Sources of genetic variation: Why the simple single gene/ 2 allele model is insufficient

Why do we see so much variation? Many answers.

- More than one gene controls trait
  - True for almost every phenotype
  - Fictional example: alleles at 6 genes control height

Fictional (simplified) example: 6 genes for women's "height"

	Person 1	2	3	4	5	6	7
Gene 1	**AA**	**aa**	**Aa**	**Aa**	**aa**	**Aa**	**AA**
Gene 2	**Bb**	**Bb**	**BB**	**Bb**	**Bb**	**bb**	**BB**
Gene 3	**CC**	**cc**	**Cc**	**CC**	**Cc**	**Cc**	**CC**
Gene 4	**Dd**	**Dd**	**Dd**	**Dd**	**Dd**	**DD**	**DD**
Gene 5	**Ee**	**ee**	**Ee**	**EE**	**Ee**	**Ee**	**Ee**
Gene 6	**ff**	**ff**	**ff**	**Ff**	**FF**	**Ff**	**Ff**
Height							

Height in inches = 5' 0" + number capital letter alleles

Hence, range 5' 0" – 6' 0"

Fictional (simplified) example: 6 genes for women's "height"

	Person 1	2	3	4	5	6	7
Gene 1	**AA**	**aa**	**Aa**	**Aa**	**aa**	**Aa**	**AA**
Gene 2	**Bb**	**Bb**	**BB**	**Bb**	**Bb**	**bb**	**BB**
Gene 3	**CC**	**cc**	**Cc**	**CC**	**Cc**	**Cc**	**CC**
Gene 4	**Dd**	**Dd**	**Dd**	**Dd**	**Dd**	**DD**	**DD**
Gene 5	**Ee**	**ee**	**Ee**	**EE**	**Ee**	**Ee**	**Ee**
Gene 6	**ff**	**ff**	**ff**	**Ff**	**FF**	**Ff**	**Ff**
Height	**5'7"**	**5'2"**	**5'6"**	**5'8"**	**5'6"**	**5'6"**	**5'10"**

Height in inches = 5' 0" + number capital letter alleles

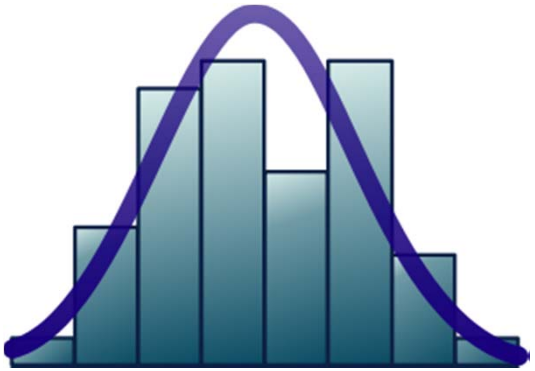
Hence, range 5' 0" – 6' 0"

Principles observed:
Fictional (simplified) example:
6 genes for women's "height"

- We used this formula:

  Height in inches = 5' 0" + number capital letter alleles

  Hence, range was 5' 0" to 6' 0"

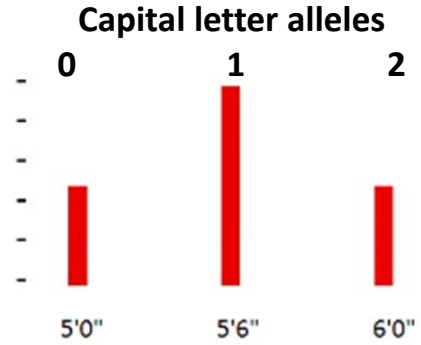


- Resulted in bell curve
  - Only one way to get 5' 0" or 6' 0"
  - Many ways to get 5' 6"
    - Just like test scores! (0 – 100%)

- "Continuous variation" from many genes
  - Despite Mendelian inheritance of each gene involved

Variation becomes apparent in F2 crosses: if 1 gene for "height"

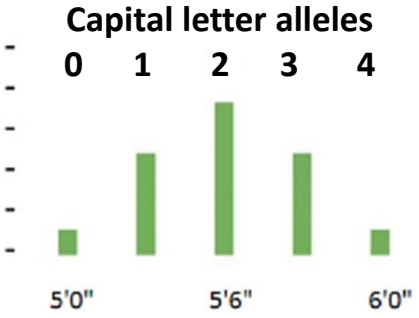
- **Start with homozygous tall AA (6') having kids with homozygous short aa (5')**
- **Offspring all heterozygous (5'6" tall): Aa**
- **What happens in F2?**
  - **Aa x Aa:**
  - **¼ AA, ½ Aa, ¼ aa**



