Medical genetics Introduction

Basic principles

Jan 29th 2020.

Chromosomal basis and inheritance

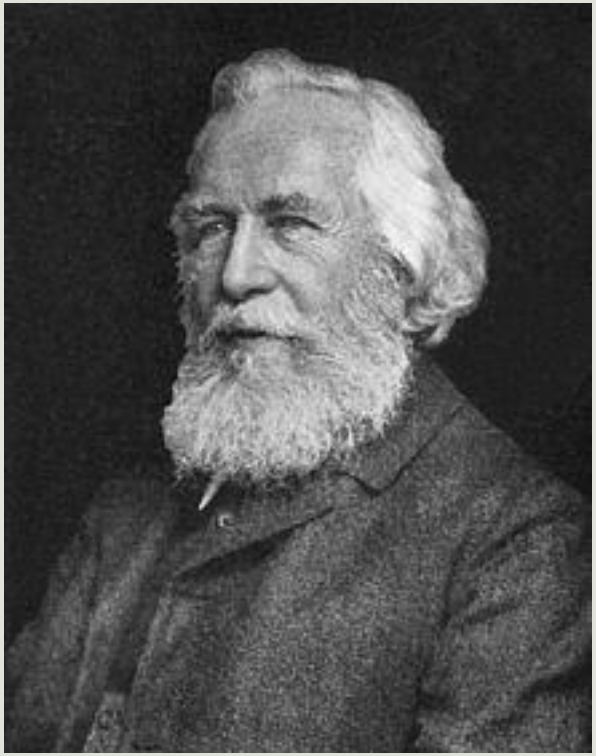
Schleiden & Schwann, (1839.)

Important concept!

cells are the living units (both plants and animals)

Chromosomal basis and inheritance

Haeckel
(1860.)



Sperm is mostly nuclear

So!

Nucleus is responsible for heredity

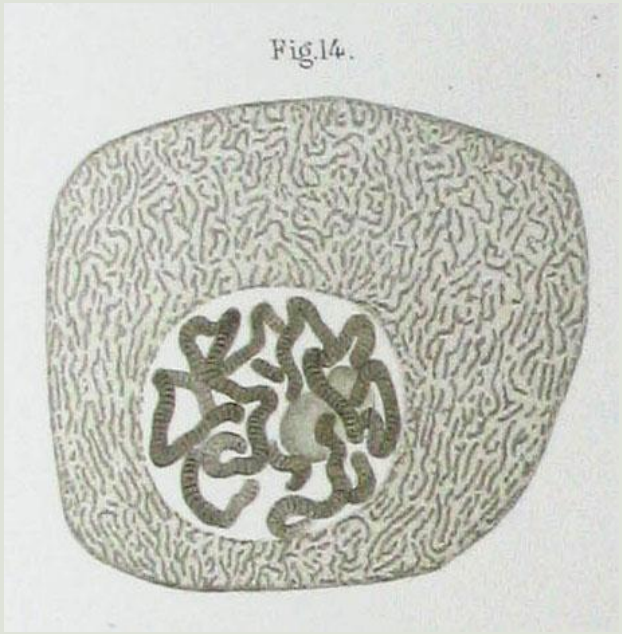
Chromosomal basis and inheritance

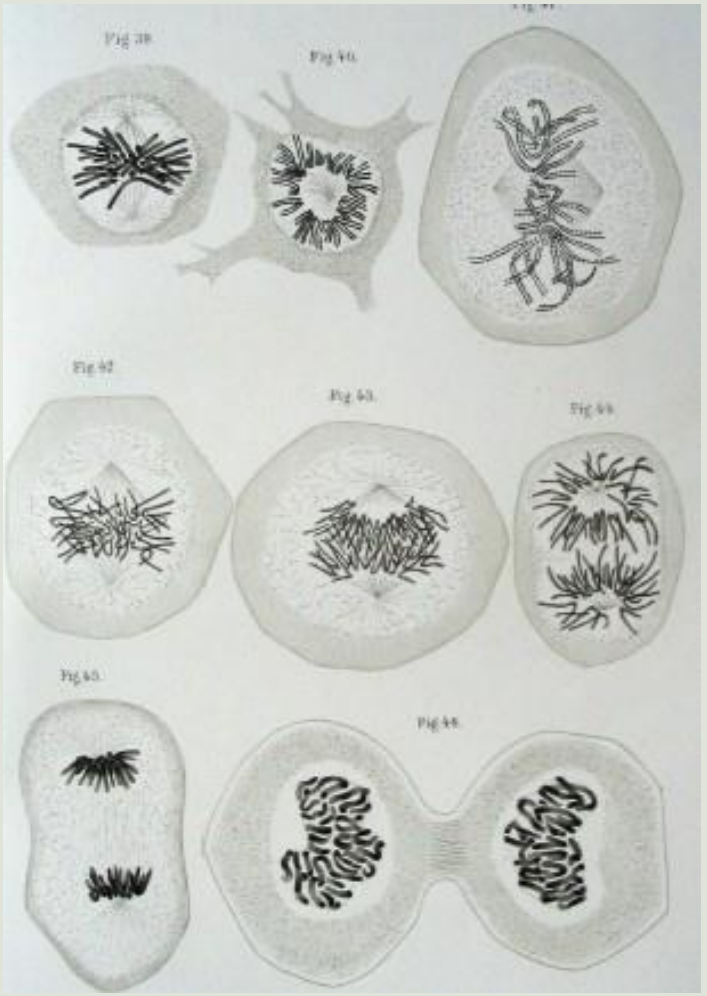
Walther Flemming (1882.)

Observed chromosomes in the cells

Chromosomal basis and inheritance

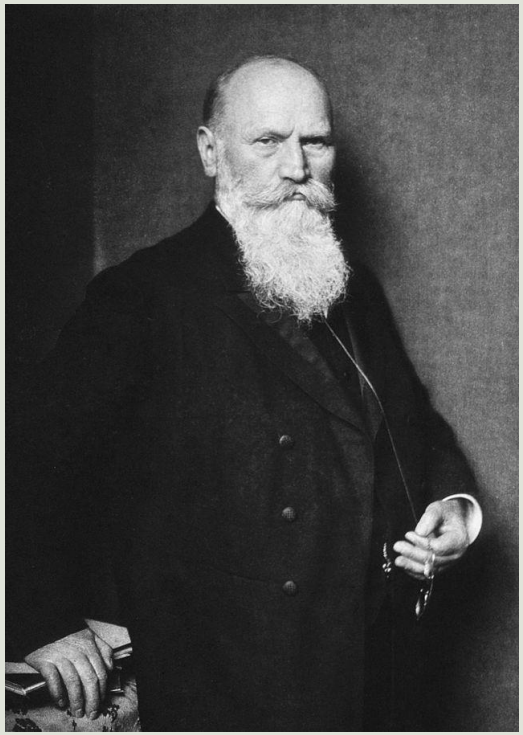
Walther Flemming (1882.)





Chromosomal basis and inheritance

Heinrich von Waldeyer-Hartz, 1888.



Named the chromosomes.

Chromosome discovery

Theodor Boveri i Walter Sutton, ~ 1900.

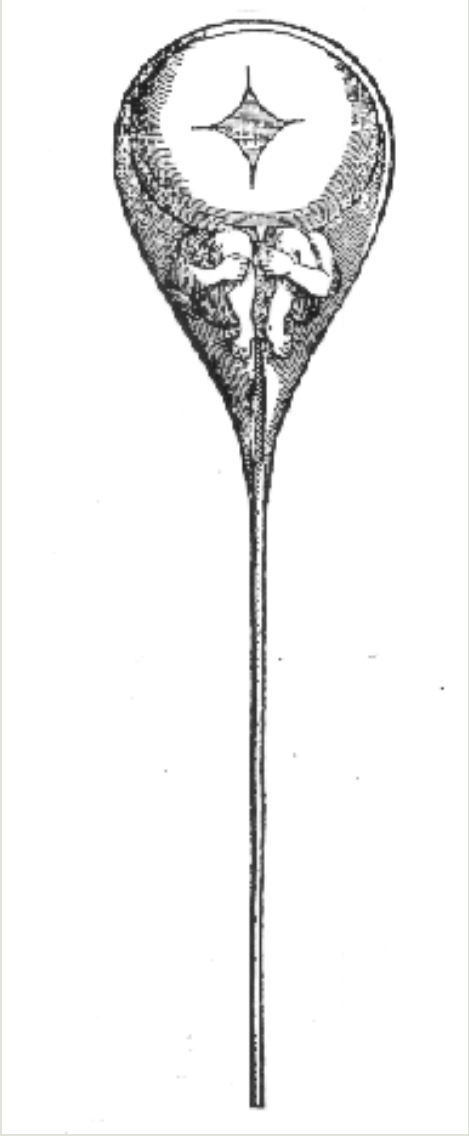
Chromosomes carry genetic material;

Chromosomes carry GENES

What was the view until then?

Homunculus (1694)

Nicolaas Hartsoeker –
Leeuwenhoek' student



All is based on …

Gregor Mendel (1850).

Hereditary elements!

Introduced:

1.homozygous/heterozygous

2.dominative/recessive

Number of chromosomes?

- Until 1956. normal number of human chromosomes in each cell = 48!

  (Theophilus Painter)

- 1956. Tjio i Levan:

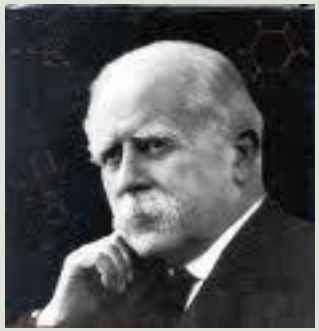
46! is the number of chromosomes in human cells!

What are genes really made of?

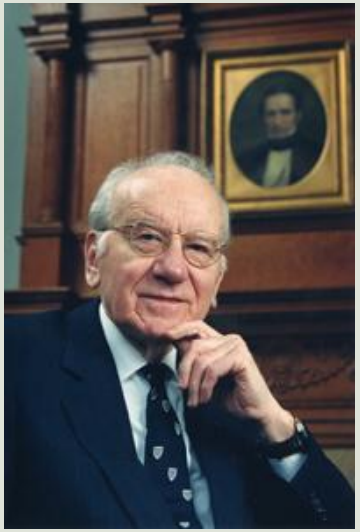
- 1953. Francis Crick & James Watson (NP1962)
- Rosalind Franklin
- Maurice Wilkins (NP1962)

Medical genetics milestones

- William Bateson i Archibald Garrod
  - alkaptonuria



- Terminology:
  - Monogenic vs. polygenic
  - Chromosomal inheritance



- Victor McKusick – Father of med.gen.
  - Catalogue of monogenic disorders

  (1966. 1500; 1998. 8500; 2010. 20000)

  - Online version 1985.

5 YEARS OMIM
Human Genetics Knowledge for the World

OMIM®

Online Mendelian Inheritance in Man®

An Online Catalog of Human Genes and Genetic Disorders

Updated January 23, 2017

Search OMIM for clinical features, phenotypes, genes, and more...

Advanced Search : OMIM, Clinical Synopses, Gene Map

Need help? : Example Searches, OMIM Search Help, OMIM Tutorial

Mirror site : mirror.omim.org

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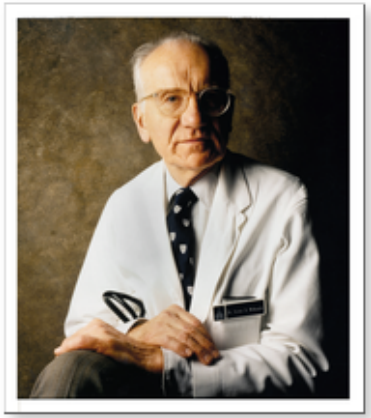


Welcome to OMIM®, Online Mendelian Inheritance in Man®. OMIM is a comprehensive, authoritative compendium of human genes and genetic phenotypes that is freely available and updated daily. The full-text, referenced overviews in OMIM contain information on all known mendelian disorders and over 15,000 genes. OMIM focuses on the relationship between phenotype and genotype. It is updated daily, and the entries contain copious links to other genetics resources.

This database was initiated in the early 1960s by Dr. Victor A. McKusick as a catalog of mendelian traits and disorders, entitled Mendelian Inheritance in Man (MIM). Twelve book editions of MIM were published between 1966 and 1998. The online version, OMIM, was created in 1985 by a collaboration between the National Library of Medicine and the William H. Welch Medical Library at Johns Hopkins. It was made generally available on the internet starting in 1987. In 1995, OMIM was developed for the World Wide Web by NCBI, the National Center for Biotechnology Information.

OMIM is authored and edited at the McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University School of Medicine, under the direction of Dr. Ada Hamosh.

NLM's Profiles in Science -- The McKusick Papers

OMIM Entry Statistics

Number of Entries in OMIM (Updated January 25th, 2019) :

MIM Number Prefix	Autosomal	X Linked	Y Linked	Mitochondrial	Totals
Gene description *	15,212	732	49	35	16,028
Gene and phenotype, combined +	46	0	0	2	48
Phenotype description, molecular basis known #	5,084	329	4	32	5,449
Phenotype description or locus, molecular basis unknown %	1,446	125	4	0	1,575
Other, mainly phenotypes with suspected mendelian basis	1,651	105	3	0	1,759
Totals	23,439	1,291	60	69	24,859

OMIM Entry Statistics

Number of Entries in OMIM (Updated January 27th, 2020) :

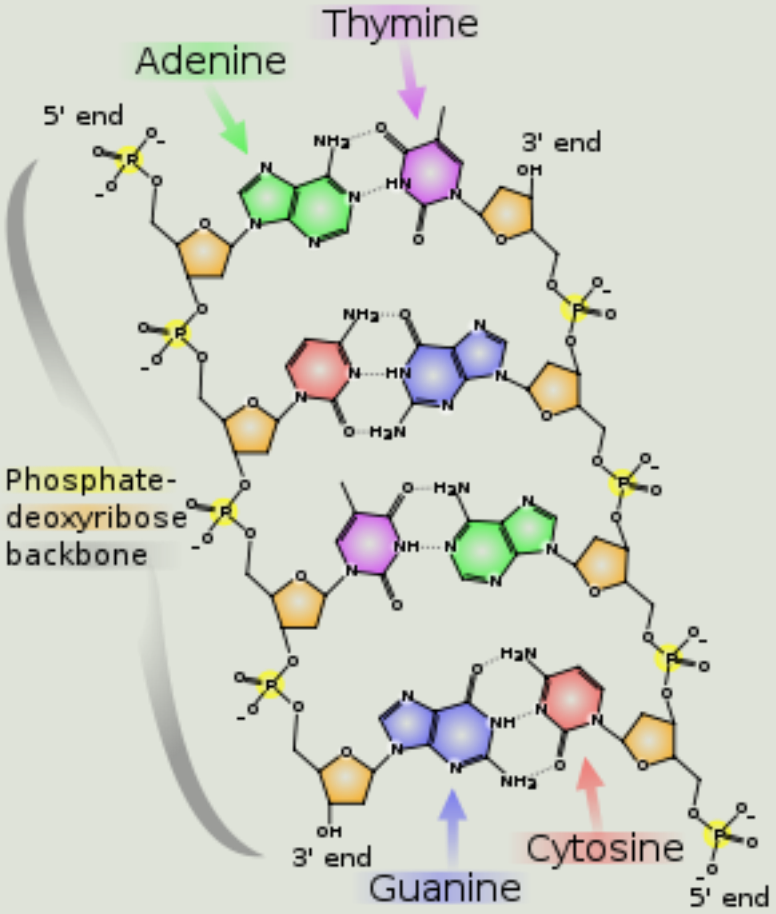
MIM Number Prefix	Autosomal	X Linked	Y Linked	Mitochondrial	Totals
Gene description *	15,433	738	51	37	16,259
Gene and phenotype, combined +	36	0	0	0	36
Phenotype description, molecular basis known #	5,338	343	5	33	5,719
Phenotype description or locus, molecular basis unknown %	1,429	118	4	0	1,551
Other, mainly phenotypes with suspected mendelian basis	1,641	104	3	0	1,748
Totals	23,877	1,303	63	70	25,313

