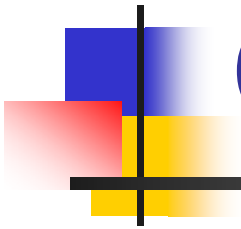


Genetic Theory - Overview

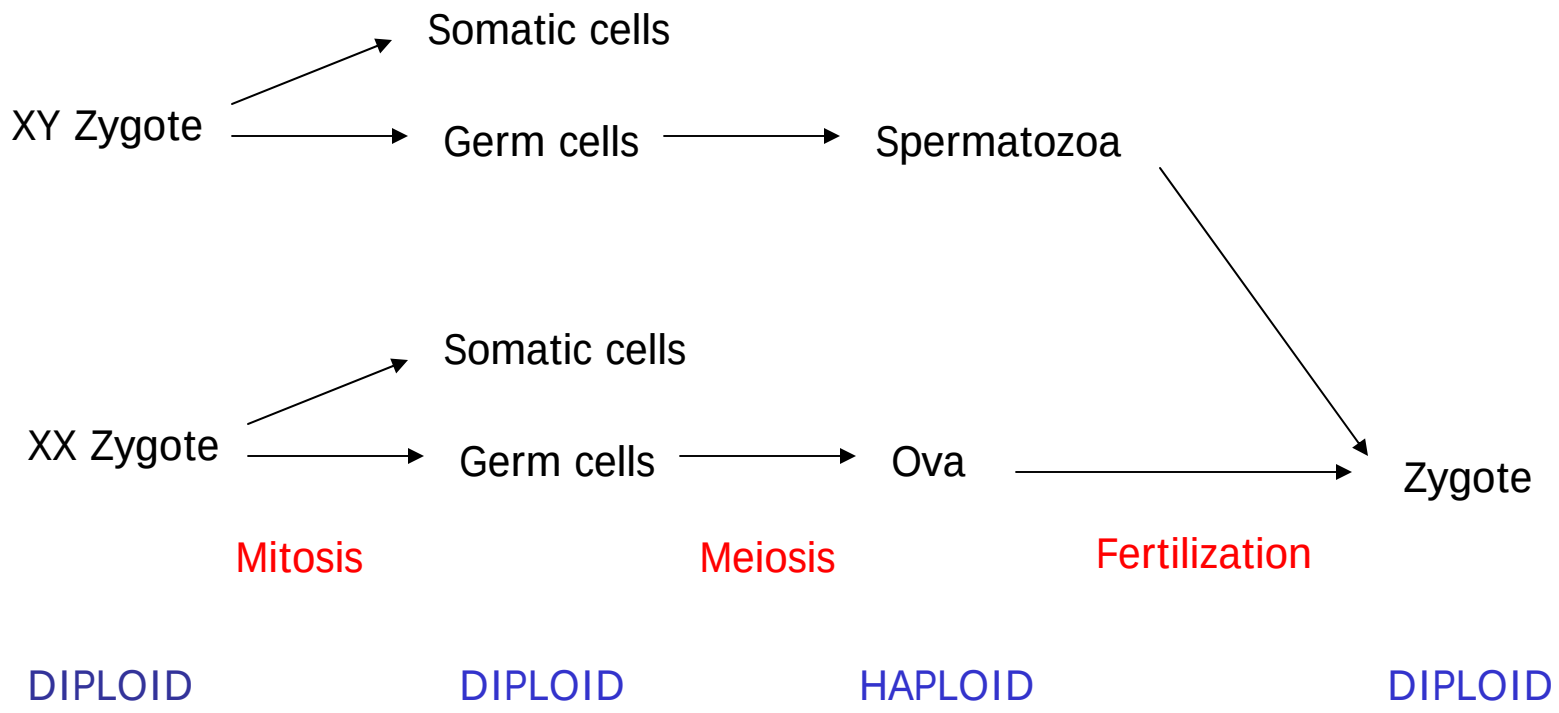
Pak Sham

International Twin Workshop
Boulder, 2005

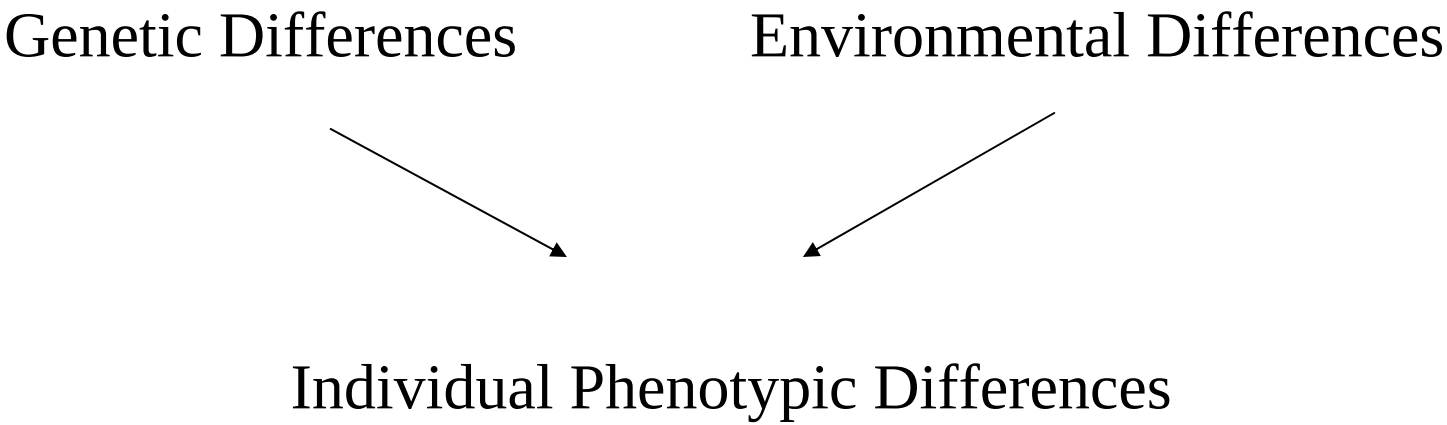
The Human Genome

- 23 Chromosomes, each containing a DNA molecule (Watson and Crick, 1953)
- 3×10^9 base pairs, completely sequenced (Human Genome Project, 2003)
- Approximately 24,000 genes, each coding for a polypeptide chain
- Approximately 10^7 common polymorphisms (variable sites, documented in dbSNP database)

Genetic transmission



Sources of Natural Variation



Genetic Variation

- Chromosomal anomalies
- Insertions / Deletions / Translocations
- Variable sequence repeats
  - microsatellites (e.g. CACACA….)
- Single nucleotide polymorphisms (SNPs)

Types of Genetic Disease

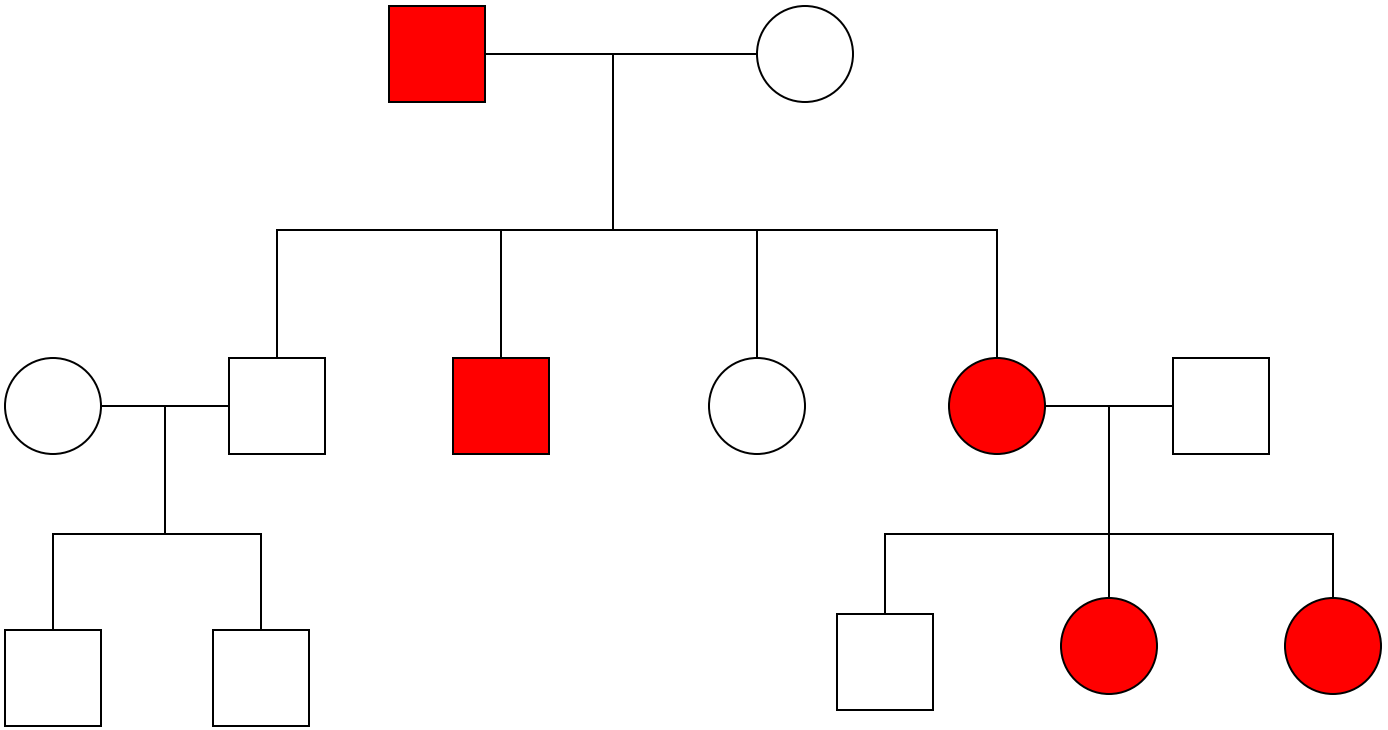
- Mendelian diseases
  - e.g. Huntington's disease, cystic fibrosis
  - A genetic mutation causes the disease
  - Environmental variation usually irrelevant
  - Usually rare
  - Occurs in isolated pedigrees

- Multifactorial diseases
  - e.g. Coronary heart disease, hypertension, schizophrenia
  - A genetic variant increases the risk of disease
  - Environmental variation usually important
  - Often common
  - Occurs in general population

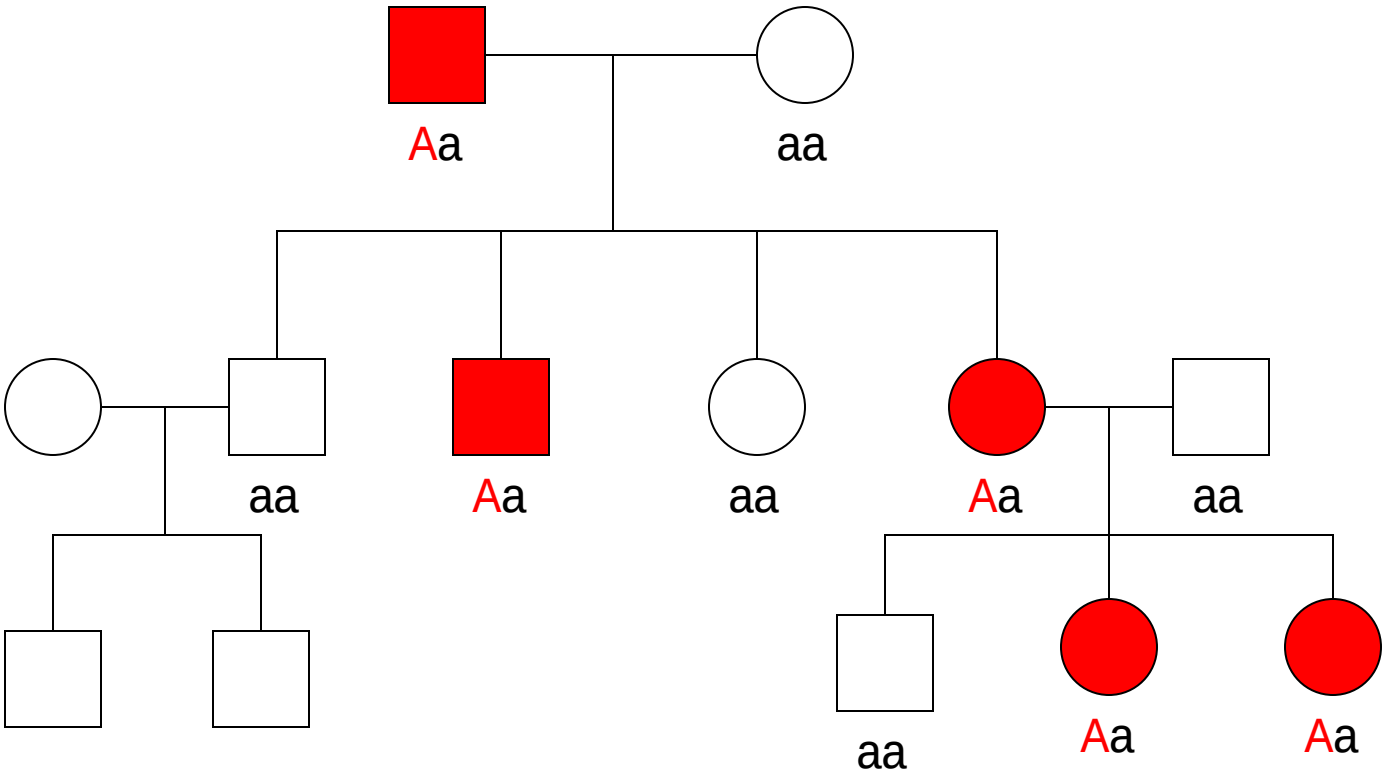
Single-Gene Disorders

- Human Genome Project completed in 2003
- Human Gene Mutation Database contains 44,090 mutations in 1,714 genes
- Gene Test web site lists genetic tests for 1,093 diseases
- dbSNP Database Build 123 contains 10,079,771 single nucleotide polymorphisms

