



Umm AL Qura University

POLYGENIC AND MULTIFACTORAIL INHERITANCE

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IMPORTANT DEFINITION

Complex or multifactorial inheritance - disease occurrences in families that do not match one of the simple Mendelian patterns of inheritance.

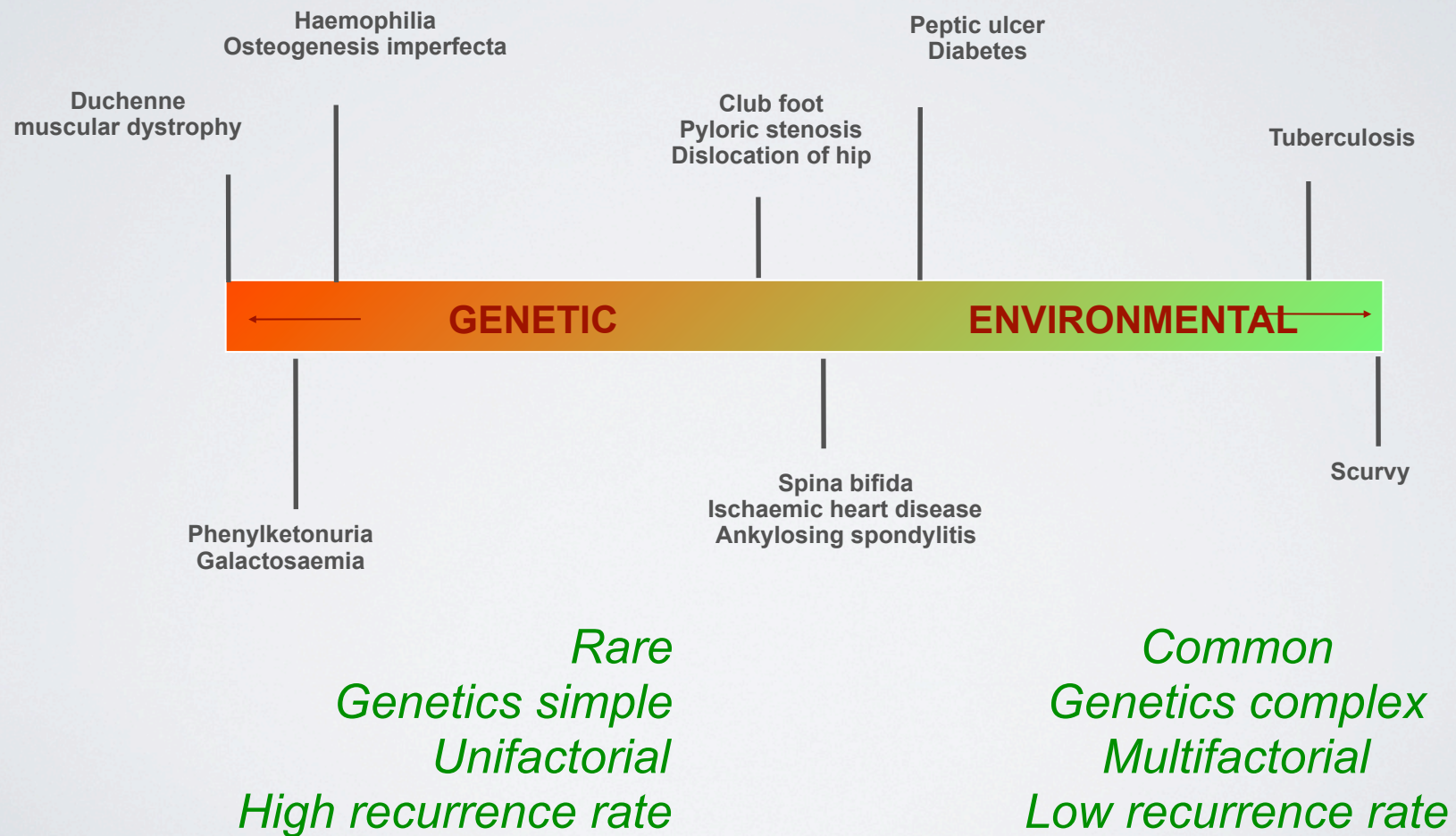
Discrete/qualitative trait - traits that are present or absent.

Continuous/quantitative trait - traits that have measurable characteristics across a range of values. This class includes the vast majority of diseases affecting humans.

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

The contributions of genetic and environmental factors to human diseases



CONTINUOUS (QUANTITATIVE) TRAIT

- Polygenic – many genes
- Large number of genetic factors, each making only a small contribution to the final phenotype

MULTIFACTORIAL INHERITANCE

- Inheritance controlled by many genes with small additive effects (polygenic) plus the effects of the environment
- Clinical clue: One organ system affected

FAMILY STUDIES OF THE INCIDENCE OF CLEFT LIP (\pm CLEFT PALATE)

<i>Anomaly</i>	<i>Risk to sibs %</i>
Bilateral cleft lip and palate	5.7
Unilateral cleft lip and palate	4.2
Unilateral cleft lip alone	2.5

The more severe the manifestation of a multifactorial condition, the greater the probability of recurrence

SOME MULTIFACTORIAL CONDITIONS HAVE AN UNEQUAL SEX RATIO

<i>Condition</i>	<i>Sex ratio (males to females)</i>
Congenital dislocation of hip	1 to 6
Rheumatoid arthritis	1 to 3
Peptic ulcer	2 to 1

For some conditions there must be a different threshold for males and females

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

MULTIFACTORIAL INHERITANCE AS A MODE OF INHERITANCE FOR A CONDITION IS MORE LIKELY IF.....

