Other causes of human diseases

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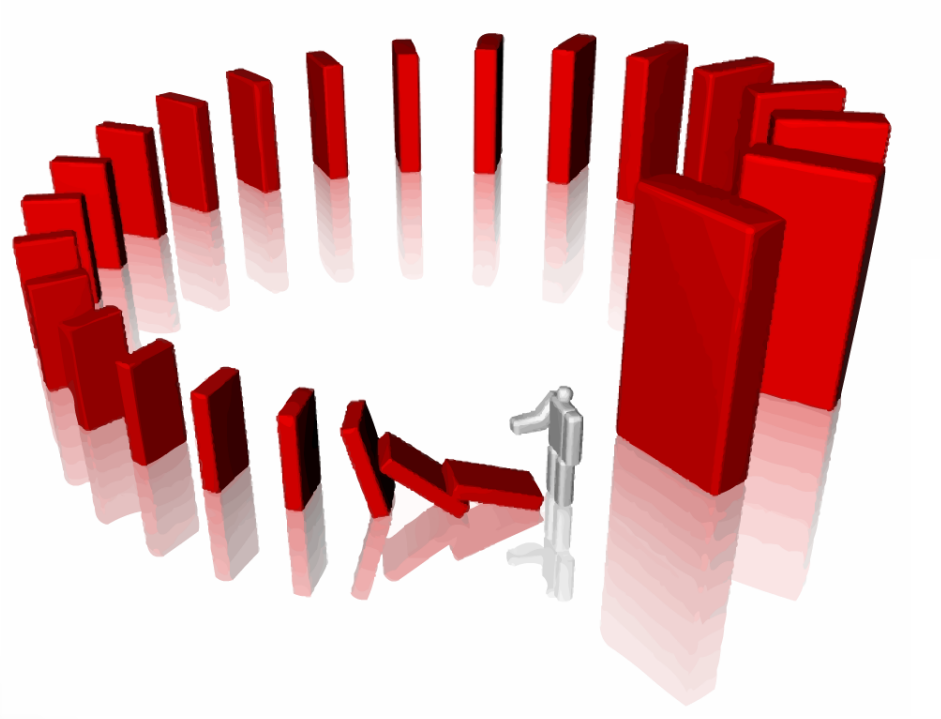

FN MOTOL

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Causes of human diseases

1) degenerative

2) hemodynamic

3) metabolic

4) inflammatory

5) neoplastic

6) imunne

7) genetic

8) developmental

9) environmental

10) infectious

Genetic causes of human diseases

Genetic causes of human diseases

- completely hereditary diseases are rare
  - usually cooperation of **inner** + **environmental** factors
  - **inner factors** = genetic predispositions based on polymorfism

    (diseases of civilization / immune ones, tumors, DM..)

- field of **Medical genetics**
  - diagnostics of **germinal** mutations (within all cells)

- genetics in pathology represents **Molecular pathology**
  - analysis of **somatic** genetic aberrations within pathological tissues (tumors)

