Introduction to QTL mapping

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Boulder Introductory Course 2006

Outline

1. Aim
2. The Human Genome
3. Principles of Linkage Analysis
4. Parametric Linkage Analysis
5. Nonparametric Linkage Analysis

1. Aim

QTL mapping

- LOCALIZE and then IDENTIFY a locus that regulates a trait (QTL)

↓

Nucleotide or sequence of nucleotides with variation in the population, with different variants associated with different trait levels.

For a heritable trait...

Linkage: localize region of the genome where a QTL that regulates the trait is likely to be harboured

Family-specific phenomenon:
Affected individuals in a family share the same ancestral predisposing DNA segment at a given QTL

Association: identify a QTL that regulates the trait

Population-specific phenomenon:
Affected individuals in a population share the same ancestral predisposing DNA segment at a given QTL

2. Human Genome

DNA structure

- ▷ A DNA molecule is a linear backbone of alternating sugar residues and phosphate groups

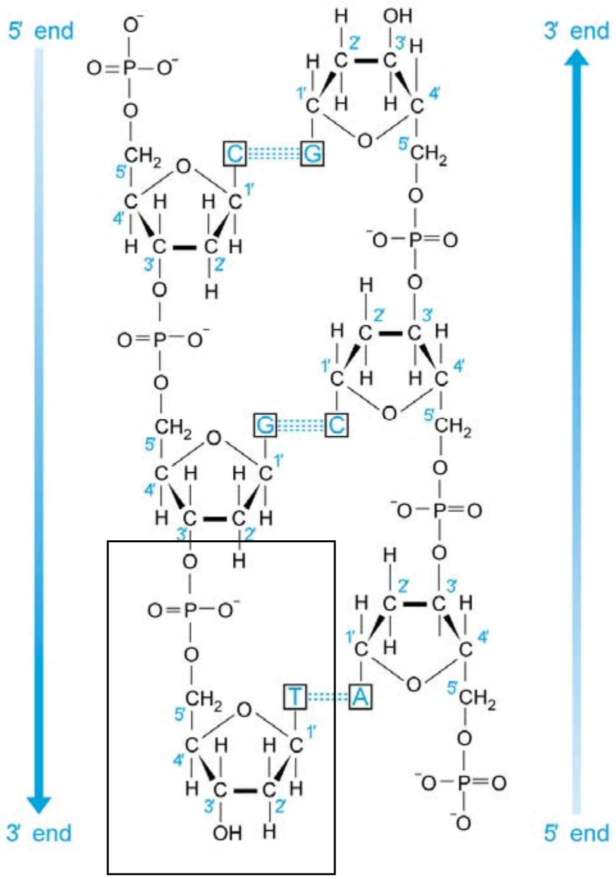
- ▷ Attached to carbon atom 1’ of each sugar is a nitrogenous base: A, C, G or T

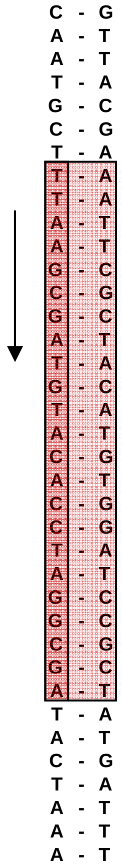
- ▷ Two DNA molecules are held together in anti-parallel fashion by hydrogen bonds between bases [Watson-Crick rules] *Antiparallel double helix*

- ▷ A gene is a segment of DNA which is transcribed to give a protein or RNA product

- ▷ Only one strand is read during gene transcription

- ▷ Nucleotide: 1 phosphate group + 1 sugar + 1 base





C - G
A - T
A - T
T - A
G - C
C - G
T - A
T - A
T - A
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A - T
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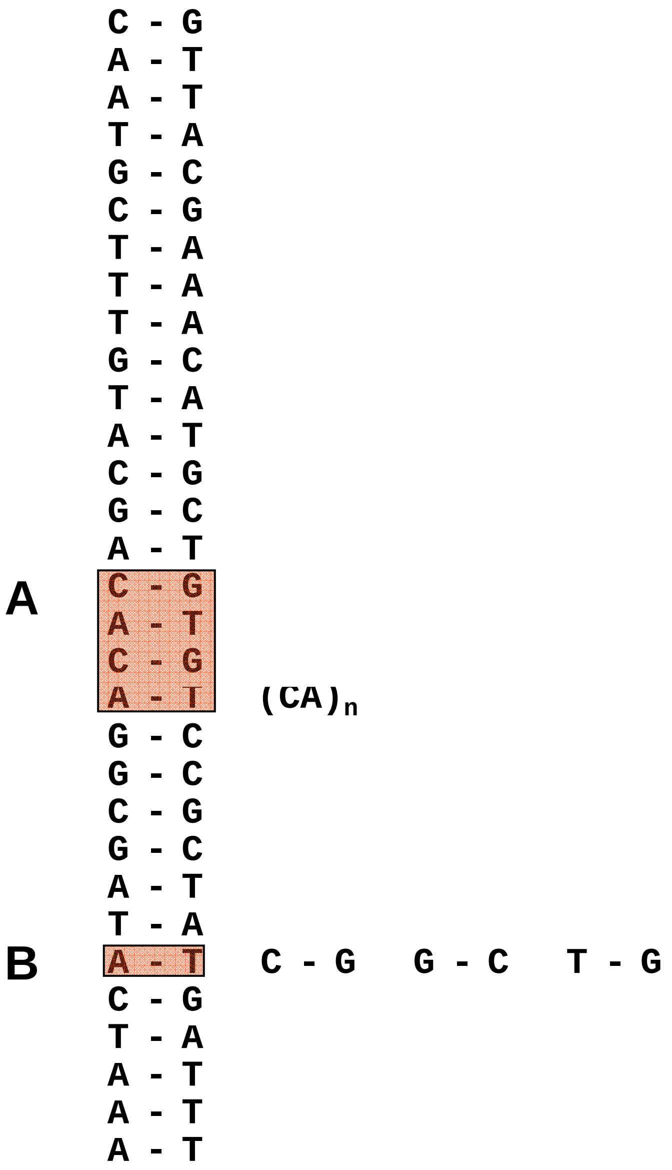
G - C
G - C
C - G
G - C
A - T
T - A
A - T
C - G
T - A
A - T
A - T
A - T

