# Graphical Models for Genetic Analyses

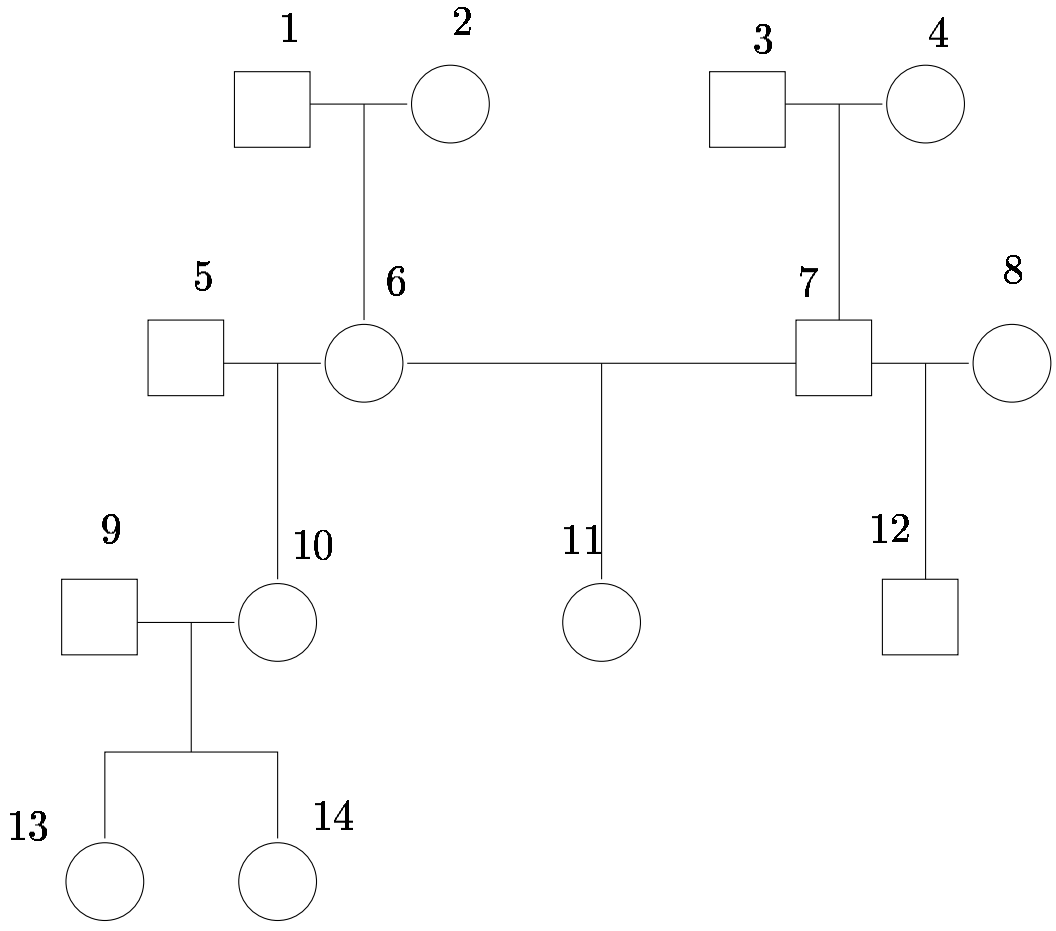
**Aarhus University, Fall 2003, Lecture 6**

Steffen L. Lauritzen, Aalborg University

# Overview

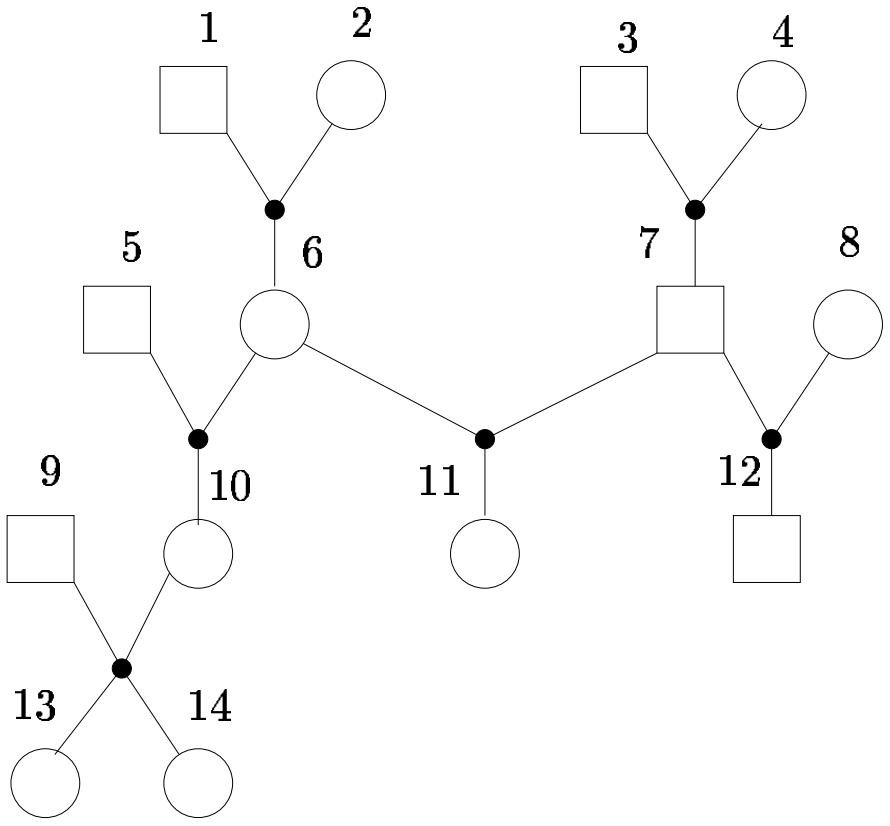
- Pedigrees
- Human DNA
- Bayesian networks and pedigrees
- Problems of linkage
- Pedigree uncertainty
- Forensic genetics

# Pedigree




Male individuals represented by squares, female by circles. Individual 6 is child of individuals 1 and 2.

