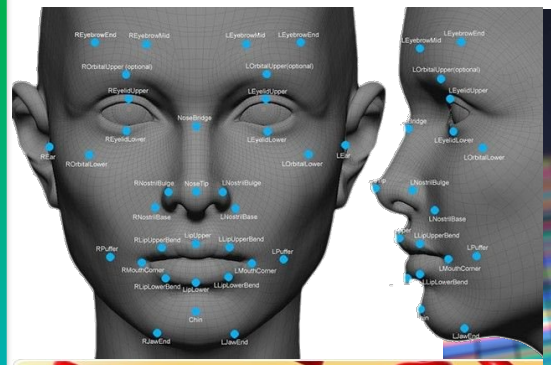
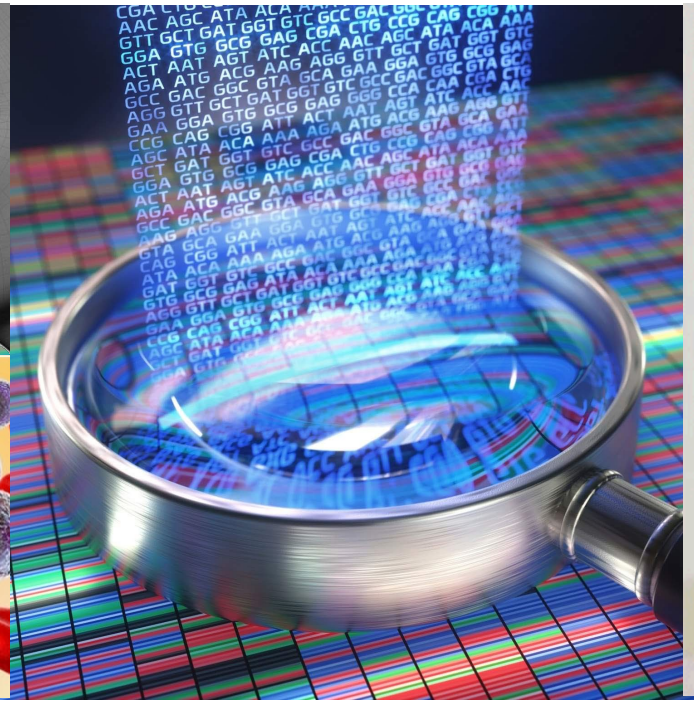
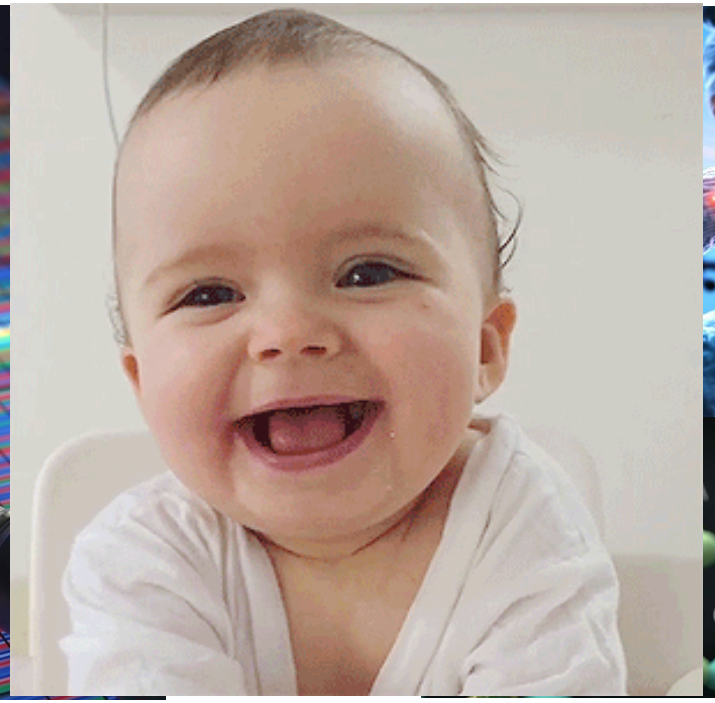
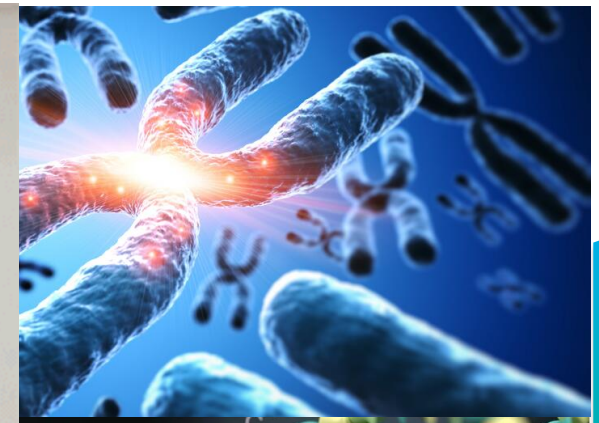
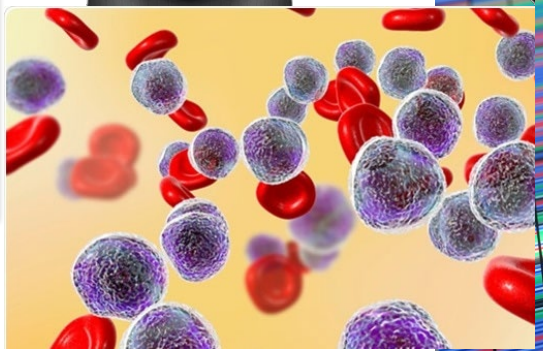
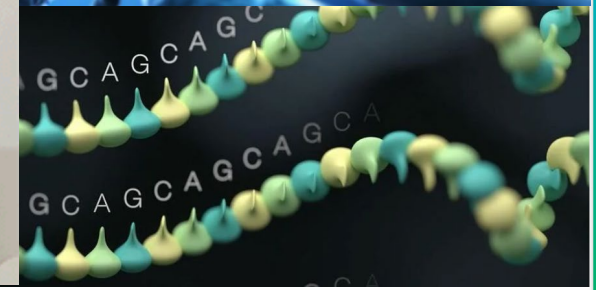
Humán Genomért Alapítvány2020

SEMMELWEIS EGYETEM 1769



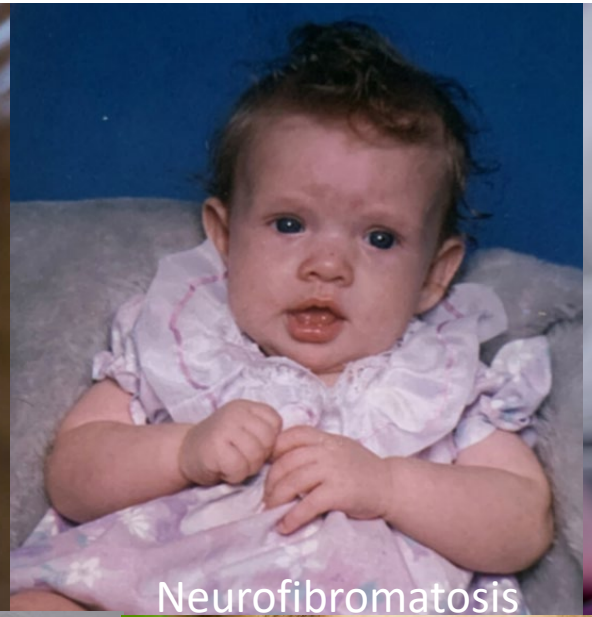






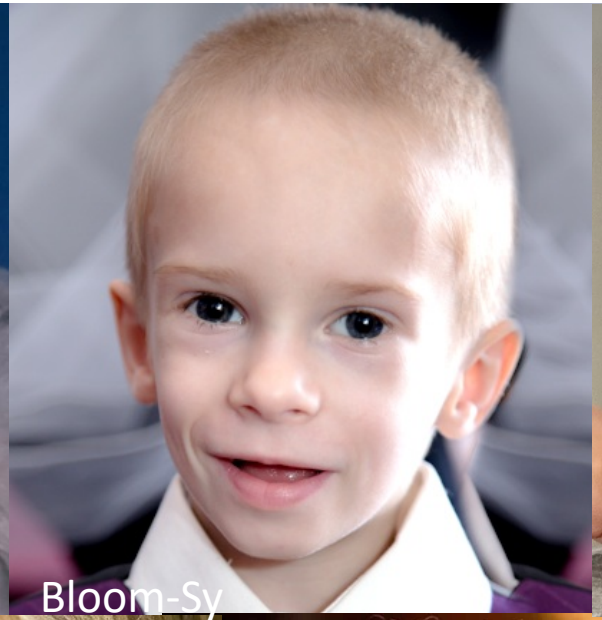
WAY TO DIAGNOSIS - MINOR ANOMALIES AND CHROMOSOMAL ABNORMALITIES RECOGNIZABLE BY MORPHOLOGICAL FEATURES

Árpád Ferenc Kovács, M.D., Ph.D

23.02.2022


Down-Sy


Neurofibromatosis


Bloom-Sy

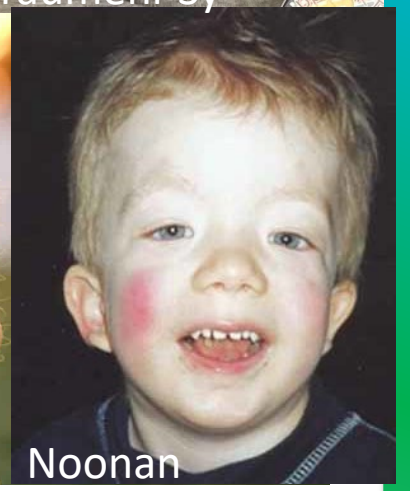

Li-Fraumeni-Sy


Kostmann-Sy


Diamond-Blackfan-Sy


Ataxia-teleangiectasia


Schwachman-Diamond


Noonan


FABRY
PROPION ACIDAEMIA
BIOTINIDASE DEF.
FENILKETONURIA
HMG-CoA LIASE DEF
FRUKTOSE 1,6 DIFOS-FATASE DEF.
SANFILIPPO
TAY-SACHS
GAUCHER
ORNITIN TRANS-CARBAMILASE DEF.
MCAD
MERRF
mtDNA POLIM. DEF.
GALACTOSAEMIA
HURLER
SANDHOFF
HEPATORENAL TIROSINAEMIA
KARNITIN TRANS-PORTER DEF
NIEMANN-PICK
PEARSON
POMPÉ
ADRENO-LEUKODISTROPHY
LESCH-NYHAN
LIPOPROTEIN LIPASE DEF.

GENETIC COUNSELLING

A.

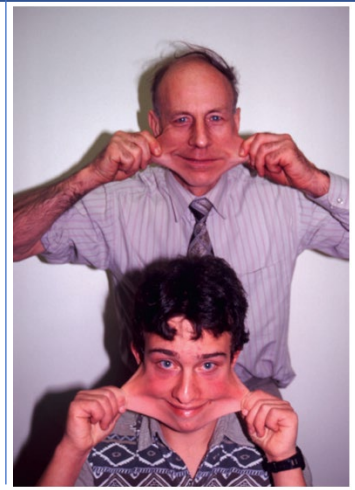
Based on family history, prior laboratory-, imaging- genetic tree and clinical findings genetic disorder can be ruled out

New signs and symptoms develop

Genetic re-counselling

B.

