Master in Cellular and Molecular Biology

Medical and Cancer Genetics course

MEDICAL GENETICS

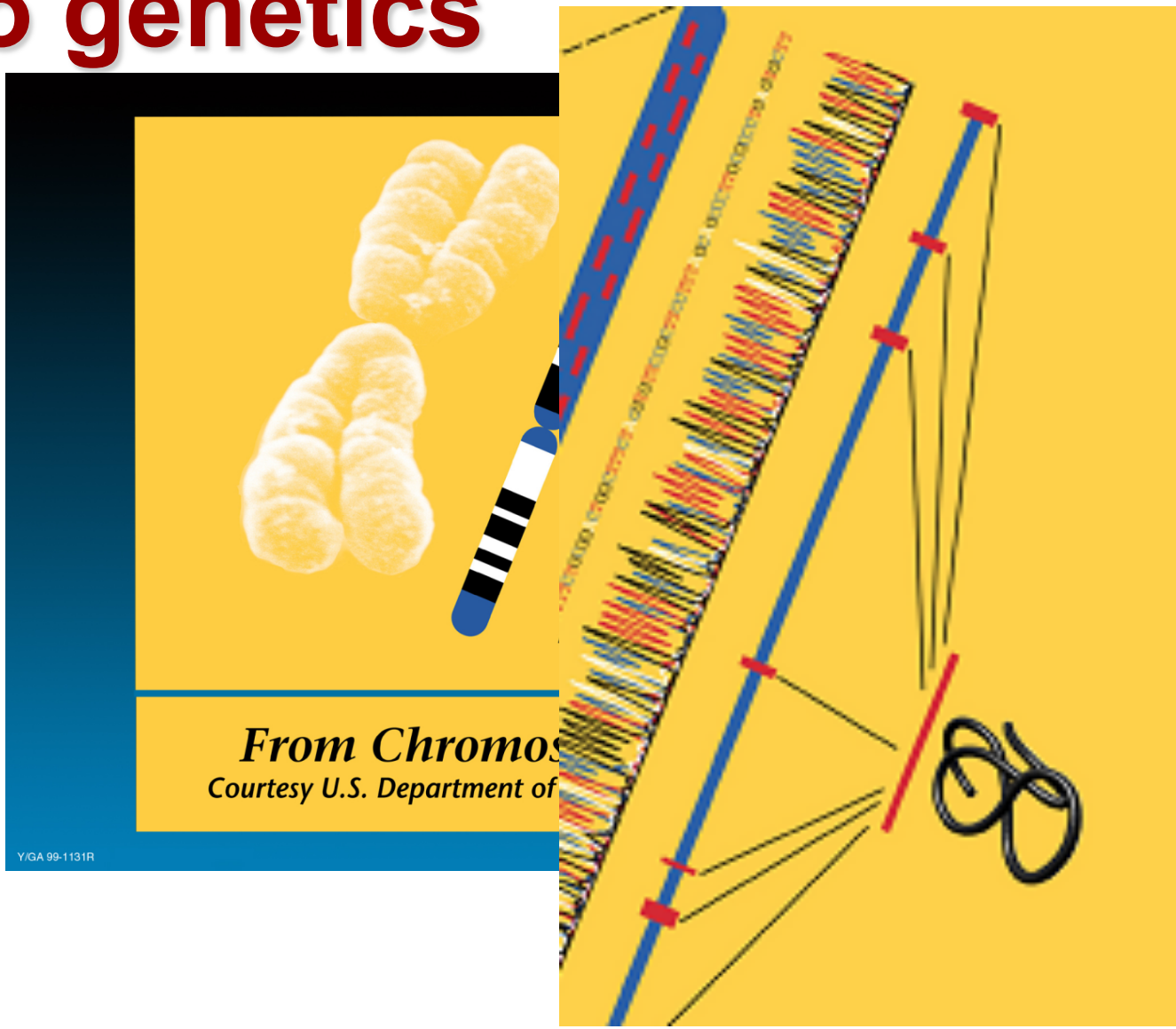
Teacher: Claudia Giachino

Lesson 3

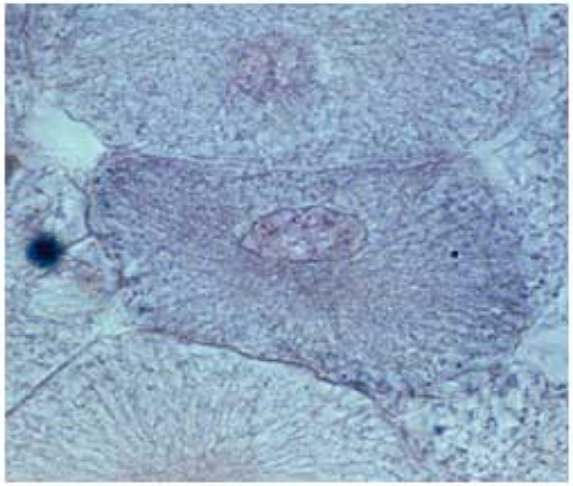
Chromosomal diseases

What diseases are attributable to genetics

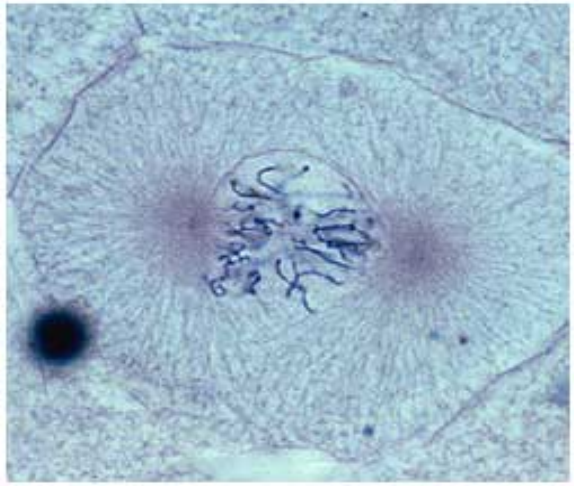
- Monogenic or hereditary diseases
- Chromosomal diseases
- Multifactorial or complex diseases



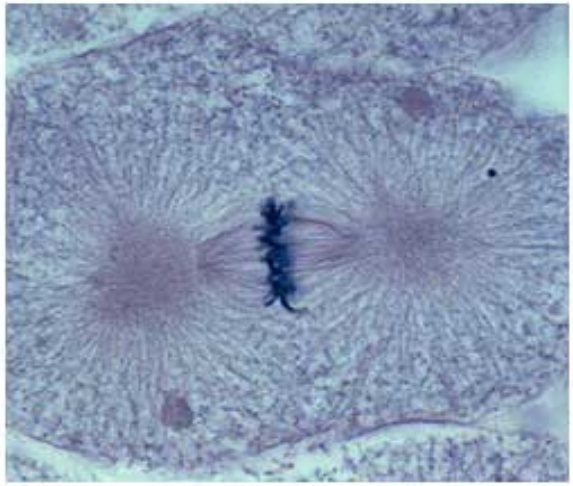
Chromosomes are [literally] the colored bodies
in latin: “chromo” “soma”



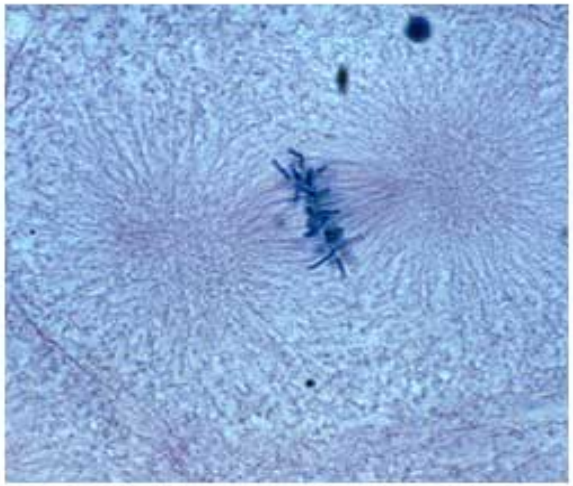
Interphase



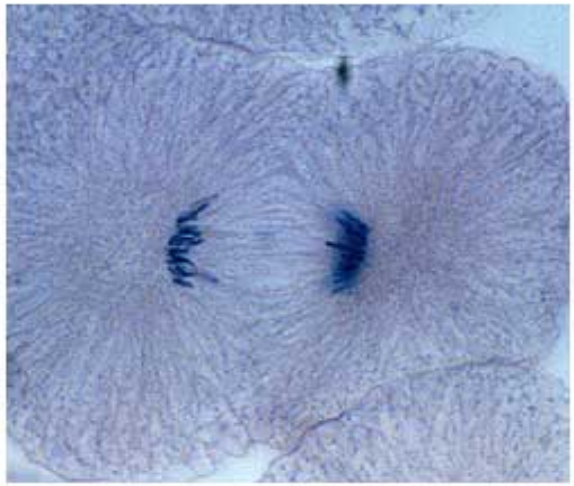
Prophase



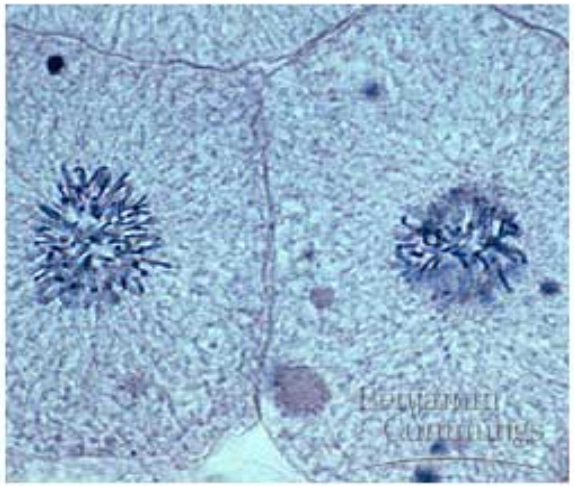
Metaphase



Anaphase

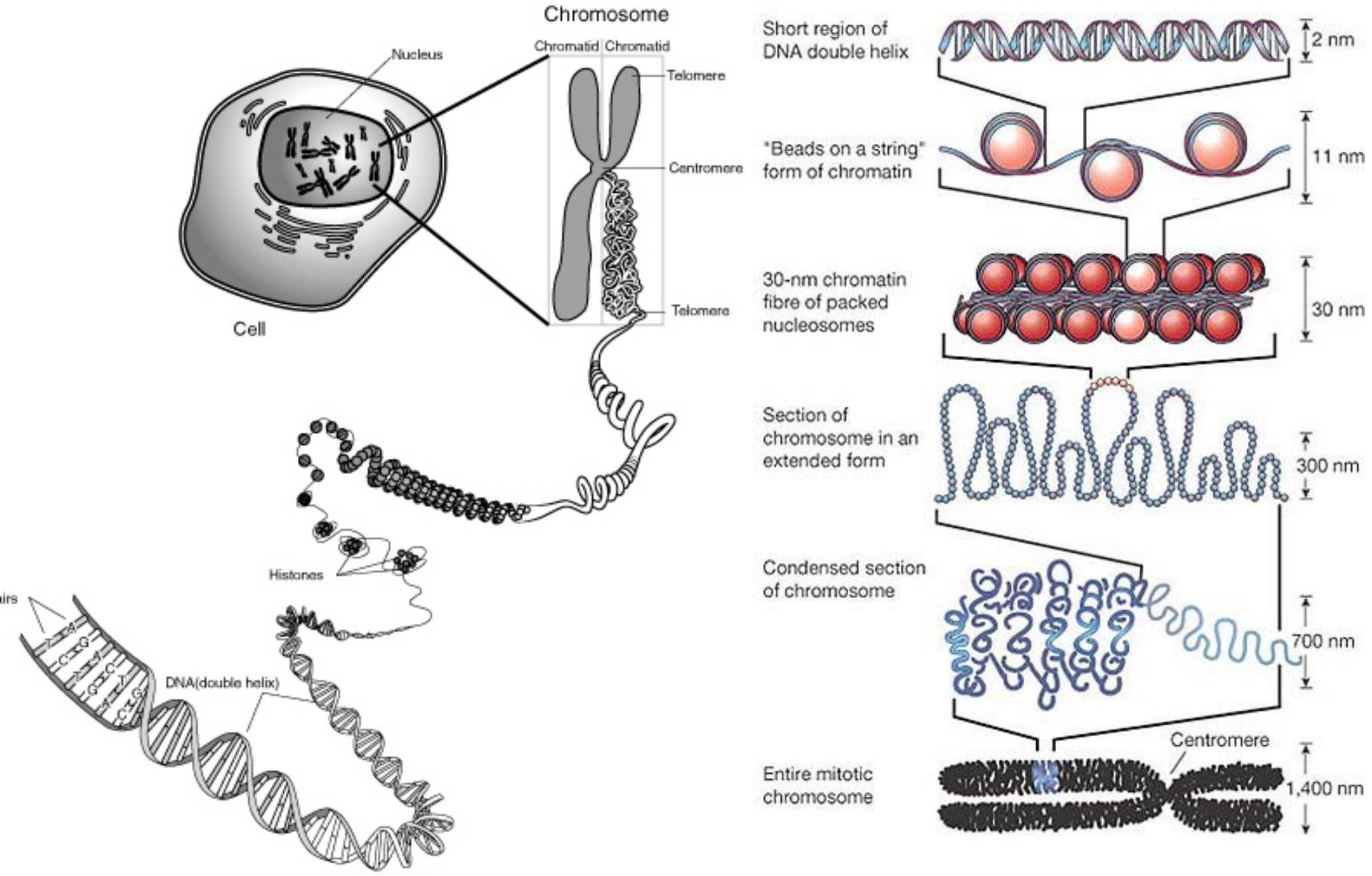


Early Telophase

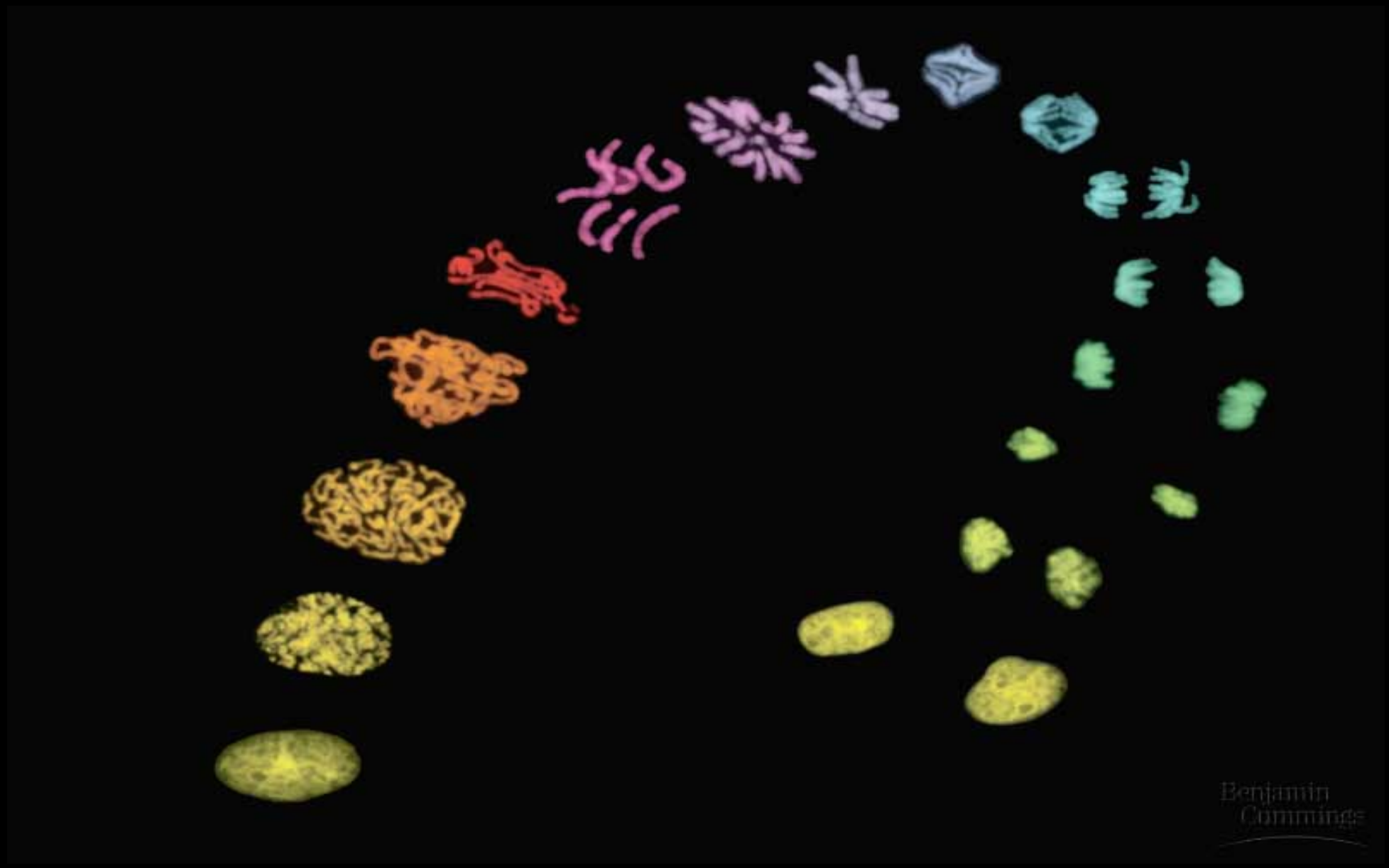


Late Telophase

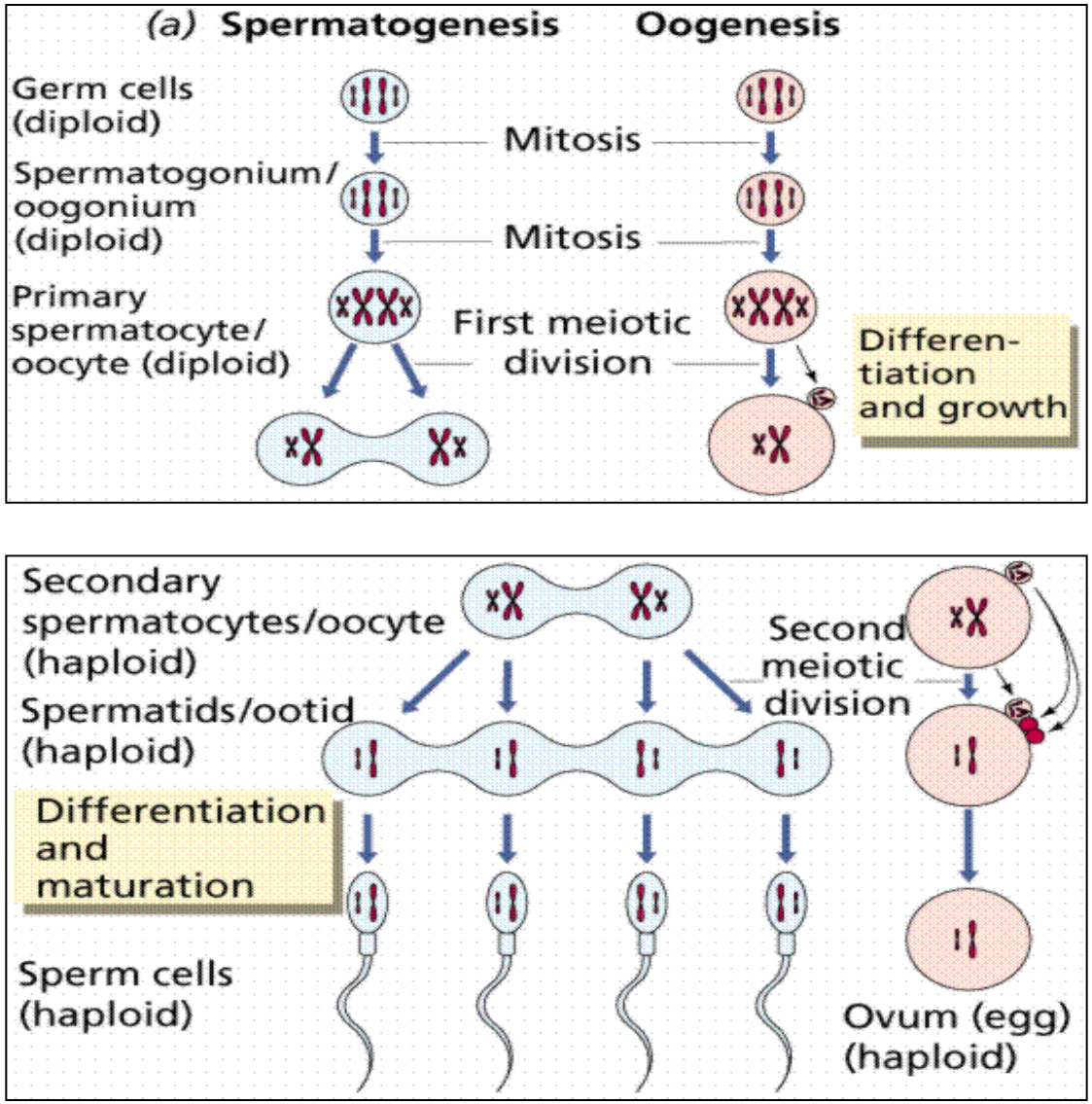
http://www.sc.edu/union/Sears/im.mitosis2.jpg


Chromosome
Chromatid
Chromatid
Nucleus
Telomere
Centromere
Telomere
Cell
Histones
DNA(double helix)
Short region of DNA double helix
2 nm
"Beads on a string" form of chromatin
11 nm
30-nm chromatin fibre of packed nucleosomes
30 nm
Section of chromosome in an extended form
300 nm
Condensed section of chromosome
700 nm
Centromere
Entire mitotic chromosome
1,400 nm

Chromosomes get duplicated in cell divisions

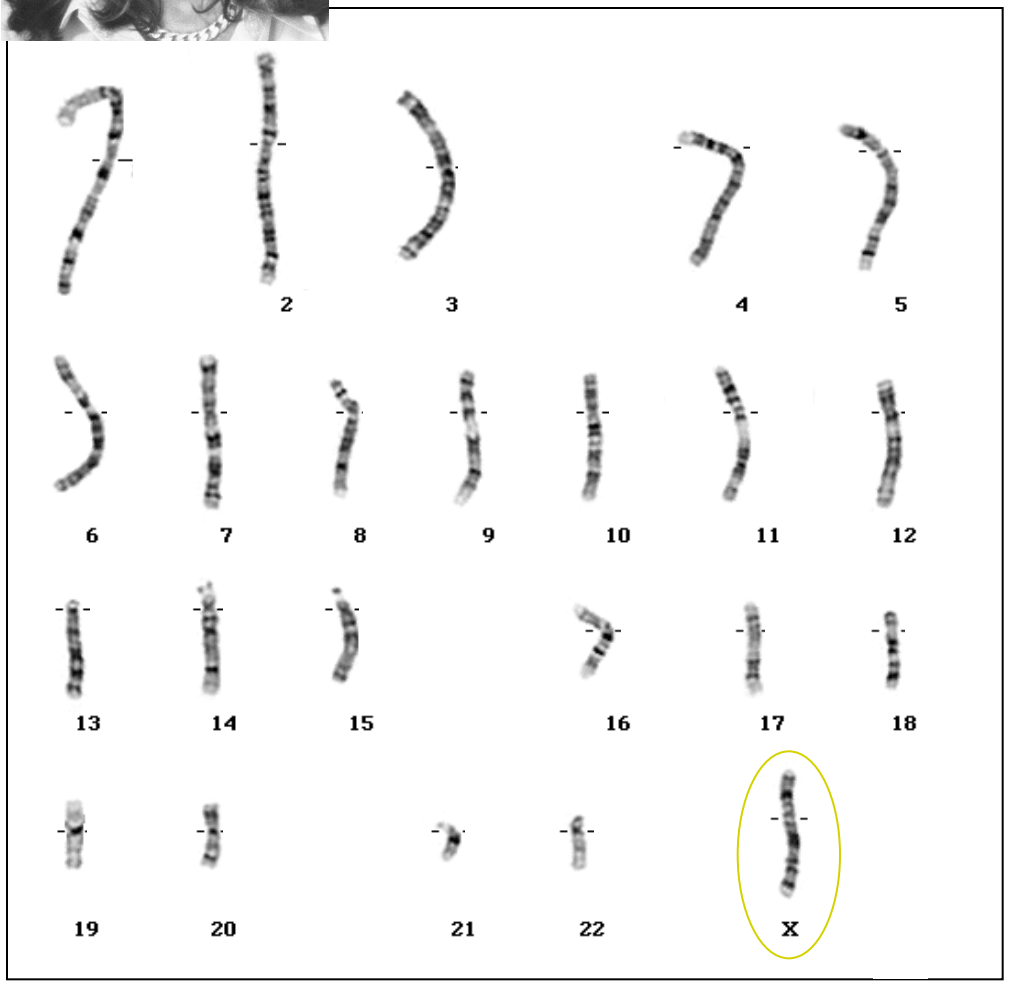


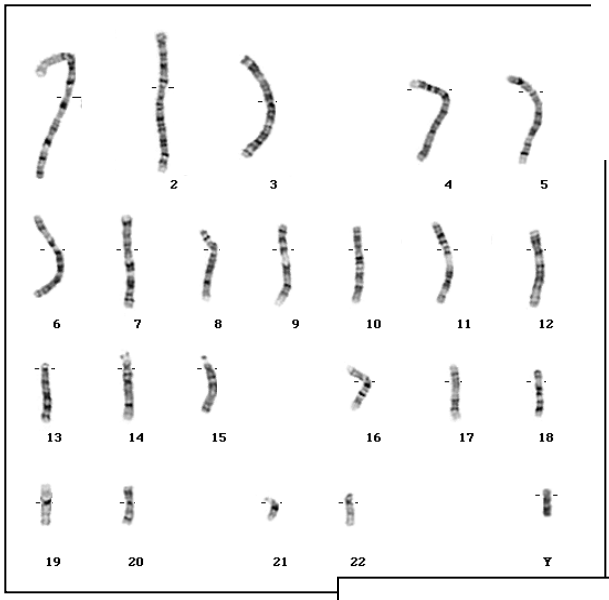
Sperm and eggs have only half the number of chromosomes found in other cells

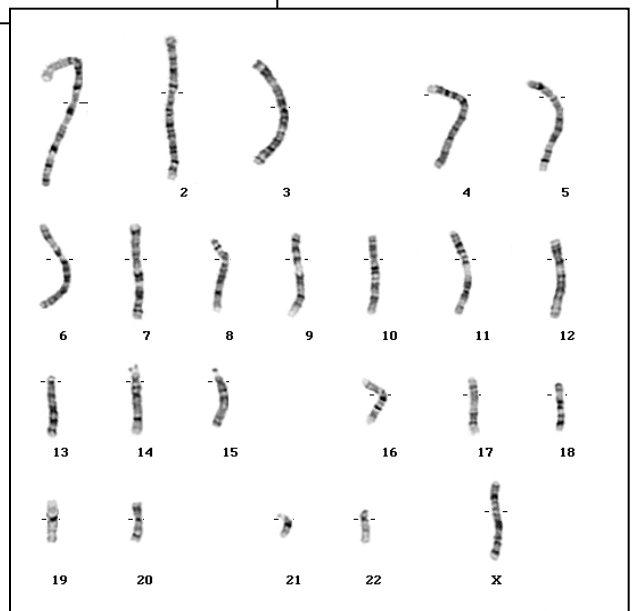


http://www.emc.maricopa.edu/faculty/farabee/BIOBK/BioBookmeiosis.html

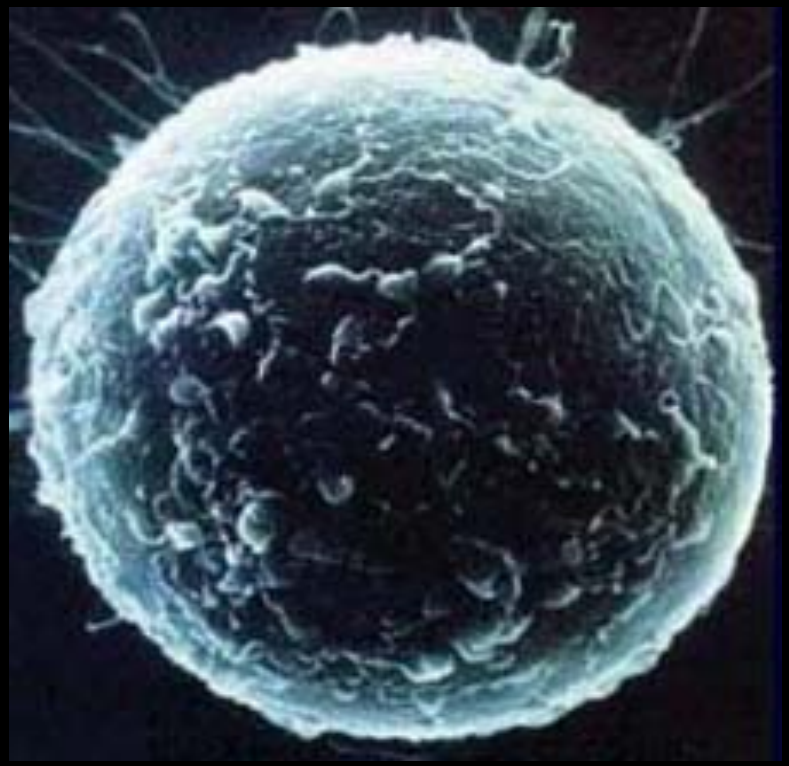
The sperm decides the sex of the offspring

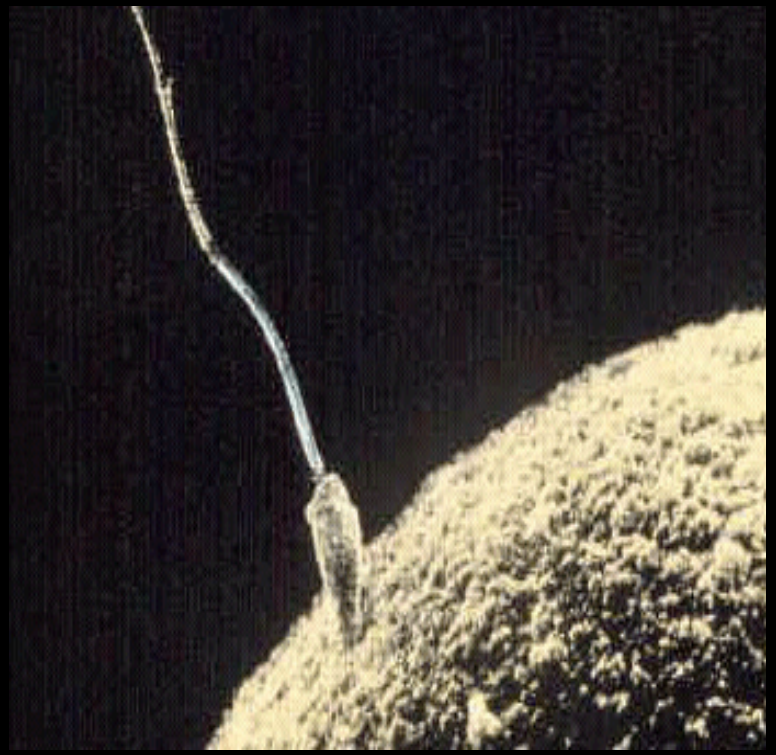






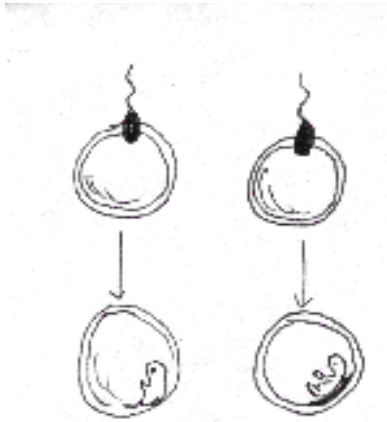
During fertilization a sperm cell joins an egg cell





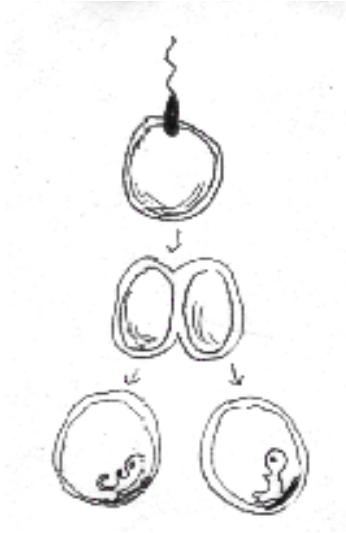
Individuals with identical chromosomes look identical

Fraternal twins

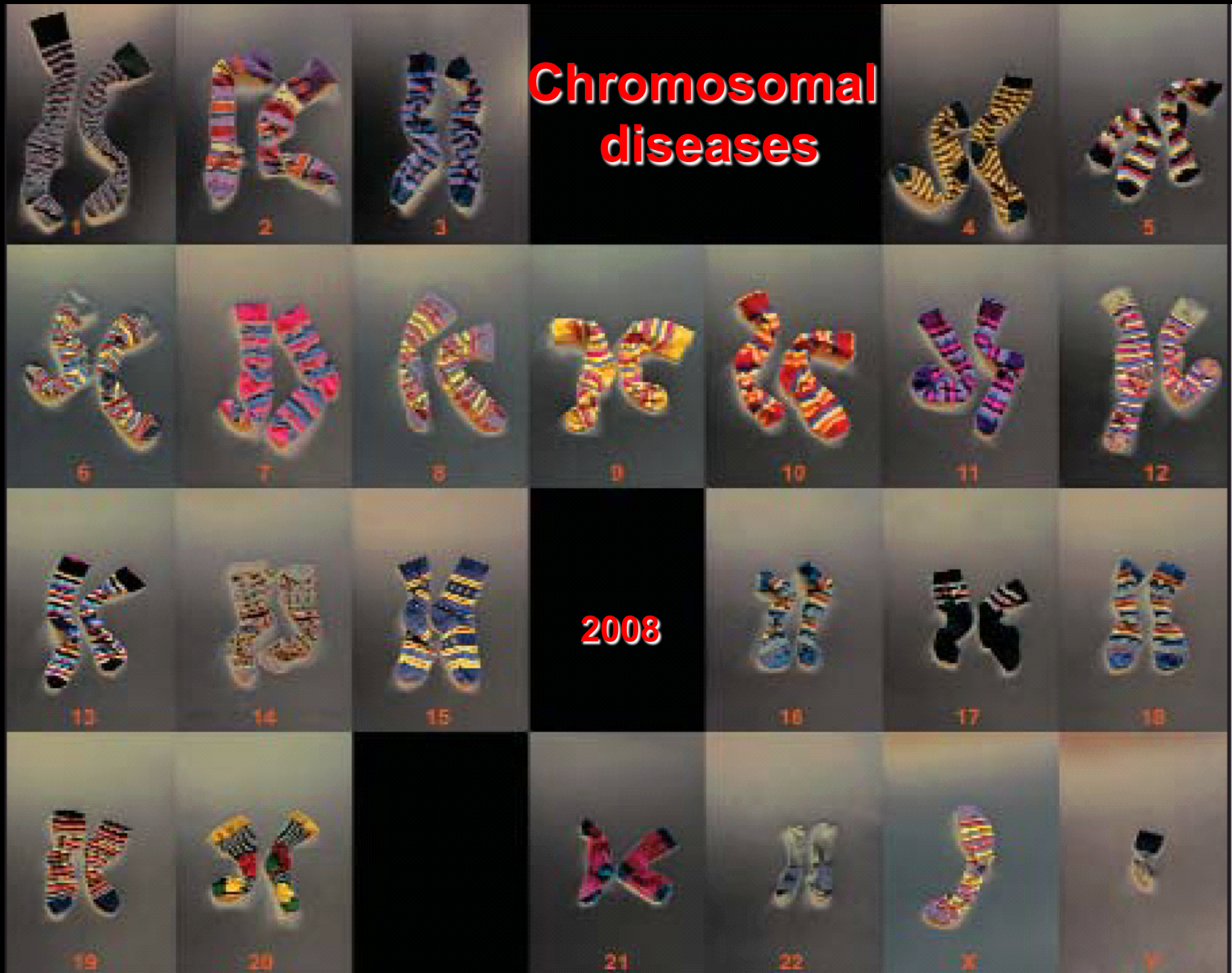


Same degree of similarity as any two siblings

Identical twins

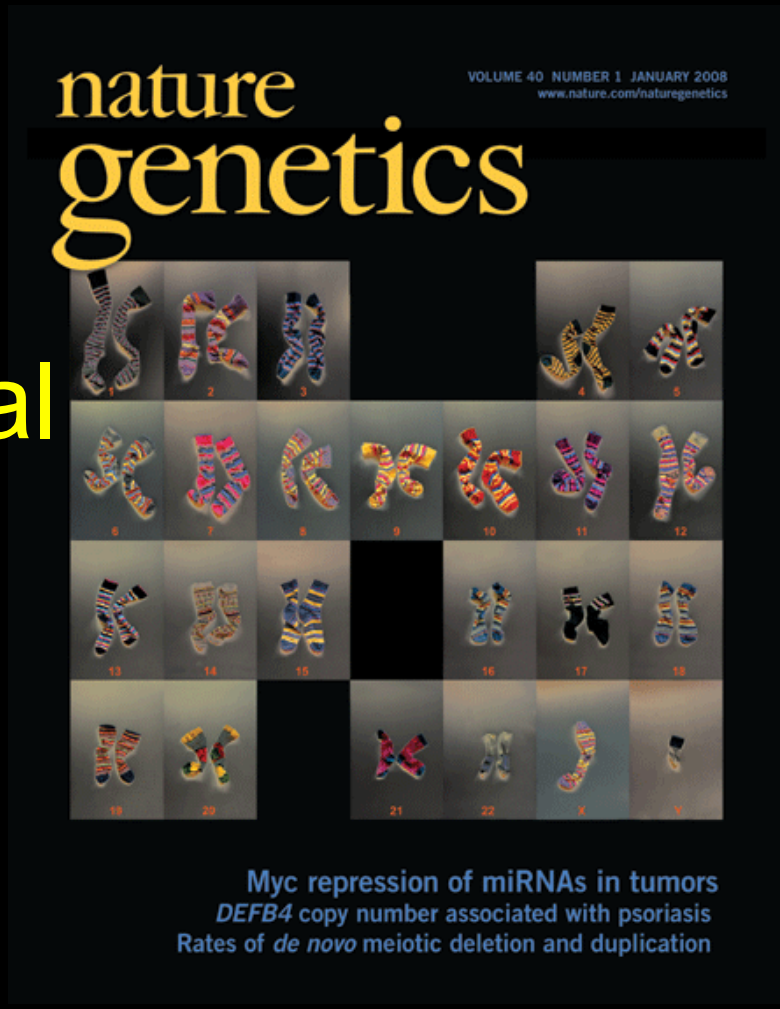


http://www.childrenofsalem.com/days/kids/ericbran/ericbran1.html


Chromosomal diseases
2008

THE STUDY OF CHROMOSOMES: CYTOGENETICS

- Principles of cytogenetics
- classification
- frequency of chromosomal diseases
- the most frequent diseases
- molecular cytogenetics methods



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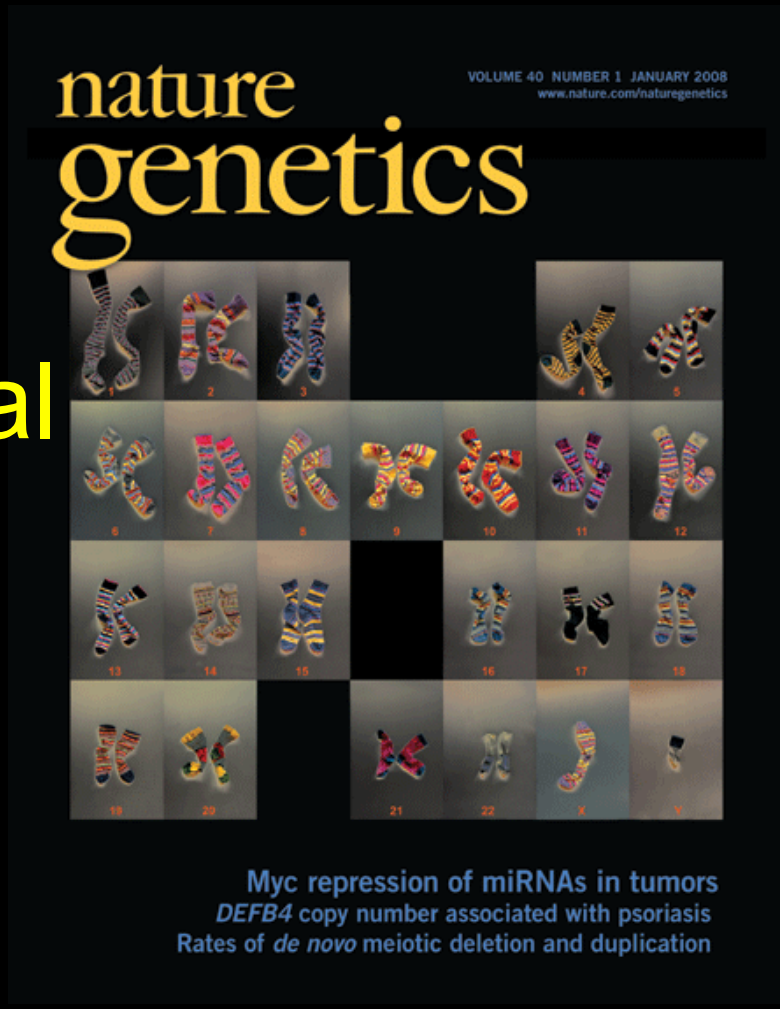
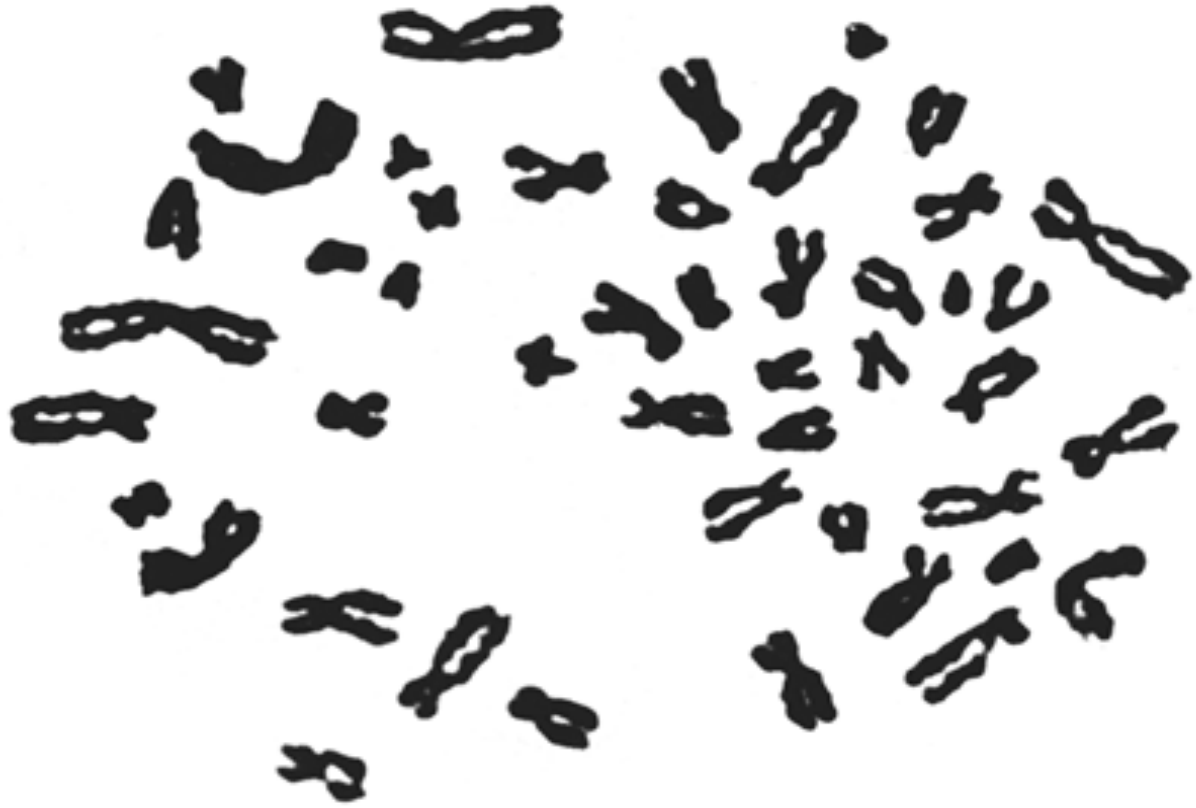




The picture that established 46 as the chromosome number in man
1955

Figure 4 | **Joe Hin Tjio.** Reproduced with permission from REF. 25 © (1979) Springer Verlag.

Nature

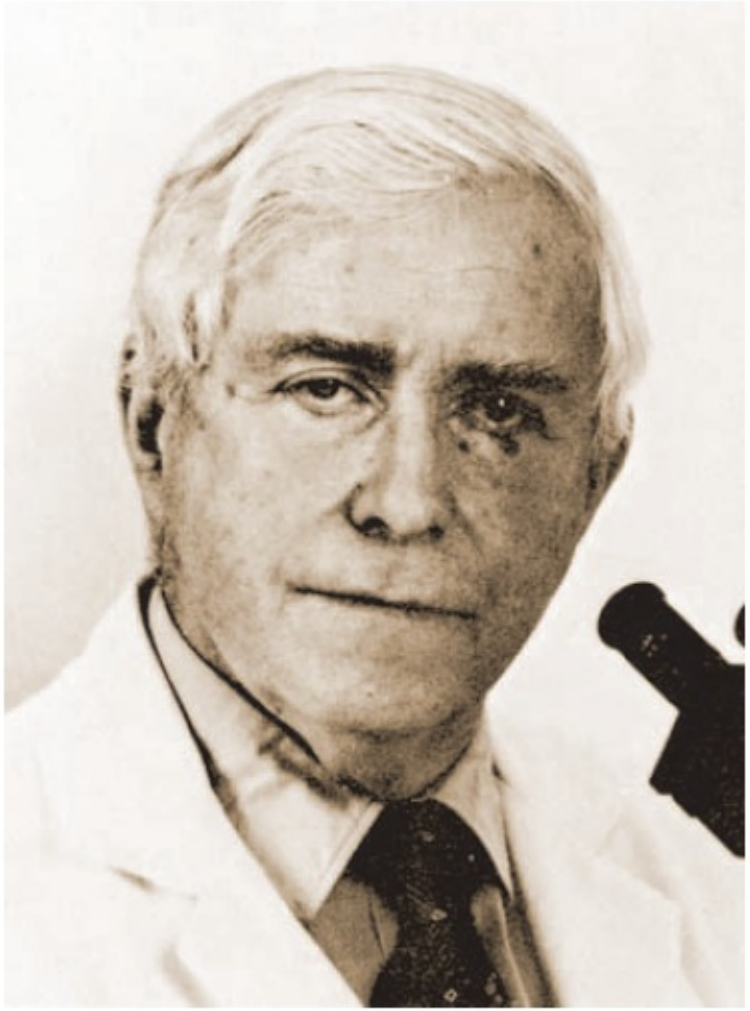


Figure 3 | **Albert Levan.** Reproduced with permission from REF. 25 © (1979) Springer Verlag.

The picture that established 46 as the chromosome number in man

Reproduced with permission from Ref. 1 © (1956) Mendelian Society of Lund for the Scandinavian Association of Genetics.

Chromosomes

Individual chromosomes of a cell differ in shape and size. The position of the centromere determines the shape of chromosomes.

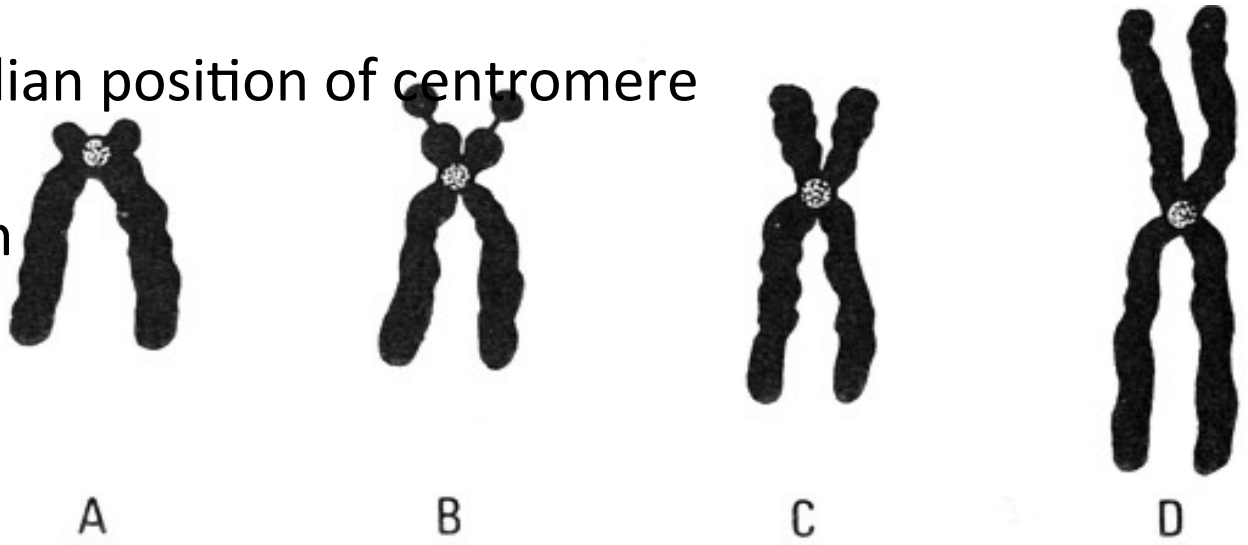
The position of the centromere allows you to classify the chromosomes into 4 types:

A: acrocentrics: terminal position of centromere

B: telocentrics: sub-terminal position of centromere (not present in humans)

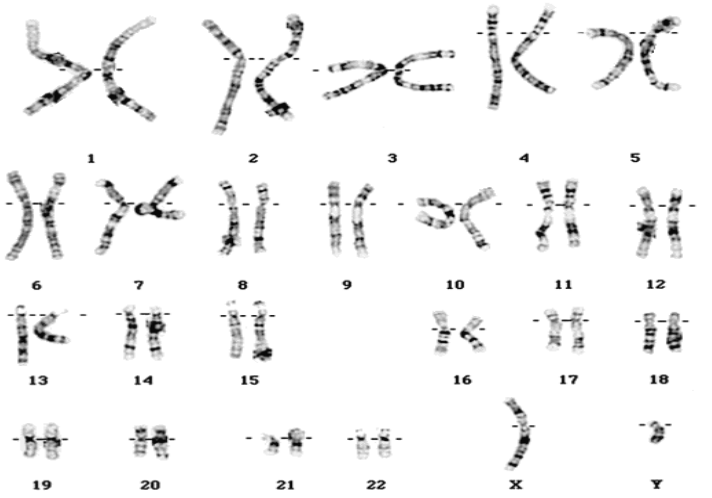
C: submetacentrics: sub-median position of centromere

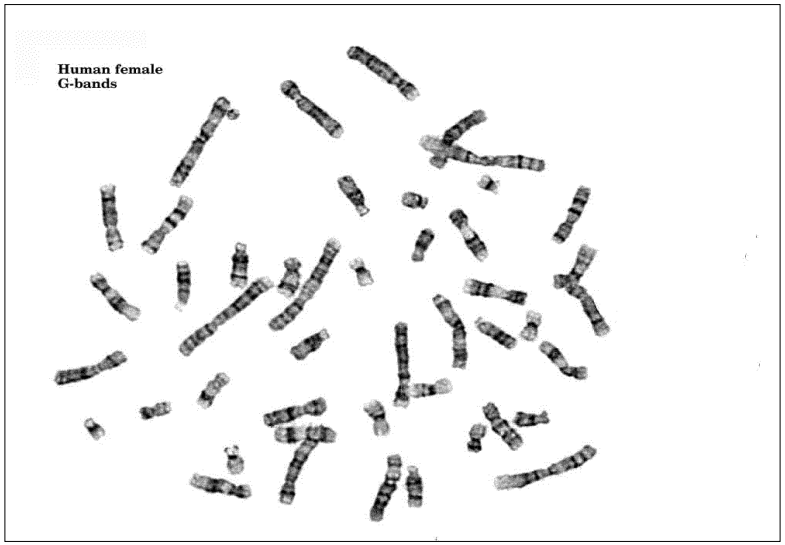
D: metacentrics: mid position of centromere

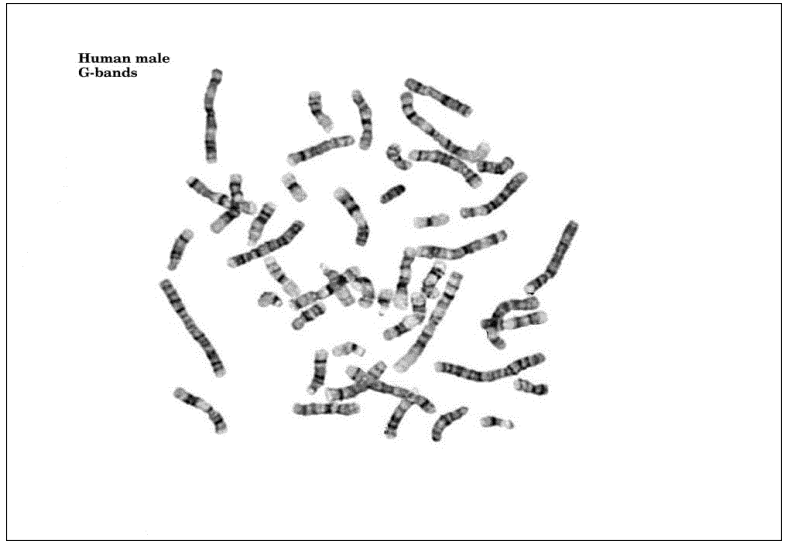


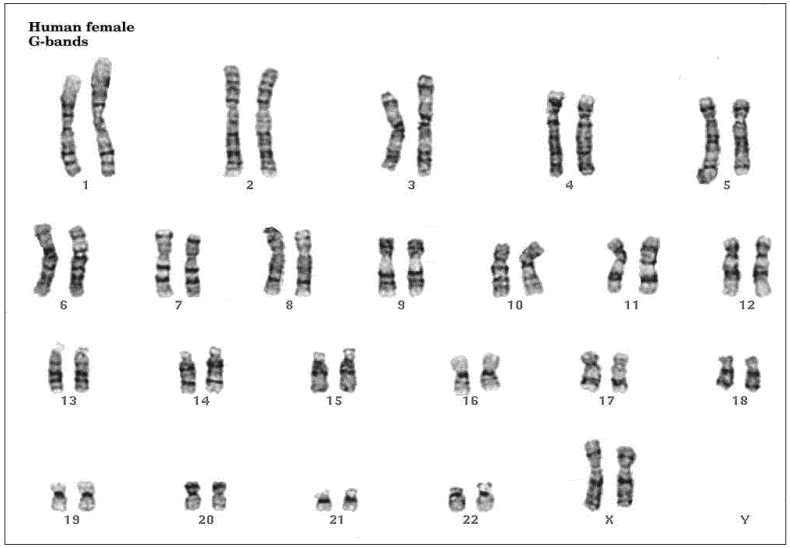
The karyotype

- The karyotype is a photographic reconstruction of the chromosomal structure of an individual.
- A karyotype is a photograph where the individual's chromosomes, duplicated and condensed as they appear under a microscope during the mitotic metaphase (highest condensation state), are sorted by their size and shape.




