Kermanshah University of Medical Sciences

Balanced Structural Chromosomal Rearrangement & Pregnancy Loss

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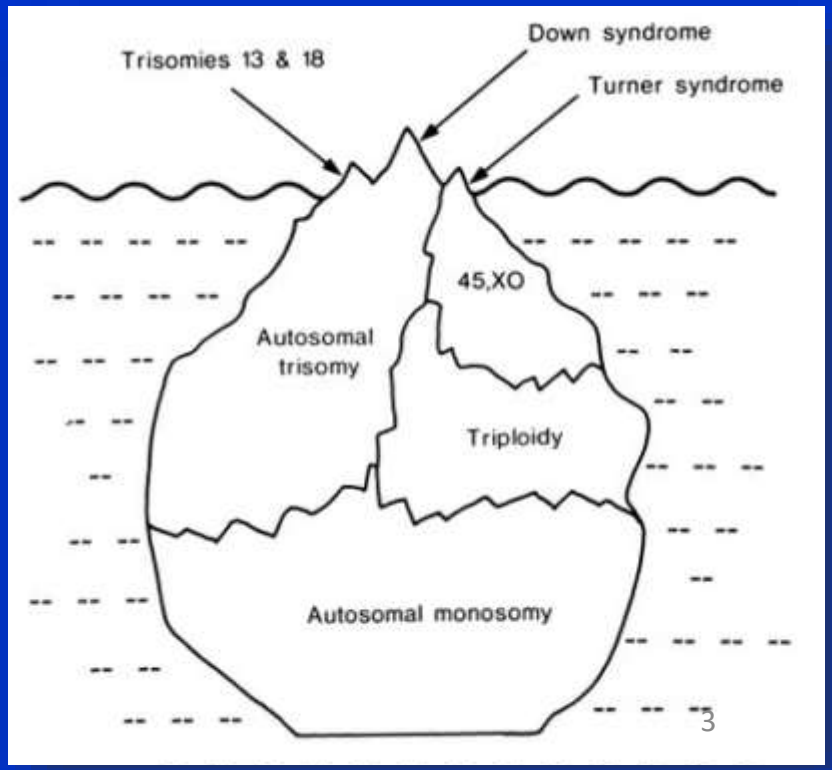
Outline

- Importance
- Subtypes
  - ✓ Reciprocal translocations
  - ✓ Robertsonian translocations
  - ✓ Inversions
  - ✓ Chromosomal heteromorphisms
- How are associated with RPL

Clinical Significance & Importance

- Human pregnancy is both a vulnerable & robust process
  - Vulnerable: large proportion of all conceptions are chromosomally abnormal with the great majority aborting
  - Robust: >99% of the time, a term pregnancy results in a chromosomally normal baby

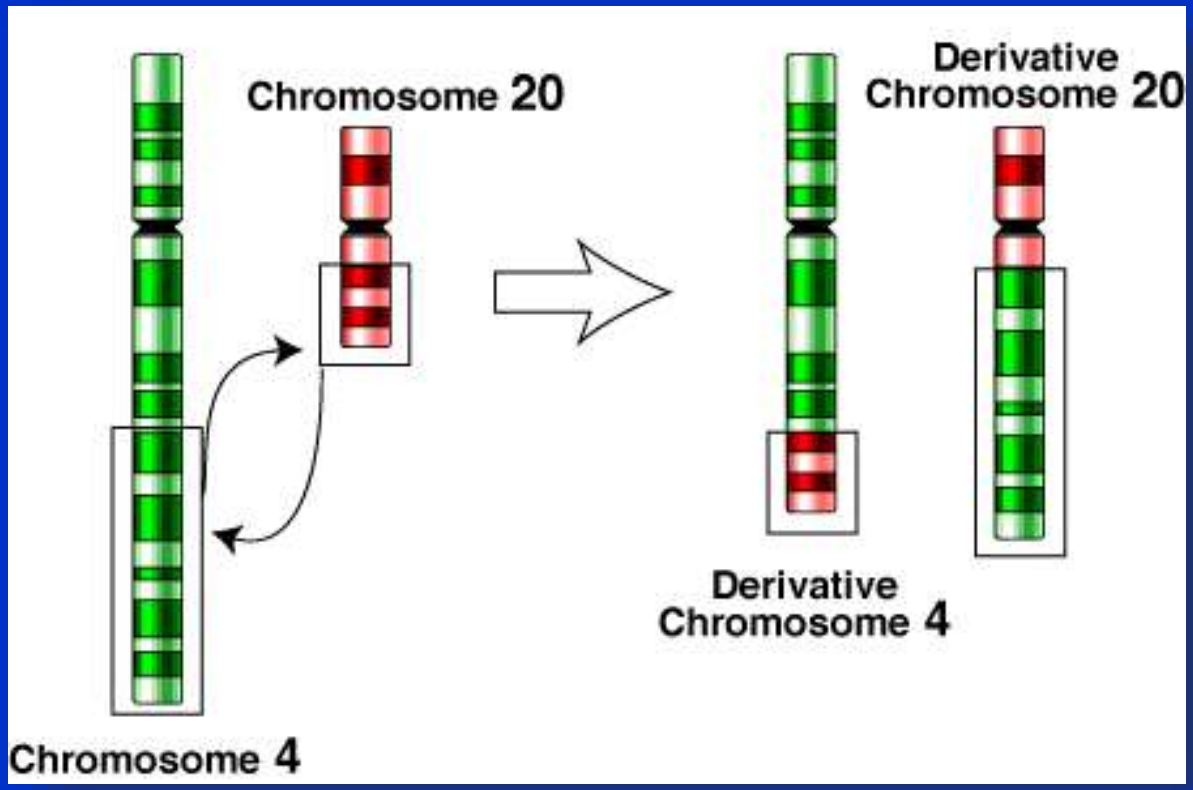
- unbalanced chromosomal abnormalities are seen in less than 1% of newborns



Balanced Structural Chromosomal Rearrangement & Pregnancy Loss

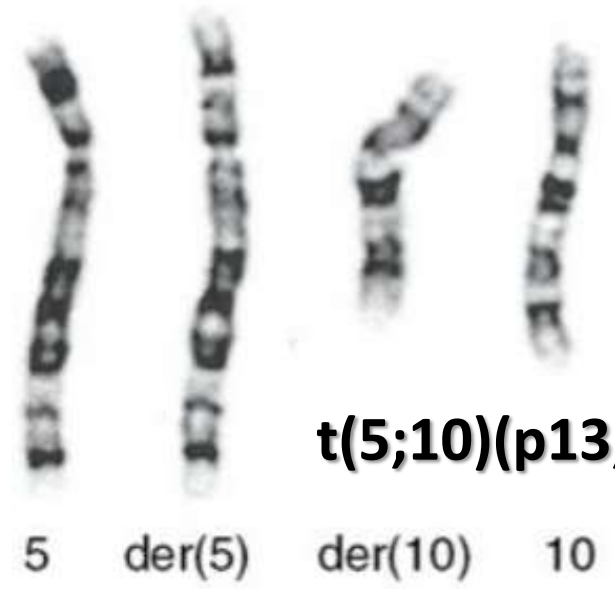
balanced chromosomal rearrangements can result in unbalanced gametes, which subsequently lead to conditions such as RPL, stillbirth, and neonates with multiple congenital anomalies

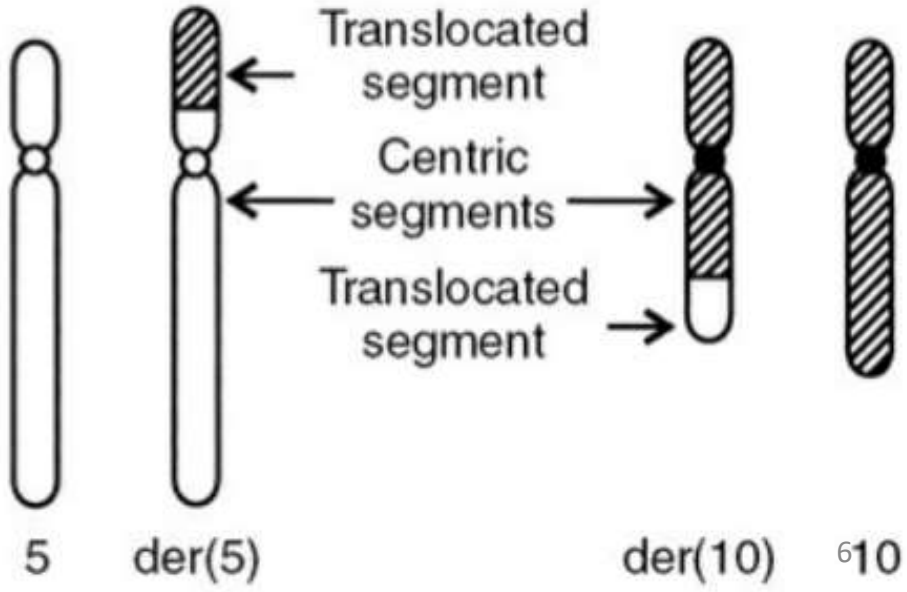
Reciprocal Translocation



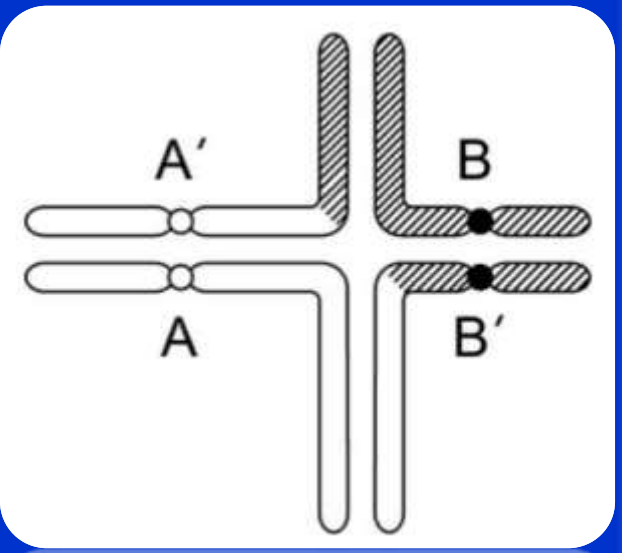
Reciprocal Translocations

- two-way exchange of material between two chromosomes
- physical apposition
- derivative (der) chromosome!
- 1 person in 500 is a reciprocal translocation heterozygote
- De novo or familial

