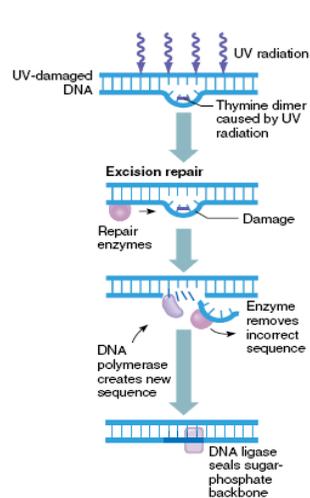


# Mutaciones Cromosómicas

Katherine Marcelain  
Tecnología Médica-2009

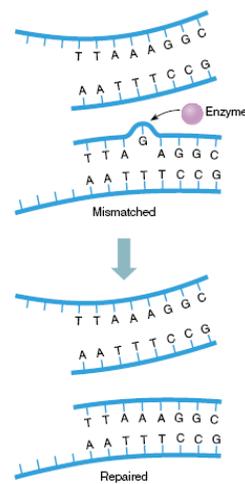
## MECANISMOS DE REPARACIÓN DEL DNA

- a. Reparación de Fracturas de Doble Hebra del DNA
- b. Reparación por Escisión de Bases (BER)
- c. Reparación por Escisión de Nucleótidos (NER)
- d. Reparación de Bases Mal Apareadas (MMR)



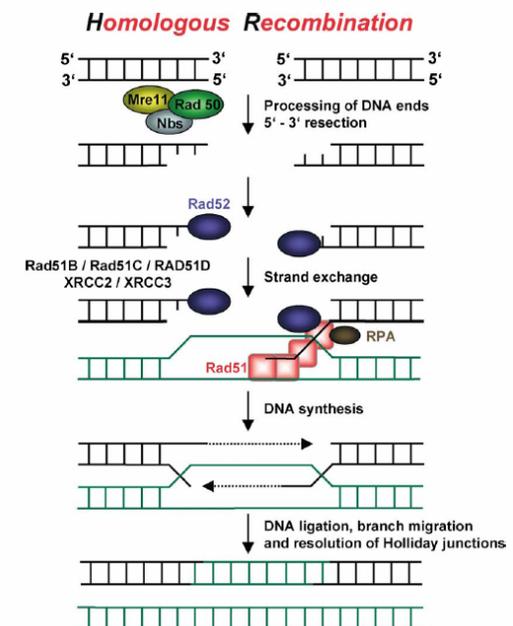
**figure 11.13**

**Excision repair.** Human DNA damaged by UV light is repaired by excision repair, in which the pyrimidine dimer and a few surrounding bases are removed and replaced.



**figure 11.14**

**Mismatch repair.** In this form of DNA repair, enzymes detect loops and bulges in newly replicated DNA that indicates mispairing. The enzymes correct the error. Highly repeated sequences are more prone to this type of error.



### Non Homologous End Joining

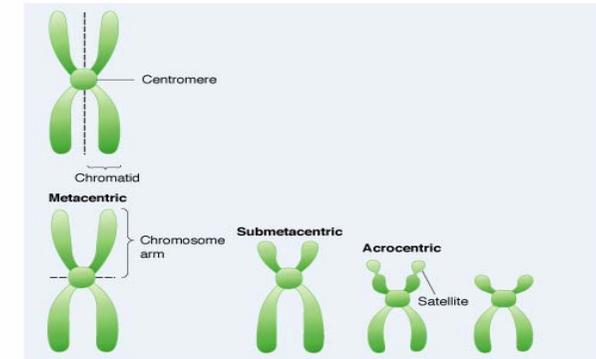
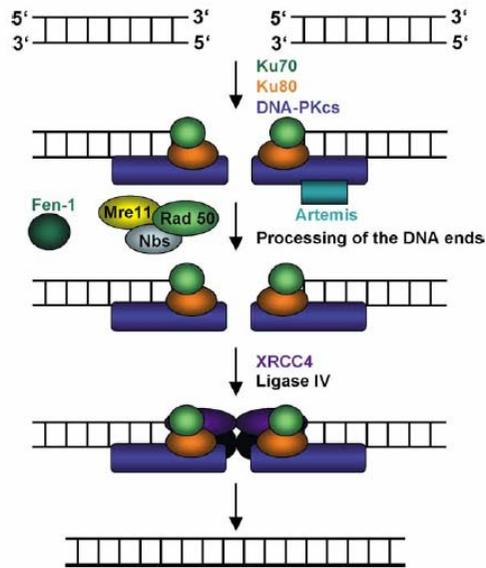
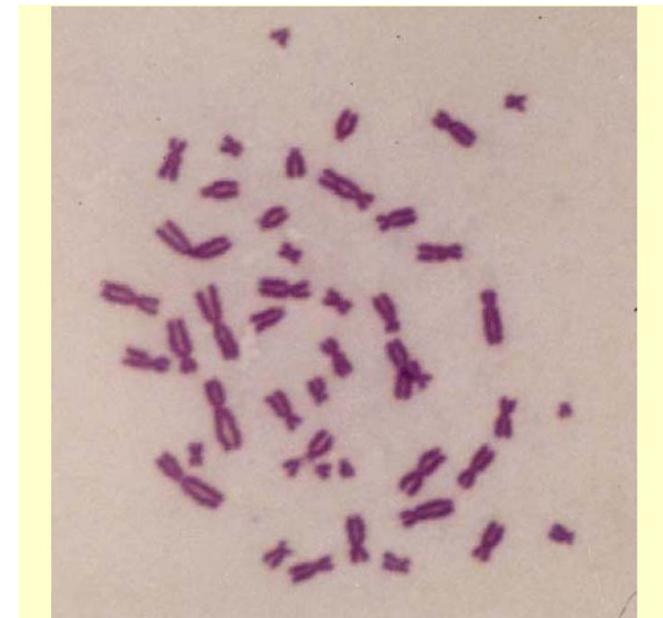


Figure 6-11 Three basic shapes and the component parts of human metaphase chromosomes. The relative size of the satellite on the acrocentric is exaggerated for visibility. (Adapted from Cormack D.H. [1993]. *Essential histology*. Philadelphia: J.B. Lippincott)

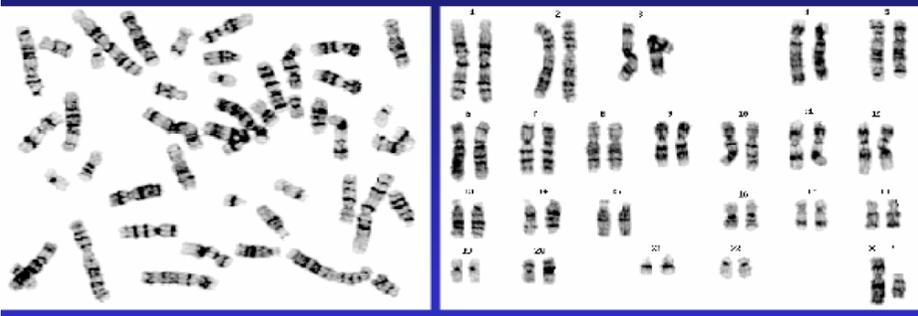
Copyright © 2005 Lippincott Williams & Wilkins. Instructor's Resource CD-ROM to Accompany *Porth's Pathophysiology: Concepts of Altered Health States*, Seventh Edition.

