Introduction to Basic Genetics

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Genetics: what is it?

- What is genetics?
  - Genetics is the study of **heredity**,
  - Heredity is the process in which a parent passes certain **genes** onto their children.
    - Not to be confused with heritability.
- What does that mean?
  - Children **inherit** their biological parents' genes that express specific **traits**:
    - Some physical characteristics
    - Natural talents
    - Performance characteristics

Difference between Genetics and Molecular Genetics

- Molecular genetics is the sub field of genetics that studies the structure and function of genes at a molecular level.
  - You have a Molecular Genetics class in junior year
- Molecular genetics employs the methods of genetics and molecular biology to explain molecular function and interactions among genes.
- It is called Molecular Genetics to differentiate it from <u>other sub fields</u> of genetics such as quantitative genetics, ecological genetics and population genetics.

Word Match Activity

- **Cell**
- **Nucleus**
- **Chromosome**
- **Double helix**
- **DNA (Deoxyribonucleic Acid)**
- **Genes**
- **Base pairs**

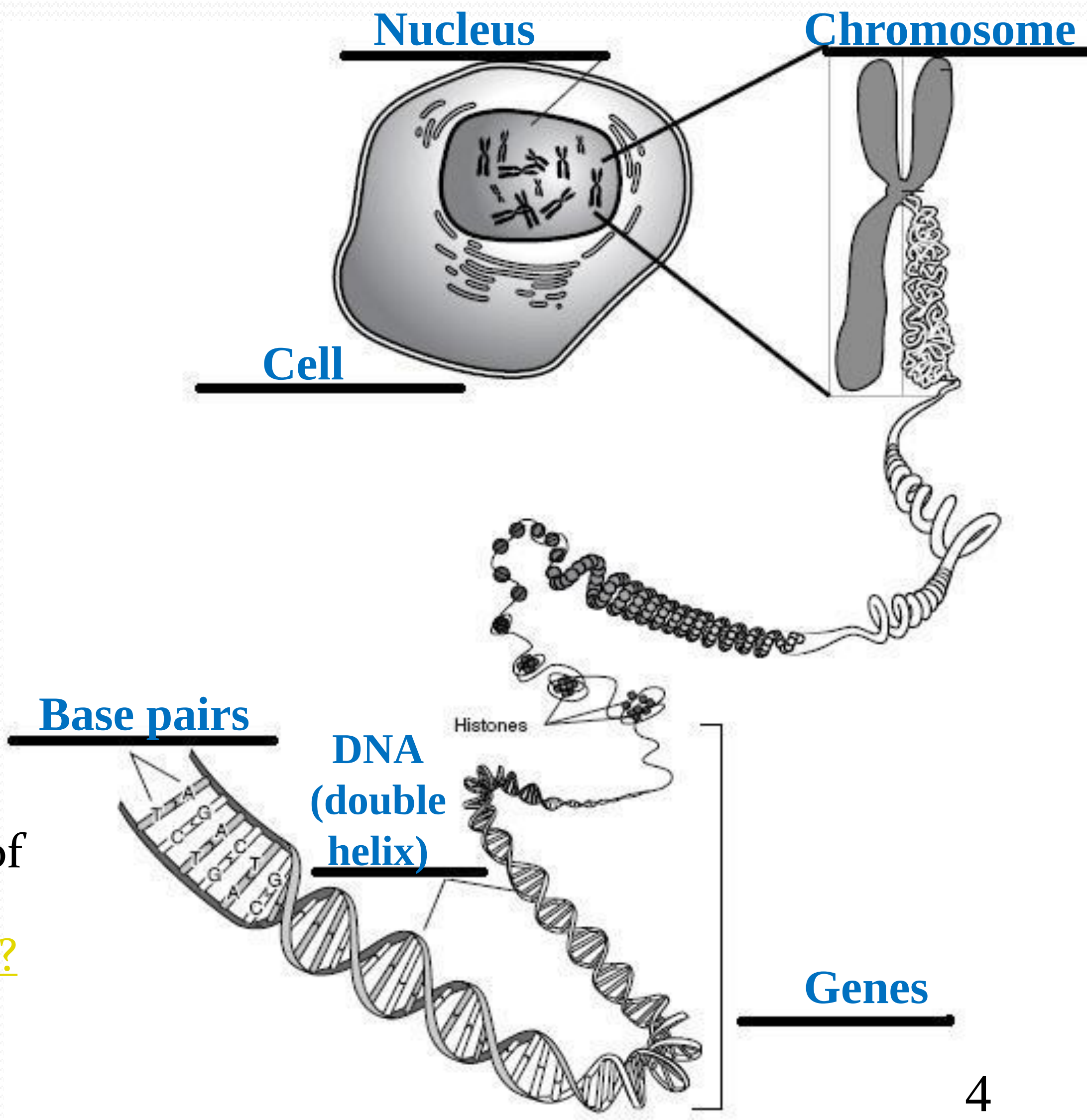


Illustration Source: Talking Glossary of Genetic Terms
http://www.genome.gov/glossary.cfm?key=chromosome

Genetic Concepts

- **H__________** describes how some traits are passed from parents to their children.
- **Heredity** describes how some traits are passed from parents to their children.
- How about **Heritability**?
  - Percentage of variation explained by genetic variation
  - Based on resemblance of relatives, such as # of ridges on fingerprints
- The traits are expressed by **g______**, which are small sections of DNA that are coded for specific traits.
- The traits are expressed by **genes**, which are small sections of DNA that are coded for specific traits.

Genetic Concepts

- Genes are found on **<u>ch____________</u>**.
- Genes are found on **<u>chromosomes</u>**.
- Humans have two sets of _____ (hint: a number) chromosomes—one set from each parent.
- Humans have two sets of **<u>23</u>** chromosomes—one set from each parent.