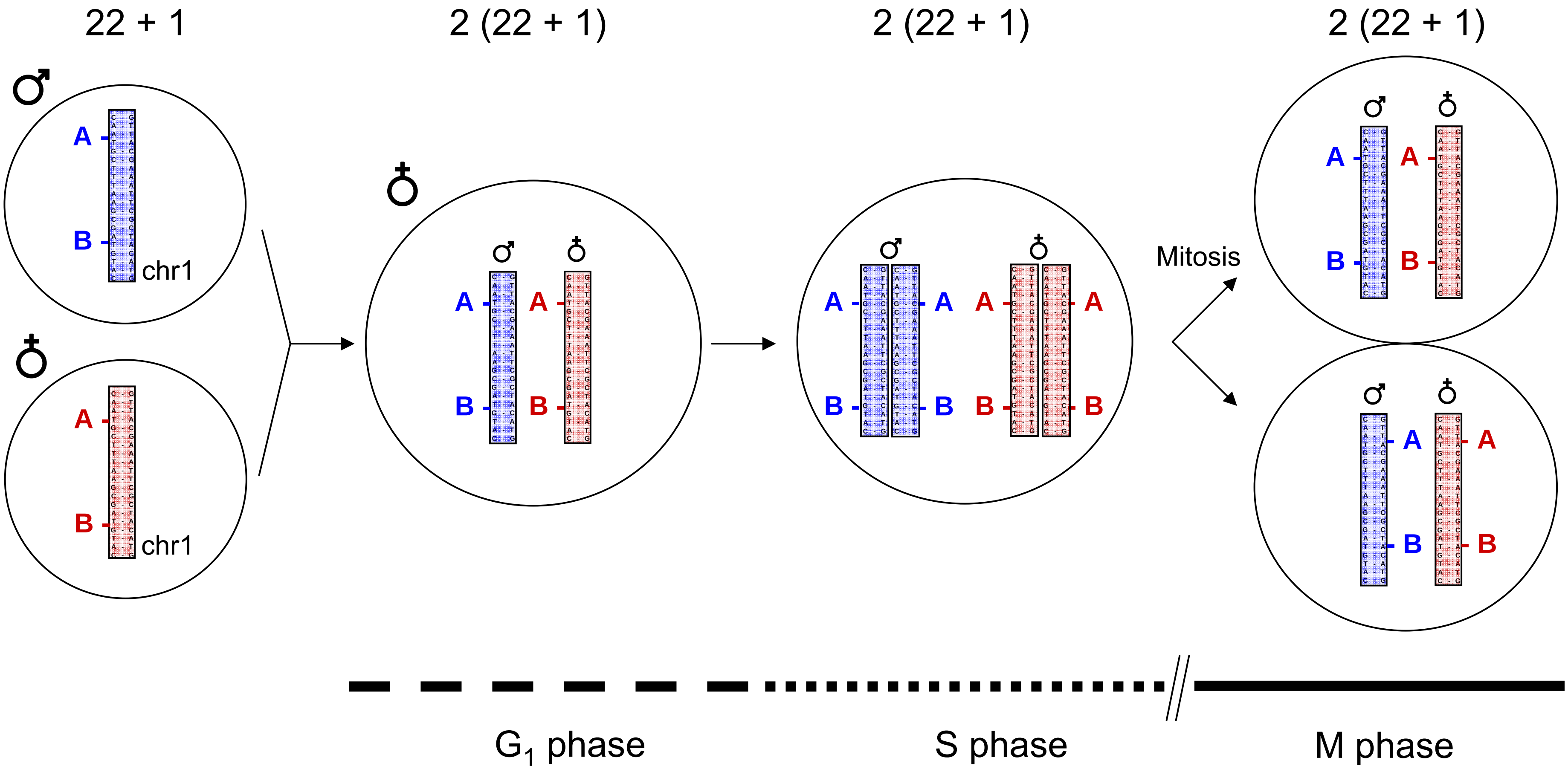
DNA polymorphisms

- ▷ Microsatellites
  >100,000
  Many alleles, $(CA)_n$, very informative, even, easily automated

- ▷ SNPs
  10,054,521 (25 Jan ‘05)
  10,430,753 (11 Mar ‘06)
  Most with 2 alleles (up to 4), not very informative, even, easily automated



DNA organization



22 + 1

2 (22 + 1)

2 (22 + 1)

2 (22 + 1)