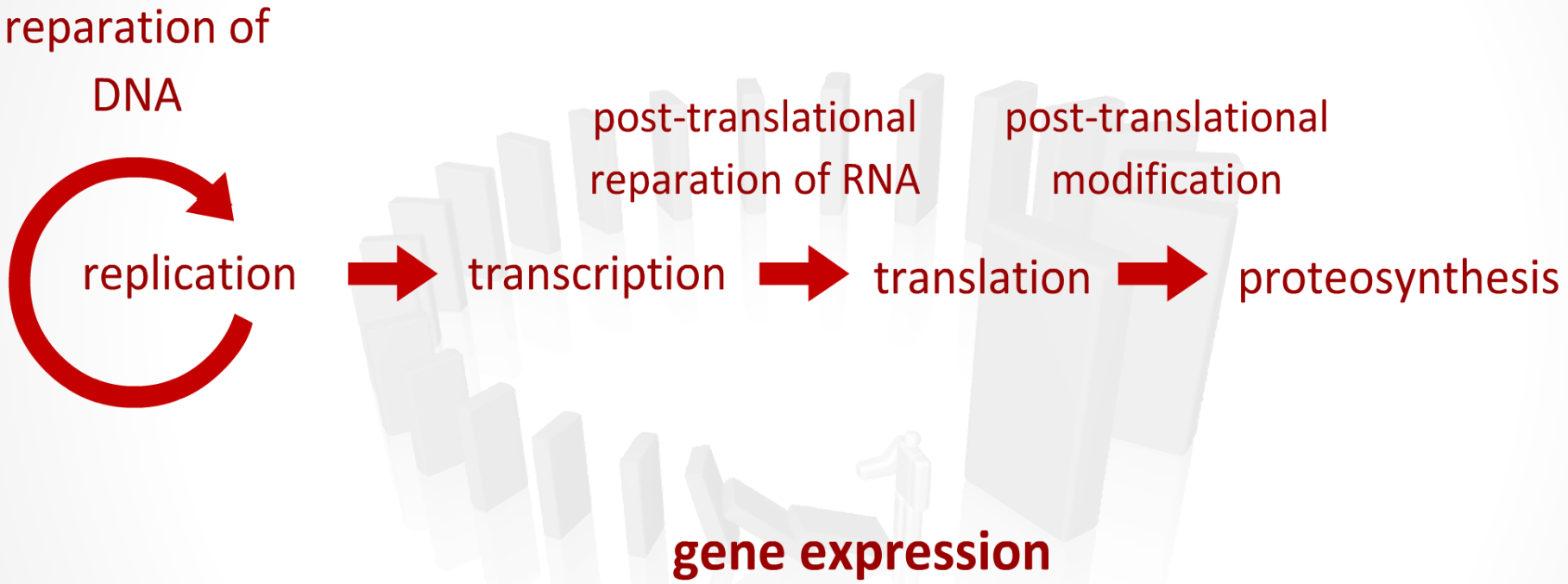
Genetic causes of human diseases

- basic **genetic vocabulary**:

  - **germinal**
    = delivered from germinal cells (all daughter cells affected, including gametes)
    = hereditary (causing syndromes)
  - **somatic (isolated, acquired)**
    = delivered from mature cells (gametes are not affected)
    = non-heritable/non-transmissible (causing tumors)

  - **hereditary** = transmitted from the genes of a parent to a child
  - **familial** = occuring in more members of a family
  - **congenital** = present from birth (hereditary / developed *in utero*)

DNA - function



gene expression

Chromosomal abberations

1) numeric

- abnormal **number** of chromosomes present

- **polyploidy** = more than 2 complete sets of chromosomes
  - euploid set = haploid (n) / diploid (2n)

- **aneuploidy** = abnormal number of single chromosomes
  - not the whole set of chromosomes

Chromosomal abberations

1) numeric

1) chromosomal polyploidy

- **triploidy** = presence of an additional set of chromosomes
  - lettal (development of 3n moles = 69 chromosomes)

- **tetraploidy** = presence of 2 additional sets of chromosomes
  - lethal (development of 4n moles = 92 chromosomes)