# Marriage graph



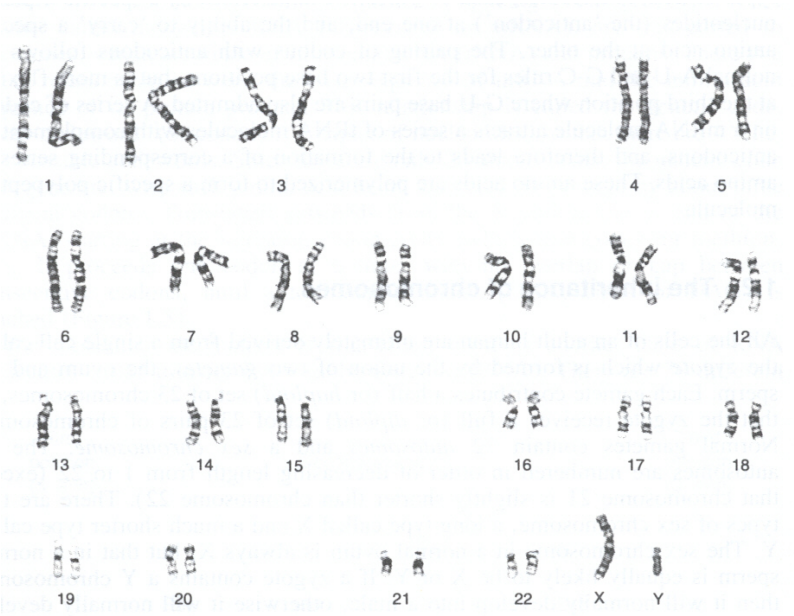

Alternative representation of a pedigree, often known as *marriage graph*.

# Pedigree analysis

Analysis of data associated with pedigrees is of interest in several contexts:

- Epidemiology of genetically affected diseases
- Animal breeding
- Genetic counseling
- Forensic identification
- Identifying and understanding genetic relationships

# Human chromosomes



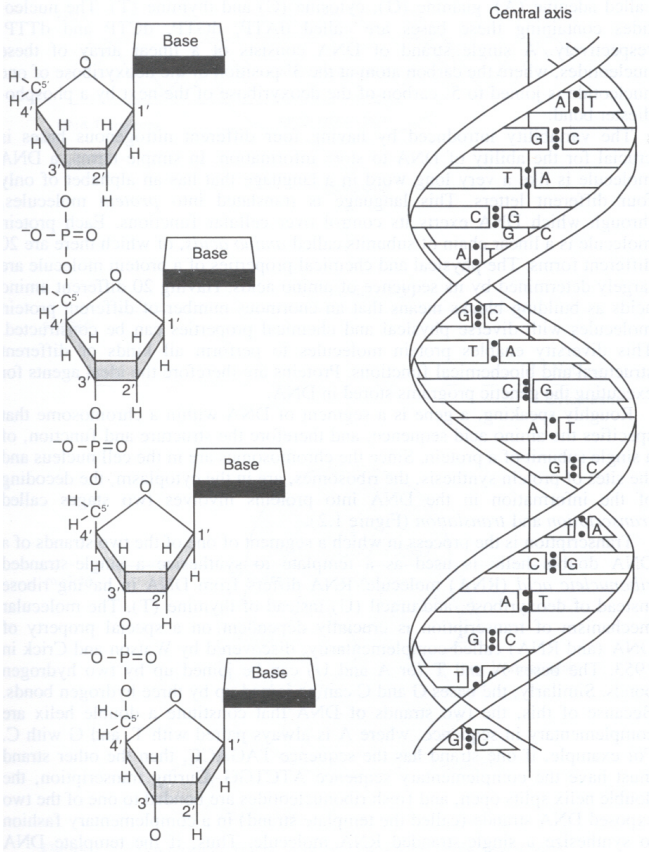

23 pairs of chromosomes in nucleus of human cell.

One pair determines gender: male XY, female XX. Other 22 are *homologous* pairs of DNA molecules.

*Only homologous pairs are considered in this lecture.*

# DNA molecules

A double helix composed by 4 different nucleotides: C, A, G, and T, binding in pairs C–G and A–T.



# Genetic markers

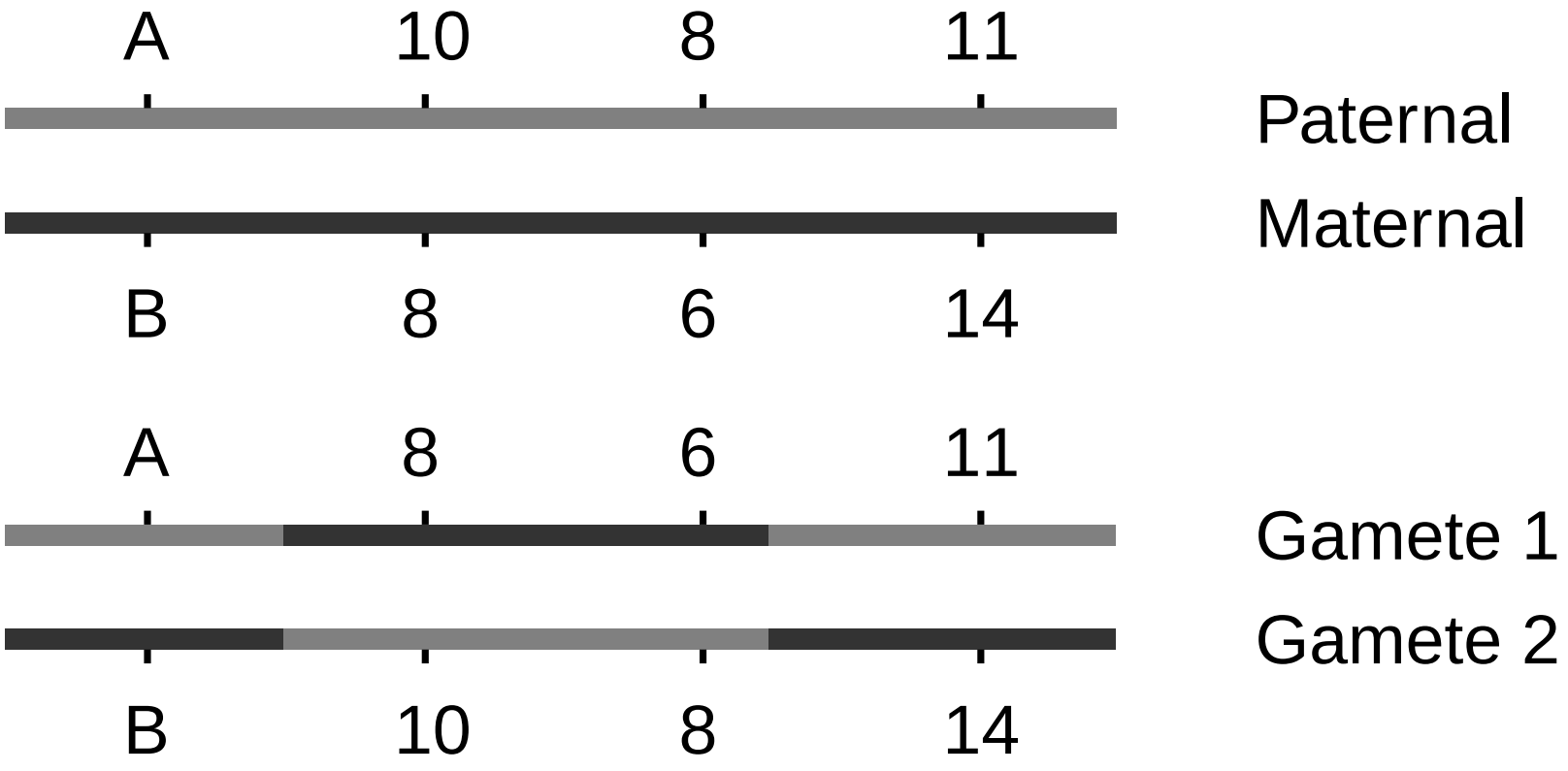
An area on a chromosome is a *locus* and the DNA composition on that area is an *allele*.

