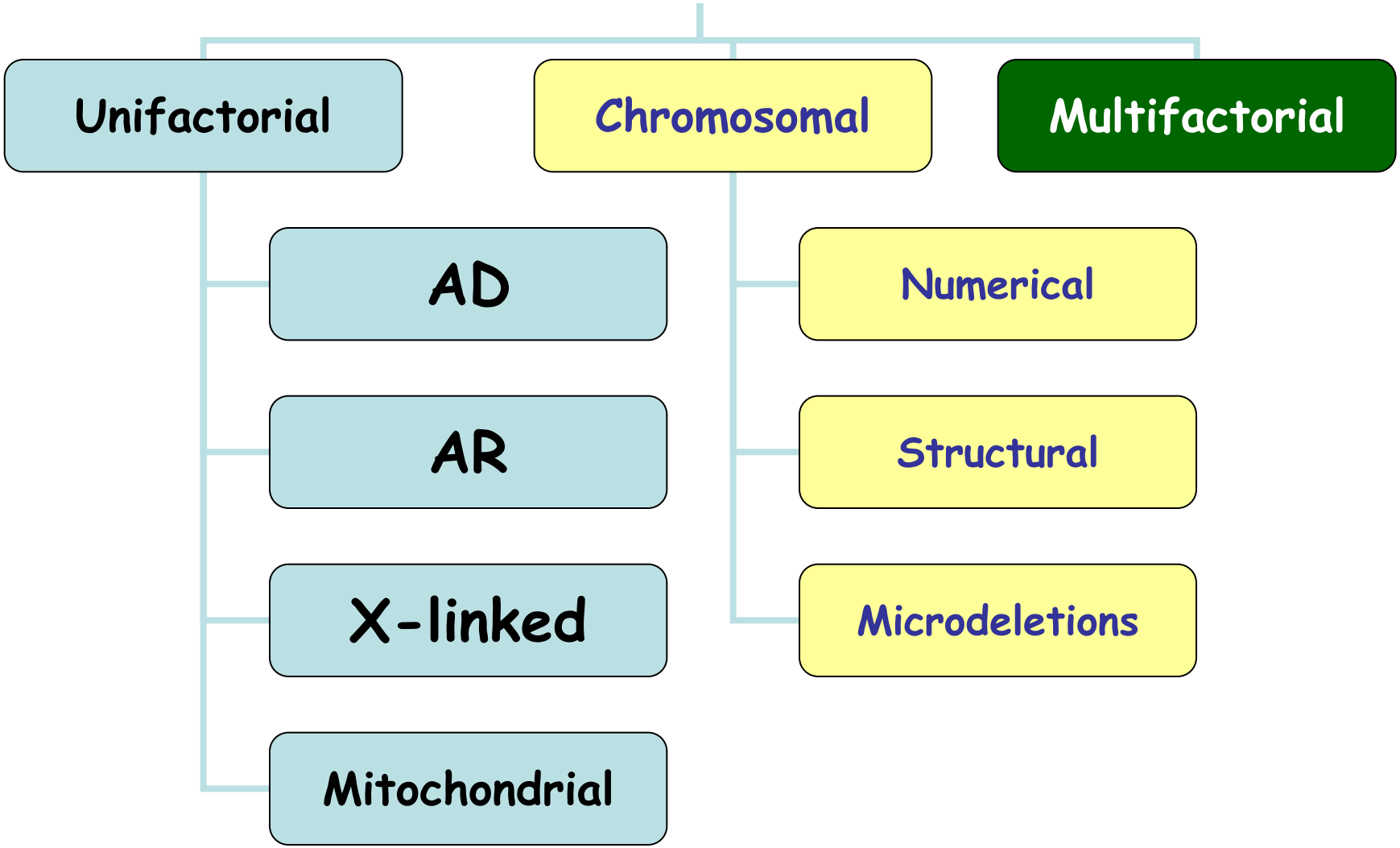
MULTIFACTORIAL DISEASES

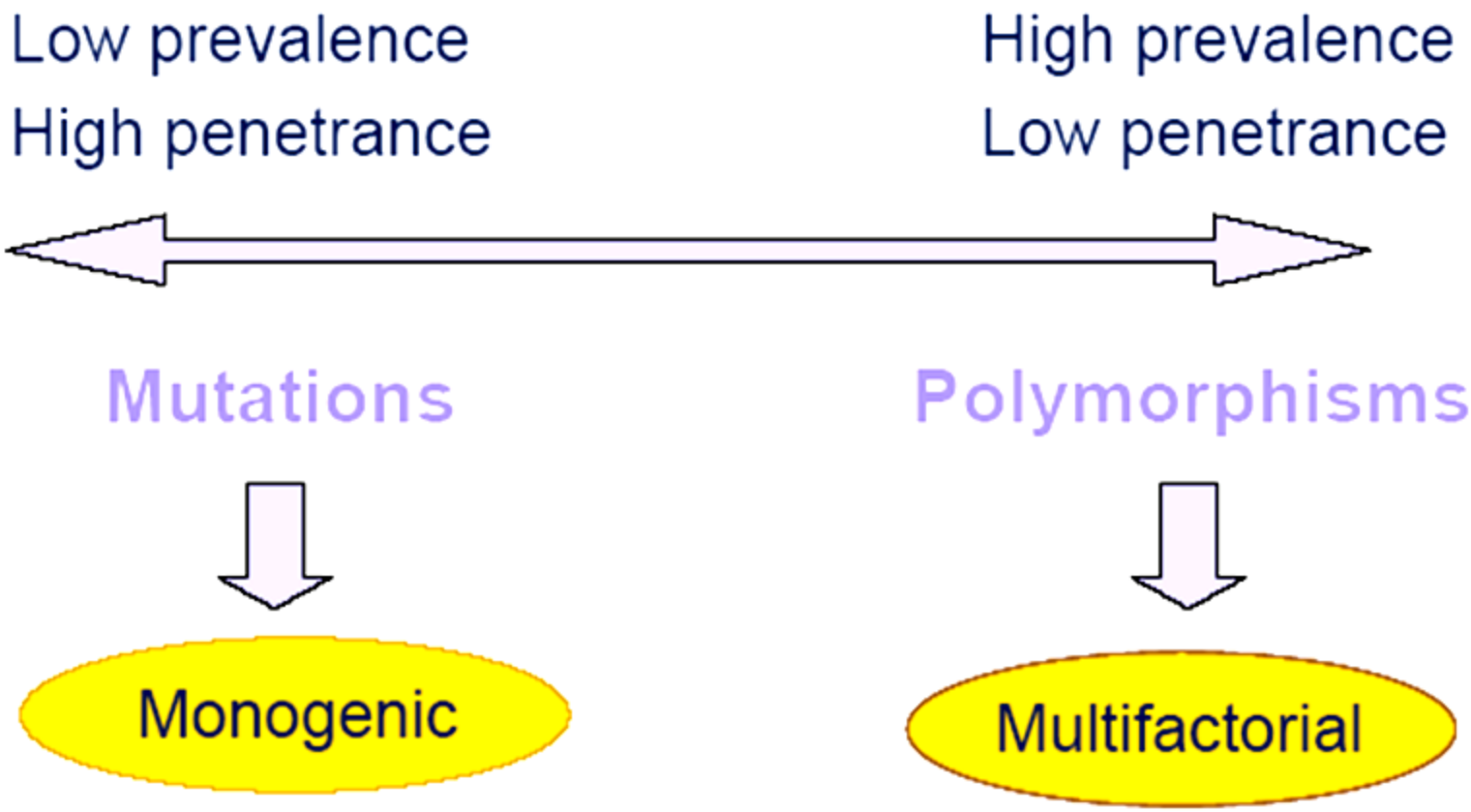
MG L-10

July 7th 2014

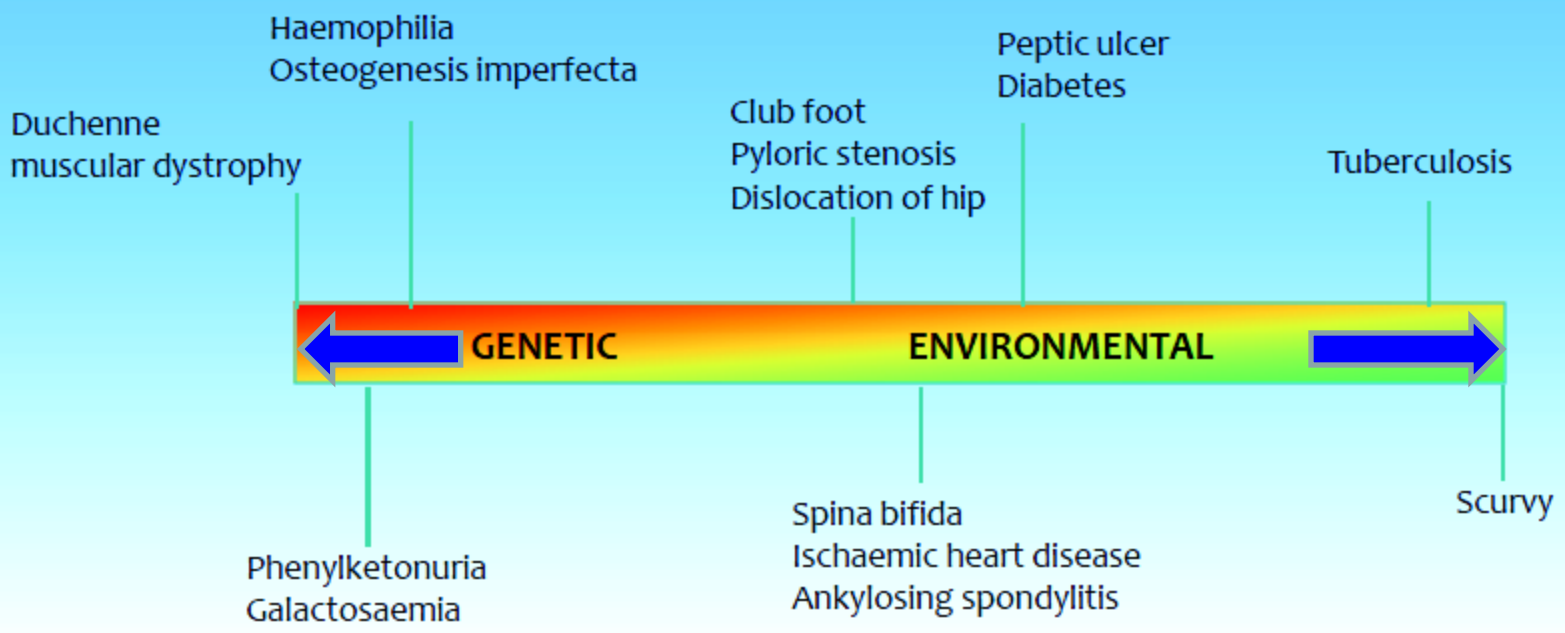
Genetic Diseases



Spectrum of Alterations in DNA Sequence



The contributions of genetic and environmental factors to human diseases



Rare	Common
Genetics simple	Genetics complex
Unifactorial	Multifactorial
High recurrence rate	Low recurrence rate

