Human Genetic Variations and Mutations
人类基因变异和突变

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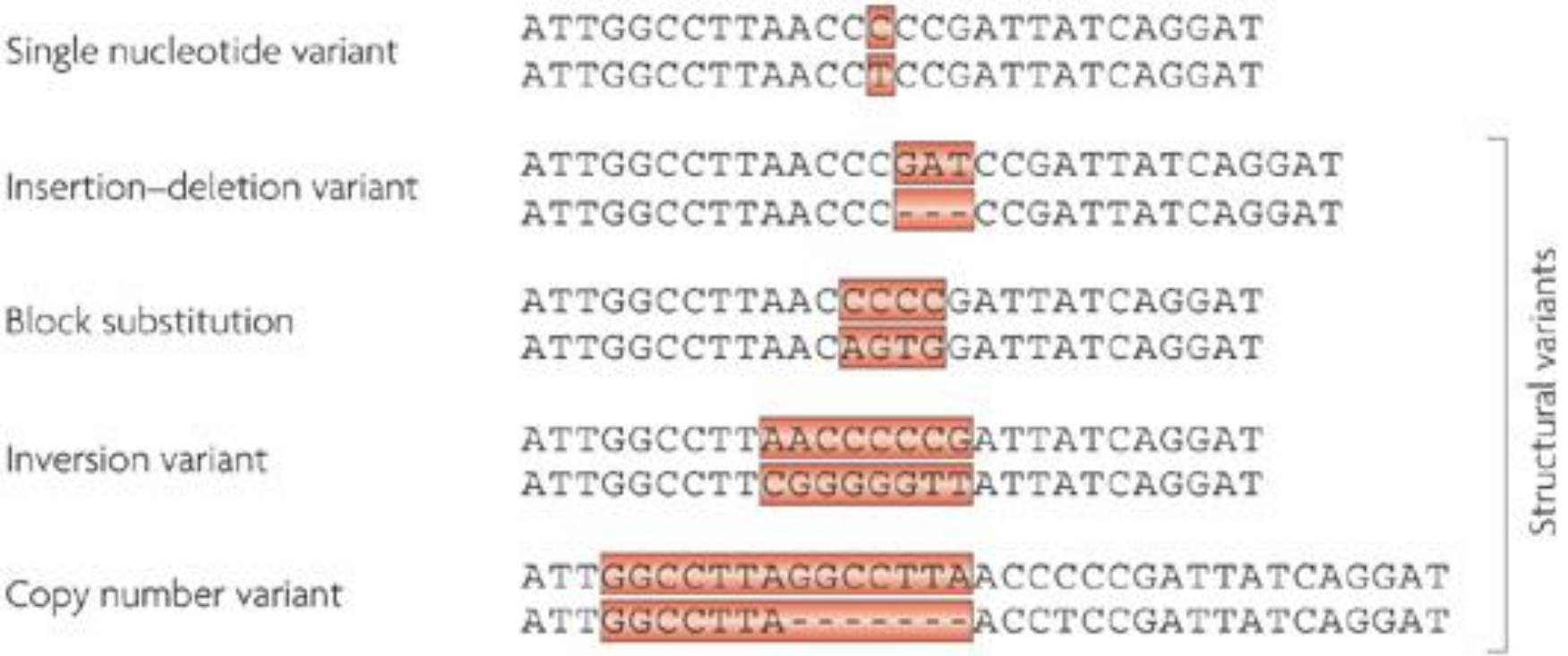
Classes of Human Genetic Variants



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Classes of Human Genetic Variants

- **Single nucleotide variants (SNV)**: DNA sequence variations in which a single nucleotide (A, T, G or C) is altered.
- **Structural variants:** all base pairs that differ between individuals and that are not single nucleotide variants.
- **Insertion–deletion variants (indels)**: one or more base pairs are present in some genomes but absent in others. A few bases - 80 kb in length.
- **Block substitutions**: a string of adjacent nucleotides varies between two genomes.
- **Inversion variant**: the order of the base pairs is reversed in a defined section of a chromosome.
- **Copy number variants(CNV)**: identical or nearly identical sequences are repeated in some chromosomes but not others.

