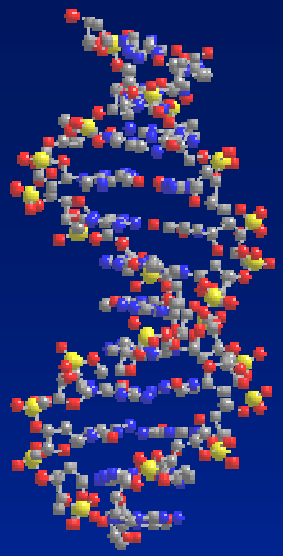
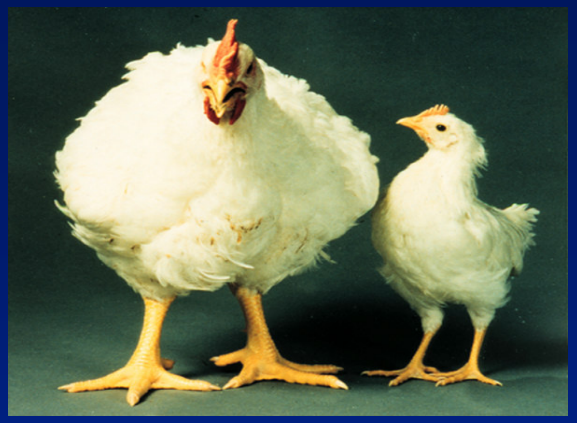
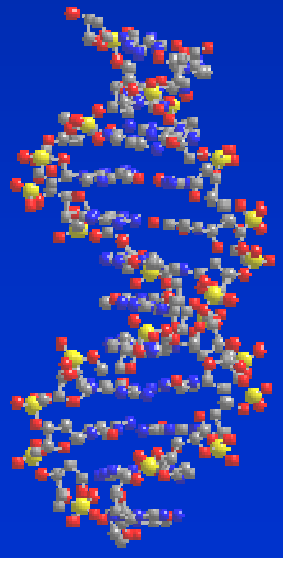




Linkage Disequilbrium to Genomic Selection



Course overview

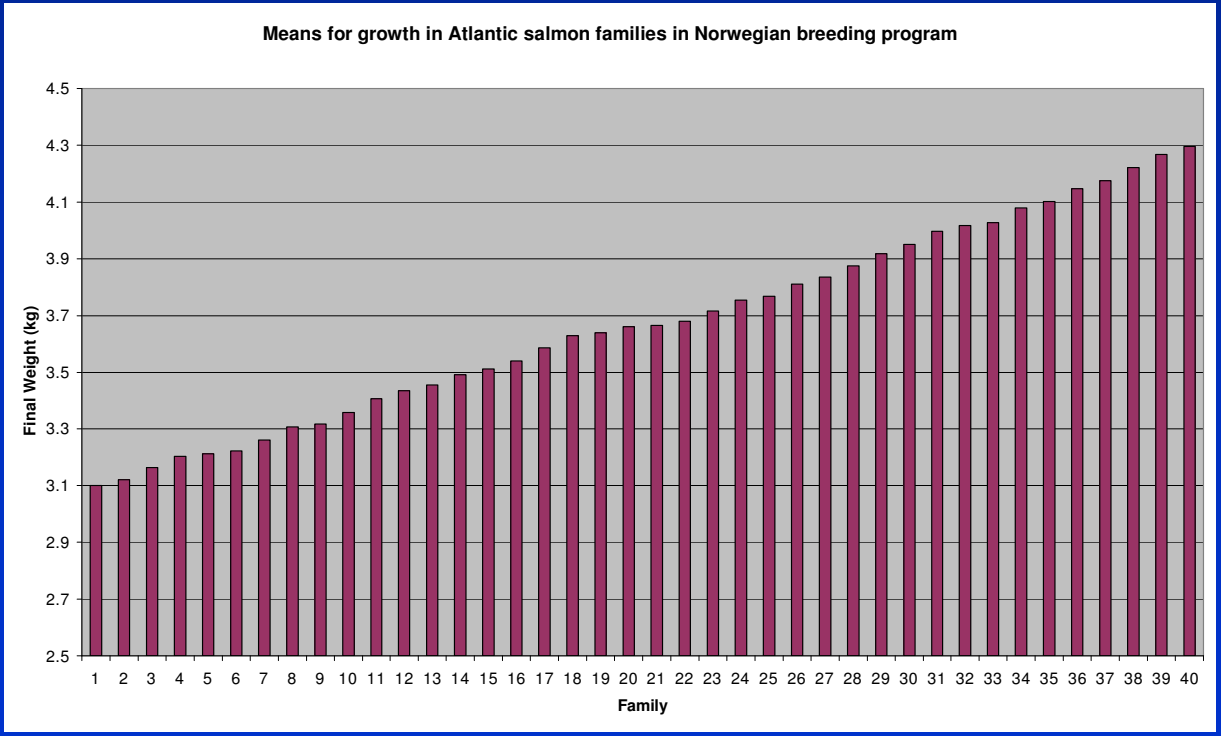
- Day 1
  - Linkage disequilibrium in animal and plant genomes
- Day 2
  - QTL mapping with LD
- Day 3
  - Marker assisted selection using LD
- Day 4
  - Genomic selection
- Day 5
  - Genomic selection continued

Linkage disequilibrium

- A brief history of QTL mapping
- Measuring linkage disequilibrium
- Causes of LD
- Extent of LD in animals and plants
- The extent of LD between breeds
- Strategies for haplotyping

A brief history of QTL mapping

- How to explain the genetic variation observed for many of the traits of economic importance in livestock and plant species



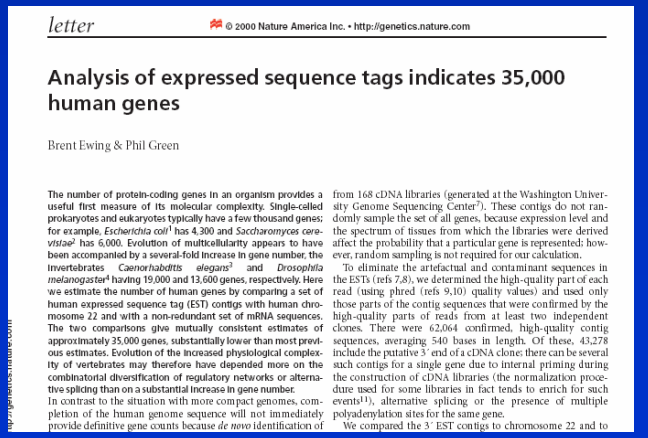
Two models…….

- Infinitesimal model:
  - assumes that traits are determined by an infinite number of unlinked and additive loci, each with an infinitesimally small effect
  - This model the foundation of animal breeding theory including breeding value estimation
  - Spectacularly successful in many cases!

Time to market weight for meat chickens has decreased from 16 to 5 weeks in 30 years

Two models…….

- *vs* the Finite loci model…..
  - But while the infinitesimal model is very useful assumption,
  - there is a finite amount of genetic material
  - With a finite number of genes……
  - Define any gene that contributes to variation in a quantitative/economic trait as quantitative trait loci (QTL)
- A key question is *what is the distribution of the effects of QTL for a typical quantitative trait* ?



letter © 2000 Nature America Inc. • http://genetics.nature.com

Analysis of expressed sequence tags indicates 35,000 human genes

Brent Ewing & Phil Green

The number of protein-coding genes in an organism provides a useful first measure of its molecular complexity. Single-celled prokaryotes and eukaryotes typically have a few thousand genes; for example, *Escherichia coli*[1] has 4,300 and *Saccharomyces cerevisiae*[2] has 6,000. Evolution of multicellularity appears to have been accompanied by a several-fold increase in gene number, the invertebrates *Caenorhabditis elegans*[3] and *Drosophila melanogaster*[4] having 19,000 and 13,600 genes, respectively. Here we estimate the number of human genes by comparing a set of human expressed sequence tag (EST) contigs with human chromosome 22 and with a non-redundant set of mRNA sequences. The two comparisons give mutually consistent estimates of approximately 35,000 genes, substantially lower than most previous estimates. Evolution of the increased physiological complexity of vertebrates may therefore have depended more on the combinatorial diversification of regulatory networks or alternative splicing than on a substantial increase in gene number.

In contrast to the situation with more compact genomes, completion of the human genome sequence will not immediately provide definitive gene counts because *de novo* identification of

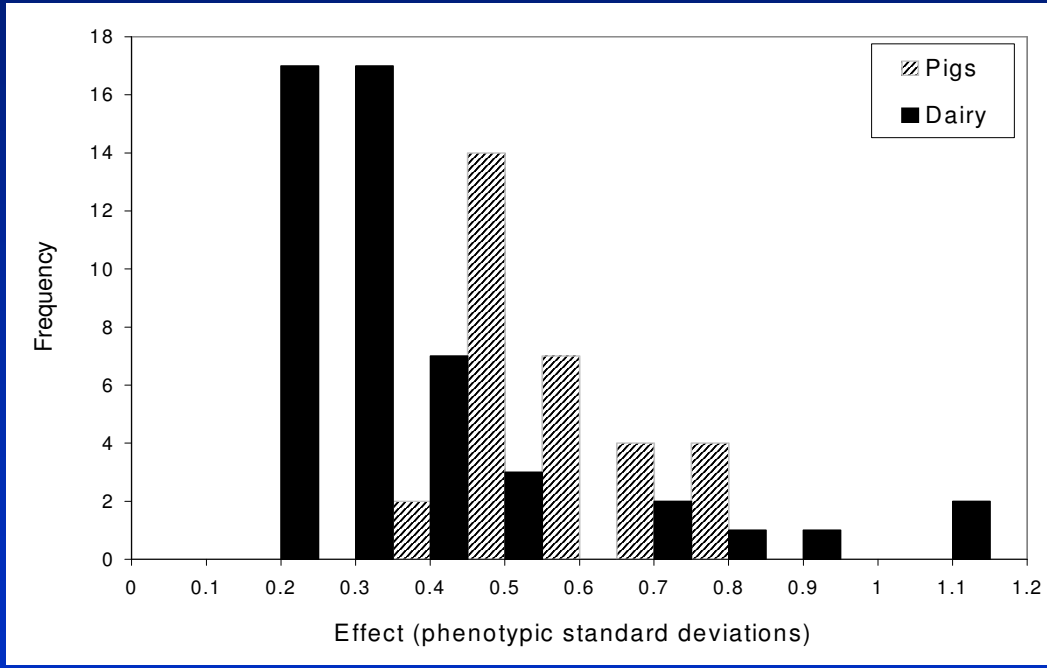
from 168 cDNA libraries (generated at the Washington University Genome Sequencing Center[7]). These contigs do not randomly sample the set of all genes, because expression level and the spectrum of tissues from which the libraries were derived affect the probability that a particular gene is represented; however, random sampling is not required for our calculation.

To eliminate the artefactual and contaminant sequences in the ESTs (refs 7,8), we determined the high-quality part of each read (using phred (refs 9,10) quality values) and used only those parts of the contig sequences that were confirmed by the high-quality parts of reads from at least two independent clones. There were 62,064 confirmed, high-quality contig sequences, averaging 540 bases in length. Of these, 43,278 include the putative 3′ end of a cDNA clone; there can be several such contigs for a single gene due to internal priming during the construction of cDNA libraries (the normalization procedure used for some libraries in fact tends to enrich for such events[11]), alternative splicing or the presence of multiple polyadenylation sites for the same gene.

We compared the 3′ EST contigs to chromosome 22 and to

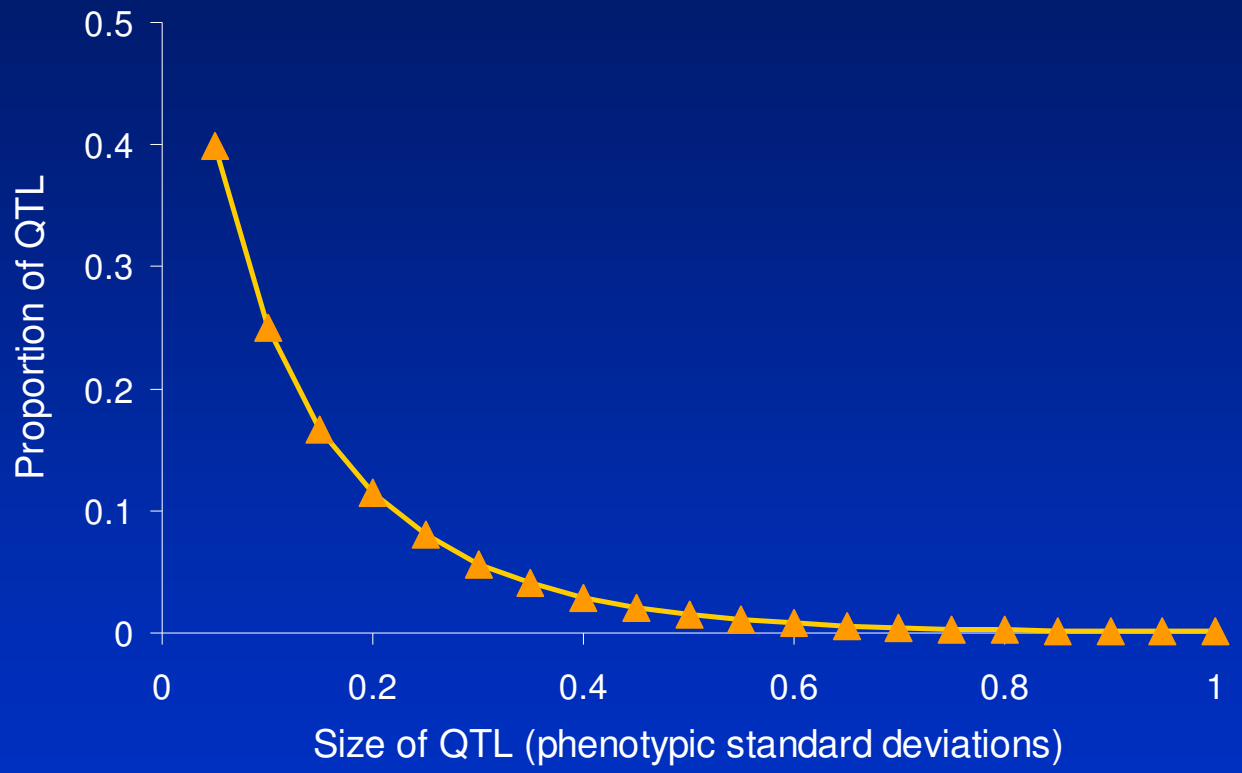
The distribution of QTL effects

- From results of QTL mapping experiments



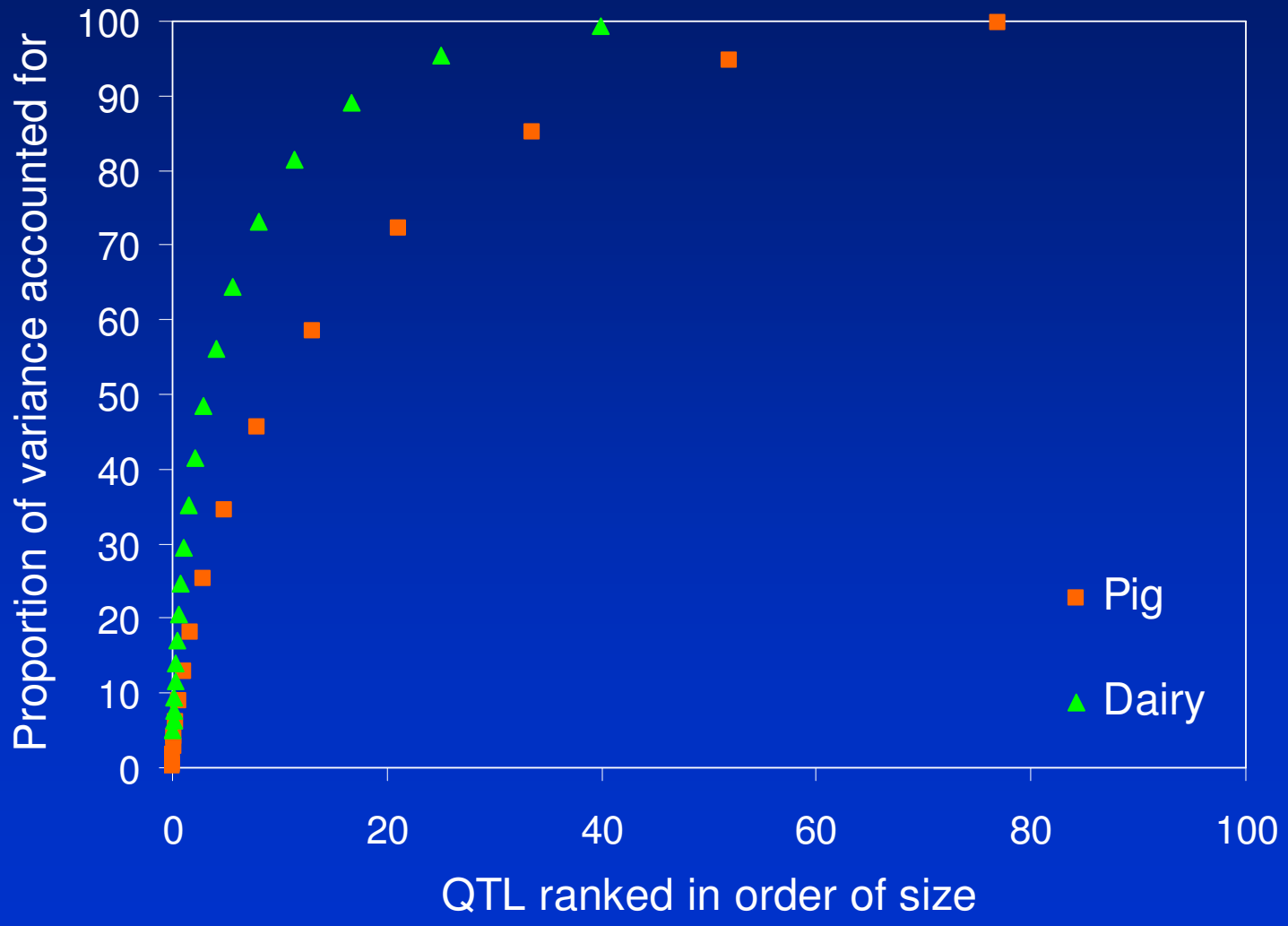
- Two problems
  - no small effects, effects estimated with error
  - Fit a truncated gamma distribution

The distribution of QTL effects



- *Many small* QTL, *few* QTL of *large* effect.
- 100 – 150 QTL sufficient to explain observed variation in quantitative traits in livestock

The distribution of QTL effects



Letter abstract

Nature Genetics
Published online: 13 January 2008 | doi:10.1038/ng.74

Common variants in the *GDF5-UQCC* region are associated with variation in human height

Serena Sanna[1,2,19], Anne U Jackson[1,19], Ramaiah Nagaraja[3], Cristen J Willer[1], Wei-Min Chen[1,4], Lori L Bonnycastle[5], Haiqing Shen[6], Nicholas Timpson[7,8], Guillaume Lettre[9], Gianluca Usala[2], Peter S Chines[5], Heather M Stringham[1], Laura J Scott[1], Mariano Dei[2], Sandra Lai[2], Giuseppe Albai[2], Laura Crisponi[2], Silvia Naitza[2], Kimberly F Doheny[10], Elizabeth W Pugh[10], Yoav Ben-Shlomo[7], Shah Ebrahim[11], Debbie A Lawlor[7,8], Richard N Bergman[12], Richard M Watanabe[12,13], Manuela Uda[2], Jaakko Tuomilehto[14], Josef Coresh[15], Joel N Hirschhorn[9], Alan R Shuldiner[6,16], David Schlessinger[3], Francis S Collins[5], George Davey Smith[7,8], Eric Boerwinkle[17], Antonio Cao[2], Michael Boehnke[1], Gonçalo R Abecasis[1] & Karen L Mohlke[18]

top

Identifying genetic variants that influence human height will advance our understanding of skeletal growth and development. Several rare genetic variants have been convincingly and reproducibly associated with height in mendelian syndromes, and common variants in the transcription factor gene *HMGA2* are associated with variation in height in the general population[1]. Here we report genome-wide association analyses, using genotyped and imputed markers, of 6,669 individuals from Finland and Sardinia, and follow-up analyses in an additional 28,801 individuals. We show that common variants in the osteoarthritis-associated locus[2] *GDF5-UQCC* contribute to variation in height with an estimated additive effect of 0.44 cm (overall $P < 10^{-15}$). Our results indicate that there may be a link between the genetic basis of height and osteoarthritis, potentially mediated through alterations in bone

Search This journal

ine publication > Letter > Abstract

Letter abstract

Nature Genetics
Published online: 13 January 2008 | doi:10.1038/ng.74

Common variants in the *GDF5-UQCC* region are associated with variation in human height

Serena Sanna[1,2,19], Anne U Jackson[1,19], Ramaiah Nagaraja[3], Cristen J Willer[1], Wei-Min Chen[1,4], Lori L Bonnycastle[5], Haiqing Shen[6], Nicholas Timpson[7,8], Guillaume Lettre[9], Gianluca Usala[2], Peter S Chines[5], Heather M Stringham[1], Laura J Scott[1], Mariano Dei[2], Sandra Lai[2], Giuseppe Albai[2], Laura Crisponi[2], Silvia Naitza[2], Kimberly F Doheny[10], Elizabeth W Pugh[10], Yoav Ben-Shlomo[7], Shah Ebrahim[11], Debbie A Lawlor[7,8], Richard N Bergman[12], Richard M Watanabe[12,13], Manuela Uda[2], Jaakko Tuomilehto[14], Josef Coresh[15], Joel N Hirschhorn[9], Alan R Shuldiner[6,16], David Schlessinger[3], Francis S Collins[5], George Davey Smith[7,8], Eric Boerwinkle[17], Antonio Cao[2], Michael Boehnke[1], Gonçalo R Abecasis[1] & Karen L Mohlke[18]

Identifying genetic variants that influence human height will advance our understanding of skeletal growth and development. Several rare genetic variants have been convincingly and reproducibly associated with height in mendelian syndromes, and common variants in the transcription factor gene *HMGA2* are associated with variation in height in the general population[1]. Here we report genome-wide association analyses, using genotyped and imputed markers, of 6,669 individuals from Finland and Sardinia, and follow-up analyses in an additional 28,801 individuals. We show that common variants in the osteoarthritis-associated locus[2] *GDF5-UQCC* contribute to variation in height with an estimated additive effect of 0.44 cm (overall $P < 10^{-15}$). Our results indicate that there may be a link between the genetic basis of height and osteoarthritis, potentially mediated through alterations in bone

top

< 1% of phenotypic variance!