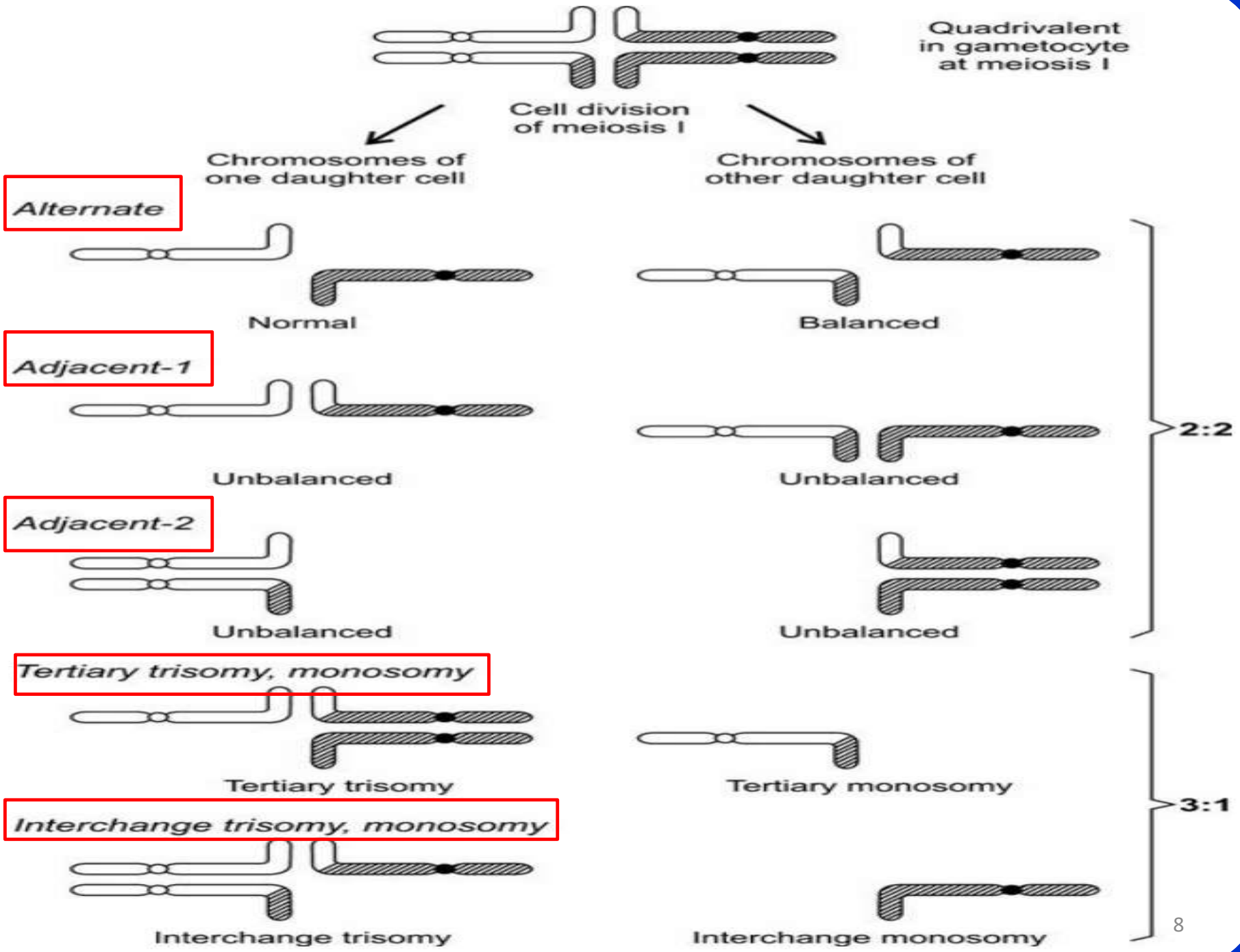




Details OF Meiotic Behavior



ONE DAUGHTER GAMETOCYTE WITH:	OTHER DAUGHTER GAMETOCYTE WITH:	SEGREGATION MODE
2:2 Segregations		
A and B	A′ and B′	Alternate segregation
A and B′	B and A′	Adjacent-1 segregation
A and A′	B and B′	Adjacent-2 segregation
3:1 Segregations		
A B A′	B′	3:1 segregation with
A B and B′	A′	tertiary trisomy or monosomy
A′ B′ and A	B	3:1 segregation with
A′ B′ and B	A	interchange trisomy or monosomy
4:0 Segregation		
A B A′ B′	None	4:0 segregation with double trisomy or monosomy


Quadrivalent in gametocyte at meiosis I
Cell division of meiosis I
Chromosomes of one daughter cell
Chromosomes of other daughter cell
Alternate
Normal
Balanced
Adjacent-1
Unbalanced
Unbalanced
2:2
Adjacent-2
Unbalanced
Unbalanced
Tertiary trisomy, monosomy
Tertiary trisomy
Tertiary monosomy
3:1
Interchange trisomy, monosomy
Interchange trisomy
Interchange monosomy

Gamete Studies

Sperm karyotyping of 45 men, heterozygous for a translocation

Oocyte karyotyping of 9 women heterozygous for a translocation

56% of sperm, and 70% of ova, were chromosomally unbalanced

Conceptions

- **Equal distribution with karyotypes in the gametes?**
  - **Female: a modest increase in the average normal fraction for embryos (45%) cf. gametes (30%)**
  - **Male: the average normal fraction of embryos (41%) is similar to that of gametes (44%)**

Viability In Utero

- **Unbalanced combinations produce:**

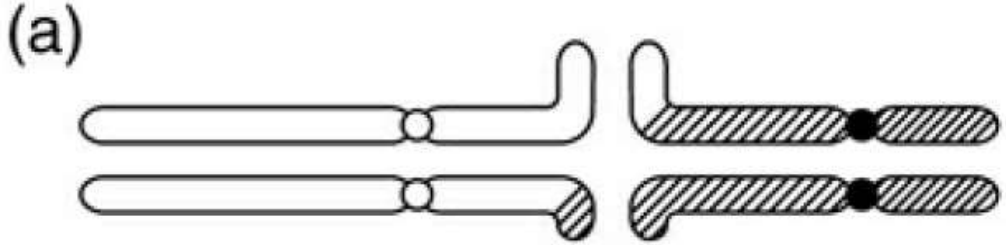
- **Enormous genetic imbalance** →
  - ✓ **conceptus lost very early in pregnancy (occult abortion), or even fail to implant**

- **Moderate imbalances** →
  - ✓ **proceed to the stage of recognizable miscarriage, or to later fetal death in utero**

- **Lesser imbalances** →
  - ✓ **result in the birth of an abnormal child.**

Predicting Segregant Outcomes (1)

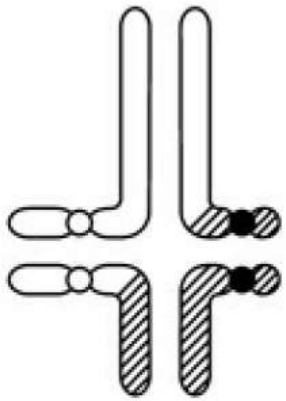
Translocated segments are small in genetic content → adjacent-1 capable of giving rise to viable abnormal offspring



Translocated segments small:
adjacent-1 most likely

Predicting Segregant Outcomes (2)

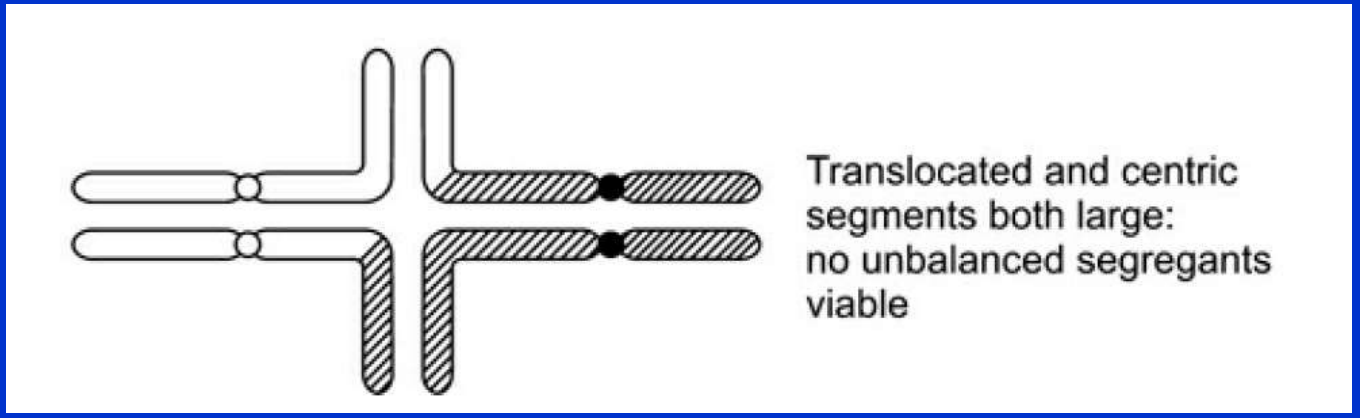
The centric segments are small in content → adjacent-2 is the most likely segregation to give a viable abnormal outcome



