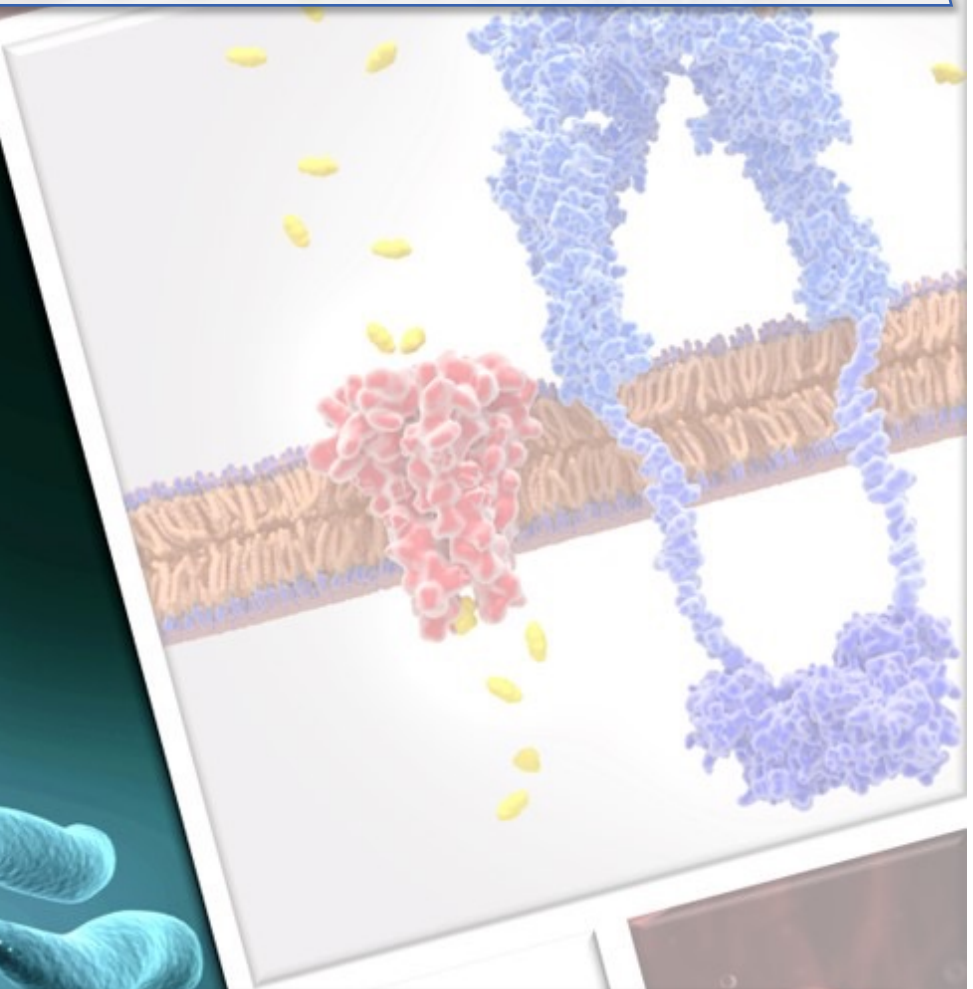
IMPERIAL

Pedigrees and Risk



Dr James Gardiner j.gardiner@imperial.ac.uk

Session Plan

Part 1

- Why draw a pedigree
- How to draw a pedigree

Part 2

- What is risk
- Modification of risk
- How to calculate risk
- Worked examples – mentimeter

Genetic disorders (POM4.2 Explain the utility of familial segregation analysis, summarise a family history by generating a pedigree diagram, generate a genetic risk assessment based on pedigree analysis.)

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Why draw pedigree

- Provides a clear simple summary of information
- Able to spot patterns easily (quiz examples added to modes insendi)
- Explain pattern to patient
- Identify potential carriers of risk gene
- Calculate risk of passing on disease or being a carrier
- Allows informed choice

(POM4.2 Explain the utility of familial segregation analysis, summarise a family history by generating a pedigree diagram, generate a genetic risk assessment based on pedigree analysis.)

