Multifactorial Inheritance

Prof. Dr. Nedime Serakinci

GENETICS

- I. Importance of genetics. Genetic terminology.
- I. Mendelian Genetics, Mendel's Laws (Law of Segregation, Law of Independent Assortment). Generations, crosses, etc.
- In humans, modes of inheritance (AR, AD, X-linked inheritance).
- II. Extensions to Mendelism; variable expressivity, incomplete penetrance, incomplete dominancy, codominancy, genetic heterogeneity, pleiotropy, environmental influences, sporadic cases, etc.
- IV. Non-Mendelian inheritance; maternal inheritance, genomic imprinting, X-inactivation, polygenetic inheritance, genetic susceptibility

Non Mendelian Genetics

- Characters Mendel studied in peas almost simple and straight-forward.

- The relationship between genotype and phenotype may be more complex in many traits.

  – Multifactorial disorders

  – Sometic cell genetic disorders

  – Mitocondrial disorders

MULTIFACTORIAL INHERITANCE

- Multi-"FACTORIAL", not just multi-GENIC

- Common phenotypic expressions governed by "multifactorial" inheritance

  - Hair color

  - Eye color

  - Skin color

  - Height

  - Intelligence

  - Diabetes, type II
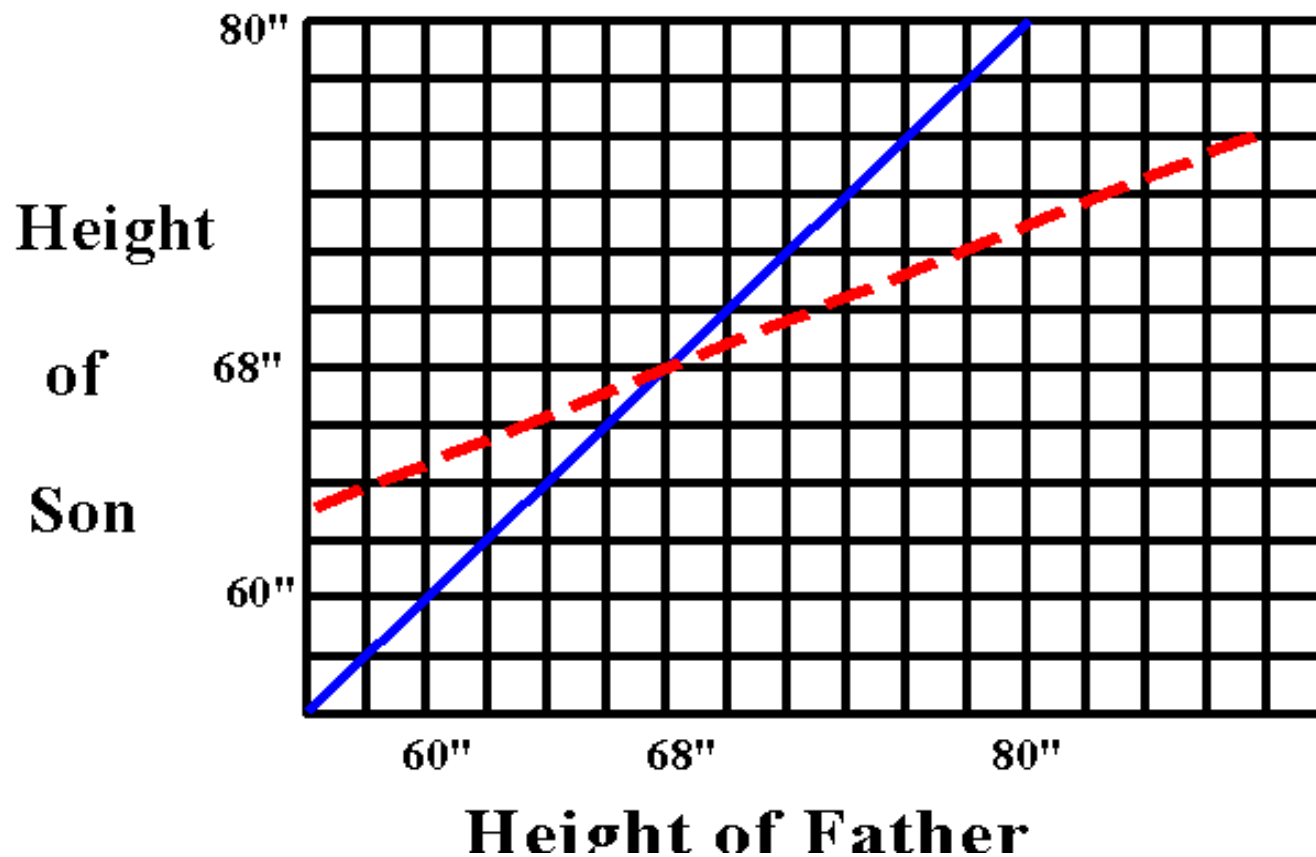
If the son's height were completely determined by the father's height, the correlation would be as shown by the solid blue line. What is observed is shown by the dashed red line. The height of the father and the average height of the son are related, but the average height of the son always regresses toward the mean. That is understandable if there is no dominance. The son only gets half of his father's genes; the other half comes from his mother

FEATURES of multifactorial inheritance

- Expression determined by NUMBER of genes

- Overall 5% chance of 1st degree relatives having it

- Identical twins >>>5%, but WAY less than 100%

- This 5% is increased if more children have it

- Expression of CONTINUOUS traits (e.g., height) vs. DISCONTINUOUS traits (e.g., diabetes)

If a disease or condition is scalable, rather than on or off, it is probably multigenic, or multifactorial, just part of the spectrum of HOMO-zygous diseases being HOMO-geneous, and HETERO-zygous diseases being VARIABLE.