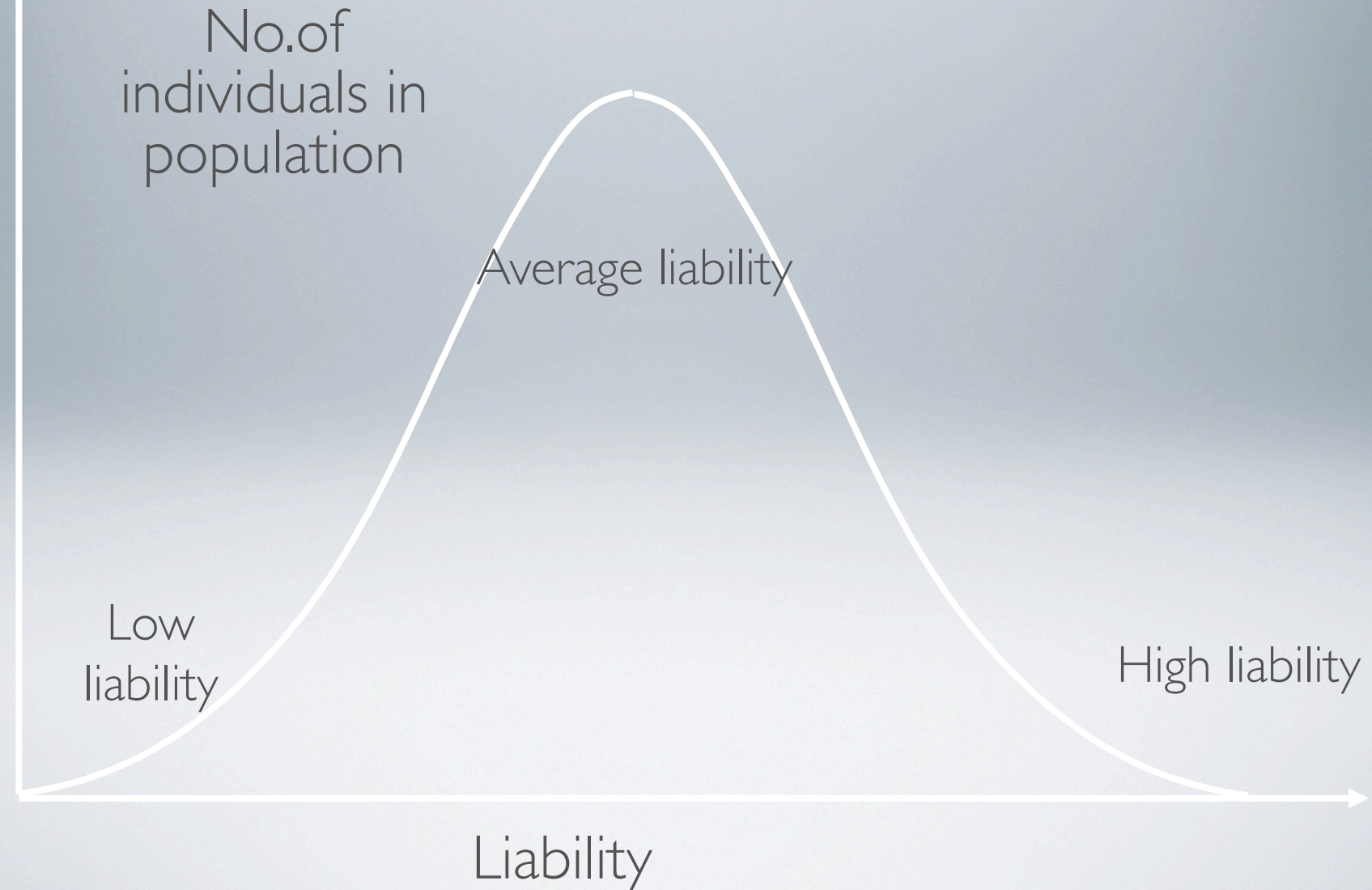
- Condition is relatively common
- Incidence in relatives lower than for single gene disorder but higher than in general population
- Risks to sibs similar to that of children
- Incidence falls rapidly in more distant relatives
- Incidence in relatives rises as the manifestations become more severe in 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 TRAITS

- Genetic predisposition likely to be due to a particular combination of genes
- The genes and environmental factors causing a particular multifactorial trait may vary from person to person

- Most diseases with a genetic component are **not** inherited in Mendelian fashion but display multifactorial inheritance
- Multifactorial disease usually polygenic -many genes each with small additive effects
- Major effort to identify common disease susceptibility genes underway
- Identification of SNPs associated with disease susceptibility

