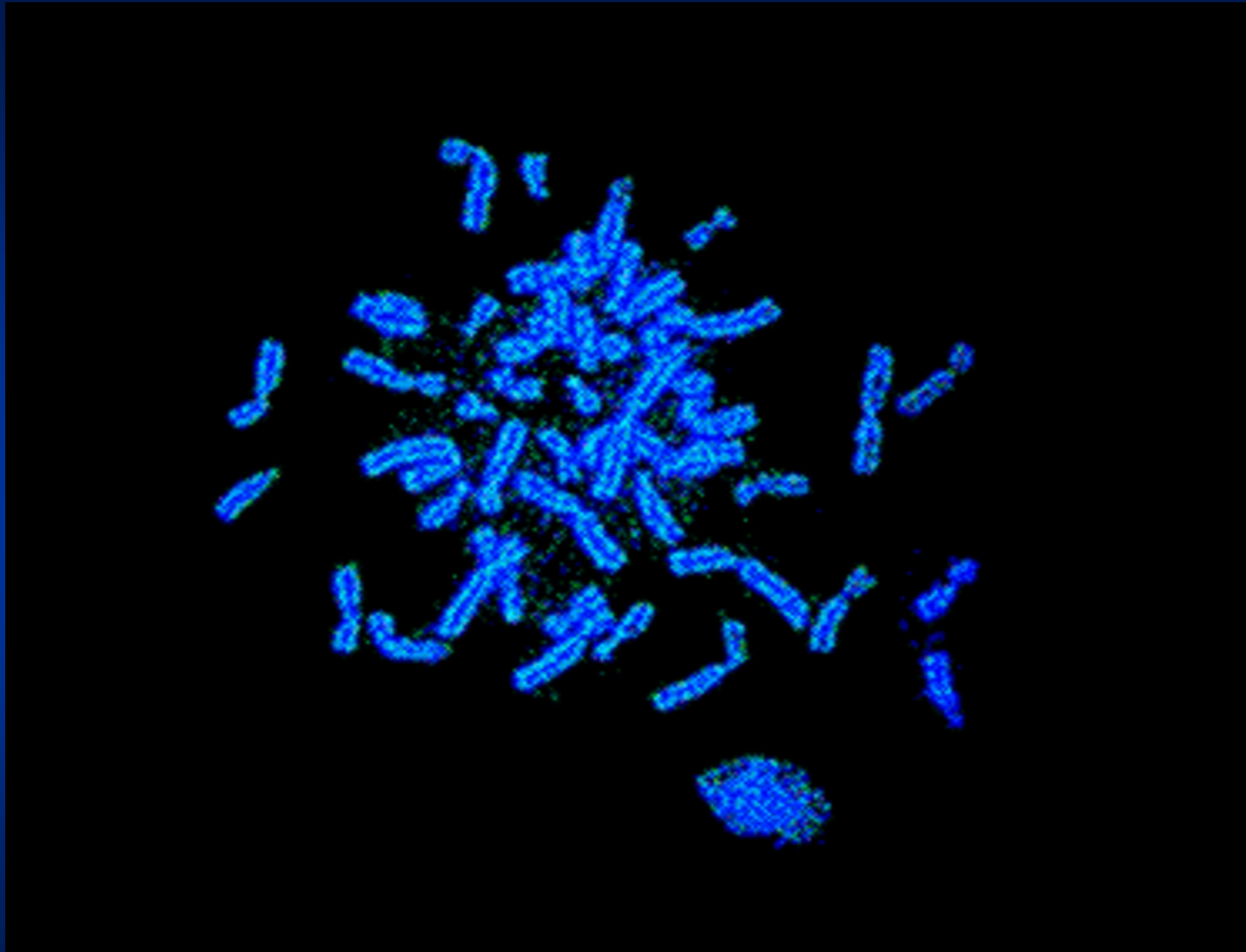


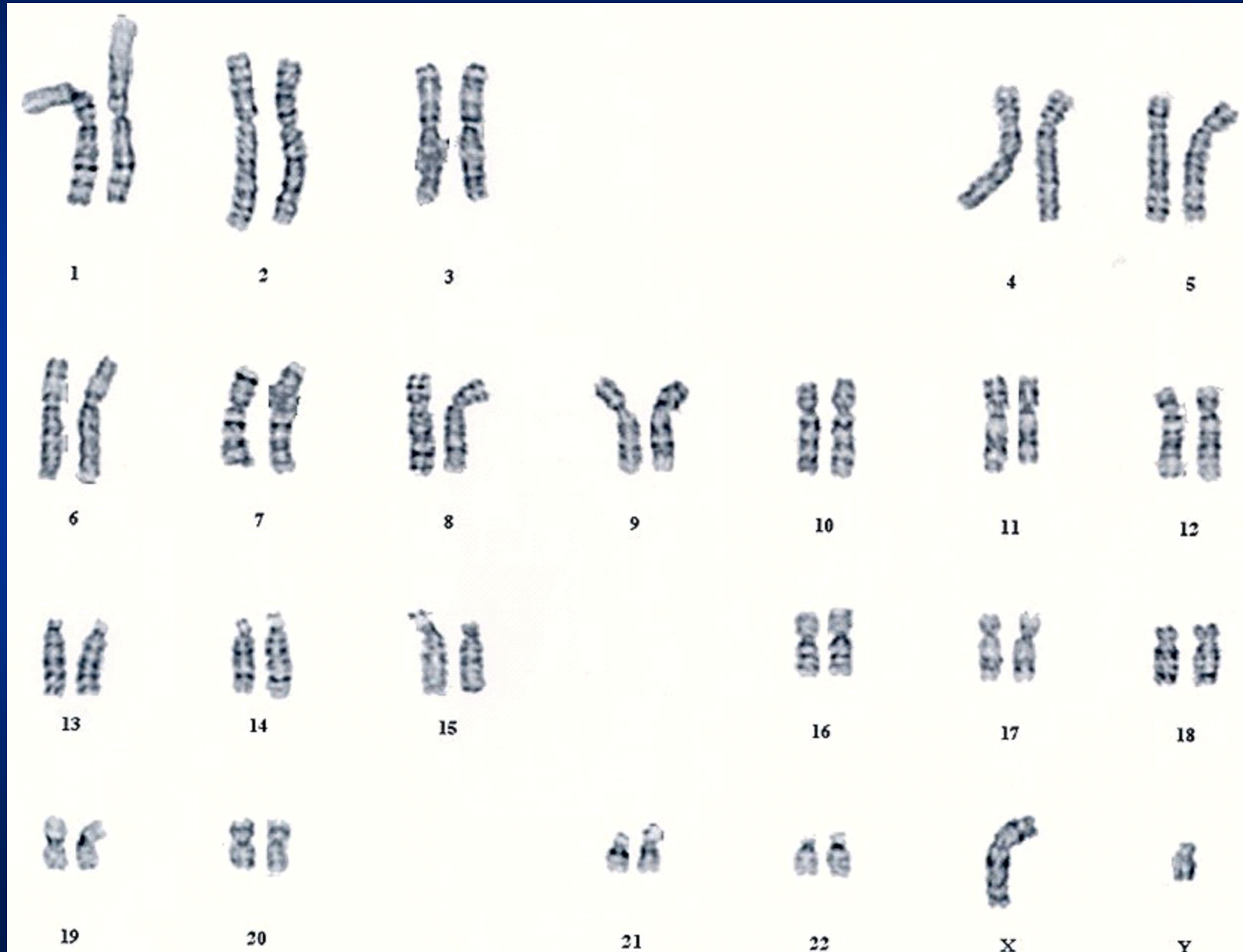
ENFERMEDADES GENETICAS

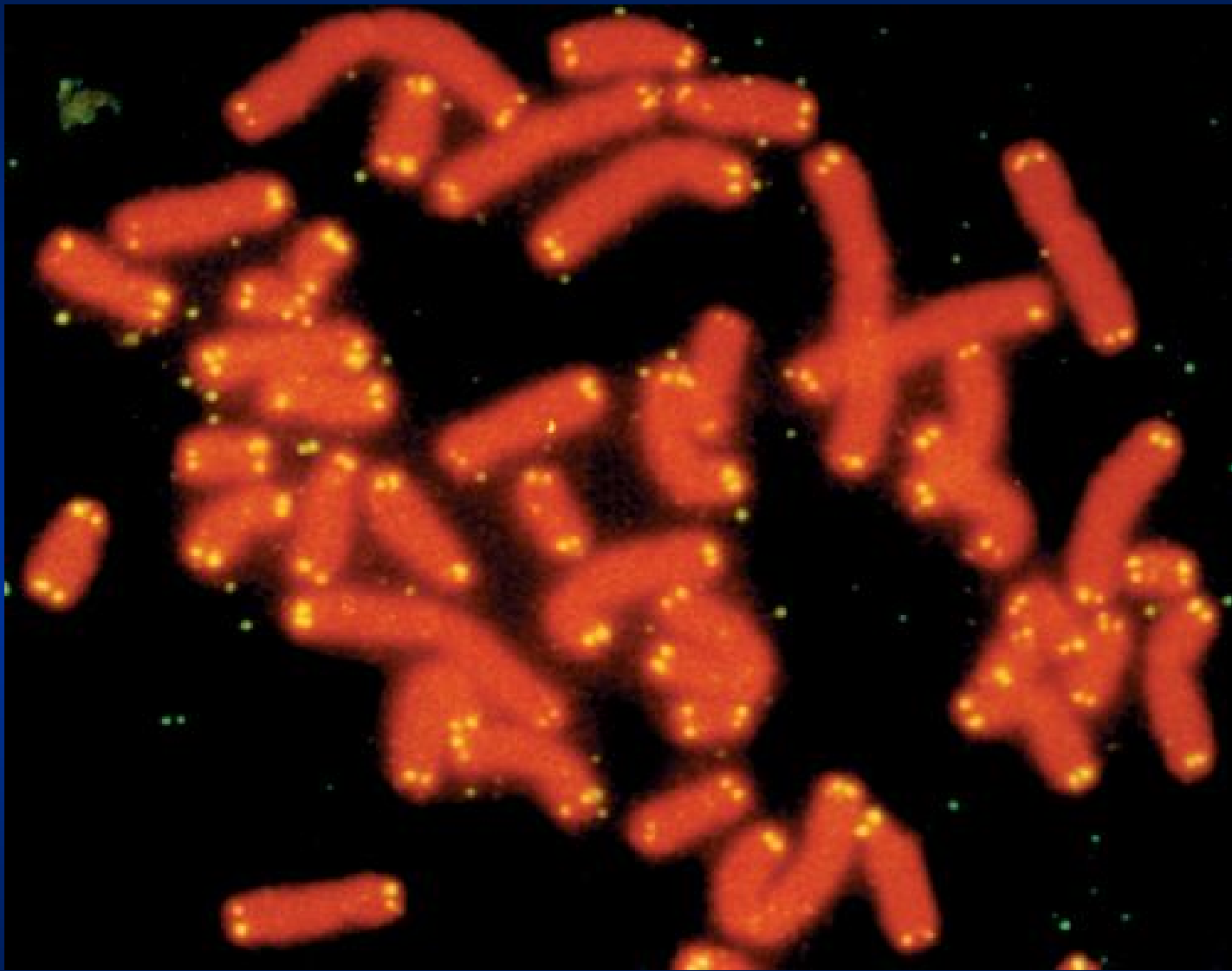
MEDICINA MOLECULAR, 2011



METAFASE DE UN LINFOCITO DE SANGRE PERIFERICA. DAPI

Cariotipo normal





DEFINICIONES

- **LOCUS:** Segmento de DNA heredado de forma Mendeliana
- **GENOTIPO:** Información contenida en un locus
- **ALELOS:** Diferencias normales en el genotipo para un gene determinado
- **HOMOCIGOTA:** Alelos idénticos
- **HETEROCIGOTA:** Alelos diferentes
- **FENOTIPO:** Características visibles de un individuo
- **DOMINANTE:** Alelo heterocigota reconocido en el fenotipo
- **RECESIVO:** Alelo heterocigota no reconocido en el fenotipo
- **CODOMINANTE:** Ambos alelos son co-expresados

Mechanisms of Gene Expression

1) X chromosome inactivation (Lyonization)

2) Genomic Imprinting

3) RNA Splicing

4) Photocopy (Transcriptional) Regulation

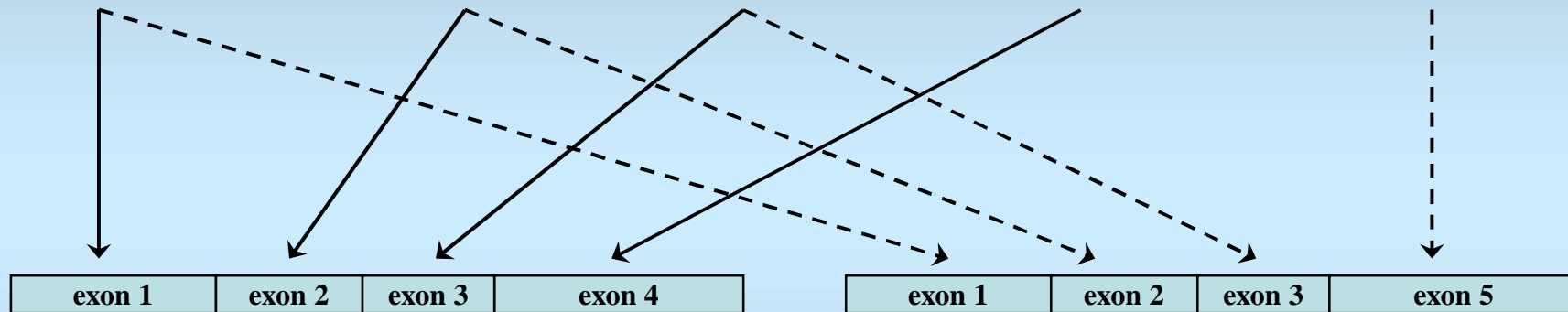
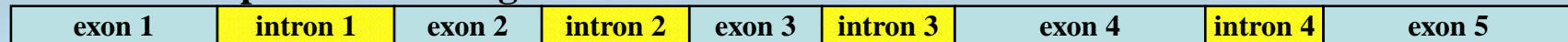
4.a) Methylation

4.b) Transcription Factors

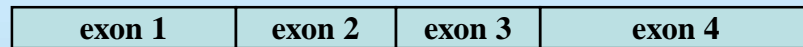
5) Packaging (Post-Translational) Regulation

RNA Splicing

RNA transcript before editing:

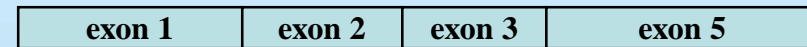


mRNA after editing:



Polypeptide 1

mRNA after editing:



Polypeptide 2

REGULACION DE LA EXPRESION GENICA POR METILACION (CpG)

INACTIVACION DEL CROMOSOMA X = LIONIZACION

GENES ACTIVOS = METILACION ↓

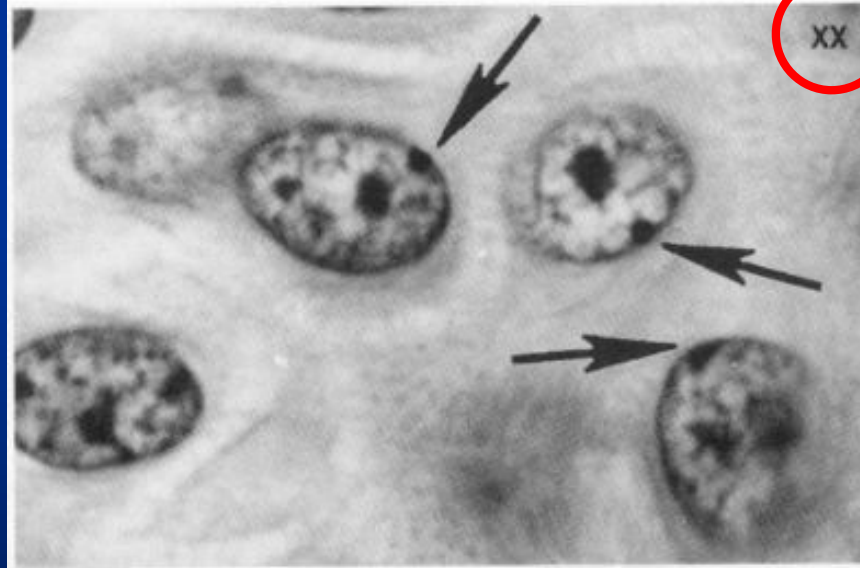
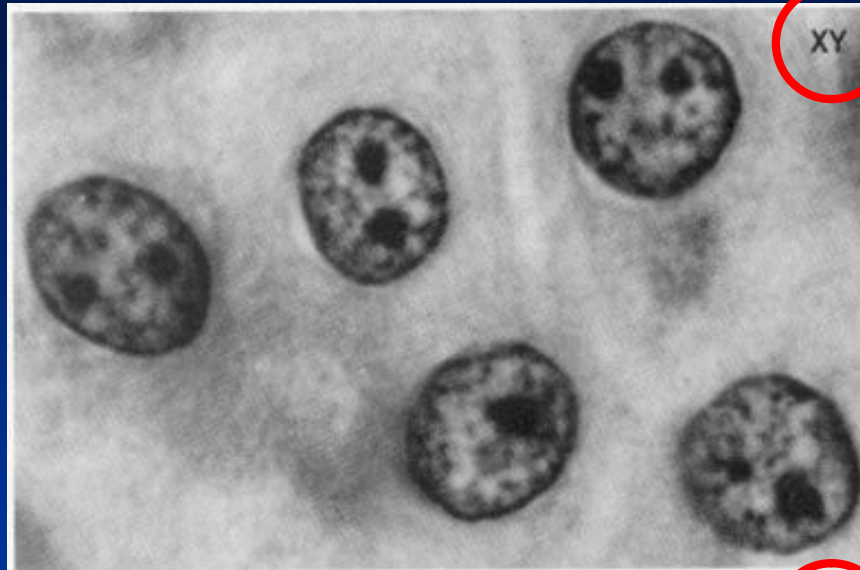
GENES INACTIVOS = METILACION ↑

Transcriptional Regulation: I: Methylation

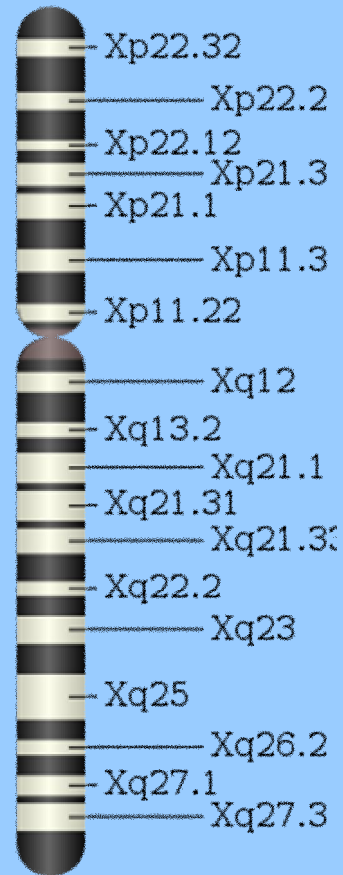
- **Methyl group (CH₃) added to DNA**
- **Shuts off genes (prevents transcription)**
- **Tissue specific (e.g., genes methylated in the MHC differ in different tissues)**
- **Human Epigenome Project (map the methylated DNA areas in the human genome)**

X Chromosome Inactivation (Lyonization)

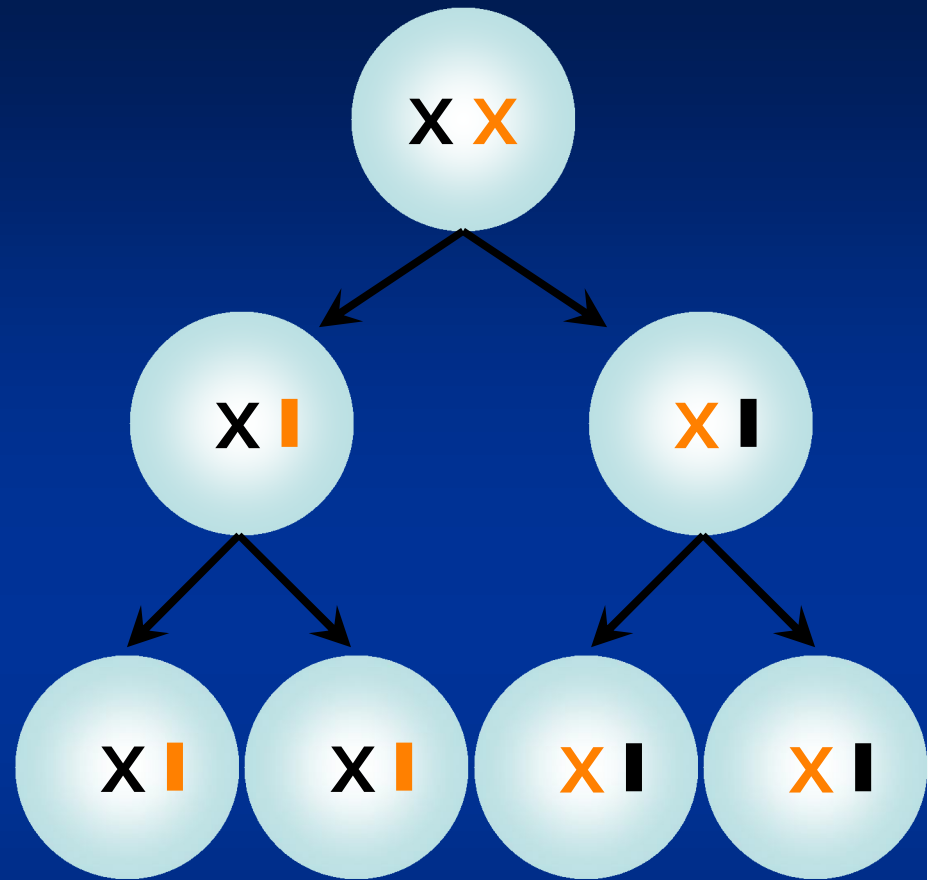
- At fertilization, both X chromosomes are active.
- Very soon, however, one of the X chromosomes in a cell, apparently taken at random, is inactivated and forms a **Barr body**.
- All other cells derived from the initial cell have the **SAME** X chromosome inactivated.
- Genes on the inactive X chromosome are not expressed.
- In humans, though, a few genes are expressed.



