Molecular genetics II

Ústav biologie a lékařské genetiky 1.LF UK a VFN, Praha

Human DNA polymorphisms used for linkage analysis, direct and indirect diagnostics

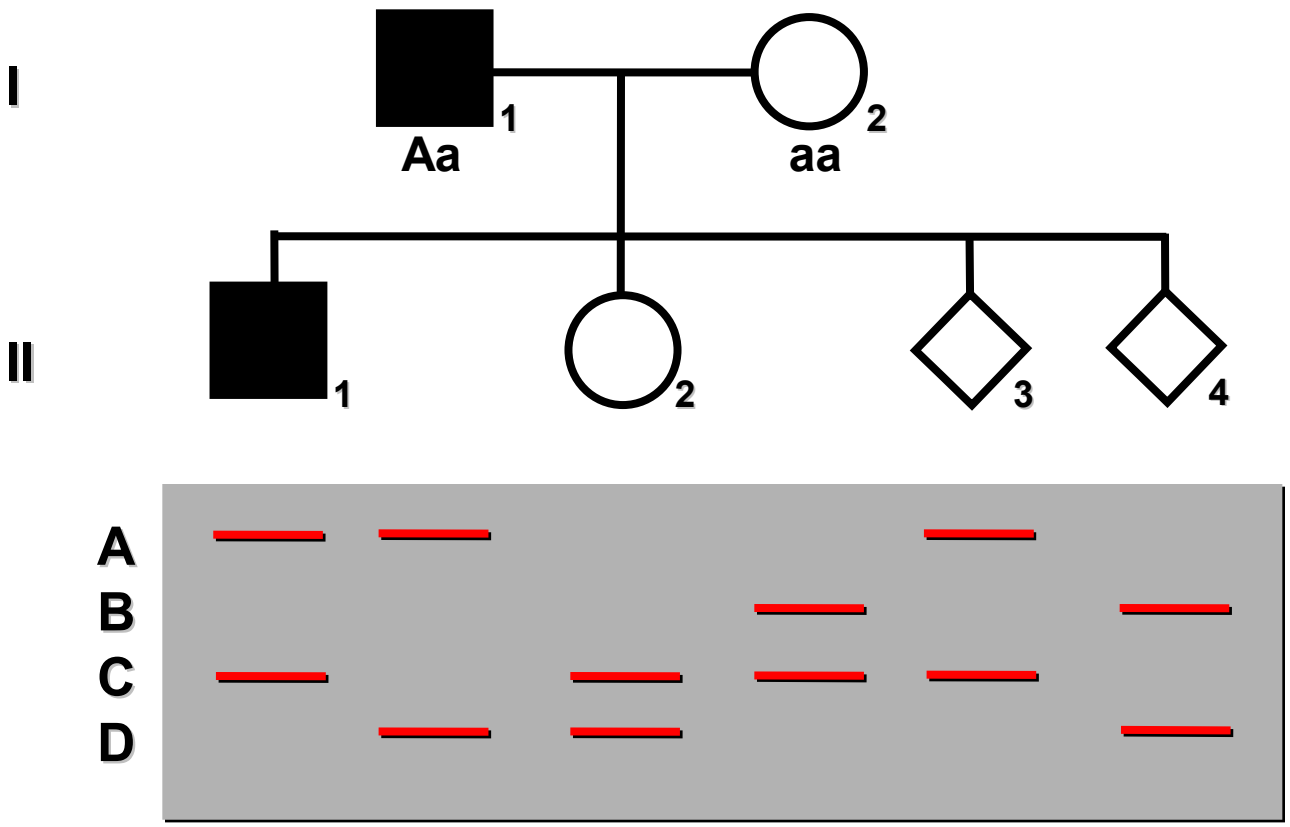
Microsatellites (or STR = short tandem repeats, SSR = simple sequence repeats)

TAGCCATCGGTACACACACACACACACAGTGCTTCAGTAGC

TAGCCATCGGTACACACACACACAGTGCTTCAGTAGCGTAG

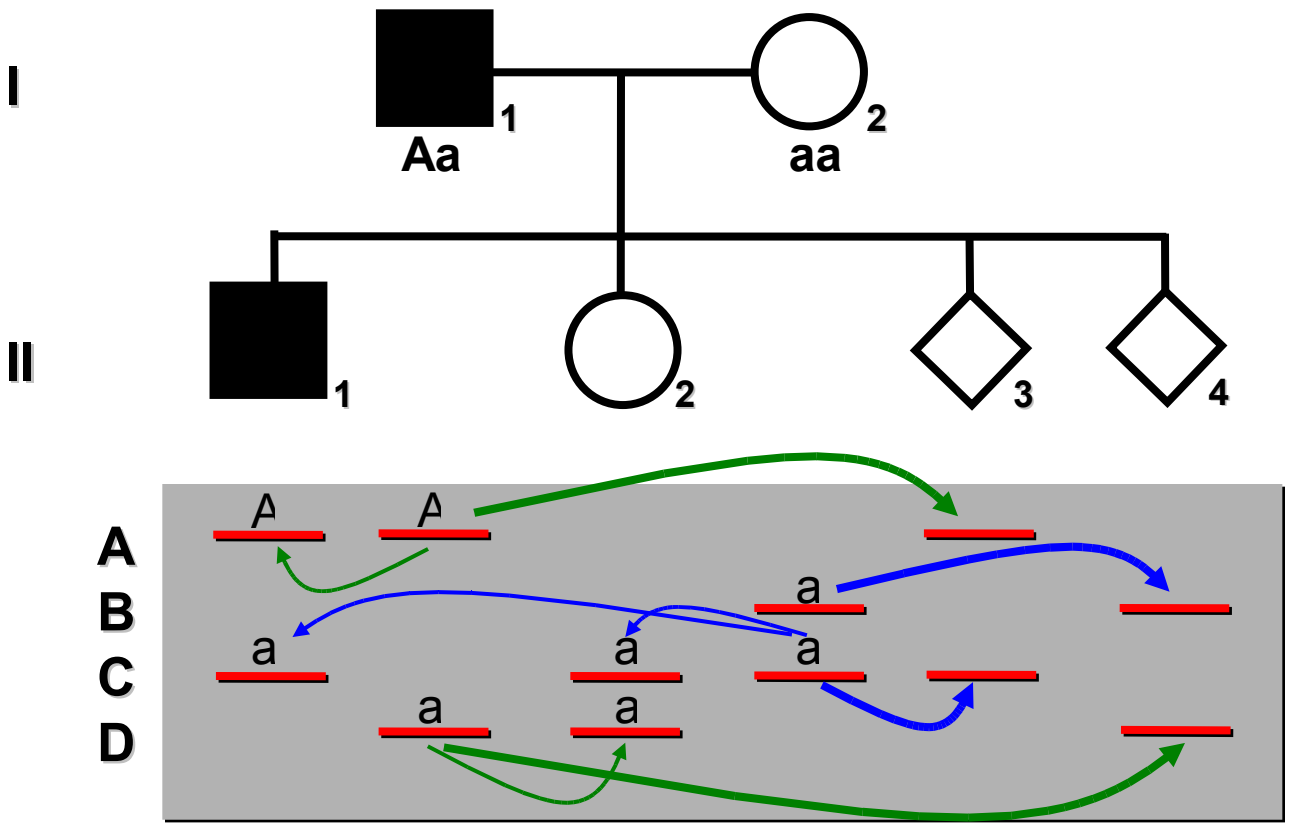
If a *detectable* polymorphism is situated closely enough to a locus, which harbors a causal mutation for the studied disease, the polymorphism will be linked to the mutated allele. In most cases, the polymorphism will be passed together with the mutated allele from the parents to the offspring („cosegregation“). Thus, the polymorphism can be used as a „marker“ for the diesase even without exact knowledge of its molecular basis.