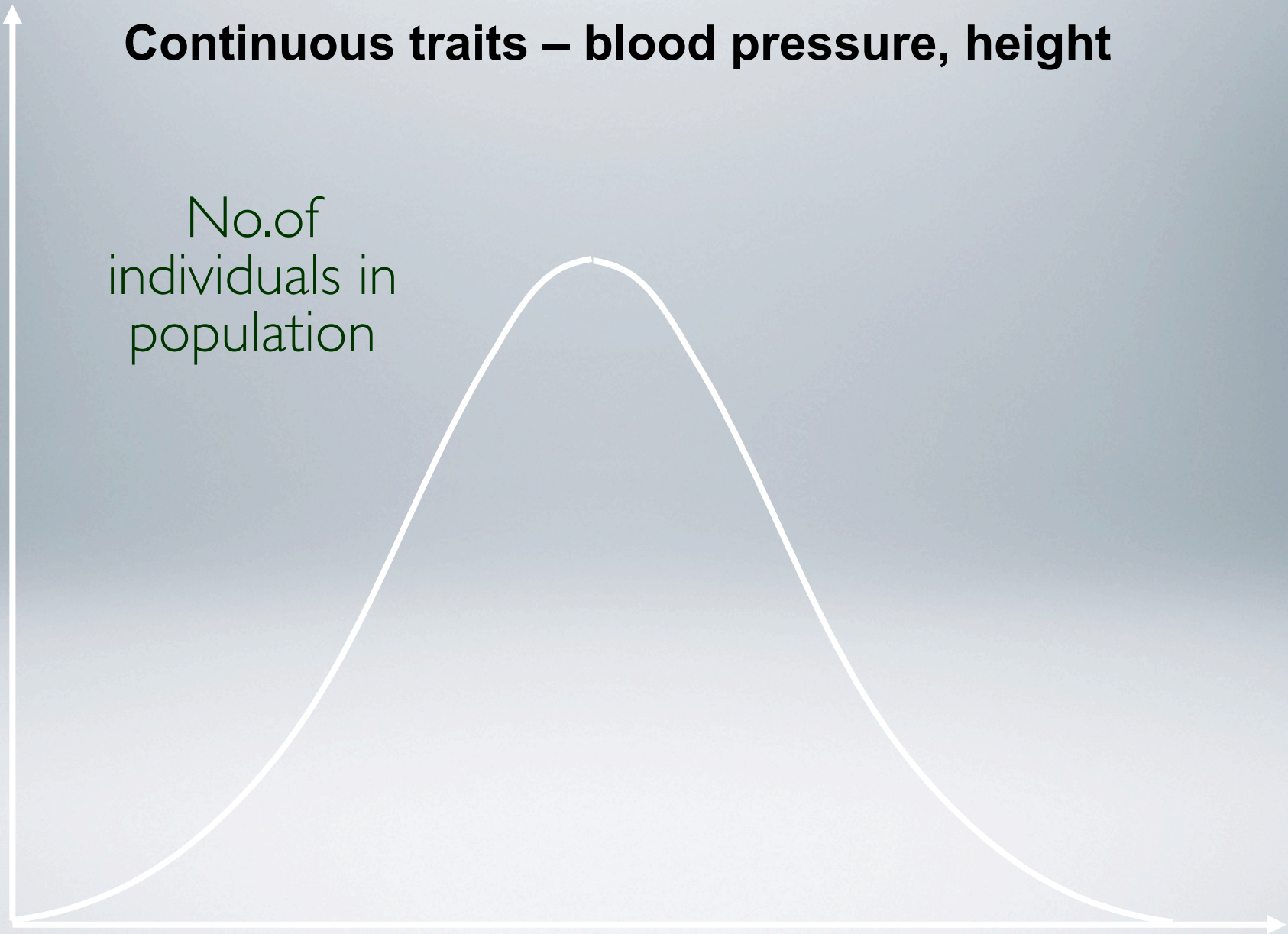
In multifactorial disorders, the liability curve is made up of genetic and environmental factors