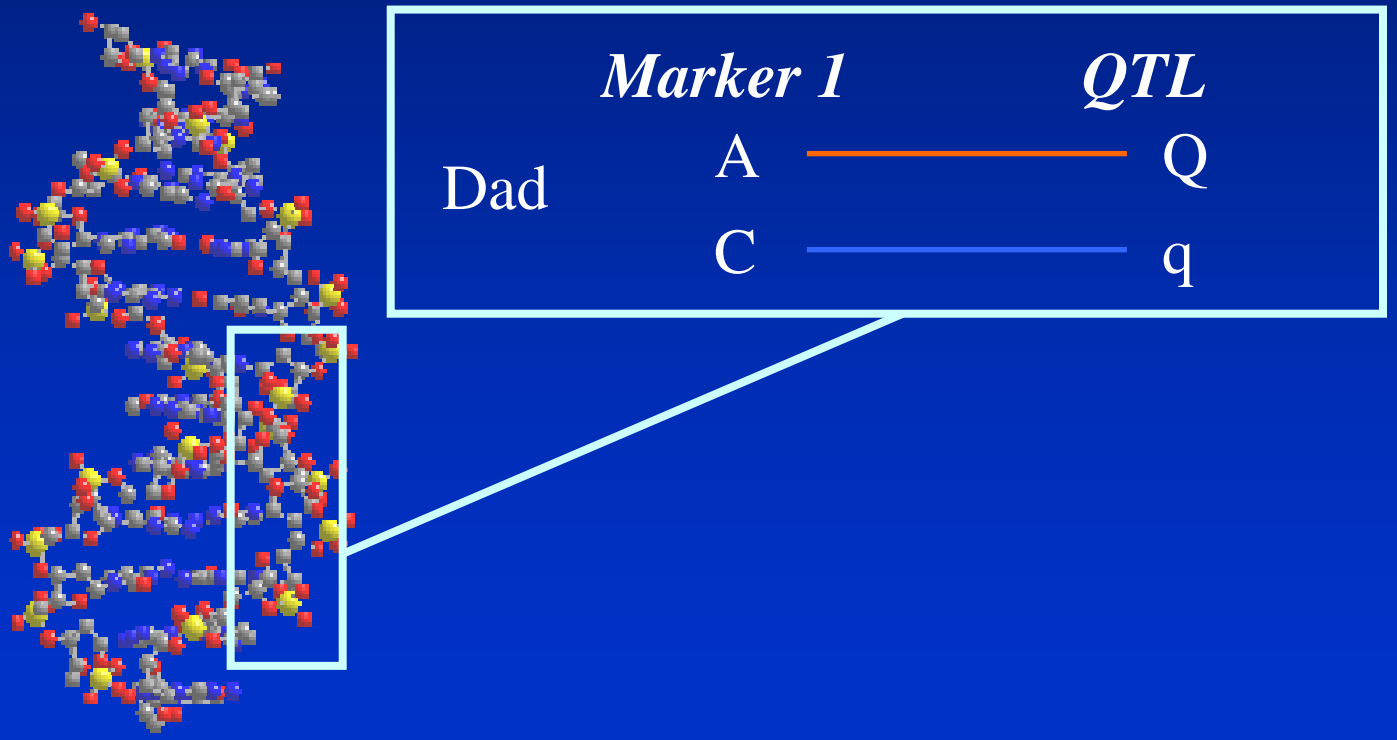
Quantitative trait loci (QTL) detection

- If we had information on the location in the genome of the QTL we could
  - increase the accuracy of breeding values
  - improve selection response
- How to find them?

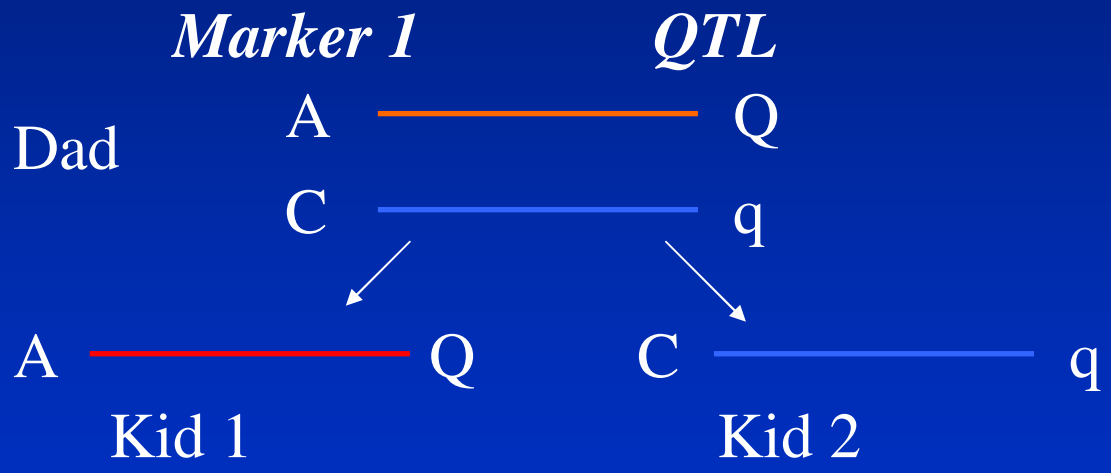
Approaches to QTL detection

- Candidate gene approach
  - assumes a gene involved in trait physiology could harbour a mutation causing variation in that trait
  - Look for mutations in this gene
  - Some success
  - Number of candidate genes is too large
  - Very difficult to pick candidates!
- Linkage mapping
  - So use *neutral markers* and exploit linkage
    - organisation of the genome into chromosomes inherited from parents

- DNA markers: track chromosome segments from one generation to the next



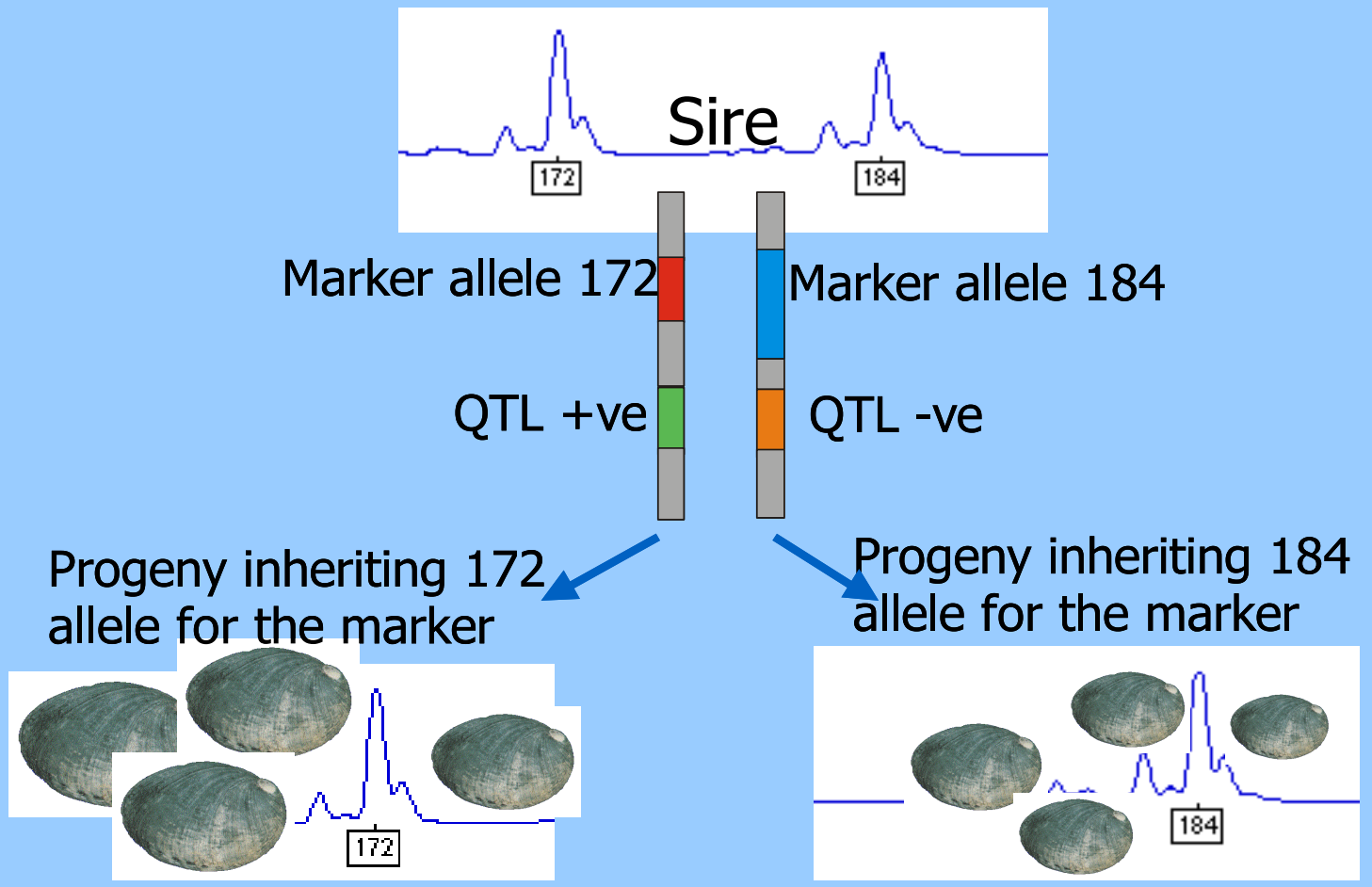
- DNA markers: track chromosome segments from one generation to the next



Detection of QTL with linkage

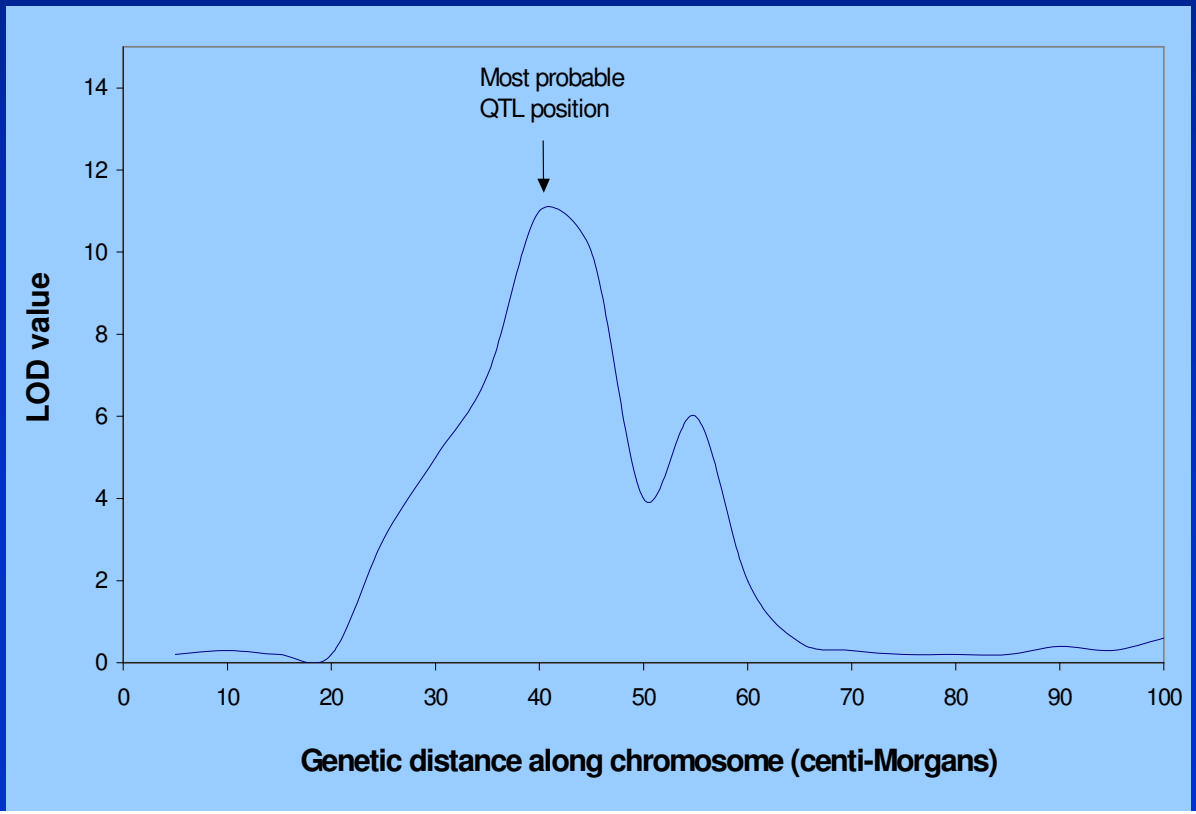
- Principle of QTL mapping
  - Is variation at the molecular level (different marker alleles) linked to variation in the quantitative trait?.
  - If so then the marker is linked to, or on the same chromosome as, a QTL

Detection of QTL



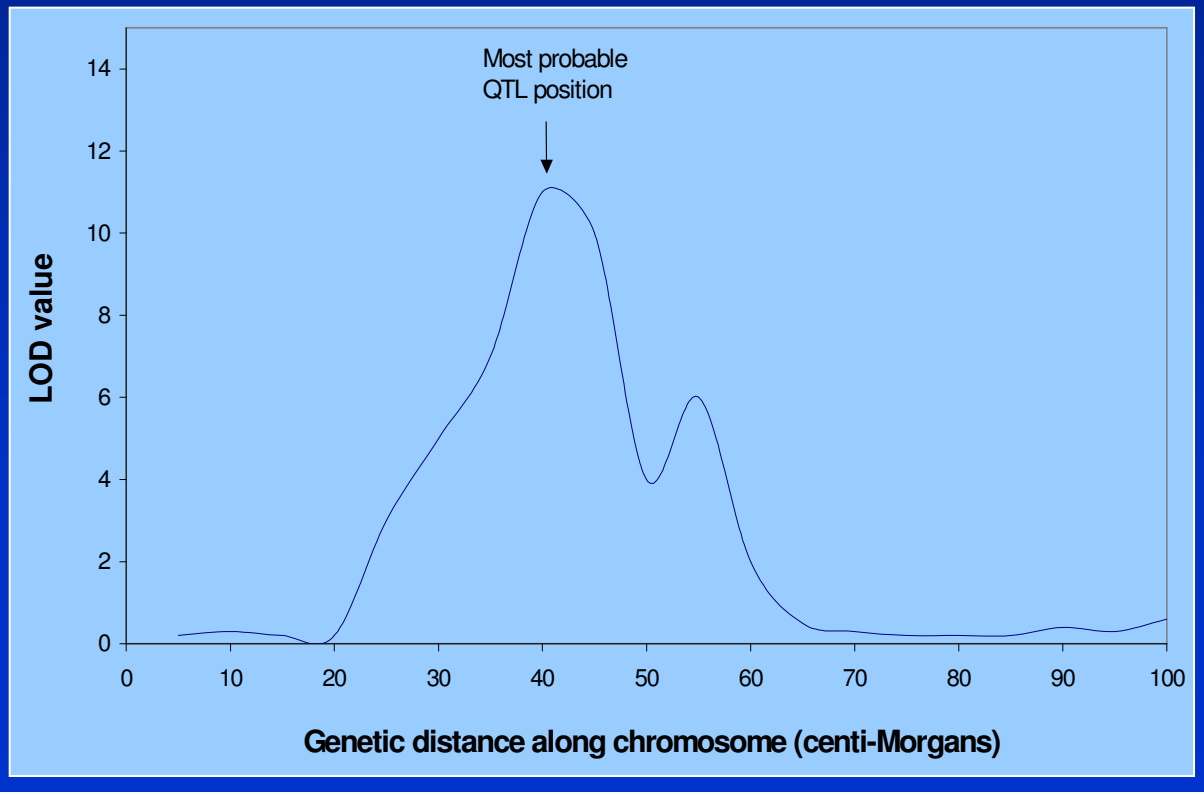
Detection of QTL with linkage

- Can use single marker associations
- More information with multiple markers ordered on linkage maps



Problems with linkage mapping

- QTL are not mapped very precisely
- Confidence intervals of QTL location are very wide

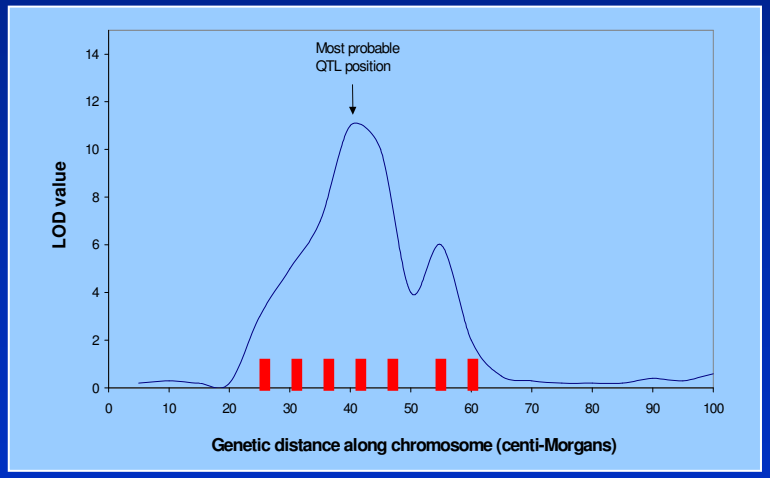


Problems with linkage mapping

- Difficult to use information in marker assisted selection (MAS)
- Most significant marker can be 10cM or more from QTL
- The association between the marker and QTL unlikely to persist across the population
  - Eg A___Q in one sire family
  - a___Q in another sire family
- The phase between the marker and QTL has to be re-estimated for each family
- Complicates use of the information in MAS
  - Reduces gains from MAS

