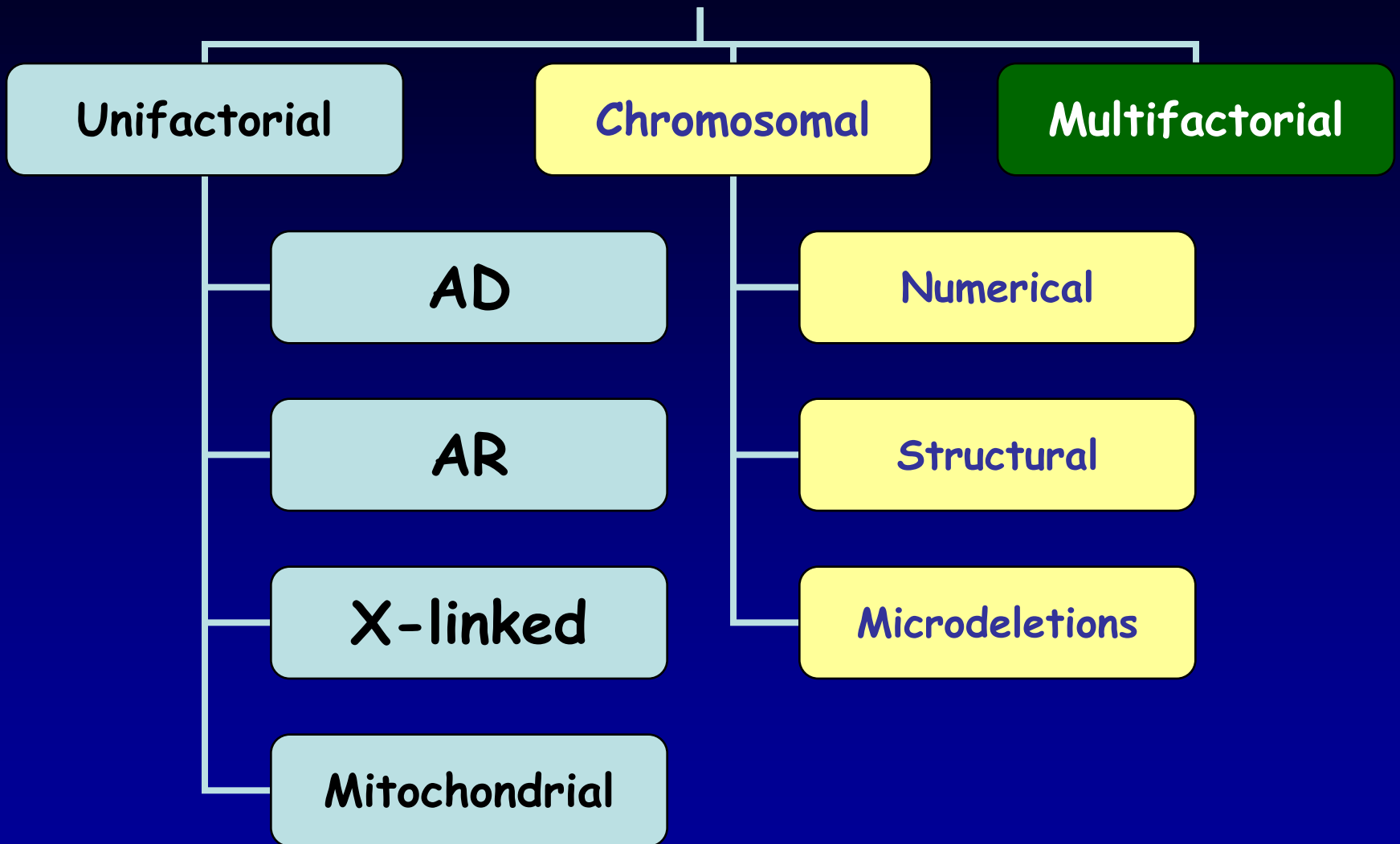


MULTIFACTORIAL DISEASES

MG L-10

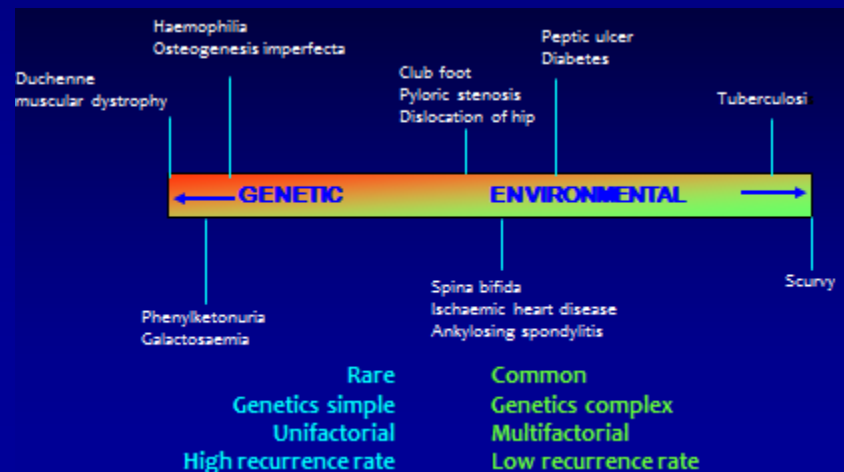
July 18th 2013

Genetic Diseases



Spectrum of Human Disease

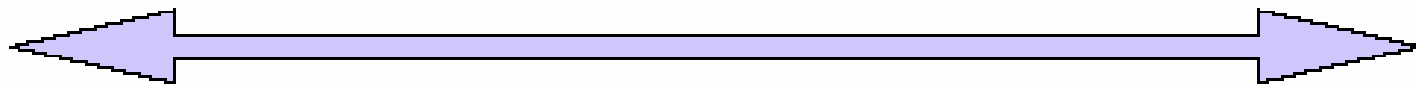
- Human diseases are caused by a multitude of genetic and environmental factors acting together.
- In certain conditions such as Down syndrome, genetic factors predominate, while in infections for example, environmental factors predominate.
- Most chronic non-communicable conditions such as schizophrenia and diabetes as well as congenital malformations are caused by an interaction of both genetic and environmental factors.



Spectrum of alterations in DNA sequence

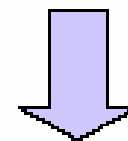
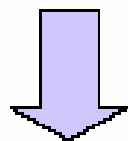
Low prevalence
High penetrance

High prevalence
Low penetrance



Mutations

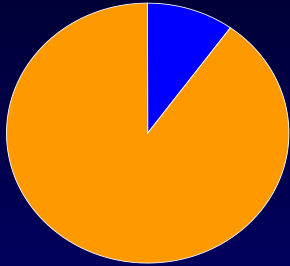
Polymorphisms



Monogenic

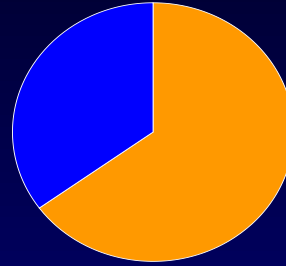
Multifactorial

Genes and Disease



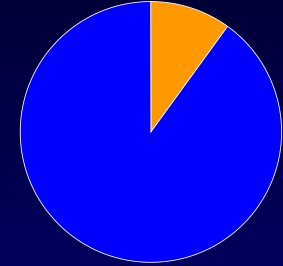
Monogenic Diseases

- Huntington Disease
- Spinocerebellar Ataxia
- Spastic Paraplegia
- Tuberous Sclerosis



Complex Diseases

- Alzheimer disease
- Cardiovascular Disease
- Autism
- Parkinson Disease



Environmental Diseases

- Influenza
- Hepatitis
- Measles

 - Environment  - Genes

Terms

- Genotype + Environment = Produce the Phenotype
- **Polygenic traits** are determined by two or more genes
- **Multifactorial traits** are controlled by two or more genes and show significant interaction with the environment
- **Complex traits** are ones where relative contribution of genes and environment are not yet established

Polygenic inheritance

- This involves the inheritance and expression of a phenotype being determined by many genes at different loci, with each gene exerting a small additive effect.
- 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

Multifactorial inheritance

- Diseases that show familial clustering but do not conform to any recognized pattern of single gene inheritance are termed multifactorial disorders.
- They are determined by the additive effects of many genes at different loci together with the effect of environmental factors.