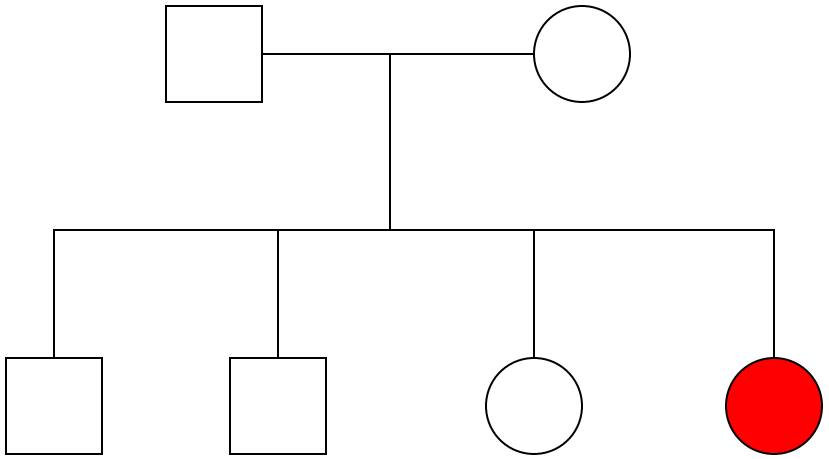
Autosomal Dominant Disorders



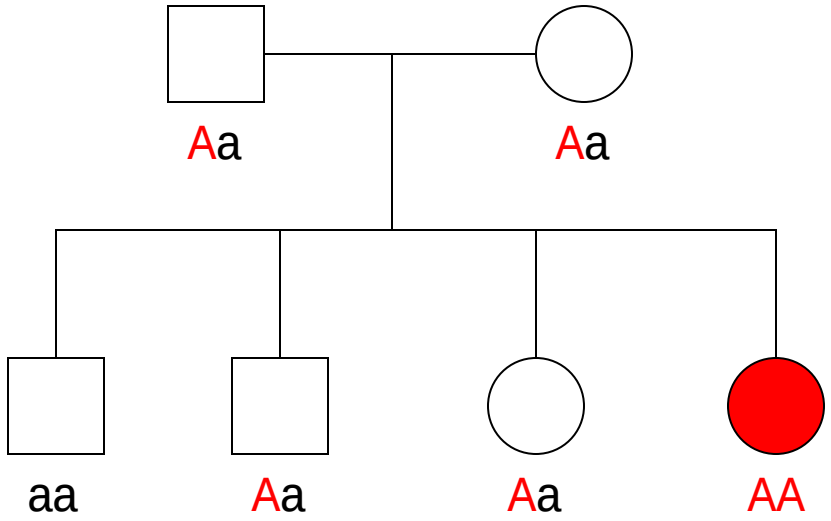
Autosomal Dominant Disorders



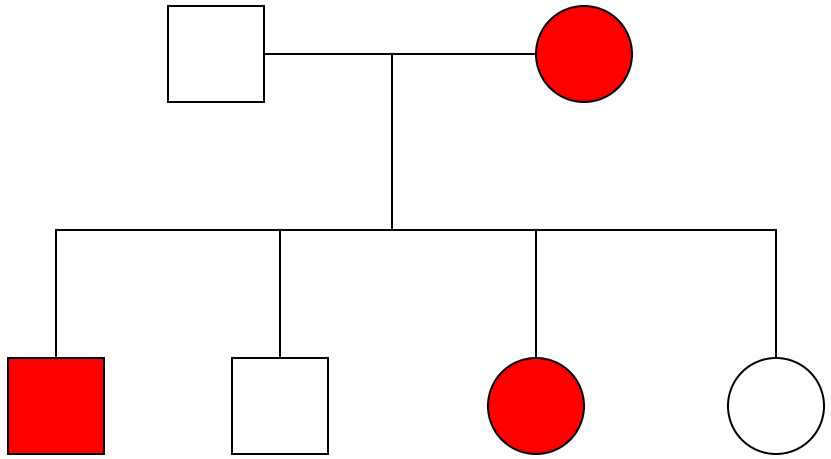
Autosomal Recessive Disorders



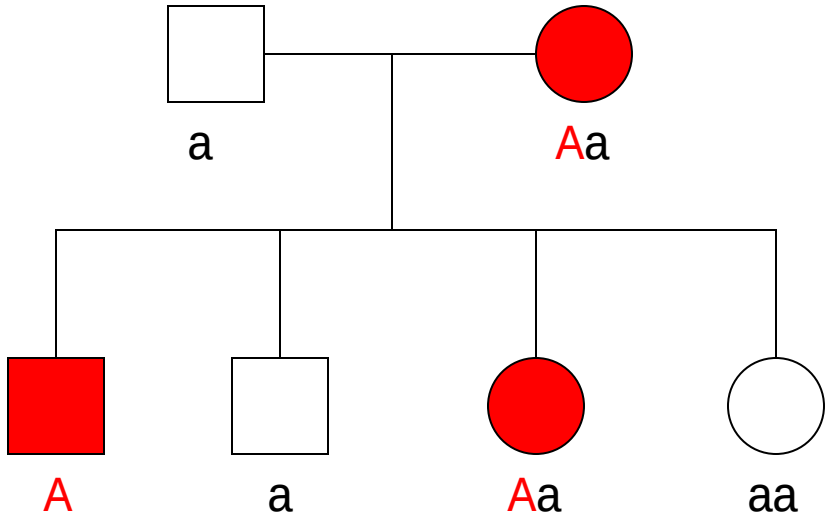
Autosomal Recessive Disorders



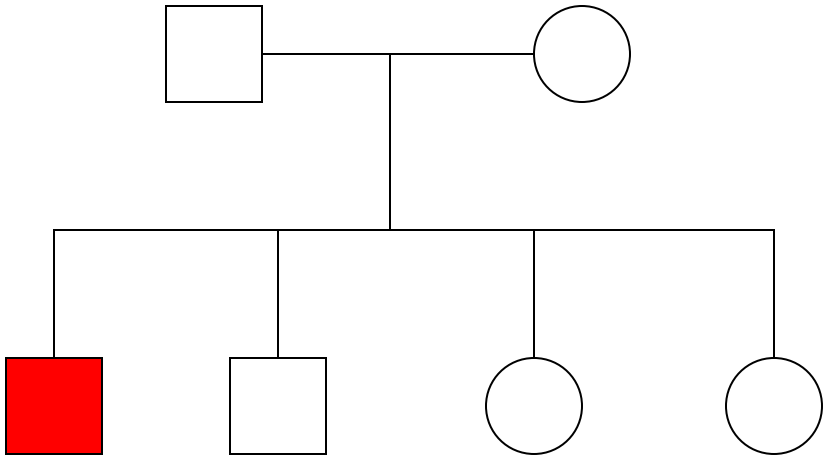
X-linked Dominant Disorders



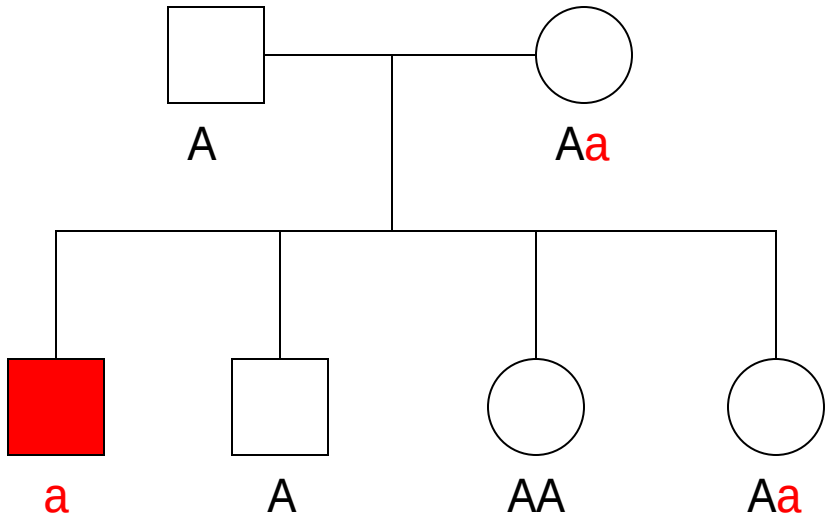
X-linked Dominant Disorders



X-linked Recessive Disorders



X-linked Recessive Disorders



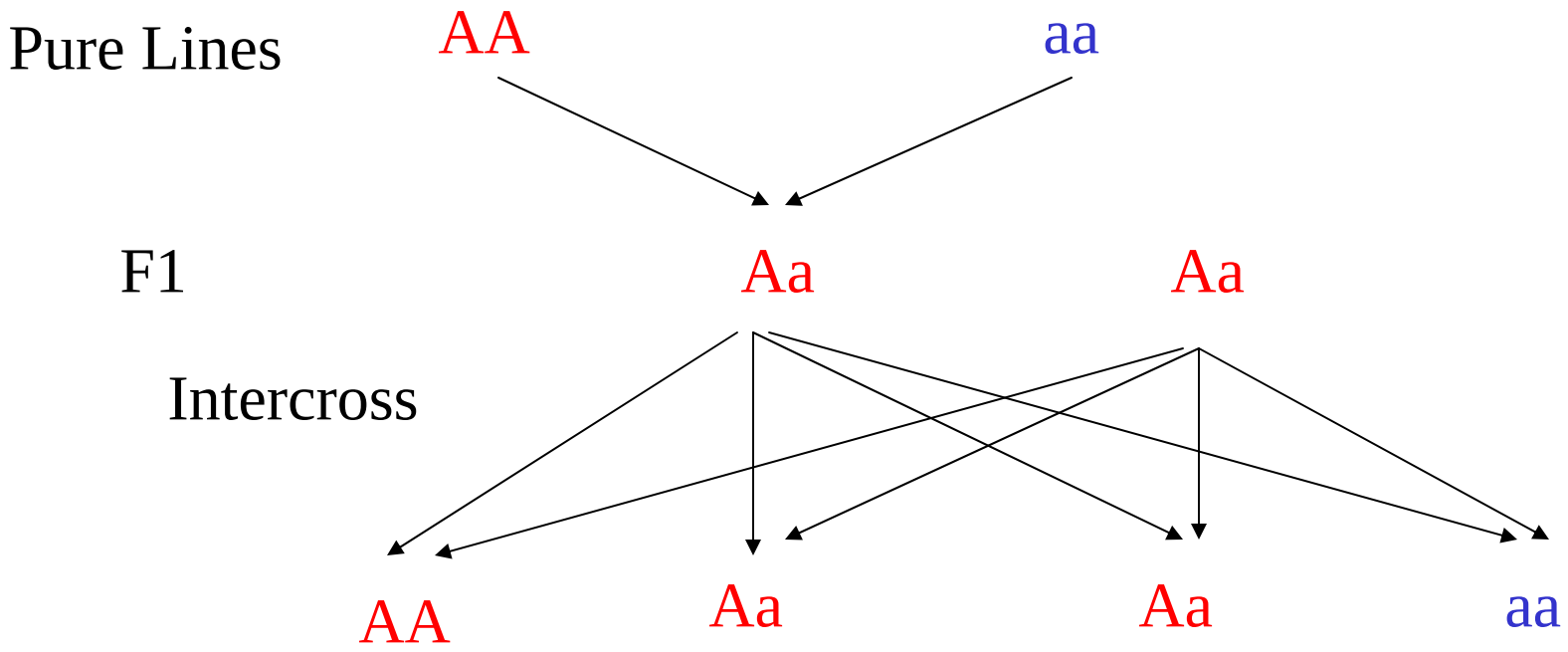
Mendelian Segregation

Segregation Ratios

- First discovered by Gregor Mendel in his experiments on the garden pea (published in 1866 and rediscovered in 1900)
- Form the basis of Mendel's first law:

  "law of segregation"
- Defined as the ratio of affected to normal individuals among the offspring of a particular type of mating.

