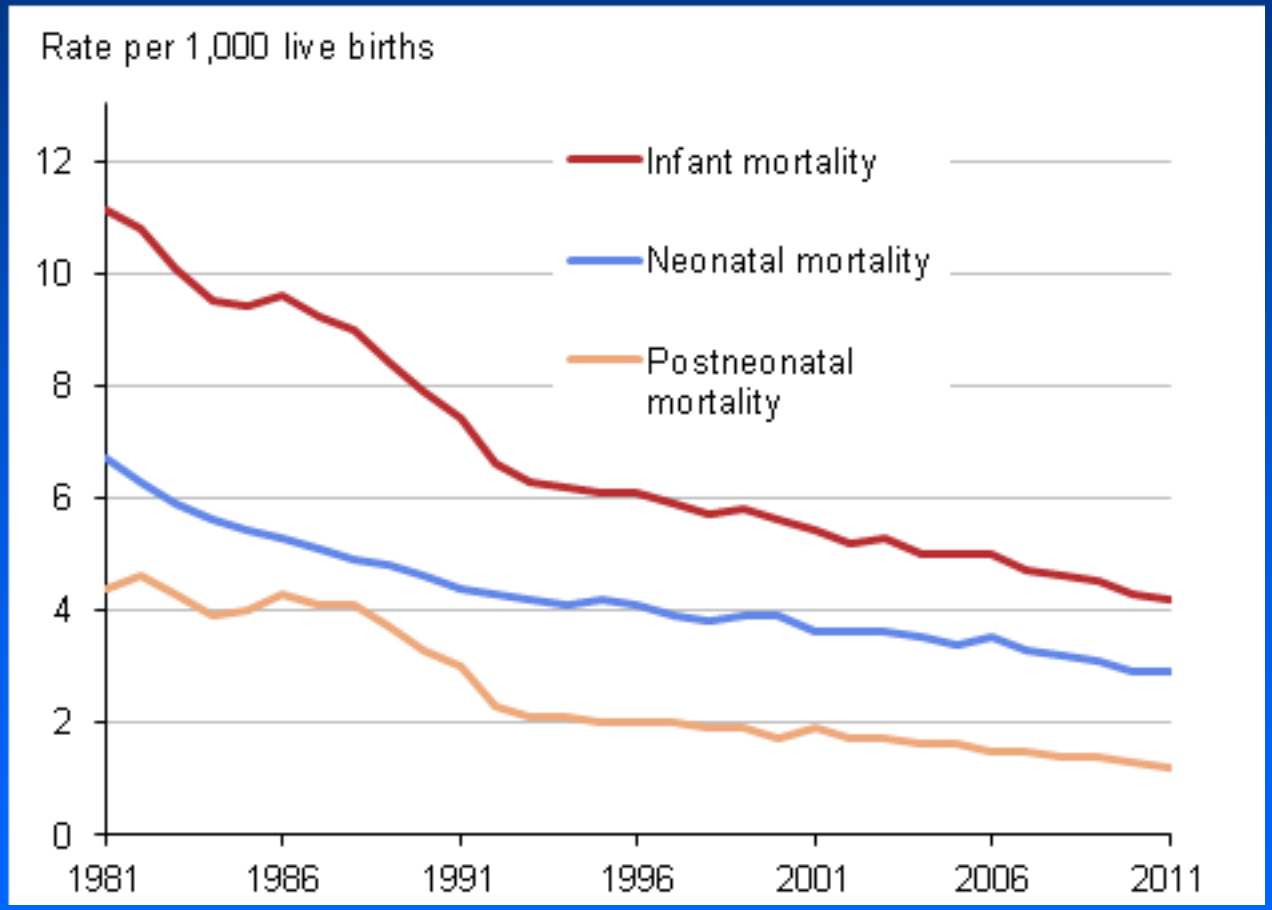
Clinical Genetics Introduction

Wayne Lam
wayne.lam@ed.ac.uk



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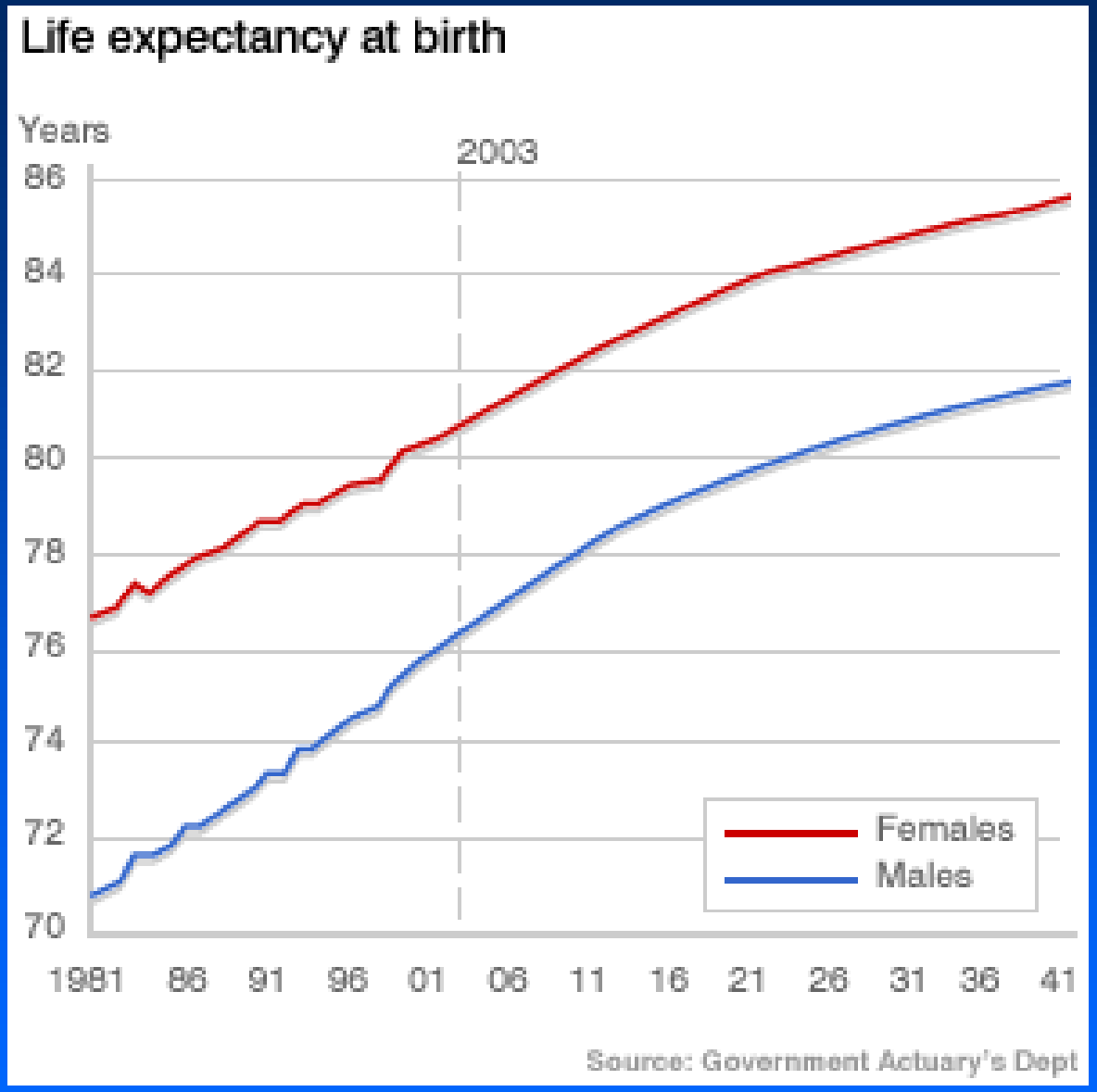

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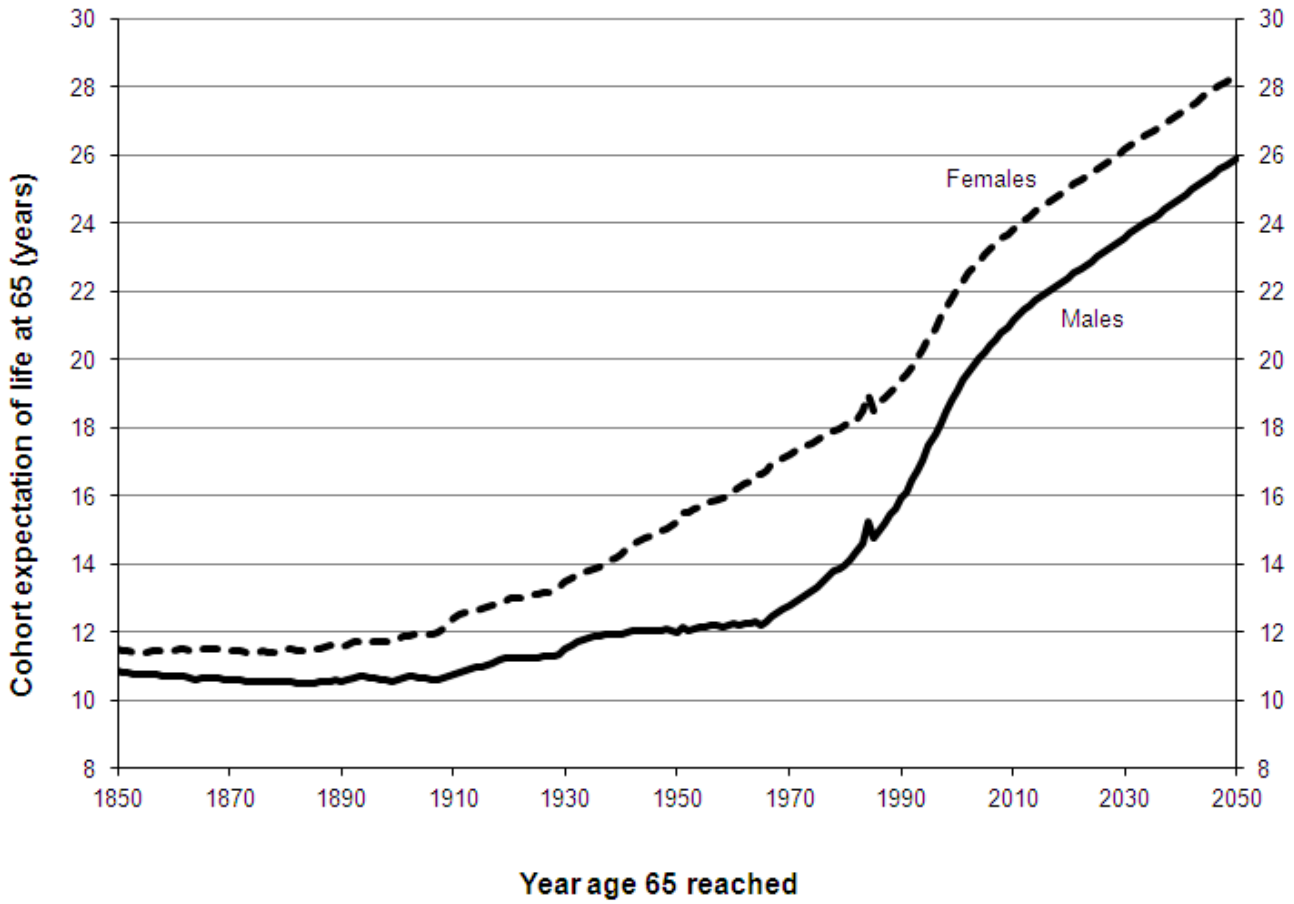
Cohort expectation of life at age 65 according to historic and projected mortality rates, persons who reached age 65 1850–2050, England and Wales