Multifactorial disorders

- These conditions show a definite familial tendency but the incidence in close relatives of affected individuals is usually around 2-4%, instead of the much higher figures that would be seen if these conditions were caused by mutations in single genes (25-50%).

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

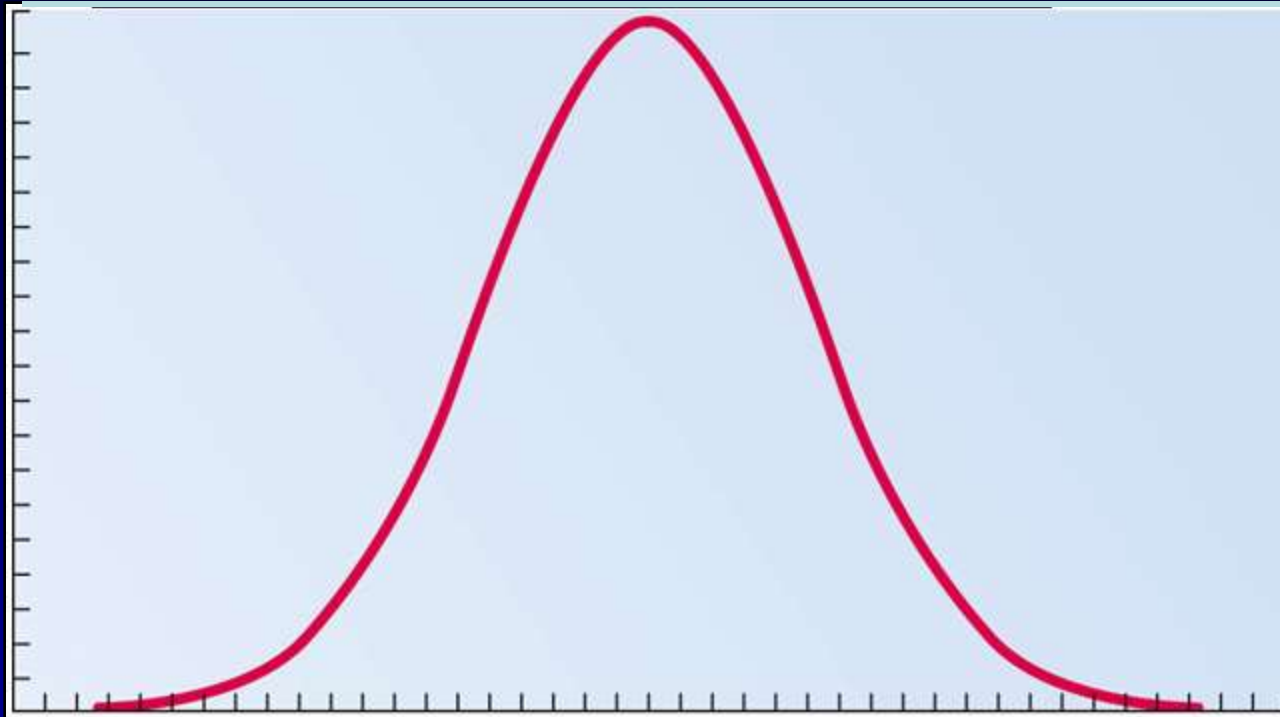
Frequency of Different Types of Genetic Disease

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

Multifactorial traits

- Several human characteristics show a continuous distribution in the general population, which closely resembles a normal distribution. This takes the form of a symmetrical bell-shaped curve distributed evenly about a mean.

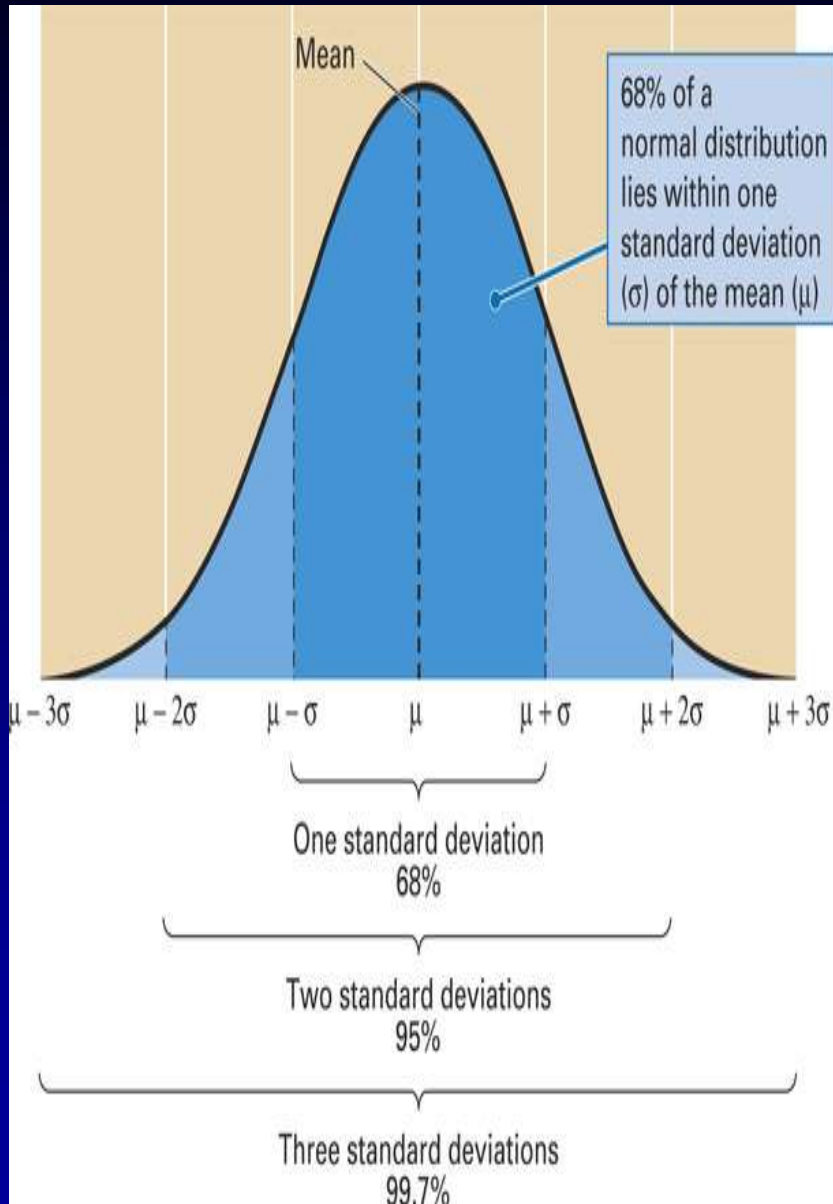
Typical Polygenic Trait in a Population



Bell curve

- Most individuals are clustered at ~average
- Few individuals at extremes of the phenotype

