Genetic Counselling

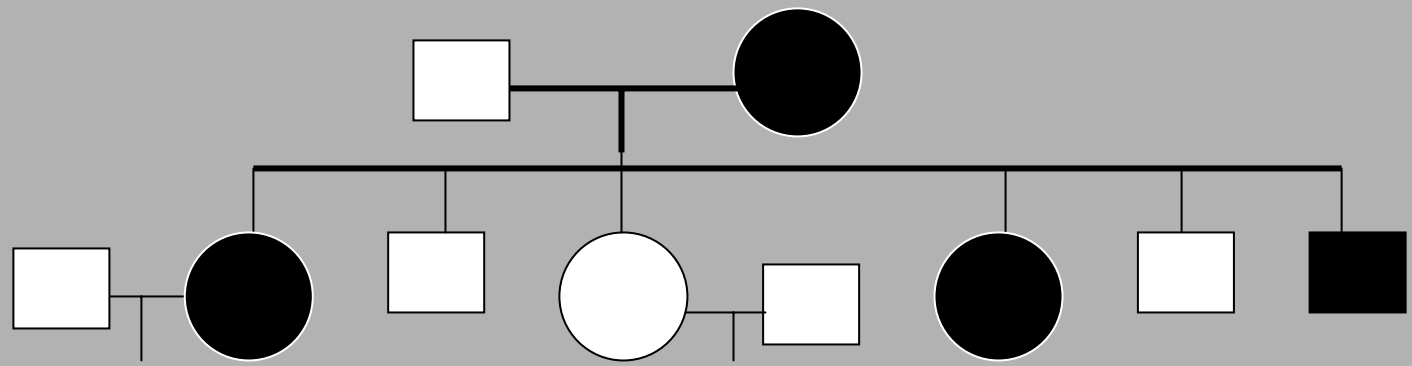
Genetic Counselling for Mendelian Disorders

- Genetic disorders:
  - Chromosomal
  - Single gene
  - Multifactorial
  - Mitochondrial
- Only single disorders follow a clearly defined pedigree pattern of inheritance “Mendelian Pattern”.
- During genetic counselling it is essential to establish whether or not the disorder is Mendelian or not and to calcualte the precise risk of recurrence.

Establishment of Mendelian Inheritance

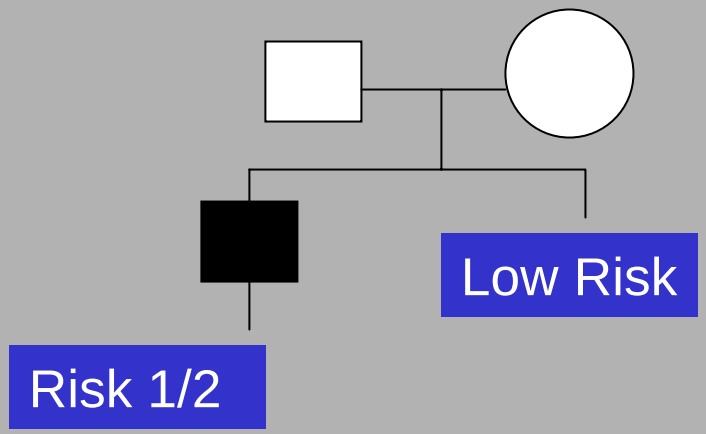
- Pattern of transmission judged from family tree. For several diseases the family tree may to conclusive even if accurate diagnosis is not made.
- For some disorders the pattern looks complicated and the exact diagnosis cannot be made.
- More common by combination of clinical diagnosis and comparable pedigree pattern.
- For some diseases pedigree pattern is not helpful and only clinical diagnosis is used.

