Recurrence risk in medical genetics.

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BeSHG course 2021 - 2022

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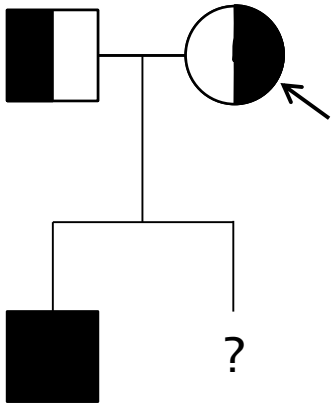
Recurrence Risk - Outline

- Monogenic disorders.
  → Mendelian laws
  → Bayesian risk calculation (AR, XL-R)
  → Bayesian risk calculation (lethal XL-R)
  → Reduced penetrance
- Chromosomal abnormalities.
- Complex phenotypes.
- Consanguinity

Single gene inheritance

- If single gene disorder and genotypes are fully known, mendelian laws apply.
- In case not all genotypes are fully known, more accurate risk calculations are possible taking into account phenotypic info.

Mendelian laws (e.g. AR)

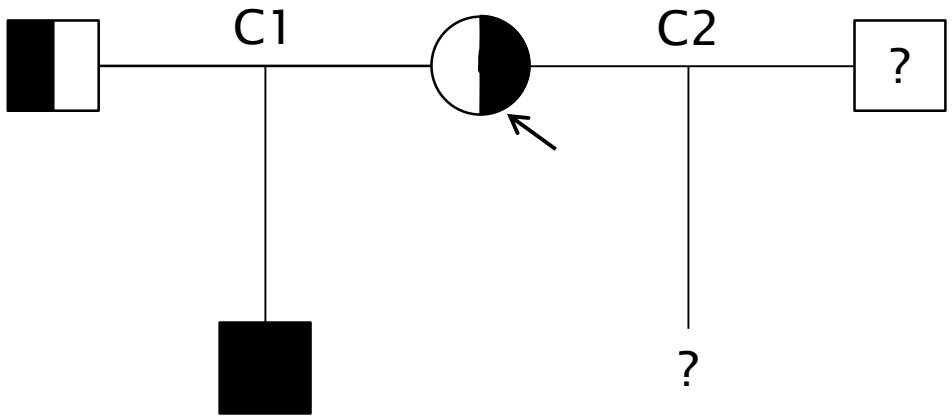


Risk calculated by mendelian laws is possible if genotypes are known or can be inferred.

1/4 Affected
1/4 carrier maternal mutation
1/4 carrier paternal mutation
1/4 Unaffected (Not carrier)

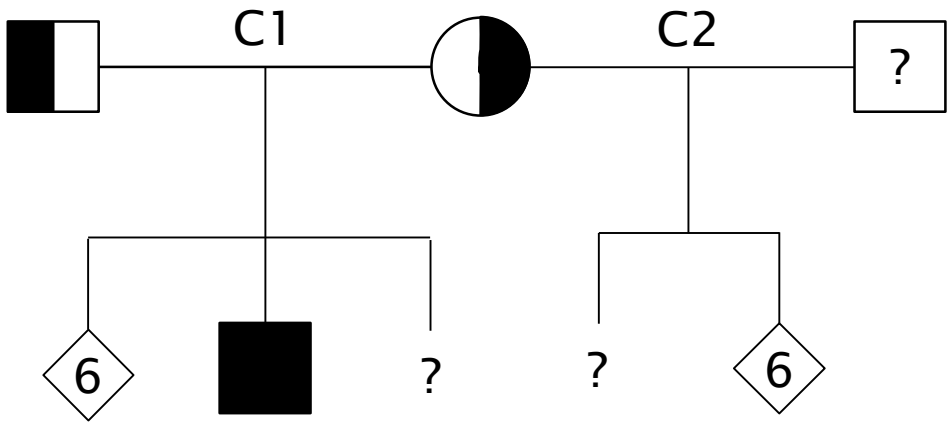
] 2/4 carrier

Cystic fibrosis (AR)



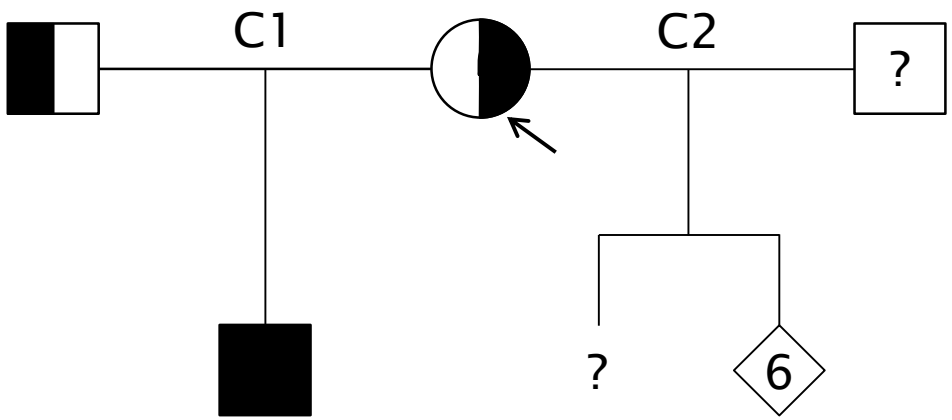
Carrier frequency CF mutation in population = 1/22
→ Risk for C1 to conceive an affected child = ¼ (mendelian)
→ Risk for C2 to conceive an affected child = 1/22 x ¼ = 1/88

Cystic fibrosis (AR)



Carrier frequency CF mutation = 1/22
→ Risk for C1 to conceive an affected child = ¼ (mendelian)
→ irrespective of the number of healthy offspring

Cystic fibrosis (AR) with posterior risk



Carrier frequency CF mutation = 1/22

→ Risk for C1 to conceive an affected child = ¼ (mendelian)

→ Risk for C2 to conceive an affected child after conception of 6 healthy children << 1/88

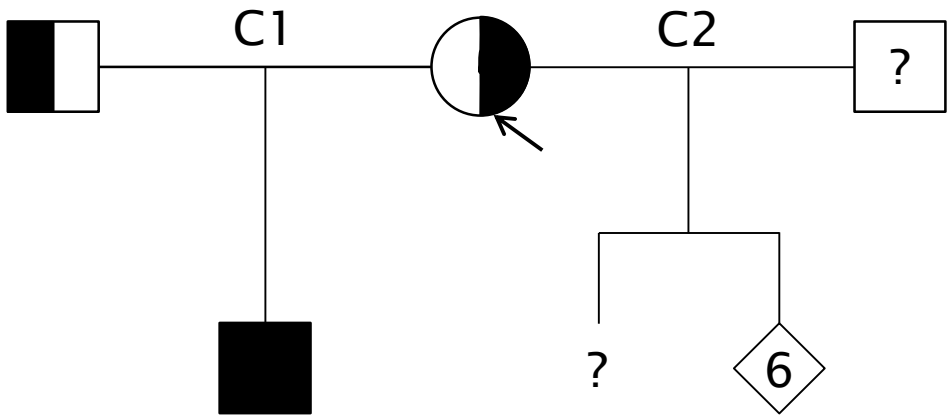
Bayesian risk analysis

- Use of phenotypic/genotypic information when not all genotypes are definitively known
- Based on all, mutually exclusive scenarios (genotypes).
- Takes into account conditional probabilities; observations with different probabilities in the different scenarios.