Why draw pedigree

- Why not test for disease gene
- Many diseases mix of familial and sporadic
- Many causative gene isn’t known

(POM4.2 Explain the utility of familial segregation analysis, summarise a family history by generating a pedigree diagram, generate a genetic risk assessment based on pedigree analysis.)

Why draw pedigree

- Amyotrophic lateral sclerosis (ALS, motor neurone disease)

~85% sporadic – cause unclear
~15% familial – four known genes account for 65% of cases

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Why draw pedigree

- Why not test for disease gene
- Many diseases mix of familial and sporadic
- Many causative gene isn’t known
- Impossible to test everyone for disease genes – may change WGS
- When disease exclusively familial and mutation known many do not want test

(POM4.2 Explain the utility of familial segregation analysis, summarise a family history by generating a pedigree diagram, generate a genetic risk assessment based on pedigree analysis.)

Why draw pedigree

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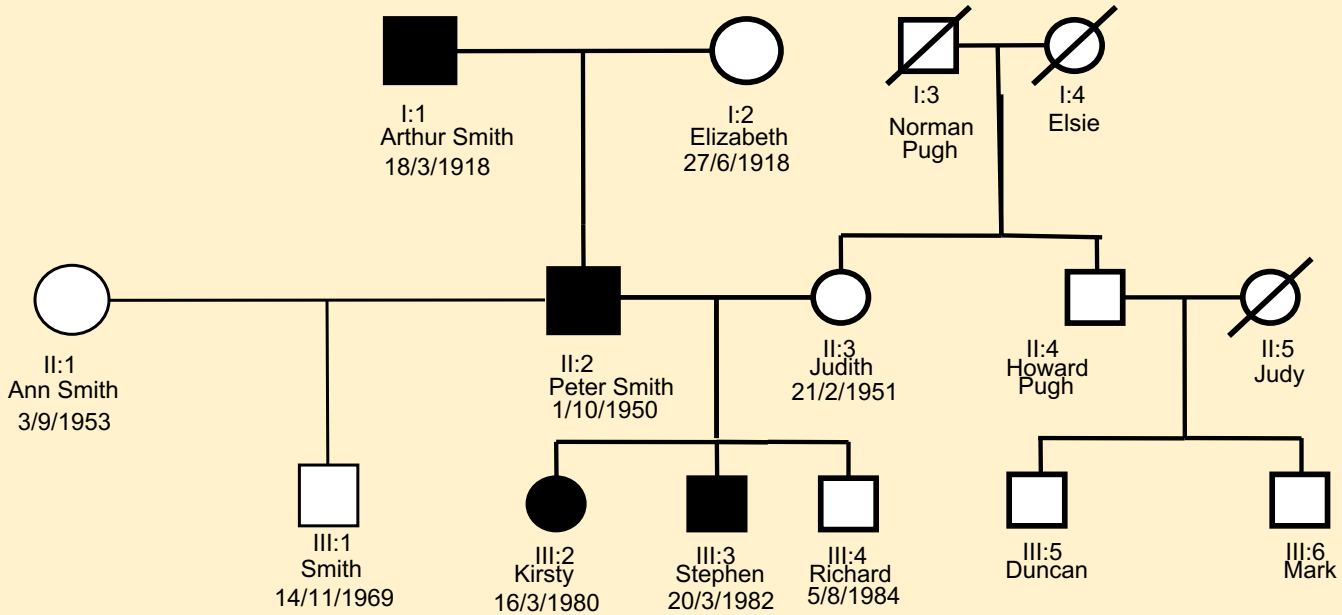
- When disease exclusively familial and mutation known many do not want test
  - >80% of people with 50% risk of inheriting Huntington's disease decline test

(POM4.2 Explain the utility of familial segregation analysis, summarise a family history by generating a pedigree diagram, generate a genetic risk assessment based on pedigree analysis.)