TABLA 1.- CLASIFICACIÓN DE LOS CROMOSOMAS HUMANOS

Grupo Cromosómico	Pares de cromosomas	Descripción de los cromosomas
A	1-3	Metacéntricos grandes
B	4-5	Submetacéntricos grandes
C	6-12 + X	Submetacéntricos medianos
D	13-15	Subtelocéntricos grandes con NOR y satélites.
E	16-18	Metacéntrico (16) y submetacéntricos (17-18) mas bien pequeños.
F	19-20	Metacéntricos pequeños.
G	21-22 + Y	Subtelocéntricos pequeños con NOR y satélites, exceptuando el cromosoma Y.



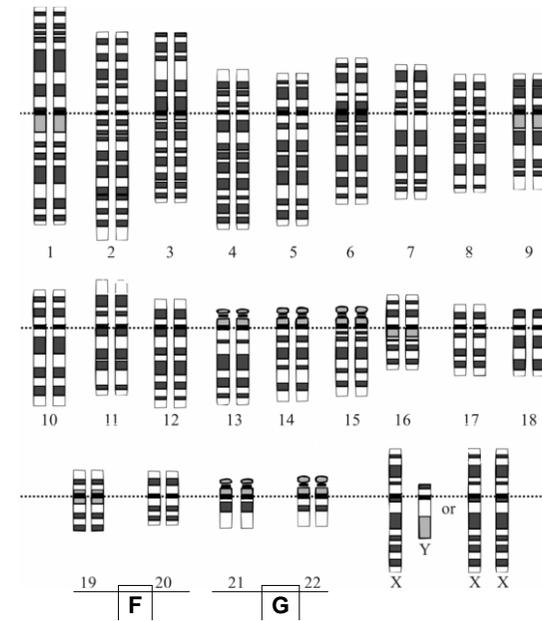
Placa metafásica humana teñida con Giemsa.



Placa metafásica y cariotipo humano con bandeo G.

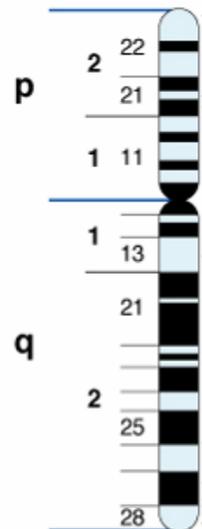
Los miembros de los pares de autosomas presentan igual morfología, tamaño y patrón de bandas G. Los cromosomas sexuales (X e Y), en cambio, difieren en todas estas características.

### Representación gráfica del cariotipo humano normal



### ISCN

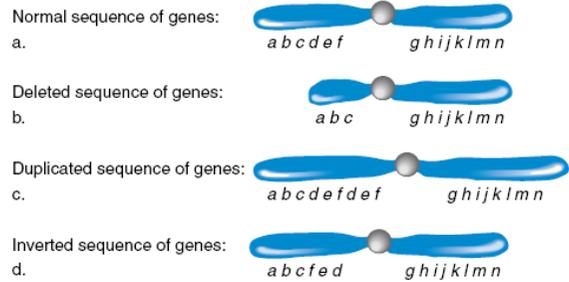
- International System for Human Cytogenetics Nomenclature
- Cariotipo Normal:
  - 46, XX
  - 46, XY



### Mutaciones cromosómicas Estructurales

- Con variación en el número de genes:
  - Deleciones-Duplicaciones
- Con variación en la disposición de los genes:
  - Inversiones, Translocaciones

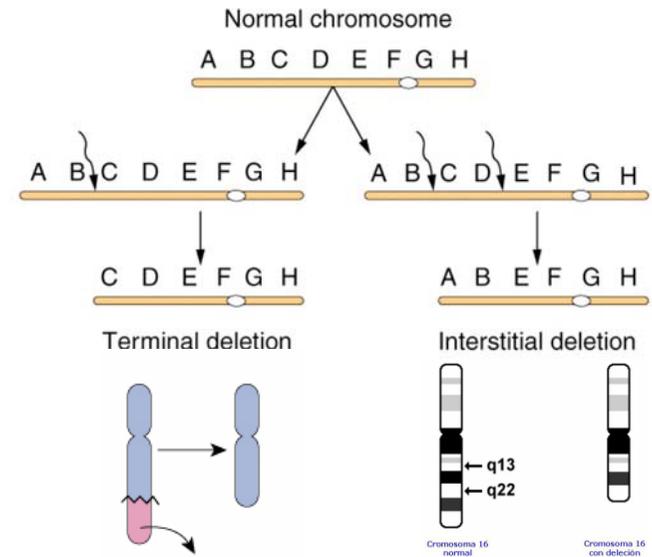
# Deleciones, duplicaciones e inversiones



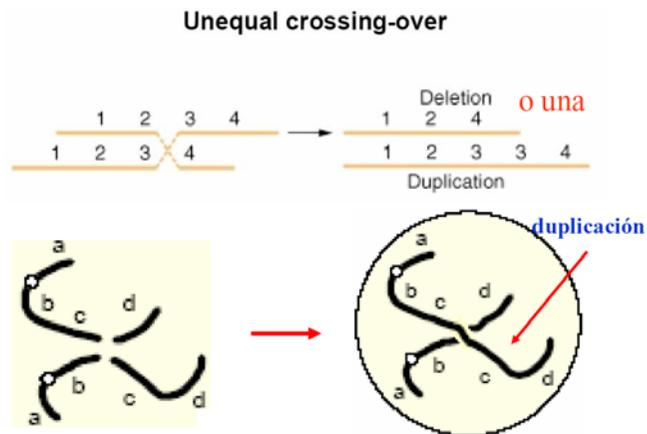
**figure 12.15**

**Chromosome abnormalities.** If a hypothetical normal gene sequence appears as shown in (a), then (b) represents a deletion, (c) a duplication, and (d) an inversion.