Mitosis

G_1 phase

S phase

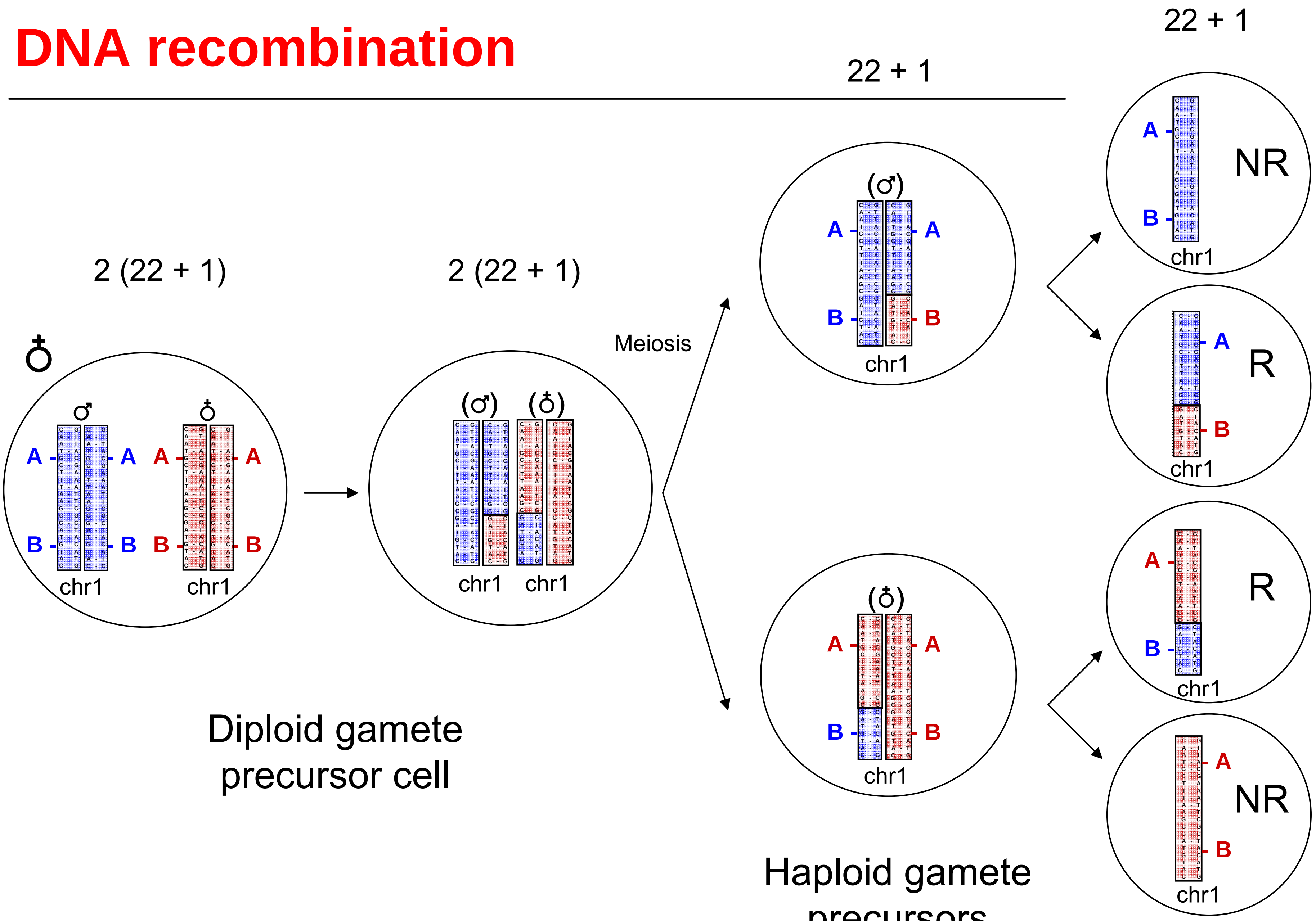
M phase

Haploid
gametes

Diploid zygote
1 cell

Diploid zygote
>1 cell

DNA recombination

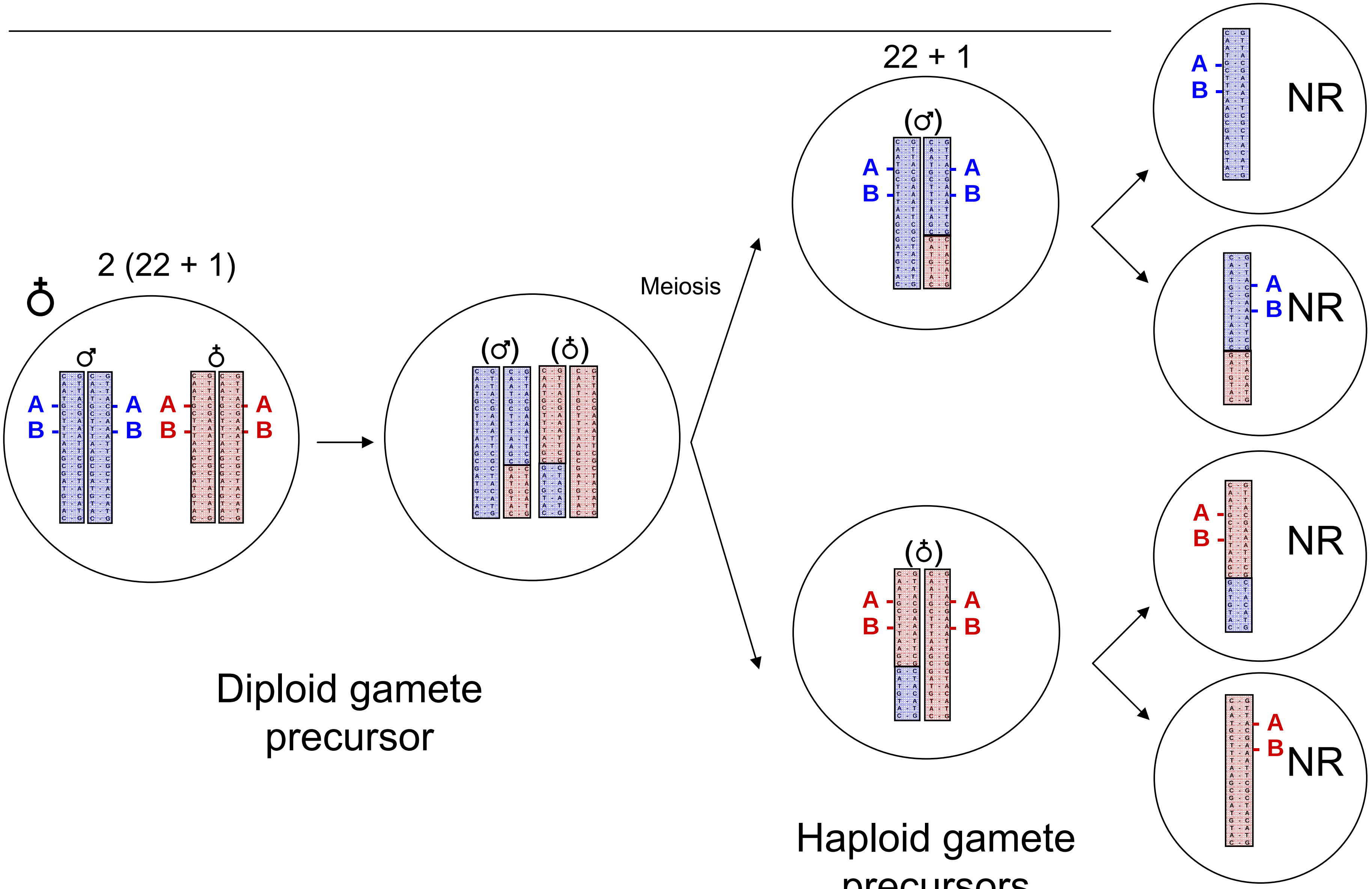


Diploid gamete precursor cell

Haploid gamete precursors

Hap. gametes

DNA recombination between linked loci



Diploid gamete precursor

Haploid gamete precursors

Hap. gametes

Human Genome - summary

- DNA is a linear sequence of nucleotides partitioned into 23 chromosomes

  Two copies of each chromosome (2x22 autosomes + XY), from paternal and maternal origins. During meiosis in gamete precursors, recombination can occur between maternal and paternal homologs

- Recombination fraction between loci A and B (θ)

  Proportion of gametes produced that are recombinant for A and B

  If A and B are very far apart: 50%R:50%NR - $\theta = 0.5$

  If A and B are very close together: <50%R - $0 \leq \theta < 0.5$

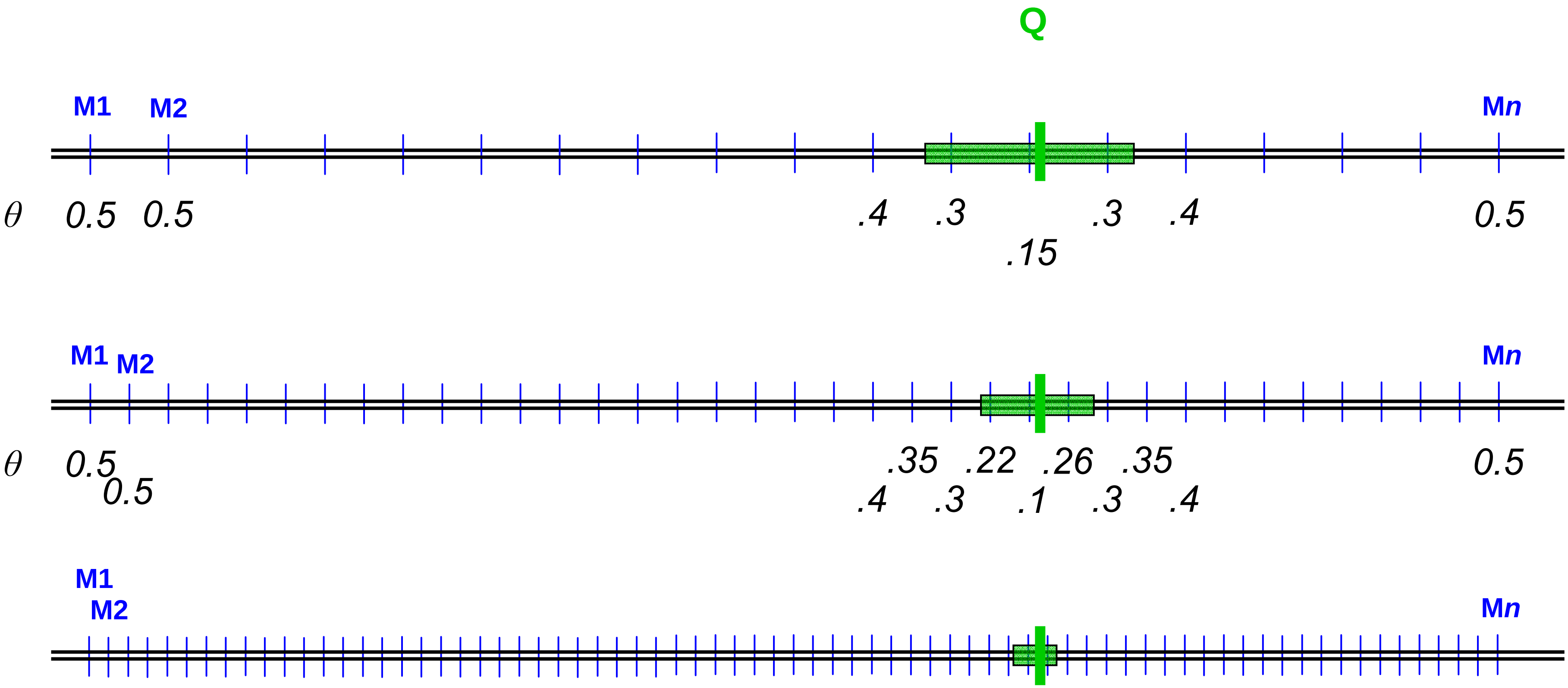
- Recombination fraction (θ) can be converted to genetic distance (cM)

  Haldane: $cM = 100 \cdot [-0.5 \cdot \ln(1 - 2 \cdot \theta)]$ eg. θ=0.17, cM=20.8

