

MALATTIE GENETICHE

1) MALATTIE CROMOSOMICHE → malattie associate ad alterazioni del numero o della struttura dei cromosomi

Es. : sindrome di Down (trisomia 21)

2) MALATTIE MENDELIANE → malattie dovute alla mutazione di un singolo gene che vengono trasmesse secondo le leggi di Mendel sull'ereditarietà

Es. : fenilchetonuria; anemia falciforme;
fibrosi cistica; talassemie.

3) MALATTIE CON EREDITA' MULTIFATTORIALE (POLIGENICHE) → malattie influenzate sia da fattori genetici che da fattori ambientali. La componente genetica di solito è data da molti geni, ciascuno con effetto limitato.

Es. : ipertensione; diabete mellito.

4) MALATTIE DOVUTE AD UN SINGOLO GENE CON PARTICOLARI MODALITA' DI TRASMISSIONE.

- a) malattie da amplificazione di triplette
- b) malattie da mutazioni del DNA mitocondriale
- c) malattie la cui trasmissione è influenzata dall'imprinting genetico o dal mosaicismo gonadico

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Le aberrazioni cromosomiche

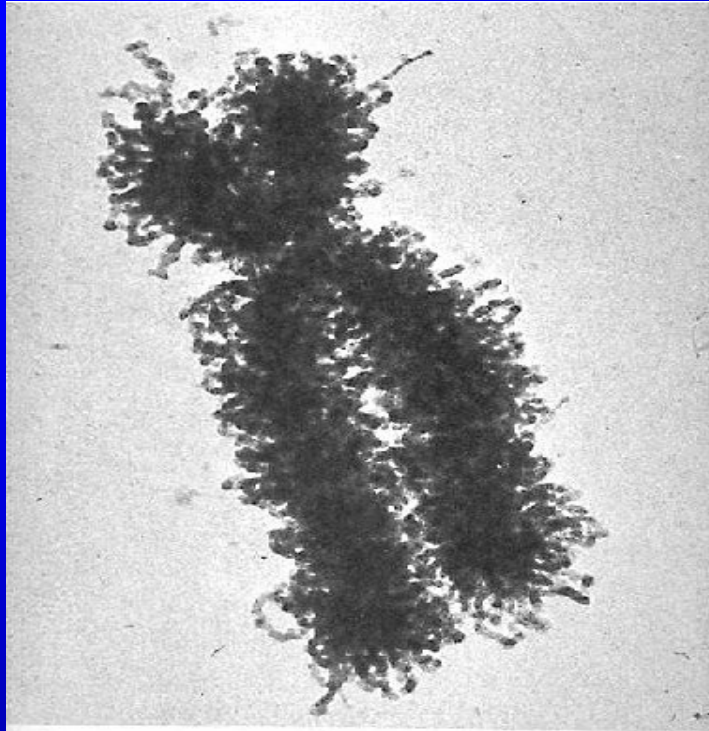
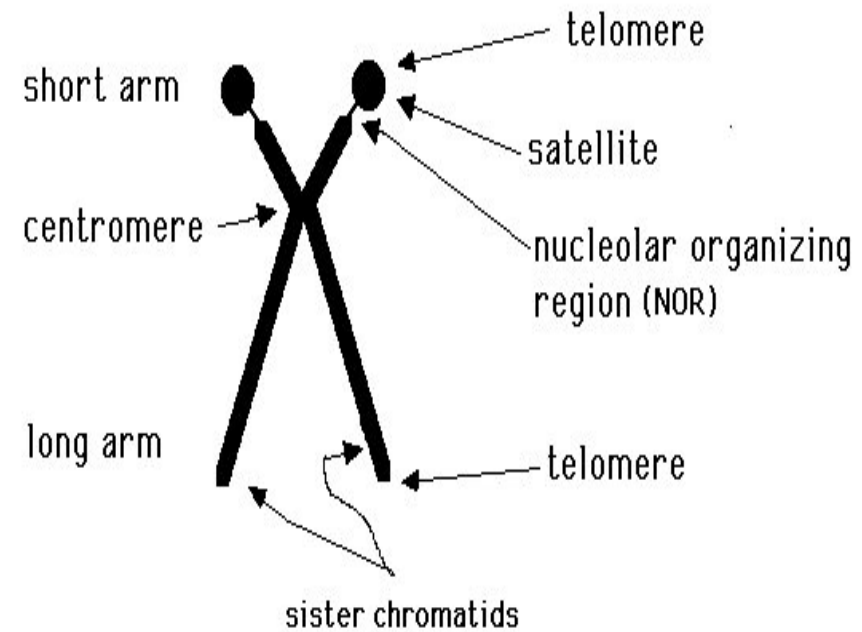


FIGURE 1-14
An electron micrograph of a human chromosome.
Chromosome XII from a HeLa cell culture. (Courtesy
of Dr. E. Du Praw.)

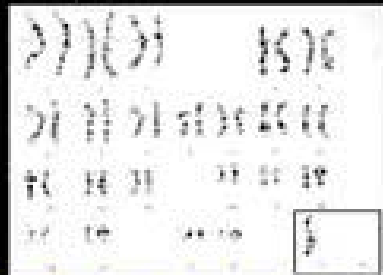


Struttura dei cromosomi

Karyotype vs Genotype vs Phenotype

♦ Karyotype

- Chromosomal pattern



♦ Genotype

- Entire genetic constitution

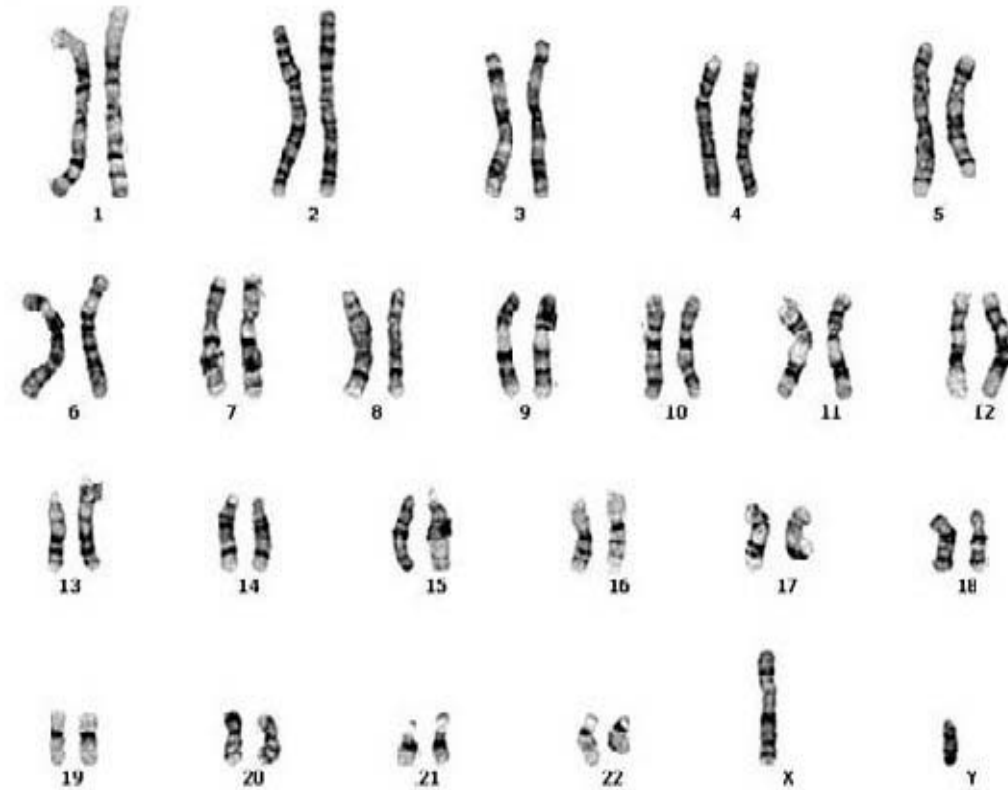
♦ Phenotype

- Physical and physiological makeup
- e.g., short stature, infertility, osteoporosis

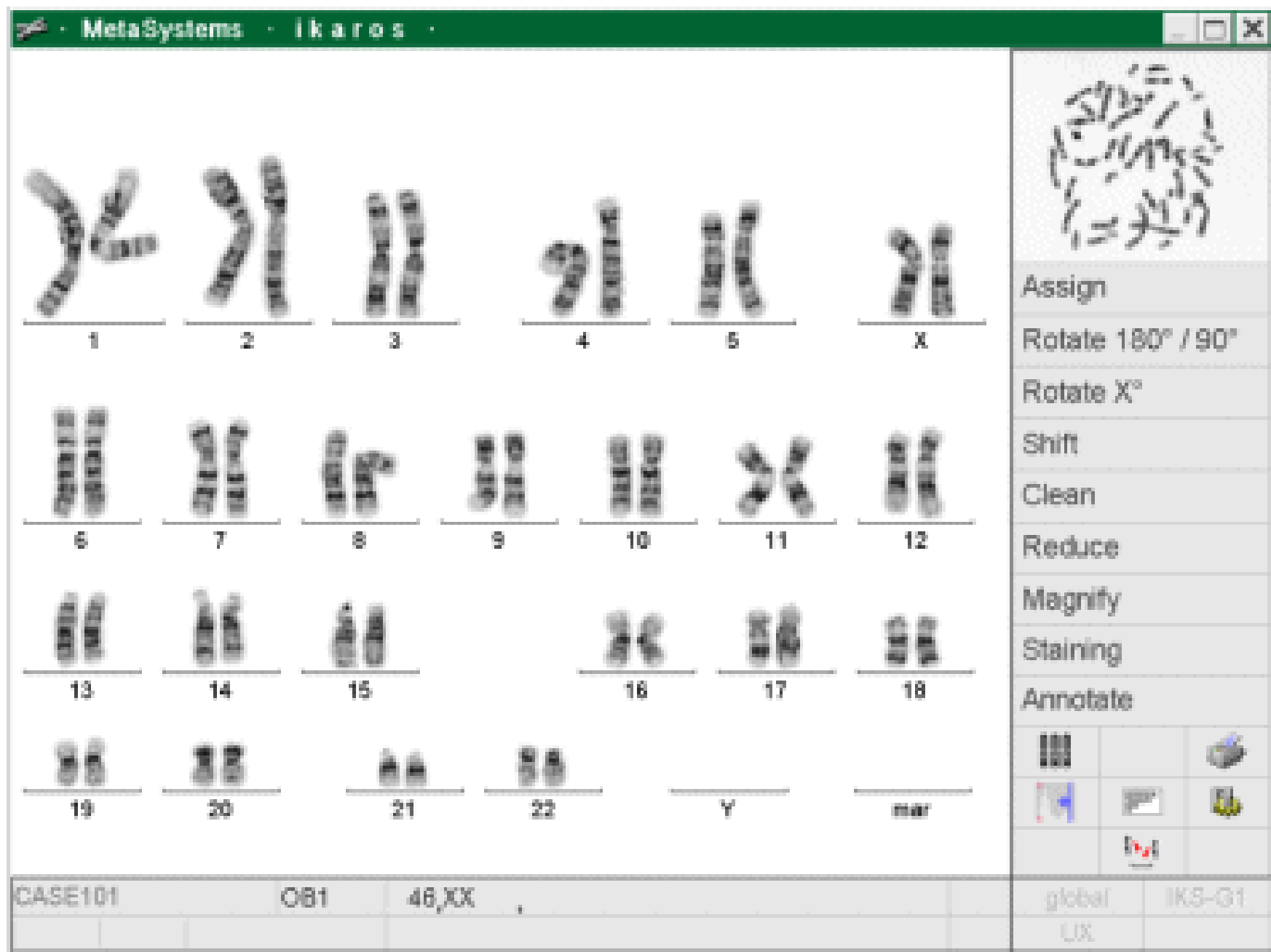


Normal Human Male Karyotype

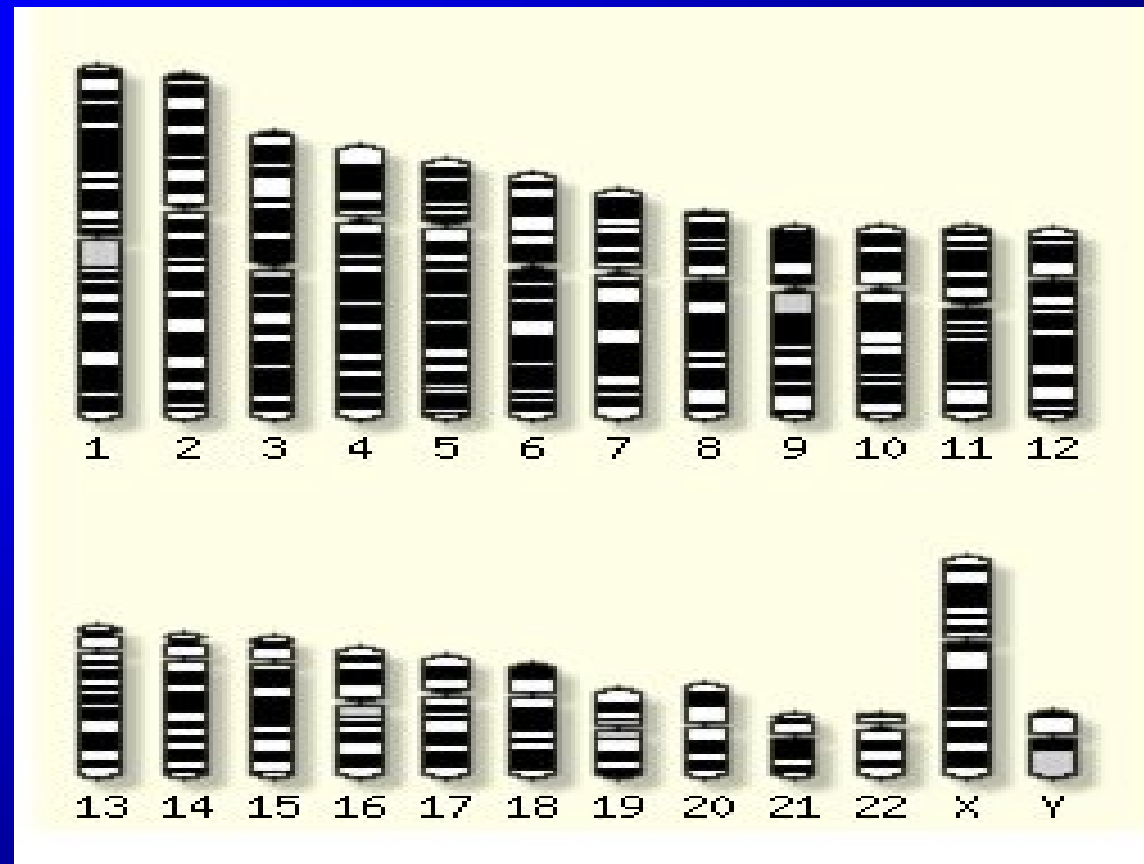
Human male
G-bands



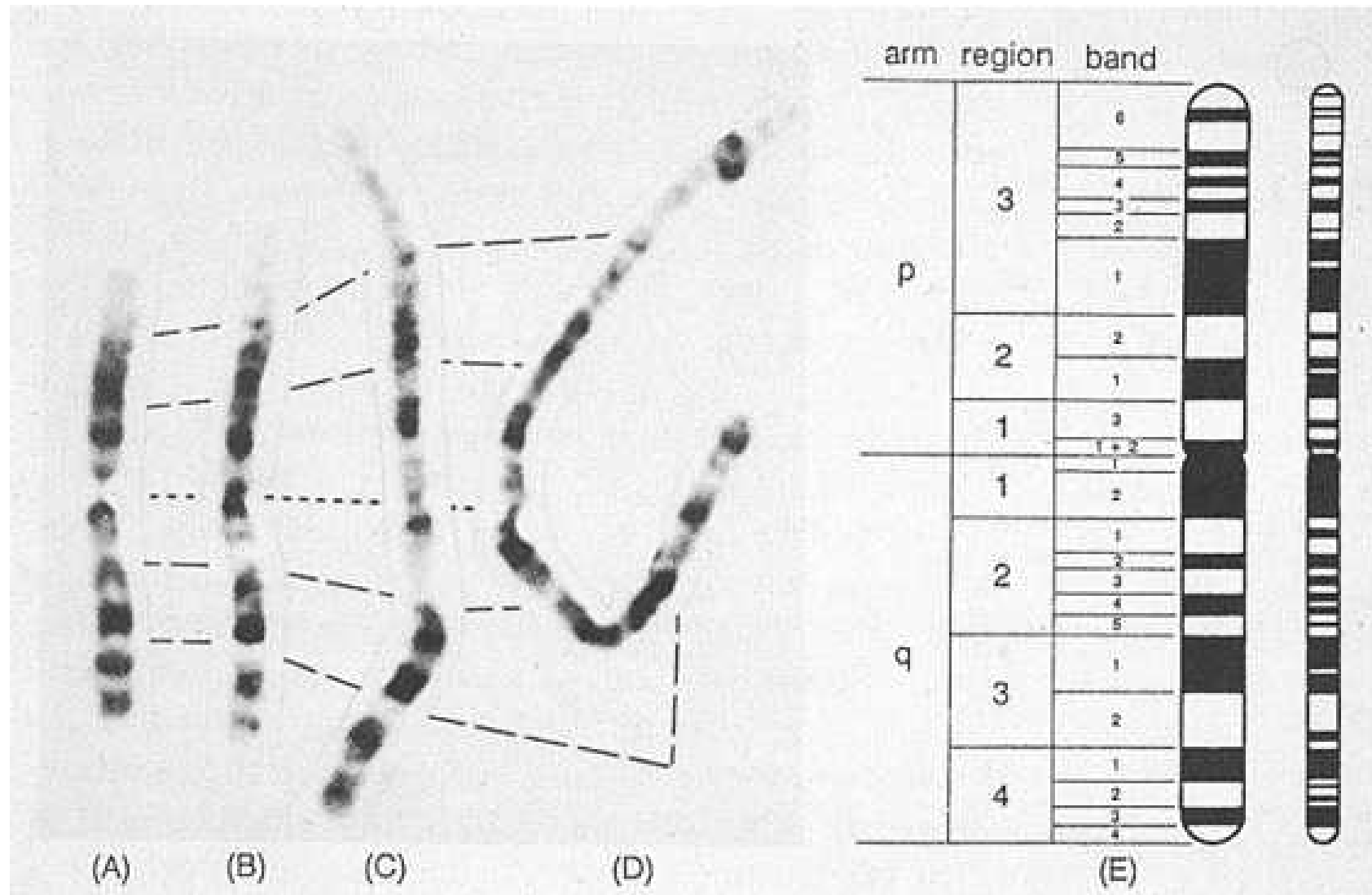
Analisi del cariotipo



a computer-assisted assembly of a karyotype from a female (46, XX)



