Master in Cellular and Molecular Biology

Medical and Cancer Genetics course

MEDICAL GENETICS

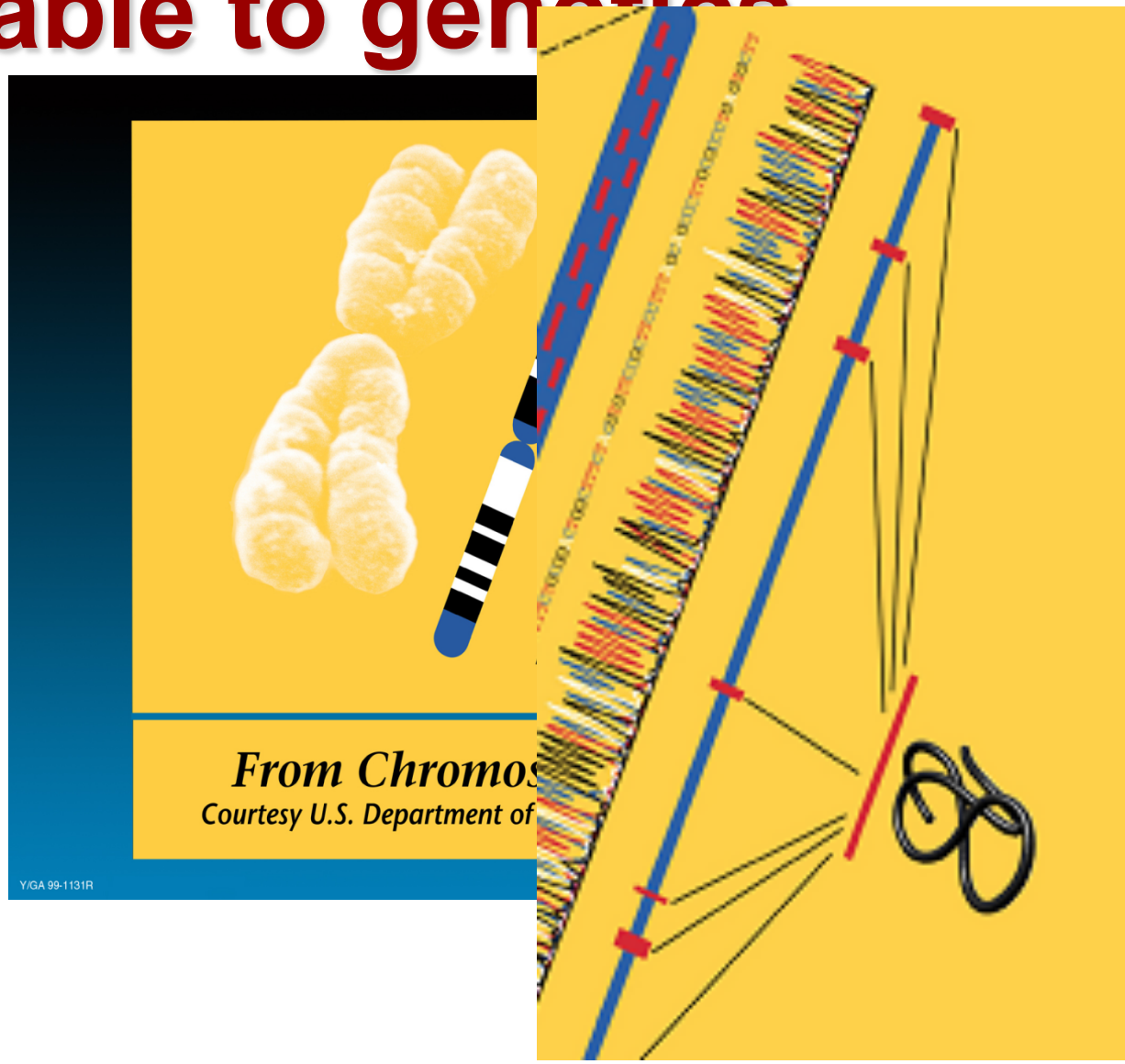
Teacher: Claudia Giachino

Lesson 2

Monogenic diseases

What diseases are attributable to genetics

- **Monogenic or hereditary diseases**
- **Chromosomal diseases**
- **Multifactorial or complex diseases**



Genetics of monogenic diseases

- How many human genes?
- How many monogenic diseases?
- Do we know the causative genes for all of them?

Genetics of monogenic diseases

- How many human genes?
- How many monogenic diseases?
- Do we know the causative genes for all of them?

http://www.ncbi.nlm.nih.gov/genome/guide/human/

NCBI Human Geno...

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NCBI » Genomes & Maps » Homo sapiens

Search All Databases (Entrez) for Go Clear

Browse your genome
Click on a chromosome to show

Genes

Find A Gene

Search for

A challenge facing researchers today is that of piecing together and analyzing the plethora of data currently being generated through the Human Genome Project and scores of smaller projects. NCBI's Web site serves an an integrated, one-stop, genomic information infrastructure for biomedical researchers from around the world so that they may use these data in their research efforts. More...

Genes and Human Health

150%

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07/10/2012

Gene home - Windows Internet Explorer

http://www.ncbi.nlm.nih.gov/gene/

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Genes and mapped phenotypes

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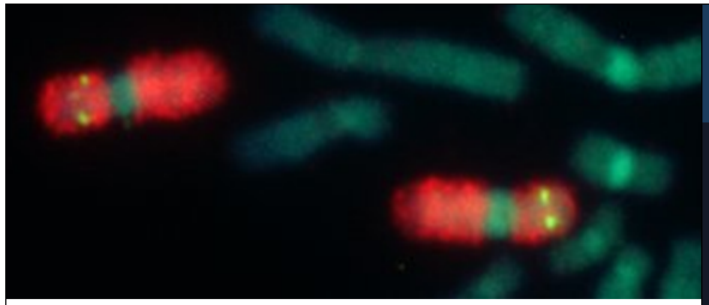
human

Search Clear



Welcome to Entrez Gene

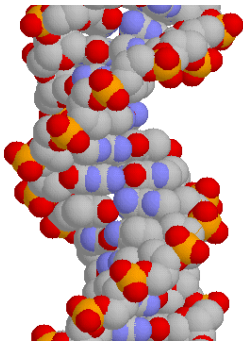
Entrez Gene maintains information about genes from genomes the RefSeq group.

Internet | Modalità protetta: attivata

175%

There are between 25,000 genes in the human genome

DNA



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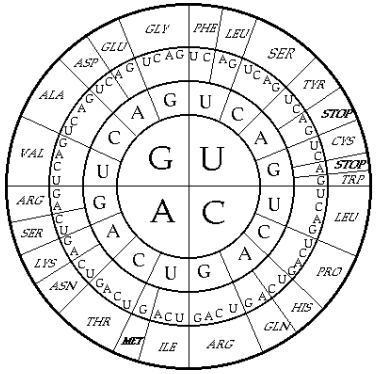
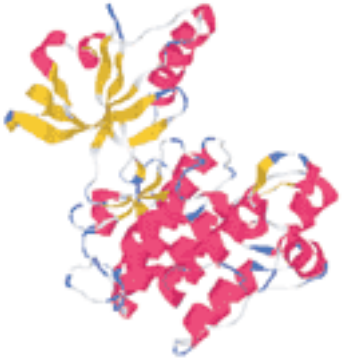
genetic code



protein



The human gene inventory corresponds to ~1.5% of the genome (coding regions)

Genetics of monogenic diseases

- How many human genes?
- **How many monogenic diseases?**
- Do we know the causative genes for all of them?


1966
1968
1971
1975
1978
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1986
1988
1990
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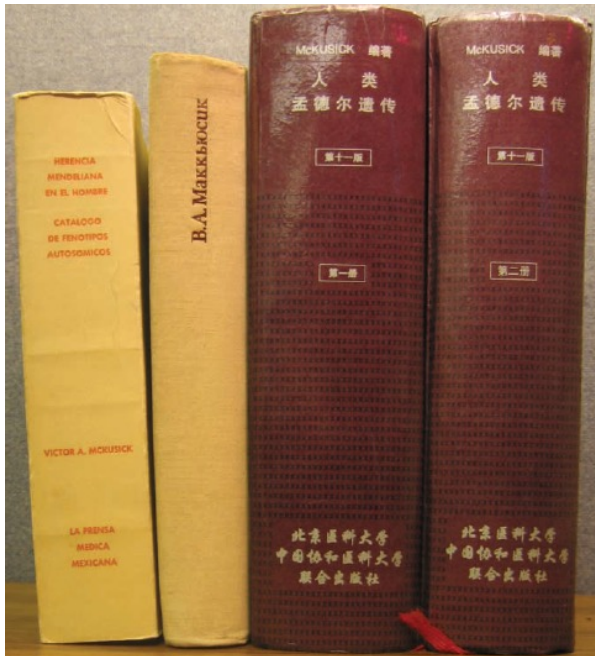
1998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http://www.ncbi.nlm.nih.gov/Omim/

OMIM - Online Mendelian Inheritance in Man - Microsoft Internet Explorer

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Indietro Cerca Preferiti Cronologia

Indirizzo http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM Vai Collegamenti

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OMIM
Online Mendelian Inheritance in Man
Johns Hopkins University

PubMed Nucleotide Protein Genome Structure PopSet Taxonomy OMIM

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Map Viewer
Sequencing Progress

- 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™

NEW OMIM is now incorporated into NCBI's Entrez system and can be queried using the same approach as the other Entrez databases such as PubMed and GenBank. The previous OMIM pages are still available here.

Welcome to OMIM, Online Mendelian Inheritance in Man. This database is a catalog of human genes and genetic disorders authored and edited by Dr. Victor A. McKusick and his colleagues at Johns Hopkins and elsewhere, and developed for the World Wide Web by NCBI, the National Center for Biotechnology Information. The database contains textual information and references. It also contains copious links to MEDLINE and sequence records in the Entrez system, and links to additional related resources at NCBI and elsewhere.

You can do a search by entering one or more terms in the text box above. Advanced search options are accessible via the Limits, Preview/Index, History, and Clipboard options in the grey bar beneath the text box. The OMIM help document provides additional information and examples of basic and advanced searches.

The links to the left provide further technical information, searching options, frequently asked questions (FAQ), and information on allied resources. To return to this page, click on the OMIM link in the black header bar or on the graphic at the top of any OMIM page.

NOTE: OMIM is intended for use primarily by physicians and other professionals concerned with genetic disorders, by genetics researchers, and by advanced students in science and medicine. While the OMIM database is open to the public, users seeking information about a personal medical or genetic condition are urged to consult with a qualified physician for diagnosis and for answers to personal questions.

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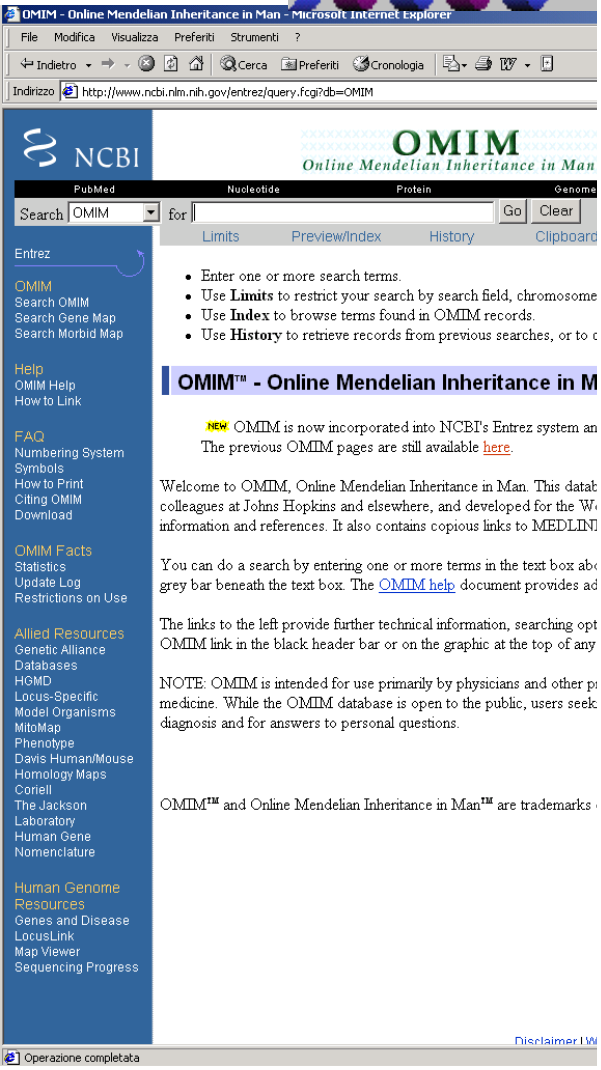
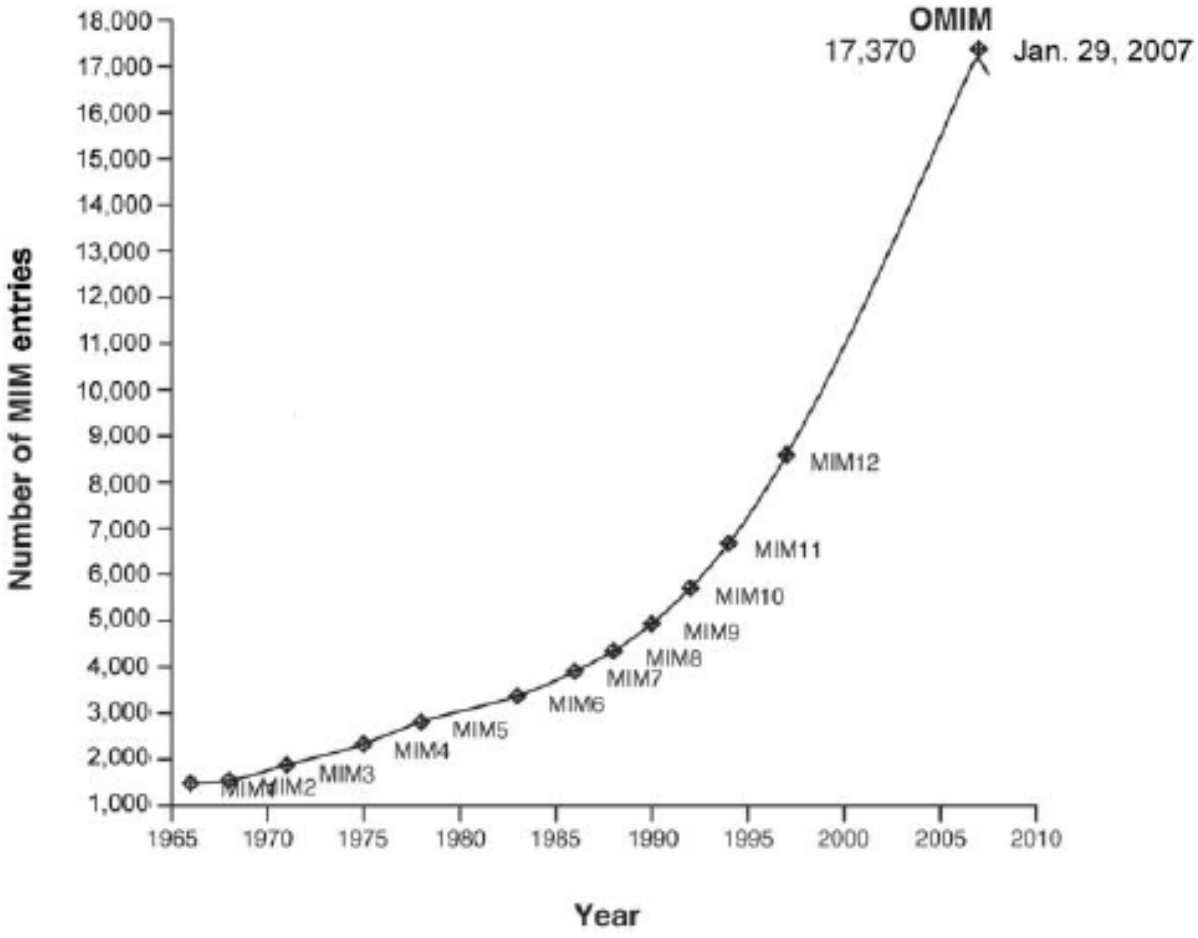
http://www.ncbi.nlm.nih.gov/Omim/

National Center for Biotechnology Information





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OMIM Statistics for August 14, 2010

Number of Entries

	Autosomal	X-Linked	Y-Linked	Mitochondrial	**Total**
* Gene with known sequence	12475	611	48	35	13169
+ Gene with known sequence and phenotype	346	20	0	2	368
# Phenotype description, molecular basis known	2576	227	4	28	2835
% Mendelian phenotype or locus, molecular basis unknown	1636	136	5	0	1777
Other, mainly phenotypes with suspected mendelian basis	1853	134	2	0	1989
Total	18886	1128	59	65	**20138**

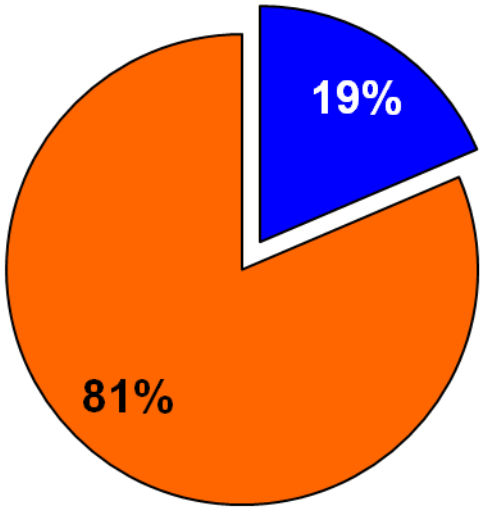
- 2835 monogenis diseases caused by mutations in known genes
- 1777 monogenic diseases for which the gene locus is known but the causative gene is unknown
- 1989 diseases suspected to have a genetic basis for which both the locus and the causative gene are unknown

Known genes

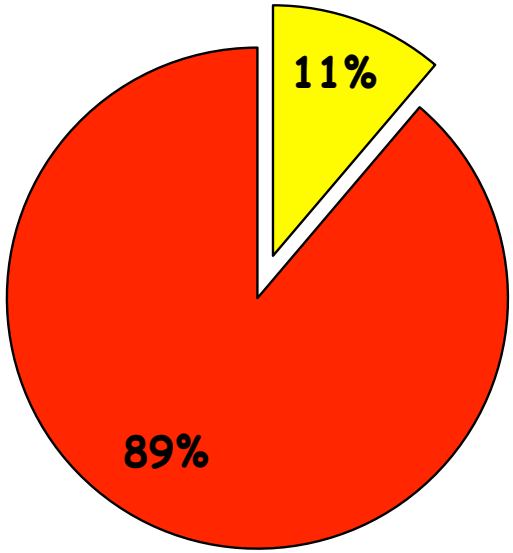
Genes which if mutated cause monogenic diseases

6601 hereditary diseases

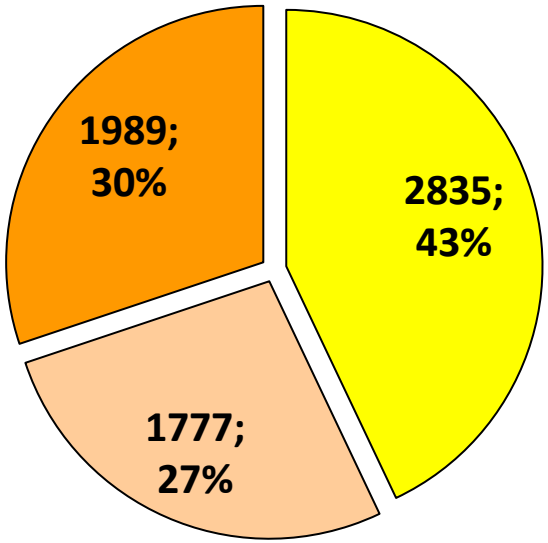
Unknown function



Known function



Known gene



Unknown gene

Total ~ 25,000 genes

Monogenic diseases or monofactorial or simple

- A quick reminder of past notions
- Examples of some of the most frequent illnesses

Gregor MENDEL (1822-1884)

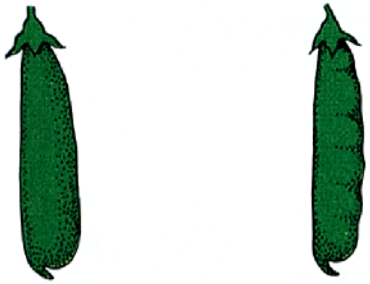
The seven characters studied by Mendel with their alternative forms.

Study conducted on pure parental lines, differing for one single character.

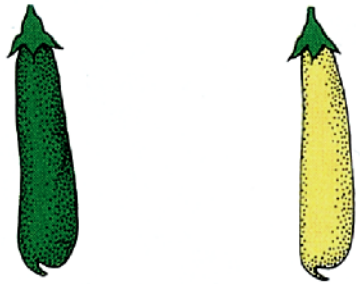
Smooth or wrinkled seed

Yellow or green seed interior

Purple or white petals



Simple or concamerate mature pod

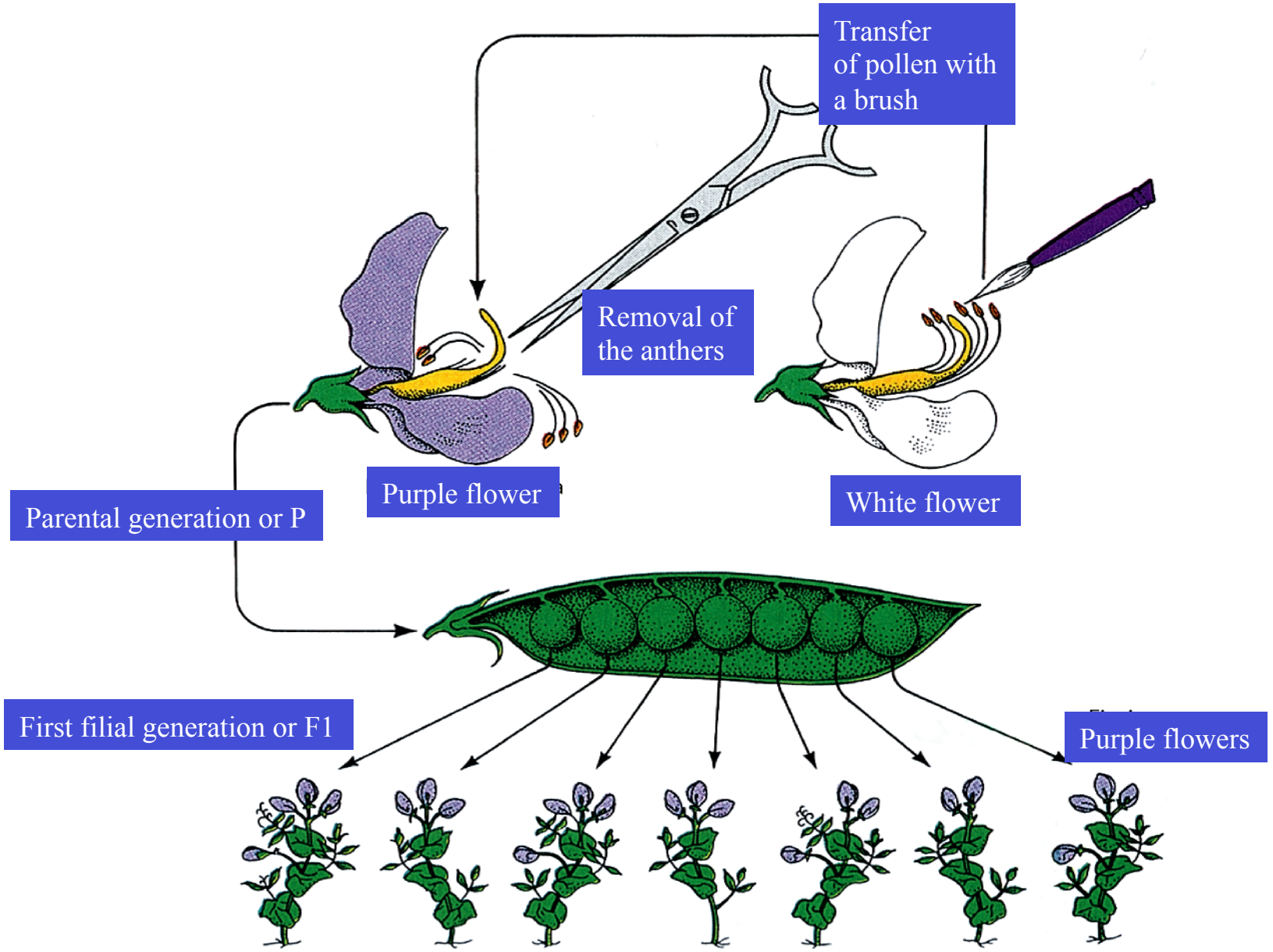


Green or yellow unripe pod

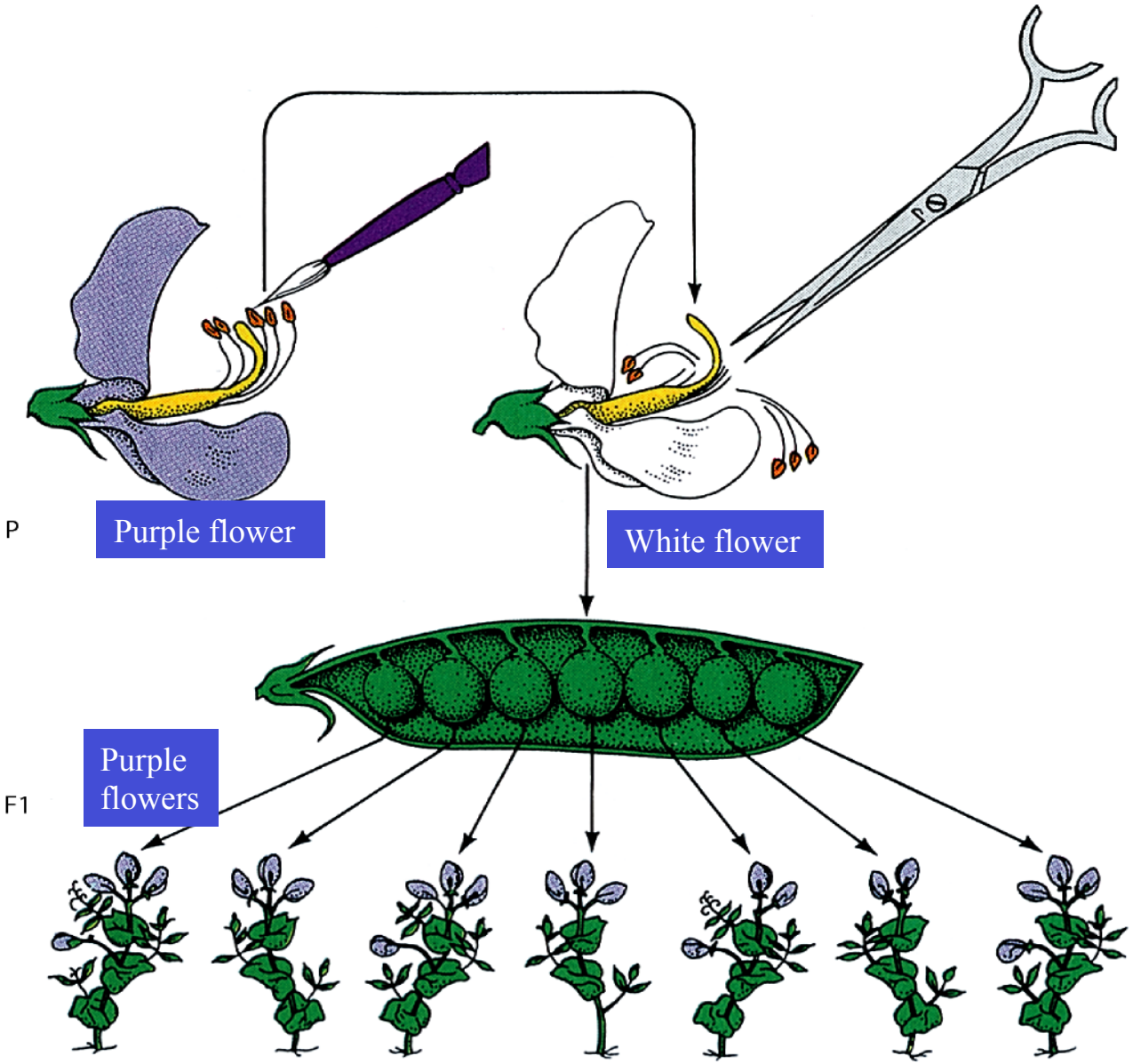
Flowers arranged along the stem of the plant (axial flowers)

Long or short stem

The crossing between female purple flowers and male white flowers conducted by Mendel produced a progeny all made of purple flowers.



The crossing between female white flowers and male purple flowers produced the same results of the reciprocal crossing, i.e. a progeny all made of purple flowers



Results of Mendel's crosses where parental types differed by only one character

In F1 a single phenotype was dominant. Mendel coined the terms of *dominant* and *recessive*.

In F2 recessive phenotype appeared again, Mendel found a ratio of 3:1.

Mendel's hypotheses

Mendel's model contemplated the following 5 concepts:

1. *The existence of genes*. Alternative phenotypic differences and how those differences were transmitted from generation to generation were attributed to hereditary particles. Today these particles are called genes.

2. *Genes are in pairs*. The gene can have different shapes, each corresponding to an alternative phenotype of a certain character. The different forms are called alleles.

3. *Segregation of gene pairs in the gametes*. Each gamete has only one member of each pair.

4. *Segregation in equal proportions*. The members of the pair of genes are distributed in equal proportions (segregate) in the gametes. The 50% of gametes will bring one of the two members of the gene pair and the remaining 50% will bring the other member.

5. *Random fertilization*. Merging a gamete of a parent with a gamete from the other parent to form the first cell (zygote) of a new individual is random. In other words, the gametes combine with one another regardless of which member of the gene pair is present in it.

First Mendel's law

- Law of uniformity.

After crossing of two homozygotes of different alleles the progeny of the first filial generation (F1) are all identical and are heterozygous.

Second Mendel's law

- Law of segregation.

The two members of a gene pair get separated (segregate) from each other in the gametes; as a result, half of the gametes carries a member of the pair in the other half carries the other member.

This law postulated 1:2:1 segregation in intercrosses of heterozygotes and 1:1 segregation in backcrosses of heterozygotes with homozygotes.

message

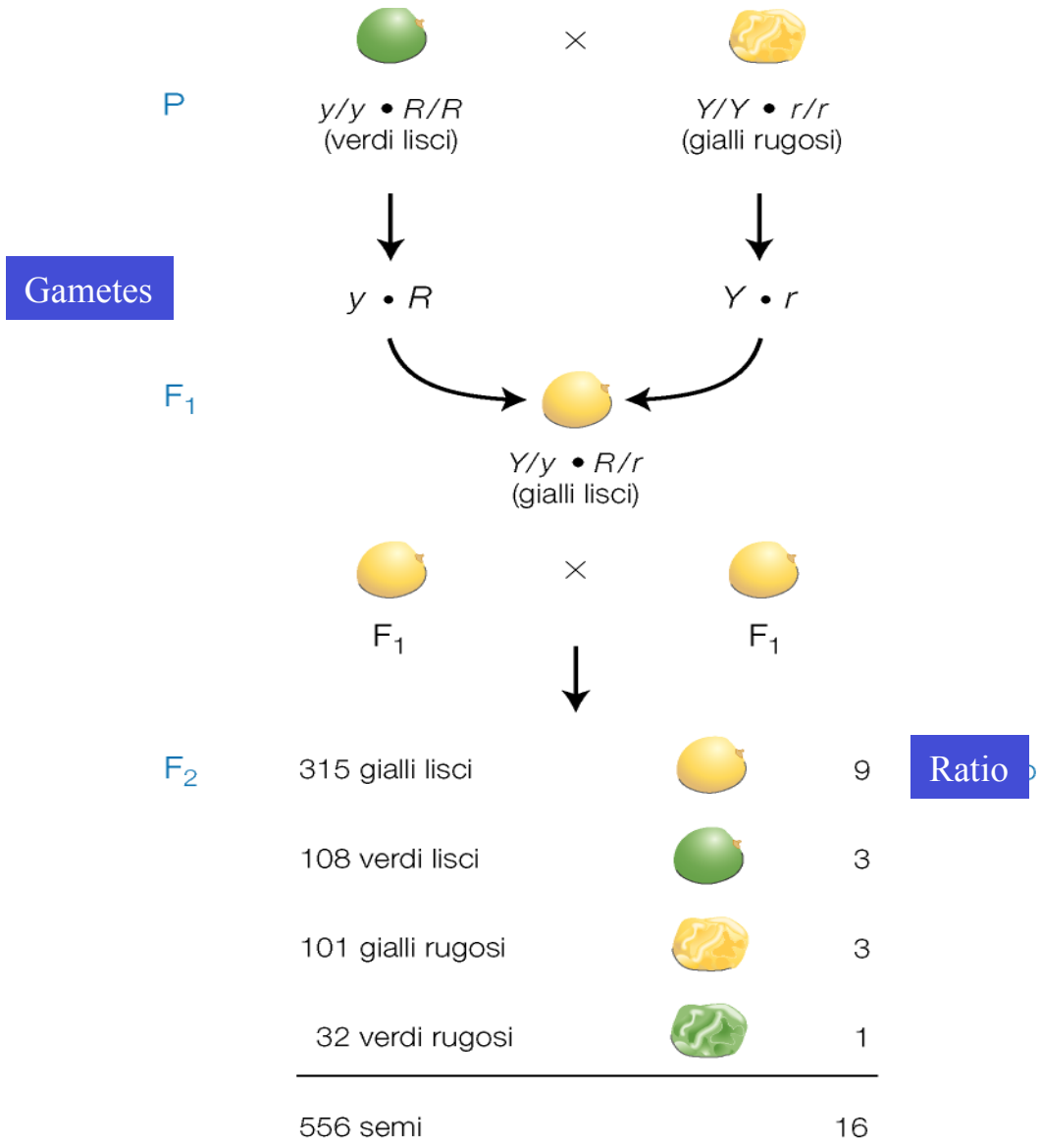
- The existence of genes was first hypothesized based on observation of specific mathematical relationships in the progeny of two parental lines showing different phenotypes.

- These general patterns of inheritance are used even today to infer the existence of specific genes underlying specific characters.

Wrikled seeds (R/R o R/r) and smooth seeds (r/r) in a pod obtained through self-fertilisation of a heterozygous plant (R/r).

The phenotypic ratio in this pod is exactly the 3:1 ratio waited on average in a progeny of this type of crossing.

A dihybrid cross produces a F2 offspring with phenotypic ratio 9:3:3:1.



Third Mendel's law

- Law of independence.

Different gene pairs are transmitted independently of each other during the formation of gametes.

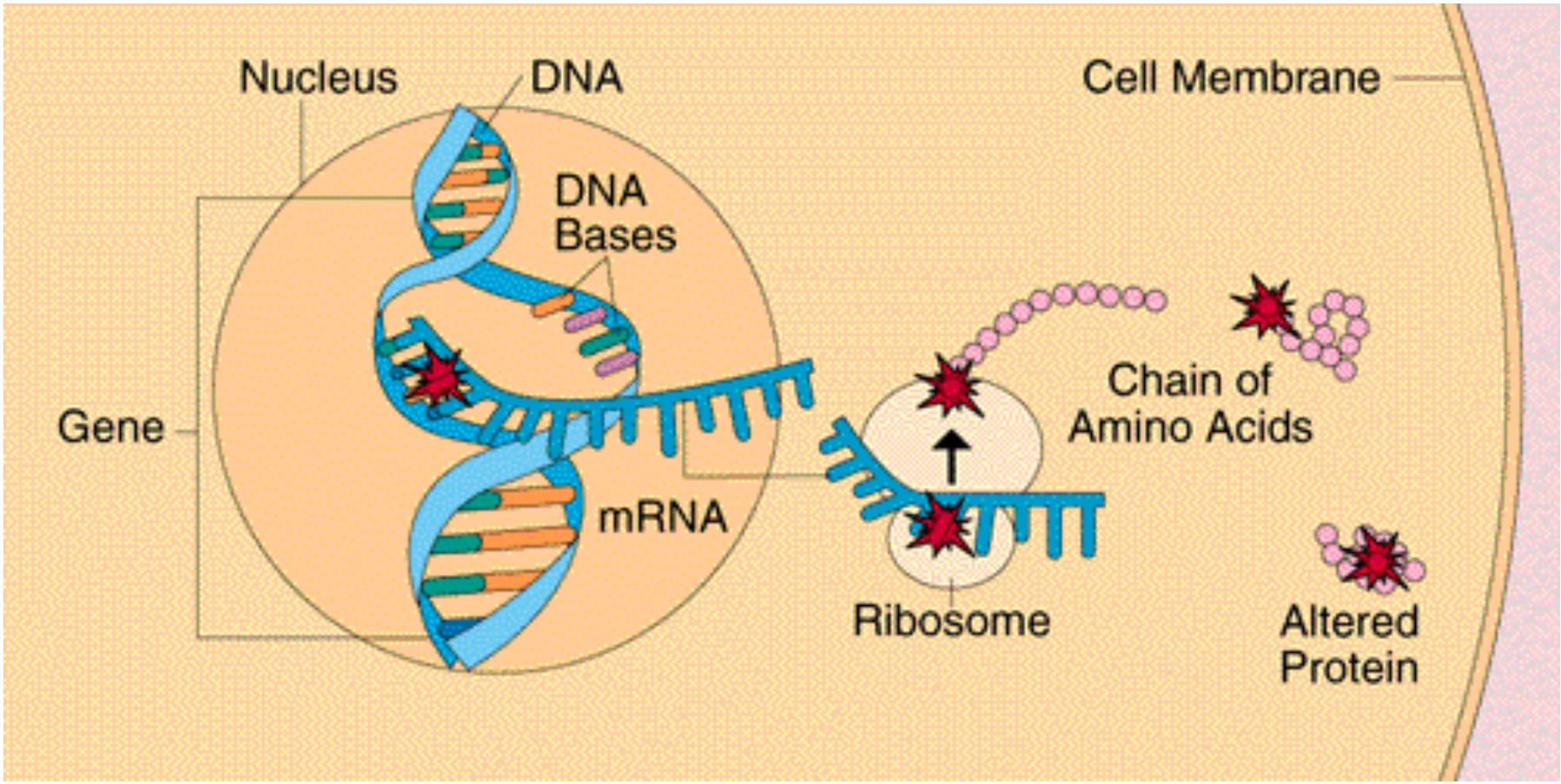
It follows that for two pairs of genes both in heterozygosity A/a and B/b the probability for the allele b going to end up in a gamete with the allele a is equal to the probability of the same allele b to finish with the allele A.

- Thanks to the discoveries of modern genetics on localization of genes, we now know that this ' law ' is true only in some cases. Most cases of independence are found for genes located on different chromosomes. The genes located on the same chromosome are not usually transmitted independently because they are physically located on the same chromosome.

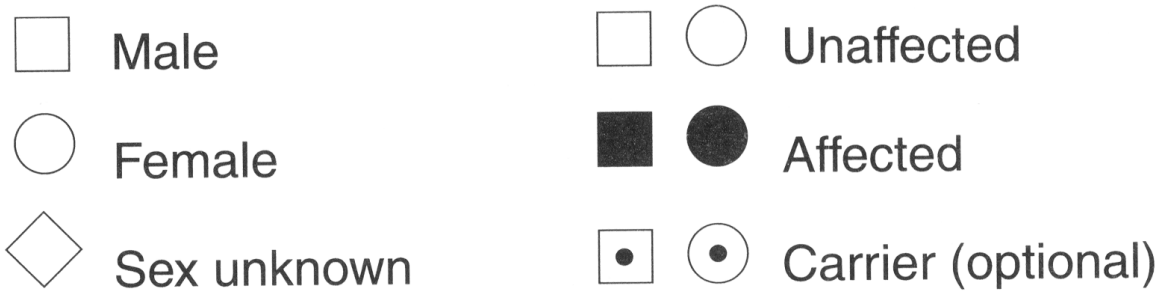
- So the modern vision of the third Mendel's law is:

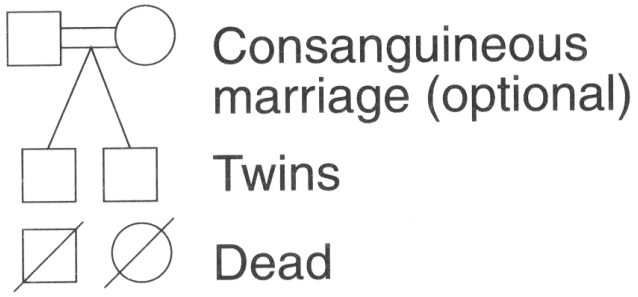
gene pairs located on different chromosomes are transmitted independently during meiosis.

Inherited disease



Mendelian pedigree patterns





= male

= female

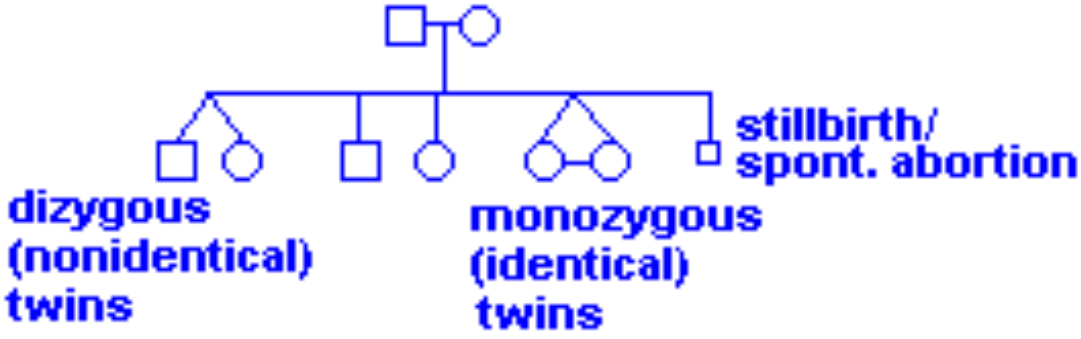
= affected

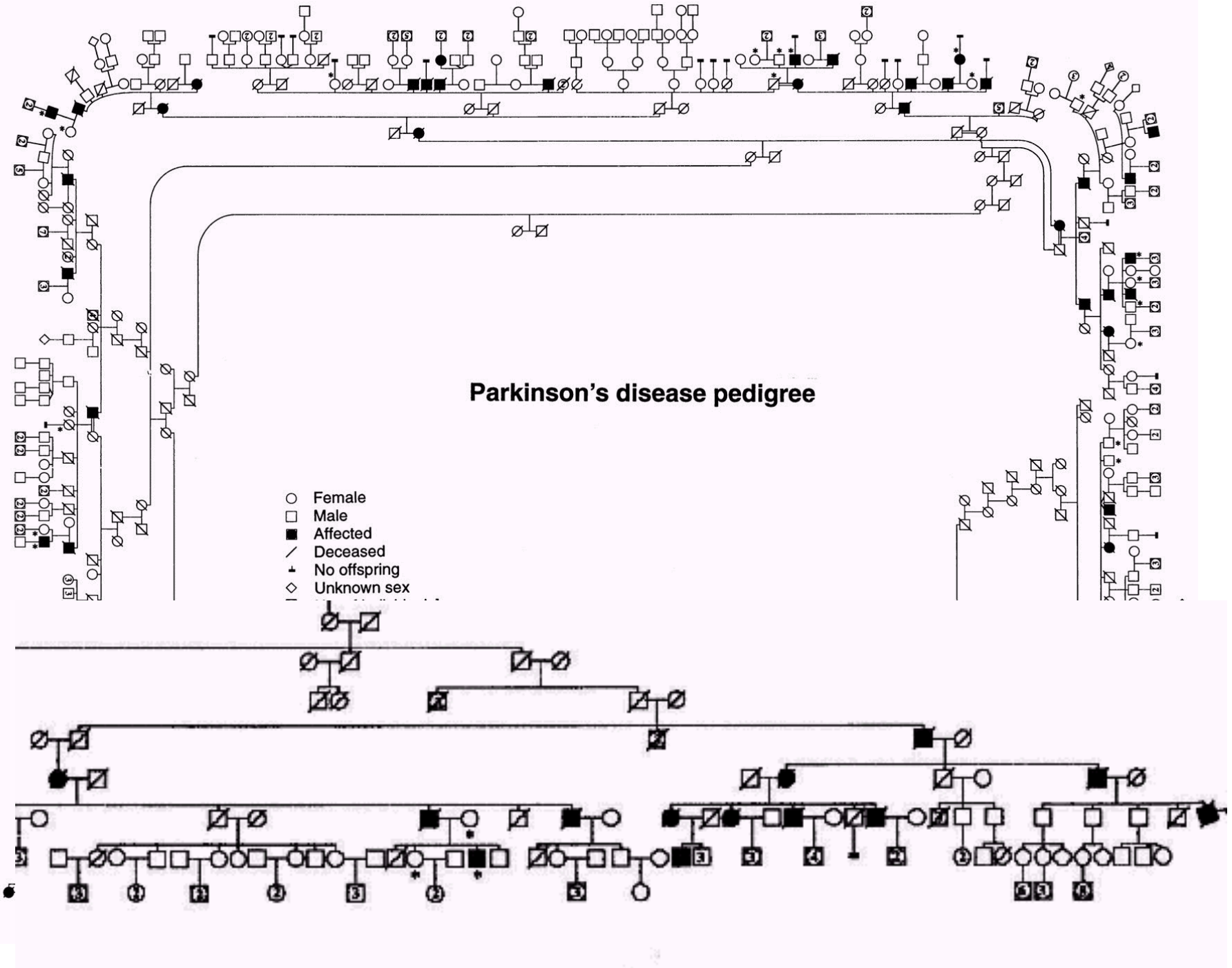
= legal mating

= consanguineous (related) mating

= deceased

= female carrier for X-linked trait




Parkinson's disease pedigree
Female
Male
Affected
Deceased
No offspring
Unknown sex
I
II
III
IV
V
VI
VII
VIII
IX
X
XI

Terminology

Locus: the position of a gene on a chromosome

eg. sex determining gene, SRY

SRY is located on chromosome Y at position p11

Alleles: alternative forms of a gene

eg. in the beta globin gene, the codon (triplette of nucleotides) encoding for the sixth aminoacid:

Normal Allele A .....GAG..... (acido glutammico)

Sickle allele S .....GTG..... (valine) **mutazione**

Mutated allele C .....AAG..... (lisina) **mutazione**

Terminology

Homozygote: carries 2 identical alleles at the same locus, βA βA o βS βS

Heterozygote: carries 2 different alleles at the same locus, βA βS

Compound heterozygote: carries 2 mutant alleles (2 different mutations) at the same locus, βSβC

Carrier (healthy): asintomatic heterozygote

Proband (Propositus): the affected individual through which a family is directed to analysis

Genotype: genetic constitution of an individual, either as a whole or referred to a specifc gene, eg. Sickle cell anemia, βS βS

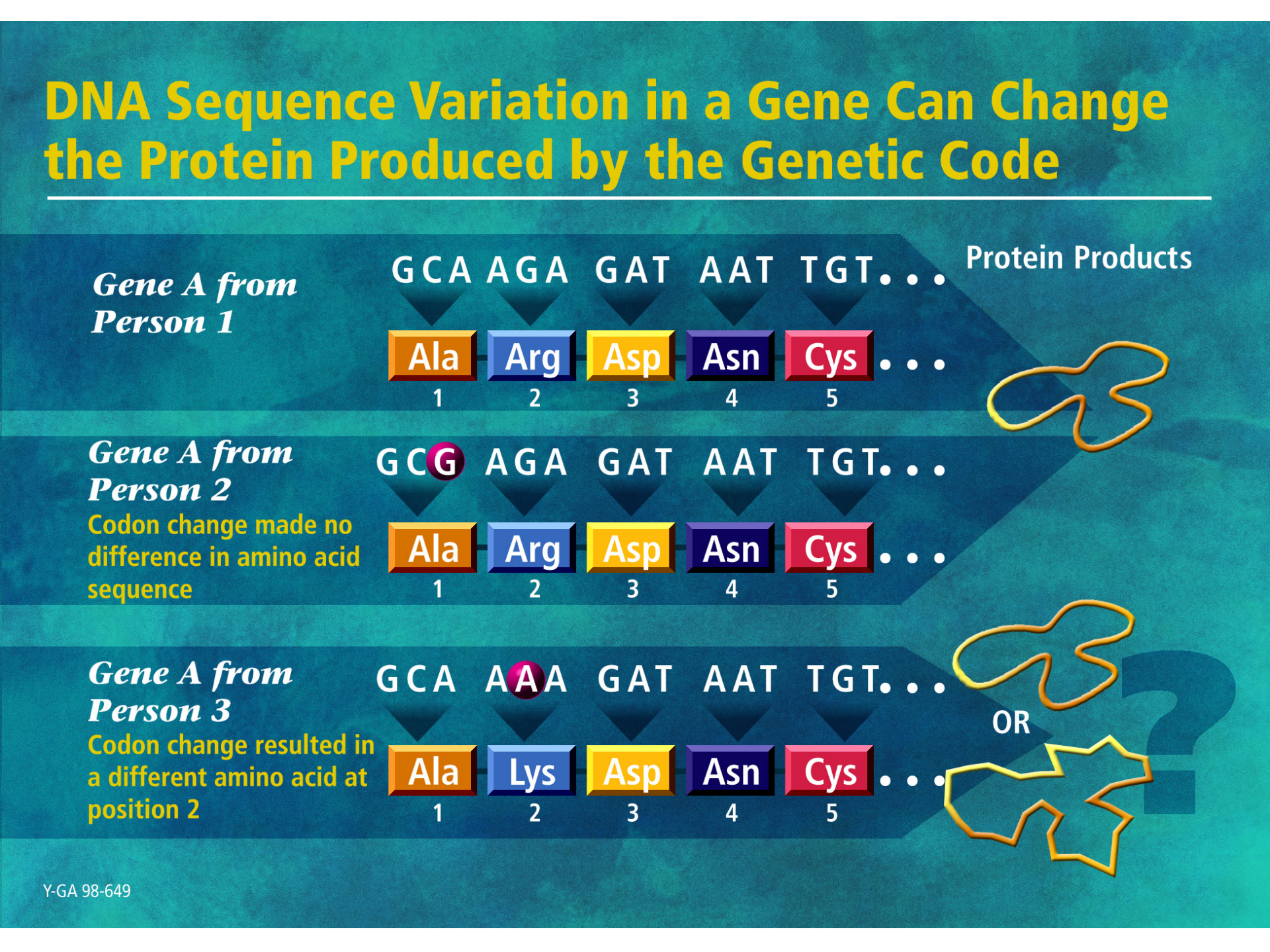
Phenotype: observable feature of an individual, or of a cell

Mendelian inheritance of tracts

- Dominant: each trait or character that is expressed in the heterozygote, that is, in case of illness, where only one copy of the defective gene is sufficient to express the affected phenotype
- Recessive: each trait or character that is expressed in the homozygote, that is, in case of illness, where both copies of the defective gene are to be present in order to express the affected phenotype
- Codominant: in cases where heterozygous state expresses a distinct phenotype respect to the two homozygous states, eg. Blood groups, blood cell enzymes etc.