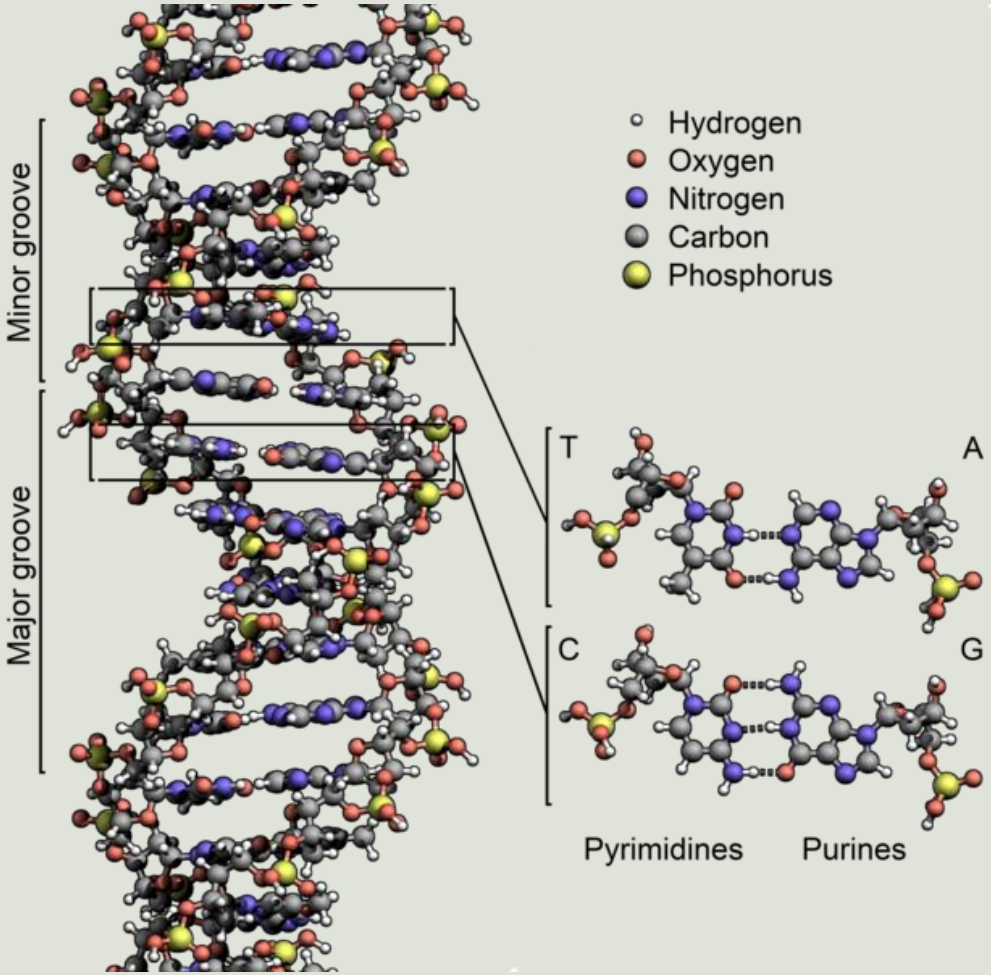
What is medical genetics?

Genetics that focuses on molecular diagnosis of hereditary diseases and disorders

Birth defects, developmental defects, mental disorders, autism, metabolic disorders, mitochondrial diseases, tumor genetics, prenatal diagnostics,…

DNA structure





Total length of human DNA (haploid) 3,28 x10^9 bp = 1m long

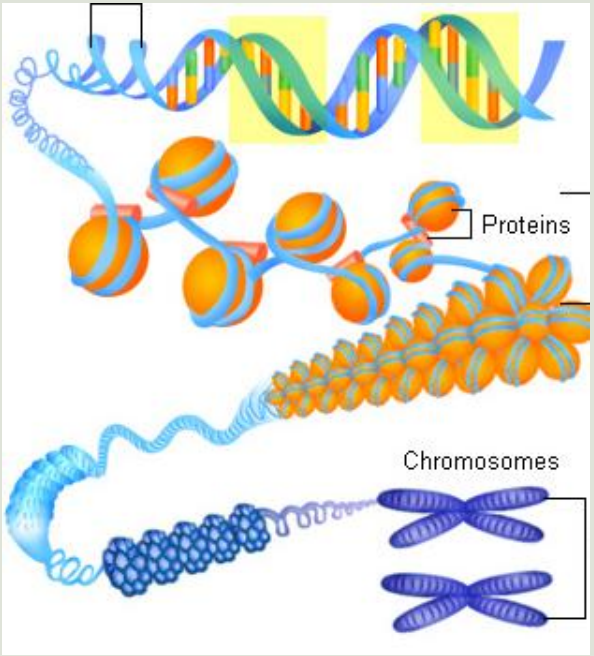
Where is DNA that is inherited?

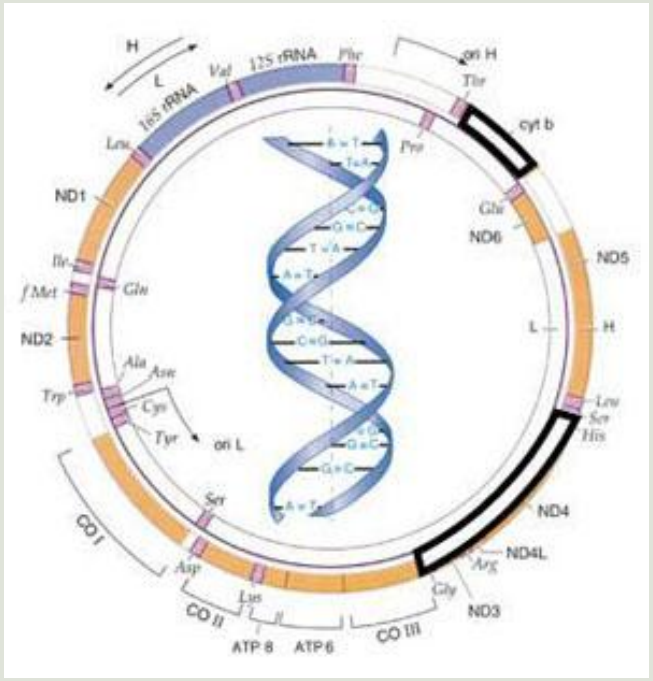
- Nuclear DNA

~20.000 genes

- Mitohondrial DNA – 37 genes

(rRNA, tRNA, cytochrome b, cytochrome oxidase...)





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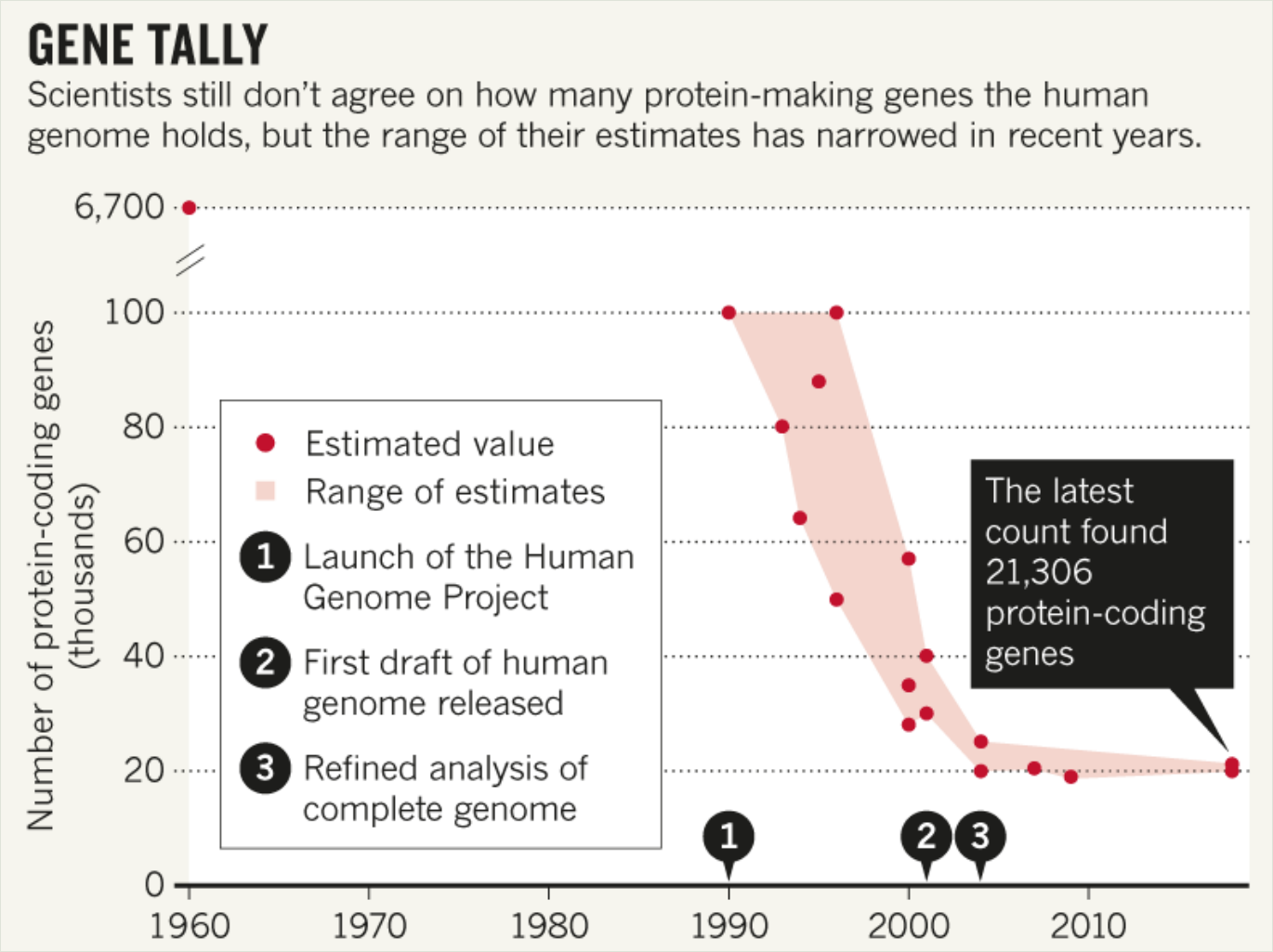

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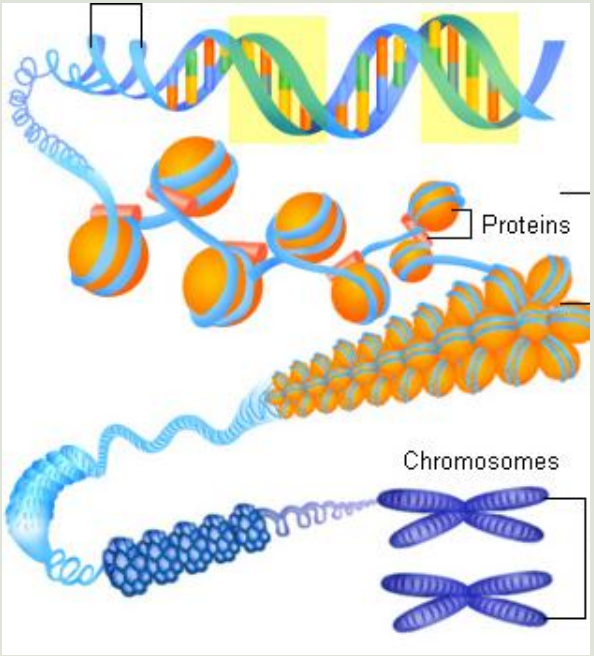
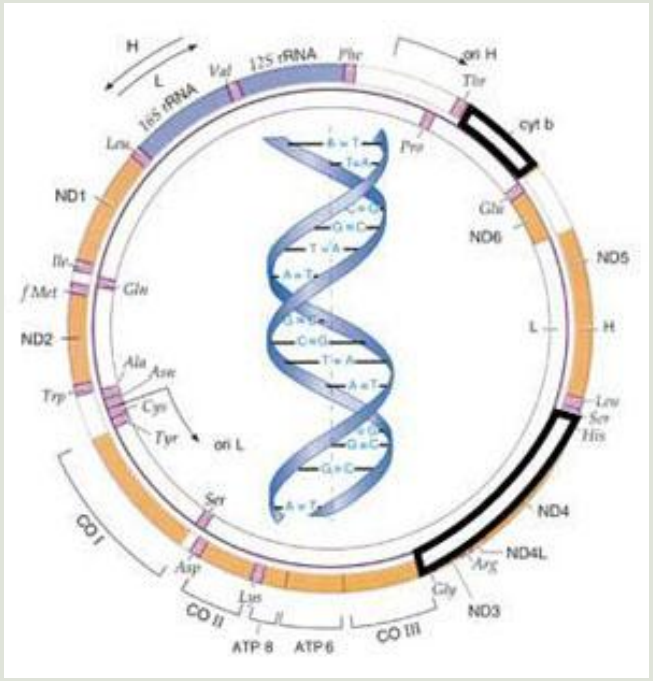
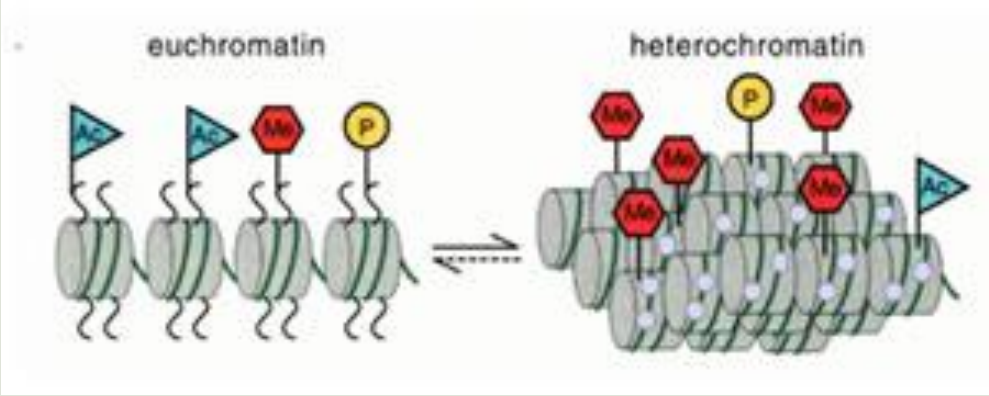




