Lectures from Pathophysiology I
General medicine 3rd year
1996-2019

Winter semester

INTERNAL FACTORS

GENETICS 2

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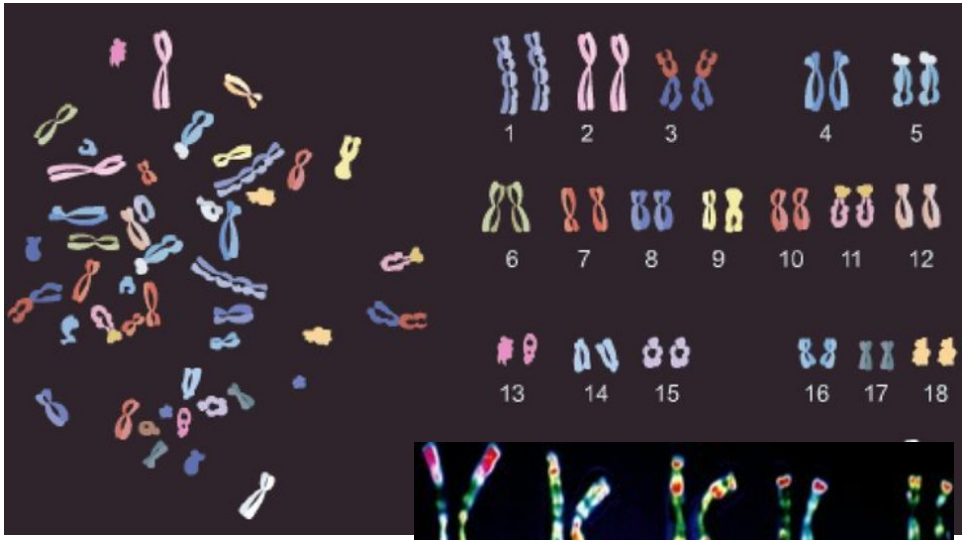
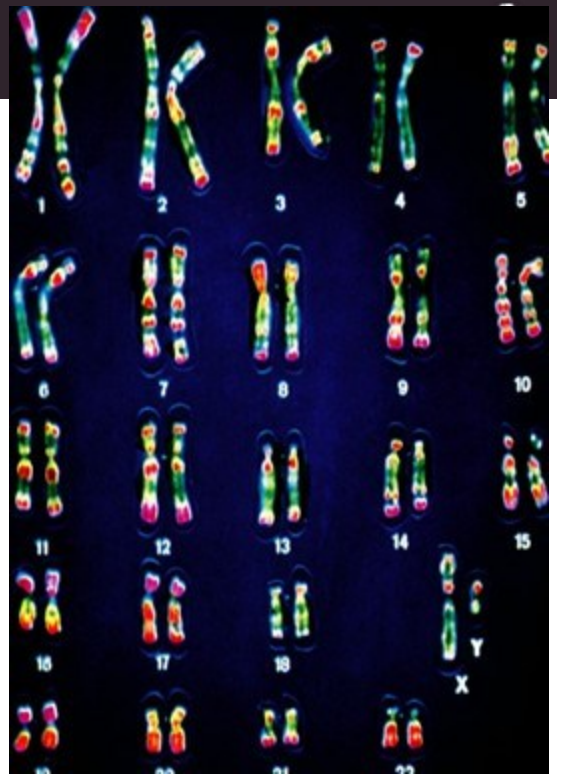
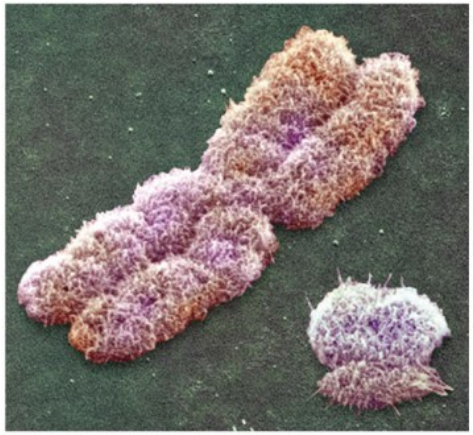
Chromosomal abberrations

Terminology - repetition

- **Karyotype =** microphotograph of chromoso- mes arranged according to a standard classification
- **Chromosome locuses** = topographical location (adress) containing certain genes
- **Homologus chromosomes (HLC)** – the same type of karyotypic chromosome e.g Ch6 from mother and Ch6 from father ; HLC contain the same locuses
- **Heterologous chromosomes** – e.g. Ch 6 and 9
- **Sister chromatides** – typical X like shaped condenzed chromatine in dichromoate chromosome
- **Chromosomal mutation:** change in the structure of chromosomes

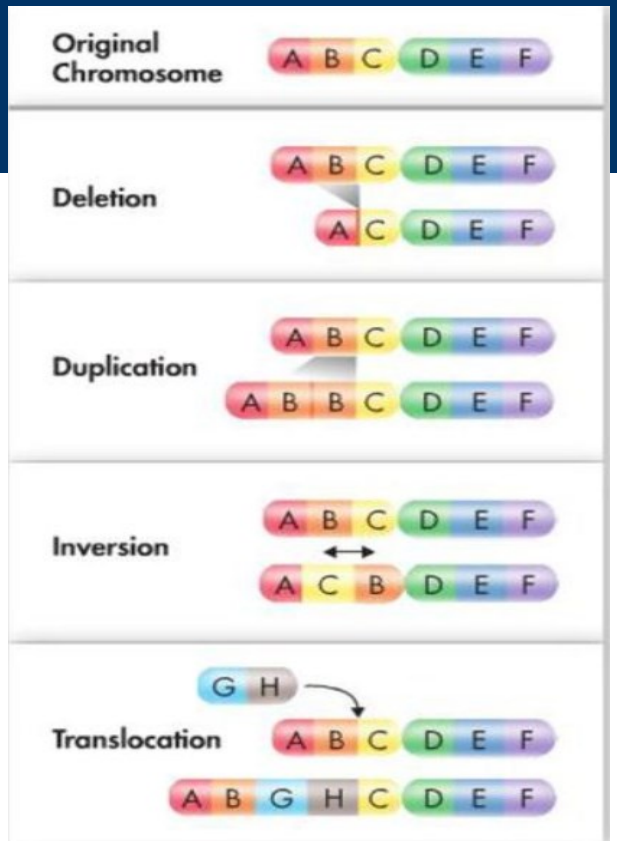


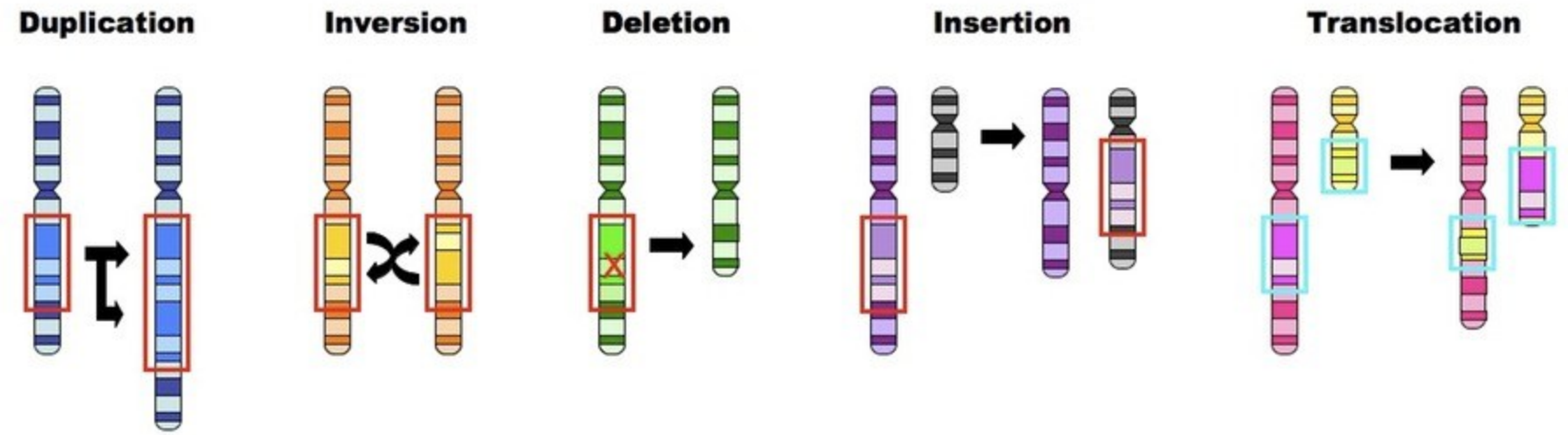




Forms of chromosomal mutations

- **Deletion –** permanent loss of a part of chromosome (small portion or entire p or q arms); Ch6 →
- **Insertion –** part of chromatide breaks off (same kind or different type; e.g. part of Ch6 → Ch6 or Ch6 → Ch21
- **Duplication** – doubling (extra copy) made of a certain structurally distinct Ch part; e.g. insertion of part of ssiter chromatide
- **Inversion** – part of chromosome breaks off and reattaches in reversed direction (can be insertion, duplication)
- **Translocation** - part of one chromosome breaks off and attaches to another chromosome
- **Ring chromosome** – fusion of the ends of chromosome after deletion of the ends (telomeres)





Structural chromosomal aberrations

C) Translocations = many chromosomal **traslocations** are associated with tumors

Lymfoid leukemia

- **Burkitt's lymphoma** - reciprocal translocation t(Ch8 (Myc)→Ch14 (IGH))
- **Follicular lymhoma -** t(Ch14 (IGH) → Ch18 (BCL2) **Acute lymphoblastic leukemia**
- **Mantle cell lymphoma/ Multiple myeloma** t(11 CCND1 → 14 IGH)
- **Anaplastic large cell lymphoma** t(2 ALK → 5 NPM1)

Myeloid leukemia

- **Chronic myeloid leukemia** – reciprocal t(9 ABL ↔ 22 BCR) Philadelphia chromosome
- **Acute myeloblasts leukemia w/ maturation** t(8 RUNX1T1 ↔21 RUNX1)
- **Acute promyelocytic leukemia** t(15 PML → 17 RARA)
- **Acute megakaryoblastic leukemia** t(1 RBM15 → 22 MKL1)

Other tumors

- **Ewing's sarcoma** t(11 FLU → 22 EWS)
- **Synovial sarcoma** t(x SYT → 18 SSX)
- **Dermatofibrosarcoma protuberans** t(17 COL1A1 → 22 PDGFB)
- **Myxoid liposarcoma** t(12 DDIT3 → 16 FUS)
- **Alveolar rhabdomyosarcoma** t(2 PAX3 → 13 FOX01) t(1 PAX7 → 13 FOX01)
- **Desmoplastic small round cell tumor** t(11 WT1 → 22 EWS)

Chromosomal abnormalities

Frequency of chromosomal abnormalities

- 1/3 of pregnancies: lost after implantation
- 10-15% conceptions: chromosomally abnormal
- 95% chromosomally abnormal conception: miscarriage
- structural abnormality of chromosomes
- **oocytes:** 20-25% aneuploidy, 1% structural abnormalities
- **Sperm cells**: 3-4% aneuploidy, 5% structural abnormalities

A) Deletions

- ***Cri du chat syndrome ("feline cry")*** *- deletion of part of the short arm of* ***Ch5 (5p-)***
- ***Prader-Willi syndrome*** *- a deletion of the long arm of* ***Ch5 (5q-)***
- ***Wolf-Hirshorn syndrome (4p-)***

B) Duplications

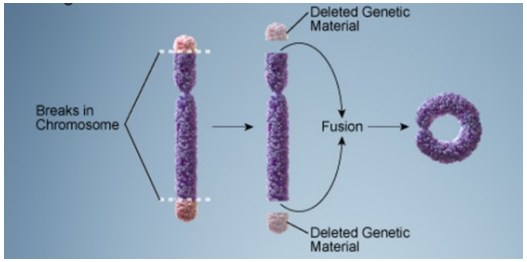
- ***Fragile X chromosome*** *- multiple duplication of DNA on the long arm chr. X*
- ***Myotonic dystrophy*** *- multiple duplication of DNA on the long arm chr. 19*