Barr Bodies

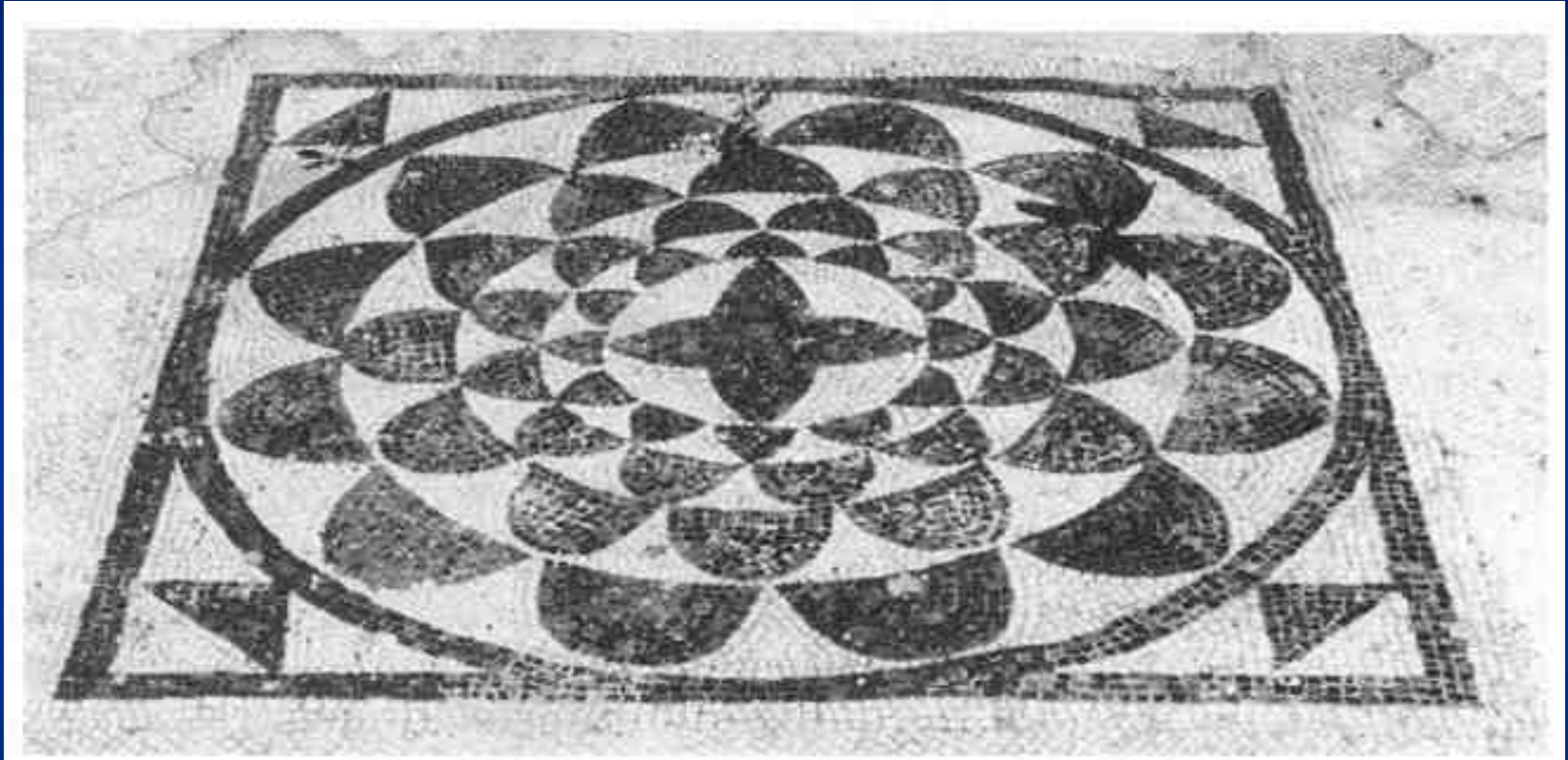


Cromosoma X. 1336 genes. Uno de ambos X se inactiva por metilación en el día 16 (al azar). Las mujeres son mosaicos.

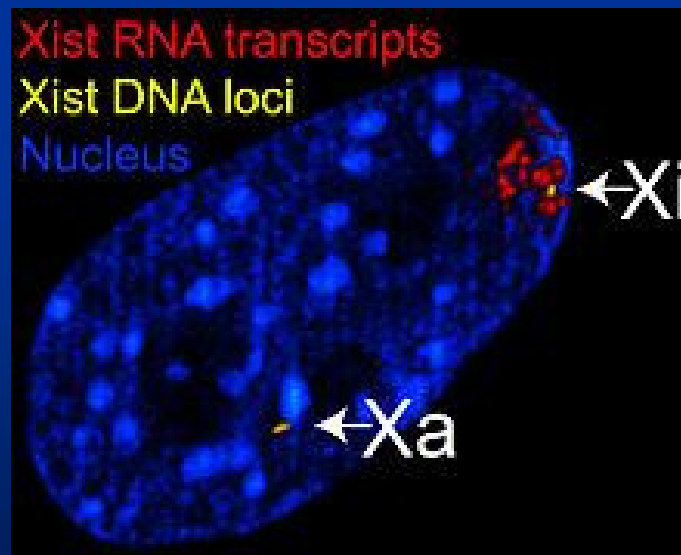
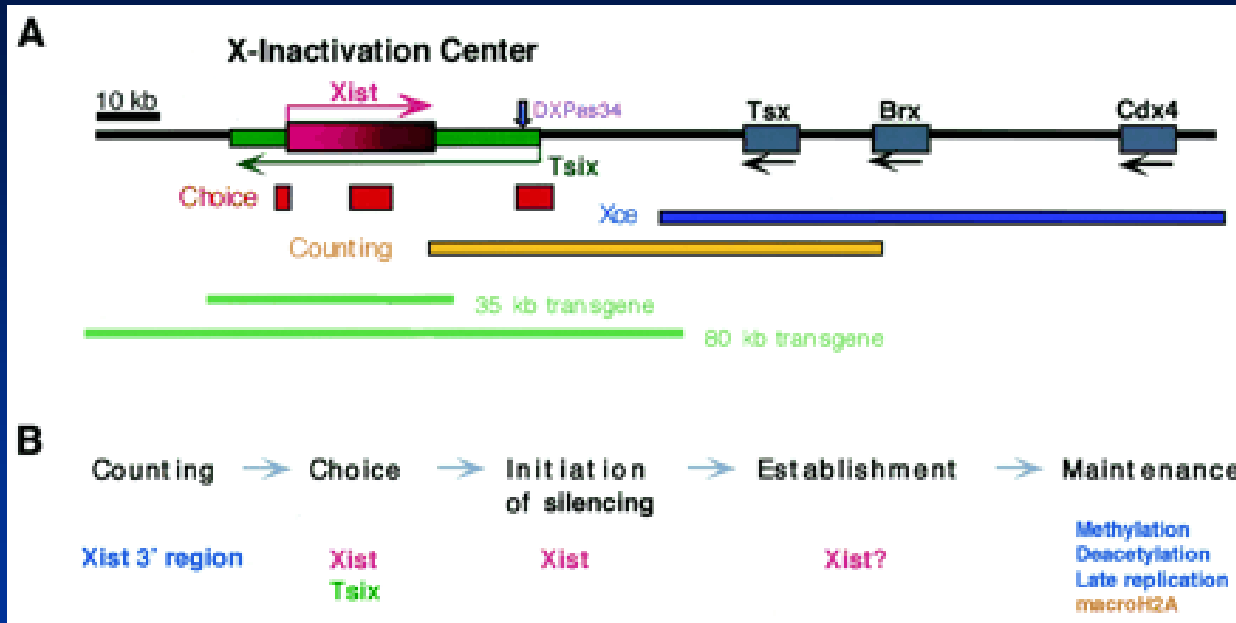


Black
Fur

Orange
Fur



Las mujeres son mosaicos. Mayor variabilidad en manifestaciones clínicas en mujeres heterocigotas que en hombres hemicigotas.

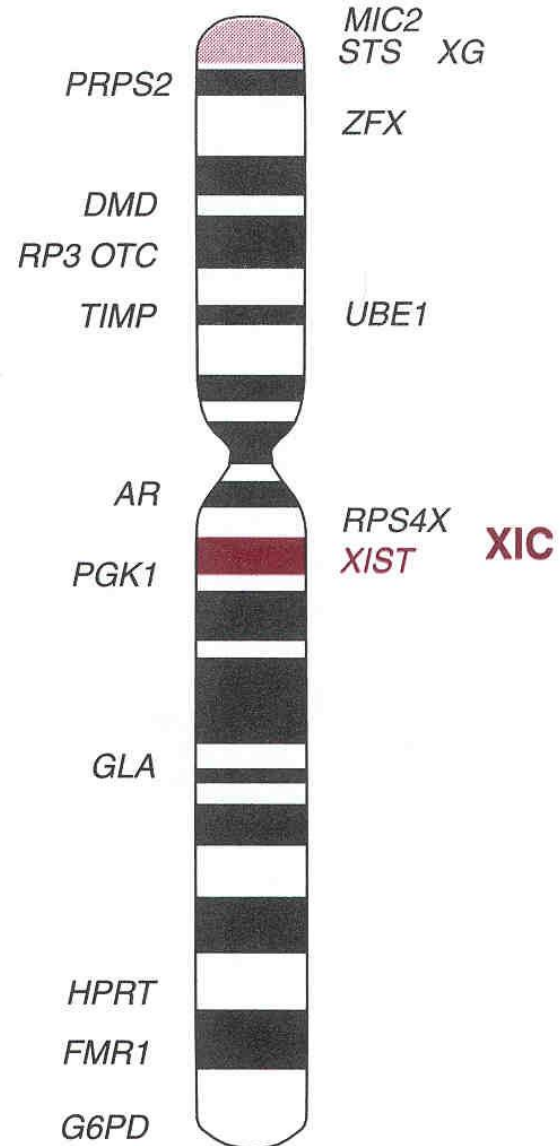


Mechanism

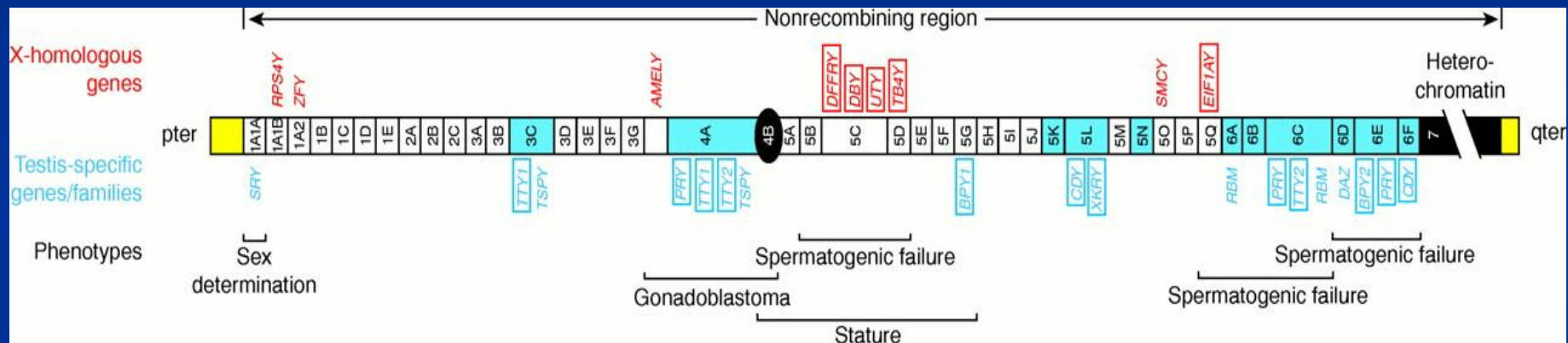
- ***XIST*** gene on the X chromosome turns on and produces ***XIST*** RNA.
- Molecules of ***XIST*** RNA accumulate along the chromosome with the active ***XIST*** gene.
- The binding of the ***XIST*** RNA with the DNA turns off the genes on that chromosome.

GENES KNOWN TO
BE SUBJECT TO
X INACTIVATION

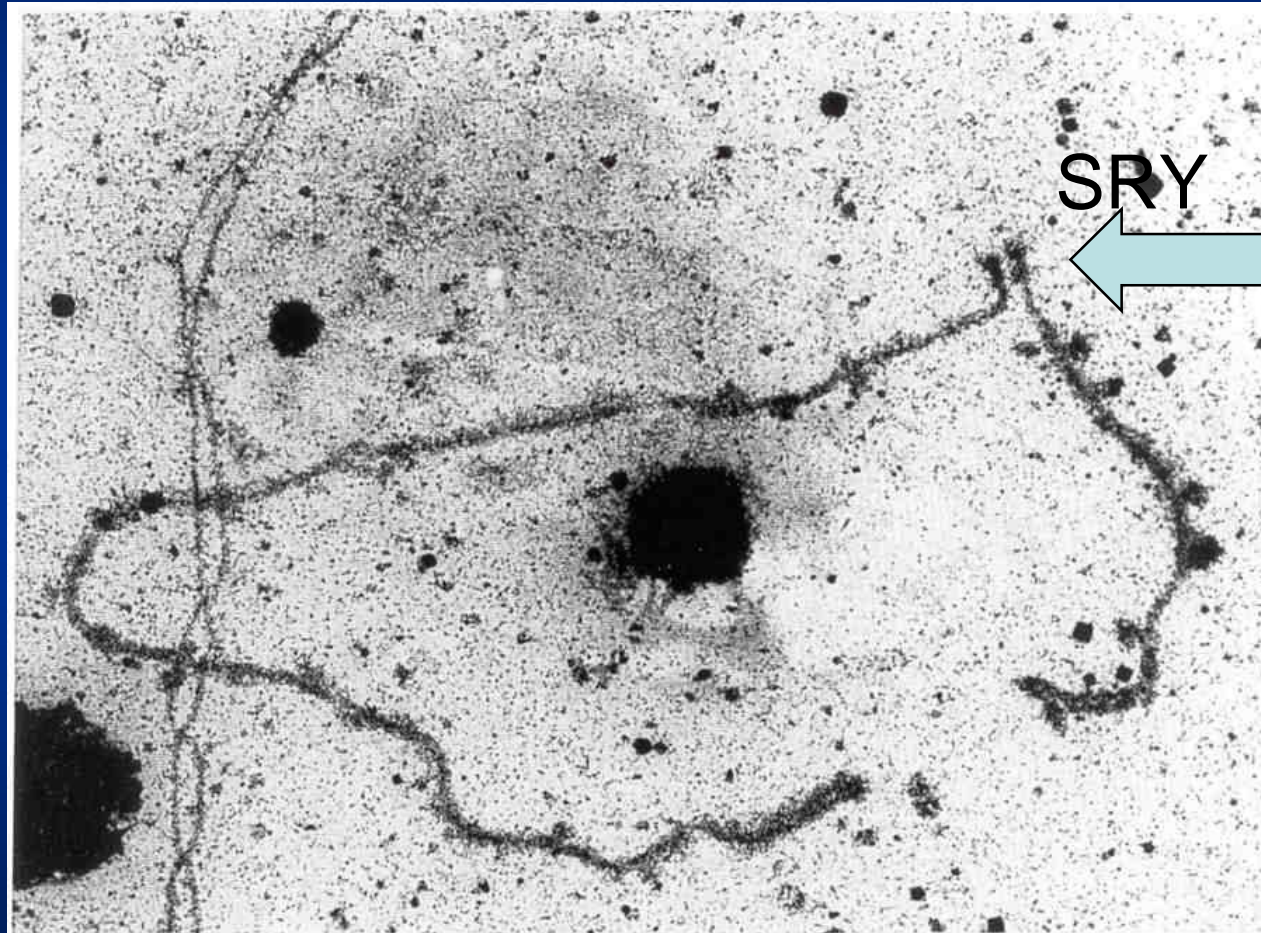
GENES KNOWN TO
ESCAPE
X INACTIVATION



Y-chromosome genes



X and Y chromosomes at meiosis



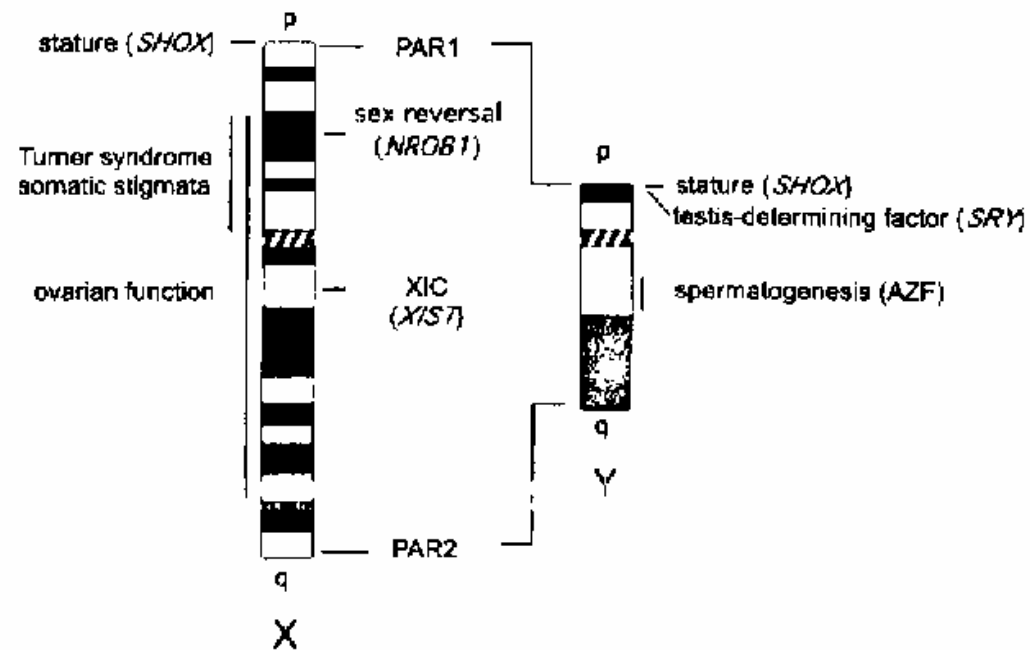


Figure 42-1 Schematic depiction of human sex chromosomes and approximate location of key genetic loci discussed in the text. Symbols for cloned genes in parentheses. p, short arm; q, long arm.

