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Genetics in Dentistry

Gregor Johann Mendel

Gregor Johann Mendel, 1822-84, an Augustinian monk noted for his experimental work on heredity. He entered the Augustinian monastery in Brno (Czech Republic) in 1843.
The Columbia Encyclopedia, Sixth Edition | 2008

Augustinian monastery in Brno (Czech Republic), May 2009

Mendel was the first to fashion a clear, analytic picture of heredity.

On the grounds of the abbey is the location of Mendel's garden and his green house.

Genetics (genomics) in 21 st century

⇒Hypothesis: every disease has its own genetic predisposition, close or distant

⇒Arguments:

- Every living being is fatal

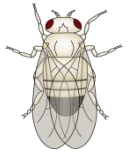
- Disease can be a state leading to death
- Ageing can be a state leading to death
- (Can be ageing considered a disease?)

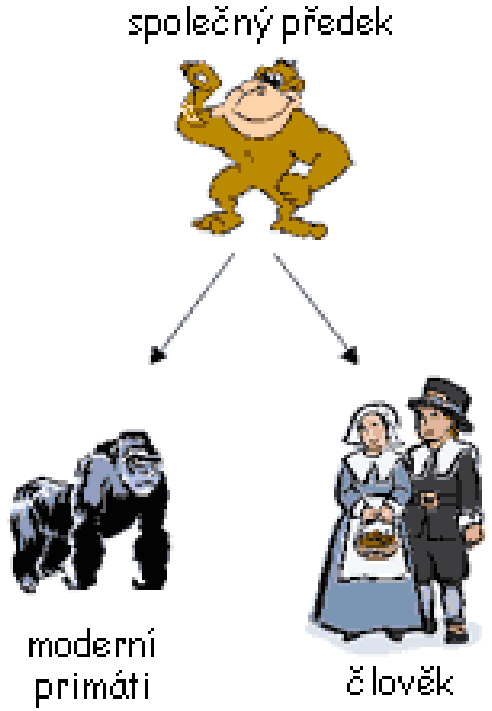
Genetics, genomics

- genetics
  - specialised biological subject focusd on variability and heritability of life beings
  - Clinical genetics- diagnostics, therapy and prevention of monogenic disorders (genetics councelling
  - Cytogenetics
    - chromosomes
  - Population genetics

genomics

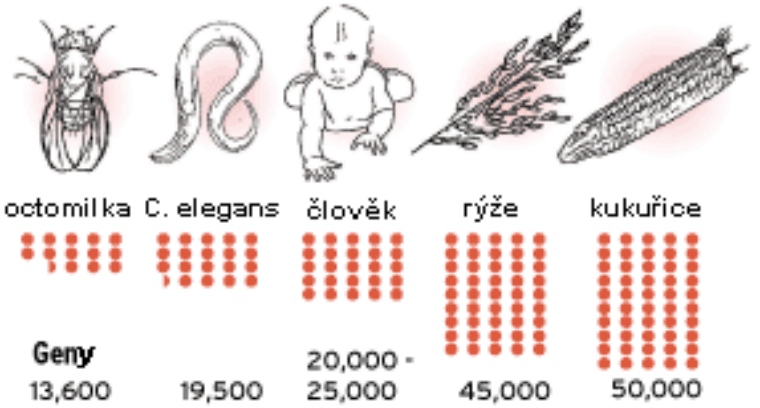
- Is focused on studies of structure and function of genome using special methods (genome mapping methods, sequencing et al.)

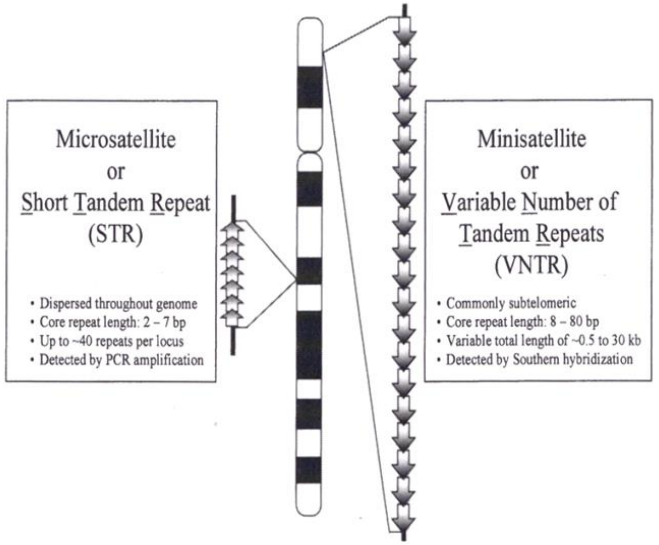




Human genome

- Human Genome Project (HUGO)
  - only ~10% -coding sequences
  - ~75% single sequences in one genome
  - Repetitive sequences
    - tandems
      - microsatelites
      - minisatelites
    - Alu-repettitions
    - L1-repetitions
- mitochondrial DNA
  - Several tens of genes coding proteins involved in mitochondrial processes
  - Only maternal heredity!





Benefit of Human Genome Project

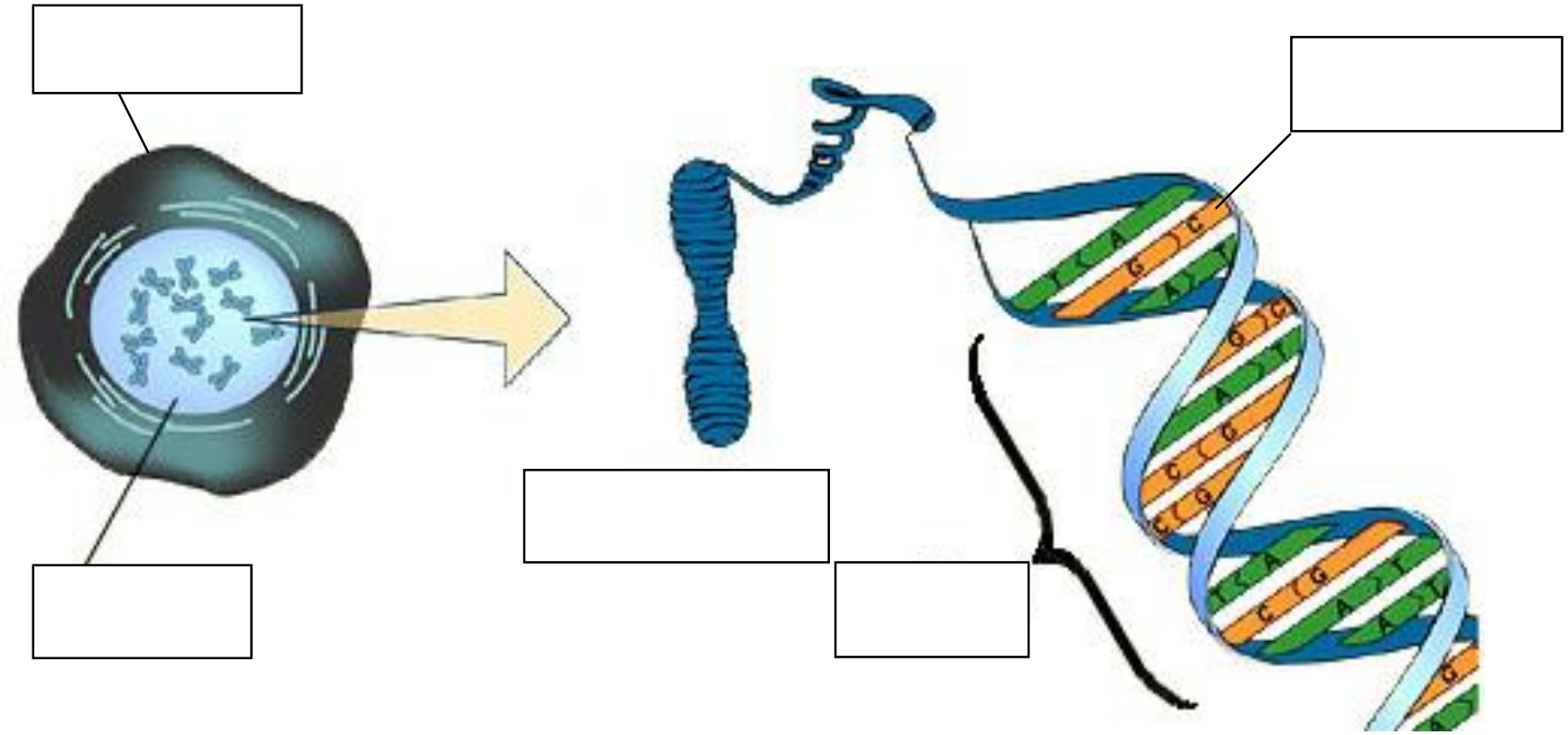
1. Faster Identification of Candidate Disease Genes:

    - Far more markers for mapping are available.
    - Candidate genes can be rapidly searched in the genome databases.
    - Mutational screens of candidate gene are greatly aided by information on the gene structure.

2. Faster Cloning of Genes of Interest by Homology Search in Genome Database:

    - Comparative Genomics
    - e-Cloning

Label IT



How many chromosomes are in a normal adult human cell?

23

23 pairs

46

46 pairs

Match IT

Gamete	A structure that is made of DNA and is found in the nucleus
Chromosome	Where a characteristic is expressed if both copies are present
Gene	Sex cells such as sperm and egg
Genotype	The alleles present
Phenotype	A small section of DNA
Dominant	Where an allele is always expressed even if only one is present
Recessive	The two alleles are different Bb
Allele	Different form of the gene
Homozygous	The alleles that are expressed
Heterozygous	The two alleles are the same e.g. BB or bb

Match IT - Answers

Gamete	Sex cells such as sperm and egg
Chromosome	A structure that is made of DNA and is found in the nucleus
Gene	A small section of DNA
Genotype	The alleles present
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Allele	Different form of the gene
Homozygous	The two alleles are the same e.g. BB or bb
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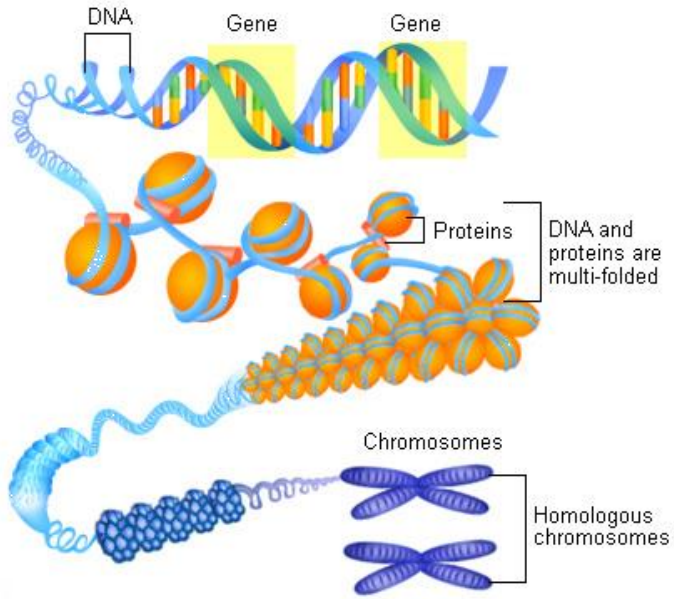
Basic terminology

