Lectures from Pathophysiology I
General medicine
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Winter semester

GENETICS 1

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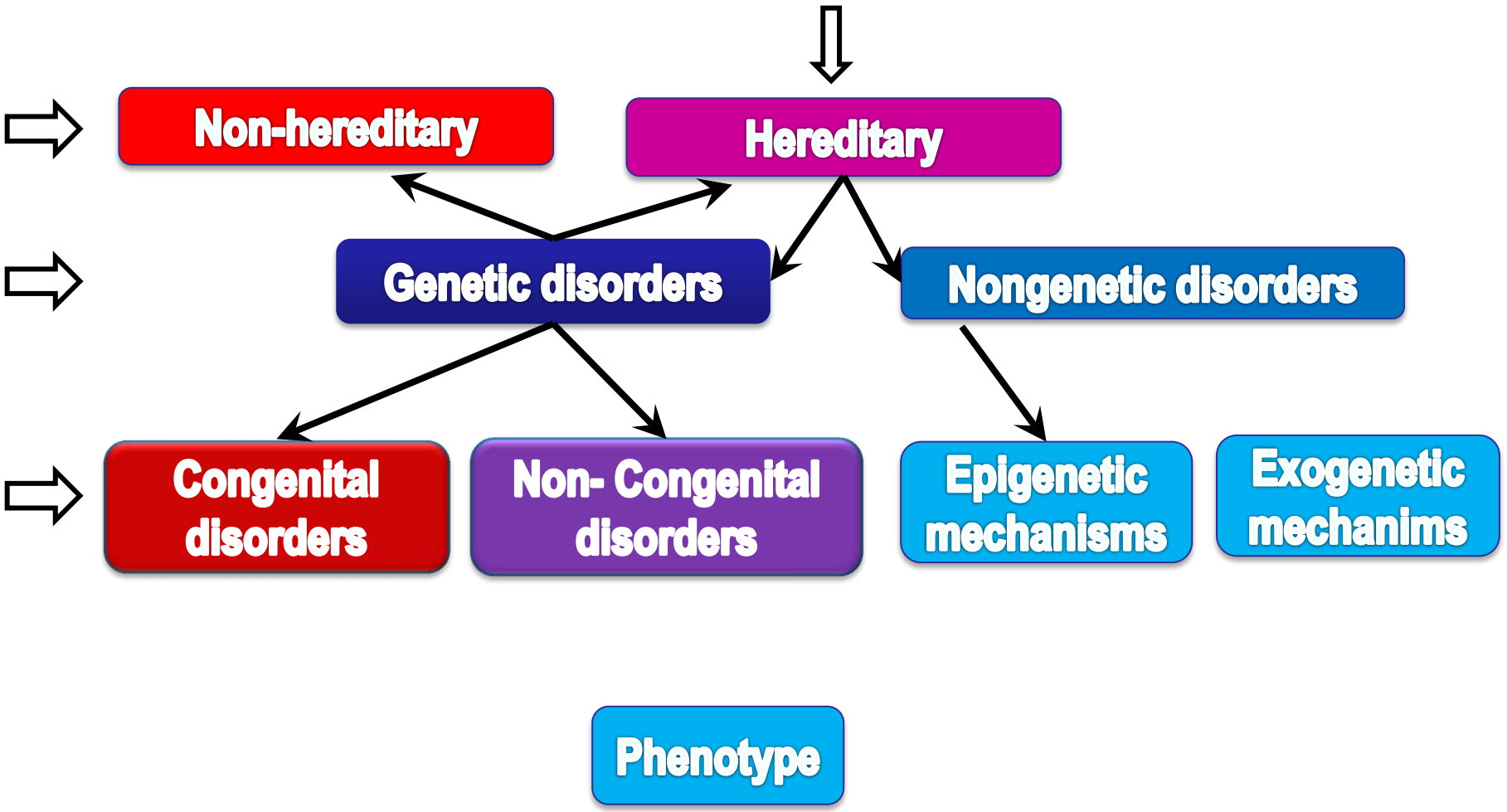
Section A

Basic terms

Terminology

examples in lecture

- Phylogenetic, Ontogenetic, Autogenetic *(lat. genus)*
- Genetic condition (diseases) – made up by changes in genetic information (genes, chrom);
  - *not all genetic disorders are hereditary ones* (e.g. all cancers)
- Epigenetic condition – implicit mechanisms which regulate how genetic information is realized (switch on and off; nonrandom, modifications) *hereditary mechanisms*
  - *part of transcriptional, translational and posttranslational machinery*
- Ectogenetic conditions – endogenous & exogenous regulations & principles which effect how genetic/epigenetic mechanism are realized – programming,
  - *non implicit, random, influence mutational rate*, in utero, postnatal ontogenesis
- Congenital diseases – diseases and pathologies present, manifested during labor or in perinatal period; hereditary disorders are not necessarily congenital and vice versa
- Hereditary condition (disease) - inheritance, biological inheritance is passing on of traits from parents to their off-springs through asexual reproduction or sexual reproduction,
  - *the offspring cells or organisms acquire the genetic properties of their predestors*
- Familiar diseases - subset of hereditary conditions; diseases, pathologies which run in families; genetic and hereditary; not all hereditary disorders are familial


Non-hereditary
Hereditary
Genetic disorders
Nongenetic disorders
Congenital disorders
Non- Congenital disorders
Epigenetic mechanisms
Exogenetic mechanims
Phenotype

Examplomania

- **Sickle cell anemia** = genetic + hereditary + non-congental
- **Hemophilia A, B** = genetic+ hereditary (X linked) + congenital
- **Cleft lip and cleft palate** = non-genetic+ non-hereditary+ congenital
- **Phacomatosis** = genetic /or/ non-genetic + non-hereditary + congenital
- **Cerebral palsy** = non-genetic + non-hereditary + congenital + nonfamilial
- **Fragile X syndrome** = genetic + hereditary (non-mendelian) + + congenital
- **Down syndrome** = genetic + non-hereditary + congenital
- **Spina bifida** = non-genetic + non-hereditary + congenital
- **Cystic fibrosis** = genetic + hereditary (AR trait) + congenital
- **Heart conditions** = genetic /or non-genetic + non-hereditary + congenital
- **Marfan syndrome.** = genetic+ hereditary (AD trait) +congenital
- **Valvuar defect** (due to rubela) = non-genetic + congenital +
- **Ca colon** = genetic+ noncongenital + nonhereditary (or) hereditary+ familal/or non-familar
- **Ca pancreas** = genetic+ non-hereditary+ non-congenital;
- **Trisomies (Down sy. Edwards sy.)** = genetic+ congenital; hereditary (1%) or non-hereditary; non-familial

Find out examples in lessons yourself

Knowledge of human genetic code

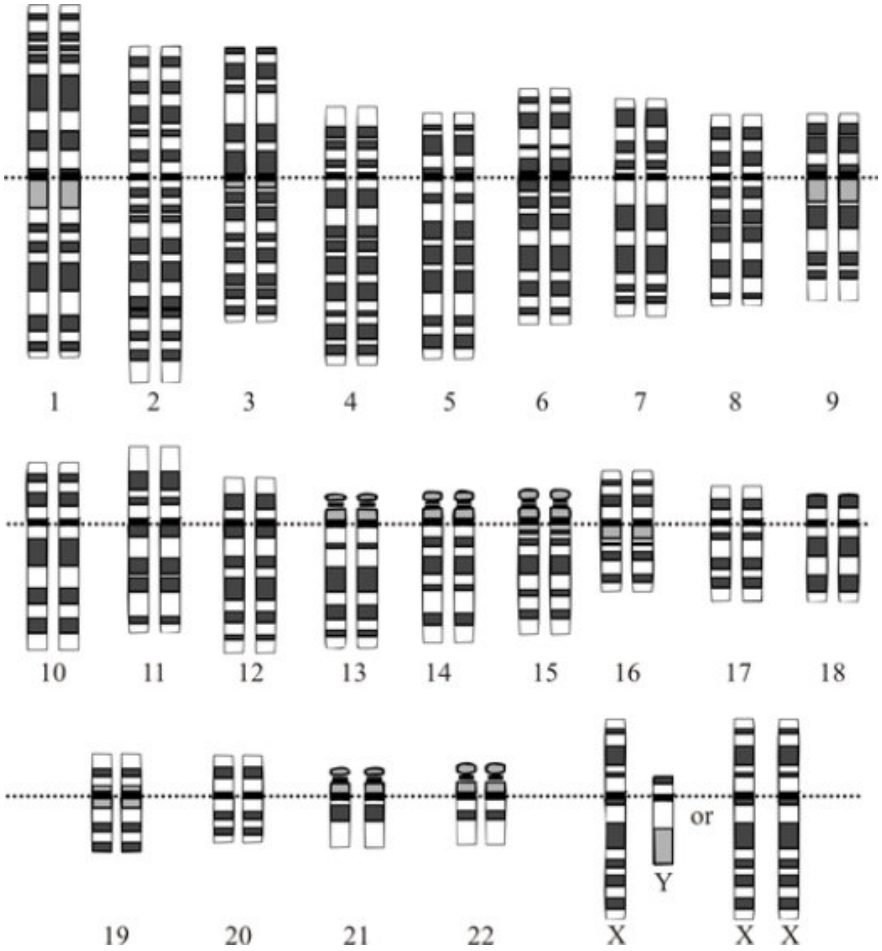
- Human Genome Project (HUGO) (started 2/2001) = complete mapping of individual human genes by DNA sequencing; first draft sequence and initial analysis being published on February 2001
- The number of initial predictions of 100,000 genes
- HGP-Write (started 6/2016) = a plan to synthesize the human genome
- A) Coding DNA (~ 1.5- 2% of the genome) = sequences that can be transcribed into mRNA and translated into proteins
- Historically, estimates of human genes ranged from up to 2,000,000 and (early1960s), 100,000 (late 1960), 40,000 (early 1970s) as low as 19,000(2005); ~ 22,000 is registered today (Uniprot; Swiss)
- Number of human protein-coding genes is not larger than that of much less complex organisms (roundworm, fruit fly). !!! There is extensive use of alternative pre-mRNA splicing in humans (large number of modular proteins through the selective incorporation of exons).
- B) Non-coding DNA (98% of genome) (~ 98% of the genome) = sequences that are not used to encode proteins; they do regulation of gene expression, organization of chromosome architecture, and control epigenetic inheritance
- non-coding RNA molecules, regulatory DNA sequences, LINEs, SINEs, introns, and sequences for which as yet no function has been determined.

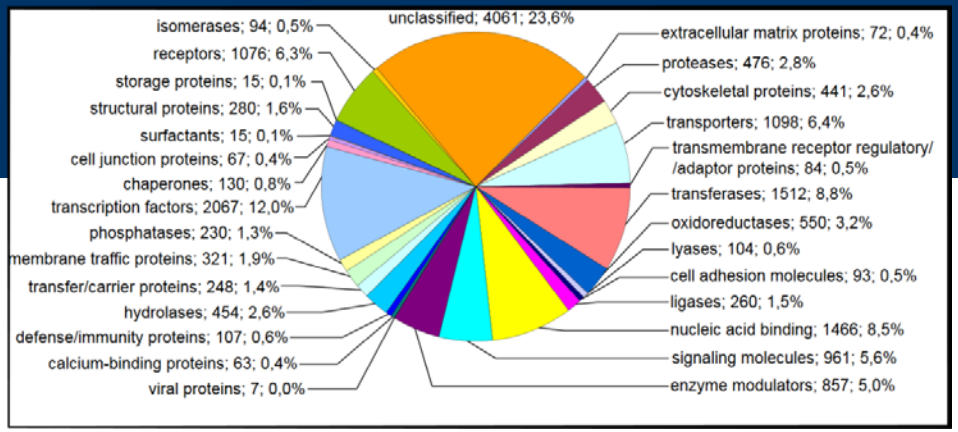
The number of chromosomes in different species (diploid stage) (2n)

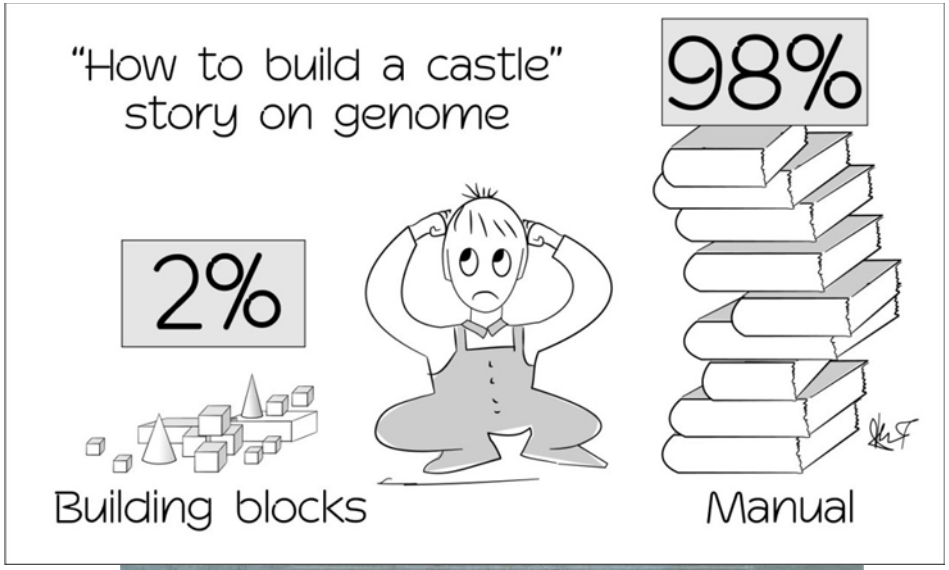
Drosophila (Drosophila melanogaster) 8
Nematode (C. elegans) 12
Housefly (Musca domestica) 12
Arabidopsis (Arabidopsis thaliana) 14
Peas (Pisum sativum) 14
Barley (Hordeum vulgare) 14
Rye (Secale cereale) 14
Chlamydomonas (n) 17
Hemp (Cannabis sativa) 20
Corn (Zea mays) 20
Rice (Oryza sativa) 24
Yeast (Saccharomyces cerevisiae) 32

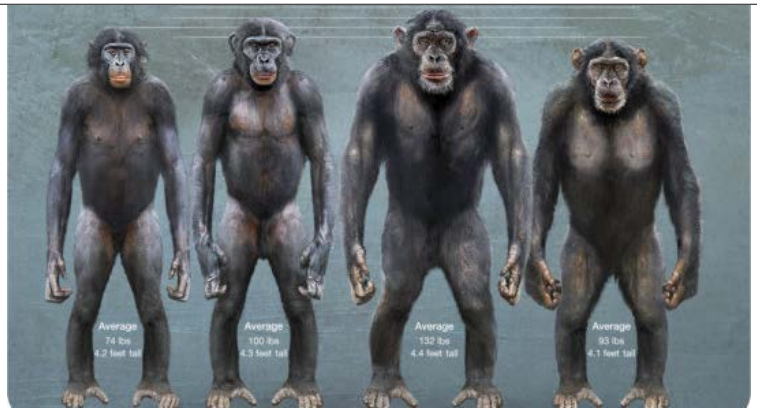
Cat (Felis catus) 38
Mouse (Mus musculus) 40
Soybean (Glycine max) 40
Wheat (Triticum aestivum) 42
Wise man (Homo sapiens sapiens) 46
Chimpanzee (Pan troglodytes) 48
Potato (Solanum tuberosum) (4 N) 48
Horse (Equus caballus ferrus) 64
Chickens (Gallus gallus) 78
Dog (Canis lupus familiaris) 78
Home Cattle (Bos taurus) 78
Carp (Cyprinus carpio) 104

Human genome









- 22 pairs of chromosomes + 2X (females) or 1X+1Y(males)
- 3,234.83 Mb (Mega-pair of bases) haploid cell
- 6,469.66 Mb diploid cell ; Variability among humans ~ 0,1%
- Difference - closest relatives chimps and bonobos (4%

Section B

Epigenetic regulations

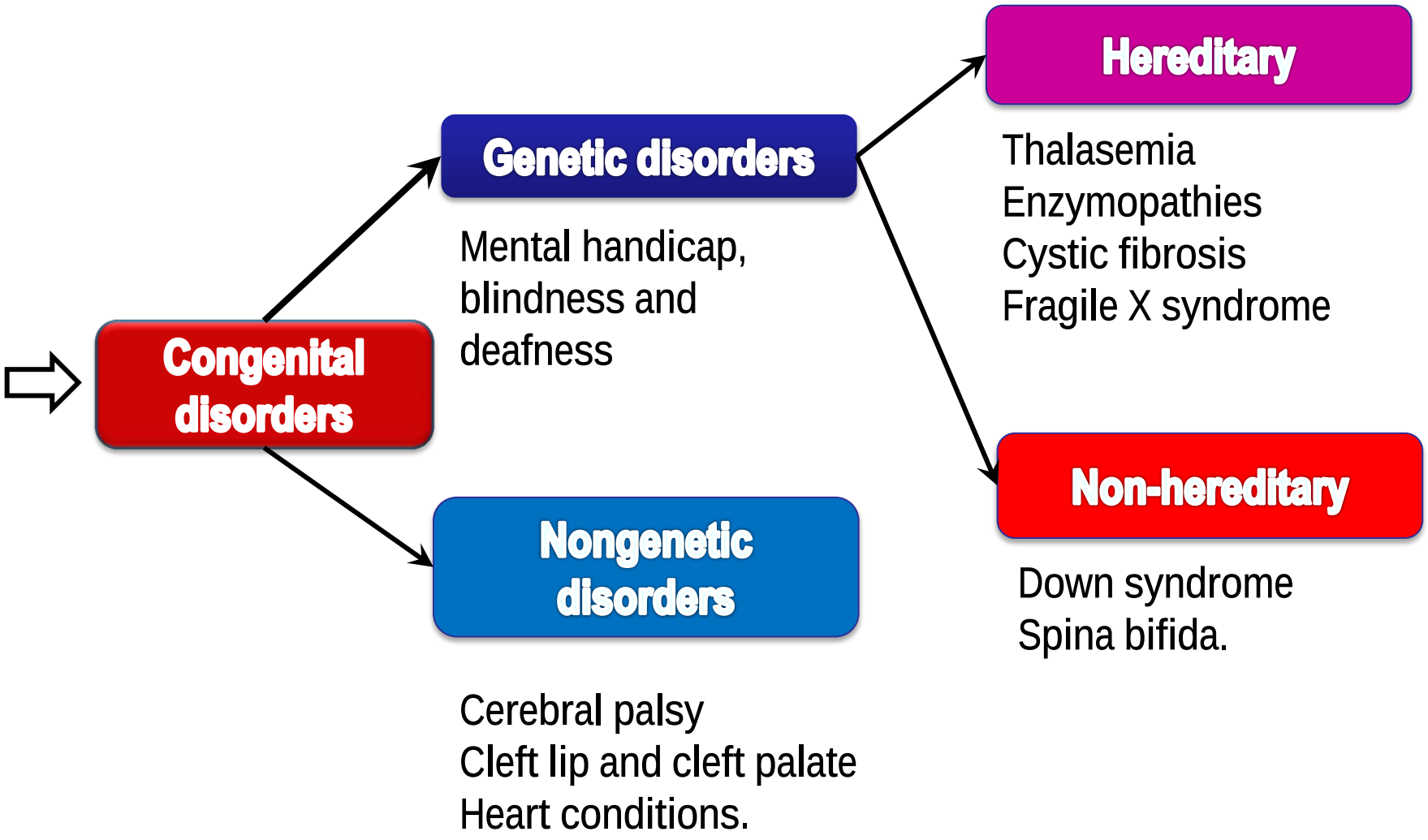
Epigenetic alterations – non genetic, hereditary

