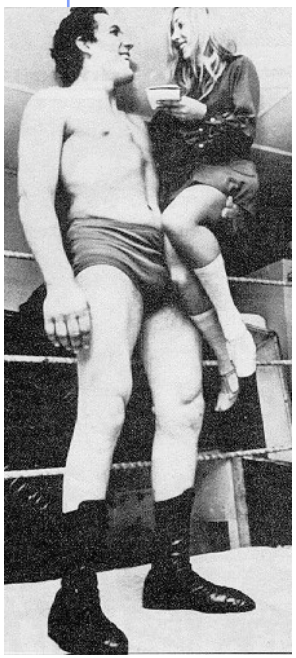
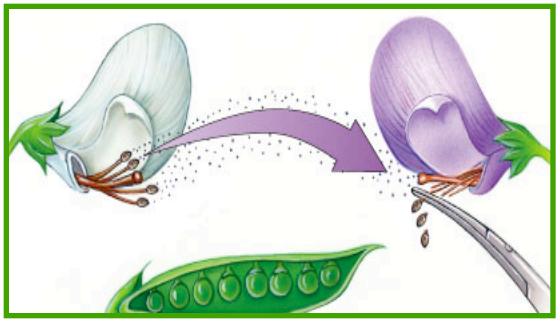
Beyond Mendel's Laws of Inheritance

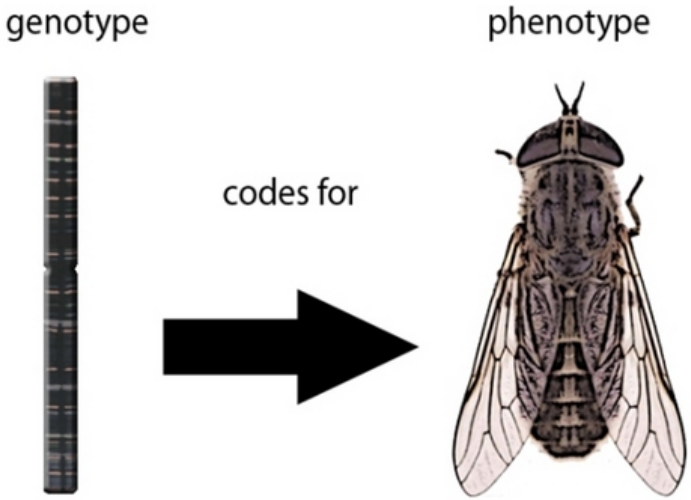


Extending Mendelian genetics

- **Mendel worked with a simple system**
  - peas are genetically simple
  - the characters he studied were controlled by a single gene
  - each gene had only 2 alleles *(gene versions)*, 1 of which is completely dominant to the other
    - When the diploid organism, which has two copies of all the genes on its autosomal chromosomes, inherits at least one dominant allele for a particular gene (the other allele being the recessive type), this organism's phenotype looks identical to the phenotype produced by an organism that inherits two dominant alleles of a gene
      - One allele of the two alleles of each gene showed COMPLETE DOMINANCE

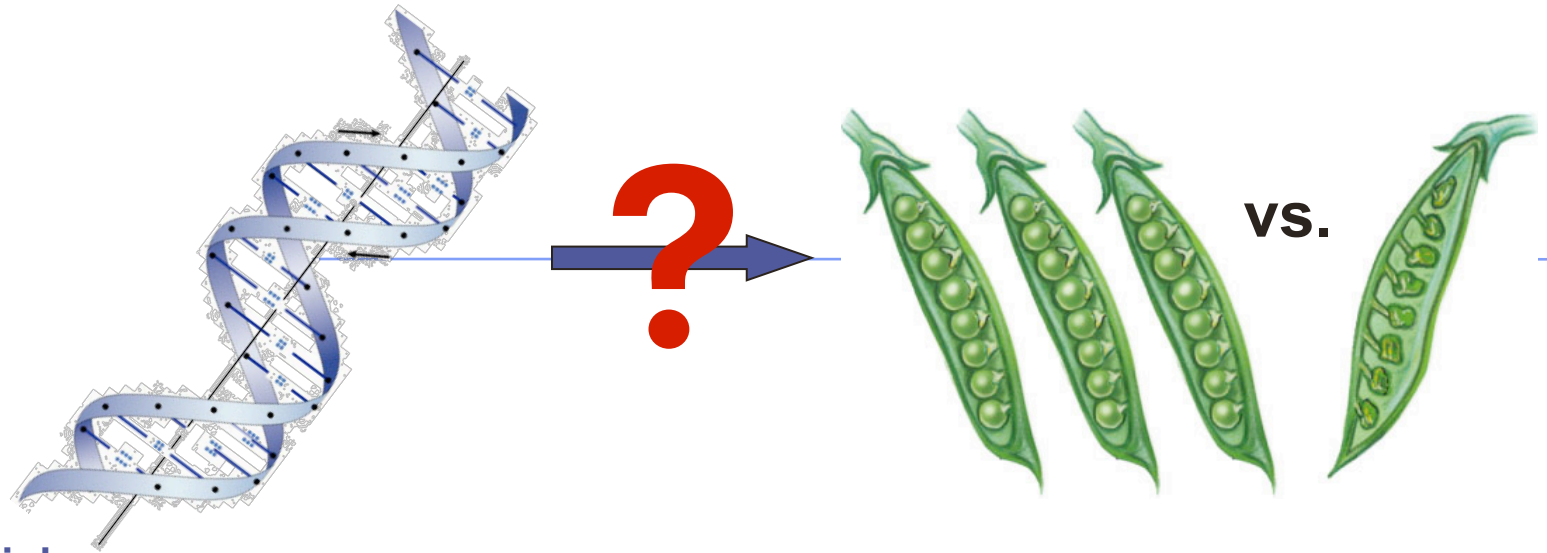


- **The relationship between genotype & phenotype is rarely that simple**



Mechanisms of Inheritance

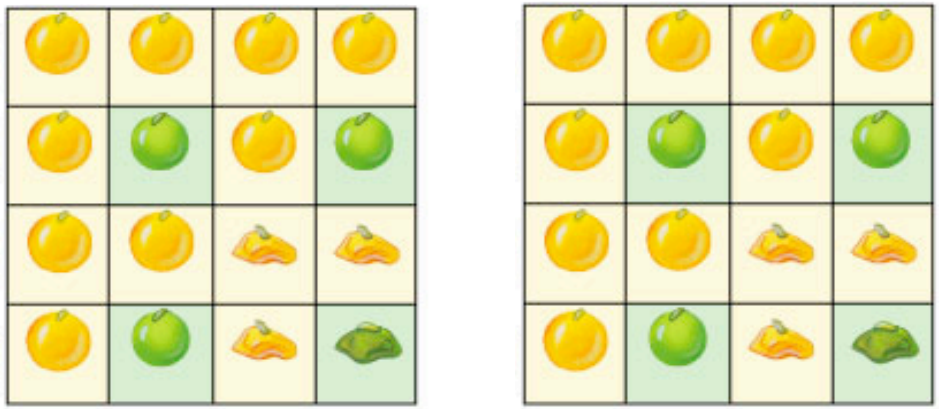
How do we go from DNA to trait?



Mechanisms of inheritance

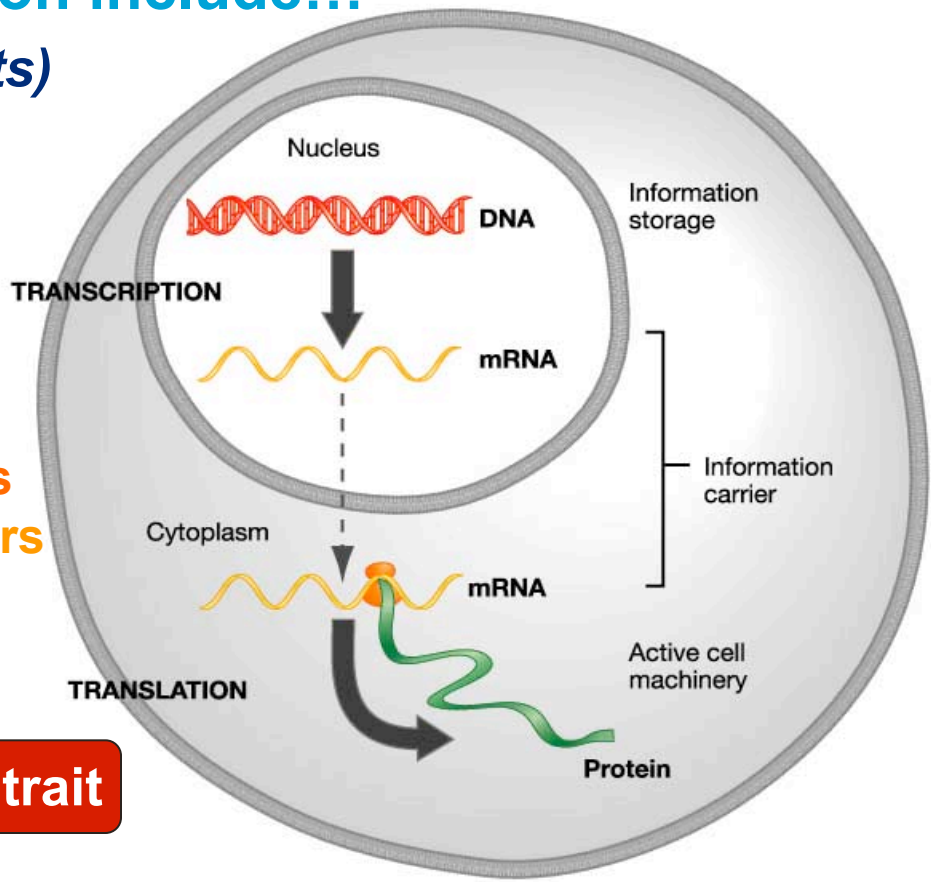
- What causes the differences in alleles of a trait?
  - yellow vs. green color
  - smooth vs. *wrinkled* seeds
  - dark vs. light skin
  - sickle cell anemia vs. no disease

- What causes dominance vs. recessive?