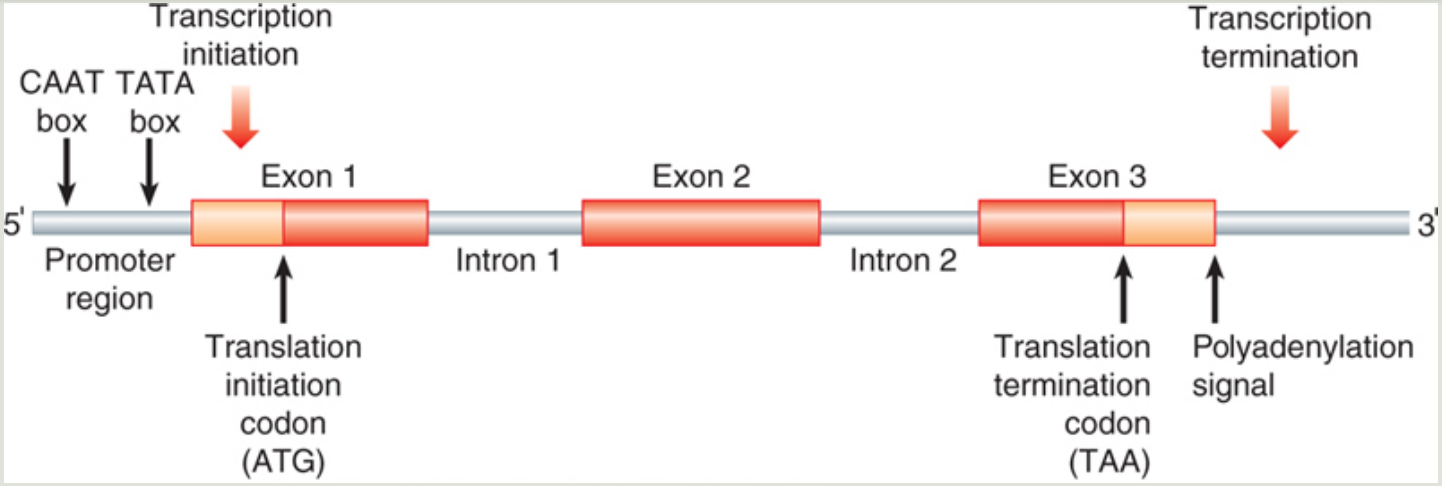
Nuclear genes

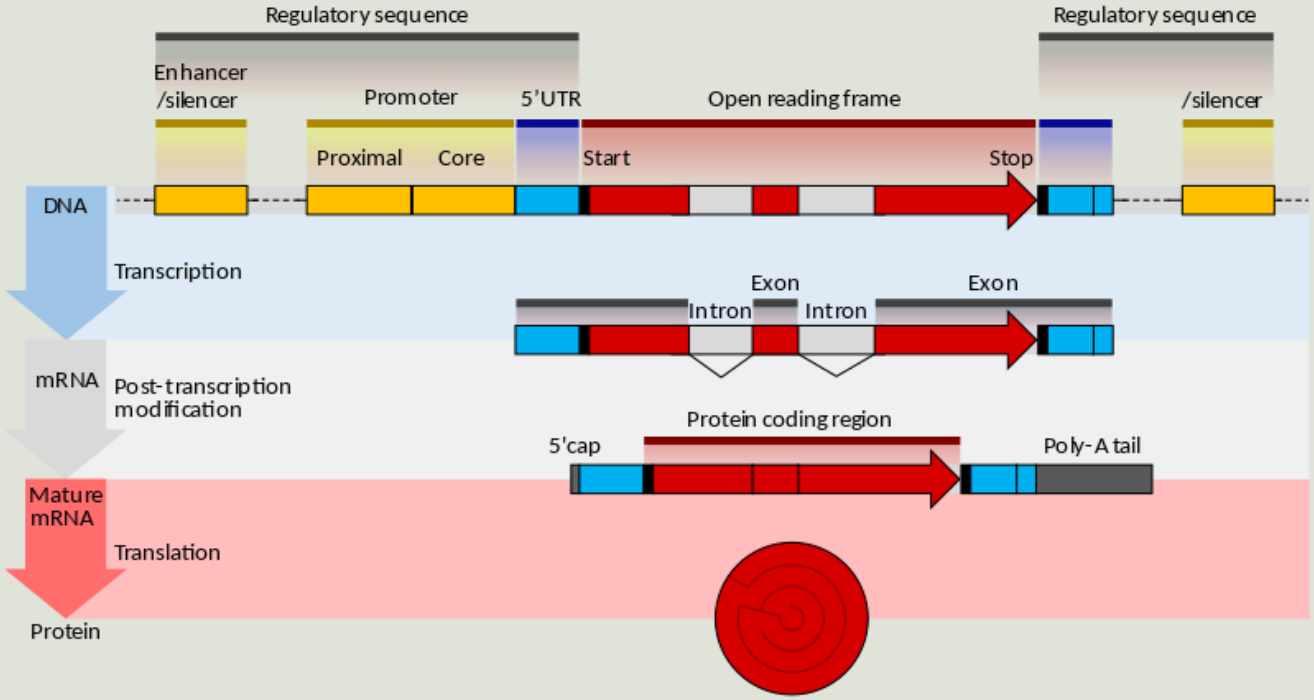
- ~ 20.000 (protein coding)
- Diversely distributed on chromosomes
  - E.g. 19. & 22. gene rich;

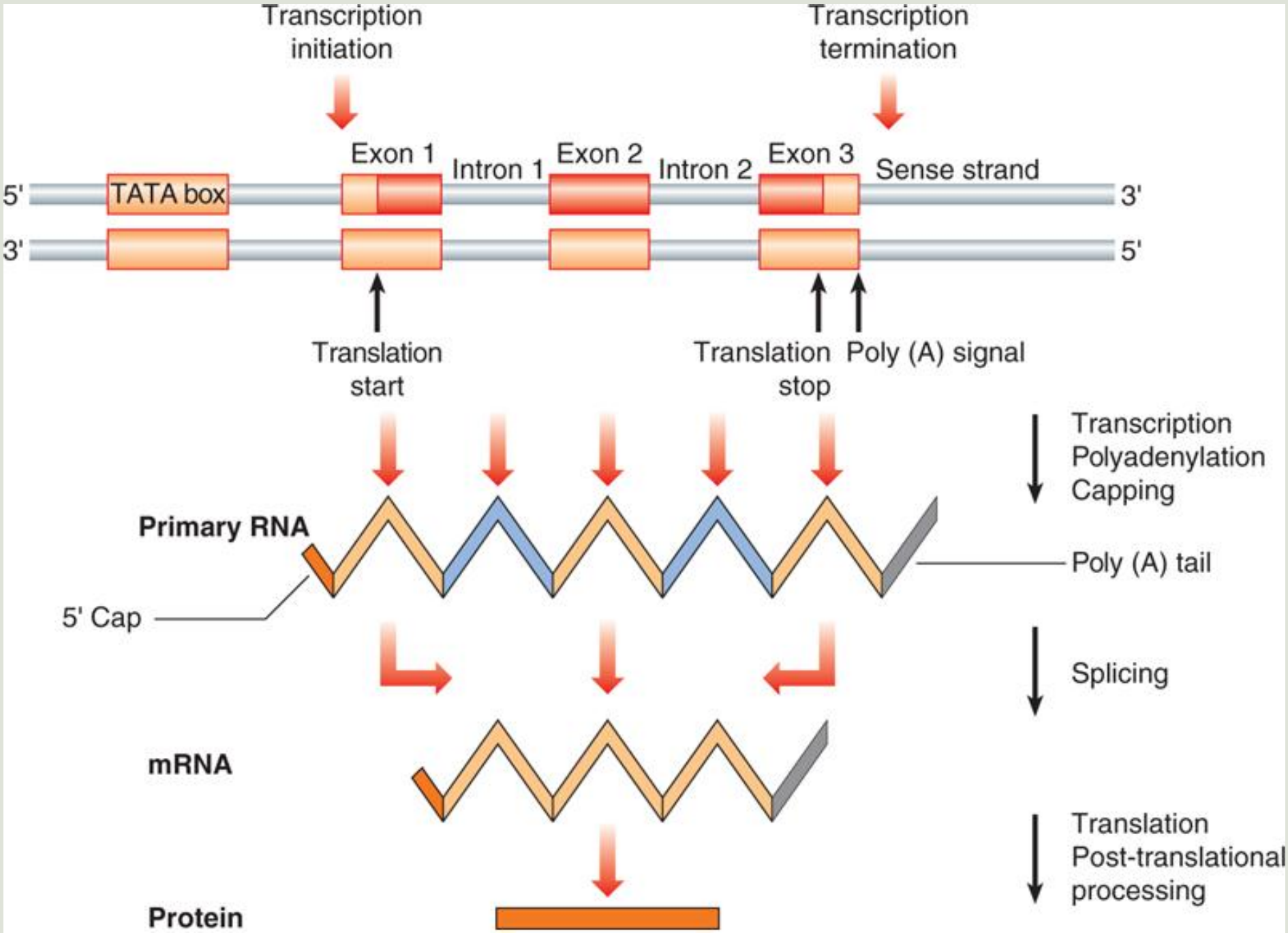
    4. & 18. gene poor
- Non-coding regions: heterochromatin & centromere & telomere



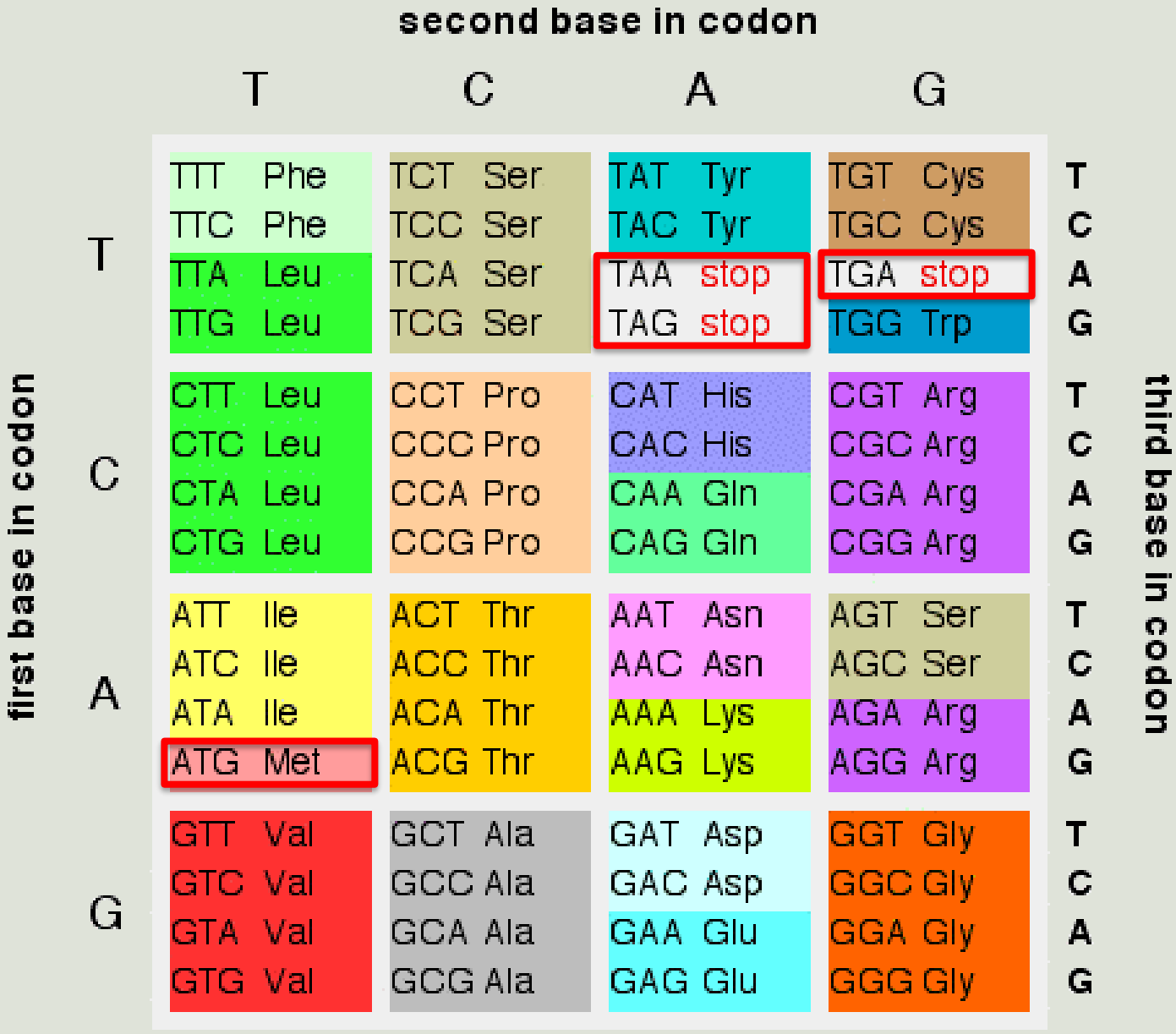
Gene structure





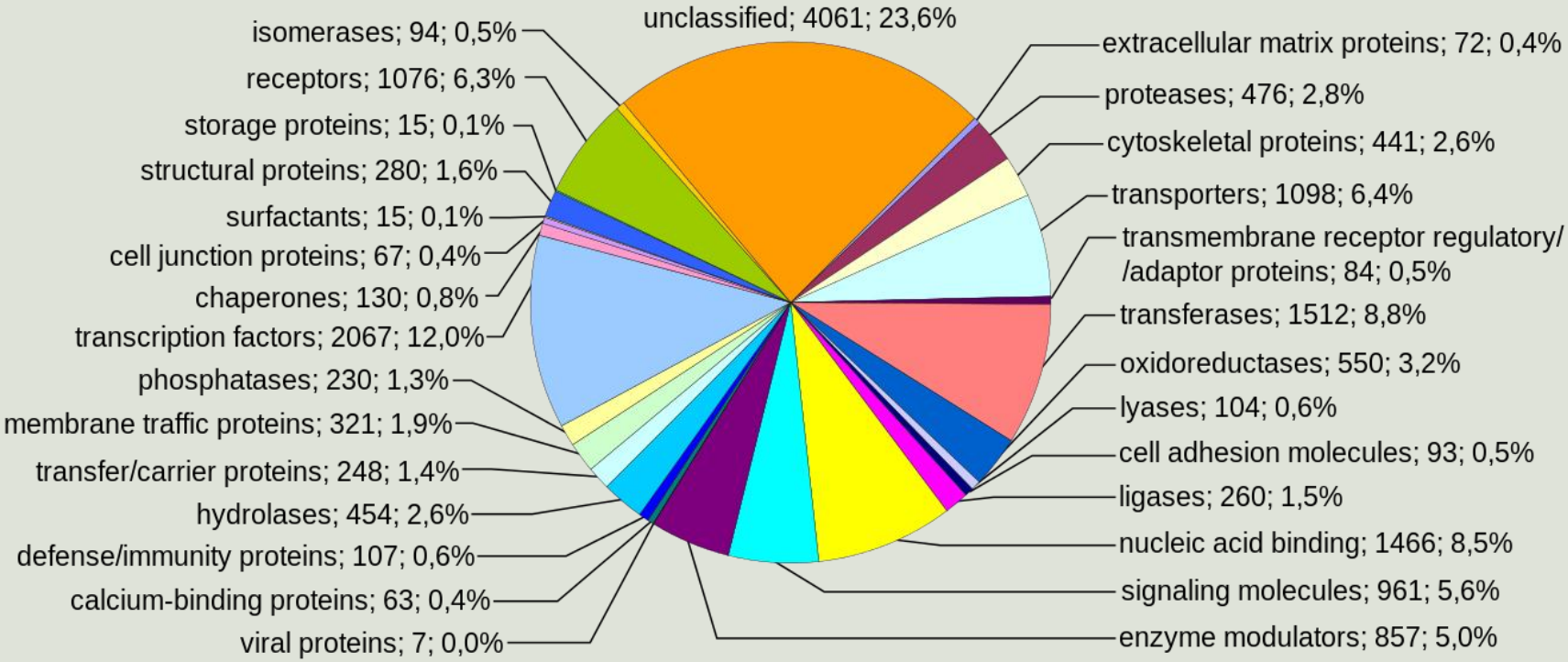

Transcription initiation
Transcription termination
Exon 1
Intron 1
Exon 2
Intron 2
Exon 3
Sense strand
5'
3'
TATA box
3'
5'
Translation start
Translation stop
Poly (A) signal
Transcription
Polyadenylation
Capping
Primary RNA
Poly (A) tail
5' Cap
Splicing
mRNA
Translation
Post-translational processing
Protein

Genetic code



Codon degeneracy (redundancy)!!!