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

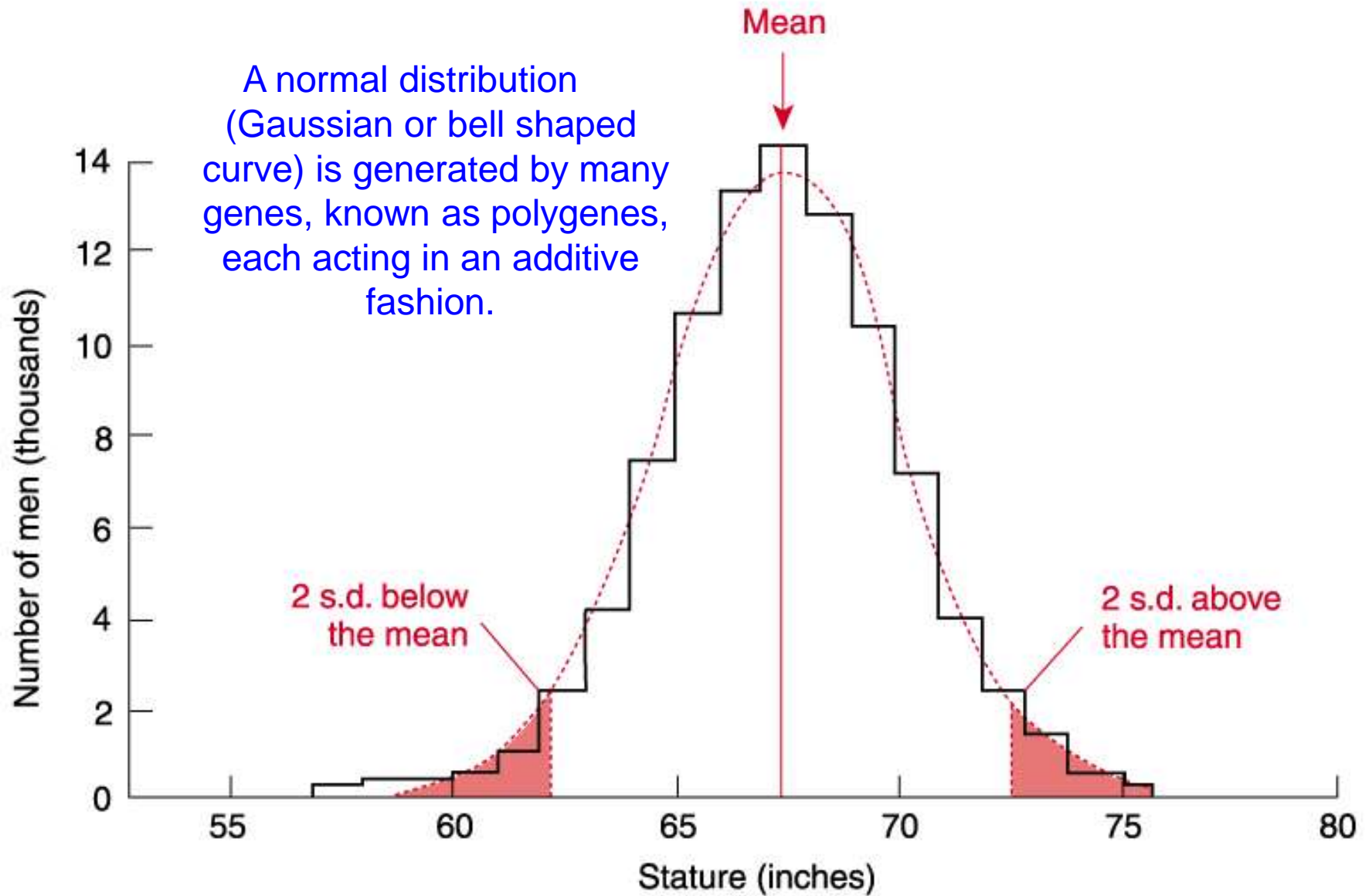
~99.7% - within 3 SD

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

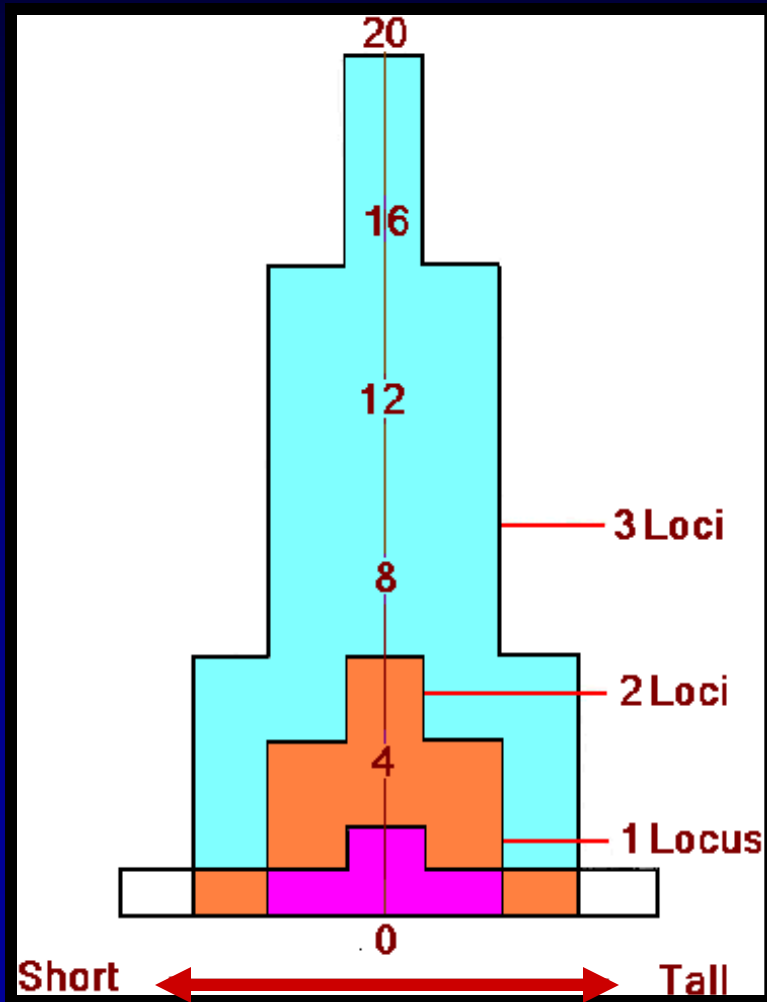
1 gene: $(a + b)^2$

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.

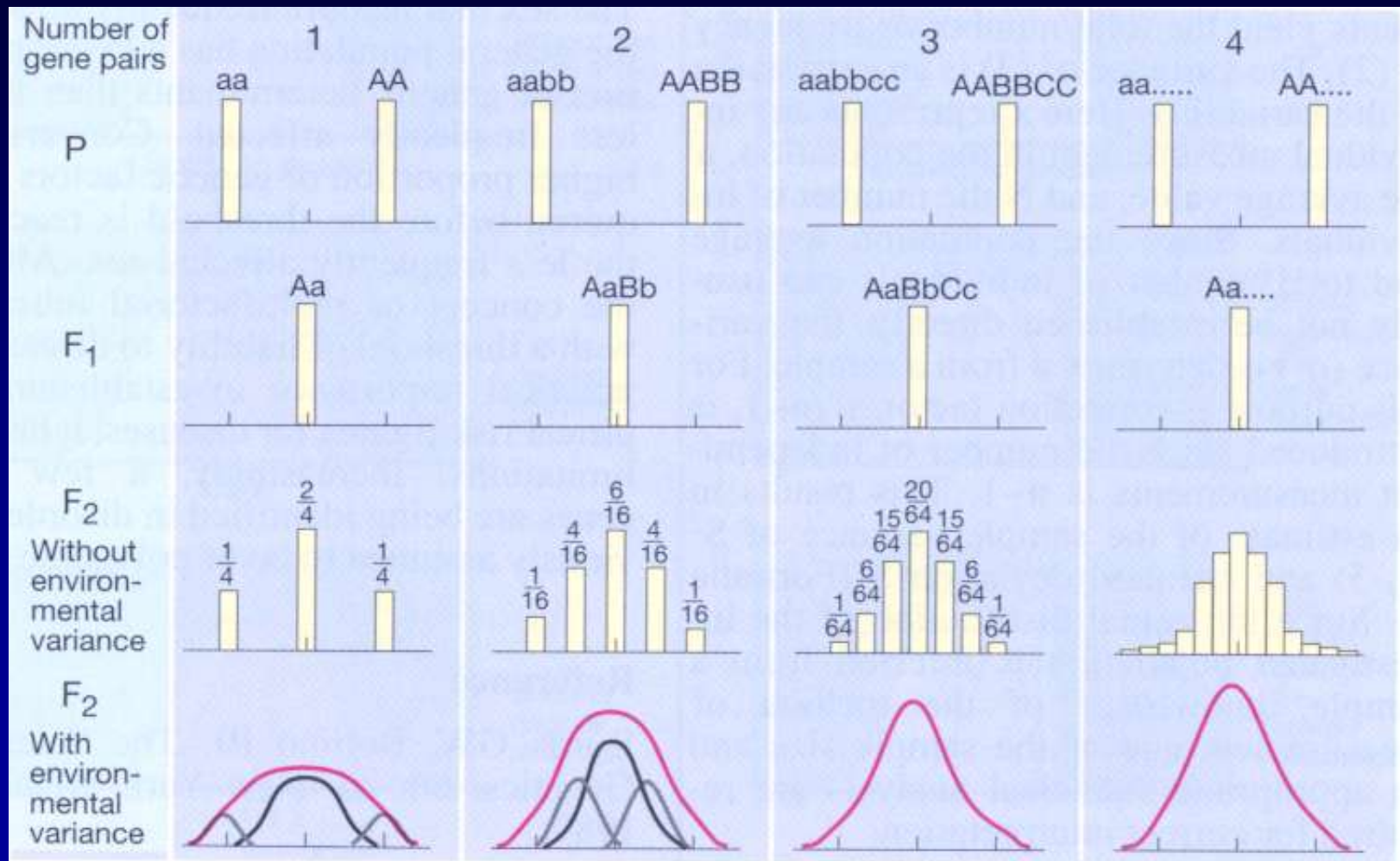


Distribution of Genotypes (Polygenic)