Molecular mechanisms of inheritance

- **Zooming into the molecular basis of inheritance:**
  - genes code for **polypeptides**
  - One or more polypeptides make up a **protein**
  - samples of proteins function include…
    - enzymes *(chemical catalysts)*
    - structural proteins
    - transport proteins
    - receptors
    - gene & cell regulators
      - Signal molecules
        - Ex: various hormones
      - gene activators & inhibitors
      - allosteric activators & inhibitors



DNA → RNA → protein → trait

How does a recessive disorder work in a diploid organism?

= allele coding for functional protein X

= allele coding for non-functional protein X

heterozygous condition

= makes 50% functional protein X → **Aa**

- [50% of protein X is nonfunctional]
- if sufficient working protein X present:
  - normal trait (phenotype) is expressed
  - normal trait-producing allele is thus called DOMINANT
    - cannot tell the difference between the phenotype of the heterozygote and the homozygous dominant organism

carrier

homozygous recessive condition

= 100% non-functional protein X → **aa**

- mutant trait (phenotype) is expressed

homozygous dominant condition

= 100% functional protein X → **AA**

- normal trait (phenotype) is expressed

Example: Nonfunctional enzyme has incorrect structure at active site and so can't catalyze a needed chemical reaction while the functional version of this enzyme has correct the form and, thus, function.

A hidden (recessive) disease reveals itself with the right allelic combination

Sickle Cell Anemia is a recessive disease

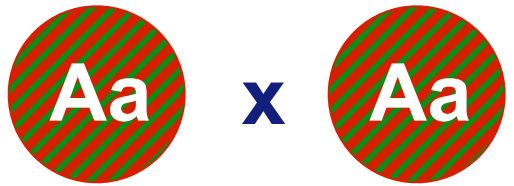
aa genotypes have disease while Aa & AA individuals have a healthy phenotype!

A = Dominant Allele = results in the making of normal hemoglobin protein

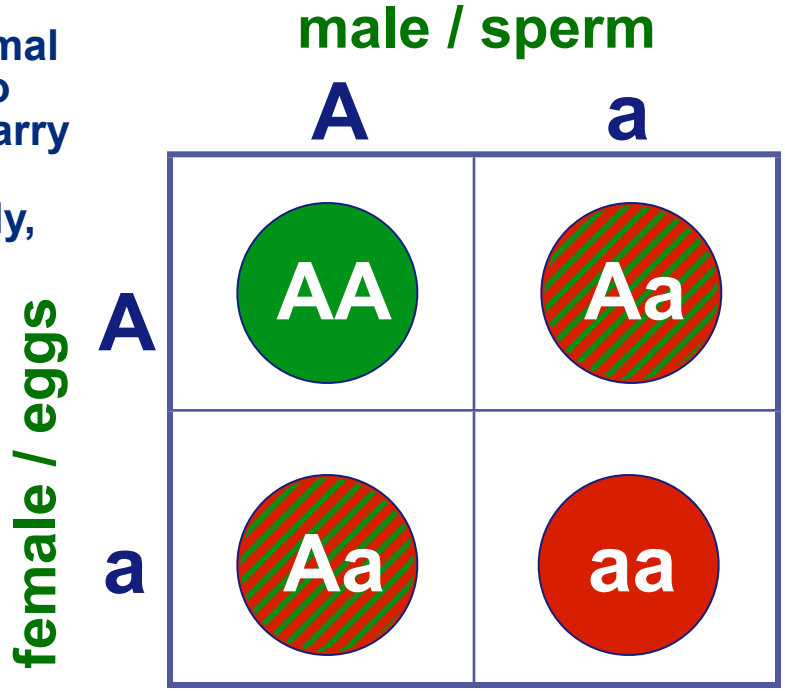
a = Recessive Allele = results in the making of abnormal hemoglobin protein, which causes hemoglobin to stick together, making hemoglobin less able to carry enough oxygen to tissues and warping the cell's shape, the cells then sticking together more easily, leading to embolism formation that can block blood flow through small blood vessels.

CARRIERS - organisms that have normal phenotypes or the phenotype of the dominant allele but carry the recessive allele in their DNA *(one of their alleles is the recessive gene version)*

- **Carriers can pass on a harmful allele!**



If carriers mate…



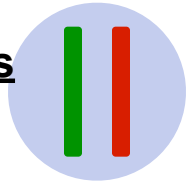
- **hidden disease may be revealed**

How does a dominant disorder work in a diploid organism?

= allele coding for functional protein X

= allele coding for abnormally functioning protein X

heterozygous condition



= makes 50% functioningly normal protein X

- other 50% of other protein X made functioning, but in a harmful way!!!
  - mutant trait (phenotype) is expressed
  - mutant trait-producing allele is thus called DOMINANT
    - the heterozygote and the homozygous dominant organism both show abnormal phenotype

→ Aa

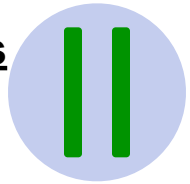
homozygous dominant condition

= 100% abnormally functioning protein X

- mutant trait is expressed as proteins are working just not in the manner intended

→ AA

homozygous recessive condition



= 100% functionally normal protein X

- normal trait is expressed
- Proteins are working *in the manner intended*

→ aa

Example: Malformed receptor protein, now "stuck on," instead of being on only when ligand bound to receptor

Example: Malformed channel protein "stuck open" continuously

Inheritance pattern of Achondroplasia - Dominantly inherited Disorder

Aa x aa

	a	a
A	Aa	Aa
a	aa	aa

50% dwarf : 50% normal or 1:1

Aa x Aa

AA = lethal

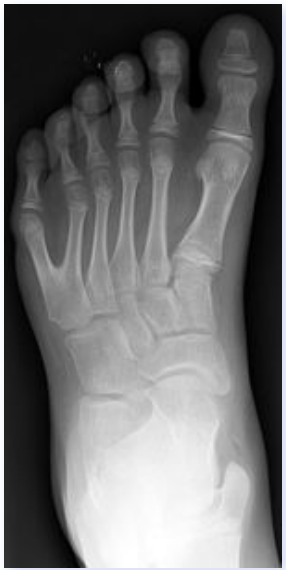
	A	a
A	~~AA~~	Aa
a	Aa	aa

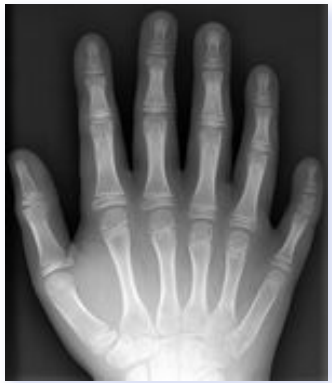
67% dwarf : 33% normal or 2:1

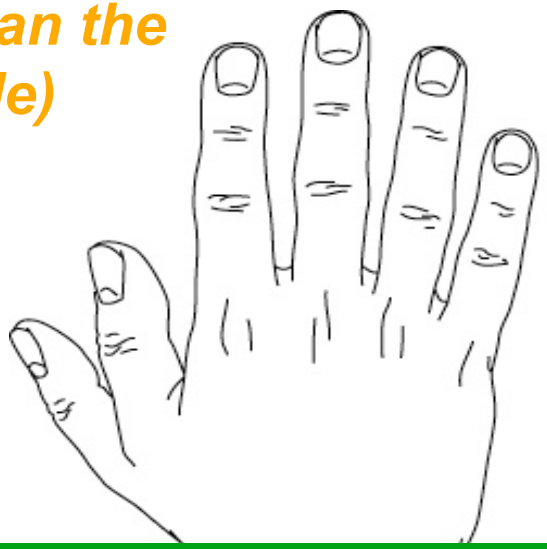
Prevalence of dominant alleles....

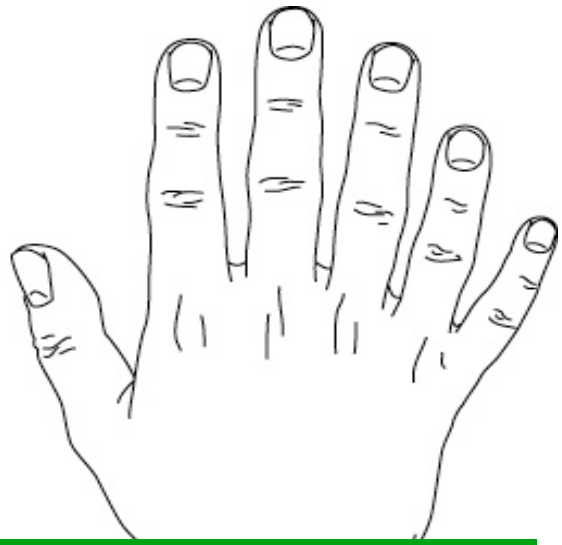
- **Just because an allele is dominant does not mean…**
  - **it is better, or**
  - **it is more common** ***(that it has a higher frequency of occurrence than the recessive allele)***