Human female
G-bands


Human male
G-bands


Human female
G-bands
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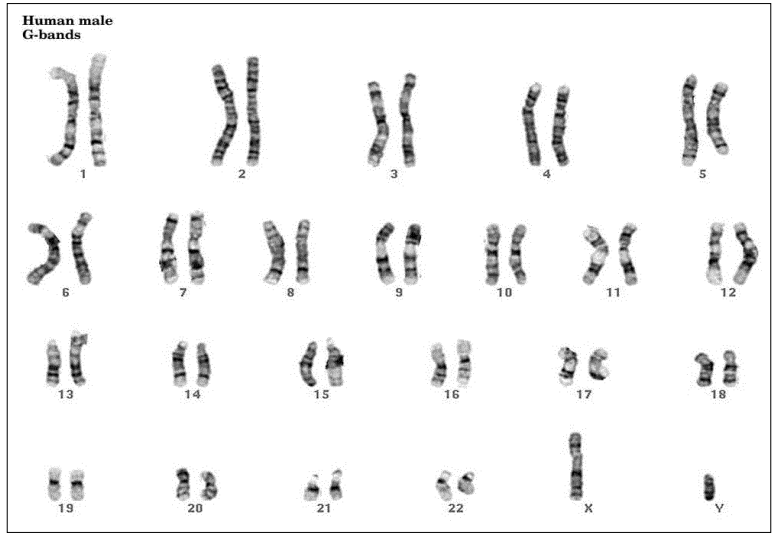
X
Y


Human male
G-bands
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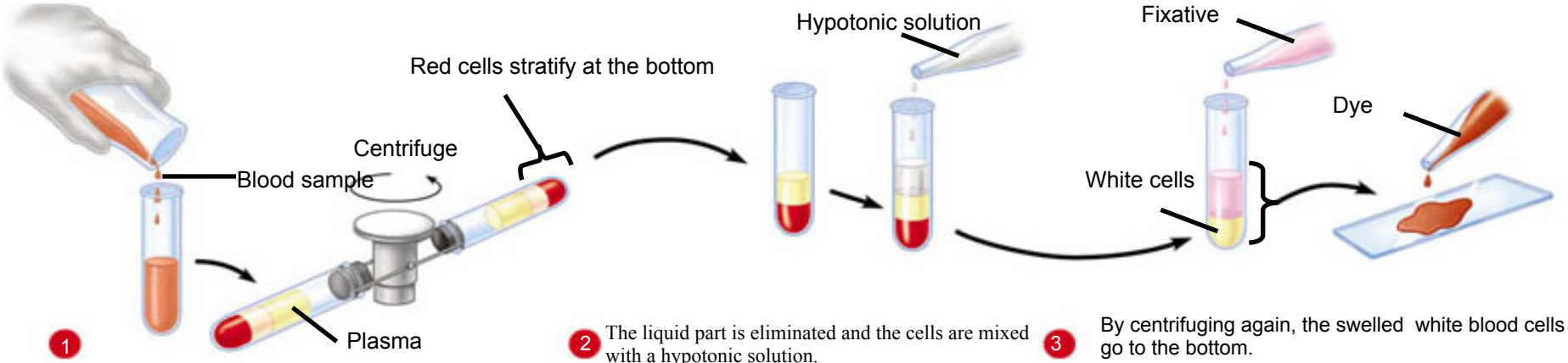
X
Y

The karyotype

Karyotype preparation from a blood sample:

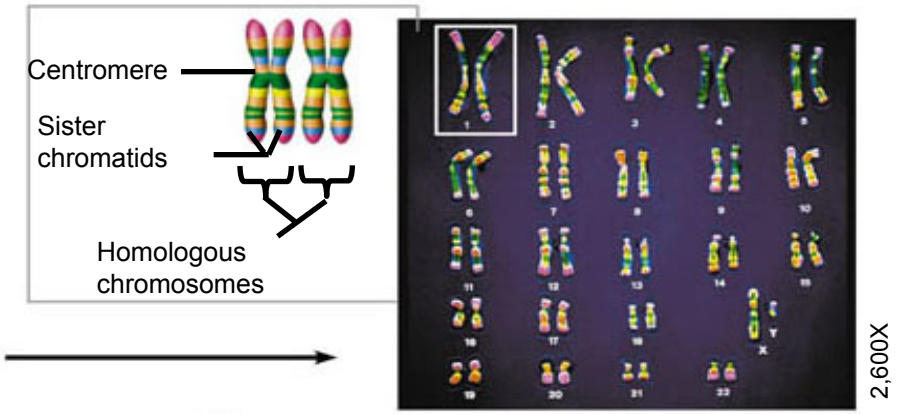


1 The blood sample is centrifuged to separate the cells from the liquid part.

2 The liquid part is eliminated and the cells are mixed with a hypotonic solution.
This procedure does inflate and break out the red blood cells. White blood cells swell but do not break, and the chromosomes move apart from each other.

3 By centrifuging again, the swelled white blood cells go to the bottom.
The liquid part containing the broken red blood cells is eliminated.
A fixative is added to the white blood cells.

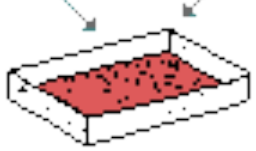
4 The preparation is observed under a microscope that is connected to a digital camera. The image is fed into a computer which sorts chromosomes by size and shape.



5 The ordered arrangement of chromosomes obtained is the karyotype.
The 46 chromosomes represented here include 22 pairs of autosomes and 2 sex chromosomes, an X and a Y. Each chromosome consists of 2 chromatids attached together so closely that they are hardly distinguishable.

add tissue sample

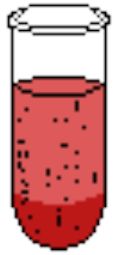
add chemical to stimulate mitosis



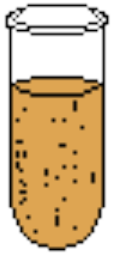
Culture in a growth medium

incubate for 2-3 days

add chemical to stop mitosis in metaphase



transfer cells to tube and centrifuge to concentrate in layers

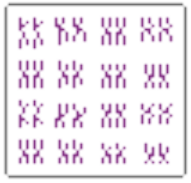


transfer to tube containing fixative

put cells onto microscope slide

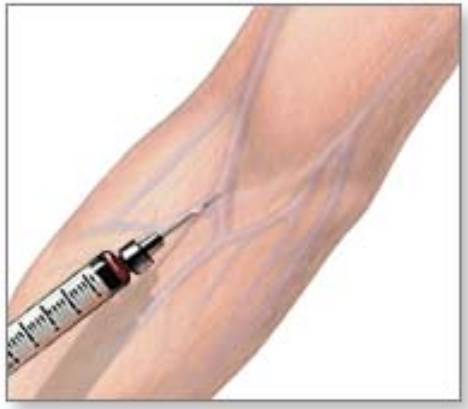
add stain to enhance chromosomes

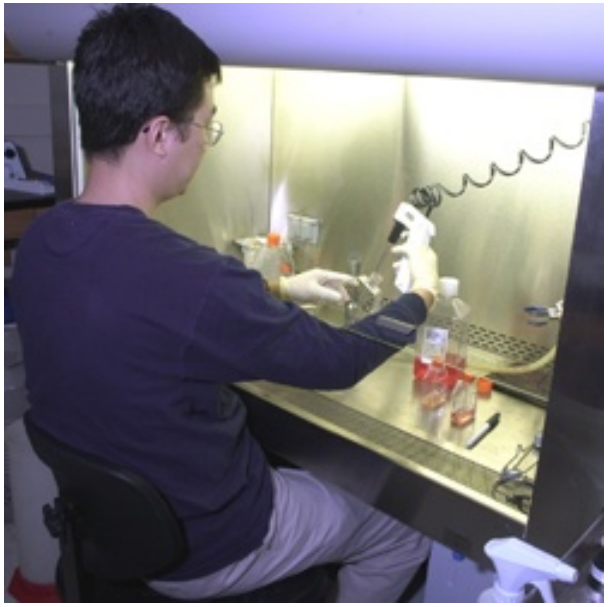
identify and photograph chromosomes

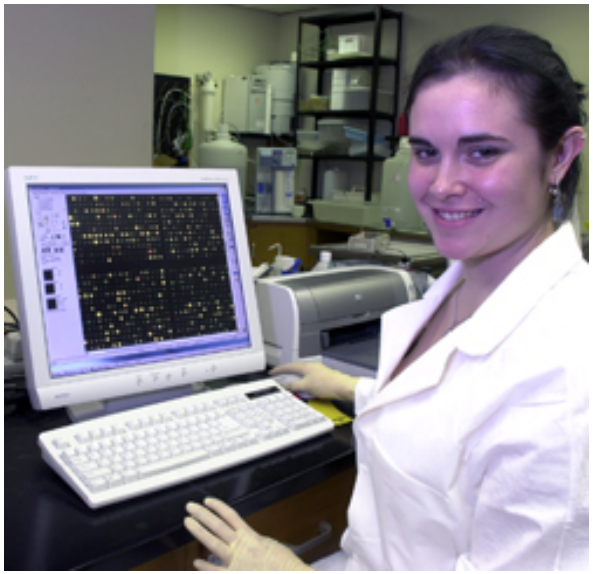


cut out chromosome pictures and arrange into karyotype

Blood sample is taken

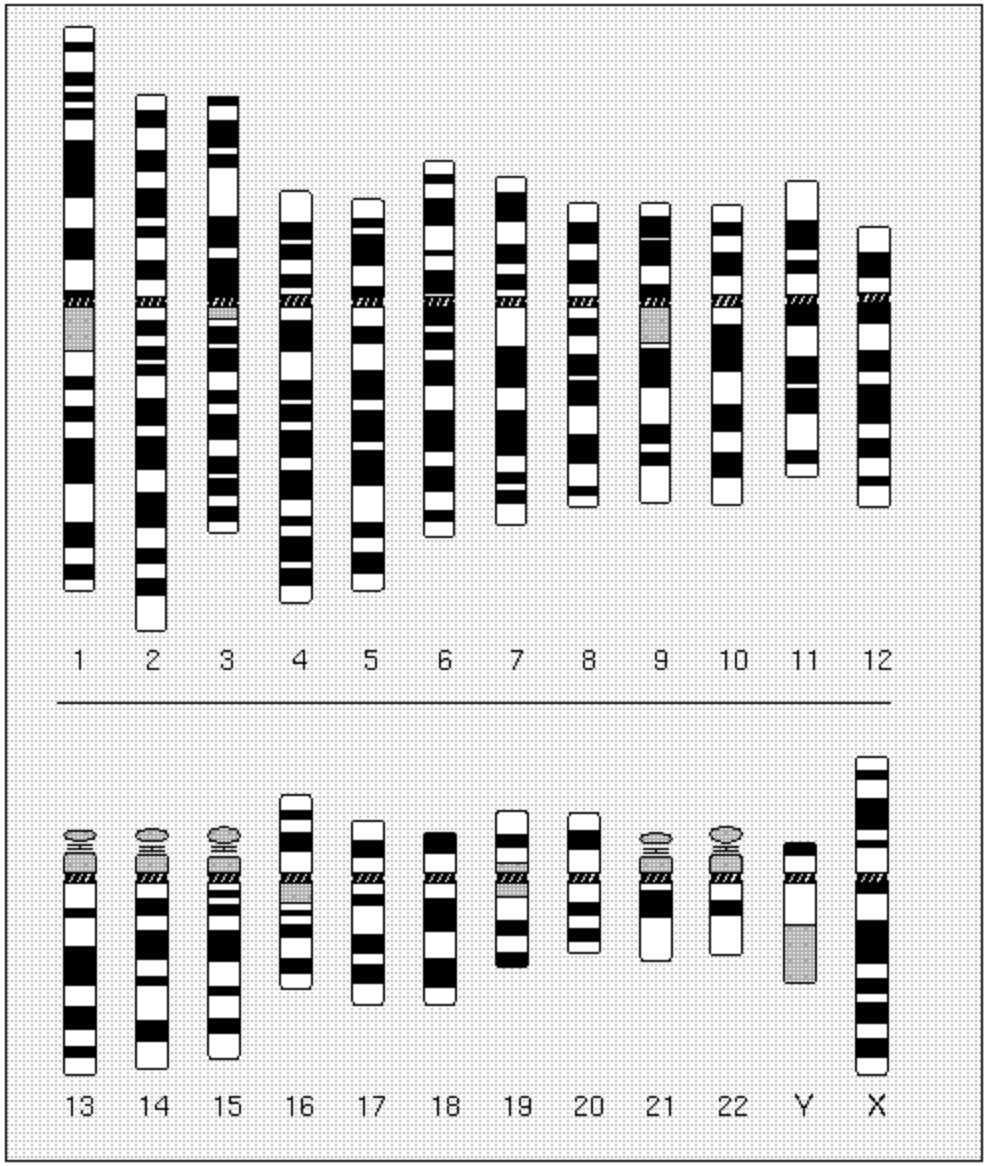




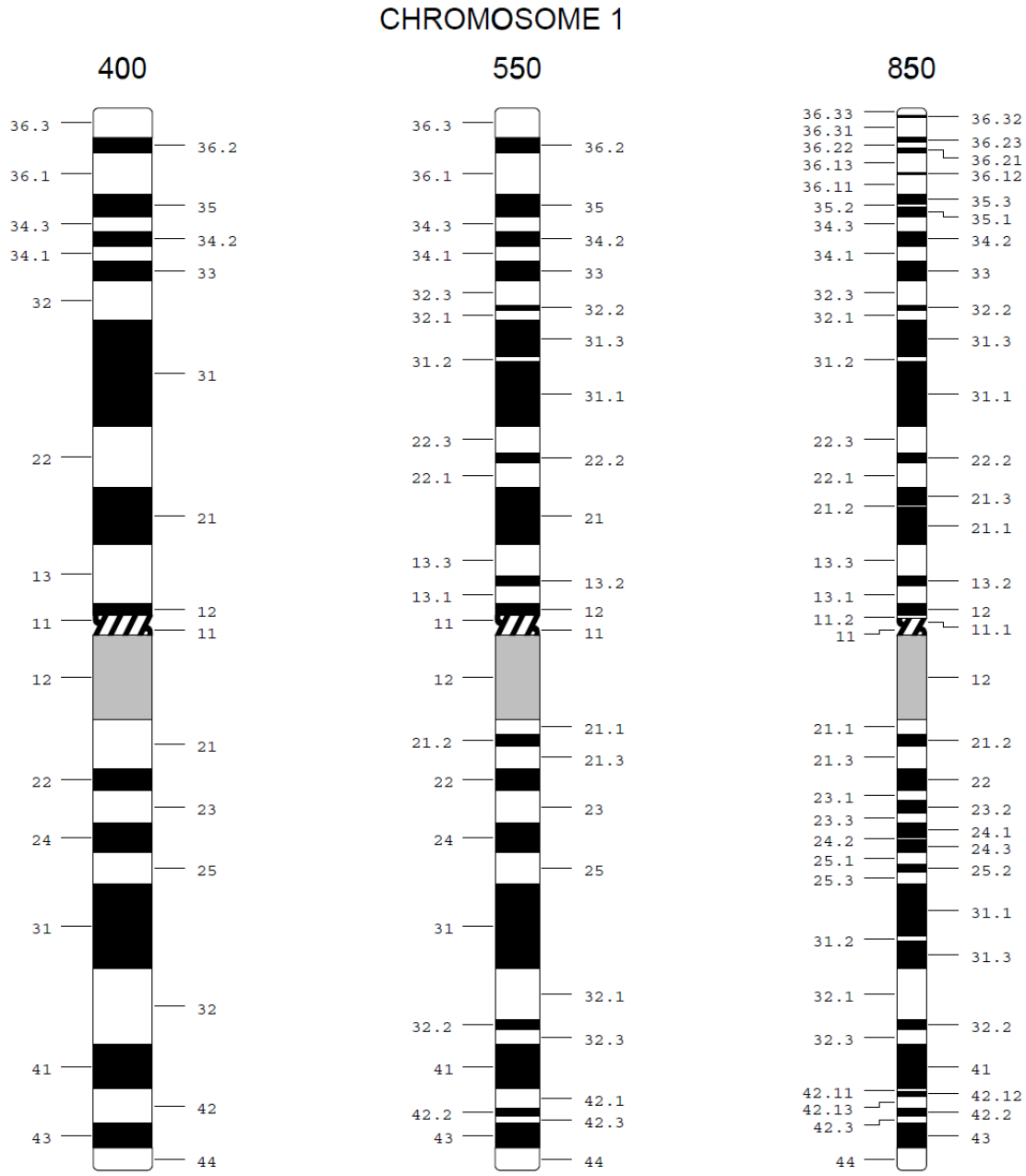


The karyotype

- The reconstruction of the karyotype is now made with a computerized image Analyzer, but until a few years ago the reconstruction took a lot of work because the individual chromosomes were cropped from the picture and pasted on a card.



Gli ideogrammi sono rappresentazioni schematiche del bandeggio di ciascun cromosoma ottenibile con ciascun tipo di metodica.
La rappresentazione del corredo cromosomico come serie di cromosomi bandeggiati è detta **cariogramma.**

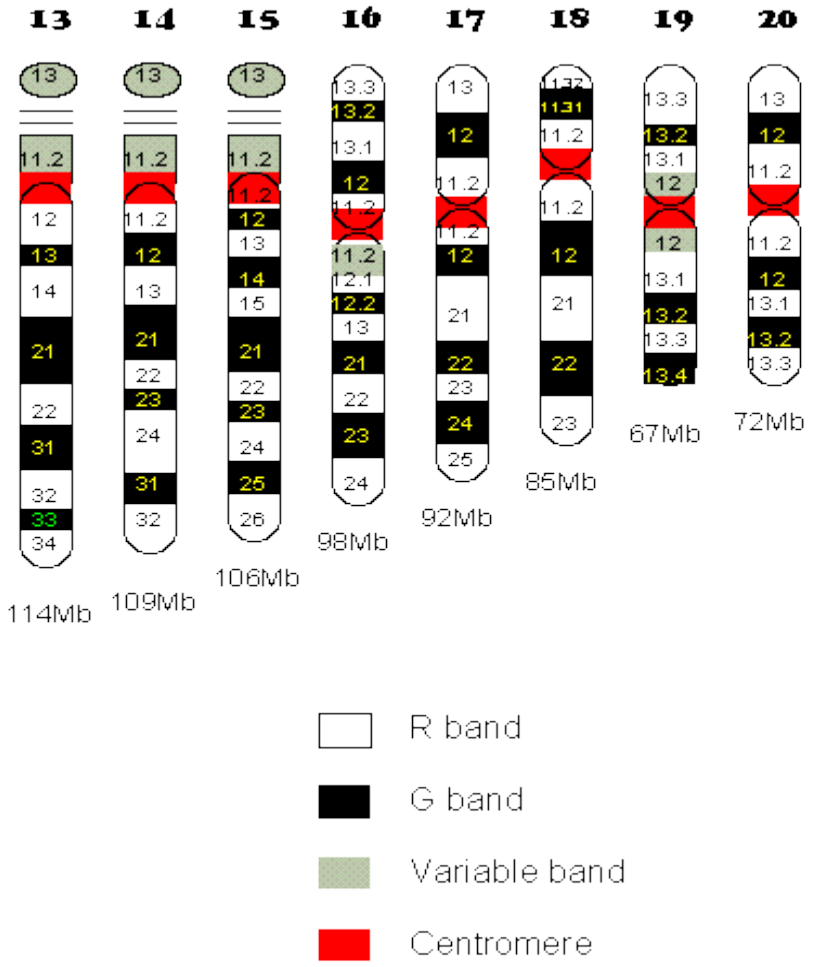


With three types of techniques, you can get in the entire human karyotype 400, 550, or 850 bands, respectively.

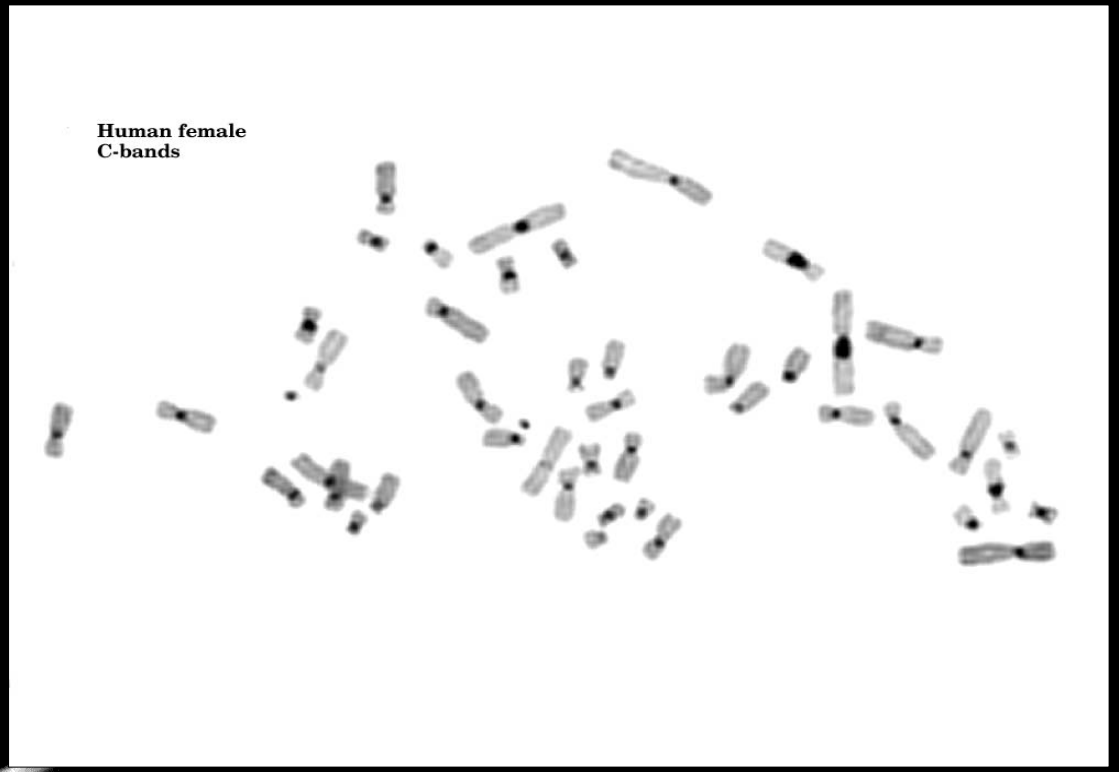
The banding

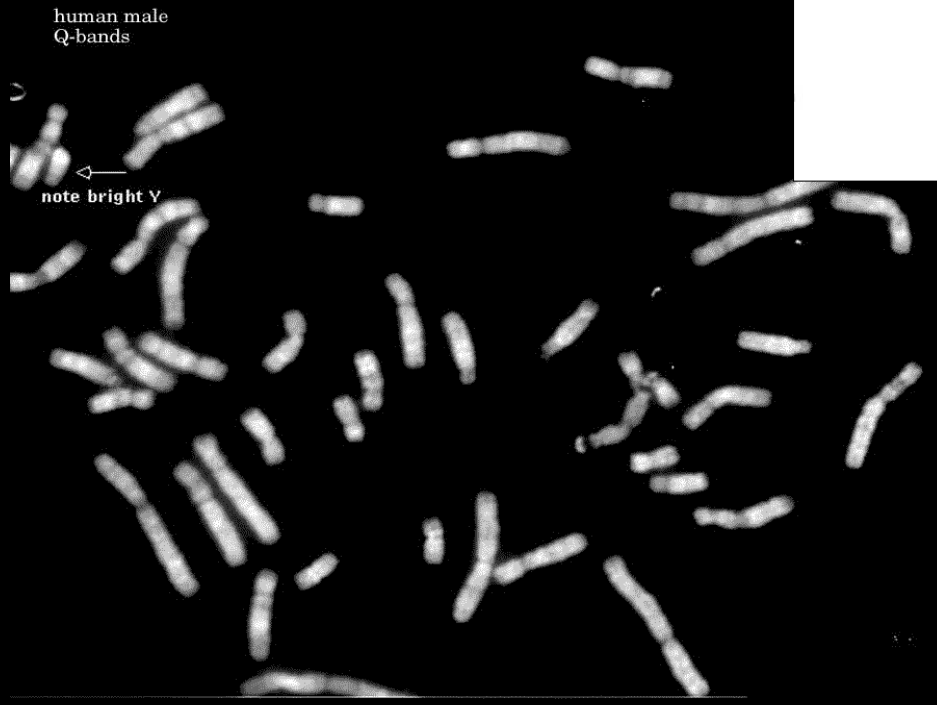
Typically, the chromosomal banding takes place with the Giemsa staining, also known as G banding, in which the slide is first treated with a saline or enzymatic solution, then it is colored in Giemsa solution, leading along the main axis of chromosomes to a sequence of regions with different staining intensity called chromosomal bands. Chromosomal bands are characteristics of each chromosome, allowing their classification according to a standardized scheme.

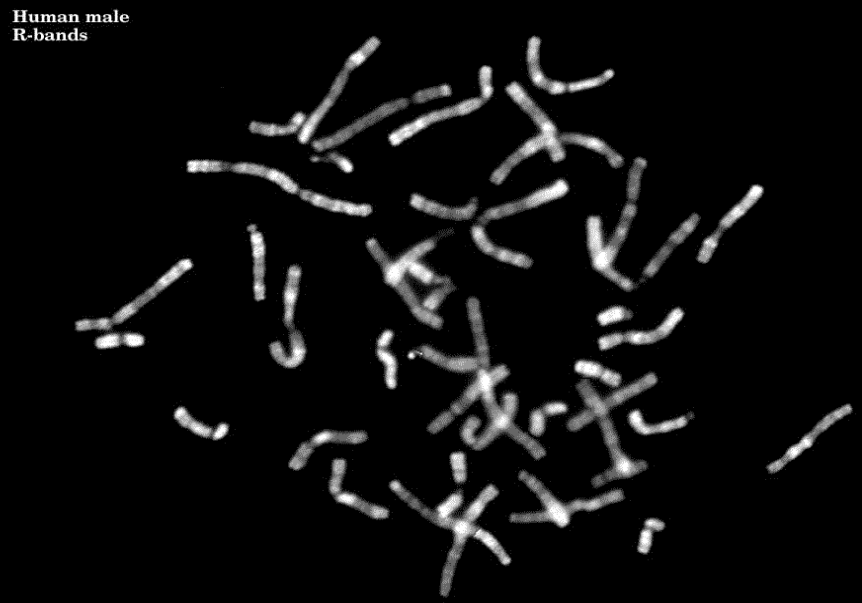
The banding is used to distinguish the different chromosomes and to study possible chromosome number and/or structure abnormalities (genomic and chromosomal mutations)

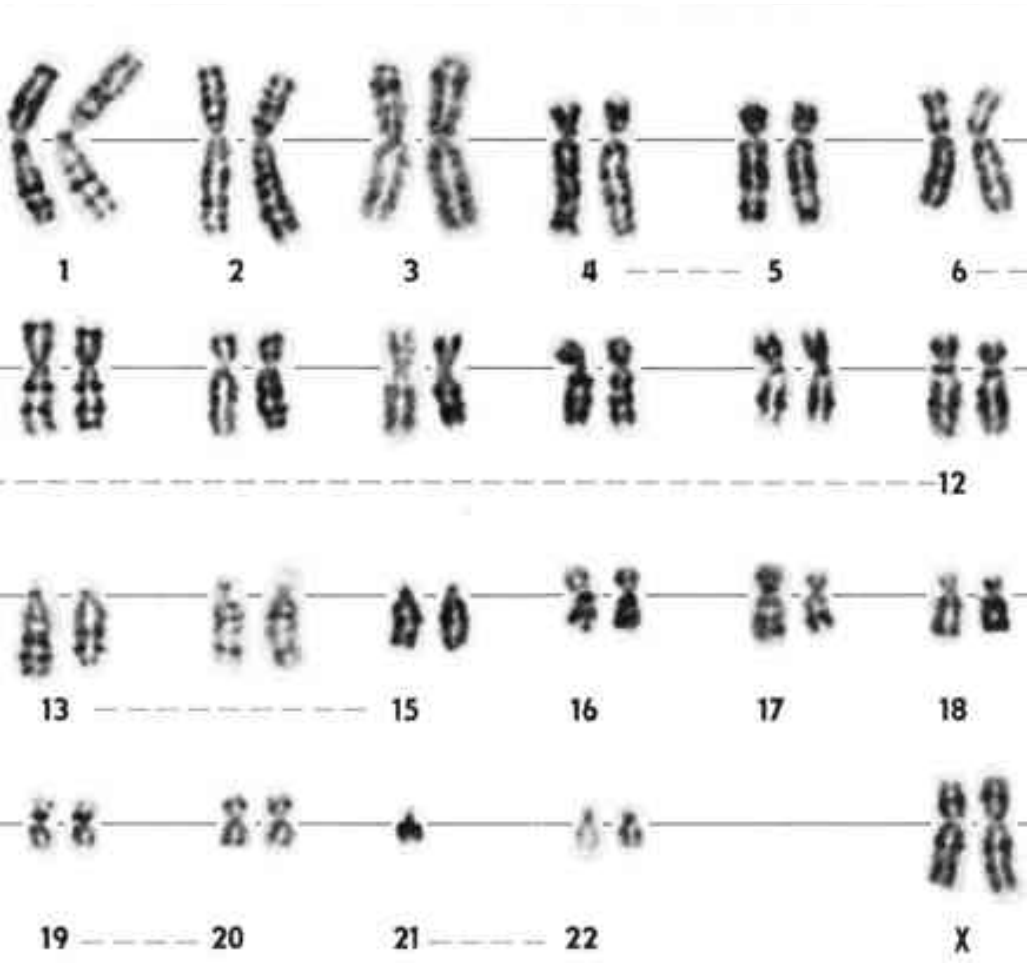


Tecniques	Procedure	Banding pattern
G banding	Partial proteolysis followed by Giemsa staining	Dark bands are rich in AT Light bands are rich in GC
R banding	Heat denaturation followed by Giemsa staining	Dark bands are rich in GC Light bands are rich in AT
Q banding	Enzymatic digestion followed by staining with a fluorescent dye, Quinacrine	Dark bands are rich in AT Light bands are rich in GC
C banding	Barium hydroxide denaturation followed by Giemsa staining	Dark bands are rich in constitutive heterochromatin


Human female
C-bands


human male
Q-bands
note bright Y


Human male
R-bands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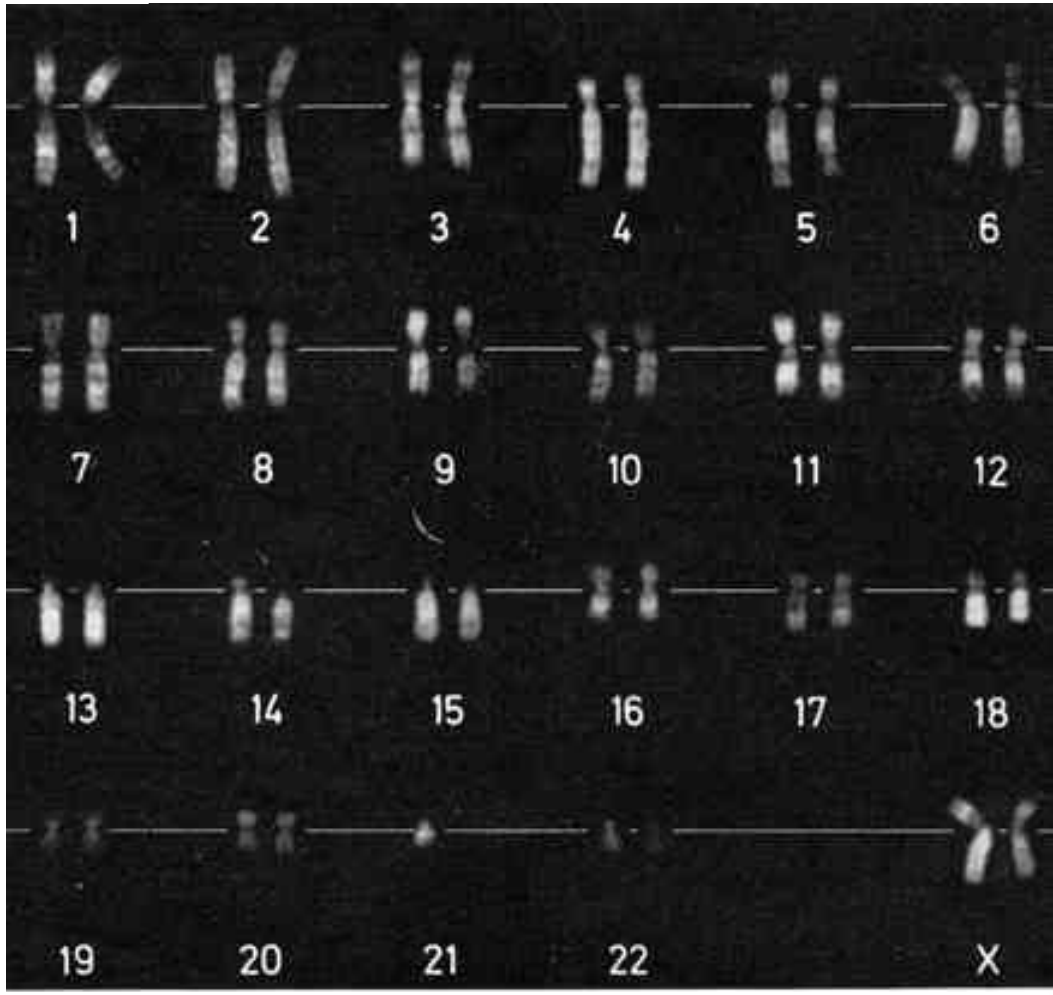
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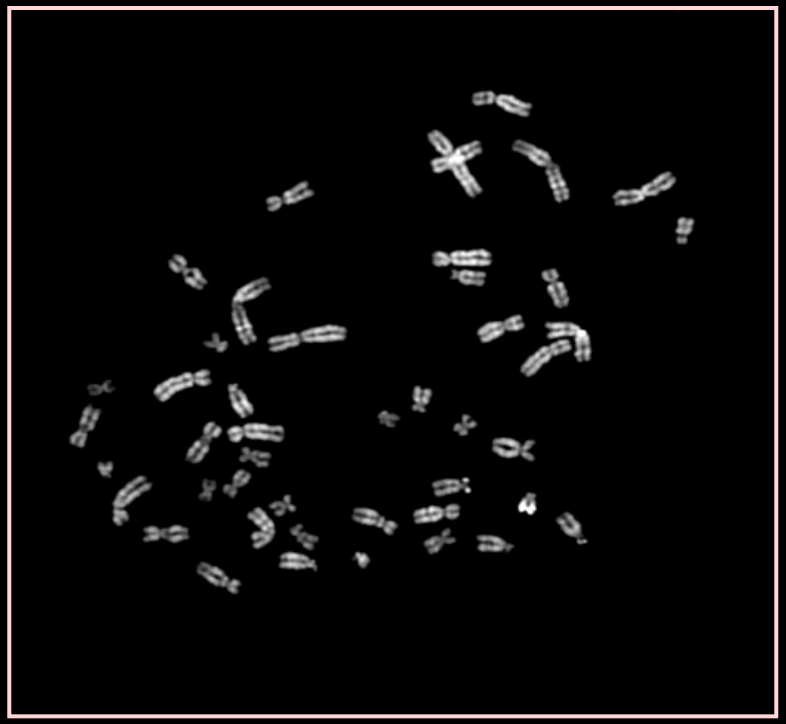
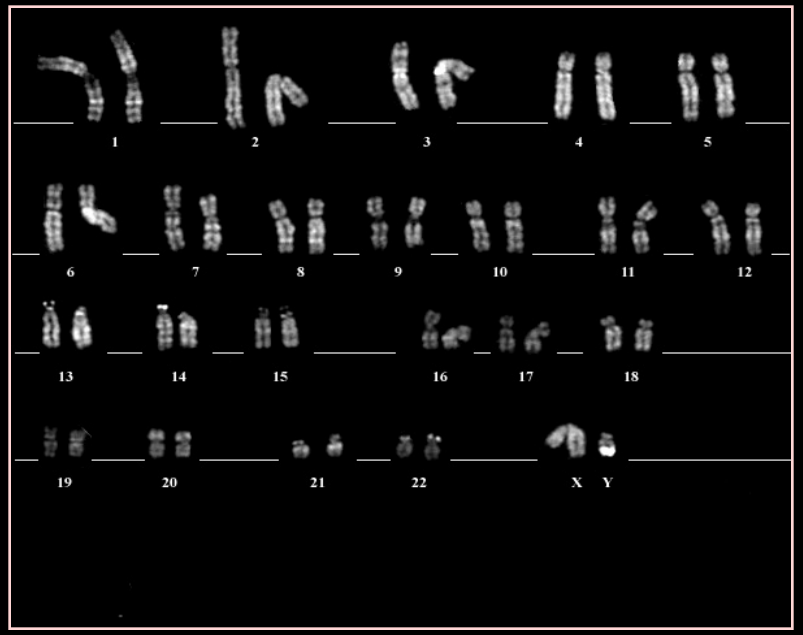
Chromosome observation through a microscope



Karyotype construction



SOME EXAMPLES

Chr. 15 x 3 !!!

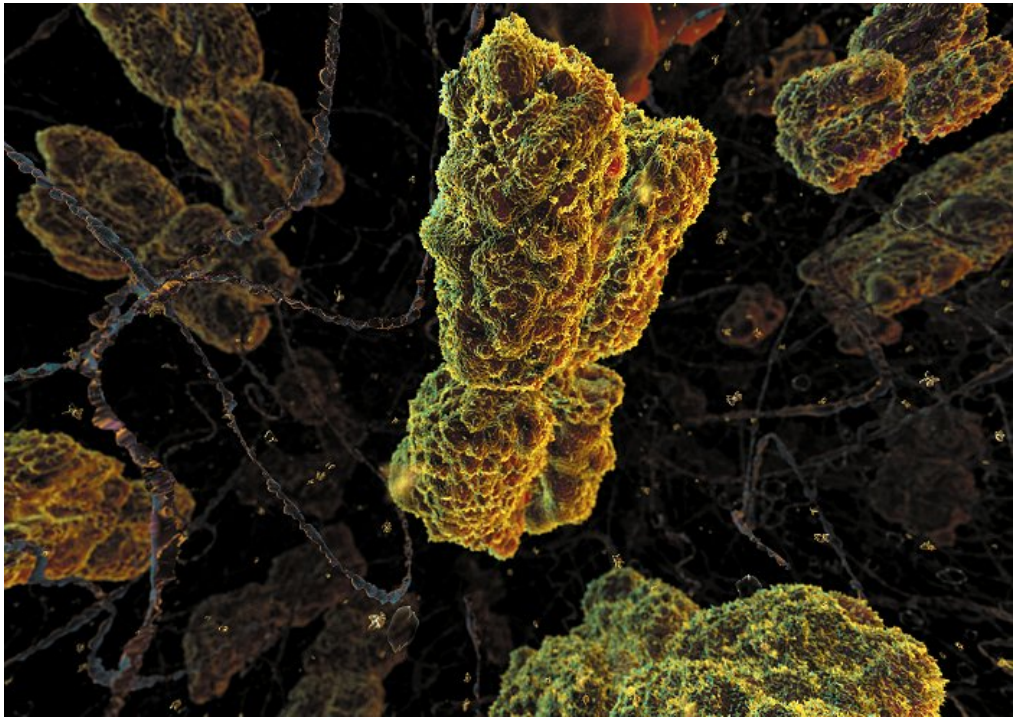
karyotype

47,XX + 15

Trisomy is the most frequent constitutional chromosomal anomaly in humans.

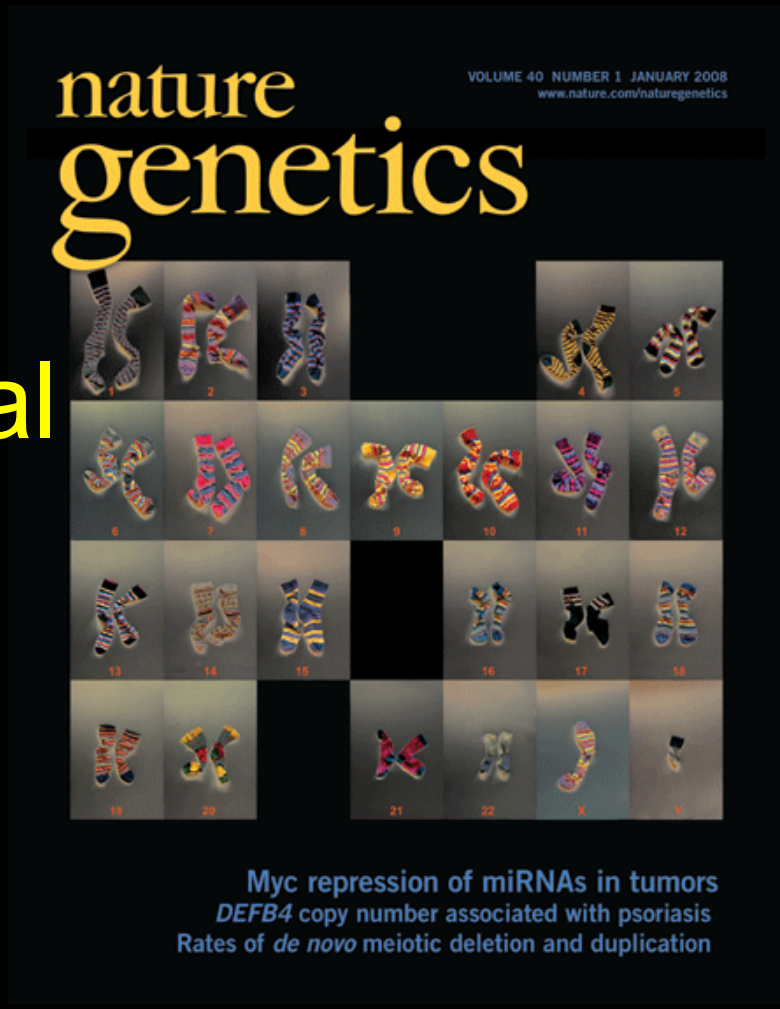
The majority of trisomies are lethal during early embryogenesis.

As the smallest alteration of one chromosome visible using standard karyotype analysis is that of a band or subband that includes a stretch of DNA on average 4 million bases long, it follows that alterations visible looking at the karyotype are those of great extension, as genomic mutations or chromosomal mutations, while you cannot highlight with this approach those alterations affecting a few bases.



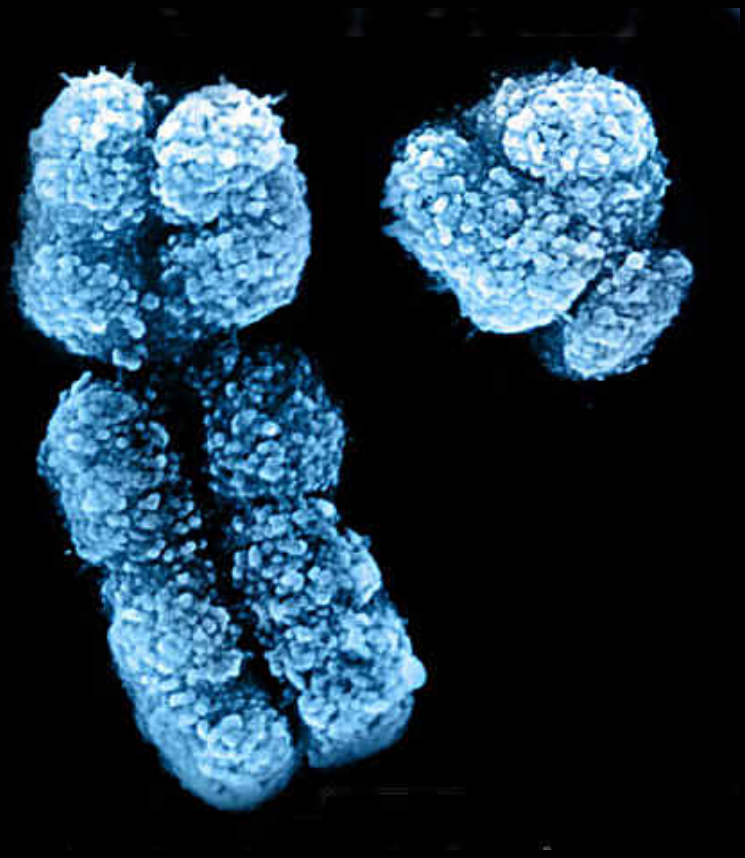
THE STUDY OF CHROMOSOMES: CYTOGENETICS

- Principles of cytogenetics
- classification
- frequency of chromosomal diseases
- the most frequent diseases
- molecular cytogenetics methods



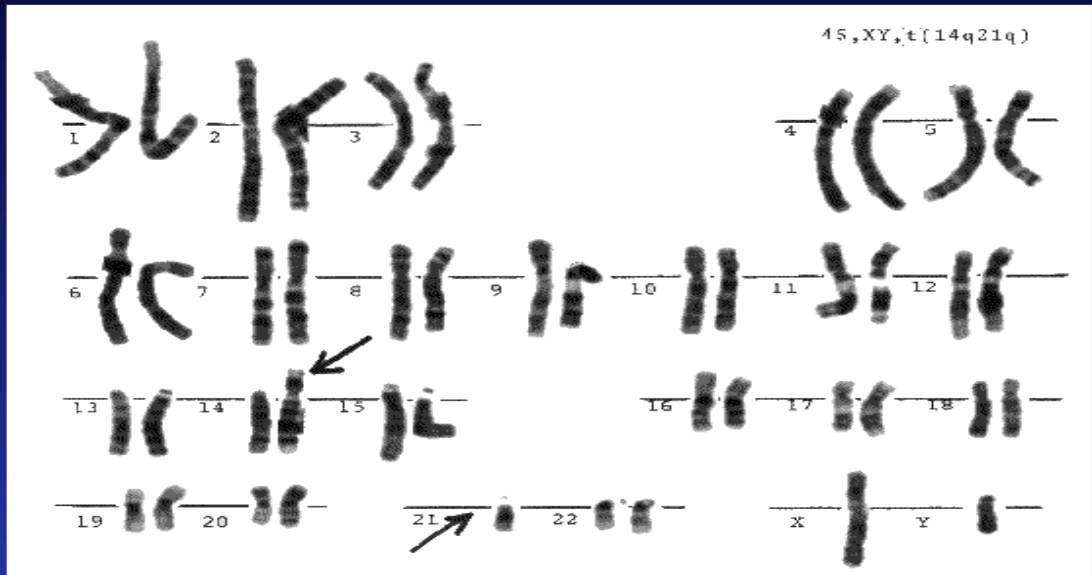
Classification criteria for chromosomal anomalies

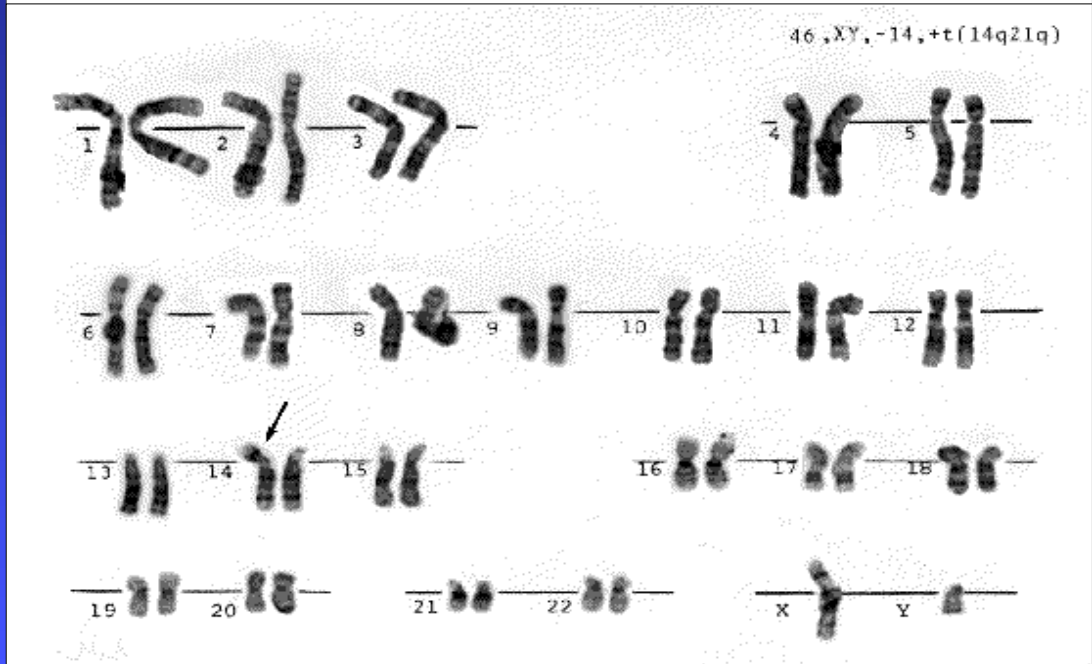
- Based on gene dosage alterations
- Based on the presence or not in all the body's cells
- Based on the type of anomaly



Gene dosage alterations

- **Balanced:**
  - In the majority of cases they are not correlated with an altered phenotype
- **Unbalanced:**
  - They are correlated with an altered phenotype (malformations and/or mental retardation)





Presence in body's cells

- **COSTITUTIONAL ANOMALIES**: present in all the body's cells.

- **SOMATIC ANOMALIES**: present in a small subgroup of cells or tissues. Different chromosomal constitutions although all cells are deriving from the same zygote. GENETIC MOSAIC.

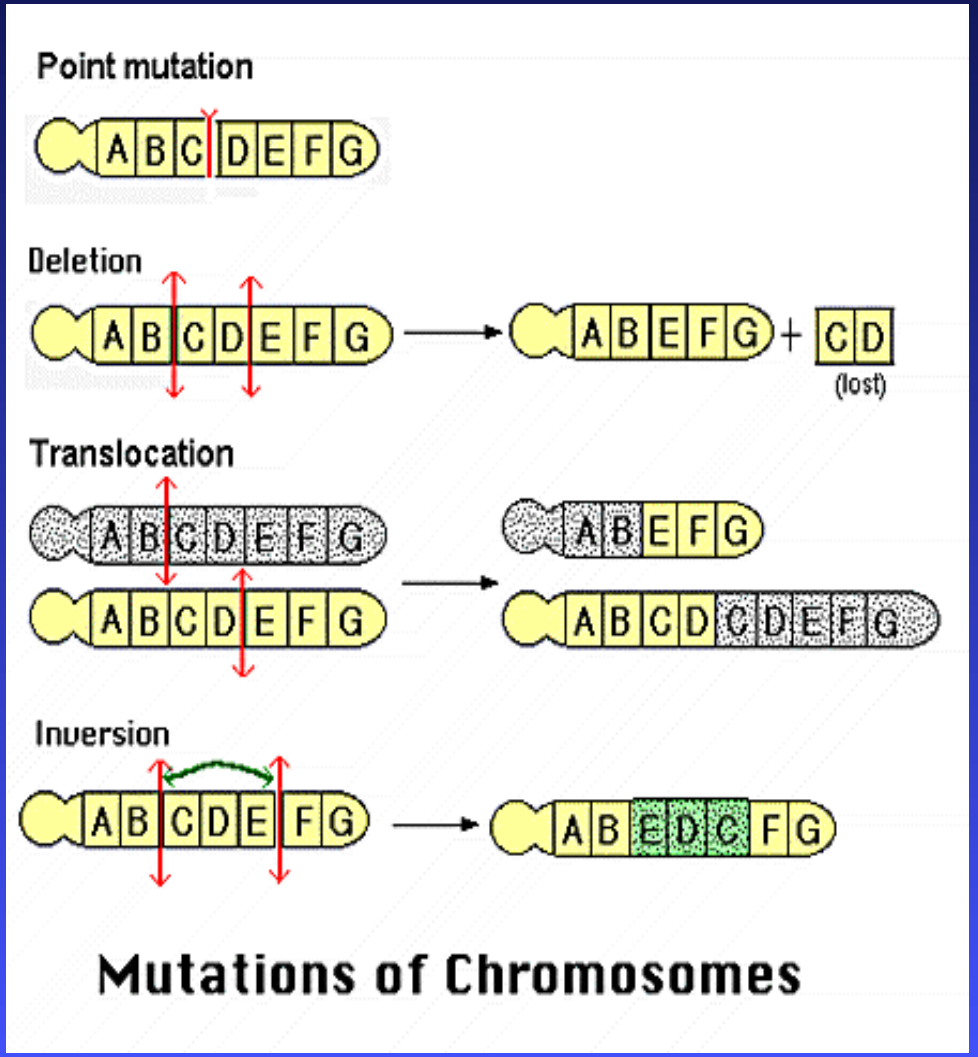
Types of anomaly

Numerical

- trisomies
- monosomies
- Triploidies
- tetraploidies

Structural

- translocations
- inversions
- deletions
- duplications

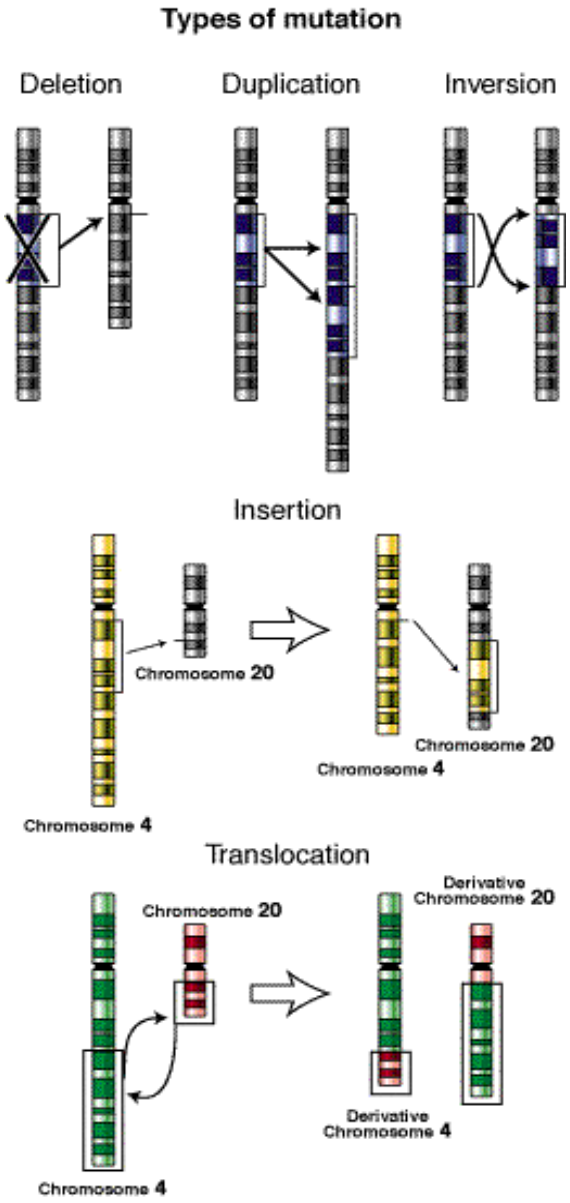


Chromosomal alterations

Alterations of chromosomal structure can cause congenital pathologies and tumors.