- **gene, allele, genome, chromosome**

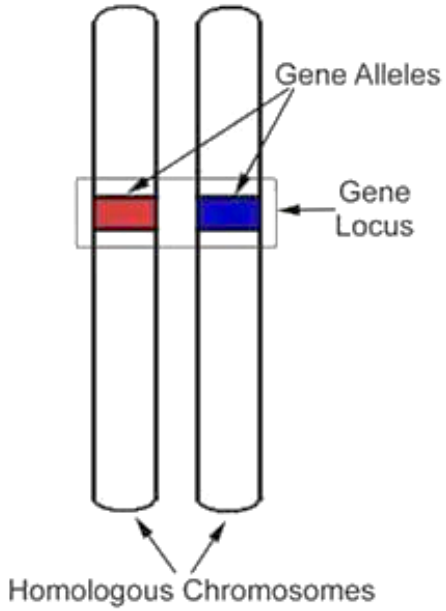


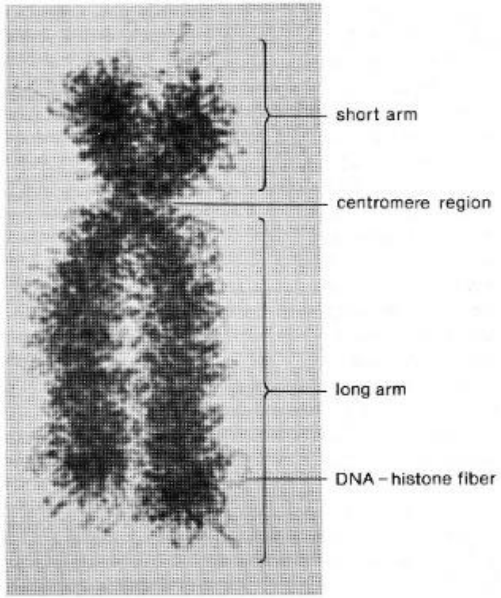
- locus
- allele

- dominant
- recessive

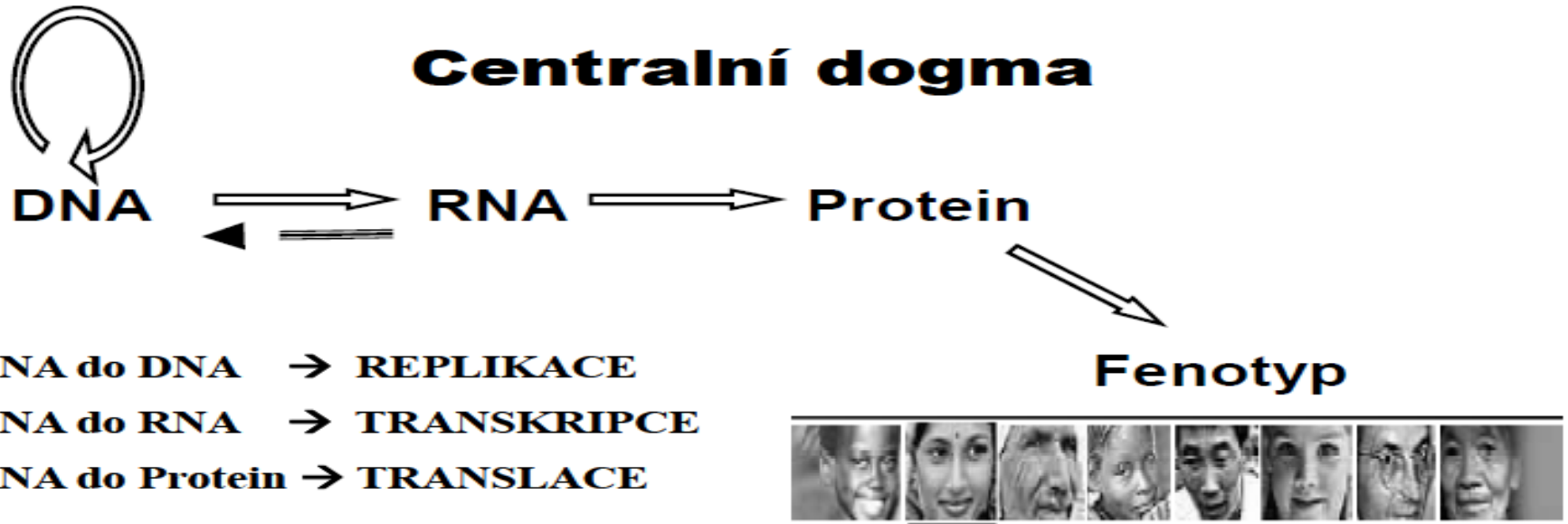
- homozygote
- heterozygote

- genotype
- phenotype



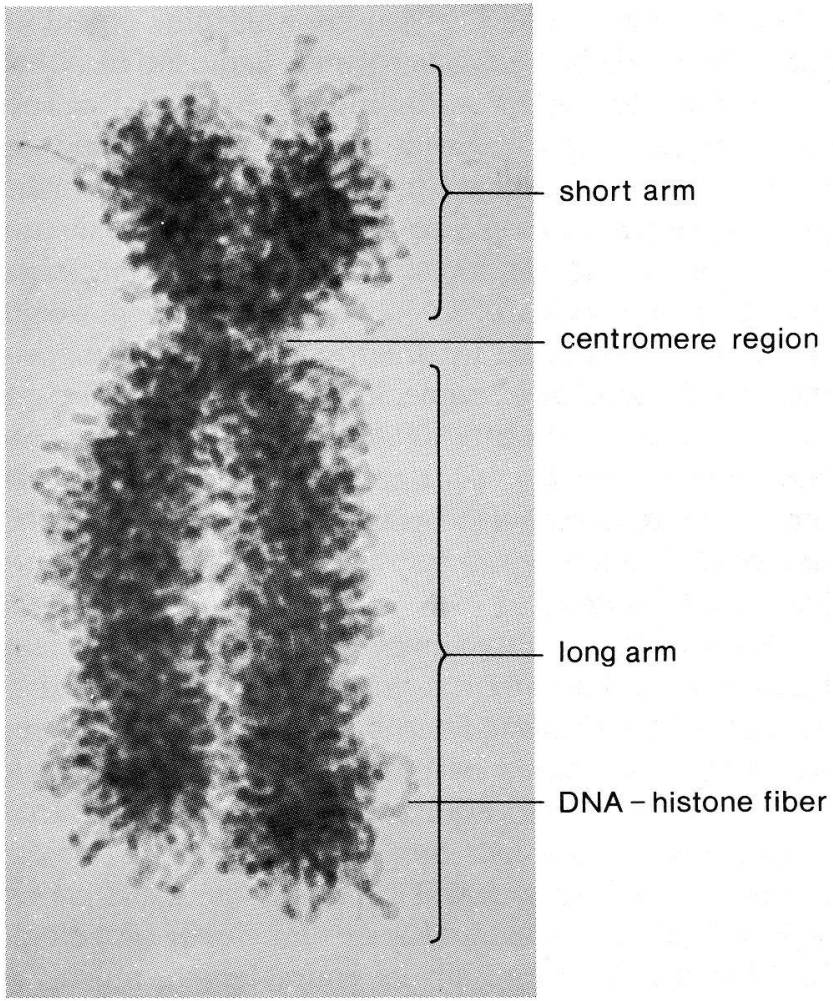


Dogma of molecular biology



Jeden gen jeden enzym (protein/polypeptid)

Human chromosomes



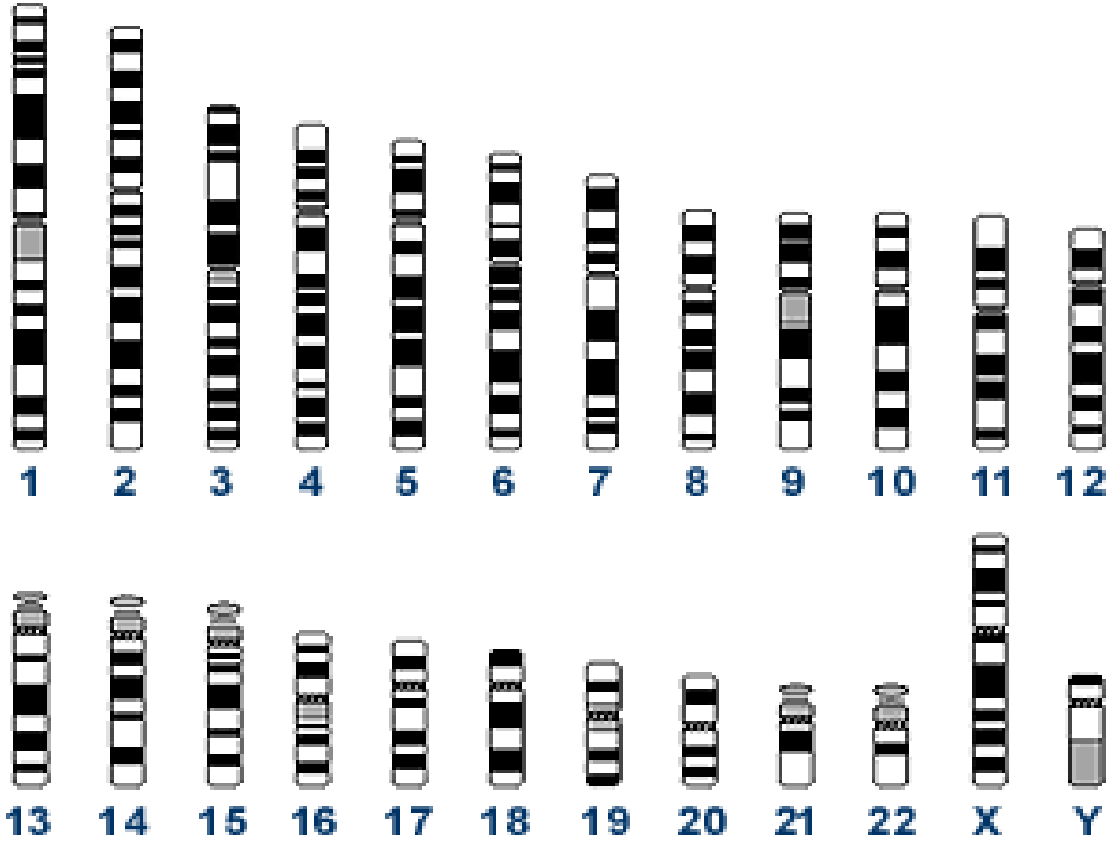
- morphologically detected only during mitosis and/or meiosis when they are condensed

- in diploid human cells - 23 pairs of homologic and 2 sex chromosomes

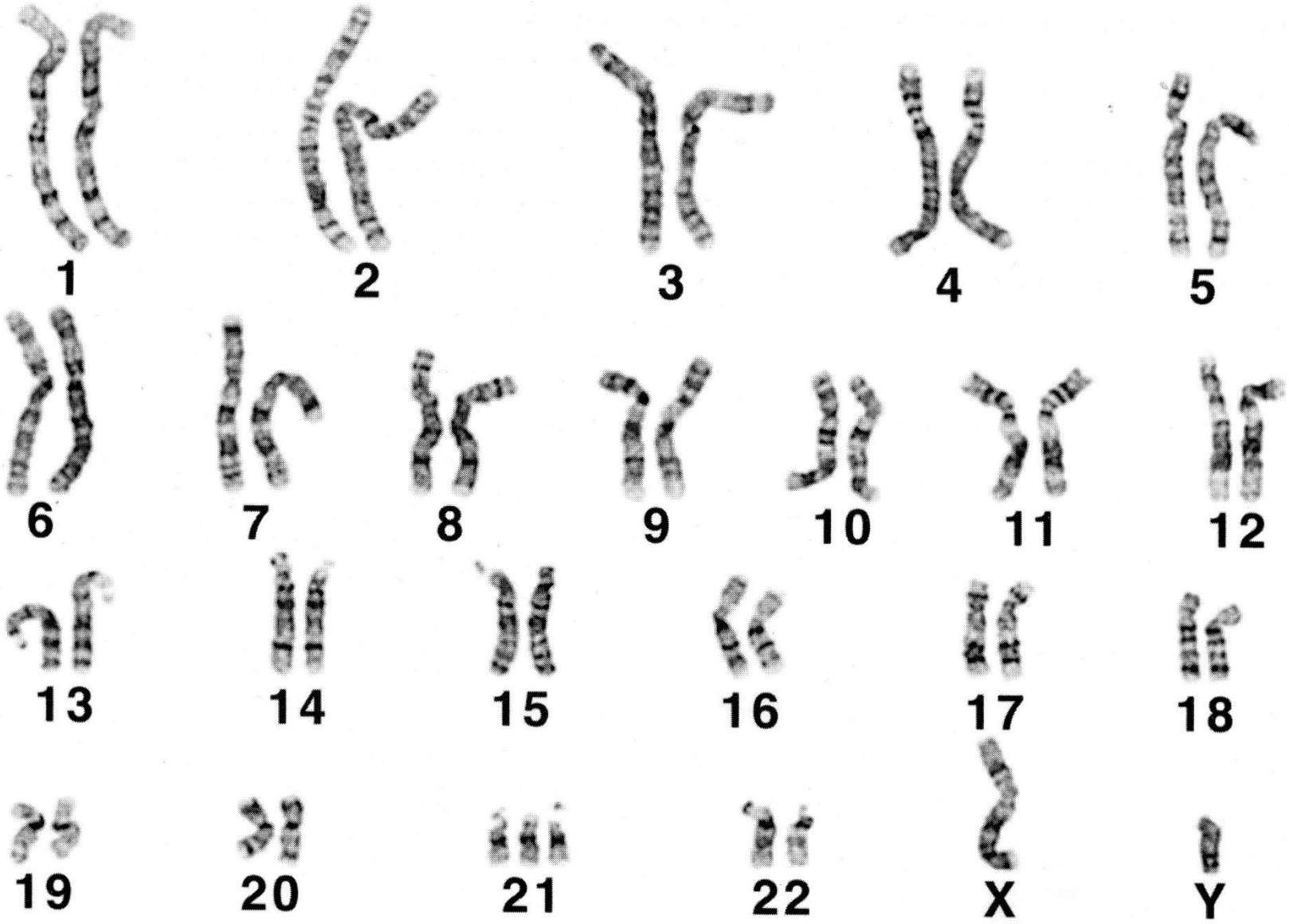
Human karyotype

- 44XX nebo 44XY
- Germ cells (egg, sperm cell)– **haploid**

- Structure of chromosomes
- centromere
  - telomers
  - long – q
  - short – p

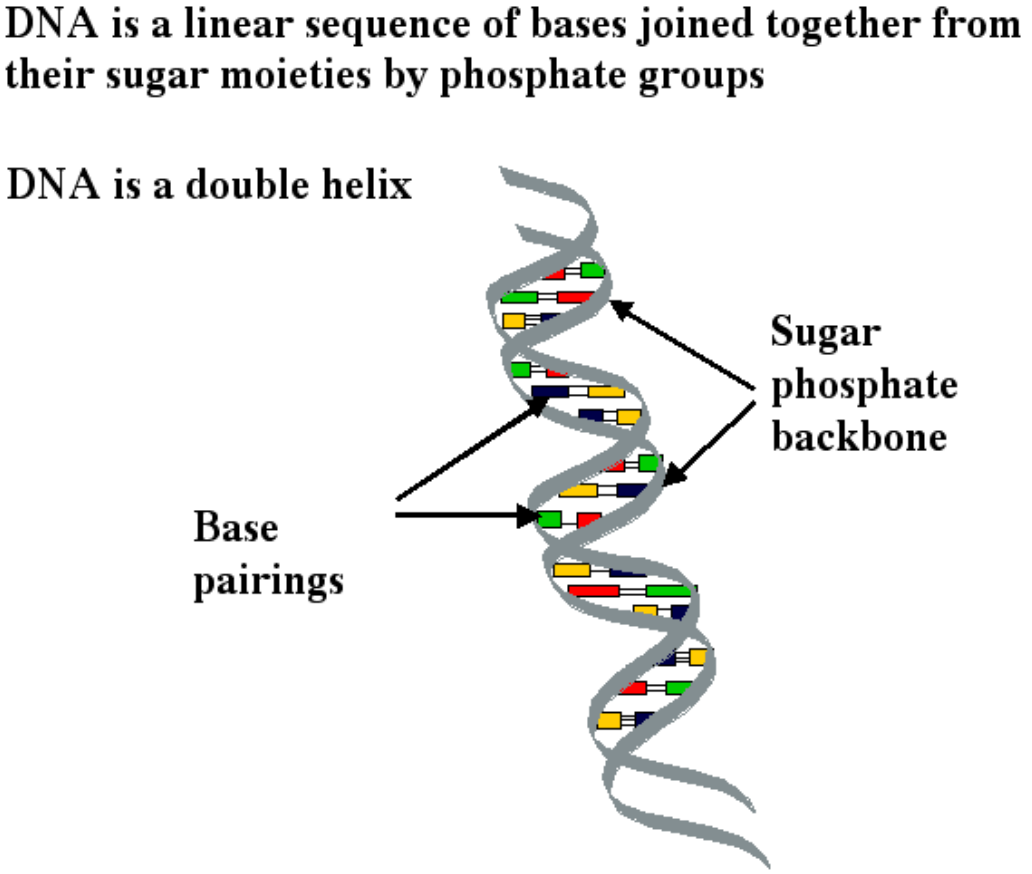


Karyotype according to the Denver´s classifications



Synthesis of DNA in animal cells

- DNA is stored in form of chromosomes.
- Each chromosome contains 2000 origins of replication. From each this place synthesis of DNA can be realized in both directions.



Multiple choice quiz

Get IT

What is a gene?

Something you get from one parent

A small section of DNA

You have 23 pairs in the nucleus

All of them

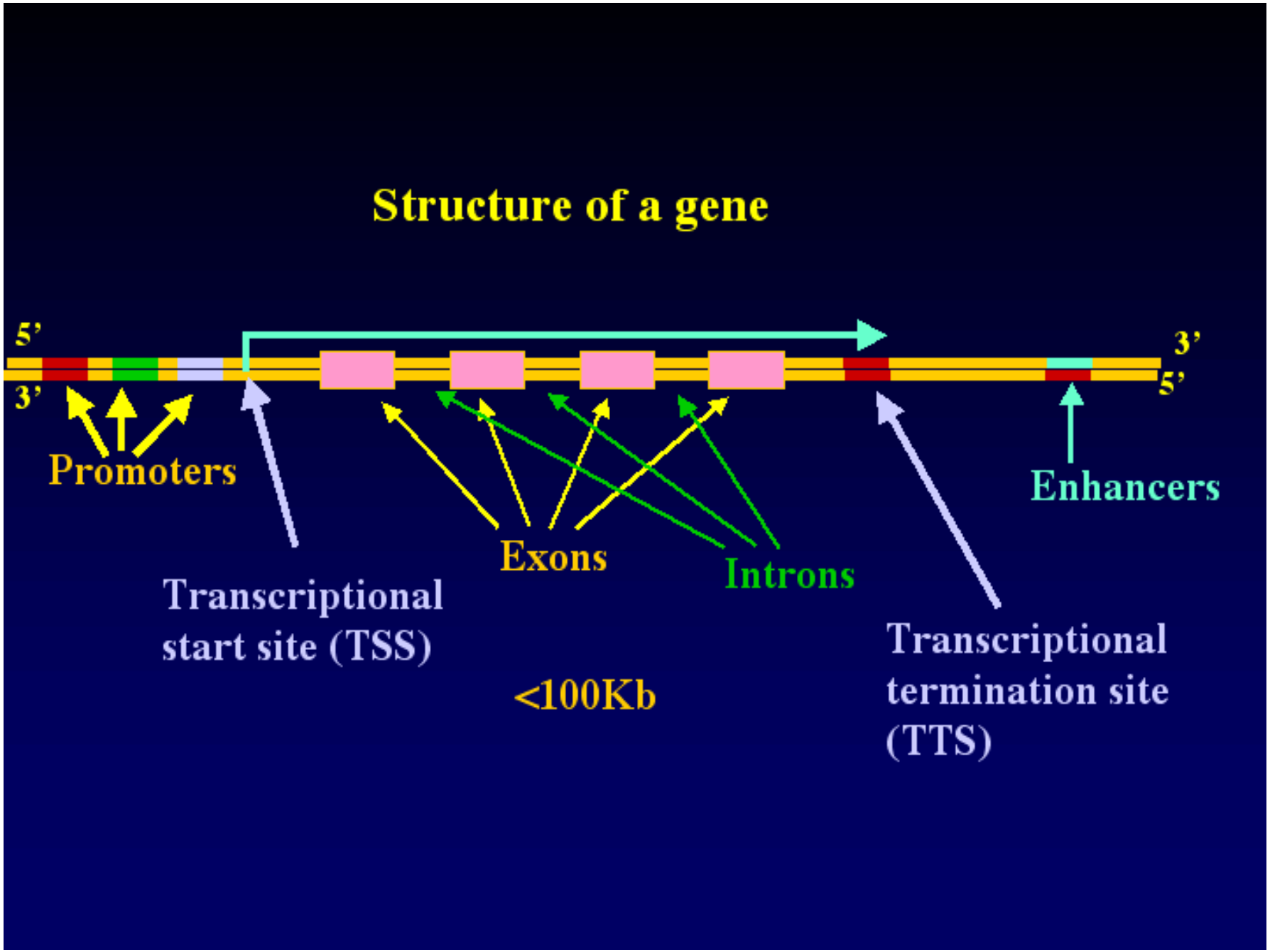
Which pair of alleles represent homozygous?

