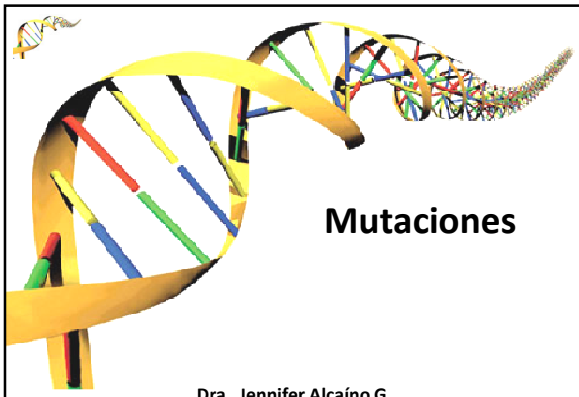


Mutaciones

Dra. Jennifer Alcaíno G
Septiembre de 2010

¿Cómo nació el término mutación?

Hugo De Vries (1902): *Oenothera lamarckiana*.

Individuos con una característica nueva que no estaba en sus antecesores.

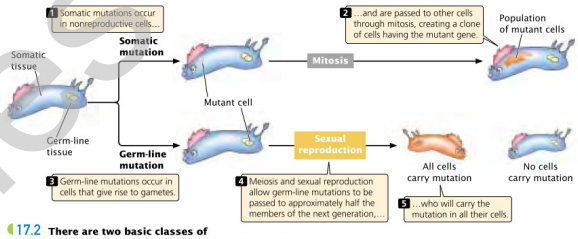
→ Cambio en el factor (gen) que determinaba el carácter y que este cambio se transmite a la progenie como cualquier otro carácter hereditario.

Hugo De Vries, around 1920.
Photo courtesy of Cold Spring Harbor Laboratory Archives

Mutación

Mutantes

Mutación es una alteración o cambio en la **información genética** (genotipo) de un ser vivo que se presenta espontáneamente (o inducida), y que se puede **transmitir** a la descendencia.



17.2 **There are two basic classes of mutations: somatic mutations and germ-line mutations.**

Mutaciones

Genómicas o cariotípicas (Número)

- ❖ Euploidía
- ❖ Aneuploidía

Cromosómicas (Estructura)

- ❖ Deleción
- ❖ Duplicación
- ❖ Inversión
- ❖ Translocación

Génicas (puntuales)

Esta clase

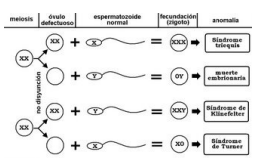
Mutaciones Genómicas

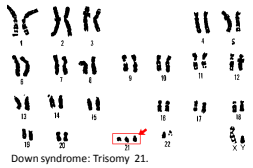
Euploidía:

Afecta al conjunto de cromosomas del genoma (set de cromosomas), aumentando el número de juegos cromosómicos (poliploidía) o reduciéndolo a una sola serie (haploidía o monoploidía).

Aneuploidía:

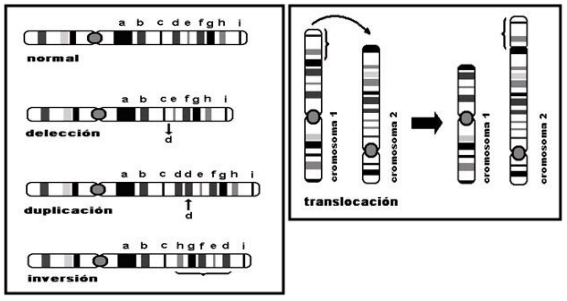
Afecta el número de cromosomas individualmente (1 par de cromosomas).





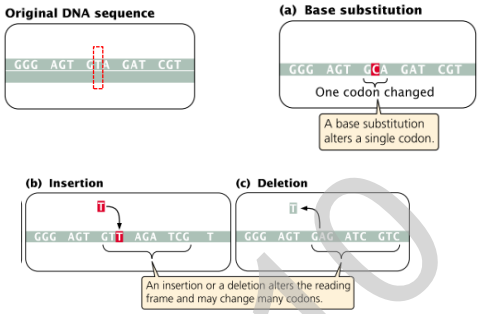
Down syndrome: Trisomy 21.