A locus thus corresponds to a (random) variable and an allele to its realised state.

The *genotype* of an individual is the unordered pair of alleles. Not always observable. The *phenotype* of an individual is an observable characteristic, e.g. eye colour.

A DNA *marker* is a known locus where genotype can be identified in the laboratory.

# Meiosis



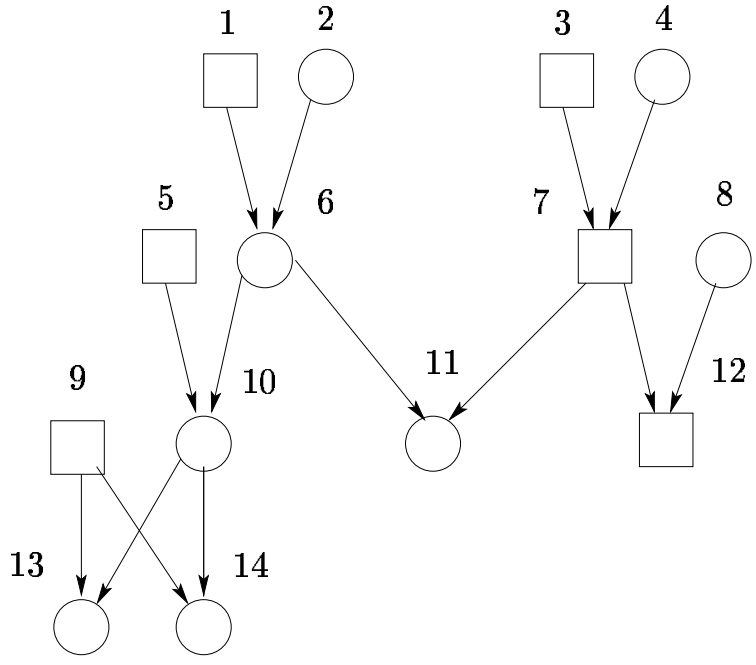

During human reproduction cells form *gametes*, where maternal and paternal DNA is mixed. A child receives one randomly chosen gamete from mother and one from father, to form a new homologous pair.

# Bayesian networks for pedigrees

Different alternatives available

- *Genotype network:* Nodes represent genotypes of individuals.
- *Allele network:* Nodes represent alleles, two for each individual.
- *Segregation network:* Nodes represent alleles, two for each individual, or *segregation indicators*, i.e. whether paternal or maternal allele is segregated during meiosis.

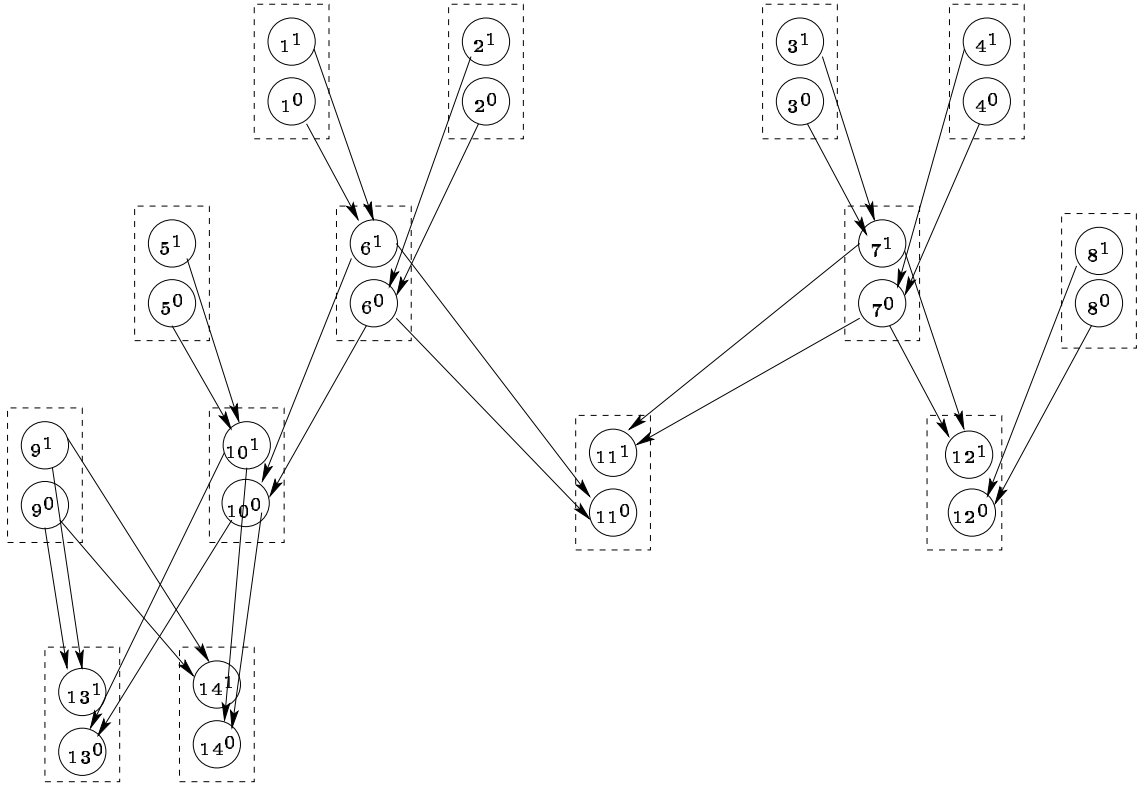
# Genotype network




*Mendel's first law* implies that local Markov property holds. State space at each node is the *genotype*, i.e. unordered pair of alleles.

Size of specification $n(a(a+1)/2)^3 = O(na^6)$.