BB

Bb

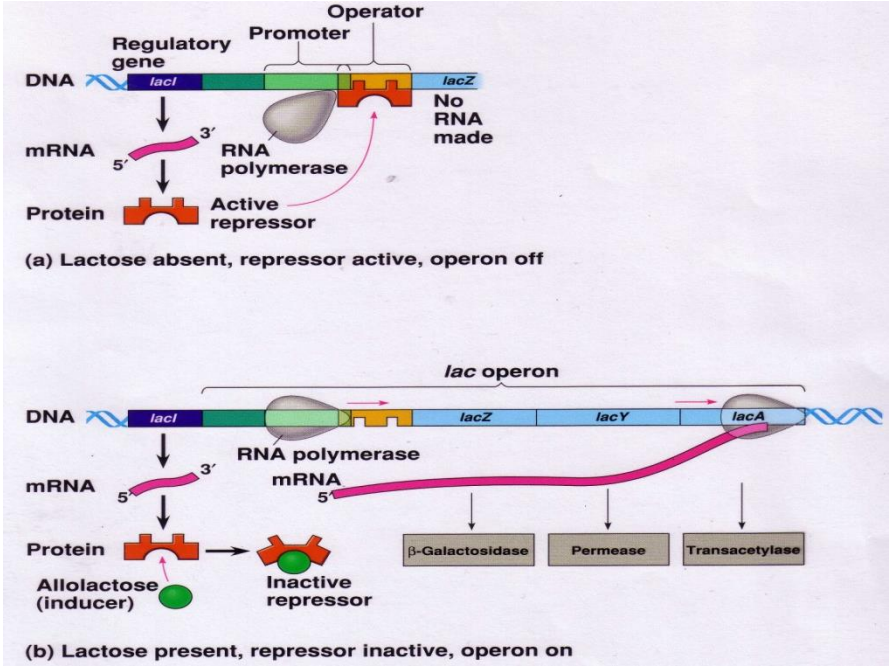
bb

bB


Structure of a gene
5'
3'
3'
5'
Promoters
Transcriptional start site (TSS)
Exons
Introns
Enhancers
<100Kb
Transcriptional termination site (TTS)

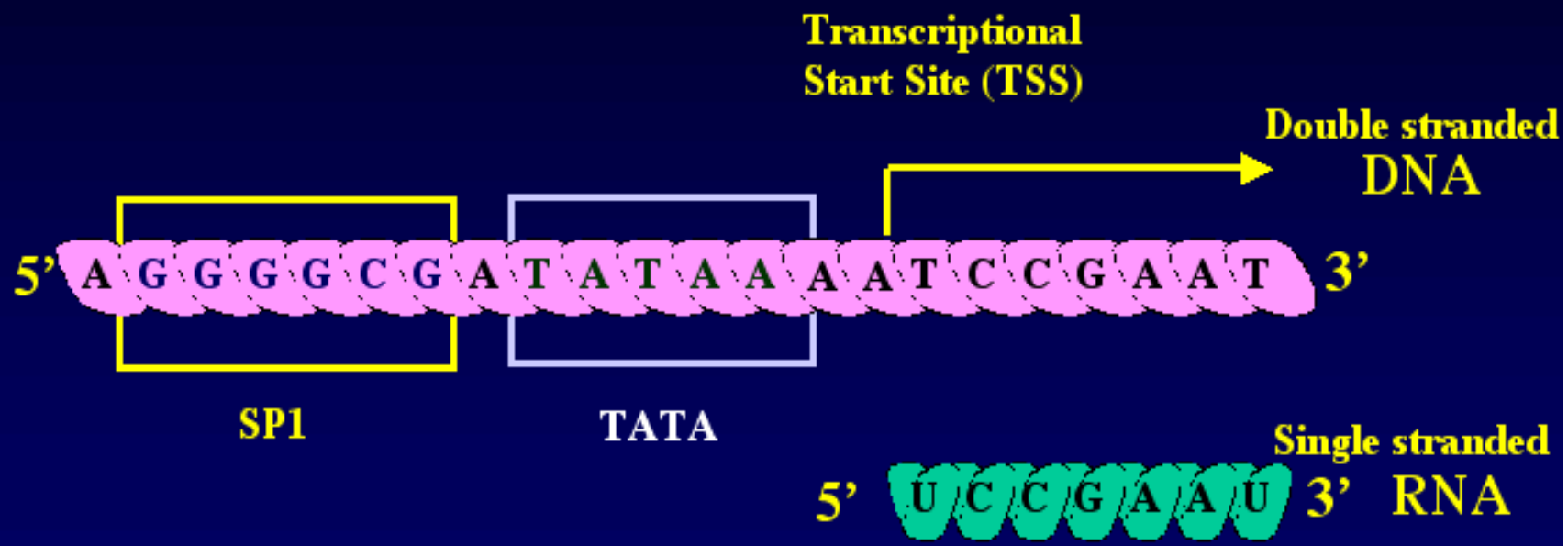
INTRONS AND EXONS

- **Eukaryotic DNA differs from prokaryotic DNA it that the coding sequences along the gene are interspersed with non-coding sequences**
- **The coding sequences are called**
  - **<u>EXONS</u>**
- **The non coding sequences are called**
  - **<u>INTRONS</u>**



Promoters

DNA sequences that are recognised by transcription factors
Transcription factors bind to this region and then start transcribing the DNA immediately downstream (5'-3')



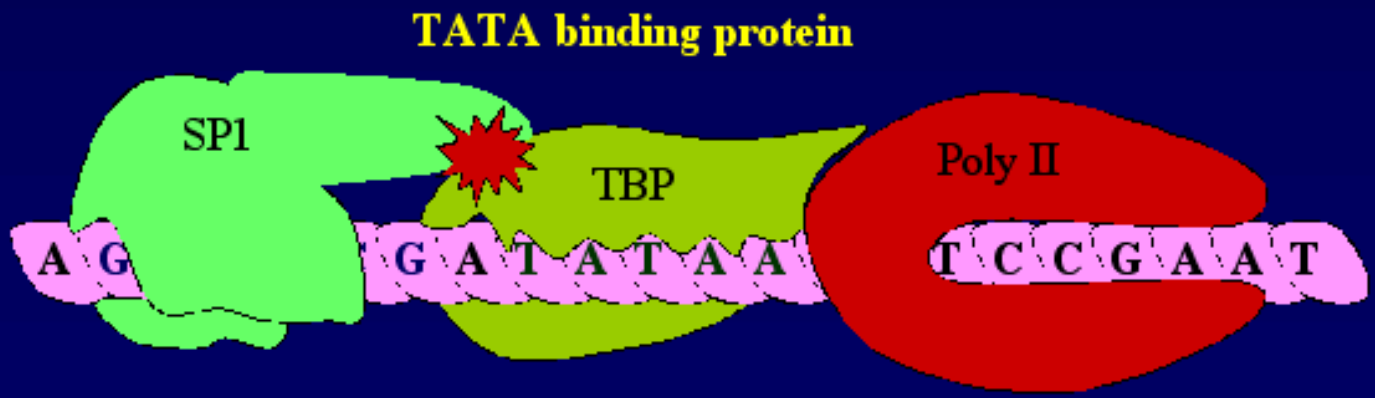
Transcription Factors

General Transcription Factors

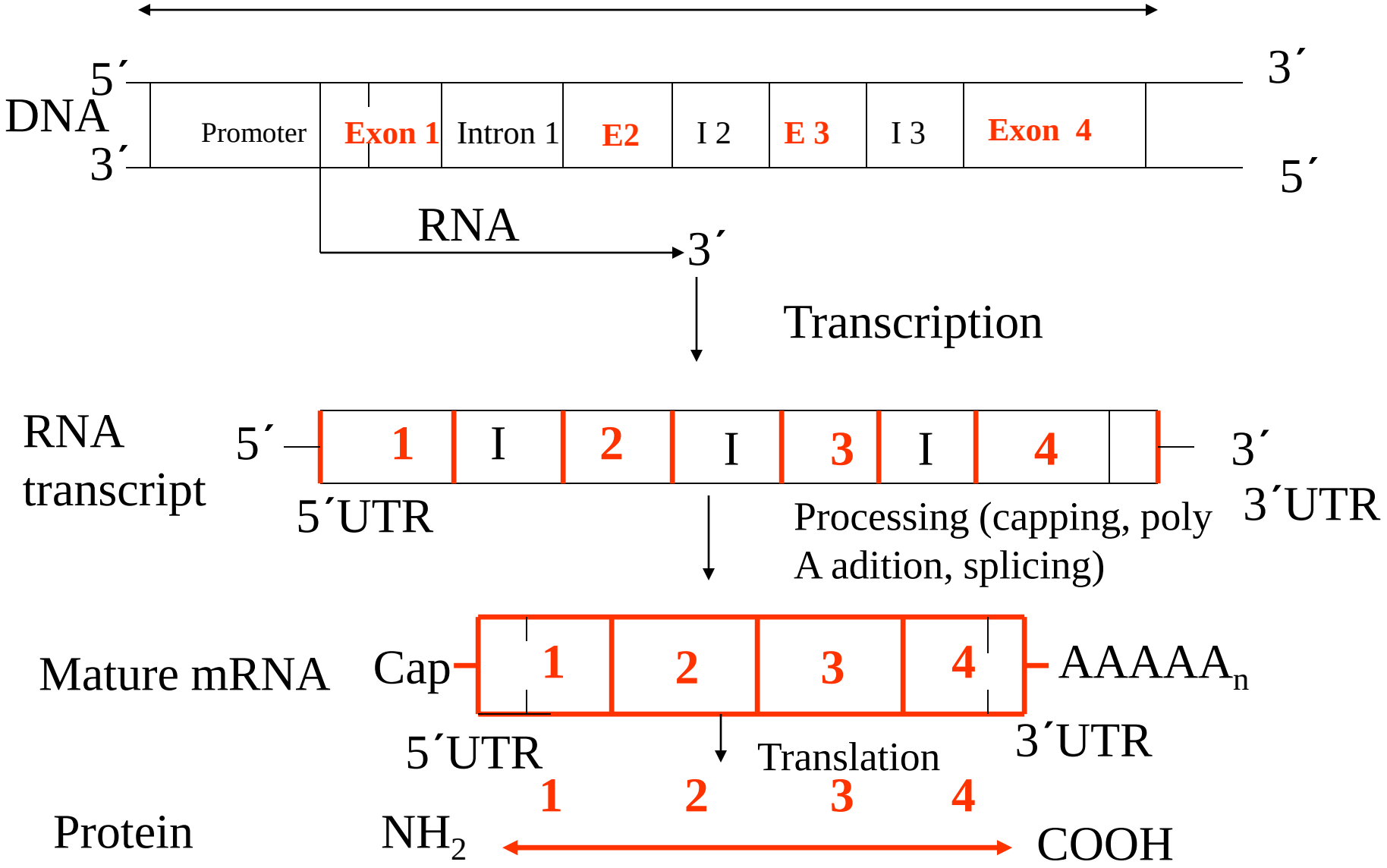
Responsible for all transcription. Binds to RNA polymerase and DNA at generic promoter sequences

Transcriptional Activators

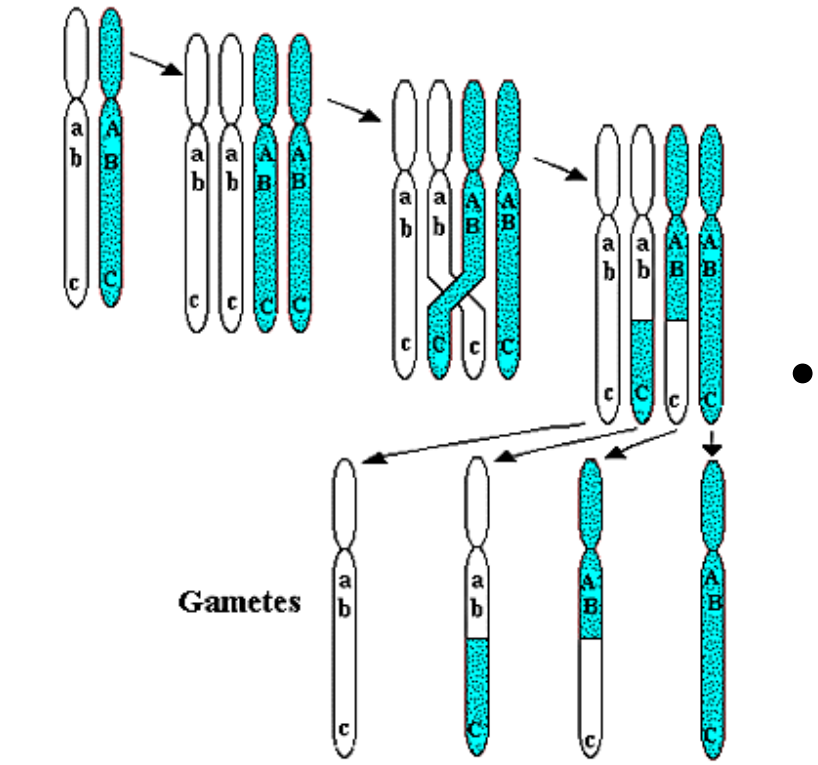
Responsible for specific regulation of transcription. Bind to DNA at specific promoter sequences and activate RNA Polymerase



Human gene


5´
DNA
3´
3´
5´
Promoter
Exon 1
Intron 1
E2
I 2
E 3
I 3
Exon 4
RNA
3´
Transcription
RNA transcript
5´
1
I
2
I
3
I
4
3´
5´UTR
3´UTR
Processing (capping, poly A adition, splicing)
Mature mRNA
Cap
1
2
3
4
AAAAA$_n$
5´UTR
Translation
3´UTR
Protein
1
2
3
4
NH$_2$
COOH

Crossing over:



Crossing-over and recombination during meiosis

- Chromatids change parts between homologous chromatids during the meiosis

- Causes redistribution of heridary material between the homologous chromosomes

→ number of genes doesn't change

→ new allele combinations are formed

Chromosome and gene aberrations

Chromosomal abnormalities

Structural

Numeric

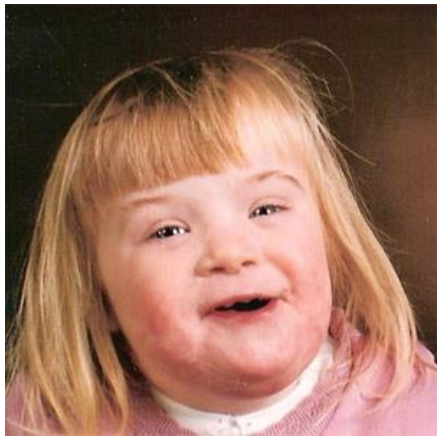
Gene mutatios

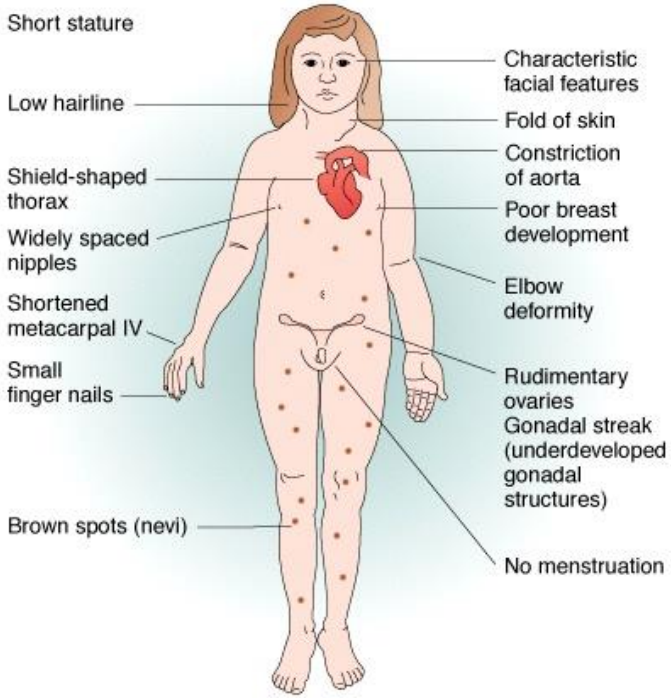
Rare alleles

Polymorphisms

Chromosomal aberrations

- aneuploidy (a difference in chromosome number)
    - meiotic non-disjunction
    - later → somatic mozaicism
  - monosomy
    - gonosomal
      - Turner´s sy. (45, X0)
  - trisomy
    - autosomal
      - Down´s sy. (47, XX/XY + 21)
      - Edwards´s sy. (47, XX/XY +18)
      - Patau´s sy. (47, XX/XY +13)
    - gonosomal
      - Klinefelter´s sy. (47, XXY)
- polyploidy -letal





Genomic disorders

- Genomic disorders represent a clinically diverse group of conditions caused by *gain, loss or re-orientation of a genomic region containing dosage-sensitive genes.*
- Determining how the *copy number variation* (CNV) affects human variation and contributes to the aetiology and progression of various genomic disorders represents important questions for the future.