Continuous traits – blood pressure, height

No. of
individuals in
population

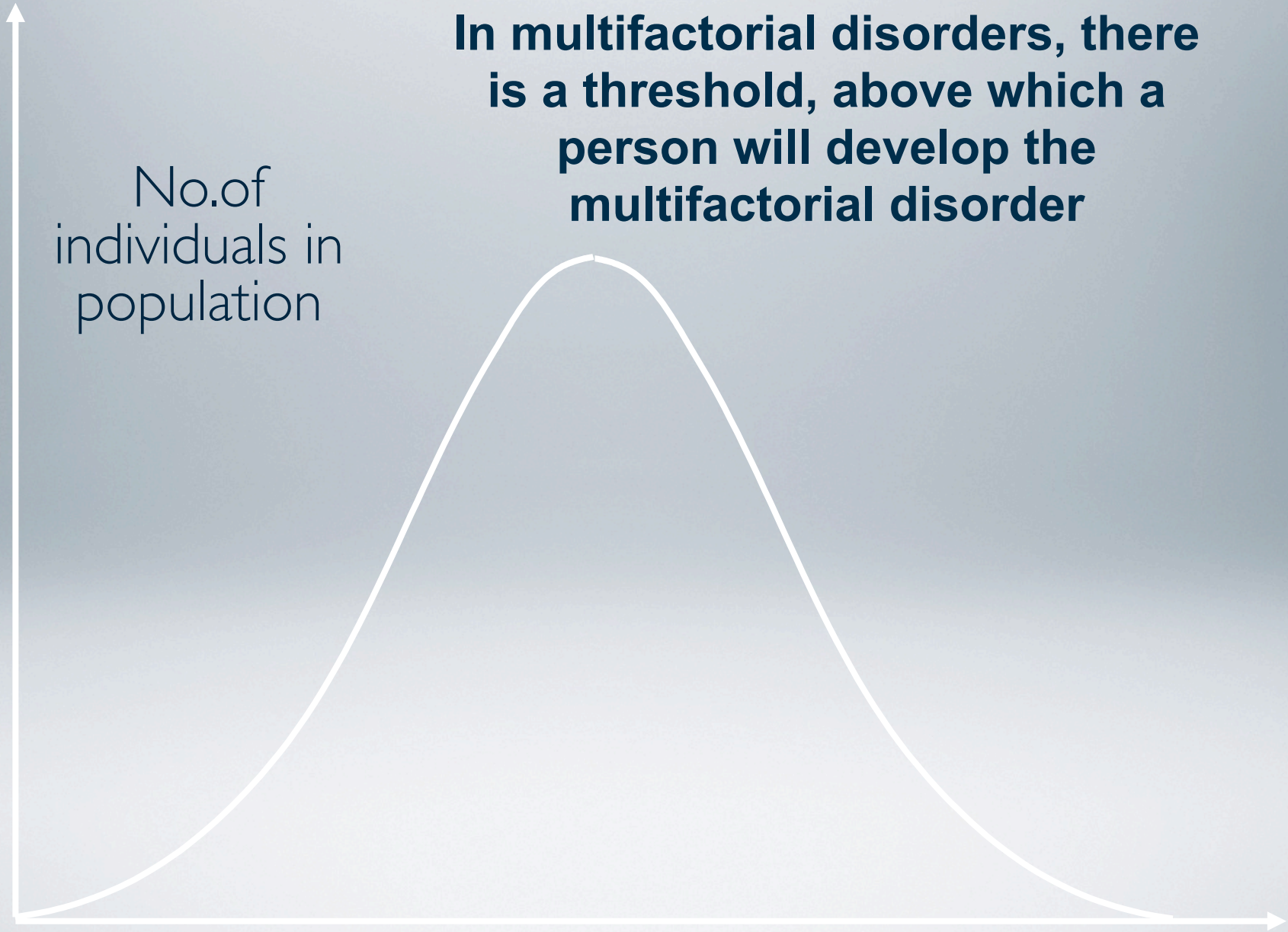
Height →



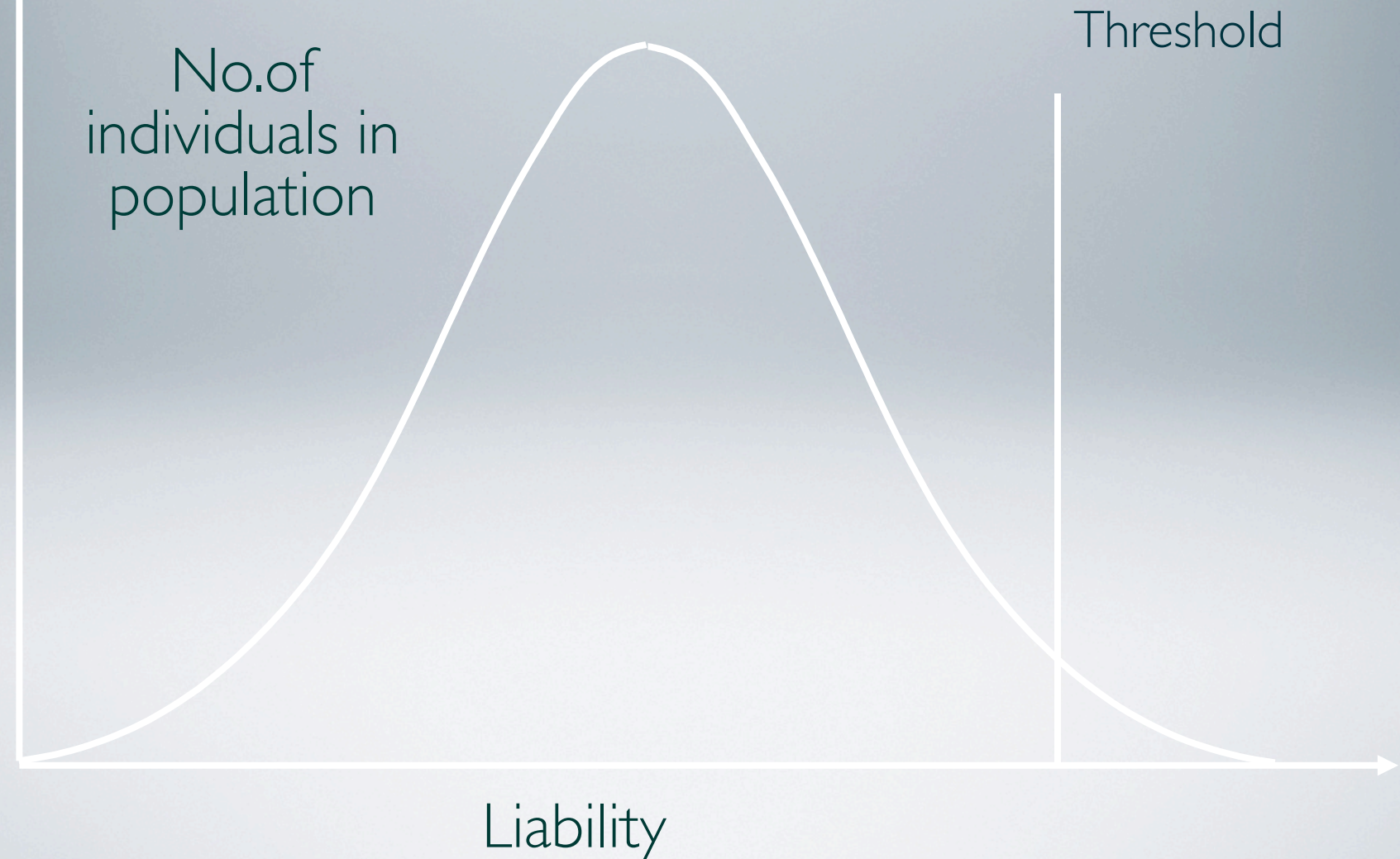
No.of
individuals in
population

**In multifactorial disorders, there
is a threshold, above which a
person will develop the
multifactorial disorder**

Liability



In multifactorial disorders, there is a threshold, above which a person will develop the multifactorial disorder



MULTIFACTORIAL DISORDERS – PRACTICE POINTS

Common
conditions

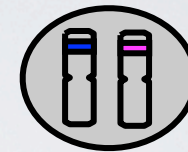
One organ
system
affected

“Environmental”
influences act
with a genetic
predisposition

Multiple genes
with
individually
small risks
often
implicated

Recurrence risks:

- “empiric figures”
- obtained from population studies
- use in population from which obtained



+ environment



**Major effort to identify common disease
susceptibility genes underway**

RISK FACTORS FOR CORONARY ARTERY DISEASE

***Uncontrollable
(but identifiable)***

Family history (genetics)

Age

Male sex

**Potentially controllable or
treatable**

Fatty diet

Hypertension

Smoking

High serum cholesterol

Low serum HDL

High serum LDL

Stress

Insufficient exercise

Obesity

Diabetes

HOW CAN THE PROBABILITY OF RECURRENCE BE DETERMINED FOR MULTIFACTORIAL DISORDERS?

- The recurrence *risk* for multifactorial disorders has to be determined through family studies
- Observe the number of affected siblings in many families (*empiric risk*)

HOW EVIDENCE IS GATHERED FOR GENETIC FACTORS IN COMPLEX DISEASES