C) Ring chromosome

- ***Ring chromosome*** *(13; 14; 15; 20)*

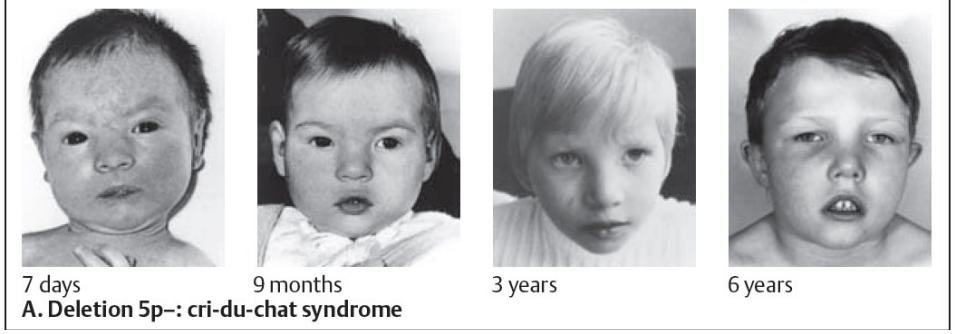
E) Orther lesions

- ***Fragile X syndrome Uniparental disomy XX male syndrome***

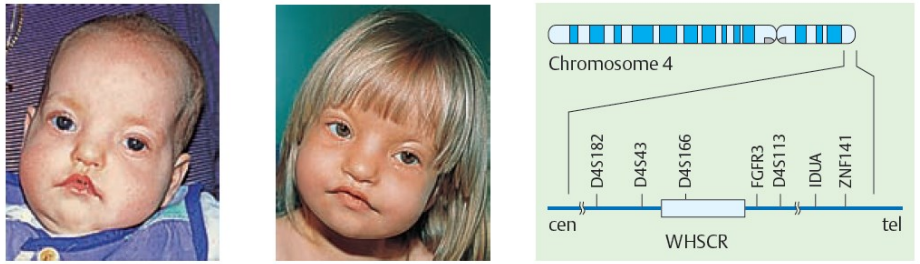


Autosomal Deletion Syndromes

- **Chromosomal arm deletions**
  - Cri-du-chat syndrome (5p-)
  - Wolf-Hirshorn syndrome (4p-)
- **Microdeletions**
  - Rubinstein-Taybi syndrome
  - Williams –Beuren (22p1), Deletion 22q11
- **Duplications**
  - Duplication 5q

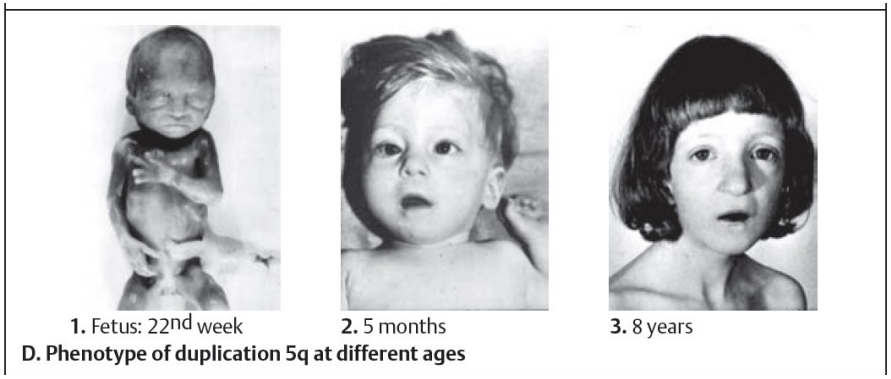


A. Deletion 5p–: cri-du-chat syndrome

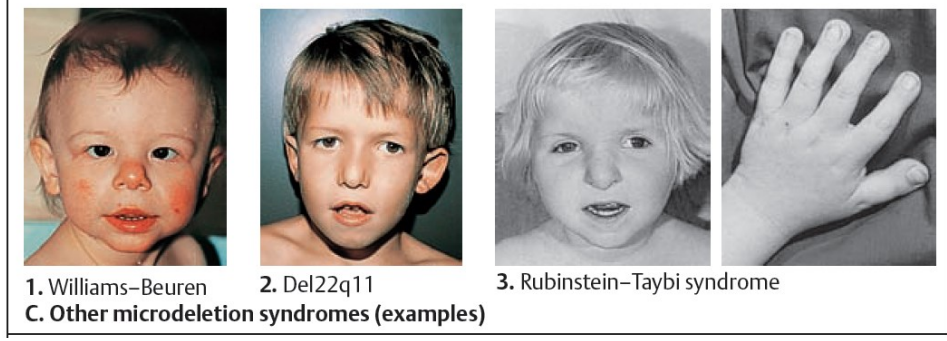


1. Age: 1 1/4 years
2. Age: 4 years
3. Scheme of physical map of 4p16

B. Deletion 4p–: Wolf–Hirschhorn syndrome

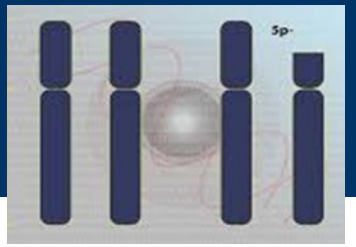


D. Phenotype of duplication 5q at different ages

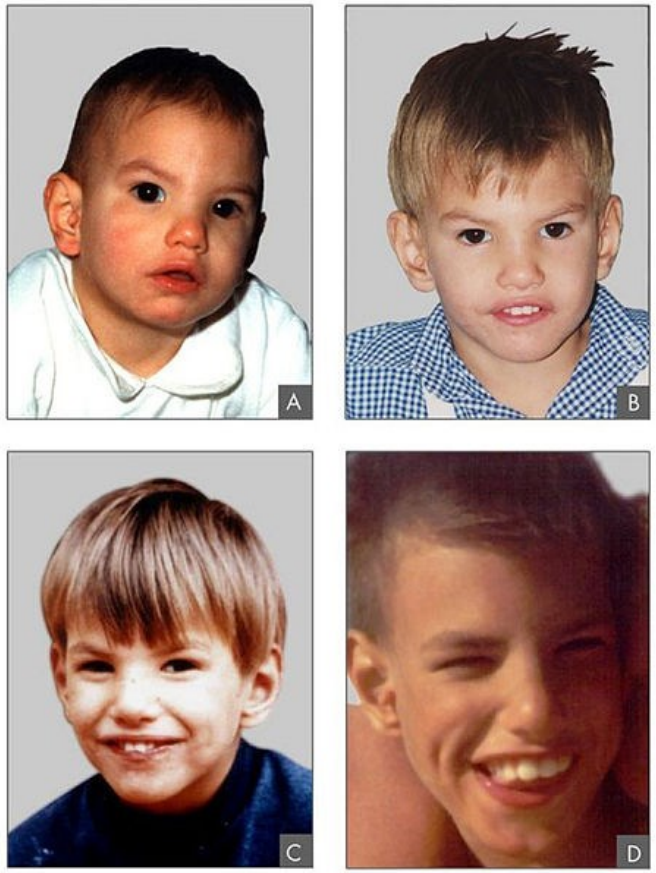


C. Other microdeletion syndromes (examples)

Cri du chat syndrome (5p minus syndrome) Lejeune's syndrome



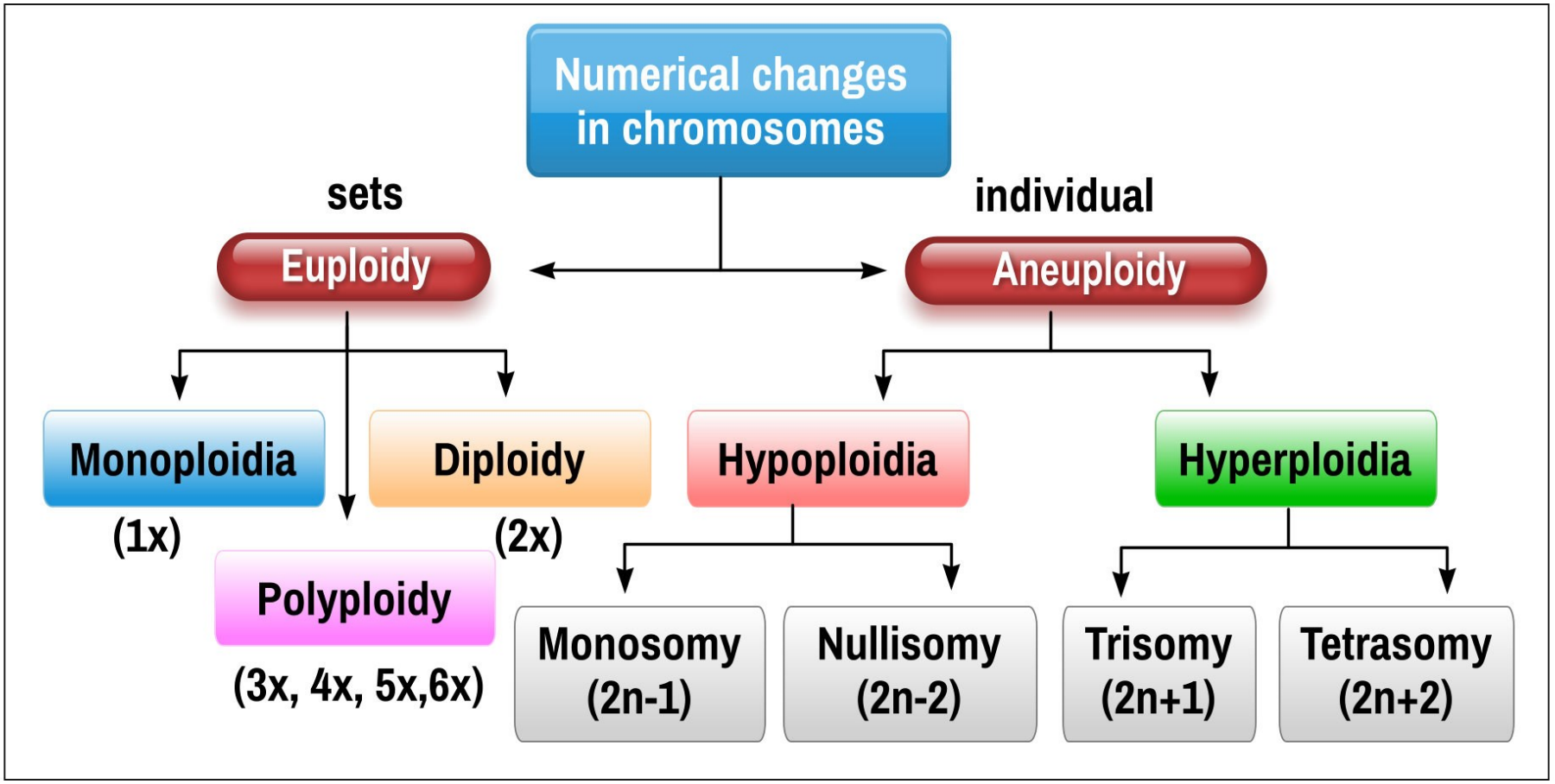
- Def.: sy. of missing of the short arm of chromosome 5 (Ch5p deletion syndrome); first described by Lejeune (1963) (cri du chat = cat-like cry of affected children).
- Epi: rare ~ 1: 50,000 live births, all ethnicities, F>M 4:3 ratio.
- Clin: unusual facial features: small head (microcephaly), and jaw (micrognathia); wide eyes; skin tags in front of eyes. Hypertelorism, epicanthal folds, down-slanting palpebral fissures, strabismus, flat nasal bridge, down-turned mouth, low-set ears,
  - characteristic cat-cry due to maldevelopment of larynx; (in 1/3 cry disappears by age 2y)
  - feeding problems (difficulty of swallowing and sucking); low birth weight and poor growth; growth retardation
  - severe cognitive, speech, and motor delays; hypotonia,,
  - short fingers, single palmar creases constipation;
  - cardiac defects (e.g., ventricular septal defect atrial septal defect patent ductus arteriosus tetralogy of Fallot).
  - behavioral problems such as hyperactivity, aggression, tantrums, and repetitive movements



