Genetic risk calculations: recessive disease

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GE02 day 3 part 4

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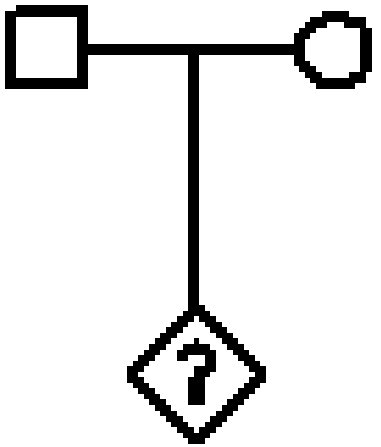
Problem

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

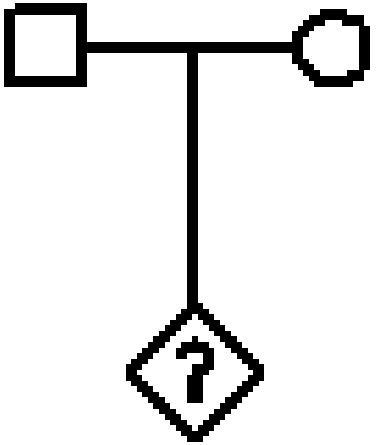


- What is the risk for “?”

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)	



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

$= 2q / (2q + 1 - q) = 2q / (1 + q)$

- if $q \to 0$ P(MN|unaffected) $\approx 2q$

- Risk for the child of unaffected parents:

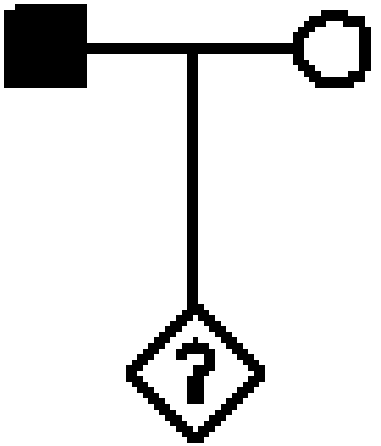
¼ P(fa=MN,mo=MN|fa,mo=Unaffected) =

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

- if $q \to 0$ 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 / (2q + p) =

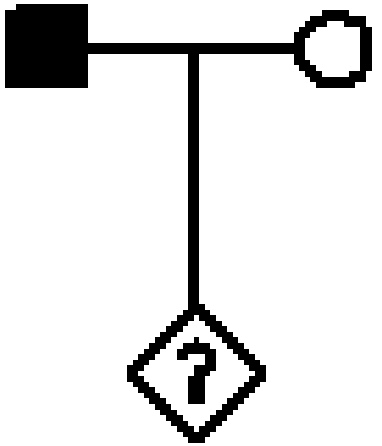
  = 2q / (2q + 1 – p) = 2q / (1 + q)

- Risk for the child:

  ½ P(mo=MN|mo=Unaffected) =

  = ½ 2 q / (1 + q) = q / (1 + q)

  - if q → 0 risk ≈ q
  - Relative risk for a child of affected person = 1/q



Task

- 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
  - Relative risk for a child of an affected parent

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
- Relative risk for a child of an affected parent
  - $1/q_a^2$ = 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
  - $1/q_e = 60.5$