Method

- Define all scenarios compatible with observed phenotypes.
- Prior probability = probability of a scenario, prior to conditioning.
- Conditional probability; probability of the other (different from prior) observations in a particular scenario.
- Joint probability : Prior x conditional
- Posterior probability = joint probability / sum of all joint probabilities → sum of posterior probabilities is always 1.

Cystic fibrosis (AR) with posterior risk



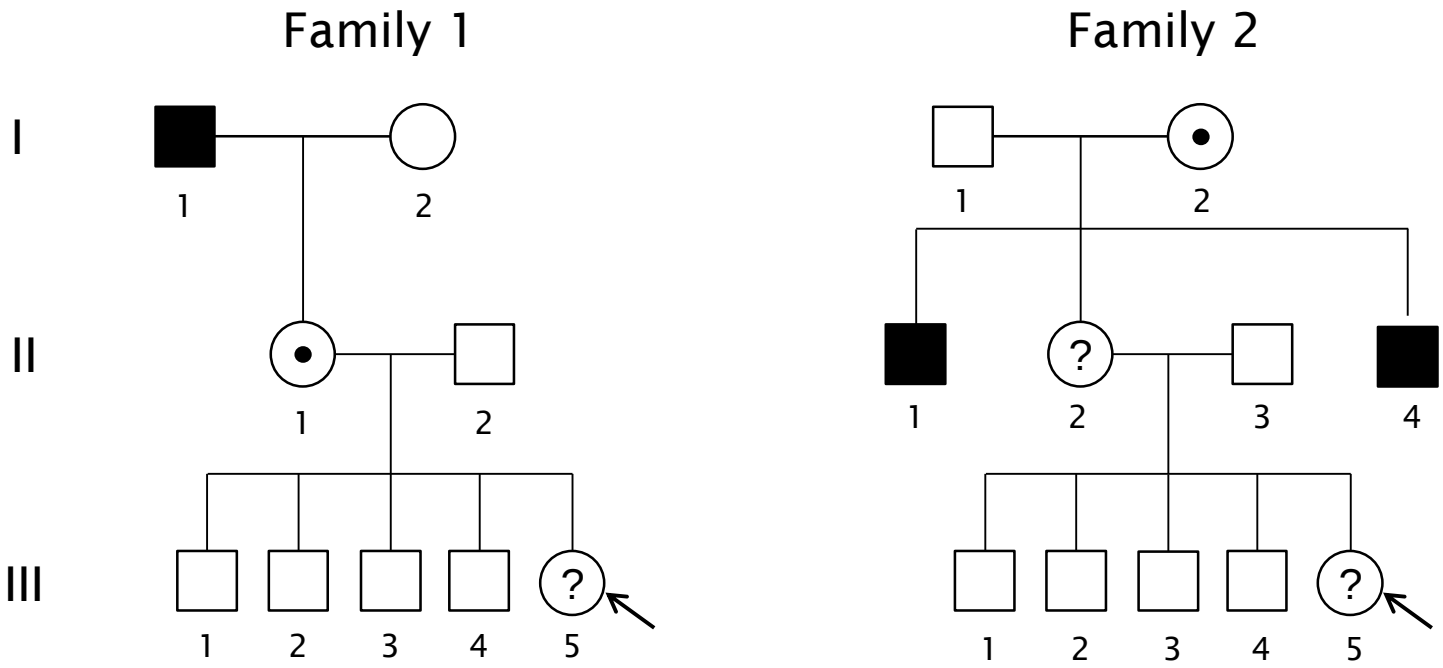
→ Intuitively we know risk for C2 to conceive an affected child after conception of 6 healthy children <<1/88.

Calculation of posterior risk for C2

-Define options;	male is carrier	male is not carrier
-Prior risk	1/22	21/22
-Conditional	$(3/4)^6$	1
-Joint risk	$(1/22)^* (3/4)^6$	21/22
-Posterior risk	$\frac{(1/22)^*(3/4)^6}{(1/22)^*(3/4)^6 + (21/22)}$	$\frac{(21/22)}{(1/22)^*(3/4)^6 + (21/22)}$
	≈1/119	≈118/119

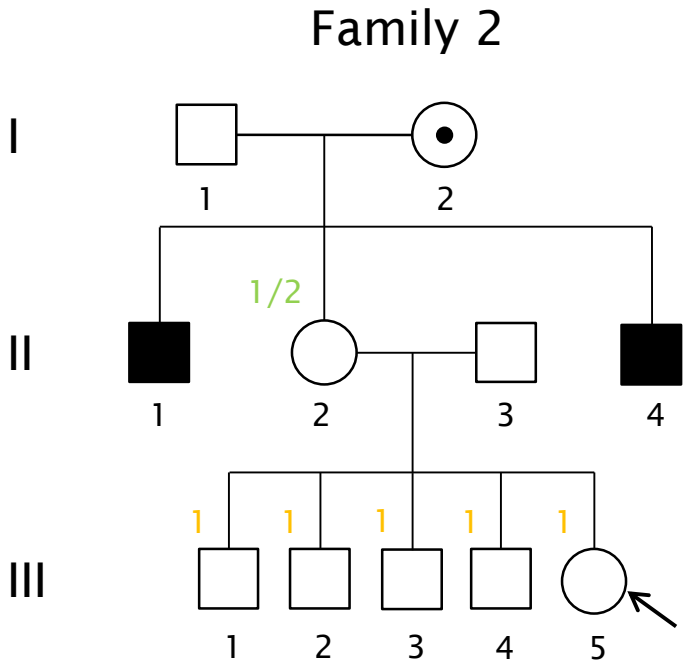
In this example the risk decreased from 1/22 (prior risk) to 1/119 (posterior risk). The risk for conceiving an affected child is (1/119)*(1/4) =1/476.

Example, X-linked Recessive (e.g. Haemophilia A)



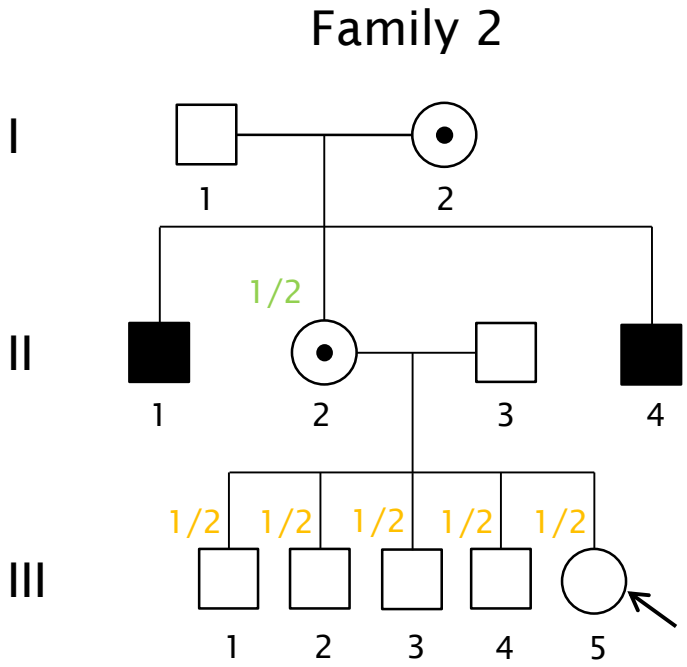
Consultand family 1 (arrow); carrier risk 50%
Consultand family 2; (arrow); carrier risk << 25%

Scenario 1; II-2 is not a carrier.



