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Medical genetics – introduction

Michael Doubek

Learning outcomes

- Basic concepts of contemporary genetics will be presented
- The student will learn principles of heredity
- Diagnostics of genetic diseases will be introduced

Lecture content

- Basic concepts of genetics
- Genome and its analysis
- Modes of inheritance
- Example from practice

Why medical genetics?

Genome role in diagnostics, therapy and prevention

= application in medical practice

It is possible to implement into practice only what I know and what I have in mind

What you should already know

What is a gene

genes: structural

for functional RNAs

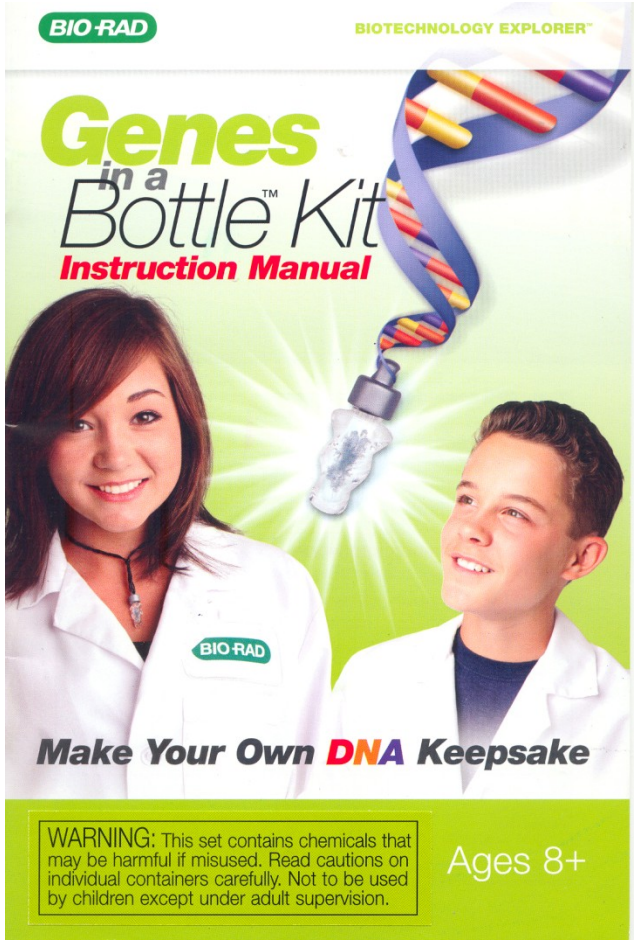
- housekeeping genes
- gene expression
- exones, introns, non-transcribed regions, promotors

Informational macromolecules

Transcription, alternative splicing, translation

Chromosomes

What is a DNA?



cold ethanol + salt + detergent
> 1 m DNA

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What is a DNA?

Cavendish Laboratory and The Eagle Pub

Watson + Crick + Wilkins + Franklin

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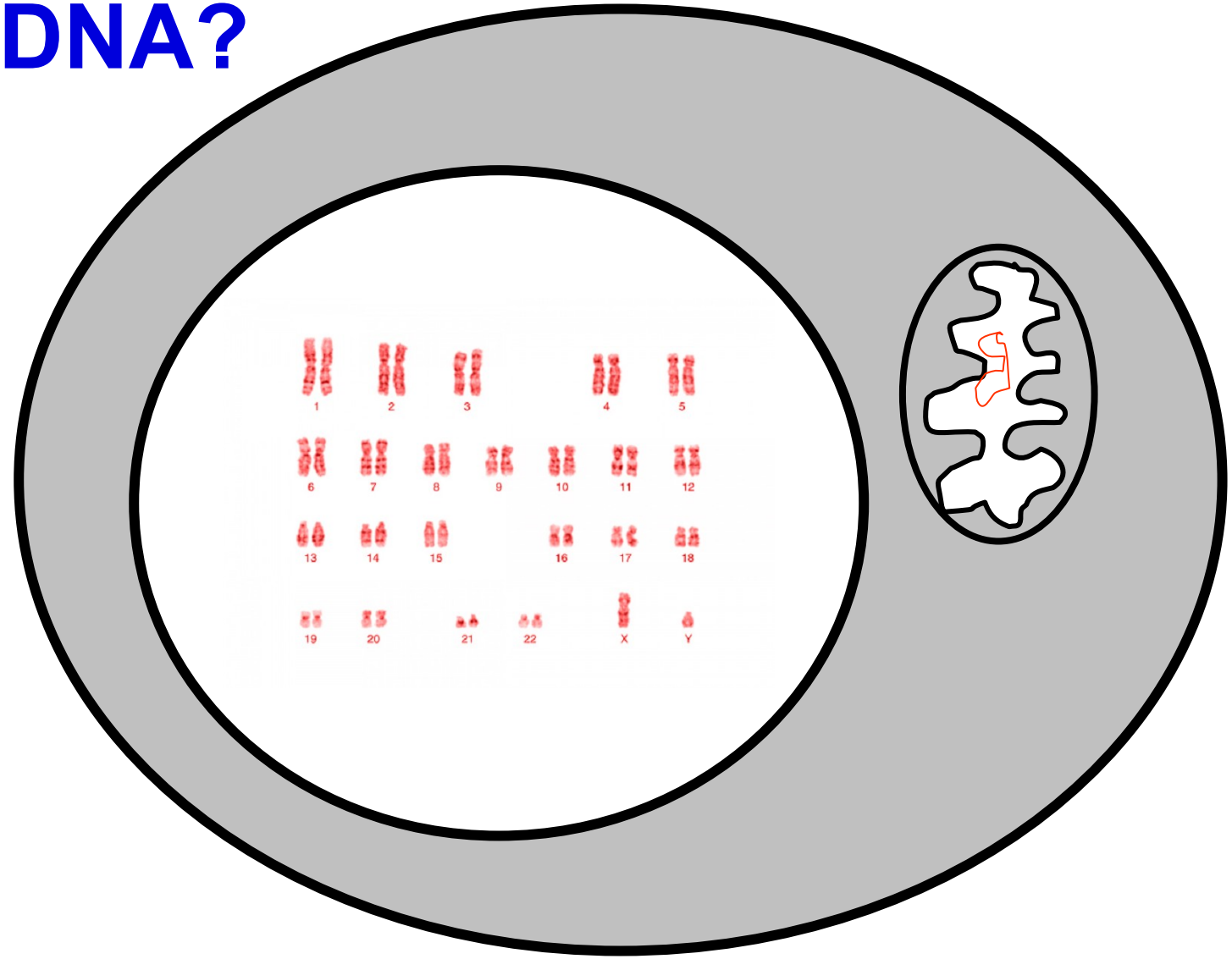
What is a DNA?



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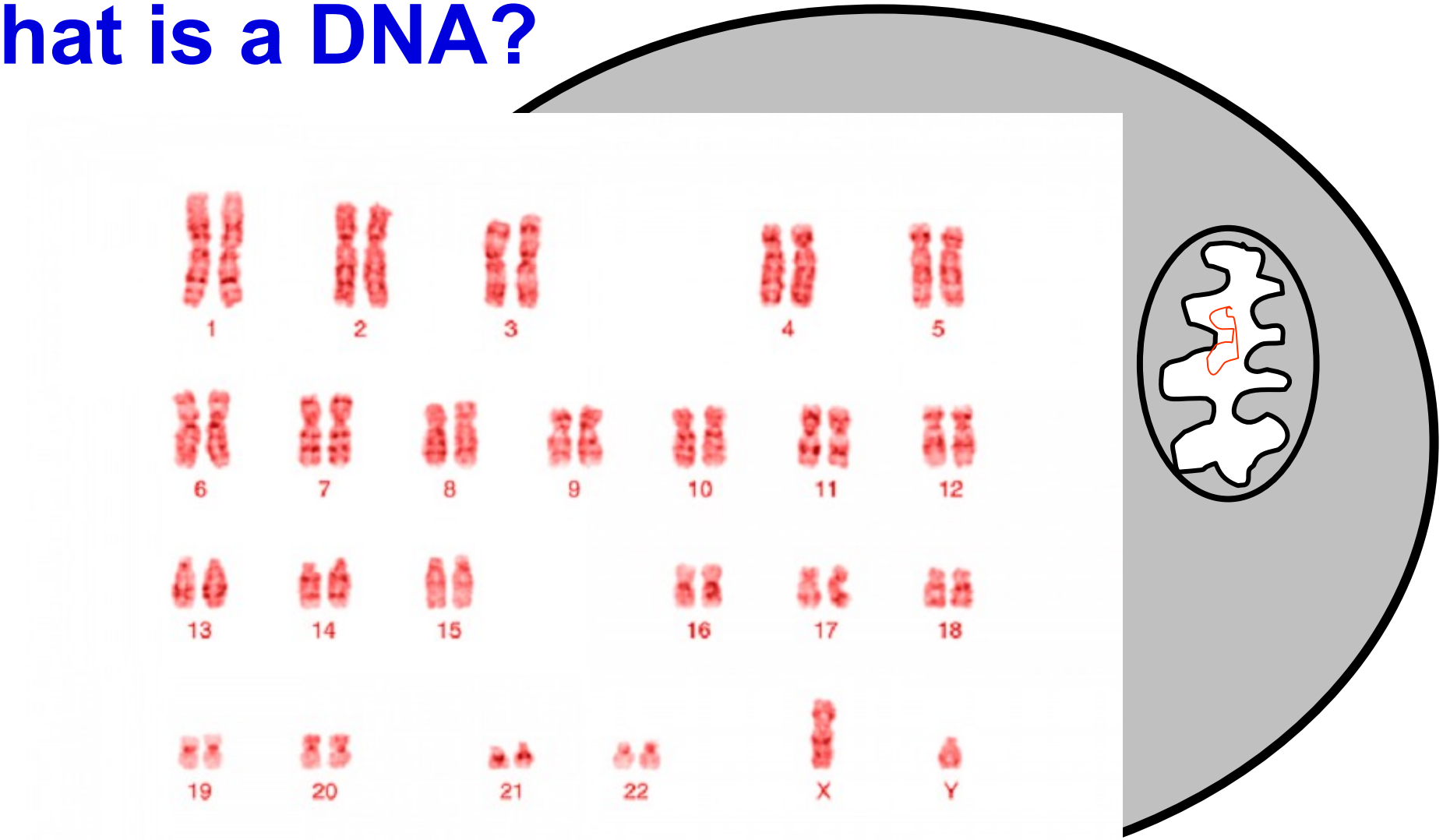
What is a DNA?