Point mutations

DNA Sequence Variation in a Gene Can Change the Protein Produced by the Genetic Code



Y-GA 98-649

functional classification for mutations

1. equivalent allele
2. hypomorphic allele
3. amorphic or null allele
4. hypermorphic allele
5. neomorphic allele
6. antimorphic allele or dominant negative

1. equivalent allele

- changes that do not alter neither the amount nor the biochemical and functional quality of the gene product
- the gene product remains unaltered and normally localised
- examples are the approximately 12,000 coding DNA sequence differences that are observed in the human population that have no pathological consequences

2. hypomorphic allele

- a type of change in which the altered gene product possesses a reduced level or activity, or in which the wild-type gene product is expressed at a reduced level
- these alleles are recessive, silent and may act more as modifiers of the phenotype than as a direct cause of pathology
- hypomorphic alleles can be cause of pathology only when in a hemizygous state
- example: hypomorphic alleles of the distrophin gene located on X chromosome, responsible for **Becker's muscular distrophy** in males as they have only a single copy of the gene

3. amorphic or null allele

- a type of change in which the altered gene product lacks the molecular function of the wild-type gene. Synonims: loss-of-function or null mutation
- an amorphic allele can be produced by other types of mutation having the same consequence of total gene deletion
- in a hemizygous state it causes a pathology when the involved gene has an essential function (eg hemophilia, **Duchenne's muscular dystrophy**)
- in a heterozygous state it is generally present in a healthy carrier of an autosomic recessive disease
- it can alone cause a disease if it relates to a gene in which 50% of the dosage (produced by the other non mutated allele) is insufficient to maintain the state of health (**haploinsufficiency**) (example **hypercholesterolemia**)

4. hypermorphic allele

- hypermorphic (hyper=augmented) is a type of change in which the altered gene product possesses an increased level of activity, or in which the wild-type gene product is expressed at an increased level
- the hypermorphic allele can be simple or have a combination of other effects such as that of being present in an improper location or at a wrong time
- it is normally bound to a dominant genetic trait, as the increased expression/function cannot be restricted or counterbalanced by the wild-type allele
- example: the increased FGF3 receptor function that causes **achondroplasia** (dwarfism dysmorphic disorder) which is transmitted in an autosomal dominant manner

5. neomorphic allele

- neomorphic (neo=new) is a type of change in which the altered gene product possesses a novel molecular function or a novel pattern of gene espression wherein the change in gene leads to an atipically new function of the gene
- it is only didactically distinguishable from the hypermorphic allele, as it is difficult to be discriminated in the individual conditions
- neomorphic alleles are usually dominant or semidominant
- in some forms of cancer the neomorphic allele is a chimera of two genes, caused by a chromosomal translocation (as for the Philadelphia chromosome fusion, with the appearance of new Bcr-abl proteins in chronic myelogeneous leukemia cases)

6. antimorphic allele or dominant negative

- antimorphic (anti=against) is a type of change in which the altered gene product possesses an altered molecular function that acts antagonistically to the wild-type allele
- antimorphic alleles are always dominant
- is the result of a change affecting a gene whose protein product works cooperatively with other proteins
- particular mutations make the protein of disturbance in any other, although the latter being perfectly normal
- one example is the collagen in which multiple genes (and two alleles for each gene) contribute to the formation of proteins each producing a portion of the base collagene chains: a mutation in only one allele produces a negative effecton the entire aggregate (example: **osteogenesis imperfecta**)

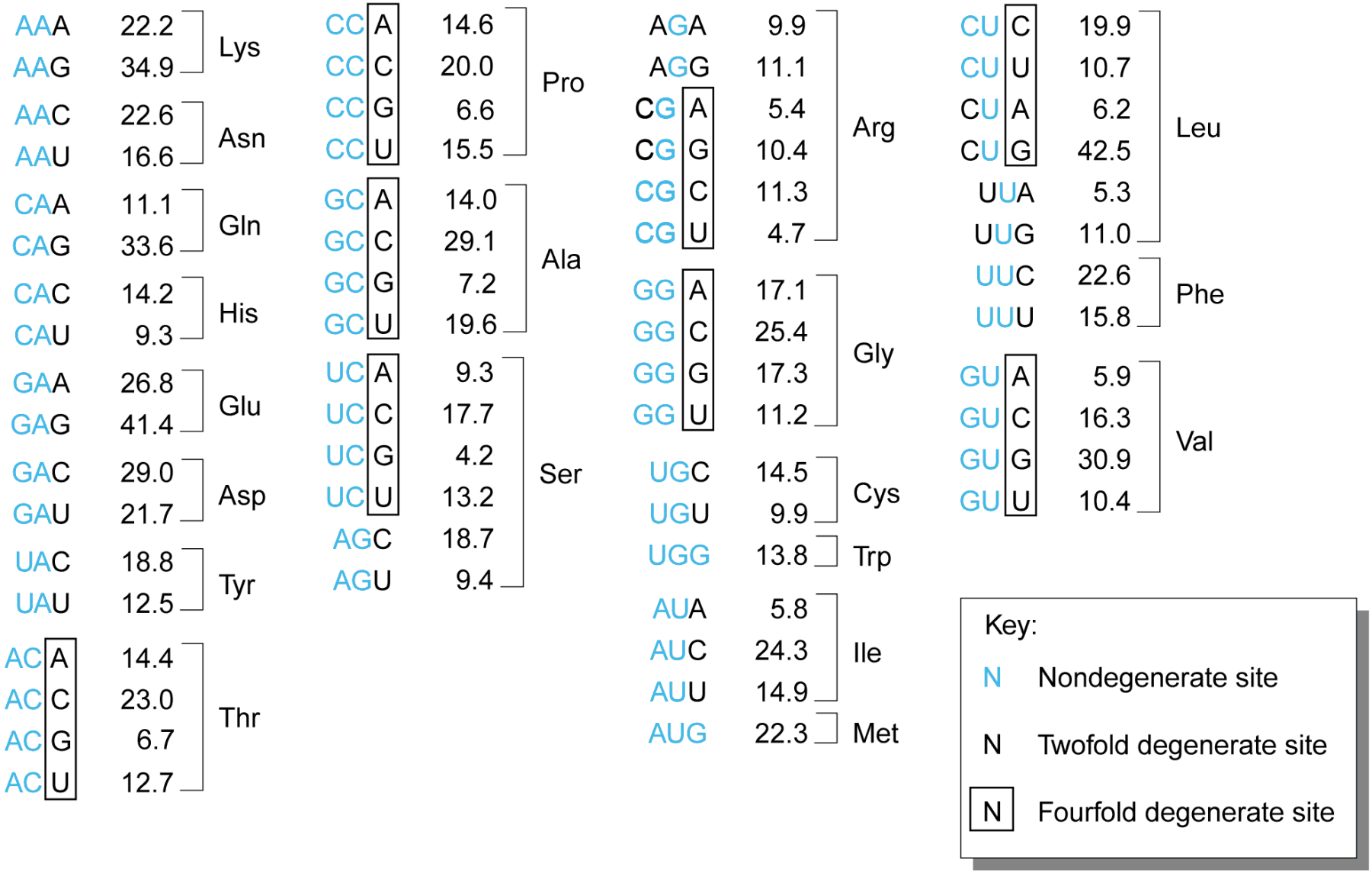
structural classification of mutations

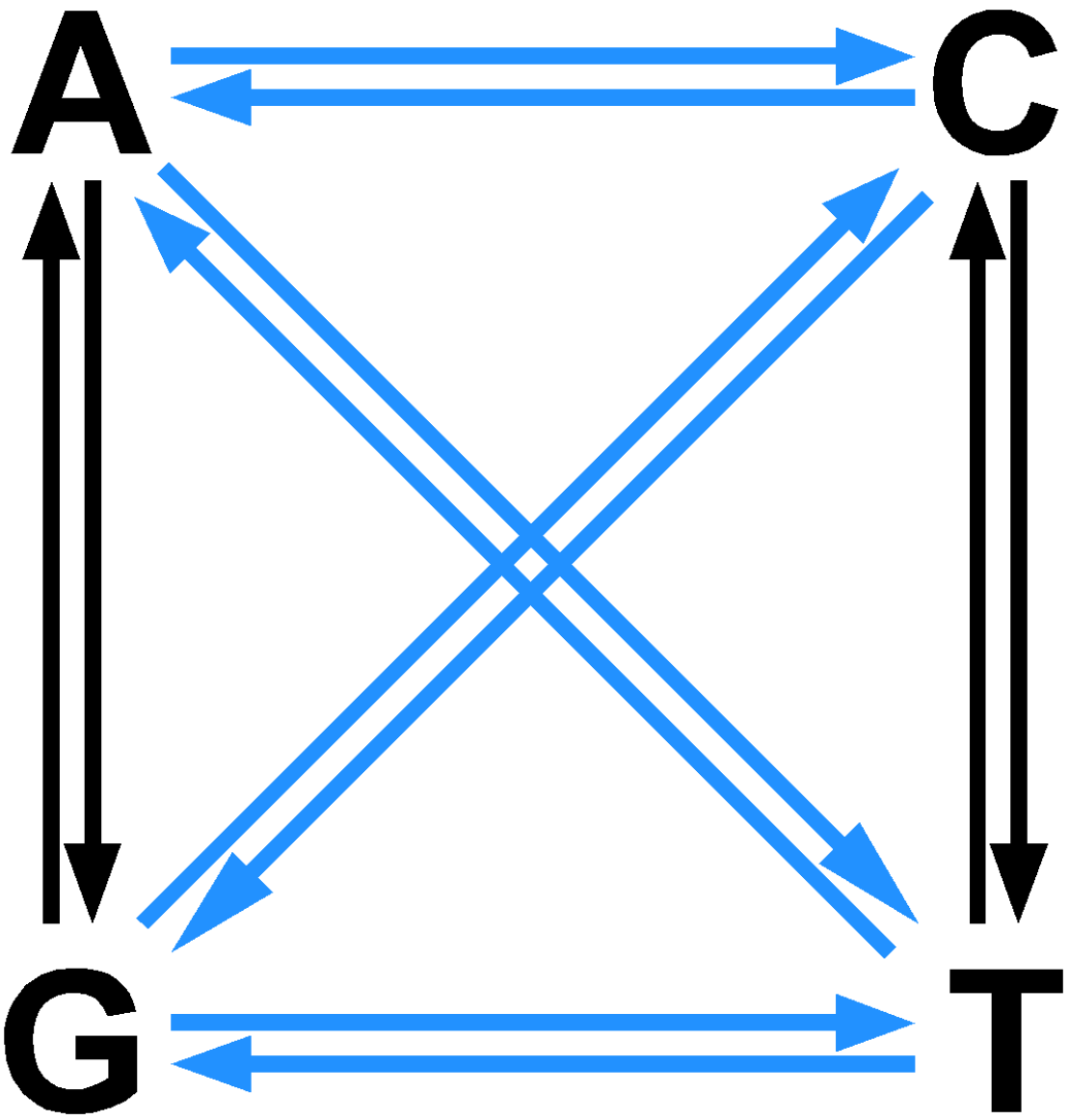
1. Substitutions
2. small insertions, deletions or simultaneously insertions + deletions (indels)
3. genomic rearrangements with two breakpoints (deletions, duplications) or more than two breakpoints (translocations, inversions, others)
4. copy number variations (CNV)

To these four classes belong both the harmless and the disease-causing mutations

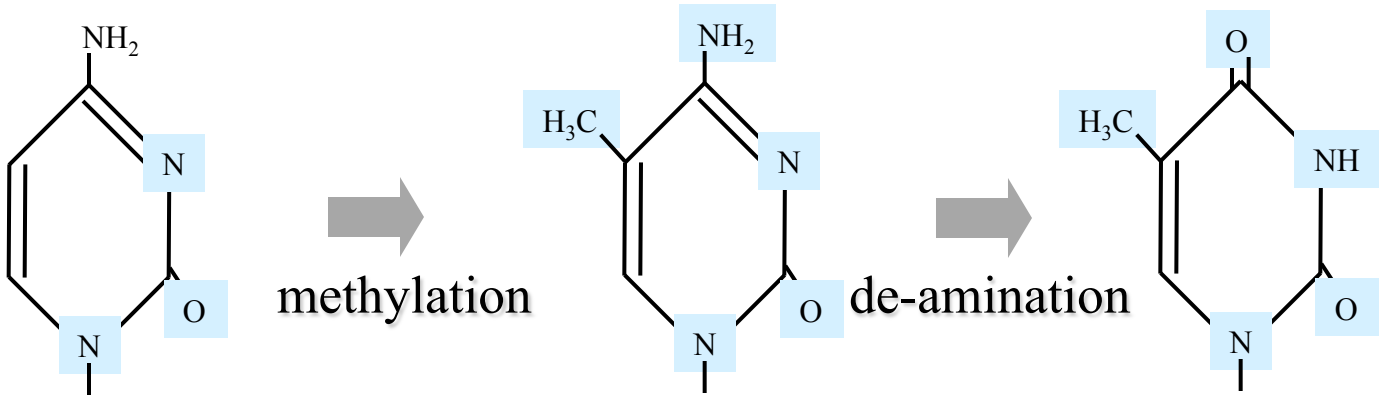
substitutions

- silent mutations, when the aminoacid does not change
- missense mutations, when one aminoacid is substituted by another aminoacid
- nonsense mutations, when an aminoacid is substituted by a premature stop codon
- nonstop mutations, when as a contrary a stop codon is substituted by another aminoacid


AAA 22.2
AAG 34.9
Lys
AAC 22.6
AAU 16.6
Asn
CAA 11.1
CAG 33.6
Gln
CAC 14.2
CAU 9.3
His
GAA 26.8
GAG 41.4
Glu
GAC 29.0
GAU 21.7
Asp
UAC 18.8
UAU 12.5
Tyr
AC A 14.4
AC C 23.0
AC G 6.7
AC U 12.7
Thr
CC A 14.6
CC C 20.0
CC G 6.6
CC U 15.5
Pro
GC A 14.0
GC C 29.1
GC G 7.2
GC U 19.6
Ala
UC A 9.3
UC C 17.7
UC G 4.2
UC U 13.2
AGC 18.7
AGU 9.4
Ser
AGA 9.9
AGG 11.1
CG A 5.4
CG G 10.4
CG C 11.3
CG U 4.7
Arg
GG A 17.1
GG C 25.4
GG G 17.3
GG U 11.2
Gly
UGC 14.5
UGU 9.9
Cys
UGG 13.8
Trp
AUA 5.8
AUC 24.3
AUU 14.9
Ile
AUG 22.3
Met
CU C 19.9
CU U 10.7
CU A 6.2
CU G 42.5
UUA 5.3
UUG 11.0
Leu
UUC 22.6
UUU 15.8
Phe
GU A 5.9
GU C 16.3
GU G 30.9
GU U 10.4
Val
Key:
N Nondegenerate site
N Twofold degenerate site
N Fourfold degenerate site


A
C
G
T

The most common mutation mechanism

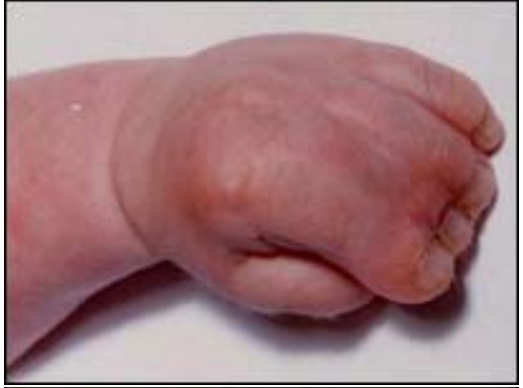


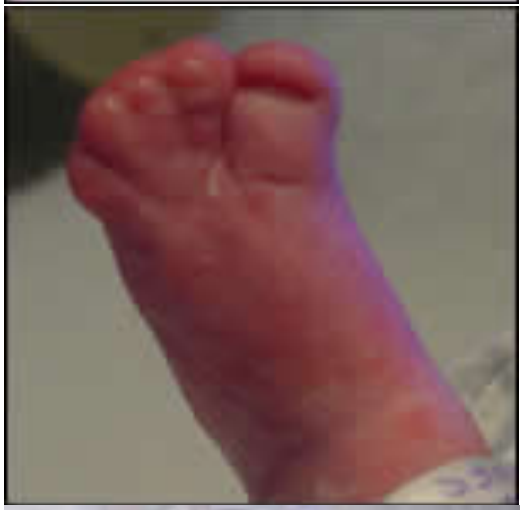
Cytosine 5-methylcytosine Thymine

CG ⇒ TG

missense point mutations

- Missense mutations are those where change determines the substitution of one aminoacid with another in the protein product
- Although these changes usually do not cause consequences in the functionality of the protein (polymorphisms, or variations), there are cases where even a slight alteration can have serious consequences



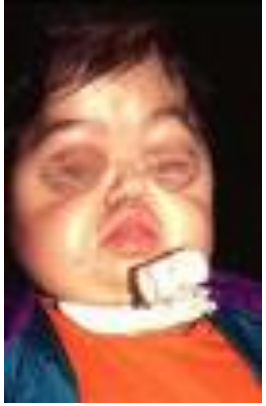


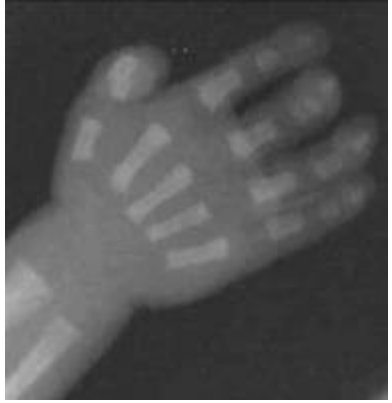
Acrocephalosyndactyly
Apert syndrome

- 1:65,000 newborns
- craniosynostosis (premature fusion of one or more craniac sutures), acrocephaly (craniac vault with a conic shape)
- endocranic hypertension
- mental retardation
- hypoplasia of the central part of the face
- syndactyly of fingers (hands) and toes (feet)
- deafness and optic atrophy

Acrocephalosyndactyly
Apert syndrome

- All patients carry the same Apert mutation (Cys755Gly) in the human fibroblast growth factor receptor 2 (FGFR2)
- Among its multiple functions, FGFR2 protein signals immature cells to become bone cells during embryonic development. The mutation causes prolonged signaling, which can promote the premature fusion of bones in the skull, hands, and feet
- The mutation is in heterozygosis
- ***de novo***
- chromosome 10q26
- This syndrome is allelic with the Pfeiffer and Crouzon syndromes





Pfeiffer syndrome

- 1:100,000 newborns
- characterised by an association of craniosynostosis, wide thumbs bend apart from the other fingers, and partial syndactyly of hands and feet
- Majority of patients carry the Pfeiffer mutation (Cys342Arg) in the human fibroblast growth factor receptor 2 gene (FGFR2)
- Some others carry the Pro252Arg mutation in FGFR1
- The mutation is in heterozygosis
- ***de novo***
- chromosome 10q26

craniofacial dysostosis Crouzon syndrome

- 1:62,000 newborns
- The premature closure of sagyttal and coronal skull sutures causes typical dysmorphic features, including pointed cranial vault, wide-set eyes (increasing orbital distance) and bulging eyes (abnormal protrusion of the eyeballs)
- Majority of patients carry the Crouzon mutation (Cys342Tyr) in the human fibroblast growth factor receptor 2 gene (FGFR2)
- The mutation is in heterozygosis
- ***de novo***
- crhomosome 10q26

The achondroplasia phenotype in man.

The photo depicts a family of 5 sisters and 2 brothers with pseudoachondroplasia.
This disease is caused by a dominant allele, called D, which interferes with the growth of bones during development.
The photo was taken at the family's arrival in Israel after the end of World War II

achondroplasia

- Dysmorphic dwarfism (1:35,000)
- Short limbs and disproportioned large head
- Prominent forehead and flattened nasal bridge
- Short stature, average adult height of 130 cm in males and 125 cm in females
- If both parents of a child have achondroplasia, and both parents pass on the mutant gene, then it is unlikely that the homozygous child will live past a few months of its life

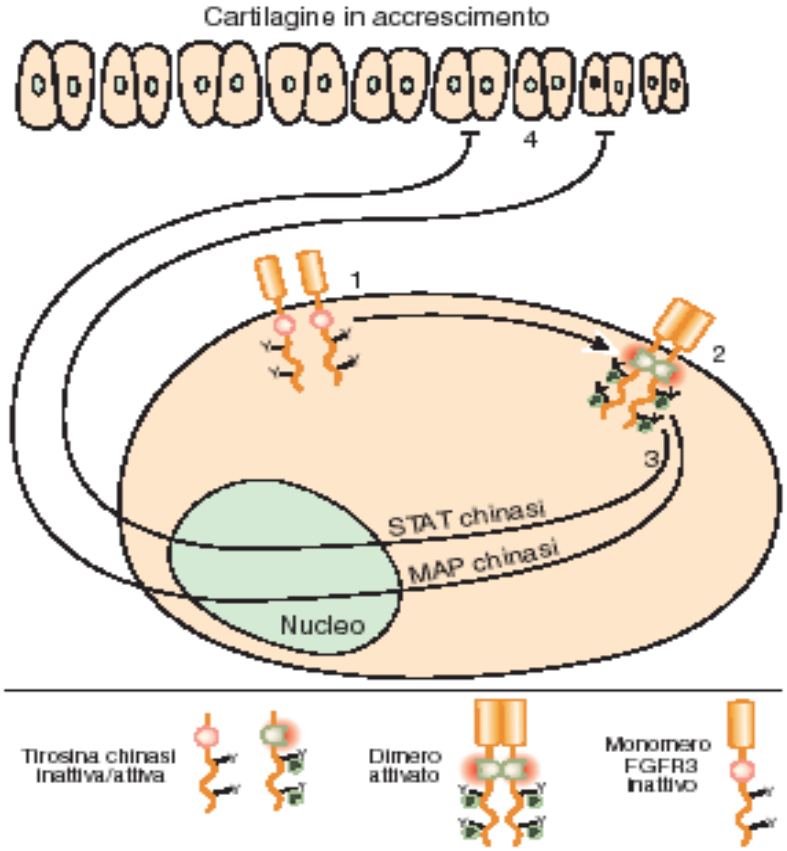
ACHONDROPLASIA

- Causative gene identified in 1994: **FGFR3**
- **Complete penetrance**
- The mutation in in heterozygosis
- Autosomal dominant
- Same recurrent mutation: **Gly380Arg** in the fibroblast growth factor receptor 3 gene (**FGFR3**) in chromosome 4p16.3
- More than 90% of the cases have a sporadic origin: **de novo mutation** from healthy parents
- These de novo mutations are of **paternal origin** and occur during spermatogenesis (it is theorized that oogenesis has some regulatory mechanism that prevents the mutation occurring in females)

achondroplasia

- The mutation confers an increased function (**hypermorphic allele**) to FGFR3, a membrane tyrosine kinase
- The receptor dimerizes and autophosphorylates even in the absence of a ligand, transducing a signal with the function of slowing down chondrocyte proliferation and thus bone growth
- Knock out mice for FGF3R have long bones and elongated vertebrae

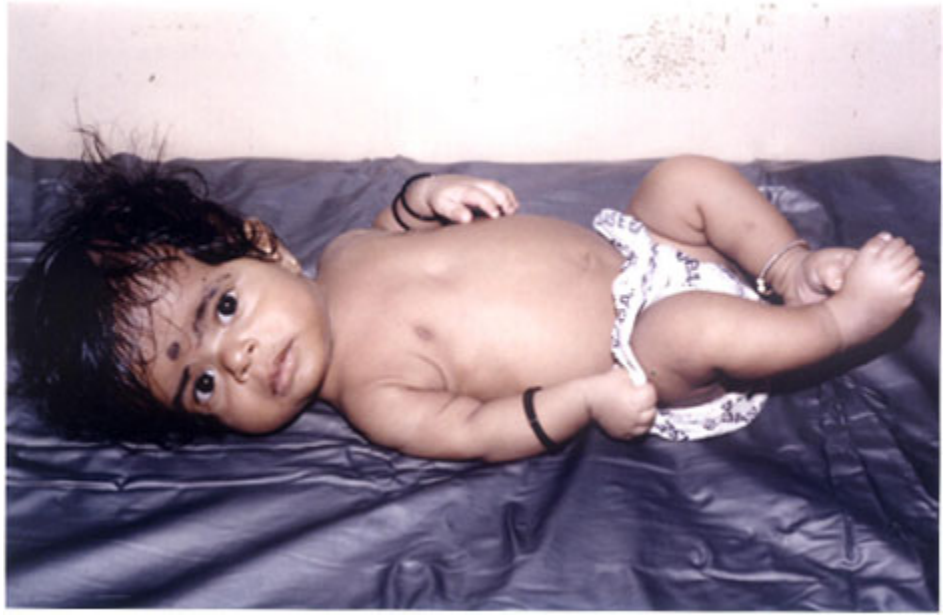
♦ **FIGURA 36.7**
Il nucleotide G 1138 (in verde) nella sequenza codificante del gene FGFR3 è mutato nei soggetti acondroplasici: si possono trovare sia transizioni G>A, sia transversioni G>C; entrambe le situazioni originano una sostituzione glicina-arginina.

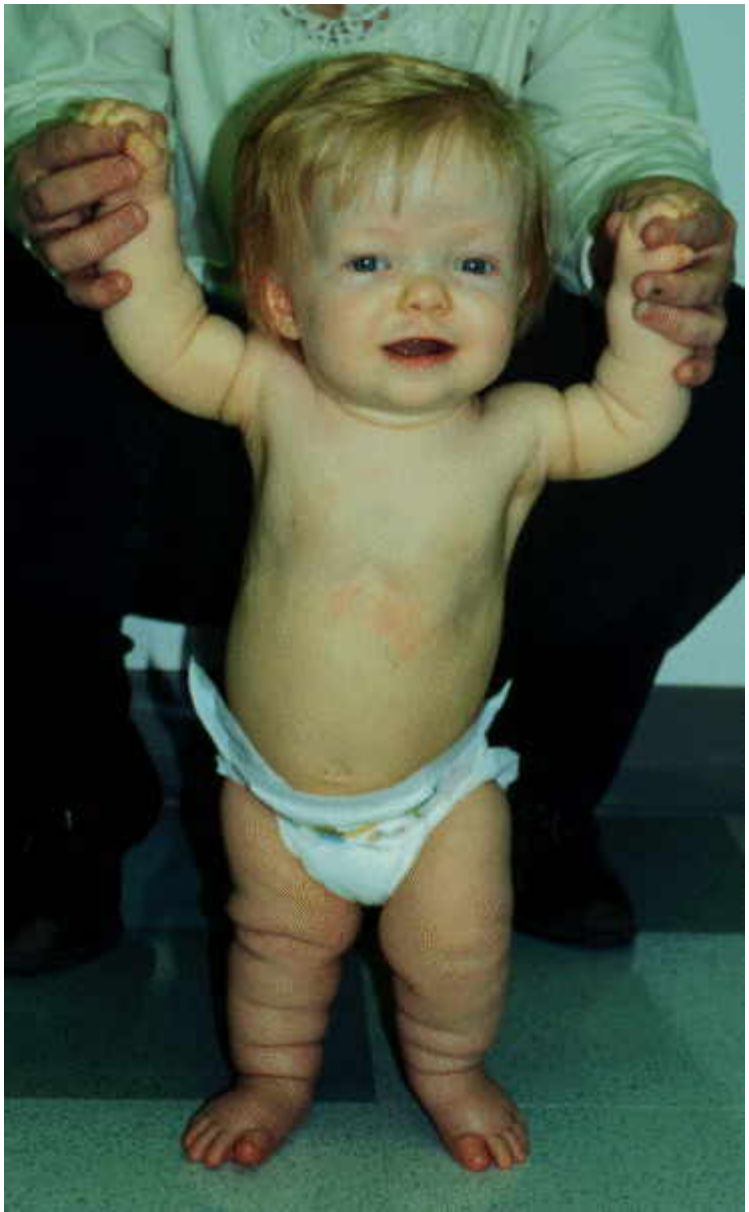


♦ **FIGURA 36.8**
Rappresentazione schematica dell'attivazione di FGFR3. L'interazione con il ligando (FGF) induce la dimerizzazione (1), che a sua volta attiva l'attività tirosina-chinasi del recettore (2). I due residui di tirosina fosforilati nel recettore attivato fungono da richiamo per molecole di segnalazione (3) (STAT e MAP chinasi) che esercitano un ruolo inibitorio sulla proliferazione dei condrociti nella cartilagine di accrescimento (4).

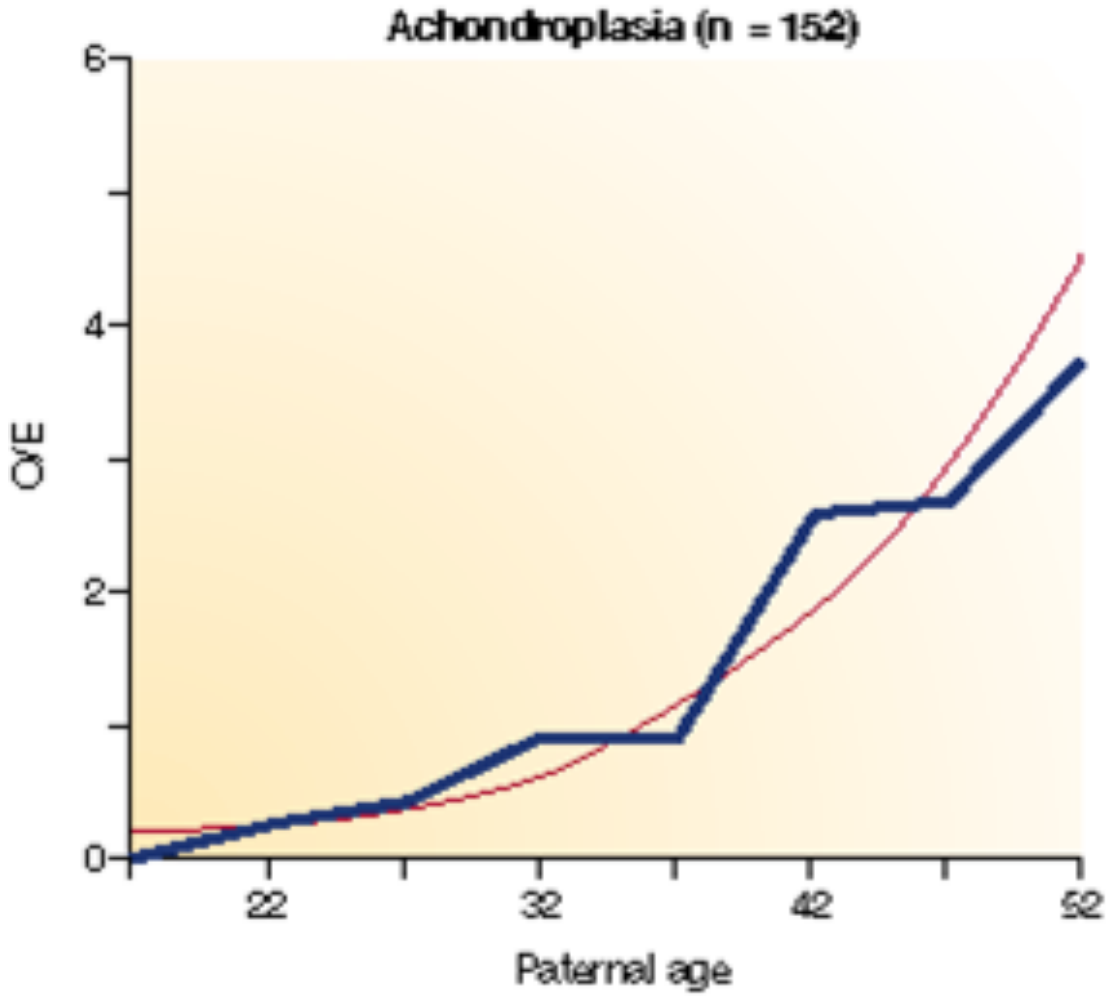
FGF Receptors

- FGF
  - family with 9 members currently known
  - mitogenesis/differentiation/angiogenesis
- FGF receptors
  - family with 4 members
  - membrane-spanning tyrosine kinases
  - three Ig-like domains





relative frequency of *de novo* mutations causing achondroplasia in relation to paternal age



Number of divisions in the male germline

Age	Chromosome replications
15	35
20	150
30	380
40	610
50	840

hypochondroplasia

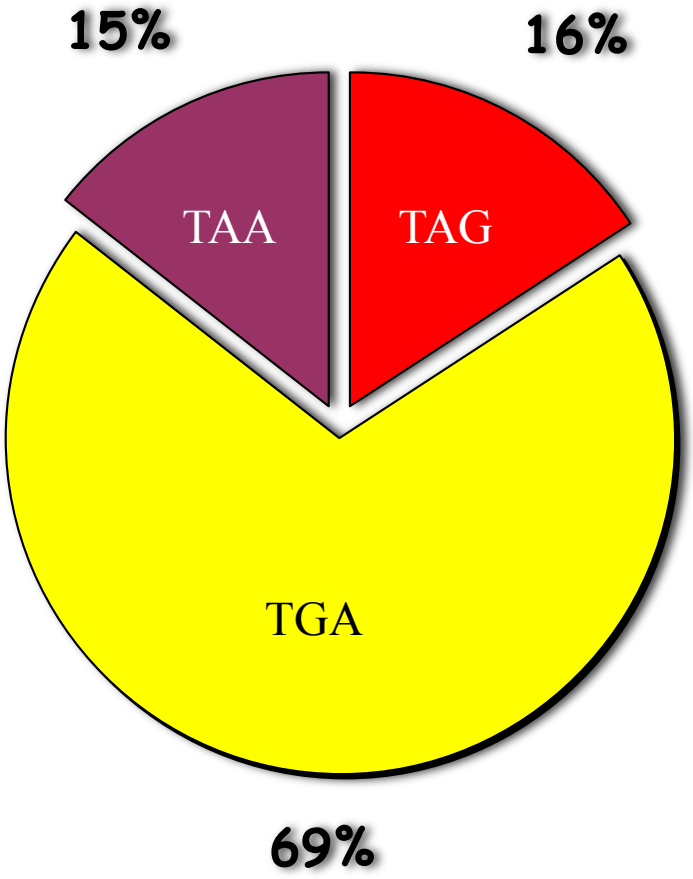
•Hypochondroplasia has characteristics similar to achondroplasia, but with a lower severity and less craniofacial involvement. The height can be in the normal range and the disease is often not diagnosed.

•Hypochondroplasia is less homogenous: about 70% of cases is due to a Asn540Lys substitution in FGFR3 gene, while in the remaining 30% of cases the mutation is not known.

nonsense point mutations

- Nonsense mutation is a change causing the creation of a stop codon, which blocks protein synthesis prematurely.
- In this case, the functionality of the protein will depend on the location of the stop.

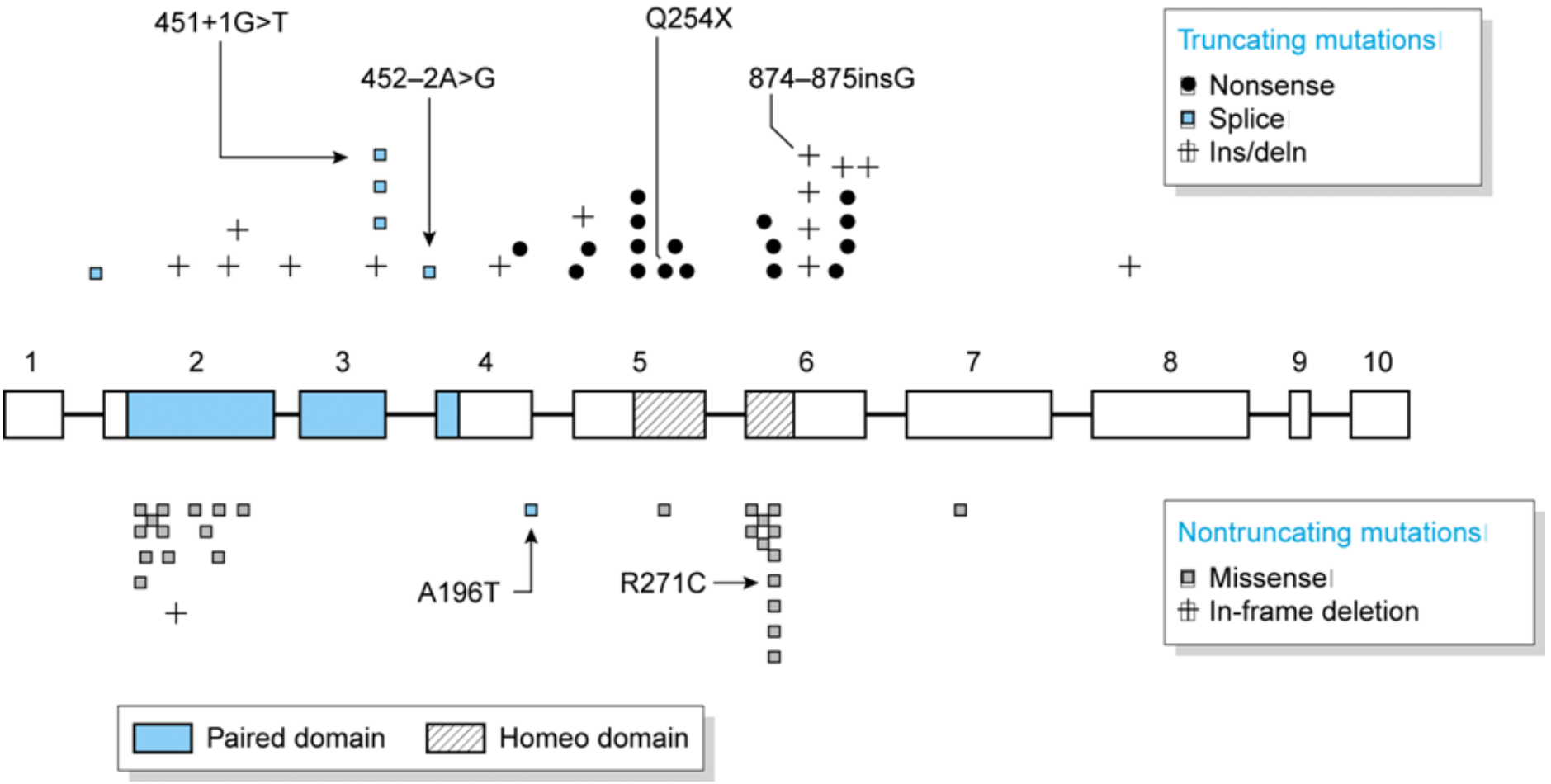
Different types of nonsense mutations in human genes

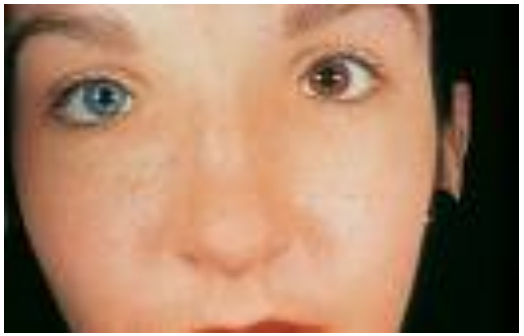


frame-shift mutations

- frame-shift mutations or slippery of the codon reading frame consist in the insertion or deletion (indels) of a number of nucleotides that is not divisible by 3 (1, 2, 4, 5, 7, 8, 10, ecc.) with subsequent change in the reading frame of mRNA.
- This mutation results in a completely different protein translation downstream from the mutation.
- The earlier in the sequence the mutation occurs, the more altered the protein.

Heterozygous PAX3 mutations
Waardenburg syndrome





Heterozygous PAX3 mutations Waardenburg syndrome

- Bilateral deafness (varying degrees, from moderate to profound)
- Pigmentation anomalies, both of hair (partial albinism, usually piebaldism) and skin
- Defects in structures arising from the neural crest migration
- Appearance of a wide-set eyes also known as *telechantus*
- Eyes of two different colors (heterochromia), often one brown and one blue
- 1:50,000 newborns

Waardenburg syndrome (WS) is an autosomal dominant hereditary disease, clinically and genetically heterogeneous, with variable penetrance and expressivity.

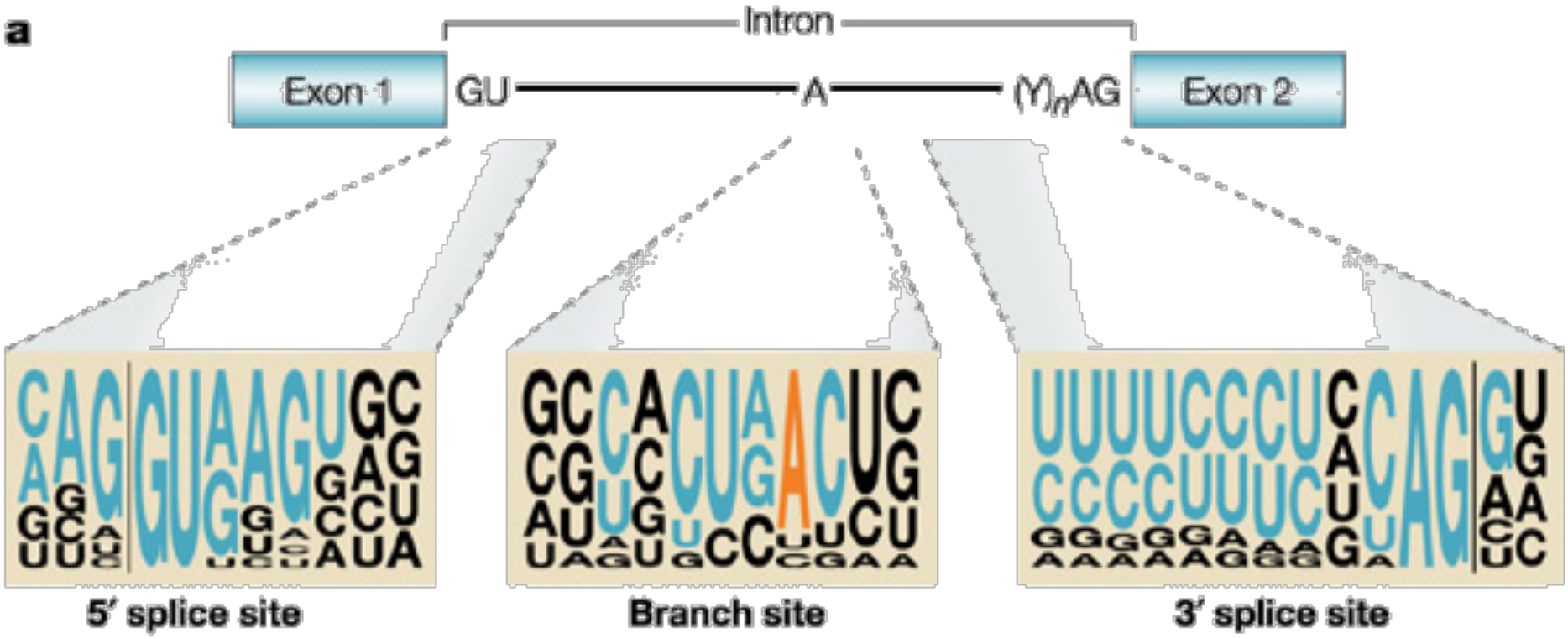
The syndrome is caused by mutations in genes (as PAX3) that control melanocytic embryogenesis and leading to a defect in the migration and differentiation of neural crest cells.

It is characterized by congenital sensorineural hearing loss of variable degree, and by pigmentary disturbances) affecting the eyes, skin, hair and cochlear stria vascularis) caused by the absence of melanocutes.

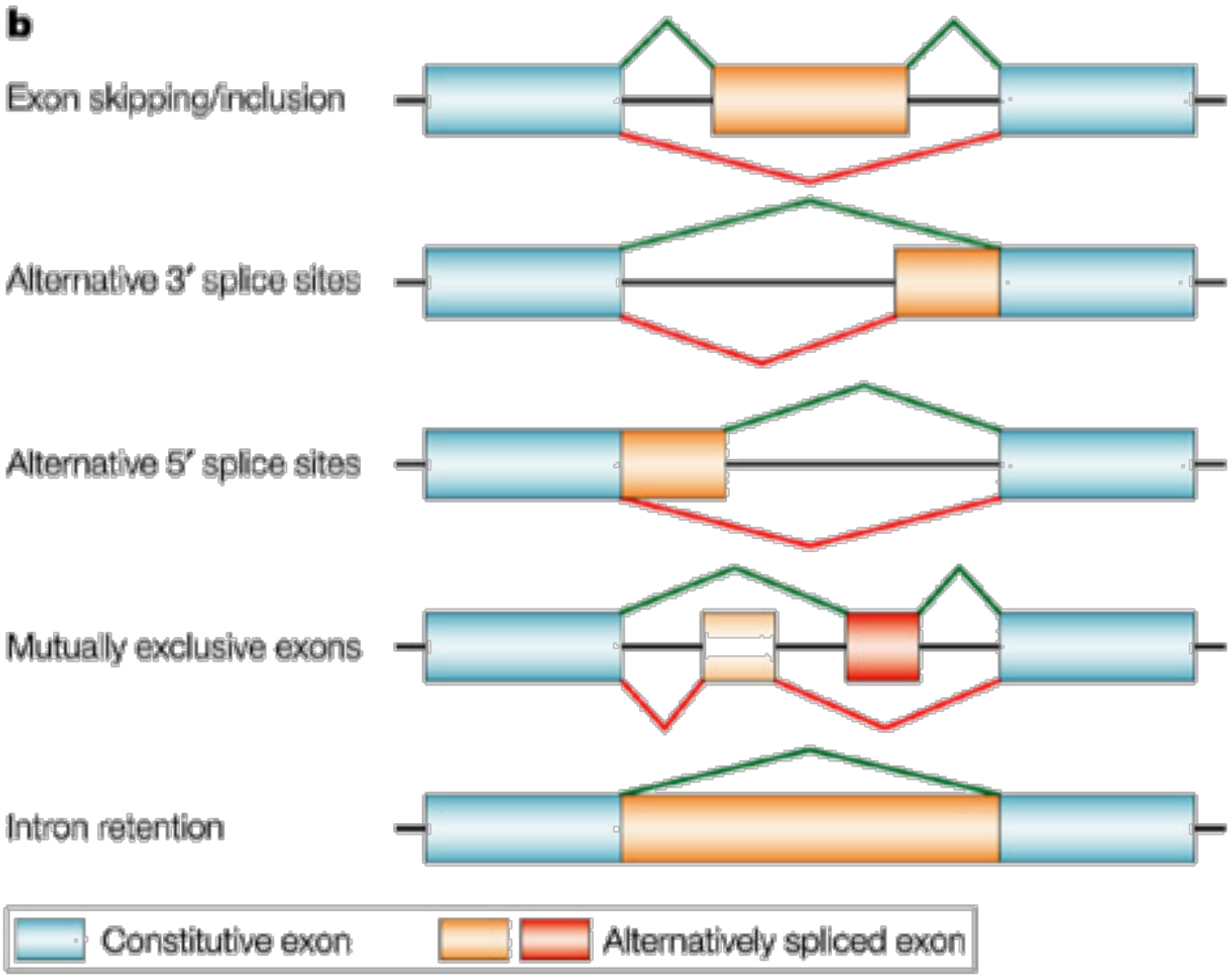
Heterozygous PAX3 mutations Waardenburg syndrome

• From a pathogenetic point of view WS is caused by a development anomaly of the neural crest, which is derived from ectodermal tissue placed at the margins of the neural tube in the early stages of embryonic development.
• the neural crest migrates slowly giving rise to different tissues: frontal bone, limb muscles, enteric ganglia, uveal melanocytes, etc.
• melanocytes are indispensable in the stria vascularis for the normal function of the cochlea. Both the hearing and pigmentation disorders are due to an error of successful melanocyte migration.

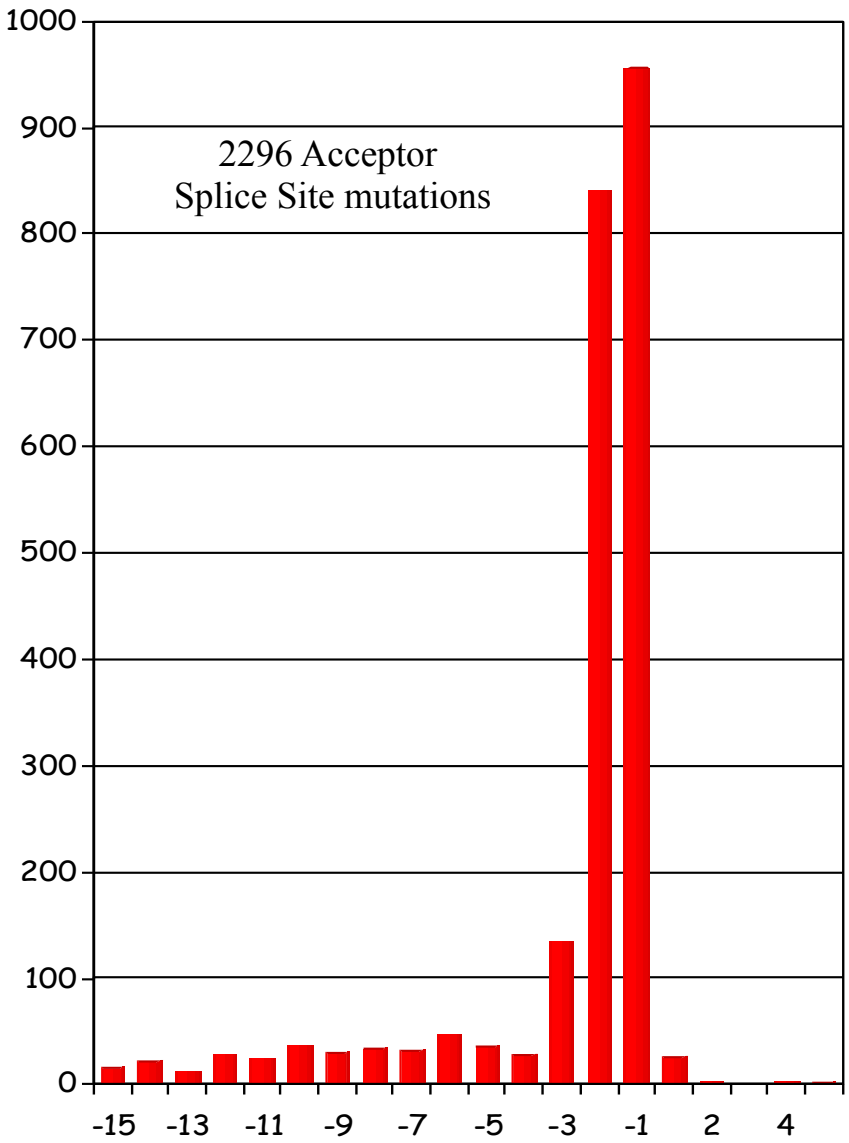
Classic splicing motifs



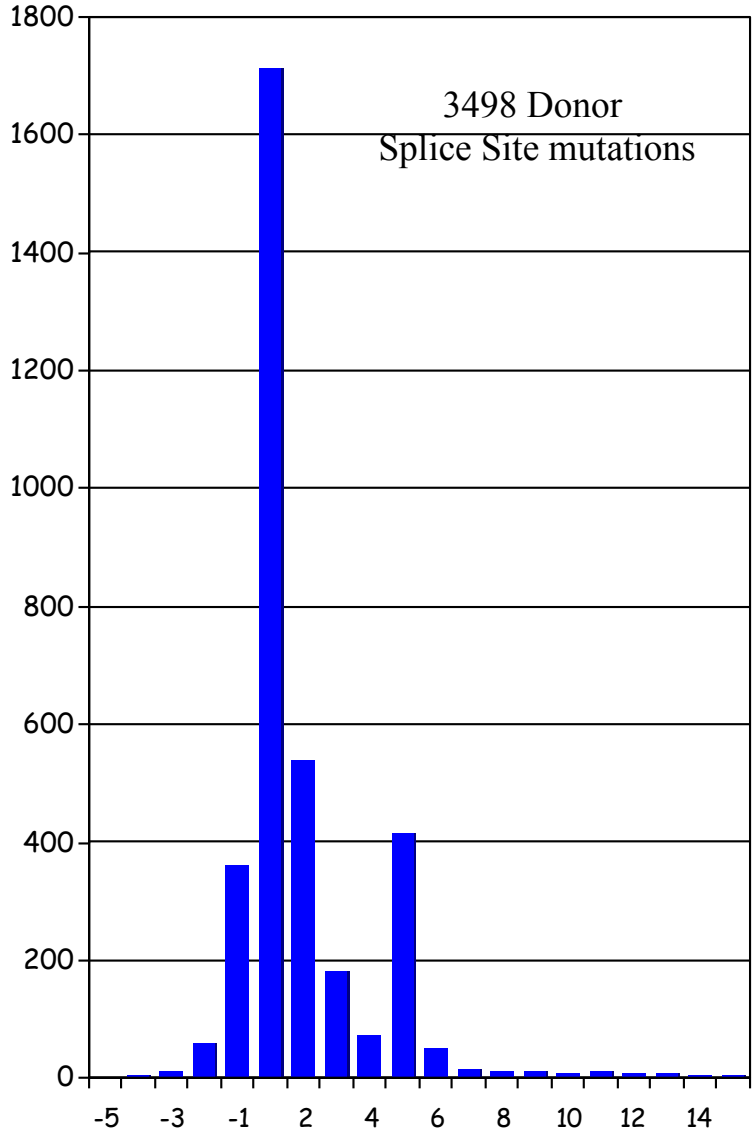
Mutations at splice sites



HGMD Mutations in Intron splice sites (5Jan07)



Nucleotide number in the acceptor site



Nucleotide number in the donor site

Hutchinson-Gilford progeria

- Premature aging
- Short stature, wrinkled skin
- baldness, absence of adipose tissue (subcutaneous fat)
- Atherosclerosis and heart attack

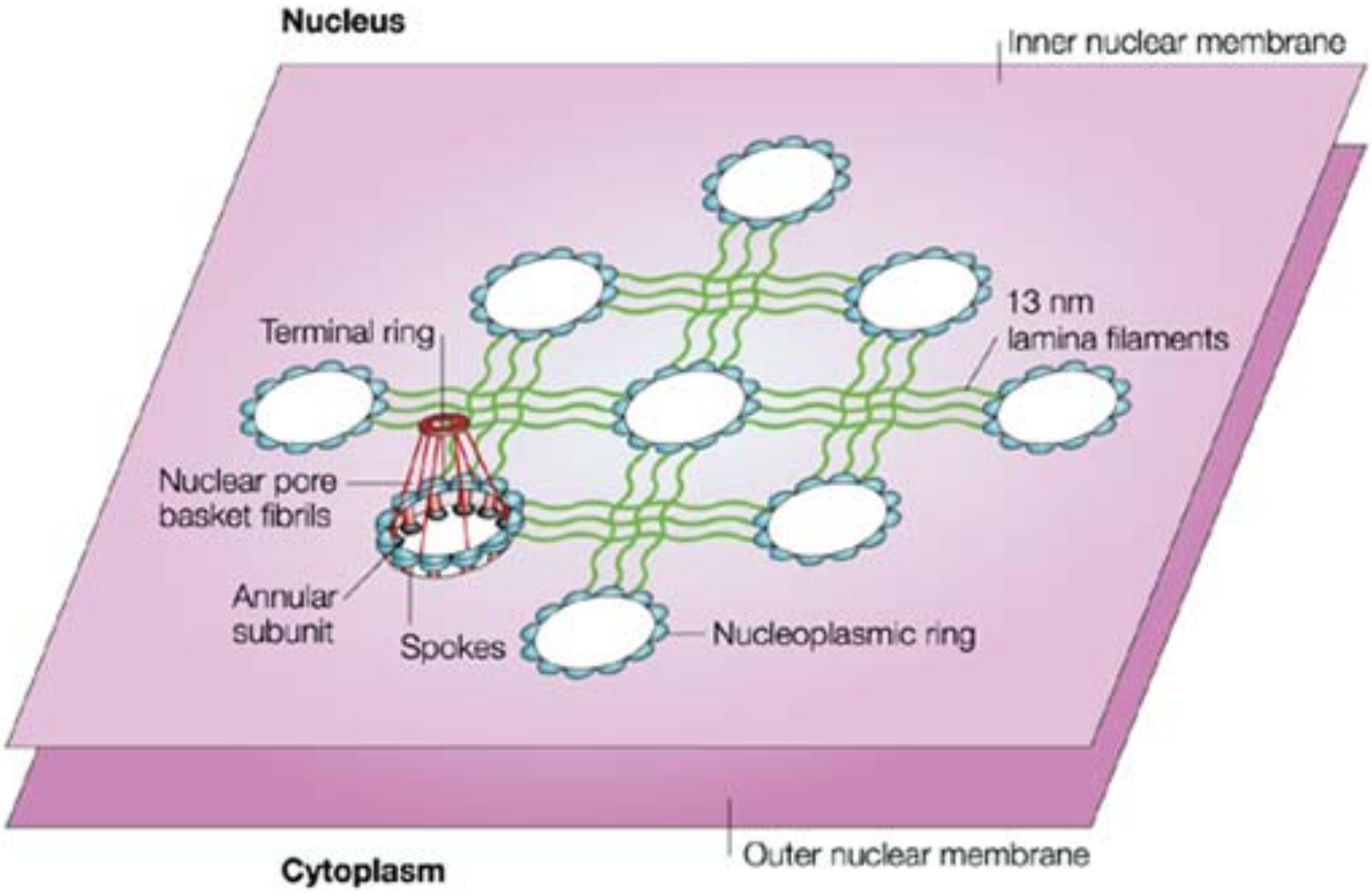
Hutchinson-Gilford progeria

• affected children appear normal until six months or one year old, but then begin to develop symptoms normally associated with aging – wrinkles on the skin, hair loss, brittle bones and atherosclerosis – and die around 13 years old.

• rare disease, 1:8.000.000 newborns.

Hutchinson-Gilford progeria

- Mutation in lamin A gene
- The mutation is in heterozygosis
- *de novo*
- chromosome 1q23
- The mutation G608G doesn't change the aminoacid glycine, but introduces a splice donor site whose consequence is a 50 aminoacid protein loss


Nucleus
Inner nuclear membrane
Terminal ring
13 nm
lamina filaments
Nuclear pore
basket fibrils
Annular
subunit
Spokes
Nucleoplasmic ring
Cytoplasm
Outer nuclear membrane

Hutchinson-Gilford progeria

• Lamin A, before acting on the nucleus, must undergo some small structural changes, which are essential to make it functional. One of these adjustments is the union of the protein with a farnesyl molecule.