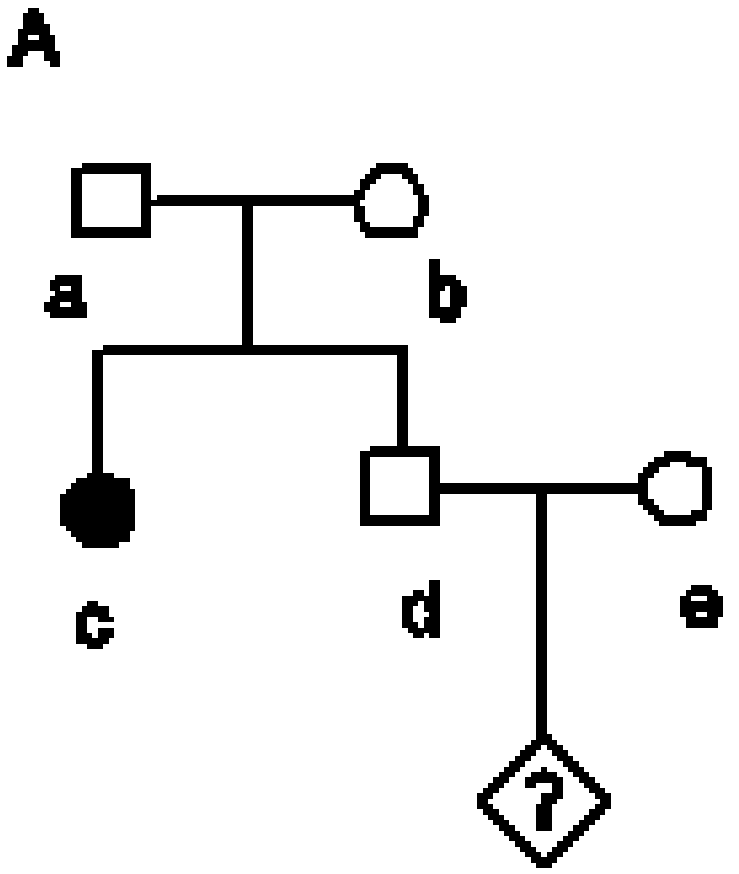
Solution, comparison

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

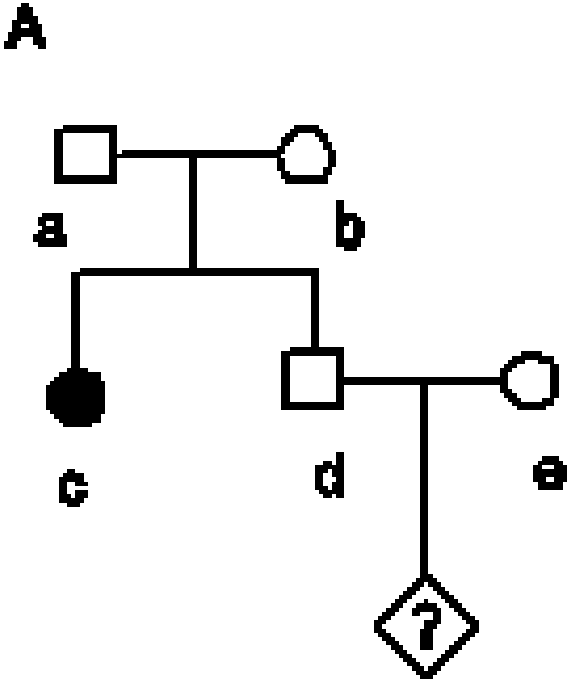
Problem

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



Solution (a)

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



H_{MM}: “e” is MM

H_{MN}: “e” is MN

H_{NN}: “e” is NN

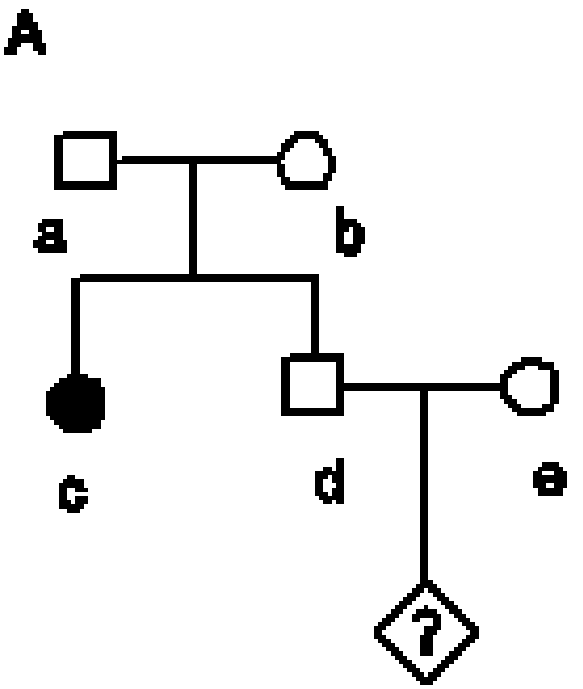
$P(H_{MM}) = 1/40*1/40 = 1/1600$

$P(H_{MN}) = 2*1/40*39/40 = 78/1600$

$P(H_{NN}) = 39/40*39/40 = 1521/1600$

Solution (a)

(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)