Branches of Genetics

- Behavioral genetics
- Classical genetics: Mendel genetics, now works with lab strains and crosses
- Developmental genetics
- Conservation genetics: applies genetic methods to the conservation and restoration of biodiversity
- Ecological genetics: study of genetics in natural populations, traits related to fitness.
- Evolutionary genetics

Branches of Genetics

- Genetic engineering
- Genomics
- Human genetics
  - Human evolutionary genetics
  - Human mitochondrial genetics
- Medical genetics
- Microbial genetics

Branches of Genetics

- Molecular genetics
- Epigenetics
- Population genetics
- Statistical genetics
- Quantitative genetics: deals with continuous variation as opposed to discrete variation, and multi genes.
  - analyzes inheritance patterns across generations and descendant lines

Molecular Genetics

- Genetic Screening (forward genetics)
  - Sequencing, SNP genotyping
- Reverse genetics
  - Gene knockout to see its effects on phenotype
    - In diploid organisms, selective breeding is required to produce homozygous knockout animals
    - CRISPR is the newest method in gene editing
- Gene Therapy
  - Adding a new gene to replace a faulty gene, done with a virus
  - Ex vivo, patients cells are cultured outside, genes transferred and then introduced to the patient,
  - In vivo gene transfer such as in brain cells (cannot remove)
  - CRISPR to the rescue, no virus ☺

Molecular Genetics Techniques

- DNA extraction
- RNA extraction
- PCR
  - DNA nucleotides, template DNA, primers and Taq polymerase (thermostable DNA polymerase isolated from the thermophilic bacterium Thermus aquaticus in hotsprings) are used
- Most techniques are based on PCR and gel electrophoresis
  - GMO detection
  - Forensic science

Molecular Genetics Techniques

- Cell culture
- Bacterial genetics
- Genome sequencing
  - Illumina
  - Ion Torrent/Proton (Life Tech)
  - 454 (Roche)

Comparison of next-generation sequencing methods

Method	Read length	Accuracy	Reads per run	Time per run	Cost per 1 million bases (in US$)	Advantages	Disadvantages
Ion semiconductor , Ion Torrent sequencing	up to 400 bp	98%	up to 80 million	2 hours	$1	Less expensive equipment abroad, more exp. in Turkey. Fast.	Homopolymer errors.
Pyrosequencing (454)	700 bp	99.9%	1 million	24 hours	$10	Long read size. Fast.	Runs are expensive. Homopolymer errors.
Sequencing by synthesis (Illumina) has Coverage, 30X	50 to 300 bp	98%	up to 3 billion Now 15 GB	1 to 10 days, depending upon sequencer and specified read length	$0.05 to $0.15	Potential for high sequence yield, depending upon sequencer model and desired application.	Equipment can be very expensive. Requires high concentrations of DNA.
Sanger sequencing	400 to 900 bp	99.9%	N/A	20 minutes to 3 hours	$2400	Long individual reads. Useful for many applications.	More expensive and impractical for larger sequencing projects.

Definitions

- **Genotype:** the alleles of an organism.
- **Phenotype:** the characteristics of an organism
  - not just appearance, enzyme levels?
- **Dominant allele:** an allele that has the same effect on the phenotype whether it is present in the homozygous or heterozygous state.
- **Recessive allele:** an allele that only has an effect on the phenotype when present in the homozygous state.

Definitions

- **Locus:** the particular position on homologous chromosomes of a gene.
- **Homozygous:** having two identical alleles of a gene.
- **Heterozygous:** having two different alleles of a gene
- **Mendelian inheritance:** inheritance of biological features that follows the laws proposed by Gregor Johann Mendel in 1865 and 1866 and re-discovered in 1900.
- **Allele:** Different copies of the same gene (A and a)

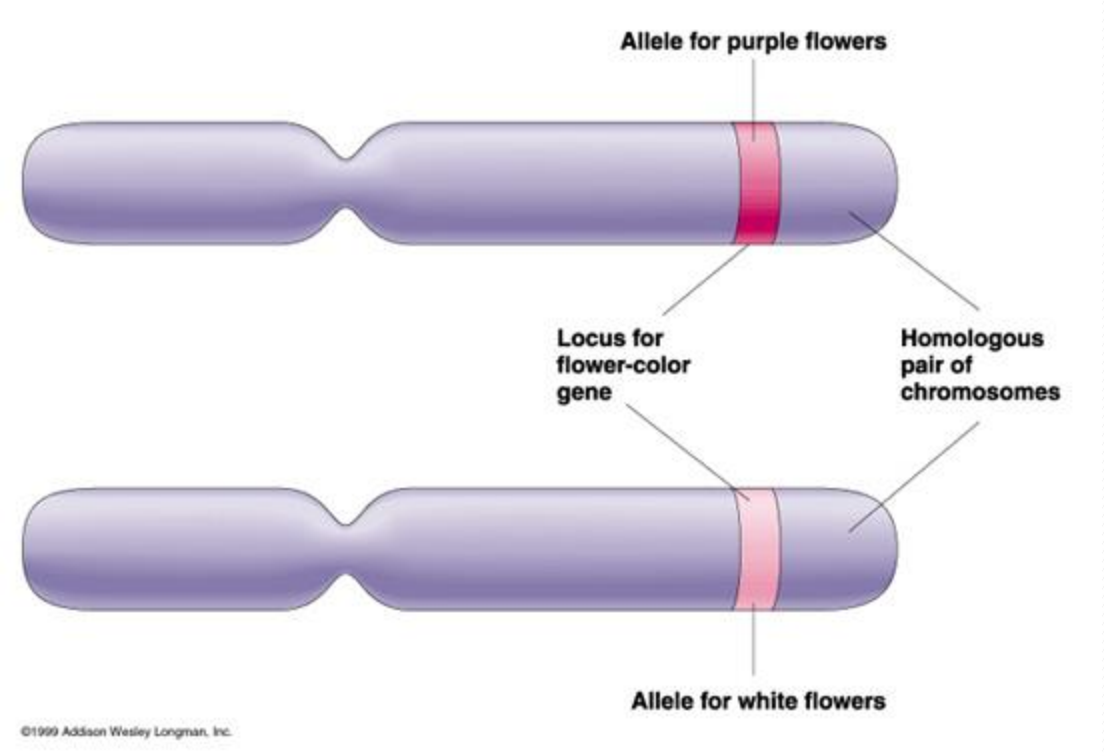
Definitions, gene vs. allele

- A gene is a stretch of DNA or RNA that determines a certain trait.
- Genes mutate and can take two or more alternative forms; an allele is one of these forms of a gene.
  - For example, the gene for eye color has several variations (alleles) such as an allele for blue eye color or an allele for brown eyes.
  - A=2, a=1;   AA=2, Aa=2, aa=1=complete dominance