(I) Genetic Councelling for AD Inheritance



Risk 1/2

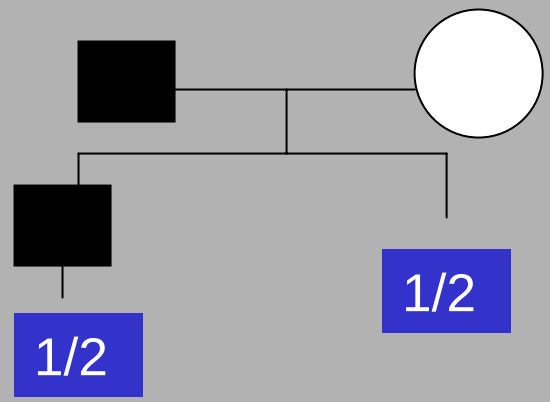
Risk not increased



Low Risk

Risk 1/2

New Mutation



1/2

1/2

Transmitted Case

Complexities in AD Disorders

1. Late or variable onset of the disease. How old will the family members be, to be certain of not developing the disease, e.g.
   - Huntington's disease, adult onset polycystic kidney disease, myotonic dystrophy.
   - For some conditions life tables have been prepared.

2. Lack of penetrance
   - Penetrance: is the index of the proportion of individuals with the gene who are affected.
   - Some disorders show lack of penetrance I.e. biochemical defect is present, but clinical features are absent, e.g.
     - Huntington disease – Penetrance decreases with age.
     - Retinoblastoma: Lack of penetrance unrelated to age.
   - The risk for children of a healthy sib never exceeds 10% even at the peak of 60% penetrance.

Complexities in AD Disorders

3. Variation in Expression:
   Several AD disorders show variation in clinical expression and hence the disorders cannot be ruled out unless careful examination is carried out.