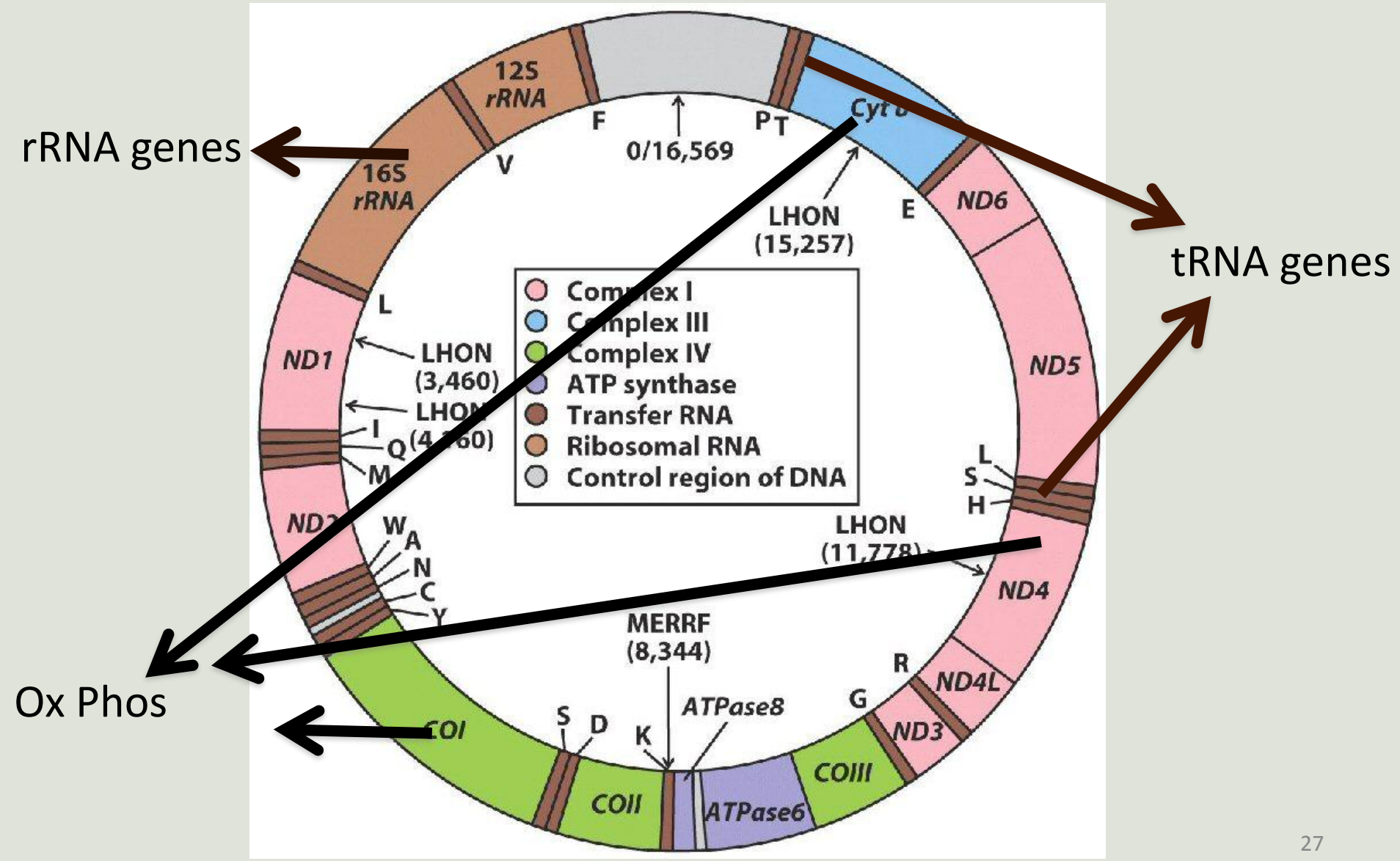
Human genes categorized by function of the transcribed proteins



Other types of nuclear DNA

- Repetitive DNA
  - Satelite
  - Minisatelite
    - Telomeric
    - Hypervariable minisatelite
  - Microsatelite
  - Transposable elements

Mitohondrial DNA



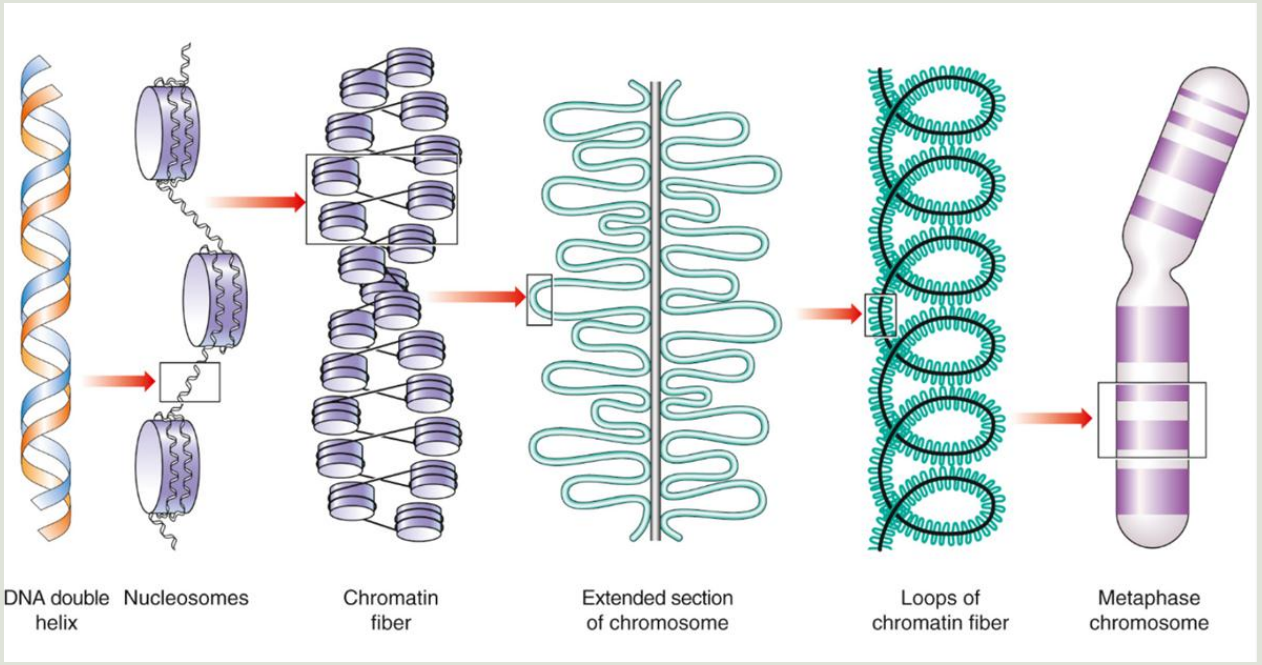
Mitohondrial inheritance

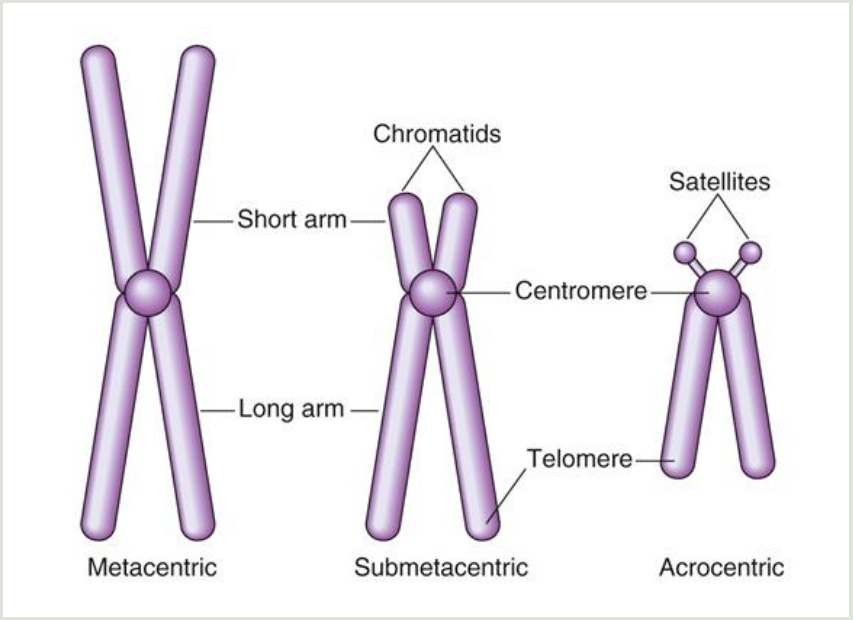
- Disorders:
  - diabetes mellitus & deafness
  - Mitochondrial myopathies
  - Leber's hereditary optic neuropathy
  - Leigh syndrome
  - neuropathy, ataxia, retinitis pigmentosa
  - ...

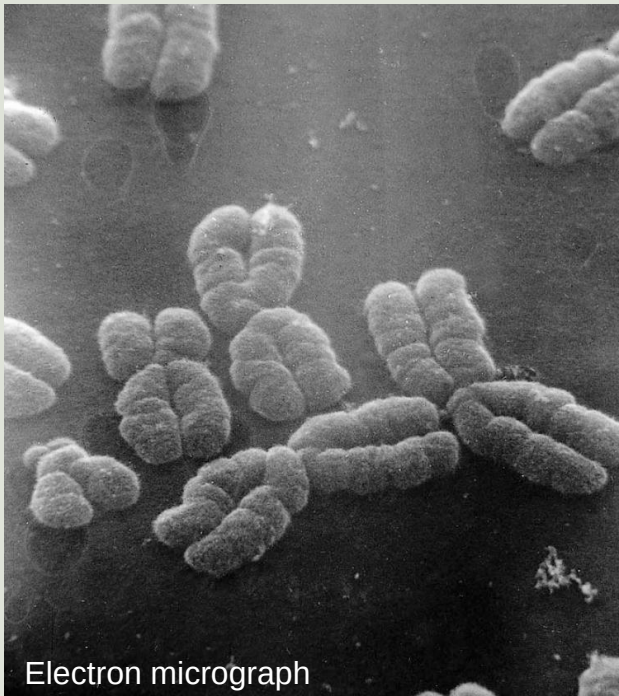
Inherited from mother!!!

