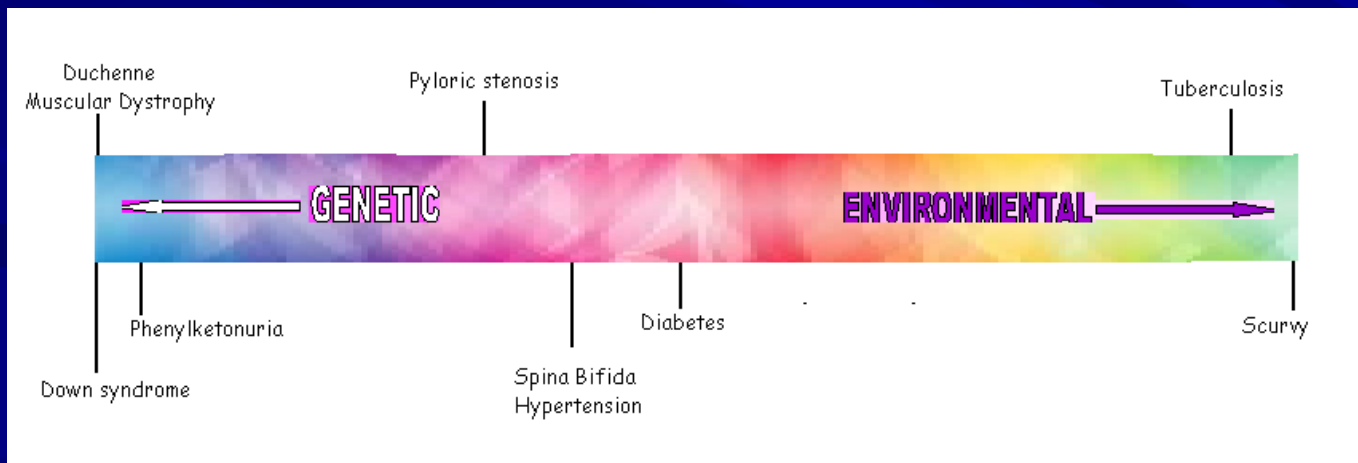# Multifactorial or Polygenic Inheritance

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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.

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

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.

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.

Polygenic / Multifactorial traits

A normal distribution (Gaussian or bell shaped curve) is generated by many genes, known as *polygenes*, each acting in an additive fashion.
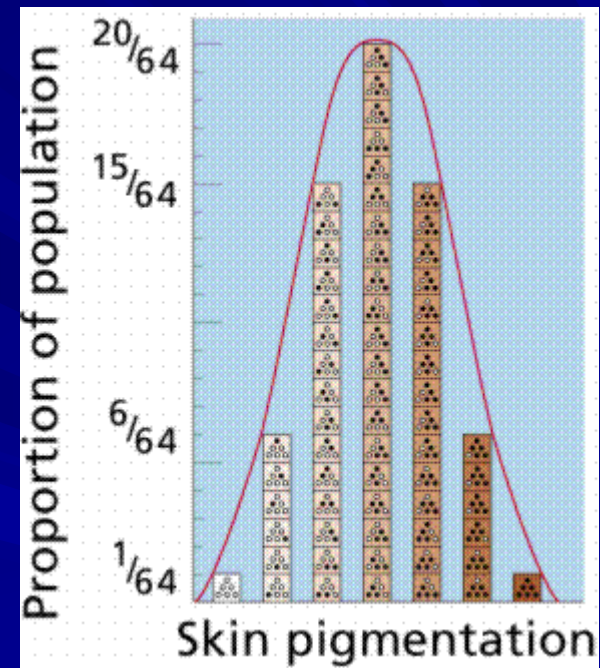
Human characteristics that show a continuous normal distribution

- Height
- Intelligence
- Blood pressure
- Skin colour

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.