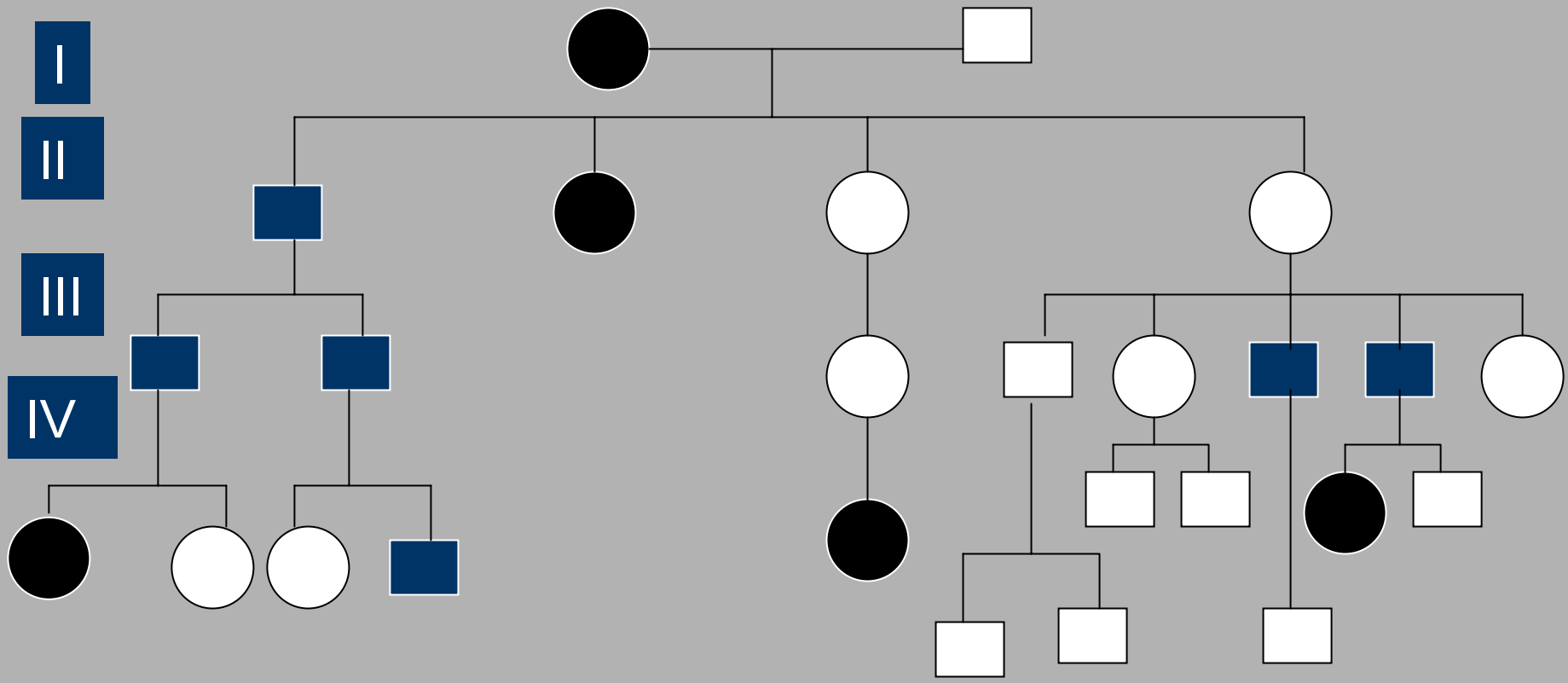
   Mild ⟷ Moderate Severe expression

   *Problems in G.C. since those who reproduce are least severely affected, but may have severely affected children e.g. Tuberousclerosis, Myotonic dystrophy, Huntingtons disease.

   *Disease severity may depend on sex of the transmitting parent.