• In the case of wild-type lamin A, the link is temporary and farnesyl is then removed; in the case of the mutated lamin A, farnesyl remains tied to the protein.

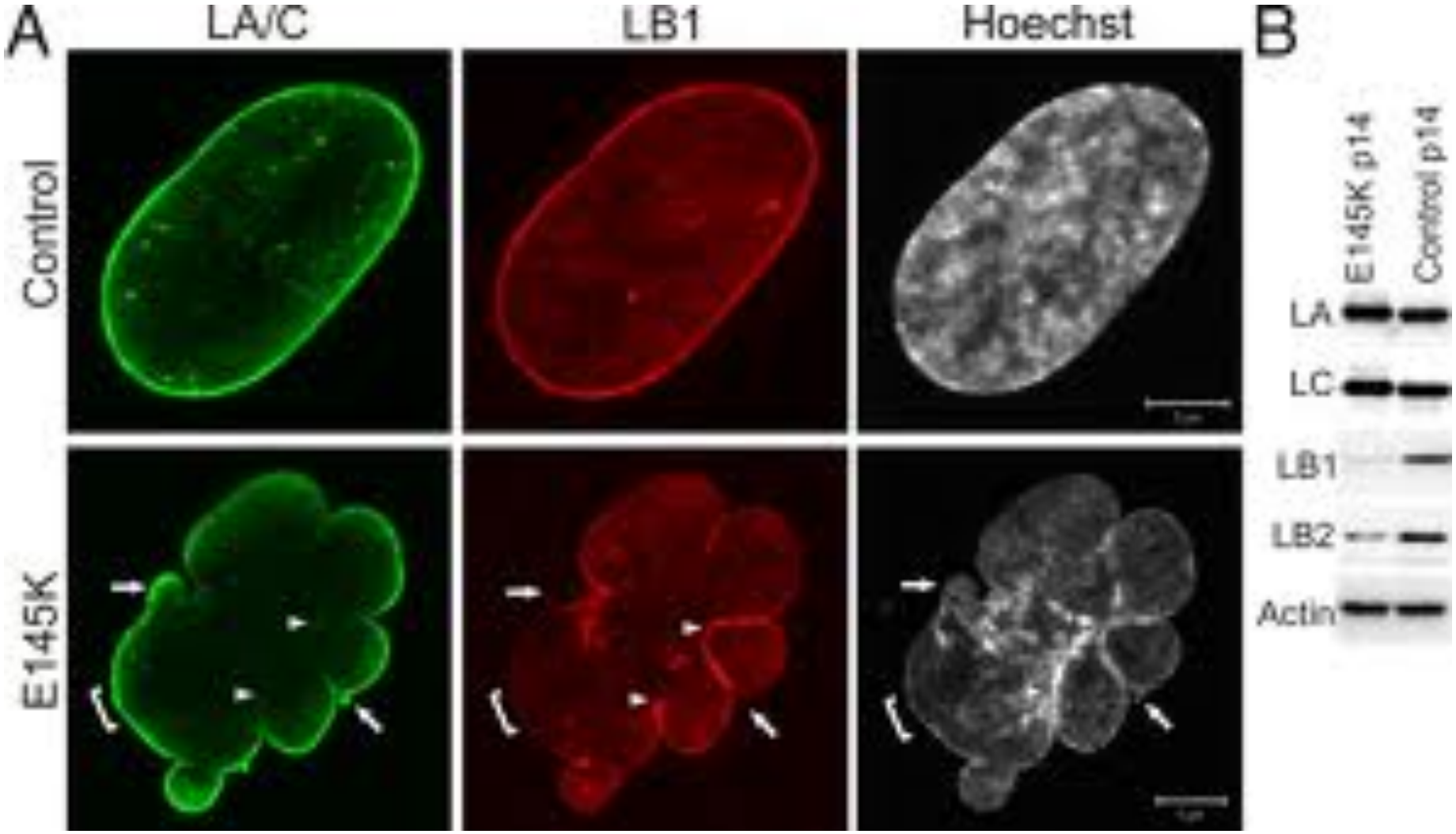
• If they remain linked, lamin A and farnesyl form an abnormal protein called **progerin**, because it determines progeria.

Hutchinson-Gilford progeria

• There is no known cure. But some studies show that a class of drugs known as farnesyl transferase inhibitors can reverse an abnormality present in cellular models of the disease.

• Instead of having round nuclei, these cells have multiple ‘lobes’ and may even look like a pile of grains or bubbles. In the laboratory, however, treatment with a farnesyl transferase inhibitor returned the cells to look normal.

Hutchinson-Gilford progeria



Hutchinson-Gilford progeria

• The drug (Lonafarnib) blocks the first step of processing the defective protein that causes the syndrome. But no word yet on whether to return to their normal nucleus may be sufficient to reverse or slow down the disease process.

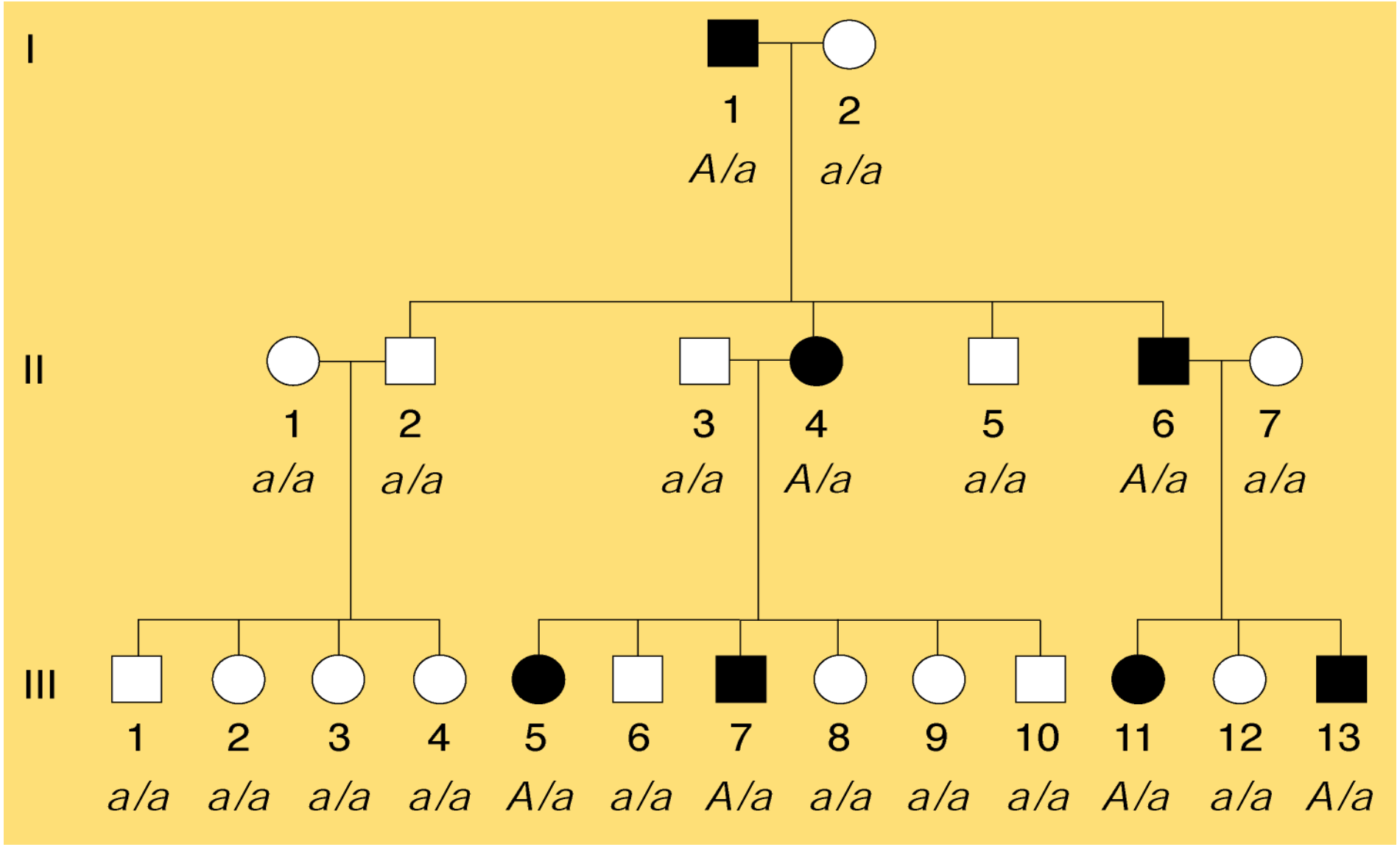
• Human trial phase II with Lonafarnib has begun and we are awaiting for further developments.

Other autosomic diseases…..

dominant

Pedigree of a **dominant** phenotype determined by a dominant allele (A).

All genotypes have been identified in this pedigree.



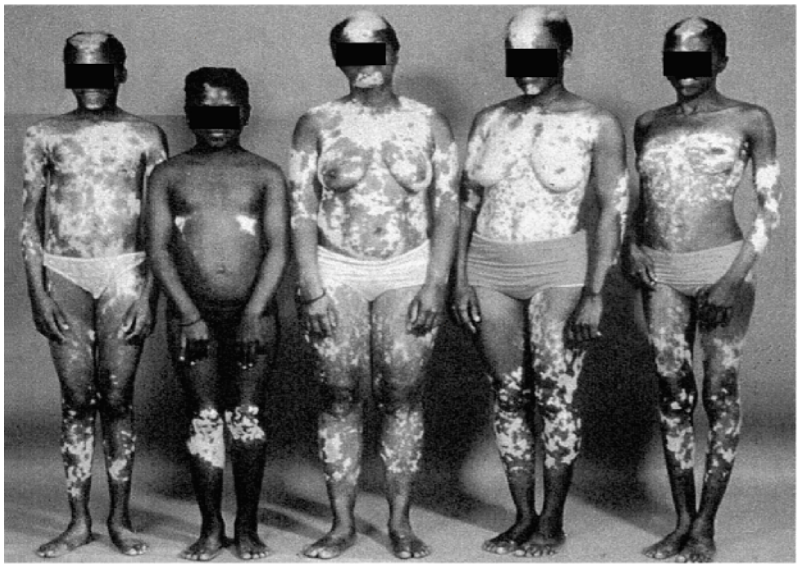
message

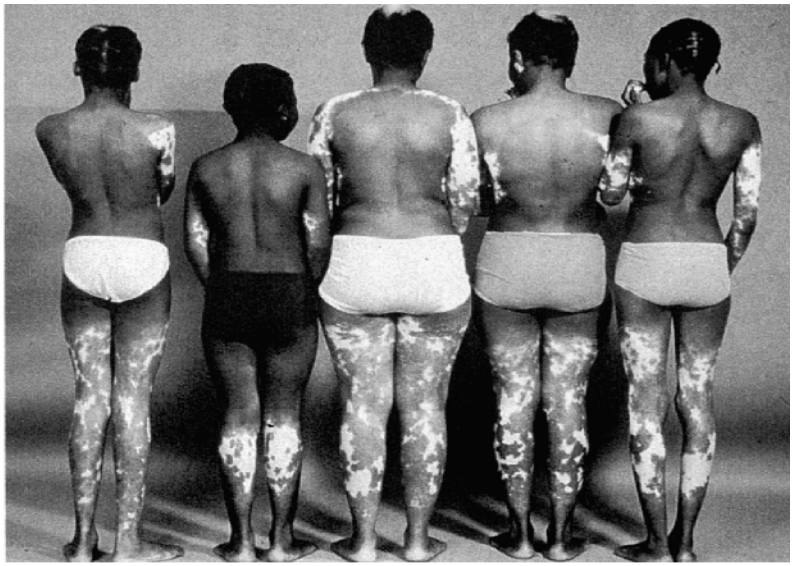
- Family trees of autosomal dominant diseases show male and female sufferers in each generation; they also show that affected men and women in equal number transmit the disease to sons and daughters.

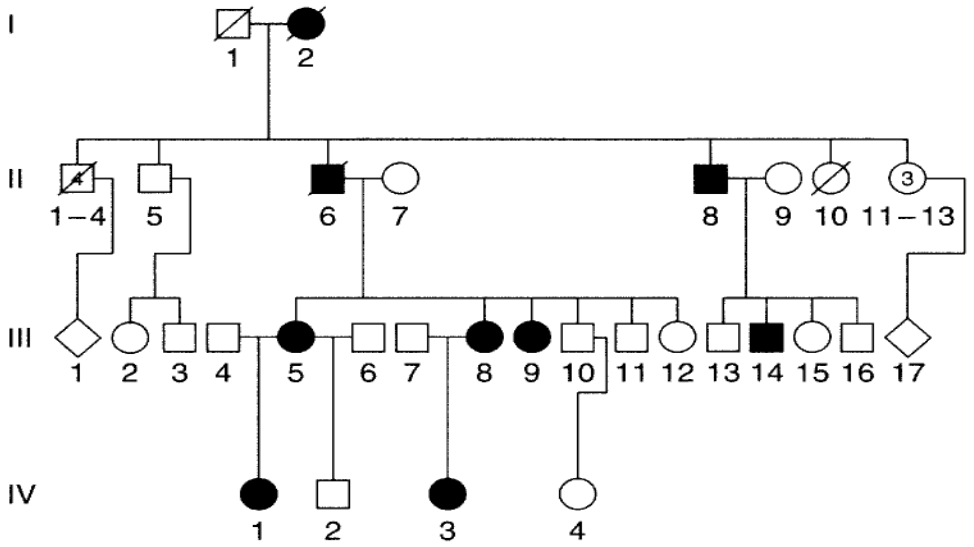
Piebaldism, a rare dominant phenotype in humans.

Although this phenotype recurs sporadically in all human races, it is particularly evident in those with dark skin.

(a) the photo shows front and back patients shown in family tree (b) as IV-1, IV-3, III-5, III-8 e III-9. Note the variability of phenotypic expression of the disease in the different family members.







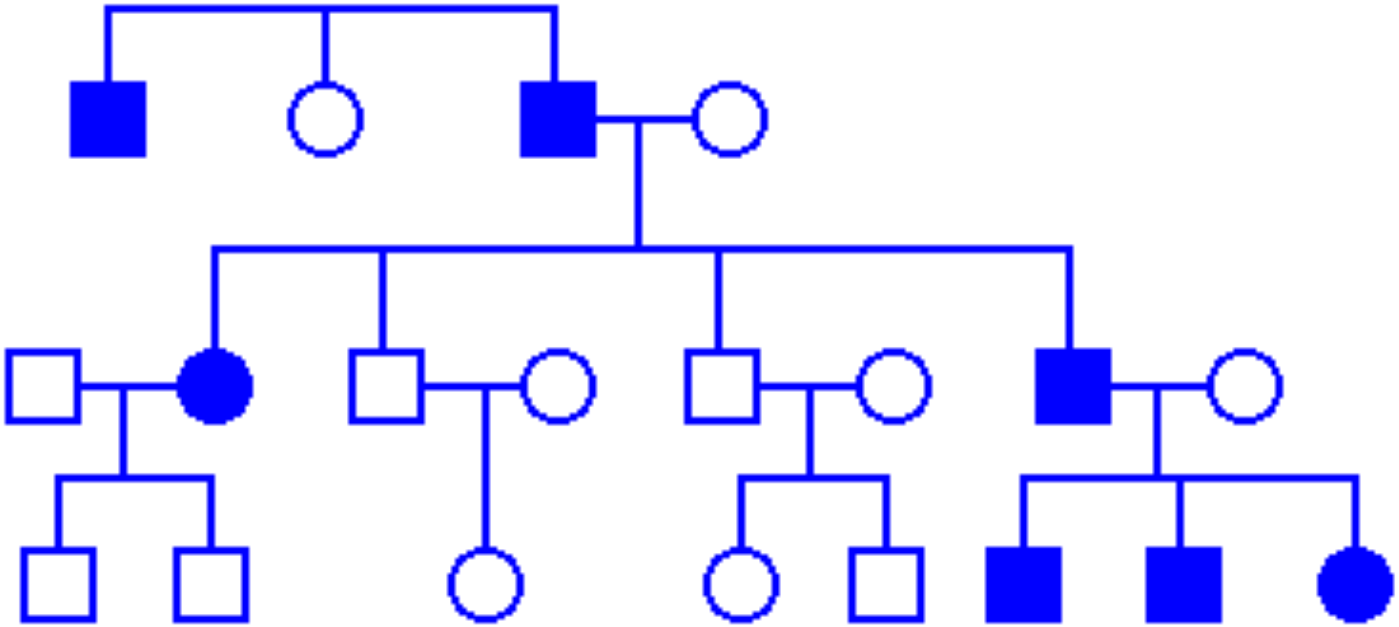
Piebaldism

- It is assumed that the ‘mottled’ drawing of the skin is caused by a dominant allele that interferes with the migration of melanocytes from the dorsal to the ventral surface during development. Common characteristics include a congenital white forelock, scattered normal pigmented and hypopigmented macules and a triangular shaped depigmented patch on the forehead.

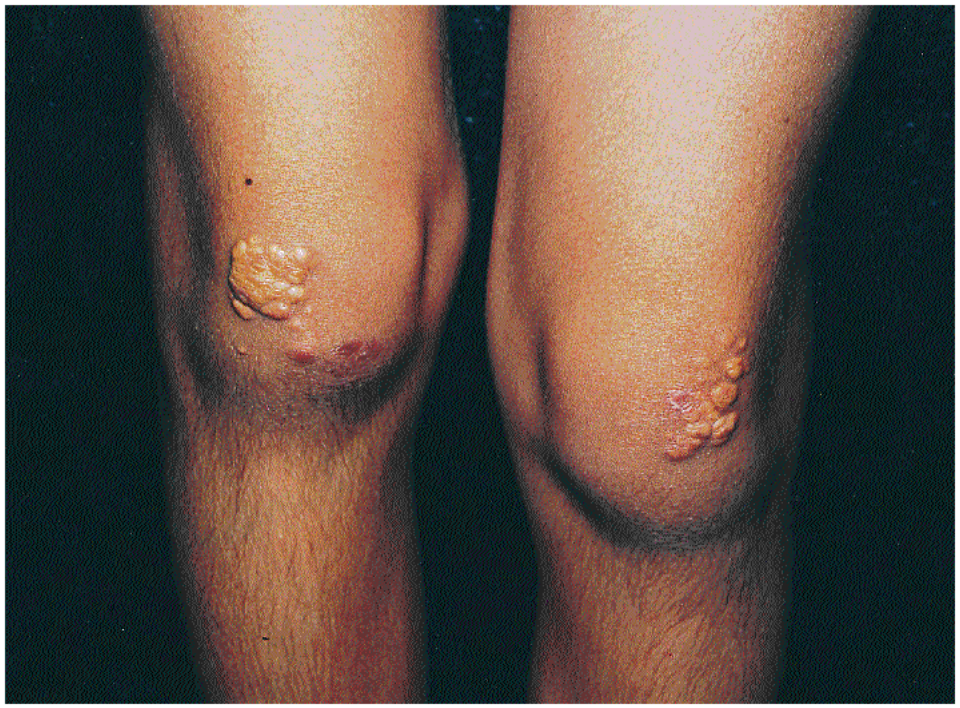
- Piebaldism is different from albinism. The cells of the white patches have the genetic potential to produce melanin, but not being melanocytes they are not ontogenetically scheduled to do so. While in true albinism cells do not have the ability to produce melanin.

- Piebaldism can be caused by mutations in c-kit, a protooncogene.

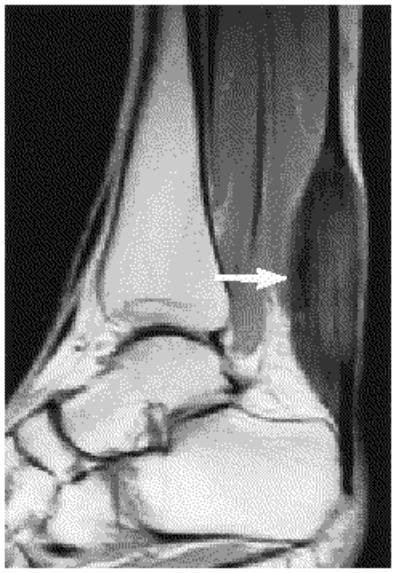
Familial hypercholesterolemia

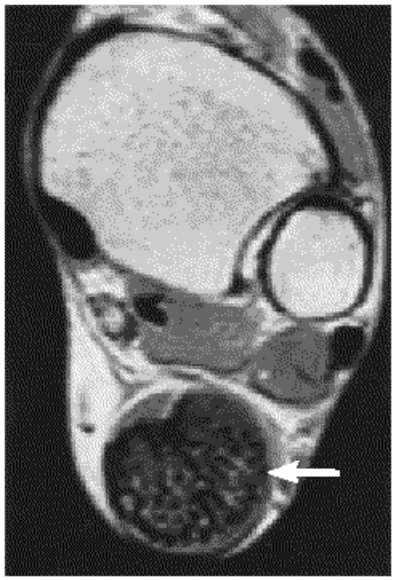


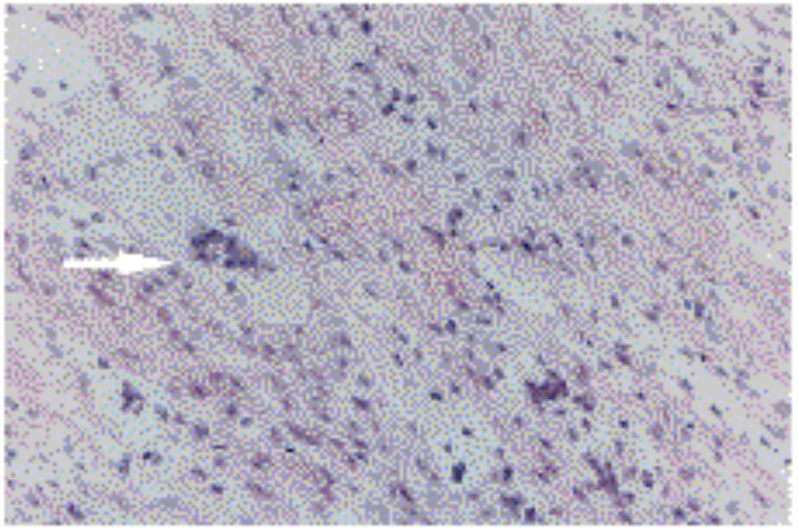
Familial Hypercholesterolemia (FHC)



A typical symptom is the appearance of xanthomas (after 30-40 years in heterozygotes and within the first four years in homozygotes), accumulation of fat tha can be formed at the level of tendons in the heterozygotes (tendon xanthomas) and the skin of the elbows and knees in the homozygotes (cutaneous xanthomas).

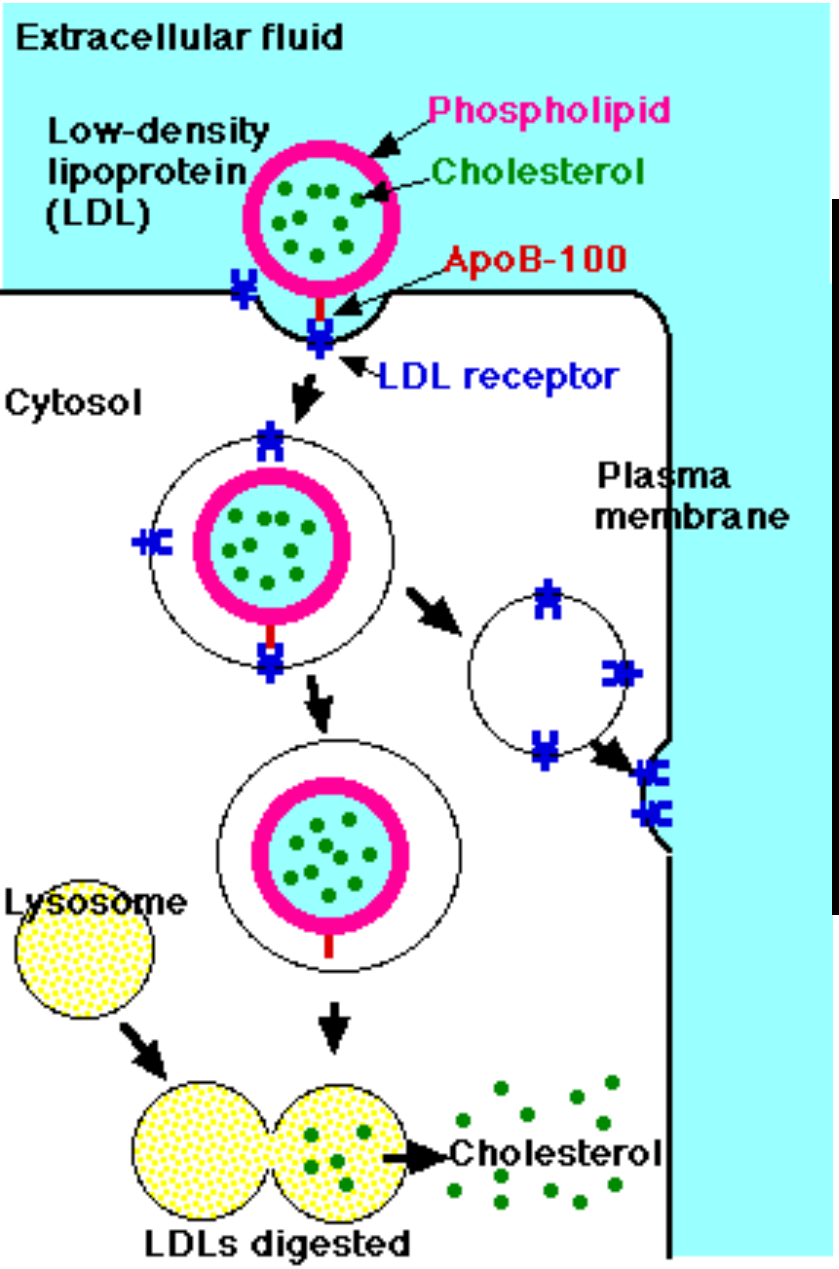


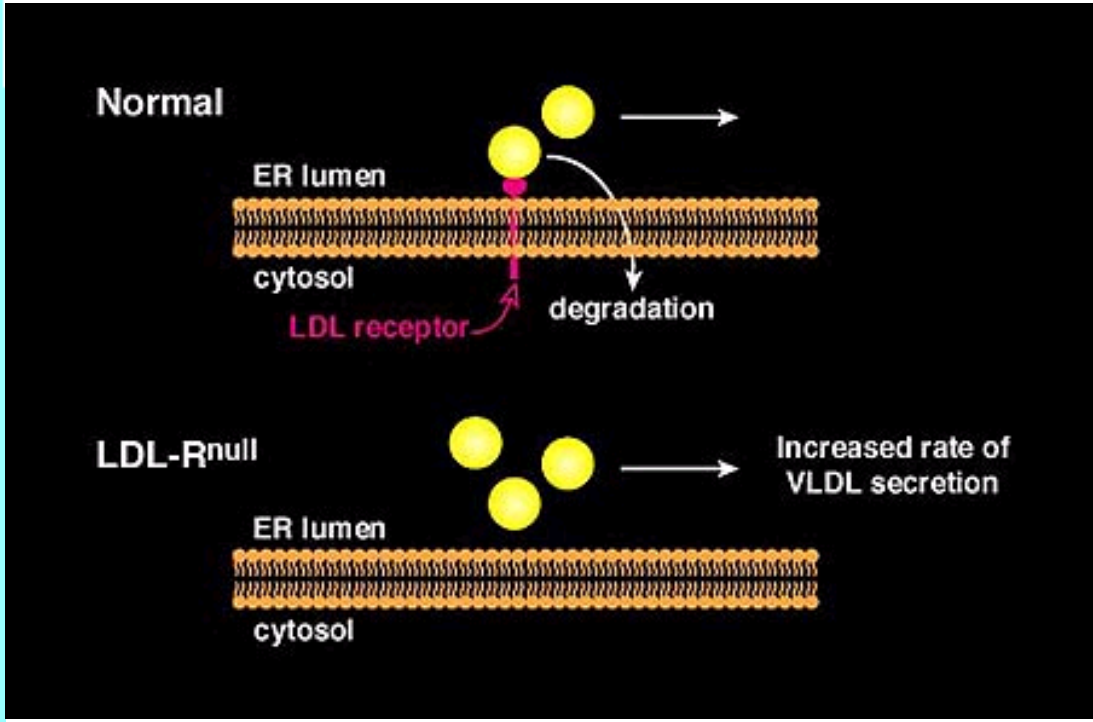




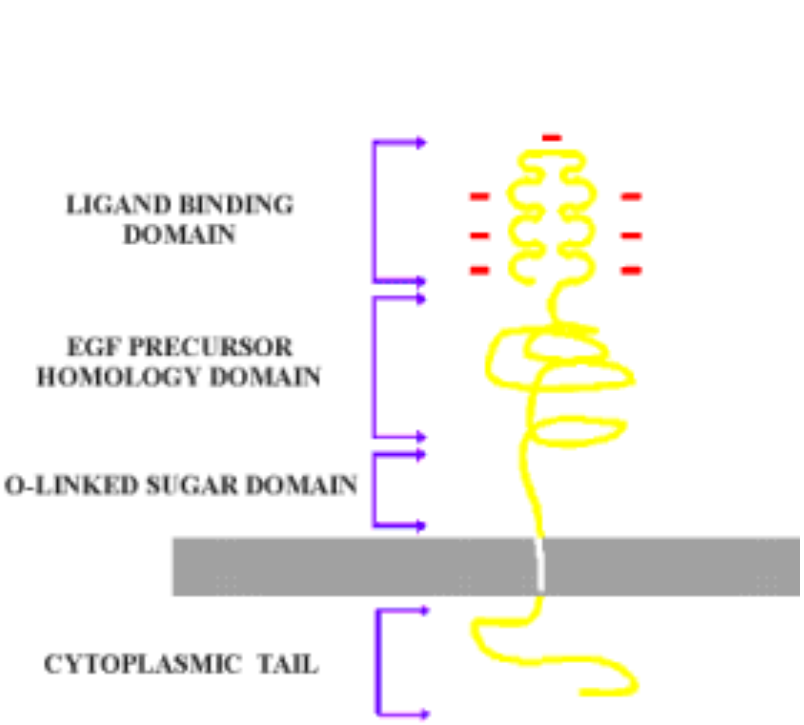
Familial hypercholesterolemia

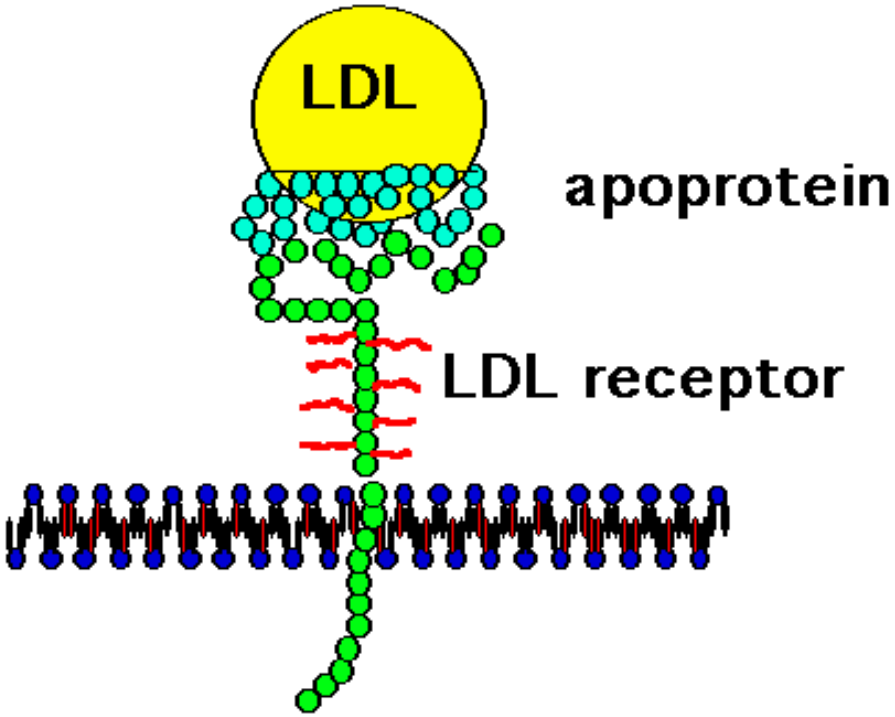
- Condition characterized by elevated levels of LDL-cholesterol in the blood (250-450 mg/dl in heterozygotes)
- At risk subjects for coronary heart disease, heart attack, stroke
- Problems occur usuallt after reproductive age
- Molecular defect resides in dominant-negative effect mutations in the gene coding for the LDL receptor
- Loss-of-function mutations, non functioning receptor
- In most populations the frequency is 1:500 (the most common mendelian disorder in humans)
- Extremely rare homozygotes (1:1.000.000), severe clinical symptoms, often do not survive until reproductive age

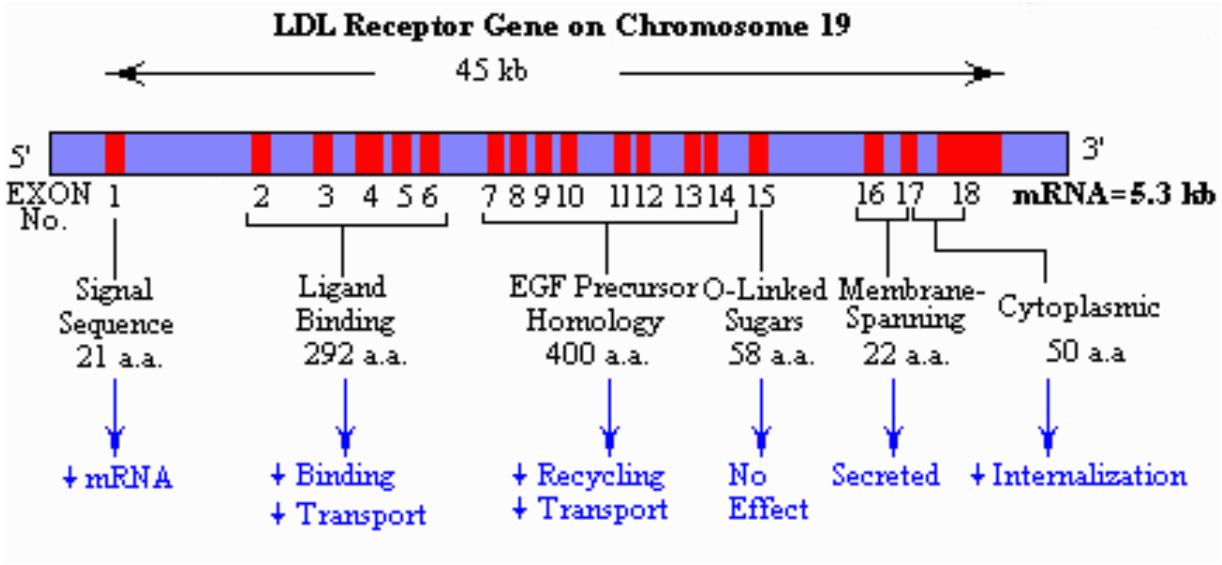

Extracellular fluid
Low-density lipoprotein (LDL)
Phospholipid
Cholesterol
ApoB-100
LDL receptor
Cytosol
Plasma membrane
Lysosome
Cholesterol
LDLs digested


Normal
ER lumen
cytosol
LDL receptor
degradation
LDL-Rnull
Increased rate of VLDL secretion
ER lumen
cytosol

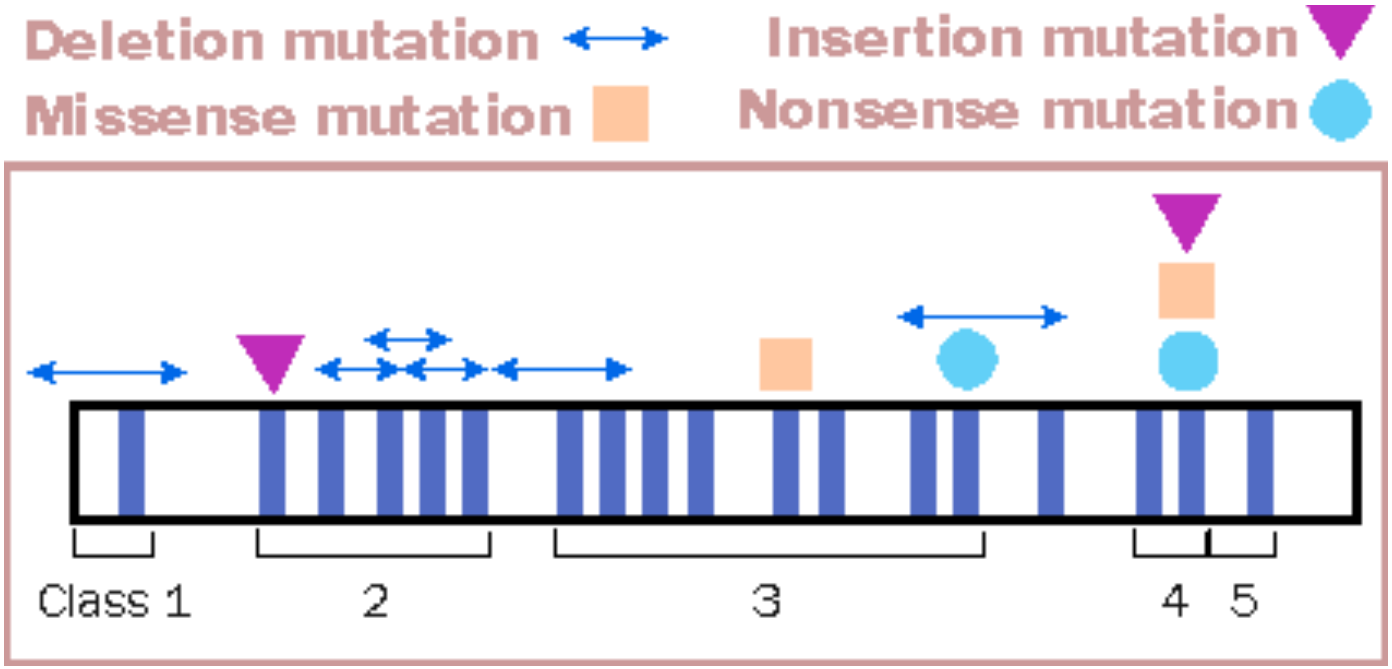
LDL RECEPTOR







Familial hypercholesterolemia

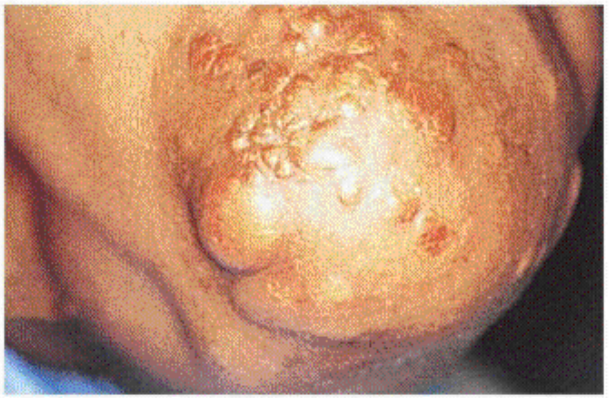


Therapeutic possibilities

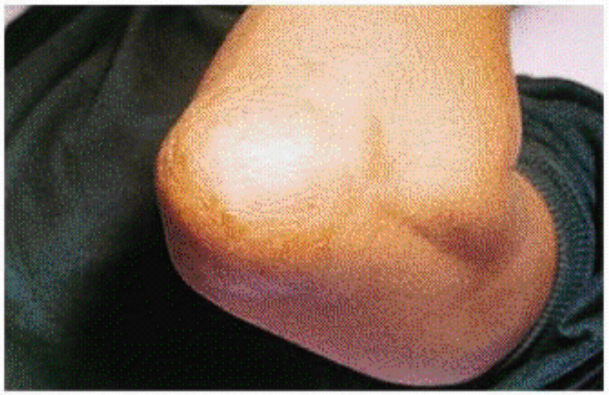
● Heterozygous patients are recommended a dietary intervention, in both children and adults, leading to lowering cholesterol. The only dietary interventions is however not enough.

● Adult heterozygous patients are treated with drugs that inhibit the production of cholesterol. These drugs are called statins. In some cases, other drugs can be used together with statins (resins) which have the effect to sequester bile acids (which derive from cholesterol), which are then excreted with feces and are not ‘recycled’ from the body.

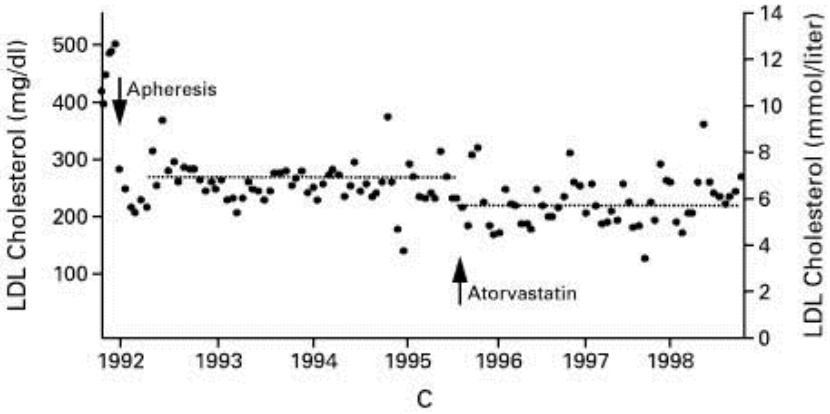
● In homozygotes drug therapy based on statins and resins generally fails. Therapeutic intervention clinically available for these patients is a treatment called LDL therapeutic plasmaphereis (or LDL apheresis) which consists in purifying the blood form these lipoproteins in extracorporeal circulation.



A



B


LDL Cholesterol (mg/dl)
500
400
300
200
100
Apheresis
Atorvastatin
1992
1993
1994
1995
1996
1997
1998
LDL Cholesterol (mmol/liter)
14
12
10
8
6
4
2
0

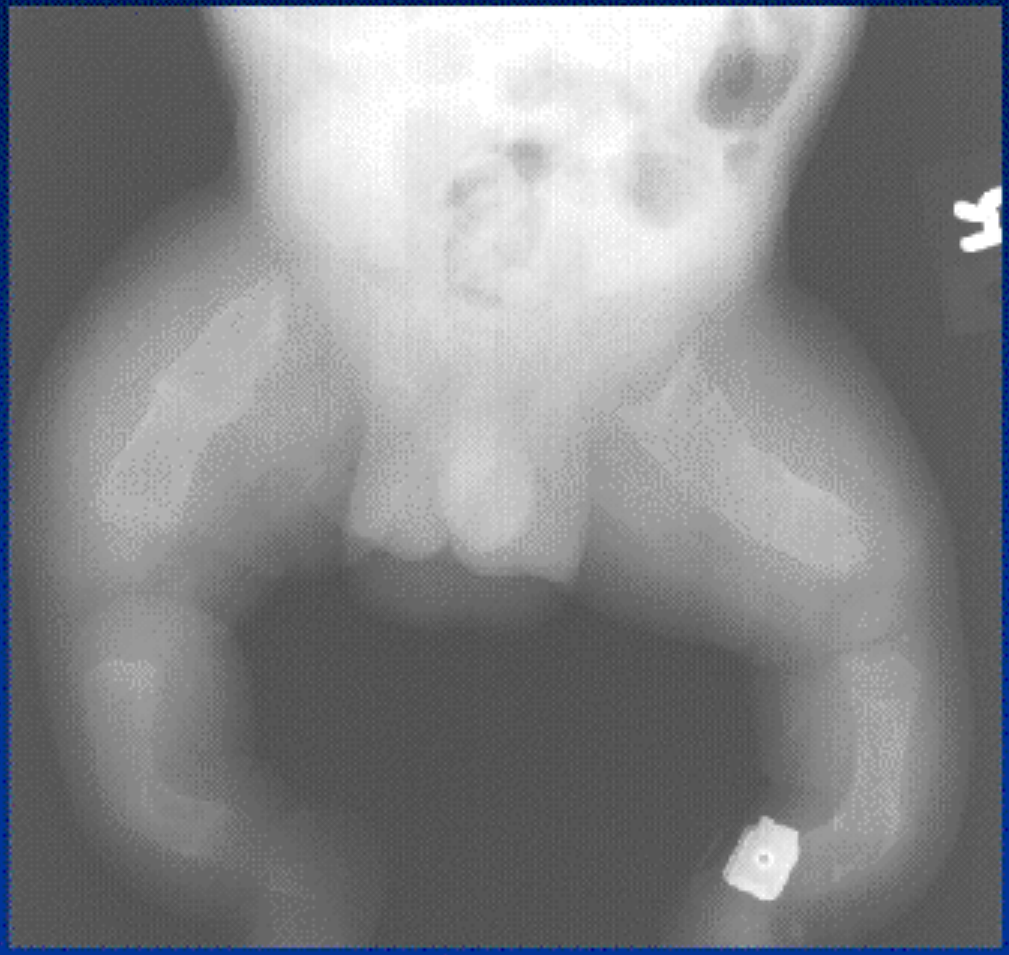
C

Population genetics hints

- Among the **Afrikaner** frequencies are 1:100 (eterozygotes) and 1:30.000 (homozygotes).
- The high frequency depends on a **founder effect**: the community has expanded from a small number of founders, weddings have taken place within a closed group, hence the high frequency of homozygotes.

- Among **Ashkenazi** jews the frequency is even higher (1:67-69 heterozygotes)
- Eight different allelic variants causing the disease are present in the Ashkenazi gene pool.
- The prevalent is G197del, of which we can estimate the origin of founder chromosome can be estimated in the 14th century.
- Also in other populations you can find high prevalence of familial hypercholesterolemia. These are all populations with stories of relative isolation: the French Canadians in Quebec, the Druze, the Finns.

Osteogenesis Imperfecta: X-ray



Osteogenesis Imperfecta

- Fragile bones/teeth
- Multiple fractures
- Hearing loss
- Blue sclerae

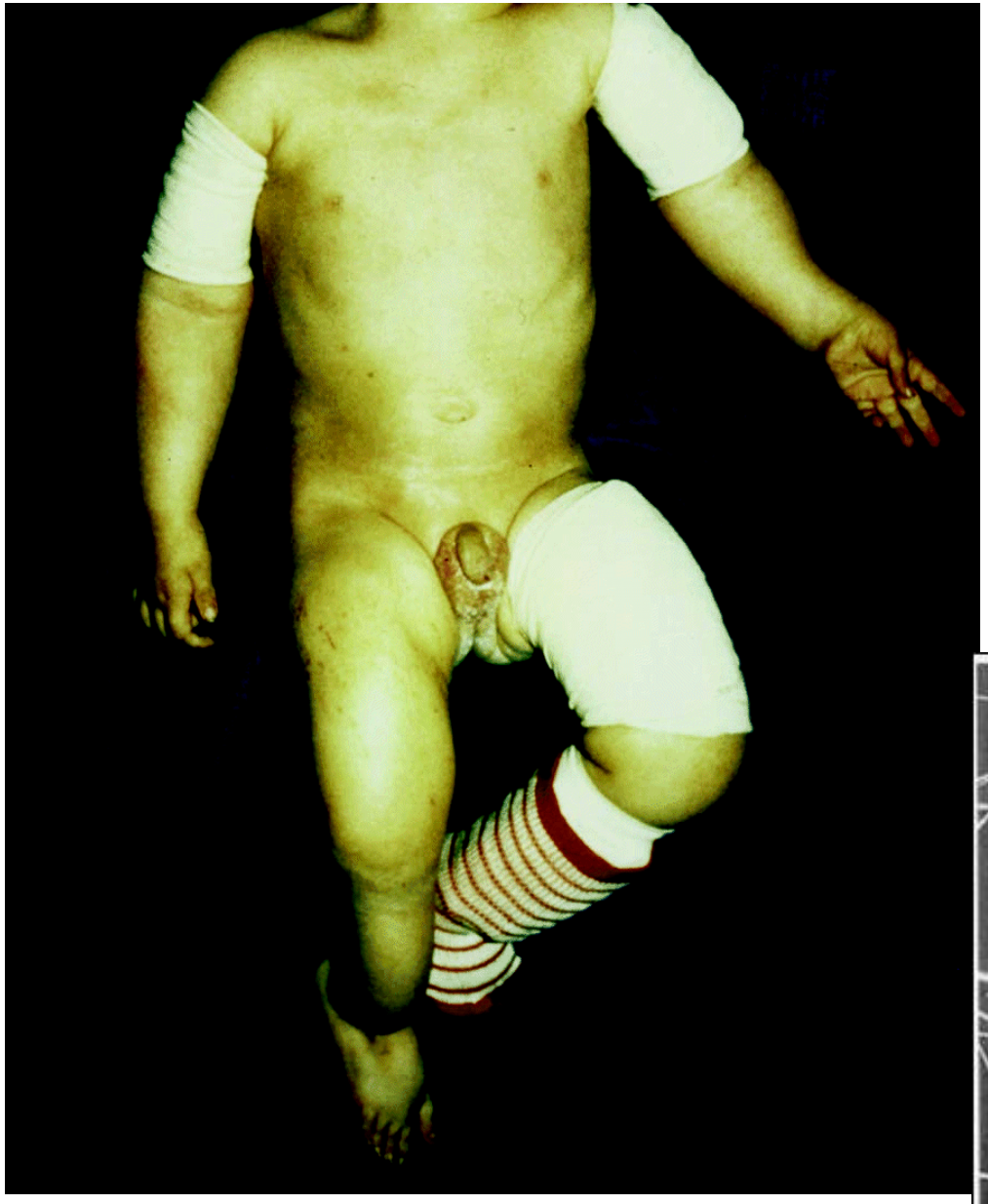
Osteogenesis imperfecta

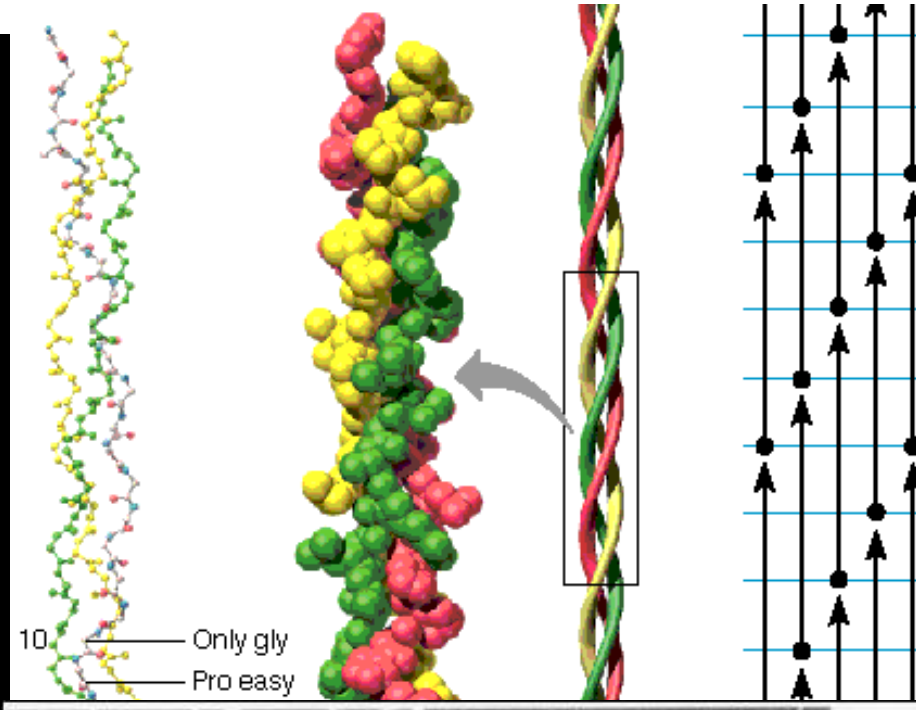
• Osteogenesis Imperfecta (OI) is a term that encompasses a very diverse group of hereditary disorders, whose common characteristics are brittleness (bone fragility) and bone deformity.

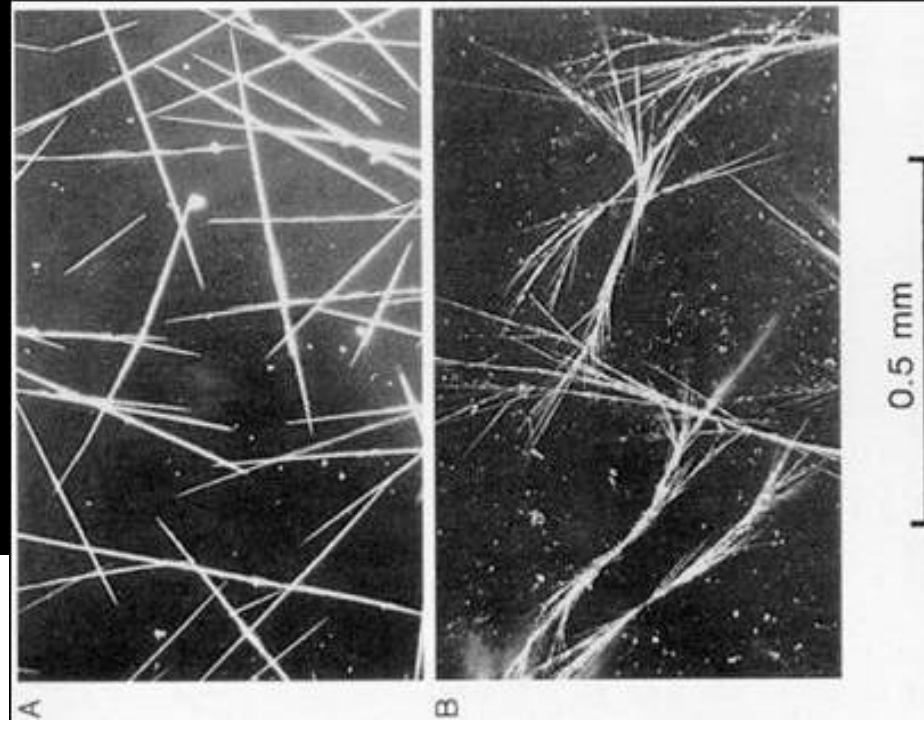
• To this are associated other nonskeletal tissue malformations like sclerae, teeth, skin, ligaments.

• they are children with short stature, enlarged head, normal intelligence.

•Brittle bones with osteoporosis: represents the most common characteristic of the syndrome. This leads to recurrent fractures, even for minimal trauma; healing occurs quickly but often with flaws, causing proneness to deformity of the spine and limbs.