- **Familial risks**

(what is the incidence of a disorder in relatives compared with the incidence in the general population?)

- **Twin studies**

(what is the incidence in monozygotic compared with dizygotic twins?)

- **Adoption studies**

(what is the incidence in adopted children of the disorders which their parent had?)

- **Population and Migration studies**

(what is the incidence in people from a particular ancestry group when they move to a different geographical area?)

Evidence from these types of studies can estimate the heritability of a condition - *the proportion of the aetiology ascribed to genetic factors rather than environmental factors*

DO BOTH TWINS SHOW THE SAME CHARACTERISTIC OR TRAIT? COMPARING MZ/DZ TWINS CAN GIVE EVIDENCE FOR GENETIC AND/OR ENVIRONMENTAL INFLUENCES

<i>Trait</i>	<i>Concordance rate</i>	
	<i>Monozygotic</i>	<i>Dizygotic</i>
Height	95%	52%
IQ	90%	60%

MZ twins share all their genes and environment

DZ twins share 50% genes and environment

DETERMINING THE INCIDENCE OF A **DISEASE** IN TWINS
HELPS DEFINE 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

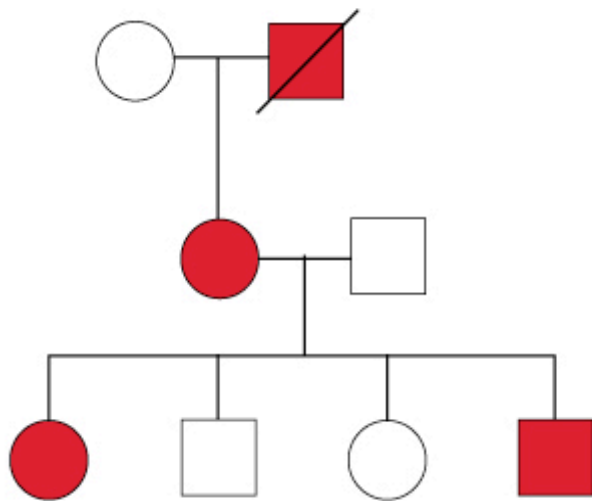
MULTIFACTORIAL



- **Examples** include some cases of cleft lip and palate; neural tube defects; diabetes and hypertension
- **Caused by** a combination of genetic predisposition and environmental influences
- **Pattern** – more affected people in family than expected from incidence in population but doesn't fit dominant, recessive or X-linked inheritance patterns