The diagnostic criteria for a defined genetic disease is fullfilled by clinical phenotype, laboratory and/ or imaging finding.

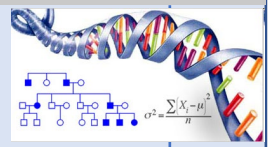


Clinical diagnosis

Family planning/ potential therapy

C.

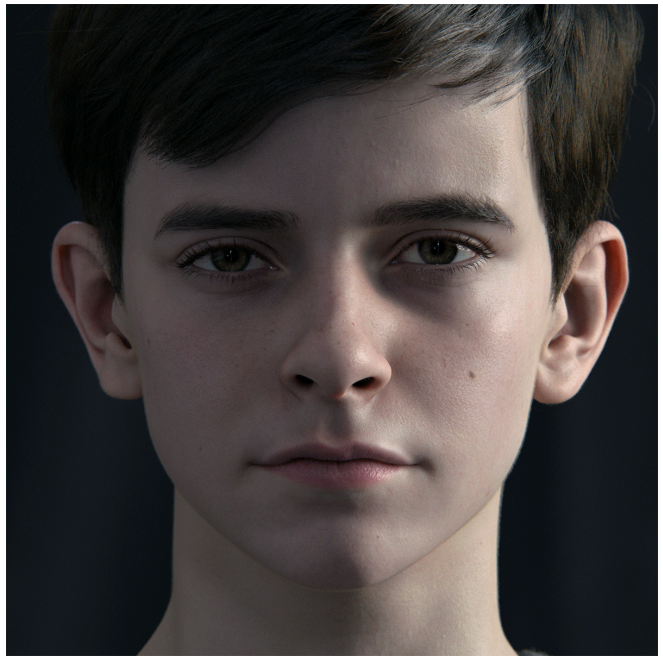
GENEDIAGNOSTICS



Post-test GENETIC COUNSELLING

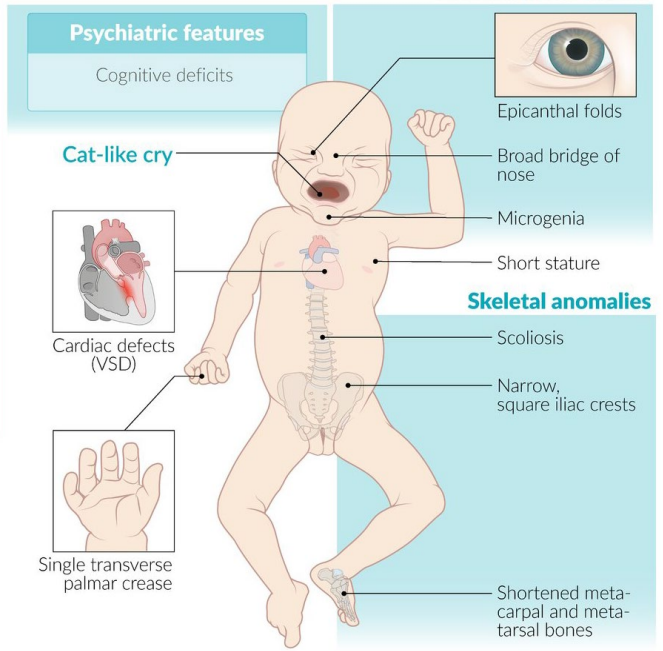
CORE CONCEPTS

MINOR ANOMALY



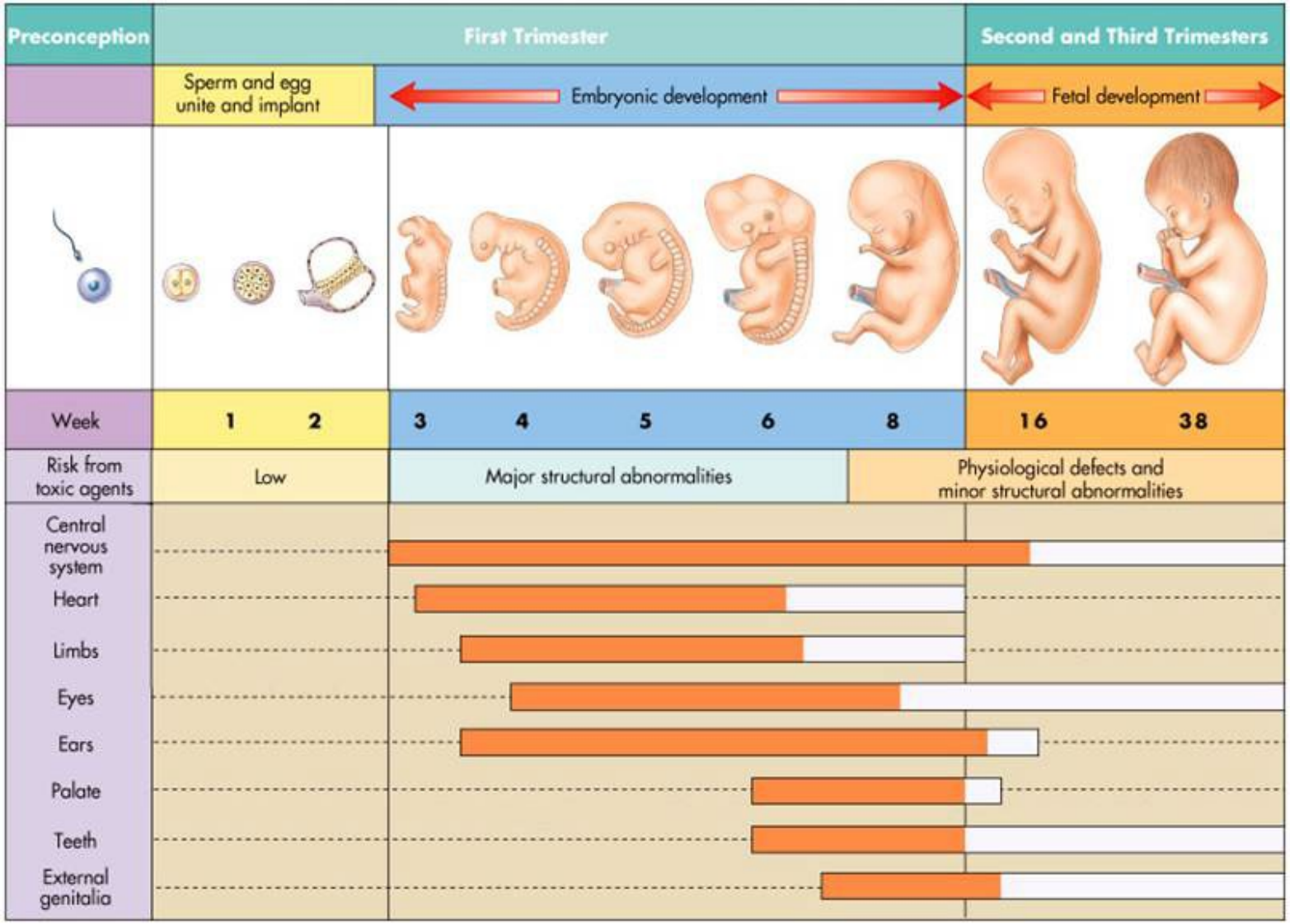
Small and unspecific inborn morphological alteration without functional consequence, that develops in the intrauterine environment.

SYNDROME



Collection of signs and symptoms involving multiple organs, that usually go together and are accompanied by various minor anomalies.

