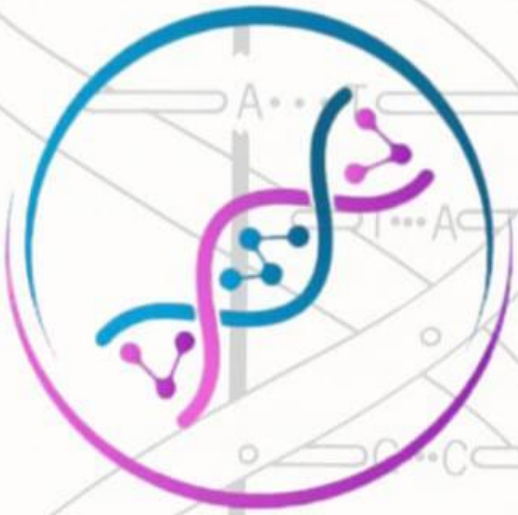
COMPLEX INHERITANCE



GENETIC VISION TEAM

Complex diseases

We discussed single gene disorders, where a mutation in a single gene causes a disease or disorder, such as sickle cell anemia, in which a mutation in one gene causes abnormal hemoglobin. These are also called Mendelian disorders because they follow Mendelian laws. Mendel stated that one factor (gene) determines the phenotype.

Single-gene disorders are very rare in the population, occurring in about 1 in 10,000, 1 in 7,000, or 1 in 5,000 individuals.

But some diseases, like cancer, cardiovascular diseases, asthma, schizophrenia, and diabetes, are more common in populations.

Genetics play a role in these diseases, but they are not the only factor. Many other factors, such as environmental factors, also play an important role in these diseases.

You may have the genetic variants that cause asthma, but you might not develop the disease because you eat healthy food and exercise regularly.

Another person may not have the variants that cause the disease, but because they eat excessive fast food and don't exercise, they could still develop the disease.

So the presence of variants associated with diseases increases the risk of developing the disease, but it doesn't necessarily that you will get the disease. also the absence of these variants does not protect you from getting the disease.

Complex diseases: Diseases caused by the interaction between genetics and environmental factors.

Complex diseases are common while single gene disorders are very rare.

Prevalence: The proportion of a population that has a specific characteristic during a given period of time.

Multifactorial disorders: Diseases caused by multiple genes and environmental factors.

Polygenic disorders: Diseases caused by multiple genes.

TABLE 9-1 Frequency of Different Types of Genetic Disease

Type	Incidence at Birth (per 1000)	Prevalence at Age 25 (per 1000)	Population Prevalence (per 1000)
Disorders due to genome and chromosome mutations	6	1.8	3.8
Disorders due to single-gene mutations	10	3.6	20
Disorders with multifactorial inheritance	≈50	≈50	≈600

Data from Rimoin DL, Connor JM, Pyeritz RE: *Emery and Rimoin's principles and practice of medical genetics*, ed 3, Edinburgh, 1997, Churchill Livingstone.

Look at this table: the prevalence of disorders caused by genome and chromosomal mutations in a certain population is approximately 4/1,000 = 0.004. What does that mean?

It means among 1000 individuals, only 4 have diseases caused by genome and chromosomal mutations.

Look at multifactorial disorders, the prevalence in the population is 600/1,000 = 0.6. What does that mean?

It means that in this population 600 out of 1,000 individuals have multifactorial disorders.

From this table we can conclude that **complex diseases are more common than single gene diseases.**

Complex diseases are classified into:

- Qualitative : The disease is either present or not.
- Quantitative: the disease shows a degree of phenotypes " **show conditions effect"**

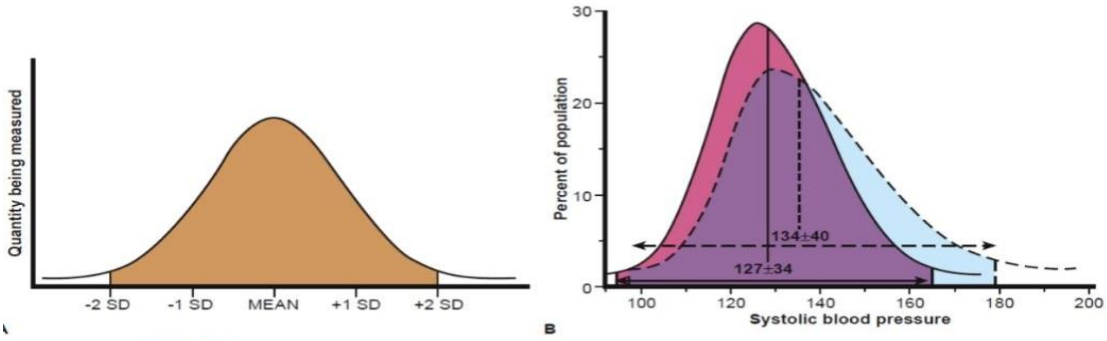
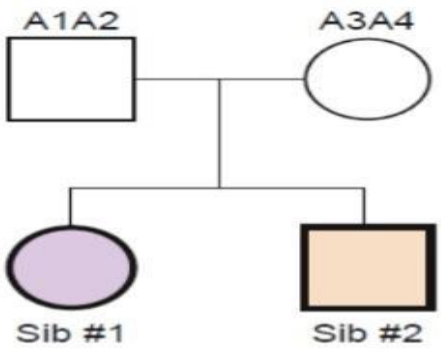


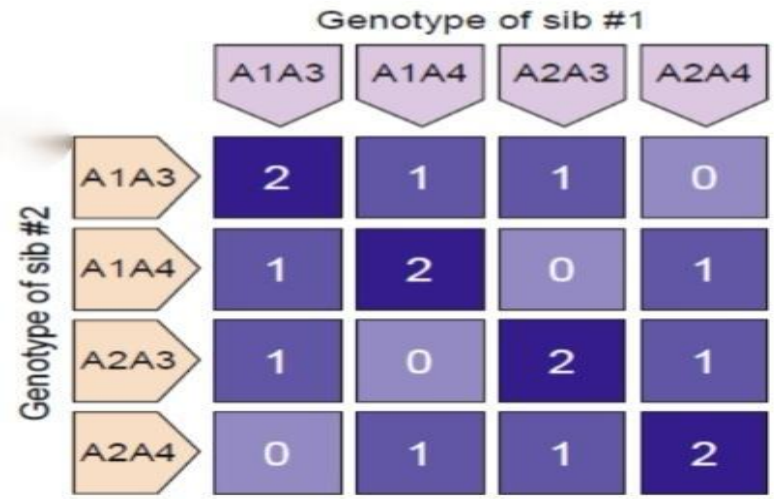
Figure 9-1 A, The normal gaussian distribution, with mean (average) and standard deviations (SDs) indicated. For many traits, the "normal" range is considered the mean ± 2 SD, as indicated by the *shaded* region. B, Distribution of systolic blood pressure in approximately 3300 men aged 40 to 45 (*solid line*) and approximately 2200 men aged 50 to 55 (*dotted line*). The mean and ± 2 SD are shown above *double-headed arrows*.