O´Driscoll M: Curr Genomics. 2008 May; 9(3): 137–146

Gene mutations as a cause of variability in genes

- Rare alleles (prevalence less than 1% in population as a result of selection pressure and/or „recent" mutation). These mutations represent „great genetic factors" causing *monogenic diseases* – subjects of clinical genetics.

- Polymorphisms (prevalence more than 1% in population, smaller genetic factors in interactions with environmental factors conditioning *complex diseases* - subjects of personalized medicine).

Gene mutations as a cause of variability in genes

- *Mutations in somatic cells*

✓ are generating in somatic cells during the lifetime

✓ are cell and/or tissue specific, without transfer to offspring

- *Mutations in germ cells*

✓ they become components of genetic predisposition

✓ they are present in all cells of the individual

✓ they are transfered to offspring

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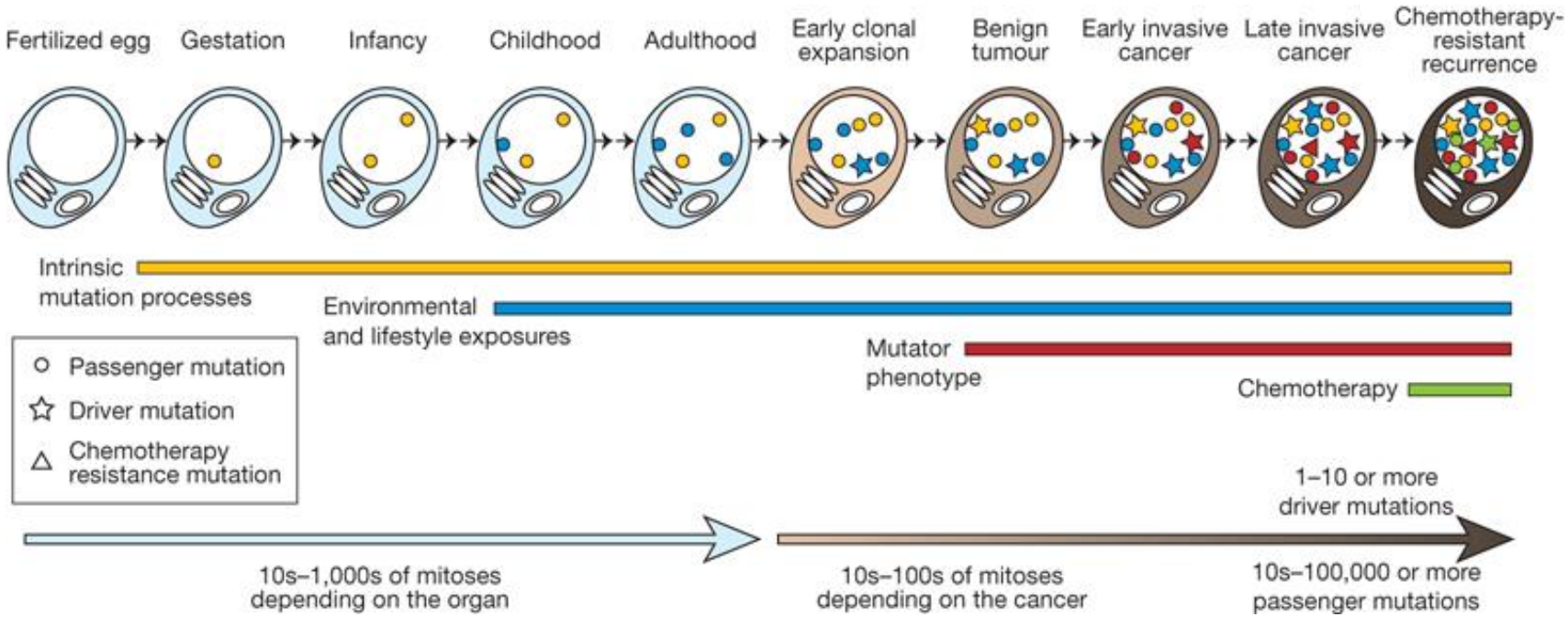
Somatic cell mutations: an example
Sporadic colorectal cancer



MR Stratton *et al. Nature* **458**, 719-724 (2009)

The lineage of mitotic cell divisions from the fertilized egg to a single cell within a cancer showing the timing of the somatic mutations acquired by the cancer cell and the processes that contribute to them.

nature

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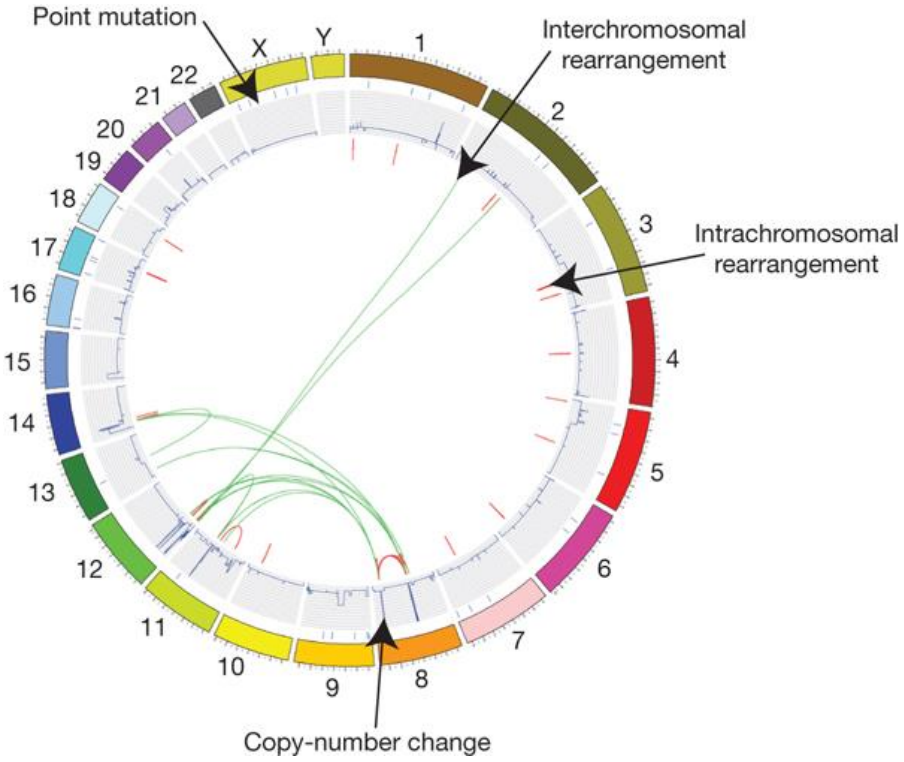
Figurative depiction of the landscape of somatic mutations present in a single cancer genome.



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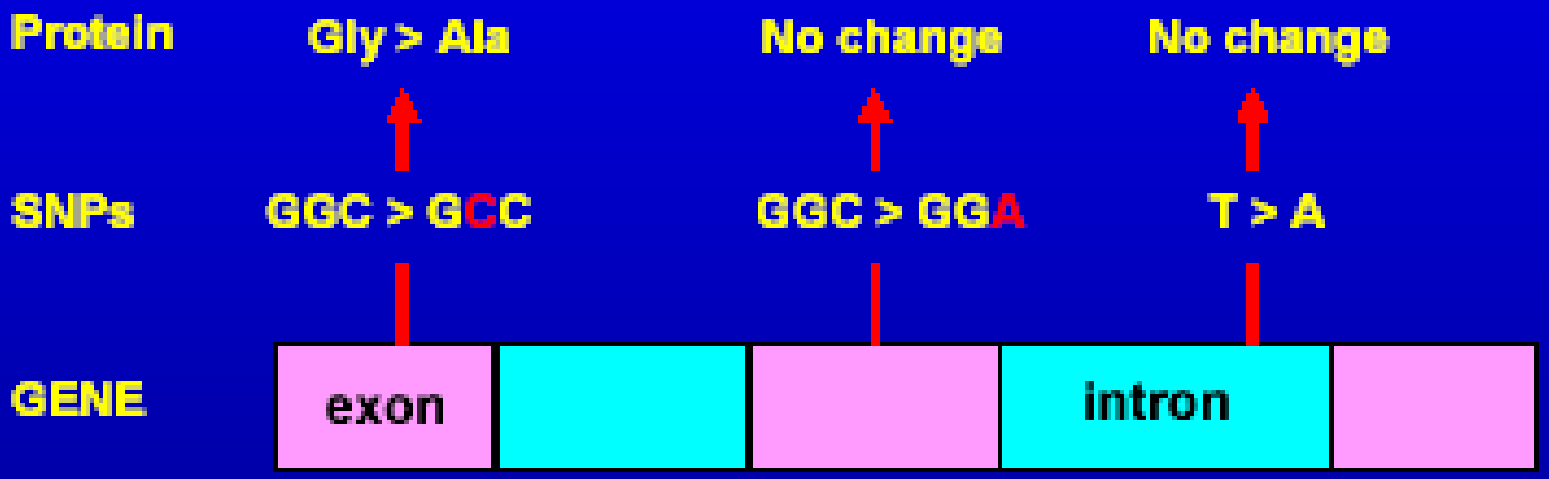
Somatic cell mutations: an example
Sporadic colorectal cancer

nature

Single Nucleotide Polymorphisms



Gene mutation - types

- Normal state
- DNA
- ATGCAGGTGACCTCAGTG
- TACGTCCACTGGAGTCAC

- RNA
- AUGCAGGUGACCUCAGUG

- PROTEIN
- Met-Gln-Val-Thr-Ser-Val

- **Mutation „missense“**
- DNA
- ATGCAG**C**TGACCTCAGTG
- TACGTC**G**ACTGGAGTCAC

- RNA
- AUGCAG**C**UGACCUCAGUG

- PROTEIN
- Met-Gln-**Leu**-Thr-Ser-Val

- **Examples-hemoglobin S in sickle cell anemia-heterozygote advantage**

Gene mutation - types

- Normal state
- DNA
- ATGCAGGTGACCTCAGTG
- TACGTCCACTGGAGTCAC

- RNA
- AUGCAGGUGACCUCAGUG
- PROTEIN
- Met-Gln-Val-Thr-Ser-Val

- **Mutation „nonsense“**
- DNA
- ATGCAGGTGACCT**G**AGTG
- TACGTCCACTGGA**C**TCAC

- RNA
- AUGCAGGUGACCU**G**AGUG

- PROTEIN
- Met-Gln-Val-Thr-Stop
- **Examples: β^0 thalasemia**

Gene mutations- types

- Normal state

- DNA
- ATGCAGGTGACCTCAGTG
- TACGTCCACTGGAGTCAC

- RNA
- AUGCAGGUGACCUCAGUG

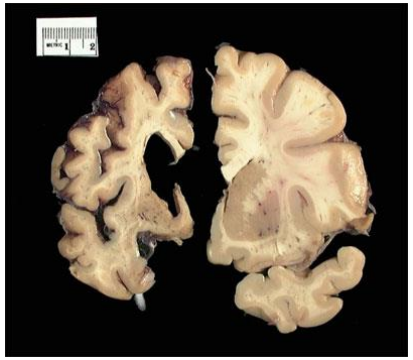
- PROTEIN
- Met-Gln-Val-Thr-Ser-Val

- Mutation type of trinucleotide expanse
- DNA
- ATG$(CAGCAGCAG)_{20}$CAGGTGACCTCAGTG
- TAC$(GTCGTCGTC)_{20}$GTCCACTGGAGTCAC

- RNA
- AUG$(CAGCAGCAG)_{20}$CAGGUGACCUCAGUG

- PROTEIN
- Met-$(Gln\text{-}Gln\text{-}Gln)_{20}$Gln-Val-Thr-Ser-Val

- **Examples: Huntington´s disease**



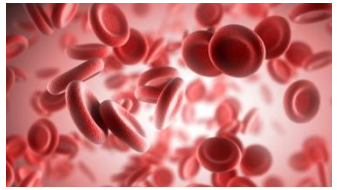
Gene mutations- types

- Normal state

- DNA
- ATGCAGGTGACCTCAGTG
- TACGTCCACTGGAGTCAC
- RNA
- AUGCAGGUGACCUCAGUG
- PROTEIN
- Met-Gln-Val-Thr-Ser-Val

- **Mutation, type „frameshift“**
- DNA
- ATGCAGGTG**A**ACCTCAGTG
- TACGTCCAC**T**TGGAGTCAC
- RNA
- AUGCAGGUG**A**ACCUCAGUG
- PROTEIN
- Met-Gln-Val-**Asn-Leu-Ser**
- **Examples:**
- **Duchenn´s muscular dystrophy, β^0 thalasemia, Tay-Sachs´s disease**

Gene mutations- types



- Normal state
- DNA
- ATGCAGGTGACCTCAGTG
- TACGTCCACTGGAGTCAC
- RNA
- AUGCAGGUGACCUCAGU G
- PROTEIN
- Met-Gln-Val-Thr-Ser-Val

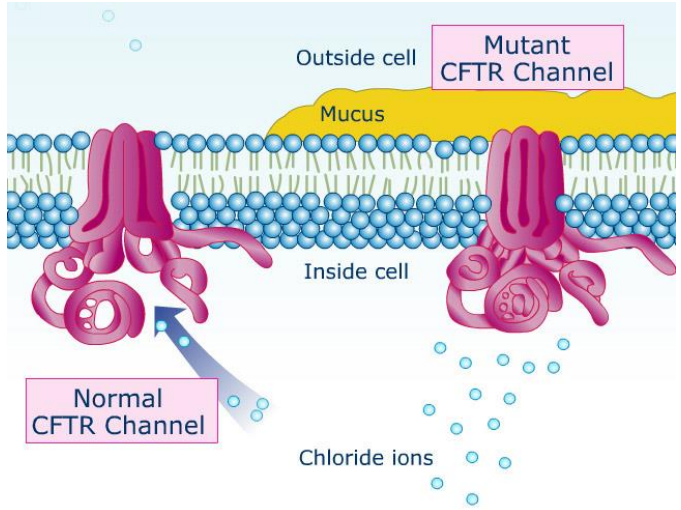
- **Mutation: type „insertion“**
- DNA
- ATGCAGGTG**-3000 bp-**ACCTCAGTG
- TACGTCCAC**-3000 bp-**TGGAGTCAC
- RNA
- AUGCAGGUG**-3000 bp-** ACCUCAGUG
- PROTEIN
- Met-Gln-Val----------?
- **Examples: Hemophilia *A***