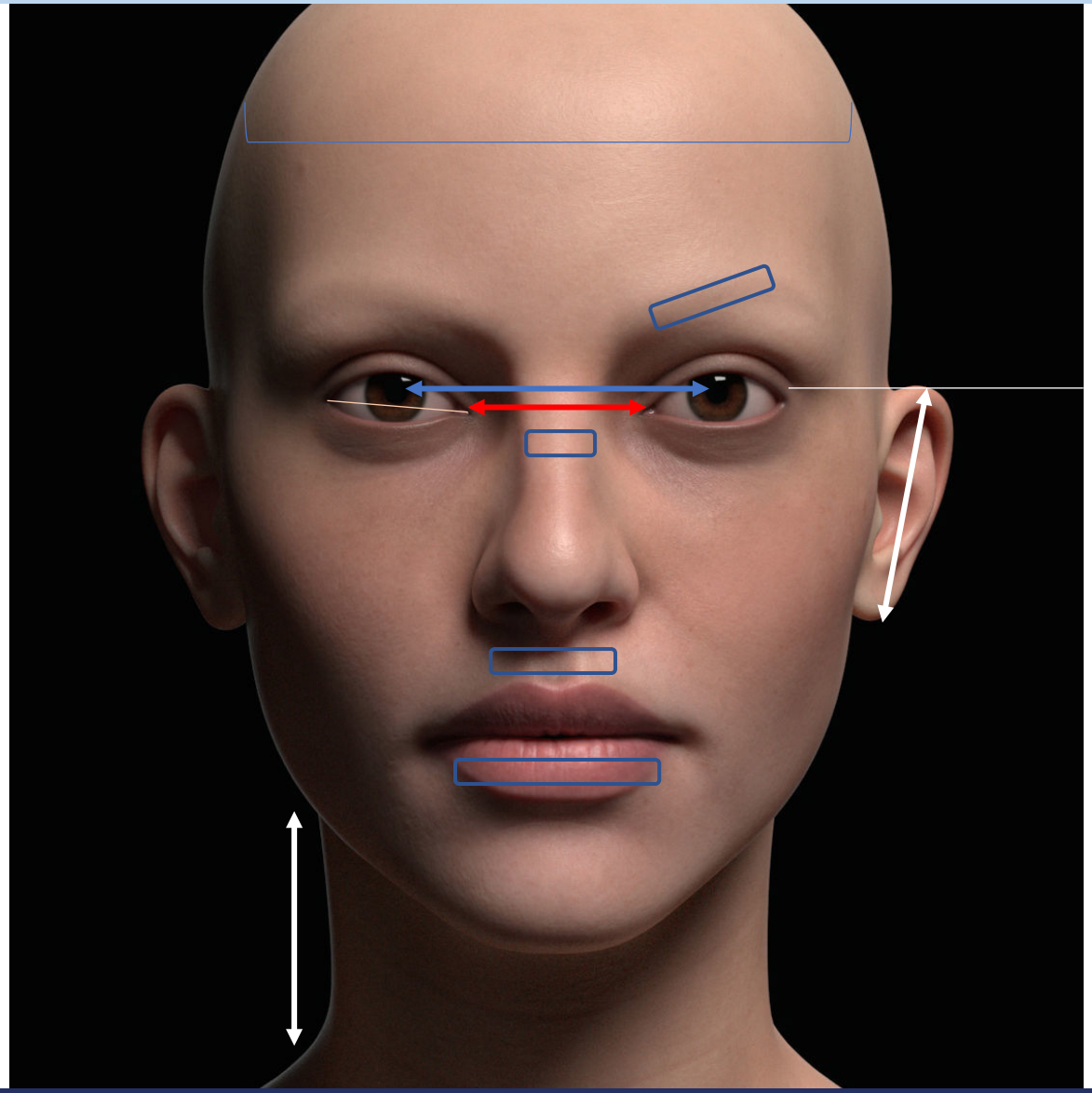
DEVELOPMENT OF MINOR ANOMALIES



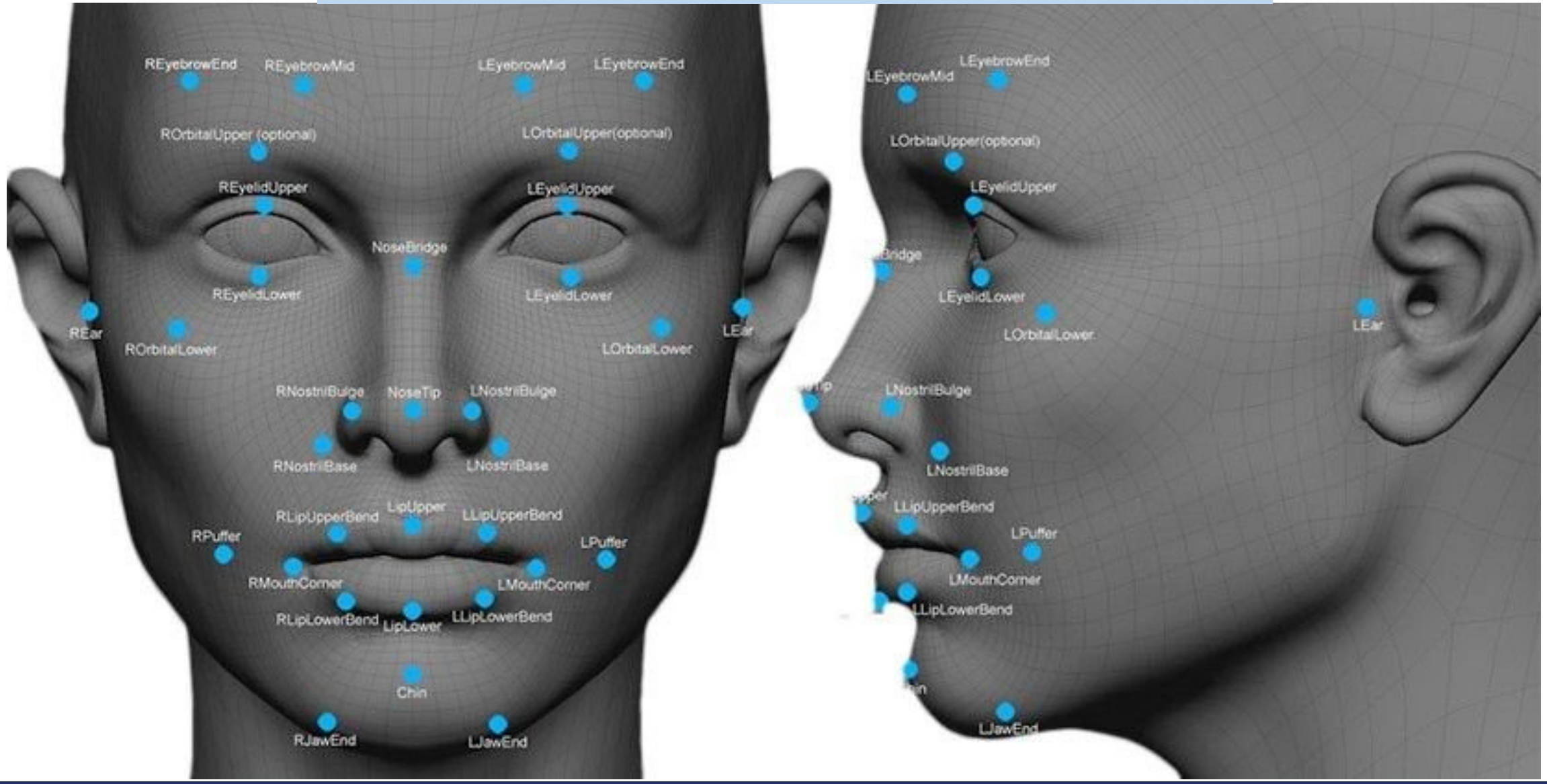
MINOR ANOMALIES: SUSPICION FOR GENETIC SYNDROMES

Required measurments for Dysmorphic features:

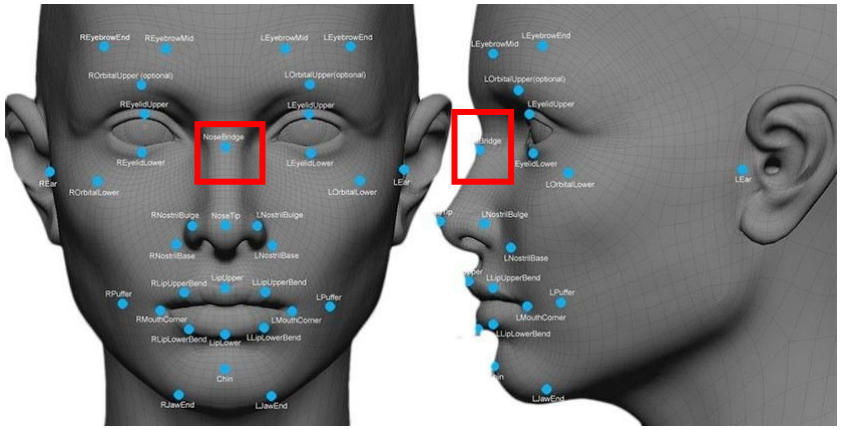
1. Height (pc)
2. Arm distance
3. Weight (pc)
4. Lower segment
5. Upper segment
6. Interpupillar distance
7. Distance between inner canthi
8. Head circumference
9. Testis volume
10. Ear length
11. Distance between philtrum- mandibular angle

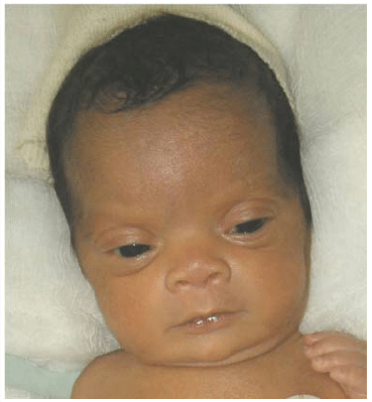
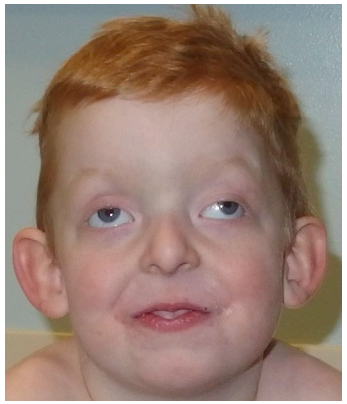
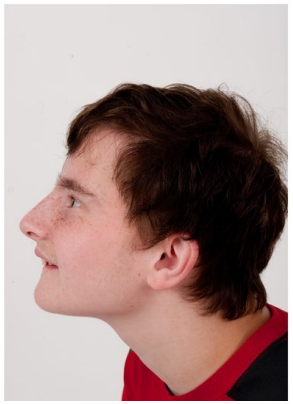
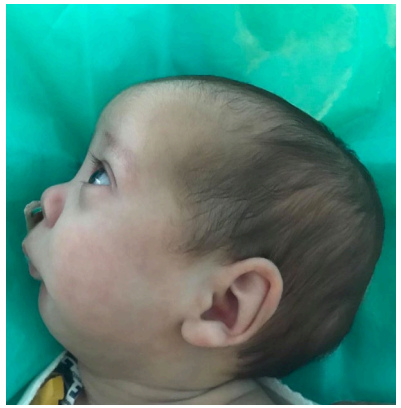
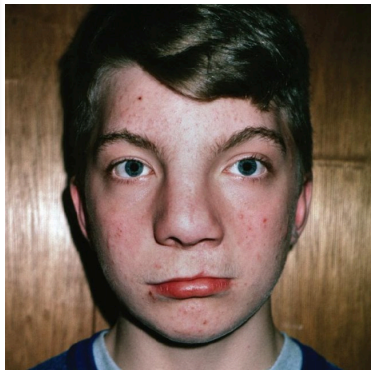
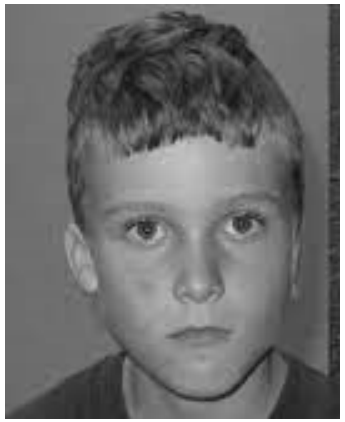
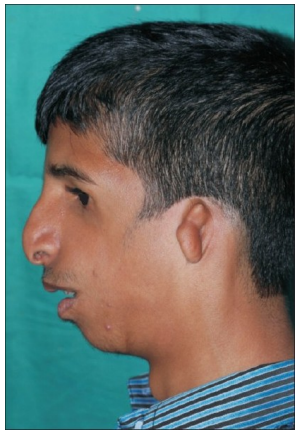


KEY FACIAL POINTS FOR THE EVALUATION OF MINOR ANOMALIES

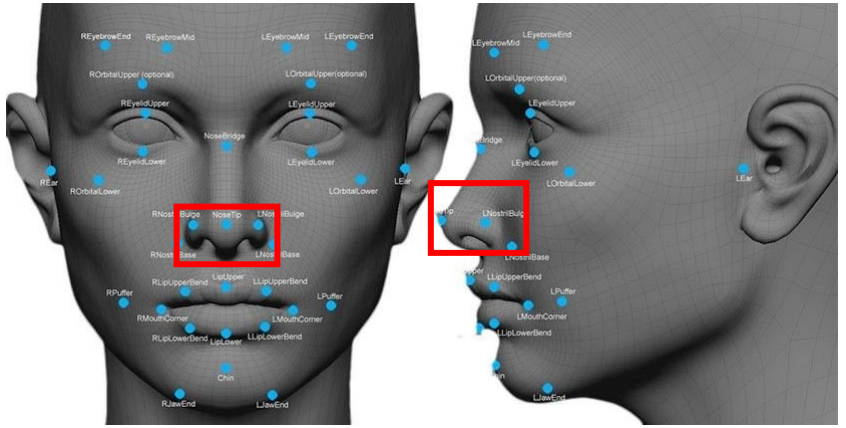


NASAL BRIDGE



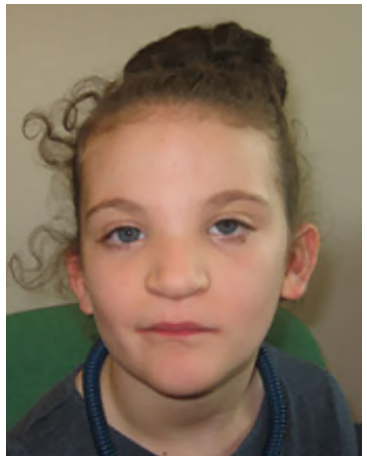
WIDE/ BROAD	NARROW	HIGH	FLATTENED
			
			