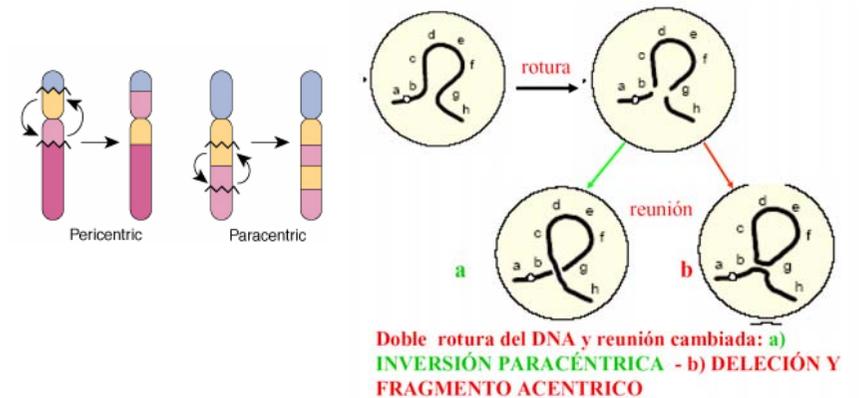
# Tipos de deleción



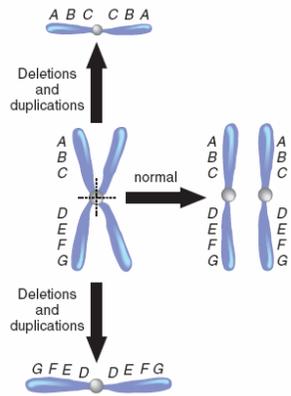
# Duplicación cromosómica



# Inversiones

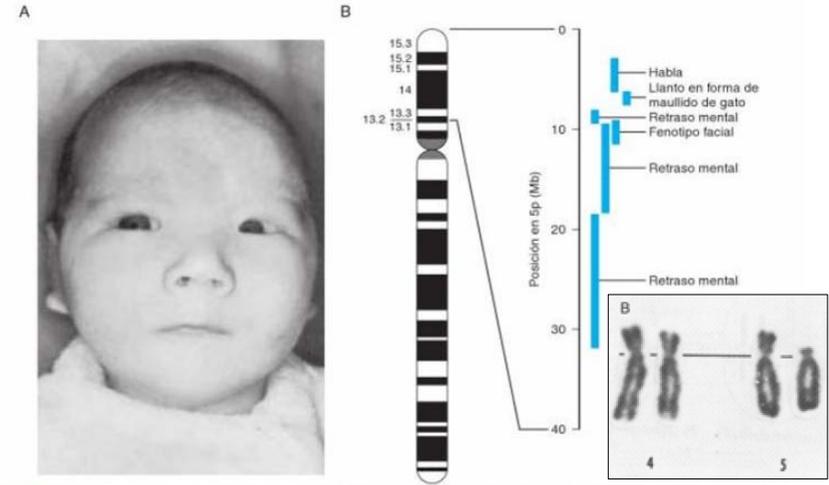


# Isocromosomas



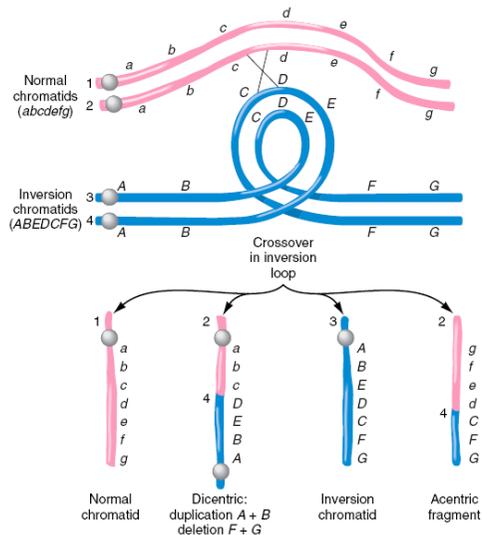
**figure 12.22**

**Isochromosomes have identical arms.** They form when chromatids divide along the wrong plane (in this depiction, horizontally rather than vertically).

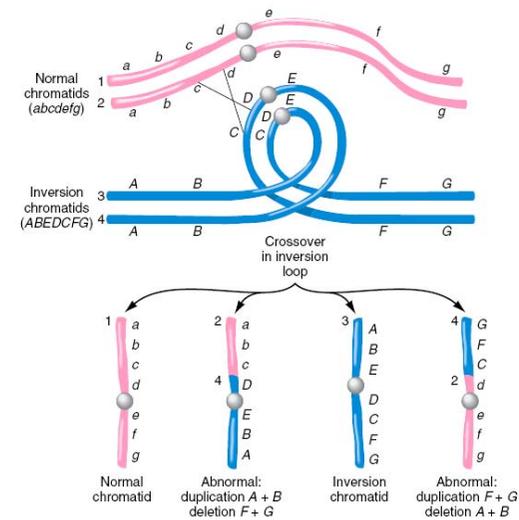


**Figura 6-7** ■ A: Lactante con el síndrome del «maullido de gato», que resulta de la delección de parte del cromosoma 5p. Nótese la cara característica con hipertelorismo, epicanto y retrognatismo. B: Mapa de la relación fenotipo-cariotipo determinada mediante análisis CGH sobre matrices de los cromosomas del (5p). (Basada en datos de Zhang X, Snijders A, Seagraves R, et al.: High-resolution mapping of genotype-phenotype relationships in cri du chat syndrome using array comparative genome hybridization. Am J Hum Genet 76:312-326, 2005.)

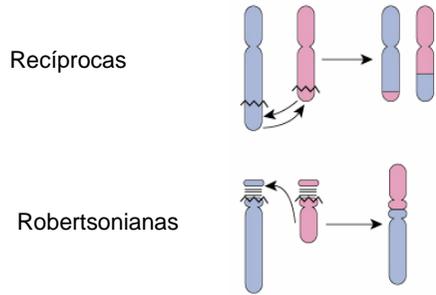
## Consecuencias inversiones paracentricas



## Consecuencias inversiones pericéntricas

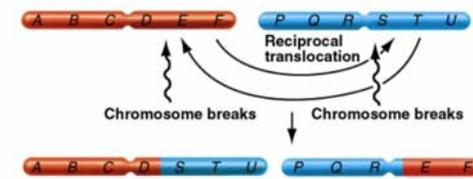


# Translocaciones

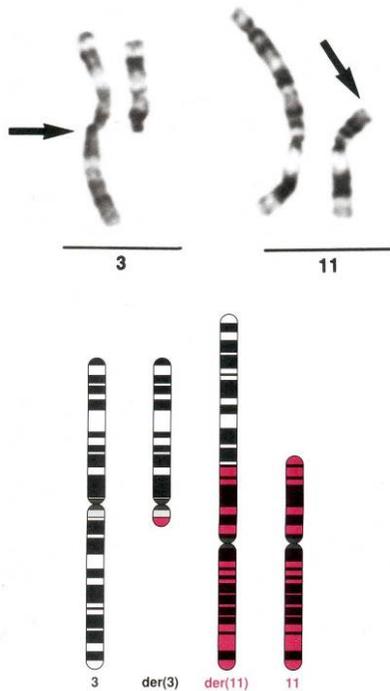


Balanceadas – No balanceadas

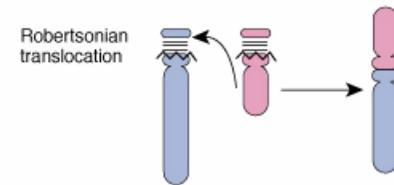
## Translocaciones



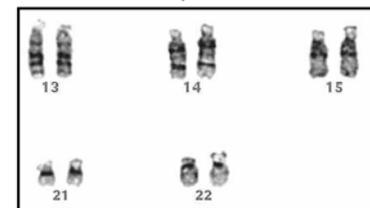
Translocación recíproca: surge del intercambio de fragmentos cromosómicos entre cromosomas **no-homólogos**



## Translocación Robertsoniana



Cromosomas acrocéntricos en el cariotipo humano



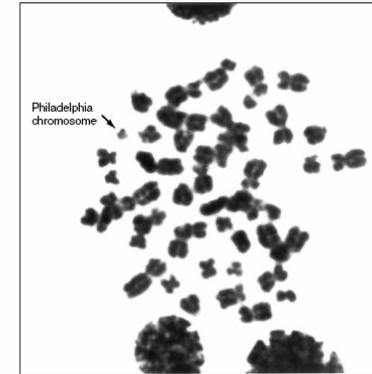
# Efectos translocación



**figure 12.19**

**A translocation syndrome.** In one family with Alagille syndrome, a reciprocal translocation occurs between chromosomes 2 and 20. Distinctive facial features are part of the condition.

