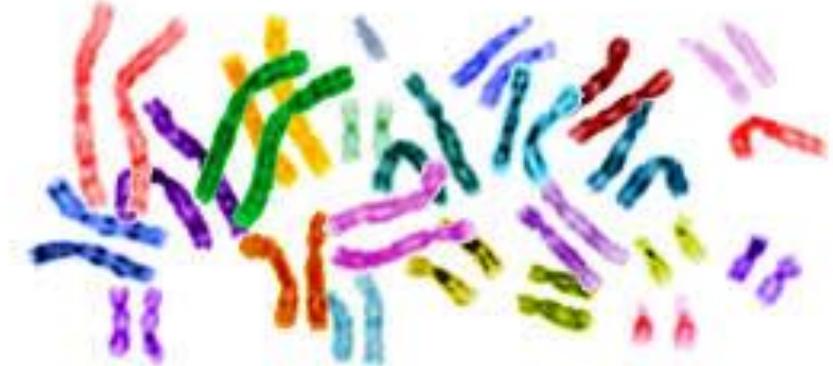


GENETICS

LECTURES 4 AND 5

Katarzyna Osmańska-Załużka, PhD



9



1



2



3



4



5



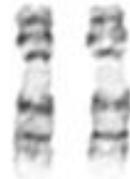
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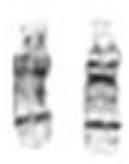
11



12



13



14



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16



17



18



19



20



21



22



X



Y

9



TETRASOMY OF SEX CHROMOSOMES

VARIANT OF KLINEFELTER SYNDROME – 48,XXYY

10



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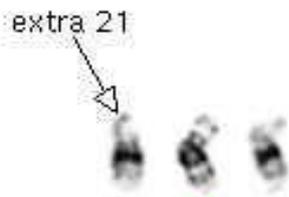
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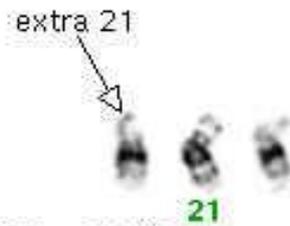


X



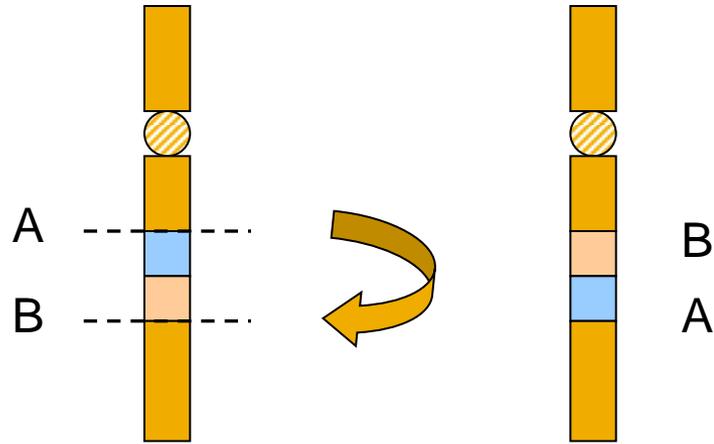
Y

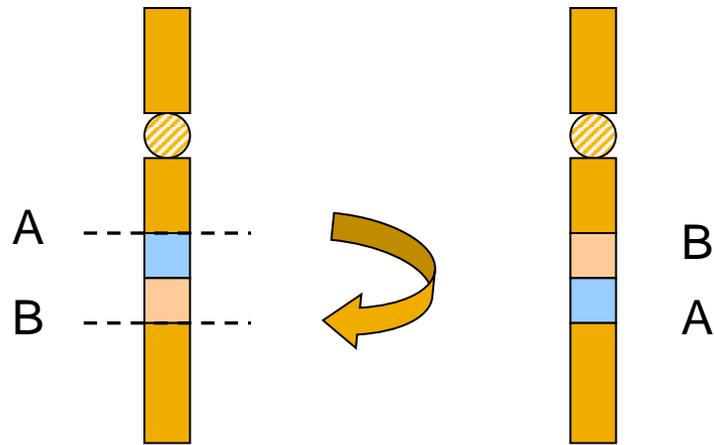
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TRISOMY

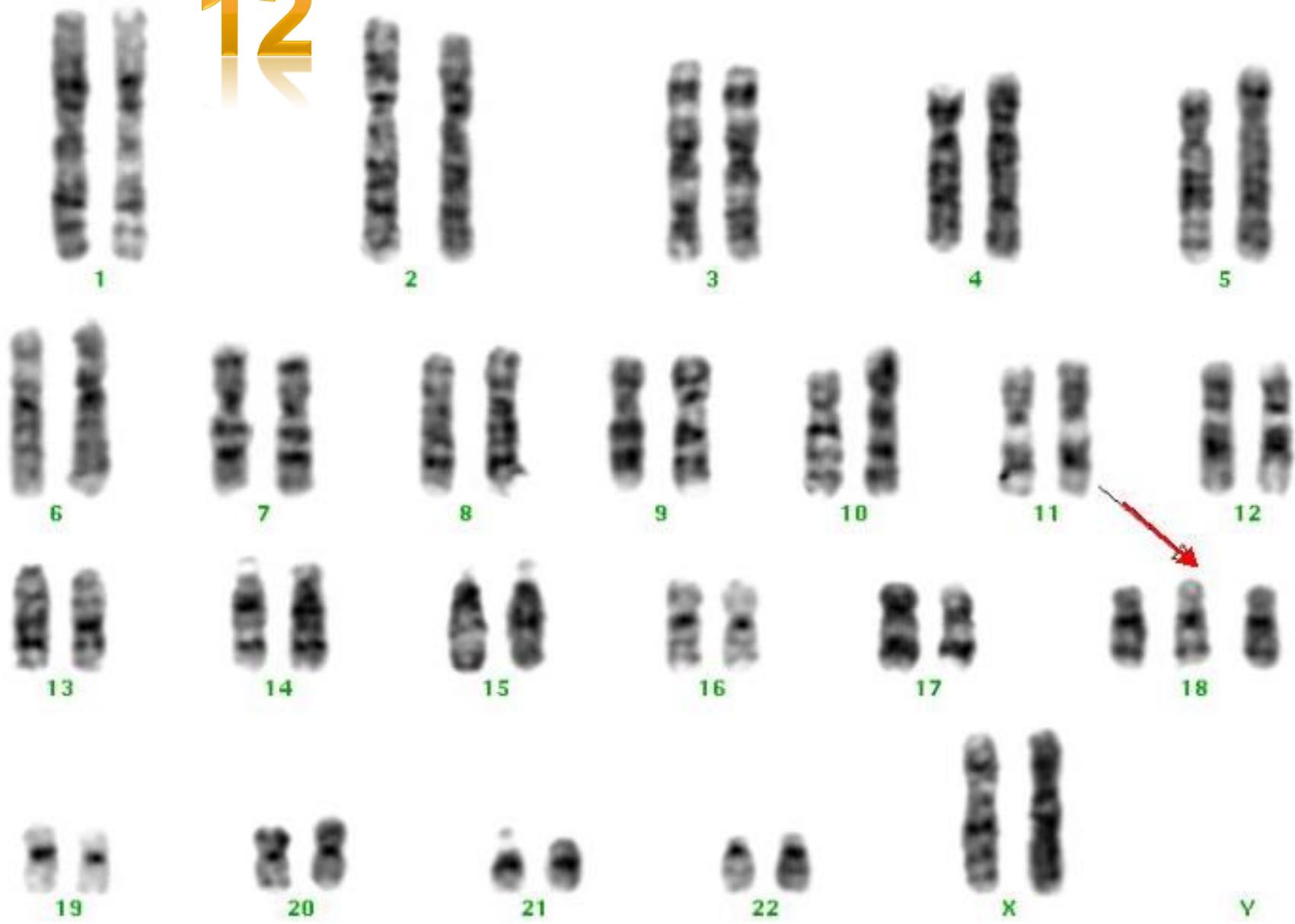
47,XY,+21 (Down syndrome)