Look at this graph which represents different data collected from two different groups in order to study systolic blood pressure, let's call them sample 1 and sample 2, sample 1 contains 3300 men aged between 40 – 45, while sample 2 contains 2200 men aged between 50- 55, for each sample, the data and the distribution of this data differ from the other sample.

Sample 1 and Sample 2 each have different means. From the distribution of the data, we can conclude that **people aged between 40-45 have lower systolic blood pressure than people aged between 50-55**.

For many traits, the normal range between (**mean + 2)** and **(mean – 2) .**





First degree relatives share **on average** 50% of their alleles. What does the word '**average**' mean?

For example, gene A has 4 alleles: A1, A2, A3, and A4. If each parent has two different alleles, with the father being A1A2 and the mother being A3A4, the offspring will inherit one allele from each parent.

The probabilities of the genotypes for the offspring are:

- **A1A3**
- **A1A4**
- **A2A3**
- **A2A4**

Siblings (Brothers and sisters) are **first degree relatives.**

If the parents have two offspring, each of them will inherit one of the four genotypes.

We will compare the four probabilities for the two siblings.

There are 16 possible probabilities when we compare the expected genotypes for both together.

0: No similar alleles are shared between the two siblings.
Example:
Sib 1: A1 A3 and Sib 2: A2 A4

1: One similar allele is shared between the two siblings.

Example:

Sib 1: A1 A3 and Sib 2: A1 A4

2: Two similar alleles are shared between the two siblings.

Example:

Sib 1: A2 A4 and Sib 2: A2 A4

Two siblings could share two similar alleles for the same gene, share one similar allele for the same gene, or didn't share any similar alleles for the same gene, on average:

1/4 (two alleles) + 1/2 (one allele) + 1/4 (one allele) =1 allele

It means that, on average two siblings could share 50% of genetic material, but **not necessarily exactly 50 %**.

To determine whether the disease is related to inheritance,

we measure the relative risk ratio.

Relative risk ratio (λr): **measures familial aggregation of a disease.**

λr = **disease prevalence in relatives of the affected / disease prevalence in the population**.

If λr = 1, it means the disease is not related to inheritance.
If λr > 1, it indicates familial aggregation.

But what does familial aggregation mean?

If you have relatives who have the disease, you are at higher risk of developing the disease than other individuals in the population.

Look at this table, which illustrates the relative risk ratio of siblings of pro-bands with diseases that show familial aggregation and complex diseases.

TABLE 9-2 Risk Ratios λ_s for Siblings of Probands with Diseases with Familial Aggregation and Complex Inheritance

Disease	Relationship	λ_s
Schizophrenia	Siblings	12
Autism	Siblings	150
Manic-depressive (bipolar) disorder	Siblings	7
Type 1 diabetes mellitus	Siblings	35
Crohn disease	Siblings	25
Multiple sclerosis	Siblings	24

For schizophrenia, what does is it mean when λr = 12?

If you have a sibling who has a schizophrenia, you are at risk 12 fold more likely to develop schizophrenia than other individuals in the population.

For Autism, what does it mean when λr = 150?

If you have one sibling with Autism, you are at risk 150 fold more likely to develop autism than other individuals in the population.

Family history case control study.

"If a person needs to know the risk of developing a certain complex disease, such as multiple sclerosis (MS), first we need a control group.

The control group must be from the same population, we calculate the prevalence of the first degree relatives who have the MS

for this person for example = 3.5,

Then, calculate the prevalence of first-degree relatives who have MS for the control person (who doesn't have multiple sclerosis), for example= 0.2.

Then, We divide them = 3.5 / 0.2 = 18

This mean you are at risk **18 fold** more likely to Develop MS than other individuals in population.

Measuring the genetic contribution to quantitative traits

Is there a relationship between the amount of cholesterol in the mother and the amount of cholesterol in the child?

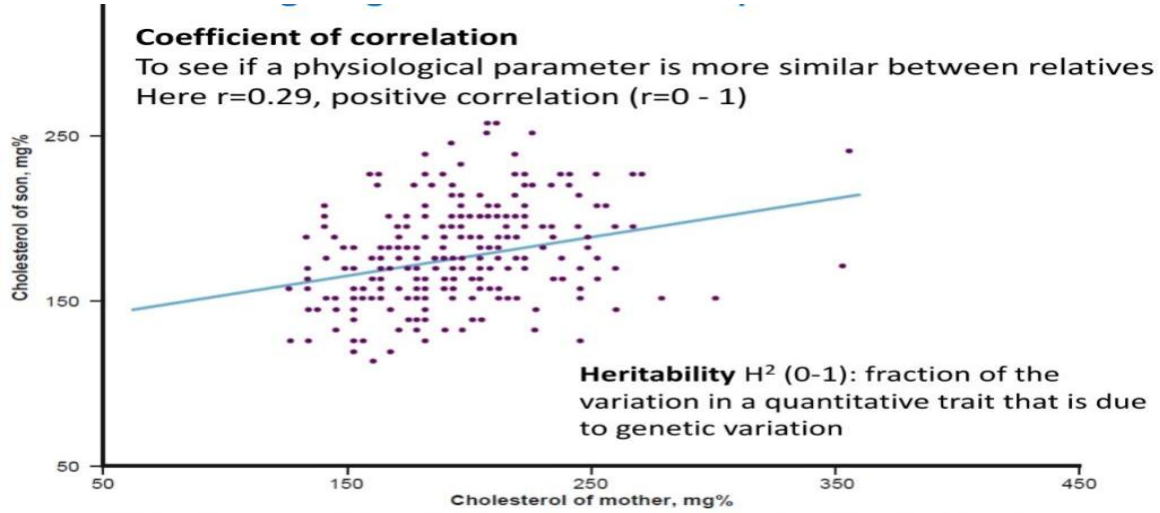


Figure 9-3 Plot of serum cholesterol levels in a group of mothers aged 30 to 39 and in their male children aged 4 to 9. Each dot represents a mother-son pair of measurements. The straight line is a "best fit" through the data points.

