Lecture 32: Numerical Chromosomal Abnormalities and Nondisjunction

- Meiosis I
- Meiosis II
- Centromere-linked markers

Female	46,XX
Male	46,XY

Human chromosomal abnormalities may be numerical or structural.

Numerical

		Total # chromosomes / cell
Trisomy =	3 copies of a single chromosome	47
Monosomy =	1 copy of a single chromosome	45
Triploidy =	3N	69
Tetraploidy =	4N	92

Structural

- Deletion
- Duplication
- Translocation (involves 2 chromosomes)

Chromosomal abnormalities manifest themselves in two ways:

1) Spontaneous abortions

- 50% of human pregnancies --> spontaneous abortion or miscarriage

  nearly all during first trimester of pregnancy, with many during the first month, when pregnancy is recognized only by hormonal assays

- 50% of spontaneously aborted embryos and fetuses have chromosomal abnormalities

- Therefore 25% of all human embryos have chromosomal abnormalities.

Breakdown of chromosomal abnormalities in spontaneous abortions:

Trisomy	
16	15%
13, 18, 21	9%
XXX, XXY, XYY	1%
All others	27%
Monosomy X (45,X or XO)	18%
Triploidy	17%
Tetraploidy	6%
Other	7%
Total	100%

Chromosomal abnormalities manifest themselves in two ways:

2) Defects in newborns: 0.5% aggregate frequency

Among the most common:

XXY	1 / 1,000 males
XYY	1 / 1,100 males
XO	1 / 7,500 females
XXX	1 / 1,200 females
Trisomy 13	1 / 15,000
Trisomy 18	1 / 11,000
Trisomy 21	1 / 900
Structural anomalies	1 / 400

Fruitflies

Female XX

Male XY

Is sex determined by presence/absence of Y?

Is sex determined by number of X's?

Fruitflies

		1916
♀ Female	XX	XXY
♂ Male	XY	XO

Sex is determined by number of X's.

	Sex chromosomes		SEX DETERMINING SIGNAL
	MALE	FEMALE	
Fruitfly	XY	XX	# of X';s
Mammals	XY	XX	Y (+ or -)
Nematodes	XO	XX hermaphrodite	# of X';s
Birds	ZZ	ZW	?
Some Reptiles			temperature

Trisomy 21 Down Syndrome

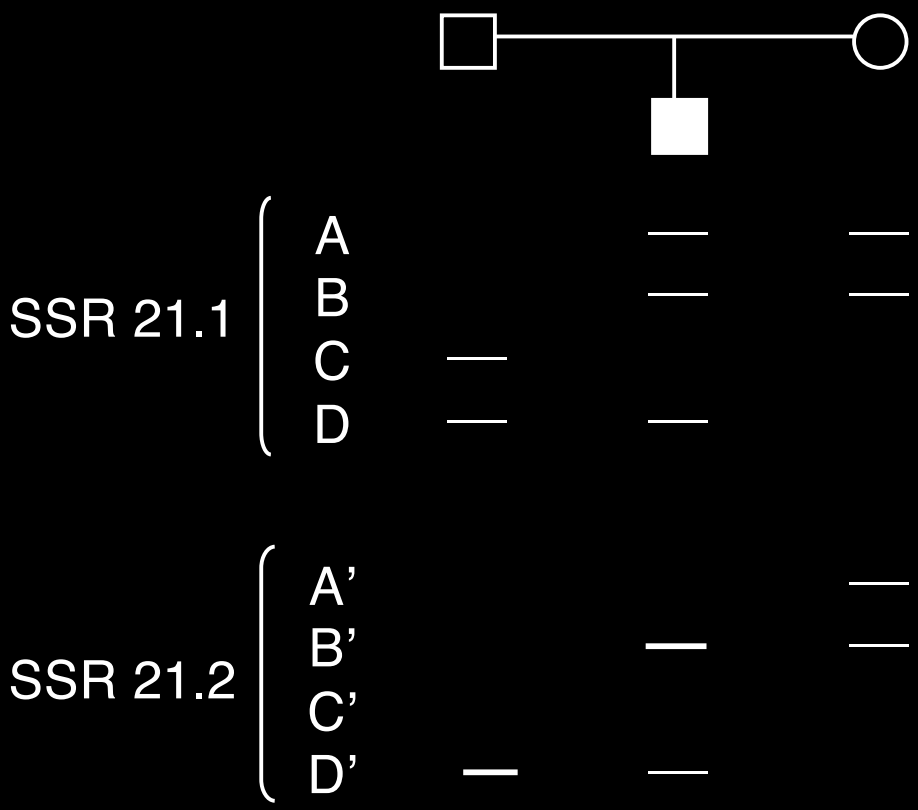
Numerical chromosomal disorders are the result of

nondisjunction = failure of chromosomes to separate normally during cell division

Nondisjunction can occur during meiosis (before fertilization)

or mitosis (after fertilization).