Mutaciones Cromosómicas



Mutaciones génicas (puntuales):

Alteración de una base (o un número pequeño de bases adyacentes).



Tipos de mutaciones génicas

Cambio de base:

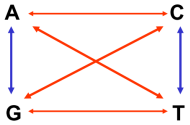
ATG ATG ATG ATG

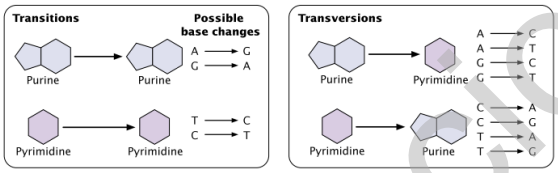
↓

ATG ACG ATG ATG : Transición

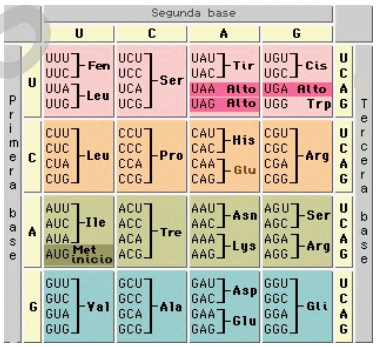
ATG AAG ATG ATG

ATG AGG ATG ATG } Transversión

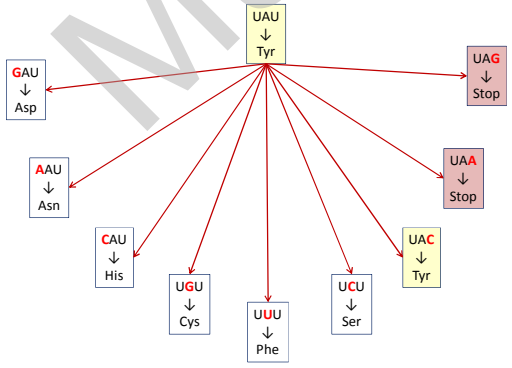




Consecuencias de las mutaciones



Consecuencias de las mutaciones



Consecuencias de las mutaciones

Mutaciones silenciosas: (mismo aa) AGG → CGG
Arg Arg

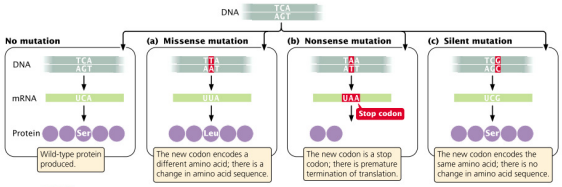
Mutaciones sentido errado "Missense": (otro aa)

Conservativa: AAA → AGA
Lys Arg
(básico) (básico)

No Conservativa: UUA → UCA
Leu Ser
(hidrofóbico) (polar)

Consecuencias de las mutaciones

Mutaciones sin sentido "Nonsense": CAG → UAG
Gln Stop



17.7 **Base substitutions can cause (a) missense, (b) nonsense, and (c) silent mutations.**

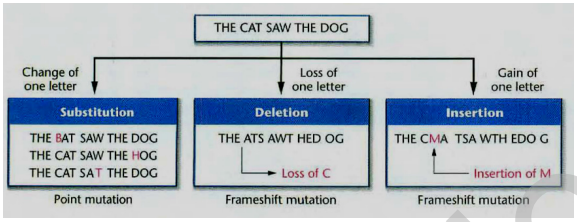
Consecuencias de las mutaciones

Mutaciones "Frameshift" (cambio en el marco de lectura):

