Genetic risk calculations: recessive disease

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GE02 day 5 part 2

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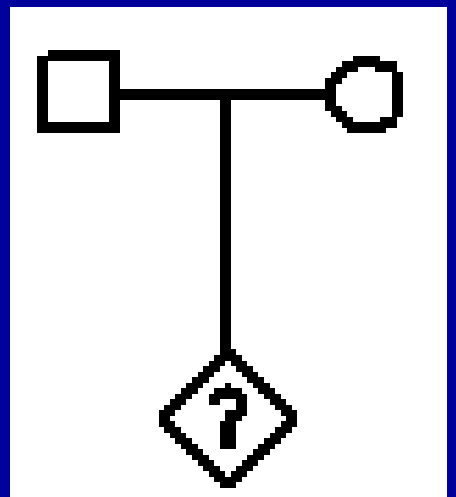
Overview

- Simple testing for recessive disease
- Incorporating molecular test information
- Risk in inbred pedigrees

Problem

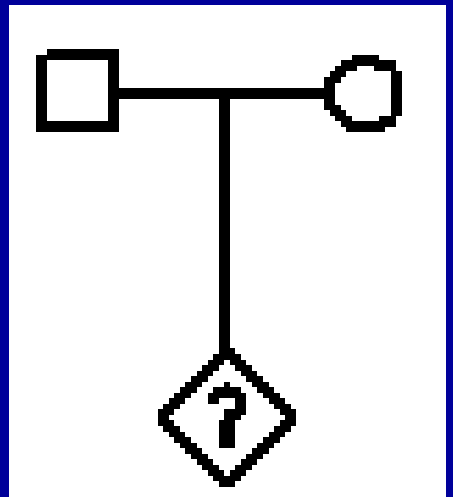
- Recessive model
  - P(M) = q
  - P(D|MM)=1
  - P(D|MN)=P(D|NN)=0
- Population prevalence
  P(D) = q^2
- What is the risk for “?”



Solution

- P(MN|person is unaffected) = ?

	H-MM	H-NM	H-NN	
Prior, P(Hi)	qq	2qp	pp	
Conditional, P(X|Hi)	0,0	1,0	1,0	Total, P(X)
Joint, P(Hi)P(X|Hi)	0,0	2qp	pp	p(2q+p)
Posterior, P(Hi|X)	0,0	2q/(2q+p)	p/(2q+p)	



$= 2q / (2q + p) = 2q / (2q + 1 – q) = 2q / (1 + q)$

- Risk for the child of unaffected parents:

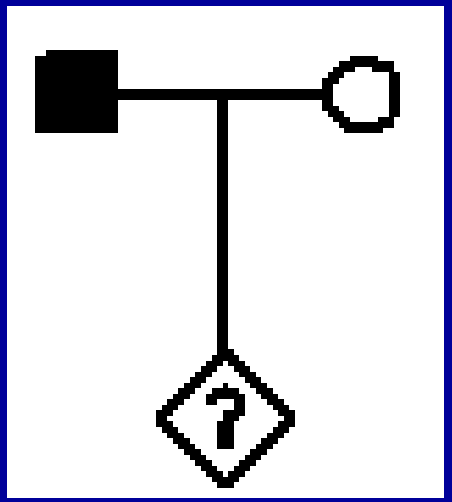
  ¼ P(fa=MN,mo=MN|fa,mo=Unaffected) =

  $= ¼ P(MN|person is unaffected)^2 = q^2 / (1 + q)^2$

- If $q \rightarrow 0$, $P(MN|unaffected) \approx 2q$, risk $\approx q^2$

Problem

- Recessive model
  - P(M) = q
  - P(D|MM)=1
  - P(D|MN)=P(D|NN)=0
- What is the risk for “?”