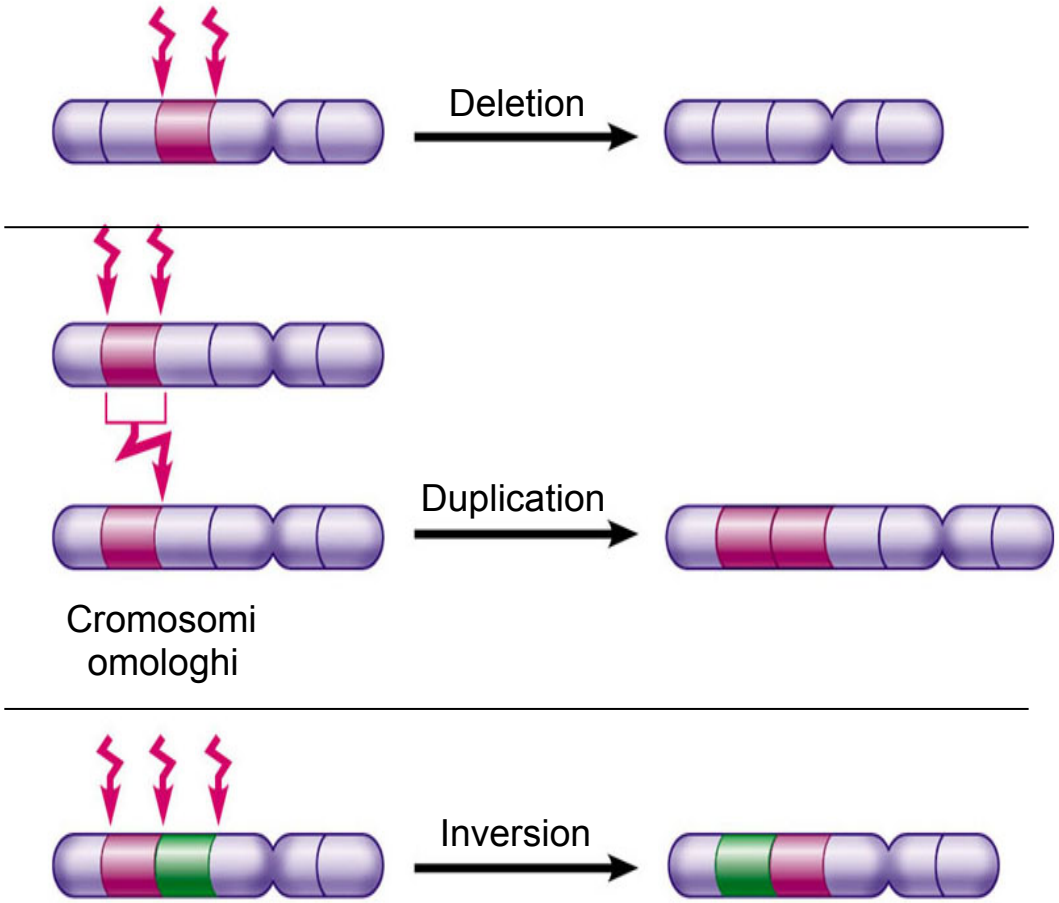
Chromosomal breakage can lead to rearrangements causing genetic disorders.

When changes occur in somatic cells they contribute to tumor formation.



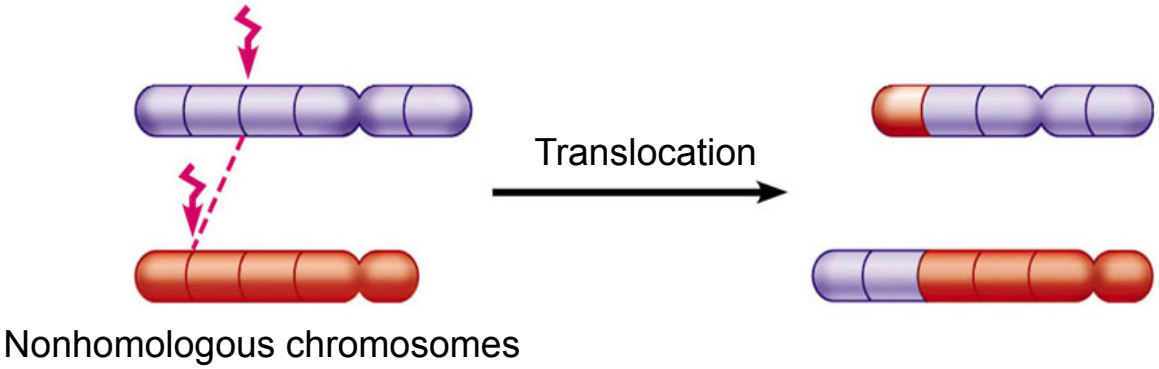
Chromosomal alterations

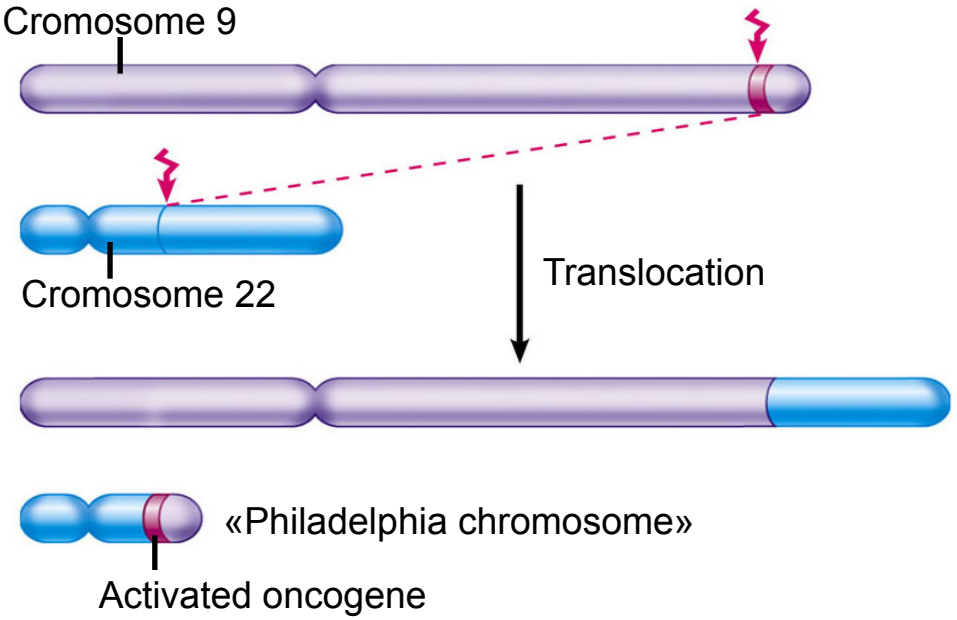
Deletions, duplications, inversions:



Chromosomal alterations

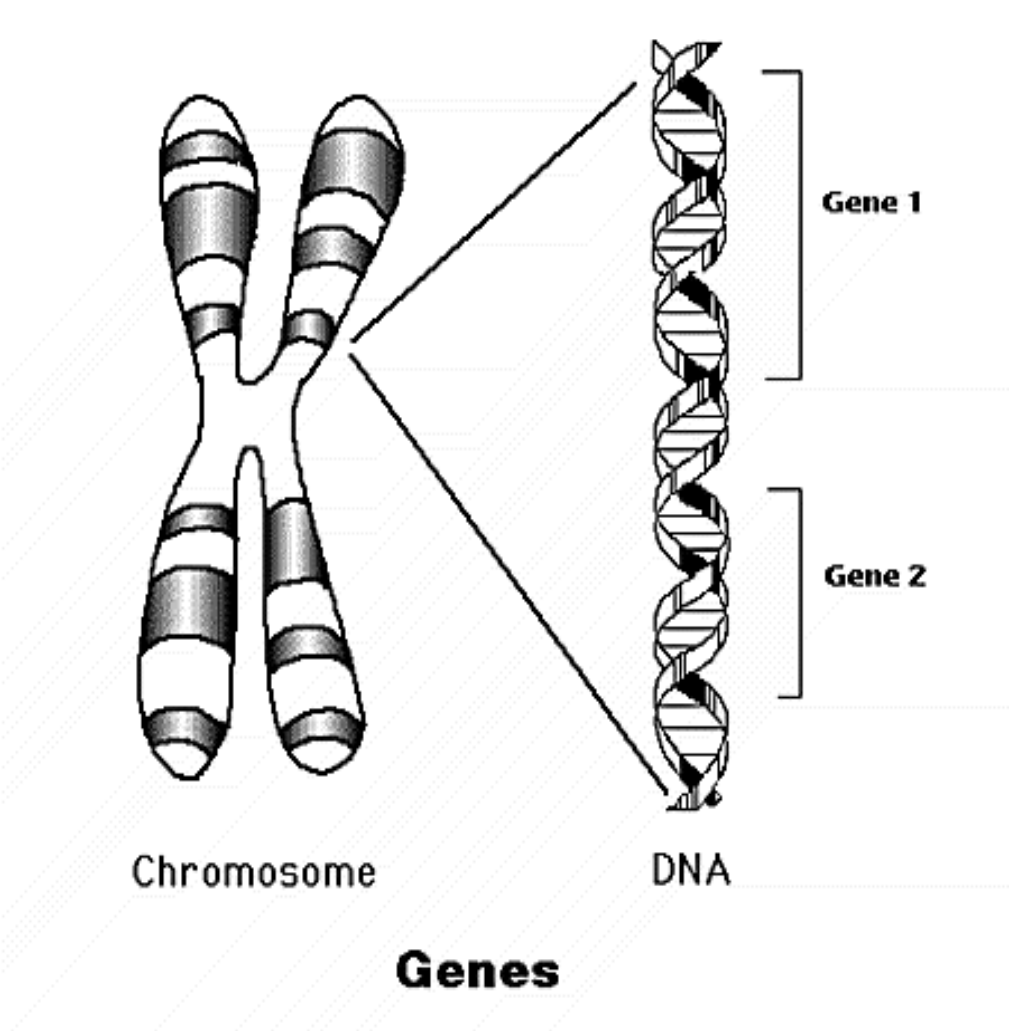
Translocations:





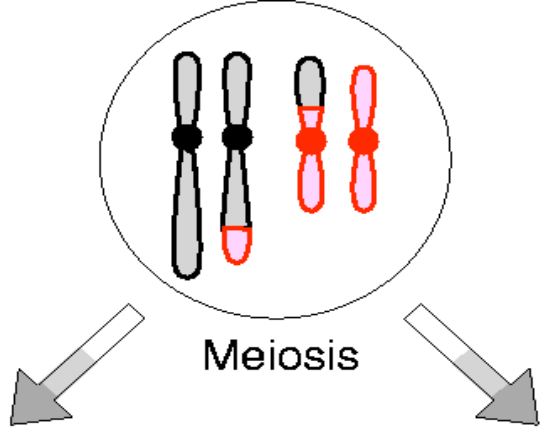
Severity of chromosomal abnormalities

- Severity is correlated to the type of chromosome and to the quantity of affected genes
- More serious is chromosomal imbalance, earlier will be termination of pregnancy

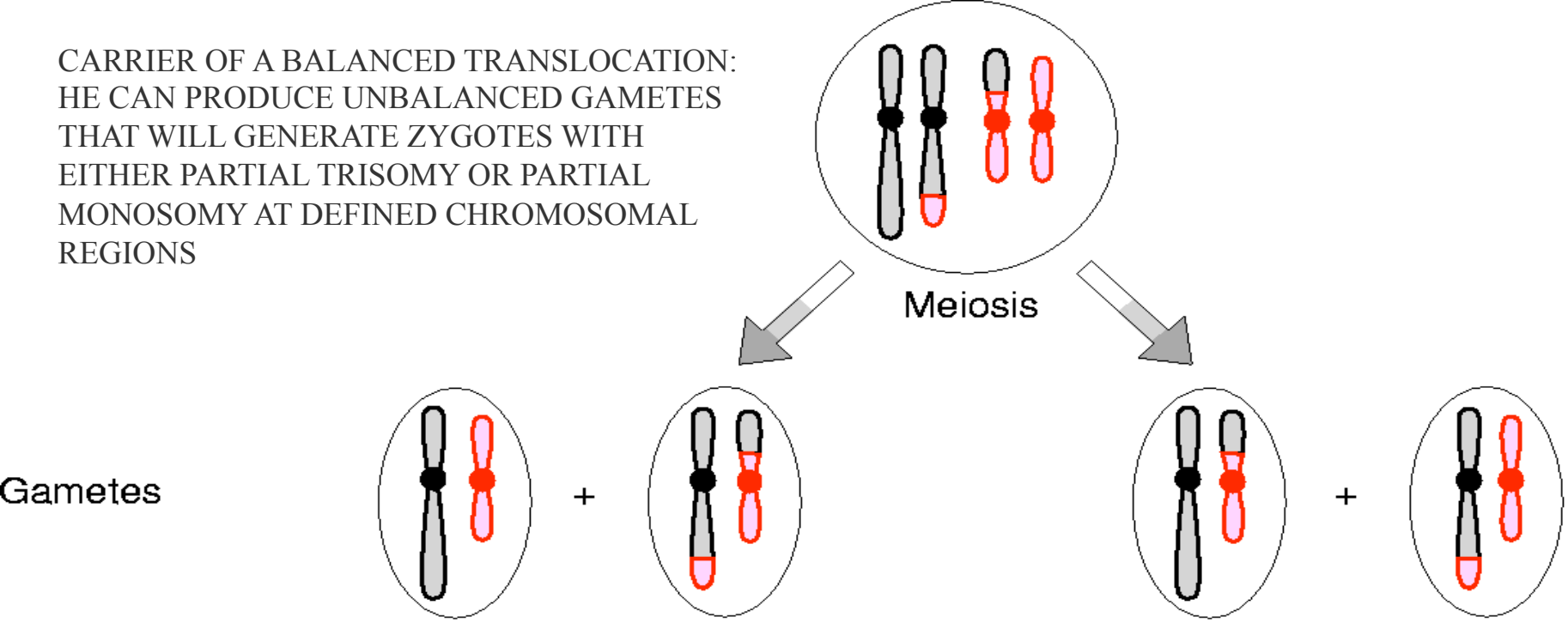


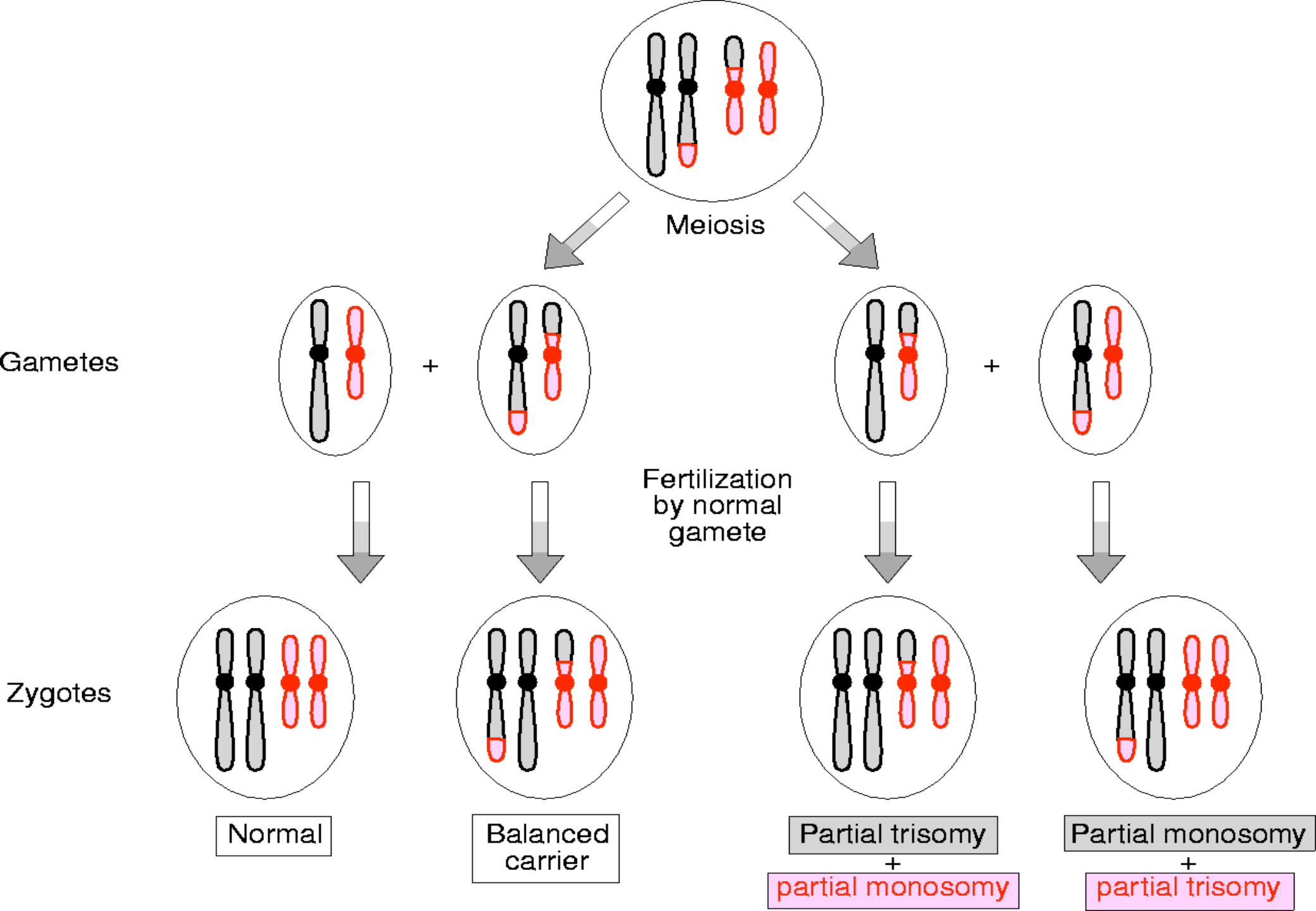
And in cases of balanced anomalies?

- The problem does not exist for the carrier itself
- but it may exist for its offspring...

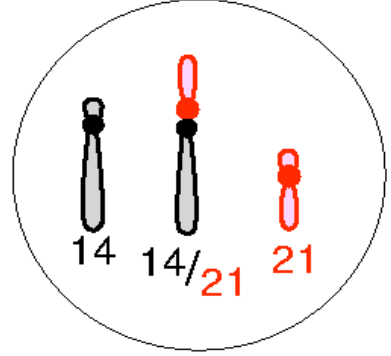

Meiosis

CARRIER OF A BALANCED TRANSLOCATION: HE CAN PRODUCE UNBALANCED GAMETES THAT WILL GENERATE ZYGOTES WITH EITHER PARTIAL TRISOMY OR PARTIAL MONOSOMY AT DEFINED CHROMOSOMAL REGIONS



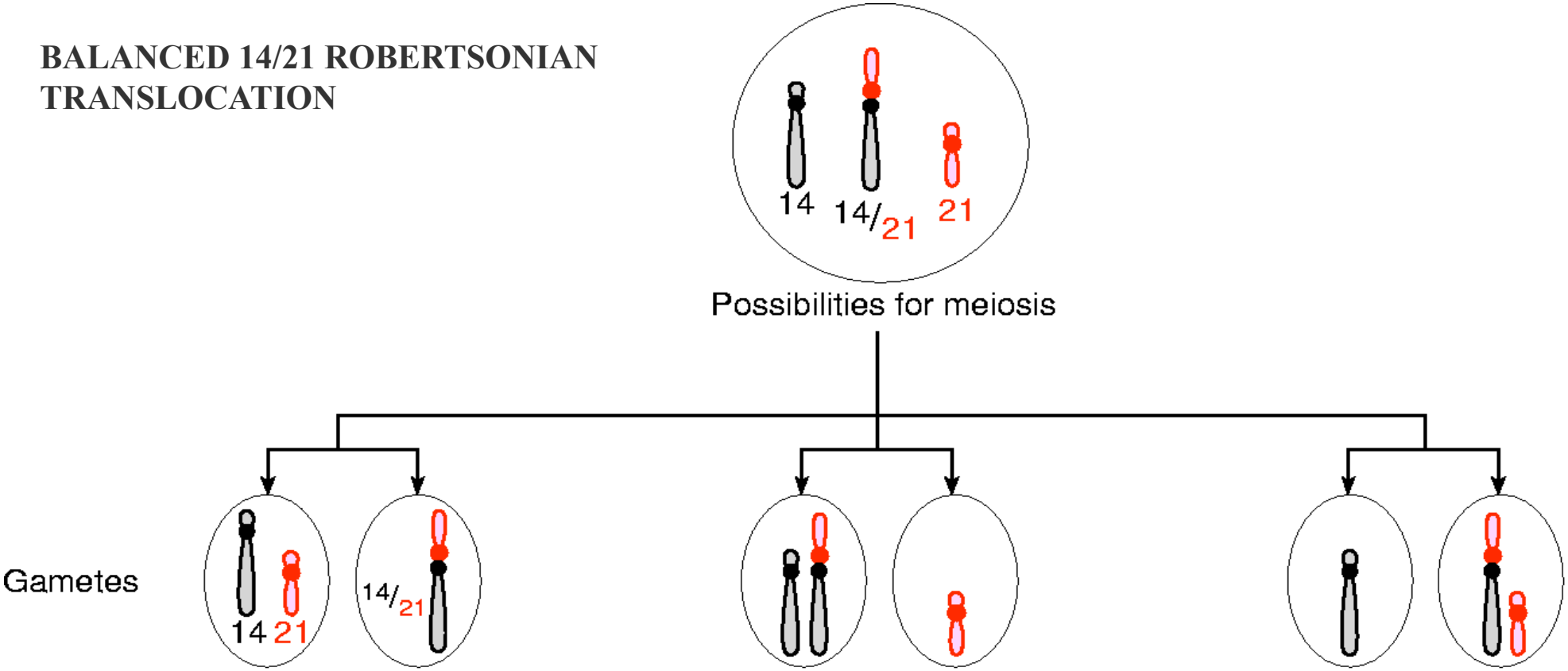

Meiosis
Gametes
+
+
Fertilization by normal gamete
Zygotes
Normal
Balanced carrier
Partial trisomy
+
partial monosomy
Partial monosomy
+
partial trisomy

BALANCED 14/21 ROBERTSONIAN TRANSLOCATION

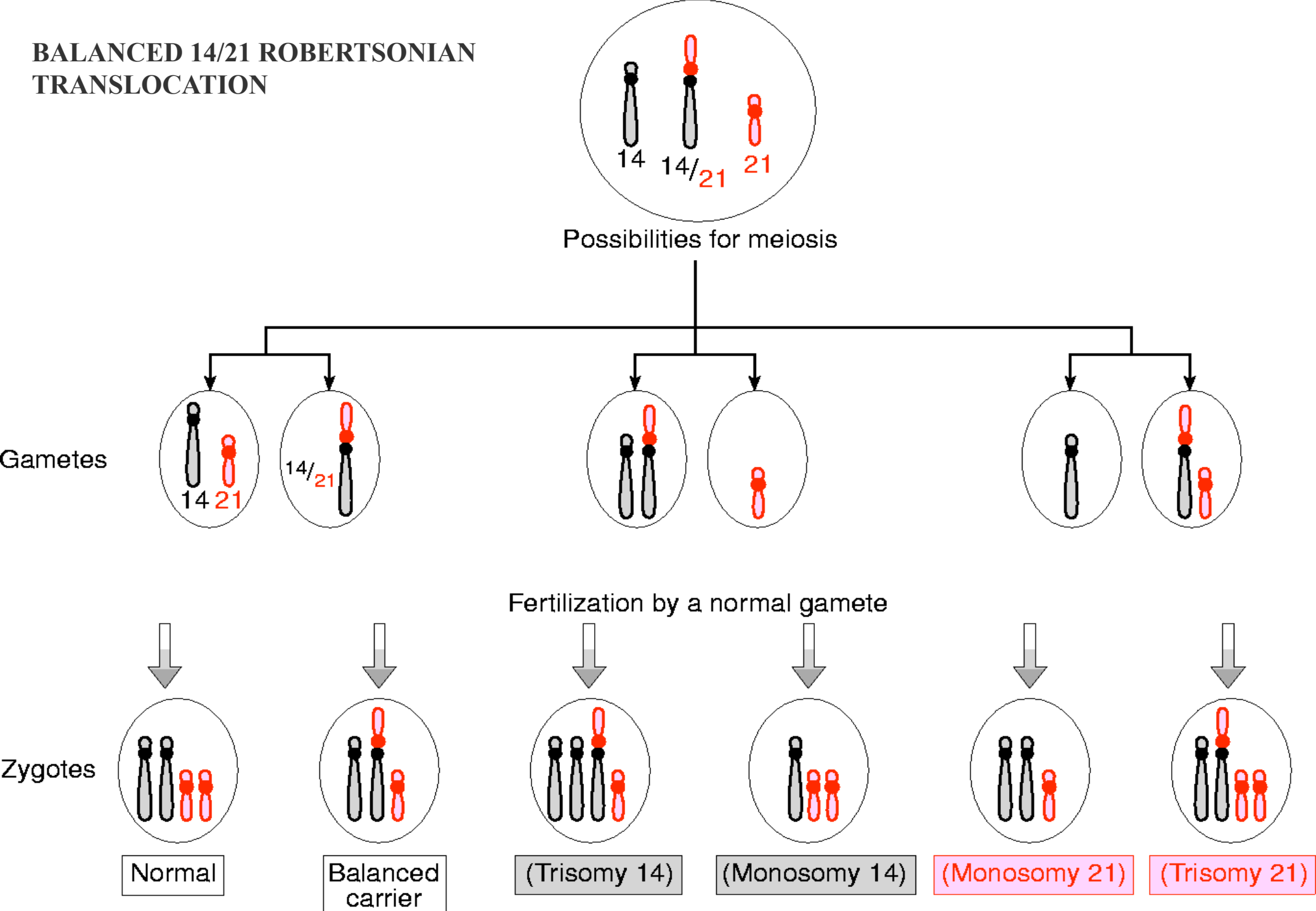


Possibilities for meiosis I

BALANCED 14/21 ROBERTSONIAN TRANSLOCATION

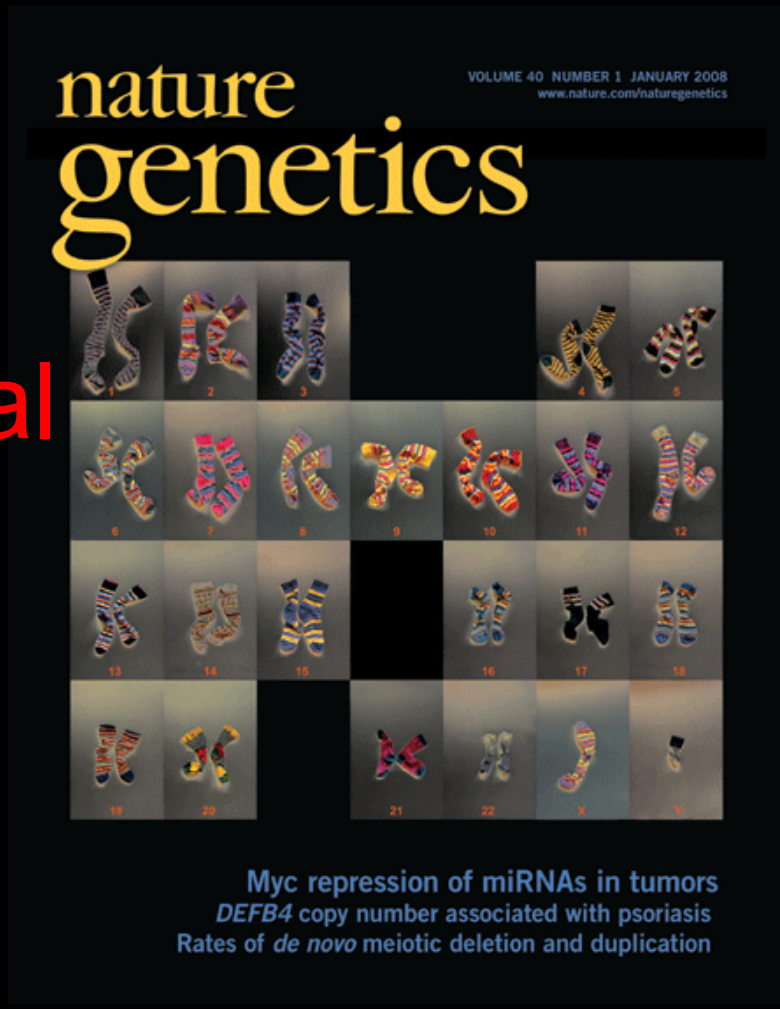


BALANCED 14/21 ROBERTSONIAN TRANSLOCATION



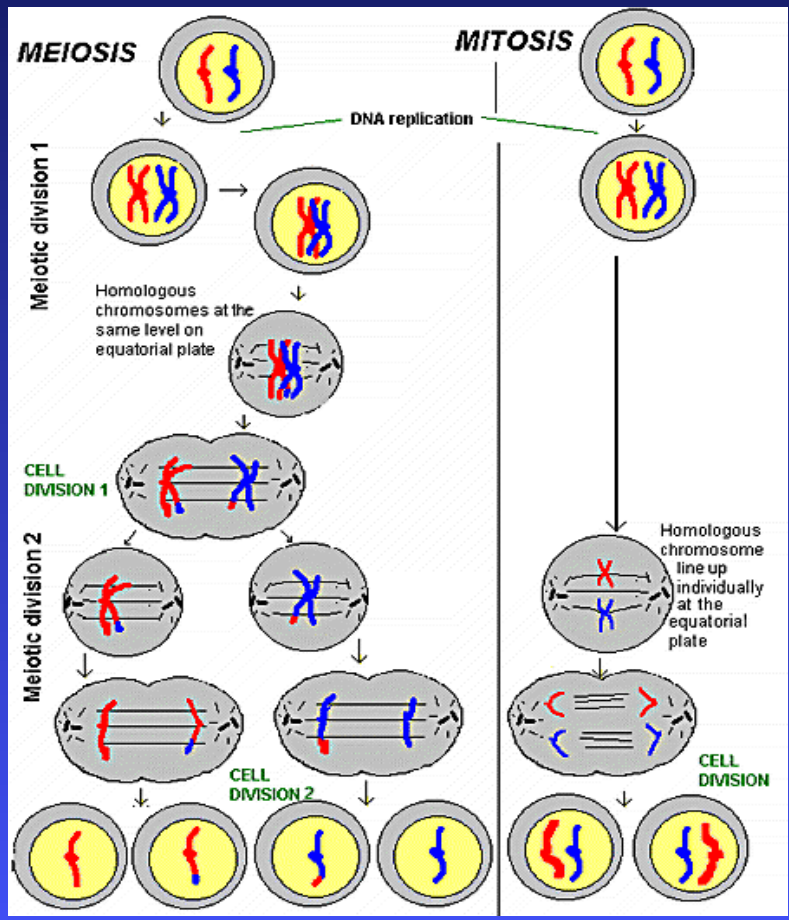
THE STUDY OF CHROMOSOMES: CYTOGENETICS

- Principles of cytogenetics
- classification
- frequency of chromosomal diseases
- the most frequent diseases
- molecular cytogenetics methods



The frequency of numerical chromosomal anomalies is:

- Directly correlated to maternal age
- Inversely correlated to gestational age

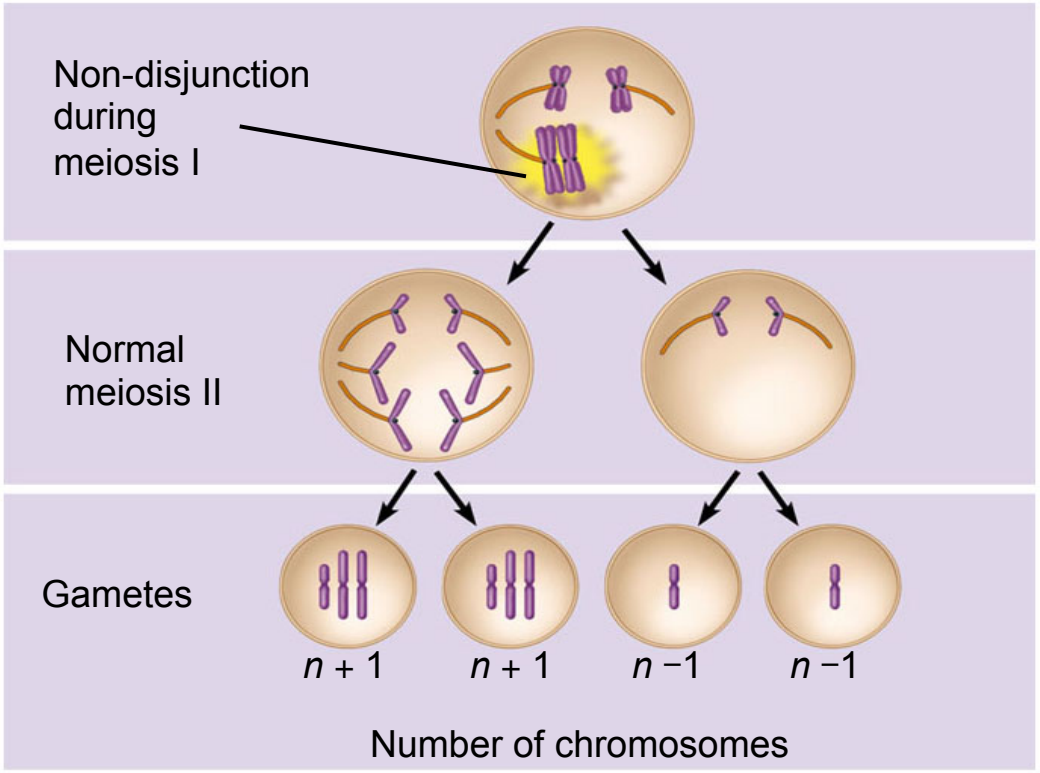


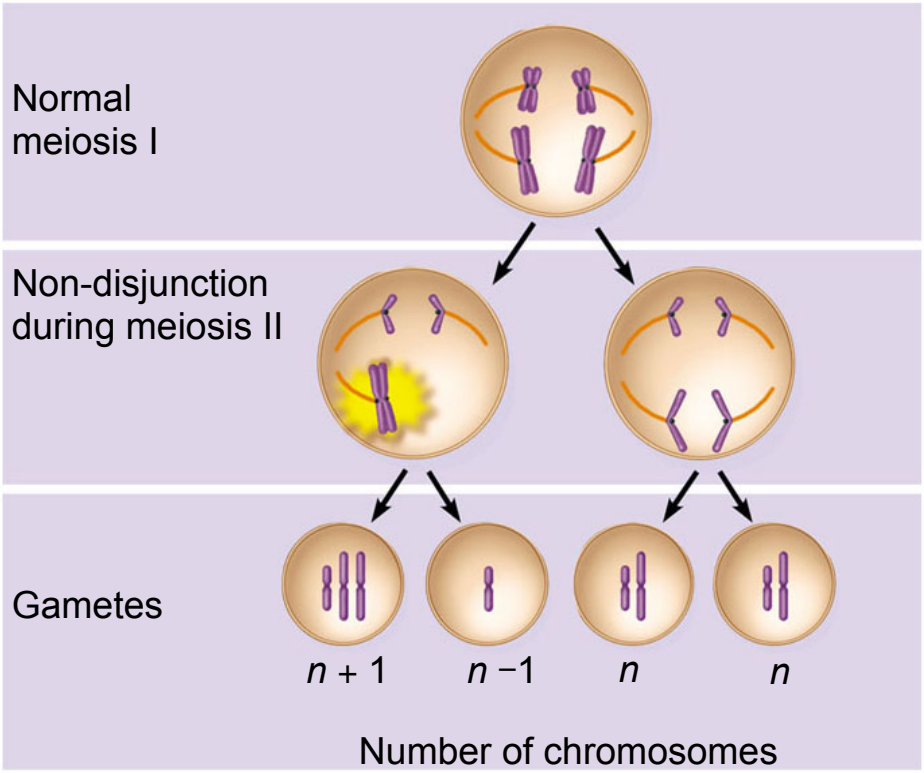
Non-disjunction

- An abnormal number of chromosomes may be the result of non-disjunction, an inconvenience that may take place in two ways:

  - homologous chromosomes of a pair do not separate during meiosis I;
  - meiosis I occurs on a regular basis, but chromatids of a couple do not divide in one of the cells during meiosis II.

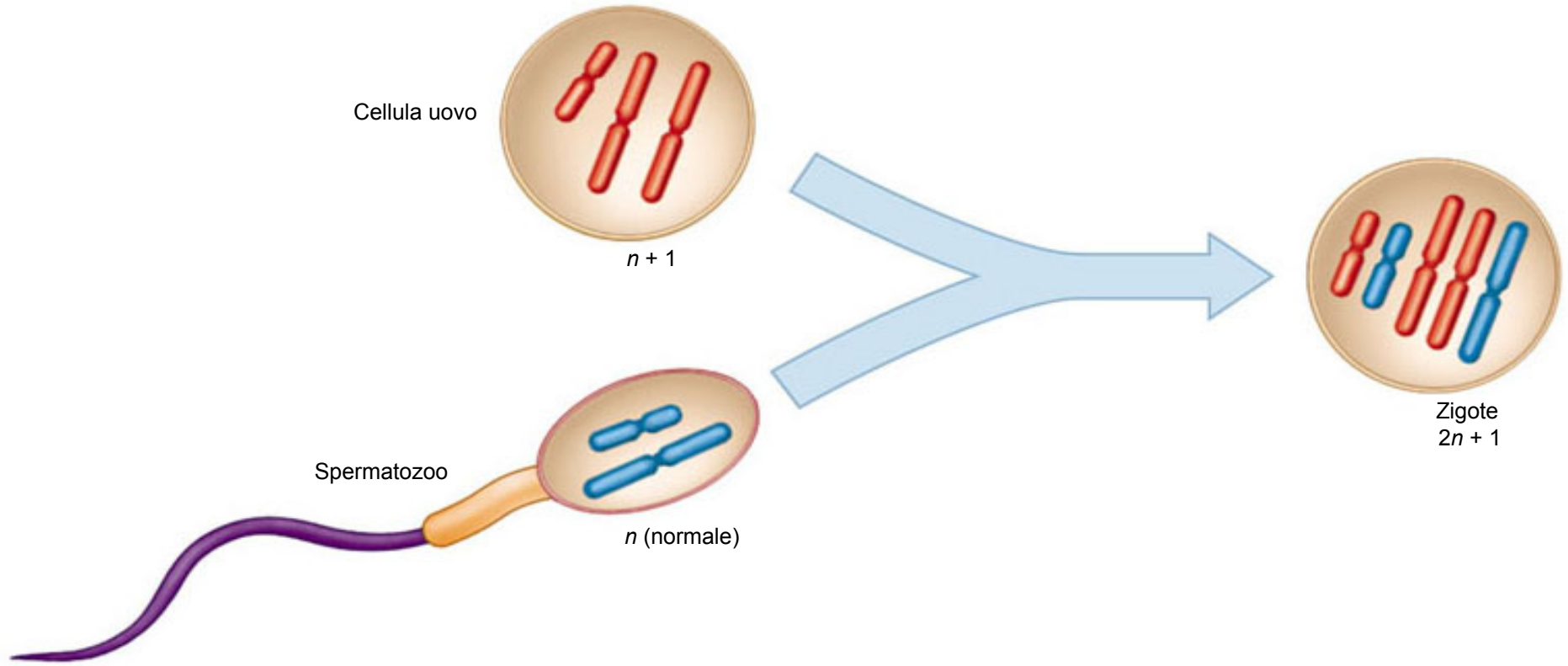
Non-disjunction





Non-disjunction

Fertilization of an egg which has undergone a non-disjunction with a normal gamete



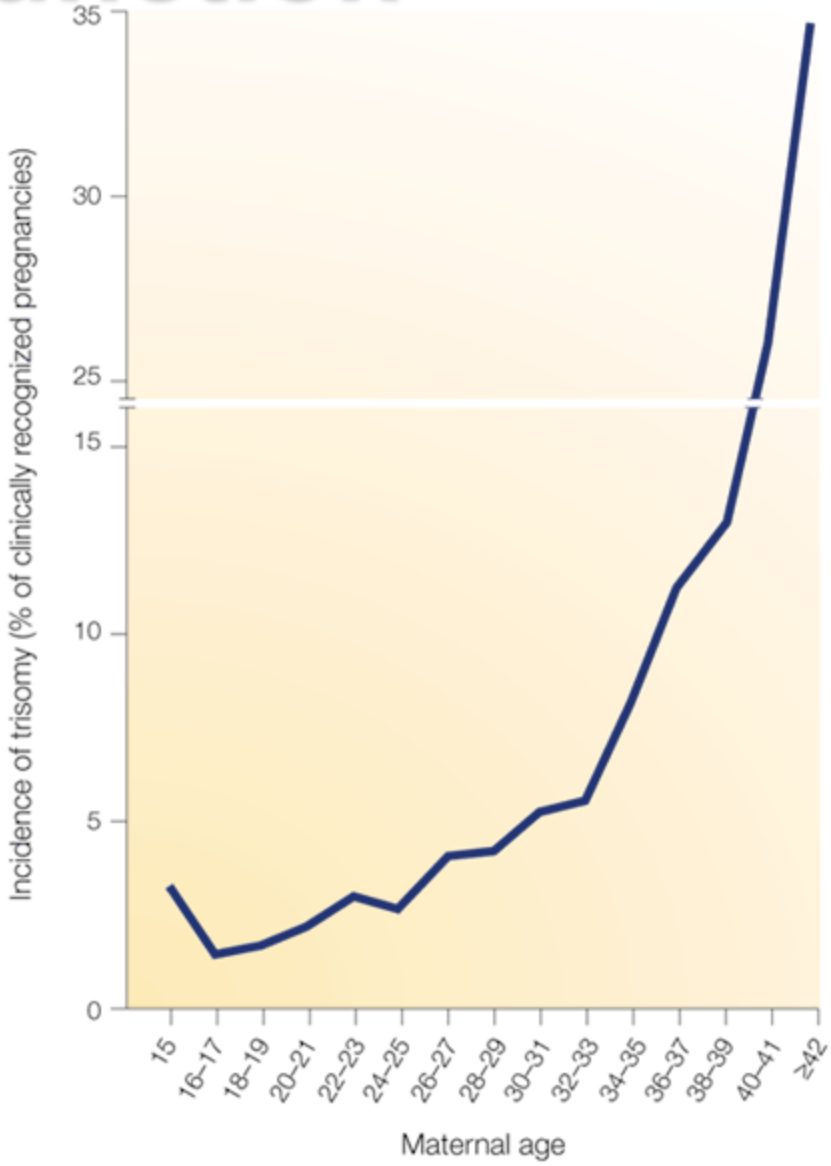
Non-disjunction

- ***Are there factors that influence the non-disjunction?***

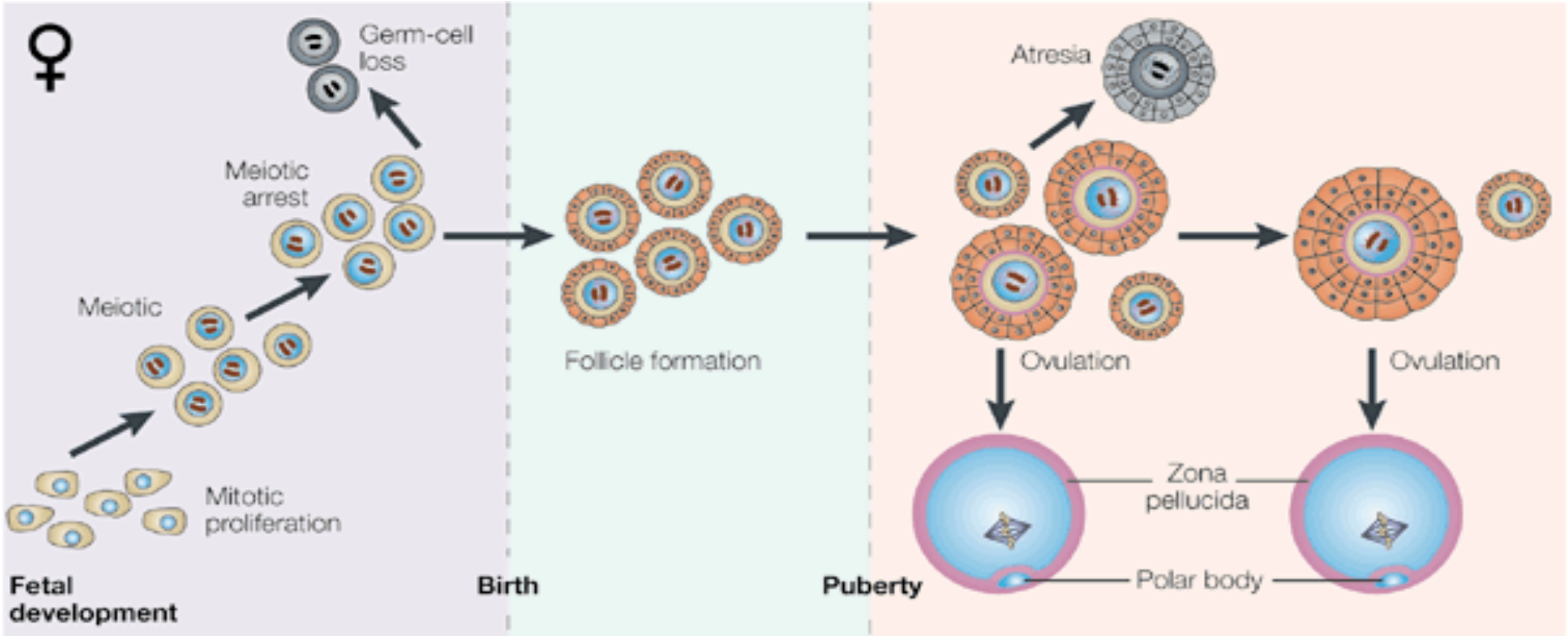
  Not well known

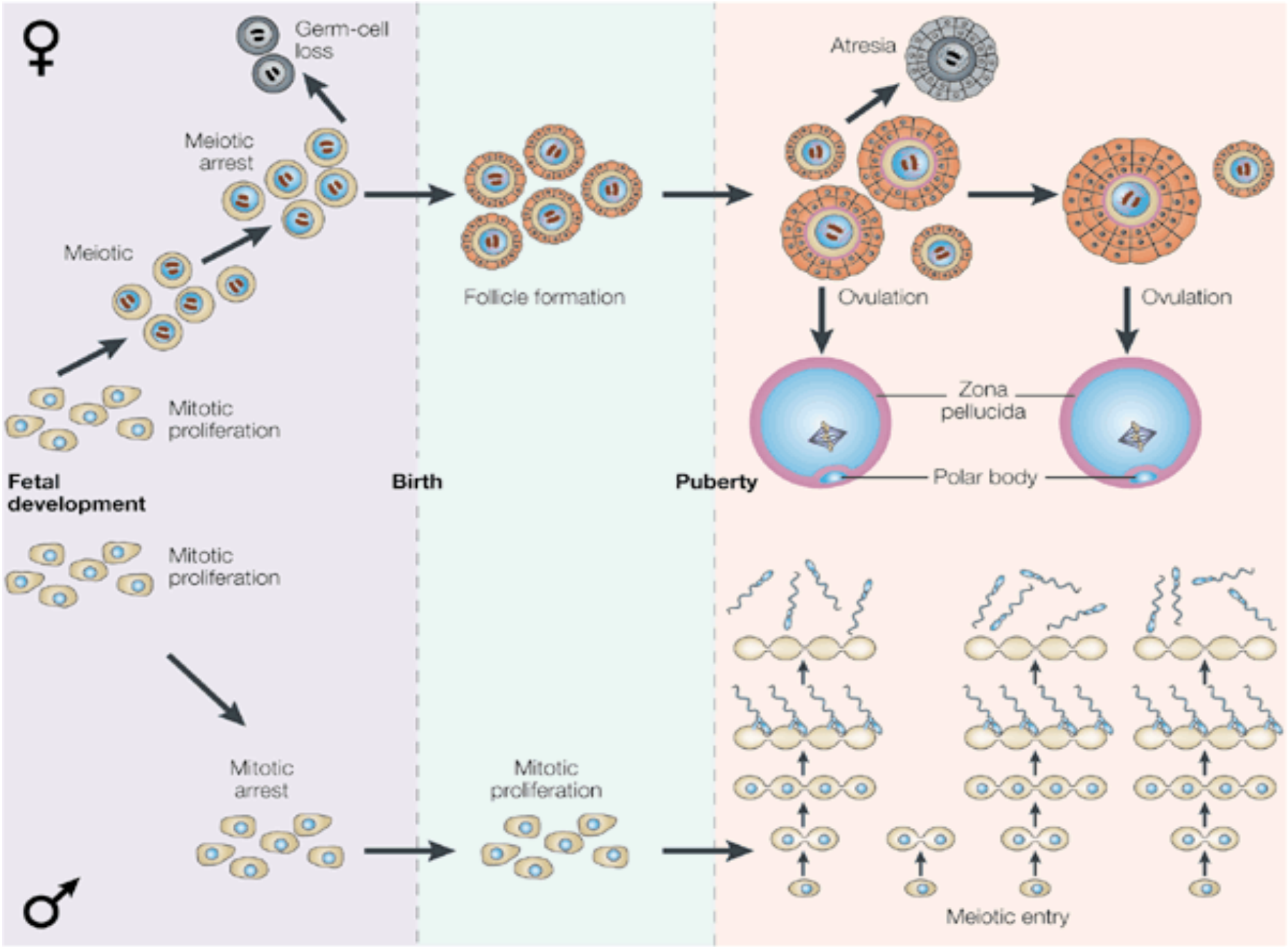
- ***Where and when does the non-disjunction occur?***

  More frequently in maternal meiosis I



Nature Reviews | Genetics


Germ-cell loss
Meiotic arrest
Meiotic
Mitotic proliferation
Fetal development
Birth
Follicle formation
Atresia
Ovulation
Ovulation
Zona pellucida
Polar body
Puberty


♀
Germ-cell loss
Meiotic arrest
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Mitotic proliferation
Fetal development
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Puberty
Follicle formation
Atresia
Ovulation
Ovulation
Zona pellucida
Polar body
Mitotic proliferation
Mitotic arrest
Mitotic proliferation
Meiotic entry
♂

The frequency of chromosomal abnormalities at birth is *0.65%*

Alteration	**Prevalence** (in 1000 born)
Numerical alterations	
Trisomies of autosomes	
+21	1,25
+18	0,13
+13	0,07
Aneuploidies of sexual chromosomes	
47,XXY	1 in 1000 males
47,XYY	1 in 1000 males
47,XXX	1 in 1000 females
45,X	0,12 in 1000 females
Structural alterations	
Balanced translocations	2
Unbalanced traslocations	0,4

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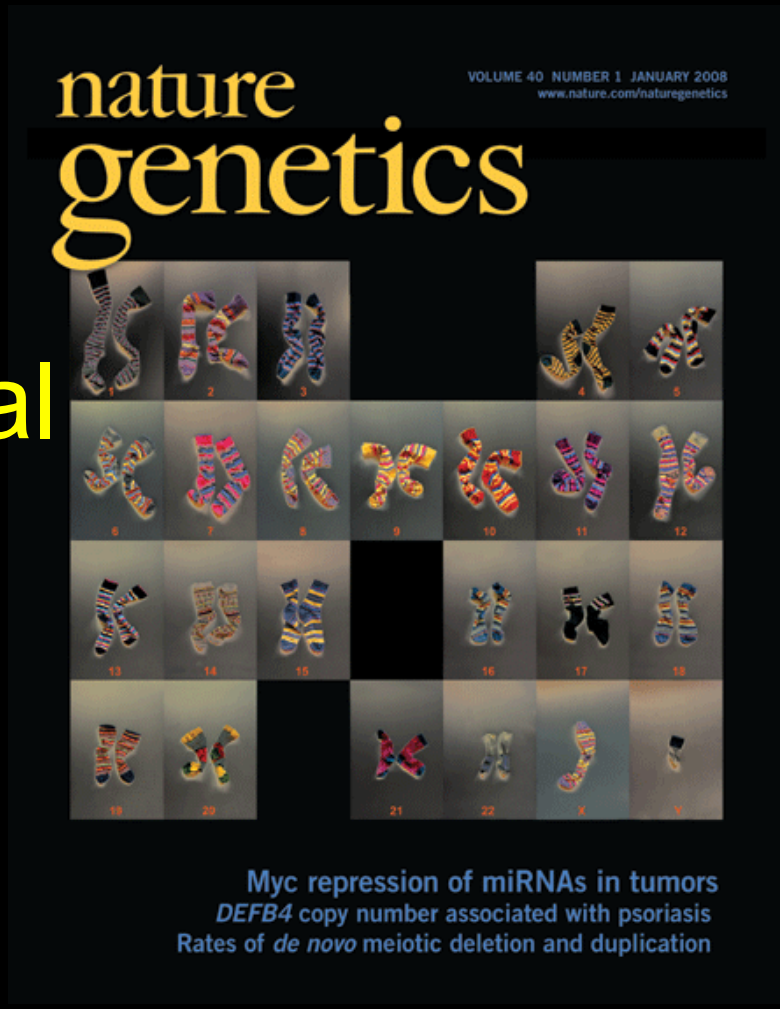
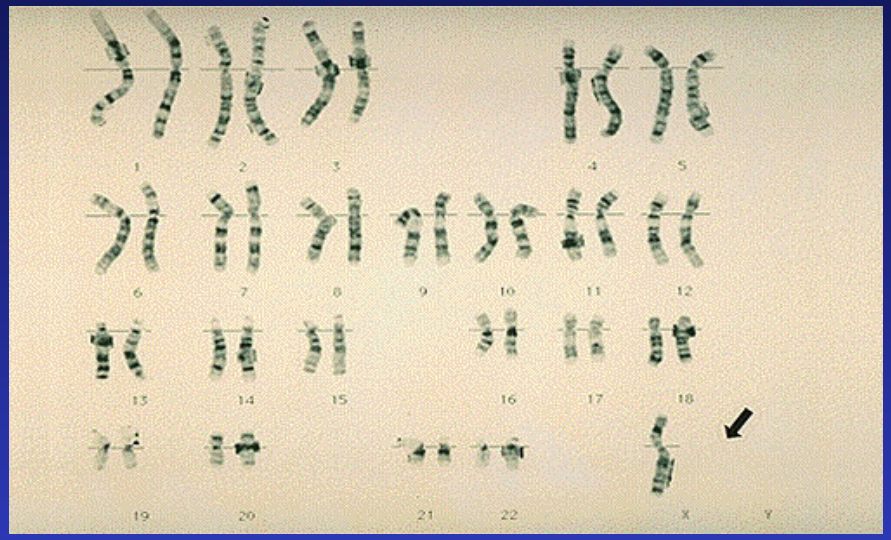
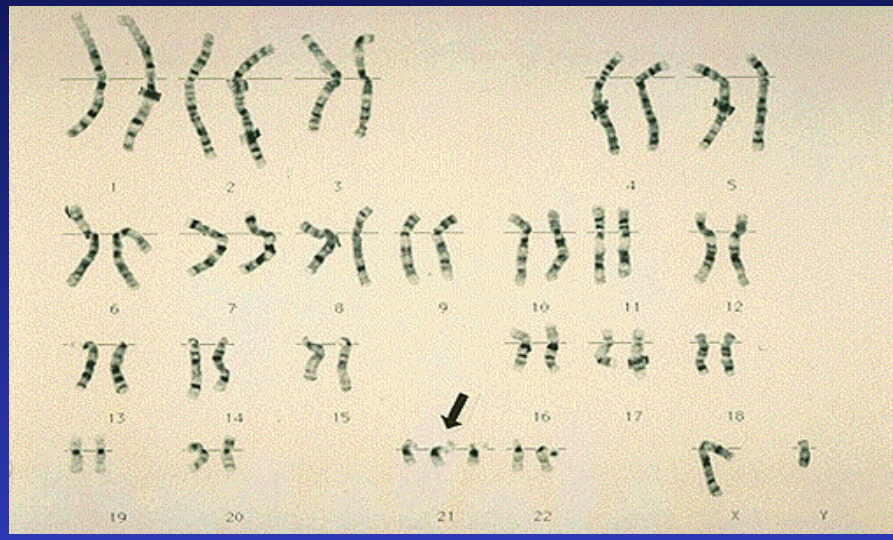
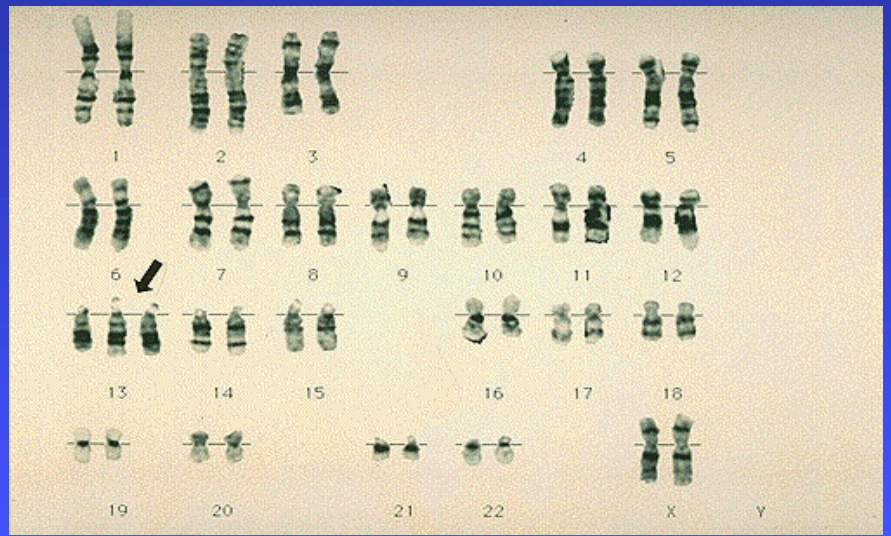
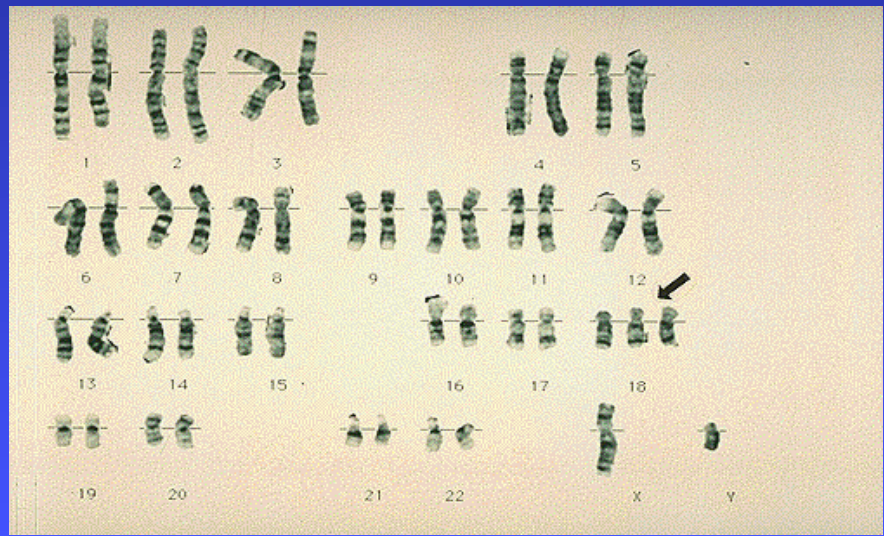


The most frequent aneuploidies at birth

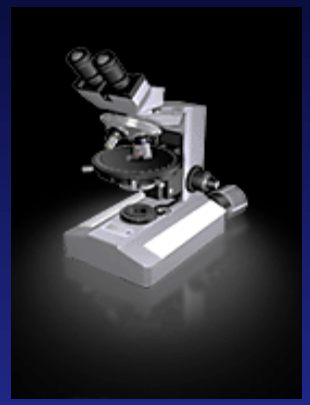








Diseases due to chromosomal aberrations.