How could you figure out whether nondisjunction for chromosome 21 had occurred during meiosis or mitosis?

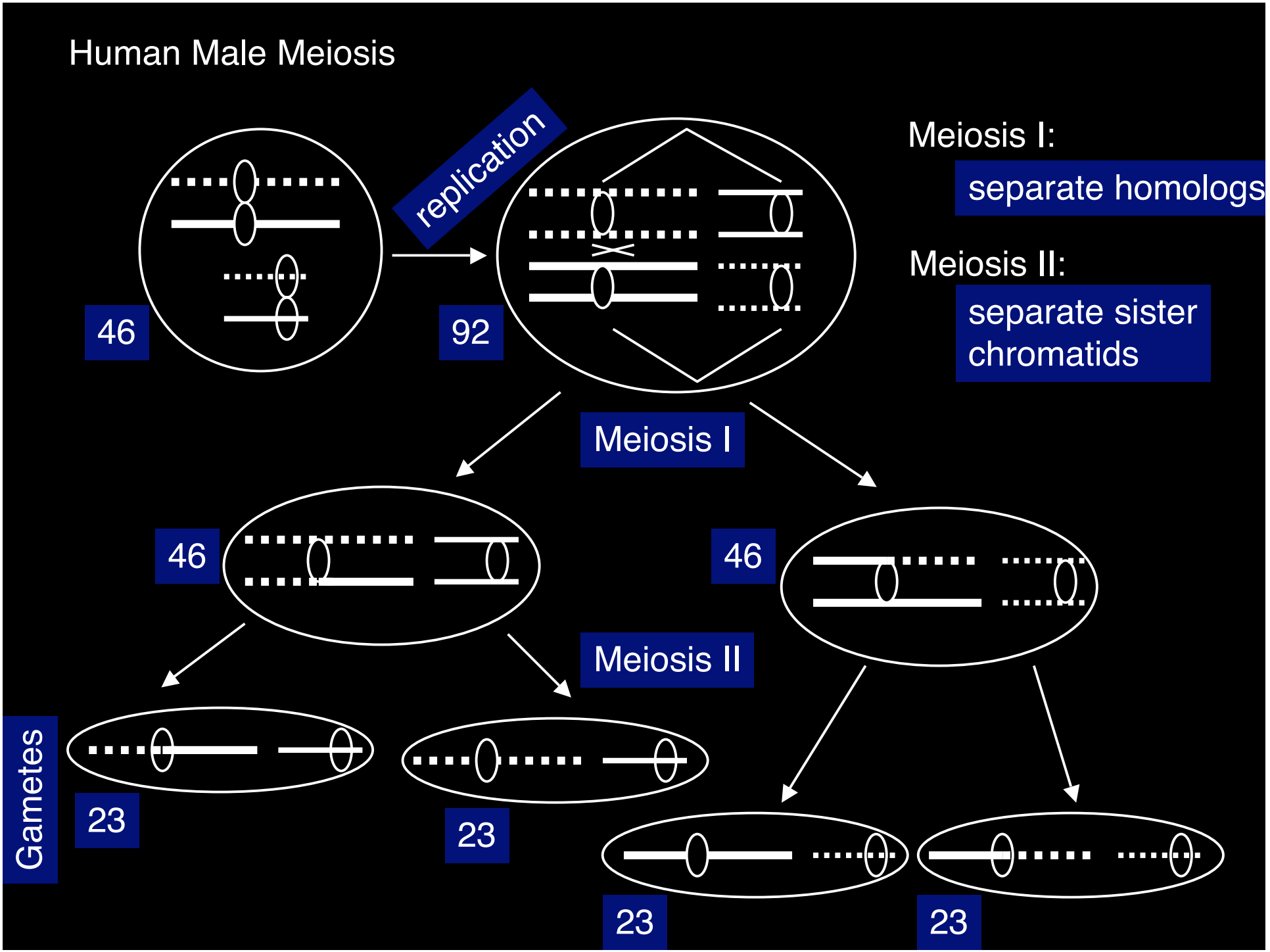


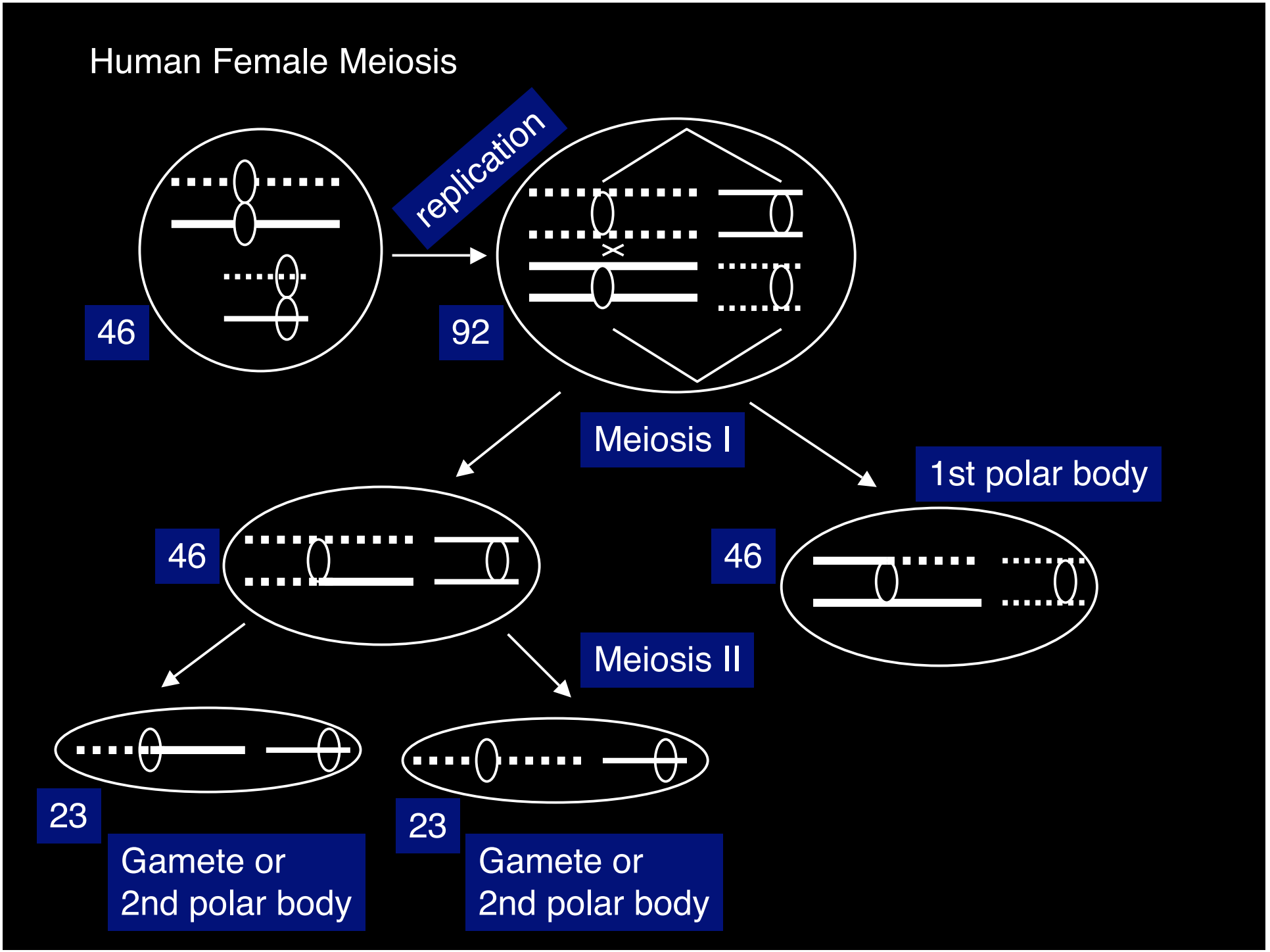
What can you conclude? At least two things:

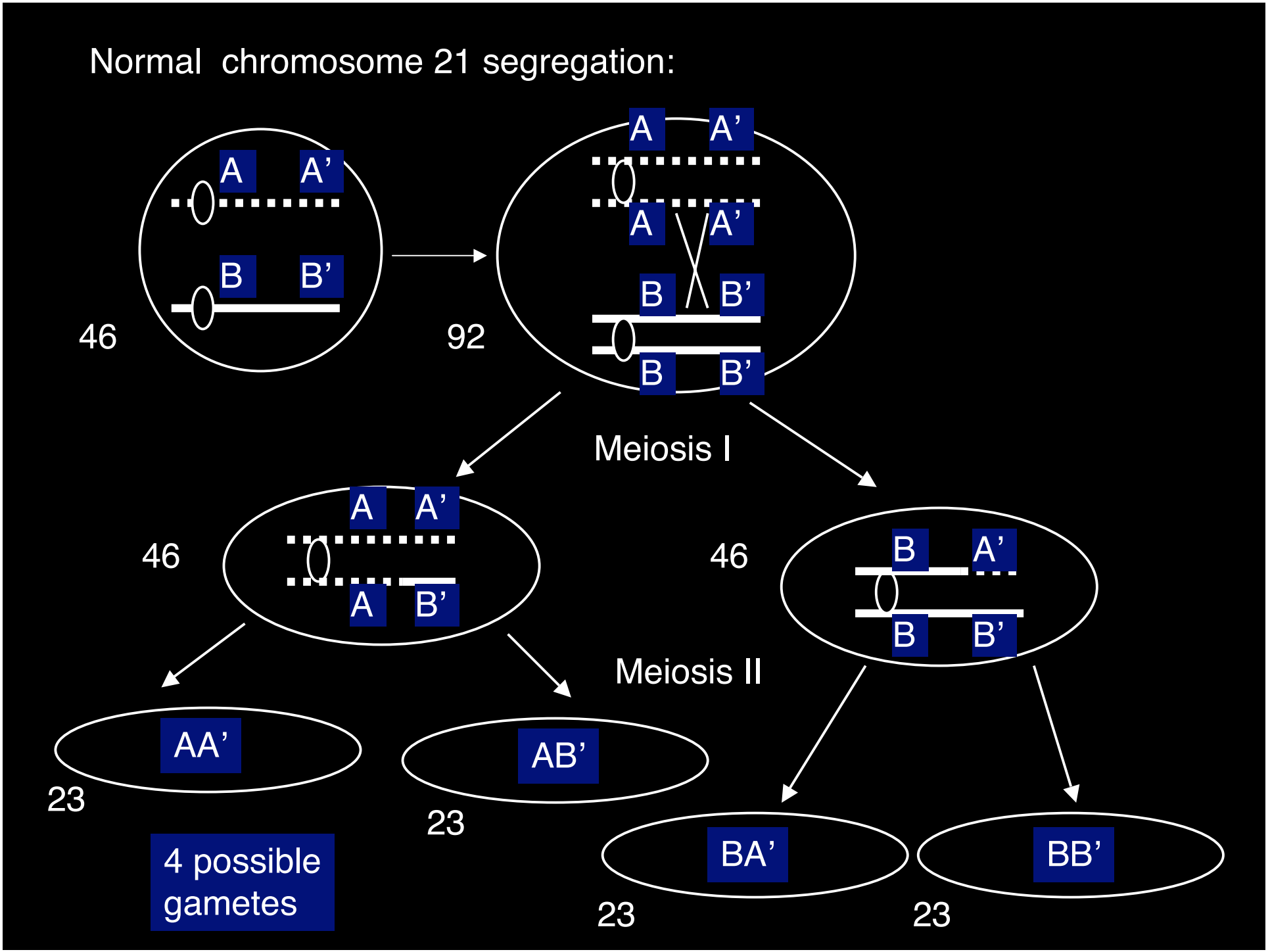
1. The presence in the affected child of two different maternal alleles for SSR 21.1 indicates that

   nondisjunction occurred before