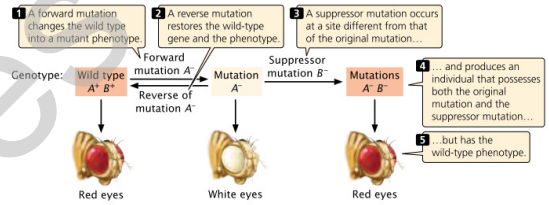
Adición: AAG ACT CCT… → AAG AGC TCC T…

Deleción: AAG ACT CCT… → AAA CTC CT…

Mutaciones "Frameshift"
(cambio en el marco de lectura):



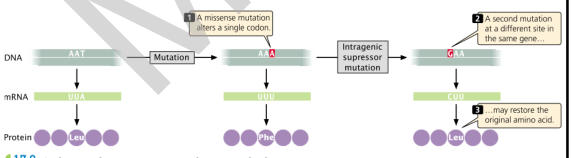
Mutaciones supresoras



17.8 **Relation of forward, reverse, and suppressor mutations.**

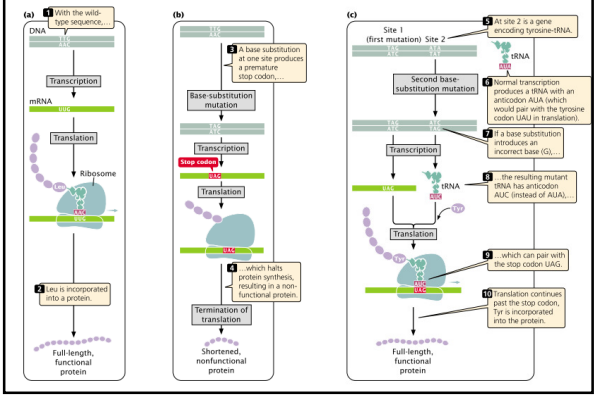
Intragénicas **Intergénicas**

Mutaciones supresoras: Intragénica



17.9 **An intragenic suppressor mutation occurs in the same gene that contains the mutation being suppressed.**

Mutaciones supresoras: Intergénica



Causas de las mutaciones

- Espontáneas
- Inducidas (mutágeno físico o químico)

Mutaciones espontáneas o inducidas

Table 14-1 Mutation Frequencies Obtained with Various Mutagens in *Neurospora*

Mutagenic treatment	Exposure time (minutes)	Survival (%)	Number of *ad*-3 mutants per 10^6 survivors
No treatment (spontaneous rate)	–	100	~0.4
Amino purine (1–5 mg/ml)	During growth	100	3
Ethylmethanesulfonate (1%)	90	56	25
Nitrous acid (0.05 M)	160	23	128
X rays (2000 r/min)	18	16	259
Methyl methanesulfonate (20 mM)	300	26	350
UV rays (600 erg/mm²/min)	6	18	375
Nitrosoguanidine (25 mM)	240	65	1500
ICR-170 acridine mustard (5 mg/ml)	480	28	2287

Note: The assay measures the frequency of *ad*-3 mutants. It so happens that such mutants are red, so they can be detected against a background of white *ad*-3⁺ colonies.

Mutaciones espontáneas

Luria y Delbrück (1943) "test de la fluctuación":

Con cierta frecuencia aparecían bacterias resistentes al fago T1:

¿Fago T1 induce un cambio fisiológico que produce la resistencia? o ¿La resistencia en las bacterias se produce de forma aleatoria?

20 cultivos independientes de *E. coli* → plaqueo en presencia de fago T1:

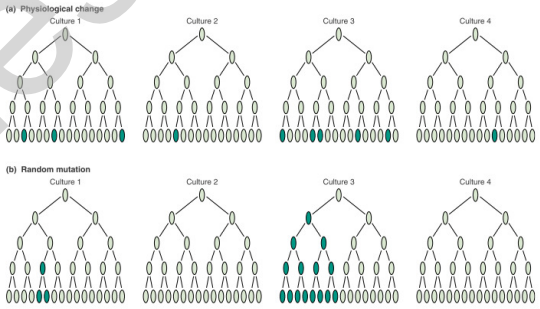
Variación en el número de colonias resistentes a T1 en los distintos cultivos.