MENDELIAN VERSUS SPORADIC

Mendelian

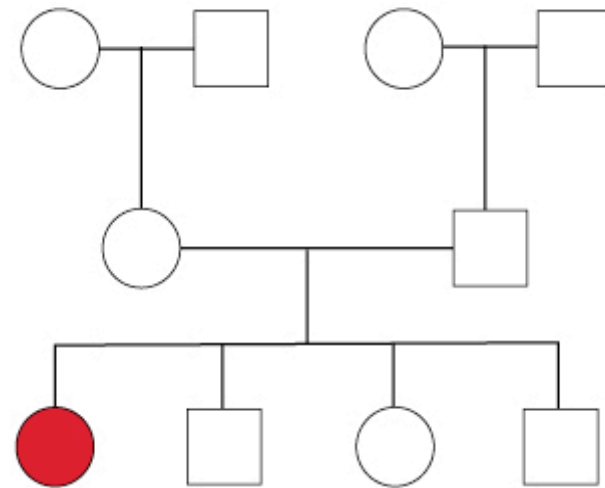


Germline mutation

Somatic mutation

Multiple tumors
Bilateral
Early-onset

Sporadic



Normal gene

Somatic mutation

Somatic mutation

Single tumors
Unilateral
Later-onset

Familial Clustering of Diseases

Relatives share a greater proportion of their alleles than with unrelated individuals in the population.

A primary characteristic of disease with complex inheritance is that affected individuals tend to cluster in families (familial aggregation).

The reverse is not necessarily true - familial aggregation of a disease does not mean that a disease must have a genetic contribution. Non-genetic factors could have the same effect - besides sharing alleles, families share culture, behavior, diet, and environmental exposure.

Familial Clustering of Diseases

Concordant - when two individuals in a family have the same disease. Affected individuals may not share the same pre-disposing alleles, in which case they are phenocopies (genetic heterogeneity).

Discordant - when some family members have a disease and others not. Discordancy could be due to one individual having the disease allele and the other not.

Alternatively, the disease may have incomplete penetrance.

Phenocopies and incomplete penetrance contribute to the difficulty of identifying genes that are responsible for multifactorial diseases.

Relative Risk

Familial aggregation can be measured by comparing the frequency of the disease in the relatives of an affected proband with its frequency (prevalence) in the general population.

Relative risk ratio (λ_r) is defined as:

$$\lambda_r = \frac{\text{prevalence of disease in a relative "r" of an affected person}}{\text{population prevalence of the disease}}$$

$\lambda_r = 1$ indicates that a relative of an affected is no more likely to develop a disease than any individual in the population.

Risk Ratios for Relatives of Proband with Diseases Showing Familial Aggregation

<i>Disease</i>	<i>Relationship</i>	λ_r
Schizophrenia	MZ twins	48
	Siblings	12
Autism	MZ twins	2000
	Siblings	150
Manic-depressive (bipolar) disorder	MZ twins	60
	Siblings	7
Type I diabetes mellitus	MZ twins	80
	Siblings	12
Crohn's disease	MZ twins	840
	Siblings	25
Multiple sclerosis	MZ twins	800
	Siblings	24

Observed Risks for Cleft Lip with/without Cleft Palate in Relatives of Affected Proband

<i>Population Affected</i>	<i>Incidence Cleft Lip</i>	$\lambda_{relative}$
General population	0.1	-----
First-degree relatives	4.0	40
Second-degree relatives	0.7	7
Third-degree relatives	0.3	3

Case-Control Studies

Another approach to assessing familial aggregation in which patients with a disease (the cases) are compared with suitably chosen individuals without the disease (the controls) with respect to family history of disease (it is also important to randomize other variables such as environmental exposures, occupation, geographical location, parity, previous illnesses, ethnicity, etc).

To assess a possible genetic contribution to familial aggregation of a disease, the frequency with which the disease is found in the extended families of the cases (positive family history) is compared with the frequency of positive family history among suitable controls that do not have the disease.

Case-Control Studies

These studies are subject to many different kinds of errors, the most troublesome being ascertainment bias.

Ascertainment bias - a difference in the likelihood that affected relatives of the cases will be reported to the epidemiologist as compared with the affected relatives of controls.

Choice of controls is also a confounding factor. Controls should differ from the cases only in their disease status and not in any other variable.

Associations found in case-control studies does not prove causation. Many variables are not independent of each other.

Separating Genetic and Environmental Factors

Disease concordance and allele sharing among relatives can be used to break down the relative contribution of genetics and environment to disease. When genetics is important, the frequency of disease concordance increases as the degree of relatedness increases.

The most extreme examples of two individuals having alleles in common are identical (monozygotic-MZ) twins. The next most closely related are first degree relatives, including fraternal (dizygotic-DZ) twins.

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 concordance in MZ versus DZ twins is strong evidence of a genetic component to the disease.

An important exception is X-linked diseases. In females, discordance could also be due to differences in the proportion of maternal versus paternal X that is inactivated.