Bandeaggiatura dei cromosomi



metaphase and prometaphase G-banded human chromosome 1 and the standard nomenclature for labeling the bands;

short arm: p (petite); long arm: q;

1 - 4 regions for each arm labeled from centromere towards telomere

each region has several bands, again numbered away from the centromere

TERMINOLOGIA CITOGENETICA

Numero cromosomi

assetto cromosomi sessuali

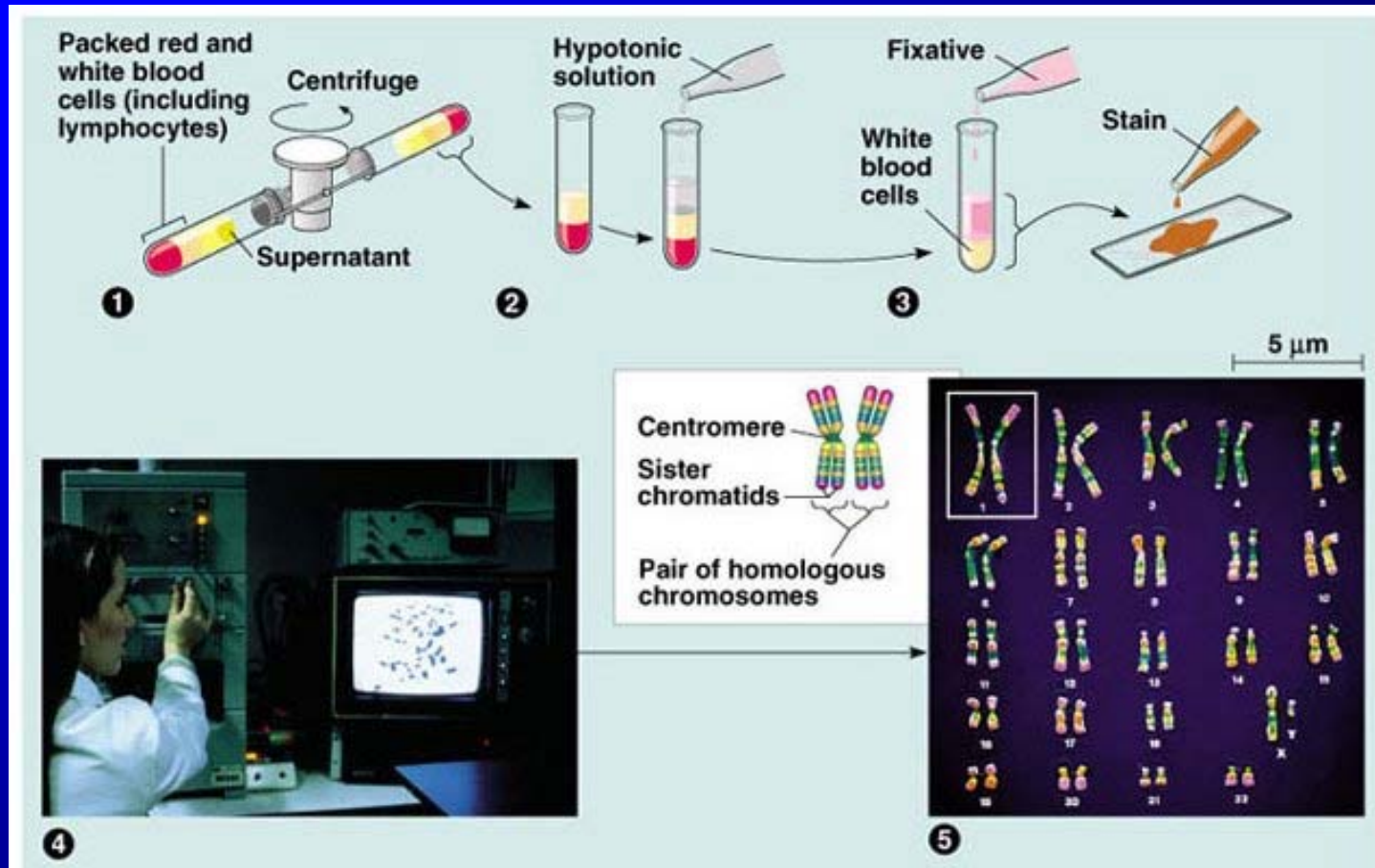
47, XY, +21

eventuali anomalie

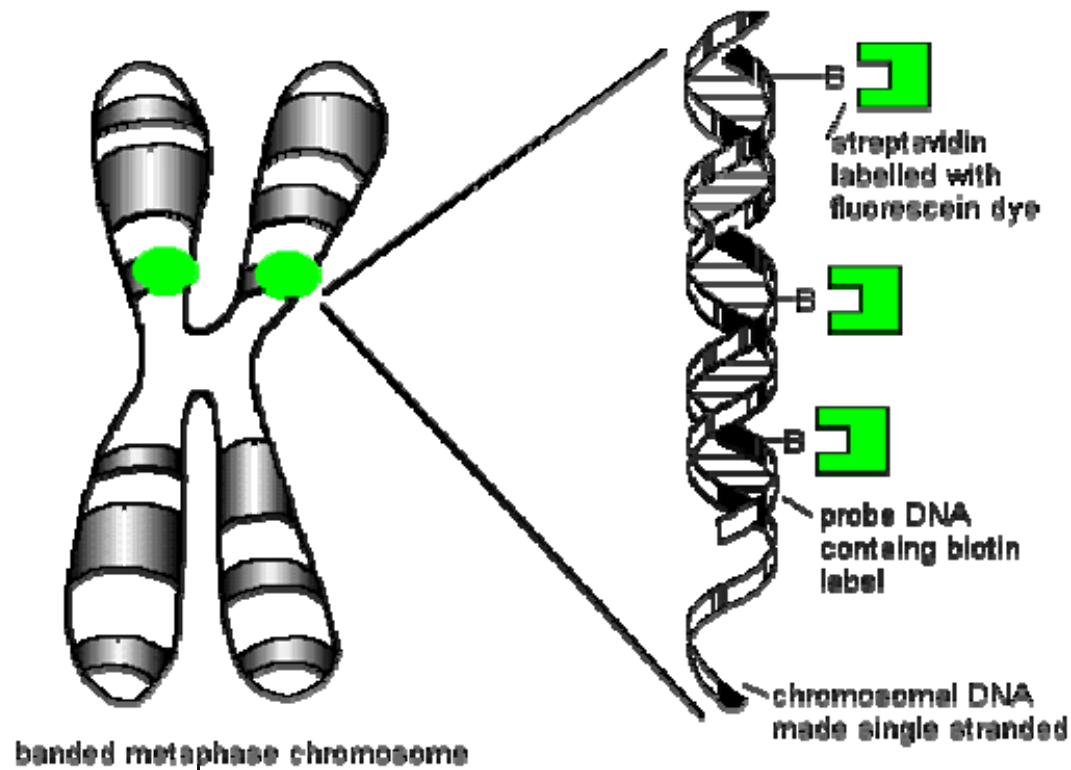
p (da *petit*) → braccio corto del cromosoma

q → braccio lungo del cromosoma

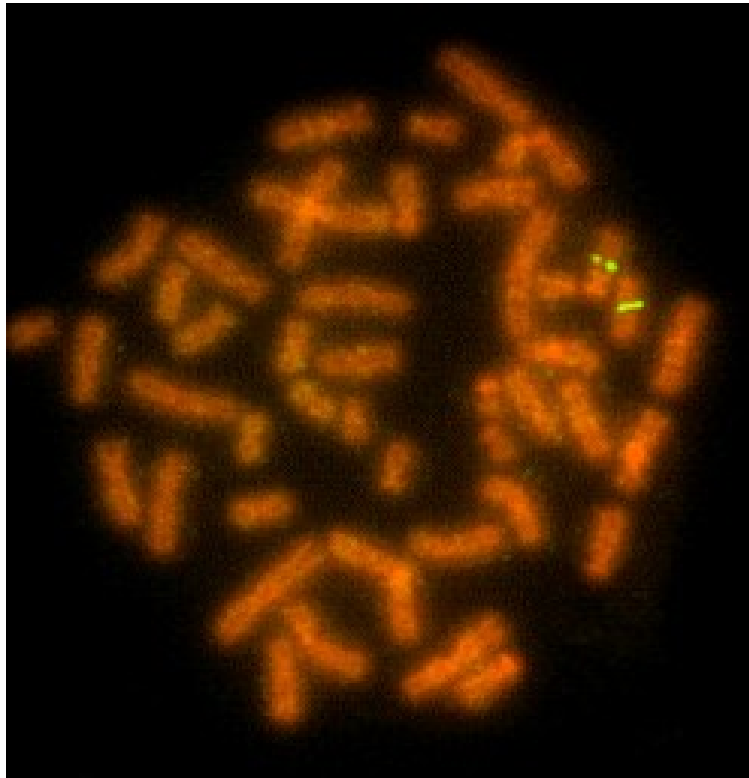
Xp21.2 = cromosoma X, braccio corto, regione 2, banda 1, sottobanda 2



FISH = Fluorescent In Situ Hybridization



The probe molecule is labelled with a hapten such as biotin. The biotin is located with streptavidin. The streptavidin is located with antibodies. A fluorescent dye may be conjugated to the streptavidin and to the antibodies. When the spread chromosomes are illuminated by a UV lamp, a point of fluorescence can be seen where the probe/streptavidin/antibody/fluorescent dye multilayer sandwich has built up. From three to five layers of fluorescent antibodies are built up to amplify the signal.



•Cytogenetic mapping by FISH

A probe is made from a genomic (or sometimes even a cDNA) clone by using the Nick Translation reaction to incorporate a biotinylated nucleotide into DNA. Metaphase chromosome spreads are made by conventional techniques, the spread chromosomes are treated to denature the DNA of the chromosomes and the probe is allowed to hybridise to the chromosomes. Later, the site(s) of hybridisation is found by using streptavidin and antibodies conjugated to a fluorescent dye. In this way the site of origin of any clone can be found in the genome.

Here is one example from the Wisconsin site which shows a cosmid hybridising specifically to a site on chromosome 13. Remember that the chromosomes are replicated ready to divide and that each therefore consists of two chromatids. The probe has hybridised to all four chromatids.