Facial features of a patient with Cri du Chat syndrome at age of 8 months (A), 2 years (B), 4 years (C) and 9 years (D)
http://en.wikipedia.org/wiki/Cri_du_chat

Genomic mutations

Numeric changes in chromosomes



Numeric mutations

- **Heteroploidy** = numerical changes in chromosomes or variations in chromosome number can be mainly of two types, namely (i) aneuploidy and (ii) euploidy.
- Aneuploidy = presence of chromosome number which is different than a multiple of basic chromosome number (2n = 15, 2n = 13)
- **Euploidy** = one or more full sets of chromosomes (2n = 7, 21, 28, 35 or 42)
- (A) Disomia = OK, normal
- (B) Monosomia + Polysomia = incompatinle with life in fetus
- **Aneuploidy** = loss of one or more chromosomes (hypoploidy) or addition of one or more chromosomes to complete chromosome complement (hyperploidy).
- chromosome number different than a multiple of basic chromosome number
- **A. Hypoploidy** = loss of 1 Ch (monosomy (2n - 1)), or one pair of chromosomes nullisomy (2n - 2)
  - **Monosomy** - lack 1 complete Ch, cannot be tolerated in diploids; could be easily produced in polyploid (has several Ch of same type and can be easily tolerated..
- **B. Hyperploidy** = addition of 1 Ch (trisomy (2n + 1)) or a 2 Ch tetrasomy (2n + 2).
  - Trisomies

Genomic mutations

- **Genomic mutations** - deviations from the basic **diploid number (2n) of chromosomes** of a somatic cell or the haploid number (n) of chromosomes of a gametic cell (**heteroploidy or polyploidy)**
  - **aneuploidy** - a change in the number of individual chromosomes
  - **euploidy** - a change in the multiplicity of the entire chromosome set

(1) Aneuploidy

- **Monosomies - Hypoploidy**
  - **Turner syndrome** - only X gonosome.
- **Trisomies Hyperploidy (>2)**

A) Autosomes

- **Down syndrome** - 21. chromosome; 1 : 700
- **Edwards syndrome** - 18. chromosome; 1 : 4000
- **Patau syndrome** - 13. chromosome; 1 : 5000

B) Gonosomes

- **Superfemale** - aneuploidy of female X gonosome - XXX,
- **Supermale** - aneuploidy of Y chromosome - XYY
- **Klinefelter's syndrome** - gonosomes are complemented by a second X chromosome - XXY

Genomic mutations

(2) Euploidy

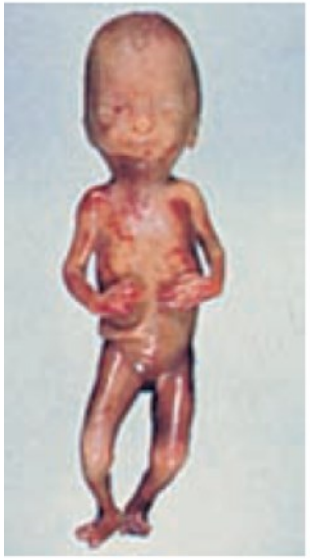
- **A) Monoploidy -** cells of an organism have 1 chromosome of that type (<2 paired (homologous) sets of chromosomes). In humans, monoploidy is lethal.
- **B) Polyploidy=** cells of an organism have > 2 homologous sets of chromosomes. lethal in humans. Triploidy is the most common (15-20% of spontaneous abortions), tetraploidy (5% of spontaneous abortions).

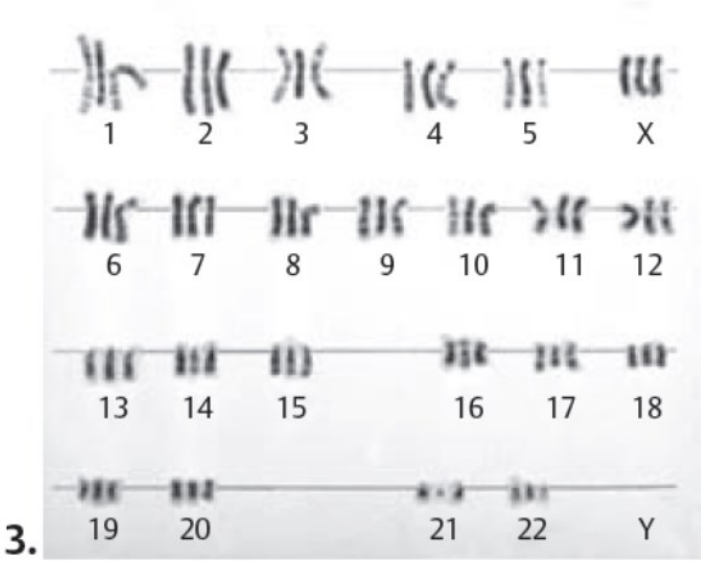
- **Triploid** – with 3 sets, e.g. seedless watermelons, banana, apple, lily, tulip
- **Tetraploid** – with 4 sets, e.g. Salmonidae fish, durum wheat, corn, cotton, potato, cabbage, leek, tobacco, peanuts, mace
- **Pentaploid** – with 5 sets, e.g. Kenai Birch (Betula papyrifera var. kenaica)
- **Hexaploid –** with 6 sets, e.g. wheat, kiwifruit, wheat, chrysanthemum, oats
- **Heptaploid** (or septaploid) – Siberian sturgeon
- **Octaploid** (or octoploid) – with 8 sets, e.g. dahlias, strawberry, dahlia, violet, sugar cane
- **Decaploid –** with 10 sets, e.g. certain strawberries
- **Dodecaploid** – with 12 sets, e.g. plant Celosia argentea, amphibian Xenopus ruwenzo
- **Tetratetracontaploid (**forty-four sets; 44x),

Polyploidy

- ***Autosomes:***
- Frequent chromosomal anomaly (15%) following spontanous abortion
- Azoospermia is as a frequent cause

- ***Gonosomes:***
- Triploidy or tetraploidy of X or Y chromosomes - ½ half of all chromosomal aberrations in man (total frequency about 1:400). accounts for about 17% of spontaneous abortions (karyotype 69,XXY or 69,XXX) or one maternal and two paternal sets (69,XXX, 69,XYY or 69,XXY)





3.

Genomic mutations

Autosomal

Trisomies

Down sy. Ch 21 *Edwards sy. Ch 18* *Patau sy. Ch 13*
Trisomy 9 *Trisomy 8/ Warkany syndrome 2*
Trisomy 22/Cat eye syndrome *Trisomy 16*

Monosomies/ Deletions

1q21.1 deletion syndrome/
1q21.1 duplication syndrome/TAR syndrome
Wolf-Hirschhorn sy. Ch4
Cri du chat/ Chromosome 5q deletion syndrome Ch5
Williams syndrome Ch7 *Jacobsen syndrome Ch11*
Miller–Dieker syndrome/ *Smith–Magenis syndrome Ch17*
DiGeorge syndrome Ch22 *(Ch22q13 deletion syndrome)*

Gonosomal

Disomies Trisomies/

Bisexual 46,XX/XY
Klinefelter syndrome (47,XXY), Triple X syndrome (47,XXX)
Supermale sy. 47,XYY

Tetrasomies Pentasiomies

48,XXYY 48,XXXY 49,XXXYY 49,XXXXY 48,XXXX, 48,XYYY
49,XXXXX 49,XYYYY

Monosomies

Turner sy. (X0)

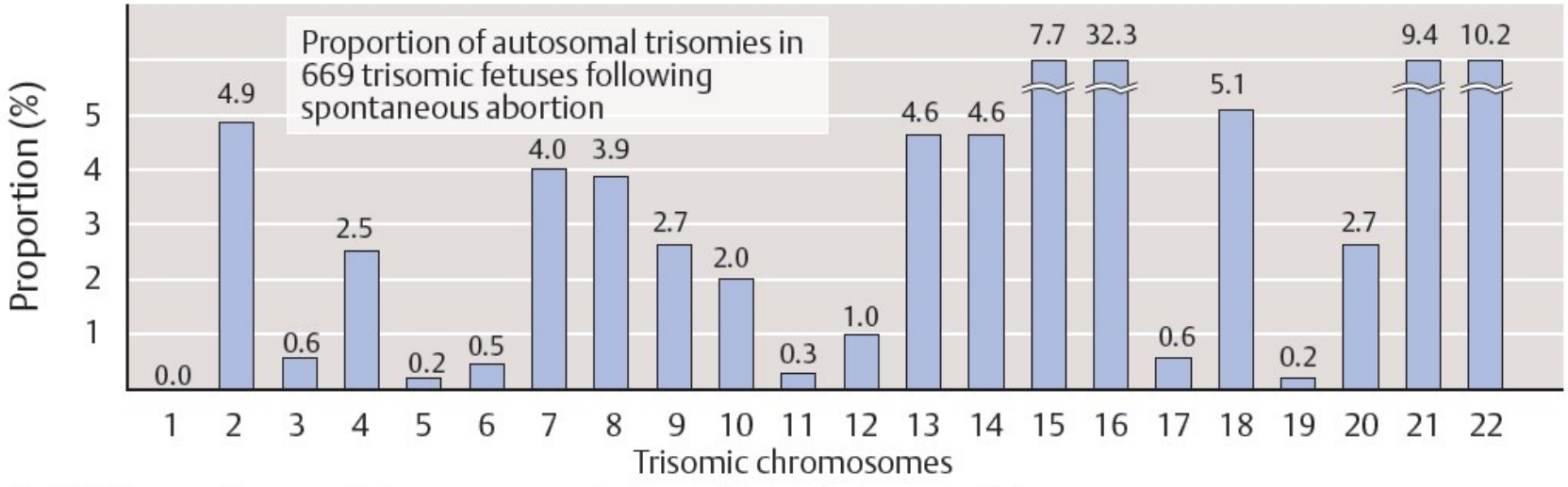
Numerical Chromosomal Deviations

- First discovered in a plant - apple (Datura stramonium) by A.F. Blakeslee in 1922. Trisomies in the mouse trisomy 12 (open skullcap and other malformations on the 14th day of fetal development),brain of a mouse with trisomy 19 is too small
- A wide spectrum of **trisomies (**and **monosomies**) occur at conception and lead to spontaneous **abortion during the second and third months of pregnancy.**
- **The most frequent is trisomy 16**; accounts for about 5% of all autosomal trisomies.
- Embryos with a **monosomy** died within the first 8 days of the 21-day gestation.
- **Sy:** severe developmental failure and severe congenital malformations cardiac defects, cleft lip and palate, skeletal defects, and others. causes include diploid spermatocyte, a diploid oocyte, or fertilization of an egg cell by two spermatozoa (dispermy).
- SHOX genes = increased stature seen in trisomies: 47,XXX, 47,XXY, and 47,XYY

Autosomal trisomiesons

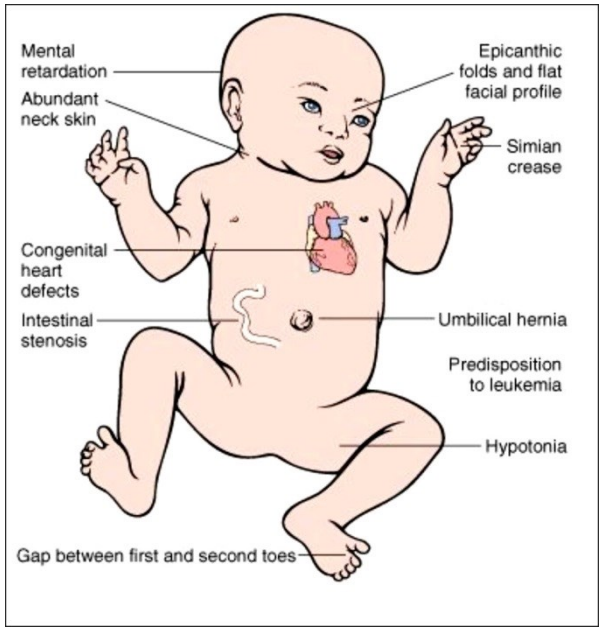
Autosomal trisomies

- **Trisomy 21 (about 1:600), trisomy 18 (about 1:5000), and trisomy 13 (about 1:8000).**
- Each has a **distinct pattern of congenital malformations** associated with variable degrees of mental impairment in trisomy 21 (Down syndrome) and complete lack of mental development in trisomies 18 and 13. Only trisomy 21 is compatible with survival into adulthood;
- **Etio:** genetic + congenital + non-familal
  - a) **inherited:** chromosome aberration = translocation (part of Ch, e.h. 18, 21)
  - b) ***prezygotic -*** not inherited; nondisjunction - meiosis I (3 chromosomes are different (1+1+1), during meiosis I;I 2 chromosomes of 3 will be identical (2 + 1).
  - c) ***postzygotic -*** mitosis in blastula/ mosaicism ; not inherited:
- more frequently with advanced maternal age; age of the father has no or very little influence.
- In humans, about 70% of nondisjunctions occur in meiosis I, and 30% in meiosis II.