Genetic Analysis of Complex Traits

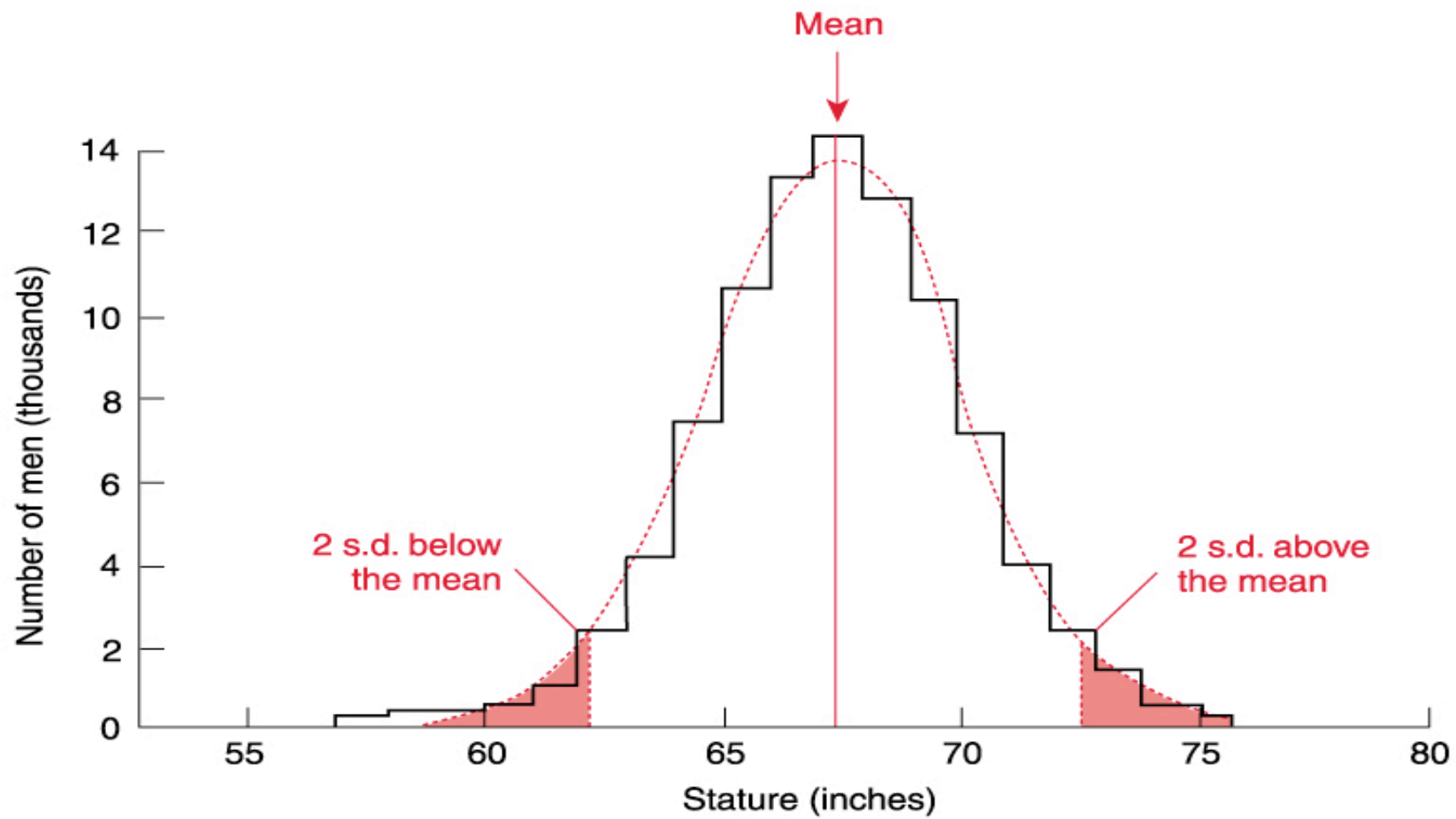
Most complex or polygenic traits have a normal (gaussian) distribution of their values when measured in a population. This is the familiar bell-shaped curve.

Two important characteristics of trait distribution are the mean (μ) and the variance (σ^2).

Mean - the arithmetic average of the values across the population. Since most people have values at the mean, the curve has its peak at the mean value.

Variance - a measure of the degree of spread of values to either side of the mean. It determines the breadth of the curve.

The variance of a measured quantity in the population is called the total phenotypic variance.