Task 5, p. 122 – Polycystic kidney disease (AD, p = 5cM)



a) Risk of being affected is 50% for II/3 and II/4.

Task 5, p. 122 – Polycystic kidney disease (AD, p = 5cM)

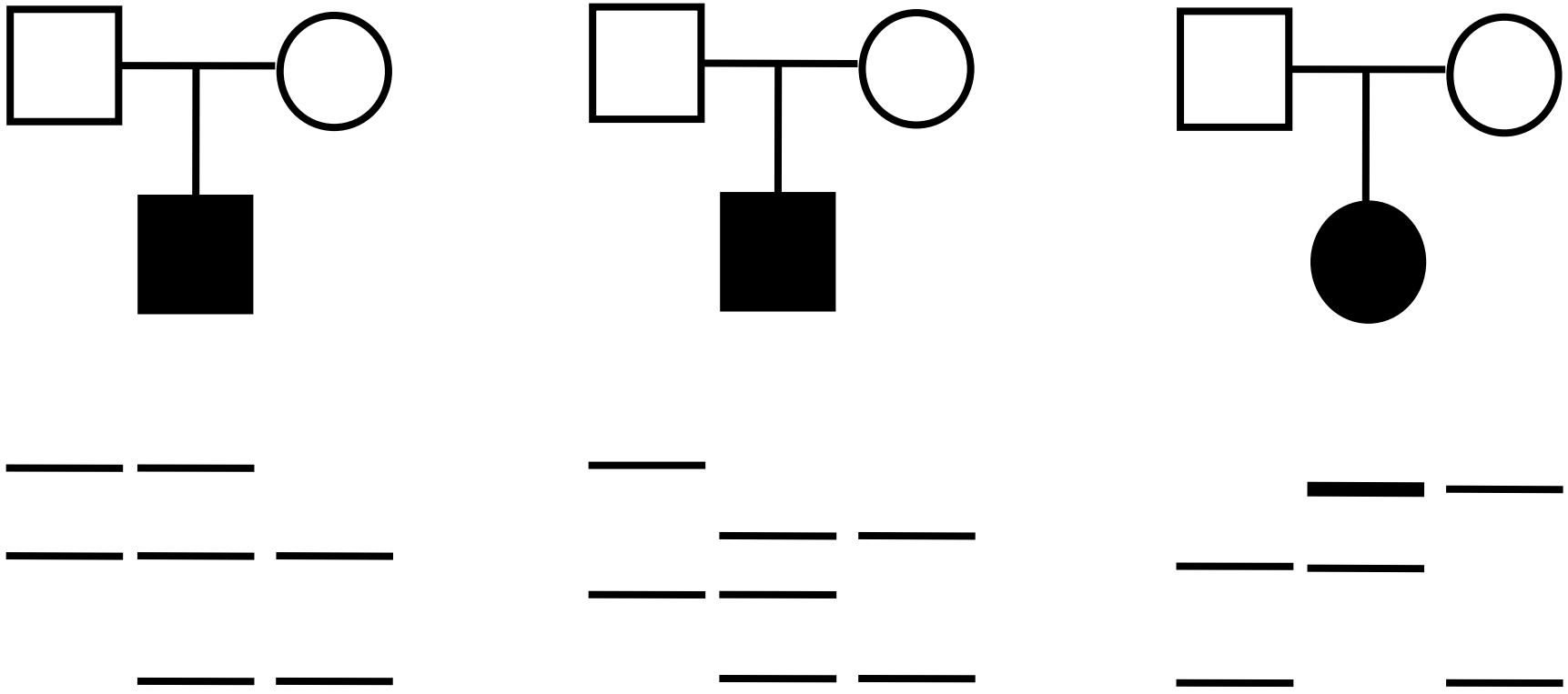


a) Risk of being affected is 50% for II/3 and II/4.

b) Risk of being affected is 95% for II/3.

b) Risk of being affected is 5% for II/4.

Nondisjunction in Down syndrome

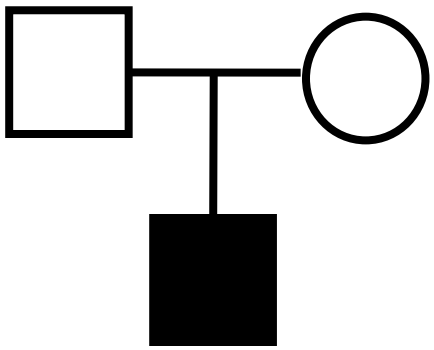


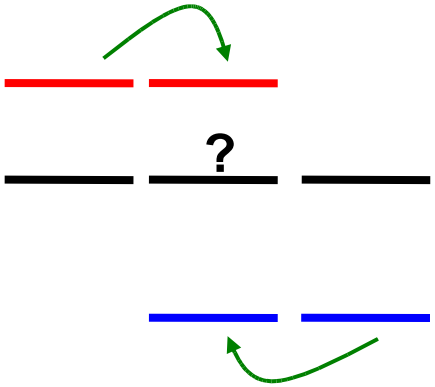
The pedigrees show families where children are affected with Down syndrome (simple trisomy). The results of DNA analysis are shown under pedigrees. Polymorphism of a tetranucleotide microsatellite on chromosome 21 was determined.