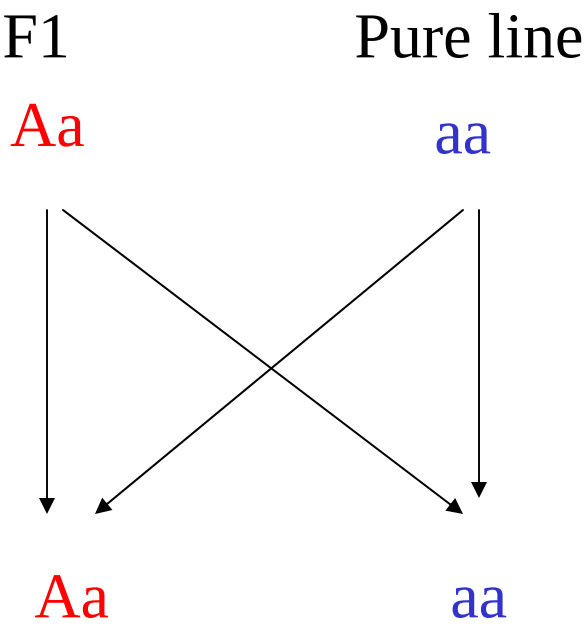
Mendel's Experiments



3:1 Segregation Ratio

Mendel's Experiments

Back cross



1:1 Segregation ratio

Segregation Ratios

Mode of inheritance	Mating type	Segregation ratio Affected:Normal
Autosomal dominant	Affected x Normal	
Autosomal recessive	Carrier x Carrier	
X-linked dominant	Nornal father x Affected mother	
X-linked recessive	Normal father x Carrier mother	

Segregation Ratios

Mode of inheritance	Mating type	Segregation ratio Affected:Normal
Autosomal dominant	Affected x Normal	1:1
Autosomal recessive	Carrier x Carrier	
X-linked dominant	Nornal father x Affected mother	
X-linked recessive	Normal father x Carrier mother	

Segregation Ratios

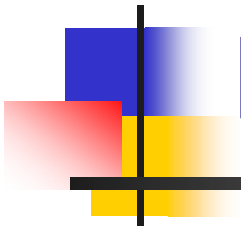
Mode of inheritance	Mating type	Segregation ratio Affected:Normal
Autosomal dominant	Affected x Normal	1:1
Autosomal recessive	Carrier x Carrier	1:3
X-linked dominant	Nornal father x Affected mother	
X-linked recessive	Normal father x Carrier mother	

Segregation Ratios

Mode of inheritance	Mating type	Segregation ratio Affected:Normal
Autosomal dominant	Affected x Normal	1:1
Autosomal recessive	Carrier x Carrier	1:3
X-linked dominant	Nornal father x Affected mother	1:1
X-linked recessive	Normal father x Carrier mother	

Segregation Ratios

Mode of inheritance	Mating type	Segregation ratio Affected:Normal
Autosomal dominant	Affected x Normal	1:1
Autosomal recessive	Carrier x Carrier	1:3
X-linked dominant	Normal father x Affected mother	1:1
X-linked recessive	Normal father x Carrier mother	1:1 in sons



Hardy-Weinberg Law

Parental Frequencies

Genotype	Frequency
AA	P
Aa	Q
aa	R

Allele	Frequency
A	P+Q/2
a	R+Q/2

Mating Type Frequencies (Random Mating)

	AA	**Aa**	**aa**
AA	P^2	PQ	PR
Aa	PQ	Q^2	QR
aa	PR	QR	R^2

Offspring Segregation Ratios

	AA	**Aa**	**aa**
AA	AA	AA:Aa 0.5:0.5	Aa
Aa	AA:Aa 0.5:0.5	AA:Aa:aa 0.25:0.5:0.25	Aa:aa 0.5:0.5
aa	Aa	Aa:aa 0.5:0.5	aa

Offspring Genotype Frequencies

Genotype	Frequency
AA	$P^2+PQ+Q^2/4 = (P+Q/2)^2$
Aa	$2PR+PQ+QR+Q^2/2 = 2(P+Q/2)(R+Q/2)$
aa	$R2+QR+Q^2/4 = (R+Q/2)^2$

Offspring Allele Frequencies

Allele	Frequency
A	$(P+Q/2)^2 + (P+Q/2)(R+Q/2) = P+Q/2$
a	$(R+Q/2)^2 + (P+Q/2)(R+Q/2) = R+Q/2$

Hardy-Weinberg Equilibrium

In a large population under random mating:

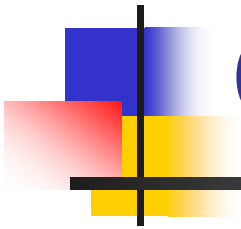
- Allele frequencies in the offspring, denoted as **p** and **q**, are the same as those in the parental generation.
- Genotype frequencies in the offspring will follow the ratios $\mathbf{p^2}$:**2pq**:$\mathbf{q^2}$, regardless of the genotype frequencies in the parents.

Hardy-Weinberg Equilibrium

	A	a	
A	p^2	pq	p
a	pq	q^2	q
	P	q	

Hardy-Weinberg Disequilibrium

	A	a	
A	p^2+d	pq-d	p
a	pq-d	q^2+d	q
	P	q	



Genetic Linkage

Genetic Markers

- Classical
  - Mendelian Disorders
  - Blood groups
  - HLA Antigens
- Molecular genetic
  - Microsatellites (e.g. CACACA...)
  - Single-nucleotide polymorphisms (e.g. C/T)

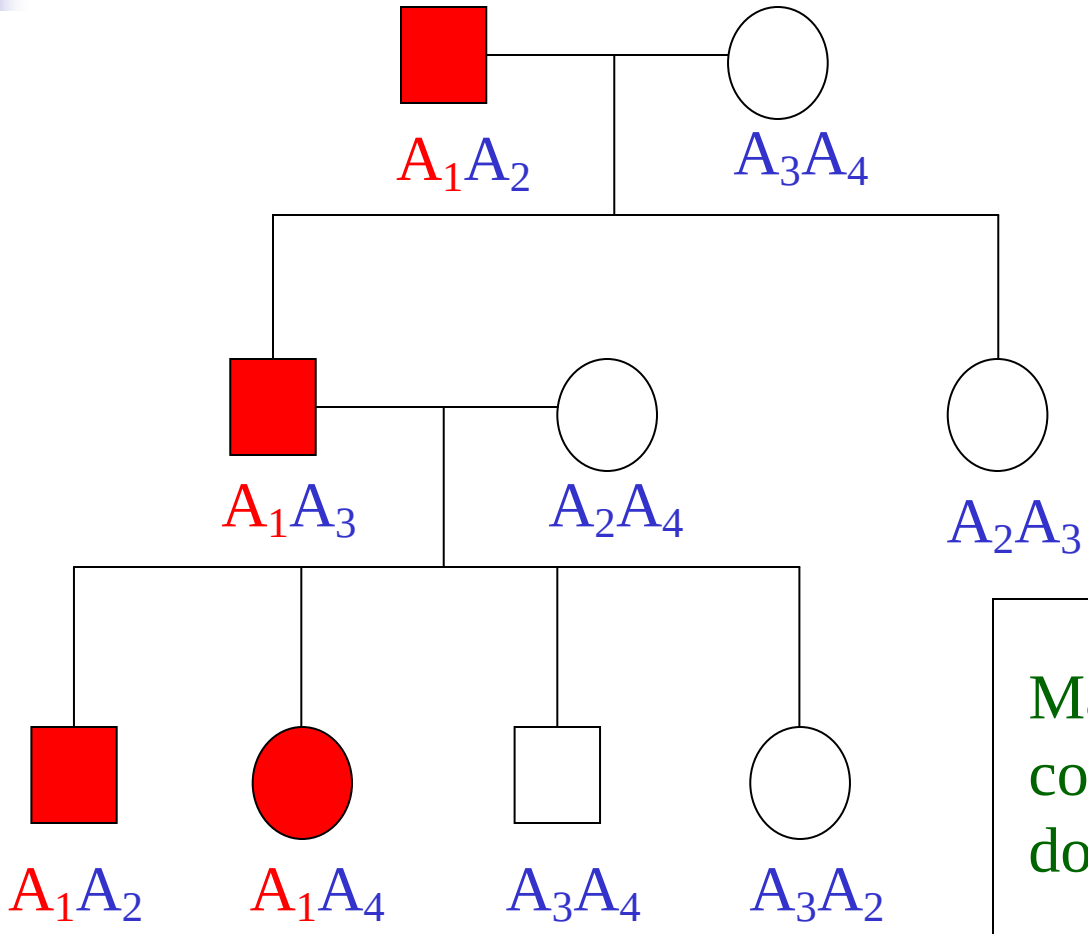
High-Throughput Genotyping

- Extreme multiplexing (multiple markers)
- DNA Pooling (multiple samples)

Maximum throughput of SEQUENOM system at the HKU Genome Research Centre is 100,000 genotypes / day, at a cost of US$ 0.2 per genotype

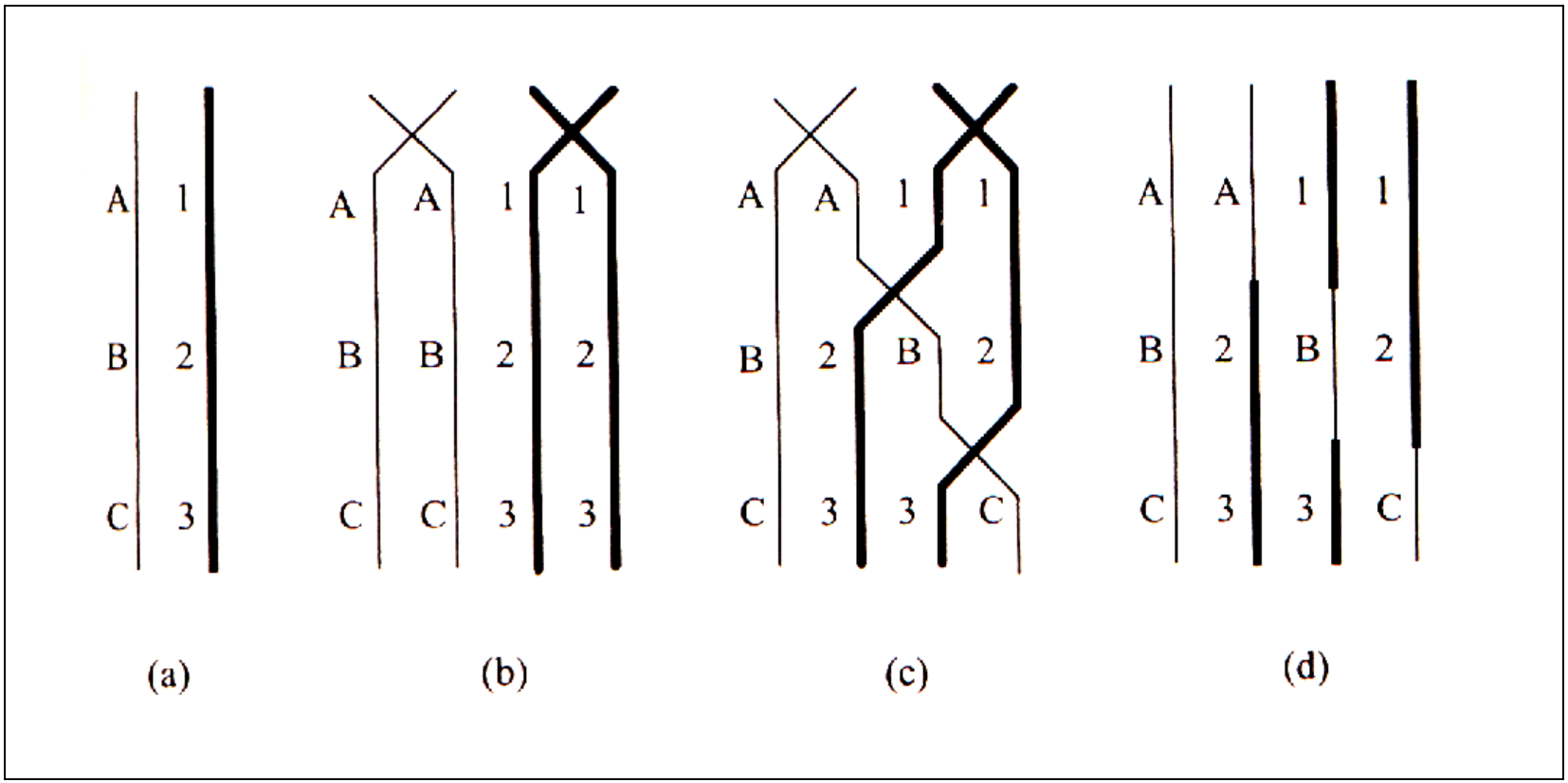
Cost of genotyping set to decrease further – eventually enabling whole-genome association studies to be done.

Linkage = Co-segregation



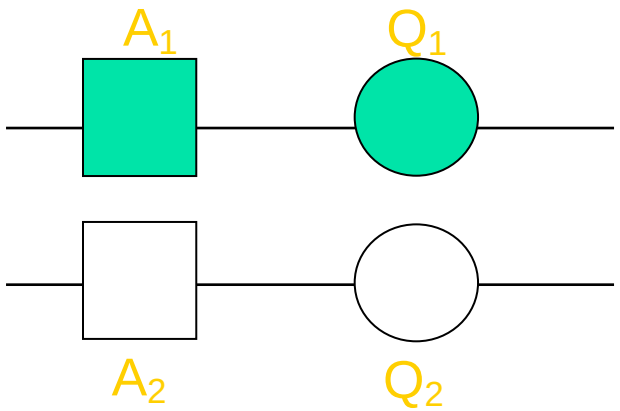
Marker allele A_1 cosegregates with dominant disease

Crossing-over in meiosis

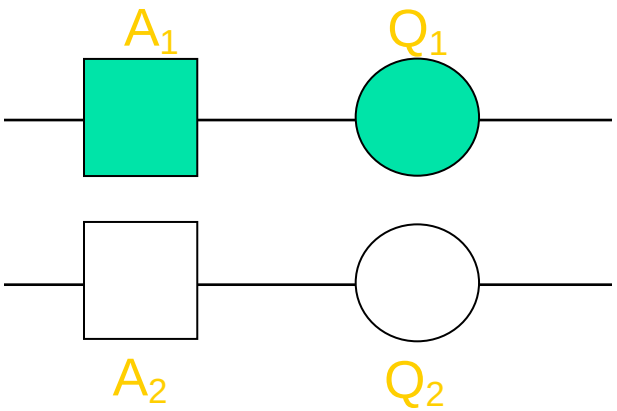


Recombination

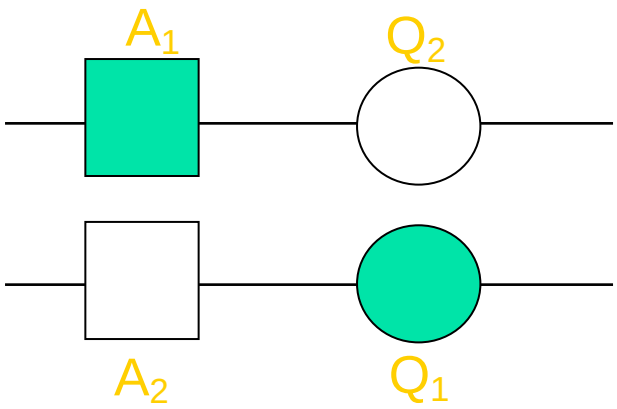
Parental genotypes



Likely gametes
(Non-recombinants)



Unlikely gametes
(Recombinants)