Look at this graph, which represents data collected from a group of

Mothers aged between 30 and 39 and their children. Each dot represents a measurement of cholesterol for both the mother and her child. The Y-axis represents the concentration of cholesterol in the sons in milligrams per percent, and the X-axis represents the concentration of cholesterol in the mothers in milligrams per percent.

Then we draw the best-fit line, r = 0.29, and r > 0, which means genetics plays a role but is not the only factor.

If genetics play a role in a certain disease, the risk of getting the disease increases as the patient is closer to you.

If your brother has the disease, you are at a higher risk of getting it than if your uncle has the disease.

Also, if you have two brothers with asthma, you are at a higher risk of developing asthma than if you have only one brother with asthma.

TABLE 9-3 Risk for Cleft Lip with or without Cleft Palate in a Child Depending on the Number of Affected Parents and Other Relatives

	Risk for CL(P) (%)		
	No. of Affected Parents		
Affected Relatives	0	1	2
None	0.1	3	34
One sibling	3	11	40
Two siblings	8	19	45
One sibling and one second-degree relative	6	16	43
One sibling and one third-degree relative	4	14	44

CL(P), Cleft lip with or without cleft palate.

Look at this table, which shows the risk of cleft lip and palate. In the case where neither parent nor siblings have CL (control), the risk of developing it is 0.1.

If you have one parent with CL and none of your Brothers or sisters have CL, what is the risk of getting a cleft lip (CL)?

$\lambda r = 3 / 0.1 = 30$

That's mean your at risk 30 fold more likely to Develop CL than other individuals in the population.

If you have a one parent and 2 siblings with CL

$\lambda r = 19 / 0.1 = 190$

That's mean your at risk 190 fold more likely to Develop CL than other individuals in the population.

We conclude the genetics play role in CL, as the shared genetic material between the person and affected relatives increase, the risk of getting CL increase.

Twins

Twins are a good model for studying Diseases specially when we need separate environmental factors from genetics.

They take advantage by allow each child to raise in different environment (reared apart).

Mono Zygote twins have the same genetic material each expose to different environmental factors because each reared in different environment.

Twins reared apart mean they raise in different environment.

TABLE 9-5 Pairwise Correlation of BMI between MZ and DZ Twins Reared Together and Apart

		Men			Women		
Twin Type	Rearing	No. of Pairs	BMI*	Pairwise Correlation	No. of Pairs	BMI*	Pairwise Correlation
Monozygotic	Apart	49	24.8 ± 2.4	0.70	44	24.2 ± 3.4	0.66
	Together	66	24.2 ± 2.9	0.74	88	23.7 ± 3.5	0.66
Dizygotic	Apart	75	25.1 ± 3.0	0.15	143	24.9 ± 4.1	0.25
	Together	89	24.6 ± 2.7	0.33	119	23.9 ± 3.5	0.27

Look at this table, which is a study of the effect of environmental differences on Body mass index (BMI)

BMI = weight / (high) ^2

If the BMI is between 22 and 25, the person is normal. If it is greater than 25 this mean there is an increase in the person weight.

They calculated the average of BMI for Mono Zygote twins (MZ) and for Di Zygote twins (DZ).

The average BMI for MZ arise together or apart are similar.

The average BMI for DZ arise to gather or apart are similar.

Pairwise correlation for BMI between a pair of twins was much higher for MZ than DZ twins.

Higher correlation between MZ versus DZ twins was independent of whether they were reared to gather or apart, **which indicate genetic material has a higher impact in BMI than environment into BMI**.

Genome wide association

Association : studying population

Linkage : study Family

Association : if we need to check whether variant or change in genetic material is present in patients higher than in controls in population that's mean this variant increase the risk of developing the disease, example, if gene X were thought had a relation ship with Asthma by a mutation that change one base pair to another base pair example change T :A to G :C , how we can test if this change related to Asthma or not?

We need two groups, group 1 contains 1000 individuals with Asthma and group2 contains 1000 normal individuals (control), both groups from the same population, We found that from the first group there were 700 people out of 1,000 who carried this mutation , We found that from the second group there were 100 people out of 1,000 who carried this mutation, **we conclude this change increases the risk of getting Asthma.**

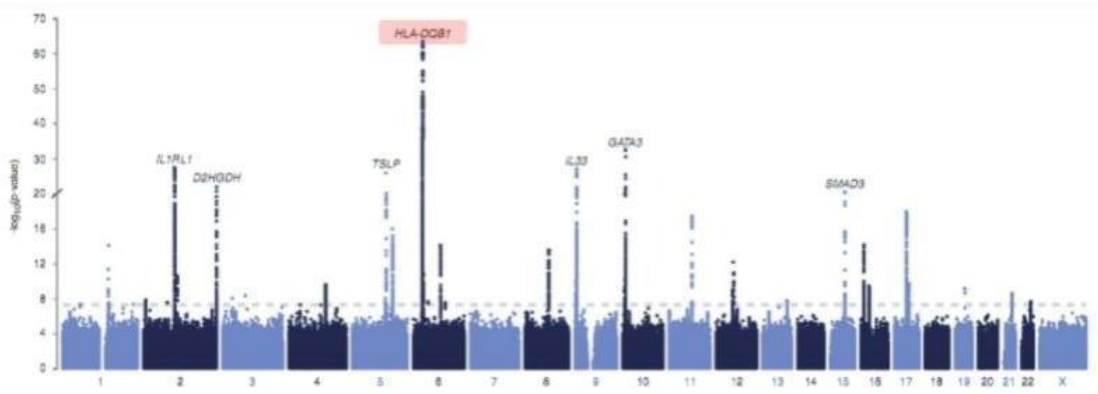
Association is used to study population, and for complex diseases

Linkage is used to study Family, and for study single gene disorders.