Examples of heritability estimates

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

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

Incidence of the disease in the general poulation

Liability curve for the general population
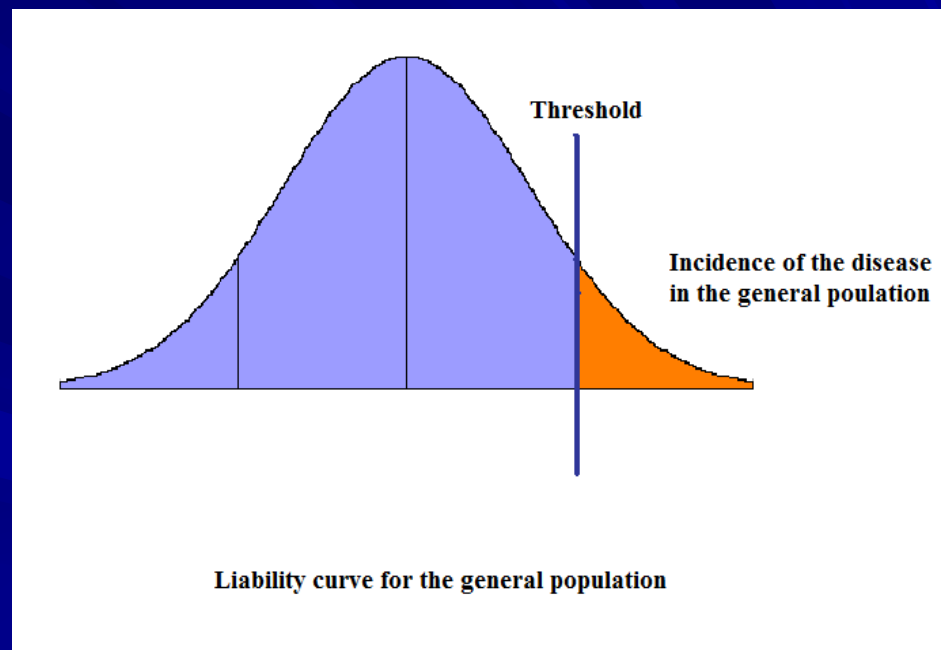
Threshold

- 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.

Liability curve for the general population

Threshold

Incidence of the disease in the general poulation

Liability curve for relatives of affecteds

Incidence of disease among relatives of affecteds
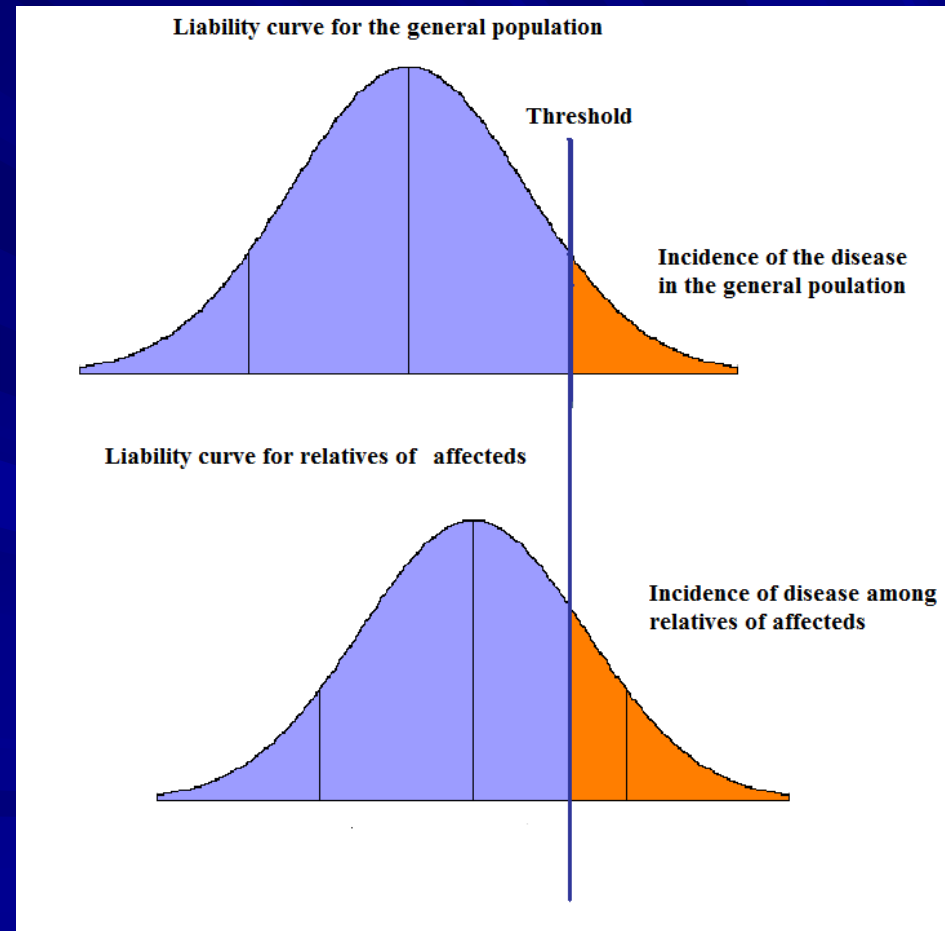
# Familial incidence versus general population incidence