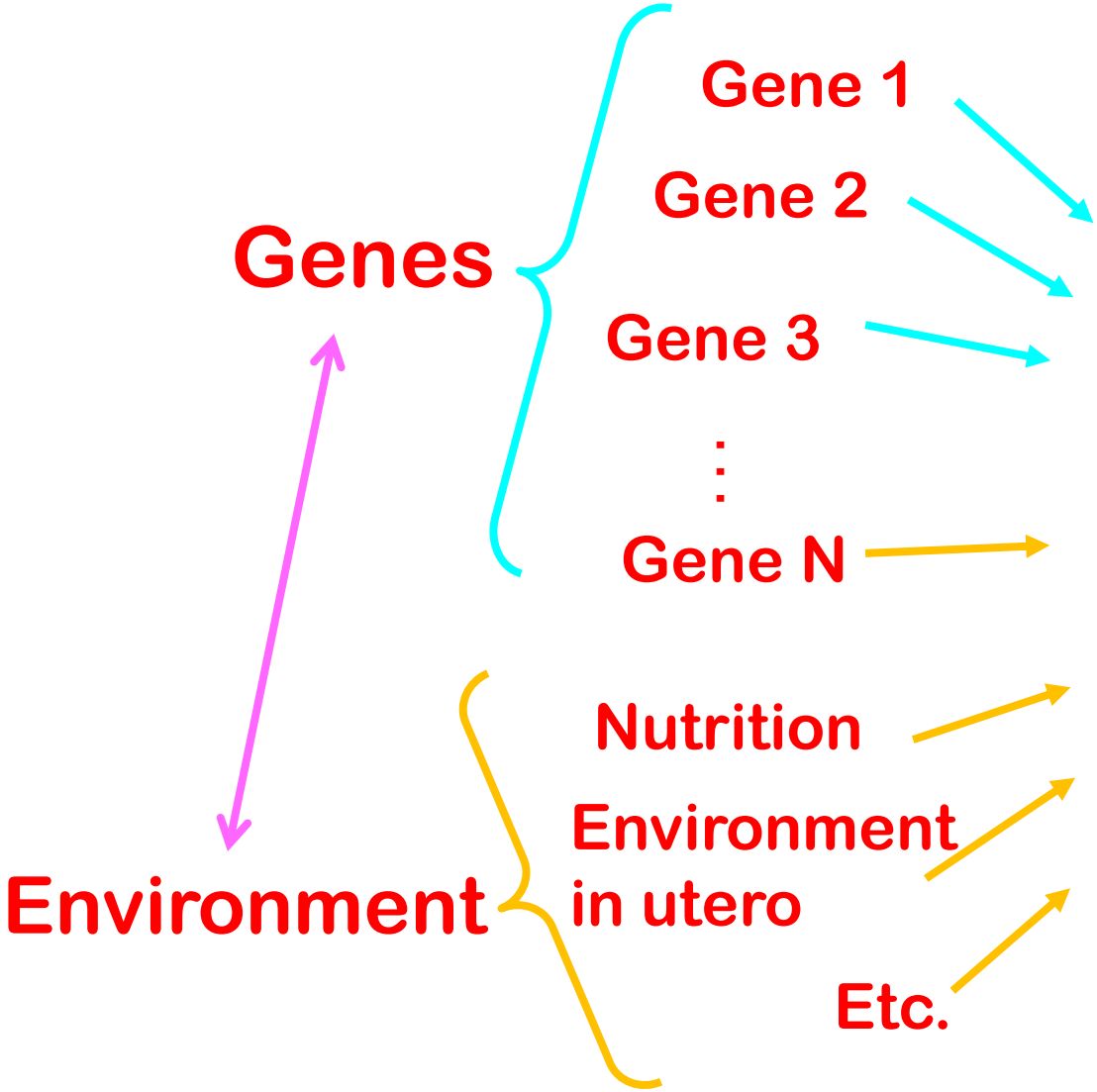
Contribution of Genes or Environment

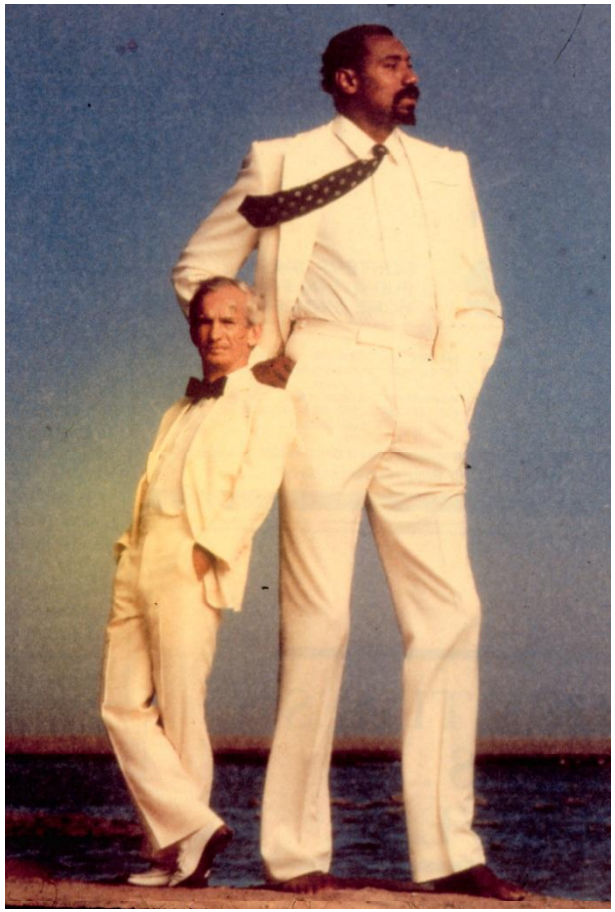
- Genes rarely act completely alone
- Environmental factors and other genes may modify expression

Traits can be described as

- **Mendelian**
- **Polygenic**
- **Multifactorial** due to an interaction between genes and the environment
- **Complex** are ones where relative contribution of genes and environment are not yet established

…but the genetic architecture is usually complex





Polygenic inheritance

- Polygenic = more than one gene Each gene separately follows Mendel's laws, but the trait overall does not
- Additive implies that the effects of the genes are cumulative, i.e. no one gene is dominant or recessive to another.
- Clinical clue: One organ system affected, ,human eye color

Genes, Environment and Traits

Single-gene traits are discrete or qualitative

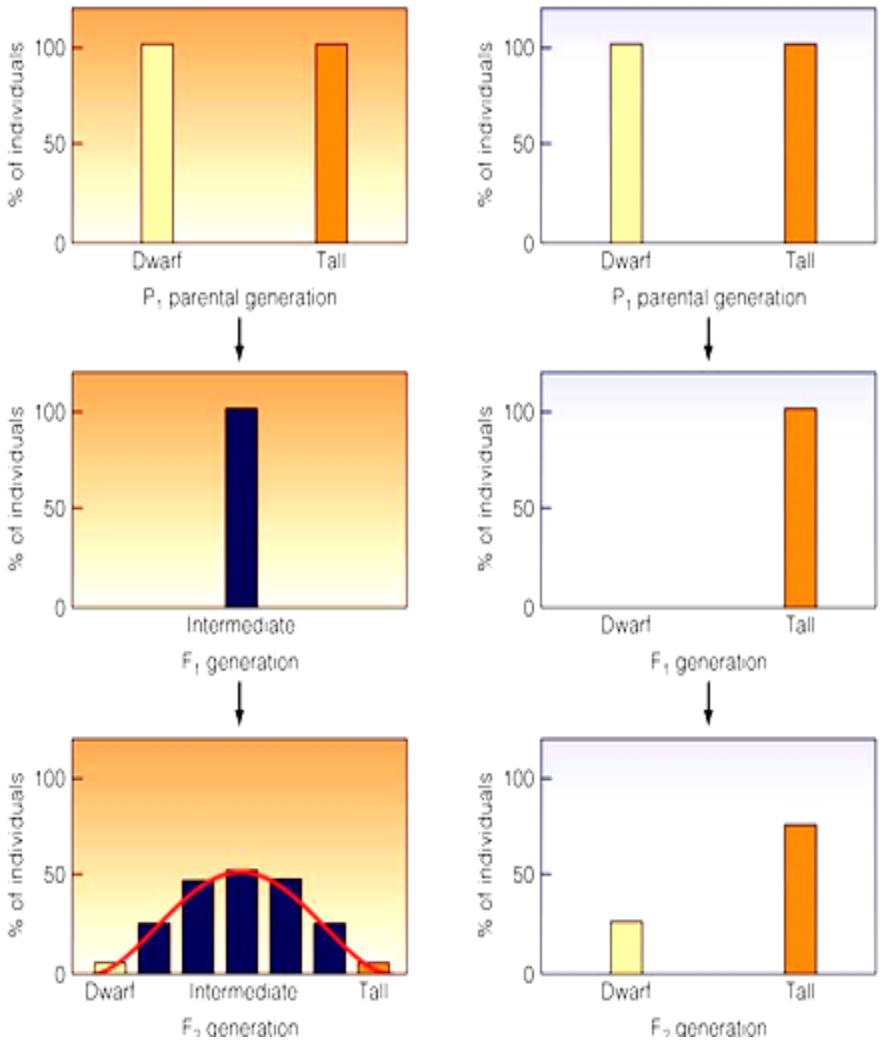
- Often produce an “all-or-none” effect

Polygenic traits produce a continuously varying phenotype

- Also called quantitative traits
- DNA sequences involved are termed **quantitative trait loci (QTLs)**