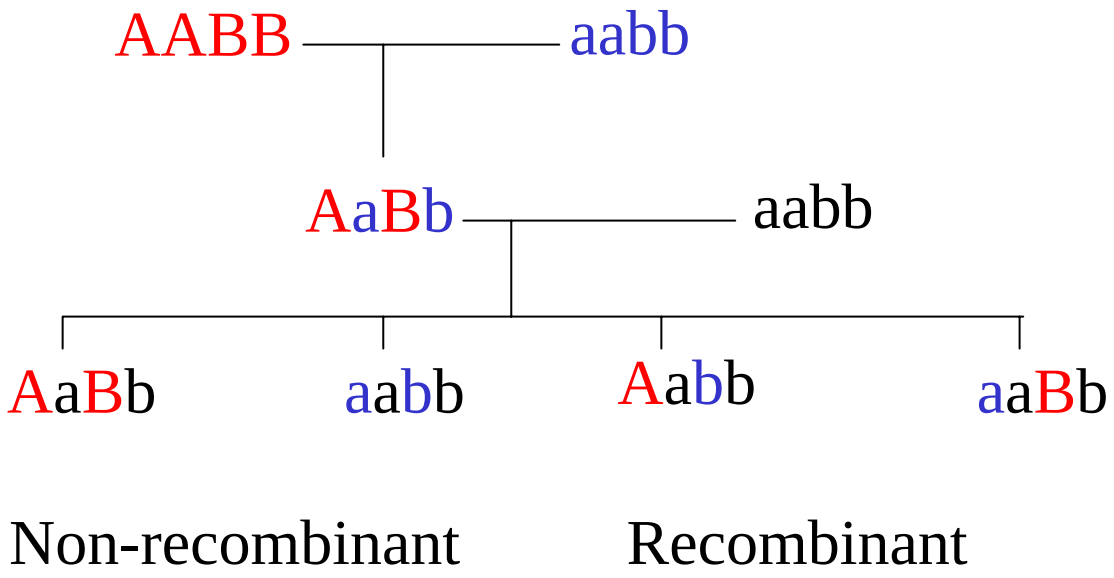


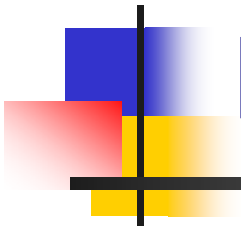
Recombination fraction

Recombination fraction between two loci

= Proportion of gametes that are recombinant with respect to the two loci

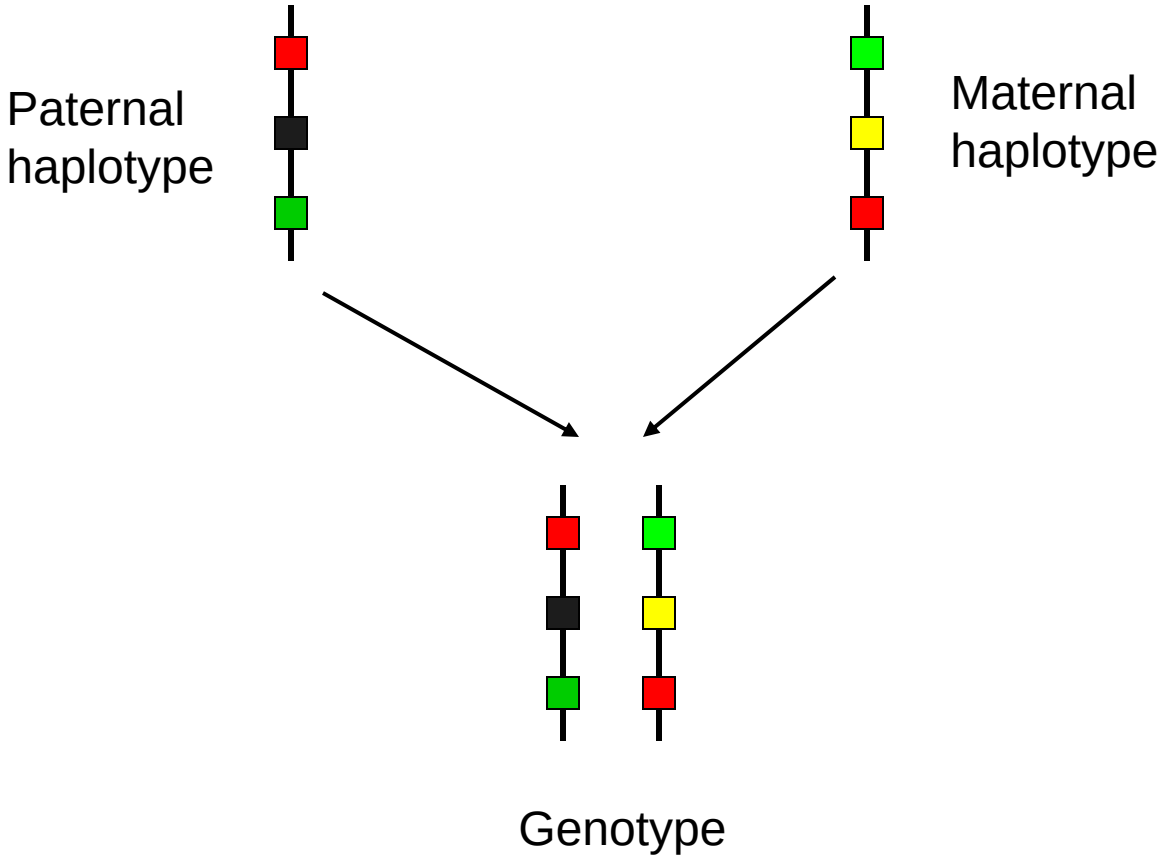
Double Backcross : Fully Informative Gametes





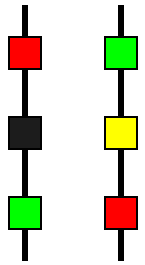
Haplotypes

Haplotypes

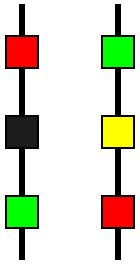


Recombination

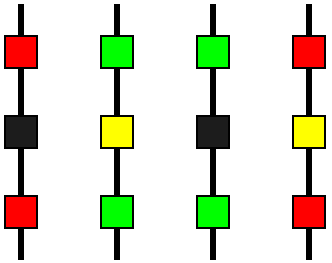
Parental haplotypes



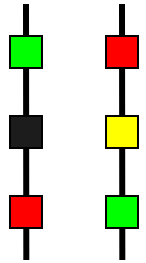
Possible transmitted haplotypes



Non-recombinants



Single recombinants



Double recombinants

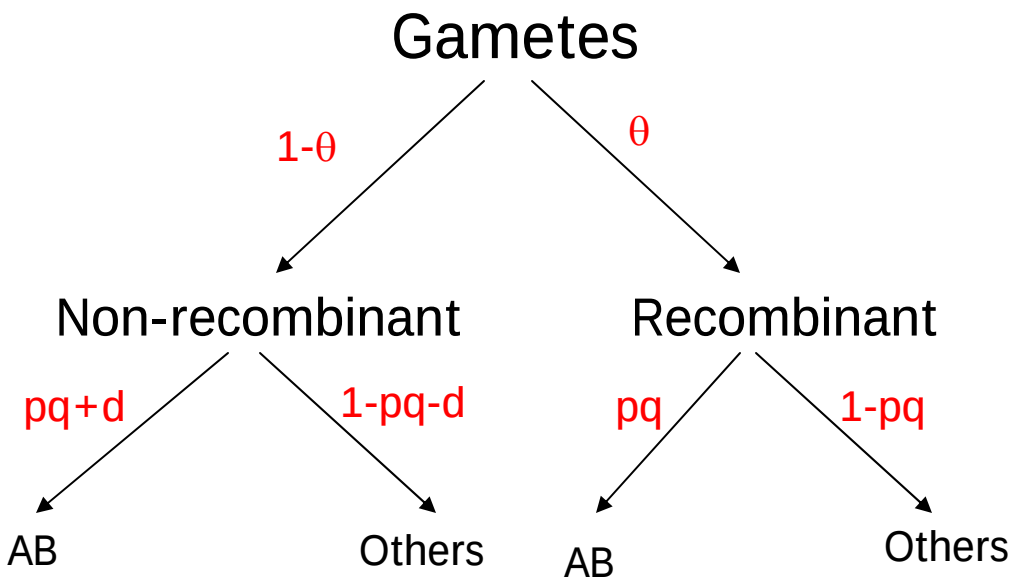
Linkage Equilibrium

	B	b	
A	pr	ps	p
a	qr	qs	q
	r	s	

Linkage Disequilibrium (LD)

	B	b	
A	pr+d	ps-d	p
a	qr-d	qs+d	q
	r	S	

Decay of LD



Frequency of AB gametes = $(1-\theta)(pq+d)+\theta pq = pq+(1-\theta)d$

Single-Gene Disorders: Some Historical Landmarks

- 1902: First identified single-gene disorder - alkaptonuria
- 1956: First identified disease-causing amino acid change: sickle-cell anaemia
- 1961: First screening program: phenylketonuria
- 1983: First mapped to chromosomal location: Huntington's disease
- 1986: First positionally cloned - chronic granulomatous disease, Duchenne muscular dystrophy
- 1987: First autosomal recessive disease cloned – cystic fibrosis

Types of Genetic Disease

- Mendelian diseases
  - e.g. Huntington's disease, cystic fibrosis
  - A genetic mutation causes the disease
  - Environmental variation usually irrelevant
  - Usually rare
  - Occurs in isolated pedigrees

- Multifactorial diseases
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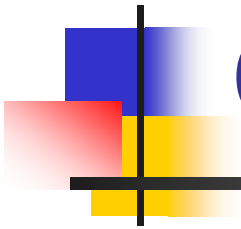


Genetic Study Designs

Family Studies

Case – Control Family Design

Compares risk in relatives of case and controls

Some terminology

- Proband
- Secondary case
- Lifetime risk / expectancy (morbid risk)

Problem: Familial aggregation can be due to shared family environment as well as shared genes

Family Studies: Schizophrenia

Relationship to Proband	Lifetime Risk of Schizophrenia (%)
Unrelated	1
First cousins	2
Uncles/Aunts	2
Nephews/Nieces	4
Grandchildren	5
Half siblings	6
Parents	6
Siblings	9
Children	13

From: Psychiatric Genetics and Genomics. MuGuffin, Owen & Gottesman, 2002

Twin Studies

Studies risk of disease (concordance rates) in cotwins of affected MZ and DZ Twin

Under the equal environment assumption, higher MZ than DZ concordance rate implies genetic factors

Problems:

- Validity of equal environment assumption
- Generalizability of twins to singletons

Twin Studies: Schizophrenia

Zygosity	Concordance (%)
Dizygotic (DZ)	17
Monozygotic (MZ)	48

From: Psychiatric Genetics and Genomics. MuGuffin, Owen & Gottesman, 2002

Adoption Studies

Adoptees' method compares

- Adoptees with an affected parent
- Adoptees with normal parents

Adoptee's family method compares

- Biological relatives of adoptees
- Adoptive relatives of adoptees

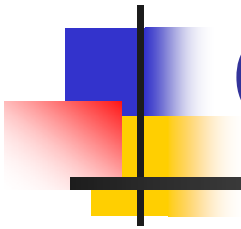
Problems:

- Adoption correlated with ill-health/psychopathology in parents
- Adoptive parents often rigorously screened

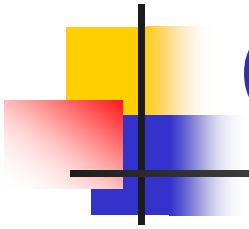
Adoption Studies: Schizophrenia

Adoptees of	Risk of Schizophrenia (%)
Schizophrenic parents	8
Control parents	2

From: Finnish Adoption Study, as summarised in Psychiatric Genetics and Genomics. MuGuffin, Owen & Gottesman, 2002



Quantitative Genetics

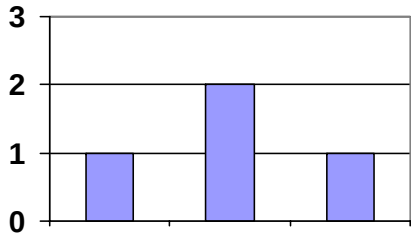


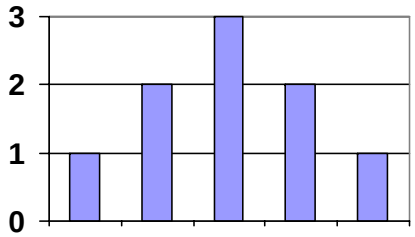
Quantitative Genetics

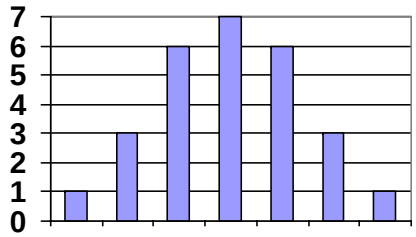
- Examples of quantitative traits
  - Blood Pressure (BP)
  - Body Mass Index (BMI)
  - Blood Cholesterol Level
  - General Intelligence (G)
- Many quantitative traits are relevant to health and disease

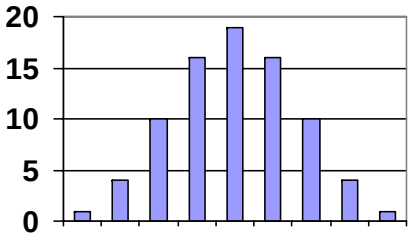
Quantitative Traits

1 Gene	2 Genes	3 Genes	4 Genes
→ 3 Genotypes	→ 9 Genotypes	→ 27 Genotypes	→ 81 Genotypes
→ 3 Phenotypes	→ 5 Phenotypes	→ 7 Phenotypes	→ 9 Phenotypes