Chromosomal abberations

1) numeric

2) chromosomal aneuploidiy

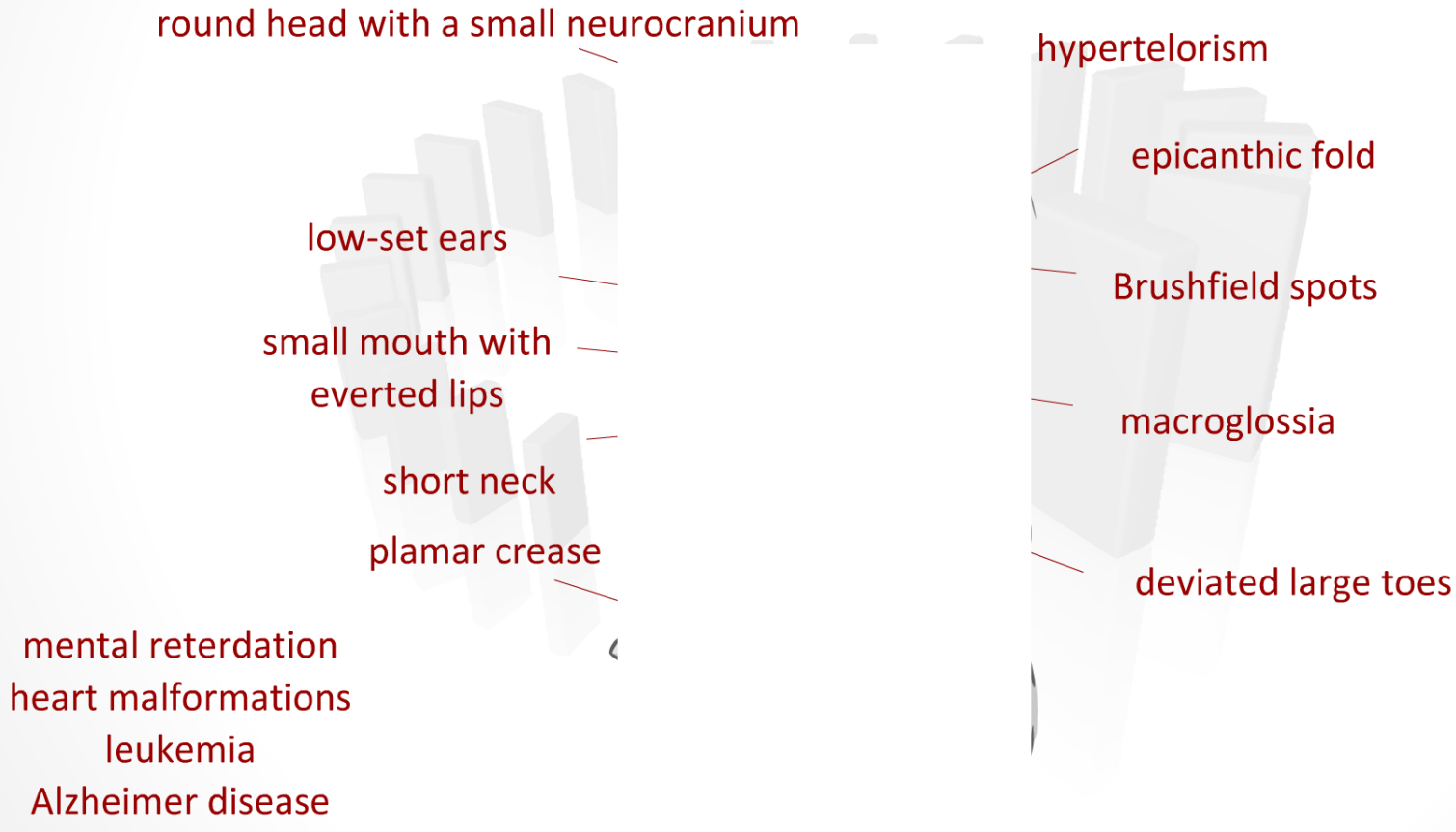
- because of **nondisjunction** during meiosis (increase with the mother's age)

- **trisomy** = third copy of a single chromosome
  - simple / translocation / mozaic **forms** are possible
  - Down (21) / Edwards (18) / Patau (13) / Klinefelter (X) / "supermale" (Y) / "superfemale" (X) syndrome

- **monosomy** = loss of the 1 chromosome
  - Turner (X) syndrome

Chromosomal abberations

1) numeric



Down syndrome (47 XX / XY; + 21)