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Introduction

TABLE 1.3 Approximate Prevalence of Genetic Disease in the General Population

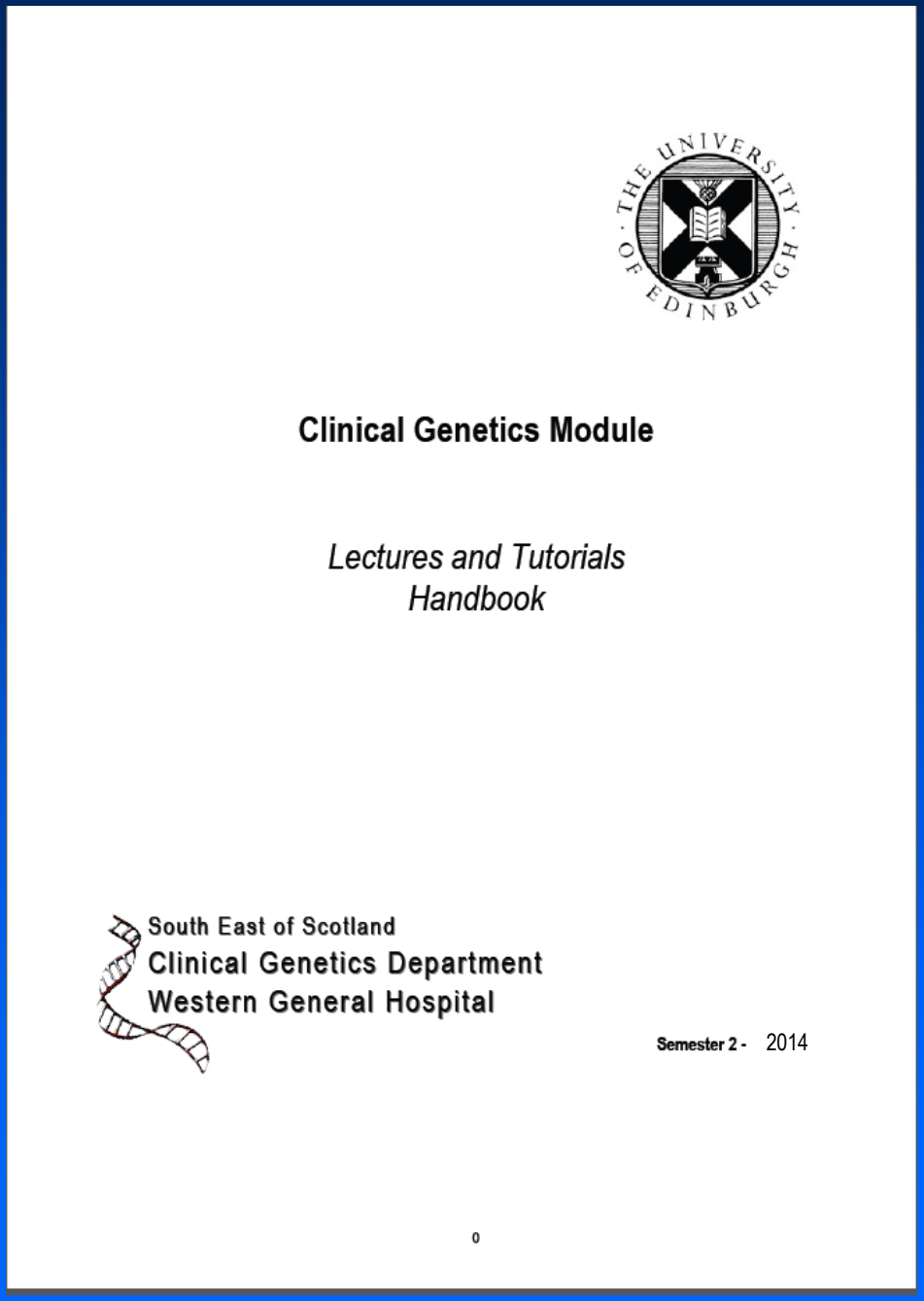
Type of genetic disease	Lifetime prevalence per 1,000 persons
Autosomal dominant	3 to 9.5
Autosomal recessive	2 to 2.5
X-linked	0.5 to 2
Chromosome disorder*	6 to 9
Congenital malformation†	20 to 50
Total	31.5 to 73

Introduction

TABLE 1.2 Percentages of Childhood Deaths in United Kingdom Hospitals Attributable to Nongenetic (e.g., Infectious) and Genetic Causes

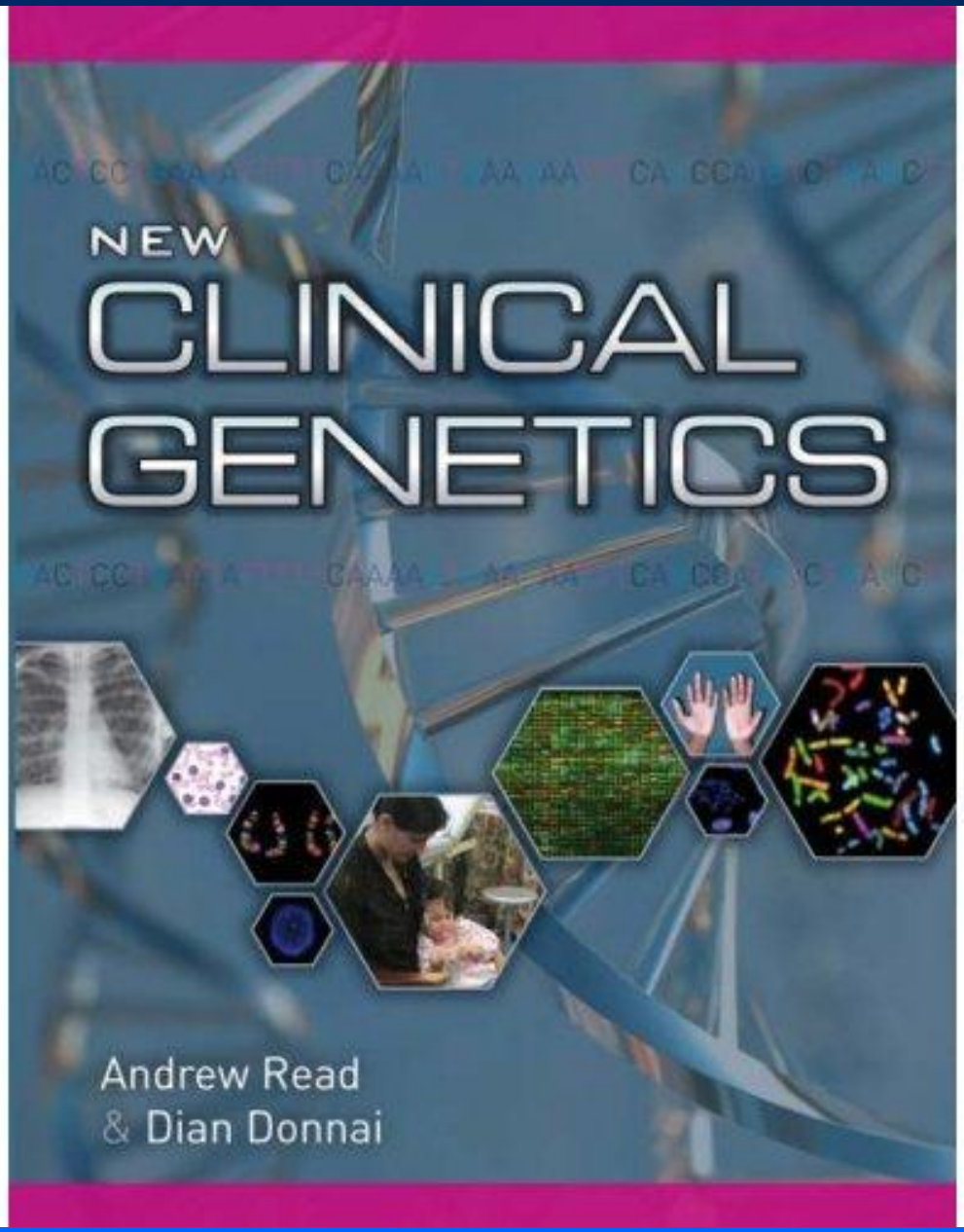
Cause	London 1914	London 1954	Newcastle 1966	Edinburgh 1976
Nongenetic	83.5	62.5	58.0	50.0
Genetic				
Single gene	2.0	12.0	8.5	8.9
Chromosomal	—	—	2.5	2.9
Multifactorial	14.5	25.5	31.0	38.2

From Rimoin DL, Connor JM, Pyeritz RE, Korf BR (2002) Emery and Rimoin's Principles and Practice of Medical Genetics. Churchill Livingstone, London.



Overview

- 9 lectures
- 3 tutorials
  - Case orientated
- 2 PBLs



Publisher: Scion Publishing Ltd

ISBN-10: 1904842313

ISBN-13: 978-1904842316

The family history

Why take a family history?

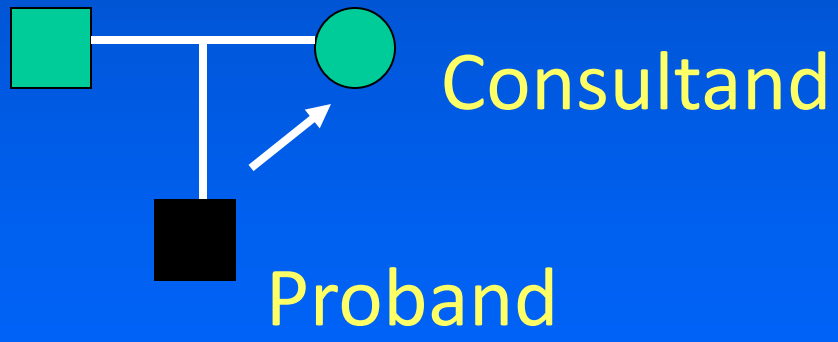
- Aid in diagnosis
  - Identify the spectrum of illnesses/medical diagnosis within the family
  - Demonstrates mode of inheritance of disease in family

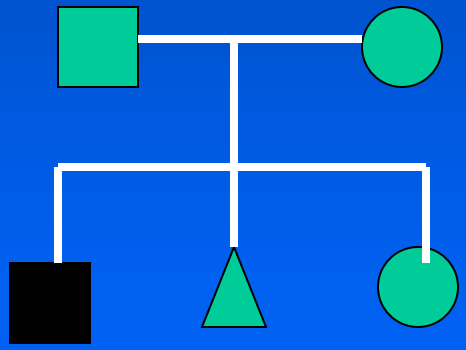
Why take a family history?

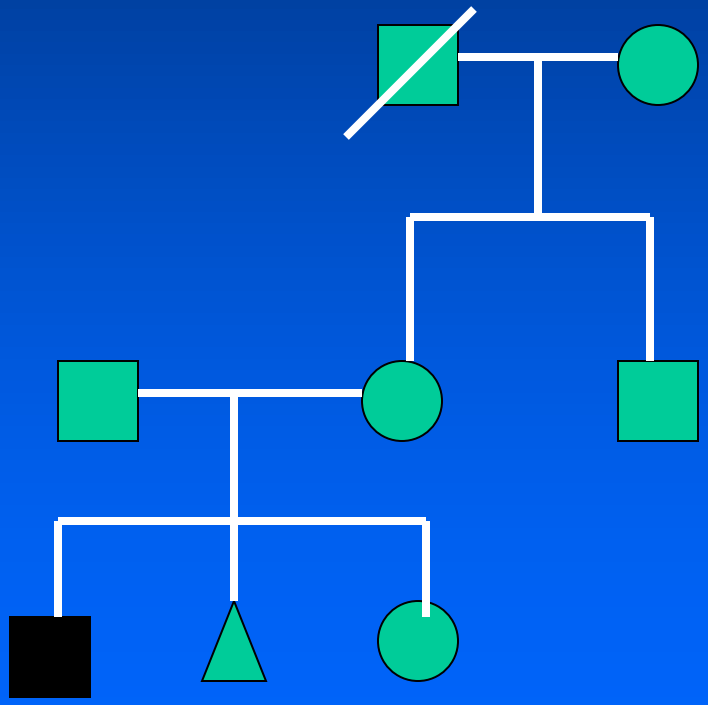
- Establishes rapport between consultand and counsellor
- Identifies consultand's concerns and perceptions
- Provides information on family relationships

