MEDICAL GENOMICS

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Medical genomics

- Big genomic data enable inference without intervention (aka reverse genetics)

- Data are just around the corner

Medical genomics

Part I. Кто виноват?
1. Mutations: origins and rates
2. Mutations: transmisson
3. Mutations in time: some basics of population genetics
4. Mutations in space: genes and consequences
5. Mutations in individuals and populations

Part II. Что делать?
6. Mendelian diseases: gene discovery and diagnostics
7. Some basics of quantitative genetics
8. Complex diseases: gene discovery and allelic architecture

Remarks

- Important info: kodomo
- English
- Molecular genetics + population genetics + medical genetics + statistical genetics + genetic epidemiology + bioinformatics $\Rightarrow$ no single textbook
- Many topics not covered: immunology, pathogens, microbiome, therapy, genome editing

- Definitions
- Questions and exercises
- Homework slides 🏠
- Summary, concepts, further reading

Textbooks

1. T.Strachan, A.Read. Human Molecular Genetics. 2011. ISBN 0815345895.
2. J. Gillespie. Population genetics. A concise guide 1998 ISBN 0-8018-5764-6
3. S. Szalai, et al. Medical genetics and genomics. 2016. https://www.researchgate.net/publication/303309837_Medical_genetics_and_genomics_2016
4. A.Griffiths et al. An Introduction to Genetic Analysis. Freeman/Worth, 11 ed. 2015 ISBN 1464109486
5. Бочков Н.П., Пузырев В.П., Смирнихина С.А. Клиническая генетика. Учебник. Под ред. Н.П. Бочкова. ГЭОТАР-Медиа, 4-е издание, 2018. ISBN 978-5-9704-4628-7

MUTATIONS: ORIGINS AND RATES

Lecture plan

- Human karyotype

- Mitosis and DNA replication

- Replication fidelity and mutation rate

- Exogenous and endogenous DNA damage

- DNA repair mechanisms

- De novo mutations: single nucleotide variants

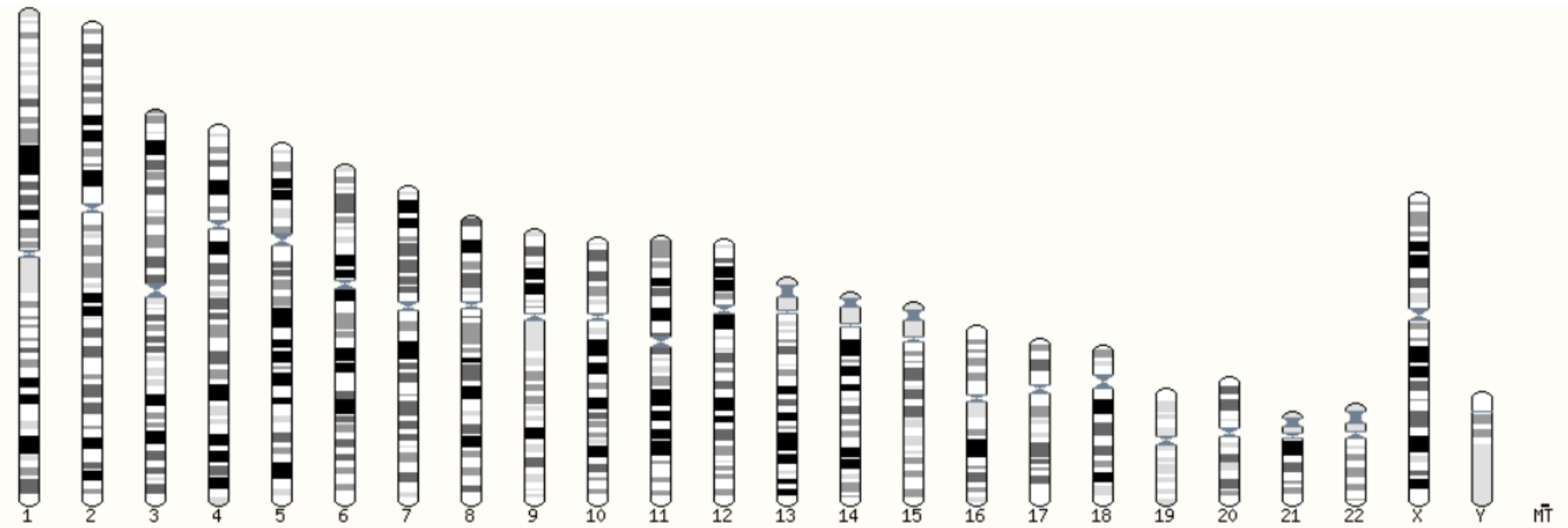- Structural variants and CNVs

- Aneuploidy

Human karyotype

22 pairs of **autosomal** chromosomes + 2 **sex** chromosomes

Human karyotype

- **Euchromatin** (2.9 Gbp): the gene-rich, transcriptionally active regions of the nuclear genome

- **Heterochromatin** (0.2 Gbp): tightly packed (condensed), transcriptionally inactive, highly repetitive DNA. Location: centromeres, telomeres.

- **Metacentric chromosomes** have the centromere in the center, such that both arms are of nearly equal length.

- **Acrocentric chromosomes** (13, 15, 21, 22) have unequal arms.
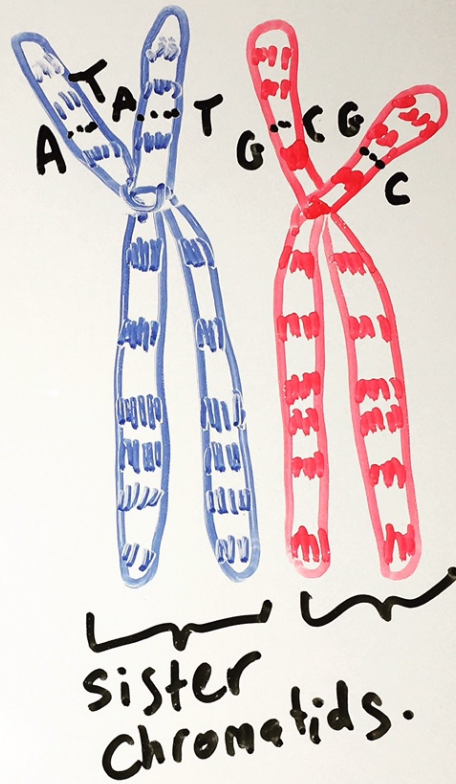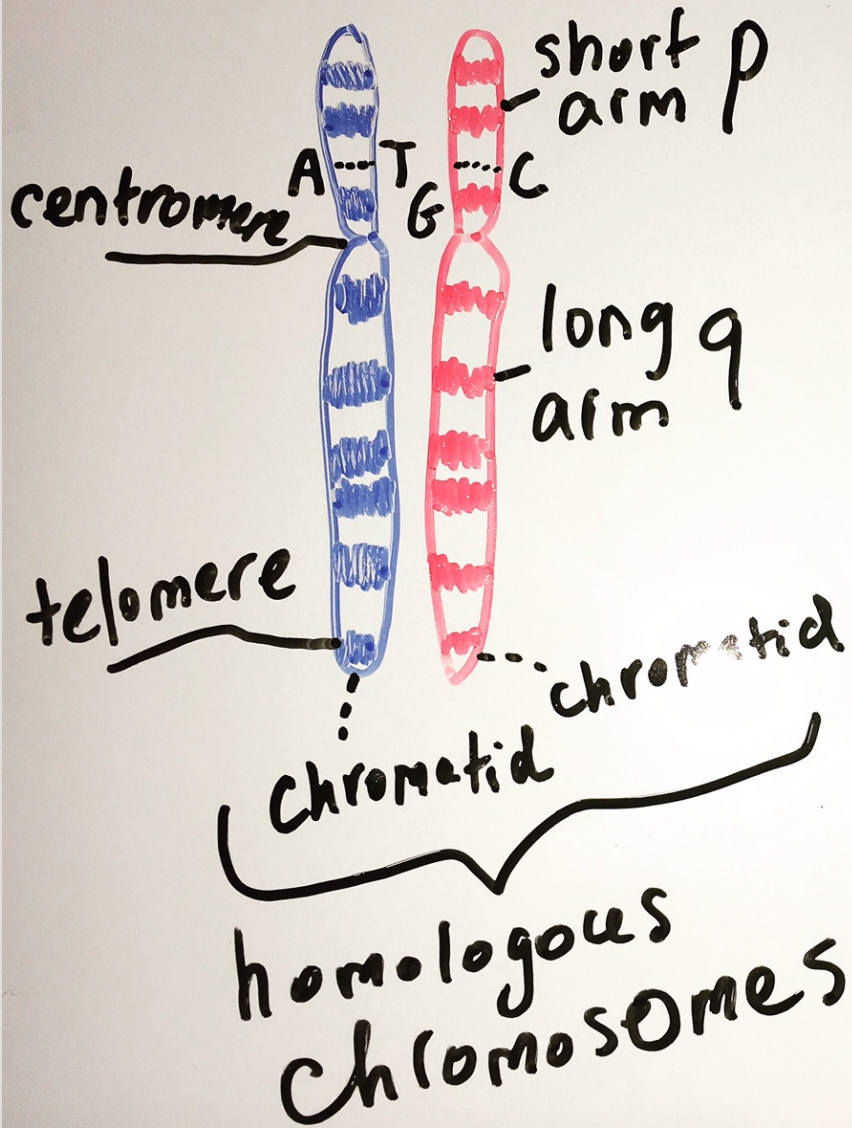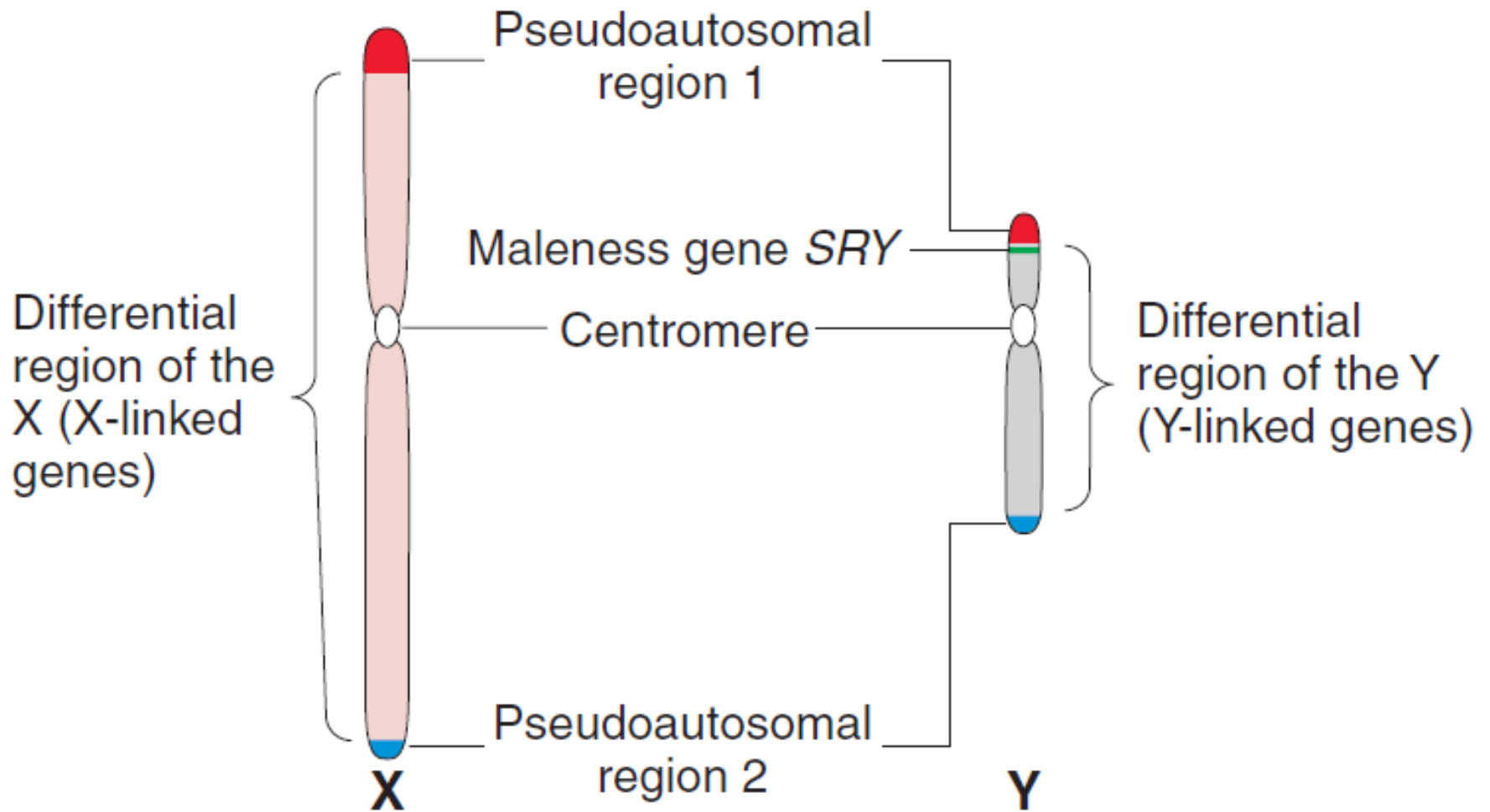
Sex chromosomes

Women: XX, men: XY

Q: transmission of Y chromosome

Griffiths -- *Introduction to Genetic Analysis*

How to check sex of an NGS sample?

How to check sex of an NGS sample?