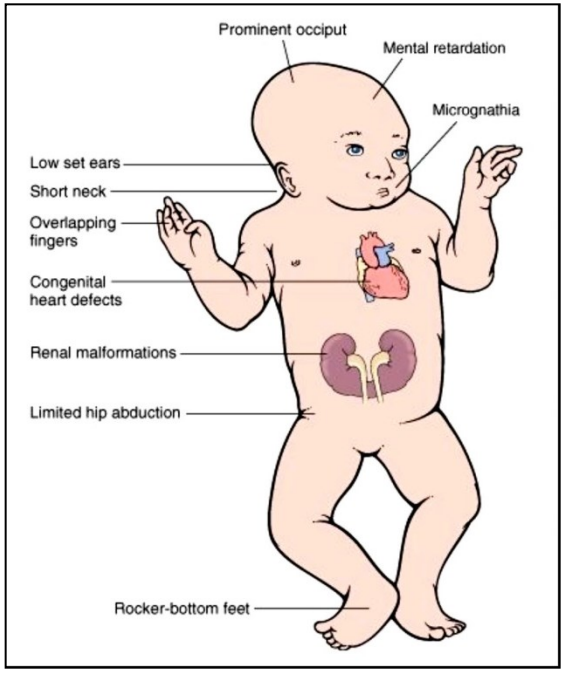
Human autosomal trisomies

Down syndrome



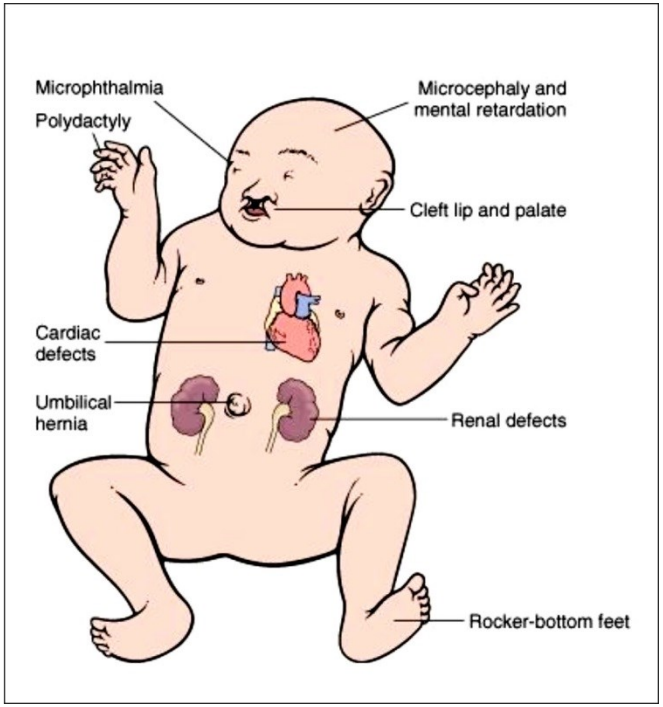
Incidence: **1 in 700 births**
Trisomy: 21 type: 47, XX. +21
Translocation type:
46.XX.der(14;21)(q10;q10).+21
Mosaic type: 46.XX/47.XX, +21

Edwards syndrome



Incidence: **1 In 8000 births**
Trisomy 18 type: 47.XX, +18
Mosaic type:46,XX/47,XX, +18

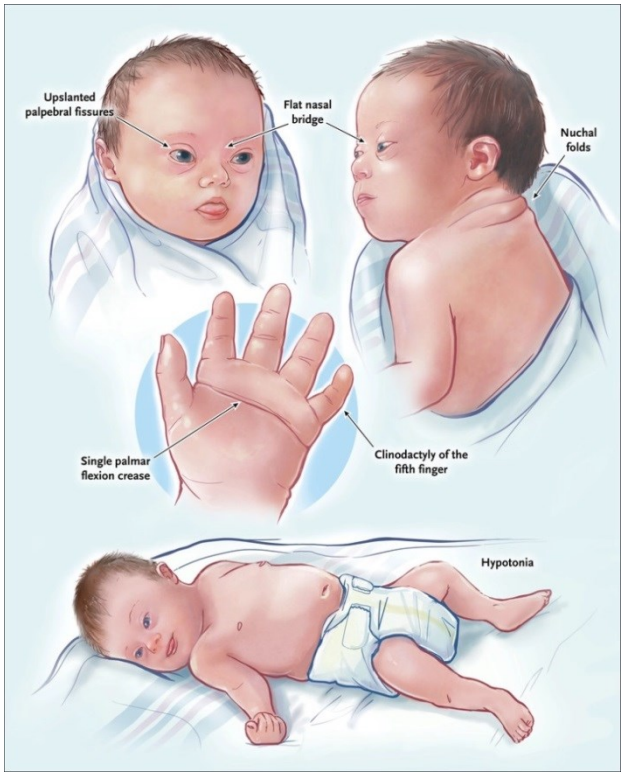
Patau syndrome



Incidence**: 1 in 15,000 births**
Trisomy 13 type:47.XX, +13
Translocation type:
46.XX,+13,der(13;14)(q10;q10)
Mosaic type: 46.XX/47.XX, +13

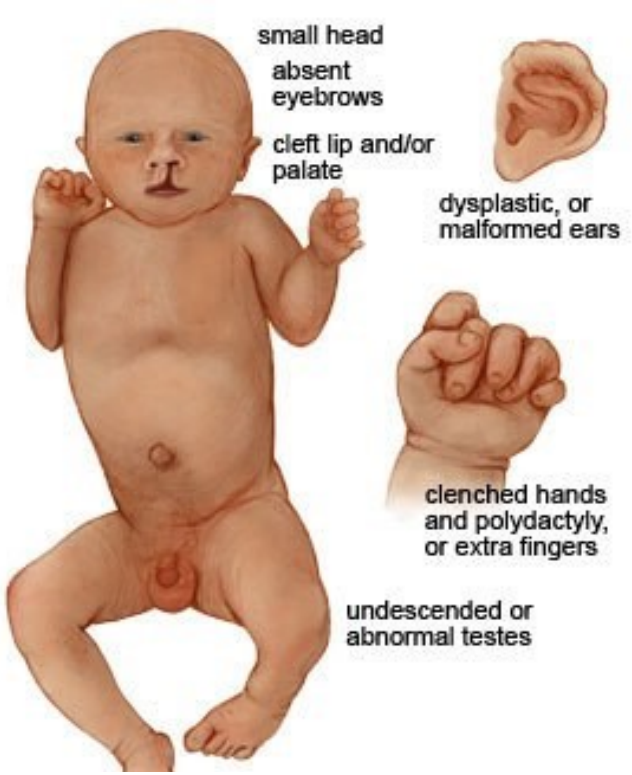
Down syndrome T21

- Def: **most severe** of autosomal trisomy, 80% of patients die within 1st month of life; 10% survive until 1. year; 1957 by Bartholini
- Etio: advanced maternal age
- Epi: **least common** (incidence 1/4000 – 1/10000 newborns); more common in girls (boys have reduced rate of survival)
- Clin:
  - **Head:** microcephaly, malformed ears.
  - **Face:** sloping forehead, broad flat nose hypertelorism, hypotelorism, microophthalmia or anophthalmia, absence of iris, cataract, cleft lip and cleft palate.
  - **Neurologic:** Holoprosencephaly (brain is not divided completely into halves),
  - **Limbs:** polydactyly, sindactyly.
  - **Cardiac: 80% of all manifestations** (patent ductus arteriosus, ventricular septal defect, interatrial septal defect, dextrocardia).
  - **Genitourinary:** polycystic kidney, renal duplicaton, double ureter, testicular agenesis and cryptorchidism in boys, clitoral hypertrophy + two-horned uterus in girls.
  - Capillary hemangiomas on the face, forehead and neck.



Patau syndrome T13

Def: most severe of autosomal trisomies, 80% of patients die within 1st month of life; 10% survive until 1. year; 1957 by Bartholini
Etio: advanced maternal age trisomy 13 (47, XY, +13) by nondisjunction or translocation
Epi: least common (incidence 1/4000 – 1/10000 newborns); more common in girls (boys have reduced rate of survival)



- **Head:** microcephaly, malformed ears.
- **Face:** sloping forehead, broad flat nose hypertelorism, hypotelorism, microophthalmia or anophthalmia, absence of iris, cataract, cleft lip and cleft palate.
- **Neurologic:** Holoprosencephaly (brain is not divided completely into halves),
- **Limbs:** polydactyly, sindactyly.
- **Cardiac: 80% of all manifestations** (patent ductus arteriosus, ventricular septal defect, interatrial septal defect, dextrocardia).
- **Genitourinary:** polycystic kidney, renal duplicaton, double ureter, testicular agenesis and cryptorchidism in boys, clitoral hypertrophy + two-horned uterus in girls.
- Capillary hemangiomas on the face, forehead and neck.

