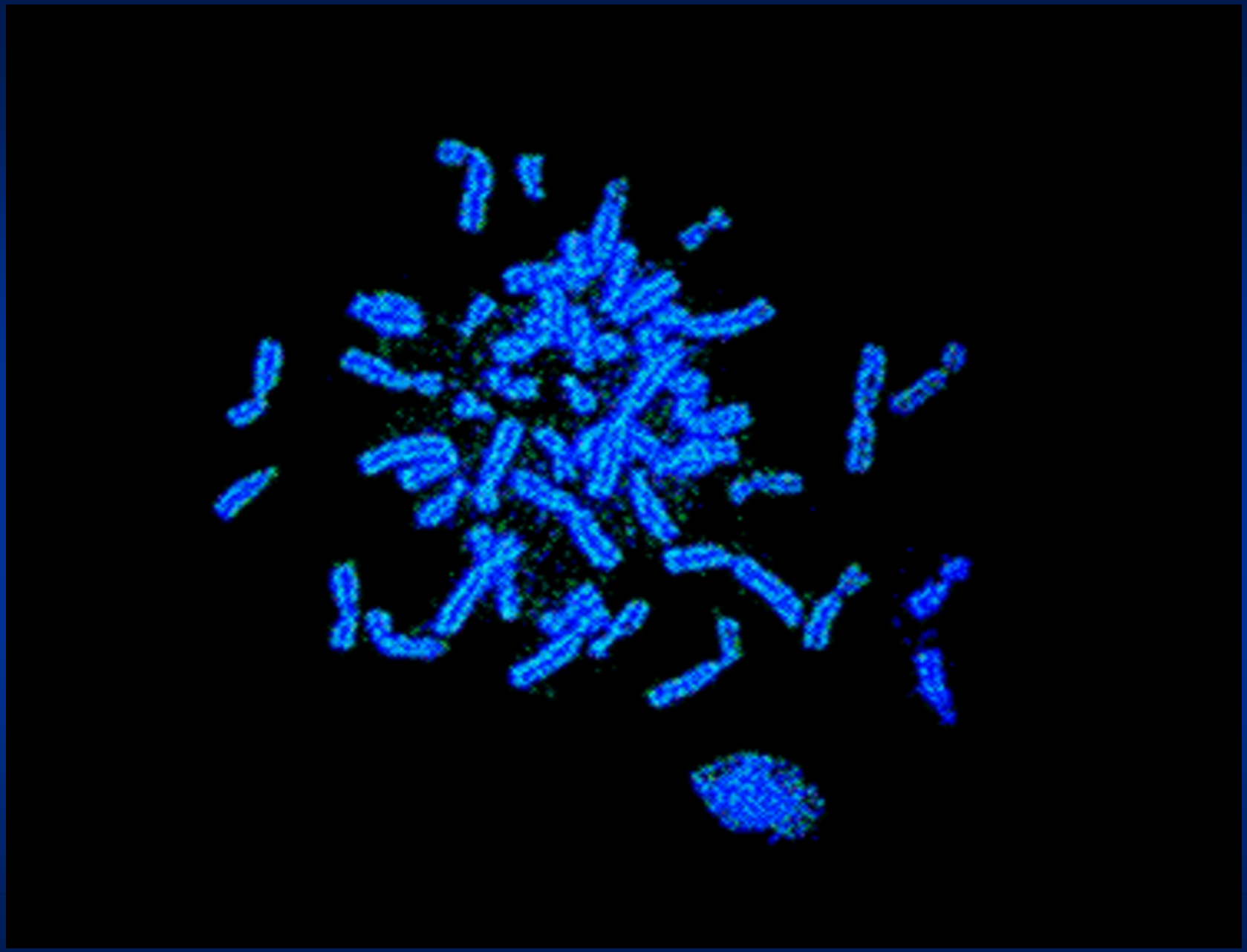
ENFERMEDADES GENETICAS

MEDICINA MOLECULAR, 2008



METAFASE DE UN LINFOCITO DE SANGRE PERIFERICA. DAPI

Size of the genome 2.91 Gbp

Percent of genome classified as repeats 35

Number of annotated genes 26,383

Percent of annotated genes with unknown function 42

Number of genes (hypothetical and annotated-2001) 39,114

Gene with the most exons Titin (234 exons)

Average gene size 27 kbp

Most gene-rich chromosome Chr. 19 (23 genes/Mb)

Least gene-rich chromosomes Chr. Y (5

Percent of base pairs spanned by genes 25.5

Percent of base pairs spanned by exons 1.1

Percent of base pairs spanned by introns 24.4

Percent of base pairs in intergenic DNA 74.5

Longest intergenic regio

Chr. 13 (3,038,416 bp)

Rate of SNP variation

1/1250 bp

Human Genome Overview

Venter et al., Science (2001)

Human Gene Content: Surprisingly Few Genes

Only 1% of genome are exons

Protein-coding Gene Number: 30,000-40,000

Human Genes:

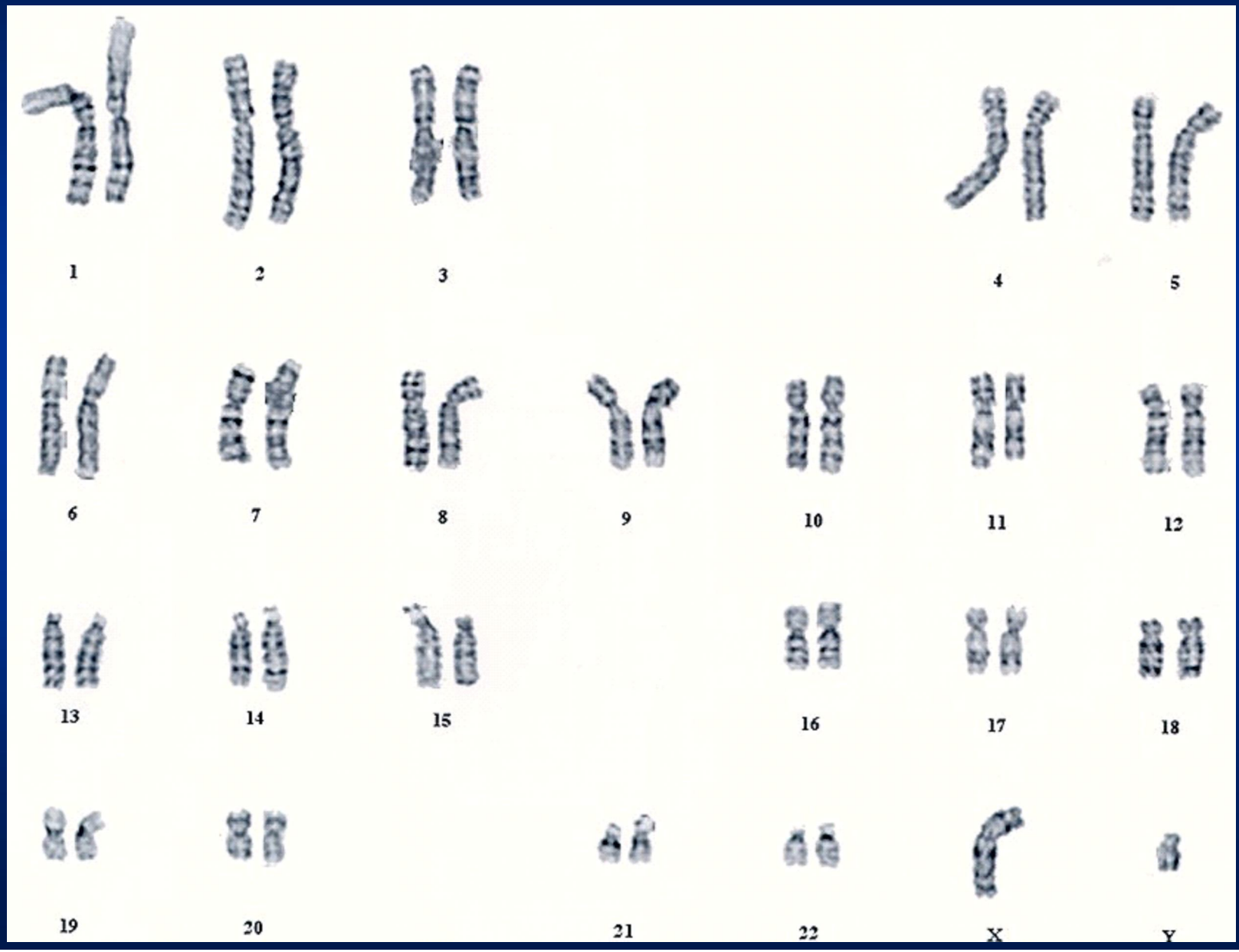
- **Tend to live in GC-rich regions**
- **Few new protein domains, many new domain architectures**
- **Big expansions of some families . . .**

Smell receptors

Immunoglobulins

Growth Factors

Cariotipo normal



REGULACION DE LA EXPRESION GENICA POR METILACION (CpG)

INACTIVACION DEL CROMOSOMA X = LIONIZACION

GENES ACTIVOS = METILACION ↓

GENES INACTIVOS= METILACION ↑

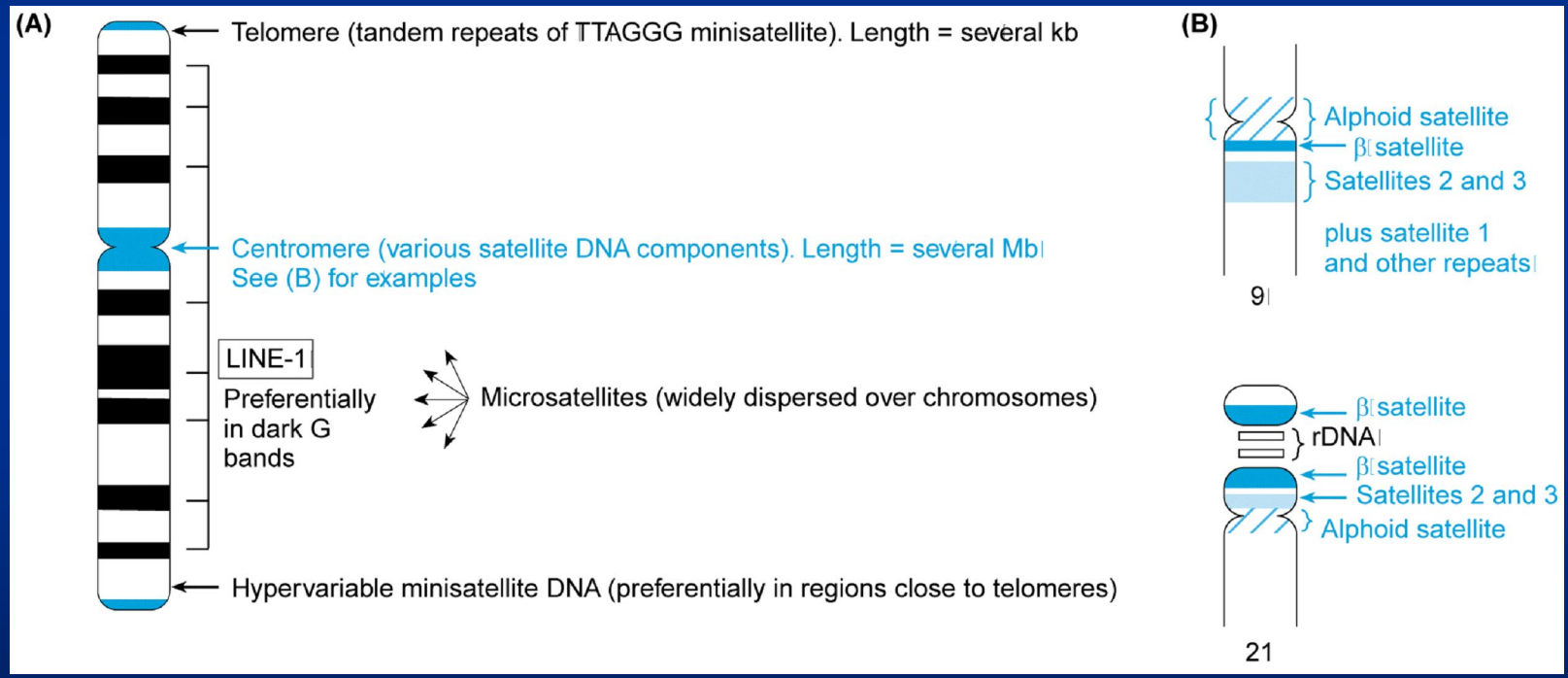
Human Populations

All individuals share genome sequences which are 99.9% identical.