1. ANEUPLOIDIES (numerical anomalies)

- Down syndrome, Patau, Edwards

- Klinefelter syndrome

- Turner syndrome

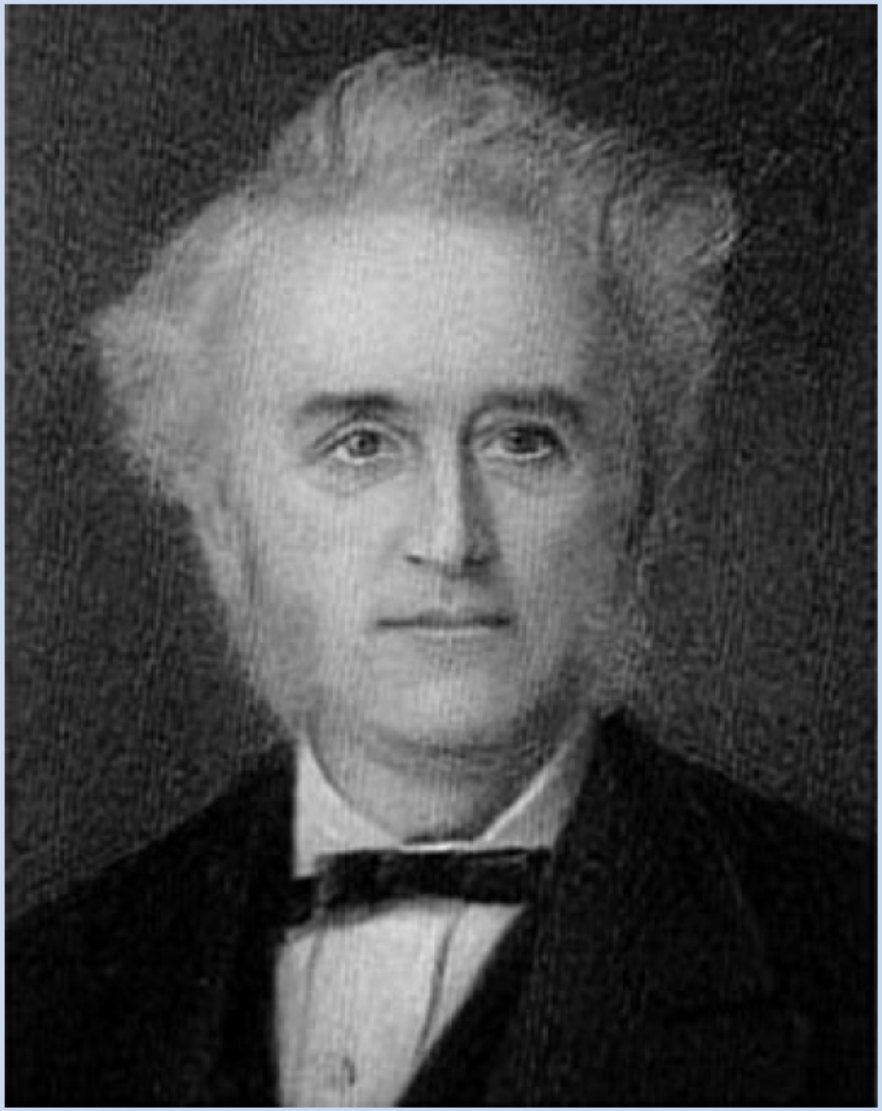
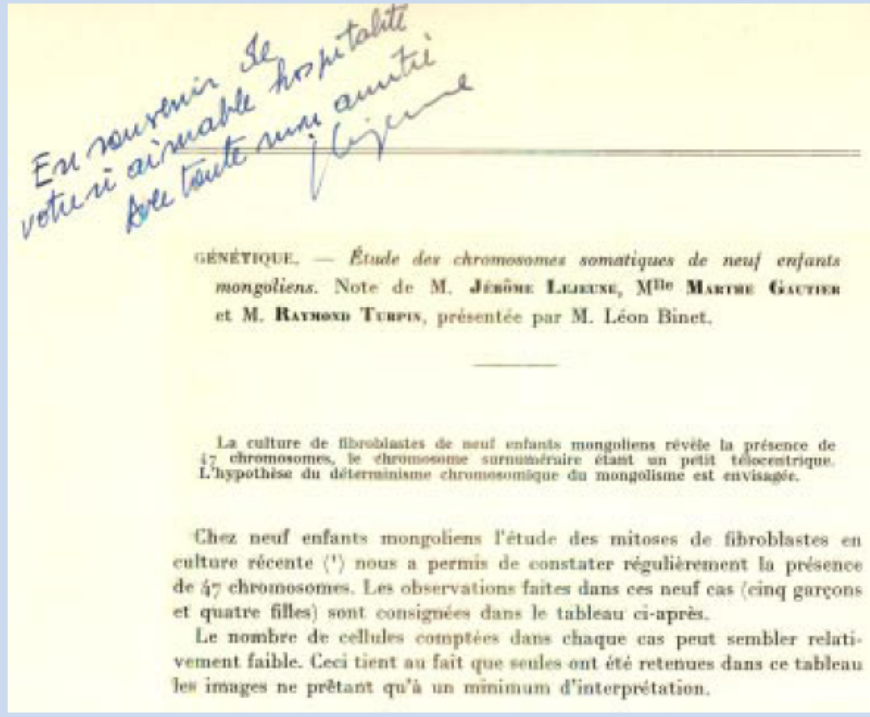


FIG. 1. Image of John H. Langdon Down. From St. George's University of London, first published ca. 1870, author unknown (http://en.wikipedia.org/wiki/Image:JLHdown.jpg).



En souvenir de votre si aimable hospitalité avec toute mon amitié
J. Lejeune

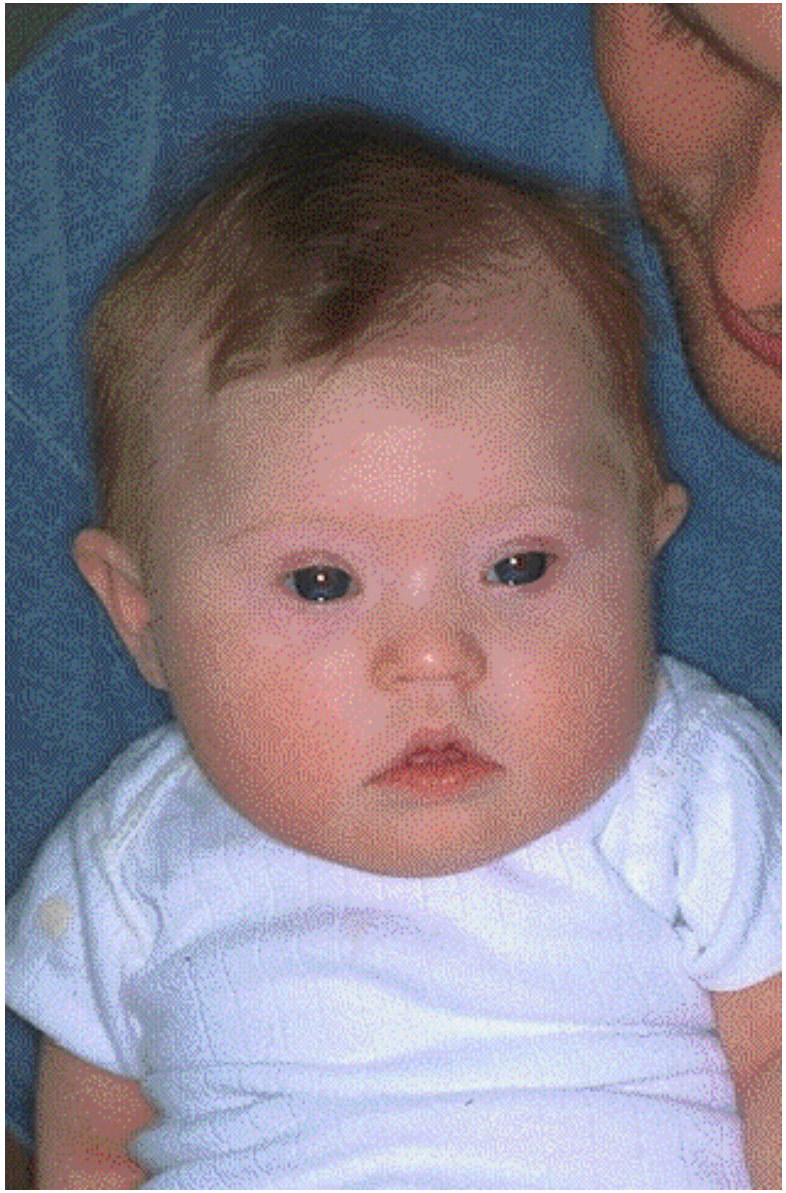
GÉNÉTIQUE. — *Étude des chromosomes somatiques de neuf enfants mongoliens.* Note de M. **Jérôme Lejeune**, M^lle **Marthe Gautier** et M. **Raymond Turpin**, présentée par M. Léon Binet.

La culture de fibroblastes de neuf enfants mongoliens révèle la présence de 47 chromosomes, le chromosome surnuméraire étant un petit télocentrique. L'hypothèse du déterminisme chromosomique du mongolisme est envisagée.

Chez neuf enfants mongoliens l'étude des mitoses de fibroblastes en culture récente (1) nous a permis de constater régulièrement la présence de 47 chromosomes. Les observations faites dans ces neuf cas (cinq garçons et quatre filles) sont consignées dans le tableau ci-après.

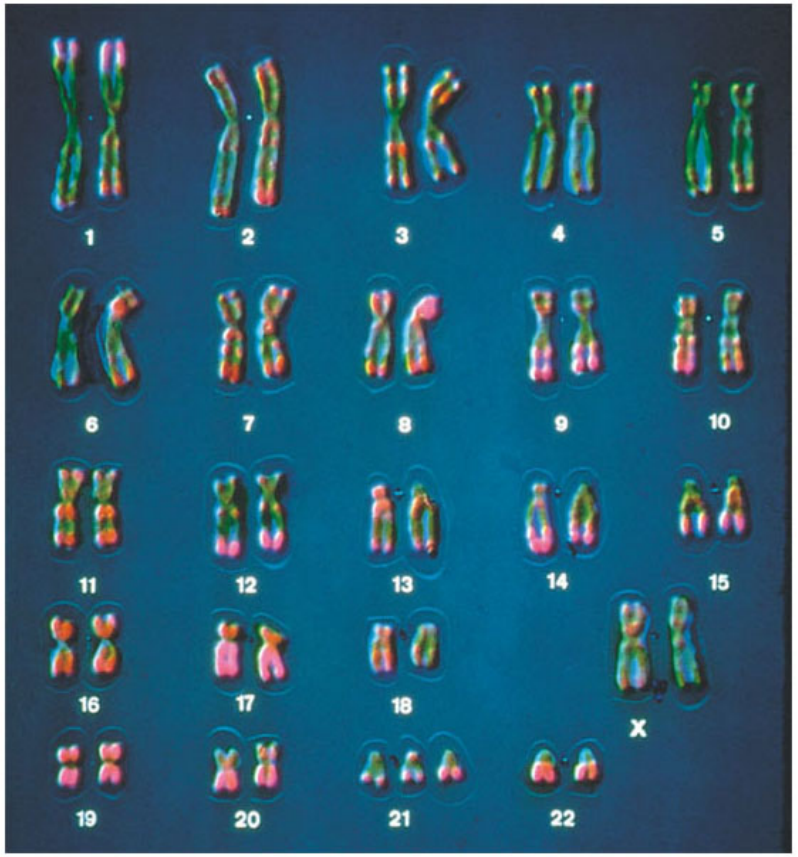
Le nombre de cellules comptées dans chaque cas peut sembler relativement faible. Ceci tient au fait que seules ont été retenues dans ce tableau les images ne prêtant qu'à un minimum d'interprétation.

FIG. 5. First page (of 2) of the historic 1959 paper by Lejeune, Gautier, and Turpin. From the library of the late Norman Horowitz.

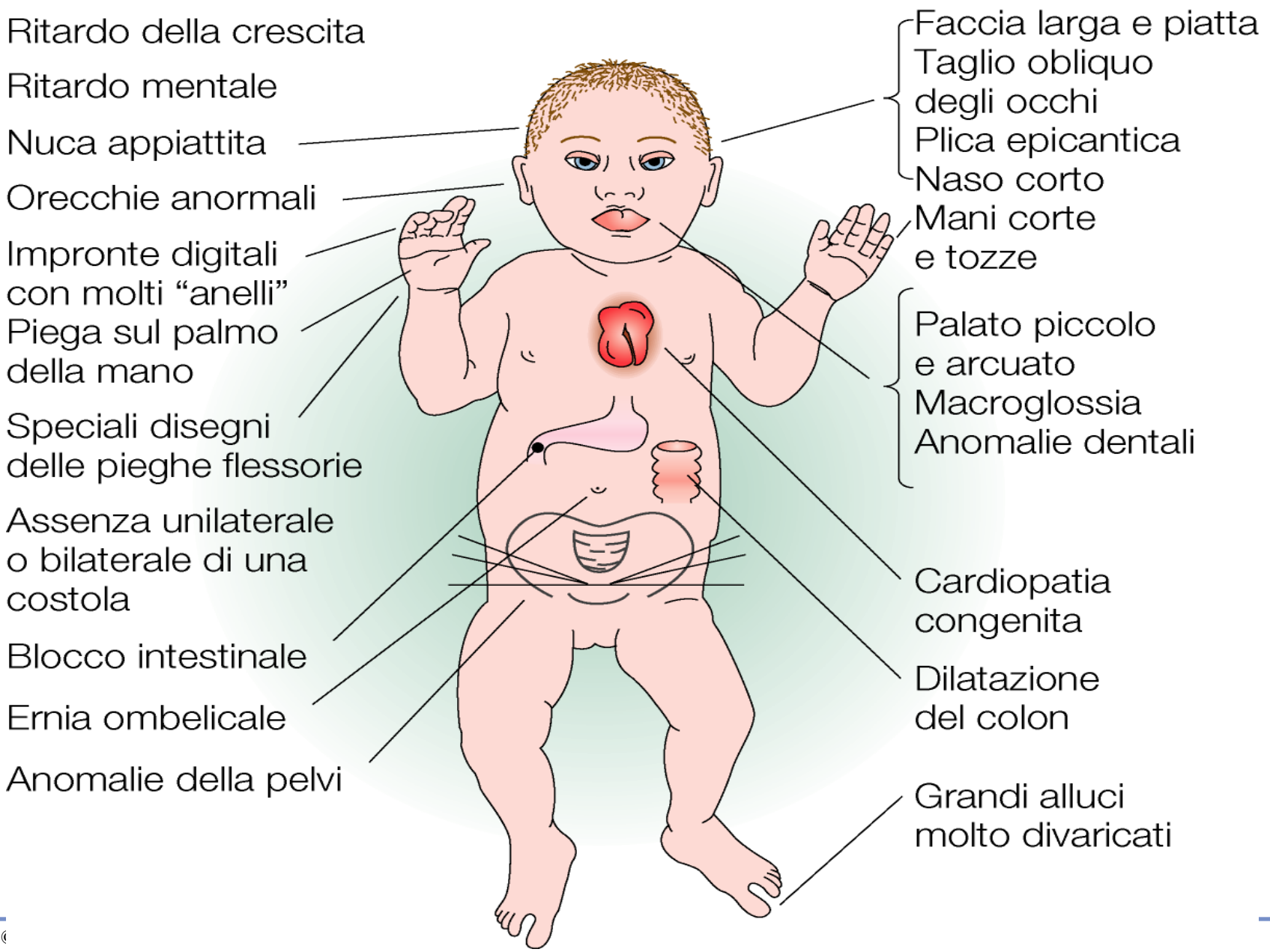


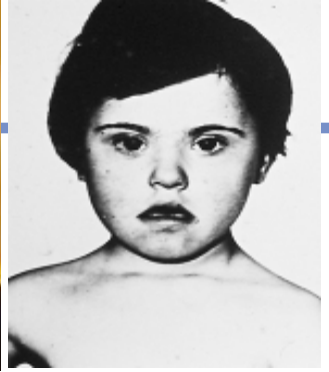
Down syndrome

Down syndrome is caused by the trisomy of chromosome 21.



Characteristic features of Down syndrome (1:700 live births)



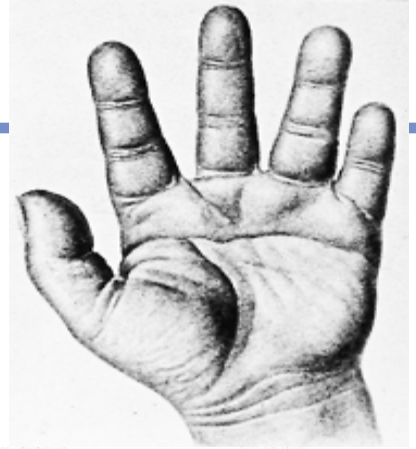
trisomy 21 Down

40.000 cases in Italy

- Neurological:
  - Mental retardation 100%
  - Alzheimer from 35y of age 100%
- Muscular hypotonia 100%
- Short stature 70%

- Head:
  - Brachycephaly 75%
  - Epicanthic fold 60%
  - Brushfield spots iris 55%
  - Protruding tongue 45%
  - Dysplastic ears 50%

trisomy 21 Down



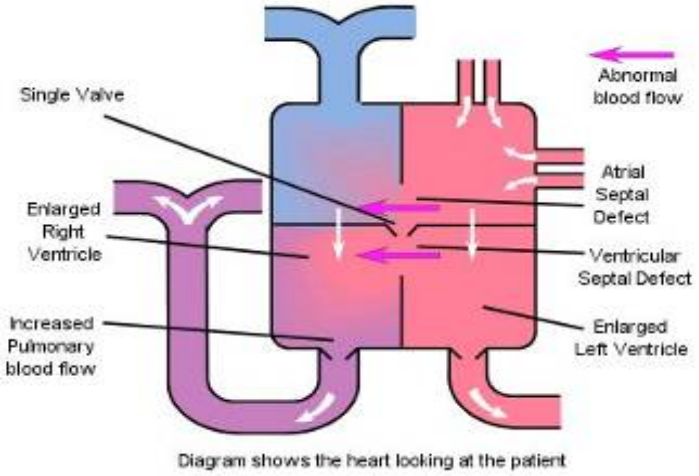
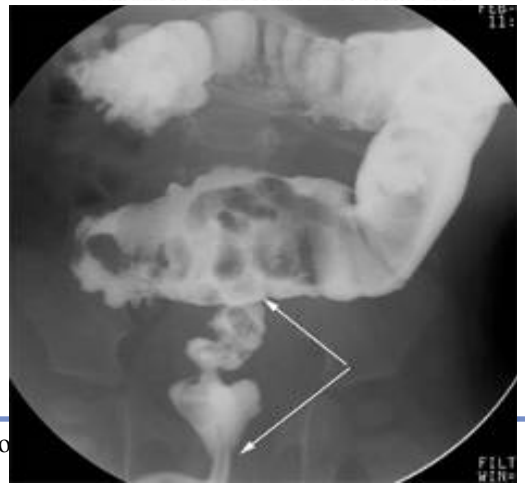


Diagram shows the heart looking at the patient



- Short limbs, wide hands 65%
- Short little finger 60%
- Palmar Simian crease 60%
- heart
  - Congenital cardiac defects 40%
- Gastrointestinal anomalies
  - Atresia/duodenal stenosis 250x
  - Imperforate anus 50x
  - Hirschsprung disease 300x
- Immune and hematopoietic systems:
  - Myeloproliferative disorders 300x
  - Leukemia (ALL e AML) 10-20x

Contributions from the Genome project: pathogenesis

- The gene content of chromosome 21 is now estimated to be 329, including 165 experimentally confirmed genes, 150 gene models based on expressed sequence tag databases, and 14 computer predictions (see http://wwweri.uchsc.edu).

- An additional, unexpected finding is that the actual fraction of chromosome 21 that is transcribed into RNA might be an order of magnitude higher than the fraction occupied by gene coding sequences.

- One striking conclusion that can be drawn from the gene content of chromosome 21 is that there are sets of genes on the chromosome that are involved in the same metabolic pathway or biological system.

Genes that may have input into Down syndrome include:

- Superoxide Dismutase (SOD1)-- overexpression may cause premature aging and decrease function of the immune system; its role in Senile Dementia of the Alzheimer's type or decreased cognition is still speculative
- COL6A1 -- overexpression may be the cause of heart defects
- ETS2 -- overexpression may be the cause of skeletal abnormalities
- CAF1A -- overexpression may be detrimental to DNA synthesis
- Cystathione Beta Synthase (CBS) -- overexpression may disrupt metabolism and DNA repa
- DYRK -- overexpression may be the cause of mental retardation
- CRYA1 -- overexpression may be the cause of cataracts
- GART -- overexpression may disrupt DNA synthesis and repair
- IFNAR -- the gene for expression of Interferon, overexpression may interfere with the imm system as well as other organ systems
- Other genes that are also suspects include APP, GLUR5, S100B, TAM, PFKL, and a few othe Again, it is important to note that *no gene has yet been fully linked to any feature associat with Down syndrome*.

Panel 5: **Management of Down's syndrome**

Evaluation

- Echocardiogram
- Ophthalmological assessment
- Hearing assessment

Prevention

- Obesity
- Periodontal disease

Monitoring

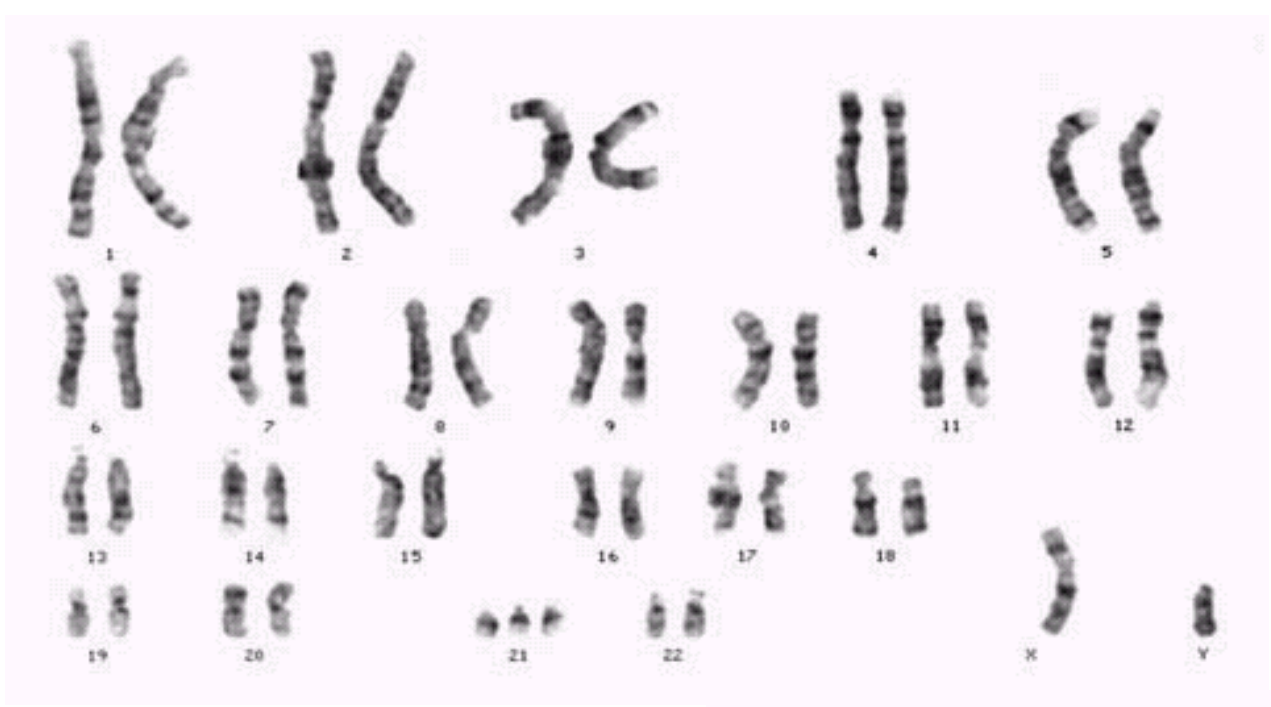
- Coeliac disease
- Thyroid function

Vigilance

- Arthritis
- Atlantoaxial subluxation
- Diabetes mellitus
- Leukaemia
- Obstructive sleep apnea
- Seizures

Other

- Sexuality and reproductive health
- Dermatological problems
- Behaviour problems
- Development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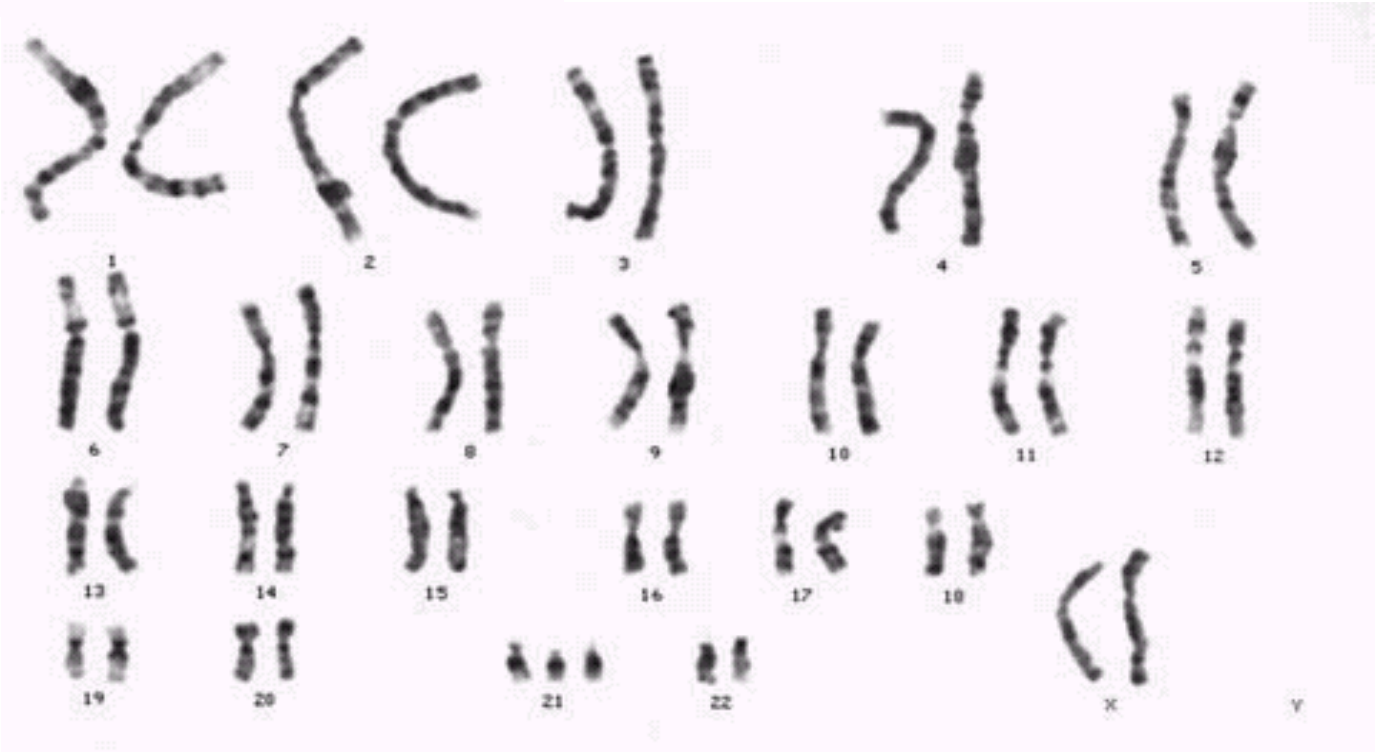
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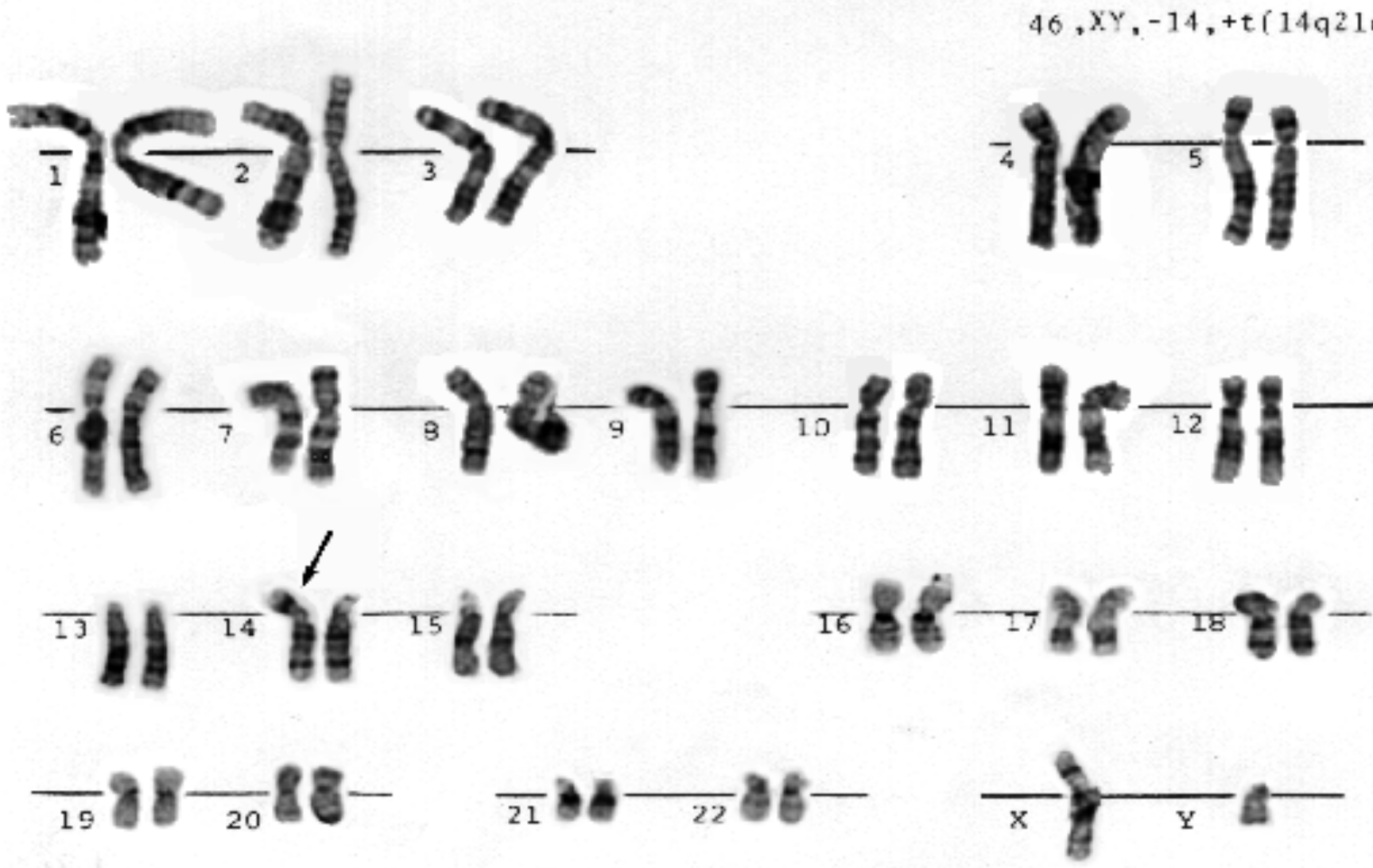
Types of anomalies in Down Syndrome

ETA' MATERNA	TIPO DI ANOMALIA (in percentuale)		
ANNI	47, +21	MOSAICO	TRASLOCAZIONE
15 -19	85	5	10
20 - 24	90	1	9
25 -29	91	2	7
30 -34	93	3	4
34 - 40	97	1	2
oltre i 40	97	2	1


46,XY,-14,+t(14q21q)
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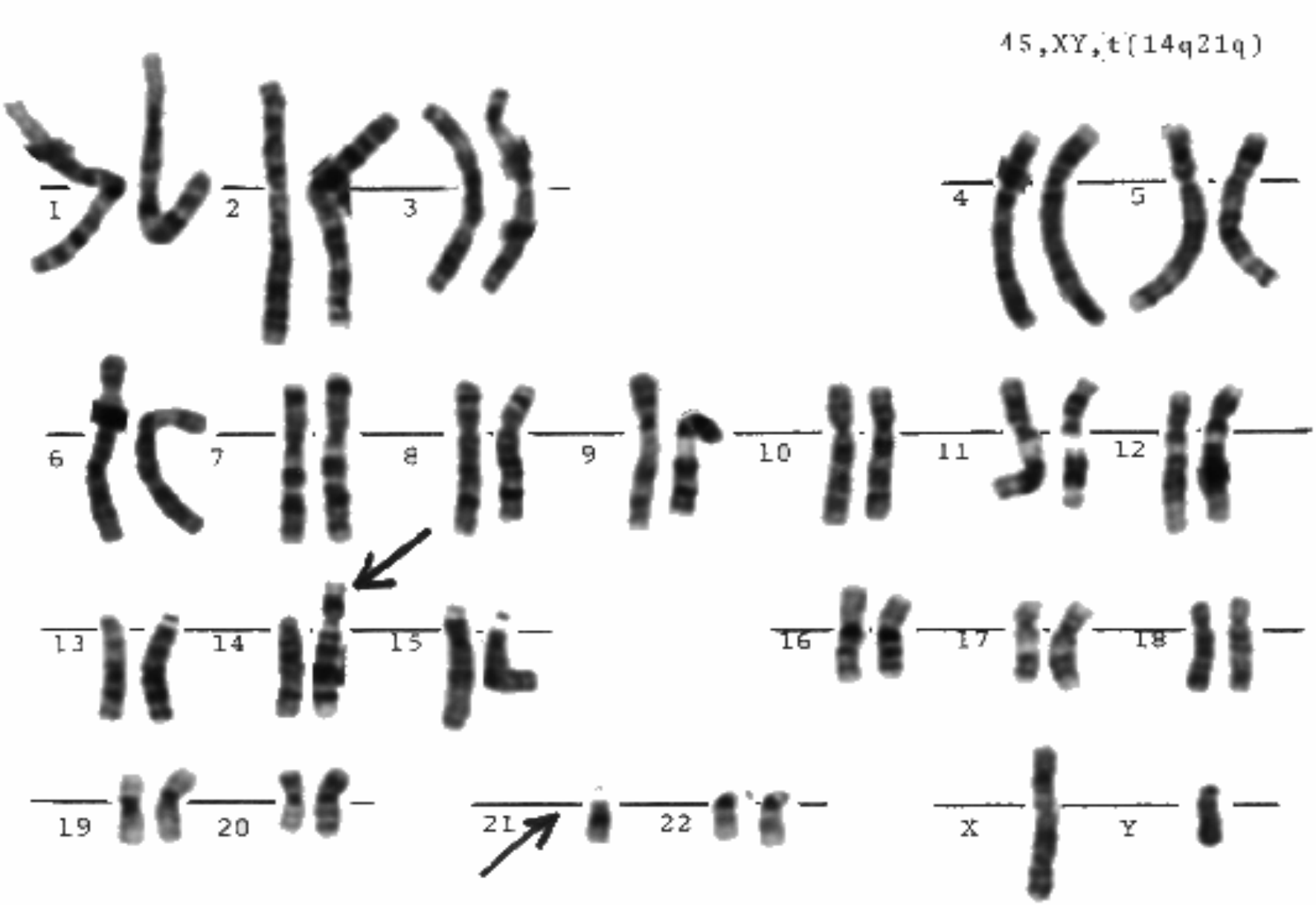
45,XY,t(14q21q)
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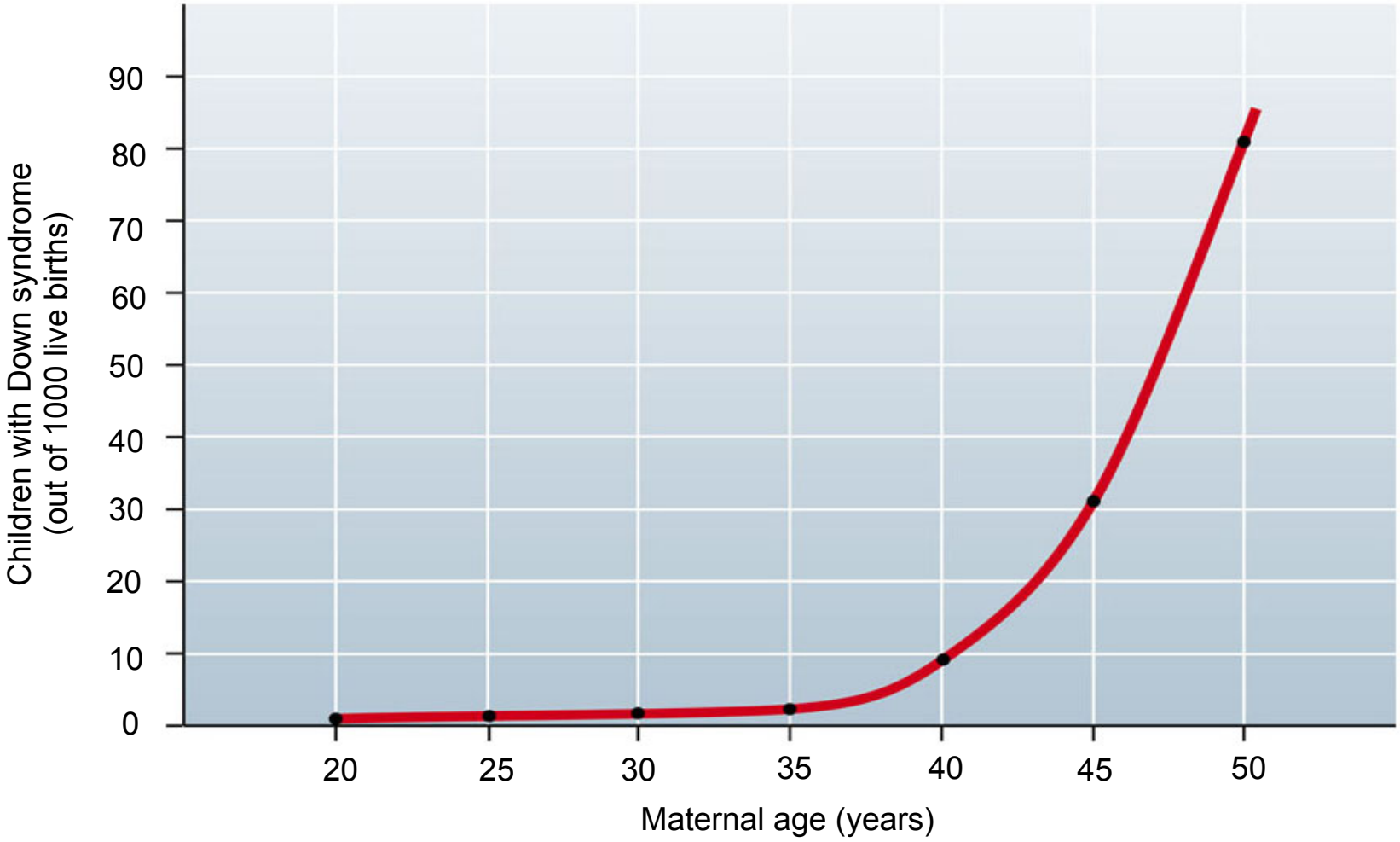
Down syndrome

The incidence of Down syndrome in the offspring of healthy parents increases with maternal age



Woman 37,5 years old anni e mezzo alla data presunta del parto

	MESI COMPLETATI										
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26	1317	1311	1306	1300	1294	1289	1283	1277	1271	1264	1258	1252
27	1245	1239	1232	1225	1219	1212	1205	1198	1191	1183	1176	1169
28	1161	1154	1146	1138	1130	1123	1115	1107	1099	1090	1082	1074
29	1065	1057	1048	1040	1031	1022	1014	1005	996	987	978	969
30	960	951	942	932	923	914	905	895	886	877	867	858
31	848	839	829	820	810	801	791	782	772	763	753	744
32	734	725	716	706	697	687	678	669	660	650	641	632
33	623	614	605	596	587	578	570	561	552	544	535	527
34	518	510	502	494	486	478	470	462	454	446	439	431
35	424	416	409	402	395	387	381	374	367	360	354	347
36	341	334	328	322	316	310	304	298	292	287	281	275
37	270	265	259	254	249	244	239	235	230	225	221	216
38	212	207	203	199	195	191	187	183	179	175	171	168
39	164	161	157	154	151	147	144	141	138	135	132	129
40	126	124	121	118	116	113	111	108	106	103	101	99
41	97	94	92	90	88	86	84	82	81	79	77	75
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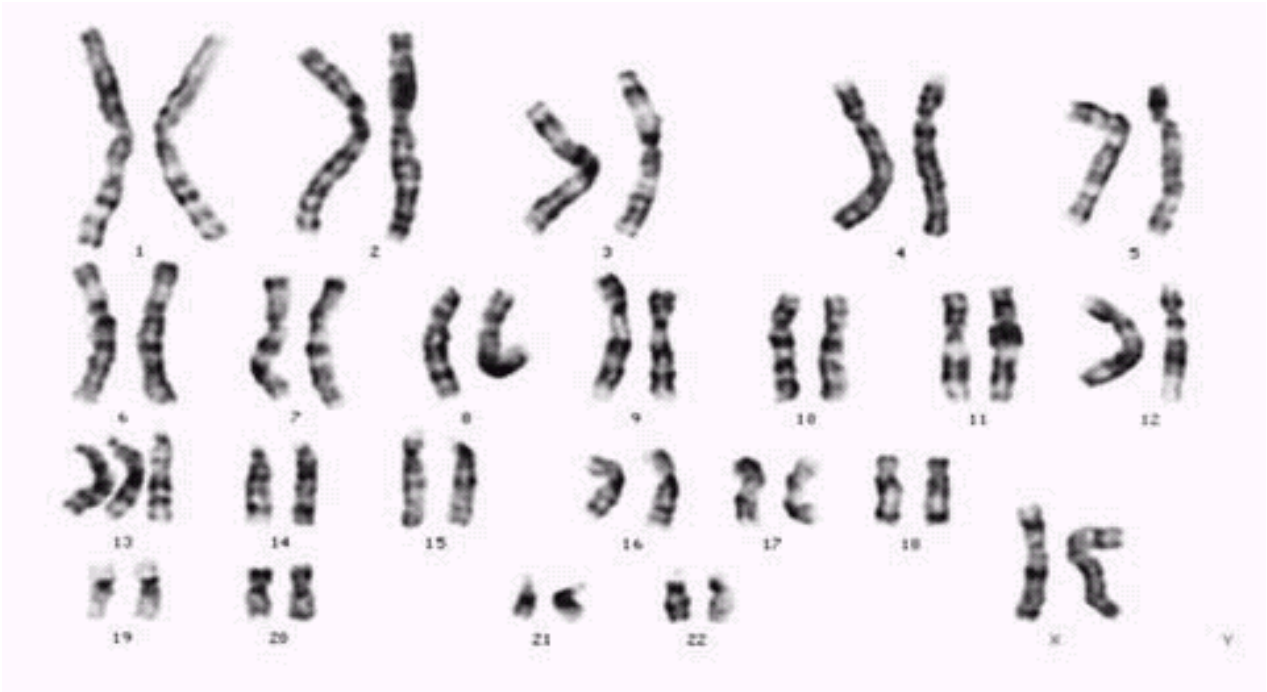
44	42	41	40	39	38	37	36	35	35	34	33	32
45	31	31	30	29	29	28	27	27	26	25	25	24

Risk of 1/239 to have a Down child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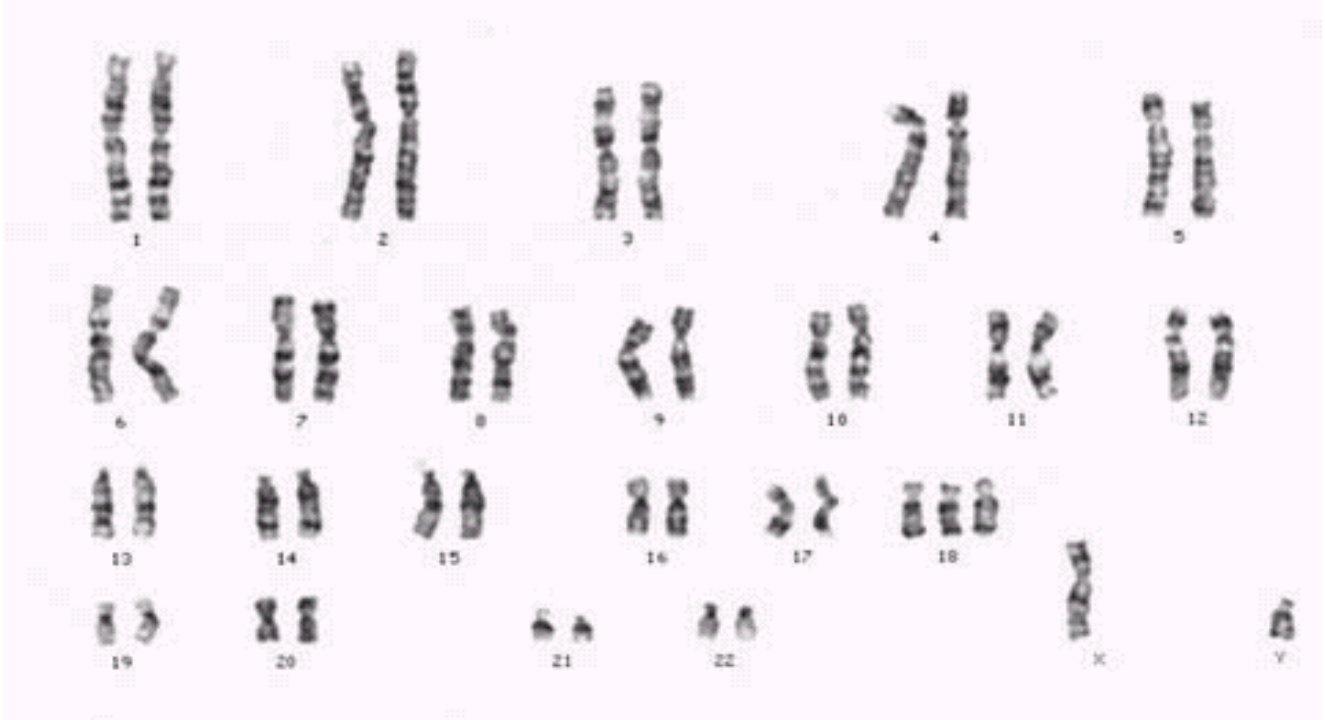
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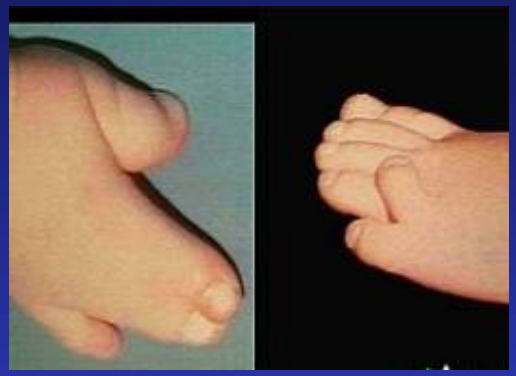
The only other human trisomies compatible with birth are:

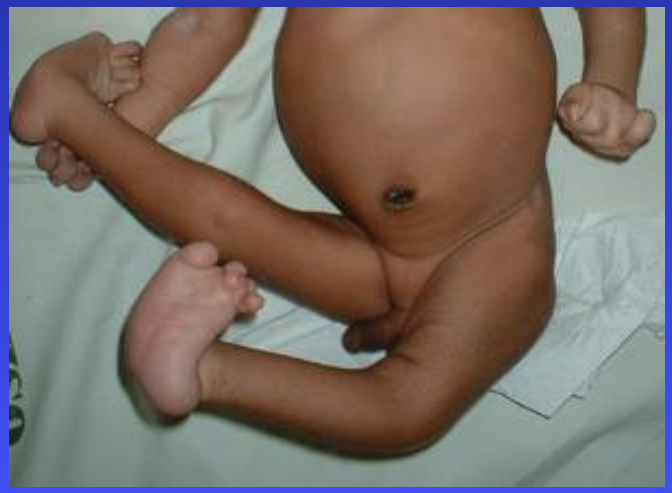
Trisomy 13 (Patau syndrome)
cleft lip, small malformed head, abnormal under foot.
Life expectancy:130 giorni

Trisomy18 (Edwards syndrome)
ears from Faun, small jaw, narrow pelvis, abnormal under foot. Life espectancy: a few weeks

For all other trisomies patients die in utero.