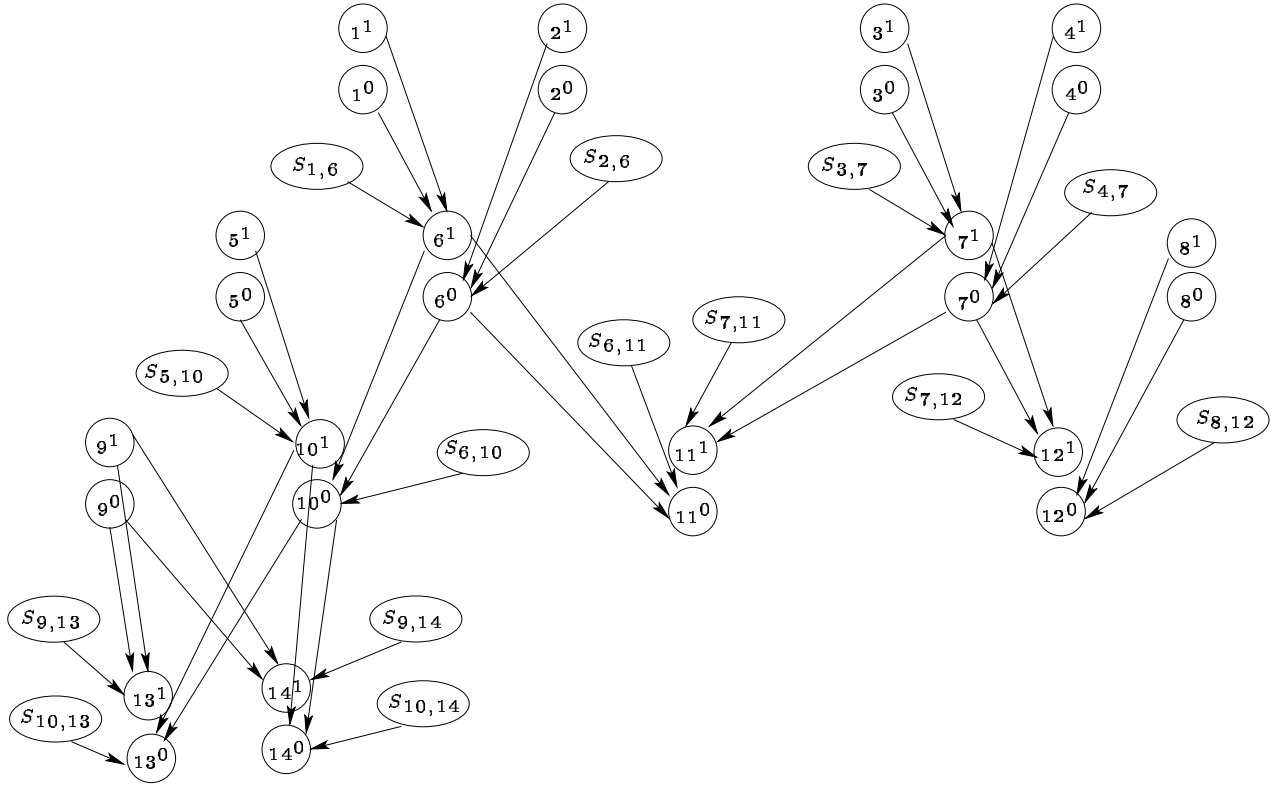
# Allele network




Each individual is represented with two alleles. Visually more complex, but computationally simpler.

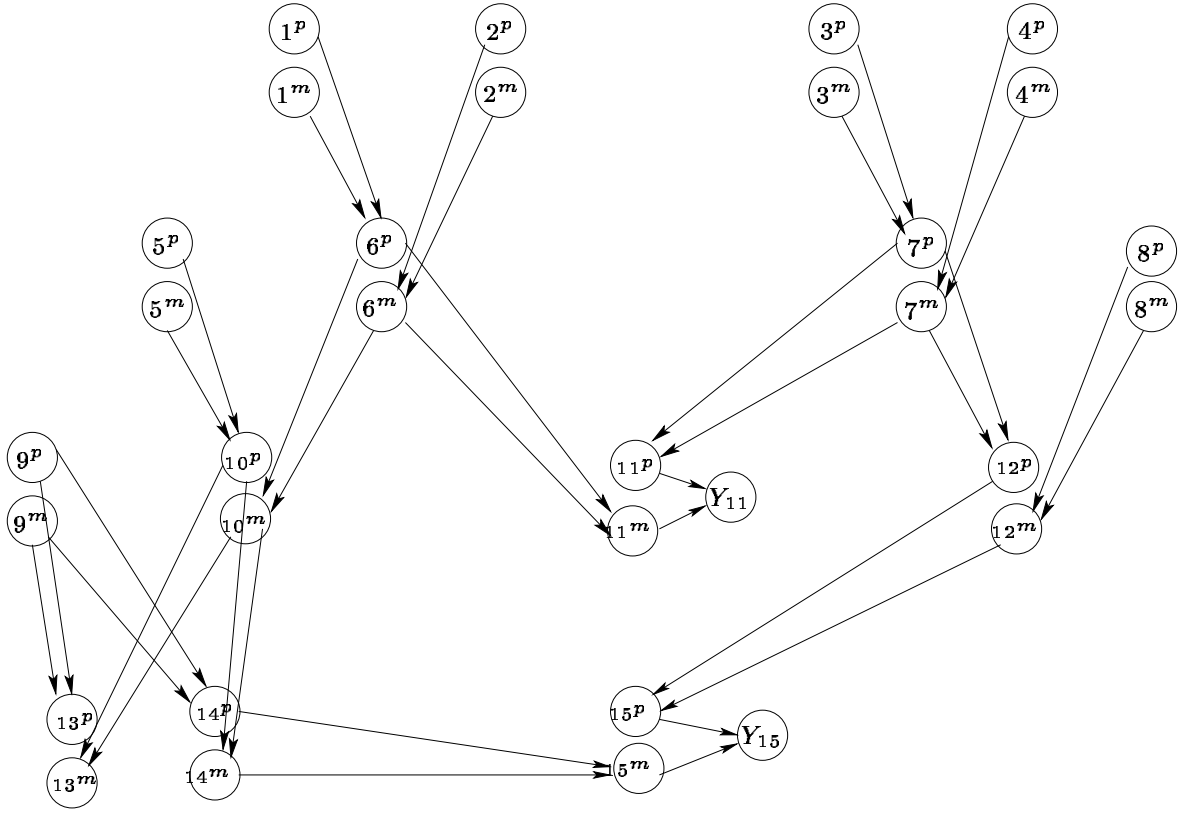
Size of specification $2na^3$.