Definitions, gene vs. allele

- Chromosomes occur in pairs so organisms have two alleles for each gene
  - one allele in each chromosome in the pair.
- Each chromosome in the pair comes from a different parent
  - organisms inherit one allele from each parent for each gene.
- The two alleles inherited from parents may be same (homozygous) or different (heterozygotes).

Mendelian Inheritance, allele



Mendelian Inheritance

- The inherited traits are determined by genes that are passed from parents to children.
- A child inherits two sets of genes—one from each parent.
- A trait may not be observable, but its gene can be passed to the next generation
  - recessive genes

Mendelian Inheritance

Each person has 2 copies of every gene—one copy from mom and a second copy from dad. These copies may come in different variations, known as **alleles**, that express different traits.

For example, 2 alleles in the gene for freckles are inherited from mom and dad:

- allele from mom = has freckles (F)
- allele from dad = no freckles (f)
- child has the inherited gene pair of alleles, **Ff** (F allele from mom and f allele from dad).

Homework: Genetic Terms

- Define the following words and write their definitions using your own words.
  - allele:
  - gene:
  - dominant :
  - recessive:
  - homozygous:
  - heterozygous:
  - genotype:
  - phenotype:
  - Mendelian Inheritance:

Chromosomes and DNA

- Humans have cells with 46 chromosomes -- 2 chromosomes that determine what sex they are (X and Y chromosomes), and 22 pairs of nonsex (autosomal) chromosomes.
- Males are "46,XY" and females are "46,XX.“

Chromosomes and DNA

- The chromosomes are made up of strands of genetic information called DNA.
- Each chromosome contains sections of DNA called genes, which carry the information needed by your body to make certain proteins.

Chromosome, gene, allele

- Each pair of autosomal chromosomes contains one chromosome from the mother and one from the father.
- Each chromosome in a pair carries basically the same information; that is, each chromosome pair has the same **genes**.

Chromosome, gene, allele

- Sometimes there are slight variations of these genes. These variations occur in less than 1% of the DNA sequence.
- The genes that have these variations are called **alleles**.

Abnormality, recessive genes

- Some of these variations can result in a gene that is abnormal.
- An abnormal gene may lead to an abnormal protein or an abnormal amount of a normal protein.
- In a pair of autosomal chromosomes, there are two copies of each gene, one from each parent.

Abnormality, recessive genes

- If one of these genes is abnormal, the other one may make enough protein so that no disease develops.
- When this happens, the abnormal gene is called **recessive**, and the other gene in the pair is called **dominant**.
- Recessive genes are said to be inherited in an autosomal recessive pattern.

Abnormality, recessive genes

- However, if only one abnormal gene is needed to produce a disease, it leads to a dominant hereditary disorder. In the case of a dominant disorder, if one abnormal gene is inherited from mom or dad, the child will likely show the disease.
- However, almost ALL genetic diseases are recessive, why?
  - Selection?

Abnormality, recessive genes

- A person with one abnormal gene is called heterozygous for that gene.
- If a child receives an abnormal recessive disease gene from both parents, the child will show the disease and will be homozygous, or compound heterozygous for that gene.

Compound heterozygote

- An organism is a compound heterozygote if it has two recessive alleles for the same gene, but with those two alleles being different from each other.
- This means that a disease arise in individuals who have two unrelated alleles, who technically are heterozygotes, but both the alleles are defective.
- A homozygous mutation is the presence of the identical mutation on both alleles of a specific gene.
- However, when both alleles of a gene harbor mutations, <u>but the mutations are different</u>, these mutations are called compound heterozygous.

Compound heterozygote

- The mutations involved are often less deleterious in combination than for a homozygous individual with the classic symptoms of the disease.
- As a result, compound heterozygotes often become ill later in life, with less severe symptoms.

Compound heterozygote

- Compound heterozygosity as a cause of genetic disease had been suspected much earlier
- Widespread confirmation of the phenomenon was feasible after the 1980s,
    - PCR techniques for amplification of DNA made it cost-effective to sequence genes and identify polymorphic alleles.

Compound heterozygote, Examples

- **Phenylketonuria.** Because PKU was the first genetic disorder for which mass post-natal genetic screening was available, beginning in the early 1960s, atypical cases were detected almost immediately.
- Molecular analysis of the genome was not yet possible, but protein sequencing revealed cases caused by compound heterozygosity.
- As molecular genomic techniques became available in the 1980s and 1990s, it became possible to explain a range of disorders in heterozygotes carrying one copy of one of the classic mutations for phenylketonuria.

Compound heterozygote, Examples

- **Sickle cell syndrome.** A variety of sickle cell disorders result from inheritance of the sickle cell gene in a compound heterozygous manner with other mutant beta globin genes.
- In the case of sickle cell anemia, an individual with one allele for hemoglobin S and one allele for hemoglobin C would still develop the disease, despite being heterozygous for both genes.

GENETIC DISORDERS

- Almost all diseases have a genetic component. However, the importance of that component varies.
- Disorders in which genes play an important role (genetic diseases) can be classified as:
  - Single-gene defects
  - Chromosomal disorders
  - Multifactorial → Quantitative Genetics

Single-gene defects

- A single-gene disorder (also called Mendelian disorder) is caused by a defect in one particular gene. Single gene defects are rare. But since there are about 4,000 known single gene disorders, their combined impact is significant.

