

## Multifactorial Inheritance

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**Several inherited disorders occur as a result of defects in one single gene or due to chromosomal abnormalities; however, some disorders can occur due to defects in several genes and these traits or features can be classified as either multifactorial or polygenic. This article will discuss commonly used terminologies, their definitions, different traits, their risk assessment and examples of multifactorial disorders.**



## Definitions

**Phenotype** is a feature or characteristic of an individual which can be either weighed, recorded or noticed e.g. hair or eye color.

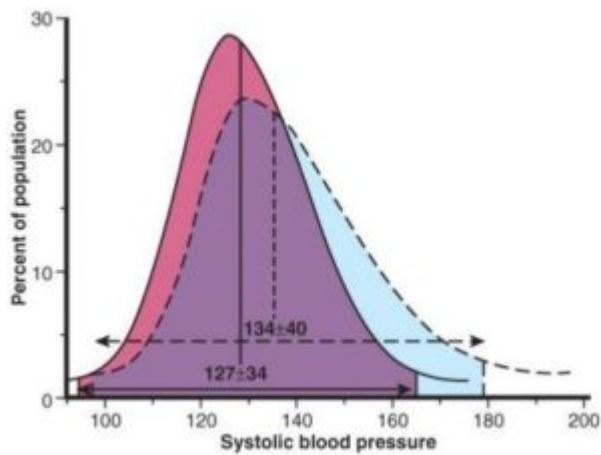
**Genotype** is a part of the feature or phenotype which is found in the progeny and is formed by alleles or gene located on different loci. It is not possible to record/measure or notice a genotype.

**Polygenic inheritance** is a mode of inheriting phenotypic traits and occurs when several gene pairs located on different loci have an additive effect leading to a particular trait or characteristic of an individual e.g. the ridges on our fingertips.

**Multifactorial inheritance** is another mode of inheritance which is polygenic but is also due to the influence of other genes and the ante and post-natal environment of the individual. e.g., height and skin color of the individual.

## Types of Phenotype Traits

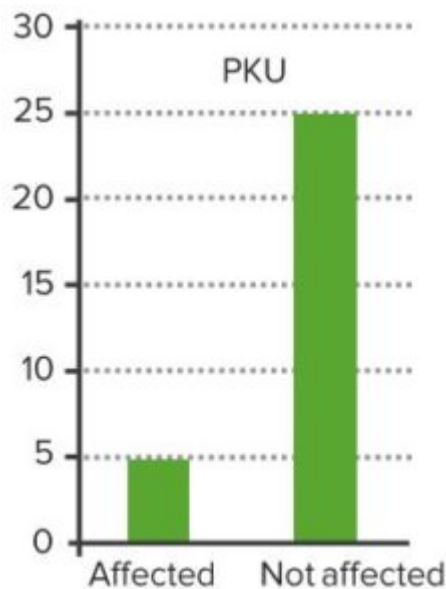
They can be classified as qualitative, quantitative and threshold traits.



"Continuous Quantitative traits are measurable" Image created by Lecturio

**Quantitative traits** occur as a result of continuous variation which is the sum total of small effects caused by a gene. Usually, several genes or a group of genes control quantitative traits. If multiple genes influence a trait, then it is called a polygenic trait, e.g., height, human intelligence and skin color. Height is considered the best example of a quantitative trait. It occurs a range of values.

**Qualitative traits** are "yes or no traits" and can be classified into categories which may not be in any particular order. This type of trait has a monogenetic pattern of inheritance i.e. the trait is only influenced by a single gene and the environment does not play a role in the development of this trait.



"Discrete Qualitative traits are either present or absent" Image created by Lecturio

E.g. inherited disorders caused by a single gene mutation, ABO blood groups. With a few rare exceptions, a majority of humans have one of the following four categories of blood groups: A, B, AB or O. Since the ABO blood group can be classified neatly into any of the four categories, it is considered a good example of a qualitative trait.

**Threshold traits** are inherited quantitatively but are expressed qualitatively. As several genes form a threshold trait, it is considered a quantitative trait in practice. Threshold traits occur in families, but their exact segregation ratio cannot be predicted unlike

diseases inherited according to the Mendelian pattern.

## Qualitative Traits: Risk Assessment

Risk of qualitative traits can be assessed using familial aggregation studies like relative risk ratios and case-control studies.

