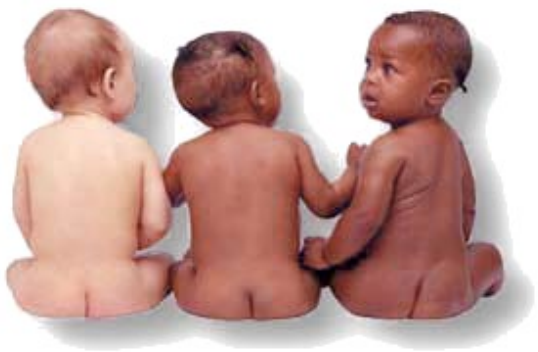
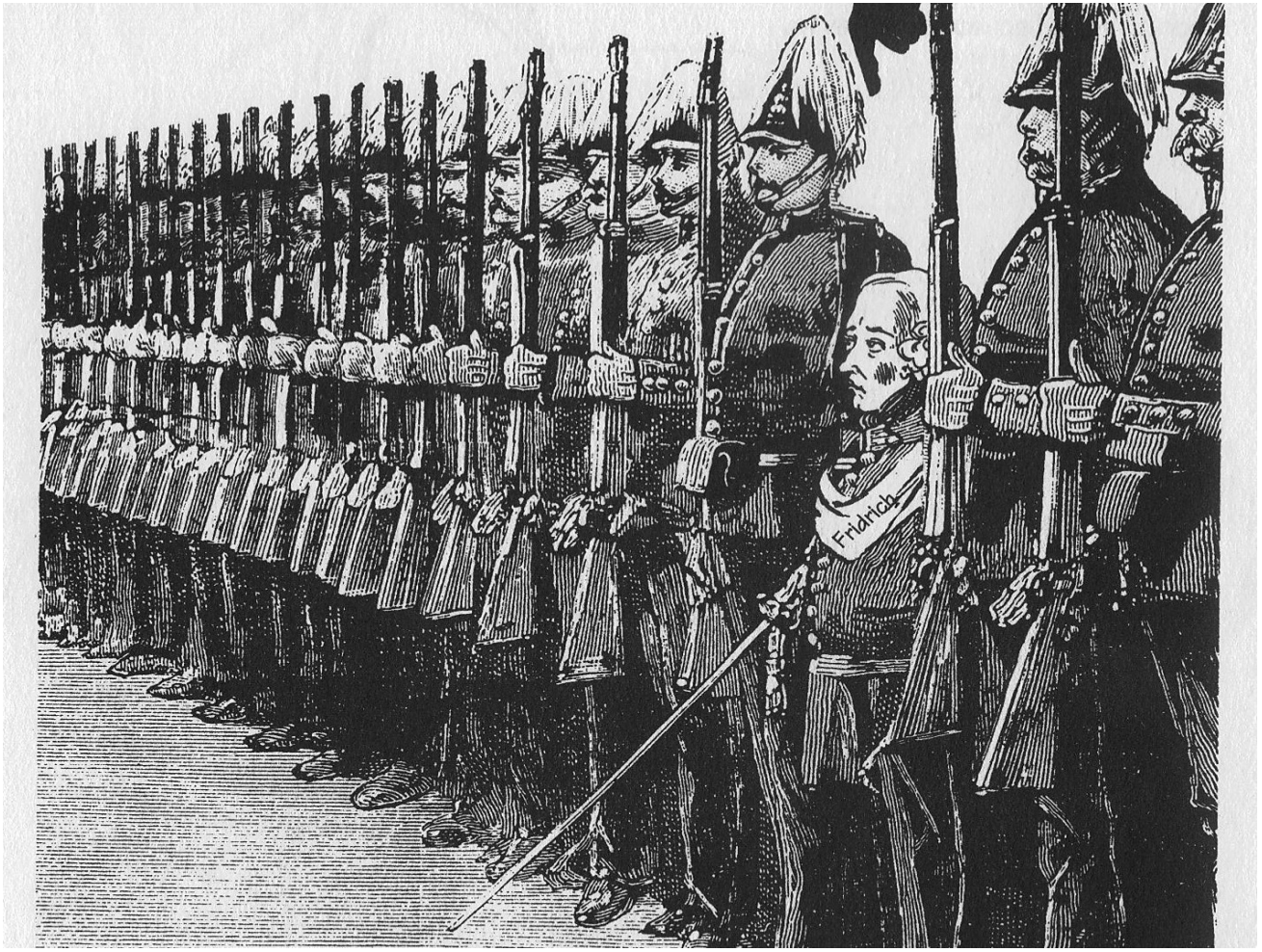
Mendel´s principles in human genetics



Peculiarities of genetic studies in humans

- Ethical standards **forbids** experiments and **selection** in human beings
- Humans have usually **small number** of offsprings
- **Phenotype** is influenced by **externa**l conditions - polygenic traits
- Generation period is too long – max **4 generations** for 1 scientists
- Complexity of human genome
- Historically, the **mating** was limited to **individuals** in certain **population** (nation, religion..) x huge number of means of transport = **migration** nowadays

Directed mating in humans?

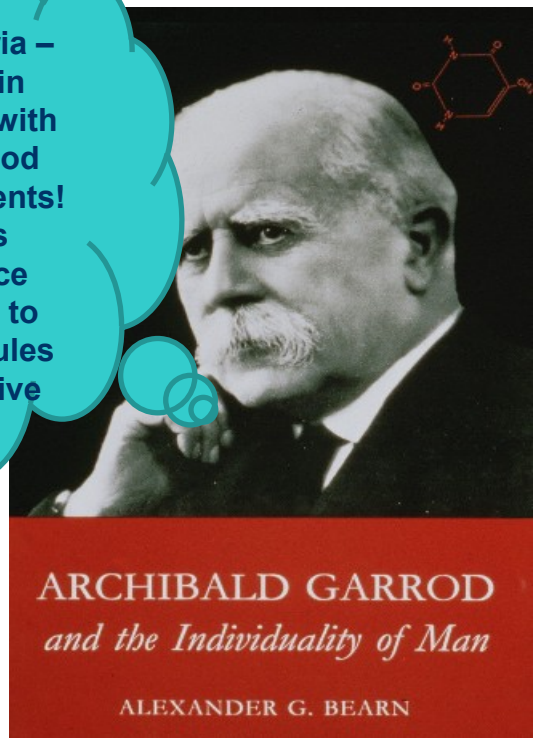


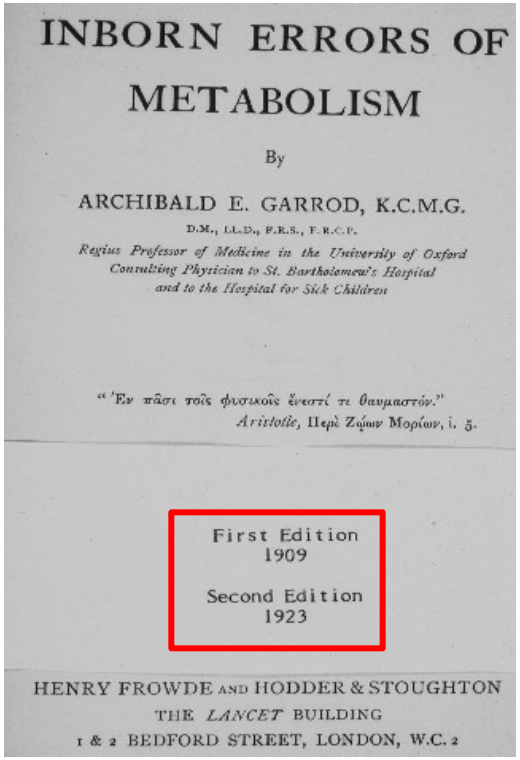
Fridrich I Prussian *had searched tall women for mating with tall men in order to produce royal guard soldiers*

Archibald Garrod – physician, verified Mendel´s principles by connecting the incicndece of metabolic abnromalilites and mutant recessive alleles (1910) – dysfnuction of enzymes!

aa

Alkaptonuria – frequent in offsprings with parent blood relative parents! Trait has inheritance according to Mendel´s rules for recessive traits




INBORN ERRORS OF METABOLISM

By

ARCHIBALD E. GARROD, K.C.M.G.

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Regius Professor of Medicine in the University of Oxford
Consulting Physician to St. Bartholomew's Hospital
and to the Hospital for Sick Children

"Ἐν πᾶσι τοῖς φυσικοῖς ἔνεστί τι θαυμαστόν."
Aristotle, Περὶ Ζῴων Μορίων, i. 5.

First Edition
1909

Second Edition
1923

HENRY FROWDE AND HODDER & STOUGHTON
THE *LANCET* BUILDING
1 & 2 BEDFORD STREET, LONDON, W.C. 2

Enzymopaties

Alkaptonuria

Albinism

Cystinuria

Pentosuria

Homogentisic acid in urine alkaptonuritic patient

Genes have influence on chemical basis of individuals… Recessive allele = enzyme non-functional!

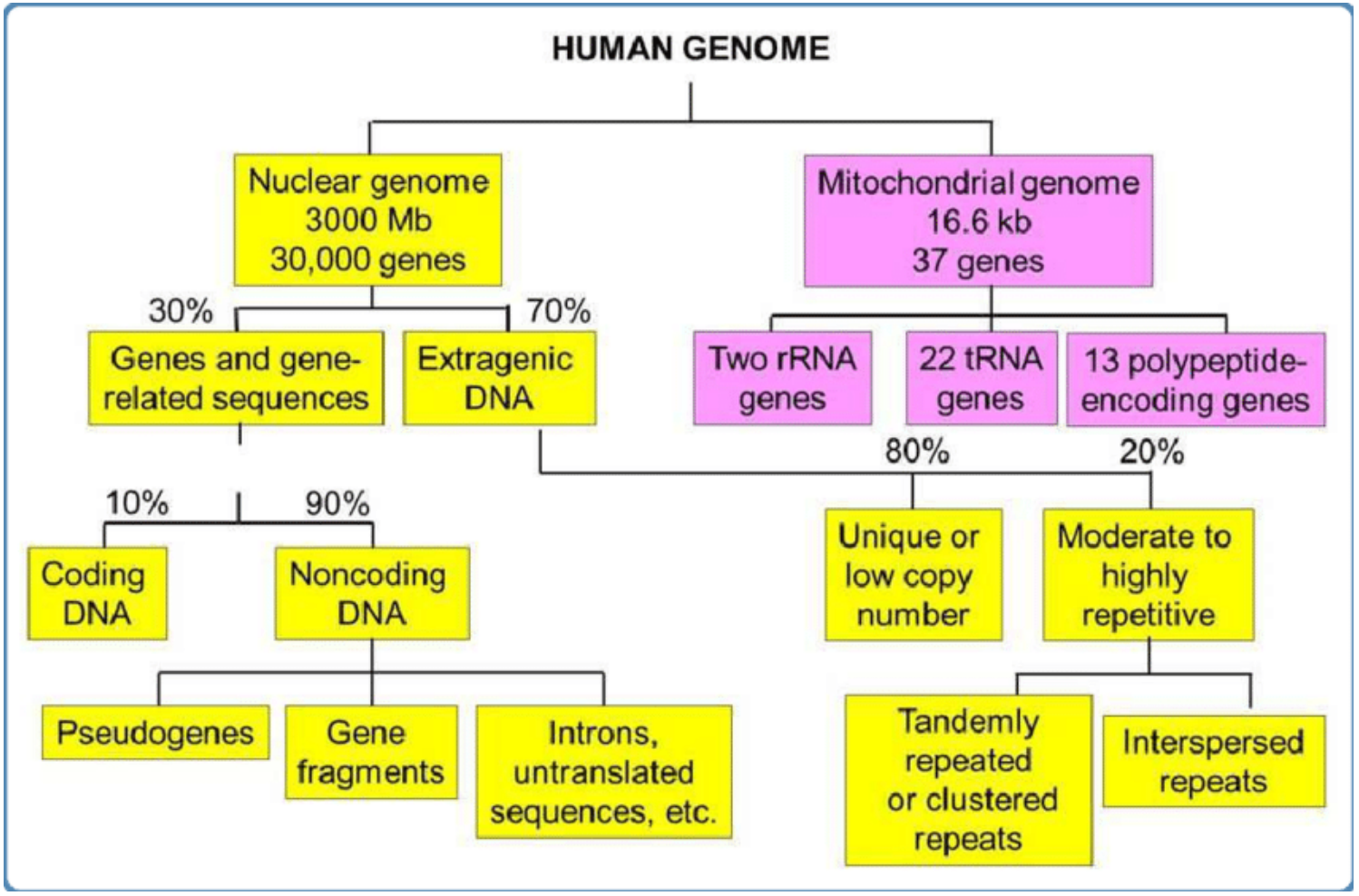
Human Genome Project

In 2003 was HGP finished. Human genome consists of 3 billion base pairs m

Genome of the individuals of the given kind is the same

Genotypes of individuals of same kind can be different ⇒ diversity of the genome

98% of human genome is non protein-coding!
> 50% of genome is consisted of repetitive sequences



Variability of human genome on DNA level
1000 Genomes Project Consortium

ARTICLE

OPEN

doi:10.1038/nature15393

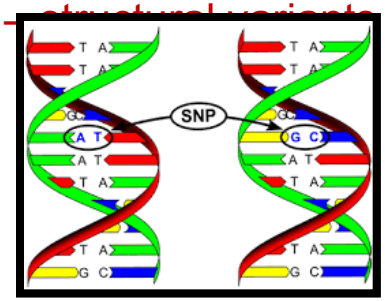
A global reference for human genetic variation

The 1000 Genomes Project Consortium*

The 1000 Genomes Project set out to provide a comprehensive description of common human genetic variation by applying whole-genome sequencing to a diverse set of individuals from multiple populations. Here we report completion of the project, having reconstructed the genomes of 2,504 individuals from 26 populations using a combination of low-coverage whole-genome sequencing, deep exome sequencing, and dense microarray genotyping. We characterized a broad spectrum of genetic variation, in total over 88 million variants (84.7 million single nucleotide polymorphisms (SNPs), 3.6 million short insertions/deletions (indels), and 60,000 structural variants), all phased onto high-quality haplotypes. This resource includes >99% of SNP variants with a frequency of >1% for a variety of ancestries. We describe the distribution of genetic variation across the global sample, and discuss the implications for common disease studies.