• **Heterozygous / Homozygous ratio on chromosome X**
Het/Hom<0.8 => M, Het/Hom>0.8 => F; suspicious : 0.5-1.0

• ***SRY* gene** (Sex-determining Region Y):
intronless sex-TF protein, responsible for
the initiation of male sex determination
in mammals
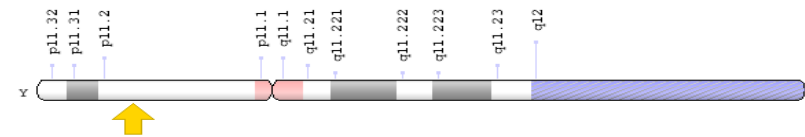
• **The human amelogenin genes: *AMELX* and *AMELY***
Short arms of X and Y sex chromosomes, share 84% sequence
identity. A 6 bp insertion/deletion difference in the first intron of the
AMELY and *AMELX* genes is typically targeted in forensic sex
identification (Tzvetkov 2010 *Pharmacogenomics*)

Genome Reference Consortium GRCh38.p13
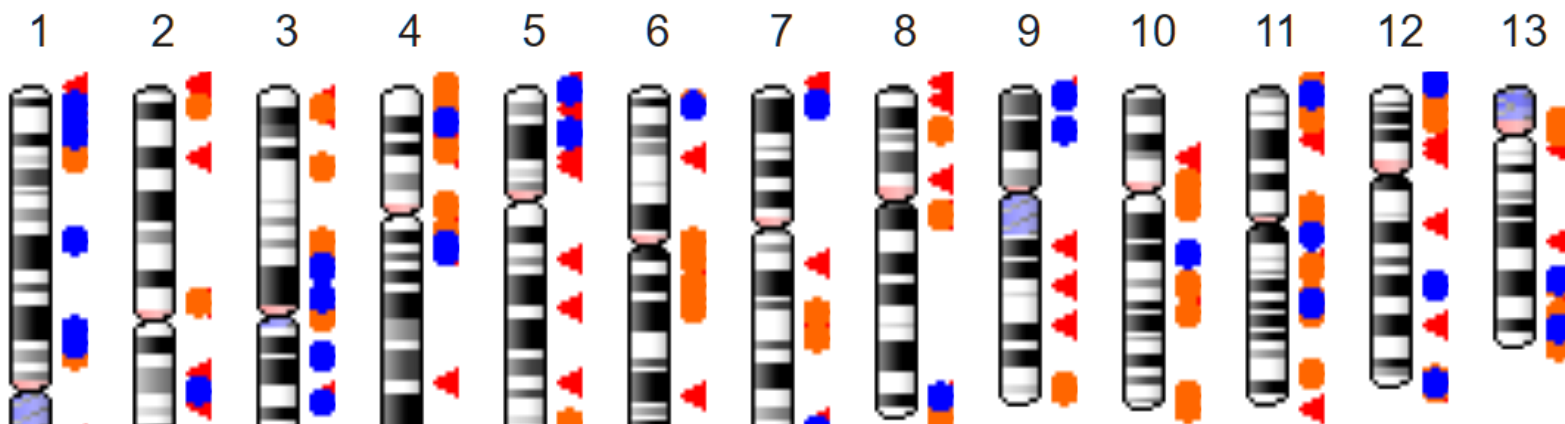
Chromosomes	Mbp
Nuclear	3088
Mitochondrial	0.017
Unknown, alt	121.0
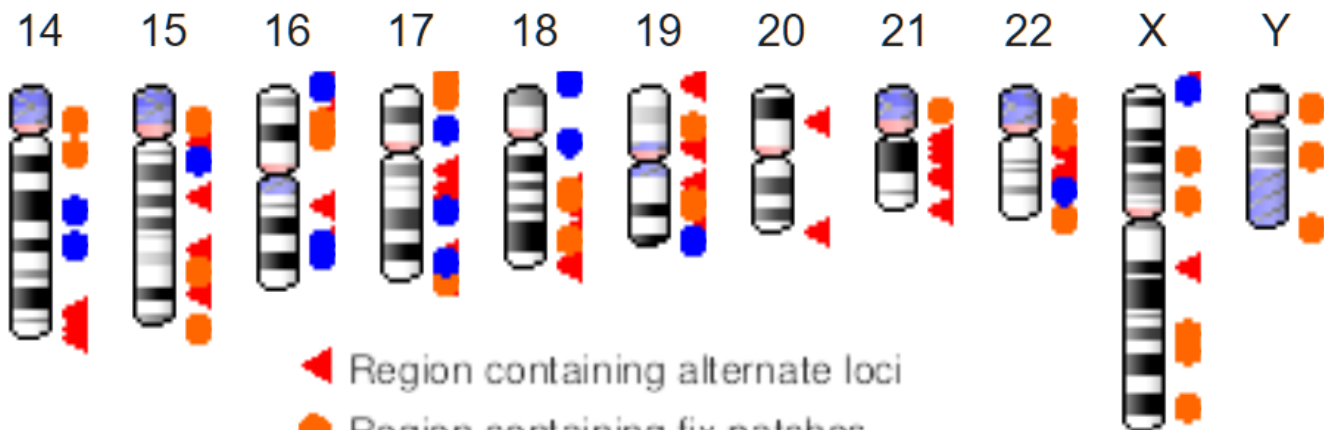
◄ Region containing alternate loci
● Region containing fix patches
● Region containing novel patches

https://www.ncbi.nlm.nih.gov/grc/human

Human genome contents

Regions	Length, Mbp	%	Description
Genes	1,200	37.5	Genomic locus where transcription occurs
Exons	48	1.5	Transcribed genomic region that remain in the RNA after splicing
Other (introns, UTRs)	1,152	36.0	Regions of a coding cDNA which are not translated
Unique and regulatory sequences	510	15.9	
Interspersed repeats	1,400	43.8	
LINEs	640	20.0	~850,000 Long Interspersed Elements (~7,000 bp). Retrotransposed elements containing open reading frames encoding (often inactive) reverse transcription machinery
SINEs, Alu repeats	420	13.1	~1,500,000 Short Interspersed Elements. Retrotransposed elements <500 bp that contain tRNA, snRNA and rRNA, which require other mobile elements to be transposed.
LTR retrotransposons	250	7.8	Transposable elements characterized by the presence of Long Terminal Repeats (LTRs) directly flanking an internal coding region
DNA transposons	90	2.8	Class II transposable elements that move through a DNA intermediate
Microsatellites	90	2.8	A region in the genomic sequence containing short tandem repeats of 2-10bp
Total	3,200	100.0	

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Human genome contents
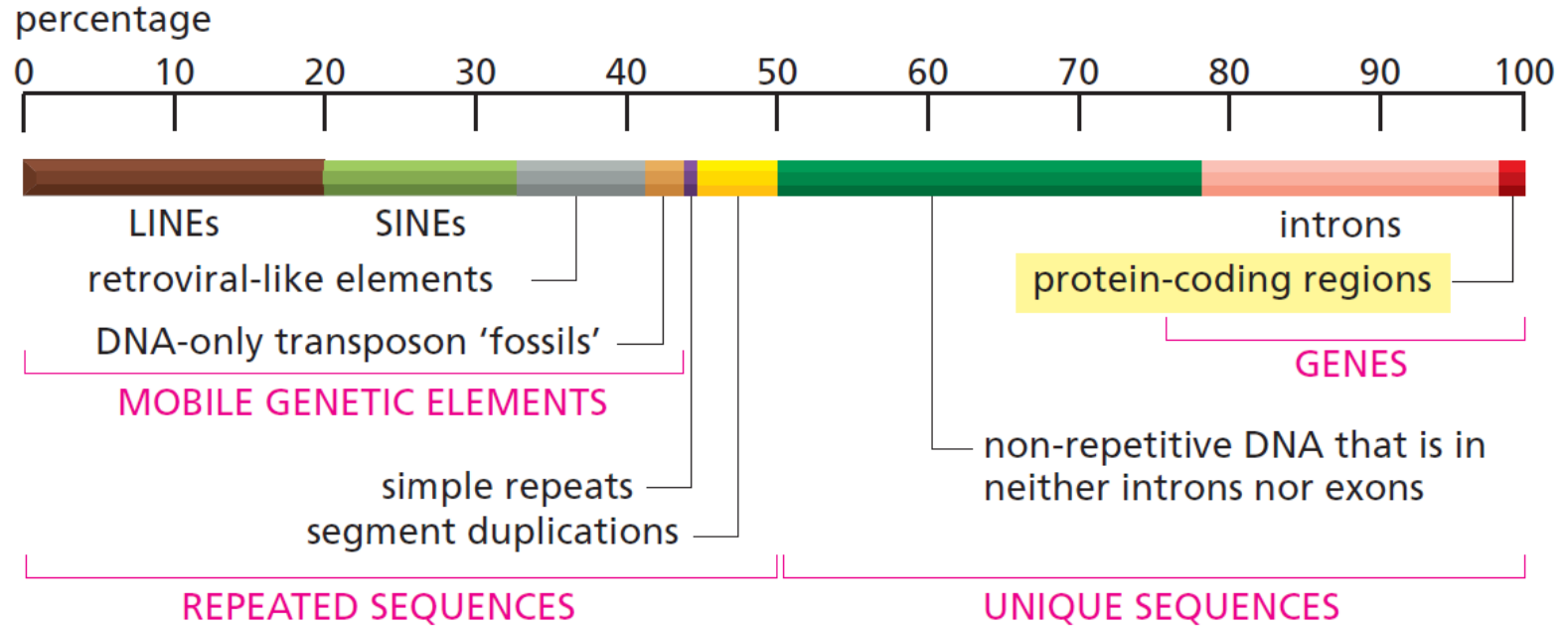
Alberts - *Essential Cell Biology*

Element	Transposition	Structure	Length	Copy number	Fraction of genome
LINEs	Autonomous	ORF1 ORF2 (pol) AAA	1–5 kb	20,000–40,000	21%
SINEs	Nonautonomous	AAA	100–300 bp	1,500,000	13%
DNA transposons	Autonomous	transposase	2–3 kb	300,000	3%
	Nonautonomous		80–3000 bp		

Griffiths -- *Introduction to Genetic Analysis*

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ENSEMBL gene annotation GRCh38 v.99

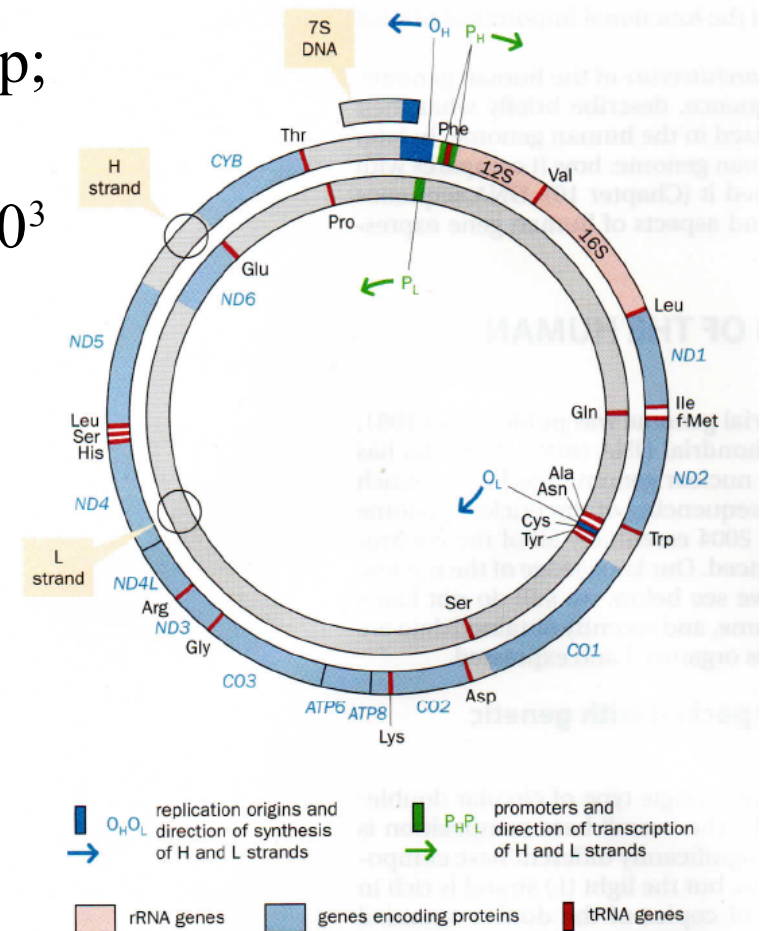| Gene biotype	Genes (Transcripts)	%	Description
Proten coding	19,968 (153,197)	32.9	Genes that contain an open reading frame (ORF)
Pseudogenes	15,263	25.2	Genes that have homology to known protein-coding genes but contain a frameshift and/or stop codon(s) which disrupts the ORF
To be confirmed	1,060	1.7	Require experimental validation
T-cell receptors, immunoglobulins	408	0.7	Undergo somatic recombination before transcription
RNA genes	23,977	39.5	
lncRNA	16,880		A non-coding gene >200bp in length
snRNA	1,910		Processing of pre-messenger RNA
miRNA	1,879		A small RNA (~22bp) that silences the expression of target mRNA
snoRNA	942		Post-transcriptional modification of other RNAs
Other	2,366		rRNA, sRNA, scRNA, scaRNA, miscRNA
Total	60,676 (227,818)	100	