20 muestras de 1 cultivo de *E. coli* → plaqueo en presencia de fago T1:

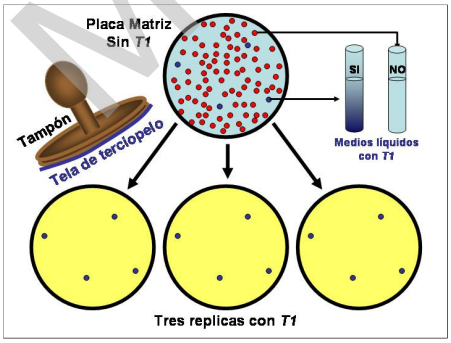
Número similar de colonias resistentes a T1 en las distintas muestras.

Mutaciones espontáneas

Si T1 induce un cambio fisiológico: No debiera existir una alta variación de resistencia en los distintos cultivos.



Demostración de la existencia de mutantes en la población antes de la selección (presencia de fago T1). Joshua y Esther Lederberg (1952).

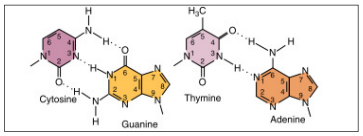


Mutaciones espontáneas:

- Errores en la replicación
  - Tautómeros
  - "Balanceo"
  - Deslizamiento de la hebra de DNA
- Cambios químicos espontáneos
  - Depurinación
  - Desaminación

Tautomerismo de las bases nitrogenadas.

Tautómeros: isómeros que se diferencian sólo en la posición de sus átomos.



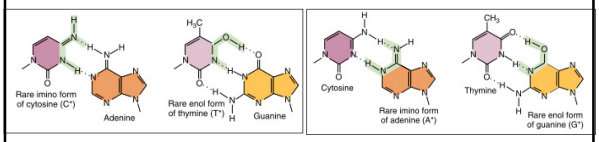
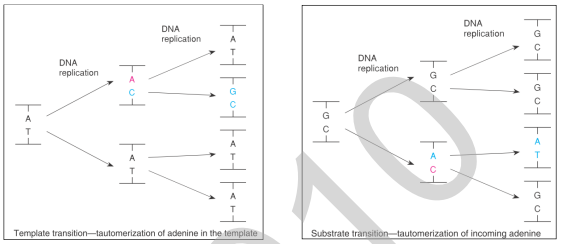


Figure 14-6 **Mismatched bases.** Rare tautomeric forms of bases result in mismatches.

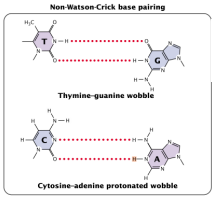
Tautomerismo de las bases nitrogenadas.

Table 12.4 **Pairing Relationships of DNA Bases in the Normal and Tautomeric Forms**

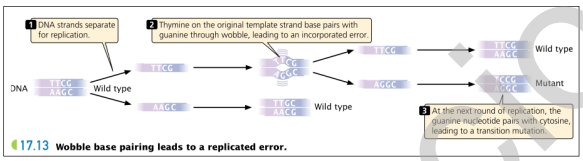
Base	In Normal State Pairs with	In Tautomeric State Pairs with
A	T	C
T	A	G
G	C	T
C	G	A



"Balanceo" por flexibilidad en la estructura del DNA.



17.12 **Nonstandard base pairings can occur as a result of the flexibility in DNA structure.** Thymine and guanine can pair through wobble between normal bases. Cytosine and adenine can pair through wobble when adenine is protonated (has an extra hydrogen).



17.13 **Wobble base pairing leads to a replicated error.**

Deslizamiento de la hebra de DNA.