- Def:: Any heritable phenotype changes ; any alterations to the genome that do not involve a change in the nucleotide sequence that do not involve alterations in the DNA sequence (non- mutational)
- Hist: british embryologist C. H. Waddington (1942) epigenetic principle in differentiation of cells ; epigenetic landscape, *canalisation*
- (1990ties) mechanisms of ***temporal and spatial control of gene activity*** during the development of complex organisms → ontogenesis (R.Holliday)
- Riggs and colleagues → mitotically and/or meiotically ***heritable changes in gene function*** that cannot be explained by changes in DNA sequence.
- "the structural adaptation of chromosomal regions so as to register, signal or perpetuate altered activity states.„ (Adrian Bird)
- Etio: external/environmental (heat stress, acclimation, food – fastening, overeating)+ many internal factors (programming ontogenesis); part of normal development+regulation (non random)
- Mech: I)switch on, off, tuning of gene activity/ inactivity/ gene expression → RNA processing → protein synsthesis; II) may last through cell divisions (G1, S, G2, M) /or for the duration of the cell's life; few / or multiple cell generations
- a) DNA methylation, histone acetylations; b) microRNA

Section C

Congenital disorders

Congenital disorders



Terminology

Congenital disorders (anomalies, malformations, birth defects) = structural or functional anomalies that occur during intrauterine life (prenatally) or happen during a labor, i.e. thery are present at birth regardless of its cause;

- may be identified before or at birth; influence neonatal and perinatal morbidity and mortality

Occ: estimated 6% of babies worldwide; 25%-35% of perinatal deaths in Saudi Arabia

- cca. 50% of congenital anomalies cannot be linked to a specific cause.
- cca 30% of congenital anomalies are hereditary: caused by single gene defects, chromosomal disorders, multifactorial inheritance,
- cca. 20% of congenital anomalies are non-hereditary genetic /or/ non genetic environmental

Etio: mutations, teratogens (chemicals), drugs, infections (TORCH) , micronutrient deficiencies.

a) non genetic defects; epigenetic (effects on programming)

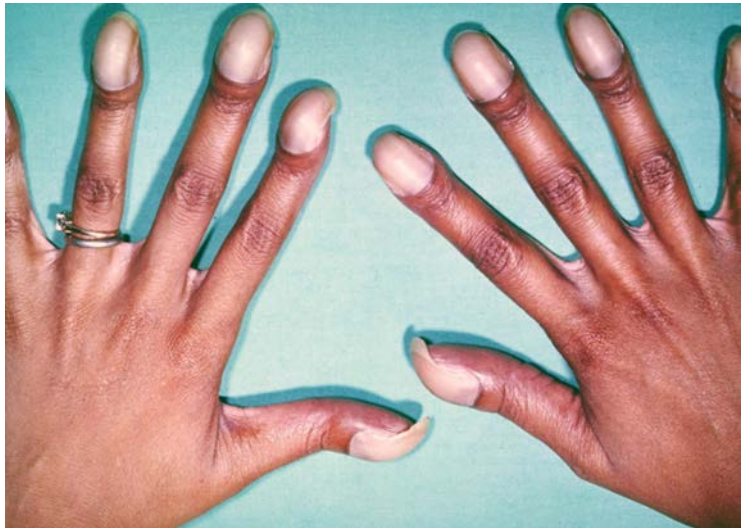
b) genetic defects (mutations)

- Chromosomal aberrations are among the most important causes of congenital malformation and mental handicap. The risk of having a child with Down syndrome increases with increased maternal age from 1 in 600 births for mothers under 30 years to 1 in 50 births for mothers over 40 years [13]. Available data for the EMR suggest that in some countries of the Region, 50% of Down syndrome children are born to mothers over 40 years [14]. The observed prevalence of Down syndrome among live births in the EMR has been reported to vary from 1.15 per 1000 in the UAE [15] to 2.5 per 1000 in Egypt [16].

examples in lecture

Congenital cardiac malformations

- Cyanotic heart defects commonly affect the atrial or ventricular walls, heart valves, or large blood vessels.
- Etio: a) genetic defects (e.g., trisomies), maternal infections (e.g., rubella), maternal consumption of drugs or alcohol during pregnancy.
- Ptg: characterized by a right-to-left shunt → deoxygenated blood entering the systemic circulation→ hypoxemia + cyanosis, failure to thrive, heart murmurs, and symptoms of heart failure.
- Clin: "Blue babies": pale gray or blue skin color caused by cyanosis, Nail clubbing , Exertional dyspnea, tachypnea, and fatigue ,Poor weight gain, failure to thrive, Characteristic heart murmurs



Congenital visceral malformations (CVM)

- CVM develop during organogenesis (first 8 w after conception; embryo).
- Gommon malformations include: gastroschisis, biliary atresia, omphalocele, anal atresia, occur on their own or together with other malformations and syndromes. All conditions require surgery.
- Anal atresia - an absent anal opening and failure to pass meconium; leads to ileus or the formation of fistulas.
- Omphalocele - is often associated with trisomies; herniation of abdominal viscera through the abdominal wall into a hernia sac.
- Gastroschisis, by contrast, herniated parts of the intestine are not covered by a sac, but exposed.
- Extrahepatic biliary atresia, the infant presents with prolonged *neonatal jaundice*, *acholic stools, dark urine, and hepatomegaly, conjugated hyperbilirubinemia* .

Section B

Genetic disorders

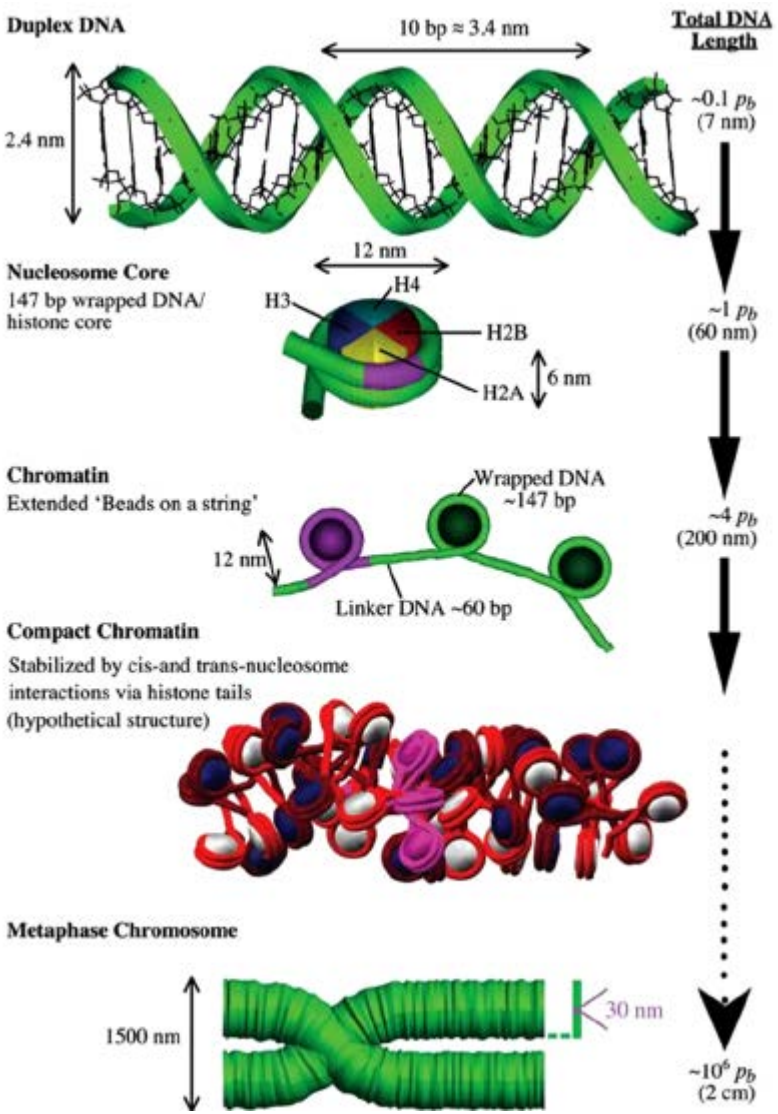
Mutations types

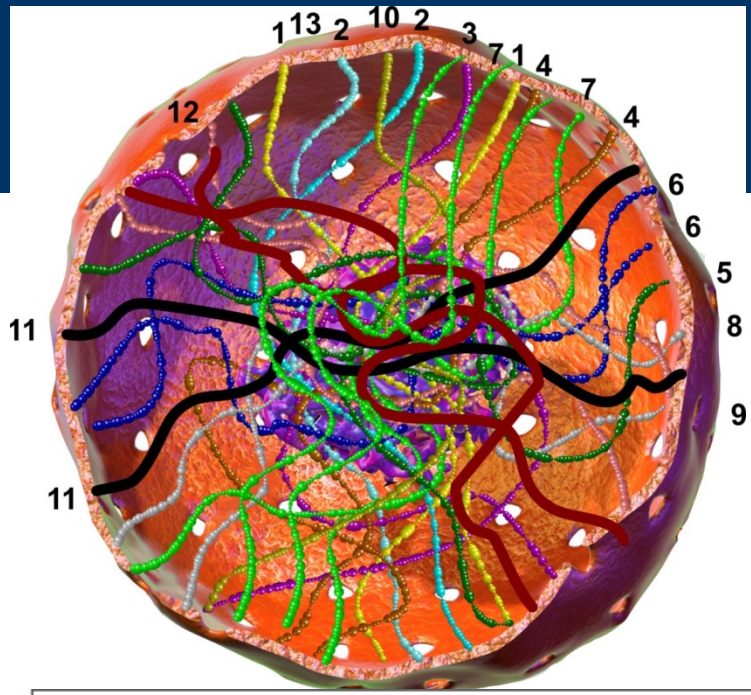
- Genetic disorders are about change in „encoded genetic informoation“; this change is called mutation.
- According to an extent of genetic information involved:
  - Gene mutations - affects nucleotide sequence limited to a single gene
  - Chromosomal mutations (aberrations) - affects the DNA at the chromosome structure and parts
  - Genomic mutations - mutations leading to a change in the number of chromosomes and chromosomal whole files
- According to „the power“ to do the disease:
  - Single gene mutations, Clustered muitations (several genes, e,.g in chromosomal traslocations), Polygenic mutations
- According to the cell types:
  - gametic mutations - genetic material in gametes (oocytes + sperm cells); occur during spermatogenesis (sperm) or oogenesis (egg formation)
  - somatic mutations - affects somatic (body) cells; not transferred to the subsequent generation; They can cause cancer
- According to mechanisms:
  - spontaneous mutations - are random phenomena
  - induced mutations - are purposefully induced mutations in laboratory conditions

Mutations

- According to the location of the mutation:
  - Nuclear mutations - occur in the DNA contained in the cell nucleus
  - Non-nuclear mutations - are formed on the DNA which is present in mitochondria, respectively. chloroplasts in plants
- According to the direction of mutating:
  - Direct mutation - when the normal allele arises mutated allele
  - Back-ward mutations - when mutated genotype changes back to the original (normal) genotype
- According to the compatibility:
  - Vital mutation - not affect the survival of the individual
  - Lethal mutation - mutant genotype does not permit the survival of the wearer (mutations in essential genes)
- Depending on the degree of phenotypic expression:
  - Dominant mutations - the mutant allele is superior to the normal allele
  - Recessive mutation - mutant allele will occur in homozygous recessive condition (most mutations)

Genes


Duplex DNA
10 bp ≈ 3.4 nm
2.4 nm
Total DNA Length
~0.1 p_b (7 nm)
Nucleosome Core
147 bp wrapped DNA/ histone core
12 nm
H4
H3
H2B
H2A
6 nm
~1 p_b (60 nm)
Chromatin
Extended 'Beads on a string'
Wrapped DNA ~147 bp
12 nm
Linker DNA ~60 bp
~4 p_b (200 nm)
Compact Chromatin
Stabilized by cis-and trans-nucleosome interactions via histone tails (hypothetical structure)
Metaphase Chromosome
1500 nm
30 nm
~10^6 p_b (2 cm)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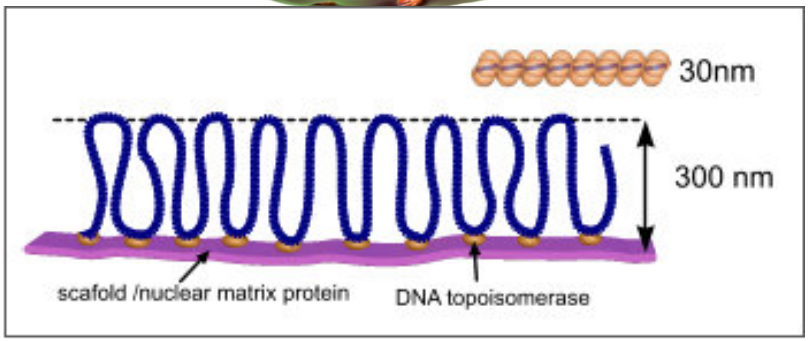
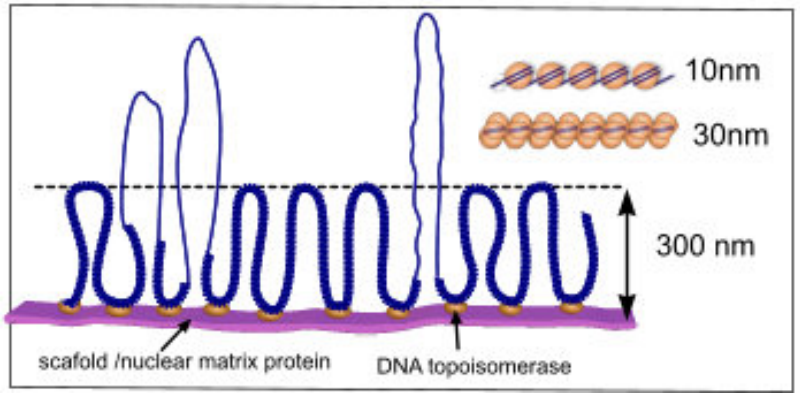
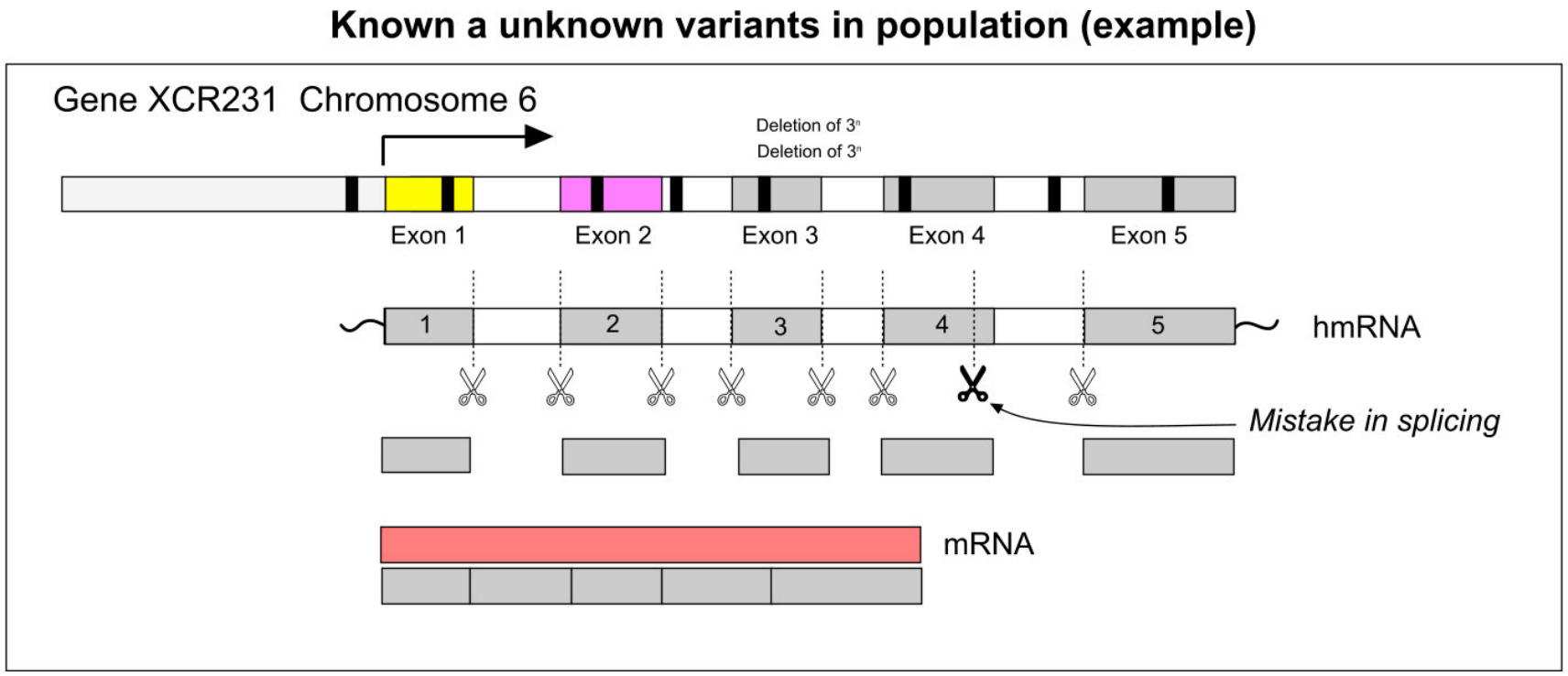