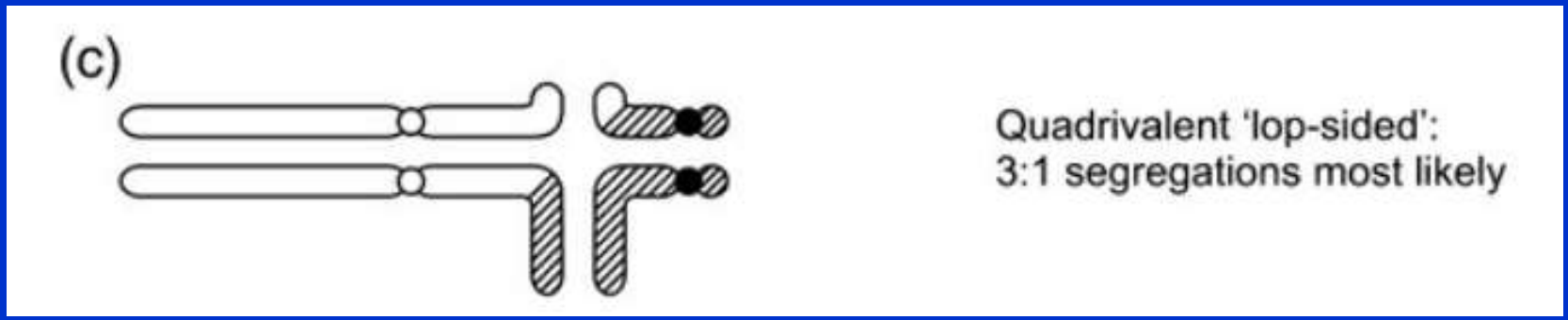
Centric segments small:
adjacent-2 most likely

Predicting Segregant Outcomes (3)

If the translocated and centric segments both have large content, no mode of segregation could produce an unbalanced gamete that would lead to a viable offspring

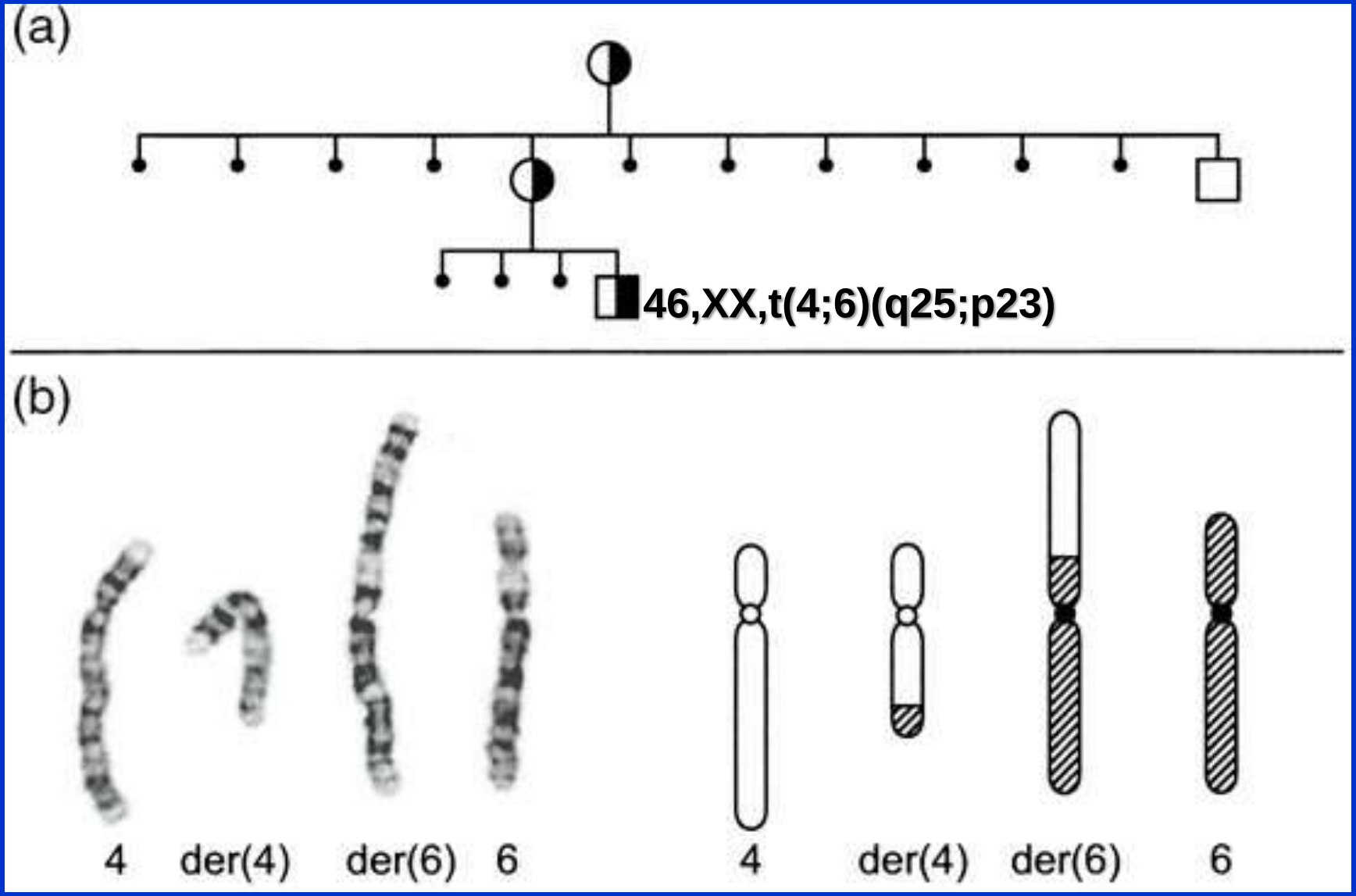


If one of the whole chromosomes of the quadrivalent is small in content, 3:1 disjunction is the most likely .
The small chromosome may be a small derivative chromosome or a chromosome 13, 18, or 21



Adjacent-1 segregation

No unbalanced product viable



Infertility

- Infrequently, gamete formation in male translocation heterozygote is disturbed → gametogenic arrest
- Not predictable from the nature of the translocation
- Same translocation compromise fertility in only some men in the family
  - ✓ effect of the genetic Background
- Consequence of failure of pairing
- The semen profiles of translocation carriers may not always predict fertility outcomes
- t(10;14) man, **normozoöspermic**, had **30%** of spermatocytes showing synaptic pairing abnormalities
- t(13;20) man, **azoöspermic**, and showed synaptic pairing abnormalities in **71%** of meiotic spreads

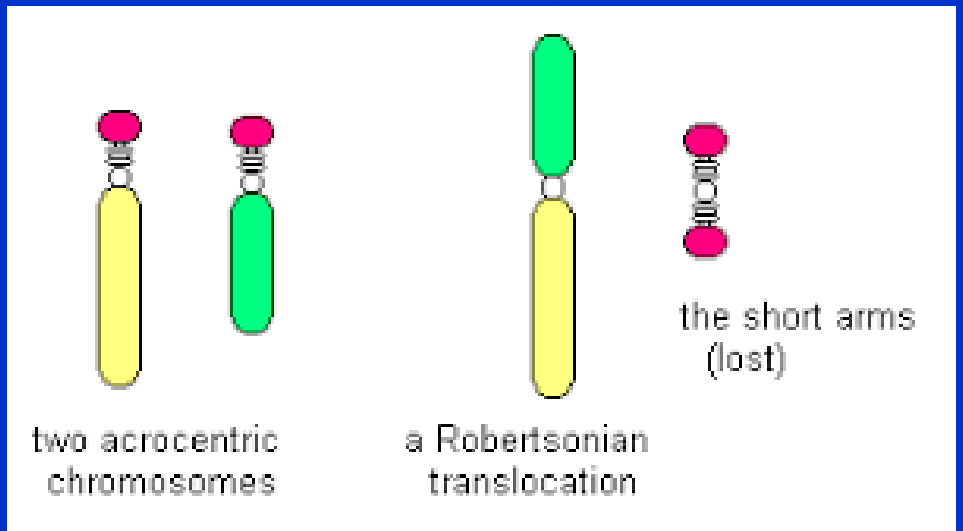
Genetic Counseling

1. Is there a risk of having an abnormal child?
2. If so, what is the magnitude of the risk?
3. What would be the abnormality, and would the child survive?
4. What if the same translocation that I have is found at prenatal diagnosis?
5. What is the risk for pregnancy loss through abortion? Is pregnancy possible?
6. Anything else I should know?

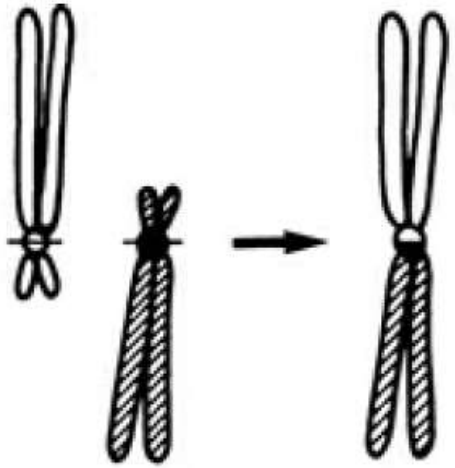
Robertsonian Translocations

Robertsonian Translocations

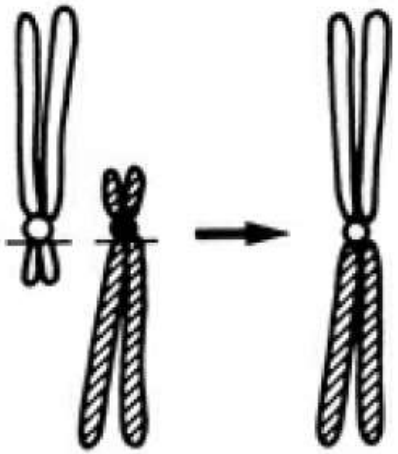
- Robertson
  - ✓ Insect cytogeneticist
- five human acrocentric autosomes—13, 14, 15, 21, & 22
- the complete long arm chromatin of the two fusing chromosomes
- Among the most common balanced structural rearrangements
- Frequency in newborn surveys of about 1 in 1,000