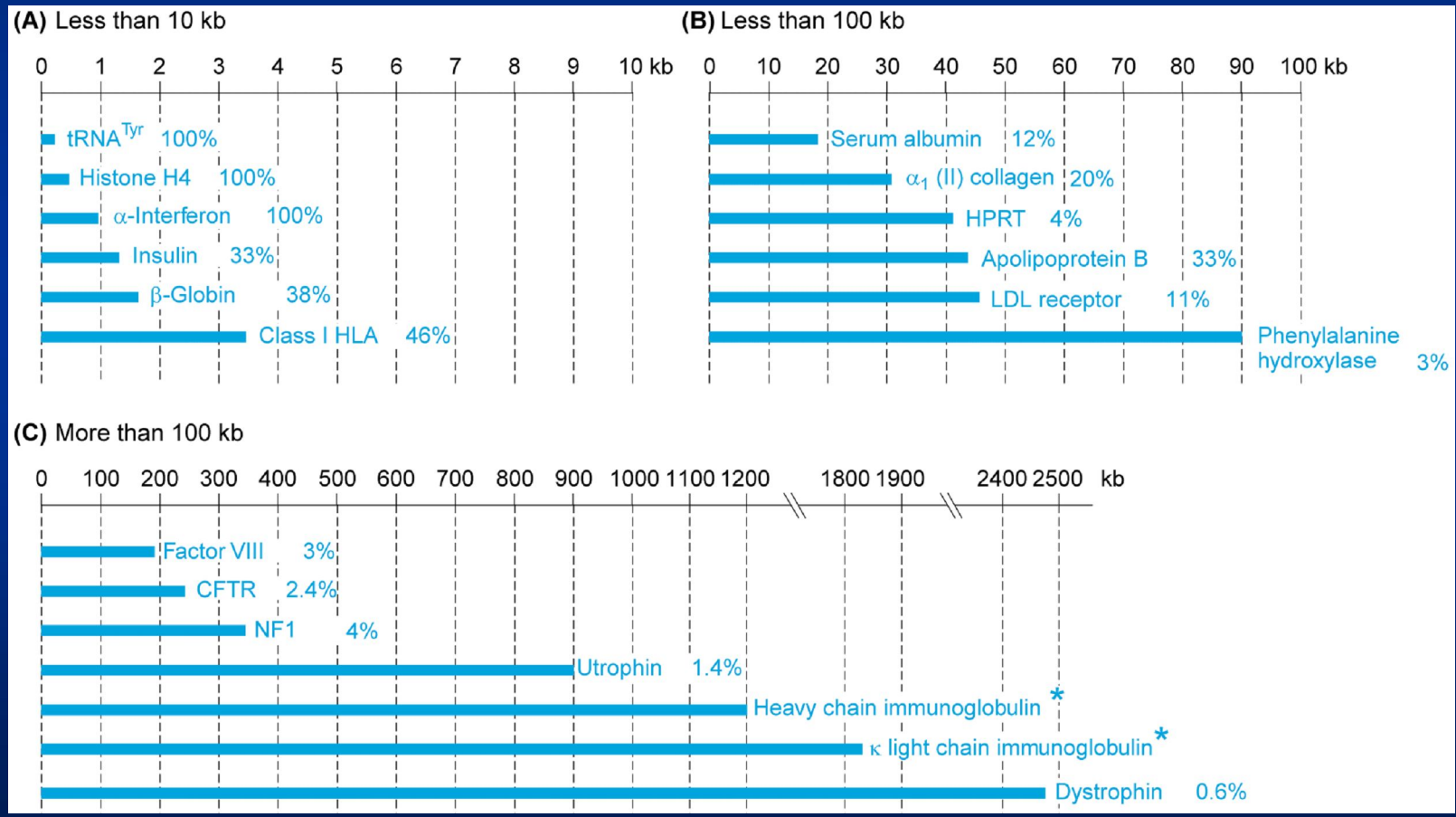
The remaining 0.1% is responsible for all of the genetic diversity between individuals.

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

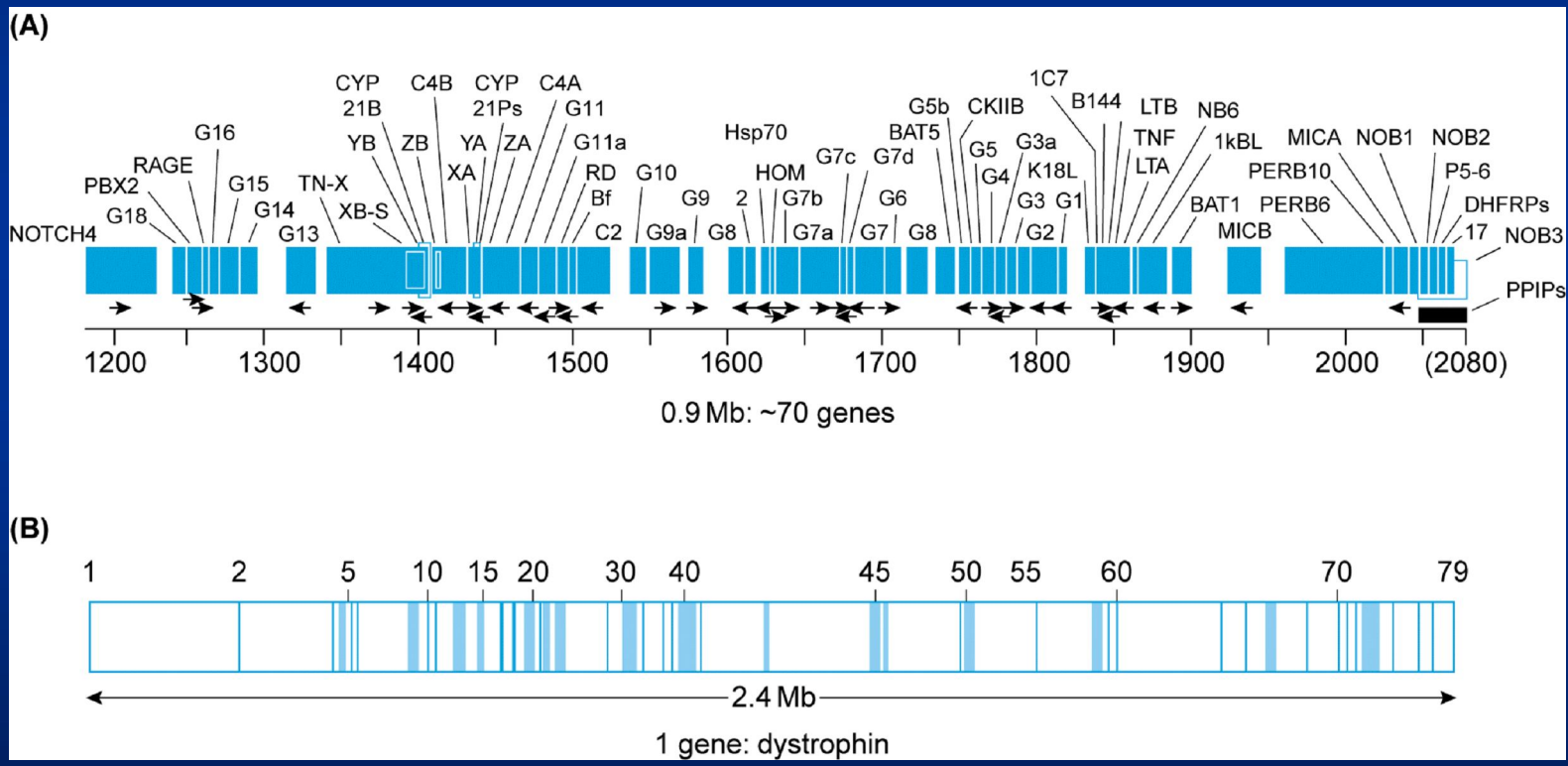
Chromosomal location of repetitive DNA



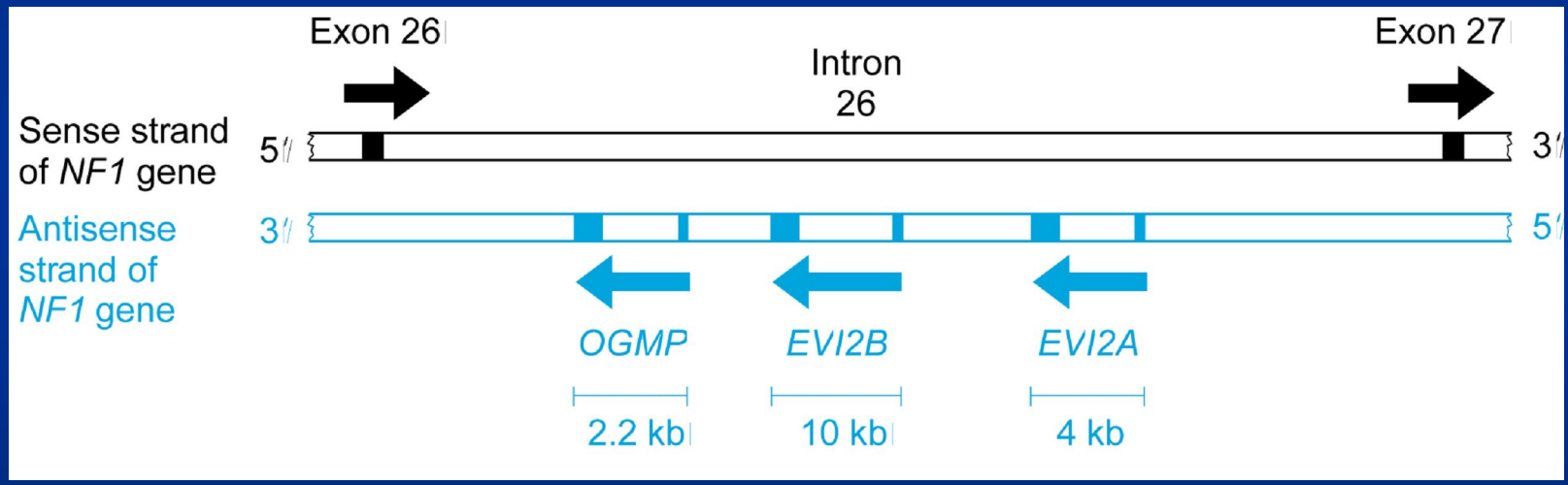
Human genes vary enormously in size and exon content



GENE DENSITIES



GENES WITHIN GENES



Gene families

- Members may exhibit high sequence homology
- sometimes contain a highly conserved domain (e.g. SOX box)
- sometimes contain a very short conserved "motif" (e.g. DEAD box, asp-glu-ala-asp RNA helicases)
- superfamilies (e.g. Ig superfamily)
- sometimes clustered (e.g. globin genes)
- Often associated with truncated and non processed pseudogenes

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

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.