### Relative risk ratios

$\Lambda_r$  = presence of the disease in relatives/presence of the disease in the population.

If an allele increases the chance of developing a disease, then one would expect the affected individual to have a greater than expected number of affected relatives.

$(\Lambda_r) = 1$  means there is little or no genetic impact.

$(\Lambda_r) > 1$  means there is a possible genetic predisposition.

Disease	Relationship	$\Lambda_r$
Schizophrenia	Siblings	12
Autism	Siblings	150
Bipolar disorder	Siblings	7
NIDDM (type I DM)	Siblings	35
Crohn's disease	Siblings	25
Multiple sclerosis	Siblings	24

**Case-control studies** are another method to calculate the risk. In this, the genetic contribution is evaluated by comparing an affected individual to an unrelated control i.e. the spouse who has shared the same environment.

Approximately 3.5% of the first degree relatives of patients with multiple sclerosis (MS) is also reported to suffer from the disease, indicating a genetic component to the disease. This can be compared to an incidence of only 0.2% of first degree relative of matched controls (married couples) who suffer from MS.

Considering the incidence of 3.5% and 0.2%, we can calculate that the incidence of MS would be 18 times greater amongst siblings than amongst unrelated individuals.

## Quantitative Traits: Risk Assessment

The risk for quantitative traits can be assessed using correlation and heritability studies.

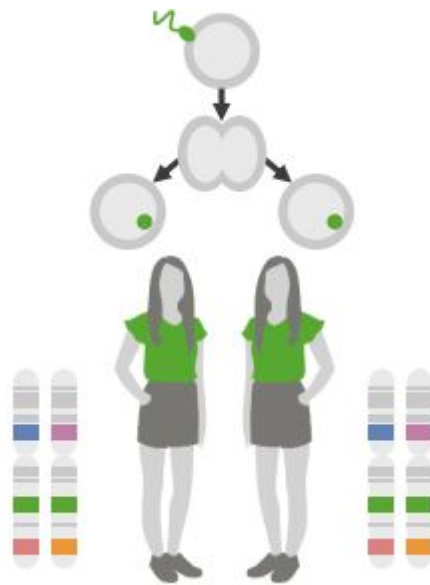
**Correlation studies:** The coefficient of correlation ( $r$ ) is a measure of similarities amongst relatives. A positive correlation is represented by an upward slope, while the negative correlation is represented by a straight line or downward slope.

**Heritability studies ( $H^2$ ):** Measures the extent of variation in a phenotypic trait attributable to a genetic variation (not environmental) amongst individuals of a population.

$H^2 = 1$  (heritability equals one means that all variations are attributable to genetics)

$H^2 = 0$  (none of the heritability is attributable to genetics or anywhere in between)

## Twin studies



"Identical. Monozygotic twins share 100% of their genetic information (theoretically)" Image created by Lecturio

Theoretically, identical or monozygotic twins share almost 100% of their genetic information with epigenetic studies providing more detailed information about this observation.

Fraternal or dizygotic twins share approximately 50% of their genetic information depending on whether they inherited maternal or paternal traits.

**Concordance values:** If one twin has a trait, then concordance value estimates the frequency of the other twin having it too. Greater concordance in monozygotic twins versus dizygotic twins provides evidence that there is a genetic component to the disease. From the concordance values in the following list, one can discern that there is a likelihood of a genetic component in these conditions:

Disorder	Monozygotic twins	Dizygotic twins
Multiple sclerosis	18	2
Schizophrenia	46	15
Bipolar disorder	62	8
Rheumatoid arthritis	12	3
Cleft lip w/wo cleft palate	30	2
Systemic lupus erythematosus	22	0

## Multifactorial Gene Disorders

Multifactorial gene disorders occur as a result of a combination of several factors. These include genetic factors, as well as environmental factors, which lead to small variations in the inherited genes. There is a different "threshold" of expression so that one gender is more adversely affected than the other. For example, congenital hip dysplasia is more common amongst females than among males.

The probability of a multifactorial trait occurring in a family depends upon how close the relationship is between the family member with the trait and the rest of the family. For

example, the incidence is higher if a sibling has the trait compared to if a first cousin has the trait as family members share a specific percentage of the genes based on the relationship.