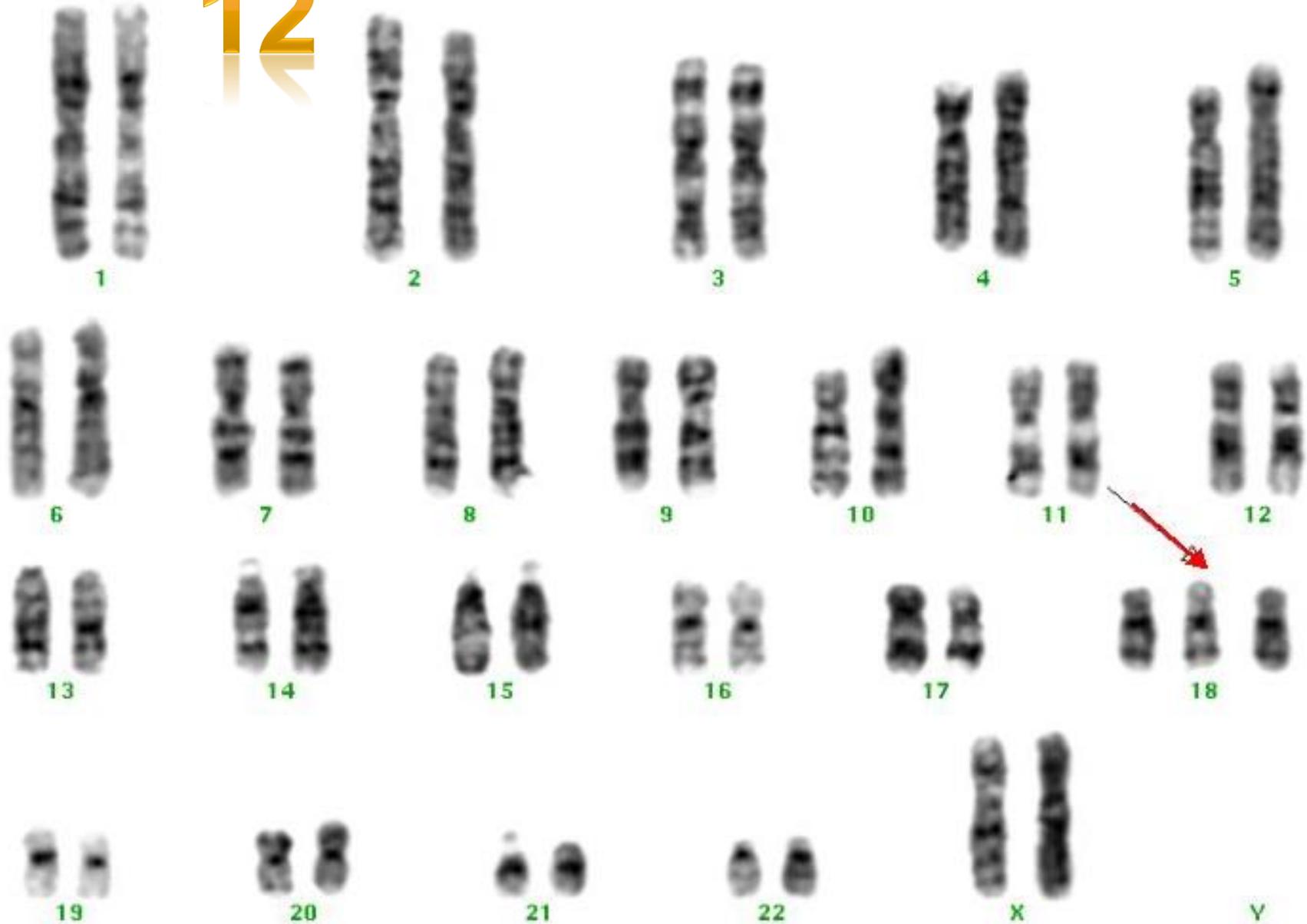


PARACENTRIC INVERSION

12

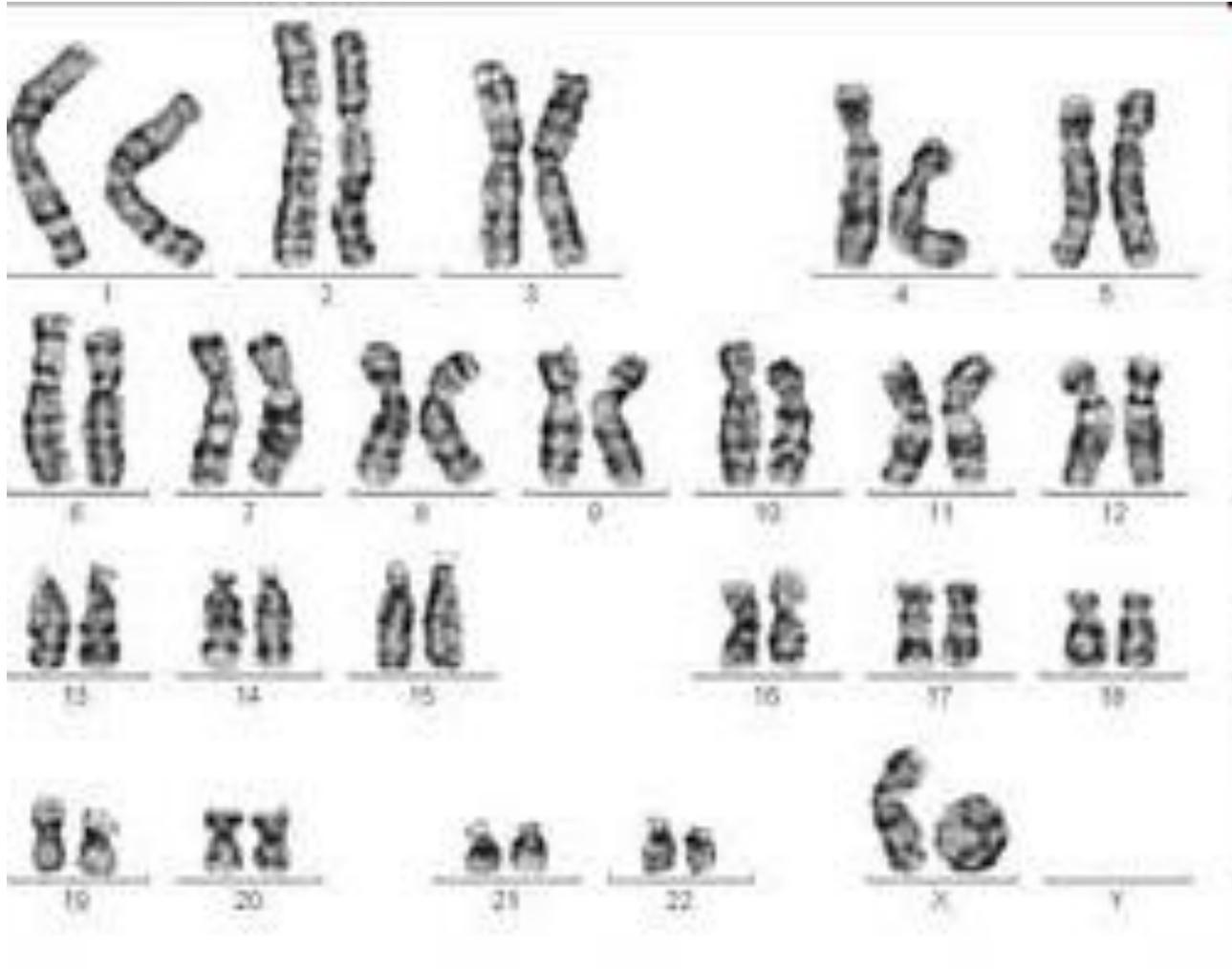


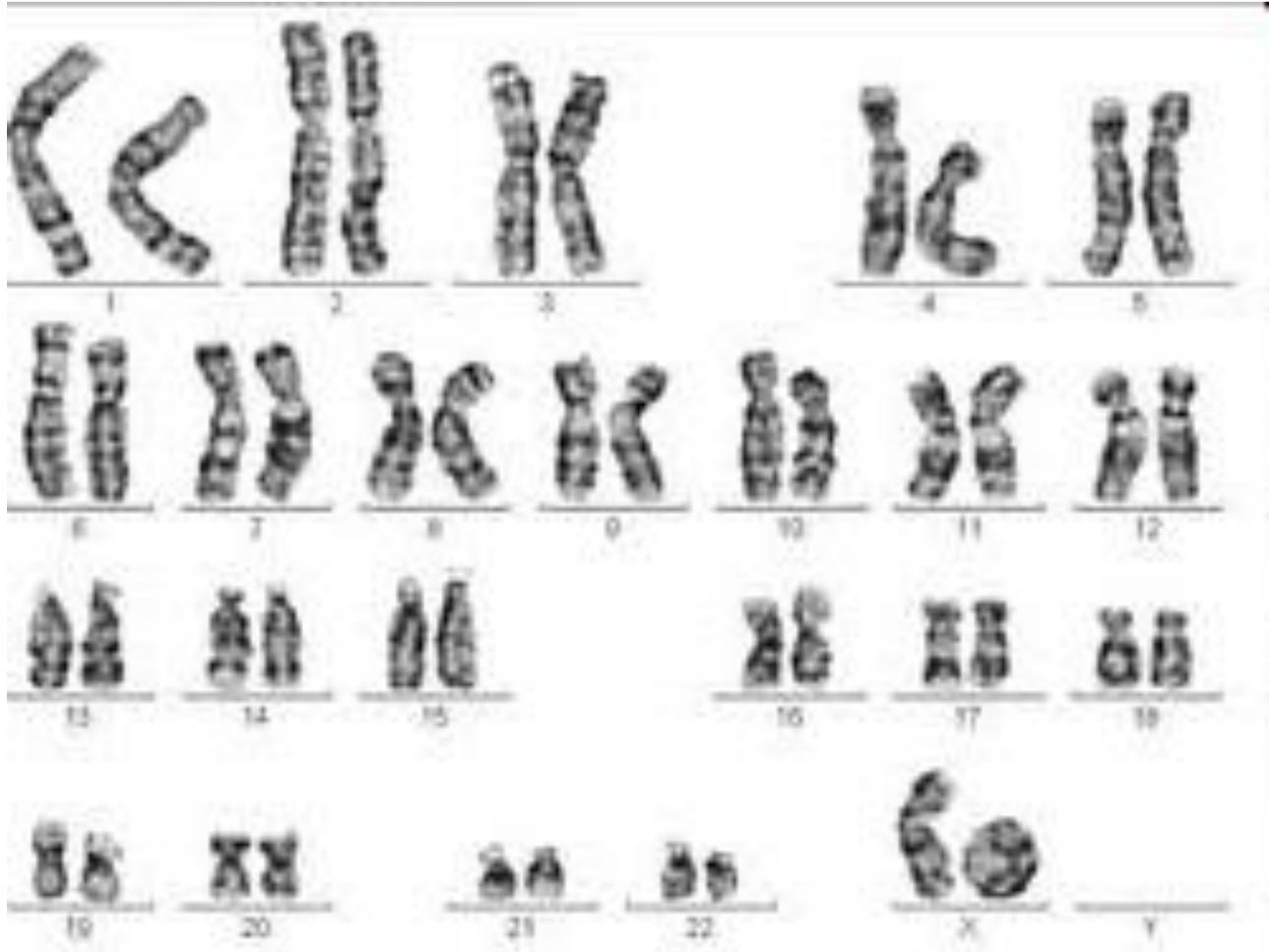
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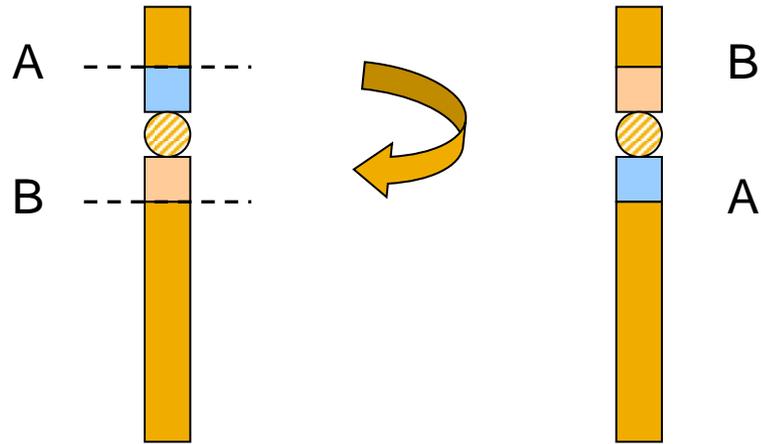
TRISOMY