Human characteristics that show a continuous normal distribution, and are therefore multifactorial.

Blood pressure

Dermatoglyphics (ridge count)

Head circumference

Height

Intelligence

Skin color

Heart disease

Many more………………

Multifactorial disorders

- Result of both environmental and genetic factors.

- Relative importance of genetic factors is variable.

- Familial tendency apparent but do not follow the characteristic pedigree patterns of single-gene disorders.

- Numerous genetic alterations may predispose individuals to the same disease

Multifactorial disorders - examples

Diseases of childhood and adult life

- Neural tube defects

- Asthma

- Diabetes mellitus

- Hypertension

- Coronary heart disease

- Cancer

- Epilepsy

- Manic depression

- Rheumatoid arthritis

- Alzheimer's Disease

Polygenic and multifactorial inheritance

- Many disorders demonstrate familial clustering that does not conform to any recognized pattern of Mendelian inheritance. Examples include several of the most common congenital malformations and many of the common acquired diseases of childhood and adult life.

- It is likely that many factors – genetic and environmental – are involved in causing these disorders that are showing multiple gene inheritance – the two types being multifactorial and polygenic.

- Multifactorial conditions show normal distribution, and are generated by many genes. Polygenic conditions show a liability threshold, where genes act in an additive, but discontinuous fashion.

Consider the following: One locus for height, with three alleles. Allele **h2** adds 2 inches to the average 68-inch height. Allele **h0** neither adds nor subtracts from the average height of 68 inches. And allele **h-** subtracts 2 inches from the average height. Suppose **h0** is twice as frequent as either **h2** or **h-**. The Punnett square for the population would be as follows:

		FATHER'S GAMETES		
		h2	2h0	h-
MOTHER'S GAMETES	h2	h2,h2 72"	2(h2,h0) 70"	h2,h- 68"
	2h0	2(h2,h0) 70"	4(h0,h0) 68"	2(h-,h0) 66"
	h-	h2,h- 68"	2(h-,h0) 66"	h-,h- 64"

If a second locus, called the tall locus, or **t**, is also involved in height, with three alleles as above, one adding two inches, one neither adding nor subtracting from the phenotype, and one subtracting 2 inches, with the neutral allele occurring twice as frequently as the either of the others
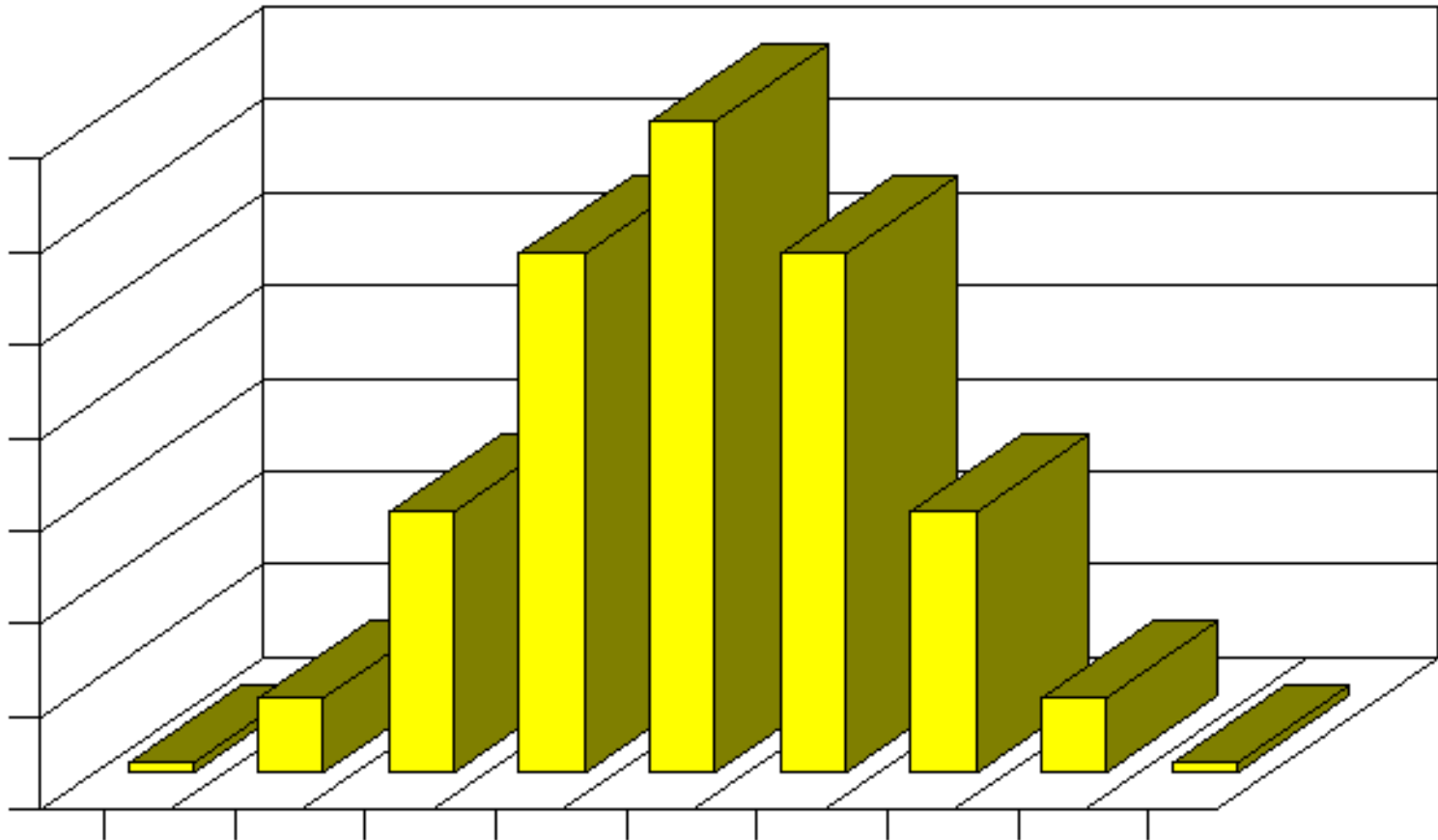
THE MULTIFACTORIAL MODEL