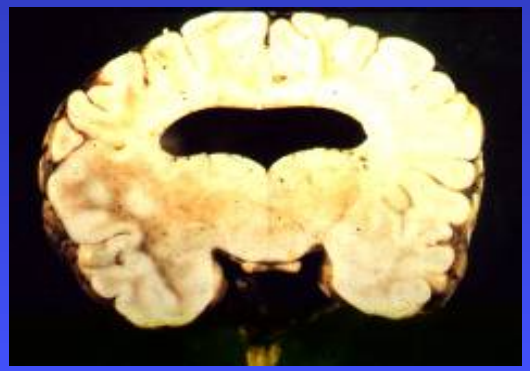
trisomy 18 Edwards



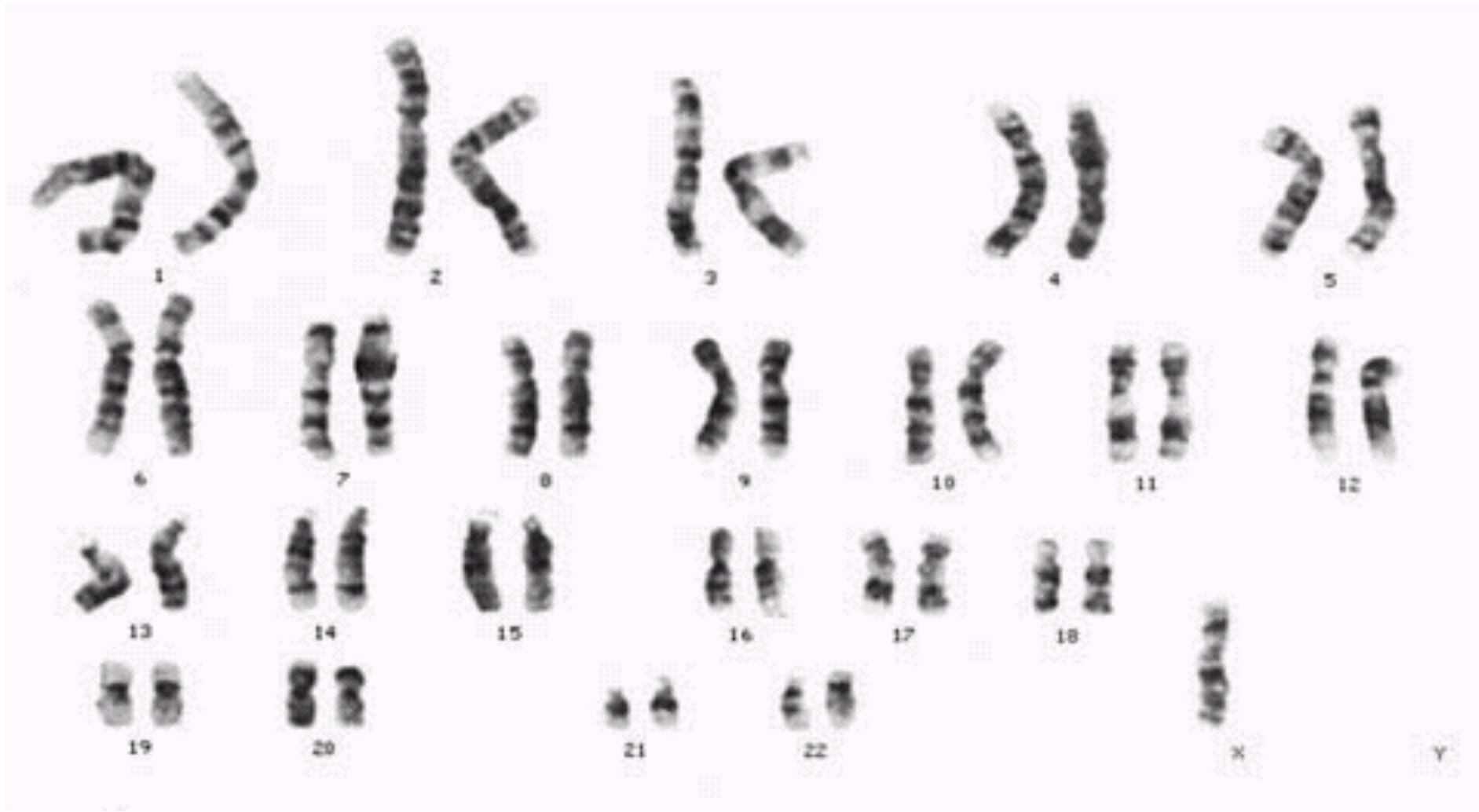


- (1/6.500 births)
- 90% caused by maternal non-disjunction
- M/F = ¼
- Only 2.5% conceptions are completed
- Of these, 33% die within 1 month from conception, 50% within 2 months
- Over 100 anomalies
  - Weight below the norm, sucking difficulties
  - Hypotonia
  - Hydrocephalus, epilepsy
  - Heart defects
  - Hypoplasia of fingernails
  - Feet with prominent heel
  - Crossed legs

trisomy 13 Patau



- (1/12.000-20.000 births)
- 90% caused by maternal non-disjunction
- Only 2.5% conceptions are completed
- Of these, 33% die within the first month, 50% within 2 months
  - Weight below the norm, sucking difficulties
  - Microcephaly
  - Blindness and deafness
  - Microphthalmia/anophthalmia
  - Labiopalatoschisis 80%
  - Epilepsy
  - Cardiac malformations
  - Feet with prominent heel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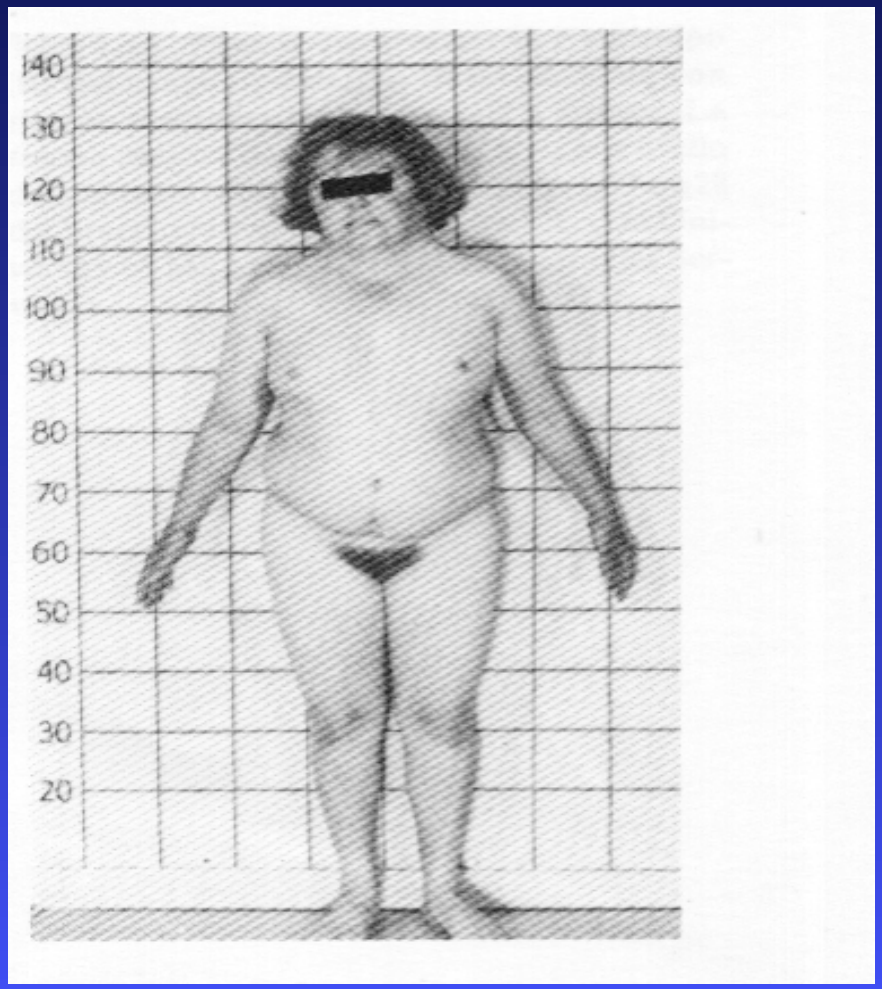
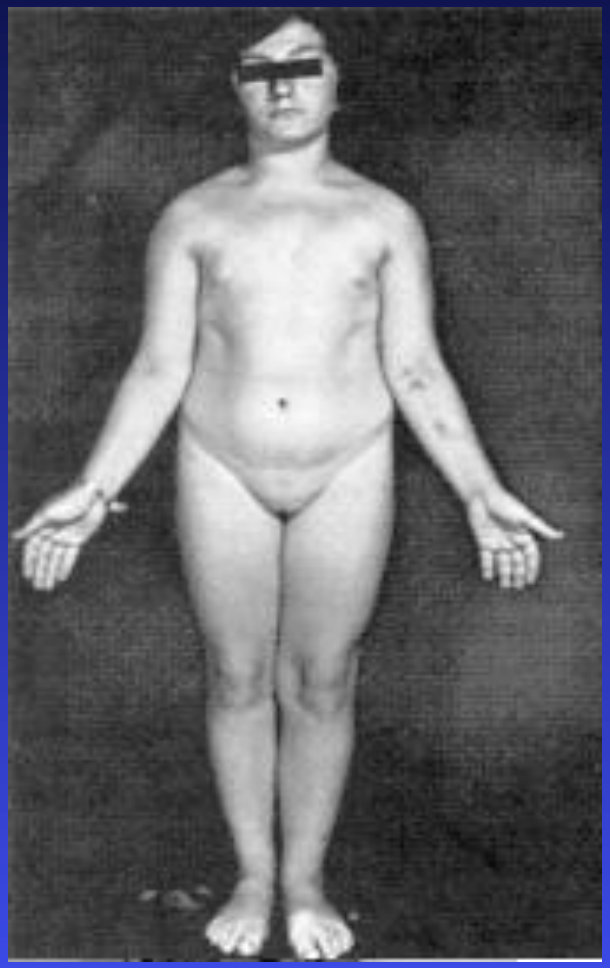
Turner syndrome



- Short stature
- Pterygium colli
- Shield-shaped thorax
- Elbow deformity (cubitus valgus)
- Poor breast development

X monosomy (45,X0) Turner



Takes its name from the endocrinologist Henry Turner who described it in 1938

Turner syndrome (TS) defines a complex female human phenotype, due to complete or partial absence of the second sex chromosome

Depends on a mistake in spermatogenesis in 80% of cases and does not correlate with parental age

A previous child with TS does not increase the reproductive risk expected for an age-matched couple

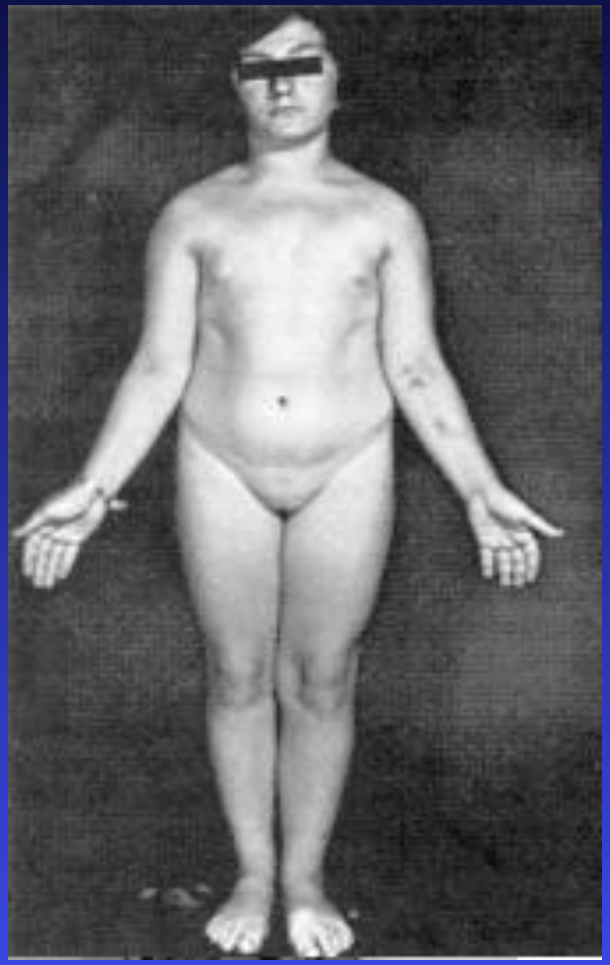
X monosomy (45,X0) Turner

Ii is the only monosomy compatible with life, but 98% of all TS monosomic fetuses undergoes spontaneous miscarriage

The incidence in abortions is about 7-10%, while at birth the incidence is 1/2500 females. It is unclear why the 45, X0 karyotype is lethal in utero while compatible with postnatal survival

The real X chromosome monosomy is responsible for 45% of TS cases; others have mosaicism (45, X/46, XX) and/or an abnormal X chromosome
A low level of somatic Turner mosaicism, less than 2%, is found in the normal population

X monosomy (45,X0) Turner



"menopause before menarche”

The ovaries are elongated and formed by stromal tissue devoid of follicles: oocytes often undergo apoptosis in 2 years of life

Prepubertal ovarian failure leads to primary amenorrhea, infertility and estrogen deficiency

In less than 10% of cases, puberty can occur and pregnancies are possible though at an increased risk of fetal loss

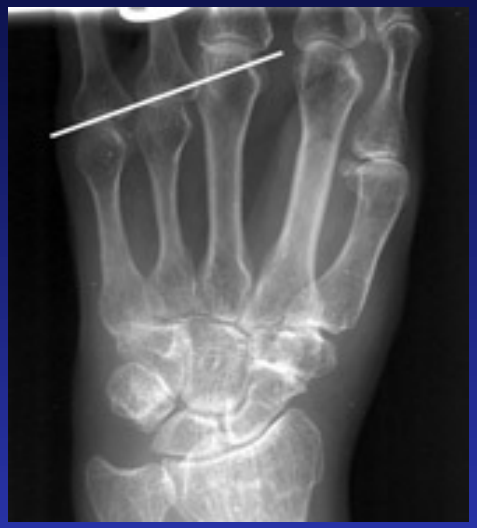
Also in relation to the heterogeneity of genotype, phenotype is manifest in a very variable manner

Incidence of Phenotypes in Turner Syndrome

Short stature	100%
Infertility	98%
Primary gonadal failure	95%
Osteoporosis	50%
Cubitus valgus	45%
Low posterior hairline	40%
Carbohydrate intolerance	30-40%
High blood pressure	25-40%
Short metacarpals	35%
High arched palate	35%
Structural abnormalities in kidney	35%
Hypothyroidism (Hashimoto thyroiditis)	35%

NIH. Electronic Citation; 2002.

X monosomy (45,X0) Turner
1:2.500



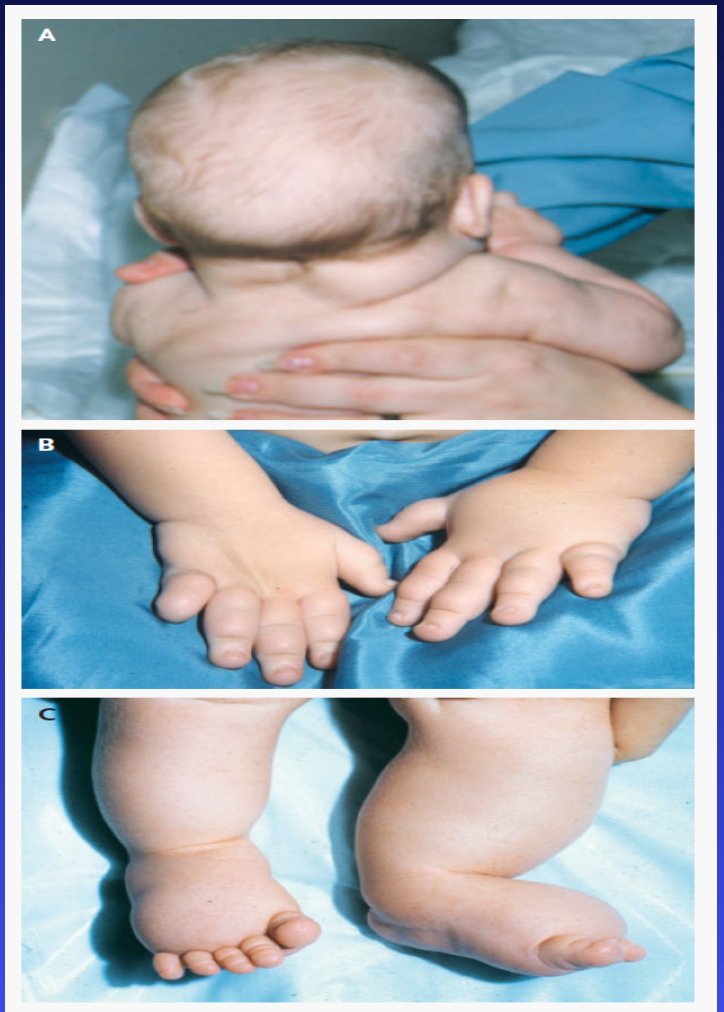


Figure 1. Redundant Nuchal Skin (Panel A) and Puffiness of the Hands (Panel B) and Feet (Panel C) in Turner's Syndrome.

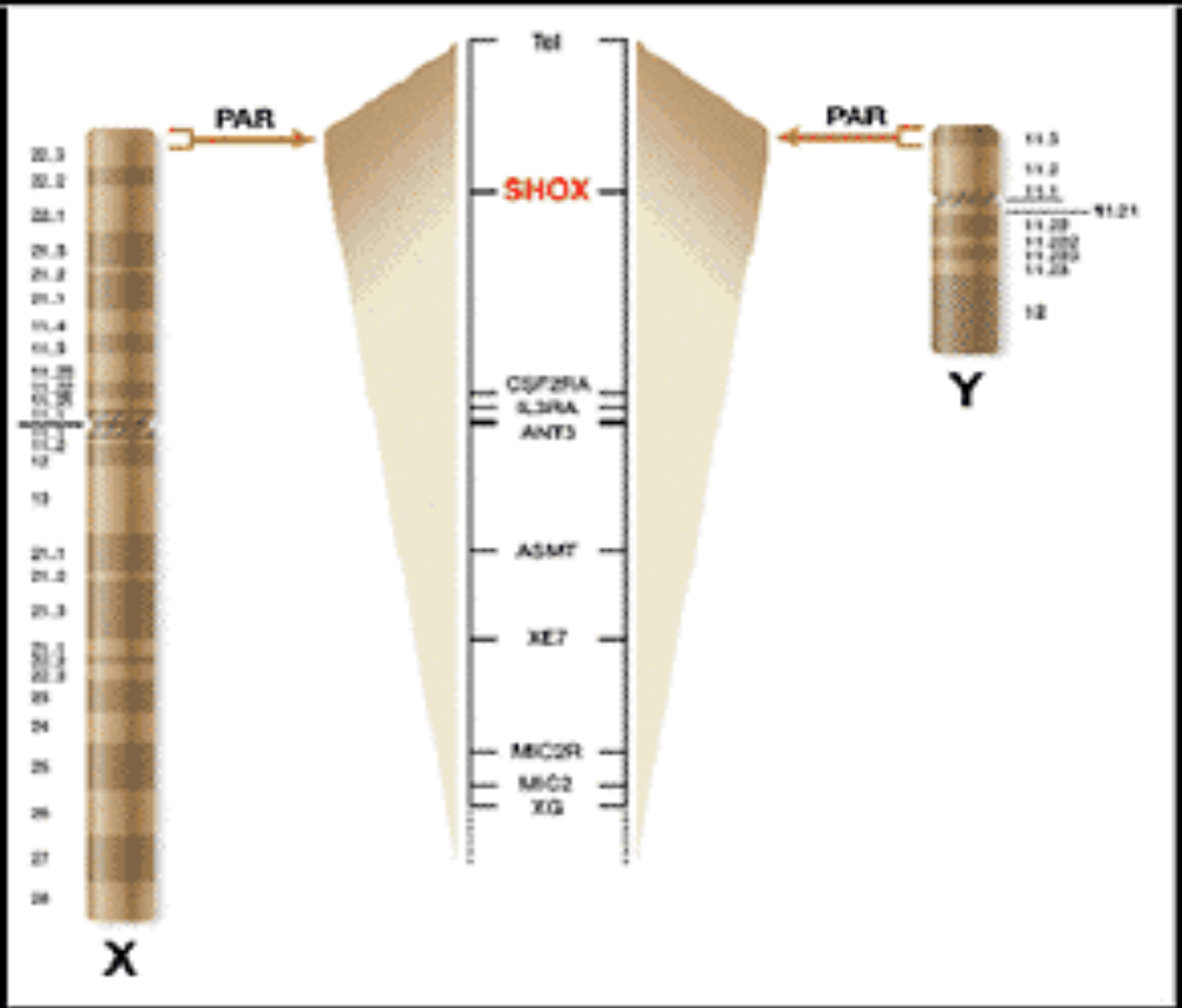
TABLE 1. Clinical Abnormalities in Individuals With Turner Syndrome

Very frequent (>50% of individuals)
- Growth deficiency
- Gonadal dysgenesis
- Lymphedema of hands and feet
- Deep set, hyperconvex nails
- Unusual shape and rotation of ears
- Narrow maxilla and dental crowding
- Micrognathia
- Low posterior hairline
- Broad chest with inverted or hypoplastic nipples
- Cubitus valgus
- Short fourth metacarpals
- Tibial exostosis
- Tendency to obesity
- Recurrent otitis media

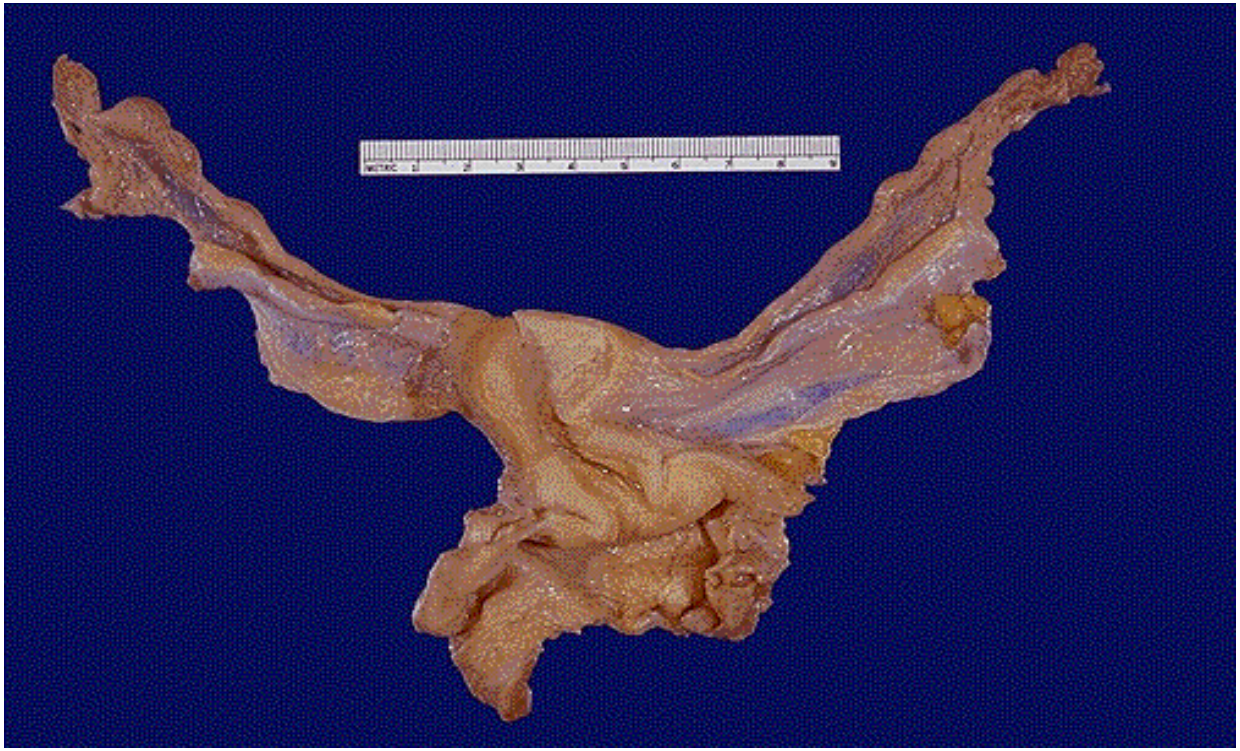
Frequent (<50% of individuals)
- Hearing loss
- Pigmented nevi
- Webbed neck
- Renal abnormalities
- Cardiovascular anomalies
- Hypertension
- Hypothyroidism
- Glucose intolerance
- Hyperlipidemia

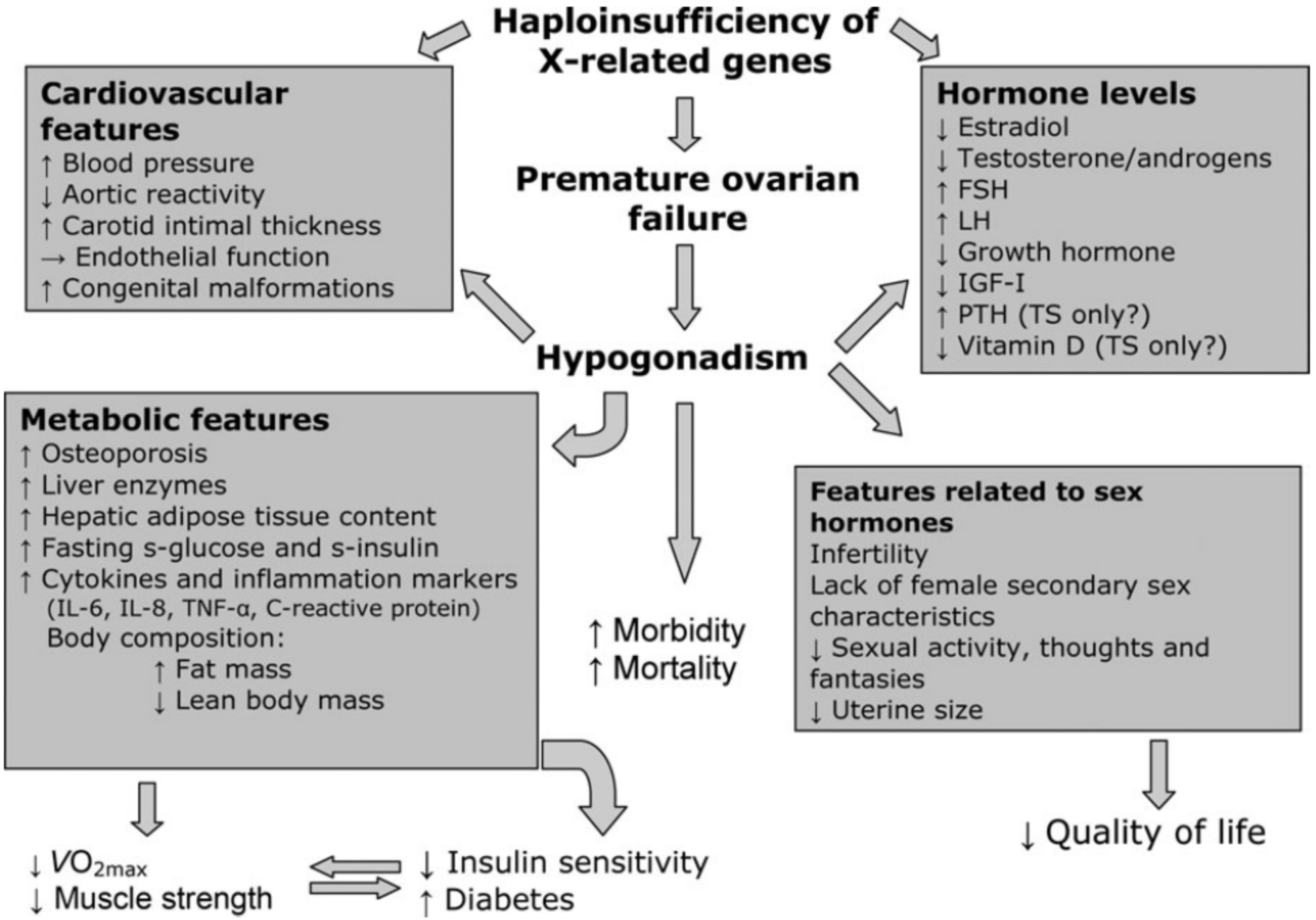
Occasional (<5% of individuals)
- Scoliosis, kyphosis, lordosis
- Osteoporosis
- Gonadoblastoma
- Inflammatory bowel disease
- Colon cancer
- Neuroblastoma
- Juvenile rheumatoid arthritis
- Liver disease

Short Stature HomeobOX (SHOX)–Containing Gene



After puberty, the ovaries should develop into plump 3 to 5 cm ovoid organs, but these "streak" ovaries are typical for Turner's syndrome.




Haploinsufficiency of X-related genes
Premature ovarian failure
Hypogonadism
Cardiovascular features
↑ Blood pressure
↓ Aortic reactivity
↑ Carotid intimal thickness
→ Endothelial function
↑ Congenital malformations
Hormone levels
↓ Estradiol
↓ Testosterone/androgens
↑ FSH
↑ LH
↓ Growth hormone
↓ IGF-I
↑ PTH (TS only?)
↓ Vitamin D (TS only?)
Metabolic features
↑ Osteoporosis
↑ Liver enzymes
↑ Hepatic adipose tissue content
↑ Fasting s-glucose and s-insulin
↑ Cytokines and inflammation markers
(IL-6, IL-8, TNF-α, C-reactive protein)
Body composition:
↑ Fat mass
↓ Lean body mass
↑ Morbidity
↑ Mortality
Features related to sex hormones
Infertility
Lack of female secondary sex characteristics
↓ Sexual activity, thoughts and fantasies
↓ Uterine size
↓ Quality of life
↓ VO2max
↓ Muscle strength
↓ Insulin sensitivity
↑ Diabetes

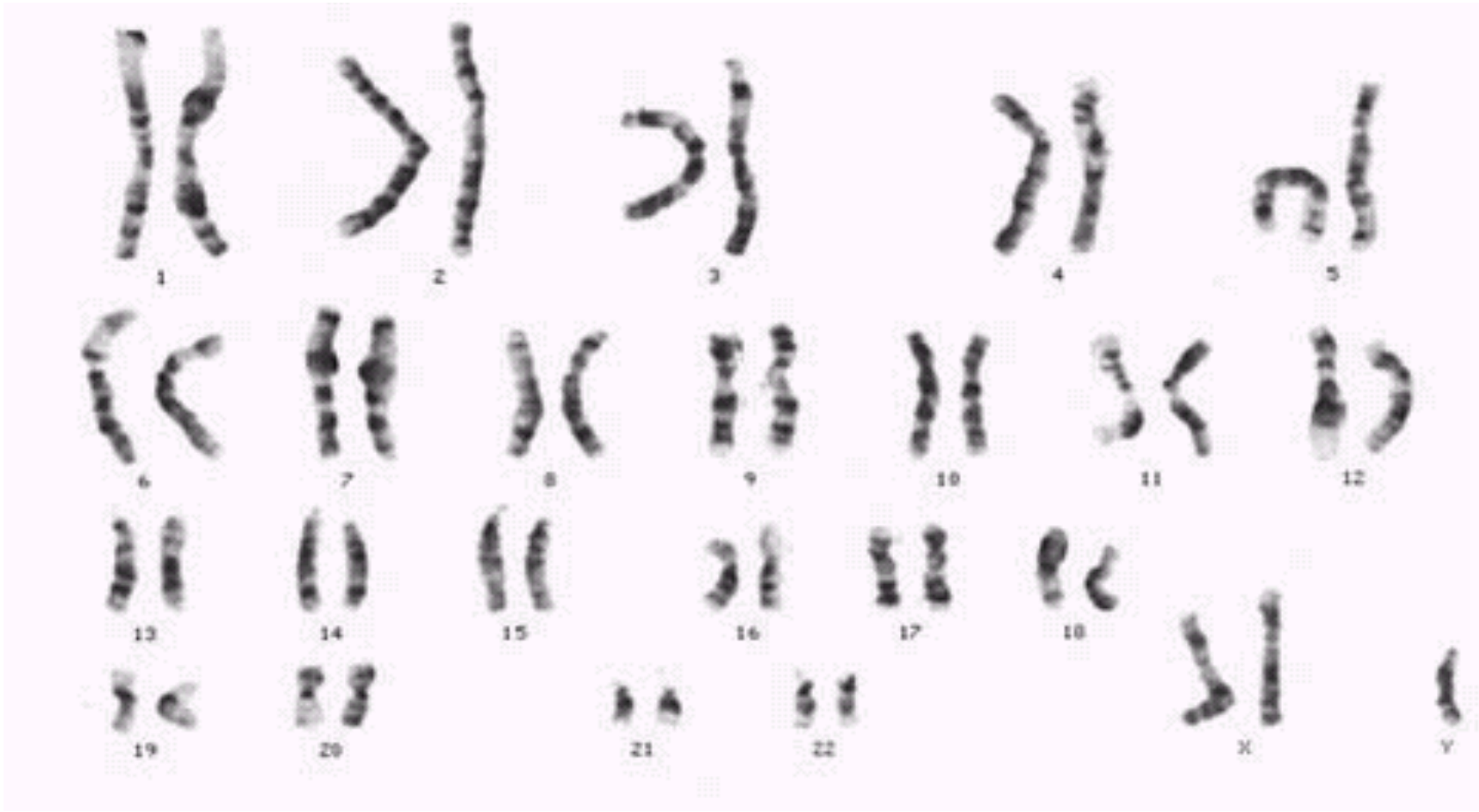
Ranke MB.

Why Treat girls with Turner Syndrome with Growth Hormone? Growth and Beyond.

Abstract

Turner Syndrome (TS) is a rare disorder, characterized by numerous signs and symptoms, which are also highly variable in their expression in individuals. The understanding of the genetic basis of the phenotype has advanced greatly during the past decades. The most consistent features, which negatively affect the quality of life in these individuals, are short stature and impaired gonadal function. After recombinant human growth hormone (rhGH) became available and was shown to improve height, it was then approved and has been used widely. Yet it remains a challenge to decide on the optimal treatment modality for individuals with TS and to evaluate the benefits and risks also in terms of karyotype of GH on growth and on other organ systems.

Pediatr Endocrinol Rev. 2015 Jun;12(4):356-65.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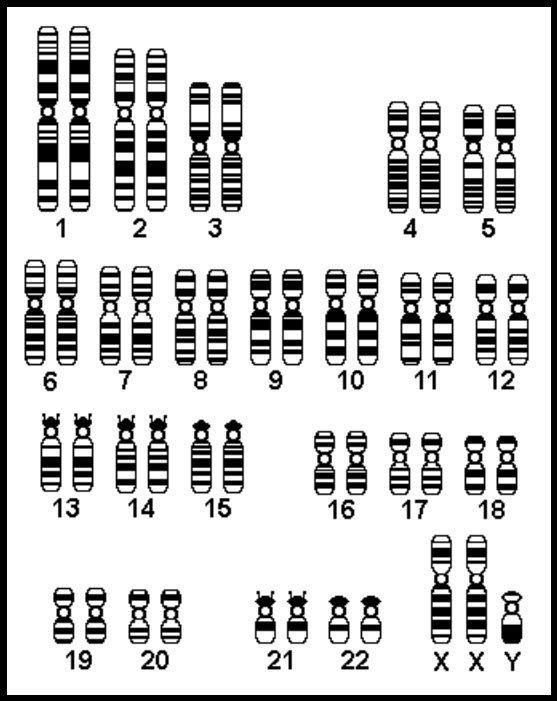
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Klinefelter syndrome.

- Tall stature
- Gynecomastia
- disproportion of limbs
- hypogonadism

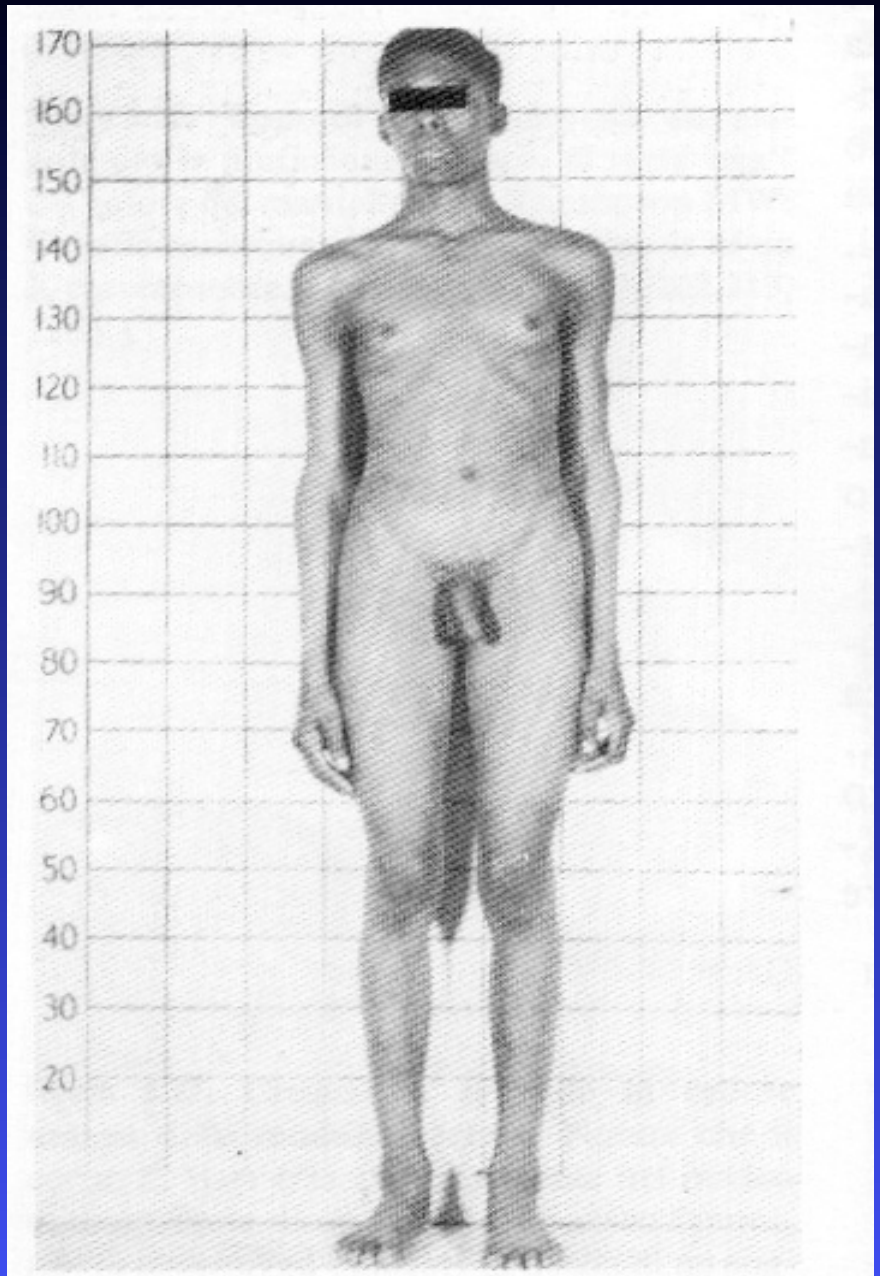
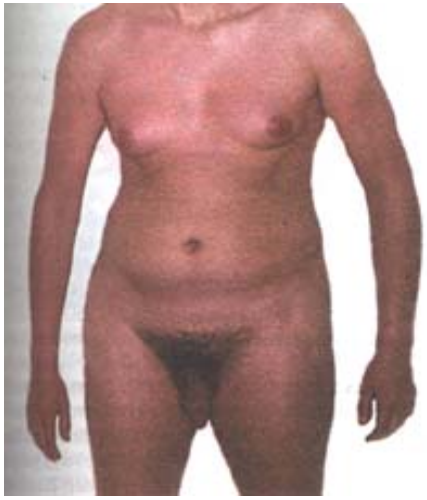


Figura 8.30. La sindrome di Klinefelter. Nota-

Klinefelter syndrome (47,XXY) 1:900-1:600 males

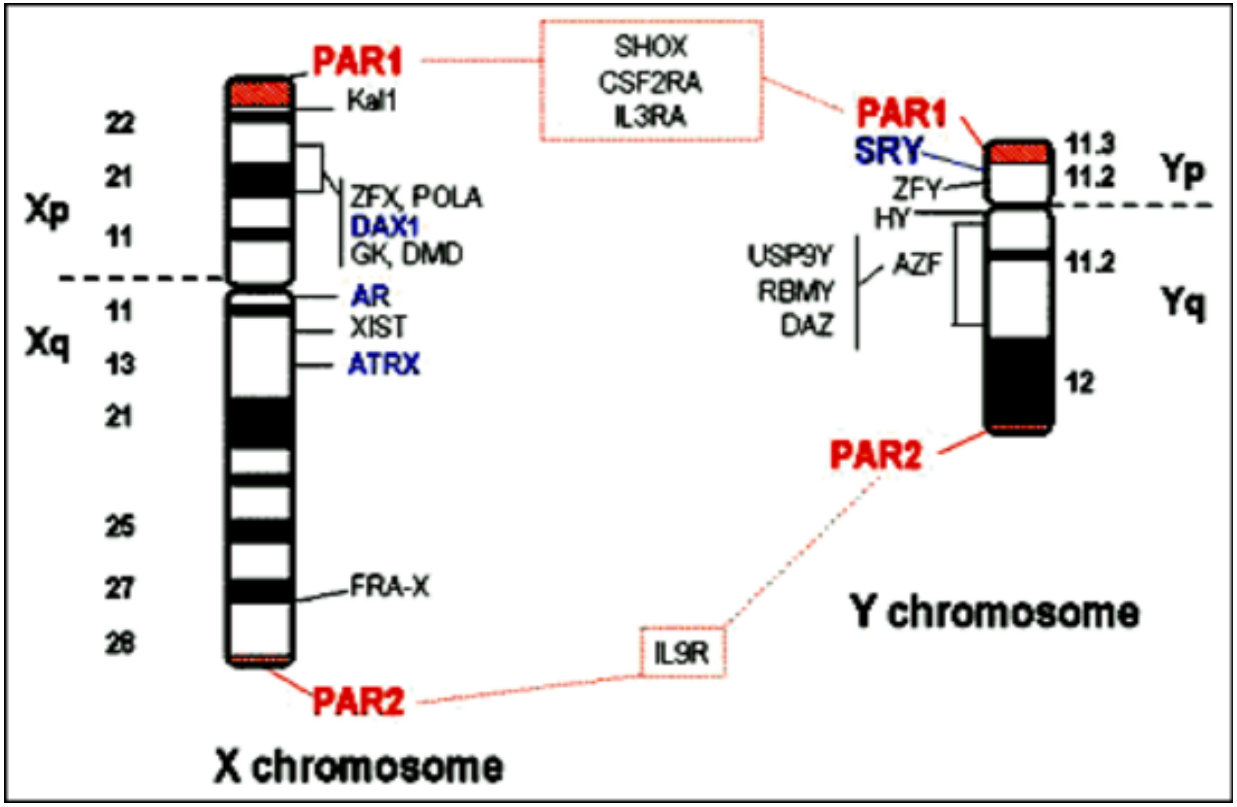


- 50% of pregnancies is successful
- male phenotype
- main features:
- Tall stature
  - hypogonadism, low testosterone levels, lack of sperm production (azoospermia) and then infertility
  - Gynecomastia
  - Both intelligence and life expectancy are almost normal

Other cytogenetics forms

- There are also Klinefeler cases **48,XXYY** and **48,XXXY** in 1 case out of 17,000 and 1 out of 50,000 born males
- **49,XXXXY** in 1 case out of 85,000 -100,000
- There are also males **46,XX** carrying a translocation of part of chromosome Y on chromosome X where translocationd includes the sex determining region (SRY)
- mosaics

The PAR regions on sex chromosomes contain non inactivated genes, as the double dosage is ensured anyway



PAR1 contains 24 genes, PAR2 only 4 genes

SHOX gene
Short stature HOmeoboX-containing

- Either mutations or deletions of SHOX gene mapping in PAR1 cause growth retardation and short stature.
- The short stature of Turner Syndrome females (X0) results from one single copy of SHOX (and also the shortened fourth metacarpus)
- The increased stature of Klinefelter syndrome males (XXY) and of triple X females (XXX) might be a consequence of 3 SHOX gene copies

Other abnormal sex chromosome combinations are:

XYY

Controversial history, has tried to associate the condition XYY in a predisposition to violence, today widely shown that there is no relationship. These males are fertile. During meiosis there is a normal XY pairing, the second Y does not pair and is not passed on to gametes.

XXX

Phenotypically normal and fertile females. During meiosis only two X chromosomes get paired, the third X chromosome does not pair and is not transmitted to gametes.

Males (47,XYY)
1:1.000 males

- Male phenotype
- Main features:
  - Tall stature
  - normal fertility
  - No correlation with paternal age
  - Both intelligence and life expectancy are perfectly normal

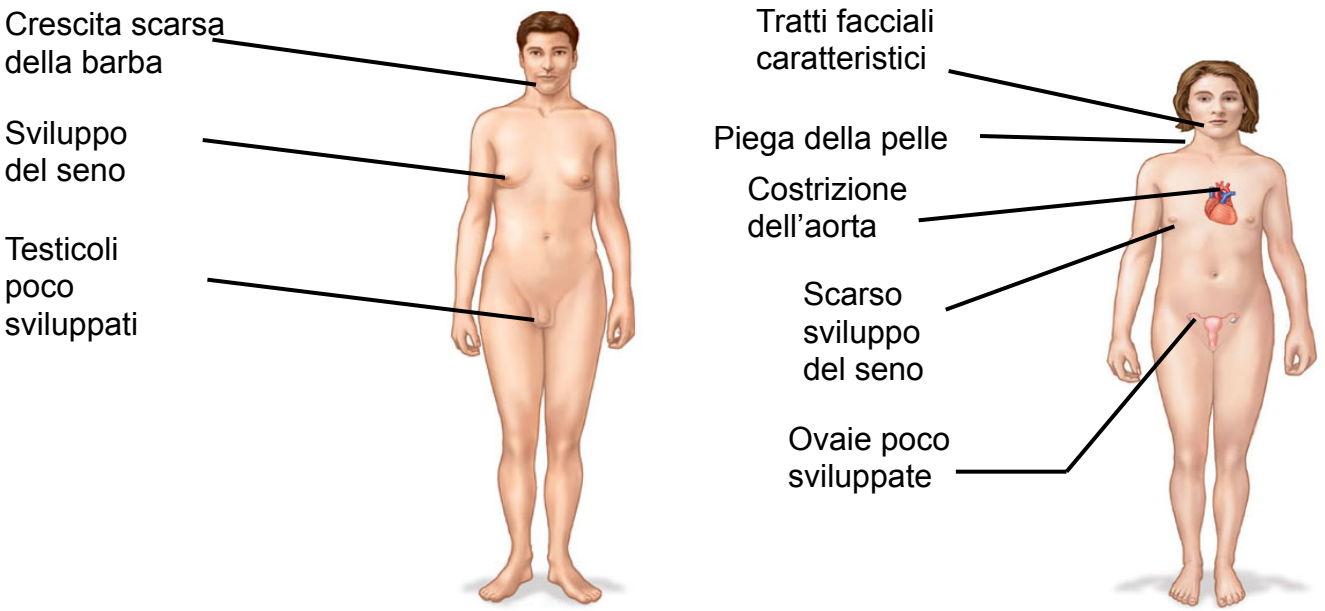
Trisomy X (47,XXX) 1:1.200

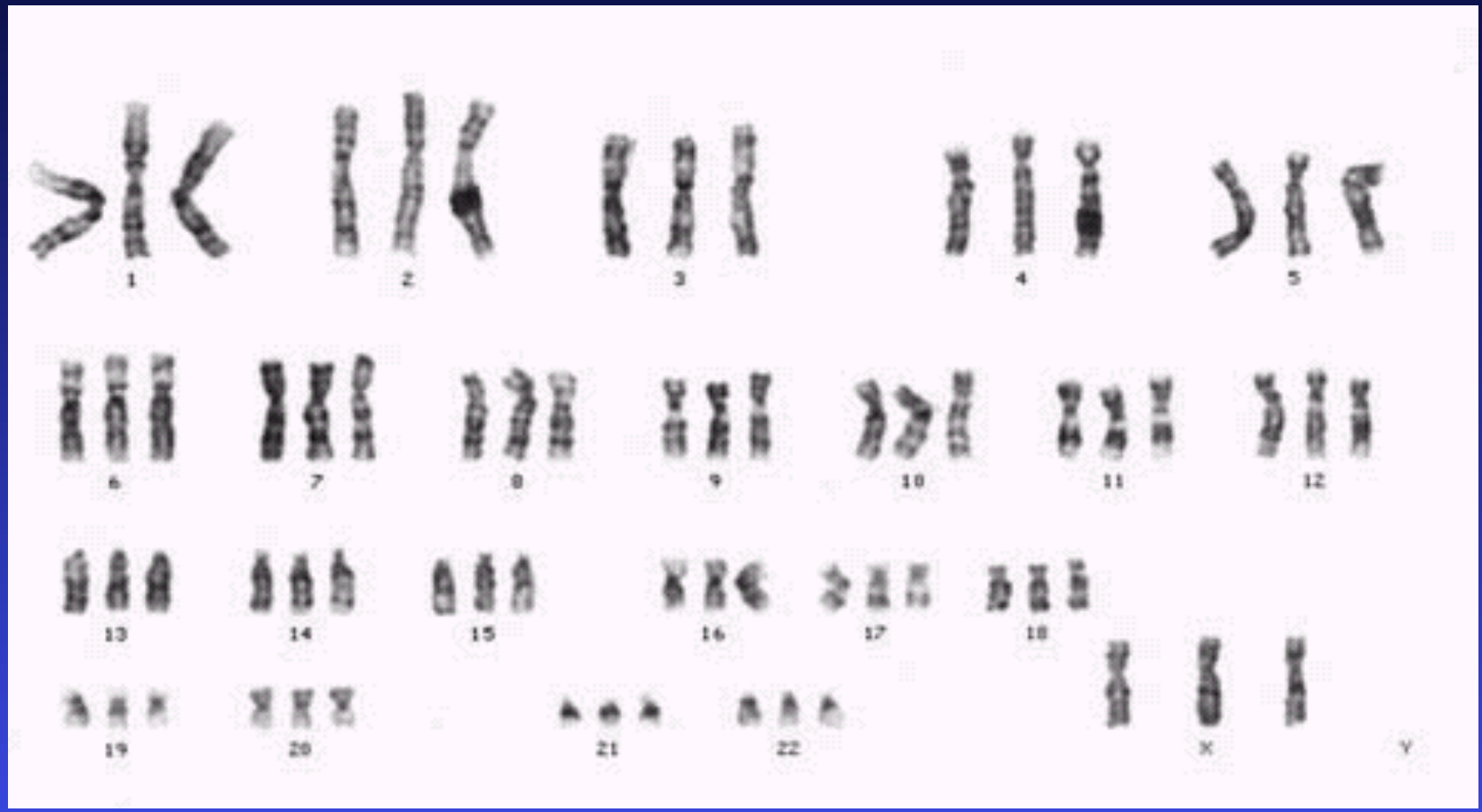
- 70% of pregnancies is successful
- Error in maternal disjunction and correlation with maternal age
- Main features:
  - Tall
  - Normal fertility, cycle irregularities
  - Both intelligence and life expectancy are normal

Sex chromosome alterations

An abnormal number of sex chromosomes usually does not compromise survival

The non-disjunction can produce gametes with an abnormal number of sex chromosomes leading to syndromes that, usually, do not compromise the survival of individuals.