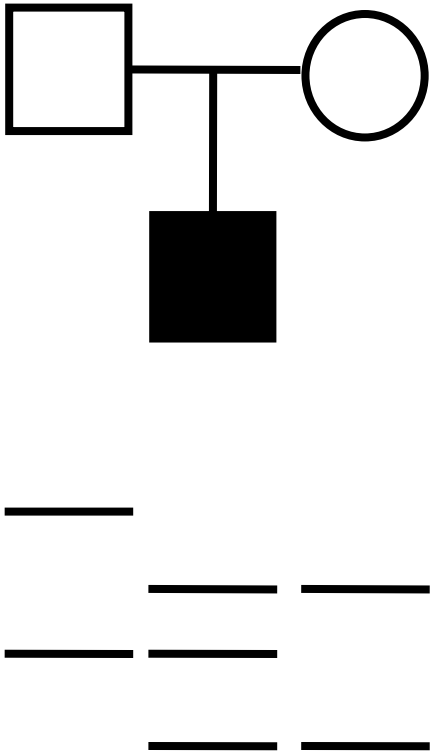
From which parent the affected child inherited an extra chromosome 21?

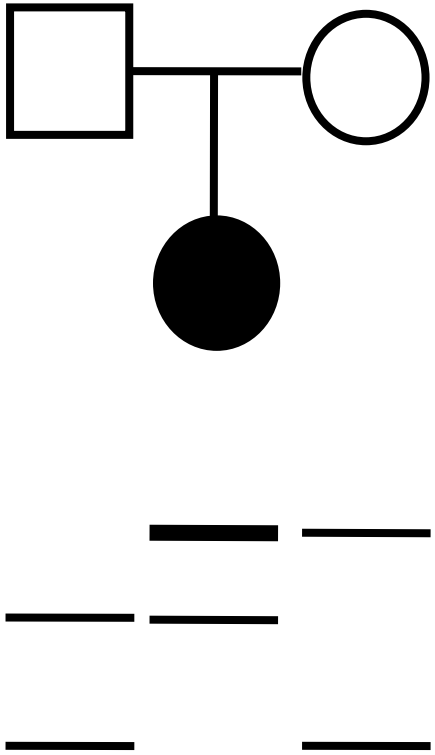
In which meiotic division the nondisjunction occurred?

Nondisjunction in Down syndrome



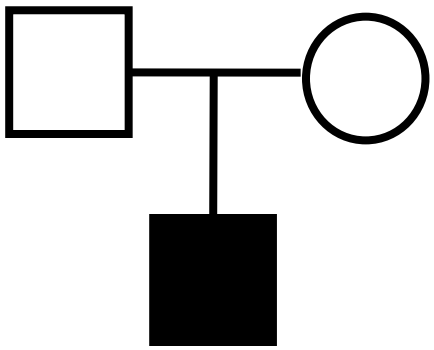


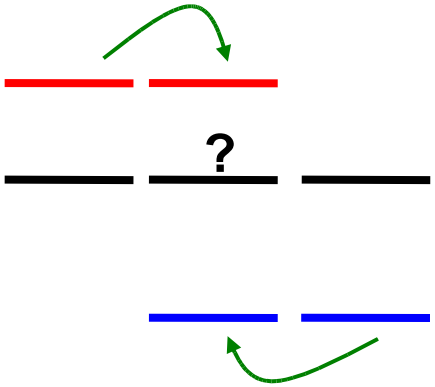




Meiosis I in mother or father

Nondisjunction in Down syndrome





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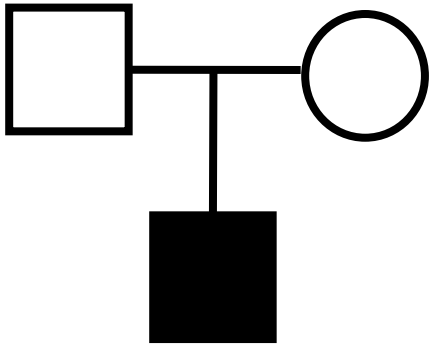
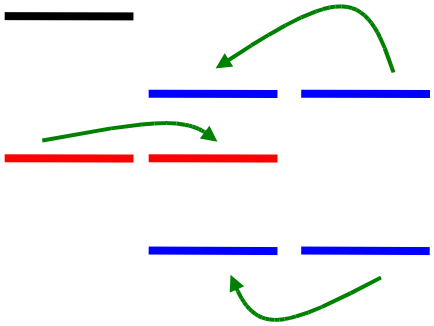
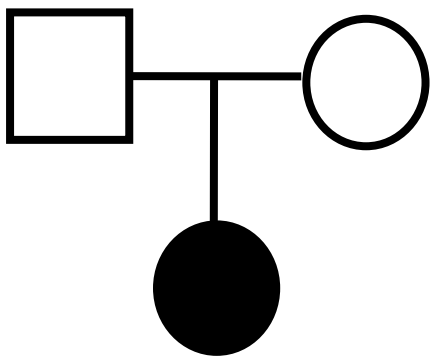
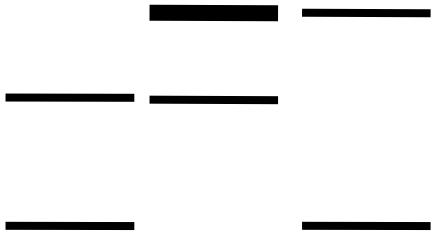