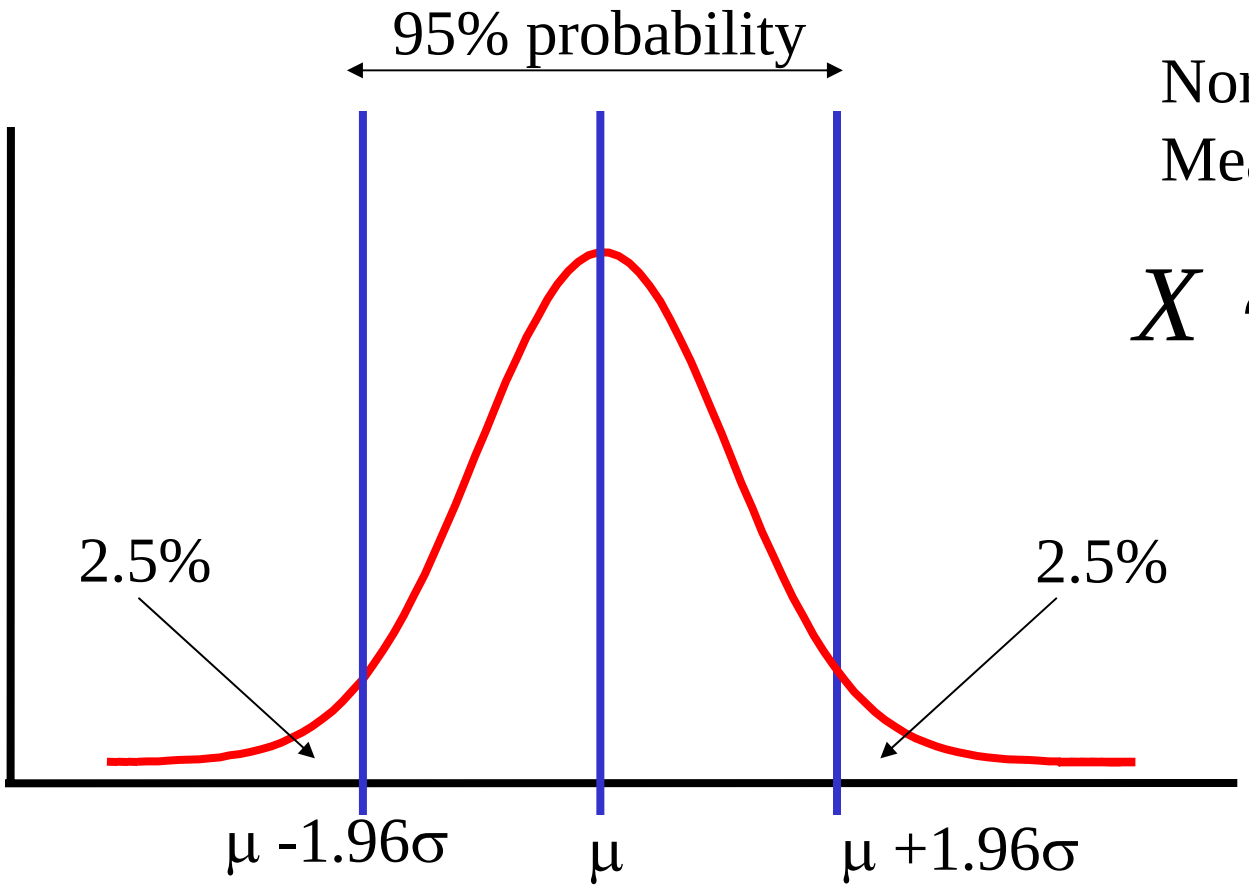






Central Limit Theorem → Normal Distribution

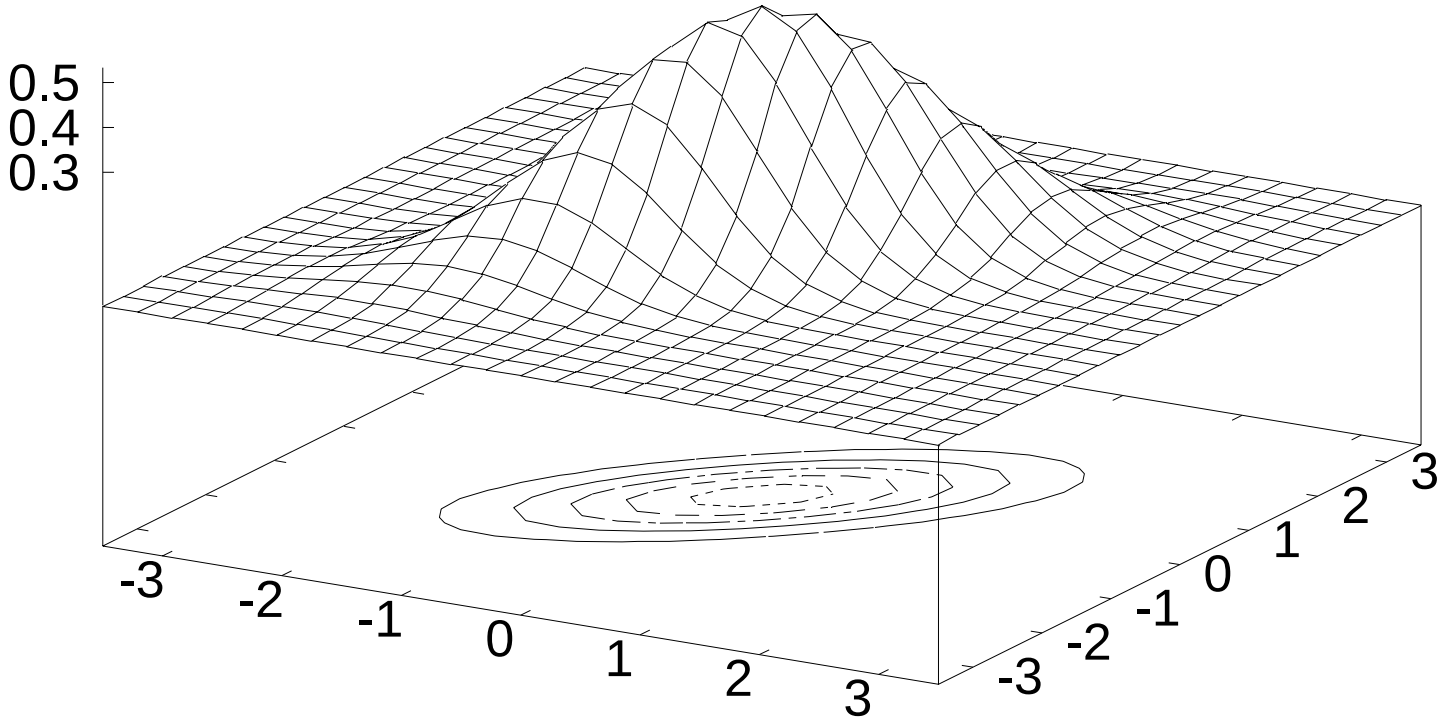
Continuous Variation



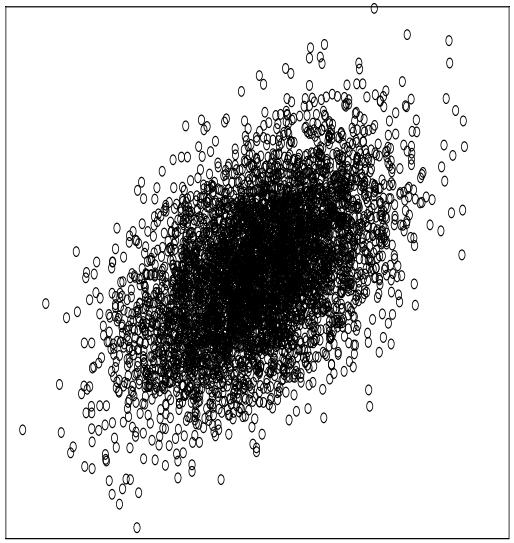
Normal distribution
Mean μ, variance σ^2

$$X \sim N(\mu, \sigma^2)$$

Bivariate normal



Familial Covariation



Bivariate normal disttribution

$$X \sim N(\boldsymbol{\mu}, \boldsymbol{\Sigma})$$

$$\boldsymbol{\mu} = \begin{bmatrix} \mu_1 \\ \mu_2 \end{bmatrix}$$

$$\boldsymbol{\Sigma} = \begin{bmatrix} \sigma_1^2 & \sigma_{12} \\ \sigma_{21} & \sigma_2^2 \end{bmatrix}$$

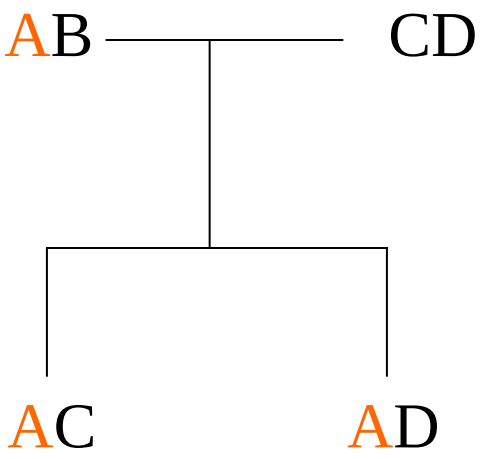
Correlation due to Shared Factors

Francis Galton: Two Journeys starting at same time

Journey Times: A+B and A+C

Shared A ⟶ Covariance ⟶ Correlation

Shared Genes



Gene A is shared:

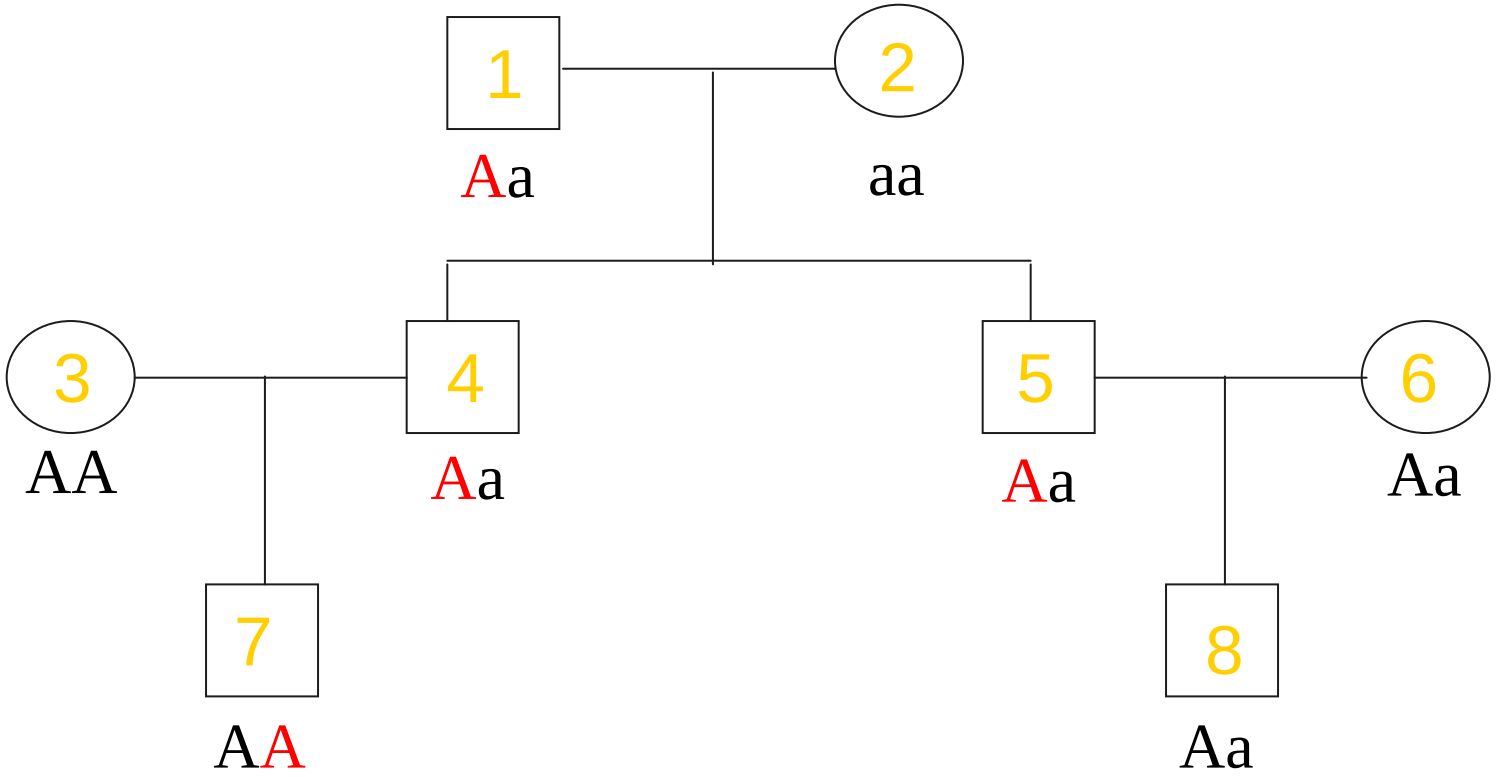
= Identity-By-Descent (IBD)

$\Rightarrow$ Shared Phenotypic Effects

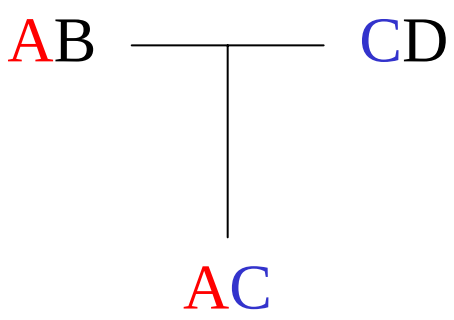
At any chromosomal location, two individuals can share 0, 1 or 2 alleles.