If the tools are few, each variant is screened separately.

In genome wide association more than one variant are screened at the same time for a group of patients and group of controls.

You can measure a thousands of variants or Millions for patients and controls instead of examine just one variant at time it's a good tool for studying complex diseases, but it doesn't good tool for studying mendelian disorders.



This is a manhattan plot of Asthma, which is a genome wide association of Asthma, we have compared Millions of genotypes variants between a group of people who have Asthma and group of controls (normal) in **UK,** the results of comparison were summarized in P values and represent on graph we call it **manhattan plot.**

If certain variant has higher spike (score) that's mean this variant is present in patients higher than controls which indicate this variant increase the **risk of get asthma**, for example **HLA-DQB1**.

There are a significant differences, they are not by chance to get this score, indicate this variant or something that related to this variant increase the risk of getting Asthma.

Having a variant of HLA-DQB1 increase the risk of developing Asthma but doesn't necessarily cause Asthma.

Miami plot

Linking two complex diseases to gather

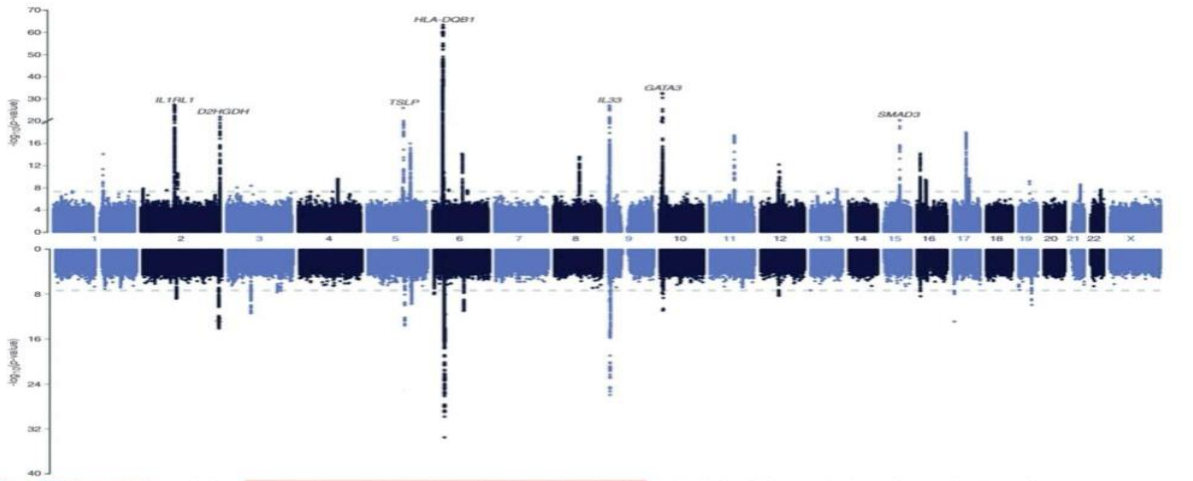


Figure 9.5 Miami plot example for a genome-wide association analysis of asthma and nasal polyps in UK Biobank. The association analysis on the top panel compares genotypes at millions of genetic variants between asthma cases, defined on the basis of diagnosis codes in their individual medical records, and controls. The analysis on the bottom panel compares genotypes at the same variants between individuals with nasal polyps and controls. Note the many shared signals between the two analyses. The results of each comparison are summarized in a *p*-value, which is plotted in the graph. The top few association signals have been labeled with the name of the nearest gene in the asthma portion of the plot.

Like mirror image, we compare two different complex diseases **Asthma and nasal polyps,** association analyzes of both diseases were compared together , as we notice **HLA - DQB1** has the highest score in **Asthma and nasal polyps,** what does this mean?

This mean that **HLA-DQE** is higher in Asthma and Nasal polyps , which suggests that this variant increase the risk of developing Asthma and nasal polyps, also if you have nasal polyps you are more likely to develop Asthma, Also if you have Asthma you are more likely to develop nasal polyps.

The variant increase risk of developing the complex diseases but it doesn't necessary for this person to Develop the disease, and the absence of the variant doesn't mean that a person is protected from Developing Asthma and Nasal polyps.

If you have Asthma, You don't have to the Nasal polyps and And vice versa.

TABLE 9-6 Some Common Congenital Malformations with Multifactorial Inheritance

Malformation	Approximate Population Incidence (per 1000)
Cleft lip with or without cleft palate	0.4-1.7
Cleft palate	0.4
Congenital dislocation of hip	2*
Congenital heart defects	4-8
Ventricular septal defect	1.7
Patent ductus arteriosus	0.5
Atrial septal defect	1.0
Aortic stenosis	0.5
Neural tube defects	2-10
Spina bifida and anencephaly	Variable
Pyloric stenosis	1,† 5*

Congenital : born with it

Heart defect : problem in heart

In Congenital heart defect : mix between oxygenated and de oxygenated blood which result from problem in heart structure.