How to draw a pedigree

- Start at the bottom with the proband and siblings
- Choose one parent ask about their siblings, children and parents
- Add other side of family
- Ask about children of other partners



(POM4.2 Explain the utility of familial segregation analysis, summarise a family history by generating a pedigree diagram, generate a genetic risk assessment based on pedigree analysis.)

Potential difficulties

- Incomplete information
  - May not have information on all or many relatives
- Incorrect information
- Family history may not be correct
- Important in clinical setting

(POM4.2 Explain the utility of familial segregation analysis, summarise a family history by generating a pedigree diagram, generate a genetic risk assessment based on pedigree analysis.)

Progress check

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- Pedigree allows identification of inheritance type if any
- Needed to calculate risk

Part 2

- Risk helps informed decision making
- Can reassure some patients if not affected
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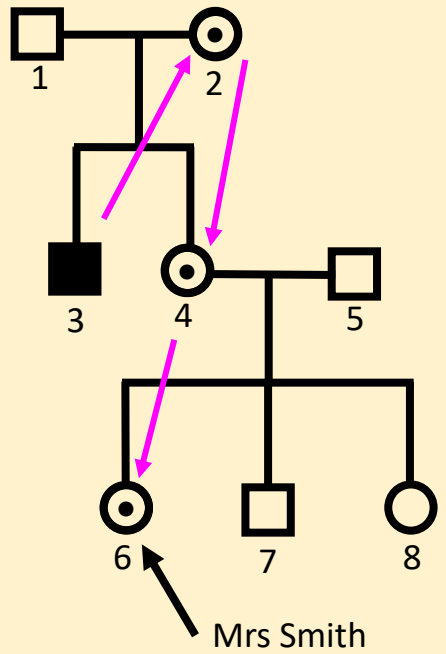
Risk

- This is a calculation of the predicated chance of having the disease or being carrier.
- Work from person with known phenotype to subject
- If more than 1 affected individual then start closest affected relative
- Calculate risk for each person on path from the start point to the subject
- Multiply risks together

Risk

- This is a calculation of the predicated chance of having the disease or being carrier.
- **Mrs Smiths maternal uncle (3) has X linked condition**
- **What is chance Mrs Smith (6) is a carrier**
- **Work from person with known phenotype to subject**
- 2 must be carrier 1 in 1 chance
- Since 2 is carrier 1 in 2 chance 4 inherited mutation
- Assume 4 carrier therefore 1 in 2 chance Mrs Smith (6) inherited mutation
- Multiply risks together 1 x 1/2 x 1/2
- Therefore 1 in 4 chance Mrs Smith (6) carrier



Risk

- Take account of all information
  - Phenotype
  - Disease characteristics
- Family distribution for X-linked and mitochondrial disease
  - which side of family disease is on
  - Which parent has the disease

Risk modifiers

- Which side of family disease is on
  - X-linked, mitochondrial
- Ethnic background
  - Many diseases have different prevalence in different populations eg CF, Sickle cell, Tay-Sachs
    - Heterozygote advantage- sickle cell, CF?
    - Founder effect- Tay-Sachs

Risk modifiers

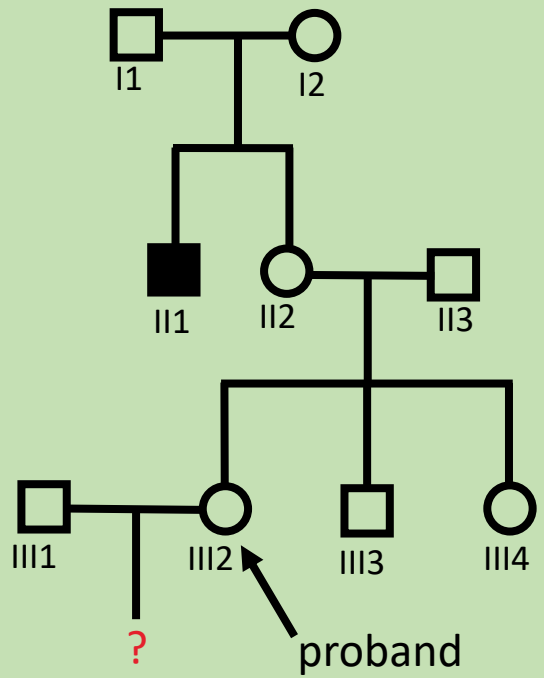
On which continent is the area with the highest prevalence of Sickle cell trait