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Chromosomes

Terminology

Genetics: study of genes, genetic variation, and heredity in living organism

Genome: complete set of DNA within a single cell of an organism

Genomics: focuses on the structure, function, evolution, and mapping of genomes

Terminology

Genetics

Genome

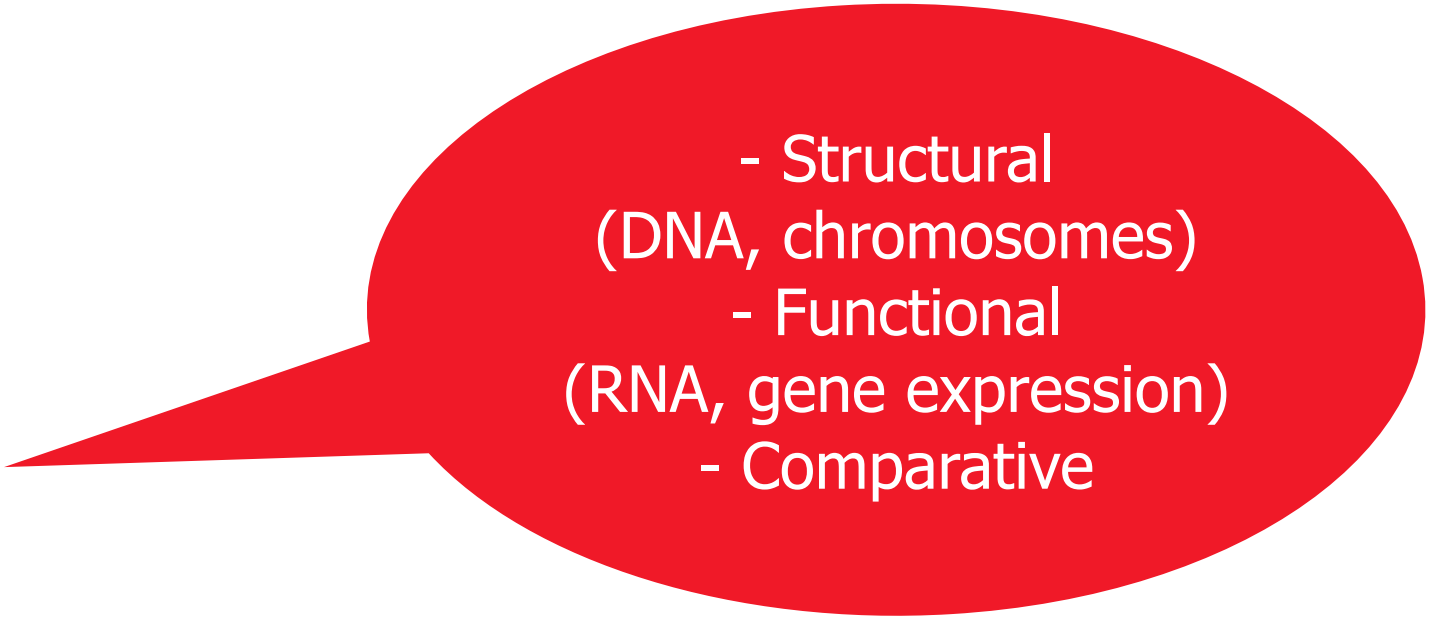
Genomics

Terminology

Genetics

Genome

Genomics



Terminology

Genetics

Genome

Genomics

Microbiome

Transcriptome

Epigenetics

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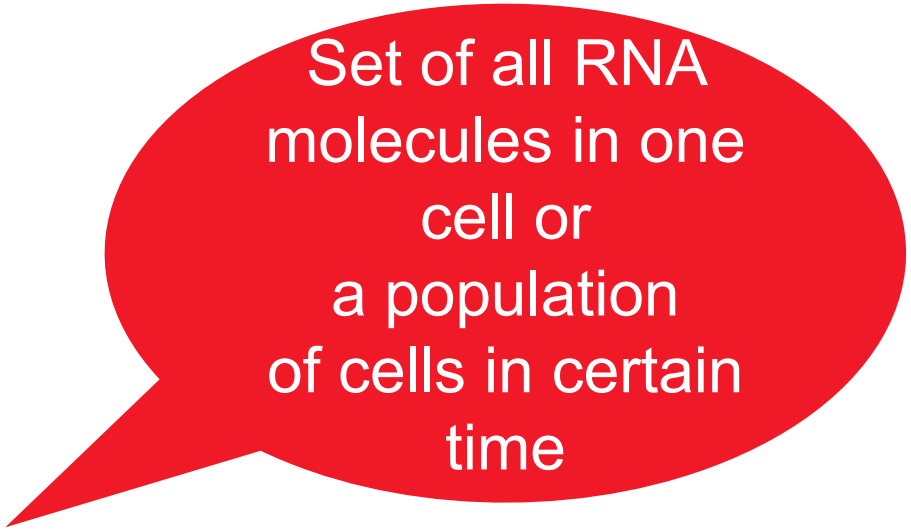

Terminology

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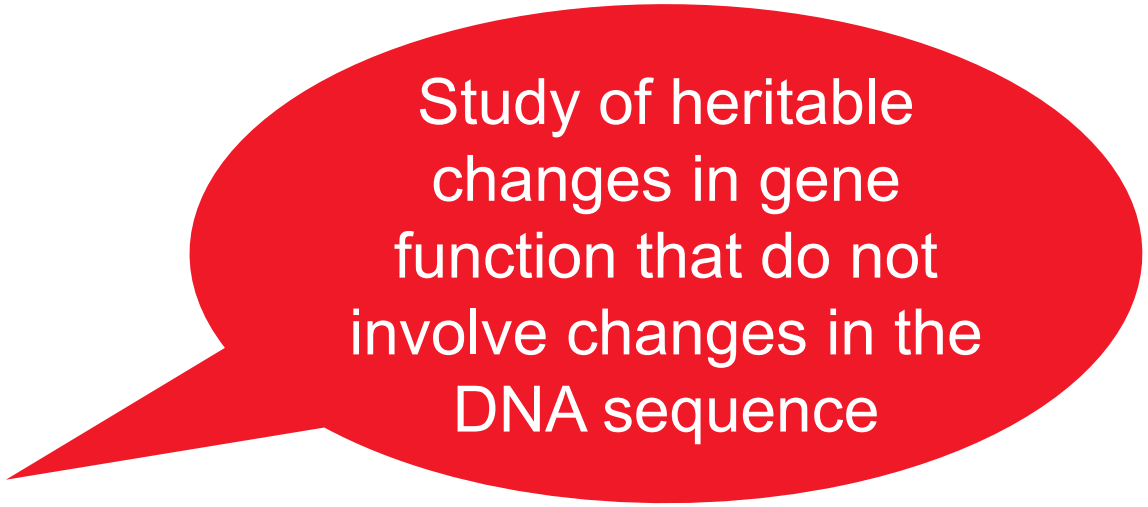
Epigenetics



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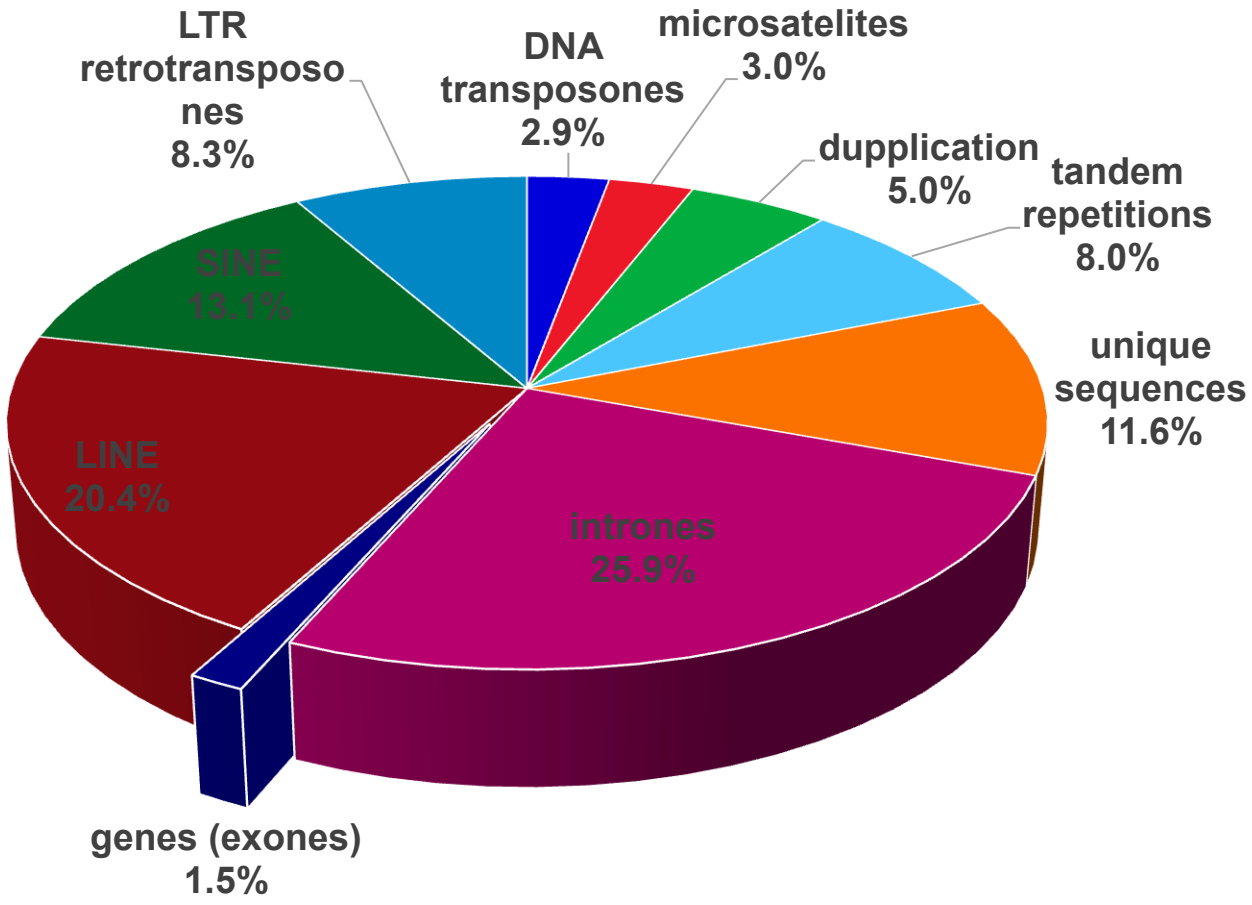
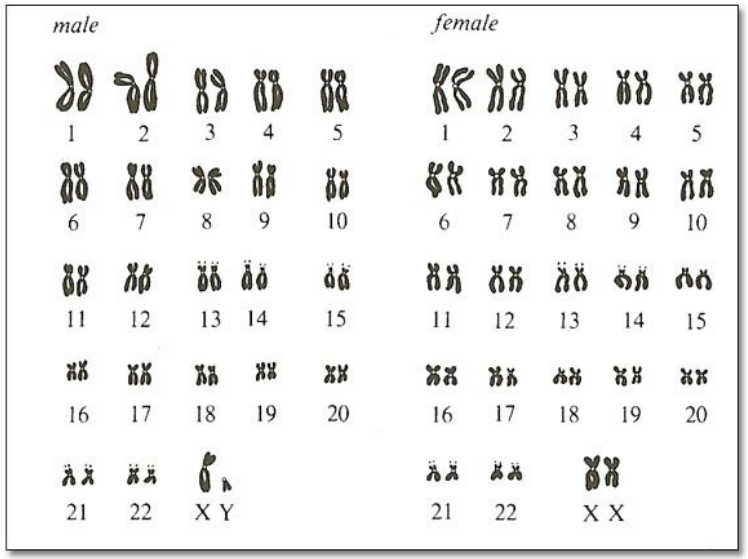
Genome