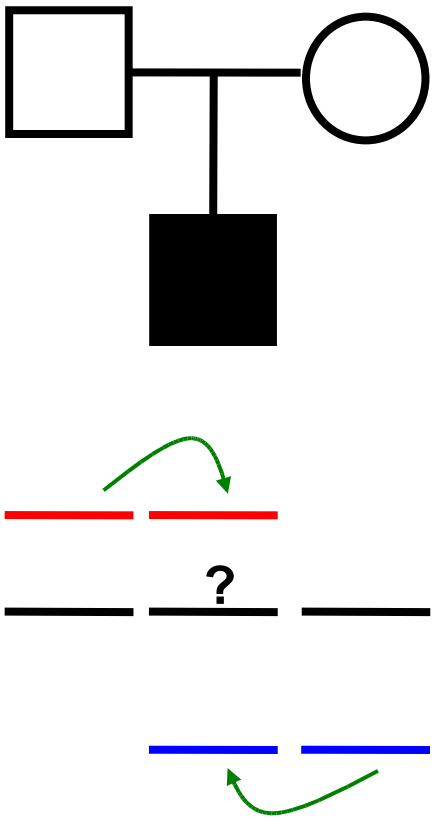


Meiosis I in mother

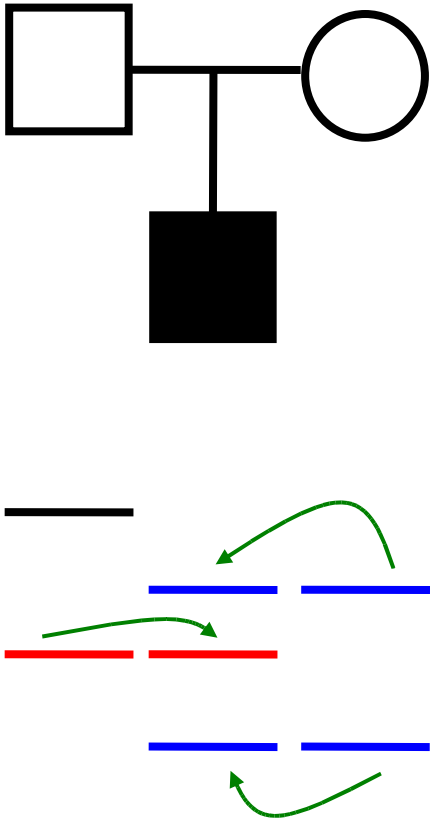




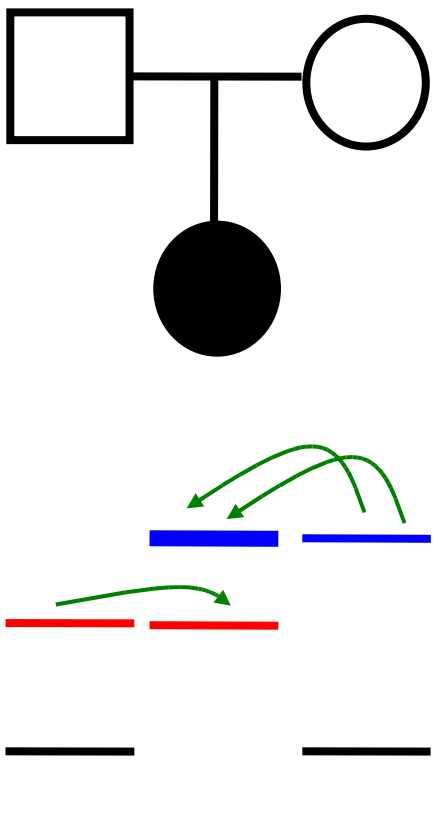
Nondisjunction in Down syndrome



Meiosis I in mother or father

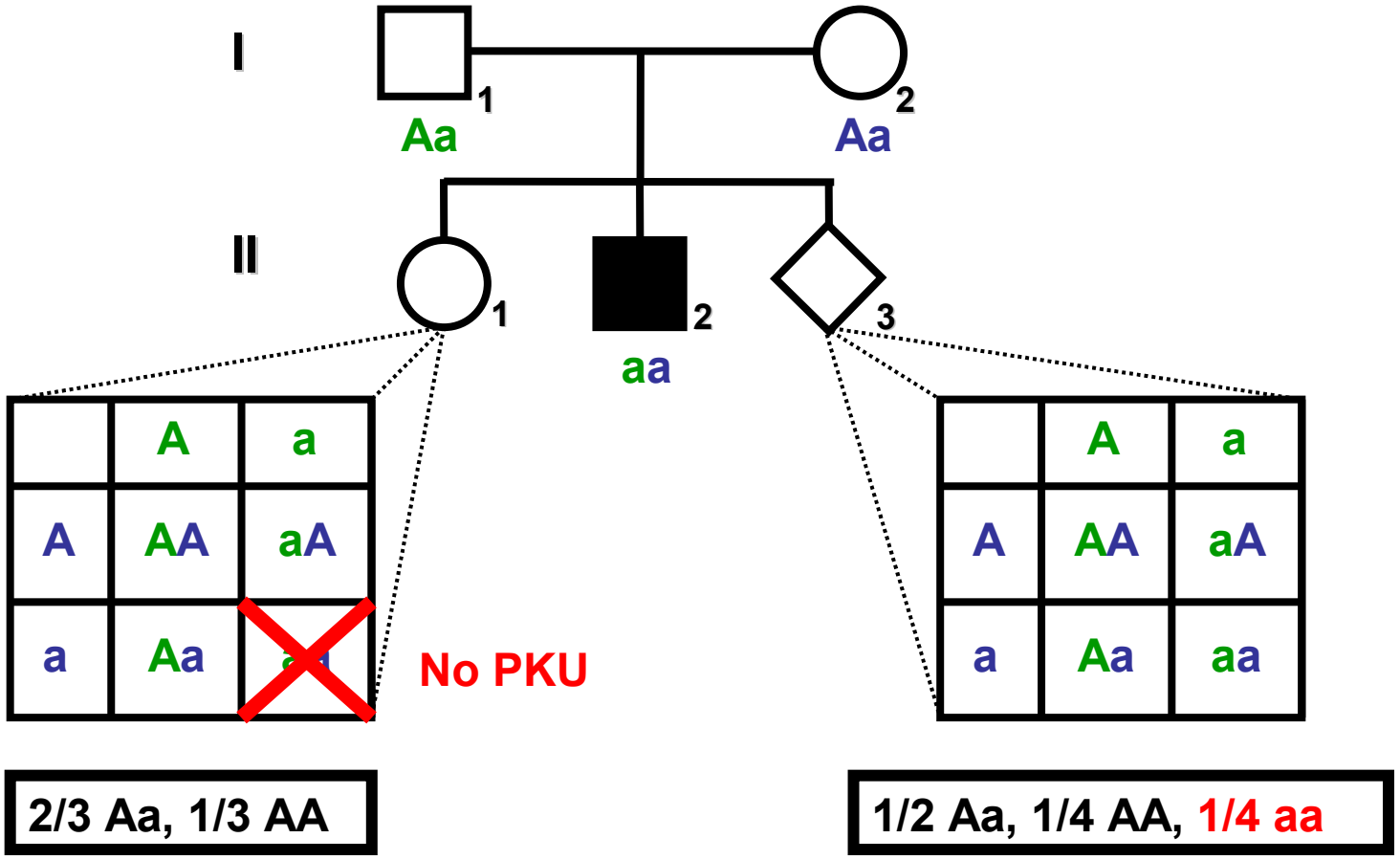


Meiosis I in mother



Meiosis II in mother

Task 3, p. 134, PKU