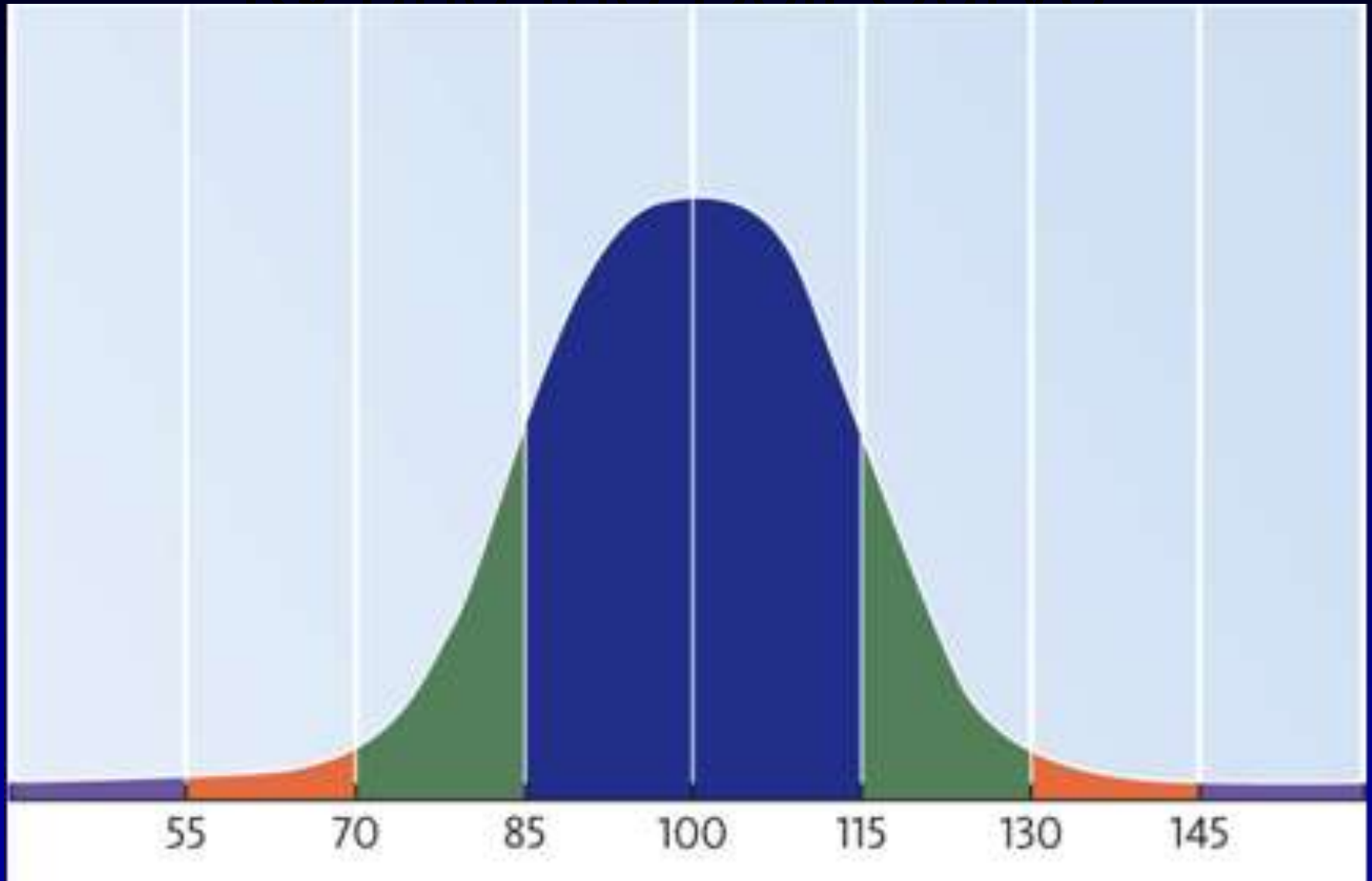
- Height with 1, 2 and 3 loci each with two alleles of equal frequency.
- The values for each genotype can be obtained from the binomial expansion $(p+q)^{2n}$ where $p = q = 1/2$ and n equals the number of loci.

Distribution A height in Population, Assuming is Controlled by Single Gene



IQ DISTRIBUTION

IQ and the Bell Curve



Phenotypic Variation

Sources of phenotypic variation

- Genotypes in the population
- Variation in the environment

Heritability – how much of the observed phenotypic variation is due to differences in genotype

Factors that Contribute to Phenotypic Variance

- **Genetic variance**

Variance attributed to the genotypic differences

- **Environmental variance**

Variance attributed to differences in the environment

- **Correlation coefficients**

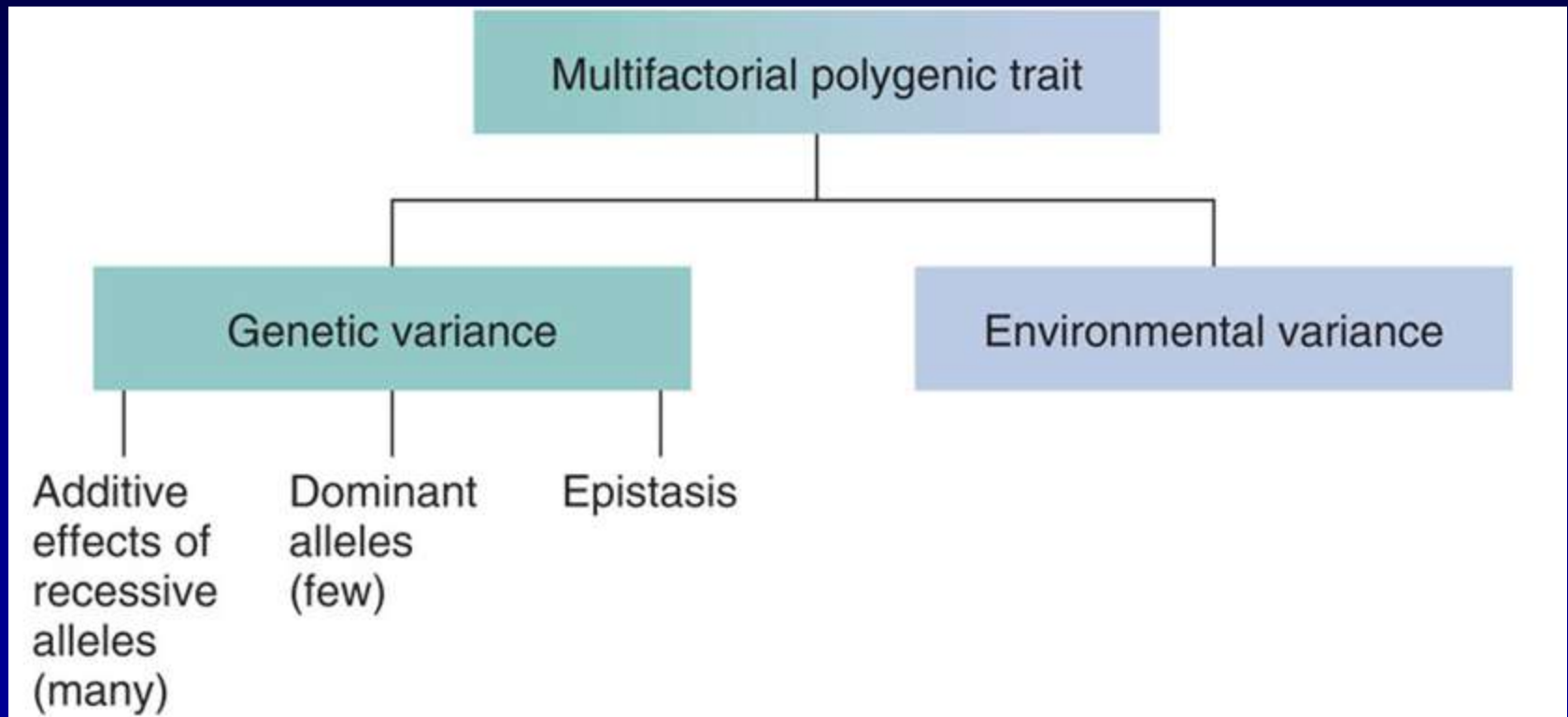
Measure the degree to which variables vary together

Heritability

- Heritability of a trait or disease is the proportion of the total variance that is genetic.
- The overall variance of the phenotype is the sum of the environmental and genetic variance.
- Heritability provides information of the importance of genetic factors in the causation of the disease.