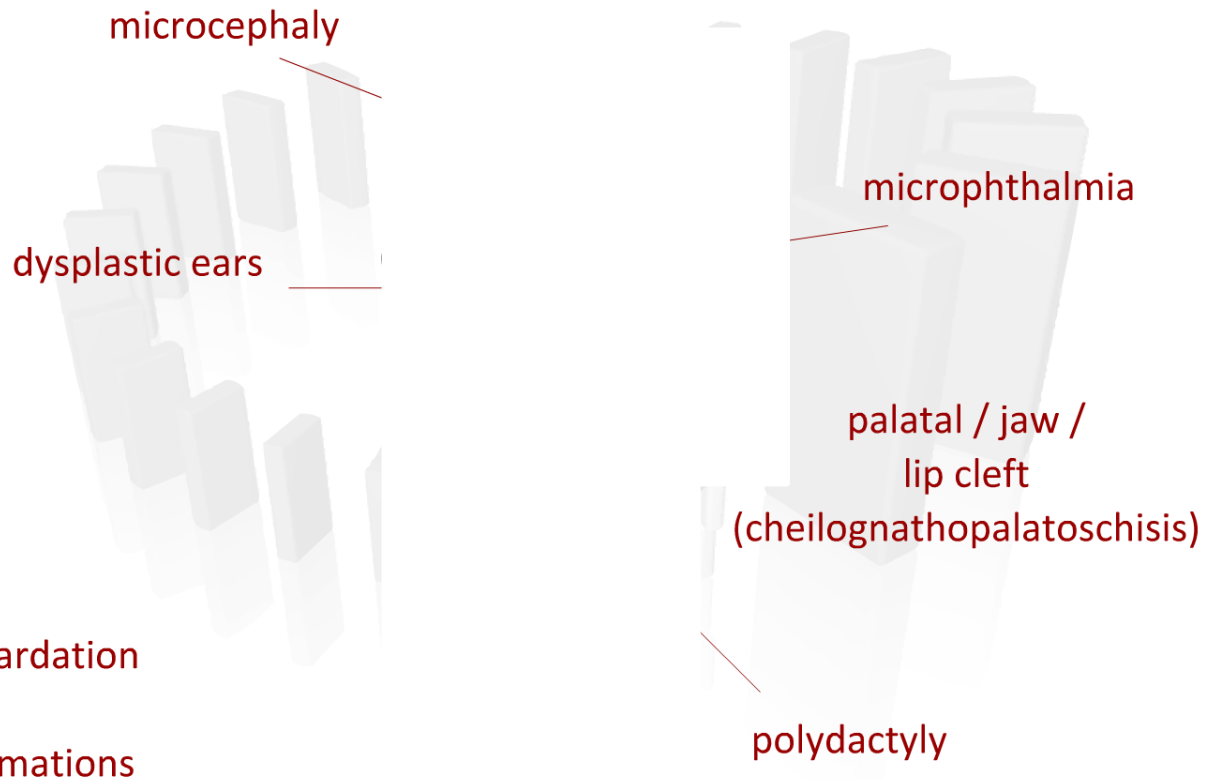
Chromosomal abberations

1) numeric

Edwards syndrome (47 XX / XY; + 18)

Chromosomal abberations

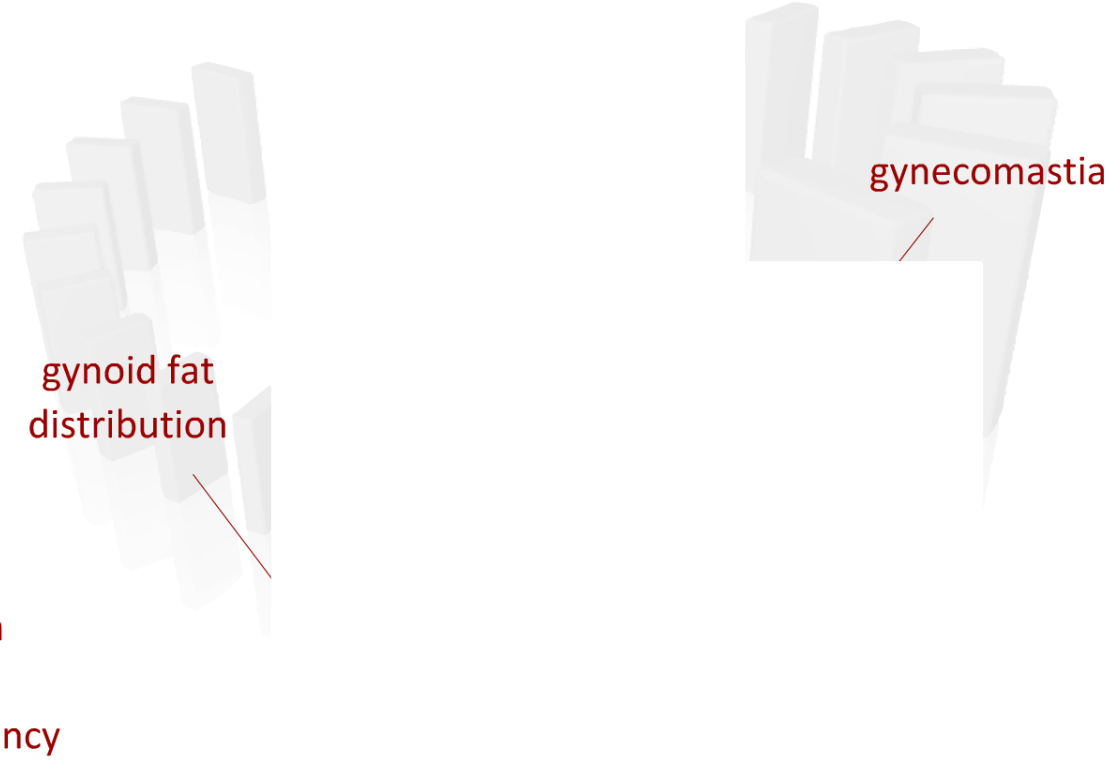
1) numeric



Patau syndrome (47 XX / XY; + 13)

Chromosomal abberations

1) numeric



Klinefelter syndrome (47 XXY; + X)

Chromosomal abberations

1) numeric

short stature
primary hypogonadism
(gonadal dysgenesis =
fibrosis of te ovaries)
amenorrhea
heart malformations
lower life expectancy