Problems with linkage mapping

- Shift to fine mapping
  - Saturate confidence interval with many markers



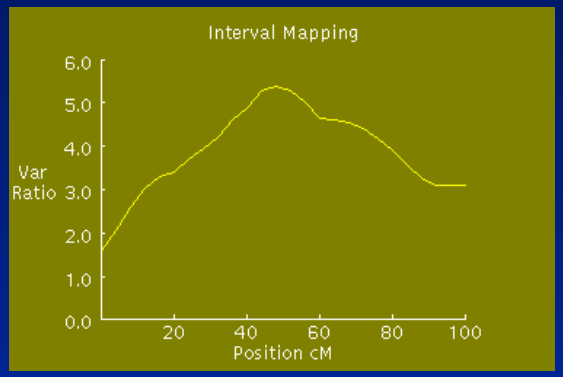
  - Use Linkage disequilibrium mapping approaches within this small chromosome segment

Problems with linkage mapping

- Shift to fine mapping
  - Saturate confidence interval with many markers
  - Use Linkage disequilibrium mapping approaches within this small chromosome segment
  - Eventually find causative mutation

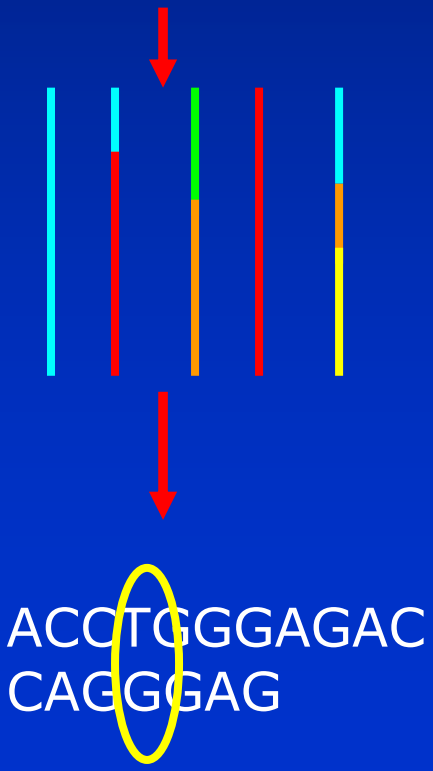
DGAT1 - A success story (Grisart et al. 2002)

1. Linkage mapping detects a QTL on bovine chromosome 14 with large effect on fat % (Georges et al 1995)



2. Linkage disequilibrium mapping refines position of QTL (Riquet et al. 1999)

3. Selection of candidate genes. Sequencing reveals point mutation in candidate (DGAT1). This mutation found to be functional - substitution of lysine for analine. Gene patented. (Grisart et al. 2002)

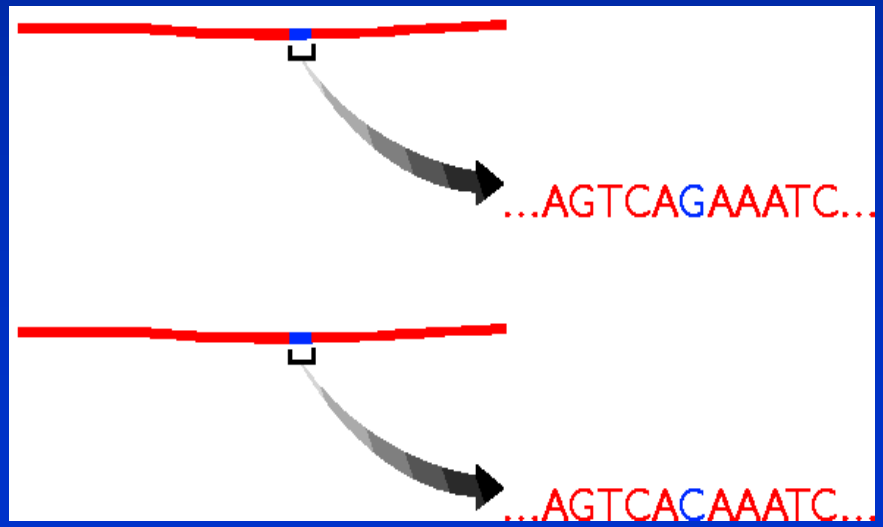


Problems with linkage mapping

- But process is very slow
  - 10 years or more to find causative mutation
  - One limitation has been the density of markers

The Revolution

- As a result of sequencing animal genomes, have a huge amount of information on variation in the genome
  - at the DNA level
- Most abundant form of variation are Single Nucleotide Polymorphisms (SNPs)





- ~10 mill SNPs
- ~7 mill SNPs with minor allele >5%
- ~100,000-300,000 cSNPs
- ~50,000 nonsynonymous cSNPs -> change protein structure

The Revolution

- 100 000s of SNPs reported for cattle, chicken, pig
- Sheep, Atlantic Salmon on the way
- Plants?

The Revolution

- Can we use SNP information to greatly accelerate the application of marker assisted selection in the livestock industries?

The Revolution

- Can we use SNP information to greatly accelerate the application of marker assisted selection in the livestock industries?
  - Omit linkage mapping
  - Straight to genome wide LD mapping
  - Breeding values directly from markers?
    - Genomic selection

Aim

- Provide you with the tools to use high density SNP genotypes in livestock and plant improvement

Linkage disequilibrium

- A brief history of QTL mapping
- Measuring linkage disequilibrium
- Causes of LD
- Extent of LD in animals and plants
- The extent of LD between breeds
- Strategies for haplotyping

Definitions of LD

- Why do we need to define and measure LD?
- Both genomic selection and LD mapping require markers to be in LD with QTL
- Determine the number of markers required for LD mapping and/or genomic selection

Definitions of LD

- Classical definition:
  - Two markers A and B on the same chromosome
  - Alleles are
    - marker A A1, A2
    - marker B B1, B2
  - Possible haploptypes are A1_B1, A1_B2, A2_B1, A2_B2

Definitions of LD

Linkage equilibrium……

		Marker A		
		A1	A2	Frequency
Marker B	B1			0.5
	B2			0.5
	Frequency	0.5	0.5	

Definitions of LD

Linkage equilibrium……

		Marker A		
		A1	A2	Frequency
Marker B	B1	0.25	0.25	0.5
	B2	0.25	0.25	0.5
	Frequency	0.5	0.5	

Definitions of LD

Linkage disequilibrium……..

		Marker A		
		A1	A2	Frequency
Marker B	B1	0.4	0.1	0.5
	B2	0.1	0.4	0.5
	Frequency	0.5	0.5	

Definitions of LD

Linkage disequilibrium……

		Marker A		
		A1	A2	Frequency
Marker B	B1	0.4	0.1	0.5
	B2	0.1	0.4	0.5
	Frequency	0.5	0.5	

within a sire family

sire haplotypes A1_B1, A2_B2

progeny A1_B1, A2_B2, A1_B1, A2_B2, A1_B2

Definitions of LD

Linkage disequilibrium……

		Marker A		
		A1	A2	Frequency
Marker B	B1	0.4	0.1	0.5
	B2	0.1	0.4	0.5
	Frequency	0.5	0.5	

within a *population*

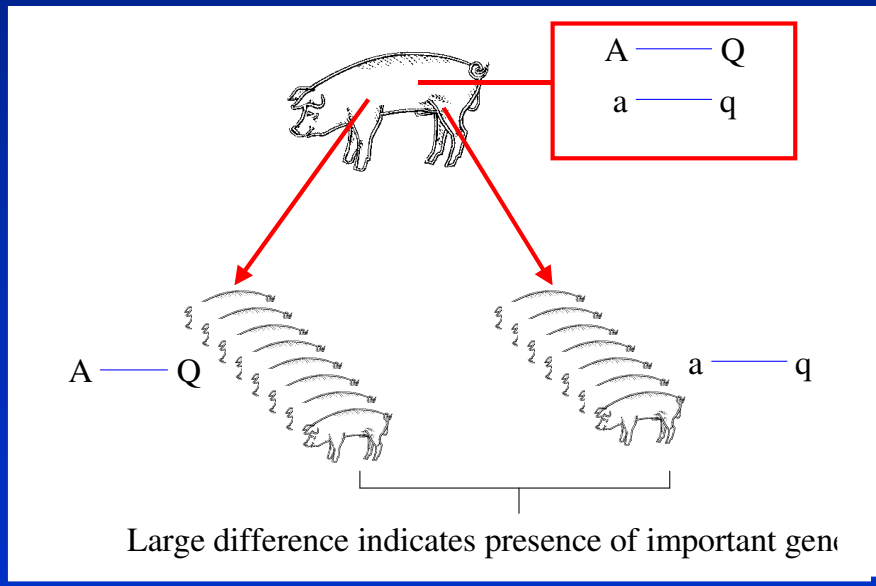
unrelated animals selected at random:

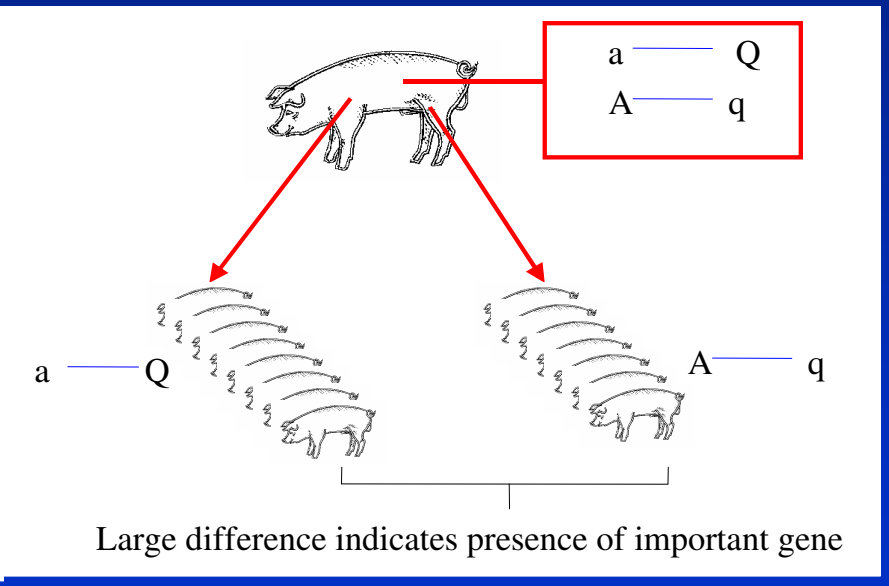
A1_B1, A2_B2, A1_B1, A2_B2, A1_B2

Definitions of LD

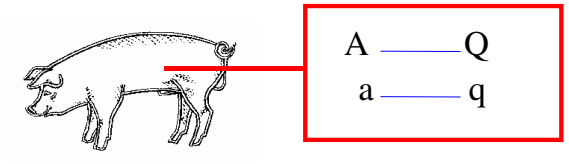
- In fact, LD required for both linkage and linkage disequilibrium mapping
- Difference is
  - linkage analysis mapping considers the LD that exists within **families**
    - extends for 10s of cM
    - broken down after only a few generations
  - LD mapping requires a marker allele to be in LD with a QTL allele across the whole **population**
    - association must have persisted across multiple generations to be a property of the population
    - so marker and QTL must be very closely linked

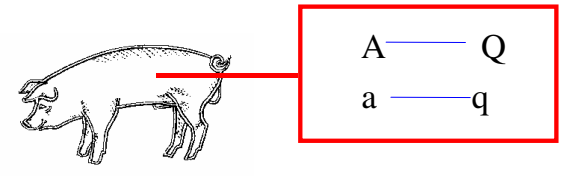
- Linkage between marker and QTL

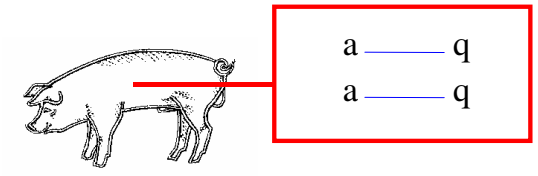


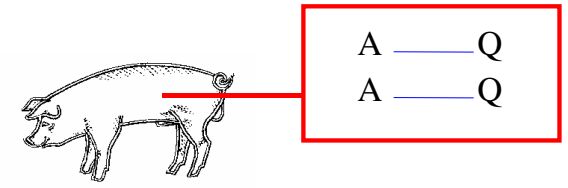


- Linkage disequilibrium between marker and QTL









Definitions of LD

Linkage disequilibrium……..

		Marker A		
		A1	A2	Frequency
Marker B	B1	0.4	0.1	0.5
	B2	0.1	0.4	0.5
	Frequency	0.5	0.5	

D = freq(A1_B1)*freq(A2_B2)-freq(A1_B2)*freq(A2_B1)

= 0.4 * 0.4 - 0.1 * 0.1

= 0.15

Definitions of LD

- Measuring the extent of LD (determines how dense markers need to be for LD mapping)

D = freq(A1_B1)*freq(A2_B2)-freq(A1_B2)*freq(A2_B1)

– highly dependent on allele frequencies
  - not suitable for comparing LD at different sites

$\mathbf{r^2}=D^2/[\text{freq}(A1)*\text{freq}(A2)*\text{freq}(B1)*\text{freq}(B2)]$

Definitions of LD

Linkage disequilibrium……..

		Marker A		
		A1	A2	Frequency
Marker B	B1	0.4	0.1	0.5
	B2	0.1	0.4	0.5
	Frequency	0.5	0.5	

D = 0.15

$r^2 = D^2/[freq(A1)*freq(A2)*freq(B1)*freq(B2)]$

$r^2 = 0.15^2/[0.5*0.5*0.5*0.5]$

$= 0.36$

Definitions of LD

- Measuring the extent of LD (determines how dense markers need to be for LD mapping)

  D = freq(A1_B1)*freq(A2_B2)-freq(A1_B2)*freq(A2_B1)

  – highly dependent on allele frequencies
    - not suitable for comparing LD at different sites

  $\mathbf{r^2}=D^2/[freq(A1)*freq(A2)*freq(B1)*freq(B2)]$

  Values between 0 and 1.

Definitions of LD

- If one loci is a marker and the other is QTL
- The r^2 between a marker and a QTL is the *proportion of QTL variance which can be observed at the marker*
  - eg if variance due to a QTL is 200kg^2, and r^2 between marker and QTL is 0.2, variation observed at the marker is 40kg^2.

Definitions of LD

- If one loci is a marker and the other is QTL
- The r^2 between a marker and a QTL is the *proportion of QTL variance which can be observed at the marker*
  - eg if variance due to a QTL is 200kg^2, and r^2 between marker and QTL is 0.2, variation observed at the marker is 40kg^2.
- Key parameter determining the power of LD mapping to detect QTL
  - Experiment sample size must be increased by $1/r^2$ to have the same power as an experiment observing the QTL directly

Definitions of LD

- If you are using microsatellites, need a multi-allele equivalent
- Use $\chi 2'$ (Zhao et al. 2005)

Definitions of LD

- Another LD statistic is D'
  - |D|/Dmax
  - Where
    - Dmax
      - = min[freq(A1)*freq(B2),(1-freq(A2))(1-freq(B1))]
      - if D>0, else
      - = min[freq(A1)(1-freq(B1),(1-(freq(A2))*freq(B2)]
      - if D<0.
  - But what does it mean?
  - Biased upward with low allele frequencies
  - Overestimates r^2

Definitions of LD

- Another LD statistic is D'
  - |D|/Dmax
  - Where
    - Dmax
      - = min[freq(A1)*freq(B2),(1-freq(A2))(1-freq(B1))]
      - if D>0, else
      - = min[freq(A1)(1-freq(B1),(1-(freq(A2))*freq(B2)]
      - if D<0.
  - But what does it mean?
  - Biased upward with low allele frequencies
  - Overestimates r^2

Definitions of LD

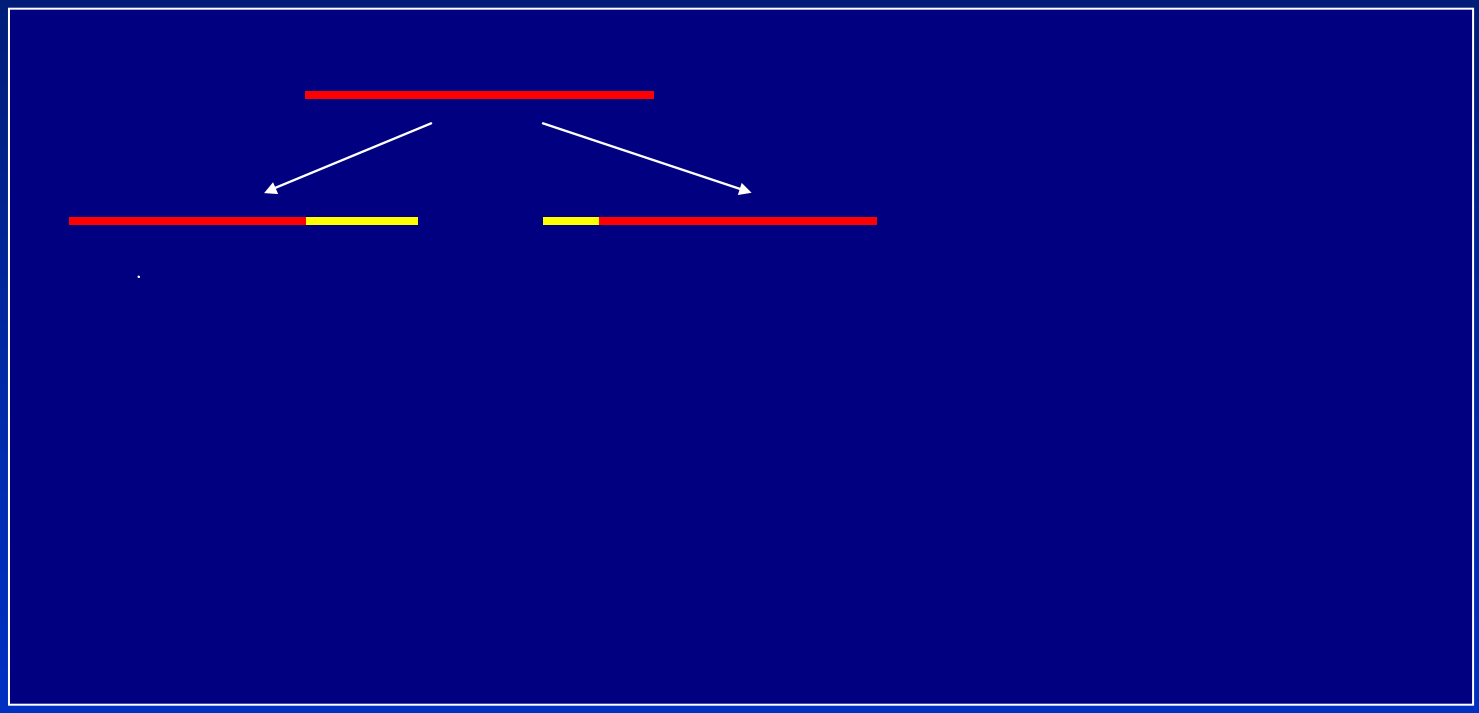
- Multi-locus measures of LD
  - r^2 is useful, easy to calculate and very widely used
    - and equivalents for loci with multiple alleles exist
  - But, only considers two loci at a time
    - cannot extract LD information available from multiple loci
    - not particularly intuitive with regards to the causes of LD