RFLP

(Restriction Fragment Length Polymorphisms)

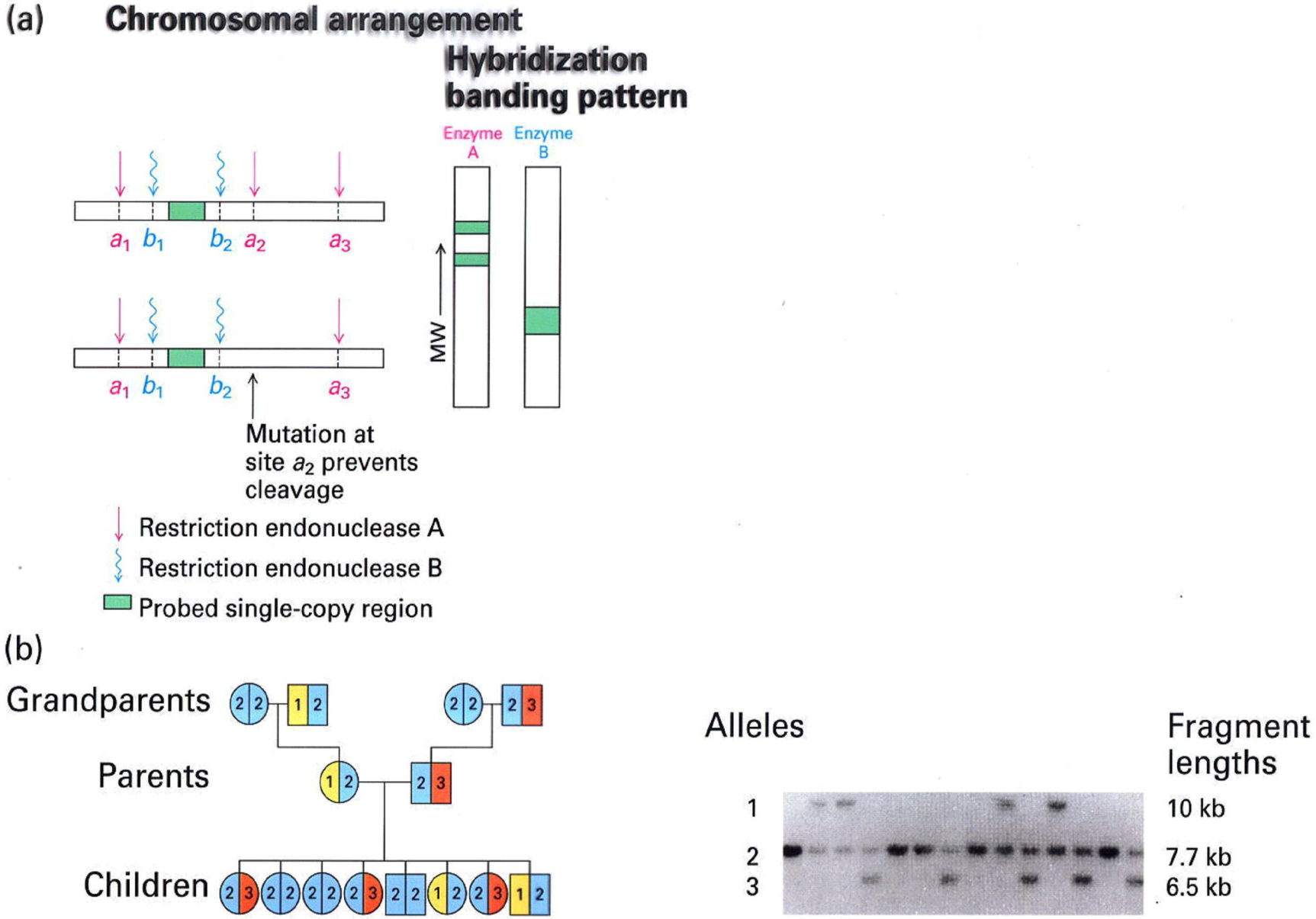


Figure 8-20
Lodish et al. MOLECULAR CELL BIOLOGY, Fourth Edition

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]

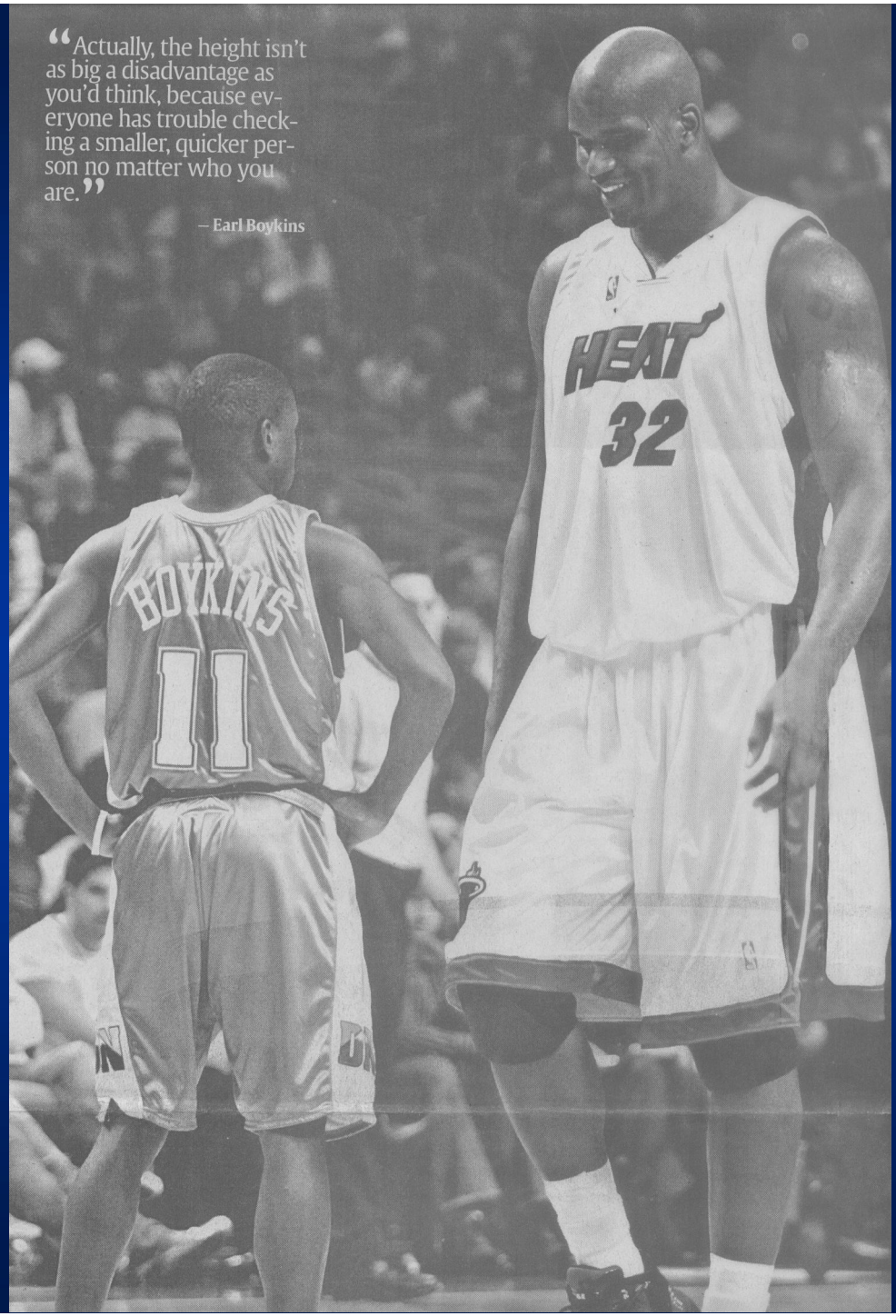
- Even in a library made from from one person's DNA, the homologous chromosomes have SNPs
- This inevitably leads to the discovery of SNPs - any single base sequence difference
- These SNPs can be valuable as the basis for diagnostic tests

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.


“Actually, the height isn’t as big a disadvantage as you’d think, because everyone has trouble checking a smaller, quicker person no matter who you are.”
– Earl Boykins
HEAT
32
BOYKINS
11

ENFERMEDADES GENETICAS (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

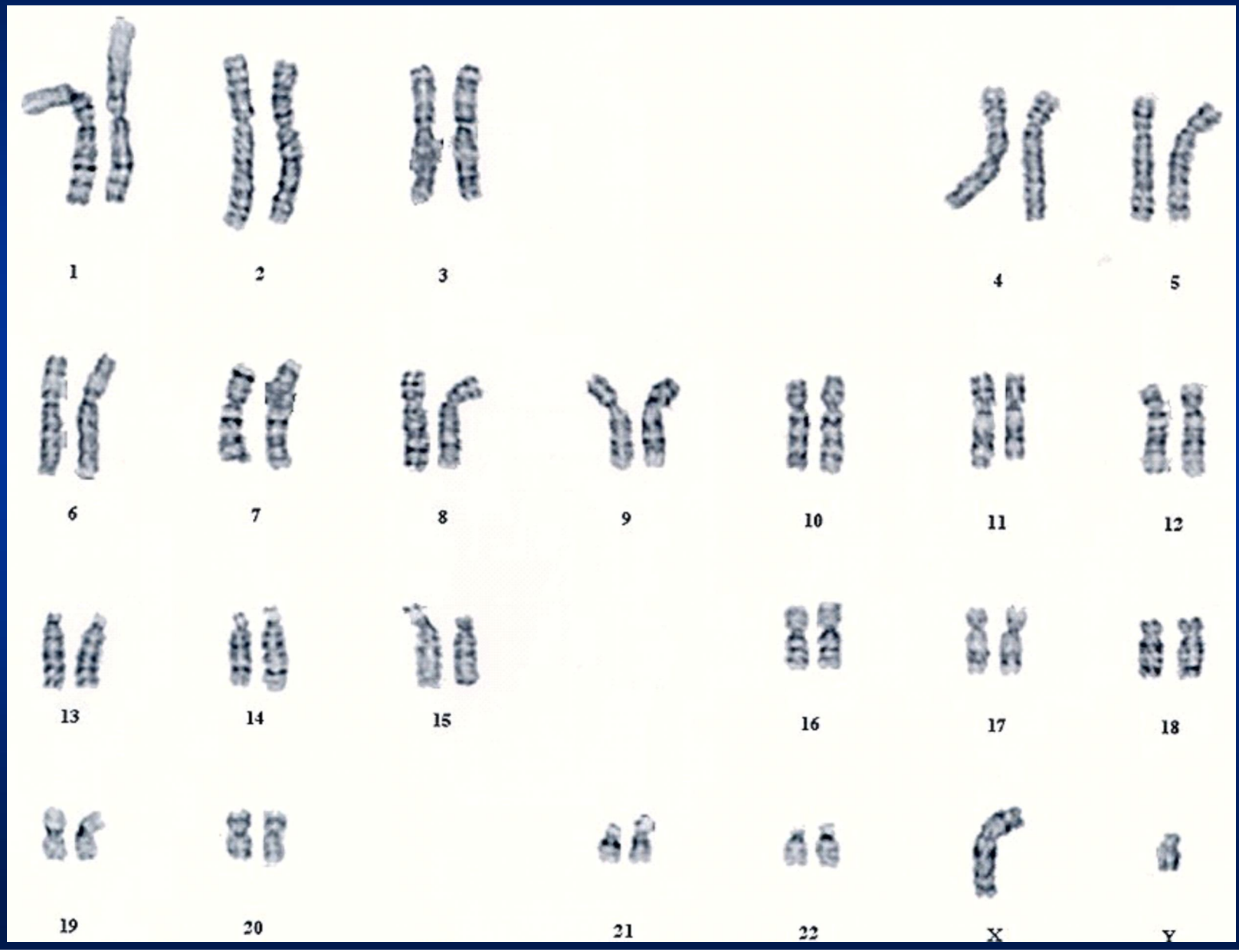
Types of Mutation

- **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 **C**GA CCC G	Insertion
AGC TTC **TTC** GAC CCG	Expansion
A**T**C TTC GAC CGG	Point mutation
ATC **TGA**	Nonsense ‘stop’