*Nature 256, October **2015***

- **2504 genomes sequenced from individuals from various areas of Earth (26 populations)**
- **88 million of genetic variants**
- 84,7 million SNP – single nucleotide polymorphisms
- 3,6 million indels
- 60 000 SV – structural variants



- typical genome differs from the reference human genome at **4.1 million to 5.0 million sites**
- **99.9% of variants consist of SNPs** and short **indels,**
- **structural variants affect more bases:** the typical genome contains an estimated **2,100 to 2,500 structural variants:** affecting **cca 20 million bases of sequence !**

Single change on DNA level can cause genetic disease!

Genetically determined pathologies in humans

- various disorders of mental and physical development are found in about **5% of newborns**
- **Approx. 0,6 - 0,7 %** population has congenital chromosomal aberration
- approx. **0,36 % newborns** is born with monogenic diseases, which will manifested in 90% of cases in pubertal age

Primary cause of genetically-based diseases is change of DNA in form of mutation or pathological variant

Types of genetic diseases

1. Monogenic diseases (AD, AR, sex-linked)
2. Chromosomal aberrations
3. Complex diseases with multifactorial type of inheritance (diabetes, allergies)
4. Genetic aberrations in somatic cells (tumors)
5. Mitochondrial genetic diseases
6. Non-mendelian inheritance diseases (uniparental disomy, unstable trinucleotide expansions

Genetics, medical genetics and medicine

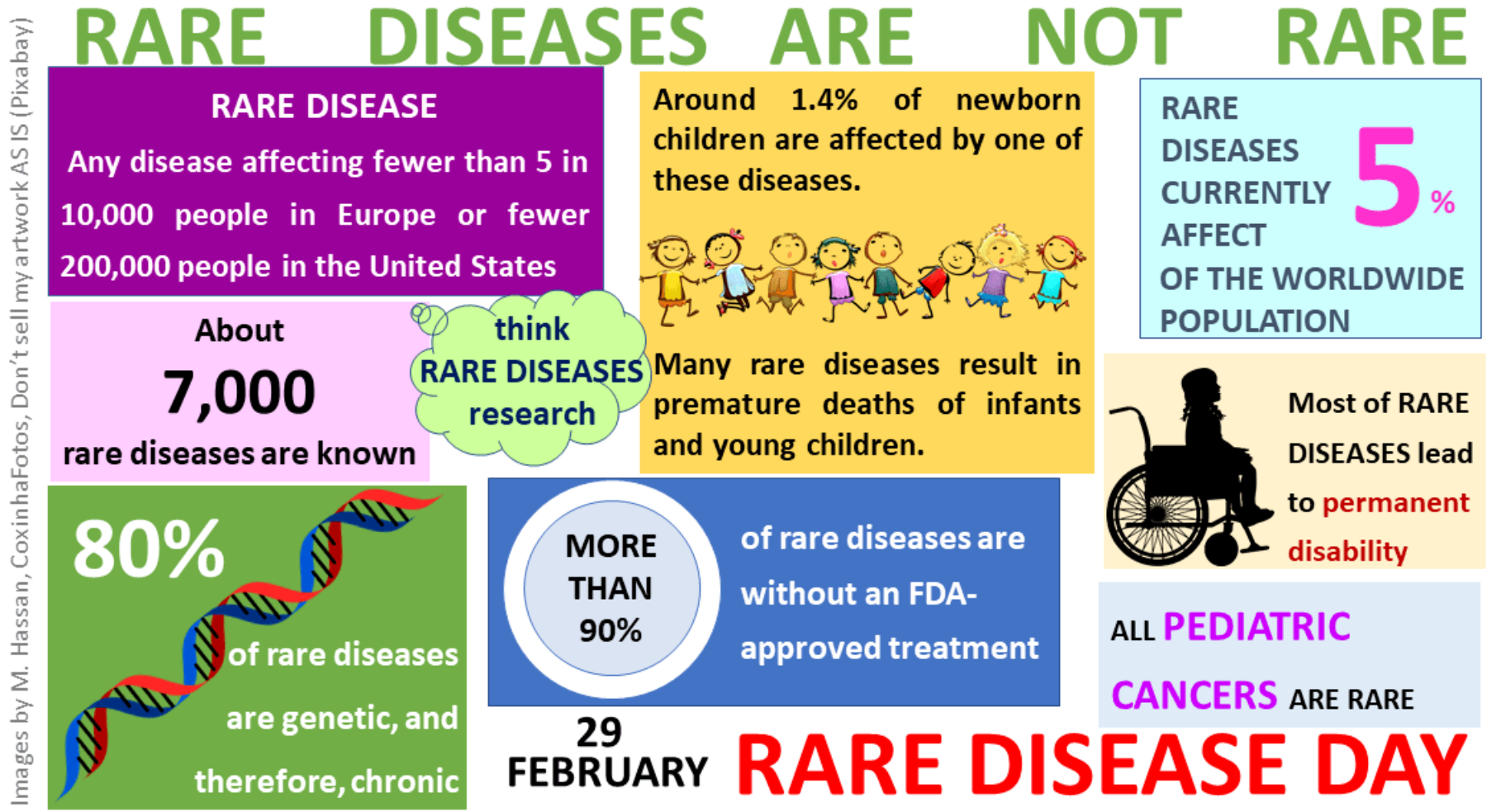
Medical genetics is widespread, multidisciplinary field of preventive medicine

- Medical genetics is any application of genetic principles to medical practice. This includes studies of inheritance, mapping disease genes, diagnosis and treatment, and genetic counseling.

- 1969 – Medical genetics recognized as standalone medical field in Czechoslovakia

- The most of the diseases has any genetic background

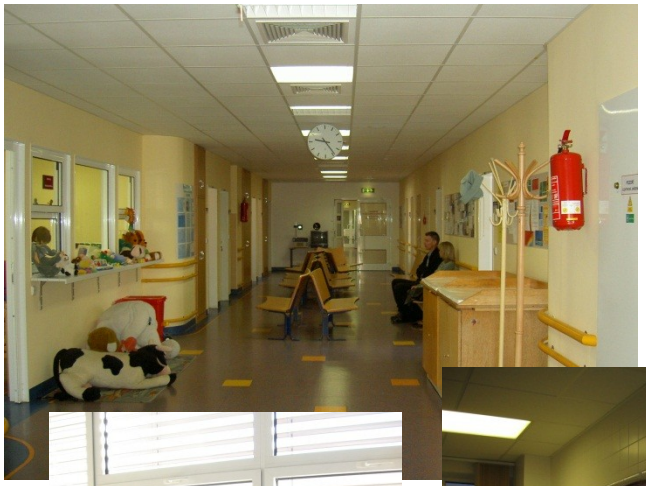
  - Nowadays, in CR are departments of medical genetic parts of most of the big hospitals in – Praha, Brno, Olomouc, Ostrava, Plzeň, Hradec Králové, České Budějovice
  - Also private companies in a form of private genetic laboratories



https://www.mdpi.com/files/multidisciplinary_topic_graphical_abstract/429/Graphical%20Abstract_def.png

- In EU, disease is called **„rare**“ when incidence is less than **5 / 10 000** individuals
- Encompass a **wide range** of **conditions**, such as movement disorders, metabolic diseases, neurological diseases or retinal dystrophy
- Most of them **lack an effective treatment** = traumatization of parents, whole families

Dpt. Of Medical Genetics, Univeristy Hospital Brno
www.fnbrno.cz/olg



Patients of DMG - children

- Children with inherited **neurodevelopmental disorders** and their families
- Children with suspicious or verified **inherited diseases** and their families (cystic fibrosis)
- Children with suspicious or verified inherited **aberration of metabolism** with and their families
- Children with suspected incidences of **inherited chromosomal** aberration including stigmatization, development delays, early births,

Patients of DMG - adults

- Blood relative pairs
- Individuals with long-term persons exposed for long periods to environmental pollutants
- Pairs treated with infertility or repeated spontaneous aborts
- Sperm and egg donors

Patients of DMG – pregnant women

- **Positive familial anamnesis** (in/dysferility, aborts, NDDs..**)**
- **Unfavorable anamnesis during** pregnancy (long disease or acute diseases, medical treatments, vaccinations, addictive substances)
- **Pathological finding in biochemical or ultrasound screening**
- **Older than 35 years**
- **Birth of dead fetus or exitus of newborn**
- **Parents are carriers of balanced translocation**

Genetic counselling

- performed by a **physician - geneticist**
- a medical **profession** dedicated to the **care of patients** with **genetic diseases** and their families.
- clinical geneticists provide the **necessary laboratory** diagnostics, identify patients who are **at increased risk** of developing or transmitting a genetic disease.
- combines the determination of **the risk of disability** of the developing individual with **psychological** and **educational activities** - informing the patient and family members

The main goal of genetic counselling is to answer the question **"What is the risk** of our child being affected by a hereditary disease?"

Genetic counselling in clinical praxis

- The basic role of genetic counselling is to provide patients with genetic diseases or their relatives with sufficient information about the nature of the condition, its future course, treatment options and, above all, the risk of recurrence in other members of the family.

- to determine the genetic prognosis !!!
- **genetic risk (%) - above 10 % unfavorable**

Genetic counselling – gathering of information

- **Personal and family anamnesis**
- **Genealogical examination, compilation of at least a three-generation family tree**
- **Ethnic information**
- **Consanguinity**
- **Nonpaternity**

Genetic counsellor is dedicated to answer during session following questions:

- is the **disease** occurring in the family **hereditary?**
- what is the **type of inheritance** of the disease in the family?
- what is the **risk of recurrence** of the disease **in the family**?
- what is the **risk o**f any hereditary disease **in offspring**?
- is it possible to **prevent the onset** and development of hereditary disease?
- is it possible to **detect an inherited disease** in the fetus during pregnancy?
- is it possible to **detect** hereditary disease **before pregnancy**?
- can the **disease be treated**?

Take care !

- **inherited**
- congenital (de novo?)
- familial (genetic and enviromental origin)

Diagnostic approaches

- **Methods of clinical genetics**

- **Pedigree analyses**

Laboratory techniques

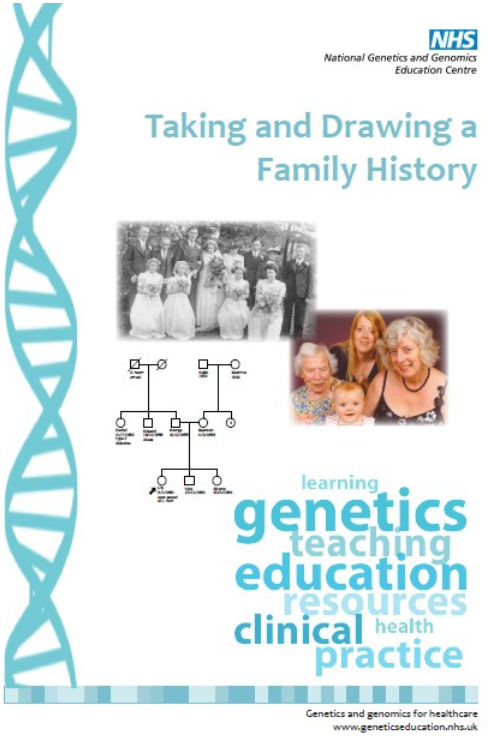
- **Cytogenetics** - karyotypes, FISH….
- **DNA or RNA diagnostics**

Clinical-genetic examination

Somatic abnormalities - stigma

- Congenital developmental defects e.g. malformations (e.g. cleft palate), dysplasia - abnormalities of certain tissues
- Psychomotor development
- Mental retardation
- Dermatoglyphics

