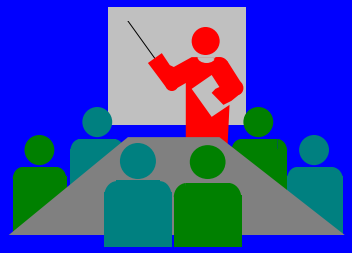
2nd year, winter semester
1st week 1.10. - 5.10.2006

REPETITION

SELECTED TASKS of summer semester



PROGRAM

REPETITION
SELECTED TASKS of summer semester

1. Nondisjunction in Down, Turner, and Klinefelter syndrome

2. Evaluation of karyotype with aberration

3. Linkage

Introduction to POPULATION GENETICS

4. Estimates of gene frequencies

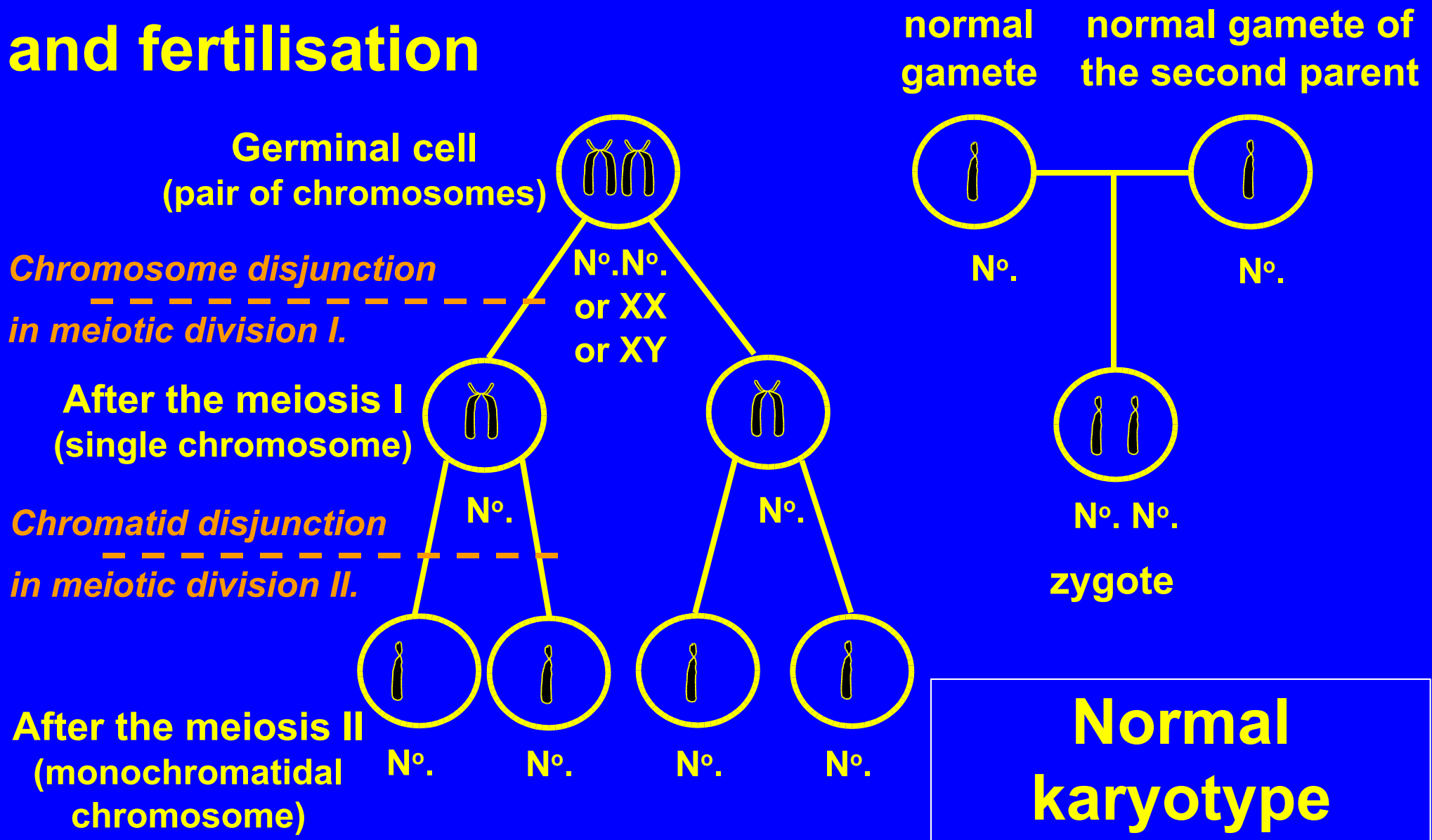
1. Nondisjunction in Down, Turner, and Klinefelter syndrome

p. 80/Task 6e, a, b (preserve this order)

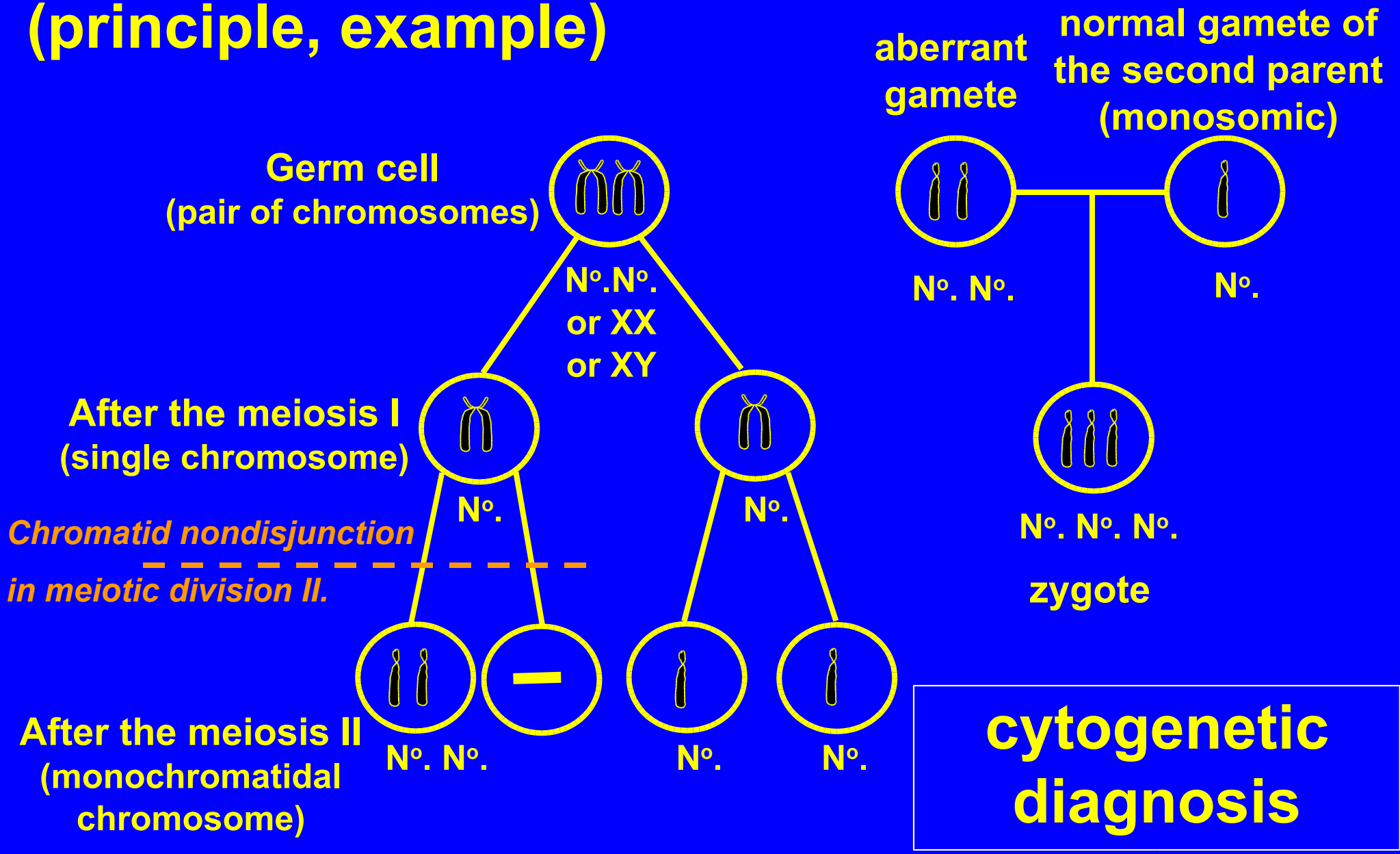
Remaining c) and d) - syndromes XXX and supermale – home work, as selfstudy!