30nm
300 nm
scafold /nuclear matrix protein
DNA topoisomerase


10nm
30nm
300 nm
scafold /nuclear matrix protein
DNA topoisomerase

Location of single gene mutations

- Promotor = part of the gene
- Exons = coding part of the gene
- Introns = cutt off nonused part of the gene
- Mechanisms of splicing = incorrect mRNA



Hypothetical phenotype consequences of mutational variants of the gene in population

Gene XCR 231 Chromosome 6

Allellic Variants	Occurence	Locus	Protein	Function	Manifestation
01.Variant	96%		156 AA	Normal	Healthy - control
02.Variant	3%	Substitution Lys 35 → Arg	156 AA	No change	No apparent change
03.Variant	0,1%	Substitution Pro 112 → Lys	156 AA	Loss of function	Disease XY variant 1
04.Variant	0,2%	Substitution Gly 104 → ILeu	156 AA	Gain in function	No disease
05.Variant	0,01%	Substitution Ala 72 → His	156 AA	Loss of function	Disease XY variant 2
06.Variant	0,1%	Substitution His 56 → Ala	156 AA	Loss of function	No apparent disease
07.Variant	0,01%	Deletion Lys148 →	147 AA	Loss of function	Disease WZ variant 3
08.Variant	0,02%	Substitution Pro 149 → Lys	156 AA	Loss of function	Disease WZ variant 1
09.Variant	0,01%	Substitution Glu 69 → Ala	156 AA	Loss of function	Disease XY variant 3
10.Variant	0,002%	Substitution Glu 69 → Ala Asp 96 → Glu	156 AA	Loss of function	Disease XY variant 4
11.Variant	0,0001%	Insertion Ile 49 →	42 AA	Loss of function	Incompatible with life
12.Variant	0,01%	Substitution Val 112 → ILeu	156 AA	Gain in function	No apparent change

Genetics

- Genomic damage - mutations : gene (one point, multiple points, chromosomal aberrations, genomic mutatonions
  - Mechanisms of mutations
  - Reasons of mutations:
  - Terminology: genetic disease vs. Hereditary vs. Familiar vs. congenital disease
- Monogeneic mutations
  - Monogenic diseases, AD traits - principles and examples
  - Monogenic diseases, AR traits - principles and examples
  - Monogenic diseases : X-linked inheritance – principles and examples
- Monogenic diseases with non- mendelian inheritance:
  - Imprinting,
  - Triplet repeat mutations,
  - Mitochondrial diseases
  - Mosaicism
- Abnormalities in number of autosomes and gonosomes
- Polygenic mutations

Mutagens

- The emergence of mutations that pass to future generations, occurs naturally at low frequency. Such so-called. spontaneous mutation, ie mutations occurring without the intentional use of mutagens, error rates related to three processes:
  - replication system - if the DNA polymerase of DNA replication placed the wrong nucleotide that does not match the rule base complementarity
  - recombination system - if the ongoing recombination in prophase of meiotic division I in the formation of gametes will take place imprecisely
  - repair system - where the enzymes repairing DNA damage they make a mistake
- Mutagens can substantially increase the frequency of mutations : directly or indirectly
  - Physical mutagens - different types of ionizing and non-ionizing radiation
  - Chemical mutagens - chemical compounds mimicking or changing the structure of nitrogen base intercalating into the DNA double
  - Biological mutagens - some oncogenic viruses and transponibilné elements
- Mutagenesis, e.g. formation induced mutations is a powerful tool of genetics and molecular biology.
- Genotoxicology sub-discipline is the science of genetics, which deals with mutagenic and classification of mutagens

Physical mutagens

- The ionizing radiation = high energy radiation,
  - X-rays, Gamma ray radiation capable to ionoze (kick off electrons the atamic shell → high doses of ionizing radiation kill cells by their toxicity, so it can be used in the treatment of certain tumors.
  - Ions have a great ability to disrupt covalent bonds in nucleotides and lead to breaking of the DNA. → cause chromosomal aberrations. H
- Non-ionizing radiation = less energy, which is not sufficient for the formation of ions.
- UV radiation / wavelength of 254-260 nm can cause mutations that lead to the formation of abnormal bonds between bases (known as the so-called. Thymine dimers impediment to DNA replication.

Chemical mutagens

- Gene mutations can be caused by exposure to various body chemicals that are found in the environment and which daily produces chemical industry.
- Chemical mutagens act in several ways:
  - base analogs
  - modifying a base mutagens
  - intercalators
- As with base analogues, as well as changing the structure chemomutagens bases we encounter with changes in base pairing; replacement of two types:
  - Transition - the replacement of a purine purine or pyrimidine a pyrimidine (e.g., C to T)
  - Transversions - replacement of the purine or pyrimidine counter (e.g., a G to A)

Classical genetics – my answers to Thomas Biedel

- Tom: We were told in Genetics lessons, that we have 2 alleles. You say that there are mary ?!
  - Me: Sure. Term allele comes from Mendel, what was ment as a different phenotype appearance of a given feature, e.g. white and red color of flowers. Now, as we know molecular base beyond, we rather use term gene variants. There is an ample evidence, that one gene may have even dosens of variants in population. To be true, some evolutionary conserved genes may have merely 2-3 or few over thousends of years, but some contain a more than 50 fixed ones. New mutation are created permanently. Yet there is a principle, that 1 of them vastly predominates (>95% or such). But even those variants with a rate of 0,0001% count, beciause this means 7 mil. pepple from 7 mld.
  - All we have 2 gene copies, 1 from mom and 1 from a dad. Thus, from all those variants you may have only 1+1 same variant - you are homozyt, or you have 2 different variants - you are heterozygot.
- Tom: Aha, we were told, that there are dominant alleles and recessive. Does it mean the prevailing one allel is dominant one, and those other are recessive, correct ?
  - Me: No. Term „dominant“, „recessive“, codominant“ refer always to comparisons - „which of those 2 different variants“ you got finally wins in phenotype. Winner is not sure and may differ. e.g. commonest variant 1 may win in combination with variant 2 or 4. But variant 3 may win (dominate) over variant 1. If variant 3 is pathological mutation and disease occurs in combination V1 + V3, i.e. in heterozygotes, V3 is dominant. If disease occurs only in combination V3 + V3, than it is recessive. Yet, V3 in combination with V2 or V4 (V3+V2 or V3+V4) may not manifest, i.e. it behavs recesivelly.
  - Many non-disease variants remain unknown.

Classical genetics – my answers to Thomas Biedel

- Tom: How this variability is achieved? Me: Thorugh mutations. This is a tool of evolution. Nature loves experimenting. It is like scientist. Life is about mutations, good or bad. Nature wants to creation new species, new characteristics, shapes, even. if not necessary. (Consider numebr of species)
- Tom: How many normal / pathological allelic variants for a given gene do exist?
  - Me: Nobody knows and will neever know. Tell me how many students from this study year has been tested genetically ? Likely none. Correct ? Why ? Well, it costs. In pactice. testing is done „routinelly“ just for few up tp 10 selected disorders in newborns.? E.g. here in Slovakia bit less than e.g. in Switzerland and USA. Further there is a additional testing on demand.
  - This means all we know about allelic variants is mostly about „bad“ varianats from sick people. Even, mostly in those which run in families discovered e.g. by researchers who get grants.
  - If freqeuncy in population > 1%, these variants are called „polymorphisms“. If not, they are called „disease allelic variants“. Some are rare and run only in 1-2 famies in the wordl (<20 persons). good data are about **diseased alleles** (lead to manifestant diseases) = **OMIM (Online Mendelian inheritance in Man) (Victor McKusick; Johns Hopkins Univ.)**
- Tom: Do all those not „main stream“ variants (alleles) of genes manifest as disease ? And are these the same diseases ? Me: Well. 1) Those variants which, do no cause discernible disease in homozygotes are technically „normal “. However, some of these polymorphisms may be „statistically „clustered“ with some diseases. This means, that even not sufficient for disease alone (monogenic), they „may be a risk“ or even. regularly controbute into complex, polygenic disordes“. 2)

Oucomes of gneetic mutations

- **Allelic heterogenity** = various muational variants in sma gene may lead to different phenotypical pathological manifest. (diseases)
- **Genetic heterogenity** = one disease can be caused by muta-ted variants in different genes.

SODIUM CHANNEL, VOLTAGE-GATED, TYPE V, ALPHA SUBUNIT; SCN5A
SCN5A 3p22.2

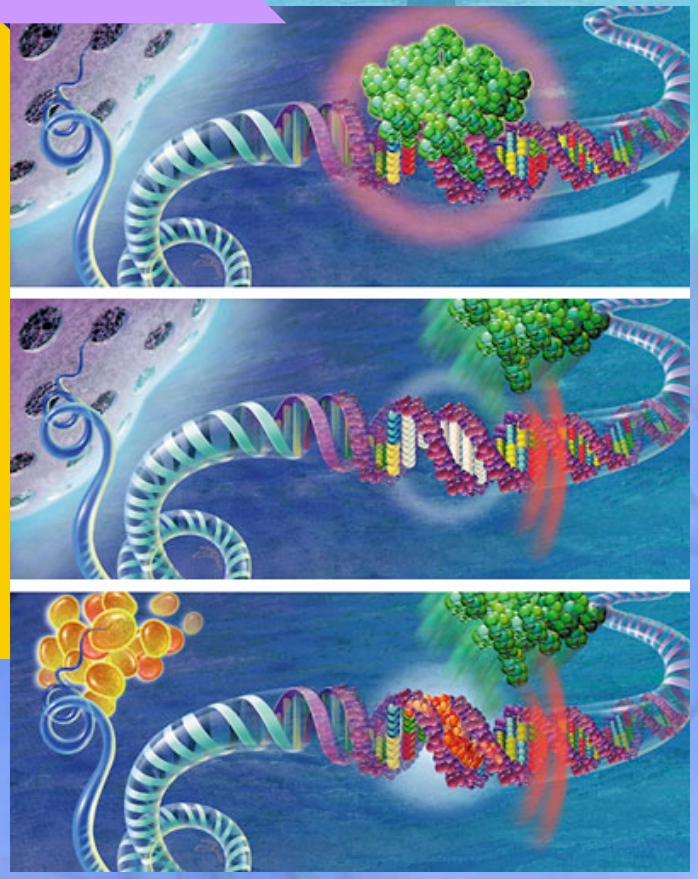
- Atrial fibrillation, familial, 10
- Brugada syndrome 1
- Cardiomyopathy, dilated, 1E
- Heart block, nonprogressive
- Heart block, progressive, type IA
- Long QT syndrome-3
- Sick sinus syndrome 1
- Ventricular fibrillation, familial, 1
- Sudden infant death syndrome

POTASSIUM CHANNEL, VOLTAGE GATED, SUBFAMILY H, MEMBER 2; KCNH2 7q36.1

- Long QT syndrome-2
- Short QT syndrome-1

POTASSIUM CHANNEL, VOLTAGE-GATED, SHAKER FAMILY, MEMBER 9; KCNA9 KVLQT1
11p15.5-p15.4

- Atrial fibrillation, familial, 3
- Jervell and Lange-Nielsen syndrome
- Long QT syndrome-1
- Short QT syndrome-2



Mendelian inheritance

1. **Autosomal dominant disorders**
2. **Autosomal recessive disorders**
3. **Gonosomal recessive disorders**
4. **Gonosomal dominant disorders**

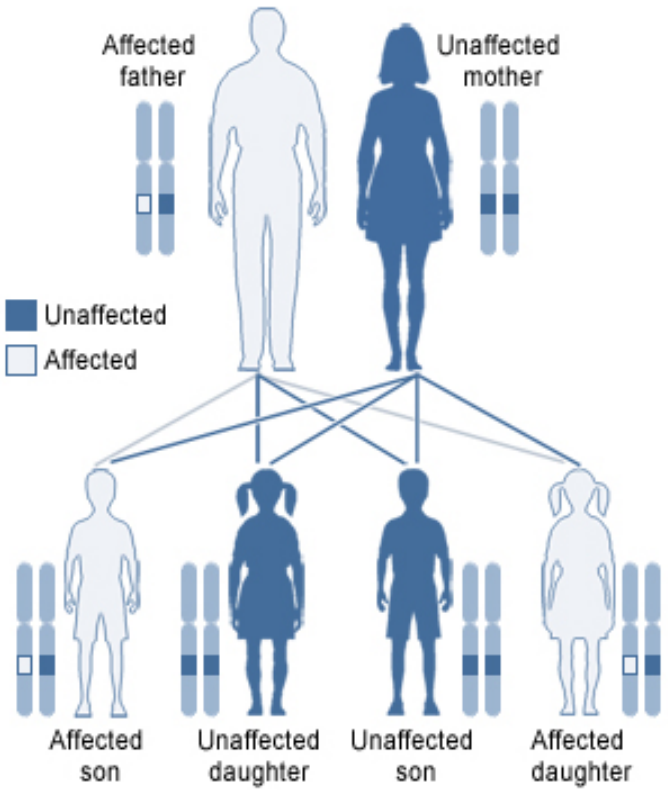
Classical genetics - history

- Gregor Mendel (1822 - 1884) austrian - czech monk from Brno postulated 4 principles concerning inheritance, dominance, segregation and independent assortment that apply to most genes of all diploid organisms; worked with plants.
  - The principle of unit inheritance. Hereditary characters are determined by indivisible units of information (genes). One particular variant of a gene = allele.
  - The principle of dominance. Alleles occur in pairs in each individual, but the effects of one allele may be masked by those of a dominant partner allele.
  - The principle of segregation. During formation of the gametes the members of each pair of alleles separate, so that each gamete carries only one allele of each pair. Allele pairs are restored at fertilization.
- Walter Sutton (1877-1916): *chromosomes occur in matched pairs of maternal and paternal chromosomes which separate during meiosis (1902);* he worked with grasshoppers;
- Theodor Boveri (1862-1915): *all chromosomes had to be present for proper embryonic development to take place;* he studied sea urchins;
- Eleanor Carothers () = definitive evidence of independent assortment of chromosomes (1913) (grasshopper).
- Thomas Hunt Morgan () = inheritance patterns may be generally explained by assuming that genes are located in specific sites on chromosomes (1915); he worked with Drosophila melanogaste

Autosomal dominant disorders (AD) - principles

Principles:

- mutated gene or genes is/are localized **on autosomes;** most common monogenic type of disease in man (~ 65 %);
- **either sex is equally involved** inrrespective of which parent is affected; **every affected person has an affected parent**
- **one mutated gene is enough** for manifestation of disease (heterozygot), i.e. one patent has to be sick/ carrier (either mother or father)
- manifestations of disease (intensity of phenotype) are **stronger in homozygotes** (both parents sick) than heterozygotes (one parent) = earlier onset and worse course (e.g. familial hypercholesterole-mia), often lethal (e.g. achondroplasia); these **are very rare** (parents with the same disease do not marry often);



Predictions:

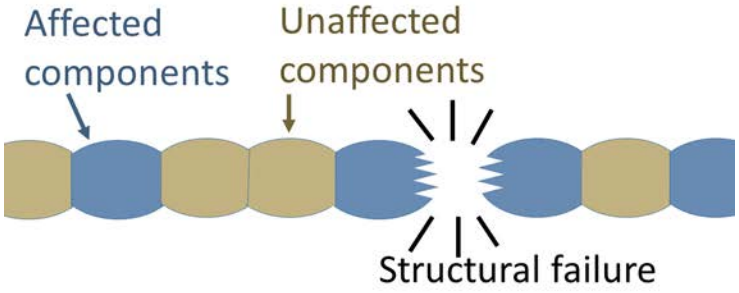
- If parents are sick and **both hetozygotes (Aa**) then **risk for kids is 75 %** (25 % homozygotes; 50% heterozygotes) ; if one is homozygot (AA) and another heterozygot (Aa) then risk for kids is 100% (*75% homozygotes, 25% heterozygotes)*
- *Because 1 mutated alelle (heterozygote) "is enough", AD - trait is the early way of manifestation of **de - novo mutations - new variants, or even new diseases** (another parent is healthy*

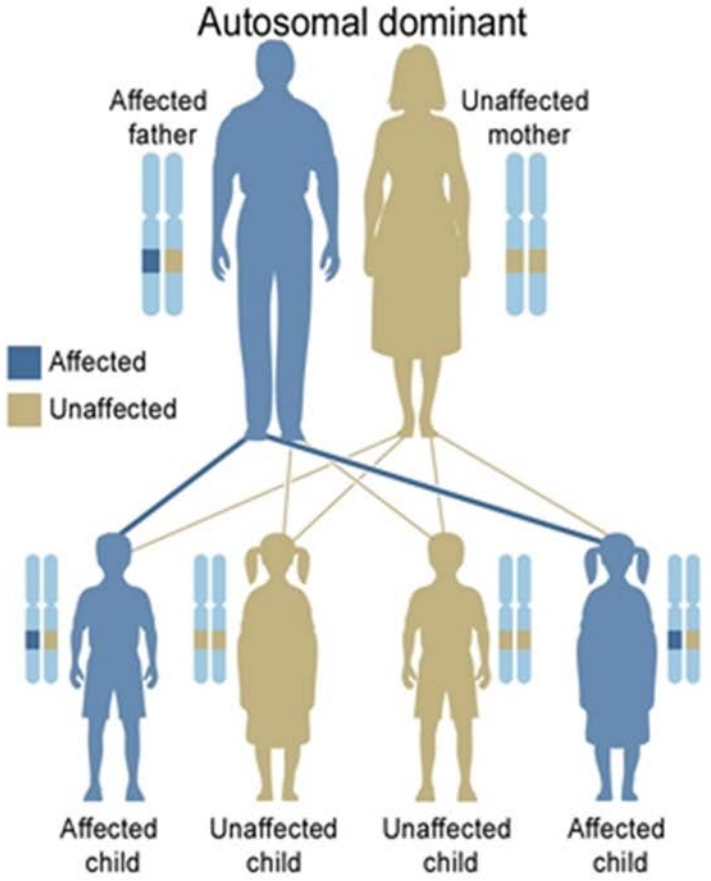
Autosomal dominant disorders (AD) - principles