Heritability (H)

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



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
• pyloric stenosis	0.3	75
• Ankylosing spondylitis	0.2	70
• Club foot	0.1	68
• Coronary artery disease	3	65
• Hypertension (essential)	5	62
• Congenital dislocation of the hip	0.1	60
• Anencephaly and spina bifida	0.1	60
• Peptic Ulcer	4	37
• Congenital Heart Disease	0.5	35

Heritability

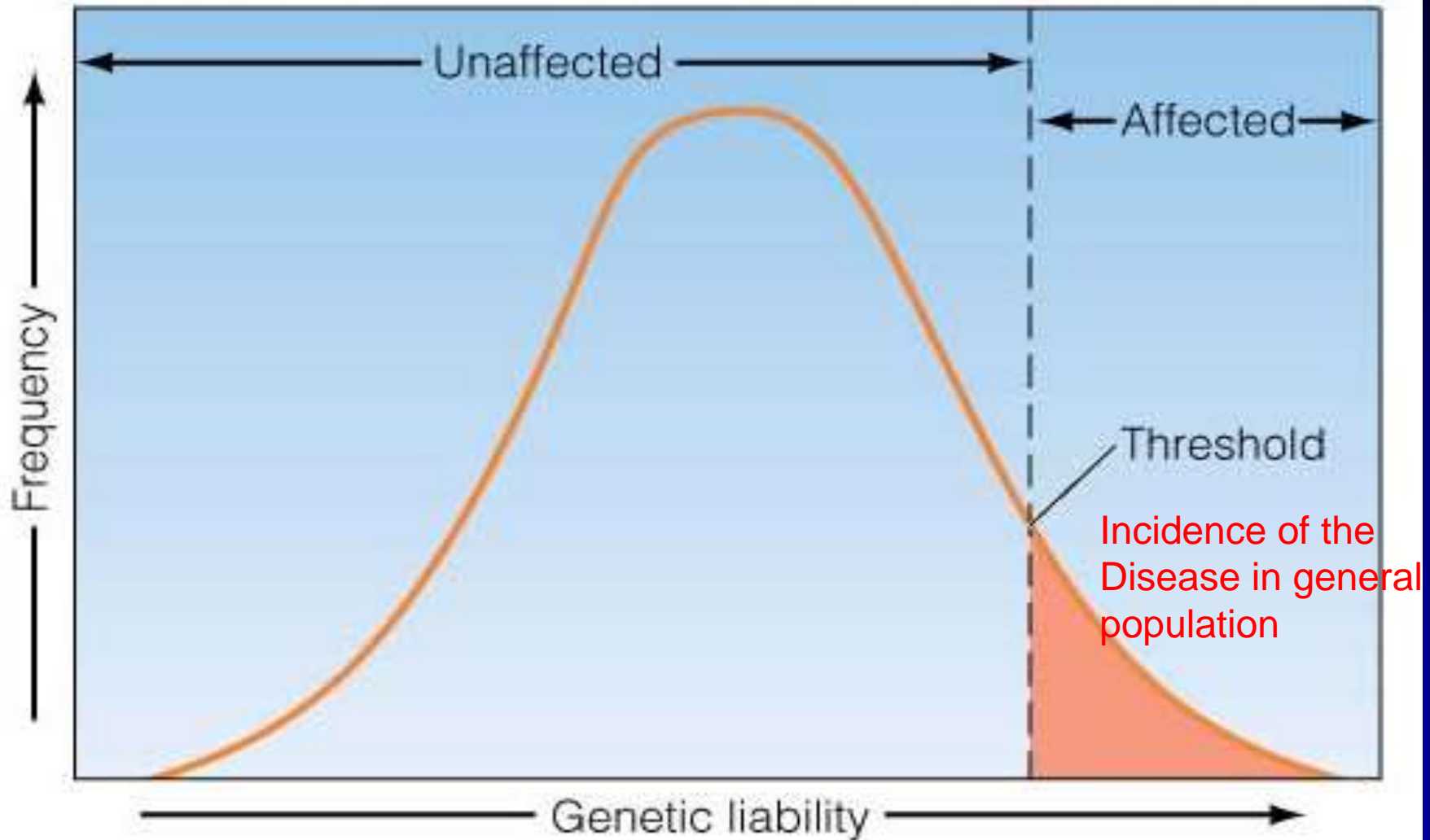
- Estimated from the proportion of people sharing a trait compared to the proportion predicted to share the trait.

Relationship	Degree	Percent shared genes
Siblings	1°	50%
Parent and child	1°	50%
Uncle/aunt and niece/nephew	2°	25%
Grandparent and grandchild	2°	25%
First cousins	3°	12.5%

Liability curve and threshold

- According to the liability/threshold model, all of the factors which influence the development of a multifactorial disorder, whether genetic or environmental, can be considered as a single entity known as **liability**.
- The liabilities of all individuals in a population form a continuous variable, which can be exemplified by a bell shaped curve.
- Individuals on the right side of the threshold line represent those affected by the disorder.