(b) compute risk that “d” is heterozygote, given pedigree data

H_{MM}: “d” is MM

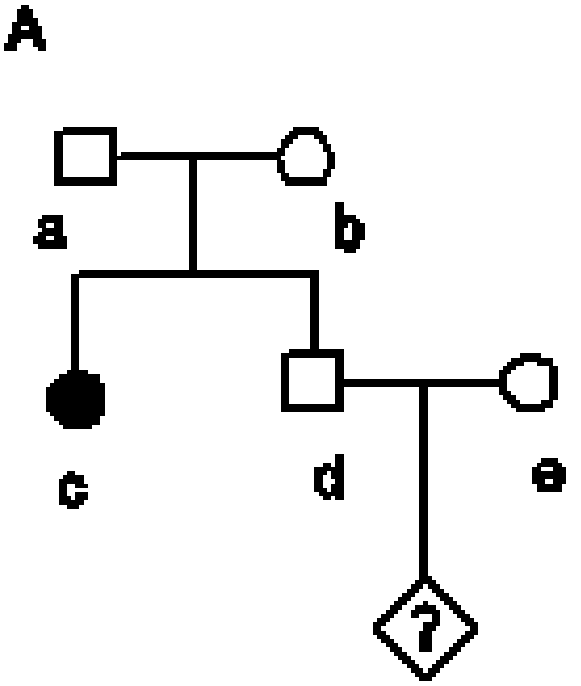
H_{MN}: “d” is MN

H_{NN}: “d” is NN

$P(H_{MM}) = 1/4$

$P(H_{MN}) = 1/2$

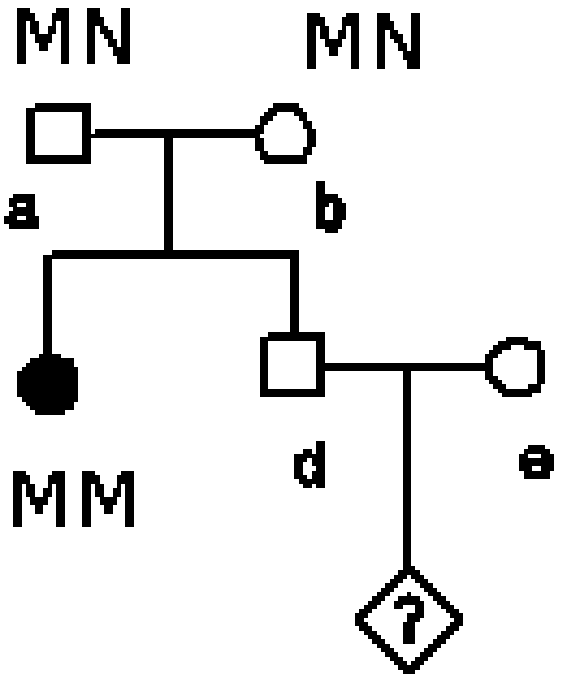
$P(H_{NN}) = 1/4$



Solution (b)

(b) compute risk that “d” is heterozygote, given pedigree data

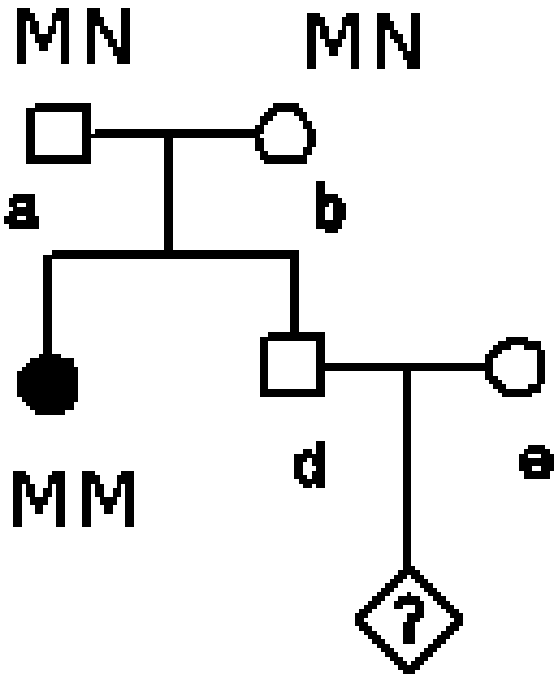
	H-MM	H-NM	H-NN	
Prior, P(Hi)	0,25000	0,50000	0,25000	
Conditional, P(X|Hi)	0,00000	1,00000	1,00000	Total, P(X)
Joint, P(Hi)P(X|Hi)	0,00000	0,50000	0,25000	0,75000
Posterior, P(Hi|X)	0,00000	0,66667	0,33333	1,00000



P(d=MN|pedigree, d is Unaffected) = 2/3

Solution (c)