- As more loci are included, this binomial distribution quickly approaches the Gaussian distribution, or the bell-shaped normal curve, observed with human quantitative traits. Three loci, each with three alleles, are enough to produce population frequencies indistinguishable from a normal curve.

The multifactorial model is then:

Several, but not an unlimited number, loci are involved in the expression of the trait.

There is no dominance or recessivity at each of these loci.

The loci act in concert in an additive fashion, each adding or detracting a small amount from the phenotype.

The environment interacts with the genotype to produce the final phenotype.

As an example of 4. above, women are, on average, three inches shorter than men with the same genome. Environmental factors (hormones) affect the final phenotype.

Not all human traits that show a continuous distribution in the population are multifactorial traits.

Any bimodal distribution is not controlled by multifactorial expression. It is more likely to be under the control of a single dominant/recessive gene with modifying environmental factors.

Multifactorial traits all show a unimodal bell-shaped distribution.

MULTIFACTORIAL INHERITANCE

- **What is known** as *multifactorial* **or** *quantitative* **inheritance?**

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

Effects of the genes are cumulative , with each gene contributing a small amount to the final expressed phenotype. No one gene is dominant or recessive to another.

Several human characteristics show a continuous distribution in the population that closely resembles a normal distribution.

Approximately 68%, 95% and 99.7% of observations fall within the mean plus or minus one, two or three standard deviations respectively.

Multifactorial trait

- Complex (conditions caused by many contributing factors are called complex or multi factorial, partly genetic

- Common medical probems, Either distinct (discontinous, e.g. disease like heart disease, Coronary artery disease (CAD), Diabetes Mellutus (DM), Alzheimer) or continous phenotypes (e.g. height, blood pressure level)

Multifactorial trait
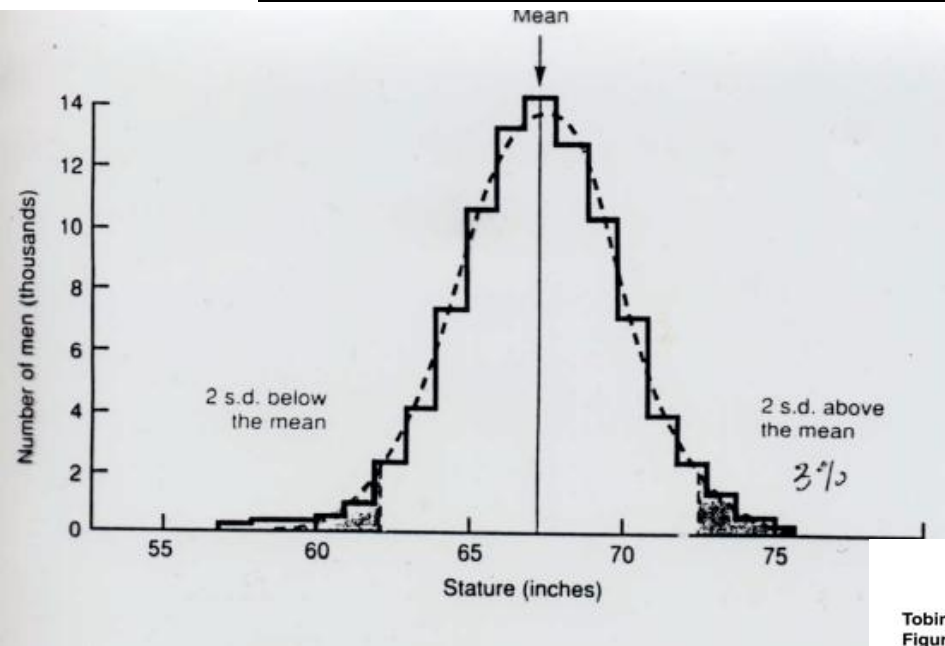
- Discontinous traits – risk to relatives of affected individual > population risk