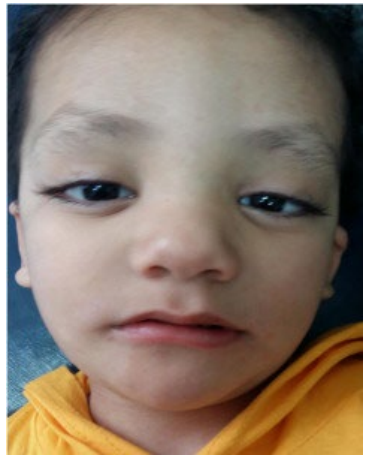
NOSE TIP AND NARES



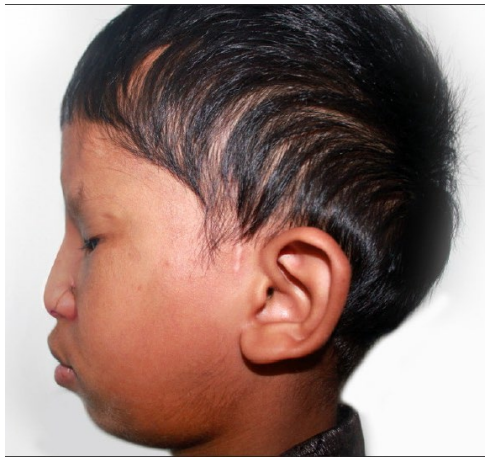
ANTEVERTED

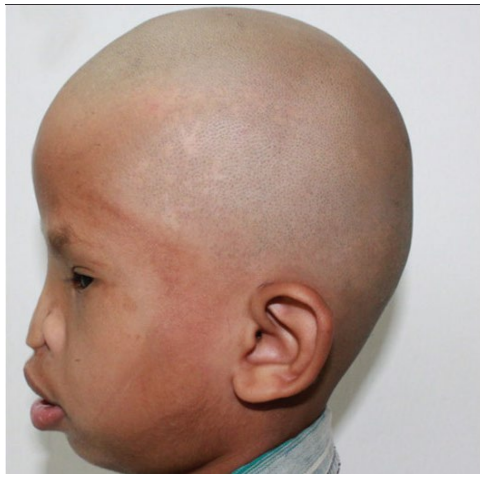
WIDE





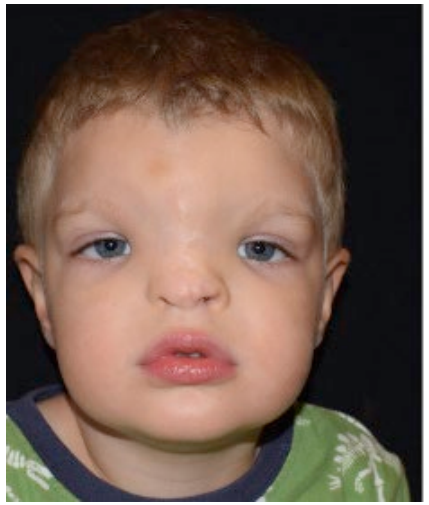
FLAT

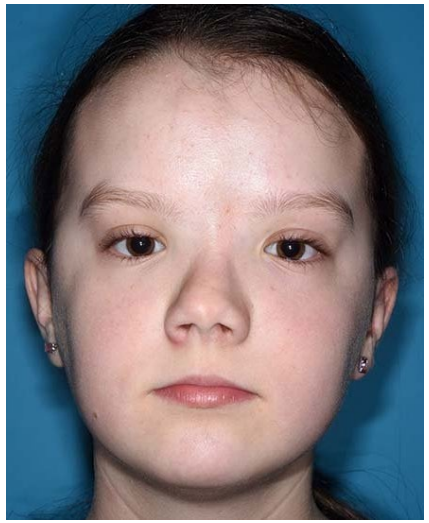




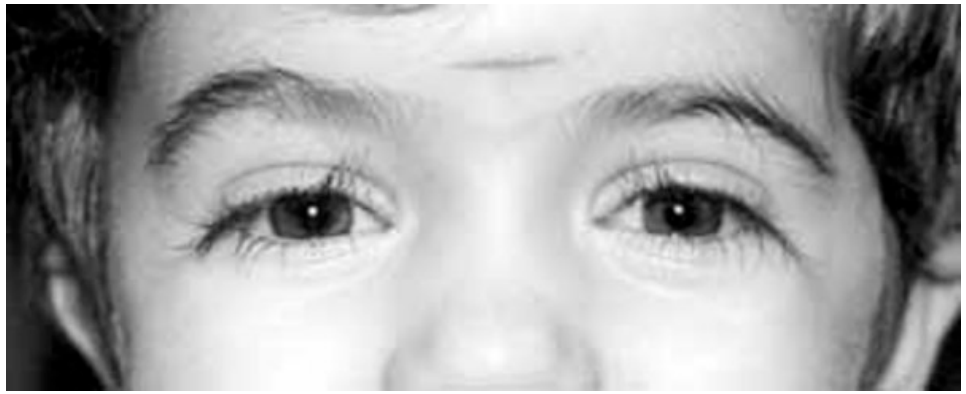
EYES

HYPERTELORISM

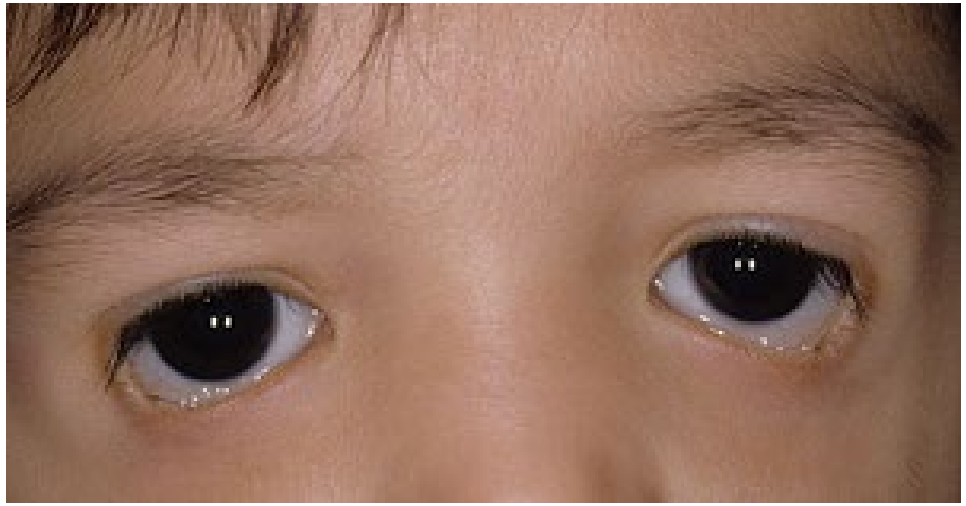


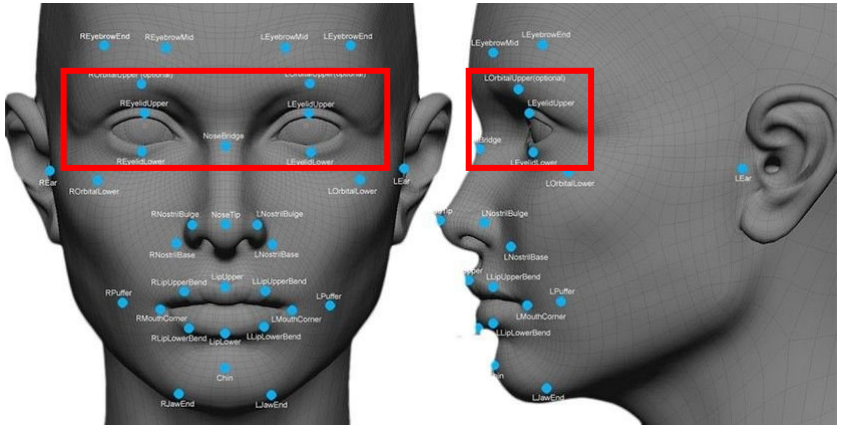


LONG EYELASH



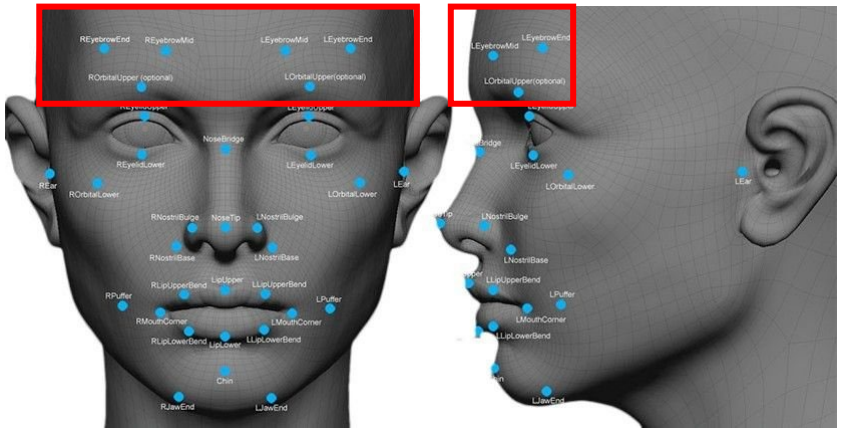
MISSING EYELASH



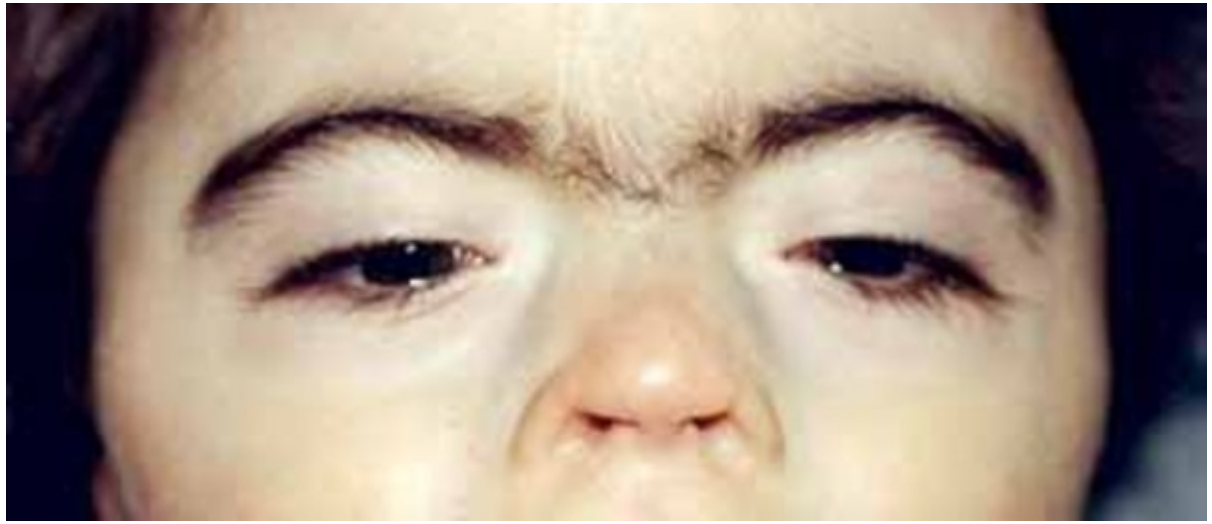


EPICANTHAL FOLDS

EYEBROWS AND FOREHEAD