Cariotipo normal



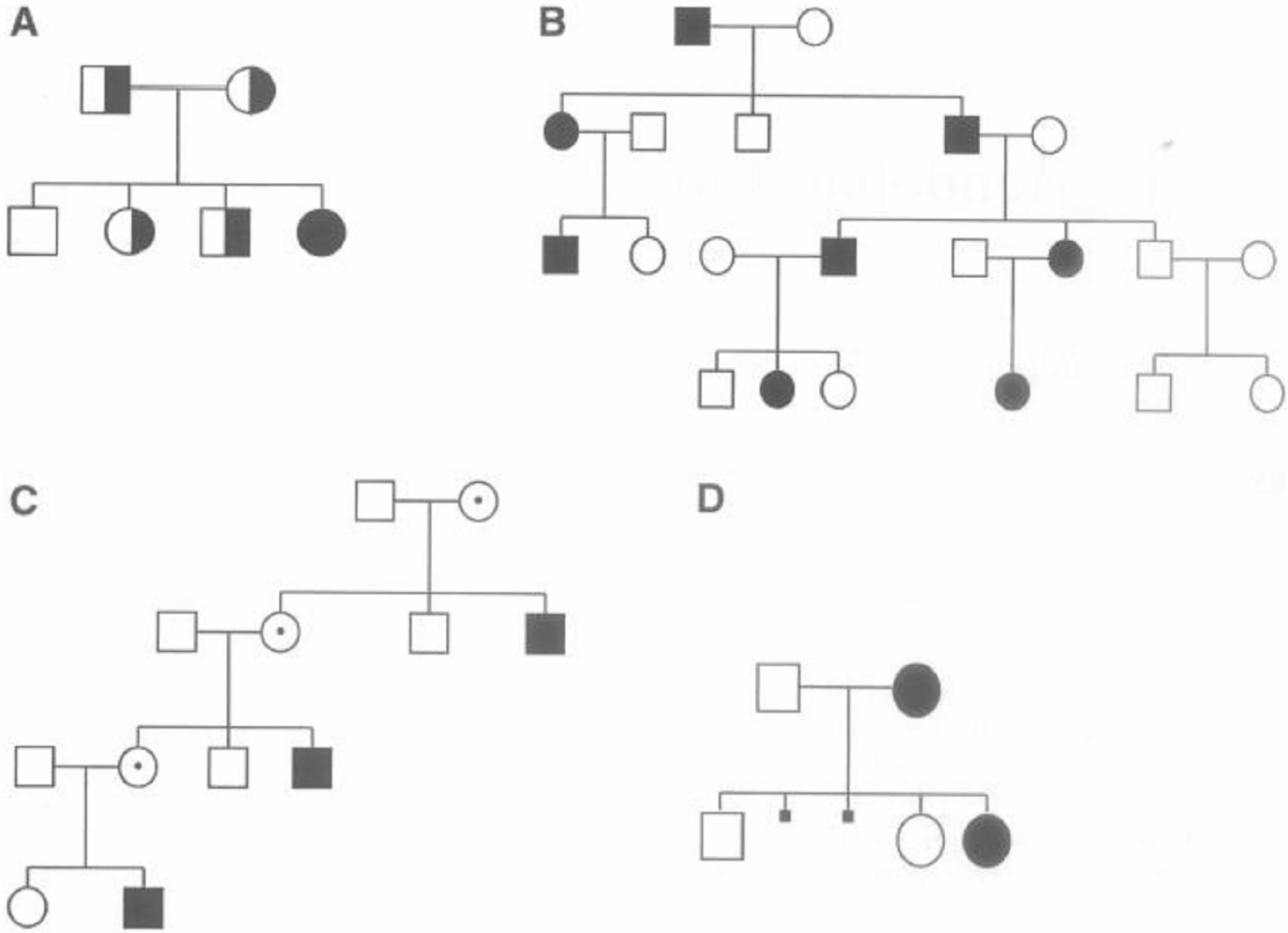


Figure 1-1 Pedigrees depicting autosomal-recessive (**A**), autosomal-dominant (**B**), X-linked-recessive (**C**), and X-linked-dominant with male lethality (**D**). By convention, squares denote males, circles females, and filled-in symbols are individuals who manifest a phenotype. Half-filled symbols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

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PENETRANCIA

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

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

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 crhomosomes		
Klinefelter syndrome	47XXY	1/1000 males
XYY-syndrome	47XYY	1/1000
Turner syndrome	45X0,45X/46X0,45X/46XY (mosaicism)	1/10.000 females
Triple-X syndrome	XXX	1/1000

Table 4-3
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 (mosaicism)	1/10,000 females
Triple-X syndrome	XXX	1/1000

SINDROMES KLINEFELTER Y TURNER

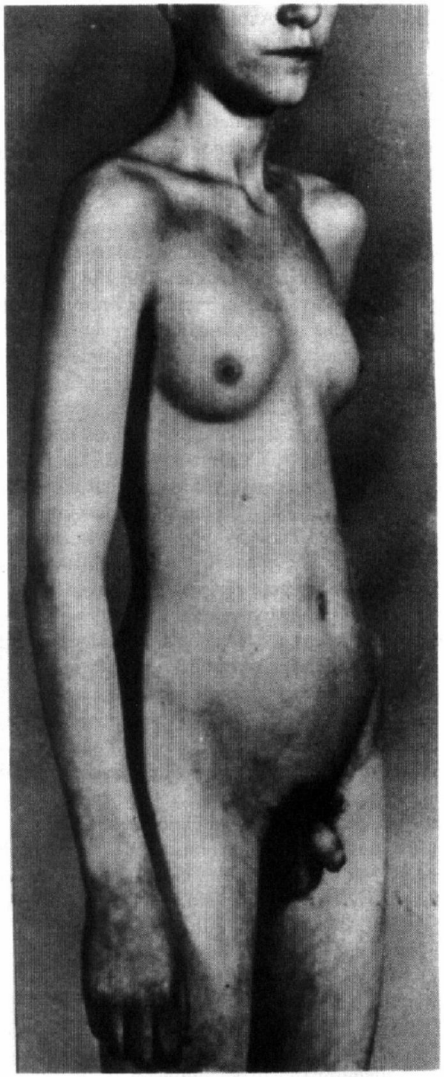

Figure 58-4 Klinefelter's syndrome. (Used with permission from Blackwell Science.)

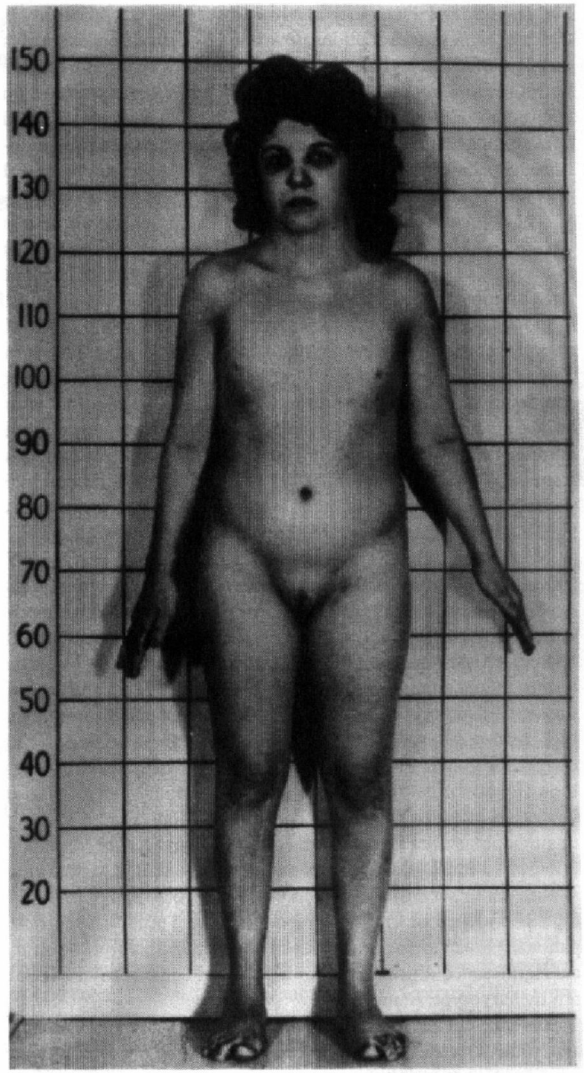

Figure 58-5 Turner's syndrome. (Used with permission from Blackwell Science.)