Types of Genetic Defects

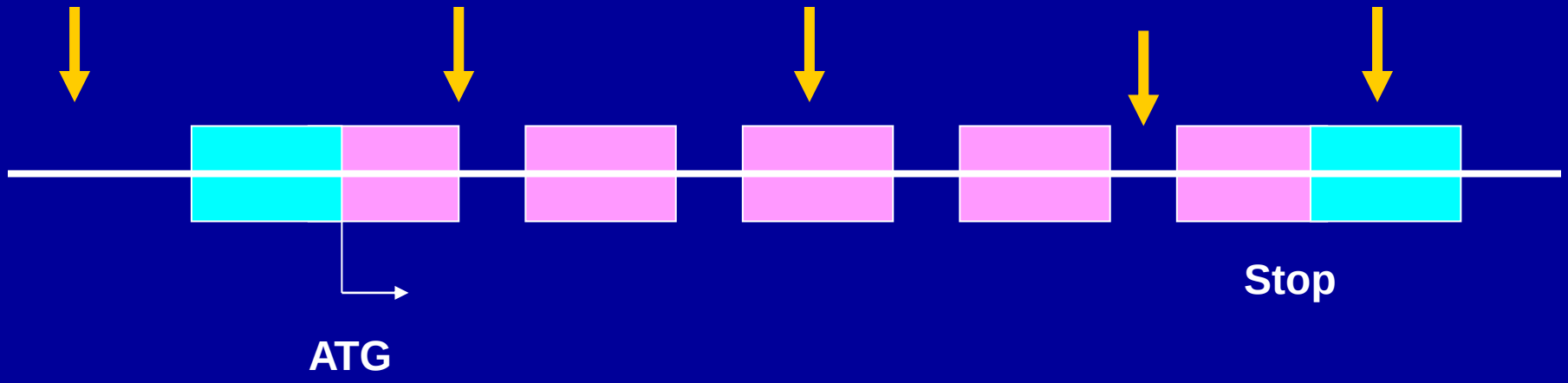
- Somatic cell genetic defects
- Multifactorial genetic defects
- Chromosomal genetic defects
- Mitochondrial genetic defects
- *Monogenic defects*

Monogenic Defects

- Over 4,500 different monogenic disorders
- The majority of them display *simple Mendelian inheritance* pattern

Effect of Disease-Causing Mutations on Function of Gene Product

- Loss of function
- Gain of function
- Acquisition of novel property
- Abnormal expression: heterochronic or ectopic


Stop
ATG

How do we differ? – Let me count the ways

- Single nucleotide polymorphisms
  - 1 every few hundred bp, mutation rate* ≈ 10^{-9}

TGCATTGCGTAGGC
TGCATTCCGTAGGC

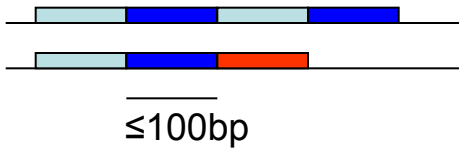
- Short indels (=insertion/deletion)
  - 1 every few kb, mutation rate v. variable

TGCATT---TAGGC
TGCATTCCGTAGGC

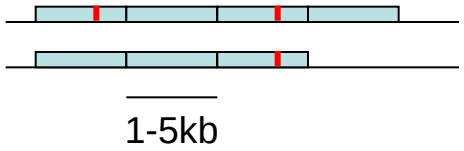
- Microsatellite (STR) repeat number
  - 1 every few kb, mutation rate ≤ 10^{-3}

TGCTCATCATCATCAGC
TGCTCATCA------GC

- Minisatellites
  - 1 every few kb, mutation rate ≤ 10^{-1}



- Repeated genes
  - rRNA, histones



- Large inversions, deletions
  - Rare, e.g. Y chromosome

*per generation

Molecular Genetic Defects

- *Single base substitution*
- Insertion or deletion

Base Pair Substitution

- **Coding Sequence:**
  - Silent mutation
  - Missense mutation
  - Nonsense mutation
- **Non-coding Sequence:**
  - Transcription mutation
  - RNA processing mutation
  - RNA polyadenylation mutation