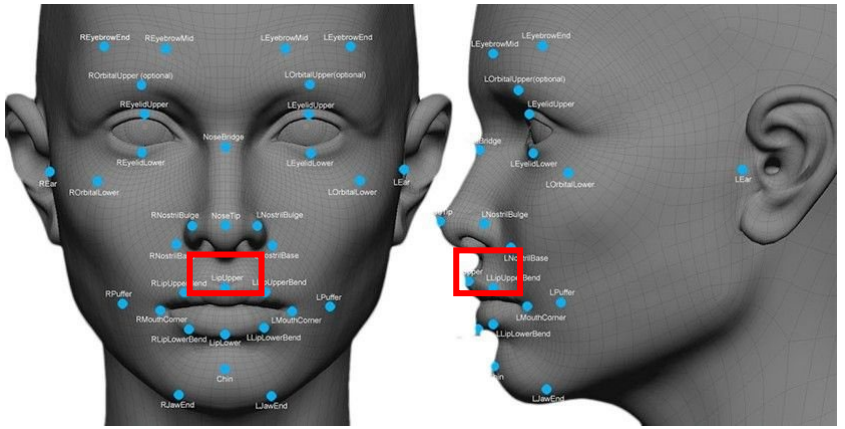


SYNOPHRYS

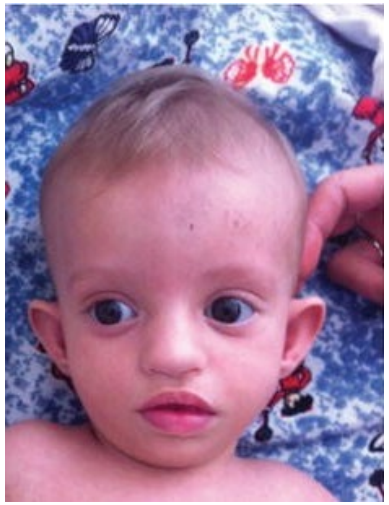


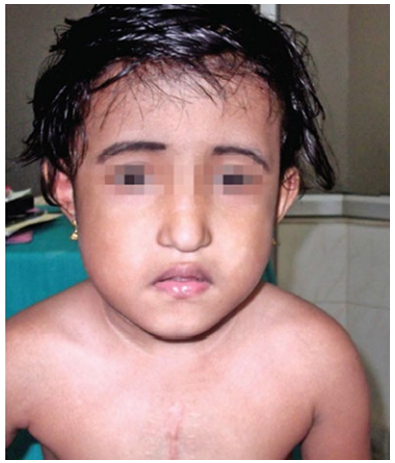
PROTRUDING FOREHEAD

PHILTRUM

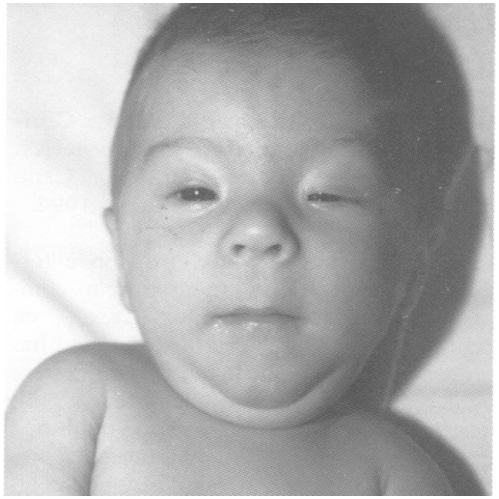


SHORT

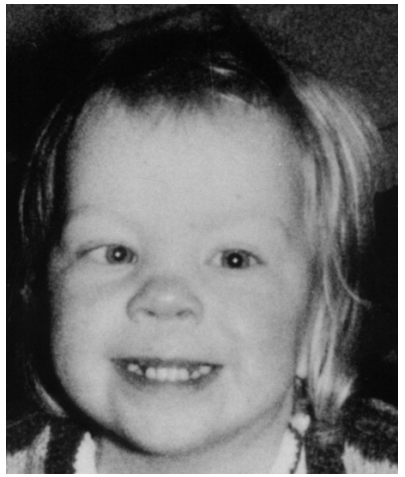


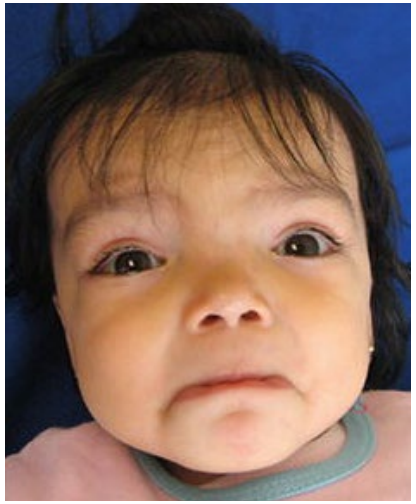


LONG

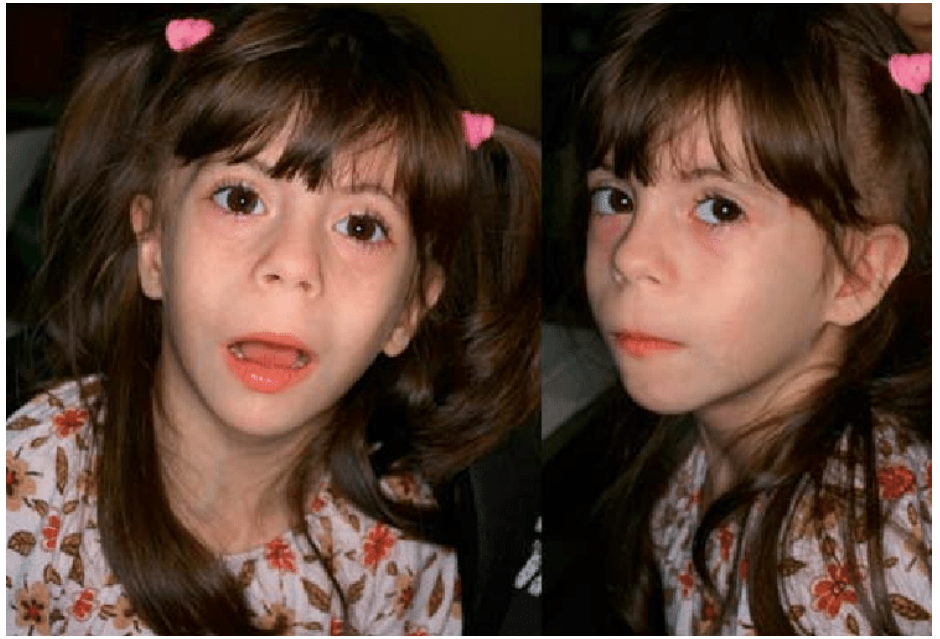


SMOOTH



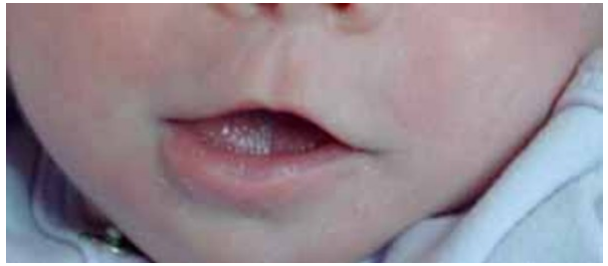


LONG AND SMOOTH

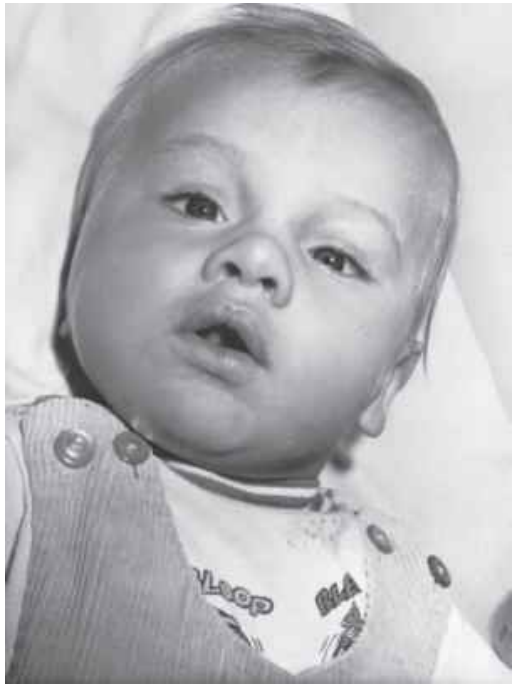


LIPS

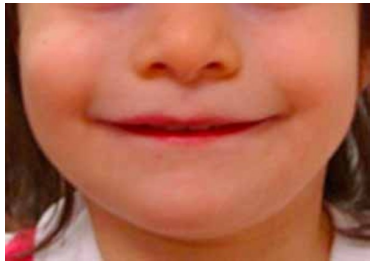
THIN UPPER LIPS

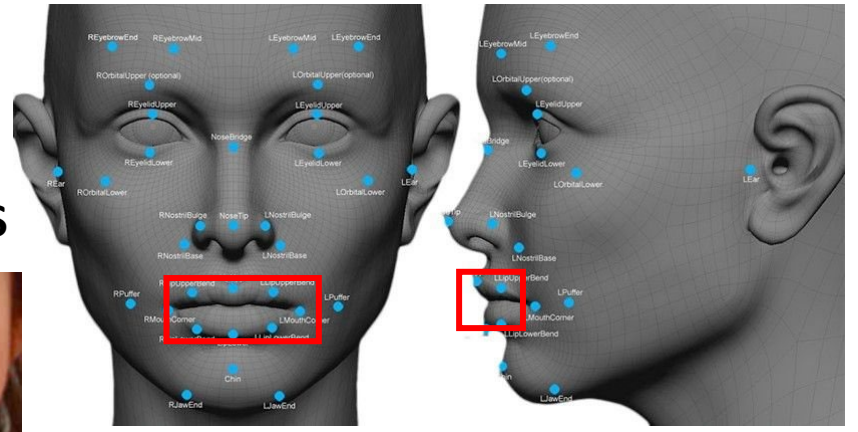


THICK UPPER LIPS