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Selected Monogenic Disorders

Autosomal dominant disorders

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

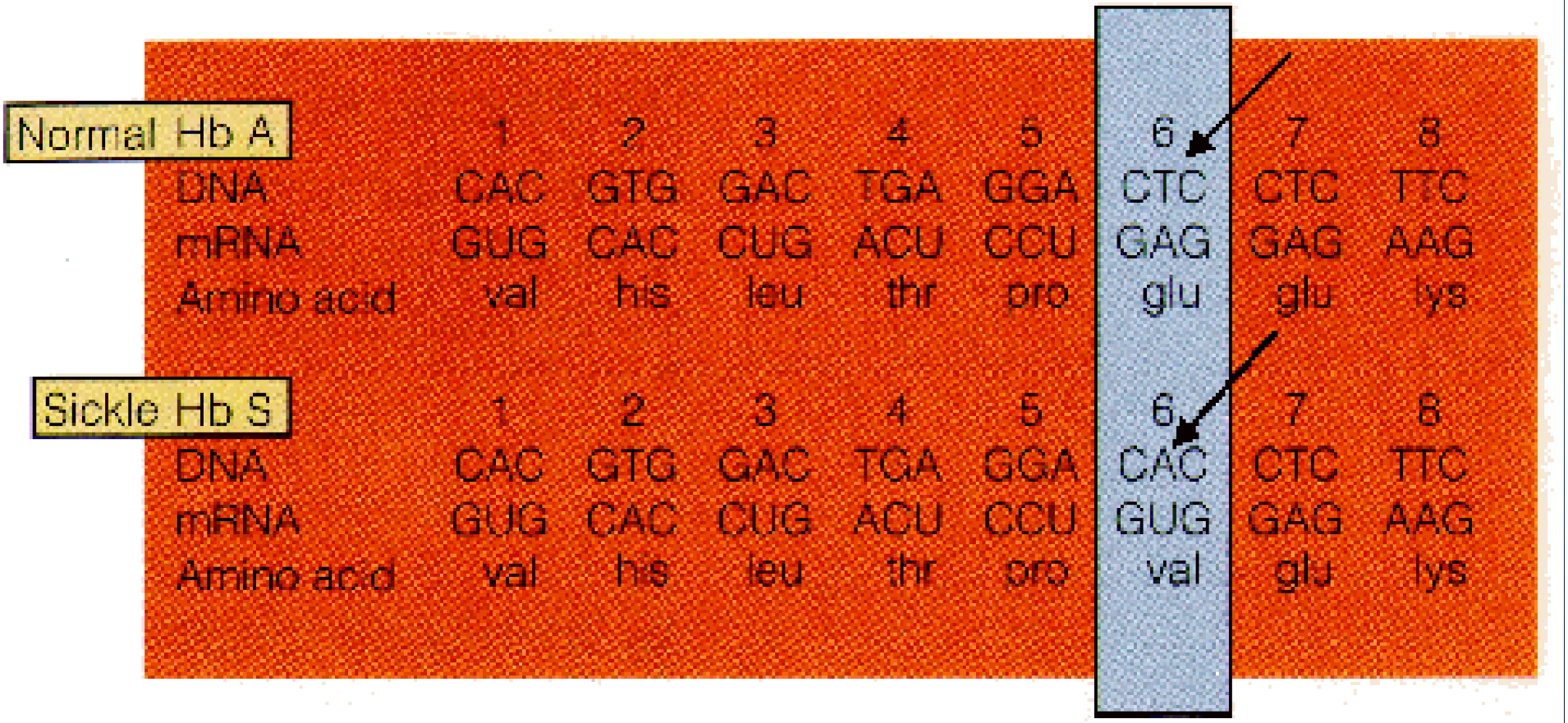
Autosomal recessive disorders

- 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



Cystic fibrosis transmembrane regulator (CFTR)

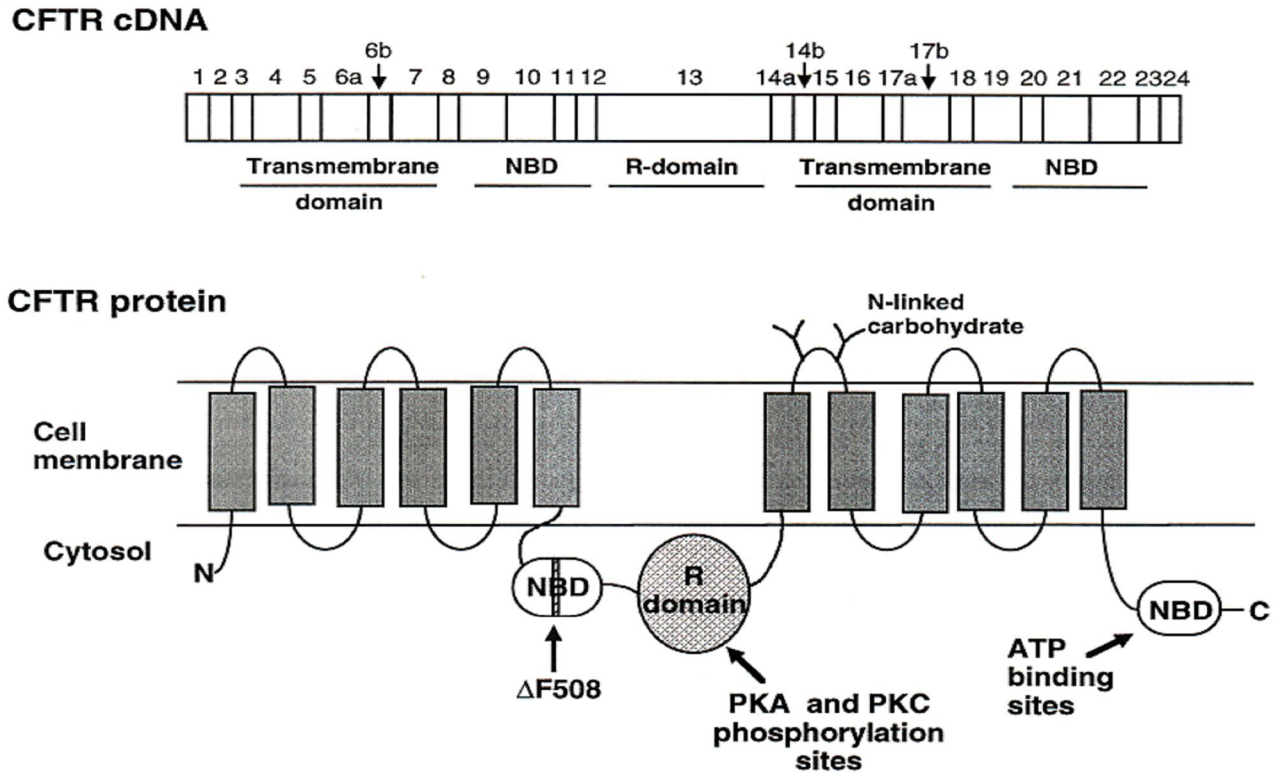


Figure 37-1 Structure of cystic fibrosis transmembrane conductance regulator (CFTR) cDNA and protein. Shown above is a schematic diagram of the structure of the CFTR cDNA with 27 exons indicated by boxes and labeled with the predicted protein domain coded for by the cDNA. A model of the CFTR protein 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 ΔF508 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

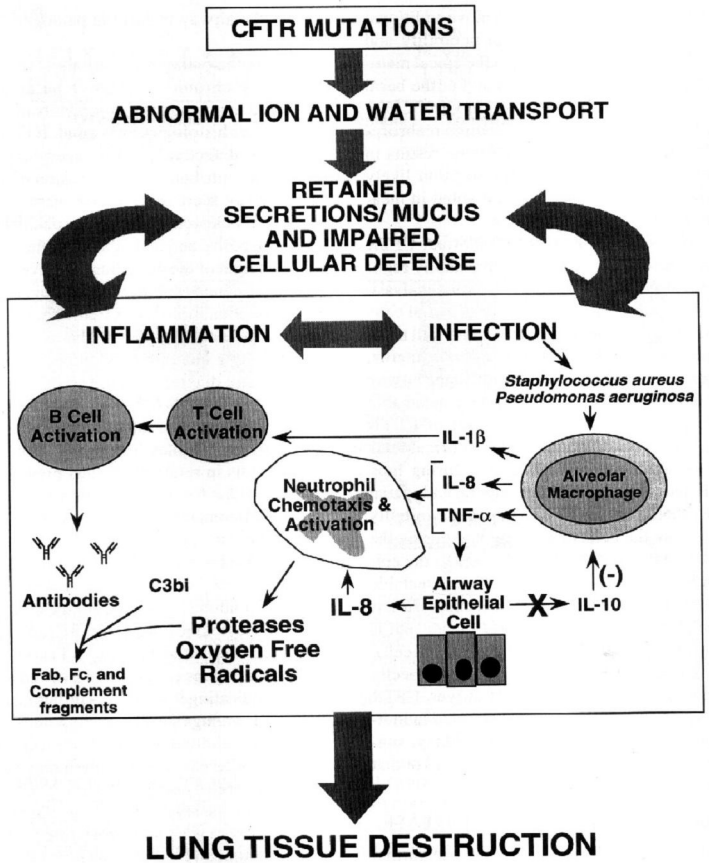


Figure 37-2 Pathogenesis of cystic fibrosis-related lung disease. Proposed mechanism for the development of CF-related lung disease. CFTR mutations lead to abnormal salt and water transport, which in turn result in retained desiccated airway secretions and possibly impaired defensin function. This results 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]

Mutation	*Frequency (%)*[b]	*Mutation class*[c]	*Phenotypic association*	*Population with increased prevalence*[b]
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	

[c]Adapted 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.

[b]Mutations 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.

[c]Mutation class designated by biochemical or physiologic effect on CFTR protein.

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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

SINDROME DE RETARDO MENTAL POR X FRAGIL

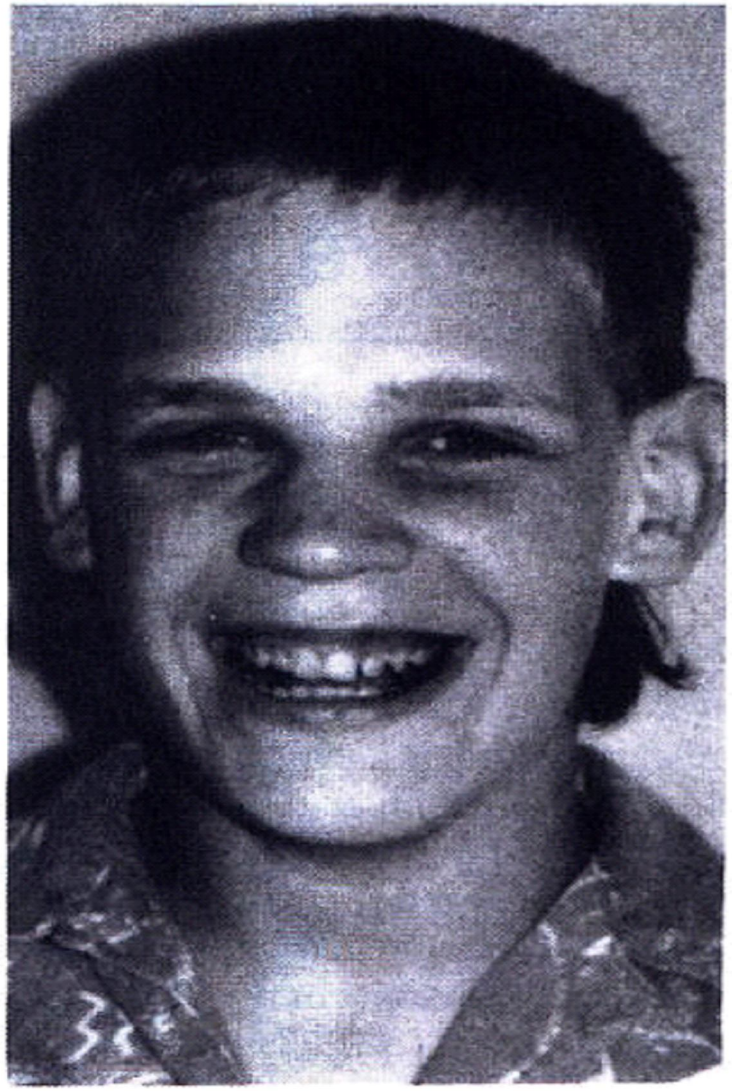

Figure 118-2 Mentally retarded adolescent male with fragile X syndrome. Note long facies with prominent forehead and ears. Typical of most patients, there is no major dysmorphia associated with this syndrome, confounding the clinical diagnosis. (Reprinted with permission from JAMA 1994;271:536–542.)