a metaphase spread of human chromosomes

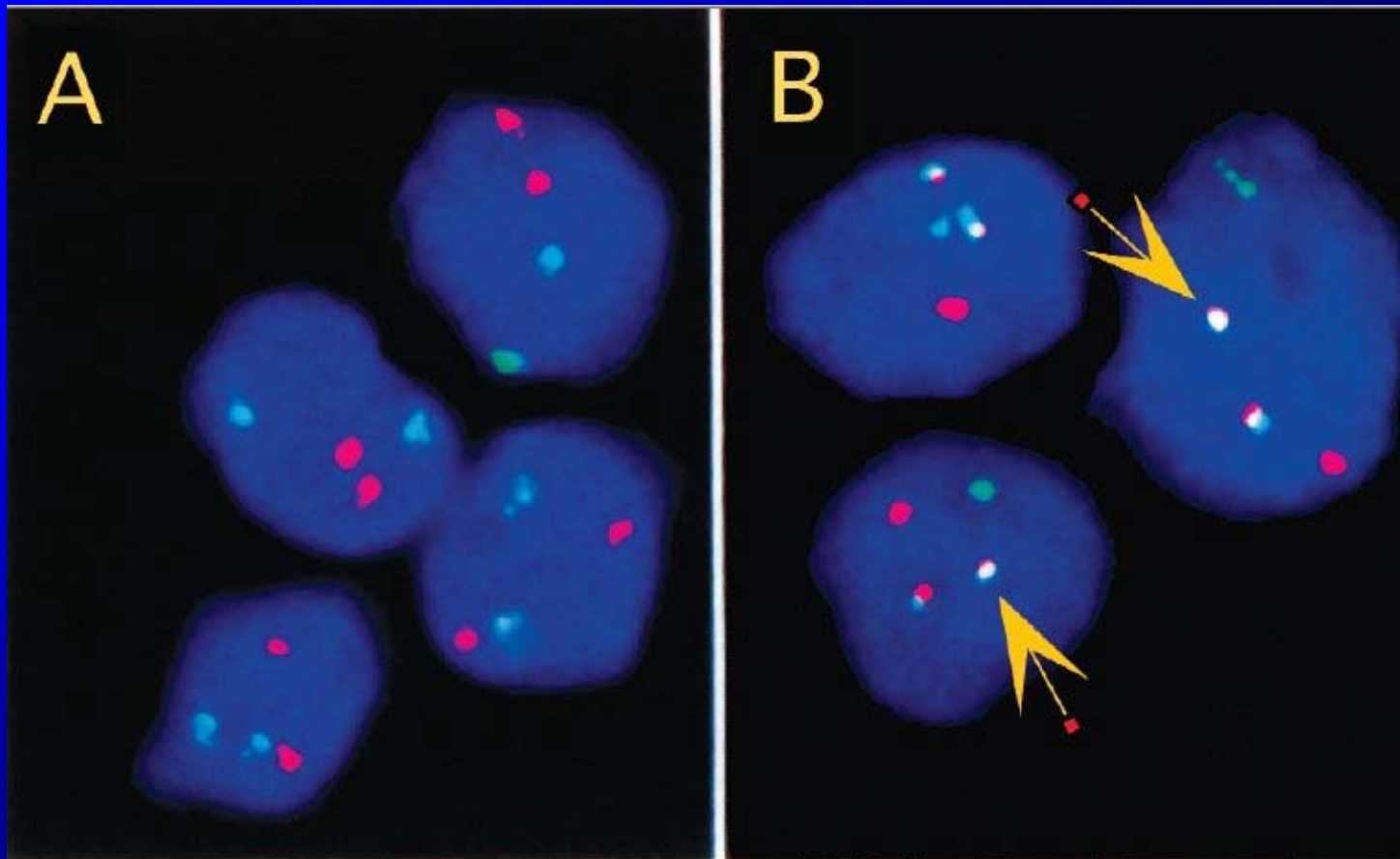
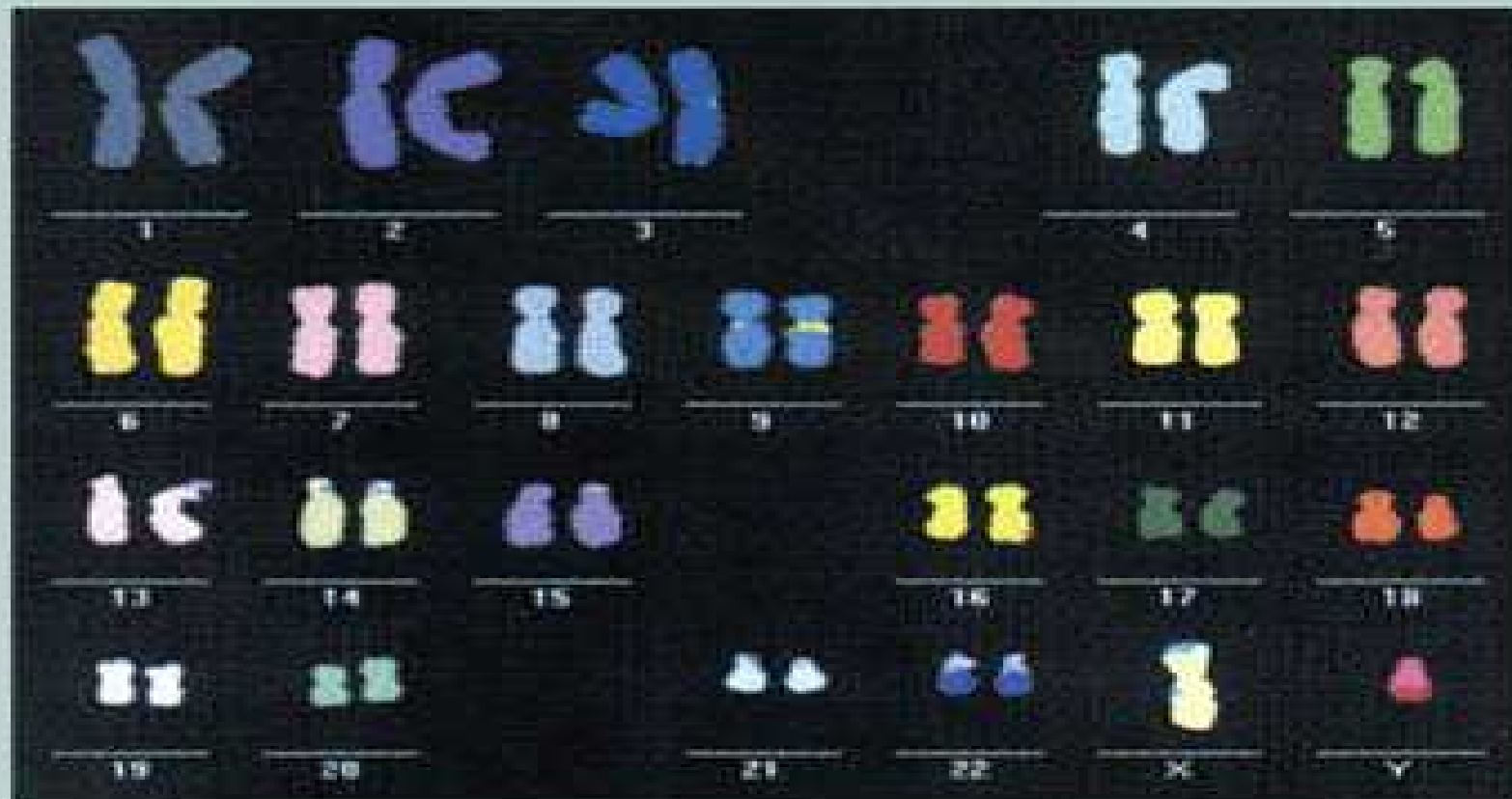
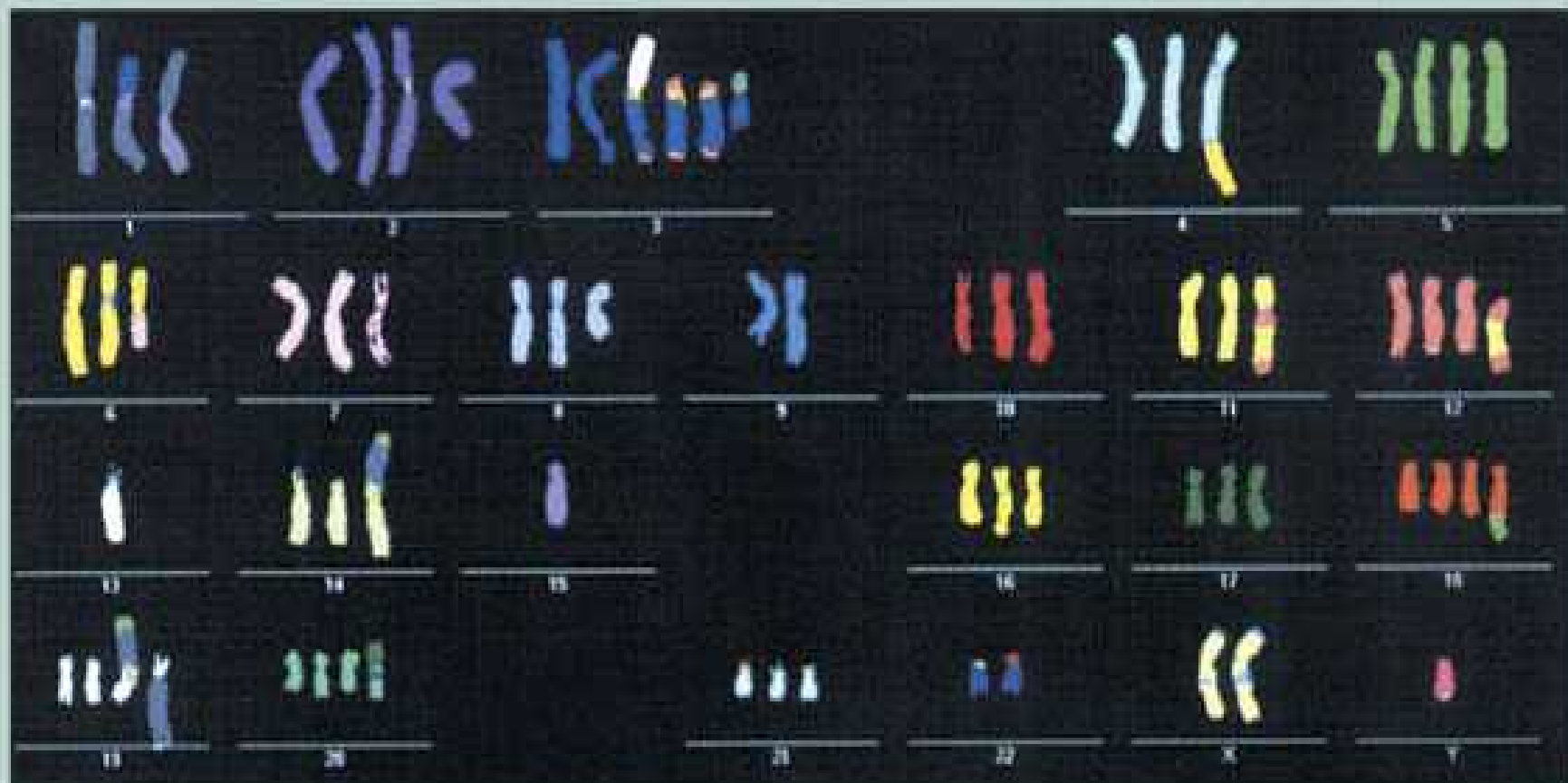


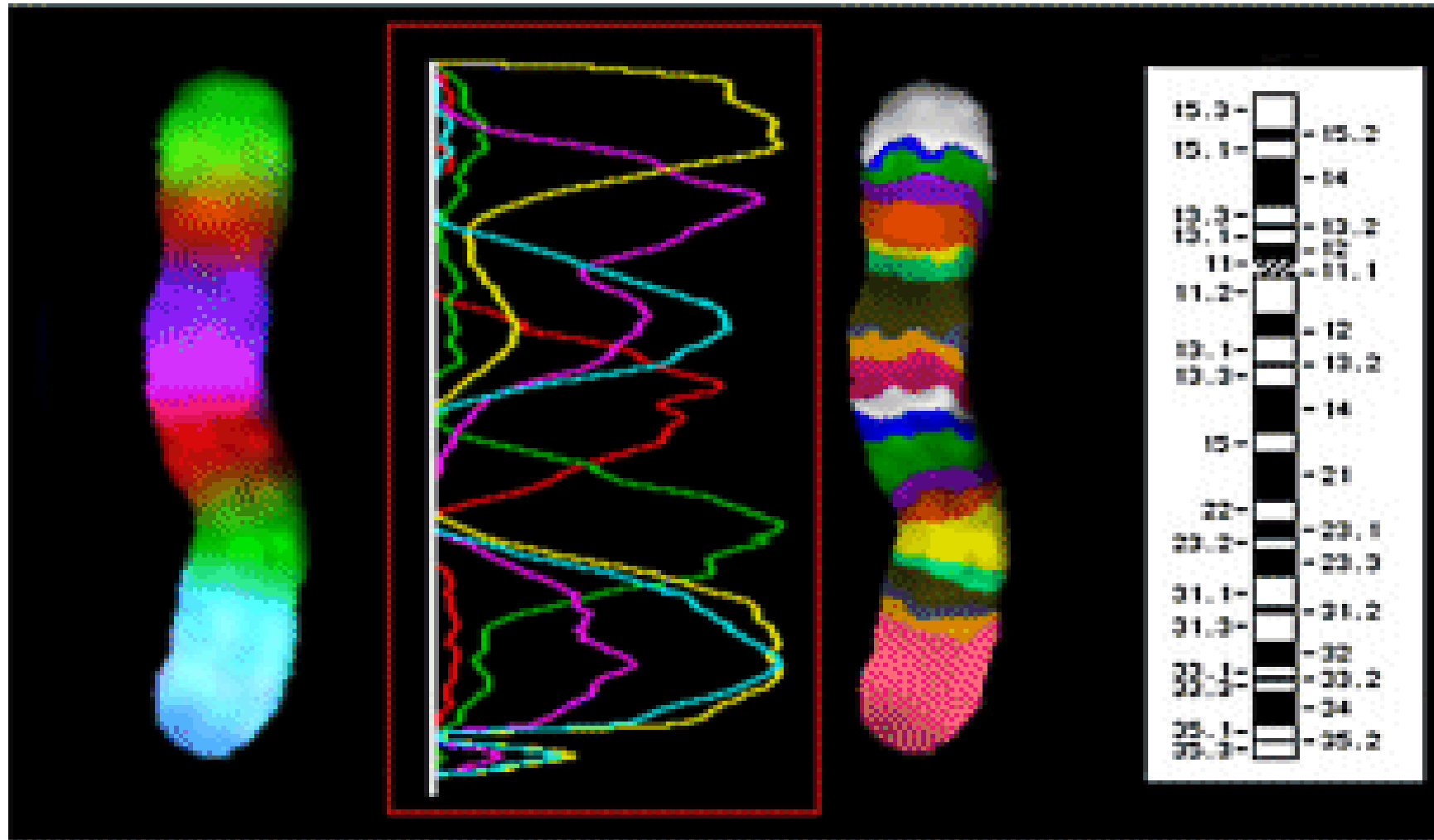
Fig. 5 FISH for t(11;14) translocation. A. Normal lymphoid nuclei (2 red-chromosome 11; 2 green-chromosome 14 signals). B. Mantle cell lymphoma t(11;14) (1 red, 1 green and 2 yellow fusion signals-arrows). Lymph node imprints x 1000.



■ Figura 3.2 - Cariotipo umano maschile normale, ottenuto mediante la tecnica del "chromosome painting", consistente nell'impiego di sonde specifiche per ogni cromosoma, marcate con fluorocromi diversi per ciascuno di essi.



■ **Figura 3.3 - Cariotipo ipertriploide da una cellula di tumore altamente anaplastico.** La tecnica del "chromosome painting" consente di definire i riarrangiamenti dei singoli cromosomi (duplicazioni, inserzioni, traslocazioni, etc.).

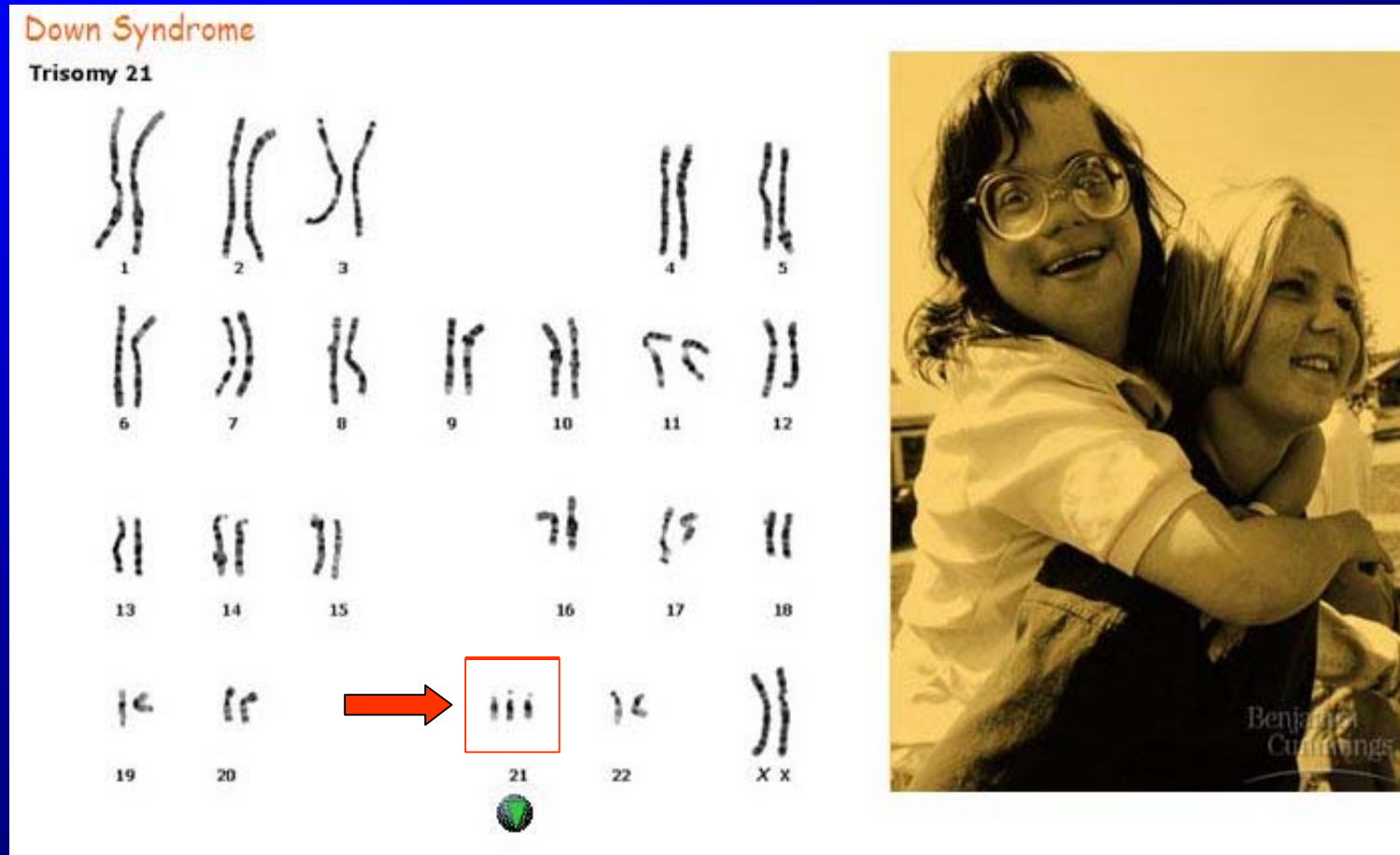


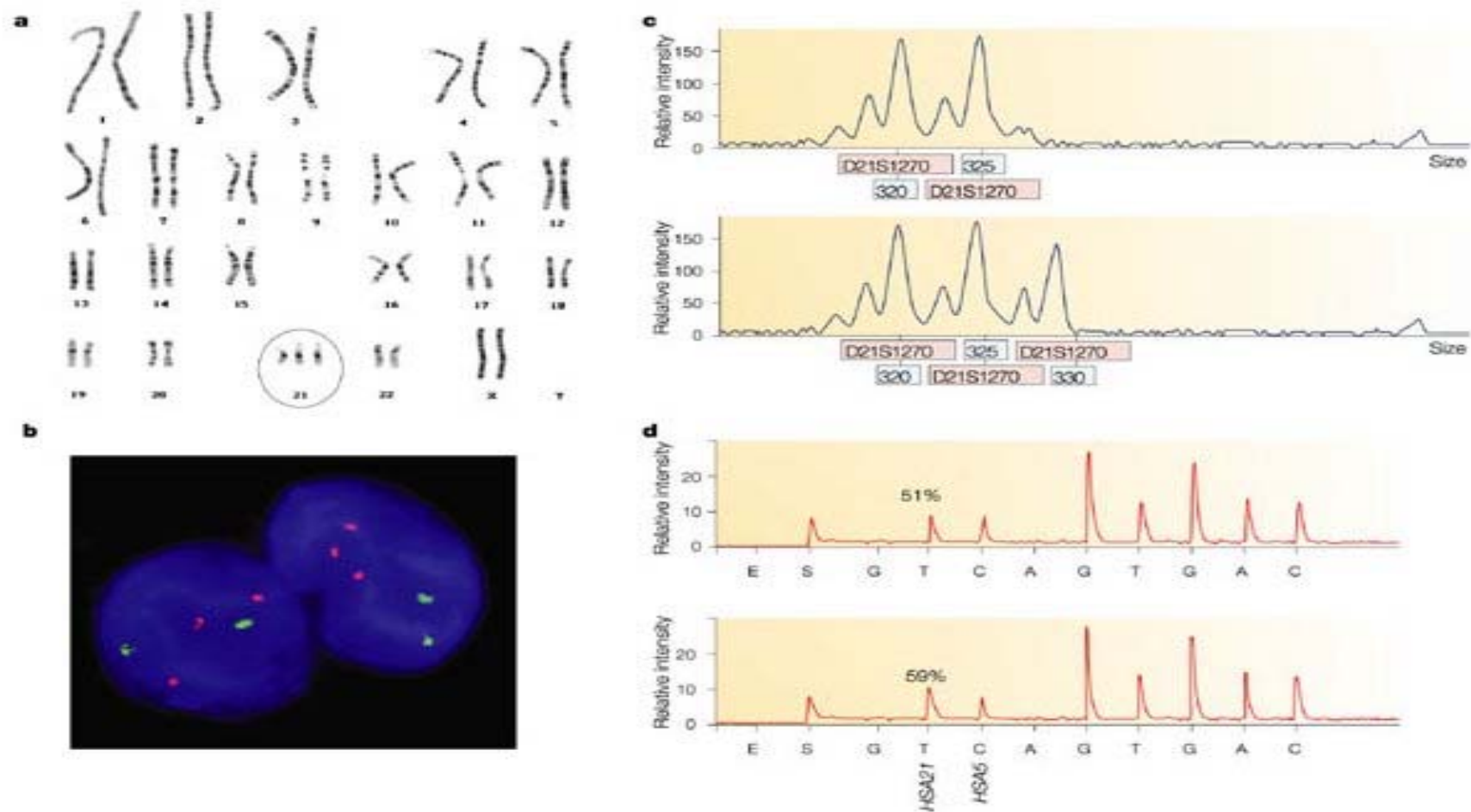
Chromosome painting with specific probes (1990s) (from MetaSystems)

This methodology is based on in situ hybridization of probes to metaphase chromosomes; different probes can be conjugated to different fluorescent chromophores;

Whole chromosomes, individual bands of a specific chromosome, or even single genes can be detected.