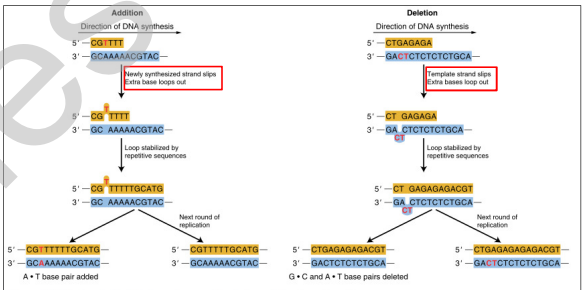
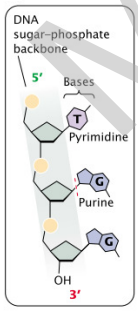


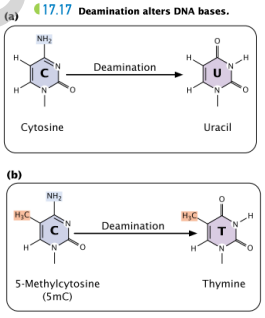
Figure 14-21 **A model for indel mutations resulting in frameshifts.** dr = deoxyribose.

Depurinización y Desaminación:



17.16 **Depurination, loss of a purine base from the nucleotide, produces an apurinic site.**

17.17 **Deamination alters DNA bases.**



Mutaciones inducidas:

- Físicos (radiación):
  - Radiación ionizante (Rayos X y gamma)
  - UV
- Químicos:
  - Análogos de Base
  - Agentes modificadores de base:
    - Alquilantes
    - Deaminación
    - Hydroxylamina
  - Reacciones oxidativas
  - Agentes Intercalantes

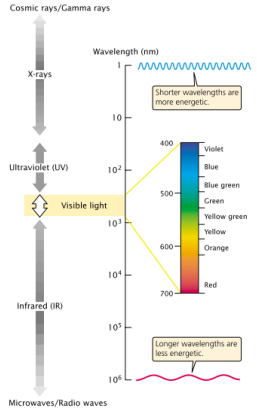
Concepts

Chemicals can produce mutations by a number of mechanisms. Base analogs are inserted into DNA and frequently pair with the wrong base. Alkylating agents, deaminating chemicals, hydroxylamine, and oxidative radicals change the structure of DNA bases, thereby altering their pairing properties. Intercalating agents wedge between the bases and cause single-base insertions and deletions in replication.

Radiación:

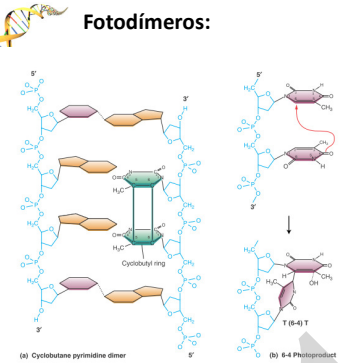
Concepts

Ionizing radiation such as X-rays and gamma rays damage DNA by dislodging electrons from atoms; these electrons then break phosphodiester bonds and alter the structure of bases. Ultraviolet light causes mutations primarily by producing pyrimidine dimers that disrupt replication and transcription. The SOS system enables bacteria to overcome replication blocks but introduces mistakes in replication.



17.23 **In the electromagnetic spectrum, as wavelength decreases, energy increases.** (Adapted from *Life 6e*, figure 8.5).

Fotodímeros:



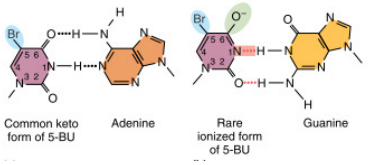
Alteran la estructura DNA

Sistema de reparación SOS

Figure 14-12 UV light–generated photoproducts. Photoproducts that unite adjacent pyrimidines in DNA are strongly correlated with mutagenesis. (Left panel adapted from E. C. Friedberg, *DNA Repair*. Copyright 1985 by W. H. Freeman and Company. Right panel from J. S. Taylor et al.)