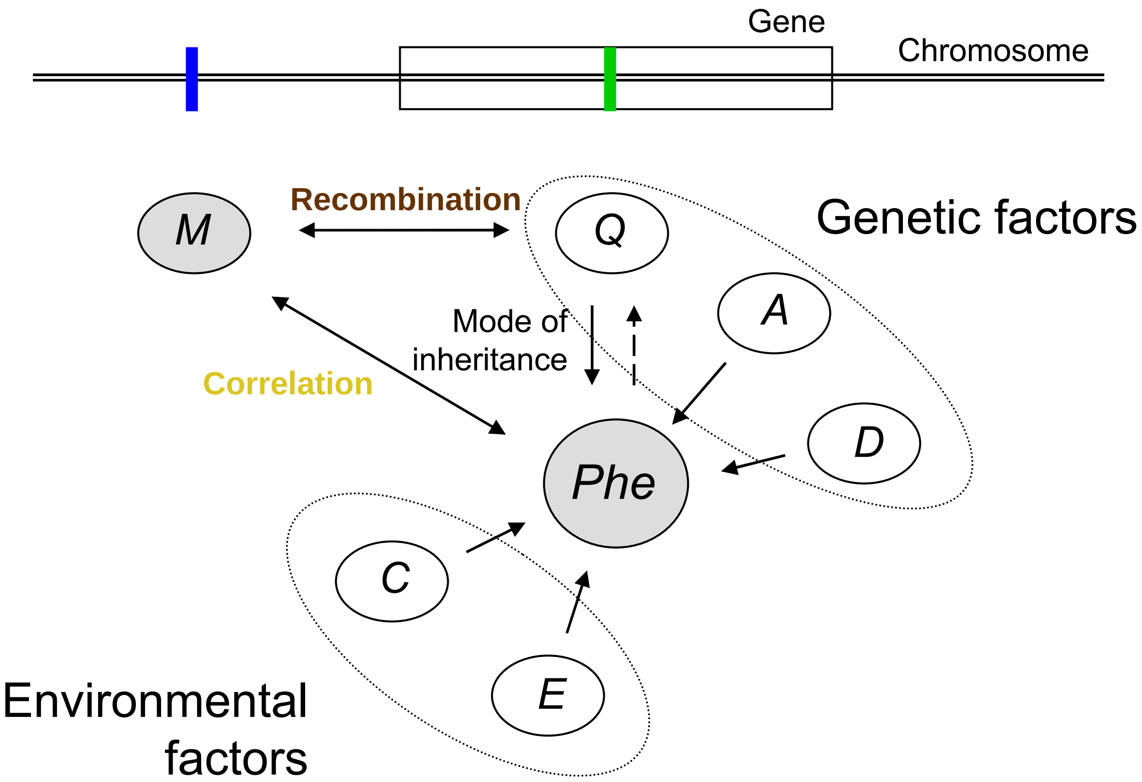
  Kosambi: $cM = 100 \cdot [0.25 \cdot \ln((1 + 2 \cdot \theta)/(1 - 2 \cdot \theta))]$ eg. θ=0.17, cM=17.7

3. Principles of Linkage Analysis

Linkage Analysis requires genetic markers



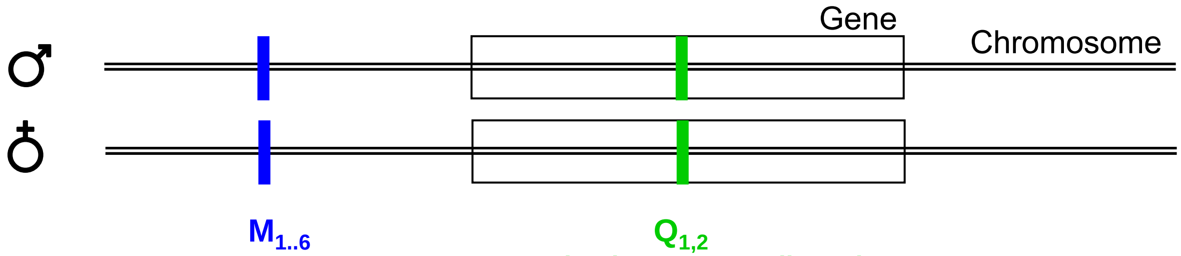
Linkage Analysis: Parametric vs. Nonparametric