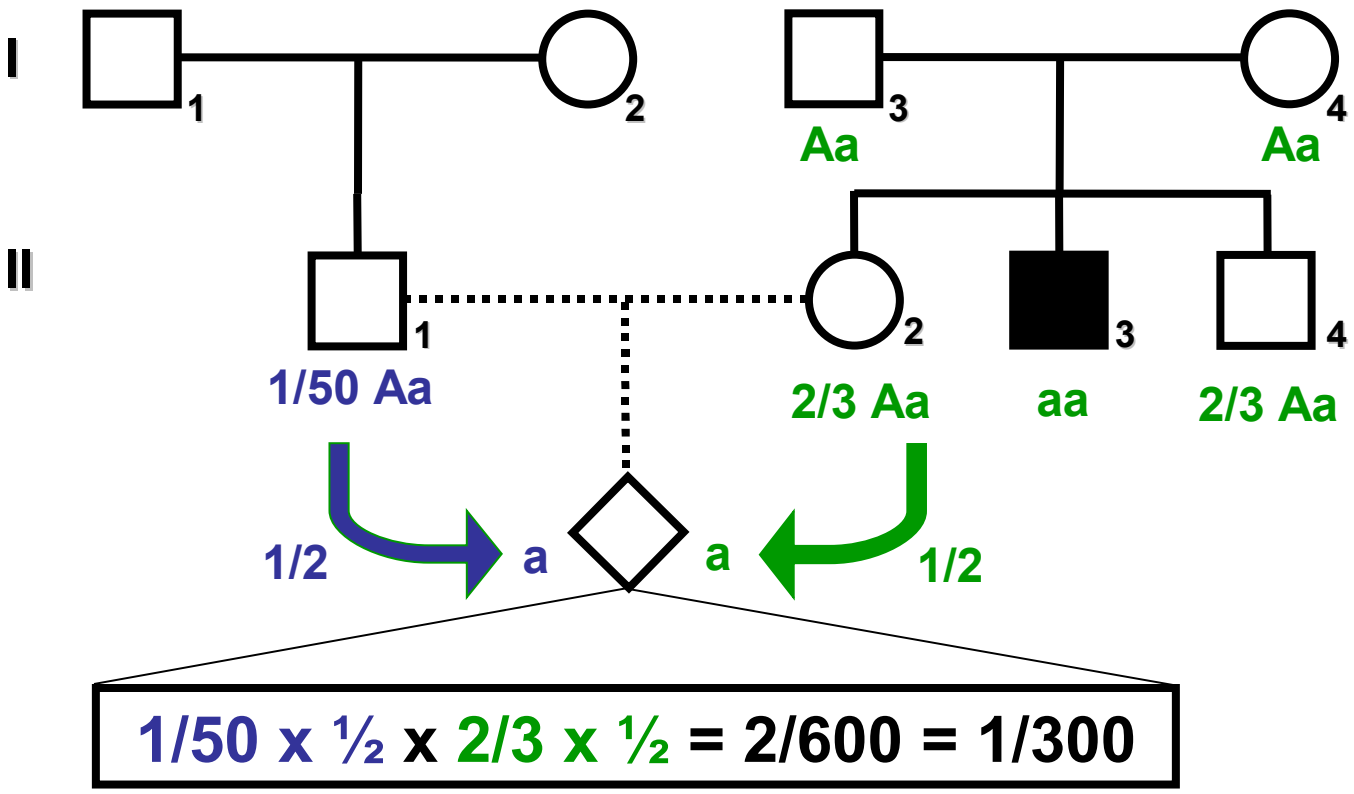


Prenatal dg. was not possible in late 1970s.

Risk 25% (i.e. > 10%) - possibility to terminate the pregnancy upon mother´s request.

In case the pregnancy continues: after the child is born, PKU screening will be performed, put on special diet if tested positive (i.e. affected).