Human Populations

All individuals share genome sequences which are 99.9% identical.

The remaining 0.1% is responsible for all of the genetic diversity between individuals.

Typing SNPs allows us to chart the evolution of the human race and its migration across the globe.

SNPs are Very Common

- SNPs are very common in the human population.
- Between any two people, there is an average of one SNP every ~1250 bases.
- Most of these have no phenotypic effect
 - Venter et al. estimate that only <1% of all human SNPs impact protein function (non-coding regions)
 - Selection against mis-sense mutations
- Some are alleles of genes.

DNA Sequence Variation in a Gene Can Change the Protein Produced by the Genetic Code

Gene A from Person 1

GCA AGA GAT AAT TGT...

Ala Arg Asp Asn Cys ...
1 2 3 4 5

Protein Products



Gene A from Person 2

Codon change made no difference in amino acid sequence

GCG AGA GAT AAT TGT...

Ala Arg Asp Asn Cys ...
1 2 3 4 5

Gene A from Person 3

Codon change resulted in a different amino acid at position 2

GCA AAA GAT AAT TGT...

Ala Lys Asp Asn Cys ...
1 2 3 4 5

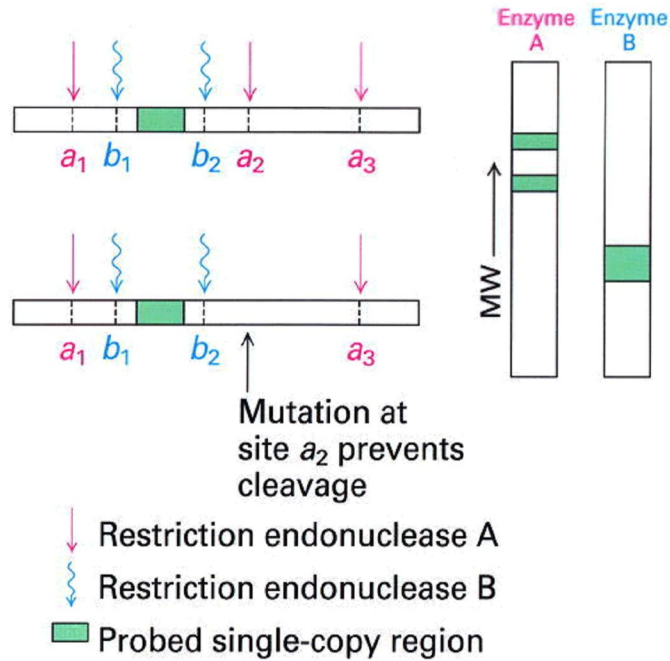
OR



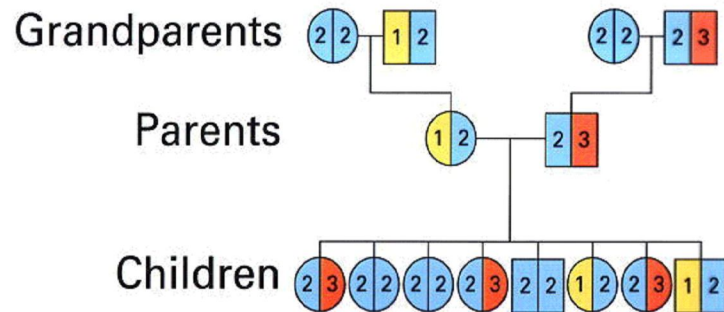
RFLP

**(Restriction Fragment Length
Polymorphisms)**

(a) **Chromosomal arrangement**
Hybridization
banding pattern

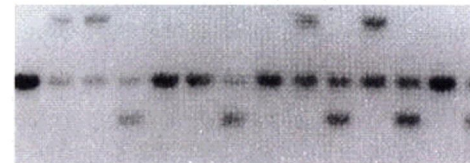


(b)



Alleles

1
2
3



Fragment lengths

10 kb
7.7 kb
6.5 kb

Figure 8-20
 Lodish et al. MOLECULAR CELL BIOLOGY, Fourth Edition
 Copyright © by W. H. Freeman and Company

Genome Sequencing finds SNPS

- The Human Genome Project involves sequencing DNA cloned from a number of different people.
[The Celera sequence comes from 5 people]
- Even in a library made from one person's DNA, the homologous chromosomes have SNPs
- This inevitably leads to the discovery of SNPs
- any single base sequence difference
- These SNPs can be valuable as the basis for diagnostic tests



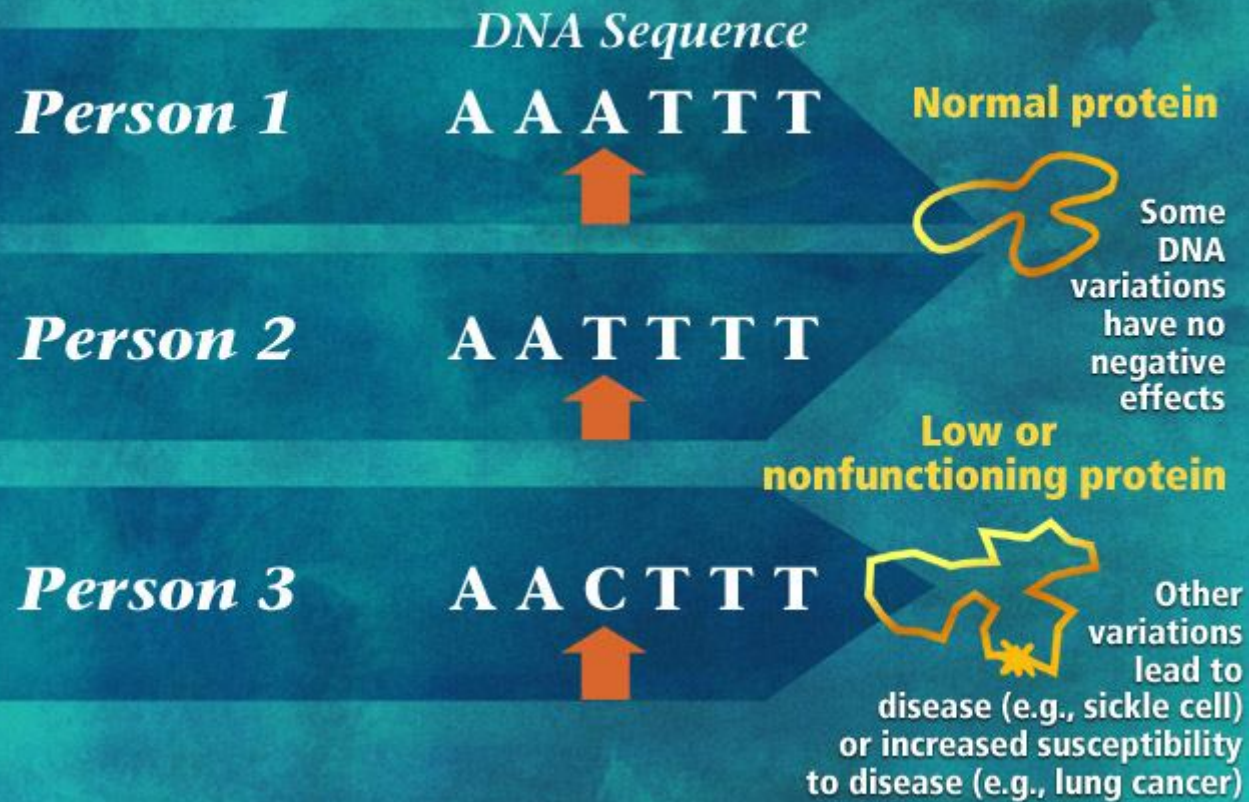
A map of human genome sequence variation containing 1.42 million single nucleotide polymorphisms

The International SNP Map Working Group*

** A full list of authors appears at the end of this paper.*

We describe a map of 1.42 million single nucleotide polymorphisms (SNPs) distributed throughout the human genome, providing an average density on available sequence of one SNP every 1.9 kilobases. These SNPs were primarily discovered by two projects: The SNP Consortium and the analysis of clone overlaps by the International Human Genome Sequencing Consortium. The map integrates all publicly available SNPs with described genes and other genomic features. We estimate that 60,000 SNPs fall within exon (coding and untranslated regions), and 85% of exons are within 5 kb of the nearest SNP. Nucleotide diversity varies greatly across the genome, in a manner broadly consistent with a standard population genetic model of human history. This high-density SNP map provides a public resource for defining haplotype variation across the genome, and should help to identify biomedically important genes for diagnosis and therapy.

Health or Disease?





ENFERMEDADES GENÉTICAS (3-5%)

- **Trastornos cromosómicos**
 - Trastornos mendelianos o monogénicos
 - Enfermedades multifactoriales
 - Formas no-clásicas de enfermedad genética (imprinting genómico, etc)
 - Trastornos mitocondriales
 - Mutaciones que surgen en células somáticas diferenciadas

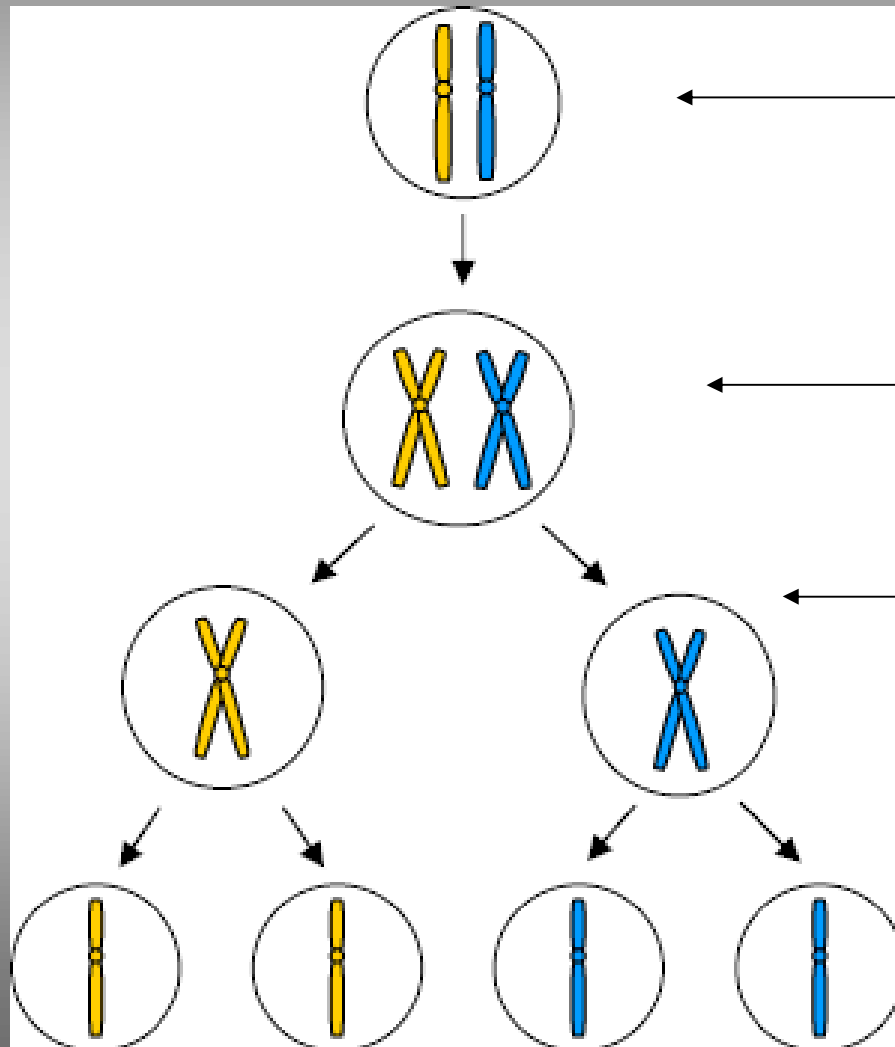
Meiosis

Cell division – ‘reduction
division’

Production of sex cells – gametes

Meiosis errors

Meiosis



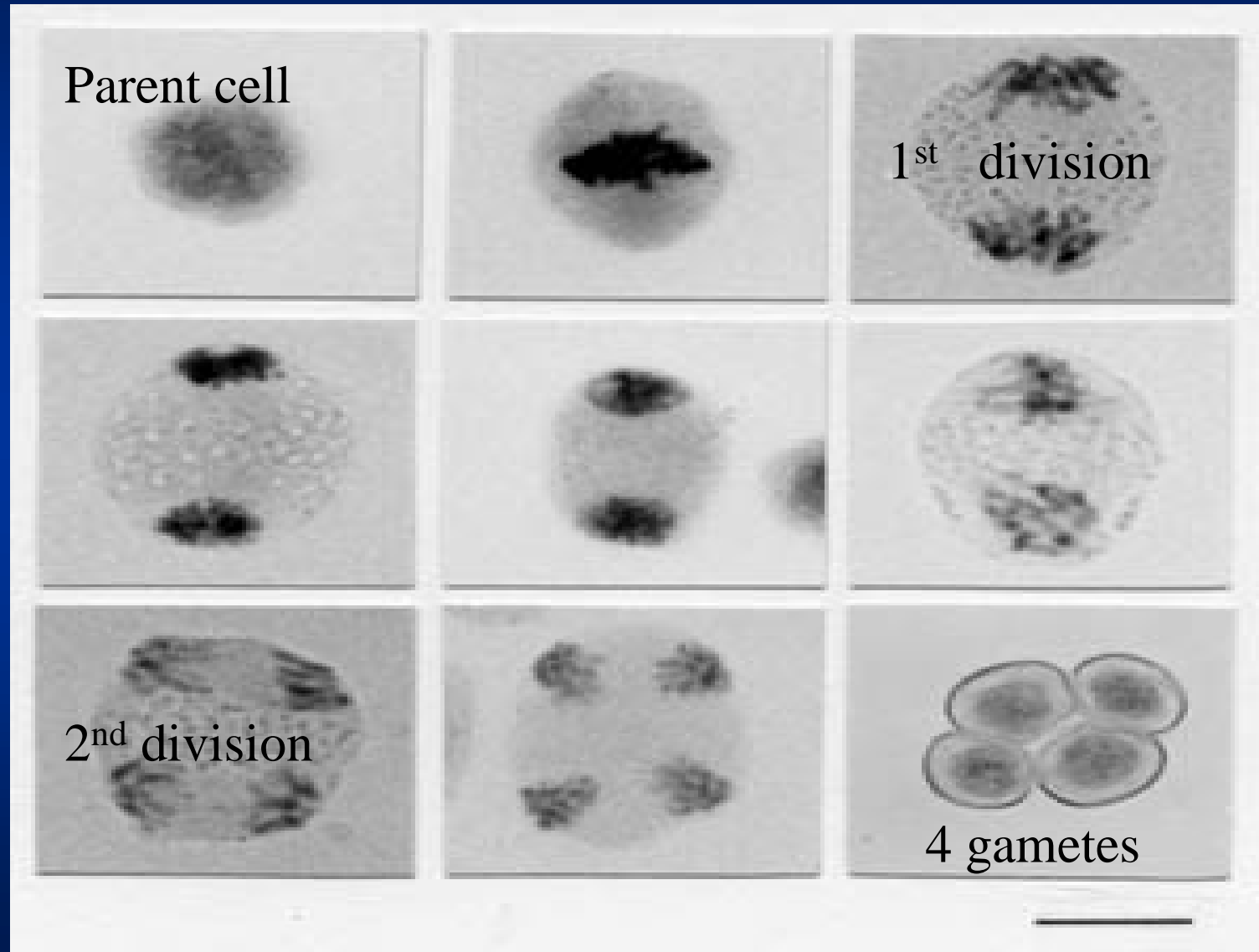
← Parent cell –
chromosome pair

← Chromosomes
copied

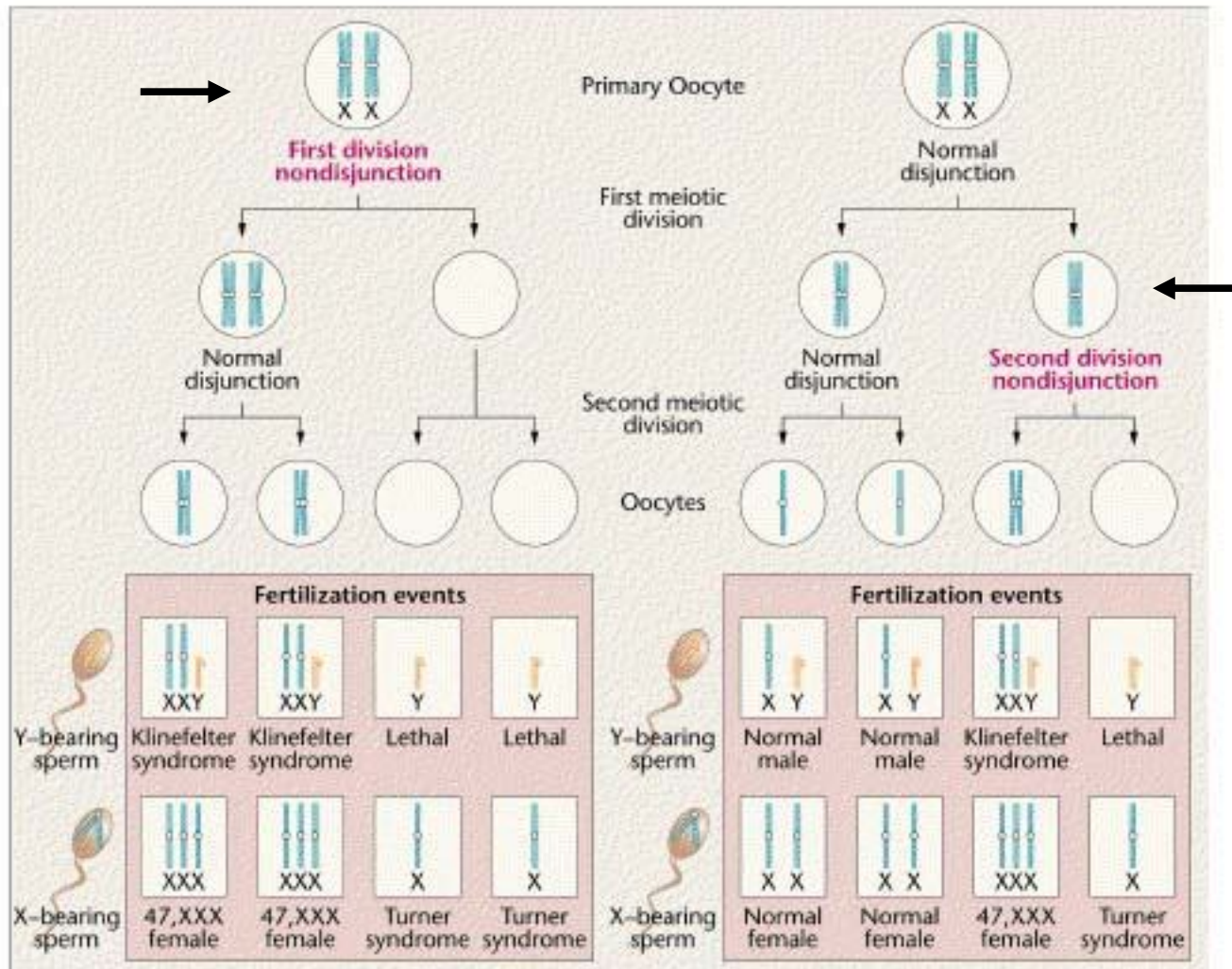
← 1st division - pairs split

← 2nd division – produces
4 gamete cells with $\frac{1}{2}$
the original no. of
chromosomes