- mtDNA mutations are very often
  - No damage control during replication

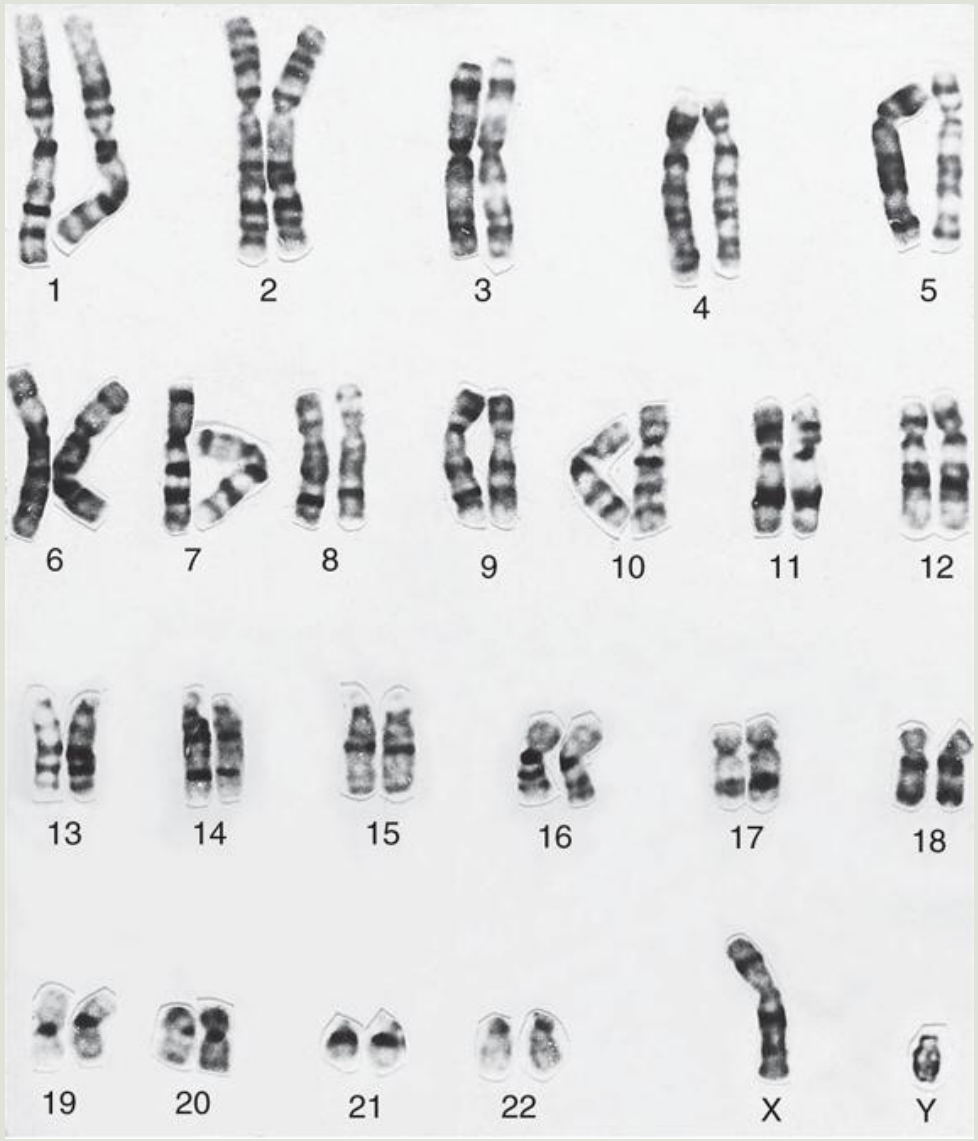
Chromosome structure

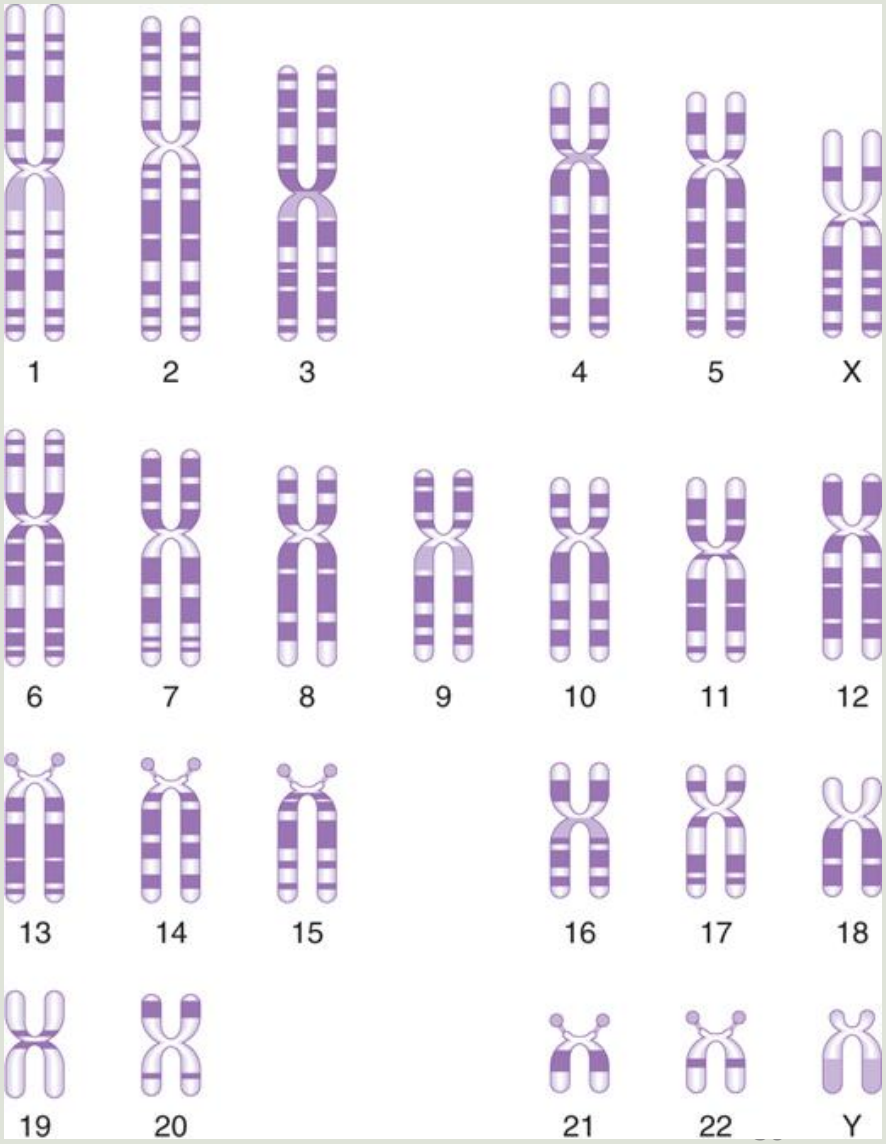


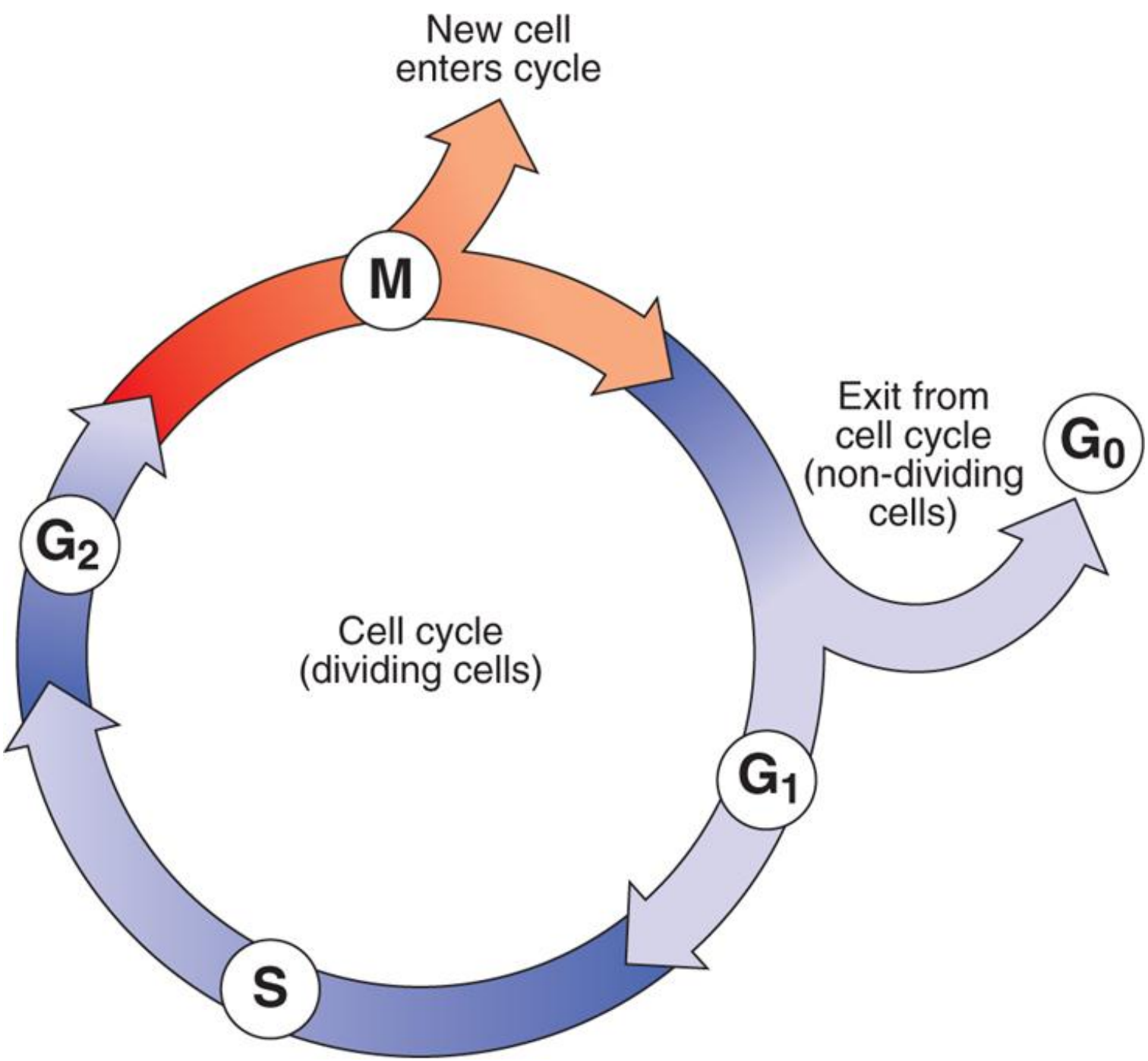



Electron micrograph

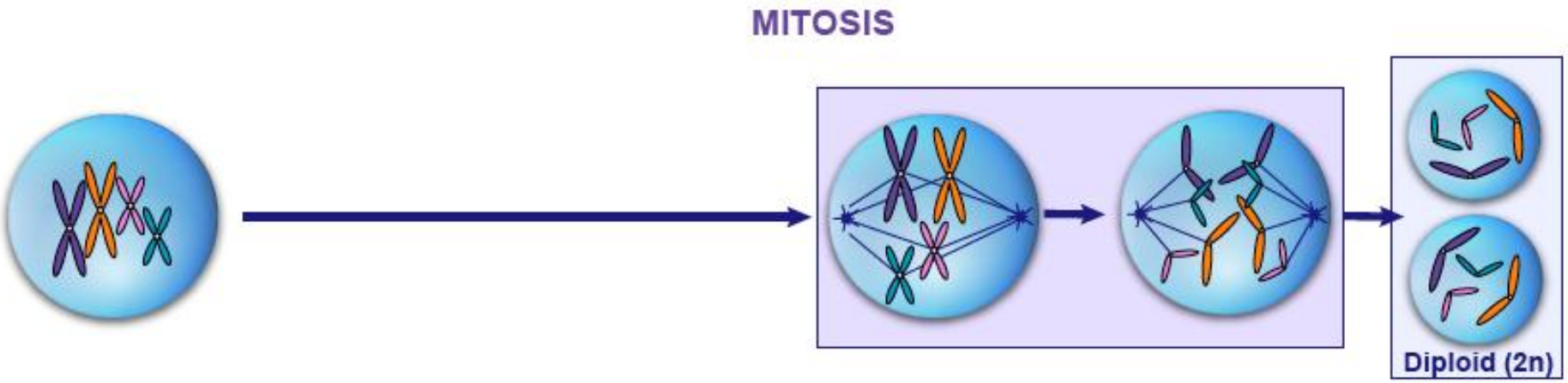
Human karyotype



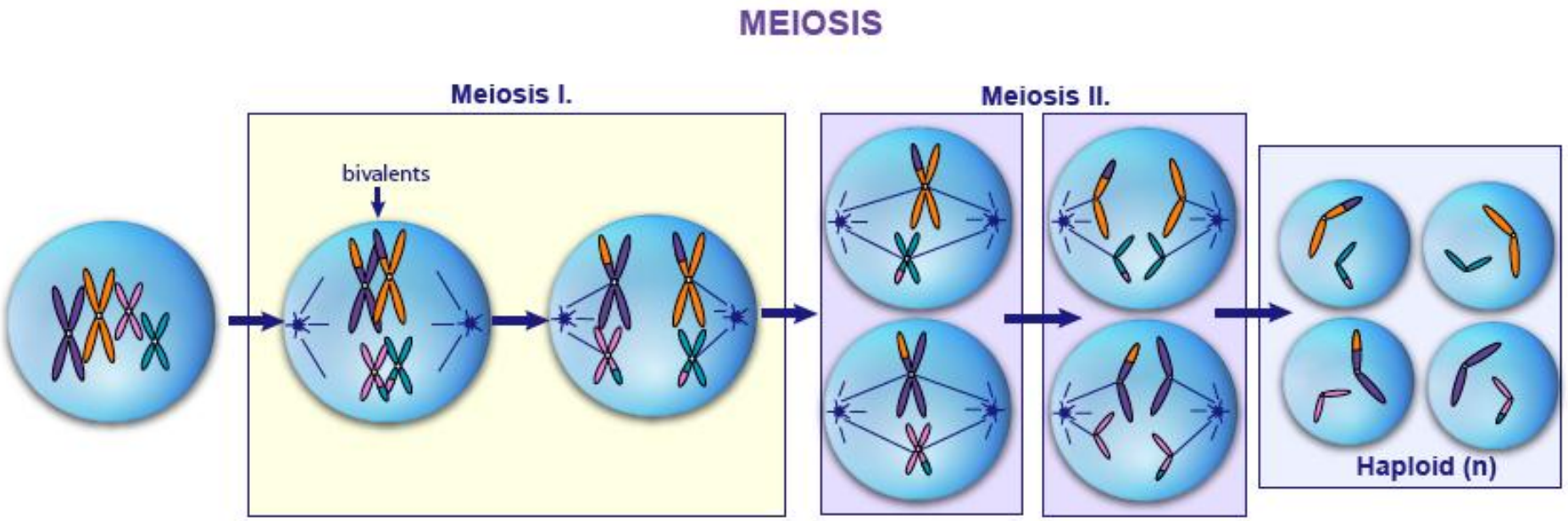


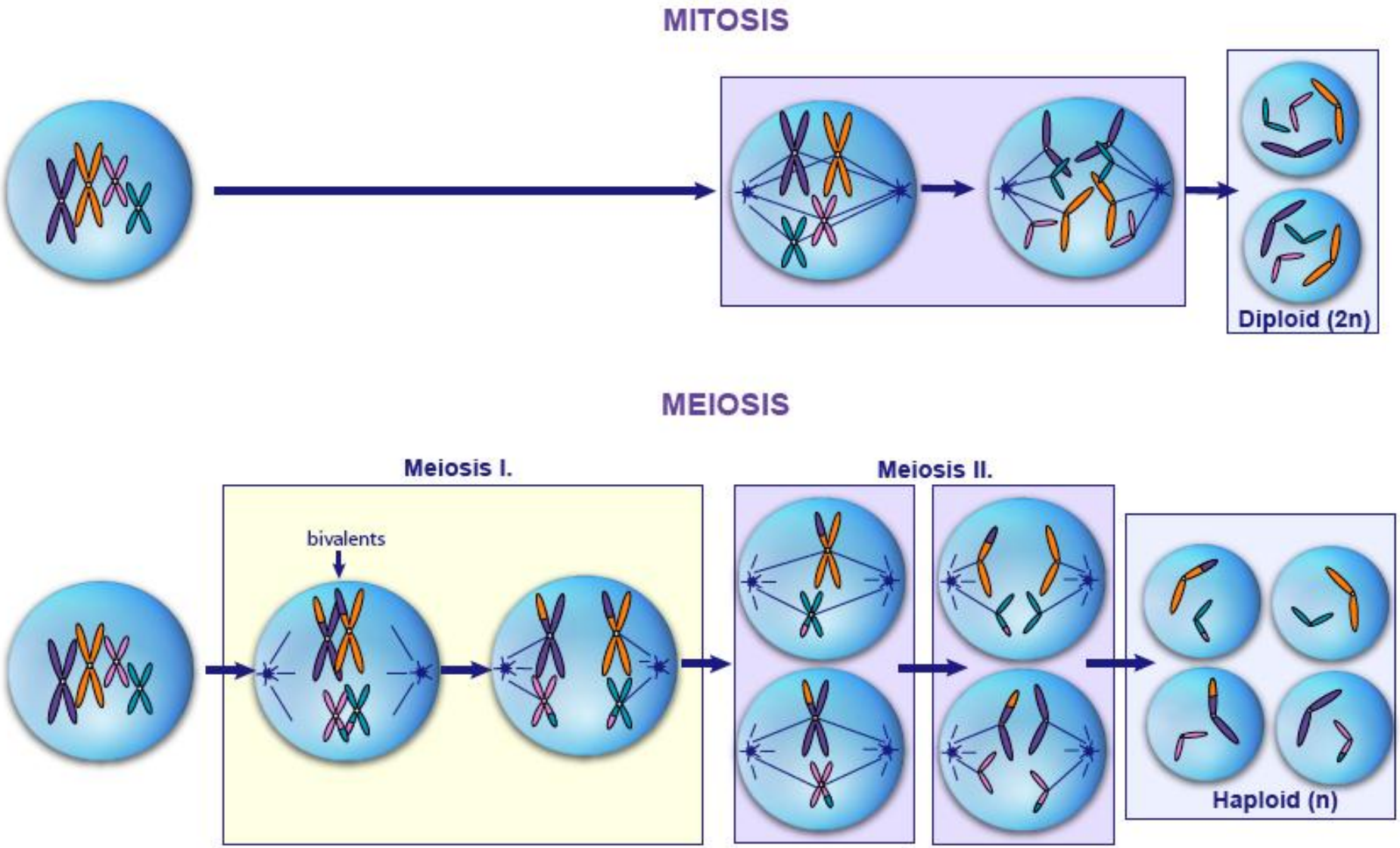

New cell
enters cycle
M
Exit from
cell cycle
(non-dividing
cells)
G0
G2
Cell cycle
(dividing cells)
G1
S