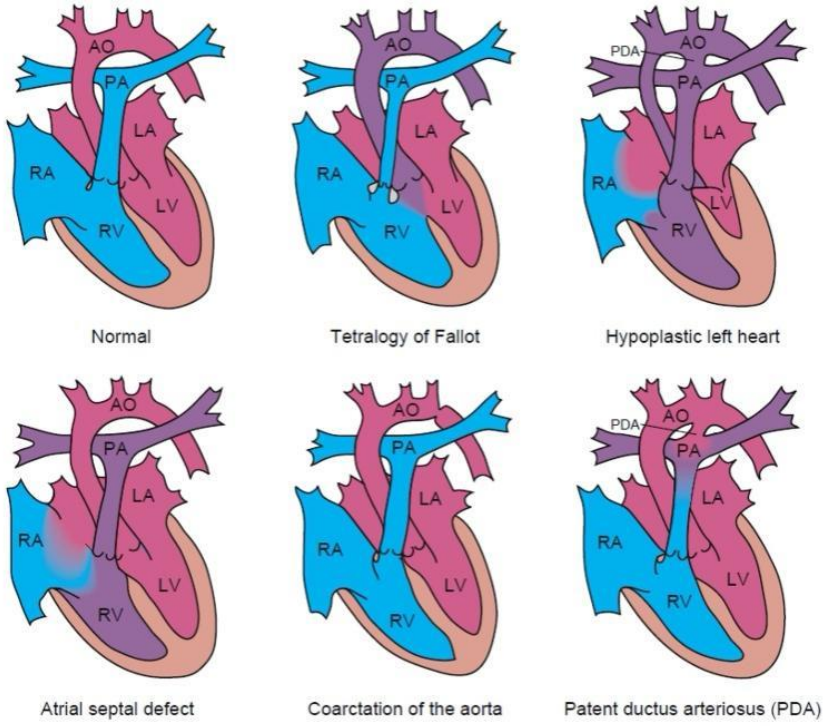


Figure 9-7 Diagram of various flow lesions seen in congenital heart disease. Blood on the left side of the circulation is shown in *red*, on the right side in *blue*. Abnormal admixture of oxygenated and deoxygenated blood is *purple*. AO, Aorta; LA, left atrium; LV, left ventricle; PA, pulmonary artery; RA, right atrium; RV, right ventricle.

Normal structure of heart in which the Oxygenated blood completely separated from de oxygenated blood, but in Congenital heart defect there is a little bit mix between oxygenated and deoxygenated blood.

TABLE 9-7 Population Incidence and Recurrence Risks for Various Flow Lesions

Defect	Population Incidence (%)	Frequency in Sibs (%)	λ_s
Ventricular septal defect	0.17	4.3	25
Patent ductus arteriosus	0.083	3.2	38
Atrial septal defect	0.066	3.2	48
Aortic stenosis	0.044	2.6	59

This table show a group of flow lesions , lets take about **patent ducts arteriosus,** if you have sibling with this disease you are at risk more than 38 fold other individuals in population to get this disease, which mean the genetics play role in this disease.

Psychic diseases

Example : Schizophrenia and Bipolar

Schizophrenia→ problems in thoughts

Bi polar→ problems in mod, some time the patient has high confidence and depress in some times.

25 % of cases of schizophrenia have a Deletion in 22q11, suggesting that genetics play role in getting schizophrenia, but also 75% of schizophrenia cases don't have Deletion 22q11 which suggesting that genetics is not the only factor which causes schizophrenia.

TABLE 9-8 Recurrence Risks and Relative Risk Ratios in Schizophrenia Families

Relation to Individual Affected by Schizophrenia	Recurrence Risk (%)	λ_r
Child of two schizophrenic parents	46	23
Child	9-16	11.5
Sibling	8-14	11
Nephew or niece	1-4	2.5
Uncle or aunt	2	2
First cousin	2-6	4
Grandchild	2-8	5

if you have a sibling has schizophrenia the risk of recurrence is

8 – 14 and λr = 11 , what does that mean?

This means that, the Probability of schizophrenia occurring again in other Family members is 8 – 14 %

And λr=11, meaning you are at risk 11 fold more likely to develop Schizophrenia than other individuals in population.

Coronary Artery disease (CAD)

Problems on coronary Artery in heart muscle which lead to thrombosis and cause heart attack.

Multiple steps cause coronary Artery

Accumulation of fats and died cells on arteries walls forms a Thick layer that constricts the blood flow , blood vessels also lose their elasticity to perform the contractile movement that helps blood movement.

Also this precipitate layers could be released and move to another smaller vessel and close it, also inflammation play role in CAD.

Both genetics and environmental factors increase the risk of Developing CAD.

TABLE 9-10 Risk for Coronary Artery Disease in Relatives of a Proband

Proband	Increased Risk for CAD in a Family Member*
Male	3-fold in male first-degree relatives 2.5-fold in female first-degree relatives
Female	7-fold in male first-degree relatives
Female <55 years of age	11.4-fold in male first-degree relatives
Two male relatives <55 years of age	13-fold in first-degree relatives

*Relative to the risk in the general population.
CAD, Coronary artery disease.

For CAD the males are more susceptible to than females to Develop CAD disease, if you have a brother with CAD you are at higher risk to get the disease, but if you have a sister with CAD your at much higher risk to get the disease, **because the females need accumulate more genetics factor in order to express the disease**.

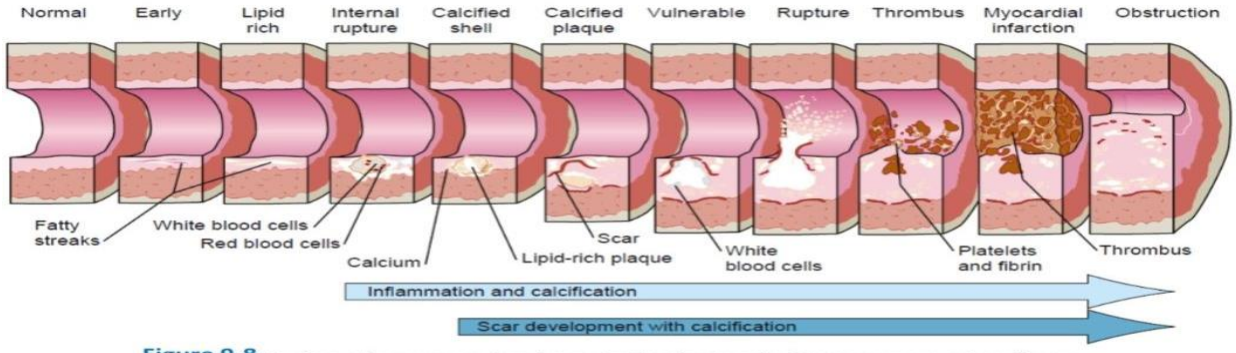


Figure 9-8 Sections of coronary artery demonstrating the steps leading to coronary artery disease. Genetic and environmental factors operating at any or all of the steps in this pathway can contribute to the development of this complex, common disease. *See Sources & Acknowledgments.*

EXAMPLES OF MULTIFACTORIAL TRAITS FOR WHICH SPECIFIC GENETIC AND ENVIRONMENTAL FACTORS ARE KNOWN .