Threshold Model



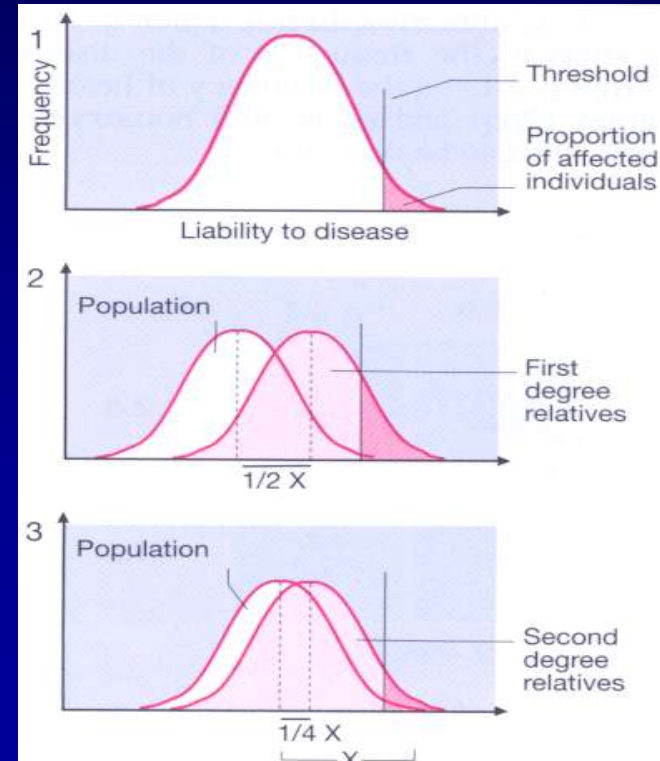
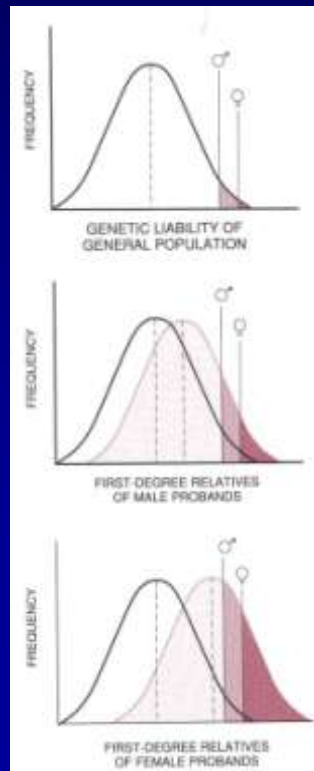
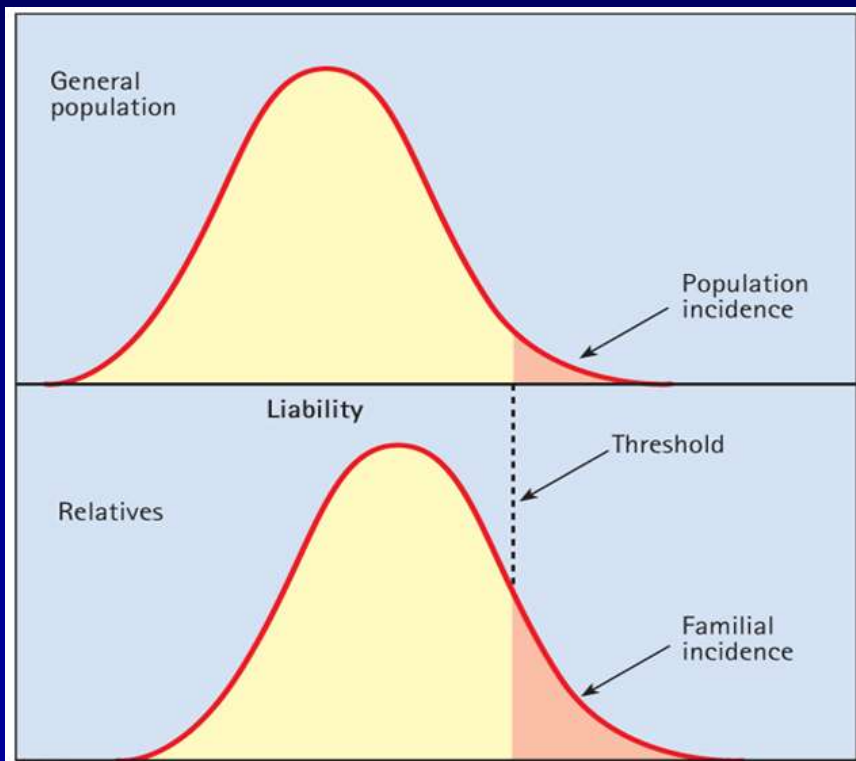
Threshold

- To account for a discontinuous phenotype (i.e. affected or not affected) with an underlying continuous distribution, it is proposed that a threshold exists above which the abnormal phenotype is expressed. In the general population the proportion beyond the threshold is the population incidence, and among relatives the proportion beyond the threshold is the familial incidence.

Liability curves of affected and their relatives

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

First degree relatives of an affected individual differ in their liability for the disorder by about half of the average of the general population $1/2 X$
 Second degree relatives = $1/4 X$



Familial incidence versus general population incidence

- The risk of recurrence for first-degree relatives, i.e. siblings and offspring of an index case approximates to the square root of the general population incidence.
- Thus if the incidence in the general population is 1 in 1000, the sibling and offspring risk will equal approximately 1 in 32 or 3% (square root of 1/1000).

Population and recurrence risks for Type 2 diabetes mellitus

- If incidence in the general population is 4-5%, then possible rate of affection in first degree relatives (brothers, sisters, sons and daughters) is around 10-15%.

Liability or susceptibility for a certain disorder

- For example : every embryo has a certain susceptibility to cleft palate.
- The susceptibility is low or high and follows a Gaussian distribution in the population.
- Embryos whose susceptibility exceeds a critical threshold value develop cleft palate, those whose susceptibility is below the threshold develop a normal palate.
- Susceptibility is the product of interaction of many genes with environmental factors in utero.

Characteristics of multifactorial inheritance

- Condition is relatively common
- Incidence in relatives lower than for single gene disorder but higher than in general population
- Risks to sibs similar to that of children
- Incidence falls rapidly in more distant relatives
- Incidence in relatives rises as the manifestations become more severe in the index case
- Risk to relatives higher when index case is of the least commonly affected sex
- Observed risk rises following the birth of two affected children

Multifactorial inheritance: ***Factors increasing probability of recurrence in a particular family***

- Close relationship to proband
- High heritability of disorder
- Proband of more rarely affected sex
- Severe or early onset disease
- Multiple family members affected

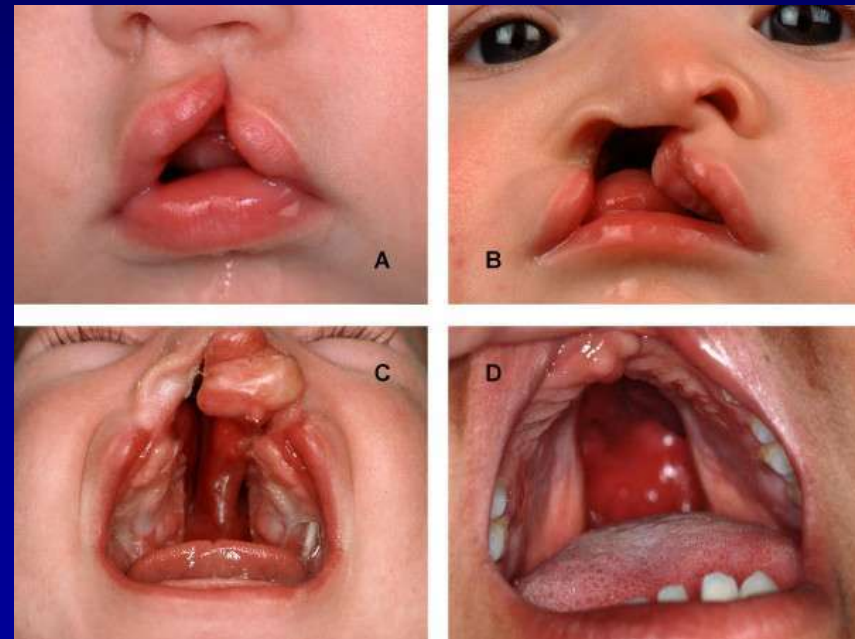
All these suggest that the family has a higher liability to the disorder – genes of higher effect or more adverse environmental influences

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 lip and 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 of cleft palate

Recurrence

Relationship

Risk

General population

0.1%

First cousin

0.3%

Niece or nephew

0.8%

Child

3.5%

Sibling

4.1%

Identical twin

40.0%



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%. It is not that having a second baby caused their recurrence risk to increase, but it makes them a couple who always had been at a high risk. For MF disorders, bad luck in the past is a predictor of bad luck in the future.



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

- In spina bifida the risks to first-, second- and third degree relatives of the index case are approximately 4%, 1% and less than 0.5%, respectively.



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.

To be affected or not depends on a balance between the number and function of good and bad genes and environmental 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