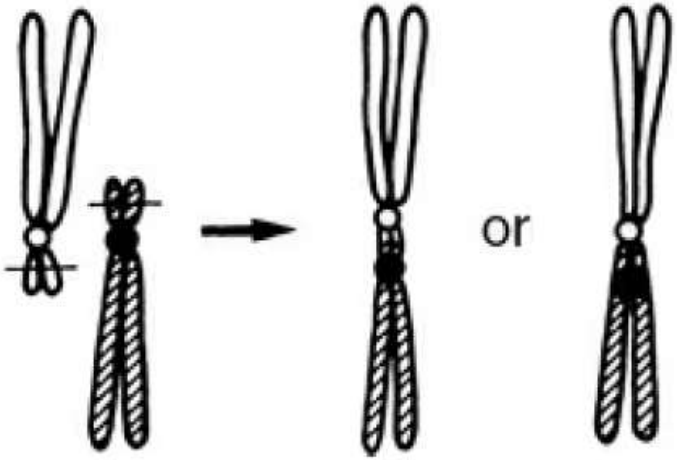
Mechanisms of Formation of Robertsonian Translocations



Centric fusion:
giving a monocentric chromosome



breakage in one short arm and one long arm:
giving a monocentric



breakage in both short arms:
giving a dicentric or, after suppression of one centromere, a monocentric

The balanced rob(14q;21q) in a Phenotypically Normal Male

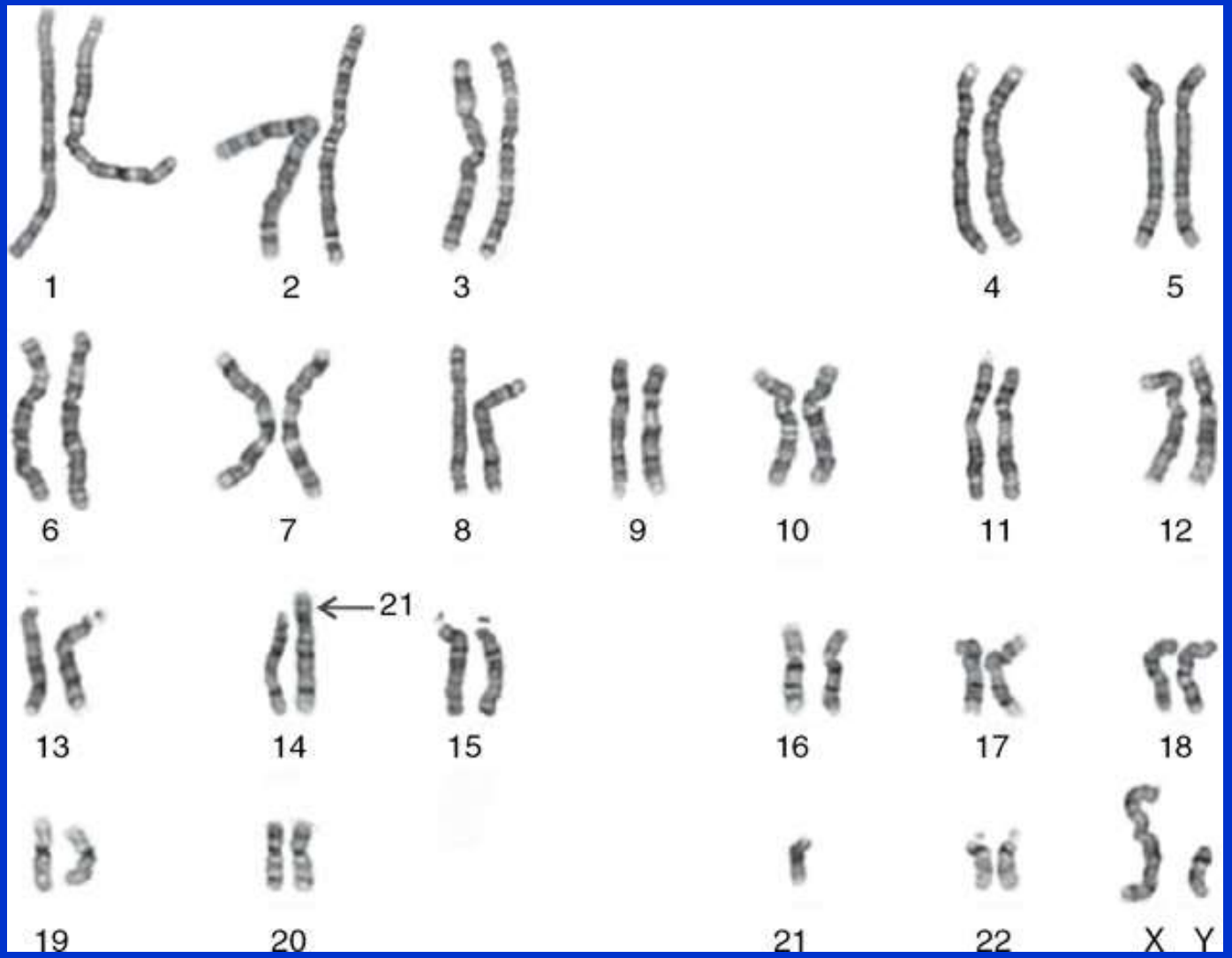


Table 7–1. The Frequency of Robertsonian Translocations

TRANSLOCATION	LITERATURE REVIEW	UNBIASED ASCERTAINMENT
13q13q	3%	2%
13q14q	33%	74%
13q15q	2%	2%
13q21q	2%	1%
13q22q	1%	2%
14q14q	½%	–
14q15q	2%	5%
14q21q	30%	8%
14q22q	1%	2%
15q15q	2%	–
15q21q	3%	½%
15q22q	½%	1%
21q21q*	17%	3%
21q22q	2%	½%
22q22q	1%	–

Meiotic Behavior of the Robertsonian Translocation

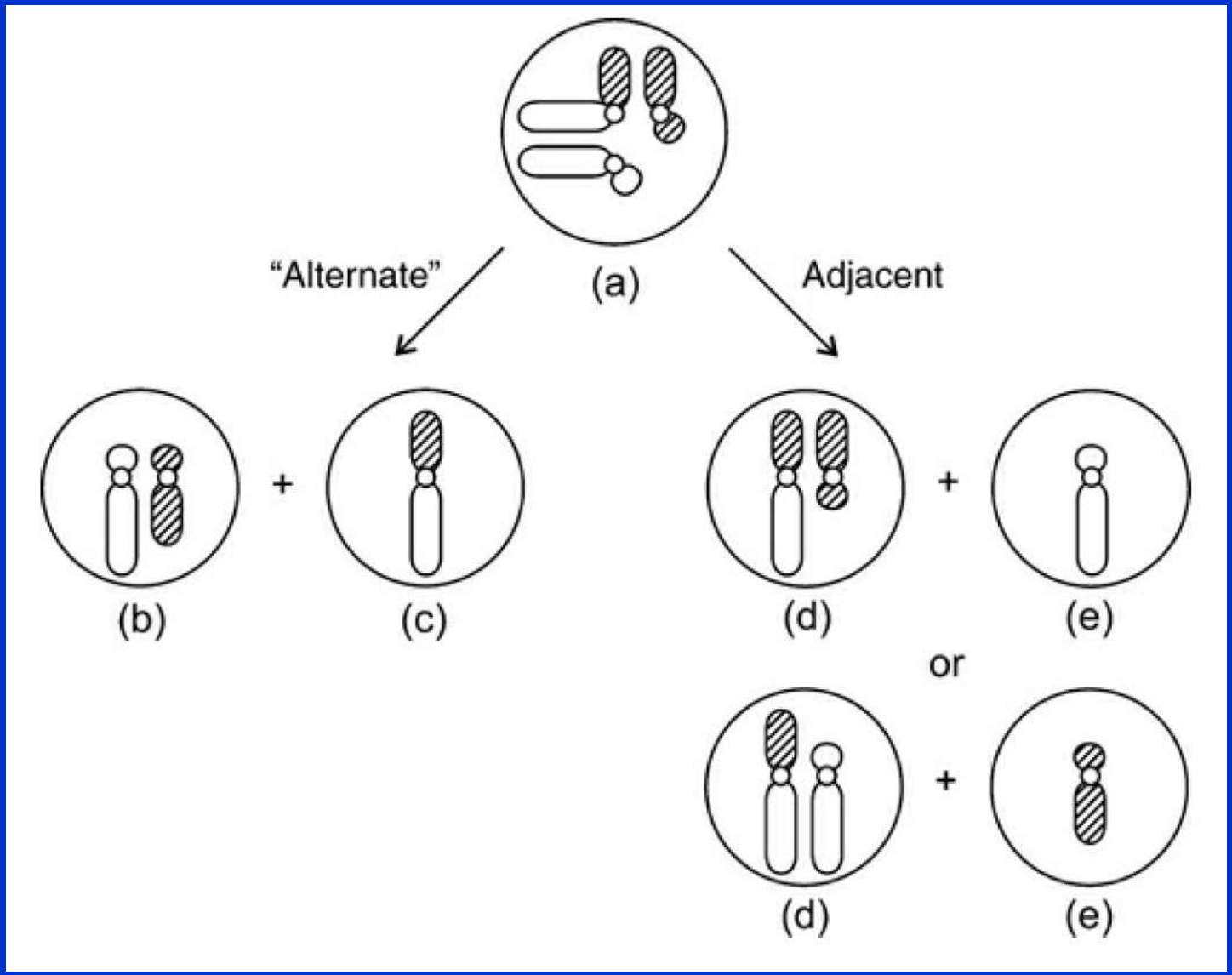


Table 7–2. Estimates of Risks to Have a Child with Aneuploidy or with a Uniparental Disomy Syndrome, for the Heterologous rob Carrier