Solution

- P(MN|person is unaffected) = 2q / (1 + q)
- Risk for the child:

  ½ P(mo=MN|mo=Unaffected) =

  = ½ 2 q / (1 + q) = q / (1 + q)
- Relative Risk = (q / (1 + q))/q^2) = 1/(q(1+q))
- if q $\longrightarrow$ 0
  - Risk for child $\approx$ q
  - Relative risk for a child of affected person = 1/q

Problem

Given the carrier frequency is 1/30 (CF case). compute

- Risk for a child of unaffected parents
- Risk for a child of affected mother and unaffected father
- Risk for a child of affected mother and affected father
- Relative risk for a child of an affected parent (other is not affected)

Solution, approximate

- Carrier frequency
  - q_a = carr.freq/2 => q_a = 1/60 = 0.0167
- risk for a child of unaffected parents
  - q_a^2 = 1/3600 = 0.000278
- risk for a child of affected mother and unaffected father
  - q_a = 1/60 = 0.0165
- Risk for a child of affected mother and affected father
  - 100% (both parents are homozygous mutant)
- Relative risk for a child of an affected parent
  - $1/q_a$ = 60

Solution, exact

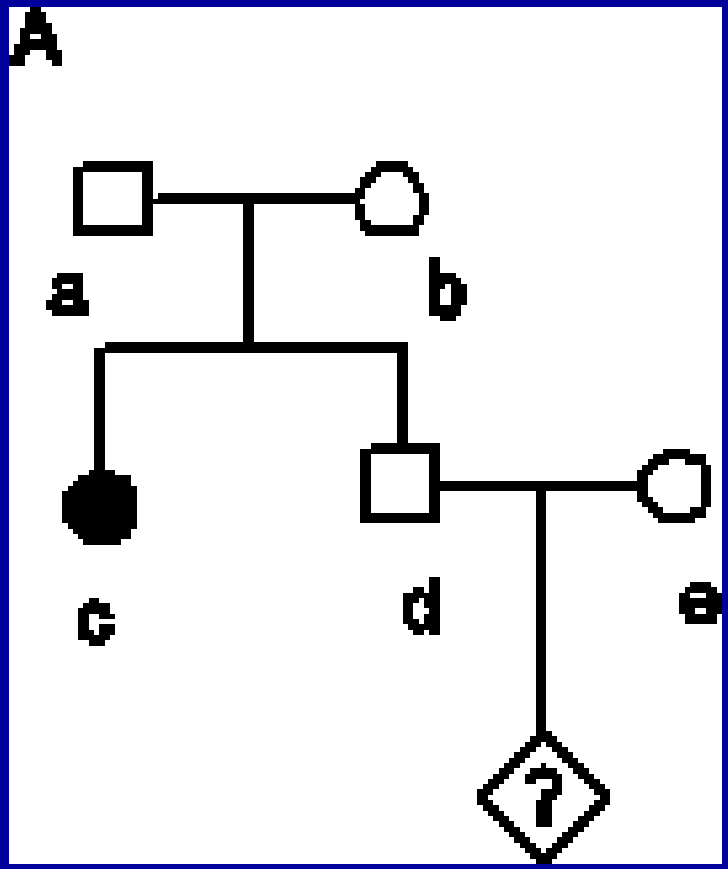
- Carrier frequency
  - $q_e = 1 - \sqrt{(1 - \text{carr.freq.})} \Rightarrow q_e = 0.0168$ (0.8% more)
- risk for a child of unaffected parents
  - $q_e^2 / (1+q_e)^2 = 0.000273$ (1.7 % less)
- risk for a child of affected mother and unaffected father
  - $q_e / (1+q_e) = 0.0165$
- Relative risk for a child of an affected parent
  - $1/q_e = 60.5$

Solution, comparison

carrier freq	0,03		
	exact	approx	Error, %
q	0,01681	0,01667	0,84
both parents U	0,00027	0,00028	-1,66
one parent D	0,01653	0,01667	-0,83
RR	60,49576	60,00000	0,82

Problem

- Recessive model
  - P(M) = 1/40 = 2.5%
  - P(D|MM)=1
  - P(D|MN)=P(D|NN)=0
- What is the risk for “?”



Outline of solution

Compute

- P1 = P(“e” is MN|”e” is unaffected)
- P2 = P(“d” is MN|”d” is unaffected, has affected sib)