   (may be related to degree of DNA methylation).

   "Anticipation: refers to the state that a genetic disease worsens with successive generation.

Lack of Penetrance in an AD Disorder



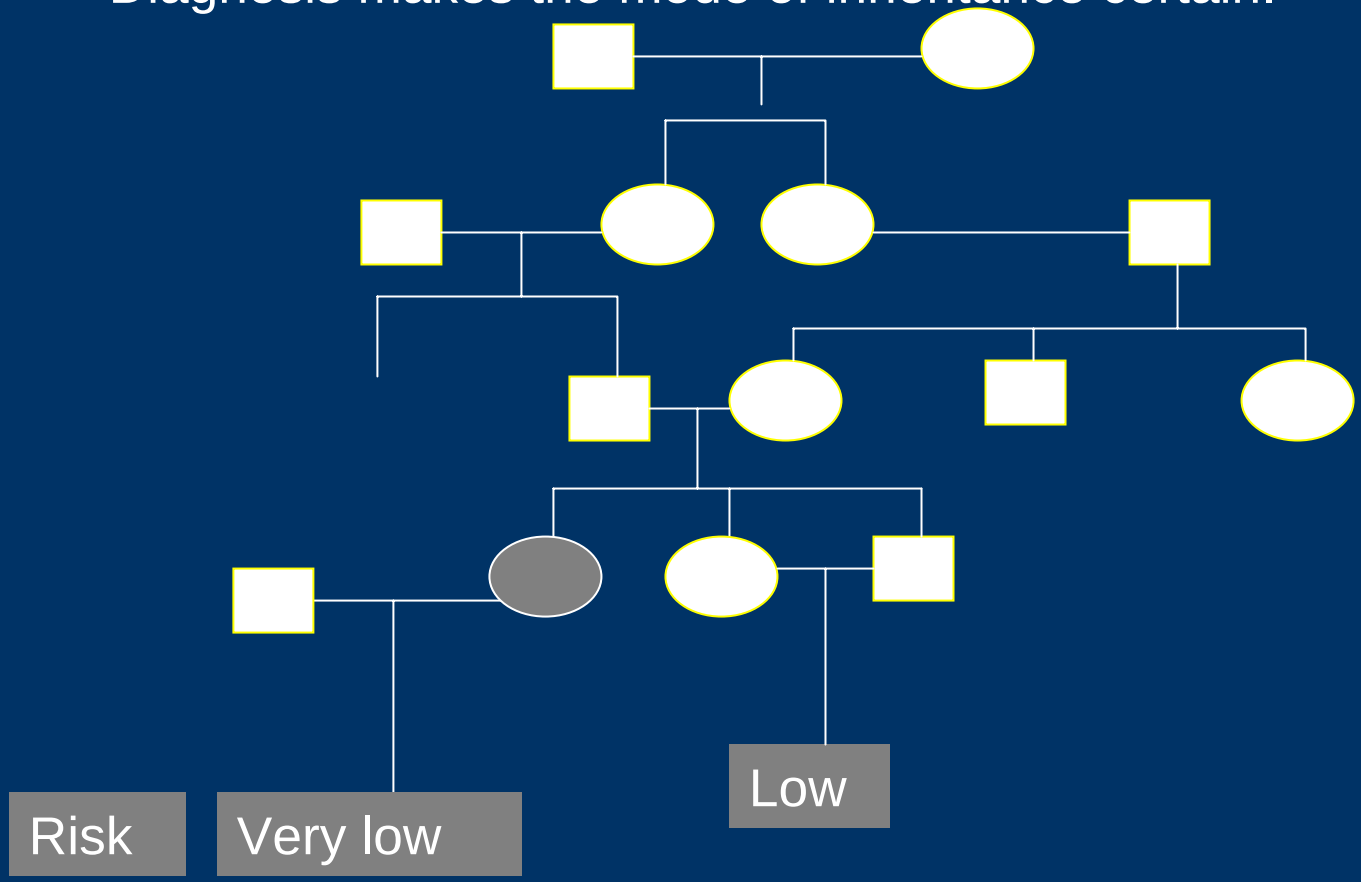
A Large kindred with hereditary pancreatitis