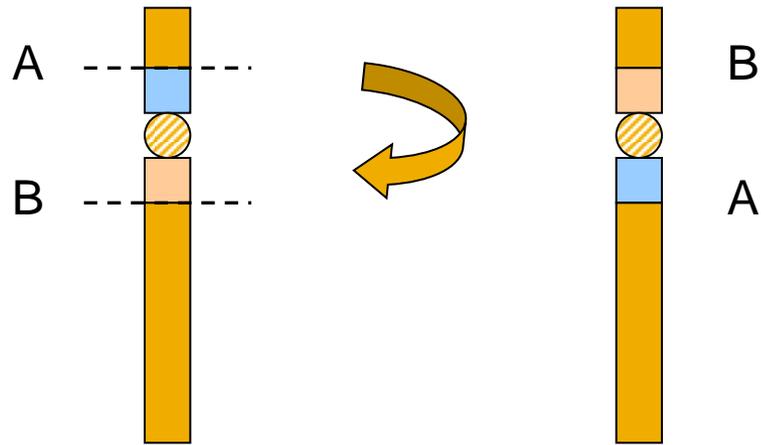
Edwards syndrome – 47,XX,+18



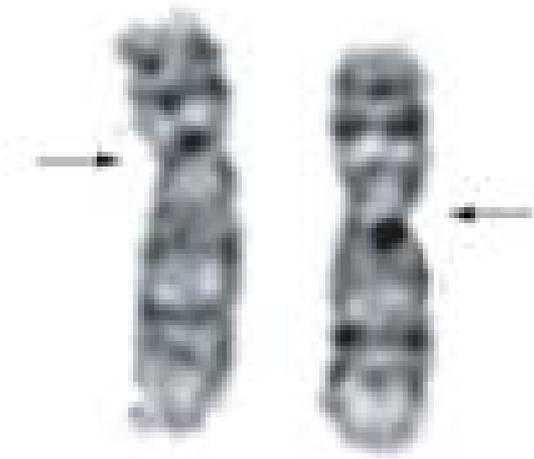


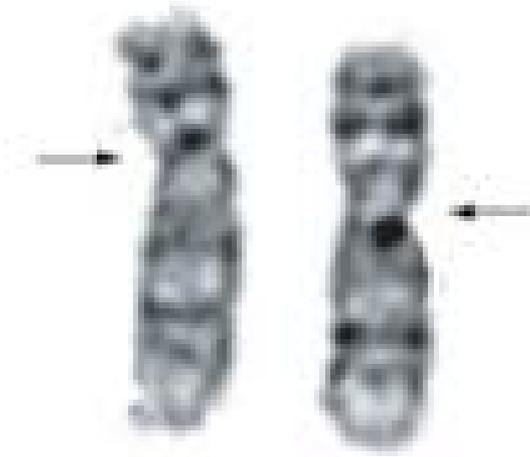
RING CHROMOSOME



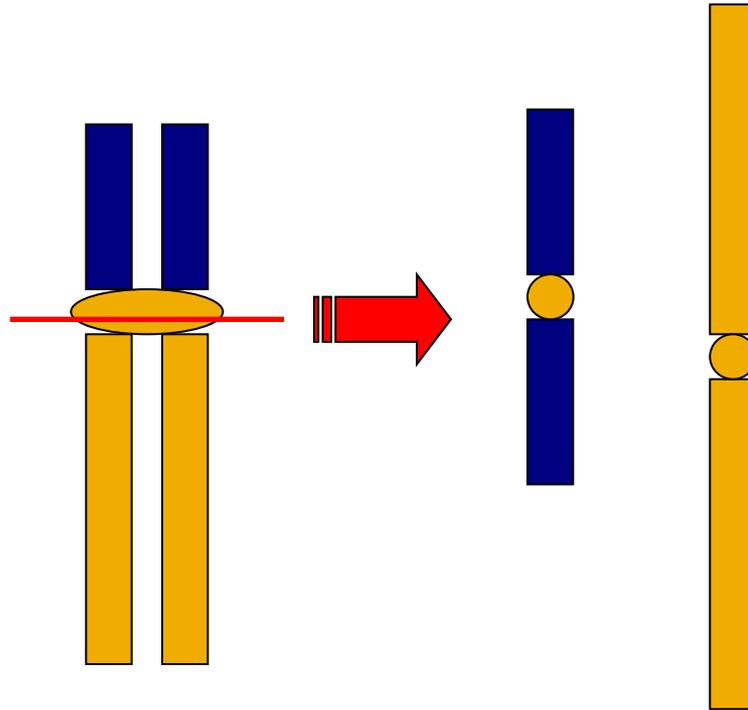


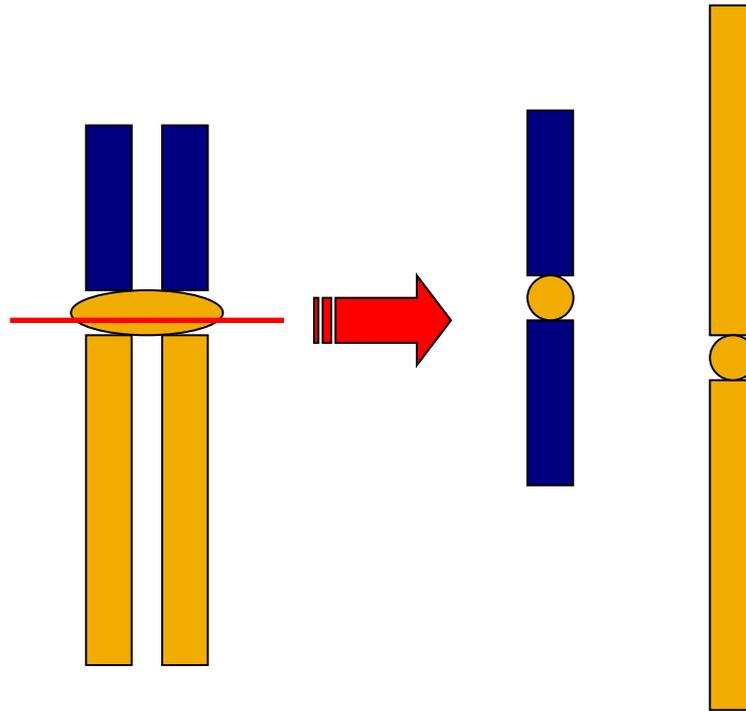
PERICENTRIC INVERSION



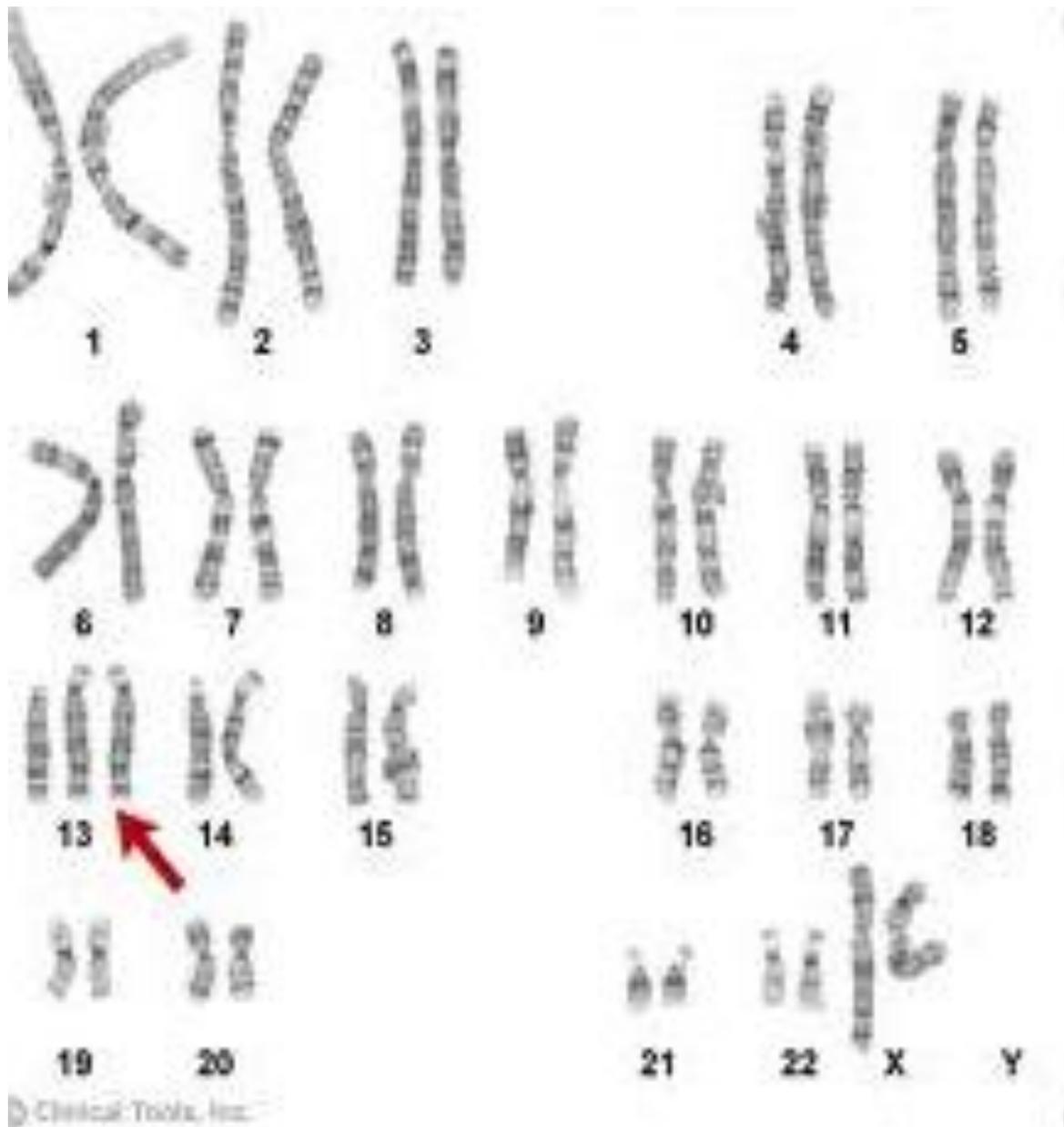


PERICENTRIC INVERSION



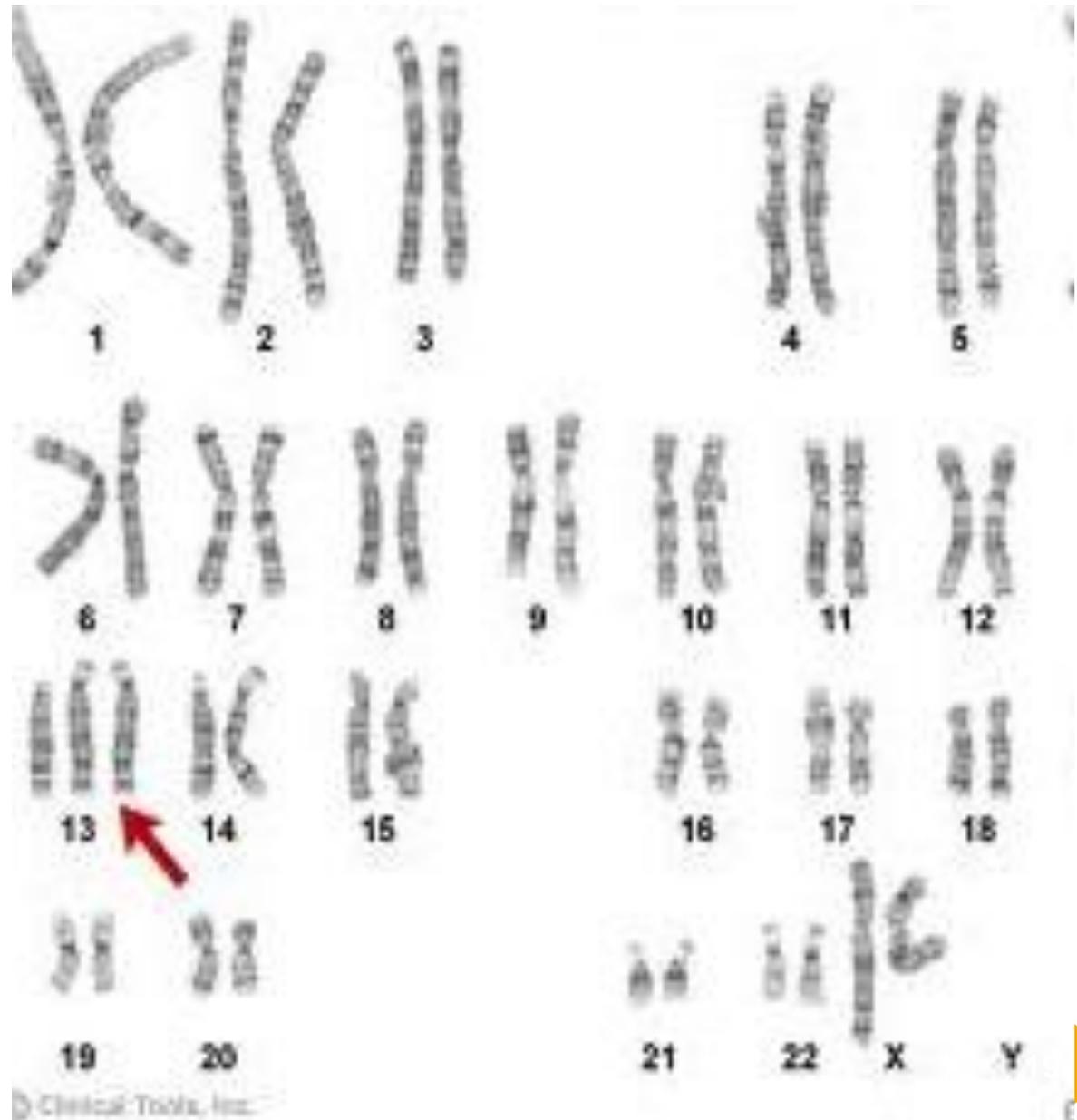


ISOCHROMOSOME(S)

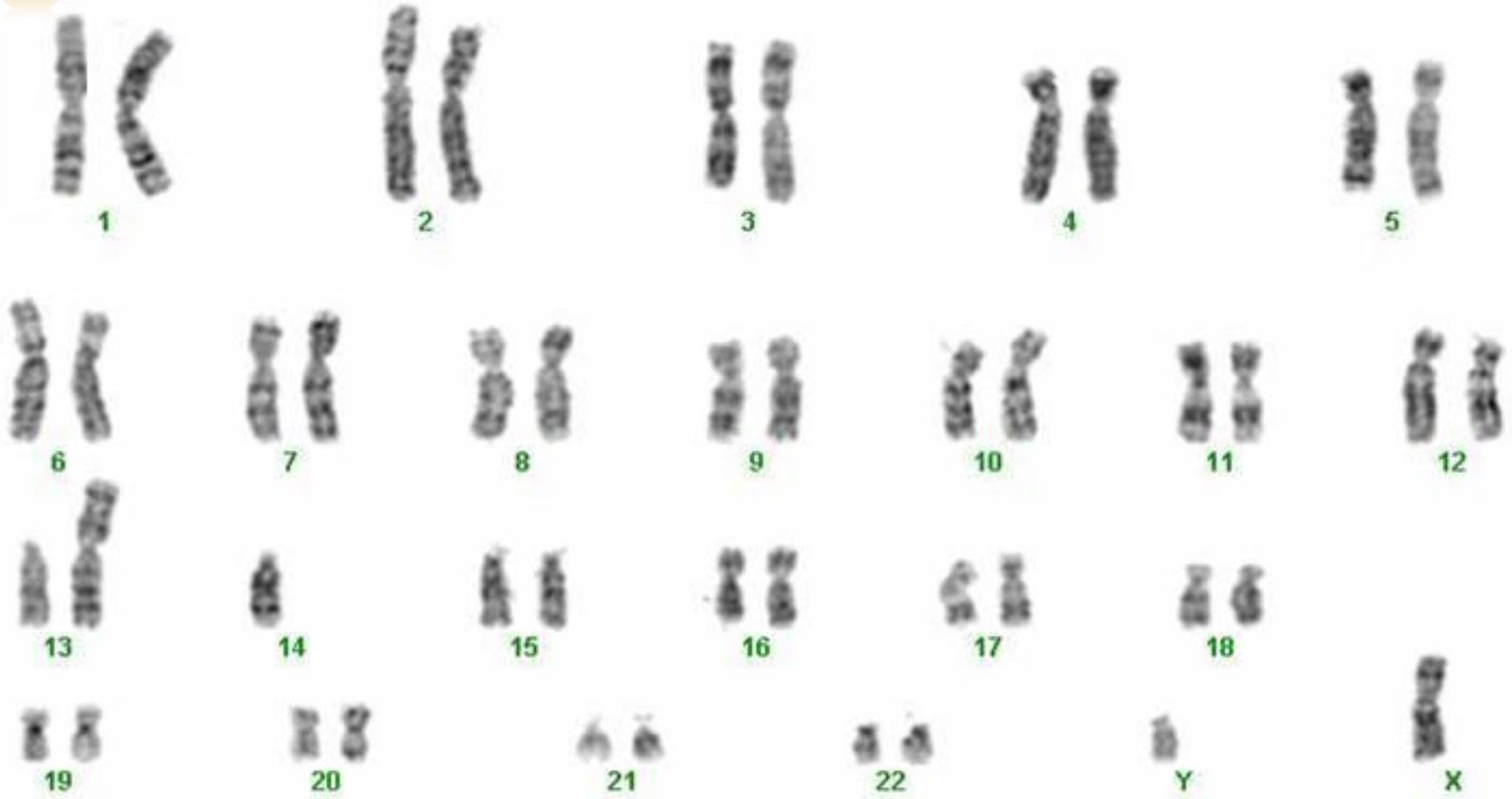


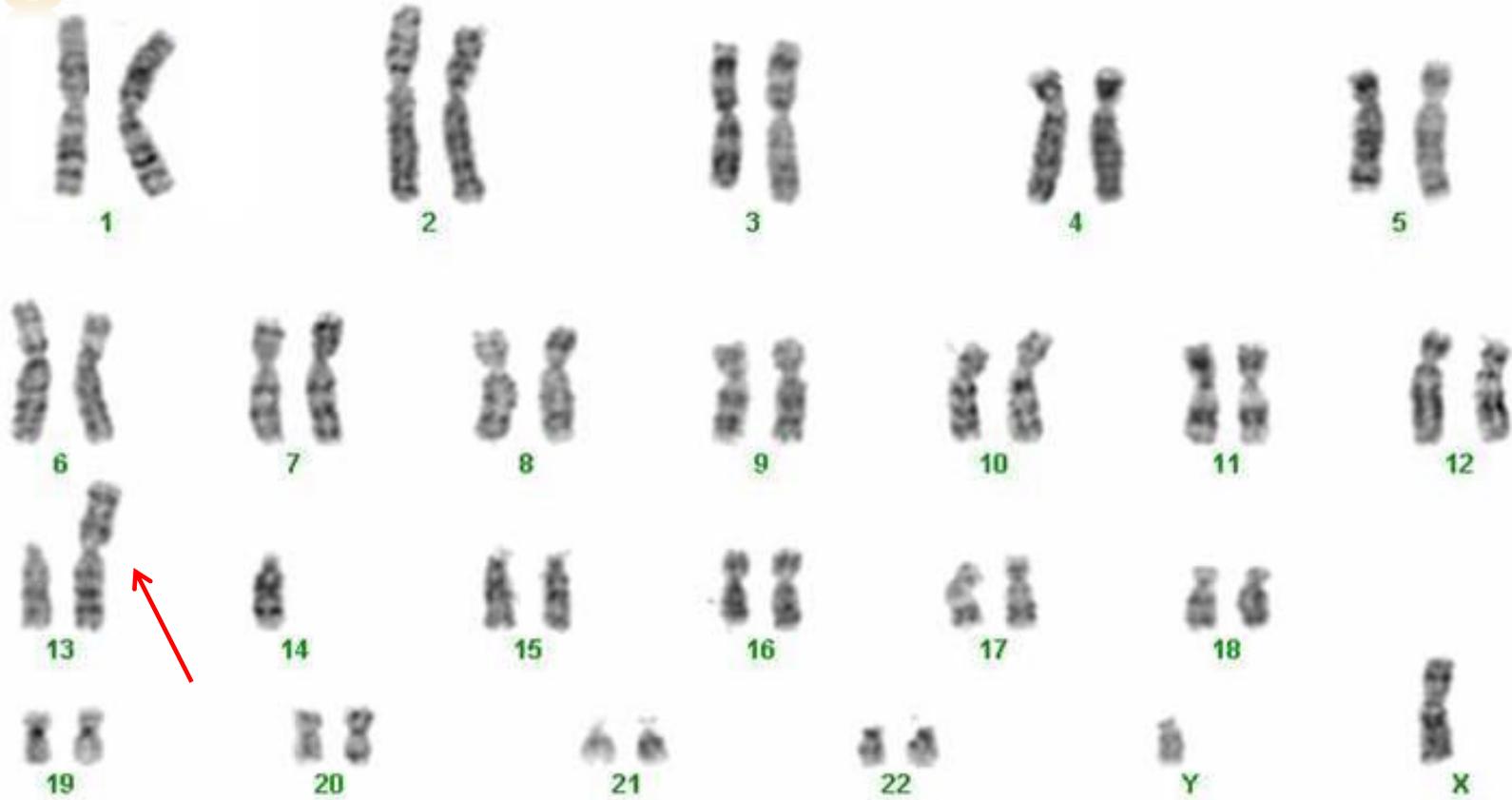
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PATAU SYNDROME
47,XX,+13

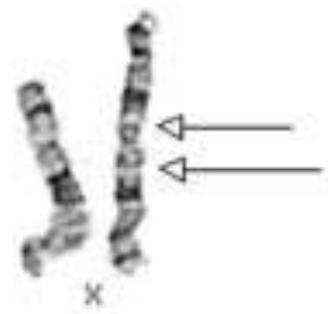
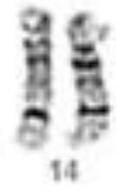