Most common form of Polydactyly dominant allele



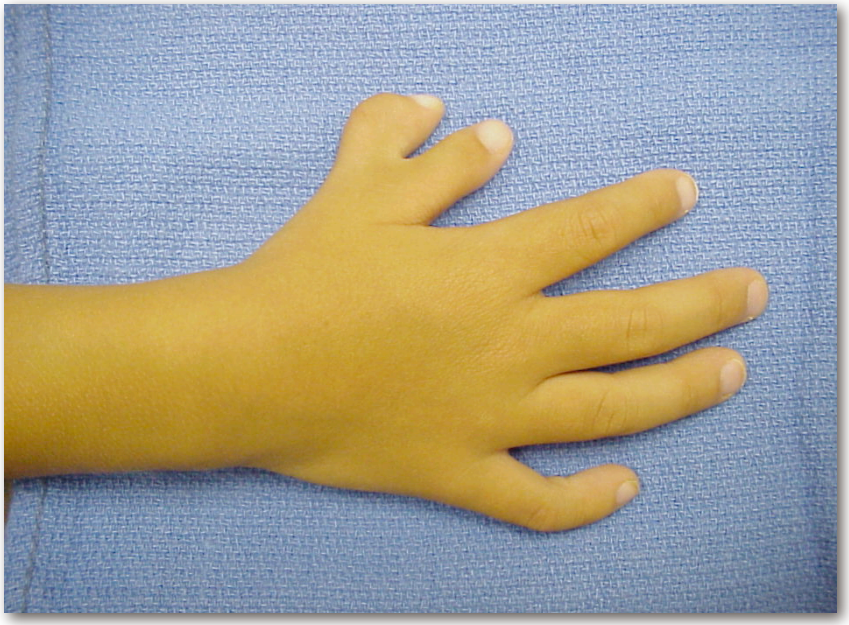






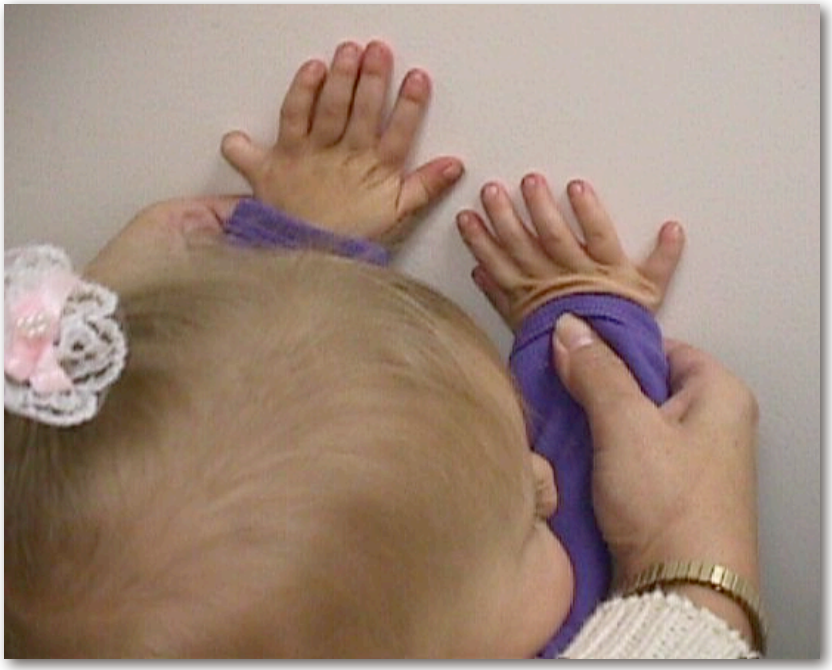
Polydactyly, however, displays a frequency of 1 in approximately 700–1,000 live births.

Polydactyly



individuals are born with extra fingers or toes

the allele for MORE THAN 5 fingers/toes is DOMINANT & the allele for 5 digits is recessive

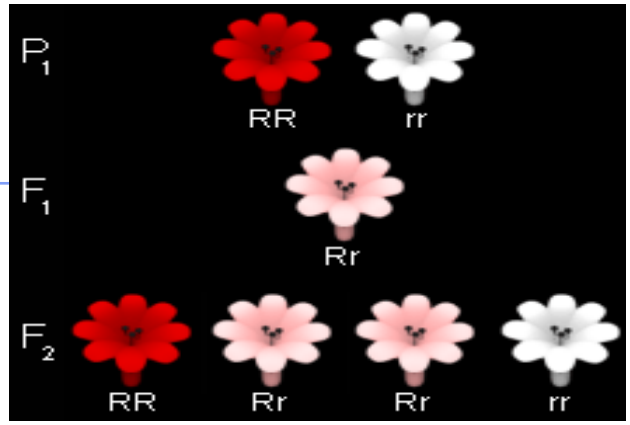


recessive allele far more common than dominant

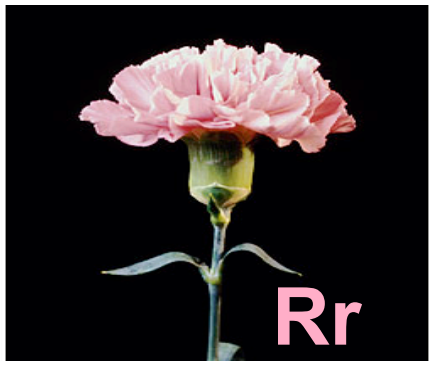
→ only 1 individual out of ~750 has more than 5 fingers/toes

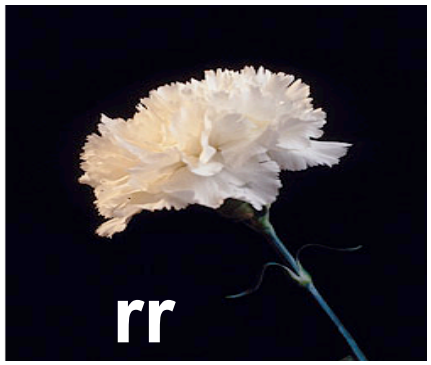
→ so ~749 out of 750 people are homozygous recessive (aa)

Incomplete/Intermediate dominance



- **For some genes, neither allele is considered completely dominant**
  - **Heterozygotes show a phenotype in between the two homozygous true breeding types!!!**
    (phenotype is a mixture of the two homozygote conditions)
    - **Heterozygotes = display an intermediate, blended phenotype**
  - **Example:**
    - **RR = red flowers**
    - **rr = white flowers**
    - **Rr = pink flowers -** ***make 50% less color & not enough color to make the flower look fully red***





Incomplete dominance in snap dragons

P

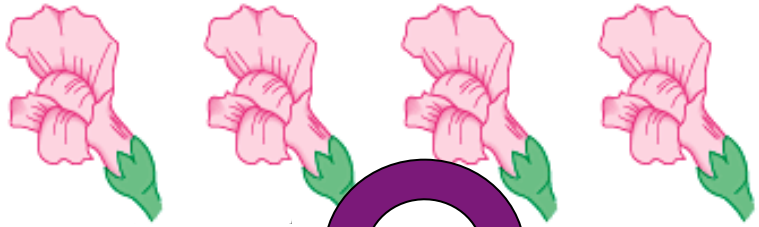
true-breeding red flowers

X

true-breeding white flowers

100% pink flowers

F_1 generation (hybrids)



100% pink

self-pollinate

F_2 generation

25% red

50% pink

25% white

1:2:1
Phenotypic ratio (not a 3:1 like is expected in complete dominance)

Incomplete dominance *[Instead of a capital vs lower case letter, the allele may be written as the "character raised to the trait" or "gene raised to the allele type" with regard to Incomplete Dominance Inheritance Patterns*

C^R = Dominant Allele
C^W = Recessive Allele

C^RC^W x C^RC^W

male / sperm

female / eggs	C^R	C^W
C^R	C^RC^R	C^RC^W
C^W	C^RC^W	C^WC^W

	% genotype	% phenotype
C^RC^R	25%	25%
C^RC^W	50%	50%
C^RC^W		
C^WC^W	25%	25%
	1:2:1	1:2:1