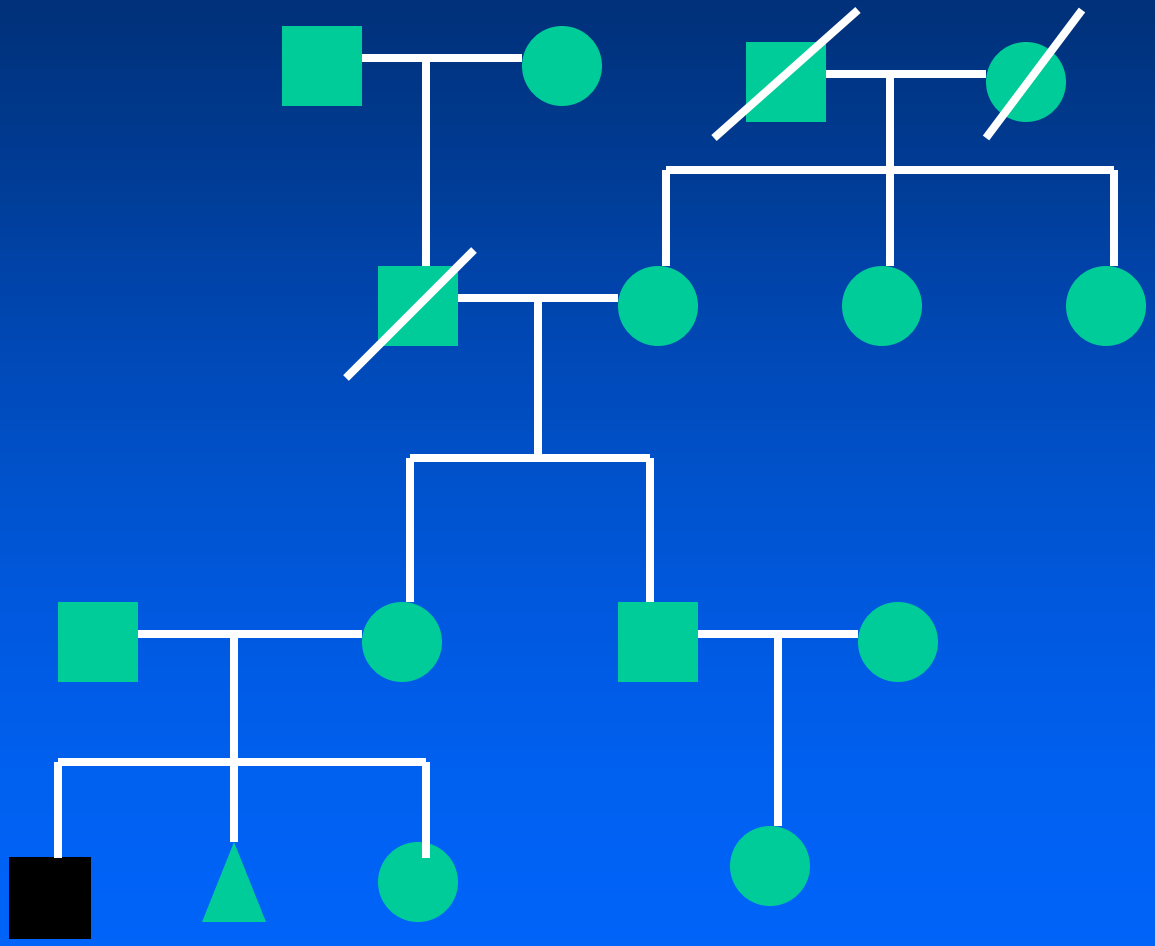
Information to be collected

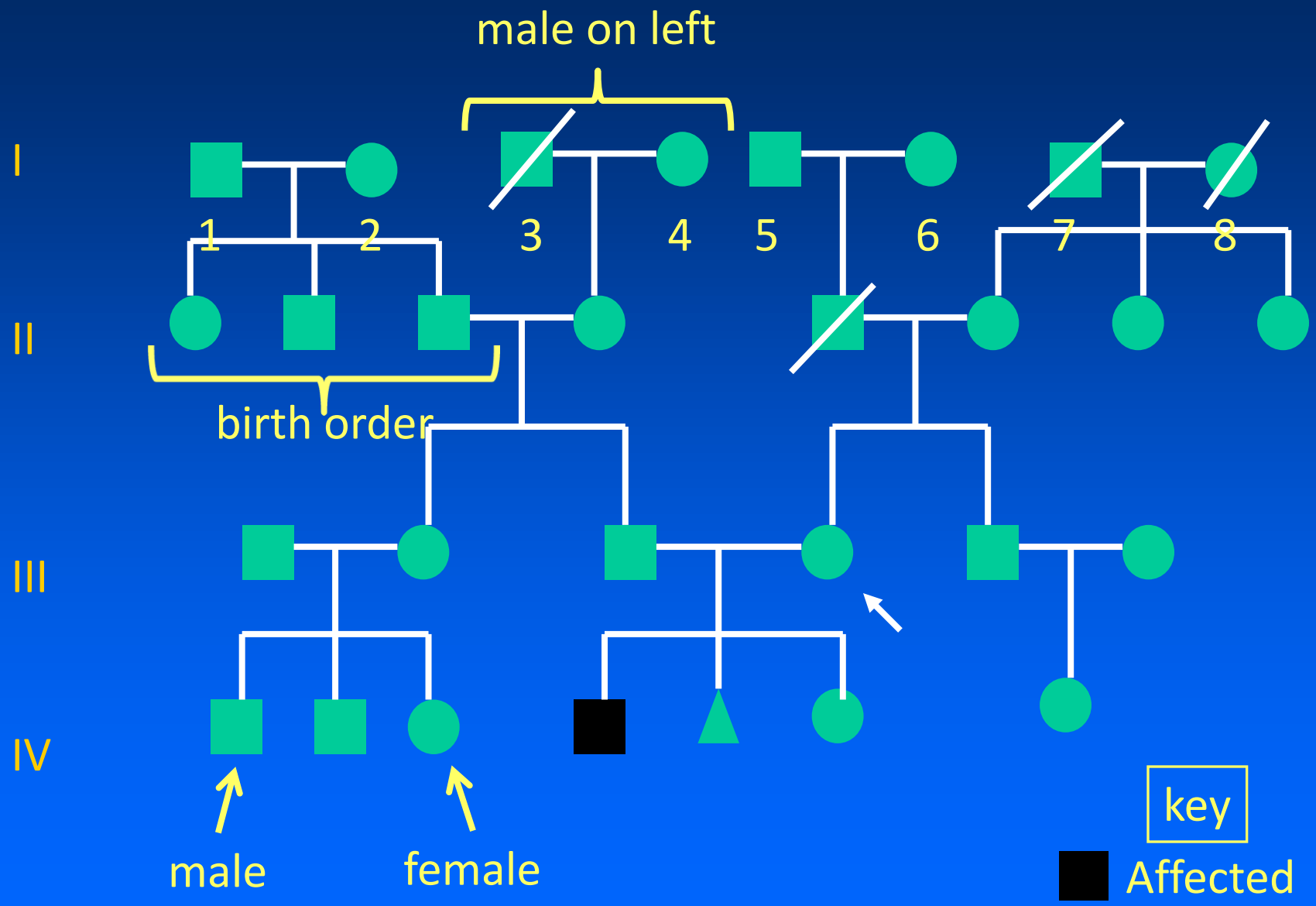
- Full name (including maiden name)
- Date of birth
- Date and cause of death
- Number of children and miscarriages
- Any specific medical diagnoses


