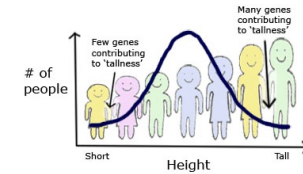


## Module – Complex Trait (Quantitative) Genetics



*Lecture 13— When many genes and many environmental effects influence trait expression and variation*

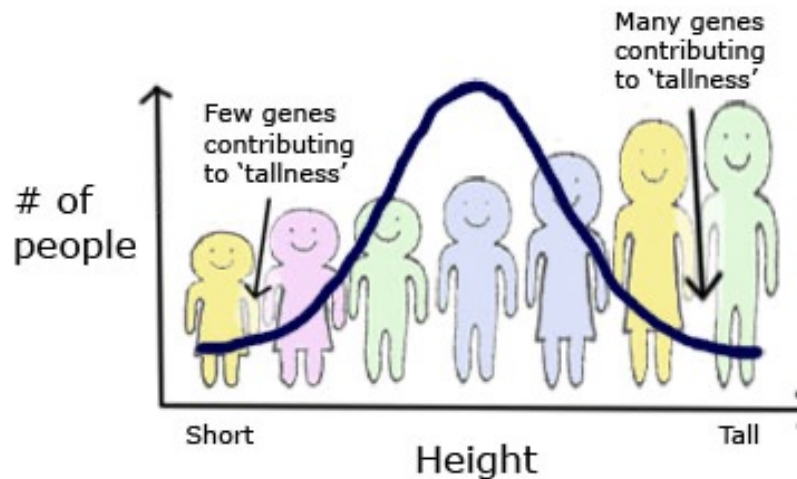
1. Complex trait variation (Ch19 Section 1)
2. Measuring components of phenotypic trait variation (Ch19 Sections 2,3)
3. Quantitative trait loci: Using molecular markers to infer the presence of genes affecting genetic variance (Ch19 Sections 4,5)

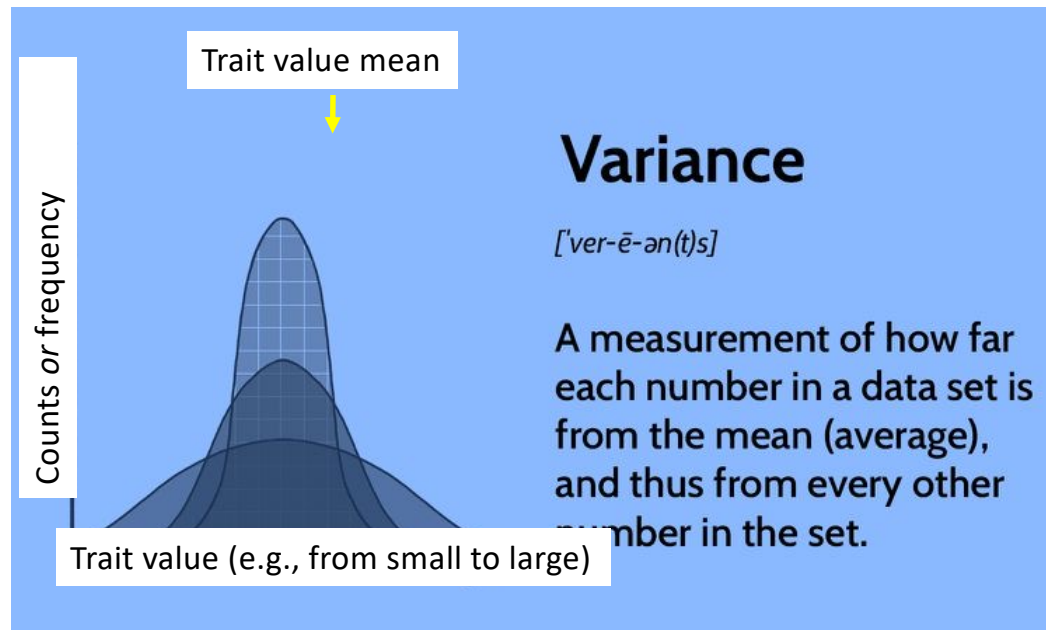
**PRIMER**—Quantitative Genetics (see myCourses page for Biology 202)

**Self-Assessment Exercise 2: Wed, 5 February at 08h55-09h25**

# Module: Complex trait genetics

*Lecture 13— When many genes and many environmental effects influence trait expression and variation*





*Sample variance*

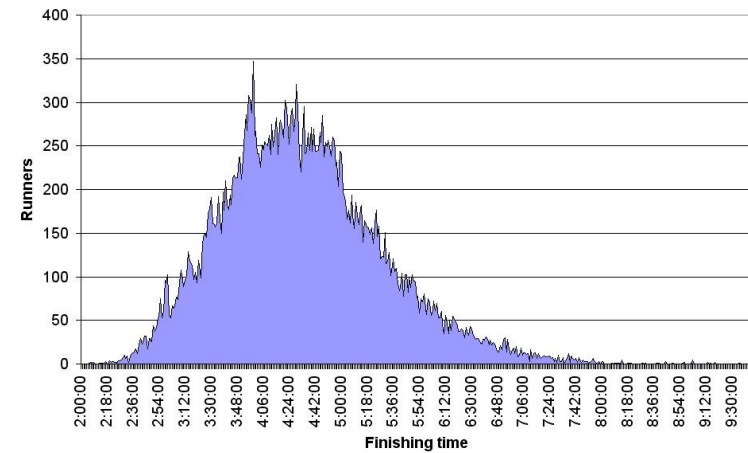
$$S^2 = \frac{\sum (x_i - \bar{x})^2}{n - 1}$$

# Types of complex traits

## Continuous



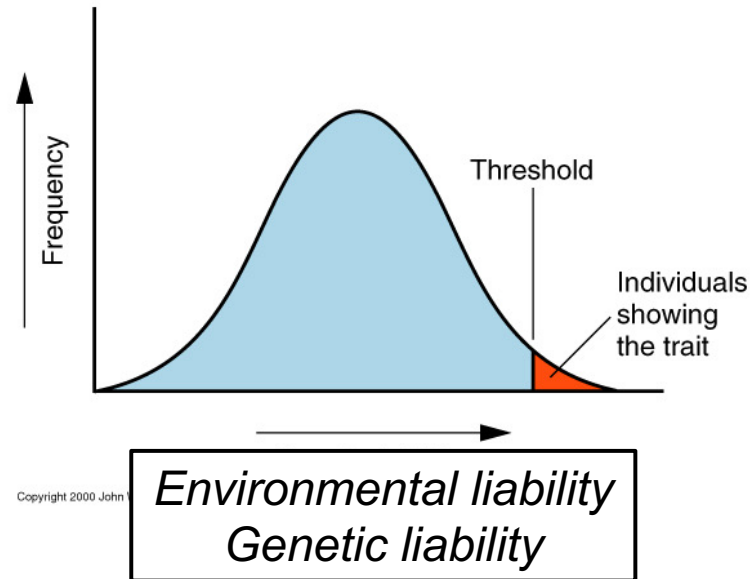
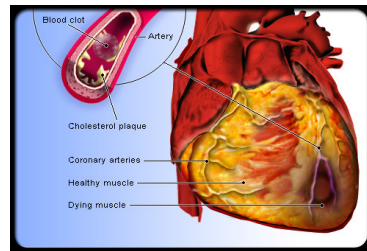
*Body size (height)*