Gene mutations- types

- Normal state
- DNA
- ATGCAGGTGACCTCAGTG
- TACGTCCACTGGAGTCAC
- RNA
- AUGCAGGUGACCUCAGUG

- PROTEIN
- Met-Gln-Val-Thr-Ser-Val

- **Mutation: type „deletion“**
- DNA
- ATGCAGGTG
- TACGTCCAC
- RNA
- AUGCAGGUG



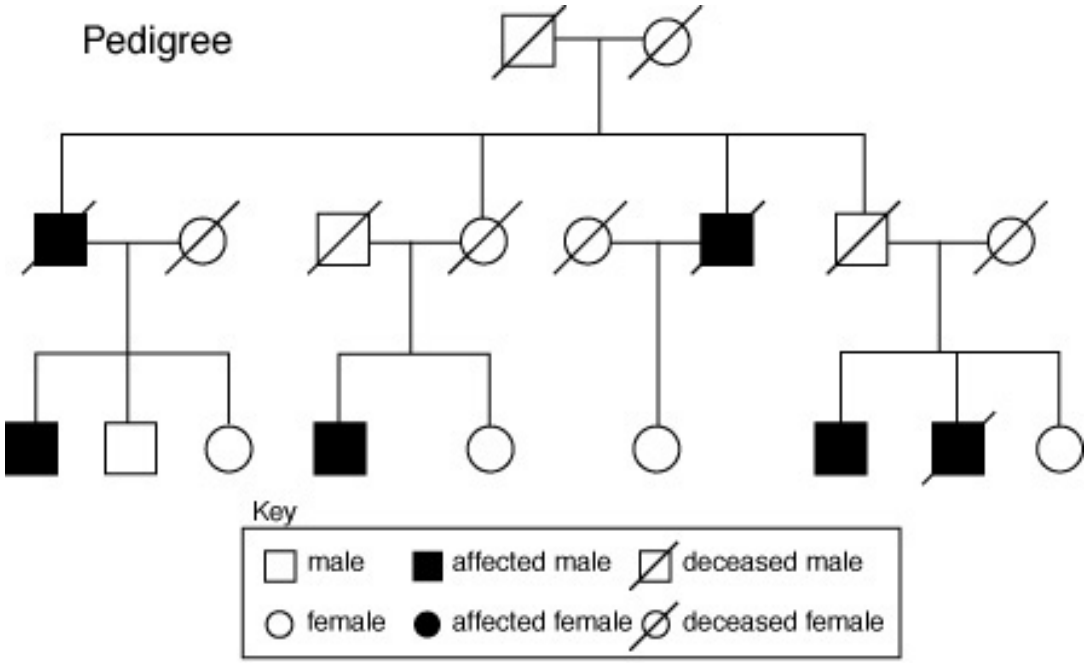
- PROTEIN
- Met-Gln-Val
- **Examples:**
- **small-cystic fibrosis**
- **large: Duchenn´s muscular dystrophy**

Four basic types of heredity

	dominant	recessive
Autosomal	autosomal dominant (AD)	autosomal recessive (AR)
X-linked	X-dominant (XD)	X-recessive (XR)

Monogenic disorders

- Determined by one locus alleli.
- Variant allele which had arosen sometimes in the history replaces original („wild“) allele on one (heterozygote) or both (homozygote) chromosomes.
- Monogenic disorders have a characteristic transfer of the genotypes in families.
- Rare alleles are associated with monogenic disorders as a „big“ factor.

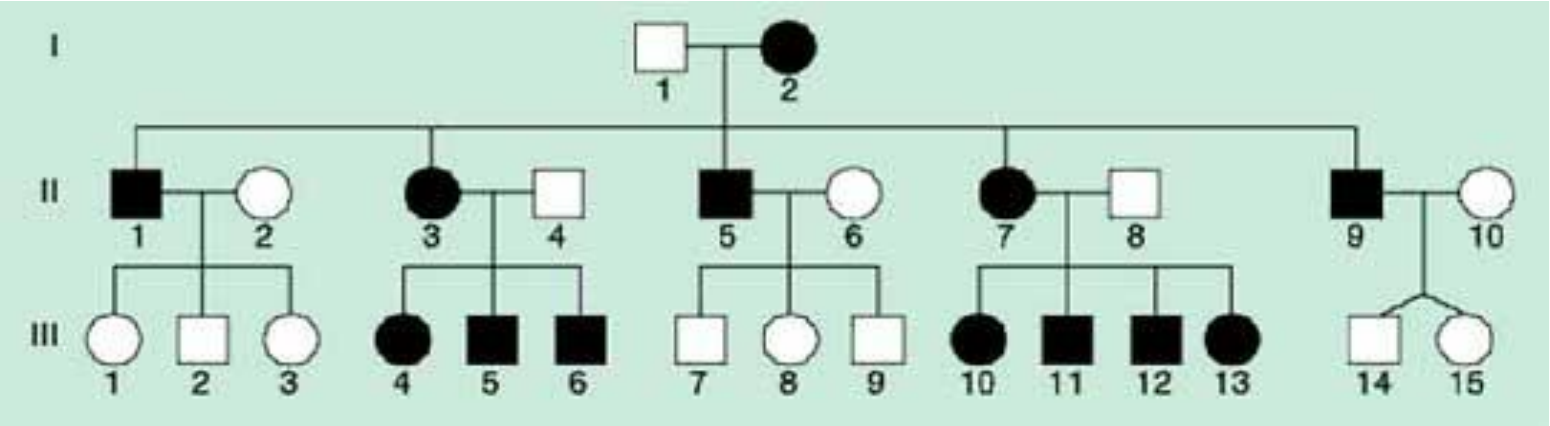


Monogenic disorders

- Clinical manifestations are observed usually in childhood.
- Less than 10% are manifested after puberty and only 1% after reproductive age.
- Prevalence about 0.36%; in 6-8% hospitalizod children some monogenic disorder is suspected.

Mitochondrial heredity

- mtDNA is transfered by mother (after fertilization, only maternal mitochondria are conserved).
- Active process in paternal mitochondria elimination is supposed.

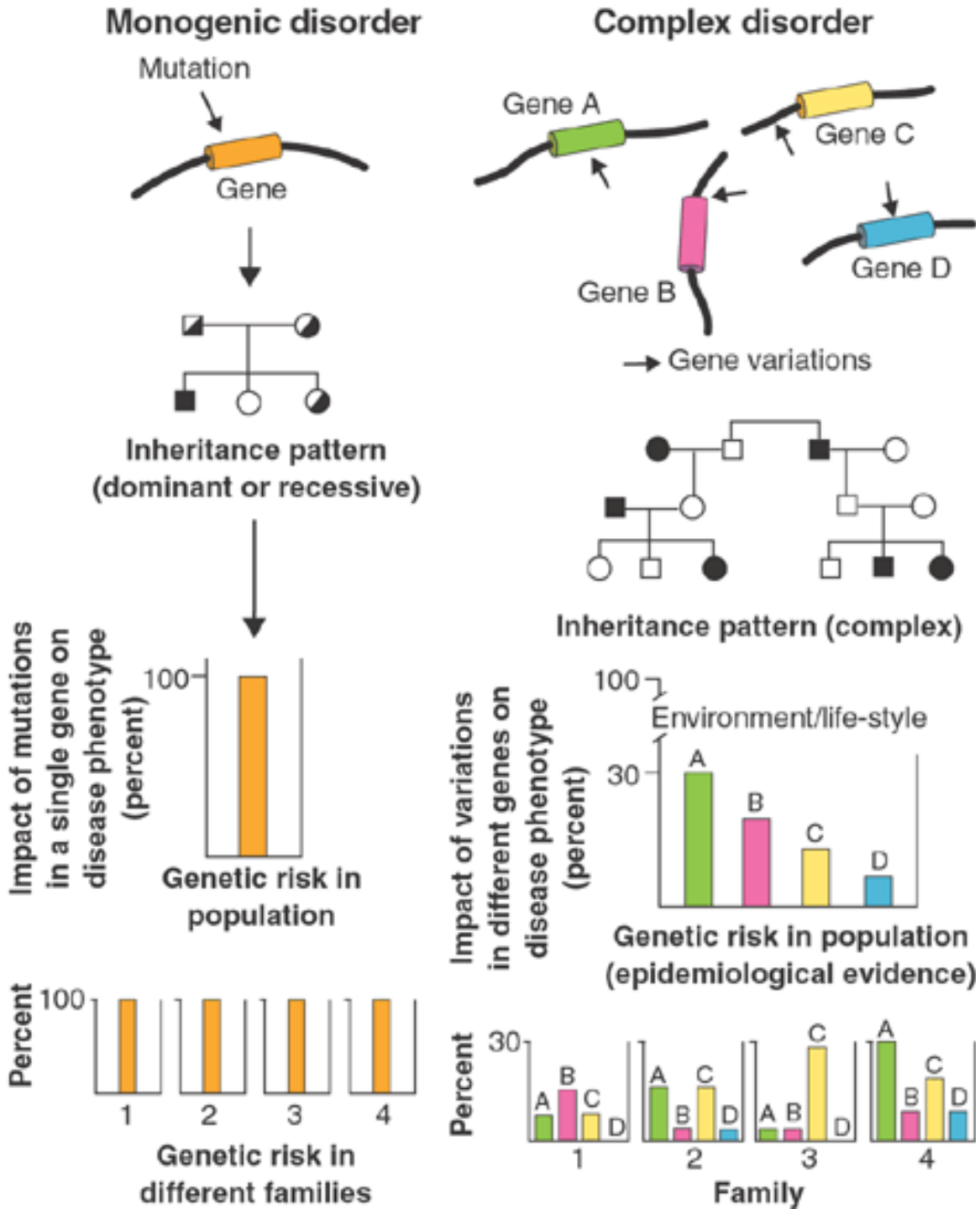


Complex (multifactorial, multigene) diseases

- *Every disease has its own genetic predisposition with different impact to clinical manifestation and/or other phenotypes of the disease.*

Complex (multifactorial, multigene) diseases

- They may be interactions of certain gene variants and certain environmental factors (and their combinations) which could be responsible for predisposition for many
- biological processes
- evolutional adaptations and/or
- complex diseases.


Monogenic disorder
Mutation
Gene
Inheritance pattern
(dominant or recessive)
Impact of mutations in a single gene on disease phenotype (percent)
100
Genetic risk in population
Percent
100
1
2
3
4
Genetic risk in different families
Complex disorder
Gene A
Gene C
Gene B
Gene D
Gene variations
Inheritance pattern (complex)
Impact of variations in different genes on disease phenotype (percent)
100
Environment/life-style
30
A
B
C
D
Genetic risk in population (epidemiological evidence)
Percent
30
A
B
C
D
1
2
3
4
Family

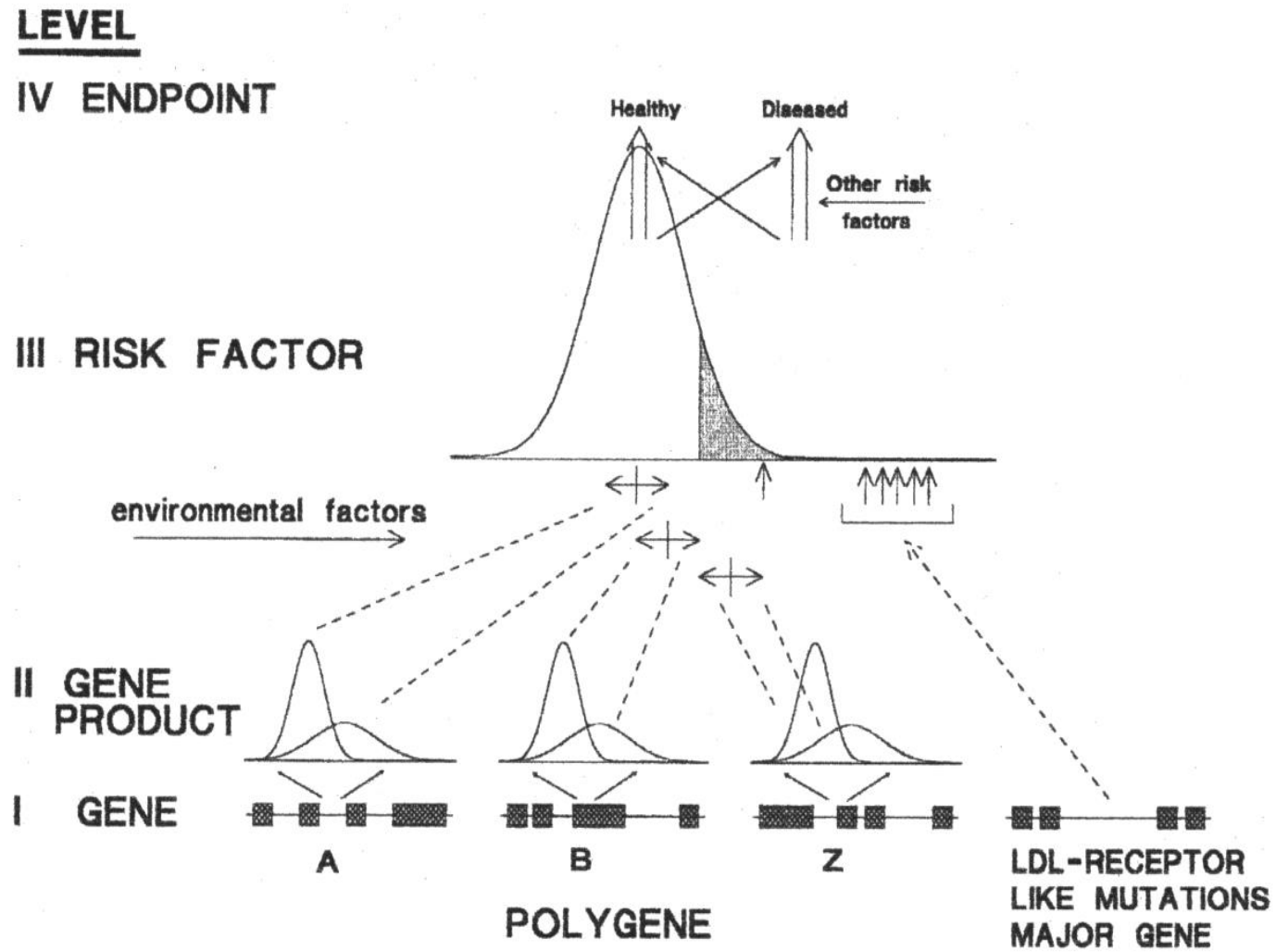


Fig. 1. A general model depicting the role of polygenes, major genes and environmental factors in the aetiology of a chronic multifactorial disease (adapted from Ref. [7] with permission from the authors and Oxford University Press, Oxford). The figure illustrates how genetic variation at level I (in polygenes, indicated by genes A, B...Z and in major genes indicated by LDLR mutations at the right) through altered gene products (level II, indicated by shifts in the distribution) and interactions between them and environmental factors contribute to variations in biological risk factors (level III) and ultimately to disease outcome (level IV). Note that the contribution of polygenic variation to biological risk factor variability is far more than that of major genes.

Candidate gene and its association with disease

✓The question is simplier in mendelistic diseases in which a change function of a gene can be easier indentified.