Modifier genes

Cystic fibrosis is a single gene disorder caused by mutation in CFTR gene, which leads to disruption in chloride ion channels.

Cystic fibrosis is Autosomal recessive disease and is a single gene disorder.

But some genes increase or decrease the complexity of the disease we call them **modifier genes.**

Variation in genetic material of Modifier genes don't cause the disease, but it cause fine tuning in disease symptoms Either increase or decrease.

MBL2 and TGFB1 are example of modifier genes that fine tune Cystic fibrosis, by change the degrees of pulmonary disease, because in cystic fibrosis the chloride ion channels are changed which lead to change the salt concentration and Accumulation of Mucus in lungs which lead to increase the risk of contamination.

Digenic inheritance

Two genes have Similar pathways interact to each other, so you have the disease only if you have mutation in both genes.

If you have heterogeneous mutation in both genes you will get the disease for example retinitis pigmentosa, two different genes related to disease, **peripherin** and **ROM 1,** heterogeneous of both genes it will. Case the disease, heterogeneous for one genes doesn't cause the disease.

1 = wild type allele

Mut = mutant allele

1/ Mut 1/ Mut → retinitis pigmentosa

1/1 1/Mut → carrier (un affected)

Digenic Inheritance

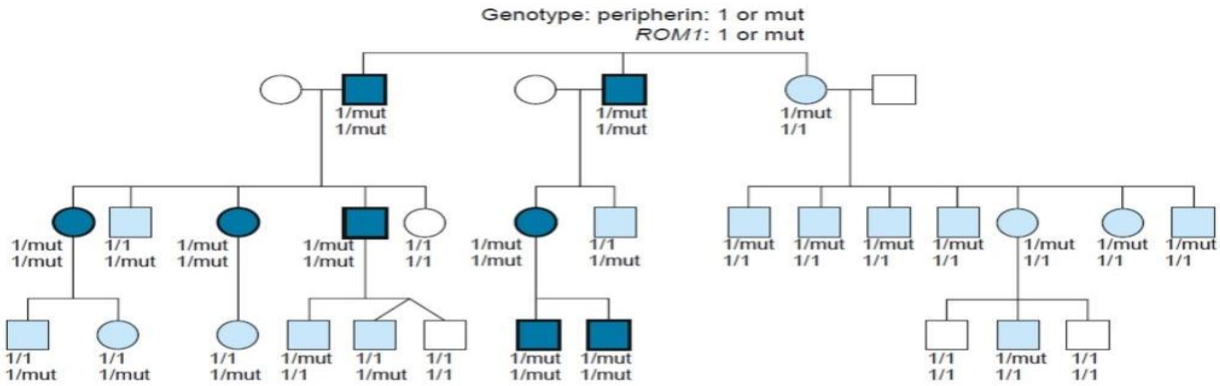


Figure 9-9 Pedigree of a family with retinitis pigmentosa due to digenic inheritance. *Dark blue* symbols are affected individuals. Each individual's genotypes at the peripherin locus (*first line*) and *ROM1* locus (*second line*) are written below each symbol. The normal allele is 1; the mutant allele is mut. *Light blue* symbols are unaffected, despite carrying a mutation in one or the other gene.

This a pedigree of retinitis pigmentosa in which mutation in two different genes give the disease, mutation only in one gene does not give the disease.

Gene-Environment Interactions in Venous Thrombosis

Two genes are related to increase the risk of get Venous Thrombosis

- **Mutation in clotting factor V gene we call it Leiden R506Q**

  R506Q →mutation at the loci 506 Arginine was changed to Glutamine

- Mutation in 3' UTR of the gene that give pro-thrombin 20210 G >A

Also environmental factors **Oral contraceptives** increase the risk of developing **Idiopathic cerebral venous thrombosis**.

If you have the mutation in gene of Clotting factor V(R506Q) you are at risk 7 folds more likely to develop Idiopathic cerebral venous thrombosis than other individuals in population .

If you have the mutation in gene of pro thrombin (20210 G> A) you are at risk of 3-6 folds more likely to develop Idiopathic cerebral venous thrombosis than other individuals in population

Oral contraceptives increase the risk of get the disease 14 – 22 fold

If you have the two mutation→ 7 x (6-3)

If you have the two mutation and you consume Oral contraceptives the risk is higher.

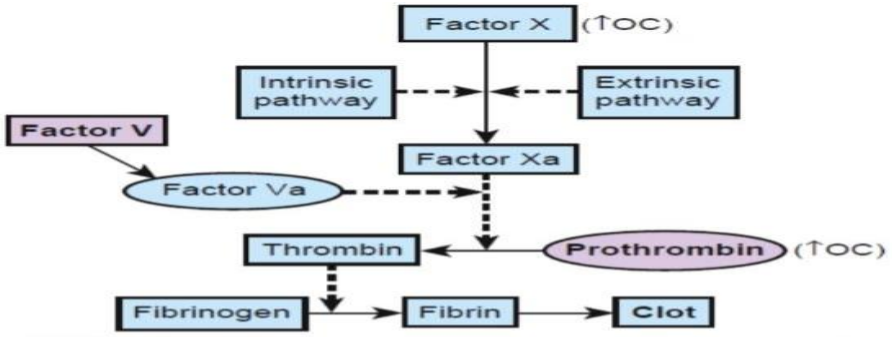


Figure 9-10 The clotting cascade relevant to factor V Leiden and prothrombin variants. Once factor X is activated, through either the intrinsic or extrinsic pathway, activated factor V promotes the production of the coagulant protein thrombin from prothrombin, which in turn cleaves fibrinogen to generate fibrin required for clot formation. Oral contraceptives (OC) increase blood levels of prothrombin and factor X as well as a number of other coagulation factors. The hypercoagulable state can be explained as a synergistic interaction of genetic and environmental factors that increase the levels of factor V, prothrombin, factor X and others to promote clotting. Activated forms of coagulation proteins are indicated by the letter *a*. *Solid arrows* are pathways; *dashed arrows* are stimulators.

The variants of Factor V and pro thrombin will increase the activity of factors V and prothrombin to accelerate the clotting pathway.

Factor X is affected by Oral contraceptives (OC), increase the activity of Factor X.

Oral contraceptives affect Factor X and prothrombin.