"streak ovaries"

Turner syndrome (45 X, - X / defective X)

Chromosomal abberations

2) structural

- abnormal **structure** of a chromosome
  - usually **breakage** followed by a loss / rearrangement of genetic material
  - **balanced** = complete set of genetic material
  - **unbalanced** = gain / loss of genetic material

Chromosomal abberations

2) structural

1) chromosomal **translocation**

- **transfer** of a segment from one chromosome to another

normal

translocation

Chromosomal abberations

2) structural

1) chromosomal **translocation**

- germinal / somatic

- **reciprocal** = segments from 2 different chromosomes are exchanged
  (balanced = asymptomatic, heritable)
- **Robertsonsonian** = fusion of long arms and a loss of short ones
  (-1 chromosome, but asymptomatic; heritable)

Chromosomal abberations

2) structural

2) chromosomal **deletions**

- **loss** of chromosomal segment (terminal / interstitial = intermedial part)

normal

deletion

Chromosomal abberations

2) structural

2) chromosomal **deletions**

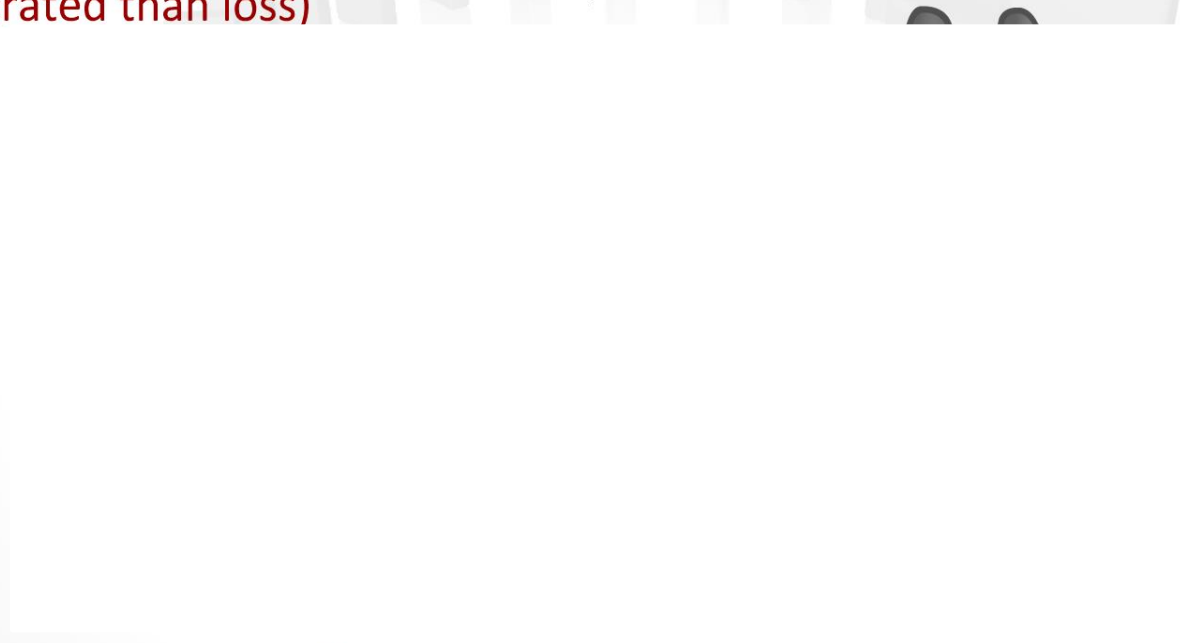
- **germinal** = **microdeletion syn.** (Prader-Willi, DiGeorge, Cri du Chat), Familial retinoblastoma, WARG sydrome
- **somatic** = development of tumors

Chromosomal abberations

2) structural

3) chromosomal **insertion**

- **gain** of chromosomal segment (redundant genetic material is better tolerated than loss)



normal

insertion

Chromosomal abberations

2) structural

4) chromosomal **inversion**

- portion of the chromosome is broken off, turned upside down, and reattached

normal

inversion

Chromosomal abberations

2) structural

5) **ring** chromosome

- portion of a chromosome has broken off and formed a **circle** or ring

normal

ring chromosome

Chromosomal abberations

2) structural

6) isochromosome

- formed by the **mirror image** copy of a chromosome segment

normal

isochromosome

Gene abberations

1) mutation

- *permanent change of the DNA sequence within gene*
  - **germinal** (heritable) / **somatic** (nontransferable)
  - new protein with an **inhibition** ("loss") / **activation** ("gain") of its function (activating mutation)