# Cromosoma Filadelfia en Leucemia mieloide crónica



**figure 17.6**

**The Philadelphia chromosome.** A tiny chromosome that appears consistently in the white blood cells of patients with chronic myeloid leukemia was named the Philadelphia chromosome in honor of the city where researchers identified it in 1960. Note the poor quality of the chromosome preparation, compared to the intricately banded and DNA-probed chromosomes we view today.

# Cromosoma Filadelfia en Leucemia mieloide crónica

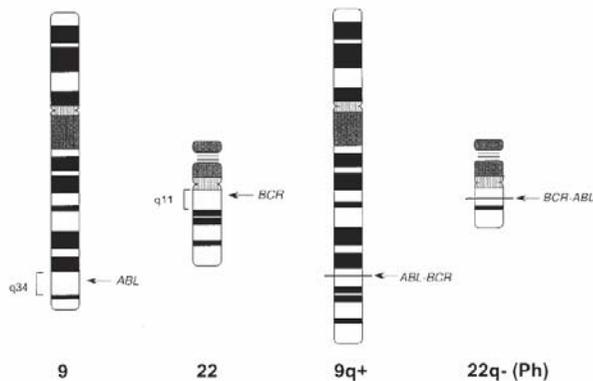
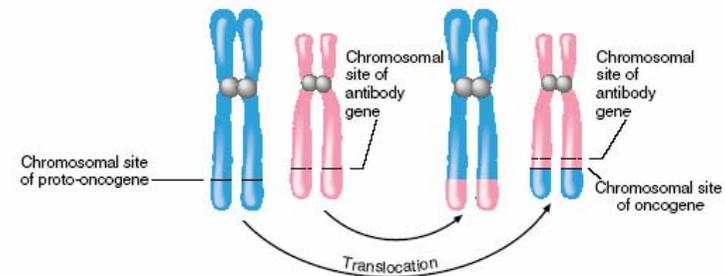


Fig. 1. Philadelphia (Ph) translocation. Reciprocal translocation of genomic material from the long arms of chromosomes 9 and 22. The resulting fusion genes are *ABL-BCR* on chromosome 9q+ and *BCR-ABL* on chromosome 22q-.

# t(8:14) en linfoma de Burkitt



**figure 17.5**

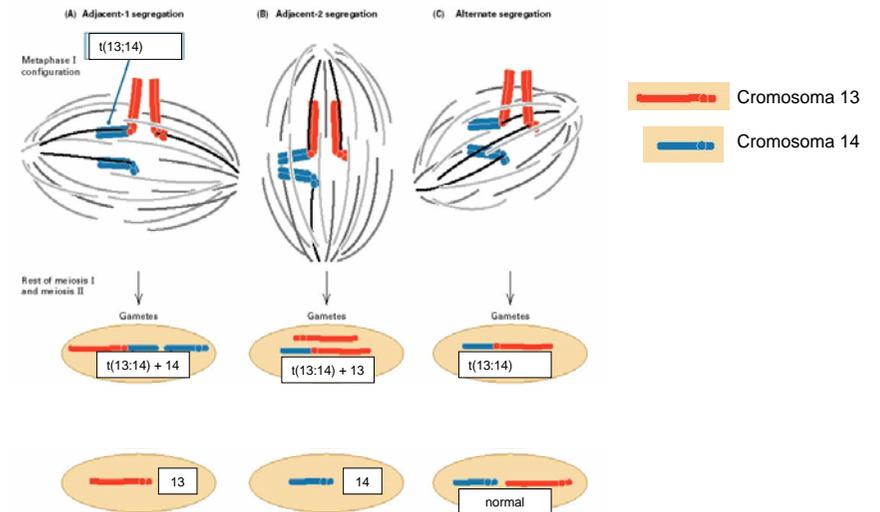
**A translocation that causes cancer.** The cause of Burkitt's lymphoma is translocation of a proto-oncogene on chromosome 8 to chromosome 14, next to a highly expressed antibody gene. Overexpression of the moved proto-oncogene, now an oncogene, triggers the molecular and cellular changes of cancer.

**Table 1**  
**Chromosomal Translocations Observed in Leukemias (Selection) (1-4)**

Translocation	Genes	Disease <sup>a</sup>
t(1;19)(q23;p13)	<i>PBX1, E2A</i>	B-ALL
t(8;14)(q24;q32)	<i>MYC, IgH</i>	B-ALL
t(2;8)(p12;q24)	<i>Igκ, MYC</i>	B-ALL
t(8;22)(q24;q11)	<i>MYK, Igλ</i>	B-ALL
t(4;11)(q21;q23)	<i>AF4, MLL</i>	B-ALL
t(12;21)(p13;q22)	<i>TEL, AML1</i>	B-ALL
t(7;19)(q35;p13)	<i>LYL1, TCR-β</i>	T-ALL
t(1;14)(p32;q11)	<i>TAL1, TCR-δ</i>	T-ALL
t(7;9)(q34;q32)	<i>TCR-β, TAL2</i>	T-ALL
t(11;14)(p13;q11)	<i>RHOM-2, TCR-δ</i>	T-ALL
t(10;14)(q24;q11)	<i>HOX11, TCR-δ</i>	T-ALL
t(15;17)(q22;q21)	<i>PML, RARα</i>	AML M3
t(6;9)(p23;q34)	<i>CAN, DEK</i>	AML M2, M4
t(8;21)(q22;q22)	<i>ETO, AML1</i>	AML M2
inv(16)(p13;q22)	<i>CBFβ, MYH11</i>	AML M4Eo
t(9;22)(q34;q11)	<i>c-ABL, BCR</i>	CML, ALL
t(8;13)(p11;q12)	<i>ZNF198, FGFR1</i>	8p11 MPD
t(9;12)(q34;p13)	<i>ABL, TEL</i>	Ph-negative CML, MDS
t(5;12)(q33;p13)	<i>PDGFR-β, TEL</i>	CMML

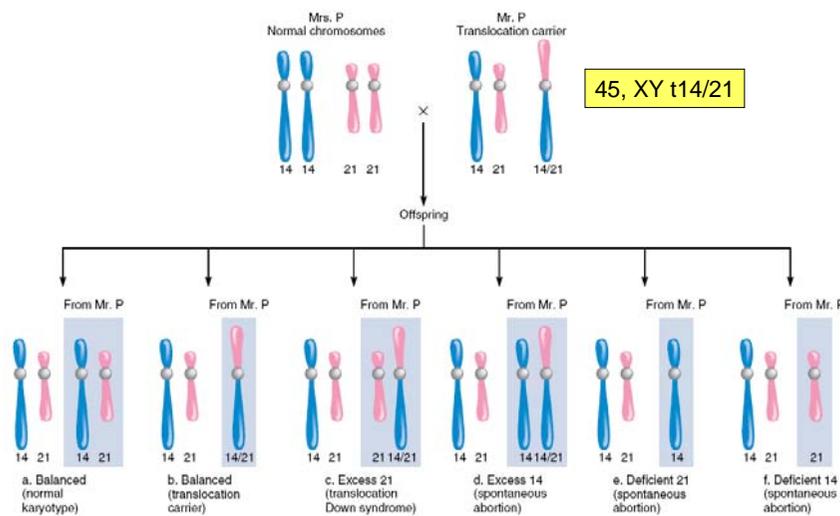
<sup>a</sup>B-ALL, B-lineage acute lymphoblastic leukemia; T-ALL, T-lineage acute lymphoblastic leukemia; AML, acute myelogenous leukemia; CML, chronic myelogenous leukemia; MDS, myelodysplastic syndrome; CMML, chronic myelomonocytic leukemia.