*Running speed  
(e.g., finishing time in a marathon)*

## Types of complex traits

### Threshold (“either / or”)

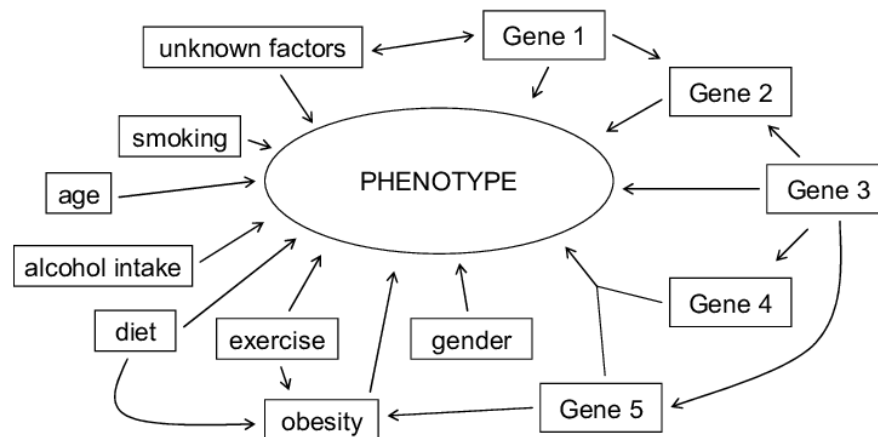


Threshold traits  
(e.g., cancers, heart diseases)

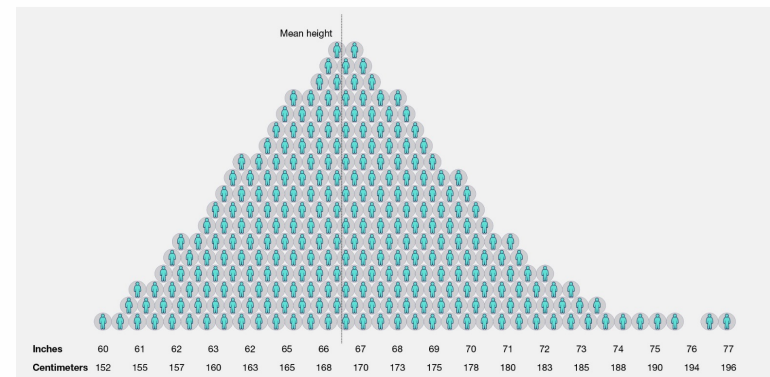
# The “Multifactorial Model” for complex trait variation

## ENVIRONMENTAL FACTORS

## GENETIC FACTORS

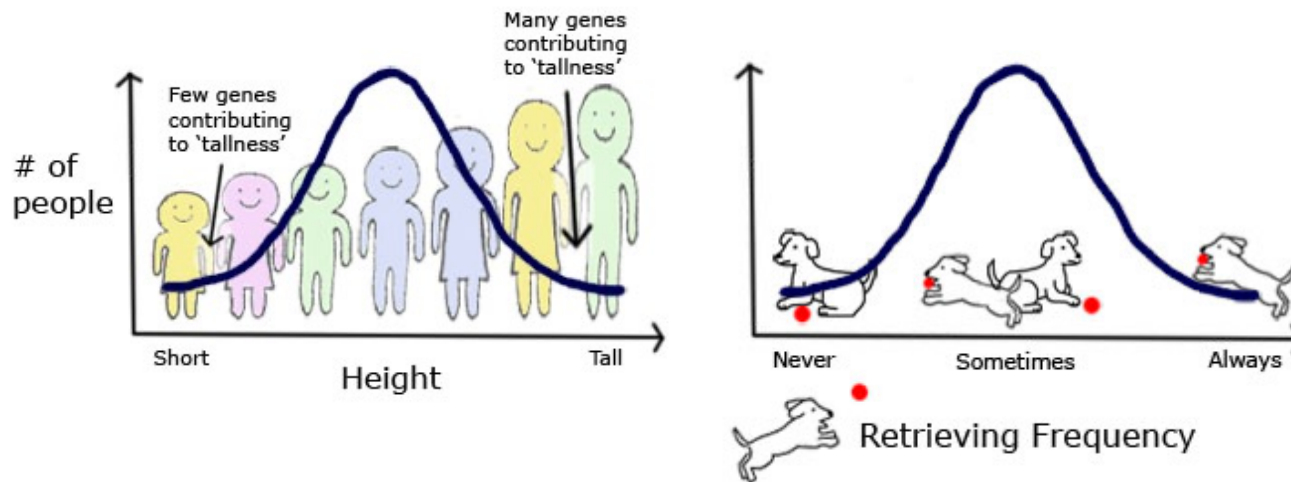


Phenotypic variance is the observed variability of a particular trait. For many measurable traits (such as height, skin color, and blood pressure) phenotypic variation can be thought of as a distribution. The variation within that distribution centers on an average or mean. Phenotypic variance is often caused by a combination of genetic and environmental factors.



# Complex (quantitative) trait genetics

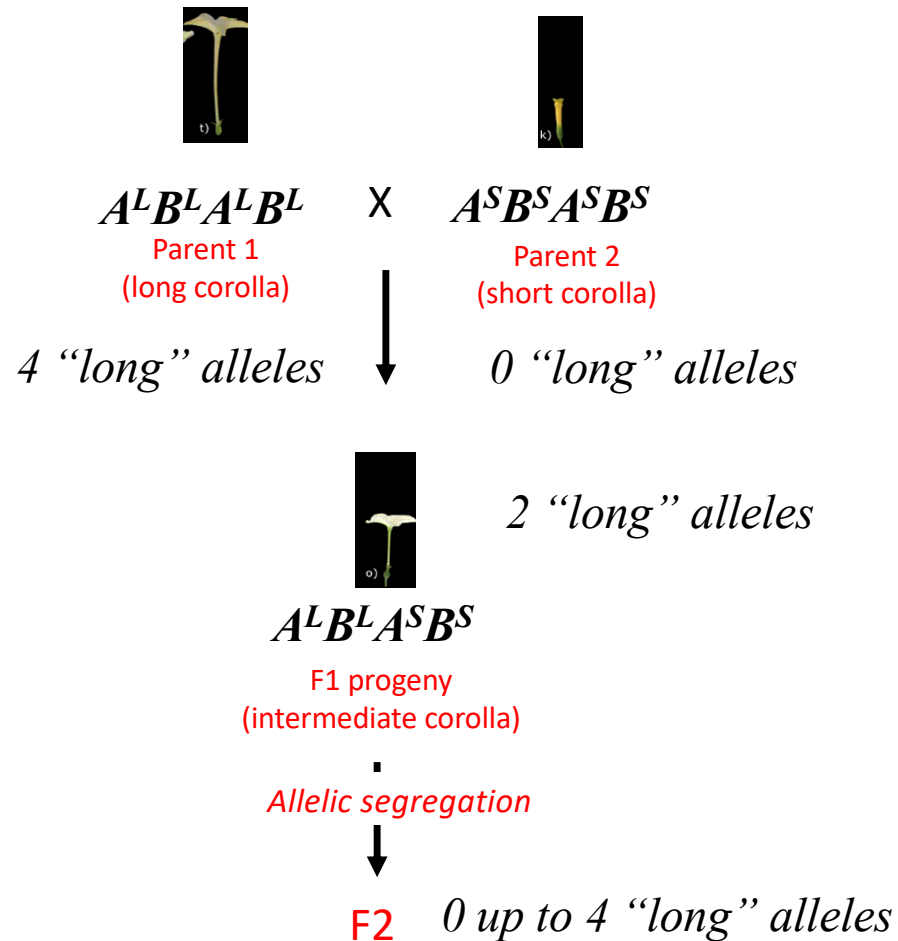
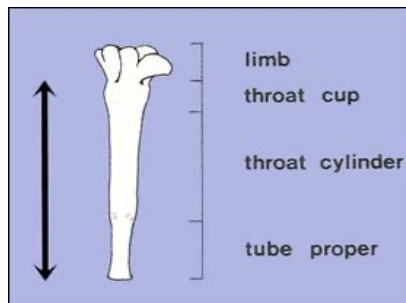
The nature of quantitative variation:  
Distribution of phenotypic states is often “bell-shaped”



Why do complex traits usually show bell-shaped distributions?