La sindrome di Down (trisomia 21)

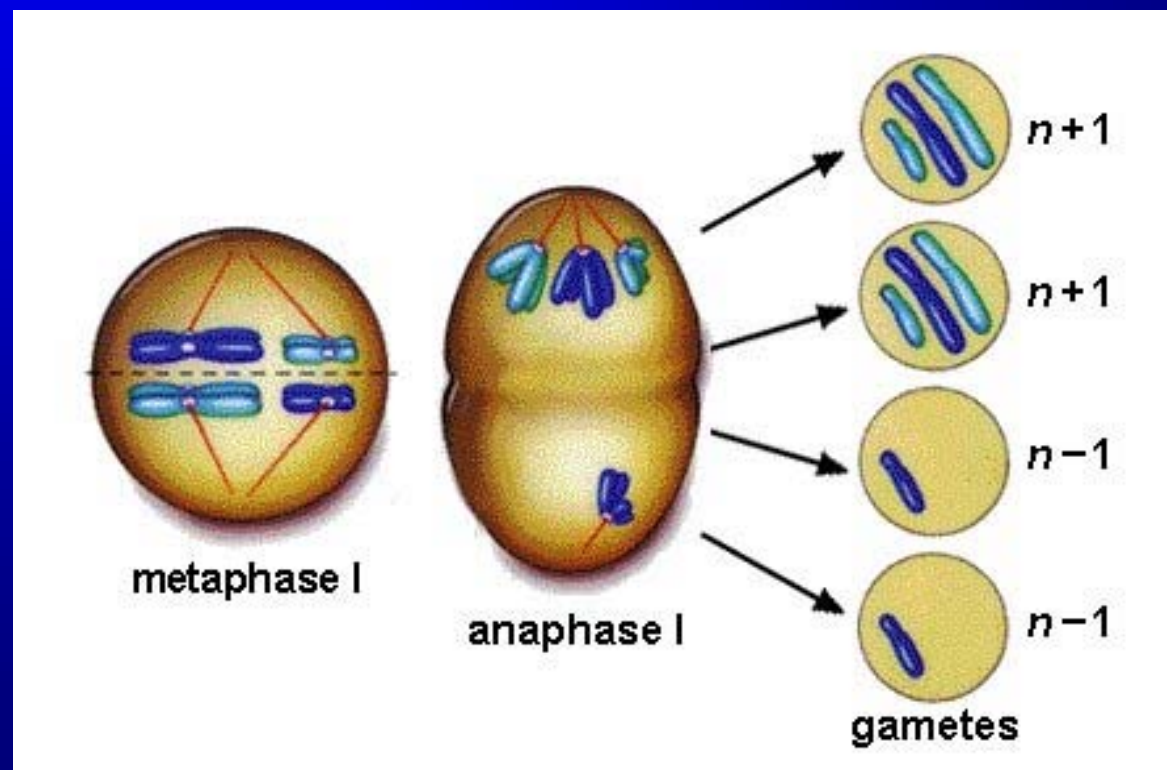


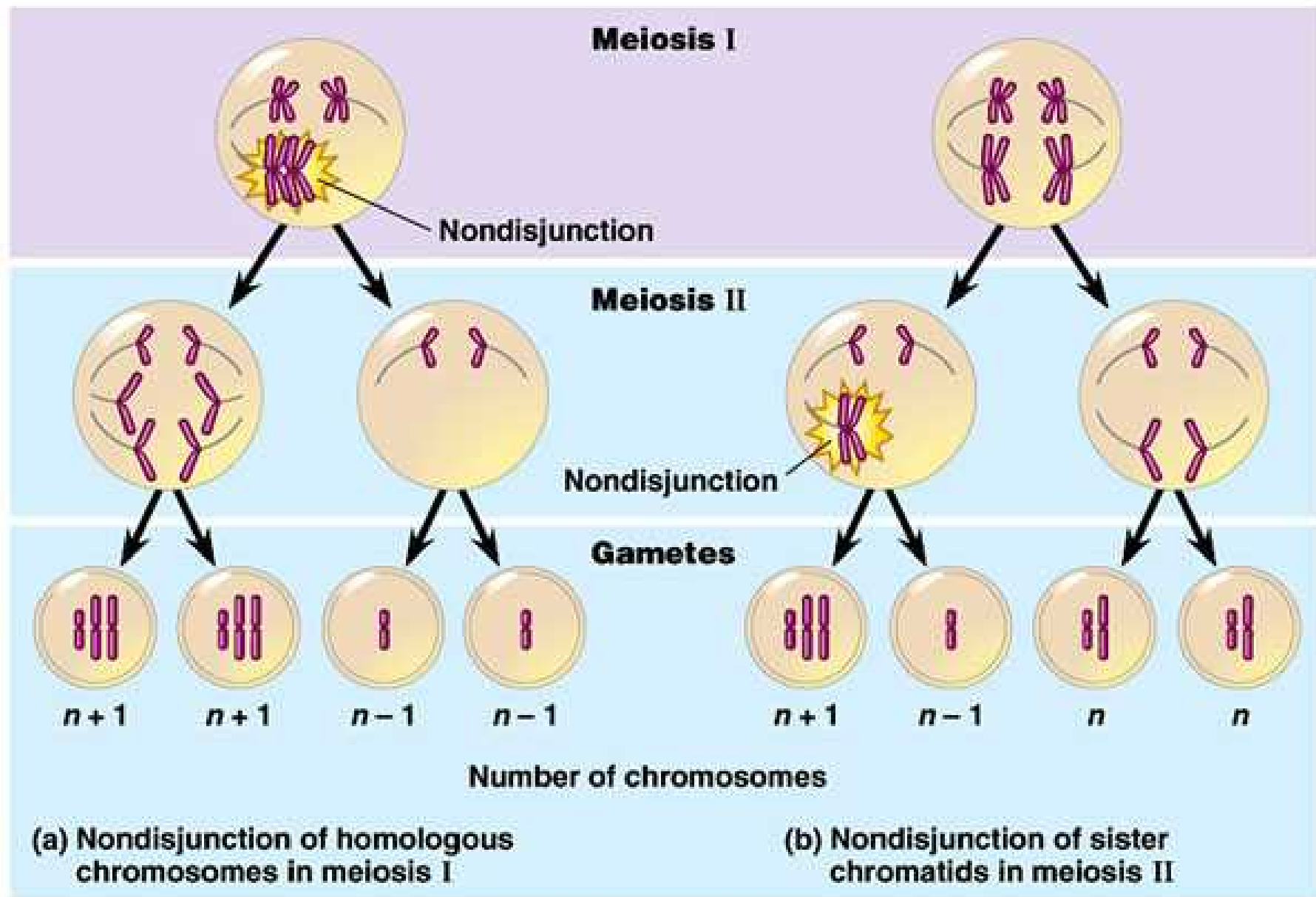


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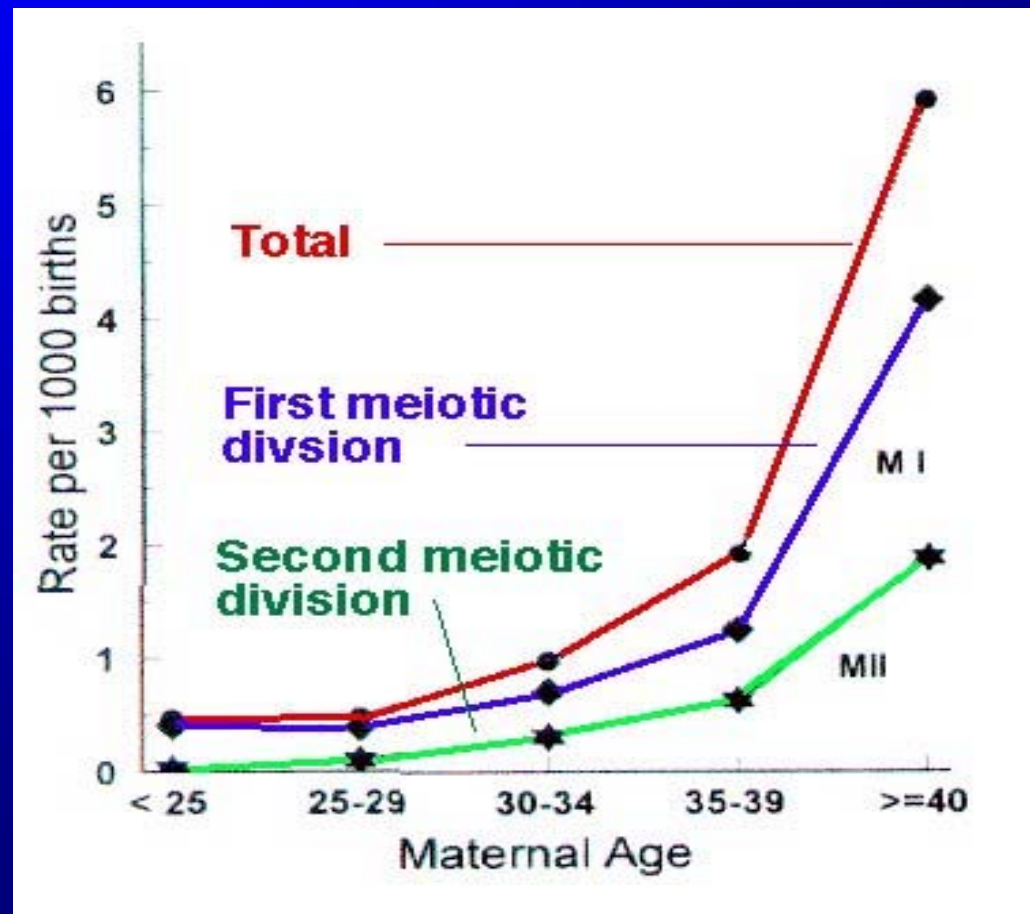
Figure 4 | Trisomy 21 diagnostic methods: old and new. **a** | G-banded karyotype of a trisomy 21 female, showing three copies of human chromosome 21 (HSA21). **b** | Fluorescent *in situ* hybridization (FISH) of interphase nuclei of a trisomy 21 fetus. In each cell there are two green spots (LSI 13 SpectrumGreen probe, Vysis) and three red spots (LSI 21 SpectrumOrange probe, Vysis) marking the 13q14 and 21q22.13-q22-2 chromosomal regions, respectively. **c** | Quantitative fluorescence PCR (QF-PCR) of marker D21S1270 of a trisomy 21 proband (bottom line) and his mother (top line). There are three different alleles in the

**La causa piu' frequente della trisomia 21
è una NON DISGIUNZIONE
dei due cromosomi 21
durante la prima divisione meiotica**

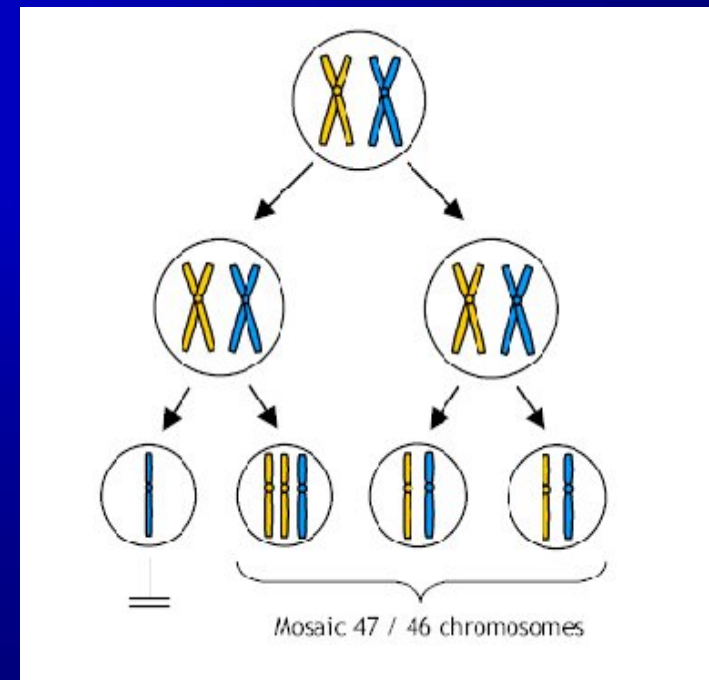
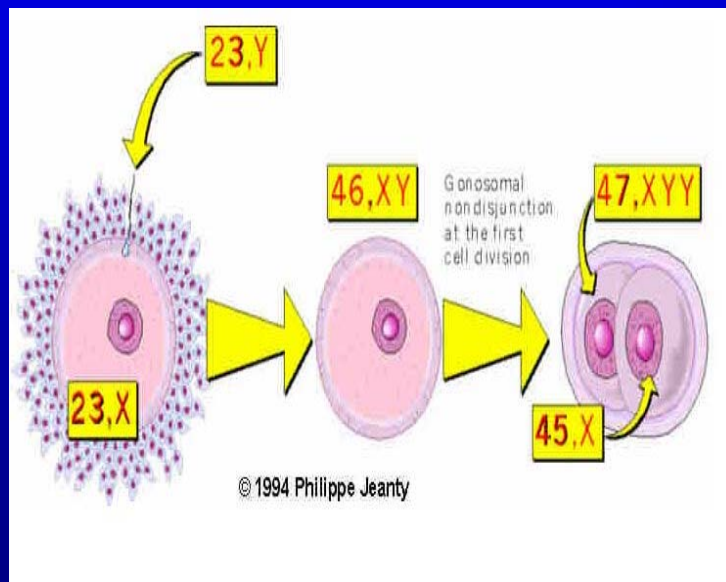




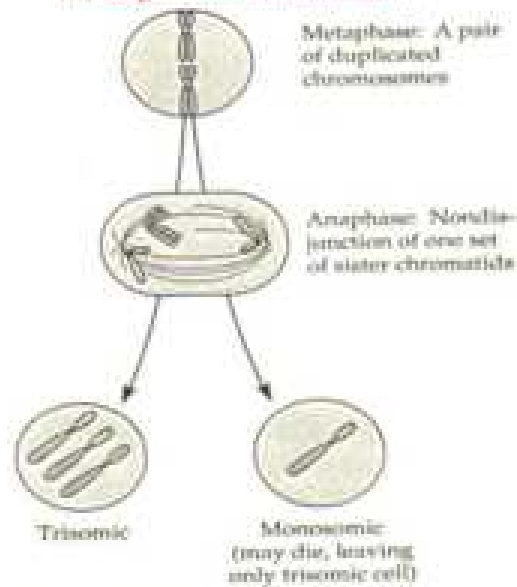
Esiste un'importante correlazione positiva fra età della madre (ma non del padre) e probabilità di avere un figlio affetto da sindrome di Down → il fenomeno della non disgiunzione meiotica si verifica più frequentemente durante la gametogenesi femminile.