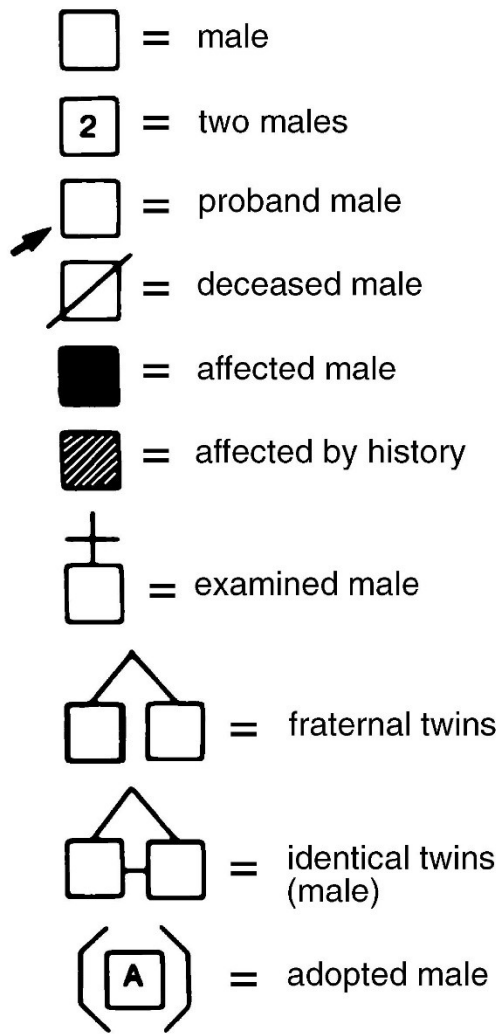
Pedigree analysis

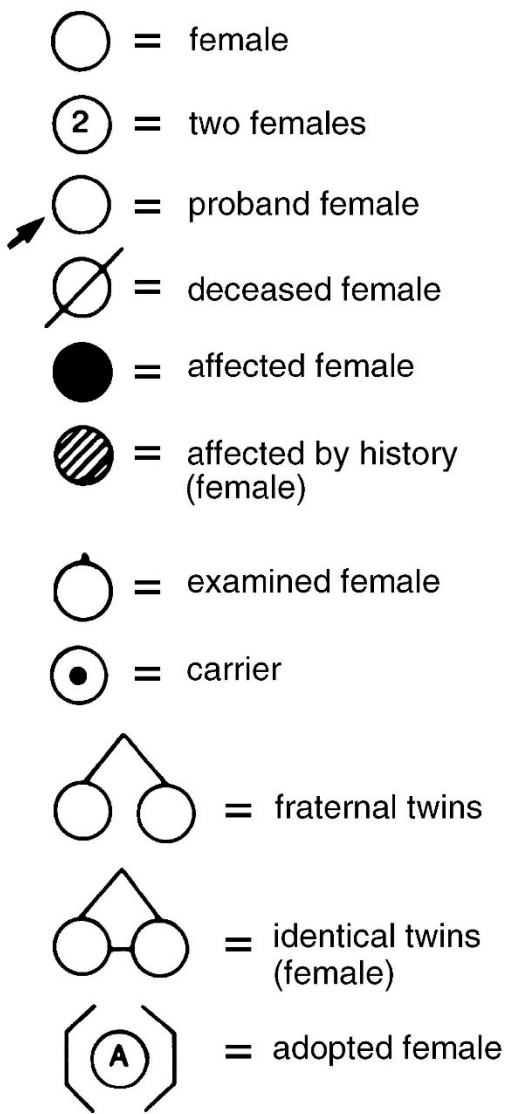


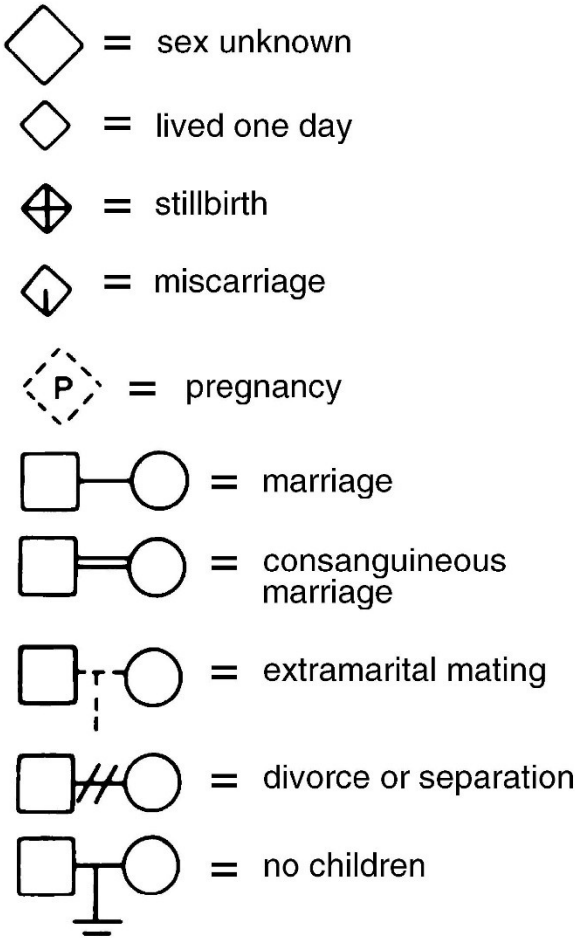
Analysis of pedigrees it is possible to find

- incidence of hereditary diseases in the family
- **type of heredity**
- diagnosis
- **probability of disability in descendants or relatives - genetic prognosis**
- influence on treatment (preventive examinations...)

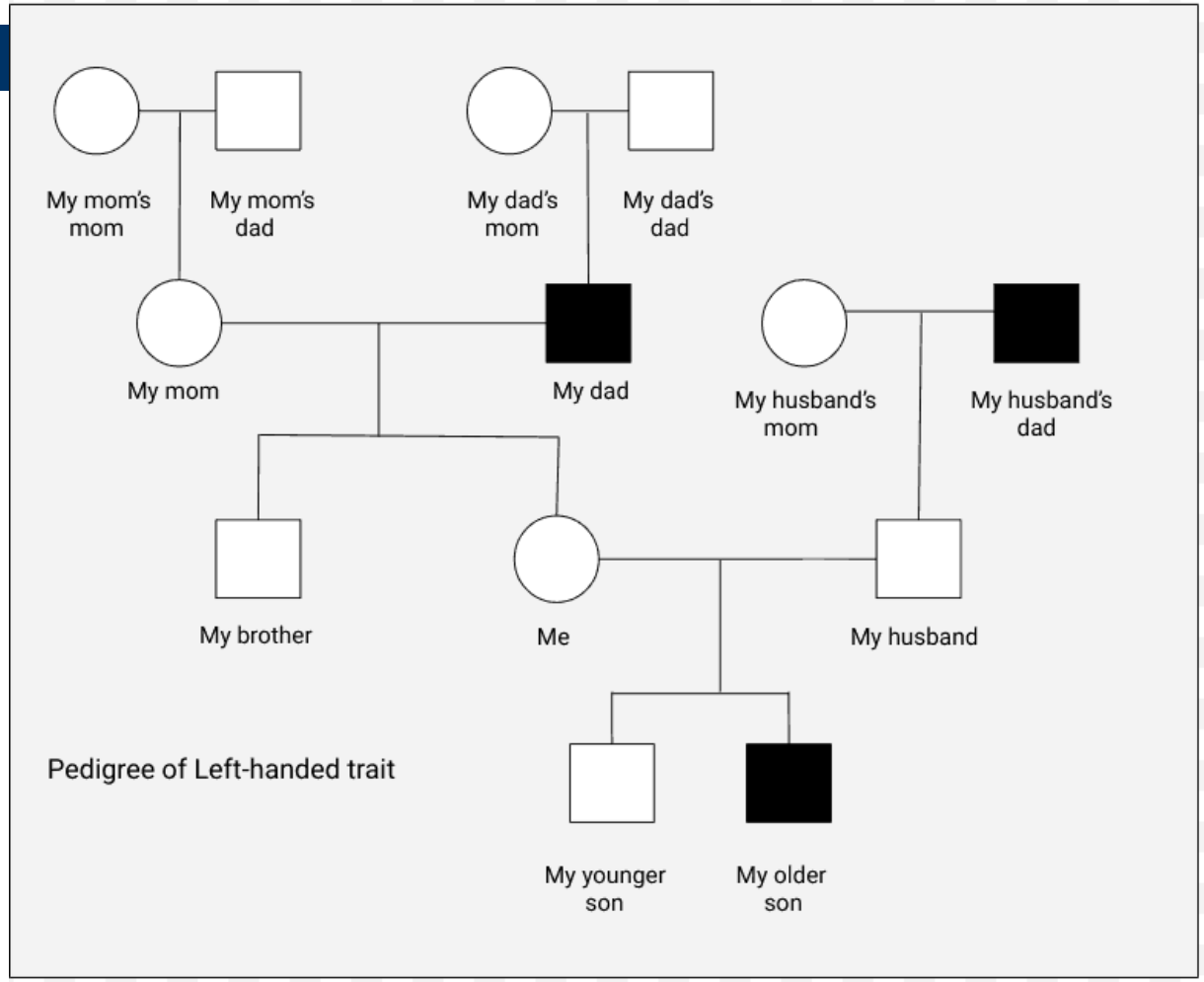
PEDIGREE SYMBOLS







Example of pedigree



https://kristinmoonscience.com/wp-content/uploads/2019/11/Incomplete-pedigree-of-left-handed-trait.png

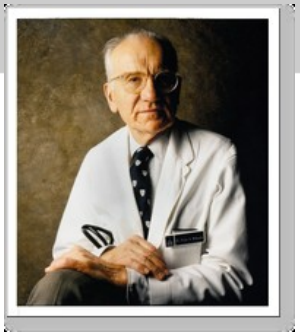
Monogenic diseases(DNA mutation at the level of one gene - change of gene product !

Most monogenic inherited diseases manifest themselves before birth, early after birth or in childhood
Mendelian inheritance is characteristic !

Types of inheritance

- Autosomal dominant - AD
- Autosomal recessive - AR
- X-linked recessive - XR
- X-linked dominant - XD

Entrez
OMIM
Search OMIM
Search Gene Map
Search Morbid Map
Help
OMIM Help
How to Link
FAQ
Numbering System
Symbols
How to Print
Citing OMIM
Download
OMIM Facts
Statistics
Update Log
Restrictions on Use
Allied Resources
Genetic Alliance
Databases
HGMD
Locus-Specific
Model Organisms
MitoMap
Phenotype
Human/Mouse/Rat
Homology Maps
Coriell



- Enter one or more search terms.
- Use **Limits** to restrict your search by search field, chromosome, and other criteria.
- Use **Index** to browse terms found in OMIM records.
- Use **History** to retrieve records from previous searches, or to combine searches.

OMIM ® - Online Mendelian Inheritance in Man ®

Welcome to OMIM ®, Online Mendelian Inheritance in Man ®. OMIM is a comprehensive, authoritative, and timely compendium of human genes and genetic phenotypes. The full-text, referenced overviews in OMIM contain information on all known mendelian disorders and over 12,000 genes. OMIM focuses on the relationship between phenotype and genotype. It is updated daily, and the entries contain copious links to other genetics resources.

This database was initiated in the early 1960s by Dr. Victor A. McKusick as a catalog of mendelian traits and disorders, entitled Mendelian Inheritance in Man (MIM). Twelve book editions of MIM were published between 1966 and 1998. The online version, OMIM, was created in 1985 by a collaboration between the National Library of Medicine and the William H. Welch Medical Library at Johns Hopkins. It was made generally available on the internet starting in 1987. In 1995, OMIM was developed for the World Wide Web by NCBI, the National Center for Biotechnology Information.

OMIM is authored and edited at the McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University School of Medicine, under the direction of Dr. Ada Hamosh.

OMIM Entry Statistics

Number of Entries in OMIM (Updated October 7th, 2016) :

Prefix	Autosomal	X Linked	Y Linked	Mitochondrial	Totals
* Gene description	14,584	715	49	35	15,383
+ Gene and phenotype, combined	78	0	0	2	80
# Phenotype description, molecular basis known	4,498	315	4	29	4,846
% Phenotype description or locus, molecular basis unknown	1,488	124	5	0	1,617
Other, mainly phenotypes with suspected mendelian basis	1,678	111	2	0	1,791
Totals	22,326	1,265	60	66	23,717

RECESSIVE/DOMINANT GENETIC DISORDERS

IDENTIFY:

1-four examples of recessive genetic disorders in humans

1-CYSTIC FIBROSIS

2-TAY-SACHS

3-ALBINISM

4-GALACTOSEMIA

5-ALKOPTONURIA

2-two examples of dominant genetic disorders in humans

1-HUNTINGTON'S

2-ACHONDROPLASIA

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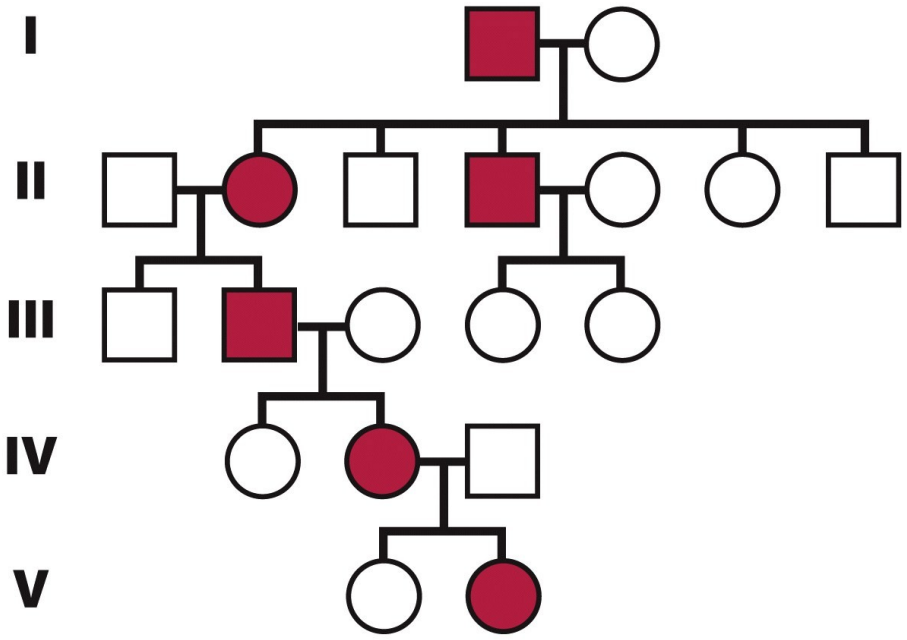
Pedigree - example of autosomal dominant inheritance



Dominant trait

Affected gene product:

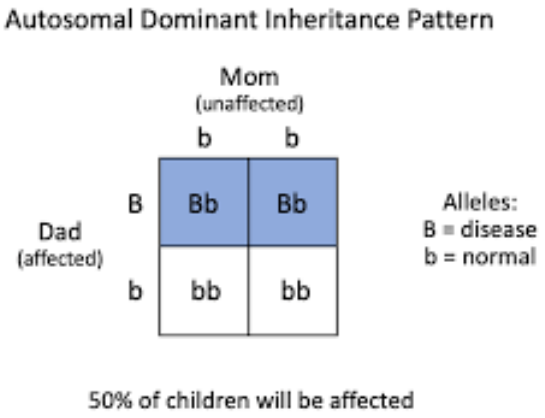
mostly proteins of morphological and structural character

biological carriers, cell receptors

Autosomal dominant inheritance
(AA, Aa – affected, aa- healthy)

- **The MOST COMMON TYPE of disease inheritance in humans**
- **vertical type of inheritance**
- dominant allele **lies on the autosome** - males and females **equally affected**
- **sex ratio 1:1**
- **heterozygotes** are also **affected** - clinical manifestation = 1 copy of the gene
- the affected person has one **parent equally affected**
- **50% risk** of recurrence for offspring and siblings of the affected person