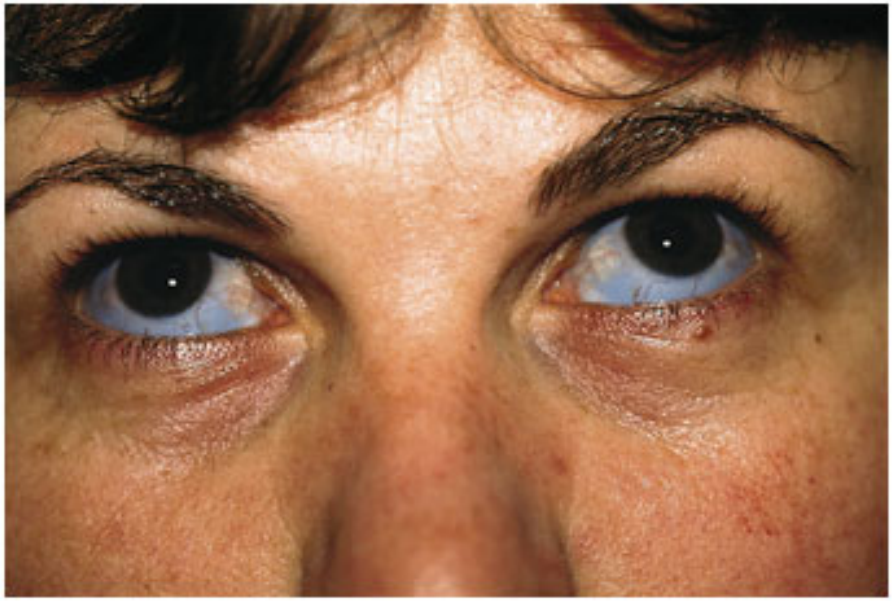



10
Only gly
Pro easy


A
B
0.5 mm

Osteogenesis imperfecta

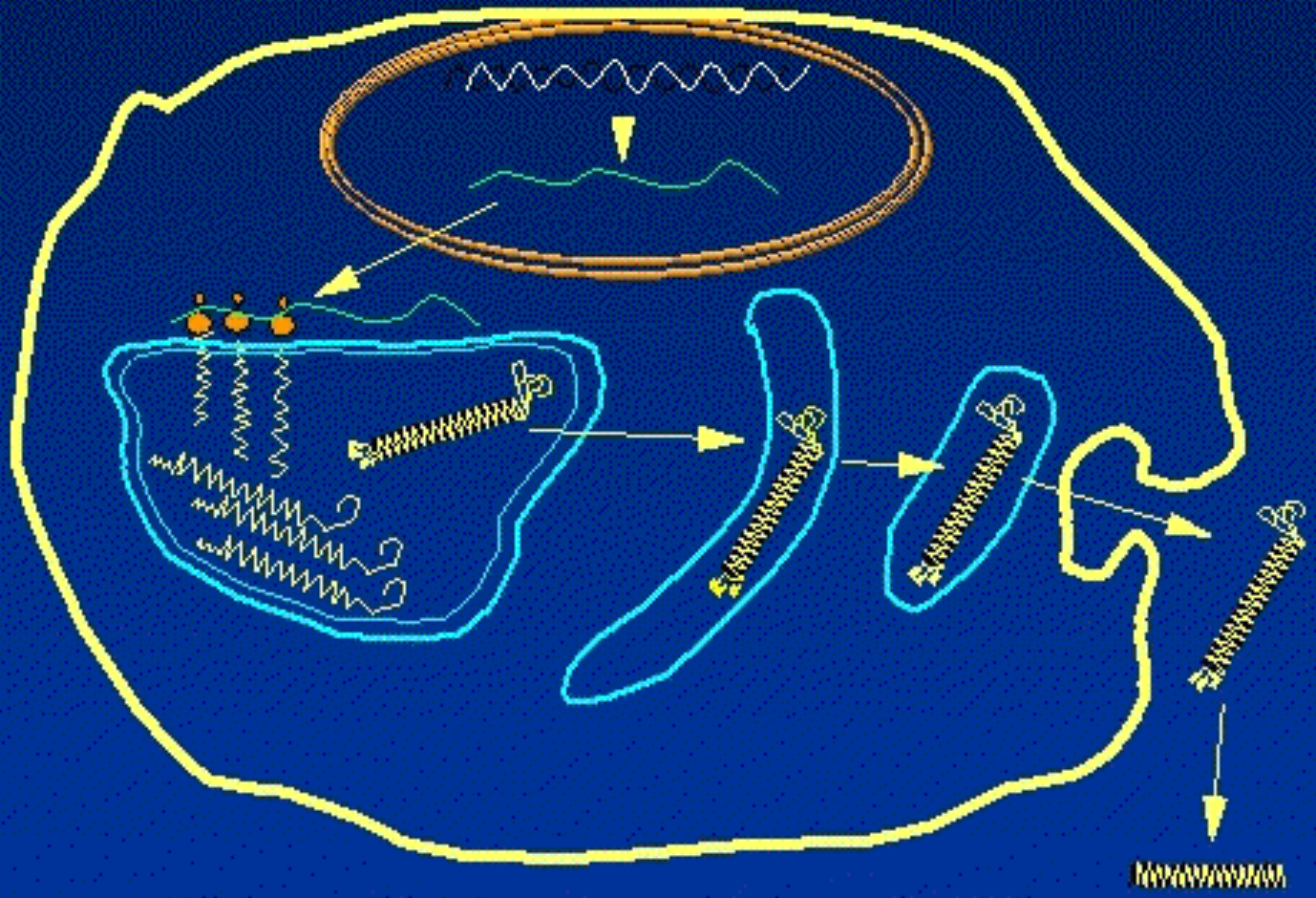
• Blue sclerae (80-90% of cases): discoloration of the sclerae, usually giving them a blue color, due to the underlying choroidal veins which show through. This is due to the sclera being thinner than normal because the type I collagen is not forming correctly.

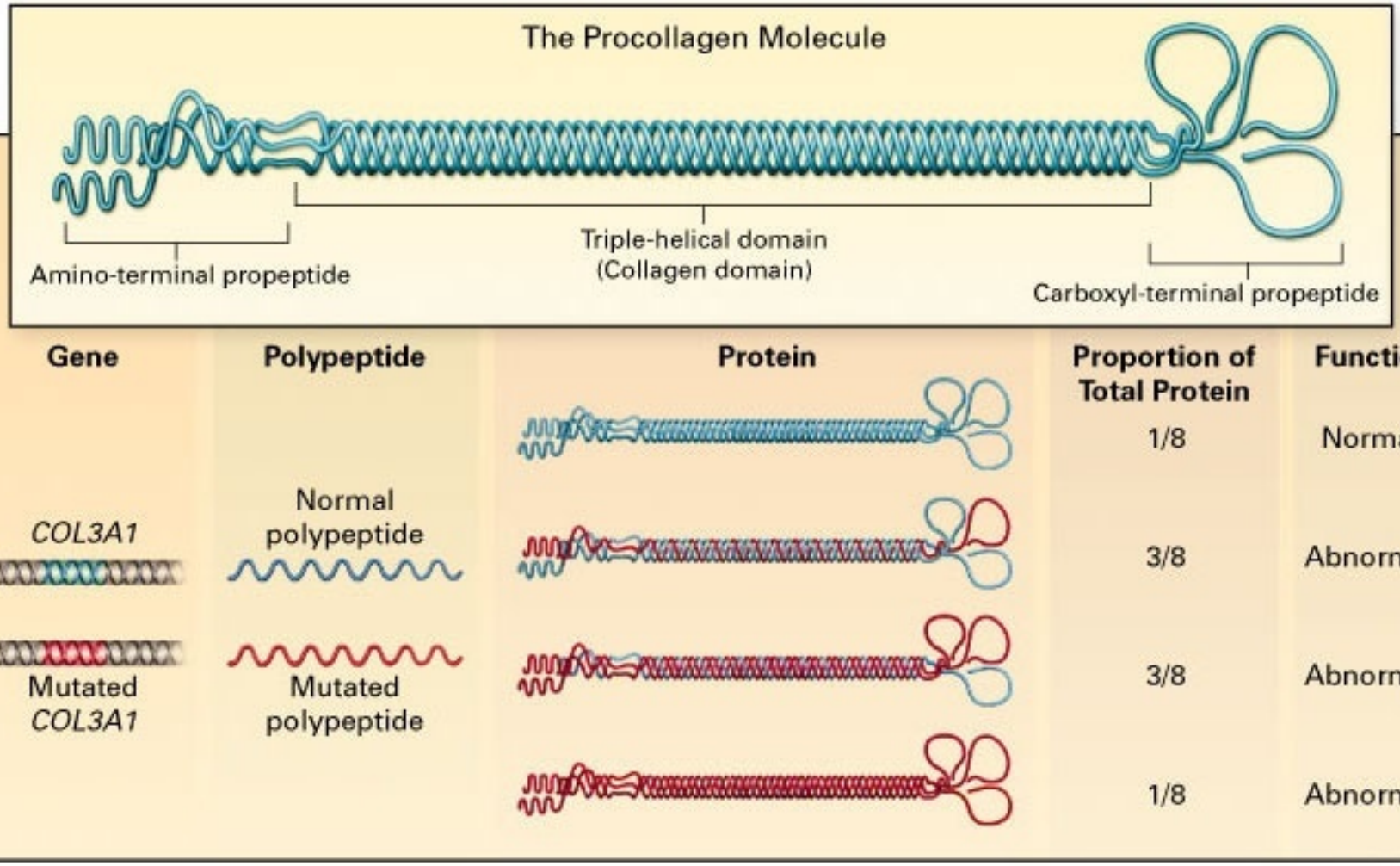


Osteogenesis imperfecta

- Dentinogenesis imperfecta (10-50% of cases): the teeth can be brown-grayish in color and opalescent and less resistant to wear, decay and caries.
- Deafness (40%): shows typically starting from the second decade and is more frequent in mild forms (OI type I). It is caused by structural abnormalities or fractures of the middle ear ossicles which ensure the transmission of vibrations to the inner ear.
- Laxity of ligaments and skin: linked to the collagen anomaly. Collagen is responsible for the mechanical resistance of these structures. Joint laxity is highly variable and may cause problems under load (knees, feet).

Collagen Synthesis




The Procollagen Molecule
Amino-terminal propeptide
Triple-helical domain
(Collagen domain)
Carboxyl-terminal propeptide
Gene
Polypeptide
Protein
Proportion of Total Protein
Function
1/8
Normal
COL3A1
Normal polypeptide
3/8
Abnormal
Mutated COL3A1
Mutated polypeptide
3/8
Abnormal
1/8
Abnormal

The Marfan syndrome and related connective tissue disorders affect at least 200,000 people in the United States.

Because connective tissue is the glue and scaffolding of the entire body, the disorder may affect the bones and ligaments, eyes, heart and blood vessels.

It is the effect on the aorta, the largest blood vessel carrying blood away from the heart, that can be fatal.

With an early diagnosis, proper treatment and a modified lifestyle, most people with the Marfan syndrome can hope to live a normal lifespan.
http://www.marfan.org

● In presurgical period (microsurgery) the average life expectancy for Marfan patients was about 40 years old; death could occur at a very young age essentially due to aortic dissection and consequest rupture of the vessel, or heart failure.

● Today, thanks to a proper lifestyle, the possibility of surgical operations on the aorta, heart and other parts of the organism, diagnostic methods and more efficient screening, life expectancy does not differ much from that of the general population. A study conducted in the United States (completed in 1995) has shown that the average age of death in Marfan patients at that time was 71 years, compared to 73 years of life expectancy of the population examined.

So how may mutations in one allele cause illness?

Dominantly inherited diseases

Mutations that cause excess function

The mutation produces a protein with altered expression or function. In some cases it can be an over-expression or an incorrect expression (in tissue or in the wrong stage of development). For example in achondroplasia, mutation of FGFR3 causes its constitutive activation -> inhibition of chondrogenesis

Insufficiency of the haploid genome (haploinsufficiency)

The reduction of one copy of the gene (50%) is harmful. For example in hypercholesterolemia, due to a mutation in the low density lipoprotein (LDL) receptor that produces a decrease in the levels of cholesterol receptor from which nearly double cholesterol amount in the circulation -> higher risk of cardiovascular disease

Dominant negative mutations

Mutations that produce a protein product that not only doesn't work, but also inhibits or interferes with the normal protein function, typically multimeric proteins. An example is osteogenesis imperfecta, as type I collagen consists of e polypeptides

message

- The recessiveness of a mutant allele is usually the result of haplosufficiency of the wild type allele for that particular gene.
- The dominance of a mutant allele is instead the result of haploinsufficiency of the wild type allele.
- This type of dominance is known as complete dominance. In this case the dominant homozygote cannot be distinguished from the heterozygote.

Codominance

A CODOMINANCE EXAMPLE

ABO Blood Groups

ABO blood groups:
a codominance example

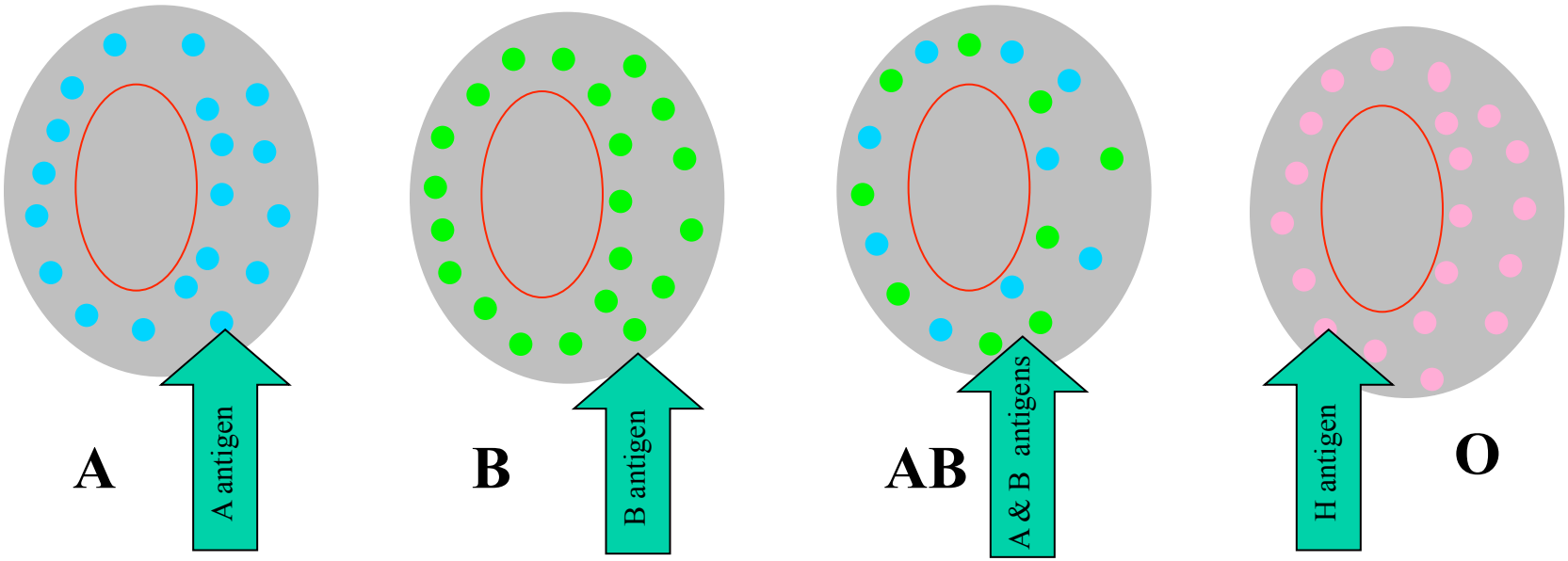
3 alleles at one gene locus: i, IA e IB.
Each individual possesses 2 copies

These alleles determine the expression of an angtigen, recognised by the immune system

Genotype	Blood group
IA/IA, IA/i	A
IB/IB, IB/i	B
IA/IB	AB
i/i	O

Blood Grouping - Antigens

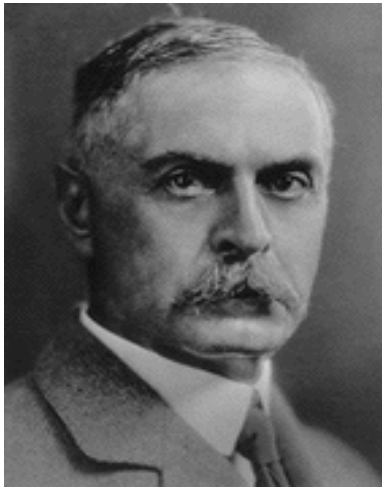
- You are type A if your red blood cells only have A antigen
- You are type B if your red blood cells only have B antigen
- You are type AB if your red blood cells have both A and B antigens
- You are type O if your red blood cells only have H antigen but no A or B antigens



Kimberley Davies -
kid1 - 011833121

Blood Grouping

- The most well known and medically important blood types are in the ABO group. They were discovered in 1900 and 1901 at the University of Vienna by Karl Landsteiner in the process of trying to learn why blood transfusions sometimes cause death and at other times save a patient. Thirty years later, he received the Nobel Prize for this discovery.



Karl Landsteiner

http://www.nobel.se/medicine/laureates/1930/landsteiner-bio.html

Blood Group	Antigens on RBCs	Antibodies in Serum	Genotypes
A	A	Anti B	AA or AO
B	B	Anti A	BB or BO
AB	A & B	None	AB
O	None	Anti A Anti B	OO

ABO Blood Donor & Recipient Compatibility

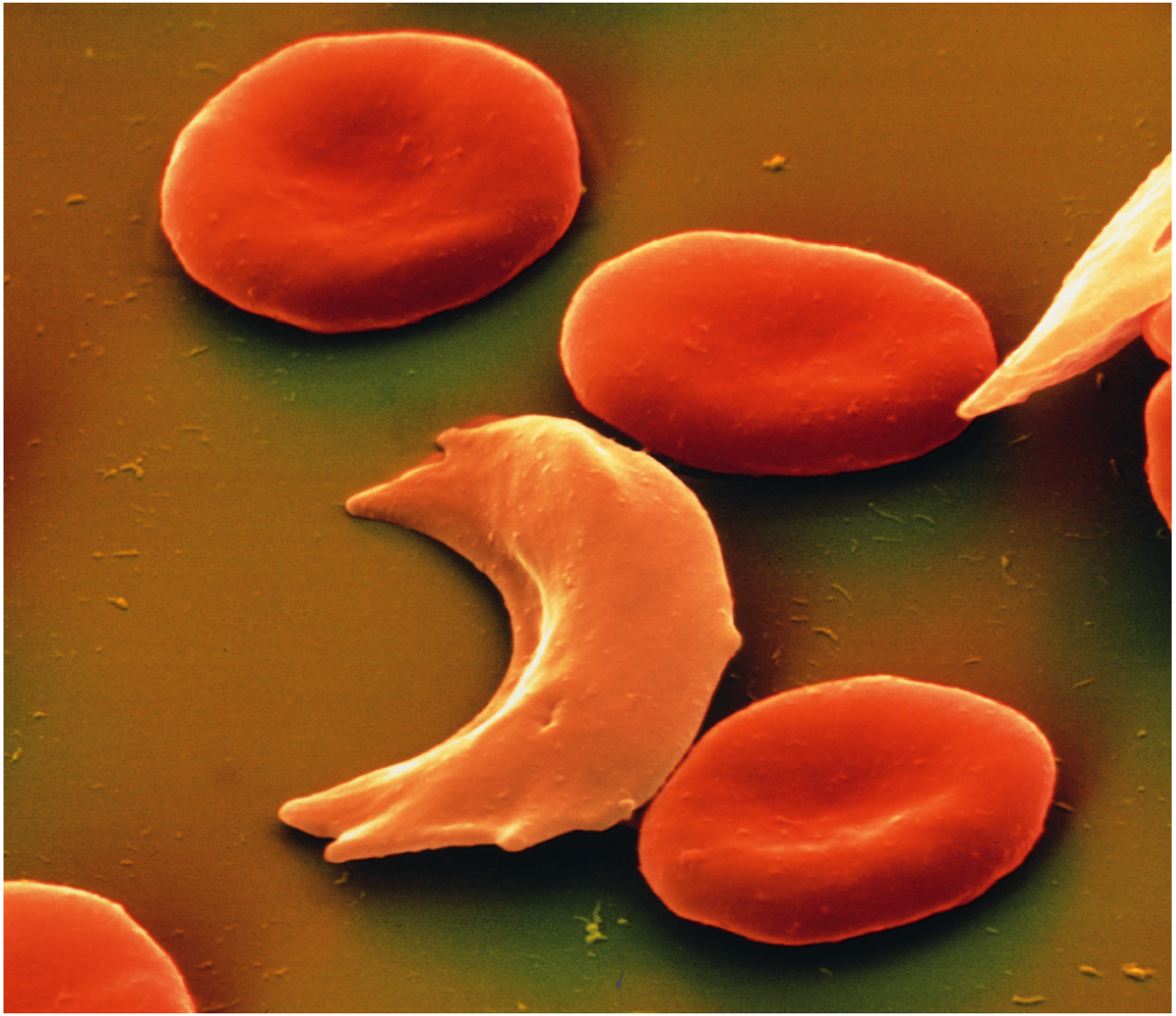
- When red cells carrying one or both antigens are exposed to corresponding antibodies, they agglutinate; that is, clump together.
- People usually have antibodies against those red cell antigens that they lack
- Table below shows who can donate blood to who, and who can receive blood from who.

	Recipient				
Donor	**Alleles and antibodies**	**O** **Anti A** **Anti B**	**A** **Anti B**	**B** **Anti A**	**AB** **None**
	O	**None**	**None**	**None**	**None**
	A	**Clumping**	**None**	**Clumping**	**None**
	B	**Clumping**	**Clumping**	**None**	**None**
	AB	**Clumping**	**Clumping**	**Clumping**	**None**

Kimberley Davies - kid1 - 011833121

Electronic microscopy photograph of a sickle-shaped red blood cell.

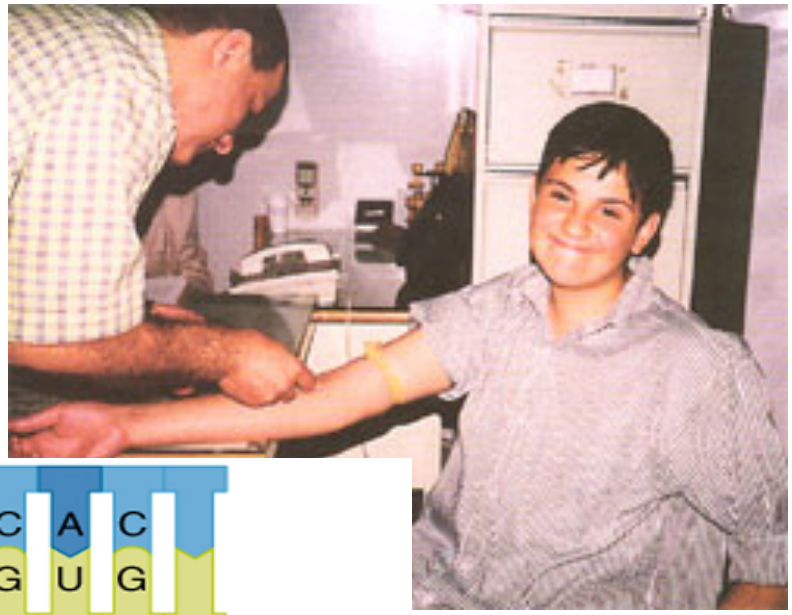
Other red blood cells have a more round morphology and look practically normal (incomplete dominance)

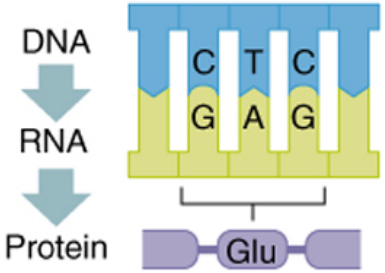


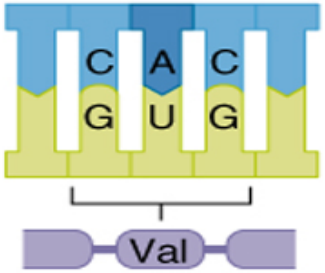
SICKLE CELL ANAEMIA

- Only 1 mutation described: A>T transversion in codon 6 of the beta globin gene
- The consequence at the protein level is a glutammic acid>valine substitution

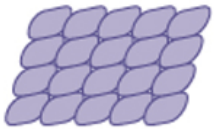
This single amino acid change alters the hemoglobin charge and causes its aggregation in rods-like structures inside the red blood cell.



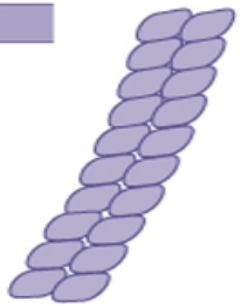




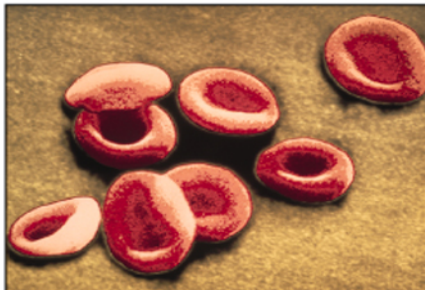
Normal folding of hemoglobin molecule



Abnormal folding of hemoglobin molecule



Normal red blood cells



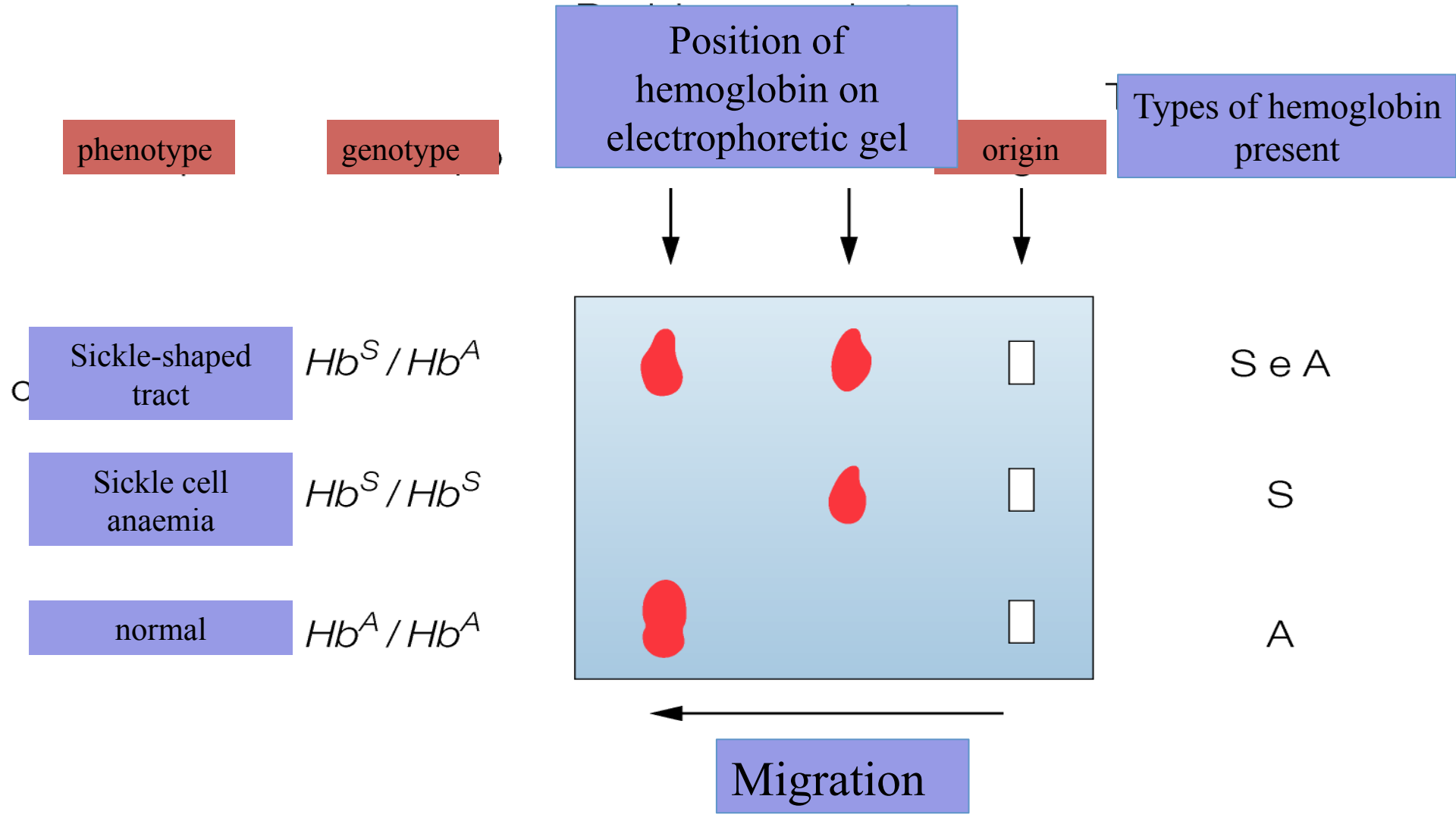
Sickled red blood cells

SICKLE CELL ANAEMIA

HbA/HbA	Normal phenotype; no sickle-shaped red blood cells
HbS/HbS	Serious anaemia, often lethal; abnormal hemoglobin gives rise to sickle red blood cells
HbA/HbS	No anaemia; some sickle-shaped red blood cells only at low oxygen tension

Electrophoresis of normal and mutant hemoglobin.

The diagram shoew the electrophoretic run of a heterozygous subject, of a sikle cell patient and of a normal subject.
The coloured spots represent the final positions reached by hemoglobin molecules in the agarose gel.
In heterozygotes codominance exists at the molecular level



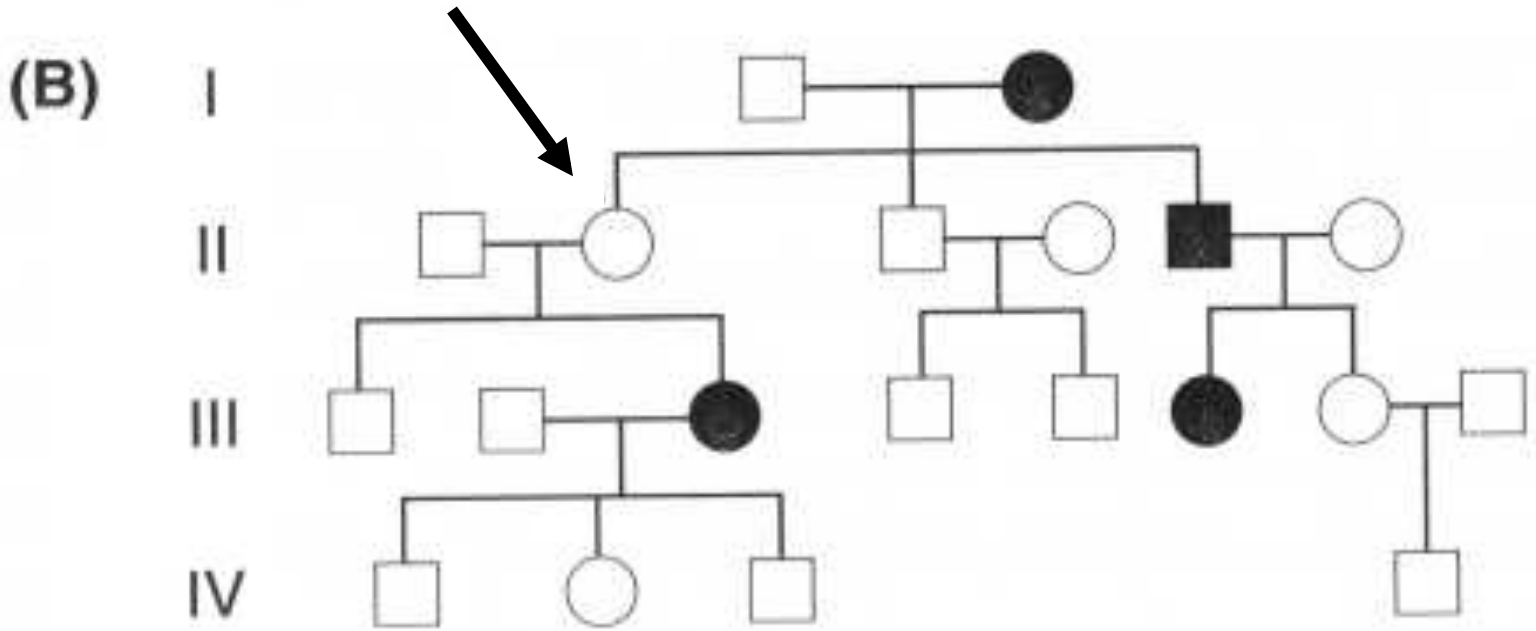
message

- The type of dominance is determined by the molecular functions of alleles and by the level of observation (organism, cell, molecule).
- Eg. Sickle cell anaemia: at the organismal level, the HbA allele is dominant (no anemia in the heterozygote). At the cellular level, the cell shape is determined for incomplete dominance (presence of a few sickle-shaped cells together with normal cells in the heterozygote). At the molecular level codominance is observed (presence of both forms of hemoglobin molecules in the heterozygote).

Sometimes there are problems in recognising dominant inheritance

Mendelian pedigree patterns

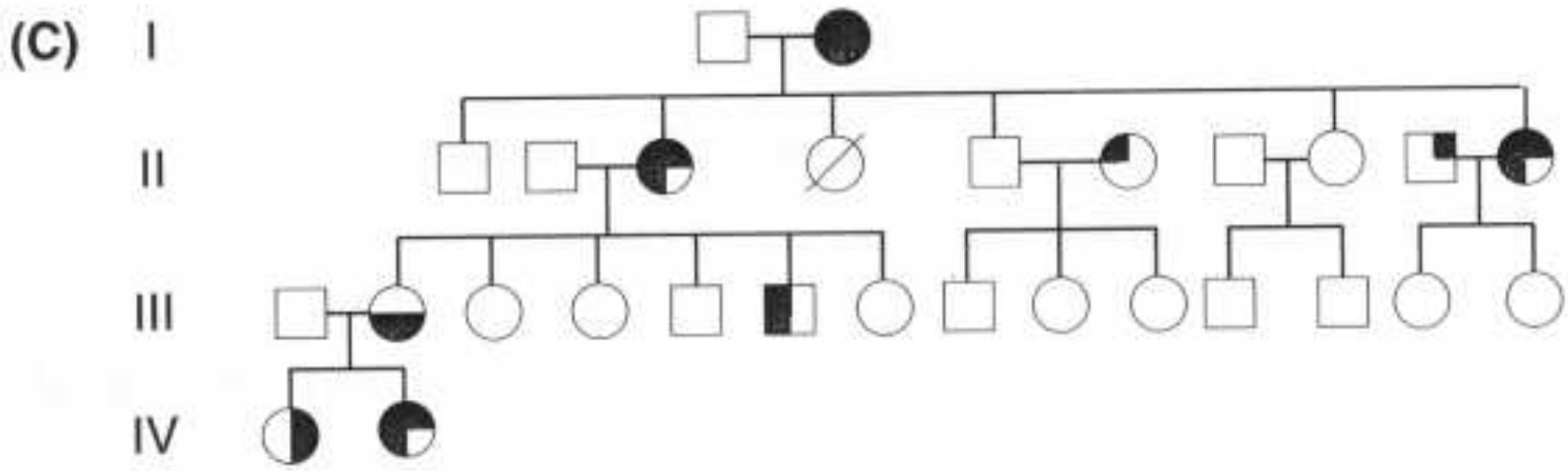
further complications



non penetrance (NP)

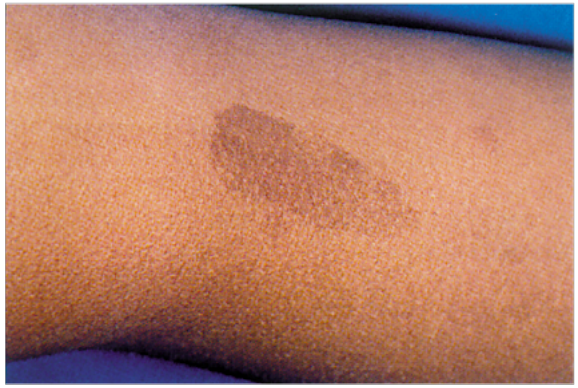
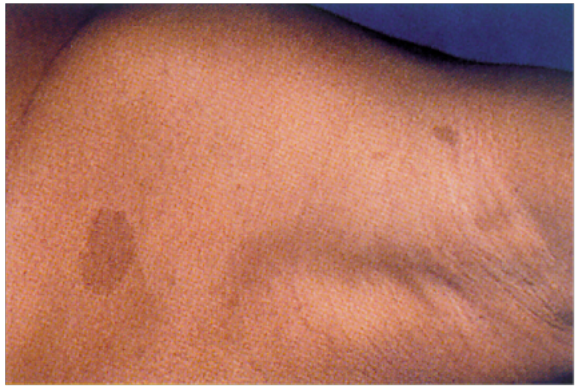
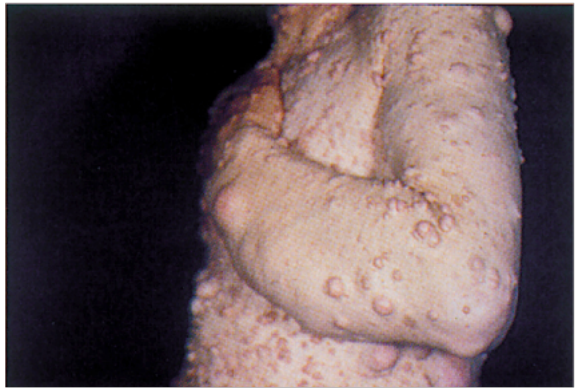
Mendelian pedigree patterns

further complications



variable expression

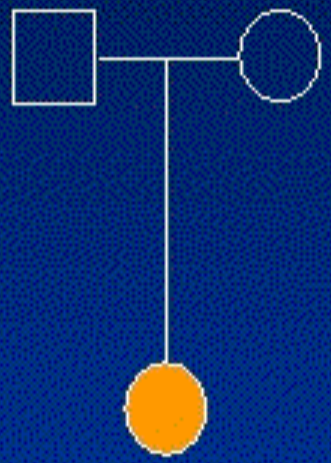
Variable expressivity

Neurofibromatosis; mutations in NF1 gene

Characterised by the presence of many benign nerve cell tumors (fibromas), but malignancy is not common. NF1 affects one in about 3500 – 4000 individuals, in 20% of cases it causes severe malformations; it is often not diagnosed because it just causes aesthetic problems.

Sporadic



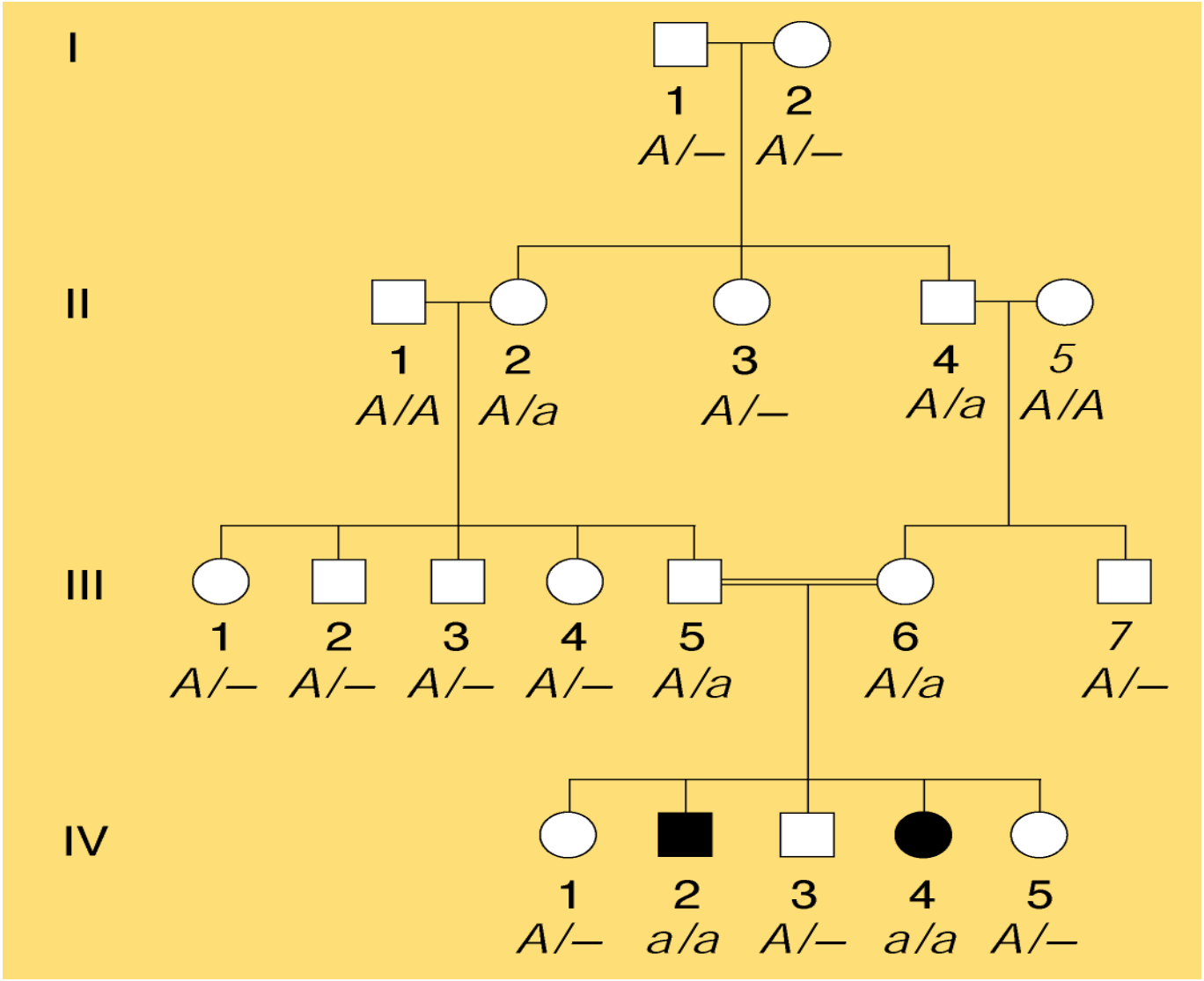
- new mutation
- non-penetrance

Other autosomal diseases…..

recessive

Pedigree of a rare recessive phenotype determined by a recessive a allele.

Genotypes are usually not included in the pedigree, but in this case they were added to facilitate understanding.
II-1 and II-5 individuals are outside the family and marry two members.
We assume they are normal because the phenotype is rare.
Note that you cannot deduce the genotype of some individuals with normal phenotype; these individuals are labeled A/-.



message

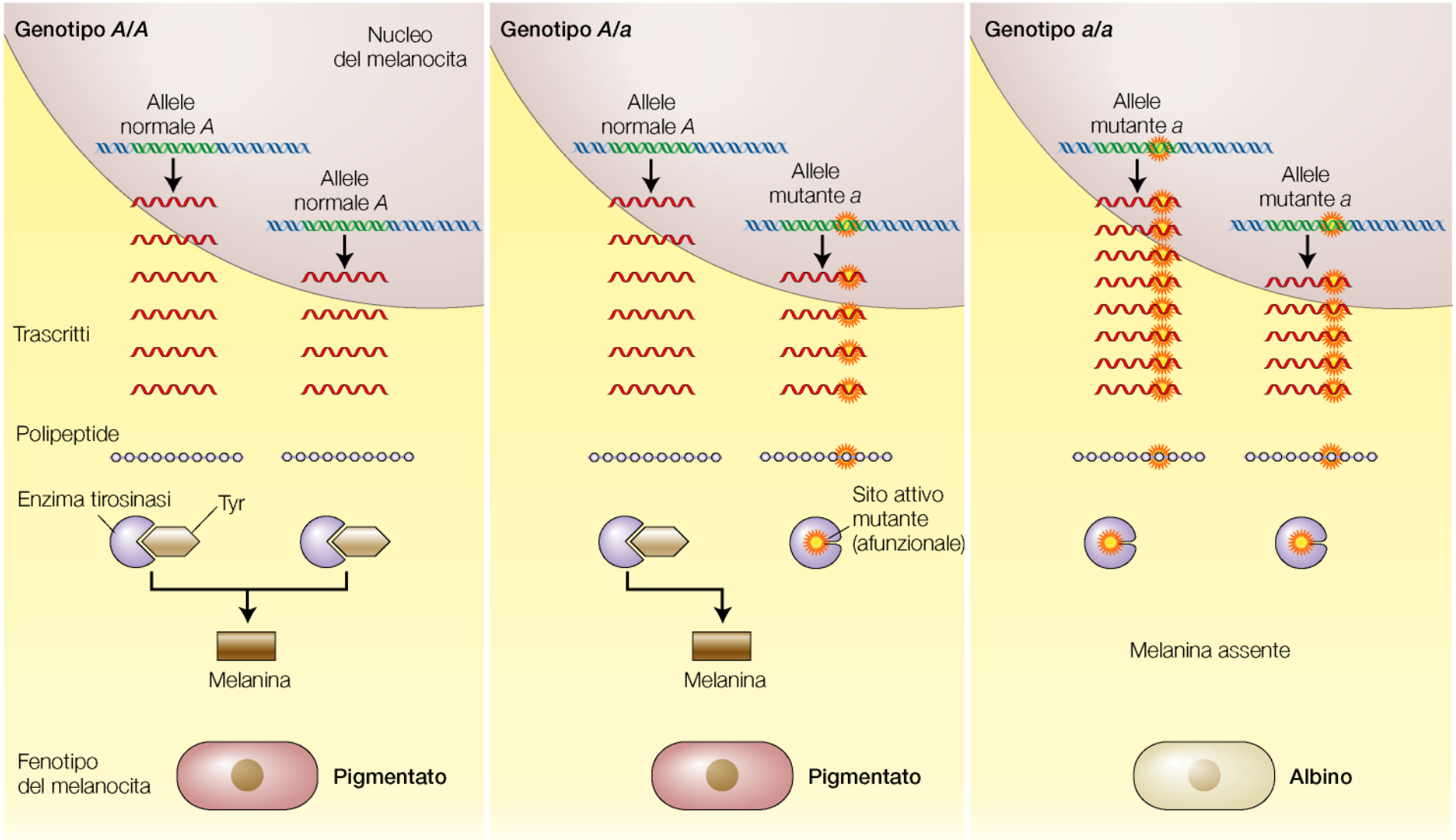
- In human family trees (pedigrees), an autosomal recessive disease is revealed by the presence of the disease in the offsprings – both male and female – of healthy parents.

Albinism.

The albin phenotype is caused by twoo copies of a recessive allele, a/a.
The dominant Aallele controls one step in the chemical synthesis of melanin found in skin cells, hair and retina.
In a/a individuals this step does not occur correctly and melanin synthesis is blocked.

Molecular bases of albinism.

Left. Melanocytes containing two copies of the normal A allele of tyrosinase gene produce this enzyme that converts tyrosine amino acid into melanin. *Centre*. Melanocytes containing only one copy of the normal allele still produce enough tyrosinase quantity to give rise to a normal, pigmented phenotype.
Right. Melanocytes containing two copies of the null mutant allele a do not produce tyrosinase enzyme.



I REMEMBER BEING JEALOUS OF THE KIDS IN "RETURN FROM WITCH MOUNTAIN" WHO NEVER FIT IN. THEY WERE FINALLY VINDICATED WHEN "THEIR PEOPLE" CAME TO TAKE THEM HOME. AND I WONDERED, WHERE WERE MY PEOPLE?

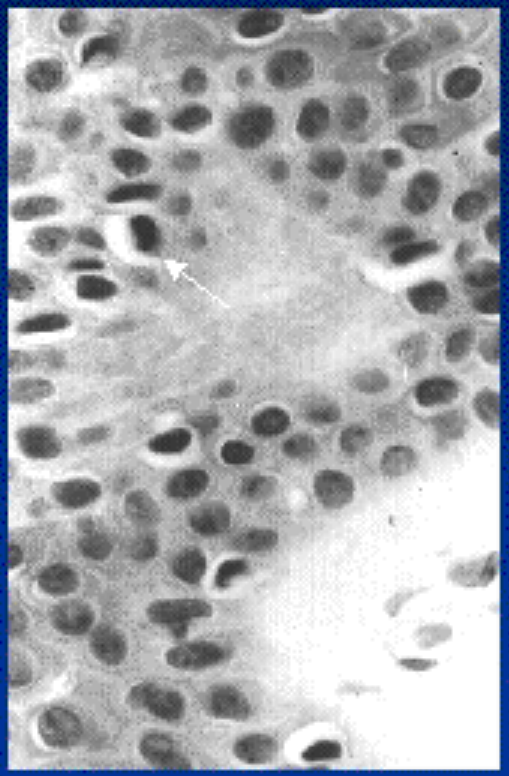
TO INSULT ME PEOPLE SIMPLY USE THE WORD "ALBINO." IN THOSE MOMENTS OF STANDING ACCUSED—ON THE BUS, IN A RESTAURANT, ON LINE AT THE GROCERY STORE—I AM STRIPPED OF MY PERSONHOOD.

Clockwise from top left: Rachel Finkel, 15; Matt Smutko, 27, musician; Meghan Petrone, 14; Kristin Cruz, 14

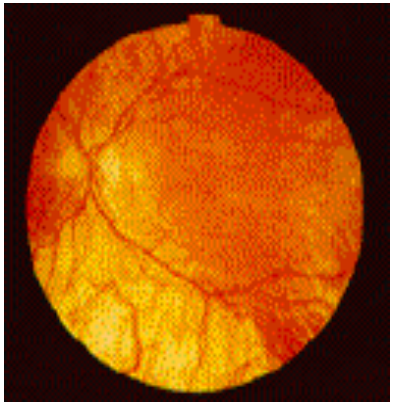
Tired of "being told what is beautiful," photographer Rick Guidotti turned his back on fashion dictators and his lens toward what his own eye found dazzling. The portraits here were inspired by a chance glimpse of a teenager with albinism. Intrigued, Guidotti sought out others and was shocked to learn how many had been stigmatized for their unconventional looks. Marshaling his industry's standard resources—hair, makeup and great clothes—he made each person see how beautiful he or she is. To help others see it as well, he asked NOAH members to tell their stories. Their words—some belonging to the people pictured, some not—are unattributed on these pages because the message, says Guidotti, is universal: "Nothing is uglier than ignorance."