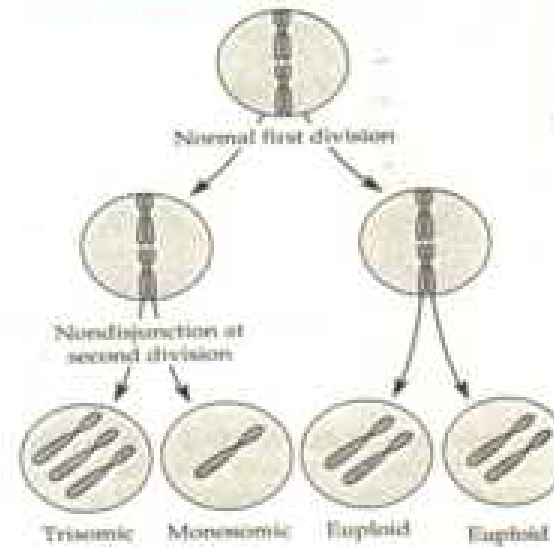
La non disgiunzione dei cromosomi 21 può anche verificarsi durante la divisione mitotica. Se questo avviene durante le prime divisioni cellulari dello zigote si può avere la formazione di un individuo con **MOSAICISMO** cromosomico.



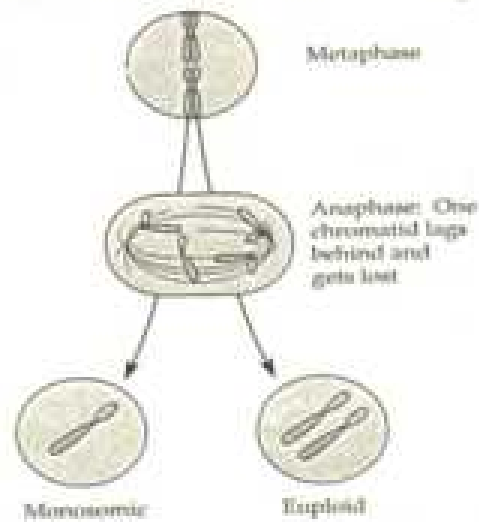
- (A) Mitotic nondisjunction during the first cleavage division of a zygote.
All daughter cells are unbalanced.



- (B) Mitotic nondisjunction during the second cleavage division. If the monosomic cell dies, the normal and trisomic lines remain.



- (C) Chromosome loss as euploid cell divides.



- (D) Chromosome loss as trisomic cell divides.

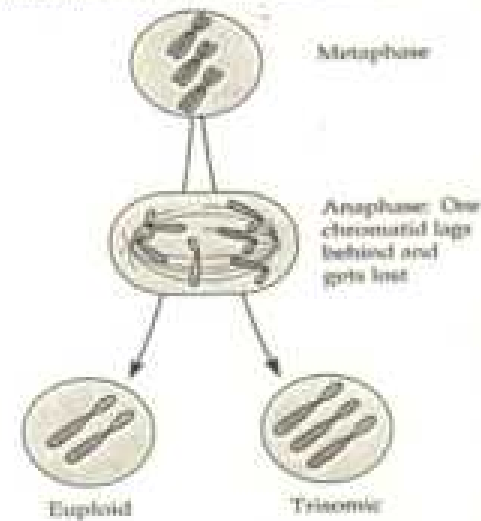
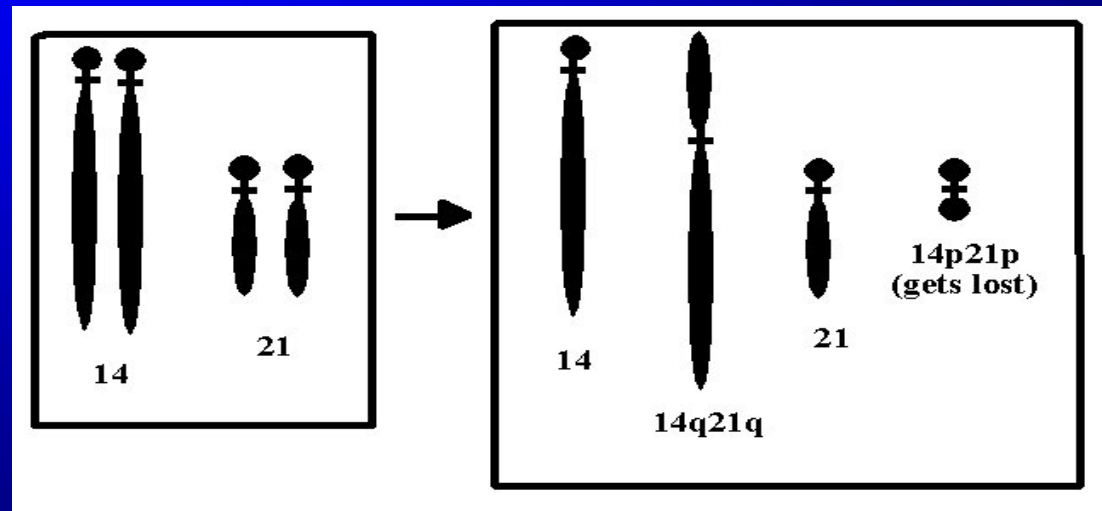
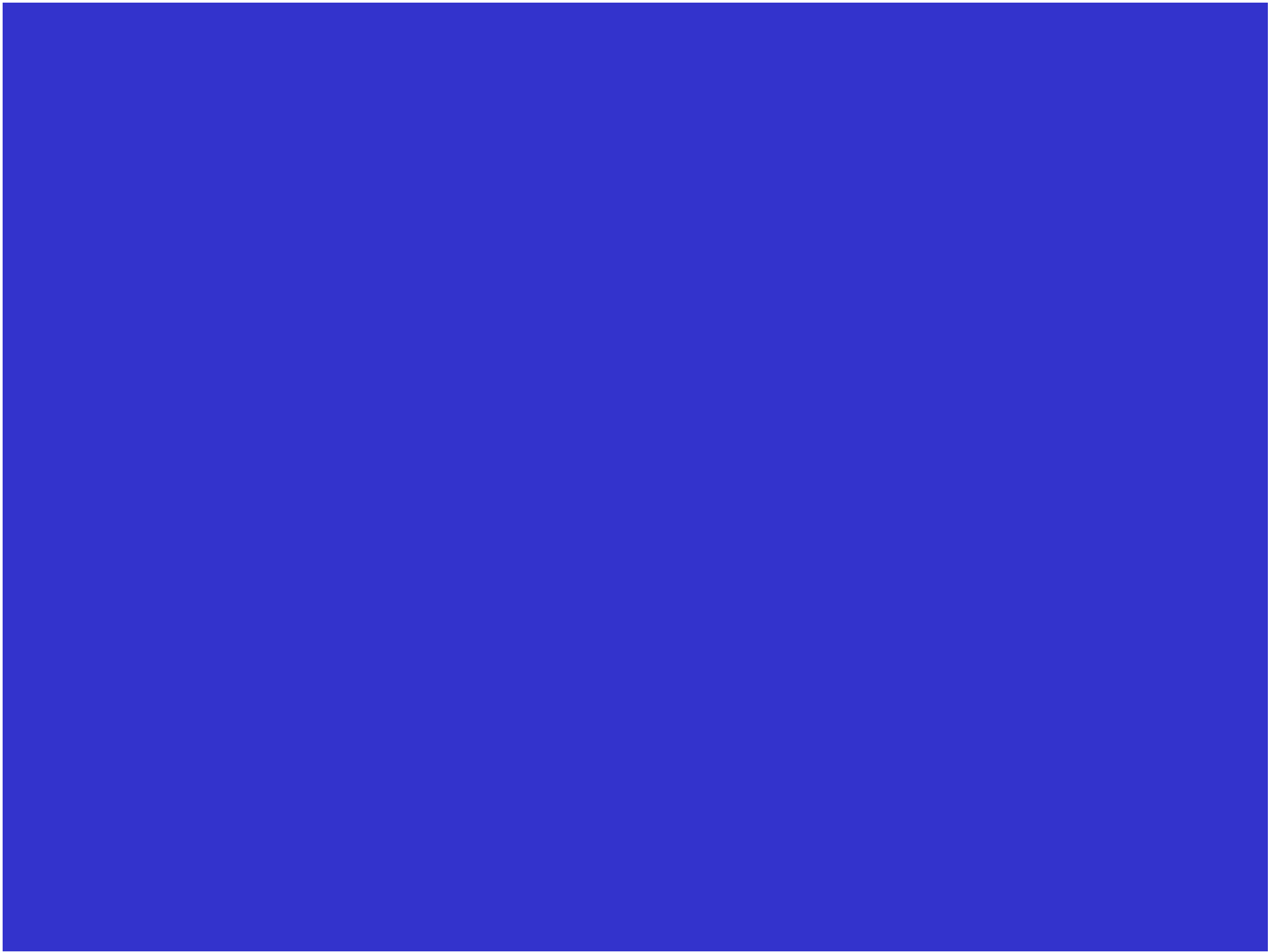


Figure 10.3
How monicism arises from mitotic nondisjunction (A and B) or from chromosome loss (C and D).

La sindrome di Down può anche essere il risultato di una **traslocazione** fra il cromosoma 21 e il cromosoma 14.

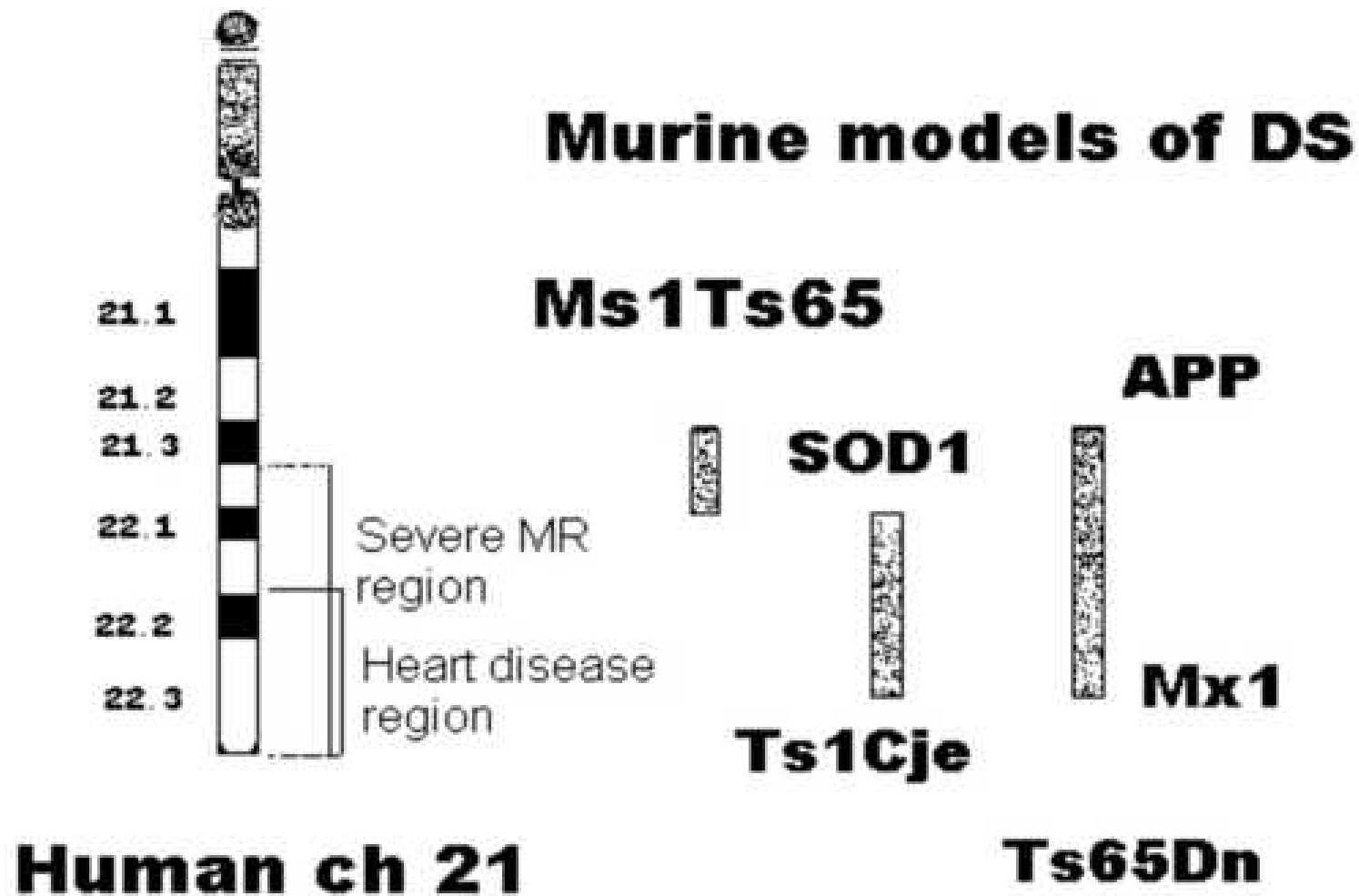


Robertsonian translocations involve two acrocentric chromosomes that fuse near the centromere region with loss of the short arms. The resulting karyotype has only 45 chromosomes since two chromosomes have fused together. The most common translocation involving chromosomes 13 and 14 is seen in about 1 in 1300 persons, making it the most common chromosome rearrangement in humans. Like most other translocations, carriers of Robertsonian translocations are phenotypically normal.



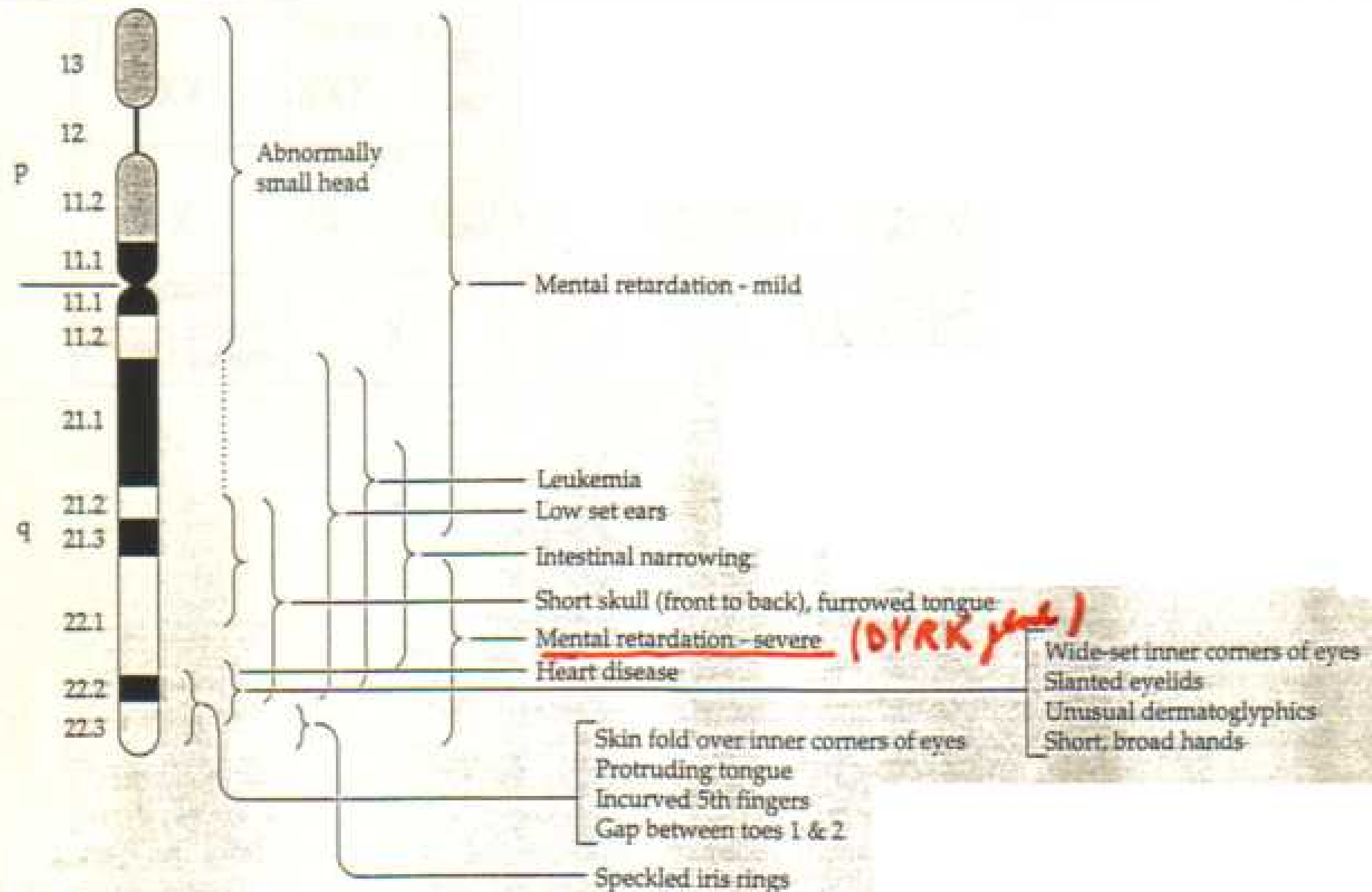
QUADRO CLINICO SINDROME DI DOWN

- Ritardo mentale
- Bassa statura
- Faccia appiattita; pliche palpebrali; orecchie malformate; macroglossia; denti irregolari
- Mani e piedi tozzi, con peculiari impronte palmari e dermatoglifi e anomalo spazio tra alluce e secondo dito
- Malformazioni cardiache; stenosi intestinale; ipotonia muscolare
- Sterilità
- Rischio sviluppo leucemia