Consultand
Proband

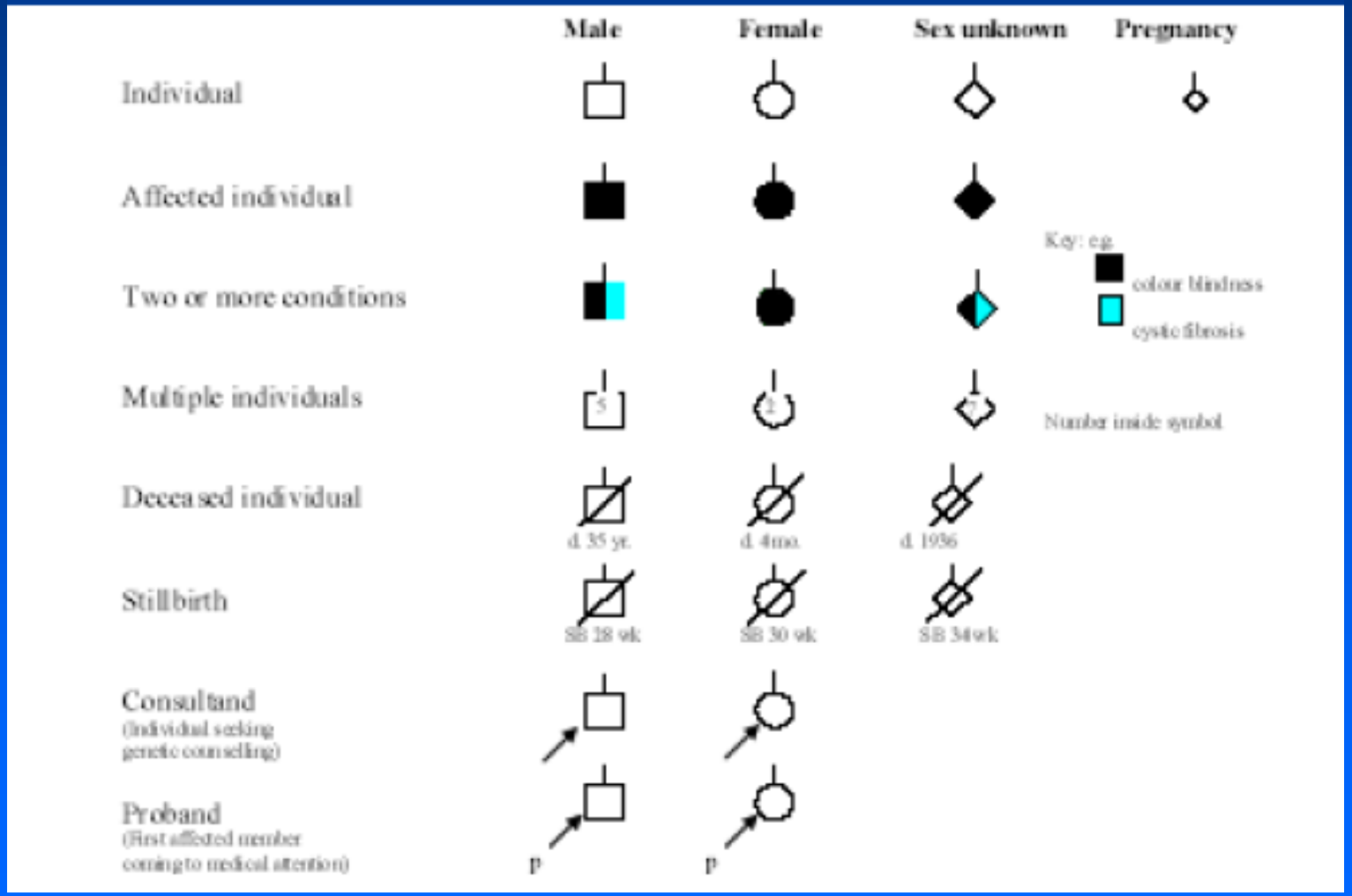




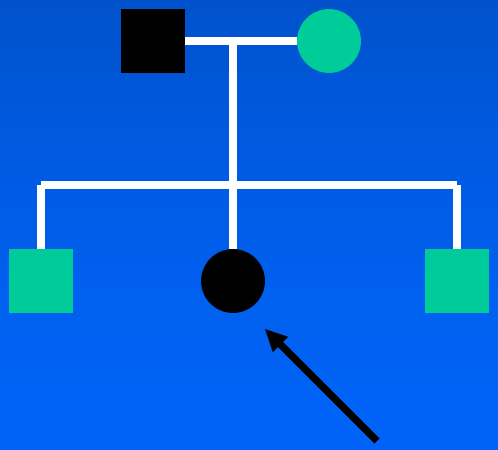



male on left
I
II
III
IV
1
2
3
4
5
6
7
8
birth order
male
female
key
Affected

Standard symbols used in drawing a family tree

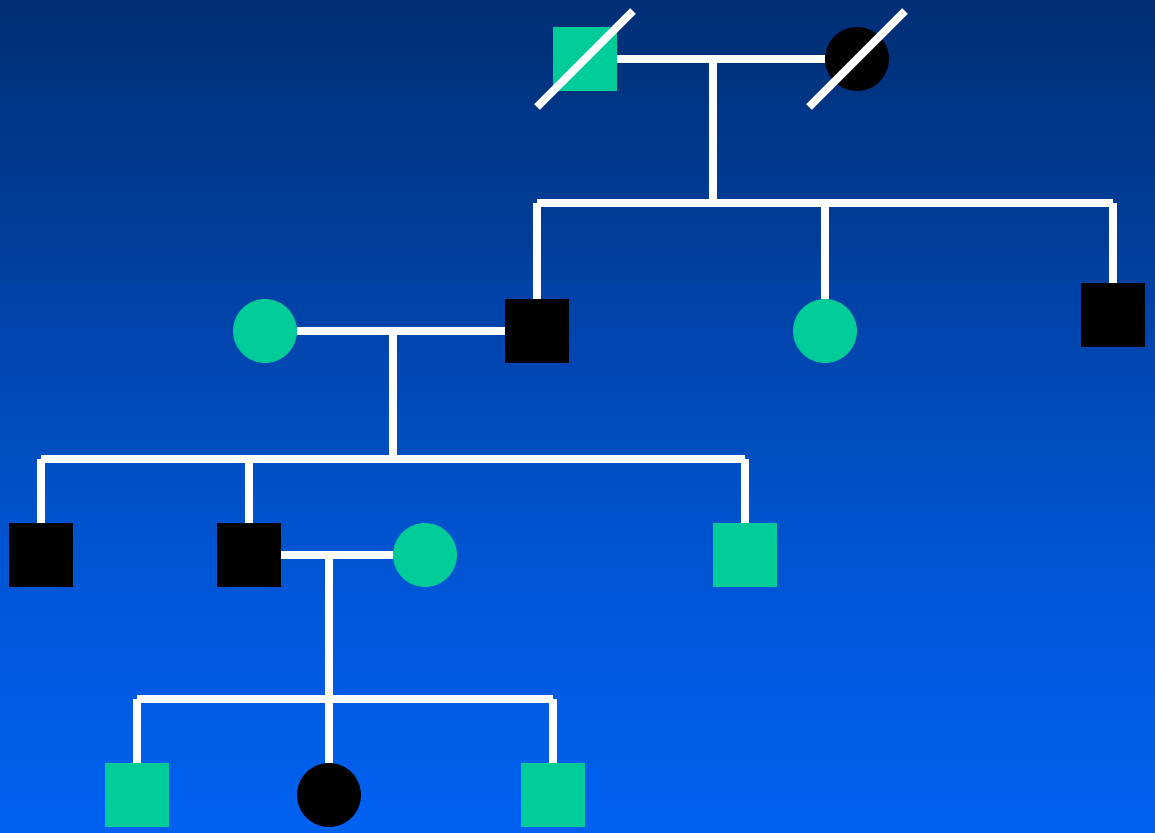


22 year old presented with acute gastrointestinal bleed



Affected

Autosomal Dominant Inheritance



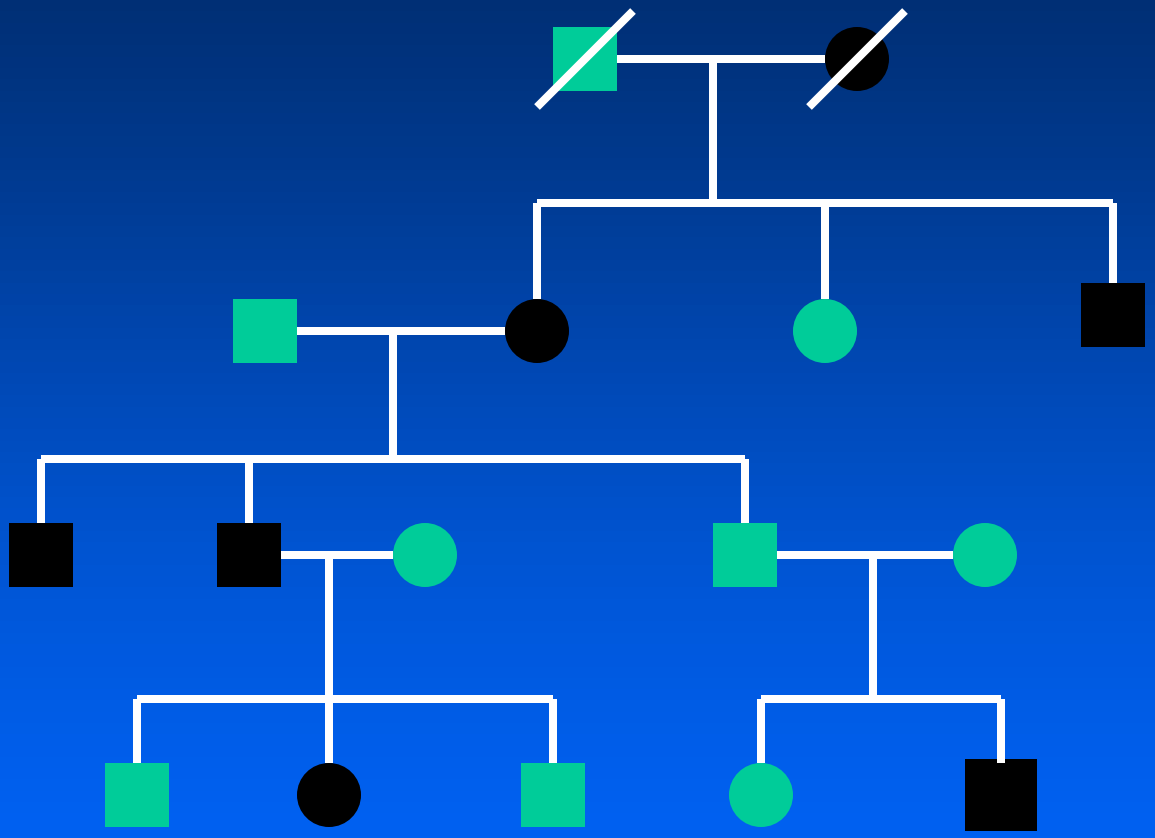
- involvement of more than one generation
- male to male transmission
- males and females affected equally

Affected

Autosomal Dominant Inheritance

- 2 further characteristics

Autosomal Dominant Inheritance



Non-penetrance

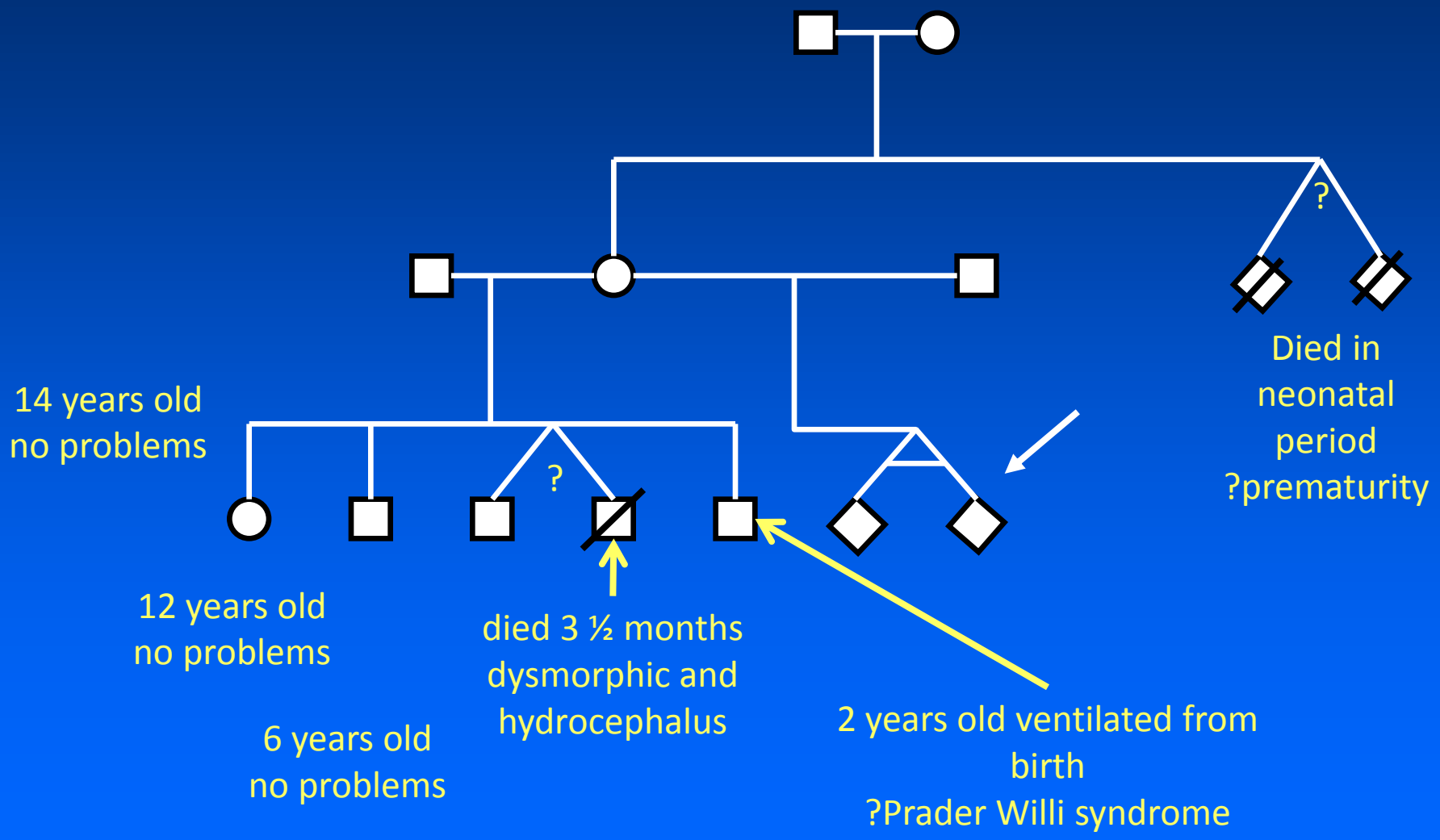
Affected

Autosomal Dominant Inheritance

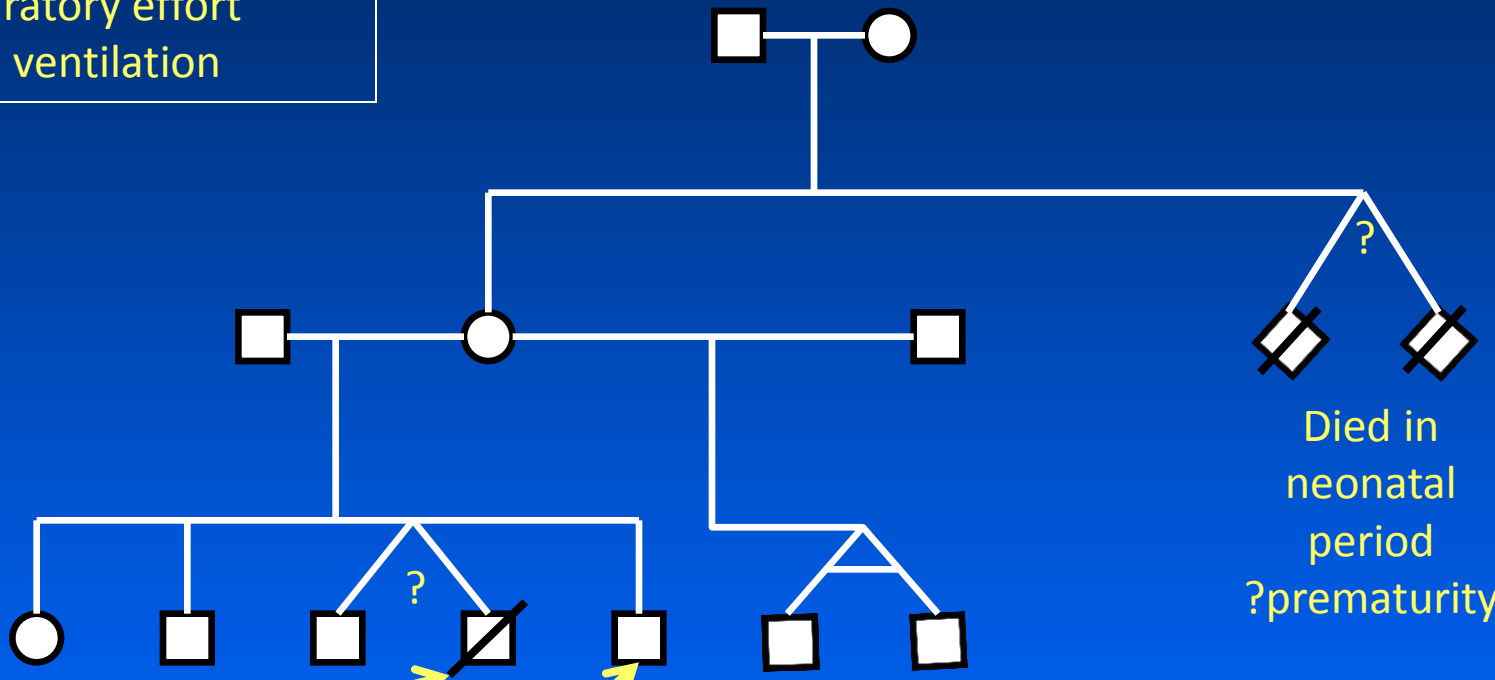
- Penetrance
  - affected person may or may not develop symptoms or show signs of the disorder

    "skipping a generation"
- Expressivity
  - variation in the clinical presentation/phenotype between patients