Tobacco



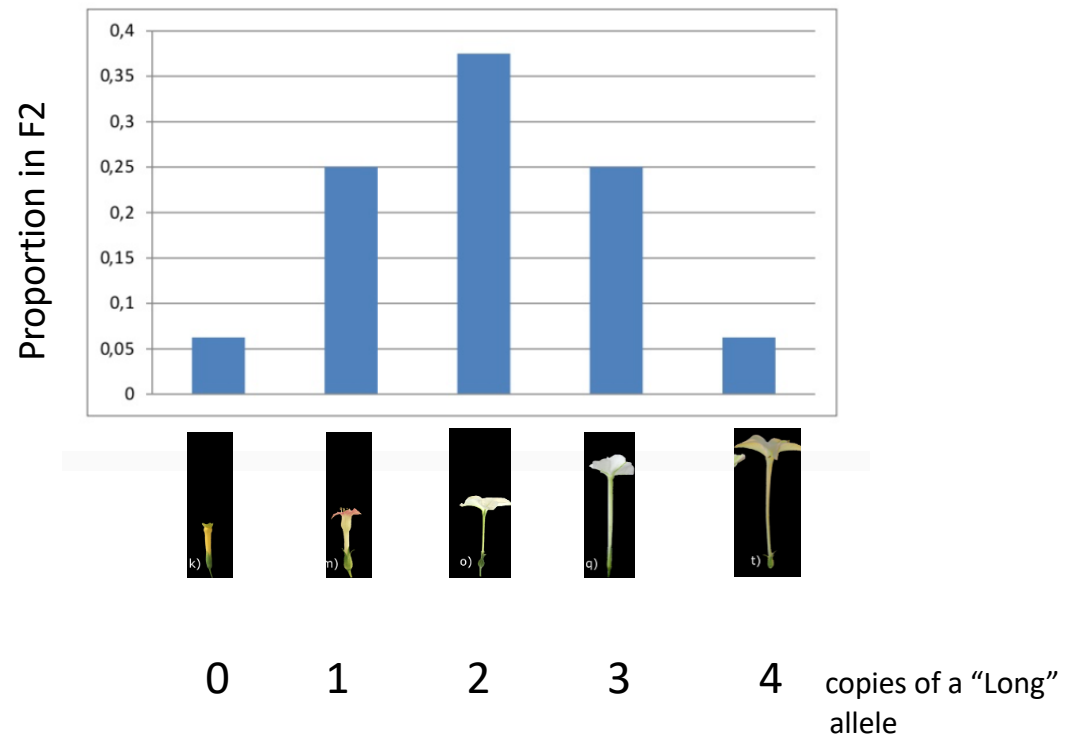


F2 generation

$$A^L B^L A^S B^S \times A^L B^L A^S B^S$$

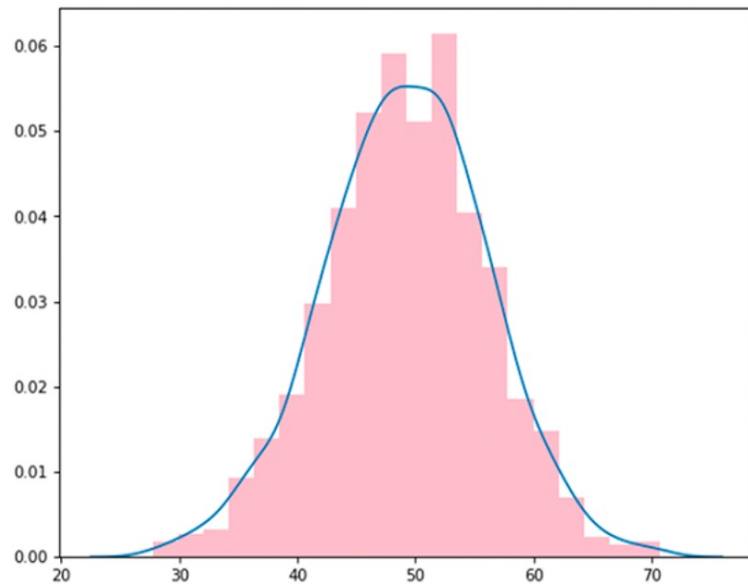
	$A^L B^L$	$A^L B^S$	$A^S B^L$	$A^S B^S$
$A^L B^L$	4	3	3	2
$A^L B^S$	3	2	2	1
$A^S B^L$	3	2	2	1
$A^S B^S$	2	1	1	0

Number of “Long” alleles



Why do complex traits usually show bell-shaped distributions?

*(apart from the genetics, there are often many environmental effects)*

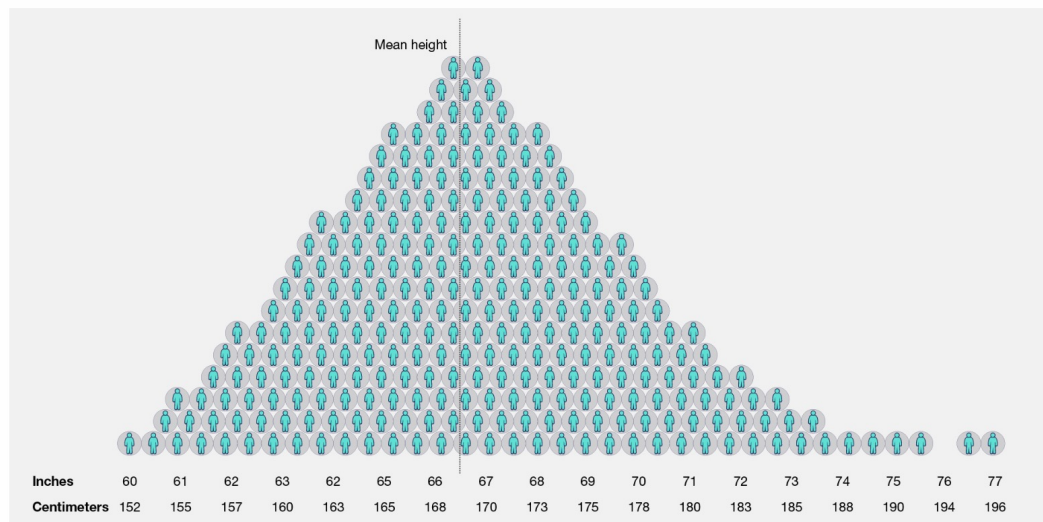


The **Central Limit Theorem** is a statistical principle stating that, under certain conditions, the distribution of the sum of a large number of independent and identically distributed random variables tends to approach a normal distribution, regardless of the original distribution's shape.