BOX A

A PRELIMINARY PHENOTYPIC MAP OF CHROMOSOME 21

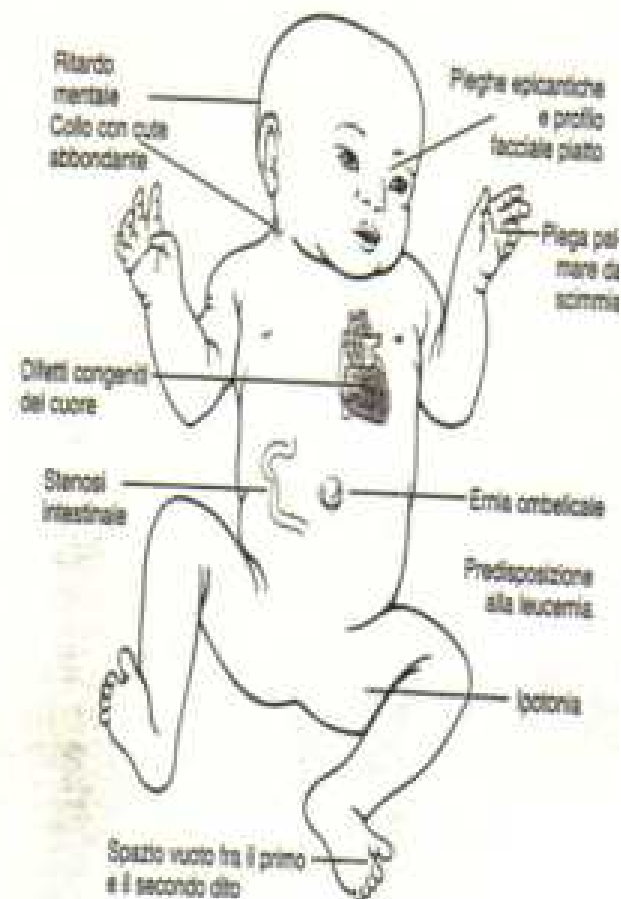


TRISOMIA 21: SINDROME DI DOWN

Incidenza: 1 su 700 nati

Cariotipi:

Trisomia 21:	47,XX, +21
Traslocazione:	46,XX,der(14;21)(q10;q10),+21
Mosaicismo:	46,XX/47,XX, +21

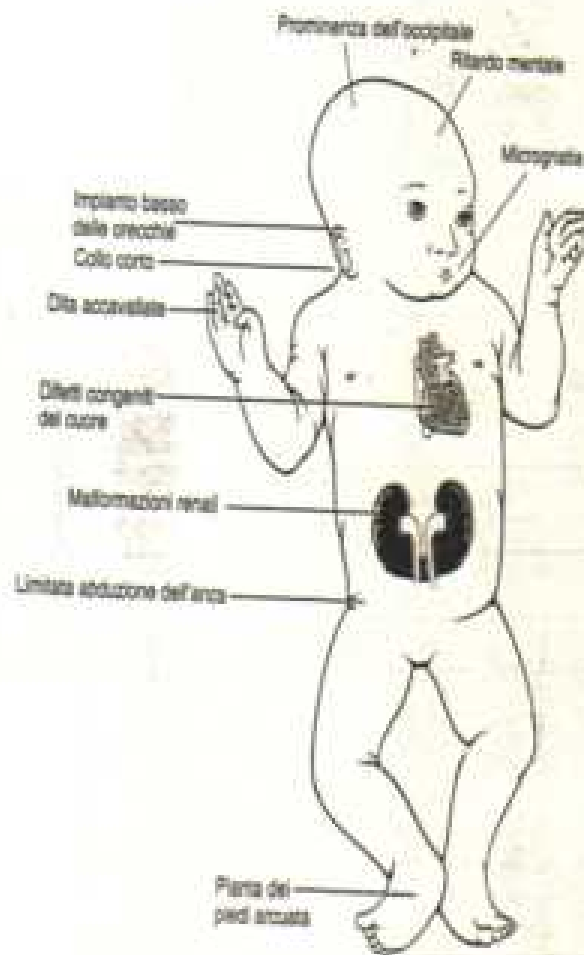


TRISOMIA 18: SINDROME DI EDWARDS

Incidenza: 1 su 8000 nati

Cariotipi:

Trisomia 18:	47,XX, +18
Mosaicismo:	46,XX/47,XX, +18

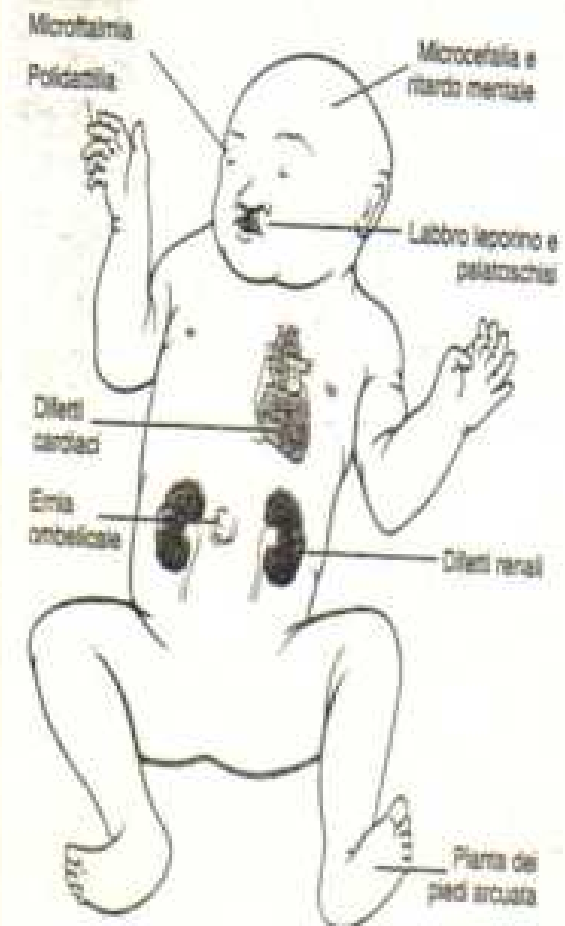


TRISOMIA 13: SINDROME DI PATAU

Incidenza: 1 su 15.000 nati

Cariotipi:

Trisomia 13:	47,XX, +13
Traslocazione:	46,XX,+13,der(13;14)(q10;q10)
Mosaicismo:	46,XX/47,XX, +13



MALATTIE CITOGENETICHE DA ALTERAZIONI DEI CROMOSOMI SESSUALI

Sono **molto più frequenti** di quelle dovute ad alterazioni degli autosomi (= sono più tollerate)

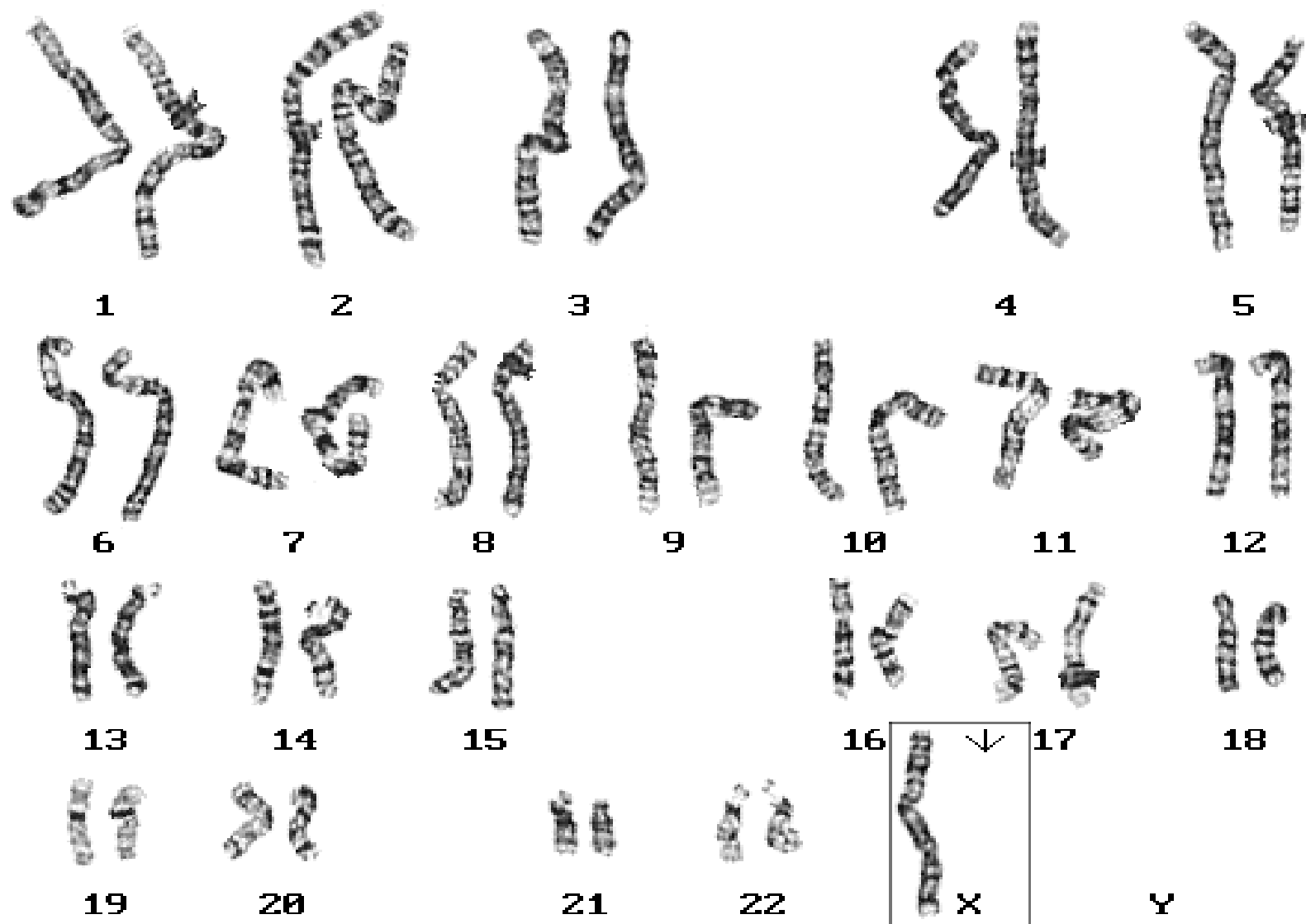
Motivi:

- Inattivazione di tutti i cromosomi X tranne uno (ipotesi di M. Lyon) [cromosoma X inattivato → **corpo di Barr**]
- Piccola quantità di materiale genetico sul cromosoma Y

Caratteristiche generali:

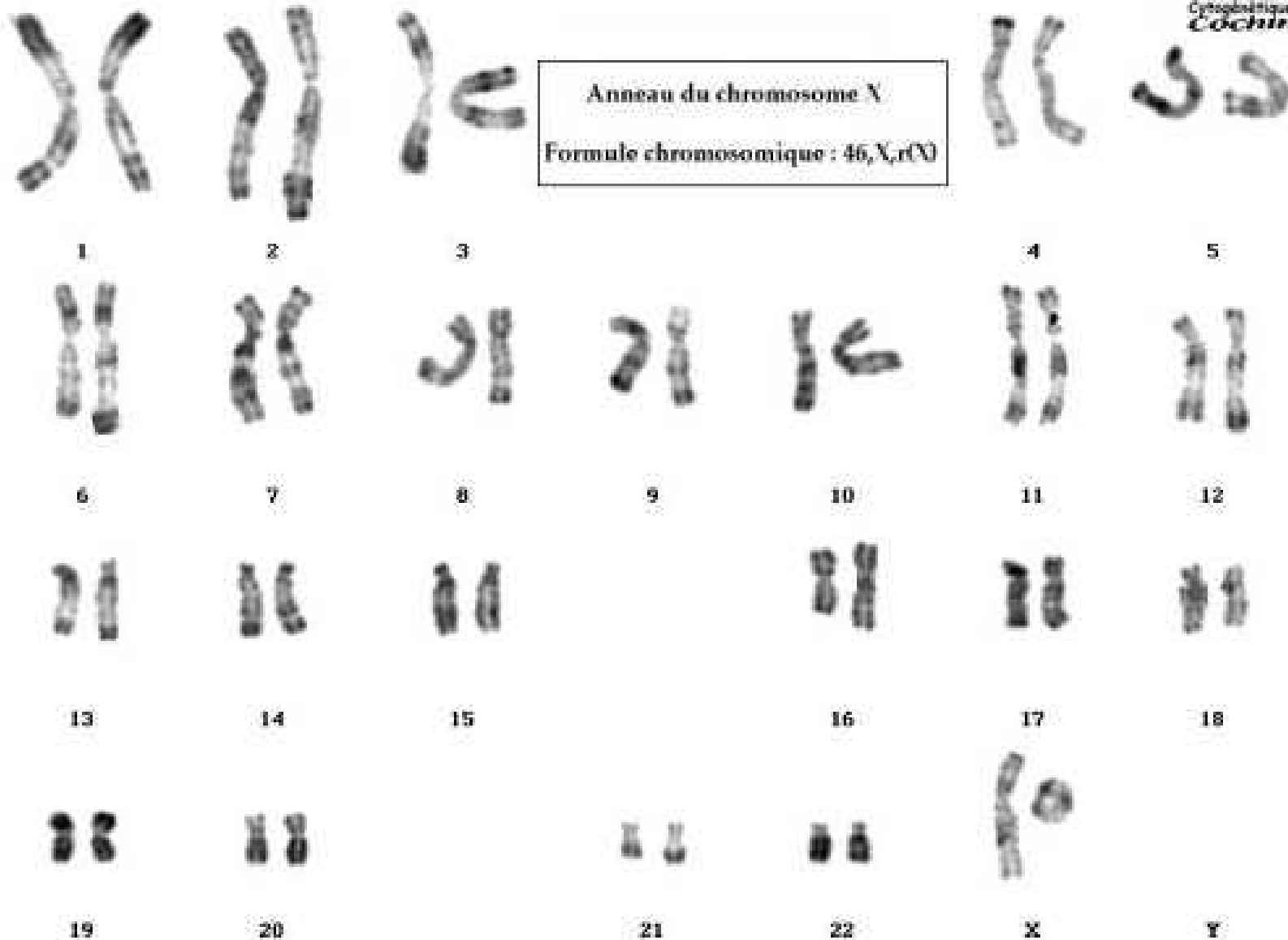
- IN GENERALE CAUSANO PROBLEMI LIEVI E CRONICI CORRELATI CON LO SVILUPPO SESSUALE E LA FERTILITA'
- SPESSO E' MOLTO DIFFICILE FARE UNA DIAGNOSI ALLA NASCITA, IN MOLTI CASI E' POSSIBILE SOLO AL MOMENTO DELLA PUBERTA'
- IN GENERALE, SIA NEI MASCHI CHE NELLE FEMMINE, PIU' ALTO E' IL NUMERO DELLE X MAGGIORE E' LA PROBABILITA' CHE SI ABBAIA RITARDO MENTALE

SINDROME DI TURNER (45, X0)