Polish couple referred for antenatal counselling

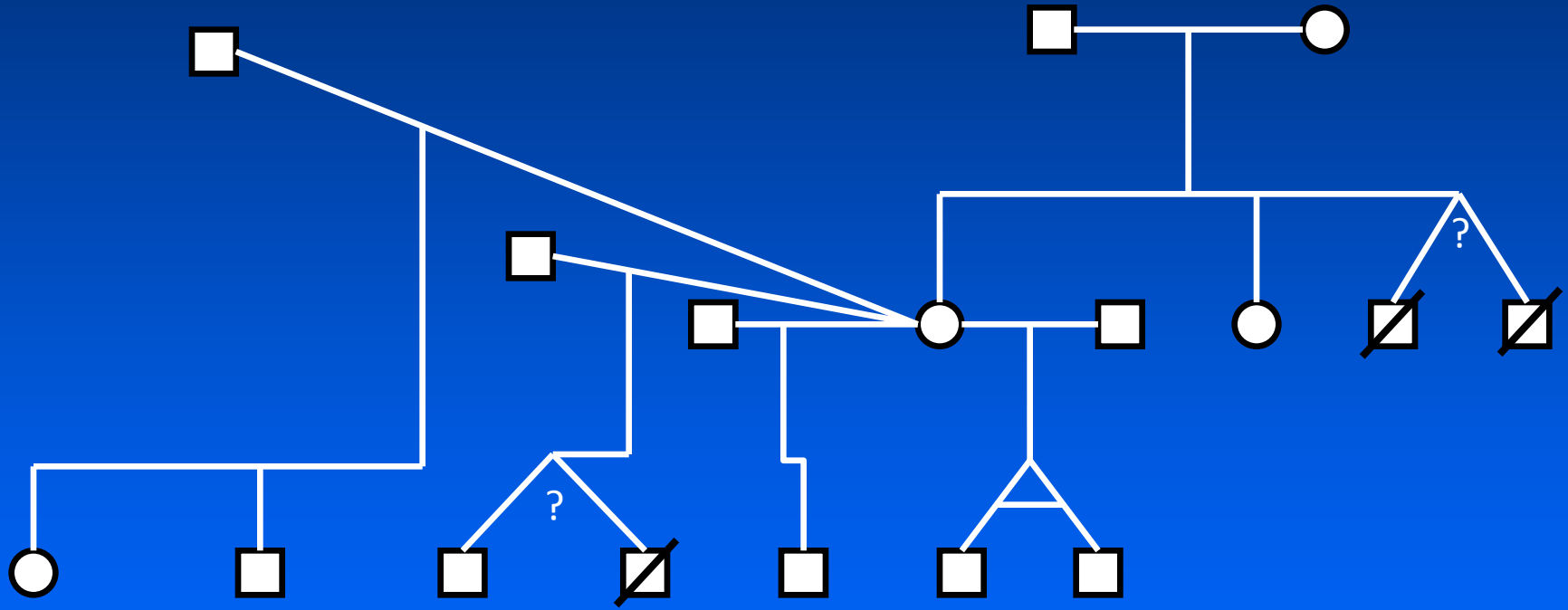


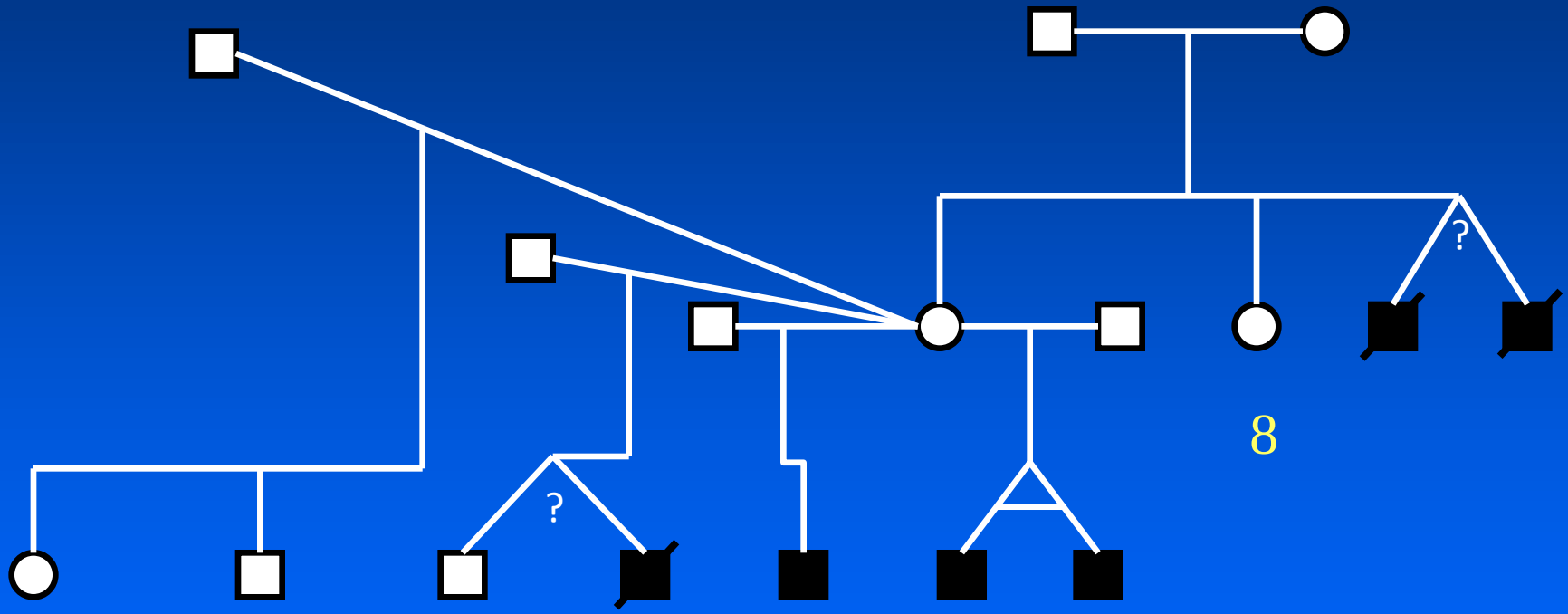
Twins born 33 weeks premature
Severe hypotonia
No respiratory effort
Require ventilation



died 3 ½ months dysmorphic and hydrocephalus

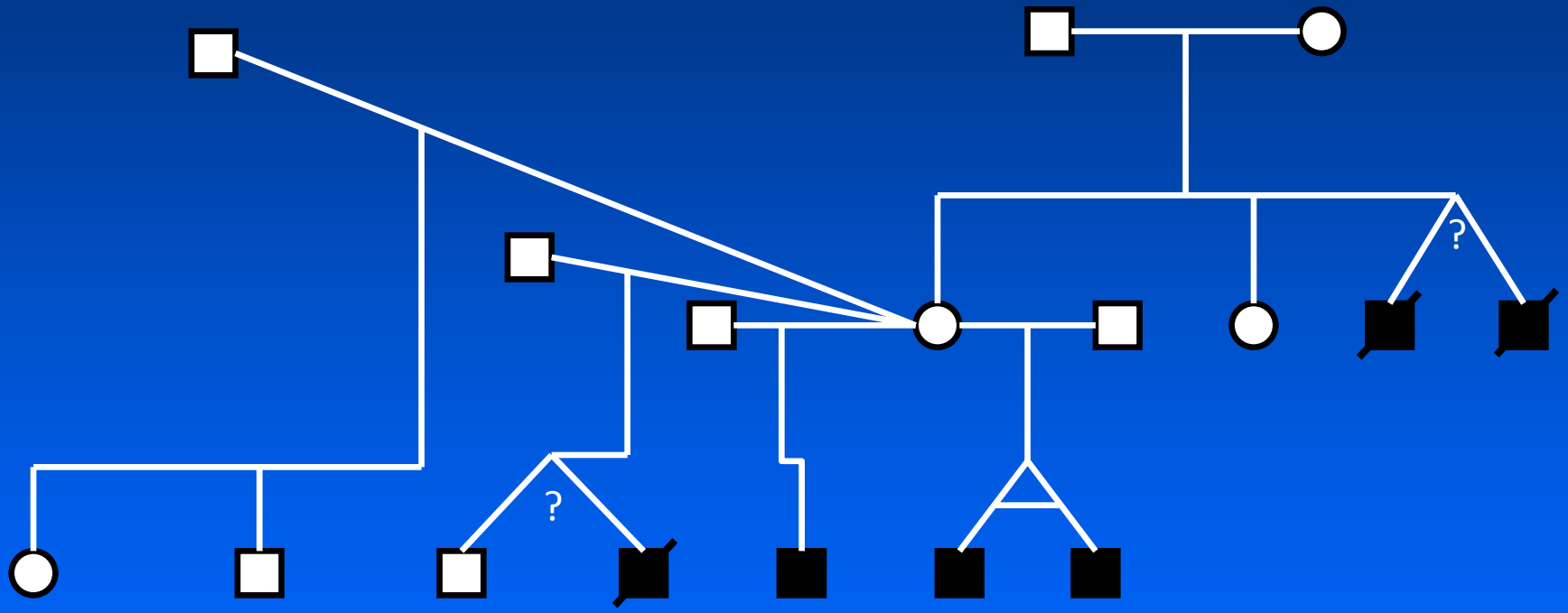
2 years old ventilated from birth
?Prader Willi syndrome





8

X-Linked Inheritance



- more than one generation affected
- no male to male transmission
- usually only males are affected

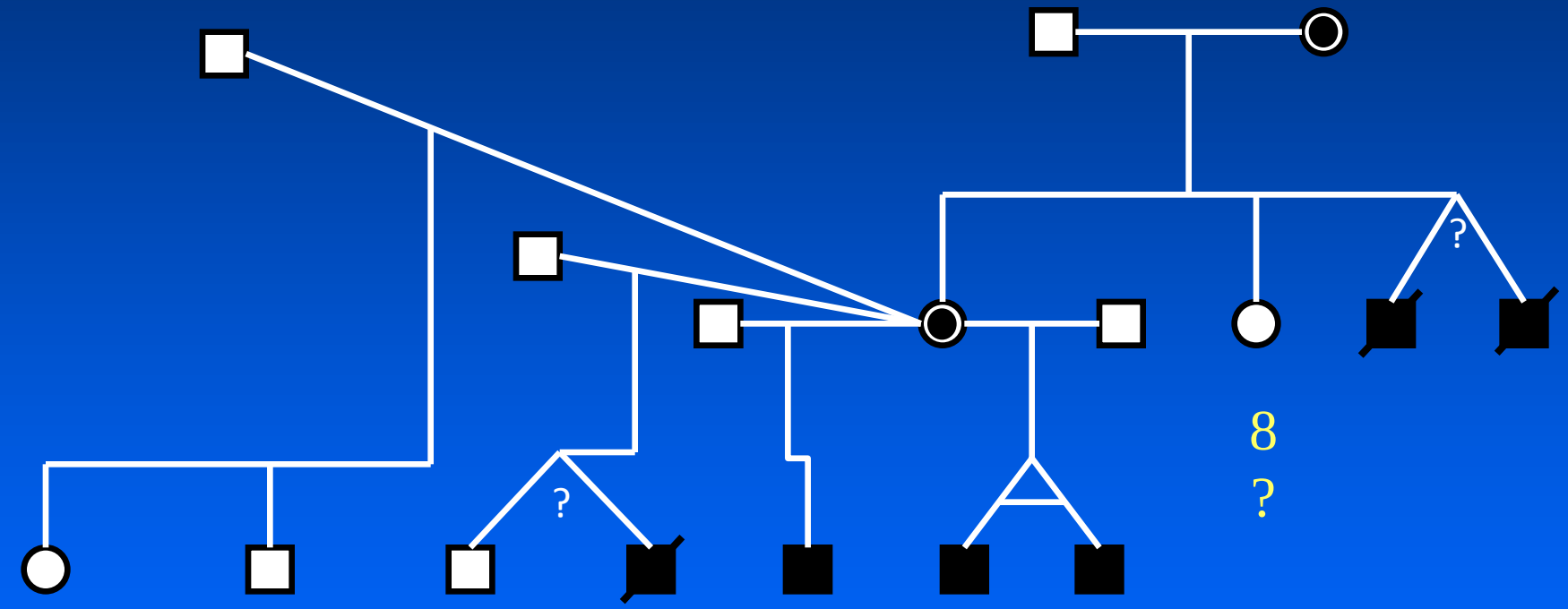
Fragile X Syndrome

- 1:4000
- Commonest none chromosome cause of mental retardation
- Mild to severe mental retardation
- Macroorchidism (post pubertal)
- Long face, prominent jaw, thick nasal bridge, large ears
- Joint hypermobility
- Autistic features, ADHD

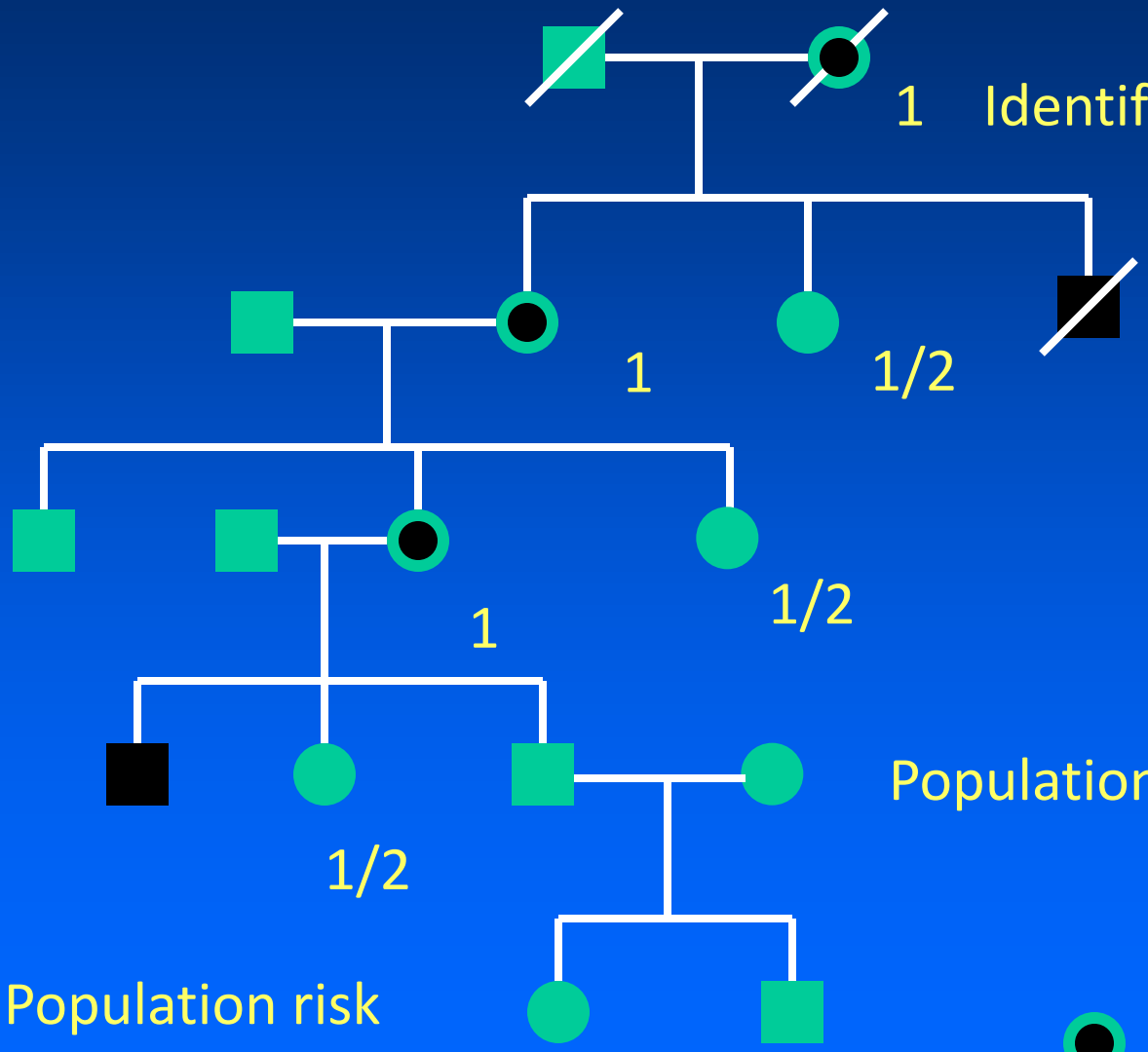
X-inactivation

- Carrier females can be affected by X-linked disorders
- Consequence of the process called X-inactivation or Lyonization
- It is an random process
- If in an excess of cells, the normal X chromosome has been switched off then a female carrier of an X-linked disorder can be affected