- Even if AD- diseses apper easyli predictable, they show many intra-familiar and/or inter-familiar inconsistencies, exceptions from predigree against the calculated presumptions
  - *Skipping generation and non-penetrance* - not rare, common; diseases omit to manifest;
  - *Irregular (incomplete) penetrance* - disease does not manifest in predicted % of members both horizontally and vertically
  - *Variable expresivity* - even if penetrated, variously affecting familes horizontal or vertical

Gene products:

- parallel precessing from both copies of the same gene is required: a) products are multimers - build from variable subunits completed tightly time-dependent way b) product is not in abundance (one working gene can not suffice to cover needs; there is no reserve)
- basic proteins mophologically and functionally defining the cell (collagen, elastin; channels, pumps, transporters, receptors)



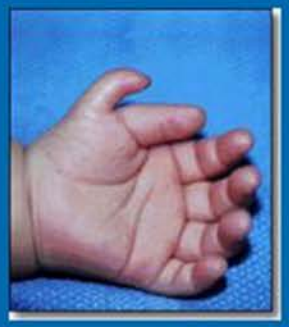


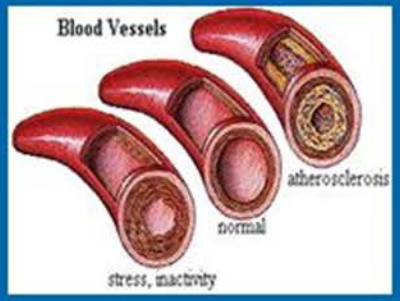
Autosomal dominant diseases - examples

Disease	Rate of occurrence
Familiar combined hyperlipidemia	1: 70-350
Familiar hypercholesterolemia (heterozygotes)	1: 500
Dominant otosclerosis	1: 1.000
Neurofibromatosis	1: 2.500
Hereditary spherocytosis	1: 5.000
Dentinogenesis imperfecta	1: 10.000
Multiple polyposis of colon	1: 10.000
Nanism	1: 12.500
Marfan syndrome	1: 25.000 - 50.000
Achondroplasia	1: 50.000
Amelogenesis imperfecta	1: 50.000
Tuberous sclerosis	1: 100.000
Acute intermittent porphyria	1: 100.000
Familar hypercholesterolemia (homozygotes)	1: 1.000.000

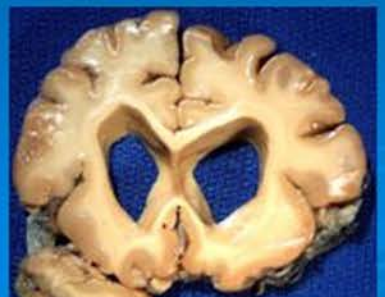
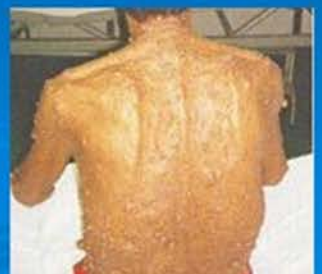
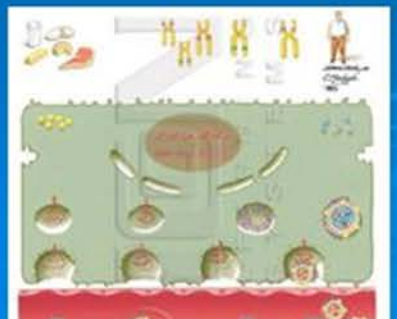
Examples of Autosomal Dominant Disorders

- **Dwarfism**
- **Polydactyly and Syndactyly**
- **Hypertension**
- **Hereditary Edema**



- **Chronic Simple Glaucoma** – Drainage system for fluid in the eye does not work and pressure builds up, leading to damage of the optic nerve which can result in blindness.
- **Huntington's Disease** – Nervous system degeneration resulting in certain and early death. Onset in middle age.
- **Neurofibromatosis** – Benign tumors in skin or deeper
- **Familial Hypercholesterolemia** – High blood cholesterol and propensity for heart disease
- **Progeria** – Drastic premature aging, rare, die by age 13. Symptoms include limited growth, alopecia, small face and jaw, wrinkled skin, atherosclerosis, and cardiovascular problems but mental development not affected.

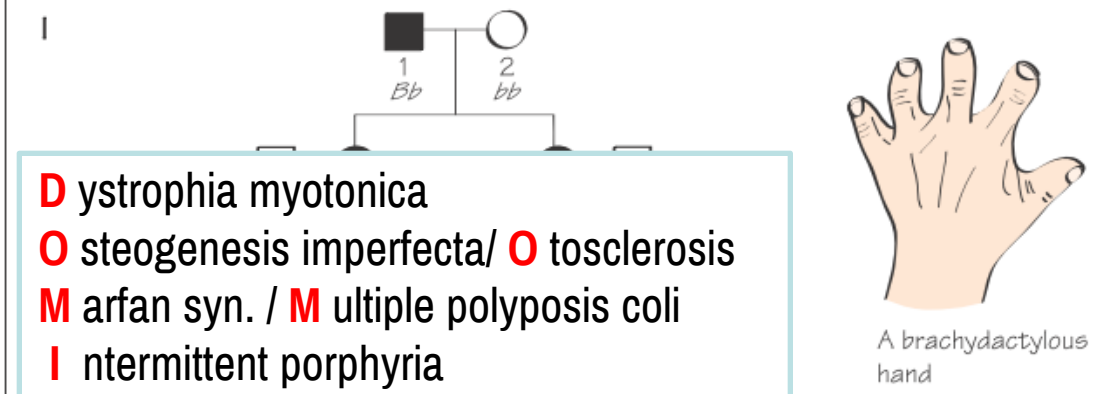






Autosomal dominant disorders (AD)

D ystrophia myotonica
O steogenesis imperfecta/ **O** tosclerosis
M arfan syn. / **M** ultiple polyposis coli
I ntermittent porphyria
N eurofibromatosis
A chondroplasia/ **A**dult polycystic kidney
N anism / **N**oonan symdrome
T uberous sclerosis

5xH
H ereditary spherocytosis
H ypercholesterolemia
H untington disease
H ypertrophic obstructive cardiomyopathy
H ereditary hemoprrhagic teleangiectasia

Figure 4.1 Part of original pedigree for brachydactyly



A brachydactylous hand

Figure 4.2 Estimation of risk for offspring, autosomal dominant inheritance

Heterozygote paired with a normal homozygote (*Bb* × *bb*)

Gametes →	*B*	*b*
b	*Bb*	*bb*
b	*Bb*	*bb*

Risk of *B*–: 2/4 = 50%

Heterozygote paired with another heterozygote (*Bb* × *Bb*)

Gametes →	*B*	*b*
B	*BB*	*Bb*
b	*Bb*	*bb*

Risk of *B*–: 3/4 = 75%

Dominant homozygote paired with a normal homozygote (*BB* × *bb*)

Gametes →	*B*	*B*
b	*Bb*	*Bb*
b	*Bb*	*Bb*

Risk of *B*–: 4/4 = 100%

Figure 5.3 Marfan syndrome

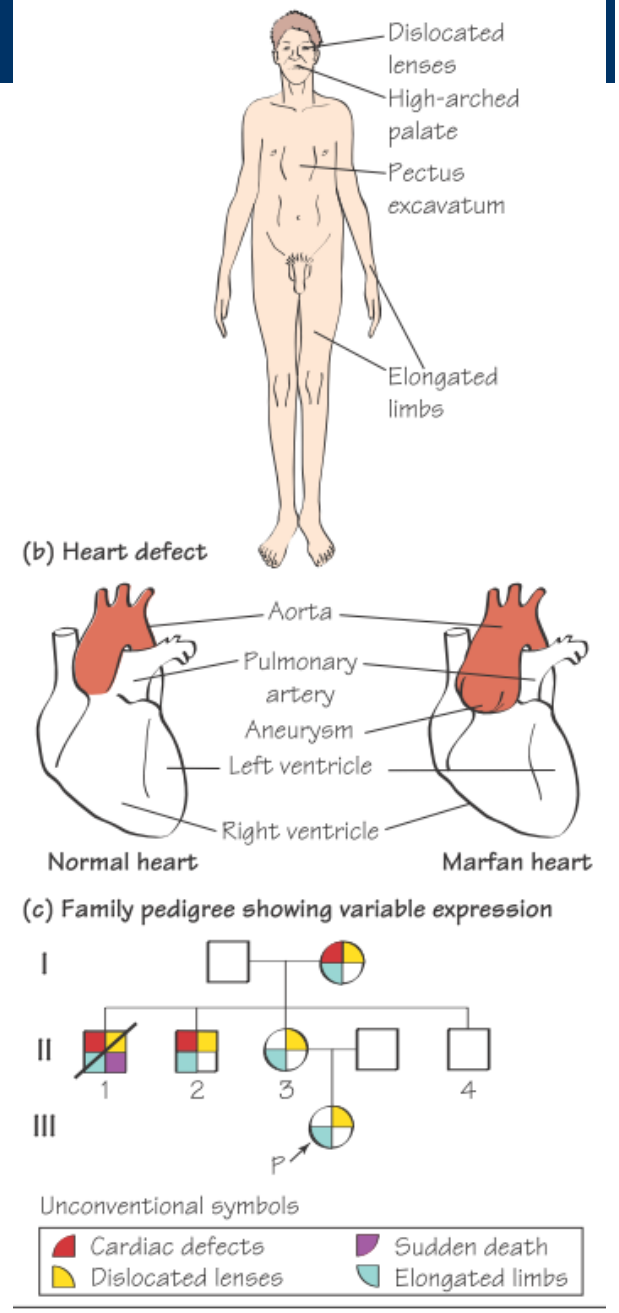


Figure 5.1 Achondroplasia

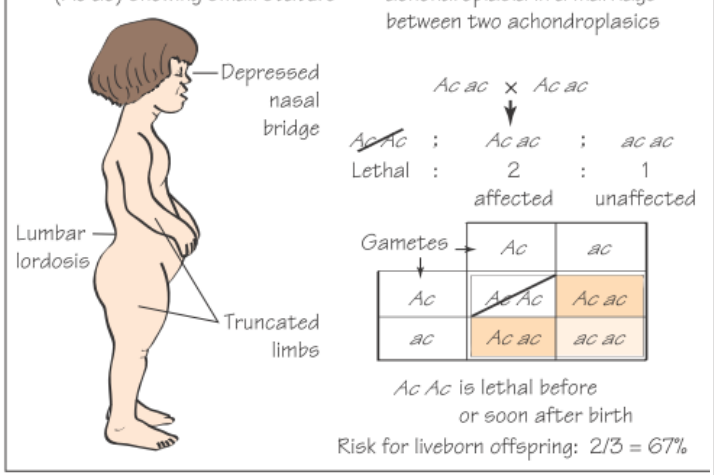


Figure 5.2 Disorders of fibroblast growth factor receptors

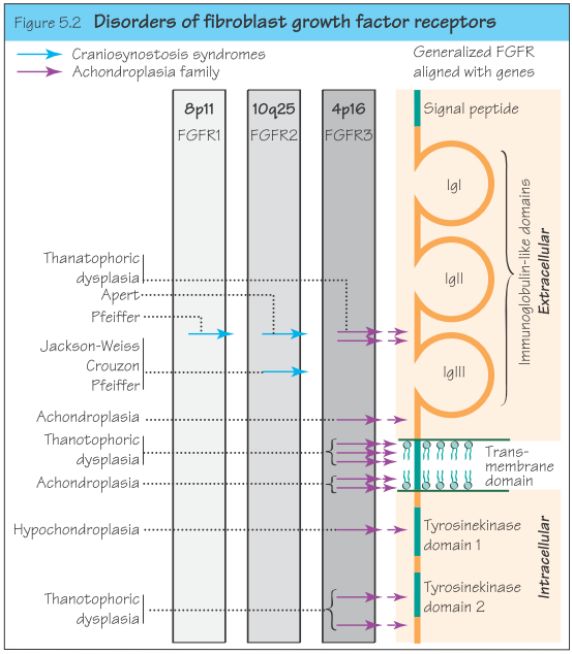
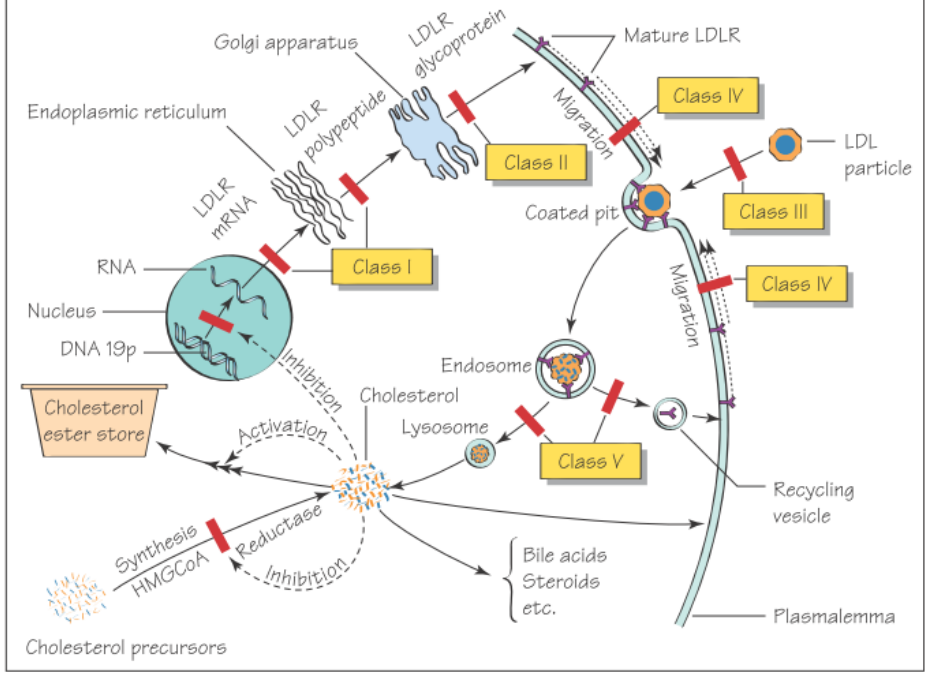


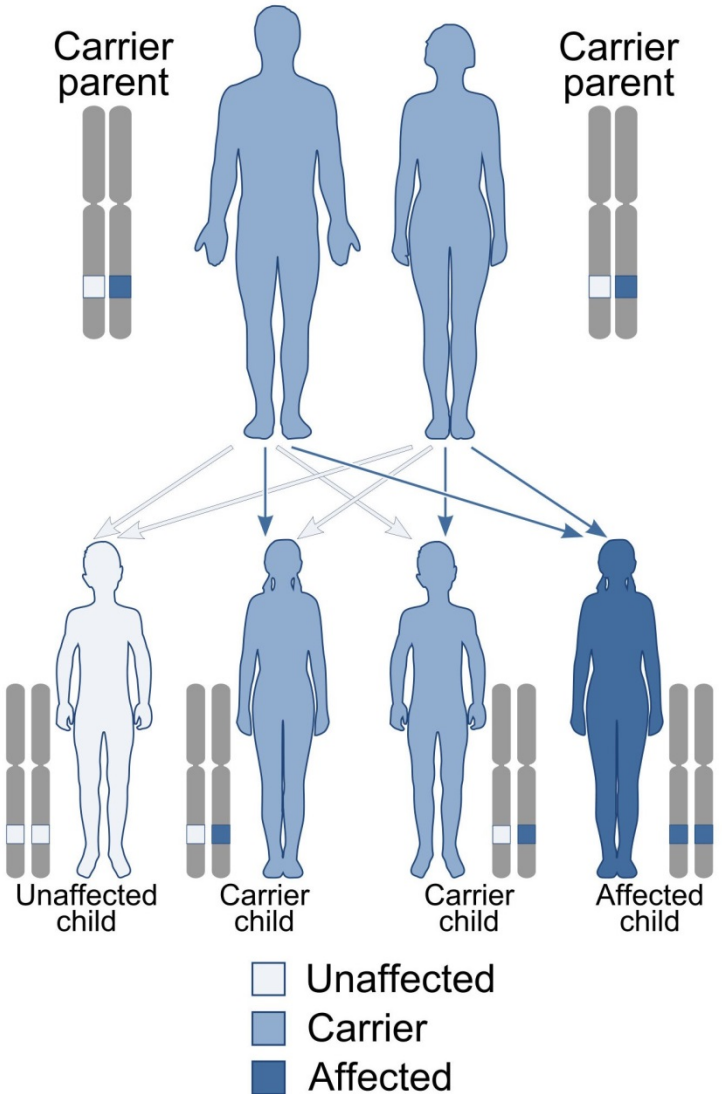
Figure 5.4 Receptor-mediated endocytosis and biosynthesis showing sites of action of mutations of classes I–IV that cause hypercholesterolaemia



Autosomal recessive disorders

Principles:

- One mutated allele is not enough for disease to be manifested (heterozygots); both genes (1 from mother and 1 from father) have to be mutated in the same way (identical pathological allele),
- Mutated genes is/are localized on homologous autosomes (e.g. Ch 2 maternal + Ch2 paternal);
- Males and females are affected with equal probability
- Parents do not need to be affected, but always are the carriers - most commonly both parents are heterozygotes; combination of affected homozygote x heterozygote is rare; all kids are affected
- Because AR require that both parents are carriers - diseases occur more common in marriages between relatives or within closed communities – geographic, ethnic, religious, etc. (imbreeding)