Mitosis



Meiosis




MITOSIS
Diploid (2n)
MEIOSIS
Meiosis I.
Meiosis II.
bivalents
Haploid (n)

Mitosis vs. meiosis

	MITOSIS	MEIOSIS
Cell type	Somatic	Germ cells
No. of daugther cells	2	4
Chromosome no. (paternal/maternal cell)	diploid	diploid
Chromosome no. (daugther cells)	diploid	haploid
Function	growth	reproduction

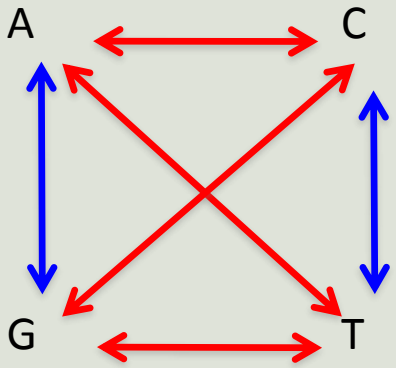
35

MUTATIONS

Mutations

- Hereditary change in genetic material

SUBSTITUTION MUTATIONS



POINT MUTATIONS

TGT → TGC

Cys → Cys

SILENT

TGT → TGG

Cys → Trp

MISSENSE

TGT → TGA

Cys → Stop

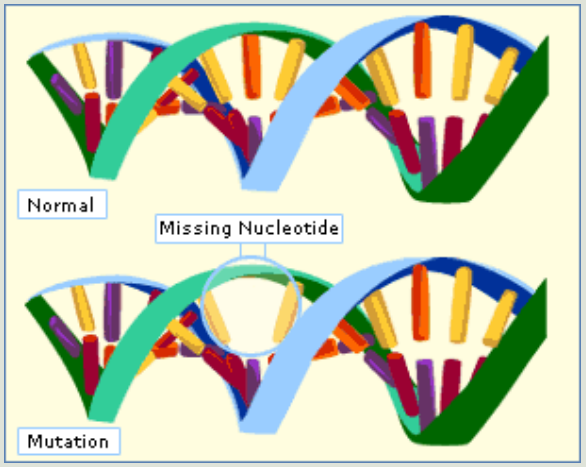
NONSENSE

Substitution mutations

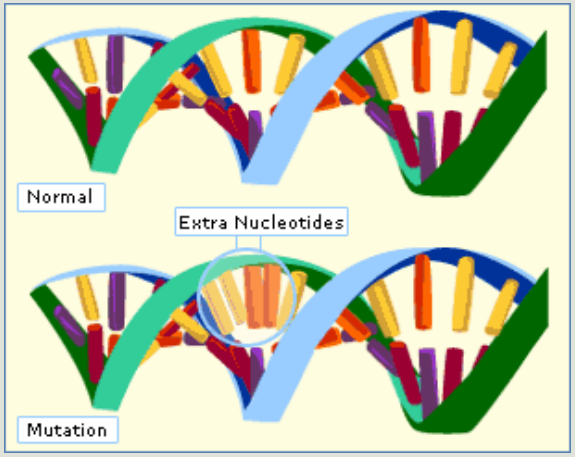
Class	Group	Type	Effect on Protein Product
Substitution	Synonymous	Silent*	Same amino acid
	Nonsynonymous	Missense*	Altered amino acid—may affect protein function or stability
		Nonsense*	Stop codon—loss of function or expression due to degradation of mRNA
		Splice site	Aberrant splicing—exon skipping or intron retention
		Promoter	Altered gene expression
		Enhancer	Altered gene expression

Mutations cont.

Deletions



Insertions



ATG TAT GCG CCA TCA ACA ATG TAT GCG CCA TCA ACA

ATG TAT GG CCA TCA ACA ATG TAT GCGA CCA TCA ACA

Met Tyr Ala Pro Ser Thr Met Tyr Ala Pro Ser Thr Thr

Met Tyr Gly His Glu Glu Met Tyr Ala Thr Ile Asp

Can lead to **frameshift mutations**

Deletions and insertions

Class	Group	Type	Effect on Protein Product
Deletion	Multiple of 3 (codon)		In-frame deletion of one or more amino acid(s)—may affect protein function or stability
	Not multiple of 3	Frameshift	Likely to result in premature termination with loss of function or expression
	Large deletion	Partial gene deletion	May result in premature termination with loss of function or expression
		Whole gene deletion	Loss of expression
Insertion	Multiple of 3 (codon)		In-frame insertion of one or more amino acid(s)—may affect protein function or stability
	Not multiple of 3	Frameshift	Likely to result in premature termination with loss of function or expression
	Large insertion	Partial gene duplication	May result in premature termination with loss of function or expression
		Whole gene duplication	May have an effect because of increased gene dosage
	Expansion of trinucleotide repeat	Dynamic mutation	Altered gene expression or altered protein stability or function

Frequency of different types of mutation

Type of Mutation	Percentage of Total
Missense or nonsense	56
Splicing	10
Regulatory	2
Small deletions, insertions, or indels*	24
Gross deletions or insertions	7
Other (complex rearrangements or repeat variations)	<1

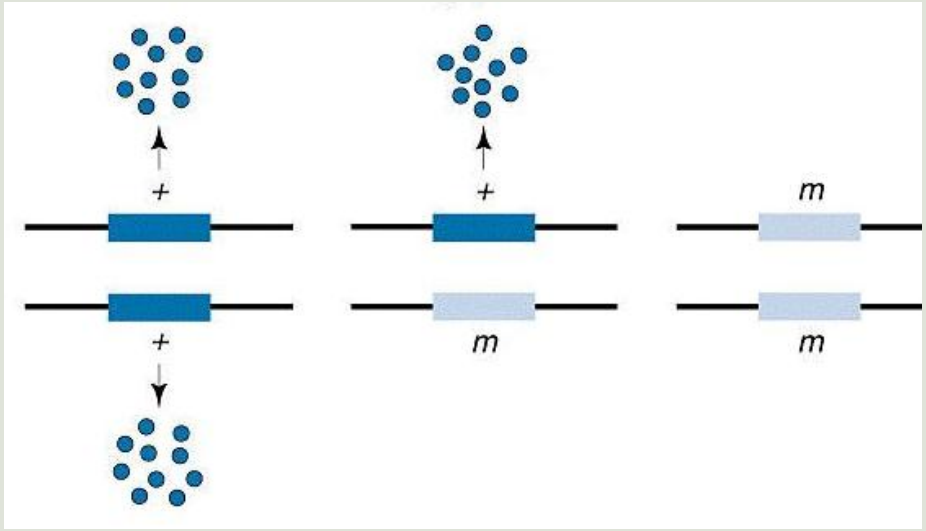
Mutations lead to...
(classification by the effect on function)

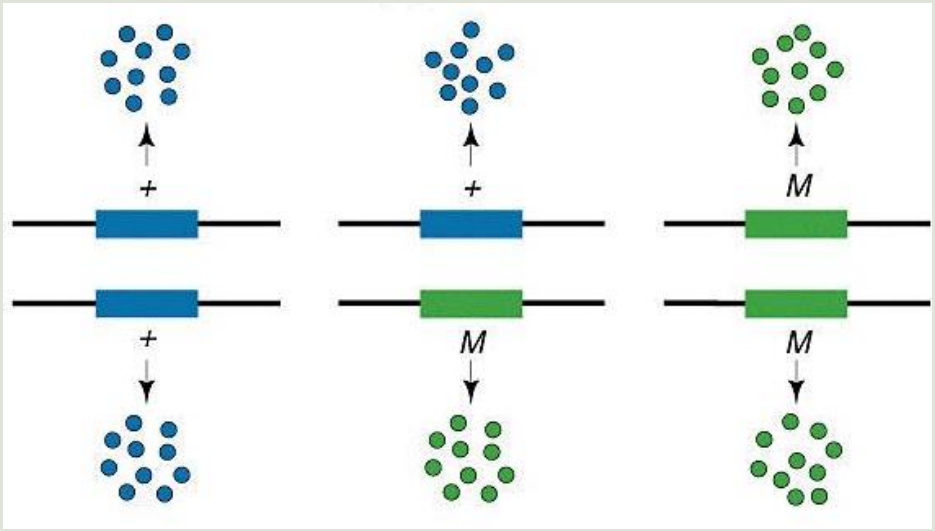
1) Loss-of-function

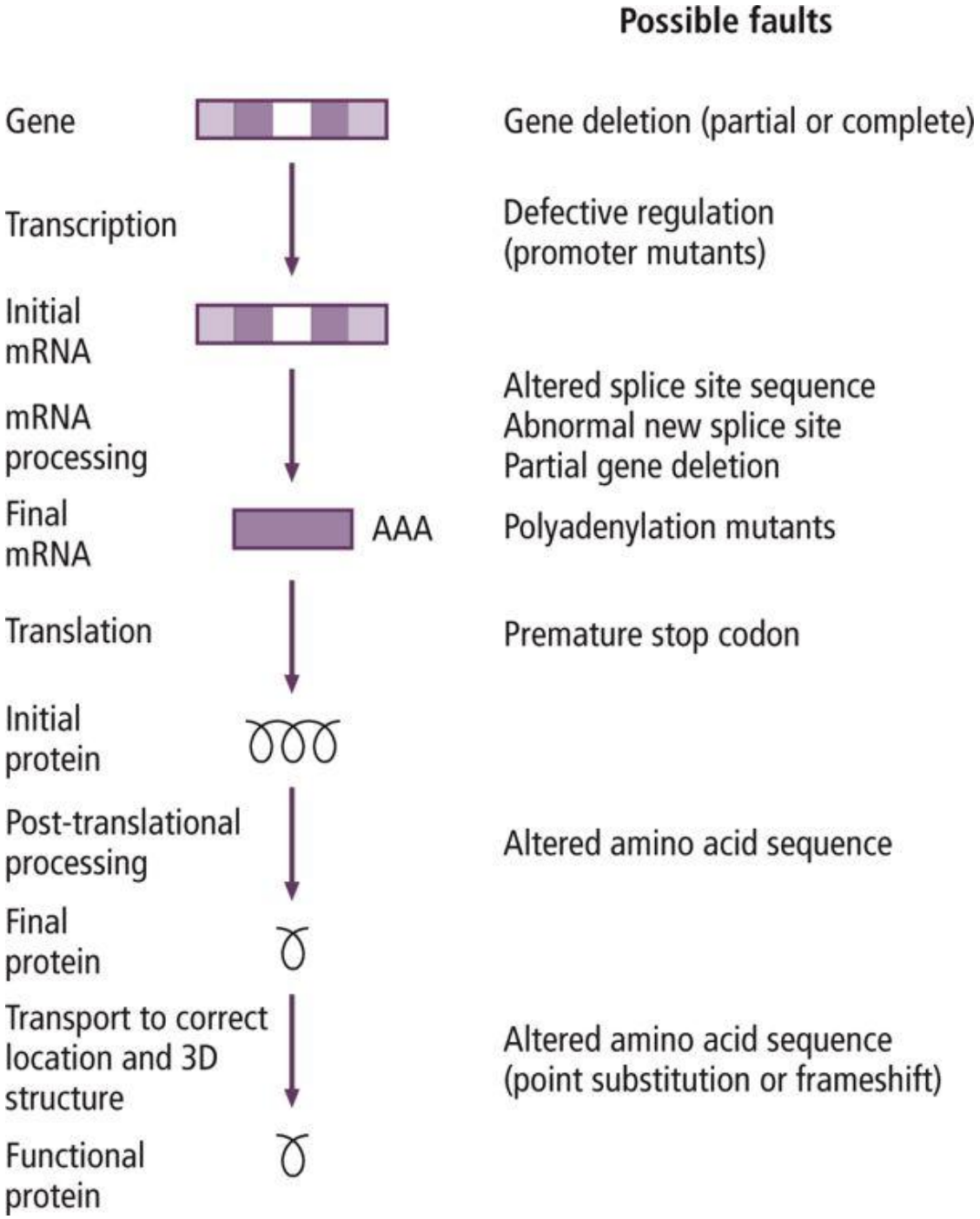
- Less gene product
- Complete loss of gene product