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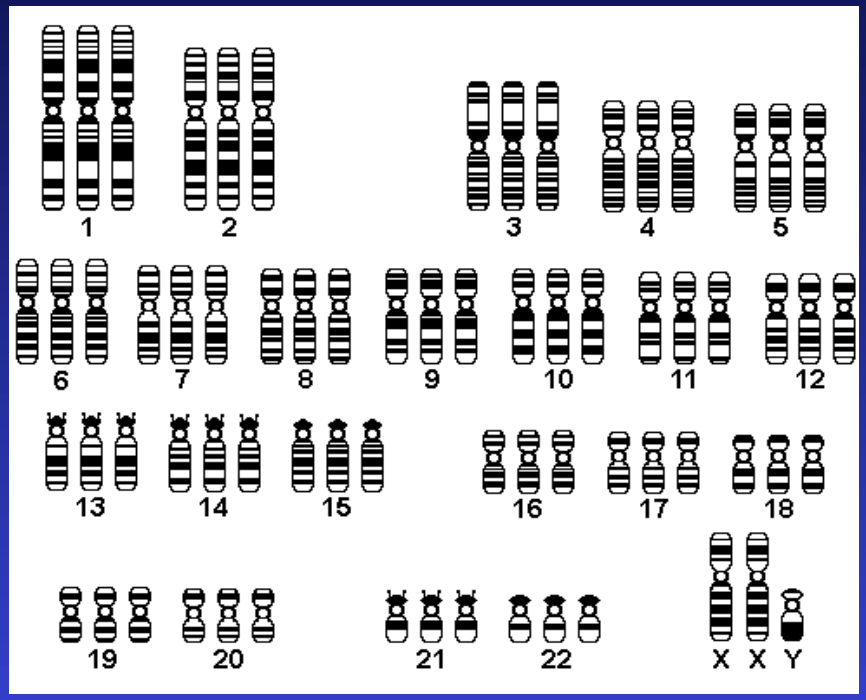
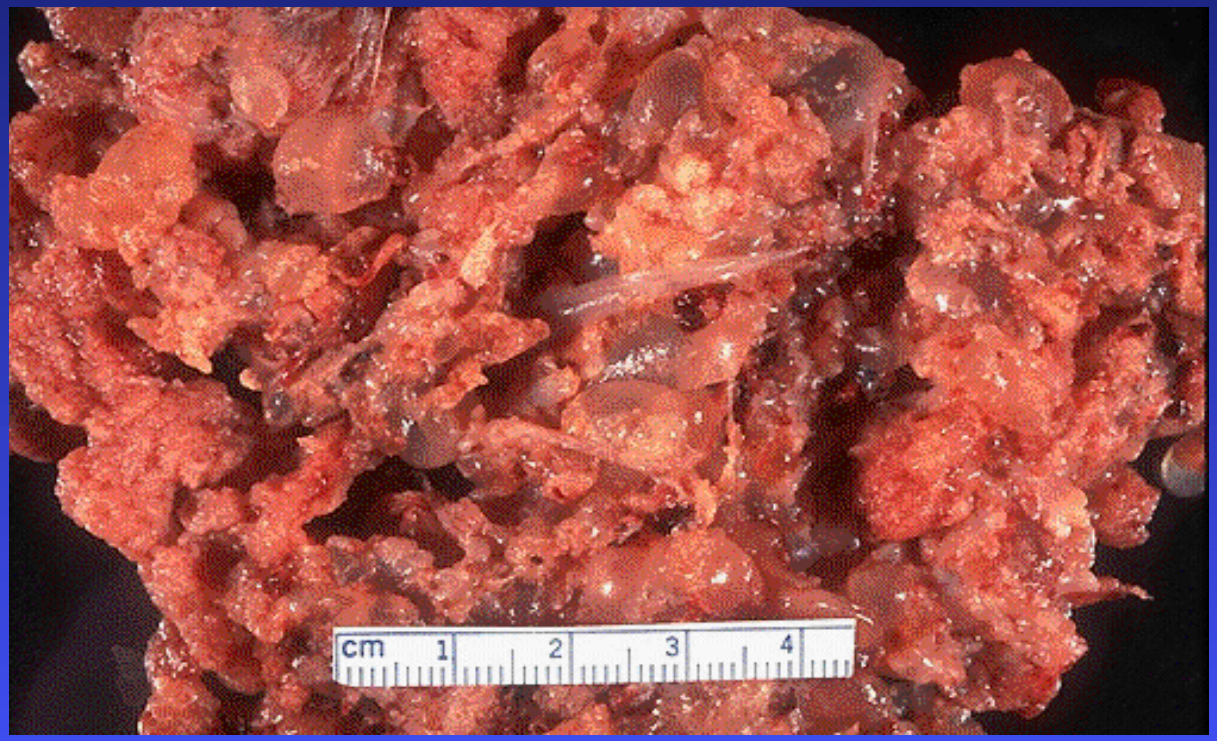
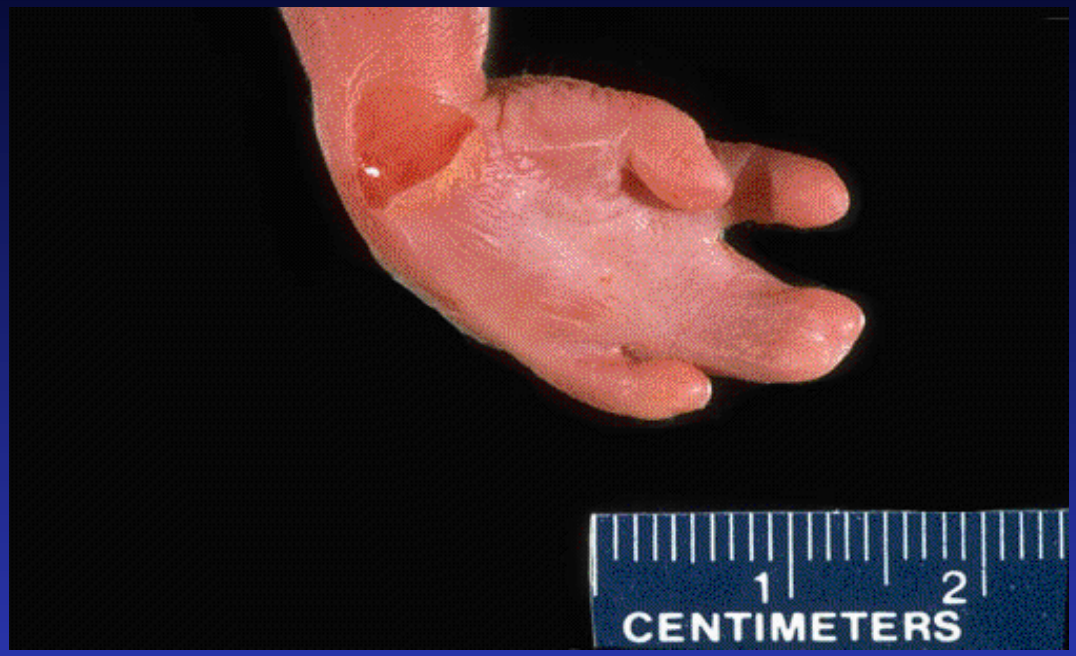


This is triploidy, which occurs when there is double fertilization of an ovum (dispermy). The result may be 69, XXX or 69, XXY or 69, XYY.

The extra set of paternal chromosomes predisposes to formation of a partial mole, features of which may or may not be grossly or microscopically apparent.

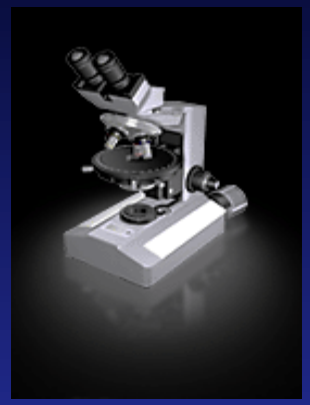
Scattered grape-like villi are present in this placenta, consistent with a partial hydatidiform mole.





A characteristic fetal finding with triploidy is syndactyly involving the third and fourth digits of one or both hands or feet.

Diseases due to chromosomal aberrations.



2. STRUCTURAL ANOMALIES

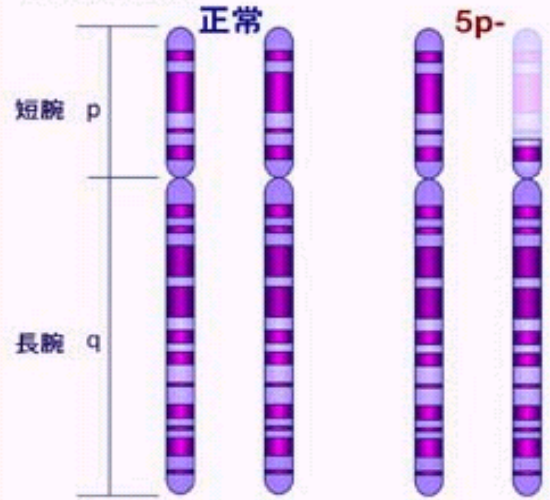
- cri du chat syndrome

- chromosome 18 anomalies

- Microdeletion syndromes (see below)

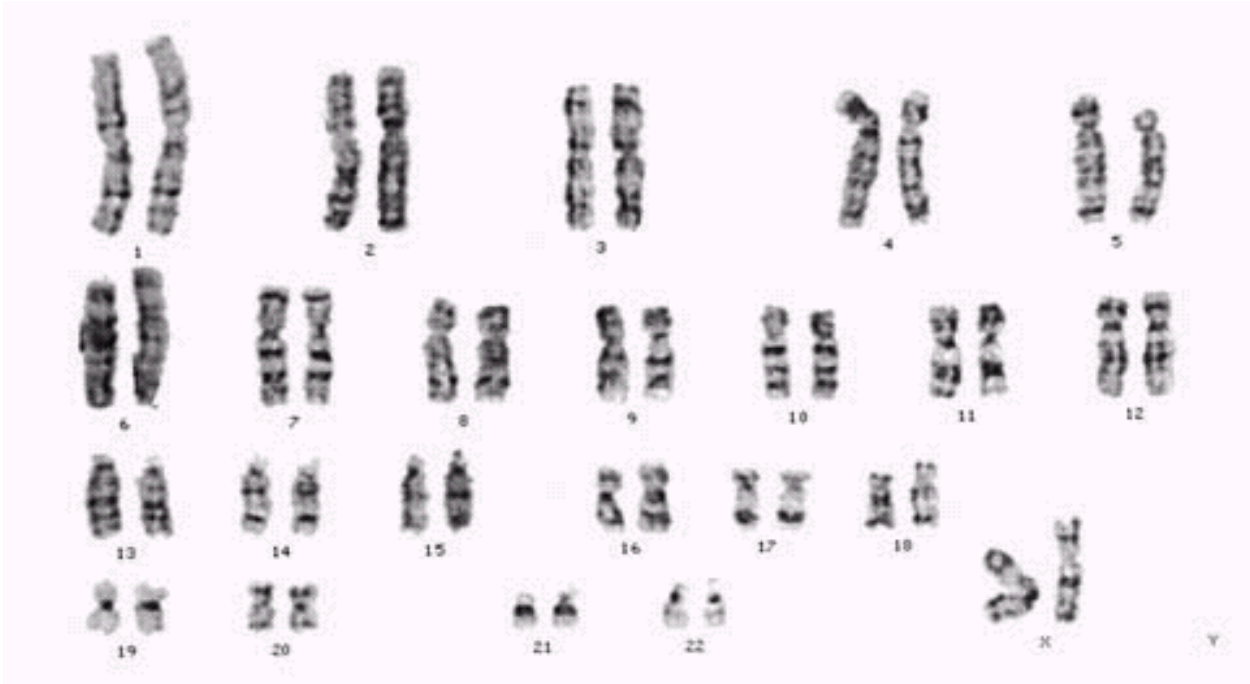
5p- syndrome = cri du chat syndrome

= ネコなき症候群



子猫の啼き声（新生児期に一過性）
円形顔貌
女児に圧倒的に多い
精神発達遅滞
1/10000
５番染色体短腕欠損

小頭，瞼裂斜下，両眼隔離，
小顎，耳介前円柱，一部に猿線，
先天性心疾患



Cat cry syndrome (or **syndrome du cri du chat**) is a rare genetic disorder caused by the deletion of part of chromosome 5 ("5 p-deletion"). Identified by the French physician Lejeune in 1963, it has an incidence of one case per 50000 births.

The syndrome is named after the cat-like cry, characteristic of affected individuals. The loss of genetic material is associated with delayed psychomotor development and severe mental retardation, but the absence of serious malformations in a significant percentage of cases can ensure a long survival.

Clinical picture:
In addition to the typical cat cry caused by hypoplasia of the laryngeal cartilages (which disappears within the first few month), there is a serious mental disability (with a tendency to self mutilation), microcephaly, growth retardation and a characteristic appearance of the face that looks roundish, enlarged nasal bridge, low-set ears and micrognathia. In 15% of cases there is a congenital heart defect.

Chromosome 18 abnormalities

- There are five major syndromes that occur when there are abnormalities of chromosome 18.
- Within each syndrome there are a variety of characteristics and a wide range in severity.
- Some individuals are mosaic or have translocations involving another chromosome and so do not fit exactly into one of these syndromes.
- The most frequent structural abnormalities of chromosome 18 are 18q-, 18p-, ring 18.

DIAGNOSIS: genetic counselling and prenatal cytogenetics

Genetic counselling

Genetic counselling is an informed and appropriate communication

In order to be **informed** it must start from the identification of a genetic defect in a patient and from calculating the risk to the other members of the family

In order to be **appropriate** it has to establish a relationship of trust and confidence without being directive, i.e. it must not direct the family towards a single goal, but leave the freedom of evaluation and choice

Genetic counselling may concern:
1. diagnosis of a clinically manifest genetic disorder
2. the reproductive risk of a couple in preconception period
3. prenatal diagnosis
4. the prediction of a future genetic disease
5. genetic susceptibility

Genetic counselling seeks to determine which family members are affected and which can be carriers of the disease, and then calculate the probability of every other person in the household (even not yet born) of being a carrier or to inherit the disease

general reproductive risk

for a couple for which personal and family medical history has excluded an increased risk in relation to the population it is

- 3-5% in case of defects detected at birth (chromosomal abnormalities 0.65%)
- 8-10% detectable within 10 years of age

Reproductive risk assessment in the preconception period

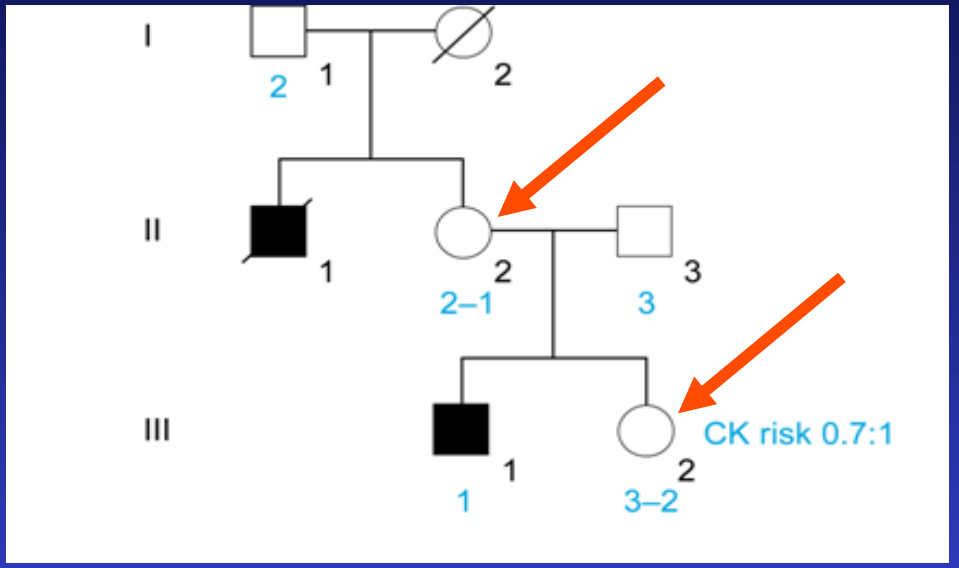
optimal time (*but more than half of pregnancies occur unexpectedly*)
data collection (visit, habits, medications, lab investigations)

PURPOSE: identification of healthy carriers of genetic disorders

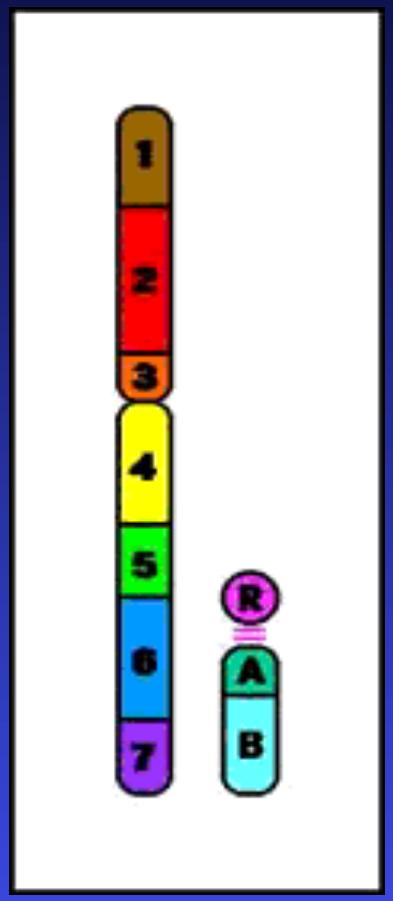
- carriers who have a reproductive risk regardless of the partner
- carriers in which the risk is manifested only in the case of marriage with a partner carrier

carriers who have a reproductive risk regardless of the partner

- women with X-linked mutations (example: Duchenne muscular dystrophy)

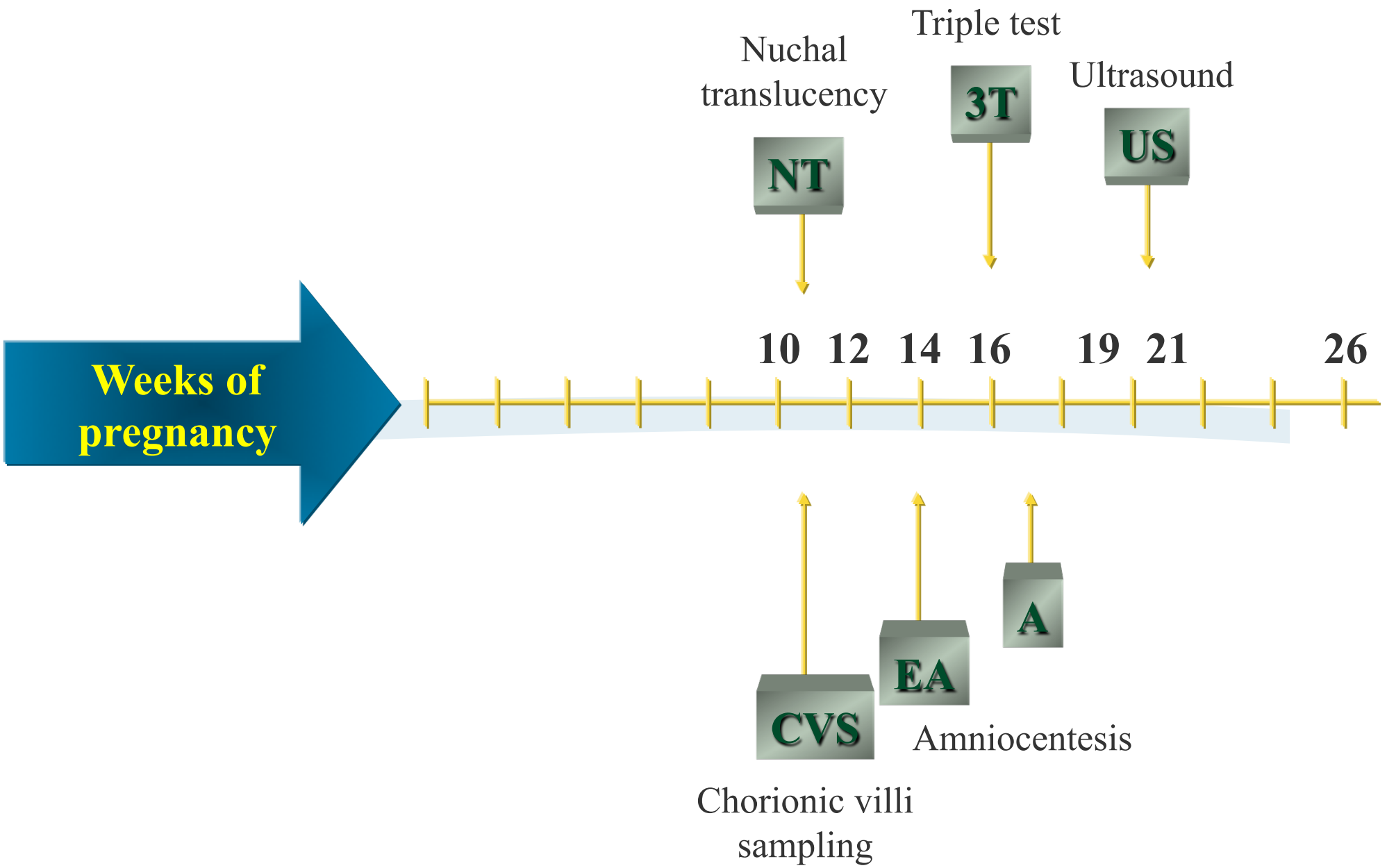


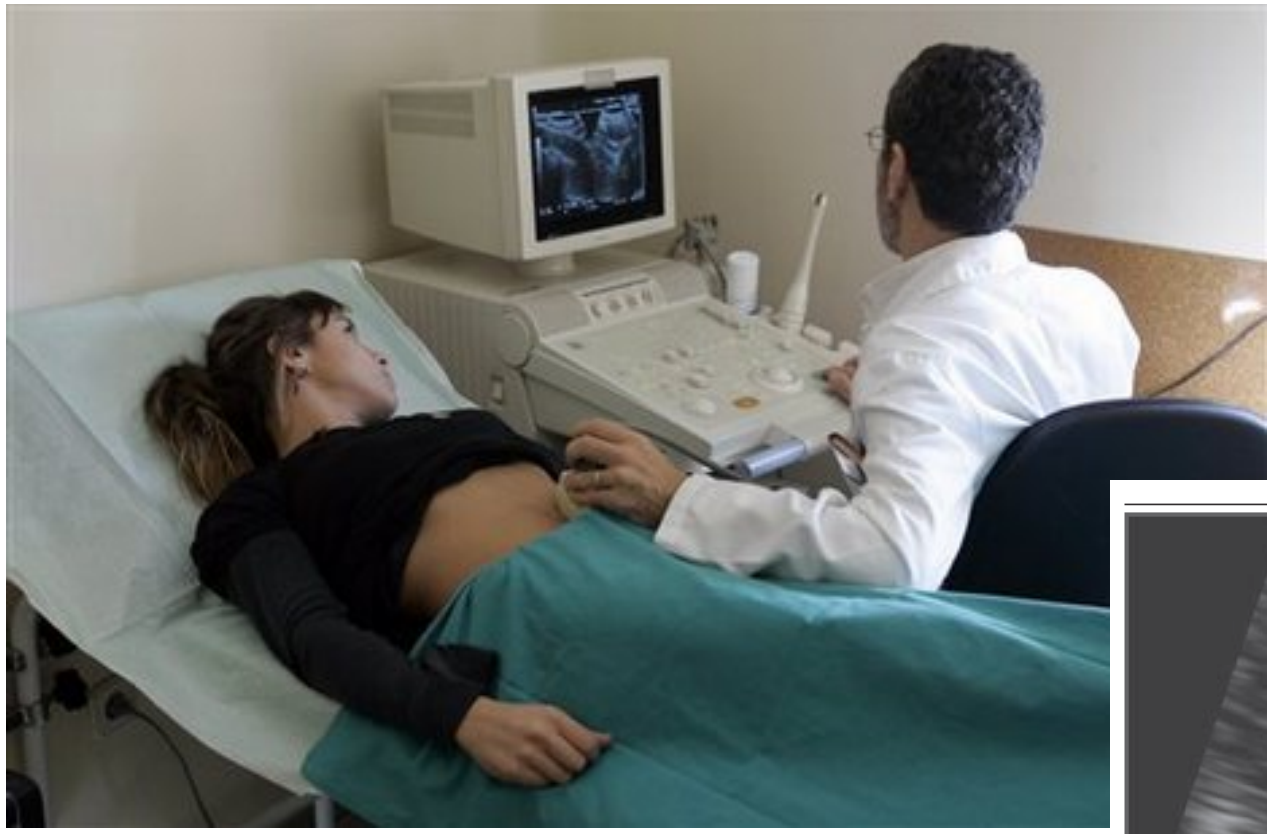
carriers who have a reproductive risk regardless of the partner



reciprocal translocation

- Carriers of a balanced chromosomal translocation (reciprocal)
- Exchange of genetic material between nonhomologous chromosomes
- No modifications in gene dosage
- frequency 1/520 newborns
- phenotypically normal


Nuchal translucency
NT
Triple test
3T
Ultrasound
US
Weeks of pregnancy
10 12 14 16 19 21 26
CVS
Chorionic villi sampling
EA
A
Amniocentesis



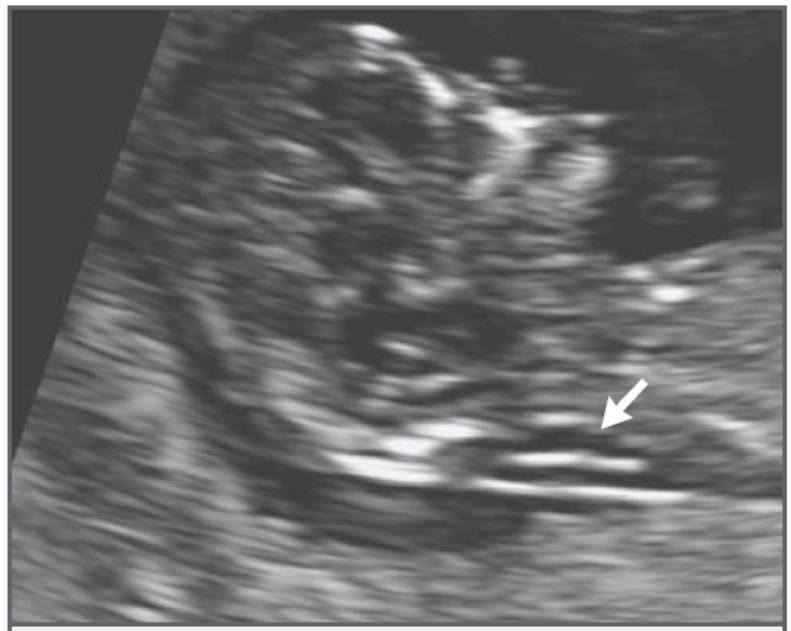
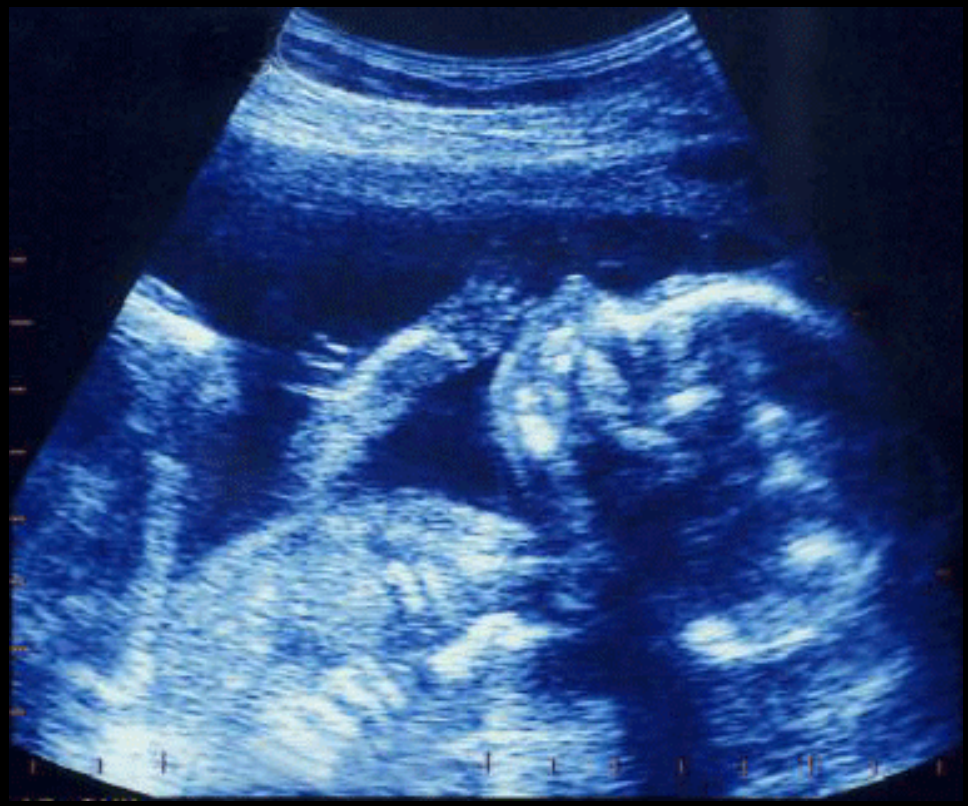


Figure 1. Nuchal Translucency in a Fetus.

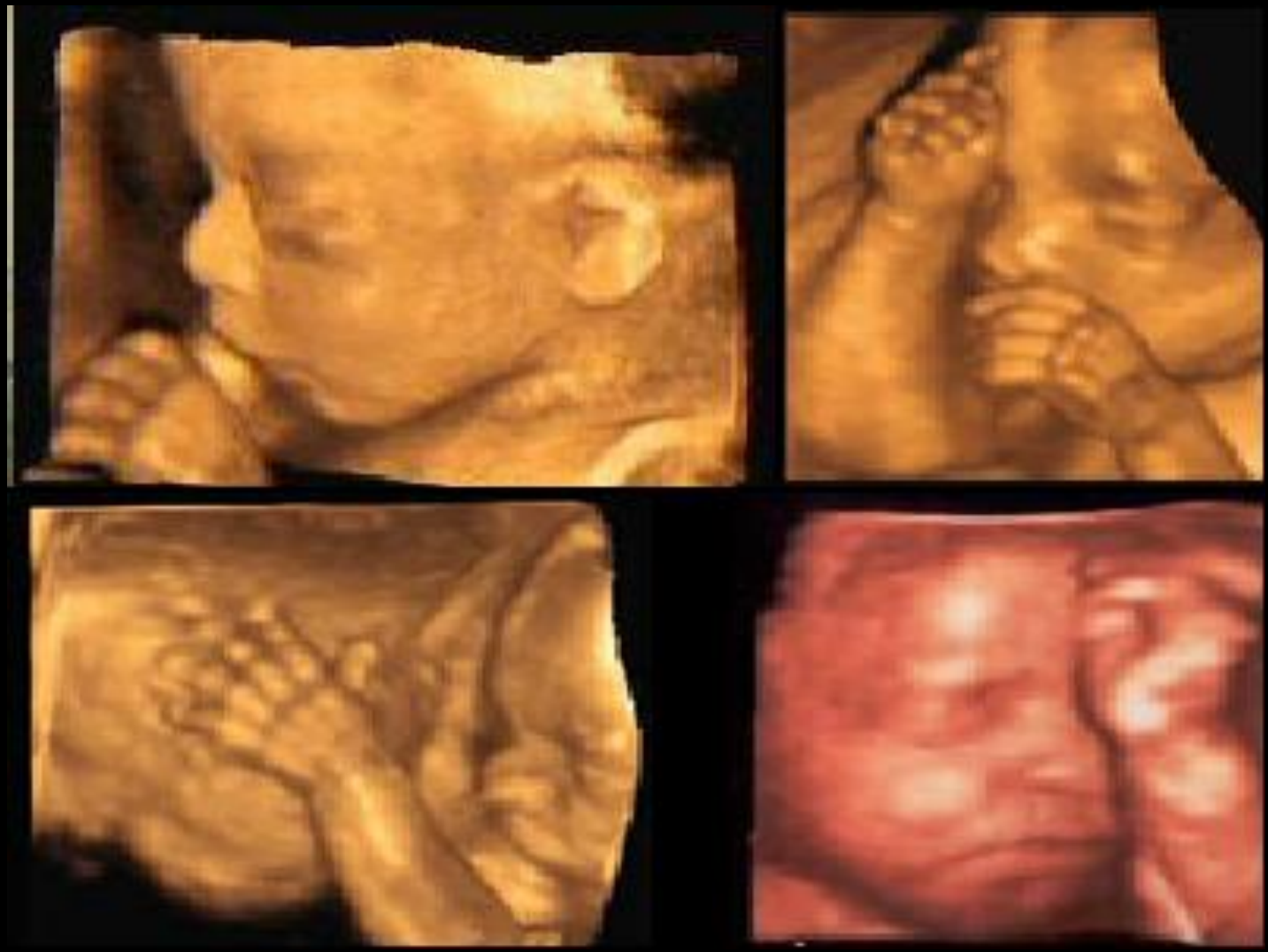
An ultrasonographic image of a fetus at 13 weeks' gestation shows the nuchal-translucency region at the back of the fetal neck (arrow).



triple test interpretation of results

Fetal anomaly	AFP Alpha-feto protein	Beta hCG Chorionic gonadothropin	uE unconjugated Estriol
NTD =neural tube defects*	↑	Normal	Normal
Trisomy 21	↓	↑	↓
Trisomy 18	↓	↓	↓

•NTD: anencephaly, spina bifida (incomplete closure of 1 or more vertebrae) and encephalocele (herniation of brain tissue)

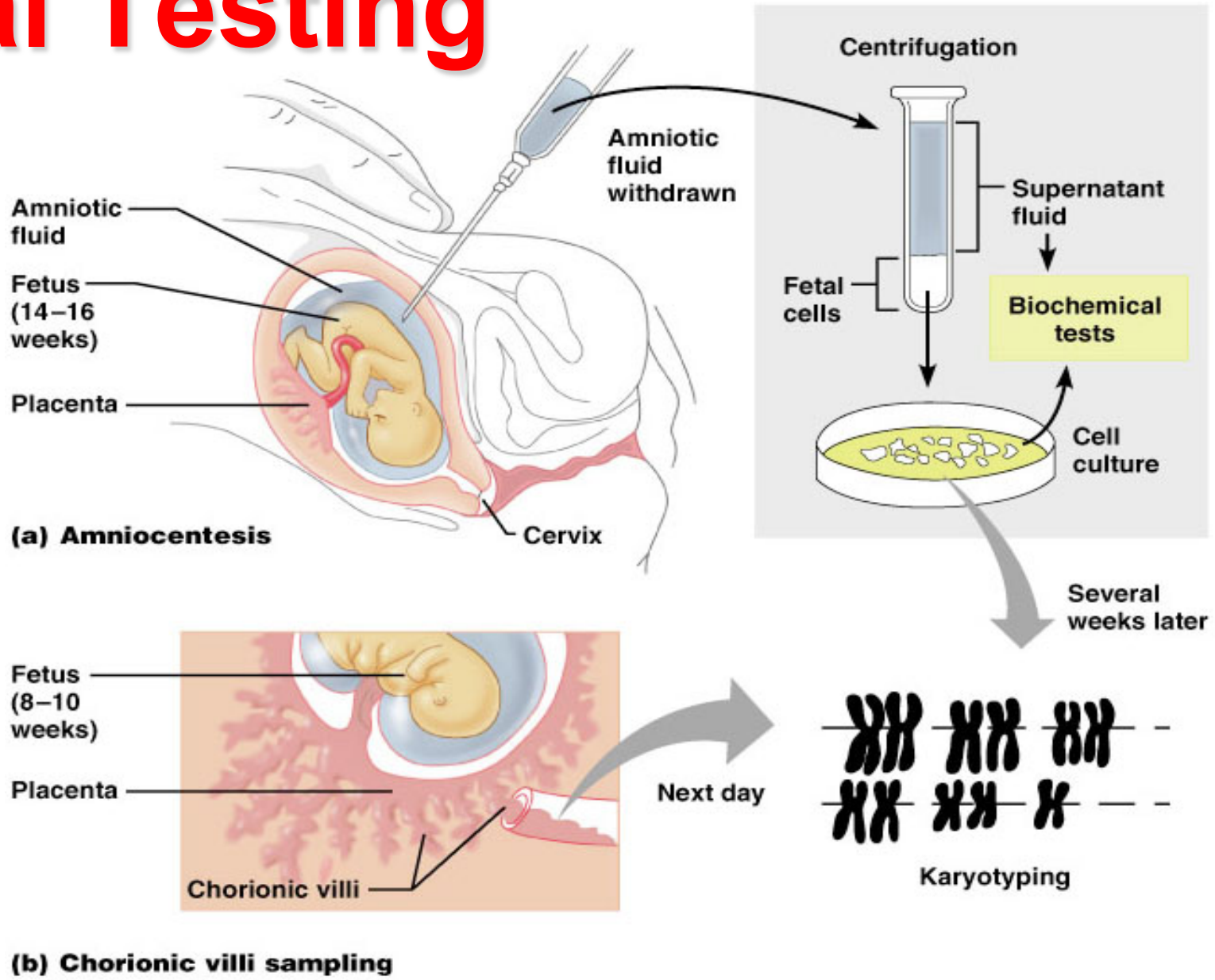


prenatal cytogenetics

- from amniocytes
- from chorionic villi
- should be representative of fetal cells
- difficult to obtain

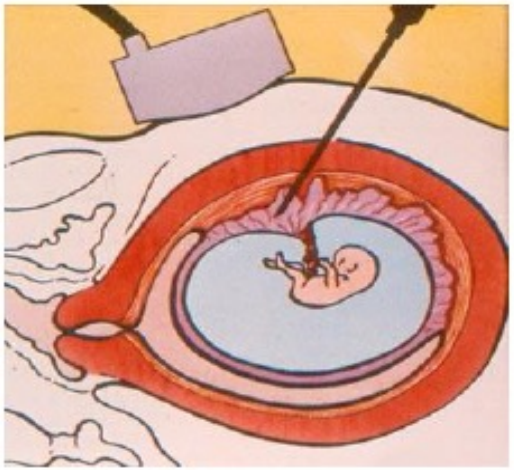
couple with family history of chromosomal abnormalities is indication of executing a fetal karyotype and extending the investigation to relatives

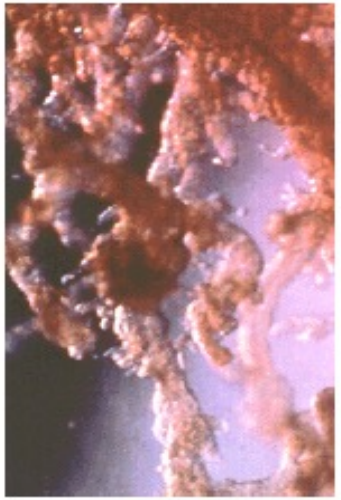
Fetal Testing



Chorionic villous sampling

Villi constitute a placental layer interposed between the basal decidua adhering to the uterus wall, and the chorial plate situated externally in the fetal side of placenta. In villi many actively reproducing cells are present which allow to study the karyotype.

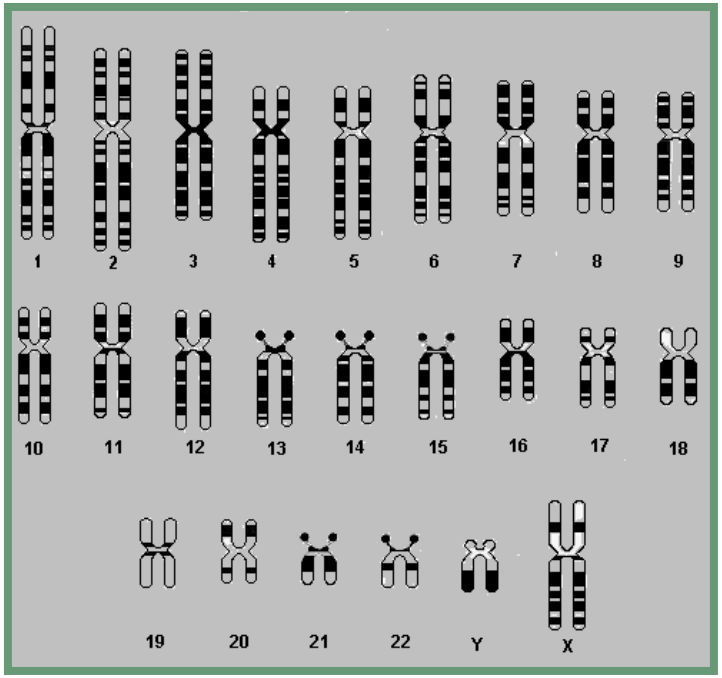




Microscopic image of chorionic villi

Chromosomal analysis

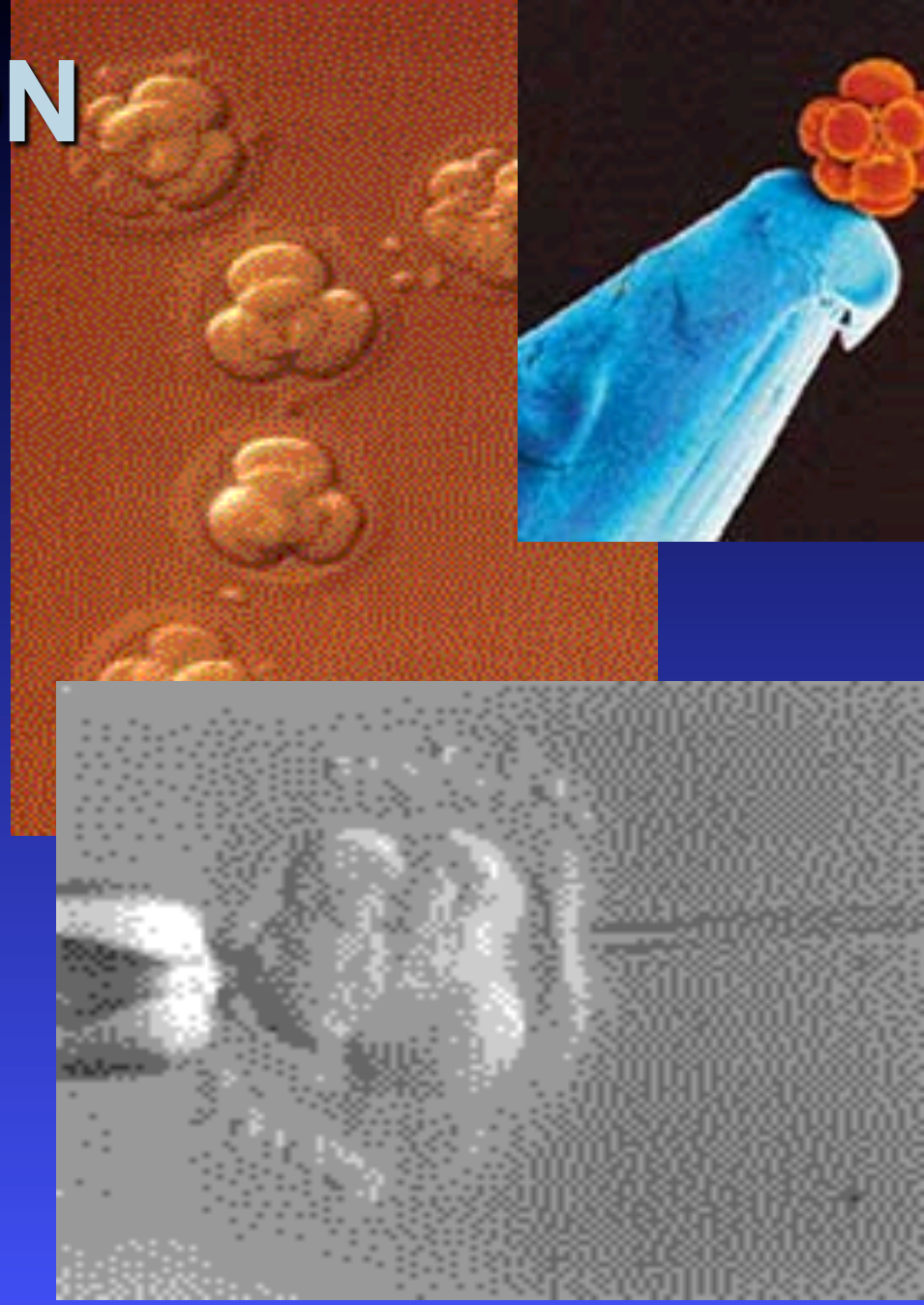
- Study of the fetal chromosomal arrangement on chorionic villous, amniotic fluid and fetal blood.



- Turnaround time varies depending on the sample analysed (1-3 weeks).

PREIMPLANTATION DIAGNOSIS

Preimplantation genetic diagnosis (PGD) is a new procedure that allows to obtain early prenatal diagnosis for chromosomal anomalies



PGD

- PGD refers to genetic profiling of embryos prior to implantation, and sometimes even of oocytes prior to fertilization.

- PGD thus is an adjunct to assisted reproductive technology, and requires in vitro fertilization (IVF) to obtain oocytes or embryos for evaluation.

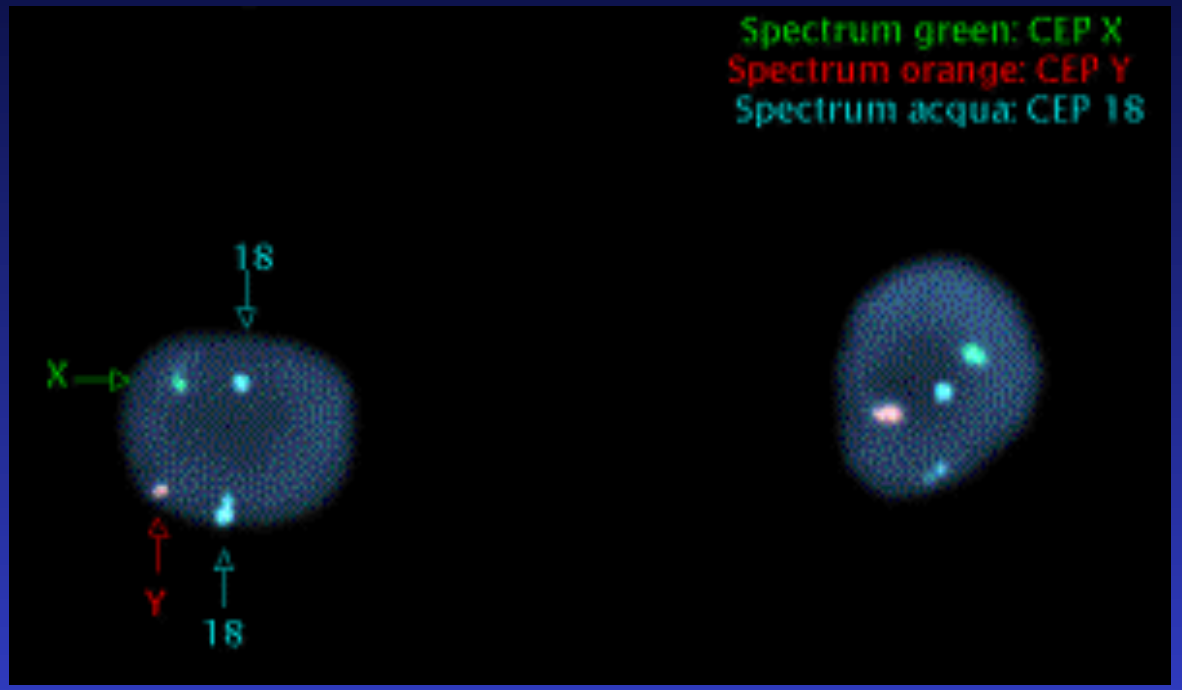
- PGD is considered in a similar fashion to prenatal diagnosis.

- When used to screen for a specific genetic disease, its main advantage is that it avoids selective pregnancy termination as the method makes it highly likely that the baby will be free of the disease under consideration.

- PGD is useful when there are previous chromosomal or genetic disorders in the family and within the context of in vitro fertilization programs.

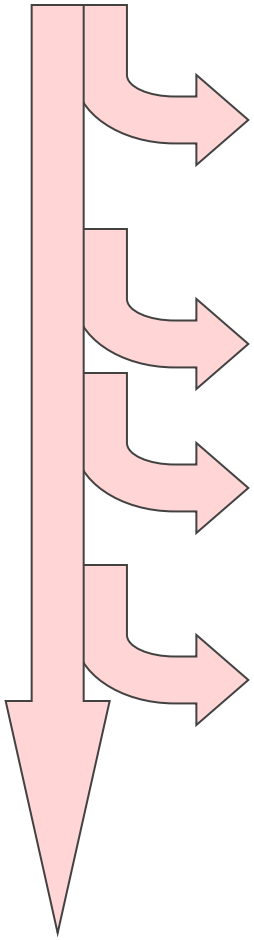
Affected
Affected
Affected
Biopsied cell
Transfer only unaffected embryos to the patient
A
B
C
(a)
Remove oocytes following superovulation
(d)
(e)
♂
1
2
3
4
5
6
8
Male-specific fragment

Preimplantation diagnosis



- **The employment of PGD by using molecular probes for different chromosomes allows the analysis of some aneuploidies in blastomeres.**

Conception



20% abortion before implantation

42% abortion within 7th week of pregnancy

10% abortion between 7th and 12th week of pregnancy

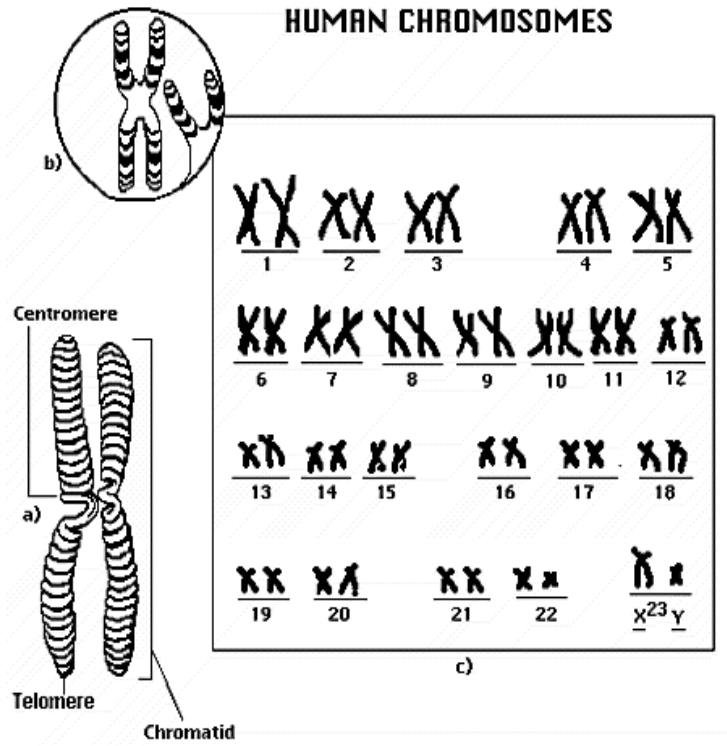
3% abortion after 12th week of pregnancy

BIRTH only 25% of conceptions

Frequency of chromosomal abnormalities in prenatal diagnosis

Maternal

Age	*A.F.*	*CVS*
35y	0.76 %	0.78 %
40y	2.50 %	3.40 %
45y	8.33 %	7.14 %



Frequency of chromosomal abnormalities in germ cells

- Chromosomal abnormalities are present normally in a certain percentage of adult gametes.