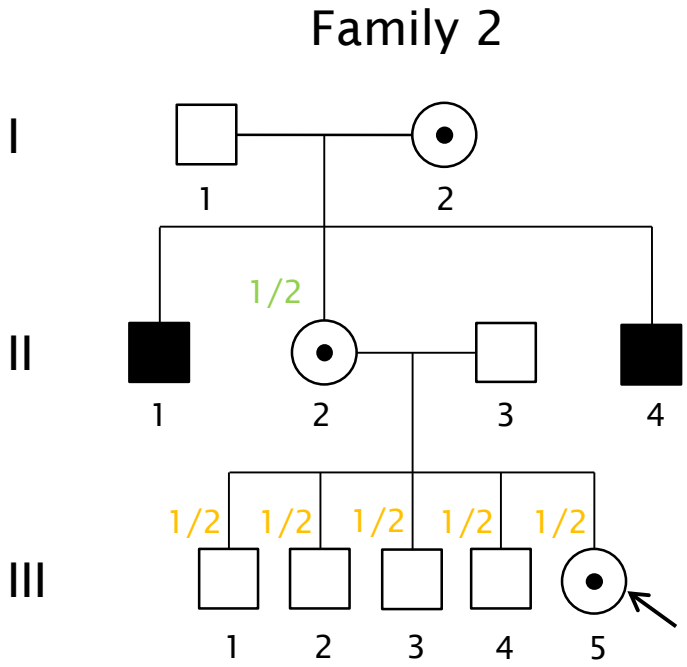
II-2; Prior probability 'no carrier': 1/2
Conditional probability: $(1)^5=1$
Joint probability: 1/2
Posterior probability: depends also on other scenarios.

Scenario 2; II-2 is carrier, III-5 is not



II-2; Prior probability 'carrier': 1/2
Conditional probability: $(1/2)^5$
Joint probability: $(1/2)^6 = 1/64$
Posterior probability: depends also on other scenarios.

Scenario 3; II-2 and III-5 are carrier



II-2; Prior probability 'carrier': 1/2
Conditional probability: $(1/2)^5$
Joint probability: $(1/2)^6 = 1/64$
Posterior probability: depends also on other scenarios.

Calculation of posterior risk

-Define options;	Scen1	Scen2	Scen3
-Prior risk	1/2	1/2	1/2
-Conditional	1	$(1/2)^5$	$(1/2)^5$
-Joint risk	1/2	$(1/2)^6$	$(1/2)^6$
-Posterior risk	$\frac{(1/2)}{(1/2) + (1/2)^6 + (1/2)^6}$	$\frac{(1/2)^6}{(1/2) + (1/2)^6 + (1/2)^6}$	$\frac{(1/2)^6}{(1/2) + (1/2)^6 + (1/2)^6}$
	=32/34	=1/34	=1/34
	≈94%	≈3%	≈3%

III-5 is only carrier in scenario 3. Her risk being a carrier is 1/34 (≈3%). Her mother is carrier in scenario's 2 and 3. The risk of II-2 of being a carrier is 2/34 or 1/17 (≈6%).

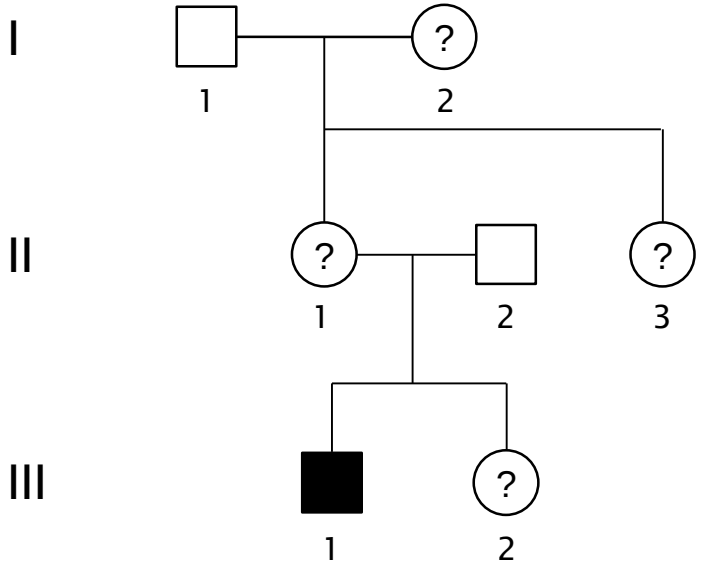
Lethal X-linked recessive disorders

- Due to lethality in males, H= carrier frequency in females is relatively low. New mutations are relatively frequent.
- The mutation rate in a gamete at an X-linked locus (μ) ranges from 10^{-4} to 10^{-6}.
- 3 mutually exclusive ways to be a carrier (H);
  - New mutation on the allele from mother (1xμ)
  - New mutation on the allele from father (1xμ)
  - She inherites the mutation from her mother (H/2)

→ $H=H/2+2\mu \rightarrow H=4\mu$ (assuming H is constant)

  - Probability due to *de novo*; 2μ
  - Probability due to an Inherited mutation; 2μ

Carrier risk for each female for DMD?



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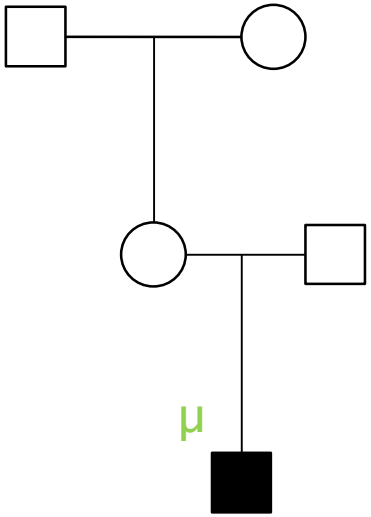
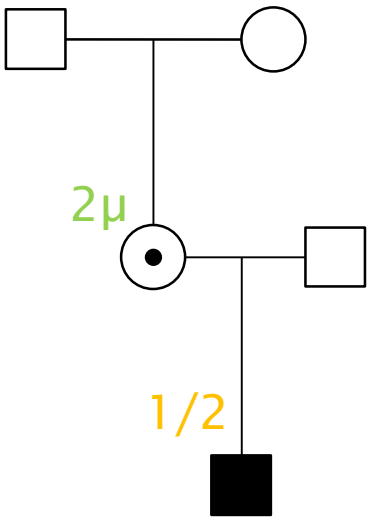
Scenarios