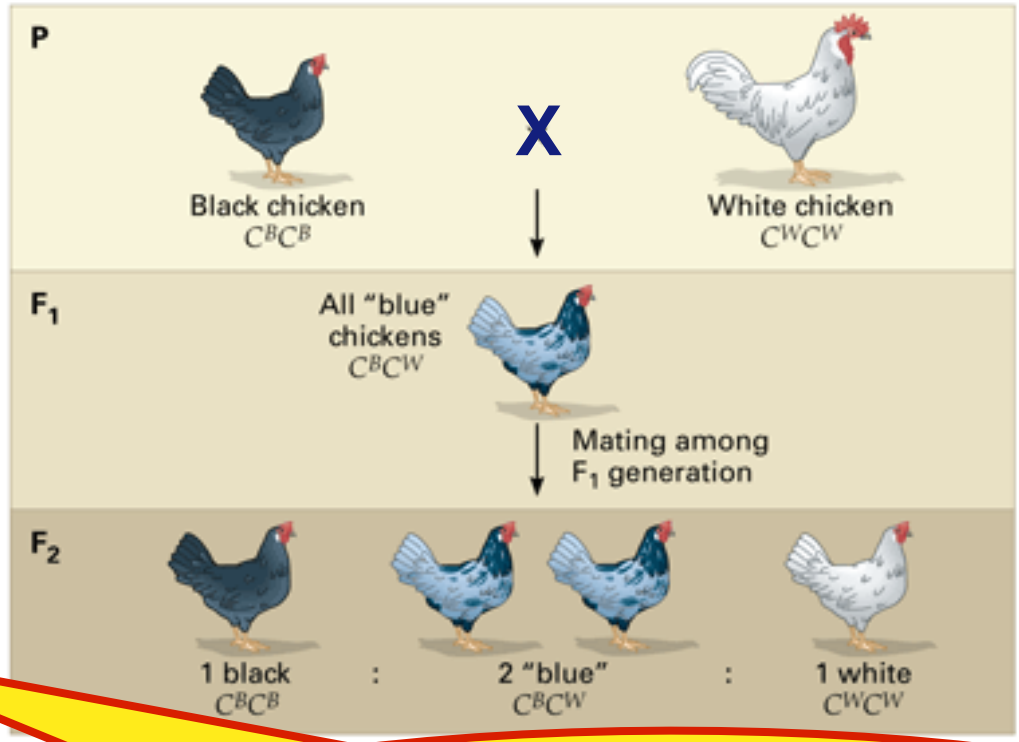
Incomplete dominance in Blue Chickens

Heterozygote turns out grayish - like a mixture of white and black

true-breeding Black

Heterozygote Gray

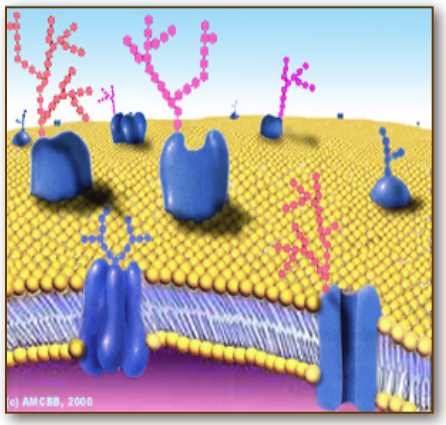
'ue-breeding white

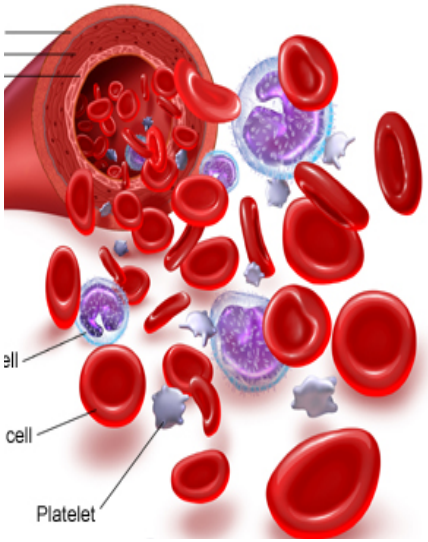


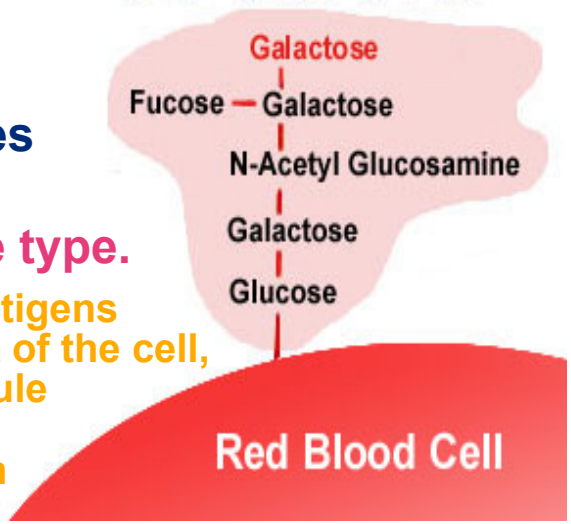
This is definitely different from Mendel's Complete Dominance Patterns of Inheritance where the heterozygote looked like the homozygous dominant parent!

Co-dominance

- **2 different alleles affect the phenotype at the same time equally yet in separate visible ways**
  - You do not see an intermediate or blended-like phenotype
    - Example: ABO blood group
      - The ABO blood type is controlled by a single gene (ABO gene) with three types of alleles
        - The gene is polymorphic (comes in multiple versions) = I^A, I^B, *i*
        - Both I^A & I^B are dominant to *i* allele
        - Alleles produce glycoprotein antigen markers on RBC cell surfaces
          - There are >30 different blood antigen groups, ABO being one type.
          - Functions of different blood group antigens include transporting molecules in/out of the cell, maintaining cell structure, cell/molecule attachment, participating in chemical reactions, self vs non-self recognition



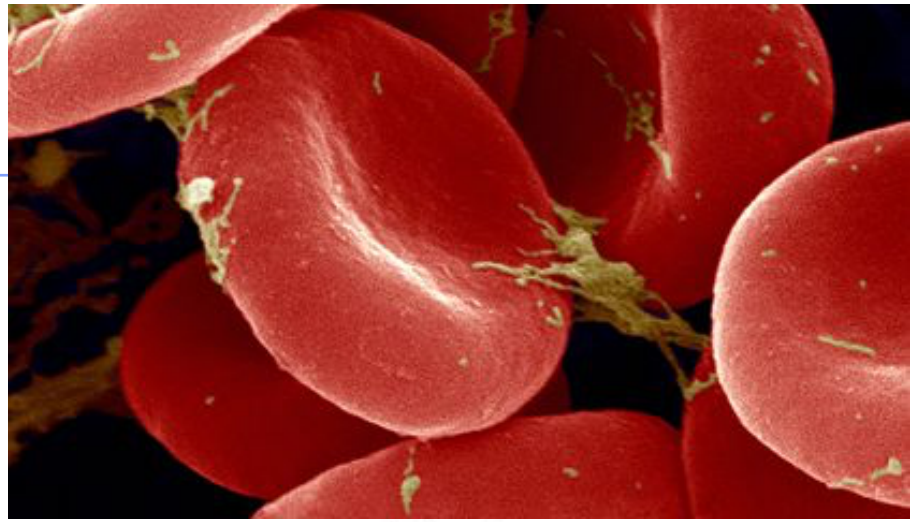




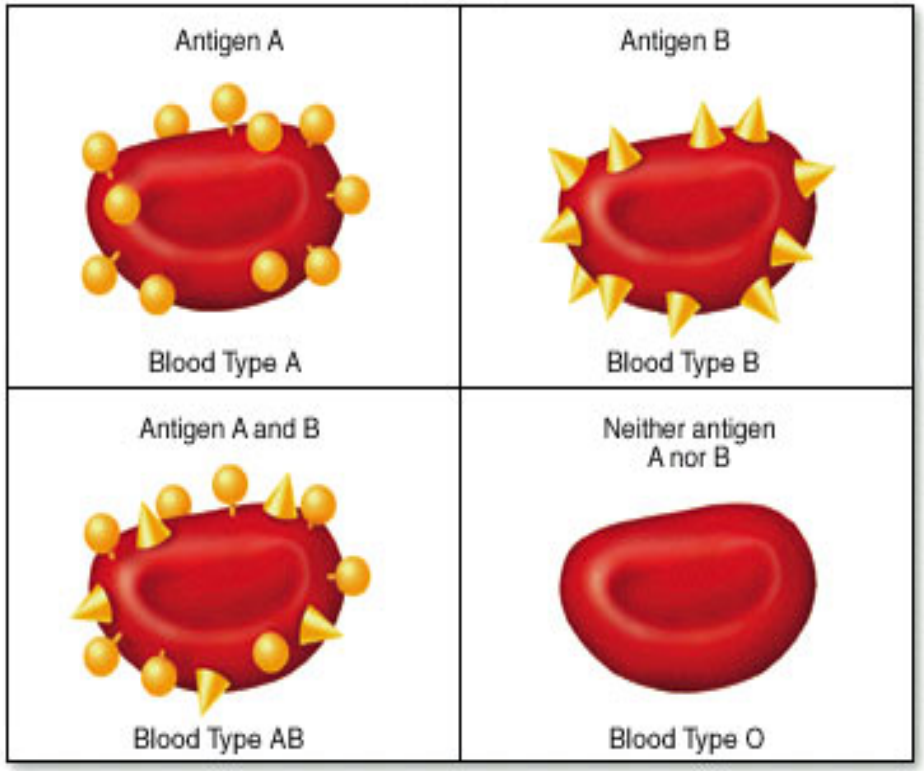
Co-dominance

- **Example**: ABO blood group
- 3 alleles
  - I^A, I^B, *i*
    - I^A adds a certain polysaccharide on the surface of red blood cells
    - I^B adds a different certain polysaccharide on the surface of a red blood cell
    - I^A I^B adds both polysaccharides (codominance)
    - *i* adds neither A nor B polysaccharides