(c) Risk is



P(e=MN|e is Unaffected) x

P(d=MN|pedigree, d is Unaffected) x

1/4 =

= 0.049 x 2/3 x 1/4 =

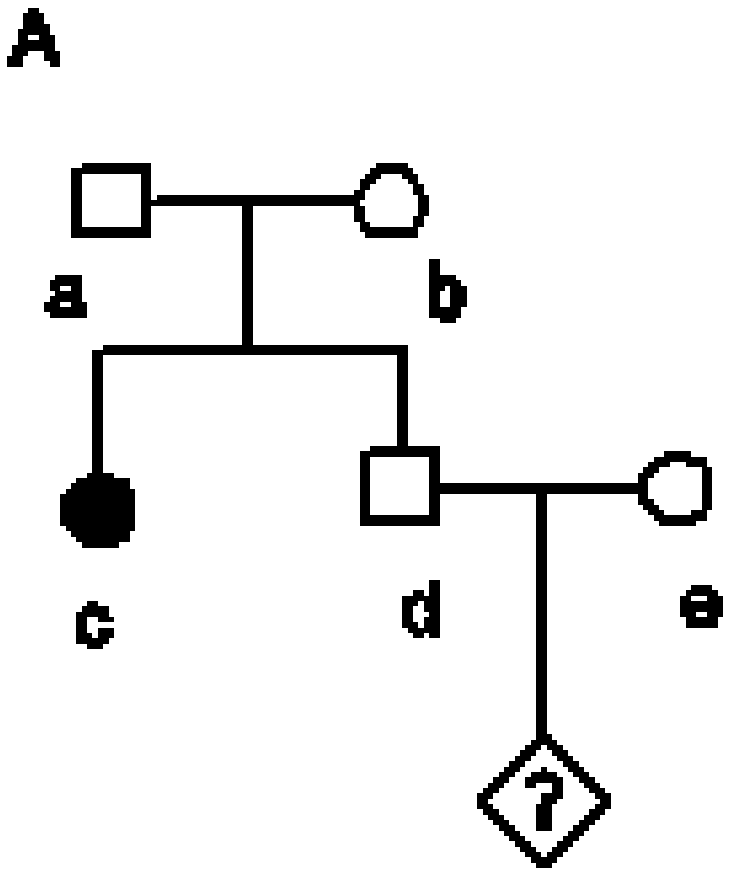
= 0.008

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 "?"

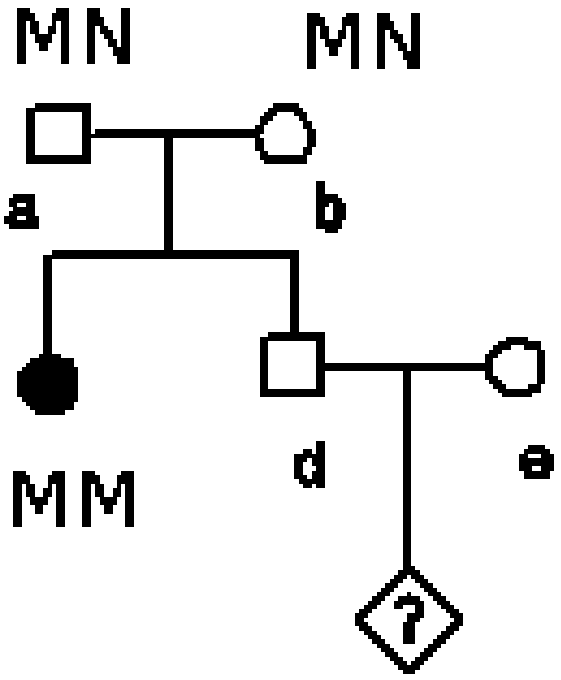


Solution for *q*

- 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) =

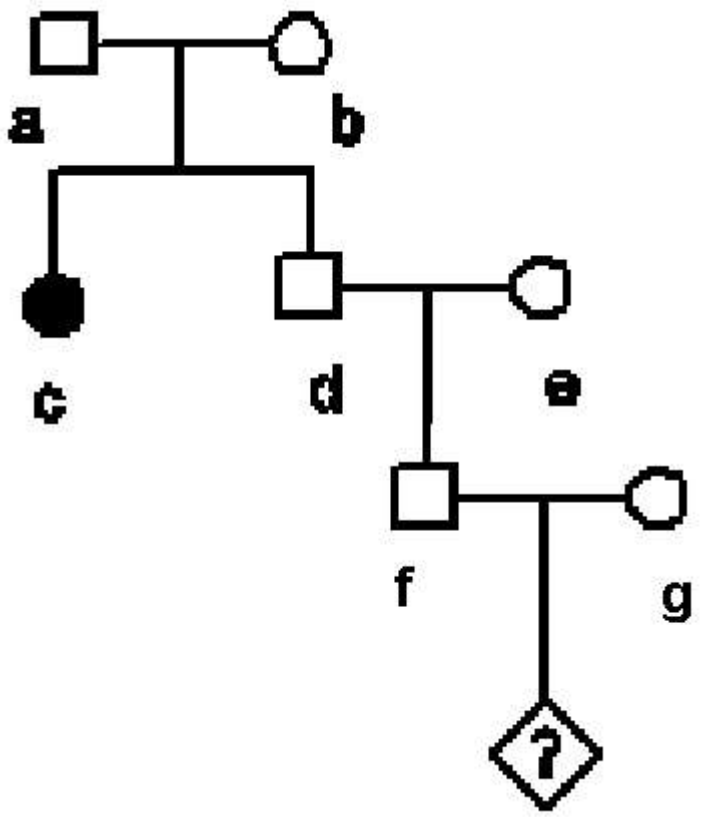
  = q / (3 (1 + q))