Principles of Molecular Medicine, 1998

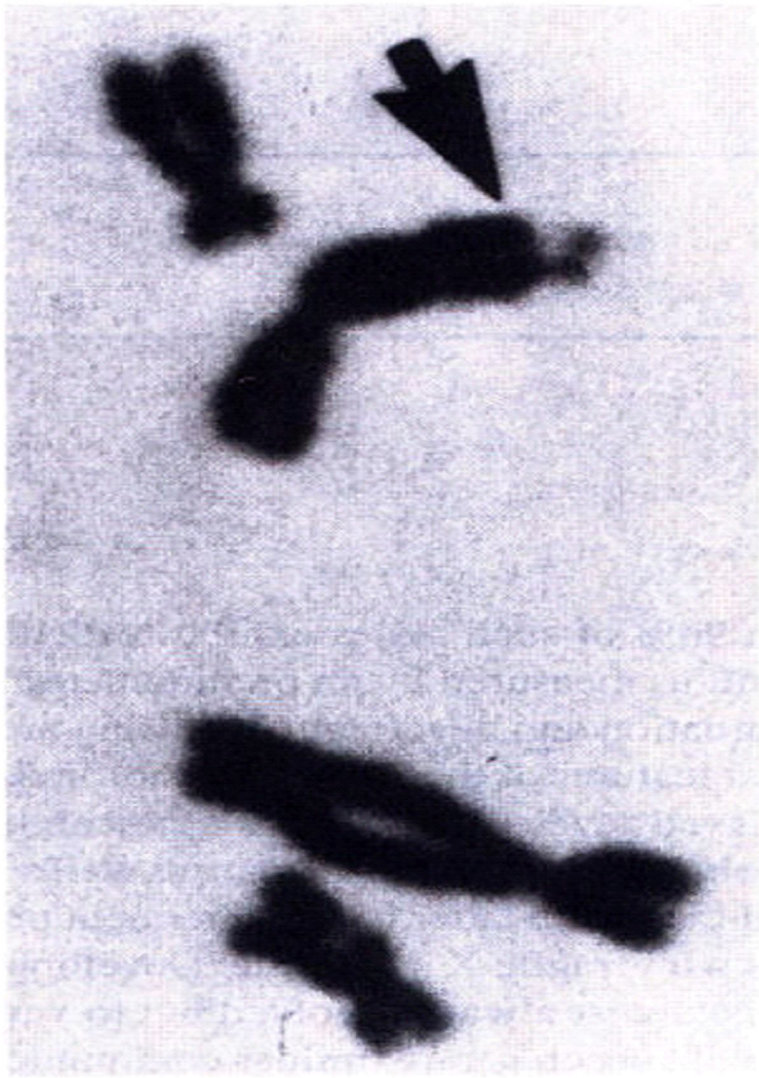

Figure 118-1 Partial karyotype of Geimsa-stained human chromosomes showing the fragile X site (arrow). (Reprinted with permission from JAMA 1994;271:536–542.)

Principles of Molecular Medicine, 1998

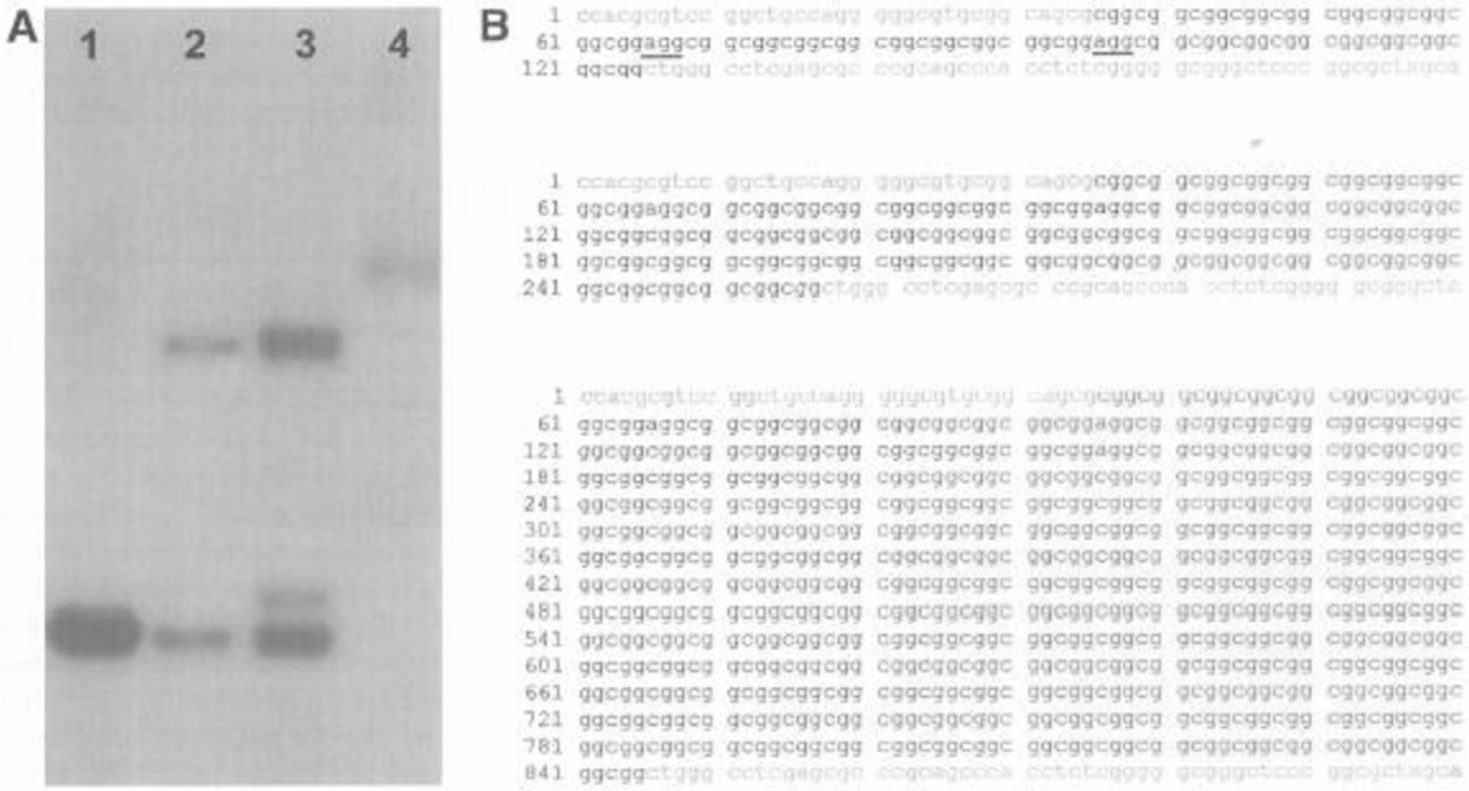

Figure 2-1 Triplet repeat expansion in fragile X syndrome. The gel (**A**) shows Southern blot-based testing for several individuals including a normal male—lane 1, a normal female—lane 2, a female premutation carrier—lane 3, and an affected male—lane 4. DNA is double digested with *Eco*RI, a restriction enzyme that cuts on either side of the triplet repeat, and *Eag*I, 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 *Eag*I 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 *Eag*I 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.)

Table 2-1
Examples of Other Triplet Repeat Expansion Disorders

Disorder	*Inheritance*	*Triplet sequence*	*Normal number of repeats*	*Number of repeats associated with disorder*
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.

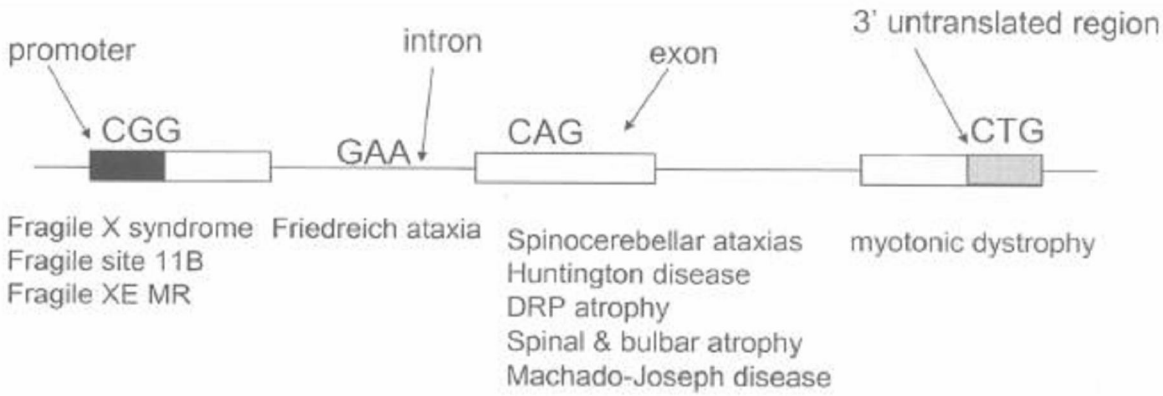

Figure 1-3 A prototypical gene, showing sites of triplet repeats that are prone to expansion, and examples of resultant disorders.

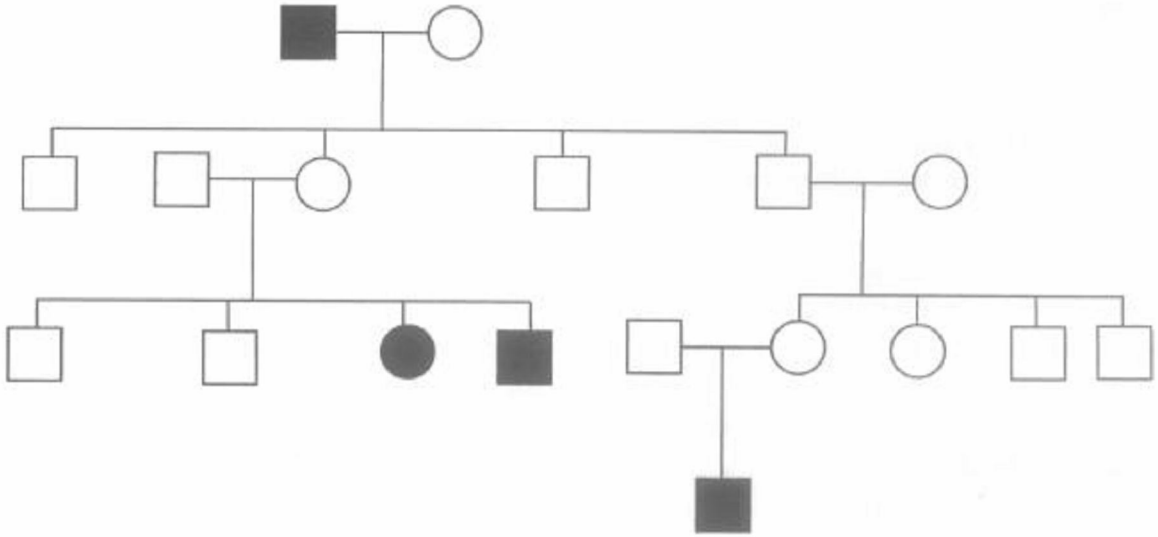

Figure 1-4 In this autosomal-dominant trait, an imprinted gene is only expressed when inherited from a female. Hence, only females can have affected offspring. Individuals who inherit the mutation from their fathers will not express the phenotype, but their daughters who carry the mutation can have affected children.