# Segregation network



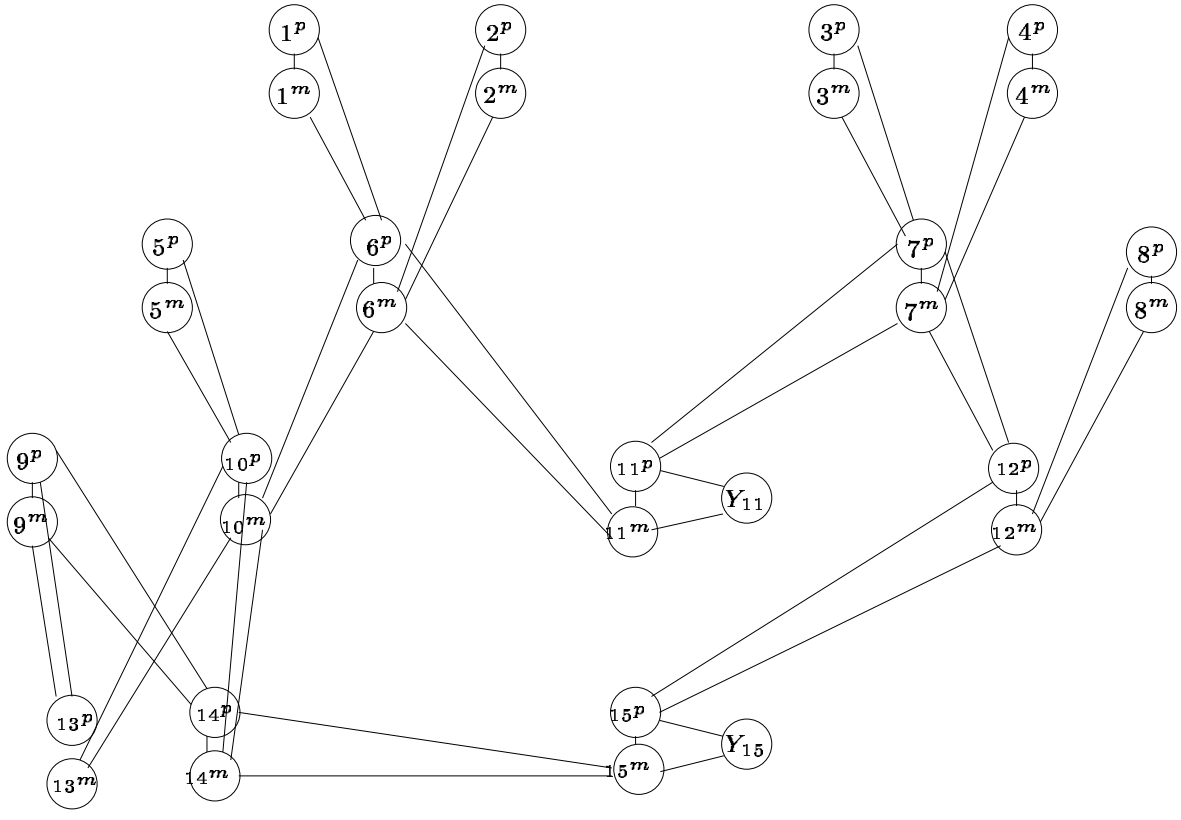

Ovals represent *segregation indicators:* 1 for paternal transmission, 0 for maternal. State at nodes of graph children is deterministic function of states at graph parent nodes. Size $4na^3$, but more expressive.

# Adding phenotypic information




Allele network with additional individual and phenotypic information on two individuals.

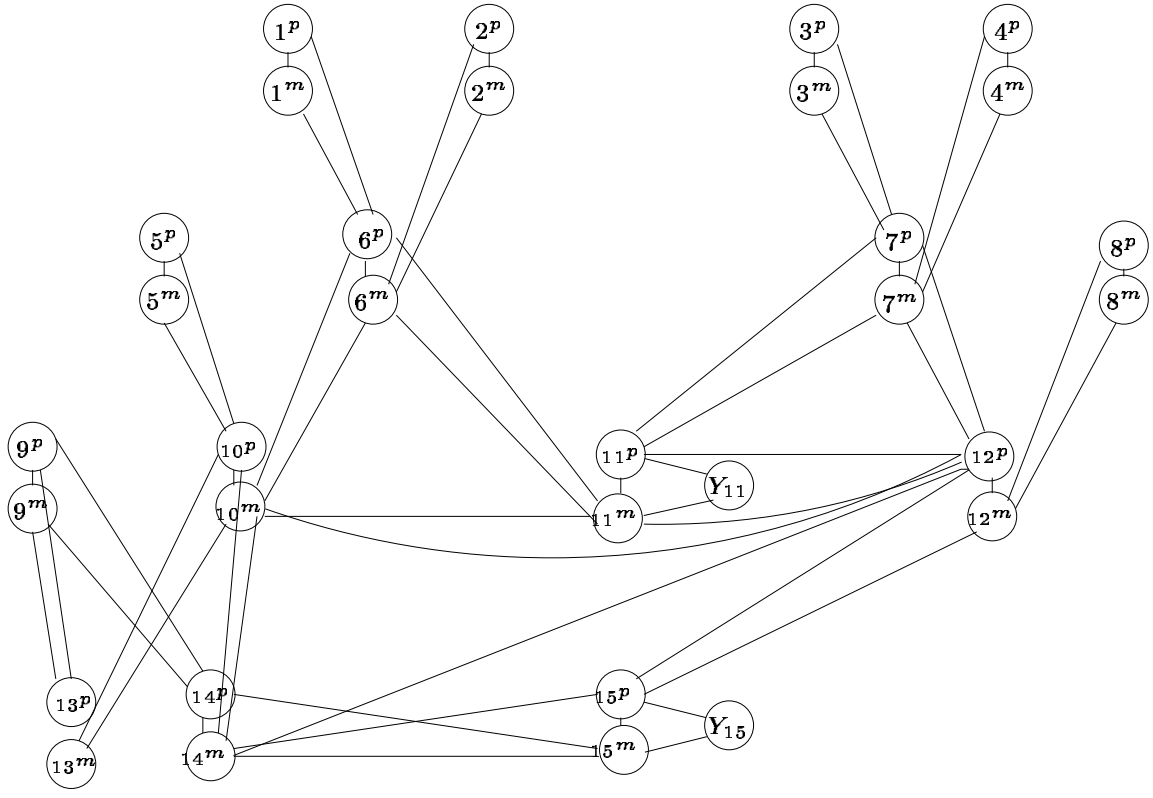
# Dependence graph




Dependence graph (moral graph) reflects factorisation of joint density into terms of form