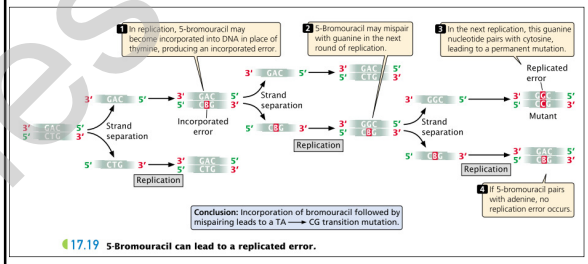
Análogos de base

Químicos con estructura similar a una base estándar de DNA.



5-BU ≈ T → 5BU --- A
5BU* --- G

Análogos de base



17.19 **5-Bromouracil can lead to a replicated error.**

Análogos de base

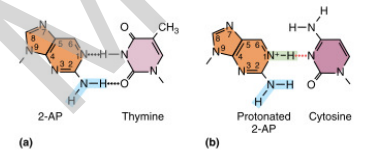
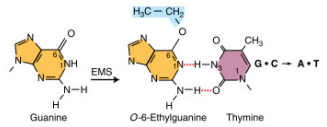


Figure 14-8 Alternative pairings for 2-aminopurine (2-AP). This analog of adenine can pair with cytosine in its protonated state (b).

2-AP ≈ A → 2AP --- T
2AP* --- C

Agentes alquilantes: químicos que donan un grupo alquilo.

-CH_3 = metilo
-CH_2CH_3 = etilo



EMS: etilmetanosulfonato (-etil)
NTG: nitrosoguanidine (-metil)

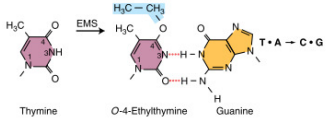
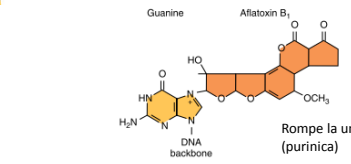


Figure 14-9 Alkylation-induced specific mispairings. Treatment with EMS alters the structure of guanine and thymine and leads to mispairings.

Modificadores de base:

	Original base	Mutagen	Modified base	Pairing partner	Type of mutation
(a)	Guanine	EMS	O^6-Ethylguanine	Thymine	CG → TA
(b)	Cytosine	Nitrous acid (HNO_2)	Uracil	Adenine	CG → TA
(c)	Cytosine	Hydroxylamine (NH_2OH)	Hydroxylamino-cytosine	Adenine	CG → TA

Sitios AP:



Rompe la unión entre el azúcar y la base (purinica)

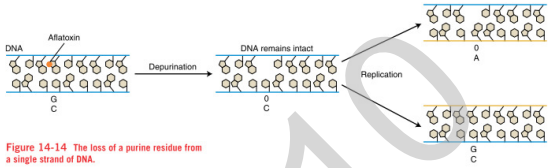
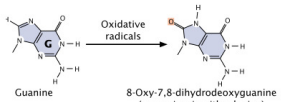


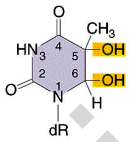
Figure 14-14 The loss of a purine residue from a single strand of DNA.

Reacciones oxidativas:

$O_2 + e^-$	→	O_2^-	: Superóxido
$O_2 + e^- + 2H^+$	→	H_2O_2	: Peróxido de hidrógeno
$H_2O_2 + e^- + H^+$	→	$H_2O + OH\cdot$	: Radical hidroxilo
$OH\cdot + e^- + H^+$	→	H_2O	



17.21 **Oxidative radicals convert guanine into 8-oxy-7,8-dihydrodeoxyguanine, which frequently mispairs with adenine instead of cytosine,**



Glicol de timidina

Agentes intercalantes:

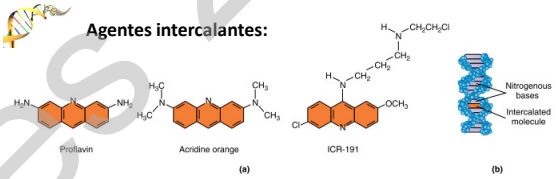
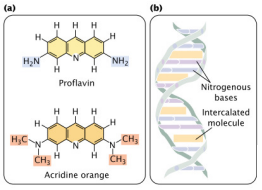


Figure 14-10 **Intercalating agents.** (a) Structures of common intercalating agents and (b) their interaction with DNA. (From L. S. Lerman, *Proc. Natl. Acad. Sci. USA* 39, 1963, 94.)