Task 4a, p. 134, PKU – incidence 1/10,000



$q^2 = 1/10000$

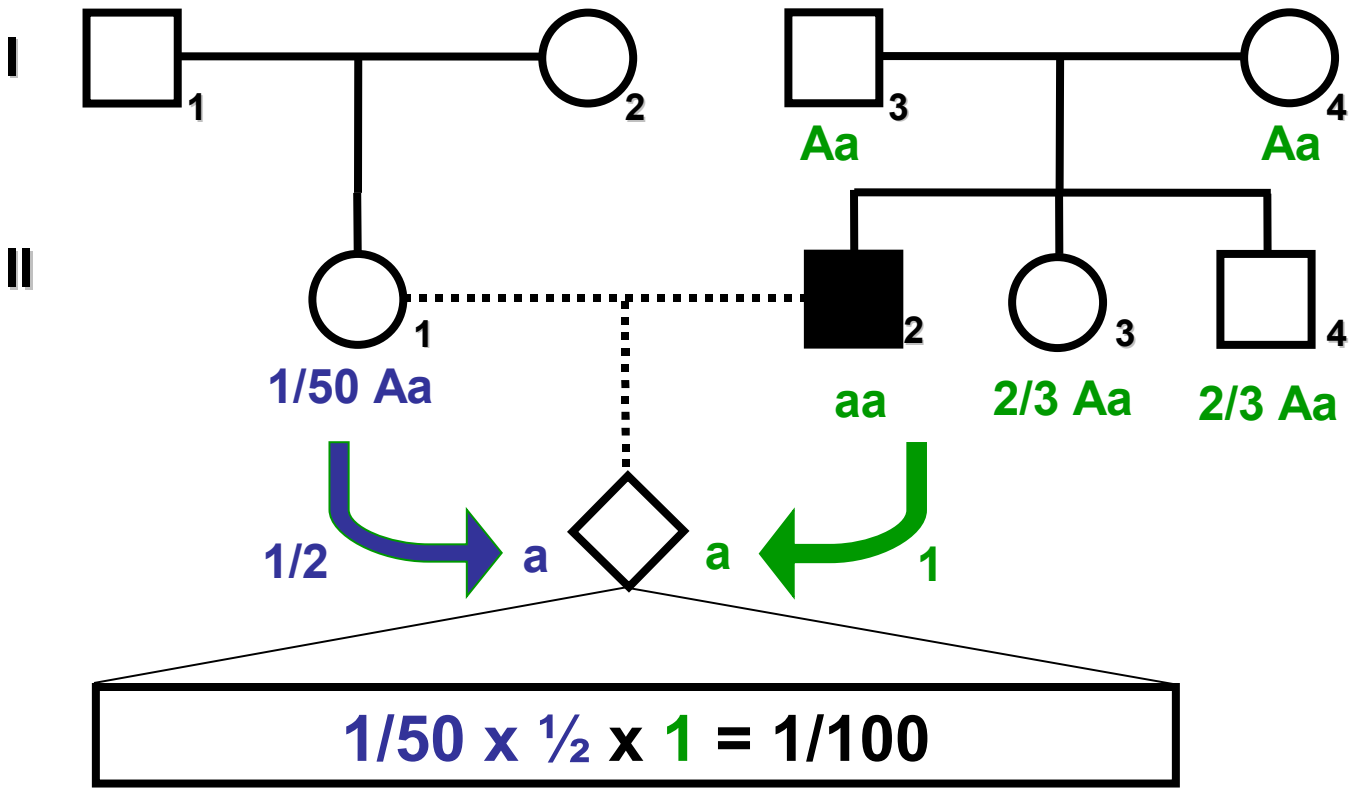
$q = 1/100$

$2pq = 2 \times 99/100 \times 1/100 = 1/50$

Low risk, DNA analysis recommended,

Importance of TIME factor….

Task 4b, p. 134, PKU – incidence 1/10,000



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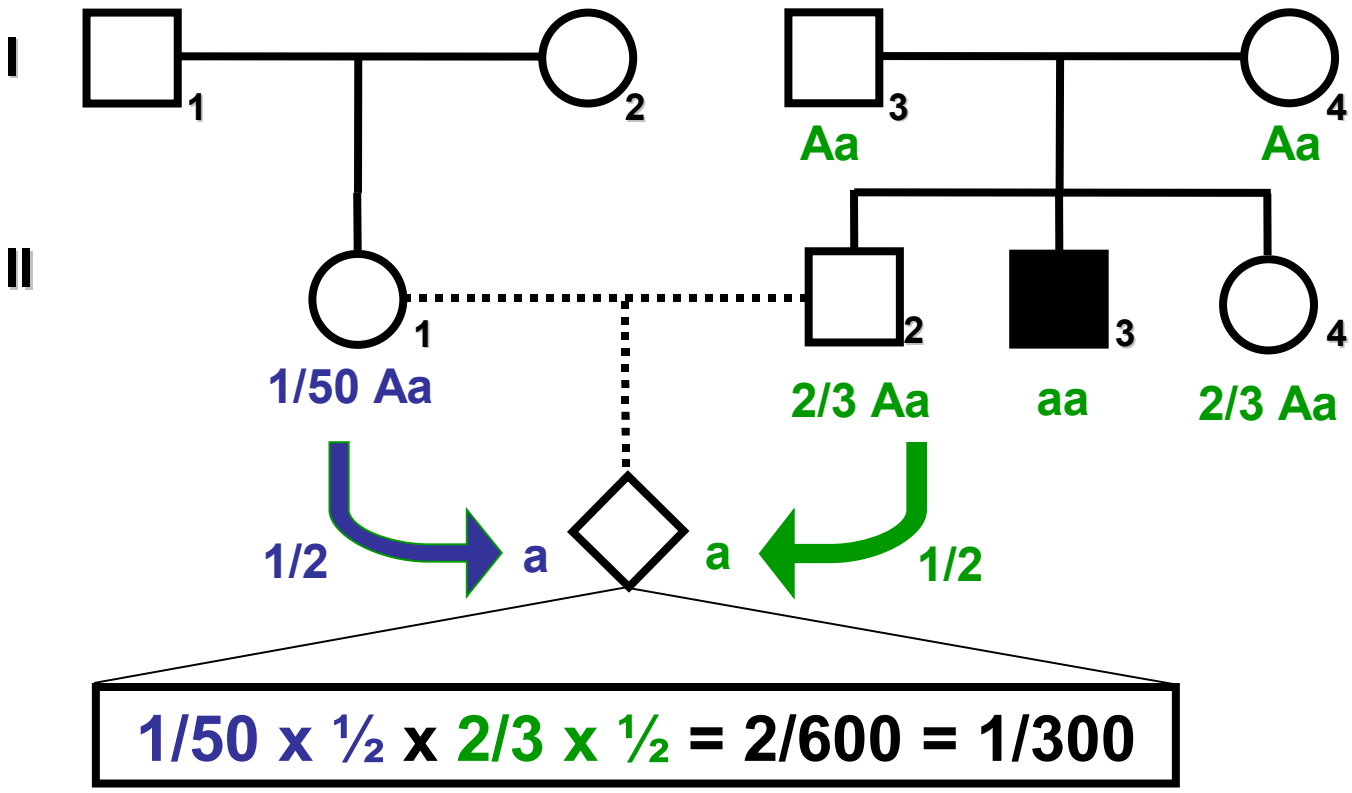
Task 4b, p. 134, PKU – incidence 1/10,000