Edwards syndrome (T18))

- **Def.:** second most common trisomy; J. H. Edwards (1960);
- **Etio:** trisomy 18 (47, XX, +18) by nondisjunction in meiosis, increases as the mother's age or translocation
- **Epi:** 1: 5,000/ 6,000 newborns; ♀: 47 XX+13; ♂: 47 XY+13, 80 % are female; 75-95% die before birth
- **Clin:** Microcephaly, holoprosencephaly; Facial anomalies (cleft lip +palate, Low-set, malformed ears; bulbous nose; small chin
  - Eyes: microphthalmia (small orbits, which may be unilateral or bilateral), possibly coloboma , ocular hypotelorism
  - Polydactyly, primarily hexadactyly, flexed fingers
  - Congenital heart defects (particularly ventricular septal defect, patent ductus arteriosis)
  - Kidney + ureters (e.g., polycystic kidney), malformations, omphalocele, diaphregmatic hernia, spina bifida, Rocker-bottom feet
  - Aplasia cutis congenita, Capillary hemangioma

Maternal Age Effect Hypotheses

older women less likely to spontaneously abort

older women increase in nondisjucional occation

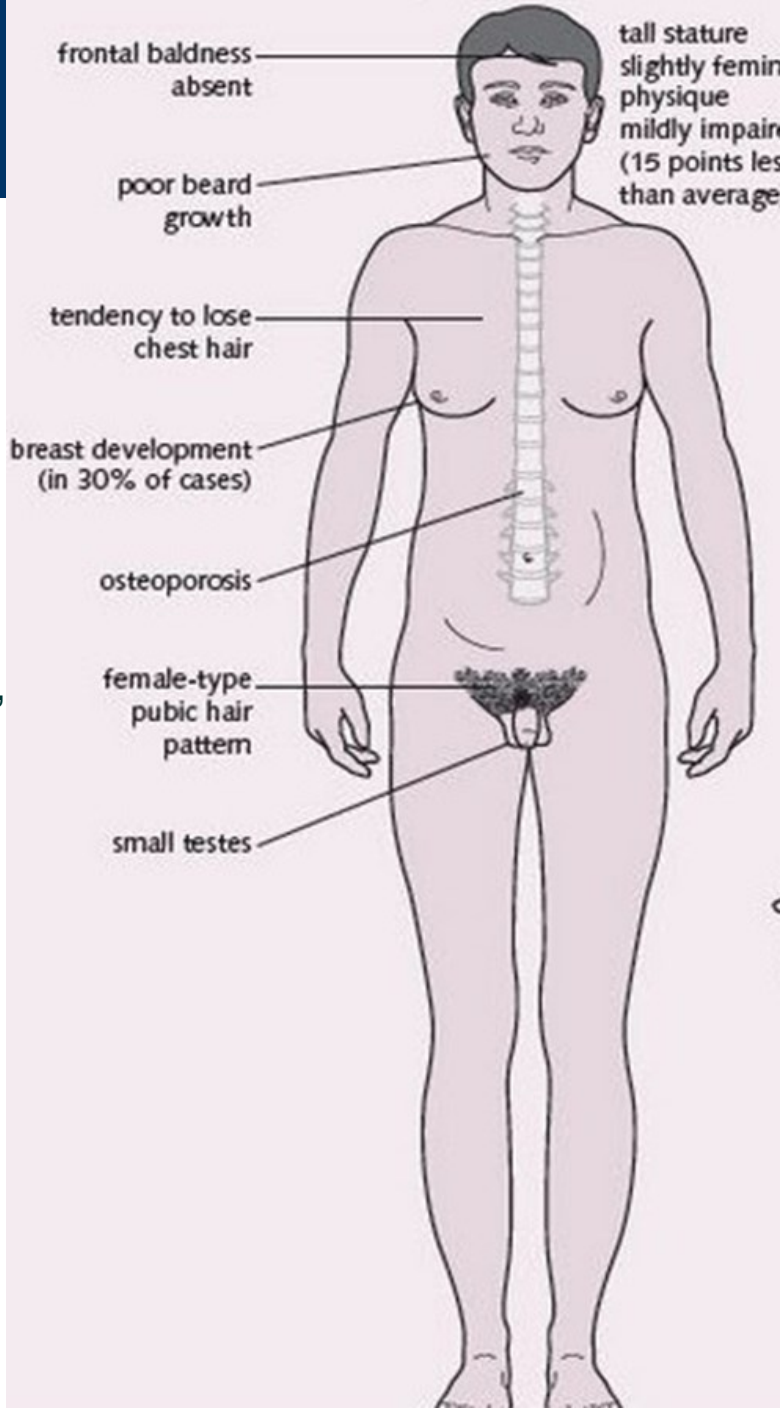
other internal and external factors

Gonosomal trisomies

Klinefelter syndrome (47,XXY)

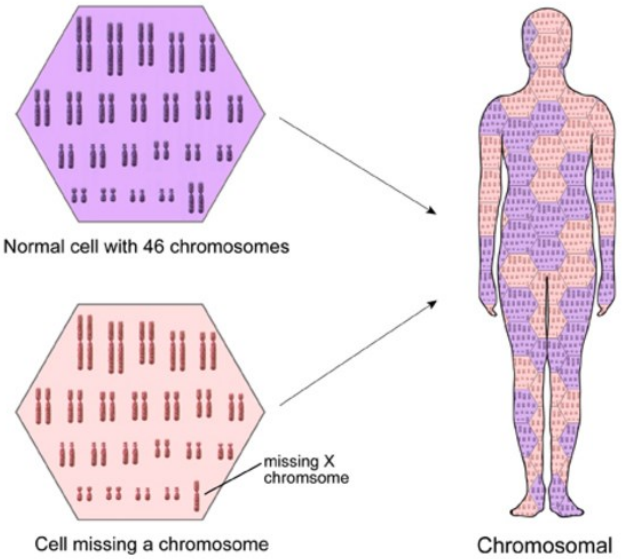
Klinefelter-Reifensteinov-Albright syndrome

- Epi: 1:1,000 male births
- Etio: 50% maternal (maternal age effect), 15% mosaicism
- 48, XXXY/ 49, XXXXY: more severe phenotype
- 50% spontaneous abortion
- Clin: tall, small and firm testes, atrophy of seminiferous tubules →absent spermatogenesis →sterility, low testosterone→ absent or minimal male secondary sex signs,
- gynecomastia, subaverage intelligence



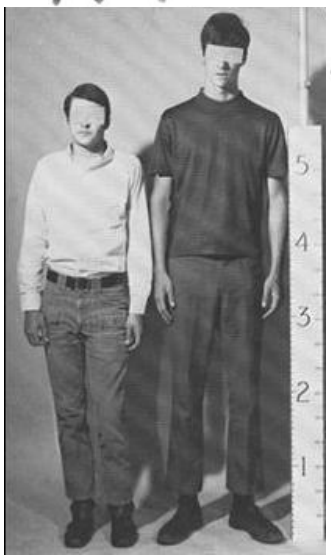
47, XYY syndrome (Supermale)

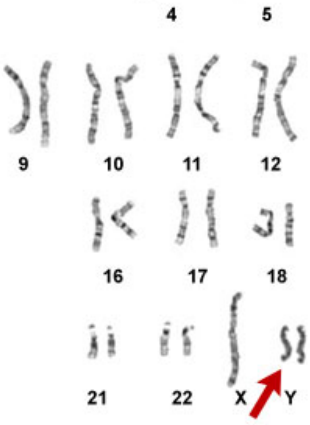
- Def: YY syndrome Jacob's syndrome
- Epi: incidence 1/ 1,000 male births; 30-50% undiagnosed;
- Sandberg (1961): frst describ; associated with criminality ?? (massive murder R Speck suspected; 46,XY proven)
- Etio: mostly non-inherited, sporadic (sperm; meiotic non disjunction) 47,XYY karyotype; mitotic nondiscunction: mosaic 46,XY+ 47,XYY.
- Clin: taller than average, acne, learning problems, normal fertility
  - prenatal or chldhood testosterone normal - not increased agressivity; normal sexual development/ normal fertility;
  - increased growth rate a bit (10cm); acne
  - IQ intelligence reduced slightly vs. normals; much less than in 47,XXX/ 47,XXY; sevelopm. delay/ behavioral def. possible,
  - 1/2 learning difficulties; aggression is not common



https://ghr.nlm.nih.gov/art/large/mosaicism.jpeg

U.S. National Library of Medicine

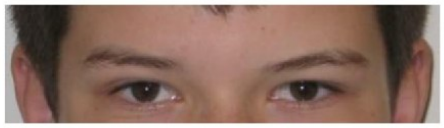




Source: Wikipedia, Licence CC 4.0

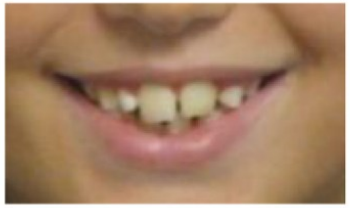
47, XYY syndrome (Supermale

A



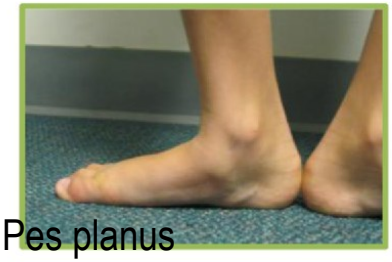
Hypertelorism

B



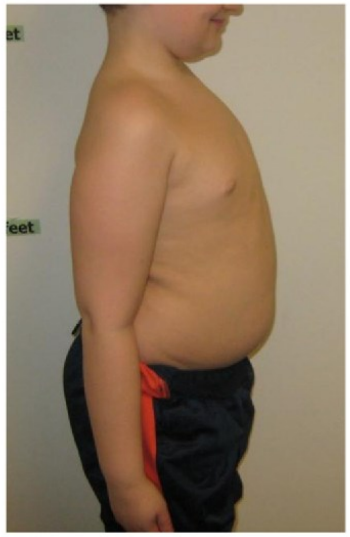
Big teeth.

C

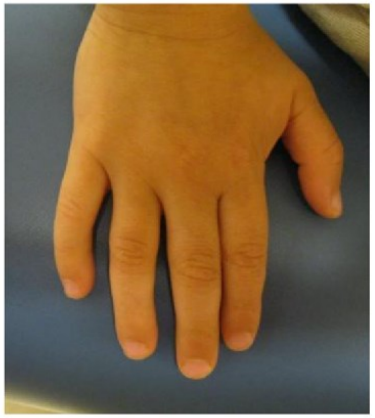


Pes planus

D



E Clinodactyly.



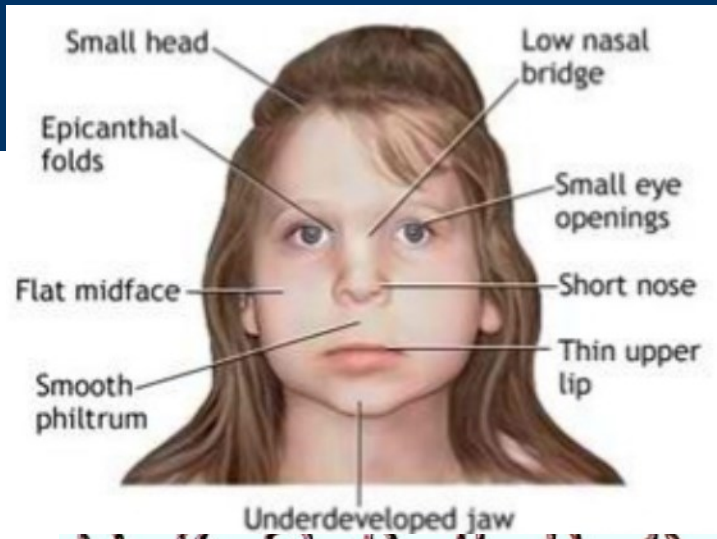
Central adiposity

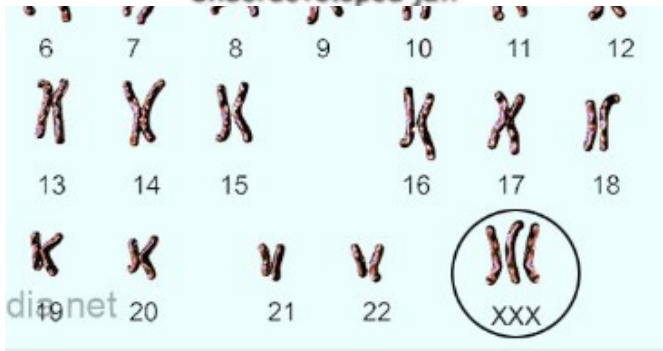
Bardsley, M. Kowal, K. et al.:47,XYY syndrome: clinical phenotype and timing of ascertainment. Journal of pediatrics 2013

Triple XXX syndrome

Triple XXX syndrome, 47, XXX (Superfemale)

- Epi: 1:1000 live births female sex ; 10% cases diagnosed
- Etio: usually not inherited; but can be
- (a) meiotic non disjunction (egg or sperm with 2X) --> conception --> zygota 3X ---in all somatic cells (47, XXX)
- (b) abnormal mitosis during the morula or blastula --> extra X only in some somatic cells ---> 46, XX/ 47, XXX mosaicism.
- Clin:
  - Neonate: no visible differences
  - Scholl: tall stature, face features (low wide nasal bridge), learning disabilities,attention-hyperactivity dis., delayed dev. of speech & language
  - Puberty: limited fertility, weak muscle tone, behavioral and emotional difficulties.