N.B.: **Fill in all possibilities of the nondisjunction events for a particular syndrome could originate. This is asked in the text, exactly as in the final exam test.**

General schedule of disjunction of chromosomes in the meiosis and fertilisation



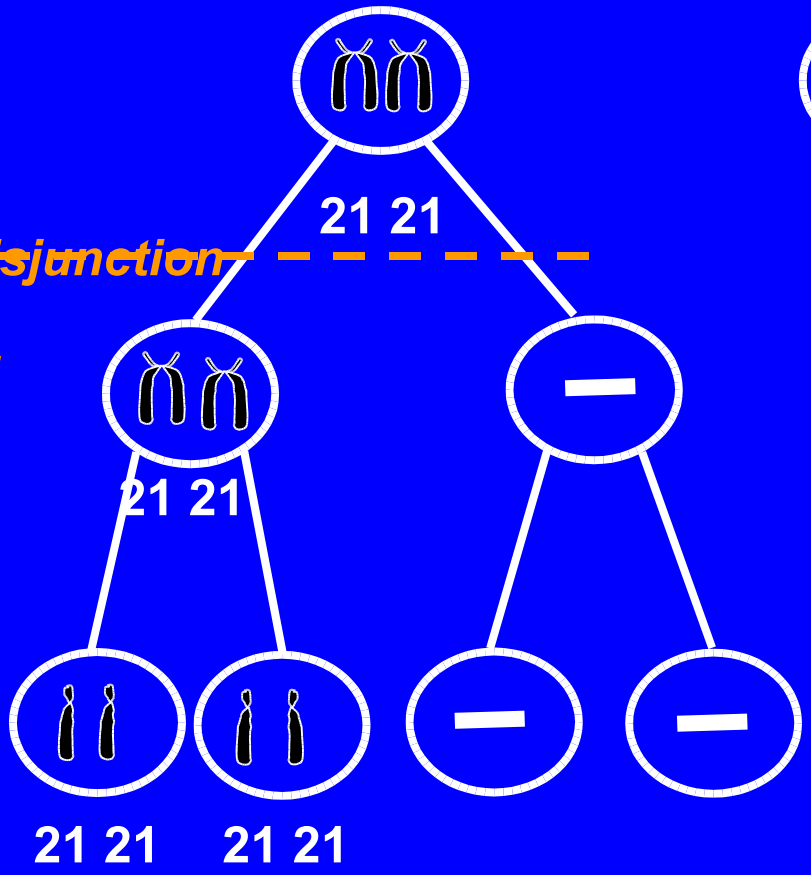
General schedule of nondisjunction (principle, example)

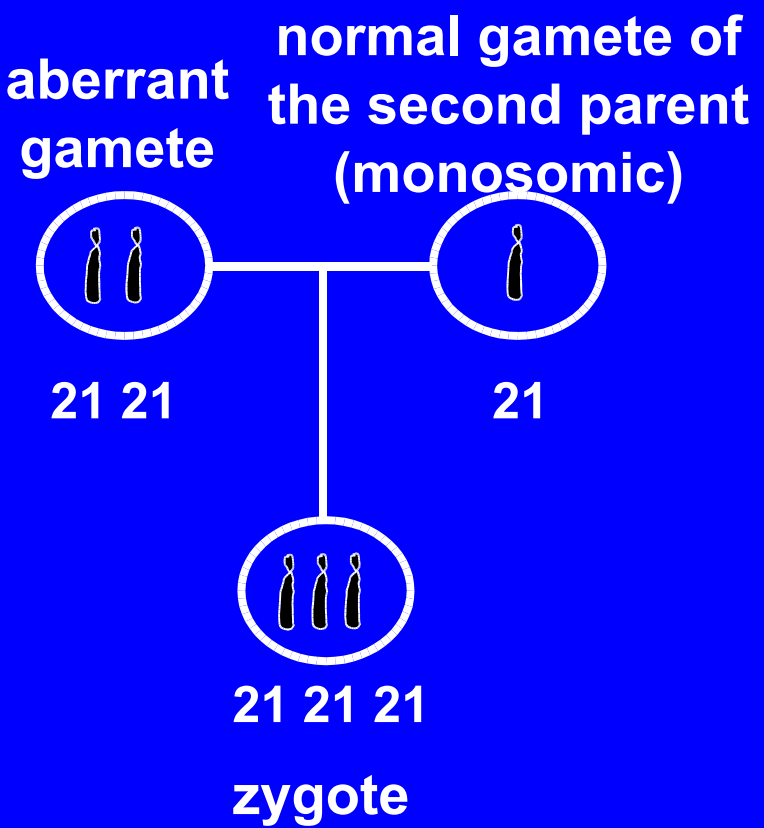


cytogenetic diagnosis

6e) Down syndrome (simple trisomy)

Nondisjunction in the meiosis I in the father or in the mother



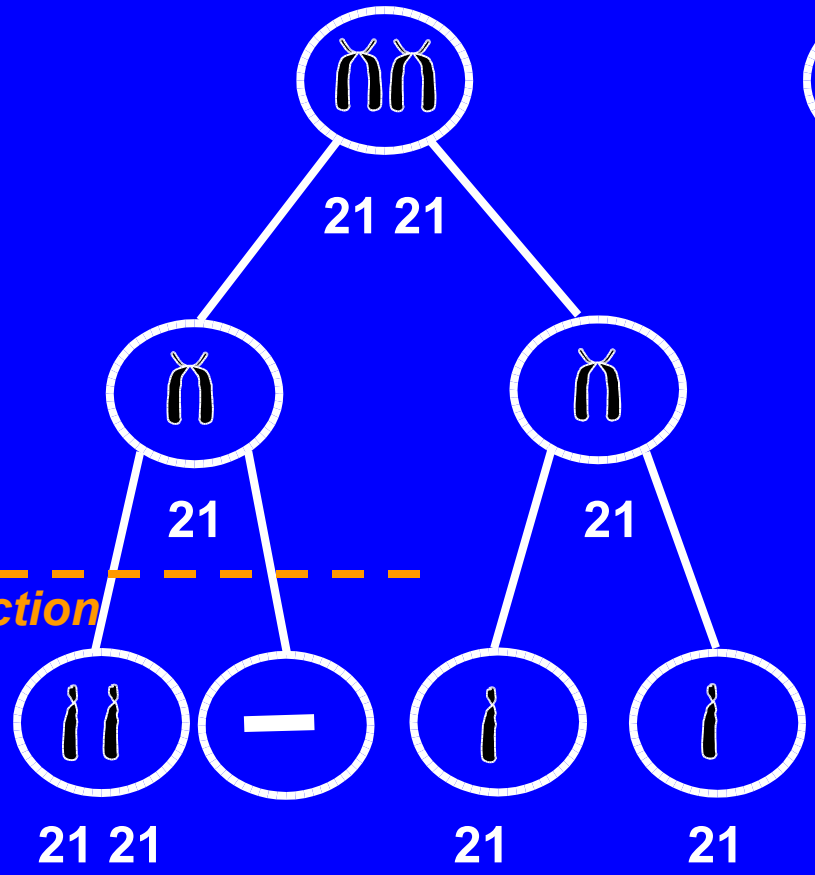


47,XX,+21

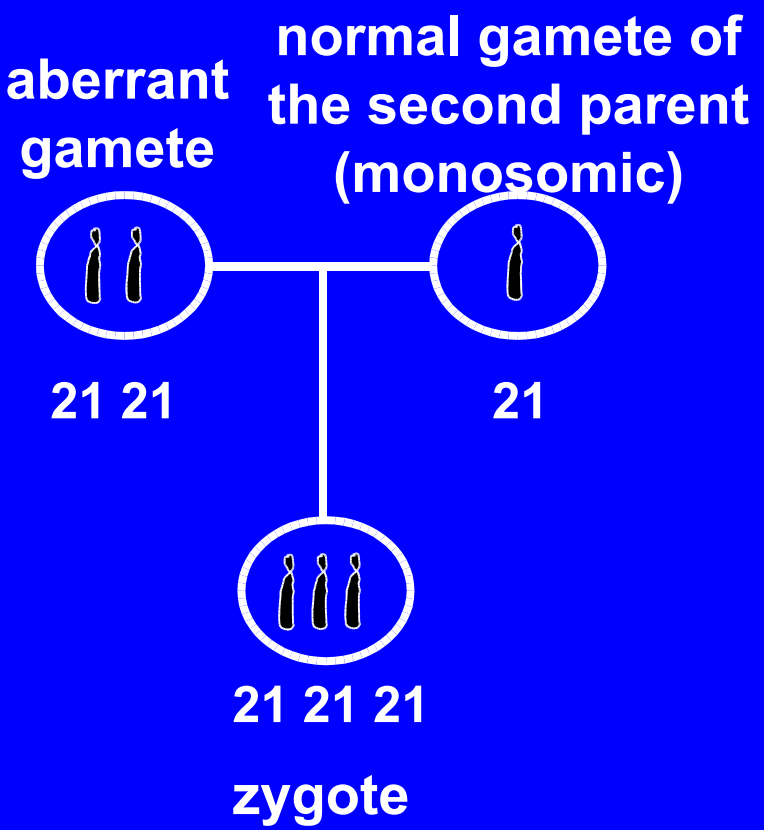
47,XY,+21

6e) Down syndrome (simple trisomy)