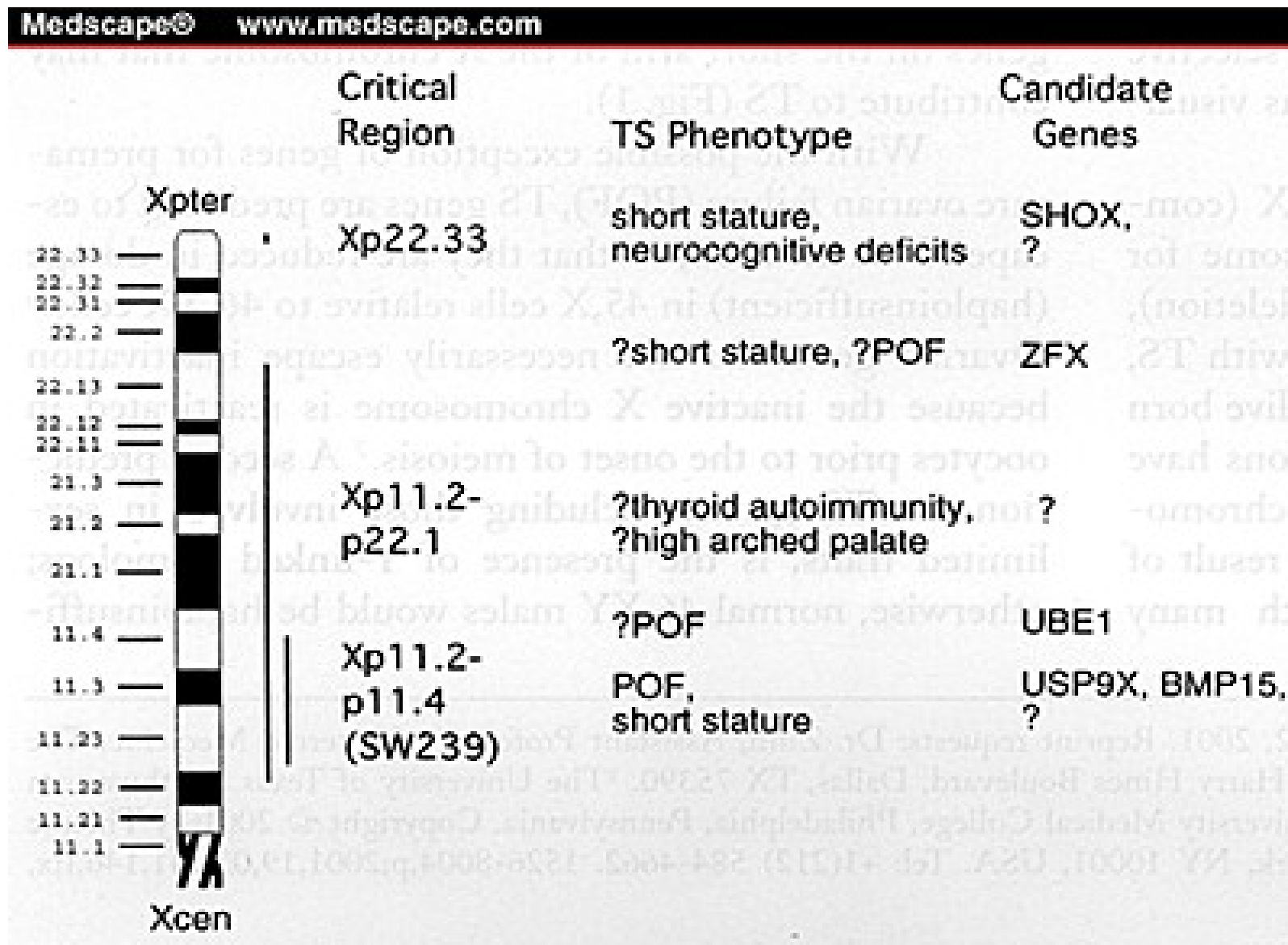


Karyotype: 45,X

Sindrome di Turner con cromosoma X ad anello: 46, X, r(X)

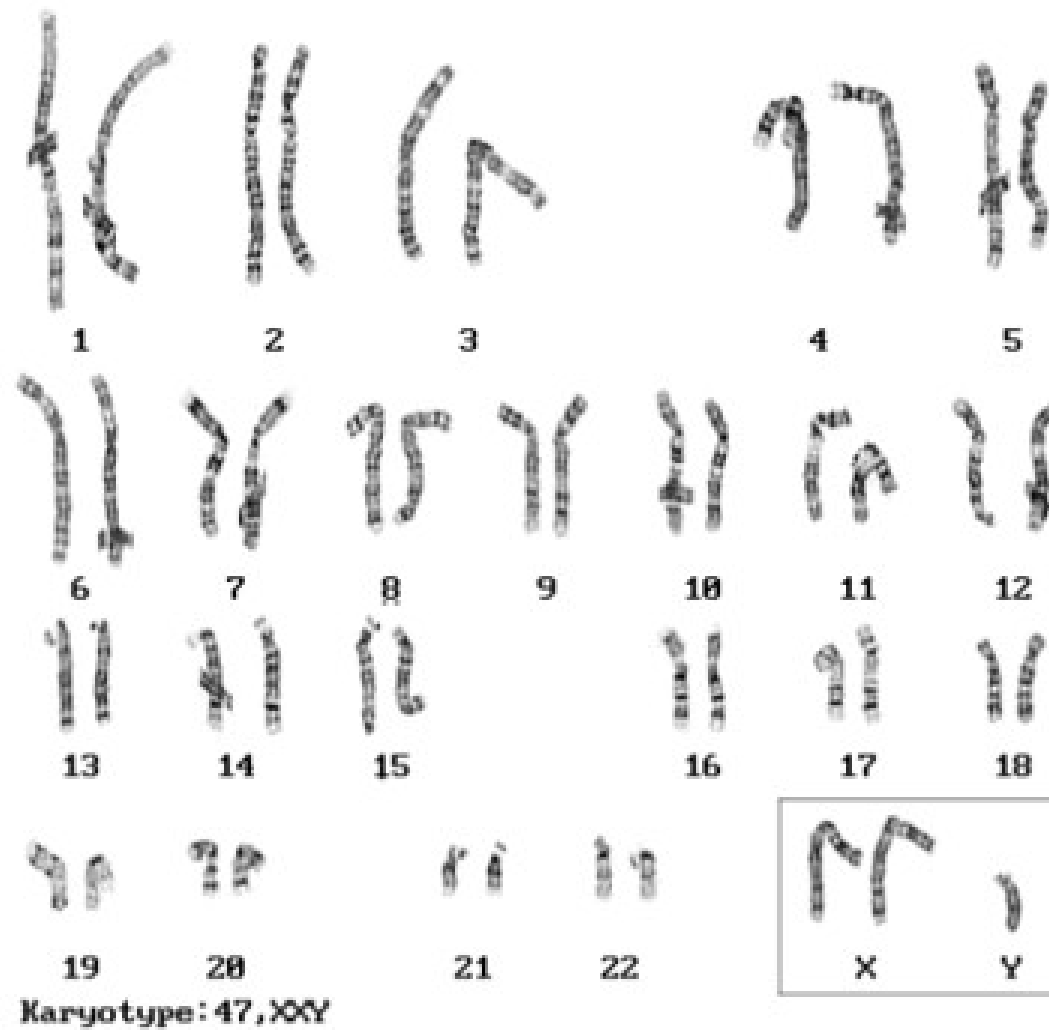


Supposte correlazioni tra Xp e fenotipo nella sindrome di Turner (TS)



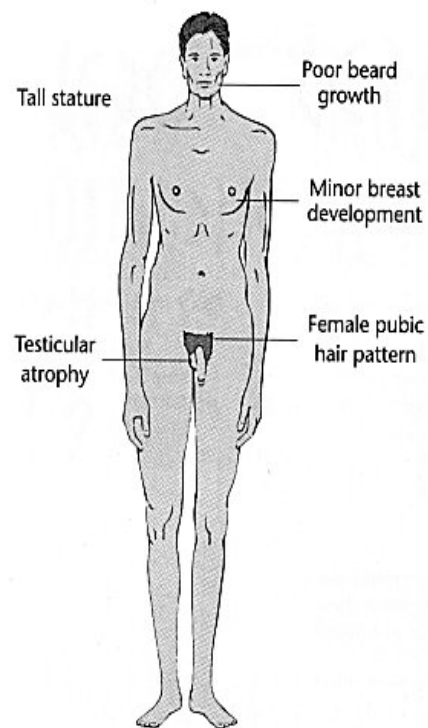
POF = premature ovarian failure

SINDROME DI KLINEFELTER (47, XXY)

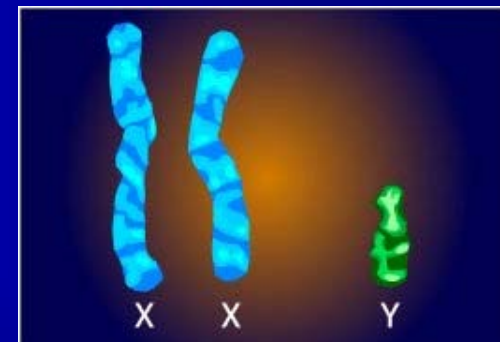
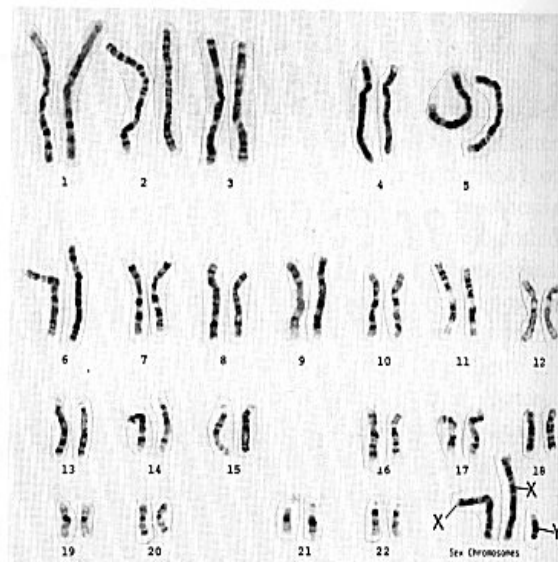


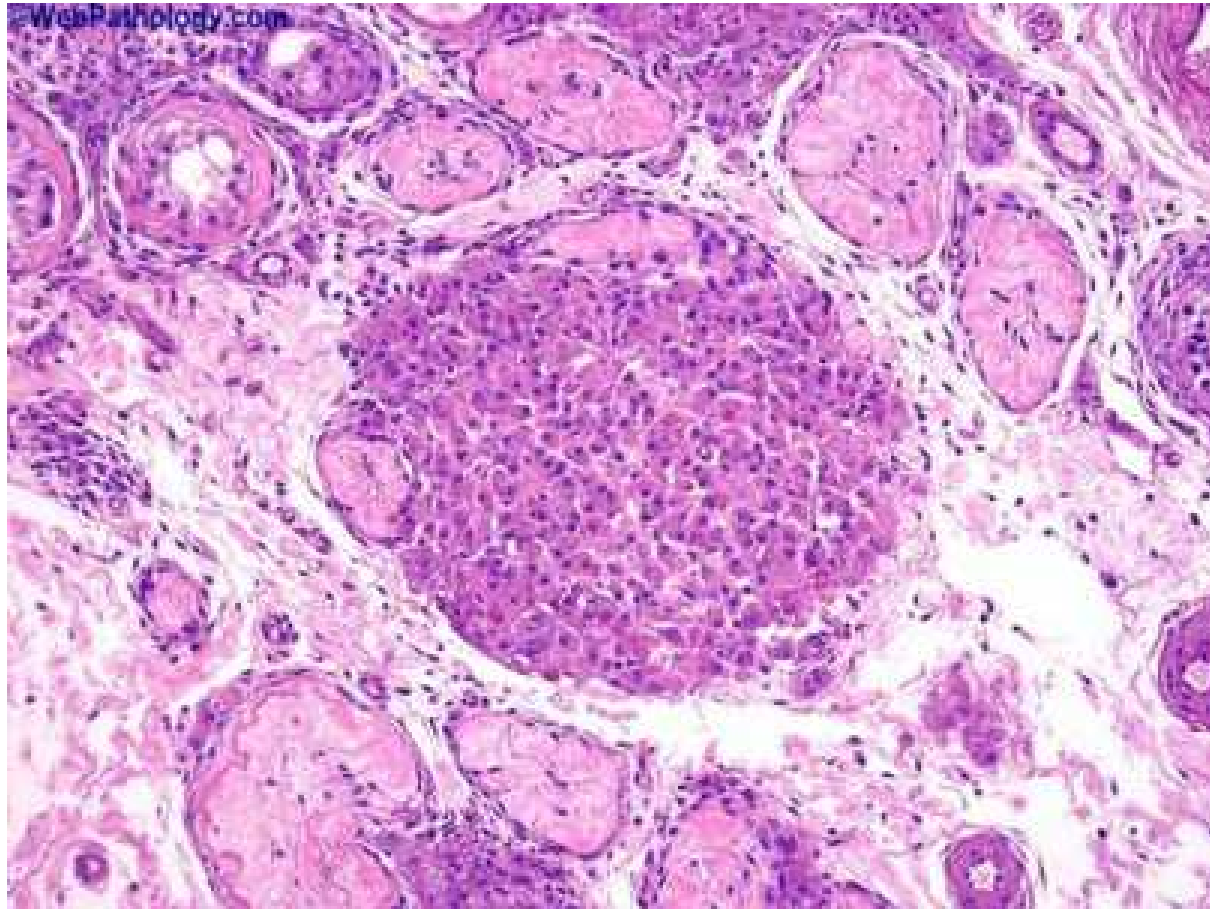
LA SINDROME DI KLINEFELTER

(47, XXY)



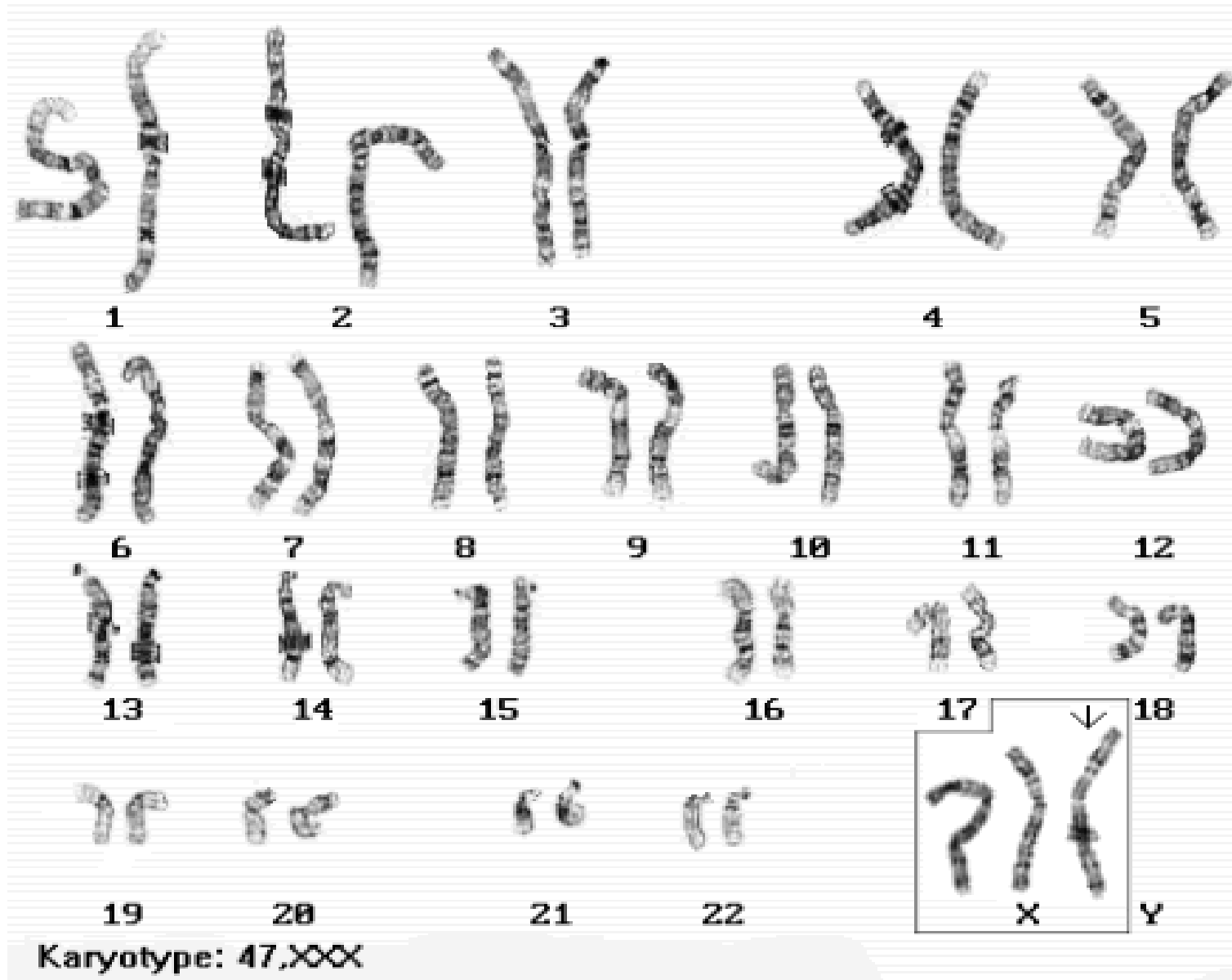
(a) Klinefelter Syndrome (47,XXY)





Testicular biopsy from an adult male with body habitus suggestive of Klinefelter's syndrome. The biopsy shows small hyalinized seminiferous tubules and pseudo-adenomatous clusters of Leydig cells.