Freeman & Herron Figure 9.2

Variation becomes apparent in F2 crosses: if 2 genes for "height"

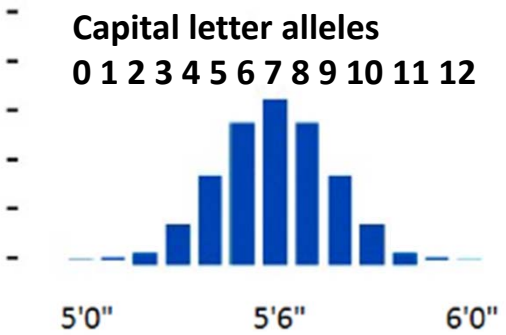
- **Start with homozygous tall AABB (6') having kids with homozygous short aabb (5')**
- **Offspring all heterozygous (5' 6" tall): AaBb**
- **What happens in F2?**
  If unlinked:
  - **Aa x Aa:**
    - **¼ AA, ½ Aa, ¼ aa**
  - **Bb x Bb:**
    - **¼ BB, ½ Bb, ¼ bb**
  - **Get more intermediates:**



Freeman & Herron Figure 9.2

Variation becomes apparent in F2 crosses: if 6 genes for "height"

- Start with homozygous all capitals (6' tall person) having kids with homozygous all lower-case (5' tall person)
- Offspring all heterozygous (5'6" tall): Aa Bb Cc Dd Ee Ff
- What happens in F2?
  - Aa Bb Cc Dd Ee Ff x Aa Bb Cc Dd Ee Ff :
  - If unlinked:
    - MANY possibilities
- Became continuous and bell-shaped



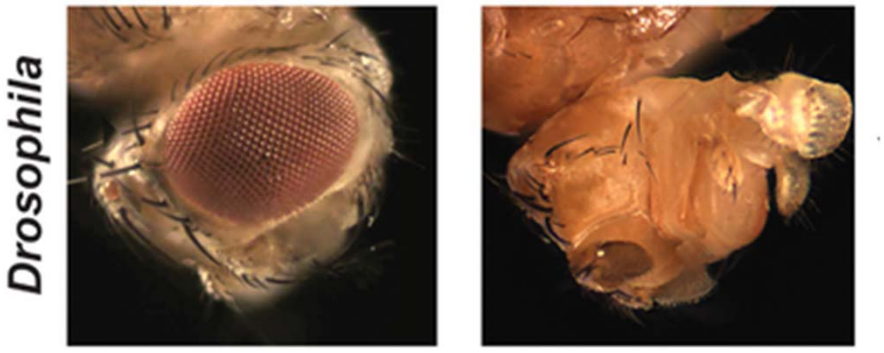
Freeman & Herron Figure 9.2

Why do we see so much variation? Many answers.

- More than one gene controls trait
  - True for almost every phenotype
- Variable “penetrance”
  - Mutant forms may “sometimes” affect phenotype but not always do so.

eyeless mutation in Drosophila

- This mutation has "variable penetrance" in that, some individuals with the mutation, have a normal or nearly-normal phenotype
  - Say the mutation is "not fully penetrant"



BRCA1 breast cancer susceptibility

- In most of population (BB or Bb), low (12%) risk of breast cancer.
- If have 2 mutant alleles at *BRCA1* (bb), 60% risk of breast cancer.
- Therefore, *BRCA1* breast cancer phenotype is **not fully penetrant**- you CAN be "bb" and still have all non-cancerous cells in breast.

Why do we see so much variation? Many answers.

- More than one gene controls trait
  - True for almost every phenotype
- Variable "penetrance"
  - Mutant forms may "sometimes" affect phenotype but not always do so.
- Interactions among genes: "epistasis"
  - Effect of genotype at one gene modifies effects of genotype at another gene.

In this example, effects of alleles at different genes was "additive": sum the effects of A, B, C, etc.

	Person 1	2	3	4	5	6	7
Gene 1	AA	aa	Aa	Aa	aa	Aa	AA
Gene 2	Bb	Bb	BB	Bb	Bb	bb	BB
Gene 3	CC	cc	Cc	CC	Cc	Cc	CC
Gene 4	Dd	Dd	Dd	Dd	Dd	DD	DD
Gene 5	Ee	ee	Ee	EE	Ee	Ee	Ee
Gene 6	ff	ff	ff	Ff	FF	Ff	Ff
Height	5' 7"	5' 2"	5' 6"	5' 8"	5' 6"	5' 6"	5' 10"

Height in inches = 5' 0" + number capital letter alleles
Hence, range 5' 0" – 6' 0"