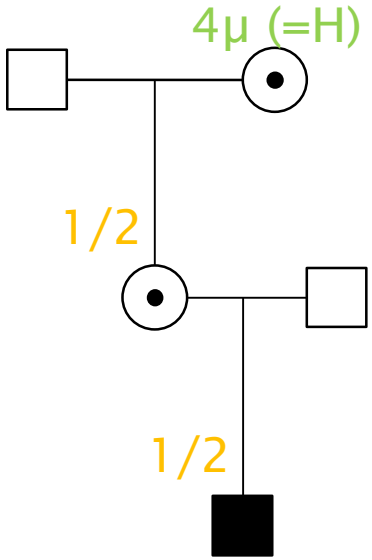
Scenario 1



Scenario 2



Scenario 3



Scenario 1: newly arisen (*de novo*) mutation in son

Scenario 2: *de novo* mutation in mother

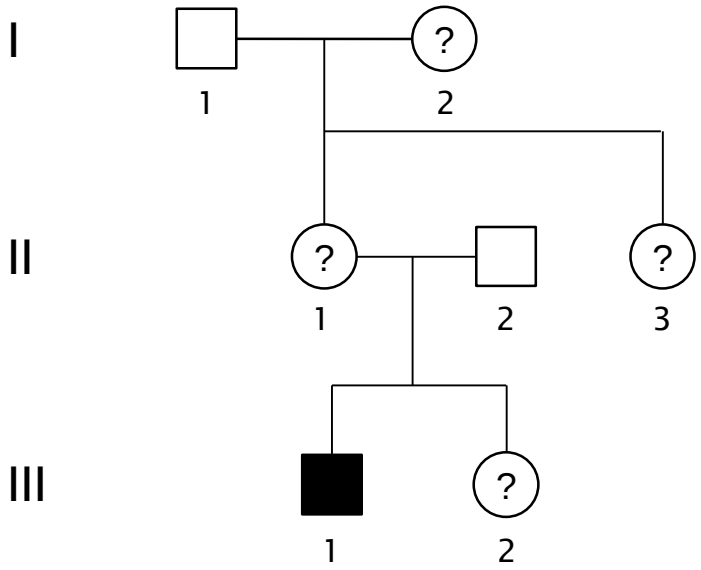
Scenario 3: grandmother is carrier (de novo in grandmother or inherited)

Calculation of posterior risk

-Define options;	Scen1	Scen2	Scen3
-Prior risk	μ	2μ	4μ
-Conditional	1	$1/2$	$(1/2)^2$
-Joint risk	μ	μ	μ
-Posterior risk	$\frac{\mu}{\mu+\mu+\mu}$	$\frac{\mu}{\mu+\mu+\mu}$	$\frac{\mu}{\mu+\mu+\mu}$
	$=1/3$	$=1/3$	$=1/3$
	$\approx 33\%$	$\approx 33\%$	$\approx 33\%$

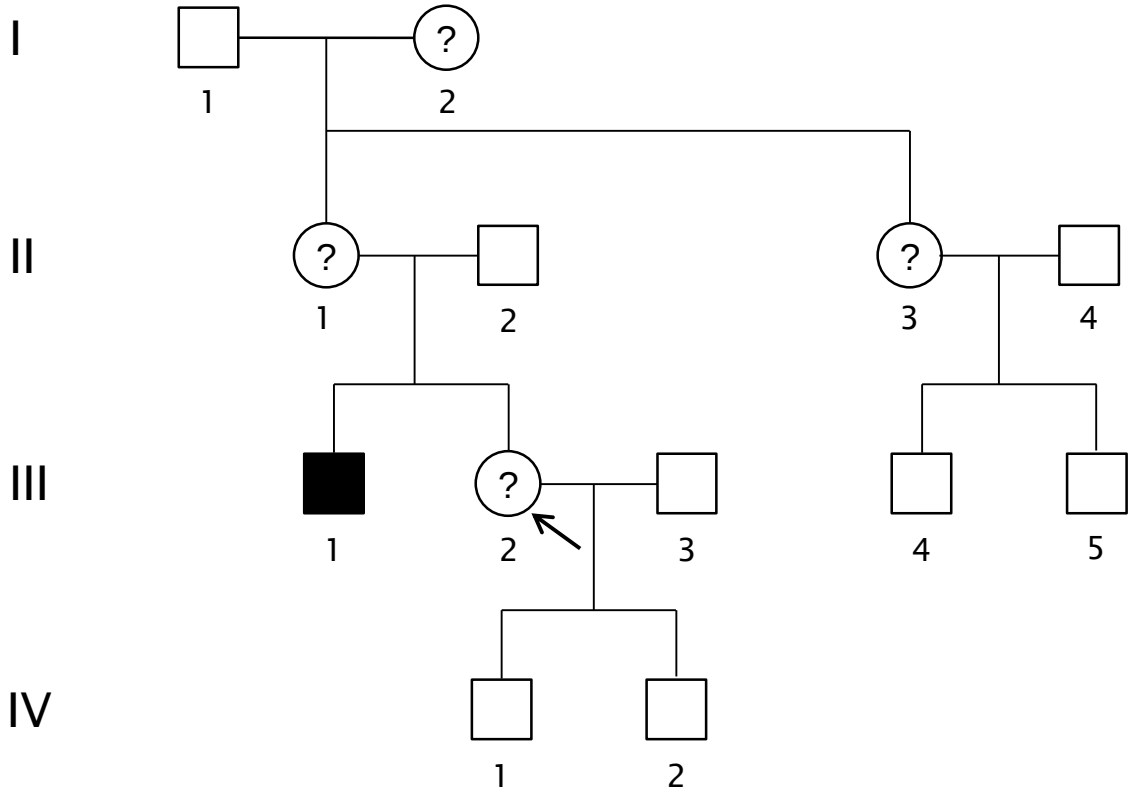
In this pedigree, every scenario is equally likely. Note that none of the females was tested, that only 1 affected male is known and no other male relatives are known (affected or unaffected). In any other situation, posterior risk would be different.

Carrier risk for each female for DMD?



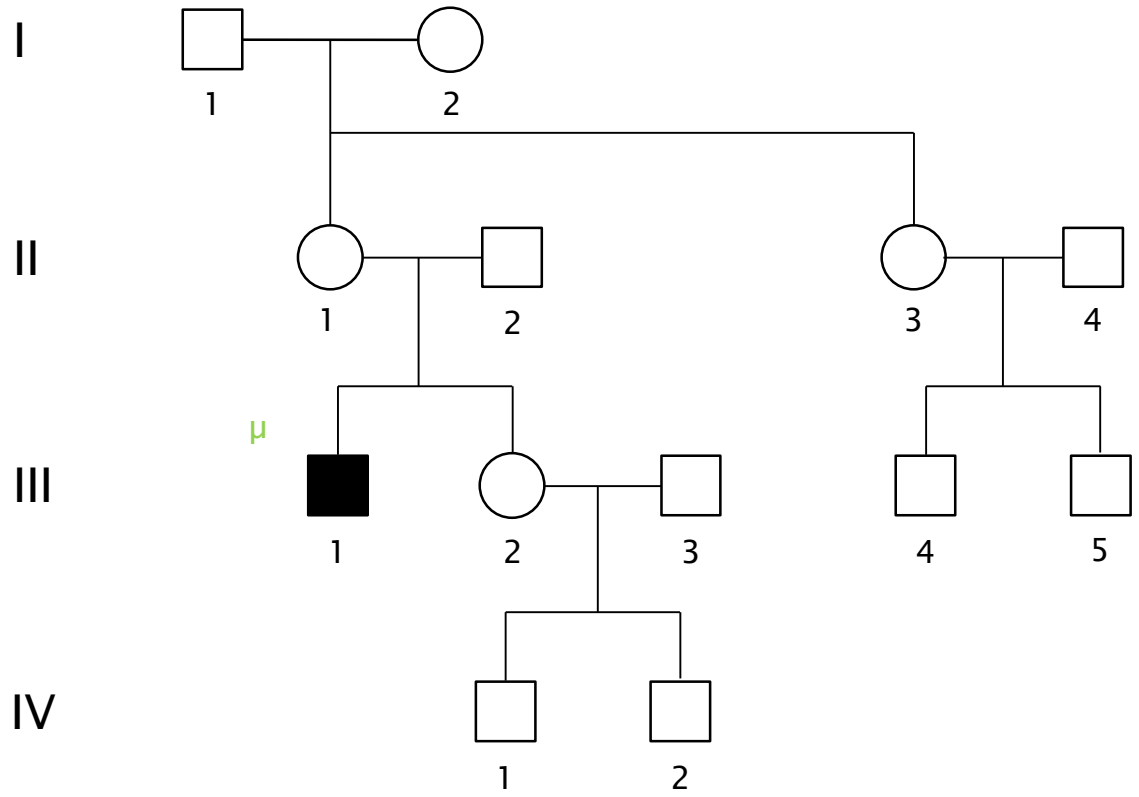
I-2; only carrier in scenario 3; probability = 1/3
II-1: carrier in scenarios 2 and 3; probability =2/3
III-2: carrier risk II-2 divided by 2 = 1/3
II-3: carrier risk I-2 divided by 2 = 1/6