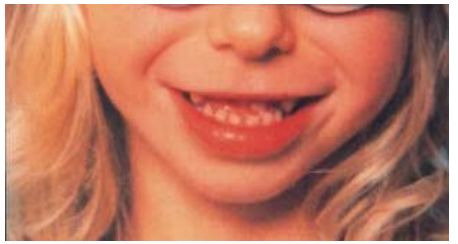


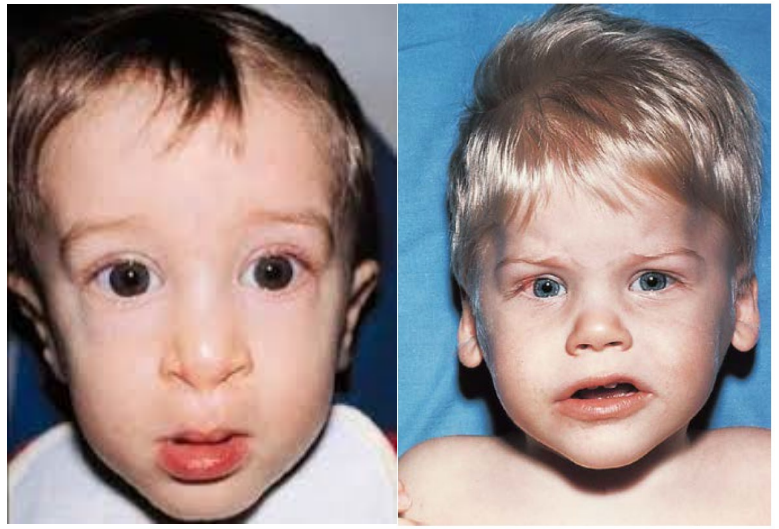
THIN LOWER LIPS





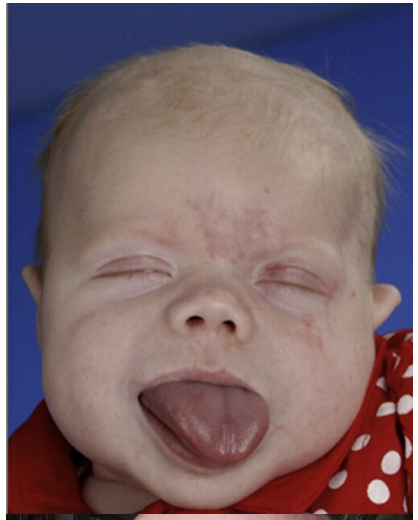
THICK LOWER LIPS

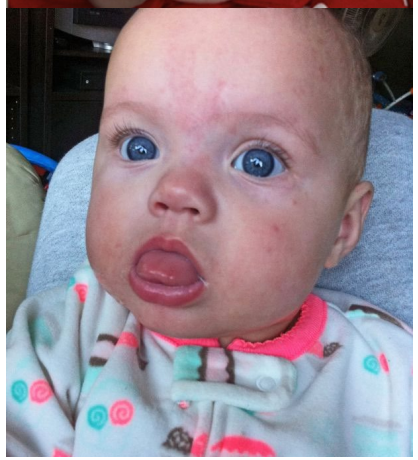




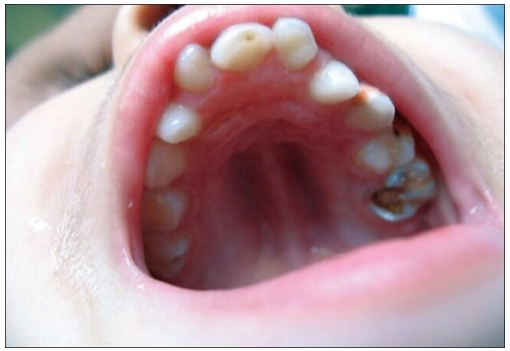
ORAL CAVITY

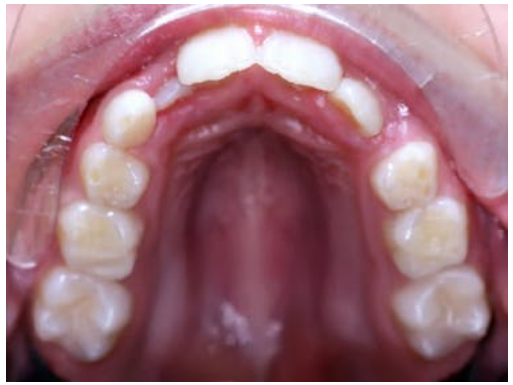
MACROGLOSSIA



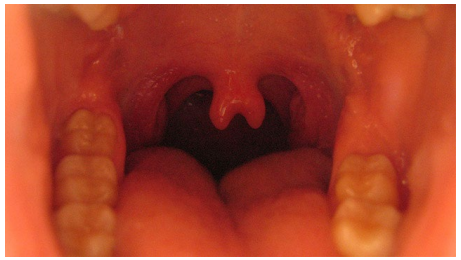


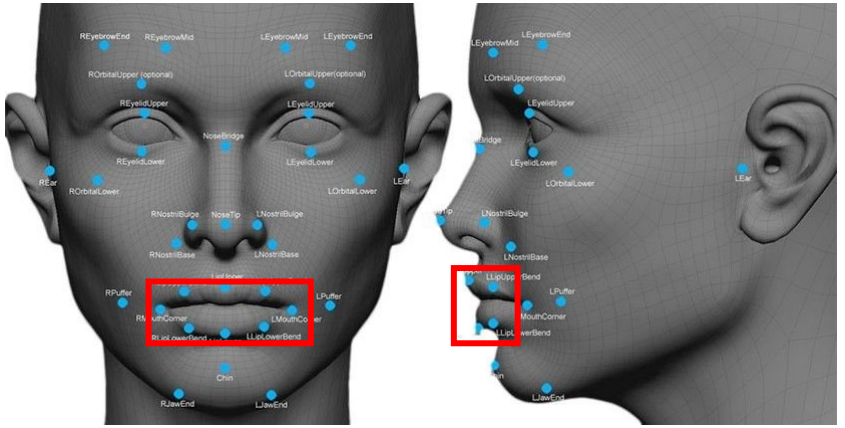
HIGH AND NARROW PALATE



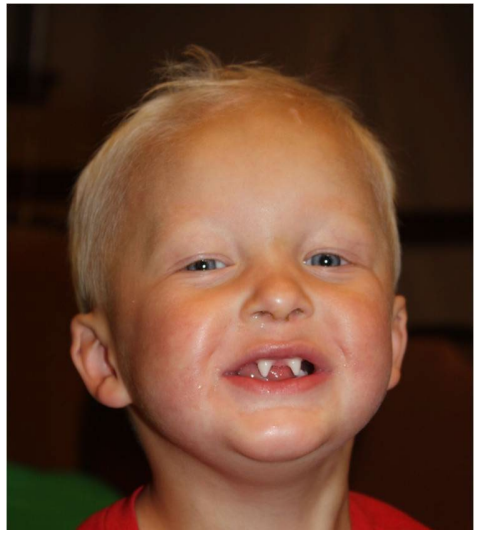


BIFID UVULA



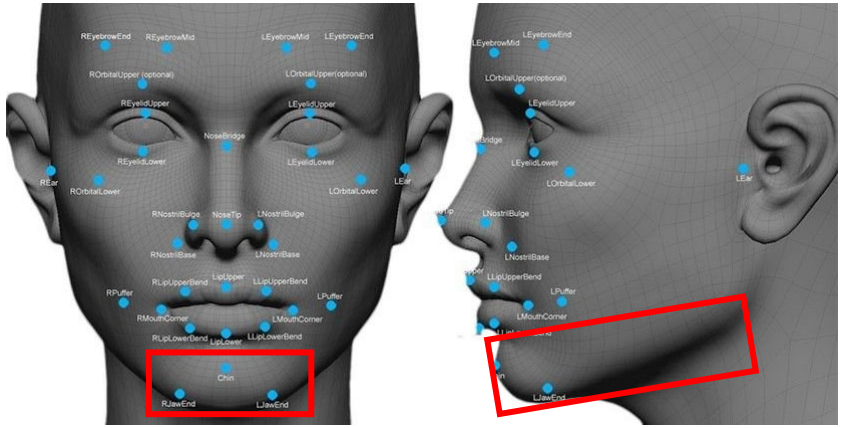


REDUCED TEETH NUMBER

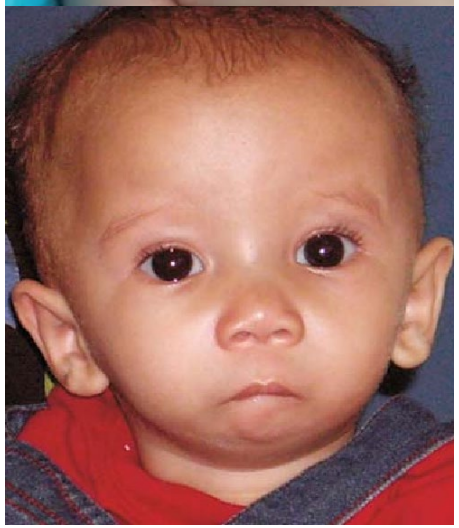