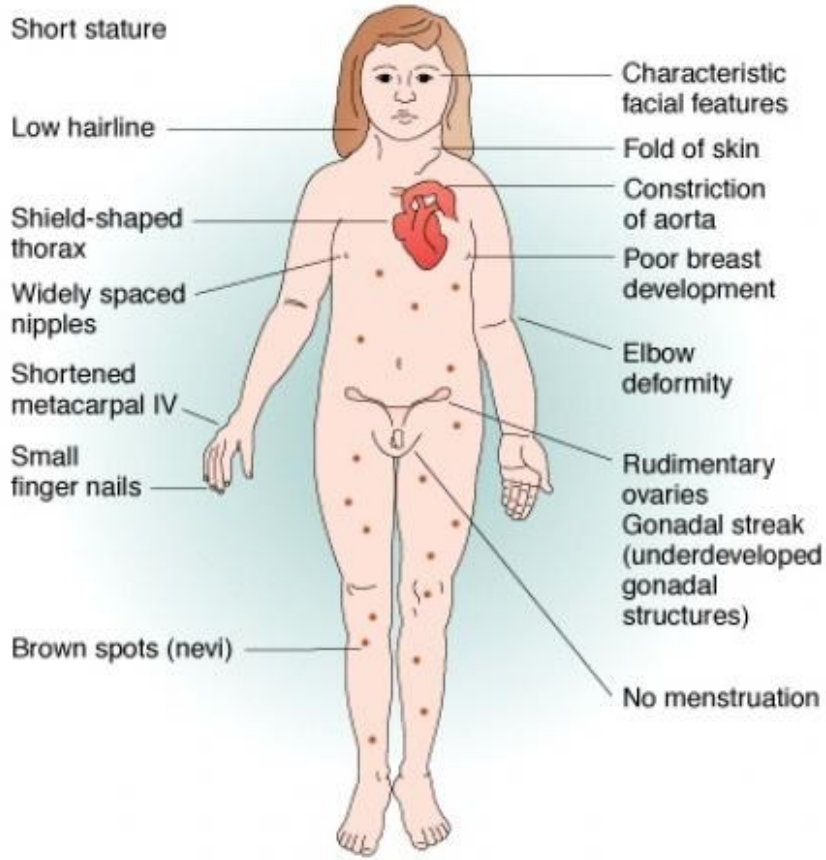


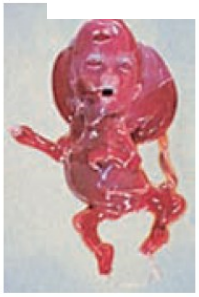


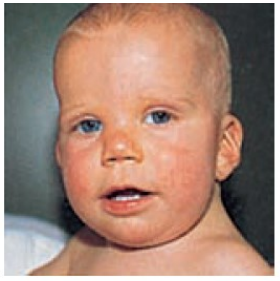
Source: Wikipedia, Licence CC 4.0
Color atlas of genetics , Thieme

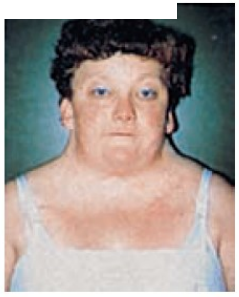
Monosomy X (Turner syndrome karyotype 45,X)

- ***Occ.:*** 5% at conception; of 40 zygotes with monosomy X, only one will develop to birth
- Most patients have chromosomal mosaicism 45,X/46,XX, deletion Xp or an isochromosome for the long arm [i(Xq)].
- ***Sy:*** wide phenotypic spectrum, ranging from severe (abortion) to very mild
- Massive lymphedema of the head and neck, large multilocular thinwalled lymphatic cysts
- Small stature (~150 cm) webbing of the neck (pterygium colli); degeneration of the ovaries
- Congenital cardiovascular defects (aorta, kidney malformations) ;
- The loss of genes on the short arm of the chromosome (Xp)



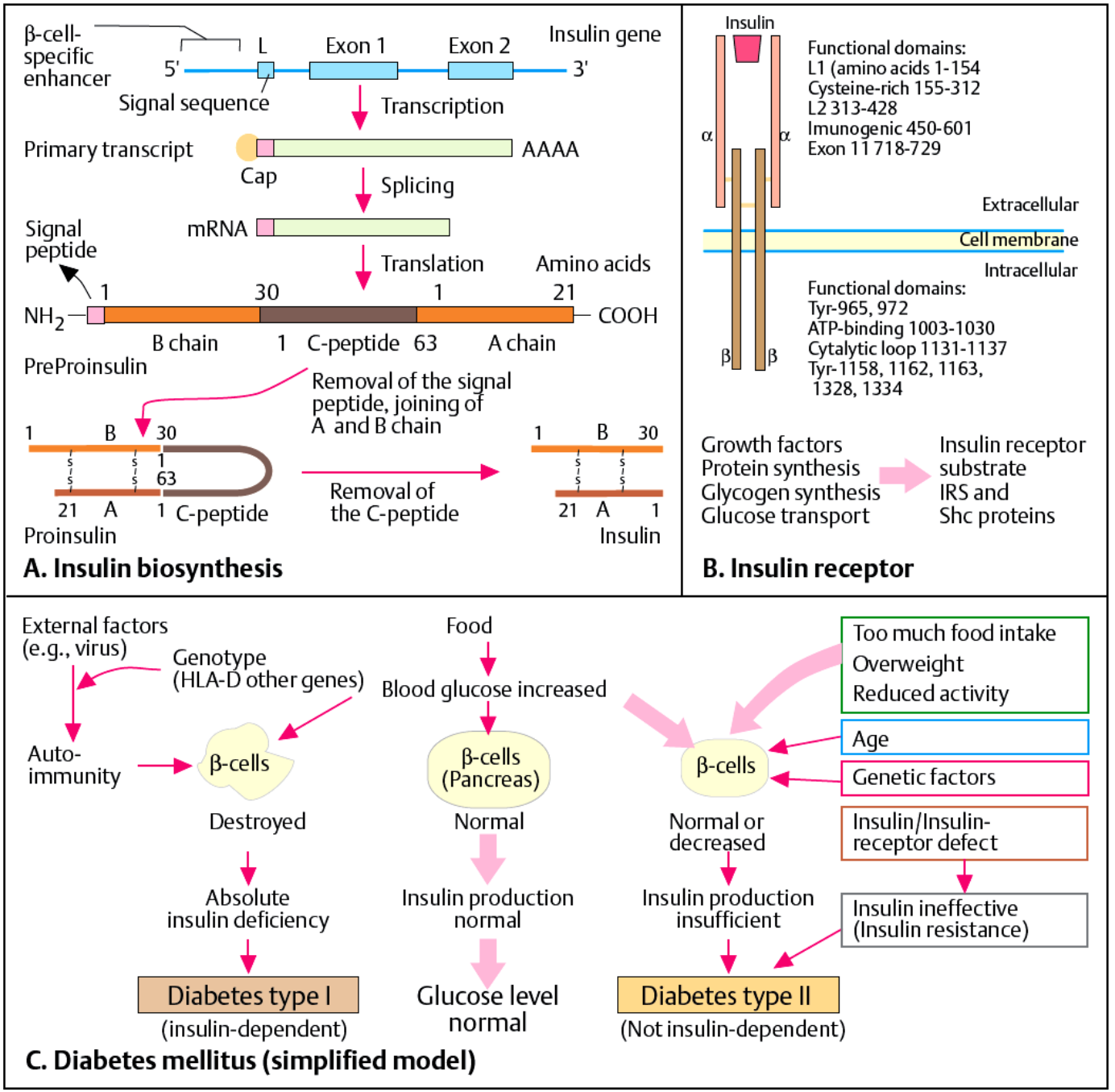

1. *Abortion*


2. *Mild form*

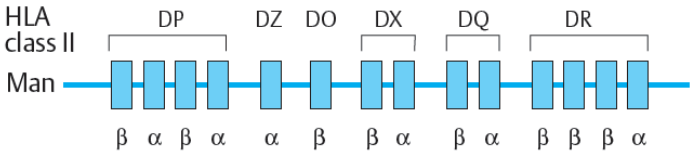

3. *Lymphedema*

Hereditary predisposition

Inheritance in diabetes



Inheritance in diabetes



Susceptible haplotypes: DR3 and or DR4 DQA1*0331, DQB1*0302, DQA1*501, DQB1*0201
(present in 40% of children with type 1A diabetes mellitus vs. 2% in the population)

Protective haplotypes: DQA1*0102, DQB1*0602

Other susceptibility loci: Xp11.23-q13.3, 12q24.2, 1p13, 6p21.3

1. Insulin-dependent diabetes mellitus type 1 (MIM 222100)

D. Genetic susceptibility to diabetes mellitus

Susceptibility loci:

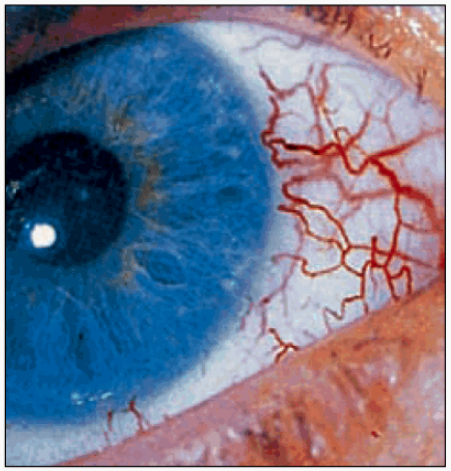
2q24.1
2q32
5q34-q35.2
6p12
6q22-q23
11p12-p11.2
12q24.2
13q12.1
13q34,
17cen-q21.3
17q25,
19p13.2
19q13.1-q13.2
20q12-q13.1

1. Non-insulin-dependent diabetes mellitus type 2 (MIM 125853)

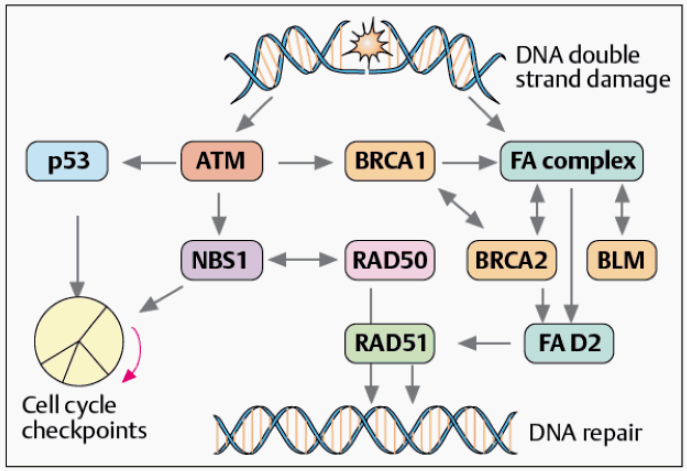
Gene repair defect

Ataxia-telangiectasia (A-T) (MIM 208900)

- **Ataxia-telangiectasia (A-T)** (MIM 208900) variable disease due toautosomal recessive mutations in the *ATM* gene 66 exons 150 kb at gene map locus 11q23. (350kD)
- protein kinase ATM 3056- amino acid activated in response todouble-strand DNA breaks regulate cellular responses to DNA damage and recombination
- characteristic telangiectasias of the conjunctivae immune defects, cerebellar ataxia in early childhoodsensitive to irradiation prone to develop lymphomas and leukemias.
- Mutations in a related gene result in the Nijmegen breakage syndrome (NBS1, MIM251260).