fertilization (in meiosis) in the mother.

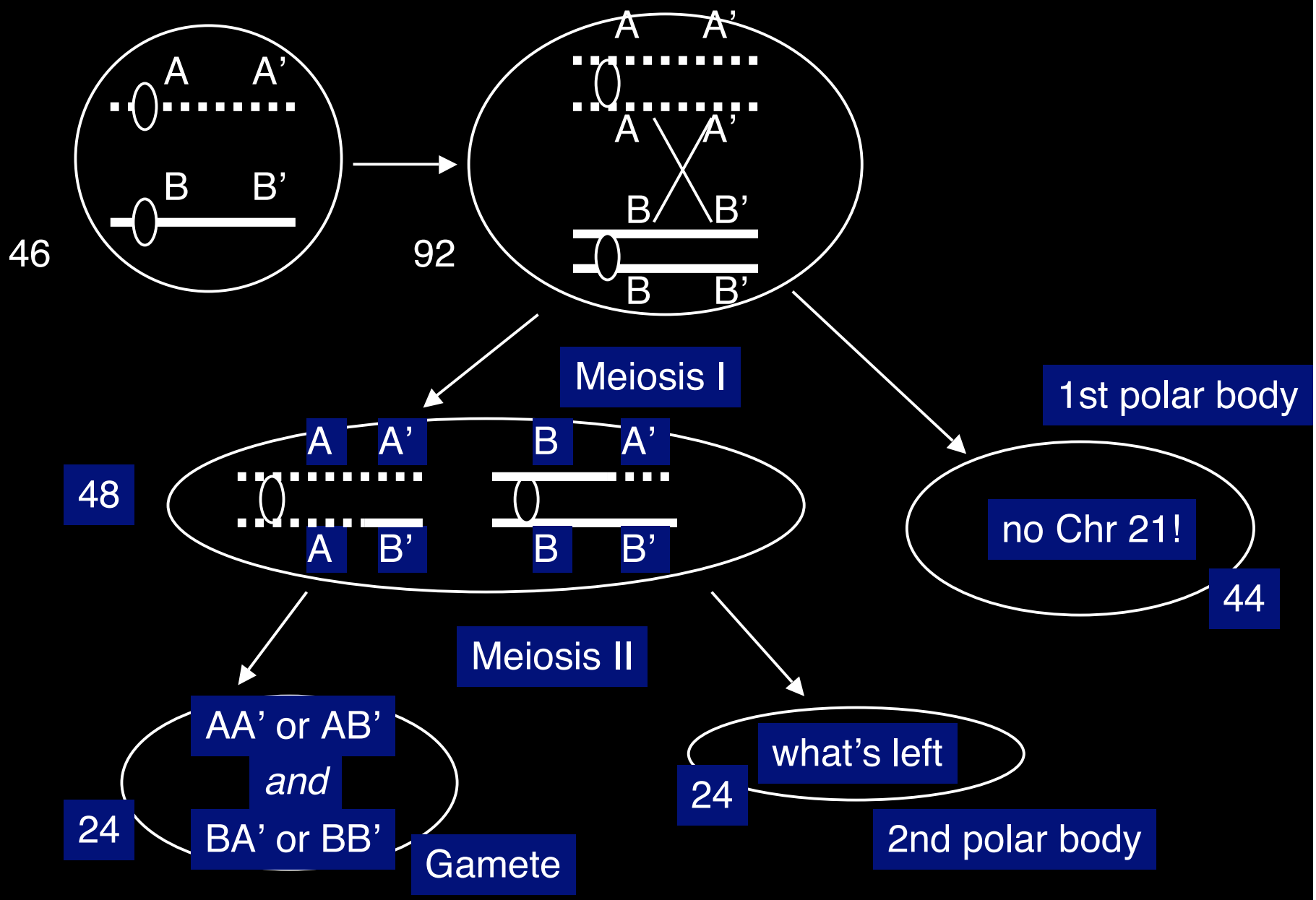
2. There has been recombination between the two chromosome 21's in the mother prior to nondisjunction.