ENSEMBL gene annotation GRCh38 v.99

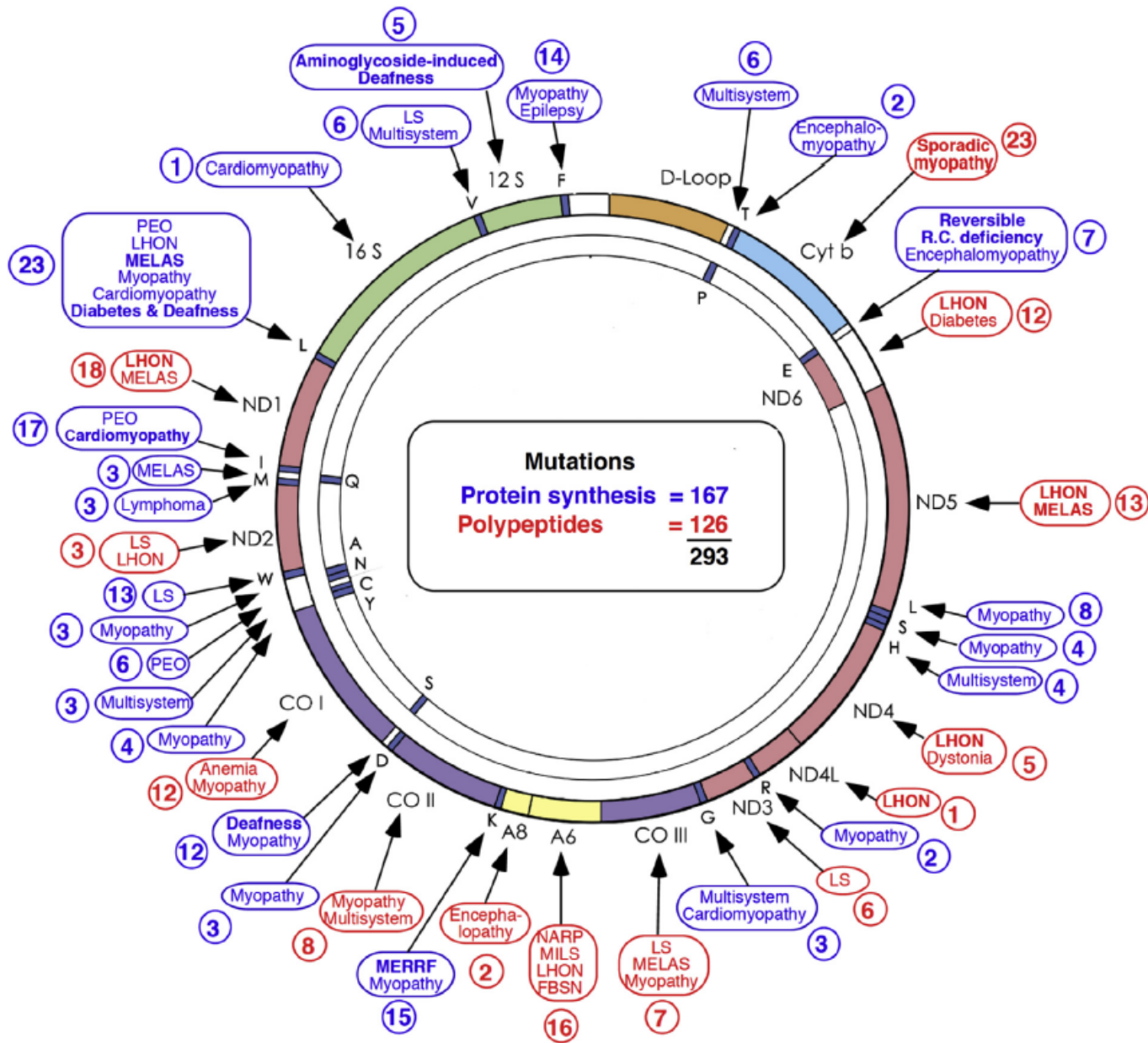| Chromosome	Approximate length (bp)	Protein-coding genes	Non-protein coding genes	Pseudogenes
1	248956422	2047	1964	1233
2	242193529	1303	1605	1033
3	198295559	1075	1160	768
4	190214555	753	984	732
5	181538259	881	1200	710
6	170805979	1041	989	803
7	159345973	989	977	893
8	145138636	670	1041	629
9	138394717	778	786	678
10	133797422	728	880	568
11	135086622	1312	1053	815
12	133275309	1036	1197	627
13	114364328	321	586	378
14	107043718	820	857	519
15	101991189	613	986	513
16	90338345	867	1033	467
17	83257441	1185	1198	531
18	80373285	269	608	246
19	58617616	1474	895	514
20	64444167	543	594	250
21	46709983	231	403	183
22	50818468	492	513	332
X	156040895	843	640	872
Y	57227415	63	108	392
Mitochondrial	16569	13	24	

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Jackson (2018) *Essays Biochem*

Mitochondrial genome

- **mtDNA**: circular, double-stranded, 16,569 bp; H and L chains; similar to bacteria
- Egg only, maternally inherited; each cell: ~10^3 copies; highly heterogeneous
- 37 genes: 22 tRNA + 2 rRNA + 13 coding
- 13 polypeptides are part of **mitochondrial respiratory complex** (Sugars → ATP), together with multiple nuclear genes
- mtDNA is to some extent autonomous, with its own genetic code
- Stop codons: TAA, TAG, AGA, AGG

- **Mitochondrial diseases**: a heterogeneous group of inherited anomalies in oxidative phosphorylation due to mutations in the mitochondrial (70%) or nuclear DNA (30%)
- ~300 disease-causing point mutations known in mtDNA

Pathogenic mutations in mtDNA

DiMauro (2017) Mitochondrial Encephalomyopathies

The cell cycle

1 During G_1, the cell grows.

2 Cells may enter G_0, a non-dividing phase.

3 After the G_1/S checkpoint, the cell is committed to dividing.

4 In S, DNA duplicates.

5 In G_2, the cell prepares for mitosis.

6 After the G_2/M checkpoint, the cell can divide.

7 Mitosis and cytokinesis (cell division) take place in M phase.

Spindle-assembly checkpoint

Cytokinesis

G_2/M checkpoint

G_1/S checkpoint

Mitosis

M phase: nuclear and cell division

Interphase: cell growth

G_1

G_0

G_2

S

2.7 The cell cycle consists of interphase and M phase.

Pierce -- *Genetics Essentials. Concepts and Connections*
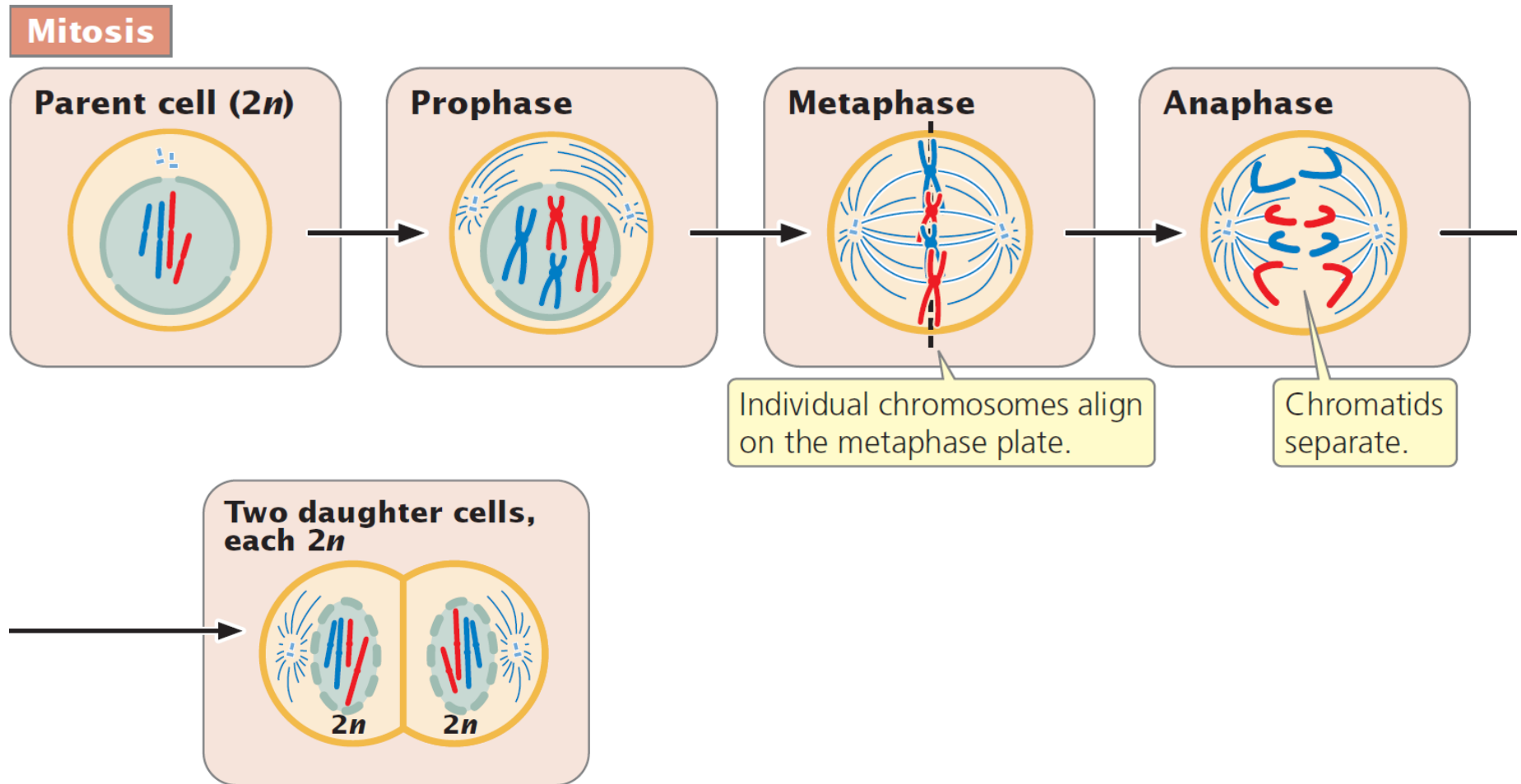
Mitosis

Mitosis: a type of cell division that results in two daughter cells with the set of chromosomes as the parent nucleus, typical of ordinary tissue growth
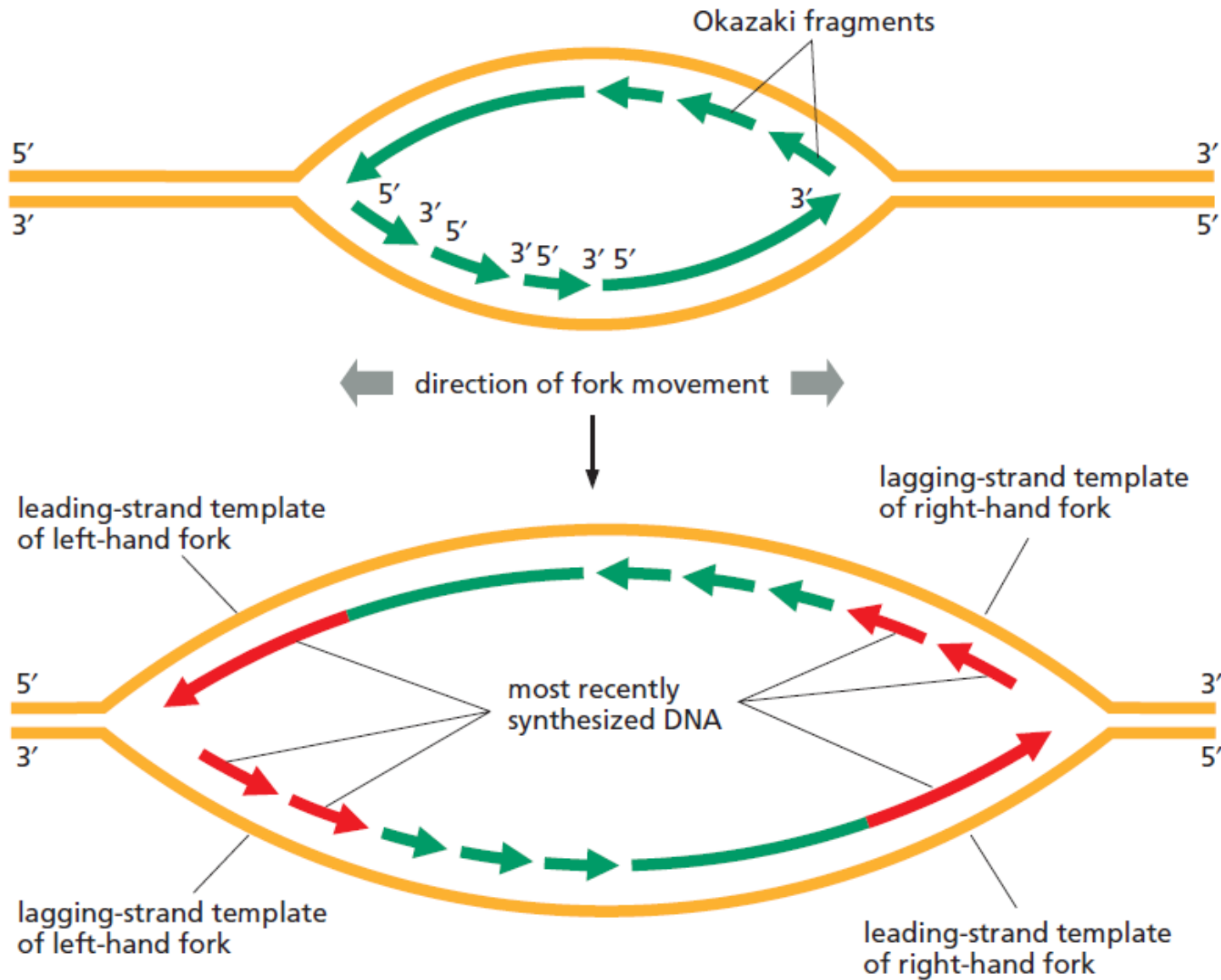
Pierce -- *Genetics Essentials. Concepts and Connections*

DNA replication forks

Alberts -- *Essential Cell Biology*

DNA replication forks

origins of replication

1

direction of
fork movement

replication forks

2

0.1 µm

3

Alberts -- *Essential Cell Biology*

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Repeat expansion during replication