Single-gene defects

- Single-gene disorders are characterized by how they are passed down in families. There are six basic patterns of single gene inheritance:
  - Autosomal dominant
  - Autosomal recessive
  - X-linked dominant
  - X-linked recessive
  - Y-linked inheritance
  - Maternal (mitochondrial) inheritance

Phenotype

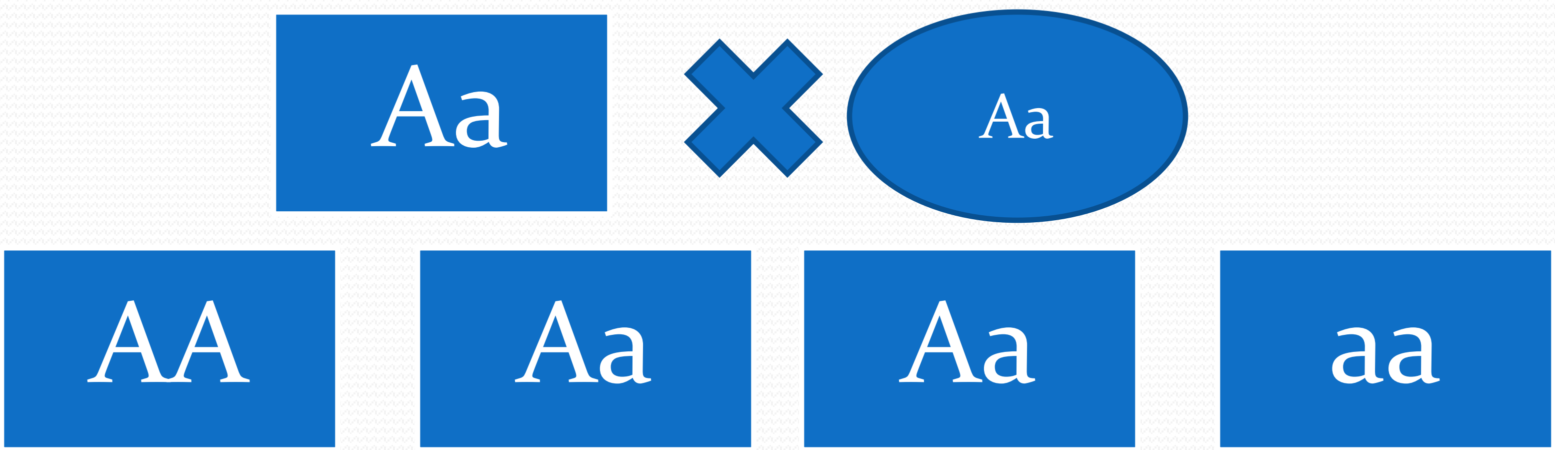
- The observed effect of a gene (the appearance of a disorder) is called the phenotype.
- In autosomal dominant inheritance, the abnormality or abnormalities usually appear in every generation.

Phenotype

- Each time an affected woman has a child, that child has a 50% chance of inheriting the disease.
- Male female probability in progeny?
- People with one copy of a recessive disease gene are called carriers. Carriers usually don't have symptoms of the disease.

Phenotype, Inbreeding

- In autosomal recessive inheritance, the parents of an affected individual may not show the disease (they are carriers).
- On average, the chance that carrier parents could have children who develop the disease is 25% every time:



Phenotype, Inbreeding

- Male and female children are equally likely to be affected.
- For a child to have symptoms of an autosomal recessive disorder, the child must receive the abnormal gene from both parents.

Phenotype, Inbreeding

- Because most recessive disorders are rare, a child is at increased risk of a recessive disease if the parents are related.
  - Inbreeding is bad because the same kind of disease genes may come together in the progeny.
- Related individuals are more likely to have inherited the same rare gene from a common ancestor.

X-linked recessive inheritance

- In X-linked recessive inheritance, the chance of getting the disease is much higher in males than females.
- Since the abnormal gene is carried on the X (female) chromosome, males do not transmit it to their sons
  - Sons will receive the Y chromosome from their fathers.
- Half of the sons will be affected:
  - $X^A X^a$ * $X^A Y$ =1/2 $X^a Y$

X-linked recessive inheritance

- Males transmit it to their daughters.
- In females, the presence of one normal X chromosome masks the effects of the X chromosome with the abnormal gene.
- So, all of the daughters of an affected male appear normal, but they are all carriers of the abnormal gene. Each time these daughters bear a son, there is a 50% chance the son will receive the abnormal gene.
- $X^A X^A$ * $X^a Y = X^A X^a$
- $X^A X^a$ * $X^A Y = X^a Y$ or $X^A Y$