- healthy fa e healthy children



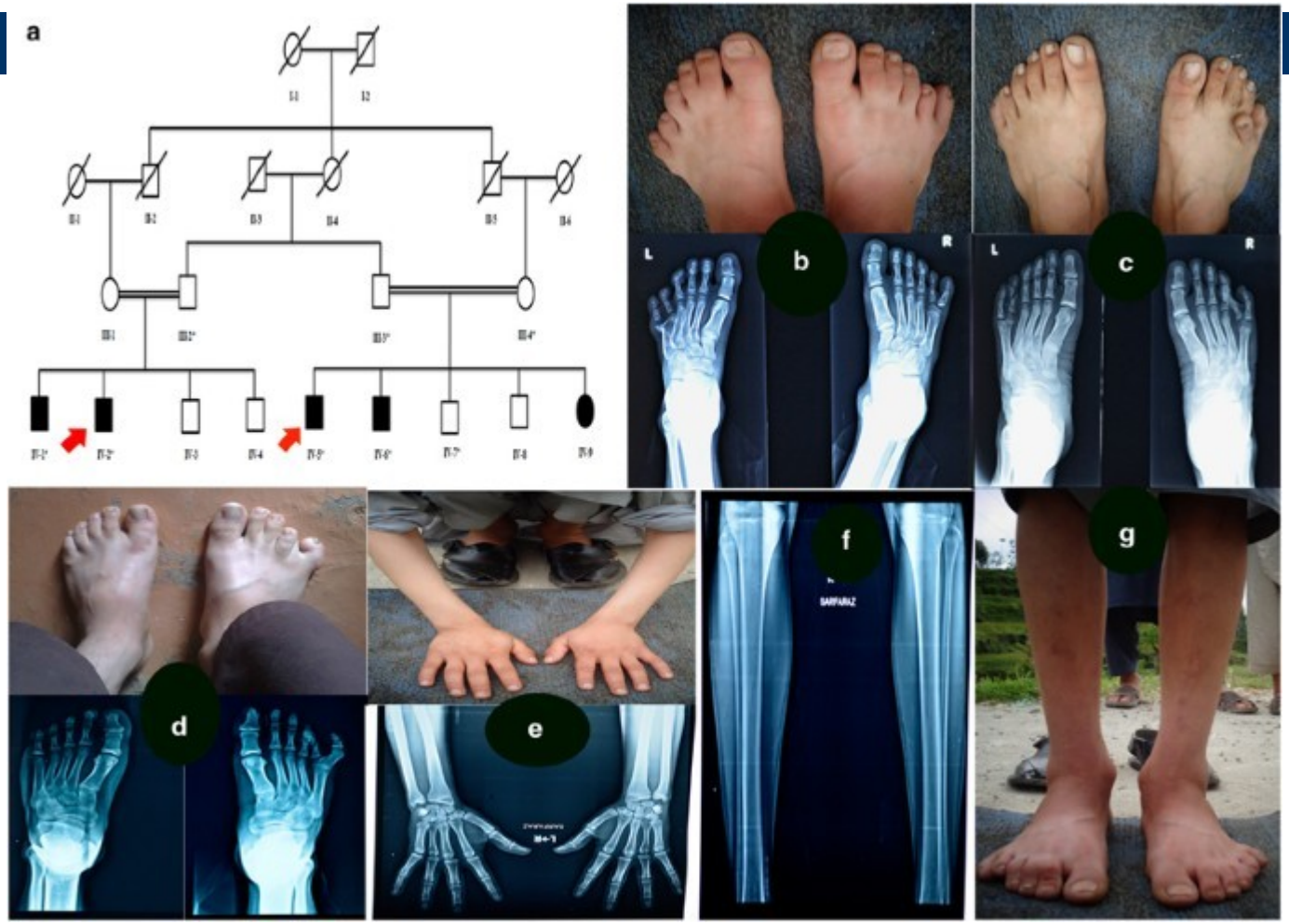
Aa x aa

AA x aa

Aa X Aa

The most common case

Polydactyly – AD inhertiance



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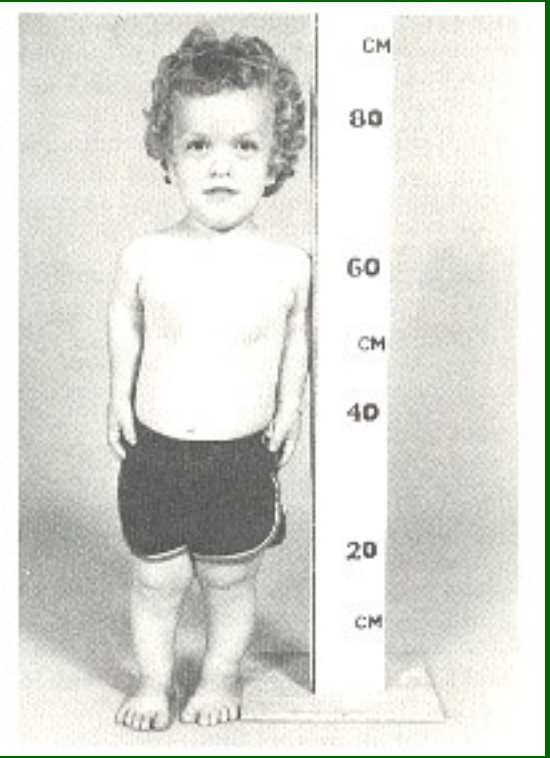
Achondroplasia – AD ihneriatnce

Achondroplasia is a genetic bone disease that accounts for a person's short stature

- translated from Greek, it means insufficient cartilage formation
- the gene responsible for this disease was discovered in 1994 : mutation in the fibroblast growth factor receptor **3 (FGFR3)** gene
- it is a congenital skeletal disorder
- arms and legs are shorter than the trunk and the head circumference increases unusually rapidly in the first few months of life.
- Other symptoms include lower muscle tension, higher joint extensibility, and susceptibility to upper respiratory tract infections and otitis media
- Because of their short limbs, people of small stature have to exert themselves a lot when walking, so many of them develop **various degrees of bowing of the legs at school age.**

Achondroplazie
autozomálně dominantní dědičnost



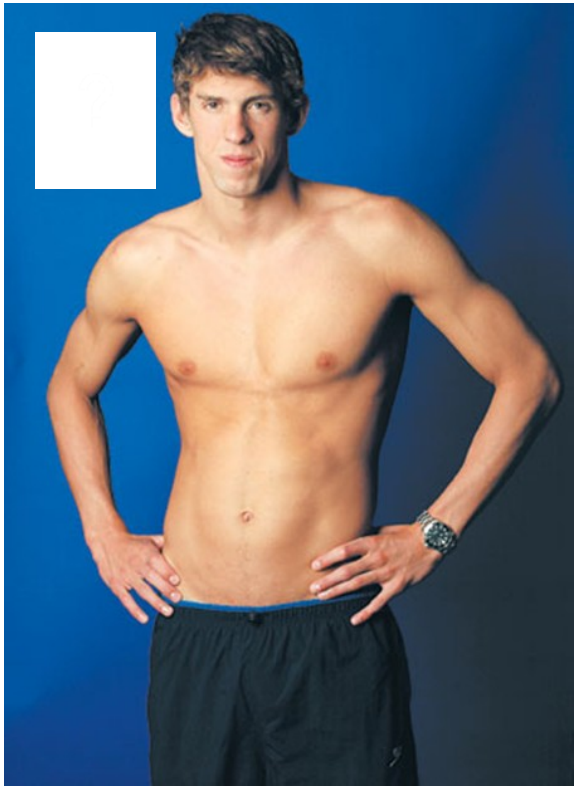
Karel van Mander:
Giacomo Favorchi (kolem r. 1600)

Achondroplazie -family

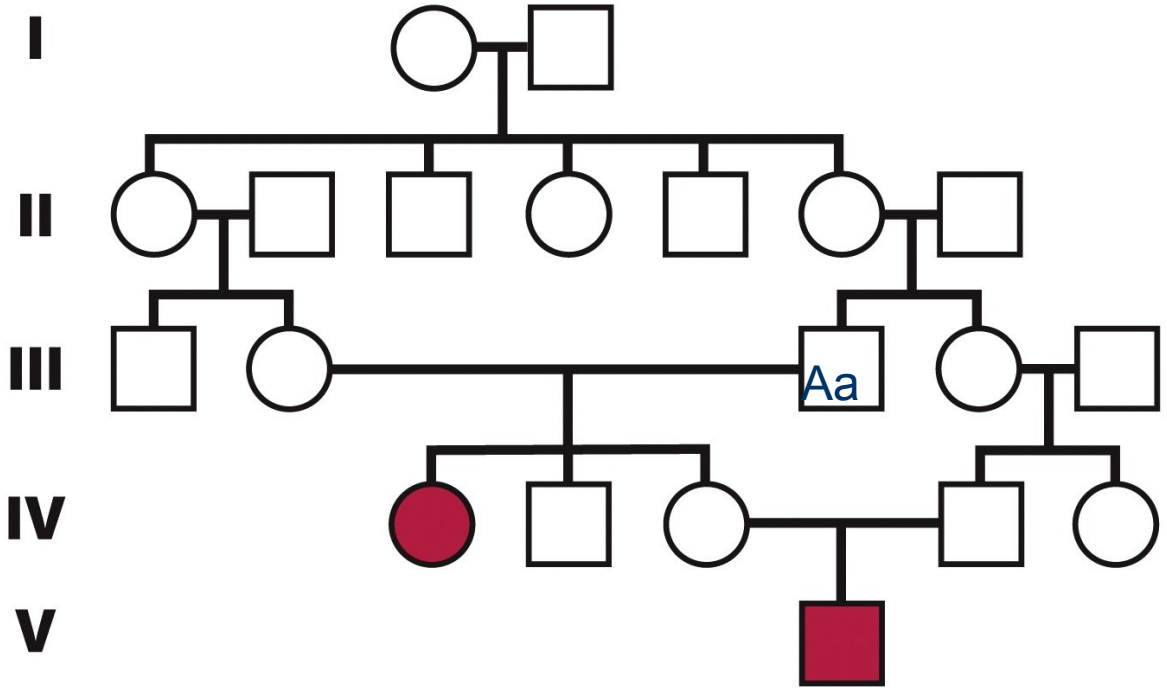
Marfan syndrome – AD inheritance

- Incidence 1:5-10000
- mutation of FBN1 – protein fibrilin 1 – a component of connective tissue)
- genetic disorder of connective tissue - ligament
- skeletal abnormalities
- tall stature, long thin limbs
- long thin fingers (arachnodactyly)
- anomalies of the heart and blood vessels

Marfan syndrome – N. Paganini?



Pedigree - example of autosomal recessive inheritance



Recessive trait

Autozomal recessive inheriatnce
(aa – affected) !

- Aa - health - the standard **heterozygote allele** is able to **compensate** for the **mutant** allele
- mutant **recessive allele** on the **autosome**
- 1:1 sex ratio
- horizontal type of inheritance
- sibling risk 25% (Aa x Aa)
- disability only occurs in homozygotes
- more common in consanguineous marriages

Genotypes

Aa x Aa...1/4 affected
Aa x aa...1/2 affected
aa x aa...all affected

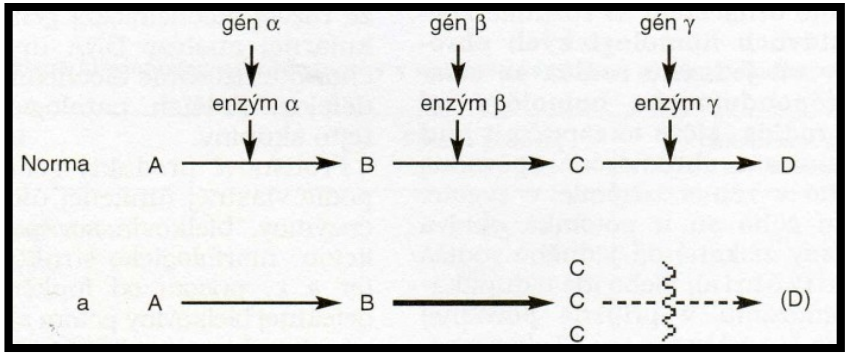
The most common type of parent....carriers !
The risk of a carrier having a disabled child depends on the likelihood that his partner is also a carrier

AR inheritance - example
Metabolic dysfunctions

Enzymopathies – enzyme disorder: almost **always AR**, heterozygotes with **50% residual allele activity** are clinically **normal (Aa)**

Metabolic blockades - all pathophysiological consequences of enzymopathies can be attributed to substrate accumulation or product deficiency

- **Substrate** $\xrightarrow{\text{enzyme}}$ **product**

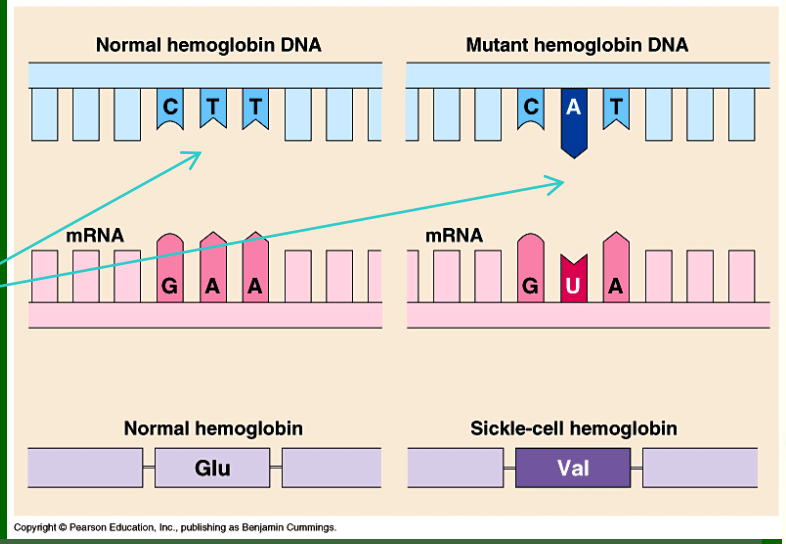


- Disorders of metabolism of amino acids, sugars, lipids, purines, pyrimidines, etc.)