Meiosis – mouse testes

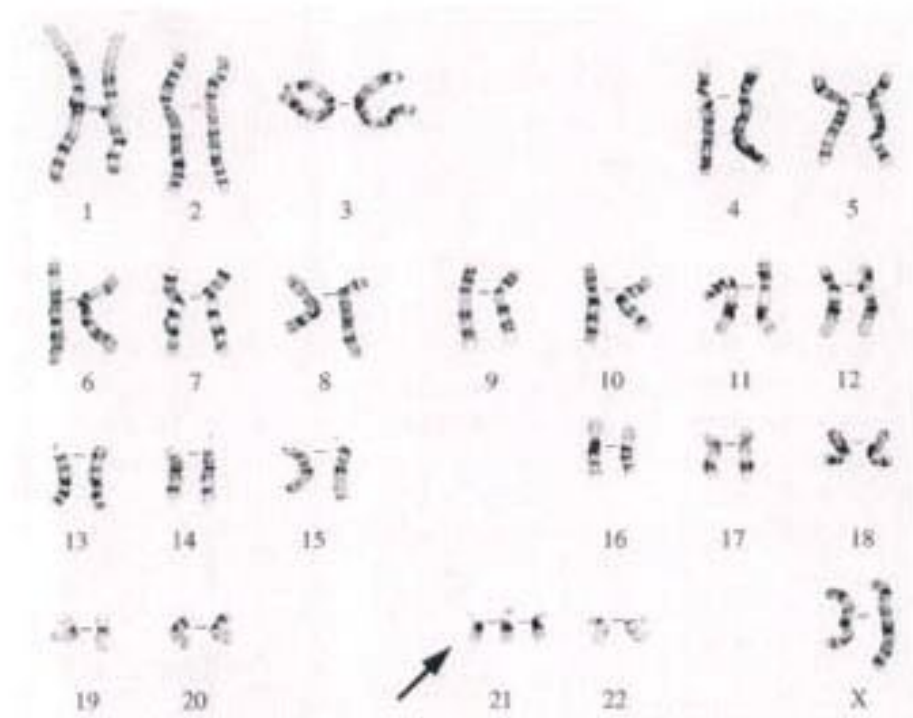


Nondisjunction of X chromosome



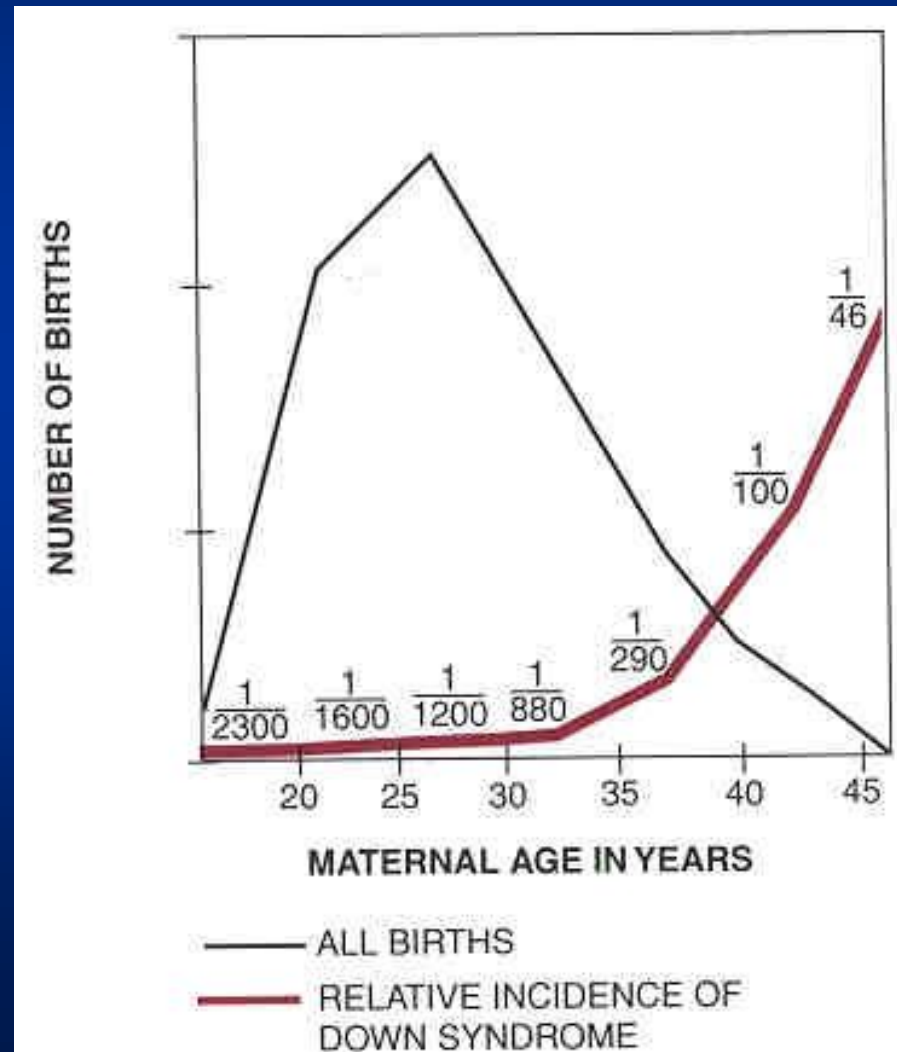
Nondisjunction also occurs with autosomes

Trisomy: Down Syndrome (47, +21)

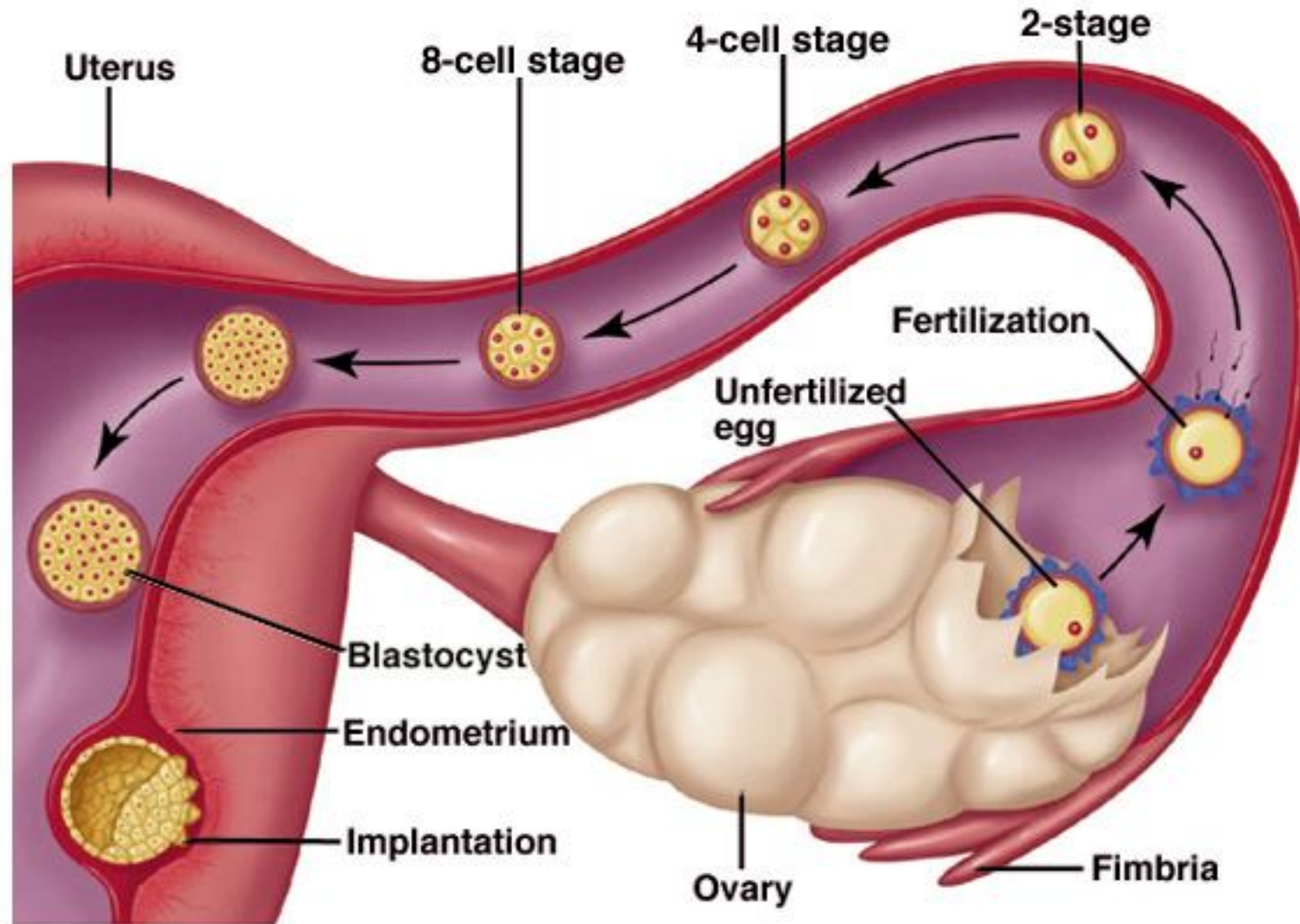


- Characteristic facial patterning, mental retardation
- 1 / 800 live births

Down syndrome—maternal age effect



Stages of Development-Early Embryo

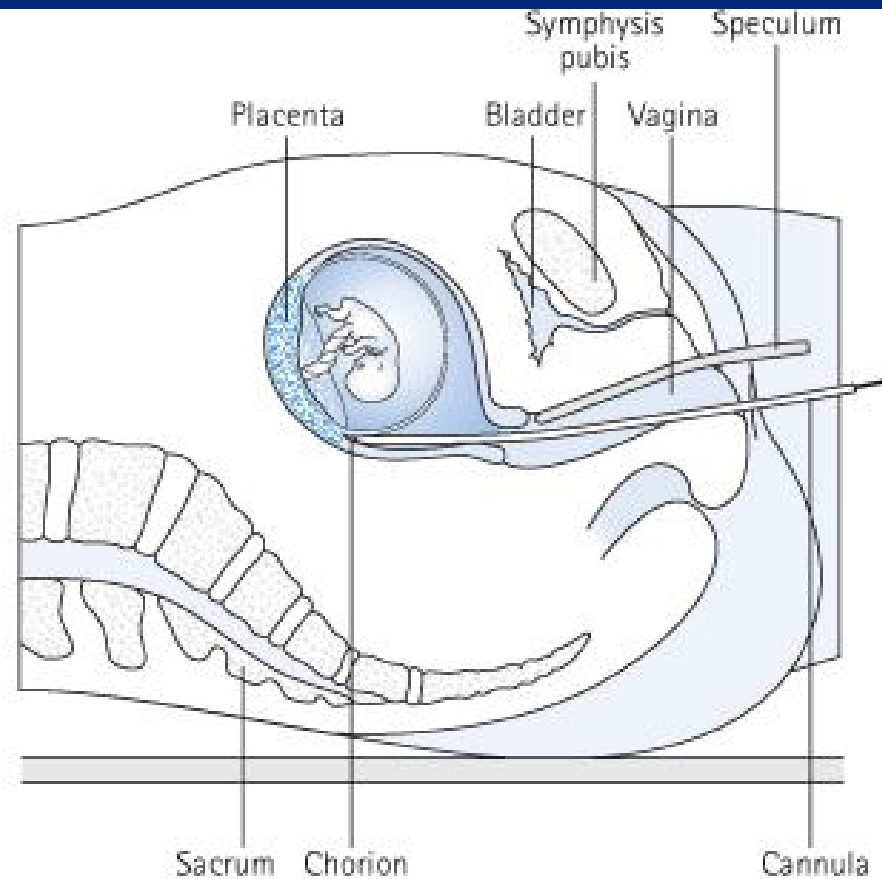


Methods of Prenatal Genetic Testing

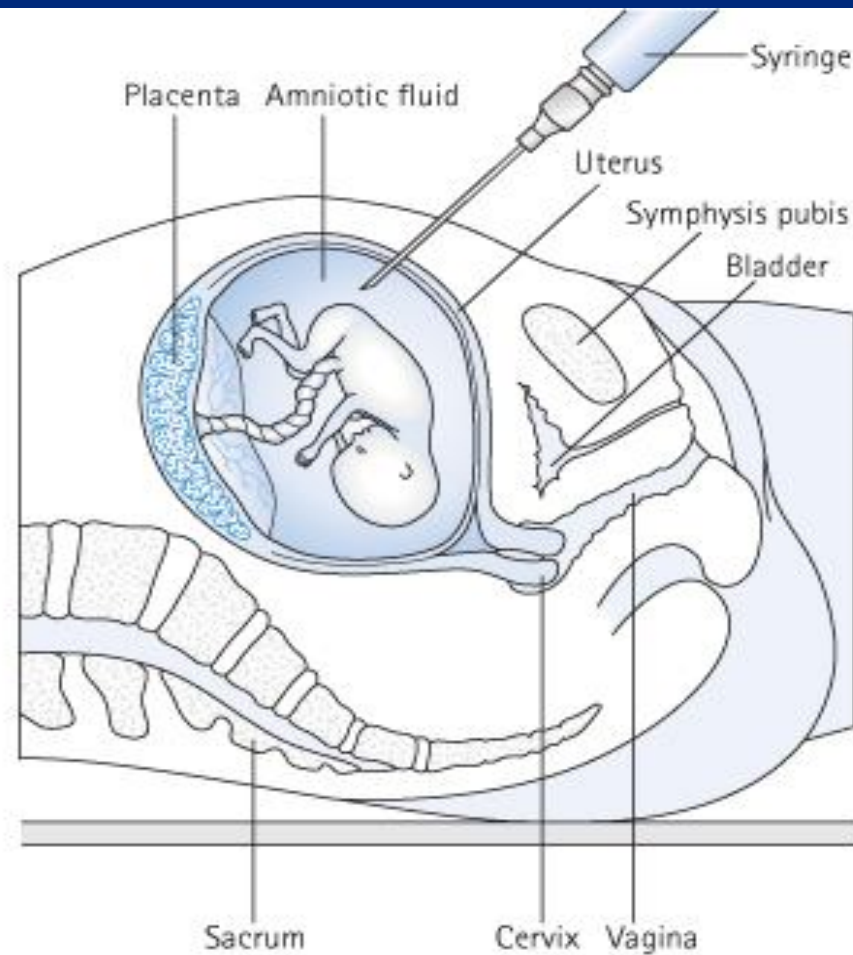
- Amniocentesis
- CVS
- Ultrasound
- Maternal serum screening (Labcorp, 2006)
 - **Four Methods of testing**
 - Cytogenic testing: analysis of the number and shape of chromosomes
 - Fluorescence in situ hybridization: protein analysis/chromosomal arrangements and study of protein markers
 - Biochemical testing: protein and enzyme analysis of the blood
 - Indirect/direct analysis of DNA strands (Carrier screening)
 - (Labcorp, 2006)



A diagram of technique of transvaginal chorionic villus sampling



A diagram of technique of amniocentesis



MOSAICISMO PLACENTARIO CONFINADO

- 1-2 % DE LOS CASOS
- GENERALMENTE TRISOMIAS
(21,13,18)
- 90 % CONFINADO A LA PLACENTA
- REQUIERE CONFIRMACION POR
AMNIOCENTESIS
- ECOGRAFIA ES MUY UTIL

Frequent Chromosome Abnormalities

Disorder	Chromosomal Genotype	Frequency
Abnormal no. of chromosome sets		
Triploidy	69XX, 69XY	Frequent in miscarriage
Tetraploidy	92XX, 92XY	Frequent in miscarriage
Abnormal no. of autosomes		
Trisomy 21		1/600
Trisomy 18		1/5000
Trisomy 13		1/15.000
Abnormal no. of sex chromosomes		
Klinefelter syndrome	47XXY	1/1000 males
XYY-syndrome	47XYY	1/1000
Turner syndrome	45X0, 45X/46X0, 45X/46XY (mosaic)	1/5.000 females
Triple-X syndrome	XXX	1/1000

SINDROMES KLINEFELTER Y TURNER

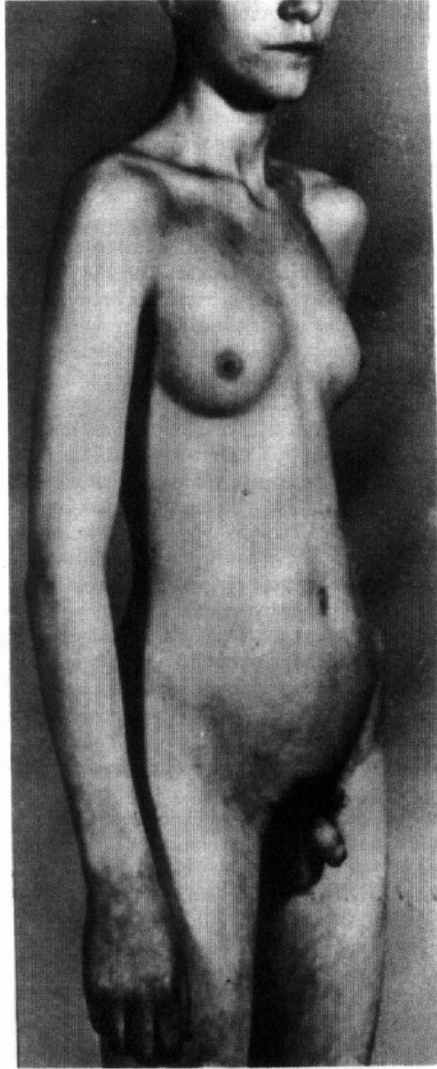


Figure 58-4 Klinefelter's syndrome. (Used with permission from Blackwell Science.)