Pierce -- *Genetics Essentials. Concepts and Connections*

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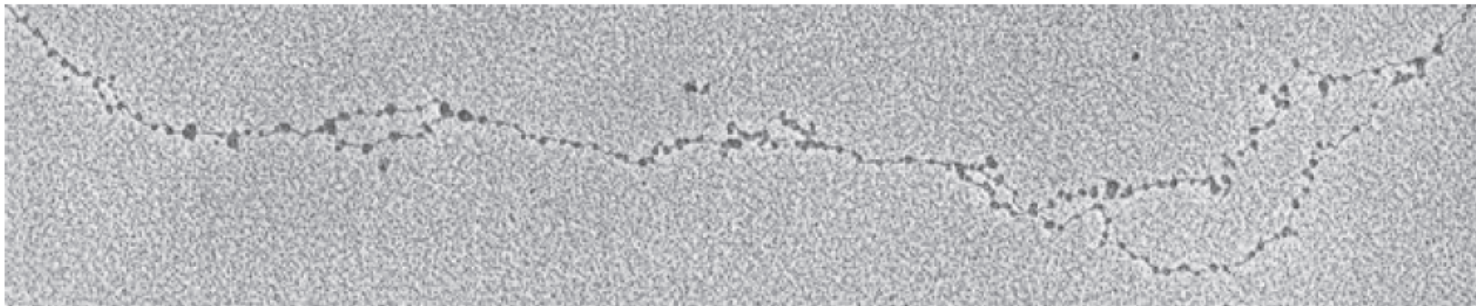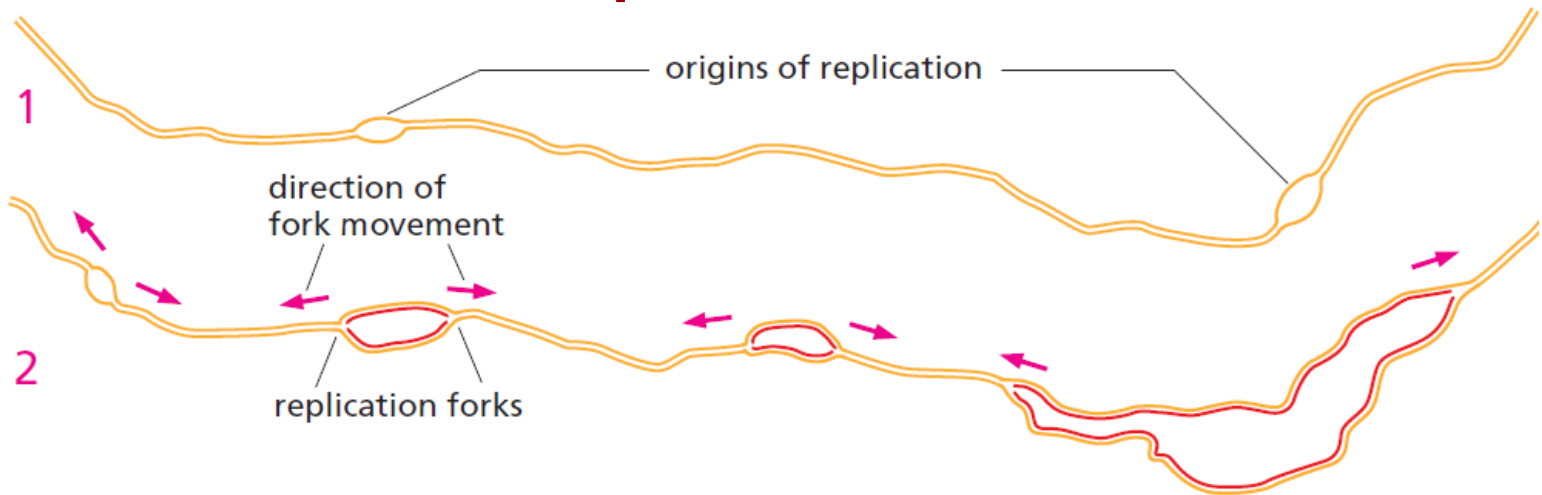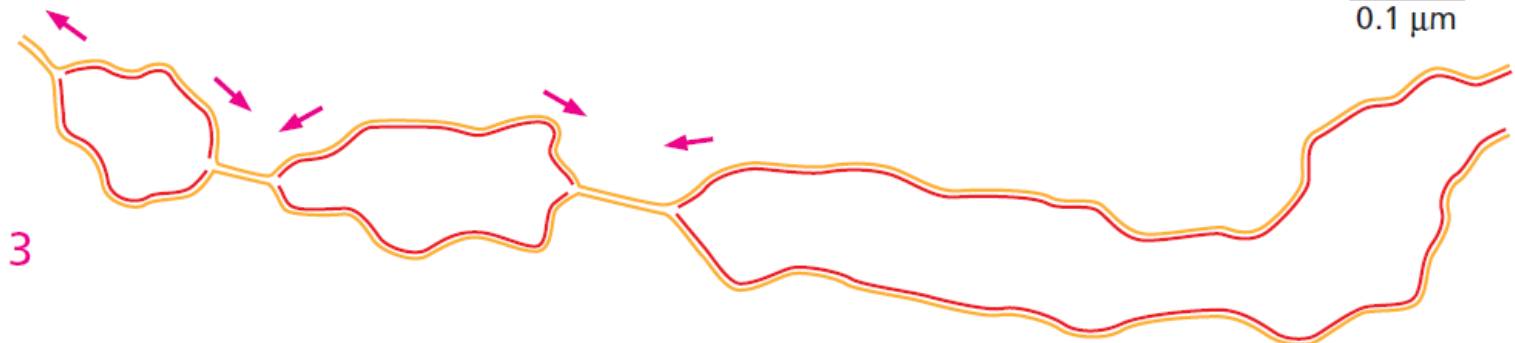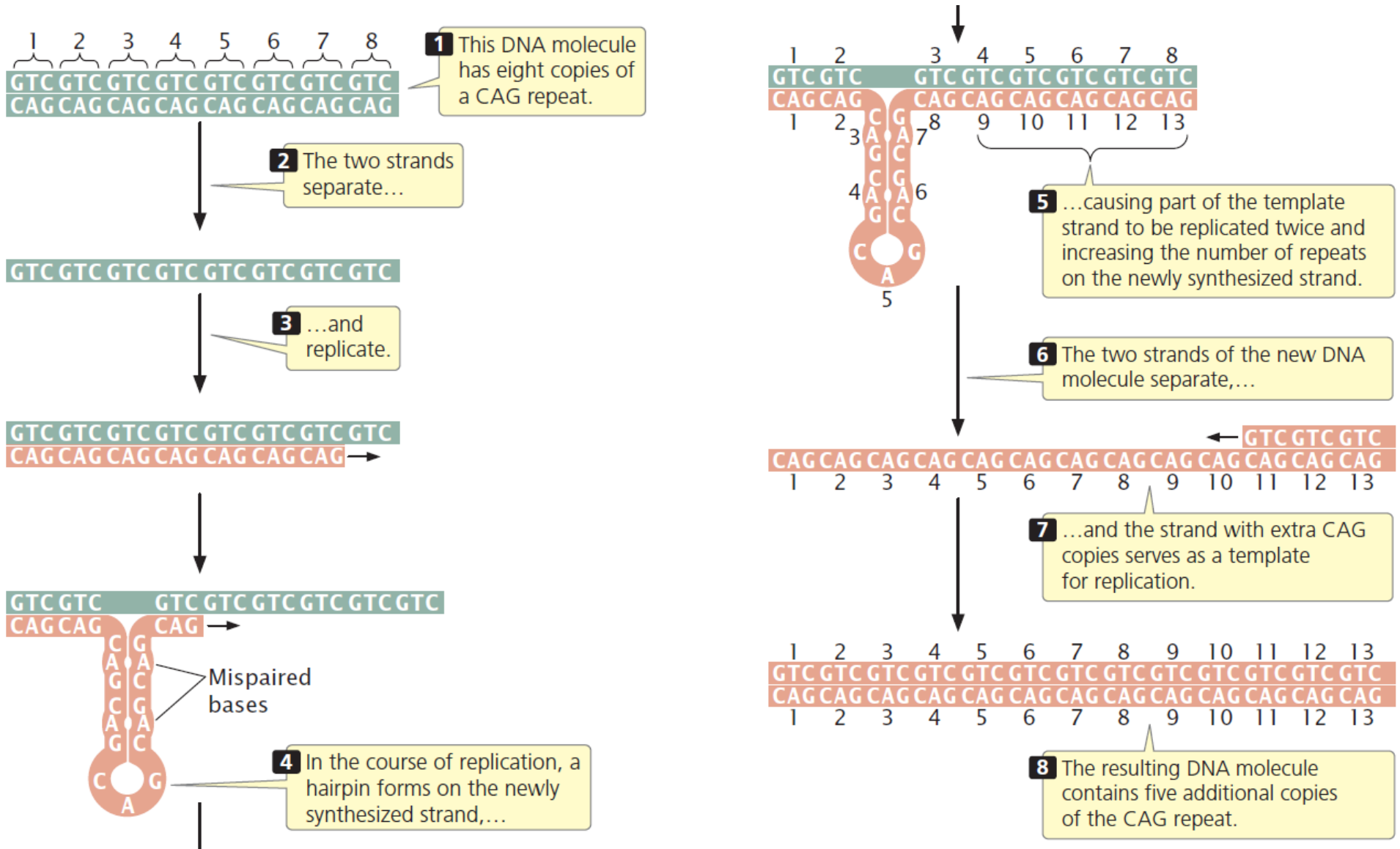
Repeat expansion during replication
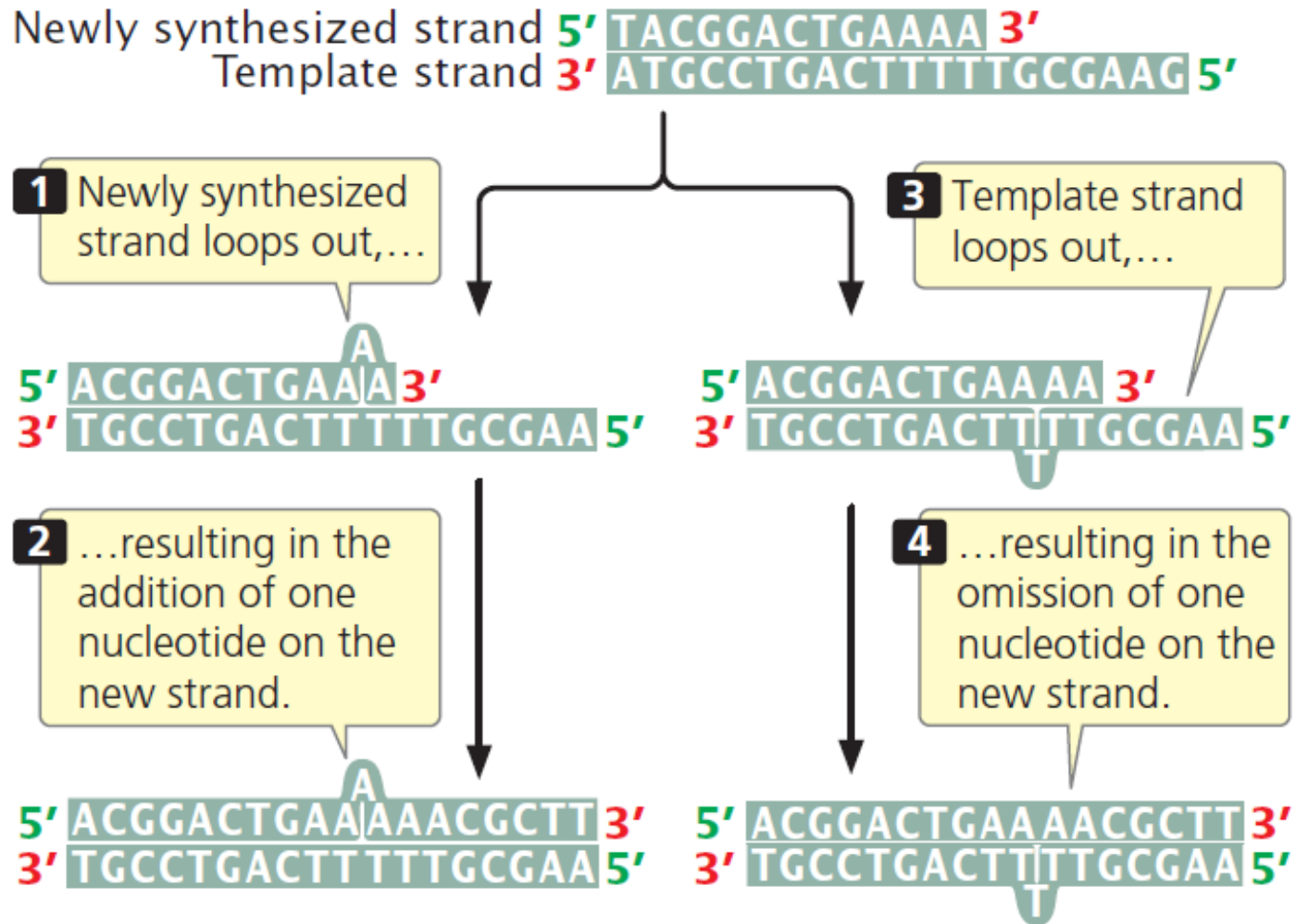
13.13 Insertions and deletions may result from strand slippage.

Pierce -- *Genetics Essentials. Concepts and Connections*

Repeat expansion and disease

Table 13.1	Examples of genetic diseases caused by expanding trinucleotide repeats		
		Number of Copies of Repeat	
Disease	**Repeated Sequence**	**Normal Range**	**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*	CCCCGCCCCGCG	2–3	12–13

Exercise: find related genes in OMIM database

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OMIM®

Online Mendelian Inheritance in Man®

An Online Catalog of Human Genes and Genetic Disorders

Updated February 12, 2021

Search OMIM for clinical features, phenotypes, genes, and m   🔍

Dissected OMIM Morbid Map Scorecard (Updated February 12th, 2021) :

Class of phenotype	Phenotype	Gene *
Single gene disorders and traits	5,740	4,006
Susceptibility to complex disease or infection	694	499
"Nondiseases"	151	119
Somatic cell genetic disease	231	130

*Some genes may be counted more than once because mutations in a gene may cause more than one phenotype and the phenotypes may be of different classes (e.g., activating somatic BRAF mutation underlying cancer, 164757.0001. and germline BRAF mutation in Noonan syndrome, 164757.0022.)

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Mutations

Mutations are random changes in DNA sequences

Mutations are the cause of all genetic variation and genetic disease.