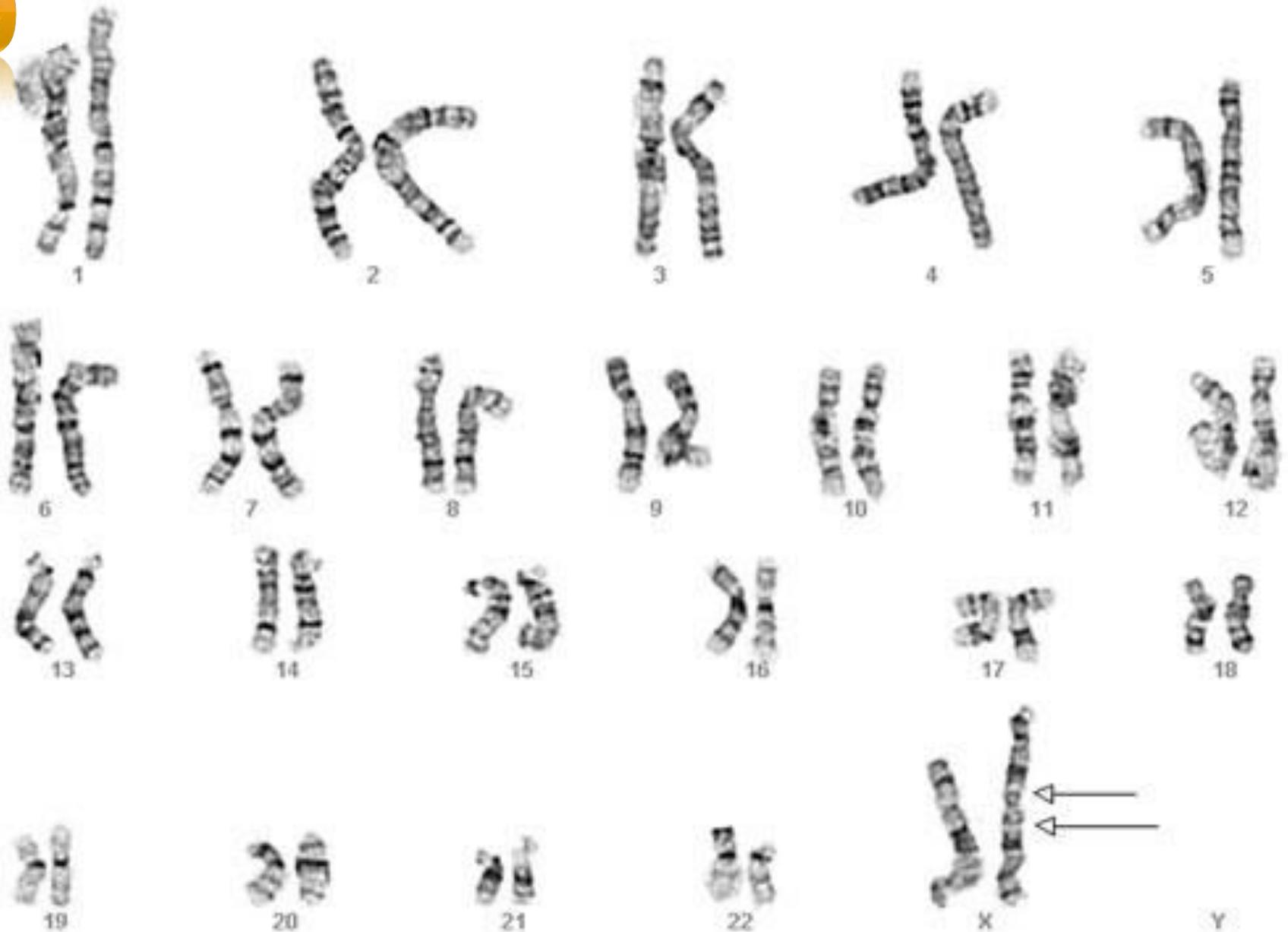
TRISOMY





45,XY,der(13;14)
CENTRIC FUSION
(ROBERTSONIAN TRANSLOCATION)





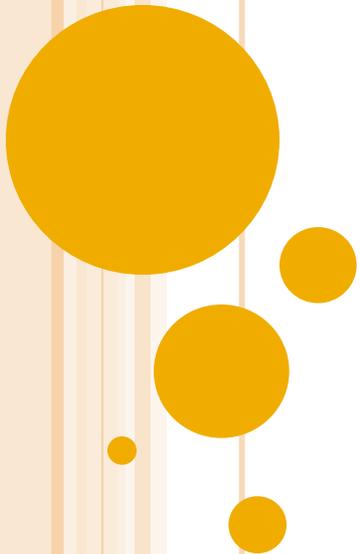
46,X,i(X)(q10)

ISOCHROMOSOME OF LONG ARM

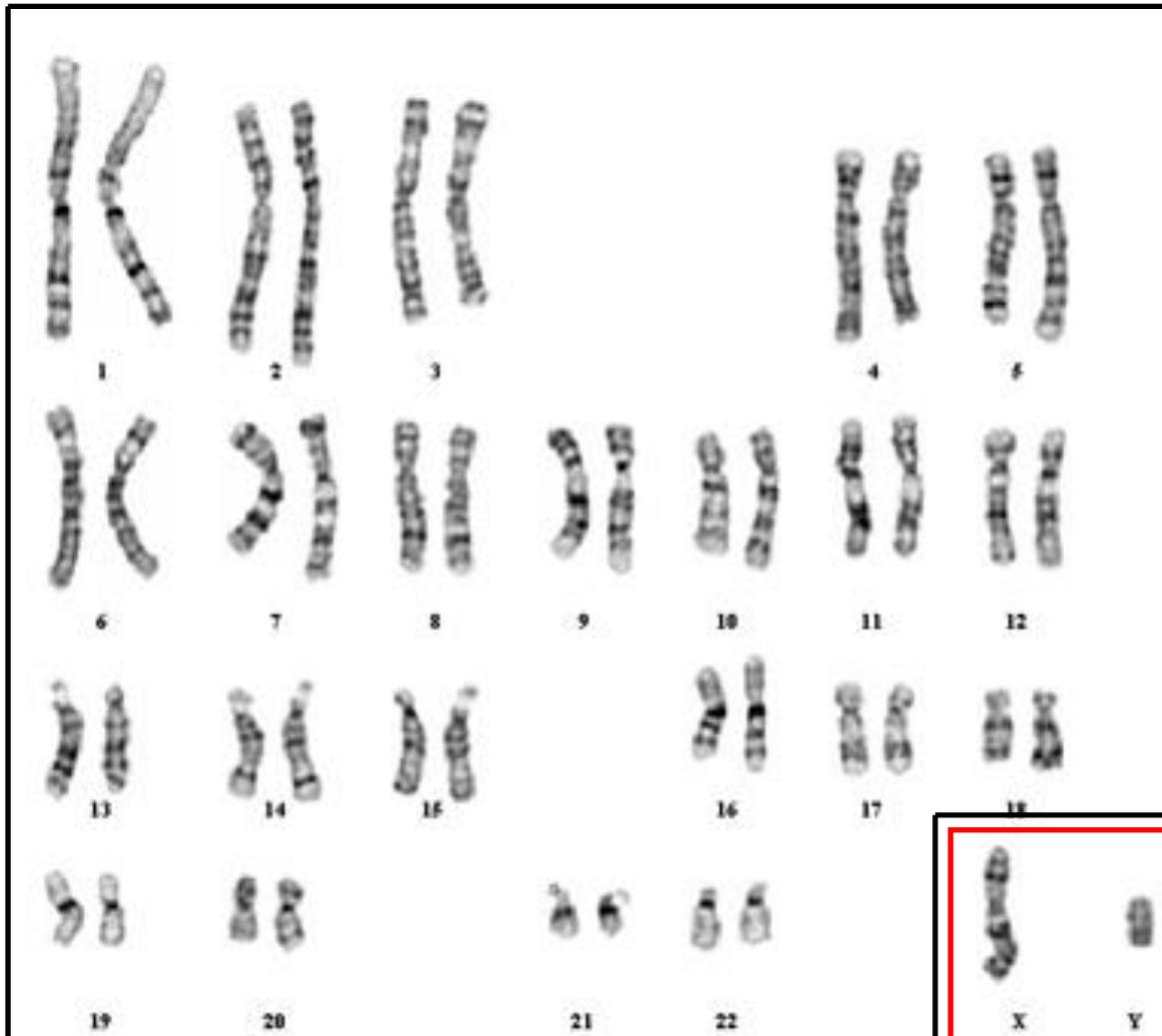
**AUTOSOMES AND HETEROSOMES
DISORDER SYNDROMES**

CONGENITAL MALFORMATIONS

DYSMORPHIC FEATURES



AUTOSOMES 1 – 22



**HETEROSOMES
X & Y**

CHROMOSOMAL ANEUPLOIDY

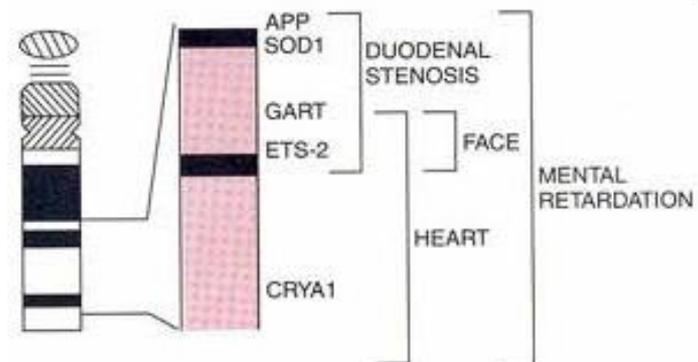
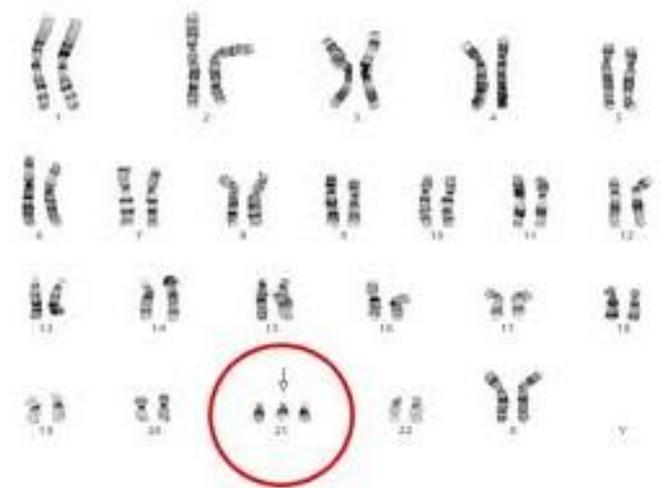
- **Nondisjunction** resulting in the addition or loss of an entire chromosome
- **Deletion** of a part of a chromosome
- **Microdeletion syndromes** (small piece missing which is usually only detected using special techniques)

COMMON CHROMOSOMAL SYNDROMES CAUSED BY NONDISJUNCTION

- Down Syndrome (trisomy 21)
- Patau Syndrome (trisomy 13)
- Edwards Syndrome (trisomy 18)
- Turner Syndrome (monosomy X)
- Klinefelter Syndrome (XXY)
- Jacob Syndrome (XYY Syndrome)

DOWN SYNDROME

- Pure trisomy 21
- Mosaic forms of trisomy 21
- $i(21)(q10;q10)$
- Parental translocation $t(21;21)(q10;q10)$ or translocation involving critical region (21q22)



DOWN SYNDROME – CLINICAL FEATURES

- Microgenia – abnormally small chin
- Macroglossia – oversized tongue
- Round face
- Almond shaped eyes
- Epicanthal fold
- Short limbs
- Single palmar crease
- Poor muscle tone
- Heart problems
- High risk of neoplasia



Characteristics	Percentage	Characteristics	Percentage
mental retardation	100%	small teeth	60%
stunted growth	100%	flattened nose	60%
atypical fingerprints	90%	clinodactyly	52%
separation of the abdominal muscles	80%	umbilical hernia	51%
flexible ligaments	80%	short neck	50%
hypotonia	80%	shortened hands	50%
brachycephaly	75%	congenital heart disease	45%
smaller genitalia	75%	single transverse palmar crease	45%
eyelid crease	75%	macroglossia (larger tongue)	43%
shortened extremities	70%	epicanthal fold	42%
oval palate	69%	strabismus	40%
low-set and rounded ear	60%	brushfield spots (iris)	35%

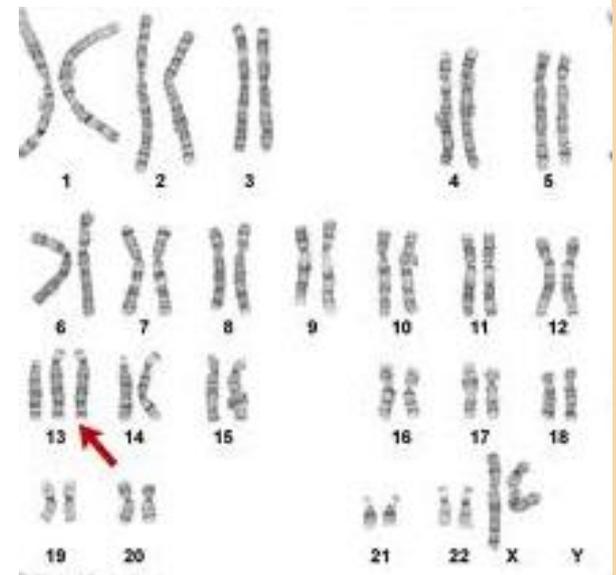
TRISOMY 21

- Trisomy 21, which causes Down Syndrome, is the most common autosomal aneuploidy seen among live births. The extra 21st chromosome is contributed by the mother in approximately 90% of cases. Mosaicism is seen in 2% to 4% of Down Syndrome cases, and it often accompanies a milder phenotype.



PATAU SYNDROME

- Trisomy 13
- Mosaic cases
- Result of balanced translocation in parent
- Most of the cases occur as random event
- Unless one of the parents is a carrier of a translocation, the chances of having another trisomy 13 child is less than 1%.
- More than 80% of children die in first year.