- Rapidly falls in distant relatives

- Pedigree analysis is not very useful as in Mendelian disorders

Continous traits

- e.g. Physical characterstics like height, weight, red cell size, hemoglobin level etc..
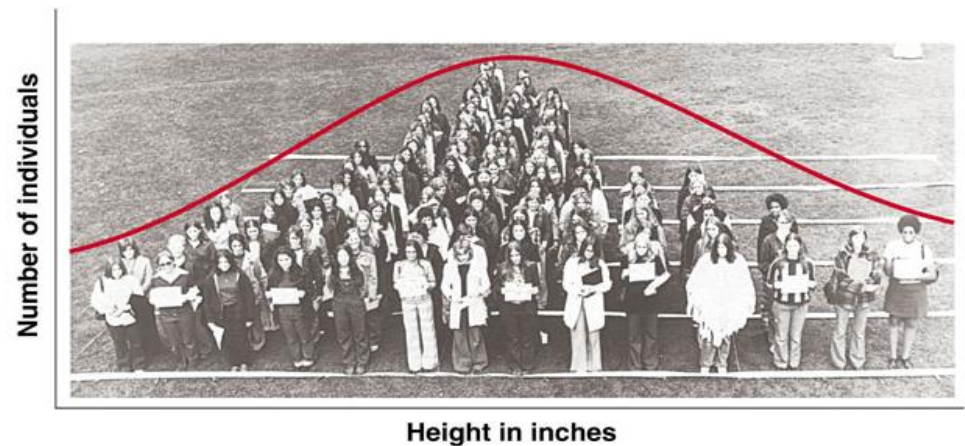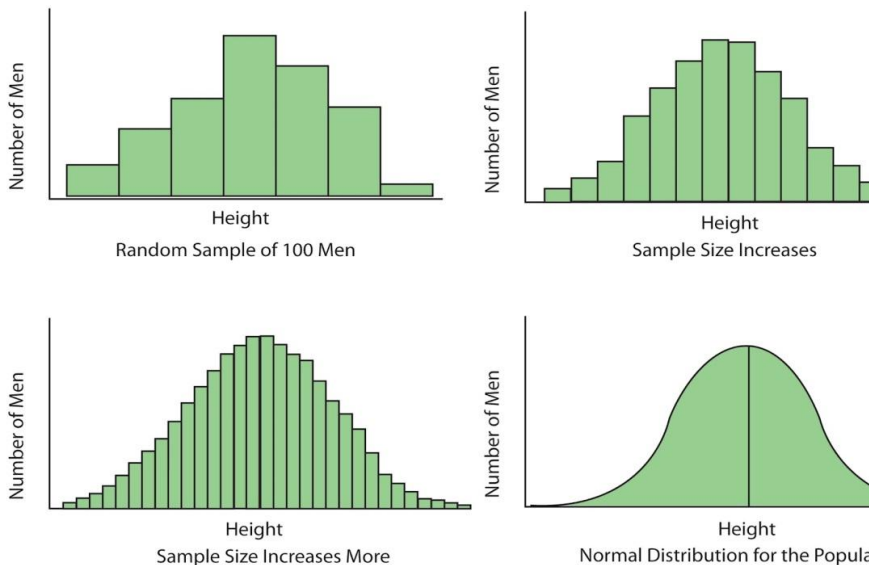
- Usually show Gaussian distribution
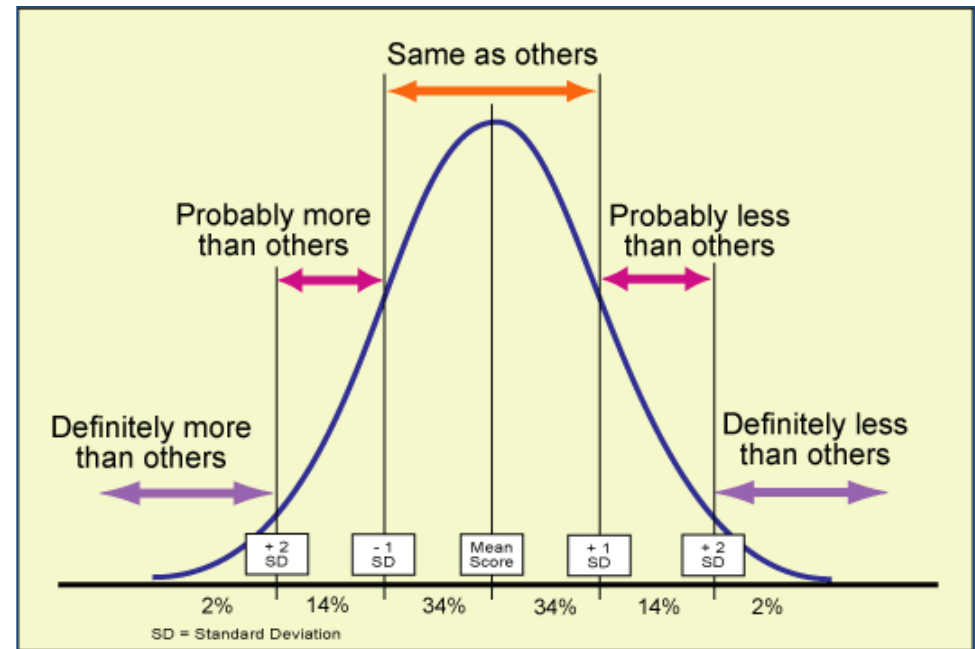
height - polygenic (additive) inheritance

Tobin/Dusheck, Asking About Life, 2/e
Figure 16.6

Polygenic Traits are quantitative rather than qualitative in nature. They are frequently distributed continuously in the population, often in a more or less bell shaped curve or they may fit the threshold model. polygenic traits include height, blood pressure, cleft lip cleft palate, NTDs .