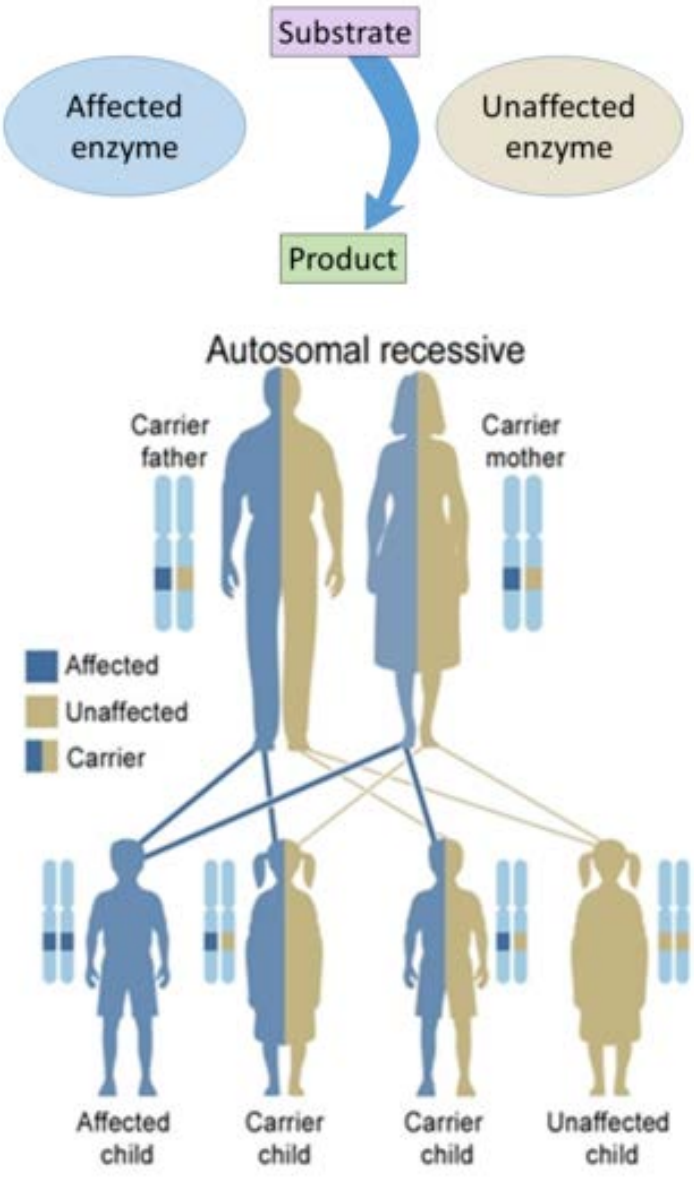


Autosomal recessive disorders

- However, characteristic pedigree pattern is rather single-hit and horizontal *(brothers, sisters,)* than vertical one passing multiple generations (i.e usual mating is between heatlhy carriers;)
- *Complete penetrance* - diseases occur in agreement with rules and calculated predictions in members of families both horizontally and vertically;
- *Non-variable expresivity* - once disease should occur than manifestatioons and intensity of symptoms (fenotype) is similar in each family member (intra-familiar) ; diseases resemble among families, too (inter-familiar)

Predictions:

- Male and female clinically normal carrriers give 25% 50% heterozygote carriers



Autosomal recessive diseases - examples

Figure 8.1 **Organ systems affected by cystic fibrosis**

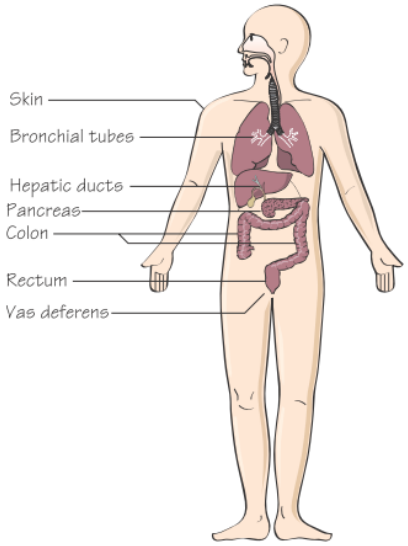
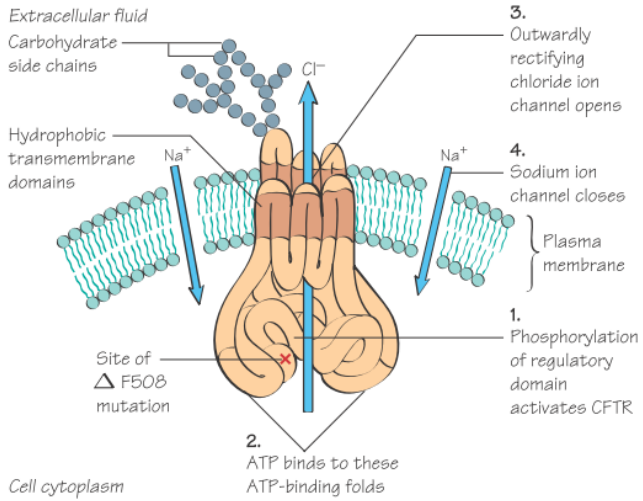
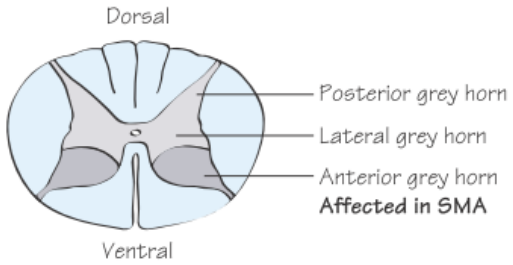


Figure 8.2 **The cystic fibrosis transmembrane conductance regulator, CFTR**



Transverse section of spinal cord



A phenylketonuria patient showing schneidersitz (tailor's posture) caused by muscular hypertonicity

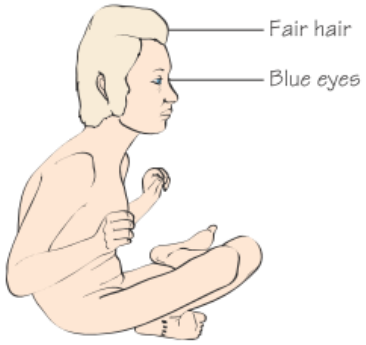
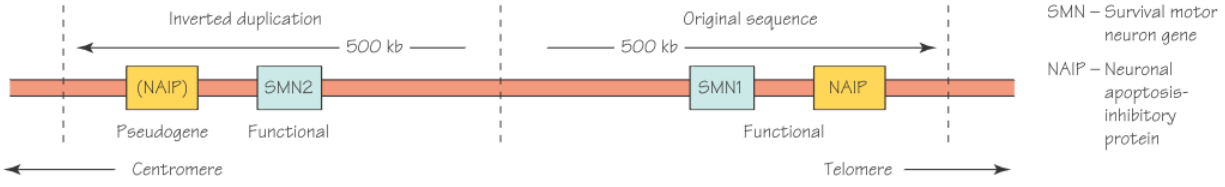


Figure 8.5 **Inverted duplication involved in spinal muscular atrophy**

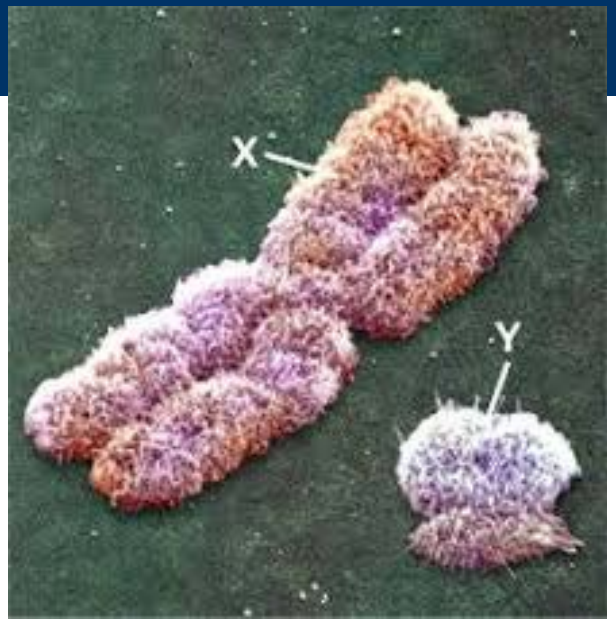


Autosomal recessive diseases - examples

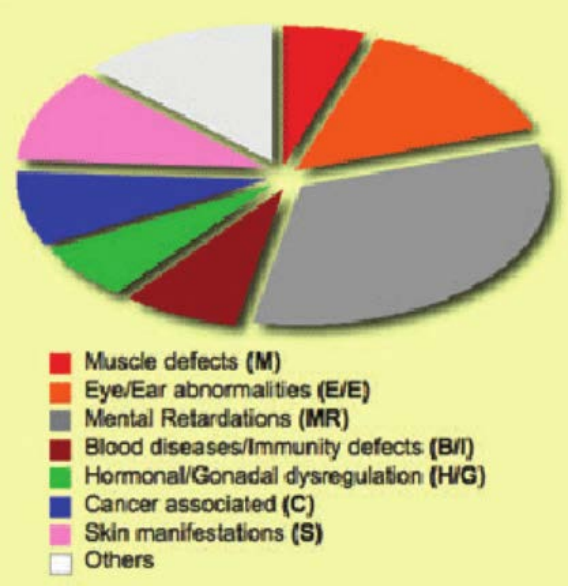
Disease	Rate of occurence
Lactase deficiency	1: 10 (whites)
Alpha - thalasemia	very high in mediterian area
Beta - thalasemia	north-african, azian countries
Dubin- Johnson-Rotor sy.	1: 300 (persian Jews)
Cystic fibrosis	1: 2000 (whites)
Gaucher disease type 1	1: 2000 (Jews in USA)
Tay - Sachs disease	1: 2000 (Jews in USA)
Alpha1 -antitrypsin deficiency	1: 3500
Congenital hypothyreosis	1: 4000
Cystinuria	1: 7000
Hyperphenylalaninemia type I	1: 10.000
Congenital adrenogenital sy.	1: 10.000
Alcaptonuria	1: 19.000
Cartagener sy.	1: 20.000
Wilson disease	1: 50.000
Cystinosis	1: 100.000
Xeroderma pigmentosum	1: 250.000

X chromosome (ChX)

"Human Genome Assembly GRCh38 - Genome Reference Consortium". NCBI

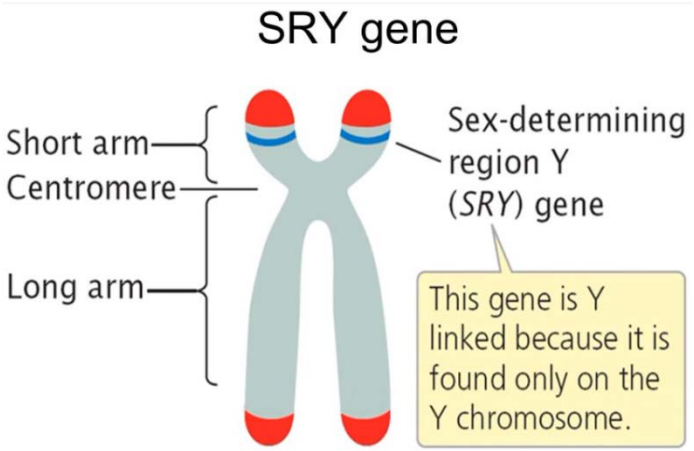


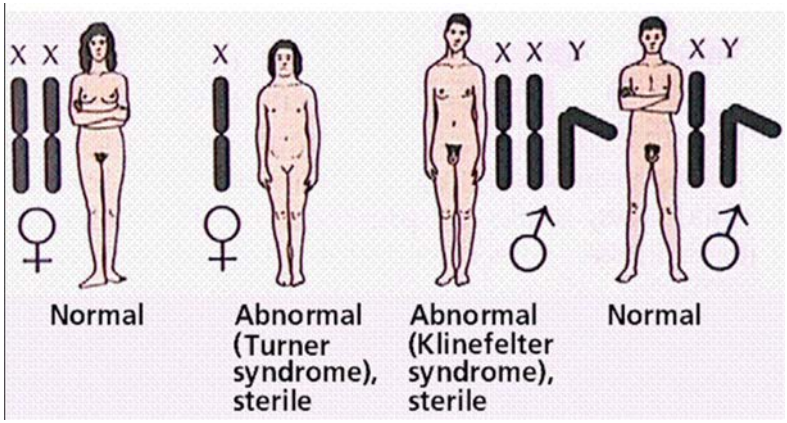
- 1890 by Hermann Henking in Leipzig
- Ch X is one of the sex determining chromosome (allosome)
- Played a crucial role in the development of sexually selected characteristics for over 300 million years
- XY sex-determination system in man
- Ch X is as big as modest autosomes (156 millions base pairs; 804 genes; behaves like autosome - encodes proteins inevitable for CNS (mental functions, intelligence; senses (eyes, ears), PNS (nerves), muscles, liver, blood, metablic disorders,
- Humans cannot live w/o any ChX; but can live w/o Y (females);
- Females must have 2 x ChX in morula to be fertile although
- Females, like males, had only one functional copy of the X; one Ch X is randomly and (permanently?) inactivated in preimplantation blastocyst in nearly all somatic cells (except eggs) = lyonization → creates a Barr body (transcriptionally inactive heterochro- matin) compacted by Polycomb Repressive Complex 2 (PRC2)
- Females may exhibit X-dominant and/or X-recessive trait in ChX geneexpression similar to autosomal genes; males are hemizygous for X

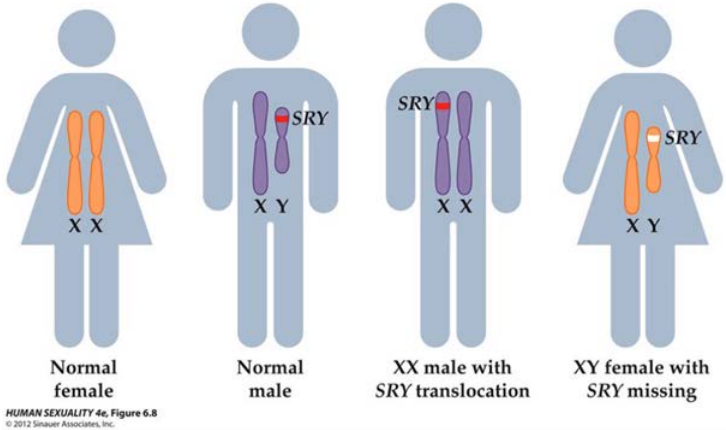


Y chromosome

- one of two sex chromosomes (allosomes) in mammals,
- 59 million base pairs; 100-200 genes, 45 - 73 protein-coding; 30% difference between humans and chimpanzees
- Y that typically determines the male or female sex
- In mammals, the Y chromosome contains the gene SRY, which triggers male development.
- one of the fastest-evolving parts of the human genome
- aneuploidy such as XYY syndrome or XXYY syndrome.
- XX male syndrome rare disorder, (translocation of the SRY gene to the X chromosome) SRY region of the Y chromosome has recombined to be located on one of the X chromosomes.
- XY female syndrome (mutations in SRY → gonadal dysgenesis → externally female



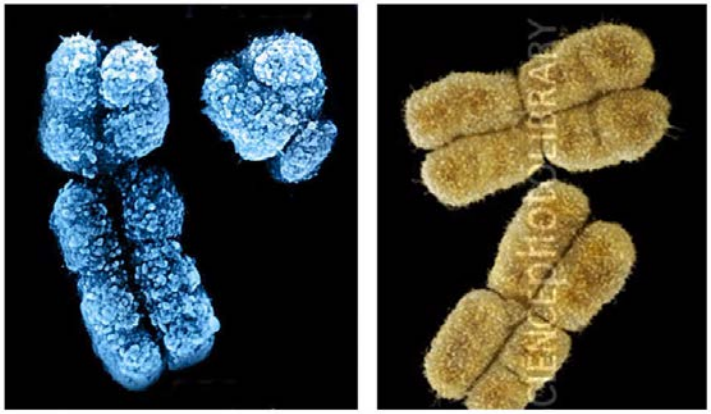




Sex-determination systems

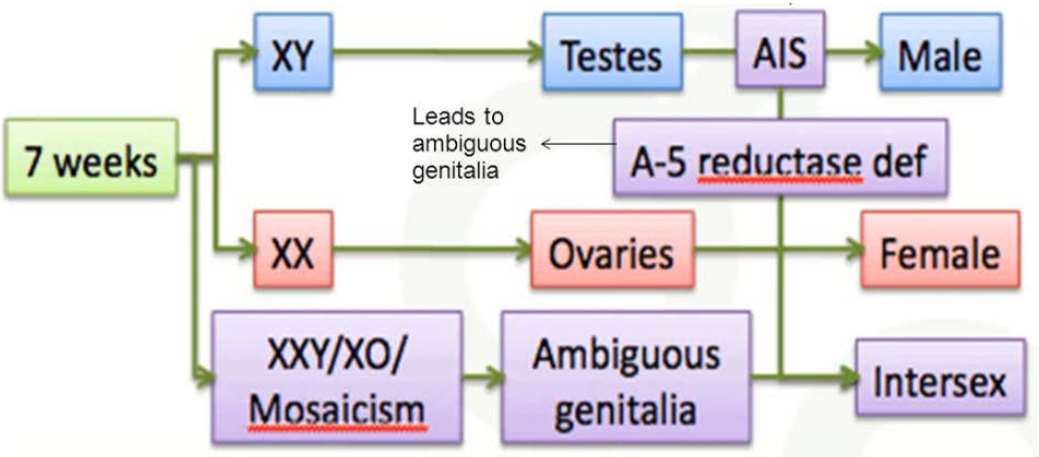
- XY sex-determination system
- mammals, primates, humans, some insects (Drosophila), some snakes (pythons, boas), some fish (guppies), plants (Ginkgo tree); sex of an individual is determined by a pair of sex chromosomes: females (XX) *homogametic sex.* Males: (XY) are *heterogametic sex.*
- Ch Y trigger male development; absence of Y → fetus will undergo develops to female
- Ch Y - SRY gene → male differentiation.