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%.
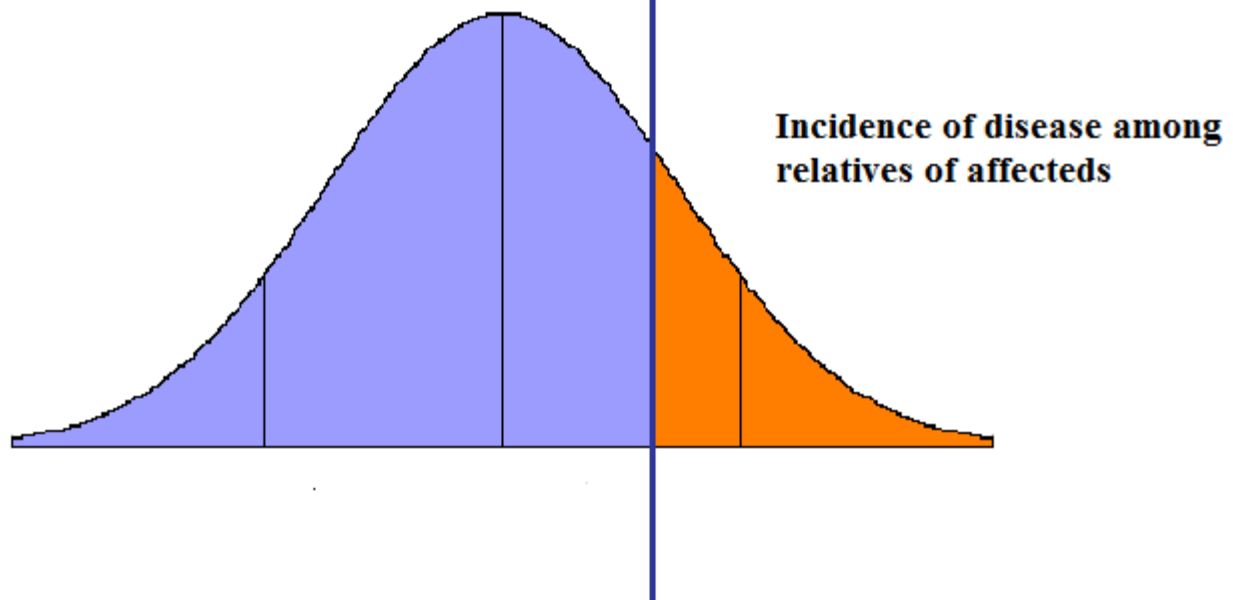