Kristen Daley, 12

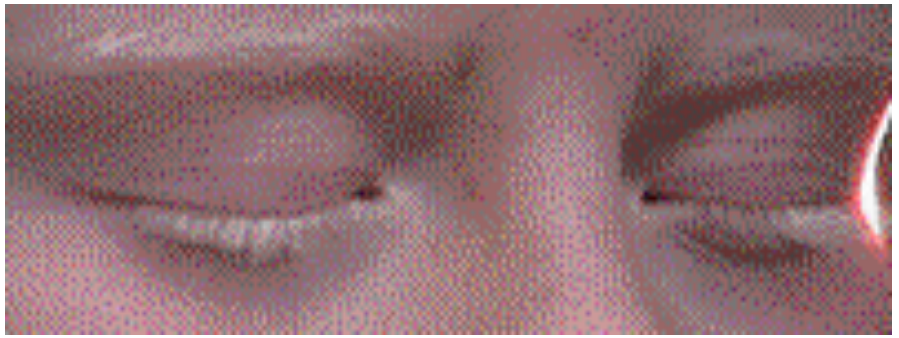
Oculocutaneous Albinism



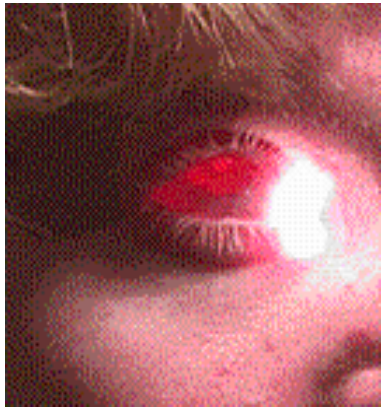
The hypopigmentation and macular/ foveal hypoplasia



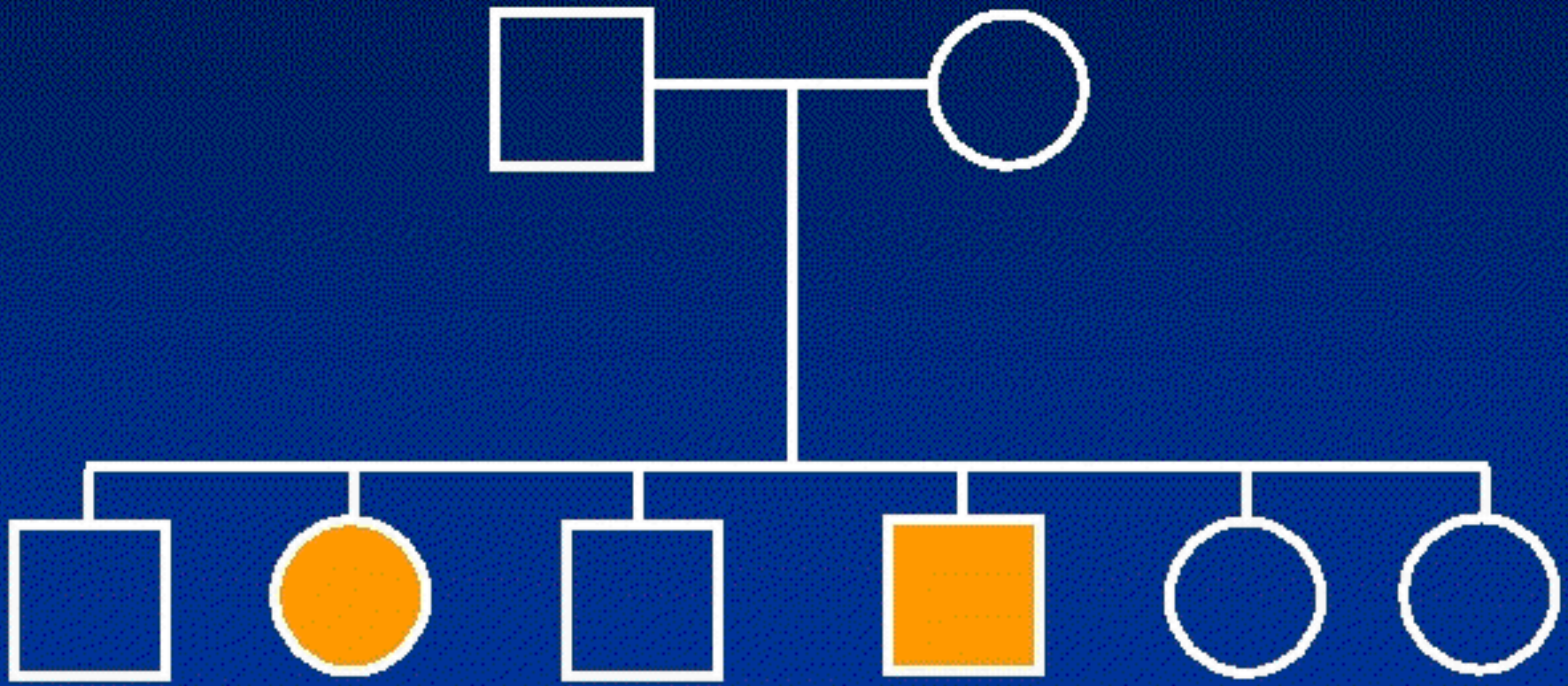
Hypopigmentation of the hair and eyelashes



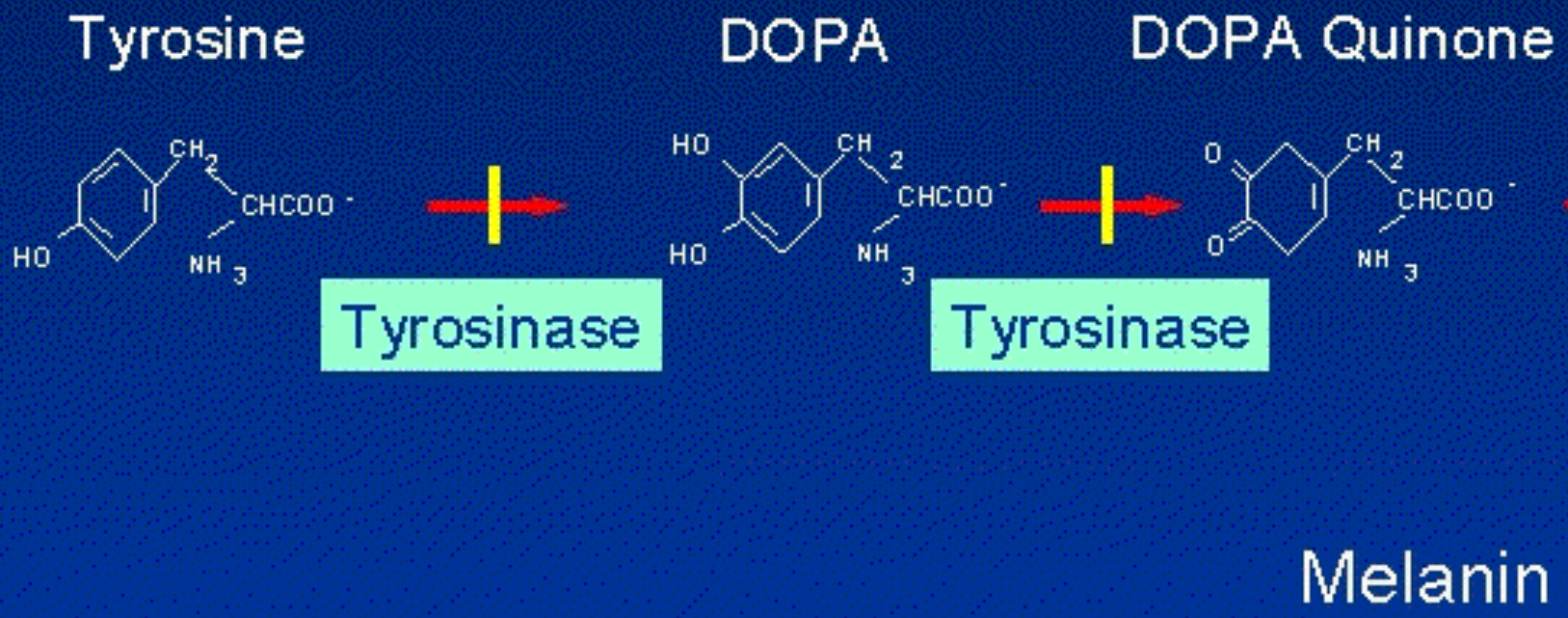
Transillumination of the iris

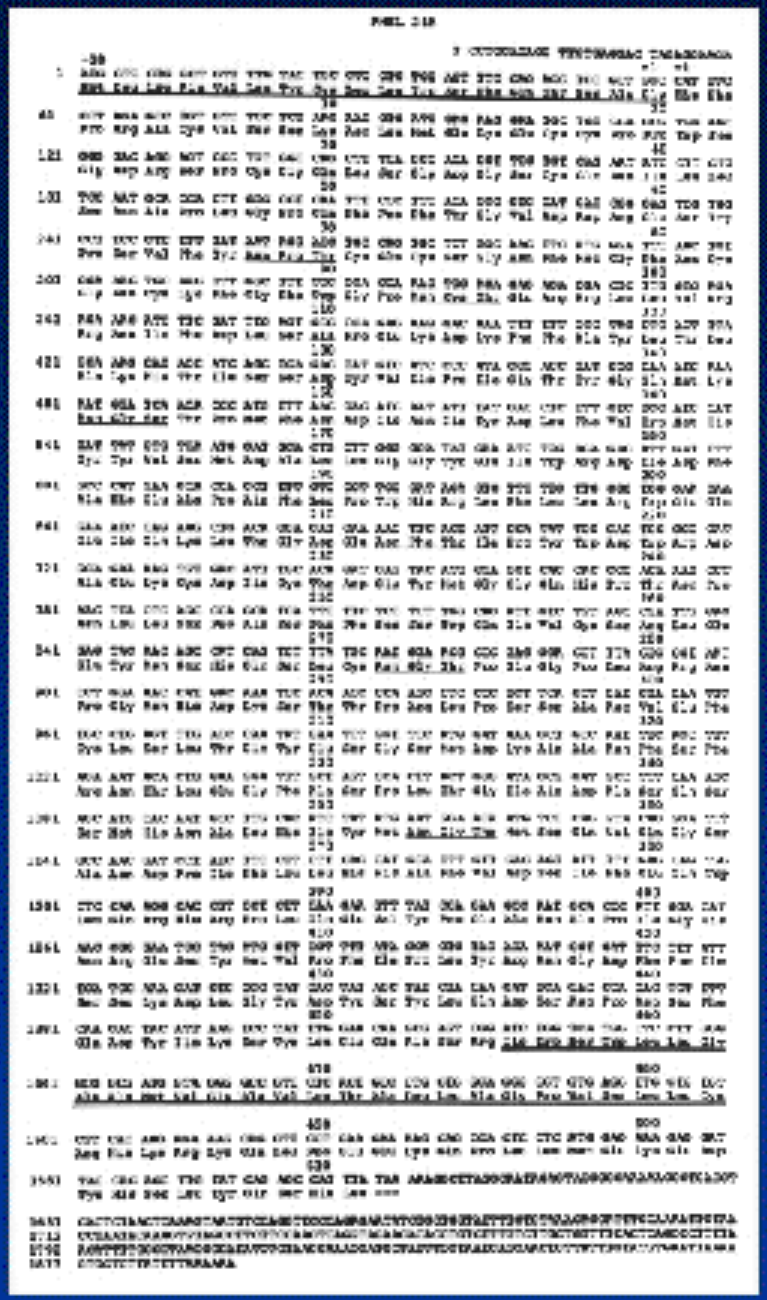


Autosomal Recessive Pedigree



Tyrosinase

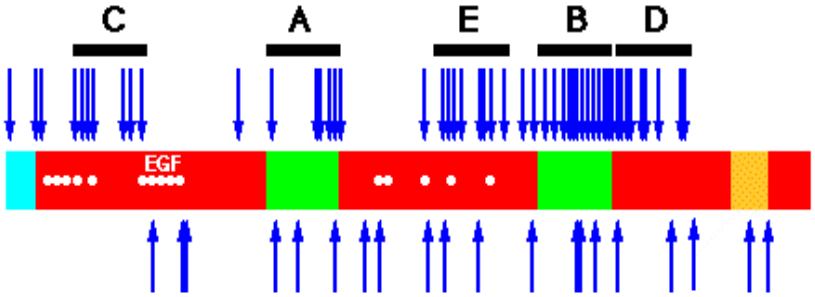

Tyrosine
DOPA
DOPA Quinone
HO
CH2
CHCOO-
NH3
Tyrosinase
Tyrosinase
Melanin



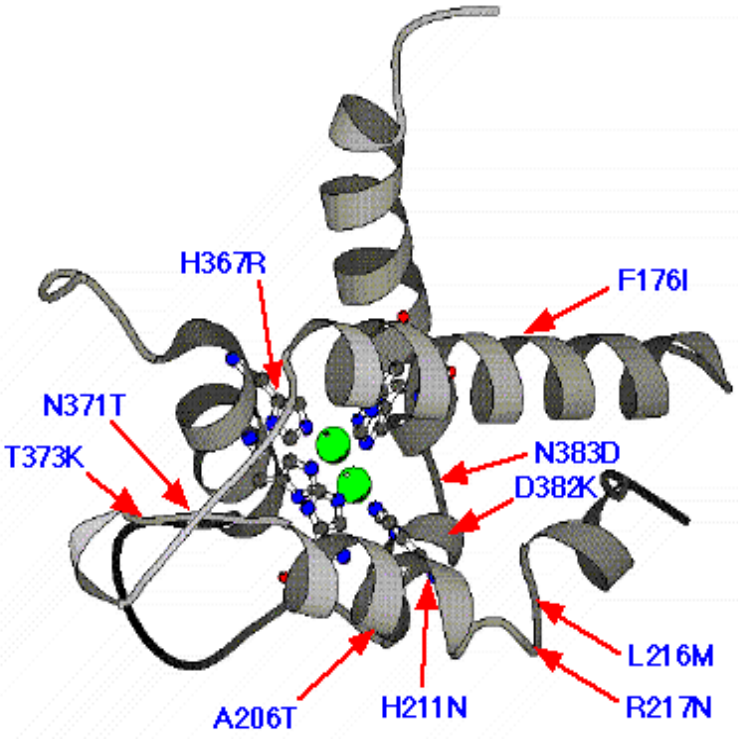
Tyrosinase Sequence

Kwon et al.,
Proc. Natl. Acad. Sci.
1987;84:7473.

Human tyrosinase protein structure and mutation location



- The red represents the coding region of the human tyrosinase polypeptide.
- The blue represents the signal peptide, the green represents the copper-binding regions and the yellow the transmembrane region.
- The white dots are cysteine residues conserved in all members of the tyrosinase-related protein family.



Wildtype

CTT AAT GCC CGG TCG ACC GTA CGT GAG

Leu Asn Ala Arg Ser Thr Val Arg Glu

single base change

CTT AAT GCC CGG CCG ACC GTA CGT GAG

Mutant

Leu Asn Ala Arg Pro Thr Val Arg Glu

Amino acid substitution

Wildtype

CTT AAT GCC CGG TCG ACC GTA CGT GAG

Leu Asn Ala Arg Ser Thr Val Arg Glu

insert one base

CTT AAT GCC CGG TAC GAC CGT ACG TGA G

Mutant

Leu Asn Ala Arg Tyr Asp Arg Thr Stop

Frameshift mutation

Other examples of autosomic recessive diseases in man

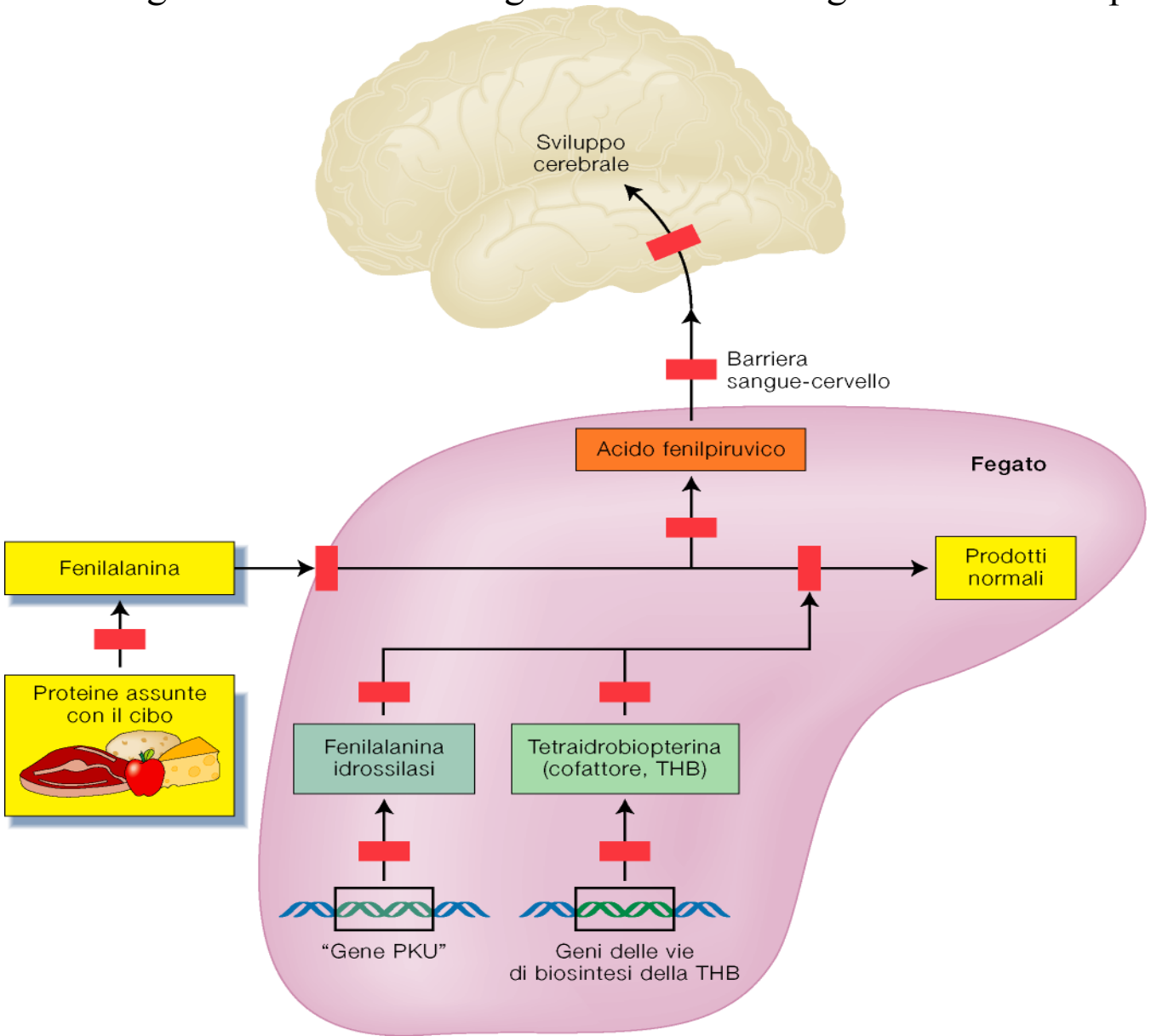
- Phenylketonuria (PKU)

Caused by a defect in the conversion of the amino acid phenylalanine, a component of all proteins we take with food. Phenylalanine is normally converted into the amino acid tyrosine by the enzyme phenylalanine hydroxylase.

If the gene that codes for this enzyme is mutated, the conversion does not take place and phenylalanine accumulates in the body, interfering with the normal development of the nervous system and causing mental retardation.

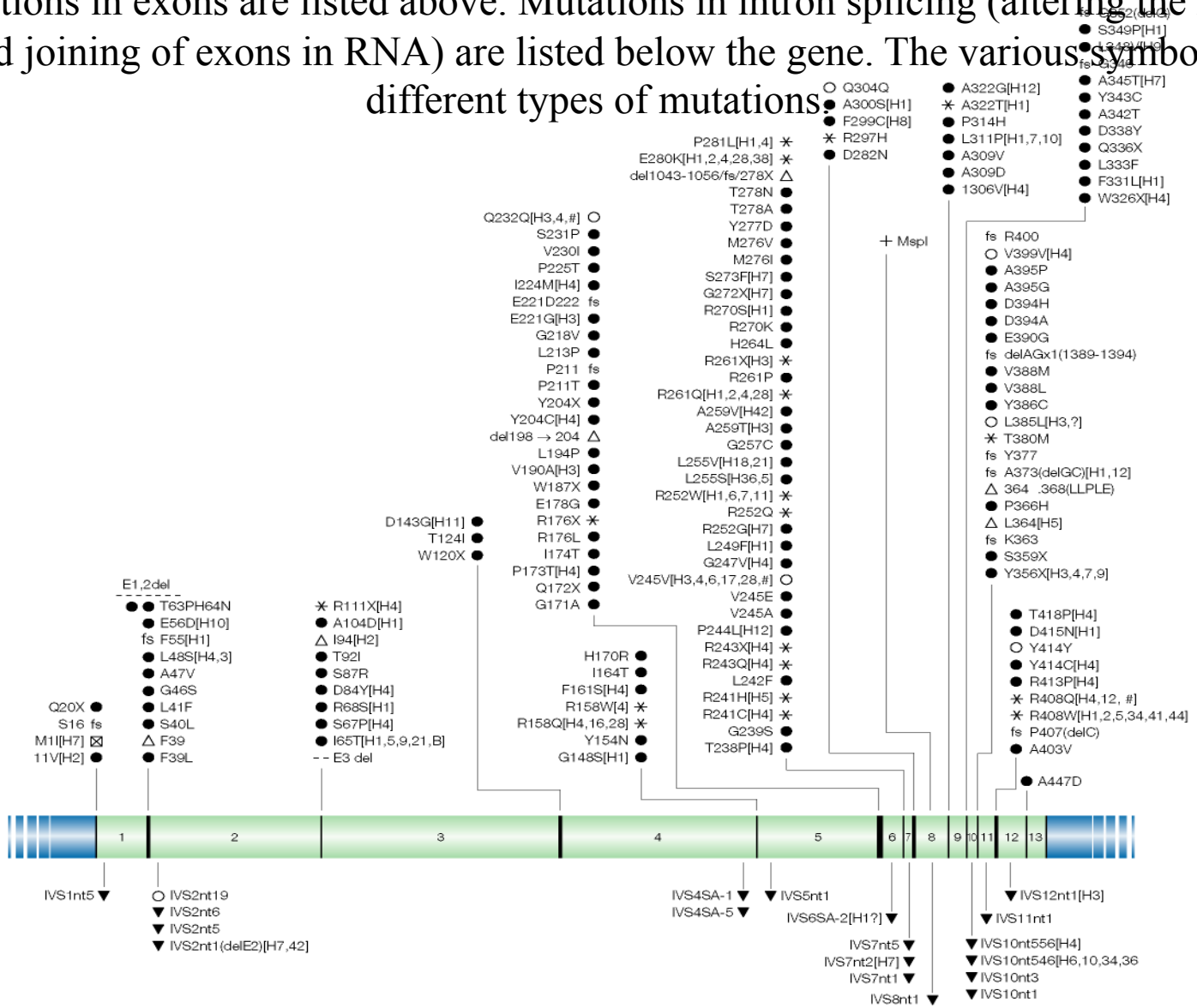
The onset of phenylketonuria is manifested through a complex sequence of stages.

The red rectangles indicate those stages in which a change or a block are possible.



Structure of the gene for the enzyme phenylalanine hydroxylase in the human species and checklist of some mutations responsible for the malfunction of the enzyme.

Gene mutations in exons are listed above. Mutations in intron splicing (altering the removal of introns and joining of exons in RNA) are listed below the gene. The various symbols indicate different types of mutations.



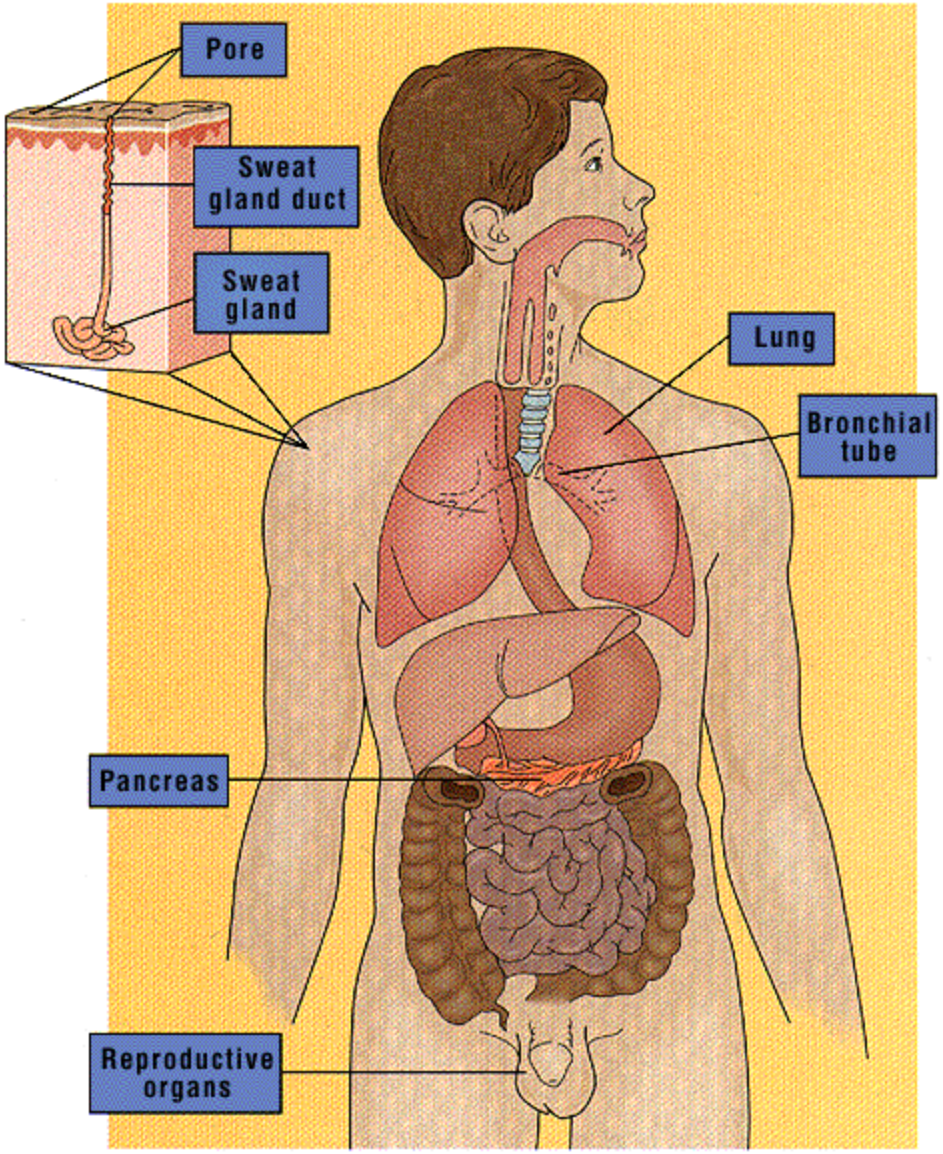
- Phenylketonuria (PKU)

Today newborns are routinely subjected to diagnostic tests to identify the deficiency at birth and, if needed, to give the child a special diet that doesn't lead to phenylalanine uptake.

Cystic Fibrosis

Cystic fibrosis

- It is the most common autosomal recessive disorder in Europe
- Caused by mutations in the CFTR gene, a chloride channel expressed by epithelial cells
- The defective chloride permeability seriously affects the mucous secretions of various organs, including the lungs and intestine
- More than 1000 allelic variants, the most common being delF508



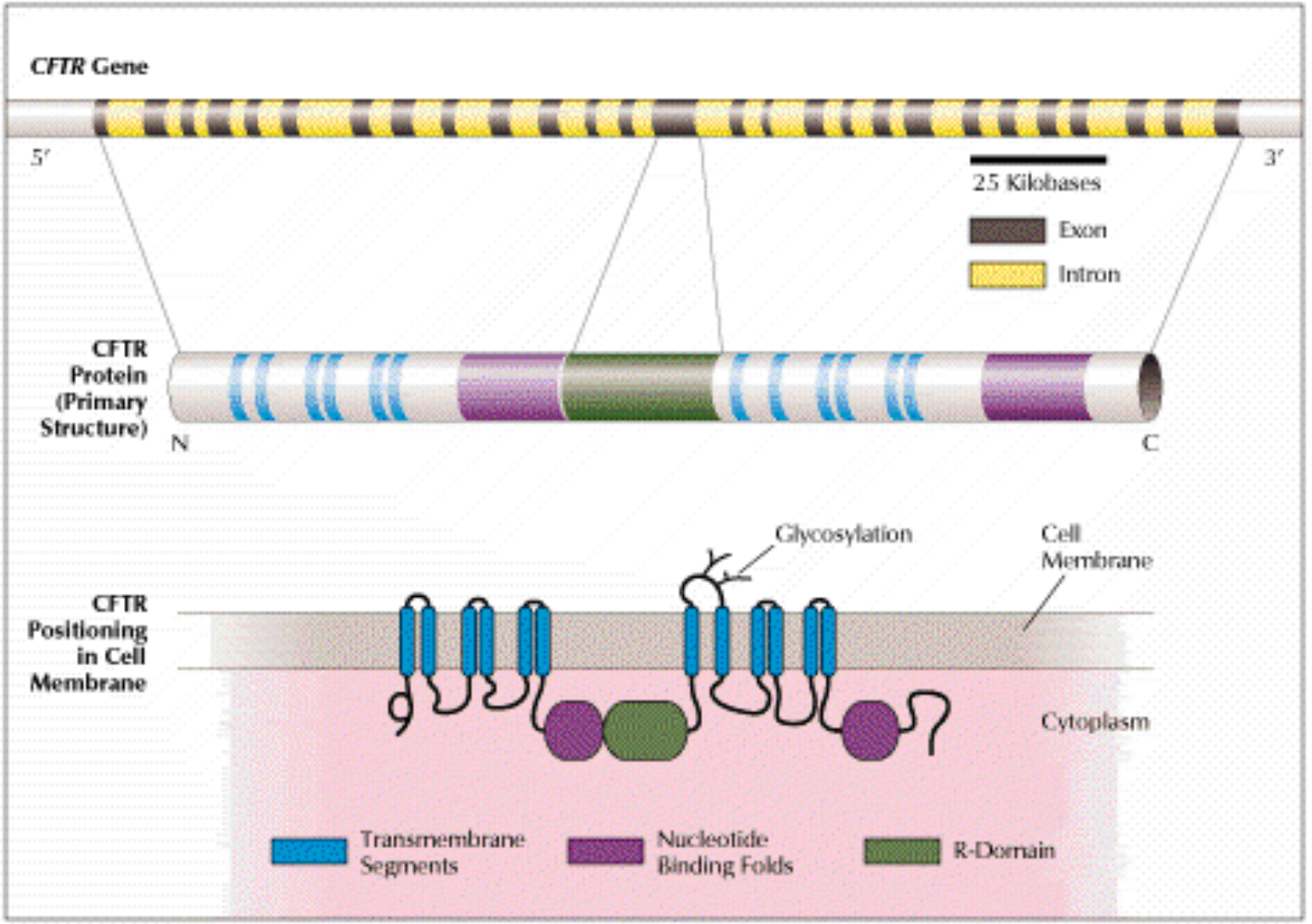


Figure 2. Human *CFTR* gene (top), identified in 1989 on the long arm of chromosome 7, uses 27 exons to specify a polypeptide consisting of 1,480 amino acids (middle). On the basis of its dual versions of a nucleotide-binding fold (NBF), the polypeptide has been classified as an ATP-binding-cassette protein (where "cassette" signifies a functional module). The polypeptide also has dual sets of six membrane-spanning segments. Unique to CFTR is a central region coded by the gene's longest exon. Suspected of having a regulatory function, it is called the R-domain. Analysis of the primary sequence of CFTR suggests that the only part of it protruding from a cell (bottom) is a short loop between transmembrane segments 7 and 8, which has attachment sites for two sidechains.

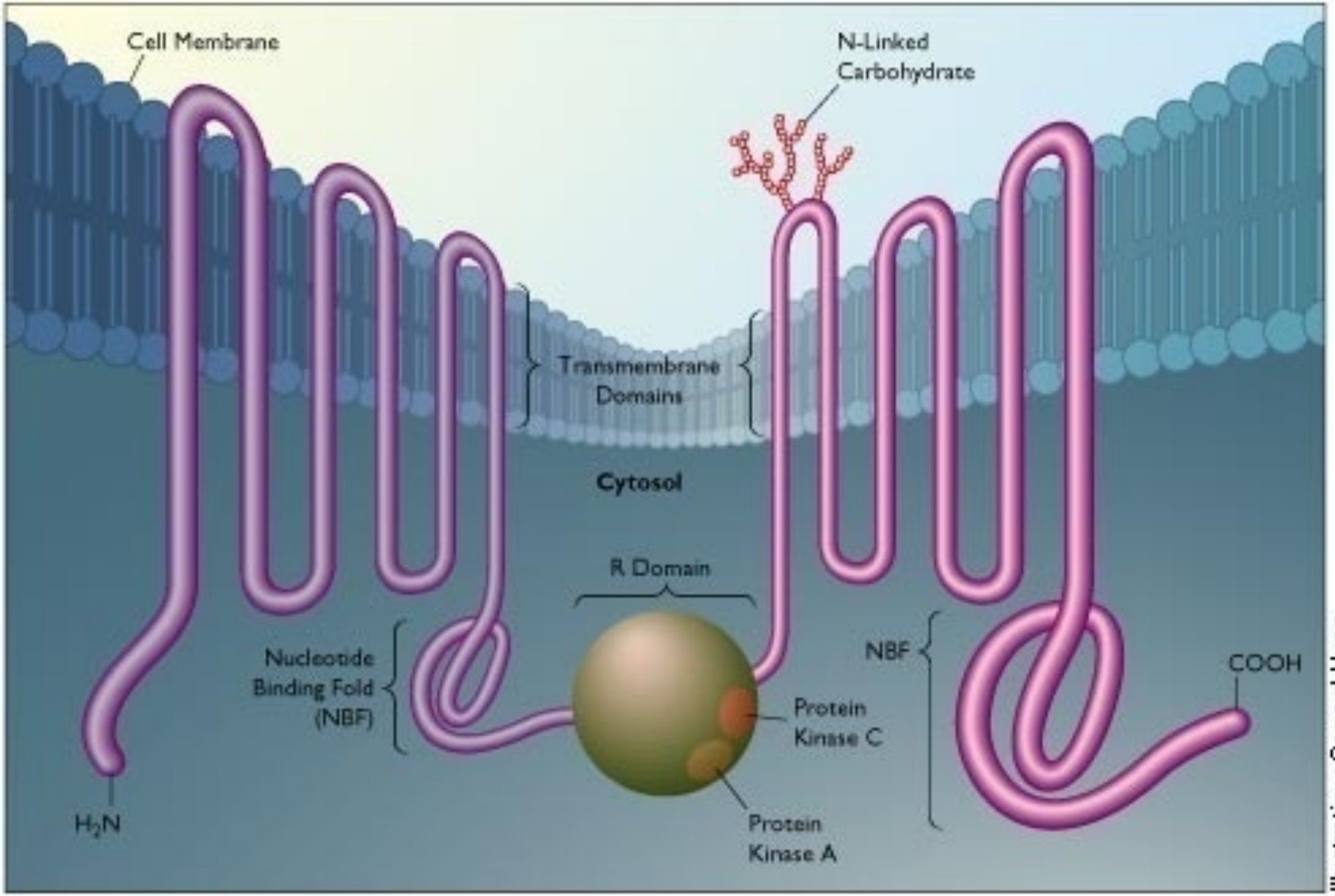


Illustration: Seward Hung

Figure 2. The amino acid sequence of CFTR suggests that it consists of two homologous structural units, each including a transmembrane domain and a nucleotide-binding fold, connected by a central regulatory (R) domain rich in phosphorylation sites. Experimental data confirm a transmembrane transport function with likely regulatory roles for adenosine triphosphate (ATP) binding and phosphorylation.

Cystic fibrosis

- progressive bronchiectasis
- exocrine pancreatic dysfunction
- recurrent sinopulmonary infections.

Introduction to population genetics

- Incidence varies from 1:2,500 in Europeans to 1:17,000 in Africans and 1:90,000 in Asians

- Many studies to understand these variations among ethnic groups and explain the high frequency of heterozygotes (> 4%) carriers

- The disease is severe and the males are sterile

- The explanation was sought in a selective advantage of heterozygotes

- Proved that the bacterium Salmonella typhi, responsible for typhoid fever, uses the CFTR channel as a receptor for introducing in the epithelial cells of the gut

- Animal models (mice heterozygous for the mutation delF508) confirmed a lower intestinal permeability to Salmonella

- It is estimated that the mutation delF508 had originated in Europe at least 10,000 years ago. In past centuries heterozygotes would have had a selective advantage during the many epidemics of typhoid that have presented

Inherited recessive diseases

Loss of function mutations

Heterozygotes (carriers) are normal, a reduction of 50% protein product is tolerated if the remaining 50% is enough for a normal function

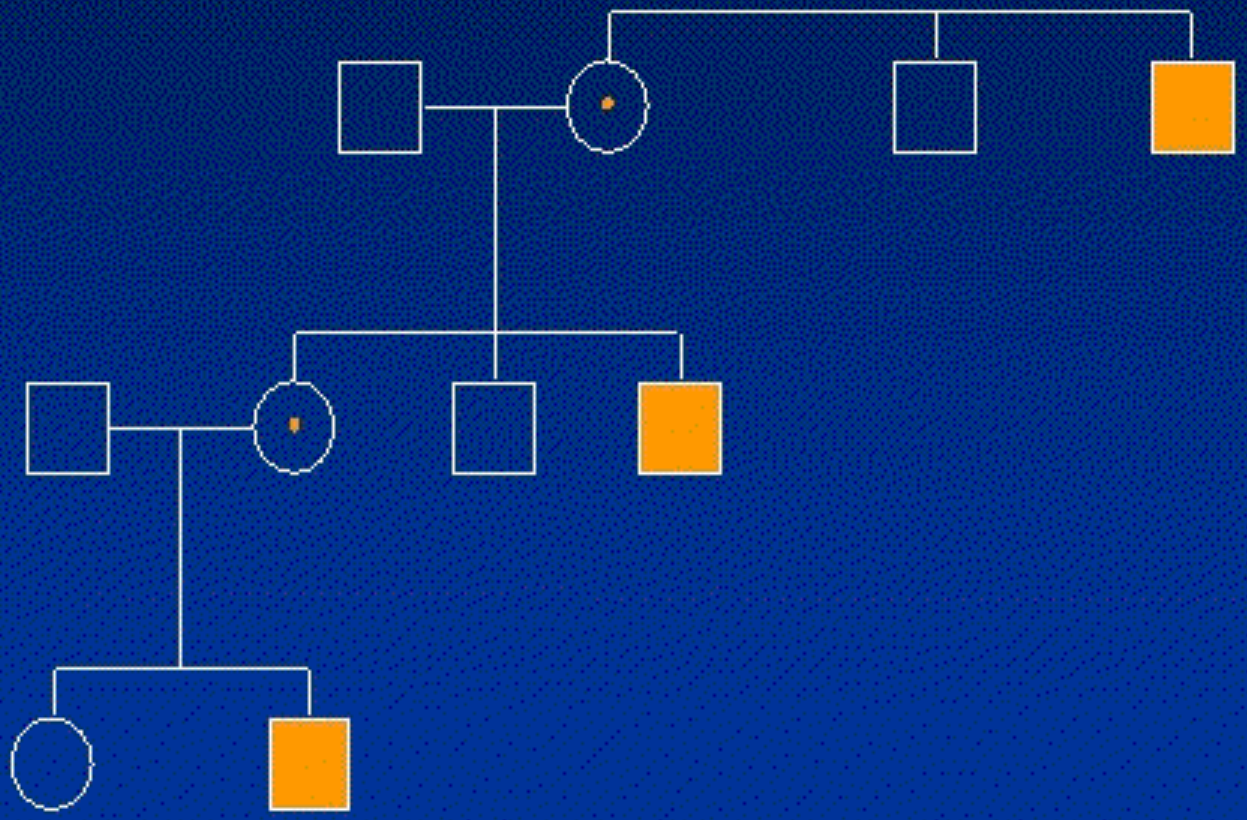
Example: falcemic trait, HbA HbS

Homozygotes are affected because protein is not produced or the one that is produced does not work normally

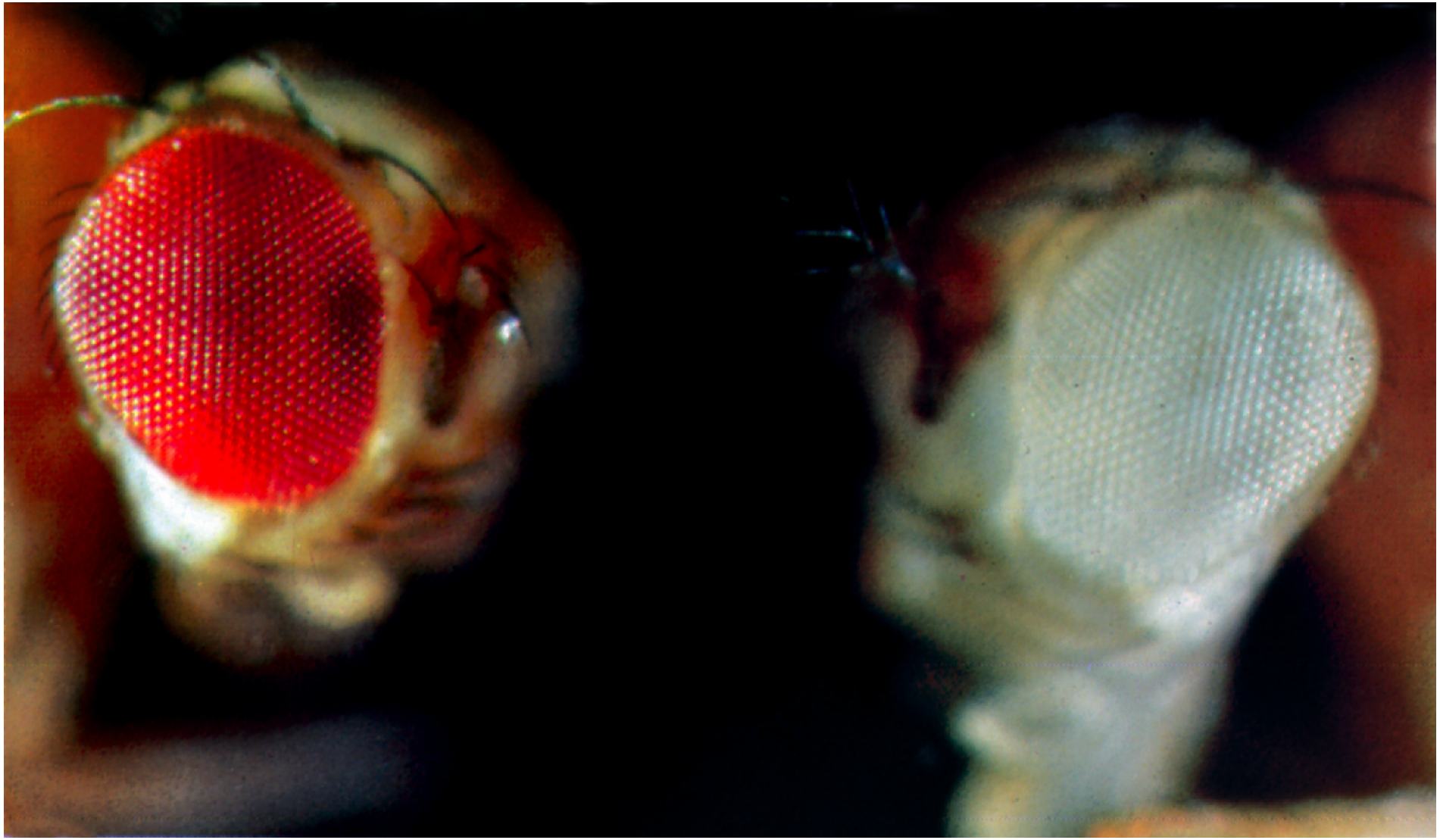
Example: sickle cell disease, HbS HbS

Sex chromosomes and sex-linked inheritance

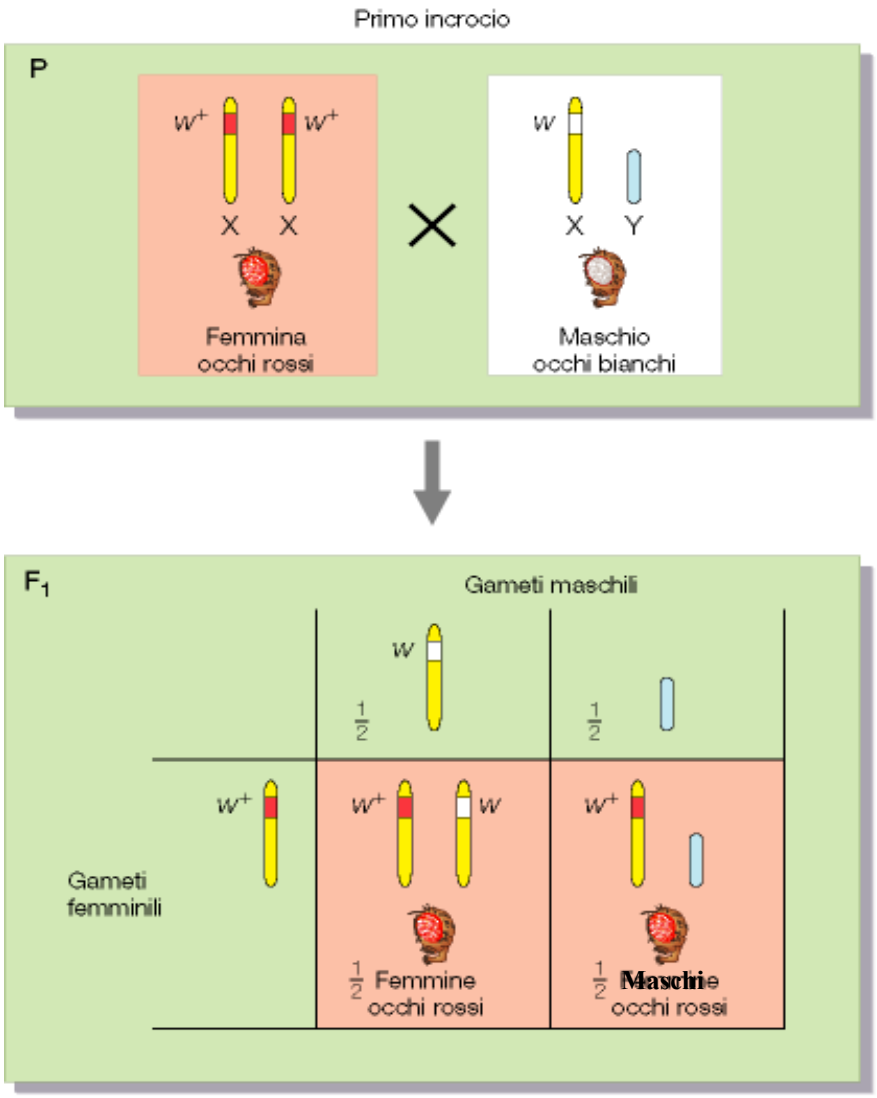
X-linked Recessive

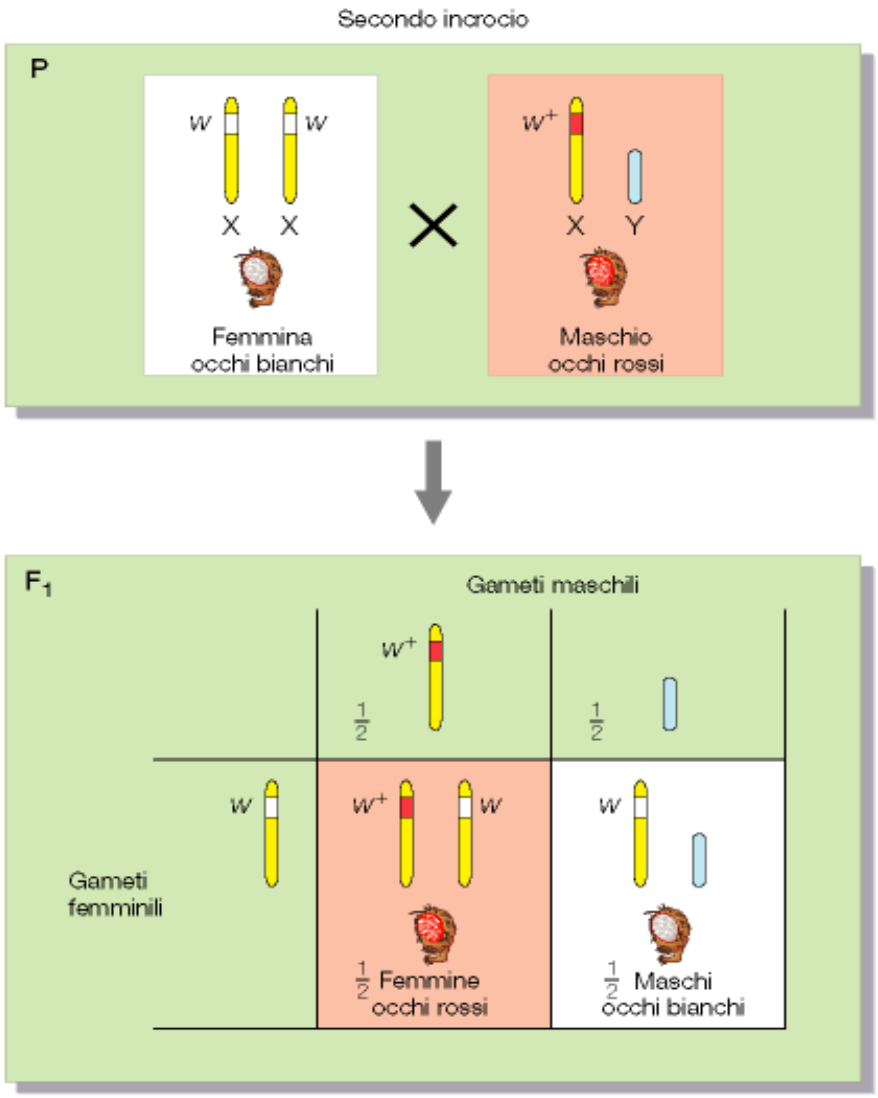


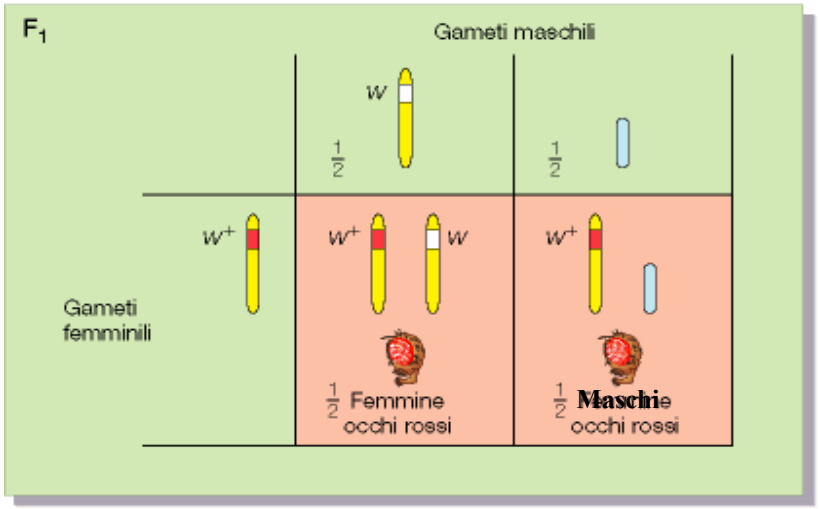
Red eyes and white eyes in *Drosophila*.
Morgan, the mid-20th century (early 1909)
Nobel, 1934

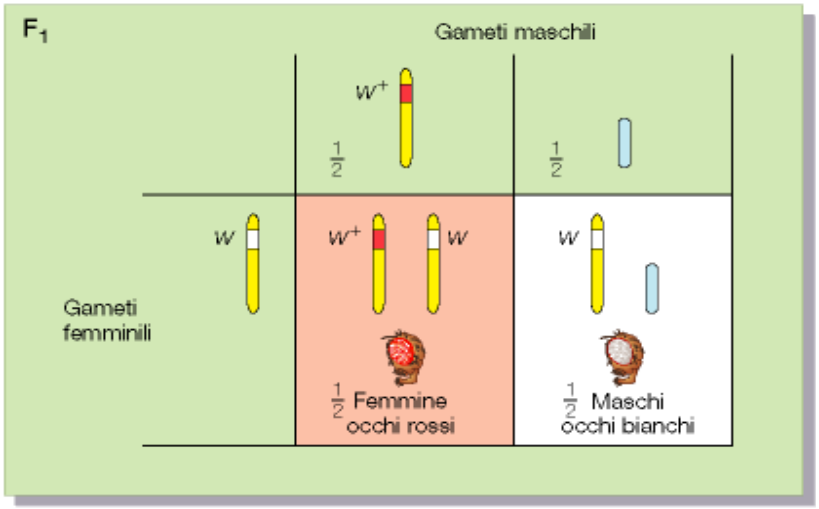


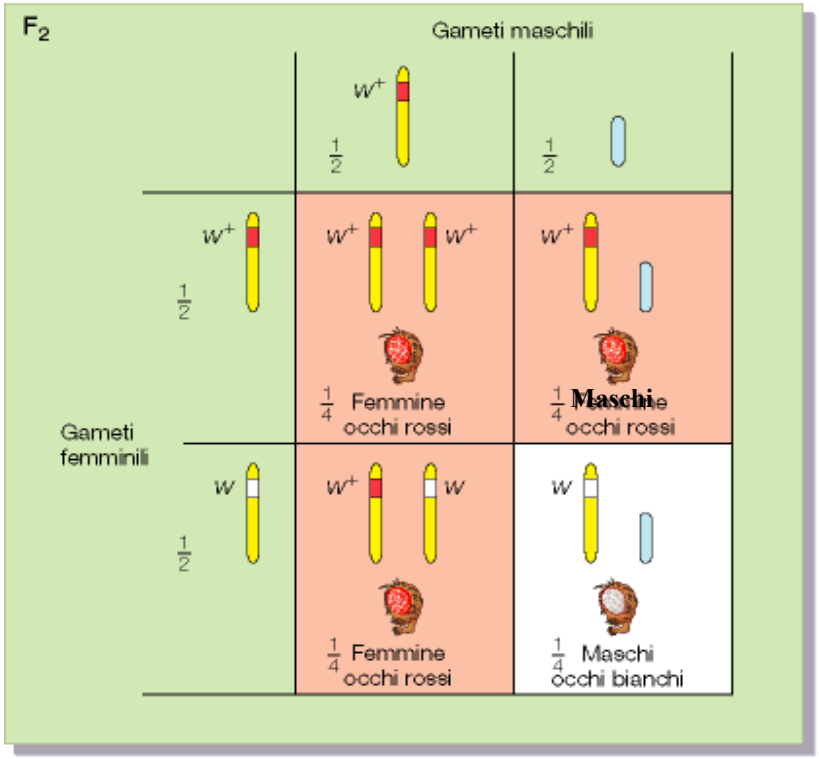
Reciprocal crosses between individuals of *Drosophila* with red eyes and individuals with white eyes give different results.






F1
Gameti maschili
w
1/2
1/2
w+
Gameti femminili
w+
w
w+
1/2 Femmine occhi rossi
1/2 Maschi occhi rossi


F1
Gameti maschili
w+
1/2
1/2
w
Gameti femminili
w+
w
w
1/2 Femmine occhi rossi
1/2 Maschi occhi bianchi


F2
Gameti maschili
w+
1/2
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Gameti femminili
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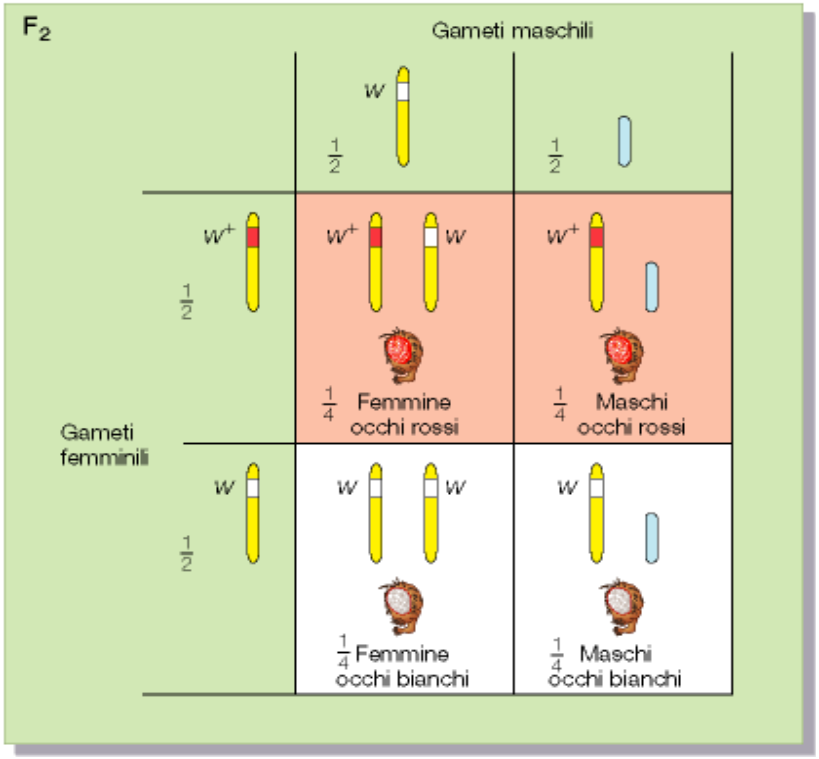
1/4 Femmine occhi rossi
1/4 Maschi occhi rossi
1/4 Femmine occhi rossi
1/4 Maschi occhi bianchi


F2
Gameti maschili
w
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Gameti femminili
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w
w
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1/4 Femmine occhi rossi
1/4 Maschi occhi rossi
1/4 Femmine occhi bianchi
1/4 Maschi occhi bianchi

Reciprocal crosses between individuals of Drosophila with red eyes and individuals with white eyes give different results. Why?

- The alleles are linked to the X chromosome. The transfer of X from one generation to the next, explains phenotypic ratios observed, which are different from those of genes carried by autosomes.

In Drosophila and in many other species used in Genetics the + sign at the top of the gene symbol indicates the normal allele, also known as wild-type allele. In this case w + = Red, w = white.