- *Two main possibilities for this strategy:*

- ***Linkage analysis***

✓needs examination of genealogy

✓is evaluating common occurrence of genetic marker and disease in related individuals

- ***Association study***

Genetic studies

- *Candidate gene selection strategy.*

✓Etiopatogenetic (pathophysiological) approach using for candidate gene selection

- *Genome- wide analysis*

✓Based on analysis of large sequences of genome

Association studies

are evaluating common occurrence of genetic marker and disease in unrelated individuals

Types of association studies

- *case-control* (healthy-ill)
- *case-case* (severity of disease, early onset of disease, risk factors for disease including gender
- *genotype-phenotype (e.g.biochemical parameters)*

Epigenetic effects

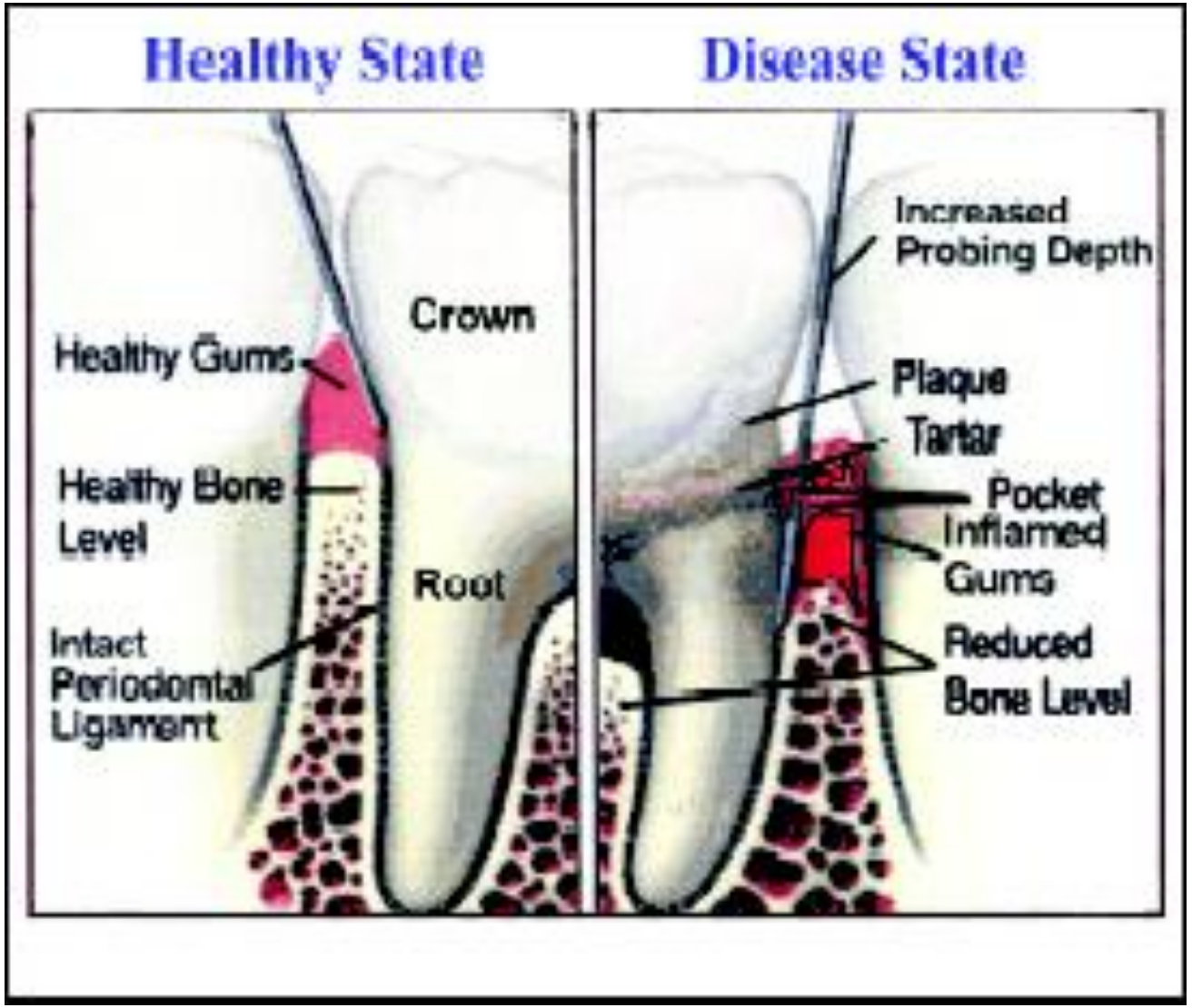
Identical Twins with Different Hair Color

Dough Burlag 2011

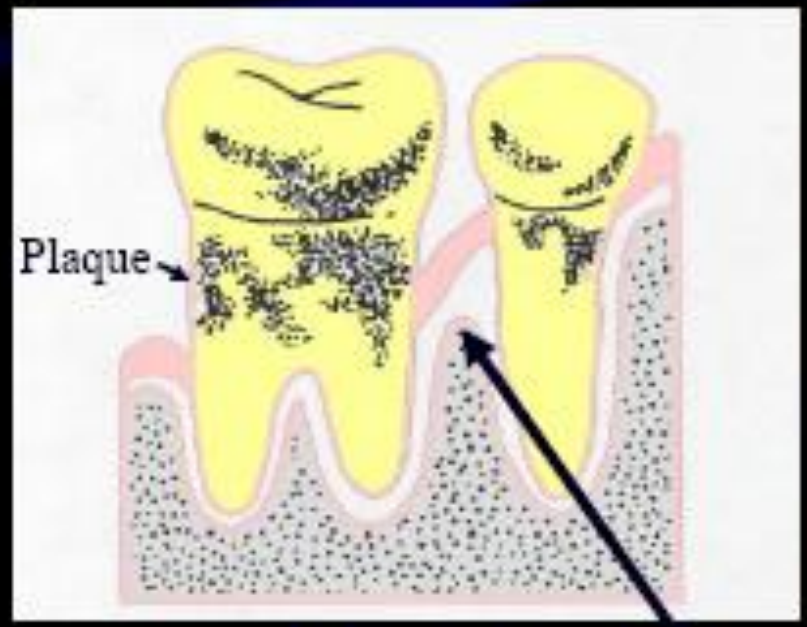
Future: genome wide analysis and cadidate gene approach

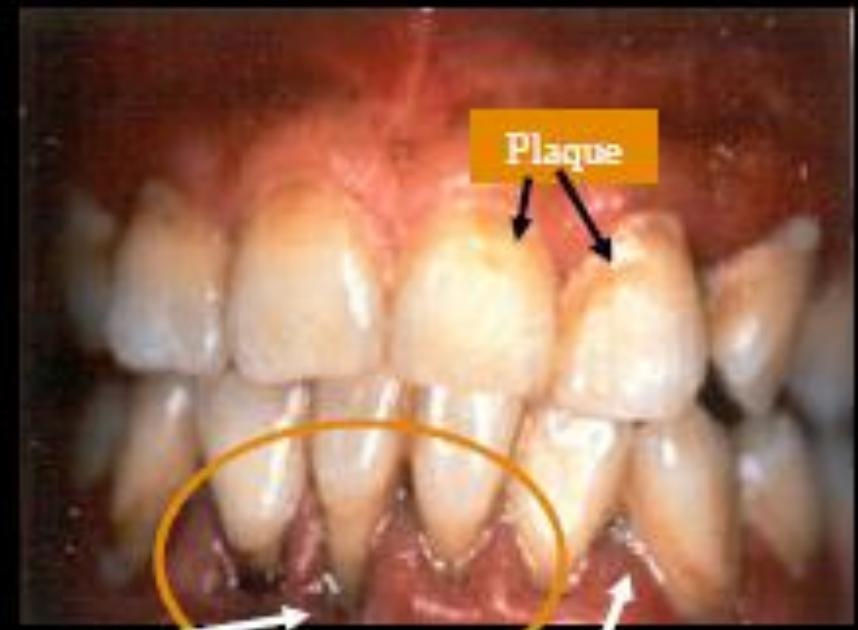
- Current genetic investigations are performed both on the basis of a rational and biologically based choice of candidate genes and through genome wide scans.
- Nonetheless, lack of replication is a common problem in different genetic fields.

Periodontal disease



Periodontal Disease





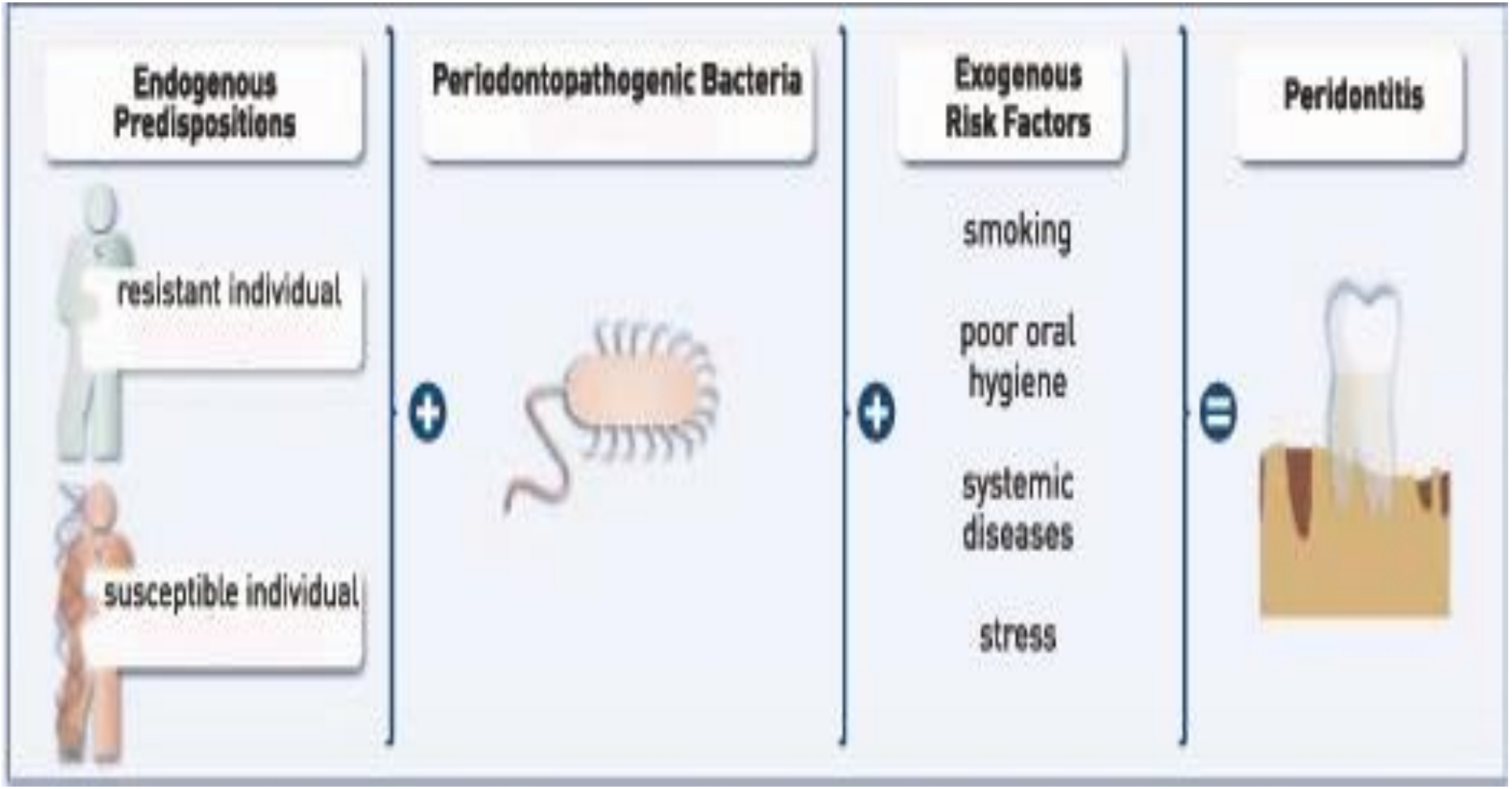
Periodontitis

- Advanced gum inflammation
- Bone loss
- Destruction of ligaments

Gingivitis

- Inflamed Gums

Multifactorial disorder



Syndromic Forms of Periodontitis

- Severe periodontitis presents as part of the clinical manisfestations of several monogenetic syndromes.

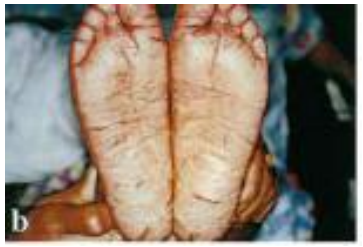
- Significance of these conditions is that they clearly demonstrate that a genetic mutation at a single locus can impart susceptibility to periodontitis.

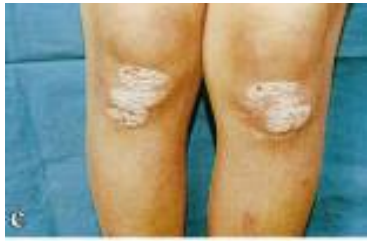
TABLE 2

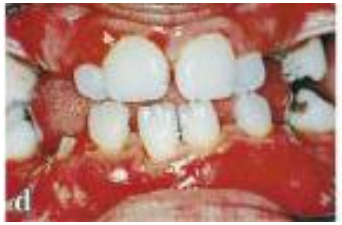
Examples of Syndromic Forms of Periodontitis in Which Inheritance is Mendelian and Due to a Genetic Alteration at a Single Gene Locus

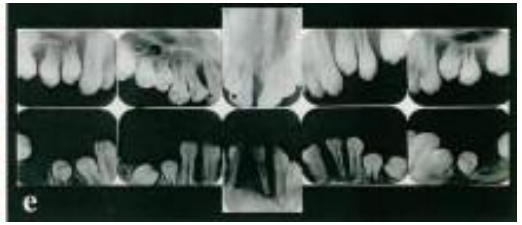
Condition	Biochemical/Tissue Defect	Inheritance	OMIM
Papillon-Lefèvre syndrome	Cathepsin C	AR	245000
Haim-Munk syndrome	Cathepsin C	AR	245100
Ehlers-Danlos syndrome type 4	Collagen	AD	130050
Ehlers-Danlos syndrome 8	Collagen	AD	130080
Cyclic neutropenia	neutrophil elastase	AD	162800
Chronic familial neutropenia	Defect unknown	AD	162700
Chediak-Higashi syndrome	lysosomal trafficking regulator gene	AR	214500
Congenital disorder of glycosylation type IIc	GDP-fucose transporter-1	AR	266265
Leukocyte adhesion deficiency type 1	Leukocyte chain adhesion molecule CD18	AR	116920

Papillon LeFevre Syndrome









- Clinically characterized by:
  - Palmoplantar hyperkeratosis
  - **Severe early onset periodontitis** that results in premature loss of the primary and secondary dentition (distinguishes PLS from other plamoplantar keratoderma)
- Prevalence 1/ 4million
- No gender or racial predilection

CTSC gene encodes for Cathepsin C protease

- **CTSC gene lies on chromosone 11q14-q21; seven exons encoding for lysosomal protease cathepsin C.**

- **It is expressed at high levels in a variety of immune cells including polymorphonuclear leucocytes, macrophages, and in epithelial regions commonly affected by PLS, including the palms, soles, knees, and oral keratinized gingiva (RT-PCR) (Hart et al., 1999).**

- **Cathepsin C is a protease enzyme that processes and activates a number of granule serine proteases critical to immune and inflammatory responses of myeloid and lymphoid white blood cells**

Mutations in CTSC gene

- **Mutations in Cathepsin C (CTSC) gene are implicated for PLS**

- **For example:**
  - **One exon 1 nonsense mutation (856C→T): introduces a premature stop codon at amino acid 286.**
  - **Three exon 2 mutations:**
    - **single nucleotide deletion (2692delA) of codon 349: introduces a frameshift and premature termination codon,**
    - **2 bp deletion (2673-2674delCT): introduces a stop codon at amino acid 343, and**
    - **G→A substitution in codon 429 (2931G→A): introduces a premature termination codon.**

- **Truncated or altered conformation of the protein may not be transported to the organelle and may not be able to activate protein kinases**

- **In other words, Cathepsin C activity in these patients is nearly absent**

Polymorphism Studies on Periodontitis

- Host response is predominantly influenced by genetic make-up.
- Several features of host's innate immune response may contribute to susceptibility to AgP and include epithelial, connective tissue, fibroblast, and PMN defects.
- Aspects of the host inflammatory response namely cytokines are crucial variants influencing host respone in periodontitis.