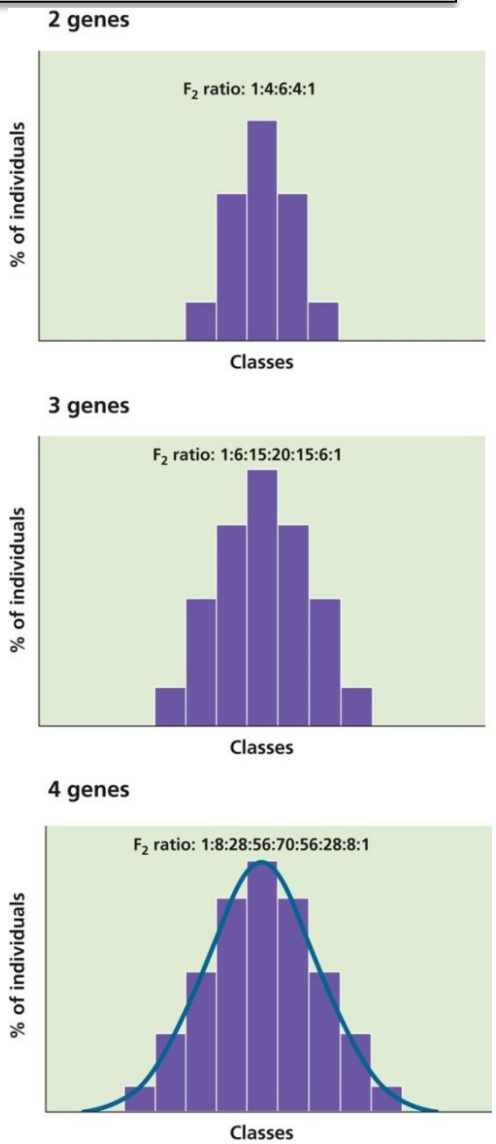
Phenotypes Can Be Discontinuous or Continuous

- **Discontinuous variation** shows distinct phenotypes
  - Short and tall peas phenotypes
- **Continuous variation** shows a series of overlapping phenotypic classes
  - Height in humans

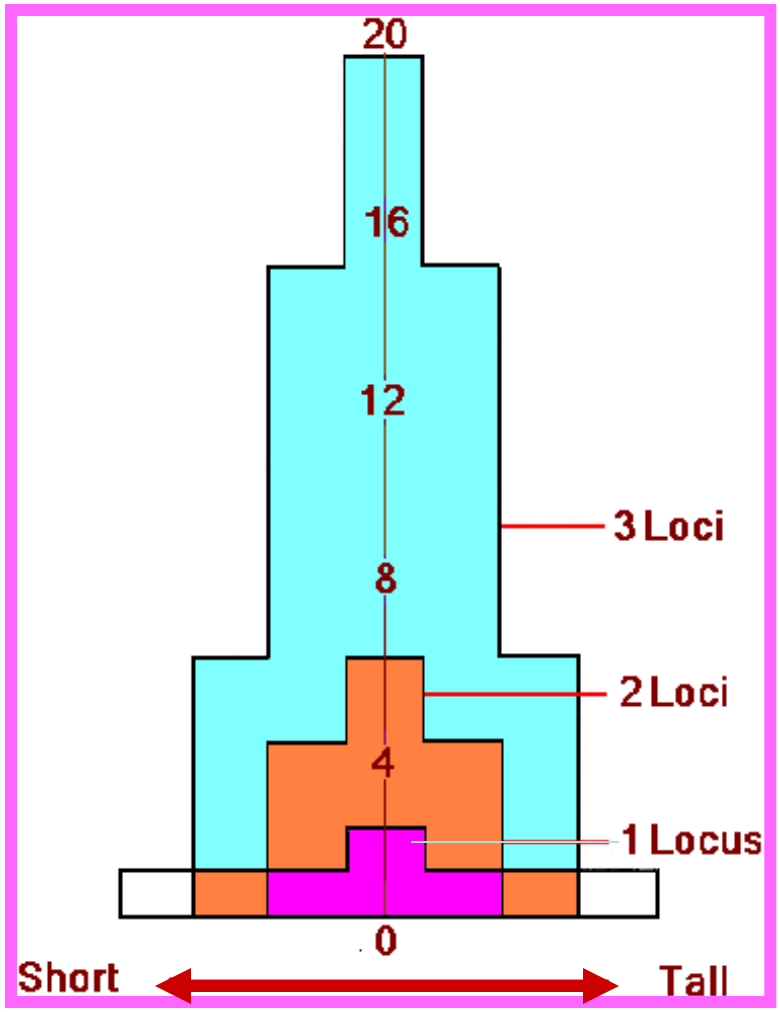


The Additive Model of Polygenic Inheritance

- The number of phenotypic classes increases as the number of genes controlling a trait increases
- As the number of genes involved increase, the number of phenotypic classes increases



Distribution of Genotypes (Polygenic)



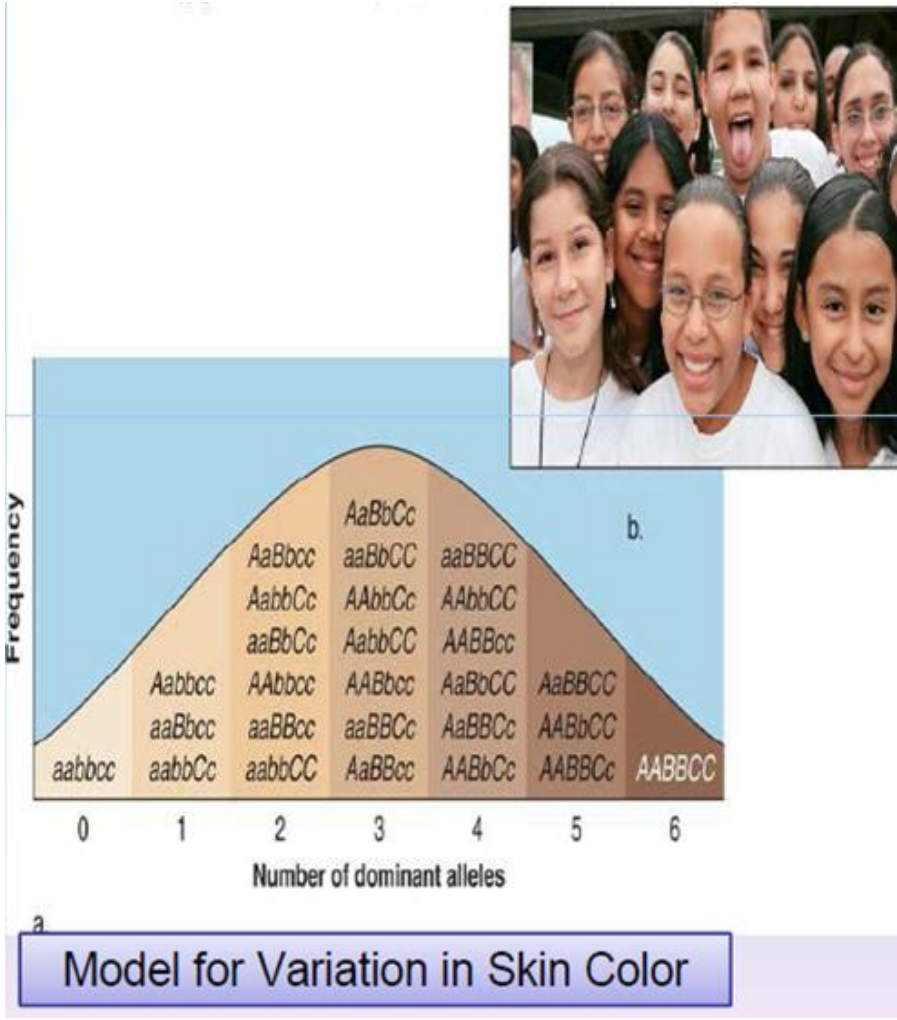
- Height with 1, 2 and 3 loci each with two alleles of equal frequency.
- The values for each genotype can be obtained from the binomial expansion $(p+q)^{2n}$ where $p = q = 1/2$ and n equals the number of loci.

