    - A cause, not the only cause

PGD: Screening for a Healthy Child

- Many debilitating human conditions have genetic causes
- Many of these conditions can be detected very early
- Embryonic cells can be gathered
  - Chromosomes and DNA can be analyzed
  - Such screening began in the 1960s

- The screening of embryos produced through in vitro fertilization is termed "Preimplantation genetic diagnosis"
  - "PGD"
- Hormones stimulate egg formation
  - 10 – 12 mature eggs removed from ovaries
  - Fertilized in laboratory

- Each fertilized egg divides to form an early embryo
  - Eight-cell embryo in three days
- One cell is removed from this early embryo
  - Undifferentiated "embryonic stem cell"
  - Embryo is unaffected

- DNA and chromosome testing is performed on removed cell from each embryo
  - e.g., Attach fluorescent molecules to each copy of chromosome 21 to allow them to be visualized easily with a microscope
- Embryos deemed "acceptable" are implanted

- PGD can be used by couples that are simply having a hard time getting pregnant
  - No known genetic risk factors in this case
    - This difficulty may be indicative of genetic issues such as aneuploidy
    - Some couples may be prone to producing such embryos

- PGD can also be used by couples affected by or carrying a genetic disorder
  - They might be likely to produce a child with genetic defects
    - Amniocentesis actually provides a more conventional assessment for such couples
      - However, if termination of the pregnancy is not a morally acceptable option to the couple, perhaps PGD is more acceptable

- Couples can use PGD to screen for many different phenotypes
  - Choosing an embryo free of genetic disease
  - Choosing the sex of the child
  - Choosing only tall, blonde-haired offspring
    - Perhaps this third choice is less morally acceptable than the others