Liability curve and threshold
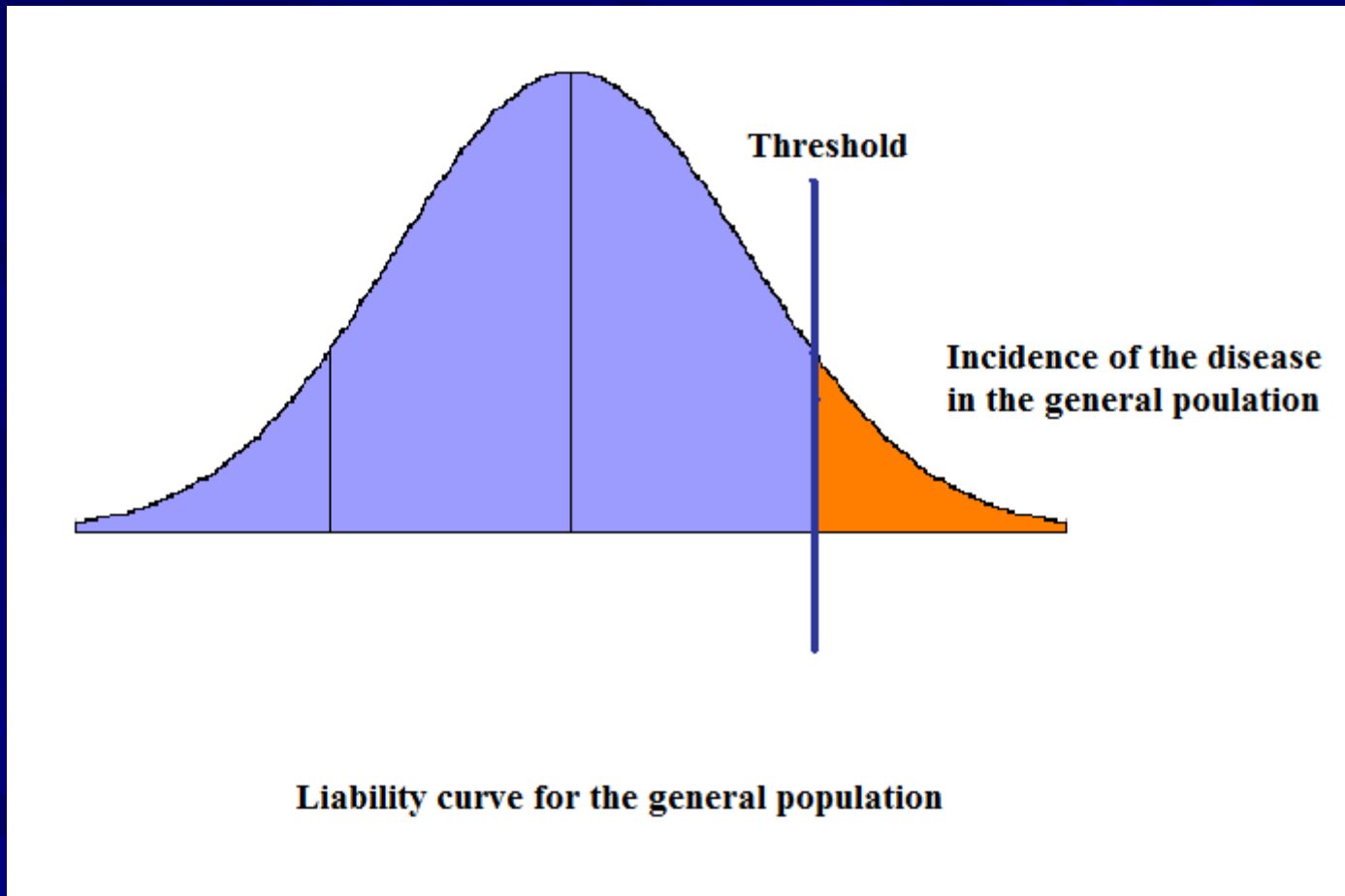
Liability curve for the general population