q^2 = 1/10000

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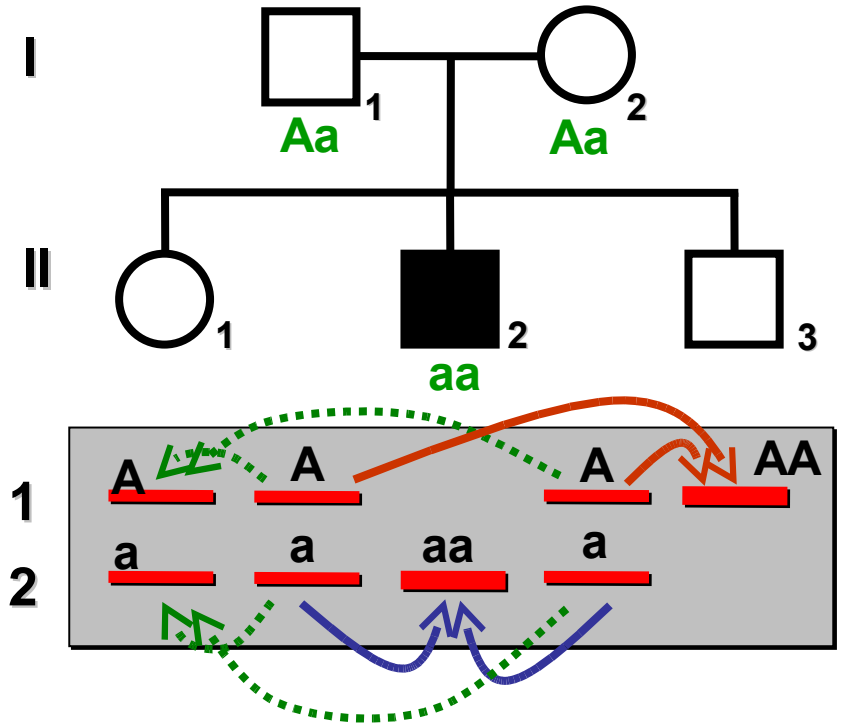
2pq = 2 x 99/100 x 1/100 = 1/50

Task 6, p. 135



a) Yes, the familiy IS INFORMATIVE concerning the genotypes of II/1-3.

b) Intragenic probe, i.e. the daughter II/1 IS HETEROZYGOUS.

c) Intragenic probe, i.e. the son II/3 IS a DOMINANT HOMOZYGOTE.

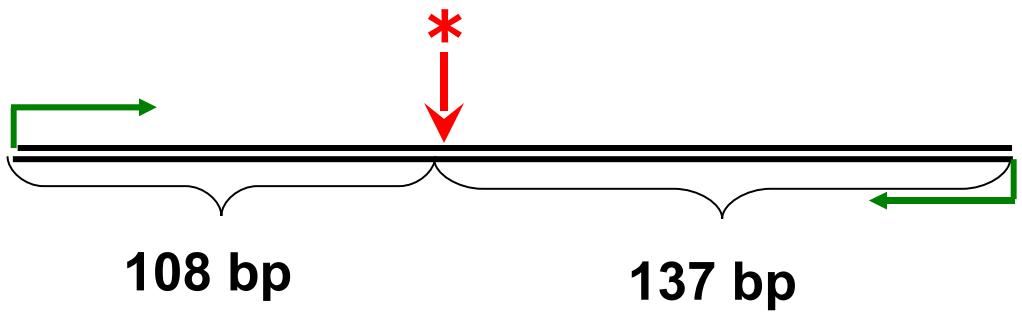
d) NO, indirect diagnostics cannot be used outside the context of the family.

Task 7, p. 135

R408W
(Sty I)