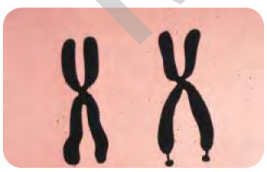


InDel

17.22 **Intercalating agents such as proflavin and acridine orange insert themselves between adjacent bases in DNA, distorting the three-dimensional structure of the helix and causing single-nucleotide insertions and deletions in replication.**

Algunos casos de mutaciones en humanos:

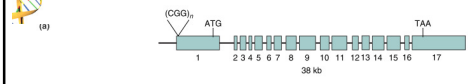
Síndrome X-frágil: retraso mental.
1 cada 1500 hombres y 1 cada 2500 mujeres



17.5 **The fragile-X chromosome is associated with a characteristic constriction (fragile site) on the long arm.** (Visuals Unlimited.)

Gen *FMR-1*:

$(CGG)_n$: se transcribe, pero no se traduce



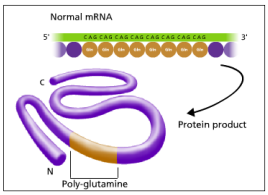
(b)

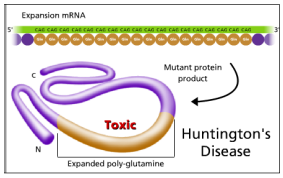
FMR-1 gene	Phenotype	Transmission	Methylation	Transcription
Normal $(CGG)_{6-39}$ ATG	Normal	Stable	No	Yes
Premutation $(CGG)_{60-200}$ ATG	Largely normal	Unstable, prone to expansion	No	Yes
Full mutation $(CGG)_{>200}$ ATG	Affected	Unstable	Yes	No

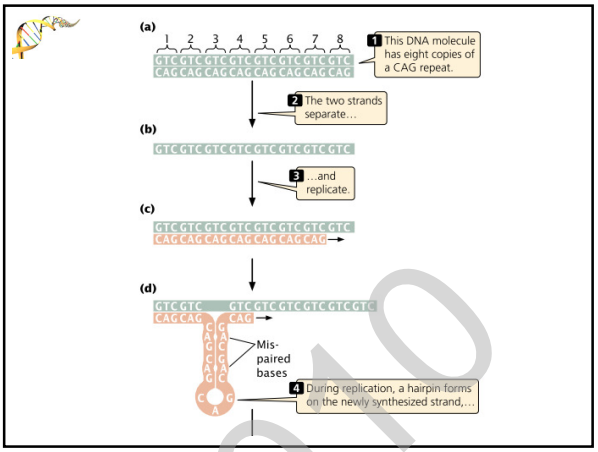
Figure 14-24 **The *FMR-1* gene involved in fragile X syndrome.** (a) Exon structure and upstream CGG repeat. (b) Transcription and methylation in normal, premutation, and full mutation alleles. The red circles are methyl groups. (W. T. O'Donnell and S. T. Warren, *Ann. Rev. Neuroscience* 25, 2002, 315–338, Figure 1.)

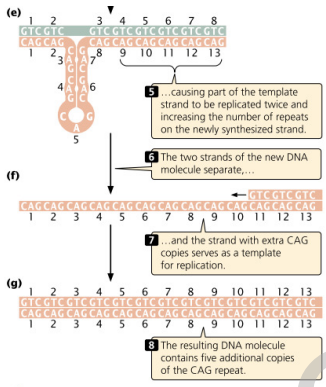
Enfermedad de Huntington: trastorno genético hereditario, trastorno neuropsiquiátrico. Degeneración neuronal constante y progresiva.