Nondisjunction <u>in the meiosis II</u> in the father or in the mother

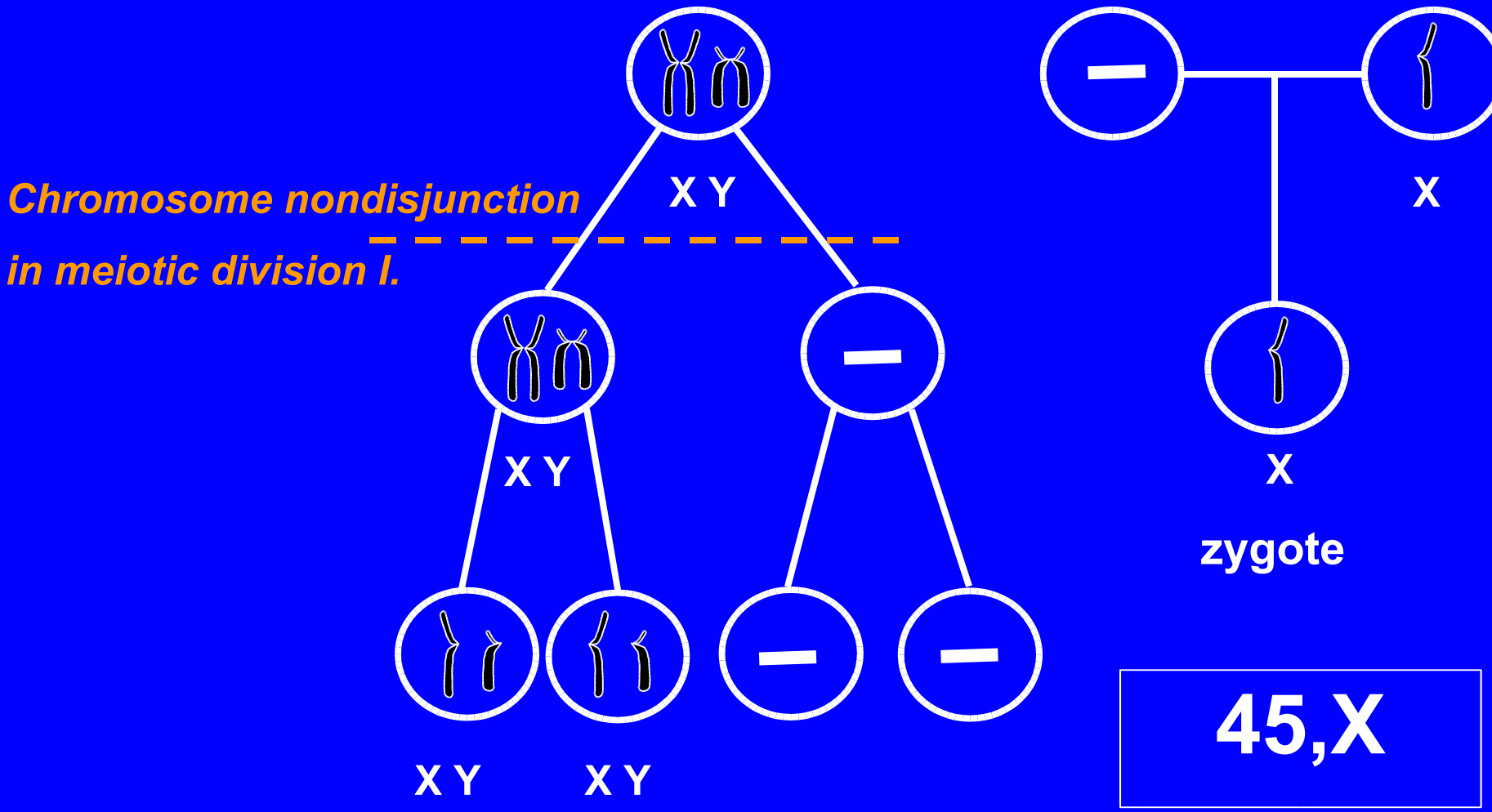


Chromatid nondisjunction in meiotic division II.

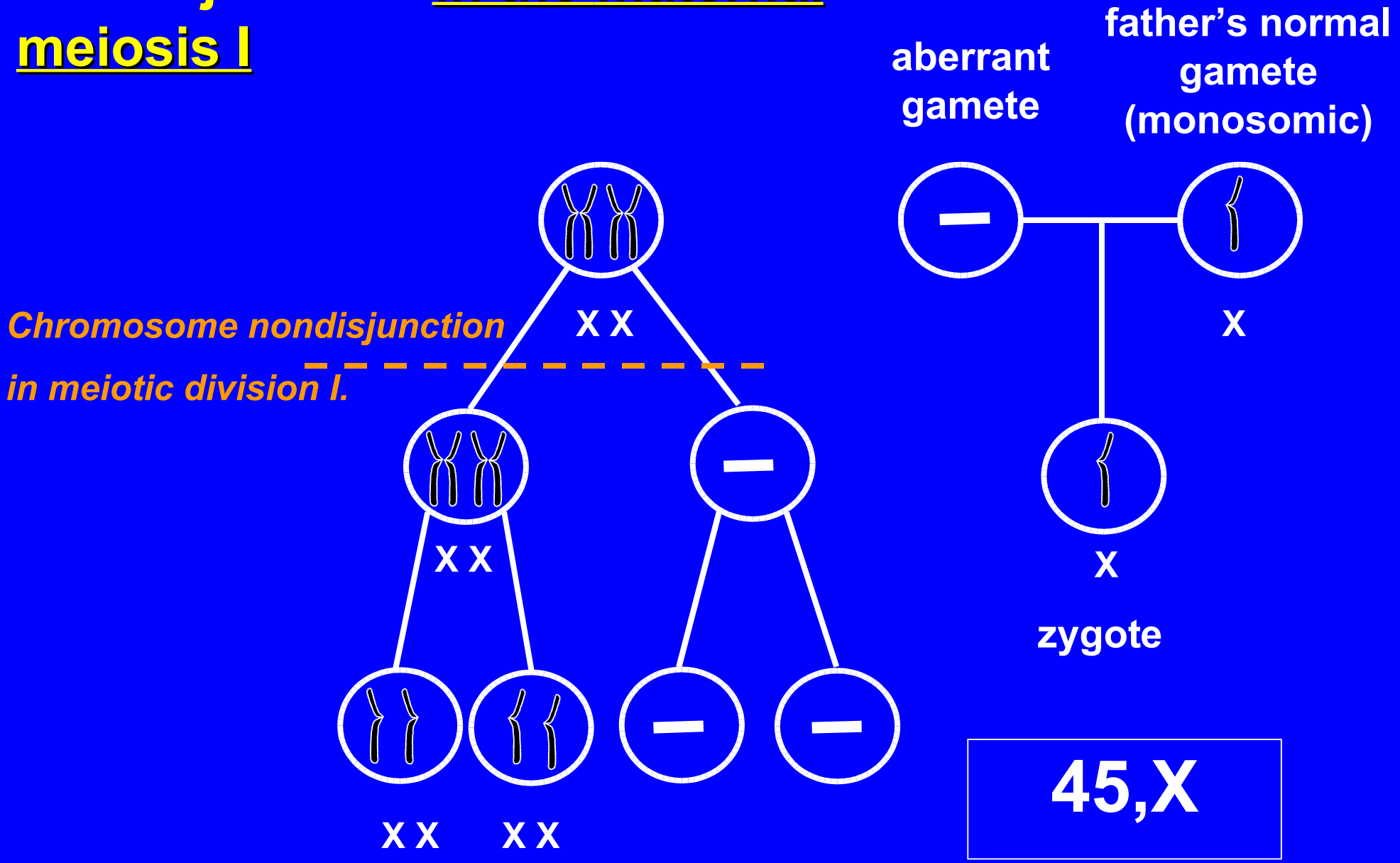


47,XX,+21
47,XY,+21

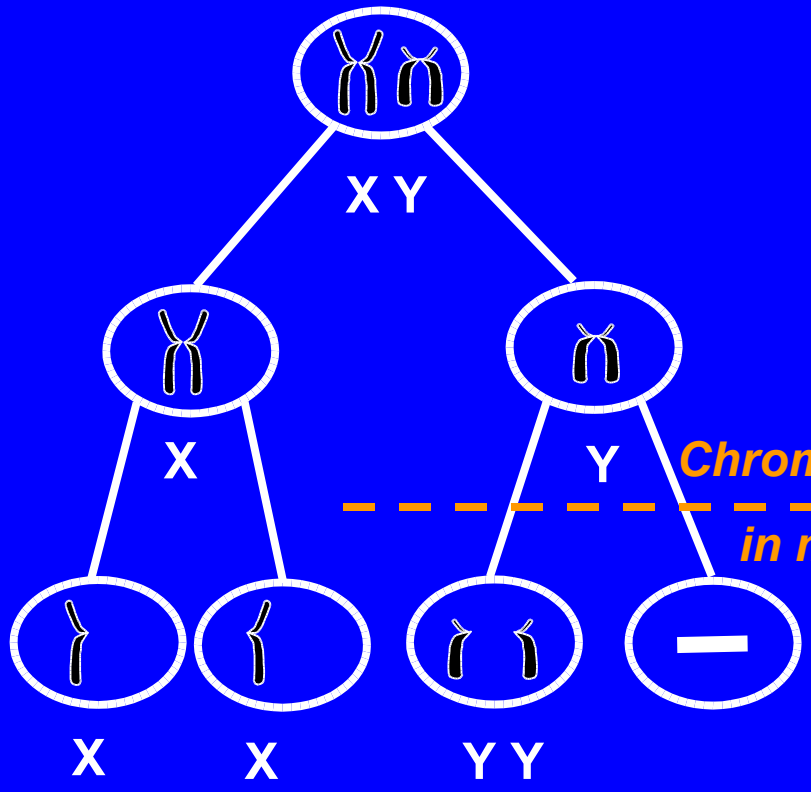
6a) Turner syndrome
Nondisjunction in the paternal meiosis I



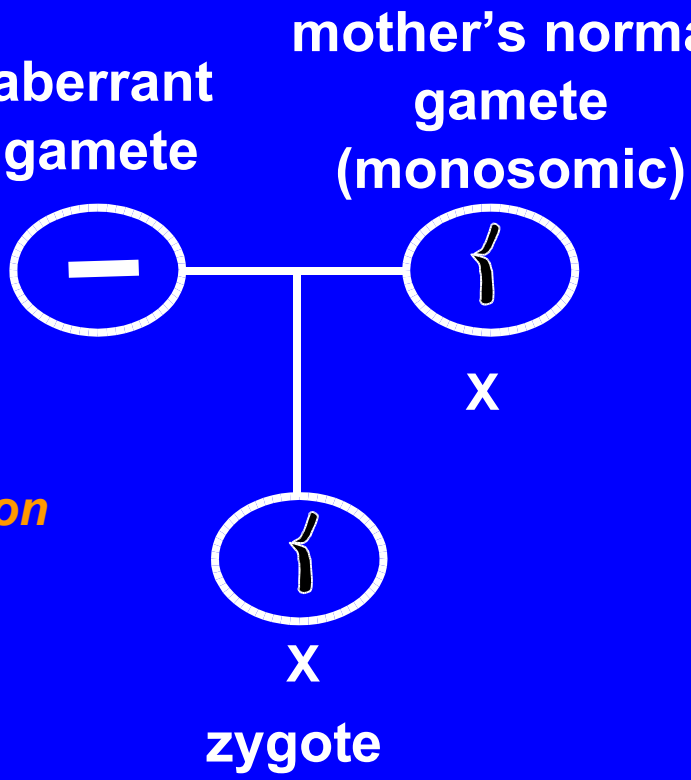
6a) Turner syndrome
Nondisjunction in the maternal meiosis I



6a) Turner syndrome
Nondisjunction in the paternal meiosis II

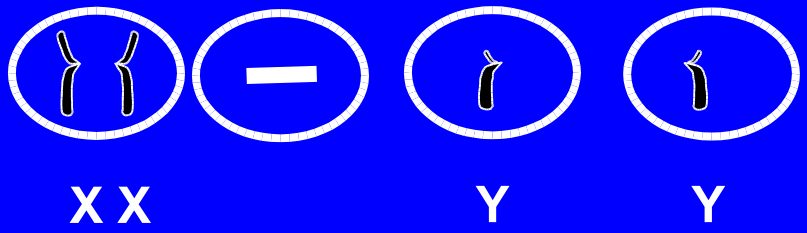


Chromatid nondisjunction in meiotic division II.