	CARRIER PARENT			
	MOTHER		FATHER	
ROB	UNBAL.	UPD*	UNBAL.	UPD*
13q14q	1%	<½%	<1%	<½%
13q15q	1%	<½%	<1%	<½%
13q21q	10%–15%	–	<1%	–
13q22q	1%	–	<1%	–
14q15q	–	½%	–	<½%
14q21q	10%–15%	<½%	<1%	<½%
14q22q	–	<½%	–	<½%
15q21q	10%–15%	<½%	<1%	<½%
15q22q	–	<½%	–	<½%
21q22q	10%–15%	–	<1%	–

Association with Infertility

- infertile couples: 7-fold excess of Robertsonian heterozygotes
- oligospermic Men: 13 fold excess among
- compromise the fidelity of the first few mitoses, affecting mitotic segregation
- Conn et al.(1998):
- two infertile couples with Robertsonian translocation:
  - 45,rob(13q14q) man
  - 45,rob(13q21q) woman
- karyotype 33, day-3 embryos from the two couples
  - 90% of embryos were chromosomally abnormal
  - 40% were trisomic or monosomic for 13, 14, or 21
  - 60% had a“chaotic karyotype”

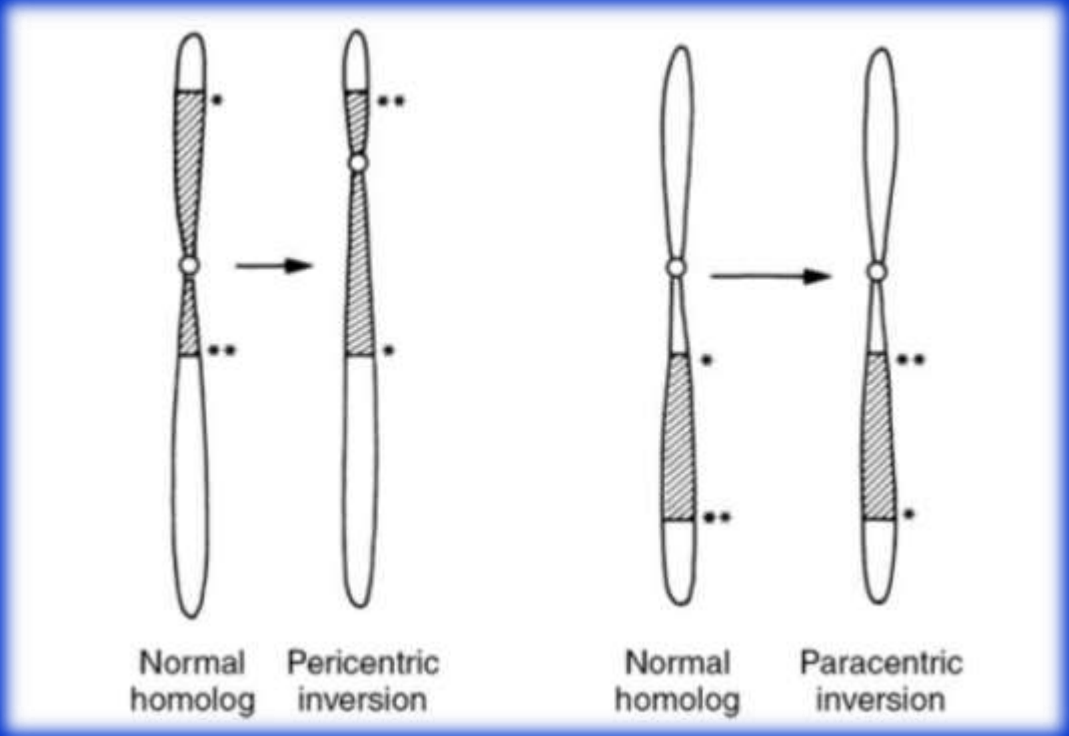
rob(14q21q)

- the most important Robertsonian translocation in frequency and *genetic risk*
- marked difference according to the sex of the parent
- Most familial translocation DS is due to the rob(14q21q)
- At amniocentesis, the *female* heterozygote has a risk for translocation trisomy 21 of about 15%
- risk of having a liveborn child with translocation DS is a little less (in the range 10%–15%):
  - the loss, through spontaneous abortion
- The risk for the *male* heterozygote is very different, and a figure of <1% is appropriate to offer

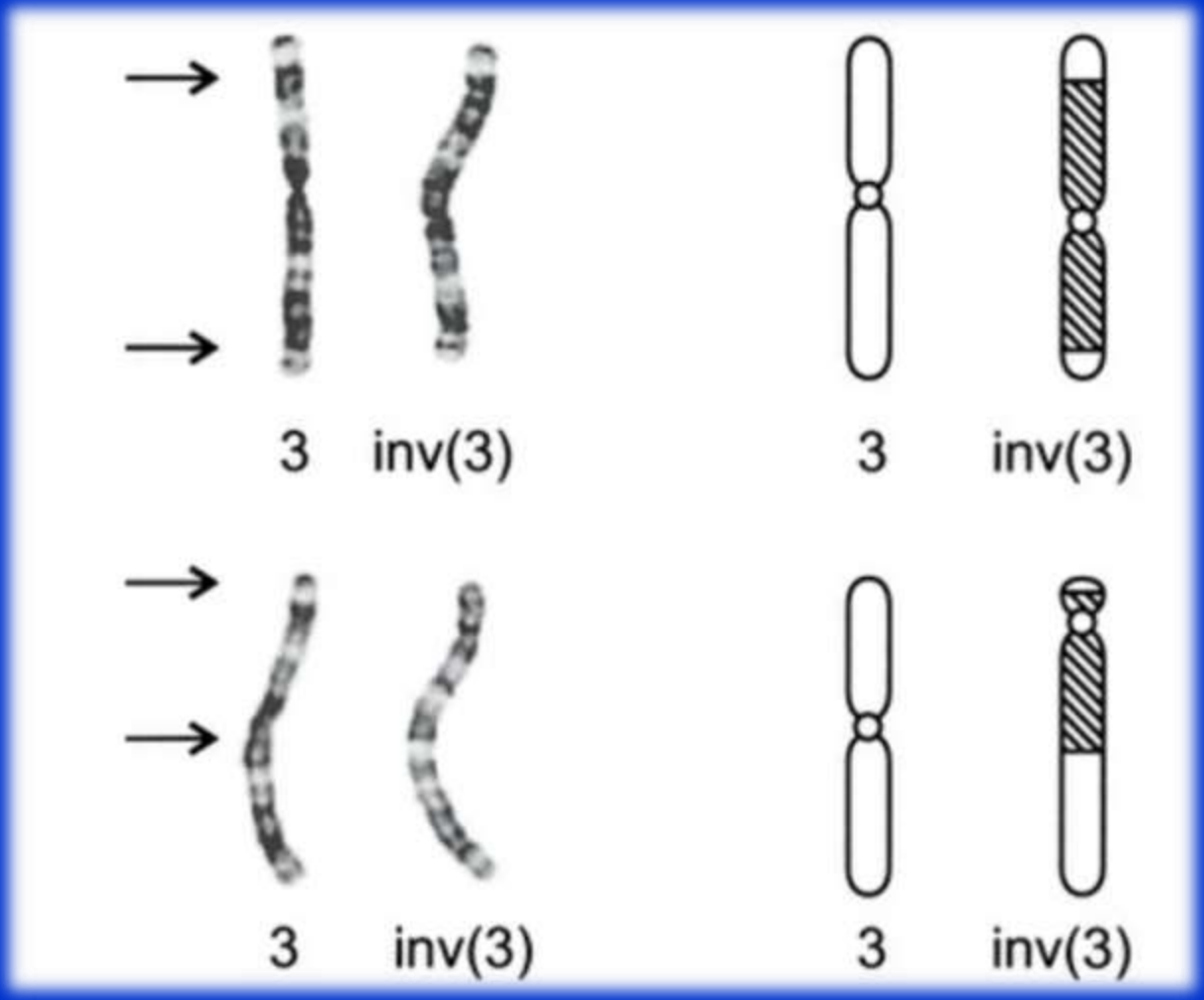
Inversions

Inversions

- a two-break event involving just one chromosome
- The intercalary segment rotates 180°, reinserts, the breaks unite
- generation of recombinant (rec) gametes that may lead to abnormal pregnancy



Two Pericentric Inversions of Chromosome 3



Both of the noninverted segments are small in one (*a*) and one is large in the other (*b*).

Frequency of Inversions

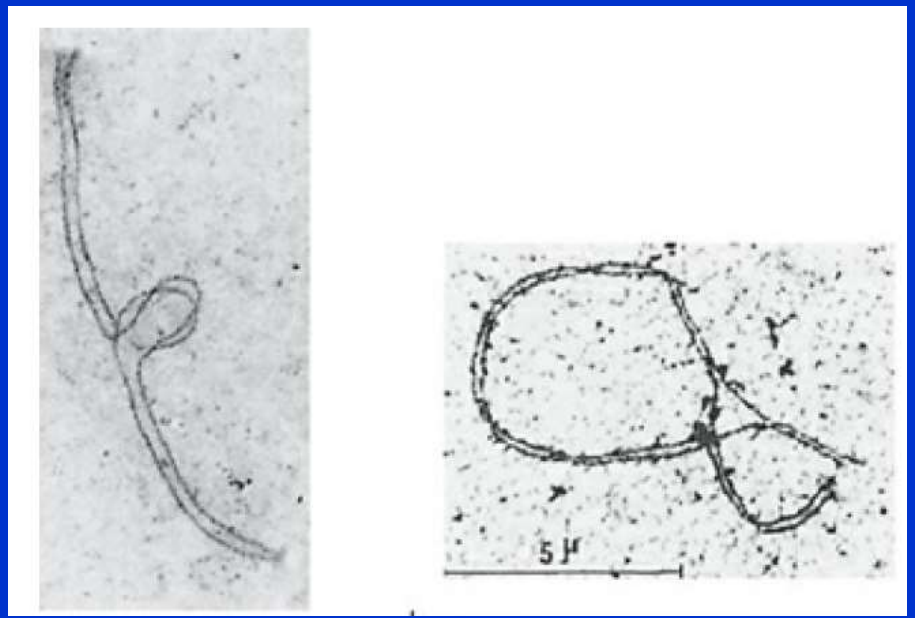
- Classical inversions are a fairly uncommon
- Estimates of frequency range from:
  - ~0.12% to 0.7% (pericentric)
  - ~0.1% to 0.5%(paracentric) of individuals
- Many small examples remain undetected
- Will not be detected by chromosome microarray