Carrier risk for each female for DMD?



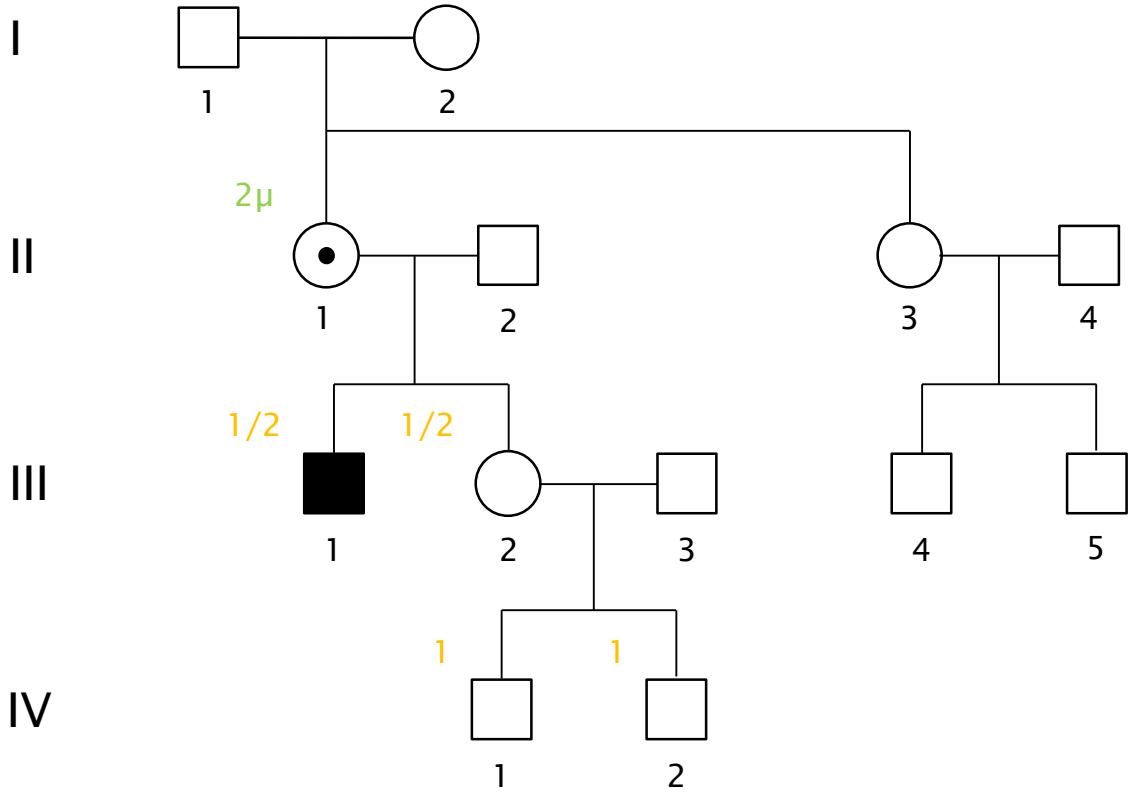
Note the difference with the family in the previous slide: healthy males known in this pedigree.

Scenario 1



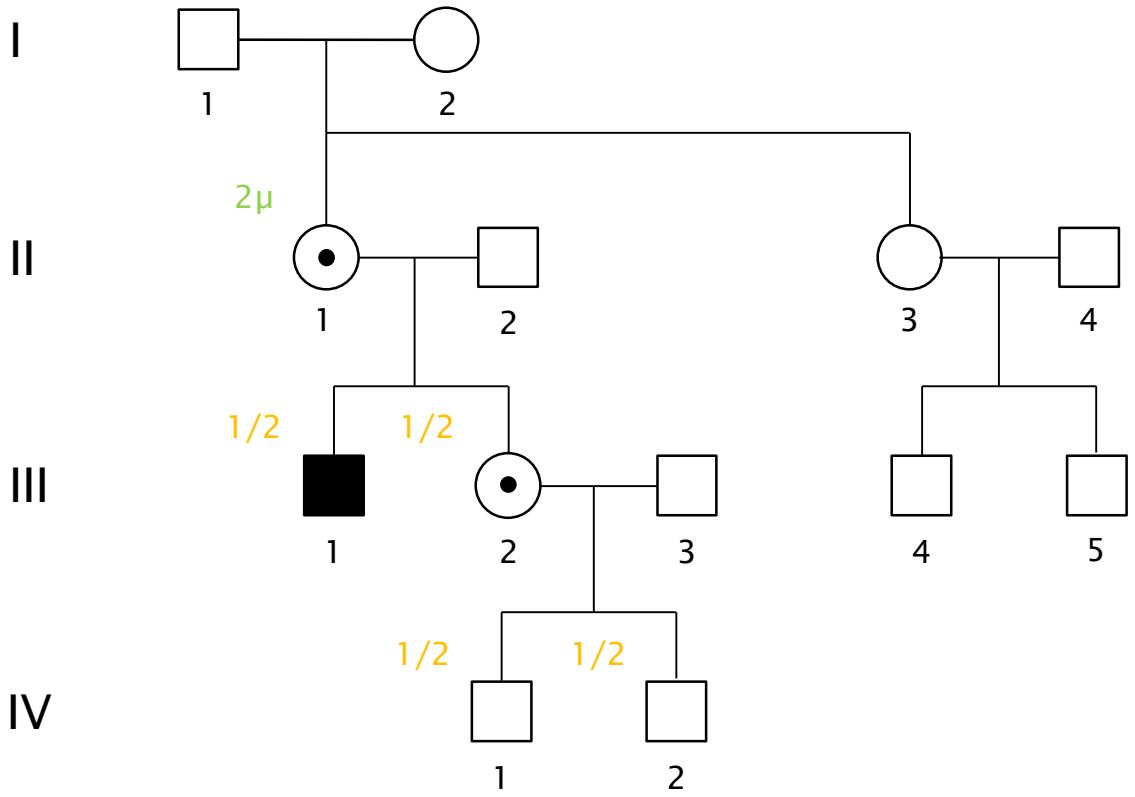
Mutation arose *de novo* in III-1.
Prior probability: μ
Conditional probability: 1
Joint probability: μ