Hirschsprung disease

Disease affect individual in birth stage, There is a decrease in the number of nerve cells that present in digestive system.

The never cells help in rhythmic contraction to allow continuous movement of food that present in digestive system (Peristaltic movement)

In hirschsprung disease the Peristaltic movement is decreased which lead to enlargement of colon (mega colon) and constipation.

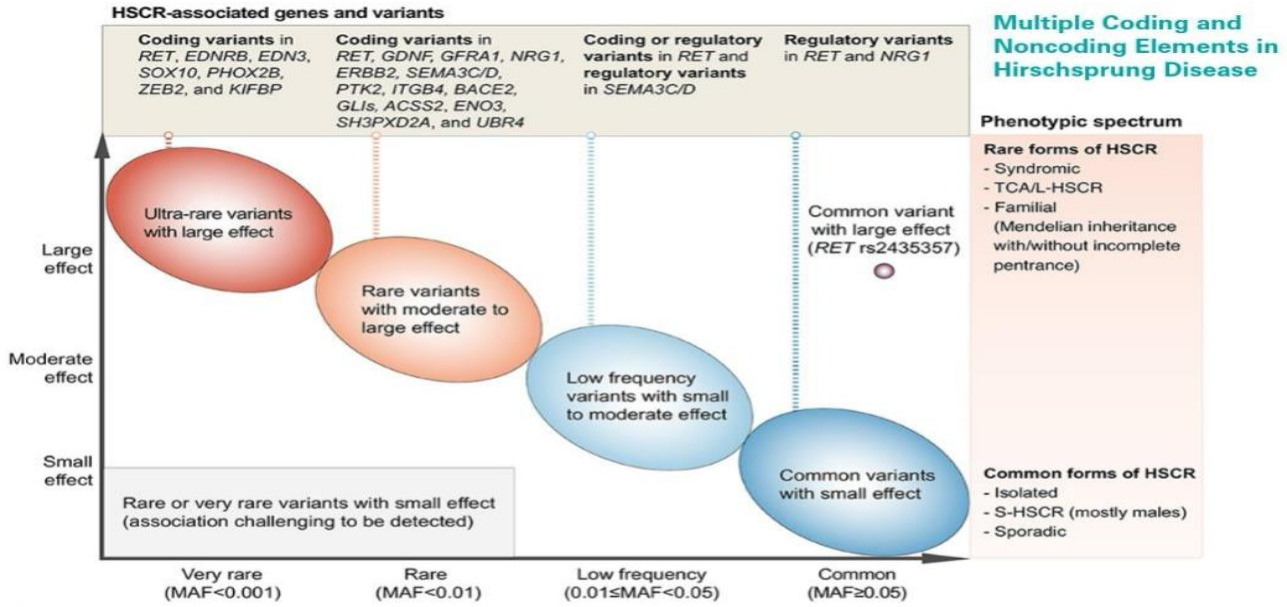


Figure 9-11 Current understanding of the genetic factors underlying inheritance of HSCR. As with most complex traits, genetic susceptibility can be explained by common variants with relatively small impacts on individual risk, and a spectrum toward very rare alleles with substantial impact on risk. HSCR shows phenotypic severity differences – syndromic HSCR and TCA/L-HSCR are more rare and severe, whereas sporadic S-HSCR is more

This graph show different genes and variants associated with Hirschsprung disease, X axis show the frequency of variants in the population, **very rare, rare**, **low Frequency** and **common**, Y axis represents the effect of these variants on population,

generally common variants have a small effect, and very rare variants have large effect on population.

Regardless of the of small effect of Common variants it increase the risk of get the complex diseases.

If we go with variants that are less and less common they have bigger and bigger impact and large effect to get the disease.

Type 1 Diabetes Mellitus

Less common, 10% of people who have diabetes

It is a Autoimmune Disease, immune cells destruct the Beta cells that produce Insulin.

Normally early aged people have Type 1 diabetes

Type 2 diabetes

Normally elder aged people have type 2 diabetes

More than 88%

People's who have diabetes, they have a continuous urination and the urine contain a lot of glucose.

Incidence of Type one Diabetes = 0.2 %

Concordance in MZ twins = 40%, what does mean?

Genetics play role, there are a lot of genetic contributions, but also concordance is not 100% which indicate environmental factors play role.

Risk in sibling of an affected is 7%

λs = 7/ 0.2= 35,

if you have a sib with Diabetes, you are at risk 35 fold more likely to develop Diabetes type 1 than other individuals in the population.

Major Histocompatibility genes : located at chromosome 6, it is a risk factor for type 1 Diabetes.

MHC very polymorphic, more than 200 genes and more than 2000 allele.

Two classes of MHC

Class 1 and class 2

Class 1 = HLA – A , HLA-B , HLA-C

Class 2 = HLA-DR, HLA-DQ, HLA-DP

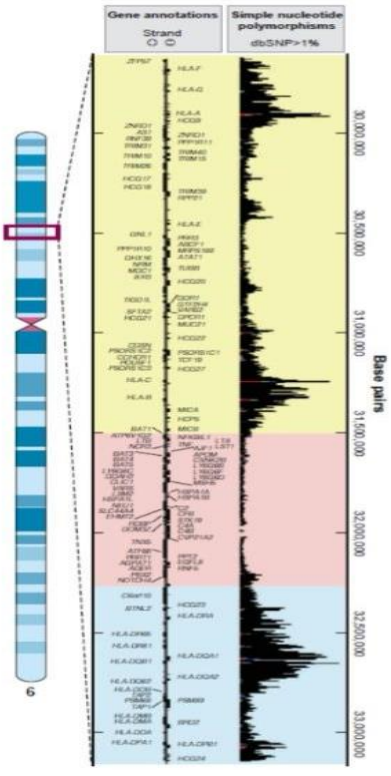


Figure 9-12 Genomic landscape of the major histocompatibility complex (MHC). The classic MHC is shown on the short arm of chromosome 6, comprising the class I region (*yellow*) and class II region (*blue*), both enriched in human leukocyte antigen (HLA) genes. Sequence-level variation is shown for single nucleotide polymorphisms (SNPs) found with at least 1% frequency. Remarkably high levels of polymorphism are seen in regions containing the classic HLA genes where variation is enriched in coding exons involved in defining the antigen-binding cleft. Other genes (*pink*) in the MHC region show lower levels of polymorphism. dbSNP, minor allele frequency in the Single Nucleotide Polymorphism database.