2) Gain-of-function

- More gene product
- New gene product



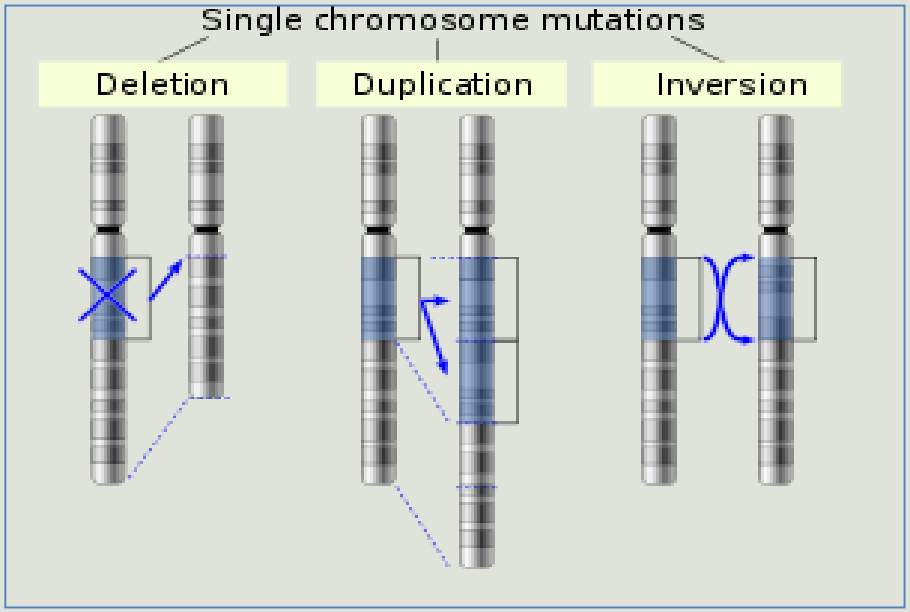


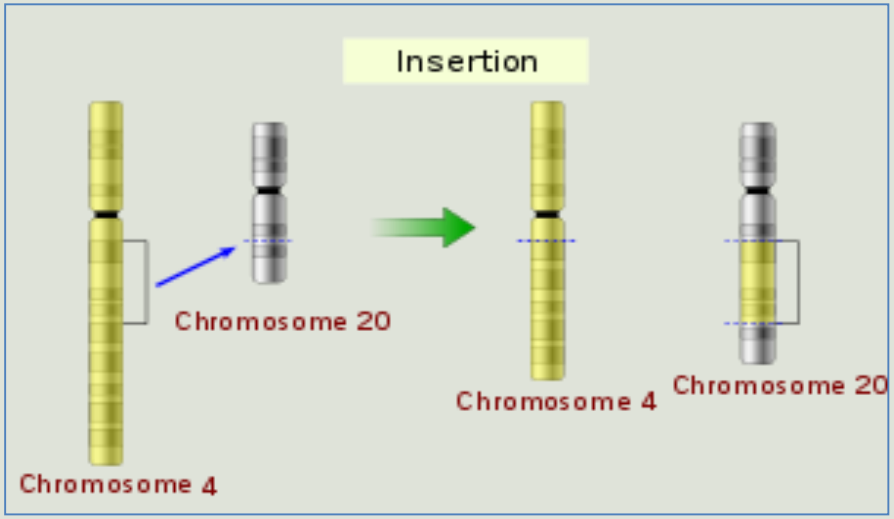

Possible faults
Gene
Gene deletion (partial or complete)
Transcription
Defective regulation
(promoter mutants)
Initial
mRNA
mRNA
processing
Altered splice site sequence
Abnormal new splice site
Partial gene deletion
Final
mRNA
AAA
Polyadenylation mutants
Translation
Premature stop codon
Initial
protein
Post-translational
processing
Altered amino acid sequence
Final
protein
Transport to correct
location and 3D
structure
Altered amino acid sequence
(point substitution or frameshift)
Functional
protein

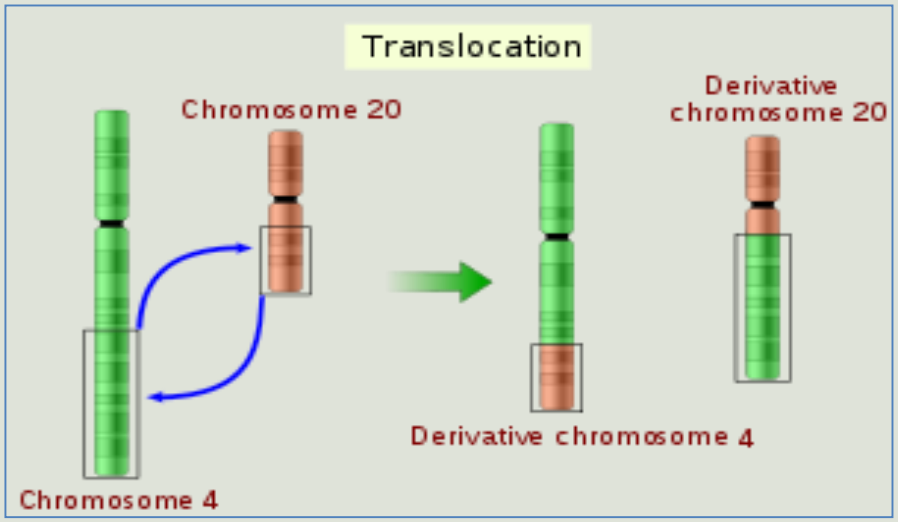
Chromosomal Abnormalities

- Numerical
  - Aneuploidy
  - Monosomy
  - Trisomy
  - Tetrasomy
  - Polyploidy
  - Triploidy
  - Tetraploidy
- Different Cell Lines (Mixoploidy)
  - Mosaicism
  - Chimerism
- Structural
  - Translocations
  - Reciprocal
  - Robertsonian
  - Deletions
  - Insertions
  - Inversions
  - Paracentric
  - Pericentric
  - Rings
  - Isochromosomes