Example in Pea Flower Color

- Pathway with two genes
  - Precursor $\xrightarrow[\text{C protein}]{}$ step1 $\xrightarrow[\text{P protein}]{}$ step 2, Anthocyanin (color)
- Blocking process at either place results in white peas
  - Homozygous *cc* OR *pp* nonfunctional

		Female Gametes			
		CP	***Cp***	***cP***	***cp***
Male Gametes	***CP***	*CCPP*	*CCPp*	*CcPP*	*CcPp*
	Cp	*CCPp*	*CCpp*	*CcPp*	*Ccpp*
	cP	*CcPP*	*CcPp*	*ccPP*	*ccPp*
	cp	*CcPp*	*Ccpp*	*ccPp*	*ccpp*

Bateson described 9:7 phenotypic ratio

Example in mouse coat color

- A dominant over a; B dominant over b

A – B –	color agouti
A – bb	color albino
aa B –	color black
aa bb	color albino (again)

- AA vs aa may be agouti vs. black, OR modified by “bb” to albino

How does epistasis happen?

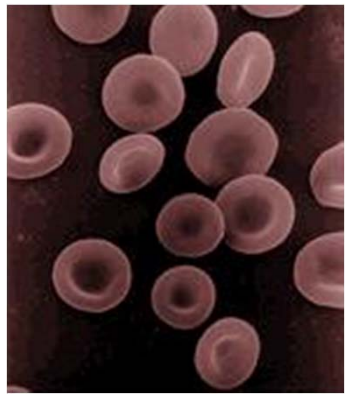
- One possibility: 2 genes
  - Gene 1 (B) is a "switch" that turns on gene 2
    - 2 variants: ON (B-) vs. OFF (bb)
  - Gene 2 (A) affects deposition of coat color
    - 2 variants: one causes deposit of black, other brown
- AA vs. aa cause deposition of black vs. brown
  - BUT, if bb, then no deposition at all →
  - Genotype at B *modifies* effect of genotype at A (and sometimes eliminates its effect)

Why do we see so much variation? Many answers.

- More than one gene controls height
  - True for almost every phenotype
- Variable "penetrance"
  - Mutant forms may "sometimes" affect phenotype but not always do so.
- Interactions among genes: "epistasis"
  - Effect of genotype at one gene modifies effects of genotype at another gene.
- There can be >2 alleles at a locus!

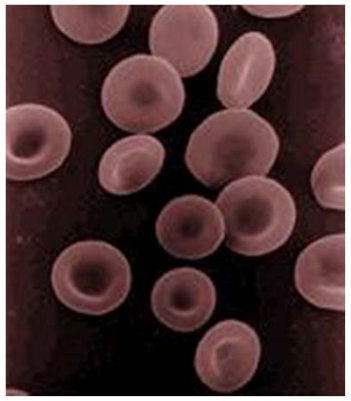
Classic example: ABO blood types

- Gene located on chromosome 9 in humans
- Three **alleles**, A and B are dominant over O
  - A and B create specific antigens, O doesn't
- Blood phenotypes: A, B, AB, or O
- Blood genotypes: AA, AO, BB, BO, AB, OO
- If get transfusion, reject if receive blood with foreign antigen
  - O blood is best to donate
  - AB best to receive blood transfusion



Classic example: ABO blood types

- Three alleles, A and B are dominant over O
  - A and B create specific antigens, O doesn't
- Blood phenotypes: A, B, AB, or O
- Blood genotypes: AA, AO, BB, BO, AB, OO
- Inheritance is as we've studied for single genes:



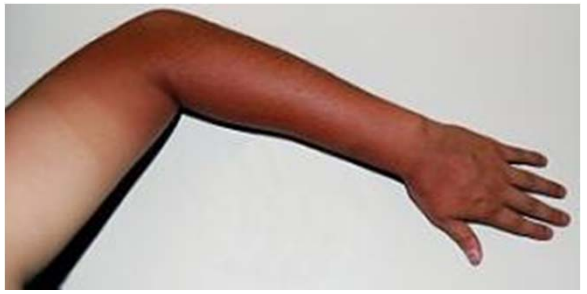
♂ \ ♀	A	O
B	AB	BO
O	AO	OO

Why do we see so much variation? Many answers.

- More than one gene controls trait
- Variable “penetrance”
- Interactions among genes: “epistasis”
- There can be >2 alleles at a locus
- **Environment, and interactions with it.**
  - We will begin “heritability” soon…

Environment can affect phenotypes (duh!)

- Can affect directly, or can interact with genotype



- Example- sun tanning
  - In absence of sun, don't tan
    - (Environmental effect)
  - Some people naturally tan easier than others
    - (Interaction of environment with genetics)

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