- These abnormalities origin as new mutations during the gametogenesis of subjects with a normal chromosomal arrangement

Chromosomal abnormalities in sperm

Around 10% of fertile male sperm possess chromosomal abnormalities:

- 45% numeric abnormalities
- 55% structural abnormalities

(prevalently breaks)

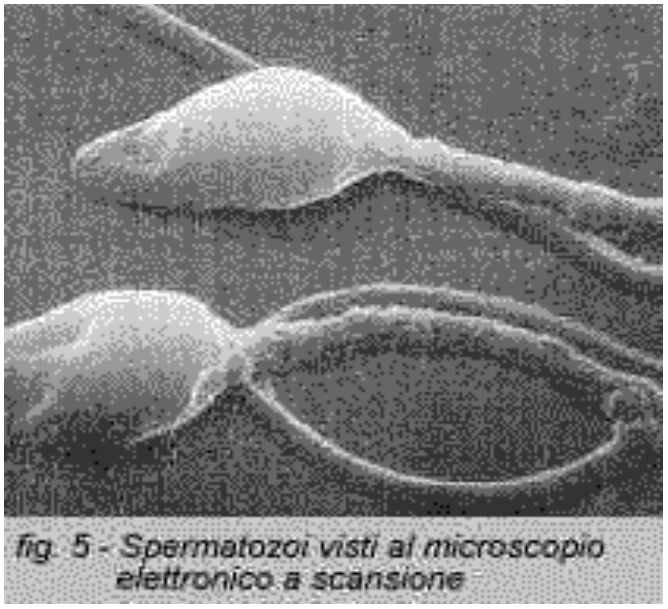
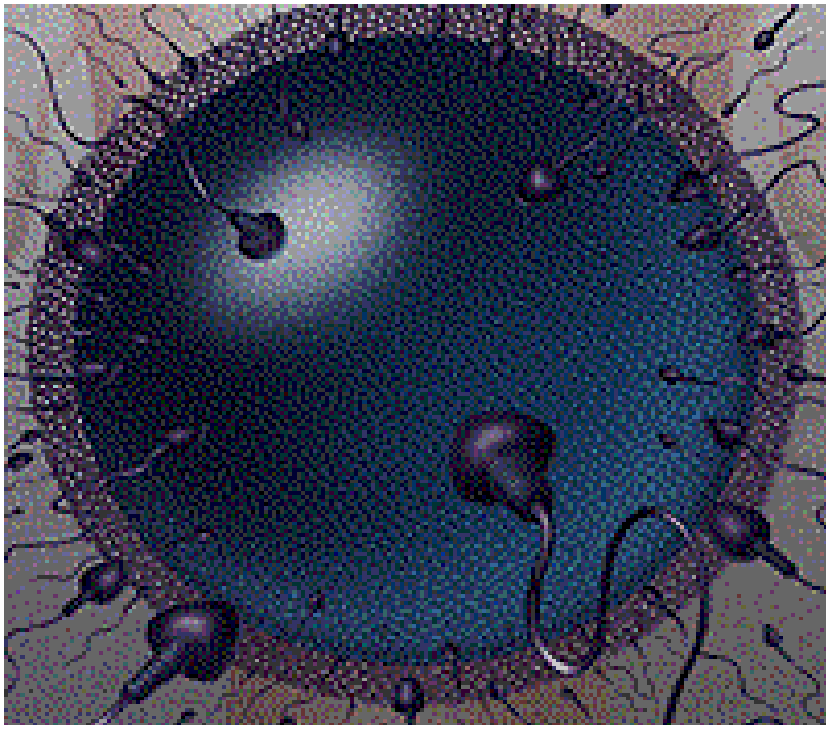


fig. 5 - Spermatozoi visti al microscopio elettronico a scansione

Chromosomal abnormalities in oocytes

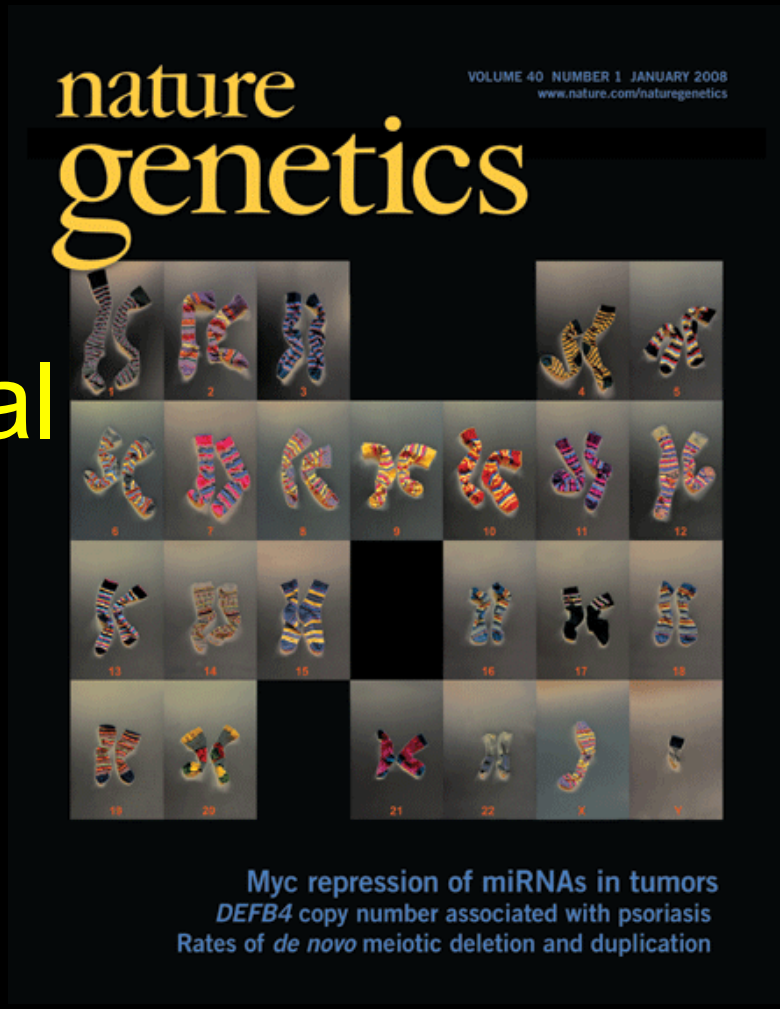
Around 25% of oocytes possess chromosomal abnormalities

(prevalently aneuploidies)



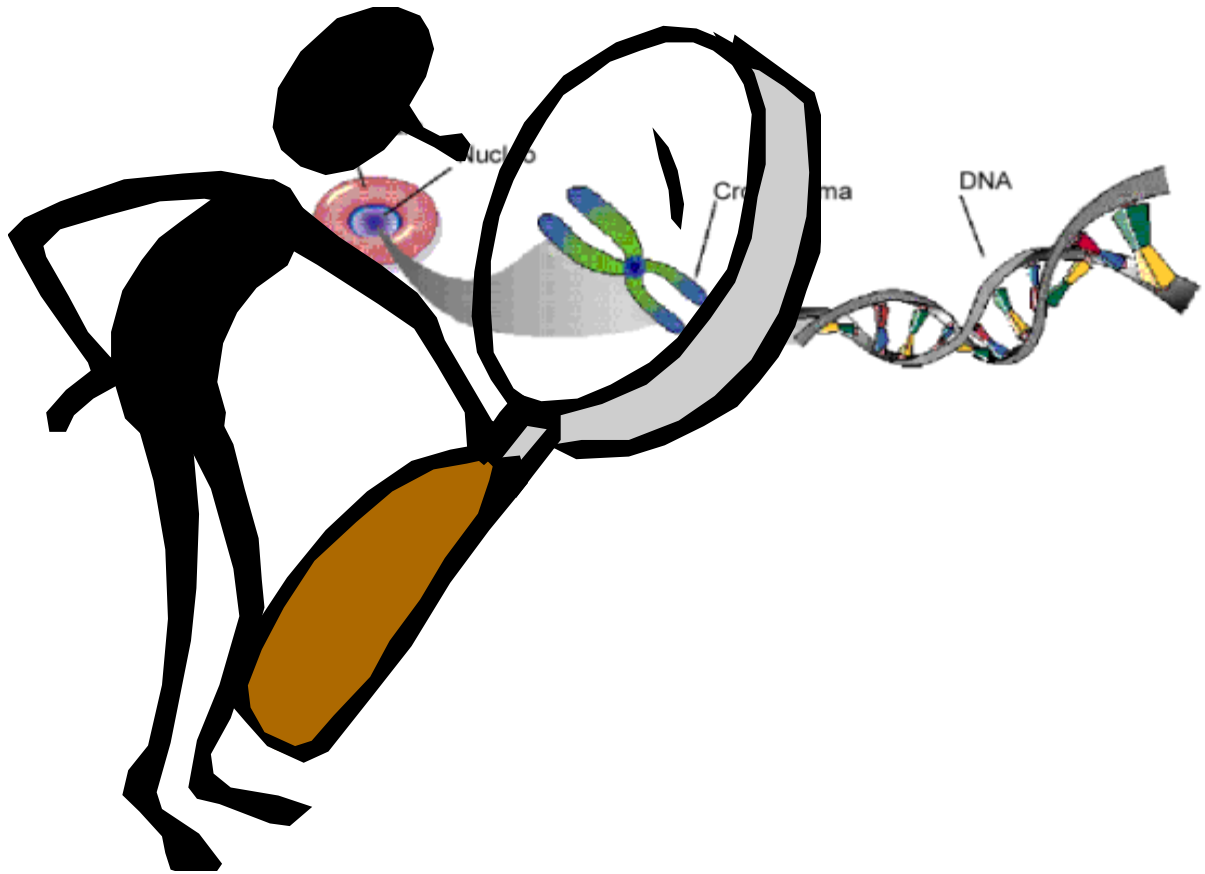
THE STUDY OF CHROMOSOMES: CYTOGENETICS

- Principles of cytogenetics
- classification
- frequency of chromosomal diseases
- the most frequent diseases
- molecular cytogenetics methods



Classical cytogenetics

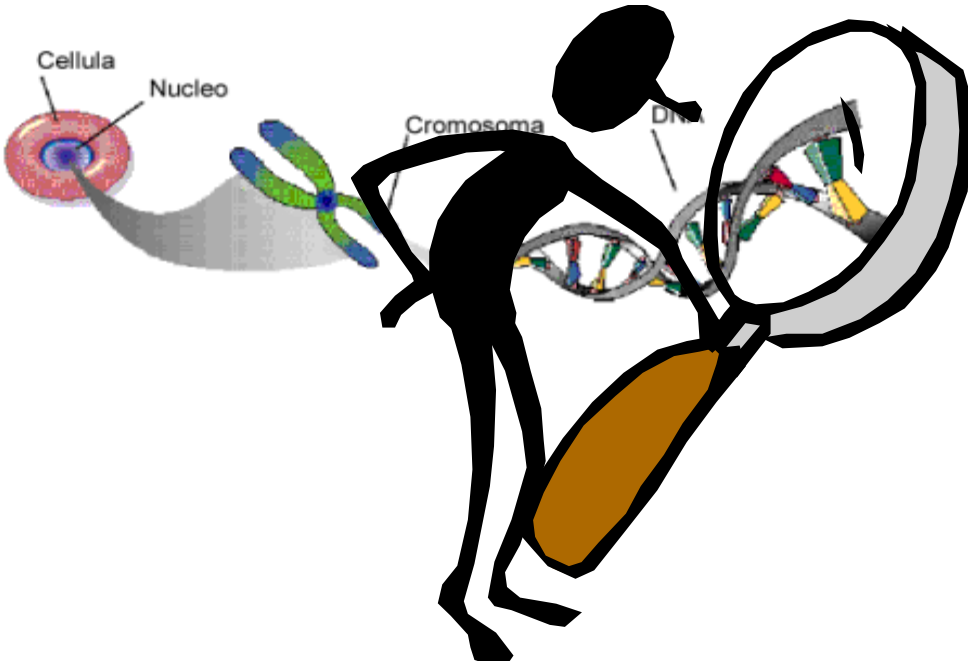
- Allows identification of chromosomal rearrangements involving no less than 5 Mb.



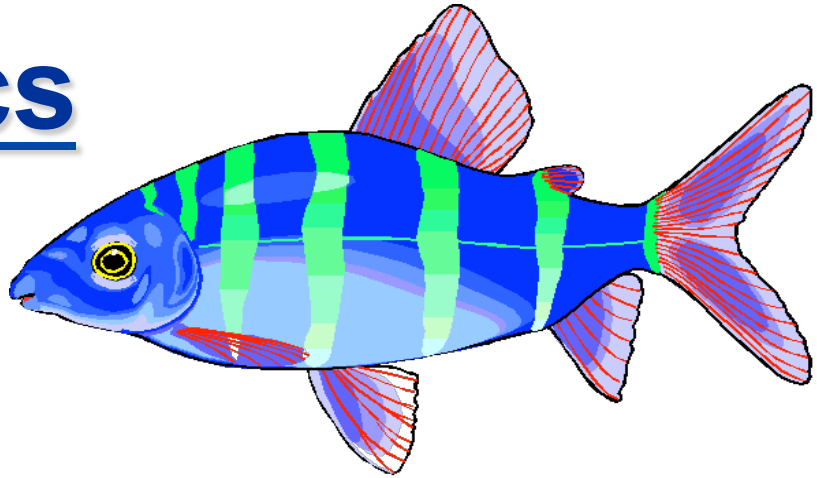
When the karyotype (classical cytogenetics) is not enough

Molecular cytogenetics

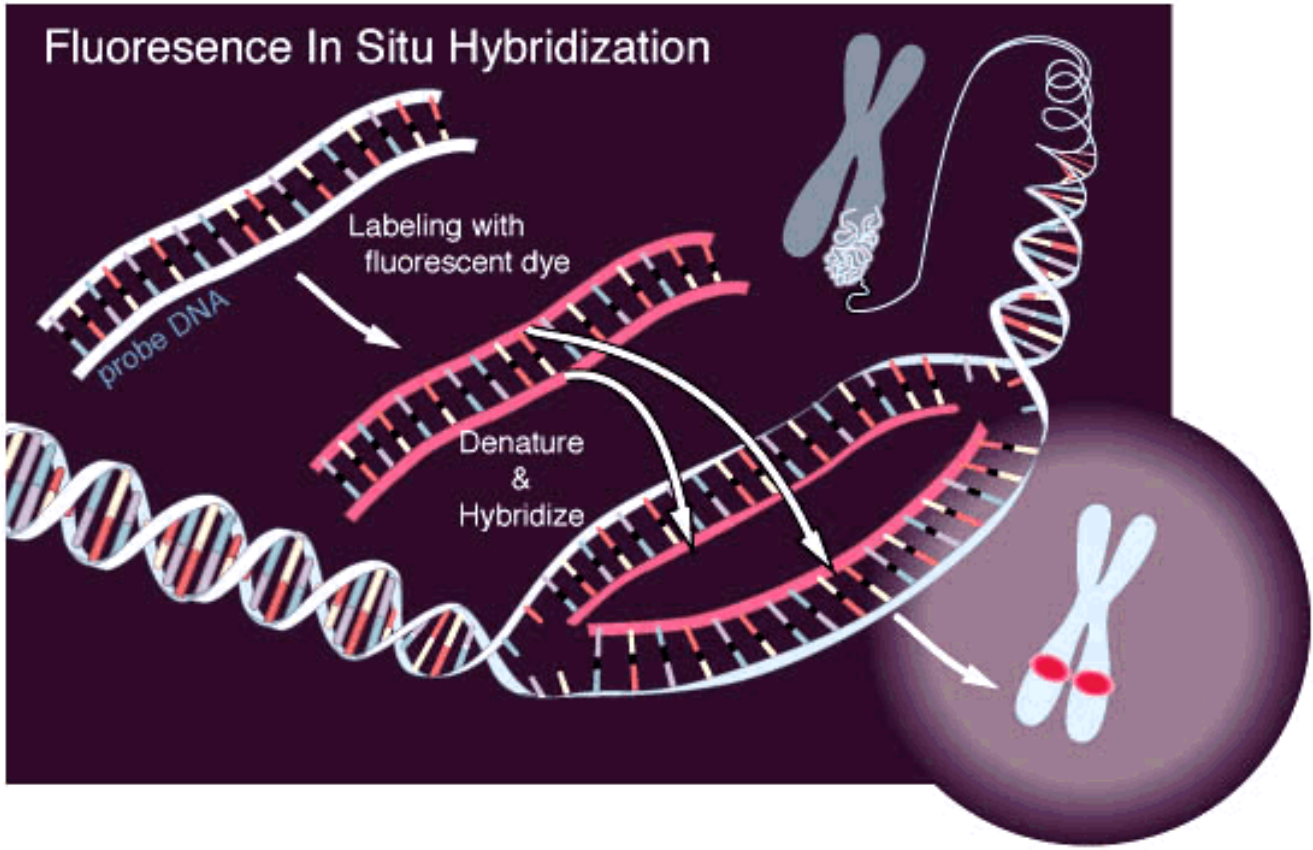
Combines the possibility of DNA analysis, proper of molecular biology techniques, with chromosome structure whose study is the subject of classical cytogenetics.



Molecular cytogenetics



Allows a targeted analysis of a chromosomal region allowing to highlight rearrangements of several hundred kilobases.



Clinical molecular cytogenetics techniques

- **FISH** (fluorescence in situ hybridization)
- **PRINS** (primed in situ labeling)
- **PCR *in situ*** (polymerase chain reaction *in situ*)
- **CGH** (comparative genomic hybridization)
- **NGS** (next generation sequencing)
- others

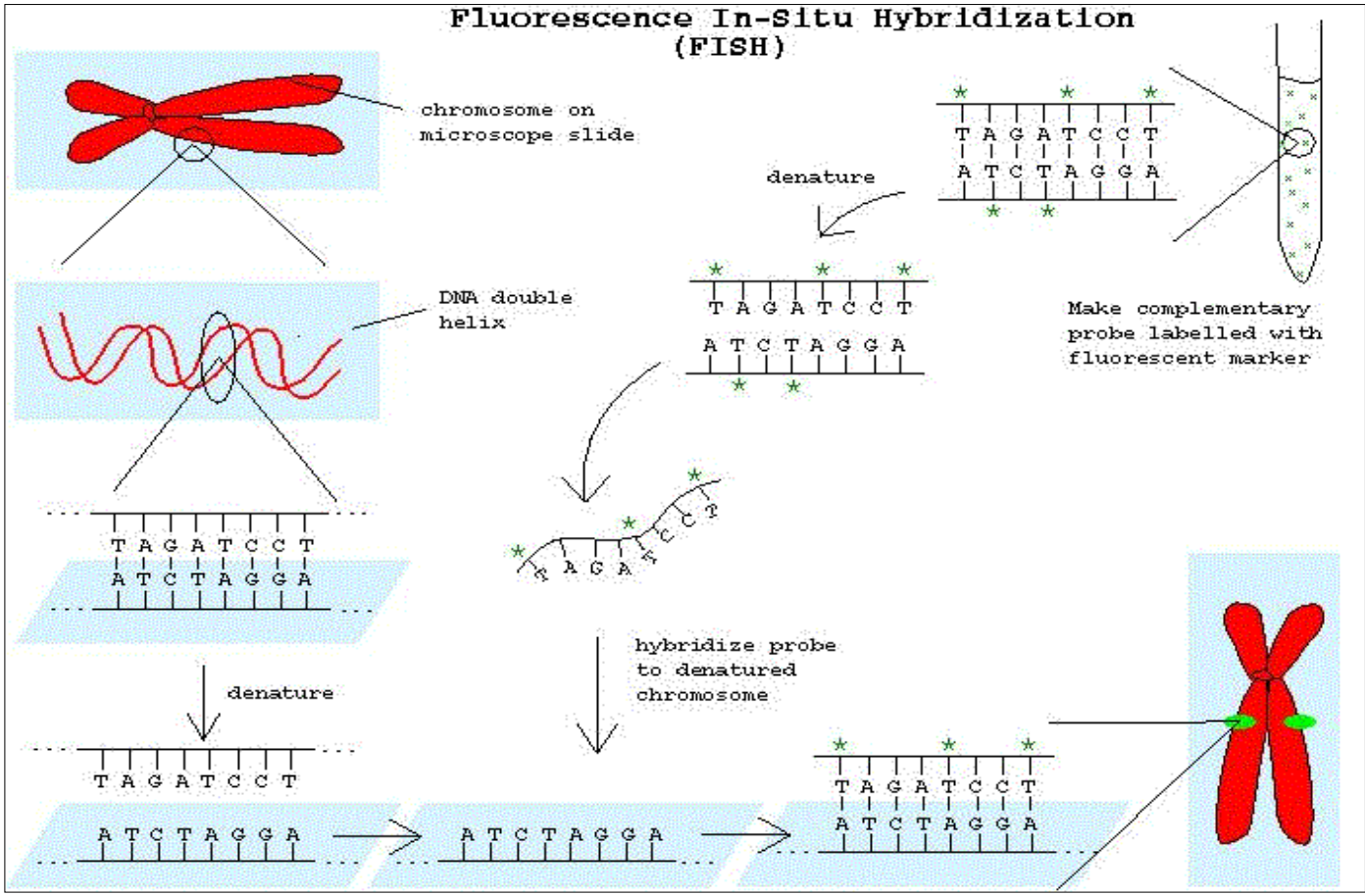
Molecular cytogenetics techniques

- **FISH** (fluorescence in situ hybridization)
- **CGH** (comparative genomic hybridization)
- ecc.

FISH (Fluorescence *in situ* hybridization)

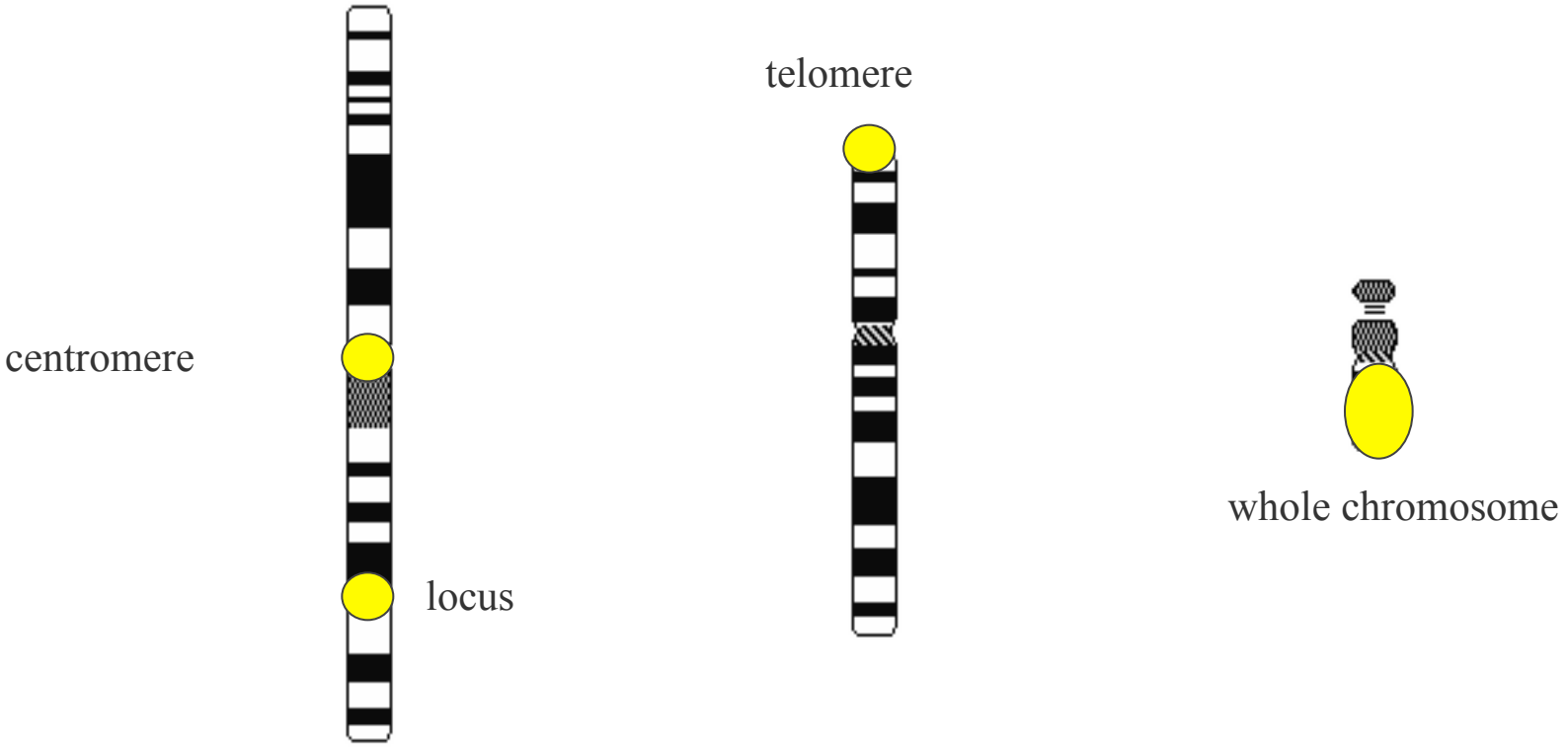
- It is a hybridization technique that allows, after fixation of metaphases and interphasic nuclei on a slide, to identify specific sequences in nucleic acids.

- This identification is made through non-isotopic labeled probes, using fluorochromes that emit at different wavelengths.

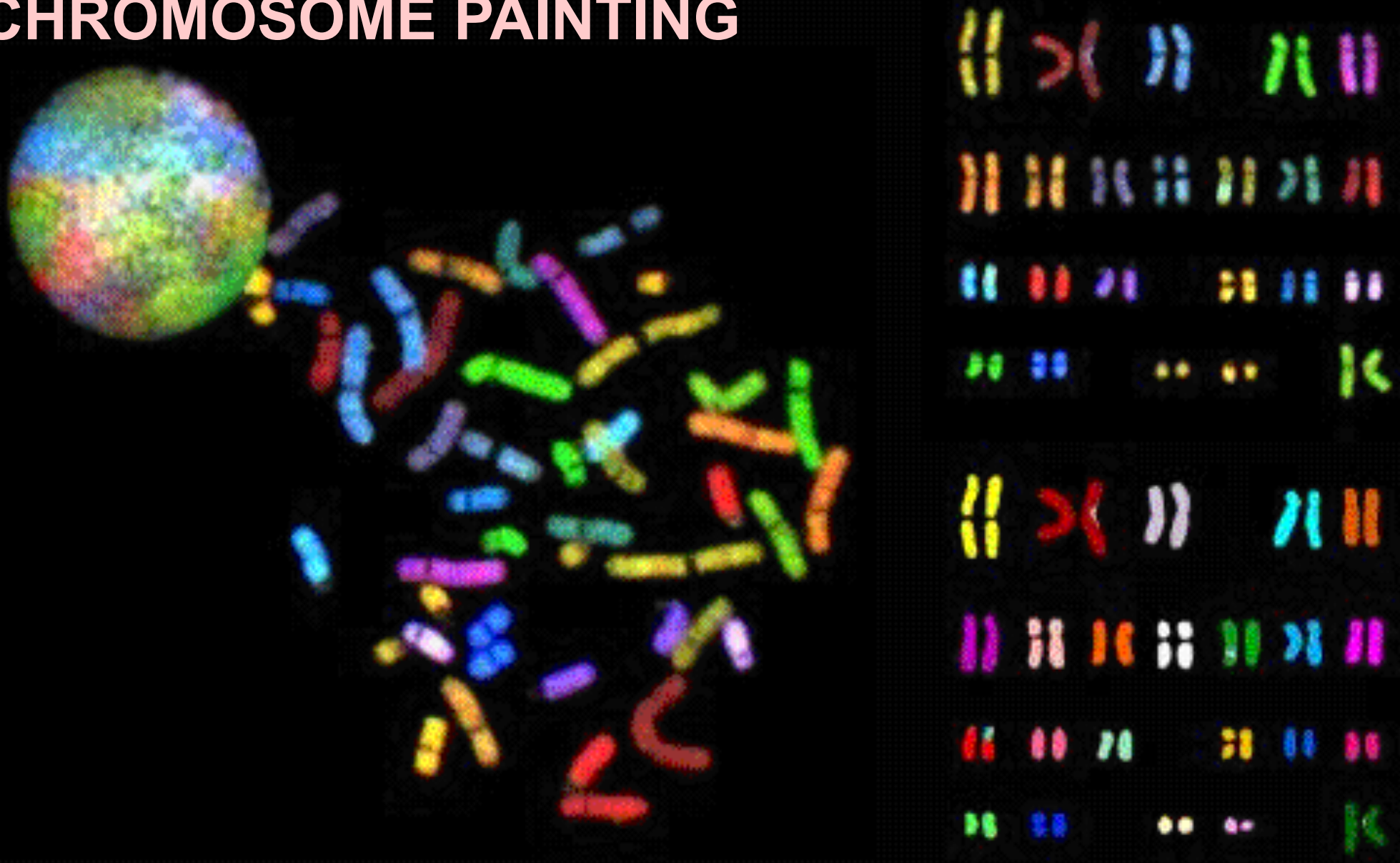


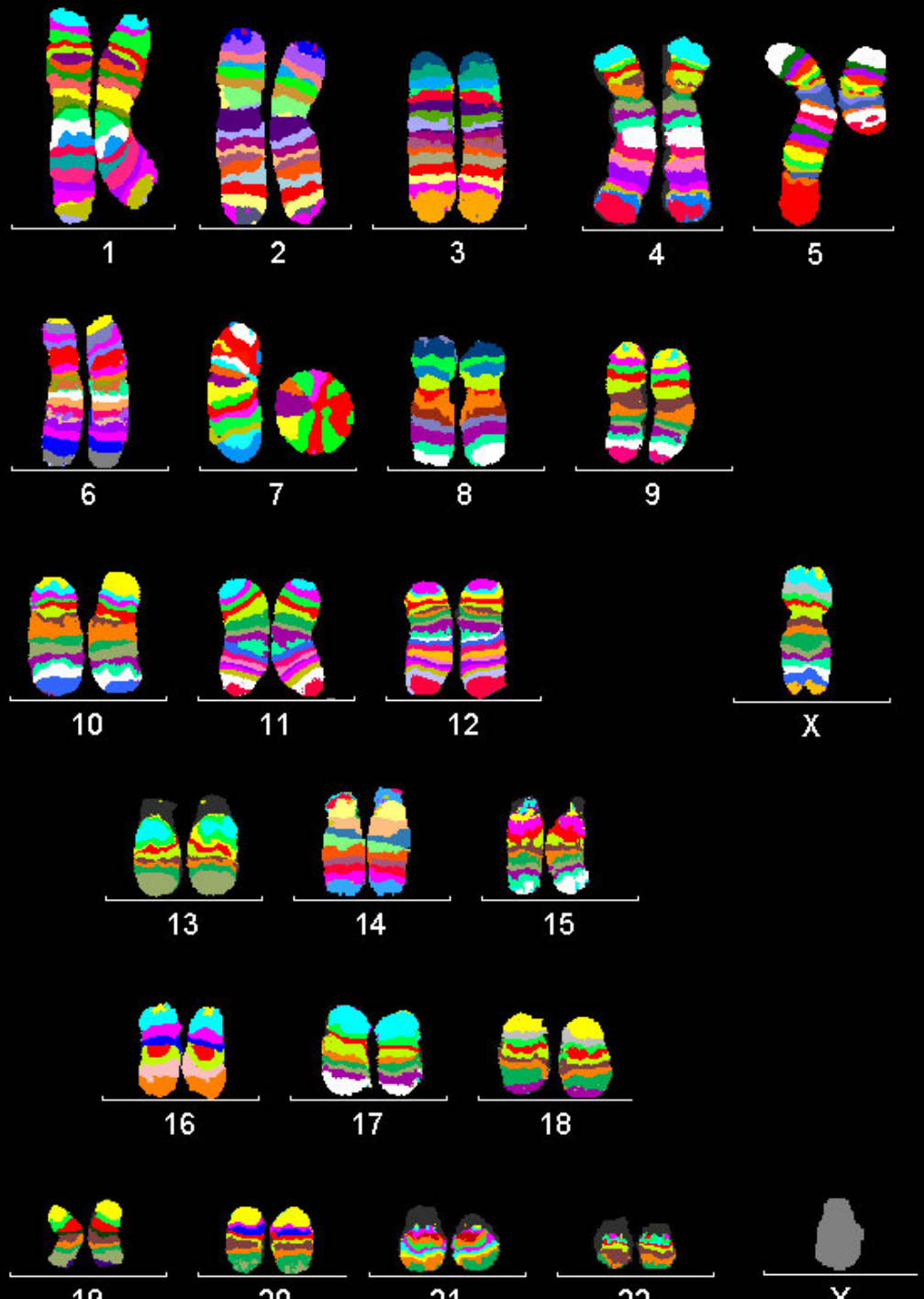
FISH probes

FISH probes must be targeted, cannot be helpful in overall genomic analyses



CHROMOSOME PAINTING




1
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X
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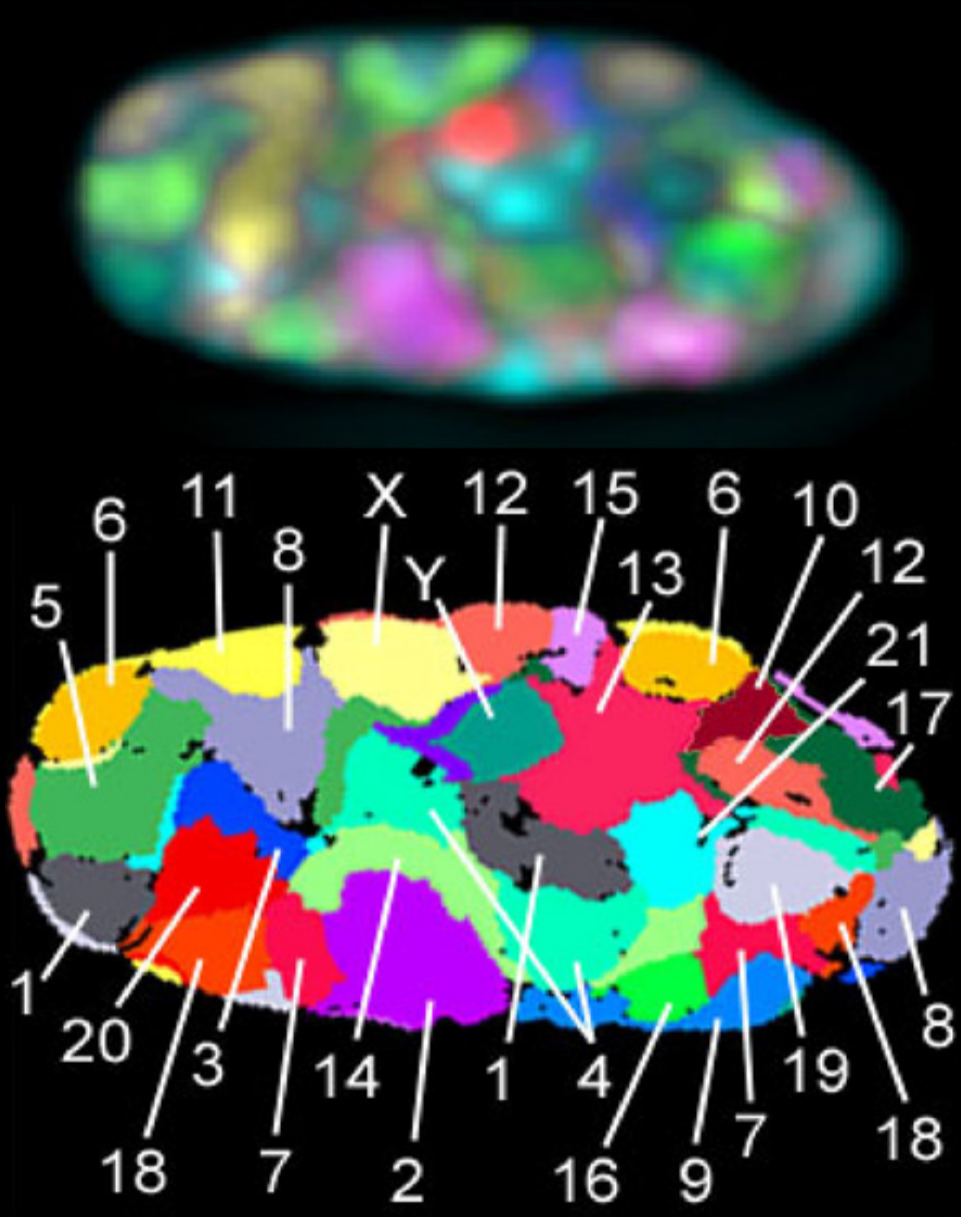
18


5
6
11
8
X
Y
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21
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1
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9
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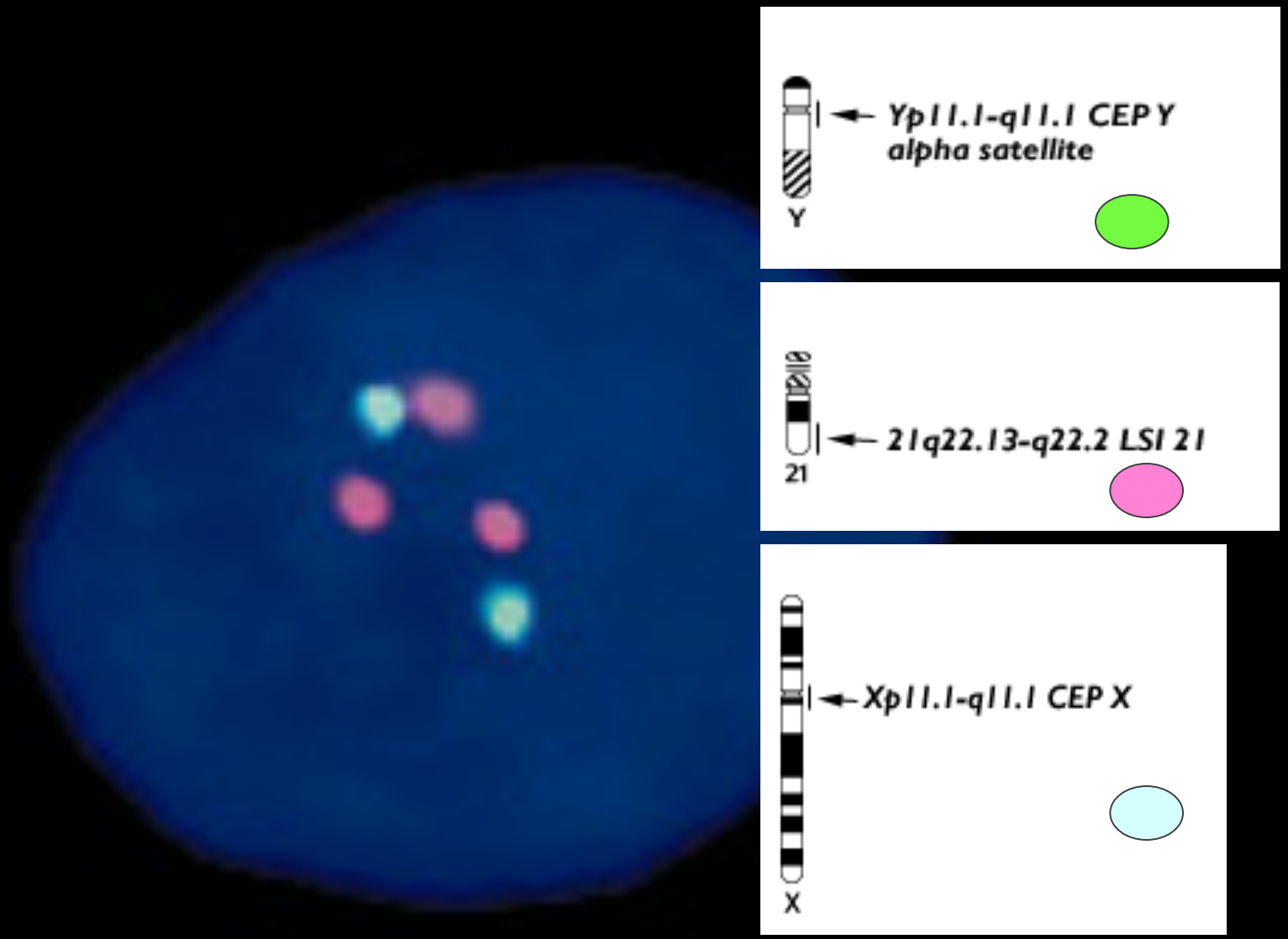
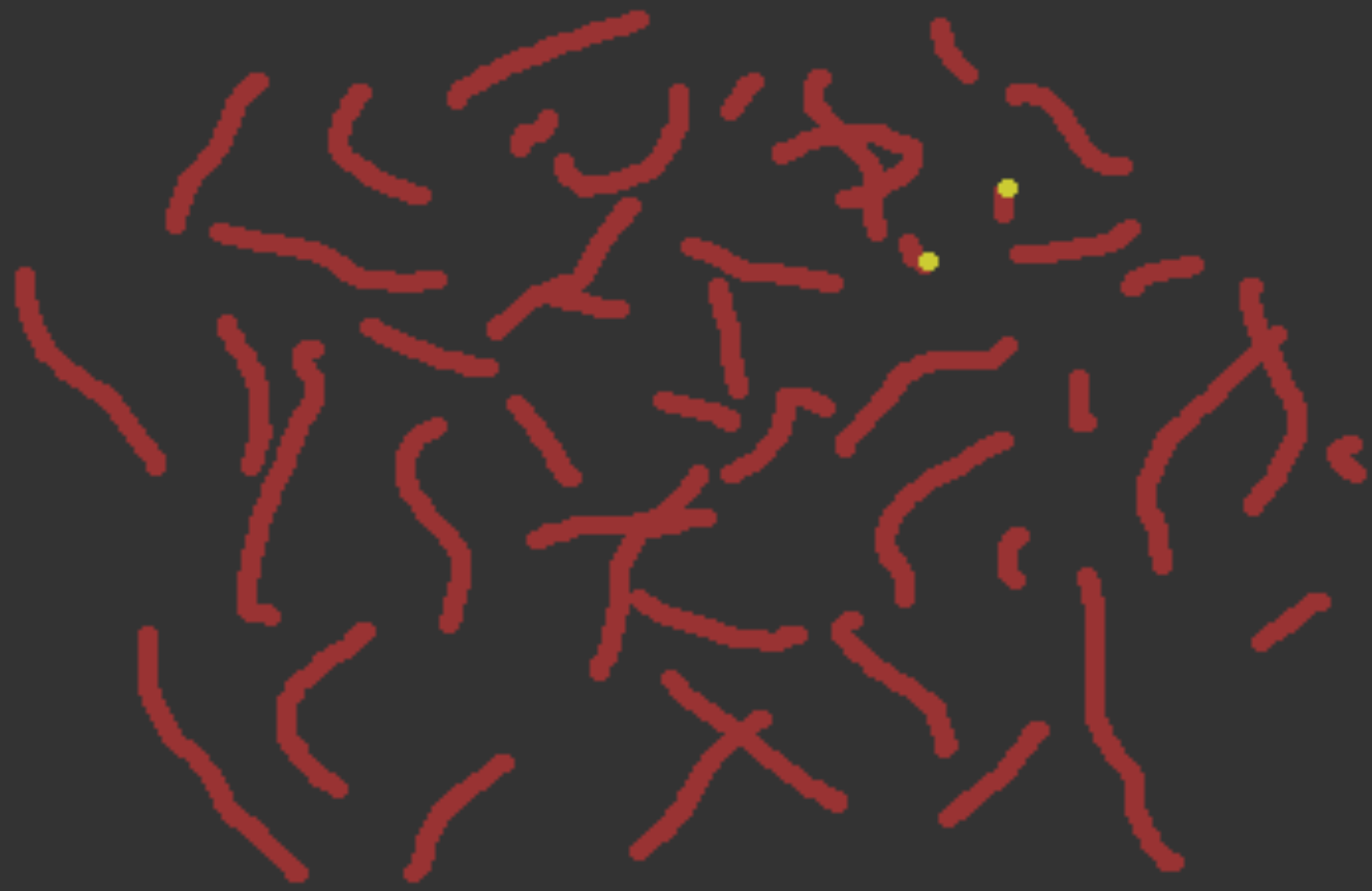
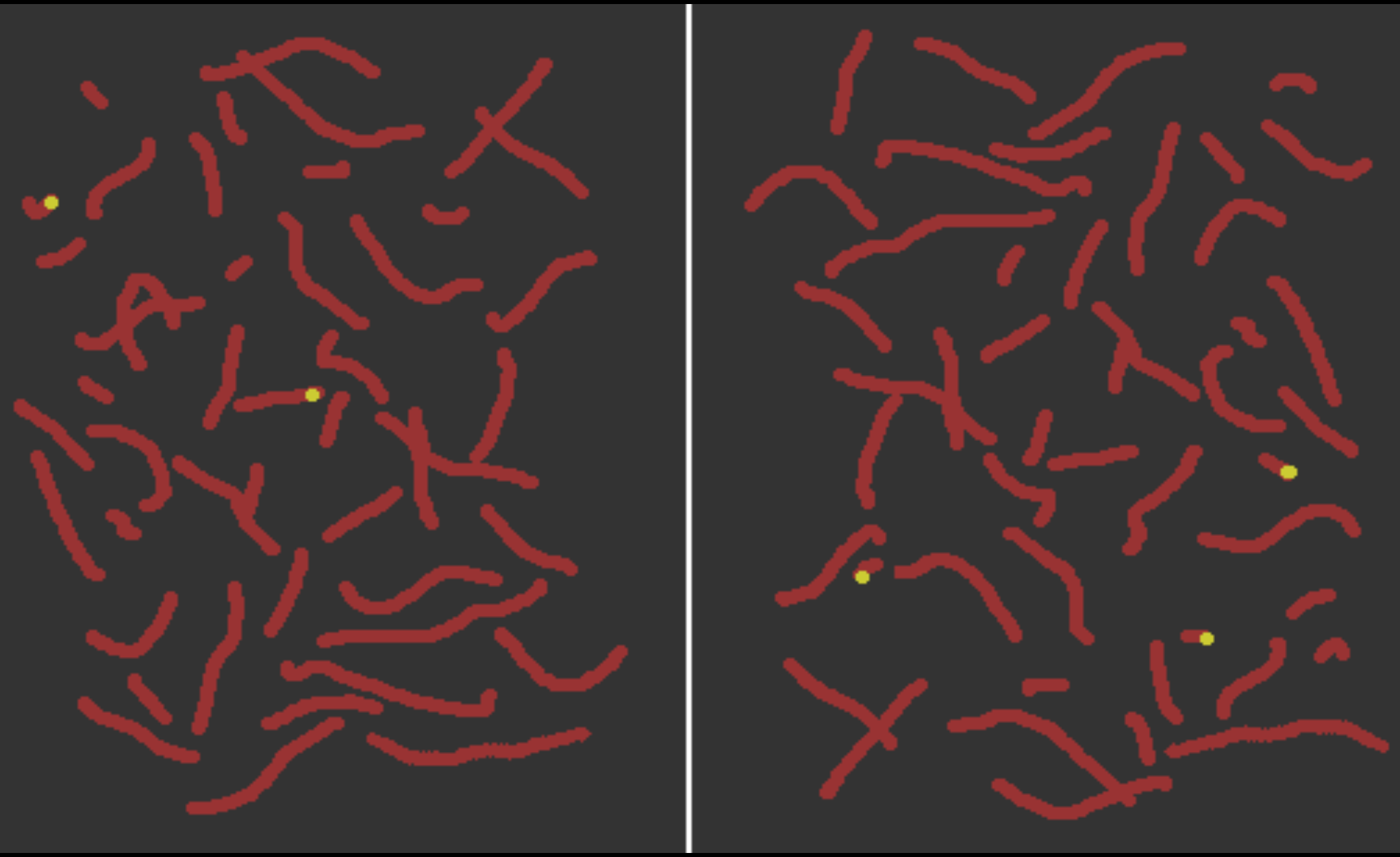
19
18
8

DIAGNOSIS OF ANEUPLOIDIES







Down syndrome

FISH IN PRENATAL DIAGNOSIS

- **from 15 ml amnyotic fluid**

  metaphase: - Karyotype
  - FISH for microdeletion diagnosis
  - FISH for chromosomal rearrangement diagnosis

- **from 2 ml amnyotic fluid**

  nucleus: - FISH for sex determination
  - FISH for numerical anomalies diagnosis

FISH

ADVANTAGES

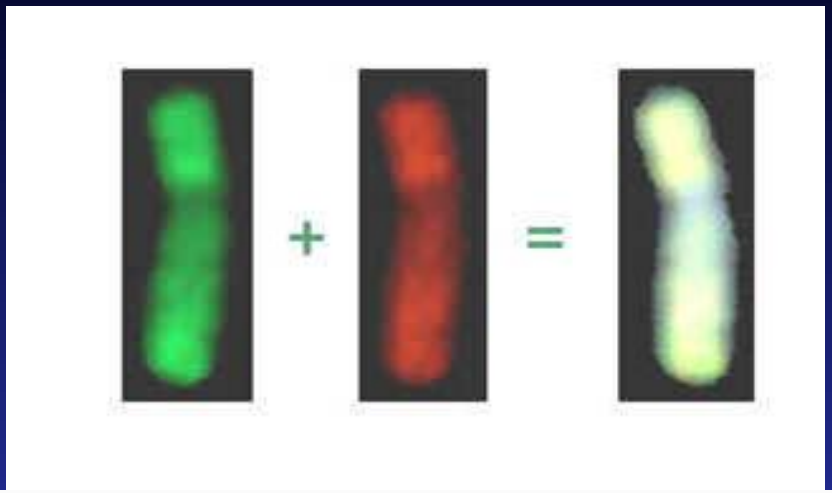
- speed
- identification of microdeletions and complex rearrangements
- diagnosis on nuclei

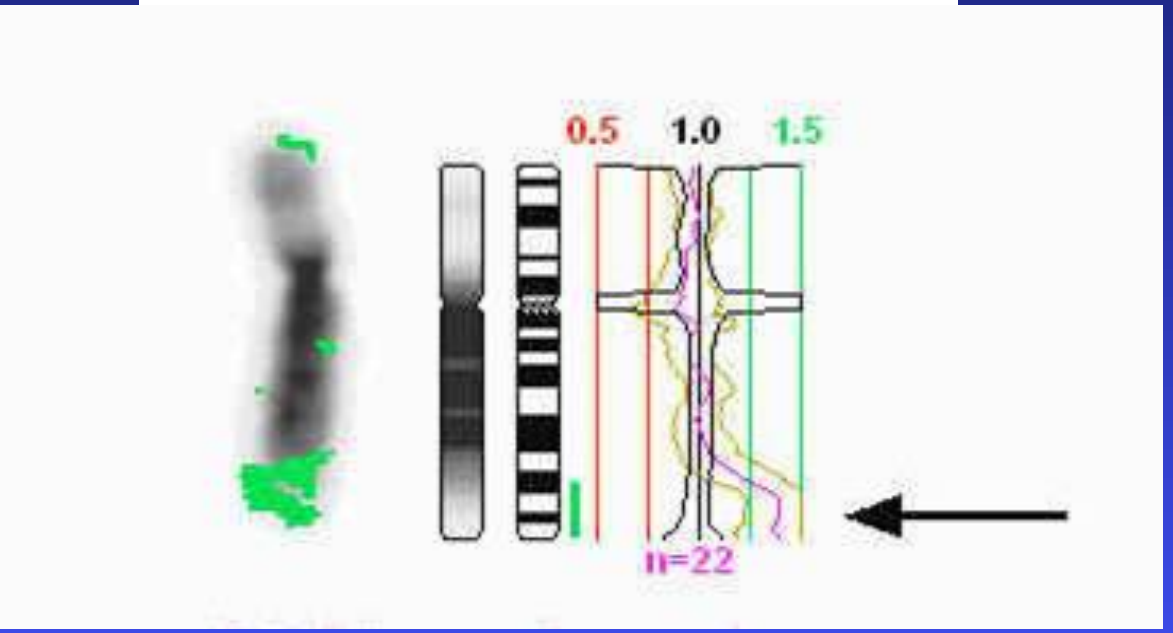
DISADVANTAGES

- expensive
- uncomplete diagnosis

Remember that..

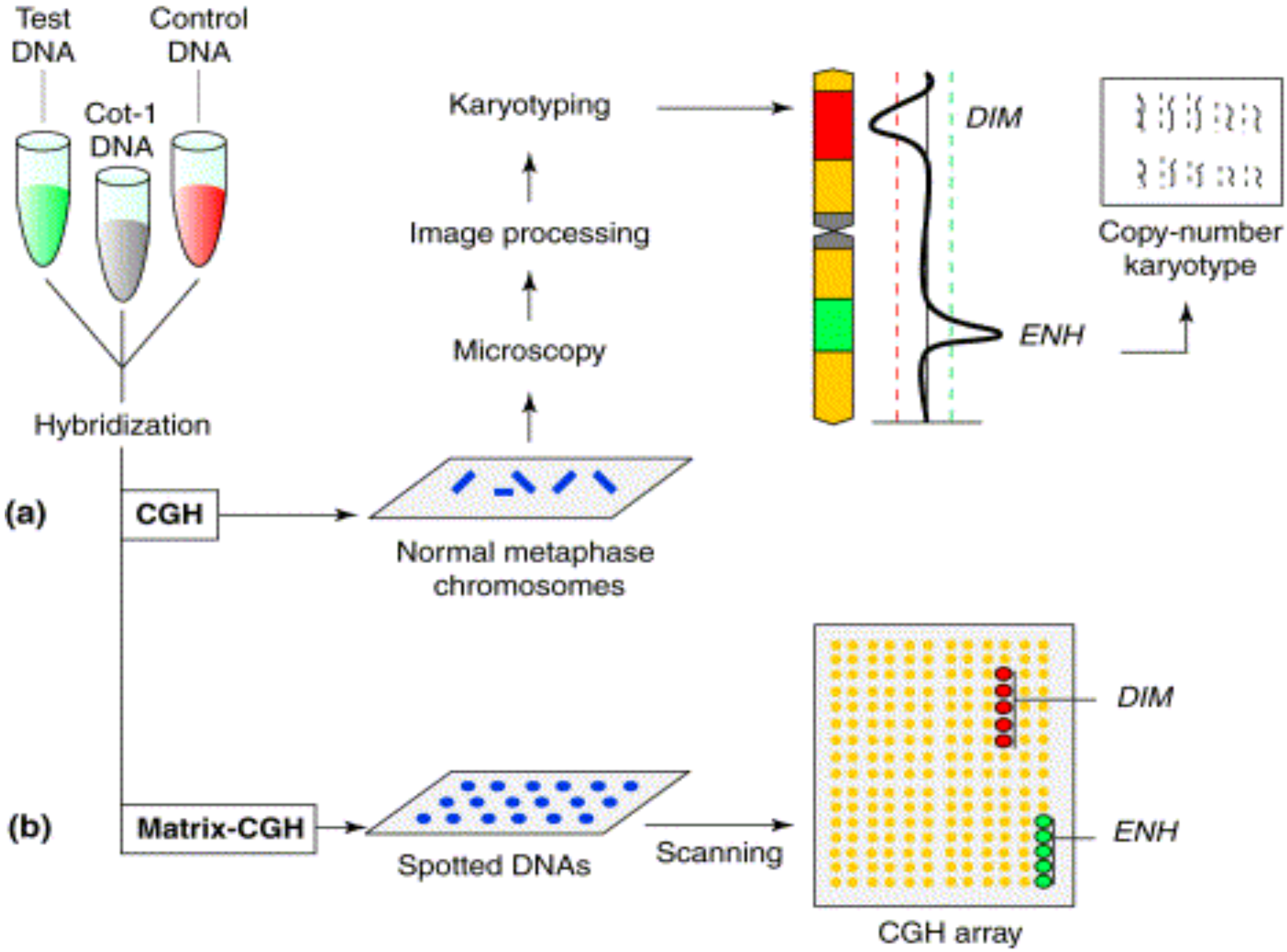
- 95% of chromosomal anomalies consist of aneuploidies involving chromosomes 21, 13, 18, X and Y.

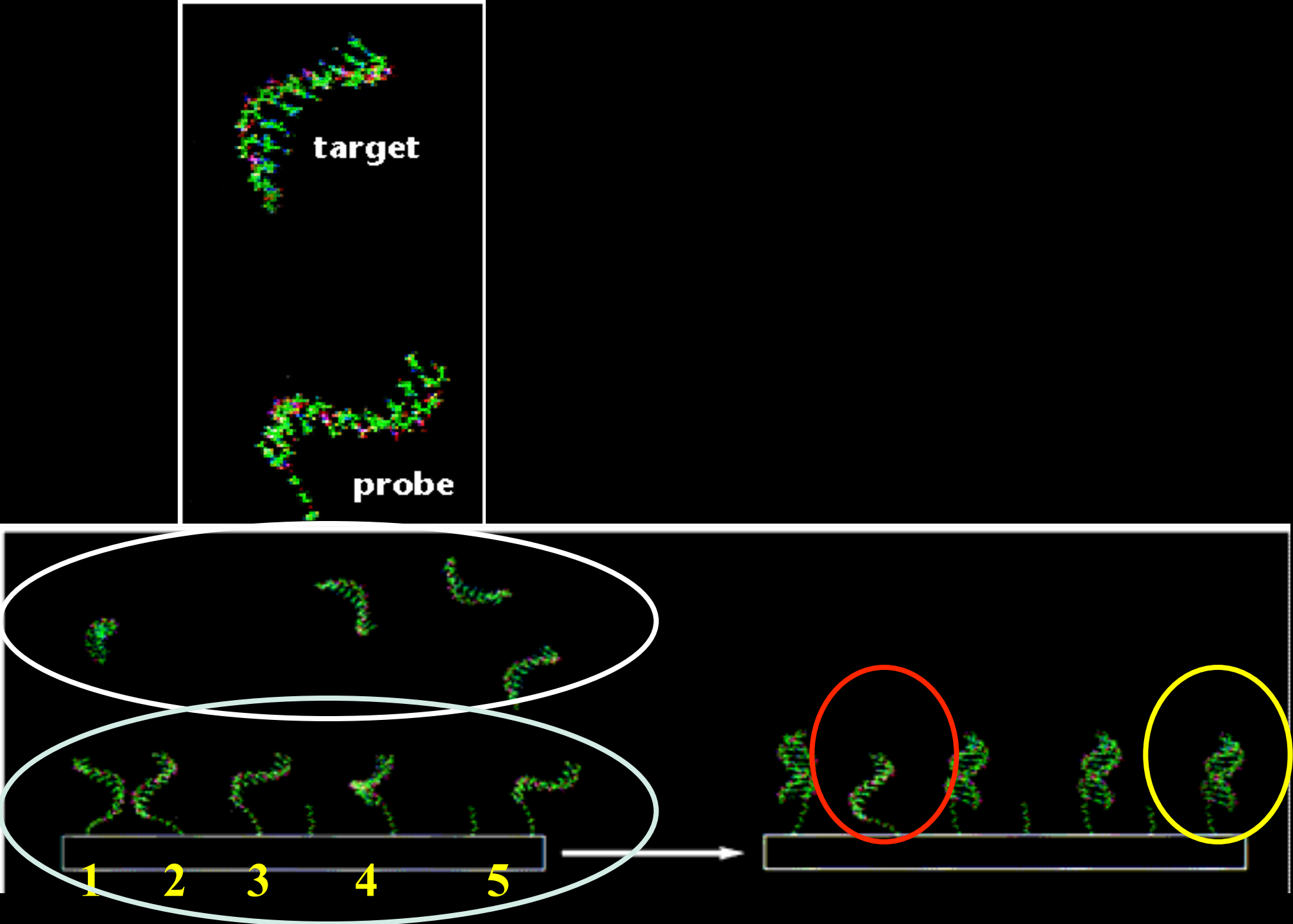


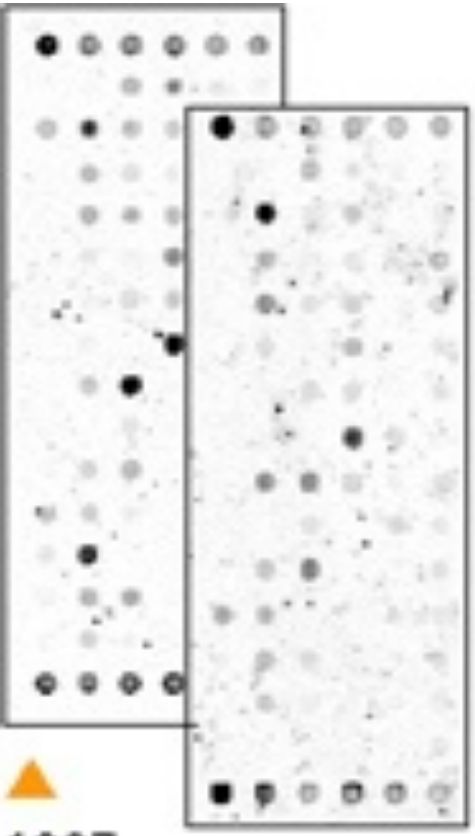


The comparative genomic hybridization (CGH) technique allows the detection of deleted or duplicated sequences in the genome to be tested (green) on the basis of a comparison with a reference genome (red).