- **(phenylketonuria, alkaptonuria, albinism, galactosemia**)

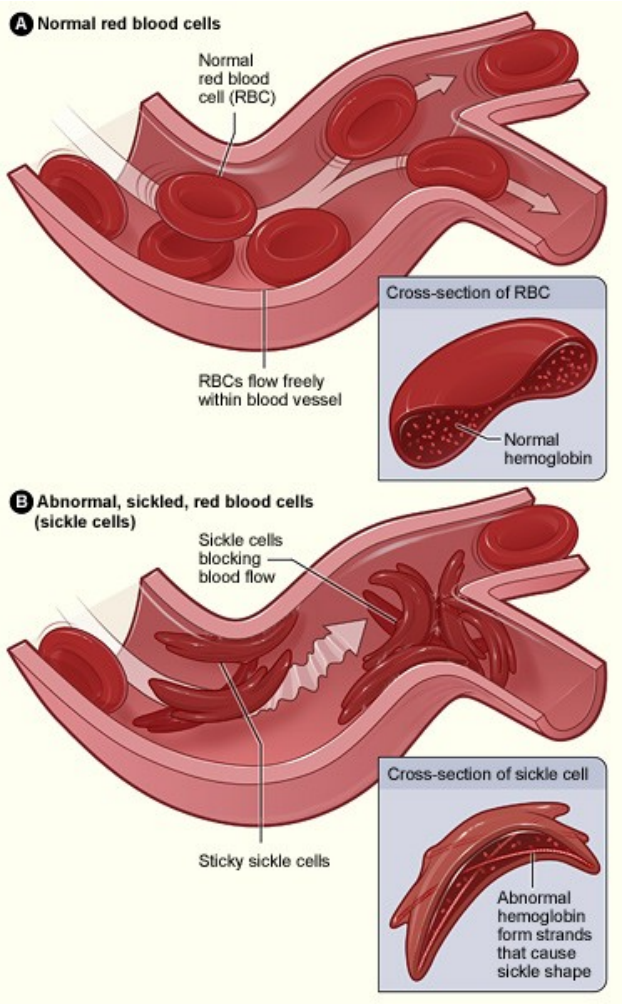
AR inheritance – sickle cell anemia

Mechanism



mutation

Mutation T – A causes change in AA sequnece: GLU - VAL



HbA

HbS

Normal adult haemoglobin (HbA) consists of 4 subunits, two alpha (α) and two beta (ß - 146 AA). each subunit is composed of a protein part, globin, and a prosthetic (non-protein) part, HEME group

Substitution of CTT for CAT in sickle cell anemia in the beta chain of hemoglobin leads to substitution of one amino acid ⇨ joining the polymeric fibers ⇨ the sickle-shaped form blood cells

HbA/HbA
homozygotes - normal

HbA/HbS
heterozygotes

HbS/HbS - sickle cell anaemia
(microcirculation disorders, capillary blockage, bone marrow infarction, tissue damage)

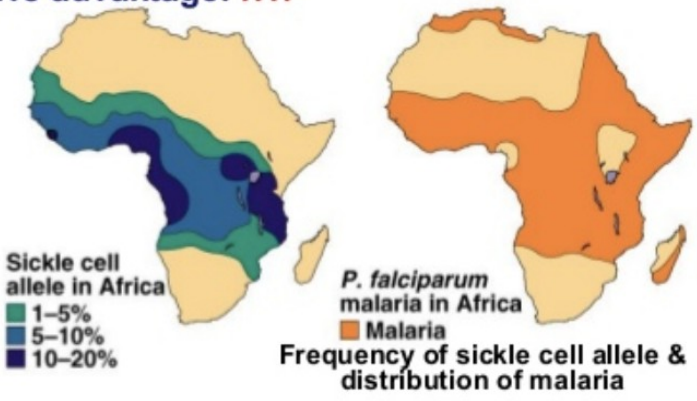
1 : 600 Afican Americans

HbA/HbA : HbA/HbS
1, 46 : 1
The mutant allele still persists in the population...?

Heterozygote Advantage

- In tropical Africa, where malaria is common:
  - homozygous dominant (normal)
    - reduced survival or reproduction from malaria: H^bH^b
  - homozygous recessive
    - reduced survival & reproduction from sickle cell anemia: H^sH^s
  - heterozygote carriers
    - survival & reproductive advantage: H^bH^s

Hypothesis:
In malaria-infected cells, the O_2 level is lowered enough to cause sickling which kills the cell & destroys the parasite.



Frequency of sickle cell allele & distribution of malaria

Cystic fibrosis – AR inheritance

- one of the most common in Caucasians (predominant disease in Northern Europeans !!!)

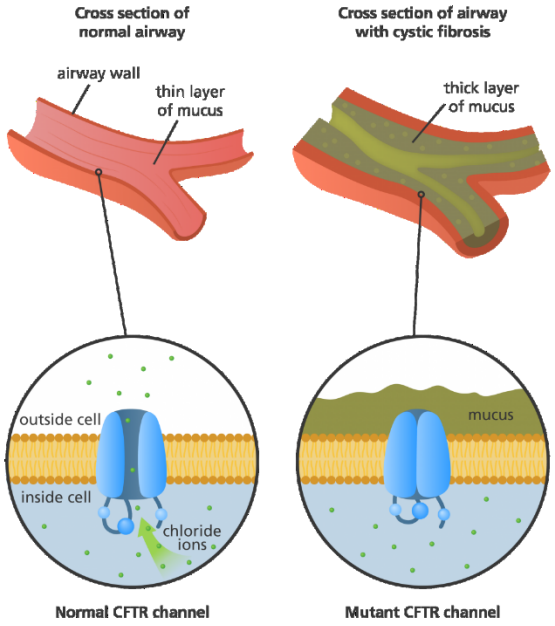
- basis - mutation in the *CFTR* gene, range about 250 kb, coding region with 27 exons
- gene discovered in 1989 (7q31)
- incidence in the Czech Republic about 1/2000 - 1/3000
- frequency of carriers in the Czech Republic about 1/25-1/29
- mean age at diagnosis 6-8 months, 66% of patients under 1 year
- severity is limited mainly by lung involvement....
- median survival in 1976 - 18 years, in 1995 - 30 years, very little improvement since 1990, now new drugs?

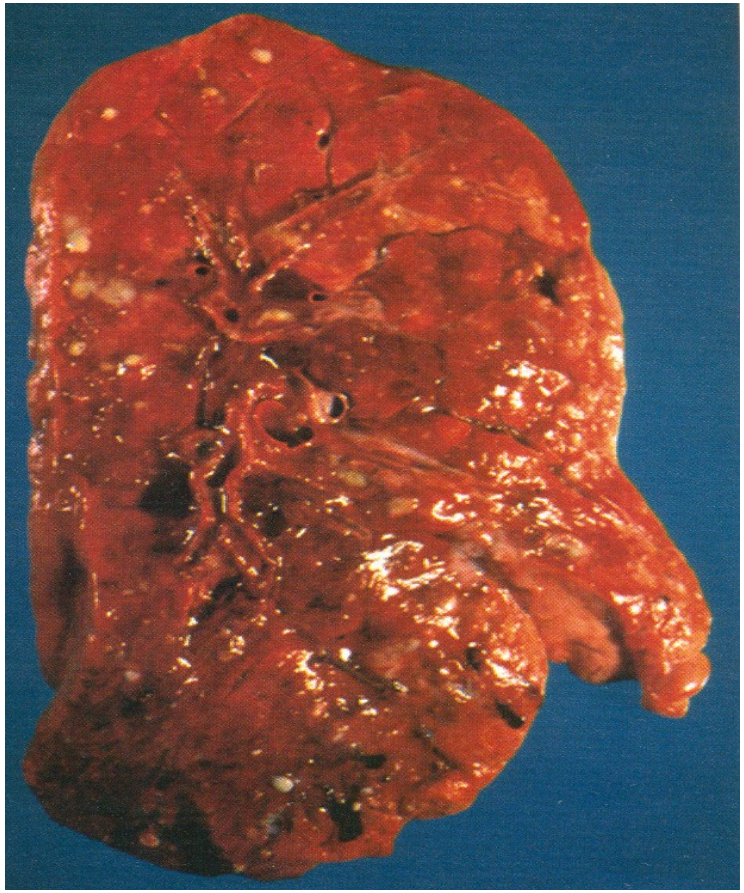
CF - pathophysiological defect - impaired ION TRANSPORT in epithelial cells

Photograph of the middle transverse section of the lung in a patient with CF (mucus plugs in the lungs)

CFTR protein - chloride channel - regulates the flow of salts and water

CF - mutation - the channel is missing or non-functional !

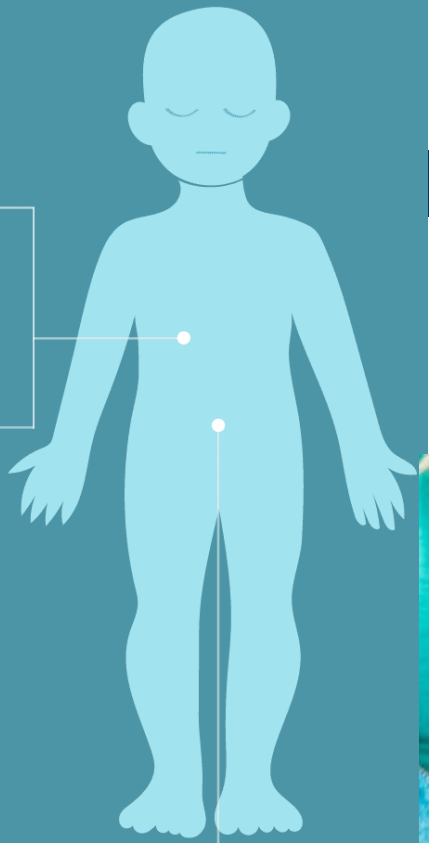


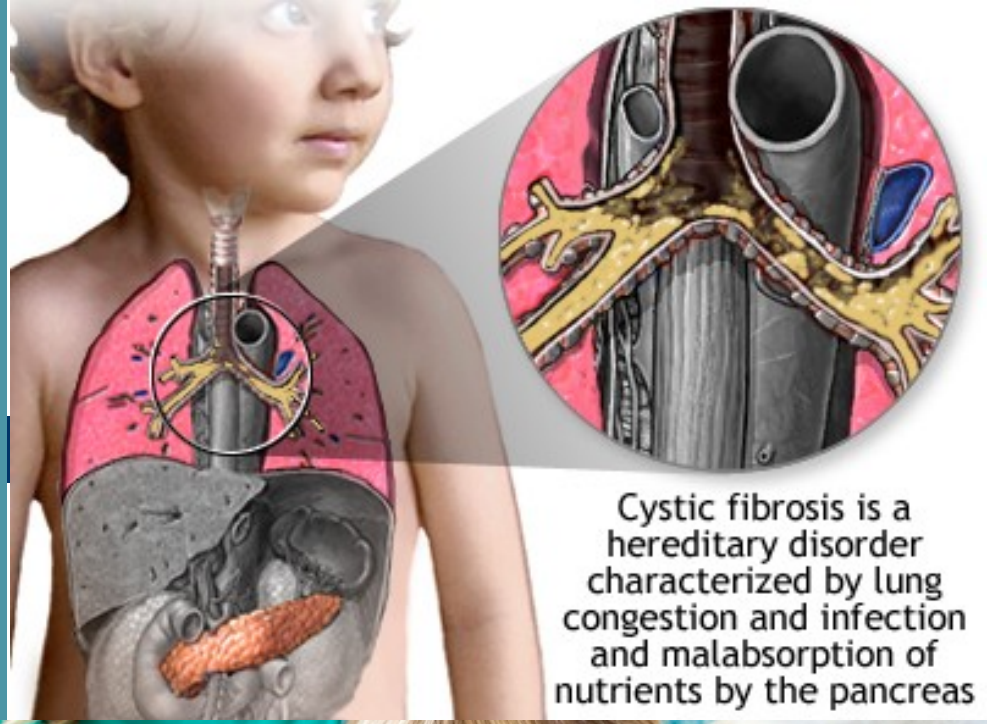


Cystic Fibrosis

Common Symptoms

- salty-tasting skin
- chronic respiratory problems
- lung infections
- poor growth/weight loss
- meconium ileus
- bulky/greasy stool