Europe
America
Africa
Asia

Risk modifiers

- Which side of family disease is on
  - X-linked, mitochondrial
- Ethnic background
  - Many diseases have different prevalence in different populations eg CF, Sickle cell, Tay-Sachs
    - Heterozygote advantage
    - Founder effect
- Information you know about the person
  - Their phenotype
  - Biological sex

Question Time:1



Mrs Smith consults you
Her maternal uncle has Haemophilia A an X-linked disease (incidence 1: 5000)

Want to know risk of having affected son?

a. 1 in 4

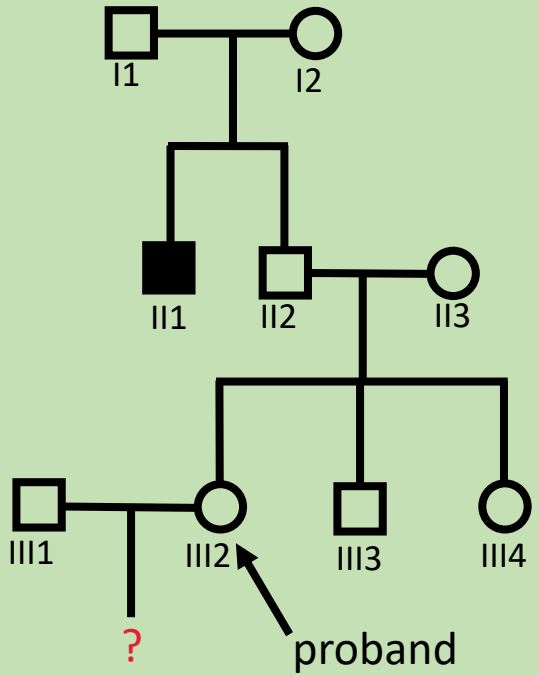
b. 1 in 8

c. 1 in 16

d. 1 in 2

e. Population risk

Question Time:2



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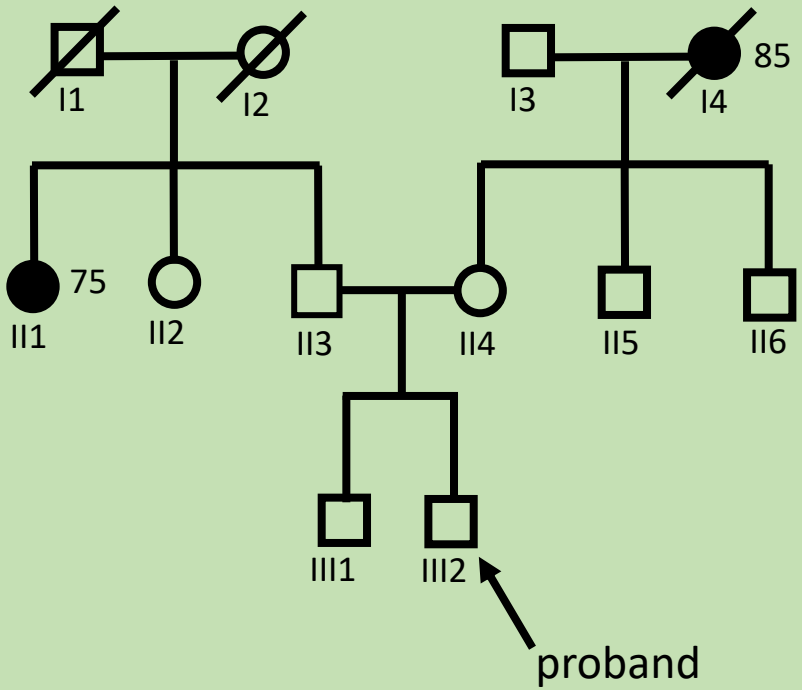