Identity by Descent (IBD)

- Two alleles are IBD if they are descended from and replicates of the same ancestral allele

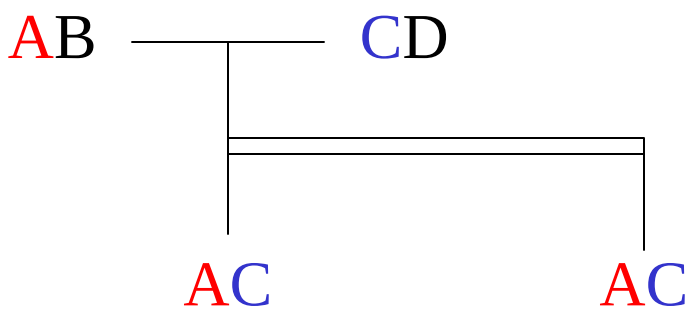


IBD: Parent-Offspring



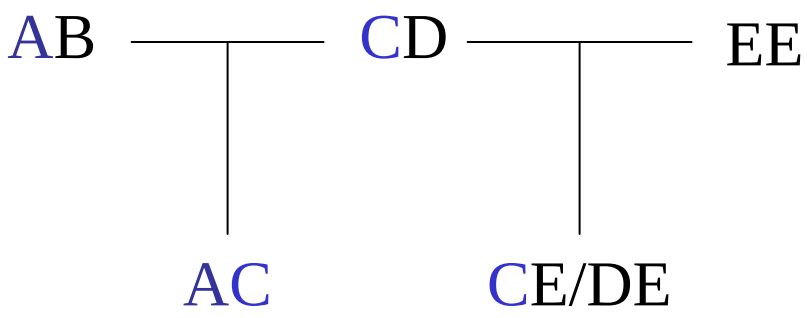
If the parents are unrelated,
then parent-offspring pairs always share 1 allele IBD

IBD: MZ Twins



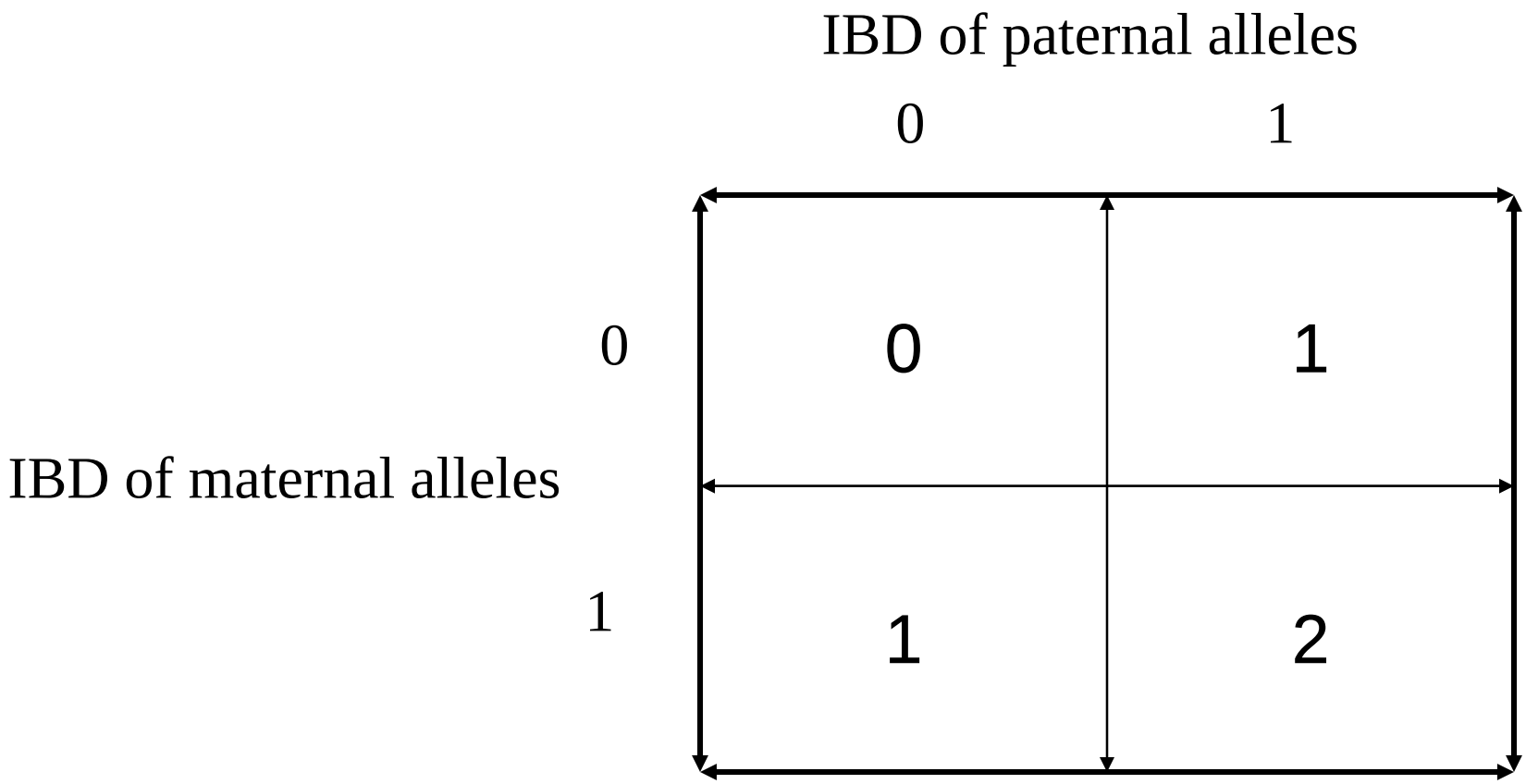
MZ twins always share 2 alleles IBD

IBD: Half Sibs



IBD Sharing	Probability
0	½
1	½

IBD: Full Sibs



IBD: Full Sibs

IBD Sharing	Probability
0	1/4
1	1/2
2	1/4

Average IBD sharing = 1

Genetic Relationships

Φ (kinship coefficient): Probability of IBD between two alleles drawn at random, one from each individual, at the same locus.

Δ: Probability that both alleles at the same locus are IBD

Relationship	Φ	Δ
MZ twins	0.5	1
Parent-offspring	0.25	0
Full sibs	0.25	0.25
Half sibs	0.125	0

Proportion of Alleles IBD (π)

Proportion of alleles IBD = Number of alleles IBD / 2

Relatiobship	Φ	E(π)	Var(π)
MZ	0.5	1	0
Parent-Offspring	0.25	0.5	0
Full sibs	0.25	0.5	0.125
Half sibs	0.125	0.25	0.0625

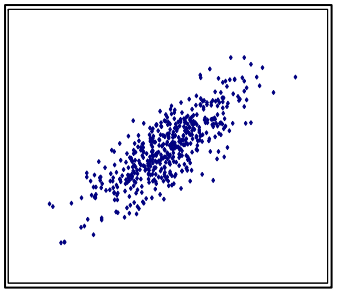
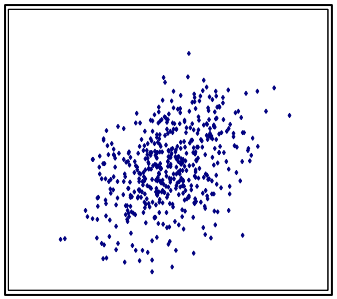
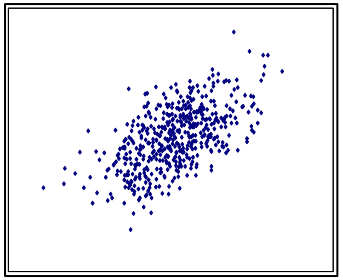
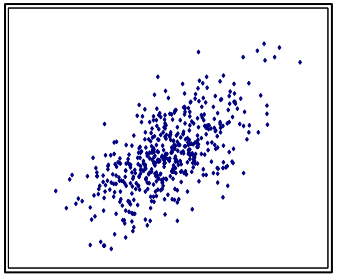
Most relationships demonstrate variation in π across the chromosomes

Genetic Relationship & Genetic Sharing

Type of Relationship	Average Genetic Sharing
MZ Twins	1
Parent - offspring	0.5
Full sibs (including DZ Twins)	0.5
Half Sibs	0.25
Aunt/Uncle – Nephew/Niece	0.25
First Cousins	0.125

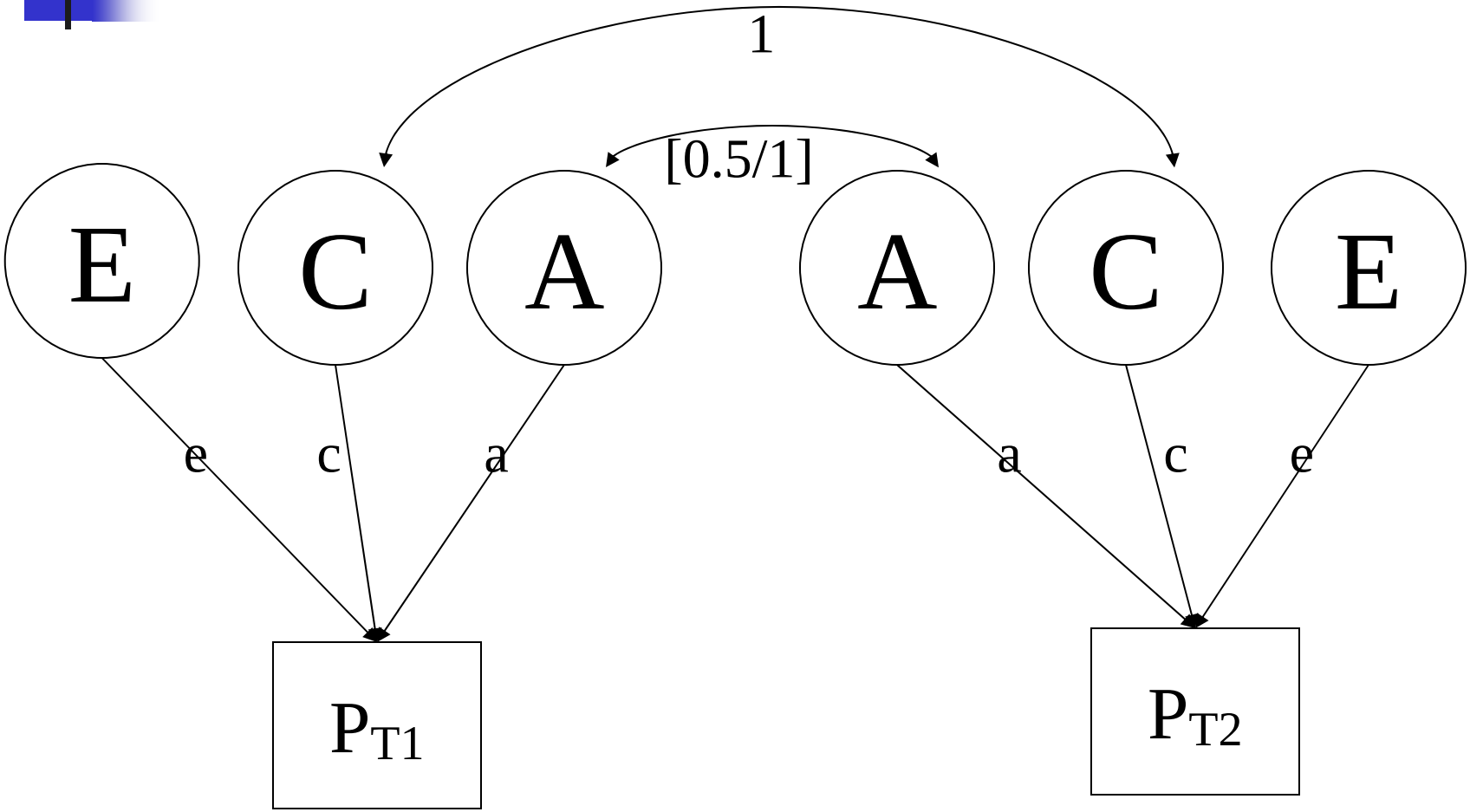
If genetic factors are involved in a disease, then the closer the relationship, the greater the similarity in disease status

Classical Twin Analysis

	MZ Twins	DZ Twins	
Average genetic sharing	100%	50%	
Phenotypic correlation			> ⇒ Genetic influences
			= ⇒ No genetic influences

Note: Equal Environment Assumption

ACE Model for twin data



Implied covariance matrices

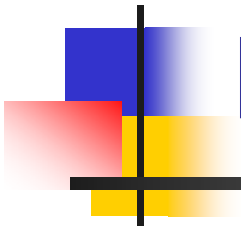
$$\Sigma_{MZ} = \begin{bmatrix} a^2 + c^2 + e^2 & \\ a^2 + c^2 & a^2 + c^2 + e^2 \end{bmatrix}$$

$$\Sigma_{DZ} = \begin{bmatrix} a^2 + c^2 + e^2 & \\ \frac{1}{2}a^2 + c^2 & a^2 + c^2 + e^2 \end{bmatrix}$$