WIDELY SPACED TEETH

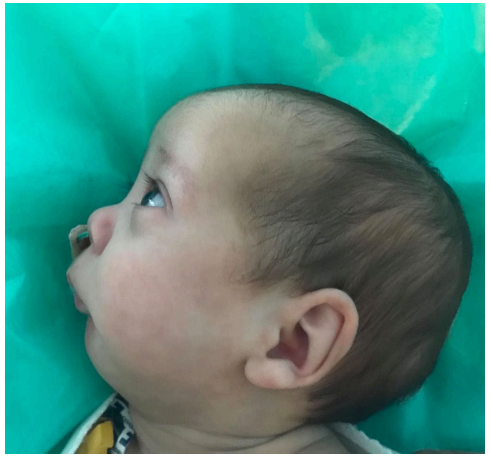
CHIN AND JAW



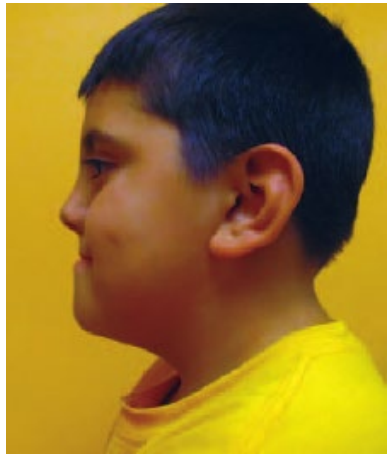
MICROGNATHIA

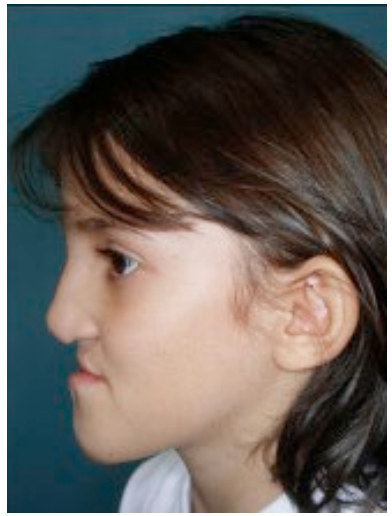


RETROGNATHIA



PROGNATHIA

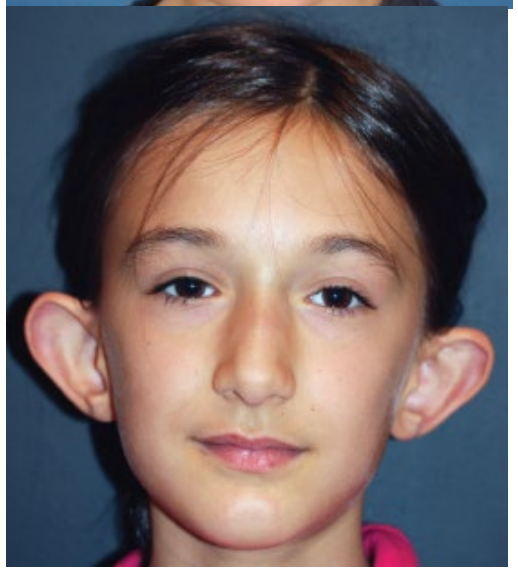




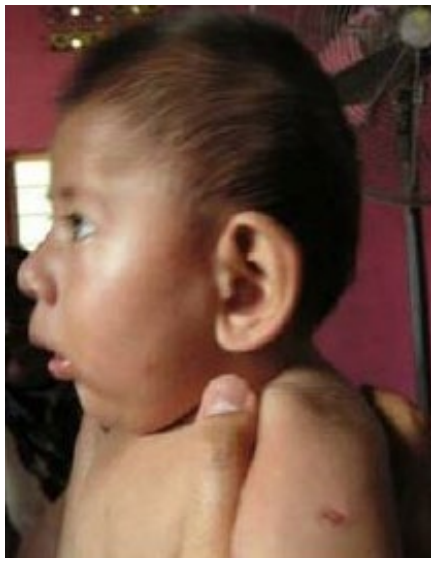
MICRO-RETROGNATHIA

EARS

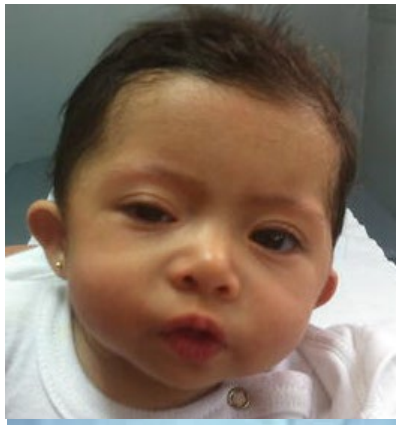
PROTRUDING EARS

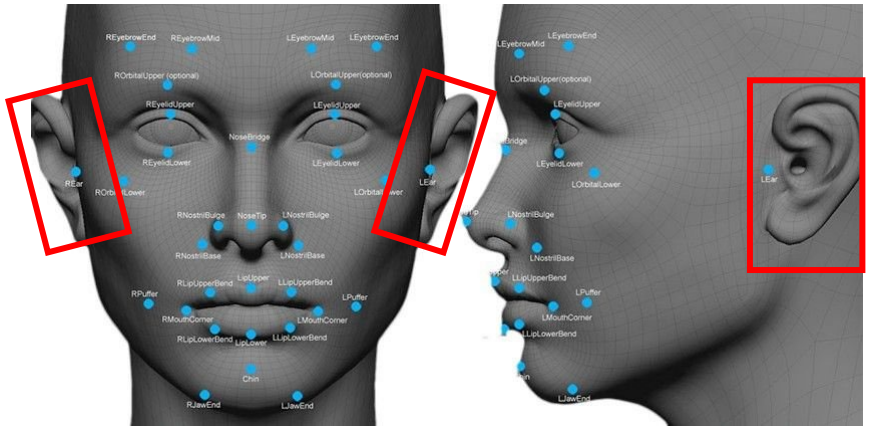


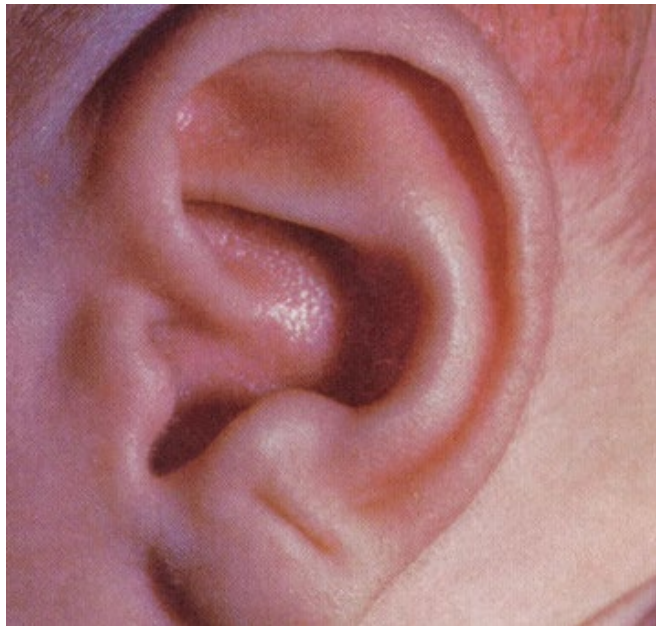
ENLARGED EARS



LOW-SET EARS

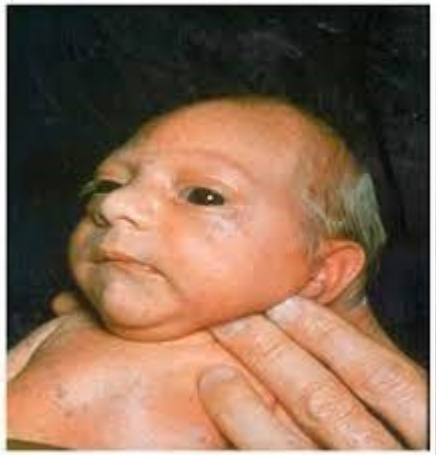


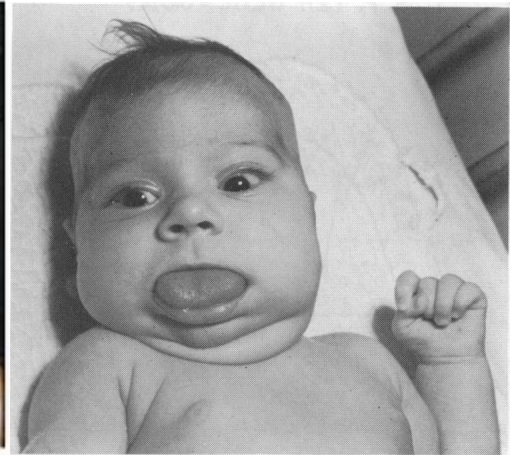