Human genome:
3.2×10^9 bp,
~ 20,000 genes

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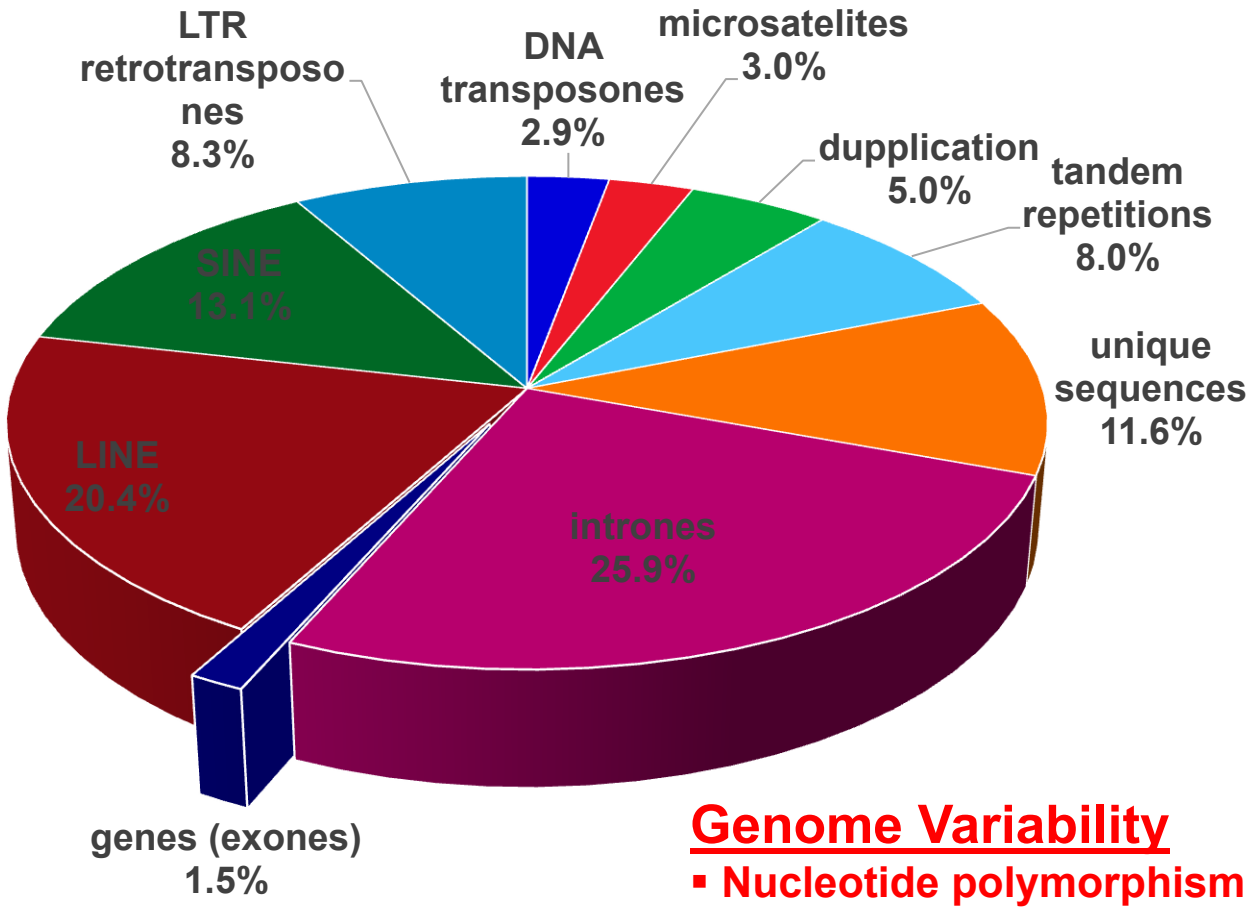
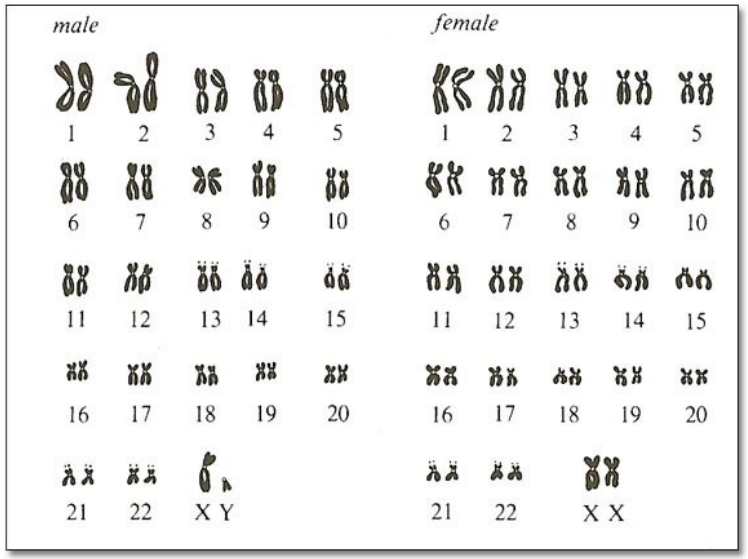
Genome





Human genome:
3.2×10^9 bp,
~ 20,000 genes

Genome Variability

- Nucleotide polymorphism
  - Single Nucleotide Polymorphisms - SNP
- Structural variations
  - Copy Number Variations – CNV
  - Short Tandem Repeats – STR (2-5)

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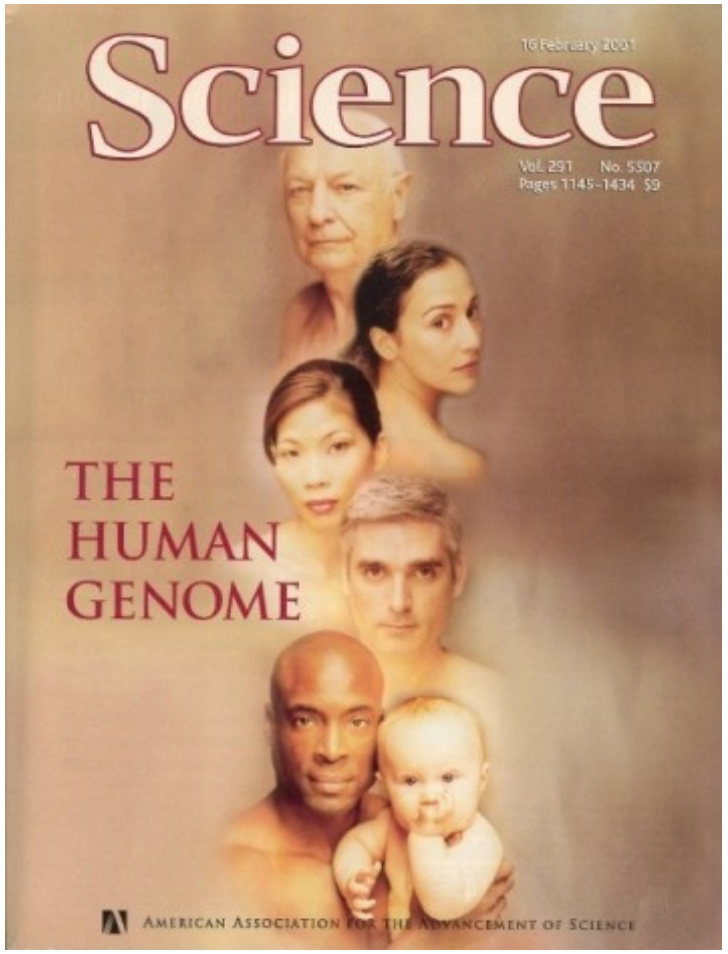
Genome



Human genome was published in 2001

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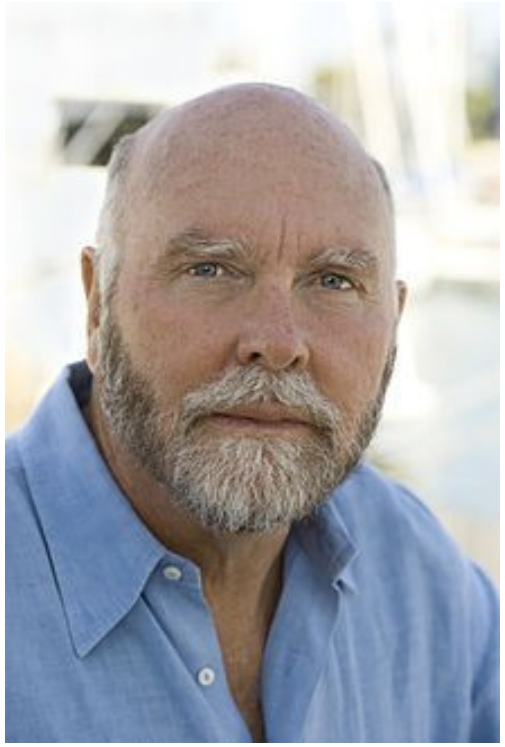
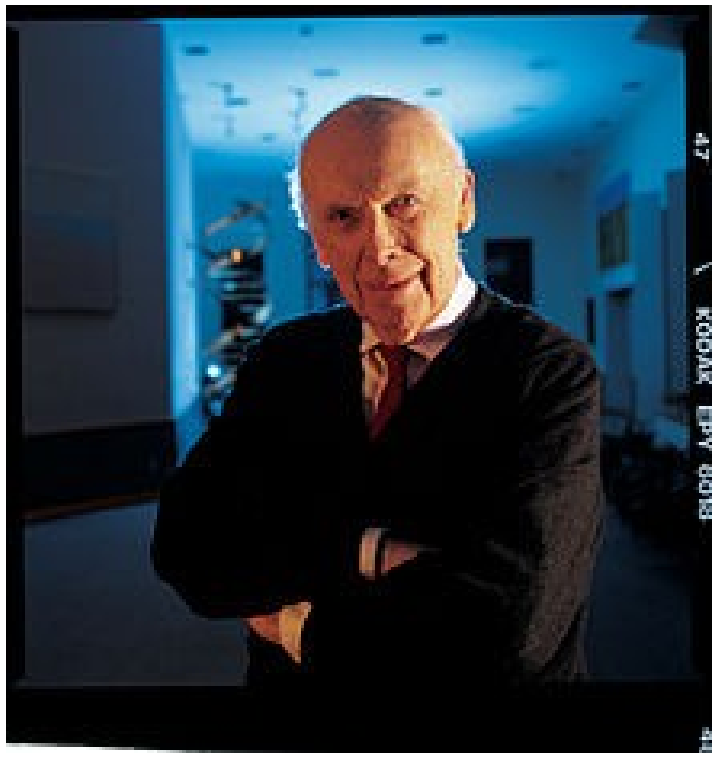
Genome