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SINDROME DE PRADER-WILLI

Hiperfagia,Hipotonia, Hipogonadismo, Obesidad

SINDROME DE ANGELMANS

“Sindrome de Happy Puppet”

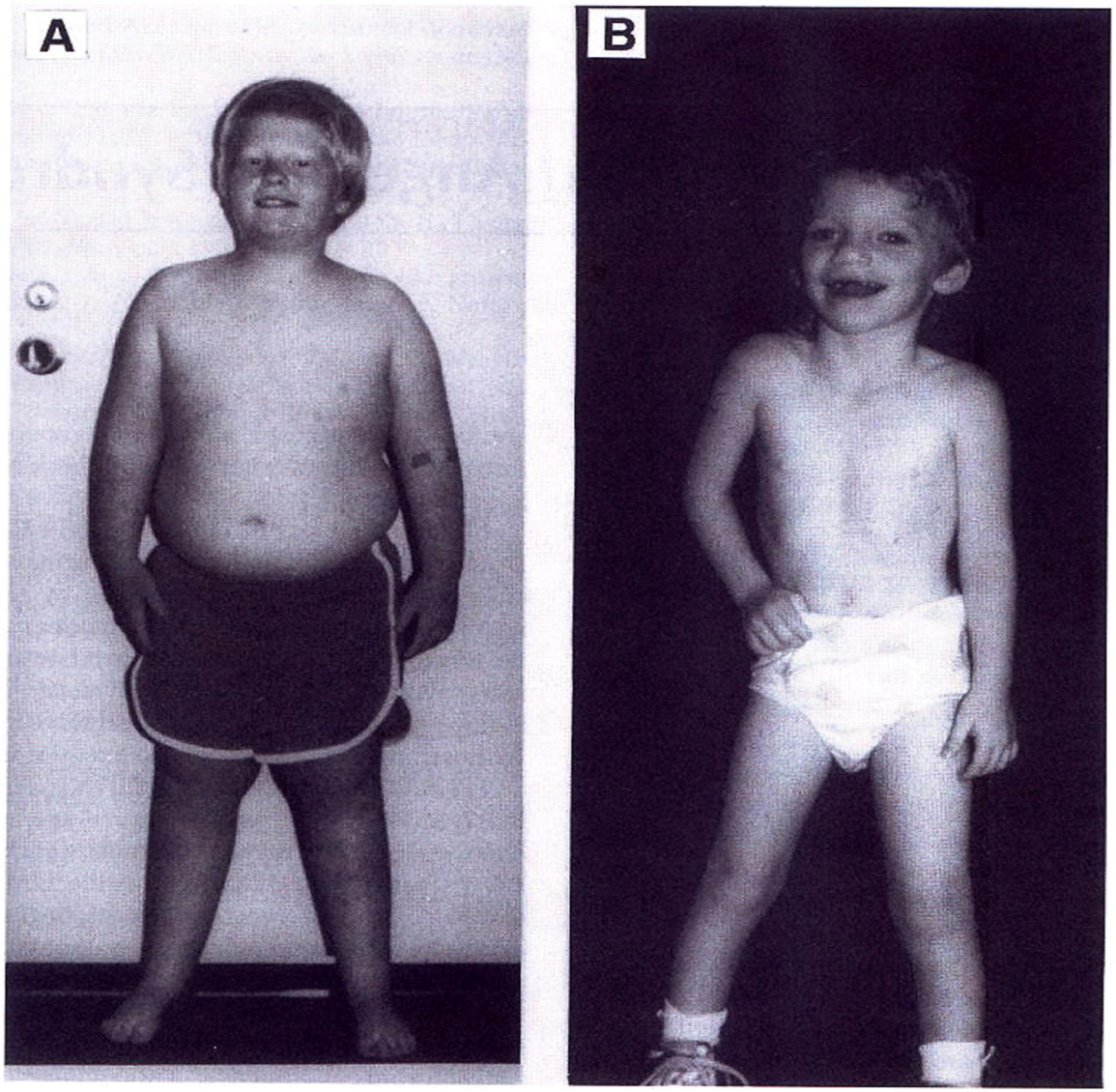

Figure 117-1 Clinical phenotype of children with **(A)** Prader-Willi syndrome or with **(B)** Angelman syndrome. Note the central obesity, short stature, small hands and feet, and almond-shaped eyes/narrow bifrontal diameter in the PWS child, and the happy disposition, wide-spaced mouth, and teeth, 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]).

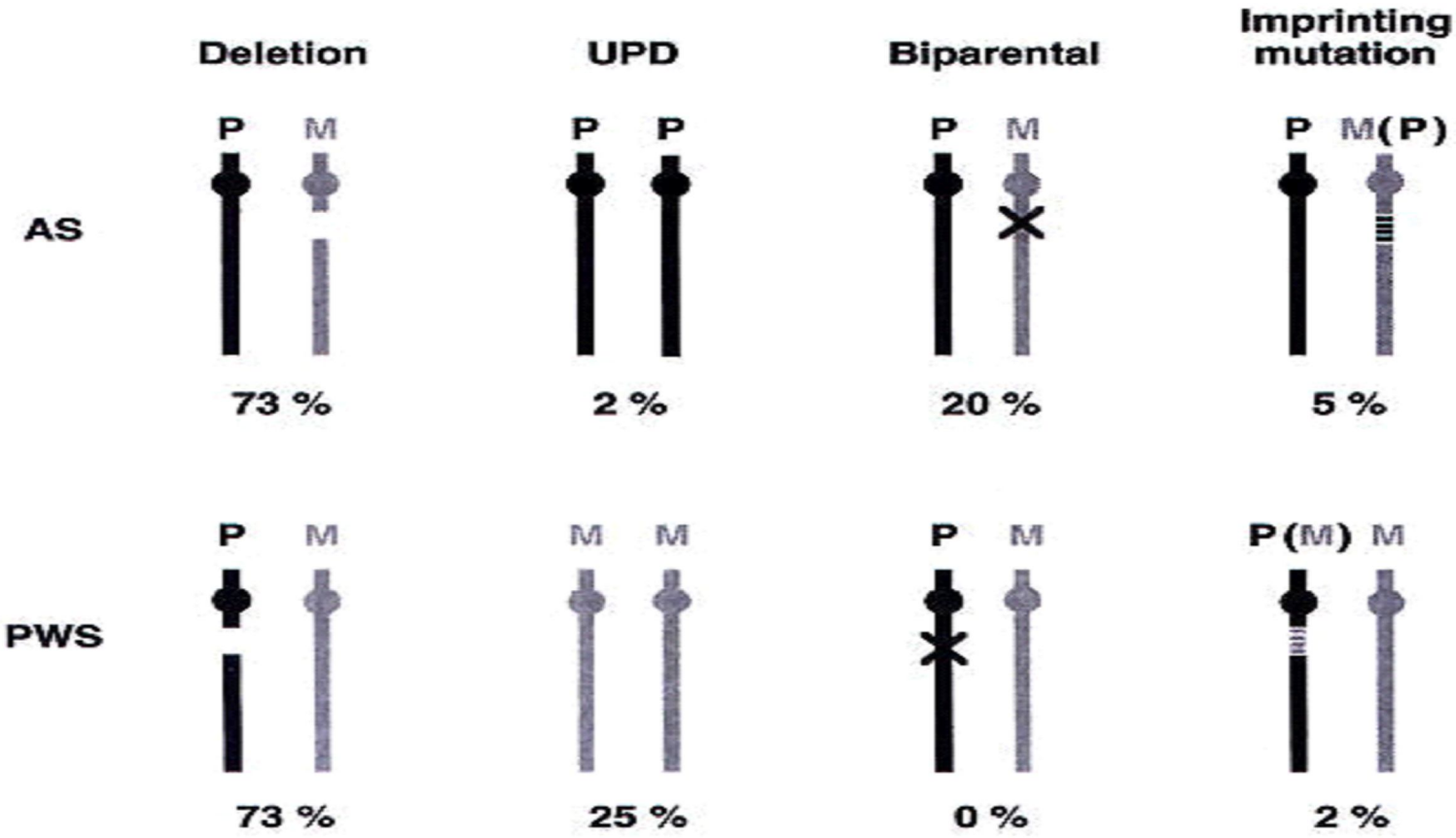

Figure 117-2 Molecular classes of Prader-Willi and Angelman syndromes. The chromosome 15 genotypes (and frequency) are shown for the major classes of AS and PWS. UPD, uniparental disomy; P, paternal (black); M, maternal (gray); M(P), maternal inheritance with paternal imprint (or epigenotype); P(M),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

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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 GENETICAS

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

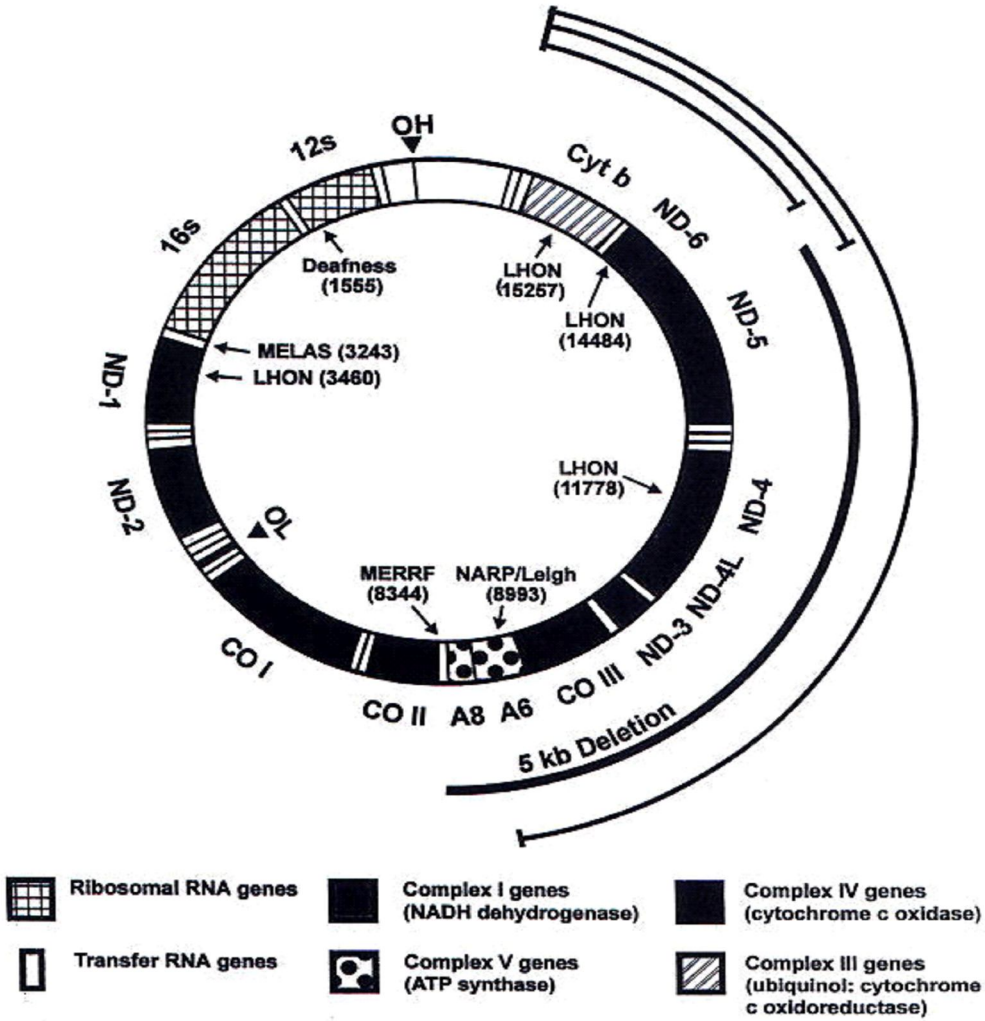

Figure 103-1 Schematic diagram of human mitochondrial DNA and the most prominent pathogenetic mutations. Inside the circle, point mutations in structural and protein-coding genes, with the clinical phenotype and the nucleotide position of the mutation; arcs outside the circle, the position of the most 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.)