Mechanisms of mutation:
- Spontaneous replication errors
- Endogenous (spontaneous) DNA damage: deamination, depurination
- Exogenous (induced) DNA damage: chemical agents, radiation

Variants = mutations (recent changes), polymorphisms (segregating in a population), engineered (non-random) changes

Mutations

Single nucleotide variant: change of the base of a single DNA nucleotide (90%)
- Transition (G>A, C>T)
- Transversion (C>G, etc)

Short deletion: removal of few (<50bp?) nucleotides (6%)
- Deletion of a unique sequence
- Contraction of a short repeat

Short insertion: addition of few (<50bp?) nucleotides (2%),
- Insertion of a unique sequence
- Expansion of a short repeat

Structural variant (2%): sequence change ~1 kbp and larger in size
- Balanced
  Inversion or translocation
- Unbalanced (aka **CNV, copy number variant**)
  Tandem or dispersed duplication, deletion, insertion

Aneuploidy: wrong number of whole chromosomes: nullisomy, monosomy, trisomy

Replication errors become mutations

1 DNA strands separate for replication.

2 Thymine on the original template strand base pairs with guanine through wobble, leading to an incorporated error.

DNA — Wild type

TTCG
AAGC

Wild type

TTCG
AAGC

3 At the next round of replication, the guanine nucleotide pairs with cytosine, leading to a transition mutation.

Wild type

TTCG
AAGC

Mutant

TCCG
AGGC

T:A > C:G

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Standard and non-standard base pairing
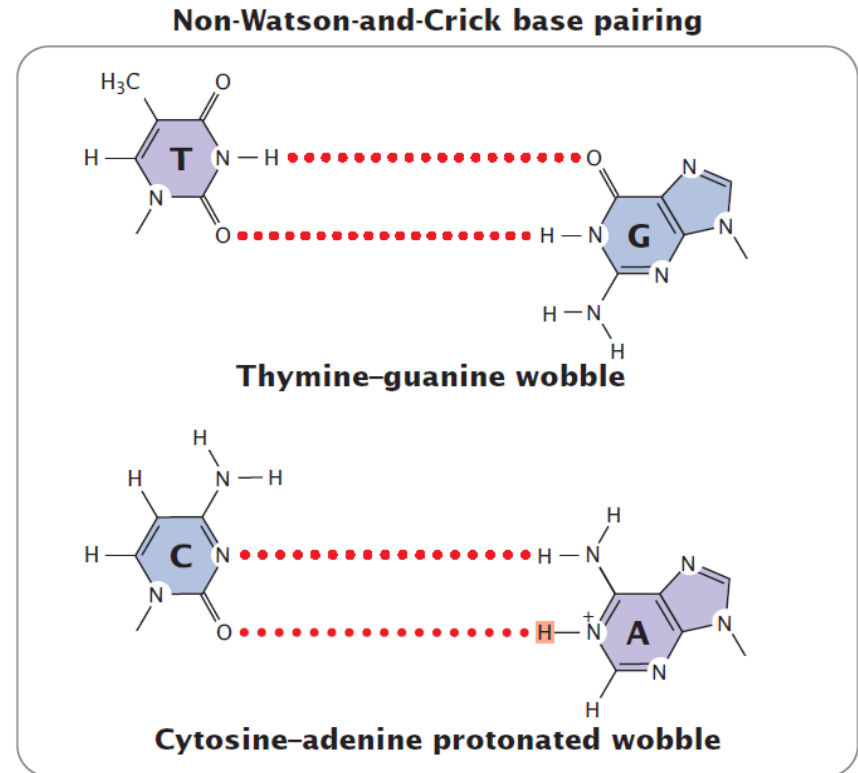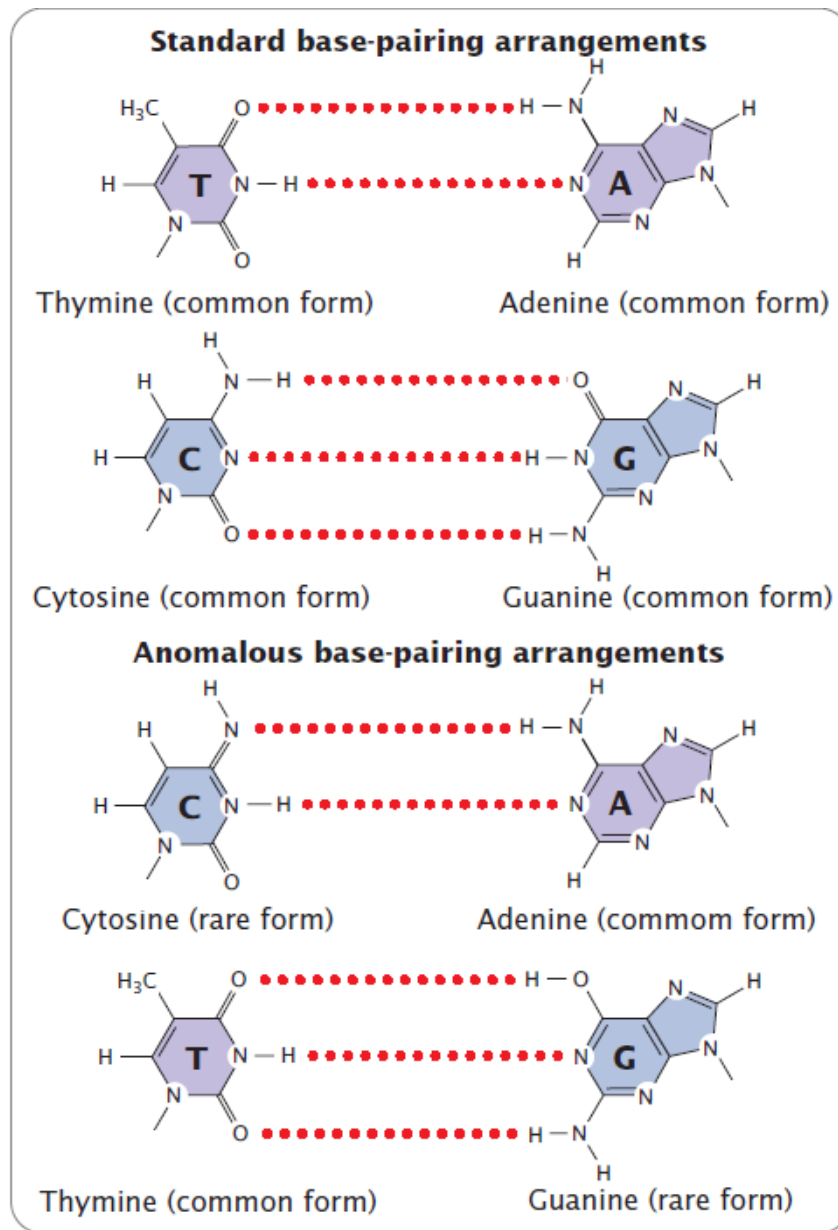
Standard base-pairing arrangements

Thymine (common form) — Adenine (common form)

Cytosine (common form) — Guanine (common form)

Anomalous base-pairing arrangements

Cytosine (rare form) — Adenine (commom form)

Thymine (common form) — Guanine (rare form)

Non-Watson-and-Crick base pairing

Thymine–guanine wobble

Cytosine–adenine protonated wobble

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Mechanisms of replication fidelity

Overall mutation rate: 10^{-10} per nucleotide per replication

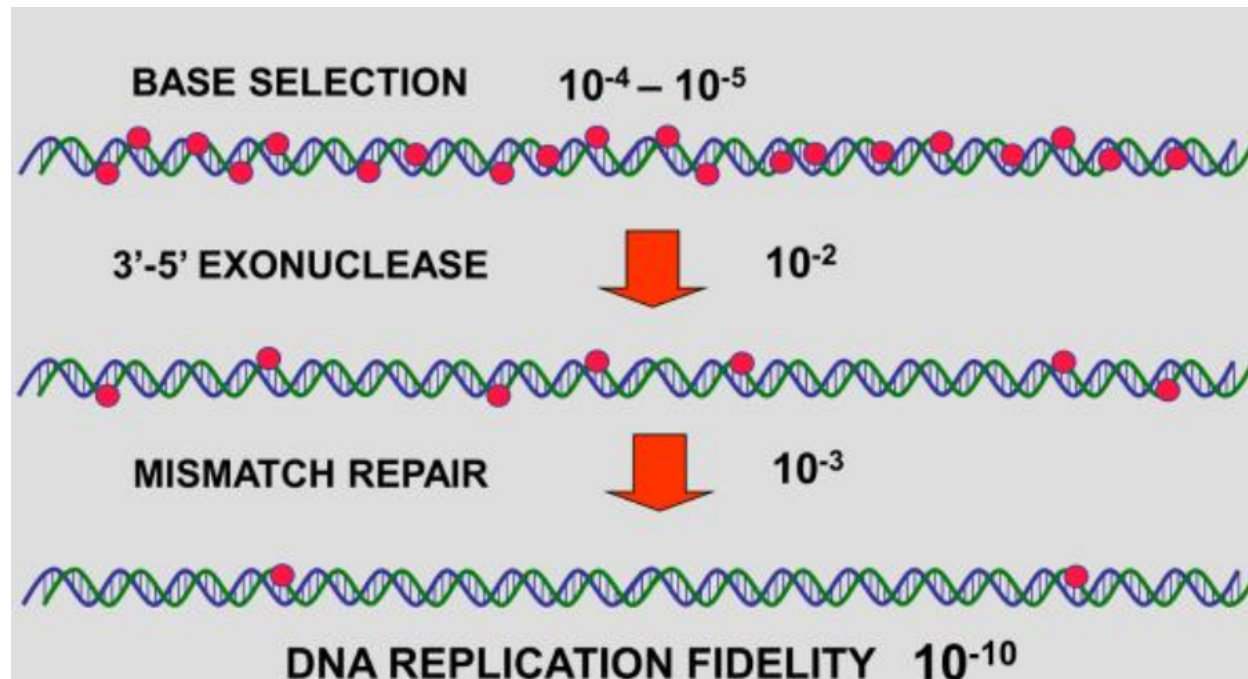1. DNA polymerase: $\sim 10^{-5}$ error rate
2. Proofreading 3'>5' exonuclease removes 99% mispairings: $\sim 10^{-2}$
3. Mismatch repair (MMR) machinery removes and restores DNA fragment around the mismatch: $\sim 10^{-3}$

BASE SELECTION $10^{-4} - 10^{-5}$

3'-5' EXONUCLEASE 10^{-2}

MISMATCH REPAIR 10^{-3}

DNA REPLICATION FIDELITY 10^{-10}

Fijalkowska (2012) *FEMS Microbiology Rev*

Mechanisms of replication fidelity

Overall mutation rate: 10^{-10} per nucleotide per replication

TABLE 6–1 ERROR RATES

US Postal Service on-time delivery of local first-class mail	13 late deliveries per 100 parcels
Airline luggage system	1 lost bag per 200
A professional typist typing at 120 words per minute	1 mistake per 250 characters
Driving a car in the United States	1 death per 10^4 people per year
DNA replication (without mismatch repair)	1 mistake per 10^7 nucleotides copied
DNA replication (including mismatch repair)	1 mistake per 10^9 nucleotides copied

Alberts – *Essential Cell Biology*

Mutation rate and its consequences

S: mutation rate per nucleotide per cell division

K: the average number of germline cell divisions per generation, from zygote to zygote (~30 in females, ~60–500 in males)

N: genome size

Mutation rate per genome: $S \times K \times N$

~10^{-10} per nucleotide per cell division (or ~10^{-8} per generation, because there are ~100 cell divisions and rounds of DNA replication per human generation $\implies$ ~100 *de novo* mutations in a newborn

1) ~1% of all newborns being affected by a serious disease due to a de novo mutation. If the mutation rate were 100 times higher, 10^{-8} per cell division, we would immediately **go extinct**.

2) 10^{14} cells in human body $\implies$ total number of somatic mutations in each person ?

Mutation rate and its consequences

Spontaneous *de novo* germline mutations in humans and mice: rates, spectra, causes and consequences

Mizuki Ohno[*]

The human body consists of approximately 10^{14} cells and undergoes approximately 10^{16} cell divisions in a lifetime, resulting in **over 10^{15} cumulative mutations per individual** (Frank, 2014).

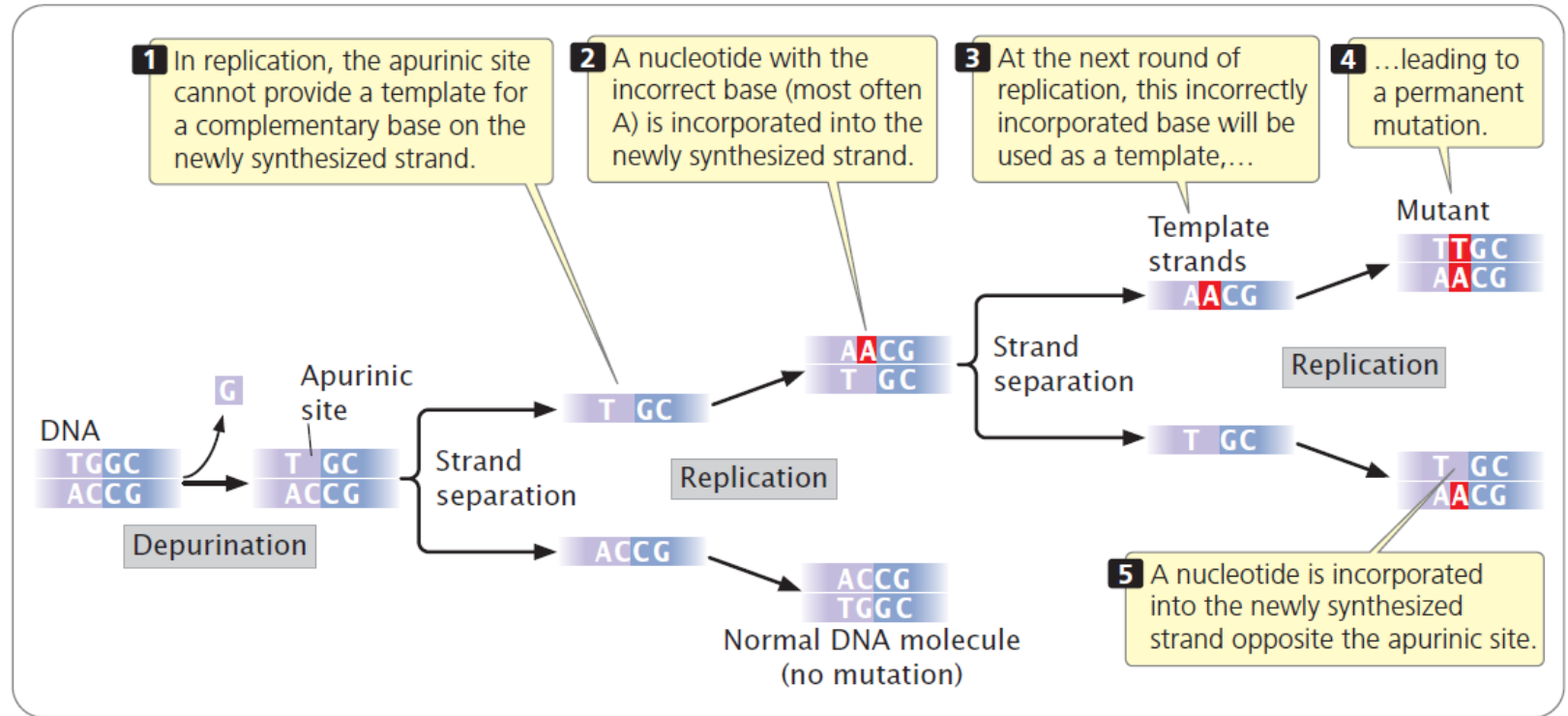If 10^6 stem cells in intestinal tissue generate transient daughter cells once a week with a mutation rate of approximately 10^{-9} per nucleotide per cell division, the intestinal epithelium of a 60-year-old human would have accumulated more than 10^9 independent mutations. Thus, **nearly every genomic site is likely to be mutated in at least one cell in this organ** (Lynch, 2010a, 2010b).