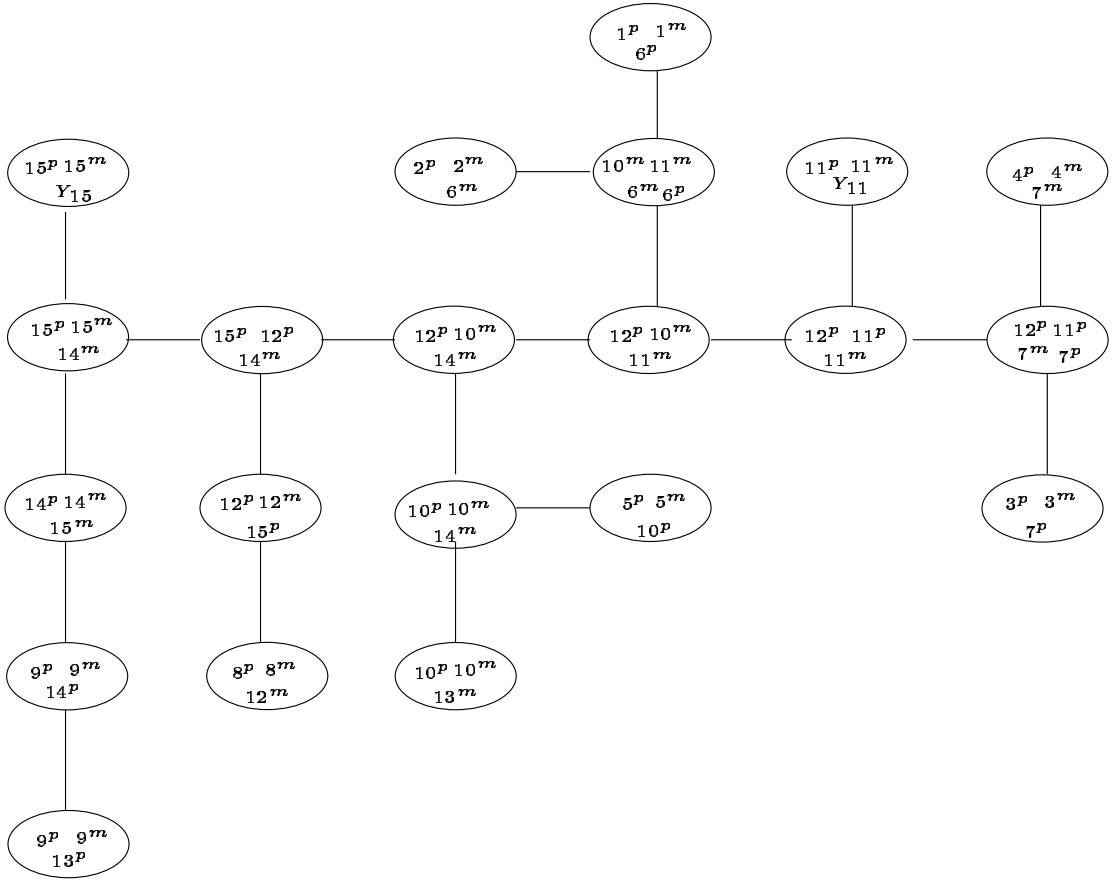
$$\phi(x_{\{v\}\cup \mathrm{pa}(v)}) = p(x_v \mid x_{\mathrm{pa}(v)}).$$

# Triangulation




Links are added to make graph *triangulated*, i.e. so that all cycles of length $\geq 4$ have chords.

# Junction tree




Cliques are arranged into a tree with $C_1 \cap C_2 \subseteq D$ for all cliques $D$ on path between $C_1$ and $C_2$.

# Result of basic computation

Normalisation constant after CollInfo gives *likelihood* for observations $p(x_E)$, useful for estimating unknown parameters of genetic model.

DistInfo gives $p(x_v \mid x_E)$ which *predicts* genetic information at other nodes, useful e.g. for identifying inheritance patterns of disease genes.

# Linkage analysis

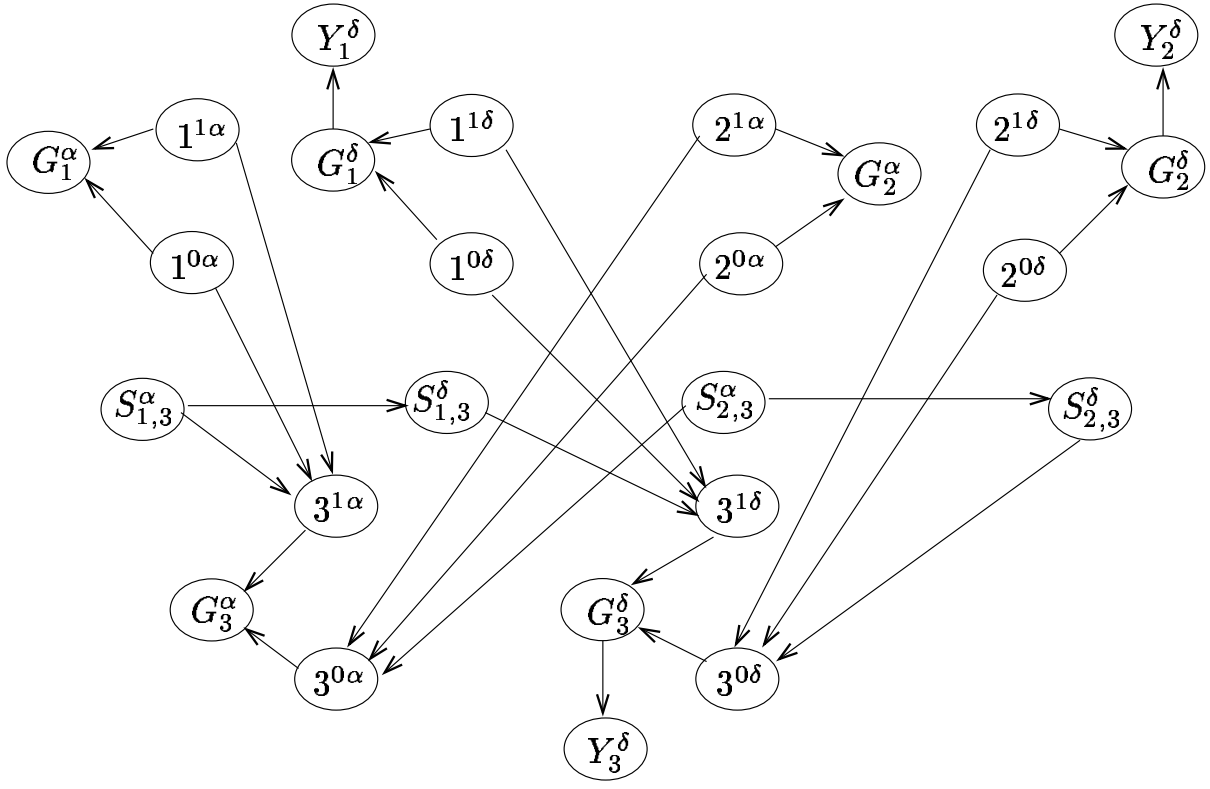
If two loci are close, it is more probable that paternal alleles are inherited together.

*recombination fraction* between two loci $r$ is the probability that the segregated alleles come from different chromosomes. $0 \leq r \leq 1/2$.

If distances along chromosome are measured in *genetic map distance* $\lambda = -\{\log(1-2r)\}/2$ measured in Morgans.

*Haldane's model* says that cross-overs happen according to a Poisson process of rate 1 per Morgan.