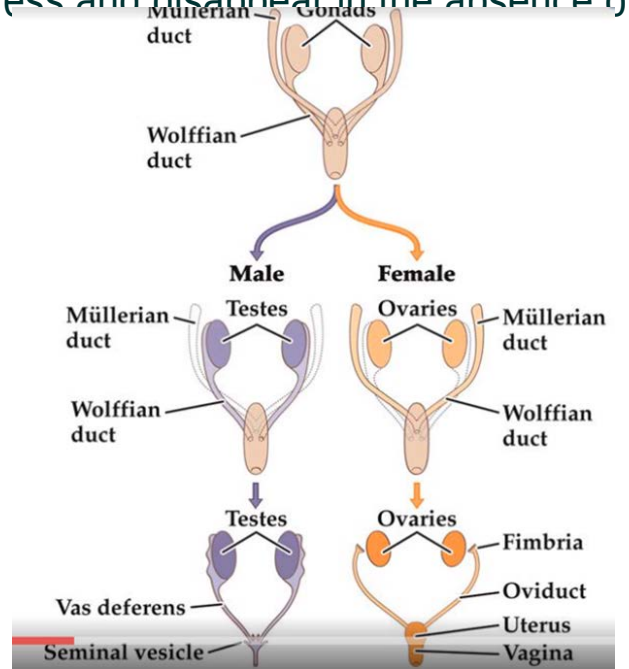
- X0 sex-determination system: most arachnids, insects (e.g. dragonflies, grasshoppers, crickets and cockroaches) nematodes, crustaceans, gastropod molluscs[3] and bony fish, several mammals (some bats ,rats) Males: X0, Females (XX)
- ZW sex-determination system: birds, some insects, many reptiles, various other animals, heterogametic is female.
- Temperature-dependent sex determination system found in some reptiles.

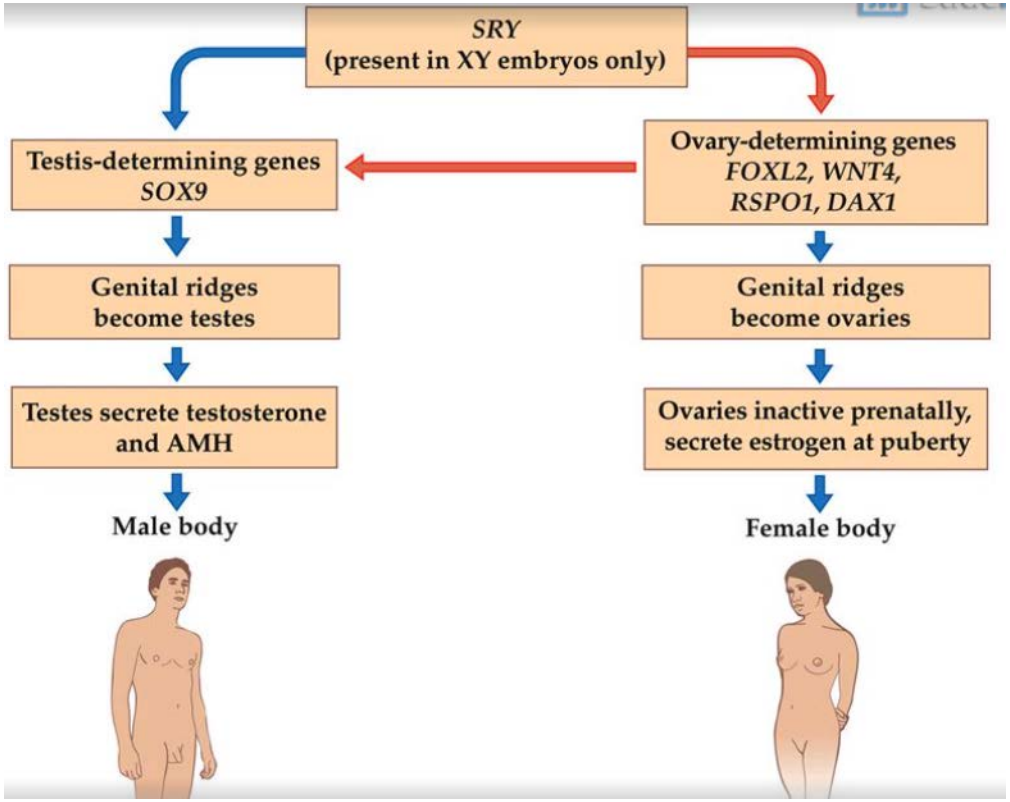


Sex determination

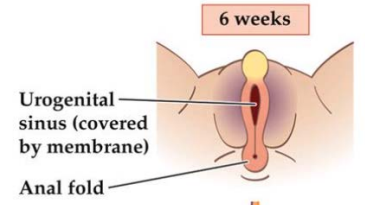
- Six week old embryos possess undifferentiated structures called "genital ridges" that will develop intoeither testes or ovaries
- Male development depends upon the presence of the SRY gene, which causes the fetus to develop testes, which secrete testosterone and antiMullerian hormone (AMH). testosterone stimulates the Wolffian ducts to develop into the epididymis, vas deferens, ejaculatory ducts, and seminal vesicles,and AMH causes the Mullerian to regress and disappear
- Female development (with the exception of ovaries) ***proceeds in the absence of specific genetic instructions,*** although several genes are involved in both stimulating ovarian development and inhibiting testis development. In absence of AMH, Mullerian ducts develop into the oviducts, uterus, and the deeper part of the vagina, while the Wolffian ducts regress and disappear in the absence of testosterone.

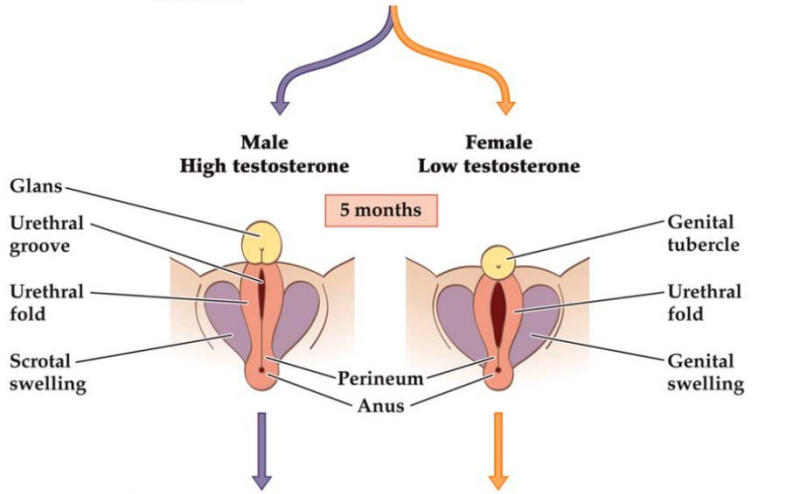


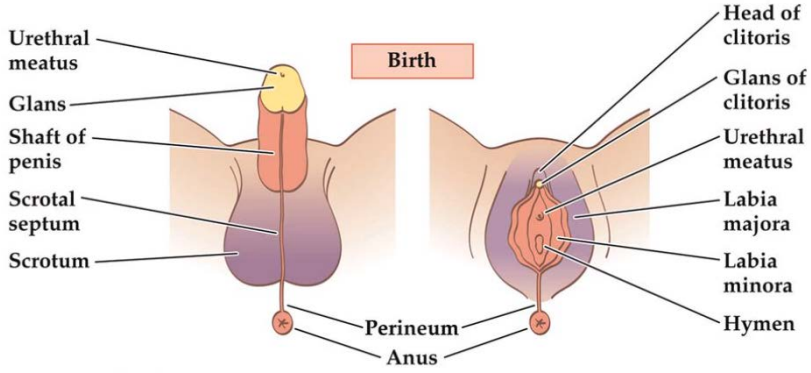



SRY
(present in XY embryos only)
Testis-determining genes
SOX9
Ovary-determining genes
FOXL2, WNT4,
RSPO1, DAX1
Genital ridges
become testes
Genital ridges
become ovaries
Testes secrete testosterone
and AMH
Ovaries inactive prenatally,
secrete estrogen at puberty
Male body
Female body


4 weeks
Genital tubercle
Cloaca (covered by membrane)
Genital Swelling
Urethral fold


6 weeks
Urogenital sinus (covered by membrane)
Anal fold

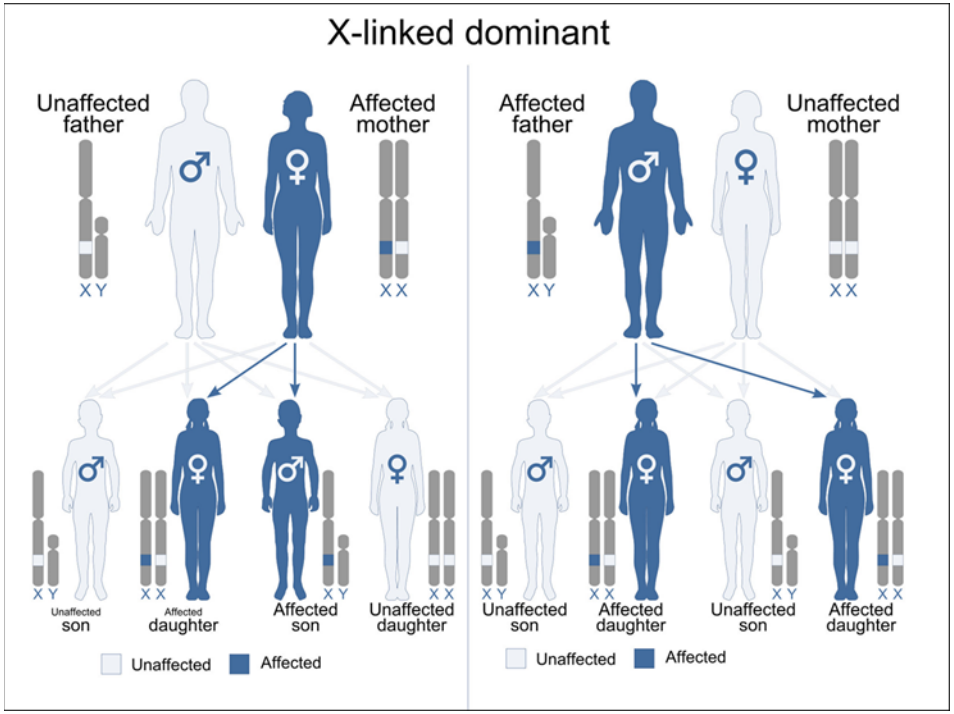

Male
High testosterone
Female
Low testosterone
5 months
Glans
Urethral groove
Urethral fold
Scrotal swelling
Perineum
Anus
Genital tubercle
Urethral fold
Genital swelling
HUMAN SEXUALITY 4e, Figure 6.12 (Part 2)


Birth
Urethral meatus
Glans
Shaft of penis
Scrotal septum
Scrotum
Perineum
Anus
Head of clitoris
Glans of clitoris
Urethral meatus
Labia majora
Labia minora
Hymen

Gonosomal dominant inheritance (XD)

Principles:

- both men and women are affected; the proportion of affected women in the population is about 2 times higher; F show higher prevalence of XD disorders because they have 2 x ChX
- pattern of inheritance varies, depending on whether the father or the mother is carrier
- affected fathers alone will have 100% affected daughters; and no disabled son
- affected mother alone might have affected sons or daugters; (50% will have the disorder; 50% unaffected)



- affected males with some XD disease are aborted (e.g. Aicardi syndrome); disease appear only in females or in Klineffelter boys (47, XXY)
- affected daughters may have either father or mother affected
- if both parents are carriers of a defective gene---> both are sick (have the disorder)--> 100% of daughers will have the disorder, 50% of the sons will have the disease, 50% will be unaffected; daughter experience a more severe form
- there is highly variable penetrance of X-linked traits in females <-- (X-inactivation or somatic mosaicism)

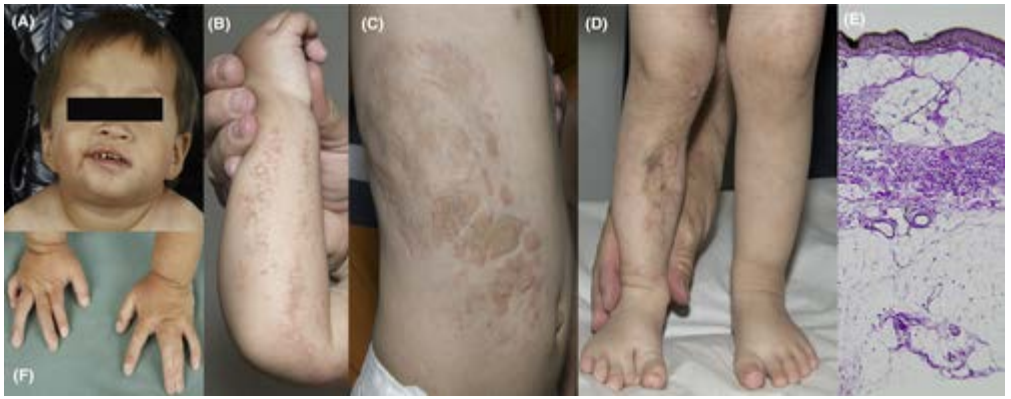
Gonosomal dominant inheritance (XD) Examples

- Alport syndrome, X-linked dominant porphyria Incontinentia pigmenti
- Fragile X syndrome, Giuffrè–Tsukahara syndrome Lujan–Fryns syndrome
- Vitamin D resistant rickets: X-linked hypophosphatemia (1:20.000 ♀♂ PHEX gene) rickets (osteomalacia) in that vitamin D supplementation does not cure
- Rett syndrome (RTT) (1: 8,500 ♀) MECP2 (95% de novo mutations; <1% hereditary) after 6–18 months of age (language,ataxia, slower growth, difficulty walking, boys die shortly after birth
- Goltz syndrome (focal ectodermal dysplasia) PORCN gene; 90% female: males die in utero multisystem dis,;:skin (atrophy, hypoplasia)at birth (yellow-pink bumps on the skin and pigmentation changes.stature short, epilepsy.
- Aicardi syndrome (thousands wordwide) partial /or complete absence of corpus callosum), retinal abnormalities, spasms - seizures (from 6th months of age) ; associated with tumors (choroid plexus papilloma), medulloblastoma), polyps, etc
- Oculofaciocardiodental syndrome (< 1>1000000; F>>M`, BCOR gene Teeth with large roots (radiculomegaly), defective enamel, small eyes (microphthalmia) early cataracts, Glaucoma Atrial and/or ventricular defects, Mitral valve prolapse, Mild mental retardation sensorineural hearing loss
- CHILD syndrome 99% females (60 cases worldwide); NSDHL gene (cholesterol synthesis) irst few weeks of life CH = Congenital Hemidysplasia (right side ribs, neck, vertebrae, internal organs etc. poorly developed) I - Ichthyosiform Erythroderma (red, inflamed patches (erythroderma); LD - limb defects (fingers may be missing; arm or leg shortened)

Gonosomal dominant inheritance (XD) Examples

Fragile X syndrome

https://en.wikipedia.org/wiki/Fragile_X_syndrome, CC licence



Goltz syndrome

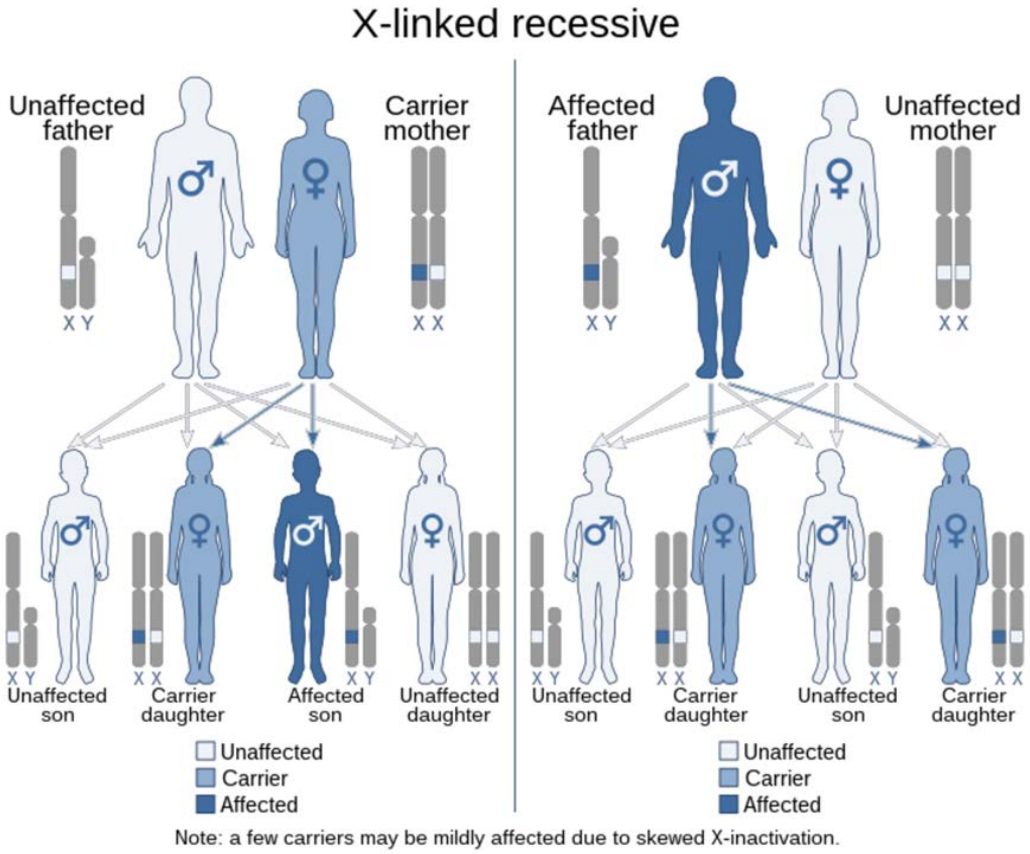
Frisk, S et al.: Clin. Case Report. 6(11): 2103-2110, 2018; CC licence