I have the Blood Group with an attitude.
B+



Erythrocytes

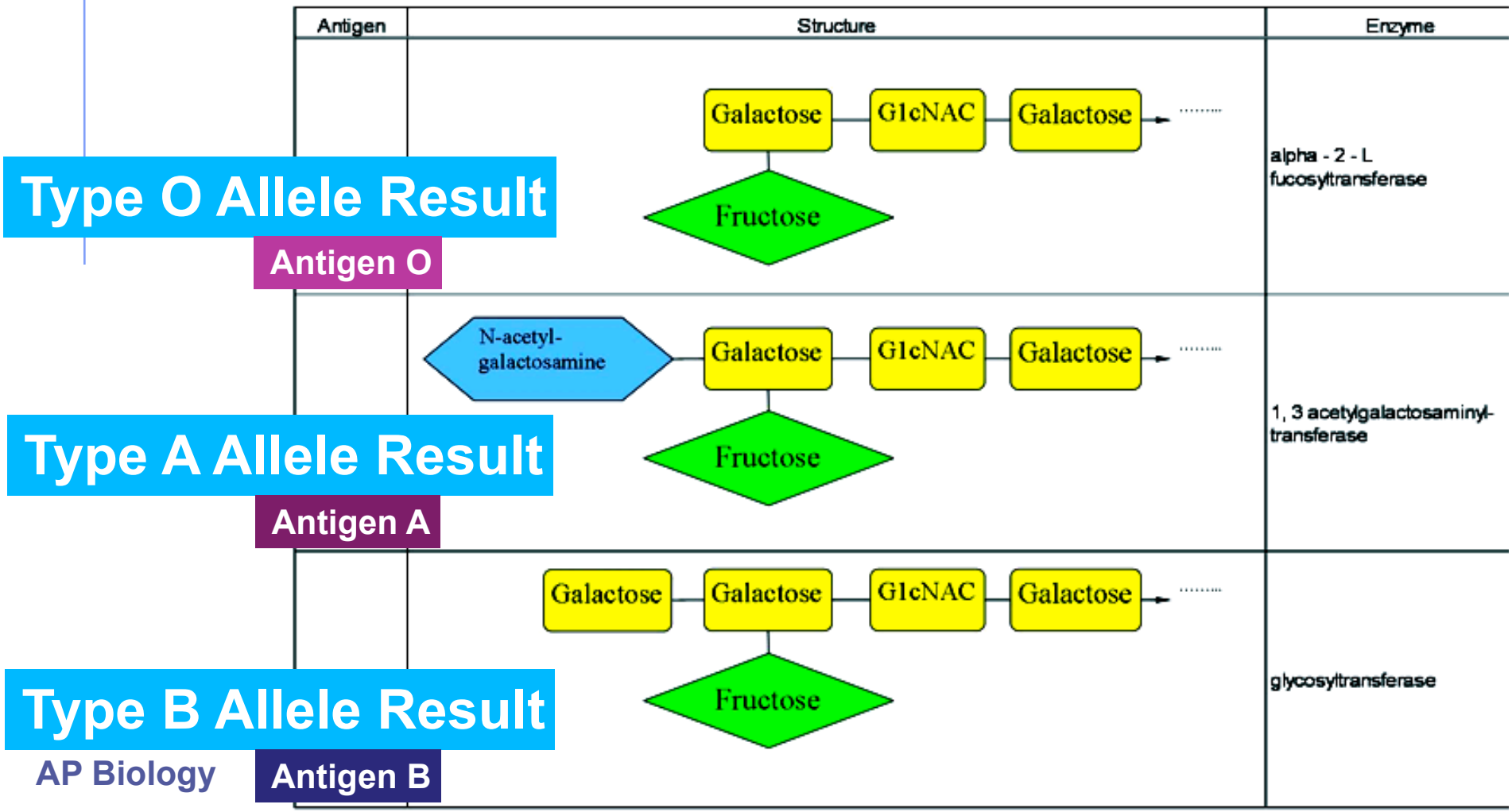


Molecular results of having the I^A, I^B, or *i alleles*

- **Regardless of having the I^A, I^B, i alleles, red blood cells make a glycoprotein, called H antigen, on their surface.** ***Additional simple sugars can be added to the fructose on this glycoprotein if you can make the enzyme to do so.***
  - **The i allele is "silent." It cannot encode the making of a necessary enzyme to modify the H antigen further.**
    - **Someone with genotype ii, cannot add any additional sugar to the H antigen. Their phenotype is called Type O.**
  - **For those who inherit the I^A or I^B alleles, an additional alpha 1,3-N acetylgalactosaminyltransferase or glycosyltransferase functional enzyme is encoded to attach an additional sugar to the "H" antigen.**
    - **Someone with an I^A allele (genotype I^AI^A or I^Ai) will add the N-acetyl-galactosamine sugar to the galactose of Antigen H. Their phenotype is called Type A.**
    - **Someone with an I^B allele (genotype I^BI^B or I^Bi) will add an extra galactose sugar to the galactose of Antigen H. Their phenotype is called Type B.**
    - **Someone with one I^A and one I^B allele (genotype I^AI^B) will add the N-acetyl-galactosamine sugar to the galactose of some Antigen H's AND will add an extra galactose sugar to the galactose of other Antigen H's. Their phenotype is called Type AB.**

RBC Glycoprotein phenotypic results based on the I^A, I^B, i allele

- **Therefore, the two alleles inherited determined if a person will remain a type O or change to type A, B, or AB.**



Blood Type & Your Immune System

The A- vs. B-type sugar groups on surface of red blood cells are ID Tags

- These glycoproteins allow your body to tell if a cell is one of its own or an invader

Antigens are molecules your immune system's antibodies can recognize

- Antibody proteins (made by immune system cells) circulate in body fluid looking for foreign antigens on invading cells
- **By attaching to antigens, antibody proteins tag foreign cells for destruction**

  You do not make antibodies that recognize your own antigens

pheno-type	genotype	antigen on RBC	antibodies in blood	donation status
A		antigens on surface of RBC	antibodies	—
B		antigens on surface of RBC	antibodies	—
AB		antigens on surface of RBC	antibodies	
O		on surface of RBC	antibodies	

Blood Type & Your Immune System

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  You do not make antibodies that recognize your own antigens

phenotype	genotype	antigen on RBC	antibodies in blood	donation status
A	$I^A I^A$ or $I^A i$	type A antigens on surface of RBC	anti-B antibodies	—
B	$I^B I^B$ or $I^B i$	antigens on surface of RBC	anti-A antibodies	—
AB	$I^A I^B$	both type A & type B antigens on surface of RBC	no antibodies	universal recipient
O	$i\ i$	no antigens on surface of RBC	anti-A & anti-B antibodies	universal donor

Blood compatibility

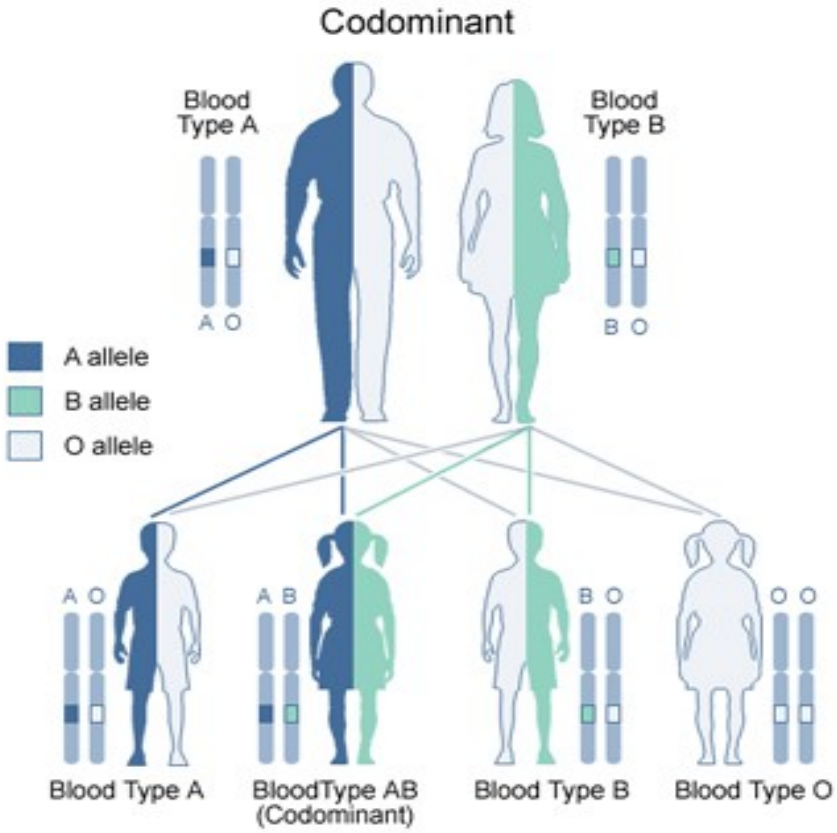
1901 | 1930

Matching compatible blood groups

- critical for blood transfusions
  - Antibodies attach to antigens and signal the immune system to destroy whatever contains that antigen.

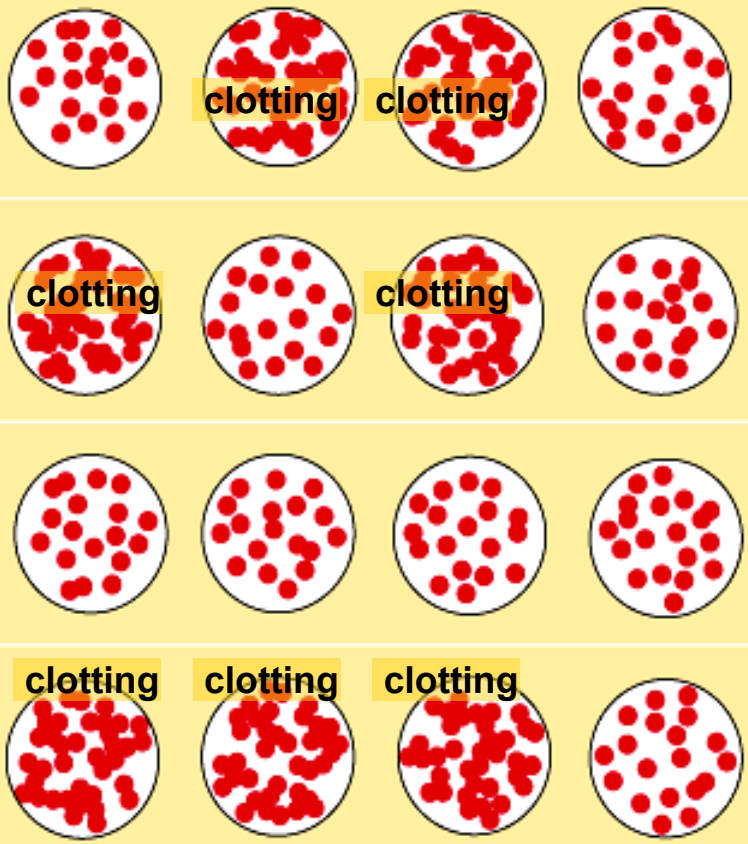
A person produces antibodies against antigens in foreign blood ***[in this case, the antigen might be a type A or B sugar, whichever your your body does <u>not</u> naturally produce]***

- If you get blood with a sugar your body recognized as foreign, you were given the wrong blood type
  - If donor's blood has the A or B antigen that is <u>foreign</u> to recipient then…
  - antibodies in recipient's blood bind to these foreign molecules on foreign RBCs
  - This causes donated blood cells to clump together as they are coated in antibodies *[forming blood clots]*
    - These blood clots can kill the recipient