Definitions of LD

- A chunk of ancestral chromosome is conserved in the current population

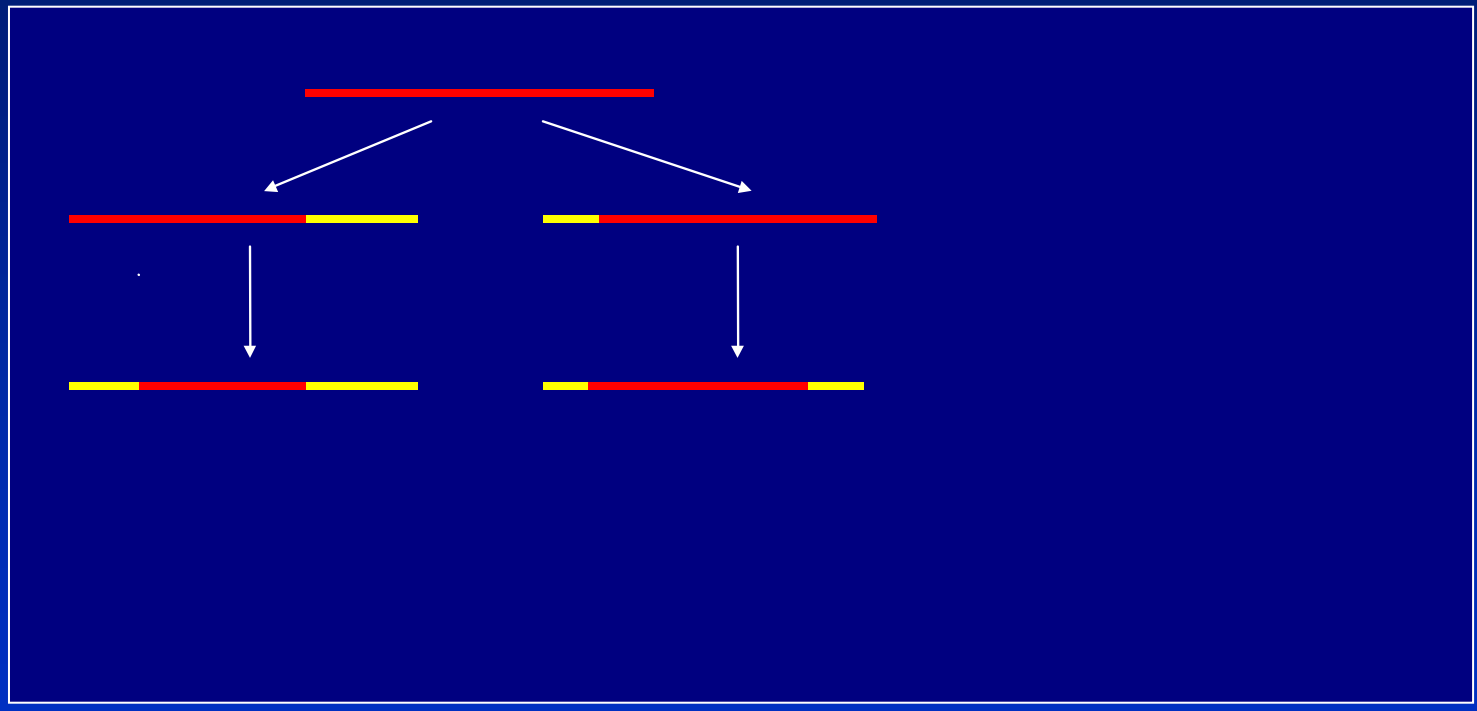
Definitions of LD

- A chunk of ancestral chromosome is conserved in the current population



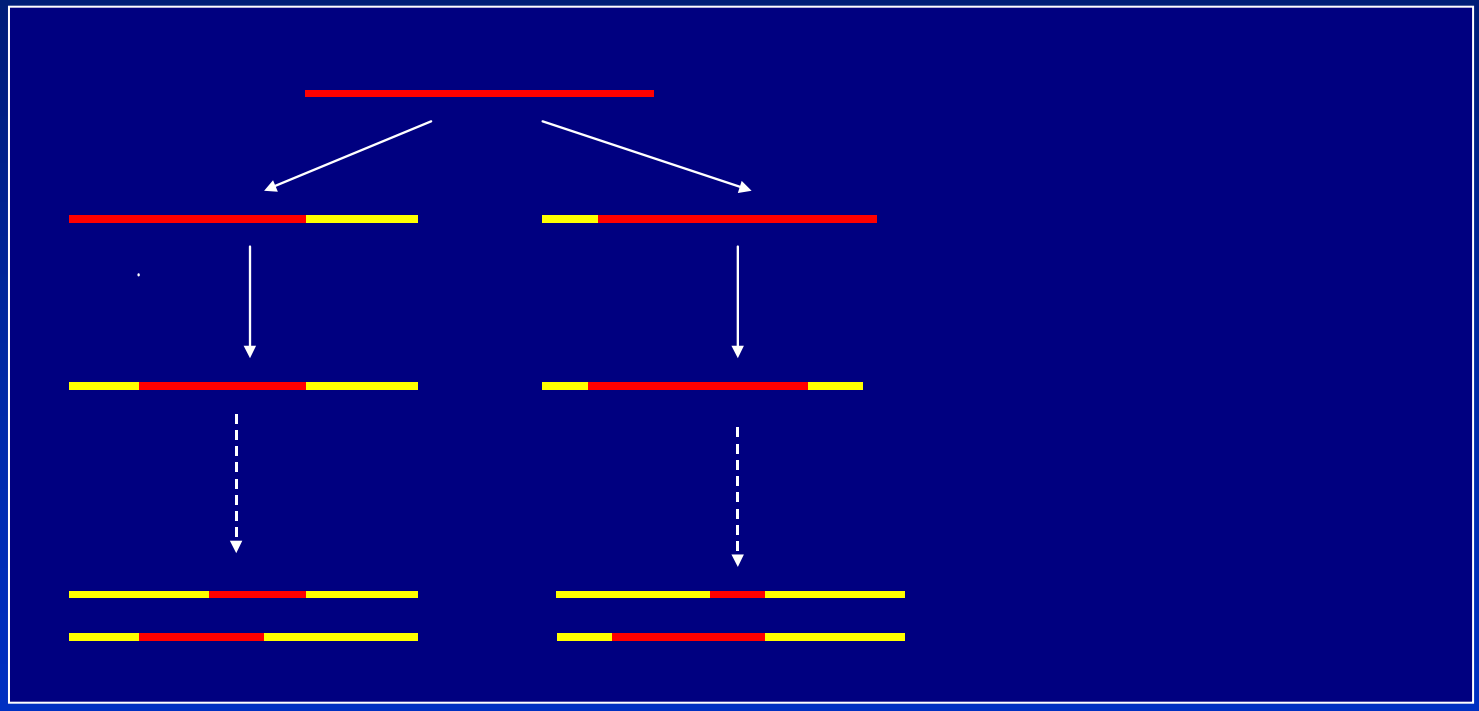
Definitions of LD

- A chunk of ancestral chromosome is conserved in the current population



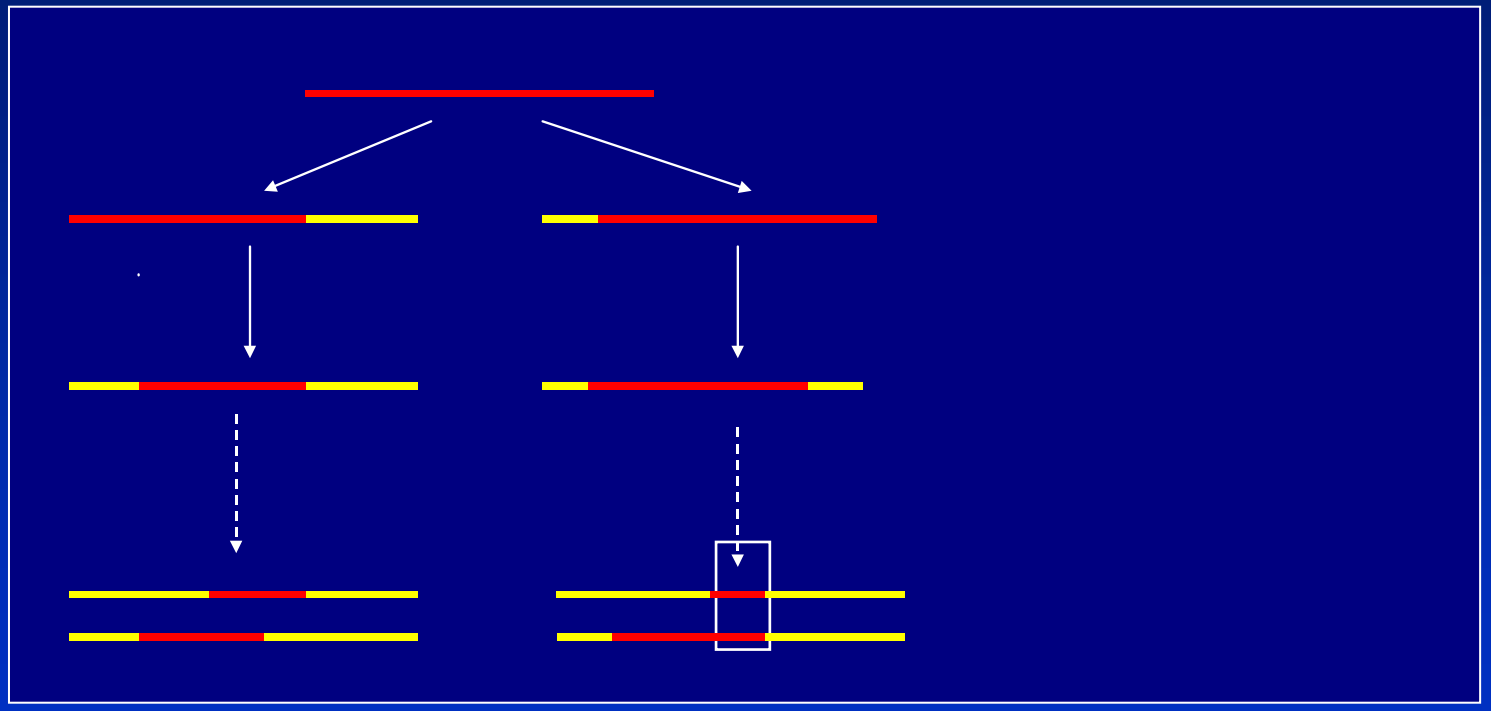
Definitions of LD

- A chunk of ancestral chromosome is conserved in the current population



Definitions of LD

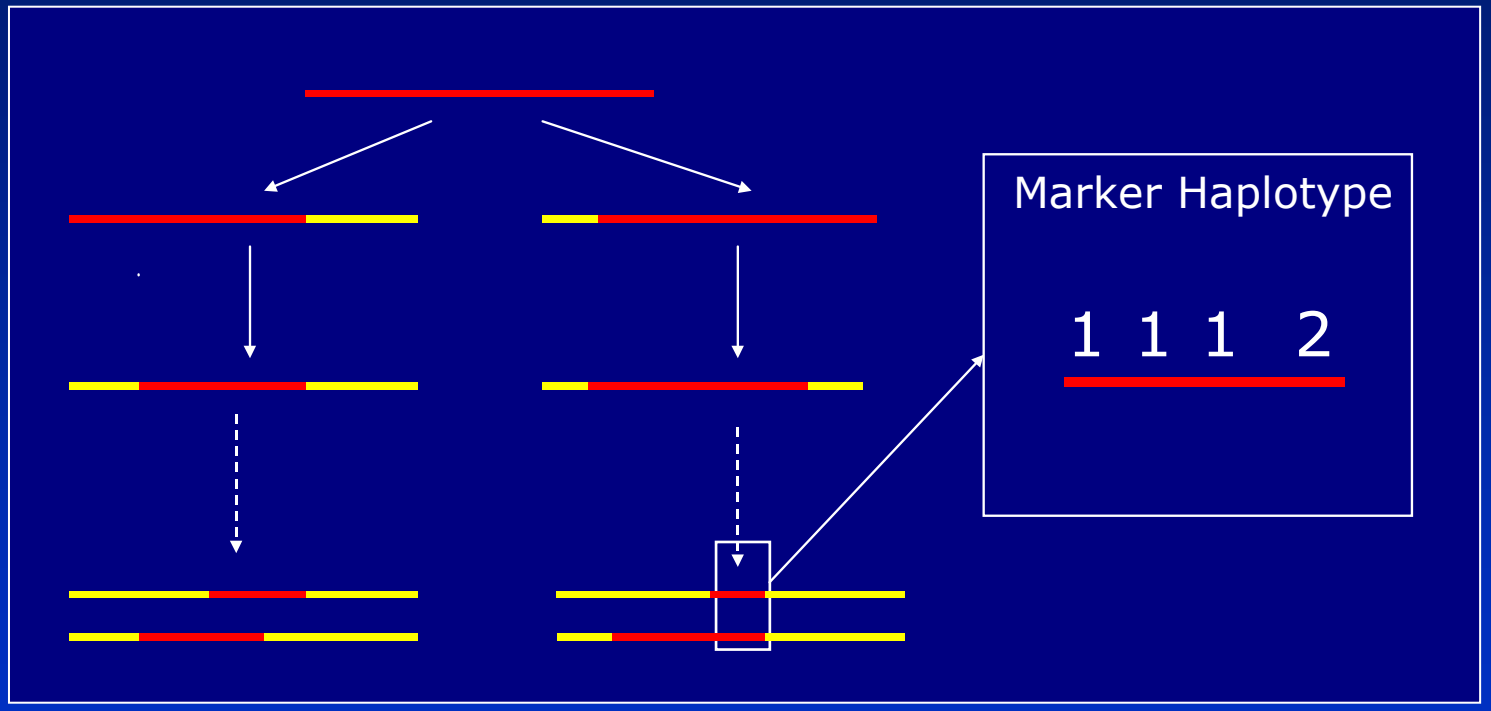
- A chunk of ancestral chromosome is conserved in the current population



- chromosome segment homozygosity (CSH) = Pr(Two chromosome segments randomly drawn from the population are derived from a common ancestor)

Definitions of LD

- A chunk of ancestral chromosome is conserved in the current population



- chromosome segment homozygosity (CSH) = Pr(Two chromosome segments randomly drawn from the population are derived from a common ancestor)

Definitions of LD

- Haplotype homozygosity = CSH + Identical chance (and not IBD)
- For two loci

  $HH = CSH + (Hom_A\text{-}CSH)(Hom_B\text{-}CSH)/(1\text{-}CSH)$
- Derivation for multiple loci similar, but more complex

Linkage disequilibrium

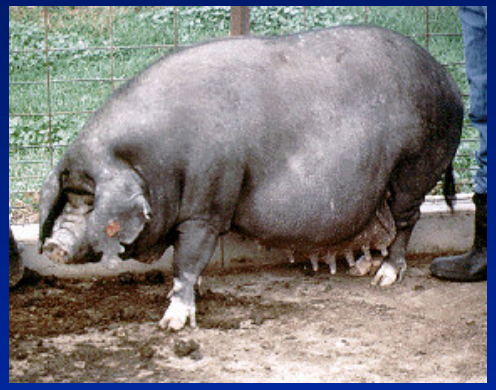
- A brief history of QTL mapping
- Measuring linkage disequilibrium
- Causes of LD
- Extent of LD in animals and plants
- The extent of LD between breeds
- Strategies for haplotyping

Causes of LD

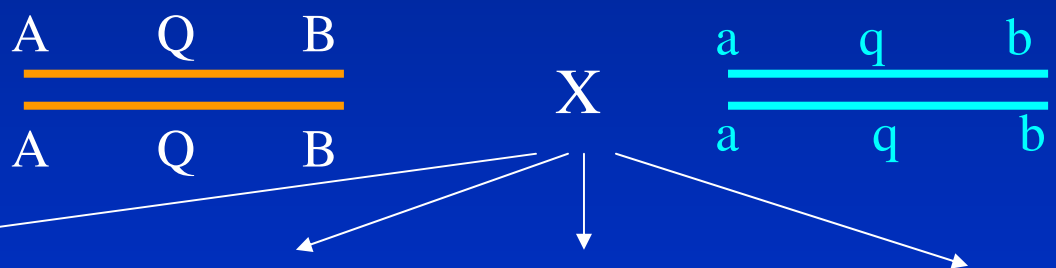
- Migration
  - LD artificially created in crosses
    - large when crossing inbred lines
    - but small when crossing breeds that do not differ markedly in gene frequencies
    - disappears after only a limited number of generations

- F2 design

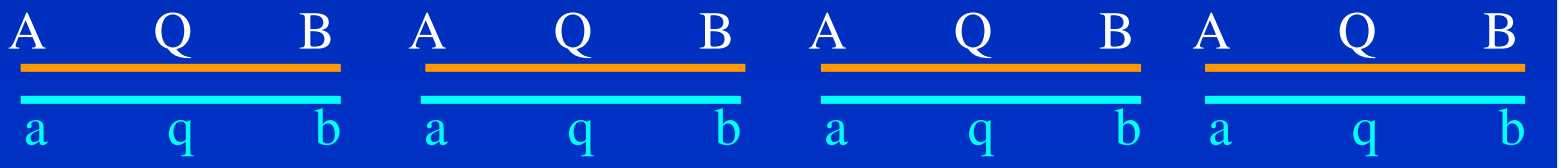
X



Parental Lines

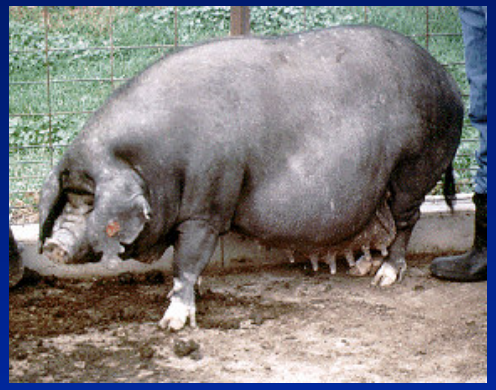


F1

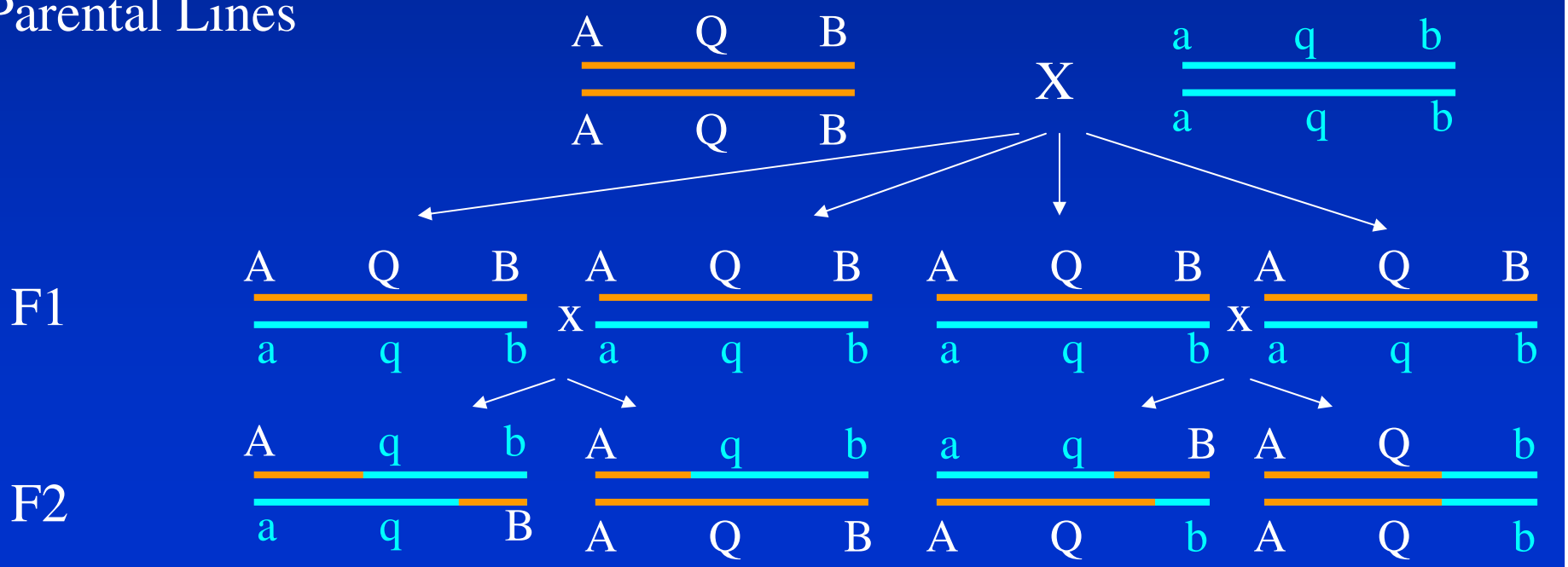


- F2 design

X



Parental Lines



Causes of LD

- Migration
  - LD artificially created in crosses designs
    - large when crossing inbred lines
    - but small when crossing breeds that do not differ markedly in gene frequencies
    - disappears after only a limited number of generations
- Selection
  - Selective sweeps