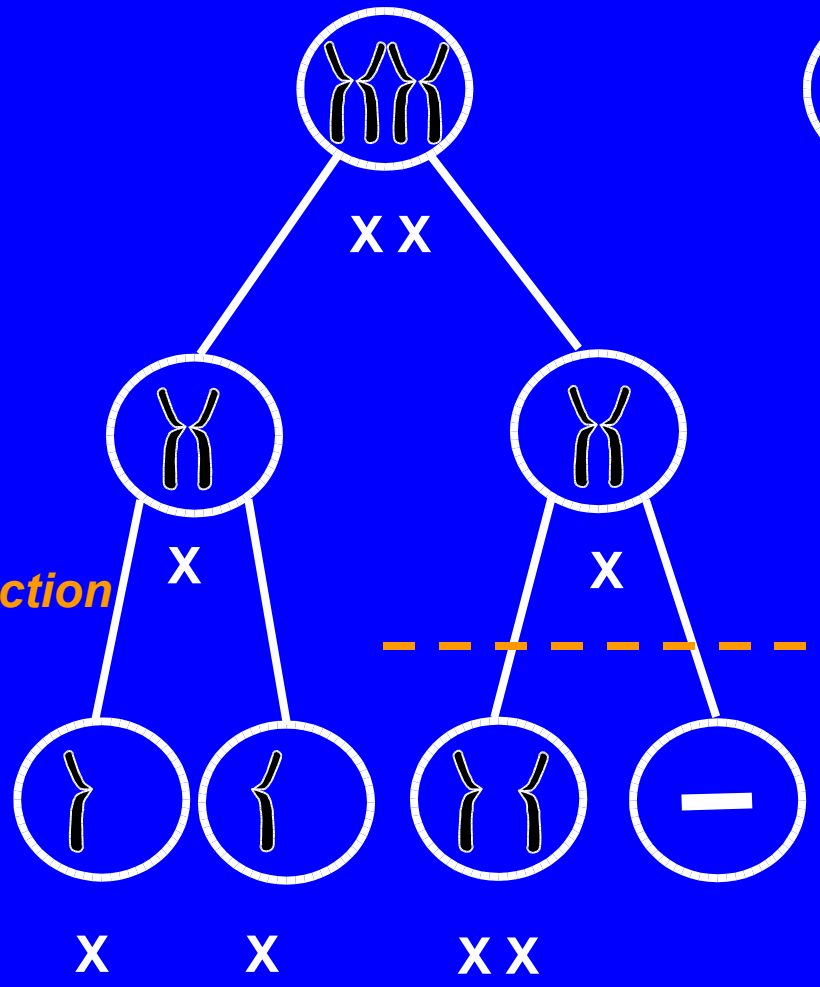


45,X

!! or:



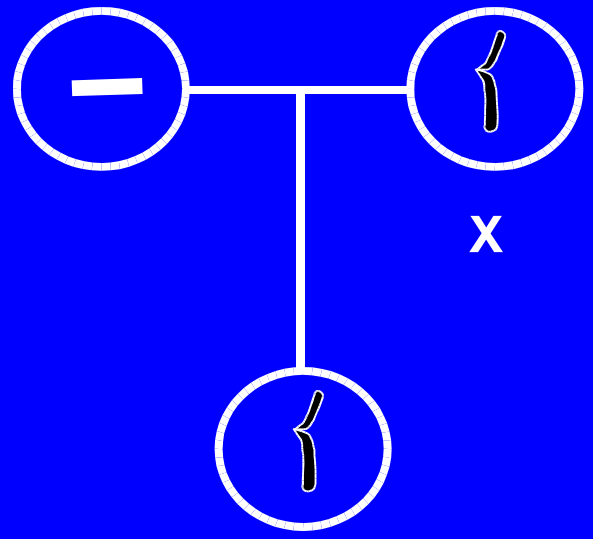
6a) Turner syndrome
Nondisjunction in the maternal meiosis II



Chromatid nondisjunction in meiotic division II.

aberrant gamete

father's normal gamete (monosomic)

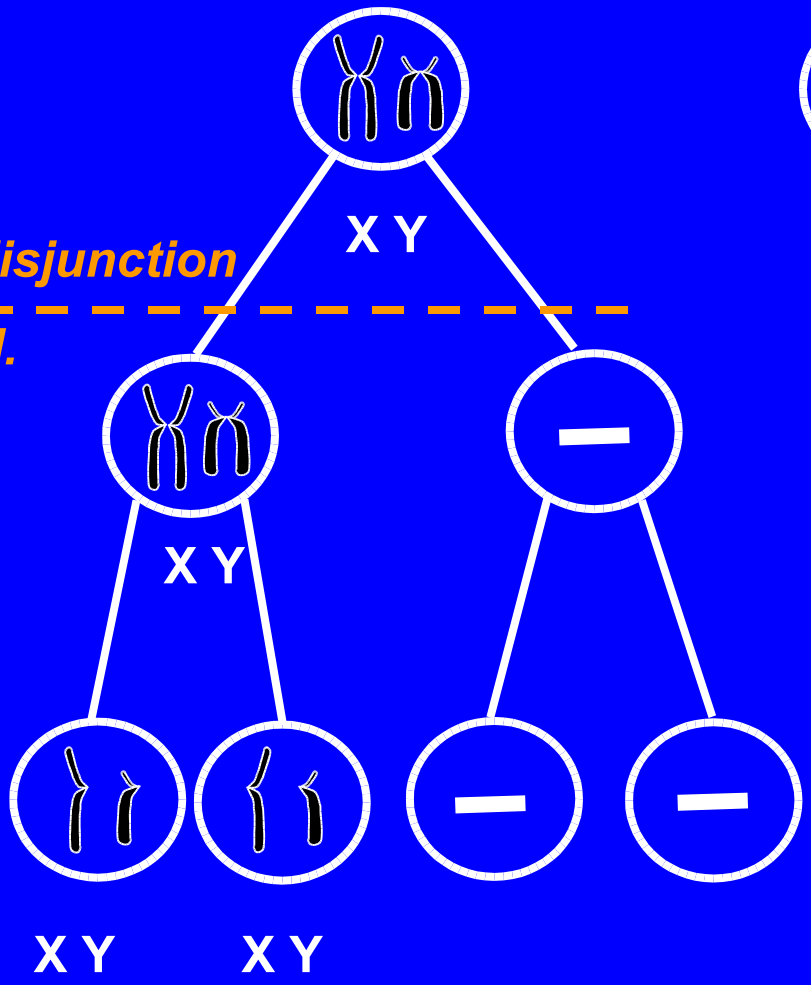


zygota

45,X

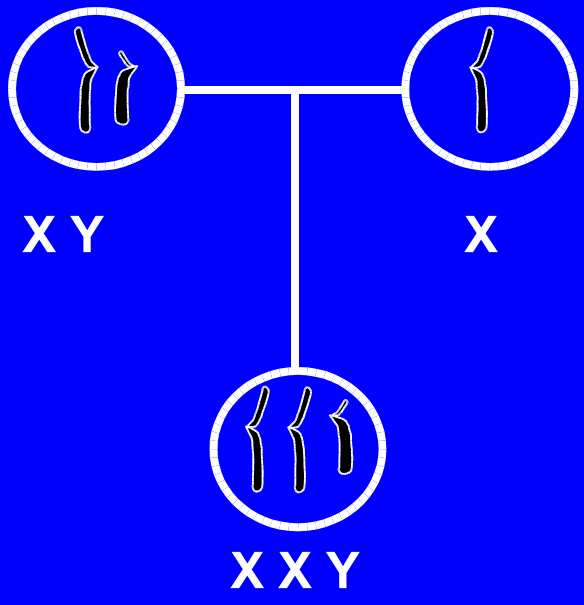
6b) Klinefelter syndrome Nondisjunction in the paternal meiosis I

Chromosome nondisjunction in meiotic division I.



aberrant gamete

mother's normal gamete (monosomic)