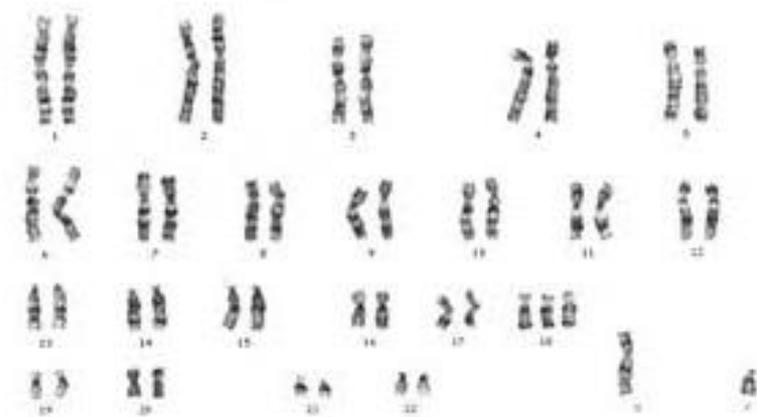
PATAU SYNDROME – CLINICAL FEATURES

- Nervous system:
 - Mental and motor challenged
 - Microcephaly
 - Holoprosencephaly
 - Structural eye defects
 - meningocele
- Musculoskeletal:
 - Polydactyly
 - Low-set ears
 - Deformed feet
 - Overlapping of fingers over thumbs
 - Cleft palate



EDWARDS SYNDROME

- Trisomy 18
- Mosaic cases (small percentage)
- Incidence increases with maternal age
- Median lifespan is 5-15 days



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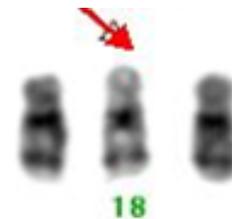
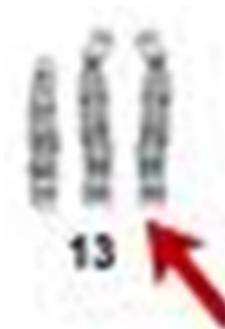
EDWARDS SYNDROME – CLINICAL FEATURES

- Nervous system:
 - Mental retardation
 - Developmental delay
 - Microcephaly
- Musculoskeletal:
 - Low-set malformed ears
 - Deformed feet
 - Micrognathia
 - Cleft lip/palate
 - Hypertelorism
- In utero:
 - Cardiac anomalies followed by central nervous system anomalies such as head shape abnormalities.



TRISOMIES

- Trisomies of the 13th and 18th chromosomes are sometimes compatible with survival to term, although 95% or more of affected fetuses are spontaneously aborted. These trisomies are much less common at birth than is trisomy 21, and they produce severer disease features, with 95% mortality during the first year of life. As in trisomy 21, there is a maternal age effect, and the mother contributes the extra chromosome in approximately 90% of cases.



TURNER SYNDROME

- Monosomy X
- Mosaic cases (partial monosomy X)

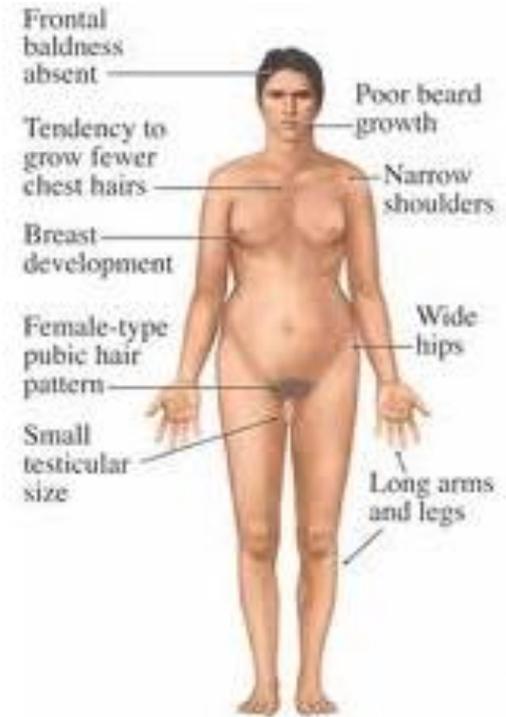
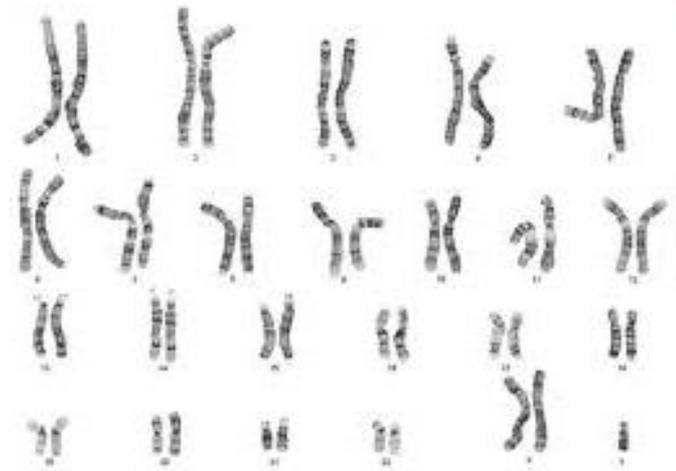
- Short stature
- Swelling
- Broad chest
- Low-set ears
- Webbed neck

- Gonadal dysfunction



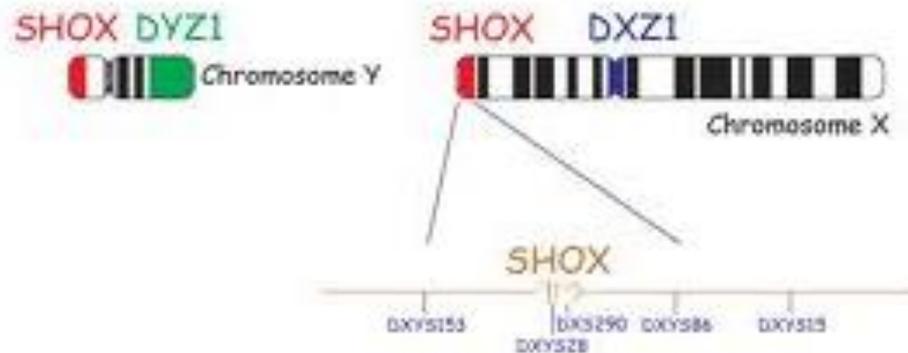
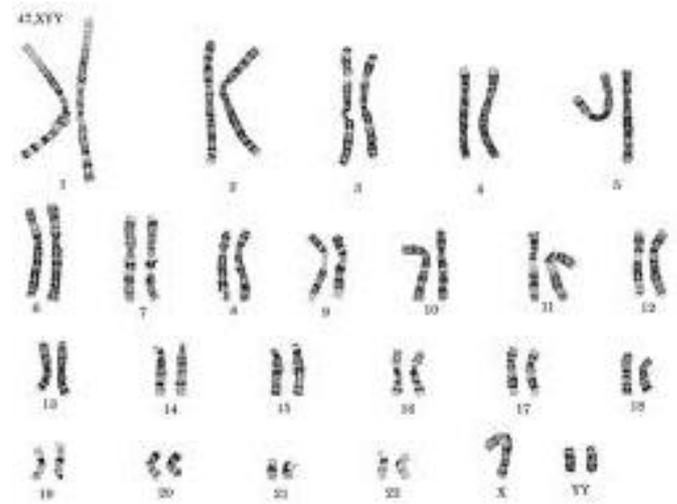
KLINFELTER SYNDROME

- Additional X chromosome in males
- Most common sex chromosome disorder in males
- 1 in 550-600 males
- Often without symptoms
- Hypogonadism
- Reduced fertility



XYY „SYNDROME”

- Phenotype is normal
- Increased growth velocity in boys
- Increased risk of learning difficulties
- The increased gene dosage of three X/Y chromosome pseudoautosomal region (PAR1) *SHOX* genes has been postulated as a cause of the increased stature seen in all three sex chromosome trisomies: 47,XXX, 47,XXY and 47,XYY

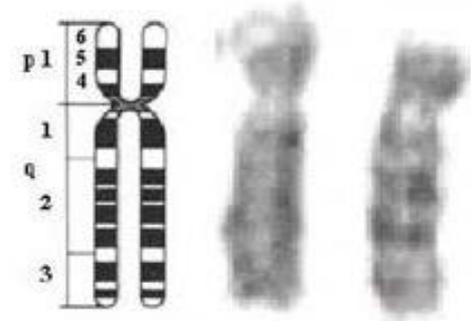


SMALL VISIBLE CHROMOSOME DELETIONS

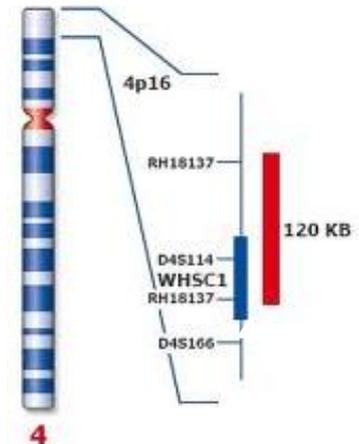
- Wolf – Hirschhorn Syndrome (4p-)
- Cri du Chat Syndrome (5p-)

WOLF – HIRSCHHORN SYNDROME (WHS)

- Deletion of terminal part of short arm of chromosome 4 (4p-)



- Can be also caused by microdeletion of critical region (*WHCR1* or *WHCR2*)



WOLF – HIRSCHHORN SYNDROME

- About 87% represent *de novo* cases
- 13% are inherited from a translocation-carrier parent
- Critical region determining phenotype is at 4p16.3

WHS – clinical features

- Craniofacial phenotype:
 - Microcephaly
 - Micrognathia
 - Short philtrum
 - Prominent glabella
 - Hypertelorism
 - Dysplastic ears
- Growth and mental retardation
- Muscle hypotonia
- Seizures
- Congenital heart defects

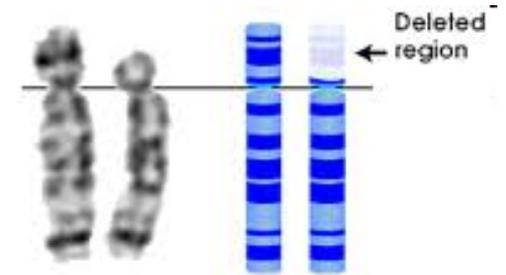
- Hypospadias
- Colobomata of the iris
- Renal anomalies
- Deafness



CRI DU CHAT SYNDROME (CDC)

- „Cat cry” syndrome
- Partial deletion of short arm of chromosome 5 (5p-)
- 85 - 90% cases – *de novo* deletion
- 10 – 15% cases – due to parental balanced translocation

- Can be caused by microdeletion of CDCS Critical Region (CDCSCR) – 5p15.2



CDC – clinical features

- Hypotonia
 - Microcephaly
 - Growth retardation
 - Hypertelorism
 - Epicanthal folds
 - Micrognathia
 - Flat nasal bridge
 - Low-set ears
-
- Cardiac defects
 - Affected patients are fertile and can reproduce



CDC – clinical features

- Characteristic cry of an infant can be first symptom
- Feeding problems (difficulties in sucking and swallowing)
- Low birth weight and poor growth
- Speech and motor delays
- Behavioral problems
- Excessive drooling

CONTIGUOUS GENE SYNDROMES

- Syndromes described before chromosomal etiology was known.
- Cytogenetic abnormalities are frequently detectable only by high resolution chromosomal analysis.
- Not all patients with the syndrome have a detectable cytogenetic abnormality.

CONTIGUOUS DELETION SYNDROMES

- Angelman syndrome
- Prader-Willi syndrome
- Beckwith-Wiedemann Syndrome (BWS)
- Miller-Dieker Syndrome (MDS or MDLS)
- WAGR Syndrome
- Williams syndrome
- Smith-Magenis syndrome

ANGELMAN SYNDROME

Chromosome 15



- Neuro-genetic disorder
- Classic example of genome imprinting
- Caused by microdeletion of 15q11-13 on maternal chromosome
- Caused by paternal imprinting of genes
- Caused by mutations of *UBE3A* gene

AS – CLINICAL FEATURES

Consistent (100% of cases)

- Severe developmental delay
- Speech impairment
- Movement and/or balance disorder
- Characteristic behavioral phenotype

Frequent (>80% of cases)

- Microcephaly
- Seizures
- Abnormal EEG

Associated (20-80% of cases)

- Strabismus
- Hypopigmentation
- Feeding problems
- Sleep disturbance
- Wide mouth
- Wide spaced teeth



PRADER-WILLI SYNDROME

Chromosome 15



- 7 genes are deleted or unexpressed
- Paternal 15q11-13 deletion
- Maternal imprinting

- Critical region contains *SNRPN* gene



PWS – CLINICAL FEATURES

In utero:

- Reduced movements
- Frequent abnormal fetal position
- Polyhydramnios (excessive amniotic fluid)

At birth:

- Hypotonia
- Feeding difficulties
- Hypogonadism



PWS – clinical features

Infancy:

- Failure to thrive
- Intellectual delay
- Strabismus
- Scoliosis

Childhood:

- Speech delay
- Hyperphagia (over-eating)
- Sleep disorders



PWS – clinical features

General physical appearance (adults):

- Prominent nasal bridge
- Small hands and feet
- High narrow forehead
- Almond-shaped eyes with downturned eyelids
- Excess fat, especially in the central part of the body
- Lack of complete sexual development



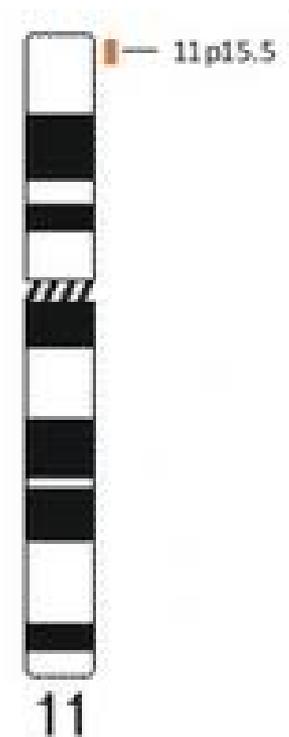
BECKWITH-WIEDEMANN SYNDROME (BWS)

- Is an overgrowth disorder
- >85% sporadic
- <15% can be familial

- 11p15 – imprinted genes
- Complex syndrome

- In 1/3 of patients unknown mutation

- Genes involved:
 - *IGF2*
 - *p57*
 - *CDKN1C*
 - *H19*
 - *LIT1*



BWS – CLINICAL FEATURES

- EMG = exomphalos-macroglossia-gigantism
- Macroglossia
- Macrosomia
- Midline abdominal wall defects
- Ear creases or ear pits
- Neonatal hypoglycemia