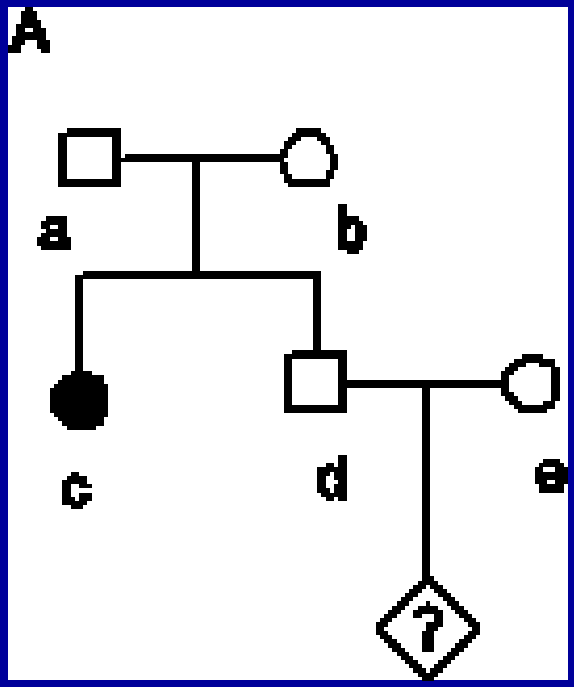
Chance for the child to be affected is (¼ P1 P2)

Solution (a)

compute risk that “e” is a heterozygote given “e” is not affected

P(e=MN|e is Unaffected) =

= 2q / (1 + q) = 0.049



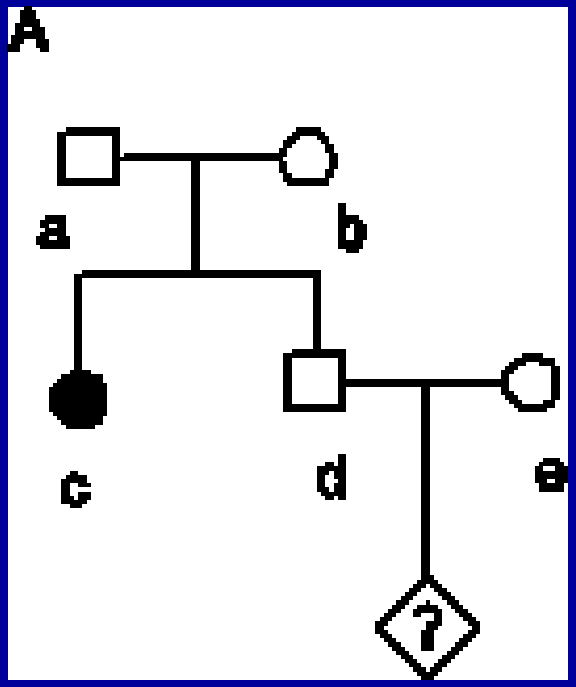
Solution (b)

compute probability that “d” has certain genotype, given sib is affected

P(d=MM|sib is A) = 1/4

P(d=MN|sib is A) = 1/2

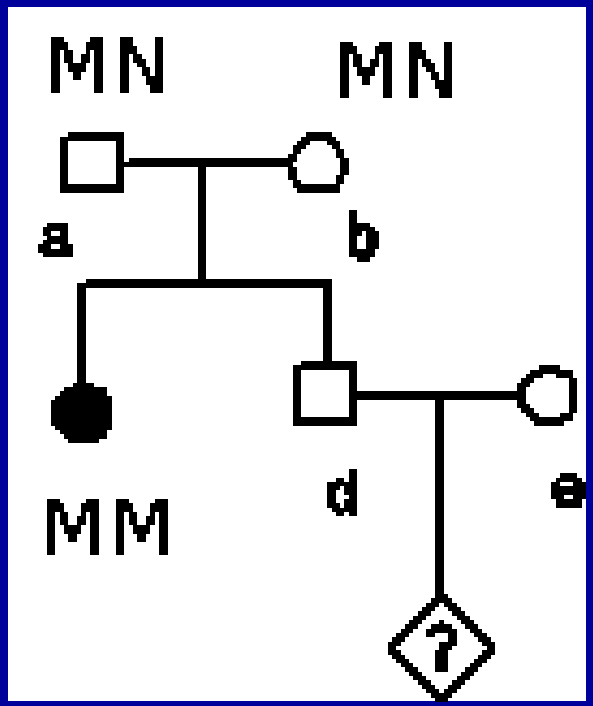
P(d=NN|sib is A) = 1/4



Solution (b)

compute risk that “d” is MN, given sib is affected AND “d” is not affected

	H-MM	H-NM	H-NN	
Prior, P(Hi)	0,25000	0,50000	0,25000	
Conditional, P(X|Hi)	0,00000	1,00000	1,00000	Total, P(X)
Joint, P(Hi)P(X|Hi)	0,00000	0,50000	0,25000	0,75000
Posterior, P(Hi|X)	0,00000	0,66667	0,33333	1,00000