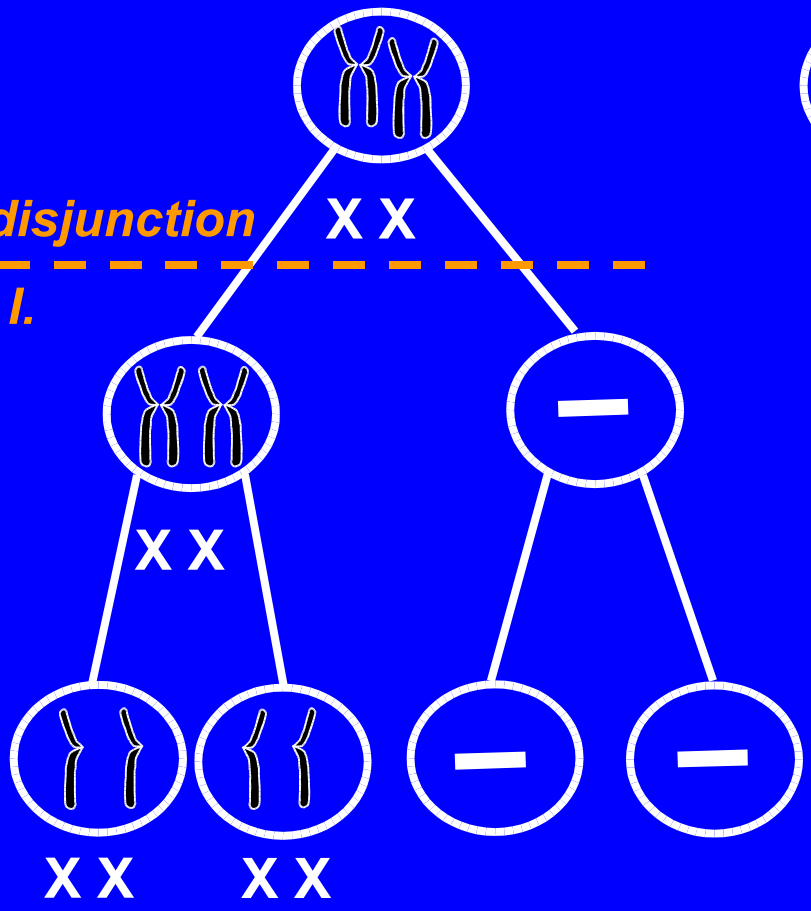


zygote

47,XXY

6b) Klinefelter syndrome
Nondisjunction in the maternal meiosis I

Chromosome nondisjunction in meiotic division I.



aberrant gamete

father's normal gamete (monosomic)

X X

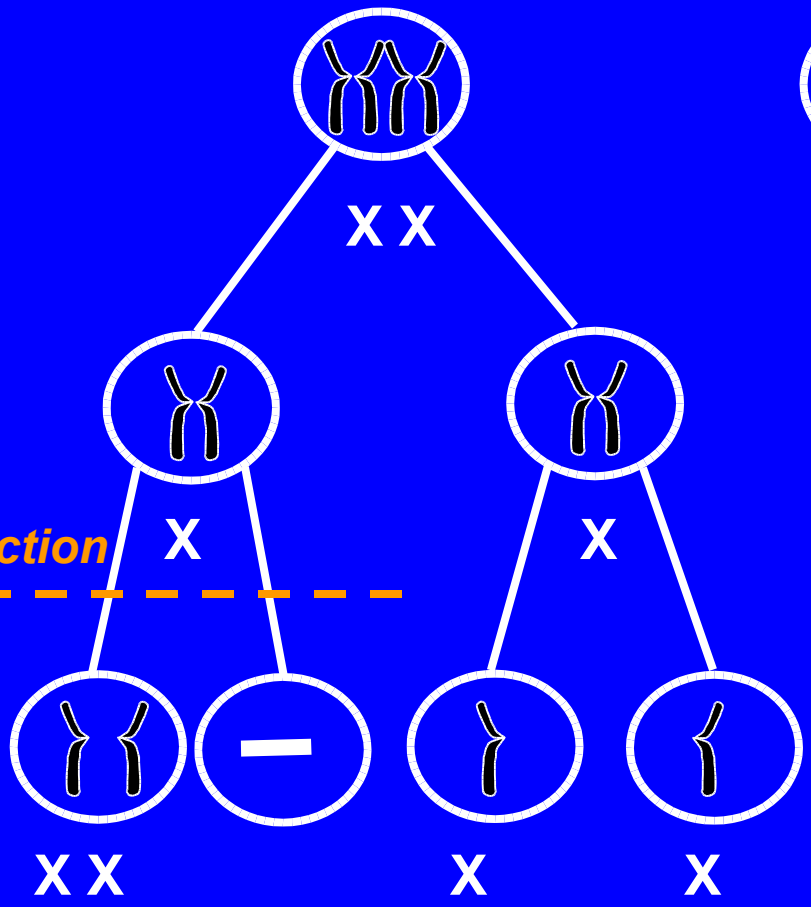
Y

X X Y

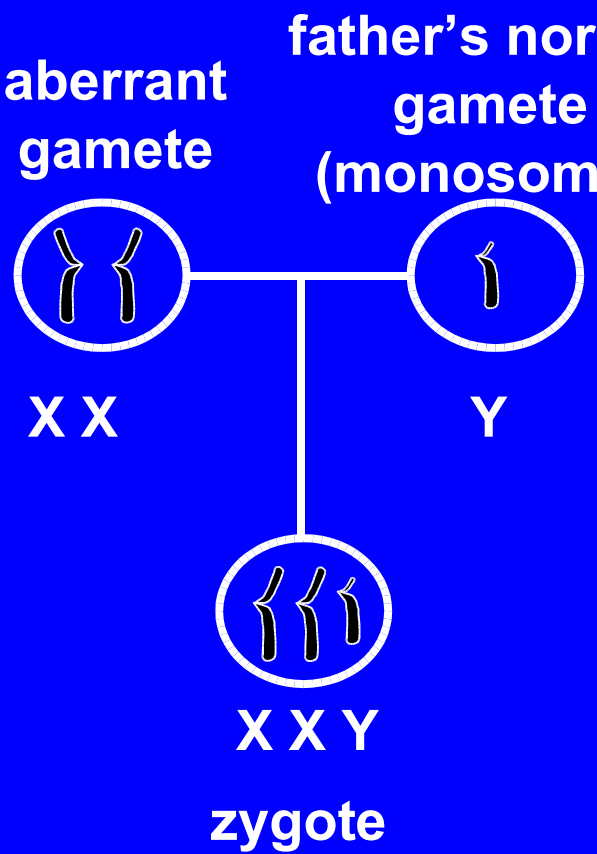
zygote

47,XXY

6b) Klinefelter syndrome
Nondisjunction in the maternal meiosis II

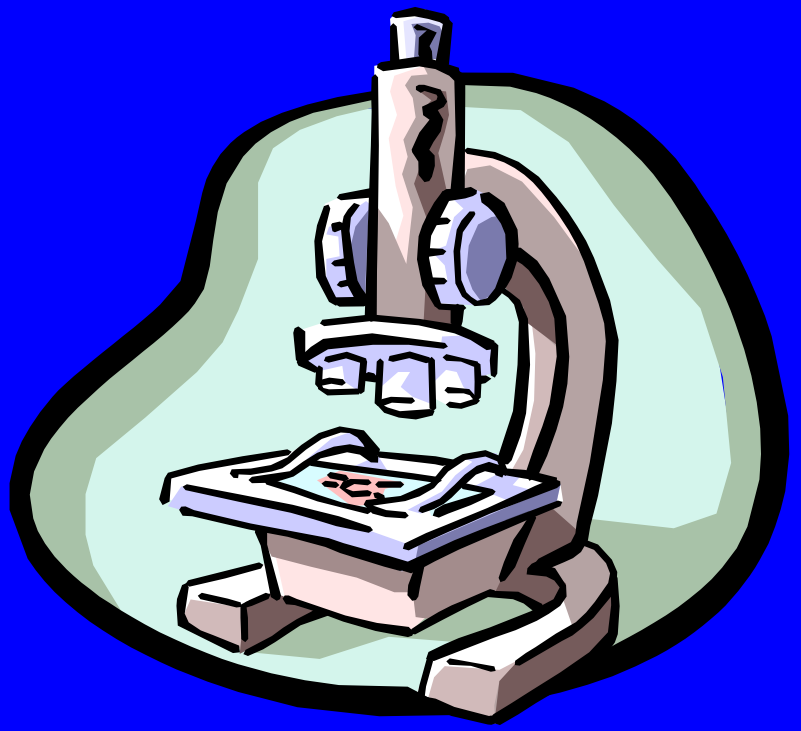


Chromatid nondisjunction in meiotic division II.