When we look at a population, we can measure the PHENOTYPIC variance

*(that phenotypic variance is usually the sum of both genetic and environmental variances)*

Phenotypic variance is the observed variability of a particular trait. For many measurable traits (such as height, skin color, and blood pressure) phenotypic variation can be thought of as a distribution. The variation within that distribution centers on an average or mean. Phenotypic variance is often caused by a combination of genetic and environmental factors.

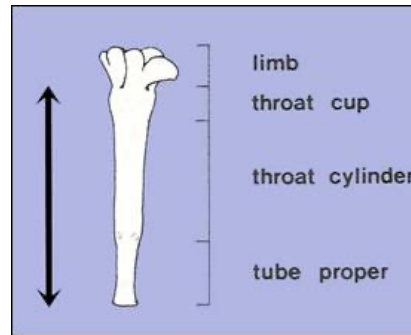


## The variance of a complex trait:

An **experiment** to estimate the genetic and environmental variances

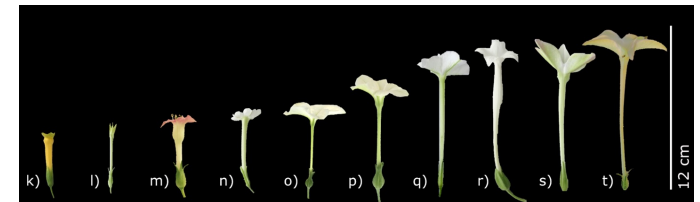
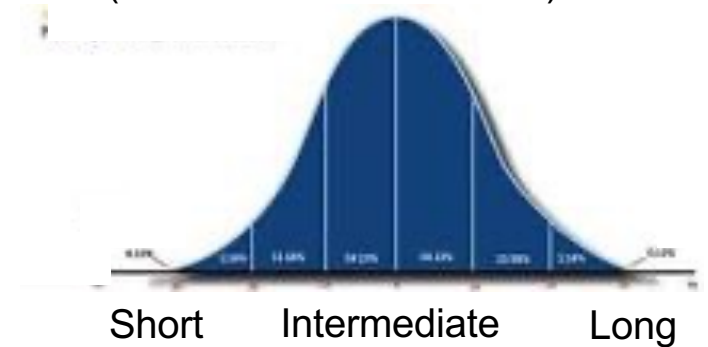


Tobacco

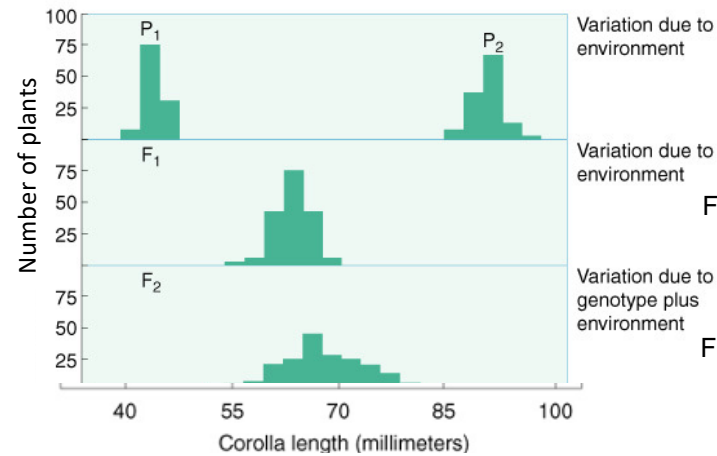


*Complex trait=*  
*Corolla length*

Corolla length in wild tobacco:  
(a **continuous** distribution)



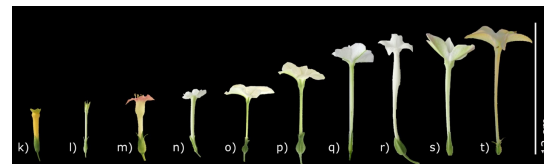
## Tobacco corolla length phenotypic variance ( $V_x$ )



P<sub>1</sub> and P<sub>2</sub> are **different inbred lines**  
 ( genetically homozygous... at some loci  
they will be homozygous for different alleles )

F<sub>1</sub> **hybrid** is heterozygous for alleles that differ in P<sub>1</sub> and P<sub>2</sub>.

F<sub>2</sub> progeny **segregate** for alleles that differ in P<sub>1</sub> and P<sub>2</sub>.



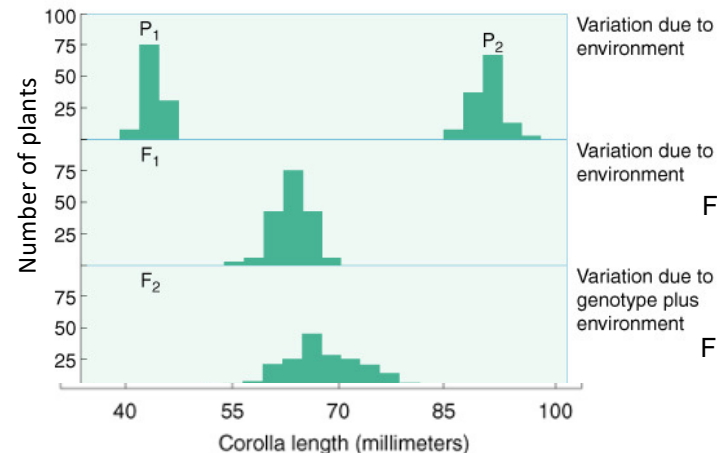
## Tobacco corolla length phenotypic variance ( $V_x$ )

### Source(s) of variance

**Parents:** Environmental differences between individuals

**$F_1$ :** Environmental differences between individuals

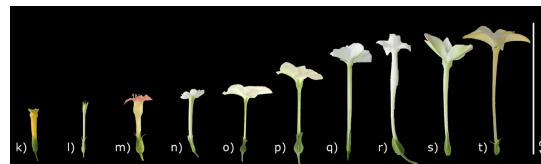
**$F_2$ :** Environmental differences between individuals  
**AND**  
 genetic differences between individuals



P<sub>1</sub> and P<sub>2</sub> are **different inbred lines**  
 ( genetically homozygous...though at some loci they will be homozygous for different alleles )

F<sub>1</sub> **hybrid** is heterozygous for alleles that differ in P<sub>1</sub> and P<sub>2</sub>.

F<sub>2</sub> progeny **segregate** for alleles that differ in P<sub>1</sub> and P<sub>2</sub>.



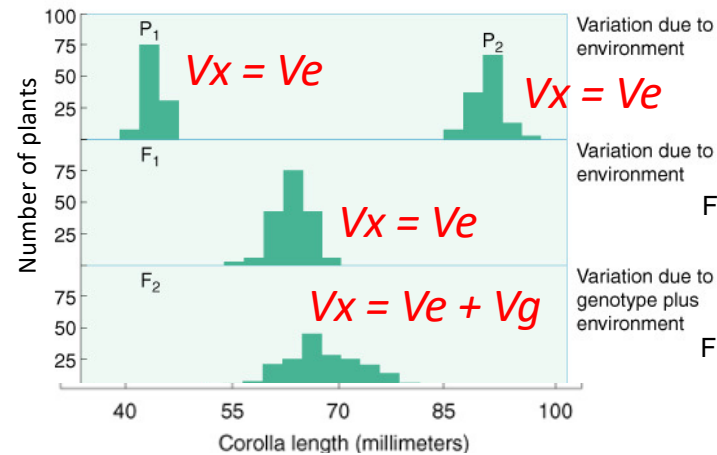
## Tobacco corolla length phenotypic variance ( $V_x$ )

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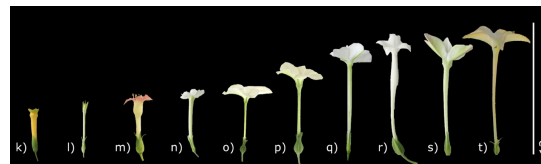
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F<sub>1</sub> **hybrid** is heterozygous for alleles that differ in P<sub>1</sub> and P<sub>2</sub>.