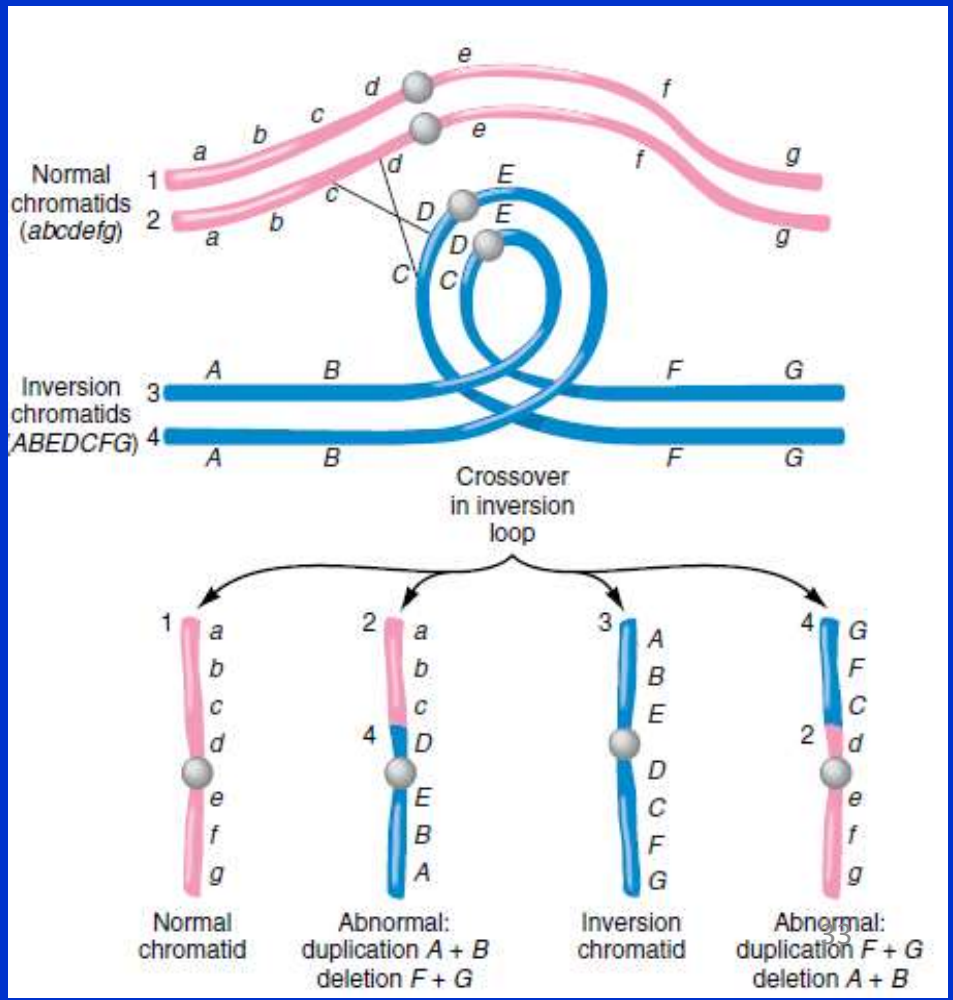
"Normal Variant" Inversions

- "Inversions" having a breakpoint within the heterochromatic regions of chromosomes 1, 9, 16, &Y
- inv(2)(p11.2q13)
- inv(3)(p11q11) and inv(3)(p11q12), inv(3)(p13q12), inv(5)(p13q13)
- inv(10)(p11.2q21.2)

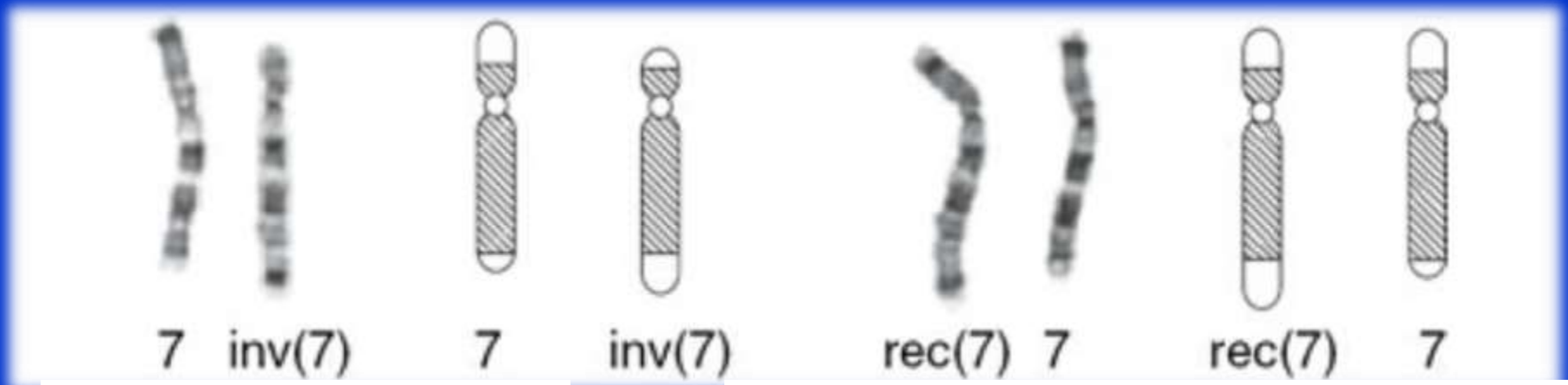
The Autosomal Pericentric Inversion: Meiotic behavior

- The inversion heterozygote may produce chromosomally unbalanced gametes
- Suffer reproductive pathology





Pericentric Inversion 7

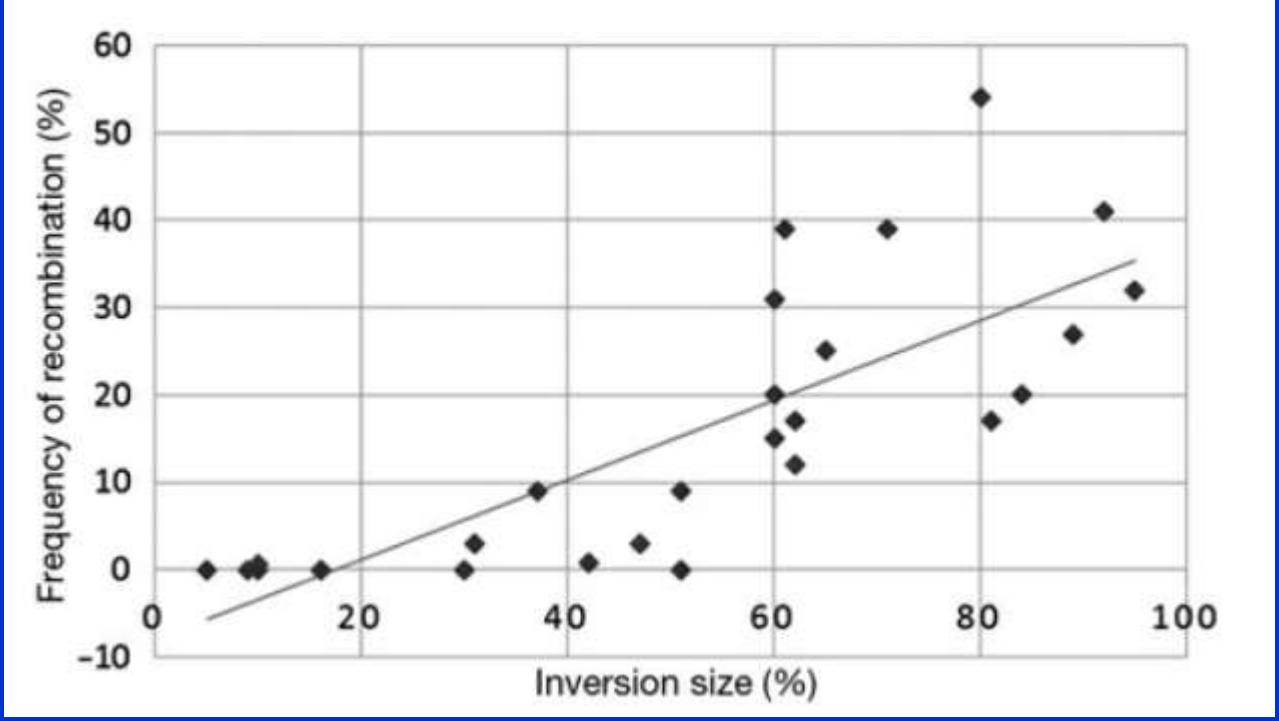


46,XY,inv(7)(p14.2q36.3)

46,XY,rec(7)dup(7p)inv(7)(p14.2q36.3)pat

- Pericentric inversion 7 in the father (*left*) of an abnormal child with a recombinant 7 (*right*)
- duplication of over half of 7p, a minuscule deletion in distal-most subband of 7q
- The child has triple amount of the segment 7p14.2pter
- The countertype form, with monosomy 7p14.2pter (& trisomy 7q36.3qter), would cause a miscarriage

The Proportion of Gametes that are Recombinant, Compared with the Relative Size of the Inversion