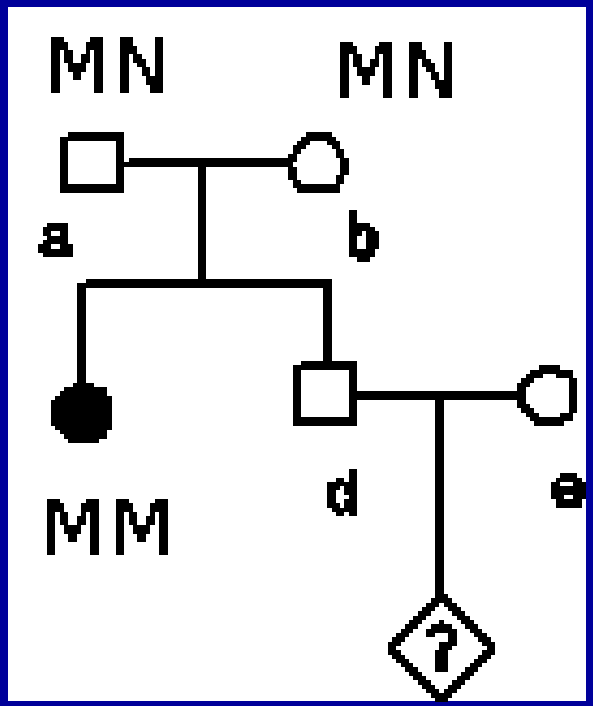
P(d=MN|sib affected, d is not) = 2/3

Solution (c)

Risk is

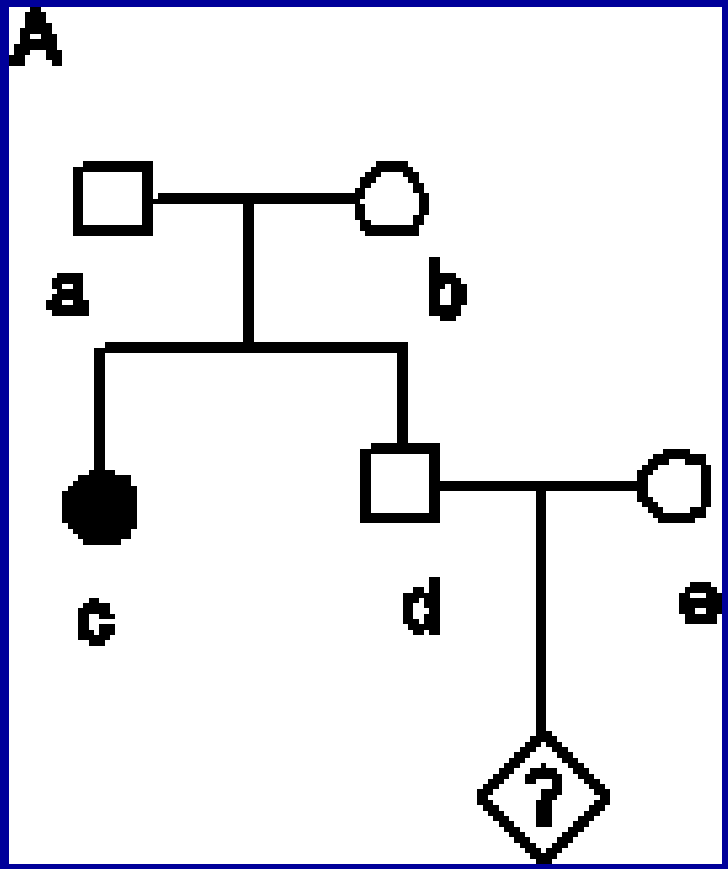
P(e=MN|e is Unaffected) x
P(d=MN|sib affected, d is Unaffected) x 1/4 =
= 0.049 x 2/3 x 1/4 =
= 0.008

RR = 0.008/(1/1600) =
1600 0.008 = 12.8



Generalization

- Recessive model
  - P(M) = q
  - P(D|MM)=1
  - P(D|MN)=P(D|NN)=0
- What is the risk for “?”