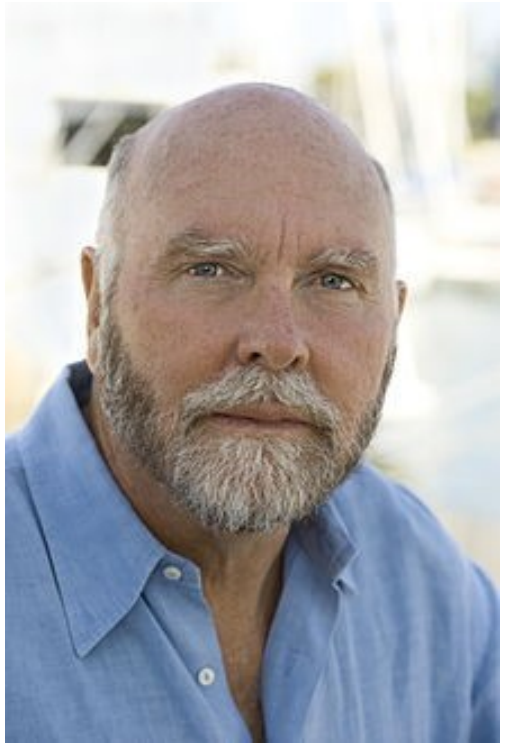
C. Venter



J. D. Watson

Individual sequences of human genomes were published in 2007 and 2008

Genome



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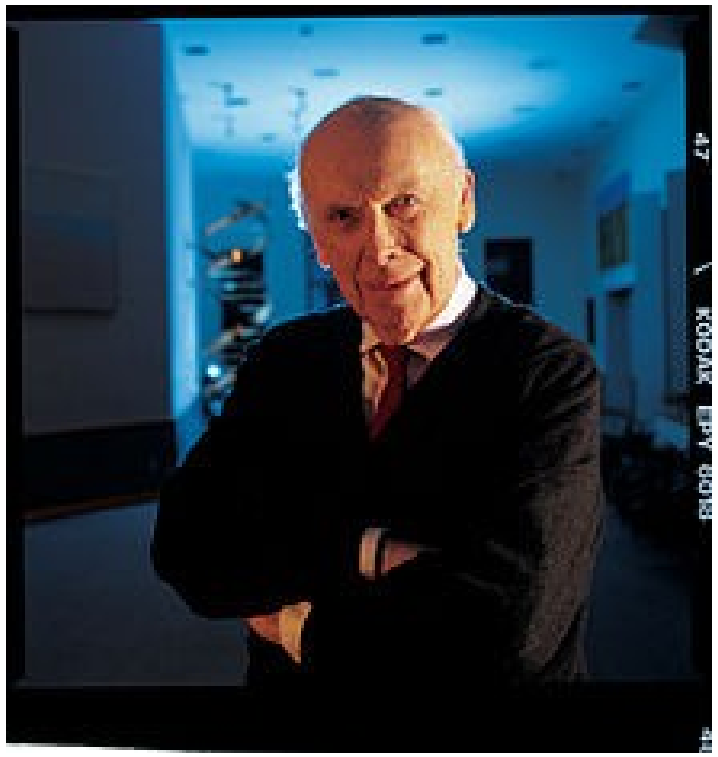
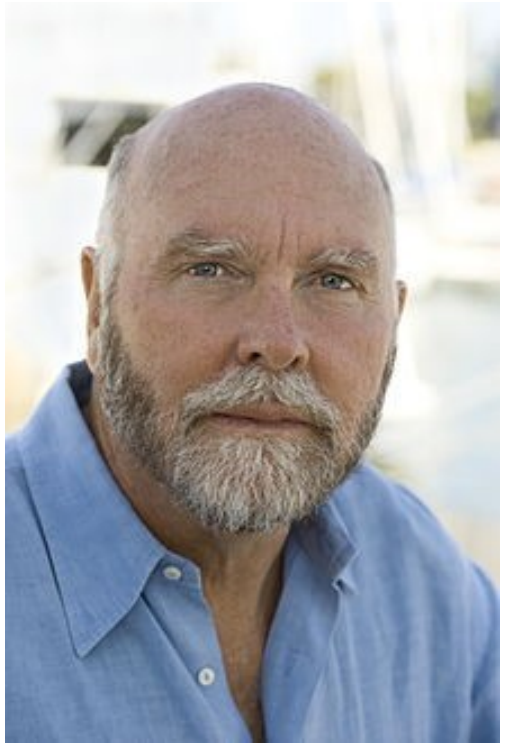


J. D. Watson

Individual sequences of human genomes were published in 2007 and 2008

Difference in 7648 amino acid substitutions

Genome



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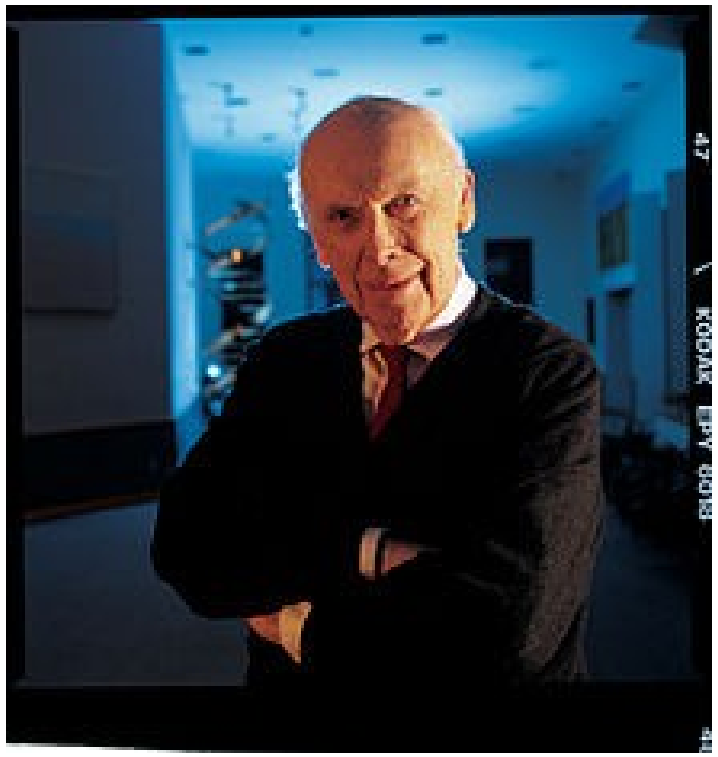
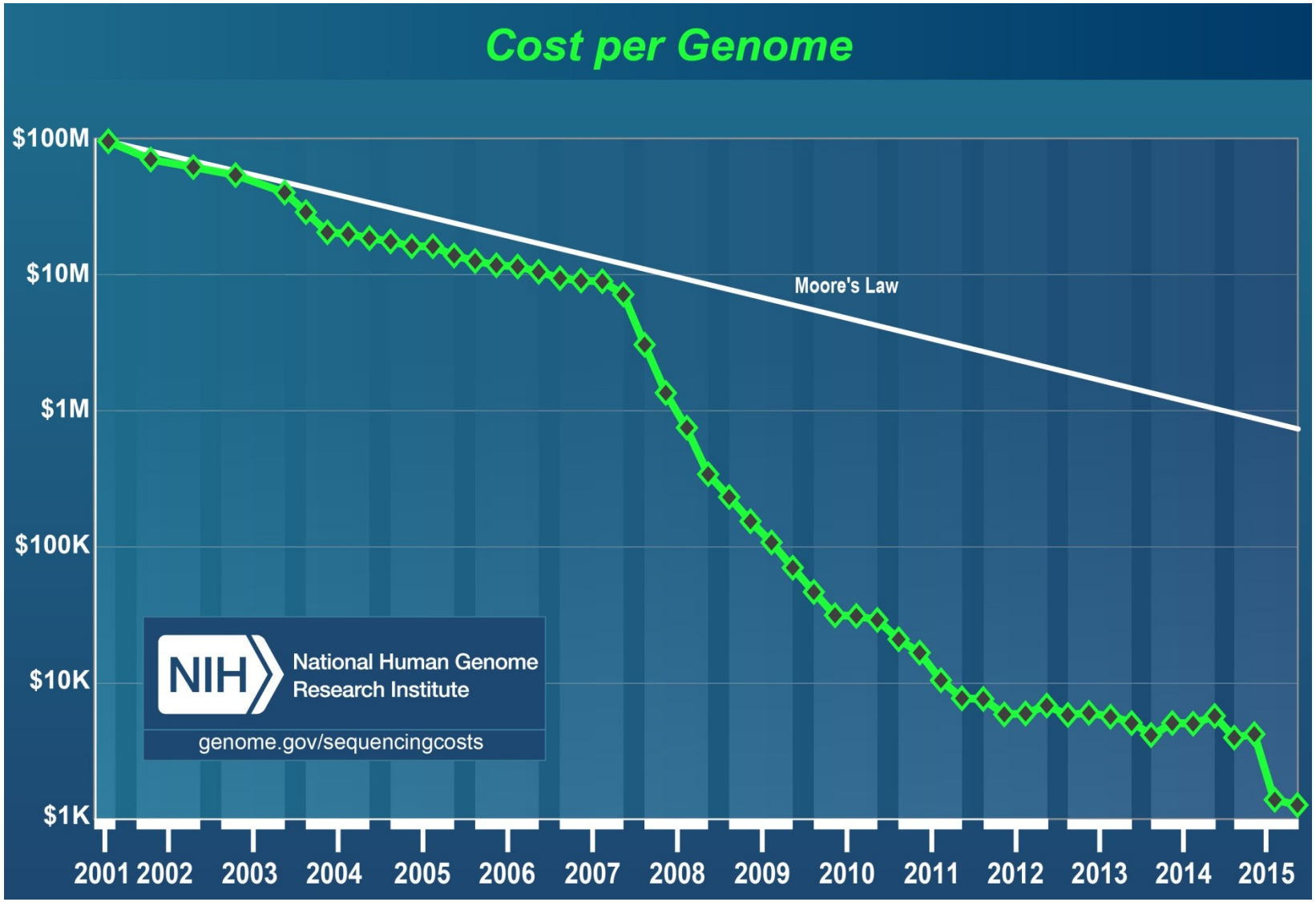