F<sub>2</sub> **progeny** segregate for alleles that differ in P<sub>1</sub> and P<sub>2</sub>.



# Heritability

broad sense

$$H^2 = \frac{V_g}{V_X}$$

- Bounded by 0 and 1
- Dimensionless
- Standardized parameter
- Comparable across traits / species



You have a population of genetically identical mice of strain A. You also have a second population of genetically identical mice of strain B. The mean and variance of body weight of the strain A population are 30 g and 400 squared grams, respectively, while the mean and variance of body weight of strain B are 10 g and 400 squared grams, respectively.

You cross the strains to obtain an F1, which you allow to *interbreed*, and then raise the F2 progeny. The mean and variance of body weight of the F2 population is 20 g and 1200 squared grams. **What is the broad-sense heritability of body weight?**

- a. 0.67
- b. 0.50
- c. 0.33
- d. 0.25

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- a. 0.67
- b. 0.50
- c. 0.33
- d. 0.25

ANSWER:

$V_e = 400$  squared grams (e.g., from the parents who are inbred lines)  
 $V_x = 1200$  squared grams (from the F2 population)

We know that  $V_x = V_e + V_g$ , and so (by subtraction)  $V_g = 800$  squared grams  
 $H^2$  is defined as  $V_g/V_x$ , and so,  $H^2 = 800/1200 = 2/3$  or *ca. 0.67*

# Heritability

broad sense

$$H^2 = \frac{V_g}{V_X}$$

- Bounded by 0 and 1
- Dimensionless
- Standardized parameter
- Comparable across traits / species

# Heritability Estimation in Humans: Twin Studies



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Twin 1      Twin 2



Twin Sisters Separated at Birth Reunite

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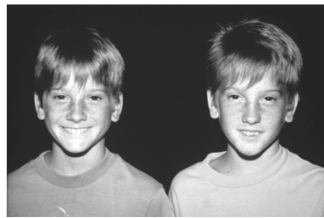
Twin 1      Twin 2

**Table 19-4** Broad-Sense Heritability for Some Traits in Humans as Determined by Twin Studies

Trait	$H^2$
<b>Physical attributes</b>	
Height	0.88
Chest circumference	0.61
Waist circumference	0.25
Fingerprint ridge count	0.97
Systolic blood pressure	0.64
Heart rate	0.49
<b>Mental attributes</b>	
IQ	0.69
Speed of spatial processing	0.36
Speed of information acquisition	0.20
Speed of information processing	0.56
<b>Personality attributes</b>	
Extraversion	0.54
Conscientiousness	0.49
Neuroticism	0.48
Positive emotionality	0.50
Antisocial behavior in adults	0.41
<b>Psychiatric disorders</b>	
Autism	0.90
Schizophrenia	0.80
Major depression	0.37
Anxiety disorder	0.30
Alcoholism	0.50–0.60
<b>Beliefs and political attitudes</b>	
Religiosity among adults	0.30–0.45
Conservatism among adults	0.45–0.65
Views of school prayer	0.41
Views on pacifism	0.38

Sources: J. R. Alford et al., *American Political Science Review* 99, 2005, 1–15; T. Bouchard et al., *Science* 250, 1990, 223–228; T. Bouchard, *Curr. Dir. Psych. Sci.* 13, 2004, 148–151; P. J. Clark, *Am. J. Hum. Genet.* 7, 1956, 49–54; C. M. Freitag, *Mol. Psychiatry* 12, 2007, 2–22.

# MZ and DZ twins



Identical

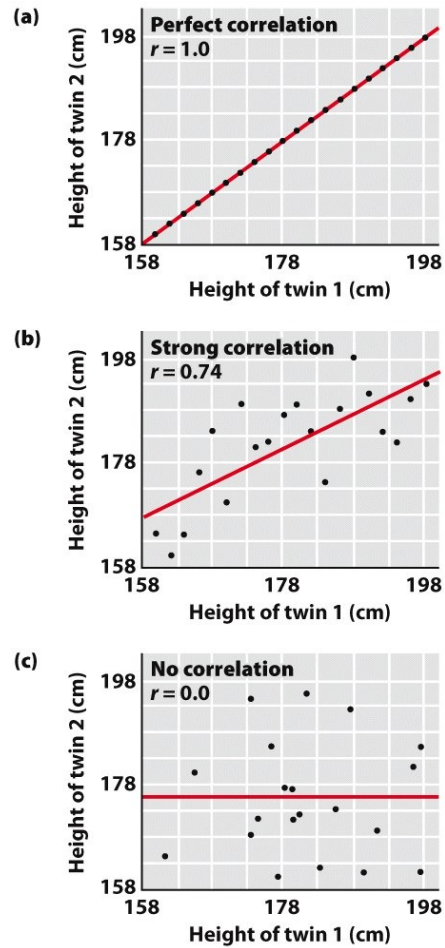


Fraternal: Same-Sex

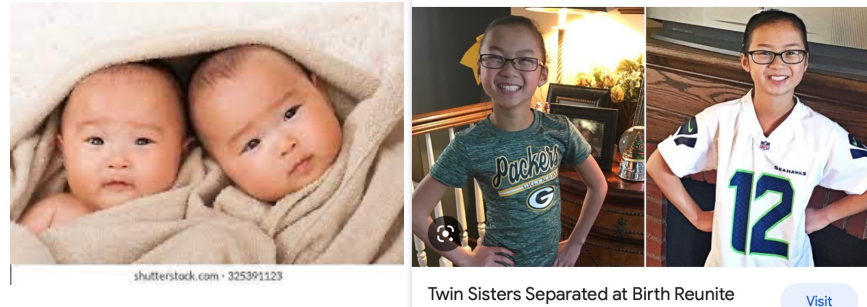


Fraternal: Opposite-Sex

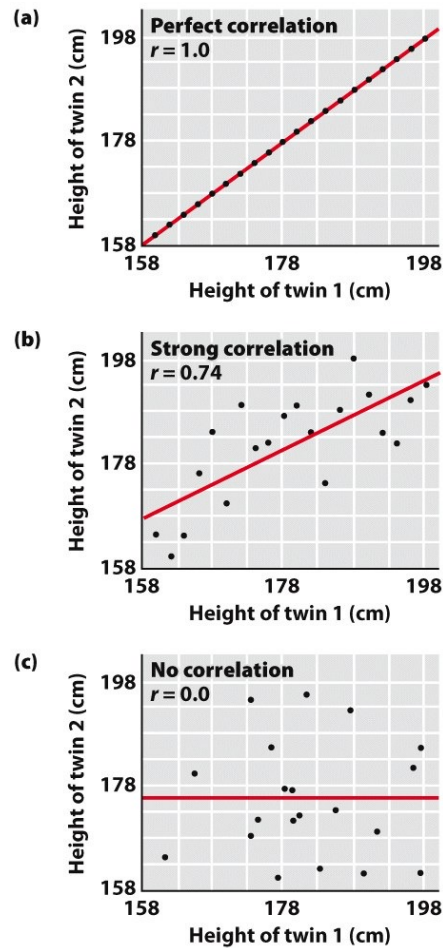
FIGURE 1. The study of twins. Photo credit: Nancy Segal.