Endogenous DNA damage

Depurination   G:C → A:T
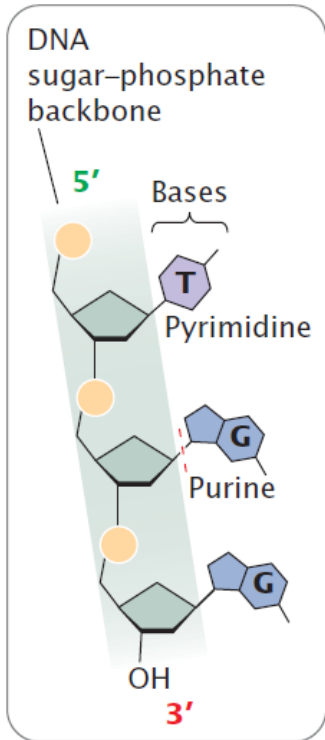
Deamination C:G → U:A → T:A   C:G → 5mC:G → T:G → T:A

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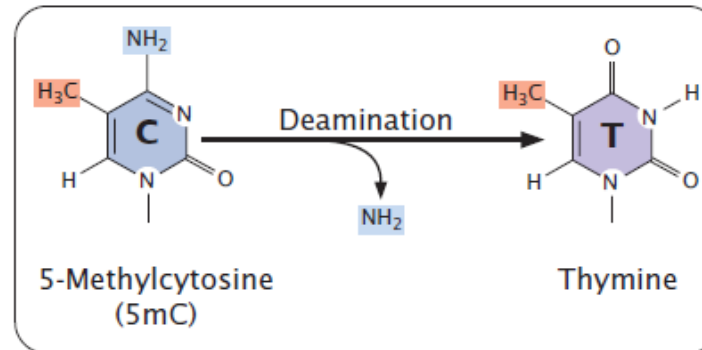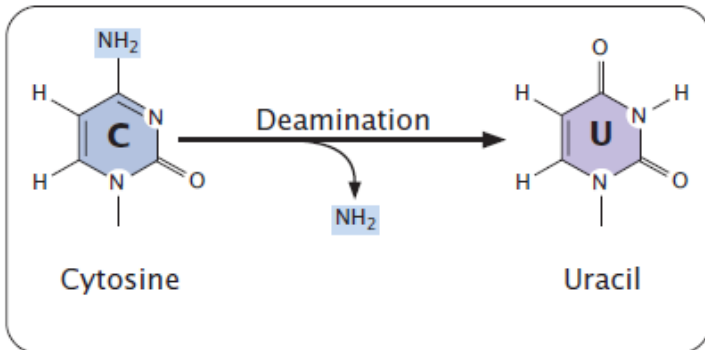
Deamination of 5'-methylcytosine

CpG → TpG

Complementary:
CpG → CpA
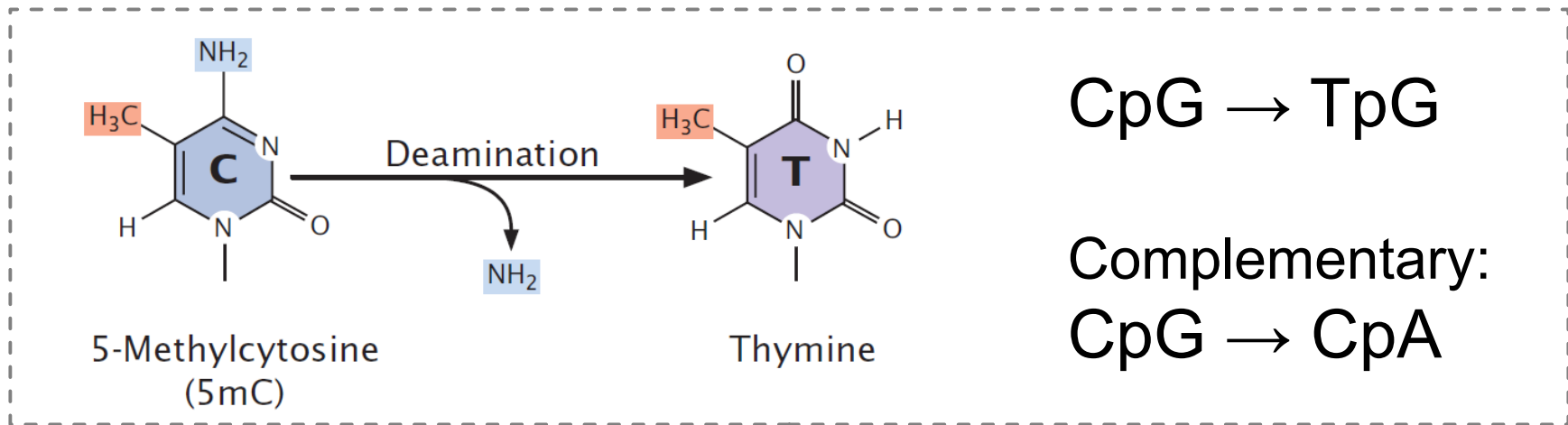
- Cannot be detected by DNA repair system, because it produces a normal base
- Most mutations occur in male germ cells (M/F = 7:1), because of heavy methylation of sperm DNA and high number of cell divisions
- Example: 46% of point mutations in coagulation factor VIII (*F8*) in unrelated hemophilia A patients
- 23% of all mutations in Human Gene Mutation Database (1998)

Exogenous DNA damage

Chemical mutagens

- **Base analogs**: 5-bromouracil, 2-aminopurine
- **Alkylating agents**: methyl ($-CH_3$) and ethyl ($-CH_3-CH_2$) groups added to nucleotide bases
- **Deamination**: nitrous acid deaminates cytosine, creating uracil
- **Hydroxylamine**: adds a hydroxyl group ($-OH$) to cytosine
- **Intercalating agents**: proflavin, acridine orange, ethidium bromide, dioxin

Radiation

- **Ionizing:** $\sim10^{-5} - 1$ nm
- **Ultra-violet:** $\sim1 - 380$ nm

Pierce -- *Genetics Essentials. Concepts and Connections*
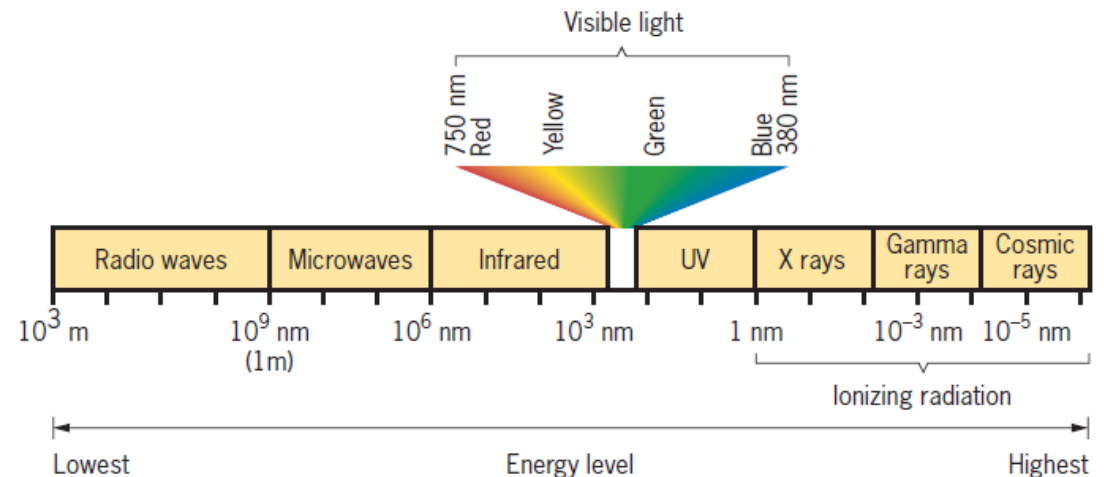
Exogenous DNA damage

Chemical mutagens: 5-bromouracil

(a)

Normal base — Thymine

Base analog — 5-Bromouracil

(b)

Normal pairing

5-Bromouracil ... Adenine

Mispairing

5-Bromouracil (ionized) ... Guanine

1 In replication, 5-bromouracil may become incorporated into DNA in place of thymine, producing an incorporated error.

3 In the next replication, this guanine nucleotide pairs with cytosine, leading to a permanent mutation.

2 5-Bromouracil may mispair with guanine in the next round of replication.

4 If 5-bromouracil pairs with adenine, no replicated error occurs.

Conclusion: Incorporation of bromouracil followed by mispairing leads to a TA ⟶ CG transition mutation.

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Chemical mutagens

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

Pierce -- *Genetics Essentials. Concepts and Connections*

Exogenous DNA damage
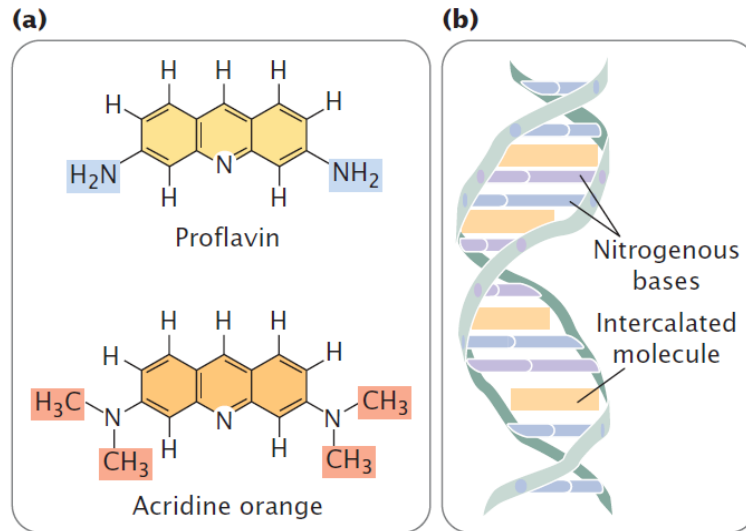
13.20 Intercalating agents such as proflavin and acridine orange insert themselves between adjacent bases in DNA, distorting the three-dimensional structure of the helix and causing single-nucleotide insertions and deletions in replication.
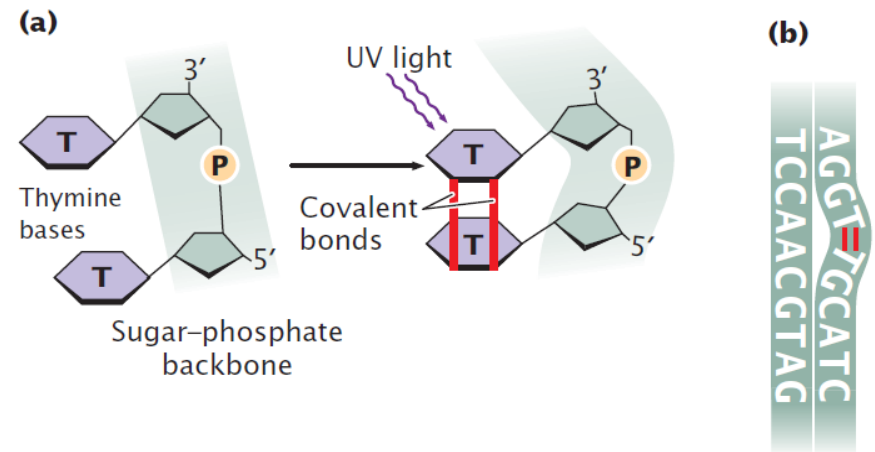
13.21 Pyrimidine dimers result from ultraviolet light. (a) Formation of thymine dimer. (b) Distorted DNA.

Intercalating agents: distorted DNA ⟹ insertions and deletions

Ionizing radiation:
- Free radicals, reactive ions ⟹ altered bases
- Double-strand breaks

UV light: Pyrimidune dimers (TpT, CpC, CpT) ⟹ distorted DNA ⟹ replication blocked ⟹ apoptosis or continued error-prone replication

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Depurination: about 5000 adenine or guanine bases are lost every day from each nucleated human cell by spontaneous hydrolysis of the base-sugar link

Deamination: at least 100 cytosines each day in each nucleated human cell are spontaneously deaminated to produce uracil.

Attack by reactive oxygen species: highly reactive superoxide anions and related molecules are generated as a by-product of oxidative metabolism in mitochondria. They can also be produced by the impact of ionizing radiation on cellular constituents. These reactive oxygen species attack purine and pyrimidine rings.

Nonenzymatic methylation: accidental nonenzymatic DNA methylation by S-adenosyl methionine produces about 300 molecules per cell per day of the cytotoxic base 3-methyl adenine, plus a quantity of the less harmful 7-methyl guanine.

Strachan, Read. *Human Molecular Genetics*, Chapter 13

Exogenous DNA damage

Ionizing radiation: gamma- and X-rays can cause single-strand or double-strand breaks in the sugar-phosphate backbone.