Beckwith-Wiedemann syndrome



Abdominal wall defects:

- Common in BWS children
 - Require surgical treatment
 - Different range of severity
 - Omphalocele (most serious)
 - Umbilical hernia (least serious)



Intestine protruding through abdominal wall defect

#ADAM



Umbilical hernia

#ADAM

Macroglossia:

- Present in >90% BWS patients
- Becomes less noticeable with age
- In severe cases can cause respiratory, feeding and speech problems

Macroglossia (abnormally large tongue)



#ADAM

Nevus flammeus (port wine stain):

- Flat, red birthmark caused by small blood vessels malformations
- In BWS patients often present on forehead or neck



Hemihypertrophy:

- Abnormal asymmetry between left and right sides of the body occurring when the one part grows faster than the other



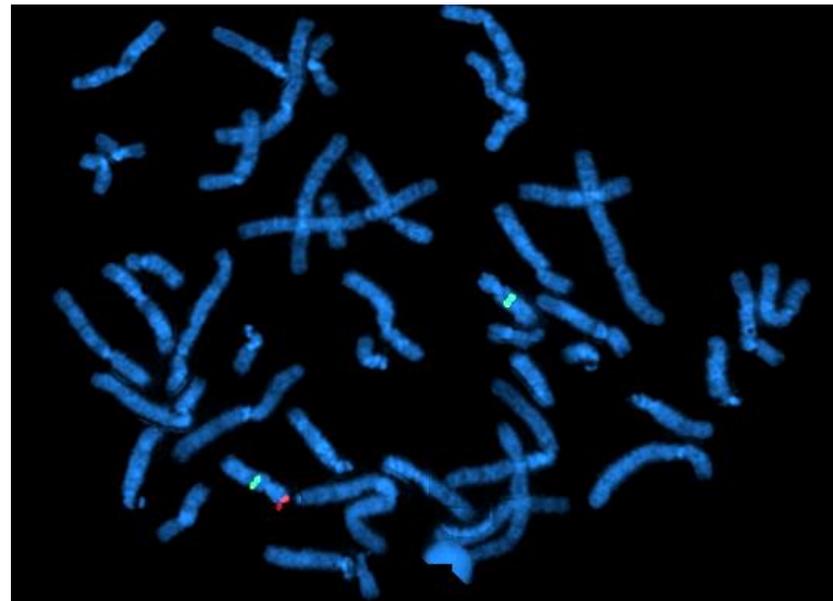
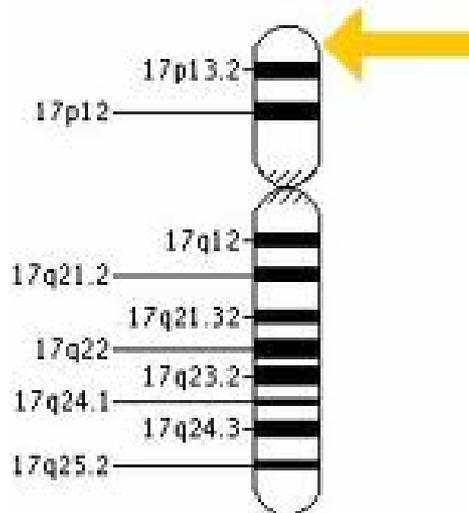
Neoplasms:

- >80% cases do not develop cancer, but children with BWS are ~600 times more likely to develop childhood cancer:
 - Wilms tumor (nephroblastoma)
 - Hepatoblastoma
 - Adrenal cortical carcinoma
 - Neuroblastoma
 - Rhabdomyosarcoma

MILLER-DIEKER SYNDROME (MDS)

- Miller-Dieker lissencephaly syndrome (MDLS)
- Chromosome 17p13.3 deletion syndrome
- Autosomal dominant congenital disorder

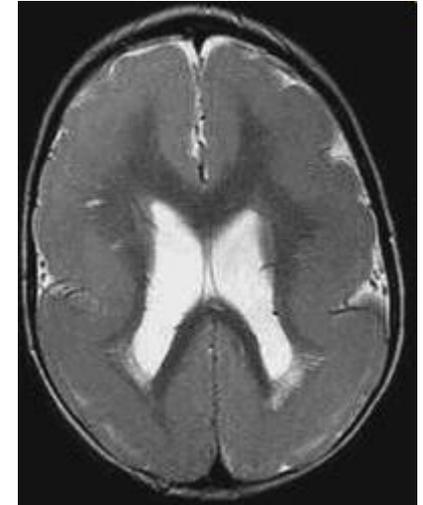
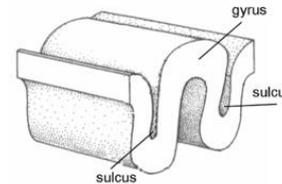
- Developmental defect of brain caused by incomplete neuronal migration



MDLS – CLINICAL FEATURES

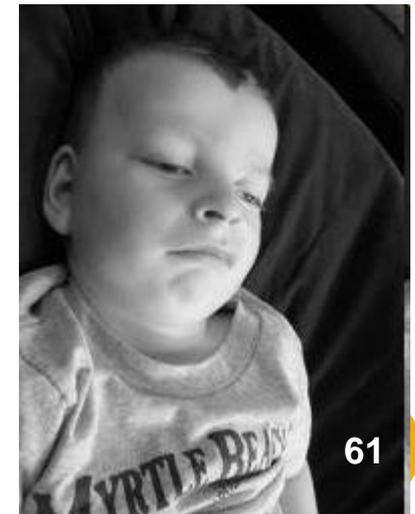
Brain:

- Lissencephaly (smooth brain)
- Absence of sulci and gyri
- 4 layers thick cerebral cortex (instead of 6)
- Microcephaly



Facial appearance:

- Prominent forehead
- Midface hypoplasia
- Small upturned nose
- Low-set ears
- Small jaw
- Thick upper lip

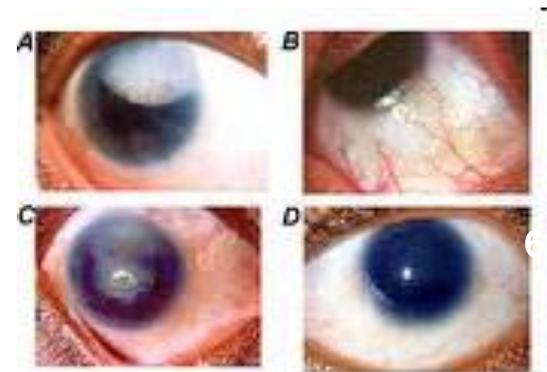


WAGR SYNDROME

- W = Wilms tumor
- A = Aniridia
- G = Genitourinary anomalies
- R = Mental Retardation

- O = Obesity

- Wilms tumor – a tumor of kidneys
- Aniridia – absence of iris



WAGR SYNDROME

- Results from chromosome 11 deletion (11p13) – loss of several genes
- Can be caused by *PAX6* and *WT1* mutations
- *PAX6* gene – „master control” gene for the development of eyes and sensory organs, certain neural and epidermal tissues and other homologous structures derived from ectodermal tissues.
- *WT1* gene – has an essential role for normal development of urogenital system.

DYSMORPHOLOGY

- The term “dysmorphology” was first coined by Dr.David Smith, USA in 1960s.
- It implies study of human congenital defects and abnormalities of body structure that originate before birth.
- The term “dysmorphic” is used to describe individuals whose physical features are not usually found in other individuals with the same age or ethnic background.
- “Dys” (Greek)=disordered or abnormal
- “Morph”=shape

CONGENITAL DISORDER

- Can be result of:
 - chromosomal abnormality
 - genetic abnormality
 - intrauterine environment
 - errors of morphogenesis
 - infection

The outcome will depend on complex interactions between the prenatal deficit and postnatal environment.

TERATOGEN – any substance that causes birth defect

CONGENITAL MALFORMATIONS (ETIOLOGY):

Multifactorial	20%
Monogenic	7,5
Chromosomal aberrations	6
Mather's health/diseases	3
Infections	2
Drugs, alkohol, radiation	1,5
Unknown	60

Dysmorphic features can be present as a single trait or in groups.

Combinations of features can result in:

1. Syndrome of congenital defects (malformation syndrome)
2. Sequence of congenital defects
3. Association of defects
4. Complex of defects

1. MALFORMATION SYNDROME

Presence of congenital anomalies in characteristic pattern

2. Sequence of malformations

Cascade of anatomical defects resulted from one anomaly

- For example: Pierre-Robin Sequence – micrognathia
- Potter Sequence – agenesis of kidneys



Pierre-Robin sequence



Potter sequence

3. Association

- Random coexistence of malformations with higher frequency than they exist separately
- Malformations (usually 5-6) coexist, but clinical picture is not constant
- From malformations A, B, C, D, E, F, in one child A, B, F can be observed and in other B, D, E, F.
- Names of associations are acronyms (come from first letters english name of malformation)
- CHARGE – Coloboma, Hear defects, choanal Atresia, Retardation of growth and development, Genitourinary defects, Ear anomalies

- **Association:** An association is a group of anomalies that occur more frequently than would be expected by chance alone but that do not have a predictable pattern or unified etiology (e.g. VATER association).



Vertebral anomalies, absence of radius & anal atresia as a part of VATER association

VATER (VACTERL)= V: vertebral, A: anal anomalies, C: cardiac, TE: tracheo-esophageal fistula, R: radial, renal anomalies, L: limb anomalies

MECHANISMS OF DISORDER FORMATION:

1. DEFORMATION - condition arising from mechanical stress to normal tissue. Deformations often occur in the second or third semester, and can be due to oligohydramnios.



- **Deformation:** Distortion by a physical force of an otherwise normal structure. This could be due to uterine malformation, twins or oligohydramnios (e.g. contractures of limbs and talipes deformity).



Multiple joint contractures (arthrogryposis)



Talipes deformity

2. DISRUPTION - involves breakdown of normal tissues (for example amniotic band syndrome).



- **Disruption:** Destruction of a tissue that was previously normal. Examples of disruptive agents include amniotic bands, local tissue ischemia or hemorrhage.



Congenital ring constrictions with amniotic bands

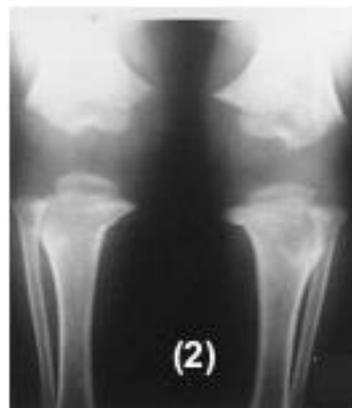


3. DYSPLASIA - disorder at the organ level that is due to problems with tissue development.

- Osteogenesis imperfecta
- Albright osteodystrophy



- **Dysplasia**: Abnormal cellular organization within tissue resulting in structural changes. For example within cartilage or bone in skeletal dysplasias (e.g. achondroplasia).



Characteristic features of achondroplasia

Radiological findings in achondroplasia: Loss of caudal widening (1), short long bones of lower limbs (2)

4. MALFORMATION - associated with a disorder of tissue development. Malformations often occur in the first trimester.

Abnormalities can be characterised by:

- Incomplete morphogenesis
 - Agenesis
 - Hipoplasia
 - Incomplete closure (cleft lip/palate)
 - Incomplete division (syndactyly)



- **A malformation / anomaly:** is a primary defect where there is a basic alteration of structure, usually occurring before 10 weeks of gestation.
- Examples: cleft palate, anencephaly, agenesis of limb or part of a limb.



Cleft lip & palate



Absence of digits (ectrodactyly)

Impact of malformations

- About 3% of all children born will have a significant congenital malformation.
- These congenital malformations are responsible for a large proportion of neonatal and infant deaths.
- They also account for about 30% of all admissions to pediatric hospitals.
- It is important to recognize both major and minor malformations as they may lead to the early detection and intervention of a genetic disorder.

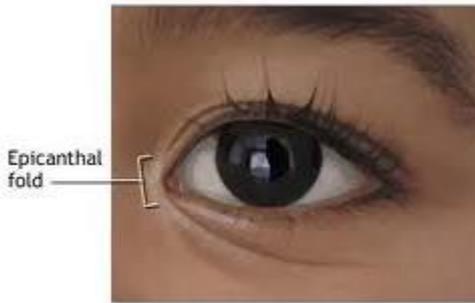
The difference between major and minor anomalies

- **Major anomalies** are severe, impair normal body function and require surgery for management (e.g. cleft palate, congenital heart disease.....).
- They may be isolated or multiple affecting different body systems.
- **Minor anomalies** are primarily of cosmetic significance (e.g. small ear, fifth finger clinodactyly.....). They occur with variable frequencies in the normal population.