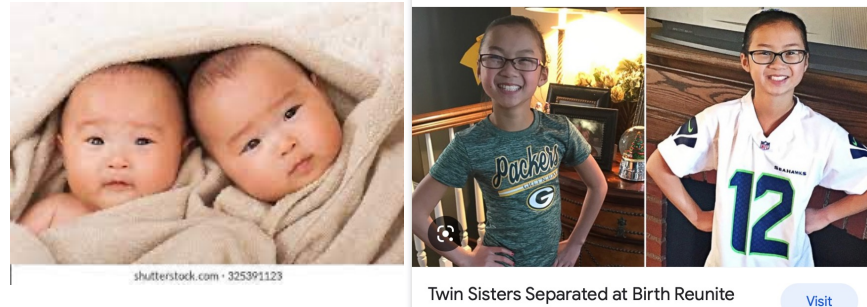
**Figure 19-4**  
*Introduction to Genetic Analysis*, Tenth Edition  
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## ***TWIN STUDIES: Correlation and Broad Sense Heritability***



**Figure 19-4**  
*Introduction to Genetic Analysis*, Tenth Edition  
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## ***TWIN STUDIES***

### ***Correlation and***

### ***Broad Sense Heritability***

$$r = \frac{\sum (x_i - \bar{x})(y_i - \bar{y})}{\sqrt{\sum (x_i - \bar{x})^2 \sum (y_i - \bar{y})^2}}$$

$r$  = correlation coefficient

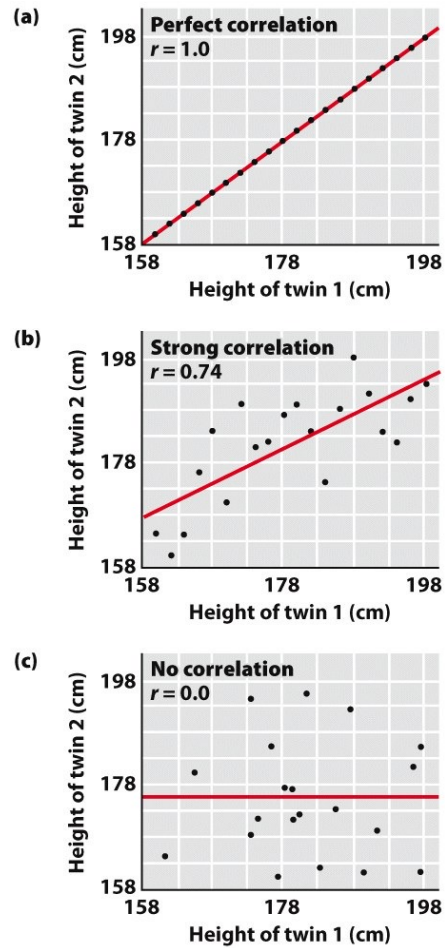
$x_i$  = values of the x-variable in a sample

$\bar{x}$  = mean of the values of the x-variable

$y_i$  = values of the y-variable in a sample

$\bar{y}$  = mean of the values of the y-variable





**Figure 19-4**  
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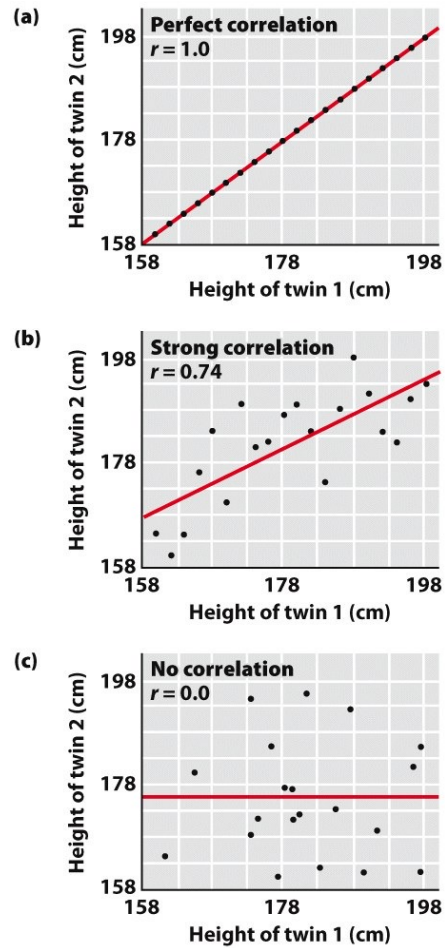
Twin Sisters Separated at Birth Reunite

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## ***TWIN STUDIES***

### ***Correlation and Broad Sense Heritability***





**Figure 19-4**  
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Twin Sisters Separated at Birth Reunite

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## ***TWIN STUDIES***

### ***Correlation and Broad Sense Heritability***

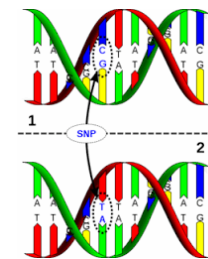
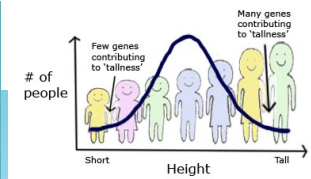
**Table 19-4 Broad-Sense Heritability for Some Traits in Humans as Determined by Twin Studies**

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# ***Complex trait genomics***