X-linked Dominant inheritance

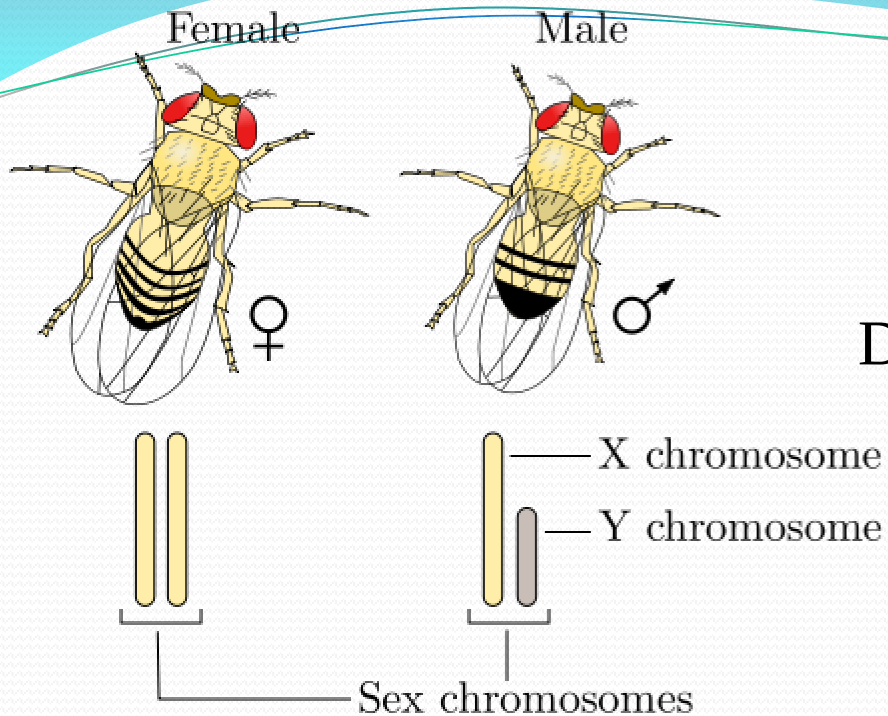
- In X-linked **dominant** inheritance, the abnormal gene appears in females even if there is also a normal X chromosome present.
- Since males pass the Y chromosome to their sons, affected males will not have affected sons.
  - All of their daughters will be affected.
- Sons or daughters of affected females will have a 50% chance of getting the disease.
  - $X^D X^d$ * $X^d Y$ =
    - Males: $X^D Y$, $X^d Y$
    - Females: $X^D X^d$, $X^d X^d$

X linked genes examples

- White Gene, abbreviated w, was the first sex-linked mutation ever discovered in the fruit fly Drosophila melanogaster.
- In 1910 Thomas Hunt Morgan and Lilian Vaughan Morgan (married) collected a single male white-eyed mutant from a population of Drosophila melanogaster fruit flies, which usually have dark brick red eyes.
- Upon crossing this male with wild-type female flies, they found that the offspring did not conform to the expectations of Mendelian inheritance.

X linked genes examples

- The first generation (the F1) produced 1,237 red-eyed offspring and three white-eyed flies, all males.
- The second generation (the F2) produced 2,459 red-eyed females, 1,011 red-eyed males, and 782 white-eyed males.
- Further experimental crosses led them to the conclusion that this mutation was somehow physically connected to the "factor" that determined gender in Drosophila.
- Morgan named this trait white gene, now abbreviated w.



Drosophila XY sex-chromosomes

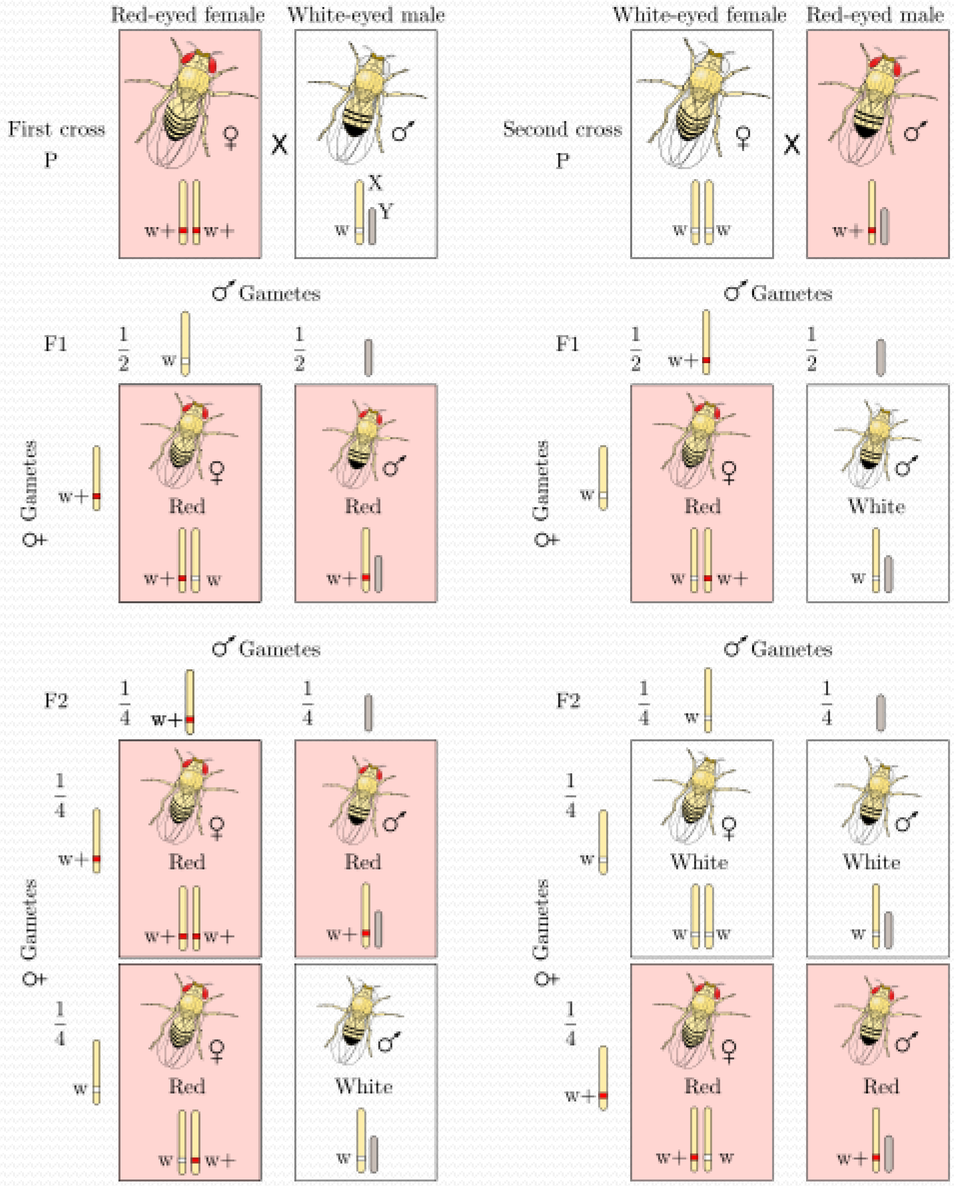
- Sex linkage is in contrast to the inheritance of traits on autosomal chromosomes, where both sexes have the same probability of inheritance.
- Since there are many more genes on the X than the Y, there are many more X-linked traits than Y-linked traits.
- The X chromosome: 2000 genes, Y chromosome: 78 genes, out of the estimated 20,000 to 25,000 total genes in the human genome. (2000 genes on chromosome 1, out of 23 pairs of chromosome)

Results from reciprocal crosses between red-eyed (Red) and white-eyed (White) Drosophila in Morgan's experiments.

w + = red allele (wild-type allele)

w = white (mutant allele).