47,XXY

2. Evaluation of karyotype with aberration



a) Task 9a, b/ p. 82

b) Task 16/ p. 88

c) Segregation of chromosomes to gametes

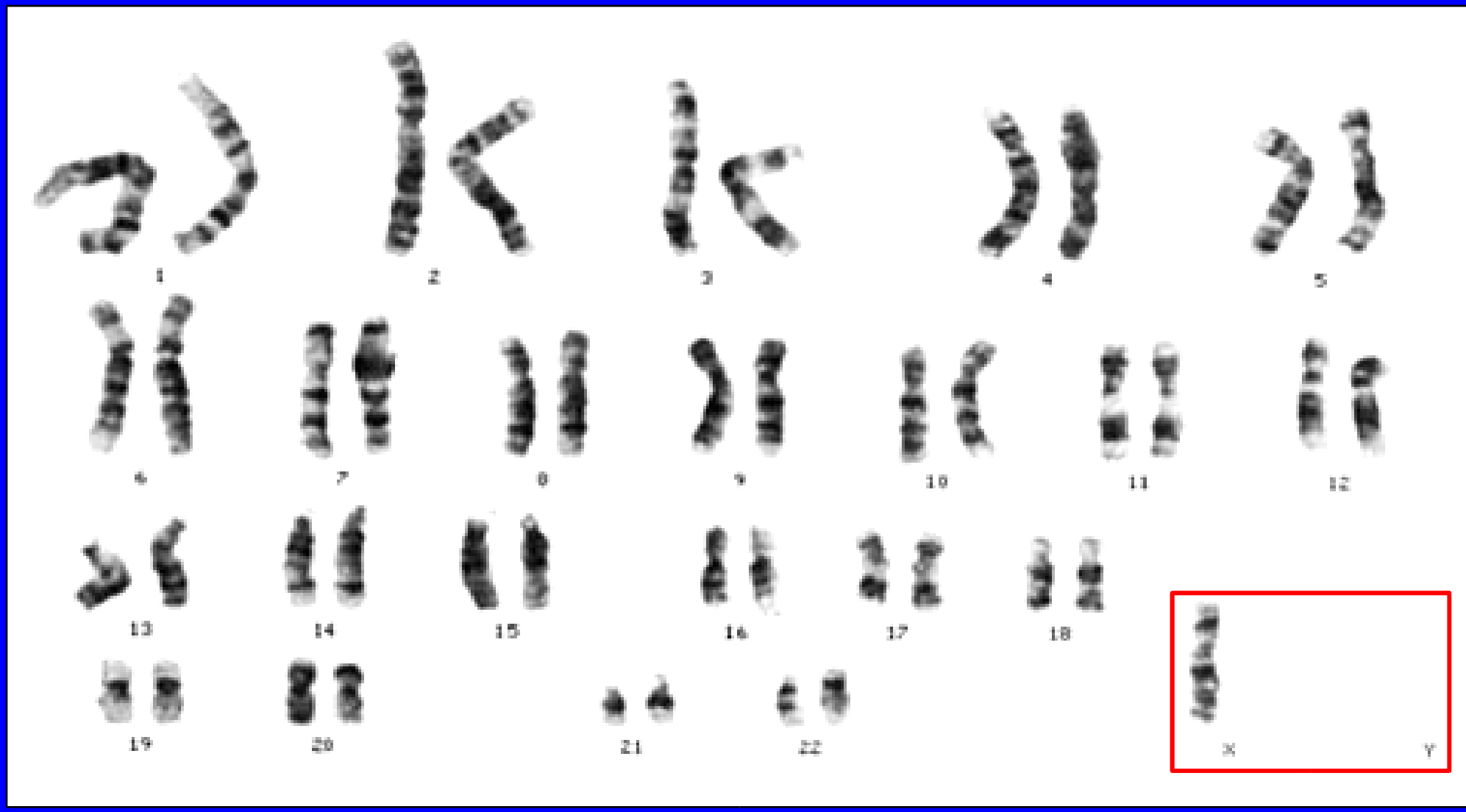
d) m. Down – conclusion of recurrent risk

Karyotype evaluation - General procedure:

- total number of chromosomes (46, 45, 47, other)
- heterochromosomal complement (XX, XY, other)
- completeness of pairs (disomy, monosomy)
- surplus (redundant) chromosomes (trisomy, markers)
- structural aberrations

a) Task 9a, b/ p. 82

Solution: **Turner syndrome** ***Formula:*** **45,X**



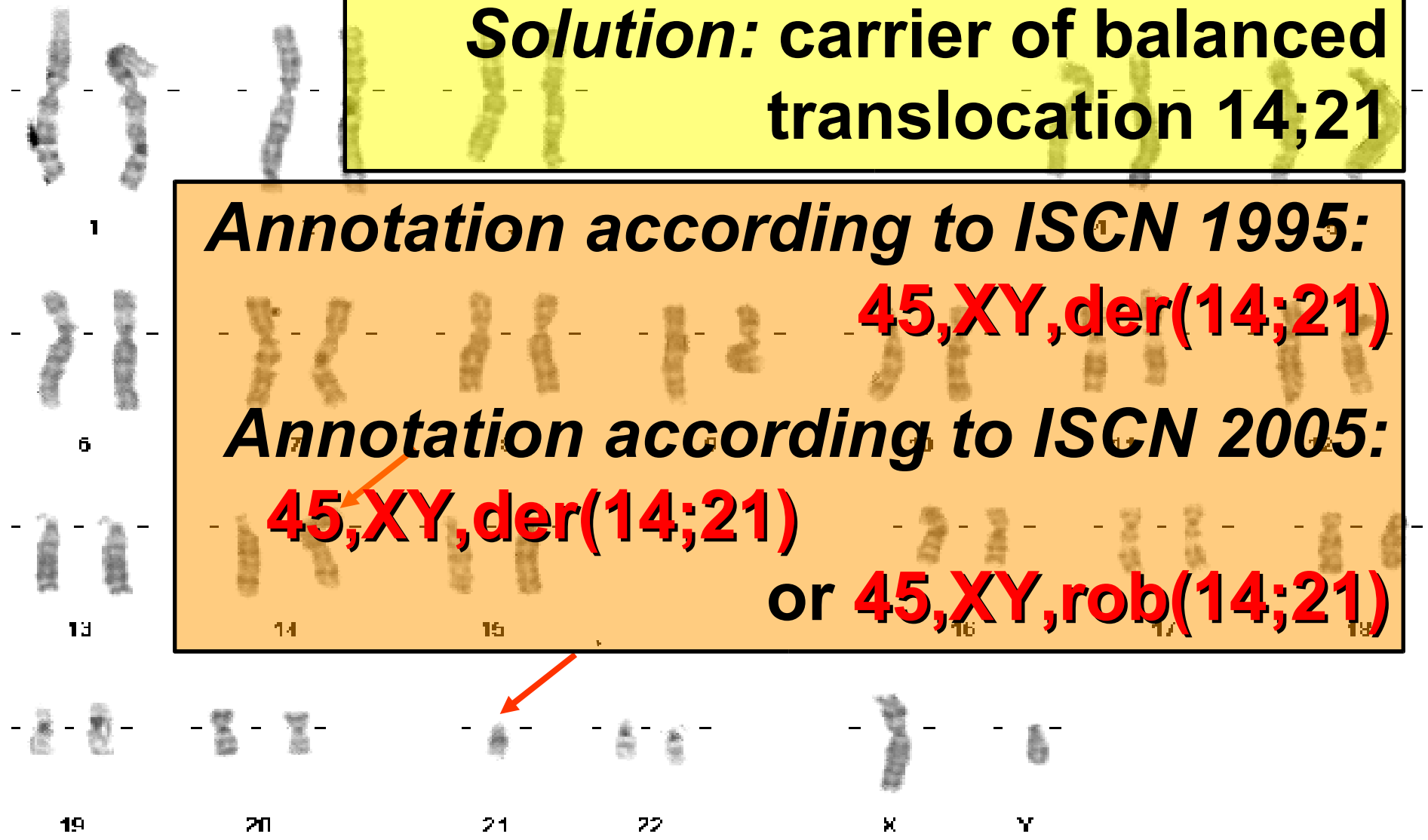
The difference between cytogenetic and clinical diagnosis

Solution: **Turner syndrome** ***Formula:*** **45,X**

Clinical diagnosis | **Cytogenetic diagnosis**

Not all individuals expressing the symptoms of a concrete (here *e.g.* Turner) syndrome have to have the same cytogenetic finding (formula, annotation, diagnosis). But all individuals sharing the same cytogenetic diagnosis usually express the same complex phenotype (syndrome, disease).

b) Task 16/ p. 88



Solution: **carrier of balanced translocation 14;21**

Annotation according to ISCN 1995:

45,XY,der(14;21)

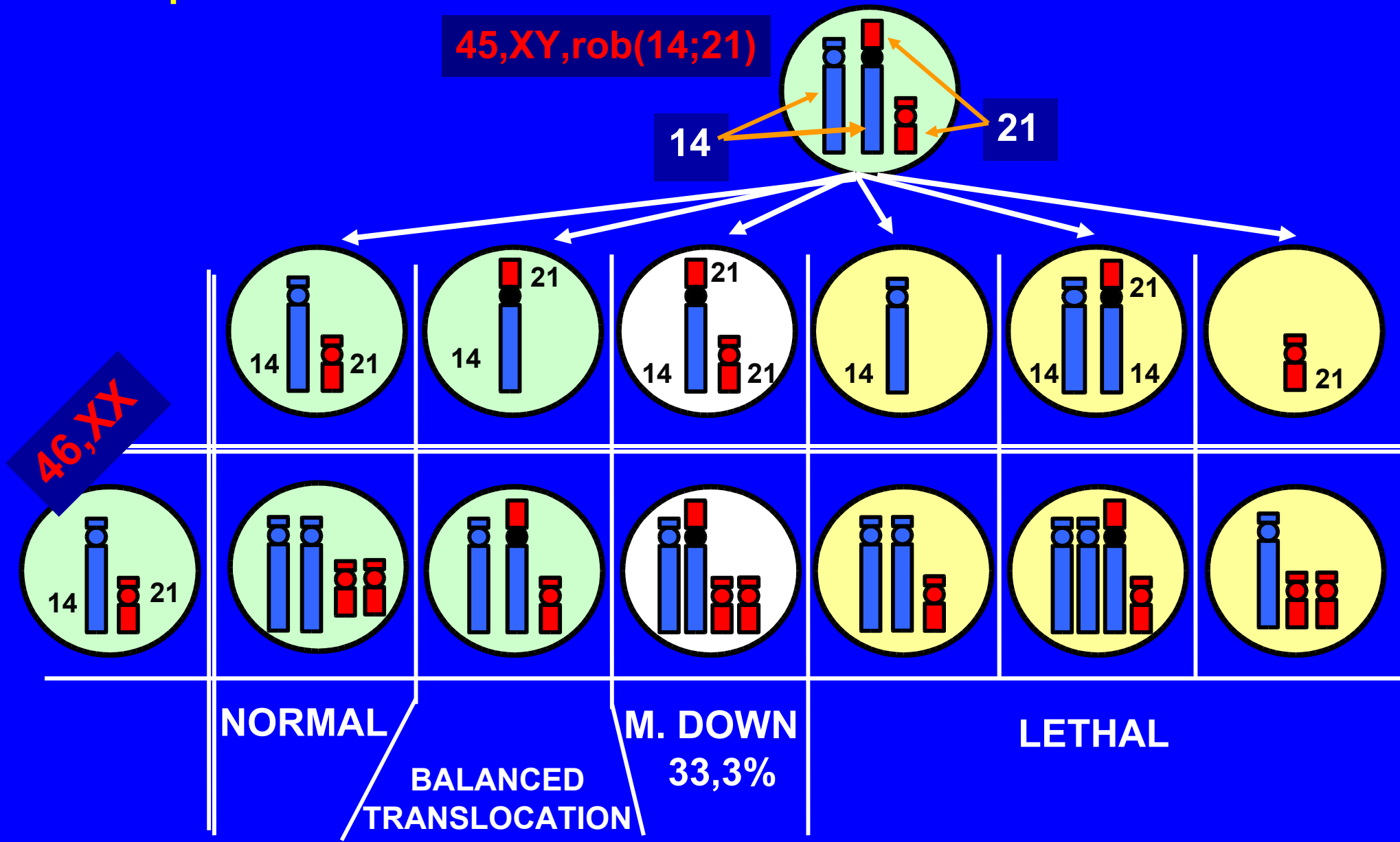
Annotation according to ISCN 2005:

45,XY,der(14;21)

or 45,XY,rob(14;21)

c) segregation of chromosomes to gametes

in previous individual



d) m. Down – conclusion of reccurent risk

(expected chromosomal findings in parents and reccurent risk in dependence on finding in m. Down affected individual)

MORBUS DOWN			
PROBAND	**PARENTS**		**RISK**
47,$X^X/_Y$,+21	46,$X^X/_Y$	46,$X^X/_Y$	> THAN POPULATION dependence on maternal age
46,$X^X/_Y$,der(21;21),+21	45,$X^X/_Y$,der(21;21)	46,$X^X/_Y$	100% THEORETICAL 100% EMPIRICAL
46,$X^X/_Y$,der(D;21),+21 46,$X^X/_Y$+21,der(21;22)	45,$X^X/_Y$,der(D;21) 45,$X^X/_Y$,der(21;22)	46,$X^X/_Y$	33,3% THEORETICAL EMPIRICAL: cca 5% - father (carrier) cca 15% - mother (carrier)
46,$X^X/_Y$,der(D;21),+21 46,$X^X/_Y$,+21,der(21;G)	46,$X^X/_Y$	46,$X^X/_Y$	NEW MUTATION NONPATERNITY
47,$X^X/_Y$,+21	47,$X^X/_Y$,+21/46,$X^X/_Y$	46,$X^X/_Y$	MOSAICISM – depends on ratio of the cell lines with normal and aberrant number of chromosome 21

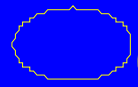
3. Linkage

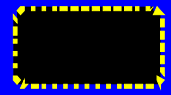
a) Task 2/p. 99 – back-cross in trans configuration, gametogenesis and phenotype frequencies

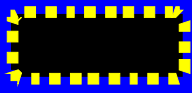
b) Task 10/p. 104 – linkage in genealogy (nail-patella sy)

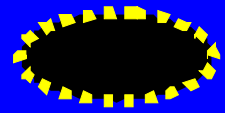
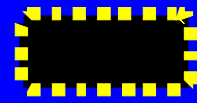
Demonstration:

back-cross in trans phase (corresponds to Task 2/p. 99), repetition of production of gametes and phenotype frequencies

Genes: A Traits: "shape"  (smooth)  (wrinkled)

B "colour"  (deep)  (pale)

	double heterozygote (F1 hybrid)	x	recessive homozygote
Phenotype	AB 		ab 
Genotype	Ab/aB		ab/ab
Gametes	Ab, aB (original)	AB, ab (recombinants)	ab

Distance p =	Genotype Phenotype	AB/ab 	Ab/ab 	aB/ab 	ab/ab 
0 cM	frequency	0	0,5	0,5	0
20 cM	frequency	0,1	0,4	0,4	0,1
50 cM	frequency	0,25	0,25	0,25	0,25

Genes: A Traits: "shape" (smooth) (wrinkled)

B "colour" (deep) (pale)

Back - cross (Bc) - trans configuration (repulsion)

double heterozygote (F1 hybrid) x recessive homozygote

Phenotype AB ab

Genotype Ab/aB ab/ab

Gametes Ab, aB (original) AB, ab (recombinants) ab

	Distance p =	Genotype Phenotype	AB/ab	Ab/ab	aB/ab	ab/ab
a)	0 cM	frequency	0	0,5	0,5	0
b)	20 cM	frequency	0,1	0,4	0,4	0,1
c)	50 cM	frequency	0,25	0,25	0,25	0,25

b) Task 10/p. 104 – linkage in genealogy (nail-patella sy)