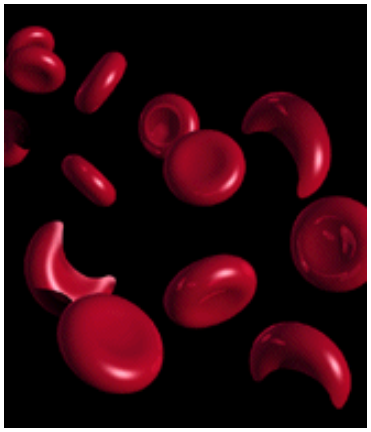
Insertion or Deletion

- Frame-shift mutation
- Codon deletion and insertion
- Partial deletion of structural gene
- Deletion of entire structural gene
- Insertion of repeated elements

Mutations

- Mutations change the sequence of DNA: spontaneous and induced
- Point mutation, deletion, insertion
- Frameshift, truncation, exon skiping
- Hotspots
- Structural change
- Epigenetics

Sickle Cell Anemia



```
HbA    -CCT GAG GAG-
       -Pro Glu Glu-

HbS    -CCT GTG GAG-
       -Pro Val Glu-
```

Instability: Mutation and DNA repair

- Higher mutation rates in males
  - Greater number of cell divisions

Instability: Mutation and DNA repair

- Sex-specific differences in mutation rates

Gene	Mutation	Ratio of male/female mutations
NF1	Point	4.5
VHL	Point	1.3
RB	Point	8.5
ZFX/ZFY	Mutations in last intron	6