A frequency distribution of systolic blood pressure determined by a two-locus two allele model was presented
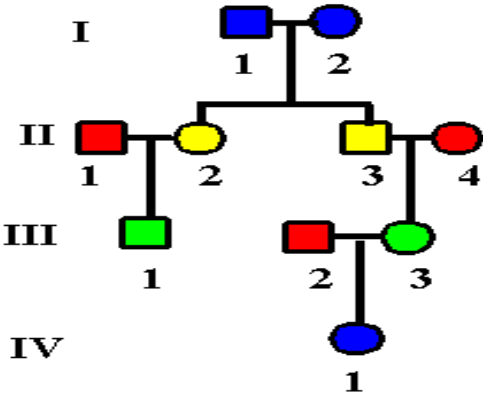

Random Sample of 100 Men

Sample Size Increases

Sample Size Increases More

Normal Distribution for the Popula
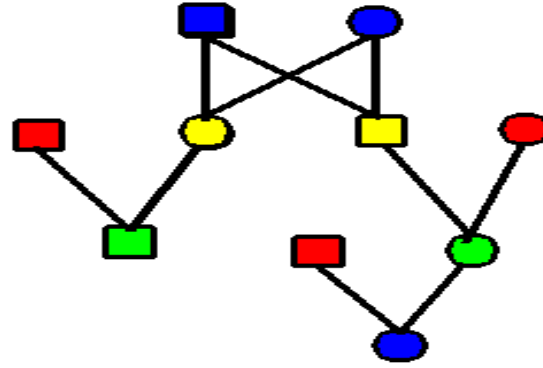

Height in inches

Discontinous traits

- Common adult diseases

- Congenital malformations

- Balance between the underactive and normally active genes is important

- Balance exceeds a threshold → phenotype

DEGREE OF RELATIONSHIP AND GENES IN COMMON

Conversion of a standard pedigree to a path coefficient pedigree for determining the fraction of genes in common.

Pedigree A

Pedigree B

I-1 and I-2. To determine the fraction of genes II-2 and II-3 have in common one simply counts all of the pathways and their connecting lines through the common ancestors. There is one line from II-2 to I-1, and a line from I-1 to II-3. That is one pathway with two lines of descent. There is another line from II-2 to I-2, and a line from I-2 to II-3. That is a second pathway with two lines of descent. These are the only pathways from II-2 to II-3. The fraction 1/2 is then raised to the power of the number of lines of descent and summed for each possible pathway, $(1/2)^2$ for the pathway through I-1, and $(1/2)^2$ for the pathway through I-2, making a total of 1/2. Brothers and sisters have, on average, 1/2 of their genes in common.

A parent and offspring, say I-1 and II-2 also have 1/2 of their genes in common. There is only one pathway between them and only one line in that pathway, $(1/2)^1$.

Other relationships follow in the same manner. In Figure 16, III-1 and III-3 are first cousins. There are two pathways connecting the two individuals, one through I-1 and the other through I-2, each with four lines. Their fraction of genes in common is then $(1/2)^4 + (1/2)^4$ or 1/8. First cousins have 1/8 of their genes in common. A grandparent and grandchild have 1/4 of their genes in common. There is a single pathway with two lines of descent. III-1 and IV-1 are first cousins once removed. Again there are two pathways, one through I-1 and the other through I-2, each with 5 lines, $(1/2)^5 + (1/2)^5$ or 1/16 of their genes in common.

The degree of relationship is often used rather than the fraction of genes in common. The degree of relationship is simply the power to which (1/2) is raised to reach the fraction of genes in common. First degree relatives have (1/2) of their genes in common. Second degree relatives have 1/4, $(1/2)^2$, of their genes in common, etc.

familial aggregation

- measured by relative risk (λ_r) =

$$\frac{\text{disease prevalence in relatives}}{\text{disease prevalence in population}}$$

- *Prevalence* is a measurement of *all* individuals affected by the disease (at a particular time) and is expressed as a proportion of the population

CONCORDANCE

Twin studies, although limited by complicating factors, provide the best source for separating genetic contributions to the trait being studied from environmental influences.

- Monozygous (identical) twins have the same genome, but not the exact environmental factors, especially if they were raised apart.