- **manifestation** is variable
  - asympt. → diversity (evolutionary adaptation) → monogenic disorders → lethal

Gene abberations

1) mutation

1) point mutation ("in-frame mutation")

- base **substitution without** shift of the way the sequence is read

- **synonymous** ("silent") mutation
  - mutated codon encodes **same** aminoacid (same protein)

- **missense** mutation
  - mutated codon encodes **different** aminoacid (different protein)

- **nonsense** mutation
  - mutated codon represents terminal **stop-codon** (shorter protein)

Gene abberations

1) mutation

2) frameshift mutation

- **insertion / deletion** within nucleotide triplet (codon) = **frameshift**
- **every** following borders of triplets and aminoacids are changed
- risk of encoding an early stop-codon (resulting in shorter polypeptide)

Gene abberations

1) mutation

3) dynamic mutation

- expansion of unstable **trinucleotide repeat expansion**
- hereditary **accumulation** of point mutations and manifestation of the disease

  (+ **anticipation** = early and more severe symptoms among generations)
- protein growth caused by trinucleotide repeat expansion and its **toxicity**
- e.g. Huntington chorea (CAG), Friedrich ataxia, Fragile X chromosome

Gene abberations

2) amplification

- increase in the number of copies of a gene in a genome ("expansion, elongation")

- **extrachromosomal** = visible "double minutes" within nucleus / **intrachromosomal** = homogeneously staining regions (HSR)
- gene copies are **not mutated** (functional = excess of proteins; oncogenes)
- e.g. ERBB2 gene (HER2 protein; conclusive for biological treatment)

Gene abberations

3) translocations

- *breakage of introns and gene rearrangement*
  - **gene fusion** (non mutated genes) from different chromosomes
  - expression of abnormal **chimeric proteins** (tyrosin kinases / TF)
  - e.g. BCR/ABL gene and Philadelphia chromosome (Ph) in t(9;22) of CML

Gene abberations

4) epigenetic changes

- regulation of gene expression **without** changes within DNA structuree

1) DNA methylation

- **methylation in promotore region** by DNA-methyltransferase
- **hypermethylation** enables the gene for RNA-polymerase, hence "silencing" it
- e.g. methylation of tumor spressor genes in tumors

Gene abberations

4) epigenetic changes

- regulation of gene expression **without** changes within DNA structure

2) histone modifications

- **histons** as nucleoproteins undergo post-translational modifications
- **modifications** change their secondary / tertiary structure and expression
- e.g activating acetylation (euchromatin) or deaktivating deacetylation (heterochromatin); possibe target for therapy

Gene abberations

4) epigenetic changes

- regulation of gene expression **without** changes within DNA structure

3) RNA interference

- large portion of DNA does not form mRNA (for proteosynthesis), but **ncRNA**
- **ncRNA** = non-coding RNA for regulation of gene expression
- main part of ncRNA is **miRNA** (microRNA; short ncRNA) inhibiting mRNA

Developmental causes of human diseases

Developmental causes of human diseases

- **congenial (inborn)** = present from birth
  - **hereditary (ancestral) diseases** = previous slides
  - **delivered *in utero*** = malformations (nontransferable)

- field of **Teratology**
  - Greek term *teratos* = monster
  - teratogen = outer factor causing malformation

Malformations

Definition

- **prenatal** delivered **abnormally** formed part of the body exceeding variability
  - **manifestation** = early (after birth) / late (functional delay, heart m.)
  - **variable** severity (asympt. anomaly → cosmetic → limiting → lethal)
  - 3% of children have isolated m. (CNS, heart, clefts), 0,7% have multiple (2^{nd} most common cause of neonatal death after prematurity)