Polygenic Traits

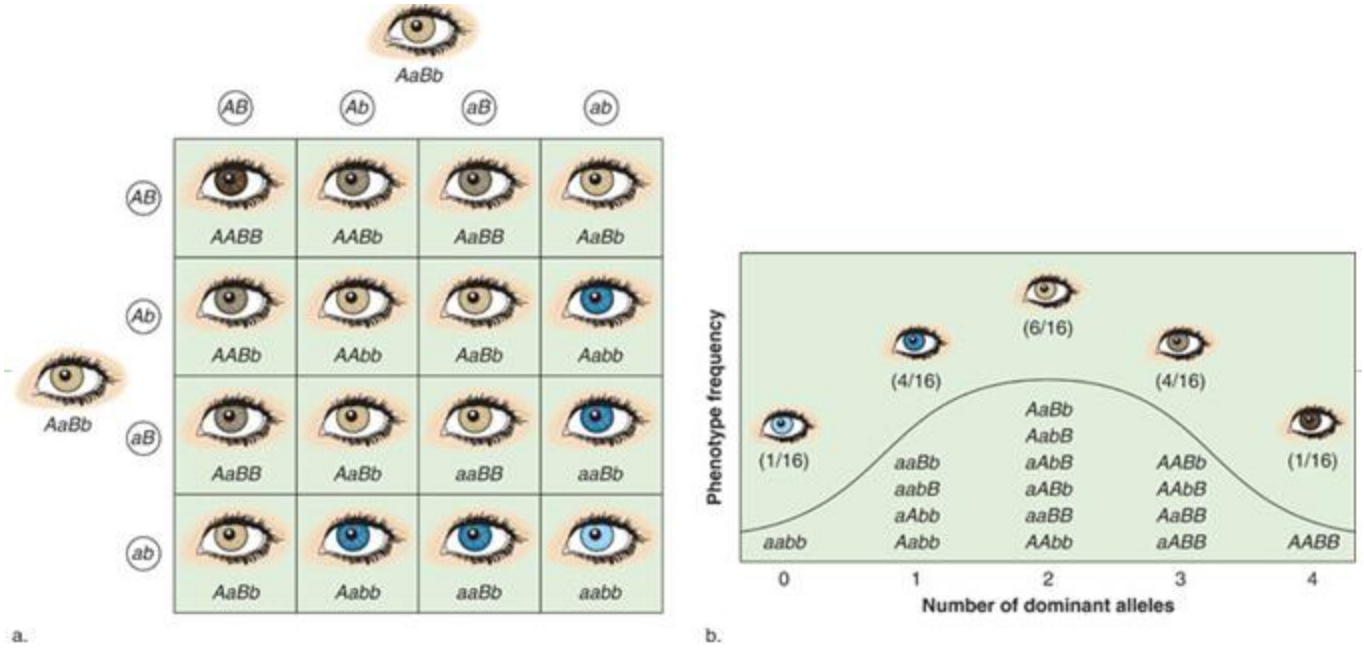
- Variation is continuous, not discrete
- Individual genes follow Mendel's laws
- Effect of genes is additive or synergistic
- Also called quantitative trait loci (QTL)
- Genes can have major or minor impacts

Examples:

- Height
- Hair color
- Body weight
- Cholesterol levels



An Example of Variations in Eye Color



- The number of human eye color genes is unknown
- Analysis will probably reveal many genes
- Mice have more than 60 eye color genes

Distinguishing Multifactorial Diseases

It is sometimes difficult to differentiate polygenic or multifactorial diseases from single-gene diseases that have reduced penetrance or variable expression. Large data sets and good family history data are necessary to make the distinction.

Risks for multifactorial diseases usually increase:

1. if more family members are affected
2. Consanguinity slightly increases the risk for an affected child.
3. the disease has more severe expression; Recurrence risk increases with severity of the defect. A more severely affected parent is more likely to produce an affected child.
4. If the two sexes have a different probability of being affected, the least likely sex, if affected, is the most likely sex to produce an affected offspring.
5. Recurrence risks decrease rapidly with more-remote degrees of relationship. In Contrast with autosomal dominant inheritance with incomplete penetrance, where the recurrence risk falls off proportionately with the degree of relationship.
6. In general, the sibling recurrence risk is approximately equal to the square root of the prevalence of the disease in the population.

Examples of disorders of Multifactorial Inheritance

- Congenital malformations:
  - congenital heart defects
  - neural tube defects
  - cleft lip/palate
  - pyloric stenosis
  - congenital hip dysplasia

- Common non-communicable diseases:
  - asthma
  - schizophrenia
  - diabetes mellitus
  - hypertension

Frequency of Different Types of Genetic Disease

Type	Incidence at Birth (per 1,000)	Prevalence at Age 25 Years (per 1,000)	Population Prevalence (per 1,000)
Diseases due to genome/chromosome mutations	6	1.8	3.8
Disease due to single gene mutations	10	3.6	20
Disease with multifactorial inheritance	~50	~50	~600

Methods Used to Study Multifactorial Traits

- **Threshold model**

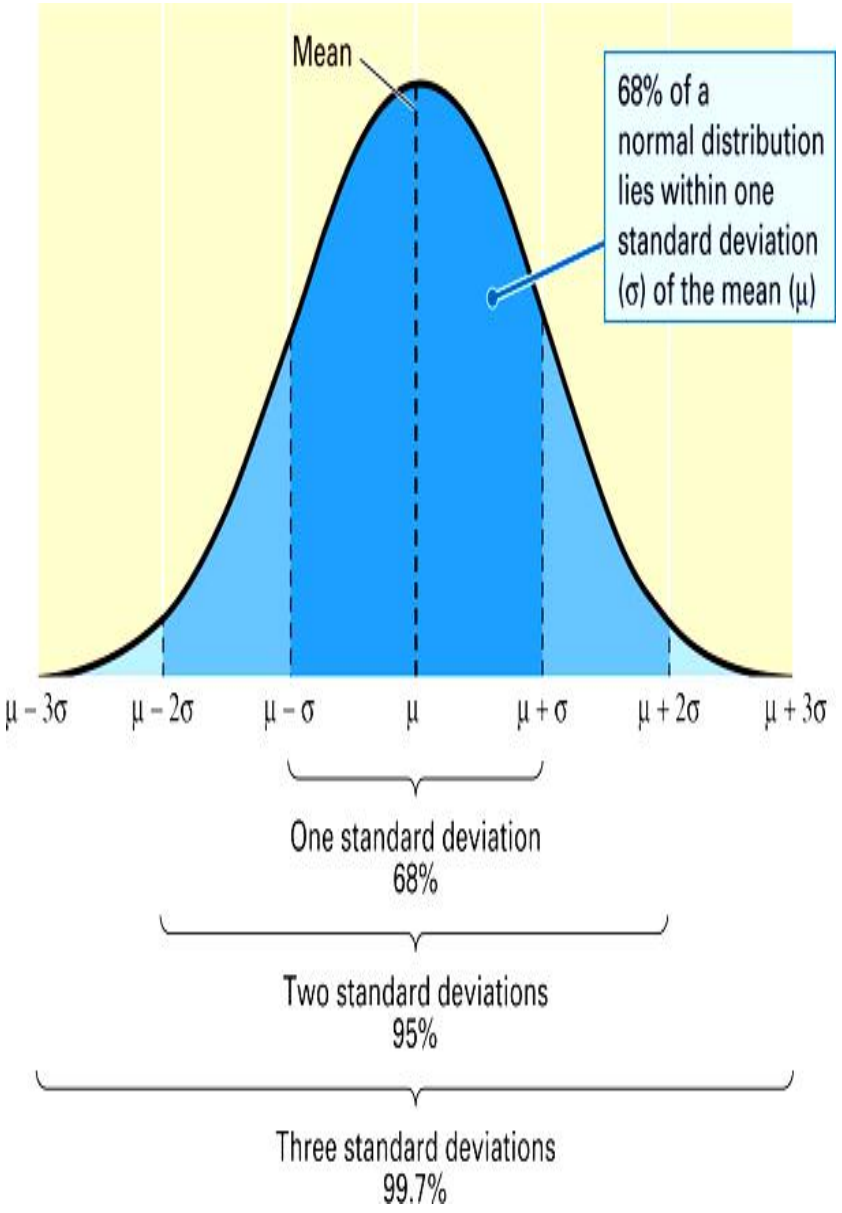
  Frequency of disorder among relatives is compared with the frequency of the disorder in the general population
- **Liability =** quantitative trait that presents a genetic risk for a threshold trait
- **Recurrence risk**

  Estimates the risk that the disease will recur

CONSEQUENCES OF THE LIABILITY/THRESHOLD MODEL

- The incidence of the condition is greatest among relatives of the most severely affected patients.
- The risk is greatest among close relatives and decreases rapidly in more distant relatives.
- If there is more than one affected close relative then the risks for other relatives are increased.

Normal Distribution



Normal distribution = symmetrical curve produced by data in which half points are above and half points are below the mean

~68% : of a population have a phenotype within one standard deviation (*s*) of the M