Instability: Mutation and DNA repair

- Mechanism of mutation
  - Simple sequence repeats and strand slippage

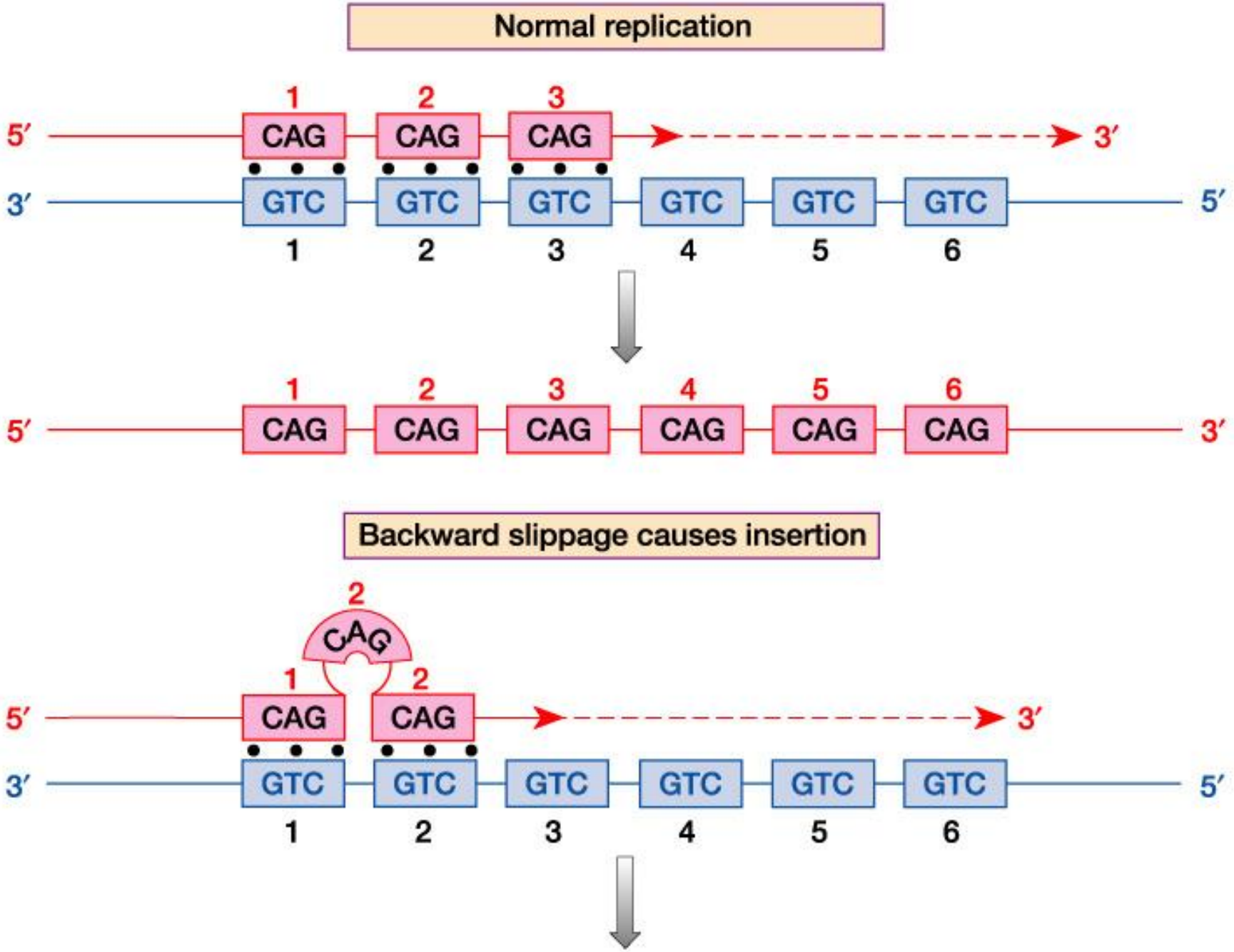


Figure 11-5 part 1 of 2 Human Molecular Genetics, 3/e. (© Garland Science 2004)

Instability: Mutation and DNA repair

- Mechanism of mutation
  - Homologous equal crossover yields fusion genes.

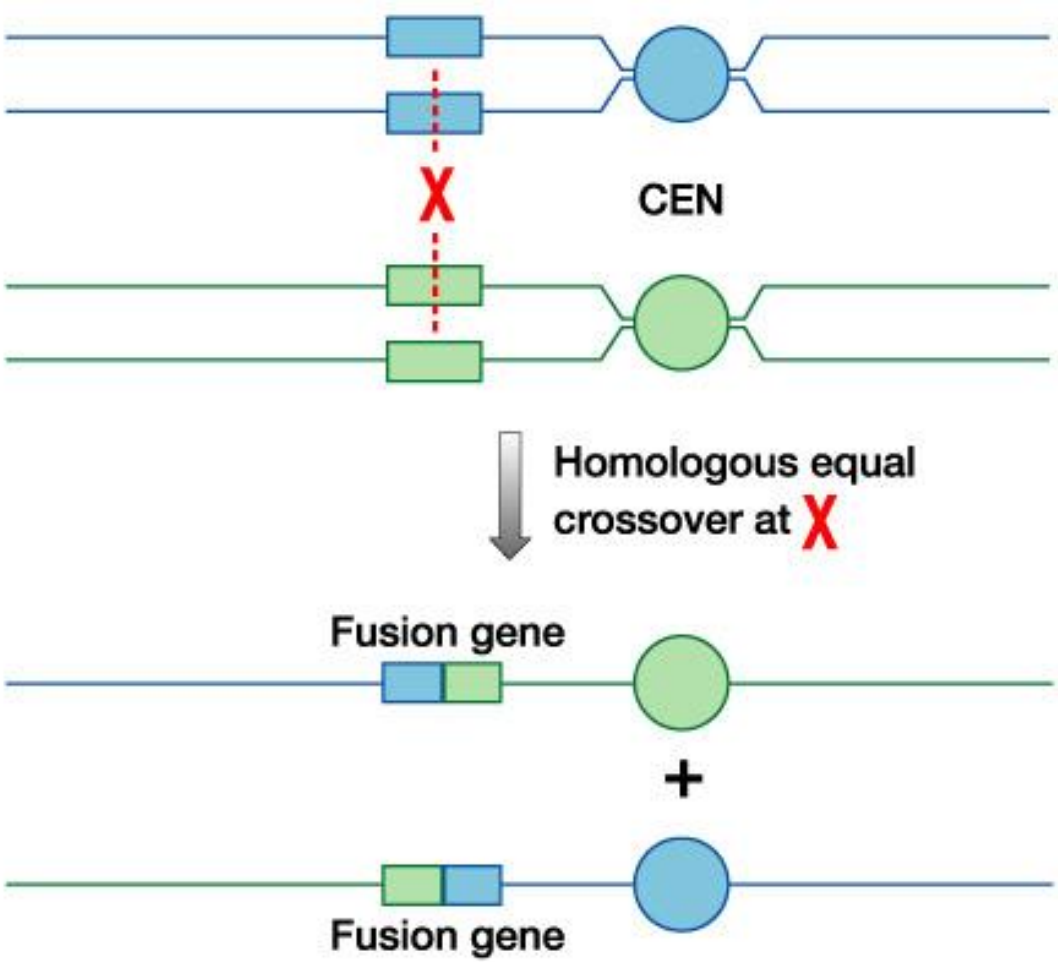


Figure 11-6 Human Molecular Genetics, 3/e. (© Garland Science 2004)

Instability: Mutation and DNA repair

- Mechanism of mutation
  - Unequal crossover causes insertions and deletions.