- The concordance rate in monozygotic twins can be compared to the concordance rate in dizygotic (fraternal) twins to estimate the genetic component (heritability) of the trait. If the trait is truly 100% genetic, as it is for total fingerprint ridge count in humans, monozygotic twins will be 100% concordant while dizygotic twins, having, on average, only half their genes in common, will have a lower concordance rate. If the trait under study is 100% environmental, monozygotic twins and dizygotic twins will have the same concordance rate. The concordance rate for a disease is calculated as follows:

- **Concordance Rate = [Both Affected / (One Affected + Both Affected)] x 100**

Twin studies

- MZ <u>rates</u> compared to DZ rates for specific traits

- The more similar rates, the less genetic contribution

Disorder	Concordance	
	Monozygotic	Dizygotic
Single gene	100%	As sibs
Chromosomal	100%	As sibs
Multifactorial	< 100% but > siblings	As sibs
Somatic cell genetic	As siblings	As sibs
Mitochondrial	100%	100%
Non-genetic	As sibs	As sibs

Essential Medical Genetics, 6th edition. Tobias, Connor, Ferguson-Smith. Published 2011 by Blackwell Published Ltd

Twin studies

- Monozygotic (MZ) or dizygotic (DZ)

- Diagnosis needs DNA marker analysis

- MZ: genetically identical

- Twins also share the environment!

Family correlation studies

- Relatives share genes

- Multifactorial traits – expressed in them according to genetic similarity

Table 10.4 Proportion of genes shared by relatives

Degree of relationship	Examples	Proportion of genes in common
First	Parent to child, sibling to sibling	50%
Second	Grandparent to grandchild, nephew or niece to aunt or uncle	25%
Third	First cousins	12.5%

Essential Medical Genetics, 6th edition. Tobias, Connor, Ferguson-Smith. Published 2011 by Blackwell Published Ltd

Degrees of relationship

| Relationship	Proportion of genes shared
First degree	**{1/2}**
Parents, Siblings, Children	
Second degree	**{1/4}**
Uncles and aunts, nephews and nieces Grandparents, grandchildren, half-siblings	
Third degree	**{1/8}**
First cousins, Great- grandparents, Great- grandchildren	

Family correlation studies

- Similarity of relatives – correlation

- 0 – 1, 1=identical

- If genetic, the closer the higher correlation

- Parents: not expected to be correlated unless blood relatives

Table 10.5 Family correlations for some continuous traits

| Trait	Correlation of first-degree relatives	
	Observed	Expected
Height	0.53	0.5
IQ	0.41	0.5
Finger ridge count	0.49	0.5
Diastolic blood pressure	0.18	0.5

Discontinous traits - liability / threshold model

- Liability: all factors which influence the development of a multifactorial disorder, whether genetic or not,

- the liabilities of all individuals in the population form a continuous variable

- the risk is distributed normally

- the disorder occurs only when a certain threshold is exceeded
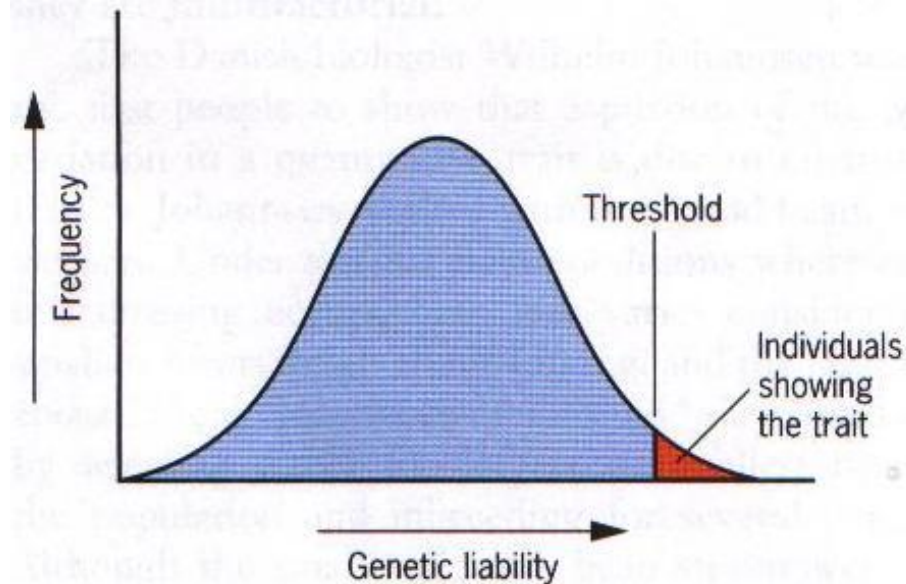
The threshold model for multifactorial traits. Below the threshold the trait is not expressed. Individuals above the threshold have the disease.