In sex-linked inheritance, alleles on sex chromosomes (XY) are inherited in predictable patterns.



X linked genes examples

- X-linked recessive allele in humans causes hemophilia
    - cannot clot the blood, lower clotting factor level of blood plasma or impaired activity of the coagulation factors
- Hemophilia is much more common in males than females
    - Males are hemizygous - they only have one copy of the gene in question
    - Express the trait when they inherit one mutant allele.
    - In contrast, a female must inherit two mutant alleles, a less frequent event since the mutant allele is rare in the population.

X linked genes examples

- Fur color in domestic cats: the gene that causes orange pigment is on the X chromosome; thus a Calico (USA name) or tortoise shell cat, with both black (or gray) and orange pigment, is always female.
- X linked locus has 2 alleles, Yellow (Y) and Orange (O). Heterozygous (YO) cats have tortoise shell color: black, white, yellow, orange all mixed up.
  - Heterozygous cats have to be female X^YX^O
  - Males are hemizygous: X^YY or X^OY

X linked genes examples, Tortoise shell heterozygous cats

X linked genes examples

- Color blindness
- A fault in the retinal cones that perceive color in light and transmit that information to the optic nerve
  - The genes that produce photopigments (photoreceptor proteins of the retina) on retinal cones are carried on the X chromosome
  - More common in males because of having only one X
    - In females, a functional gene on only one X chromosome is sufficient
    - Redundancy is good: kidneys, lungs, etc.

Y linkage

- Y-chromosome is small and does not contain many genes, few traits are Y-linked.
- Y-linked traits are passed only from father to son.
- Y-Chromosome deletions are a frequent genetic cause of male infertility.
  - Having hairy ears was once thought to be a Y-linked trait in humans, but that hypothesis has been discredited. A lot of Turkish books still report this as fact under the heading of Y-linkage.

Y linkage

- Sex-determining region Y (SRY) protein or Testis-determining factor (TDF), is a DNA-binding protein (gene-regulatory protein/transcription factor)
- SRY gene is on the Y chromosome and its protein initiates male sex determination in humans.
- Its expression causes the development of primary sex cords, which later develop into seminiferous tubules. These cords form in the central part of the yet-undifferentiated gonad, turning it into a testis.

Y linked diseases

- Male Infertility
- XYY syndrome is another proof that the Y chromosome doesn't have really many genes that determine human structure.
  - These patients have no specific physical features except perhaps for increased height. But they usually have slight learning disabilities, aggressive behavior, and severe acne.
    - Sounds like Recep Ivedik

Examples of Single Gene Disorders

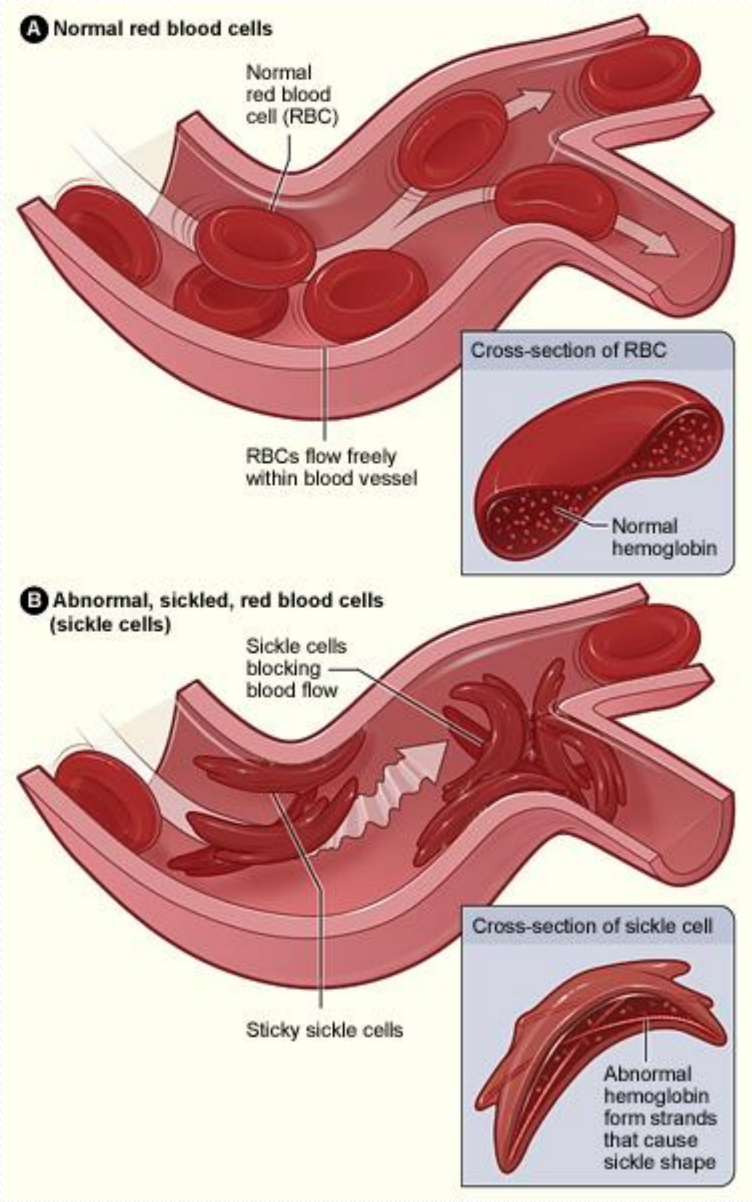
Autosomal recessive

- ADA (Adenosine deaminase enzyme) deficiency
  - Immune system cannot develop, so it is sometimes called the "boy in a bubble" disease (bubble boy episode on Seinfeld)
- Alpha-1-antitrypsin (AAT) deficiency
  - Lung and liver disease, wheezing, swollen abdomen, feet
  - Neutrophil elastase enzyme is released by white cells to fight infection, and AAT prevents it from attacking lungs and liver
- Cystic fibrosis (CF)
  - Mucus is thickened, preventing respiration and digestion
- Phenylketonuria (PKU)
- Sickle cell anemia

