

Chapter 2

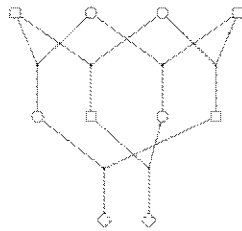
Data on related individuals:
one locus

2.1.1 Pedigrees and relationships

- **Related** : individuals having a common ancestor (implies a biological relationship)
- **Inbred**: individuals whose parents are related (implies the maternal and paternal genes can descend from single ancestral gene).
- **Unilateral (one-sided) and bilateral (two-sided) relationships** (see page 1.2.3):
 - unilateral: half-sibs, aunt, niece, cousins
 - bilateral: sibs, double first cousins, etc.
- **Cousin-type relationships**:
 - Half, full, and double (cousin) relationships
 - Cousins of different degree:
 - n th cousins k times removed

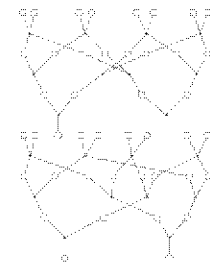
Example of a complex relationship: quadruple half first cousins.

- The figure on this page shows quadruple half first cousins (QHFC).
- This is a relationship in which each of the mother and the father of each individual is related to both the mother and the father of the other.
- The two parents of each individual are not related. There is no inbreeding.
- We will see this example again in 2.3.4.



Another example: two versions of quadruple second cousins

- This figure shows two versions of quadruple second cousins, one above the other.
- In the upper version the fathers are double-first-cousins, and so are the mothers.
- In the lower version there is a cyclic pattern of marriage among four grandparental sib pairs.
- In both cases, the two individuals at the bottom of each half-pedigree are second cousins 4 times over, but there is no inbreeding.



2.1.2 GENE IDENTITY BY DESCENT (ibd)

- **RELATIVES ARE SIMILAR** because they have ibd genes, that are copies of the same gene in a common ancestor.
- ibd genes are of the same allelic type, non-ibd genes are of independent types. See the mother-baby pairs in 1.4.3.
- **NOTE**: ibd is defined relative to given pedigree or time point.
- Pedigree or relationship determines probabilities of ibd, which determine probabilities of joint genotypes which determine probabilities of joint phenotypes that is, similarity among relatives.

2.2.1 KINSHIP and INBREEDING

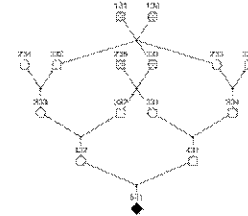
- The simplest pedigree-defined probabilities of gene ibd are the coefficients of kinship (ψ) and inbreeding (f), which measure ibd between two genes.
- $\psi(B,C) = P(\text{homologous genes segregating from B and C are ibd})$.
- $f(B) = P(\text{homologous genes in B are ibd}) = \psi(M(B), F(B))$.
- where $M(B)$ and $F(B)$ are the parents of B.

2.2.2 PATH COUNTING METHOD

- Half sibs: $(1/2) \times (1/2) \times (1/2) = 1/8$.
- Two genes from an inbred (f) parent:
 $1 \times f + (1/2) \times (1-f) = (1/2)(1+f)$.
- Half sibs with inbred (f) parent: $(1+f)/8$.
- Full sibs: $1/8 + 1/8 = 1/4$.
- First cousins: $(1/4) \times (1/2) \times (1/2) = (1/16)$.
- Double first cousins: $(1/16) + (1/16) = 1/8$.
- General formula (Wright, 1922):
 $\psi = \sum_A \sum_{\{P(A)\}} (1/2)^{n_1(P(A)) + n_2(P(A))}$
 where A are common ancestors, P(A) are paths of descent from ancestors, and n1 and n2 the counts of meioses down each side of the path.

EXAMPLE: The JV pedigree (Goddard et al. 1996)

To find $f(531)$ or $\psi(431,432)$
 2 ancestors (236, 231),
 each with $n_1=n_2=2$ and
 2 ancestors (131, 132),
 each with 3 paths,
 each with $n_1=n_2=3$.
 Total $f(531) = \psi(431,432) =$
 $2 \times 3 \times (1/2)^7 +$
 $2 \times 1 \times (1/2)^5 = 7/64$.



2.2.3 RECURSIVE METHOD

- $\psi(B,C) = (1/2)(\psi(M(B),C) + \psi(F(B),C))$
 provided B is not C nor an ancestor of C.
- Also $\psi(B,C) = \psi(C,B)$, so only other equation needed is
 $\psi(B,B) = (1/2)(1 + f(B)) = (1/2)(1 + \psi(M(B),F(B)))$
- Boundary conditions: $\psi(A,A) = (1/2)$ and $\psi(A,C) = 0$
 if A is a founder, and not an ancestor of C
- Expanding up the JV pedigree, among the grandparents, we have 3 first-cousin pairs and a sib pair.
- The kinship of first cousins is $1/16$, and of sibs is $1/4$, so overall we have $(1/4)(3 \times (1/16) + (1/4)) = 7/64$.

2.2.4 INBREEDING and GENOTYPE FREQUENCIES

- MYTH: Recessive diseases are more frequent in genetic isolates, because isolates are "more inbred".
- TRUTH 1: the more inbred individuals within any population have higher probability of homozygosity.
- Consider a recessive allele *a* with freq *q*, and an individual with inbreeding coefficient *f*:
 $P(aa) = q^2(1-f) + fq = q^2 + fq(1-q)$
 $P(Aa) = 2q(1-q)(1-f)$
 $P(AA) = (1-q)^2 + fq(1-q)$.
- See population mixtures and Wahlund variance (1.3.5)
 In population subdivision, people marry those more similar, hence more homozygosity in offspring.
 In inbreeding, people marry relatives, who are hence more similar, and hence more homozygosity in offspring.

INBREEDING and IBD

- NOTE 1: Inbreeding is a form of population subdivision.
- NOTE 2: Autozygous means having ibd genes: inbred means having non-zero probability of being autozygous.
- TRUTH 2: affected individuals have higher probability of ibd (autozygosity)
 $P(\text{ibd} | \text{affected}) = fq/(q^2 + fq(1-q)) = f/(q + f(1-q)) > f$.
- TRUTH 3: the affected people in a population have higher probability of being inbred. Suppose a proportion α of the population (Pop1) has inbreeding coefficient *f* and others (Pop2) are not inbred:

Inbreeding and IBD: ctd

- $P(\text{affected } aa) = (1-\alpha)q^2 + \alpha(q^2 + fq(1-q))$
 $P(\text{Pop1} | \text{affected}) = \frac{\alpha(q^2 + fq(1-q))}{(1-\alpha)q^2 + \alpha(q^2 + fq(1-q))}$
 $= \frac{\alpha(q + f - fq)}{(q + \alpha f - \alpha fq)}$
 which is always at least α and tends to 1 as *q* tends to 0.
- TRUTH 4: The affected inbred people in a population have higher probability of being autozygous (ibd).
- $P(\text{autozyg} | \text{affected}) = \frac{\alpha fq}{(q + \alpha f - \alpha fq)}$
 $= \frac{\alpha f}{(q + \alpha f - \alpha fq)}$
- Same form as before with *f* now becoming αf .