Liability - threshold

Molecular Genetics, 3'e. (© Garland Science 2004)
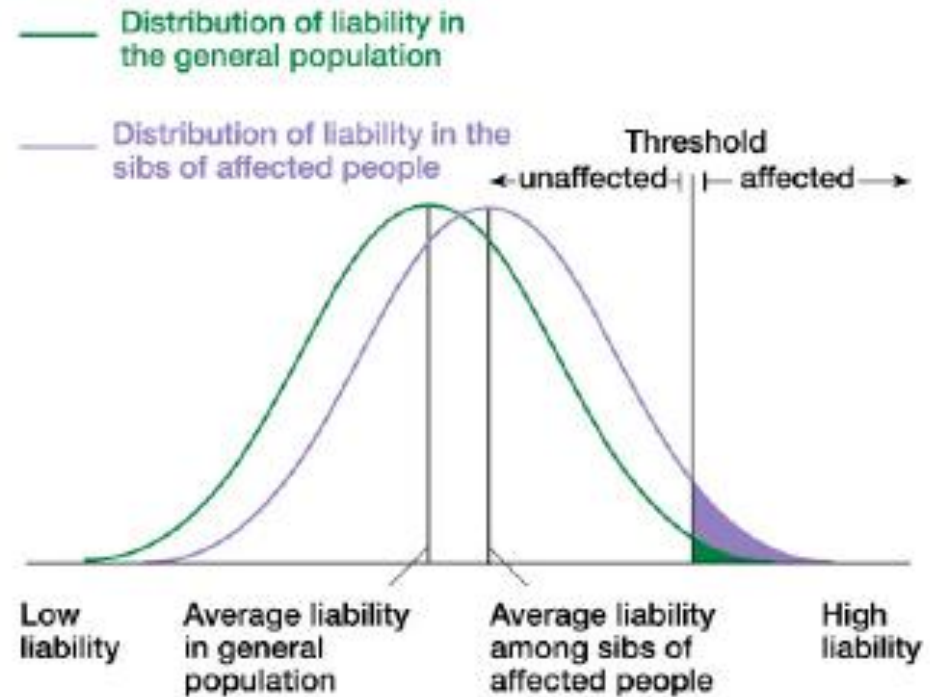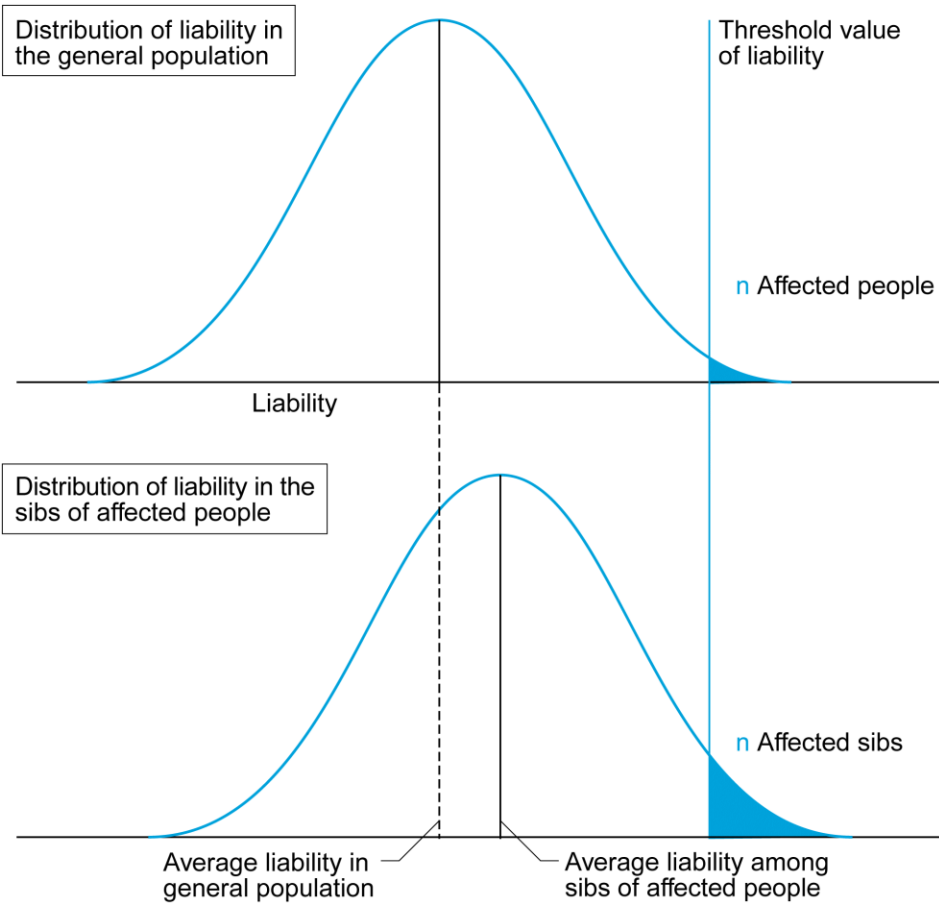
Liability/threshold model - summary

- Recurrence risk: biggest for the most close relatives, decreases rapidly in more distant ones

- Incidence: biggest among relatives of most severly affected ones

- The more affected in a family, the bigger the risk for others

- If the trait is expressed more in one sex than in the other, the risk of recurrence is greater in the offspring if the affected parent belongs to the less frequently affected sex

MULTIFACTORIAL inheritance.

- In reality, human characteristics such as height and intelligence are also influenced by environment, and possibly also by genes that are not additive in that they exert a dominant effect.

- These factors probably account for the observed tendency of offspring to show what is known as a "regression to the mean".

- This is demonstrated by tall or intelligent parents (the two are not mutually exclusive!) having children whose average height or intelligence is slightly lower than average or mid-parental value.

- Similarly, parents who are very short or of low intelligence tend to have children whose average height or intelligence is lower than the general population average, but higher than the average value of the parents.

POLGENIC Inheritance – More on the Liability/Threshold Model

- According to the *liability/threshold* model, all of the factors that 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 has a normal distribution in both the general population and relatives of affected individuals.

- However, the curves for these relatives will be shifted to the right, and the extend to which they are shifted is directly related to the closeness of their relationship to the affected index case.