Sickle Cell anemia

Sickle cells are stiff and sticky. They block blood flow in the blood vessels. Blocked blood flow can cause pain and organ damage. It can also raise the risk for infection.

Anemia is a condition in which your blood has a lower than normal number of red blood cells, The bone marrow can't make new red blood cells fast enough to replace the dying sickle cells.



X-linked recessive

- Duchenne muscular dystrophy
  - muscle degeneration and eventual death
  - the protein dystrophin provides structural stability to the dystroglycan complex of the cell membrane in muscle.
  - Usually males exhibit symptoms, muscle weakness and are wheelchair dependent by age 12. Females have two copies, so if one does not produce the protein, the other can. Females are carriers.
  - Progressive loss of movement, leading to paralysis.
  - Average life expectancy is 25.
- Hemophilia A, bleeding spontaneously, first during circumcision. Nosebleeds, bleeding into joints. Treatment replaces the missing clotting factor.

Autosomal dominant only one copy of the defective gene is enough to develop the disorder

- Familial hypercholesterolemia
  - LDL, low density lipoprotein ("bad") cholesterol levels
- Huntington disease
  - Breakdown of nerve cells in the brain. It affects functional abilities (Involuntary jerking) movement, thinking (Slowness in "finding" words, outbursts, focusing) and psychiatric (irritability, depression, death thoughts) disorders.
  - Symptoms in 30s and 40s.
  - Dominant because you catch it after you reproduce.

X-linked dominant

- Only a few, rare disorders are X-linked dominant.
- Hypophosphatemic rickets
  - also called vitamin D -resistant rickets.
- Low levels of phosphate (salt of phosphoric acid)
- Phosphate helps formation and growth of bones in childhood and maintains bone strength in adults.
- Phosphate levels are controlled by the kidneys.
- Only a small fraction of the phosphate in the diet comes from Cola. Most comes from meat and dairy products.

CHROMOSOMAL DISORDERS

- In chromosomal disorders, the defect is due to either an excess or lack of the genes contained in a whole chromosome or chromosome segment.
- Chromosomal disorders include:
  - Down syndrome
  - Klinefelter syndrome
  - Turner syndrome

CHROMOSOMAL DISORDERS

- Down syndrome
  - Abnormal cell division results in three copies of chromosome 21 (instead of the usual two copies) in all cells, which causes lifelong intellectual disability and developmental delays
  - It's caused by a mistake in cell division during the development of the egg, sperm or embryo.
  - Older eggs have a greater risk of improper chromosome division.
    - by age 35, a woman's risk is about 1 in 350
    - by age 40, the risk is about 1 in 100
    - by age 45, the risk is about 1 in 30
    - Most children with Down syndrome are born to women under age 35 because younger women have far more babies.

CHROMOSOMAL DISORDERS

- Klinefelter syndrome
  - 2 X chromosomes in males (Classic: XXY, extreme: XXXY or XXXXY)
  - small testes and less testosterone, breast enlargement, reduced hair, an inability to have biological children (infertility).

MULTIFACTORIAL DISORDERS

- Many of the most common diseases are caused by interactions of several genes and factors in the environment (illnesses in the mother and medications).
- Cancer
- Coronary heart disease
- Hypertension
- Stroke
- Genotype (Add., Dom., Ep), Env (Perm., Temp., Mat.) and Gen X Env Int. affects quantitative/threshold traits.

MITOCHONDRIAL DNA-LINKED DISORDERS

- Mitochondria are small organisms found in most of the body's cells. They are responsible for energy production inside cells. Mitochondria contain their own private DNA.
- In recent years, many disorders have been shown to result from changes (mutations) in mitochondrial DNA. Because mitochondria come only from the female egg, most mitochondrial DNA-related disorders are passed down from the mother.

MITOCHONDRIAL DNA-LINKED DISORDERS

- Mitochondrial DNA-related disorders can appear at any age. They have a wide variety of symptoms and signs. These disorders may cause:
  - Blindness
  - Developmental delay
  - Gastrointestinal problems
  - Hearing loss
  - Heart rhythm problems
  - Metabolic disturbances
  - Short stature

UK says yes to three-person babies

- http://www.bbc.com/news/health-31069173
- One man, two woman
- Defective mitochondria are passed down only from the mother.
- They can lead to brain damage, muscle wasting, heart failure and blindness.
- This procedure (new in 2015) results in babies with 0.1% of their DNA from the second woman and is a permanent change that would be passed down through the generations.