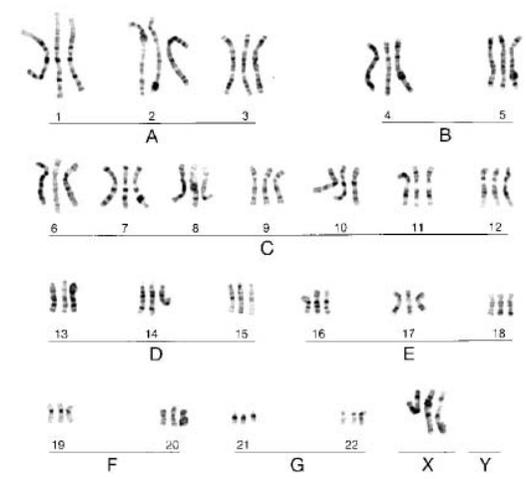
### Meiosis para una translocación Robertsoniana



### Mutaciones cromosómicas numéricas

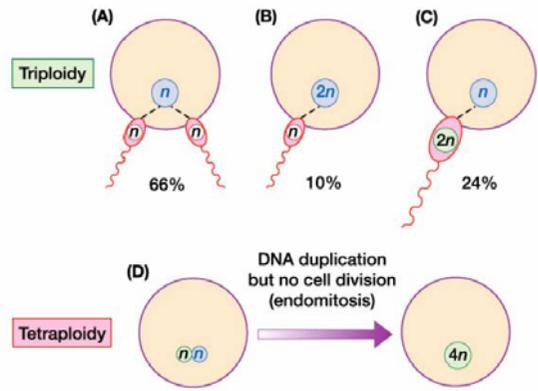
- Poliploidía: → Aumento del set completo de cromosomas. Múltiplos de 23. → triploidía, tetraploidía...
- Aneuploidía: Pérdida o ganancia de uno o más cromosomas → 2n+1; 2n-1





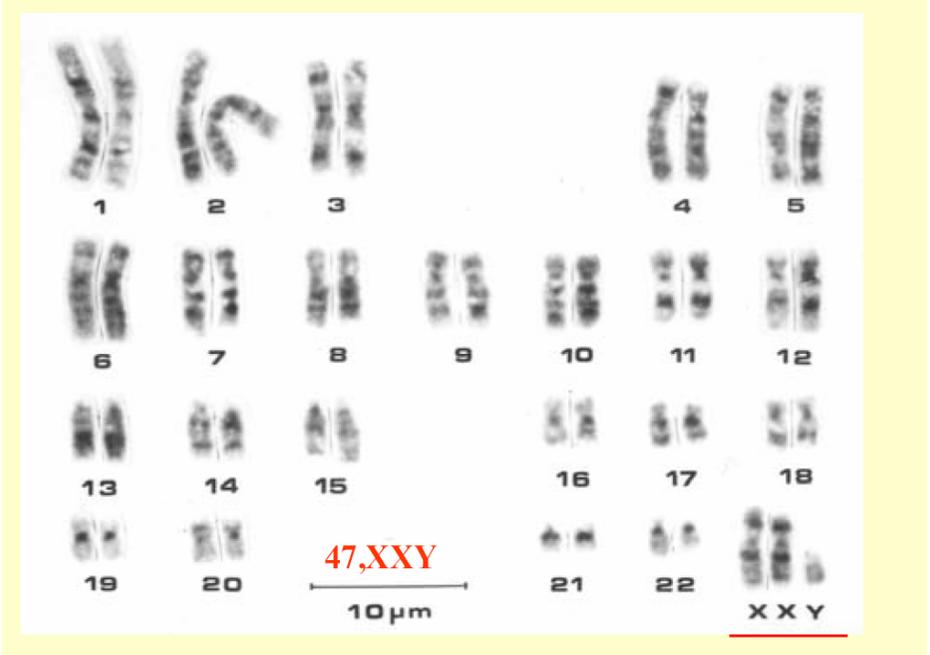
**figure 12.11**  
**Polyoids in humans are lethal.** Individuals with three copies of each chromosome (triploids) account for 17 percent of all spontaneous abortions and 3 percent of stillbirths and newborn deaths.

## Origen de poliploidías



ire 2-19 Human Molecular Genetics, 3/e. (© Garland Science 2004)

## Cariotipo bandeado G de un individuo que presenta el síndrome de Klinefelter



cariotipo Turner 45.X

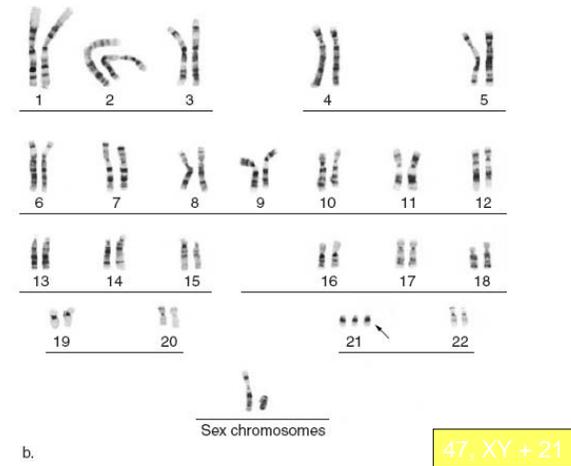
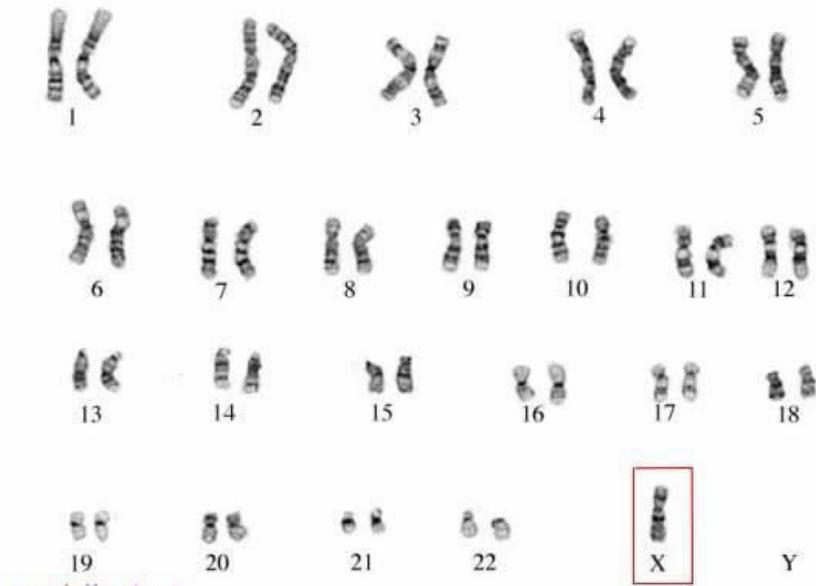
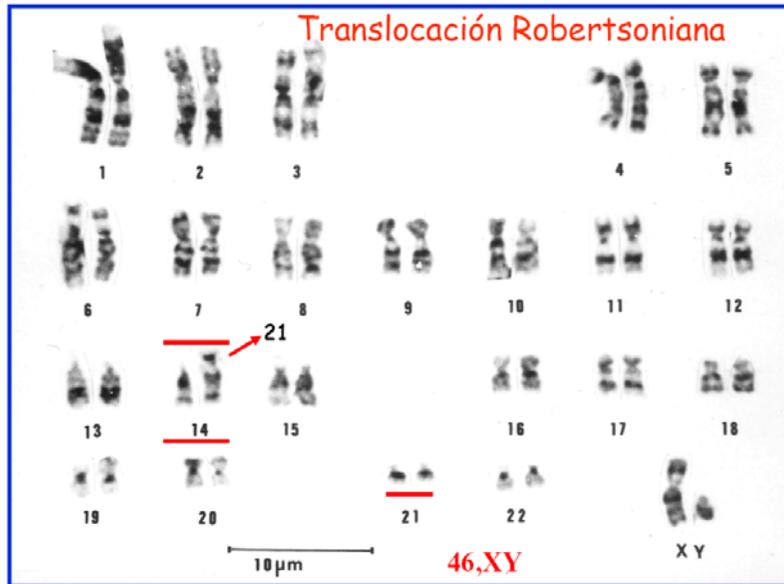