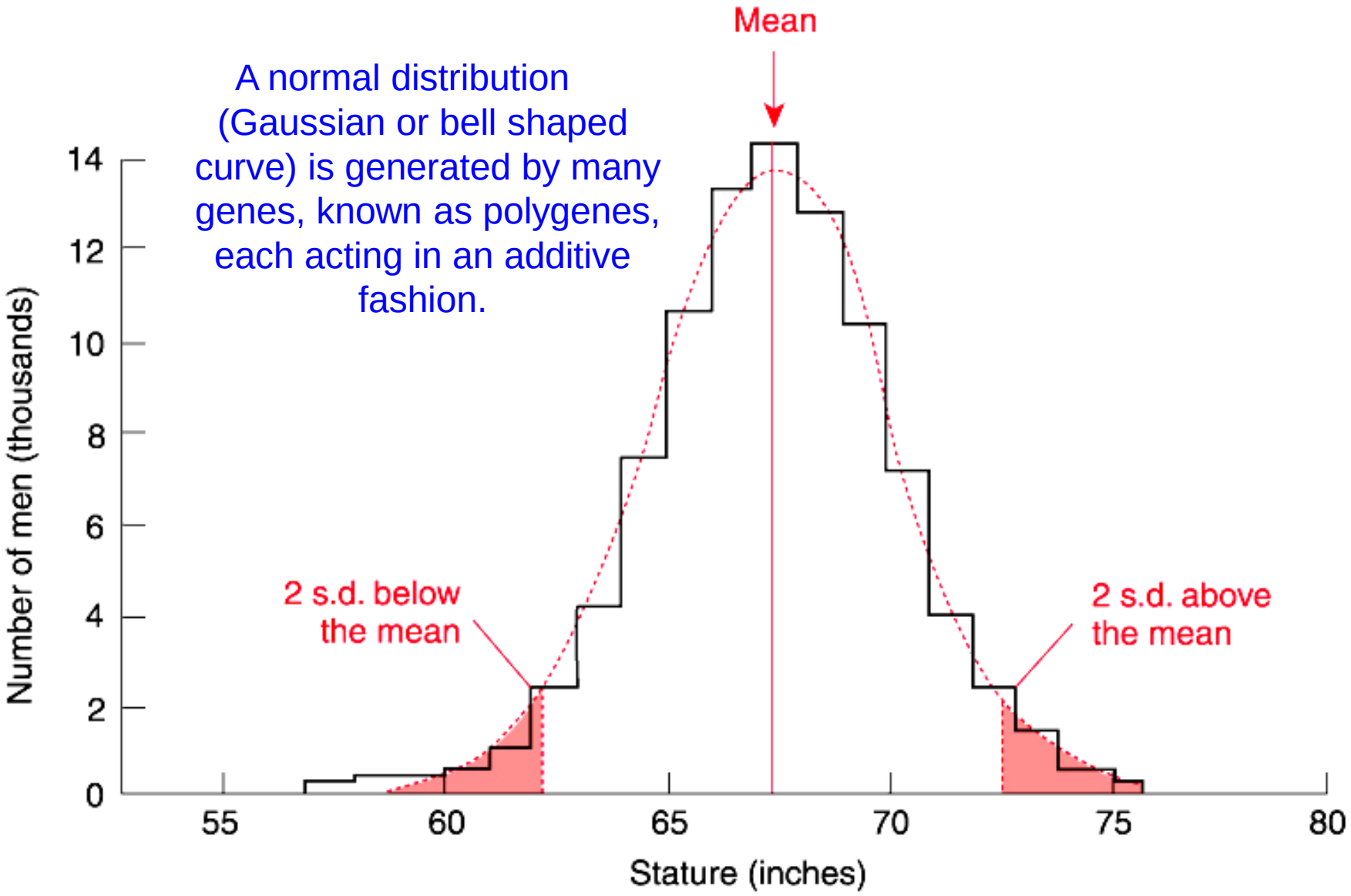
~95% - within 2 *SD*

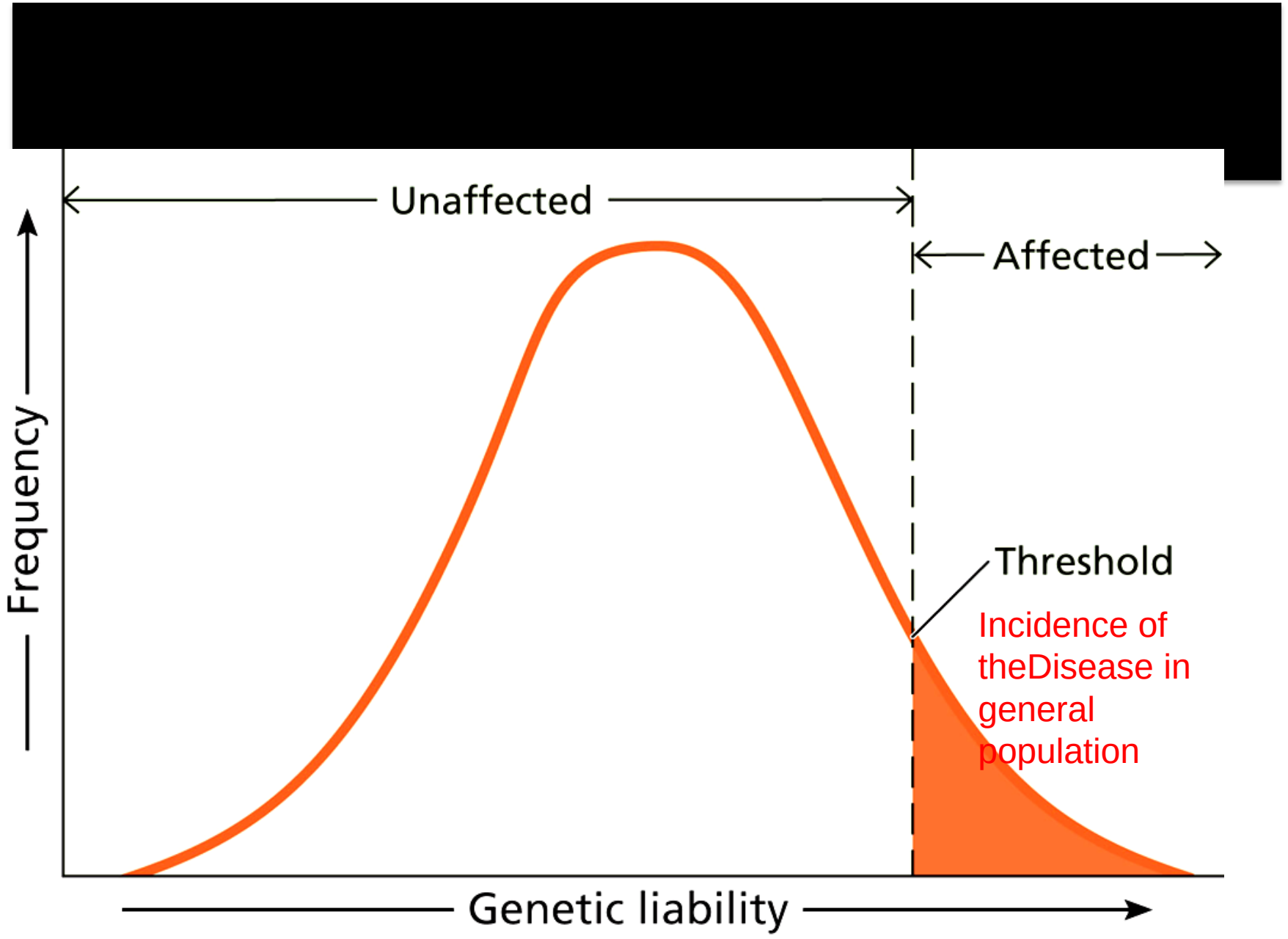
~99.7% - within 3 *SD*

•The distribution of a trait in a population implies *nothing* about its inheritance

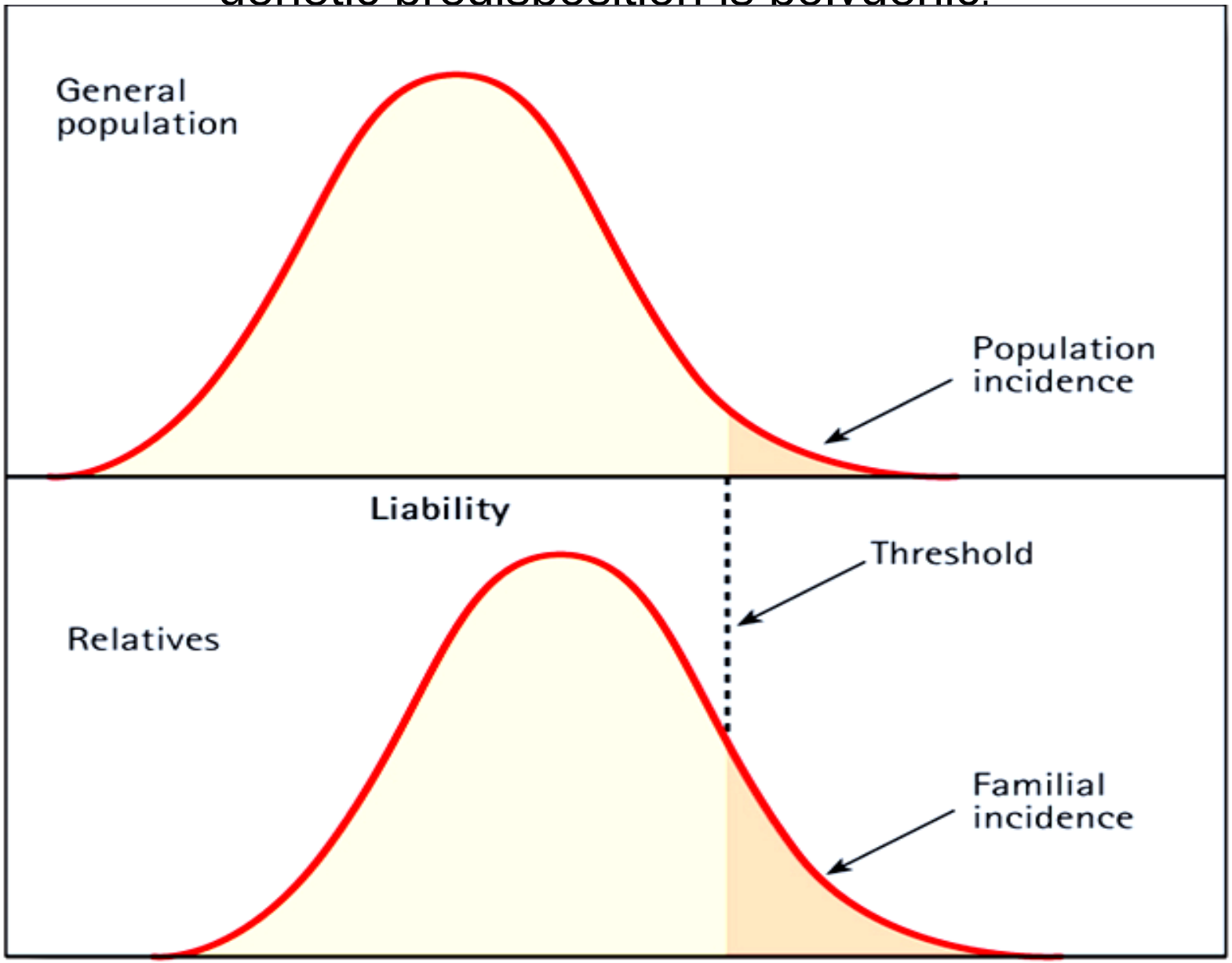
1 gene: $(a + b)^2$

2 genes: $(a + b)^3$


A normal distribution (Gaussian or bell shaped curve) is generated by many genes, known as polygenes, each acting in an additive fashion.
Mean
2 s.d. below the mean
2 s.d. above the mean
Number of men (thousands)
0
2
4
6
8
10
12
14
55
60
65
70
75
80
Stature (inches)