$\Rightarrow$ Difference between MZ and DZ covariance ~ Genetic Variance / 2

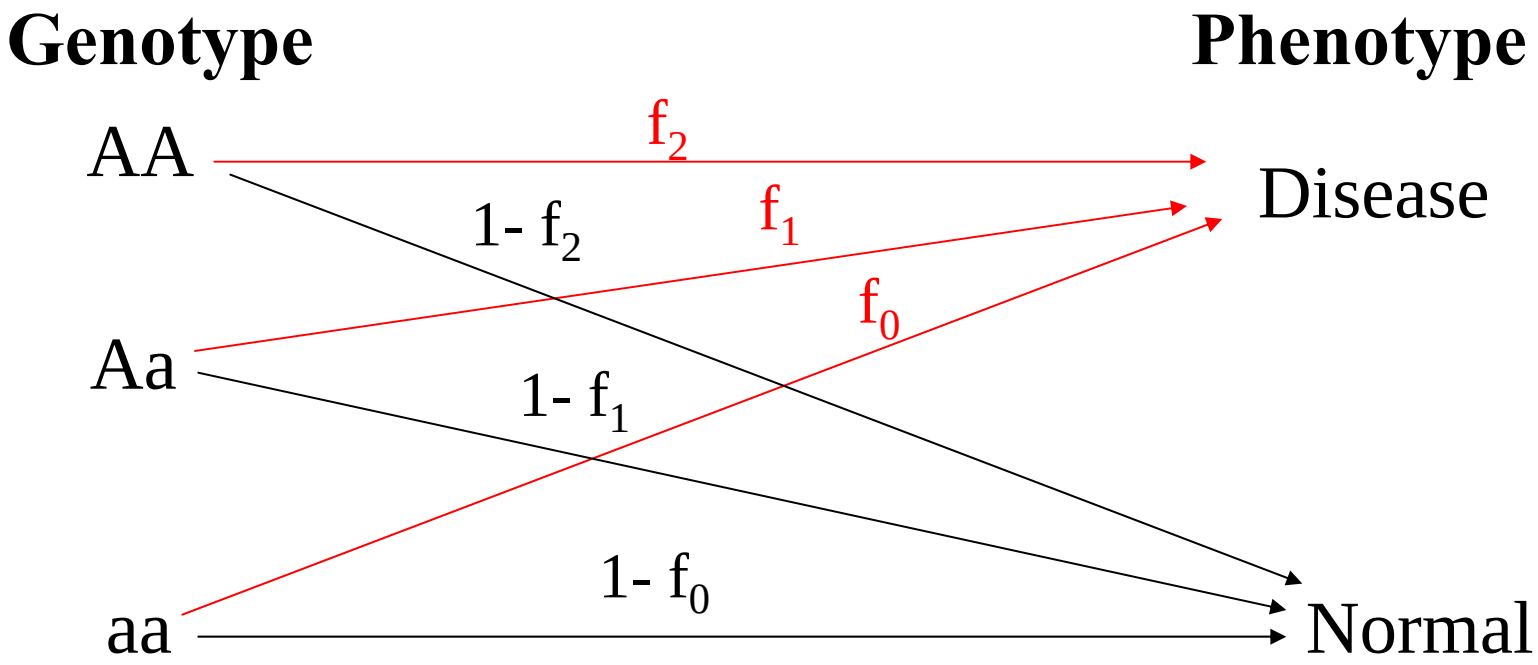
Heritability

- Is proportion of phenotypic variance due to genetic factors
- Is population-specific
- May change with changes in the environment
- A high heritability does not preclude effective prevention or intervention
- Most human traits have heritability of 30% – 90%



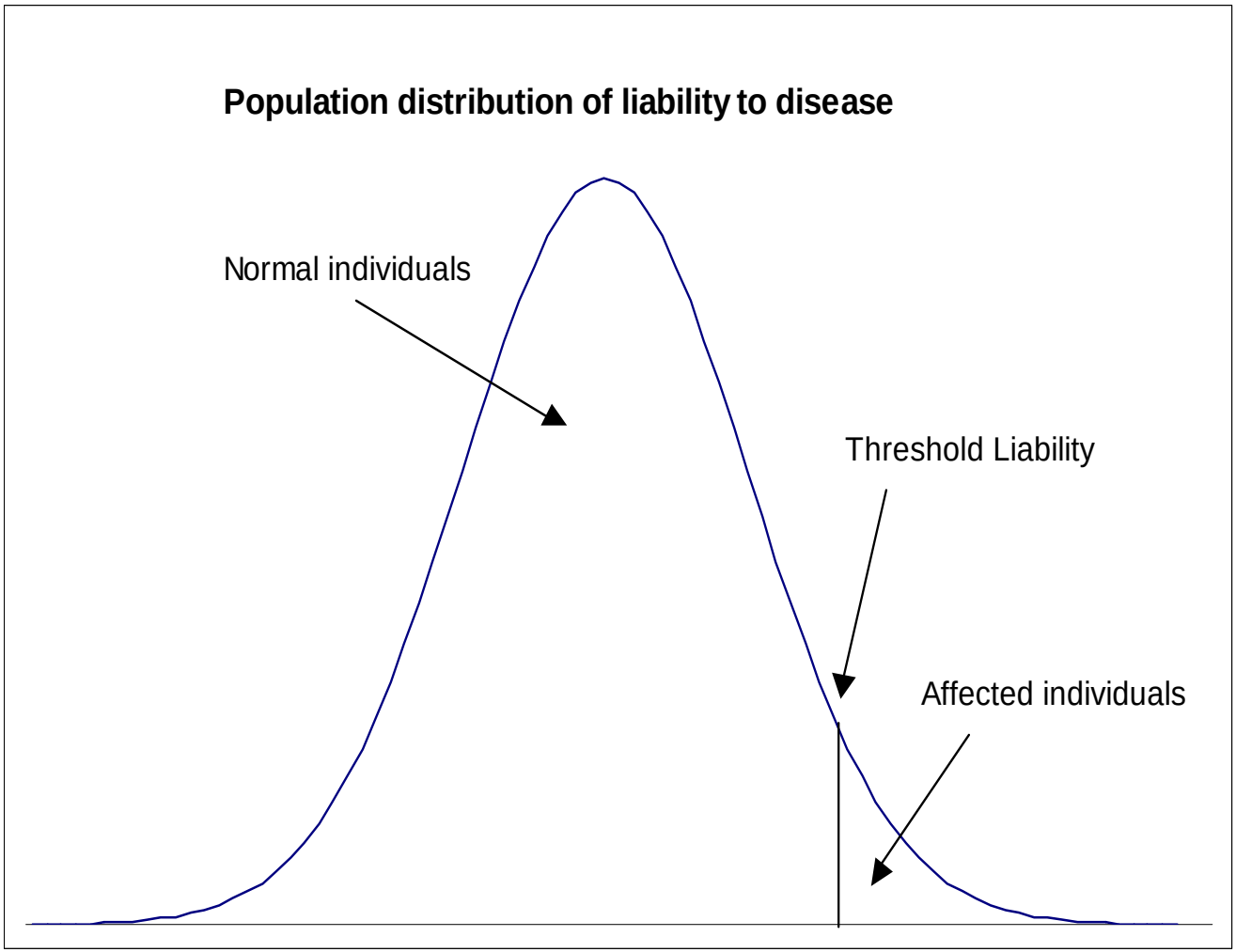
Liability-Threshold Models

Single Major Locus (SML) Model

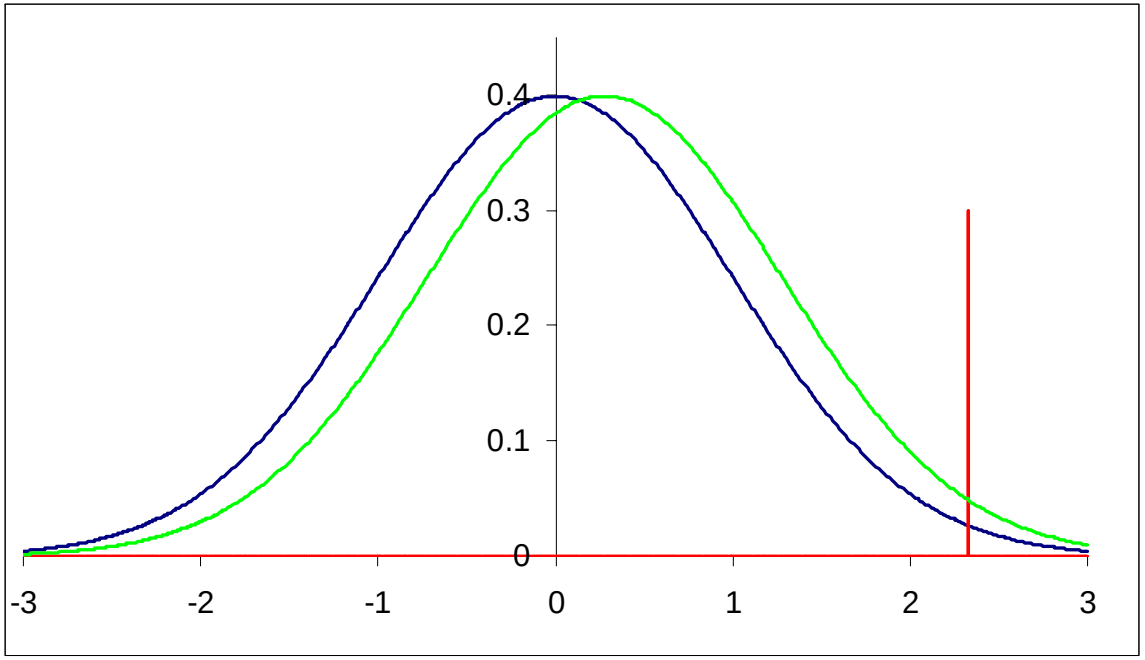


"Penetrance parameters"

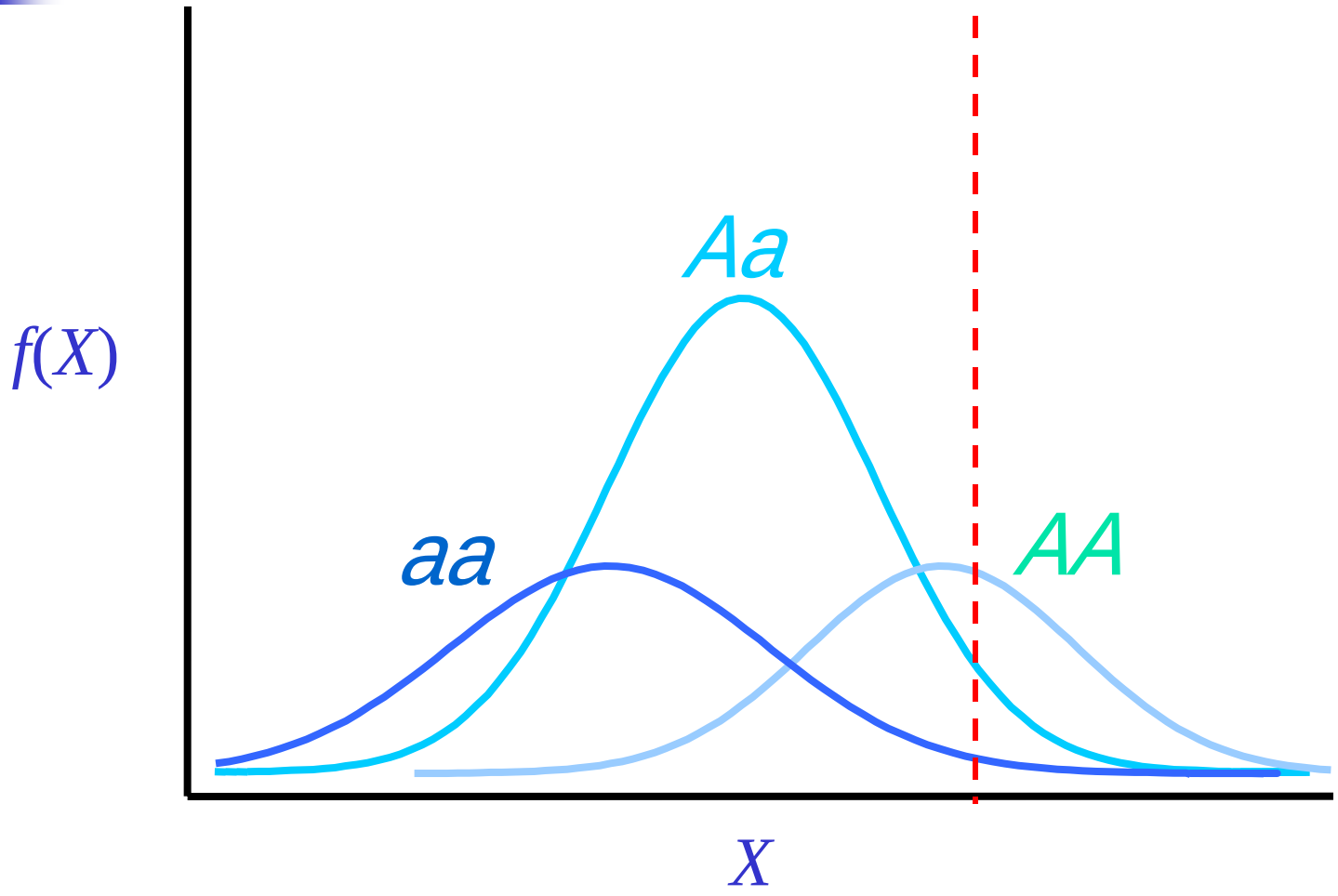
Liability-Threshold Model

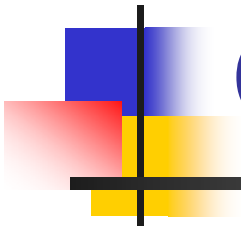


Liability-threshold model



Threshold Model with SML

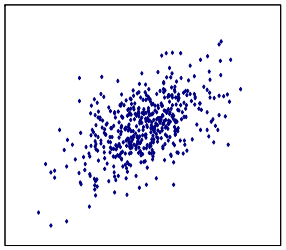
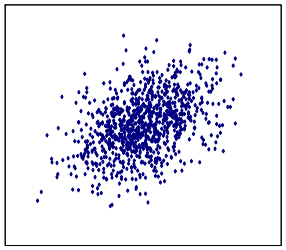
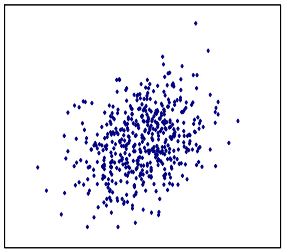
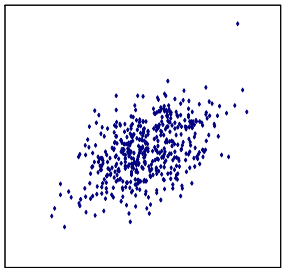
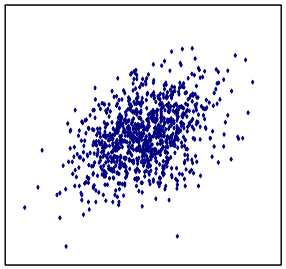
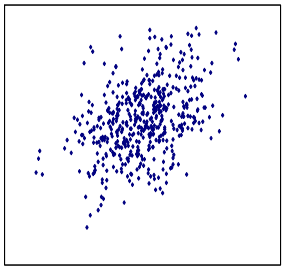