Factors underlying variability in Mendelian Disorders

Factors	Effect
• Genomic imprinting	Phenotype varies according
• Anticipation due to unstable DNA	More severe phenotype in successive generation
• Mosaicism	Mild or non-penetrant phenotype
• Modifying alleles	Influence of unaffected parent
• Somatic mutations also required. (e.g. familial cancers)	Variable penetrance
• New mutations	Sudden appearance of (AD) disorder in normal parent

III. Complexities in AR Disorders

- Difficult to confirm as homozygote born to normal parents, who are normal and may not have an affected relative.
- Horizontal transmission.
- Diagnosis makes the mode of inheritance certain.



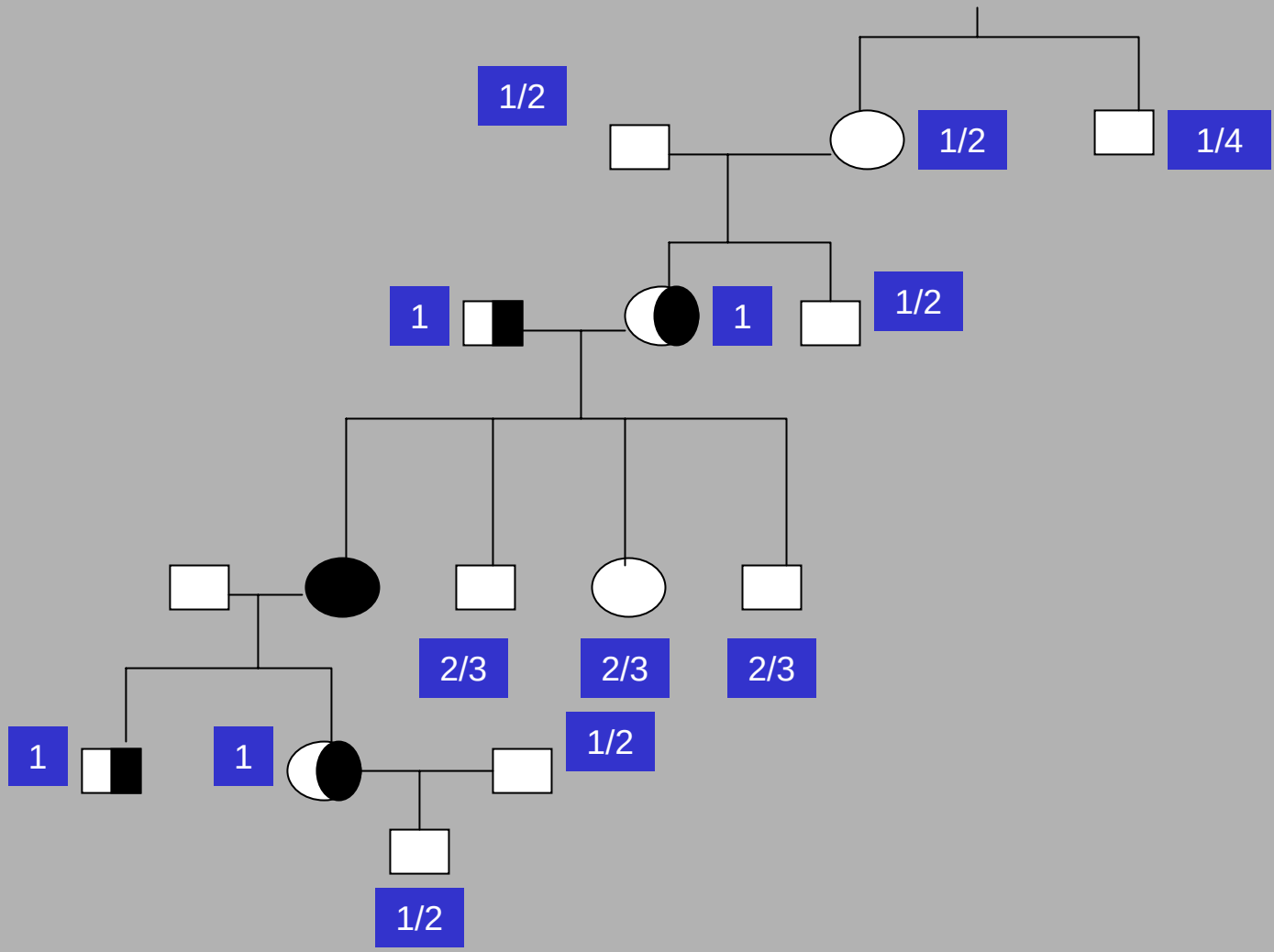
- If consanguinity present the risk is increased:

  (a) 2 brothers → 2 sisters ---- Not consanguinity

  (b) Rare disorder → increase in effected children due to consanguinity

  (c) Extensive consanguinity → Appear like AD inheritance (pseudo AD)

Risk of being a carrier in AR inheritance



Problems with AR disorders

- Genetic heterogeneity.
- Lack of penetrance and variation in expression are much less.

Population Risk

Can be calculated from:

- Hardy Weinberg Equilibrium

  $p + q = 1$ $[p^2 + q^2 = 2pq = 1]$

  q^2 = Abnormal homozygote (disease frequently)

  p^2 = Normal

  $2pq$ = Heterozygote

e.g. 2 patients of PKU in 10000 screened.

$q^2 = 2$; $q = \sqrt{0.0002} = 0.014$

$p = 1 - q = 0.986$

(hetero)$2pq = 0.0276$

Risk of transmitting an AR disorder in relation to disease incidences (the spouse is healthy)