TRISOMIA X (47, XXX)



ABERRAZIONI CROMOSOMICHE

Si possono distinguere due tipi principali di aberrazioni cromosomiche:

- Variazioni del numero dei cromosomi → **ANEUPLOIDIE**

- **ALTERAZIONI STRUTTURALI**

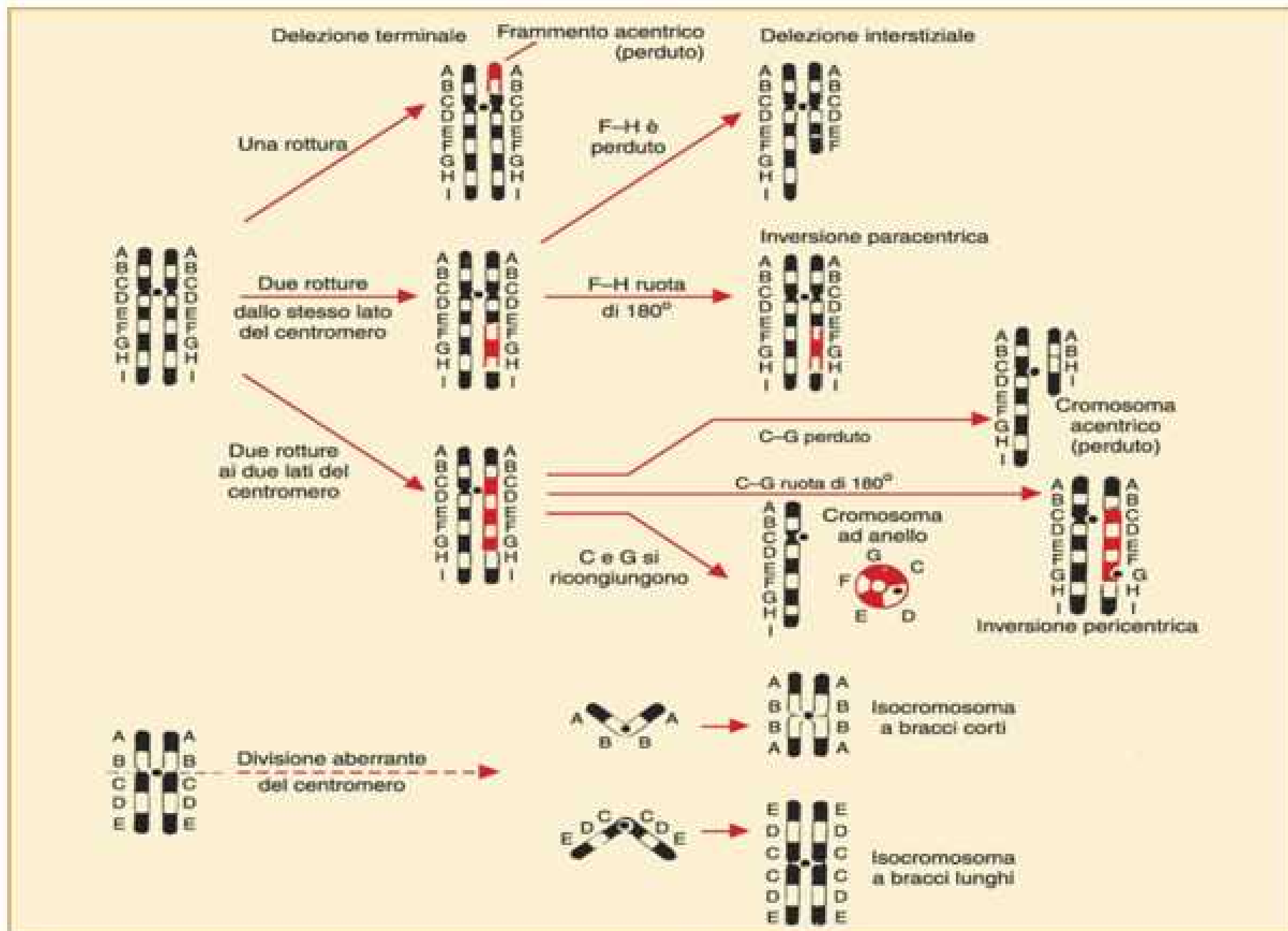
- a) **Delezione** → perdita di una parte del cromosoma osservabile all'esame microscopico

- b) **Duplicazione** → ripetizione di una parte del cromosoma nel suo stesso contesto

- c) **Inversione** → il frammento centrale risultante da due rotture di un cromosoma ruota di 180° e si inserisce tra gli altri due frammenti ricostituendo l'integrità morfologica di esso ma con sequenza genica modificata

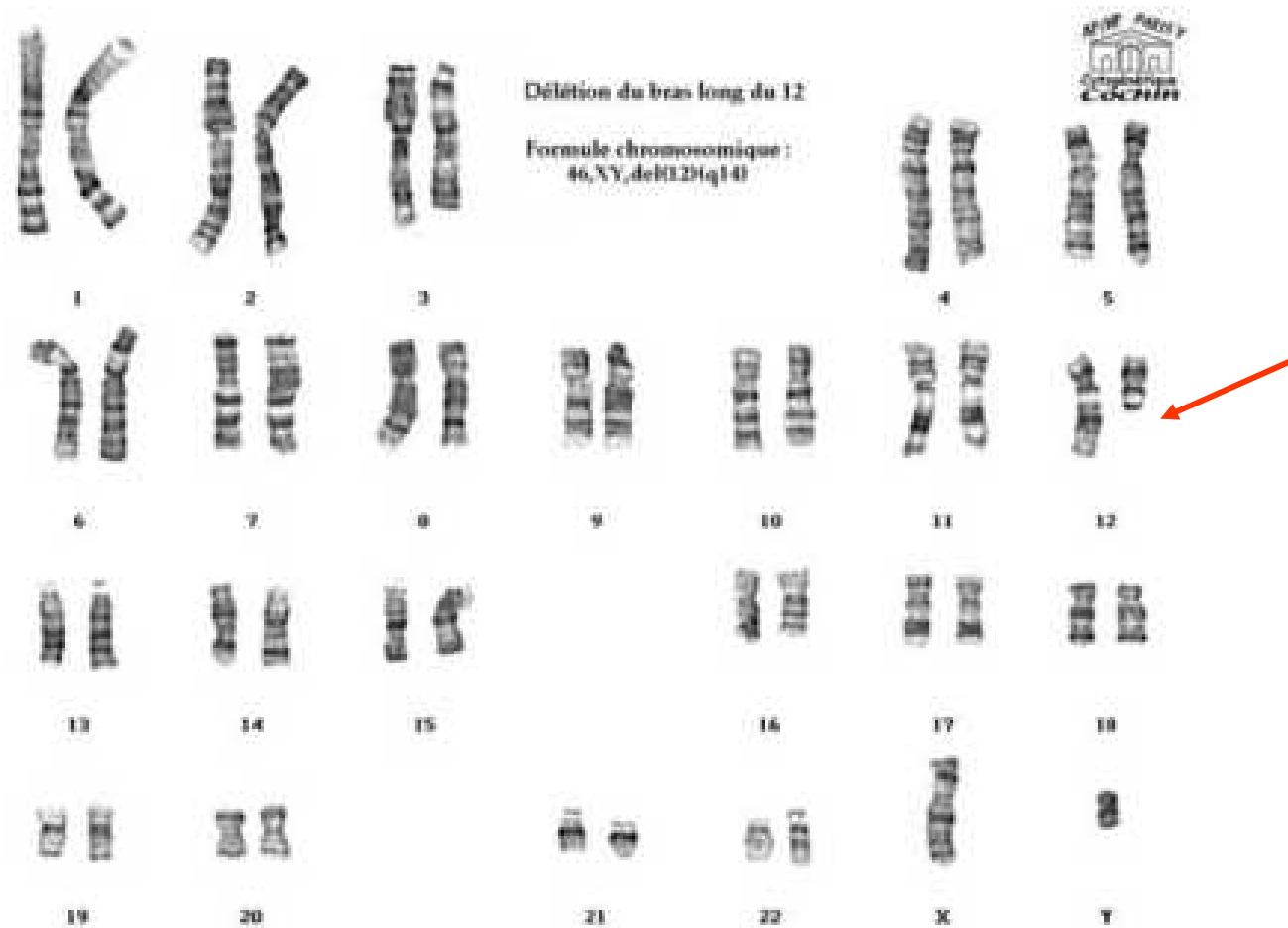
- d) **Traslocazione** → inserimento su di un cromosoma diverso di un pezzo di un cromosoma staccatosi dal cromosoma di appartenenza (t. semplice) o scambio fra due cromosomi non omologhi di frammenti cromosomici formati per rottura (t. doppia)

POLIPLOIDIA → numero di cromosomi multiplo di quello normale

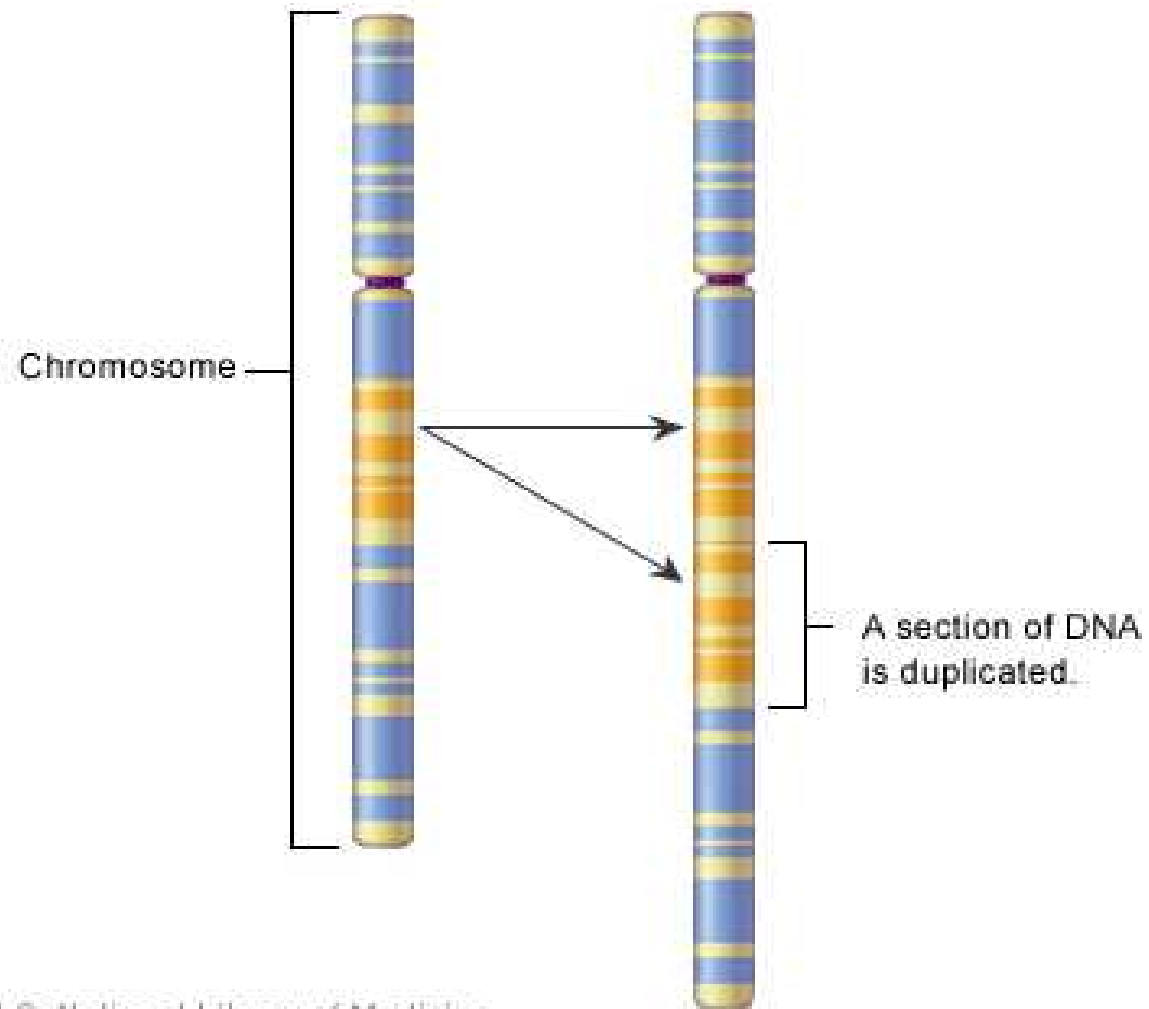


■ Figura 3.4 - Schema delle più comuni alterazioni strutturali dei cromosomi.

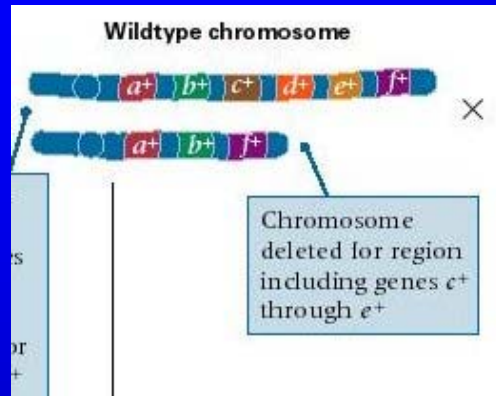
DELEZIONE BRACCIO LUNGO CR. 12



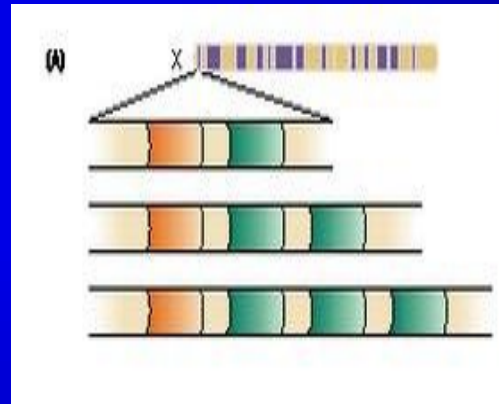
Duplication mutation



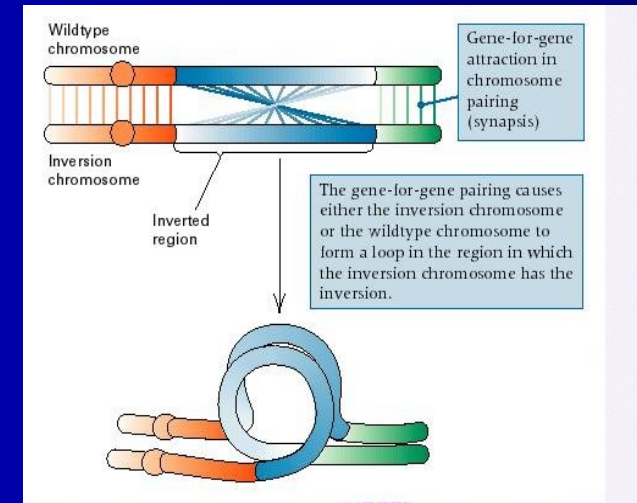
ALTERAZIONI STRUTTURALI



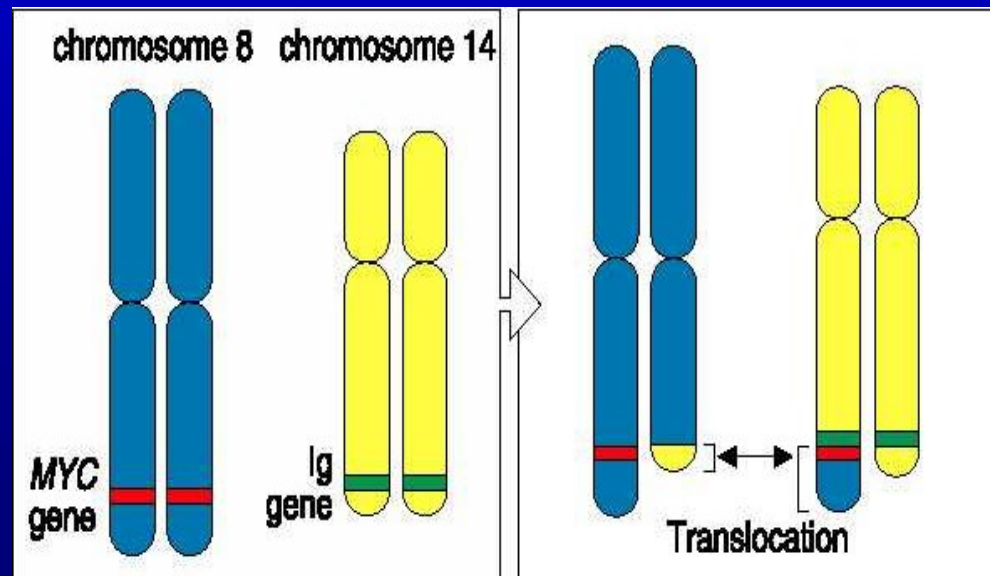
DELEZIONE



DUPLICAZIONE



INVERSIONE



TRASLOCAZIONE