Human Male Meiosis
replication
46
92
Meiosis I:
separate homologs
Meiosis II:
separate sister chromatids
Meiosis I
46
46
Meiosis II
Gametes
23
23
23
23

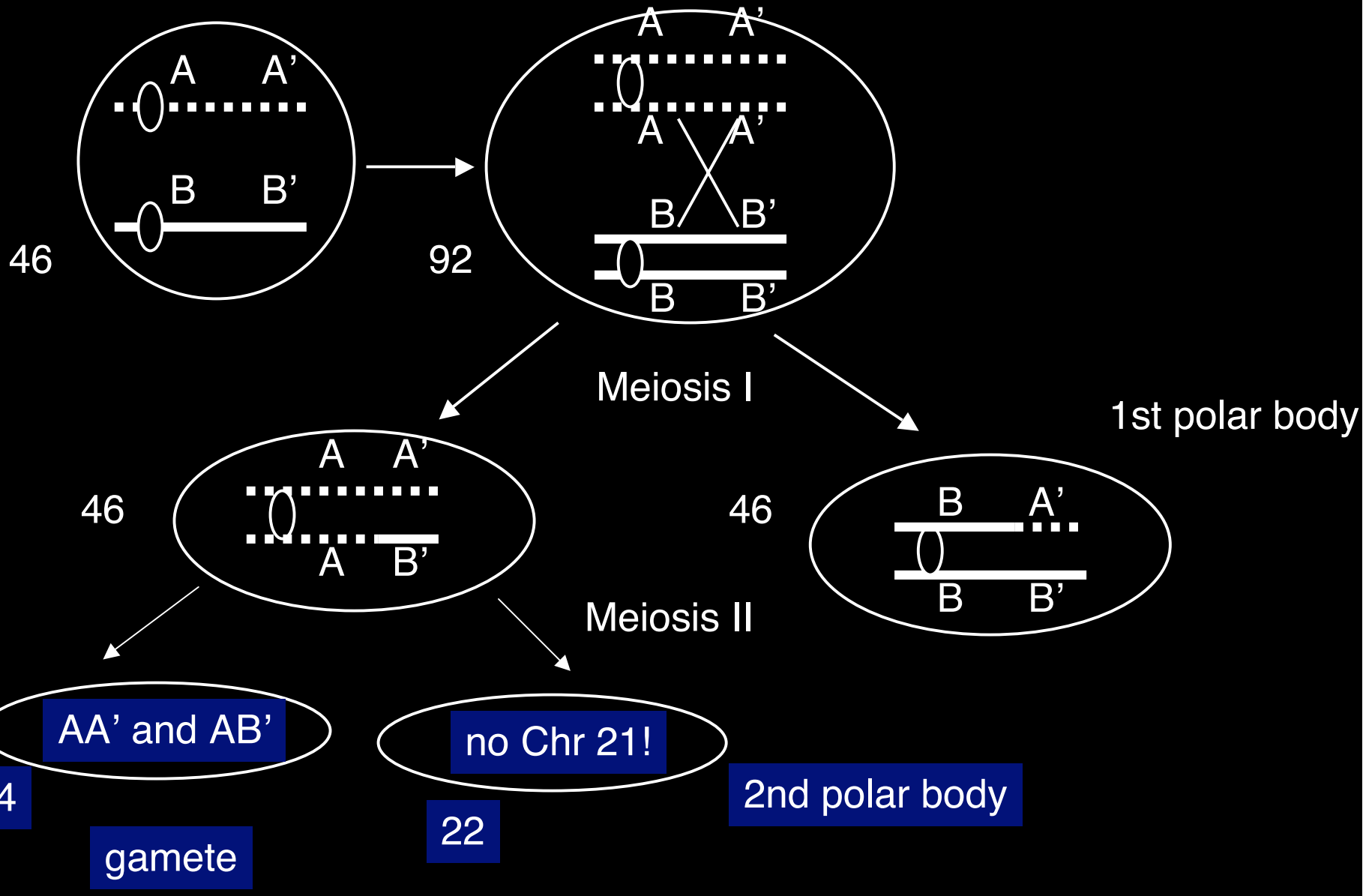

Human Female Meiosis
replication
46
92
Meiosis I
1st polar body
46
46
Meiosis II
23
Gamete or
2nd polar body