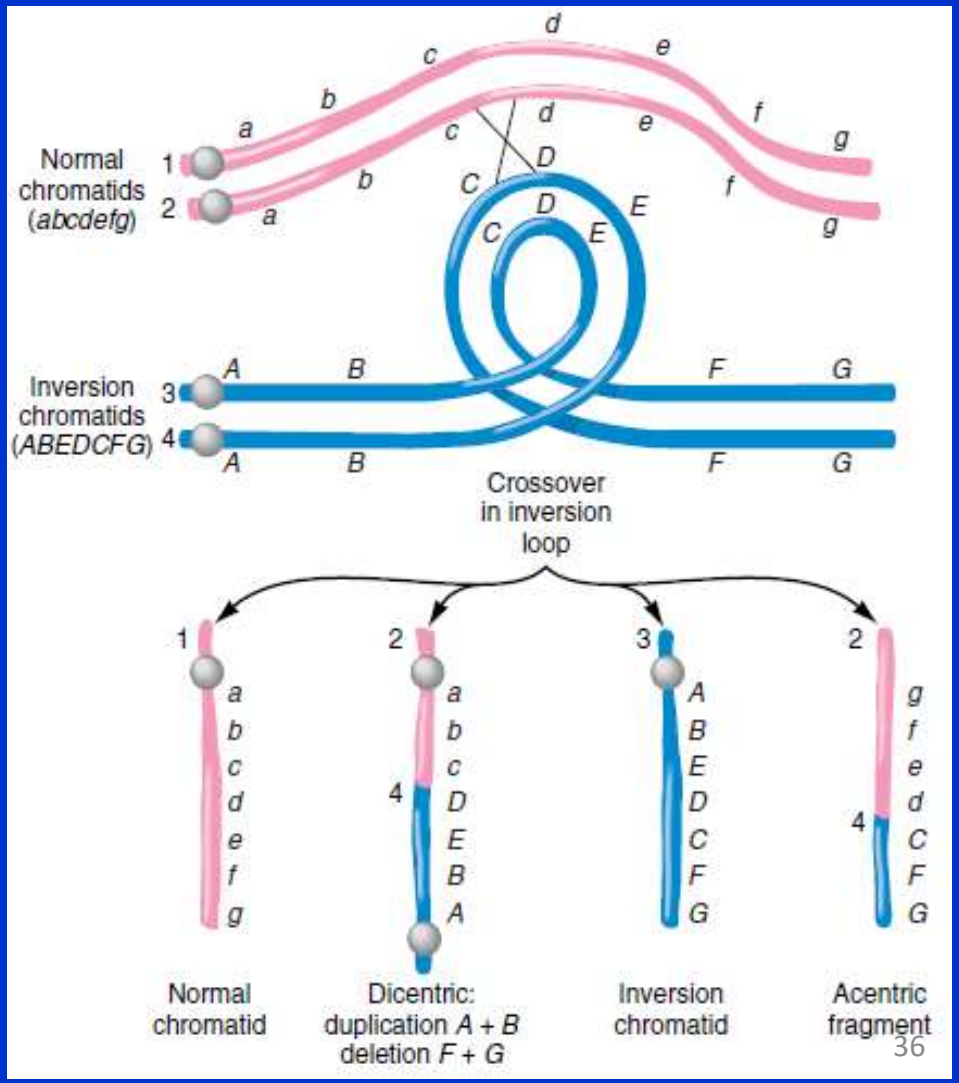


- The larger the inversion size, the more frequently recombinants
- inversion length:
  - ✓ >50% : high risk of recombination
  - ✓ between 30% and 50%: small risk
  - ✓ <30% no recombination appears to take

THE PARACENTRIC INVERSION: DETAILS OF MEIOTIC BEHAVIOR

- **Classic Theory:**

only have children who are karyotypically normal?



What are the Findings on Direct Observation of Gametes?

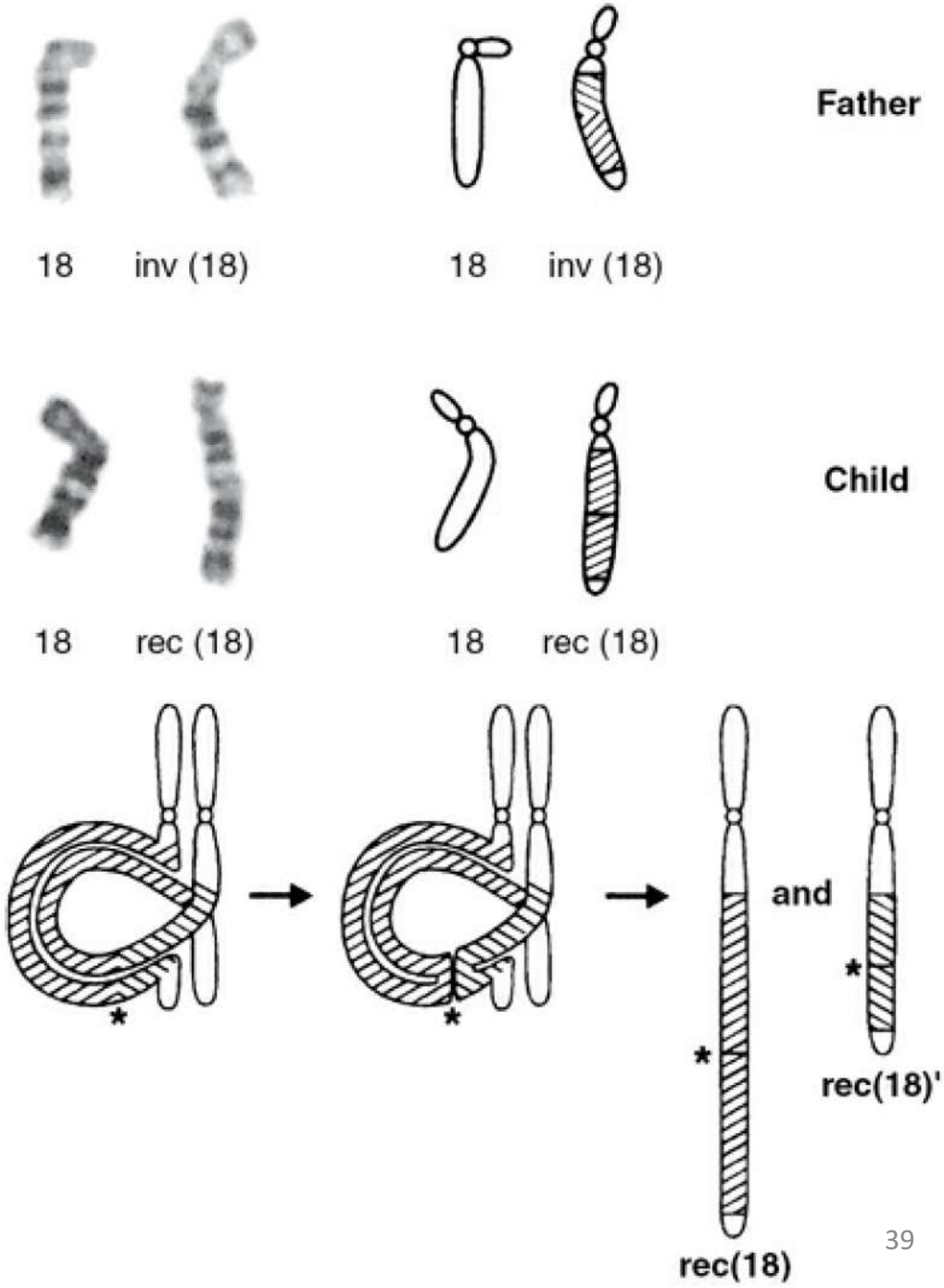
- recombination is scarcely ever seen
- Anton et al. (2005):
- inversion segments ranging from 6% to 32%
- The fractions of recombinant sperm ranged from zero to 0.81%
- Similar findings in similar studies!!!

What is the possible alternative mechanism?

Recombination/Reunion with Viable Products

- Classical theory remains valid in essence
- The abnormal process of "U-loop recombination
- *Reunitant* rather than *Recombinant*
- The crossover within the inversion loop, instead of
- continuing on in the same direction along the chromatid, reverses upon itself as a "U-loop."
- have either:
  - ✓ duplication of that part of the inversion loop proximal to the crossover
  - ✓ deletion of that part distal to it, or vice versa

Proposed mechanism of U-loop exchange



GENETIC COUNSELING

- The vast majority of paracentric inversions likely to be harmless
- refute a complete harmlessness in the parental paracentric inversion, whether due to classic recombination or to other forms of Rearrangement➔
  - A matter for debate
- Inversions with a demonstrated recombinant offspring should offer of prenatal diagnosis:
- inv(7)(q31.31q31.33), inv(9)(p13p24), inv(9)(q22.1q34.3), inv(14)(q24.2q32.3), inv(17)(p11.2p13), inv(18)(q12.1q23), inv(18)(q21.1q22.3), and inv(18)(q21.32q23).