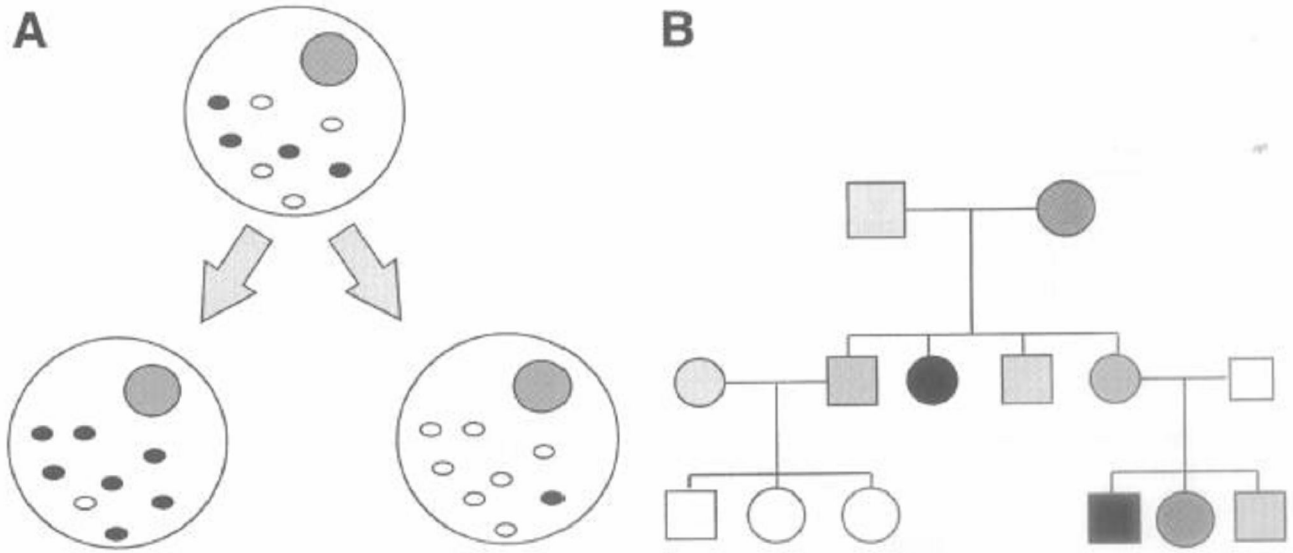

Figure 1-2 **(A)** Mutant and wild-type mitochondrial DNA may coexist in a cell, referred to as heteroplasmy. Mitochondrial DNA molecules segregate passively when a cell divides, so daughter cells may differ in their proportions of mutant and wild-type mitochondrial DNA. **(B)** Essentially, all the 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

Disease/syndrome	*MIM no.*
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

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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

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- **Trastornos cromosómicos**
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- **Formas no-clásicas de enfermedad genética (imprinting genómico, etc)**
- **Trastornos mitocondriales**
- **Mutaciones que surgen en celulas somaticas diferenciadas**

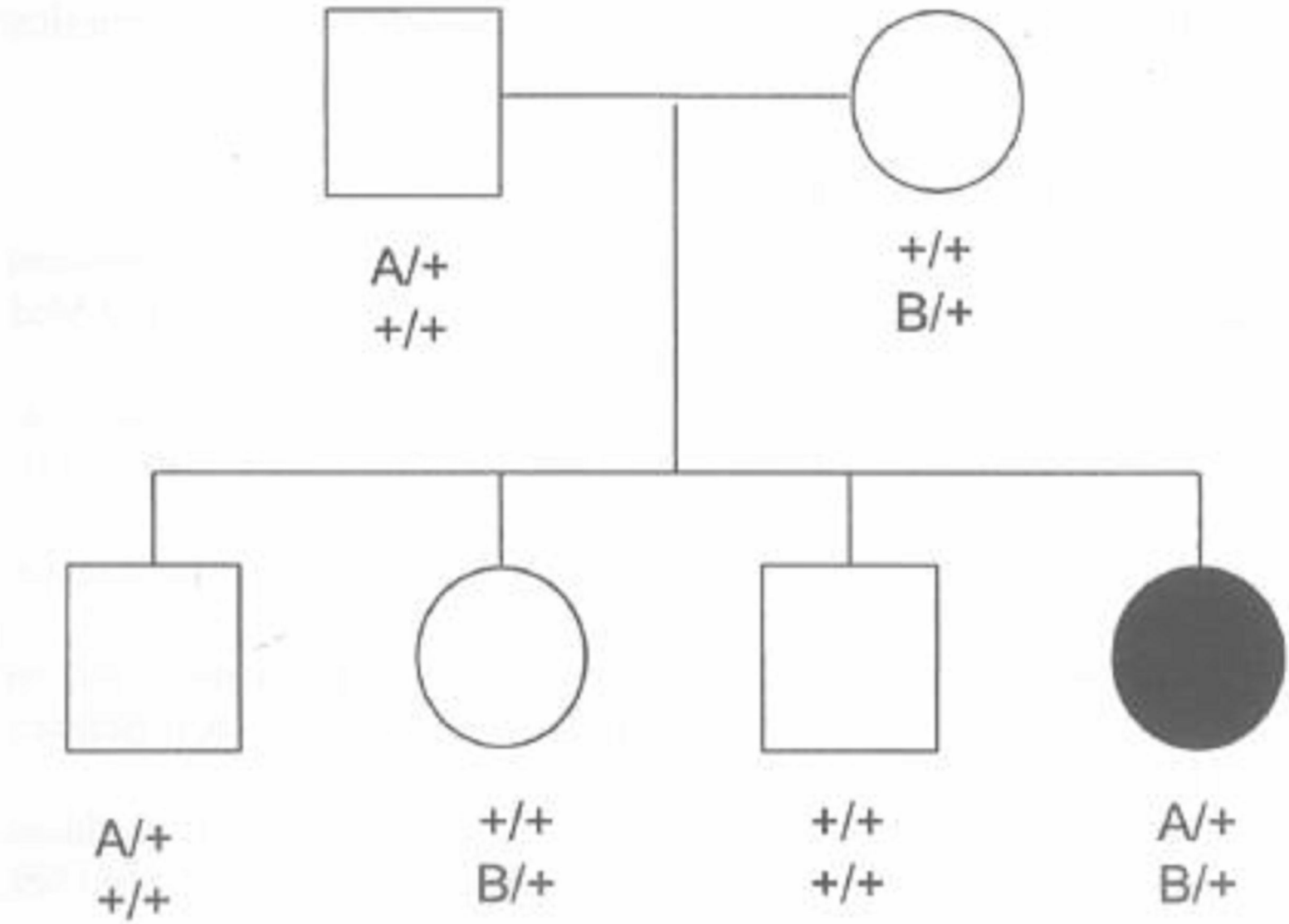

Figure 1-5 Pedigree illustrating digenic inheritance. Each parent is heterozygous for a different gene. The child who is heterozygous for both expresses the phenotype.

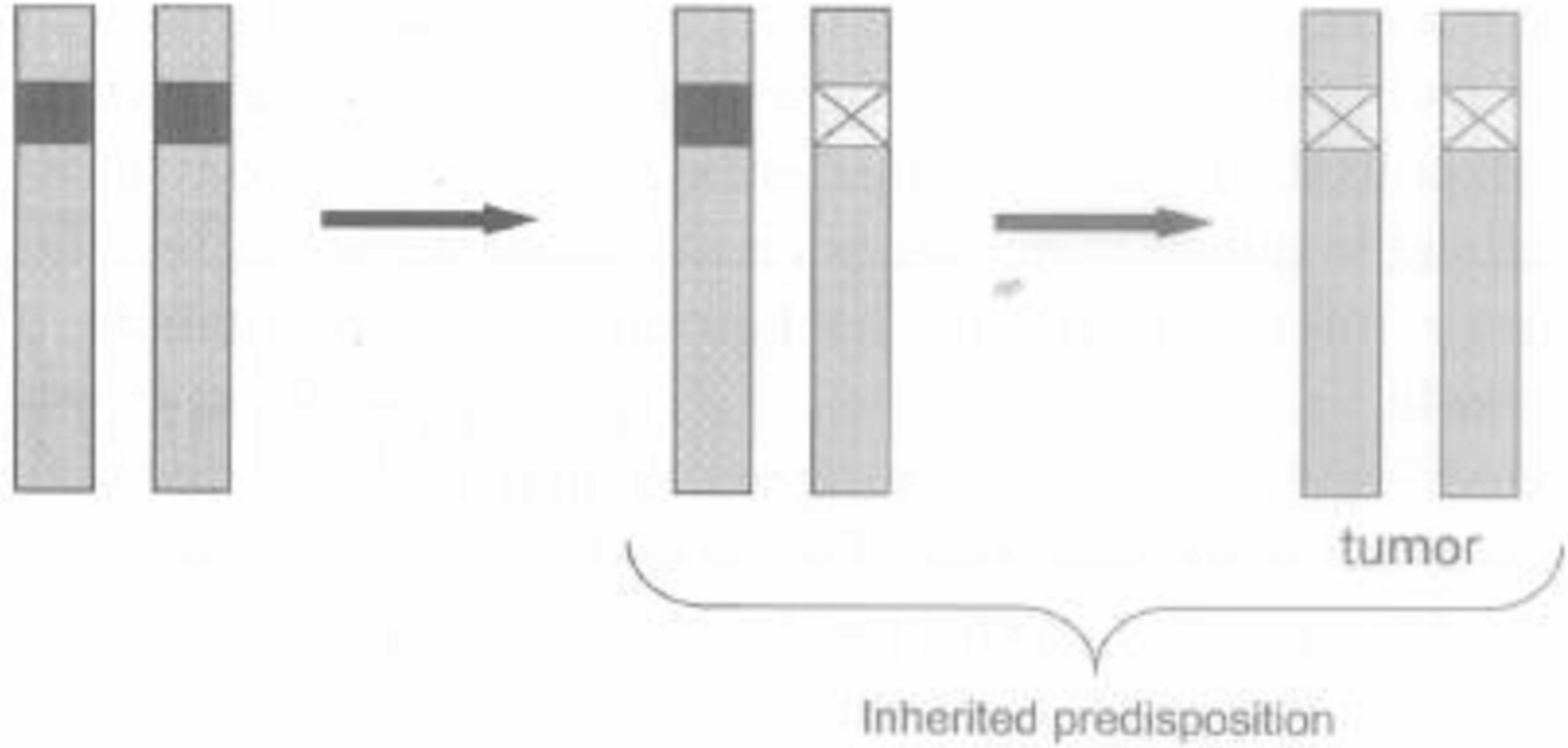

Figure 1-6 Tumor suppressor concept. A tumor suppressor gene is homozygously mutated in a tumor cell. Those who inherit a heterozygous mutation as a dominant trait are at increased risk of cancer if the remaining wild-type allele is mutated.