Identify obligate carriers



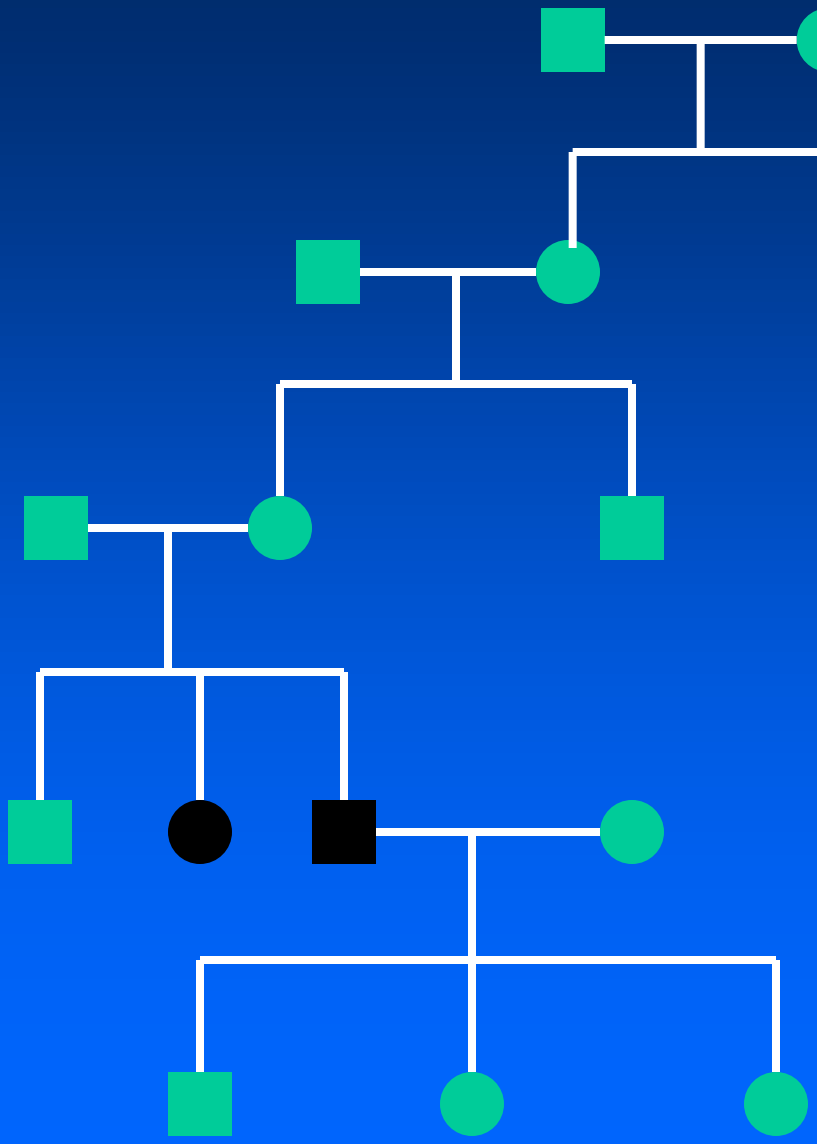
X-Linked Inheritance



Identify obligate carriers

Obligate carrier

Autosomal Recessive Inheritance



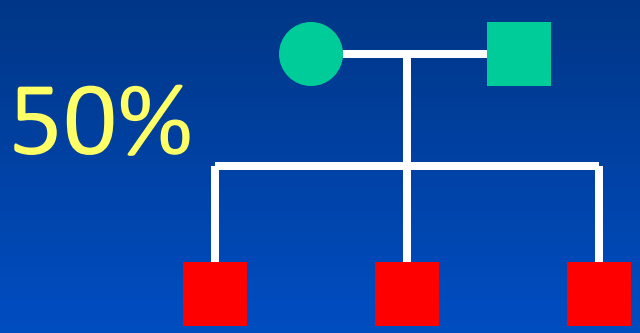
- one or more affected children with unaffected parents
- usually only one generation affected
- males and females affected with equal frequency and severity
- a higher incidence of consanguinity

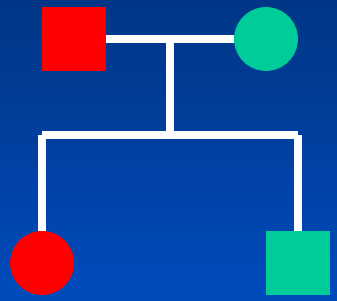
Cystic Fibrosis

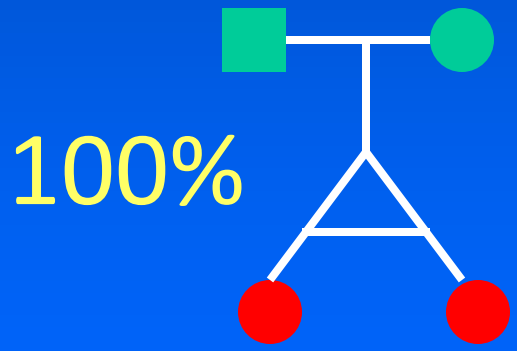
Disease onset in childhood

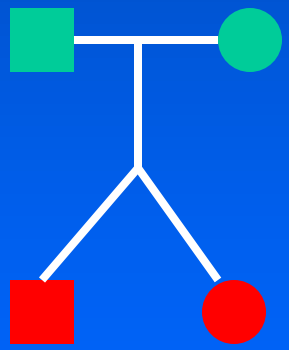
- Recurrent chest infections
- with progressive Loss of Lung Function
- May present with failure to thrive secondary to pancreatic insufficiency