Scenario 2



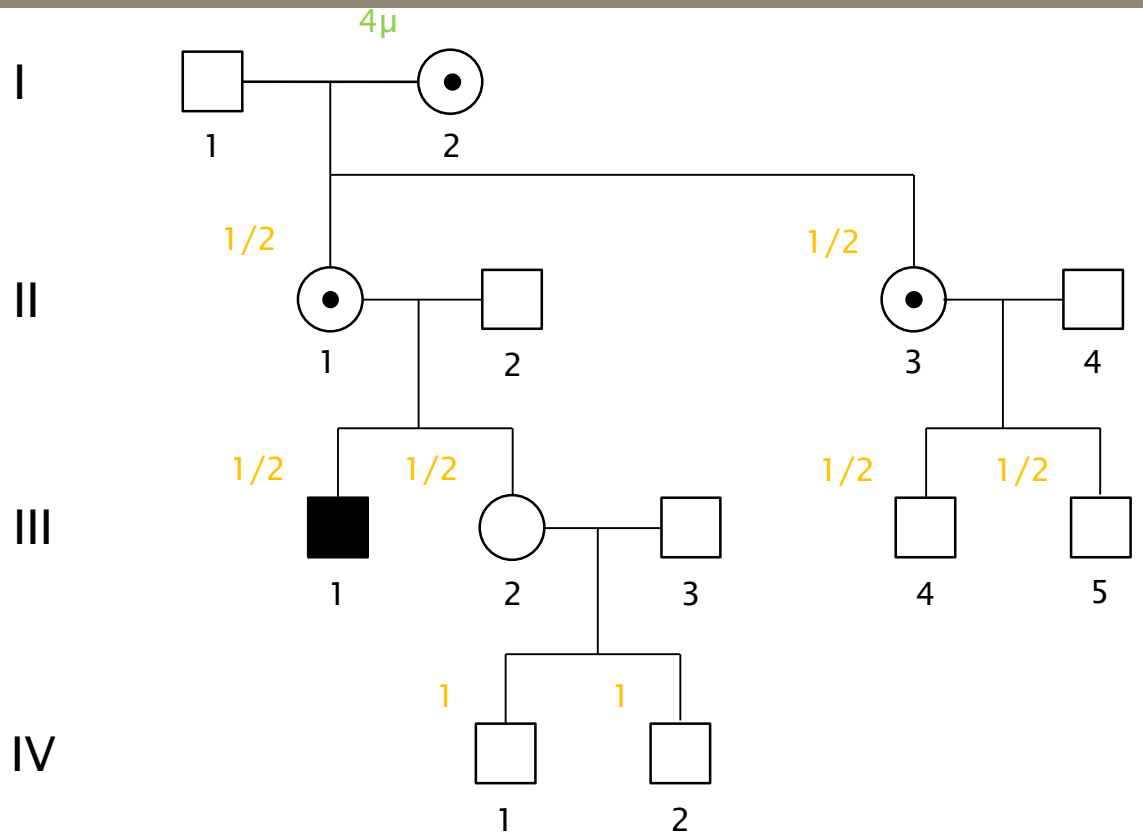
Mutation arose *de novo* in II-1. III-2 did not inherit the mutation.
Prior probability: 2μ
Conditional probability: $(1/2)^2*(1)^2$
Joint probability: μ/2

Scenario 3



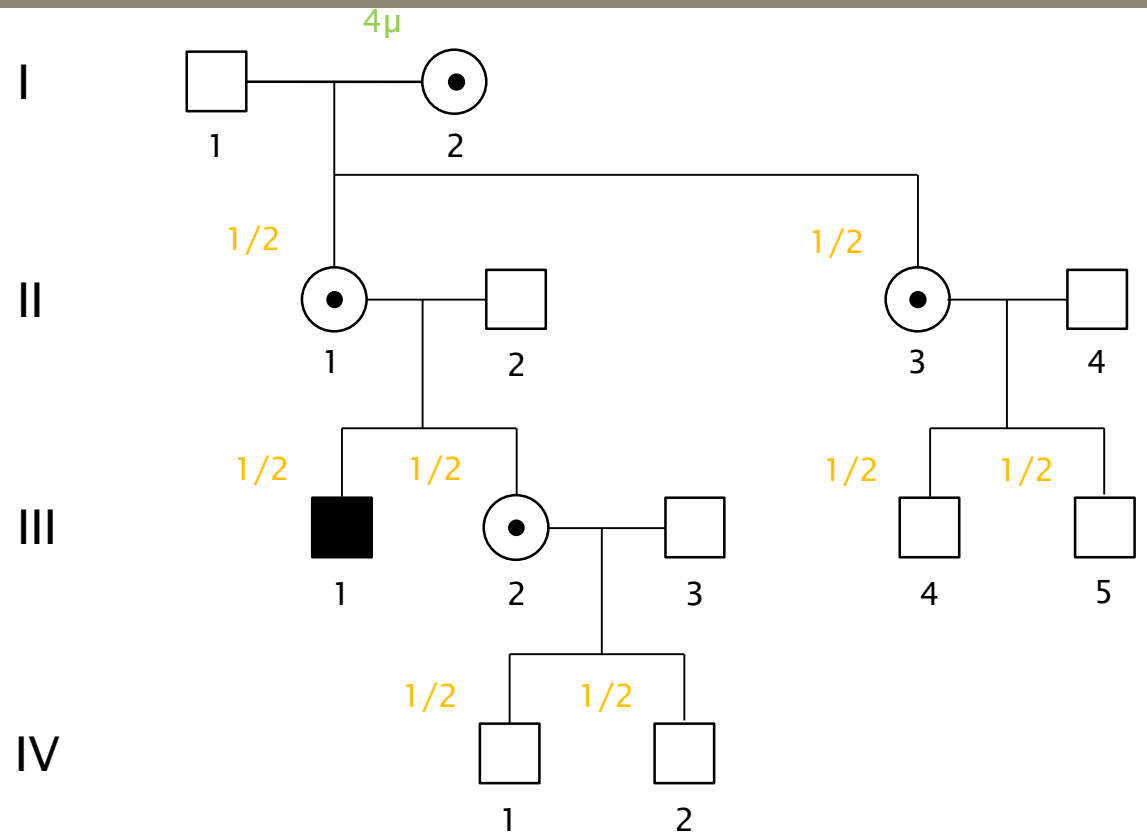
Mutation arose *de novo* in II-1. III-2 did inherit the mutation.
Prior probability: 2μ
Conditional probability: $(1/2)^4$
Joint probability: μ/8

Scenario 4



I-2, II-1 and II-3 are carrier, III-2 is not.
Prior probability: 4μ
Conditional probability: $(1/2)^6*(1)^2$
Joint probability: $(1/2)^4 *\mu$

Scenario 5



I-2, II-1, II-3 and III-2 are carrier.
Prior probability: 4μ
Conditional probability: $(1/2)^8$
Joint probability: $(1/2)^6$ *μ