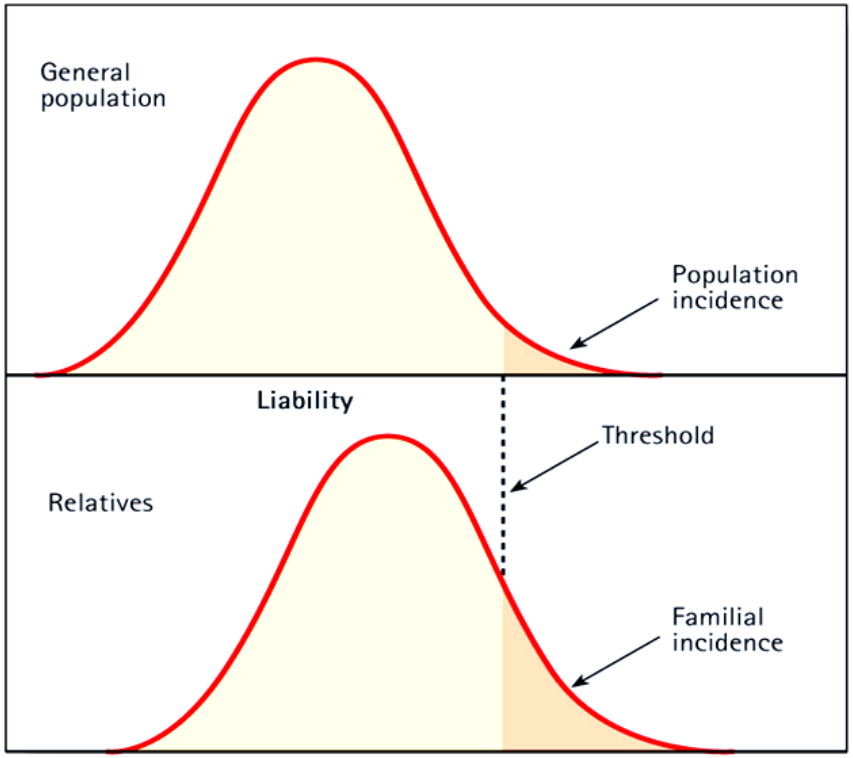

Unaffected
Affected
Frequency
Threshold
Incidence of theDisease in general population
Genetic liability

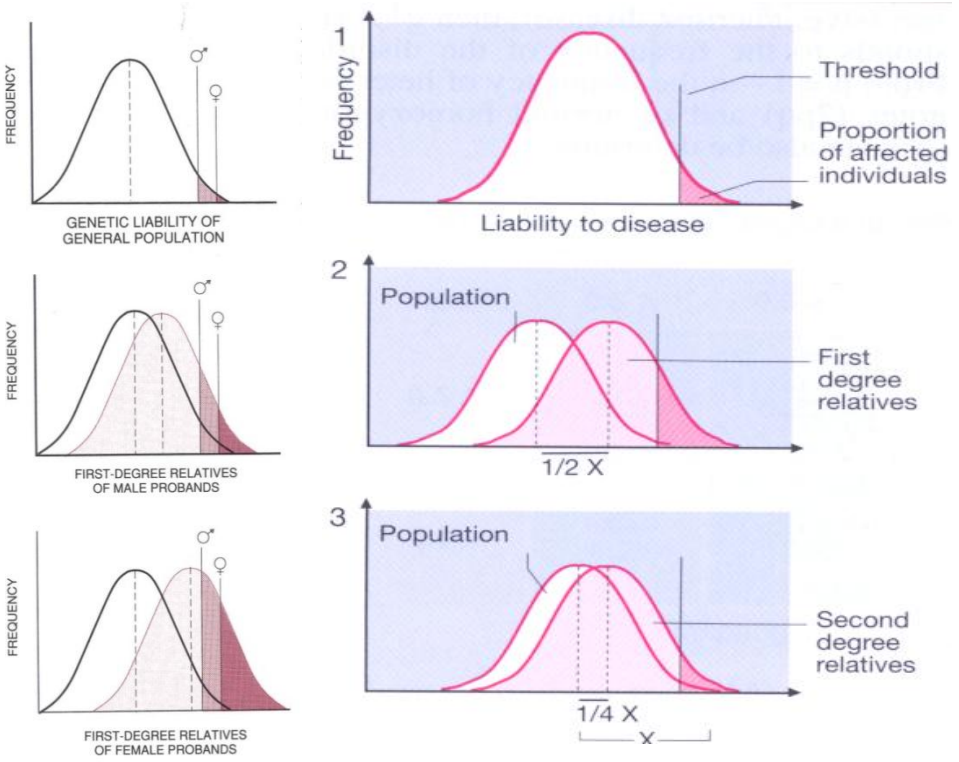
Hypothetical liability curves in the general population and in relatives for a hereditary disorder in which the genetic predisposition is polygenic.



Liability curves of affected and theirrelatives

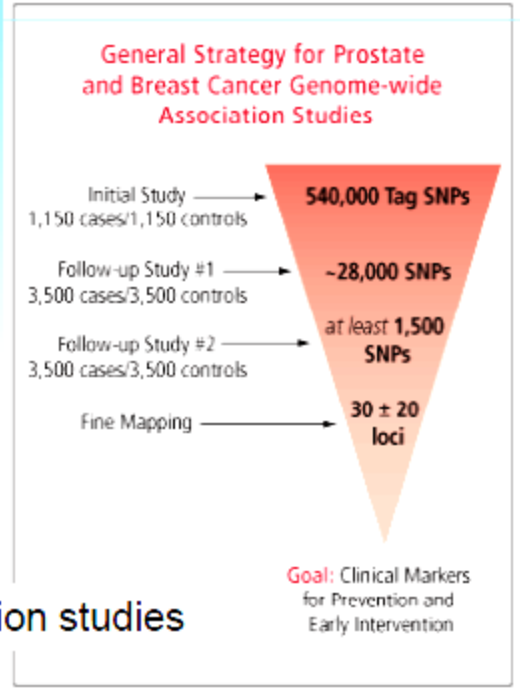
The curve for relatives of affected will be shifted to the right; so the familial incidence is higher than the general population incidence.





Analyzing Multifactorial Traits

- Difficult, requires multiple techniques
- Use human genome sequences, population, and family studies
- The frequency in a specific population = **Empiric risk**
- The amount of inheritance due to genes = **Heritability**
- Comparisons between and within families
  - Twins dizygotic and monozygotic
  - Twins raised apart
  - Adopted children
- **Association studies** - case-control design searching for common change in cases



SNP linkage Association studies

Investigating Multifactorial Traits

Empiric risk measures the likelihood that a trait will recur based on incidence

Incidence is the rate at which a certain event occurs

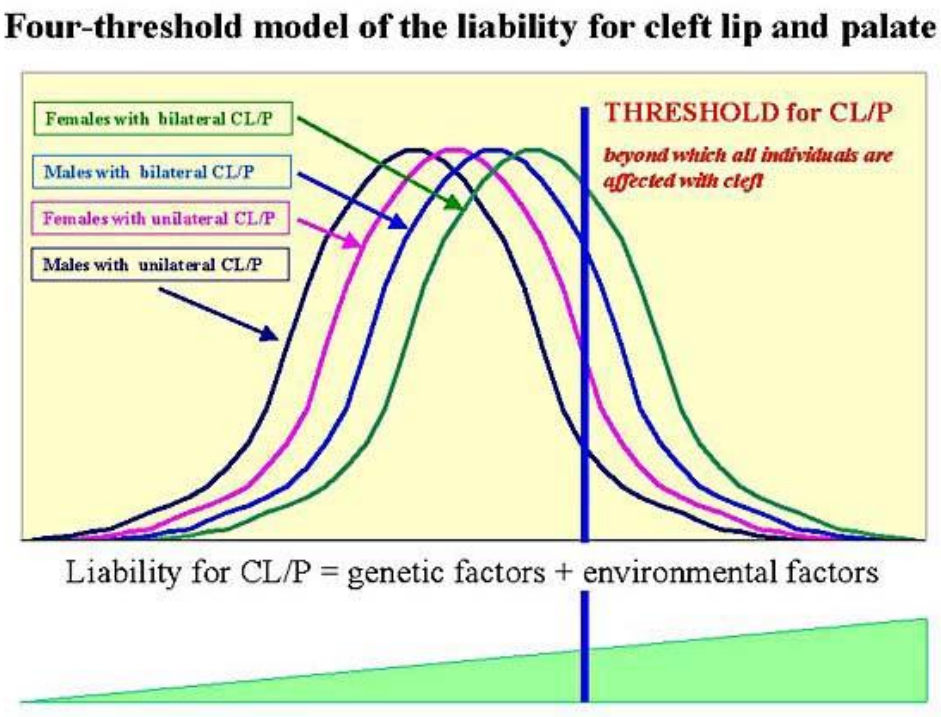
Prevalence is the proportion or number of individuals who have a particular trait at a specific time

Empiric risks

- Recurrence risks are empiric risks derived from population studies. So they are observational and do not depend on theory as the Mendelian characters.
- **Empiric risks vary according to several factors.**

1- The incidence of the condition is greatest among relatives of the most severely affected patients.

- If the index patient has bilateral cleft lipand palate, the risk to future sibling is 6%.
- If the index patient has unilateral cleft lip, the risk to future sibling is 2%.