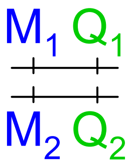
Adapted from Weiss & Terwilliger 2000

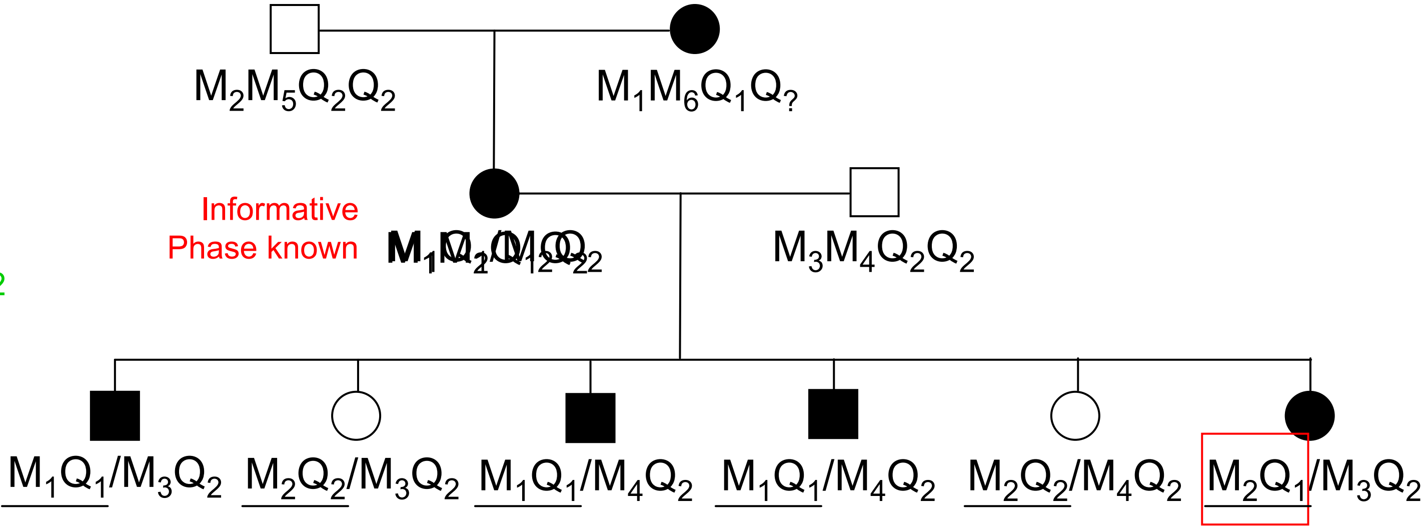
4. Parametric Linkage Analysis

Linkage with informative phase known meiosis



Autosomal dominant, Q_1 predisposing allele





NR: M_1Q_1

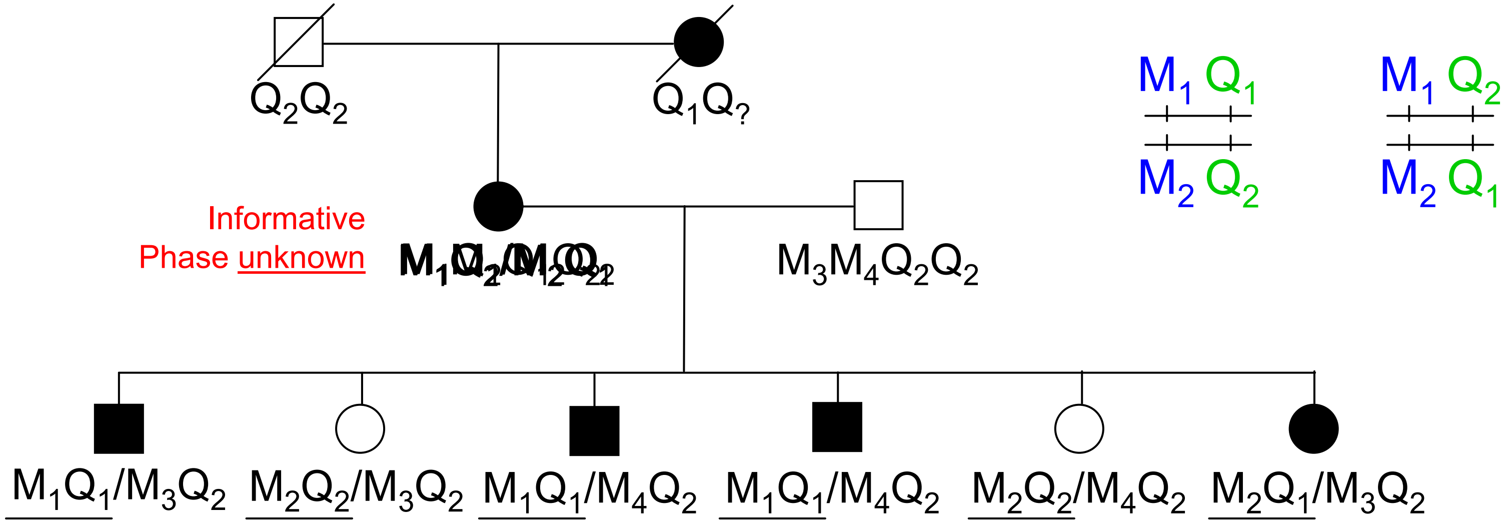
NR: M_2Q_2

R: M_1Q_2

R: M_2Q_1

$$\theta_{MQ} = 1/6 = 0.17 \quad (\sim 20.8\ cM)$$

Linkage with informative phase unknown meiosis



M_1Q_1/M_2Q_2	*P*	*N*
NR: M_1Q_1	½(1-θ)	3
NR: M_2Q_2	½(1-θ)	2
R: M_1Q_2	½θ	0
R: M_2Q_1	½θ	1

M_1Q_2/M_2Q_1	*P*	*N*
R: M_1Q_1	½θ	3
R: M_2Q_2	½θ	2
NR: M_1Q_2	½(1-θ)	0
NR: M_2Q_1	½(1-θ)	1

$$L(X\mid\theta)=\frac{1}{2}\cdot\left[\theta^1\cdot(1-\theta)^5\right]+\frac{1}{2}\cdot\left[\theta^5\cdot(1-\theta)^1\right]$$

$$L(X\mid\theta=0.5)=\frac{1}{2}\cdot\left[0.5^1\cdot(1-0.5)^5\right]+\frac{1}{2}\cdot\left[0.5^5\cdot(1-0.5)^1\right]=(0.5)^6$$

Parametric LOD score calculation

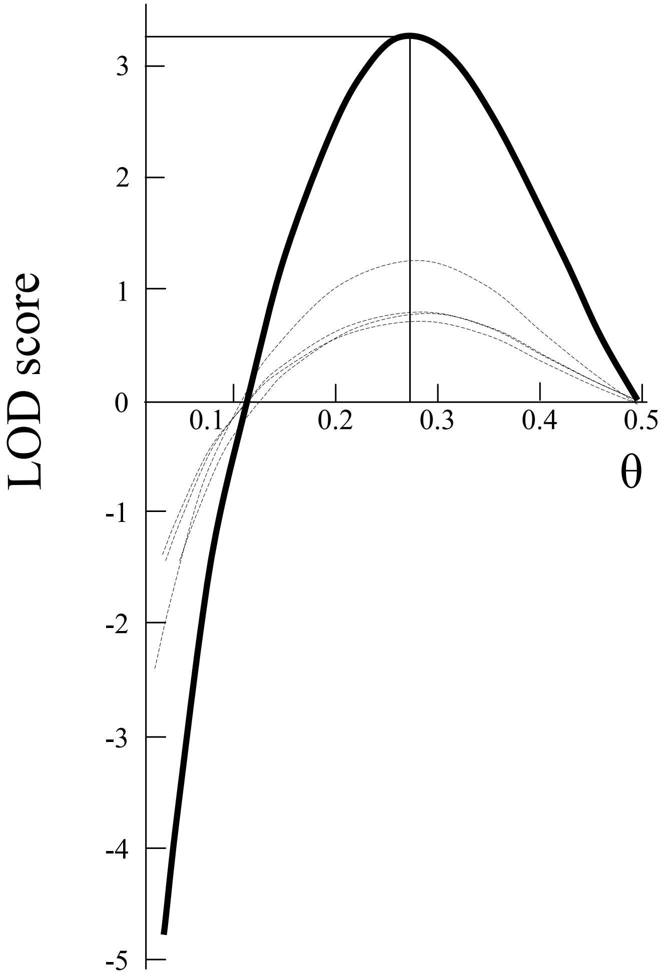
$$OD = \frac{L(X \mid \theta)}{L(X \mid \theta = 0.5)} \qquad LOD = \log_{10} \frac{L(X \mid \theta)}{L(X \mid \theta = 0.5)}$$

$$LOD = \log_{10} \frac{\frac{1}{2} \cdot \left[\theta^1 \cdot (1-\theta)^5\right] + \frac{1}{2} \cdot \left[\theta^5 \cdot (1-\theta)^1\right]}{(0.5)^6}$$

$$OD = \prod_{i=1}^{n} \frac{L(X_i \mid \theta)}{L(X_i \mid \theta = 0.5)}$$

$$LOD = \log_{10} \left(\prod_{i=1}^{n} \frac{L(X_i \mid \theta)}{L(X_i \mid \theta = 0.5)} \right)$$

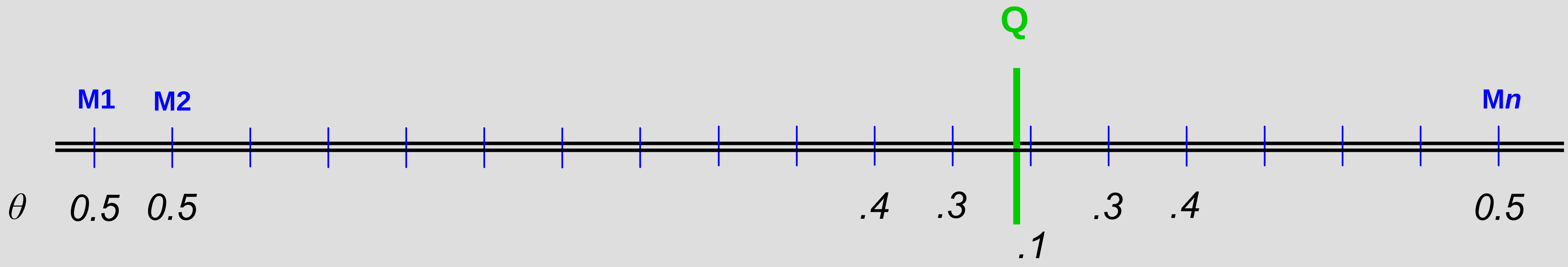
$$LOD = \sum_{i=1}^{n} \log_{10} \left(\frac{L(X_i \mid \theta)}{L(X_i \mid \theta = 0.5)} \right) = \sum_{i=1}^{n} LOD_i$$



- ▷ Overall LOD score for a given θ is the sum of all family LOD scores at θ

eg. LOD=3 for θ=0.28

Parametric Linkage Analysis - summary



- For each marker, estimate the θ that yields highest LOD score across all families

- This θ (and the LOD) will depend upon the mode of inheritance assumed

  MOI determines the genotype at the trait locus Q and thus determines the number of meiosis which are recombinant or nonrecombinant. Limited to Mendelian diseases.

- Markers with a significant parametric LOD score (>3) are said to be linked to the trait locus with recombination fraction θ

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5. Nonparametric Linkage Analysis

Approach

- Parametric: genotype marker locus & genotype trait locus

  (latter inferred from phenotype according to a specific disease model)

  Parameter of interest: θ between marker and trait loci

- Nonparametric: genotype marker locus & phenotype

  If a trait locus truly regulates the expression of a phenotype, then two relatives with similar phenotypes should have similar genotypes at a marker in the vicinity of the trait locus, and vice-versa.