Mr Jones (age 30) consults you regarding Alzheimer's disease
Mr Jones is worried as he has recently read about an inherited form of AD
AD (~3% familial ~97% sporadic) overall prevalence ~1.6%
Age onset FAD 40-50
FAD autosomal dominant disease
His paternal aunt who is now 80 developed symptoms of dementia at 75
His maternal grandmother developed symptoms at 85
No one else affected (mother is 58; father 60)
Worried he may have disease

a. 1 in 4

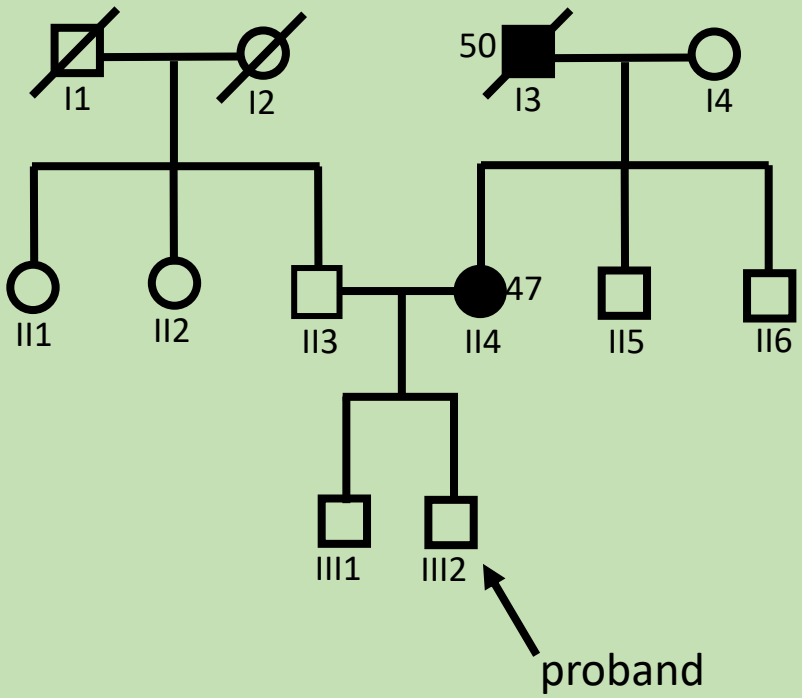
b. 1 in 8

c. 1 in 16

d. 1 in 2

e. Population risk

Question Time:4



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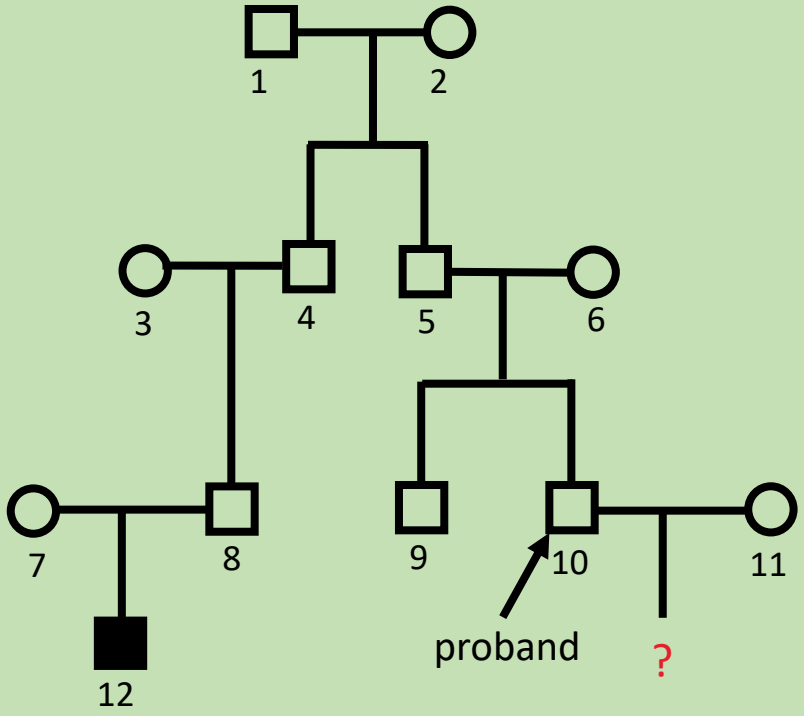