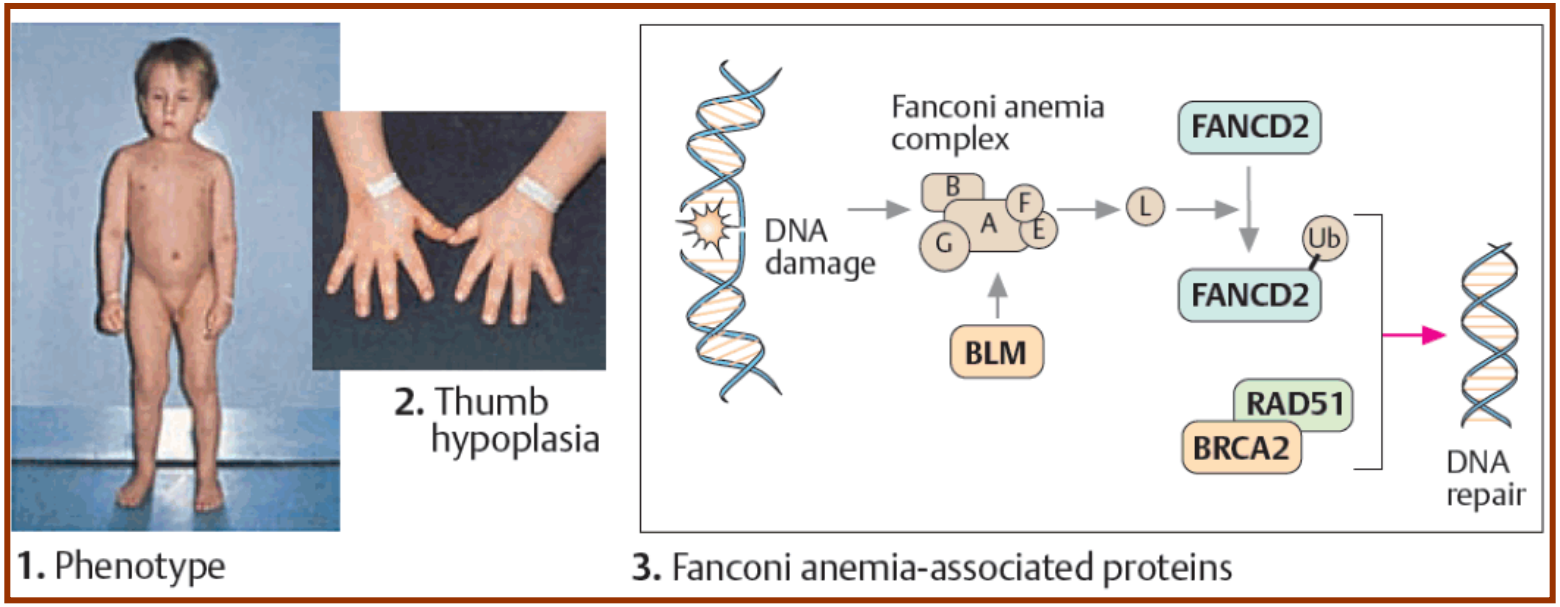
1. Telangiectasias of the conjunctiva
A. Ataxia-telangiectasia (AT)



2. Relation of ATM to other proteins maintaining genomic stability

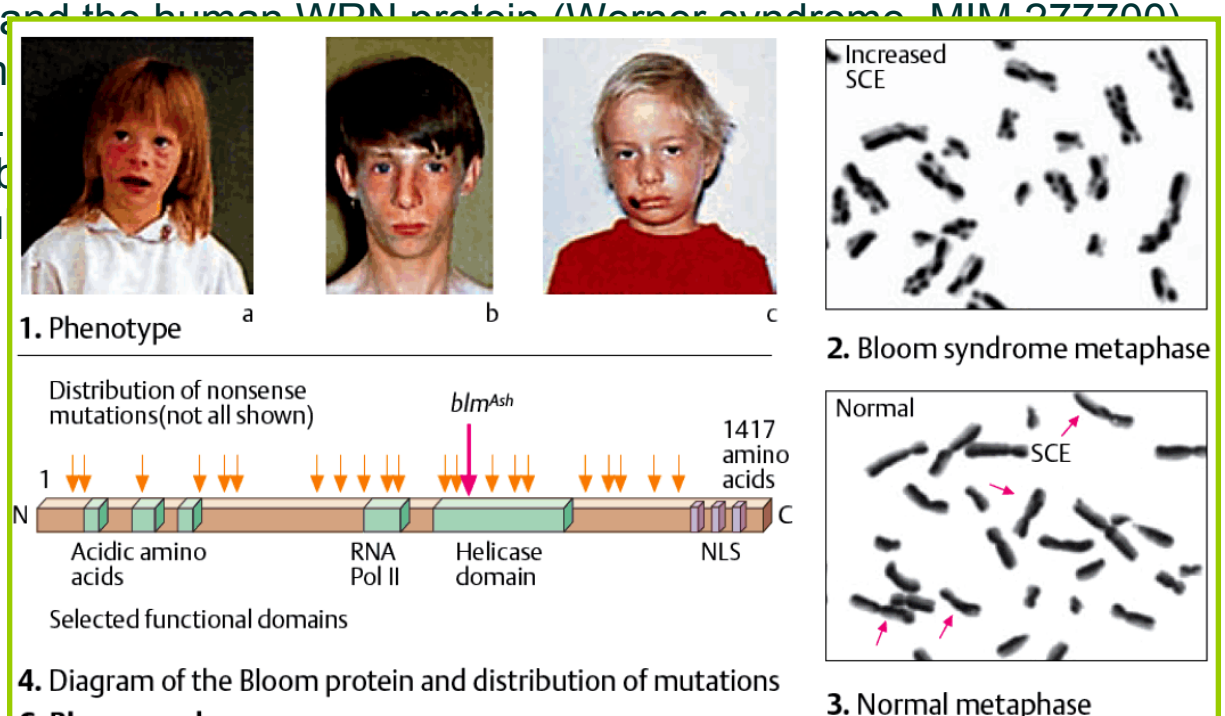
Fanconi anemia FA (MIM 227650)

- heterogeneous group of autosomal recessive and X-chromosomal diseasesmanifest in early childhood as pancytopenia, hypoplastic radius often with hypoplastic or absent thumbs and other malformations. growth deficiency
- About eight FA genesform a complementation group (see table in appendix). The proteins encoded by these genes form the FA complex. Together with other proteins, they detect DNA damage or errors in replication. The most prevalent mutation is of FA-A(also called FANCA), in about 65% of patients. FA cells are hypersensitive to DNA-crosslinking agents, such as diepoxybutane (DEB), which induceschromosomal breaks. (Diagram adaptedfrom Rahman & Ashworth, 2004.)

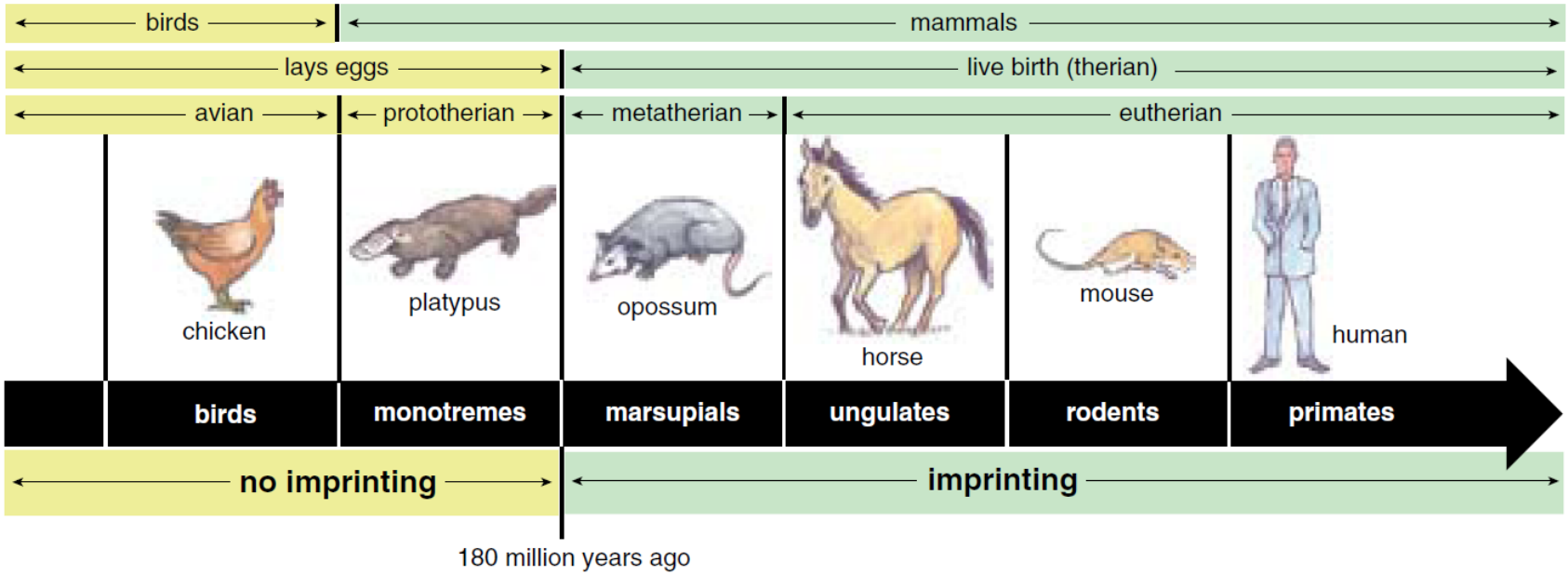


Bloom syndrome BLM (210900

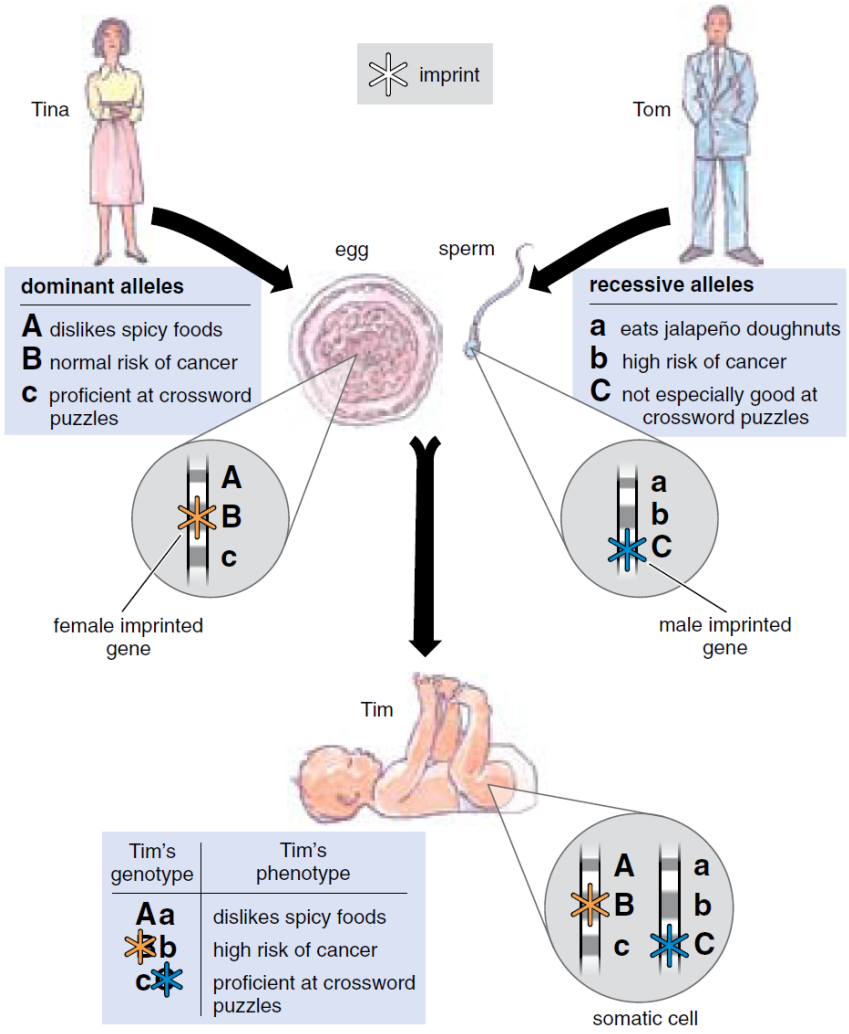
- prenatal and postnatal growth deficiency disease (birth weight 2000g, birth length 40 cm, adult height ca. 150 cm) with a distinct phenotype (1) including a narrowface, sunlight-induced facial erythema, variable immune deficiency, and a greatly increasedrisk of different malignancies (about 1in 5 patients). Chemotherapy is very poorlytolerated. The hallmark is a tenfold increase in the spontaneous rate of sister chromatid exchanges(SCE, see glossary) (2, 3). Breaks in one or bothchromatids and exchanges between homologouschromosomes occur in about 1–2% of metaphase cells.
- BLM results from autosomal recessive mutationsin the BLM gene at gene map locus15q26.1, encoding a member of the RecQ familyof DNA helicases. The 1417-amino acid BLMprotein interacts with the FA complex and is involved in meiotic recombination. It is homologousto yeast Sgs1 (slow growth suppressor) and the human WRN protein (Werner syndrome, MIM 277700). Mainly protein-truncatingnonsen
some missense mutations exist.
Jewish origin, consisting of a 6-b
mutations in the BLM gene resu