Aicardi syndrome

https://www.assignmentpoint.com/science/medical/aicardi-syndrome.html

Gonosomal recessive disorders (XR)

- X chromosome is like autosome; males are hemizygous; females may exhibit dominant and/or recessive properties of their X-linked genes, as with autosomal genes. at the cellular level, however, some genes on the X are expressed either; inactivation – Barr body



Characteristics:

- The incidence of disease is very much higher in males than in females.
- The mutant allele is passed from an affected man to all of his daughters, but they do not express it. The mutant allele is NEVER passed from father to son.
- A heterozygous woman – is carrier and passes the allele to half of her sons, who express it, and half her daughters who do not.
- A homozygous woman – is partially affetcted (mosaicism) zygosity ; passes the allele to all sons and all daughters

Gonosomal recessive linked on X

- Red–green color blindness 7-10% mužov, 0.49-1% žien
- Hemophilia A (factor VIII)
- Hemophilia B (factor IX)
- Duchenne muscular dystrophy
- Becker's muscular dystrophy,.
- X-linked ichthyosis 1: 2,000 - 6,000 males
- X-linked agammaglobulinemia (XLA),
- Glucose-6-phosphate dehydrogenase deficiency
- Adrenoleukodystrophy - progressive brain damage,
- Alport syndrome; glomerulonephritis
- Androgen insensitivity syndrome
- Barth syndrome
- Centronuclear myopathy;
- Charcot–Marie–Tooth disease
- Fabry disease; A lysosomal storage disease
- Hunter syndrome
- Spinal and bulbar muscular atrophy; muscle cramps and progressive weakness
- Lesch–Nyhan syndrome;hyperuricemia)
- Lowe syndrome; hydrophthalmia, cataracts, vitamin D-resistant rickets
- Menkes disease
- Wiskott–Aldrich syndrome;
- X-linked severe combined immunodeficiency (SCID);

Gonosomal recessive disorders

Figure 10.1 **The X chromosome showing region of homology with the Y and the map locations of some significant genes**

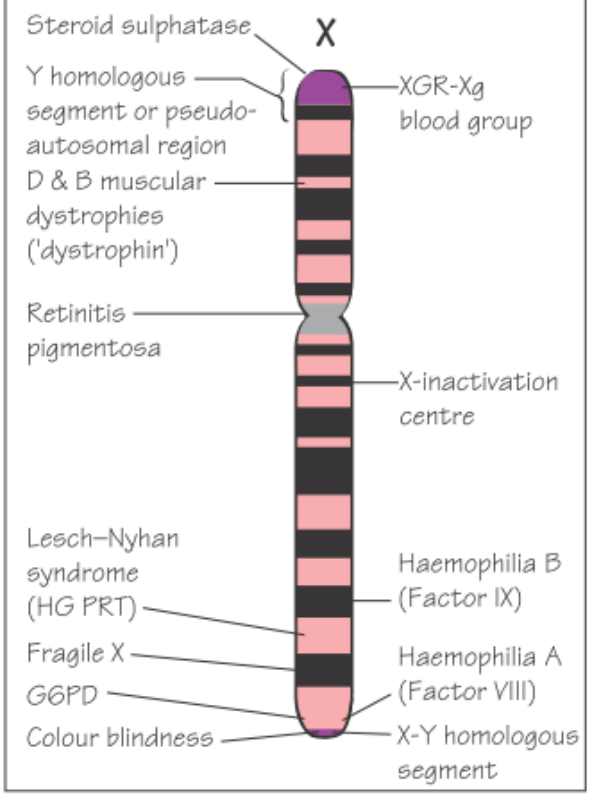


Figure 10.2 **X-linked recessive inheritance**

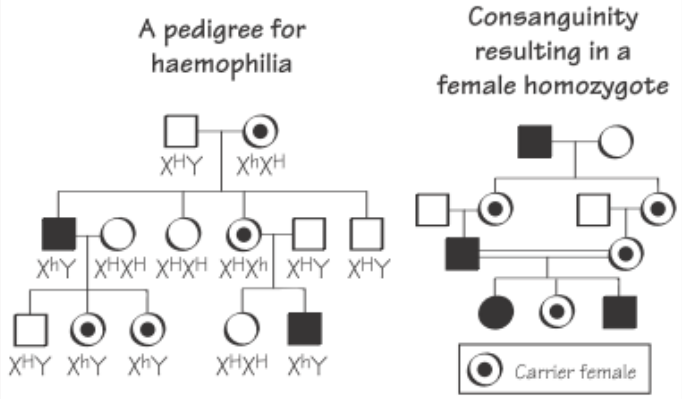


Figure 10.3 **X-linked dominant inheritance**

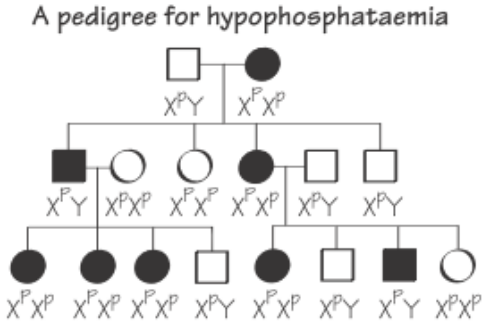
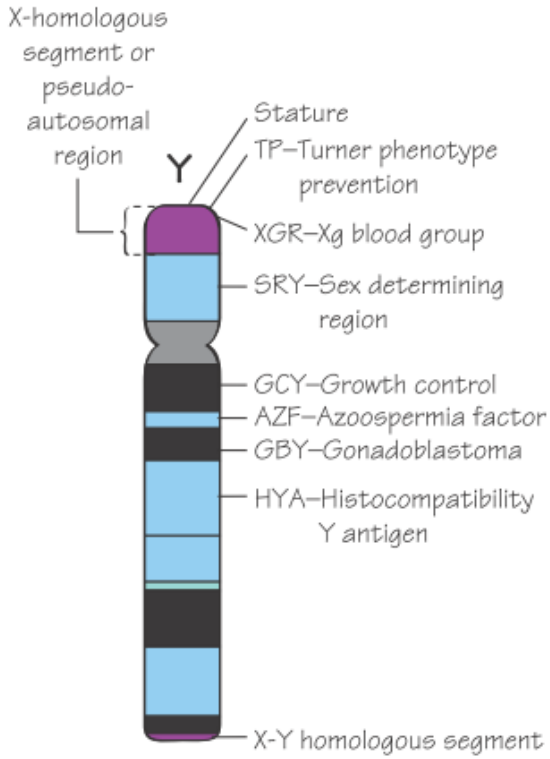
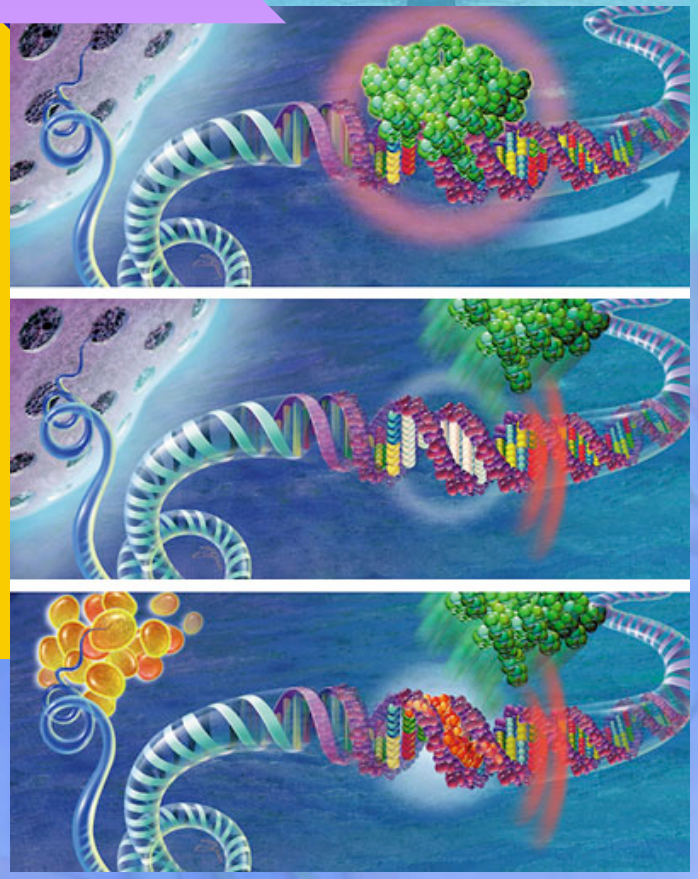


Figure 10.4 **The Y chromosome showing region of homology with the X and locations of significant genes**



Holandric inheritance (Y)

- Special type of inheritance based on the Y-chromosome.
- Yet no evidence of pathological feature that would transmit this way
- Typical indications holandrickej inheritance feature of the pedigree:
  - affected are only men
  - all the children of affected men are also affected



Non-Mendelian inheritance

1. **Trinucleotide repeate mutation' disorders**
2. **Disorders implying the genomic impring**
3. **Mosaicism phenomenon**
4. **Mitochondrial disorders**

1. Trinucleotide repeate disorders

1. Dynamic mutations

- Do no follown Mendelian rules:
  - a) remain predominant paternal inheritance – thay are trasmited by paternal lineage) or maternal lineage
  - b) unstable fenotype - manifestations worsen from generation to generation; that reset may occur;
- Mutation type: **trinucleotide repeat expansion** = increases the number of the same 3-nucleotide sequences (CAG or CTG or CGG or GCC or GAA in different diseases) in transcibed part of the gene (exon) or in introns
- They comormise the coded protein function by different ways; e.g. porolongation of peptide by reapeated sequences in aminoacid repeates
- Normal number - certain numbers of abunfant 3-nucleotide repeates is present normally; reasoin unknown
- At least 22 inherited disorders, all involving the neuraxis, are now known to be caused by expanded repeats (Table 1). Repeat expansion diseases include some of the most common inherited diseases, such as Huntington's disease (HD) and myotonic dystrophy.

Dynamic mutations

Categories

- Category I includes Huntington's disease (HD) and the spinocerebellar ataxias that are caused by a CAG repeat expansion in protein-coding portions of specific genes.
- Category II expansions tend to be more phenotypically diverse with heterogeneous expansions that are generally small in magnitude, but also found in the exons of genes.
- Category III includes fragile X syndrome, myotonic dystrophy, two of the spinocerebellar ataxias, juvenile myoclonic epilepsy, and Friedreich's ataxia. These diseases are characterized by typically much larger repeat expansions than the first two groups, and the repeats are [illegible] regions of the genes.

Repeat count	Classification	Disease status
<28	Normal	Unaffected
28–35	Intermediate	Unaffected
36–40	Reduced Penetrance	+/- Affected
>40	Full Penetrance	Affected

1. Polyglutamine (PolyQ) Diseases)

Type	Gene locus (protein)	Repeated codon	Normal number	Pathogenic number
DRPLA Haw River Syndrome (Dentatorubropallidoluysian atrophy) Naito-Oyanagi disease	ATN1 12p13.31 (Atrophin-1)	(CAG)n	6 - 35	49 - 88
HD (Huntington's disease)	HTT 4p16.3 (Huntingtin)	(CAG)n	10 - 35	35+
SBMA (Spinobulbar muscular atrophy Kennedy disease, SMAX1)	AR; Xq12 (Androgen receptor)	(CAG)n	9 - 36	38 - 62
SCA1 (Spinocerebellar ataxia Type 1)	ATXN1 6p22.3 (Ataxin 1)	(CAG)n	6 - 35	49 - 88
SCA2 (Spinocerebellar ataxia Type 2)	ATXN2 12q24.12 (Ataxin-2)	(CAG)n	14 - 32	33 - 77
SCA3 (Spinocerebellar ataxia Type 3) Machado–Joseph disease	ATXN3 14q32.12 (Ataxin-3)	(CAG)n	12 - 40	55 - 86
SCA6 (Spinocerebellar ataxia Type 6)	CACNA1A 19p13.2 voltage-dependent, Ca2+ channel P/Q type, a1A subunit	(CAG)n	4 - 18	21 - 30
SCA7 (Spinocerebellar ataxia Type 7)	ATXN7 3p14.1 (Ataxin-T)	(CAG)n	7 - 17	38 - 120
SCA17 (Spinocerebellar ataxia Type 17)	TBP 6q27 TATA-binding protein	(CAG)n	25 - 42	47 - 63

2. Non-Polyglutamine Diseases

Type	Gene (chromosome)	Codon	Normal	Pathogenic	Area affected
FRAXA (Fragile X syndrome)	FMR1, (Xq27.3) Fragile X mental retardation 1	CGG	6 - 53	230+	Brain hemisphere Polytopic
FXTAS (Fragile X-associated tremor/ ataxia syndrome)	FMR1 (Xq 27.3) Fragile X mental retardation 1	CGG	6 - 53	55-200	Hemispheres cerebellum, etc.
FRAXE (Fragile XE mental retardation)	AFF2 or FMR2 (Xq28) AF4/FMR2 family member 2 (transc. act.)	GCC	6 - 35	200+	Brain; Polytopic
SCA8 (Spinocerebellar ataxia Type 8)	OSCA or SCA8	CTG	16 - 37	110 - 250	Brainstem Cerebellum
SCA12 (Spinocerebellar ataxia Type 12)	PPP2R2B or SCA12	nnn On 5' end	7 - 28	66 - 78	Brainstem Cerebellum
FRDA (Friedreich's ataxia)	FXN or X25, (frataxin reduced expression)	GAA	7 - 34	100+	Spinal cord
DM (Myotonic dystrophy)	DMPK	CTG	5 - 37	50+	Muscles

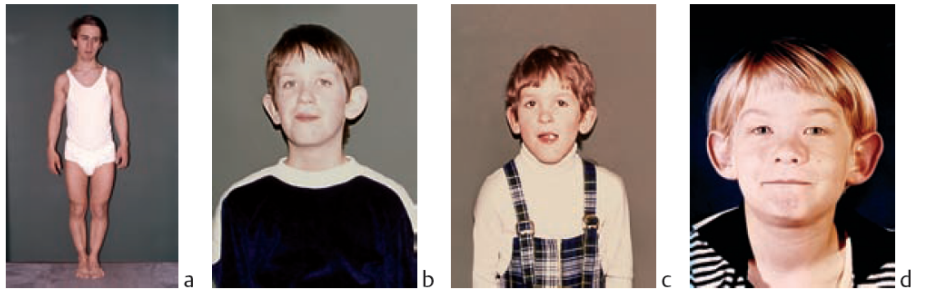
Fragile X syndrome
Escalante's syndrome

FMR1 (Martin-Bell syndrome) - identified in 1991; mental retardation; prevalence 1:3000 – 6000 males.

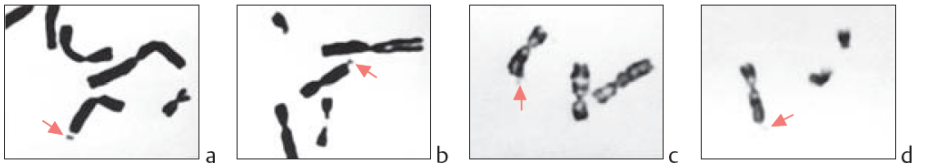
CP*:* varying intellectual delay associated with behavioral and physical features (connective tissue weakness;

Forms:

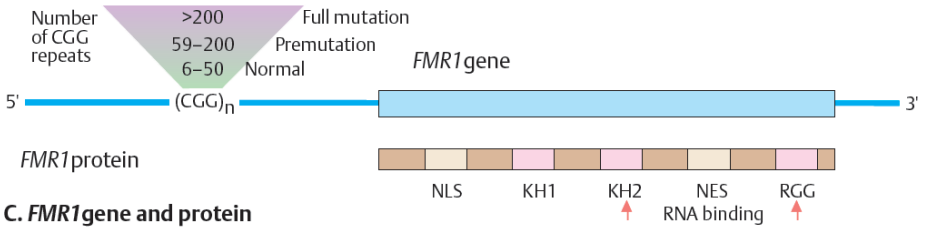
- FRAXA expansion of an unstable CGG repeats in FMR1 gene on Xq27.3 resulting in hypermethyla - tion + transcriptional silencing (->lack of FMR1 protein). FRAXE at Xq28
- FMR1 gene (17 exons); transcript is alternatively spliced and translated into at least 20 protein isoforms of protein (FMRP)
- normal allele (6–50). premutation (59–200), full mutation allele (~ 200 CGG trinucleotides)
- *Premutation* can be transmitted by either a female (I-2, II-3, III-2) or a male (II-2). A premutation allele may expand into a full mutation when passed from a mother to her children. All daughters of a normal male transmitter will be heterozygous.
- *Full mutation* males transmit a premutation to all their daughters. Carriers of a premutation allele do not usually have signs of fragile X syndrome, but 50–60% of girls with a full mutation have significant cognitive deficits.