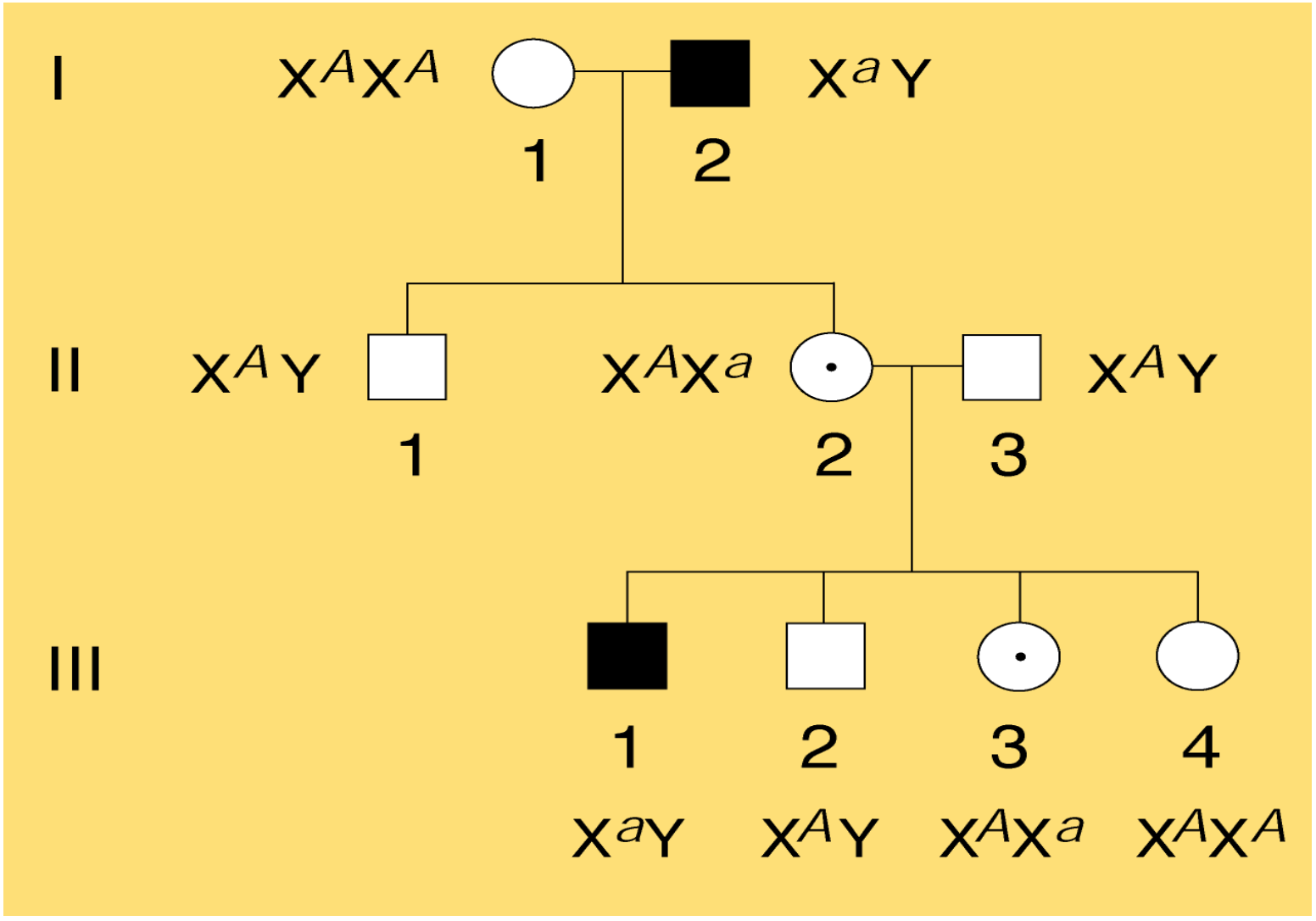
message

- The inheritance of sex-linked traits as a rule gives rise to different phenotypic ratios in both sexes and different ratios of progeny in reciprocal crosses.

Pedigree showing the expression of X-linked recessive alleles in males.

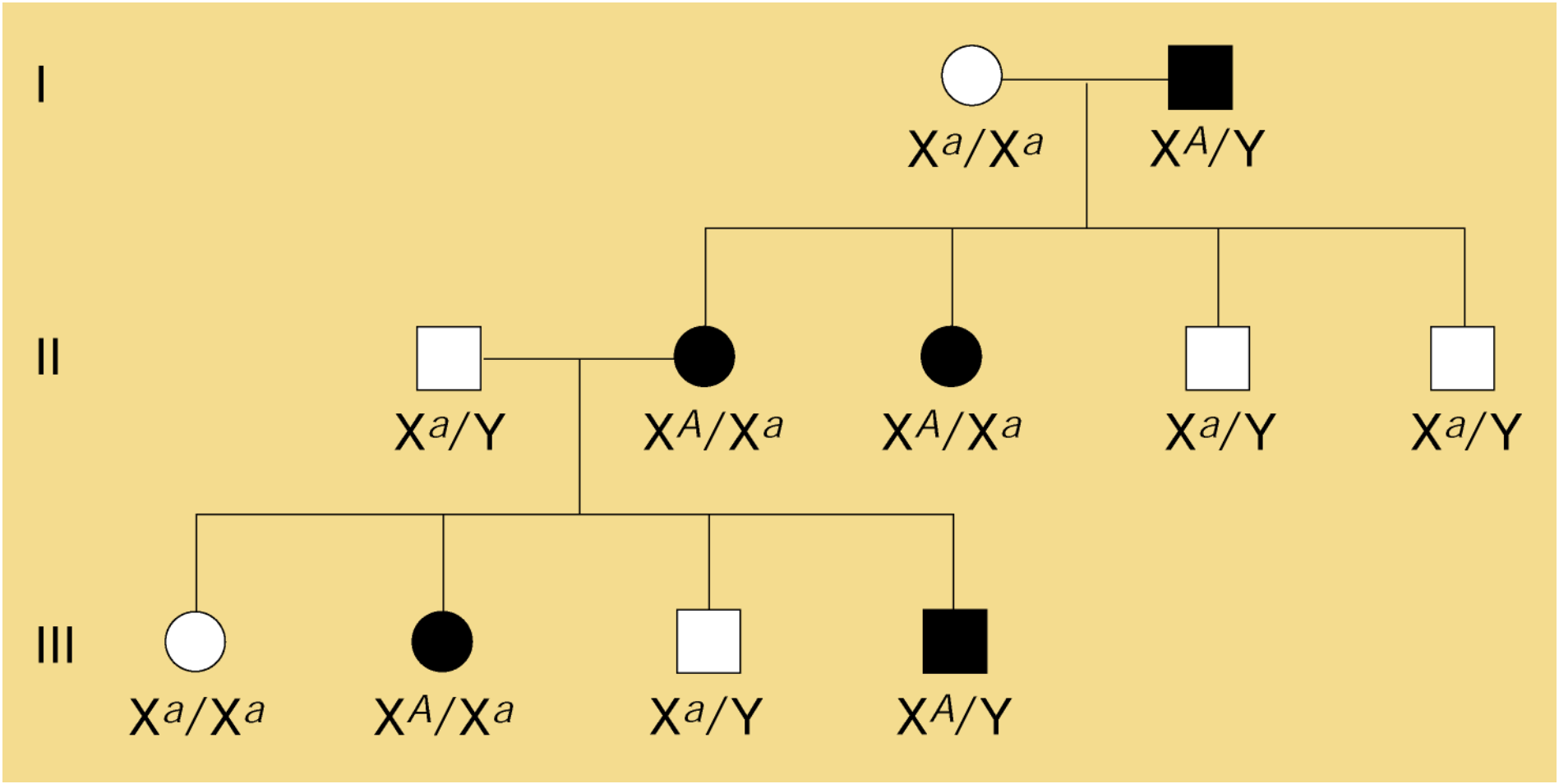
The daughters of males who exhibit the phenotype will bring the recessive allele, but this will not be expressed. These daughters will transmit the recessive allele to their sons, in which the phenotype will again be expressed.

Note that females III-3 and III-4 are phenotypically indistinguishable.



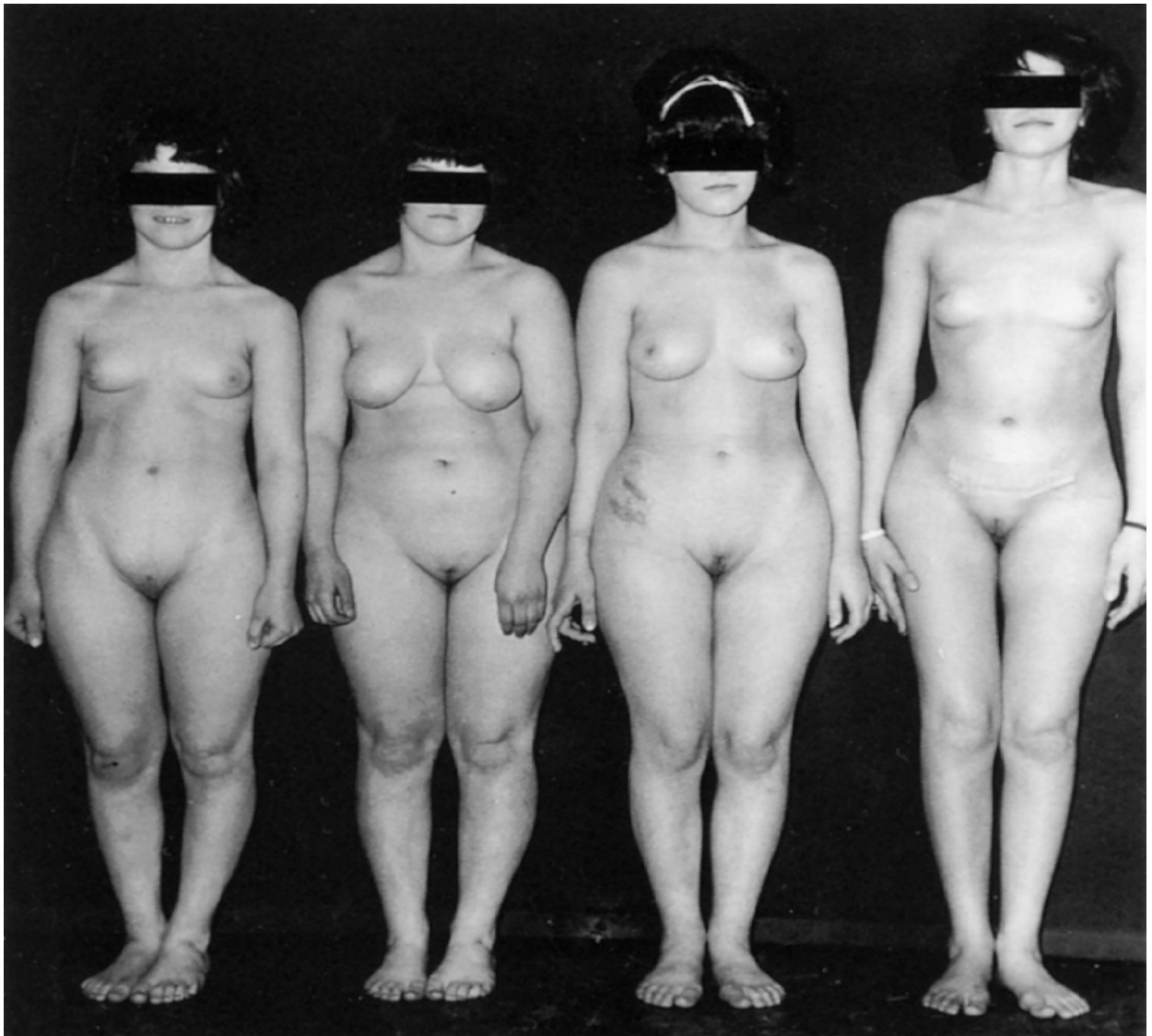
Family tree of an X-linked dominant condition.

All daughters of the male expressing a dominant X-linked phenotype exhibit the phenotype. The females heterozygous for an X-linked dominant allele convey the condition in half of the offspring, both males
and females.

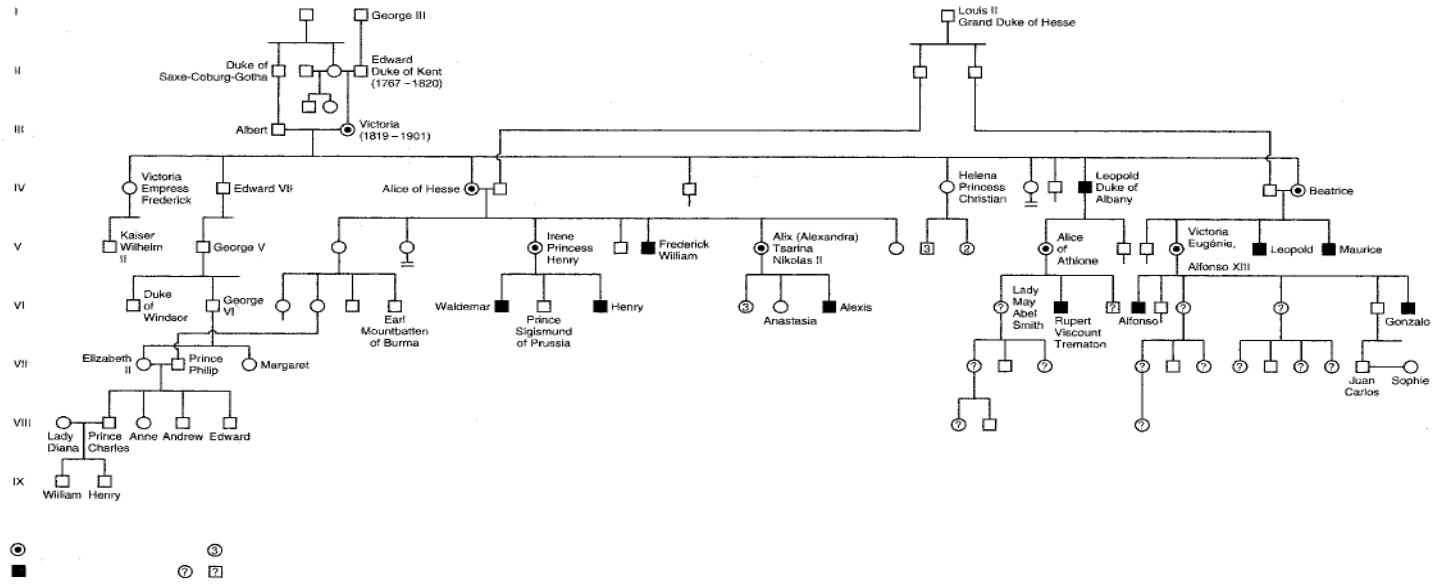


Four brothers suffering from testicular feminization syndrome and congenital insensitivity to androgens.

All four subjects shown have one X chromosome and a Y chromosome plus 44 autosomes, but they inherited an X-linked recessive allele conferring insensitivity to androgens (male hormones).



The transmission of hemophilia (X-linked recessive disorder) in the Royal families of Europe.



(a)

(b)

The transmission of hemophilia (X-linked recessive disorder) in the Royal families of Europe.

- In the germ-line cells of Queen Victoria or one of her parents appeared a recessive allele that causes hemophilia (clotting deficiency). This allele became widespread in other European royal houses as a result of marriages between members of different families.

- Partial pedigree shows affected males and female carriers (heterozygous).

TABLE 1. GENERAL FEATURES OF INHERITED DEFICIENCIES OF COAGULATION FACTOR ASSOCIATED WITH BLEEDING DISORDERS.

DEFICIENT COAGULATION FACTOR	INCIDENCE IN GENERAL POPULATION	CHROMOSOME INVOLVED	MODE OF INHERITANCE
Fibrinogen	1:1 million	4	Autosomal recessive
Prothrombin	1:2 million	11	Autosomal recessive
Factor V	1:1 million	1	Autosomal recessive
Factor VII	1:500,000	13	Autosomal recessive
Factor VIII	1:10,000	X	X-linked recessive
Factor IX	1:60,000	X	X-linked recessive
Factor X	1:1 million	13	Autosomal recessive
Factor XI	1:1 million	4	Autosomal recessive
Factor XIII	1:1 million	6 (subunit A) 1 (subunit B)	Autosomal recessive

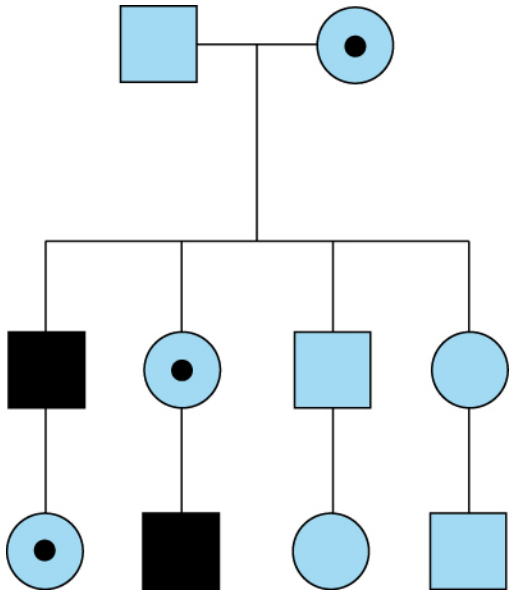
Color blindness: an example of inheritance of genes present on the X chromosome

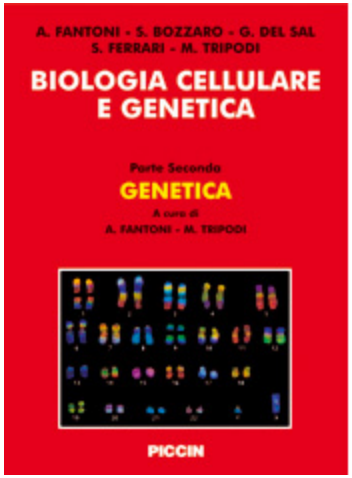
Fairly common color vision defect. Inability to distinguish red from green

In our population 1 male out of 12 is color blind

J. Dalton (UK, 1766-1844)

One of the fathers of modern physics.
He had a dichromatic vision.
About 150 years after his death, some Cambridge scientists showed on a fragment of his eyes a deletion of the gene coding for the Green opsin





FANTONI, BOZZARO, DEL SAL,
FERRARI, TRIPODI
BIOLOGIA CELLULARE
E GENETICA (Parte 2°)

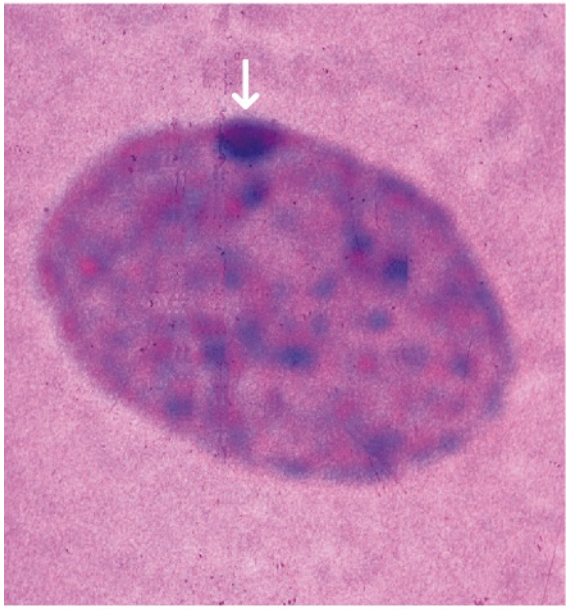
The first scientific paper on the subject of color blindness, ‘Extraordinary facts relating to the vision of colours’, was published by the English chemist John Dalton in 1798 after the realization of his own color blindness. Because of Dalton's work, the general condition has been called daltonism, although in English this term is now used only for deuteranopia.

Monochromacy, also known as "total color blindness", is the lack of ability to distinguish colors; caused by cone defect or absence. Monochromacy occurs when two or all three of the cone pigments are missing and color and lightness vision is reduced to one dimension.

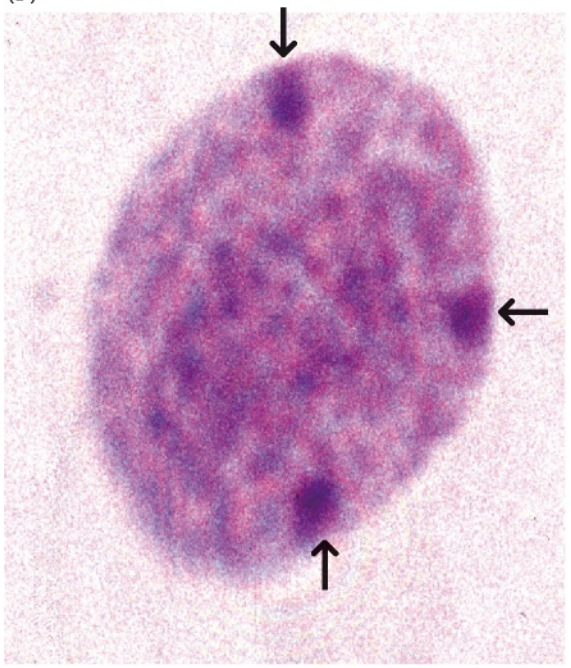
Dichromacy is a moderately severe color vision defect in which one of the three basic color mechanisms is absent or not functioning. It is hereditary and, in the case of protanopia or deuteranopia, sex-linked, affecting predominantly males. Dichromacy occurs when one of the cone pigments is missing and color is reduced to two dimensions. Dichromacy conditions are labeled based on whether the "first" (Greek: prot-, referring to the red photoreceptors), "second" (deuter-, the green), or "third" (trit-, the blue) photoreceptors are affected.

Sex determination in humans: an overview

(A)



(B)



In humans, with a system of sex determination of the type XX/XY, there must be systems that allow normal development despite the different number of chromosomes in males and females.

For this purpose several mechanisms have evolved: for the Y chromosome the workaround is to accommodate a very limited number of genes, which are linked to the normal development of male sexual functions.

In contrast, the X chromosome carries many essential genes. Humans, like all other mammals, uses the mechanism of X inactivation.

The inactivation is random and occurs in the embryo at the stage of about 10-20 cells.

Consequence of this is that the heterozygote female is a patchwork of cell clones each of which expresses alternative alleles of X chromosome of either paternal or maternal source.

If there is a mutation in a gene on the X chromosome, each cell clone of a female expresses either the wildtype or the mutant allele.

1. When the phenotype depends on a diffusible factor, as in the case of haemophilia (inability to clot blood) you will have a medium effect between clones that express the normal allele and those that express the mutated allele, so the female carriers can be abnormal from a biochemical point of view, but are usually healthy from a clinical point of view.

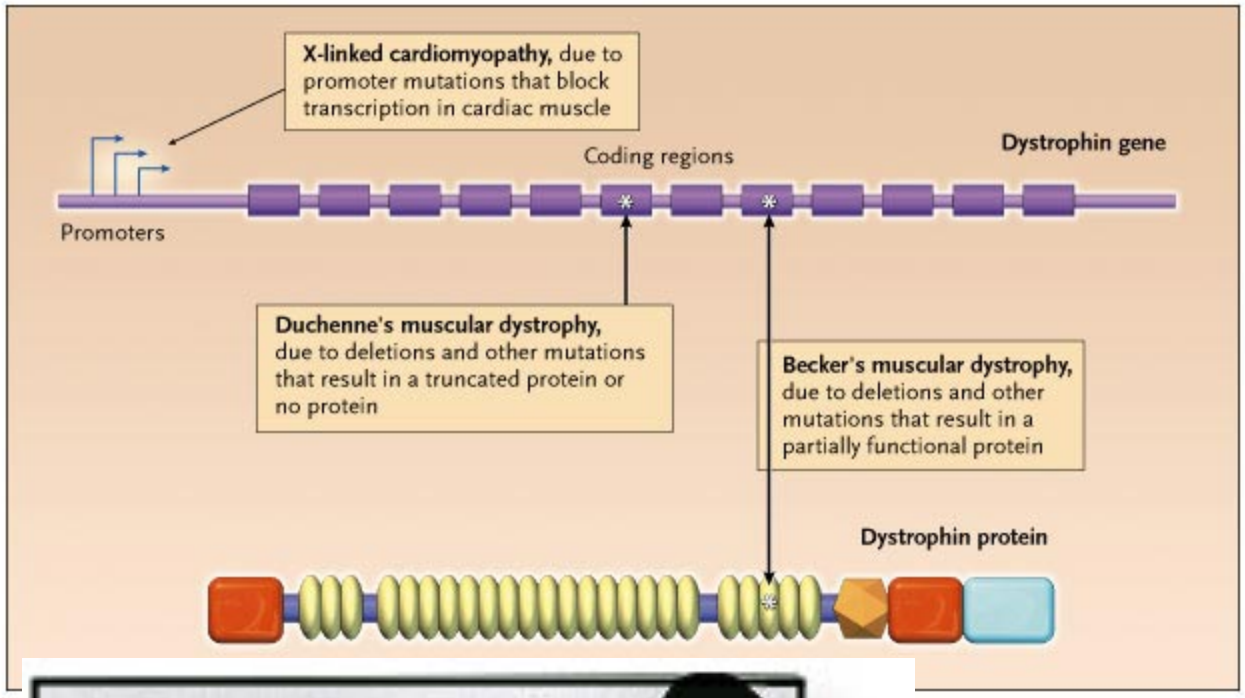
2. When the phenotype is represented by a property restricted to a group of cells, such as in hypohidrotic Ectodermal Dysplasia (lack of sweat glands accompanied by teeth and hair anomalies), female carriers have on the skin areas of healthy tissue and abnormal tissue.

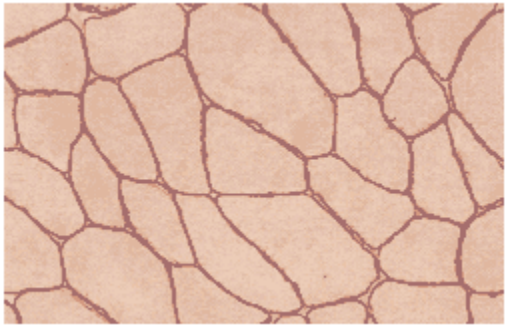
3. If an X-linked trait is pathogenic in males because of the absence of a certain category of cells, the same cells will show an X-inactivation in females that differs greatly from the 50% expected.
For example, men with Bruton's agammaglobulinemia do not produce mature B lymphocytes, while heterozygous women have mature B lymphocytes, but each of these has inactivated the X chromosome carrying the mutated allele. During embryogenesis many cells have inactivated chromosomes with the normal allele, but the cells descended from these do not develop into mature lymphocytes, so the population of lymphocyte B consists entirely of cells where it was inactivated the mutated X.

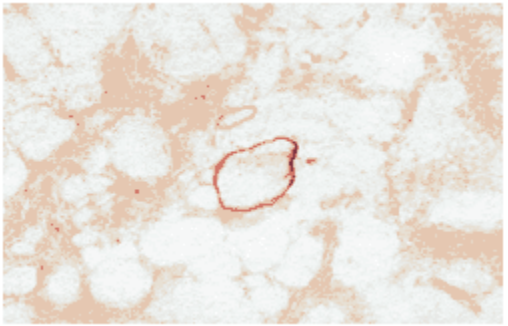
Women carriers of recessive X-linked pathological characters often have very mild symptoms of the disease. Occasionally, though, some very severe symptoms develop, because most critical tissue cells inactivated the X that brings the normal allele. These women are referred to as manifesting carrier.

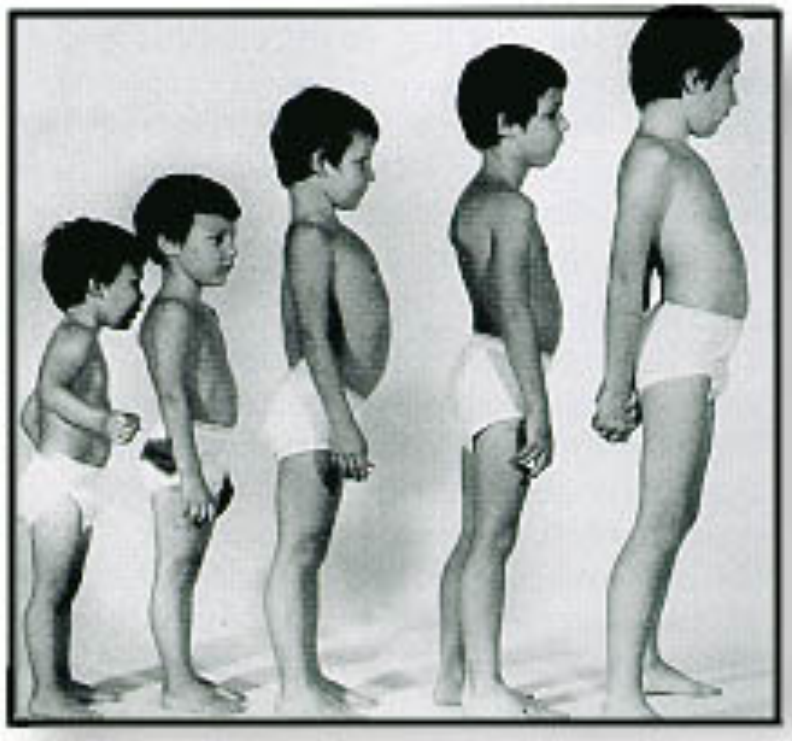
Similarly, female carriers of dominant X-linked diseases have a much less severe clinical picture of variable intensity that do men, as in many of their cells the normal allele is expressed.

G B A Duchenne


X-linked cardiomyopathy, due to promoter mutations that block transcription in cardiac muscle
Dystrophin gene
Coding regions
Promoters
Duchenne's muscular dystrophy, due to deletions and other mutations that result in a truncated protein or no protein
Becker's muscular dystrophy, due to deletions and other mutations that result in a partially functional protein
Dystrophin protein

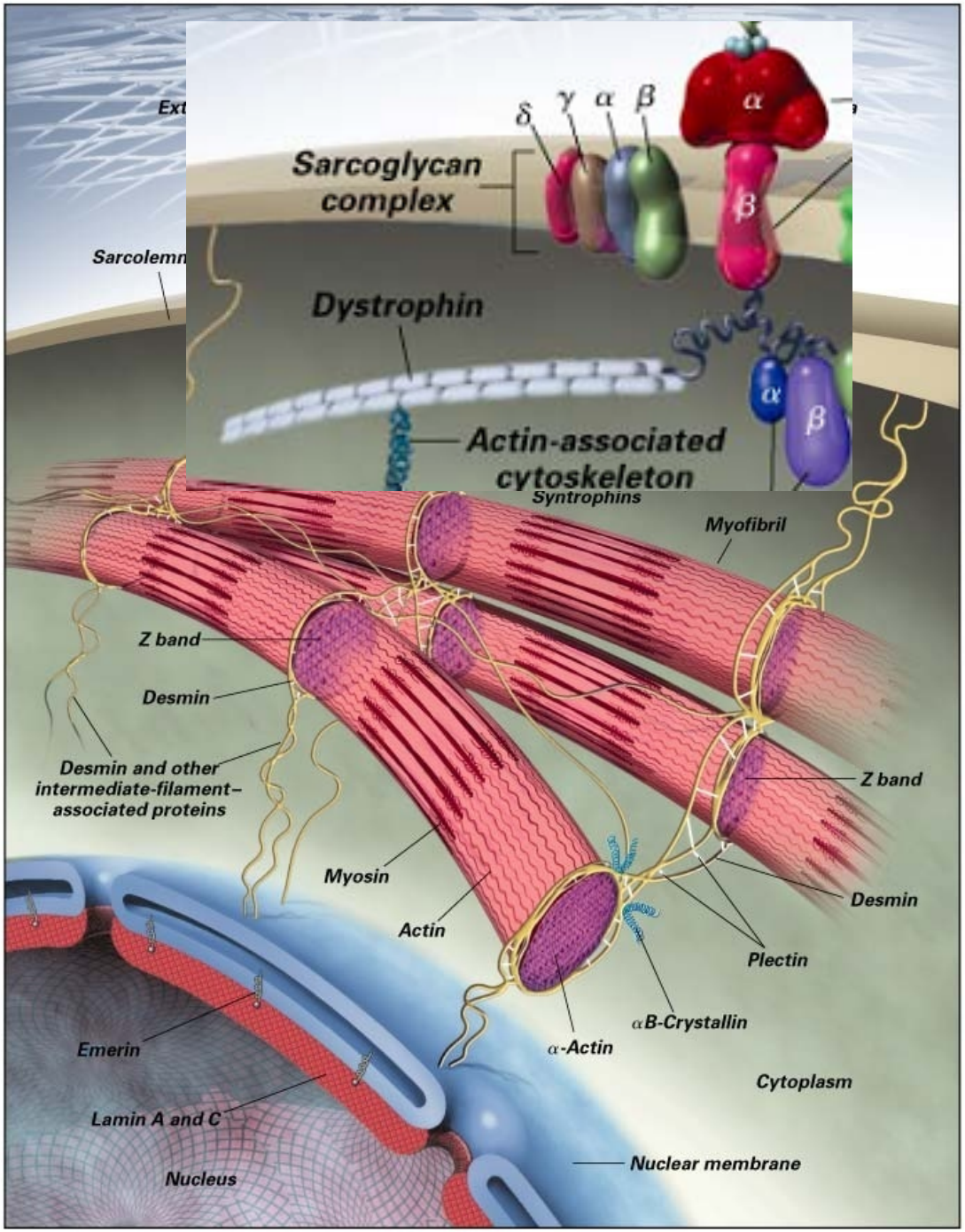






Duchenne muscular dystrophy

- Progressive muscle weakness
- Onset between 2-4 years of age
- >95% in wheel chair by 12 years of age
- Death between 15-25 years of age
- Variable mental retardation
- Frequent cardiac involvement
- Orthopaedic deformities

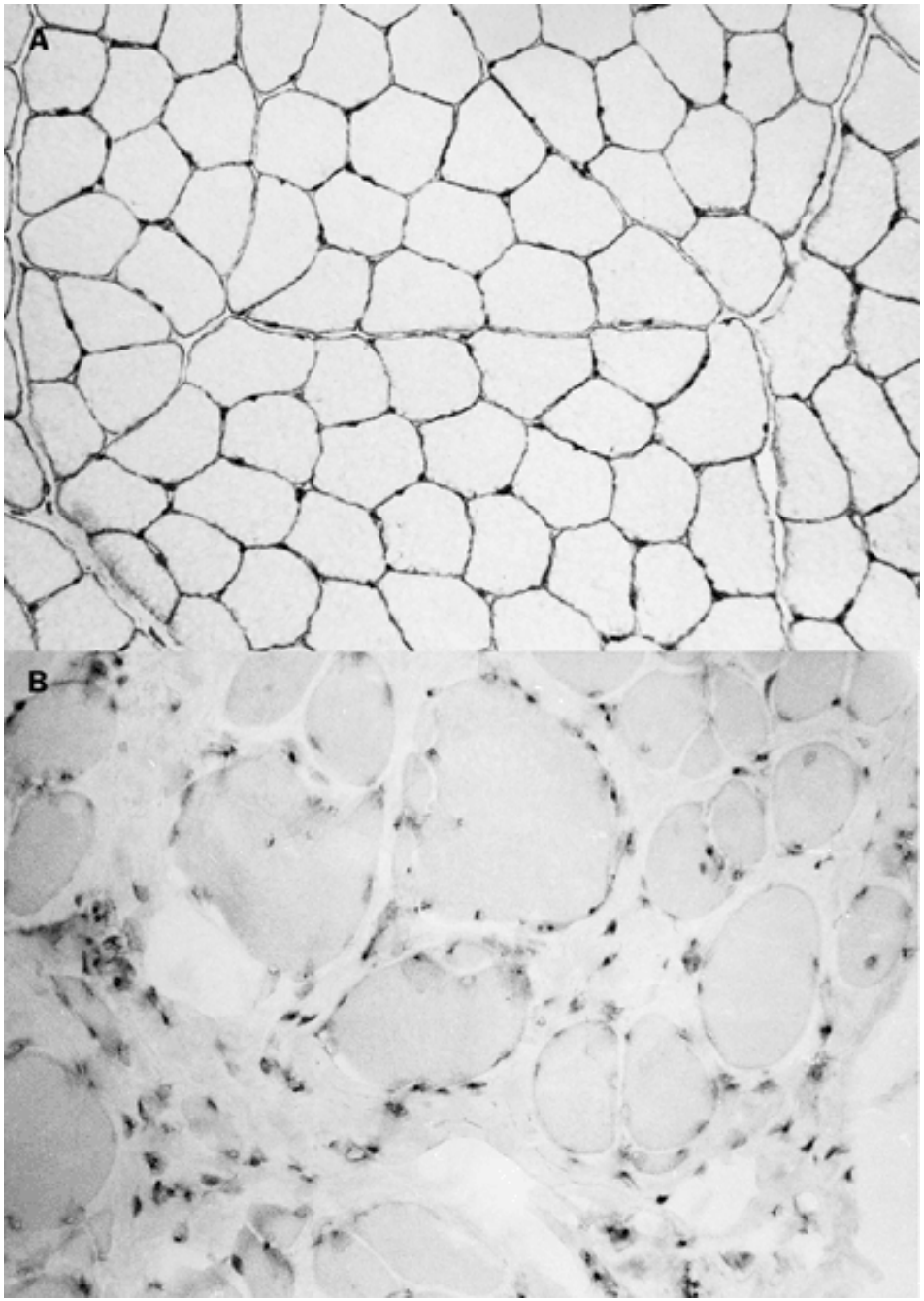


In people with Duchenne muscular dystrophy we observe the progressive death of muscle fibers, first at the level of arms and legs, then at the level of heart and respiratory system: this is because due to a genetic defect the cells are unable to produce dystrophin, a protein located on the surface of muscle cells in combination with a number of other proteins.

For the identification of the gene for Duchenne dystrophy it was employed for the first time a molecular genetic technique, called positional genetics, used when you do not know the protein produced by the altered gene.

It is based on the fact that it is possible to identify a gene by localising it on a chromosome, using DNA markers specific to a particular chromosomal locus.

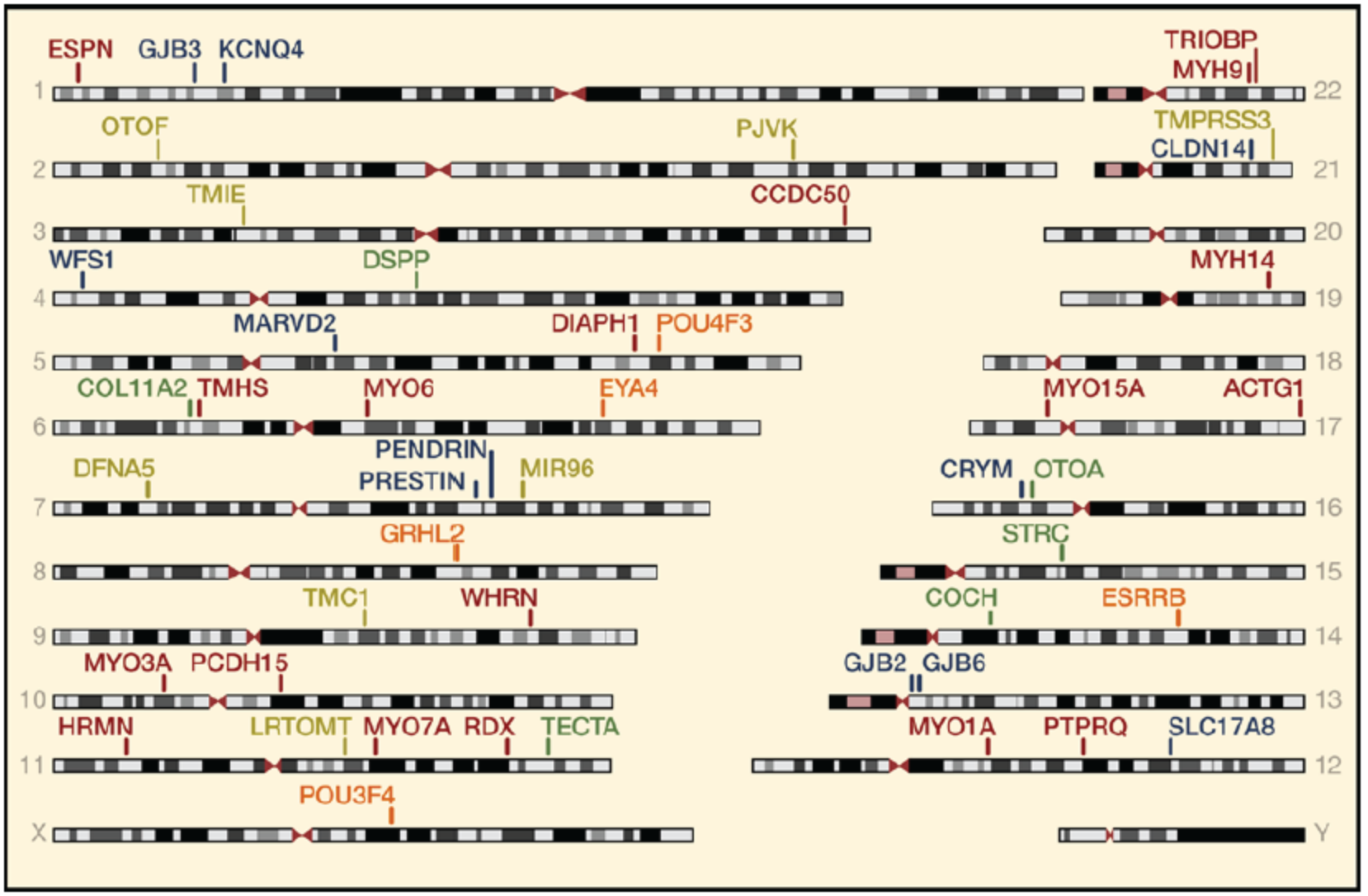
For Duchenne muscular dystrophy, it was known for many years that the gene was located on chromosome X (since the disease is inherited as a recessive trait associated with sex). In 1986, Kunkel and coworkers isolated the responsible gene and named it dystrophin.


A
B

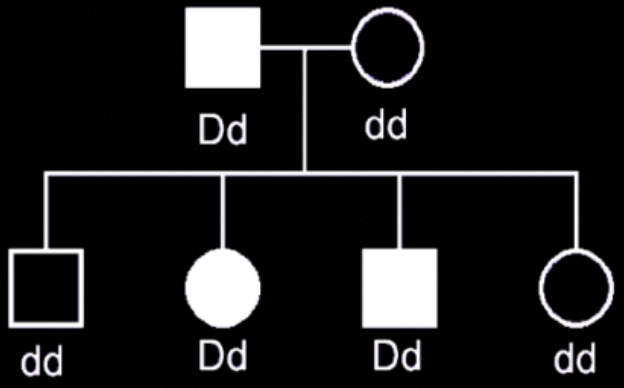
Early Childhood Hearing Loss

1 out of every 1,000 children is born deaf.

Approximately 1 out of every 300 children
has a hearing impairment
significant enough to affect speech
and language development, education,
and social development.

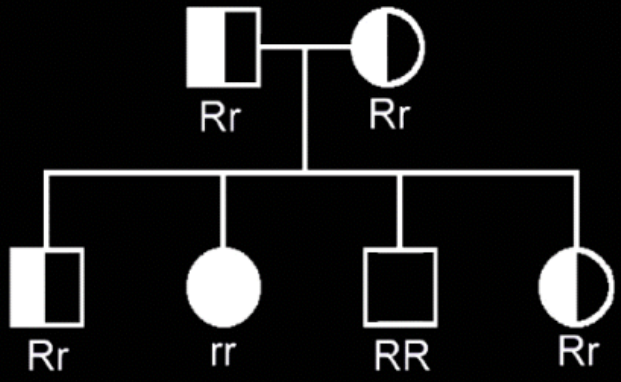

ESPN
GJB3
KCNQ4
TRIOBP
MYH9
1
22
OTOF
PJVK
TMPRSS3
CLDN14
2
21
TMIE
CCDC50
3
20
WFS1
DSPP
MYH14
4
19
MARVD2
DIAPH1
POU4F3
5
18
COL11A2
TMHS
MYO6
EYA4
MYO15A
ACTG1
6
17
PENDRIN
DFNA5
PRESTIN
MIR96
CRYM
OTOA
7
16
GRHL2
STRC
8
15
TMC1
WHRN
COCH
ESRRB
9
14
MYO3A
PCDH15
GJB2
GJB6
10
13
HRMN
LRTOMT
MYO7A
RDX
TECTA
MYO1A
PTPRQ
SLC17A8
11
12
POU3F4
X
Y

Modes of Inheritance



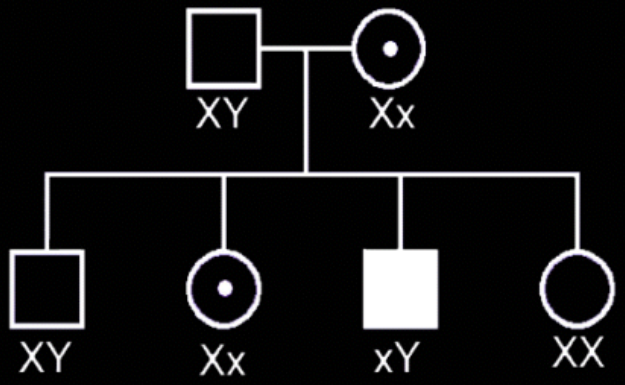
Autosomal Dominant

DFNA#



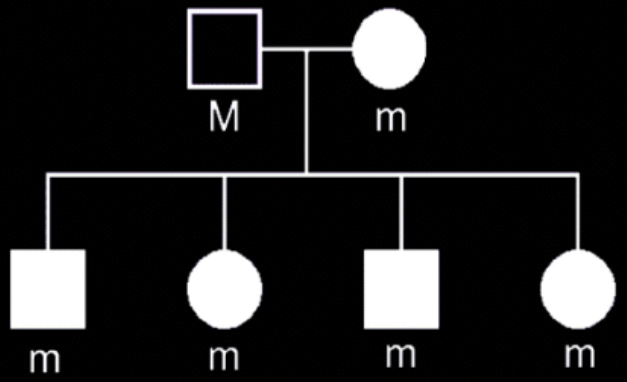
Autosomal Recessive

DFNB#



X-Linked

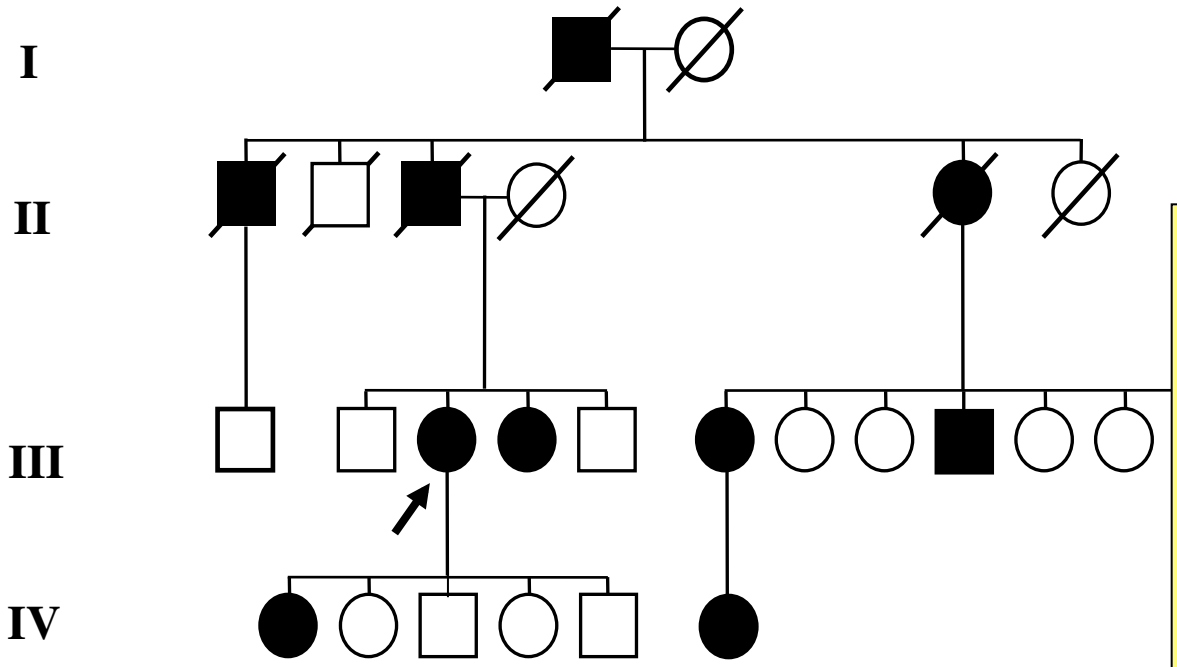
DFN#



Mitochondrial

from:

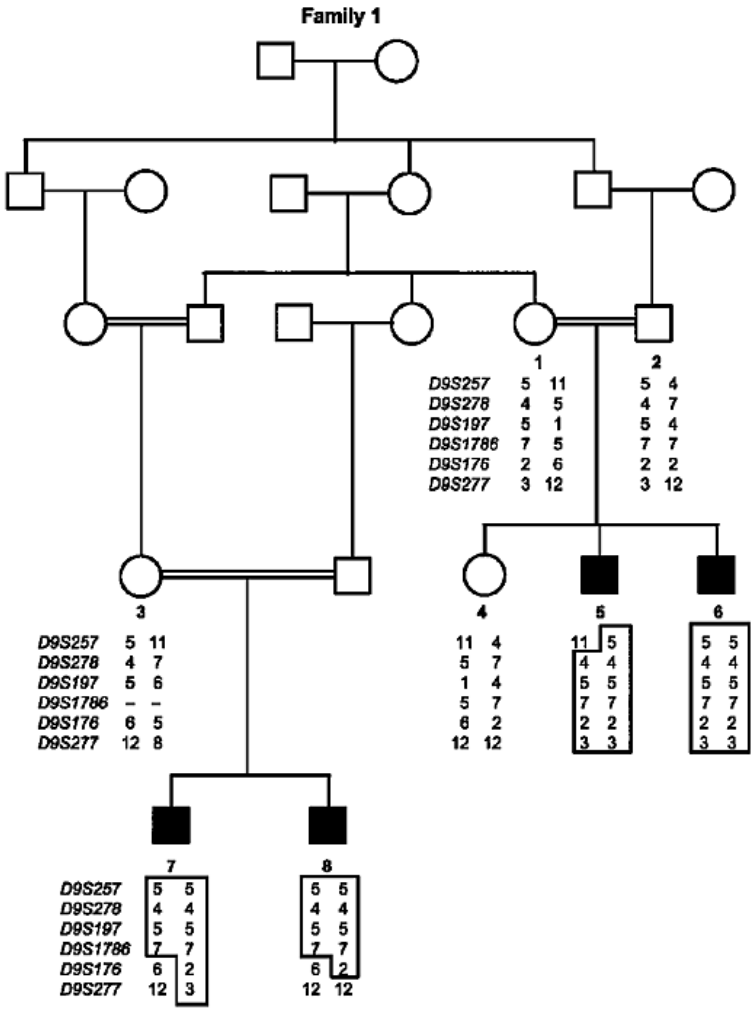
Heidi L Rehm,



What is the mode of transmission of this disease?

- autosomic?
- X-linked?

- dominant?
- recessive?



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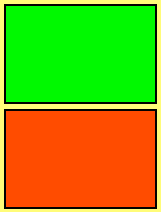
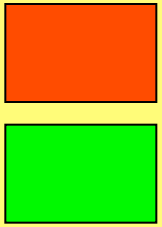


- dominant?
- recessive?



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- dominant?
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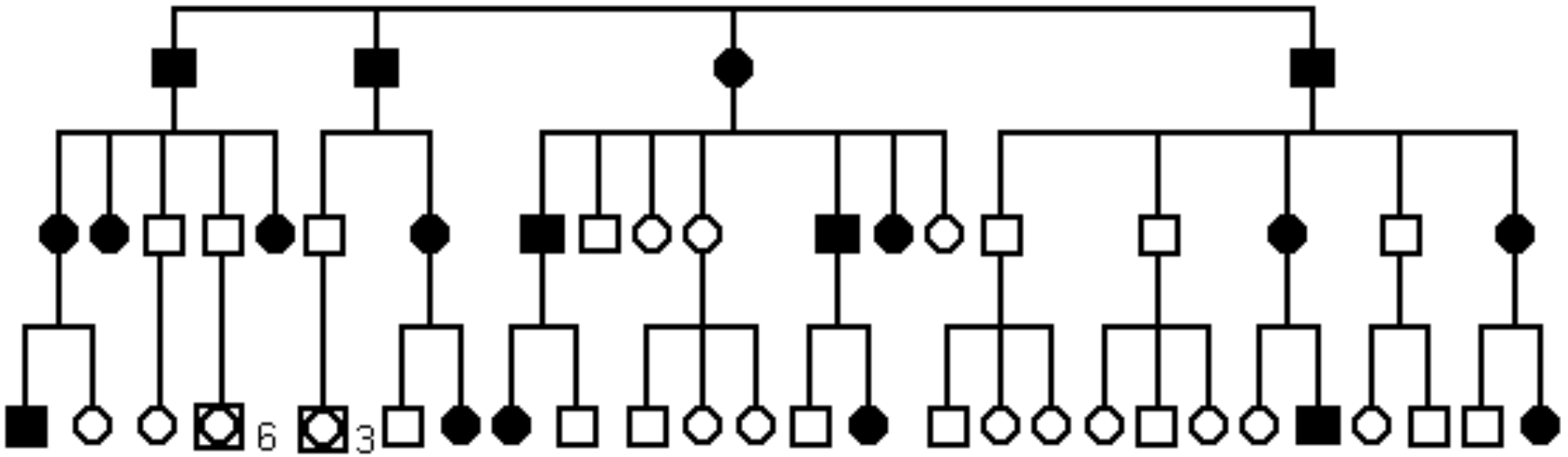
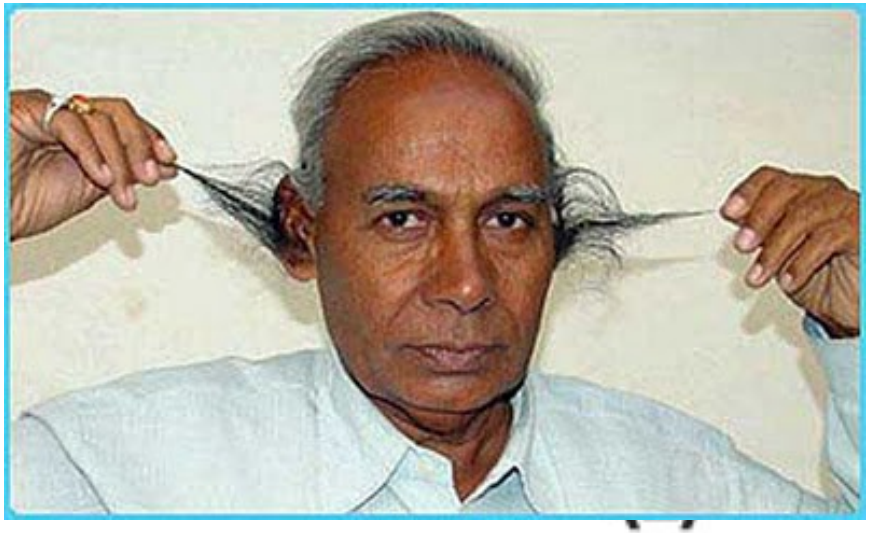
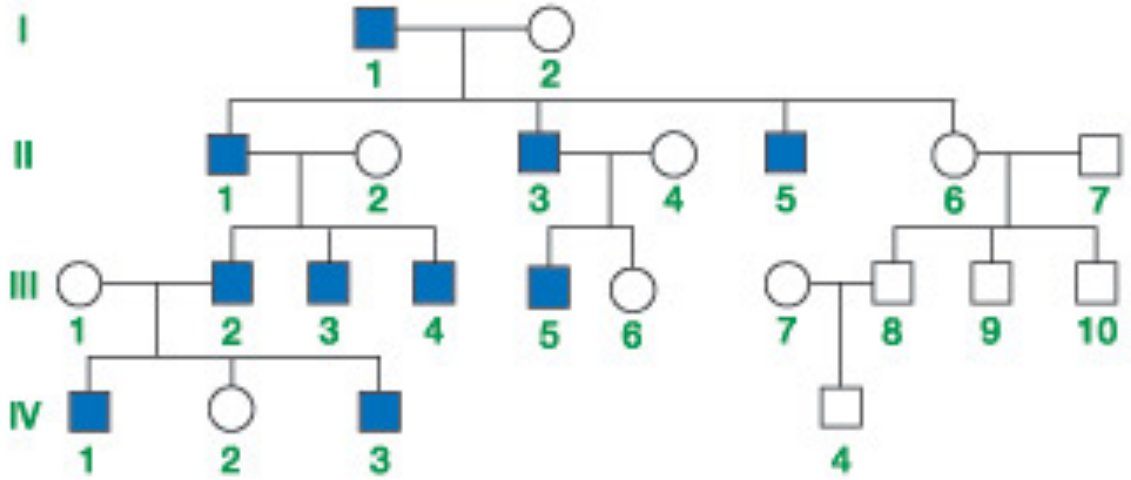


- autosomic?
- X-linked?