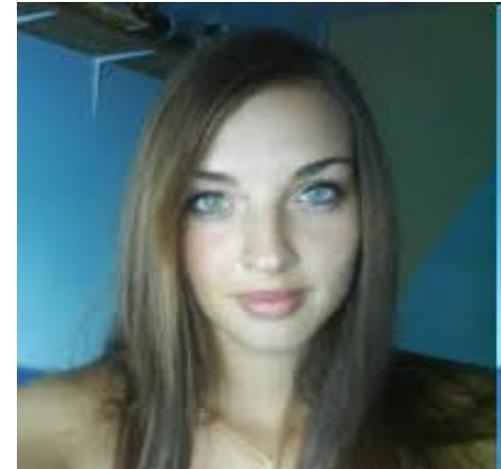
DYSMORPHIC FEATURES:

- Small anomalies without major health consequences
- Can occur separately
- Some of them can be polymorphic variants

- Epicanthal fold



- Hypertelorism



- Clinodactyly

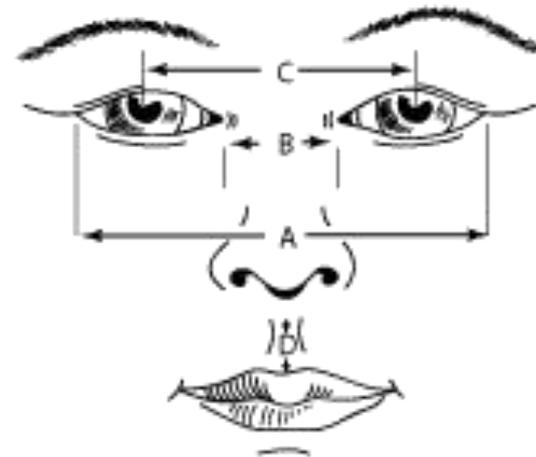
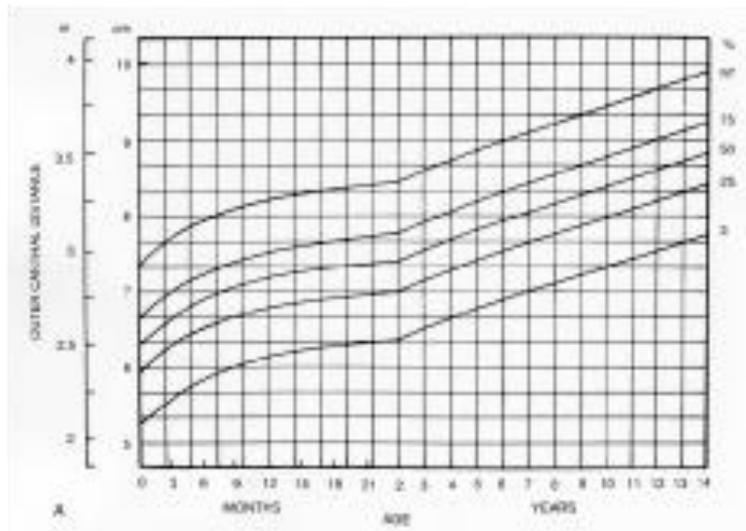
#ADAM

- Café au lait marks



FACIAL DYSMORPHOLOGY

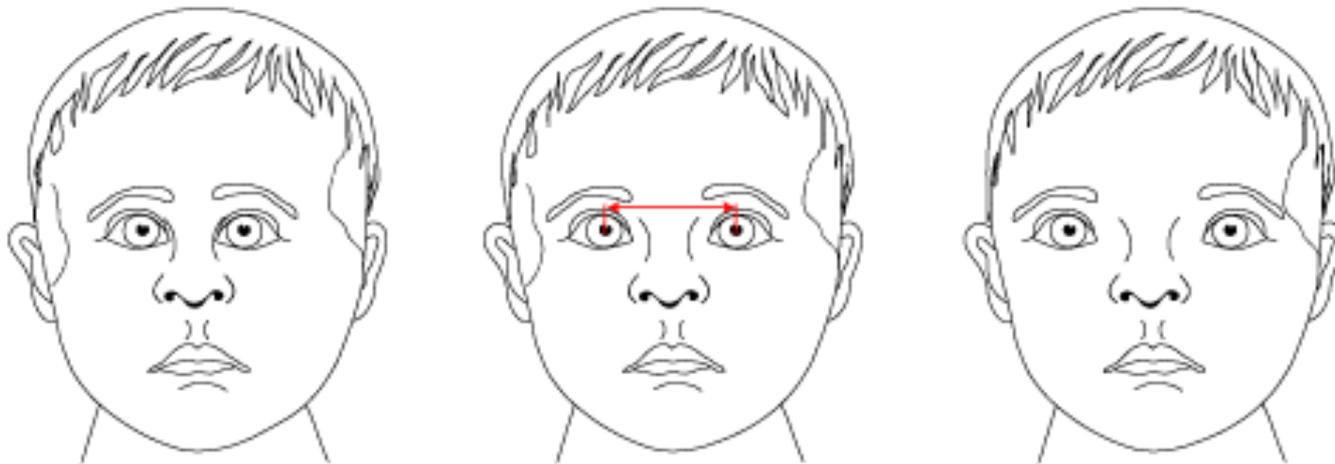
- Facial measurements can be made of certain facial regions (as noted below for example using A for outer canthal distance), and when indicated, can be measured and plotted on growth charts.



Adapted from Smith's Recognizable Patterns of Human Malformation, 5 th Ed., ed. Jones, KL

ORBITAL PLACEMENT

- Hypertelorism is defined by an increased interpupillary distance. Hypertelorism (right); normal (middle); hypotelorism (left).



Facial features

- **Eyebrows**

e.g. Synophrys (fused eyebrows)



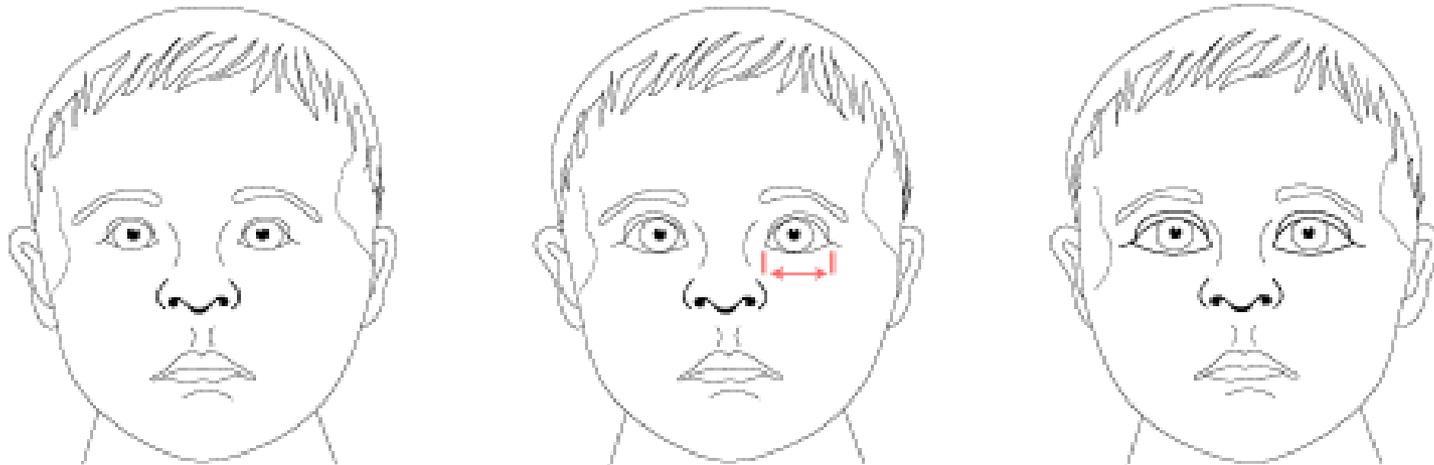
- **Innecanthal distance**

e.g. Hypotelorism (decreased inner canthal distance or
hypertelorism (increased inner canthal distance)



PALPEBRAL FISSURE LENGTH

- Often this length is actually measured and plotted. Short (left); normal (middle); large (right).



- **Palpebral fissures (length)**

Short palpebral fissures (the length of the palpebral fissure is usually equal to the distance between the two eyes i.e. innercanthal distance)



Blepharophimosis



Unilateral microphthalmia (small eye)



Unilateral anophthalmia
(absent eye globe)

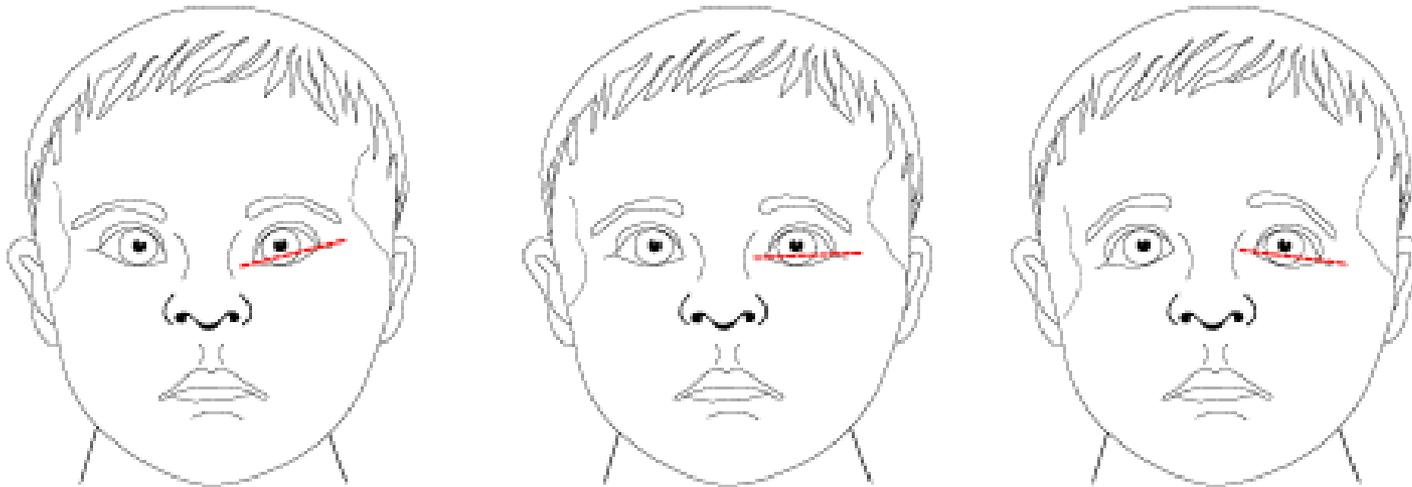


Bilateral anophthalmia



PALPEBRAL FISSURE SLANT

- This varies greatly with ethnic origin. Up (left); normal (middle); down (right).



- **Palpebral fissures (slanting)**

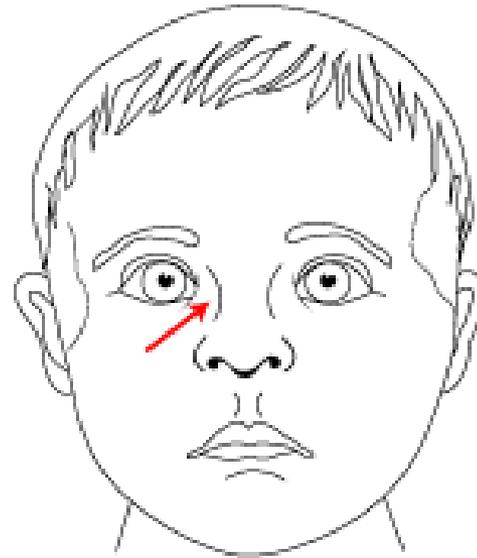
Upslanting of palpebral fissures (e.g. Down syndrome)



or downslanting of palpebral fissures (e.g. Noonan syndrome & Rubinstein-Taybi syndrome)



EPICANTHAL FOLDS



- Eyes

e.g. corneal opacities, heterochromia or other eye abnormalities



Corneal opacity



Heterochromia



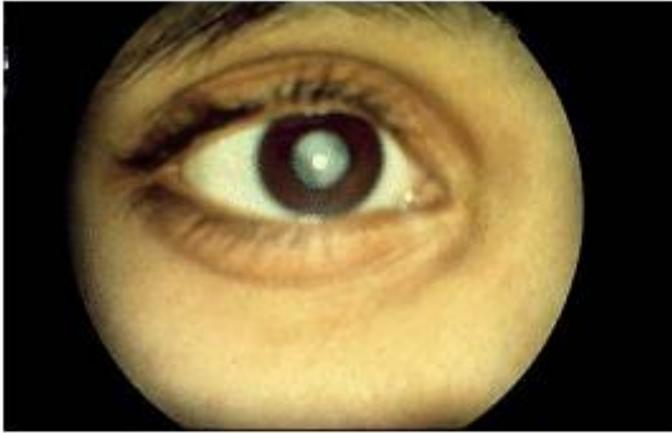
Albinism



Squint



Congenital glaucoma



Cataract



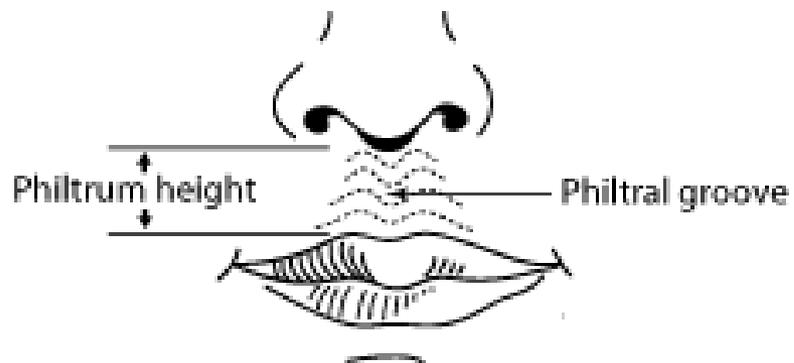
Epibulbar dermoid



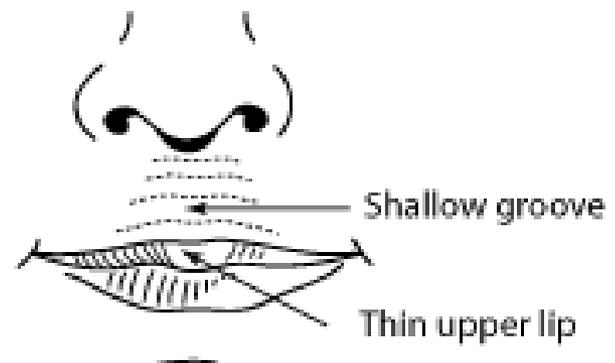
Bilateral ptosis of eyelids

PHILTRUM SHAPE

Normal



Smooth philtrum
with thin upper lip

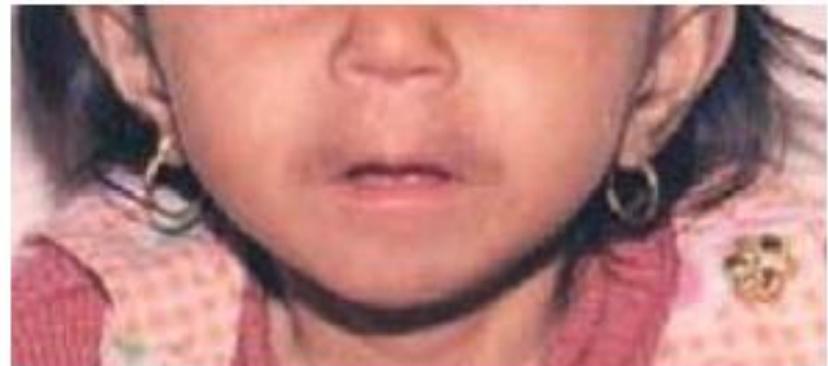
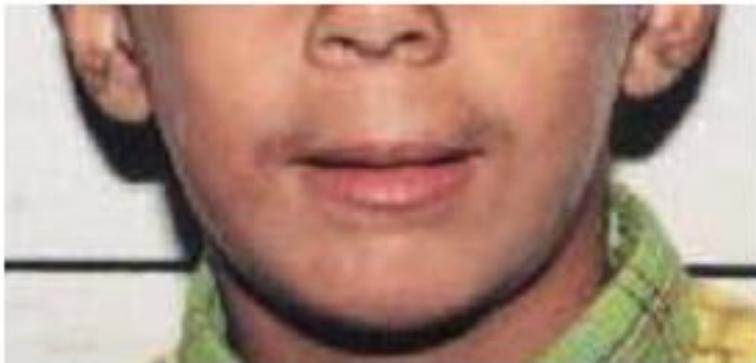