Empiric risk for Recurrence cleft Lip

Relationship to Affected Person	Empiric Risk of Recurrence
Identical twin	40.0%
Sibling	4.1%
Child	3.5%
Niece/nephew	0.8%
First cousin	0.3%
General population risk (no affected relatives)	0.1%

2- Recurrence risk increases with increasing number of previously affected children

If a couple have a baby with neural tube defect, recurrence risk is about 2-4%. If they have 2 children with neural tube defects, the recurrence risk rises to 10%.

3- The risk is greatest among close relatives of the index case and decreases rapidly in more distant relatives

.

4- If the condition is more common in individuals of one particular sex, recurrence risk varies according to sex of index case

- Pyloric stenosis shows a male to female ratio of 5 to 1. The threshold must be higher for girls than boys.
- Relatives of an affected girl must have a higher susceptibility than relatives of an affected boy.
- Offspring of male index patients are 6.4% risk for sons and 2.5% risk for daughters.
- The risks to the offspring of female index patients are 22.9% for sons and 11.4% for daughters.

Frequency of pyloric stenosis in relatives

Relationship	*Frequency %*	*Increase on general population risk for same sex*
Male relatives of a male patient	5	x10
Female relatives of a male patient	2	x20
Male relatives of a female patient	17	x35
Female relatives of a female patient	1	x70

Some Multifactorial conditions have an unequal sex ratio

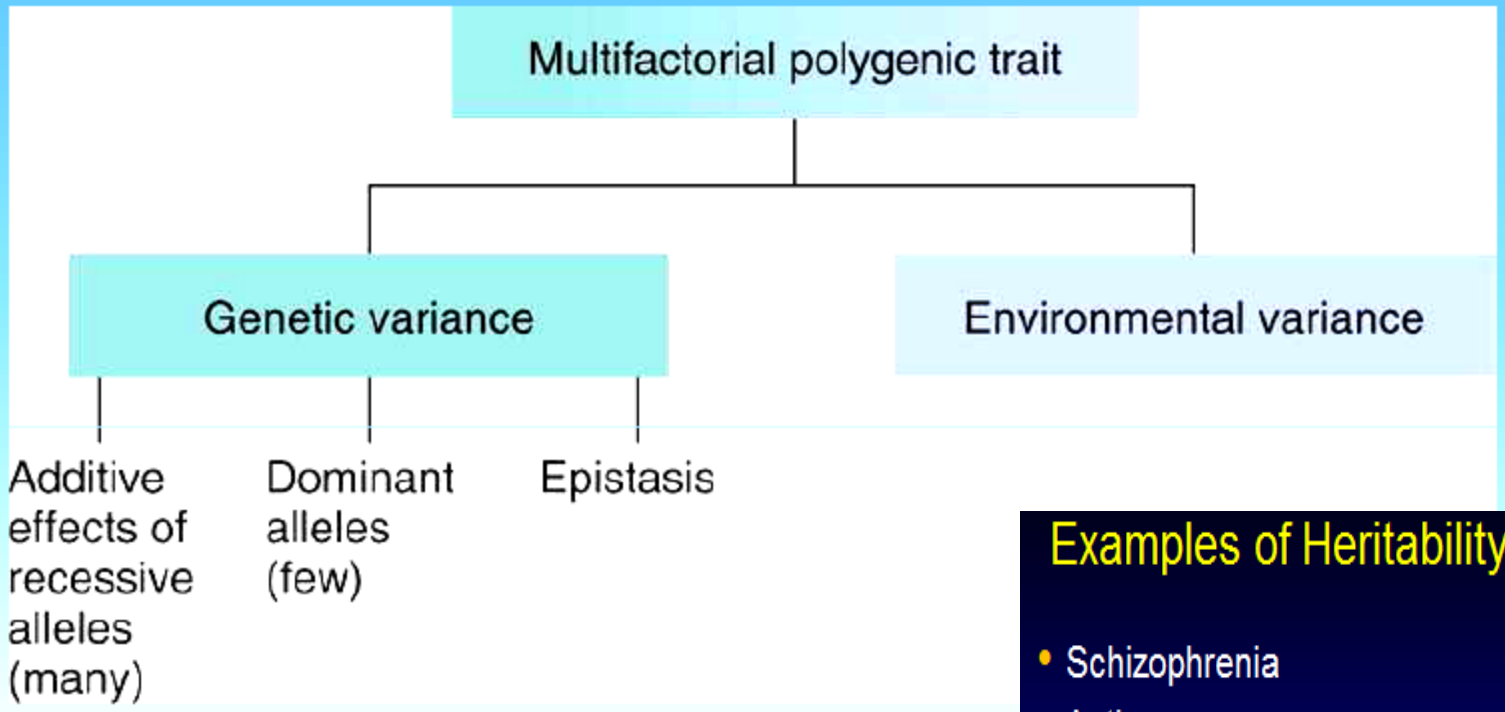
Condition	*Sex ratio (males to females)*
Pyloric stenosis	5 to 1
Hirschprung disease	3 to 1
Congenital dislocation of hip	1 to 6
Talipes	2 to 1
Rheumatoid arthritis	1 to 3
Peptic ulcer	2 to 1

Calculation of Relative Risk of a Disease Association

Marker	positive	negative
• Patients	a	b
• Controls	c	d
• Reletice Risk	= a/c ÷ b/d	
	= ad/bc	

Heritability (H)

Estimates the proportion of the phenotypic variation in a population due to genetic differences



- Heritability is estimated from the proportion of people sharing a trait compared to the proportion predicted genetically to share the trait
- May vary between populations and time period

Examples of Heritability Estimates

• Schizophrenia	85
• Asthma	80
• Pyloric stenosis	75
• Ischaemic heart disease	65
• Essential hypertension	60
• Spina bifida	60
• Diabetes mellitus	40

Estimates of Heritability of Some Disorders

Disorder	Frequency (%)	Heritability
Schizophrenia	1	85
Asthma	4	80
Cleft Lip = Cleft palate	0.1	76
pylonc stenosis	0.3	75
Ankylosingspondylitis	0,2	70
Club foot .	0.1	68
Coronaryartery dlsease	3	65
Hypertension {essential)	5	62
Congenital dislocction of the hip	0.1	60
Anencephaly and spina pifida	0.1	60
Peptic Ulcer	4	37
Congenital Heart Disease	0.5	35

Heritability Measures the Genetic Contribution to Phenotypic Variation

- The degree of phenotypic variation produced by a genotype in a specific population can be estimated by calculating the heritability of a trait

- **Heritability** summarizes how much of the variation in a trait is due to variation in genetic factors.

Analyzing Multifactorial Traits

- Comparisons between and within families
  - Twins dizygotic and monozygotic
  - Twins raised apart
  - Adopted children

- Association studies – compare SNP patterns between affected and unaffected groups, identify important DNA regions

Separating Genes and Environment

- Dizygotic twins: Shared environment and 50% of genes
- Monozygotic twins: Identical genotype, and shared environmen
- Twins raised apart: Shared genotype but not environment
- Adopted individuals: Shared environment but not genes

Concordance

- **Concordance** - the percentage of pairs in which both twins express the trait
- Used to determine heritability
- Has limitations, assumes both type of twins share similar environments
- MZ twins often share more similar environments

Twins

Concordance Values for Traits in Twins

Trait	MZ (identical) twins	DZ (fraternal) twins
Acne	14%	14%
Alzheimer disease	78%	39%
Anorexia nervosa	55%	7%
Autism	90%	4.5%
Bipolar disorder	33–80%	0–8%
Cleft lip with or without cleft palate	40%	3–6%
Hypertension	62%	48%
Schizophrenia	40–50%	10%

Concordance in MZ and DZ Twins

	Concordance Values (%)	
Trait	MZ Twins	DZ Twins
Blood types	100	66
Eye color	99	28
Mental retardation	97	37
Hair color	89	22
Down syndrome	89	7
Handedness (left or right)	79	77
Epilepsy	72	15
Diabetes	65	18
Tuberculosis	56	22
Cleft lip	42	5

Twin studies provide an insight into the interaction of genotypes and environment

Degree of Relationship and Alleles in Common

Relationship to Proband	Proportion of Alleles in Common with Proband
Monozygotic (MZ) twins	1
Dizygotic (DZ) twins	1/2
First-degree relative	1/2
Second-degree relative	1/4
Third-degree relative	1/8

Quantitative Traits

Rather than genes people often talk about:

- Quantitative Trait Loci (QTL) = chromosomal regions that have been associated with a complex trait
- If a QTL is correct then one of the genes residing in this region should be directly involved in causing trait

Remember – More than one gene!

therefore – more than one QTL too

QTL Mapping

- Start with a complex trait of interest
- Phenotype a large group of individuals for trait – quantitatively
- Genotype everyone
- Do people who share the trait also share specific genomic regions (QTL) more often than chance?