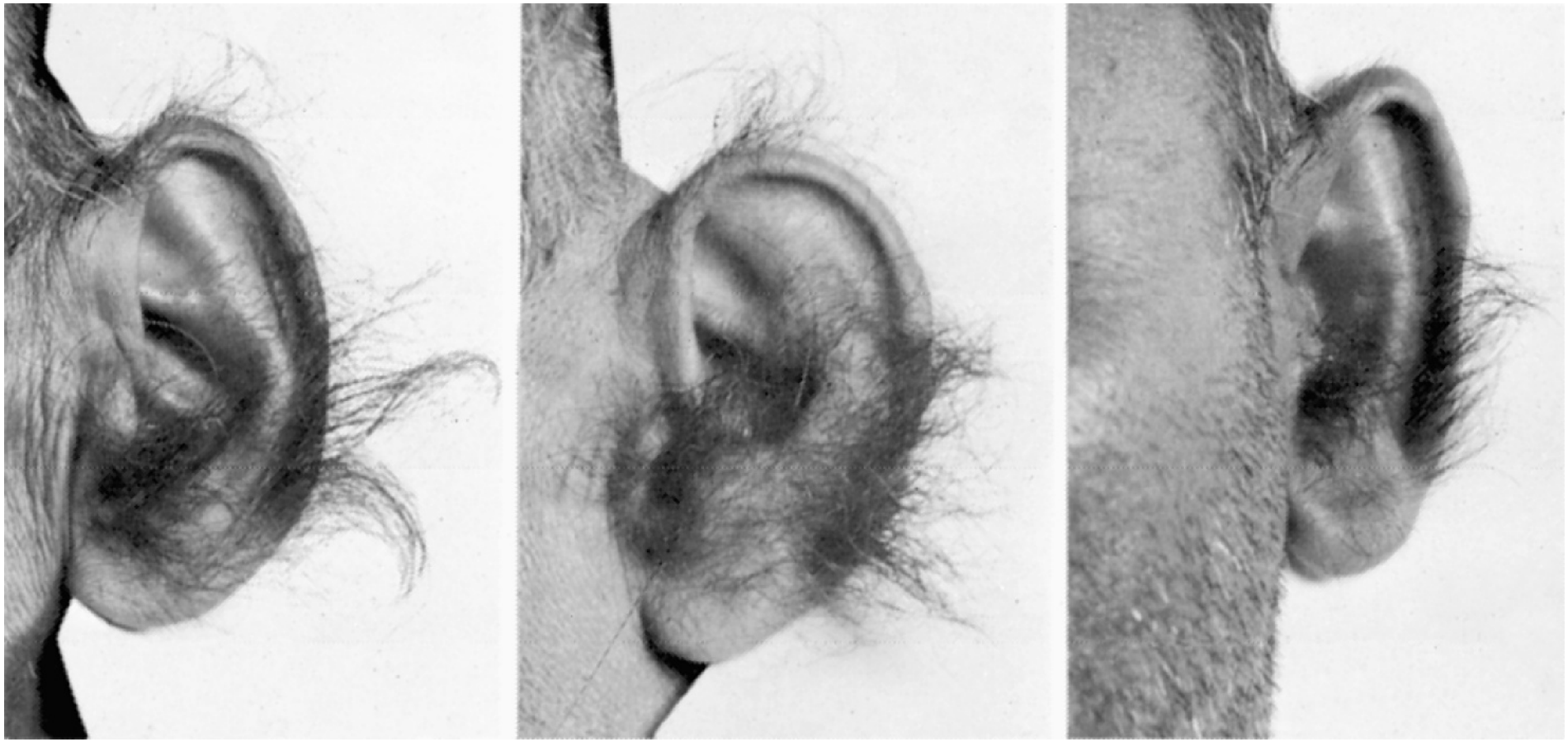


Y-linked inheritance



Hairiness in margins of pinnae (auricles).

It is supposed that this phenotype is determined by an allele of a gene linked to the Y.



message

- The pattern of inheritance in which a certain phenotype is manifested in unequal proportions in males and females allows one to locate involved genes on one of the sex chromosomes.

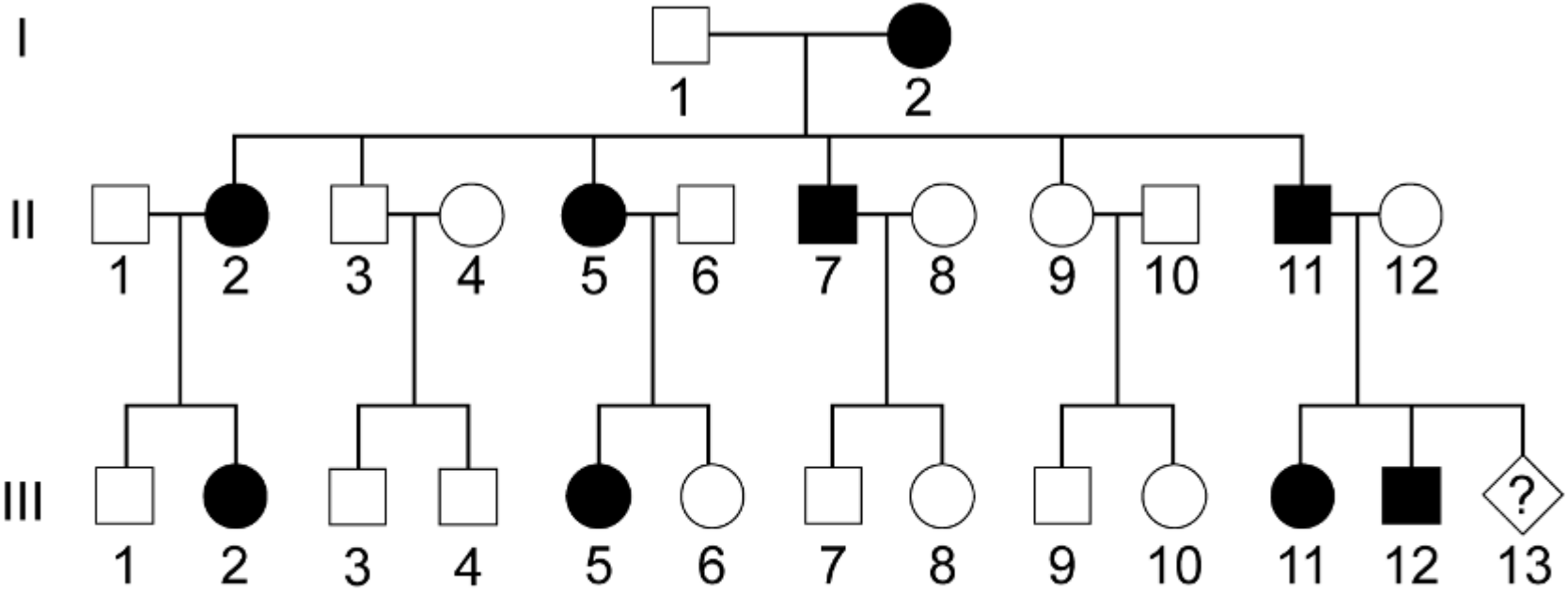
- Summarising…

Genetic diseases by mutation in one allele

Monoallelic mutations can cause autosomal dominant disorders or X-linked dominant disorders (or X-linked recessive in men)

- If the dominant transmitted disease is severe during fertile age and therefore limits or annuls the reproductive capacity (low fitness), monoallelic mutations are new and often randomly distributed
- If the dominant disease is not serious during fertile age and in no way limits the reproductive capacity (normal fitness), monoallelic mutations are inherited from a parent and often handed down for many generations

Autosomal dominant inheritance with complete penetrance (no fitness modifications)



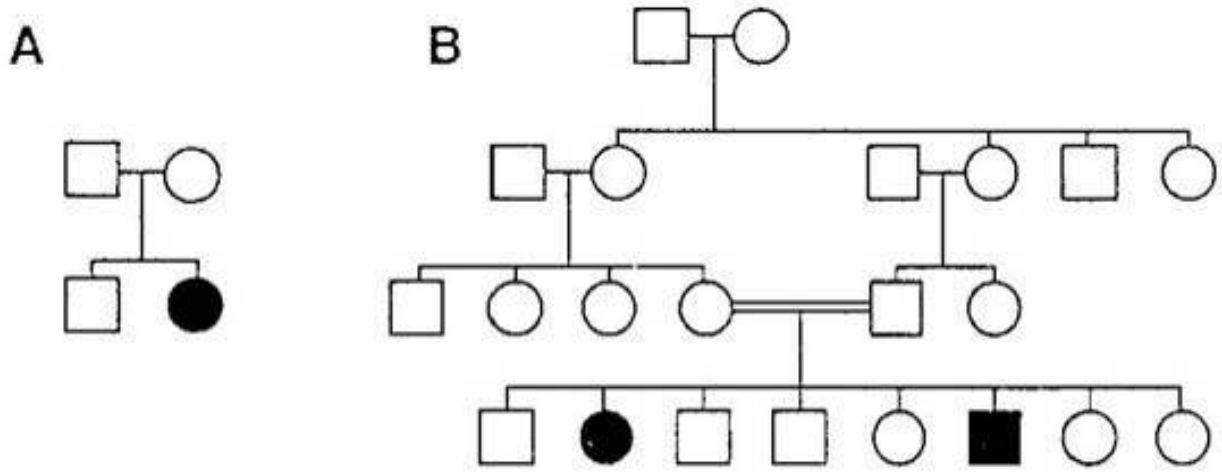
Genetic diseases by mutation in two alleles

Biallelic mutations can cause autosomal recessive disorders

- If the recessively transmitted disease is severe during fertile age and limits or annuls the reproductive capacity (low fitness), mutations do not disappear anyway because the carriers are 10-10,000 times as many as the affected
- Mutations usually are transmitted to 100-1000 generations, while new mutations are rare
- Only if the disease is due to biallelic mutations it has a signature that characterizes an ethnic origin and a common healthy heterozygous founder

Genetic diseases by mutation in two alleles

- The high number of carriers is a risk factor for compound heterozygosity (two different mutations in both alleles). This could be caused by a better fitness of heterozygotes against a negative factor (see A)
- Inbreeding is a risk factor for homozygosity (two identical alleles) even if the mutation is rare (see B)



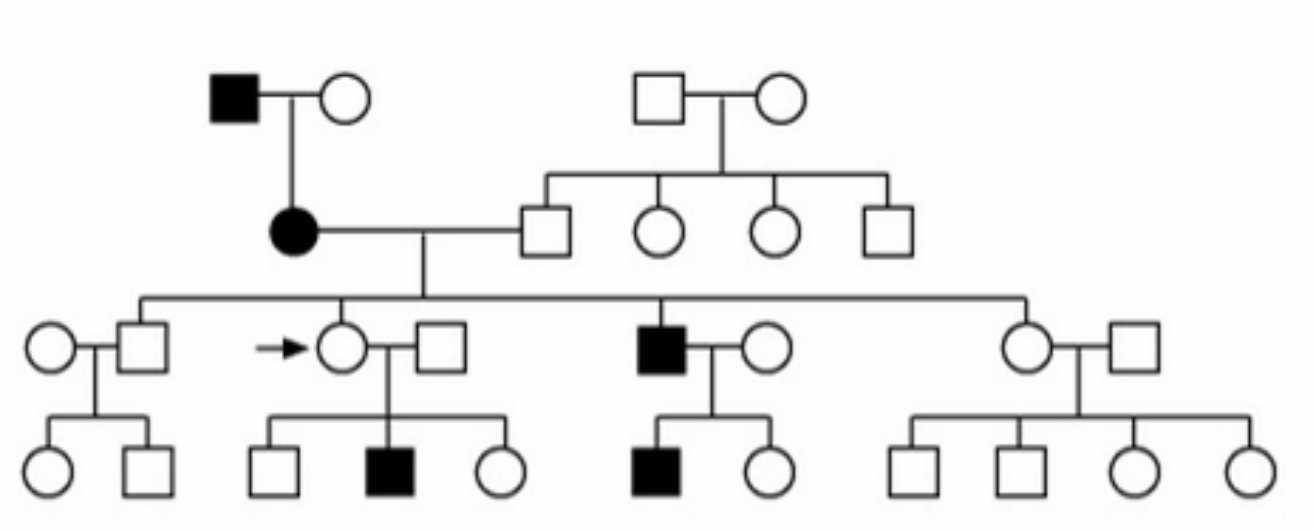
What is a causative mutation?

A variation of DNA sequence…

- .. which is found only in affected individuals
- .. which is never found in those not affected
- .. that explains the disease process
- .. that, when corrected for time, restores a normal phenotype

- .. which is found only in affected individuals
- .. which is never found in those not affected

incomplete penetrance



which is found more frequently in affected than non-affected individuals...

Dinamic mutations

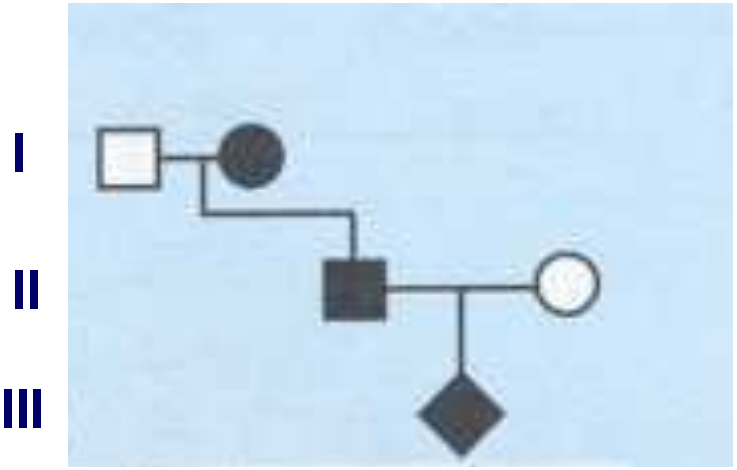
Diseases associated with the expansion of trinucleotide repeats

Disease	Gene Locus/Protein	Repeat	Location
Fragile X syndrome	Xq27.3/FMR-1 protein	CGG	Noncoding
Fragile XE syndrome	Xq28/FMR-2 protein	GCC	Noncoding
Friedreich ataxia	9q13-9q21.1/frataxin	GAA	Noncoding
Myotonic dystrophy 1	19q13/myotonic dystrophy protein kinase	CTG	Noncoding
Myotonic dystrophy 2	3q21	CCTG	Noncoding
Spinobulbar muscular atrophy	Xq13-Xq21/androgen receptor	CAG	Coding
Huntington disease	4p16.3/huntington	CAG	Coding
Dentatorubralpallidoluysian atrophy	12p13.31/atrophin-1	CAG	Coding
SCA type 1	6p23/ataxin-1	CAG	Coding
SCA type 2	12q24/ataxin-2	CAG	Coding
SCA type 3 (Machado-Joseph disease)	14q32.1/ataxin-3	CAG	Coding
SCA type 6	19p13/α-1A (voltage-ependent calcium channel subunit)	CAG	Coding
SCA type 7	3p12-3p13/ataxin-7	CAG	Coding
SCA type 8	13q12/none identified	CTG	?
SCA type 12	5q31-5q33	CAG	Noncoding

Mendelian pedigree patterns

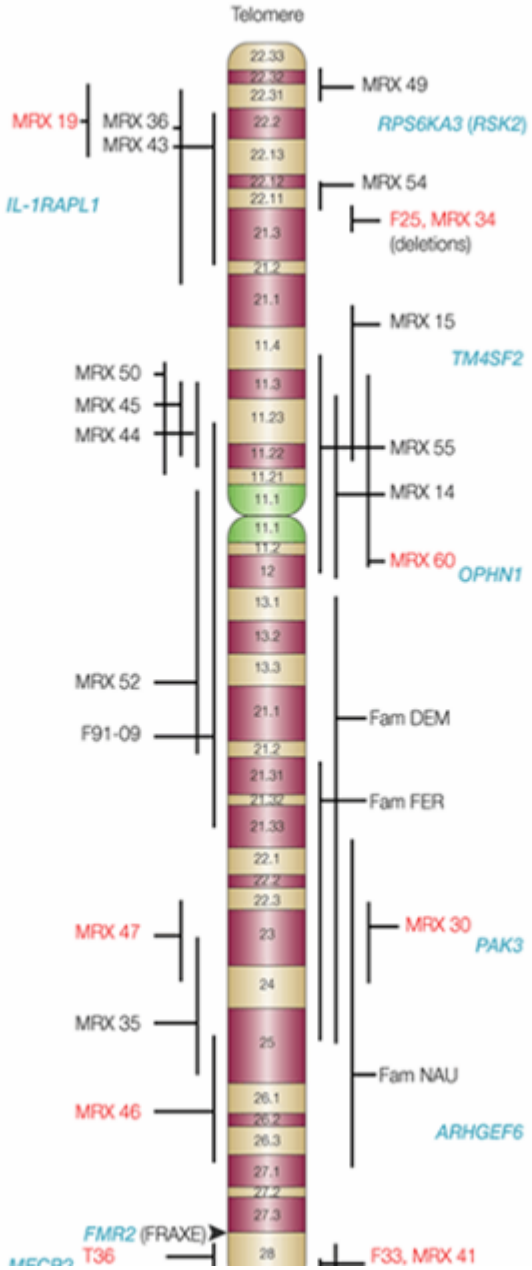
further complications

anticipation = phenotypic severity increases with each generation



Age of onset grandmother > father

Anticipation: the earliest onset and increasingly severe phenotype in successive generations



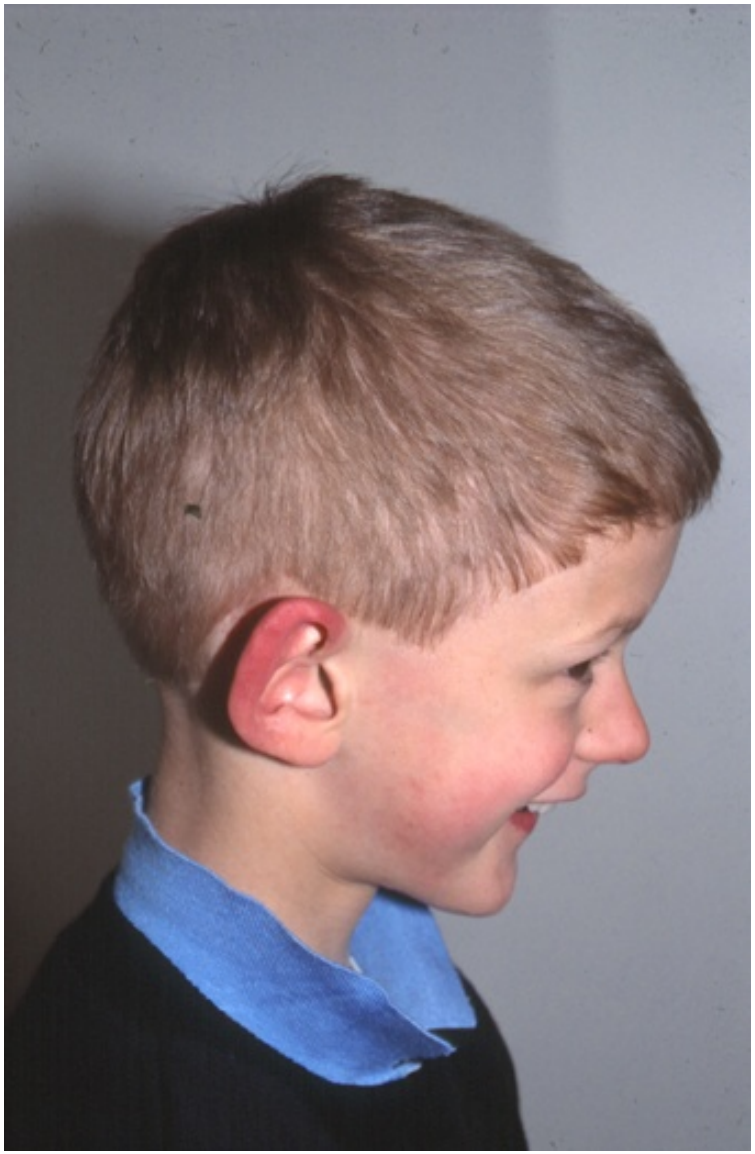
- About 2% of the population has an IQ < 70 (mental retardation)
- the 15-20% of all mental retardations are attributable to genes on chromosome X
- X-linked mental retardation is genetically heterogeneous with 202 loci responsible for shapes that overlap clinically
- 46 genes have been identified to date
- the locus which contributes to the major fraction causes Martin-Bell syndrome, now known as

fragile X syndrome

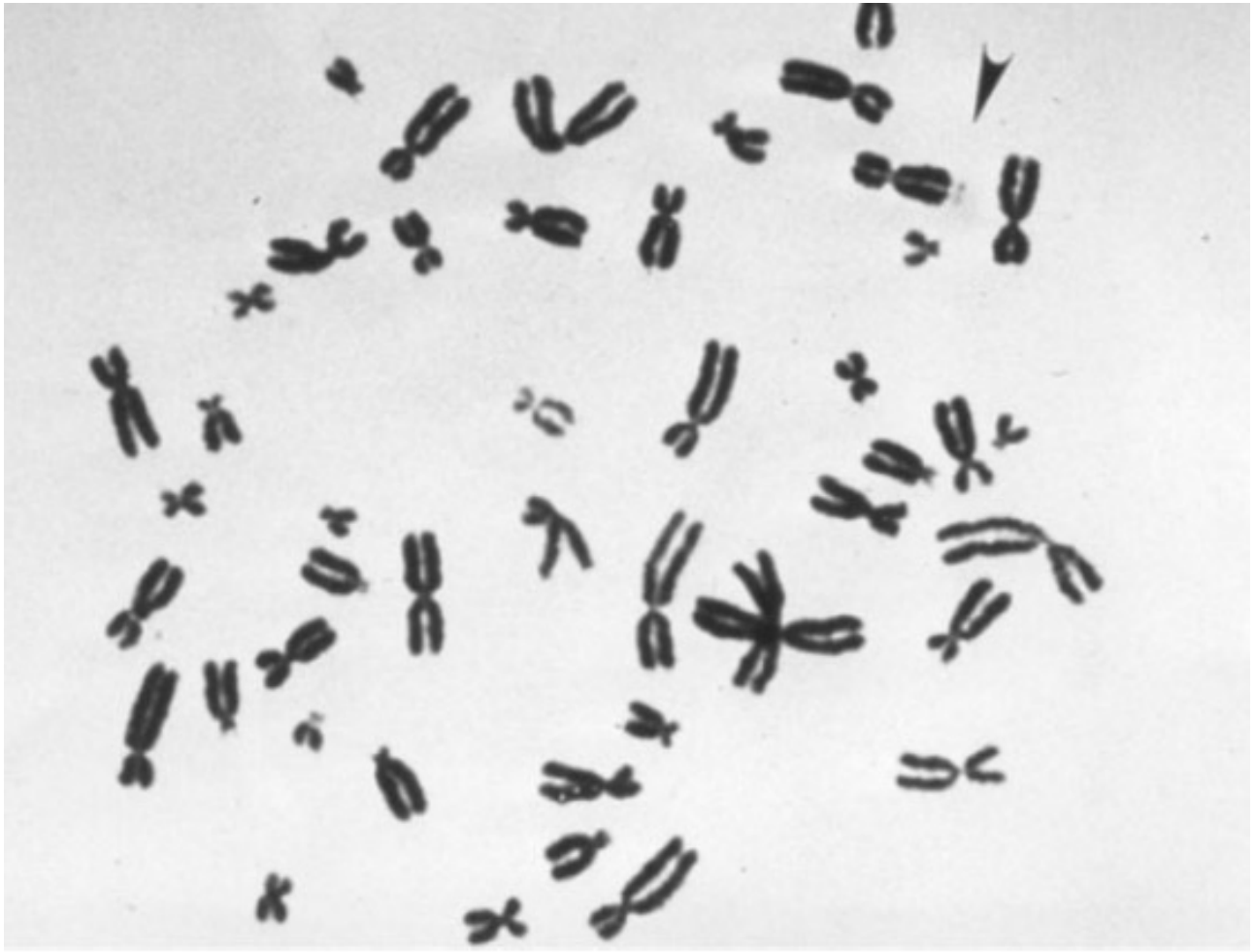
fragile X syndrome

- short-term memory deficits of complex information
- delay in language
- reduced visuo-spatial abilities
- hypersensitivity to stimuli
- hyperactivity with attention deficit
- autistic behavior

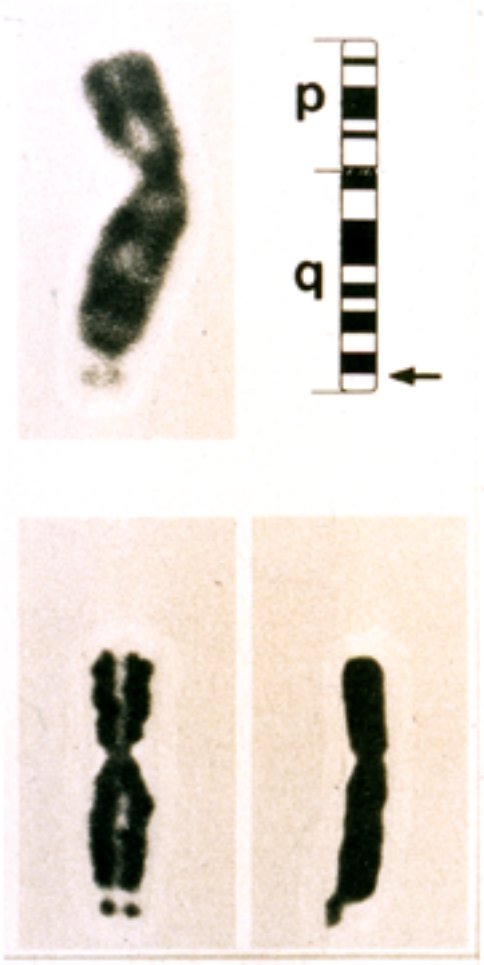
- Macrocephaly with protruding forehead, chin, and ears
- Macroorchidism (enlargement of the testicles) after puberty
- Connective tissue abnormalities



In 1969 Lubs observed a constraint (marker X) on the long arm of chromosome X in four affected males and three obliged carriers from the same family



The fragile site in Xq27.3



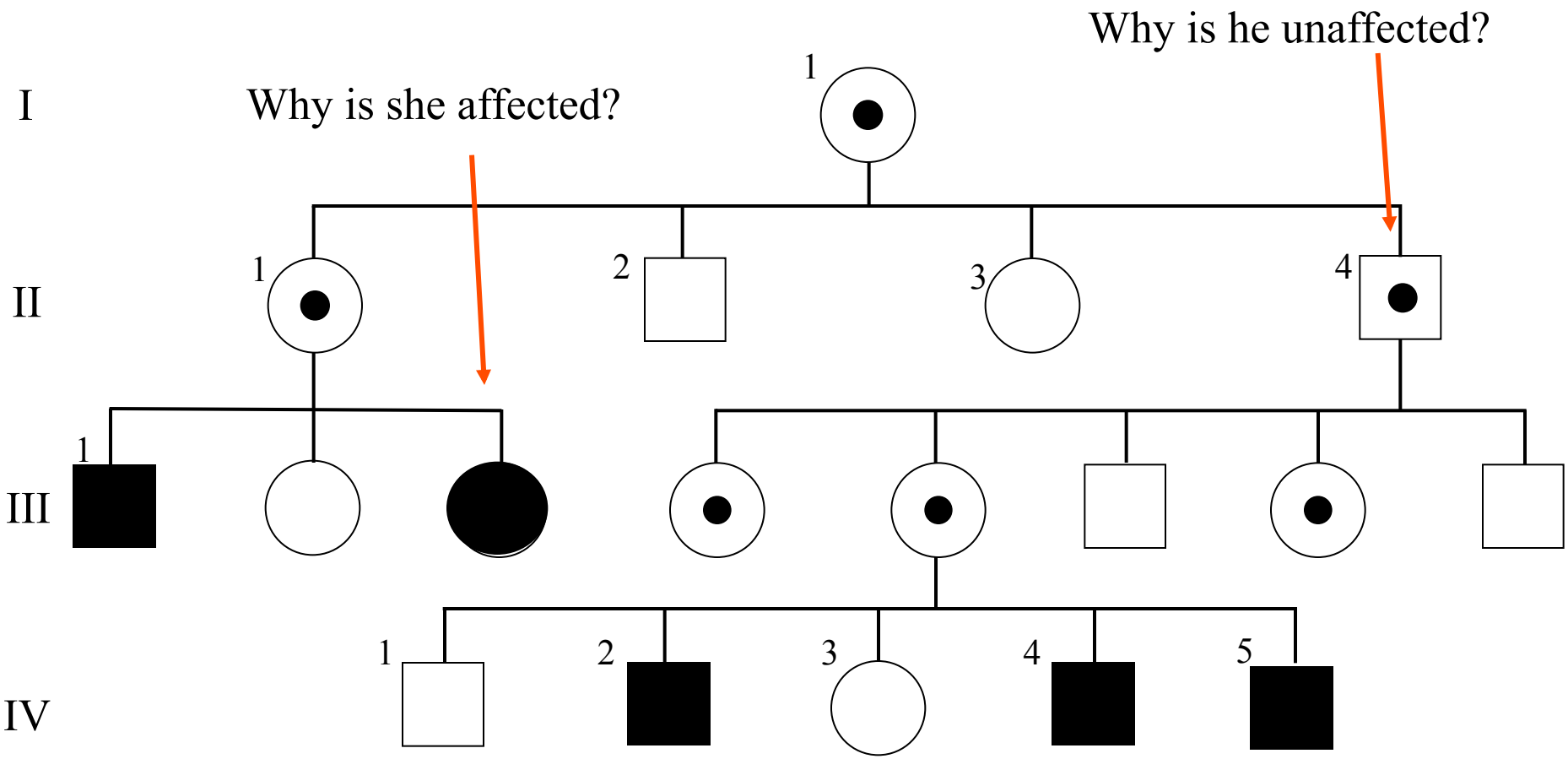
breakage or constriction of metaphase chromosomes that occurs when cells are exposed to a disruption of DNA replication

fragile sites are on all chromosomes and are named from the chromosomal band, e.g. between (X) (q 27.3)

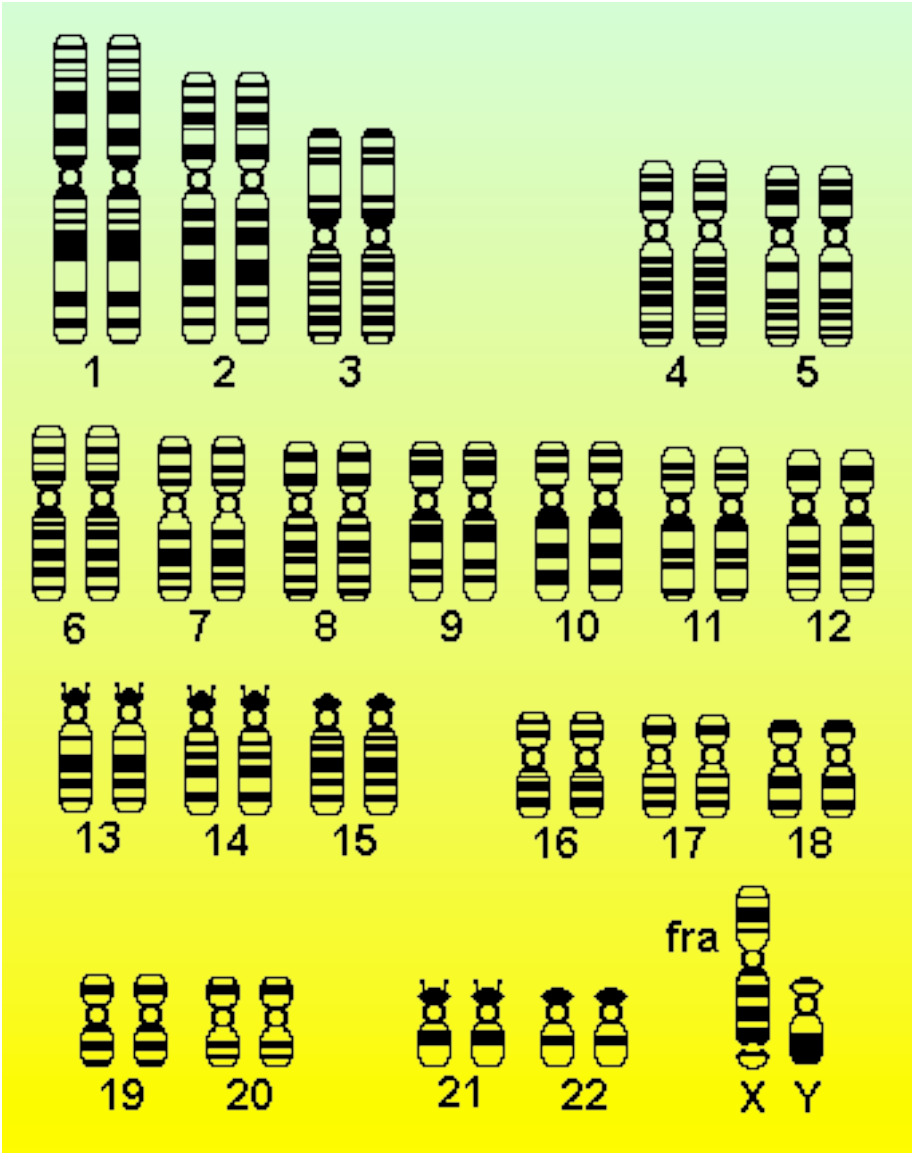
HUGO nomenclature calls this site FRAXA, the first fragile site identified on chromosome X

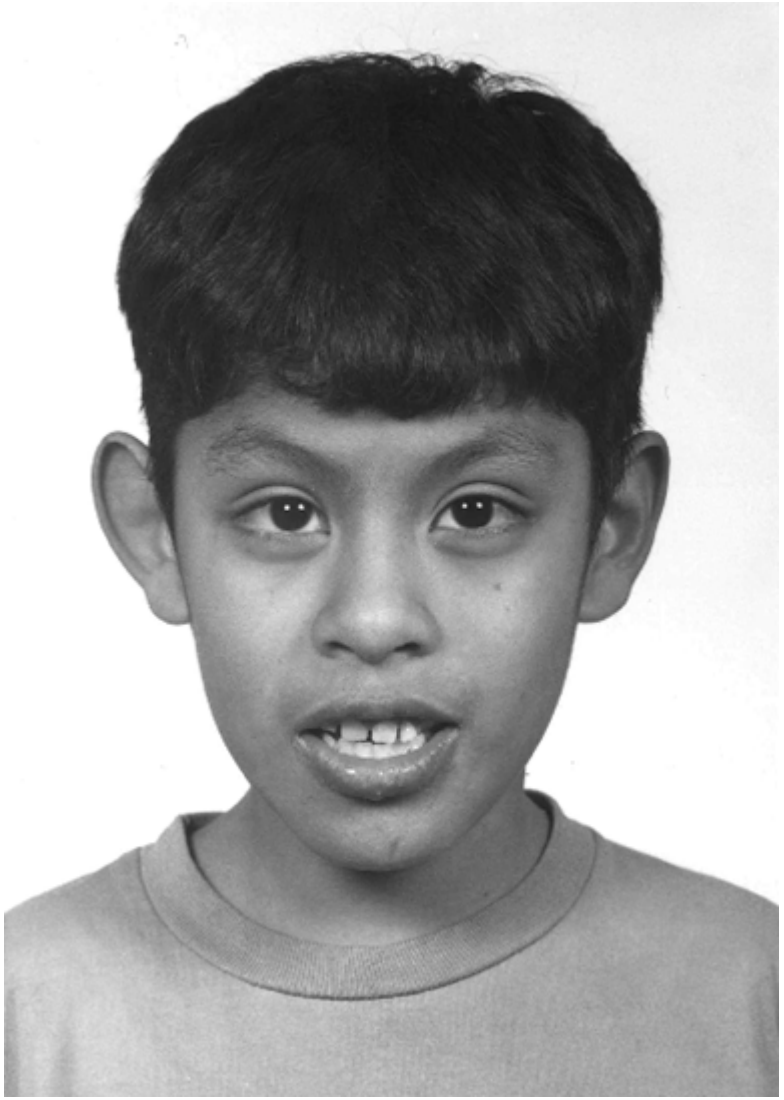
Segregation, Sherman's paradox

20% of males who carry the mutated allele is normal (NTM)
30% of female carriers has mental retardation

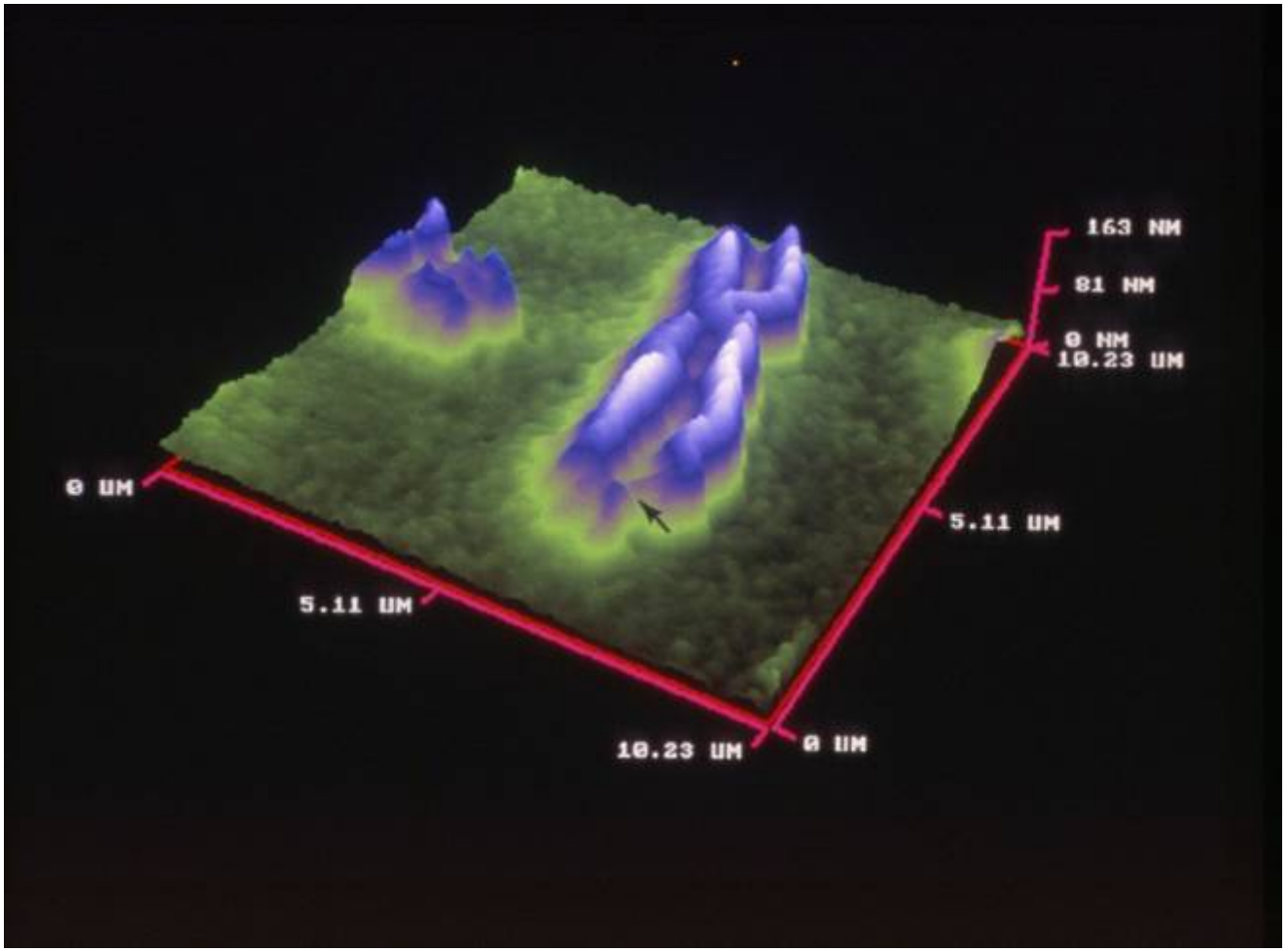


Fragile X syndrome

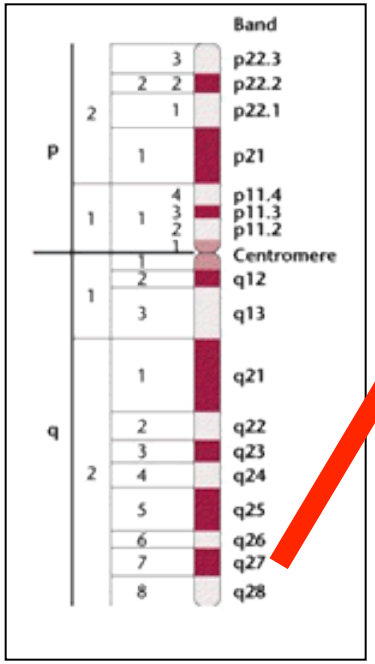


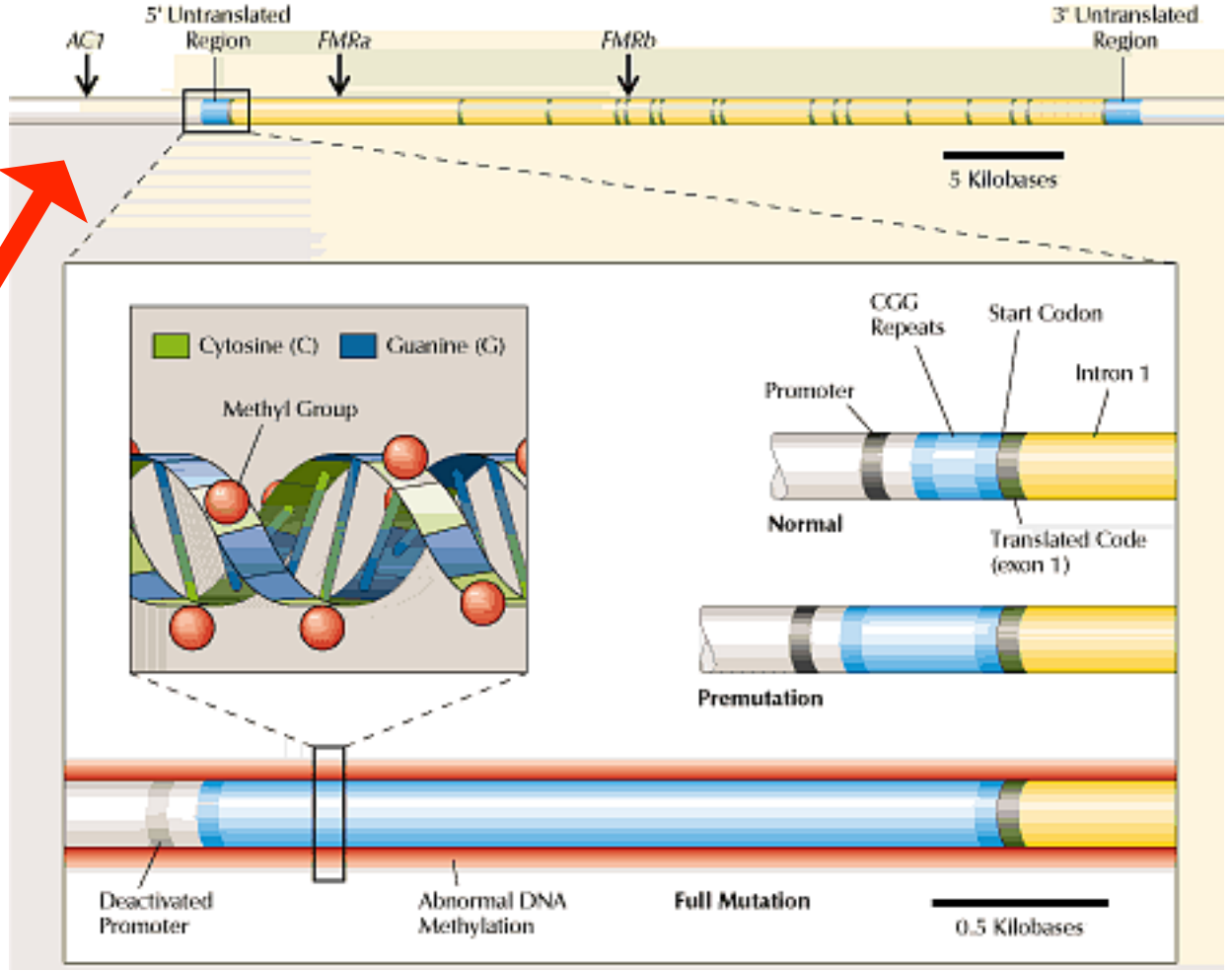


fragile X chromosome made visible by atomic force microscopy (AFM)



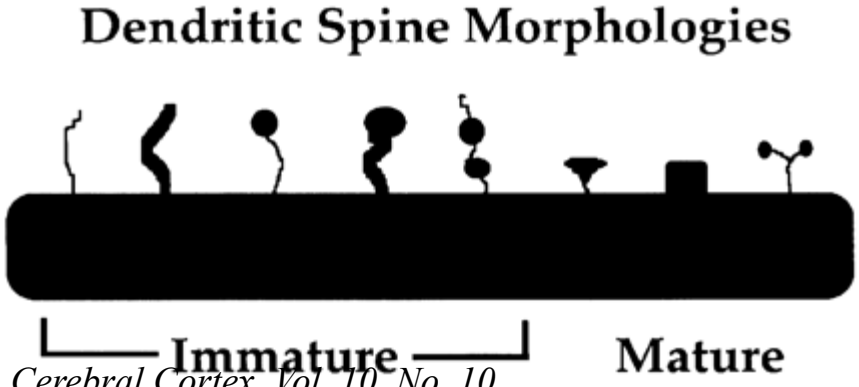
FMR1 gene


Band
P
q
p22.3
p22.2
p22.1
p21
p11.4
p11.3
p11.2
Centromere
q12
q13
q21
q22
q23
q24
q25
q26
q27
q28


5' Untranslated Region
3' Untranslated Region
AC7
FMRa
FMRb
5 Kilobases
Cytosine (C)
Guanine (G)
Methyl Group
CGG Repeats
Start Codon
Intron 1
Promoter
Normal
Translated Code (exon 1)
Premutation
Deactivated Promoter
Abnormal DNA Methylation
Full Mutation
0.5 Kilobases

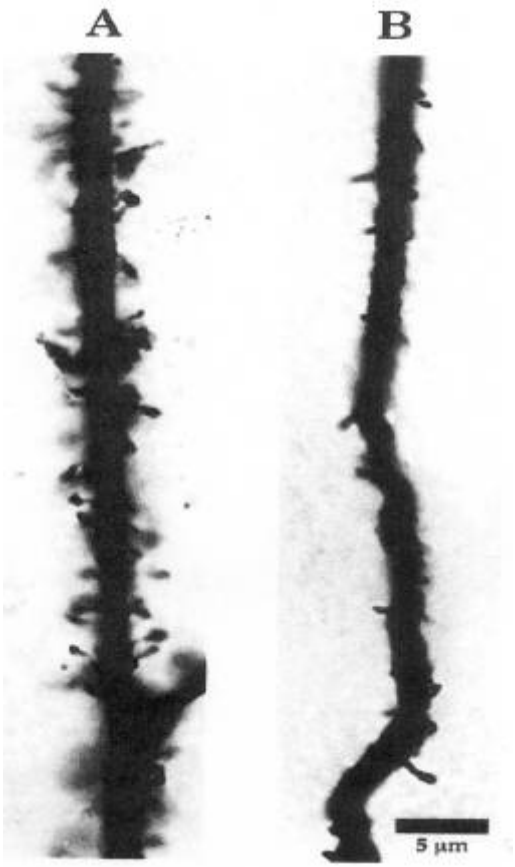
What does the FMR1 gene do?

- Encodes for the FMRP, an RNA-binding protein selectively associated with polyribosomes and expressed in neurons
- in Dendritic spines (discovered by Cajal, they are small protrusions of the dendrites that receive excitatory glutamate-sensitive signals. The density of dendritic spines of a neuron is related to the number of connections associated with the axes endings and can be considered as a measure of the complexity of its functions) regulates mRNA translation, crucial role in synaptic plasticity and neuronal maturation
- interacts with mRNA and miRNA pathway
- In fragile X dendritic spines are immature and long



Cerebral Cortex, Vol. 10, No. 10, 1038-1044, October 2000

Abnormal dendritic spines have been also found in the FMR1 KO mouse

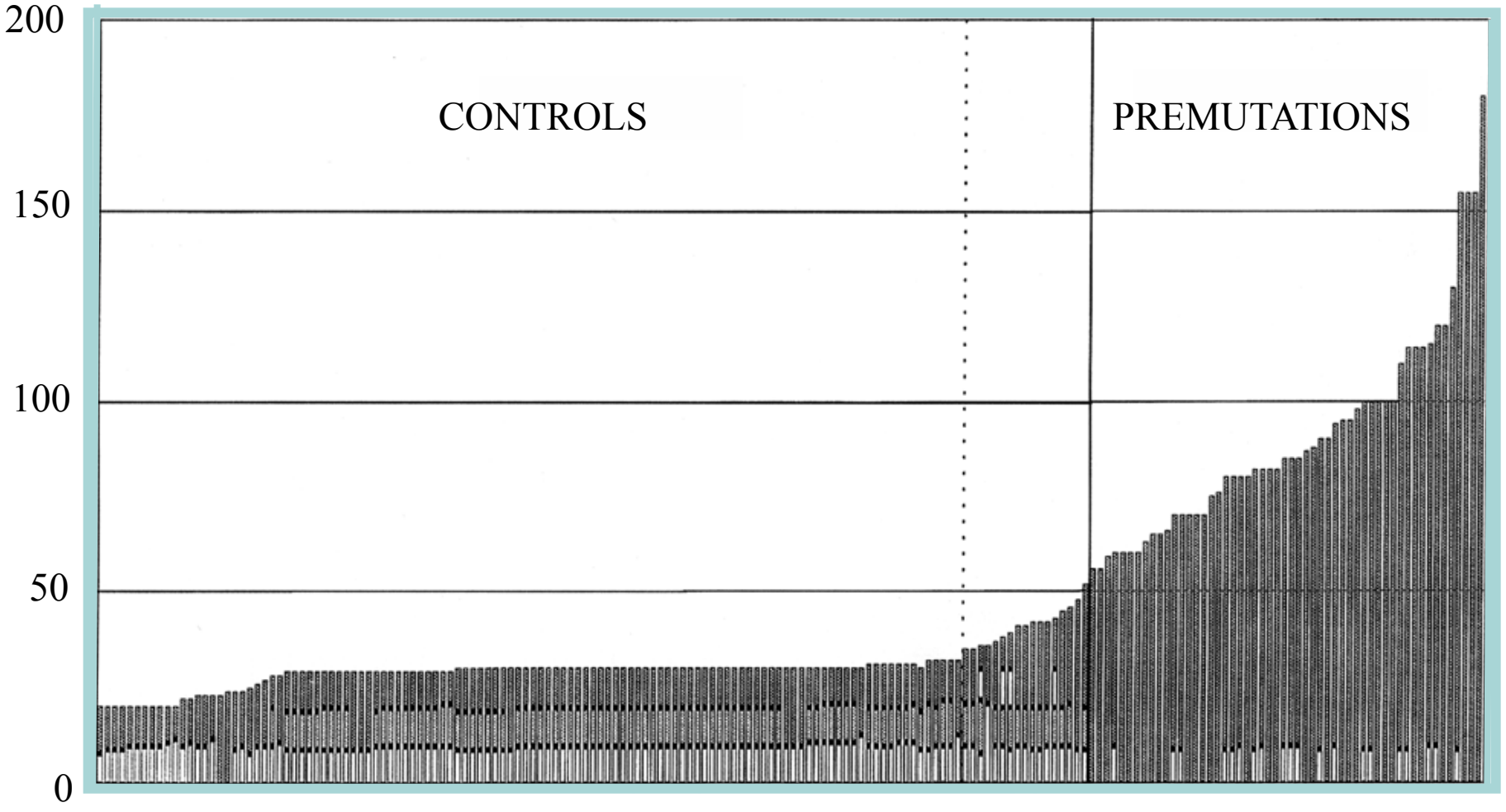


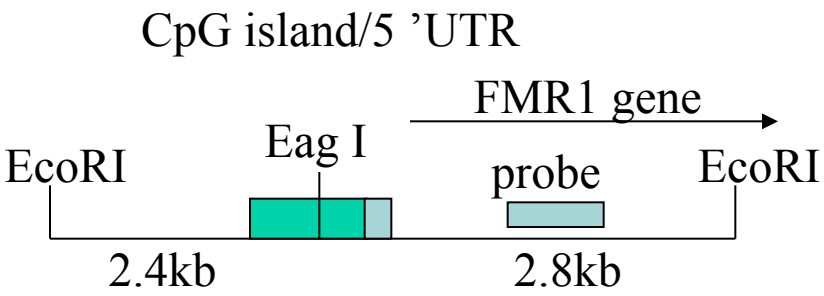
•As already mentioned, the main phenotypic trait of Fragile X syndrome is mental retardation. Other typical features are enlarged testis in almost all affected males, and often a characteristic facial phenotype with long face, prominent forehead and large inverted ears. Patients also have behavioural problems, they are often hyperactive and show poor interpersonal contact.