J. D. Watson

Individual sequences of human genomes were published in 2007 and 2008

The 1000 genome project published in 2010

Genome



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Postgenomic era

Genomes were described

Ongoing genomes annotations

Genetics today

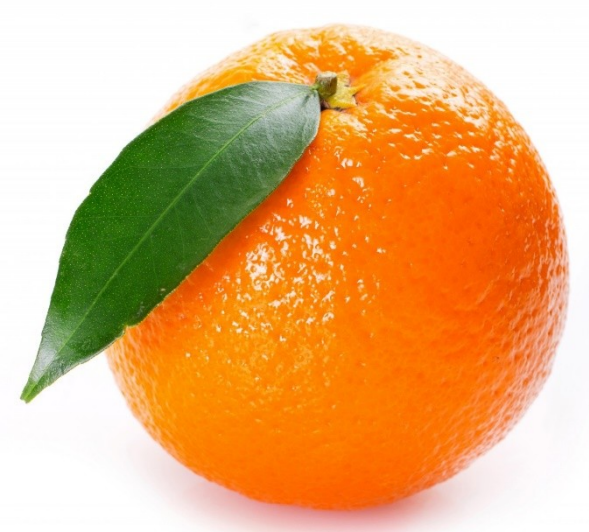
from phenotype to genotype

from genotype to phenotype

Modern techniques of genome analysis

NGS flexibility

whole genome



3 200 000 000 bp
30 x coverage

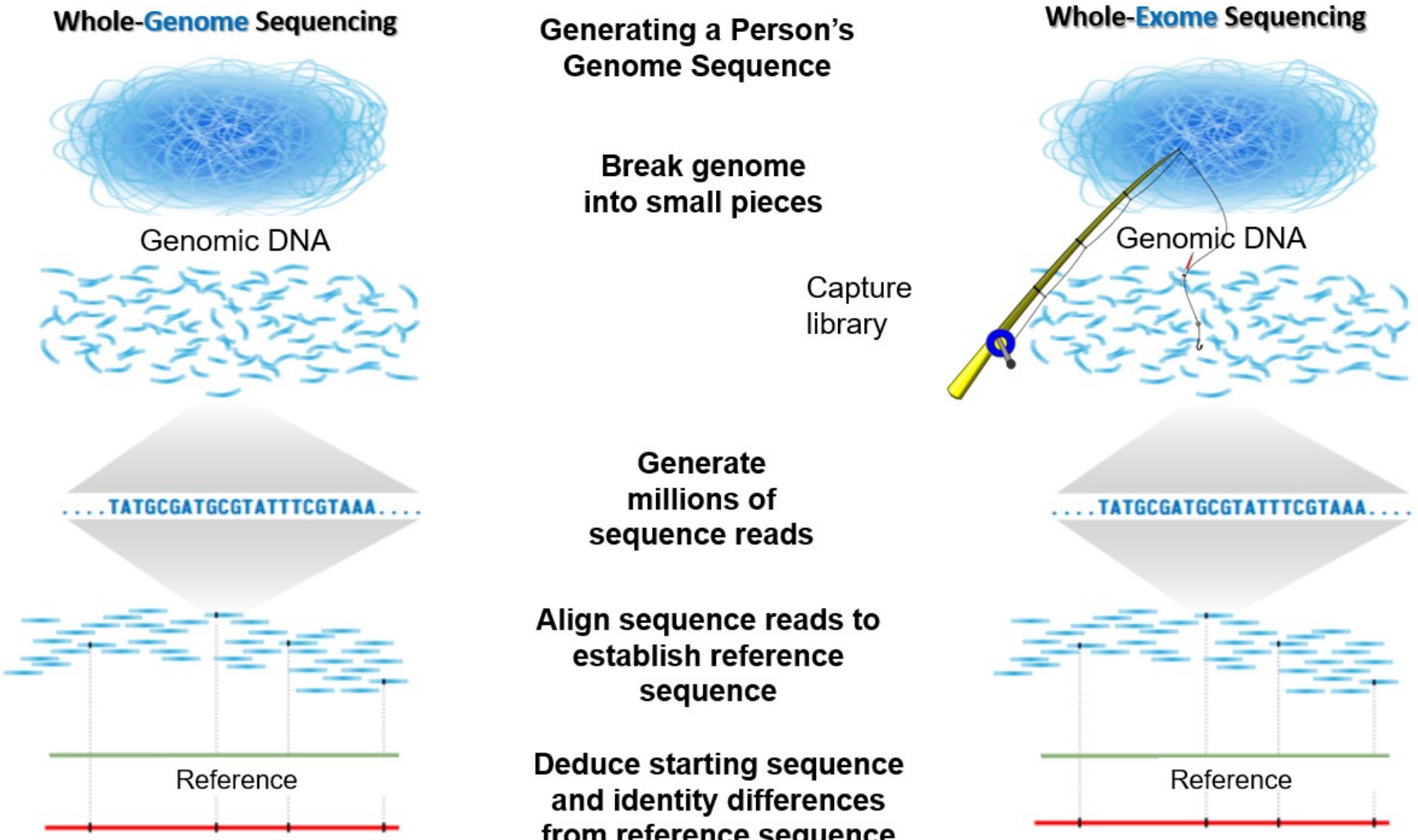
exome

20 000 genes
100 x coverage

targeted genes or hotspots

< 100 genes
≥ 1000 x coverage

Modern techniques of genome analysis



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Mutation vs. genome variability

- Every 1000th base could be mutated $\Rightarrow$ 3.2 x 10^6 variants
- One men has approx. 0.5 x 10^6 variants
- Exome analysis (1.5% of genome) $\Rightarrow$ tens thousands of variants

Which of the found variants is the disease causing one?

Mutation vs. genome variability

- Every 1000th base could be mutated ⇒ 3.2 x 10^{6} variants
- One men has approx. 0.5 x 10^{6} variants
- Exome analysis (1.5% of genome) ⇒ tens thousands of variants

Which of th mutations x polymorphisms **he disease causing one?**

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Mutation vs. genome variability

Mutations: **spontaneous** vs. **induced**

gene vs. **chromosomal**

Mutations: **missense**
nonsense (terminating triplet)
same sense
frameshift

Mutation vs. genome variability

Single nucleotide polymorphisms (SNPs)

cgcgcggcctcctccttgtggccatcctggtcctcctaaaccacctggac

cgcgcggcctcctccttgtggtcatcctggtcctcctaaaccacctggac

Insertions/deletions (indels)

cgcgcggcctcctccttgtggccatcctggtcctcctaaaccacctggac

cgcgcggcctcctccttgtgg------ctggtcctcctaaaccacctggac

Mutation vs. genome variability

Microsatelites (STR)

cgcgcggcctcctccttgtgg**cacacacacaca**catcctggtcctcctaaaccacctgga

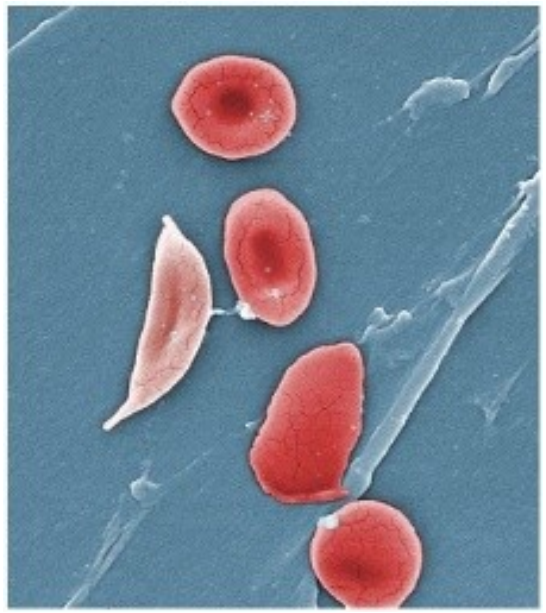
cgcgcggcctcctccttgtgg**cacacacaca**catcctggtcctcctaaaccacctgga

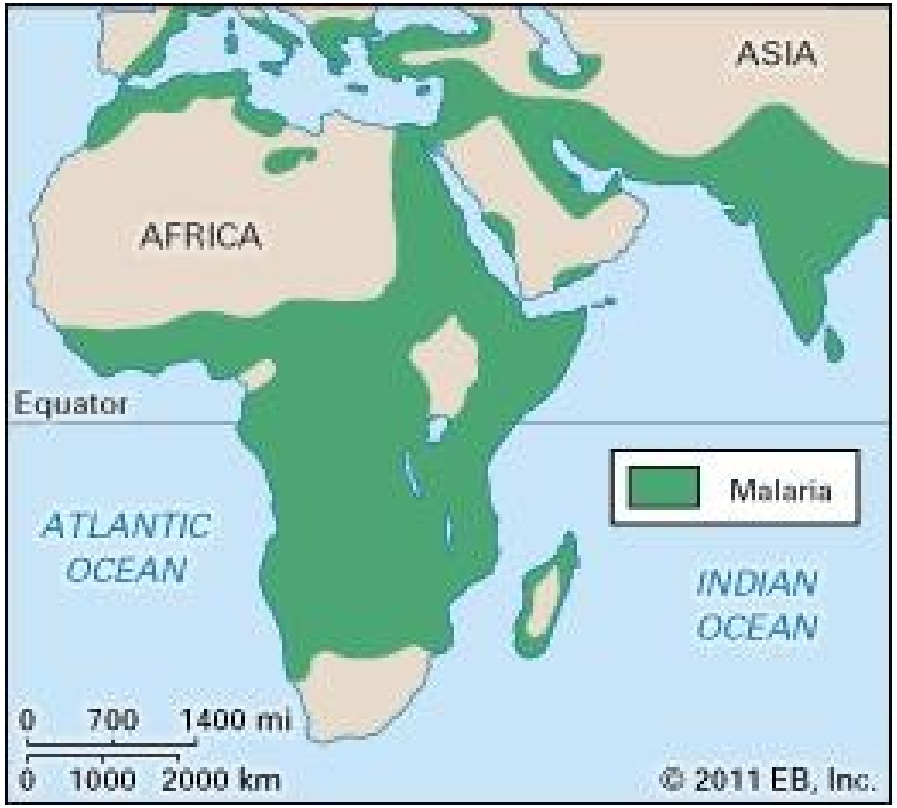
Copy number variants (CNV)