Ultraviolet radiation: UV-C rays (with a wavelength of about 260 nm) are especially damaging, but the major source of UV damage in humans is from the UV-B rays (260-315 nm) in sunlight that can penetrate the ozone layer. UV radiation causes cross-linking between adjacent pyrimidines on a DNA strand to form cyclobutane pyrimidine dimers and other abnormal photoproducts.

Environmental chemicals: these include hydrocarbons (for example, in cigaretre smoke), some plant and microbial products such as the aflatoxins found on moldy peanuts, and chemicals used in cancer chemotherapy. Alkylating agents can transfer a methyl or other alkyl group onto DNA bases and can cause cross-linking between bases within a strand or between different DNA strands.

Strachan, Read. *Human Molecular Genetics*, Chapter 13

Sources of point mutations

Seplyarskiy and Sunyaev (2021) *Nat Rev Genet*
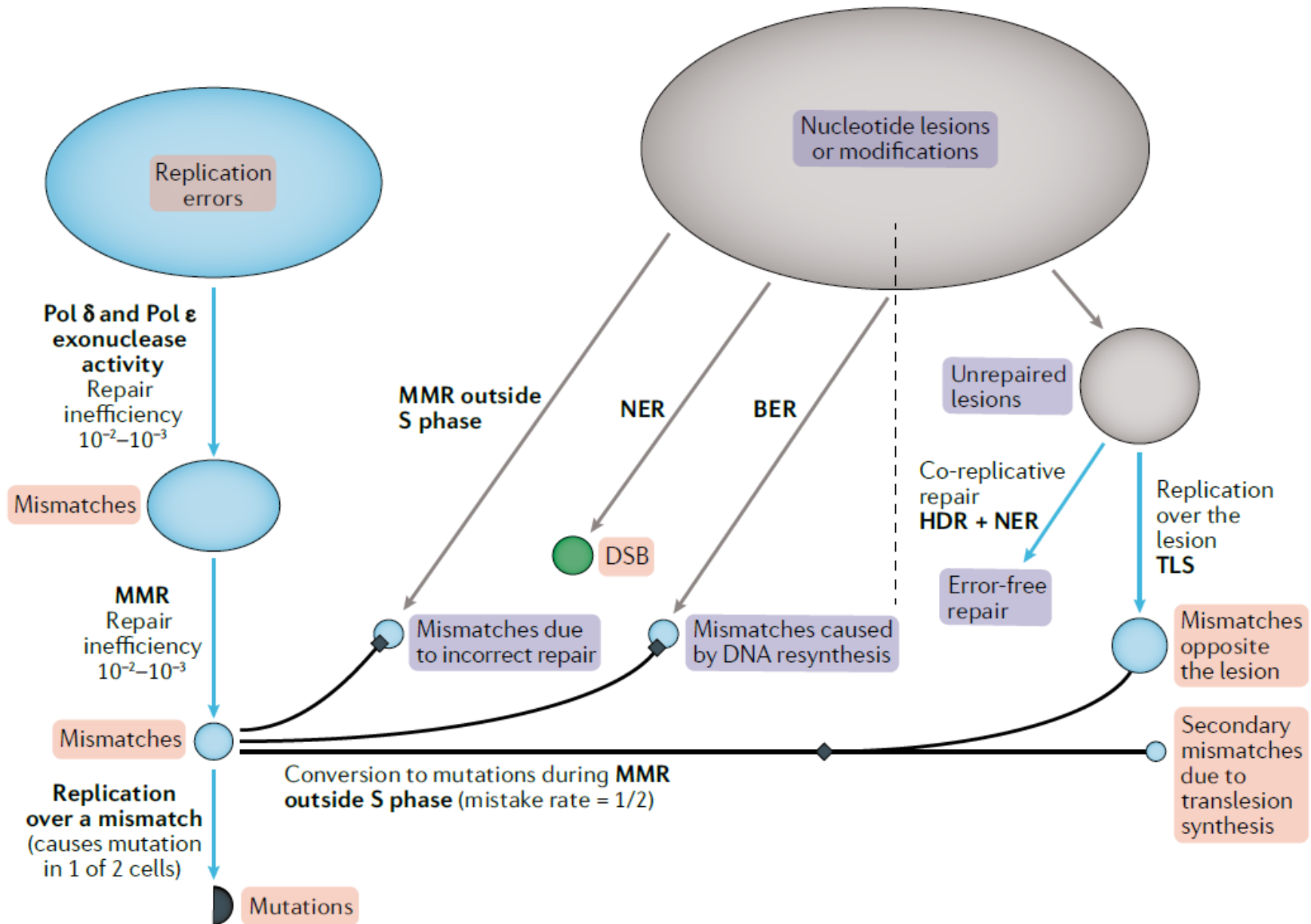
REVIEWS

The origin of human mutation in light of genomic data

Vladimir B. Seplyarskiy[1,2] _and Shamil Sunyaev_[1,2] ✉

Abstract | Despite years of active research into the role of DNA repair and replication in mutagenesis, surprisingly little is known about the origin of spontaneous human mutation in the germ line. With the advent of high-throughput sequencing, genome-scale data have revealed statistical properties of mutagenesis in humans. These properties include variation of the mutation rate and spectrum along the genome at different scales in relation to epigenomic features and dependency on parental age. Moreover, mutations originated in mothers are less frequent than mutations originated in fathers and have a distinct genomic distribution. Statistical analyses that interpret these patterns in the context of known biochemistry can provide mechanistic models of mutagenesis in humans.

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DNA repair mechanisms

One strand affected:

- **Mismatch repair (MMR)** during replication
- **Direct reversal**
- **Base excision repair (BER)** before replication
- **Nucleotide excision repair (NER)** before replication

Both strands affected:

- **Non-homologous end joining (NHEJ)**: ionizing radiation; errors at the replication fork; strong oxidizing agents; metabolites produced in the cell
- **Homologous recombination (HR)**: when a double-strand break occurs shortly after a stretch of DNA has been replicated; at that time, the duplicated helices are still in close proximity to one another

DNA mismatch repair mechanism (MMR) (I)

(a)
1. In DNA replication, a mismatched base was added to the new strand.
2. Methylation at GATC sequences allows old and newly synthesized nucleotide strands to be differentiated: a lag in methylation means that, immediately after replication, the old strand will be methylated but the new strand will not.

New DNA

GATC
CTAG

Old (template) DNA

Methyl group

Mismatch-repair complex

(b) Nick — Methyl group
GATC
CTAG

Mismatch-repair complex

3. The mismatch-repair complex brings the mismatched bases close to the methylated GATC sequence, and the new strand is identified.

(c) 5' GATC
CTAG

Methyl group

4. Exonucleases remove nucleotides on the new strand between the GATC sequence and the mismatch.

T
3'

DNA bases

(d) GATC
CTAG

Methyl group

5. DNA polymerase then replaces the nucleotides, correcting the mismatch, and DNA ligase seals the nick in the sugar–phosphate backbone.

T
A

Incorrectly paired bases distort the three-dimensional structure of DNA, and mismatch repair enzymes detect these distortions. A complex of mismatch-repair enzymes **cuts out the distorted section of the newly synthesized strand and fills the gap with new nucleotides**, by using the original DNA strand as a template. The template strand is recognized by the presence of methyl groups on special sequences of the old strand.

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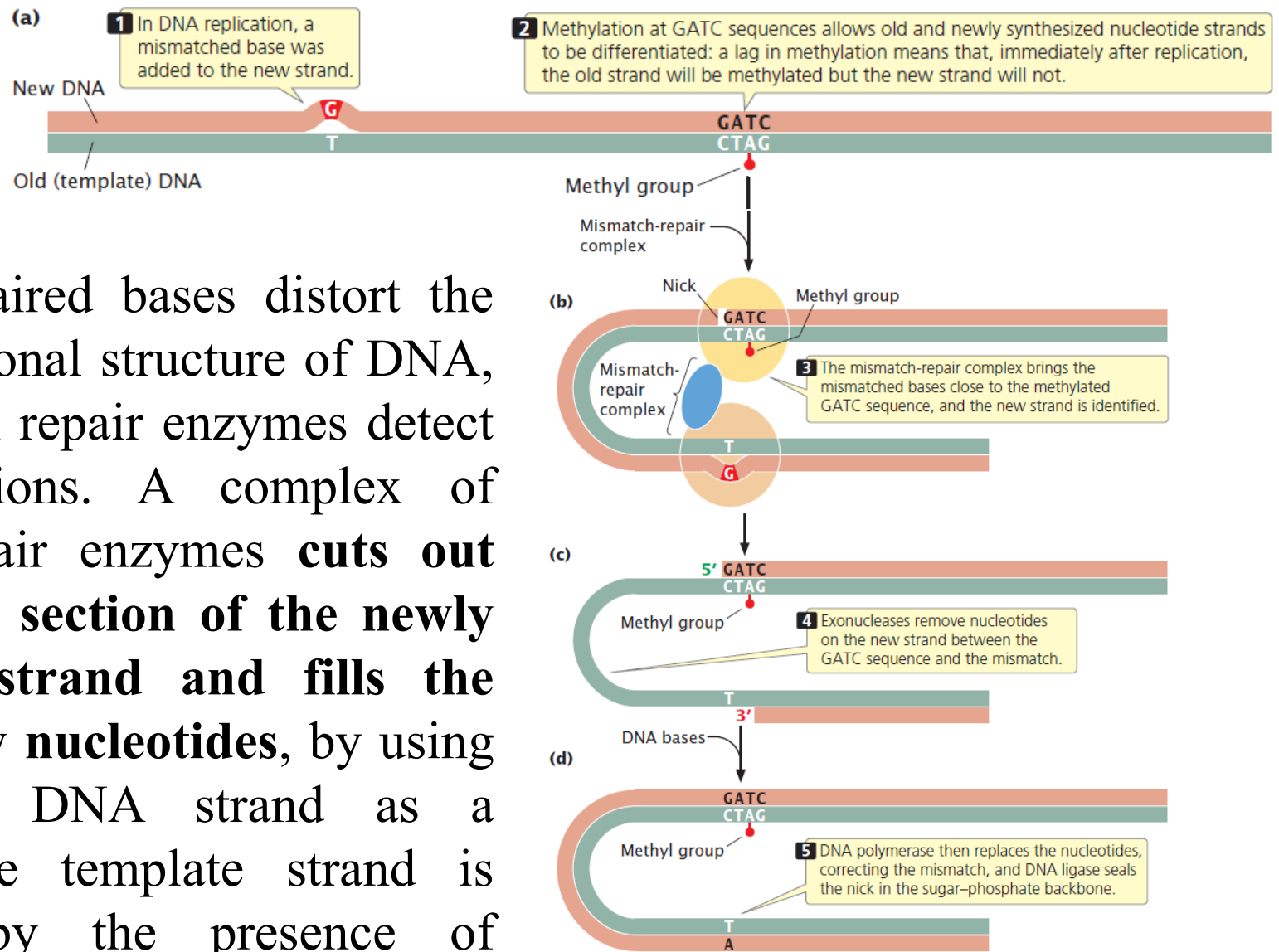
Repair by direct reversal (2)
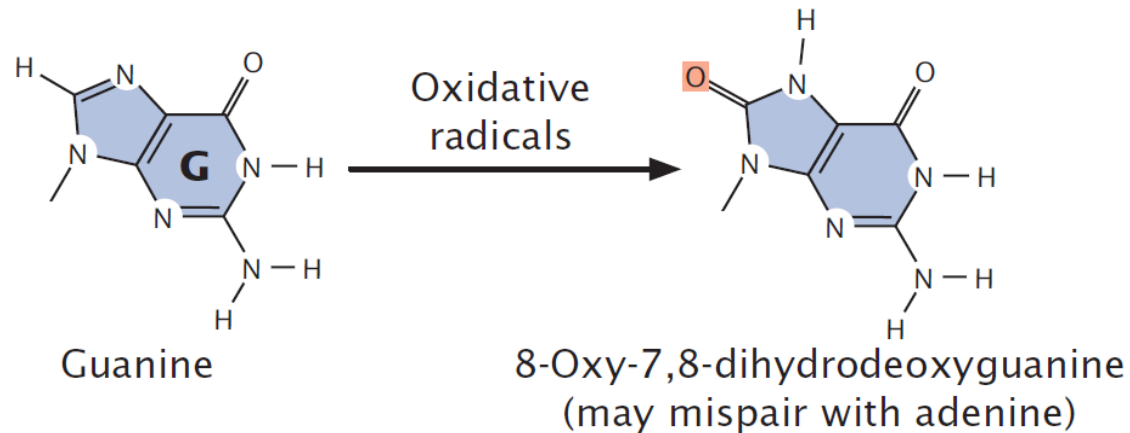
13.28 Direct repair changes nucleotides back into their original structures.

Direct repair does not replace altered nucleotides but, instead, changes them back into their original structures. For example, direct repair corrects O^6-methylguanine, an alkylation product of guanine that pairs with adenine, producing G:C→T:A transversions. An enzyme called O^6-methylguanine-DNA methyltransferase removes the methyl group from O^6-methylguanine, restoring the base to guanine.