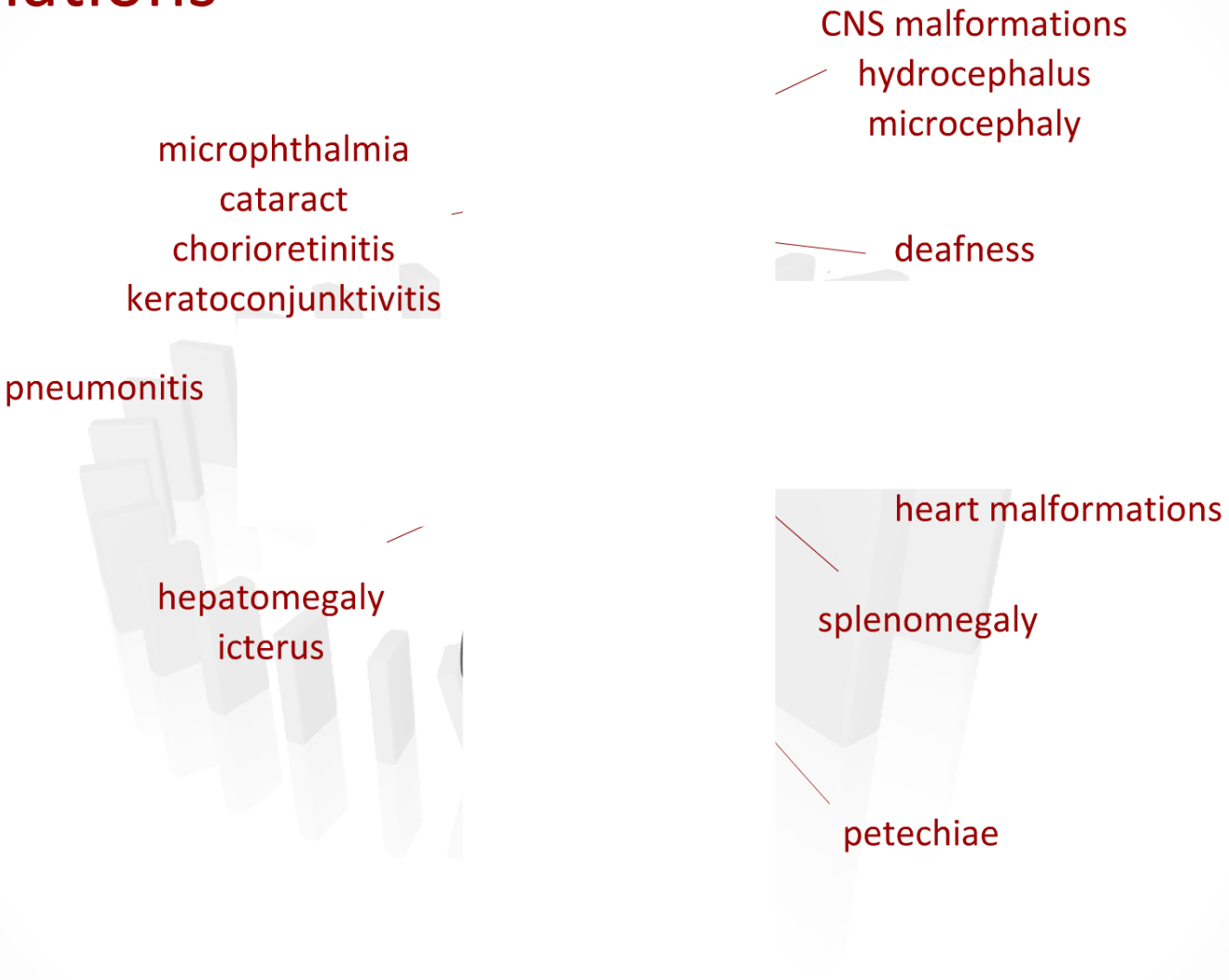
Malformations

Causes (etiology)

- multifactorial influence of inner + outer f. resulting in **disruption** of development
  - **inner** = genetic abberations (previous slides)
  - **outer** = teratogens

- classification of **teratogens**:
  - **biological** = TORCHES CLAP (Toxoplasma + Rubeolla + CMV + HSV + Enterovirus + Syphilis + Variolla + Lym. d. + AIDS + Parvovirus) infection of the mother, DM of the mother (diabetic fetopathy)
  - **physical** = radiation, trauma, pressure (leiomyoma, oligohydramnios), fetal amputation by amniotic bands)
  - **chemical** = drugs (Tetracyclines, Thalidomid...), alcohol, nicotine, illegal d.