Task

- Recessive model
  - P(M) = 1/40 = 2.5%
  - P(D|MM)=1
  - P(D|MN)=P(D|MM)=0

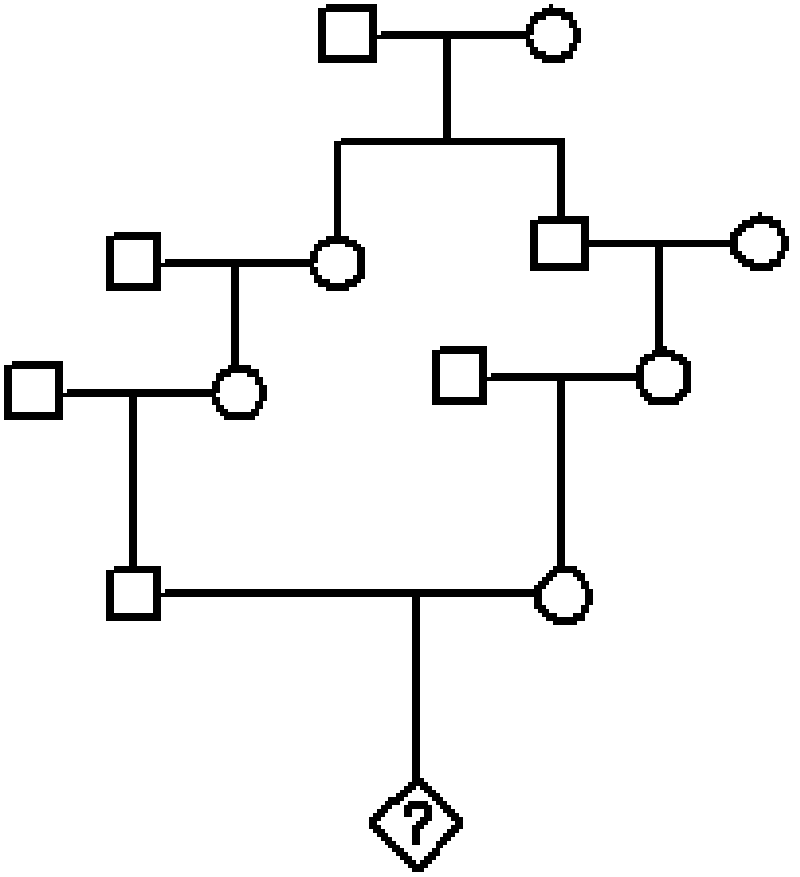
- What is the risk for "?"