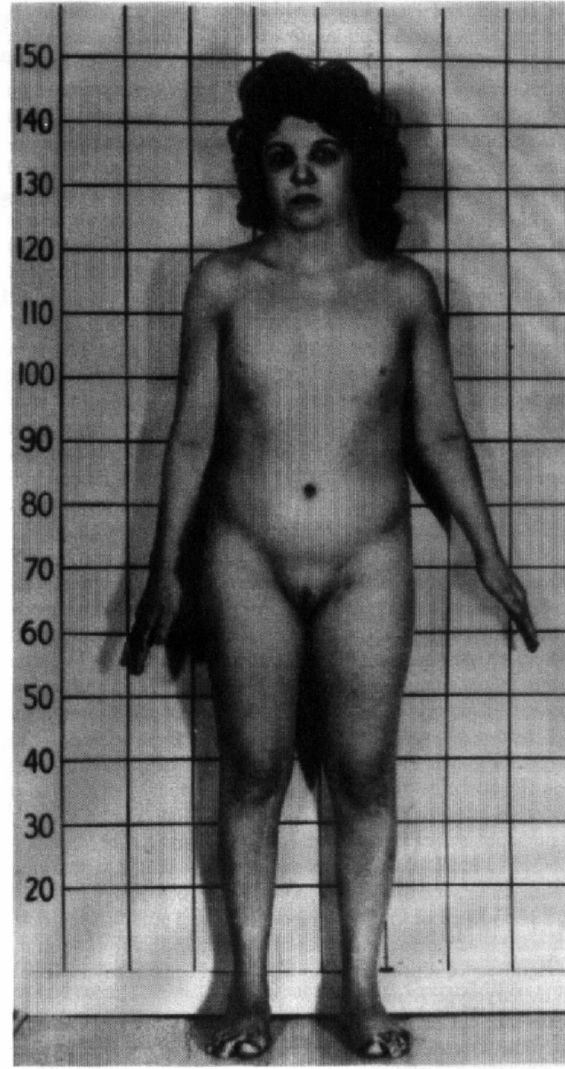
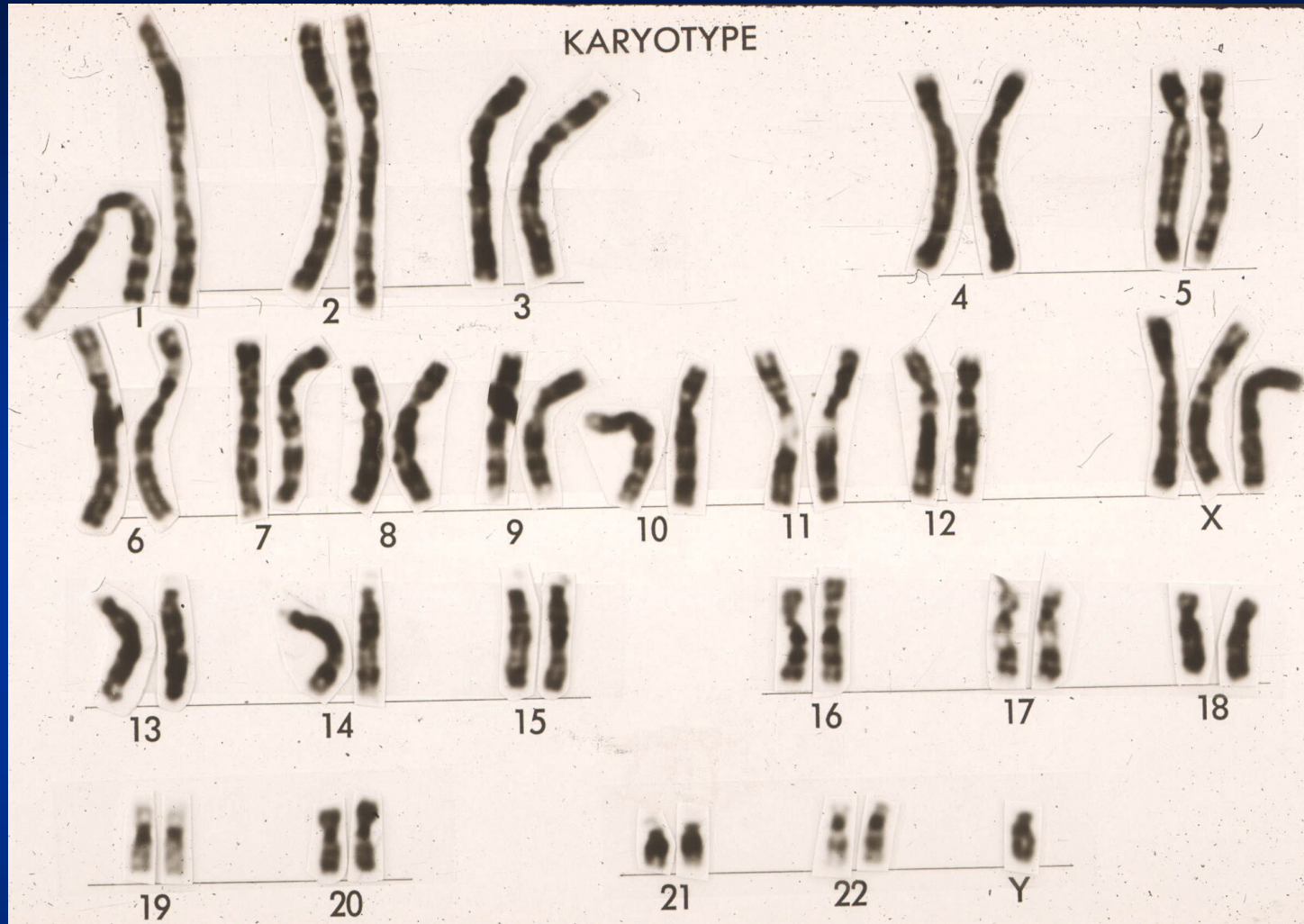


Figure 58-5 Turner's syndrome. (Used with permission from Blackwell Science.)



48,XXXY

Síndrome XXXY (análogo Klinefelter)

Turner syndrome

- 1/5,000 females
- Gonadal dysgenesis, disappearance of eggs
- Sexual immaturity
 - Amenorrhea
 - Infertility
- Short stature
- Somatic abnormalities
- Something wrong with the second X in some cells

SINDROMES KLINEFELTER Y TURNER

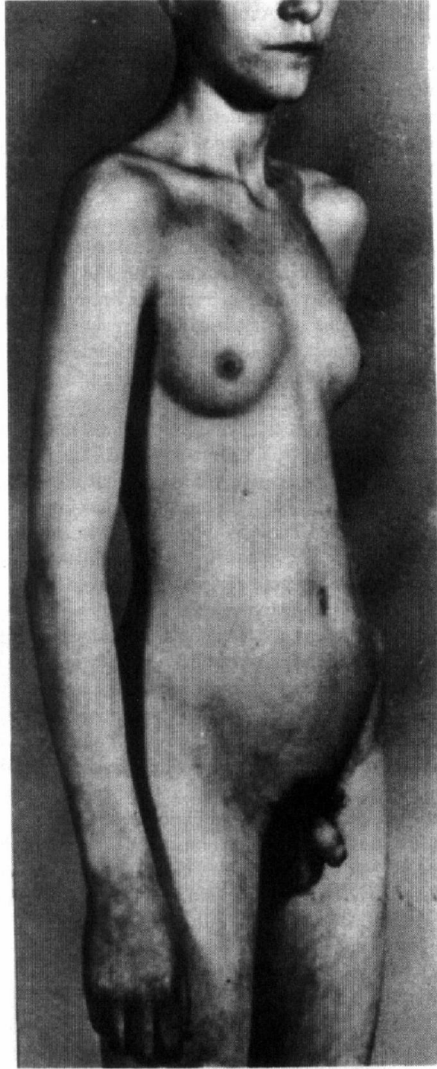


Figure 58-4 Klinefelter's syndrome. (Used with permission from Blackwell Science.)

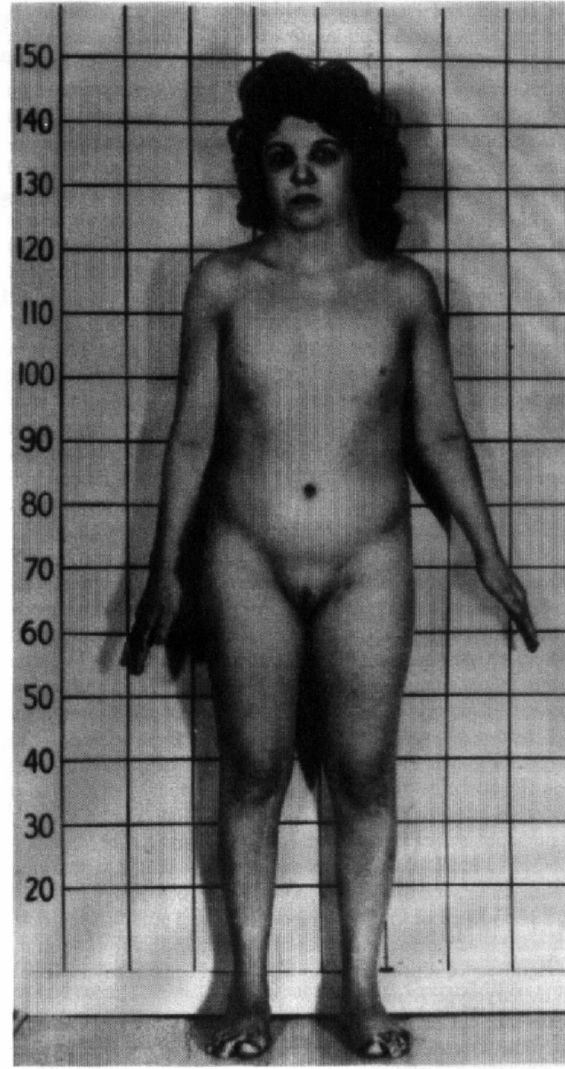


Figure 58-5 Turner's syndrome. (Used with permission from Blackwell Science.)

Turner syndrome



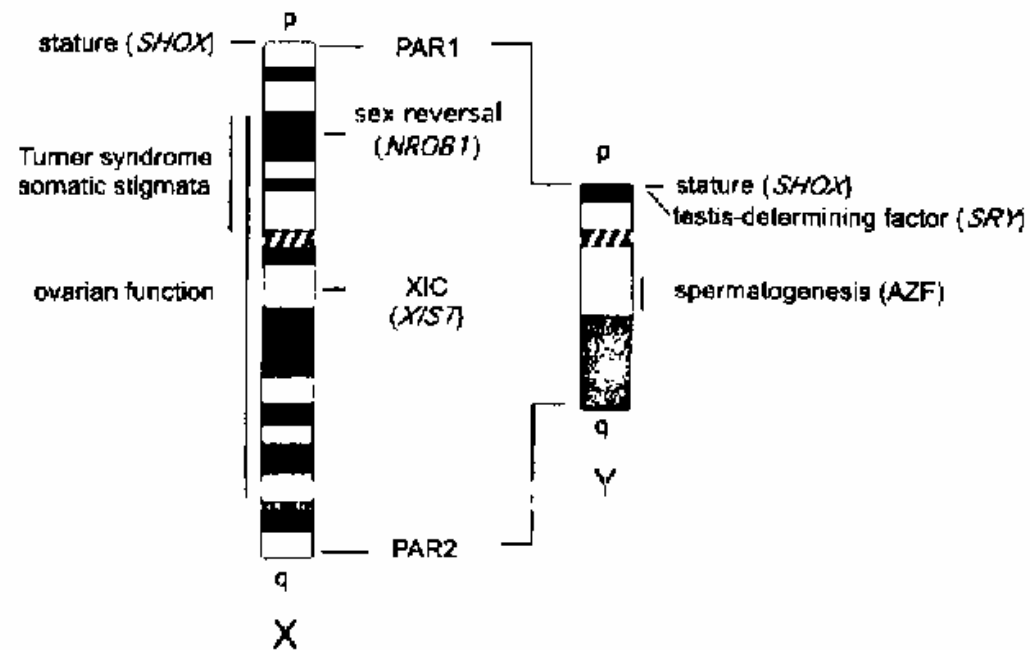
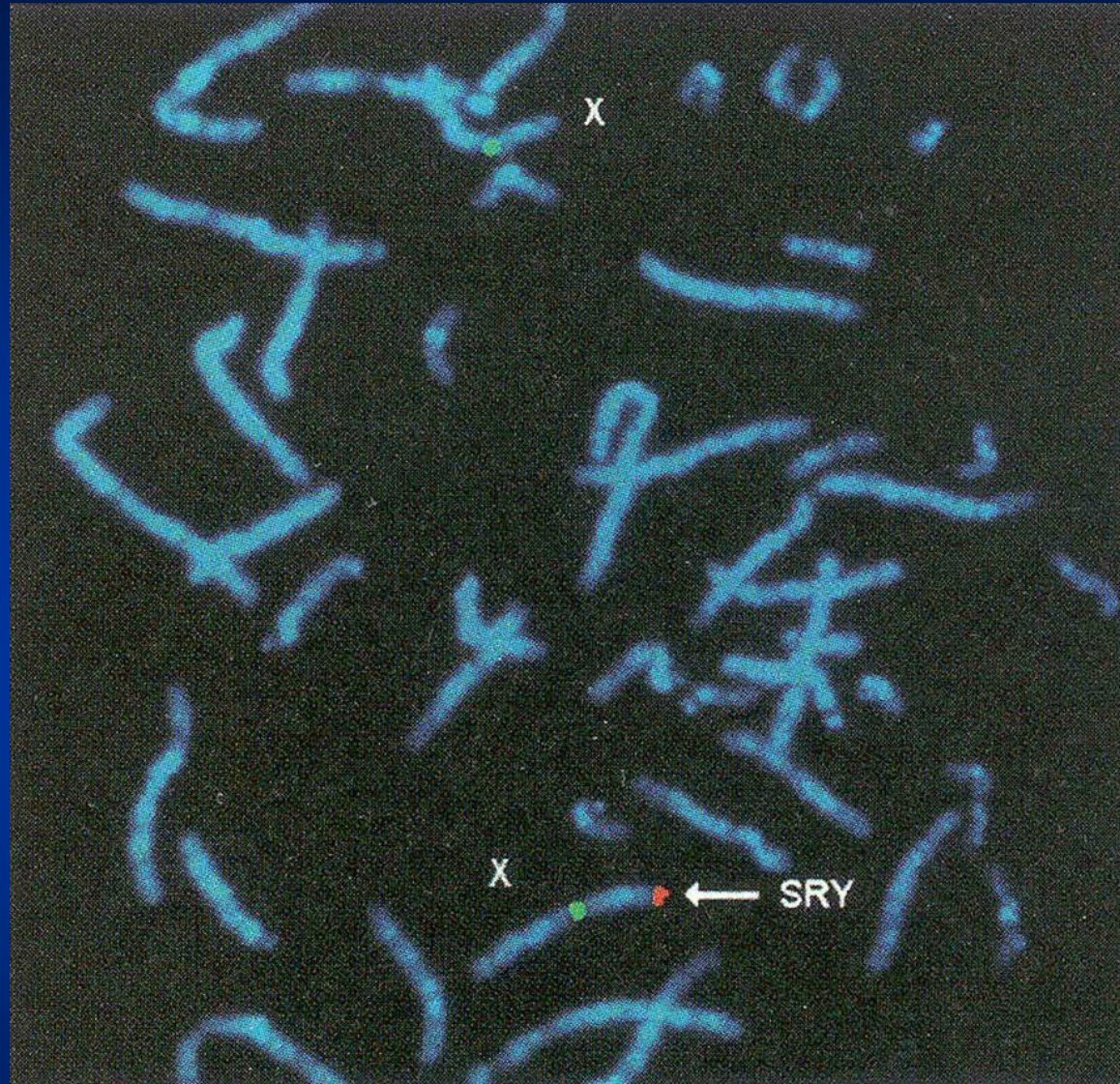


Figure 42-1 Schematic depiction of human sex chromosomes and approximate location of key genetic loci discussed in the text. Symbols for cloned genes in parentheses. p, short arm; q, long arm.

BASES MOLECULARES DEL SINDROME DE TURNER

- **Presencia de un solo gen pseudoautosomal SHOX**
- **SHOX codifica un miembro de la flia. de proteínas “homeodomain box” (60 aa) que actúan sobre promotores de genes que regulan patrones de desarrollo anatómico. En este caso, sobre las células osteogénicas durante el desarrollo de los miembros.**



Síndrome del fenotipo masculino y genotipo femenino

SINDROME DE RETARDO MENTAL POR X FRAGIL

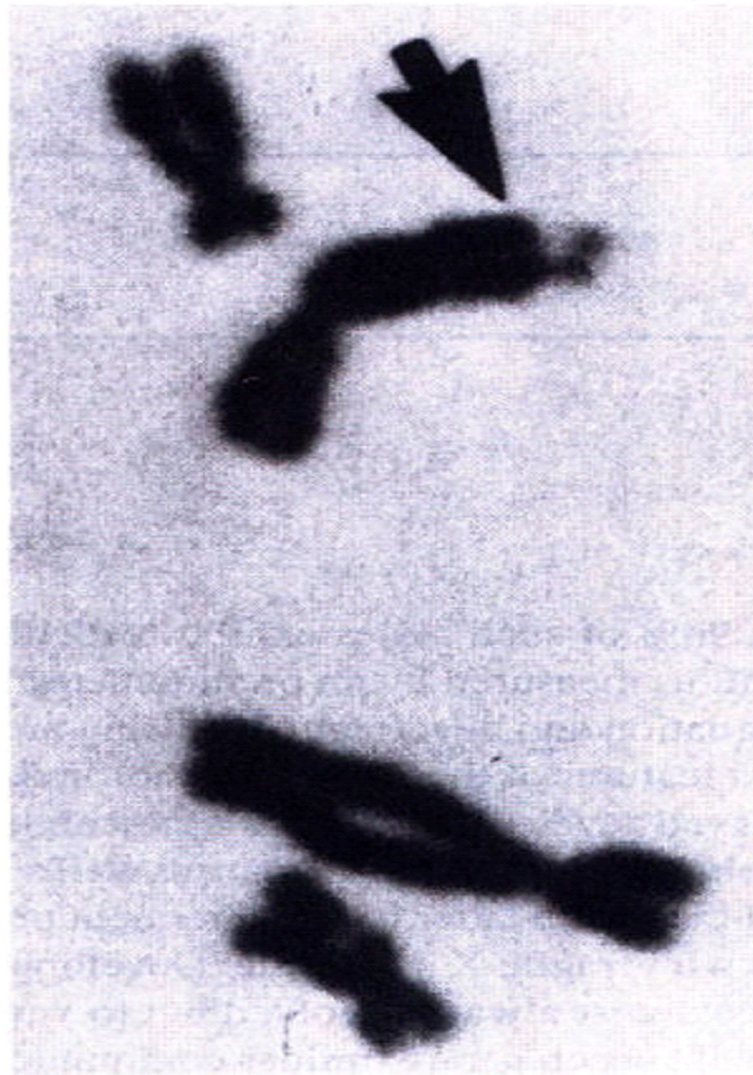
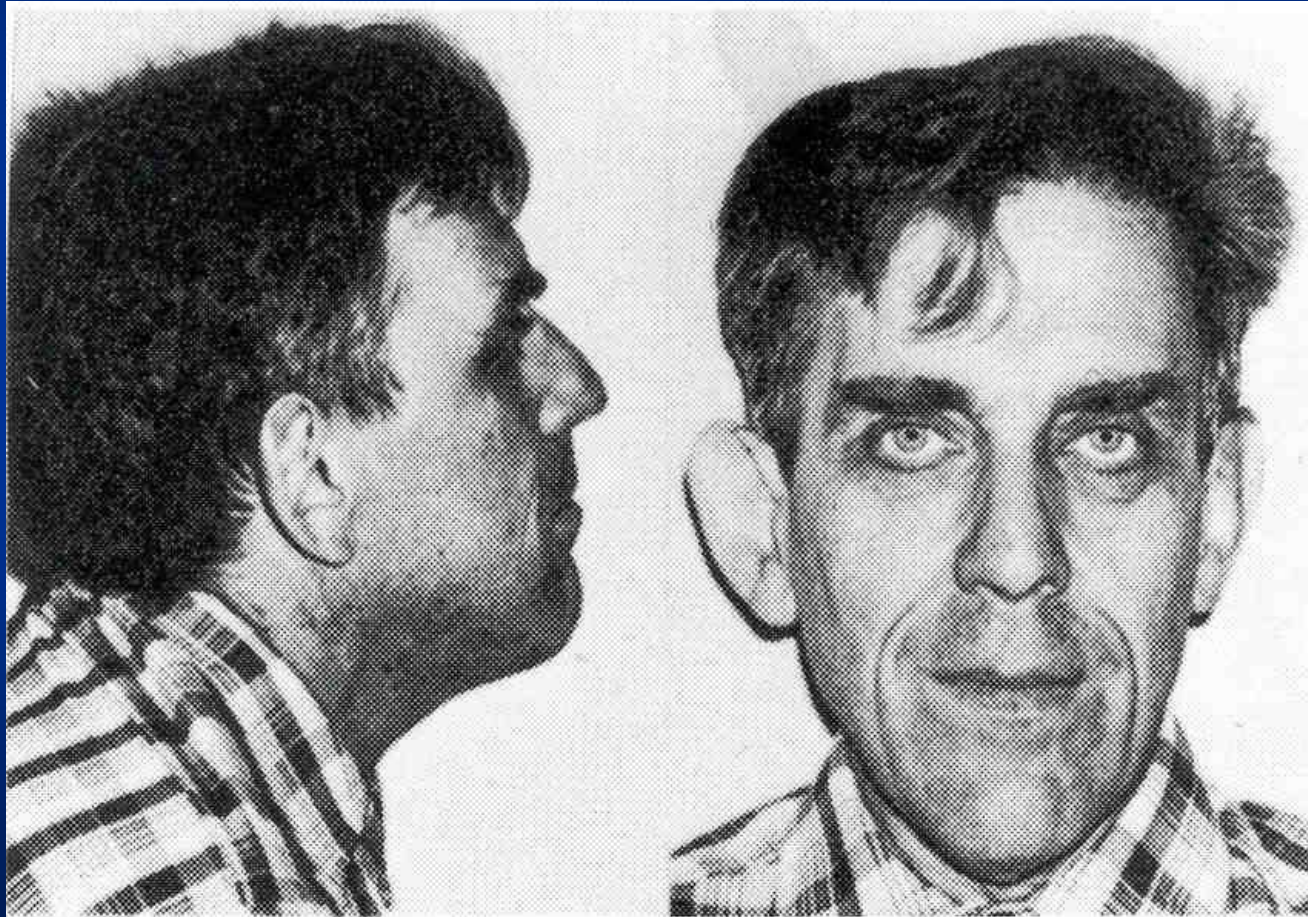