Chromosomal Heteromorphisms

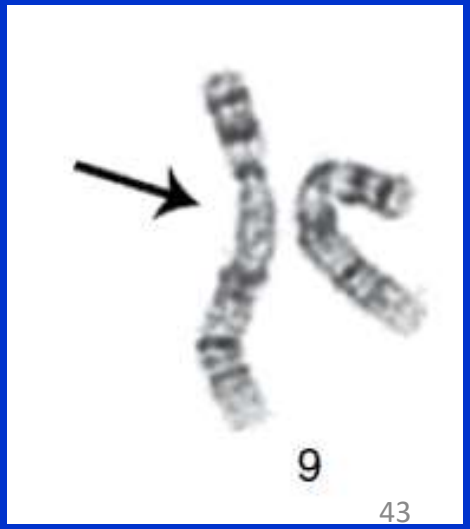
Normal Chromosomal Variation

- **Variation:**
  - **I. normal traits e.g. height, blood pressure, & intelligence**
  - **II. Abnormal variation: may be clear-cut, dwarfism,hypertension, and intellectual deficiency**
  - **III. distinction may blur at the edges: short stature, borderline blood pressure, and low-normal IQ**

- **somewhat of a parallel in the study of chromosomes**
- **Some variation is quite normal, and well understood**
- **observation such as a large deletion is abnormal**
- **But some chromosomal variation does not admit of straightforward interpretation**

Large Heterochromatic Regions

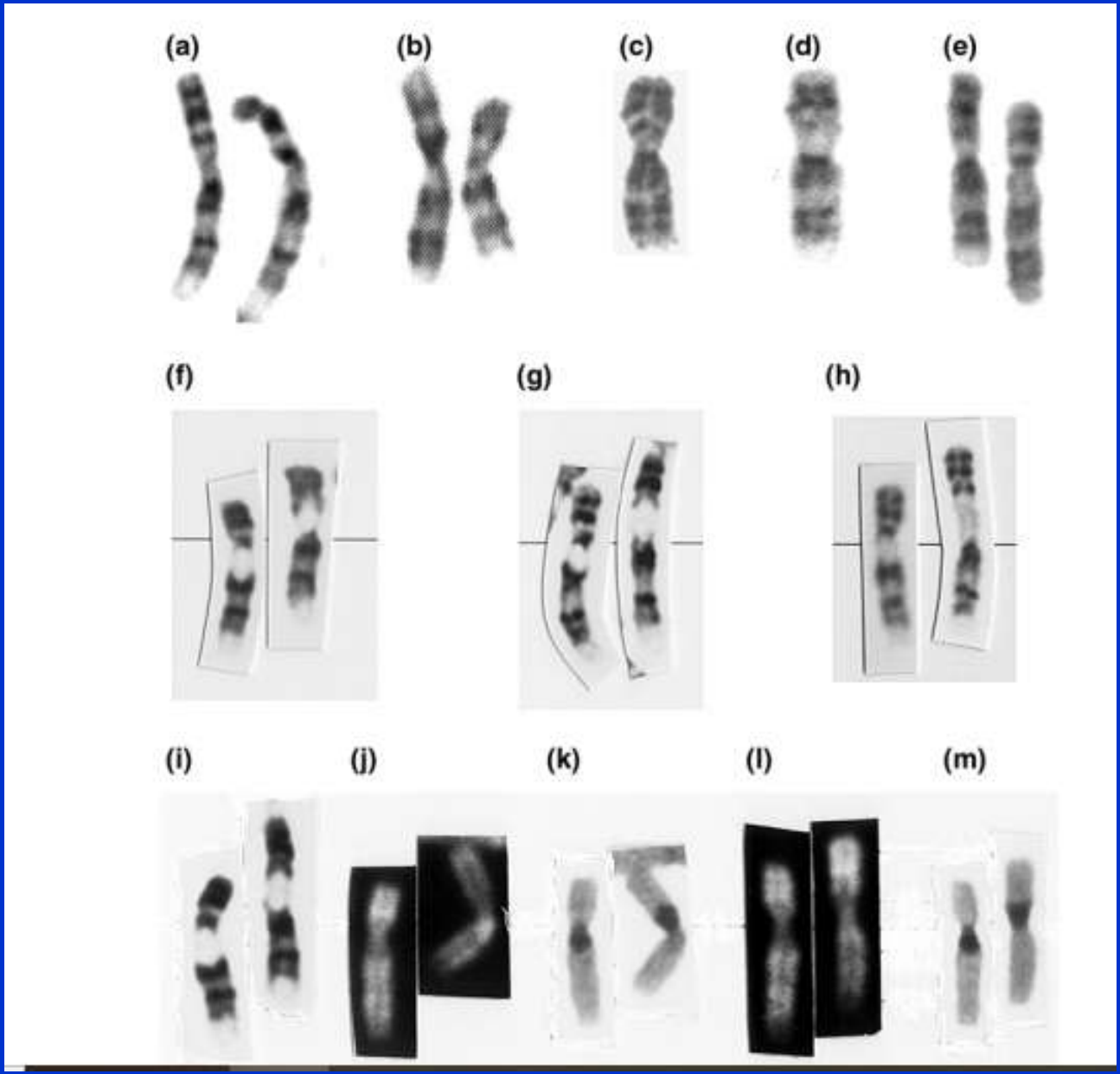
- variable amount of heterochromatin below the centromere in the proximal long arm of specific chromosomes
  - 1, 9 and 16
- no clinical consequence
- do not even include them in clinical reports, unless desired



Variant Pericentric Inversions around the Centromere

- One of the most common chromosome genetic variants is inv(9)(p12q13)
- a change in the heterochromatin to the proximal
- short arm
- an inversion of the centromeric region of chromosomes 1, 2 and 16 is also seen
- have no clinical consequence
- some laboratories do not even include them in clinical reports, although some do add a comment in the interpretation of the report

Pericentric Inversion of Chromosome 9



Variant Satellite Regions

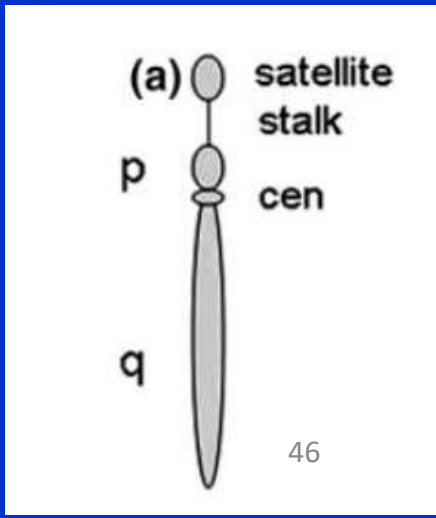
- The most variable chromosomes in the human karyotype are the acrocentric chromosomes, 13, 14, 15, 21 & 22

- The features in common are:

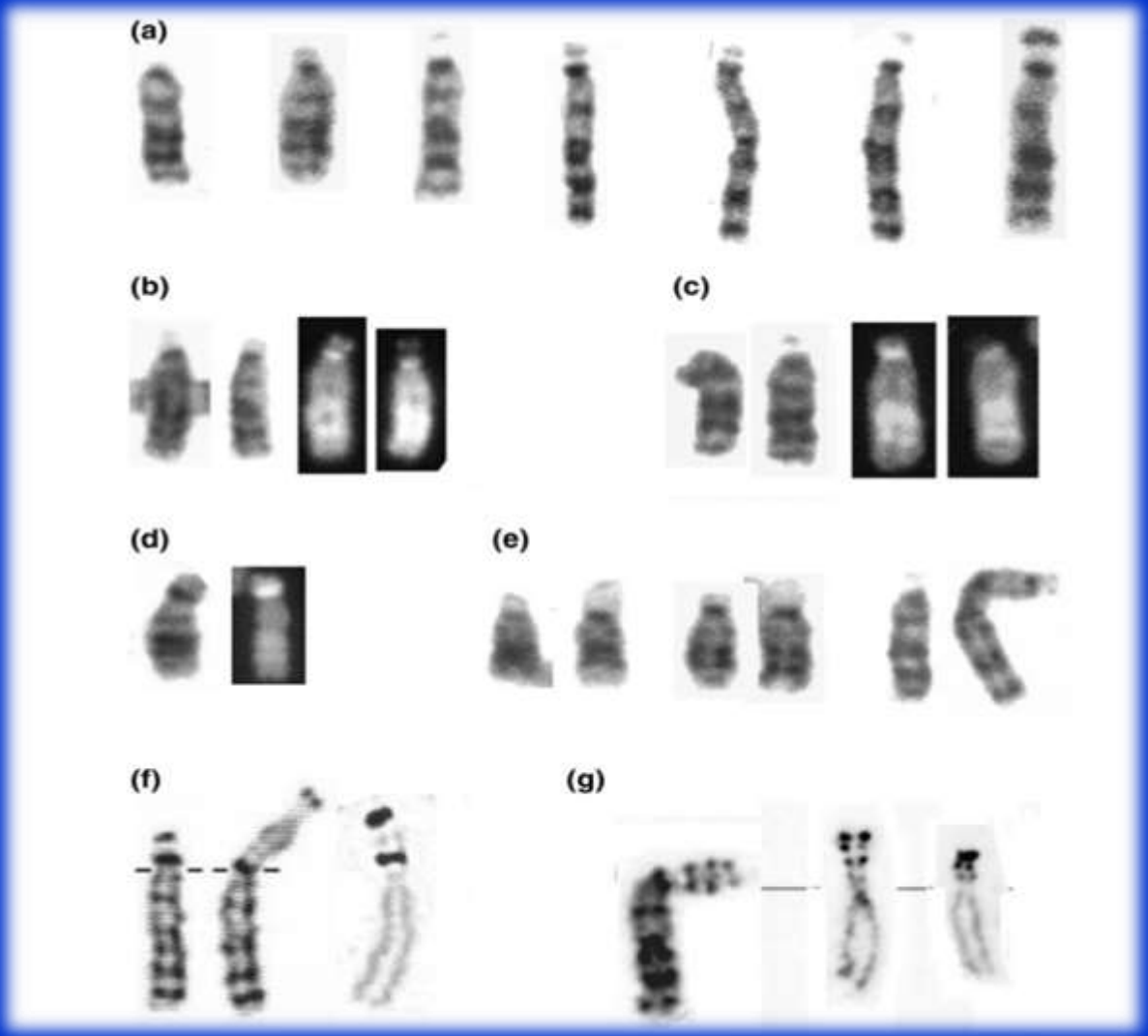
(1) they all carry nucleolar organizing regions (NORs) revealed by silver staining;

(2) they all have four distinct regions (satellite, stalk, short arm and centromere) that can vary in size and/or may have different staining properties

(3) all are involved in Robertsonian translocations



Normal chromosomes 13 showing increasing band resolution & variations in size and staining of short arms, stalks and satellites



Variant Yqh

- Y chromosome:
  - unique genes on its short arm and proximal long arm
  - heterochromatin in the distal long arm (Yqh region)
- quite variable in size
- Normal variant
- C-banding
- comment in the report regarding this region

Inversion of Chromosome Y

- a structural variant of the human Y chromosome
- prevalence of males with this structural abnormality is 1 per 1000
- generally not associated with specific phenotypic abnormalities or fertility problem


Thank you!