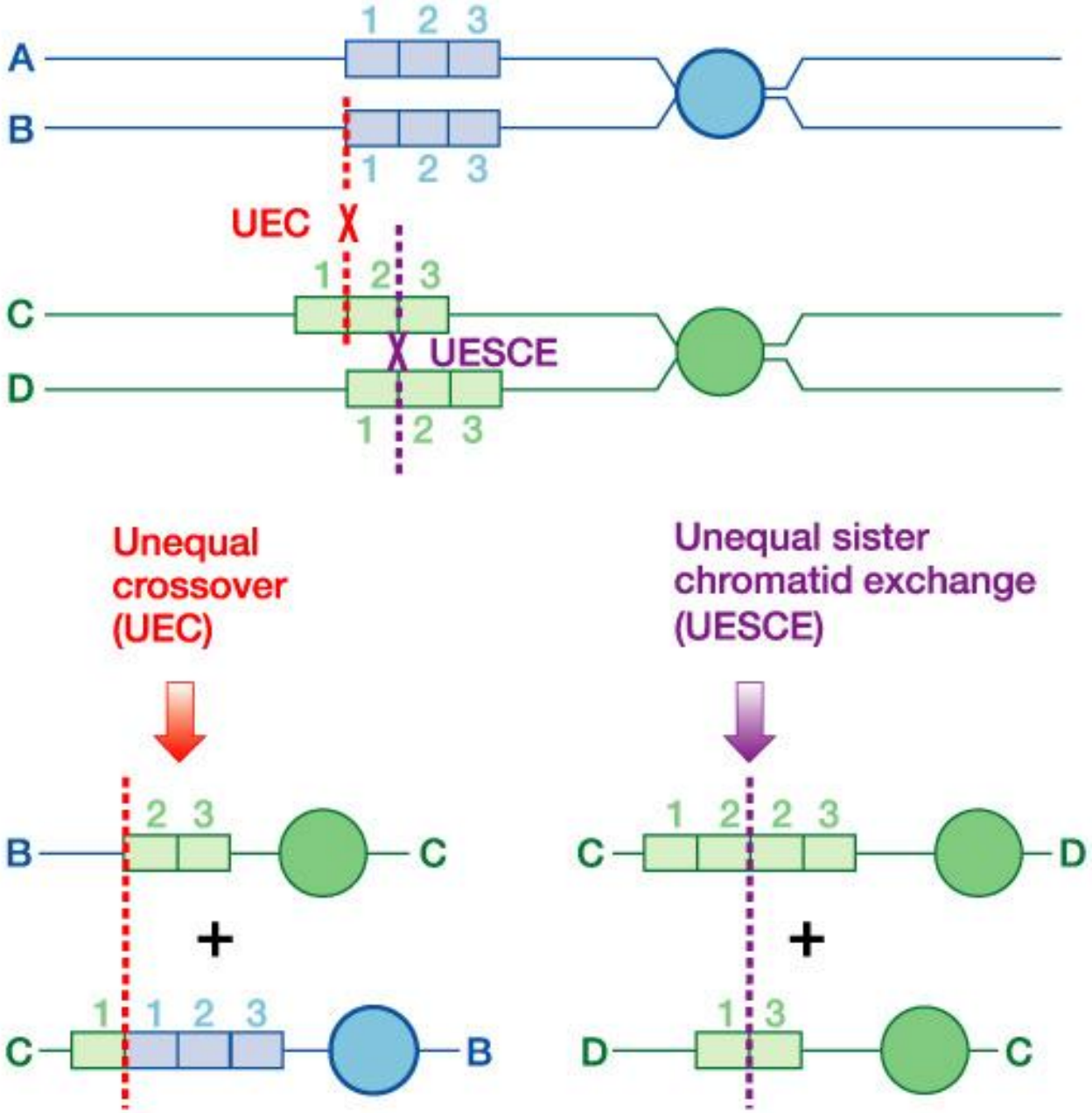


Figure 11-7 Human Molecular Genetics, 3/e. (© Garland Science 2004)