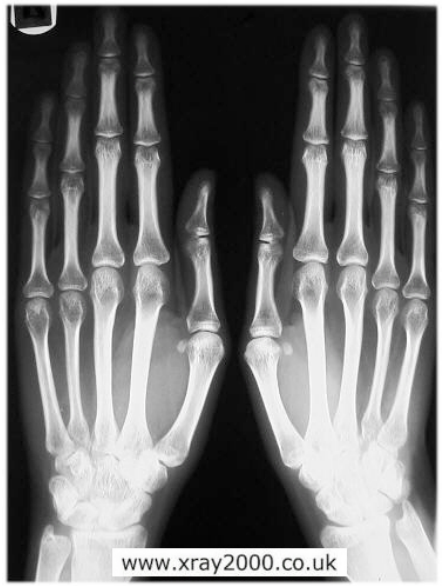
Blood donation requires matching blood type between donor and recipient

(a) Phenotype (blood group)	(b) Genotypes (see p.258)	(c) Antibodies present in blood serum	(d) Results from adding red blood cells from groups below to serum from groups at left			
			A	B	AB	O
A	$I^A I^A$ or $I^A i$	Anti-B		clotting	clotting	
B	$I^B I^B$ or $I^B i$	Anti-A	clotting		clotting	
AB	$I^A I^B$	—				
O	*ii*	Anti-A Anti-B	clotting	clotting	clotting	



Pleiotropy

- **Most genes are pleiotropic** (Greek 'pleion' = more)
  - one gene affects more than one phenotypic character & not just one aspect of your phenotype
    - wide-ranging effects can often be seen due to a single gene because this gene is turned on in numerous different tissues at different times so the effects of making a certain form or an incorrect form of the protein is noticeable in multiple body locations
      - dwarfism (achondroplasia)
      - gigantism (acromegaly)
    - Pleiotropy is responsible for the large numbers of symptoms seen with many hereditary diseases
      - Cystic fibrosis
      - Sickle-cell anemia



Acromegaly: André the Giant

- When there is too much growth hormone in the body, certain tissues grow larger than normal including bone, muscle, organs etc...
  - Other effects include enlargement of jaw and other facial bones; overgrowth of bone and cartilage in the joints, causing arthritis, back pain, and curvature of the spine (kyphosis); swelling of the face, lips, and tongue; thickening of the skin; carpal tunnel and other nerve entrapment syndromes
  - Untreated, acromegaly is linked to early heart disease, high blood pressure, heart rhythm disorders, diabetes, and colonic polyps, a precursor of colon cancer.

Inheritance pattern of Achondroplasia - Dominantly inherited Disorder

Aa x aa

	a	a
A	Aa	Aa
a	aa	aa

50% dwarf : 50% normal or 1:1

Aa x Aa

AA genotype are nonviable

	A	a
A	~~AA~~	Aa
a	Aa	aa

67% dwarf : 33% normal or 2:1

Epistasis

- One *gene* when expressed affects the phenotypic expression of another separate *gene*
  - Ex: coat color in mice = controlled by 2 separate genes
    - C/c which codes for depositing pigment is epistatic to the gene that codes for black or brown pigment molecule creation B/b

B_C_

bbC_

_ _cc

- C/c: Depositing Color is dominant to not depositing color
  - pigment (C) or no pigment (*c*)
- B/b: Black is dominant to brown
  - more pigment (black=B) or less (brown=b)
- *cc* = albino, no matter B allele

Epistasis

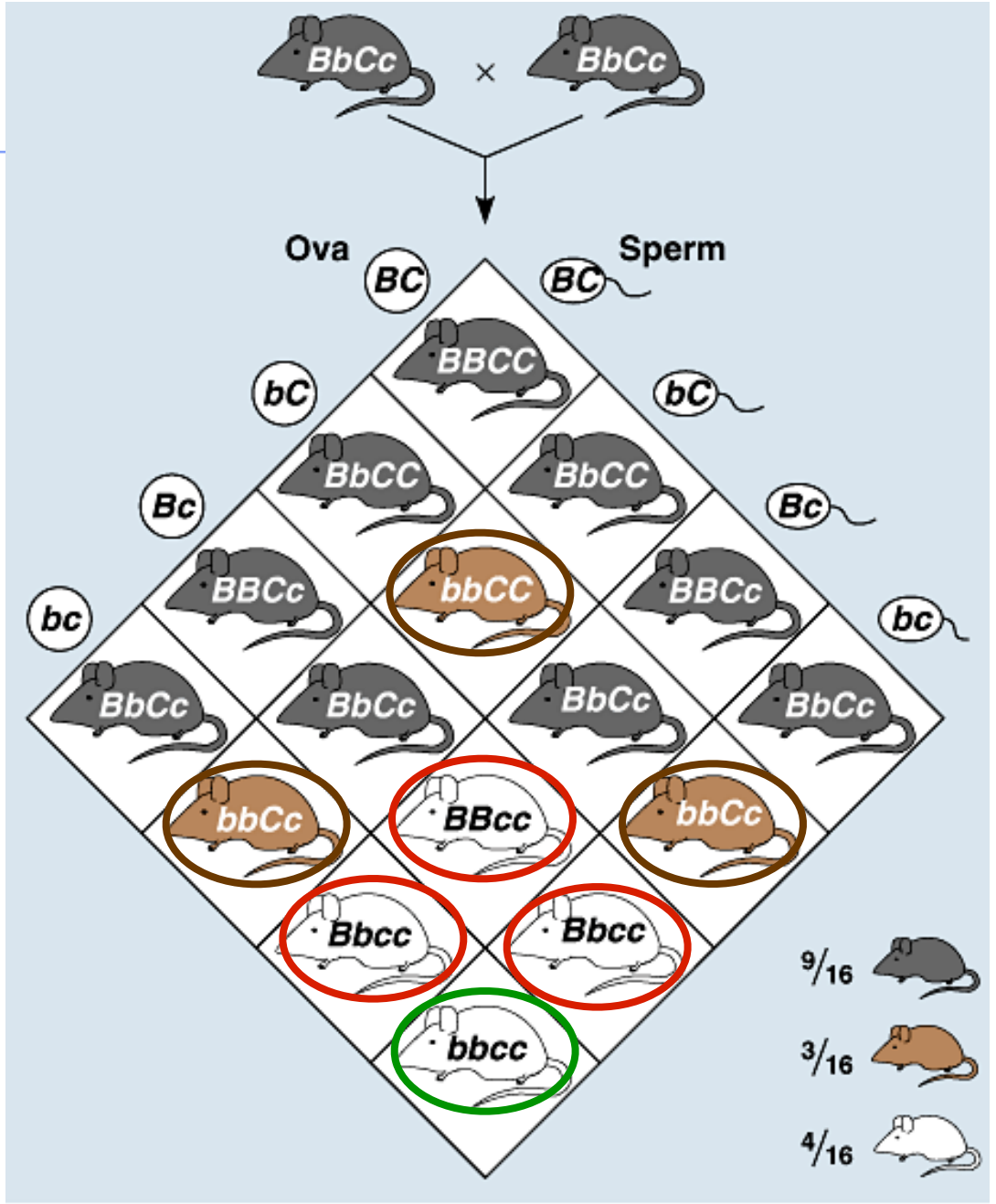
- One *gene* affects the phenotypic expression of another separate *gene*