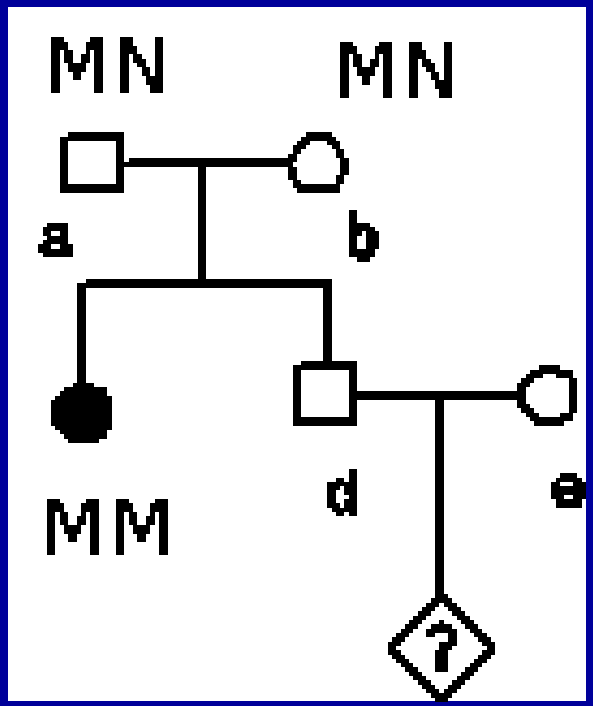


Solution for *q*

- P(e is MN|X1,q) = 2q / (1 + q)
- P(e is MN|X1,q) = 2/3
- Risk for “?” is

  ¼ P(e is MN|X1,q) P(e is MN|X1,q) =

  = q / (3 (1 + q))

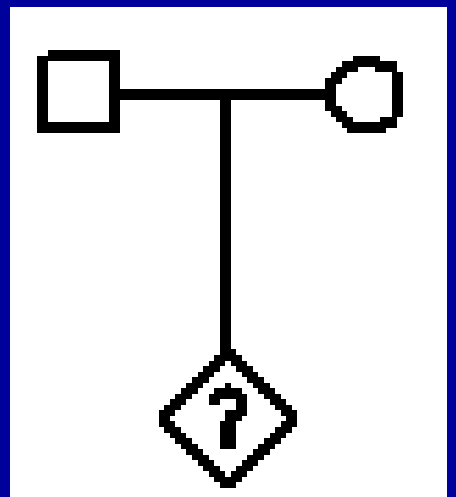


Overview

- Simple testing for recessive disease
- **Incorporating molecular test information**
- Risk in inbred pedigrees

Incorporating more information

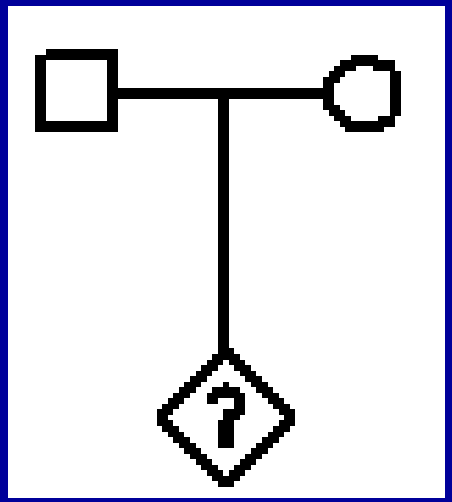
- Performing a molecular test detecting known prevalent mutations in the gene
- Test has some “sensitivity”: detects **S**% of the mutations (miss some rare mutations) present in the population
- **S** of a test is population-specific



- Assume non-carriers never test positive

Problem

- Recessive model
  - P(M) = q
  - P(D|MM)=1
  - P(D|MN)=P(D|NN)=0



- Both parents test negative at the test with 85% sensitivity

- What is the risk for “?”