This graph is a genome wide association of Diabetes type 1 , some specific changes that are visible In HLA, they are associated in increase the risk of having type 1 Diabetes.

TABLE 9-12 Empirical Risks for Counseling in Type 1 Diabetes

Relationship to Affected Individual	Risk for Development of Type 1 Diabetes (%)
None	0.2
MZ twin	40
Sibling	7
Sibling with no DR haplotypes in common	1
Sibling with 1 DR haplotype in common	5
Sibling with 2 DR haplotypes in common	17*
Child	4
Child of affected mother	3
Child of affected father	5

*20%-25% for particular shared haplotypes.
MZ, Monozygotic.

Still less than 40%, thus, other genes are involved

If you have a sibling with variation in 2 DR haplotypes the Probability of you developing this disease is 17% which is suggests that there are other genes contribute to cause the disease other than HLA because still not reach

40 %, also environmental factors play role because the concordance in MZ is 40 % not reach 100% .

Alzheimer Disease

Affects 1-2% of the population,

most common cause of dementia in older adults

Risk factors: age, sex, and family history

Can be diagnosed definitively only postmortem (after died)

As the age increase the risk of get Alzheimer disease increase.

The fits, usually female at higher risk for Developing Alzheimer Disease than males, but at older age the difference of risk between male and females for Developing Alzheimer decrease but female still higher than males.

TABLE 9-13 Cumulative Age- and Sex-Specific Risks for Alzheimer Disease and Dementia

Time Interval Past 65 Years of Age	Risk for Development of AD (%)	Risk for Development of Any Dementia (%)
65 to 80 years		
Male	6.3	10.9
Female	12	19
65 to 100 years		
Male	25	32.8
Female	28.1	45

AD, Alzheimer disease.

Apolipoprotein E gene : is related to clearing Low density Lipoprotein (LDL) through interaction with high-affinity receptors in the liver.

Mutation in this gene give variant (ε4) which the increase risk for developing Alzheimer disease, if you have two Allele the risk of developing the disease increase further and the age of Developing the Diseases also decrease.

TABLE 9-14 Association of Apolipoprotein E ε4 Allele with Alzheimer Disease*

	Frequency			
	United States		Japan	
Genotype	AD	Control	AD	Control
ε4/ε4; ε4/ε3; or ε4/ε2	0.64	0.31	0.47	0.17
ε3/ε3; ε2/ε3; or ε2/ε2	0.36	0.69	0.53	0.83

*Frequency of genotypes with and without the ε4 allele among Alzheimer disease (AD) patients and controls from the United States and Japan.

The Frequency of genotypes that have ε4 either one copy or two copy is higher in Alzheimer Disease which indicate this Allele increase the risk of developing the disease.

The Frequency of genotypes that have other alleles ε3 and ε2 without ε4 is higher in the control than AD patients also this suggest that ε4 increase the risk of developing AD disease.

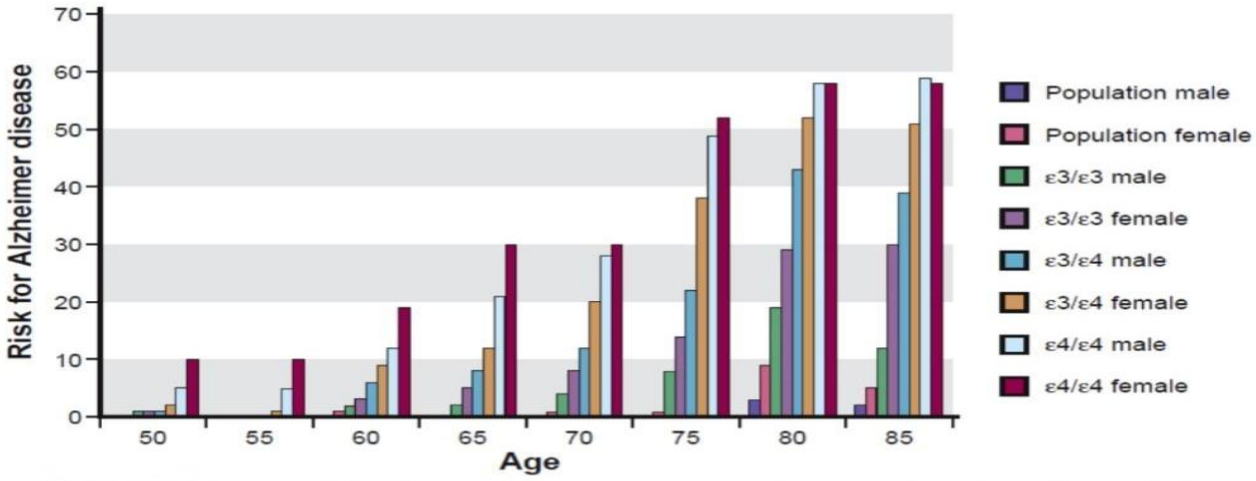


Figure 9-13 Chance of developing Alzheimer disease as a function of age for different *APOE* genotypes for each sex. At one extreme is the ε4/ε4 homozygote, who has ≈40% chance of remaining free of the disease by the age of 85 years, whereas an ε3/ε3 homozygote has ≈70% to ≈90% chance of remaining disease free at the age of 85 years, depending on the sex. General population risk is also shown for comparison.

This figure show effect of ε4 of developing Alzheimer, X axis indicate the age, Y axis indicate risk of Alzheimer Disease, as the age increase the risk of developing Alzheimer Disease increase, in the General population the risk of developing Alzheimer Disease increase in people who have alleles that increase the risk to Develop the disease, the individuals who have two ε4 alleles they are higher risk than others, also females who have two ε4 alleles are at higher risk than males who have Two ε4 alleles for Developing Alzheimer Disease.

The difference in the risk to get Alzheimer males and females is decreased at older ages 75-85

The £4 variant of APOE represents a prime example of a predisposing allele:

It predisposes to a complex trait in a powerful way but does not predestine any individual carrying the allele to the disease.