Relationship degree	Percentage of common genes	Examples
1 <sup>st</sup> degree relative	50%	Parents, children, siblings
2 <sup>nd</sup> degree relative	25%	Aunts, uncles, nieces, nephews & grandchildren
3 <sup>rd</sup> degree relative	12.5%	First cousins

## Examples of Multifactorial Gene Disorders

### Multifactorial disorders without a clear genetic component

Multifactorial disorders without a clear genetic component are, for example, congenital heart disorders (ventricular septal defect, patent ductus arteriosus, atrial septal defect, and aortic stenosis), neuropsychiatric disorders and coronary artery disease. Although the exact genes responsible for the disorders are yet unknown, genome studies are likely to reveal the details in the near future.

#### Congenital heart disorders:

Defect	Incidence in the population	Frequency in siblings in %	$\lambda_r$
Ventricular septal defect	0.17	4.3	25
Patent ductus arteriosus	0.083	3.2	38
Atrial septal defect	0.060	3.2	48
Aortic stenosis	0.044	2.6	59

Table: Congenital heart disorders

The high relative risk ratio (lambda value) in the above table indicates a probable genetic component.

**Schizophrenia:** This is a neuropsychiatric multiple personality disorder which affects approximately 1% of the population with a concordance value of 40 - 60% in monozygotic twins and 10 - 16% in dizygotic twins. This suggests that there is a strong genetic component to the disorder.

**Bipolar disorder:** This disorder affects approximately 0.8% of the population with twin and family aggregation studies indicating a strong genetic component.

**Coronary artery disease (CAD):** Concordance rates in monozygotic twin studies indicate a strong genetic component in CAD, although non-genetic and environmental components (diet, physical activities, and smoking) can influence the development of this condition too.

**Neural tube defects (NTD):** The incidence of NTDs, spina bifida, and anencephaly are approximately 1 to 2 cases per 1,000 live births with females being affected more than males. They occur as a result of inheritance of genes from both parents combined with environmental factors such as uncontrolled maternal diabetes, anti-epileptic medications prescribed to the mother etc.

A couple who have a child with NTD has a 3 - 5% probability of having another child with

the same disorder, although the type of NTD may be different from that child. While the first child may have anencephaly, the second may have spina bifida.

**Congenital hip dysplasia (CHD):** As mentioned earlier, this is more common amongst females than males. Maternal hormones are the environmental factor contributing to the development of CHD. A couple who have a child with CHD have a 6% probability of having another child with CHD.

## Multifactorial disorders which most probably have a genetic contribution

**Venous thrombosis:** It is now known that there are three factors involved in the development of idiopathic cerebral thrombosis – two genetic factors and one environmental factor (oral contraceptive pill). However, the genetic factors contributing to lower limb thrombosis are not yet known.

Other examples include factor V mutation which increases the incidence of thrombosis and mutation in prothrombin which leads to accelerated clot formation. Environmental factors like oral contraceptive pills, smoking etc. individually increase the risk of thrombosis several fold and, when combined with the genetic factors, can lead to an exponential increase in the incidence of thrombosis.

**Hirschsprung disease:** This is a developmental abnormality associated with an absence of enteric ganglia leading to symptoms of constipation and intestinal obstruction. Missense, loss of function, the mutation in the RET gene, as well as mutations in the non-coding regulatory regions near the RET locus, are now known to cause this condition.

**Type I diabetes:** It is now known to be an autoimmune disorder with complex inheritance associated with Major Histocompatibility Complex (MHC) genes on chromosome 6. Twin studies have reported 40% concordance amongst monozygotic twins.

**Alzheimer's disease:** With increasing lifespans, the incidence of this condition is currently reported to be 1 – 2% of the elderly. There are several forms of Alzheimer's disease. Three autosomal dominant forms result in the late onset of Alzheimer's (>60 years of age). Twin studies indicate concordance values of 50% in monozygotic twins. Genetic studies have found that individuals with two copies of E 4 allele for the Apolipoprotein E have an early-onset form of Alzheimer's disease.

## References

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[Polygenic and multifactorial inheritance](#) via bogari.net

[Complex and Multifactorial Inheritance](#) via carolguze.com

[The Difference Between Qualitative & Quantitative Traits in Genetics](#) via education.seattlepi.com

[Frequently Asked Questions About Genetic Disorders](#) via genome.gov

[Multifactorial inheritance](#) via chw.org

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