Immunological Polymorphisms

- MHC or HLA genes determine our response to particular antigens.
- Japanese study of AgP pts found a significant association for pts with atypical BamH1 restriction site in the HLA.DQB gene (Takashiba et al. 1994).
- Hodge & Kinane (1999) found no assoc. in caucasian AgP pts and this restriction site.

IL-1 Gene Polymorphisms

- In 1997 Kornman et al found an association between polymorphisms in genes enconding for IL-1a(-889) and IL-1B(+3953) and an increased severity of periodontitis.
- The specific genotype of the polymorphic IL-1 cluster (called PST-periodontitis susceptibility trait) was associated with severity of PD in only non-smokers, and distinguished individuals with severe periodontitis from those with mild disease.

Genetic control of IL-1: Genes and Locus of SNPs associated with controlling IL-1 biological activity

Genes	Polymorphism Locus	Current Locus assessed with test	Controlled product
IL-1A	Allele 2 -889	Allele 2 IL-1A +4845	IL-1 alpha
IL-1B	Allele 2 +3953	Allele 2 IL-1B +3954	IL-1 beta
IL-1RN			Protein receptor antagonist (impedes IL-1 alpha and beta)

Genetic Susceptibility Test for periodontitis: tests for the presence of at least one copy of allele 2 at the IL-1A +4845 loci and at least one copy of allele 2 at the IL-1B +3954 locus.

**IL-1A +4845 is being used because it is easier to identify than IL-1A -889 and it is essentially concordant with it.*

*** IL-1B +3953 has been now renumbered as IL-1B +3954 because the current convention indicates that the numbering of the transcription should begin at +1 instead of zero.*

Interleukin 1

- A proinflammatory multifunctional cytokine.
- Enables ingress of inflammatory cells into sites of infection
- Promotes bone resoroption
- Stimulates eicosanoid (PGE2) release by monocytes and fibroblasts
- Stimulates release of MMP’s that degrades proteins of the ECM.
- Forms IL-1α and IL-1B

IL-1 as modulator for Periodontitis

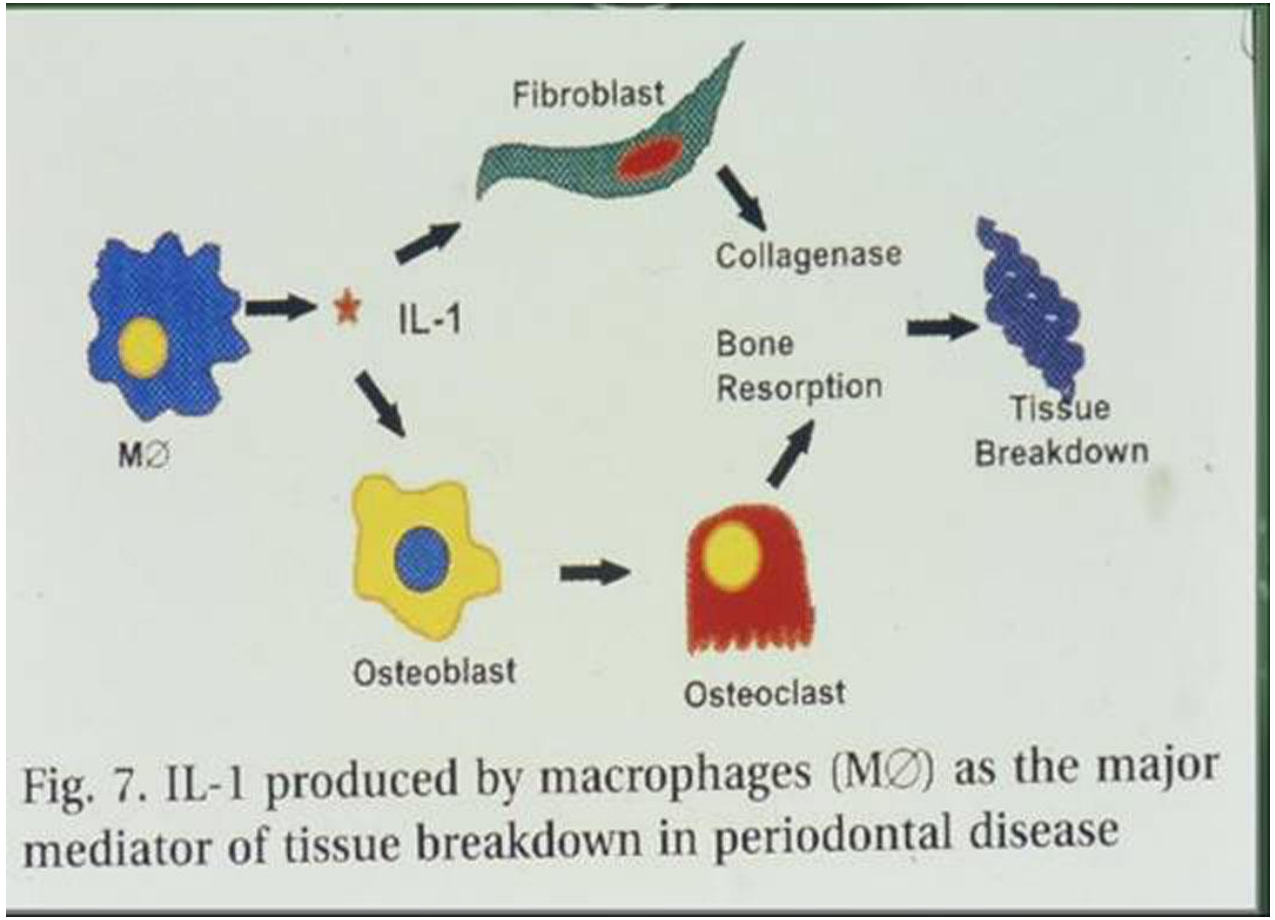


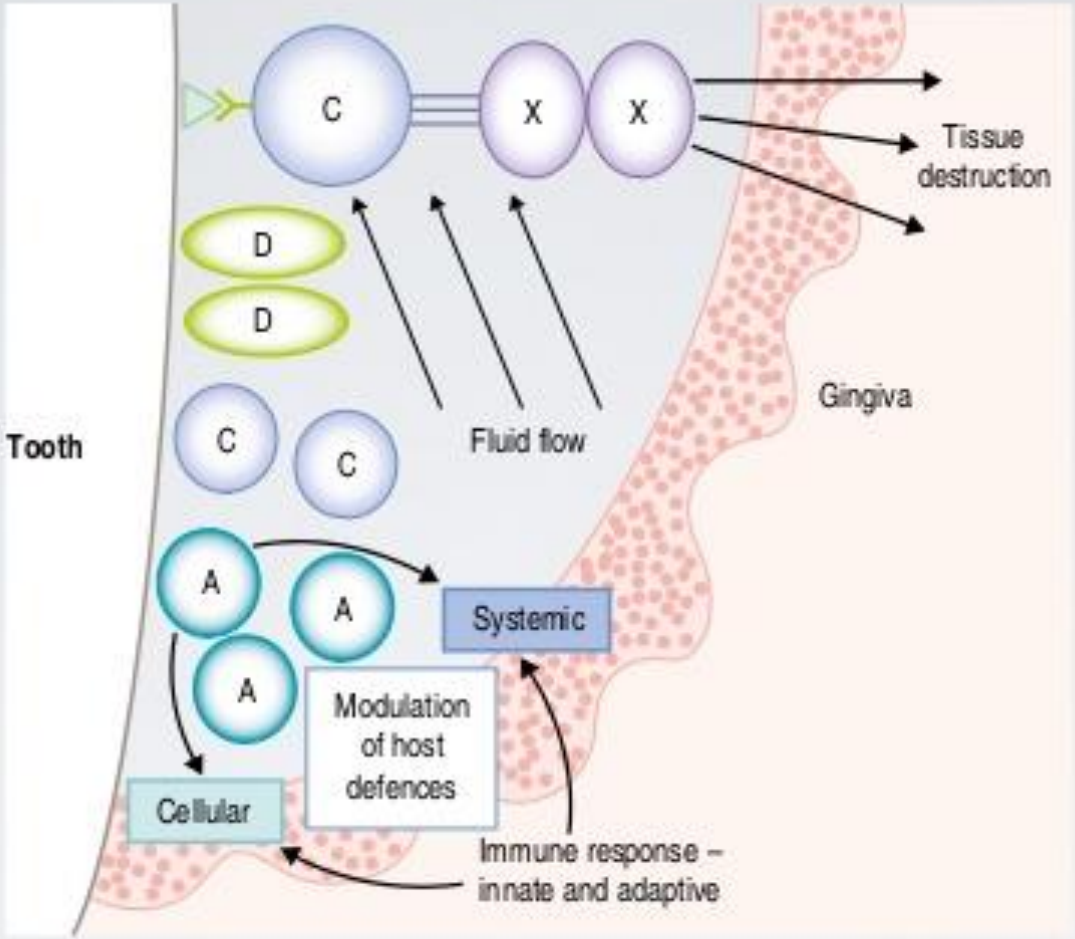
Fig. 7. IL-1 produced by macrophages (MØ) as the major mediator of tissue breakdown in periodontal disease

Prevalence of genotype positive individuals in different ethnic groups

- Frequency of many genetic alleles varies between ethnic groups, therefore, it is necessary to establish allele frequencies in populations before genetic test can be evaluated and used.

  - **Caucasions:**
    - 29% of northern european caucasions were genotype positive (Kornman et al., 1997)
  - **African Americans:**
    - 14.5% of non-diseased individuals and 8% of patients with localized form of aggressive periodontitis were genotype-positive. (Walker et al., 2000)
  - **Chinese:**
    - 2.3% of sample of 132 mod-severe periodontitis cases were genotype-positive (Armitage et al., 2000)
  - **Hispanics:**
    - 26% of hispanic individuals with peridontitis were genotype-positive (Lopez et al., 2005)

Take home message: Dissimilarity in the prevalence of genotypes in different ethnic groups precludes extrapolating data from one group to another.



Pathogenic synergy in the aetiology of periodontal diseases. Bacteria capable of causing tissue damage directly (e.g. species X) may be dependent on the presence of other cells (e.g. organisms C and D) for essential nutrients or attachment sites so that they can grow and resist the removal forces provided by the increased flow of GCF. Similarly, both of these groups of bacteria may be reliant for their survival on other organisms (e.g. A and C) to modulate the host defences. Individual bacteria may have more than one role (e.g. organism C) in the aetiology of disease.

Microbial factors

- *Porphyromonas gingivalis*
- *Bacteroides forsythus*, newly *Tanarella forsythensis*

- *Actinobacillus Actinomycemcomitans*
- …….

BUT

- The bacteria themselves are not able to cause disease:
  - A wide range of host susceptibility
  - Differences in prevalence and extent between the teeth

Dental plaque biofilm infection

- Ecological point of view
    - Ecological community evolved for survival as a whole
    - Complex community of more than 400 bacterial species
- Dynamic equilibrium between bacteria and a host defense
    - Adopted survival strategies favoring growth in plaque
    - “Selection” of “pathogenic” bacteria among microbial community
    - Selection pressure coupled to environmental changes
    - Disturbed equilibrium leading to pathology
    - Opportunistic infectio

Reaction of the organism to bacterial infection

- Gate input - usually mucosal surfaces (violation of integrity)
- The fate of the host depends on:
  - Immunity (largely genetically determined)
  - Pathogenicity of bacteria (invasive ability, production of toxins, the ability to resist the defense mechanisms of the host)

non-invasive - multiply the point of entry into the body
threatening in case of toxin production
(defense - only neutralizing Pt)

Invasive - penetrate into the organism (x extracellular intracellular)
(defense are Pt, complement, phagocytosis vs. macrophages)