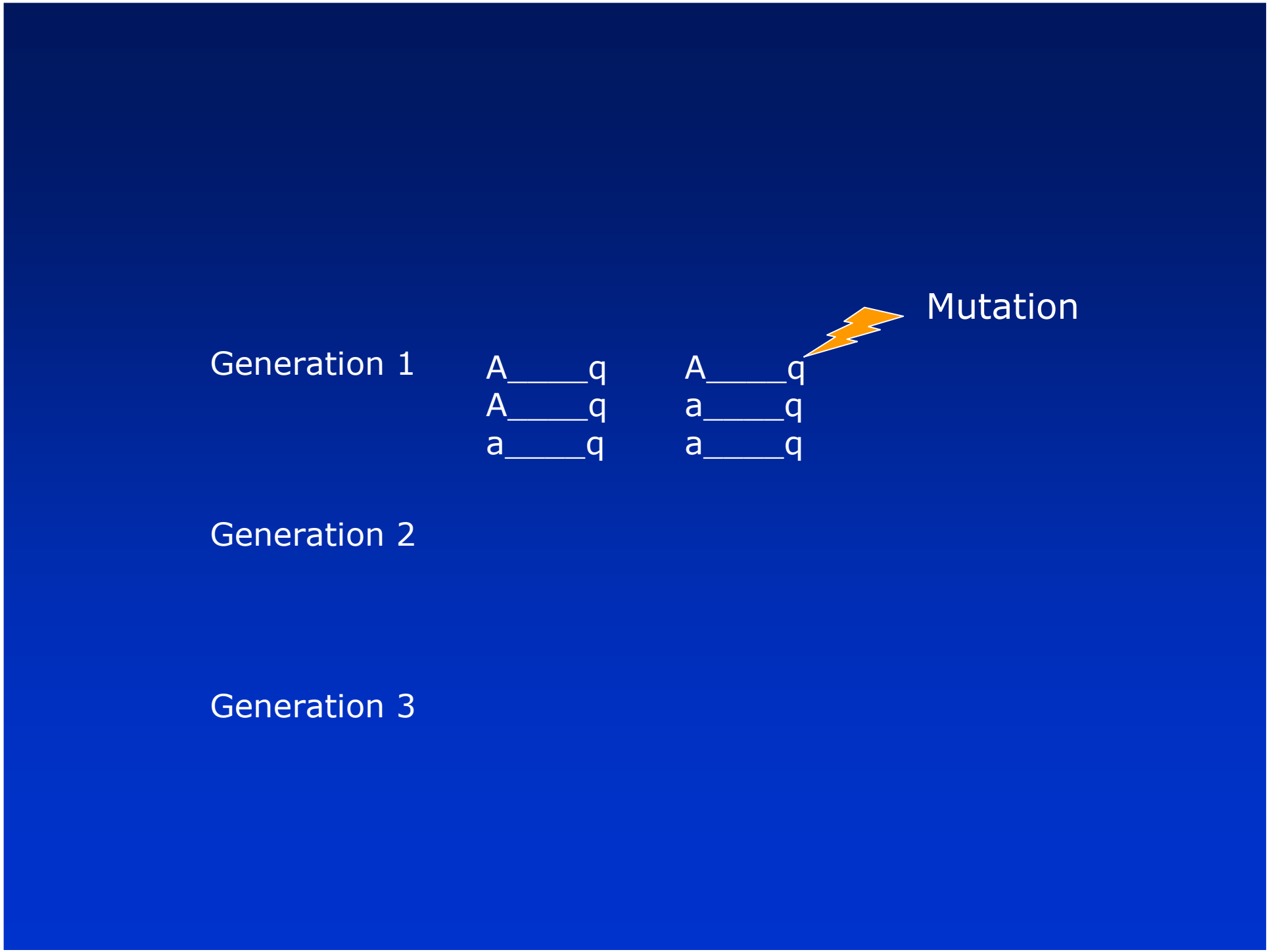
Generation 1

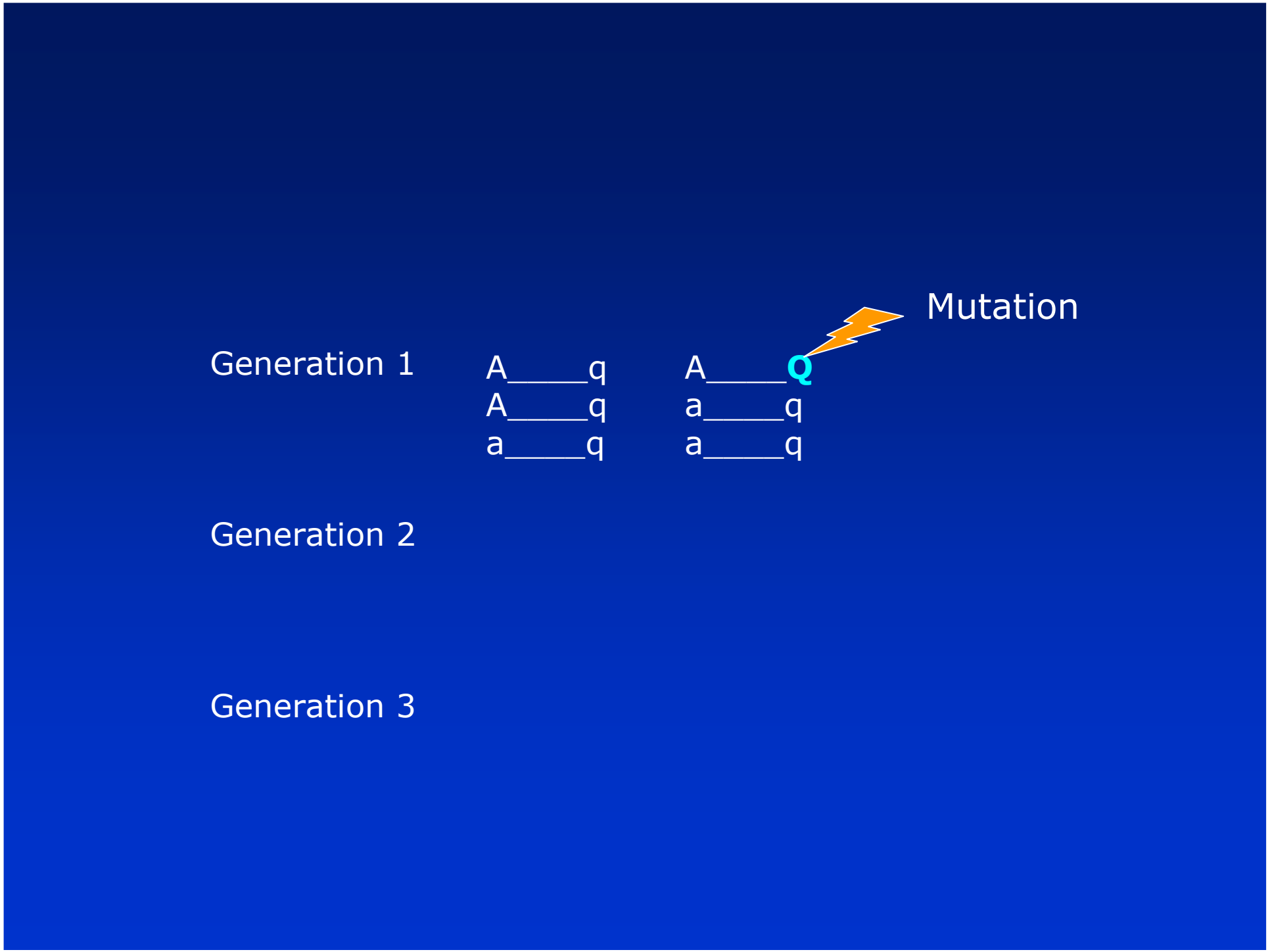
A_____q
A_____q
a_____q

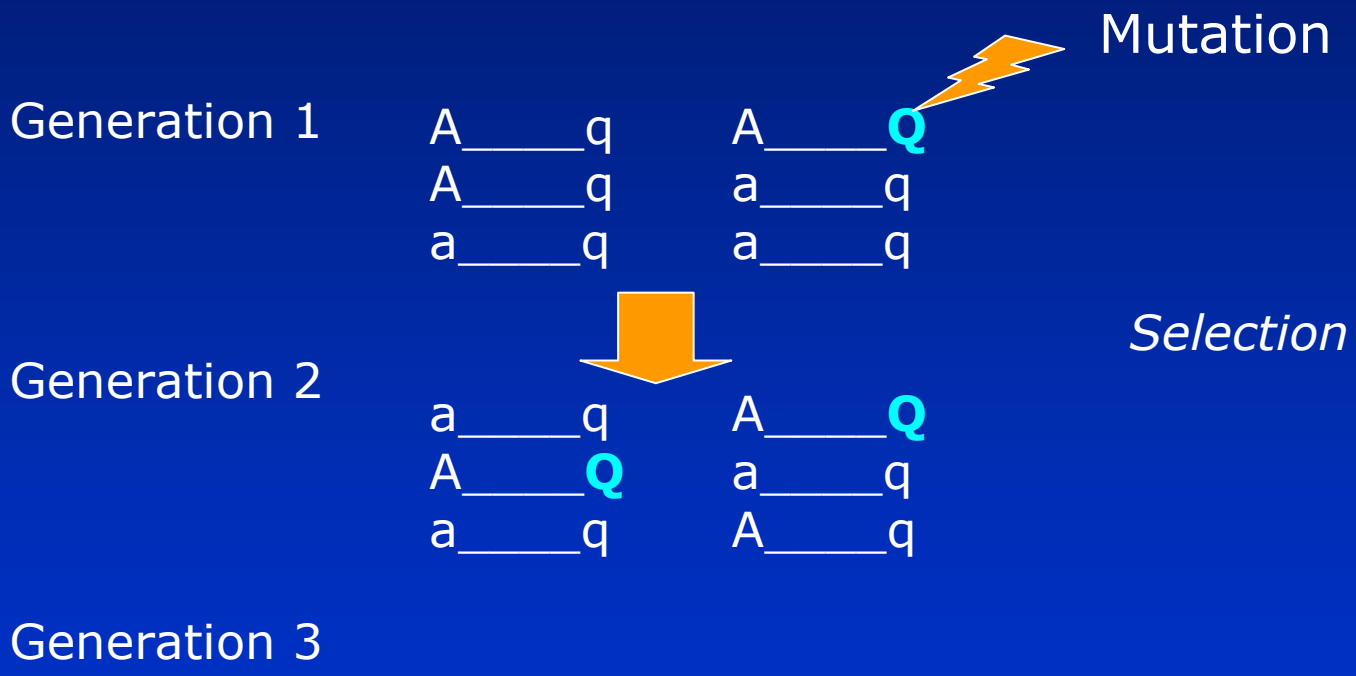
A_____q
a_____q
a_____q

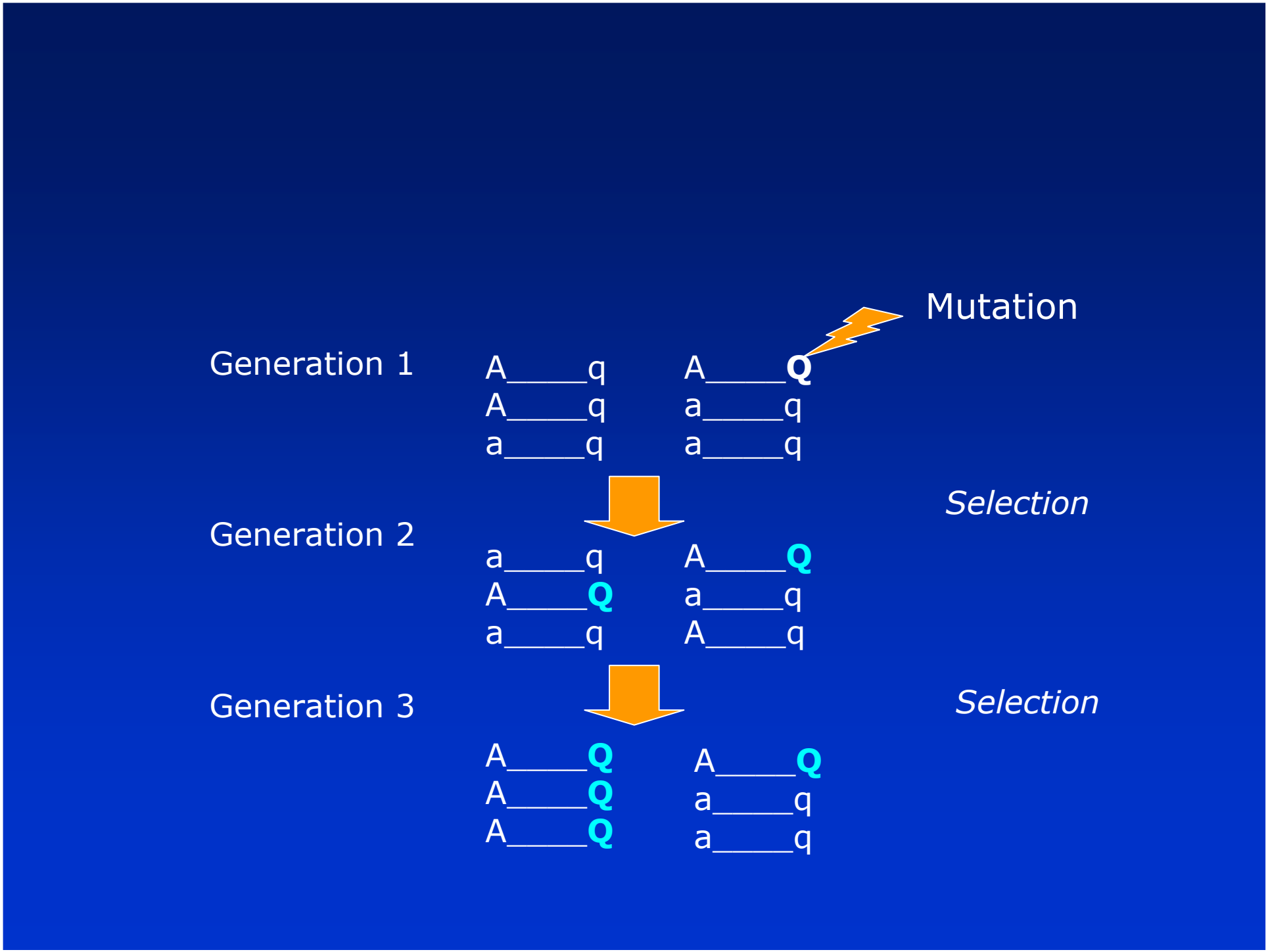
Generation 2

Generation 3


Mutation
Generation 1
A_____q
A_____q
a_____q
A_____q
a_____q
a_____q
Generation 2
Generation 3


Mutation
Generation 1
A_____q
A_____q
a_____q
A_____Q
a_____q
a_____q
Generation 2
Generation 3


Mutation
Generation 1
A_____q
A_____q
a_____q
A_____Q
a_____q
a_____q
Selection
Generation 2
a_____q
A_____Q
a_____q
A_____Q
a_____q
A_____q
Generation 3

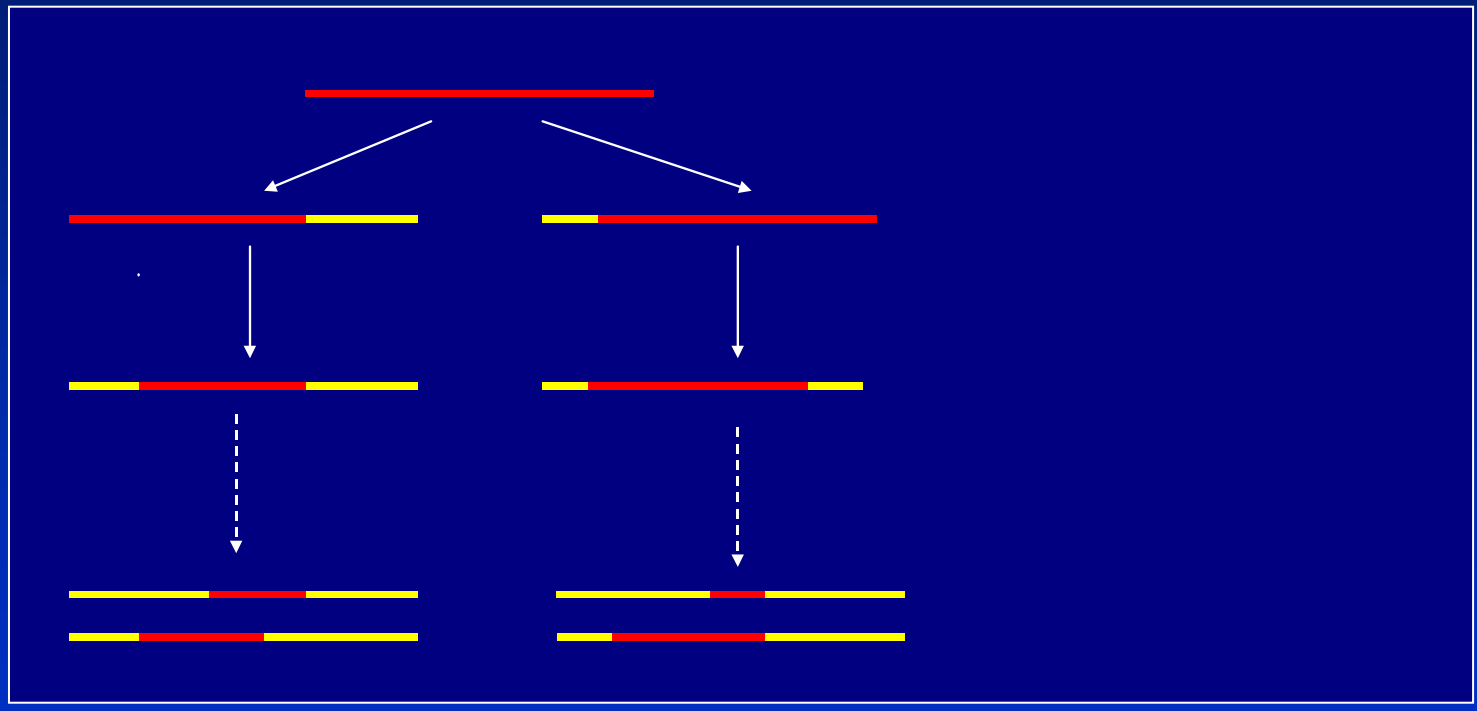

Mutation
Generation 1
A_____q
A_____q
a_____q
A_____Q
a_____q
a_____q
Selection
Generation 2
a_____q
A_____Q
a_____q
A_____Q
a_____q
A_____q
Selection
Generation 3
A_____Q
A_____Q
A_____Q
A_____Q
a_____q
a_____q

Causes of LD

- Migration
  - LD artificially created in crosses designs
    - large when crossing inbred lines
    - but small when crossing breeds that do not differ markedly in gene frequencies
    - disappears after only a limited number of generations
- Selection
  - Selective sweeps
- Small finite population size
  - generally implicated as the key cause of LD in livestock populations, where effective population size is small