Instability: Mutation and DNA repair

- Mechanism of mutation
  - Splicing mutations
    - Intron retention
    - Exon skipping
    - Activation of cryptic splice sites

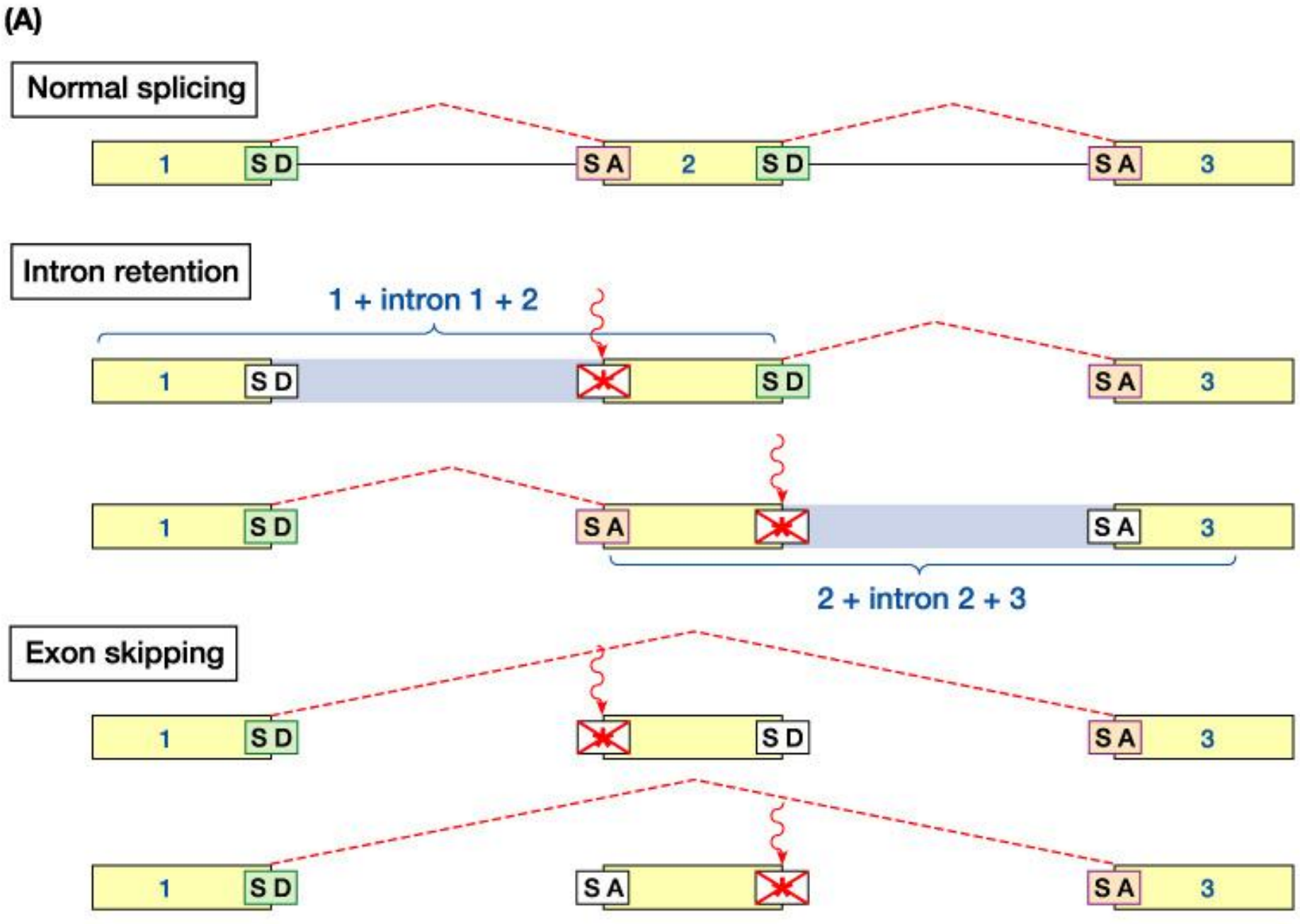


Figure 11-11 part 1 of 2 Human Molecular Genetics, 3/e. (© Garland Science 2004)