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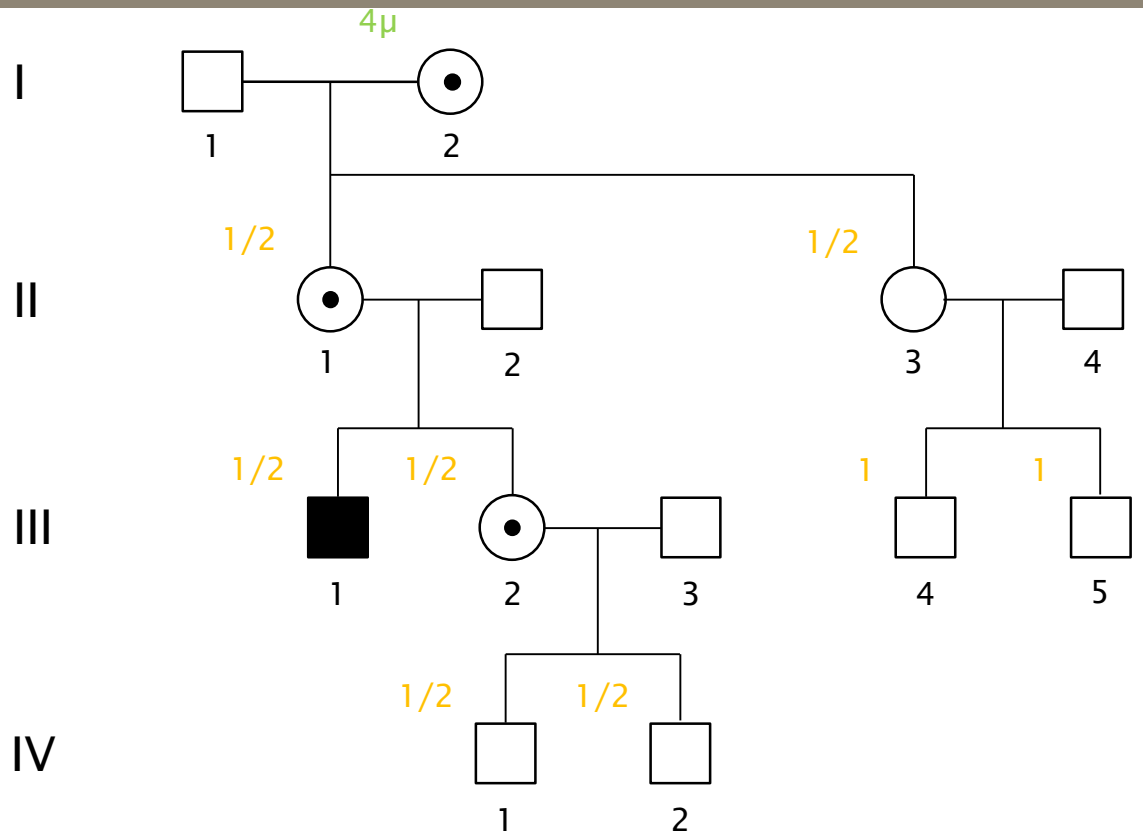
Scenario 6



I-2, II-1 and III-2 are carrier, II-3 is not.
Prior probability: 4µ
Conditional probability: $(1/2)^6*(1)^2$
Joint probability: $(1/2)^4$ *µ

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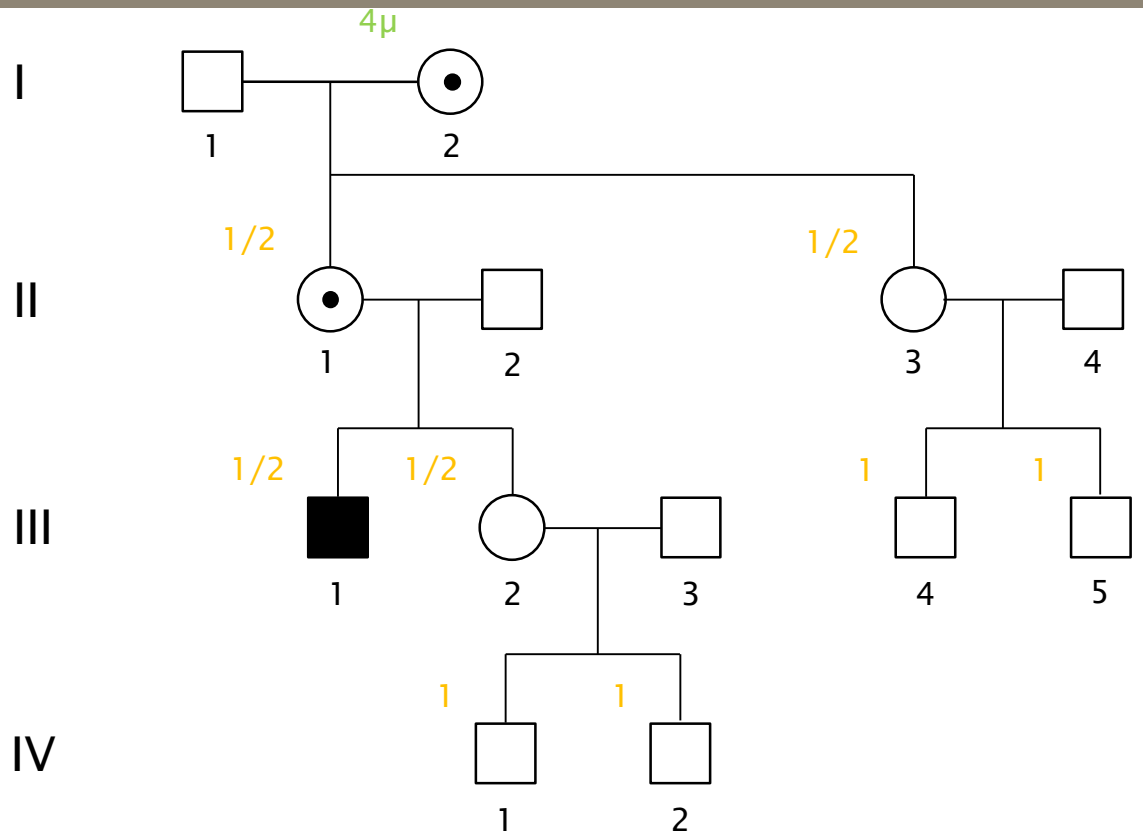
Scenario 7



I-2, and II-1 are carrier. II-3 and III-2 are not.
Prior probability: 4μ
Conditional probability: $(1/2)^4*(1)^4$
Joint probability: $(1/2)^2$ μ

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Calculation of posterior risk

- Sum of joint risks
  → (denominator of fraction to calculate posterior risk)

$$=\mu+(1/2)\mu+(1/8)\mu+(1/16)\mu+(1/64)\mu+(1/16)\mu+(1/4)\mu$$

$$=\frac{(64+32+8+4+1+4+16)\mu}{64} = (129/64)^*\mu$$

Calculation of posterior risk

- Risk III-2 is carrier?