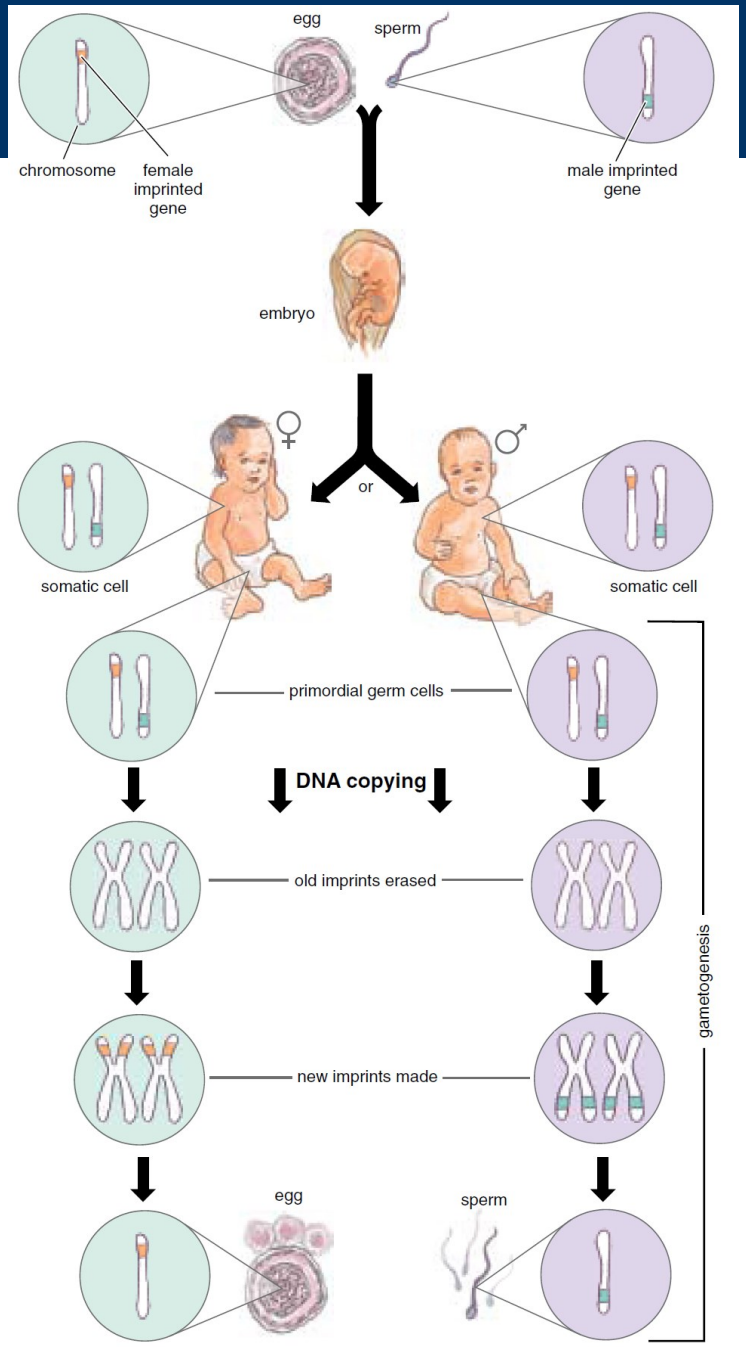
Imprinting



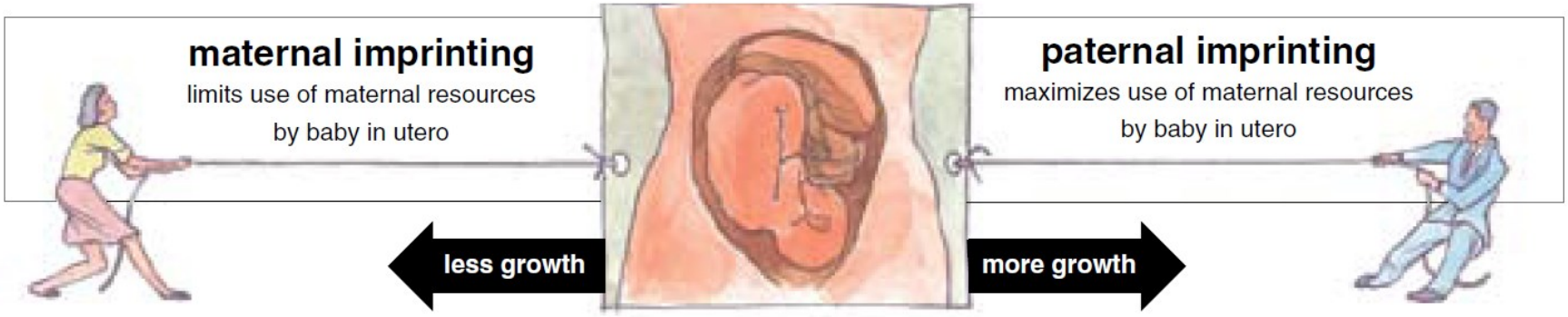
- Roughly 180 million years ago, genomic imprinting and the practice of live birth coevolved in primitive mammals. Egg-laying monotremes such as the platypus are the most ancient group of mammals and do not have imprinted genes. The first examples of imprinting appeared in a common, now-extinct ancestor of marsupials and eutherian, or placental, mammals.



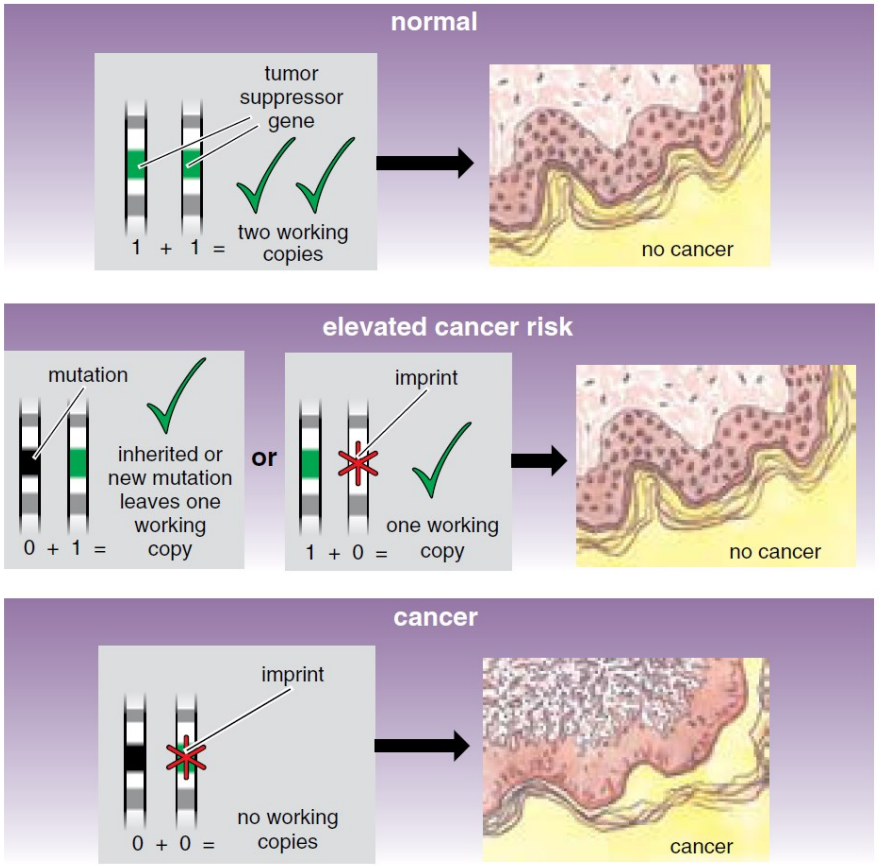
- Imprinting makes terms like *dominant* and *recessive* meaningless in the context of
- mammalian inheritance. For an imprinted gene, the important attribute is which parent it
- come from. In this cartoon, Tina and Tom are the parents of baby Tim. For a fictional spicyfood
- gene, the allele (gene variant) that leads Tina to dislike fiery edibles is dominant; the
- allele that has Tom craving hot peppers is recessive. Thus, baby Tim will share his mother's
- preference for mild meals. For two other imaginary traits, cancer predisposition and crossword-
- puzzle proficiency, maternal and paternal imprints dictate which allele will manifest
- itself in the child.

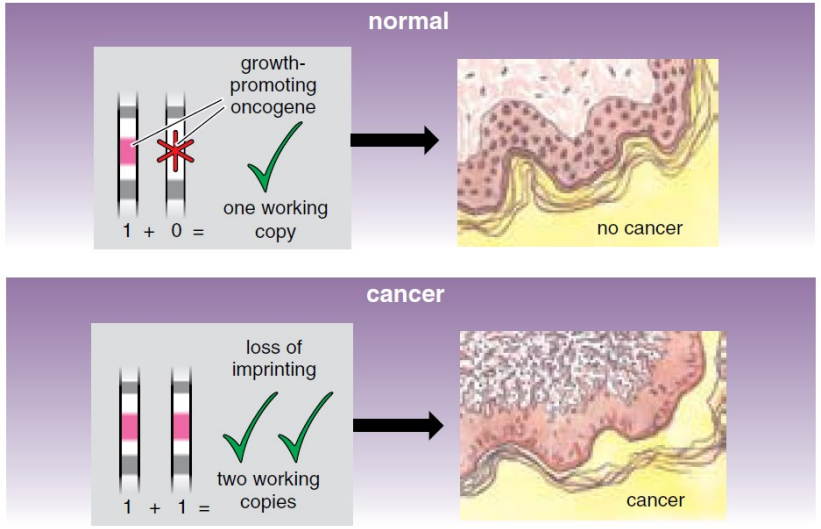


- Imprints must be reset in each new generation to ensure appropriate gene activity.
- The sex-specific imprints on DNA from the sperm and egg persist in somatic cells throughout the child's body—every cell, that is, except those destined to become the child's own gametes.
- In primordial germ cells, DNA copying is followed by the erasing of old imprints and the reestablishment of newly uniform imprints that reflect the offspring's own sex.



- The conflict hypothesis suggests that imprinting arose because of a genomic tug-of-war between mothers and fathers over the use of maternal resources by the fetus. In mammals that bear live offspring, the male's evolutionary fitness is maximized if his offspring monopolizes the female's energy reserves during gestation. The female's best strategy demands that she not invest all of her resources in a single offspring.
- If the embryo were a car on the highway of growth and development, paternal imprinting would try to speed the car up; maternal imprinting would try to slow it down.





The second way that imprinting entails greater genetic risk is the potential for genetic or epigenetic changes that result in loss of imprinting. If the normal physiological state rests on leaving only one functional copy of some growth-promoting gene, the loss of imprinting can unveil a second functional copy, thereby causing unrestrained growth, leading to cancer.