Malformations



TORCH complex

Malformations

eformities of the extremities

— renal agenesis

amnion nodosum

ng hypoplasia

face stigma
(*facies Pottera*)

smorphic ears

normal amount of amniotic fluid

oligohydramnios

Malformations

mental retardation
hypotrophy
premature birth

fetal alcohol syndrome

Malformations

Development (pathogenesis)

- it matters most which **period of organogenesis** is affected by teratogens

- **blastogeneis** = conception - 4th week ("all or nothing" mechanism, abortion)
  + non-teratogenous division of blastomeres
  (conjoined twins, teratoma)
- **embryogenesis** = 3rd-8th week (mono- to polytrophic / lethal maformations)
- **fetal period** = 9th week - labor (milder malformations)

Malformations

Morphology

- **abnormally formed** part of the organ / its part:
  - **agenesis** = completely undeveloped organ
  - **aplasia** = rudimentary development of an organ
  - **hypoplasia** = stoppage of the growth (smaller organ)
  - **ectopia (heterotopia)** = normally developed organ in pathological locality
  - **dystopia** = normally developed organ with defective migration
  - **dysplasia** = abnormal microscopic structure of an organ (CAVE)
  - **atresia** = undevelopement of a cavity or lumen
  - **dysraphia** = fusion defect of a pair structures (clefts)
  - **persistence** = defect of an abolishment of fetal / embryonal structures
  - **deformation** = mechanical fetal damage by pathological location / pressure

Malformations

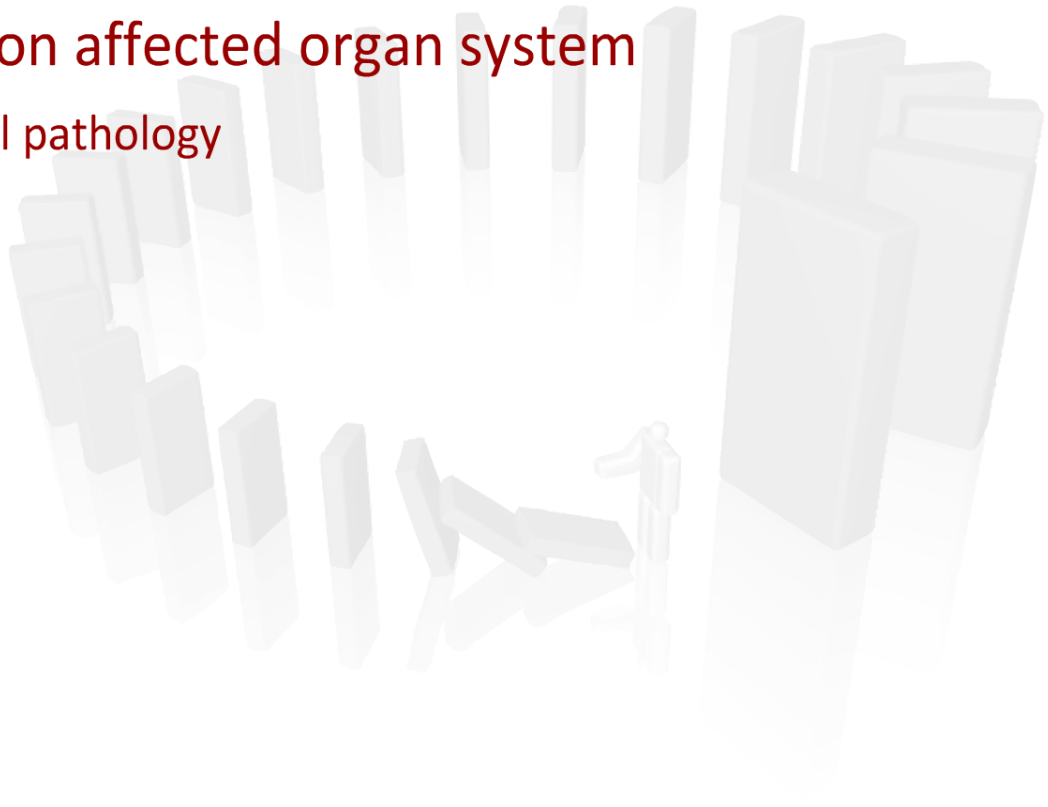
Morphology

- in cases of **multiple malformations**:
  - **syndrome** = multiorgan malformations caused by 1 factor (usually genetics)
  - **asociation** = usual idiopathic combination of malformations (VACTERL...)
  - **sequence** = secondary malformation caused by primary one (Potter's)

Malformations

Clinical manifestations

- depends on affected organ system
  - see Special pathology



Environmental causes of human diseases

Environmental causes of human diseases

- self study

1) diet problems

- malnourishment
- obesity
- vitamin deficiency + hypervitaminosis
- mineral disorders

2) physical

- thermal damage
- electric damage
- mechanical damage
- radiation damage

3) chemical

- intoxications (poisoning)

Infectious causes of human diseases

Infectious causes of human diseases

- self study + microbiology
  - general principles (transmision, spread...)
  - **CAVE** sepsis / bacteremia / pyemia

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