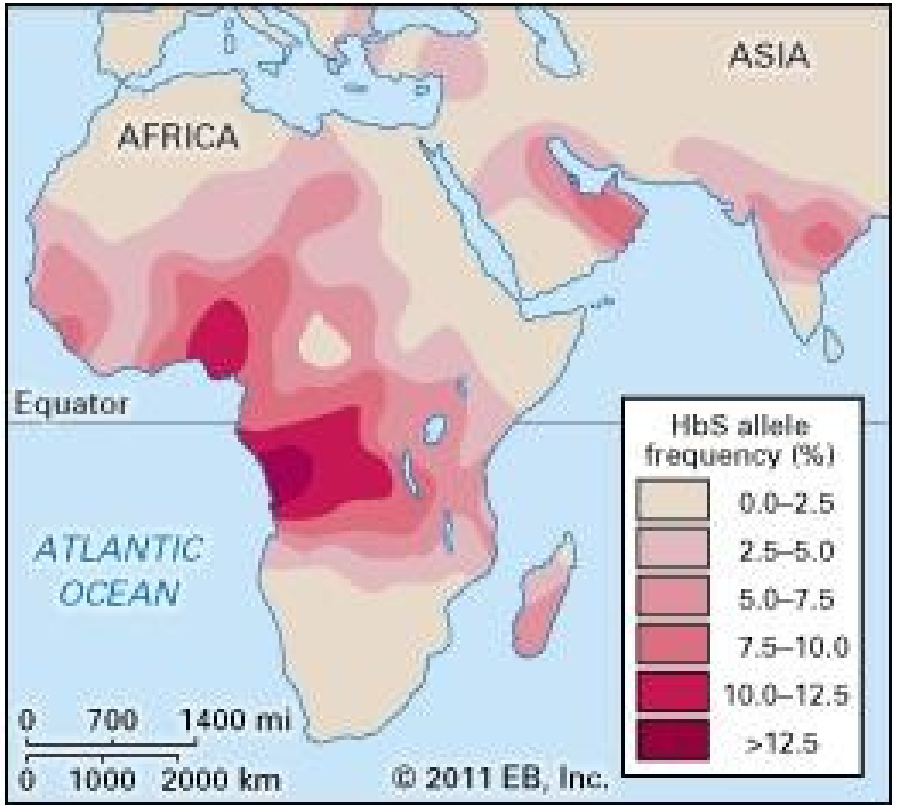
>1 kb – 1MGb

Mutation vs. genome variability

Sickle-cell anemia







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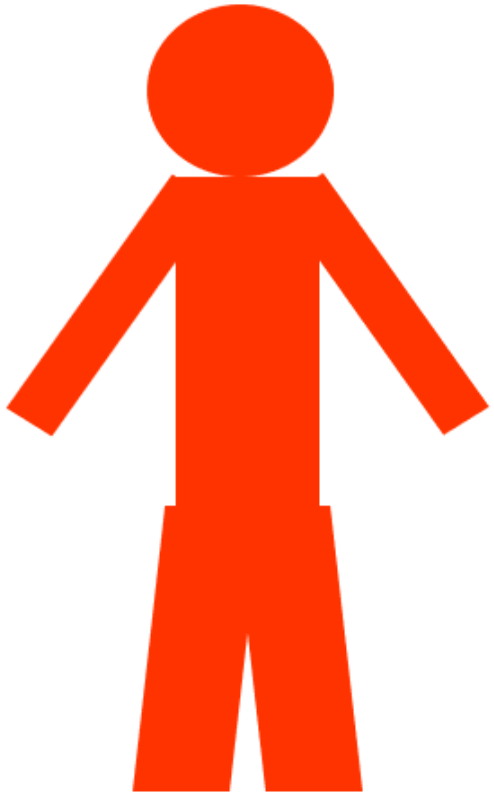
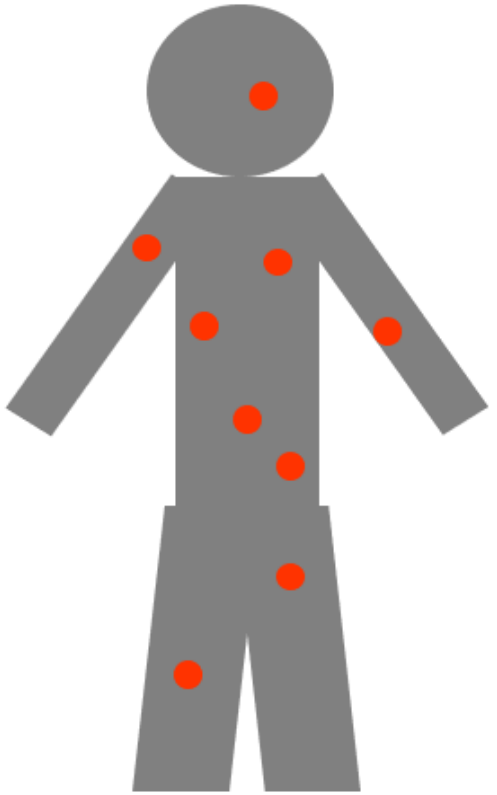
Germline vs. somatic mutations



Germline mutation



Somatic mutation

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The role of genome in the disease onset

Mendelian hereditary diseases 8%

Multifactorial 90%

Other 2%

Inheritance types

Mendelian
monogenic: one gene ⇒ one feature

X-linked and Y-linked (sex-linked disorders)

Polygenic
several genes ⇒ one feature

Mitochondrial

Environmental factors

What is the procedure of hereditary diseases tracing?