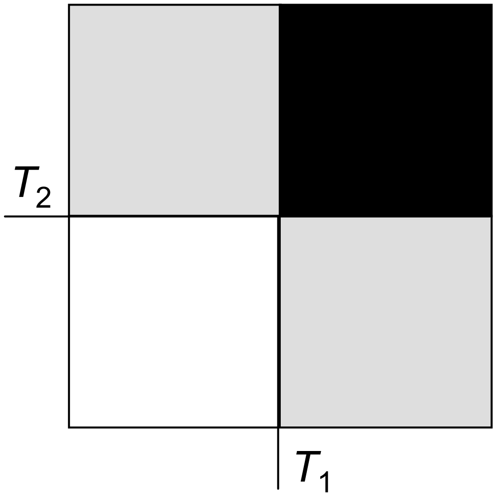
  Interest: correlation between phenotypic similarity and marker genotypic similarity

  No need to specify mode of inheritance, allele frequencies, etc...

Phenotypic similarity between relatives

- Squared trait differences $(X_1 - X_2)^2$
- Squared trait sums $(X_1 + X_2)^2$
- Trait cross-product $[(X_1 - \mu)\cdot(X_2 - \mu)]$
- Trait variance-covariance matrix $\left\{\begin{matrix} Var(X_1) & Cov(X_1X_2) \\ Cov(X_1X_2) & Var(X_2) \end{matrix}\right\}$

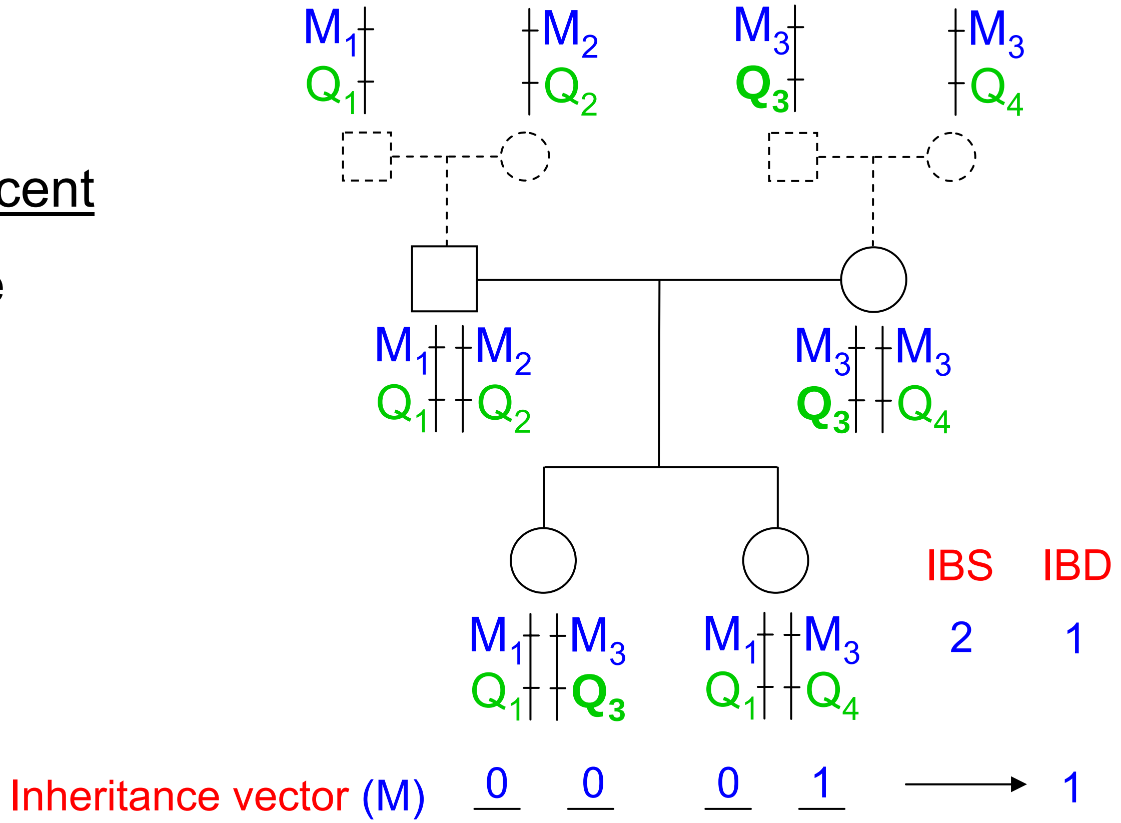
- Affection concordance



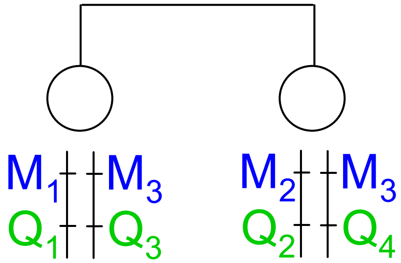
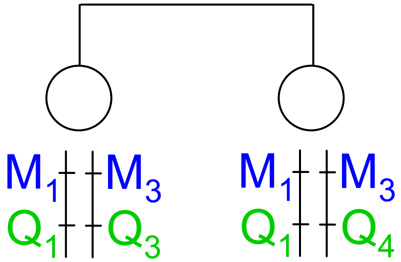
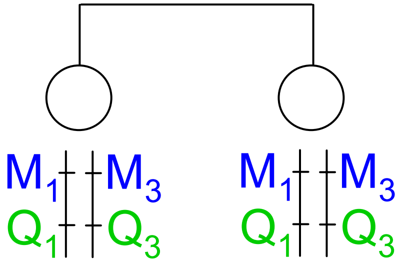
Genotypic similarity between relatives

- IBS Alleles shared Identical By State “look the same”, may have the same DNA sequence but they are not necessarily derived from a known common ancestor

- IBD Alleles shared Identical By Descent are a copy of the same ancestor allele

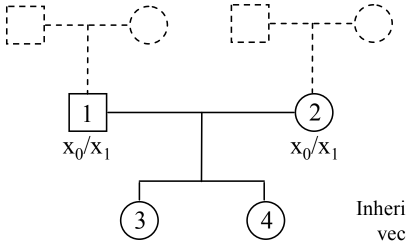


Genotypic similarity between relatives - π

	Inheritance vector (M)	Number of alleles shared IBD	Proportion of alleles shared IBD - π
	0 0 1 1	0	0
	0 0 0 1	1	0.5
	0 0 0 0	2	1

Genotypic similarity between relatives - $\hat{\pi}$

A **B** **C** **D**



2^{2n}

3	4	Inheritance vector	IBD
x_0/x_0	x_0/x_0	0000	2
x_0/x_0	x_0/x_1	0001	1
x_0/x_0	x_1/x_0	0010	1
x_0/x_0	x_1/x_1	0011	0
x_0/x_1	x_0/x_0	0100	1
x_0/x_1	x_0/x_1	0101	2
x_0/x_1	x_1/x_0	0110	0
x_0/x_1	x_1/x_1	0111	1
x_1/x_0	x_0/x_0	1000	1
x_1/x_0	x_0/x_1	1001	0
x_1/x_0	x_1/x_0	1010	2
x_1/x_0	x_1/x_1	1011	1
x_1/x_1	x_0/x_0	1100	0
x_1/x_1	x_0/x_1	1101	1
x_1/x_1	x_1/x_0	1110	1
x_1/x_1	x_1/x_1	1111	2

P (IBD=0)
P (IBD=1)
P (IBD=2)

$$\hat{\pi} =$$

Practical

▷ **Aim** (1) Estimate IBD with MERLIN; (2) IBD estimation can be influenced by genotyped individuals and allele frequencies; (3) compute $\hat{\pi}$

```
H:\manuel  -     Copy folder “Linkage” to C:\
```

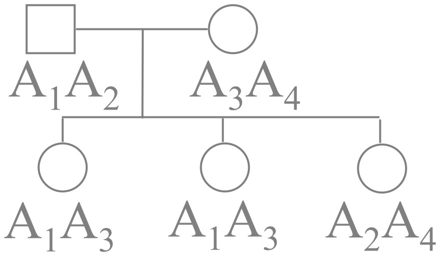
1. Open with Notepad: pr1.ped pr1.dat pr1.map pr1.freq
2. Start>Run>C:/Linkage/pfe32.exe
3. Run Command Prompt
4. Keep a File Explorer window open