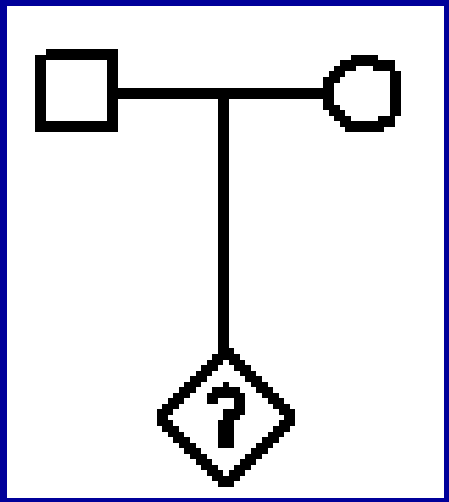
Solution

- For a parent, probability to be MN given he/she is unaffected is

  P(MN|U) = 2 q / (1 + q)

  and P(NN|U) = 1 – 2 q / (1 + q)

- X, information, is that it tests negatively



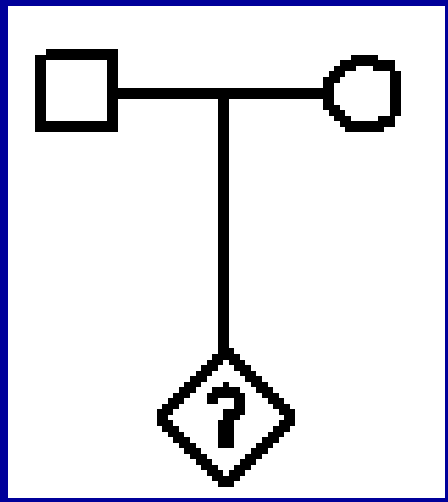
$$P(MN \mid U, test-) = \frac{P(U, test- \mid MN)P(MN)}{\sum_{g=MM,MN,NN} P(U, test- \mid g)P(g)}$$

$$= \frac{P(U, test- \mid MN)P(MN)}{P(U, test- \mid MN)P(MN) + P(U, test- \mid NN)P(NN)} =$$

$$\frac{1 \cdot P(test- \mid MN)P(MN)}{1 \cdot P(test- \mid MN)P(MN) + 1 \cdot P(NN)} = \frac{(1-S) \cdot 2q(1-q)}{(1-S) \cdot 2q(1-q) + (1-q)^2}$$

Example

- Assume that mutation frequency, q is 1/60 (CF gene)
- Test sensitivity is 85%
  - What is the probability for a child to be affected with CF if both parents are unaffected and test negatively for CF gene?
  - How test information modifies the risk?



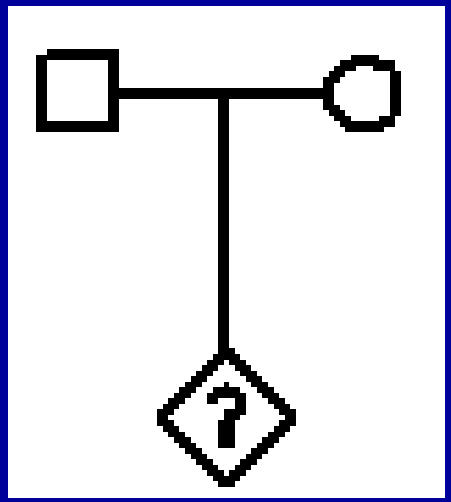
Solution

- P(test=negative|MN) = 0.15
- P(test=negative|NN) = 1.0
- P(MN/U,test) = 0.005

  P(both parents are MN | U,U,test,test) =

  =P(MN/U,test) P(MN/U,test) =

  = 0.000025

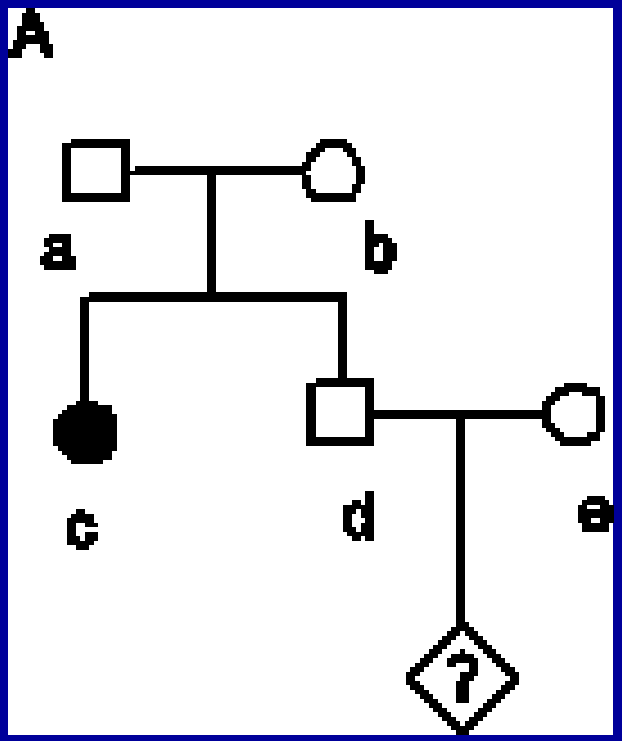


Risk for child is 0.000006 (vs pop. risk of 0.00028)

is 43 times lower then risk before the test

Problem

- Assume CF model
- Both parents “**d**” and “**e**” test negative at the test with 85% sensitivity



- What is the risk for “?”
- What is RR for “?”