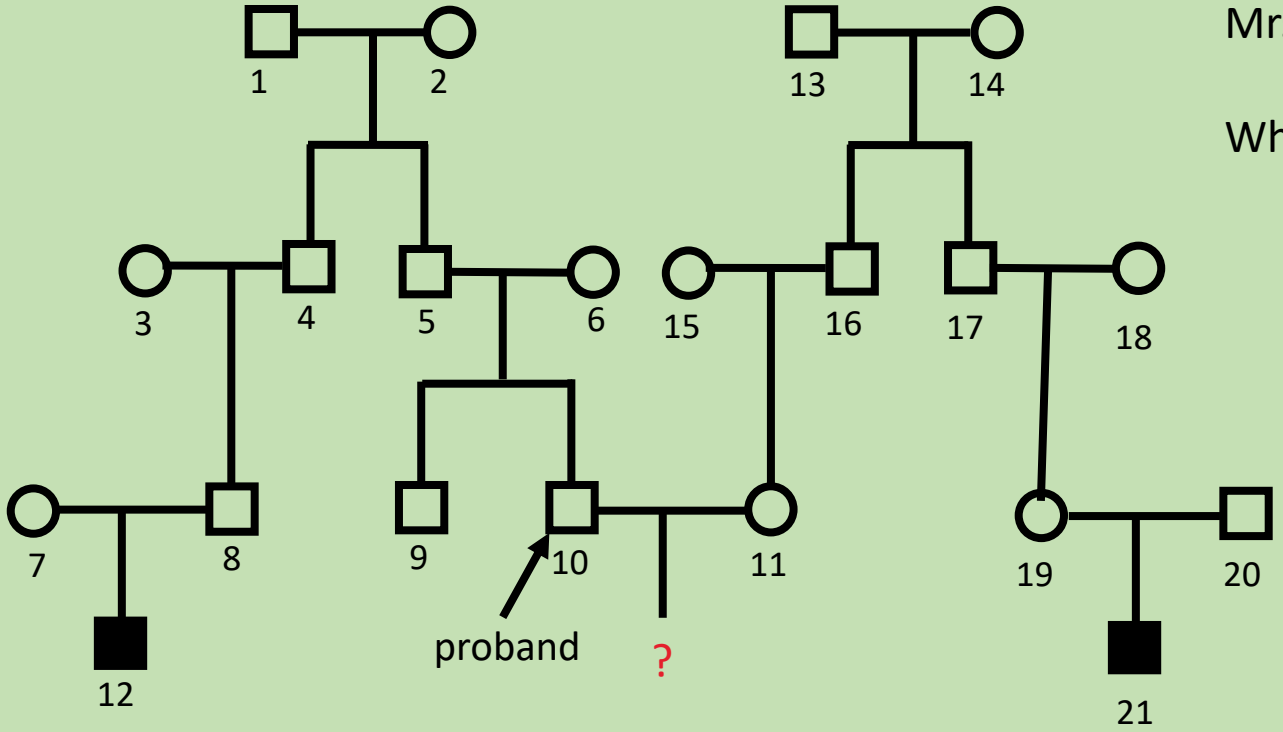
Age onset FAD 40-50
FAD autosomal dominant disease
His mother who is now 50 developed symptoms of dementia at 42
His maternal grandfather developed symptoms at 50
Neither of his two maternal uncles who are now in their late 60s are affected
No one on his fathers side is affected.
Worried he may have inherited gene and develop disease

Question Time:5



Mr & Mrs Taylor consult you both of NW European descent
Mr Taylor's first cousin has a son diagnosed with CF
No one with disease in Mrs Taylors family
They are thinking of starting a family and want to know risk of having child with CF
CF autosomal recessive
1:22 NW European descent carriers