B_C_

bbC_

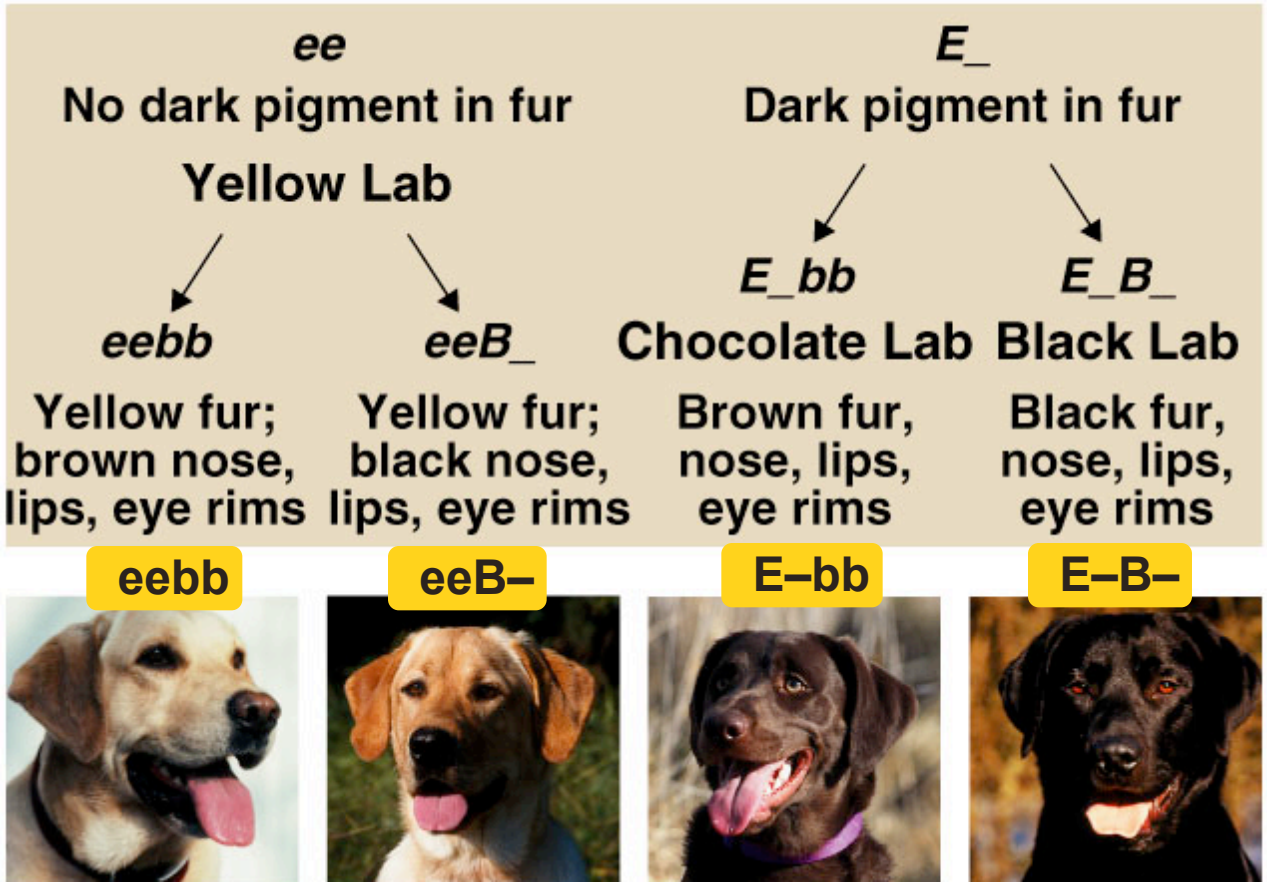
_ _cc

9:3:3:1
Phenotypes are not seen.
Instead, a 9:3:4 or another ratio of phenotypes results



Epistasis in Labrador retrievers

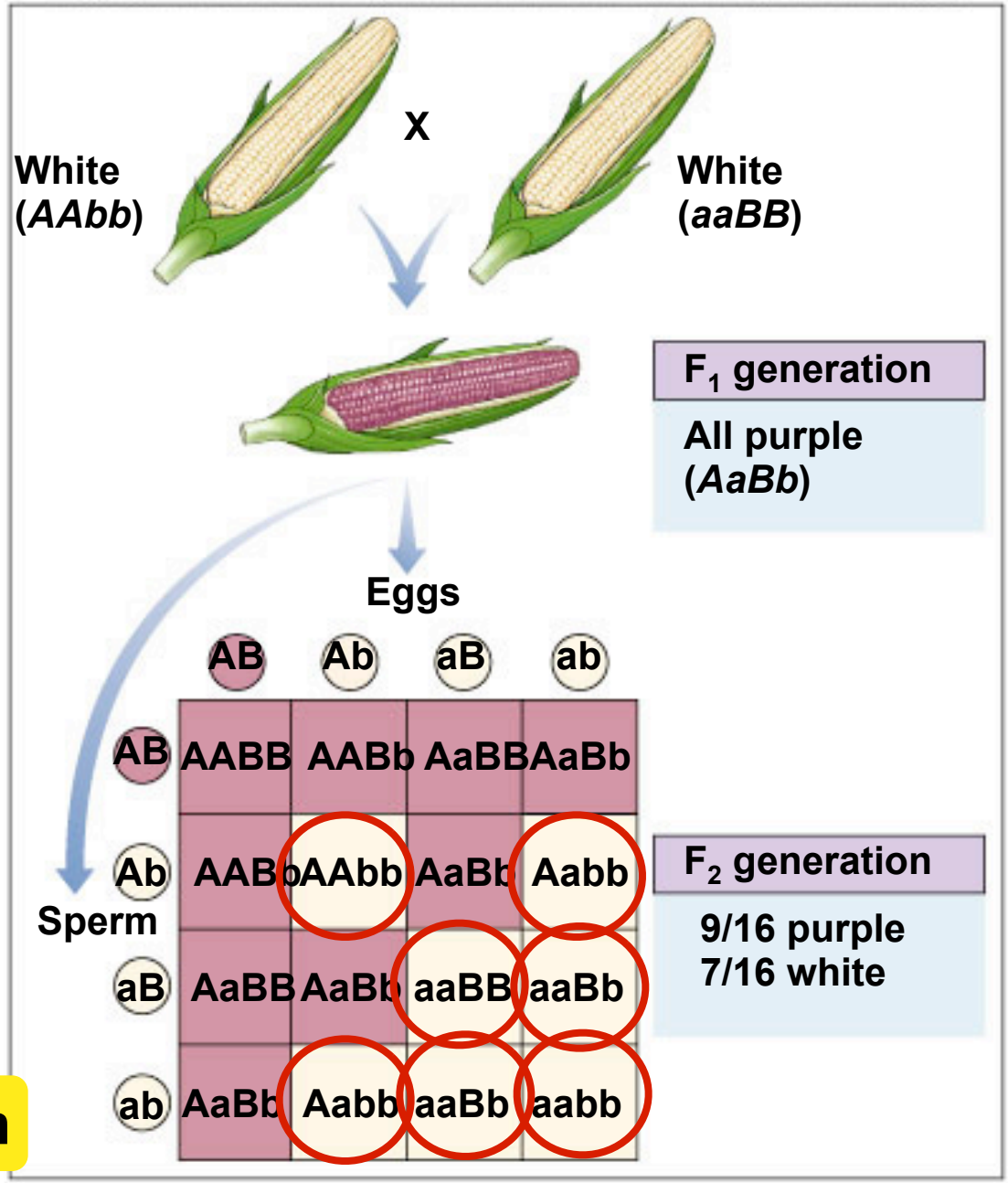
- 2 genes: (E/e) & (B/b)
  - pigment (E) or no pigment (e)
  - pigment concentration: black (B) to brown (b)



If the animal inherits the homozygous recessive genotype of the "E" gene, "ee", then it's fur will be yellow, *regardless of whether it is dominant or recessive for the "B" gene.*

Epistasis in corn color

A = enzyme 1
+
B = enzyme 2
↓
purple color (anthocyanin)



9:3:3:1 phenotype is not seen

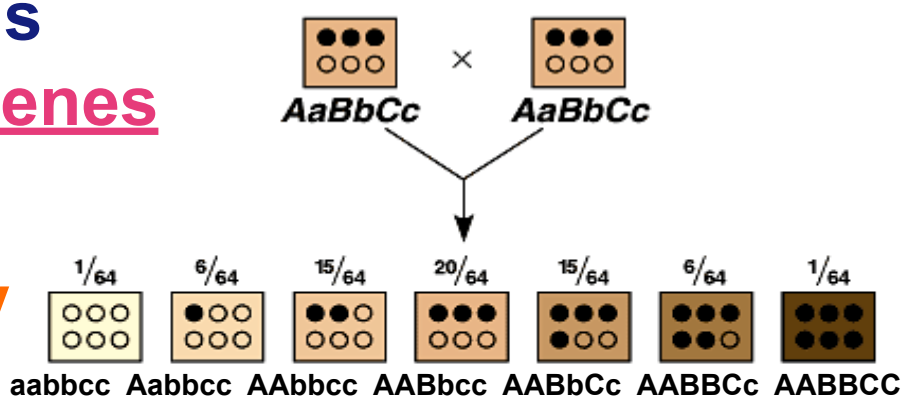
9 purple : 7 white is seen

Polygenic inheritance

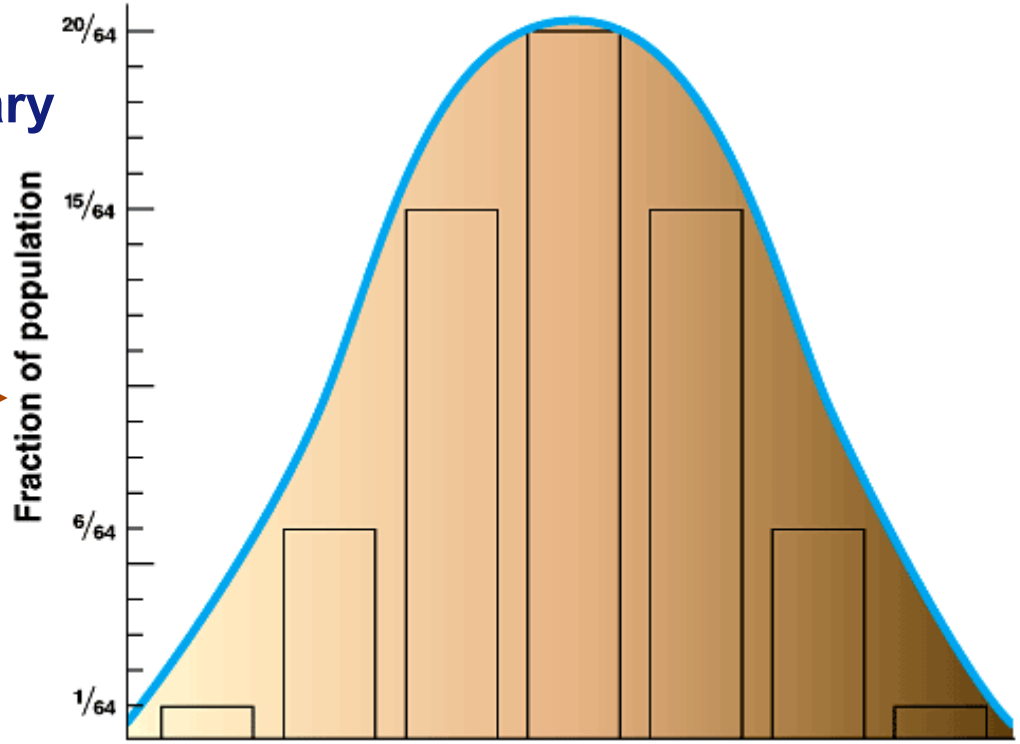
Both the amount and type of skin pigment produced is controlled by a number of genes that operate under incomplete dominance

When a single phenotype is determined by 2 or more genes

(opposite of pleiotropy)



- **Quantitative traits usually indicate polygenetic inheritance**
  - These are traits that vary in the population along a continuum
    - Ex: human traits
      - skin color
      - height
      - weight
      - eye color
      - intelligence
      - behaviors

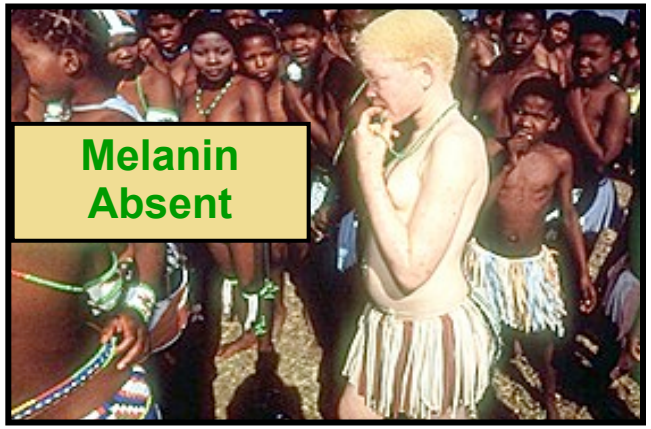


Skin color: Albinism

While UV radiation can assist in the production of Vitamin D, excessive exposure to UV can damage DNA & thus health.