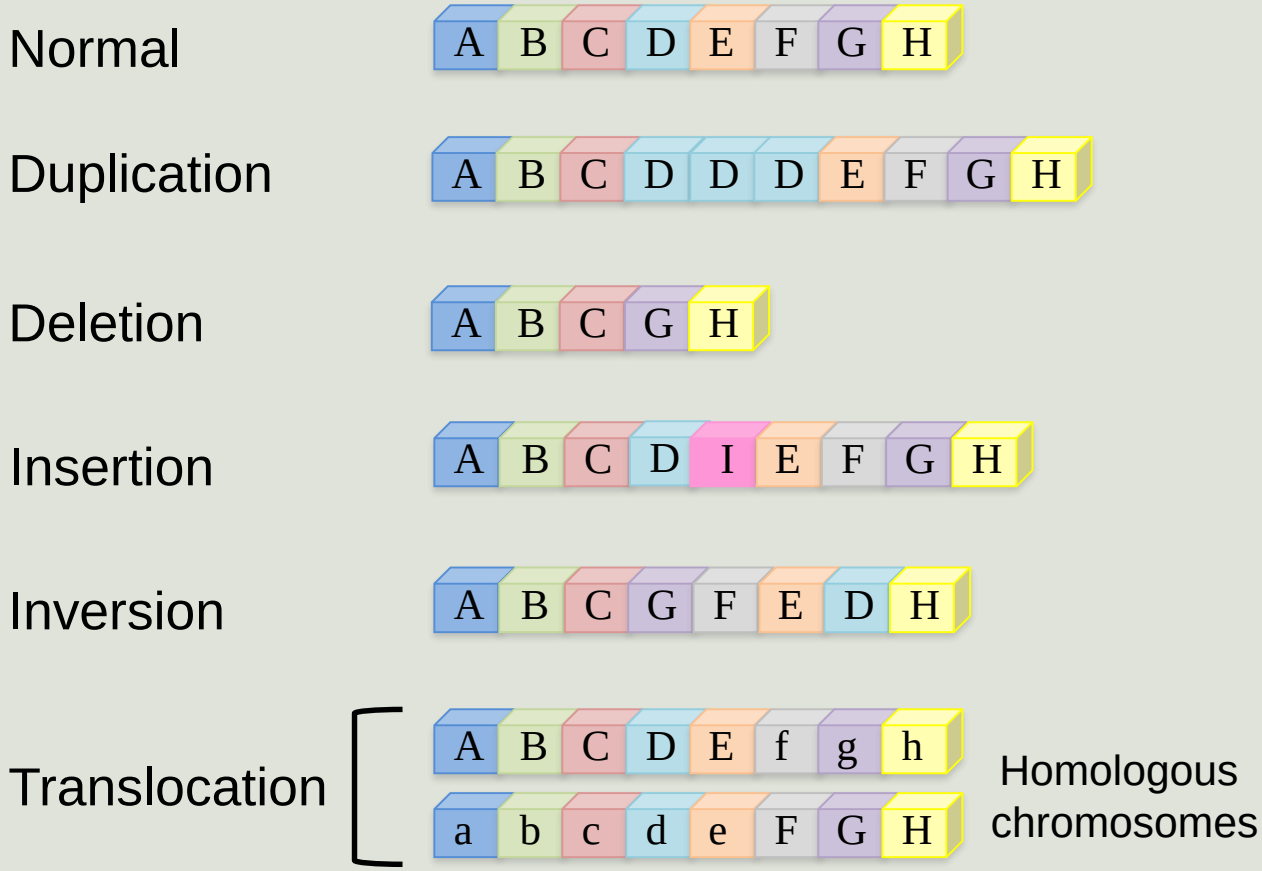
Chromosomal mutations



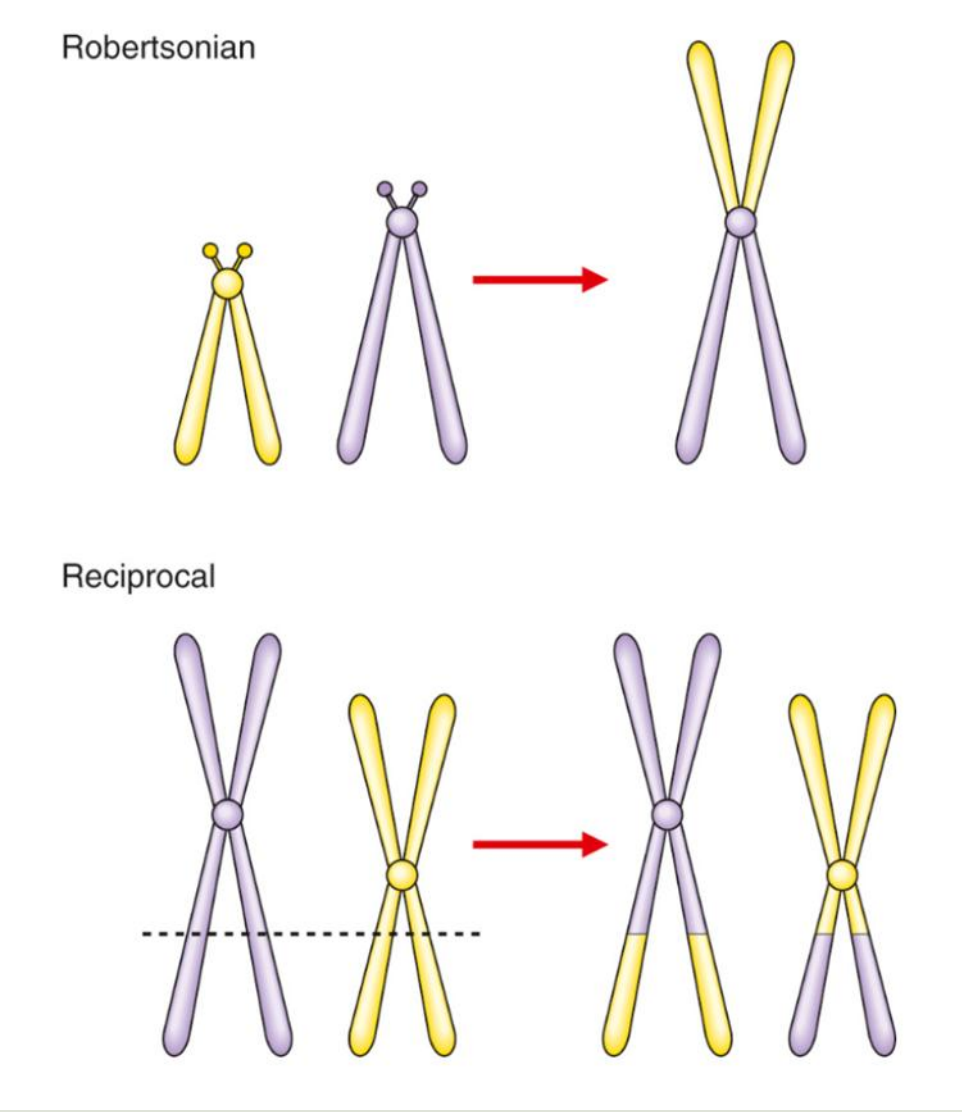




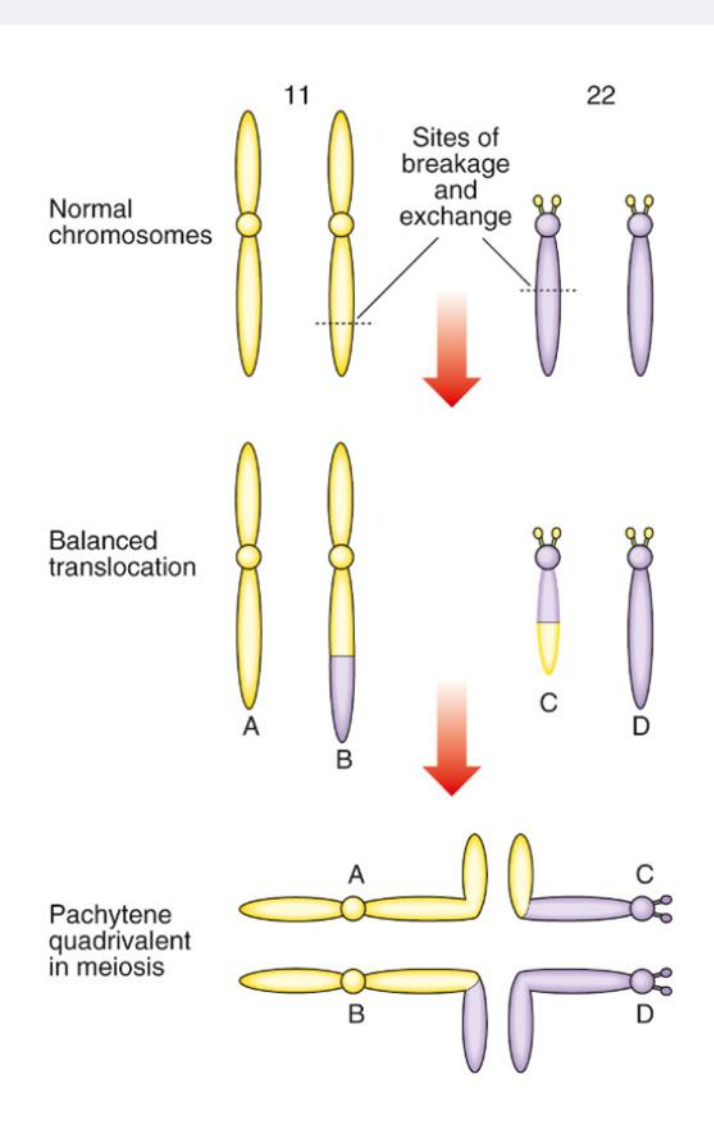
Structural chromosomal aberrations

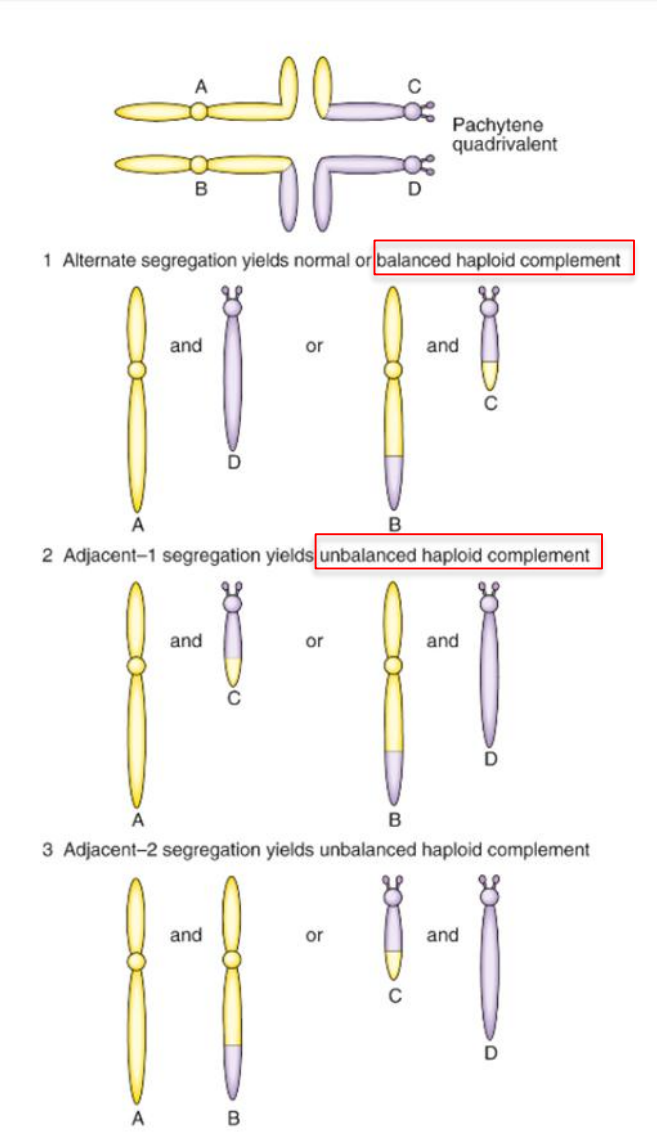


Translocations

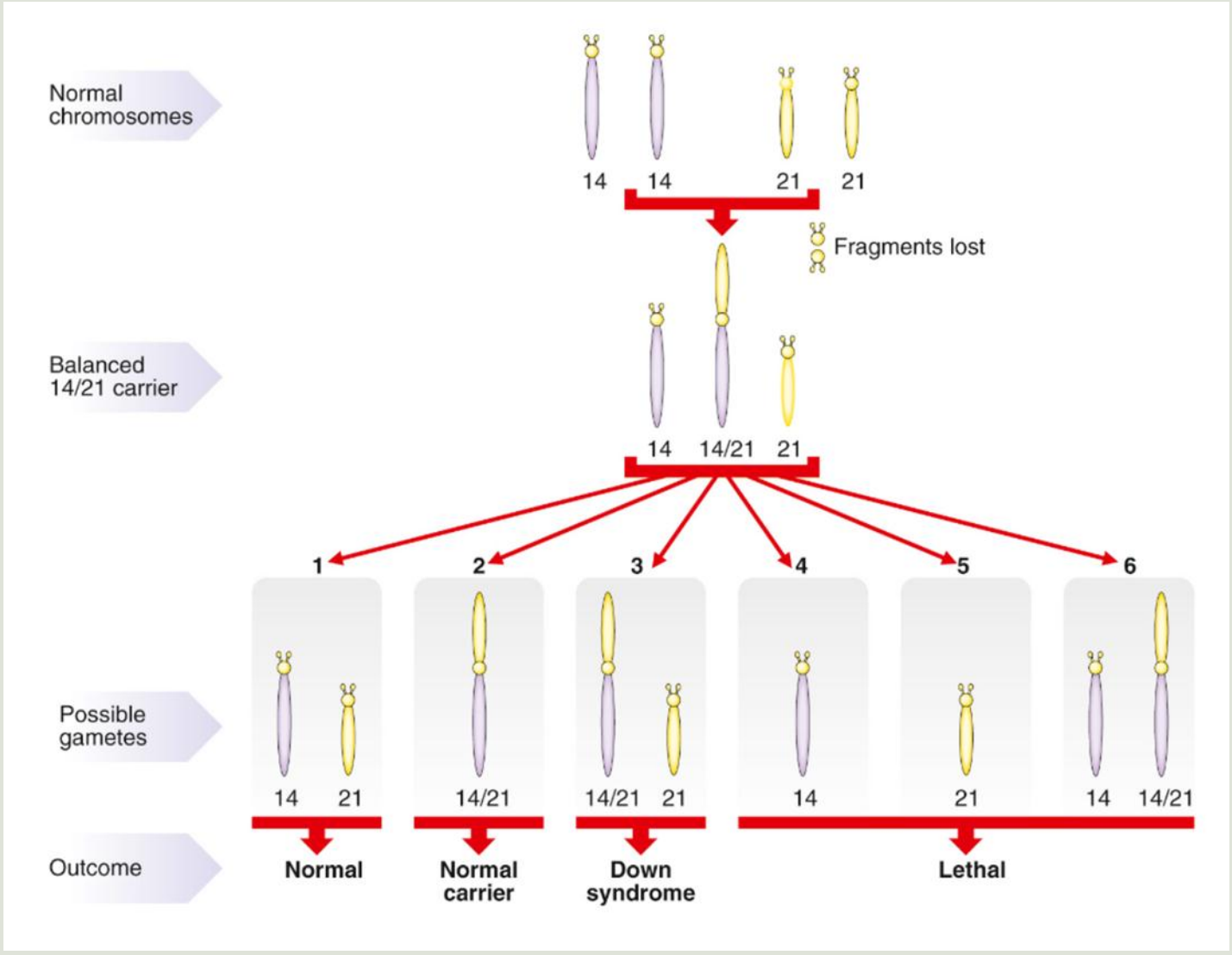


Reciprocal translocations





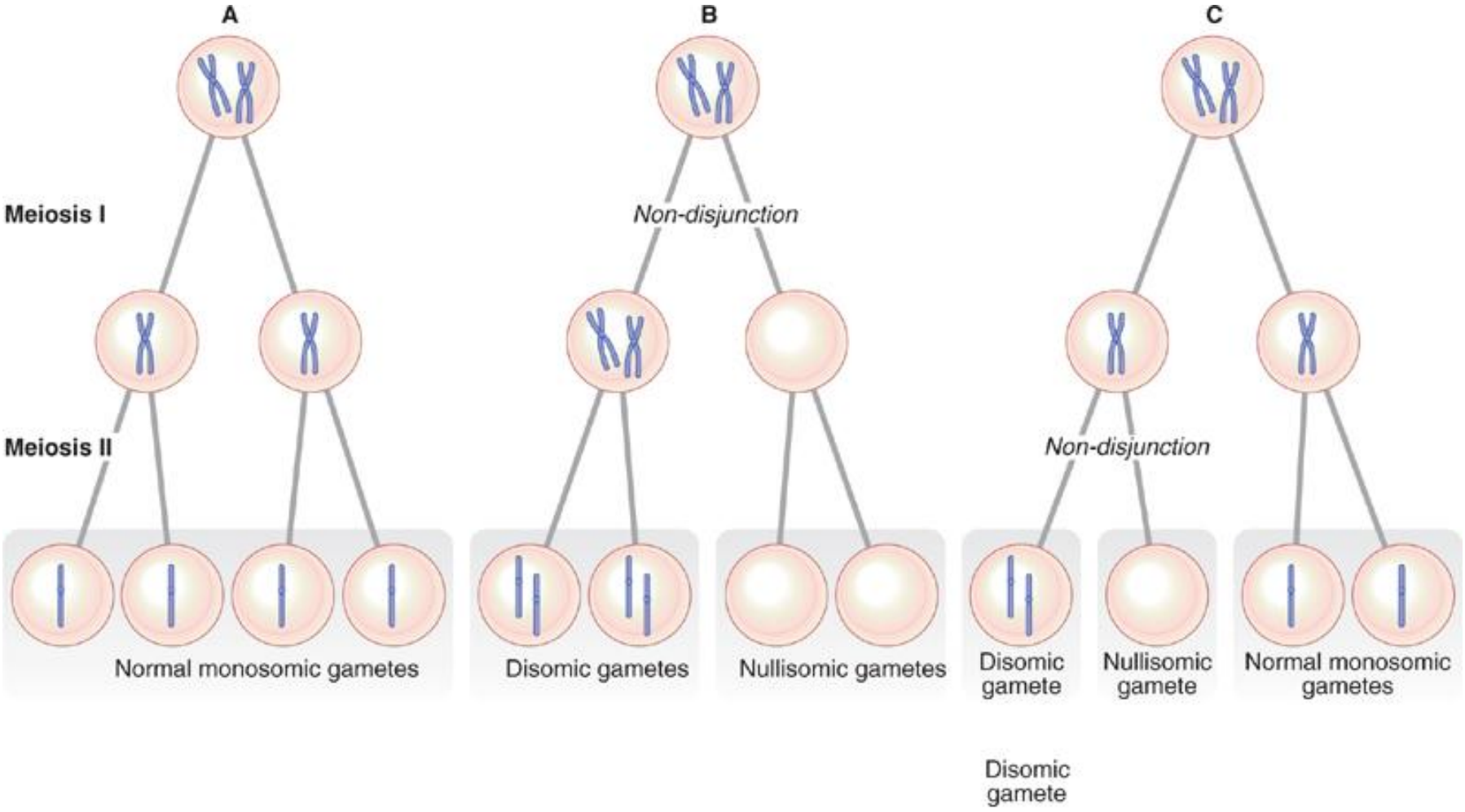
Robertsonian translocation

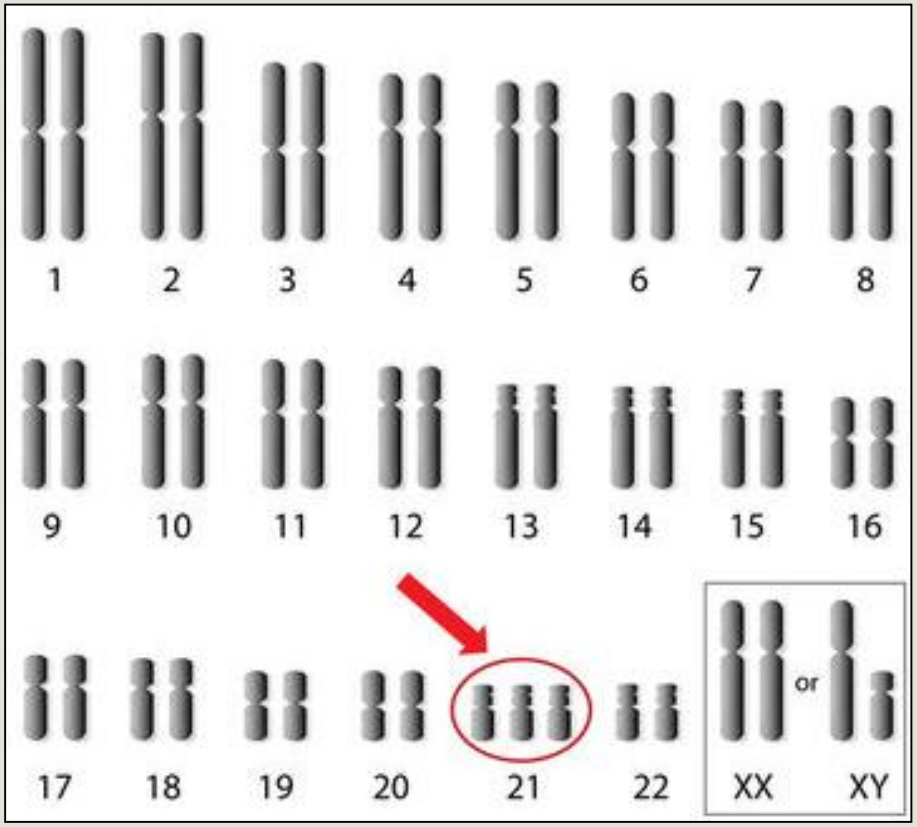


Numerical Abnormalities

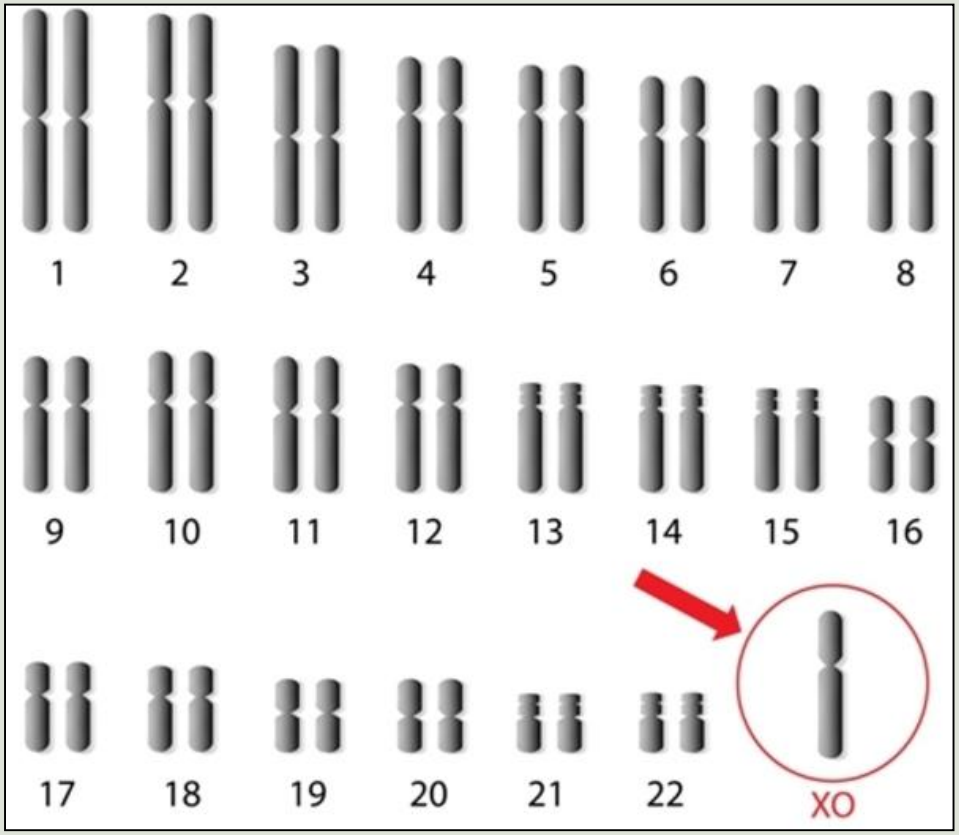
- Aneuploidy - the loss or gain of one or more chromosomes
- Polyploidy - the addition of one or more complete haploid complements
- Monosomy – sex chromosomes (45,X)
- Trisomy – Down syndrome (21), Patau syndrome (13), Edwards syndrome (18), additinal sex chromosome (47,XXX; 47,XXY; 47,XYY)

Segregation of meiosis





Trisomy



Monosomy

Chromosomal Abnormalities

- Numerical
  - Aneuploidy
  - Monosomy
  - Trisomy
  - Tetrasomy
  - Polyploidy
  - Triploidy
  - Tetraploidy
- Different Cell Lines (Mixoploidy)
  - Mosaicism
  - Chimerism
- Structural
  - Translocations
  - Reciprocal
  - Robertsonian
  - Deletions
  - Insertions
  - Inversions
  - Paracentric
  - Pericentric
  - Rings
  - Isochromosomes

For the practicals (P6), please, bring your LAB COAT!