Gen de la huntingtina: expansión de repeticiones del trinucleótido **CAG** (Gln).









17.6 The number of copies of a trinucleotide may increase by strand slippage in replication.

Table 17.1 Examples of genetic diseases caused by expanding trinucleotide repeats

Disease	Repeated Sequence	Number of Copies of Repeat: Normal Range	Number of Copies of Repeat: Disease Range
Spinal and bulbar muscular atrophy	CAG	11–33	40–62
Fragile-X syndrome	CGG	6–54	50–1500
Jacobsen syndrome	CGG	11	100–1000
Spinocerebellar ataxia (several types)	CAG	4–44	21–130
Autosomal dominant cerebellar ataxia	CAG	7–19	37––220
Myotonic dystrophy	CTG	5–37	44–3000
Huntington disease	CAG	9–37	37–121
Friedreich ataxia	GAA	6–29	200–900
Dentatorubral-pallidoluysian atrophy	CAG	7–25	49–75
Myoclonus epilepsy of the Unverricht-Lundborg type*	CCCGCCCCGCG	2–3	12–13

*Technically not a trinucleotide repeat but does entail a multiple of three nucleotides that expands and contracts in similar fashion to trinucleotide repeats.

Concepts

Expanding trinucleotide repeats are regions of DNA that consist of repeated copies of three nucleotides. Increased numbers of trinucleotide repeats are associated with several genetic diseases.

Table 17.2 Characteristics of different types of mutations

Type of Mutation	Definition
Base substitution	Changes the base of a single DNA nucleotide
Transition	Base substitution in which a purine replaces a purine or a pyrimidine replaces a pyrimidine
Transversion	Base substitution in which a purine replaces a pyrimidine or a pyrimidine replaces a purine
Insertion	Addition of one or more nucleotides
Deletion	Deletion of one or more nucleotides
Frameshift mutation	Insertion or deletion that alters the reading frame of a gene
In-frame deletion or insertion	Insertion or deletion of a multiple of three nucleotides that does not alter the reading frame
Expanding trinucleotide repeats	Repeated sequence of three nucleotides (trinucleotide) in which the number of copies of the trinucleotide increases
Forward mutation	Changes the wild-type phenotype to a mutant phenotype
Reverse mutation	Changes a mutant phenotype back to the wild-type phenotype
Missense mutation	Changes a sense codon into a different sense codon, resulting in the incorporation of a different amino acid in the protein
Nonsense mutation	Changes a sense codon into a nonsense codon, causing premature termination of translation
Silent mutation	Changes a sense codon into a synonymous codon, leaving unchanged the amino acid sequence of the protein
Neutral mutation	Changes the amino acid sequence of a protein without altering its ability to function
Loss-of-function mutation	Causes a complete or partial loss of function
Gain-of-function mutation	Causes the appearance of a new trait or function or causes the appearance of a trait in inappropriate tissues or at inappropriate times
Lethal mutation	Causes premature death
Suppressor mutation	Suppresses the effect of an earlier mutation at a different site
Intragenic suppressor mutation	Suppresses the effect of an earlier mutation within the same gene
Intergenic suppressor mutation	Suppresses the effect of an earlier mutation in another gene

Bibliografía Recomendada:

Klug W. S., Cummings M. R., Spencer C. A., Palladino M. A. (2009) Concepts of Genetics. Ninth Edition. Pearson/Benjamin Cummings, Inc.

Griffiths A. J., Wessler S. R., lewontin R. C., Carroll S. B. (2008) Introduction to Genetics Analysis. 9 TH edition. W. H. Freeman and Company, New York.

Pierce B. A. (2008) Genetics. A conceptual Approach. Third Edition. W. H. Freeman and Company, New York.

Tamarin R. (2001) Principles of Genetics. Seventh Edition. The McGraw-Hill Companies.