Figure 118-1 Partial karyotype of Geimsa-stained human chromosomes showing the fragile X site (arrow). (Reprinted with permission from JAMA 1994;271:536–542.)

Fragile X syndrome



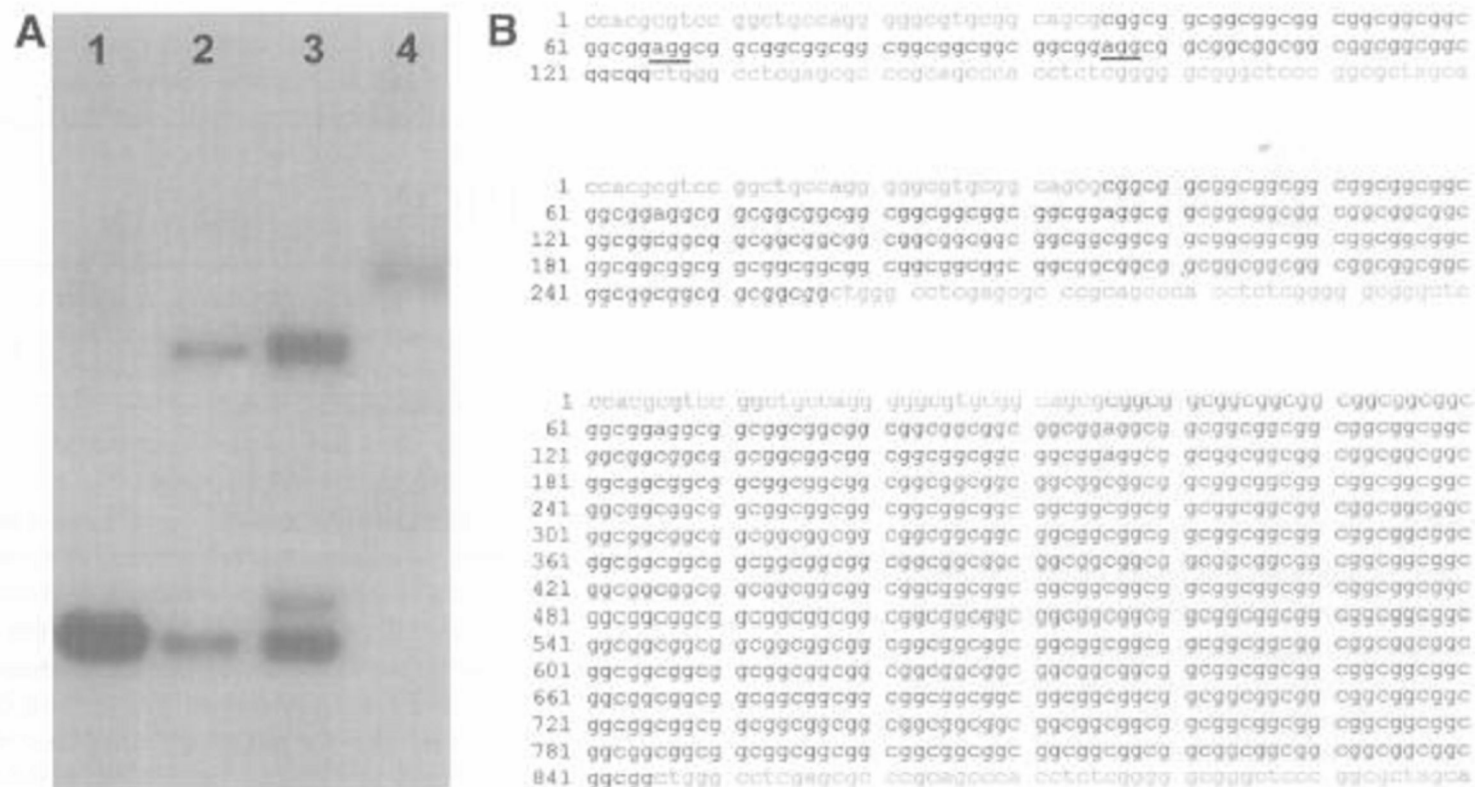


Figure 2-1 Triplet repeat expansion in fragile X syndrome. The gel (A) shows Southern blot-based testing for several individuals including a normal male—lane 1, a normal female—lane 2, a female premutation carrier—lane 3, and an affected male—lane 4. DNA is double digested with *EcoRI*, a restriction enzyme that cuts on either side of the triplet repeat, and *EagI*, a methylation-sensitive enzyme that only cuts unmethylated DNA (including one site near the Fragile X triplet repeat). DNA is loaded from the top of the gel and separated by electrophoresis. A radioactively labeled probe, which binds near the triplet repeat, is used to visualize the bands of interest. Because *EagI* only cuts unmethylated DNA, the methylated (inactive) allele is not cut and is seen as a 5.2-kb fragment (containing the triplet repeat). The unmethylated (active) allele is cut by *EagI* and is seen as a 2.8-kb fragment (also containing the triplet repeat). Normal males have only the 2.8-kb fragment, representing the unmethylated allele from the active X chromosome, as seen in lane 1. Because they have two X chromosomes, normal females have both a 2.8-kb fragment and a 5.2-kb fragment, representing the methylated (inactive) and the unmethylated (active) alleles (lane 2). The female premutation carrier (lane 3) has two bands around 2.8 kb, one slightly larger because of the triplet repeat expansion of about 70 repeats (210 nucleotides). These additional 210 nucleotides represent approx 8% of the 2.8-kb fragment, so two lower bands are seen. The upper, methylated, fragment also has two bands, but because the 210 extra nucleotides only account for approx 4% of the whole fragment, the two bands do not separate enough to be visualized. The affected male in lane 4 has only one allele, seen as a fragment larger (above) than the 5.2-kb alleles in the female premutation carrier (lane 3) because of the increased size of the triplet repeat region of the fragment (estimated to be 330–530 repeats). Because males have only one X chromosome, this band represents a full-size expansion of the triplet repeat, which leads to methylation (inactivation) of the gene, resulting in Fragile X syndrome. Examples of the sequence (B) are shown for normal, a pre-expansion carrier and an affected allele, with the expansion shown in black and flanking sequence shown in gray. The normal allele in this figure has 30 CGG repeats, the premutation 74, and the full expansion 270. (Fig. 2-1A is courtesy of Stuart Schwartz and Linda Jeng.)

Triplet Repeat Diseases

Location of Trinucleotide Repeats in Disease Genes

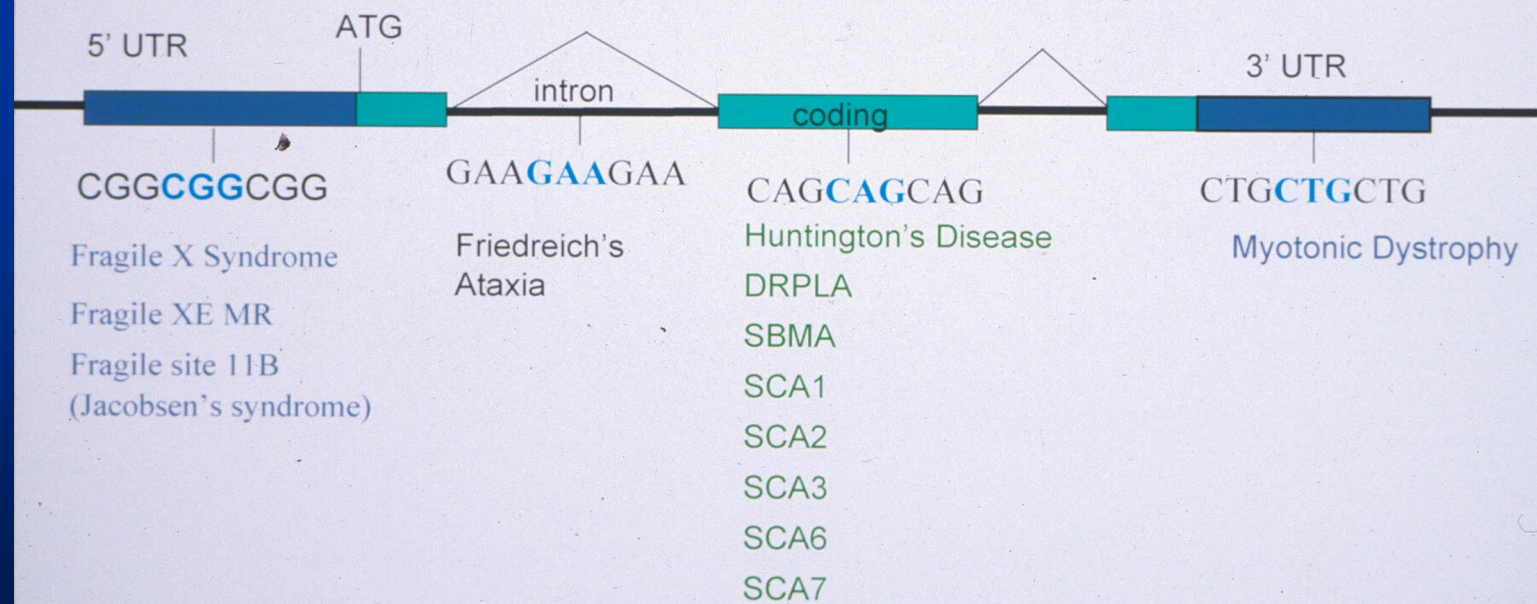


Table 2-1
Examples of Other Triplet Repeat Expansion Disorders

<i>Disorder</i>	<i>Inheritance</i>	<i>Triplet sequence</i>	<i>Normal number of repeats</i>	<i>Number of repeats associated * with disorder</i>
Myotonic dystrophy	AD	CTG	5–27	>50 to >1000
Huntington disease	AD	CAG	9–37	>37
Spinocerebellar ataxia type I	AD	CAG	19–38	40 to >80
Friedreich ataxia	AR	GAA	7–20	>200
Fragile X syndrome	XLR	CGG	6–52	>200
X-linked spinobulbar atrophy	XLR	CAG	19–25	>40

AD, autosomal-dominant; AR, autosomal-recessive; XLR, X-linked-recessive.

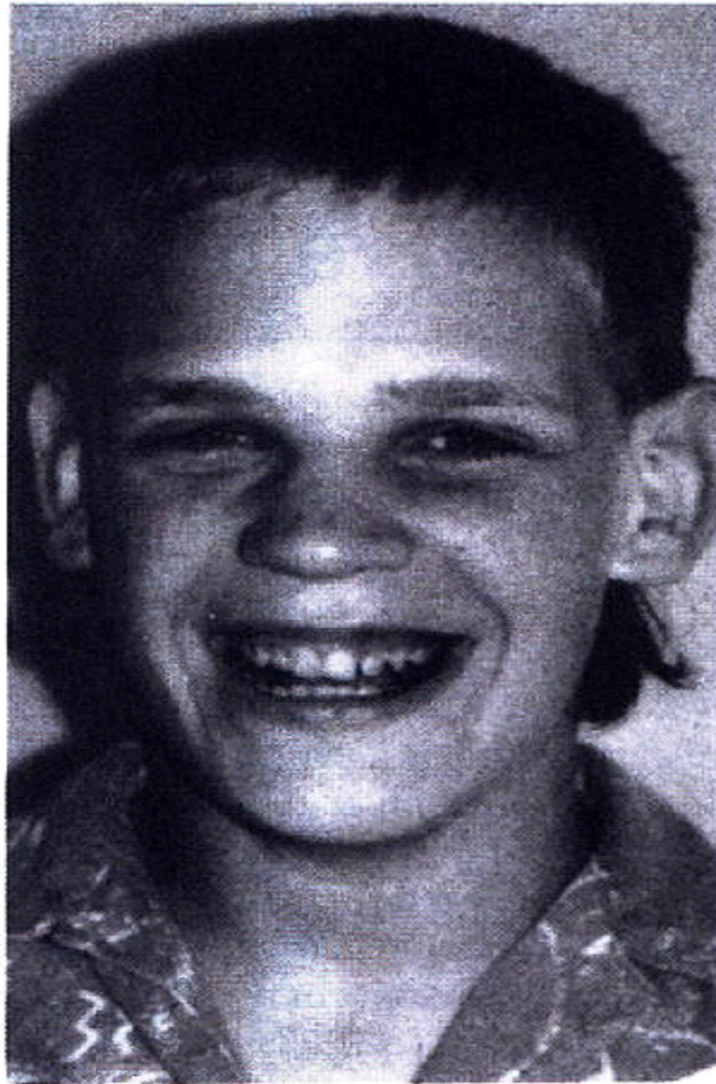


Figure 118-2 Mentally retarded adolescent male with fragile X syndrome. Note long facies with prominent forehead and ears. Typical of most patients, there is no major dysmorphism associated with this syndrome, confounding the clinical diagnosis. (Reprinted with permission from JAMA 1994;271:536–542.)

EXAMPLES OF DIFFERENT TYPES OF MUTATIONS

Type of mutations	Example
Genome	
Abnormal Chromosome set	Triploidy, tetraploidy
Chromosome	
Abnormal number of autosomal chrom.	Trisomy 21, 18, 13
Abnormal number of sex chromosomes	Klinefelter and Turner syndrome
Translocation	Acute myeloid leukemia t (9;22) (q34;q11) "Philadelphia chromosome"
Deletion	Cri du chat syndrome 5p-
Gene	
Deletion	Duchenne muscular dystrophy. Thalassemia
Duplication, insertion	Charcot-Marie-Tooth Type I
Triplet expansion	Fragile X syndr., Huntington disease
Missense point mutation	Cystic fibrosis
Splicing mutation	β Globin

ENFERMEDADES GENÉTICAS (3-5%)

- Trastornos cromosómicos
- **Trastornos mendelianos o monogénicos**
- Enfermedades multifactoriales
- Formas no-clásicas de enfermedad genética (imprinting genómico, etc)
- Trastornos mitocondriales
- Mutaciones que surgen en células somáticas diferenciadas

Mutations

- ✍ A change in the DNA sequence of the gene
- ✍ All cells acquire mutations as they divide
 - ✍ rate of approx 10^{-6} per gene per cell
- ✍ Mutations can alter protein product of DNA, stop gene working or activate gene

Types of Mutation

- **Deletion** - DNA missing
- **Insertion** - extra DNA inserted
- **Expansion** - DNA repeat size has increased
- **Point Mutation** - change in one base

Types of Mutation (in coding sequence)

AGC TTC GAC CCG	Wild type
AGC TCG ACC CG	Deletion
AGC TTC CGA CCC G	Insertion
AGC TTC TTC GAC CCG	Expansion
ATC TTC GAC CGG	Point mutation
ATC TGA	Nonsense 'stop'

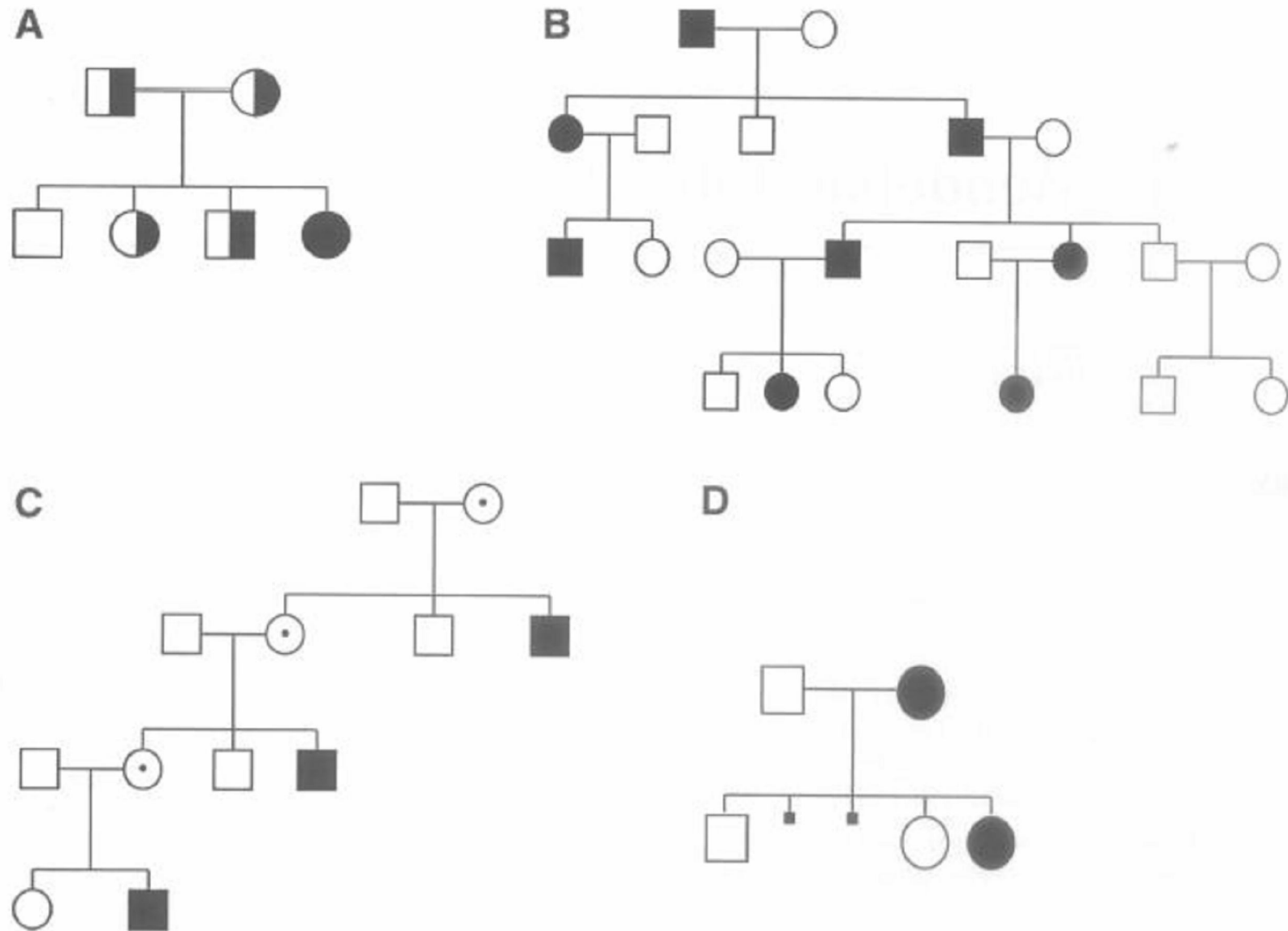


Figure 1-1 Pedigrees depicting autosomal-recessive (A), autosomal-dominant (B), X-linked-recessive (C), and X-linked-dominant with male lethality (D). By convention, squares denote males, circles females, and filled-in symbols are individuals who manifest a phenotype. Half-filled symbols in the recessive pedigree are carriers, and females with dots in the X-linked recessive pedigree are heterozygotes.