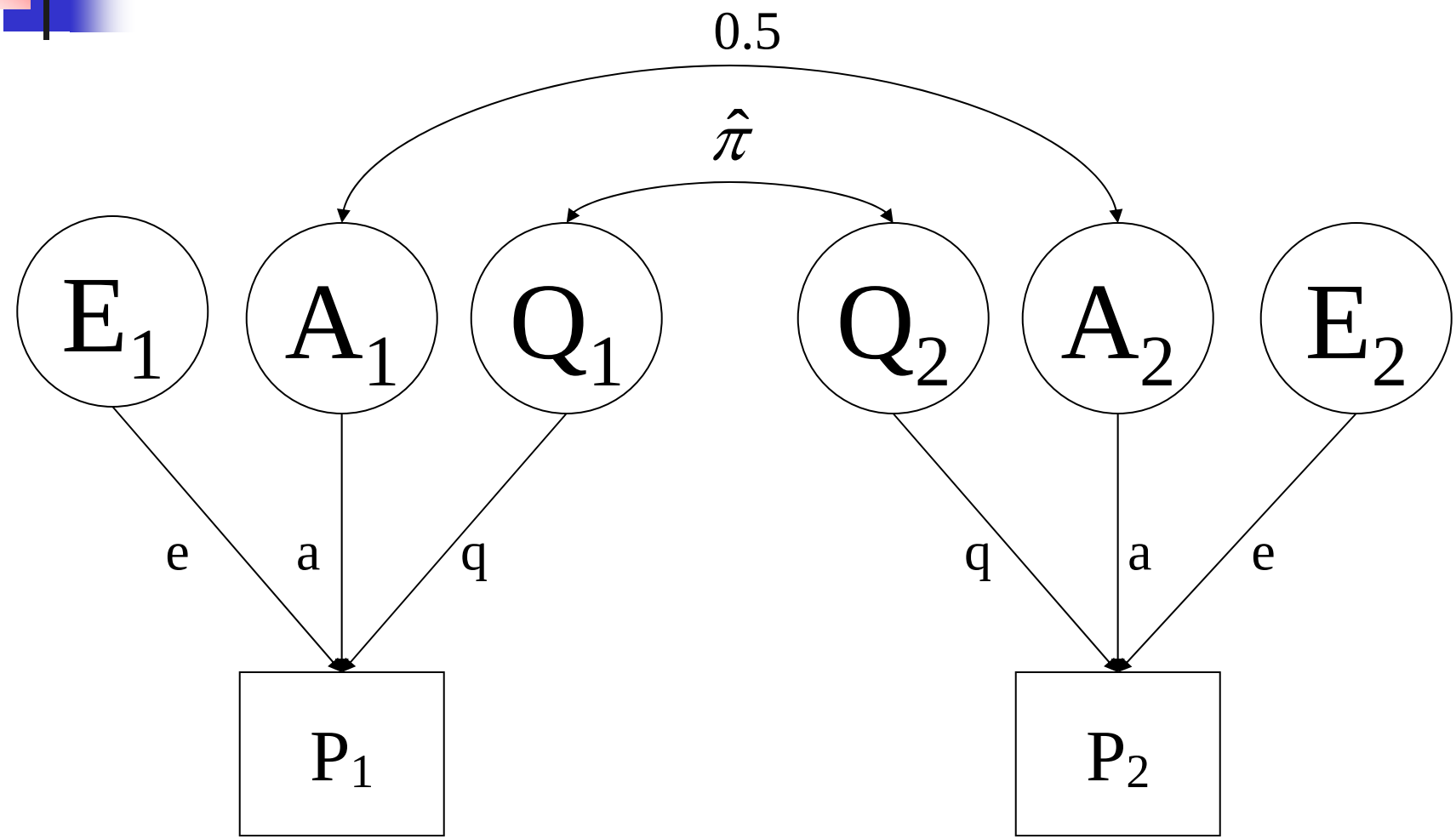
Quantitative Trait Linkgage

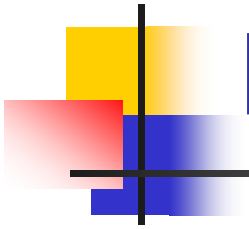
QTL Linkage Analysis

DZ Twins / Sibling Pairs

Local genetic sharing	2	1	0	
Phenotypic correlation				Linkage
				No linkage

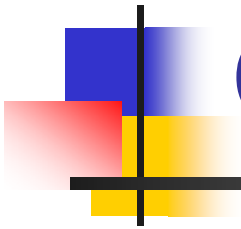
QTL linkage model for sib pairs





Exercise

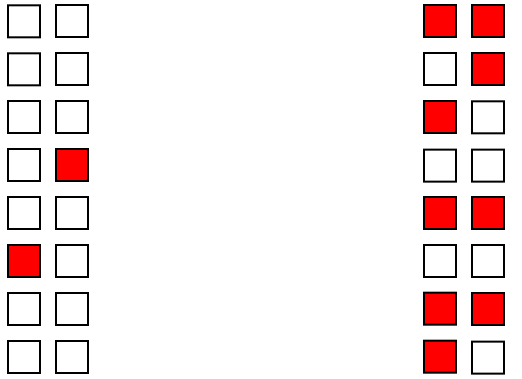
- From the path diagram write down the implied covariance matrices for sib pairs with proportion IBD sharing of 0, 0.5 and 1.



Quantitative Association

Allelic Association

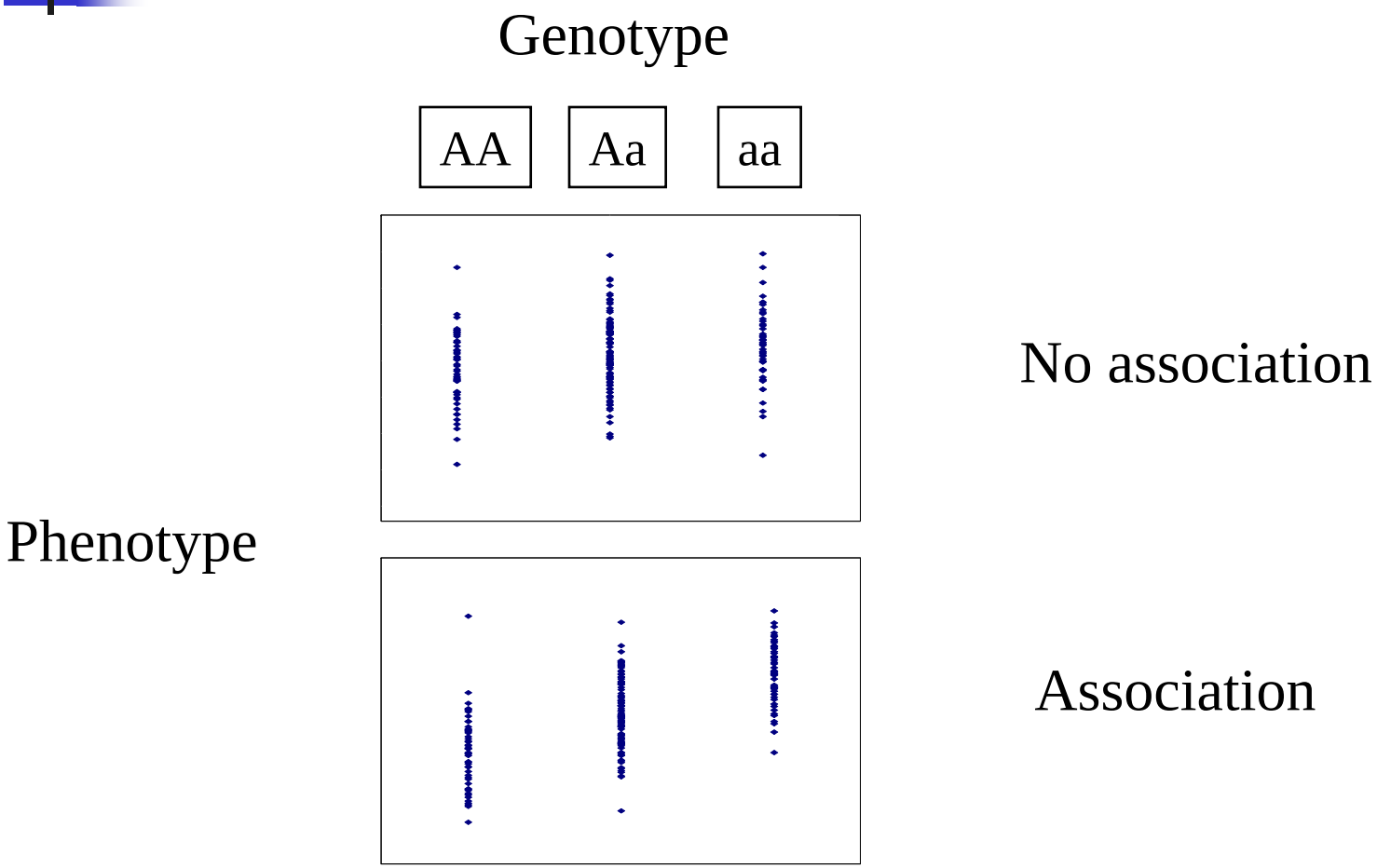
- disease susceptibility allele is more frequent in cases than in controls



Controls Cases

Example: Apolipoprotein E ε4 allele increases susceptibility to Alzheimer's disease

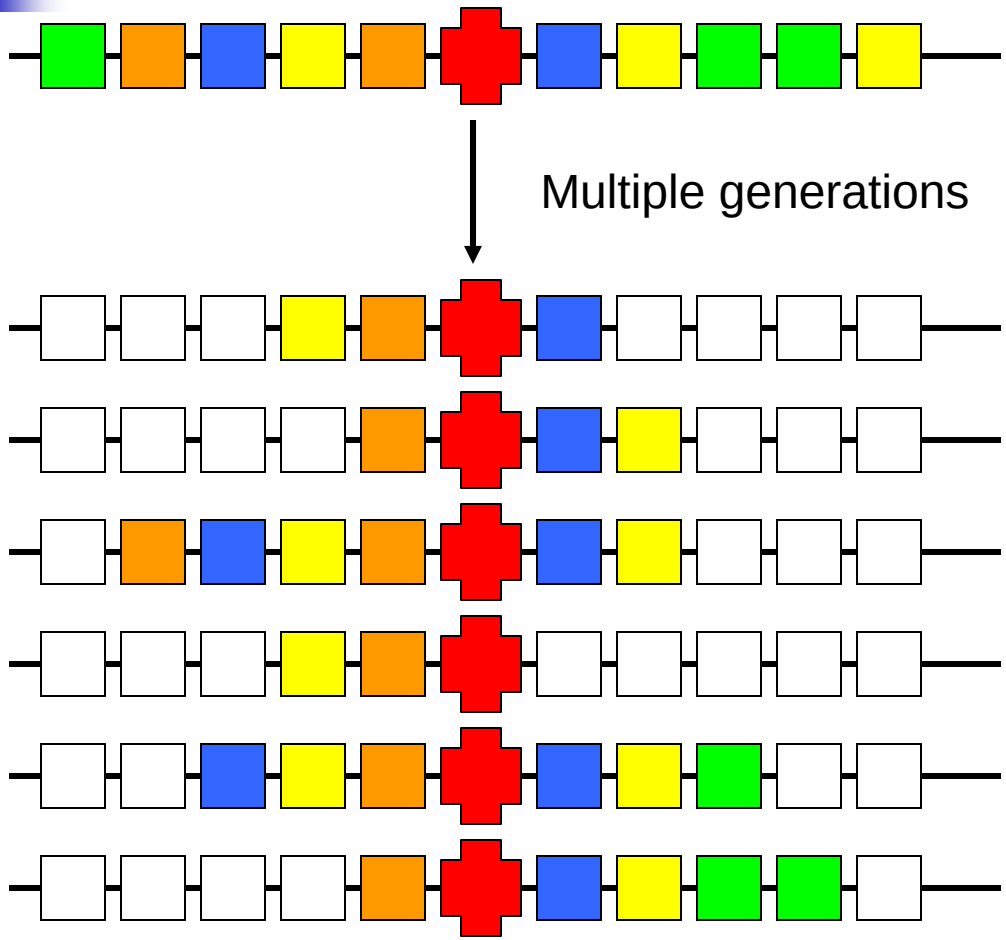
Analysis of Means



Causes of association

- Direct: allele increases risk of disease
- Indirect: allele associated with a risk-increasing allele through tight linkage
- “Spurious”: allele associated with disease through confounding variable (e.g. population substructure).

Haplotype association



Mutational event on ancestral chromosome

Present mutation-bearing chromosomes with variable preserved region

Complex Disorders: Some Historical Landmarks

- 1875: Use of twins to disentangle nature from nurture (Galton)
- 1918: Polygenic model proposed to reconcile quantitative and Mendelian genetics (Fisher)
- 1965: Liability-threshold model postulated for common congenital malformations (Carter)
- 1960's: Association between blood groups and HLA antigens with disease
- 1990's: Identification of APOE-e4 as a susceptibility allele for dementia
- 2000's: International HapMap Project