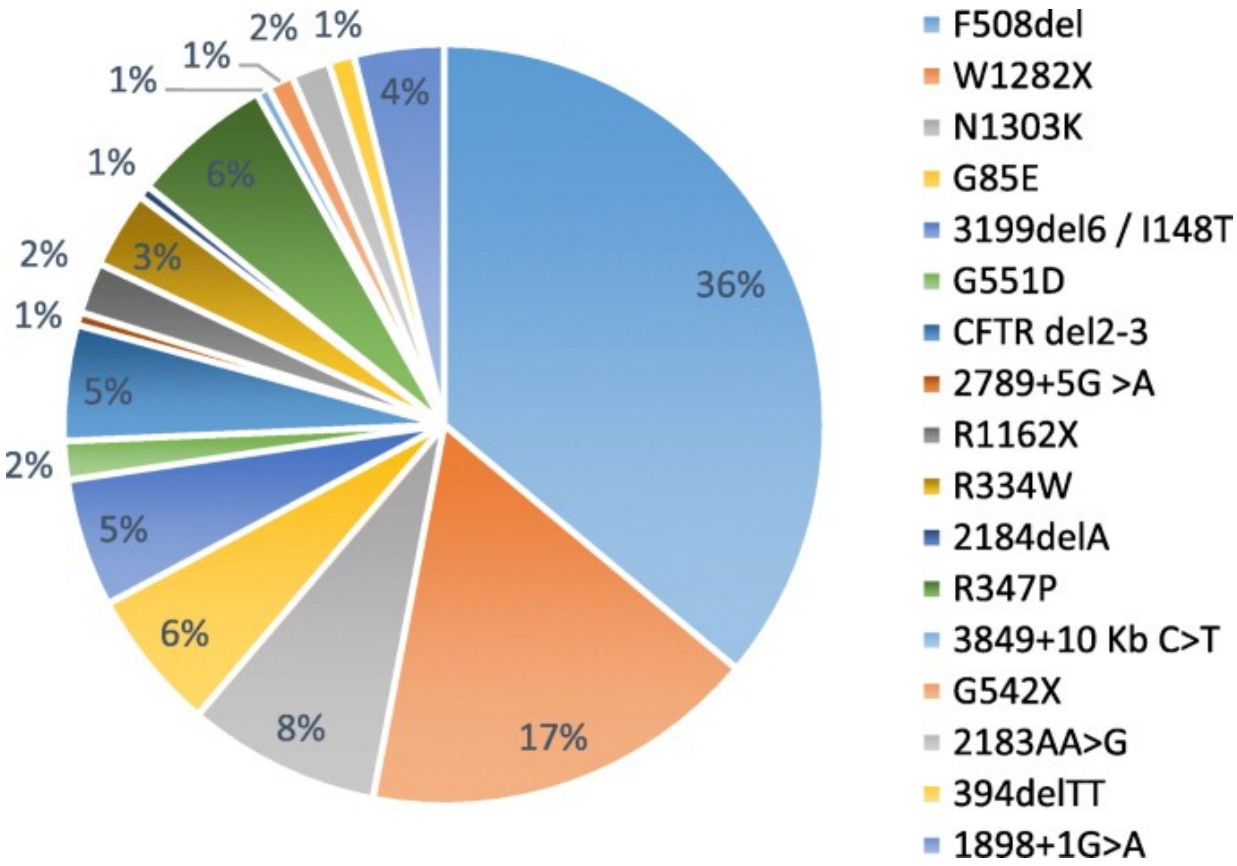




Cystic fibrosis is a hereditary disorder characterized by lung congestion and infection and malabsorption of nutrients by the pancreas

verywell

CF – mutation types in Europe



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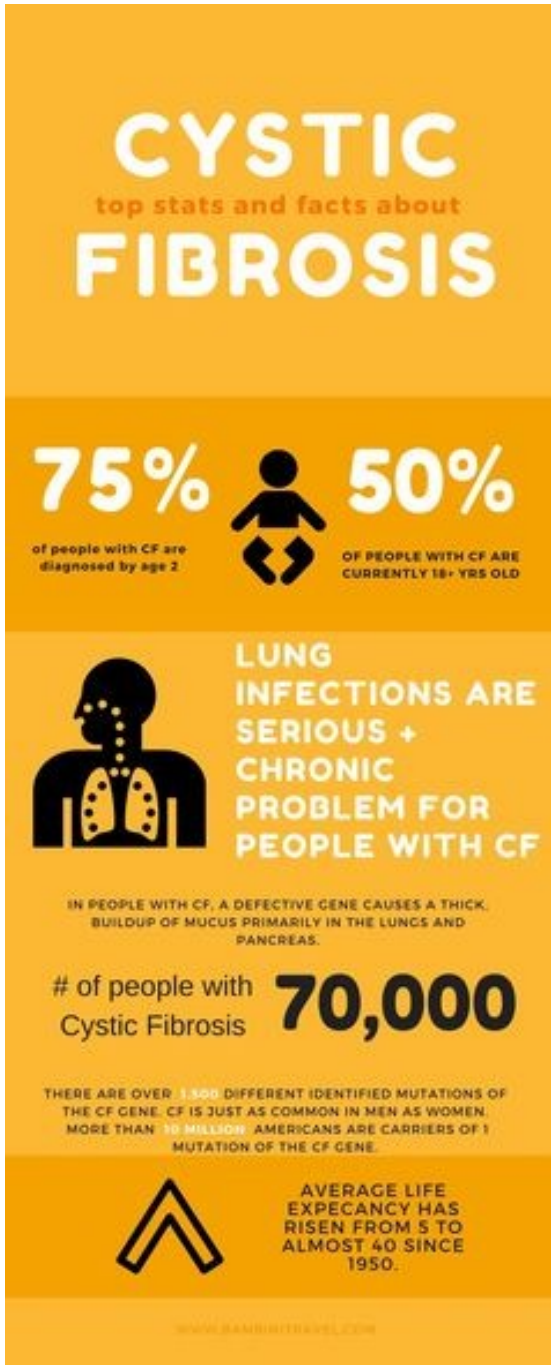


Higher concerntartion of NaCL in sweat…. „Salty children“

- **about 2000 mutations have been detected in the CFTR gene...!!!!**
- there are 5 classes of mutations...different severity of disability
- **only 7 mutations above 1% of CF patients**

Patients:

50% homozygous for dF508/dF508

40% compound heterozygous - dF508 and other mutant allele

A standard.... a1 a2 a3 ... mutations a1a2 a1a3 ... patients

Allelic heterogeneity !

F508del = delta F508 = ΔF508

- the most common mutation among Caucasians(70%)
- deletion of three basepairs in exon 10 of DNA
- resulting in deletion of a Phe F508 from CFTR protein

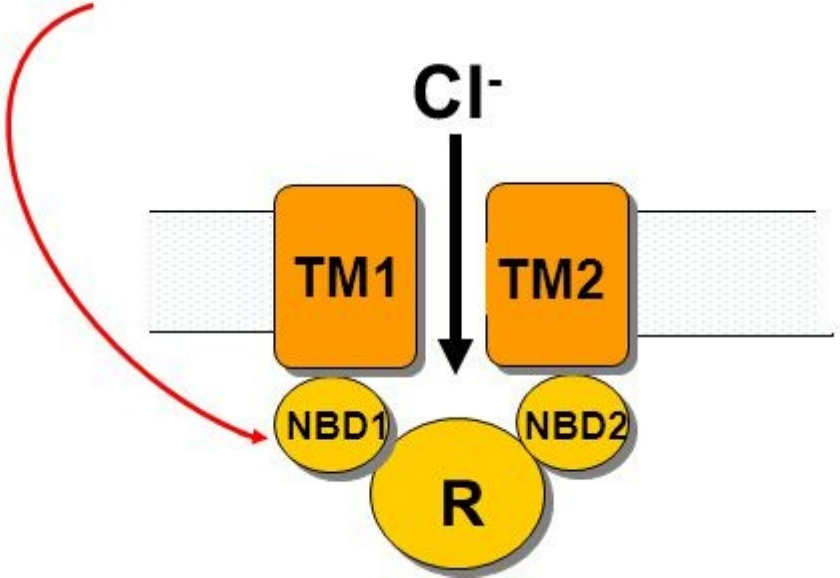
508

...E N I I F G V S Y D...

.....GAA AAT ATC ATC TTT GGT GTT TCC TAT GAT....

.....GAA AAT ATC ATT GGT GTT TCC TAT GAT....

...E N I I G V S Y D...



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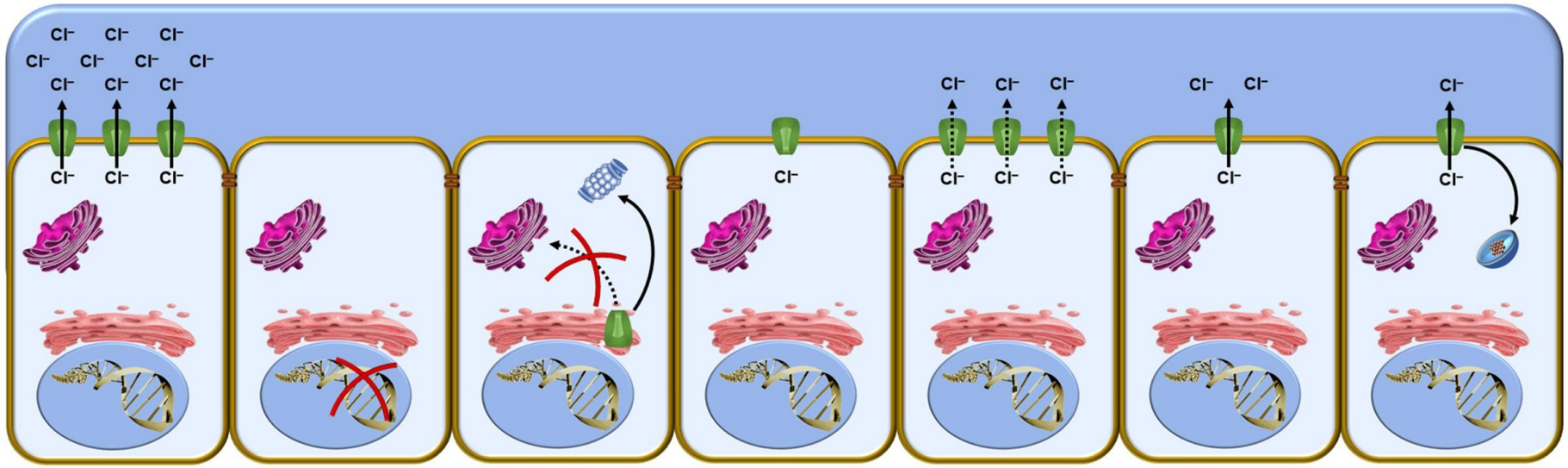
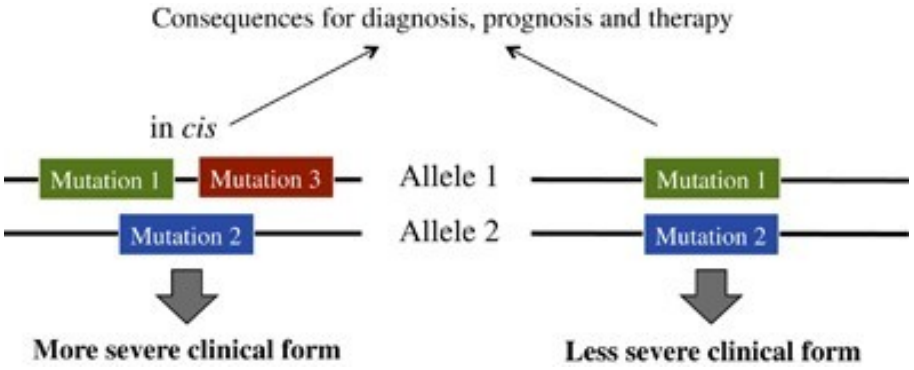
The most common *CFTR* gene mutations in the Czech population - allelic heterogeneity - multiple mutations at the same locus = composition of heterozygotes

MUTATION	FREQUENCY IN CF PAC.	EXON (26)
1. dF508	68,8%	10
2. CFTRdele 2,3 (21kb)	4,64%	2, 3
3. G551D	4,03%	11
4. N1303K	3,02%	21
5. G542X	2,22%	11
6. 1898+1 G-A	2,04%	intron
7. 2143delT	1,11%	12
8. R347P	0,74%	7
9. W1282X	0,55%	20
10. E92X	0,37%	4
11. R1162X	0,37%	19



	wt-CFTR	I	II	III	IV	V	VI
Defect types		**No protein**	**No traffic**	**No function**	**Less function**	**Less protein**	**Less stable**
Mutation examples		G542X R553X W1282X	G85E ΔI507 **ΔF508** N1303K	V520F S549R G551D	R117H R334W S1235R	A455E 1680-886A>G 2657+5G>A	**rΔF508** Q1412X
Required approaches		Rescue protein synthesis	Correct protein folding	Restore channel conductance	Restore channel conductance	Maturation / Correct misplicing	Promote protein stability



CF newbron screening

Definition of NS

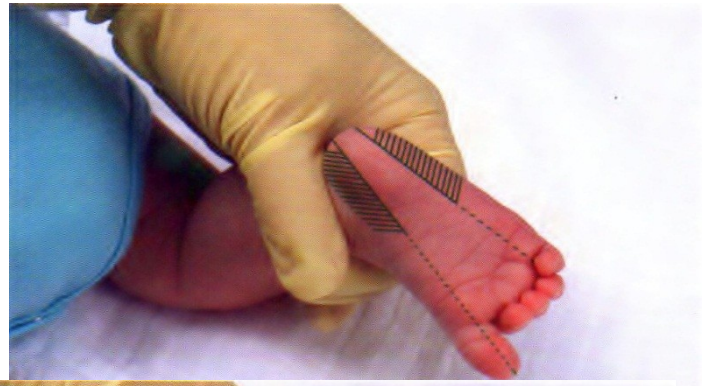
The active, nationwide **search** for a disease in **the population** of all **newborns** in its preclinical stage so that these **diseases** are diagnosed and **treated before** they have time to manifest and **cause** irreversible **damage to** the newborn's **health**

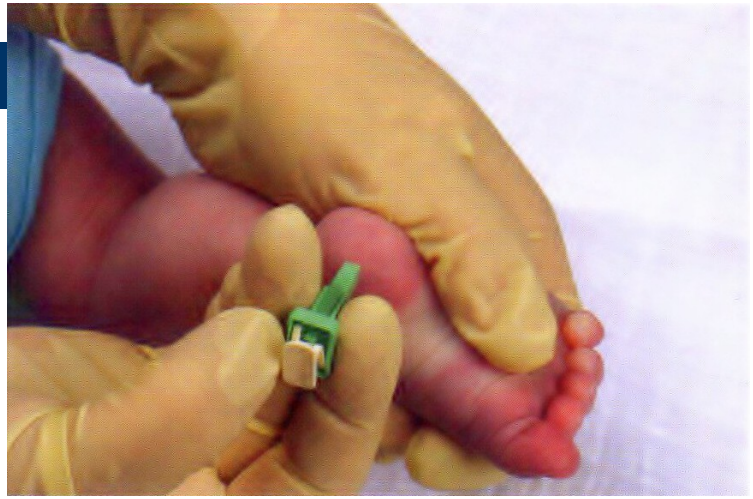
As of October 2009, 13 diseases are being screened for as part of newborn screening in the Czech Republic