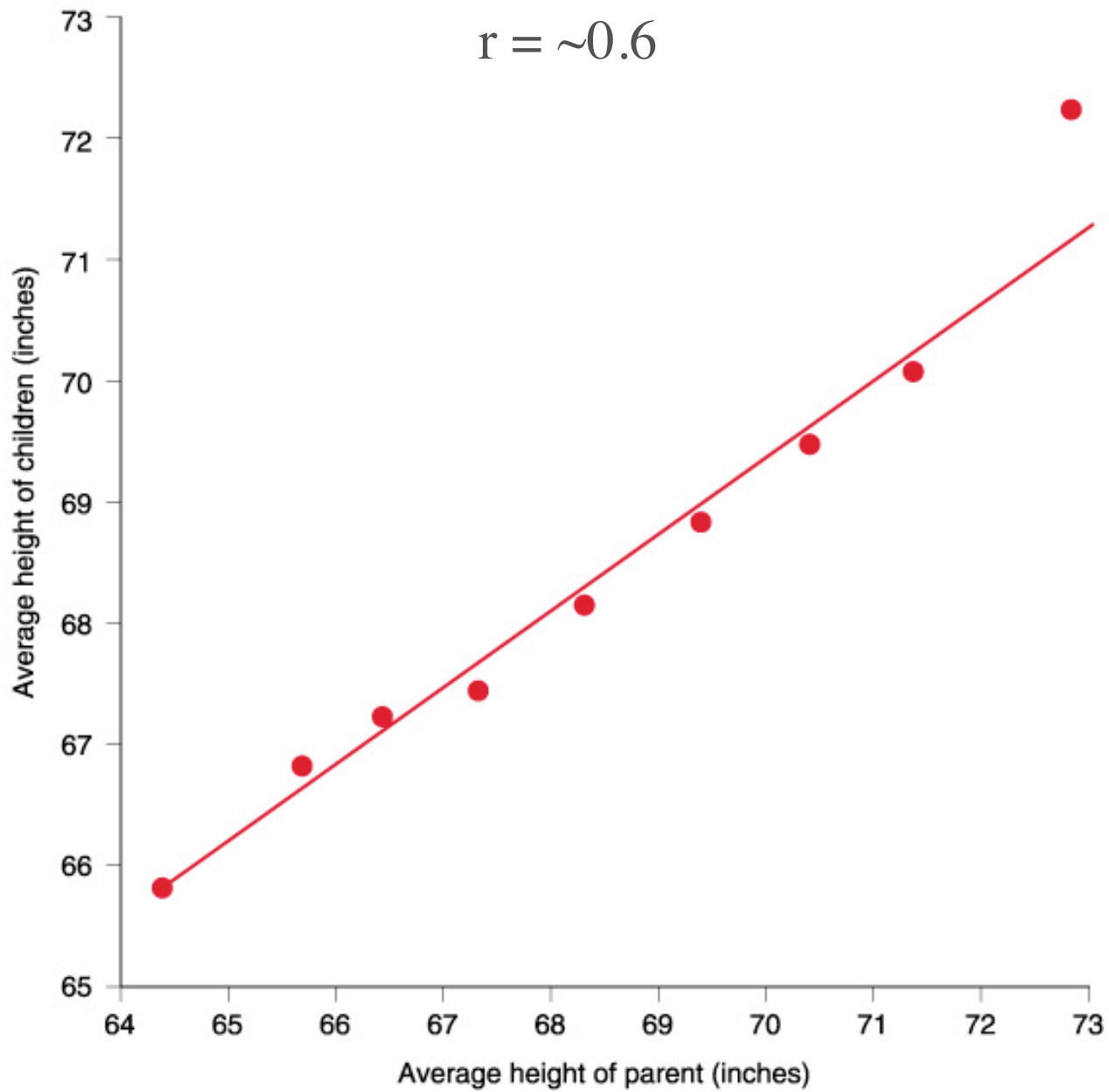


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The concept of a normal range for traits is fundamental to clinical medicine. However, the distance a measurement is from the mean before it is considered abnormal is somewhat random. In general, a trait is considered abnormal (out of the range of normal values) if the value of the trait is greater than 2 standard deviations away from the population mean.

Family studies can also be used to determine the role of genetics versus environment in the expression of complex traits. With families, the coefficient of correlation (r) provides a measure of correlation of particular traits among relatives compared to the general population.

r can range from 0, no correlation, to +1 for perfect positive correlation and to -1 for perfect negative correlation.



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Heritability (h^2) - developed to quantify the role of genetic differences in determining variability of quantitative traits

Defined as the fraction of the total phenotypic variance of a quantitative trait that is caused by genes and is, therefore, a measure of the extent to which different alleles at various loci are responsible for the variability in a given trait across a population.

The higher the heritability, the greater is the contribution of genetic differences among people in causing variability of the trait.

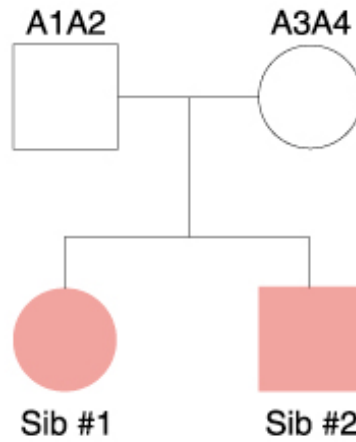
Estimating Heritability from Twin Studies

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

Genetic Mapping of Complex Traits

Two major approaches have been developed (with many variants of these for special disease models).

Affected pedigree method - type of linkage analysis that relies on pairs of family members who are concordant for the trait. Sibling-sibling or parent-sibling pairs are based upon the concept of identity-by-descent. The pairs share stretches of DNA in common through a direct inherited lineage.



Genotype of sib #1

		A1A3	A1A4	A2A3	A2A4
Genotype of sib #2	A1A3	2	1	1	0
	A1A4	1	2	0	1
	A2A3	1	0	2	1
	A2A4	0	1	1	2

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Genetic Mapping of Complex Traits

Association method - is based upon the presumption that there is an increased frequency of particular alleles in affected compared with unaffected individuals in the population.

Mapping Models

Typical linkage analysis, like used for single gene Mendelian traits, is rarely applicable to complex traits. This approach is model-based (parametric) because it assumes that there is a particular mode of inheritance.

With complex traits, the mode of inheritance is not known. Therefore, model-free (non-parametric) approaches are used. These approaches make no assumptions about the number of loci, the role of environment, or penetrance.

Model-free methods solely depend on the assumption that two affected relatives will have disease-predisposing alleles in common.

Limitations of Complex Trait Analysis

Complex epistatic interactions

Genetic heterogeneity

Pleiotropy

History of mutations/polymorphisms

Population stratification