PENETRANCIA

Está definida por la edad y frecuencia con que se expresa una mutación determinada

Selected Monogenic Disorders

Autosomal dominant disorders

- Familial hyperlipidemia
- Familial hypercholesterolemia
- Huntington disease
- von Willebrand disease

Autosomal recessive disorders

- Cystic fibrosis
- Sickle-cell anemia
- β -Thalassemia
- α 1-antitrypsin deficiency
- Hereditary nonpolyposis colon cancer
- Phenylketonuria
- Hemochromatosis
- Tay-Sachs disease
- Polyposis of the colon
- Familial breast cancer

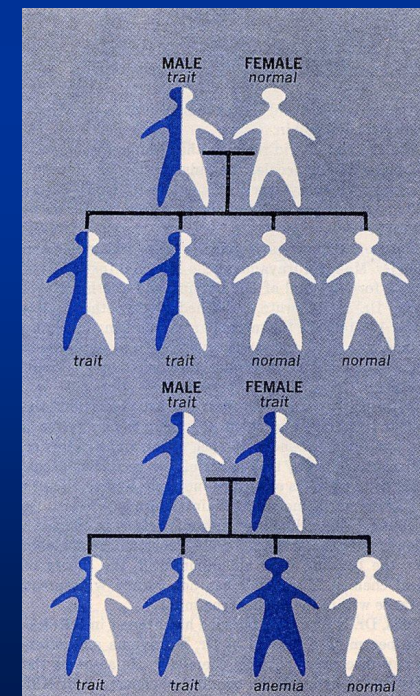
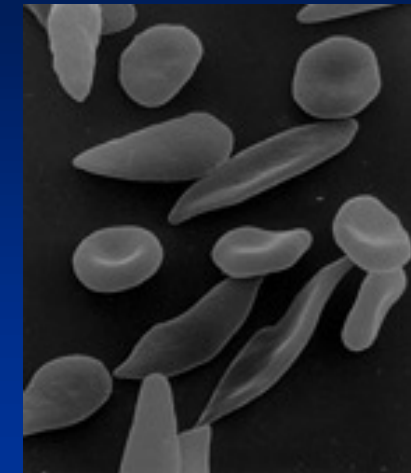
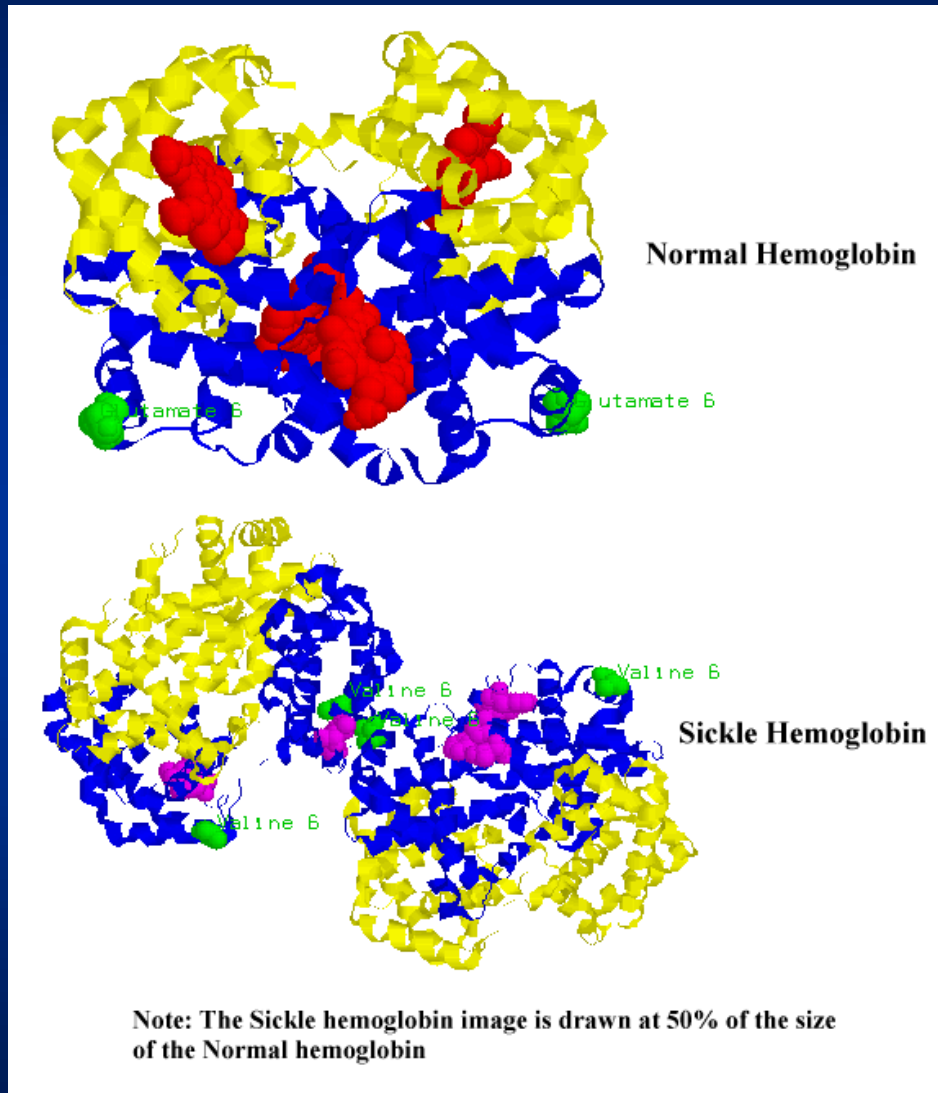
X-linked disorders

- Color blindness
- Hemophilia A
- Hemophilia B
- Duchenne muscular dystrophy
- Becker muscular dystrophy
- Fragile X syndrome

Sickle-cell anemia is due to a single base change -- a mutation

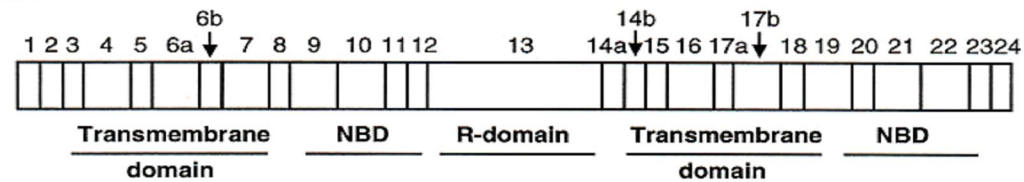
	1	2	3	4	5	6	7	8
Normal Hb A								
DNA	CAC	GTG	GAC	TGA	GGA	CTC	CTC	TTC
mRNA	GUG	CAC	CUG	ACU	CCU	GAG	GAG	AAG
Amino acid	val	his	leu	thr	pro	glu	glu	lys
Sickle Hb S								
DNA	CAC	GTG	GAC	TGA	GGA	CAC	CTC	TTC
mRNA	GUG	CAC	CUG	ACU	CCU	GUG	GAG	AAG
Amino acid	val	his	leu	thr	pro	val	glu	lys

ANEMIA CELULAS FALCIFORMES



Cystic fibrosis transmembrane regulator (CFTR)

CFTR cDNA



CFTR protein

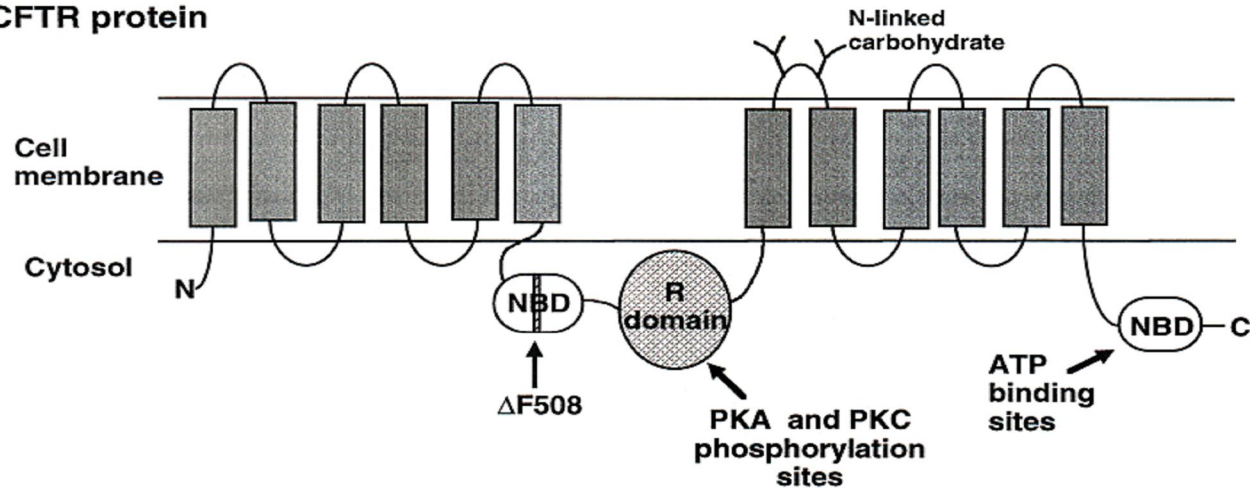


Figure 37-1 Structure of cystic fibrosis transmembrane conductance regulator (CFTR) cDNA and protein. Shown above is a schematic diagram of the structure of the CFTR cDNA with 27 exons indicated by boxes and labeled with the predicted protein domain coded for by the cDNA. A model of the CFTR protein positioned in the apical membrane of the epithelial cell is shown below. The transmembrane domains are flanked by nucleotide-binding domains (NBD) that bind ATP. The regulatory domain (R domain) contains sites for protein kinase A (PKA) and C (PKC) phosphorylation. The location of the $\Delta F508$ mutation is indicated. N is the amino-terminus and C is the carboxy-terminus of the protein. Sites of posttranslational glycosylation by amino (N)-lined carbohydrates are indicated. (Adapted from Zielenski and Tsui with permission from the *Ann Rev Gen*, 1995; 29; 777-807. © 1995 by Annual Reviews Inc.)

Destrucción del tejido pulmonar en Fibrosis Quística

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SECTION V / PULMONOLOGY

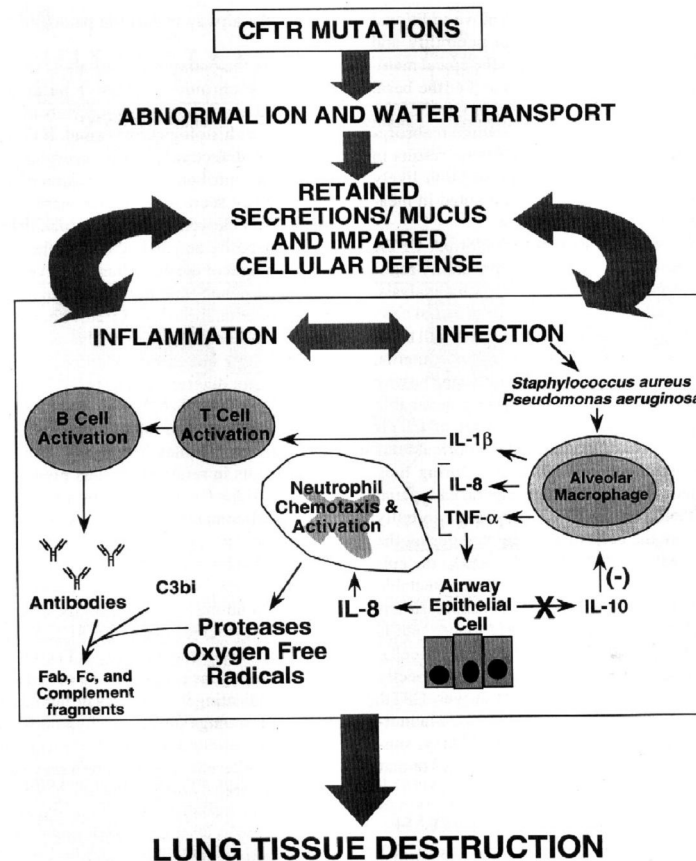


Figure 37-2 Pathogenesis of cystic fibrosis-related lung disease. Proposed mechanism for the development of CF-related lung disease. CFTR mutations lead to abnormal salt and water transport, which in turn result in retained desiccated airway secretions and possibly impaired defensin function. This results in chronic airways infection and inflammation that culminates in lung tissue destruction. The neutrophil is the central component of the inflammatory response being attracted to and activated in the CF airway by IL-8, TNF- α , and components of complement. Proteases and cytokines released by neutrophils attract additional inflammatory cells to CF airways, directly damage the airway, and may even perpetuate infection by cleaving antibodies and complement. (See text for further details.)

Table 37-1
Common Cystic Fibrosis Mutations^a

<i>Mutation</i>	<i>Frequency (%)^b</i>	<i>Mutation class^c</i>	<i>Phenotypic association</i>	<i>Population with increased prevalence^b</i>
ΔF508	66	II	Severe disease	
G542X	2.4	I	Severe disease	Spanish
G551D	1.6	III	Severe disease	English
N1303K	1.3	II	Severe disease	Italian
W1282X	1.2	I	Severe disease	Ashkenazi-Jewish
R553X	0.7	I	Severe disease	German
621 + 1G→T	0.7	I	Severe disease	French Canadian
1717-1G→A	0.6	I	Severe disease	Italian
R117H	0.3	IV	Pancreatic sufficiency	
3849+10 kb C→T	0.2	V	Pancreatic sufficiency normal sweat chloride	

^aAdapted from: Zielenski J, Tsui LC. Cystic fibrosis: genotypic and phenotypic variations. In: Annual Reviews of Genetics. Palo Alto: Annual Reviews, 1995;777-807. Used with permission of Annual Reviews, Inc.

^bMutations are designated by the code letter for the normal amino acid, followed by the amino acid position, and the letter of the substituted amino acid or an X, which denotes a nonsense mutation. A Δ indicates deletion of the amino acid whose letter follows it at the noted position. A + or - indicates mutations at various positions within introns relative to the cited position.

^cMutation class designated by biochemical or physiologic effect on CFTR protein.

ENFERMEDADES GENÉTICAS

- Trastornos cromosómicos
- Trastornos mendelianos ó monogénicos
- **Enfermedades multifactoriales**
- Formas no clásicas (imprinting genómico)
- Trastornos mitocondriales
- Mutaciones en células somáticas diferenciadas

**ENFERMEDADES
MULTIFACTORIALES O RASGOS
GENETICOS COMPLEJOS**

ASMA

ARTRITIS REUMATOIDE

DIABETES MELLITUS

ESQUIZOFRENIA

HIPERTENSION

DESVIACIONES DE LEYES MENDEL

- **PENETRANCIA / NO PENETRANCIA**
- **MUTACIONES NUEVAS**
- **MOSAICISMO**
- **ANTICIPACION**
- **IMPRINTING**
- **HERENCIA DIGENICA**

ENFERMEDADES GENÉTICAS

- Trastornos cromosómicos
- Trastornos mendelianos ó monogénicos
- Enfermedades multifactoriales
- **Formas no clásicas (imprinting genómico)**
- Trastornos mitocondriales
- Mutaciones en células somáticas diferenciadas

Genomic Imprinting

- **Some genes are turned off when inherited from the father and turned on when inherited from the mother.**
- **Other genes are turned on when inherited from father but turned off when inherited from mother.**
- **Mechanisms: methylation; phosphorylation of histones.**

SINDROME DE PRADER-WILLI

**Hiperfagia, Hipotonia,
Hipogonadismo, Obesidad**

SINDROME DE ANGELMANS

“Síndrome de Happy Puppet”

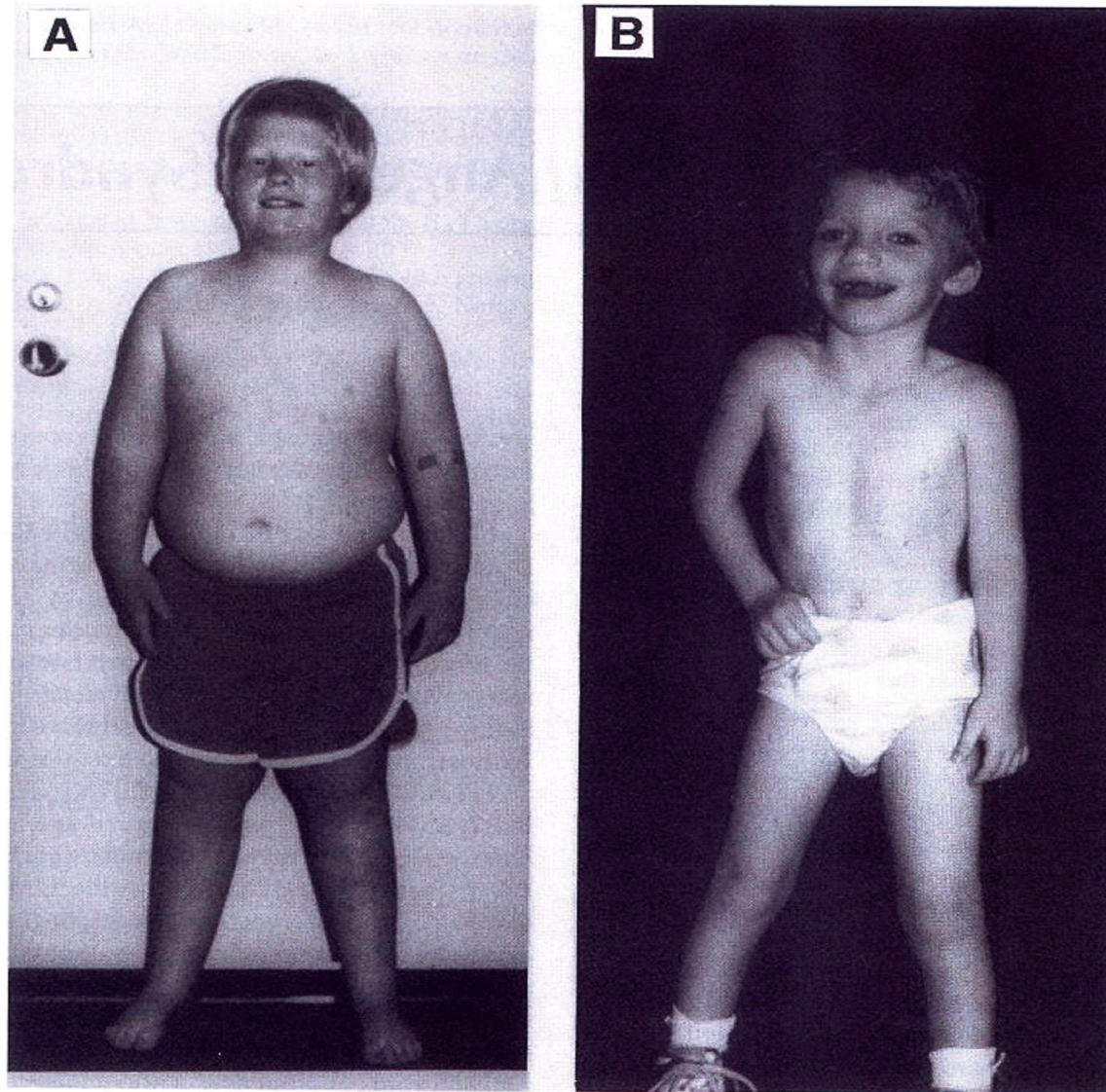


Figure 117-1 Clinical phenotype of children with (A) Prader-Willi syndrome or with (B) Angelman syndrome. Note the central obesity, short stature, small hands and feet, and almond-shaped eyes/narrow bifrontal diameter in the PWS child, and the happy disposition, wide-spaced mouth, and teeth, and broad stance of the AS child. (Reprinted with permission from Butler MG. Prader-Willi syndrome: current understanding of cause and diagnosis. *Am J Med Genet* 1990;35:319–332 [A]; and Williams CA, Zori RT, Stone JW, et al. Maternal origin of 15q11–13 deletions in Angelman syndrome suggests a role for genomic imprinting. *Am J Med Genet* 1990;35:350–353 [B]).