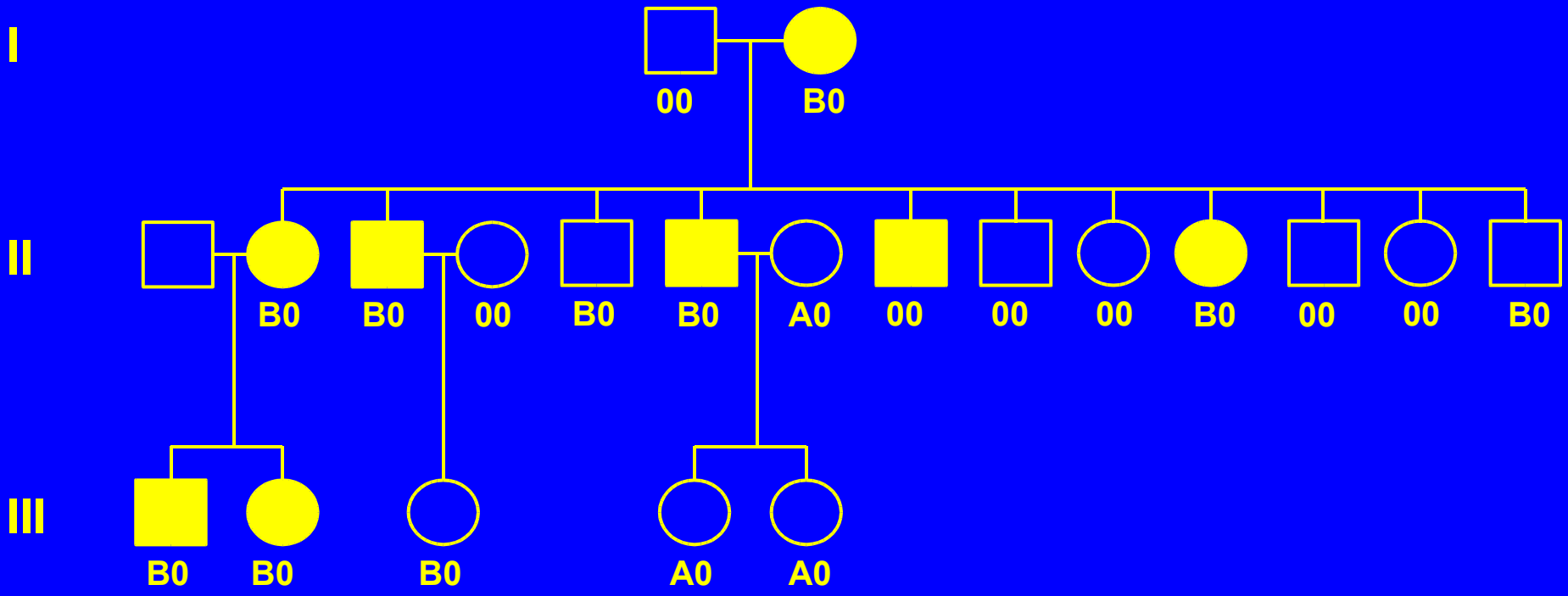


Fig. N°. VII/2

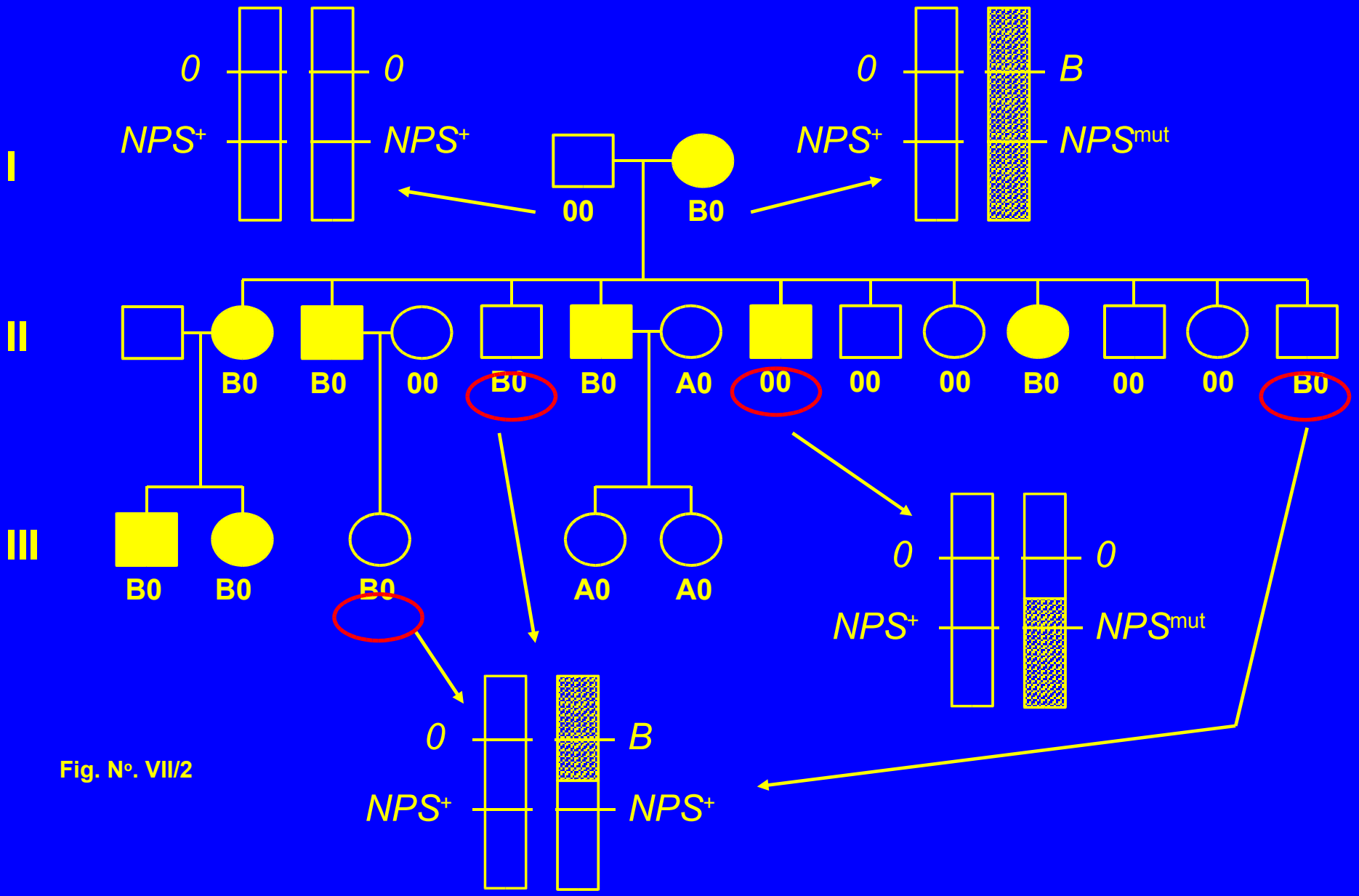

I
II
III
0
0
NPS+
NPS+
00
B0
0
B
NPS+
NPSmut
B0
B0
00
B0
B0
A0
00
00
00
B0
00
00
B0
B0
B0
A0
A0
0
0
NPS+
NPSmut
0
B
NPS+
NPS+

Fig. N°. VII/2

Answers:

a) AD (give alleles names, *e.g.* NPS^{mut} a NPS^{+}),

b) yes (*Note*: localization known today, 9q34),

c) homologous chromosomes (haplotypes) in grand-father I/1 are 0 NPS^{+} / 0 NPS^{+}, and in grand-mother I/2 are B NPS^{mut} / 0 NPS^{+},

d) recombination is present in sons II/5, II/8 a II/14, as well as in grand-daughter III/3,

e) recombination ratio is 4/16 = 0,25, *i.e.* 25 % of recombinations between the genes,

f) yes – recombination present in III/3 originated in meiosis in man II/3.

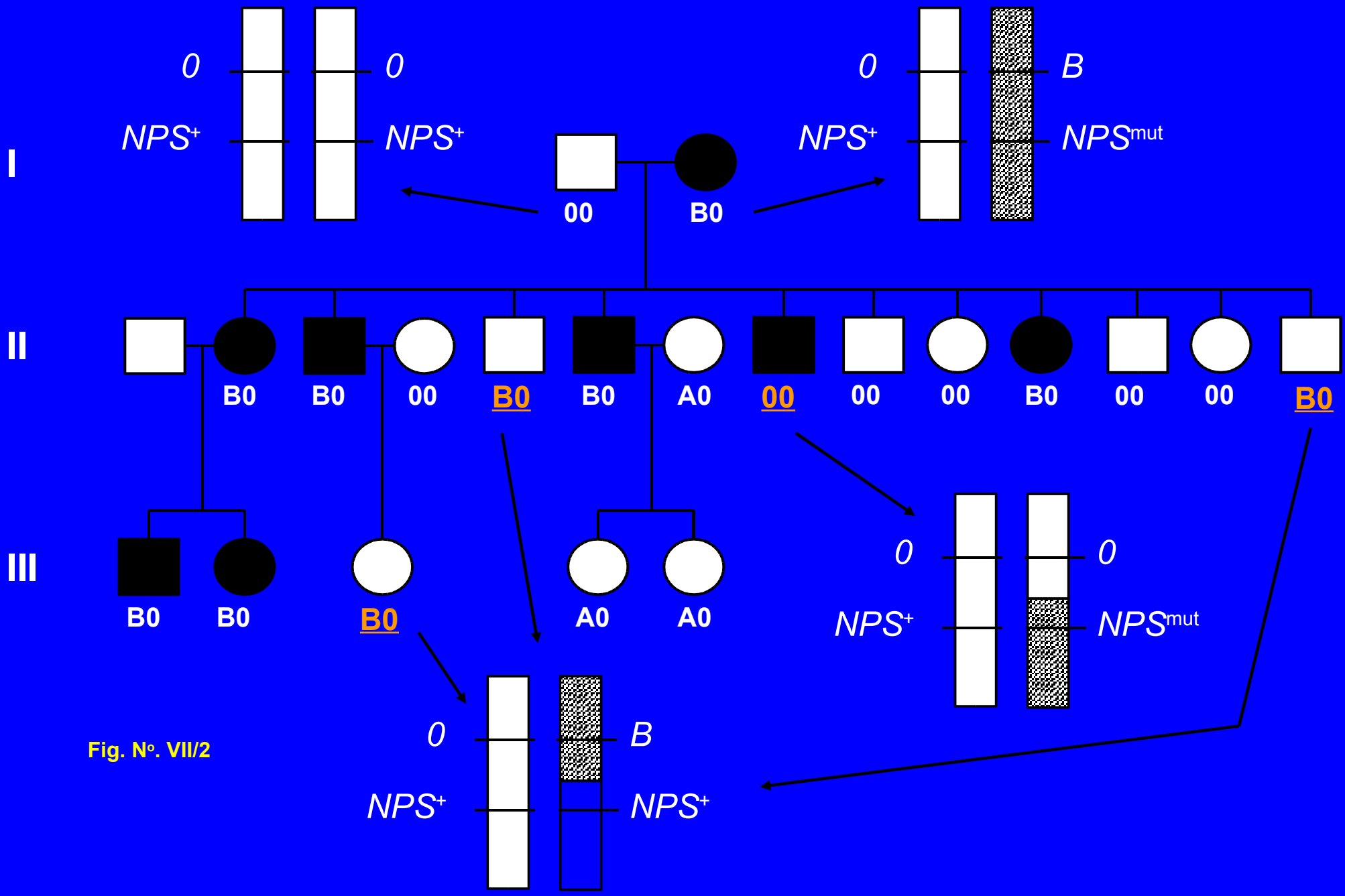

I
II
III
0
NPS+
0
NPS+
00
B0
0
NPS+
B
NPSmut
B0
B0
00
B0
B0
A0
00
00
00
B0
00
00
B0
B0
B0
B0
B0
A0
A0
0
NPS+
0
NPSmut
0
NPS+
B
NPS+

Fig. N°. VII/2

4. Introduction to population genetics – estimates of gene frequencies

a) Task 1/p.139 – frequencies of alleles in MN system

b) Task 4/p. 140 – estimates of frequencies of deleterious (recessive) alleles

The lecture has taken place in the last semester – see short introductory text and formulas [3] and [4] on pp. 138 and 139.

Castle-Hardy-Weinberg law

$$p^2_{(AA)} + 2pq_{(Aa)} + q^2_{(aa)} = 1$$

Applied on panmictic population under the assumption of limiting conditions

Castle-Hardy-Weinberg law

Basic relation for a system with two alleles in a given gene

$$p_{(A)} + q_{(a)} = 1$$

$$p_{(A)} = 1 - q_{(a)}$$

approximation

$2pq_{(Aa)} \doteq 2q$, **if** $p_{(A)}$ **approaches** 1

a) Task 1/p.139 – frequencies of alleles in MN system

Phenotype	Number of persons
M	406
MN	744
N	332

Task 1/p.139 – frequencies of alleles in MN system

Solution:

- **direct calculation of the frequency of one of alleles according to formula [3] on p. 138**

$$p_{(A)} = \frac{2 \times \text{number of homozygotes } (AA) + \text{number of heterozygotes } (Aa)}{2 \times \text{number of all individuals in the sample}}$$

- **Calculation of the frequency of the second allele $q_{(a)}$ as addition to 1.**

Task 1/p.139 – frequencies of alleles in MN system

phenotype	Number of		
	persons	alleles M	alleles N
M	406	812	0
MN	744	744	744
N	332	0	664
Total	1 482	1 556	1 408

$$p = \frac{2 \times 406 + 744}{2 \times 1482} = \frac{1556}{2964} = 0{,}525$$

$$q = 1 - p = 0{,}475$$

Task 4/p. 140 – estimates of frequencies of deleterious (recessive) alleles

Disease	Abbrev.	population frequency
phenylketonuria	PKU	1/8100
cystic fibrosis (mucoviscidosis)	CF	1/2500

Task 4/p. 140 – estimates of frequencies of deleterious (recessive) alleles

Solution: estimate calculated according to formula [4] on p. 139 (top),

$$q = \sqrt{\frac{\text{number of recessive homozygotes}}{\text{number of all individuals in the sample}}} =$$

$$= \sqrt{\text{frequency in population}}$$

Task 4/p. 140 – estimates of frequencies of deleterious (recessive) alleles

disease	Frequency in population	estimate		
		q	$p = 1 - q$	$2pq \doteq 2q$
PKU	1/8100	1/90	$89/90 \doteq 1$	2 x 1 x 1/90 = 1/45
CF	1/2500	1/50	$49/50 \doteq 1$	2 x 1 x 1/50 = 1/25

Home study of population genetics required – no other lecture with this topic will be.