## **THE NEW FRONTIER**

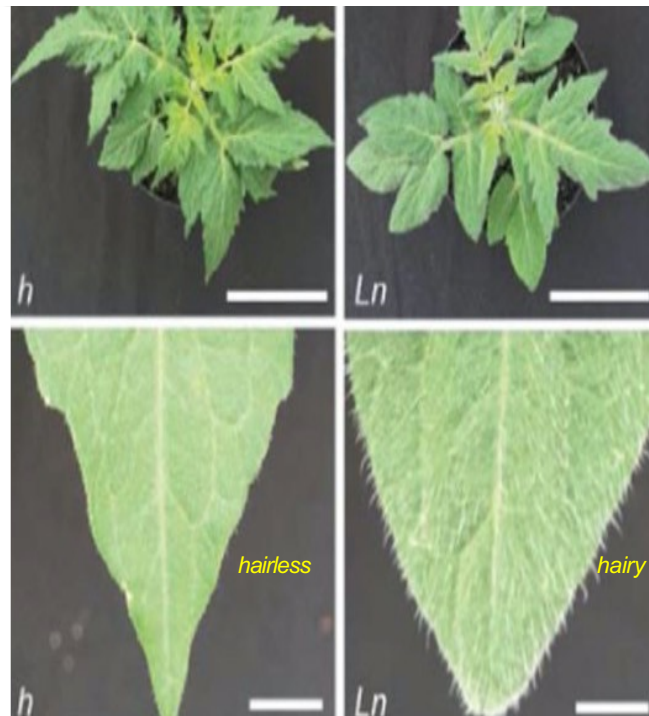


# Using molecular markers to infer the presence and effects of genes that influence genetic variance (QTL and GWAS)



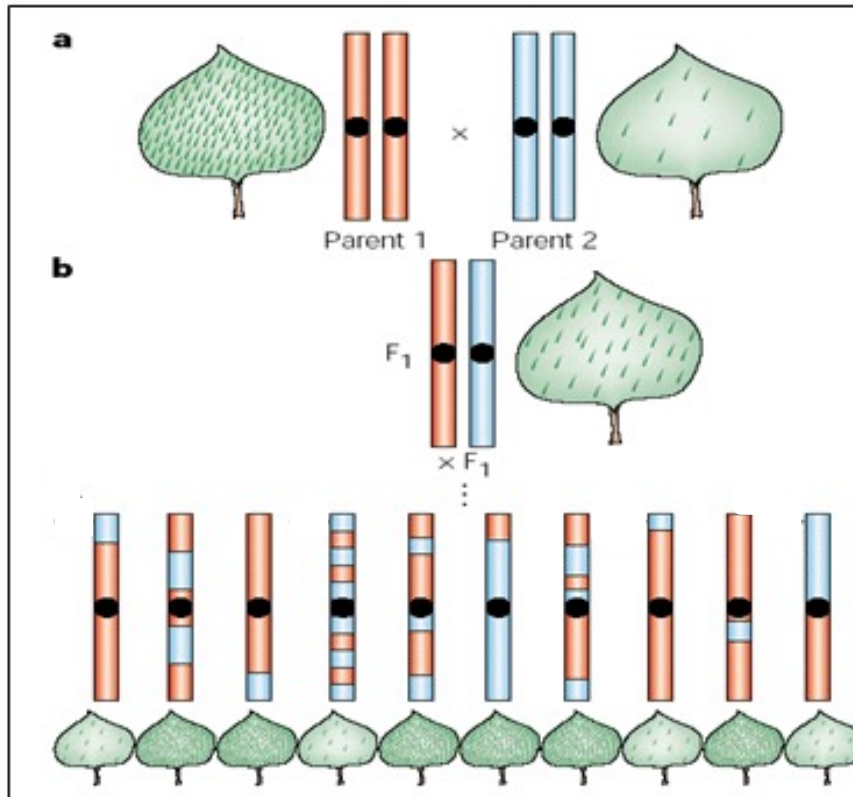
- **QTL mapping**...resembles classical mapping approaches (controlled crosses used)...**co-segregation of a marker with a trait's phenotypic** value helps you to locate the region of the genome where a gene with influence on the phenotype resides....there may be many such genes (called quantitative trait loci or QTL's)
- **Association mapping** or **genome-wide association studies (GWAS)**...relies on population surveys that look for correlation between markers and phenotypic trait values in samples taken from large populations.

**Principles of QTL mapping:** Co-segregation (co-inheritance) of phenotypes and marker alleles (*usually SNPs*)



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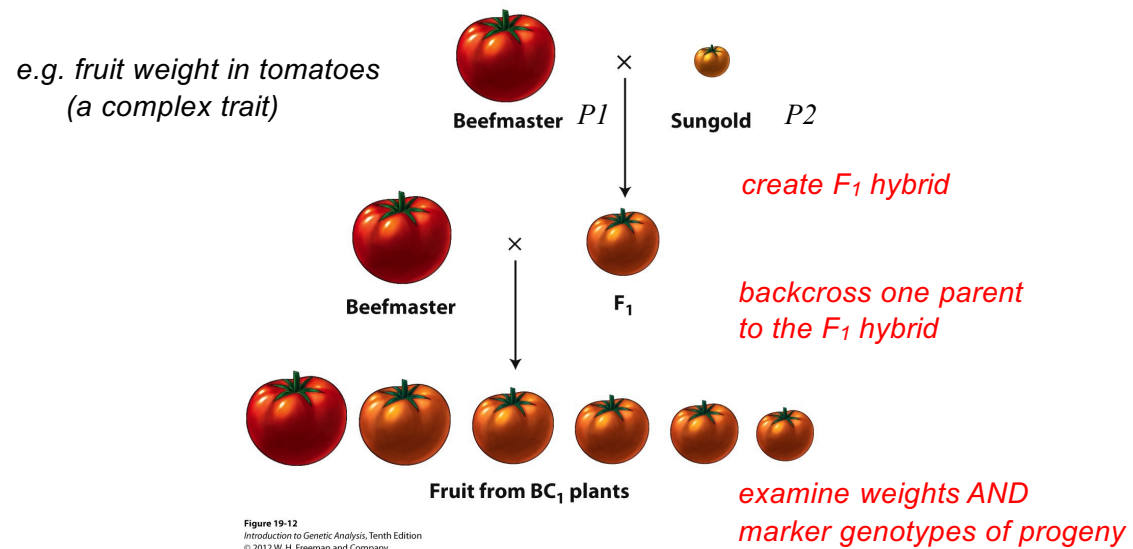
QTL mapping.....the basic approach:



Where is the gene that influences “hairiness”?

- A. At the bottom of the chromosome.
- B. In the middle of the chromosome.
- C. At the top of the chromosome.
- D. Can't tell from the information.

QTL mapping begins with crosses of **two inbred lines**  
(that differ in the trait of interest and their molecular marker genotypes)



## QTL mapping

(Parents are homozygous for different "marker" alleles)

Markers (e.g., SNPs, Microsatellites, etc. on a **chromosome segment**)

**Positions of markers**

<i>M1</i> .....	<i>M2</i> .....	<i>M3</i> .....	<i>M4</i> .....	<i>M5</i>
-----------------	-----------------	-----------------	-----------------	-----------

Beefmaster alleles:

<i>B/B</i> .....	<i>B/B</i> .....	<i>B/B</i> .....	<i>B/B</i> .....	<i>B/B</i>
------------------	------------------	------------------	------------------	------------

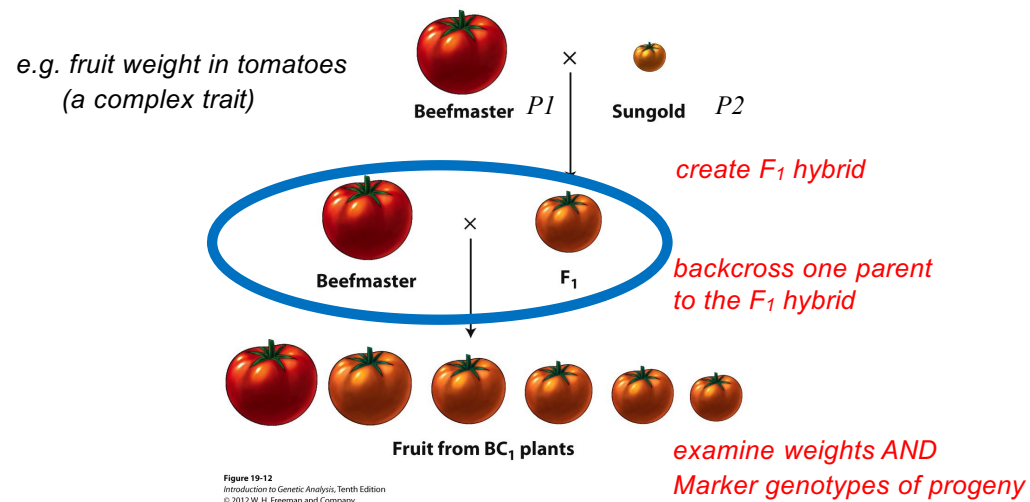
Sungold alleles:

<i>S/S</i> .....	<i>S/S</i> .....	<i>S/S</i> .....	<i>S/S</i> .....	<i>S/S</i>
------------------	------------------	------------------	------------------	------------

Genes (QTLs) affecting the complex trait (fruit weight) could be anywhere in the chromosome segment...but **WHERE** are they and what are their effects?



QTL mapping begins with crosses of two inbred lines  
(that differ in the trait of interest and their molecular marker genotypes)



## QTL mapping (Recombination in F1 and crossovers)

Markers (e.g., SNPs, Microsatellites, etc.)