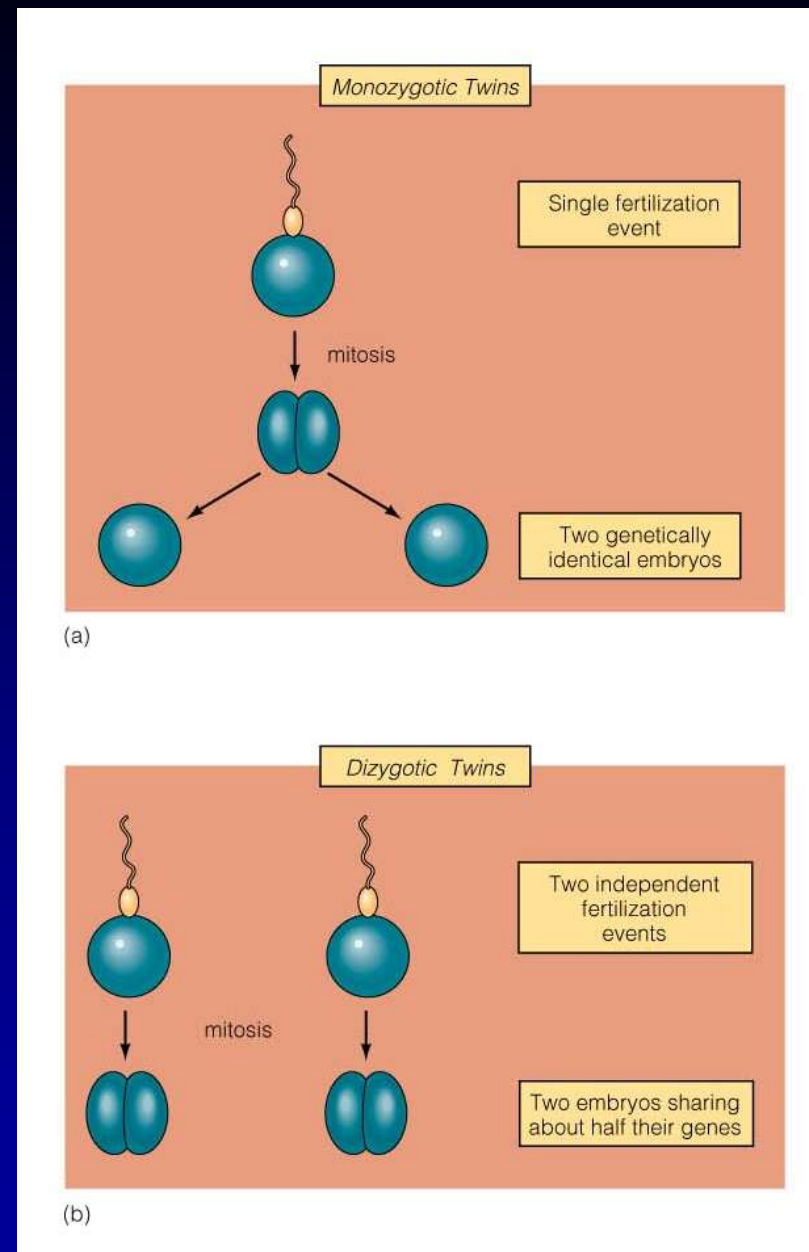
- Dizygotic twins: Shared environment and 50% of genes
- Monozygotic twins: Identical genotype, and shared environment
- Twins raised apart: Shared genotype but not environment
- Adopted individuals: Shared environment but not genes

Concordance

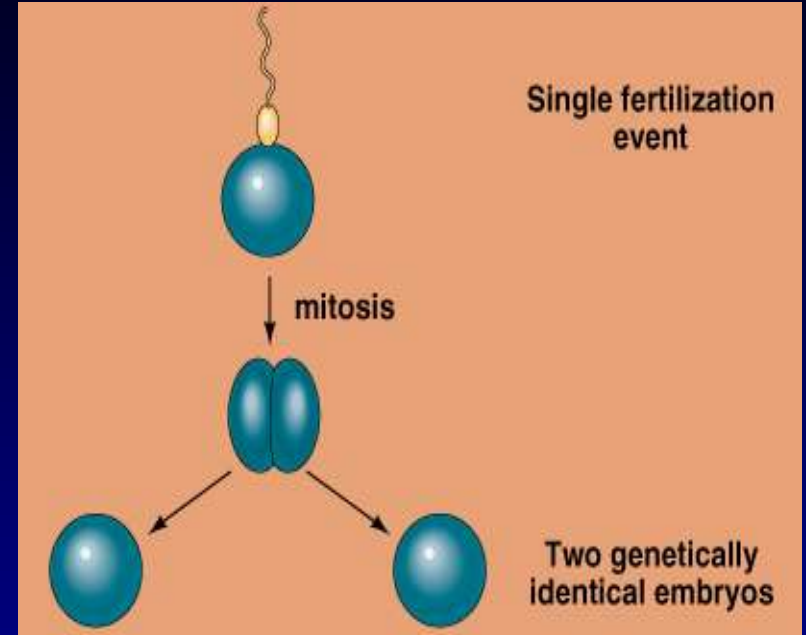
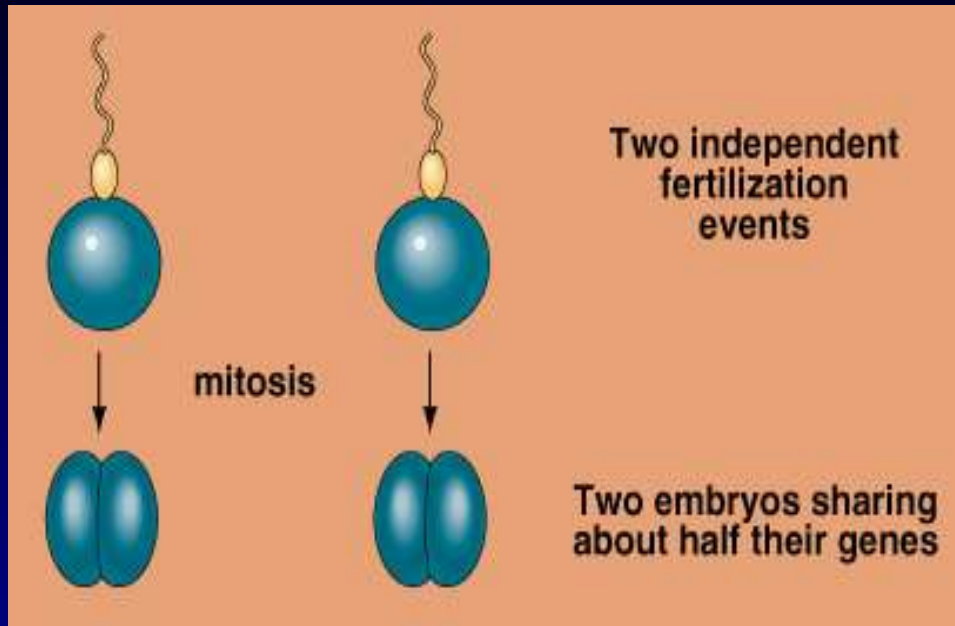
- **Concordance** - the percentage of pairs in which both twins express the trait
- Used to determine heritability
- Has limitations, assumes both type of twins share similar environments
- MZ twins often share more similar environments

Twin Studies

- **Monozygotic twins**
 - Single fertilization
 - Genetically identical
- **Dizygotic twins**
 - Independent fertilizations
 - Share approximately half their genes



Heritability



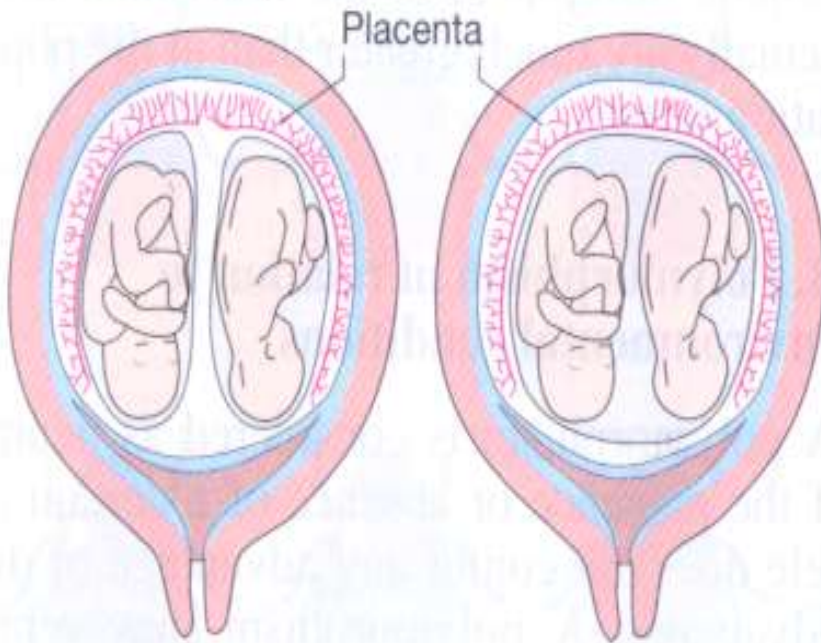
Concordance % of pairs of individuals that share the trait
(both affected or both unaffected)

Language skills (measured by vocabulary at age 2)

<u>Relation</u>	<u>%concordance</u>	<u>% expected</u>
MZ twins	.81	1.00
DZ twins	.42	0.5