First degree relatives



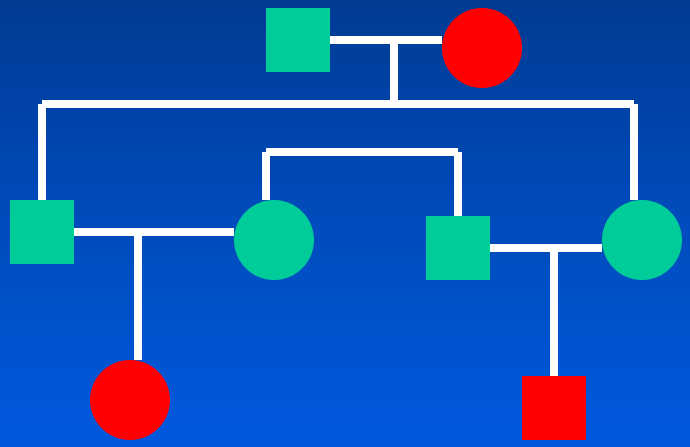




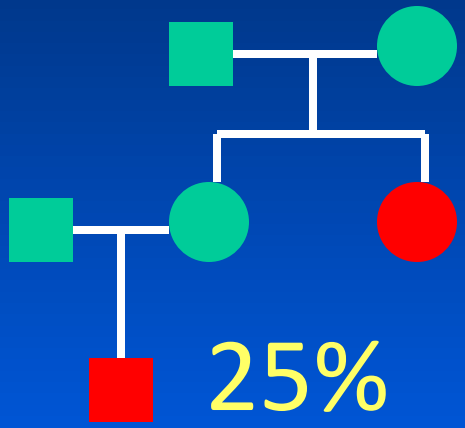


Percentage of genes shared

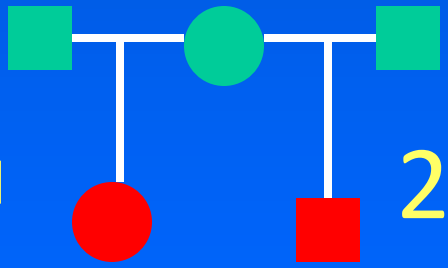
Second degree relatives



25%



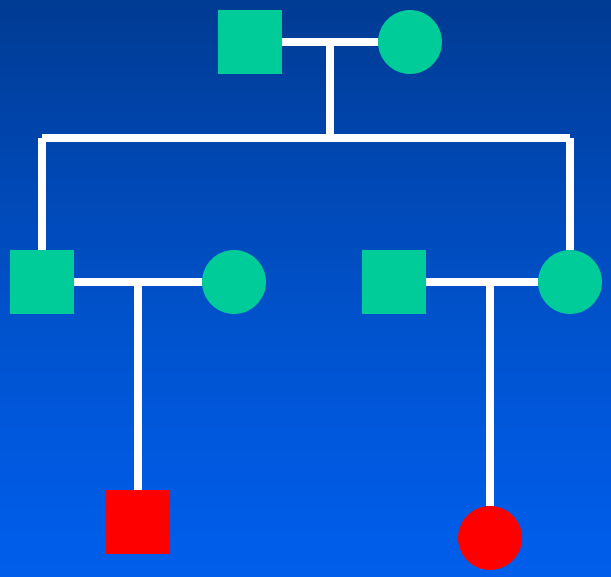
25%



25%

Percentage of genes shared

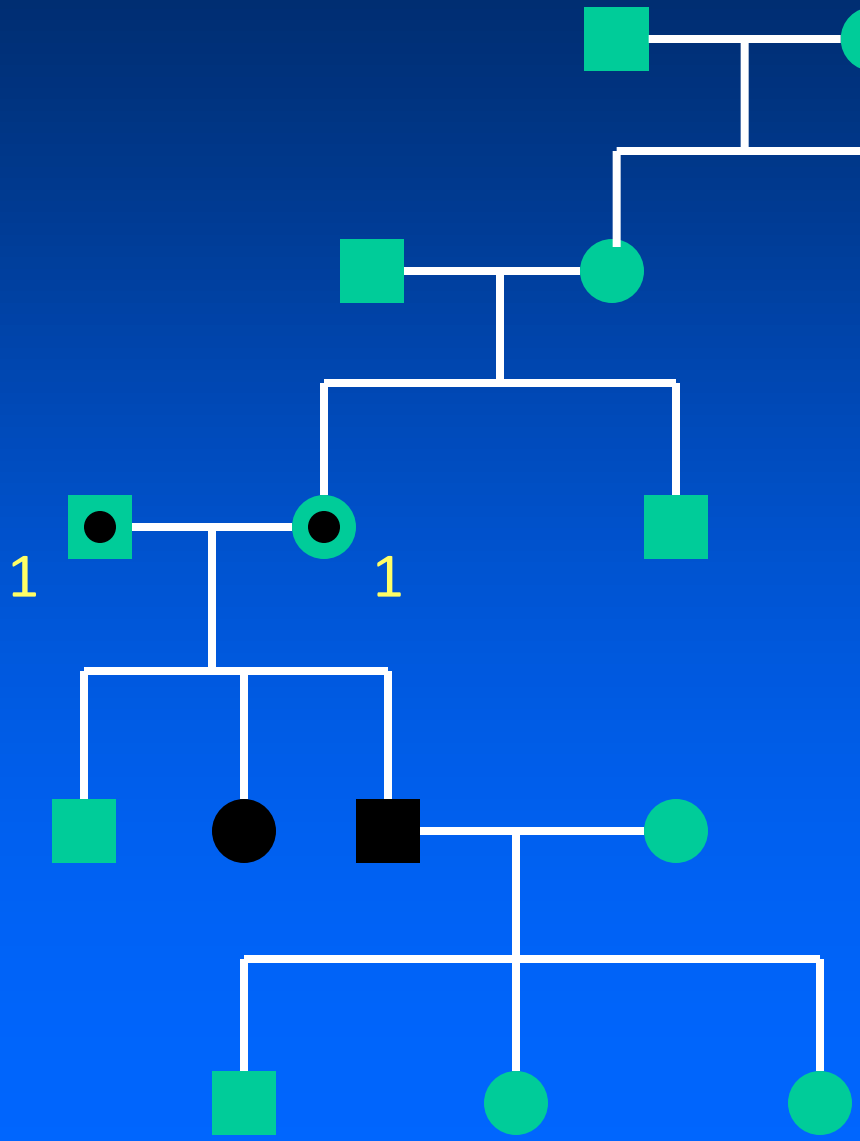
Third degree relatives



12.5%

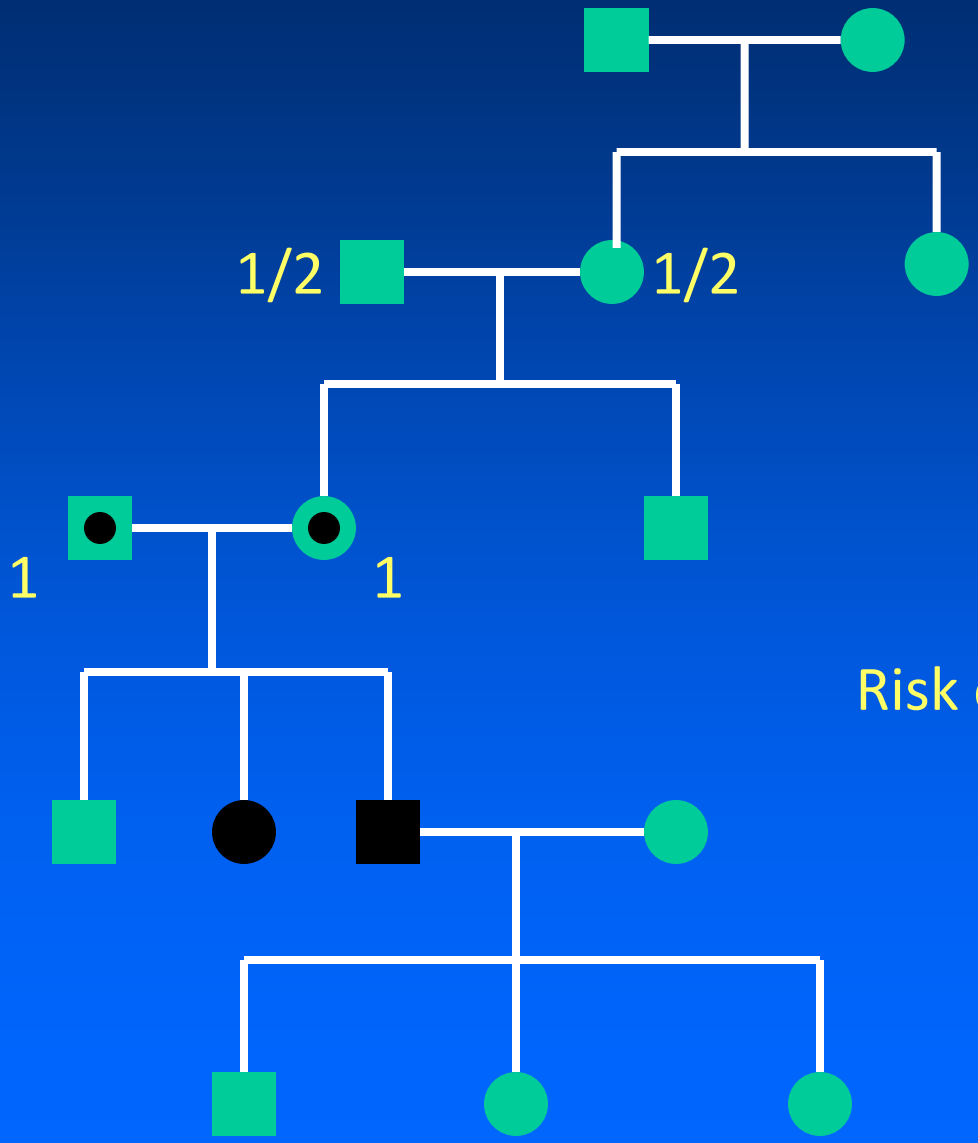
Percentage of genes shared

Autosomal Recessive Inheritance



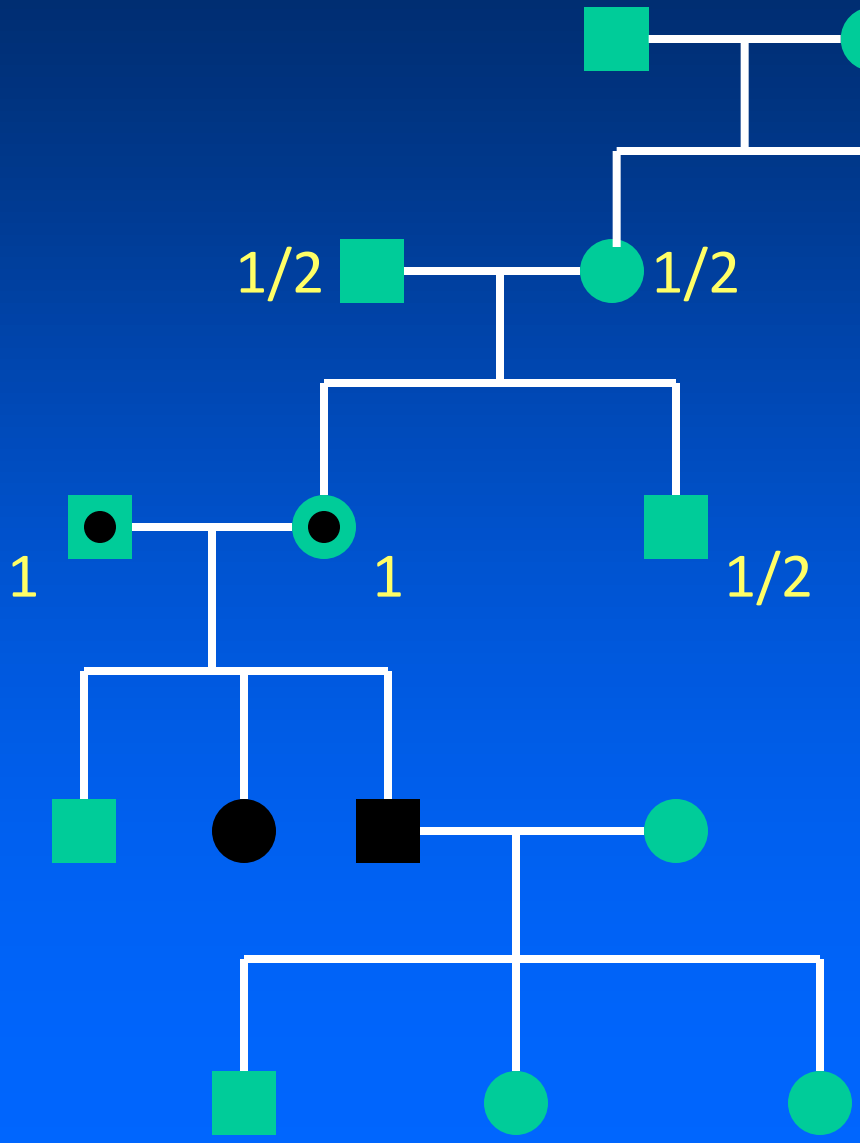
Risk of being a carrier

Autosomal Recessive Inheritance



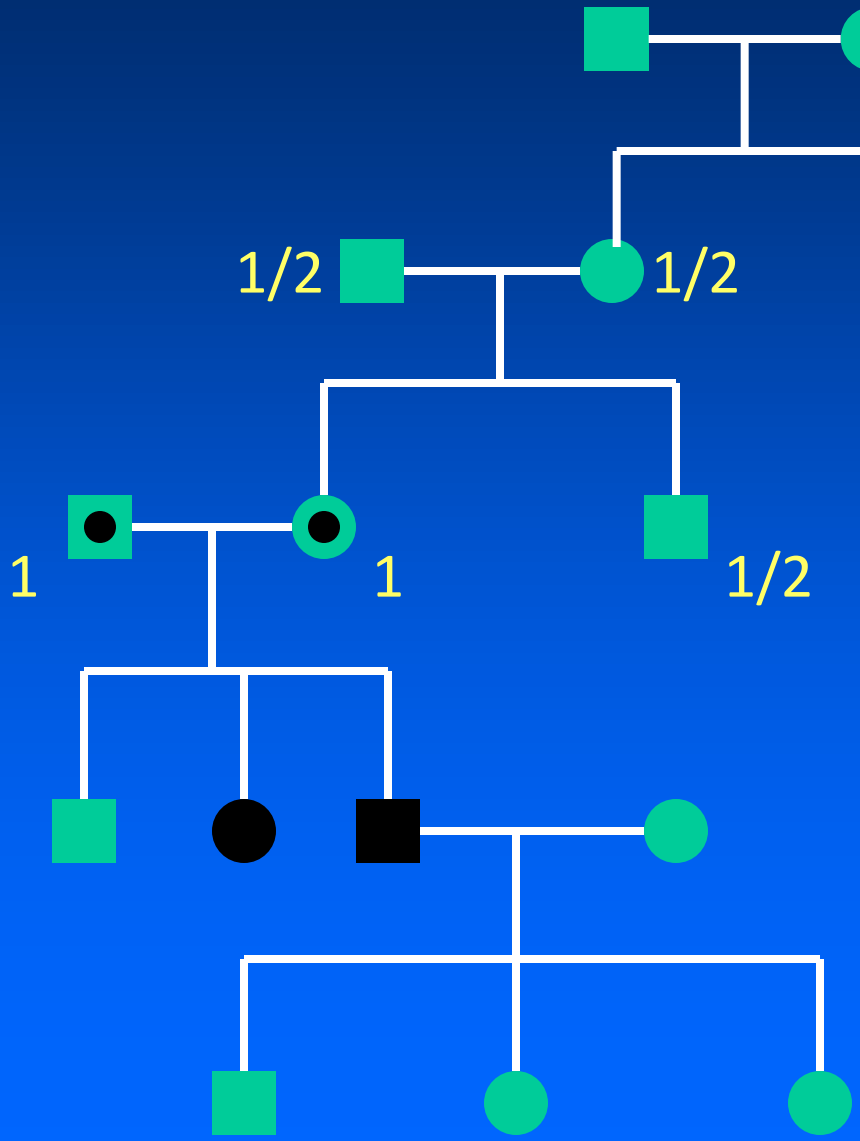
Risk of being a carrier

Autosomal Recessive Inheritance



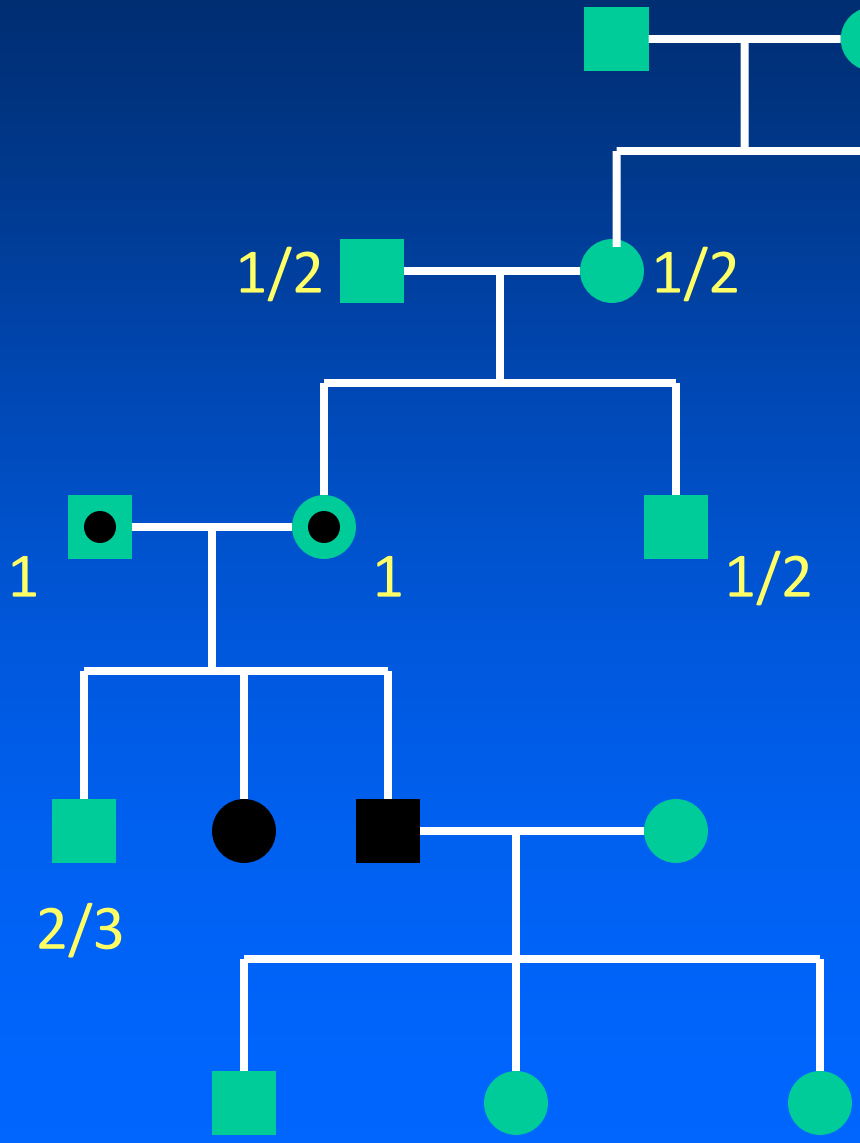
Risk of being a carrier

Autosomal Recessive Inheritance



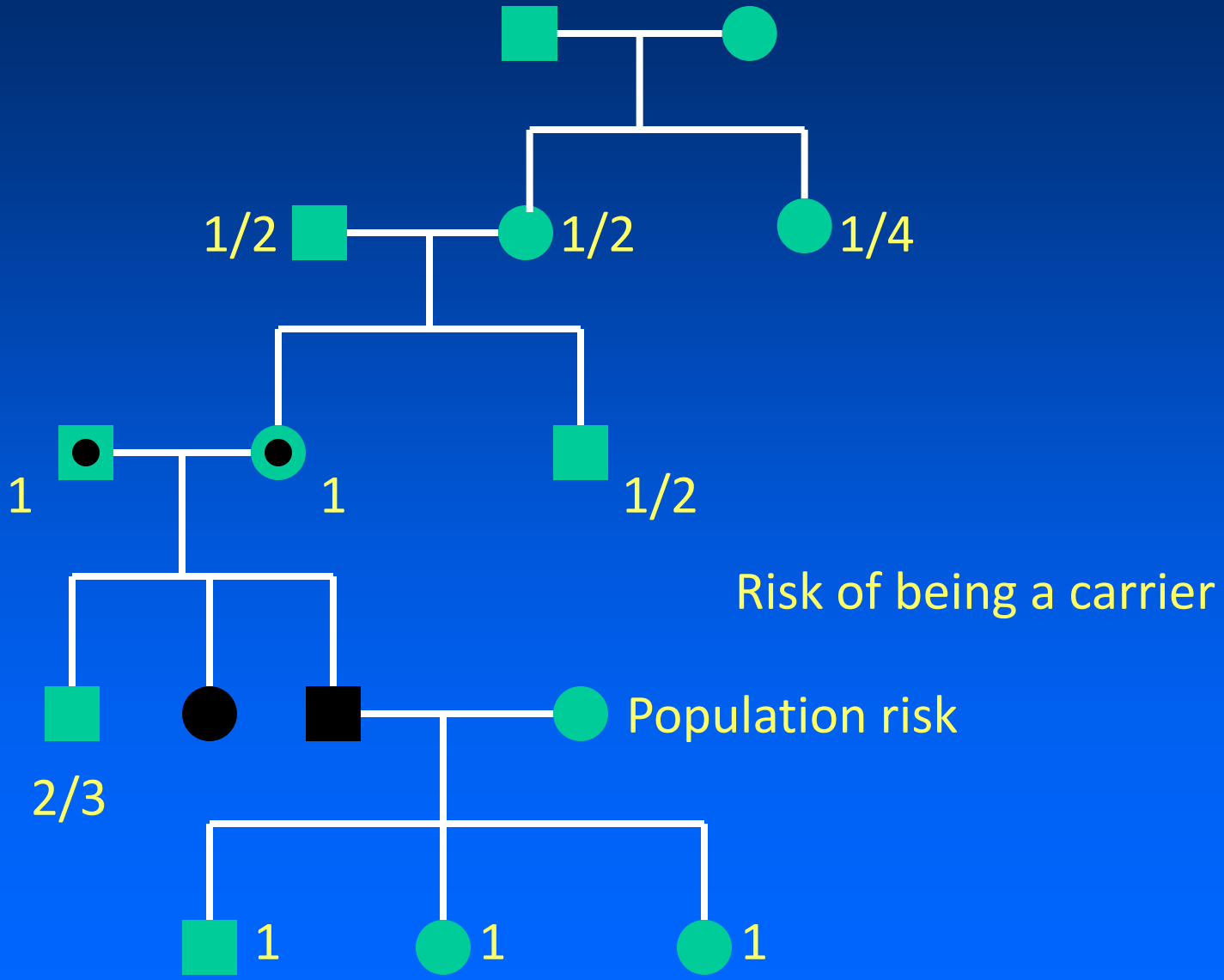
Risk of being a carrier

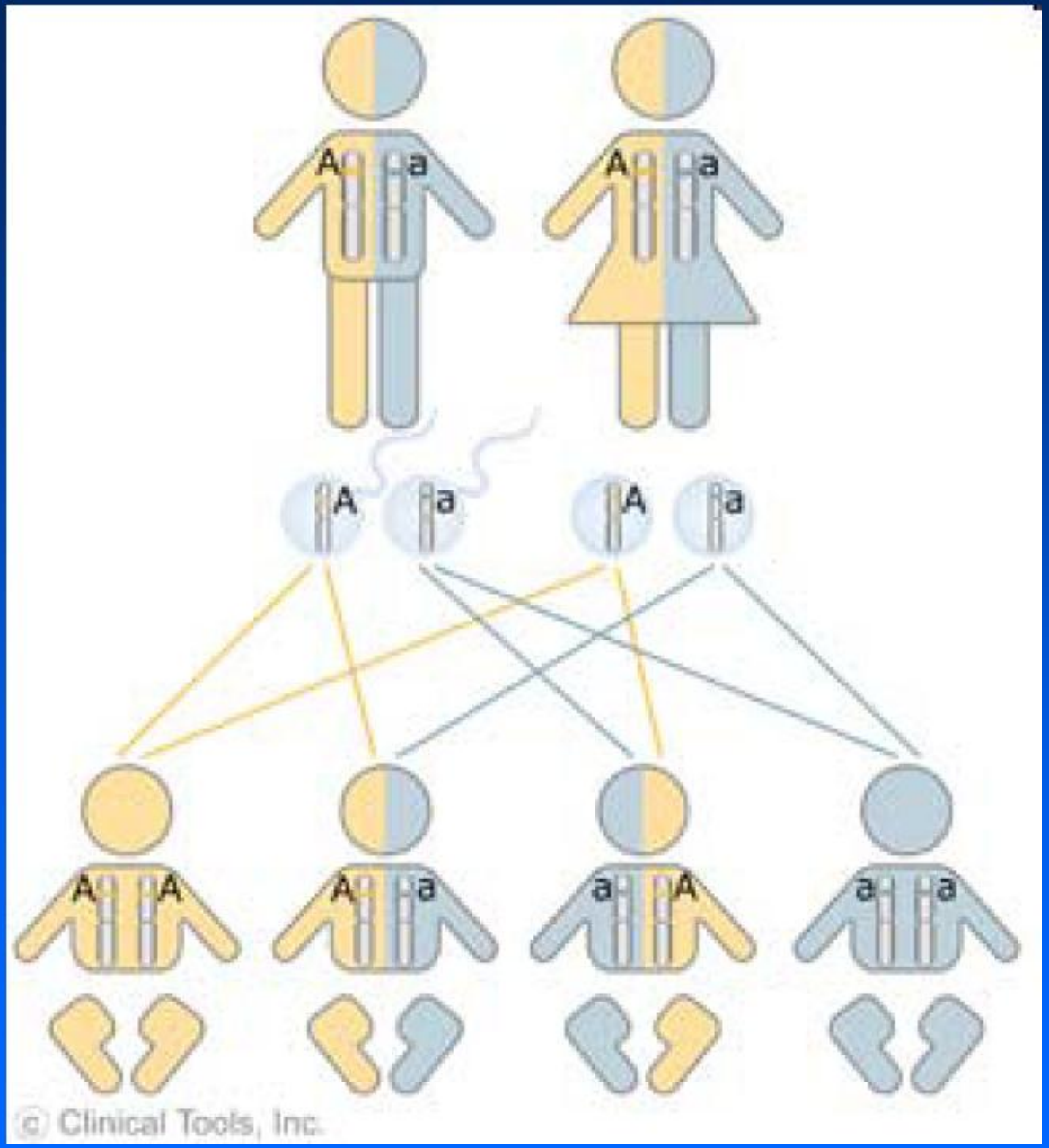
Autosomal Recessive Inheritance



Risk of being a carrier

Autosomal Recessive Inheritance





Why 2/3?

Population risk?

Hardy-Weinberg Principle

"Where in a randomly mating large population with no outside influences, the relative proportion of genotypes for any condition remains constant from one generation to another"

Population risk?

Population carrier frequency

Requires 2 disease alleles for manifestation of condition

- Therefore if p = normal allele
  q =disease allele

- Use Hardy-Weinburg Equilibrium

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

Proportion of the population who are unaffected

Proportion of the population who are carriers

Proportion of the population who are affected

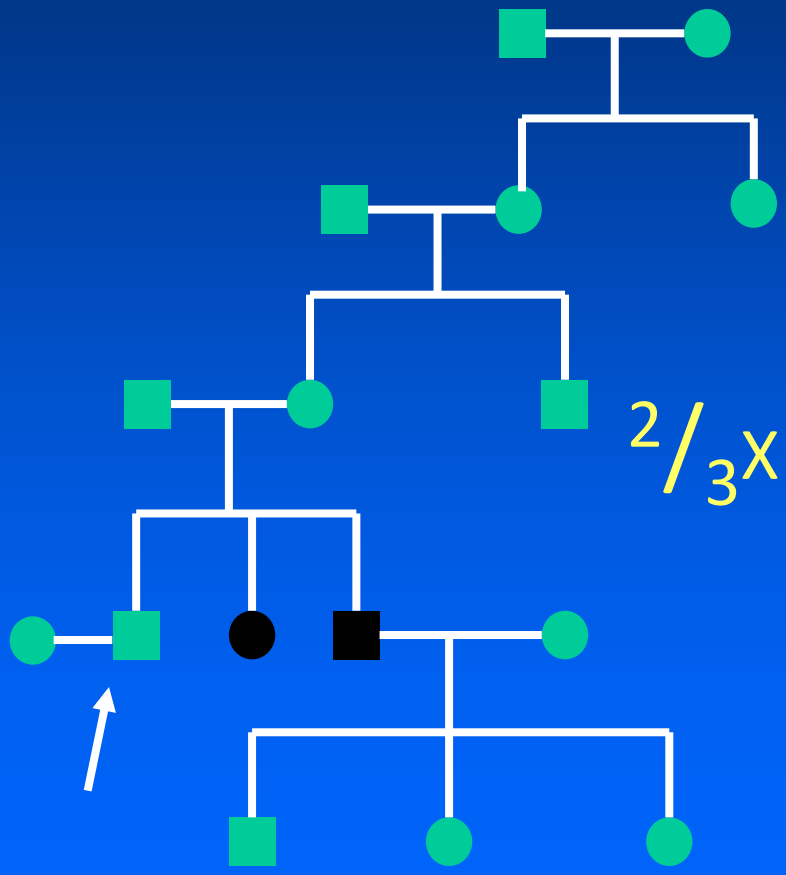