Liability curve for the general population

Threshold

Incidence of the disease in the general poulation

Liability curve for relatives of affecteds
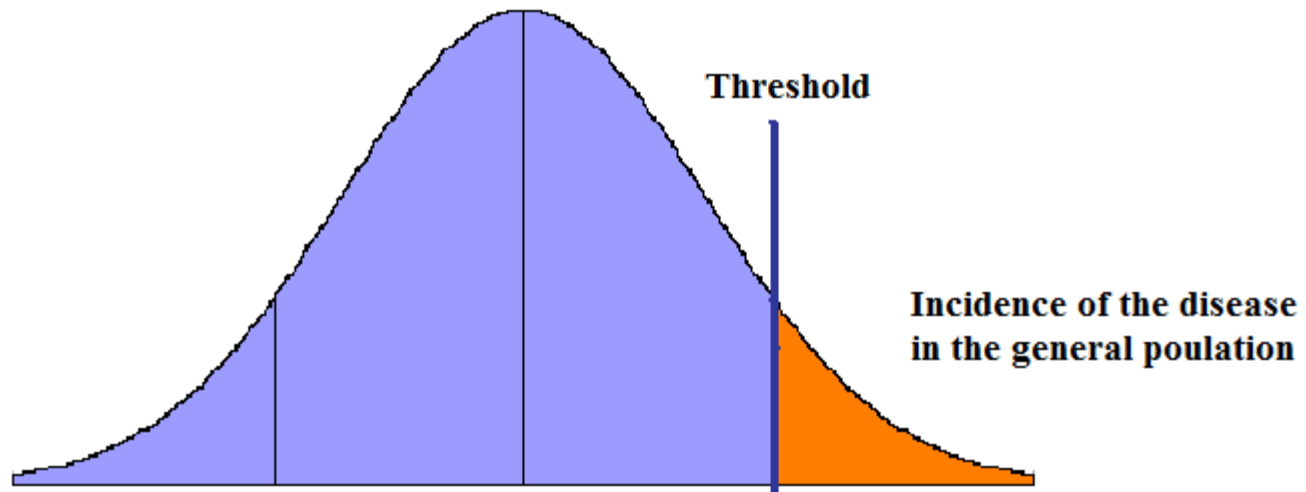
Incidence of disease among relatives of affecteds

Liability or susceptibility for a certain disorder

- For example : every embryo has a certain susceptibility to <u>cleft palate.</u>

- 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.
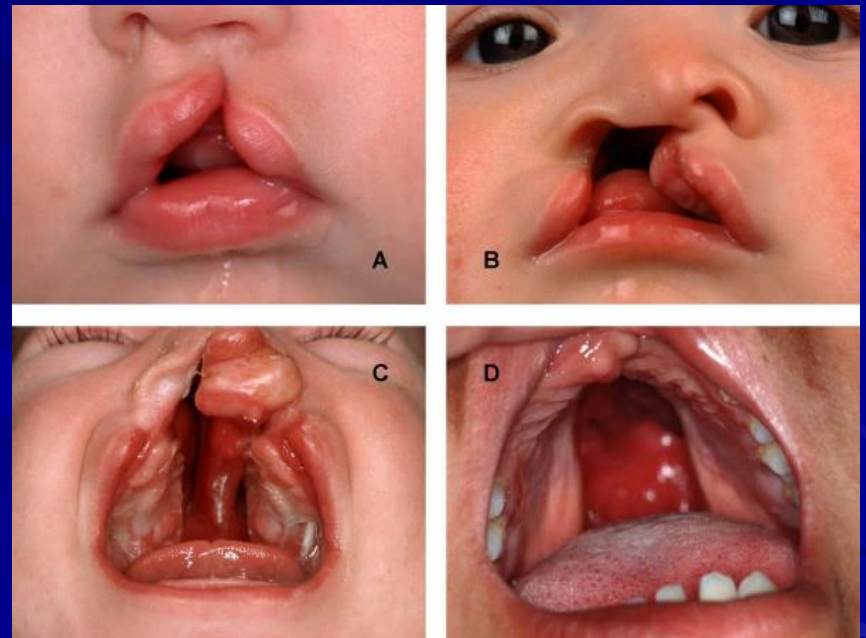
Characteristics of multifactorial inheritance

- Polygenic threshold characters tend to run in families because affected individuals have relatives who share their genes with them.

- Parents who have several affected children will have more high risk alleles than parents with only one affected child.

- Thus recurrence risk increases with increasing number of previously affected children.

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%.

- 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

Conclusions

- Multifactorial disorders are more common than single gene and chromosomal disorders
- They are caused by the interaction of many genes with environmental factors

Conclusions

- 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 non-communicable diseases counseling.