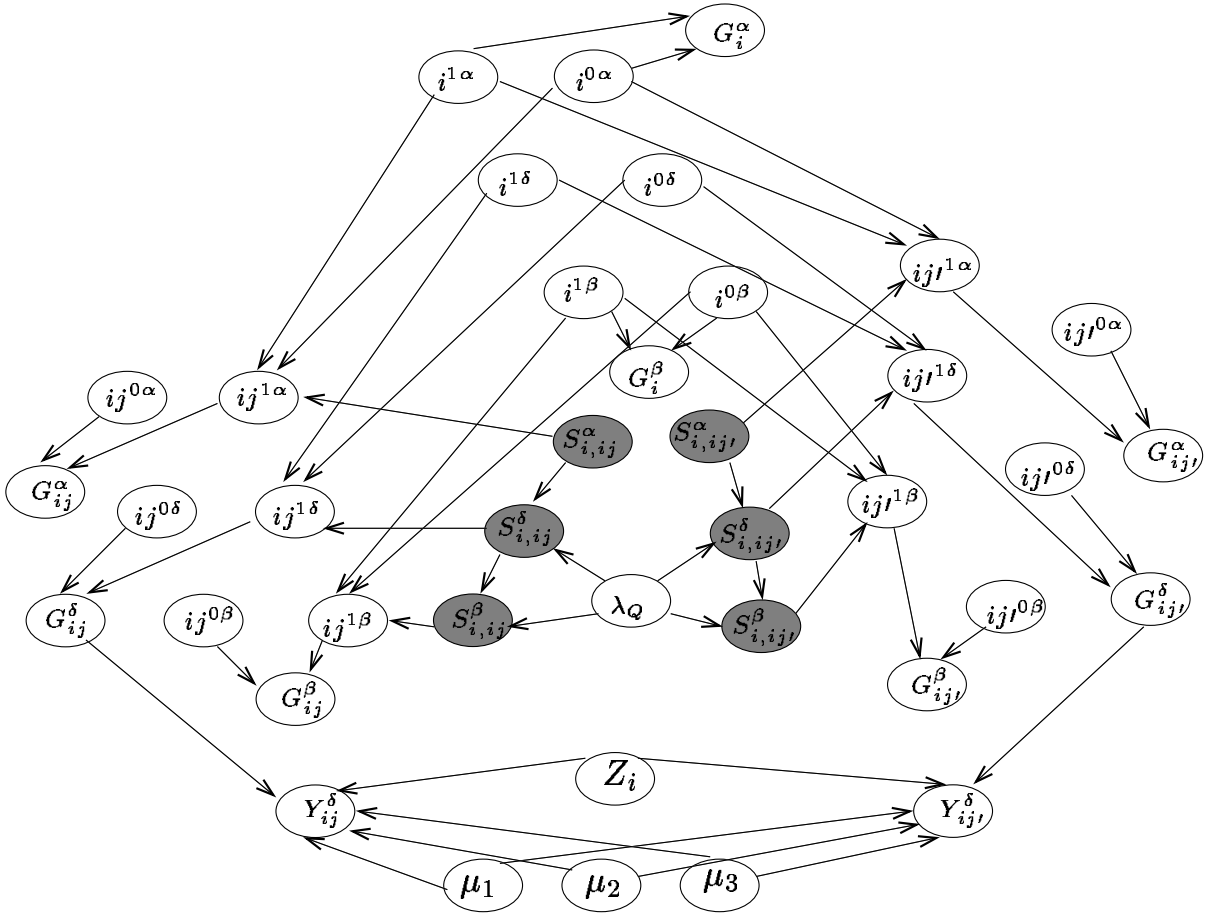
# Linkage analysis




Segregation network can express dependence between loci. Here two loci of which one is a known marker.

$P(S_{i,j}^\delta = 1 \mid S_{i,j}^\alpha = 1) = 1 - r$, etc.

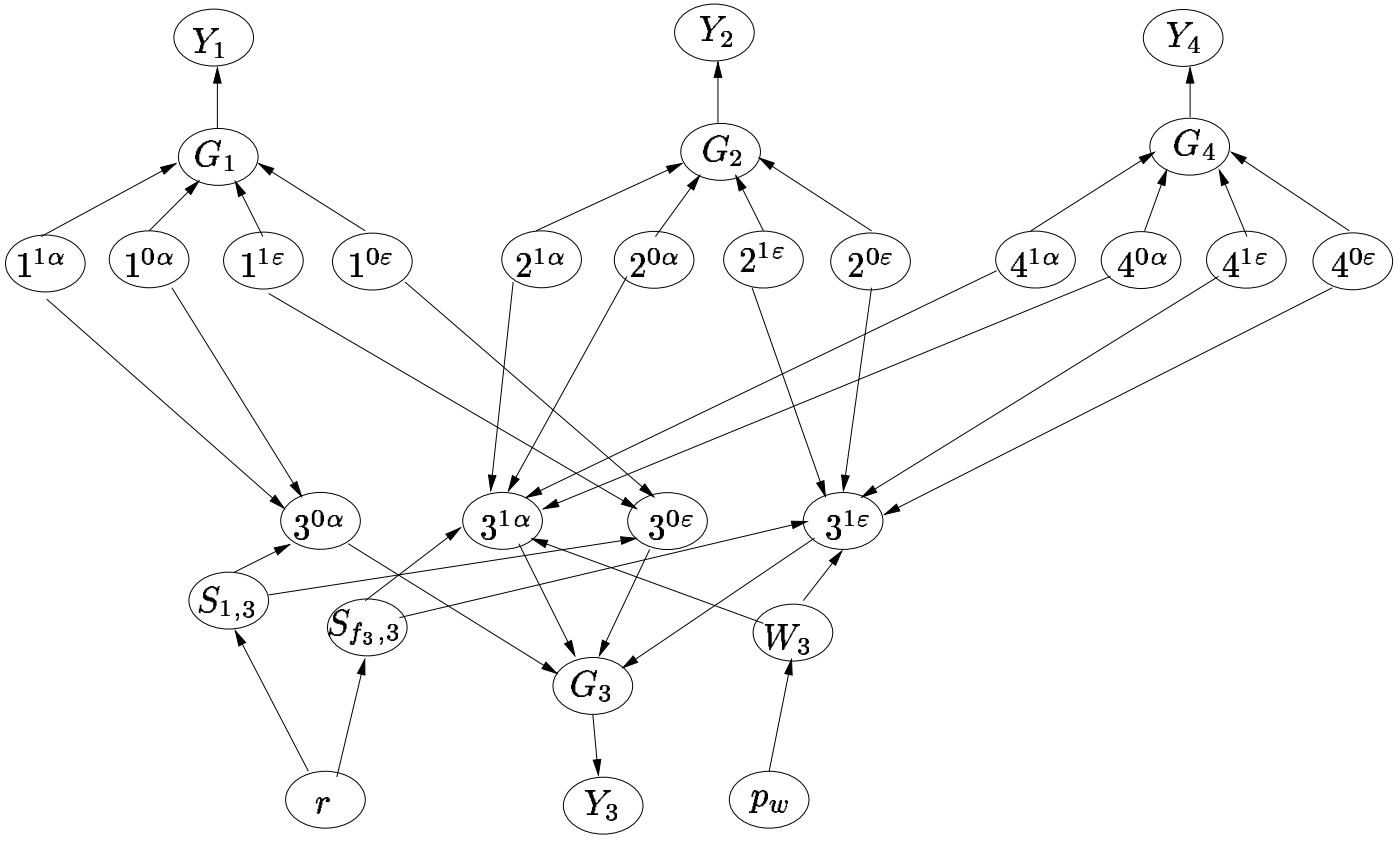
# QTL mapping




Three loci: Two known markers, and a possible major gene for a quantitative trait (milk yield) is hunted.