  - The size of the infectious dose

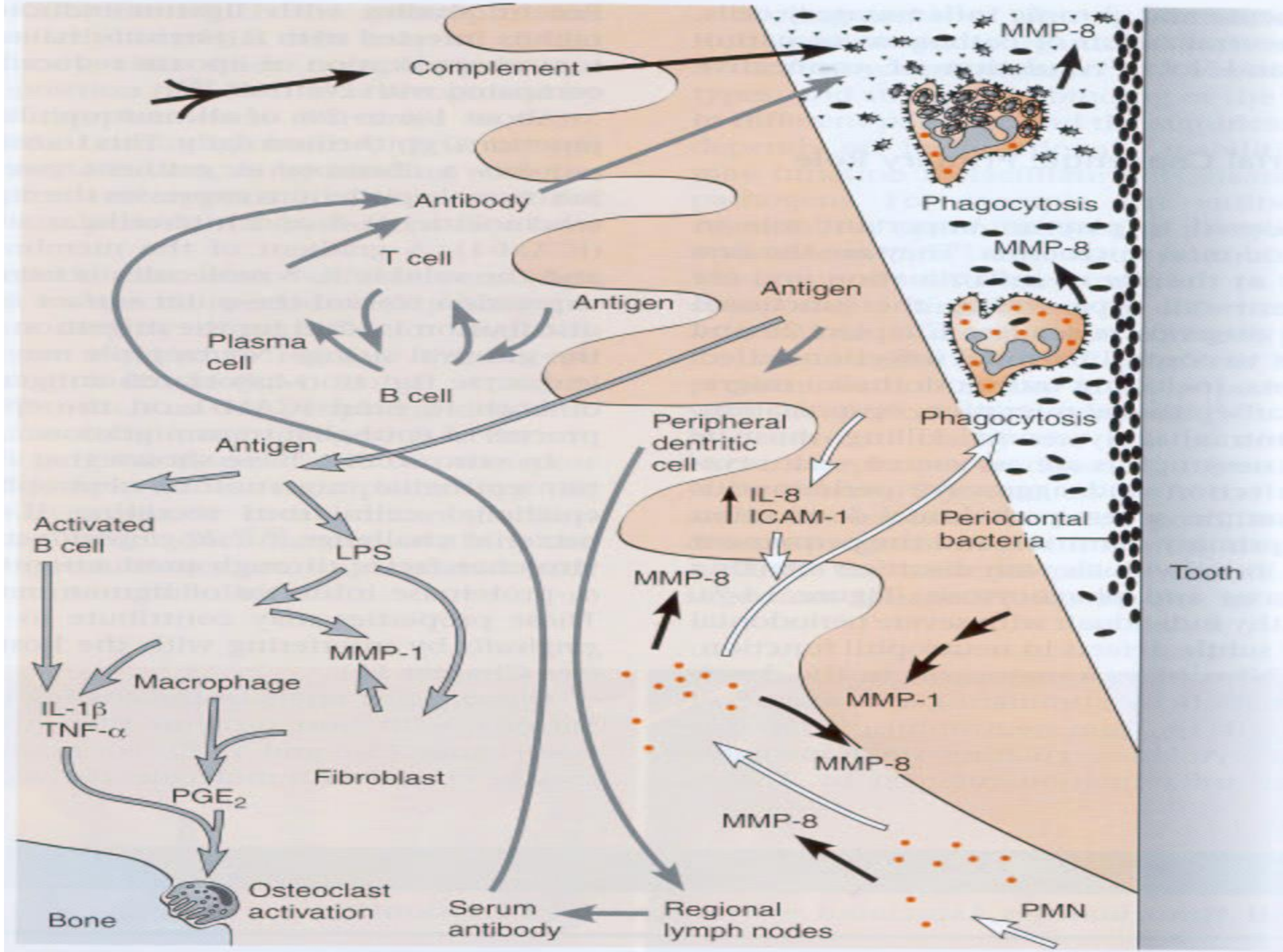
Identifying virulence factors

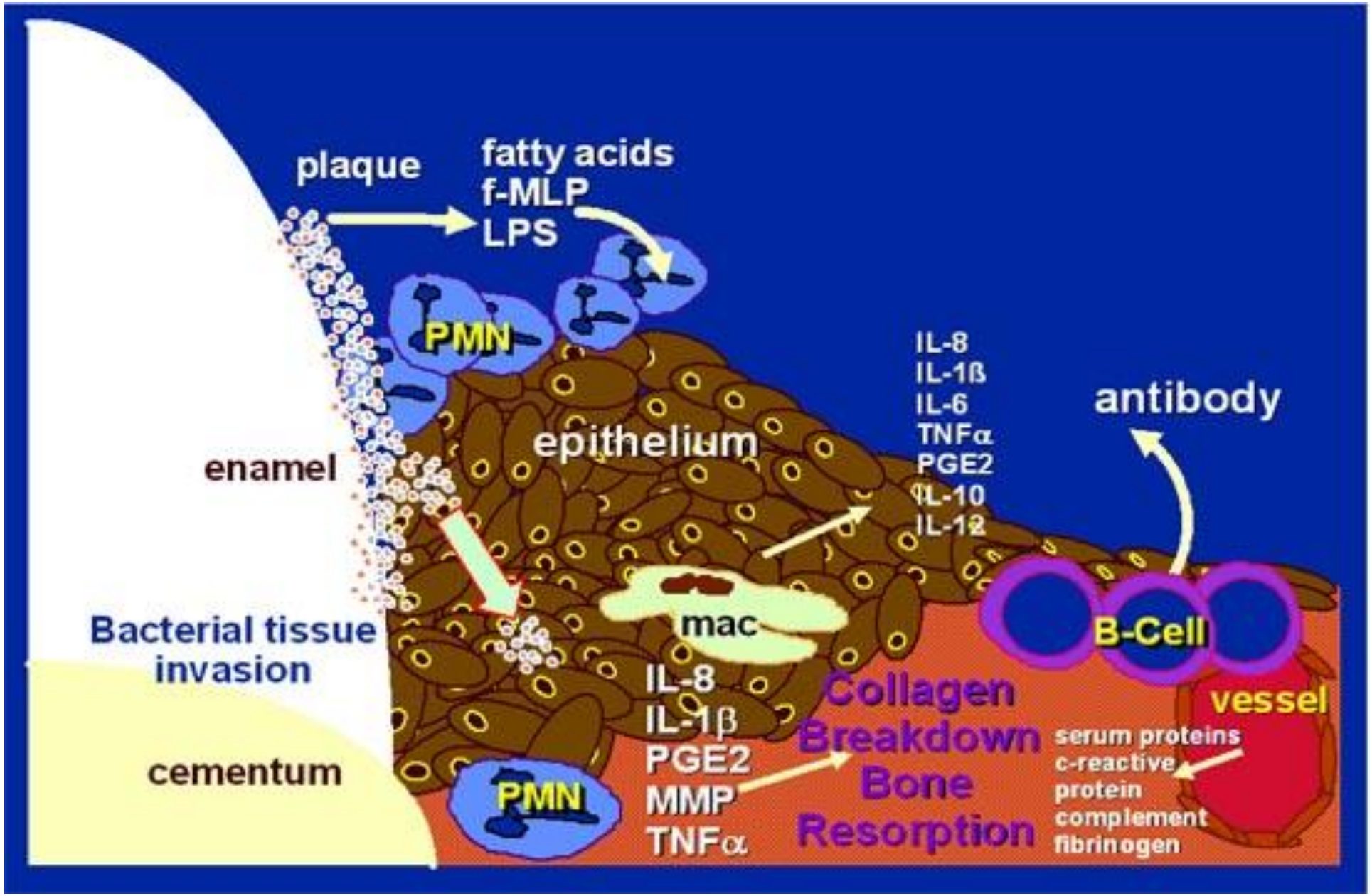
- Microbiological and biochemical studies
    - *In vitro isolation and characterization*
    - *In vivo systems*
- Genetic studies
    - Study of genes involved in virulence
    - Genetic transmission system
    - Recombinant DNA technology
        - Isogenic mutants
        - Molecular form of Koch’s postulates (Falkow)

Koch’s postulates

- A Molecular form of Koch’s postulates
  - The phenotype should be associated with pathogenic species (strains)
  - Specific inactivation of genes associated with virulence should lead to a decrease in virulence
  - Complementing inactivated genes with the wildtype genes should restore full virulence

Falkow, 1988


Complement
MMP-8
Antibody
Phagocytosis
T cell
MMP-8
Antigen
Antigen
Plasma cell
B cell
Phagocytosis
Peripheral dentritic cell
Antigen
IL-8
ICAM-1
Periodontal bacteria
Activated B cell
LPS
Tooth
MMP-8
MMP-1
Macrophage
MMP-1
IL-1β
TNF-α
MMP-8
Fibroblast
PGE2
MMP-8
Osteoclast activation
Bone
Serum antibody
Regional lymph nodes
PMN


plaque
fatty acids
f-MLP
LPS
PMN
epithelium
enamel
IL-8
IL-1ß
IL-6
TNFα
PGE2
IL-10
IL-12
antibody
Bacterial tissue
invasion
mac
B-Cell
IL-8
IL-1β
PGE2
MMP
TNFα
Collagen
Breakdown
Bone
Resorption
vessel
serum proteins
c-reactive
protein
complement
fibrinogen
cementum
PMN

TLRs

- First described as a gene for type I transmembrane receptor

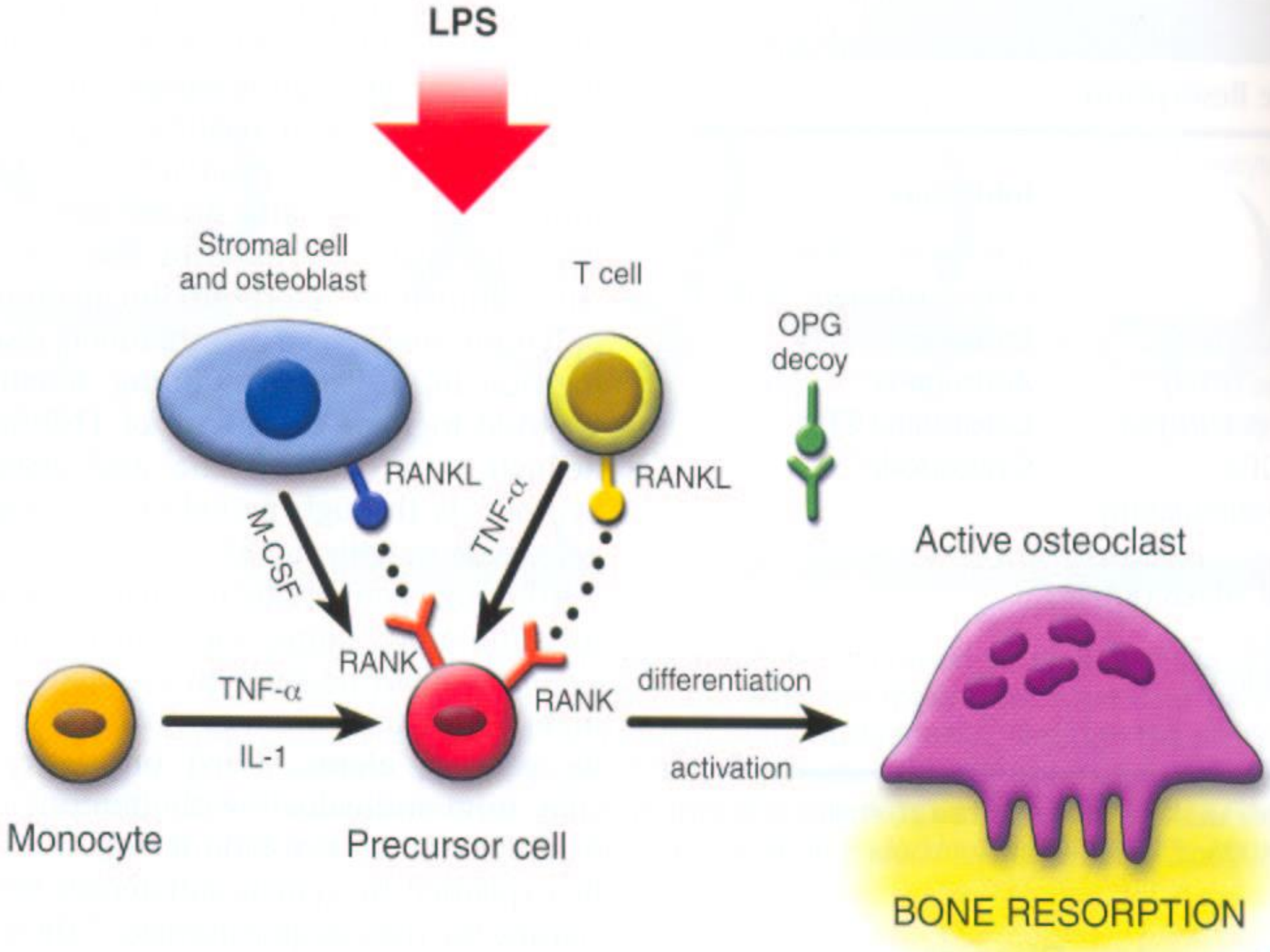
$\rightarrow$ important role in dorzoventral embryonic development of Drosophila

$\rightarrow$ absence of tolls has led to a serious brake-down of defense against fungi and bacteria G+

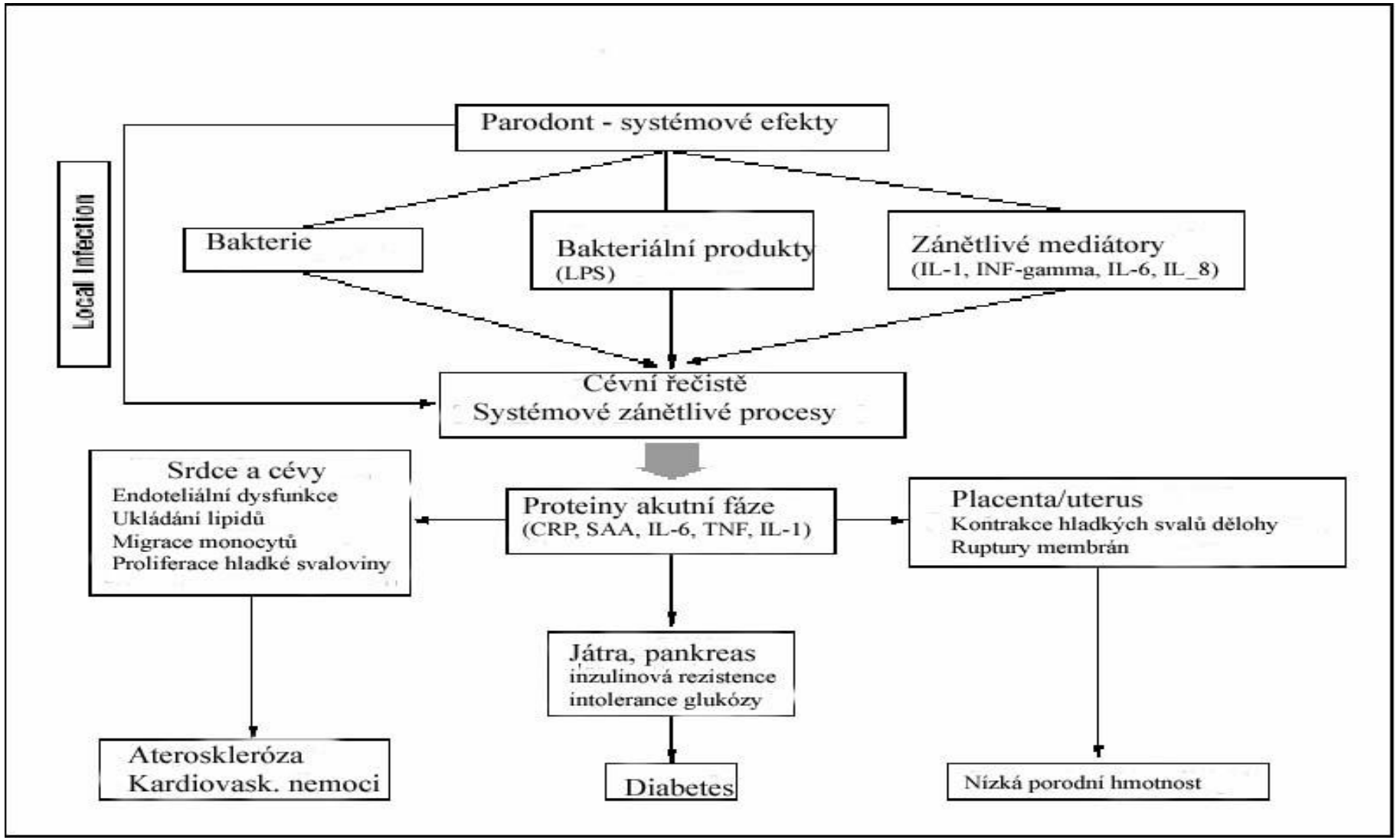
$\Rightarrow$Mammalian homologues - similar role??

TLRs receptors and ligands in periodontal disease

PRR	PAMP	Periodontal Pathogen
TLR-2	Lipoproteins	*Bacteroides forsythus**
	Atypical LPS	*P. gingivalis, C. ochracea*
	Outer membrane proteins	Oral treponemes
	Fimbriae	*P. gingivalis*
	Nonendotoxic glycoprotein	*P. intermedia*
TLR-4	HSP-60 (GroEL)	*P. gingivalis*
	LPS	*A. actinomycetemcomitans, F. nucleatum*
TLR-9	CpG-containing DNA	*A. actinomycetemcomitans, P. gingivalis, P. micros*


LPS
Stromal cell
and osteoblast
T cell
OPG
decoy
RANKL
RANKL
M-CSF
TNF-α
RANK
RANK
TNF-α
IL-1
differentiation
activation
Active osteoclast
Monocyte
Precursor cell
BONE RESORPTION

Local problem?



Periodontitis

- follows the loss of pulp vitality - the dead tooth

- Infection is usually odontogenic
- Trauma - one-time or repetitive microtrauma
- Acute periodontitis (apical)
- Hyperemia and serous exudation
- Suppuration, osteoclastic bone remodeling

- Strong pain at all stages, swelling in the later stages

- **Relationship of polymorphisms in genes IL1B, IL1RN, FcγRIIIb, VDR and TLR4 with an aggressive type of periodontitis.**

Periodontitis

Chronic periodontitis (periapical)

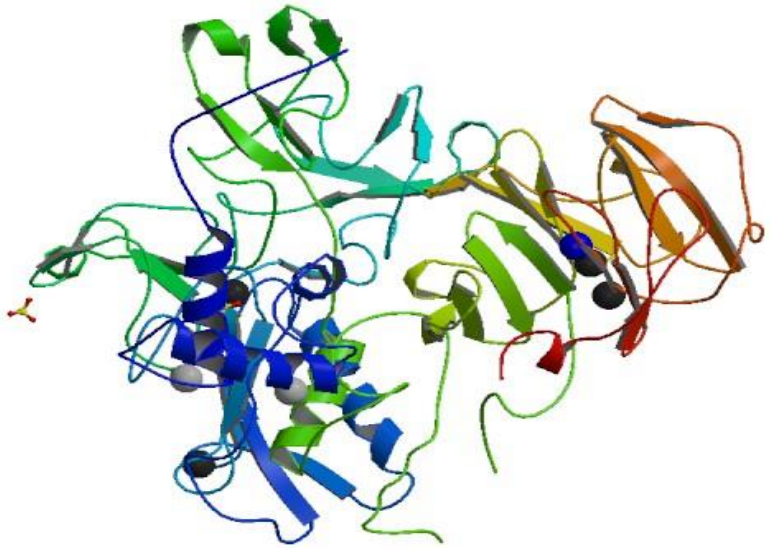
- Secondarily from acute periodontitis
  Primarily chronic (more frequent)
- Forms:
  Granulomatous
  Granulomatous progressive - fistula (mucosal and cutaneous)
  Diffusion - dismantled and alveolar bone

- granulation tissue
  macrophages
  Possibility of creating radicular cysts

- The type of chronic periodontitis is associated with polymorphisms in genes for IL1B, IL1RN, IL6, IL10, VDR, CD14, TLR4 and MMP1.

- Meta-analysis of published data have associated variants ofpolymorphisms IL1A-889, IL1B 3954, IL1B-511, TNFA-308 and IL6-174 to aggressive and chronic periodontitis.

Thank you for your attention



„I just need a closer look...“