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

© Elsevier. Turnpenny & Ellard: Emery's Elements of Medical Genetics 13e - www.studentconsult.com
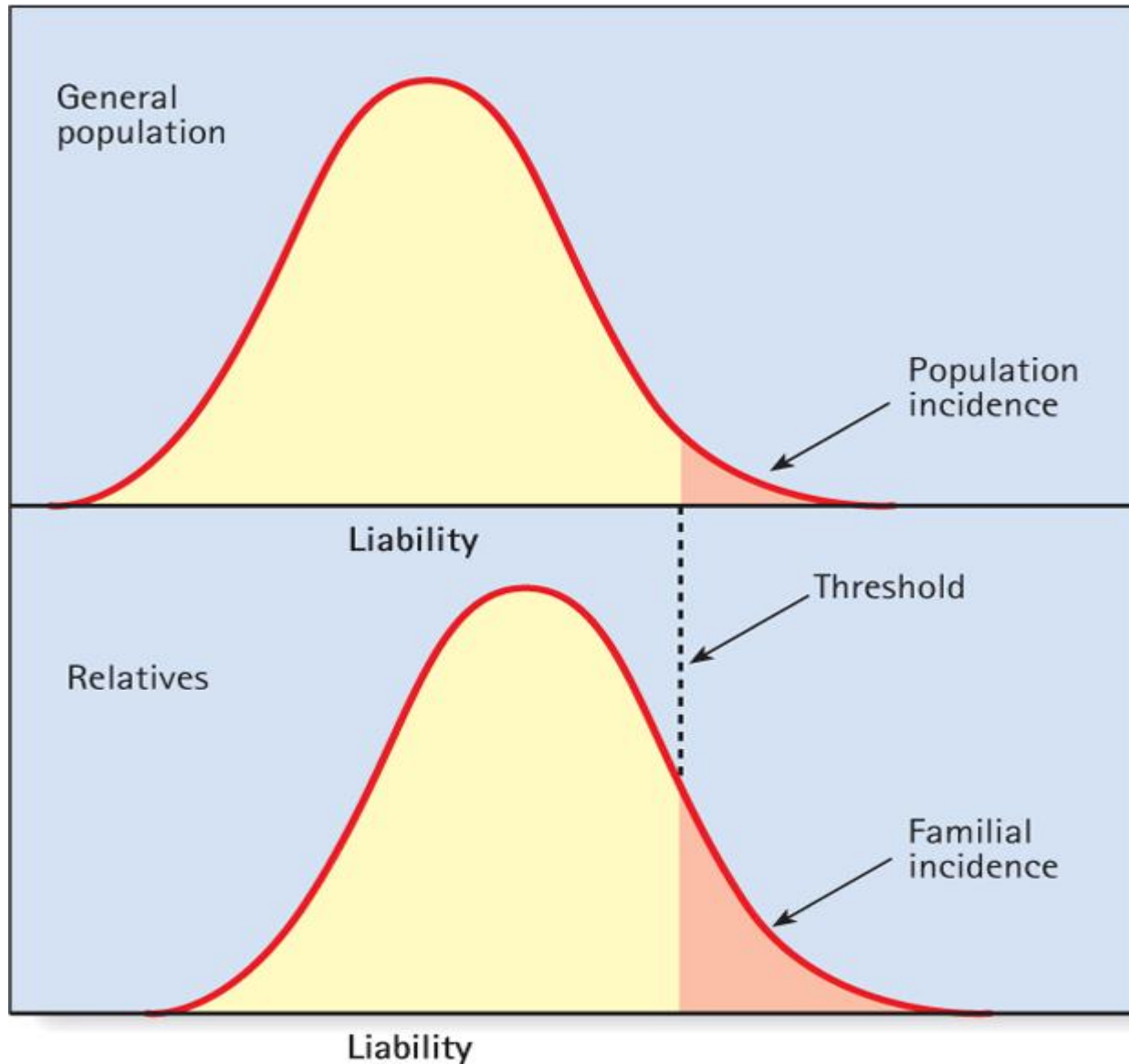
CONSEQUENCES OF THE LIABILITY/THRESHOLD MODEL

- 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.

IDENTIFYING GENES THAT CAUSE EITHER A MULTIFACTORIAL OR A POLYGENIC DISORDER

- Multiple gene disorders are common and make a major contribution to human morbidity and mortality.

- A number of strategies have been used to search for disease susceptibility genes.

- Mapping multiple gene disorders is much more difficult than mapping single gene disorders for the following reasons:

 - it is extremely difficult mathematically to develop strategies for

 detecting linkage of additive "polygenes', only because the phenotype does not show up until a liability threshold is exceeded.

 - many multifactorial diseases show a variable age of onset

 - most families where a multifactorial disease exists, have only one or two

 living affected members, owing to the severity of many of them.

 - all multiple gene disorders are etiologically heterogeneous, with different genetic and environmental mechanisms involved in different subtypes.

Analysing multifactorial trait genetically

- Linkage analysis

- Sibling-pair study

- Marker association analysis

- Candidate gene analysis

- Genome-wide SNP association

Sources

- https://www.uic.edu/classes/bms/bms655/lesson11.html

  http://mymds.bham.ac.uk/genetics/d2/multifactorial.htm

- Essential Medical Genetics, Edition, 5th or 6th EditionEdward S. Tobias, Michael Connor, Malcolm Ferguson-Smith March 2011, ©2011, Wiley Blackwell