The actual skin color of different humans is affected by many substances like blood and connective tissue, although the single most important substance is the pigment melanin.

- Melanin is produced within the skin cells called melanocytes. It controls the amount of ultraviolet (UV) radiation that penetrates the skin. People having different skin colors because of different numbers of melanocytes, and because their melanocytes produce different amounts and versions of melanin.
  - Albinism can be inherited as a single gene trait caused by a recessive allele. *You either have albinism or you do not.*



melanin = universal brown color

Johnny & Edgar Winter

Nature vs. nurture

- Some phenotype for certain characters are controlled by both environment & genes = multifactorial traits

Human skin color is influenced by both genetics & environmental conditions

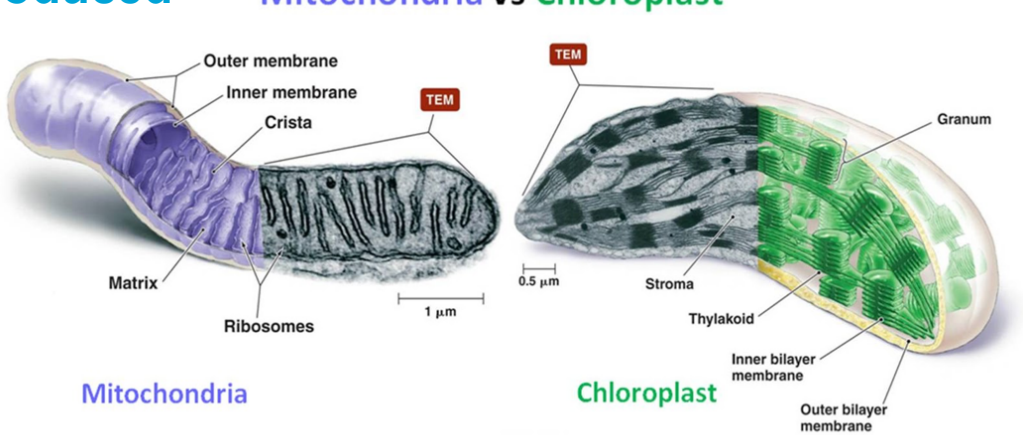
Color of Hydrangea flowers is influenced by soil pH

(a)

Coat color in arctic fox influenced by heat sensitive alleles

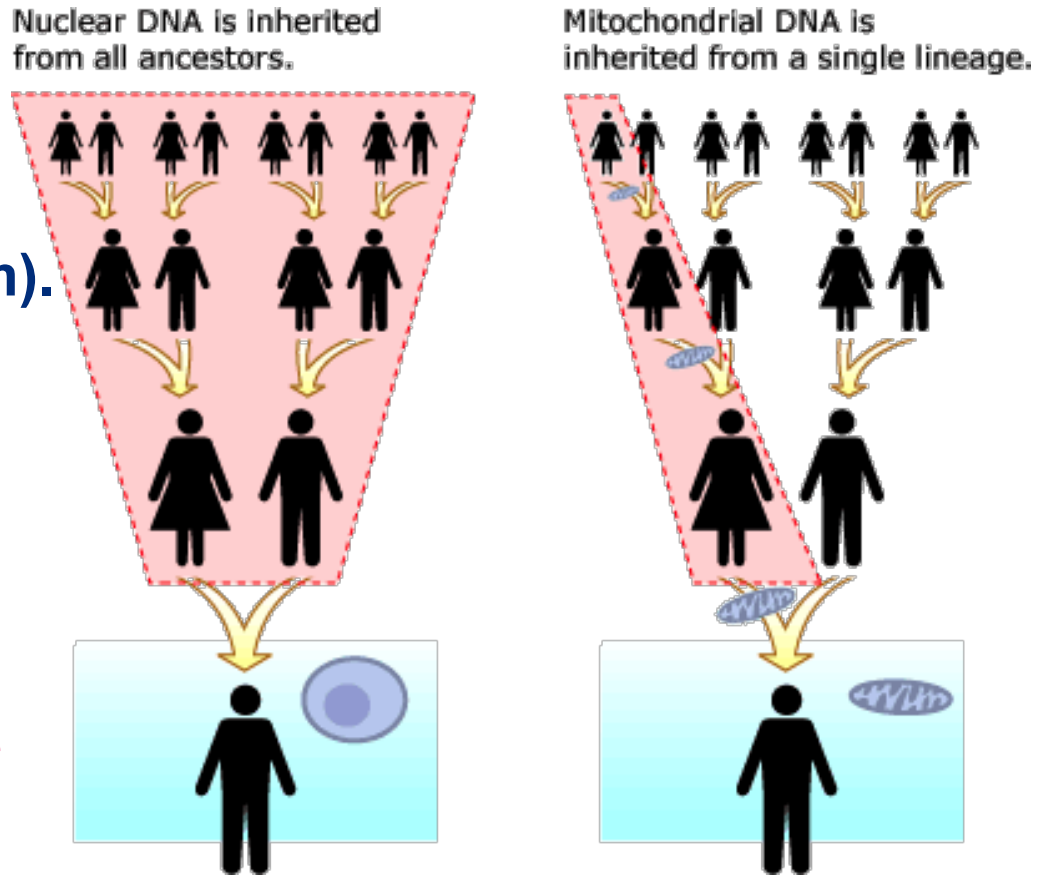
Additional Deviations from Mendelian Inheritance Patterns

- **Sometimes we see deviations from Mendel's model of the inheritance of traits because of the location of the gene and how it is passed down from one generation to the next.**
  1. **Some eukaryotic traits result from genes on sex chromosomes instead of autosomes** ***(more on this in Ch.15)***
  2. **Some traits result from non-nuclear inheritance - genes located on DNA outside of the nucleus**
     - **Recall that Chloroplasts and mitochondria contain circular DNA**
     - **Chloroplasts and mitochondria are randomly assorted into gametes or daughter cells in meiosis or mitosis, respectively.**
     - **Though most proteins used by these organelles are produced based on the information stored in nuclear DNA genes, some proteins and RNAs are produced from a limited number of nonnuclear DNA genes.**
       - **Traits determined by chloroplast and mitochondrial DNA do not follow simple Mendelian rules**



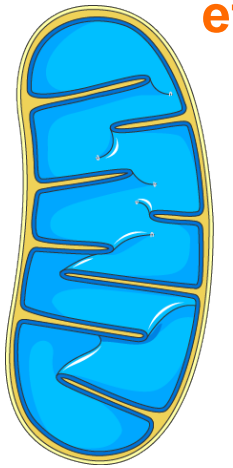
Mitochondrial Inheritance

- **Mitochondrial genomes (MtDNA) are about 16,500 bp long, containing only 37 genes (compared to the over 20,000 genes in human nuclear DNA).**
  - **Each contains 13 protein-coding (enzyme) genes, 22 tRNAs, and 2 rRNAs.**
- **MtDNA is maternally inherited – males and females inherit their MtDNA from their mother, through her gamete (ovum).**
  - **In plants, mitochondria and chloroplasts are transmitted in the ovule and not in the pollen**
  - **Nuclear DNA, on the other hand, is inherited equally from both parents**
  - **A child will inherit 50% of their nuclear DNA from the mother and the other 50% from their father.**



Mitochondrial Inheritance

- If the mitochondria do not function properly, disease symptoms arise.
  - Remember, mitochondria help transfer chemical energy from high energy organic molecules on to ATP, which carries the energy the cell needs to do work with.
    - When mitochondria don't function well, tissues may not be able to produce enough ATP for doing necessary functions.
  - Mitochondria also help store calcium levels, play a role in signal transduction, regulate metabolic process, play a role in cell death etc...
    - Though the majority of mitochondrial diseases are due to defects in the nuclear DNA that controls the synthesis of almost all mitochondrial proteins, around 15% of mitochondrial diseases are due to a defect in the mitochondrial DNA itself.
    - If the mother has *genetically* defective mitochondria, 100% of her children inherit defective mitochondria (with defective MtDNA).
      - Sometimes genes develop a mutation of their own due to external factors like exposure to radiation or toxins that damage the MtDNA, the mutation then not being inherited from a parent.



Mitochondria divide independently of the cell in which they reside. These organelles replicate by dividing in two, using a process similar to the binary fission, the simple, asexual form of cell division employed by bacteria, **passing their MtDNA on to daughter mitochondria within a cell.**

MATERNAL INHERITANCE OF MITOCHONDRIAL DNA MUTATIONS