Sum of Probabilities of scenarios 3, 5 and 6

$$=\frac{(1/8)\mu + (1/64)\mu + (1/16)\mu}{(129/64)\mu}$$

$$=\frac{(8/64)\mu + (1/64)\mu + (4/64)\mu}{(129/64)\mu}$$

$$=13/129 = 10\%$$

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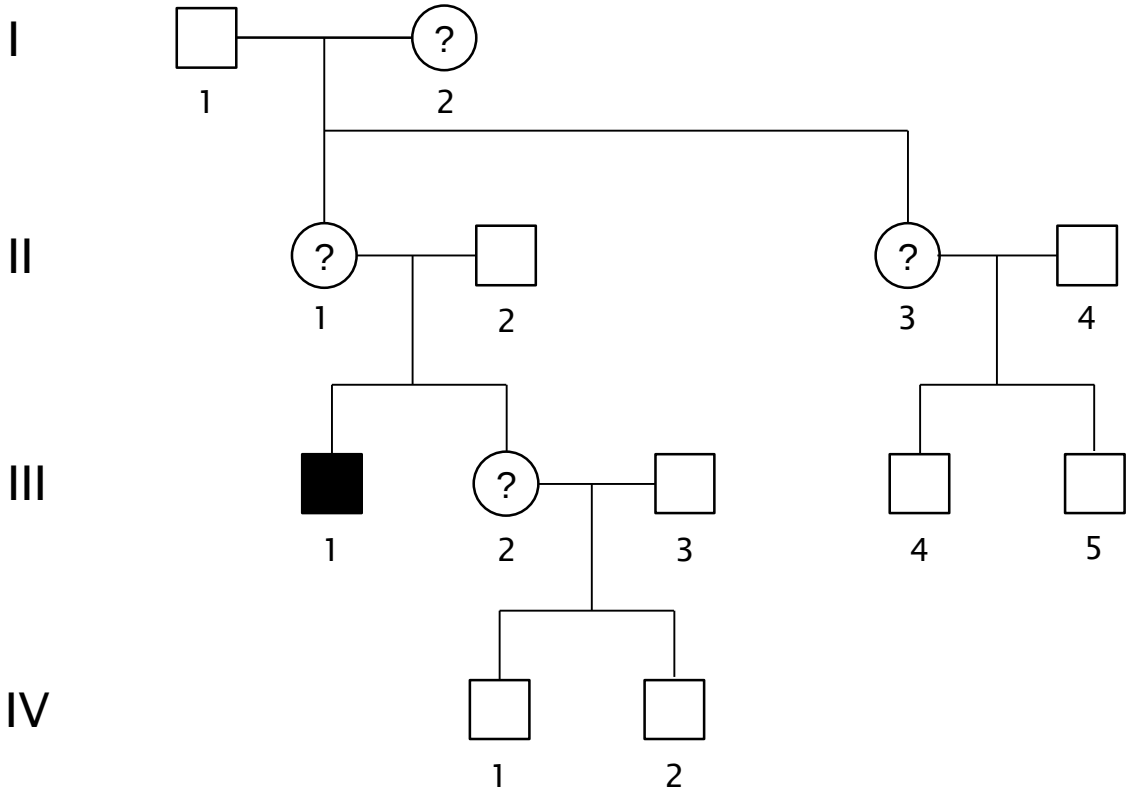
Comparison of both calculations



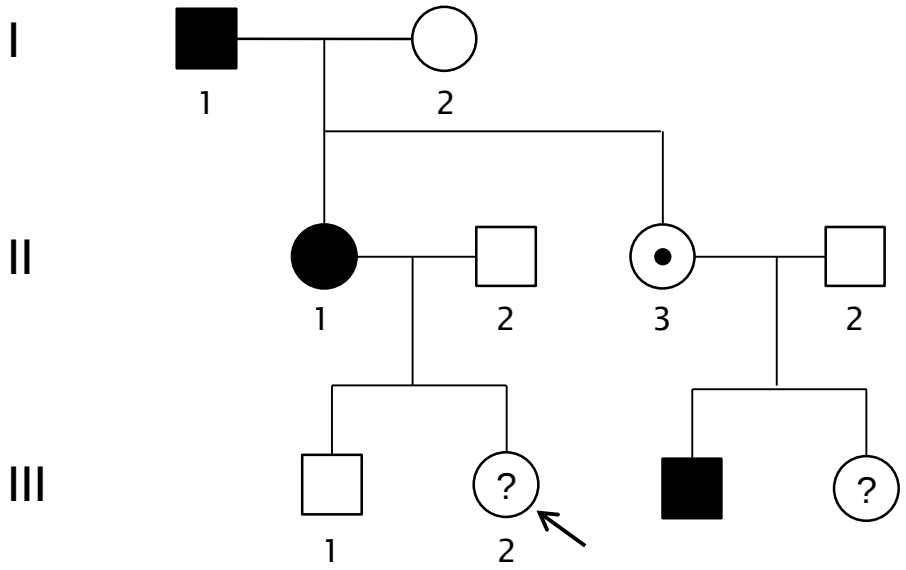
4 unaffected males in this pedigree (III-4, III-5, IV-1 and IV-2) reduce risk of III-2 being a carrier from 33,3% to 10%

Other possibilities

-Risk calculation is also possible in case of other types of uncertainty

- -Reduced penetrance
- -Age-modified risk in late onset diseases
- -Anticipation in triplet repeat disorders
- -…

Risk split-hand split-foot malformation (AD)?



Reduced penetrance; only 70% of individuals with mutation show the malformation. What is the risk for III-2 to be a carrier?

Calculation of posterior risk

-Define options;	Carrier	No carrier
-Prior risk	1/2	1/2
-Conditional	3/10	1
-Joint risk	3/20	1/2
-Posterior risk	$\frac{(3/20)}{(3/20)+(1/2)}$	$\frac{(1/2)}{(3/20)+(1/2)}$
	≈23%	≈77%

→ Having no symptoms decreases her risk to carry the mutation from 0,5 (prior risk, not taking into account her phenotype) to 0,23 (posterior risk).

Recurrence risk of chromosomal abnormalities

Recurrence risk depends on type of abnormality (eg; recurrence down syndrome due to trisomy v.s. rob. translocation involving chr. 21)

Complex disorders

-Disorders with a strong genetic component, but also environmental factors.

-Risk for recurrence is estimated using empirical recurrence risk.

- → Only useful in a particular population, at a particular time.
- → Average of heterogeneous disorder with different subgroups having different recurrence risks
- → Useful as best estimate. To be reevaluated upon additional info.
- → E.g; Cleft lip, mental retardation, cardiac malformations, bipolar disorder…

Cleft lip, palate

E.g. Cleft palate (Emery)

Parent	Sib	Recurrence risk
0	1	4,3%
0	2	14%
1	1	12,2%
1	2	25,8%
0	1, male	3,9%
0	1, female	5,0%

Consanguinity

-About 2x higher risk for birth defects in first cousins (Stoltenberg et al., 1999);

-3% in first cousins

-1,5% for non-consanguineous couples.

-Includes single gene disorders, complex disorders and chromosomal abnormalities.

References / Further reading

-Thompson & Thompson, genetics in Medicine, edition 8, Chapter 16.

-Ogino S. and Wilson R.B.: Bayesian analysis and risk assessment in genetic counseling and testing. J Mol Diagn 6:1-9, 2004.

-Stoltenberg C., Magnus P., Skrondal A., Lie R.T.: Consanguinity and recurrence risk of birth defects: a population-based study. Am J Med Genet 82:424-428, 1999.