Causes of LD

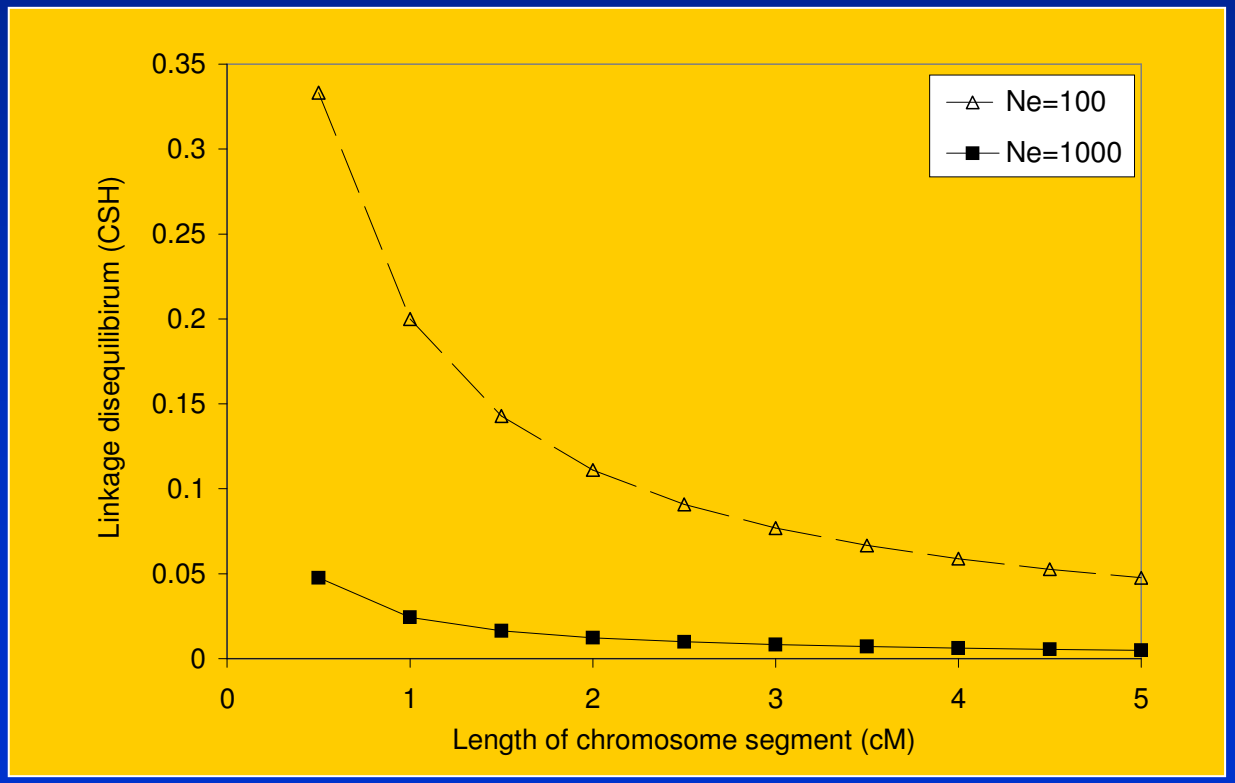
- A chunk of ancestral chromosome is conserved in the current population



- Size of conserved chunks depends on effective population size

Causes of LD

- Predicting LD with finite population size
- $E(r^2)$ and E(CSH) =1/(4Nc+1)
  - N = effective population size
  - c = length of chromosome segment

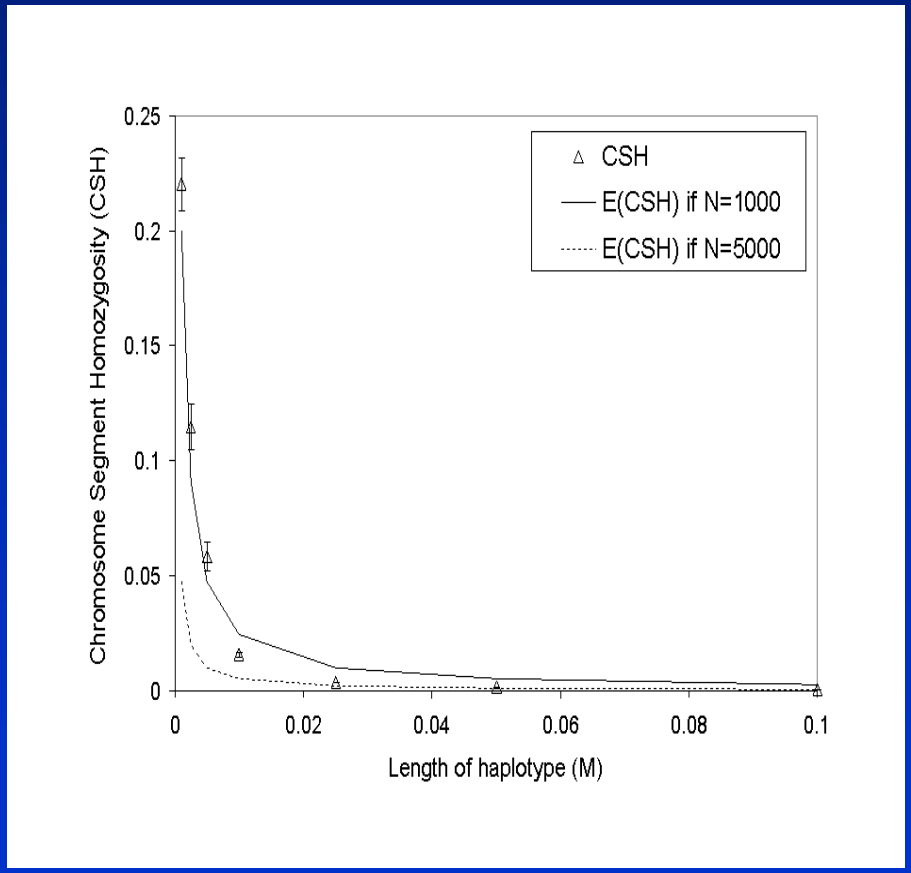


Causes of LD

- But this assumes constant effective population size over generations
- In livestock, effective population size has changed as a result of domestication
- 100 000 -> 1500 -> 100 ?
- In humans, has greatly increased
- 2000 -> 100 000 ?

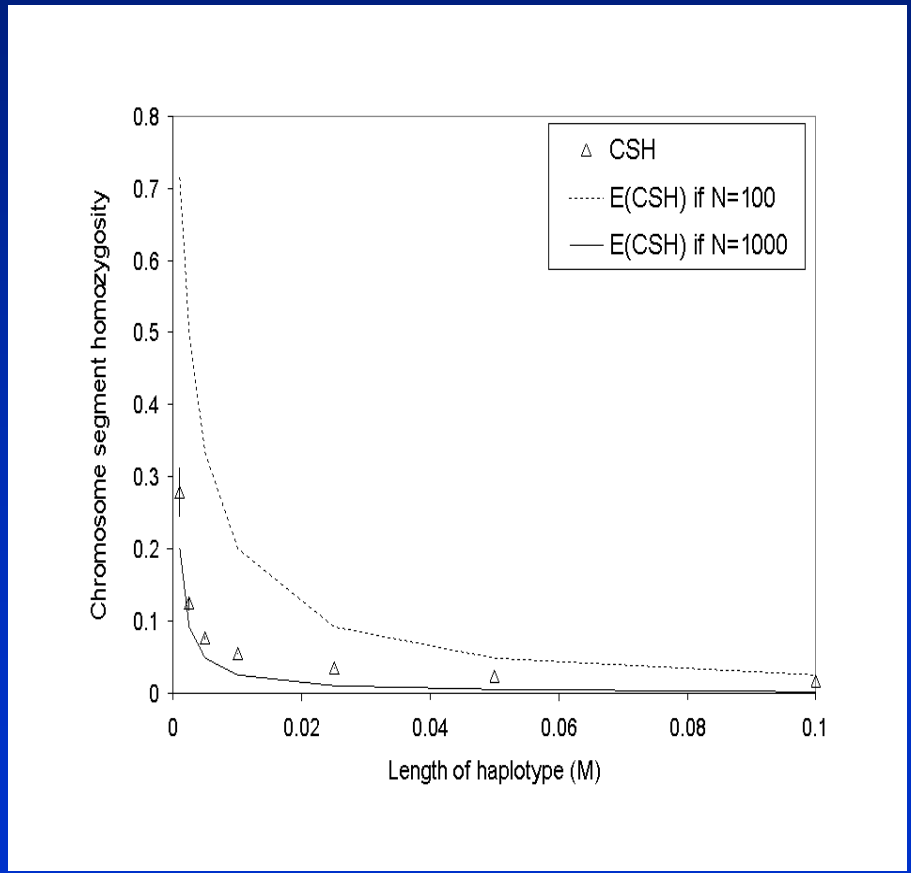
Causes of LD

1000 to 5000



A

1000 to 100



B

Causes of LD

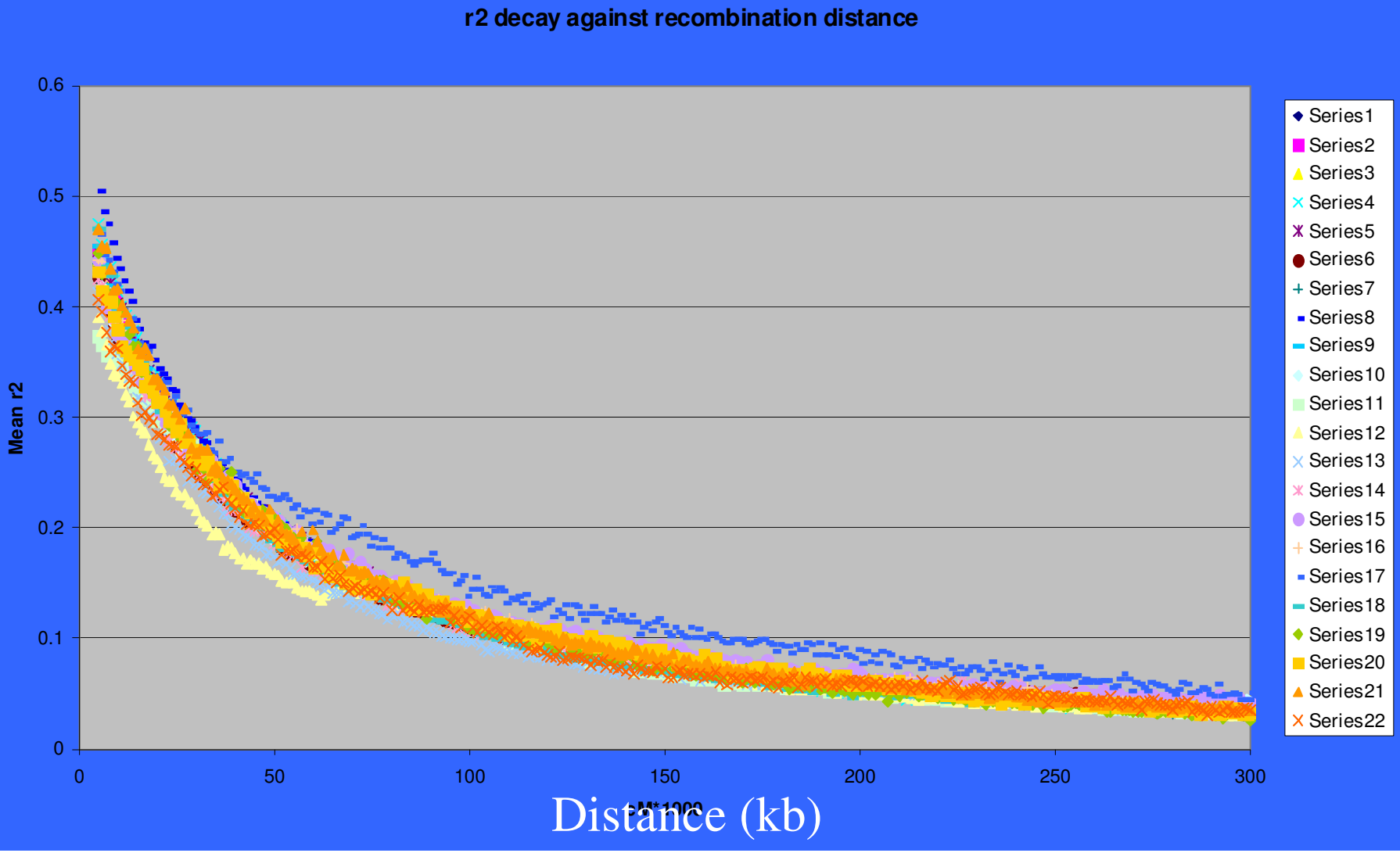
- $E(r^2) = 1/(4N_tc+1)$
- Where t = 1/(2c) generations ago
  - eg markers 0.1M (10cM) apart reflect population size 5 generations ago
  - Markers 0.001 (0.1cM) apart reflect effective pop size 500 generations ago
- LD at short distances reflects historical effective population size
- LD at longer distances reflects more recent population history

Linkage disequilibrium

- A brief history of QTL mapping
- Measuring linkage disequilibrium
- Causes of LD
- Extent of LD in animals and plants
- The extent of LD between breeds
- Strategies for haplotyping

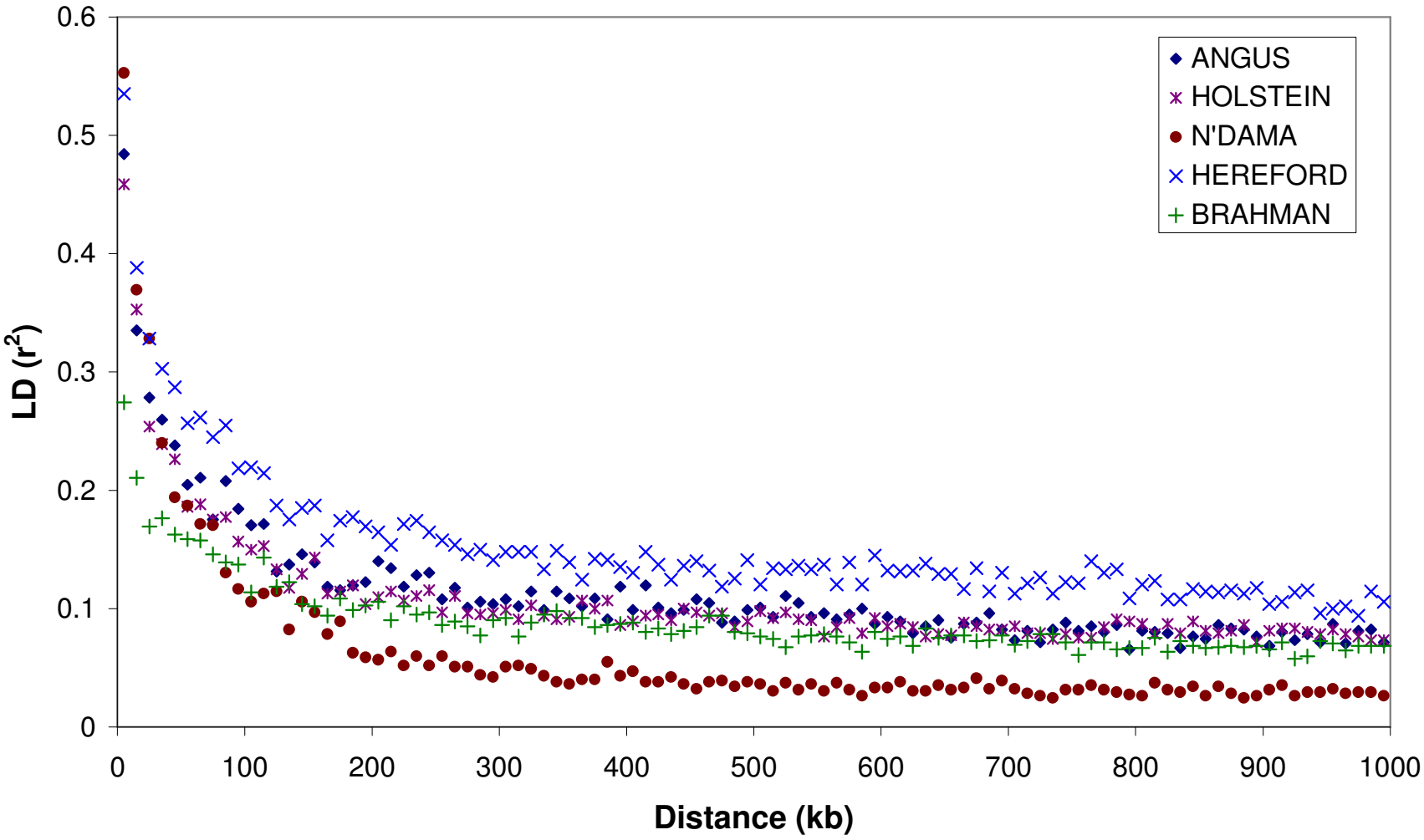
Extent of LD in humans and livestock

Humans…….(Tenesa et al. 2007)



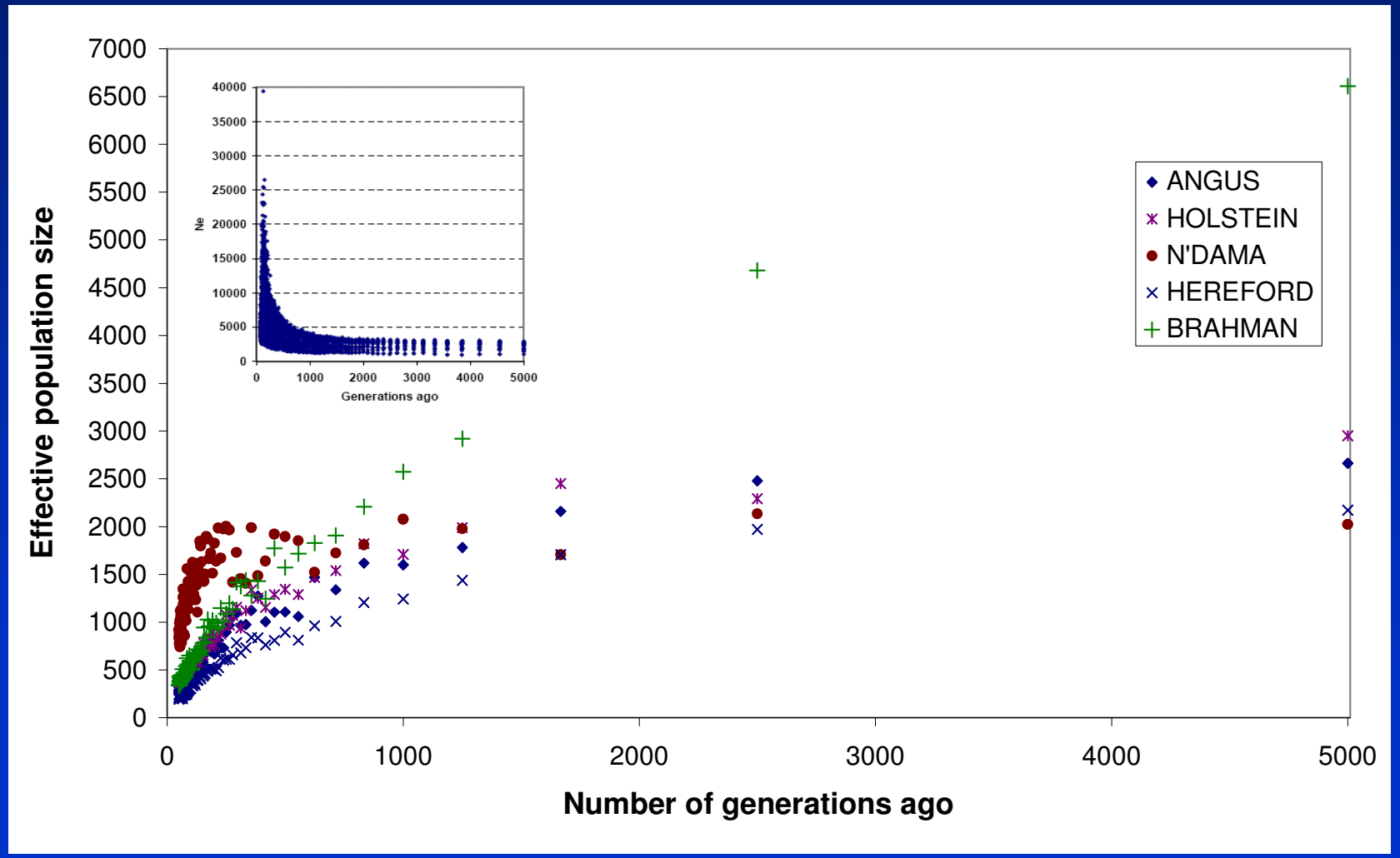
Extent of LD in humans and livestock

And cattle……



Extent of LD in humans and livestock

Population size humans and cattle…..



Implications?

- In Holsteins, need a marker approximately every 200kb to get average r^2 of 0.2 between marker and QTL (eg. 100kb marker-QTL).

Implications?

- In Holsteins, need a marker approximately every 200kb to get average r^2 of 0.2 between marker and QTL (eg. 100kb marker-QTL).
- This level of marker-QTL LD would allow a genome wide association study of reasonable size to detect QTL of moderate effect.

Implications?