Disease frequency (q2)/10000	Gene frequency (q) (%)	Carrier frequency =2pq(%)	Risk for offspring homo. (%) (affected sib)	Risk for offspring healthy sib
100	10.1	18.0	9.0	3.0
50	7.1	13.2	6.6	2.2
20	4.5	8.6	4.3	1.4
10	3.3	6.2	3.1	1.0
8	2.8	5.4	2.7	0.9
6	2.4	4.7	2.3	0.78
5	2.2	4.3	2.1	0.72
4	2.0	3.9	2.0	0.65
2	1.4	2.8	1.4	0.46
1	1.0	2.0	1.0	0.33
0.5	0.71	1.4	0.7	0.23
0.1	0.32	0.64	0.32	0.11
0.05	0.22	0.44	0.22	0.07
0.01	0.10	0.2	0.10	0.03

X-Linked Disorders

- Occupy a prominent place in genetic counselling.
- >100 X-linked disorders recognised.
- Majority XR; some dominant (often lethal in hemizygous male).
- X-chromosomes inactivation (lyonns phenomenon). applies to almost all human X-chromosomes but to a few loci it does not apply.

Recognition of X-Linkage

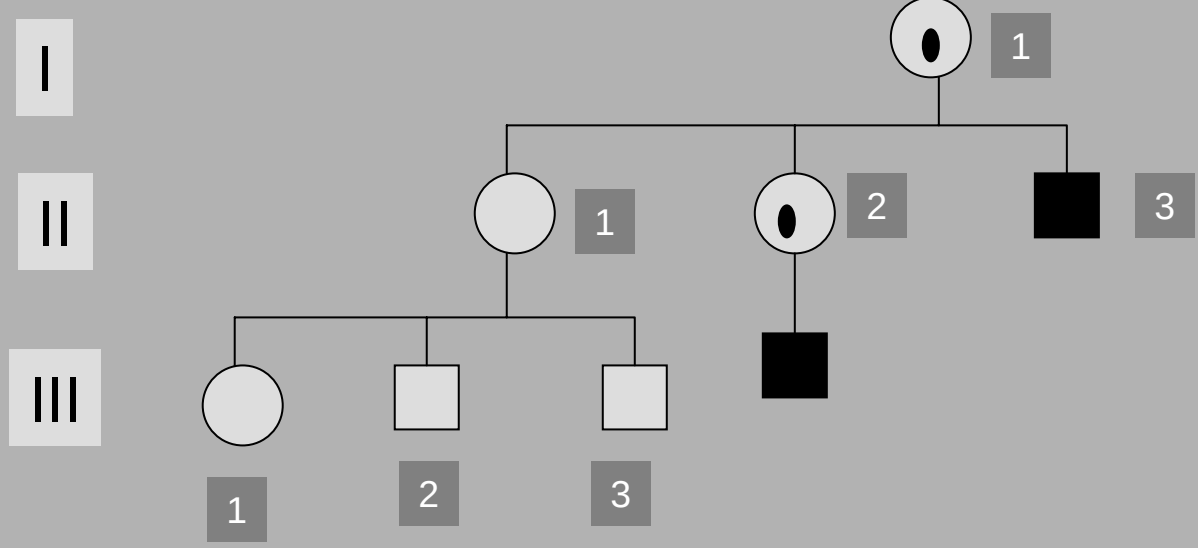
- No male-to-male transmission.
- Affected male → All daughters carriers (XR).
  → All daughters affected (XD).
- Unaffected males never transmit disease to either sex.
- A definite carrier women → risk ½ sons affected.
- Carrier women → ½ daughters carrier (XR)
  → ½ daughters affected (XD).
- Homozygous affected women are few → affected male are much more.

These guidelines will cover most genetic councelling problems.

Mitochondrial Inheritance

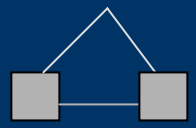
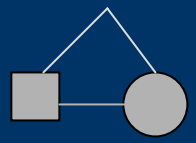
- No transmission in descendents of males, affected or not.
- Both sexes may be affected.
- Females may be symptom less carriers.
- All daughters of an affected or carrier female are at risk of transmitting the disorders or of becoming affected. All sons may become affected.
- The precise proportion of offsprings M or F, who will become affected is variable.