Exercice1

(1) Estimate IBD for pedigrees **A**, **B** and **C** in the previous slide

(2) Change allele frequencies (pr1.freq) from 0.25 0.25 0.25 0.25 to
(i) 0.45 0.25 0.25 0.05 and
(ii) 0.05 0.25 0.25 0.45

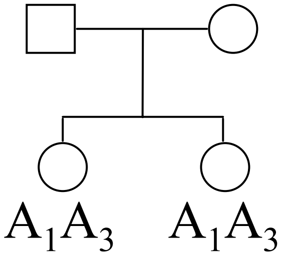
Practical



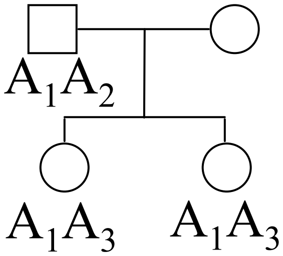
Exercice 2

(1) Modify pr1.ped and estimate IBD probabilities and $\hat{\pi}$ between twin 1 and twin 2 for pedigrees **E**, **F** and **G**:

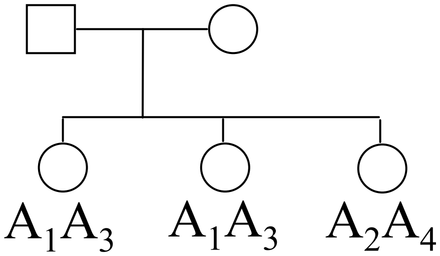
E



F



G



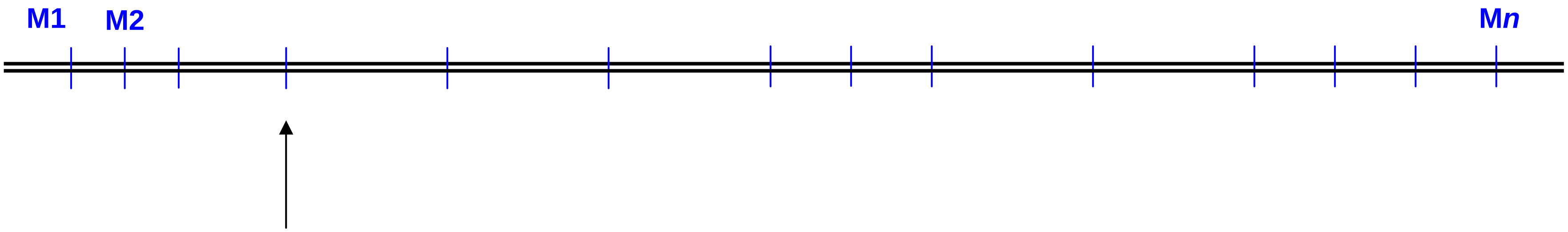
P(IBD=0)

P(IBD=1)

P(IBD=2)

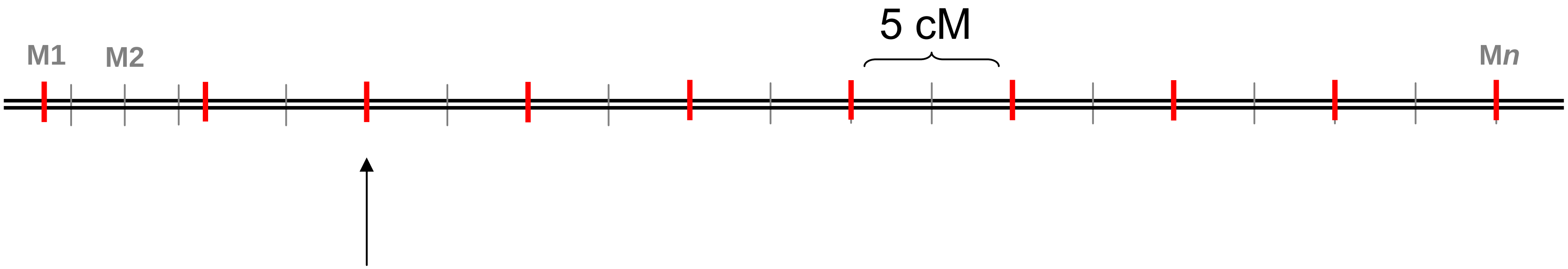
$\hat{\pi}$

Allele frequencies on pr1.freq: 0.25 0.25 0.25 0.25



IBD at a marker

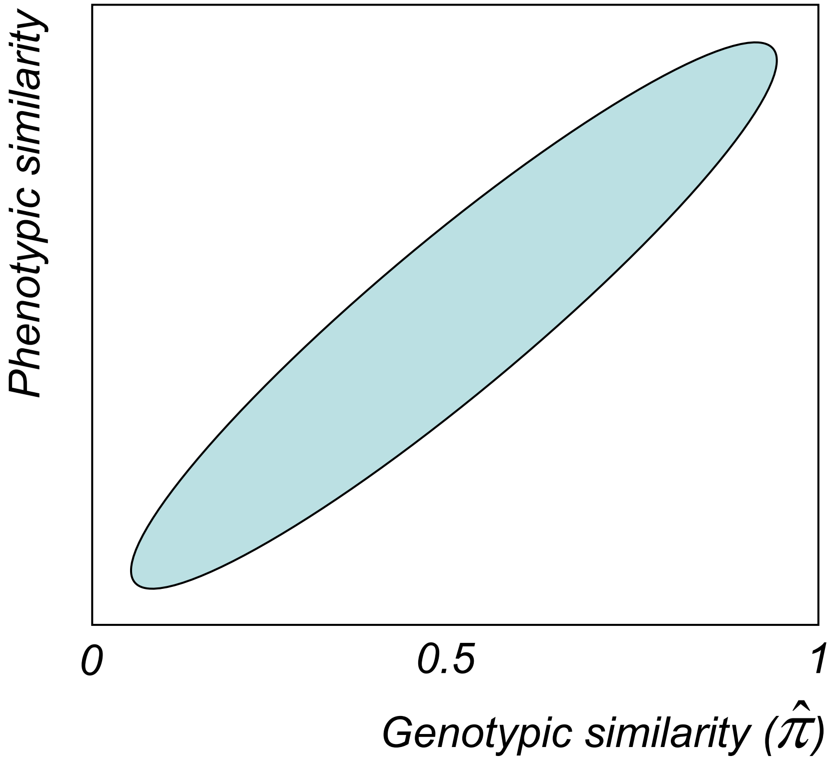
Singlepoint IBD



IBD at a 'grid'

Multipoint IBD

Statistics that incorporate both phenotypic and genotypic similarities

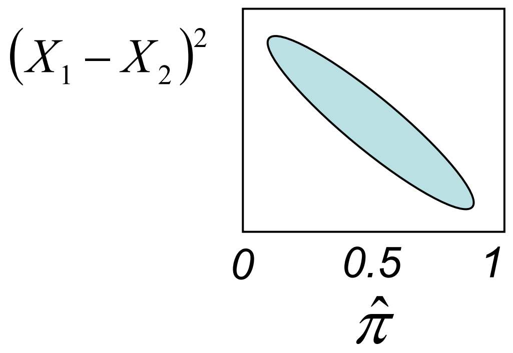


Haseman-Elston regression – Quantitative traits

$$E\left[\left(X_1 - X_2\right)^2 \mid \hat{\pi}\right]$$

$$= E\left[\left(X_1^2 + X_2^2 - 2 \cdot X_1 \cdot X_2\right) \mid \hat{\pi}\right]$$

$$= Var\left(X_1\right) + Var\left(X_2\right) - 2Cov\left(X_1 X_2 \mid \hat{\pi}\right)$$



$$Var\left(X_1\right) = Var\left(X_2\right) = V_Q + V_A + V_C + V_E$$

$$Cov\left(X_1, X_2 \mid \hat{\pi}\right) = \hat{\pi} \cdot V_Q + \frac{1}{2} \cdot V_A + V_C$$