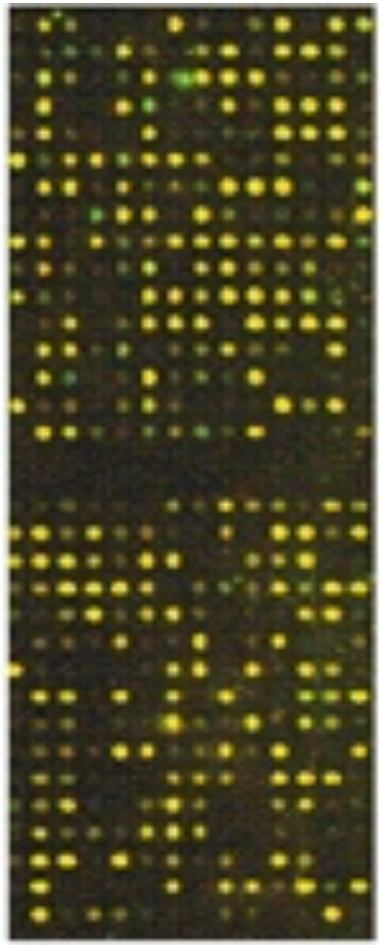
Two differently colored fluorescent probes are prepared that hybridize simultaneously on chromosomes. If in a chromosomal region prevails the color related to the reference genome (red) this means that the genome to be tested (green) has a deletion in that region. Duplications are indicated instead by prevalence of the green color.


Test DNA
Control DNA
Cot-1 DNA
Hybridization
(a)
CGH
Normal metaphase chromosomes
Microscopy
Image processing
Karyotyping
DIM
ENH
Copy-number karyotype
(b)
Matrix-CGH
Spotted DNAs
Scanning
DIM
ENH
CGH array
TRENDS in Molecular Medicine

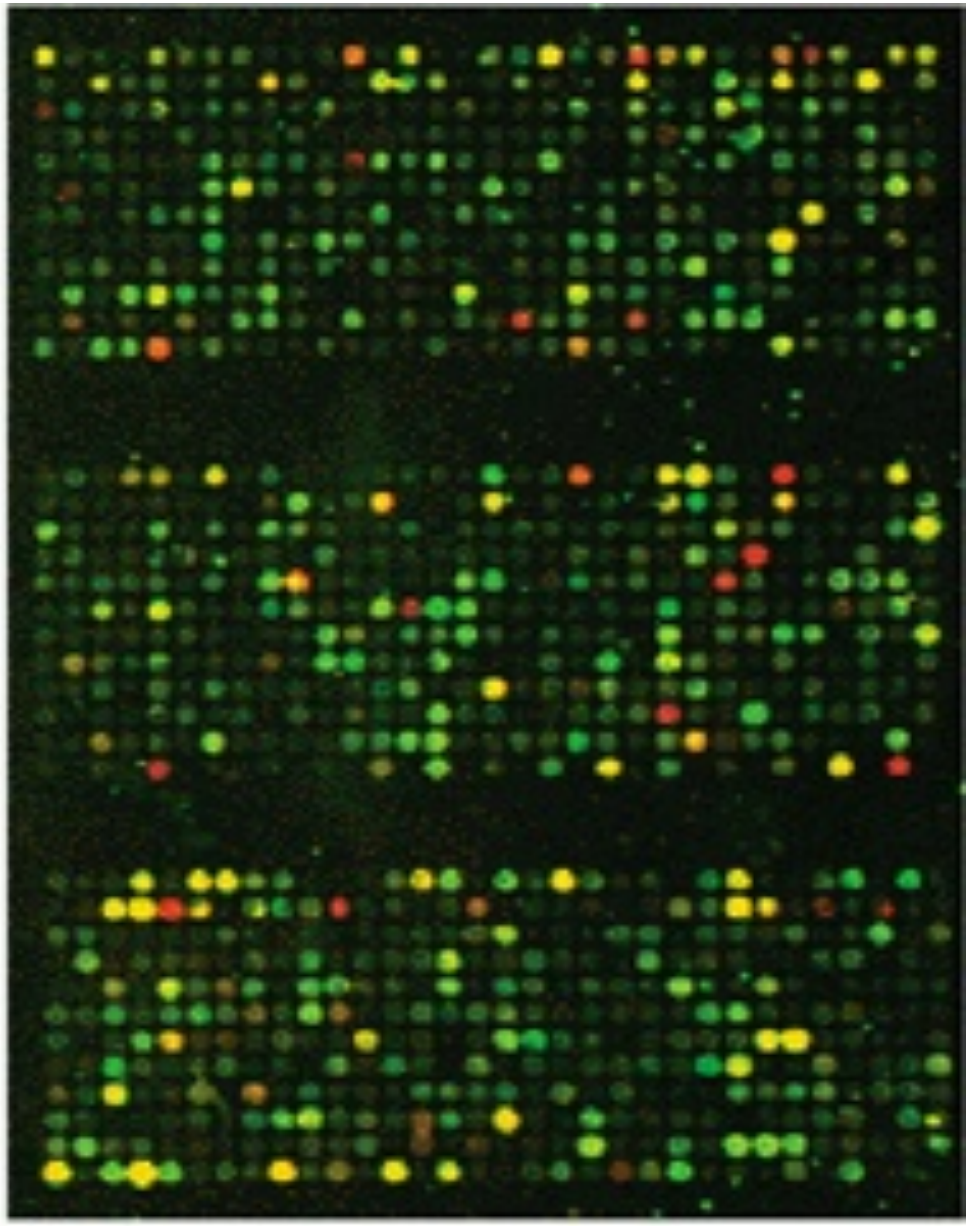

target
probe
1
2
3
4
5



1997

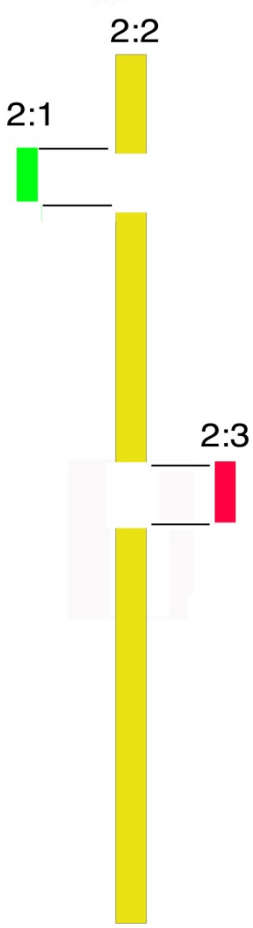


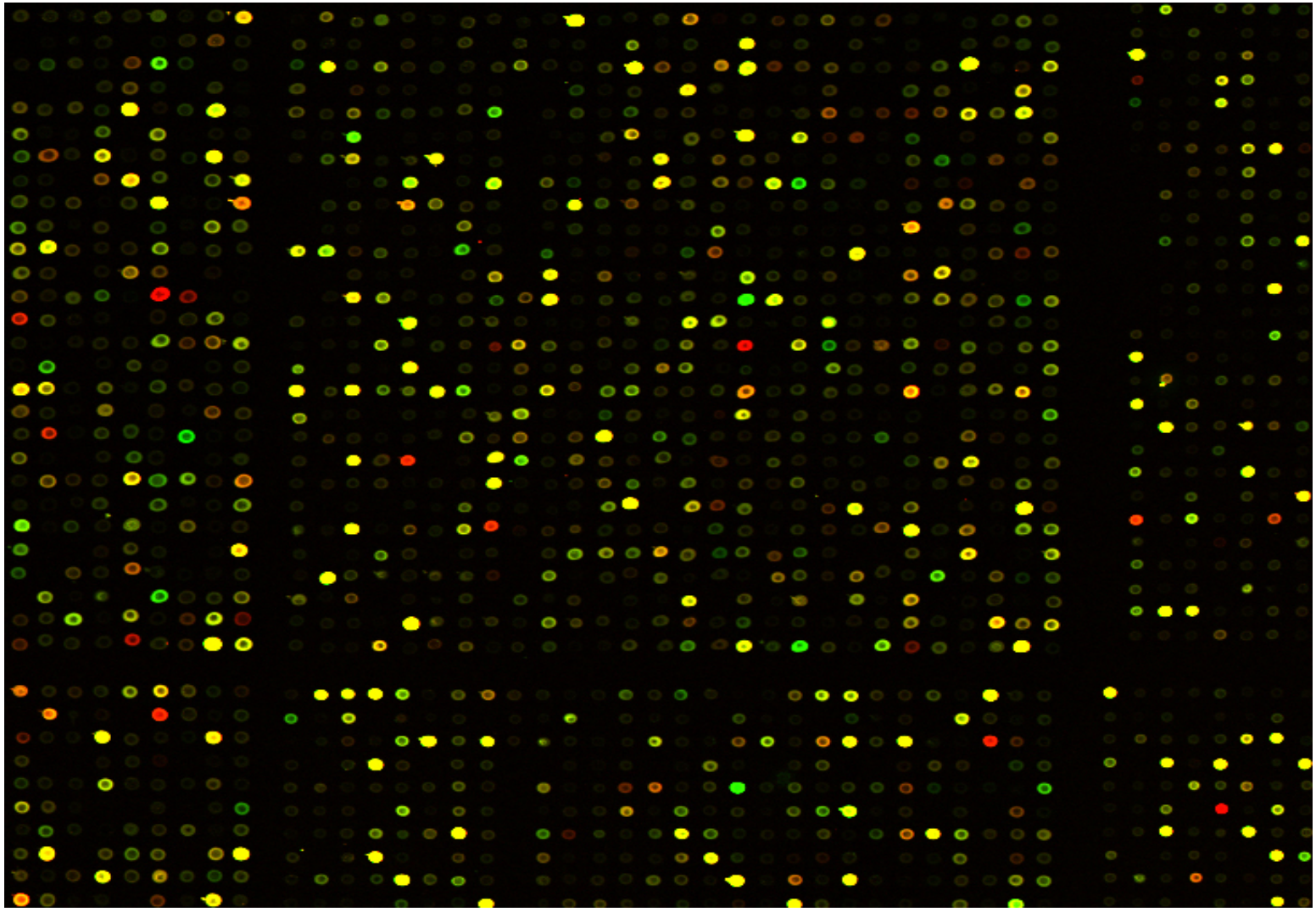
1998



Today

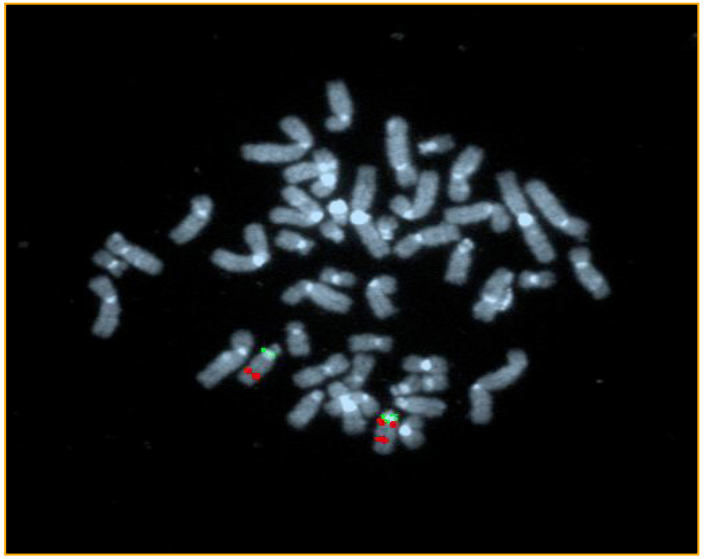
The array interrogates in a single experiment thousands portions of DNA that cover the entire genome at very high resolution (100 kb, 20 kb, 1 kb, …)

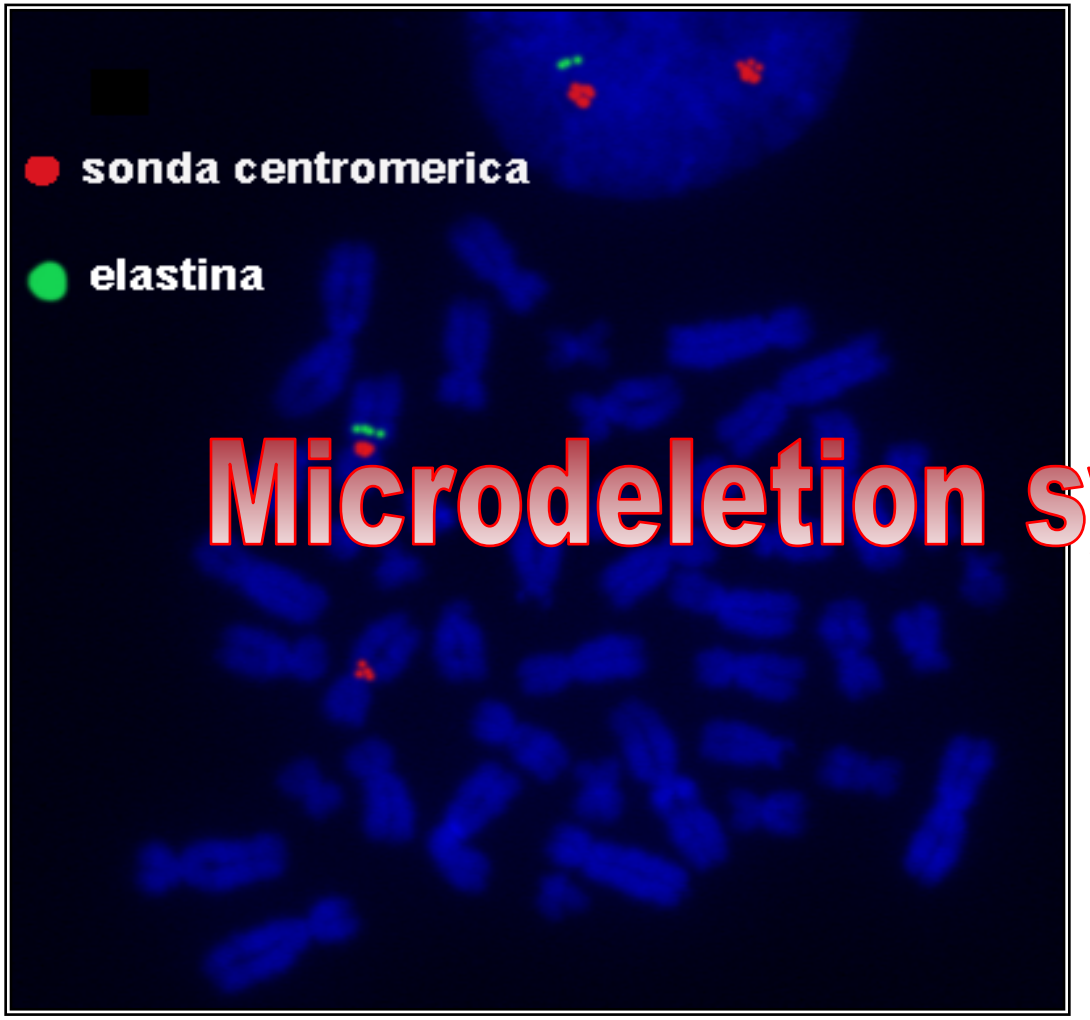




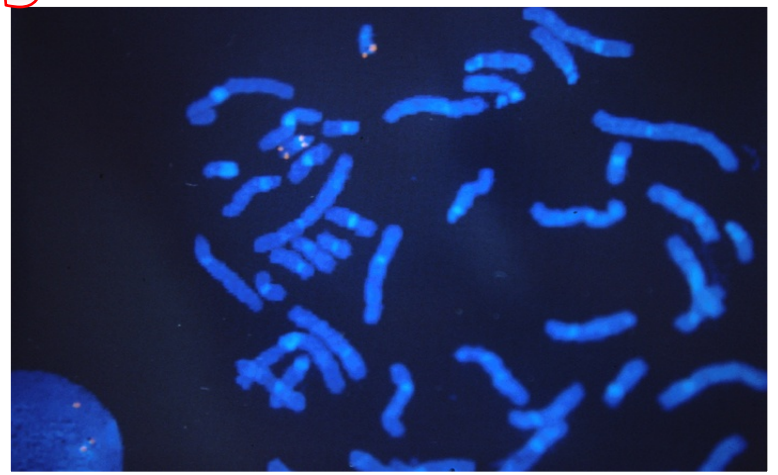
deletions/duplications easily detectable; balanced rearrangements not detectable

High resolution banding (1980) and
FISH technologies (1990):

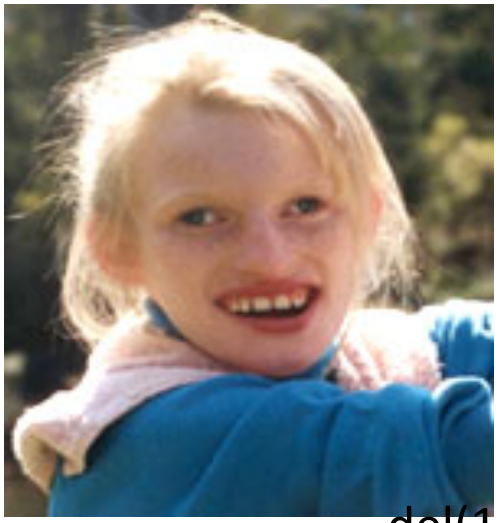




Microdeletion syndromes



del(7)(q11.23)



del(15)(q11-13)

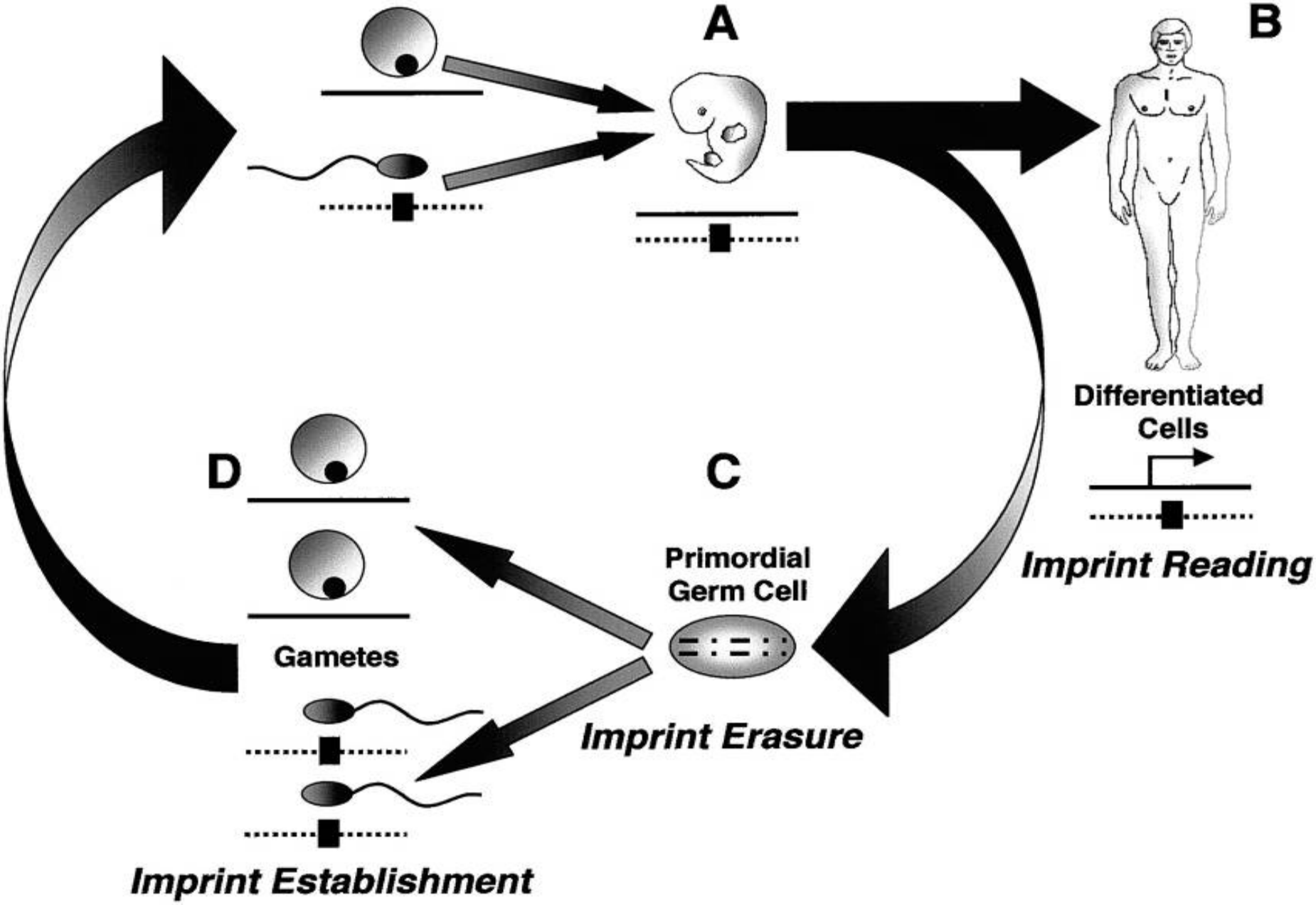
del(22)(q11.2)

Clinicians started to request FISH analysis for patients having even minor signs related to these syndromes

MAIN MICRODELETION SYNDROMES

SYNDROME	CHROMOSOMAL LOCALIZATION	PATIENTS WITH MICRODELETION
Prader Willi/Angelman	15q11.13	70%
Williams	7q11.23	90%
DiGeorge/Velocardiofacciale	22q11.2	75%
Smith-Magenis	17p11.2	95%
Miller-Dieker	17p13.3	90%

Imprinting


A
B
Differentiated
Cells
Imprint Reading
D
C
Primordial
Germ Cell
Gametes
Imprint Erasure
Imprint Establishment

Imprinting

- In primordial germ cells imprinting is completely erased and DNA is demethylated

- Later in the male germline a new imprinting pattern is determined that in some loci is complementary to that of the female germline

- The chromosomes on which the imprinting occurs (7, 11, 15) will retain this pattern and will reproduce it at each mitosis

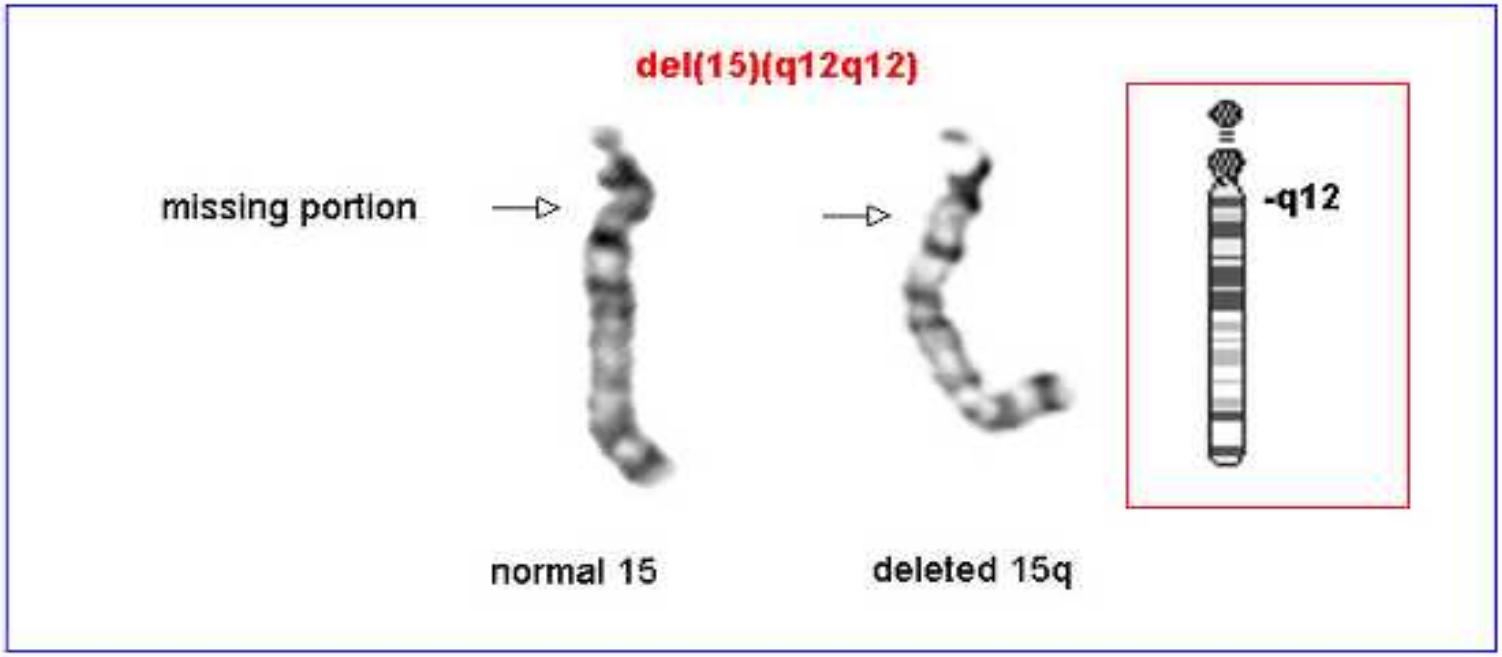
- You can always distinguish between maternal and paternal chromosome gene expression

Uniparental disomy

- Two copies of the same chromosome are inherited from only one parent
- Often this occurs through a transient trisomic stage, followed by loss of the single chromosome and maintainance of the double chromosome

PRADER WILLI OR ANGELMAN SYNDROME

del(15q12)



Prader Willi/Angelman

- Chromosomal region 15q11-q13, in man, contains both genes with exclusively maternal expression and genes with exclusively paternal expression
- Mutations and deletions of exclusively maternally expressed genes cause the Angelman syndrome
- Mutations and deletions of exclusively paternally expressed genes cause Prader Willi syndrome
- Genes with exclusively maternal (or paternal) expression can be altered through 4 different mechanisms:
  - microdeletion
  - maternal (or paternal) uniparental disomy
  - imprinting defects
  - Mutations of UBE3A, a ubiquitin ligase gene with exclusively maternal expression (Angelman)

Angelman

- “happy puppet syndrome” you can identify it in puppy (Dopey) "aslept", the youngest of the dwarfs who never learned to speak
- mental retardation with absent speech, difficulty in balance, excessive good mood

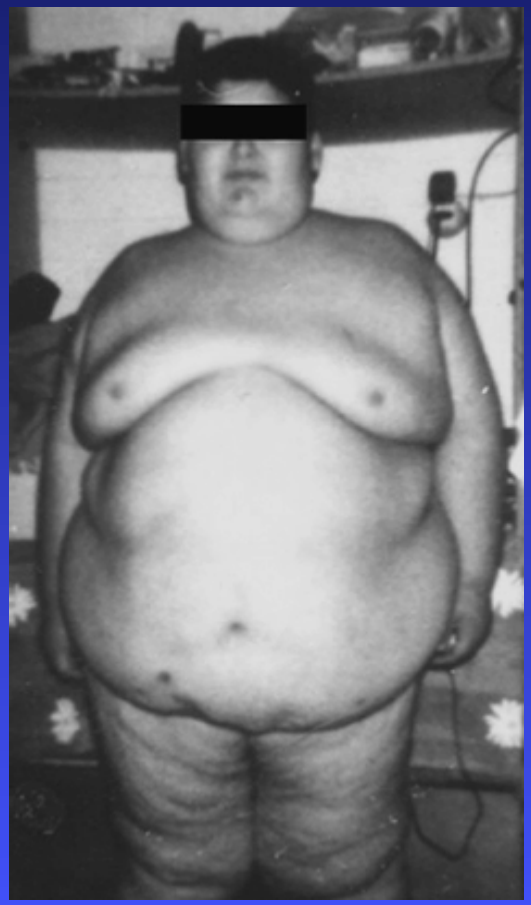
Angelman

- Prevalence of 1/20.000 newborns
- Seizures and/or EEG alterations and microcephaly

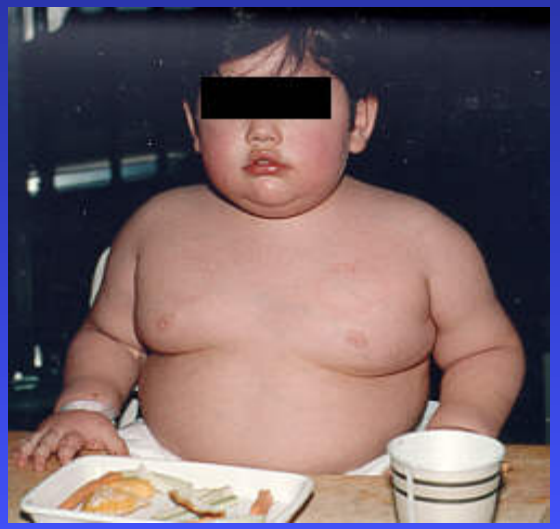
Prader-Willi

- Prevalence 1/15.000
- hyperphagy>obesity
- Excessive intake of liquids
- Abnormal reactions to sedatives
- acromicria (reduced limb size)
- Insensitivity to pain, skin lesions
- Mood swings

Prader-Willi



1/15.000



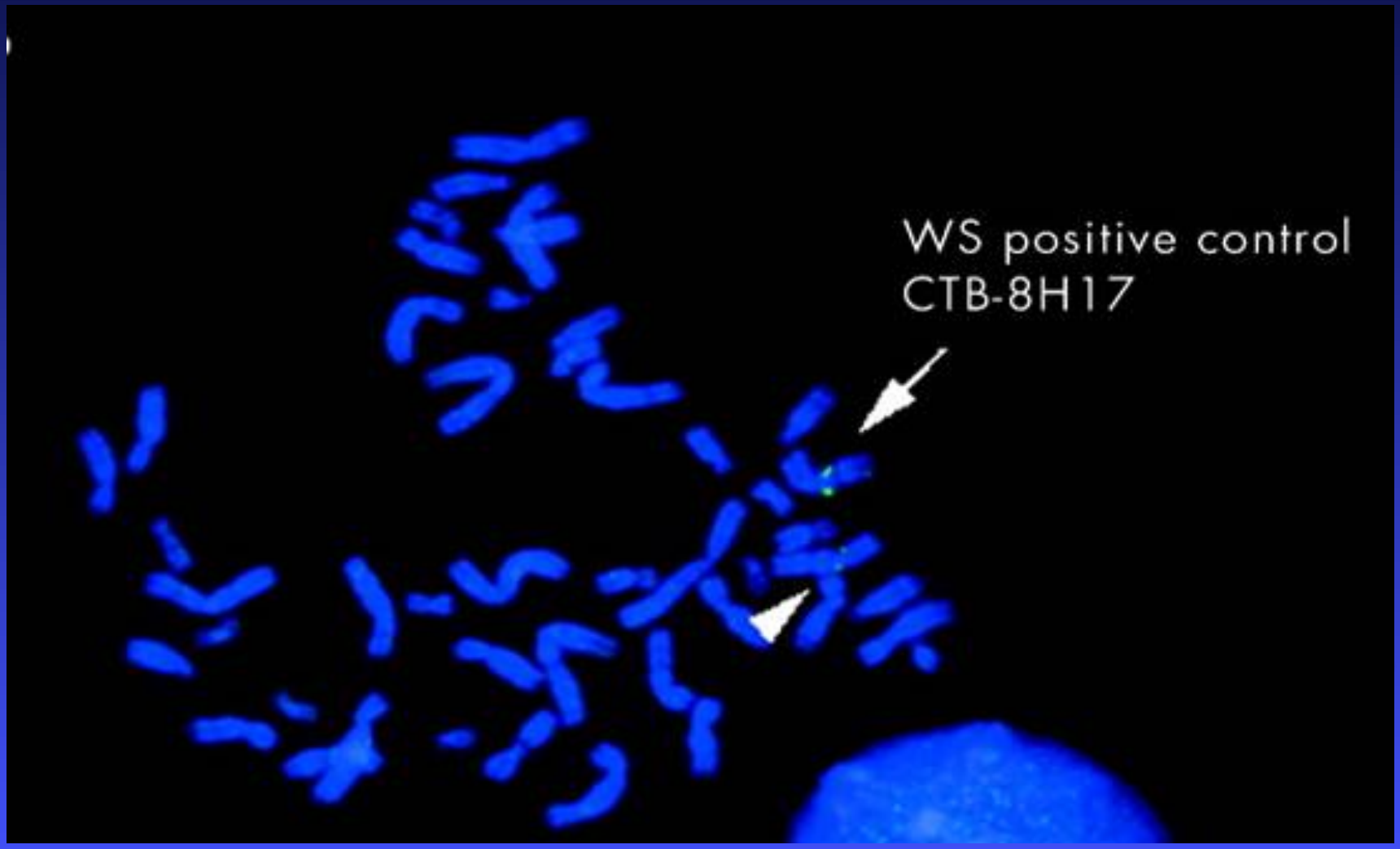
WILLIAMS SYNDROME

- Typical facies (elfin facial feature with low nasal bridge)
- Failure to thrive
- Cardiac problems
- Psychological problems

- Incidence at birth 1/7.500-1/20.000, but can remain undiagnosed

Williams genetics

- “de novo” deletion
- autosomal dominant inheritance
- Deletion of 1.6MB involving 21 contiguous genes in heterozygosity at locus 7q11.23
  - Elastine gene
  - LIM kinase 1 (LIMK1)
  - CLIP-115 that binds microtubules
  - Transcription factors GTF2I and GTF2IRD1
  - positional effect on other genes surrounding the deletion



- Evidenced through FISH but not through kariotype

Williams behaviour

- mild or medium mental retardation (IQ between 41 and 80)
- poor concentration skills
- delay in learning the language and then exaggerated loquacity
- friendly and affectionate personality
- easily give confidence to strangers
- anxiety, often worried about the welfare of others
- hypersensitivity to sounds
- visual and auditory memory often out of the ordinary
- remember people, places and musical motives
- predisposition to learn languages and music

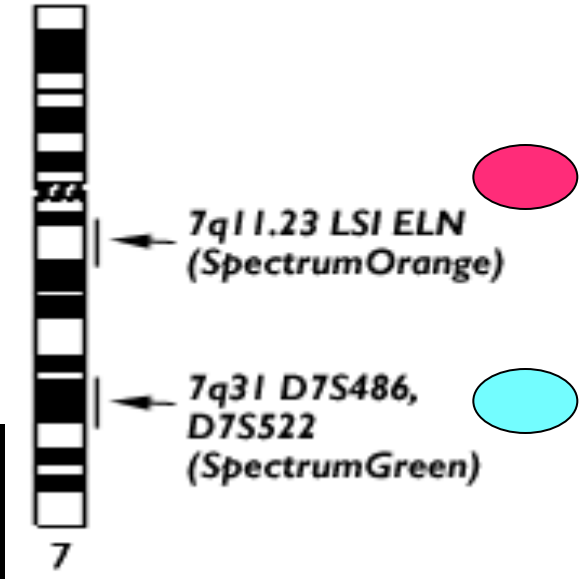
Williams signs and appearance

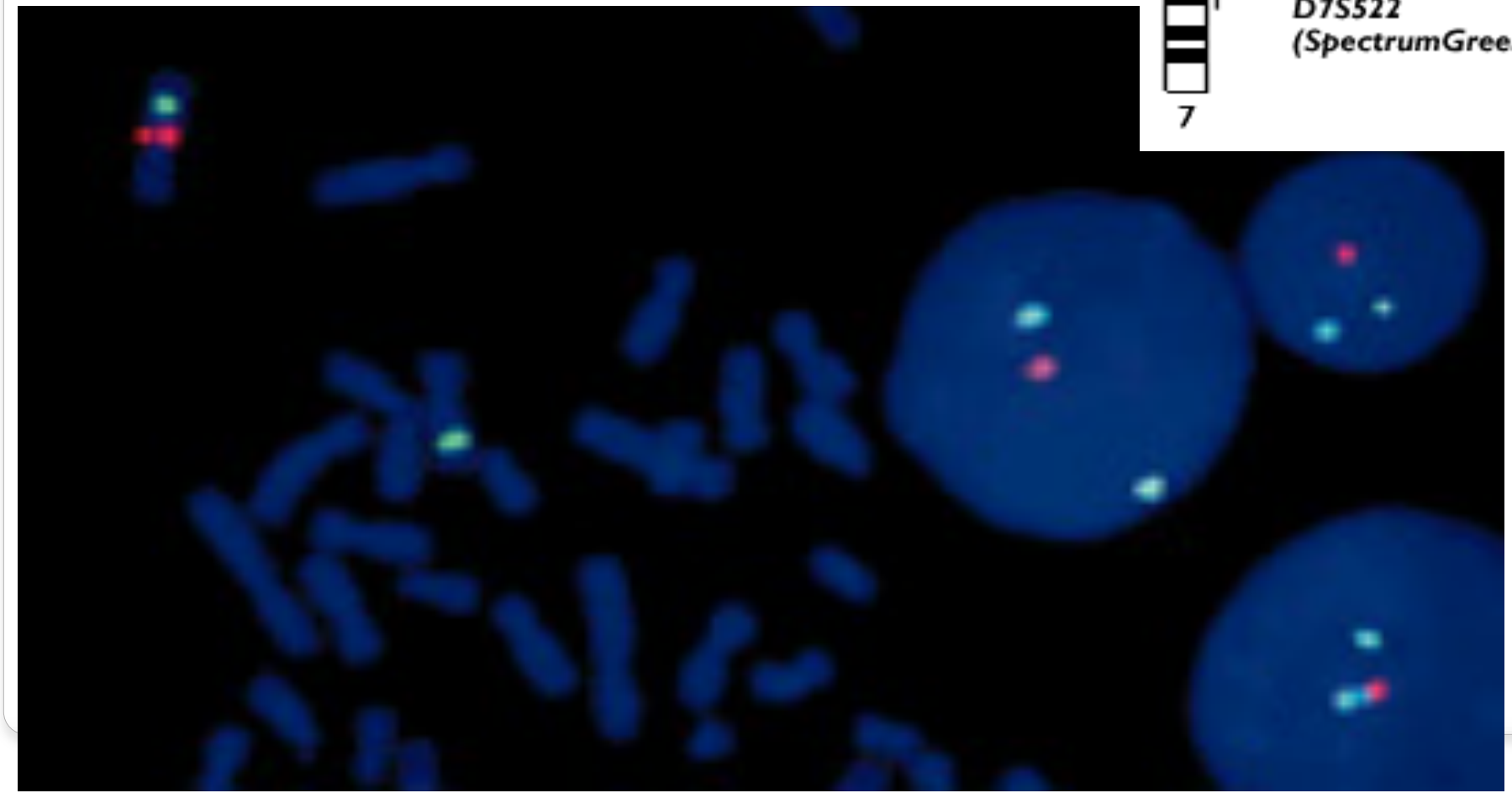
- Elfin facial feature
- blu eyes (77%) with starry iris pattern (74%) in North-European, squint (40%)
- Nose with bulbous tip
- Wide mouth and chubby cheeks
- microdontia e micrognathia
- height 10 cm less than normal
- hypercalcemia
- Peripheral pulmonary artery stenosis
- aortic stenosis, supravalvular

http://www.wsf.org/family/photoalbum/wsfphoto.htm

Williams photos

WILLIAMS SYNDROME

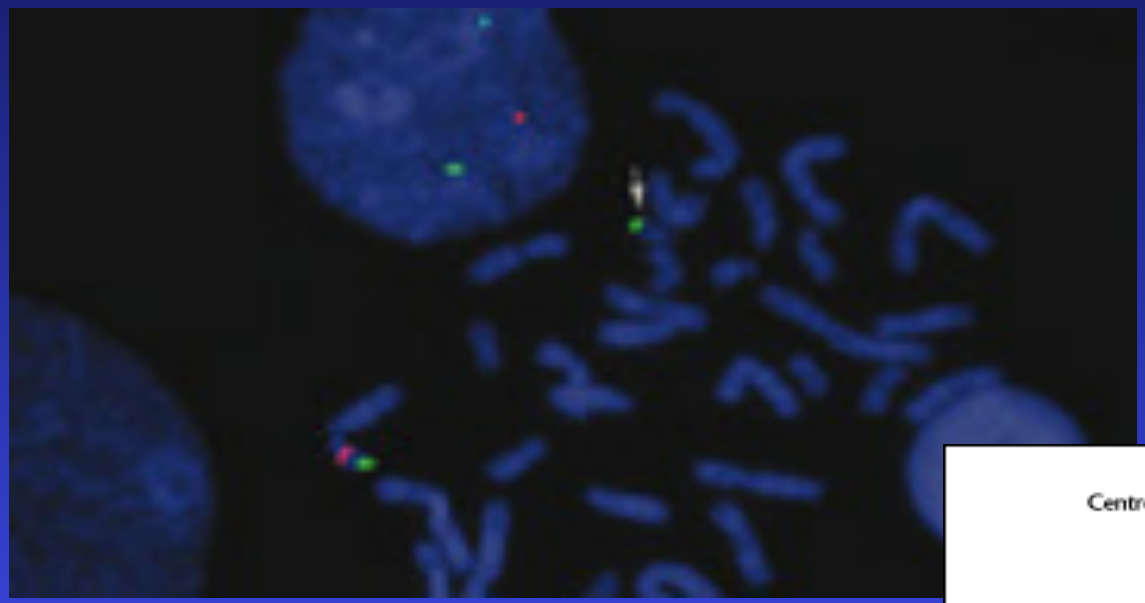


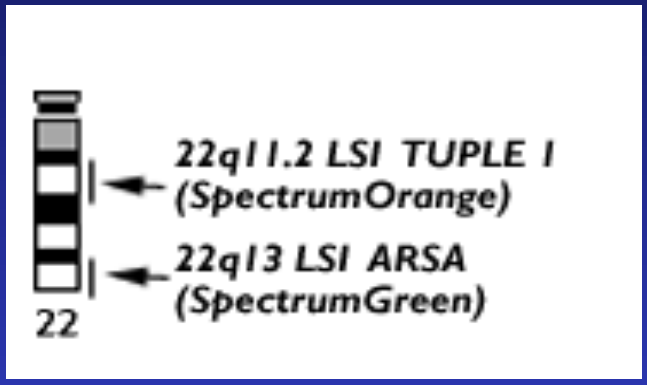


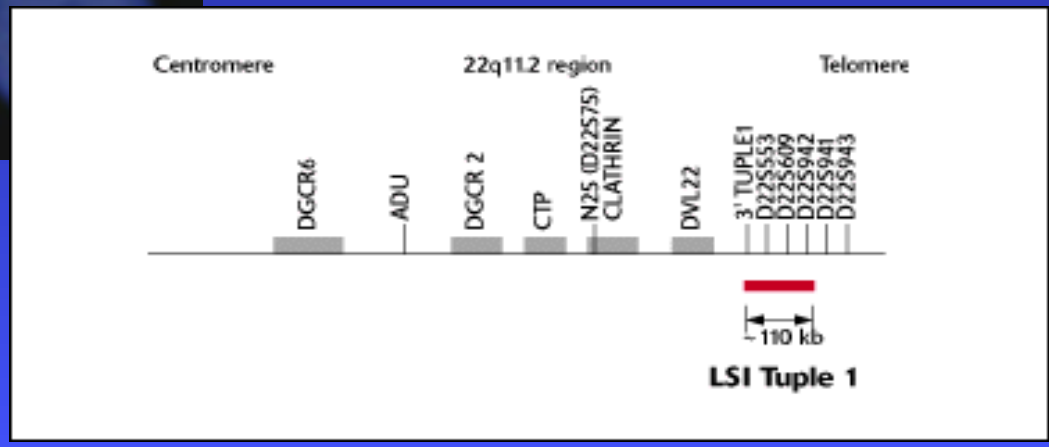
DiGeorge (velocardiofacial) syndrome

DiGeorge syndrome caused by del22q11.2 is the most frequent microdeletion syndrome, with an incidence of 1 out of 4000—5000 born

The deletion includes 3Mb and at least 30 genes

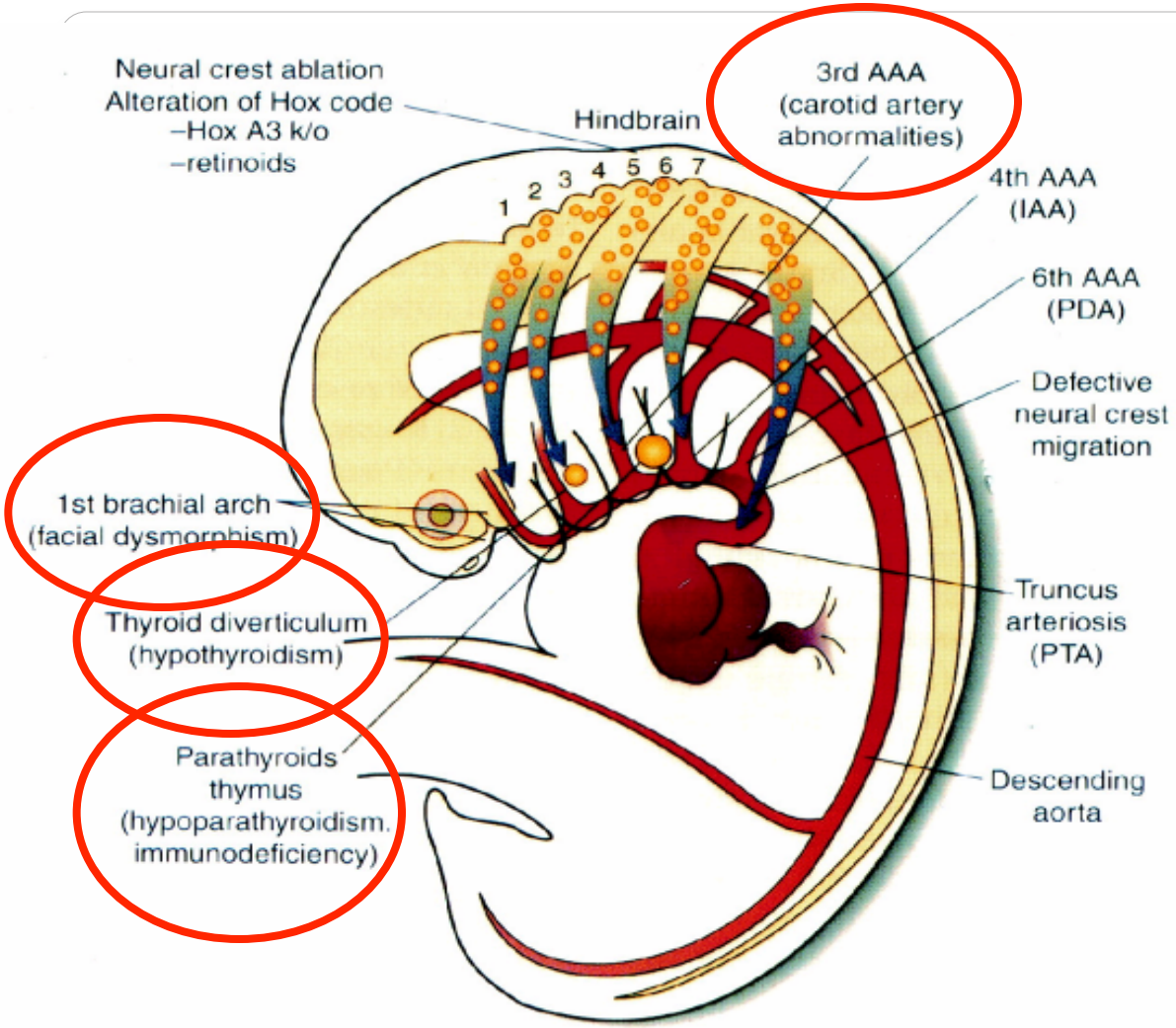




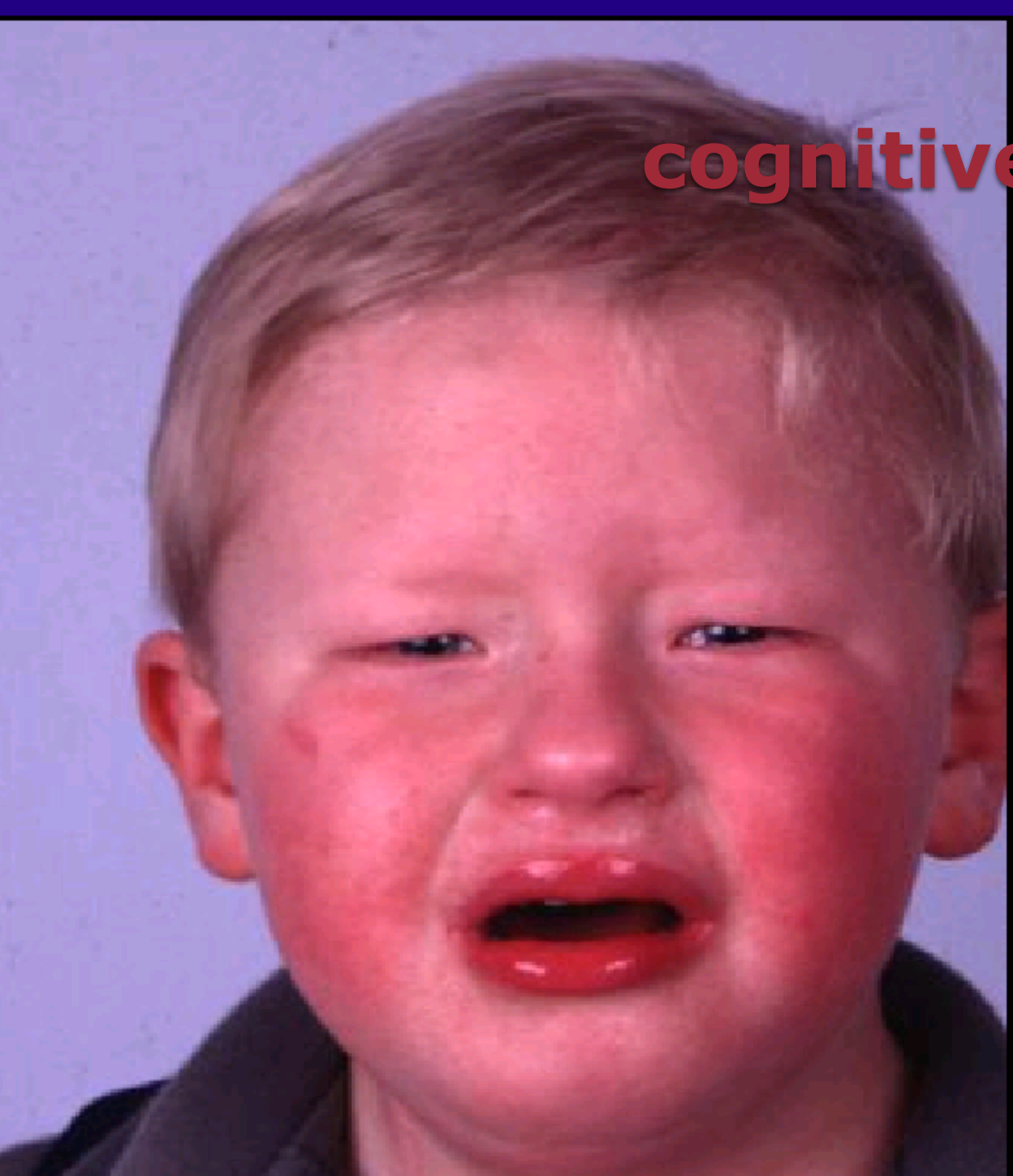


DiGeorge

- It is characterised by
  - Cardiac abnormalities (commonly interrupted aortic arch, persistent truncus arteriosus)
  - T-cell deficiency (recurrent infections)
  - Cleft palate
  - Facial abnormalities
  - hypocalcemia (low blood calcium, leads to convulsions)



- Migrating neural crest cells make a contribution to the embryonic structures affected in DiGeorge syndrome.
- The cartoon represents a human embryo at 4–6 weeks gestation.
- The migration of neural crest cells from the hindbrain to the branchial arch/ pharyngeal pouch system and cardiac outflow tract is indicated by the arrows.
- Examples of malformations associated with perturbation of this process are listed and these overlap substantially with those seen in 22q11DS AAA, arch arteries; PDA, persistent ductus arteriosus; IAA, interrupted aortic arch.



DiGeorge cognitive impairments

- Patients usually have a below-borderline normal IQ
- The severity of hypocalcemia early in childhood is associated with autism-like behavioral difficulties
- Adults with DiGeorge syndrome are a specifically high-risk group for developing schizophrenia.

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"[illegible] Paul Davies