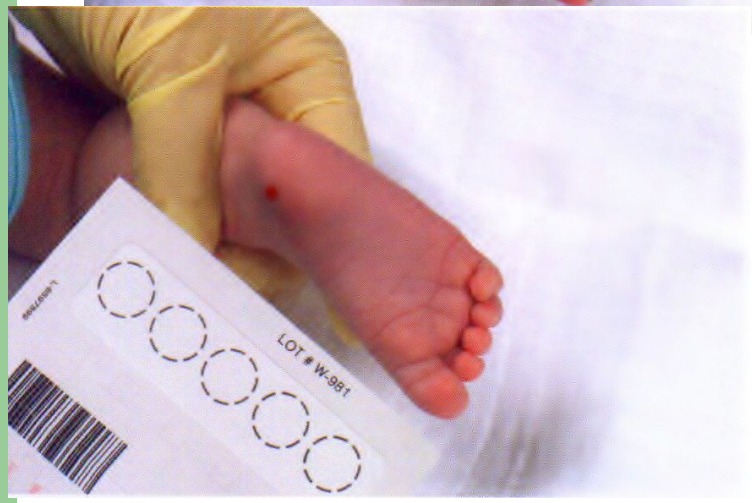
(CF, phenylketonuria, hyperphenylalaninemia, …)

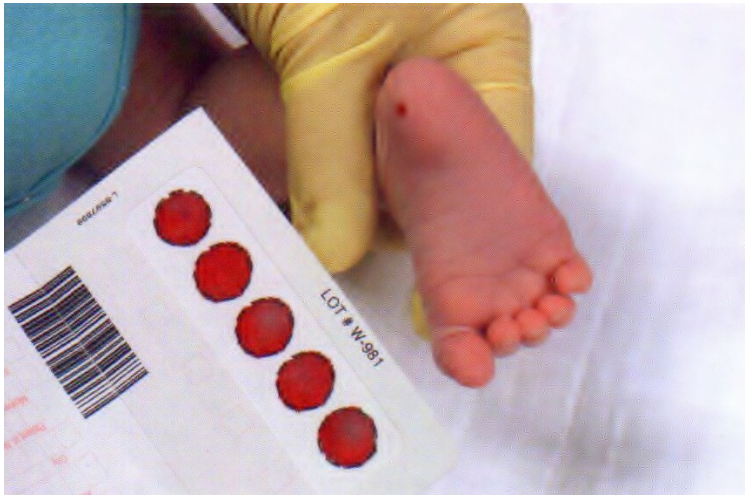
Searching by laboratory method - the principle of analysis of a so-called dry drop of blood on filter paper taken in a standard way

Blood aspiration for newborn screening









Causal treatment of CF – new drugs?

February 12, 2018

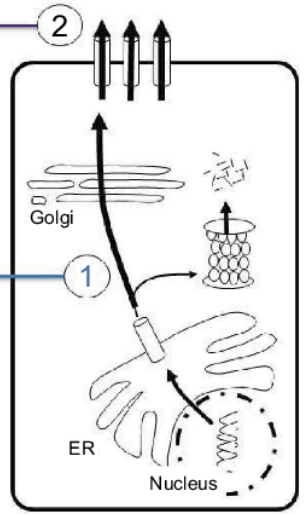
The U.S. Food and Drug Administration (FDA) approved SYMDEKO™ (tezacaftor/ivacaftor and ivacaftor) to treat cystic fibrosis (CF) in people ages 12 years and older who have two copies of the *F508del* mutation or one mutation that is responsive to SYMDEKO. SYMDEKO is Vertex's third CF medicine and offers an important option for many patients, including those eligible who may be interested in a different treatment.

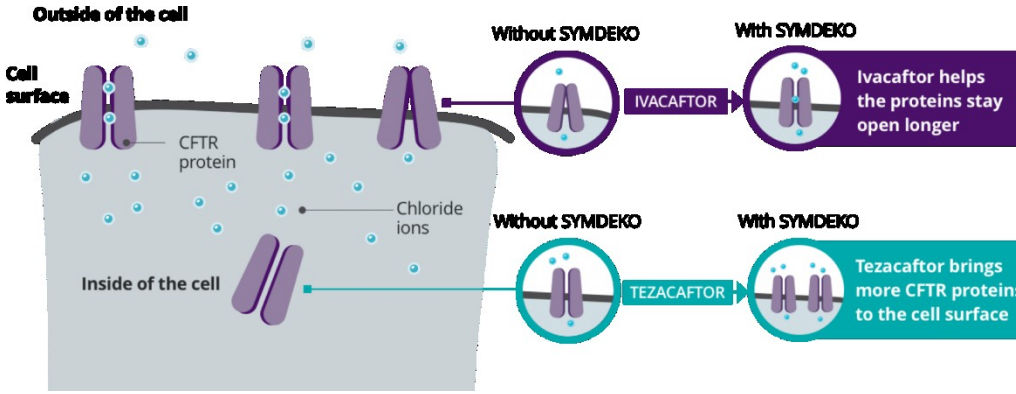
Molecular therapy of CF

- Ivacaftor
- Lumacaftor
- Symdeko

CFTR Potentiator:Ivacaftor
Potentiates the channel-open probability (channel gating) of CFTR at the cell surface

CFTR Corrector:Lumacaftor
Facilitates the processing and trafficking of CFTR to increase the amount of CFTR at the cell surface





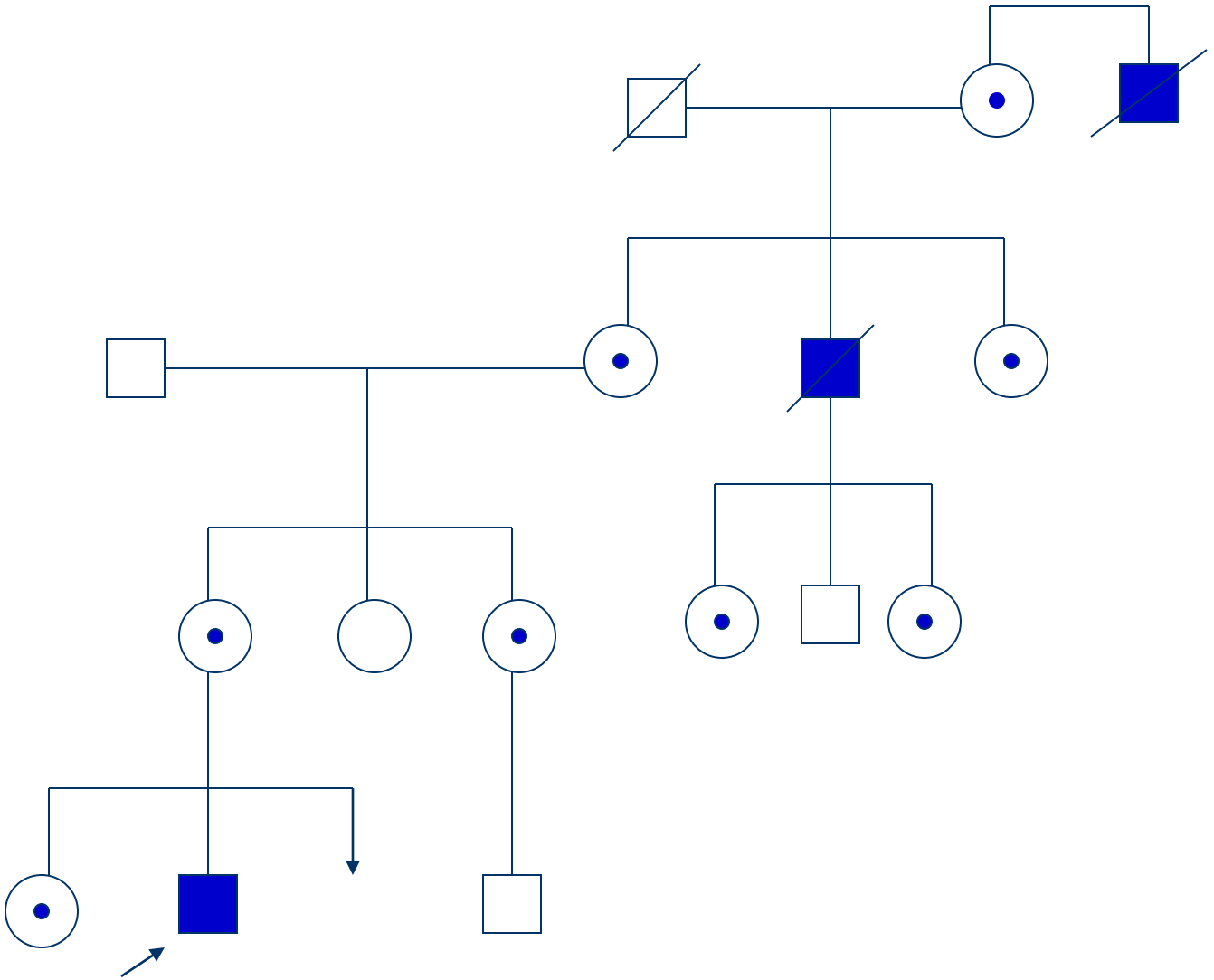
X-linked recessive inheritance

- **Sex chromosomes:** **women** $X^{A}X^{a}$, **men** $X^{a}Y$

Hemizygoteous state

- the **affected** person is usually **a man**, his sons are healthy and his **daughters are carriers** of the disease
- female carriers have **1/2 sons who are sick** and 1/2 daughters who are carriers
- **rare** occurrence in women - daughter of affected man and female carriers, women with karyotype **46,XaXa 45,Xa,** ...
- example - haemophilia

Pedigree of X-linked recessive disease



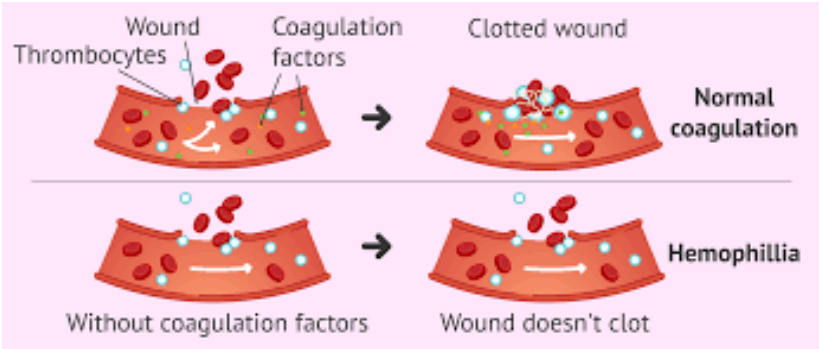
Disorders	Signs or Symptoms and Comments
Albinism: ocular[a]	Nystagmus; normal pigmentation
Ectodermal dysplasia[a]	Hypohidrotic type: abnormal teeth, sparse hair, lack of sweating
Hemophilia A	Factor-VIII deficiency: bruising, bleeding
Hemophilia B	Factor-IX deficiency
Lesch-Nyhan syndrome	Mental retardation, self mutilation
Mental retardation	Many types: some with fragile X-chromosome abnormality
Mucopolysaccharidosis II (Hunter Syndrome)	Mental retardation, hepatosplenomegaly joint contractures
Muscular dystrophy Duchenne	Delay in walking, weak shoulder & pelvic girdles, pseudohypertrophy of valves, in wheelchair by 12 years and death by 20 years; sometimes mental retardation
Becker	Much milder version of above: may be ambulant into late 20's
Nephrogenic diabetes insipidus	Failure to concentrate urine, failure to thrive, thirsty, growth delay

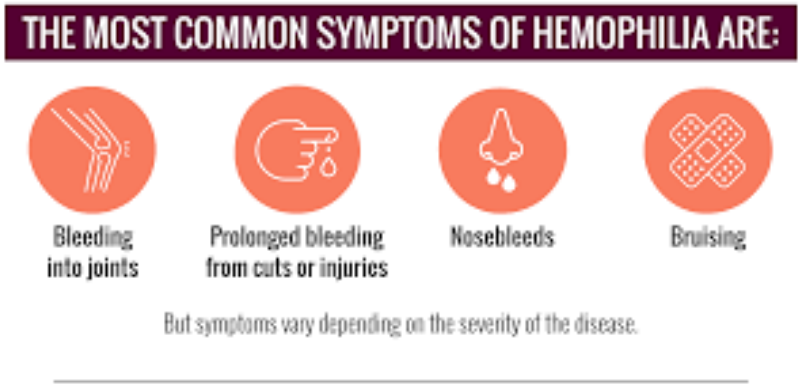
a. Indicates genetic heterogeneity.