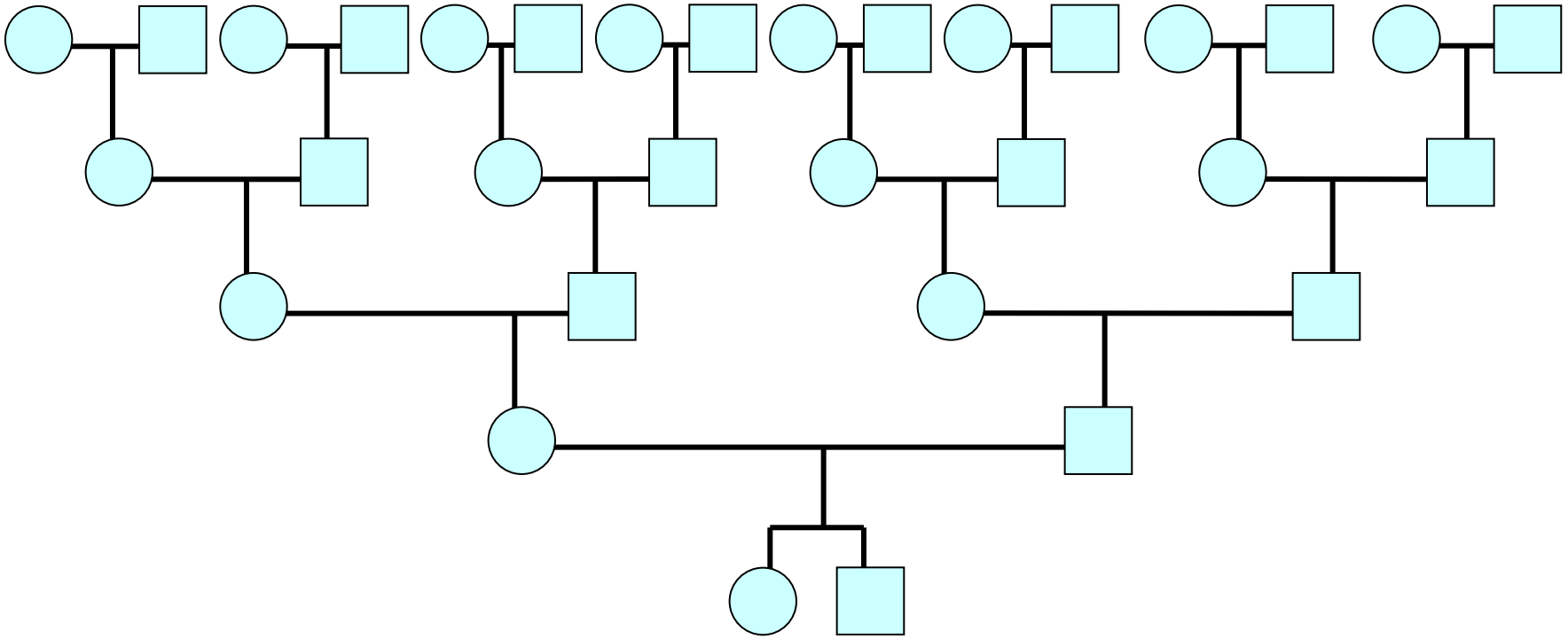
pedigree

disease frequency in population

molecular biology methods

functional tests

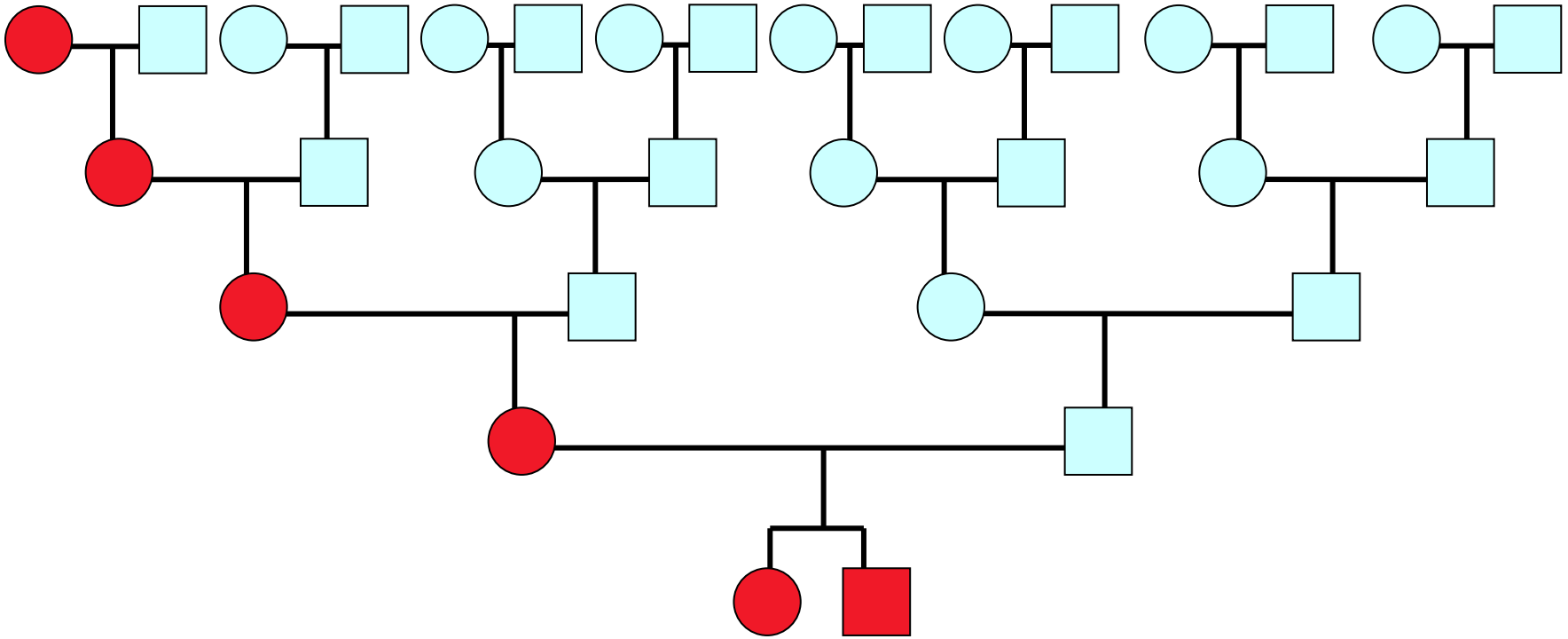
Pedigree



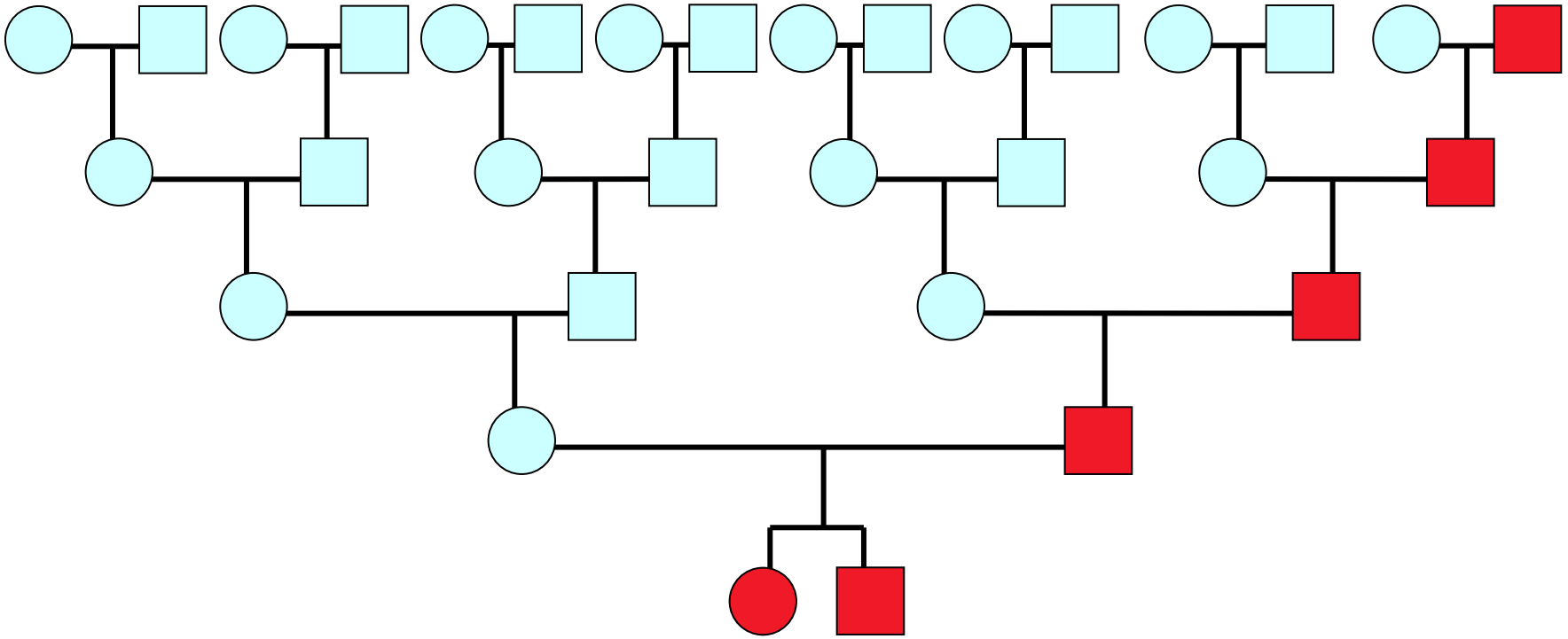
Pedigree

- two common ancestors in previous generation: parents
- 4 grandparents, 8 great-grandparents
- the number of ancestors in generation n is 2^n

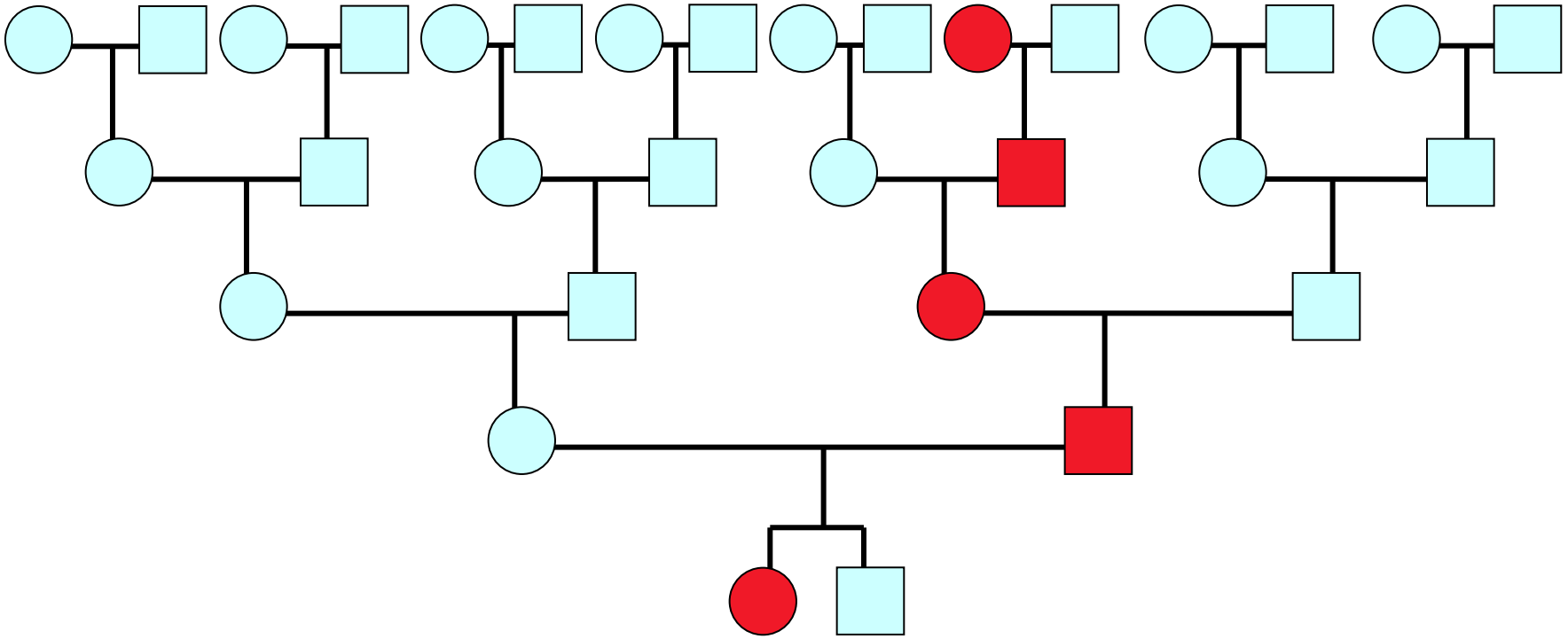
Mitochondrial inheritance



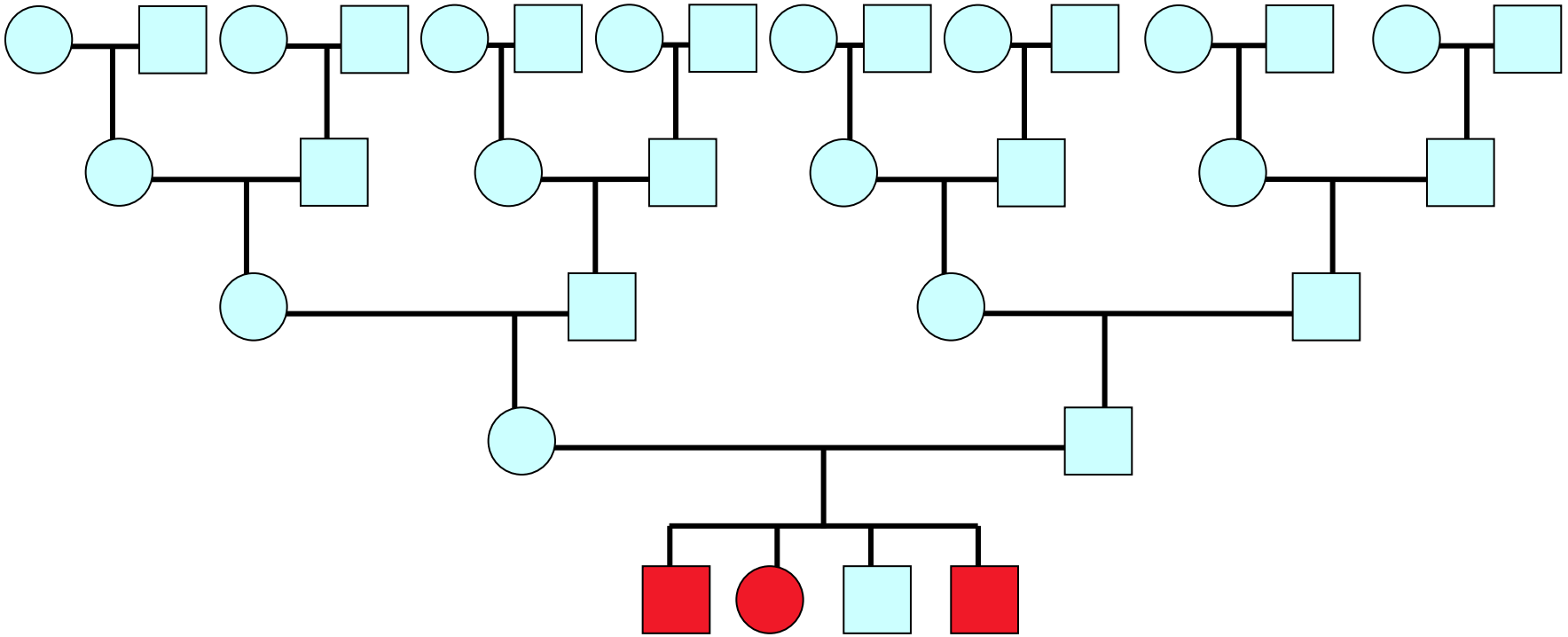
Y chromosome inheritance



Autosomal dominant inheritance



Autosomal recessive inheritance



Enviromental factors





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Monogenic disorders

Autosomal recessive disorders

hemochromatosis (1:10)

factor V Leiden mutation (1:20)

cystic fibrosis (1:25)

spinál muscular atrophy (1:40)

Autosomal recessive disorders

Founder effect

Small closed populations:

Ashkenazi Jews
franco-Canadiens
Iceland
surroundings od Maracaibo lake…

Marriages of relatives

Consanguinity

Homozygous mutation
***BLM* gene**
c.1642C>T, p.(Gln548*)

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Syndrome Nijmegen breakage, NBS