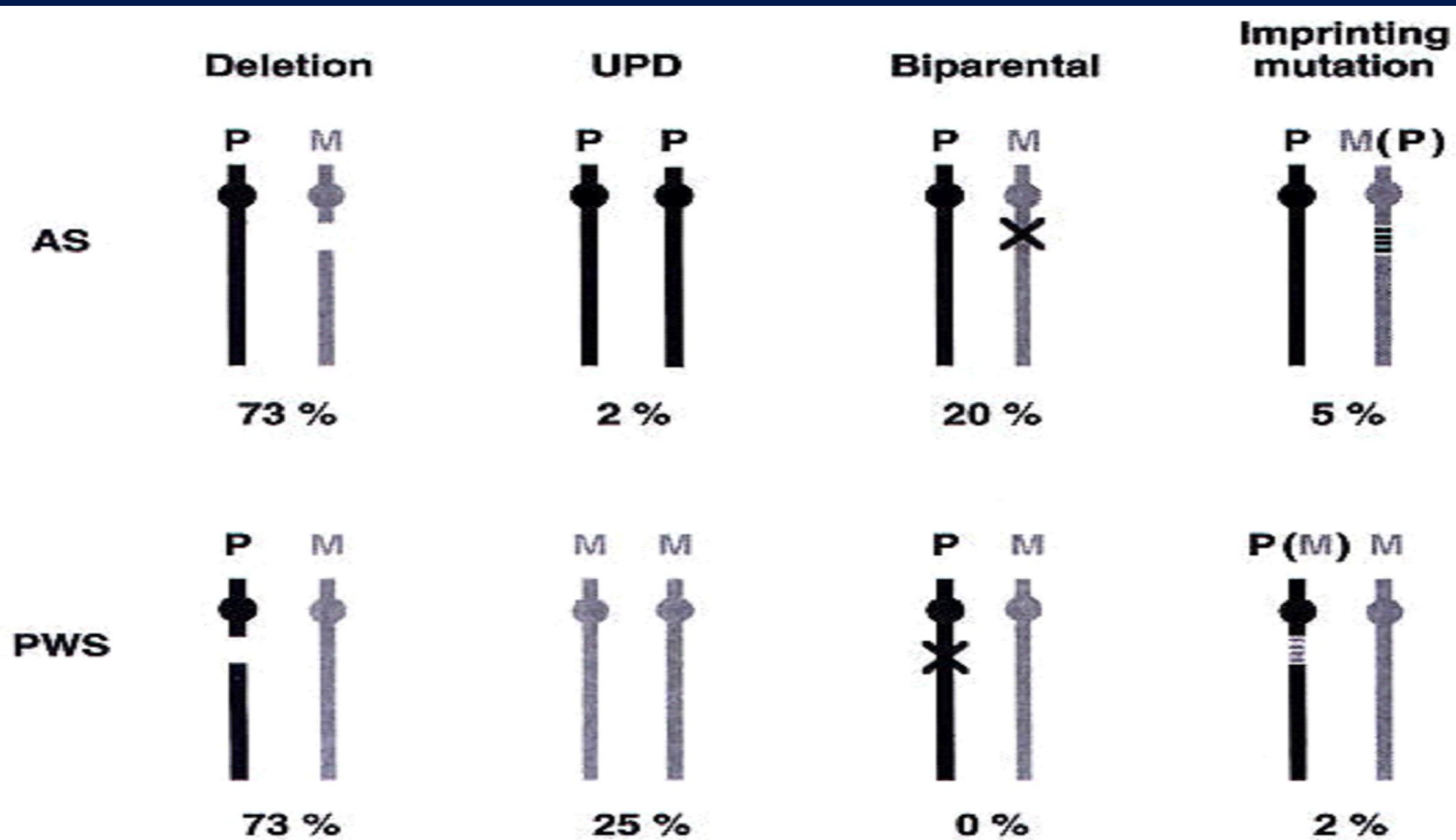


Figure 117-2 Molecular classes of Prader-Willi and Angelman syndromes. The chromosome 15 genotypes (and frequency) are shown for the major classes of AS and PWS. UPD, uniparental disomy; P, paternal (black); M, maternal (gray); M(P), maternal inheritance with paternal imprint (or epigenotype); P(M), paternal inheritance with maternal epigenotype; X, structural gene mutation. (See text for details.)

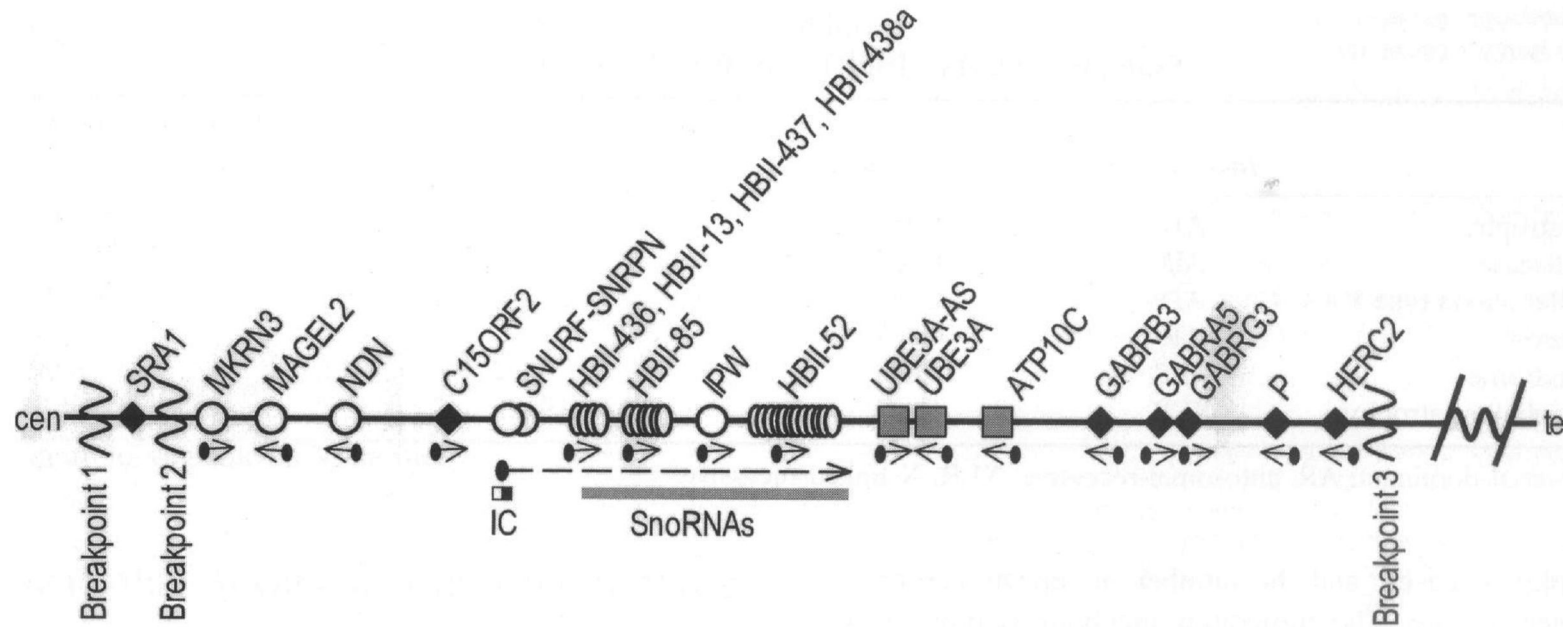


Figure 2-2 Gene map of Prader-Willi syndrome/Angelman syndrome region of chromosome 15. This represents approx 4–5 Mb of chromosome 15 just below the centromere. The common breakpoints of the recurrent deletions are shown. Open circles represent maternally imprinted (expressed only from the paternally inherited chromosome) genes. Gray squares are paternally imprinted genes, and black diamonds represent nonimprinted genes. The open ovals represent clusters of small nucleolar RNAs (SnoRNAs) that have been identified. The function of these RNAs is not known, but they are distributed in intronic regions between the 144 purported exons of SNURF/SNRPN. Arrows show the direction of transcription of genes, with the long, dashed arrow showing the direction and extent of the SNRPN exons. Any of the maternally imprinted genes potentially could contribute to the PWS phenotype, although evidence does not suggest a role for MKRN3 or IPW. The imprinting center is shown as two pieces, with the open rectangle representing the region controlling paternal imprinting (AS), and the filled portion representing the maternal imprint control (PWS) region.

ENFERMEDADES GENÉTICAS

- Trastornos cromosómicos
- Trastornos mendelianos ó monogénicos
- Enfermedades multifactoriales
- Formas no clásicas (imprinting genómico)
- **Trastornos mitocondriales**
- Mutaciones en células somáticas diferenciadas

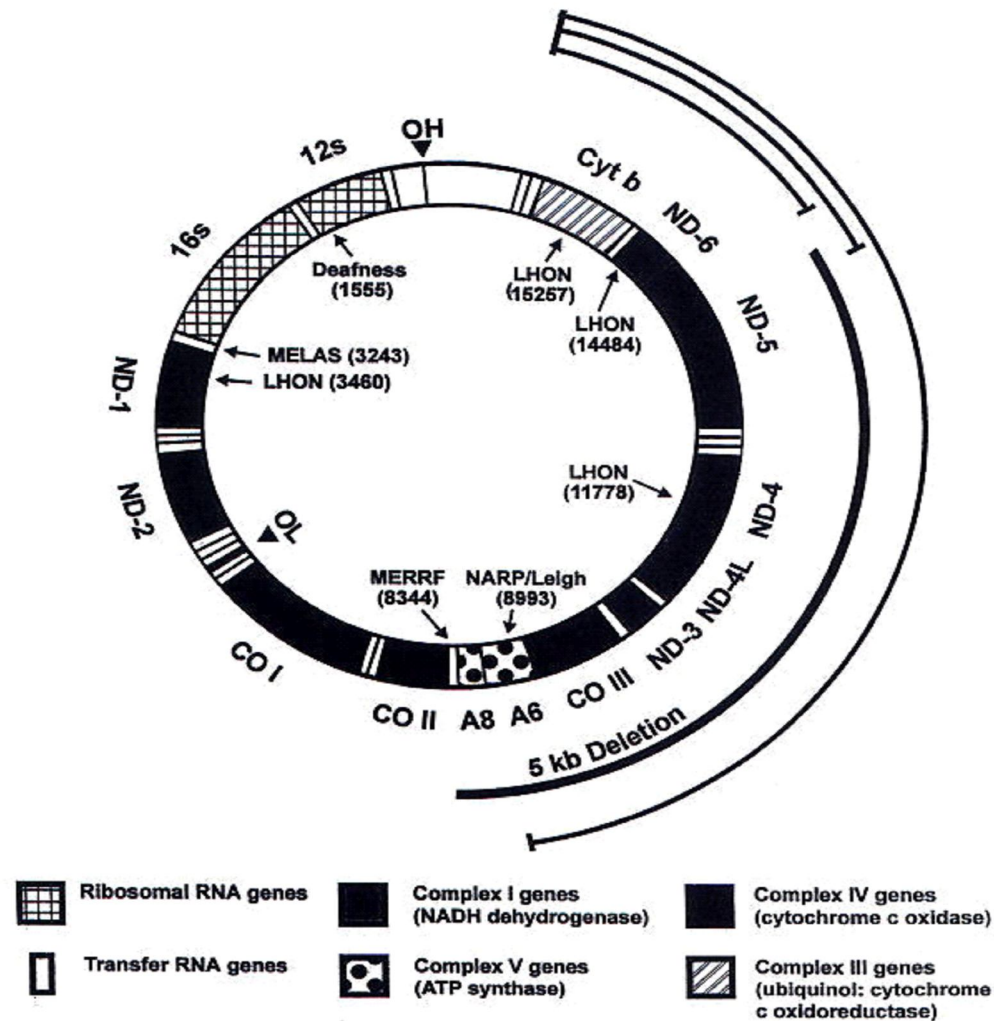


Figure 103-1 Schematic diagram of human mitochondrial DNA and the most prominent pathogenetic mutations. Inside the circle, point mutations in structural and protein-coding genes, with the clinical phenotype and the nucleotide position of the mutation; arcs outside the circle, the position of the most common single deletion, which is 5 kilobases in length, and the multiple deletions; *MERRF*, myoclonic epilepsy with ragged red fibers; *MELAS*, mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes syndrome; *LHON*, Leber's hereditary optic neuropathy; *NARP*, neuropathy, ataxia, and retinitis pigmentosa; Leigh, maternally inherited Leigh's disease. (Reproduced with permission from NEJM 1995;333:638-644.)

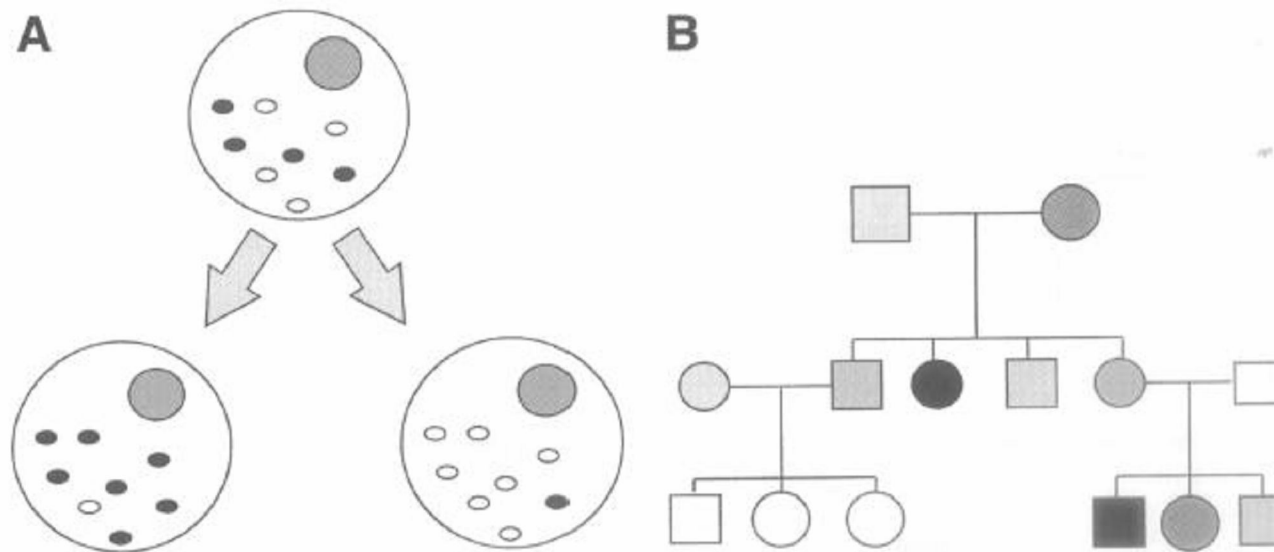


Figure 1-2 (A) Mutant and wild-type mitochondrial DNA may coexist in a cell, referred to as heteroplasmy. Mitochondrial DNA molecules segregate passively when a cell divides, so daughter cells may differ in their proportions of mutant and wild-type mitochondrial DNA. (B) Essentially, all the mitochondrial DNA is maternally transmitted. Hence, a female with a mitochondrial disorder will transmit it to all her offspring, whereas a male will not transmit the trait. Offspring may differ in their degree of expression of the phenotype because of heteroplasmy.

Table 4-6
Selected Mitochondrial Diseases

<i>Disease/syndrome</i>	<i>MIM no.</i>
MELAS syndrome: mitochondrial myopathy with encephalopathy, lactic acidosis, and stroke	540000
Leber optic atrophy: hereditary optical neuropathy	535000
Kearns-Sayre syndrome (KSS): ophthalmoplegia, retinal pigment degeneration, cardiomyopathy	530000
MERRF syndrome: myoclonic epilepsy and ragged red fibers	545030
Maternally inherited myopathy and cardiomyopathy (MMC)	590050
Neurogenic muscular weakness with ataxia and retinitis pigmentosa (NARP)	551500
Progressive external ophthalmoplegia (CEOP)	258470
Pearson syndrome (PEAR): bone marrow and pancreatic failure	557000
Autosomal dominant inherited mitochondrial myopathy with mitochondrial deletion	157640

Table 103-1

Neurological Manifestations of Mitochondrial Diseases

Ophthalmoplegia	Sensorineural hearing loss
Stroke-like episodes	Ataxia
Seizures	Dementia
Myoclonus	Peripheral neuropathy
Optic neuropathy	Vascular headache
Myopathy	Myelopathy

ENFERMEDADES GENETICAS

- Trastornos cromosómicos
- Trastornos mendelianos o monogénicos
- Enfermedades multifactoriales
- Formas no-clásicas de enfermedad genética (imprinting genómico, etc)
- Trastornos mitocondriales
- **Mutaciones que surgen en células somáticas diferenciadas**

- Further more it is vital that we, as health care professionals, along with prospective parents, are mindful that one genetic mutation is only a characteristic of the child. It does not define them entirely. (Asch, 1999)