- In Holsteins, need a marker approximately every 200kb to get average r^2 of 0.2 between marker and QTL (eg. 100kb marker-QTL).
- This level of marker-QTL LD would allow a genome wide association study of reasonable size to detect QTL of moderate effect.
- Bovine genome is approximately 3,000,000kb
  - 30,000 evenly spaced markers to capture every QTL in a genome scan
  - Markers not evenly spaced ~ 60 000 markers required

Extent of LD in other species

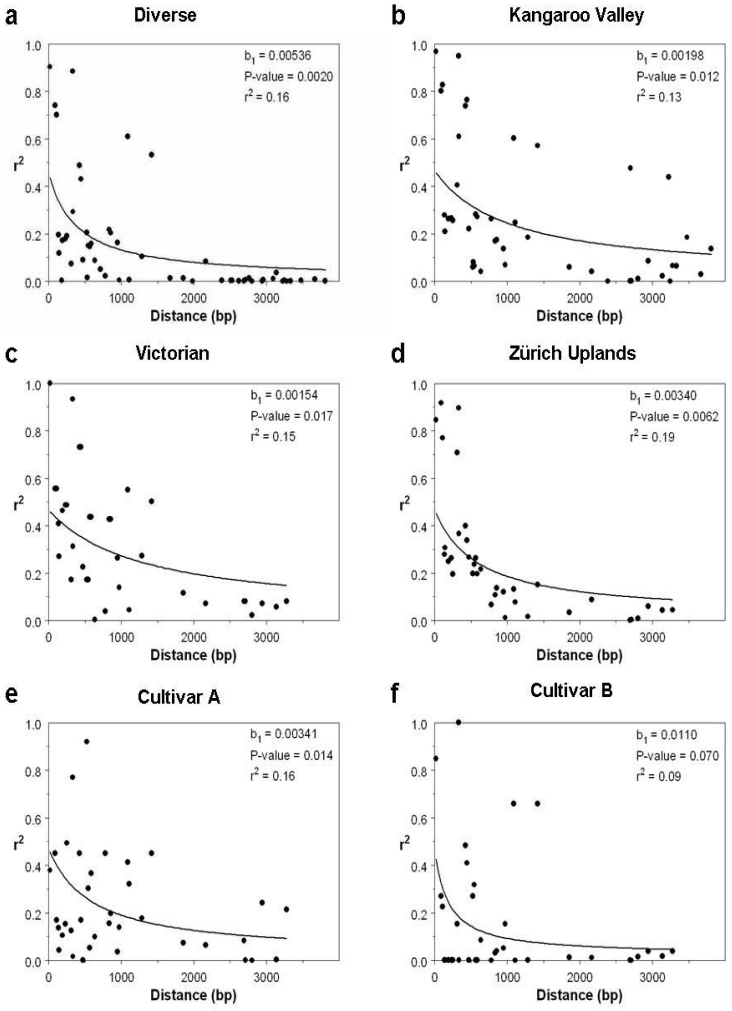
- Pigs
  - Du et al. (2007) assessed extent of LD in pigs using 4500 SNP markers in six lines of commercial pigs.
  - Their results indicate there may be considerably more LD in pigs than in cattle.
  - r^2 of 0.2 at 1000kb.
  - LD of this magnitude only extends 100kb in cattle.
  - In pigs at a 100kb average r^2 was 0.371.

Extent of LD in other species

- Chickens
  - Heifetz et al. (2005) evaluated the extent of LD in a number of populations of breeding chickens.
  - In their populations, they found significant LD extended long distances.
  - For example 57% of marker pairs separated by 5-10cM had $\chi 2' \geq 0.2$ in one line of chickens and 28% in the other.
  - Heifetz et al. (2005) pointed out that the lines they investigated had relatively small effective population sizes and were partly inbred

Extent of LD in other species

- Plants?
  - Perennial ryegrass (Ponting et al. 2007), an outbreeder
  - very little LD
  - Extremely large effective population size?



Linkage disequilibrium

- A brief history of QTL mapping
- Measuring linkage disequilibrium
- Causes of LD
- Extent of LD in animals and plants
- The extent of LD between breeds
- Strategies for haplotyping

Persistence of LD across breeds

- Can the same marker be used across breeds?
  - Genome wide LD mapping expensive, can we get away with one experiment?
- The r^2 statistic between two SNP markers at same distance in different breeds can be same value even if phases of haplotypes are reversed
- However they will only have same value and sign for *r* statistic if the phase is same in both breeds or populations.

Persistence of LD across breeds

		Marker A		
		A1	A2	Frequency
Marker B	B1	0.4	0.1	0.5
	B2	0.1	0.4	0.5
	Frequency	0.5	0.5	

Breed 1

$$r = \frac{\left(freq(A1\_B1) * freq(A2\_B2) - freq(A1\_B2) * freq(A2\_B1)\right)}{\sqrt{freq(A1) * freq(B2) * freq(B1) * freq(B2)}}$$

Persistence of LD across breeds

		Marker A		
		A1	A2	Frequency
Marker B	B1	0.4	0.1	0.5
	B2	0.1	0.4	0.5
	Frequency	0.5	0.5	

Breed 1

$$r = \frac{(0.4*0.4 - 0.1*0.1)}{\sqrt{0.5*0.5*0.5*0.5}}$$

Persistence of LD across breeds

		Marker A		
		A1	A2	Frequency
Marker B	B1	0.4	0.1	0.5
	B2	0.1	0.4	0.5
	Frequency	0.5	0.5	

Breed 1

$$r = 0.6$$

Persistence of LD across breeds

		Marker A		
		A1	A2	Frequency
Marker B	B1	0.4	0.1	0.5
	B2	0.1	0.4	0.5
	Frequency	0.5	0.5	

Breed 1

$$r = 0.6$$

		Marker A		
		A1	A2	Frequency
Marker B	B1	0.3	0.2	0.5
	B2	0.2	0.3	0.5
	Frequency	0.5	0.5	

Breed 2

$$r = 0.2$$

Persistence of LD across breeds

		Marker A		
		A1	A2	Frequency
Marker B	B1	0.4	0.1	0.5
	B2	0.1	0.4	0.5
	Frequency	0.5	0.5	

Breed 1

$$r = 0.6$$

		Marker A		
		A1	A2	Frequency
Marker B	B1	0.2	0.3	0.5
	B2	0.3	0.2	0.5
	Frequency	0.5	0.5	

Breed 2

Persistence of LD across breeds

		Marker A		
		A1	A2	Frequency
Marker B	B1	0.4	0.1	0.5
	B2	0.1	0.4	0.5
	Frequency	0.5	0.5	

Breed 1

$$r = 0.6$$

		Marker A		
		A1	A2	Frequency
Marker B	B1	0.2	0.3	0.5
	B2	0.3	0.2	0.5
	Frequency	0.5	0.5	

Breed 2

$$r = -0.2$$

Persistence of LD across breeds

- For marker pairs at a given distance, the correlation between their r in two populations, corr(r1,r2), is equal to correlation of effects of the marker between both populations
  - If this correlation is 1, marker effects are equal in both populations.
  - If this correlation is zero, a marker in population 1 is useless in population 2.
  - A high correlation between r values means that the marker effect persists across the populations.

Persistence of LD across breeds

- Example

Marker 1	Marker 2	Distance kb	r Breed 1	r Breed 2
A	B	20	0.8	0.7
C	D	50	-0.4	-0.6
E	F	30	0.5	0.6
	Average kb	33	corr(r1,r2)	0.98

Persistence of LD across breeds

- Example

Marker 1	Marker 2	Distance kb	r Breed 1	r Breed 2
A	B	20	0.8	0.7
C	D	50	-0.4	-0.6
E	F	30	0.5	0.6
	Average kb	33	corr(r1,r2)	0.98

Marker 1	Marker 2	Distance kb	r Breed 1	r Breed 2
A	B	500	0.4	0.2
C	D	550	-0.4	-0.2
E	F	450	0.2	-0.3
	Average kb	500	corr(r1,r2)	0.54

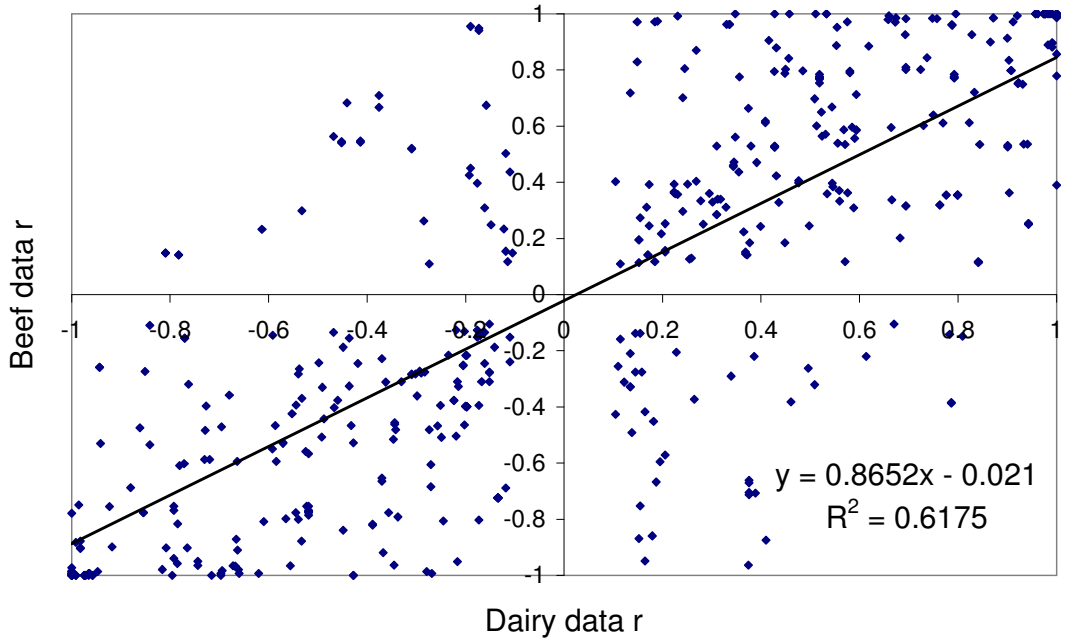
Experiment

- Beef cattle
  - 384 Angus animals chosen for genotyping from Trangie net feed intake selection lines
  - genotyped for 10 000 SNPs

- Dairy Cattle
  - 384 Holstein-Friesian dairy bulls selected from Australian dairy bull population
  - genotyped for 10 000 SNPs

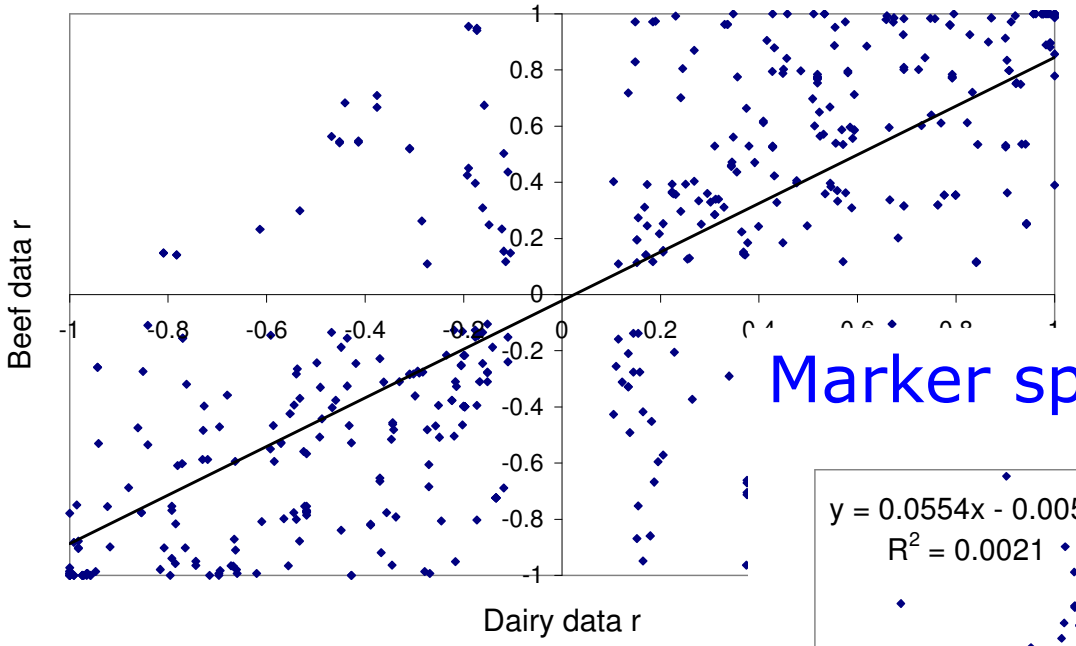
Holstein-Angus example

Marker spacing 10kb-50kb

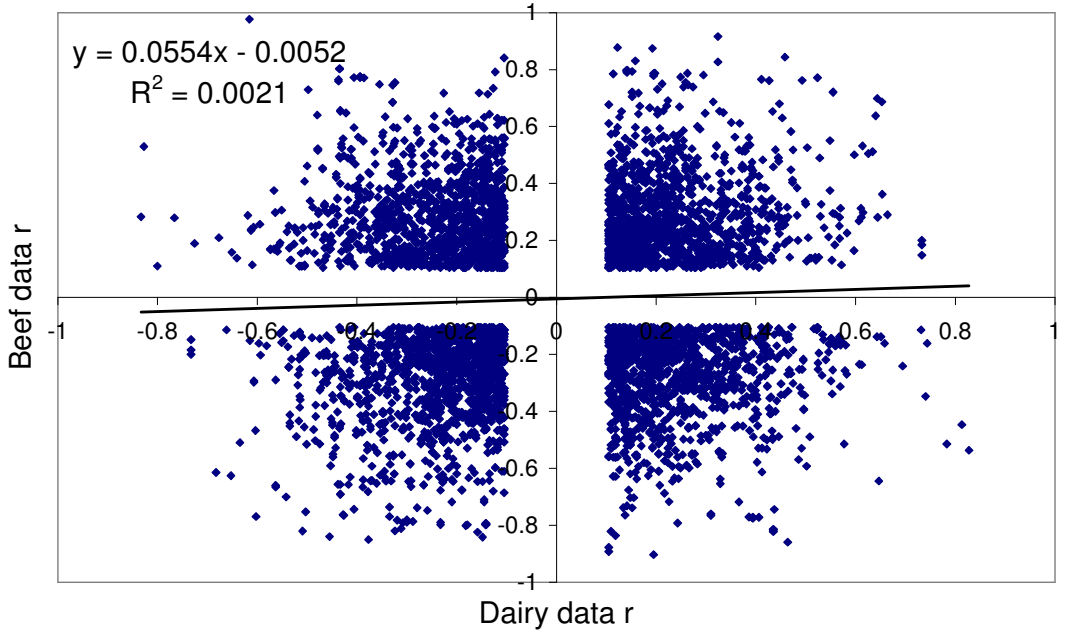


Holstein-Angus example

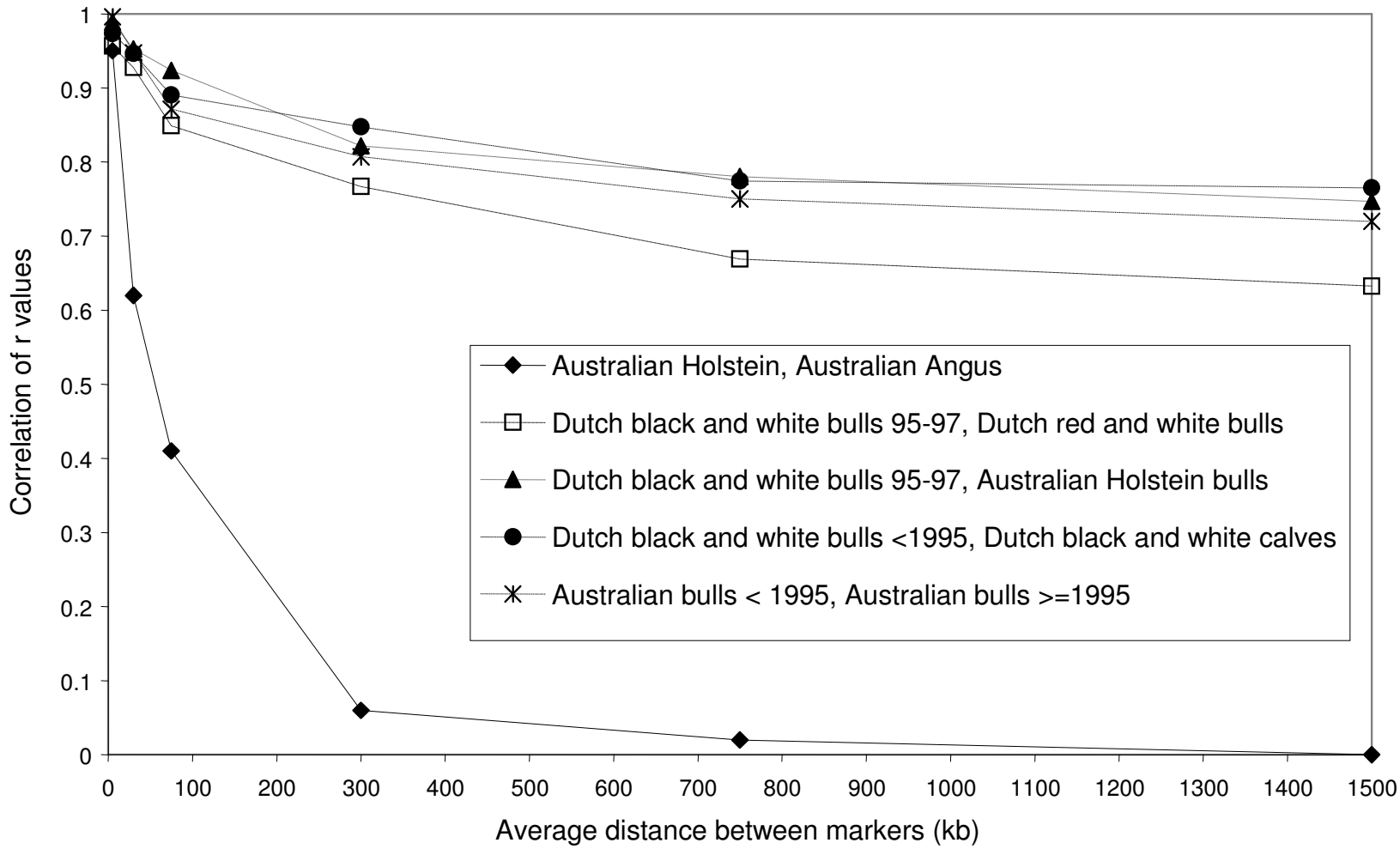
Marker spacing 10kb-50kb



Marker spacing 1000kb-2000kb



LD across breeds



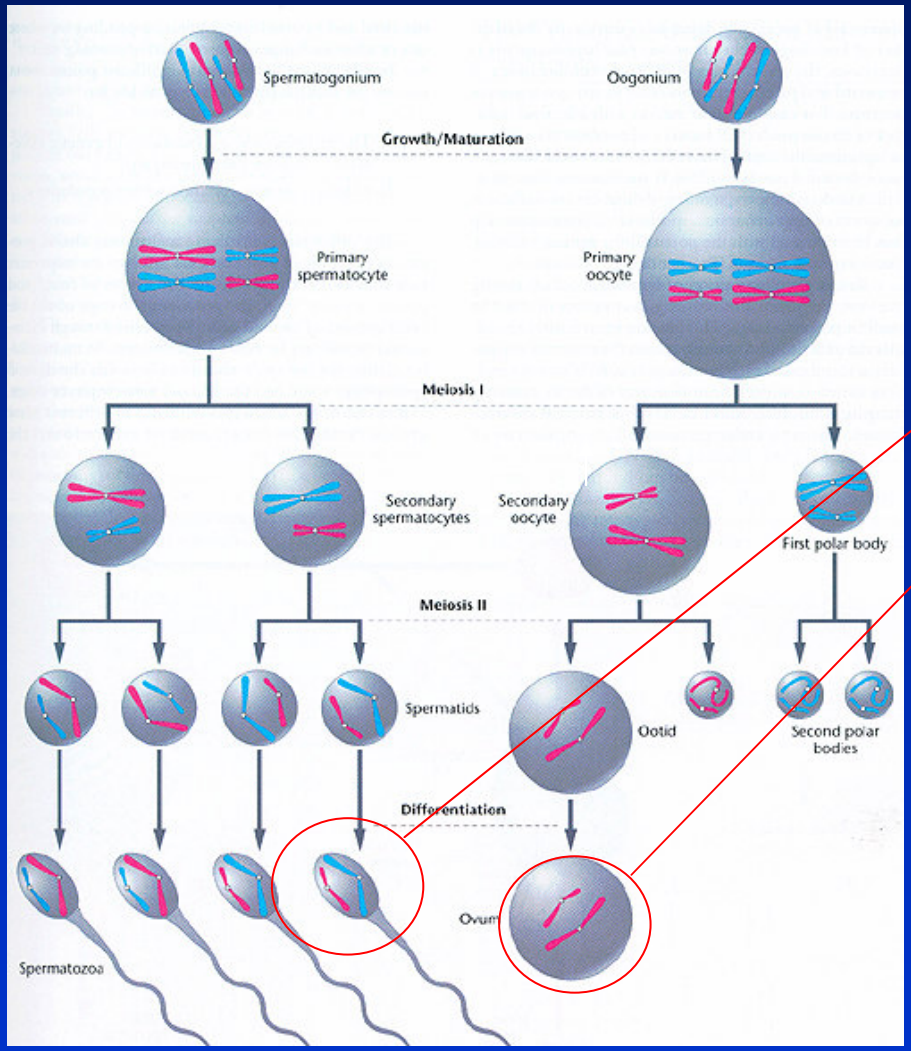
Persistence of LD across breeds

- Recently diverged breeds/lines, good prospects of using a marker found in one line in the other line
- More distantly related breeds, will need very dense marker maps to find markers which can be used across breeds
- Important in multi breed populations
  - eg. beef, sheep, pigs