NBN gene for nibrin in 8q21
Heterozygotes 1:130-150
Common ancestor

Seemanová, 1985

Autosomal dominant disorders

Achondroplasia

Huntington chorea

Marfan syndrome

Polycystic kidneys

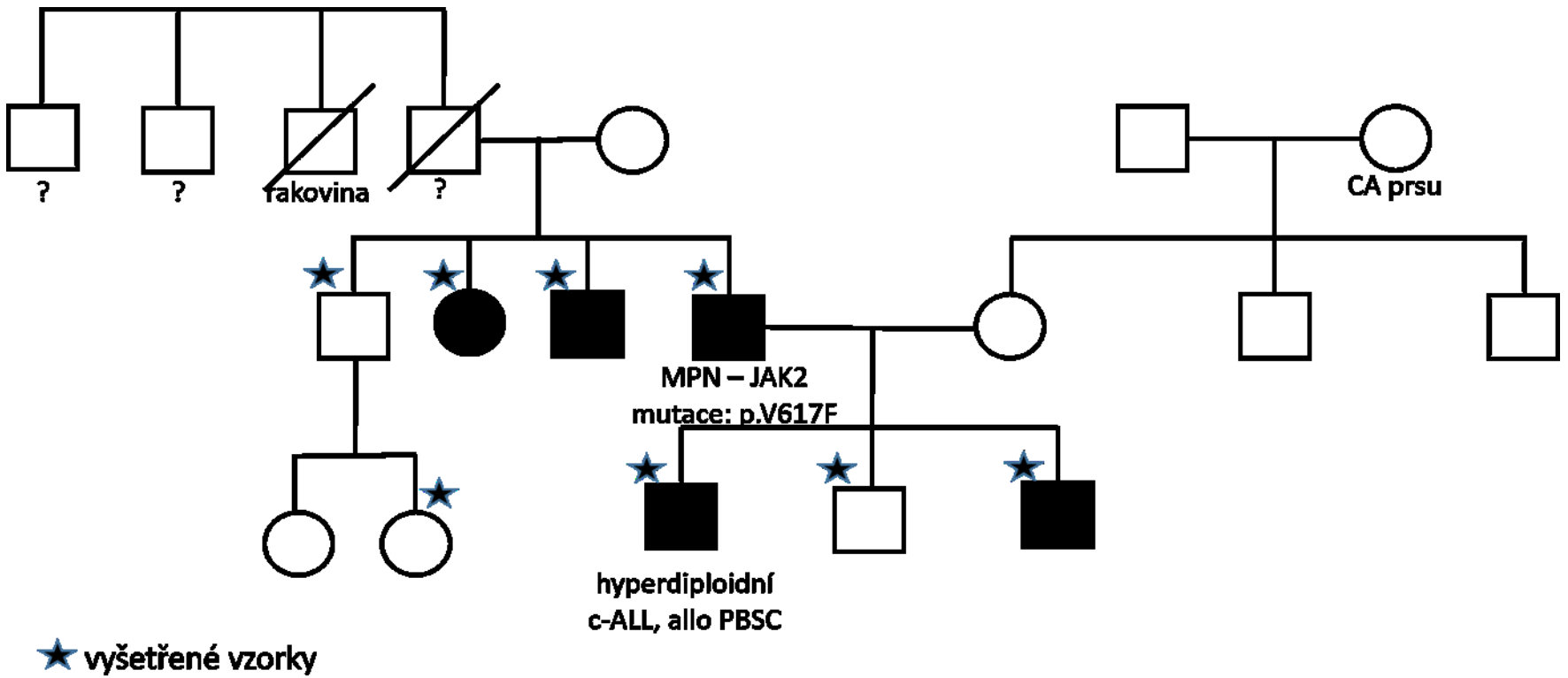
Neurofibromatosis

Gonosomal disordres

Gonosomal dominant
- vitamin D resistant rachitis

Gonosomal recessive
- hemofilia A, B
- Duchenne muscular dystrophy

Clinical case from practice



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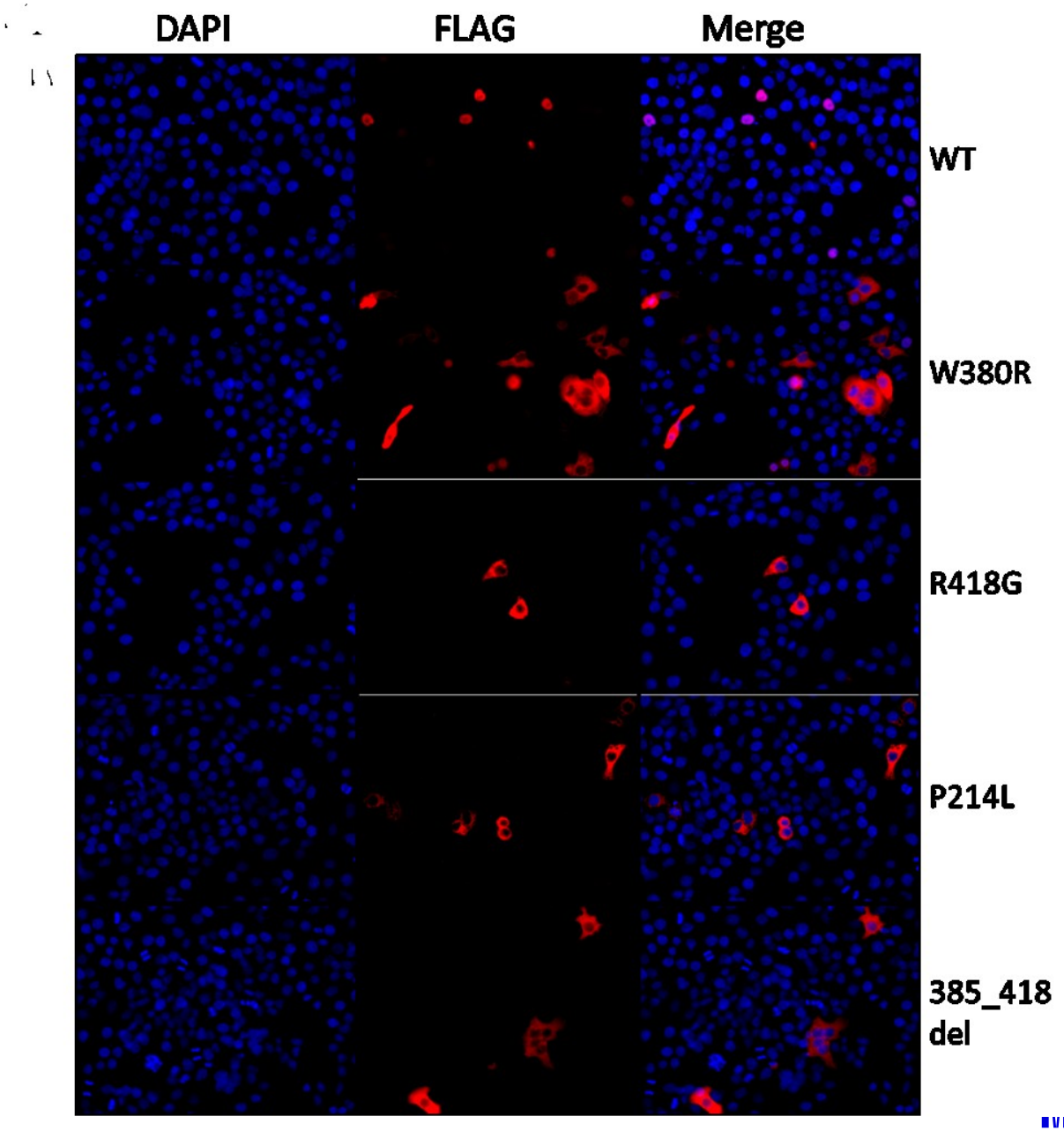
Clinical case

Functional analysis of *ETV6* :

fluorescence microscopy



What are the skills of clinical geneticist?

complex examination

gene/s analysis indication

- exome sequencing
- genome sequencing
- functional tests

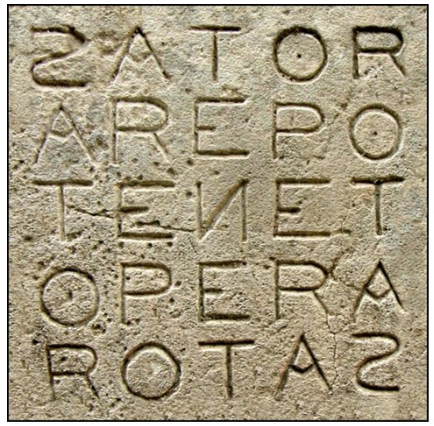
results interpretation

(from practitioners to clinical geneticists)

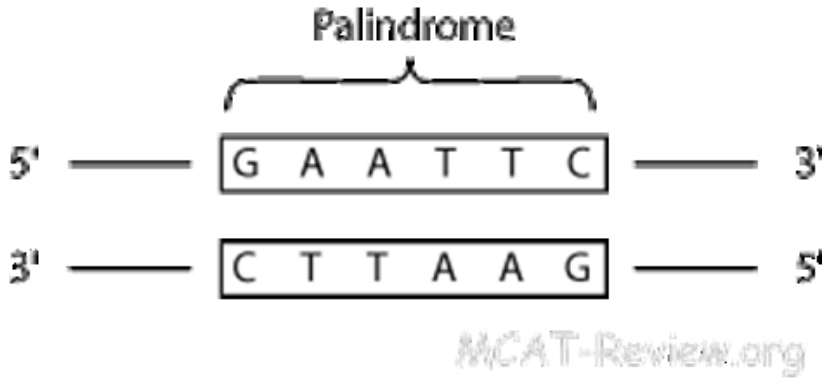
therapeutic and preventive intervenation proposal

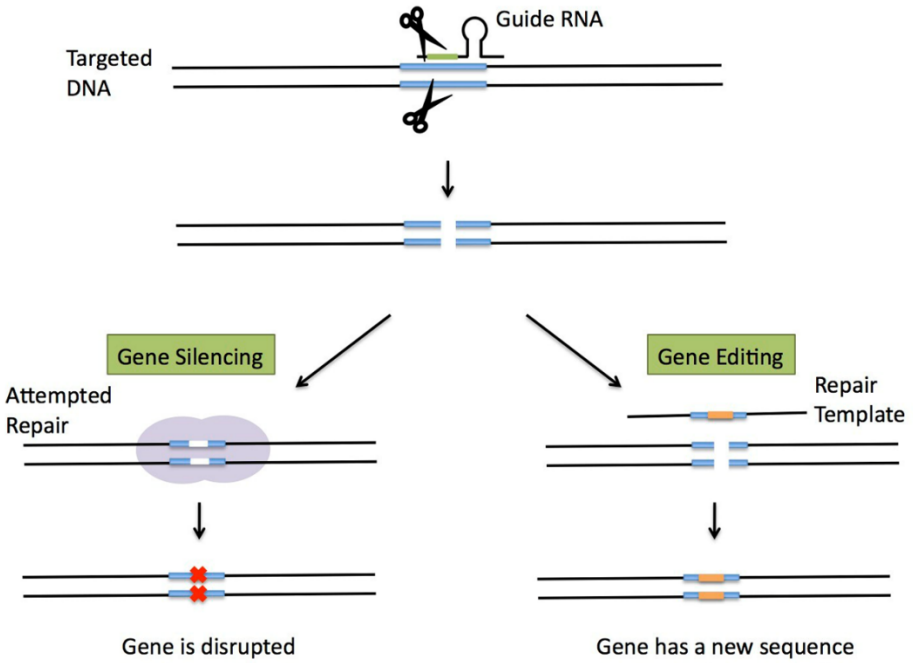
- respecting wishes of affected individuals together with ethical aspects

CRISPR/Cas9



Pompeie, 79AD





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Take home message

- The genome is all the DNA in a cell / organism
- Exome is DNA coding sequence
- We have about 20,000 genes
- Modern methods of DNA analysis make it possible to analyze whole genomes
- Human genome variability - what causes disease?
- Genetics skills
- Genome editing

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2021