UK says yes to three-person babies

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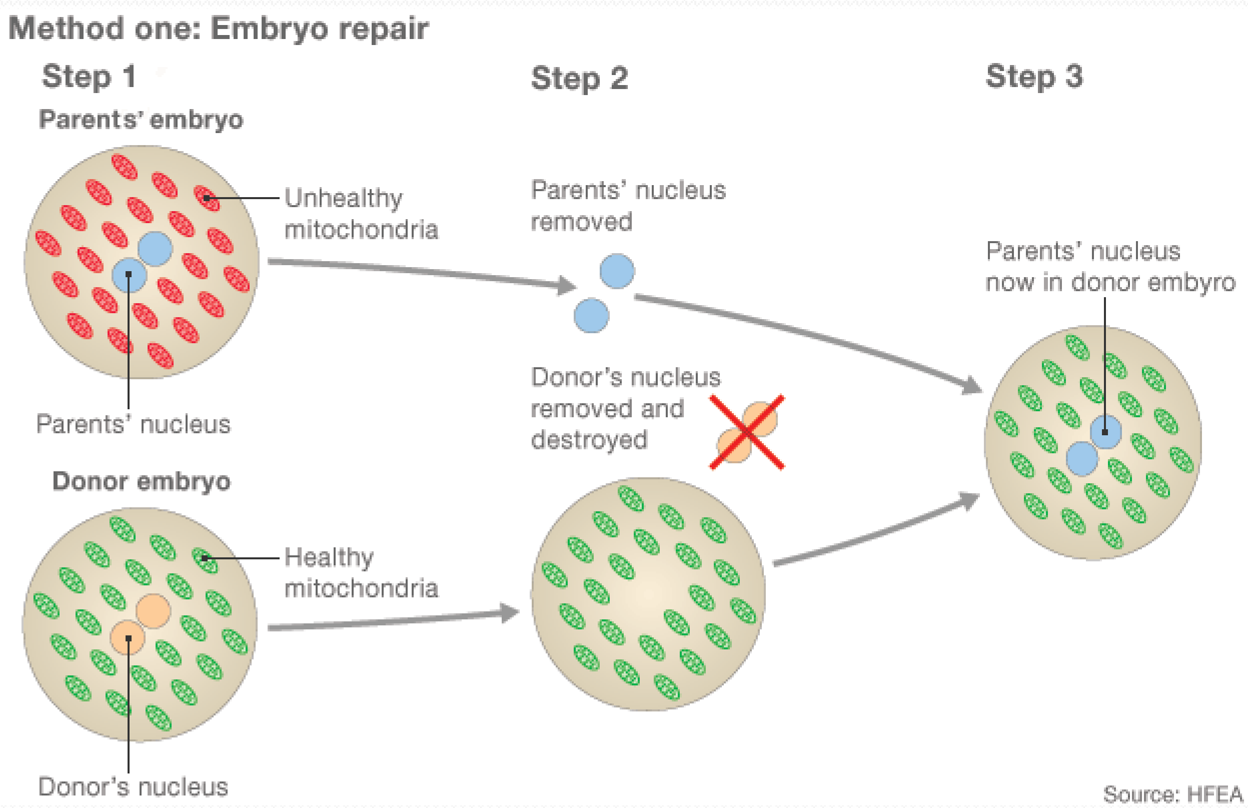

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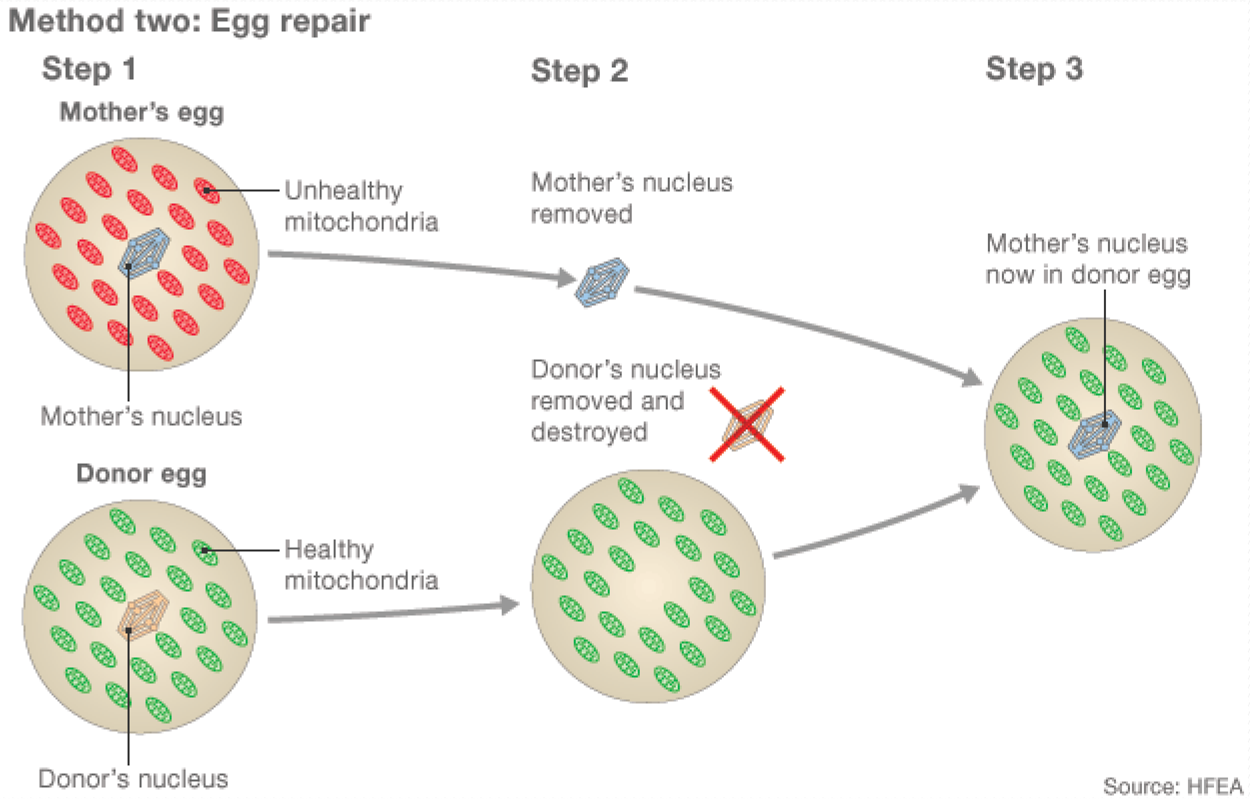

Additive Genetics

Genetics, fixing nitrogen from air