Answer

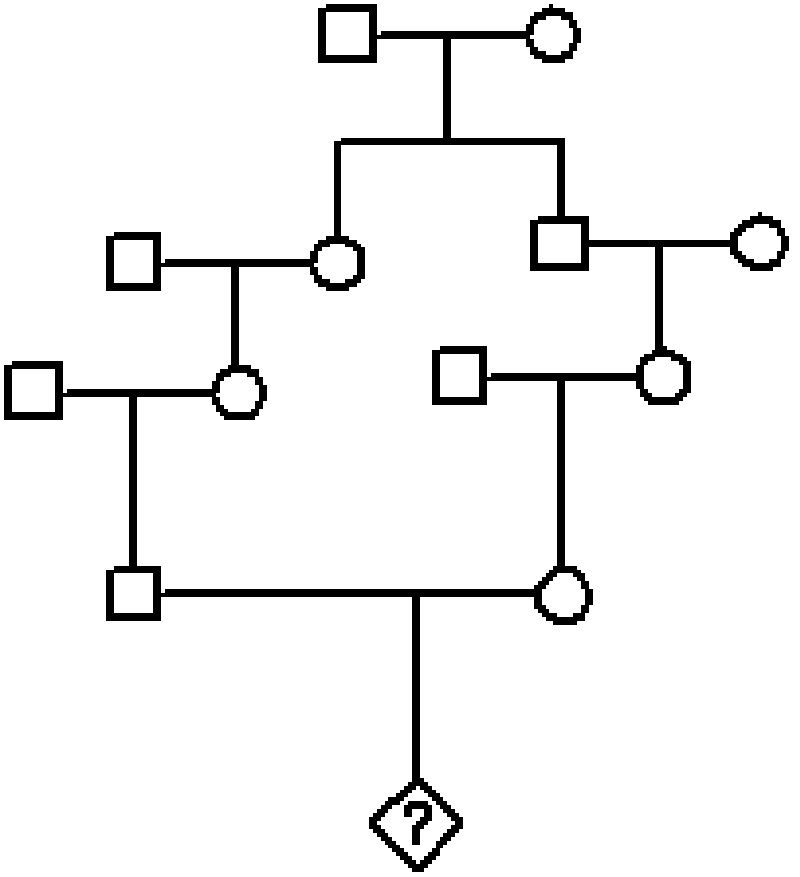
Problem

- Recessive model
- Let $q \rightarrow 0$
  - then only one source of mutation must be in the pedigree
- ...What is the risk for "?"



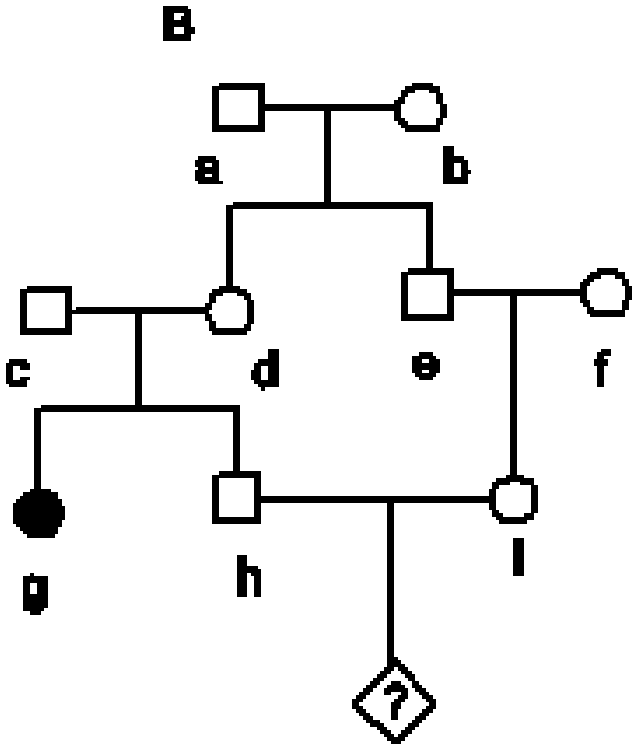
Solution

- ...What is the risk for "?"
  - Parents at first generation must be MN x NN
  - Pr(MN x NN) ≈ 2 2 q = 4 q
  - Probability that M is transmitted to both parents of the child of interest is $\frac{1}{2}^6 = 1/64$
  - Risk for child is
    - 4 q 1/4 1/64 = q / 64 = q *F*
  - Relative risk fo a child of first cousin marrige is
    - $(qF)/q^2 = F/q = 1 / (64\ q)$
  - if q = 0.1% then RR = 15.6



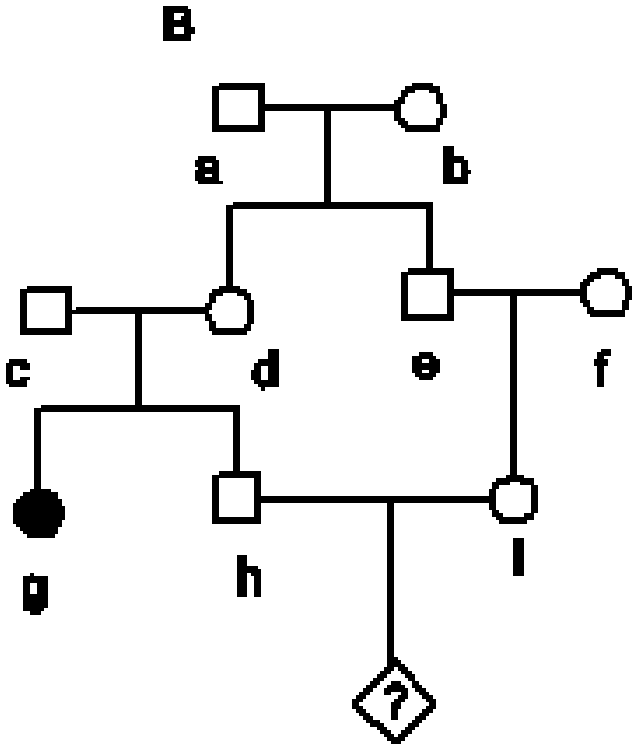
Task

- Recessive model
  - P(M) = q
  - P(D|MM)=1
  - P(D|MN)=P(D|MM)=0
- What is the risk for "?"
  - P(h=MN|X) = 2/3
  - P(i=MN|X) = ?
  - Risk = ¼ 2/3 P(I=MN|X)