23
Gamete or
2nd polar body


Normal chromosome 21 segregation:
A
A'
B
B'
46
92
Meiosis I
Meiosis II
AA'
AB'
BA'
BB'
23
23
23
23
4 possible gametes

Nondisjunction in female meiosis I leading to trisomy:



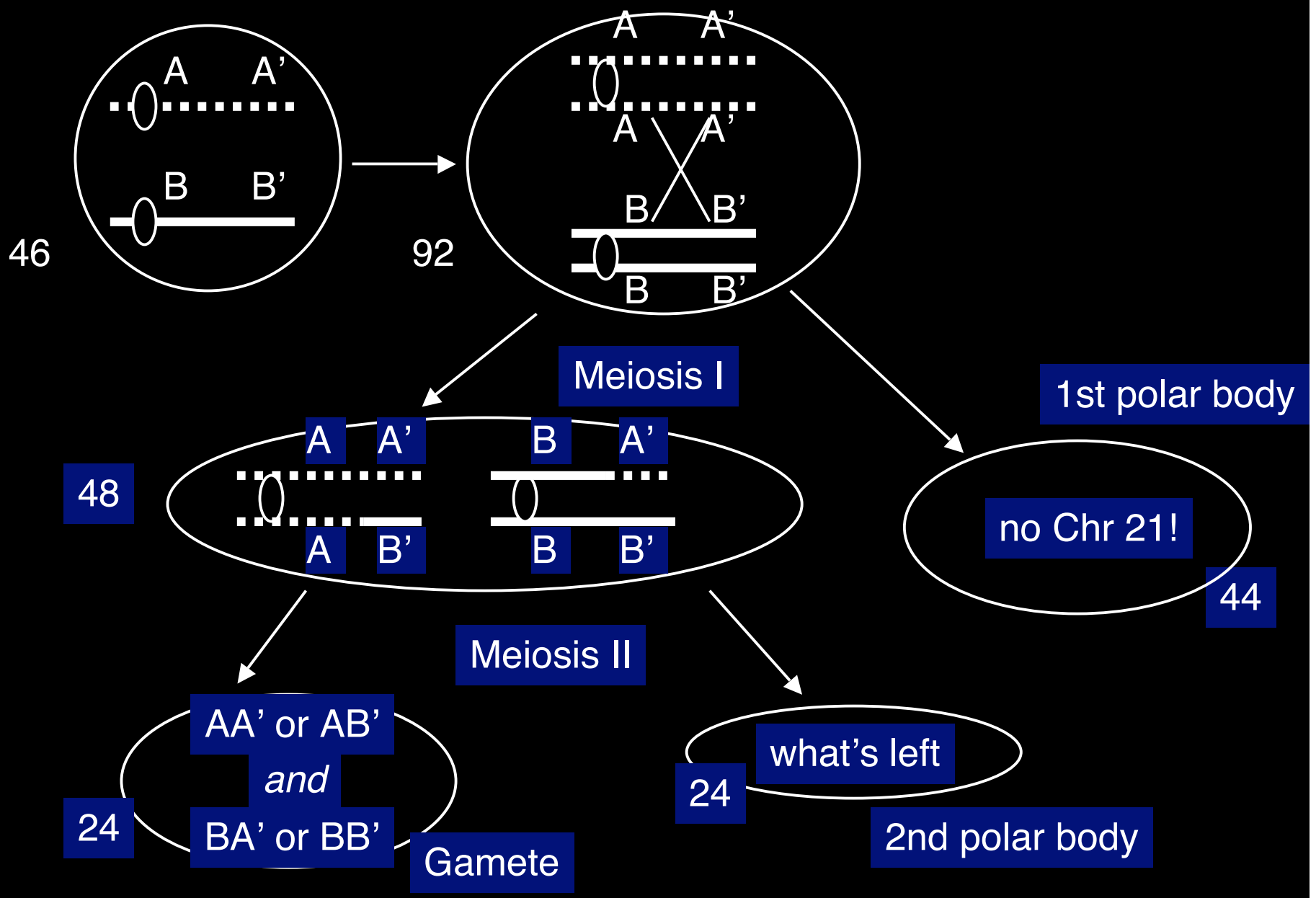
Nondisjunction in female meiosis II leading to trisomy:



The key to distinguishing Meiosis I vs Meiosis II nondisjunction is the centromere-linked marker, which will segregate as follows:

Proper disjunction	A or B
Meiosis I nondisjunction	A and B
Meiosis II nondisjunction	(A and A) or (B and B)

Nondisjunction in female meiosis I leading to trisomy:



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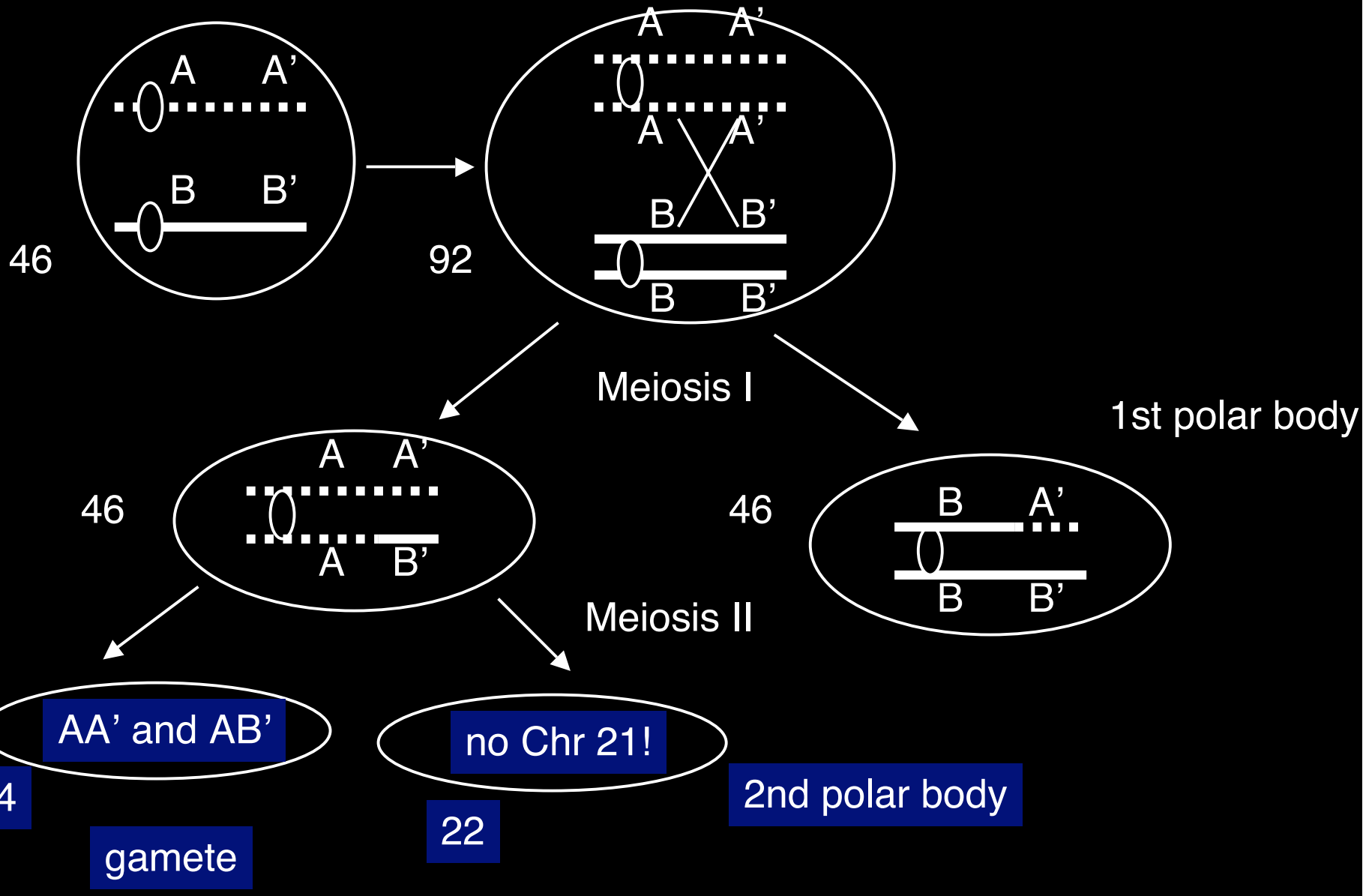
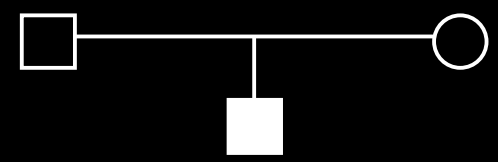
Nondisjunction in female meiosis II leading to trisomy:





very close to centromere

SSR 21.1

A
B
C
D

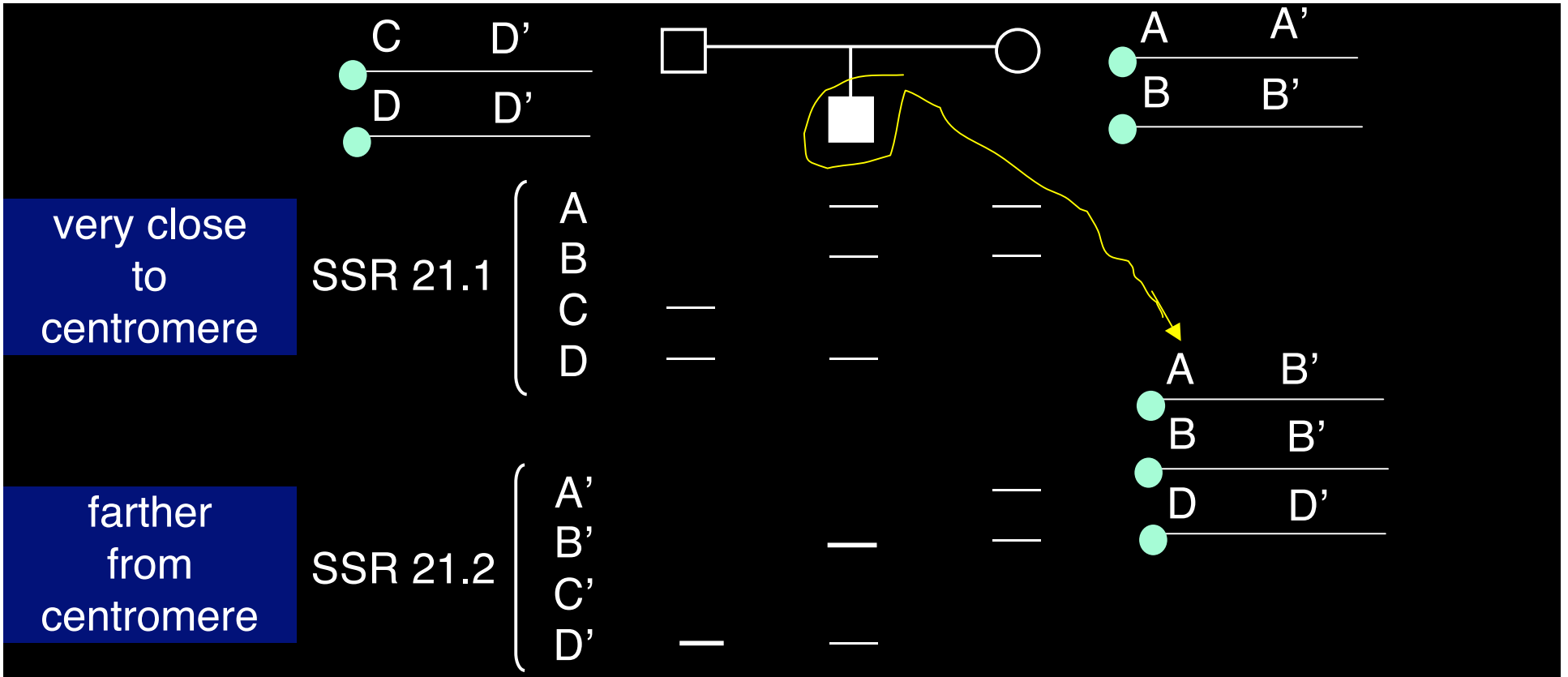
farther from centromere

SSR 21.2

A’
B’
C’
D’

Interpretation: The data for SSR21.1, the centromeric marker, demonstrate that nondisjunction occurred in maternal meiosis I.

Taken together, the SSR21.1 and SSR21.2 data demonstrate that recombination between the mother's two chromosome 21’s occurred prior to nondisjunction.



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Studies of many individuals with trisomy 21 using centromere-linked markers have revealed following breakdown of cases:

Nondisjunction in maternal meiosis: 88%

Meiosis I: 65%

Meiosis II: 23%

Nondisjunction in paternal meiosis: 8%

Meiosis I: 3%

Meiosis II: 5%

Post-zygotic mitosis: 3%

The risk of trisomy 21 rises dramatically with increasing maternal age:

Age of Mother	Incidence of trisomy 21
20	1 per 1925 births
30	1 per 885 births
35	1 per 365 births
40	1 per 110 births
45	1 per 32 births
50	1 per 12 births

Trisomy 21 provides the major rationale for advising pregnant women 35 years of age or older to undergo amniocentesis (examination of fetus' chromosomes by light microscopy).

In human females, oocytes enter but arrest in prophase of

meiosis I during fetal development.

Each oocyte remains arrested in prophase of meiosis I until that individual oocyte is ovulated, as much as 50 years later!

An oocyte proceeds through meiosis II only after (and if) it is fertilized.