How to identify QTL

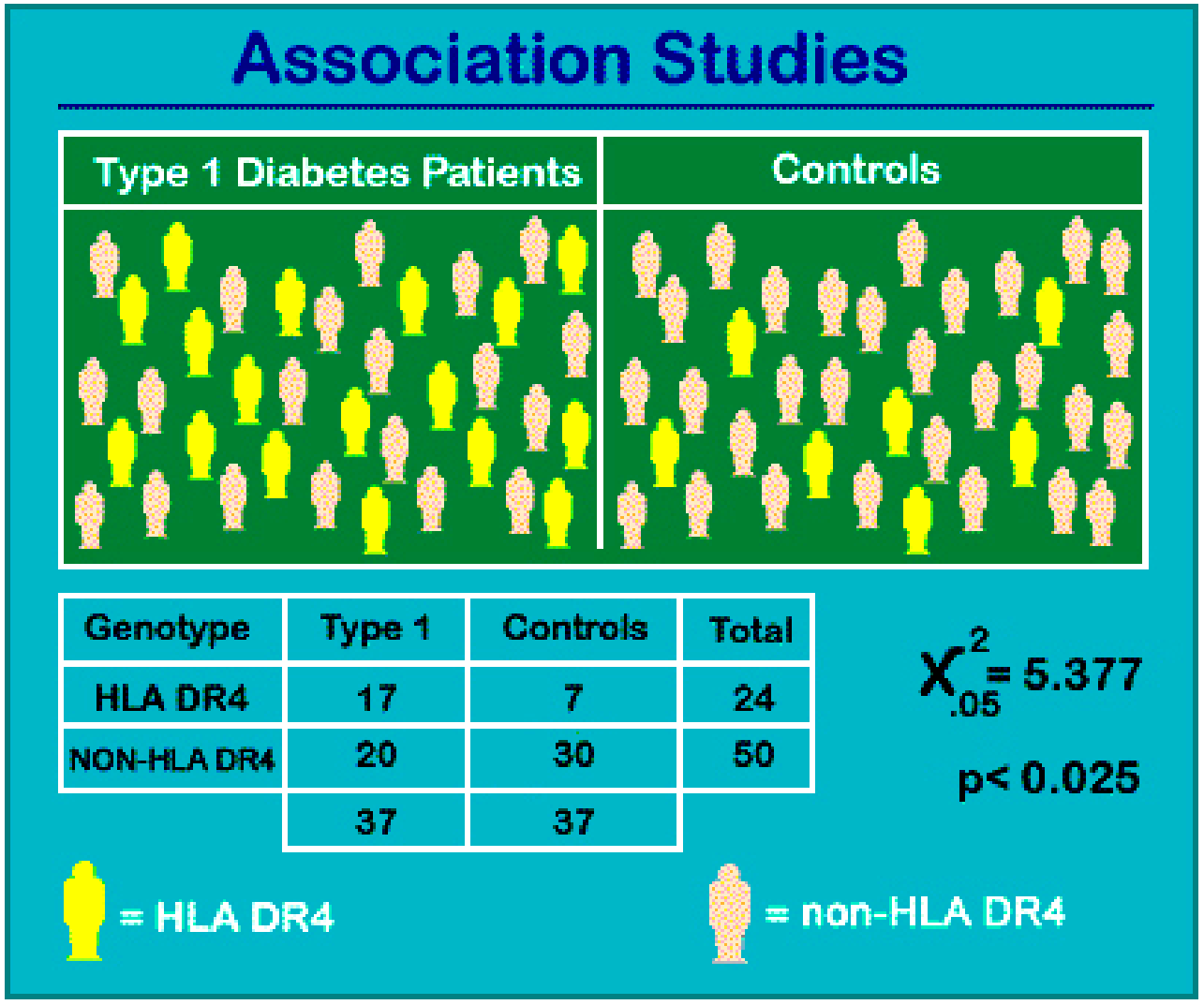
Linkage and Association Studies

"Linkage Disequilibrium" – alleles are inherited together (rather than genes)

- LD only ranges a short distance
- ~ 10,000 bases
- Because alleles are so close they are always inherited together (no crossing over)

- Association comparing alleles
- Linkage usually done in families, association usually done case vs. control

Association studies in diabetes type 1



Correlation

- Correlation coefficient
  - ✓The fraction of genes shared by two relatives
- Identical twins have 100% of their genes in common (correlation coefficient = 1.0)
  - ✓When raised in separate environments identical twins provide an estimate of the degree of environmental influence on gene expression

Association Studies

- Studies which compare a group of interest (cases) to a control group for the presence of a gene or SNP.
- Controls are matched to cases for characteristics that may confound results: age, ethnicity, gender, environment.
- If the SNP is present more often in cases than controls, it is associated with the trait and implies that the SNP may be near a gene impacting the trait.

Type of Information Used in Genome-Wide Association Studies

Marker Type	Definition
SNP	A single nucleotide polymorphism is a site in the genome that is a different DNA base in >1% of a population.
CNV	A copy number variant is a tandemly repeated DNA sequence, such as CGTA CGTA CGTA
Gene expression	The pattern of genes that are overexpressed and/or overexpressed in people with a particular trait or disease.
	Epigenetic signature

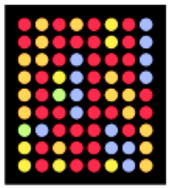
Genome-wide association studies seek SNPs that are shared with much greater frequency among individuals with the same trait than among others

People with disorder

People without disorder

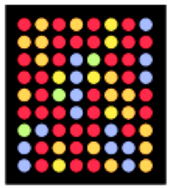
Patient DNA

Non-Patient DNA



Disease-specific SNPs

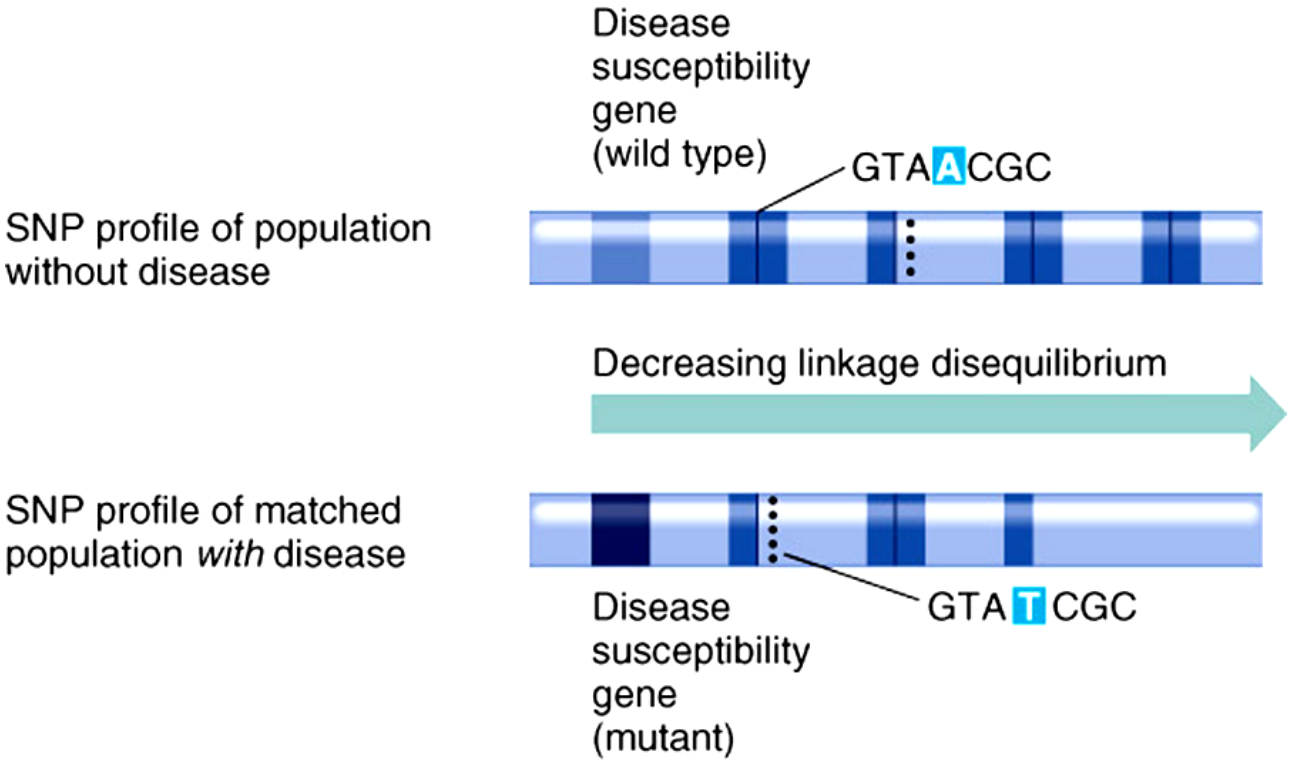
Compare differences to discover SNPs associated with disease



Nondisease SNPs

SNP (single nucleotide polymorphism)

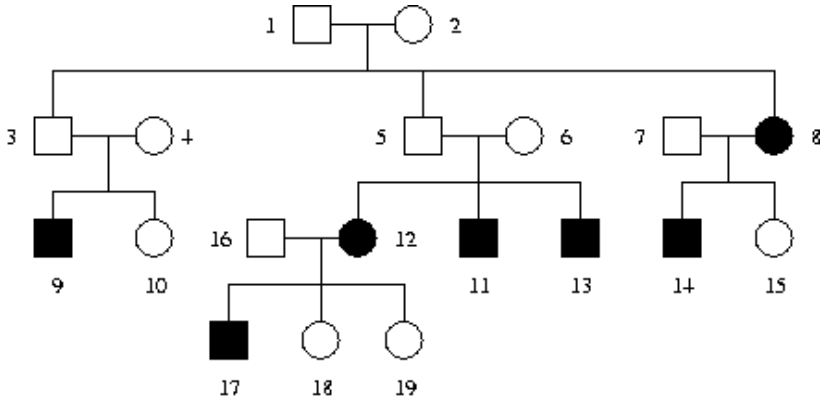
Nucleotide site with more than one allele is a polymorphism.



- **On average between two random individuals, there is one SNP every 1000 bases => 3 million differences!**

Genetic linkage and linkage analysis

- Two loci are **linked** if they appear closeby in the same chromosome.
- The task of linkage analysis is to find markers that are linked to the hypothetical disease locus
- Complex diseases in focus $\rightarrow$ usually need to search for one gene at a time
- Requires mathematical modelling of meiosis
  - One of the two main approaches in gene mapping.
  - Uses pedigree data



Conclusions

- Multifactorial disorders are more common than single gene and chromosomal disorders
- They are caused by the interaction of many genes with environmental factors
- Optimum preventive measures rely on avoidance of the bad environmental factors since avoidance of inheriting the bad genes is at present not possible.
- These measures can be explained through counseling such as periconception and chronic noncommunicable diseases counseling.