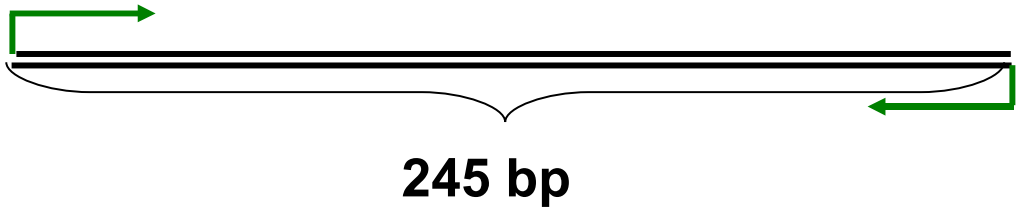
Mutated allele

R408W

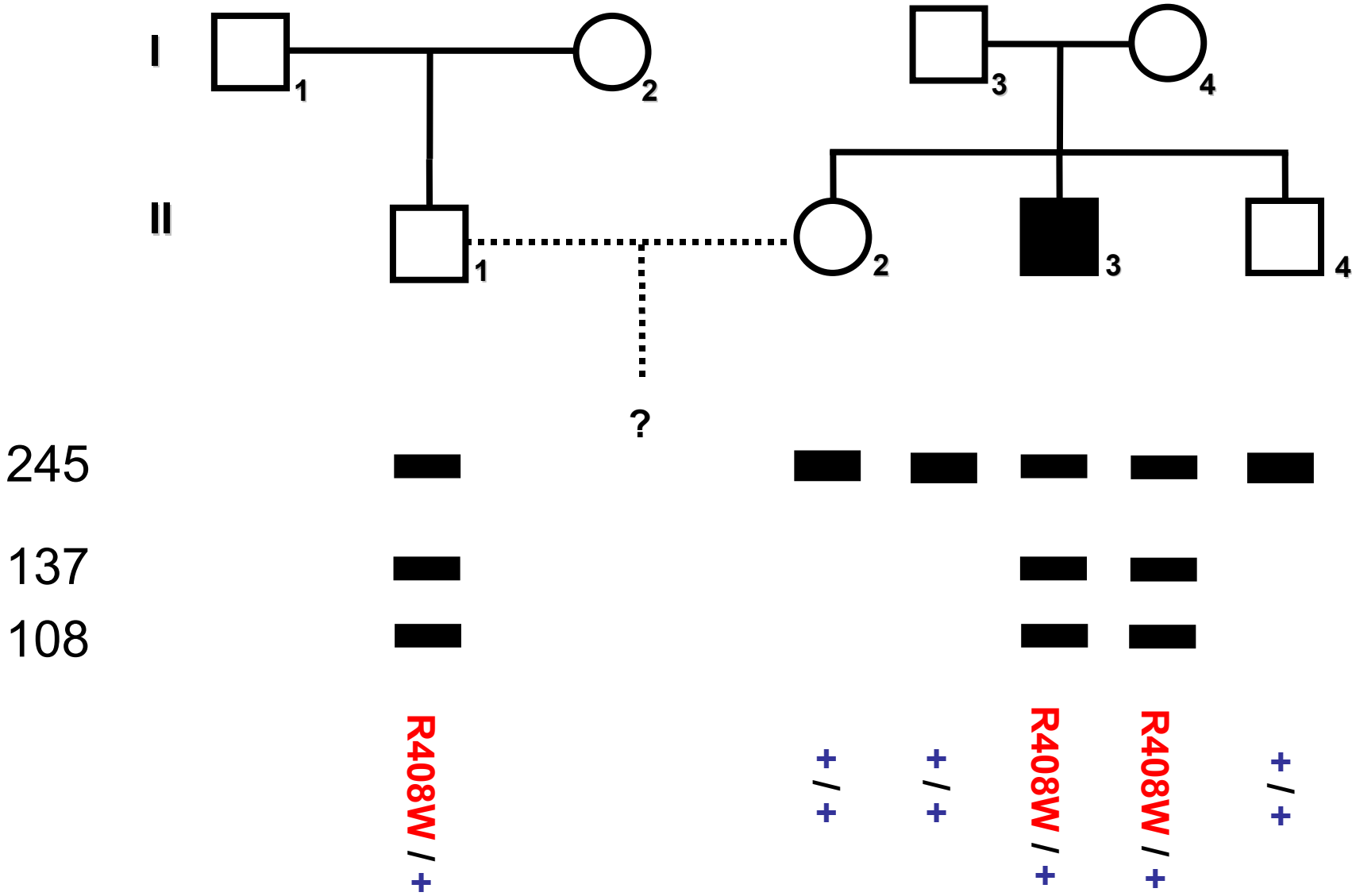


Normal allele

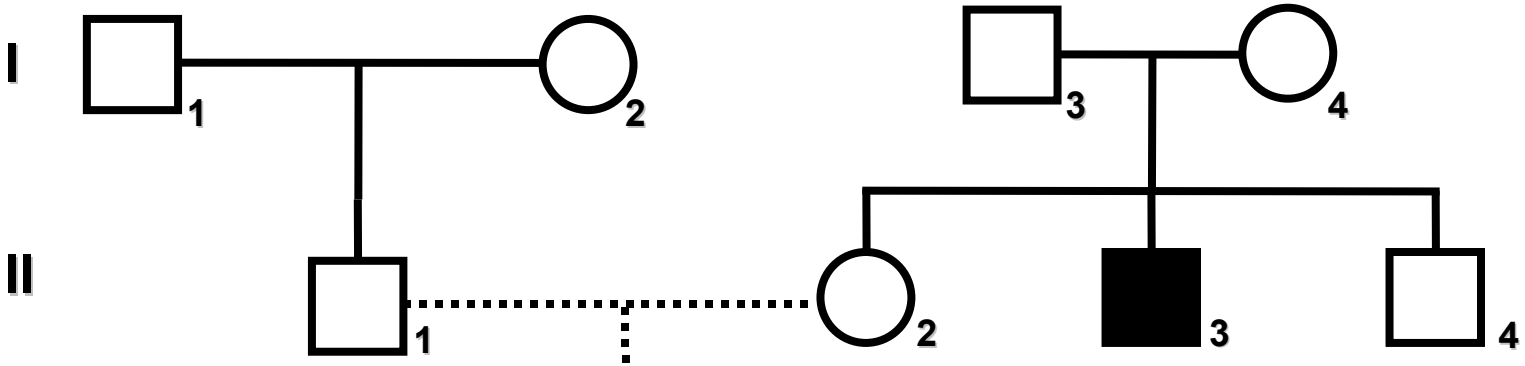
+



Task 7a, p. 135



Task 7b, p. 135



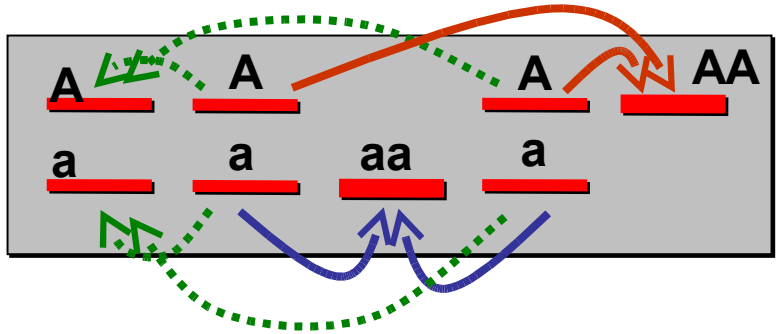
Aa

R408W / +

Aa

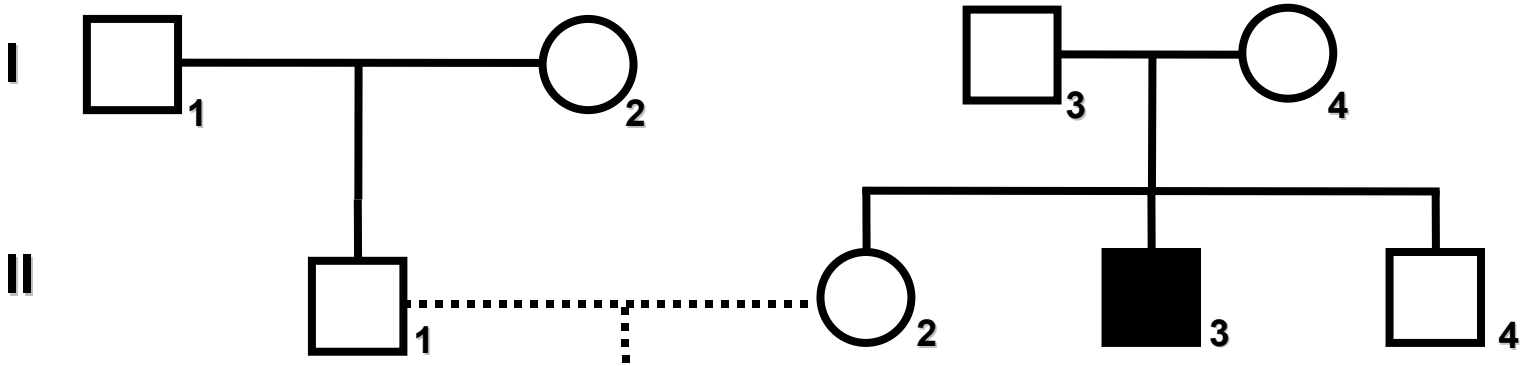
mut / +

	+	R408W
+	+/+	+/R408W
mut	+/mut	mut/R408W



1/2 Aa, 1/4 AA, 1/4 aa

Task 8, p. 136 SSCP for EXON 6.



b) CVS (10 – 12 week of pregnancy),

AMC (15th – 20th week)

PUBS (KDC) - later

?

GENOTYPE

6mut / +

R408W / +

Mutation in 6 exon (6mut)