<i>M1</i>	<i>M2</i>	<i>M3</i>	<i>M4</i>	<i>M5</i>
-----------	-----------	-----------	-----------	-----------

*F1*

<i>B</i>	<i>B</i>	<i>B</i>	<i>B</i>	<i>B</i>
<i>S</i>	<i>S</i>	<i>S</i>	<i>S</i>	<i>S</i>

*X*

*Beefmaster*

<i>B</i>	<i>B</i>	<i>B</i>	<i>B</i>	<i>B</i>
<i>B</i>	<i>B</i>	<i>B</i>	<i>B</i>	<i>B</i>



**Table 19-6** Simulated Fruit Weight and Marker-Locus Data for a Backcross Population between Two Tomato Inbred Lines—Beefmaster and Sungold

Plant	Fruit wt. (g)	Markers				
		M1	M2	M3	M4	M5
Beefmaster	230	B/B	B/B	B/B	B/B	B/B
Sungold	10	S/S	S/S	S/S	S/S	S/S
BC <sub>1</sub> -001	183	B/B	B/B	B/B	B/S	B/S
BC <sub>1</sub> -002	176	B/S	B/S	B/B	B/B	B/B
BC <sub>1</sub> -003	170	B/B	B/S	B/S	B/S	B/S
BC <sub>1</sub> -004	185	B/B	B/B	B/B	B/S	B/S
BC <sub>1</sub> -005	182	B/B	B/B	B/B	B/B	B/B
BC <sub>1</sub> -006	170	B/S	B/S	B/S	B/S	B/B
BC <sub>1</sub> -007	170	B/B	B/S	B/S	B/S	B/S
BC <sub>1</sub> -008	174	B/S	B/S	B/S	B/S	B/S
BC <sub>1</sub> -009	171	B/S	B/S	B/S	B/B	B/B
BC <sub>1</sub> -010	180	B/S	B/S	B/B	B/B	B/B
BC <sub>1</sub> -011	185	B/S	B/B	B/B	B/S	B/S
BC <sub>1</sub> -012	169	B/S	B/S	B/S	B/S	B/S
BC <sub>1</sub> -013	165	B/B	B/B	B/S	B/S	B/S
BC <sub>1</sub> -014	181	B/S	B/S	B/B	B/B	B/S
BC <sub>1</sub> -015	169	B/S	B/S	B/S	B/B	B/B
BC <sub>1</sub> -016	182	B/B	B/B	B/B	B/S	B/S
BC <sub>1</sub> -017	179	B/S	B/S	B/B	B/B	B/B
BC <sub>1</sub> -018	182	B/S	B/B	B/B	B/B	B/B
BC <sub>1</sub> -019	168	B/S	B/S	B/S	B/B	B/B
BC <sub>1</sub> -020	173	B/B	B/B	B/B	B/B	B/B
Mean of B/B	-	176.3	179.6	180.7	176.1	175.0
Mean of B/S	-	175.3	173.1	169.6	175.3	176.4
Overall mean	175.7					

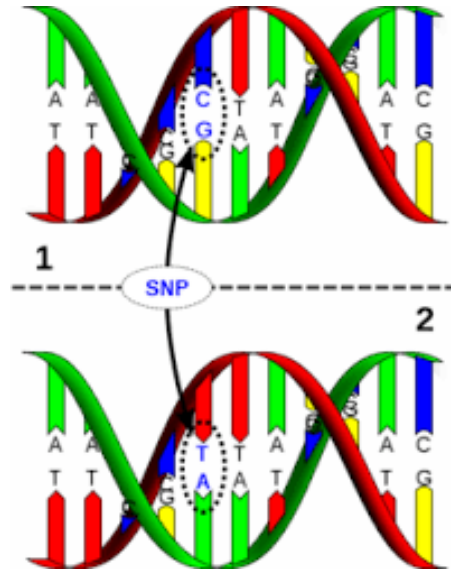
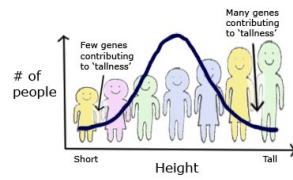
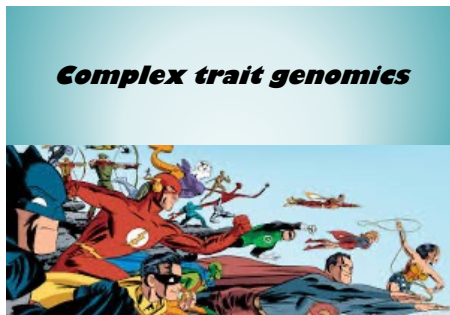
*QTL mapping (Recombination in F1 and crossovers)*

**Table 19-6** Simulated Fruit Weight and Marker-Locus Data for a Backcross Population between Two Tomato Inbred Lines—Beefmaster and Sungold

Plant	Fruit wt. (g)	Markers				
		M1	M2	M3	M4	M5
Beefmaster	230	B/B	B/B	B/B	B/B	B/B
Sungold	10	S/S	S/S	S/S	S/S	S/S
BC <sub>1</sub> -001	183	B/B	B/B	B/B	B/S	B/S
BC <sub>1</sub> -002	176	B/S	B/S	B/B	B/B	B/B
BC <sub>1</sub> -003	170	B/B	B/S	B/S	B/S	B/S
BC <sub>1</sub> -004	185	B/B	B/B	B/B	B/S	B/S
BC <sub>1</sub> -005	182	B/B	B/B	B/B	B/B	B/B
BC <sub>1</sub> -006	170	B/S	B/S	B/S	B/S	B/B
BC <sub>1</sub> -007	170	B/B	B/S	B/S	B/S	B/S
BC <sub>1</sub> -008	174	B/S	B/S	B/S	B/S	B/S
BC <sub>1</sub> -009	171	B/S	B/S	B/S	B/B	B/B
BC <sub>1</sub> -010	180	B/S	B/S	B/B	B/B	B/B
BC <sub>1</sub> -011	185	B/S	B/B	B/B	B/S	B/S
BC <sub>1</sub> -012	169	B/S	B/S	B/S	B/S	B/S
BC <sub>1</sub> -013	165	B/B	B/B	B/S	B/S	B/S
BC <sub>1</sub> -014	181	B/S	B/S	B/B	B/B	B/S
BC <sub>1</sub> -015	169	B/S	B/S	B/S	B/B	B/B
BC <sub>1</sub> -016	182	B/B	B/B	B/B	B/S	B/S
BC <sub>1</sub> -017	179	B/S	B/S	B/B	B/B	B/B
BC <sub>1</sub> -018	182	B/S	B/B	B/B	B/B	B/B
BC <sub>1</sub> -019	168	B/S	B/S	B/S	B/B	B/B
BC <sub>1</sub> -020	173	B/B	B/B	B/B	B/B	B/B
Mean of B/B	-	176.3	179.6	180.7	176.1	175.0
Mean of B/S	-	175.3	173.1	169.6	175.3	176.4
Overall mean	175.7					

Where is the gene that influences tomato size?

- A. Near SNP1
- B. Near SNP2
- C. Near SNP3
- D. Near SNP4
- E. Near SNP5



## Main points—Complex traits

- Complex traits show continuous variation or liability
- Many genes and many environmental effects affect complex phenotypes
- We are interested in quantifying how much of the overall phenotypic variation for the trait is due to variation in the genetic make-up of individuals (the **heritability** of the trait)
- QTL analysis allow us to map genes that influence complex trait variation, and to assess their effects.