Add information from other side of family

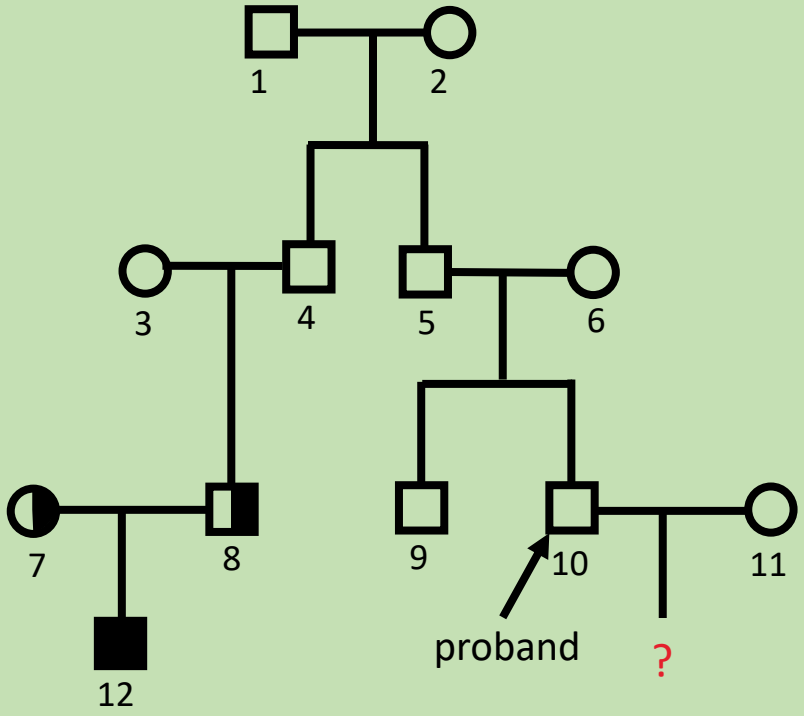


Mrs Taylors first cousin has now had a child with CF

What is the risk of Mrs and Mr Taylor having an affected child

How more information modifies risk

More information and risk



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CF autosomal recessive
1:22 NW European descent carriers
What is risk if
3 carrier
4 carrier
5 carrier
10
10 and 11

Question Time:6

Couple who are both known to be carriers of recessive disease (Aa)
Have unaffected child want to know risk of them being a carrier (Aa)
A- normal allele a- disease allele

Parent Allele	**A**	**a**
A	AA	Aa
a	Aa	aa

a. 1 in 4

b. 1 in 3

c. 1 in 2

d. 2 in 3

e. 3 in 4

Hereditary haemochromatosis

“So THAT'S why you're feeling tired all the time! The thousands of patients told they're healthy when they really have genetic condition which can damage your liver and even cause kidney failure”

Daily Mail

Haemochromatosis 'bigger threat than we thought'
BBC

How a simple blood test got me thinking about our behaviour and choices
Guardian

Killer haemochromatosis is ‘most common genetic disease’ – often mistaken for extreme tiredness
The Sun

‘Stealth disease’ written off as old age may be behind thousands of cancers and joint problems, study shows
Genetic disorder dubbed ‘Celtic curse’ afflicts one in five men who carry mutation with liver disease or joint issues
Independent

Genetic disorders (POM4.2 Explain the utility of familial segregation analysis, summarise a family history by generating a pedigree diagram, generate a genetic risk assessment based on pedigree analysis.)

Hereditary haemochromatosis

Hereditary (Familial) Haemochromatosis autosomal recessive disease

Mutation in Human homeostatic iron regulator protein (HFE)

Result excess iron absorption. Humans cannot excrete excess iron so builds up in tissues

Wide range of symptom including tiredness

Hereditary haemochromatosis – a common cause of tiredness ?

Prevalence

HH approximately 1 in 200 northern Europeans homozygous 0.5%

Of these only 10% have clinically relevant iron accumulation 0.05%

Chronic tiredness/fatigue main symptom of 7% all primary care patients

So even if all HH in tiredness group 1 in 140 have HH

In UK men cause 1.6% hip fractures, 5.8% liver cancer.

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