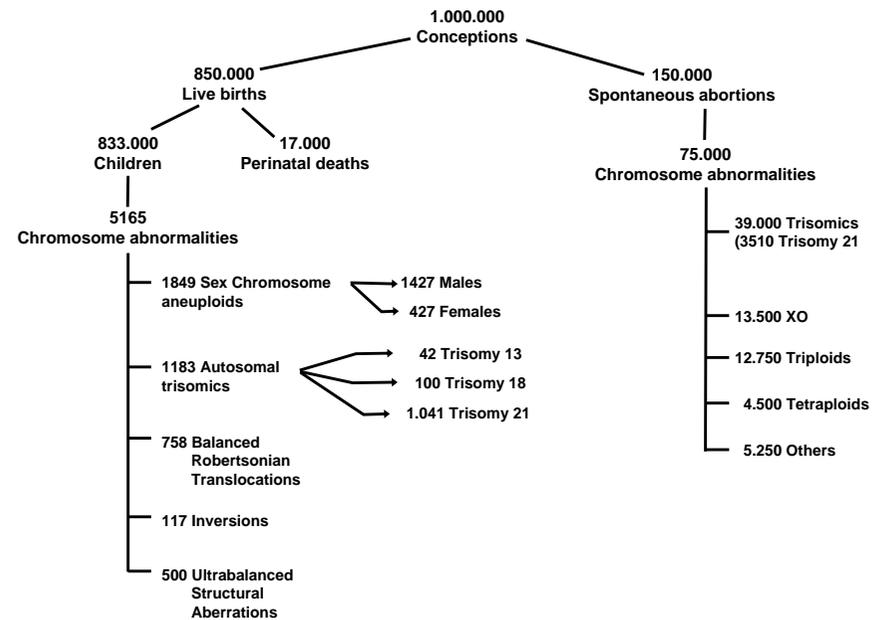
figure 12.1

Trisomy 21 Down syndrome. (a) Wendy Weisz enjoys studying art at Cuyahoga Community College. (b) A karyotype (chromosome chart) for trisomy 21 Down syndrome shows the extra chromosome 21.

Translocación Robertsoniana



The Fate of a Million Implanted Human Zygotes



# Aneuploidías

Table 1 | Incidence of aneuploidy during development

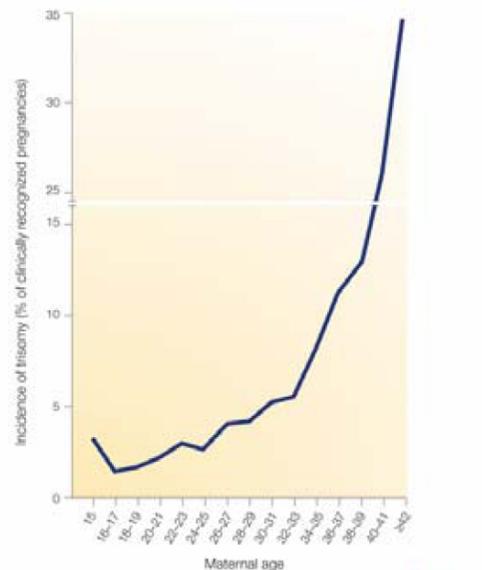
Gestation (weeks)	0		6-8		20		40	
	Sperm	Oocytes	Pre-implantation embryos	Pre-clinical abortions	Spontaneous abortions	Stillbirths	Livebirths	
Incidence of aneuploidy	1-2%	~20%	~20%	?	35%	4%	0.3%	
Most common aneuploidies	Various	Various	Various	?	45,X; +16; +21; +22	+13; +18; +21	+13; +18; +21 XXX; XXY; XYY	

table 12.5

## Comparing and Contrasting Trisomies 13, 18, and 21

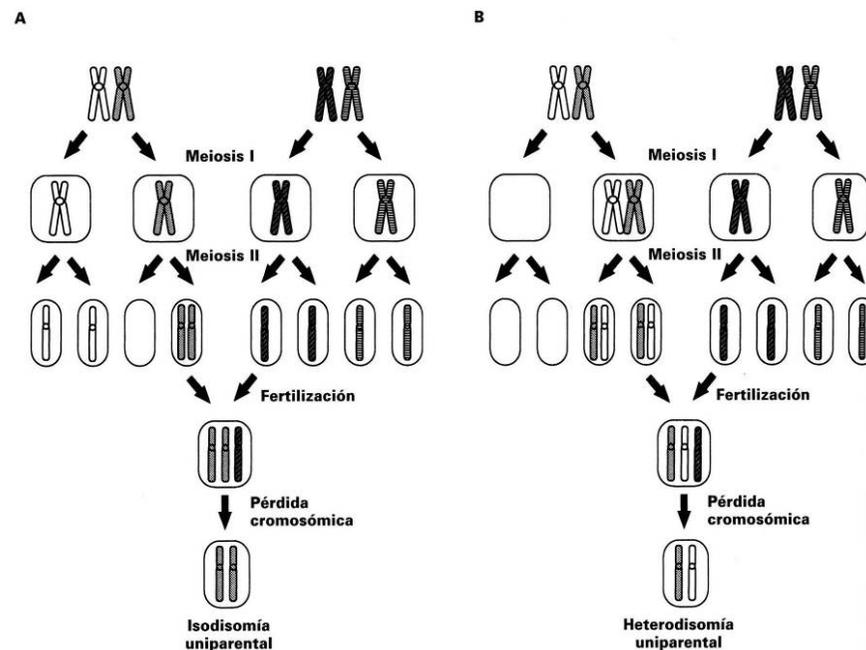
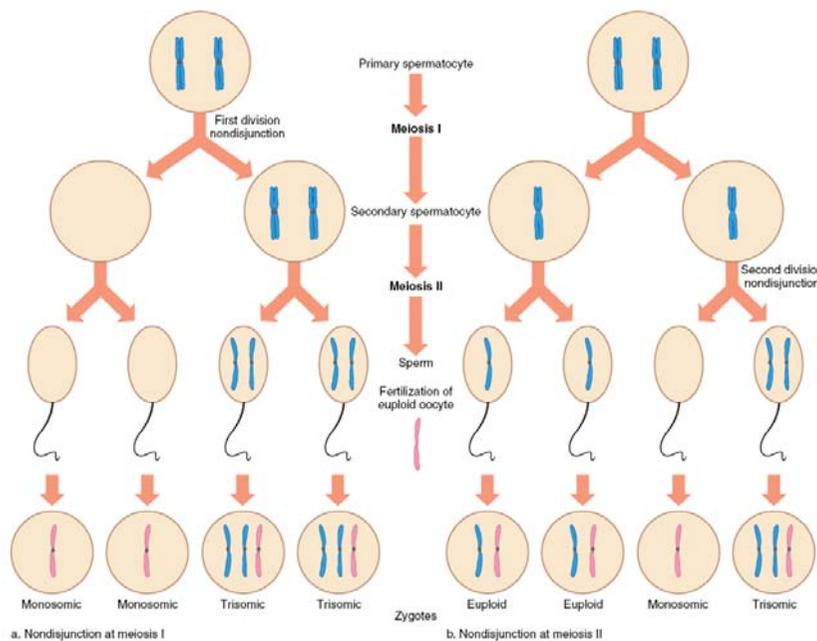
Type of Trisomy	Incidence at Birth	Percent of Conceptions That Survive 1 Year After Birth
13 (Patau)	1/12,500-1/21,700	<5%
18 (Edward)	1/6,000-1/10,000	<5%
21 (Down)	1/800-1/826	85%