TWINS

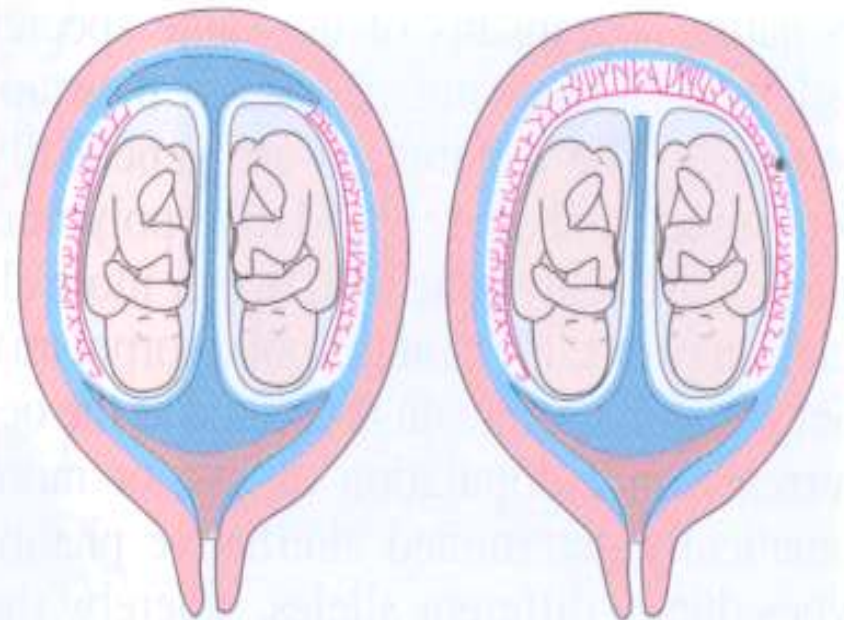
Monozygotic twins



Monoplacental,
diamniotic

Monoplacental,
monoamniotic

Dizygotic twins



Diplacental,
diamniotic

Monoplacental,
diamniotic

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

- **Disease concordance less than 100% in MZ twins is strong evidence that non-genetic factors play a role in the disease.**
- **Greater concordancy in MZ versus DZ twins is strong evidence of a genetic component to the disease.**
- **An important exception is X-linked diseases. In females, discordancy could also be due to differences in the proportion of maternal versus paternal X that is inactivated.**
- **Ascertainment bias can also affect twin studies.**

Determining the incidence of a disease in twins helps delineate whether there are genetic and environmental components

<i>Disease</i>	<i>Concordance</i>	
	<i>Identical (MZ)</i>	<i>Non-identical (DZ)</i>
Manic depressive psychosis	67%	5%
Cleft lip and palate	38%	8%
Rheumatoid arthritis	34%	7%
Asthma	47%	24%
Coronary artery disease	19%	9%
Diabetes mellitus	56%	11%

Both genetic and environmental factors important

Do both twins show the same characteristic or trait?

Comparing MZ/DZ twins can give evidence for genetic and/or environmental influences

Trait	Concordance rate	
	Monozygotic	Dizygotic
Height	95%	52%
IQ	90%	60%

MZ twins share all their genes and environment DZ twins share 50% genes and environment

Heritability Based on Twins Data

Heritability estimates the contribution of genetic elements to the phenotype

DISEASE	MZT	DZT	Gen. Pop
High blood pressure	0.6-0.8	0.3-0.5	0.6
Asthma	0.1-0.9	0.0-0.5	0.72-0.8
Type 1 Diabetes	0.25-0.35	0.03-0.05	0,72
Type 2 Diabetes	0.5	0.37	0.26
Rheumatic arthritis	0.15	0.04	0.32

Estimating Heritability from Twin Studies

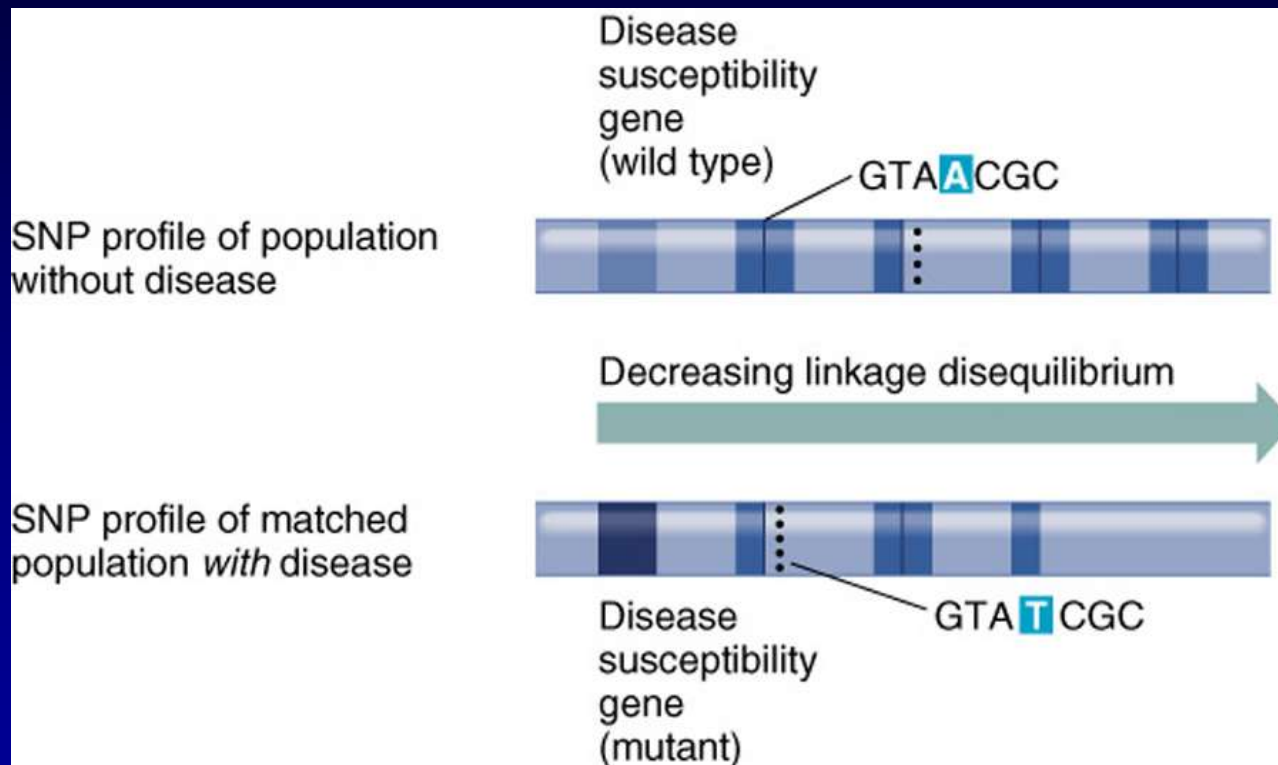
$$h^2 = \frac{\text{variance in DZ pairs} - \text{variance in MZ pairs}}{\text{variance in DZ pairs}}$$

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.

SNP (single nucleotide polymorphism)

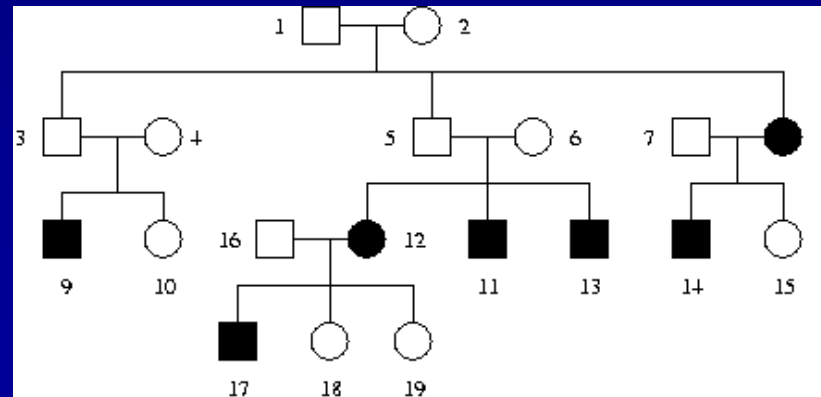
Nucleotide site with more than one allele is a polymorphism.



• 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 → 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.