QTL abbreviates Quantitative Trait Locus.

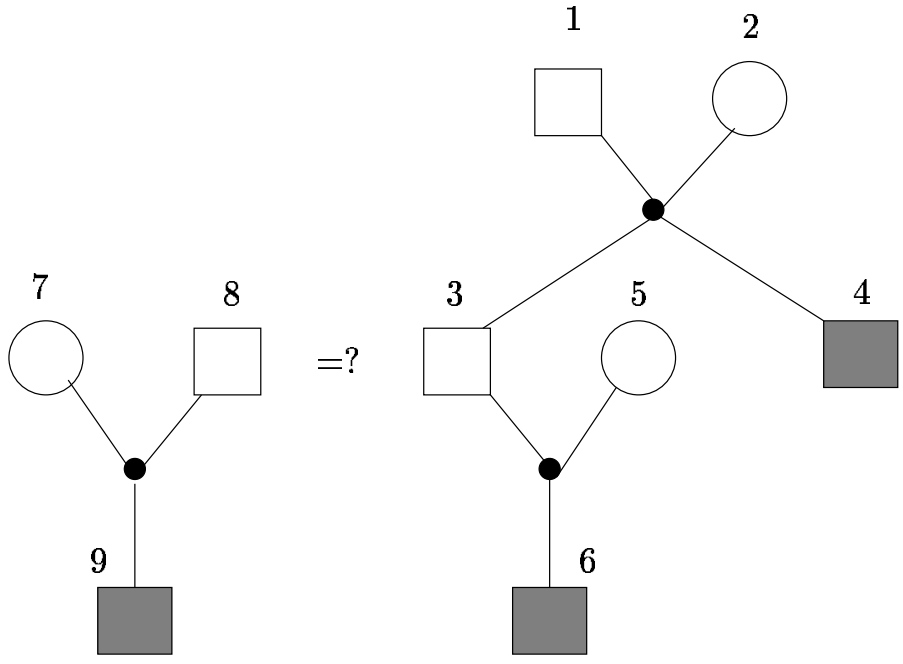
# Fur colour of foxes




Female foxes are mated with two males.

Network describes a two-locus linkage model for fur colour of foxes.

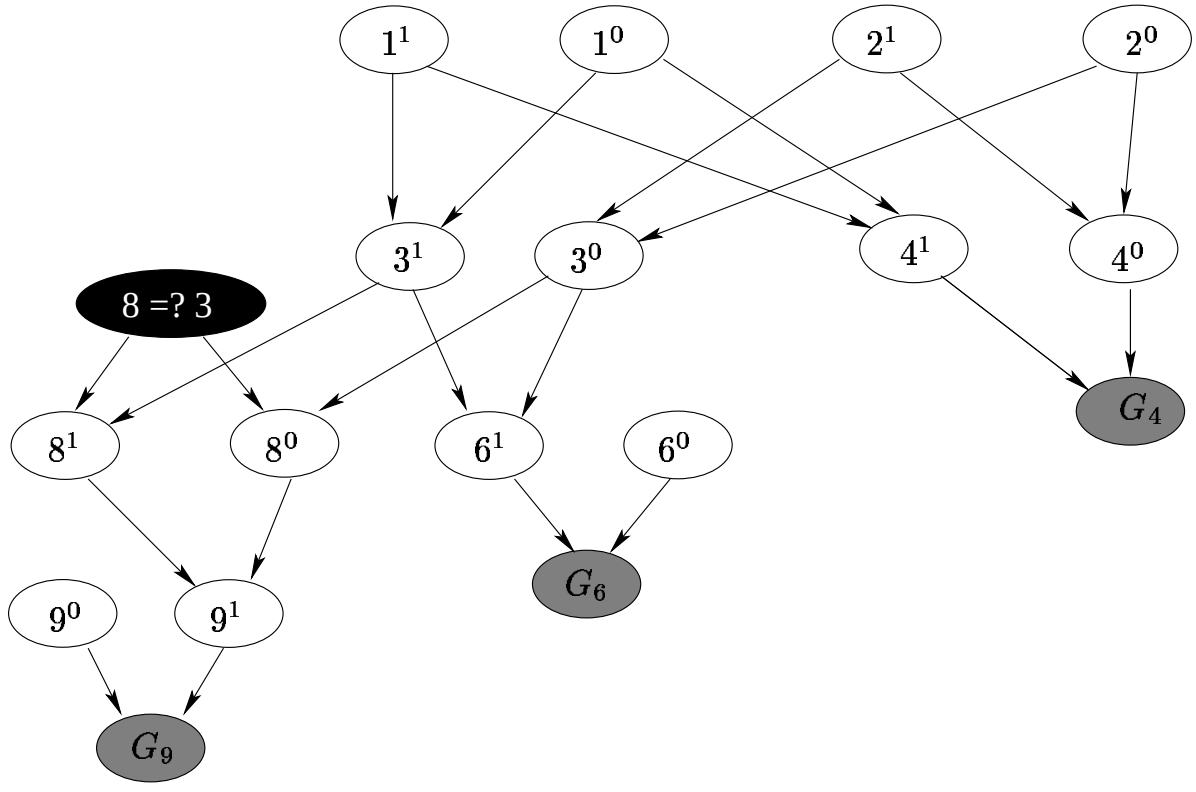
# Disputed paternity




Individual 9 claims to be son of individual 3, but with different mother. DNA is available from individuals 9, 6, and 4.

6 is a known son of 3, and 4 is known brother of 3.

# BN representation




Bayesian network representation of paternity problem. The black “target node” is binary and indicates whether the alleles from individual 8 are drawn at random or equal to those of 3.

# Conclusions

- Many problems associated with pedigree analysis have a natural formulation in terms of Bayesian networks
- Flexibility and modularity of Bayesian networks yields possibilities for incorporating variations of pure pedigree problems
- General local computational algorithm makes case-specific algorithms redundant.
- Variant of algorithm (random propagation) makes efficient basis for developing Markov chain Monte Carlo methods when exact computation becomes unfeasible.