Haemophilia

rare congenital bleeding disorder that occurs in people with a limited amount of either clotting factor VIII/ 8 (haemophilia A) or clotting factor IX/ 9 (haemophilia B)

Severity of haemophilia	Percentage of normal factor activity in blood	Number of international units (IU) per millilitre (ml) of whole blood
normal range	50%-150%	0.50–1.5 IU
mild haemophilia	5%-40%	0.05–0.40 IU
moderate haemophilia	1%-5%	0.01-–0.05 IU
severe haemophilia	less than 1%	less than 0.01 IU





Haemophillia – clinical features

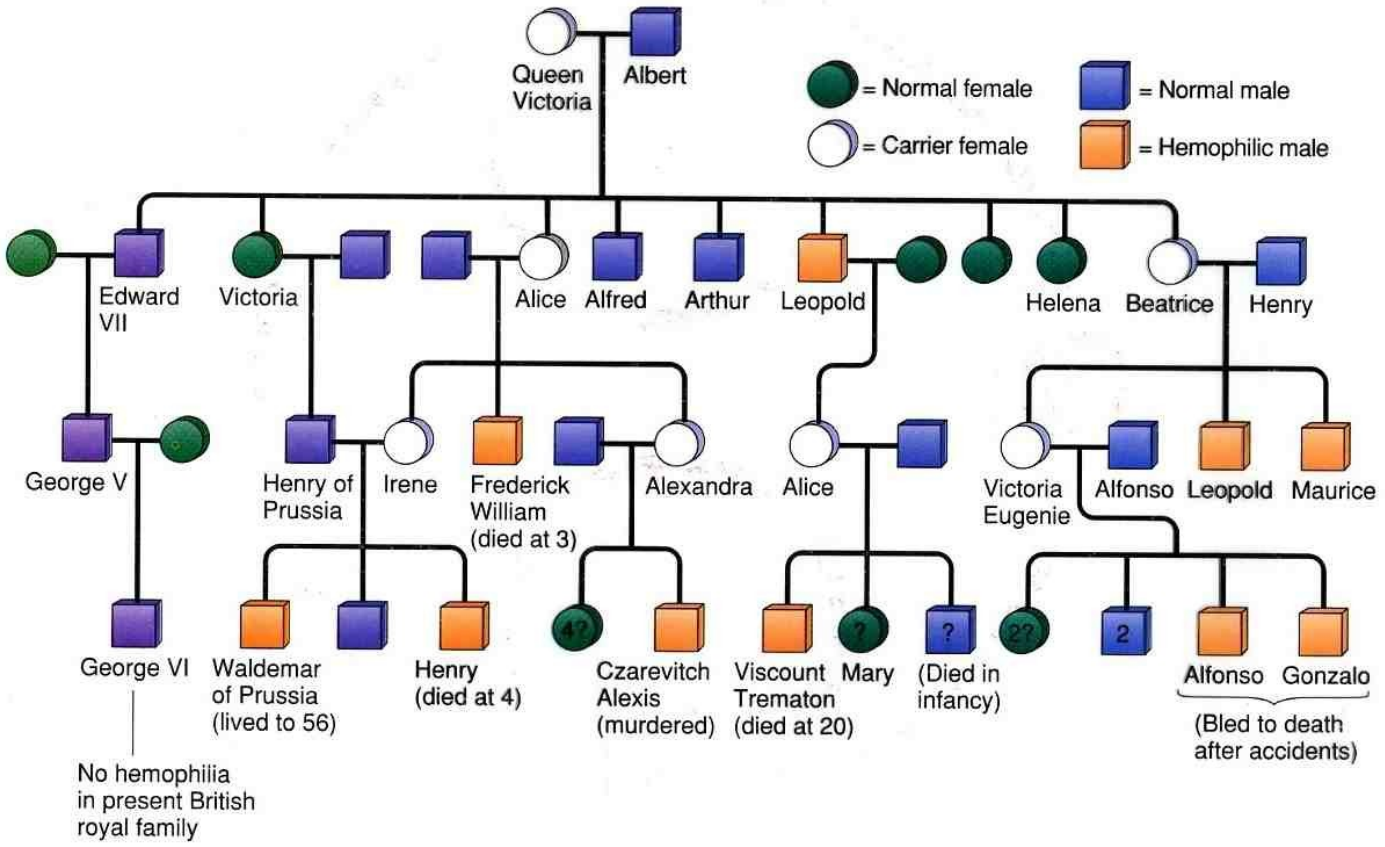
Features	Hemophilia A	Hemophilia B
Prevalence	1:5,000 males	1:30,000 males
Common clinical symptoms	Hemarthroses, muscle hematoma	Hemarthroses, muscle hematoma
Bleeding frequency[a] (episodes/year)	12–30, in severe patients	12–30, in severe patients
Age at first joint bleed (y)[a]	1–2, in severe patients	1–2, in severe patients
FVIII/FIX in vivo recovery (U/ dL)/(U/kg)	1.5–2	0.8–1
FVIII/FIX half-life (h)	12	18
Inhibitor incidence	25–30%, in severe patients	3–5%, in severe patients
Anaphylaxis	Rare and not associated with inhibitor development	Often observed in inhibitor patients
ITI success	60–80% of cases	< 50% of cases
Nephrotic syndrome	Not reported	May complicate ITI course
Most frequent FVIII/FIX gene defects	Intron 22 inversions	Missense mutations
Plasma FVIII/FIX:Ag	Rarely detectable in severe patients	Frequently detectable in severe patients

Abbreviations: ITI, immune tolerance induction treatment; h, hours; y, years.

[a]High interpatient variability in both diseases; some studies reporting a milder bleeding phenotype in hemophilia B (see text for details and references).

A Royal Disease

Queen Victoria of England, who ruled from 1837-1901, is believed to have been the carrier of hemophilia B, or factor IX deficiency. She passed the trait on to three of her nine children.



Kinship crossing - consanguinity

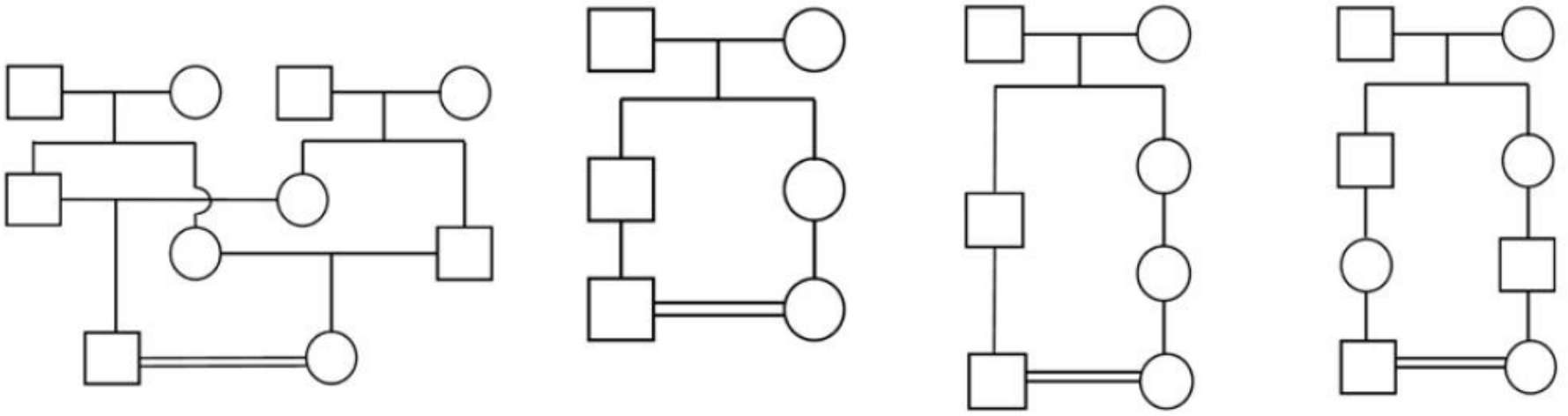


FIG. Family trees of consanguineous marriages with corresponding coefficients of inbreeding (F)

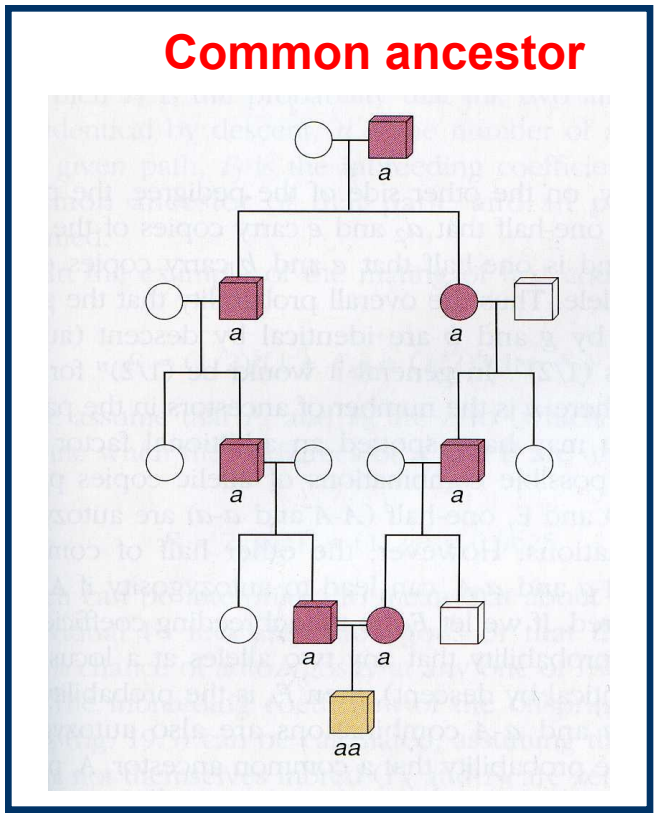
Inbreeding

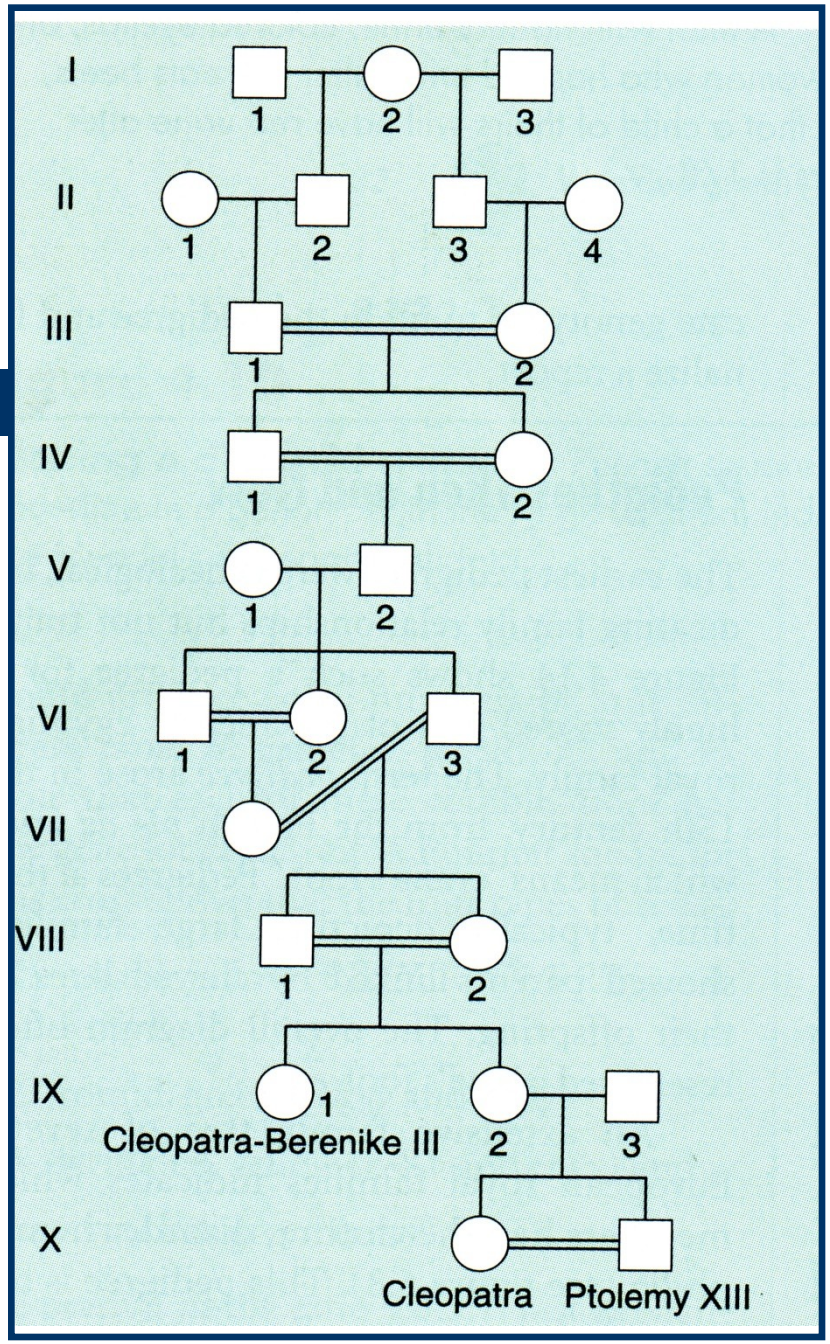
- **inbreeding** occurs when parents have **common ancestors** and are therefore related to each other.
- Inbreeding between relatives is referred to as **consanguinity** from the Latin term **"of the same blood„**
- example - crosses between siblings, half-siblings and first cousins - the offspring are inbreed
- inbreeding increases the frequency of homozygotes and decreases the frequency of heterozygotes and is quantified by the inbreeding coefficient F

F = probability that an individual has two copies of the gene identical in origin (autozygous) because they come from a common ancestor
(if they are identical, the individual is homozygous)

F value range from 0 to 1 **1 = all alleles have same origin**

Part of Ptolemy peidgree





Incidence of albinism in Amish community

I
II
III
IV
V
VI
VII
VIII

1 2

1 2 3

1 2 3 4

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18

1 2 3 4 5 6

Key:

albinism

unaffected

consanguineous mating

Nance, W. E., Jackson, C. E., and Witkop, C. J., Jr. 1970. *American Journal of Human Genetics* 22:579-586. Used with permission of the University of Chicago Press.

Habsburgs - frequent hereditary mental and psychological illnesses due to consanguineous marriages

Joanna of Castile (Mad)

Married with Habsburg 1496

Philip I (Handsome)
Archduke of Austria

What destroys House of Habsburgs? Inbreeding

In the Habsburg dynasty, uncles and nieces, aunts and nephews, as well as cousins often married each other. The so-called inbreeding coefficient, which is a measure of how closely related individuals are.

While the first Spanish king of the Habsburgs, Philip I the Magnificent, had an **inbreeding coefficient of 0.025** - meaning that **2.5%** of his genes **were identical** to those of his relatives. Seven generations and **200 years later** - in the case of Charles II - the inbreeding coefficient was already tenfold, i.e. **0.25 (25%!!!)**