Linkage disequilibrium

- A brief history of QTL mapping
- Measuring linkage disequilibrium
- Causes of LD
- Extent of LD in animals and plants
- The extent of LD between breeds
- Strategies for haplotyping

Definition of Haplotype



Paternal gamete

Maternal gamete

SNP1 SNP2 SNP3 SNP4

----A—----T—----C----—G—

Haplotyping

- LD statistics such as r^2 use haplotype frequencies

  D = freq(A1_B1)*freq(A2_B2)-
  freq(A1_B2)*freq(A2_B1)

  $\mathbf{r^2}=D^2/[freq(A1)*freq(A2)*freq(B1)*freq(B2)]$

- Need to infer haplotypes

Haplotyping

- In large half sib families
  - which of the sire alleles co-occur in progeny most often
    - Dam haplotypes by subtracting sire haplotype from progeny genotype
- Complex pedigrees
  - Much more difficult, less information per parent, account for missing markers, inbreeding
  - *SimWalk*
- Randomly sampled individuals from population
  - Infer haplotypes from LD information!
  - *PHASE*

Haplotyping

- PHASE program:
  - Start with group of unphased individuals

Genotypes

121122
121122

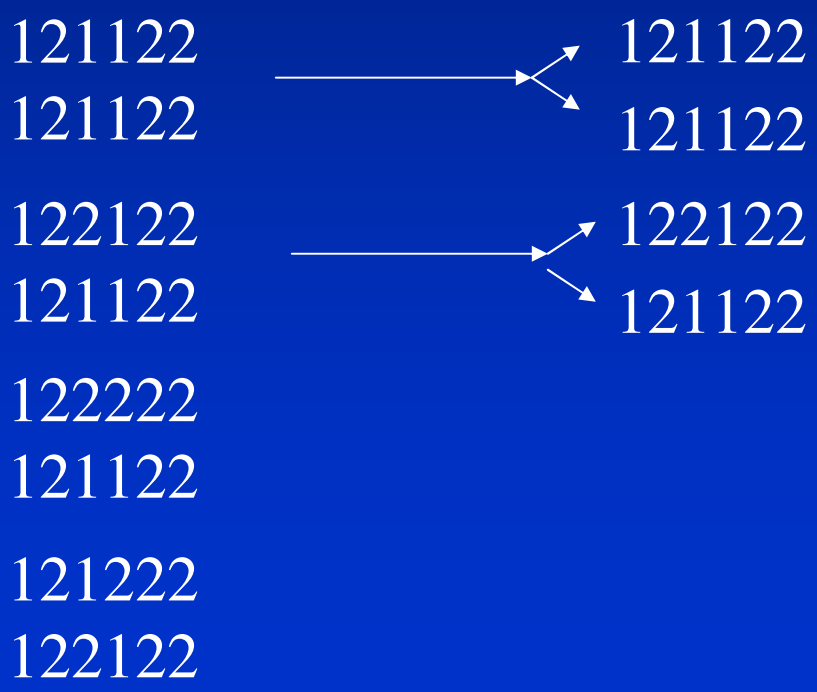
122122
121122

122222
121122

121222
122122

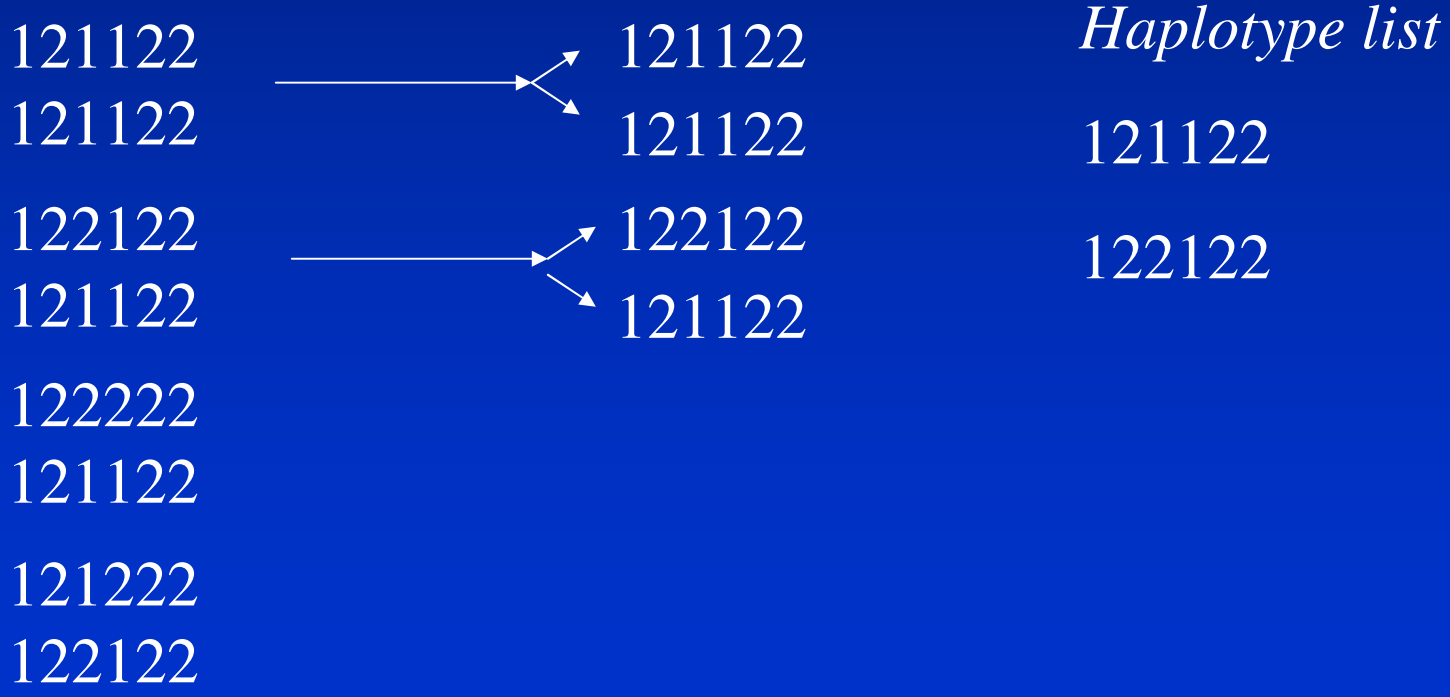
Haplotyping

- PHASE program:
  - Sort haplotypes for unambiguous animals



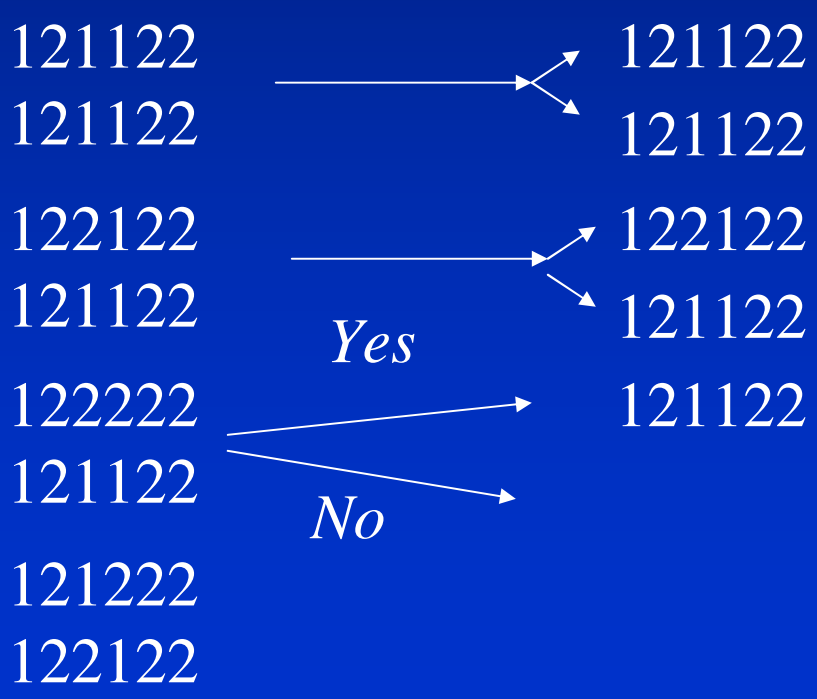
Haplotyping

- PHASE program:
  - Add to list of haplotypes in population



Haplotyping

- PHASE program:
  - For an ambiguous individual, can haplotypes be same as those in list (most likely=most freq)?



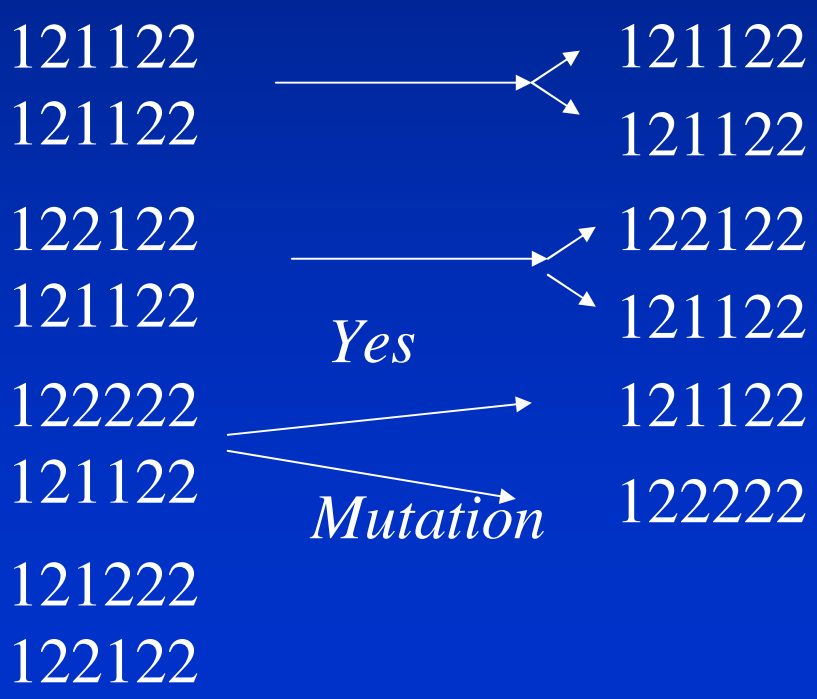
Haplotype list

121122

122122

Haplotyping

- PHASE program:
  - If no, can we produce haplotype by recombination or mutation (likelihood on basis of length of segment and num markers)



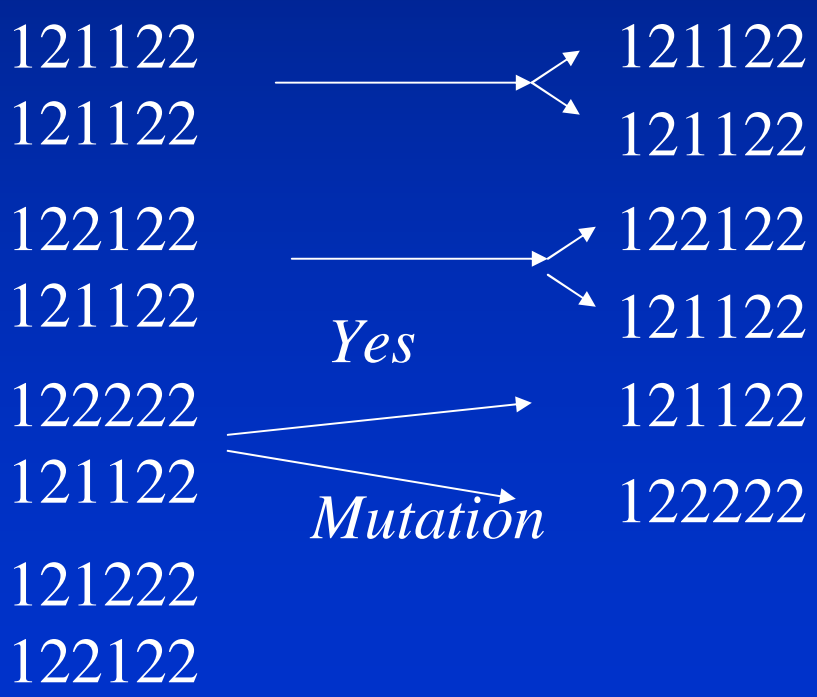
Haplotype list

121122

122122

Haplotyping

- PHASE program:
  - Update list



Haplotype list

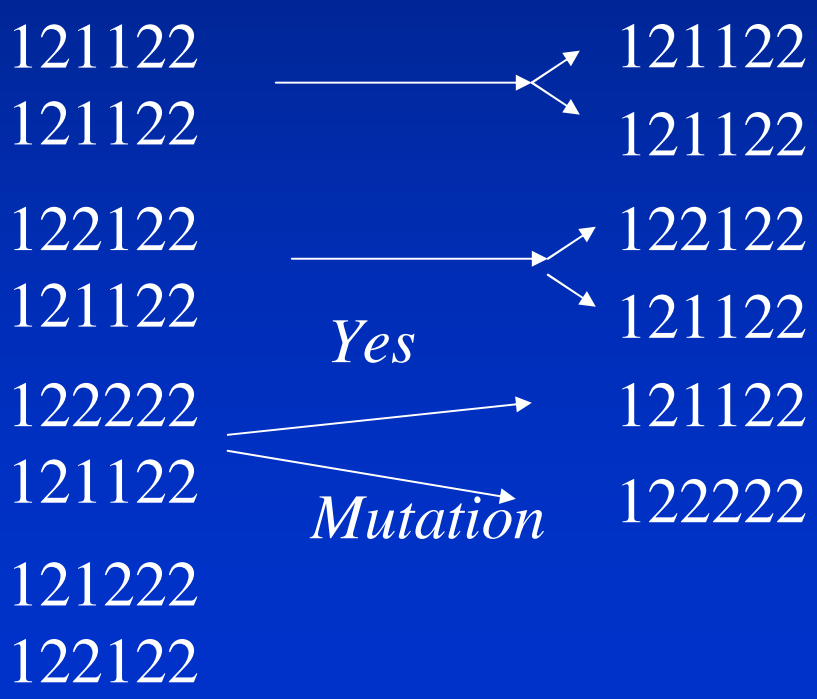
121122

122122

122222

Haplotyping

- PHASE program:
  - If we randomly choose individual each time, produces Markov Chain



Haplotype list

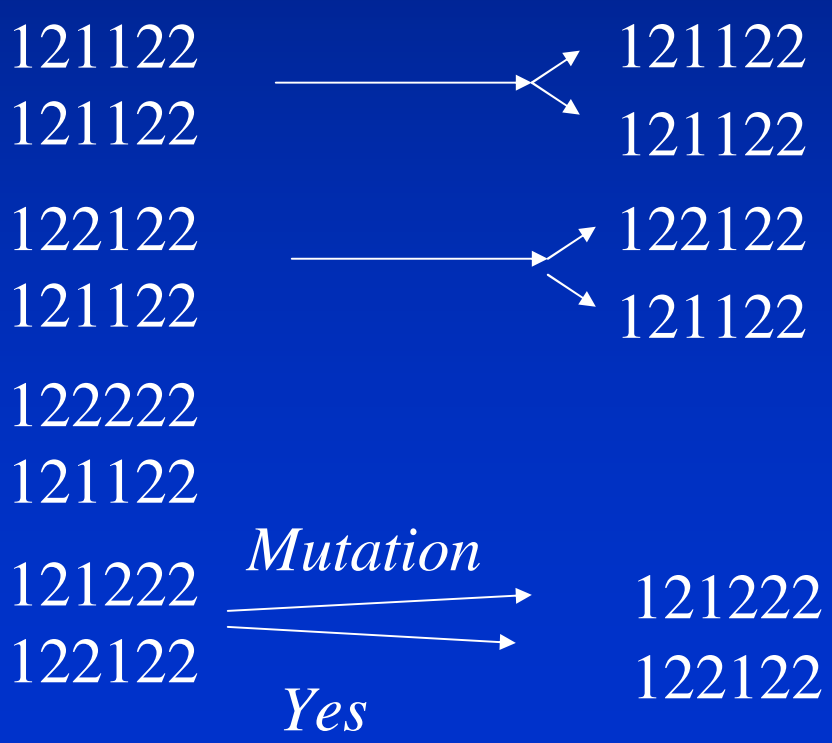
121122

122122

122222

Haplotyping

- PHASE program:
  - If we randomly choose individual each time, produces Markov Chain



Haplotype list

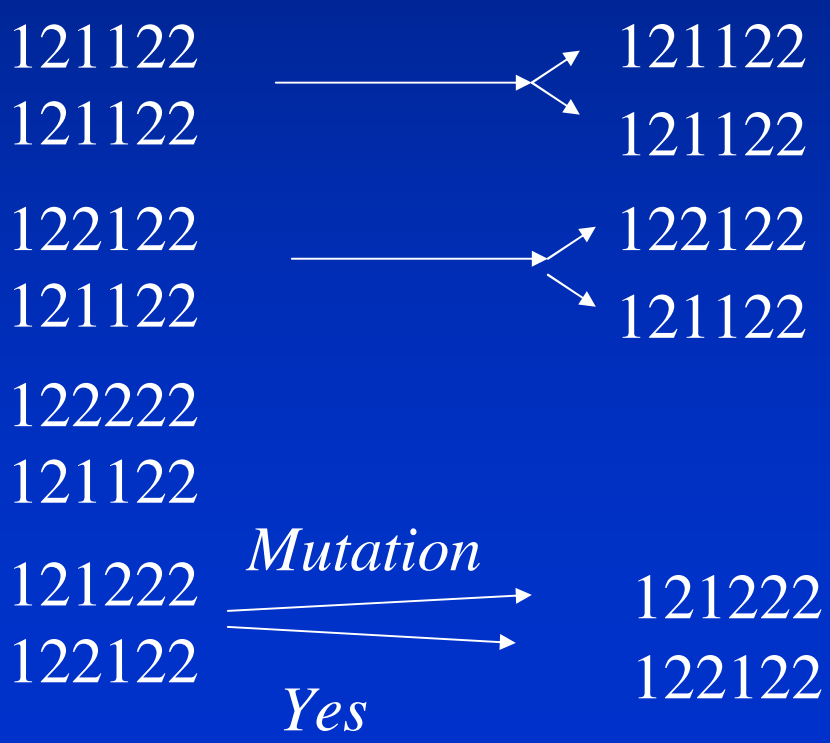
121122

122122

122222

Haplotyping

- PHASE program:
  - If we randomly choose individual each time, produces Markov Chain



Haplotype list

121122

122122

122222

121222

Haplotyping

- PHASE program
  - After running chain for large number of iterations,
    - End up with most likely haplotypes in the population, haplotype pairs for each animal (with probability attached)
  - Only useful for *very short intervals, dense markers*!
  - But very accurate in this situation
  - Used to construct human hap map

Linkage disequilibrium

- Extent of LD in a species determines marker density necessary for LD mapping
- Extent of LD determined by population history
- In cattle, r^2~0.2 at 100kb ~ 60 000 markers necessary for genome scan
- Extent of across breed/line LD indicates how close a marker must be to QTL to work across breeds/lines