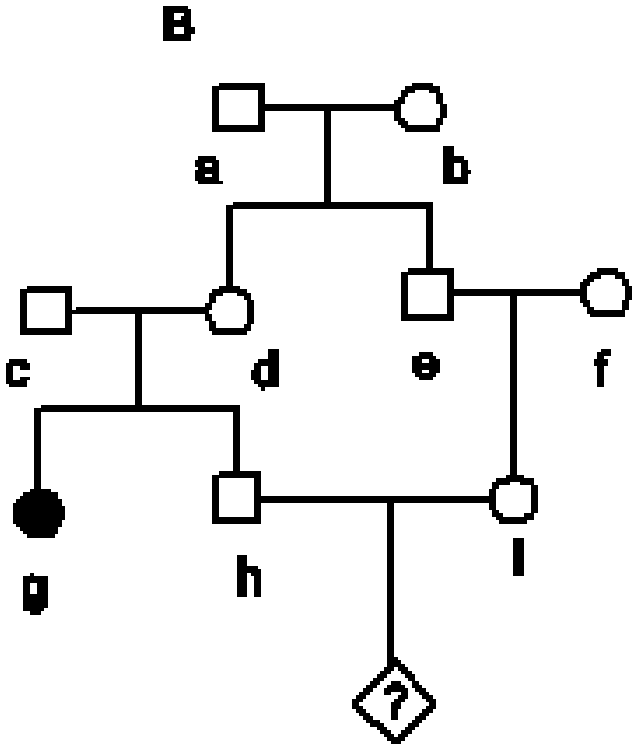
Ideas

- Let $q \rightarrow 0$
  - then only one source of mutation must be in the pedigree
  - we know that “d” is a carrier
  - ...



Solution

- Let $q \rightarrow 0$
  - we know that “d” is a carrier
  - thus “a” or “b” is carrier
  - the chances that the mutation segregates also to “i” is ¼



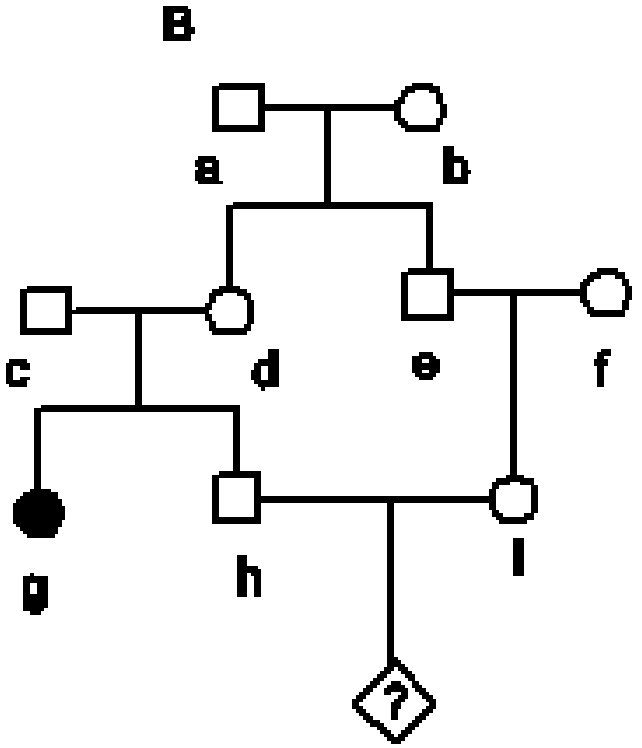
Solution

- Risk =

  = 1/4 2/3 P(I=MN|X)

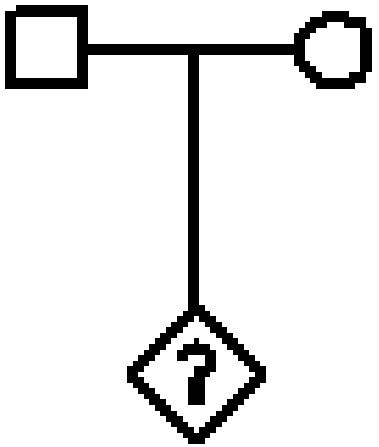
  = 1/4 2/3 1/4 = 1/24 = 0.042

- Does not depend on q! (but we assumed it is small)