- **Philtrum**

e.g. short, long or flat



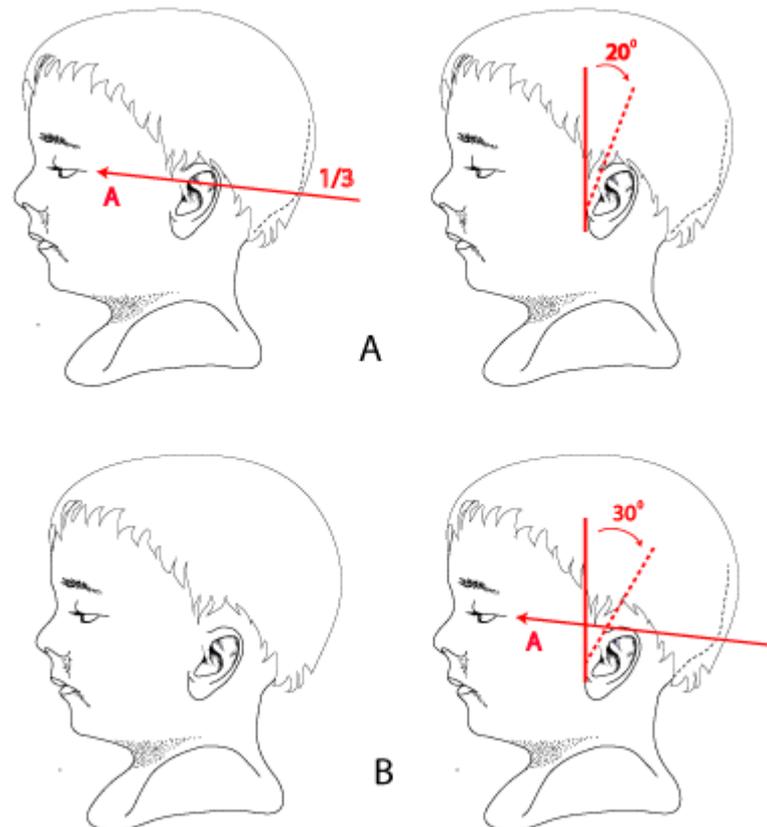
Short philtrum



Long flat philtrum

EAR PLACEMENT

- Images A show normal ear position. Low set ears are positioned below the horizontal line as illustrated in B.



Abnormal shape or size of the ears



Cupped simple ears



Preauricular pit



Cauliflower ears

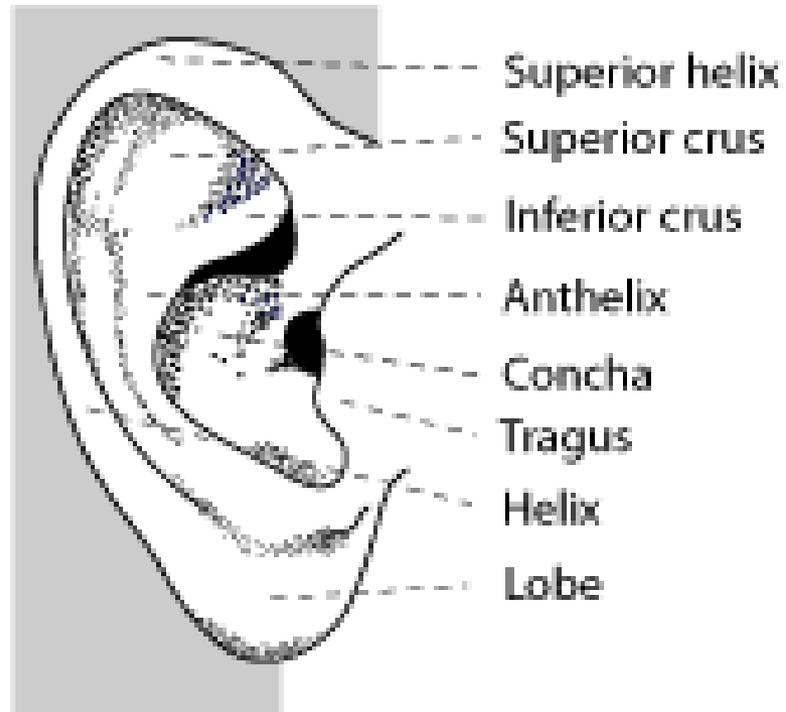


Microtia (small or dysplastic ears)

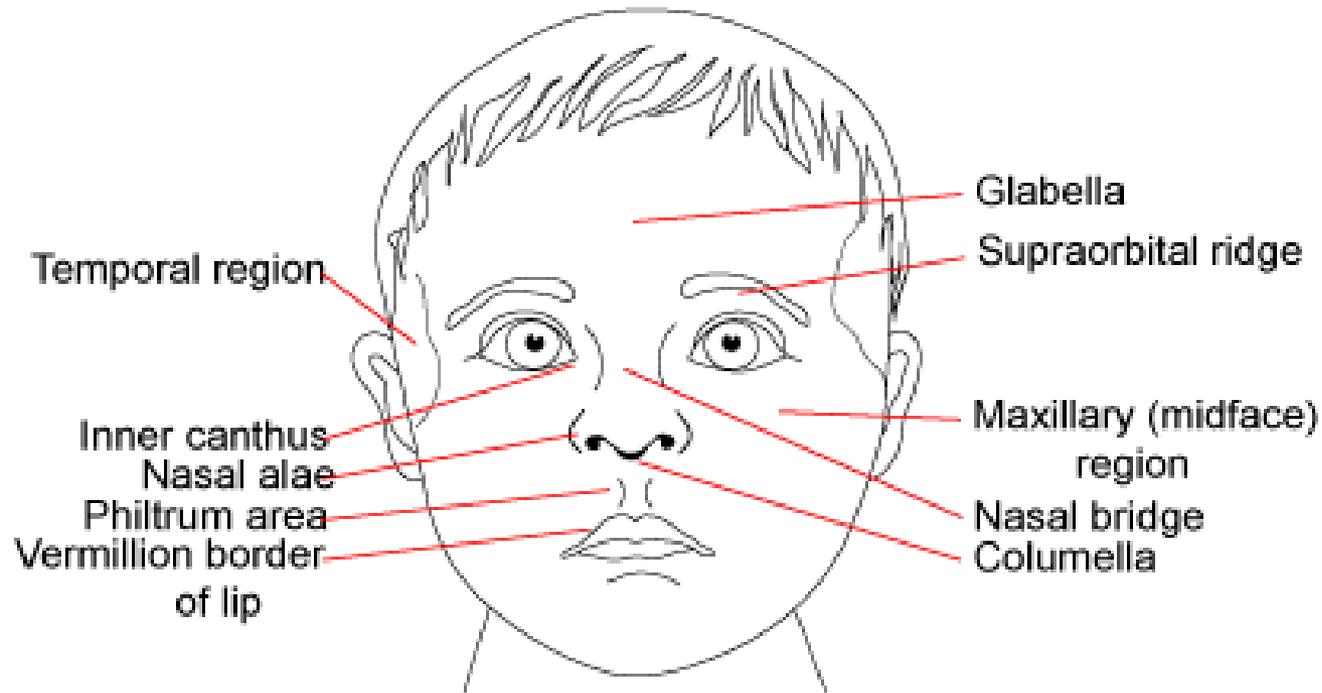


Preauricular skin tags

ANATOMIC LANDMARKS, EAR



OTHER ANATOMICAL LANDMARKS, FACE



- Mouth & lips

Abnormal lips (thin/full, tented, down turned, cleft), big or small mouth (macrostomia or microstomia)



Thin tented lips



Thick patulous lips



Cleft lip



Macrostomia



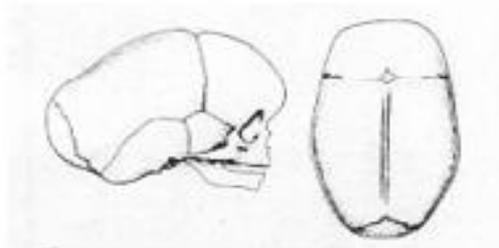
Lip pits



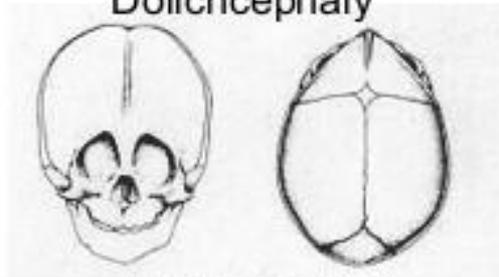
Microstomia

Specific organ anomalies

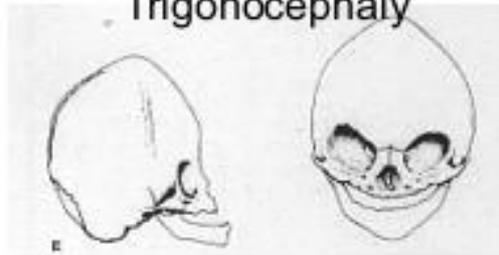
Unusual head shape



Dolichocephaly



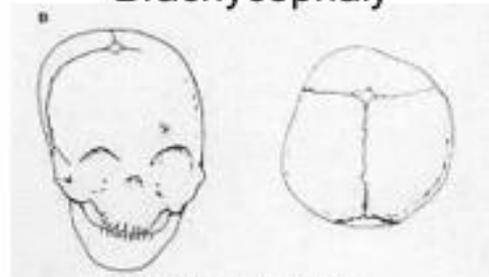
Trigonocephaly



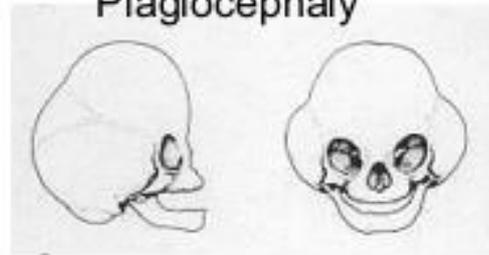
Oxycephaly



Brachycephaly



Plagiocephaly



Cloverleaf skull



Brachycephaly (flat occiput)

Head circumference

e.g. small head “microcephaly” (head circumference below $-3SD$)
or large head “macrocephaly”) (HC above $+3SD$)



Microcephaly



Macrocephaly
(Hydrocephalus)

Body proportions

e.g. short spine, short limbs or long limbs...



Disproportionate shortening in patients with mucopolysaccharidosis (1) & an autosomal recessive type of spondylo-epi-metaphyseal dysplasia (2)

Hands & feet

Brachydactyly (short fingers or toes)



Arachnodactyly (long fingers or toes)



Clinodactyly (incurved fingers, usually fifth finger)



Syndactyly (fusion of digits)



Reduction (absence) defect



Hemimelia (absent forearm & hand))



Ectrodactyly (absent toes)



Apodia (absent foot)



Axial hand reduction (split hands)

Polydactyly (preaxial, postaxial extra digits)



Postaxial polydactyly
(pedunculated post minimus)



Complete postaxial polydactyly

Camptodactyly (contracture of fingers)



Polysyndactyly (preaxial polydactyly with syndactyly)



Other limb anomalies



Macrodactyly (large digits)



Rocker bottom feet with sandal gap
between 1st & 2nd toes



Clasped thumb (adducted & flexed)

Neck

e.g. short, webbed...

Webbed neck



Short neck

Chest

Abnormal chest shape (e.g. pectus carinatum, pectus excavatum, short sternum)



Pectus carinatum



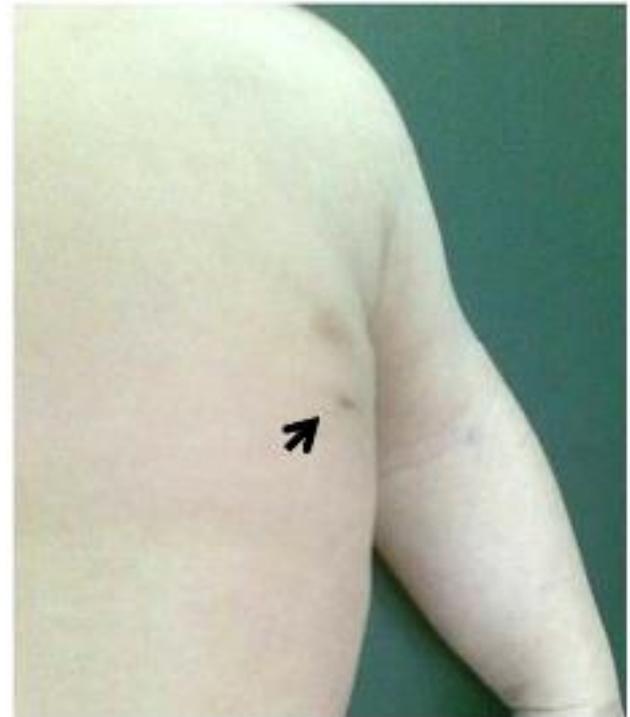
Pectus excavatum

Nipples

e.g. widely spaced, supernumerary, inverted....



Widely spaced nipples



Supernumerary nipple

RESEARCH ARTICLE

Elements of Morphology: Standard Terminology for the Hands and Feet

Leslie G. Biesecker,^{1*} Jon M. Aase,² Carol Clericuzio,³ Fiorella Gurrieri,⁴ I. Karen Temple,⁵ and Helga Toriello⁶

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Judith E. Allanson,^{1*} Christopher Cunniff,² H. Eugene Hoyme,³ Julie McGaughan,⁴ Max Muenke,⁵ and Giovanni Neri⁶

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