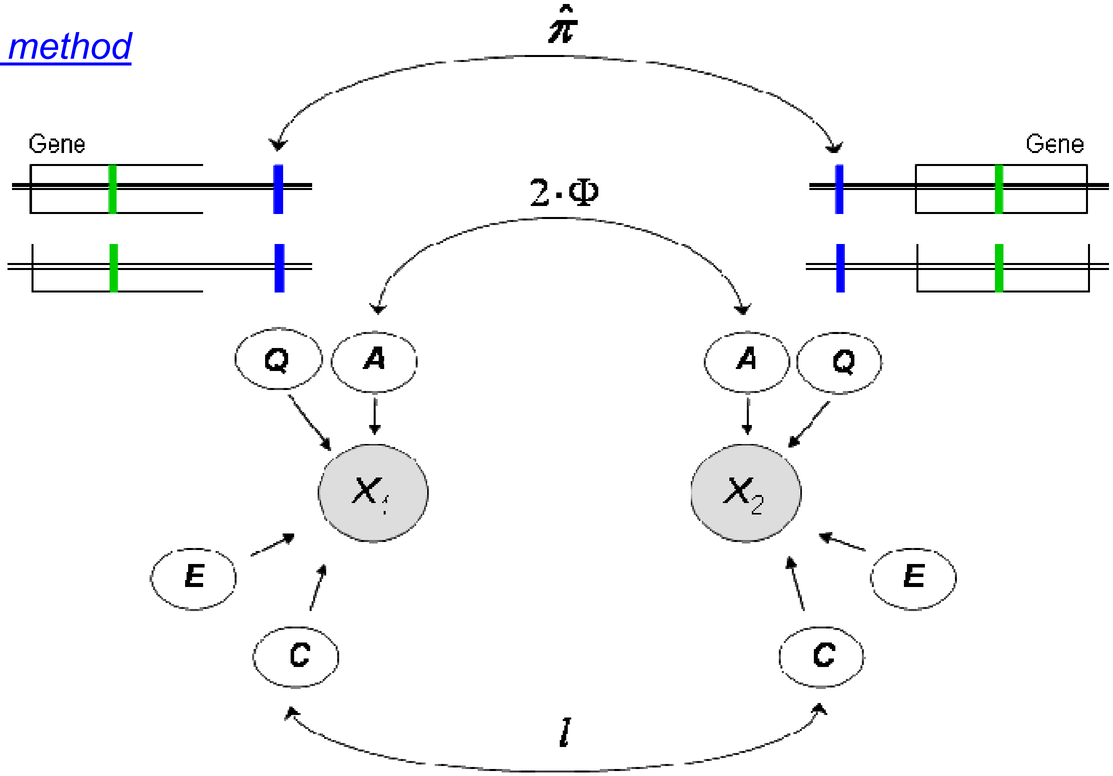
	X_1	X_2	$(X_1-X_2)^2$	$\hat{\pi}$
1	2.2	2.1	0.01	0.9
2	1.9	2.3	0.16	0.6
3	2.3	2.6	0.09	0.7
4	3.4	1.6	3.24	0.1
5	2.5	2.3	0.04	0.8
…				
1000	2.4	2.4	0	0.9

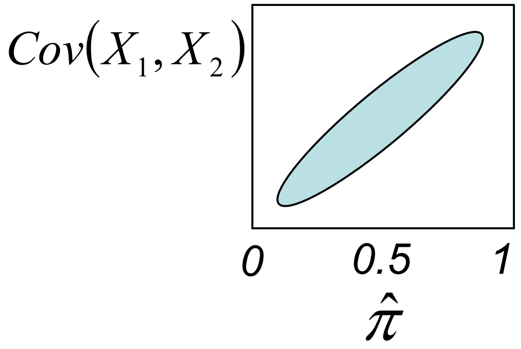
$$E\left[\left(X_1 - X_2\right)^2 \mid \hat{\pi}\right] = -2 \cdot V_Q \cdot \underset{\uparrow}{\hat{\pi}} + \underset{\uparrow}{\underline{2 \cdot V_Q + V_A + 2 \cdot V_E}}$$

Phenotypic dissimilarity = ***b* ×** Genotypic similarity **+ *c***

VC ML – Quantitative & Categorical traits

$\hat{\pi}$ method





H_1:

$$Var(X_1) = Var(X_2) = V_Q + V_A + V_C + V_E$$

$$Cov(X_1, X_2 \mid \hat{\pi}) = \hat{\pi} \cdot V_Q + 2 \cdot \Phi \cdot V_A + l \cdot V_C$$

H_0:

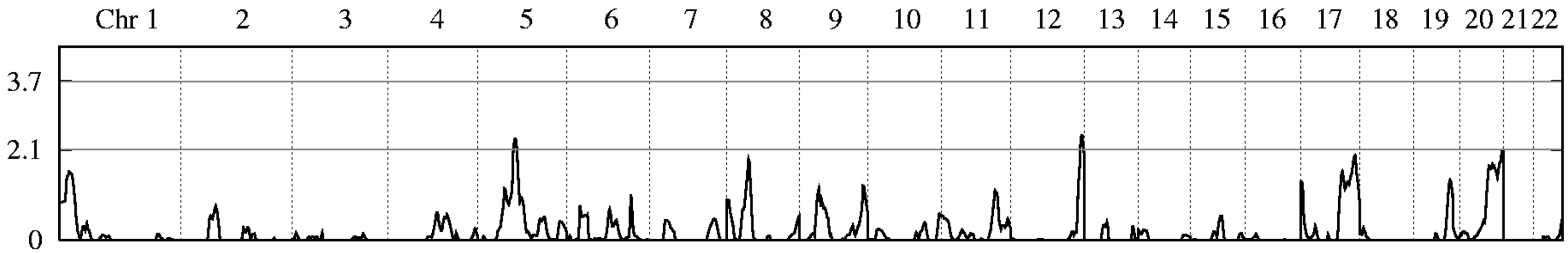
$$Var(X_1) = Var(X_2) = \qquad V_A + V_C + V_E$$

$$Cov(X_1, X_2 \mid \hat{\pi}) = \qquad 2 \cdot \Phi \cdot V_A + l \cdot V_C$$

$$LOD = \log_{10} \frac{L(H_1)}{L(H_0)}$$

e.g. LOD=3

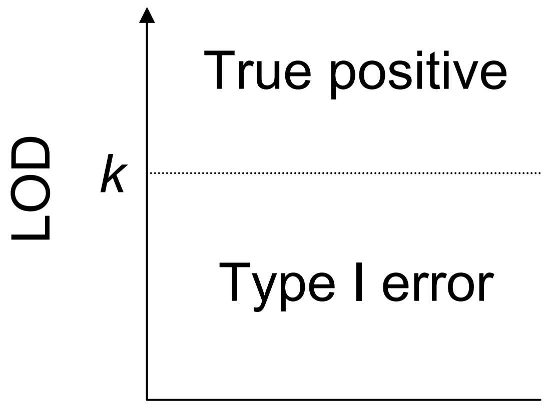
Genome-wide linkage analysis (e.g. VC)



Individual LOD scores can be expressed as *P* values (Pointwise)

LOD $\xrightarrow{(x4.6)}$ Chi-sq (n-df) → *P* value

2.1 9.67 0.0009



True positive

Type I error

→ Theoretical (Lander & Kruglyak 1995)

LOD = 3.6, Chi-sq = 16.7, *P* = 0.000022

Nonparametric Linkage Analysis - summary

- No need to specify mode of inheritance
- Models phenotypic and genotypic similarity of relatives
- Expression of phenotypic similarity, calculation of IBD
- HE and VC are the most popular statistics used for linkage of quantitative traits
- Other statistics available, specially for affection traits