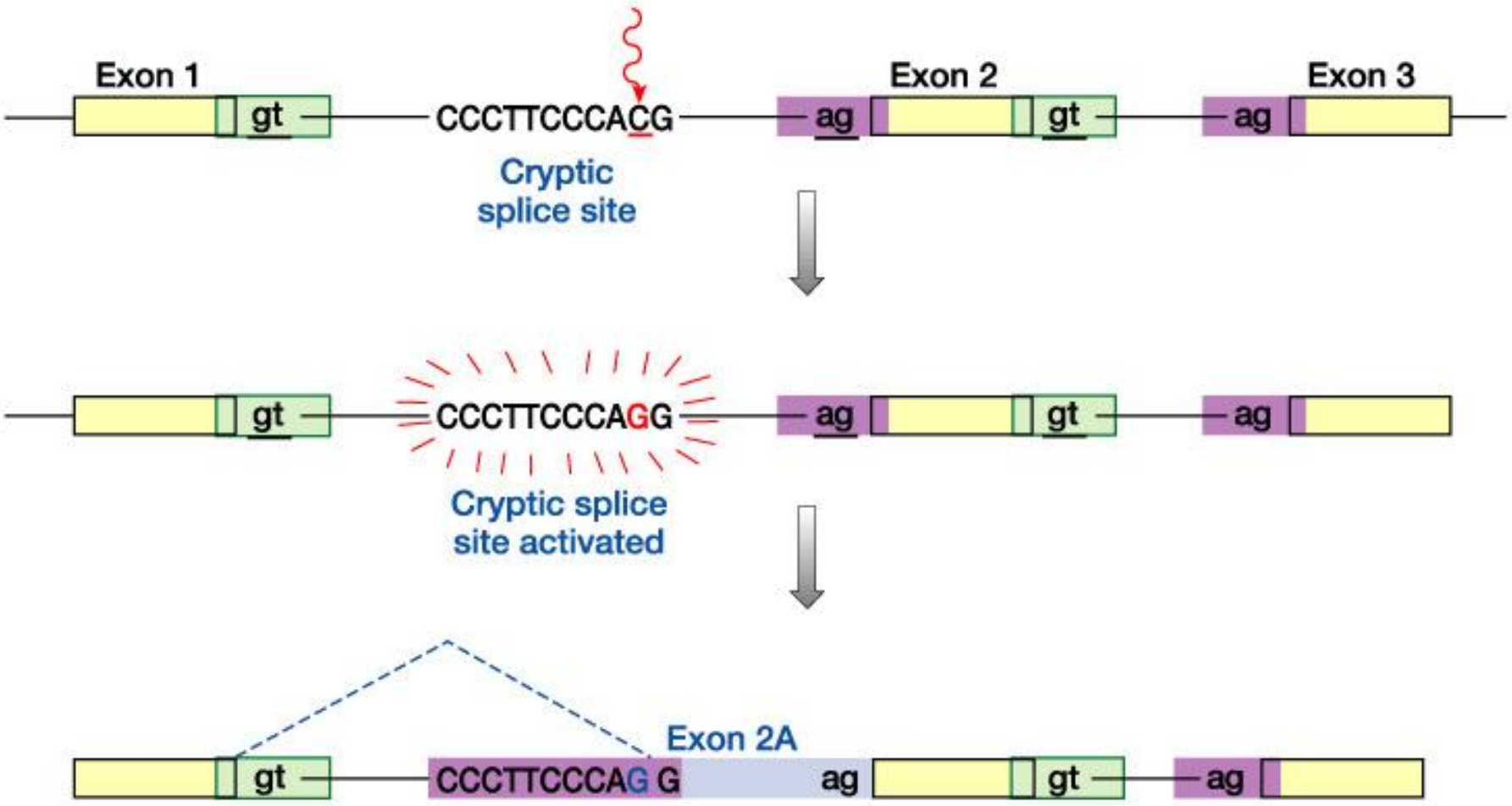


Figure 11-13 Human Molecular Genetics, 3/e. (© Garland Science 2004)

Possible mechanisms of disease-causing mutations