ie disease incidence

Example calculation

- Disease is present in $^{1}/_{10,000}$ population
- $q^2 = {}^{1}/_{10,000}$ so $q = {}^{1}/_{100}$

  $p + q = 1$
- $p = (1-q) = 1 - {}^{1}/_{100} = {}^{99}/_{100} \sim 1$
- $2 \times p \times q = 2 \times 1 \times {}^{1}/_{100}$
- $2pq = {}^{1}/_{50}$
- $^{1}/_{50}$ of the population carry the faulty gene

Calculating risk of having child with recessive condition



e.g. Cystic Fibrosis

- population carrier frequency is 1/22
- therefore chance of an affected child is

$$^{2}/_{3} \times {}^{1}/_{2} \times {}^{1}/_{22} \times {}^{1}/_{2} = {}^{1}/_{132}$$

Recessive risk

What is genetic counselling?

- The process by which patients or relatives at risk of a disorder that may be hereditary are advised of the consequences of the disorder, the probability of developing or transmitting it, and of the ways in which this may be prevented, avoided or ameliorated

  – Peter Harper

What is genetic counselling?

Help individual or family to:

- comprehend the medical facts, including the diagnosis, probable course of the disorder and the available management
- appreciate the way heredity contributes to the disorder and the risk of recurrence in specified relatives
- understand the alternatives
  for dealing with the risk of recurrence
- choose the course of action
  which seems to them appropriate in view of their risk, their family goals and their ethical and religious standards and to act in accordance with that decision
- make the best possible adjustment
  to the disorder in an affected family member and /or the risk of recurrence of that disorder