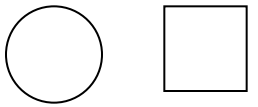
•Postmortem examination of the brains of some fragile X patients has shown that the only consistent difference in their brain architecture are abnormally developed dendritic spines of neurons, which are observed in different regions of the brain. When compared with the normal structures, those spines appear too long, thin and also slidely more numerous.

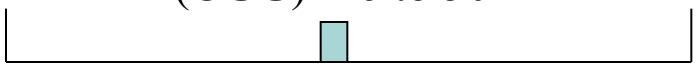
•Dendritic spines are the major sites of synaptic input one neuron gets from another and therefore it seems likely that this abnormality is the structural basis underlying mental impairment in fragile X patients.

Zhong et al. Am J Hum Genet 1995





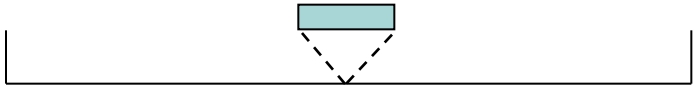




Normal alleles :

Stable in the family and in the individual

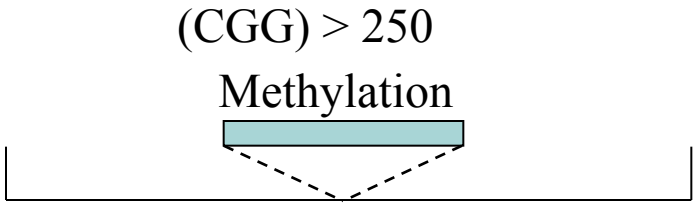
Unstable in the population (Polymorphism)



Premutation :

Unstable in the family

Stable in the individual

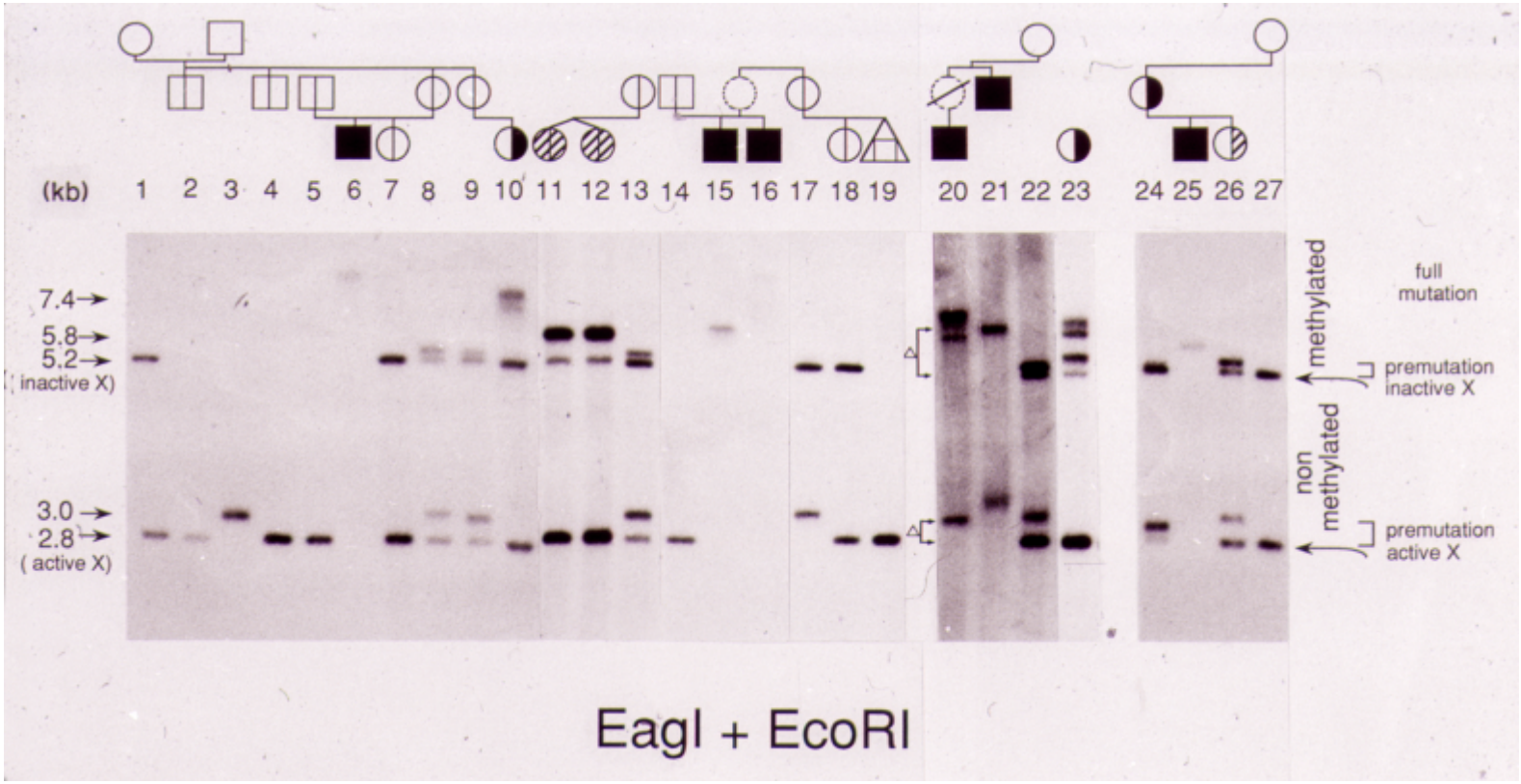


Full mutation :

Unstable in the individual (somatic mutations)

<u>Represses FMR1 transcription</u>

Fragile X diagnosis: Southern blot analysis of expansion and methylation



Rousseau et al. NEJM 1991

Pre-mutations and mutations

- The premutations expand when they are transmitted from the mother
- The woman with premutations has a greater risk of premature menopause or POF (premature ovarian failure)
- The shorter allele described, that in one generation became full mutation, is 59 triplets

Stable expansion (CGG)**9**-AGG-(CGG)**9**-AGG-(CGG)**9**

At least 2 A interrupting the series of 9 triplets

Unstable expansion (CGG)**9**-(CGG)**9**-(CGG)**9-** (CGG)**9……**

Does NOT have any A interrupting the series

Myotonic muscular dystrophy

Myotonic dystrophy MD1

- It is the most common muscular dystrophy of adults
- It is caused by a CTG (in RNA CUG) repeat expansion in the 3 ' UTR of the DMPK gene in 19q13.3
- inherited almost exclusively from female carriers
- anticipation, the repeat has a tendency to expand in subsequent generations and disease severity correlates with repeat length
- RNA binding proteins have been identified that interact with the CUG expansion

Myotonic dystrophy MD1

- "myotonic phenomenon", difficulty in muscle relaxation after a contraction
- facial hypotonia, weakness although not important
- early cataract
- heart rhythm abnormalities
- thyroid dysfunction
- autosomal dominant (1/8000)
- congenital form with severe neonatal hypotonia

Myotonic dystrophy MD2

- a similar expansion in intron 1 of a CCUG repeat in ZNF9 gene (zinc finger protein 9) causes myotonic dystrophy 2
- MD2 is also called proximal myotonic myopathy

Huntington disease

- described by George Huntington in 1872, it is also called chorea which in Greek means the dance

- its starting point is a genetically programmed degeneration of neurons of the basal ganglia (caudate nucleus and putamen) and cortex

- prevalence of 1/10.000

- presents the phenomenon of anticipation

- It is transmitted as an autosomal dominant trait in 97% of cases associated with the huntingtin gene on chromosome 4p16.3

- only 3% of cases are due to new mutations

- a dynamic expansion of the CAG triplet coding for glutamine

Huntington disease

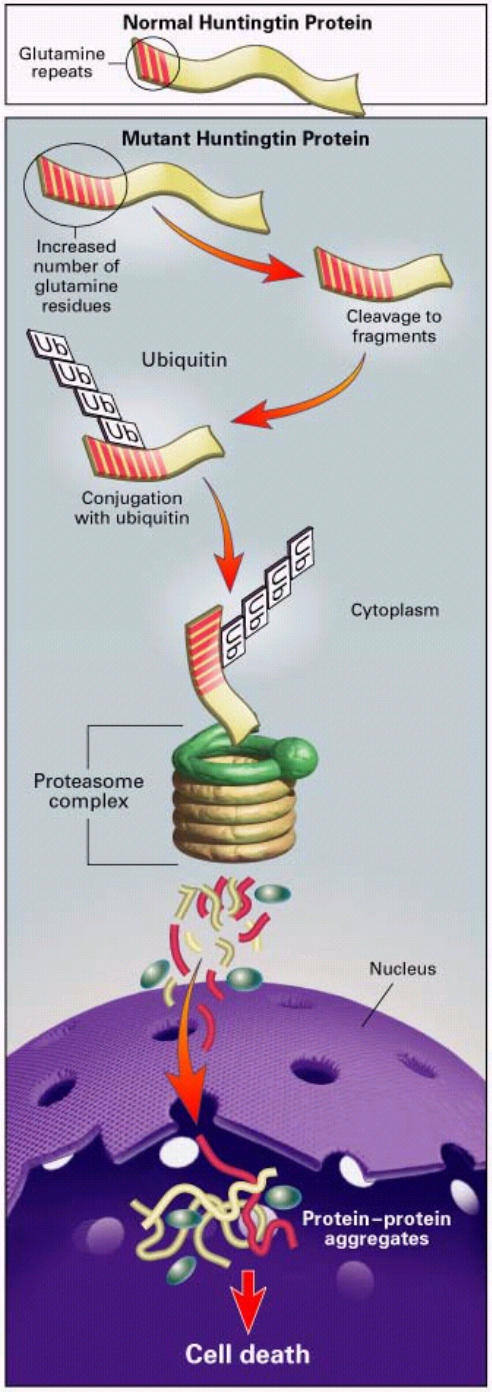
- The HTT gene encodes a protein called huntingtin, evolutionarily highly conserved, expressed in neurons and in many other tissues.

- It probably plays a role in nucleus-cytoplasm transport.

- The expanded triplets (CAG) are in the first exon

- The expansion causes the production of an abnormal protein, with a variable series of glutamine

- The dominant negative effect is a gain of cytotoxic function.


Normal Huntingtin Protein
Glutamine repeats
Mutant Huntingtin Protein
Increased number of glutamine residues
Cleavage to fragments
Ubiquitin
Ub
Conjugation with ubiquitin
Cytoplasm
Proteasome complex
Nucleus
Protein–protein aggregates
Cell death

Huntington disease

- The pathogenic mechanisms are still under discussion, but it is known that the mutant protein forms aggregates which tend to seize other proteins important in cell metabolism

- The damage occurs mainly in certain areas of the central nervous system

- The length of the expansion is correlated with the age of onset and severity of the phenotype.

- In healthy people the repeats (CAG) vary from n = 8 n = 28.

- In HD families can be found asymptomatic individuals with n = 39. These represent situations of transition from pre-mutation to mutation, a kind of ' gray area ' in which disease penetrance is incomplete.

- Individuals with 40-50 repeats develop clinical symptoms at around 35-40 years, while a number of repetitions > 60 gives rise to the juvenile onset of the disease.

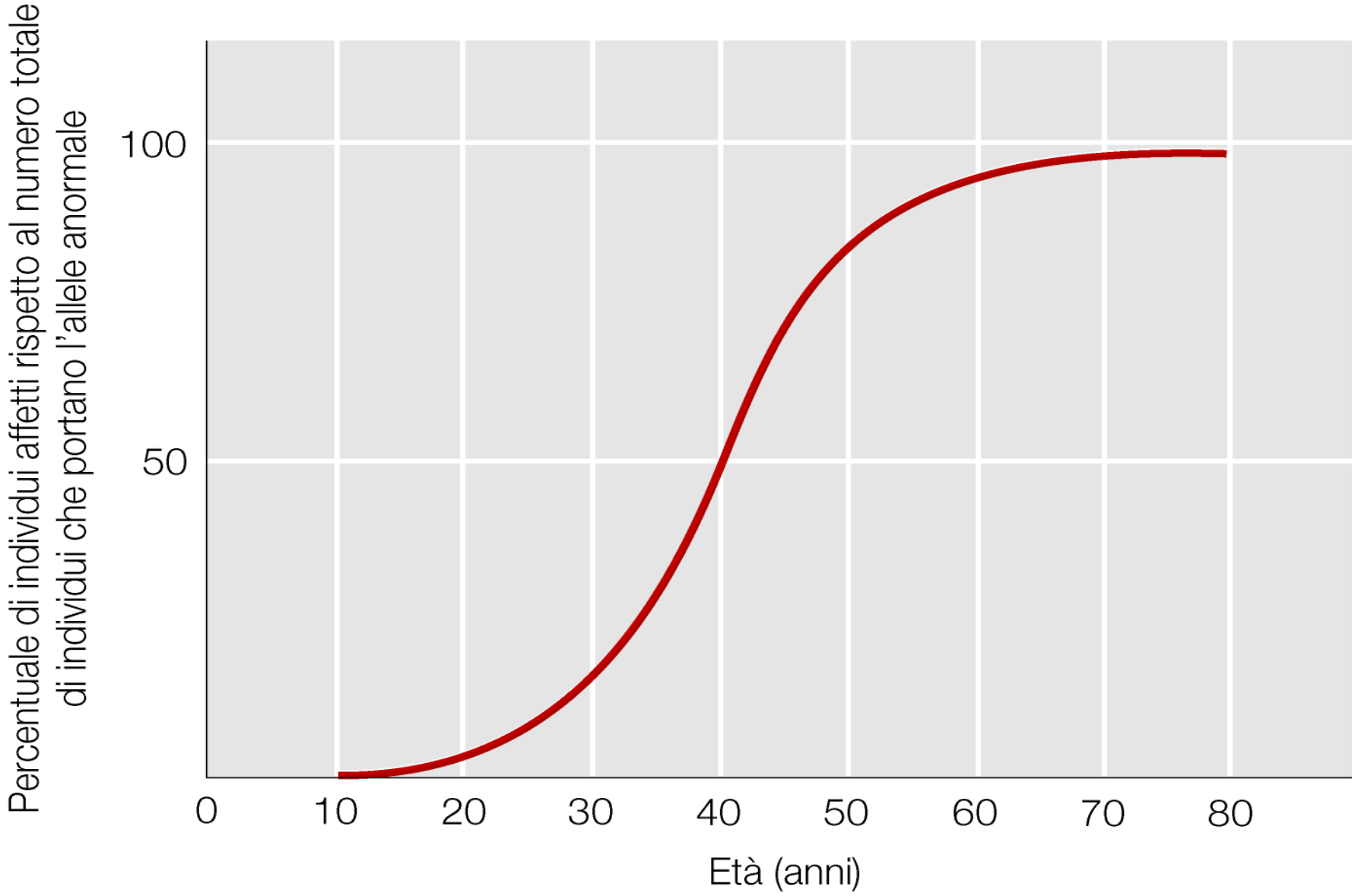
- Anticipation passes paternally, it is linked to specific events of spermatogenesis.

- This disease affects almost exclusively Western Europeans with an incidence of 1:10,000, while it is very rare in other populations.

- It is thought that, coincidentally, in Western Europe appeared a premutated allele particularly predisposed to expansion. The onset of clinical symptoms in post-reproductive age allowed the affected individuals to transmit the disease from generation to generation, maintaining relatively high frequency.

Age of onset of Huntington disease

(nerve degeneration, seizures and premature death) The graph shows that persons who bring the allele for this disease generally manifest symptoms only after reproductive age.

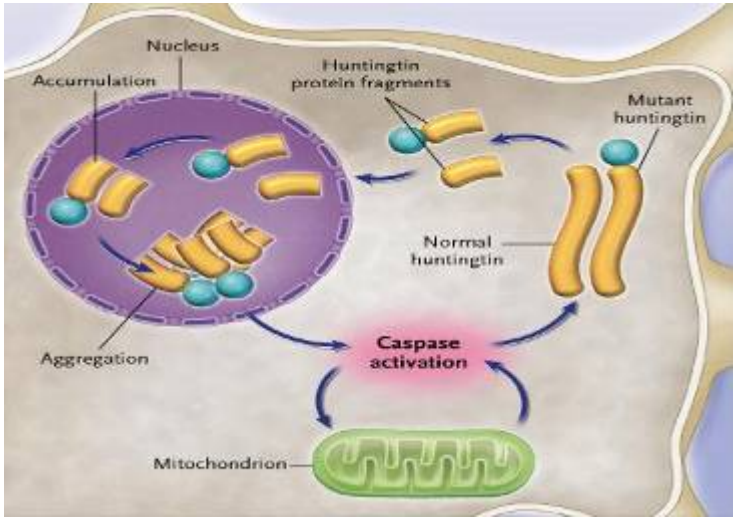


How many glutamines?

- up to 28 = maximum number of CAG for a not at risk person
- 29-39 CAG disease might present to the next generation (pre-mutation)
- From 40 CAG the subject is considered affected even though the disease has not yet manifested
- the test is able to predict that the disease will manifest itself in the future
- Test run in healthy individuals raises ethical problems

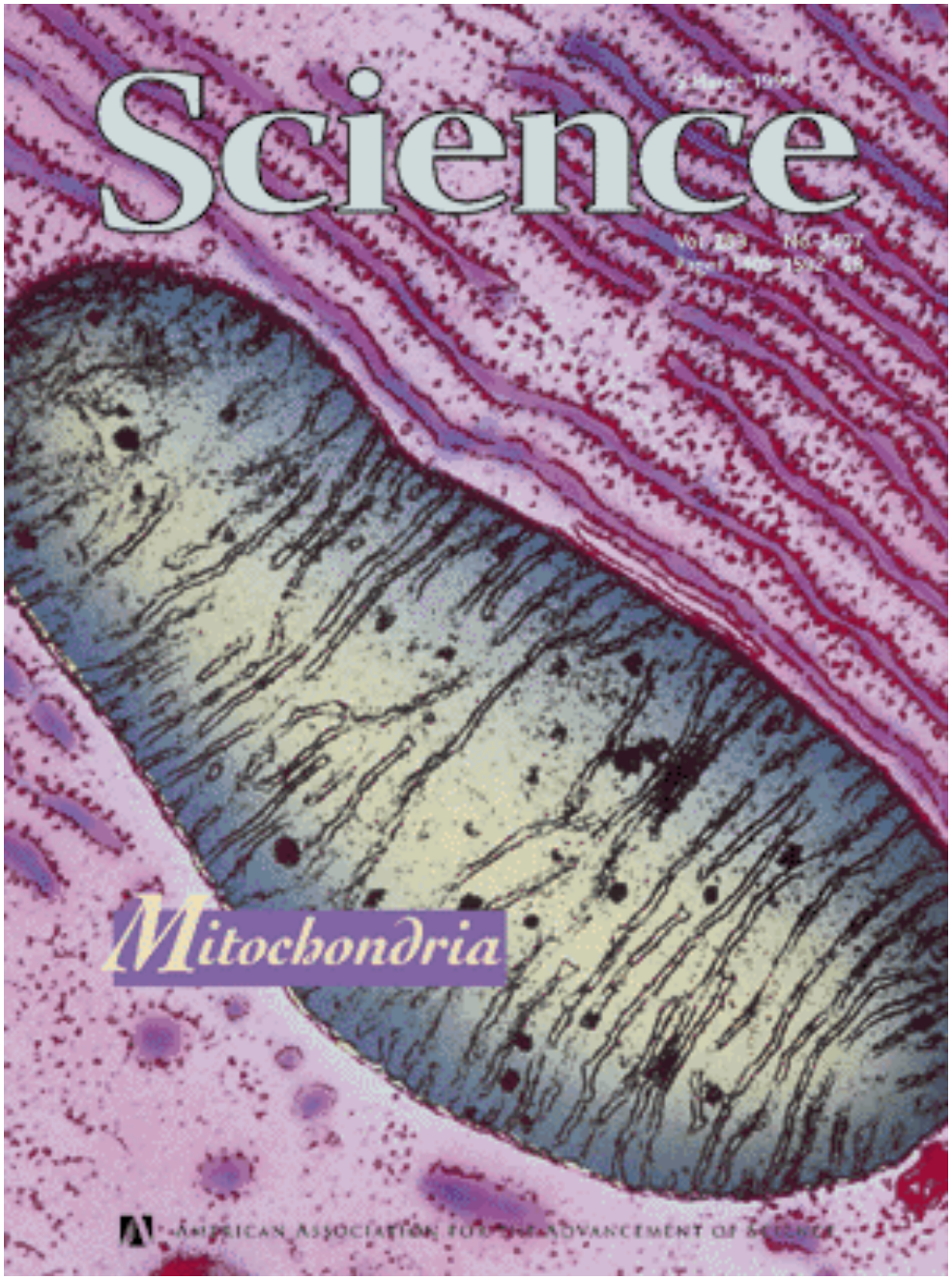
•The Huntingtin with polyglutamine aggregates in neurons causing their death

•At first psychiatric symptoms such as depression, irritability, difficulty in taking decisions, then presents uncontrolled movements similar to a dance and dementia



•even with a great individual variability, the disease progresses inexorably until death

•Therapeutic attempts are ongoing with cystamine, inhibiting transglutaminase involved in the formation of aggregates



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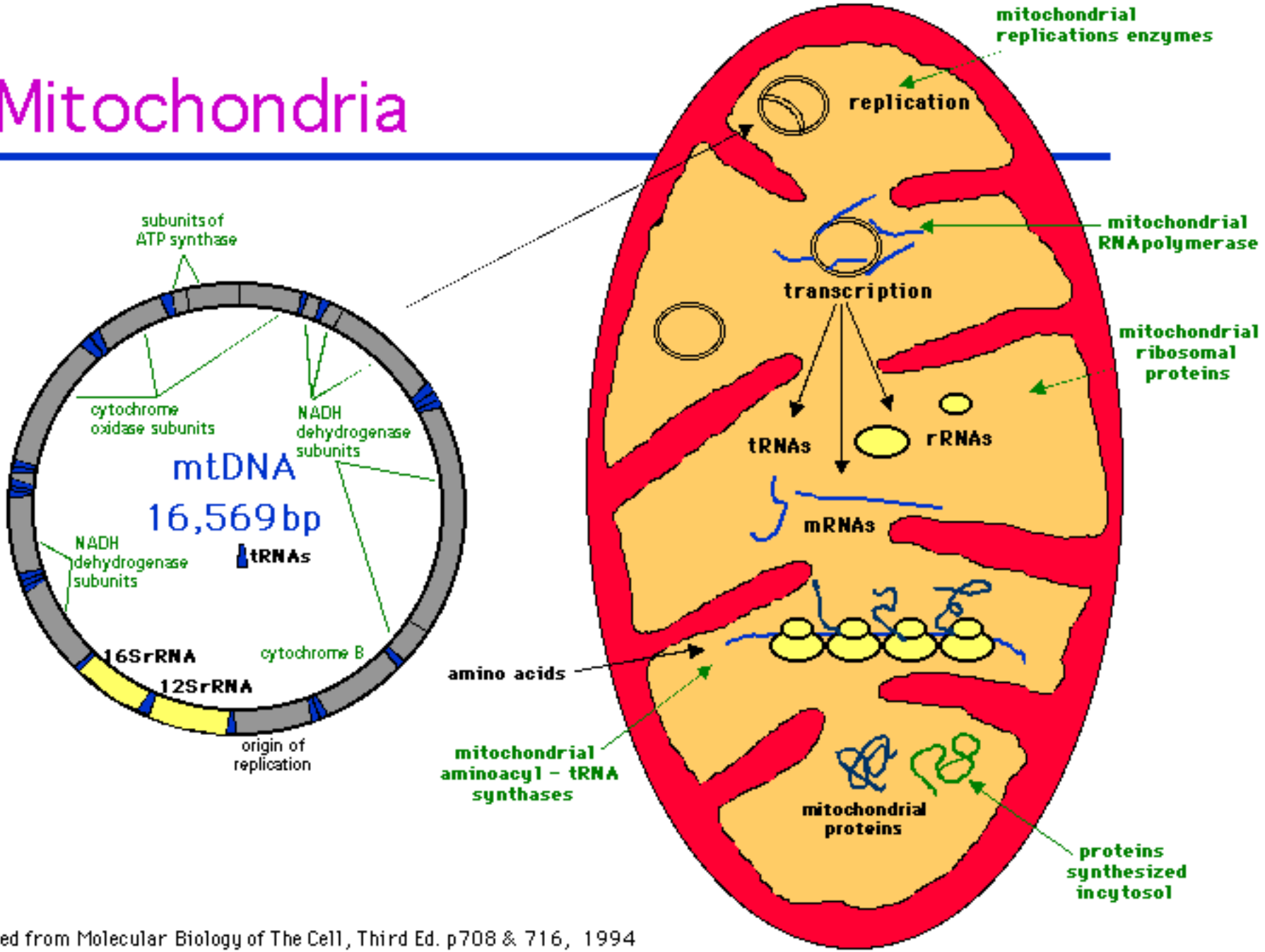
"Mitochondria"

Mitochondrial Inheritance

- maternal inheritance
  - mitochondria and mitochondrial DNA (mtDNA) from the mother are contributed to all offspring
    - » no risk to offspring from an affected father
- mitochondria
  - several hundred – thousands / cell
  - ~10 copies of circular mtDNA / organelle
- somatic mutations
  - 10 fold higher rate of mutations than nuclear DNA
- threshold effects
  - over 85% of mtDNA must be mutant for cellular function to be affected

Mitochondria



adapted from Molecular Biology of The Cell, Third Ed. p708 & 716, 1994

Mitochondrial Genome

- mtDNA is circular, 16,569 bp
  - **bidirectional**
    - » replication, transcription on both strands
  - **lacks introns, 5' and 3' untranslated regions**
- mtDNA encodes
  - **13 polypeptides**
    - » subunits of oxidative phosphorylation enzymes
  - **2 rRNAs**
  - **22 tRNAs**
- codon changes
  - **UAG, tryptophan** (stop codon in cytoplasmic translation)
  - **AUA, methionine** (isoleucine codon in cytoplasmic translation)

93% of mitochondrial DNA is coding

- chromatin structure is different: not protected by the histones

- By going through many cycles of replications it is more subject to replicative machine errors (source of mutations also for nuclear DNA)

-Repair mechanisms are less efficient than for nuclear DNA

all this causes the fact that a number of genetic diseases are due to alterations in mitochondrial function.

Mitochondrial inheritance

- Due to the transmission of characters encoded by mitochondrial DNA

- Defects in the mitochondrial DNA show maternal inheritance

- The absence of controlled segregation generates at each mitosis cells with varying proportions of mitochondria with normal or mutant DNA

- Characteristics of mitochondrial diseases are incomplete penetrance, variable expressivity and pleiotropy

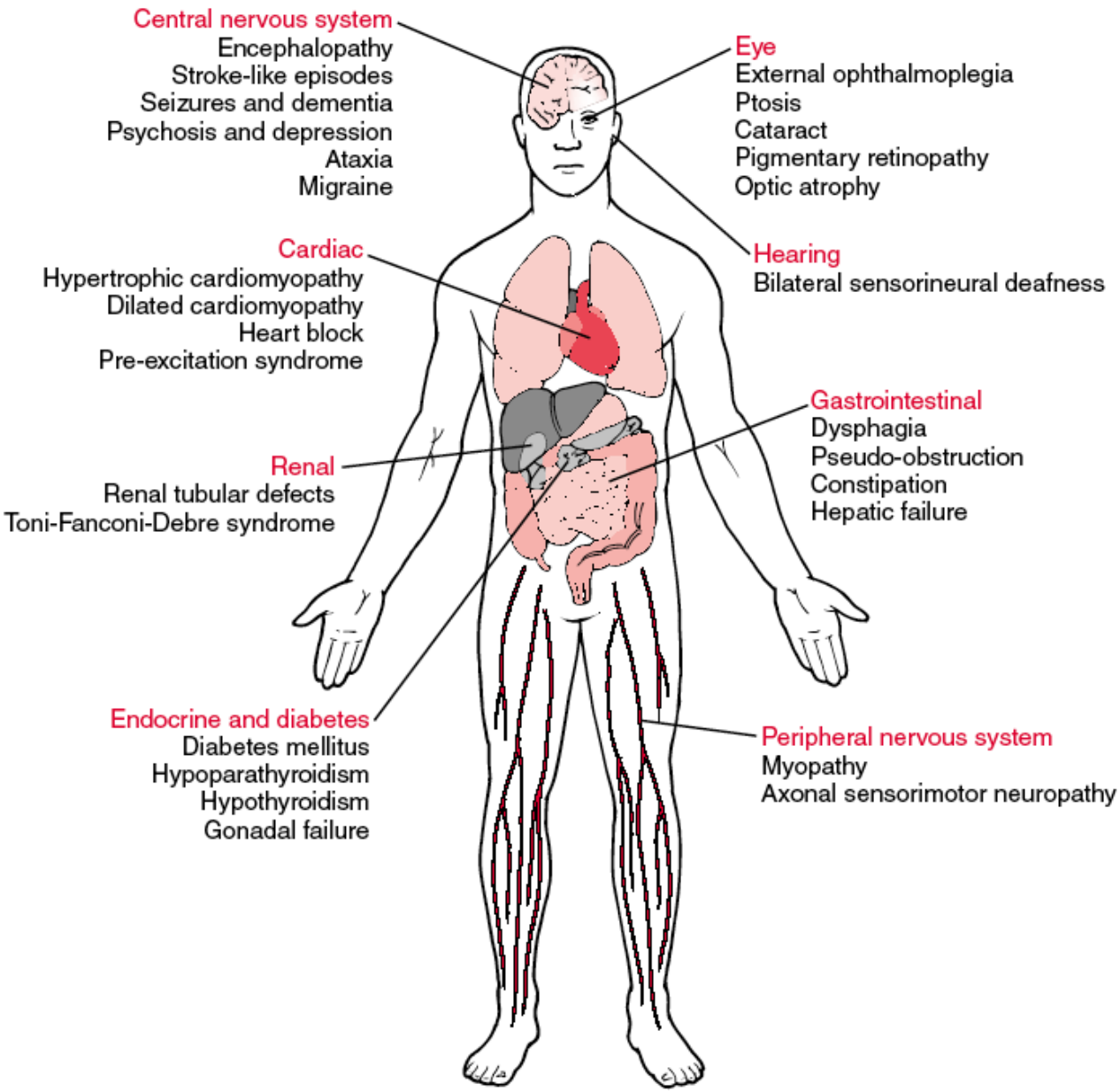
Examples of mitochondrial diseases

- Leber's syndrome: optic neuropathy with progressive loss of vision associated with cardiac arrhythmia; mutation in a complex I component (subunit ND1)

- MELAS: myopathy, encephalopathy, lactic acidosis, and stroke; mutation of mitochondrial $tRNA^{leu}$

Mitochondrial diseases are manifested in those districts of the organism in which it's required a higher energy production: nervous system, muscle, eyes, liver ... and have high clinical variability even within the same family.

Involved tissues and clinical pictures



A mitochondrial inheritance pattern

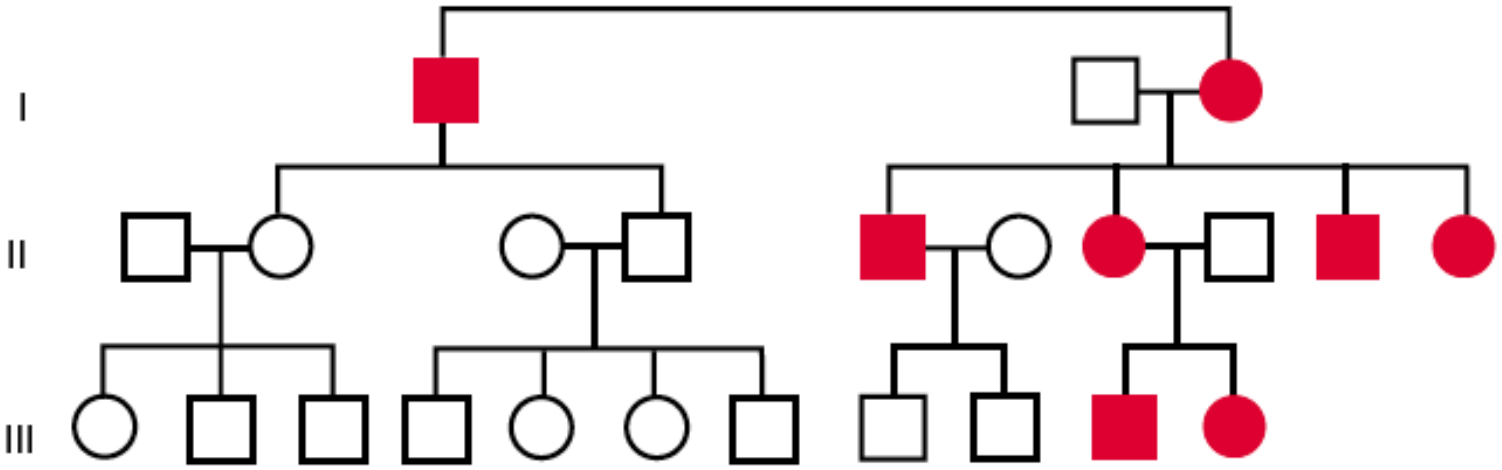


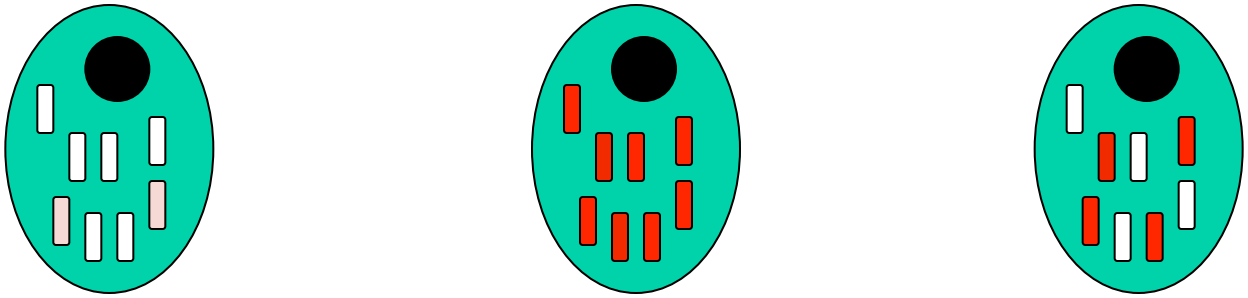
Figure 12–32. Pedigree of Leber's hereditary optic neuropathy, a disorder caused by a defect in mitochondrial DNA. Inheritance is only through the maternal lineage, in agreement with the known maternal inheritance of mitochondrial DNA. No affected male transmits the disease.

Mitochondrial DNA is a hotspot of pathogenic mutations

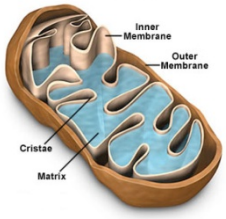
Mitochondrial diseases are more frequent than expected

HOMOPLASMY AND HETEROPLASMY

- Each cell contains thousands of mtDNA molecules
- A mutation in mtDNA is transmitted to mitochondria randomly
- A cell can receive from the mother cell a population of homogenous, healthy or mutant mtDNA (homoplasmy)
- Alternatively a cell can receive a mixed population of normal and mutated molecules (heteroplasmy)



Heteroplasmy



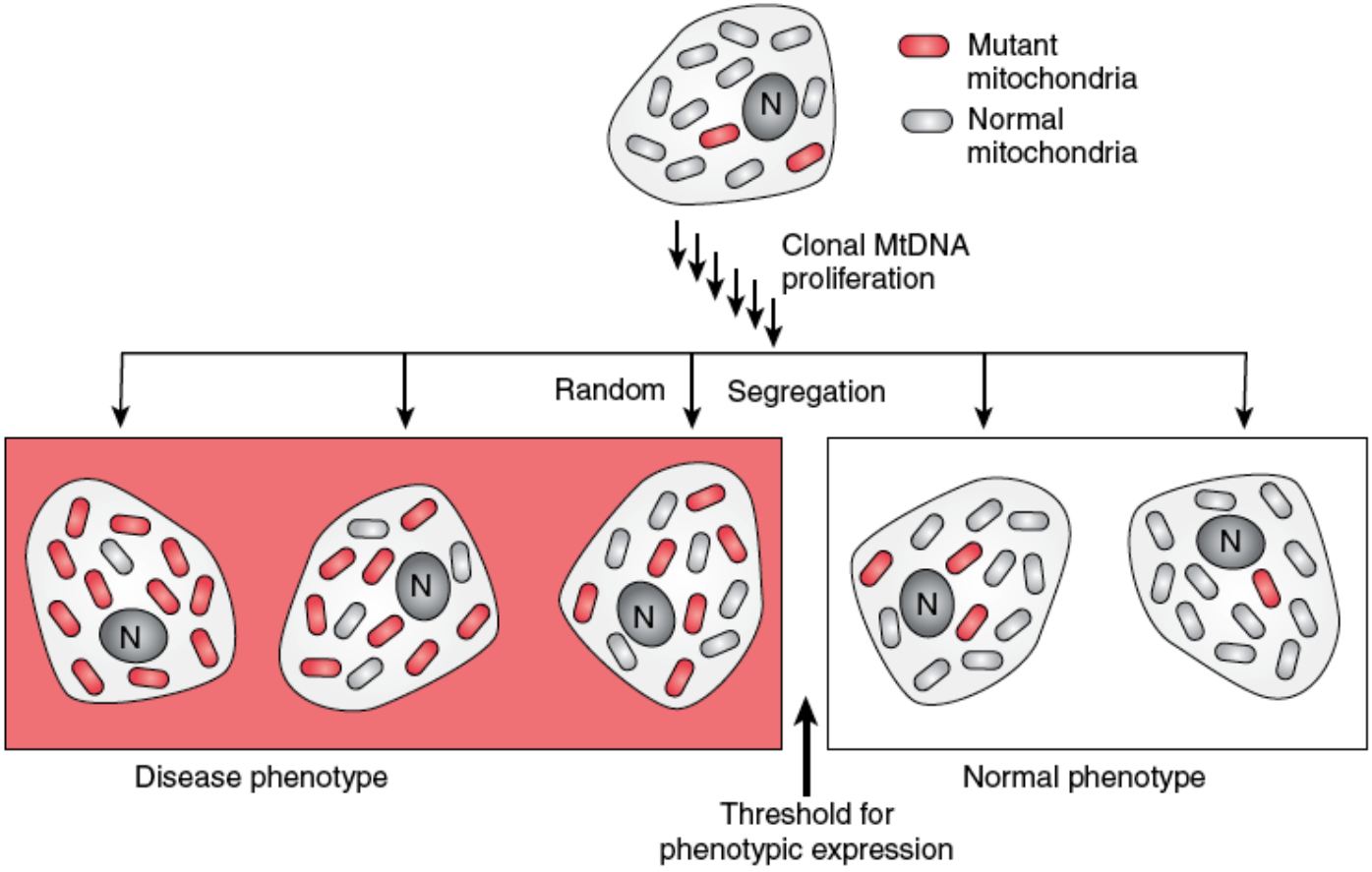
Heteroplasmy contributes greatly to explain the clinical variability

The relative amounts of normal and mutant mitochondria may vary from tissue to tissue and this partly explains the expression differences

Also it is not certain that a woman carrying a mitochondrial mutation should convey to the offspring both normal and mutated mitochondria, as this may even not occur or may be difficult to prove.

when you run a test for mtDNA mutation it is often necessary to use different tissues, as, due to heteroplasmy, some tissues may contain few mutated mitochondria or may even contain none

The expression of the phenotype of mitochondrial disorders depends on the ratio of normal and mutated mtDNA present in the cells of various tissues

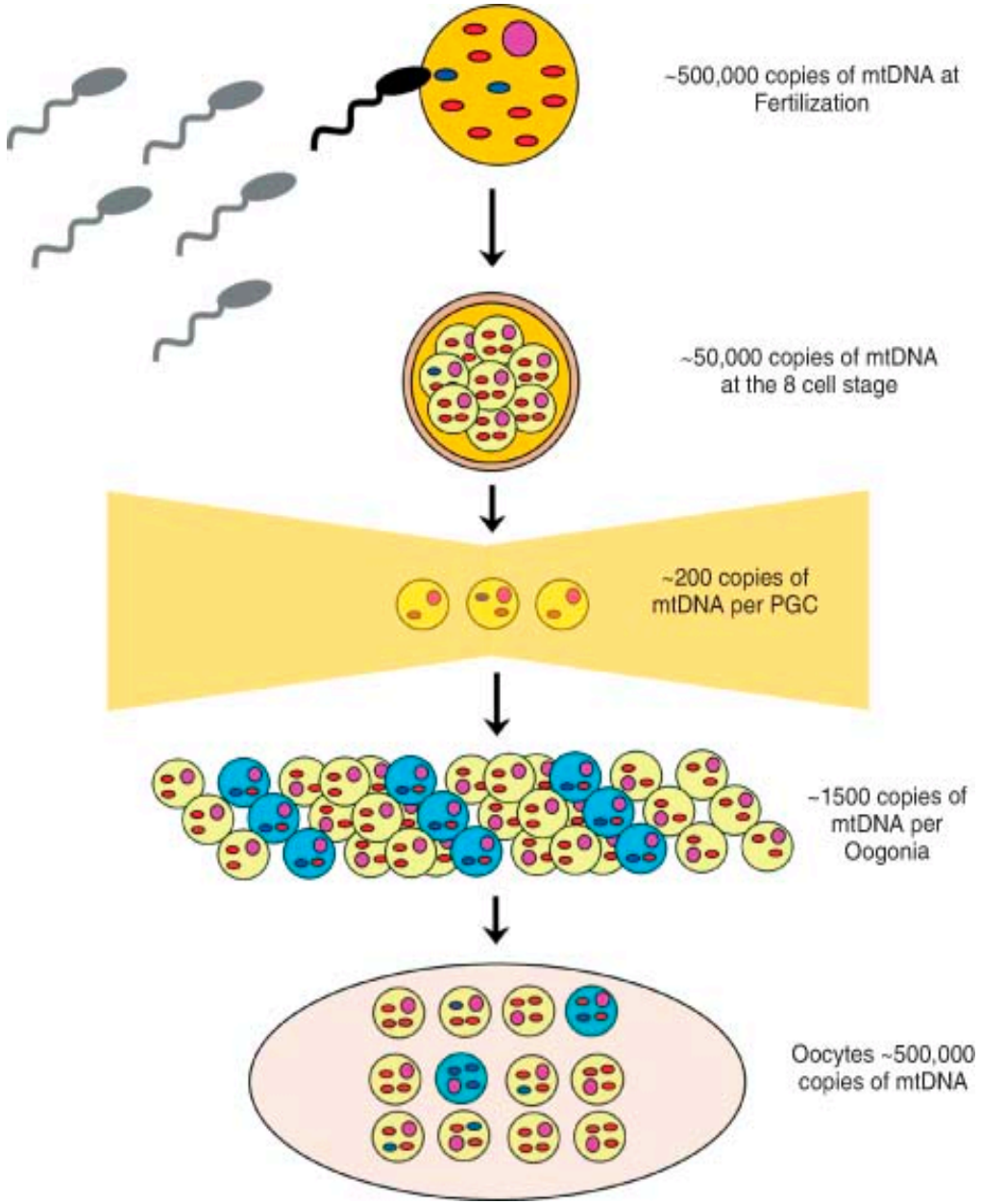


Heteroplasmy variability

- Mothers with a larger proportion of mutated molecules have a higher chance of having affected children

- Bottleneck effect during oogenesis

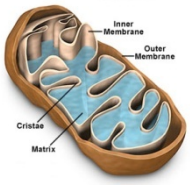
Bottleneck effect during oogenesis



primordial germ cell (PGC)

The mitochondrial genetic bottleneck. Schematic diagram showing a heteroplasmic oocyte being fertilized followed by the development of the embryo. During this development primary oocytes develop from a founder population of 40 PGCs recruited by induction from the epiblast in the posterior-proximal embryonic pole. The PGCs are believed to have a low mitochondrial number of around 200. The red circles represent wild-type mtDNA, blue circles represent mutant-type mtDNA; cells with mutant mtDNA having passed a threshold will have a biochemical defect and are shown in blue.

Mitochondrial DNA polymorphisms



It is estimated that the rate of accumulation of DNA alterations for mitochondria is 5 to 10 times that of nuclear DNA

☛ **the absence of a recombination step renders it easier to follow the inheritance of mitochondrial DNA polymorpisms**

Applications

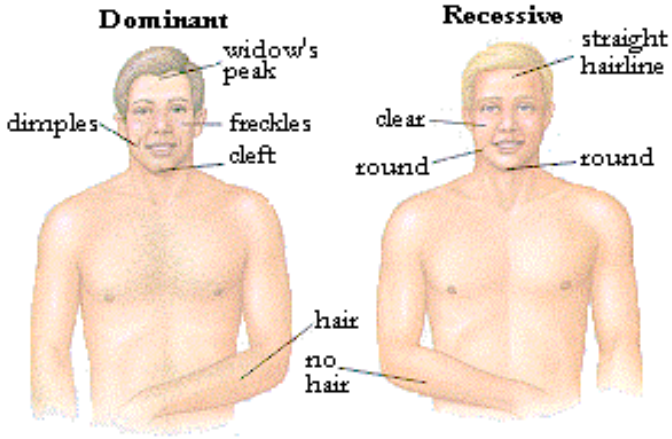
antropology

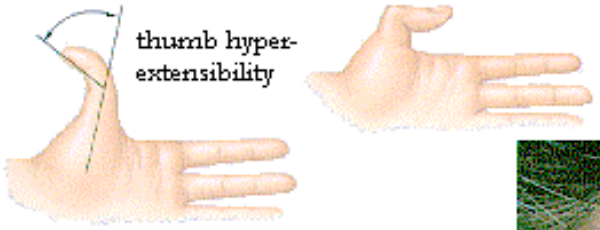
the origin of human mitochondrial DNA variation dates back to 150,000 years ago in Africa

legal medicine

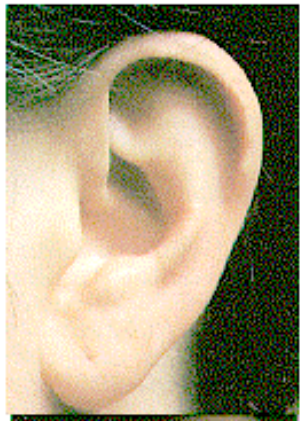
genetic markers are used to compare the genotype of the suspects with items found at the scene of the crime

NOT ONLY DISEASES….



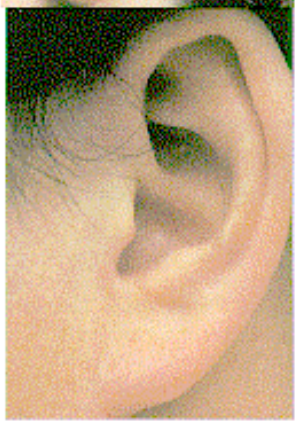


non attached ear lobes

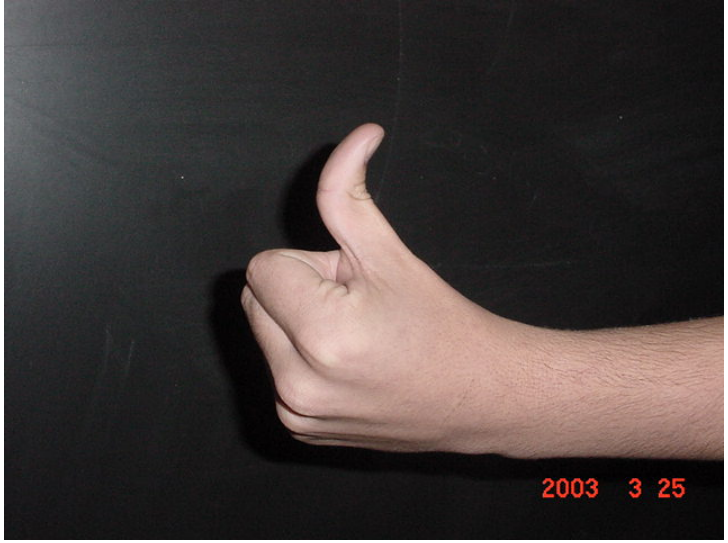


widow's peak

straight hairline



attached ear lobes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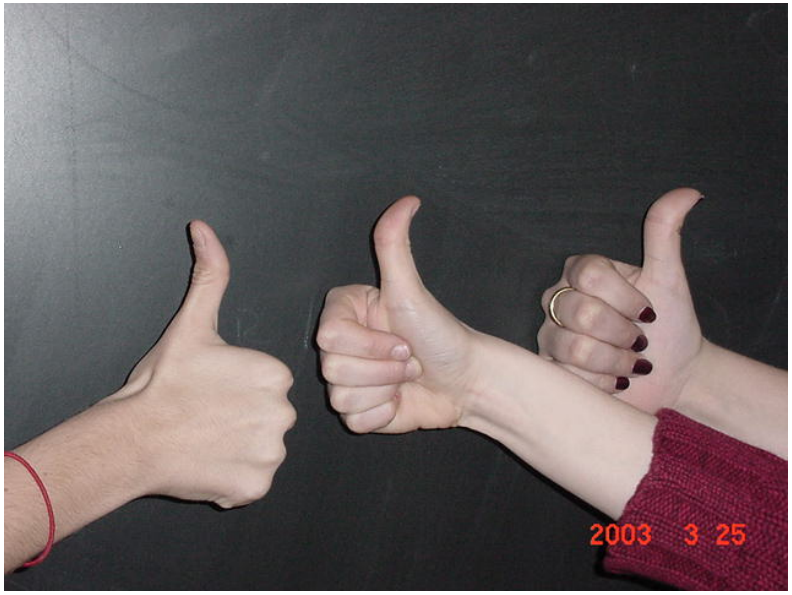
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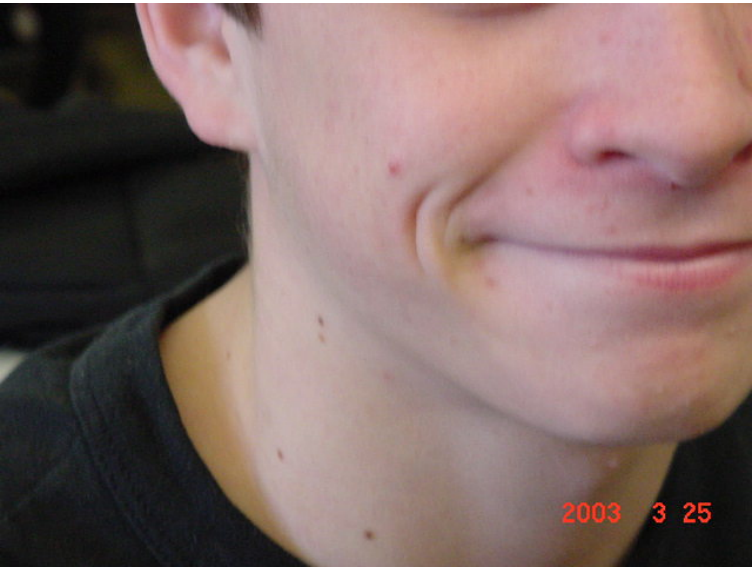

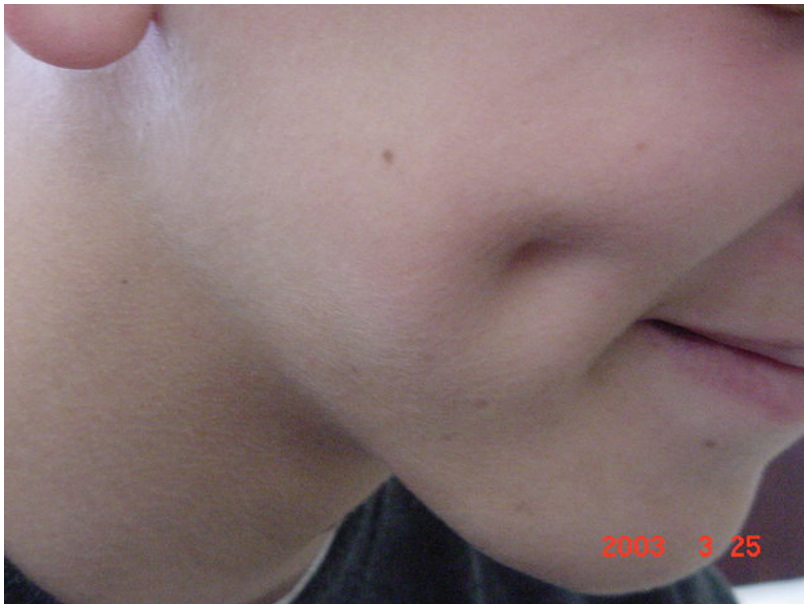

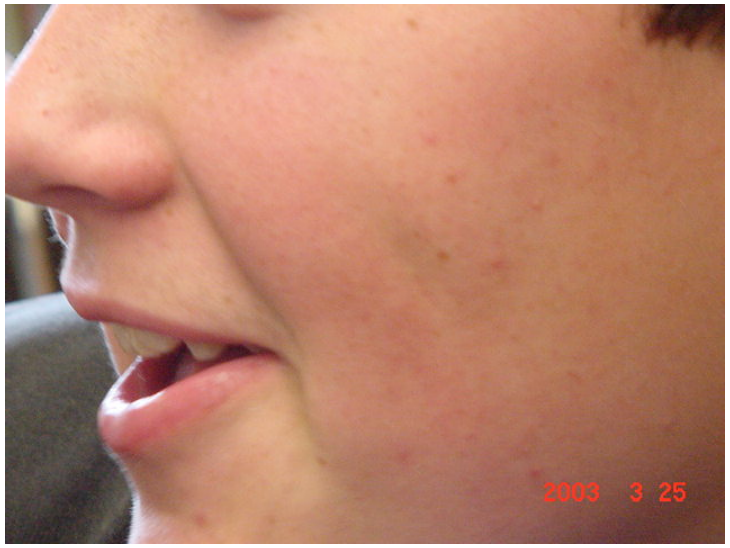

N.W.R. Dimples…..

Tongue rolling…a dominant trait!

a

b

c

Pattern baldness is a sex-influenced trait and was a genetic hallmark of the illustrious Adams family. (a) John Adams (1735-1826) was the second President of the United States. He was the father of (b) John Quincy Adams (1767-1848) who was the sixth President. John Quincy was the father of (c) Charles Francis Adams (1807-1886) who was a diplomat and the father of (d) Henry Adams (1838-1918) who was an historian.

d

claudia.giachino@unito.it

"[illegible]" Davies