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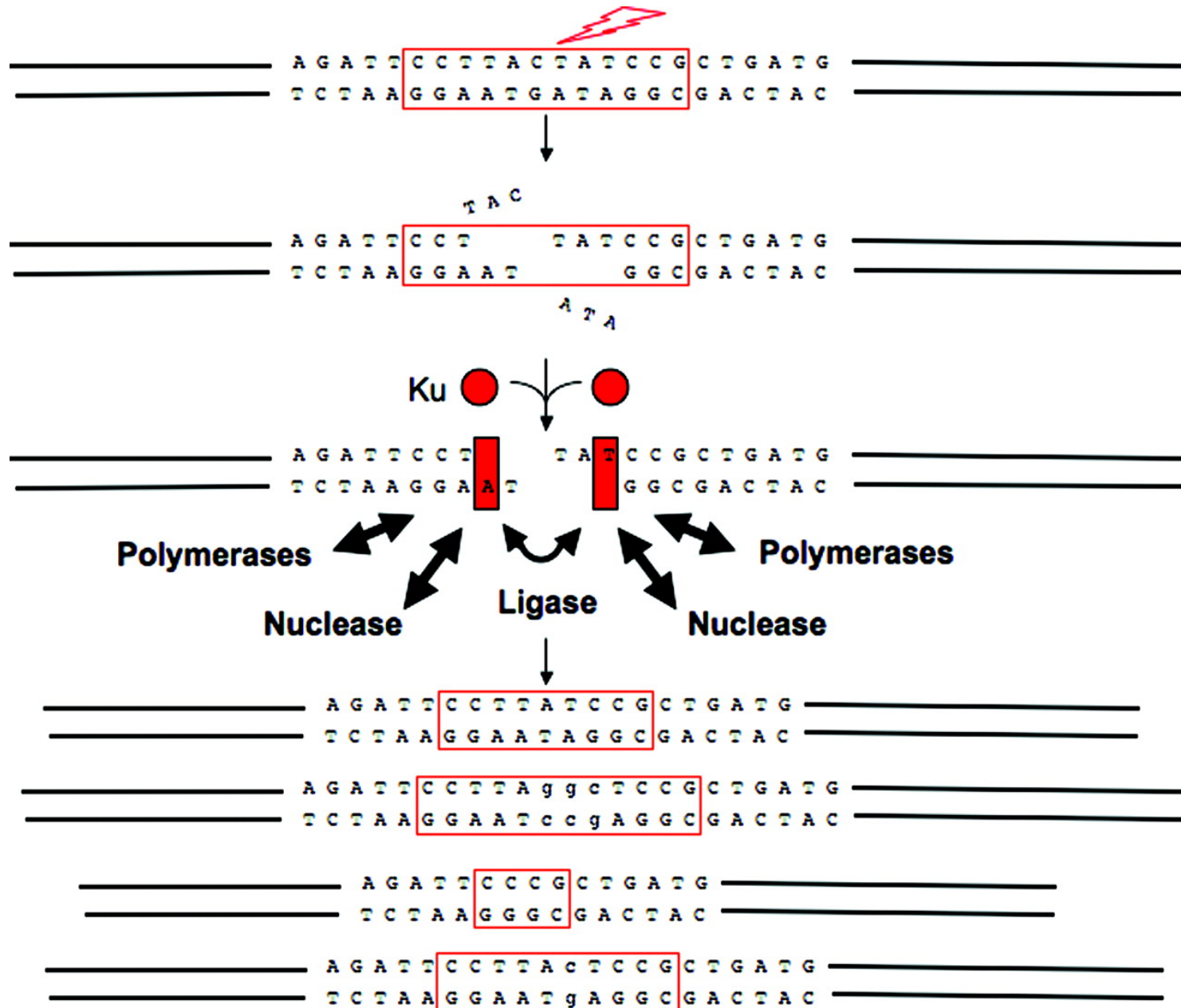# Base and nucleotide excision repair (3, 4)
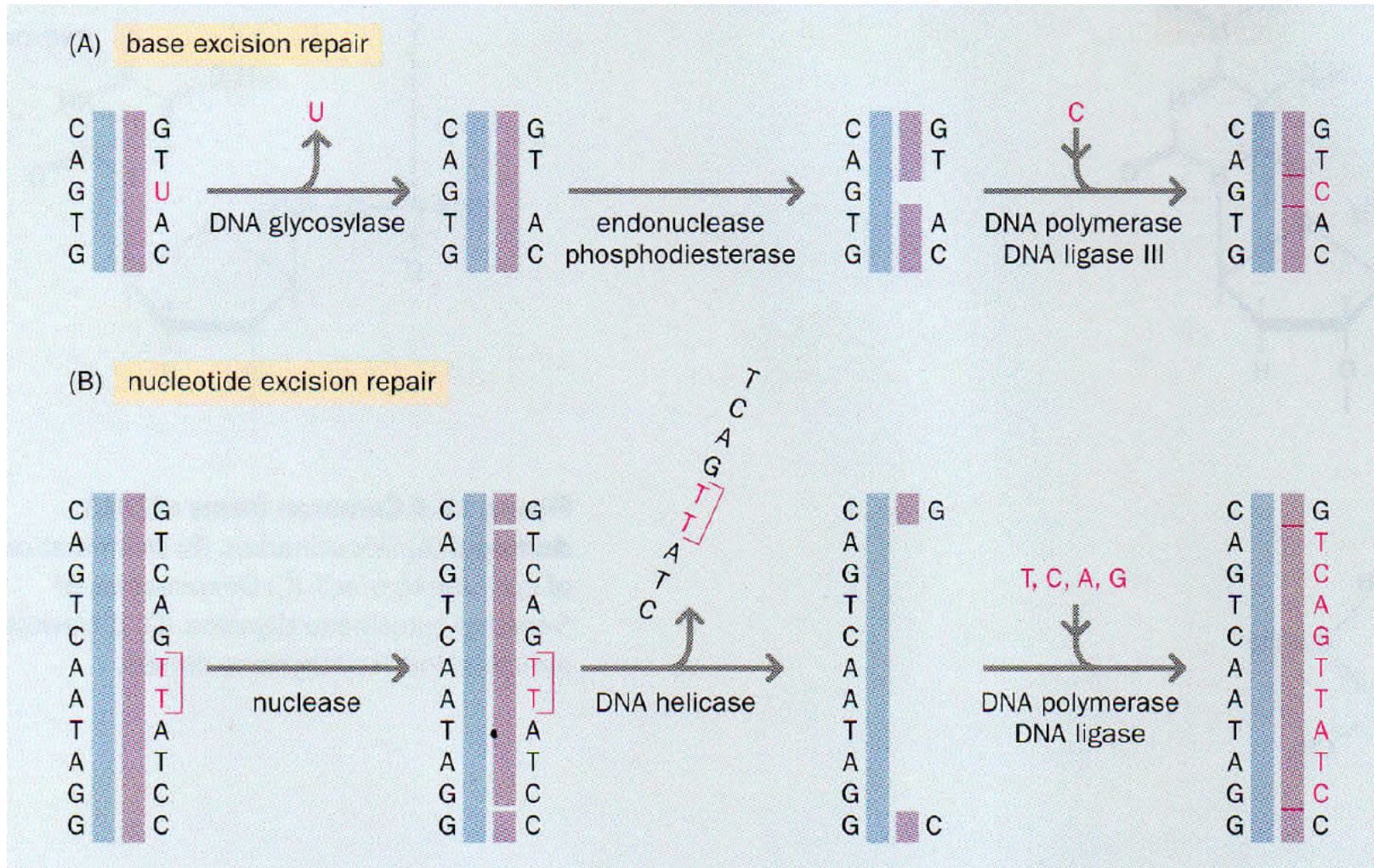
(A) **Base excision repair (BER)** corrects most common DNA damages: ~20,000 bases in each cell per day
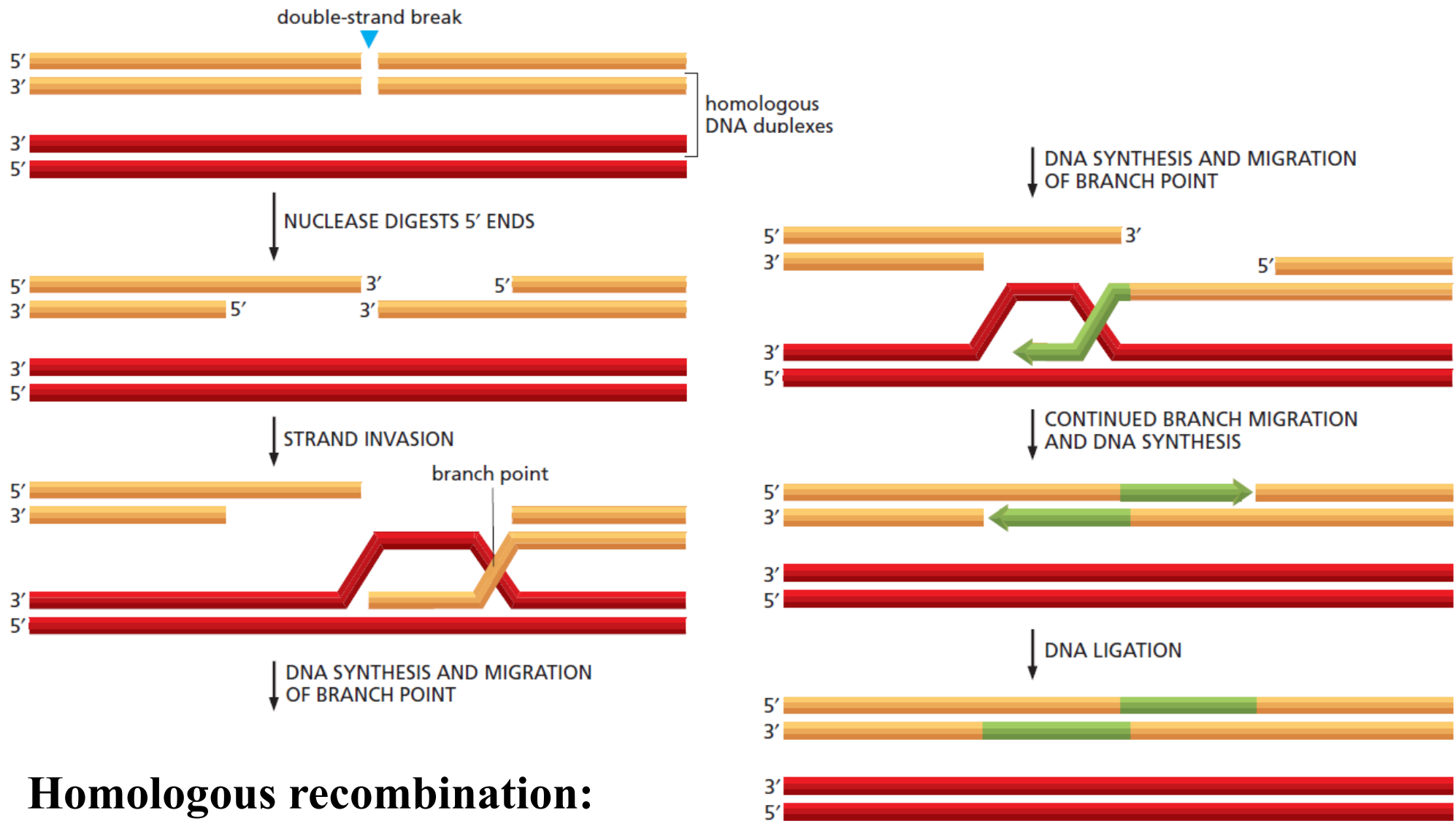
(B) **Nucleotide excision repair (NER)** remove thymide dimers and large chemical alterations

Strachan, Read. *Human Molecular Genetics*

Non-homologous end joining (NHEJ)

Michael R. Lieber (2008) *J. Biol. Chem.*

Repair by homologous recombination (HR)

double-strand break

5′
3′

homologous DNA duplexes

3′
5′

NUCLEASE DIGESTS 5′ ENDS

5′   3′   5′
3′   5′   3′

3′
5′

STRAND INVASION

branch point

5′
3′

3′
5′

DNA SYNTHESIS AND MIGRATION OF BRANCH POINT

DNA SYNTHESIS AND MIGRATION OF BRANCH POINT

5′   3′
3′   5′

3′
5′

CONTINUED BRANCH MIGRATION AND DNA SYNTHESIS

5′
3′

3′
5′

DNA LIGATION

5′
3′

3′
5′

NET RESULT: DOUBLE-STRAND BREAK IS ACCURATELY REPAIRED

Homologous recombination: exchange of genetic information between homologous DNA molecules

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Alberts – *Essential Cell Biology*

Genetic diseases associated with defects in DNA-repair systems

Disease	Symptoms	Genetic Defect
Xeroderma pigmentosum	Frecklelike spots on skin, sensitivity to sunlight, predisposition to skin cancer	Defects in nucleotide-excision repair
Cockayne syndrome	Dwarfism, sensitivity to sunlight, premature aging, deafness, mental retardation	Defects in nucleotide-excision repair
Trichothiodystrophy	Brittle hair, skin abnormalities, short stature, immature sexual development, characteristic facial features	Defects in nucleotide-excision repair
Hereditary nonpolyposis colon cancer	Predisposition to colon cancer	Defects in mismatch repair
Fanconi anemia	Increased skin pigmentation, abnormalities of skeleton, heart, and kidneys, predisposition to leukemia	Possibly defects in the repair of interstrand cross-links
Ataxia telangiectasia	Defective muscle coordination, dilation of blood vessels in skin and eyes, immune deficiencies, sensitivity to ionizing radiation, predisposition to cancer	Defects in DNA-damage detection and response
Li–Fraumeni syndrome	Predisposition to cancer in many different tissues	Defects in DNA-damage response

Exercise: find related genes in OMIM database

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Genetic diseases associated with defects in DNA-repair systems

Location	Phenotype	Phenotype MIM number	Inheritance	Phenotype mapping key	Gene/Locus	Gene/Locus MIM number
17p13.1	Li-Fraumeni syndrome	151623	AD	3	TP53	191170

- **Li–Fraumeni syndrome** is a rare, autosomal dominant, hereditary disorder that predisposes carriers to cancer development.

- The risk of developing any invasive cancer (excluding skin cancer) is about 50% by age 30 (1% in the general population) and is 90% by age 70.

- The syndrome is linked to germline mutations of the *TP53 tumor suppressor gene*, which encodes a transcription factor P53 that normally assists in the control of cell division and growth. TP53 typically becomes expressed due to cellular stressors, such as DNA damage, and can halt the cell cycle to assist with either the repair of repairable DNA damage, or can induce apoptosis of a cell with irreparable damage.

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Genetic diseases associated with defects in DNA-repair systems

Xeroderma pigmentosum, a rare autosomal recessive condition that includes **abnormal skin pigmentation and acute sensitivity to sunlight**. Persons who have this disease also have a **strong predisposition to skin cancer**, with an incidence ranging from 1000 to 2000 times that found in unaffected people.

The cells of most people with xeroderma pigmentosum are defective in nucleotide excision repair, and many of their pyrimidine dimers (UV from sunlight) remain uncorrected and may lead to cancer.

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