Solution

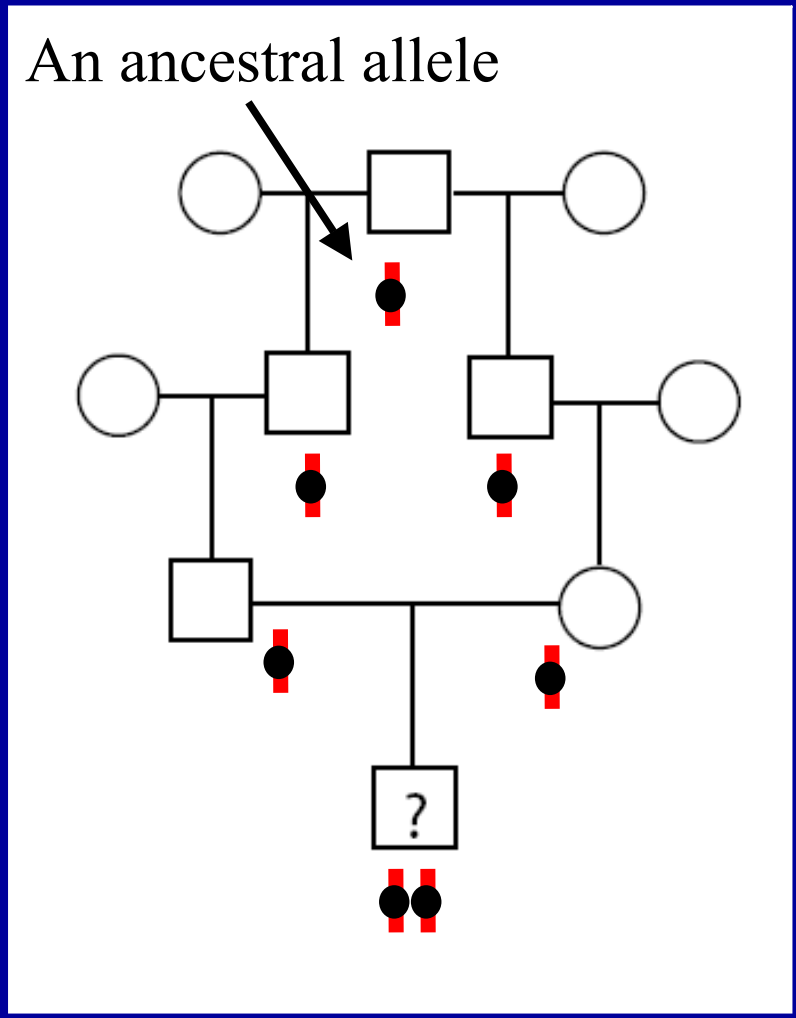
- Probability to be carrier before the test
  - D: 2/3
  - E: 2q = 1/30
- Probability to be carrier after the test
  - D: 2/3 x 0.15 = 30/300 = 1/10
  - E: 1/30 x 0.15 = 15/3000 = 5/1000 = 1/200
- Risk for child
  - 1/10 1/200 ¼ = 1/4000
- RR = (1/4000) / (1/3600) = 36/40 = 0.9

Overview

- Simple testing for recessive disease
- Incorporating molecular test information
- **Risk in inbred pedigrees**

Consanguineous marriages

- There is possibility for autozygosity in consanguineous marriages
- For “?” expected genotypic distribution is p^2+pqF, $2pq(1-F)$, q^2+pqF, where F is the coefficient of inbreeding
- Recessive disease: relative risk for “?” is $(1+pF/q)$



Computing F

- For an allele from ancestor 5 or 6, the chance to become autozygous is $\frac{1}{2}^6$
- There are 4 such alleles, hence
  - $F = 4\ \frac{1}{2}^6 = \frac{1}{2}^4$