	Counsellee (Consultand) A carrier	Counsellee (Consultand Not a carrier
• Prior risk	1/4	3/4
• Conditional risk (2 normal sons)	1/2 : 1/2 : 1/4	1
• Joint risk	1/16	3/4 : 12/16
• Relative risk	1	12
• Final risk	1/13	12/13



Risk for II-1	Carrier	Not a carrier
• Prior risk	1/2	1/2
• Conditional risk	1/2 x 1/2 : 1/4	1
• Joint risk	1/8	1/2 (4/8)
• Relative risk	1	4
• Final risk	1/5	4/5
• Prior risk for III-1	1/10	

Degree of Relationship	**Proportion of gene shared**
• First degree……	1/4
• Sibs	
• Dizygotic twins	
• Parents	
• Child	
• Second degree ……..	1/4
• Half sibs	
• Uncles, aunts	
• Nephew, nieces	
• Double first cousins	
• Third degree: ……	1/8
• First cousins	
• Half uncles, aunts	
• half nephew, nieces	
•	

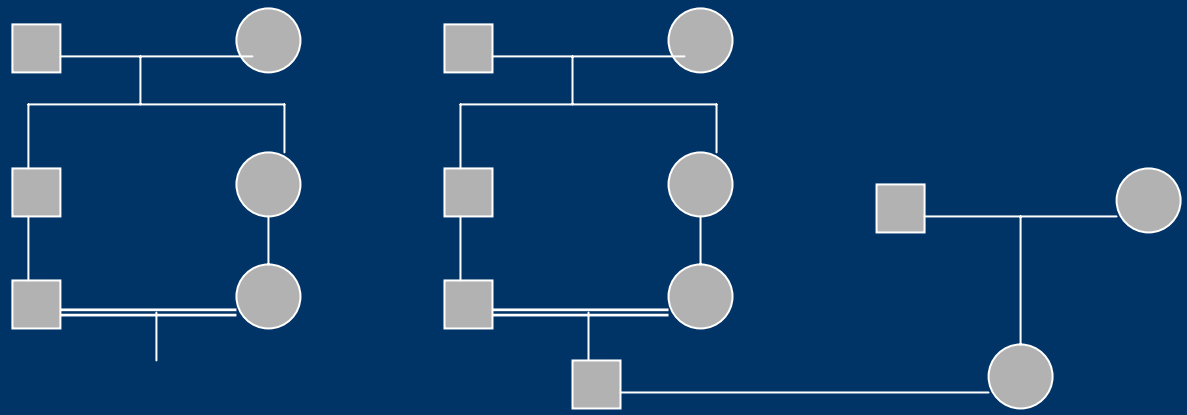
	Relation	Gene show	Chance of Homo.
 Monozygotic twin	-	1	-
 Di monozytotic twin	1st	1/2	1/4
Sibs	1st	1/2	1/5
Uncle-nephew (aunt-niece)	2nd	1/4	1/8
Half-sibs	2nd	1/4	1/8
Double 1st cousin	2nd	1/4	1/8
First cousin	3rd	1/8	1/6

The risk of being a carrier for an X-linked disorder

- Obligatory carriers must be recognised II and II-2.
- The prior genetic risk of the individual requiring advice should be calculated. ↑ it is in 1 in 4 as her mothers risk is ½.
- Other relevant information must be considered I.e. counsellee has 2 normal sons, so she is less likely to be a carrier.

Consanguinity

- Only relevant to genetic risks if it involves both parental lives not just. one.



Consanguinity relevant Not relevant

- 2 brothers marrying 2 sisters is not consanguinity but it may affect genetic risk.
- The rarer the disorder the higher the proportion of affected individuals from consanguineous marriages.
- Consanguinity must be seen in the context of particular community. An apparent relationship of a particular disorder is much less certain if 30% cousin marriages, compared to non-consanguineous mating.
- Extensive consanguinity (AR) appears like AD.