## RELACIÓN ENTRE EDAD MATERNA Y TRISOMÍAS CROMOSÓMICAS



Nature Reviews | Genetics

(Tomado de Hassold T and Hunt P: "To err (meiotically) is human: the genesis of human aneuploidy", Nature Rev Genet 2: 280-291, 2001).



## Origen parental de las aneuploidías

	Paterno %	Materno %
Trisomía 13	15	<b>85</b>
Trisomía 18	10	<b>90</b>
Trisomía 21	5	<b>95</b>
45,X	<b>80</b>	20
47,XXX	5	<b>95</b>
47,XXY	45	55
47,XYY	<b>100</b>	0

- Un individuo 47,XXY puede originarse por...
- Una mujer 45,XO puede originarse por....

- Aprox. 2% de casos con Síndrome de Down corresponde a mosaicos.

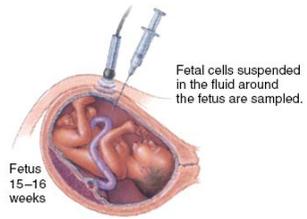
Ej. 50% de células 46,XY

50% de células 47,XY +21

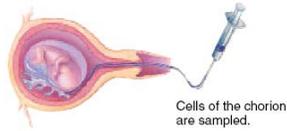
¿Cómo se explica?

## Métodos diagnósticos de anomalías cromosómicas

- Bando G
- Fish (**F**luorescent **i**n **s**itu **h**ybridization)
- SKY (Spectral Karyotype)



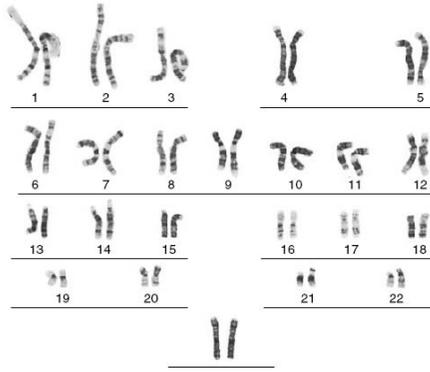
a. Amniocentesis



b. Chorionic villi sampling



c. Fetal cell sorting



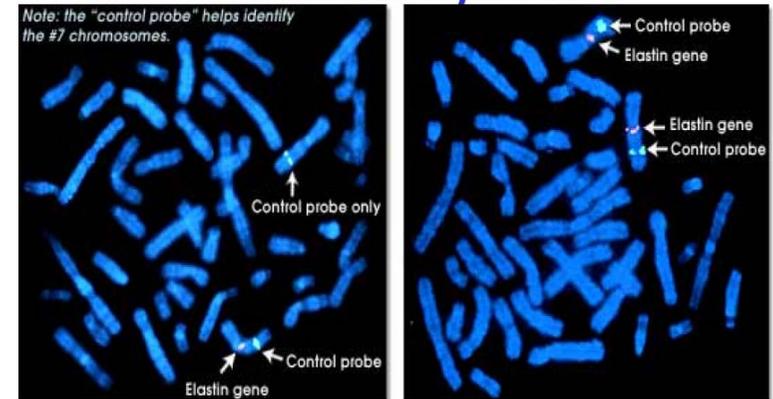
d. Fetal karyotype (normal female)

**figure 12.6**

**Three ways of checking a fetus's chromosomes.** (a) Amniocentesis harvests fetal cells shed during development into the amniotic fluid by drawing out some of the fluid. (b) Chorionic villus sampling removes cells that would otherwise develop into the placenta. Since these cells come from the fertilized ovum, they have the same chromosomal constitution as the fetus. (c) Improved techniques at identifying and extracting specific cells allow researchers to detect fetal cells in a sample of blood from the woman. (d) For all three techniques, the harvested cells are allowed to reach metaphase, where chromosomes are most visible, and then broken open on a slide. The chromosomes are stained or their DNA probed, then arranged into a karyotype.

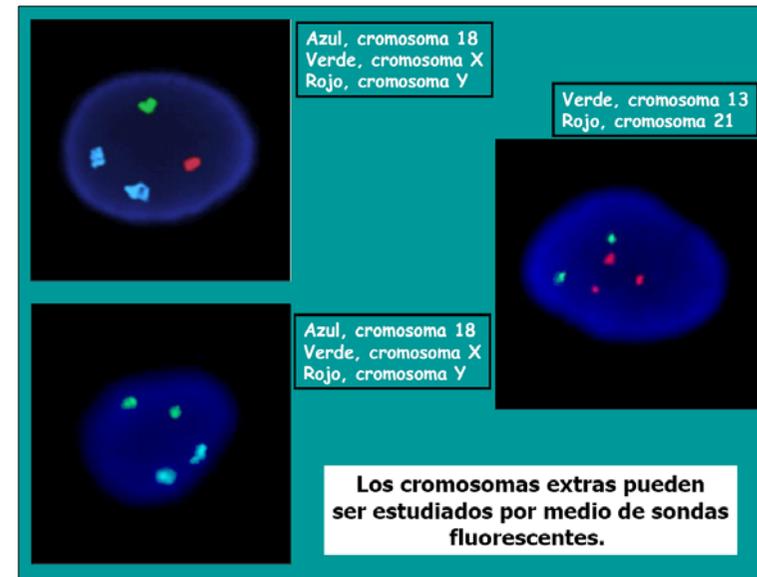
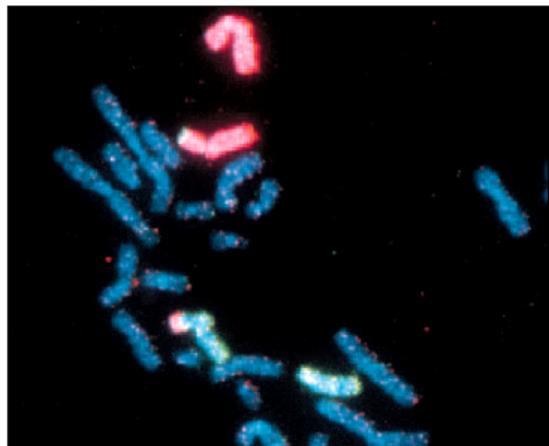
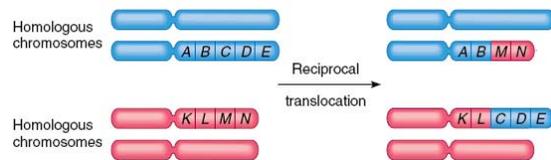
# FISH