Incorporating more information

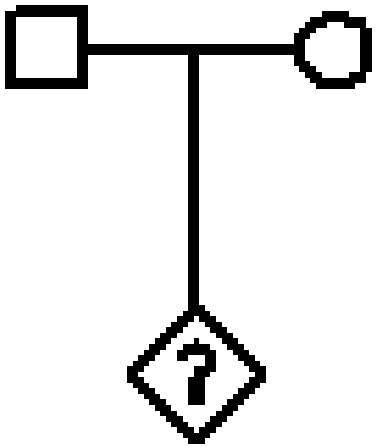
- Performing a test checking for known mutations in the gene



- Test has some “sensivity”: detects X% of the mutations (miss some rare mutations)

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% sensivity



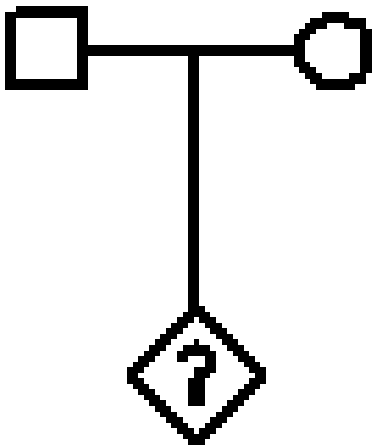
- What is the risk for “?”

Solution

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

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

  and $P(NN|U) = 1 - 2q / (1 + q)$

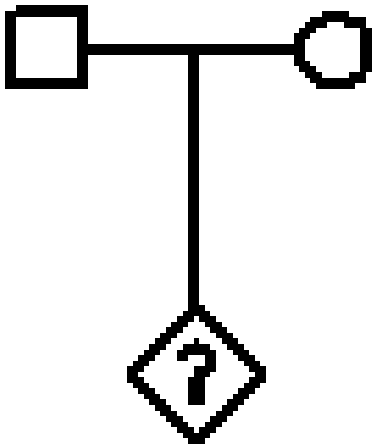


- X, information, is that it tests negatively

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

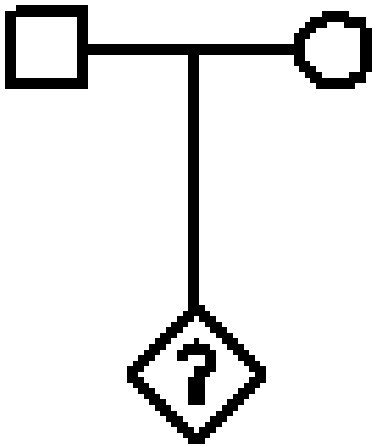
Example

- Assume that mutation frequency, *q is 1/60 in the CF gene*
- Test sensivity 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(MN|U) = 2 q / (1 + q) = 0.033
- P(NN|U) = 0.97
- 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) =

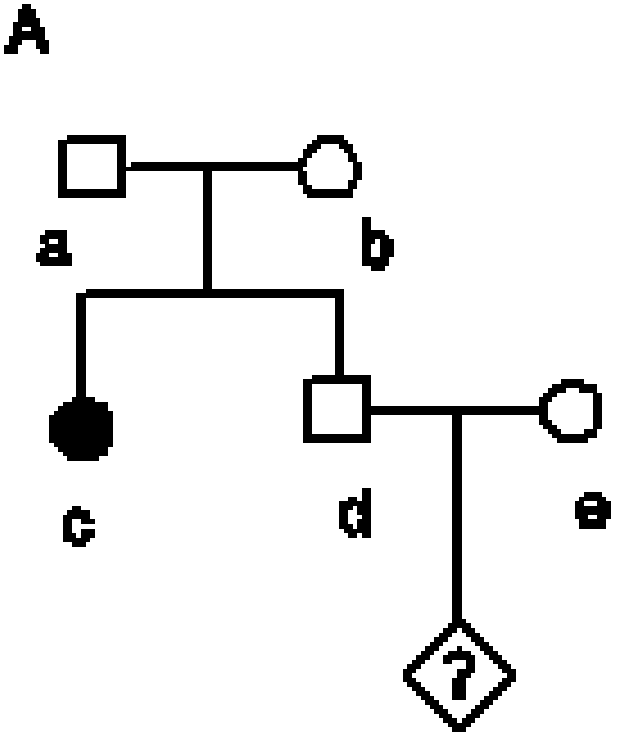
= 0.00003

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

is 43 times lower then risk before the test

Task

- Assume CF model
- Both parents "**d**" and "**e**" test negative at the test with 85% sensivity



- What is the risk for "?"
- What is RR for "?"

Answer