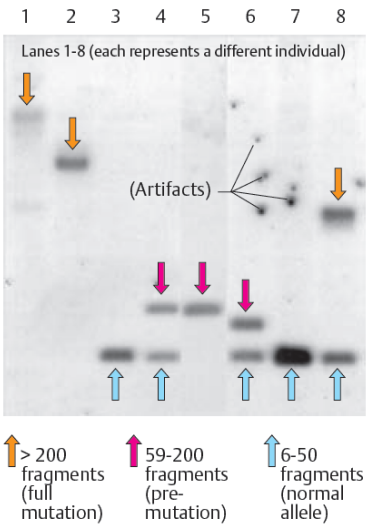
A. Phenotype



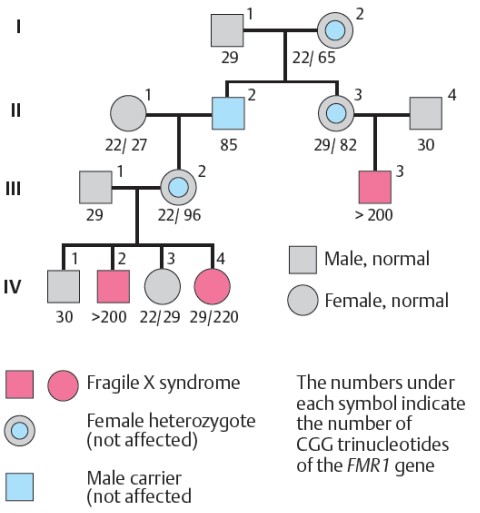
B. Fragile site Xq27.3



C. *FMR1*gene and protein



1. Southern blot analysis for Fra X syndrome



2. Phenotypic effects of expanded CGG repeats

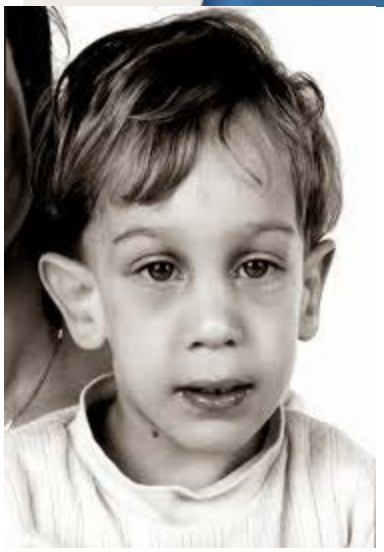
D. Inheritance and genetic testing

Fragile X syndrome

- Skeletal-motor
  - elongated face (vertical maxillary excess), large or protruding ears
  - flat feet, high-arched palate, hyperextensible finger joints, thumbs` low muscle tone;
  - stereotypic movements (e.g., hand-flapping)

- Other tissues
  - Soft skin, larger testes (macroorchidism)
  - recurrent otitis media (middle ear infection)
  - sinusitis is common during early childhood.

- Mental status
  - Intellectual disability, luttered nervous speech
  - atypical social behaviour (shyness, limited eye contact, memory problems, Autism (rarely)
- Males - virtually complete penetrance (symptoms are severe)
- Females - penetrance ~ 50% symptoms range from mild to severe



Fragile X chromsome

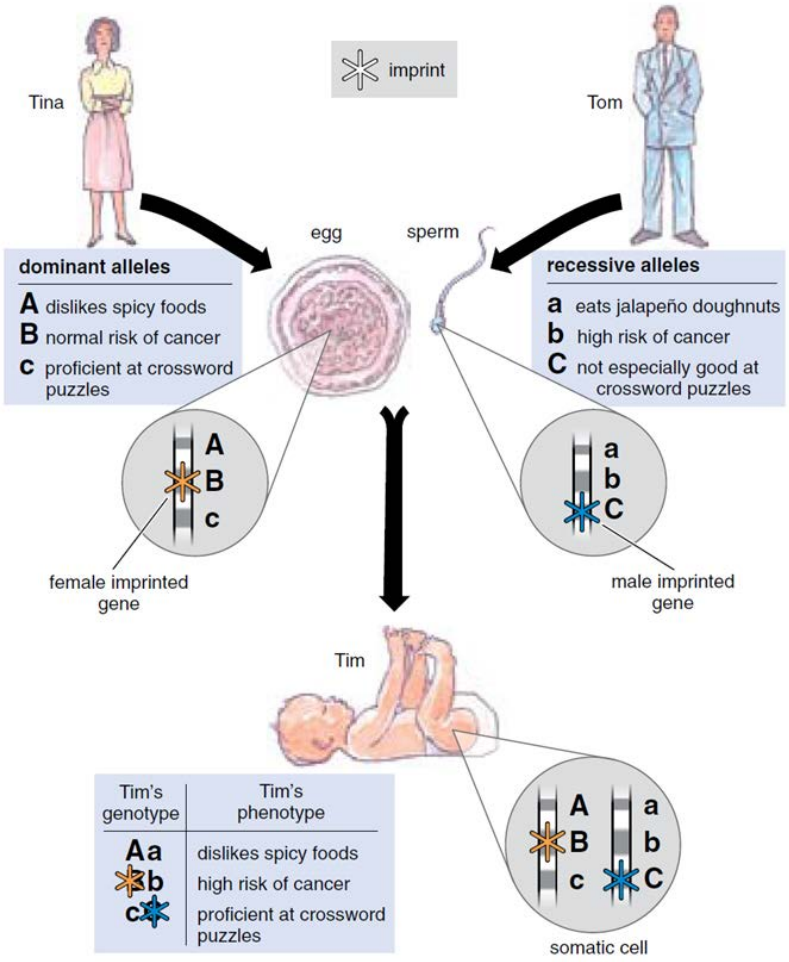
Khandjian, E. et al.: (2017). The Fragile X Syndrome (version2).

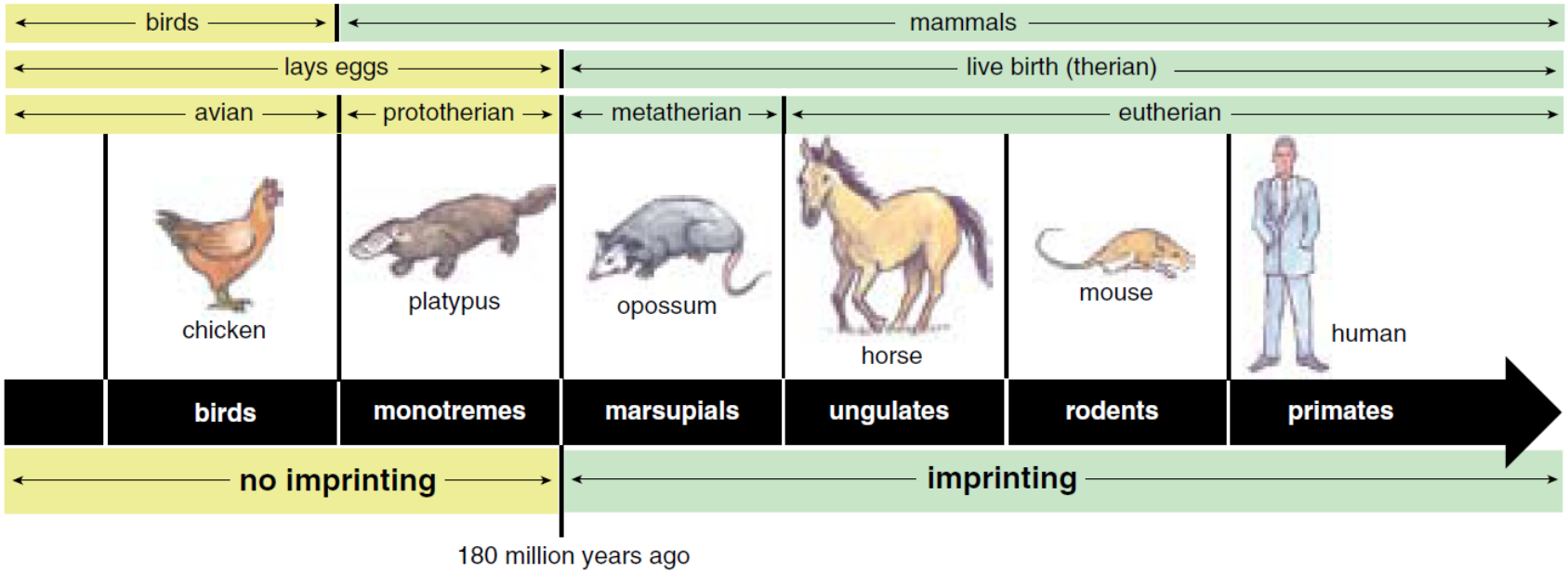
2. Disorders implying genomic imprinting

- Neurological neurodegenerative disorders
- Fragile X chromosome

Principles

- Cells can distinguish parernal and maternal chromosome: an epigenetic process that can involve DNA methylation and histone modulation; marks are established in the germline and can be maintained through mitotic divisions
- Different cell lineages in the tissues may selectively use either paternal or maternal genes/ group of genes, or even whole chromosomes – called imprinted genes or imprinted chromosomes
- Way how to achieve monoallelic gene expression without altering the genetic sequence: a) strict, i.e. other copy is never used in replace or b) facultative

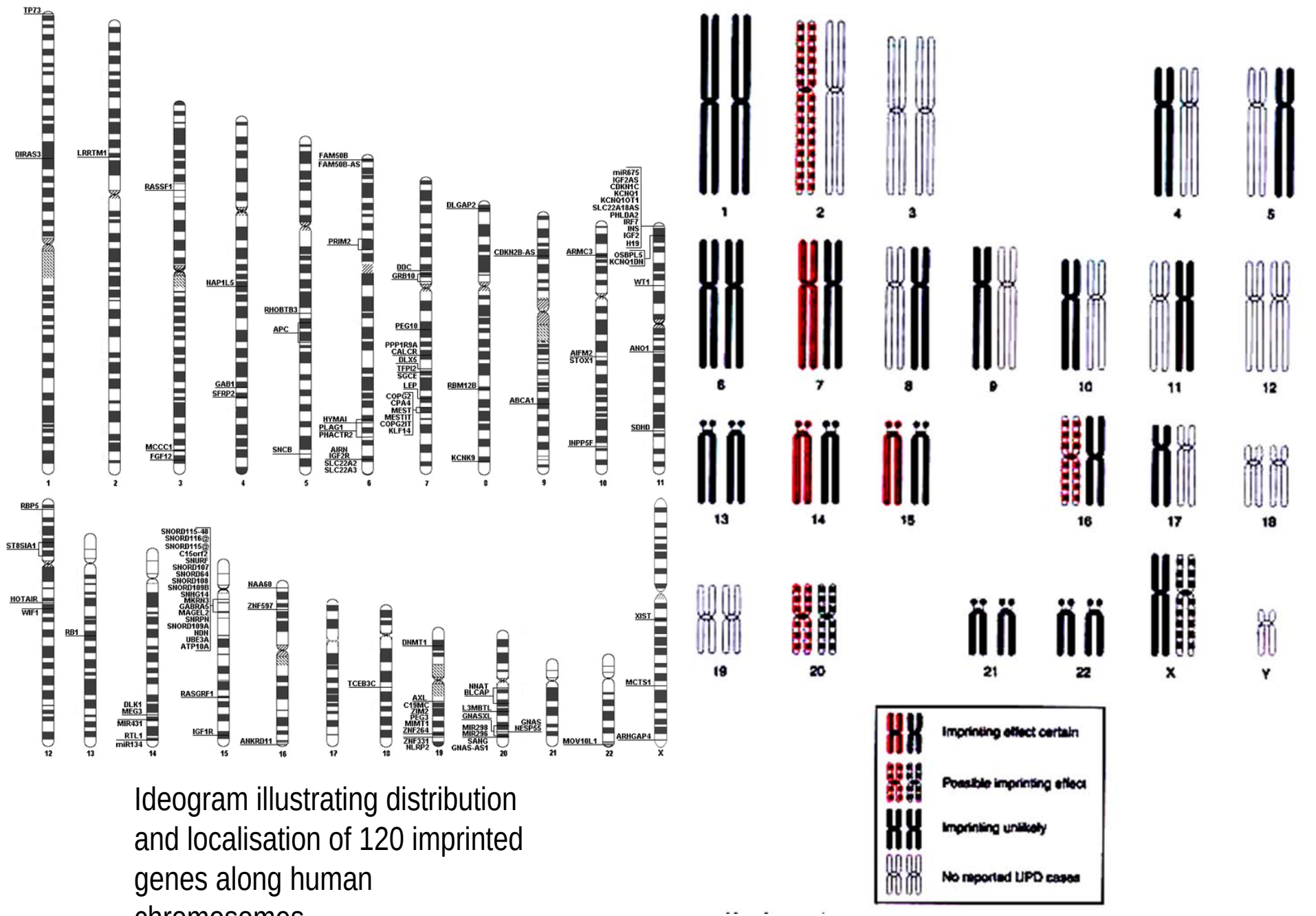




- 180 million years ago, genomic imprinting and the practice of live birth coevolved in primitive mammals.
- Egg-laying monotremes such as the platypus are the most ancient group of mammals and do not have imprinted genes.
- The first examples of imprinting appeared in a now-extinct ancestor of marsupials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

Genomic imprinting

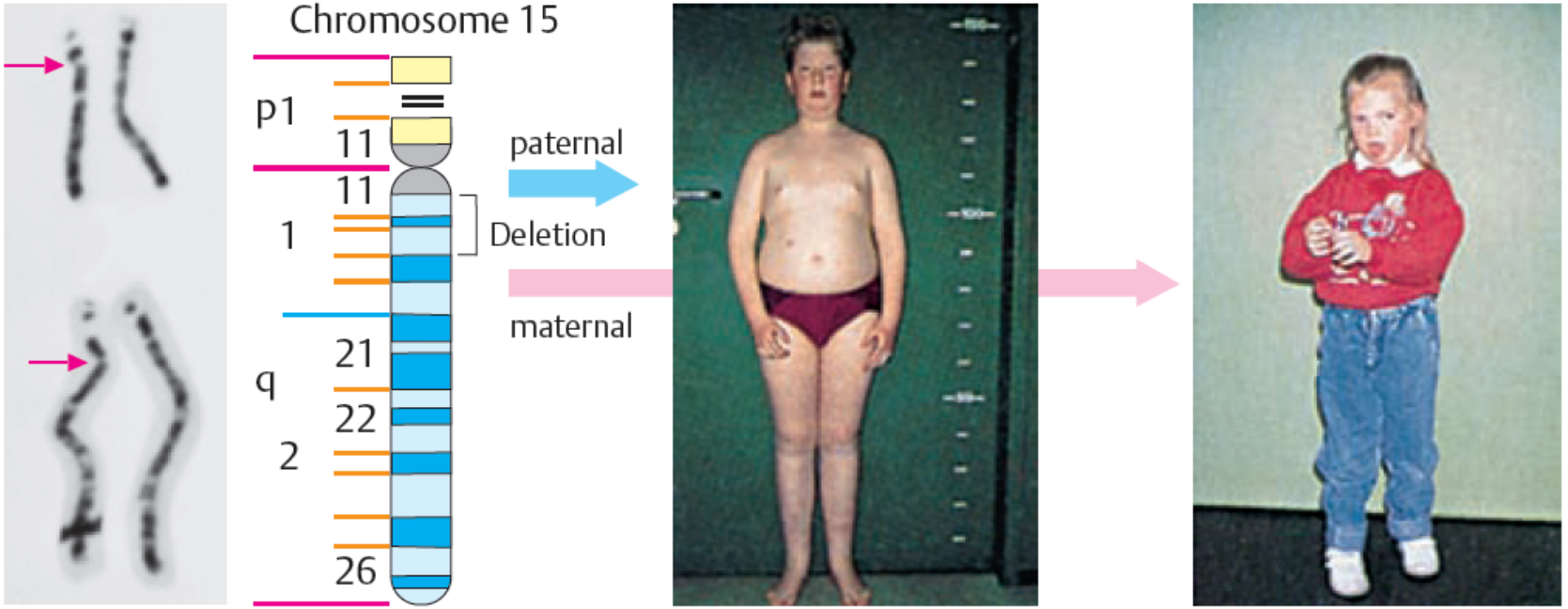
- Parental genomic imprinting (marking up) is an epigenetic phenomenon by which certain genes can be expressed in a parent-of-origin-specific manner.
- It may also ensure transposable elements remain epigenetically silenced throughout gametogenic reprogramming to maintain genome integrity.
- inheritance process independent of the classical Mendelian inheritance.
- imprinted alleles are silenced such that the genes are either expressed only from the non-imprinted allele inherited from the mother (e.g. H19 or CDKN1C), or in other instances from the non-imprinted allele inherited from the father (e.g. IGF-2).
- genomic imprinting was demonstrated in fungi, plants and animals; in plants parental genomic imprinting can refer to gene expression both solely or primarily from either parent's allele.
- Appropriate expression of imprinted genes is important for normal development,
- Beckwith–Wiedemann syndrome, Silver–Russell syndrome, Angelman syndrome and Prader–Willi syndrome



Ideogram illustrating distribution and localisation of 120 imprinted genes along human chromosomes.

Disorders implying the genomic imprinting
Prader-Willi syndrome & Angelman syndrome

- Def: group of dis. caused by different mechanisms affecting one or more active genes normally expressed in only one parental allele in an imprinted region. Best known are Prader–Willi syndrome Angelman syndrome and Beckwith-Wiedemann syndrome (MIM 130650), at 11p15.5.
- Prader–Willi syndrome (PWS) and Angelman syndrome (AS) - neurogenetic developmental disorders resulting from different genetic lesions (interstitial deletion) in an imprinted region of human chromosome 15 (15q11–13) extending over 2 Mb. Ch15 of paternal origin – PWS; Ch 15 of maternal origin AS.
- Prader–Willi syndrome - neonatal muscular weakness, feeding difficulties, lack of satiation control in childhood ⇨ massive obesity in many patients
- Angelman syndrome - the developmental retardation is usually severe; nearly complete lack of speech development, an abnormal electroencephalogram + tendency to seizures + hyperactivity



1. Interstitial deletion 15q11-13 **2.** Prader–Willi syndrome **3.** Angelman syndrome

Prader-Willi syndrome (PWS) & Angelman syndrome (AS) - Mechanisms

- **Deletion and uniparental disomy -** deletion of of 15q11-q13 in paternal chromosome 15 PWS In ***uniparental disomy (UPD)*** both chromosomes are of the same parental origin. In ***isodisomy*** they are identical (1–1 in lane 1 on the left); in ***heterodisomy*** they are of the same parent but differ (1–2 in lane 3 on the right).
- Imprinted region 15q11-q13: some genes are expressed in certain tissues depending on their parental origin.
  - **Prader–Willi** sy. results from loss of function of paternally expressed genes (blue)
  - **Angelman sy.** results from loss of function of the maternal gene. UBE3A gene (ubiquitin - protein ligase E3) is expressed from maternal copy only (red). Mono-allelic expression occurs in brain cells only.
- In addition, point mutations in this region may cause PWS in about 5–10% of patients.
- The **imprinting center (IC)**, controlling the entire imprinted region, appears to consist of two elements.