## Williams Syndrome



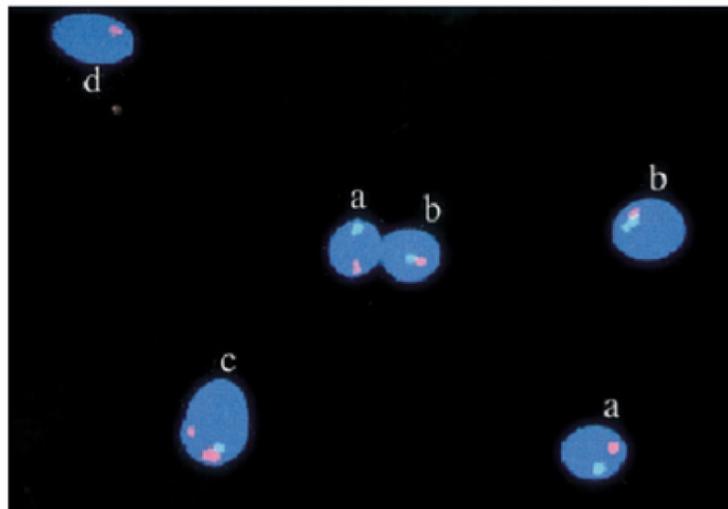
S. Williams

wild-type FISH



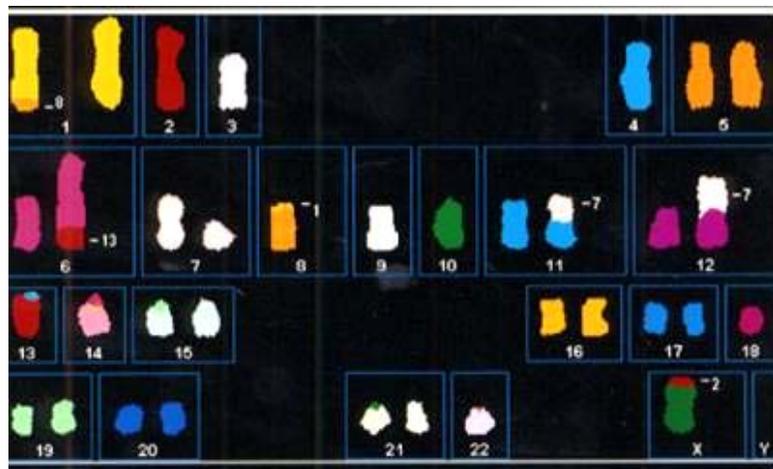
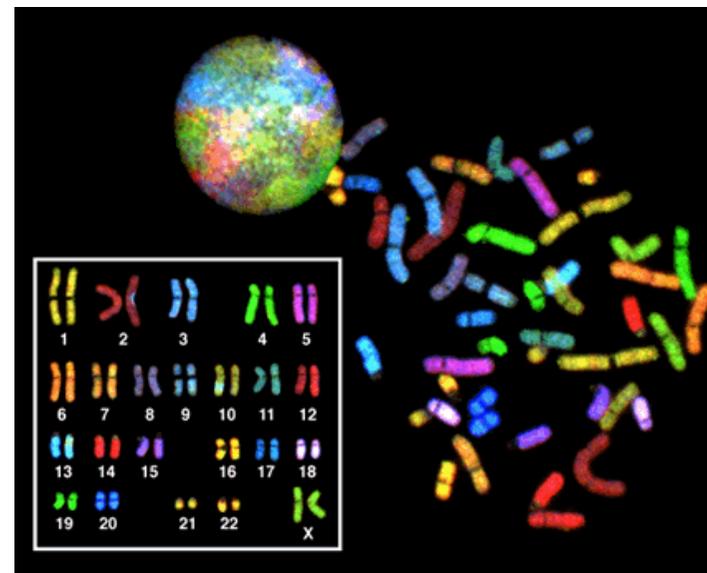
## TRANSLOCACIÓN ROBERTSONIANA 13/14 EN CÉLULAS DE LA LÍNEA GERMINAL

Figura 4. Espermatozoides de un portador de una translocación Robertsoniana [t(13;14)], tratados con la técnica de FISH aplicando sondas específicas para los cromosoma 13 (rojo) y 14 (verde). Las cabezas de los espermatozoides fueron teñidas con DAPI (azul).

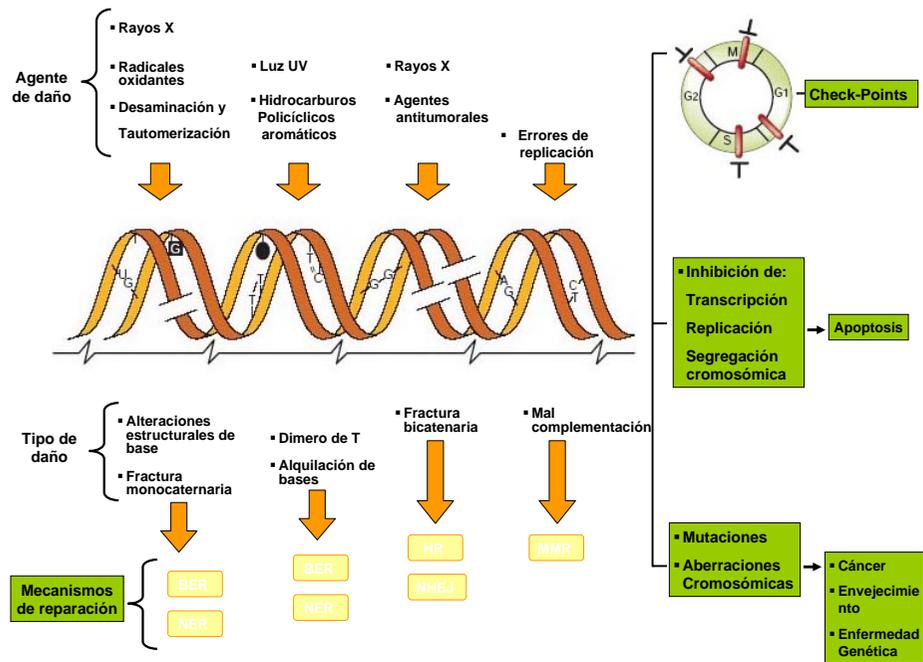


Tomado de Morel et al. (2001). *Mol Hum Reprod* 7:483-488

## SKY



• Fig. 3. Karyotype of cell line LAPC-4. Spectral karyotype of representative cell at passage 20. A: Classified image; B: Band image. *The Prostate* 57:226-244 (2003)



# Mutaciones: la base del cambio.....



**figure 11.1**

**Red hair.** This child's red curls make her the proud possessor of an unusual genetic variant.