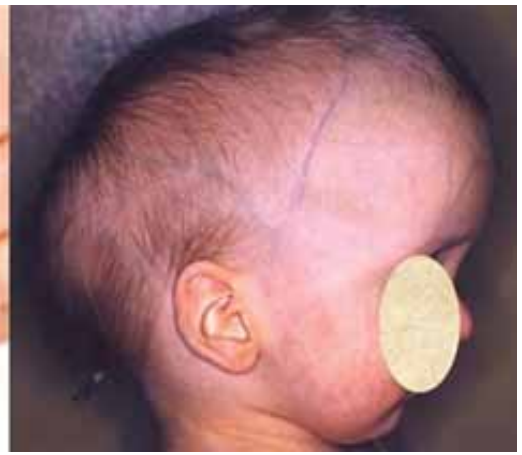
HEAD

MICROCEPHALY

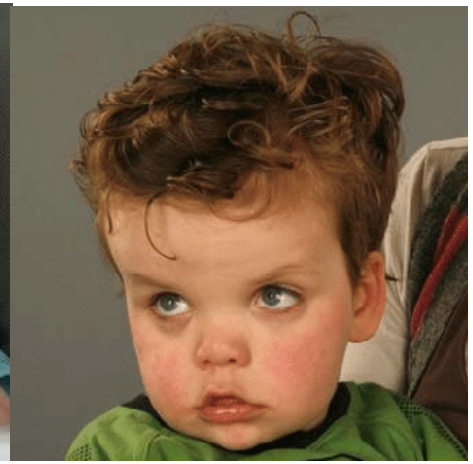




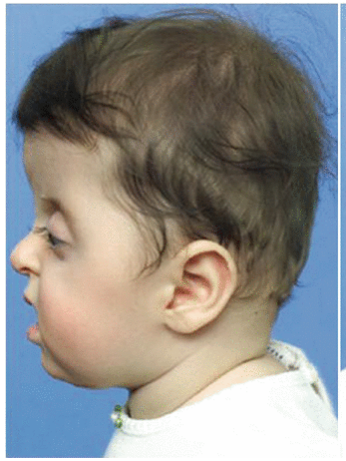
DOLICOCEPHALY

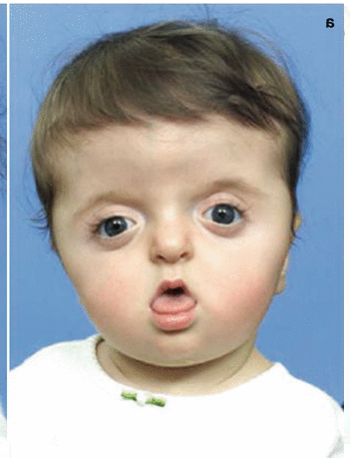


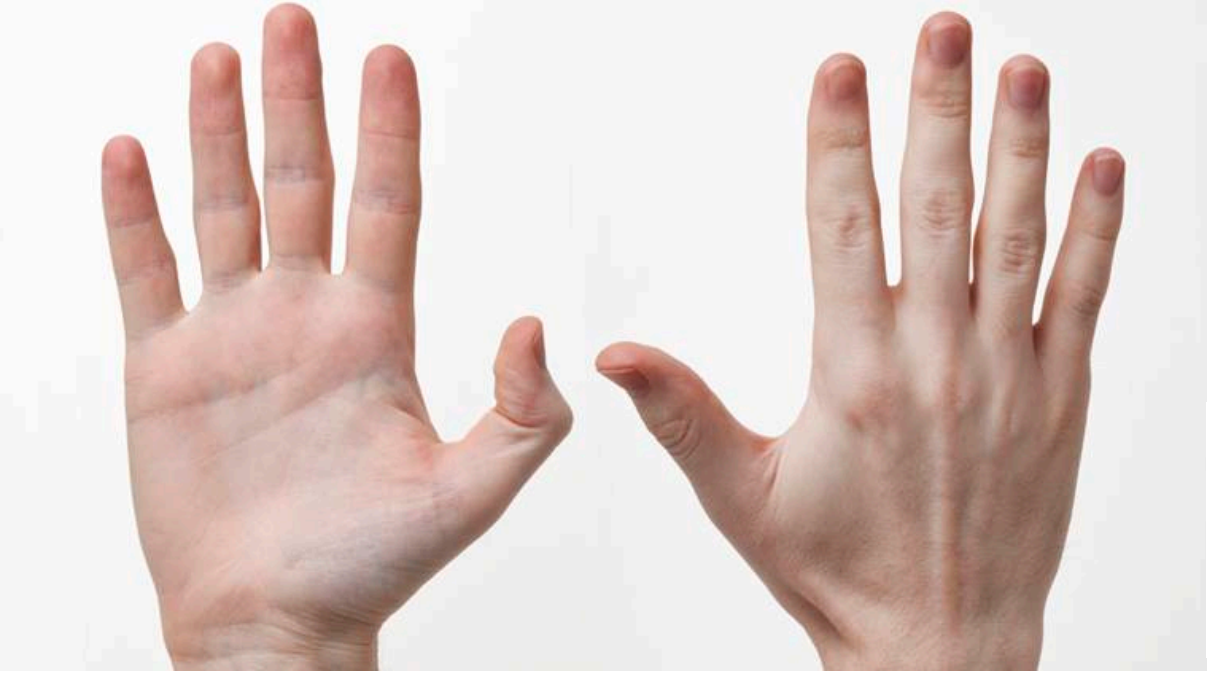
MACROCEPHALY

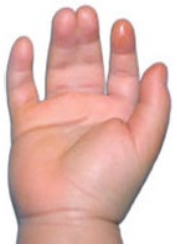


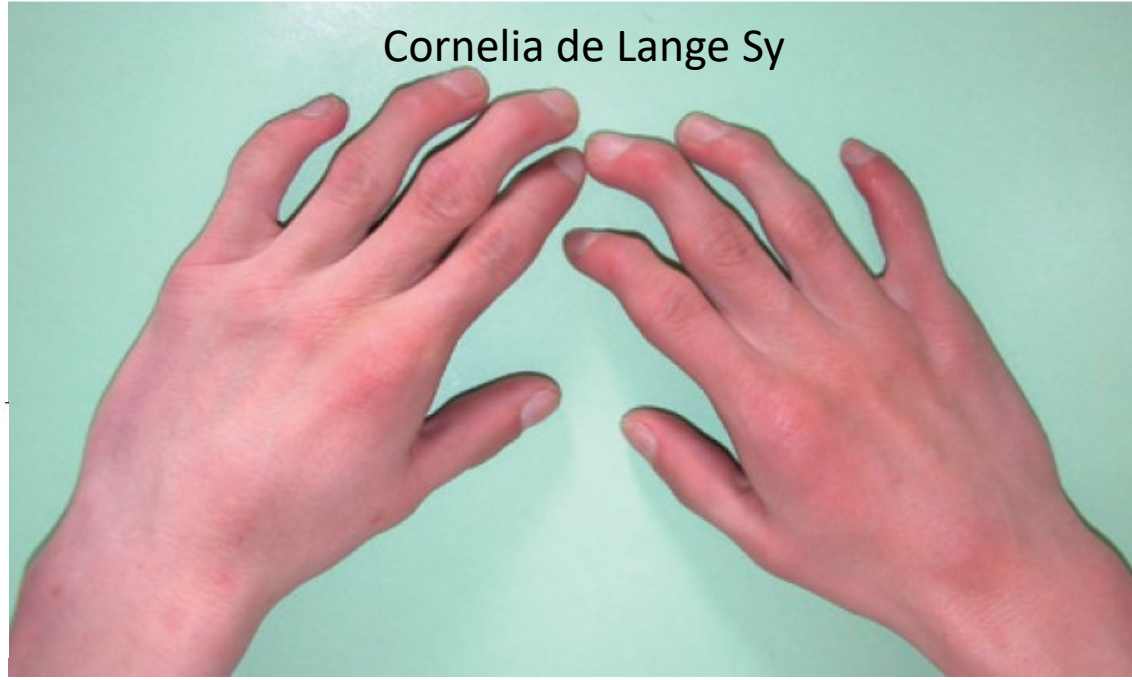
PLAGIOCEPHALY

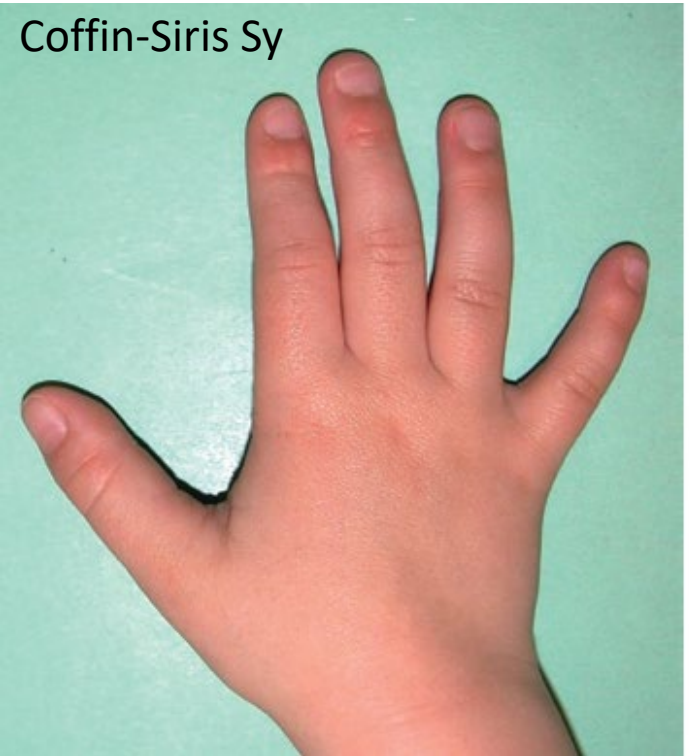


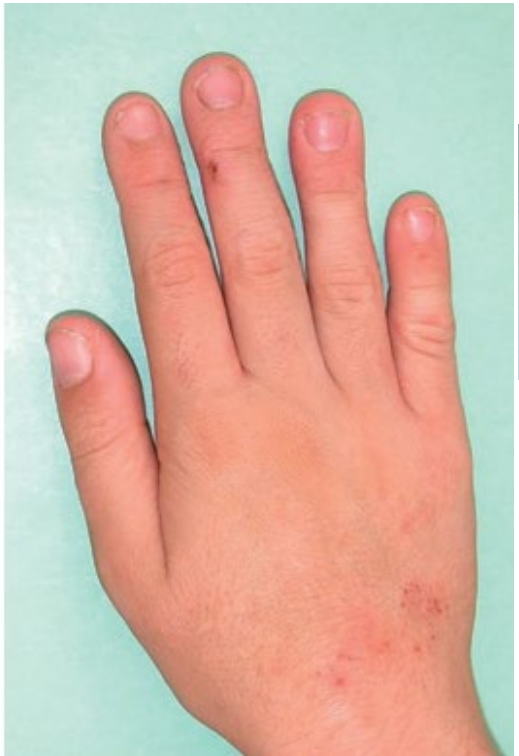


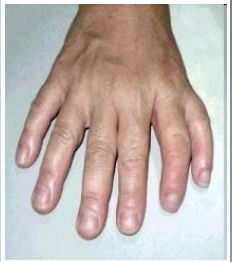


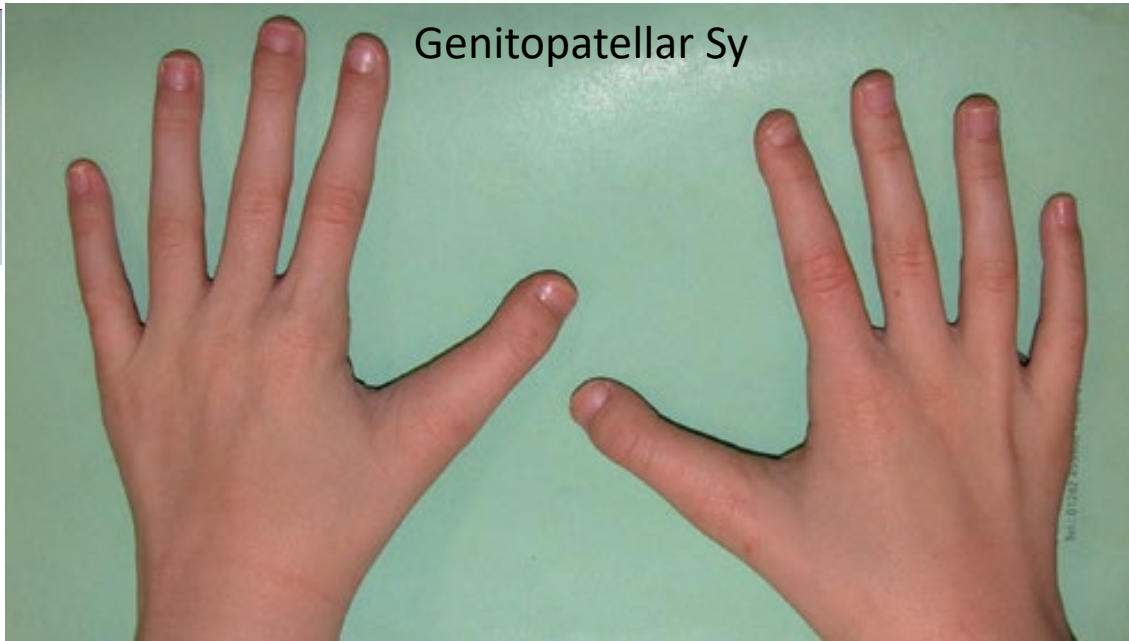


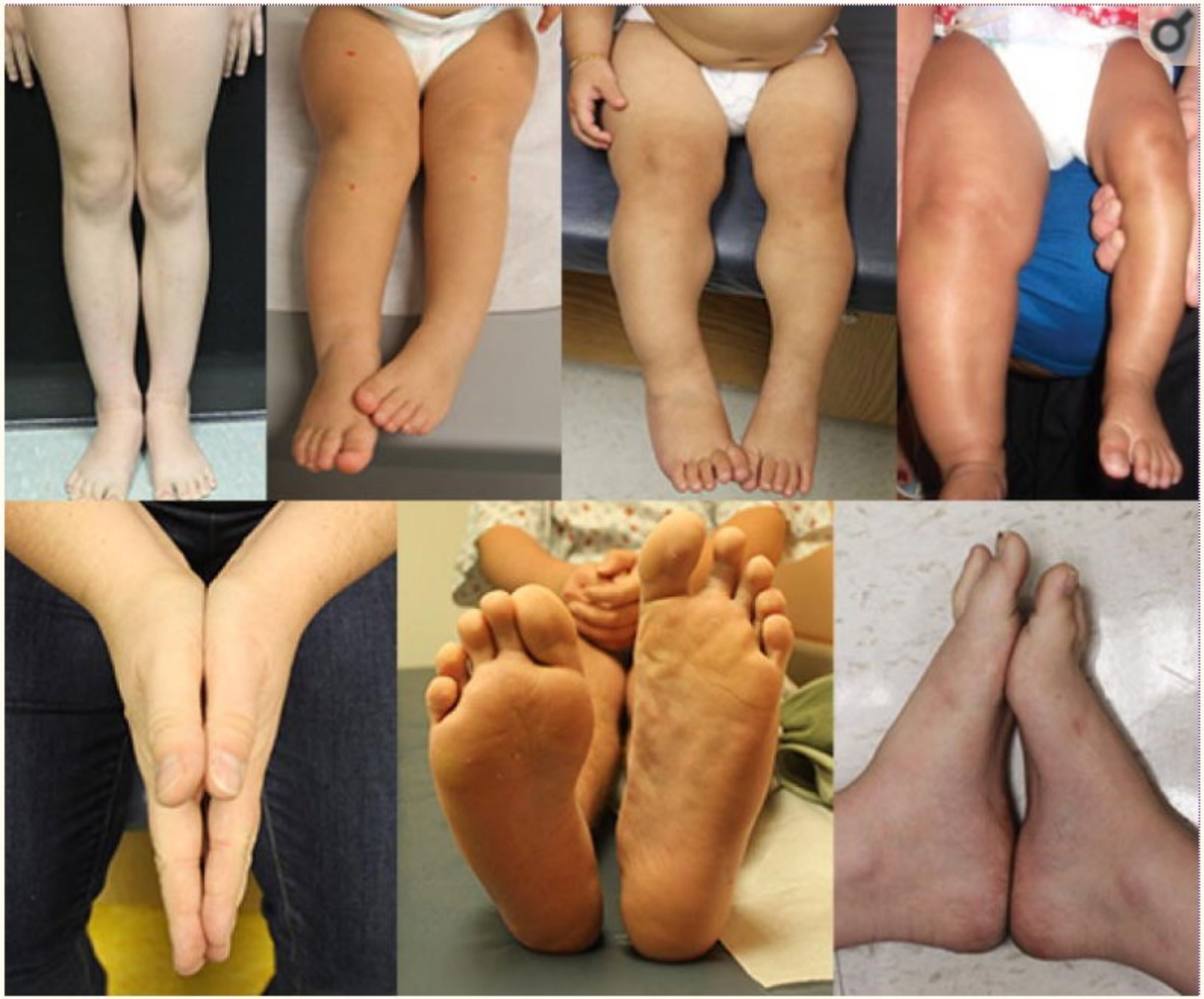

Cornelia de Lange Sy

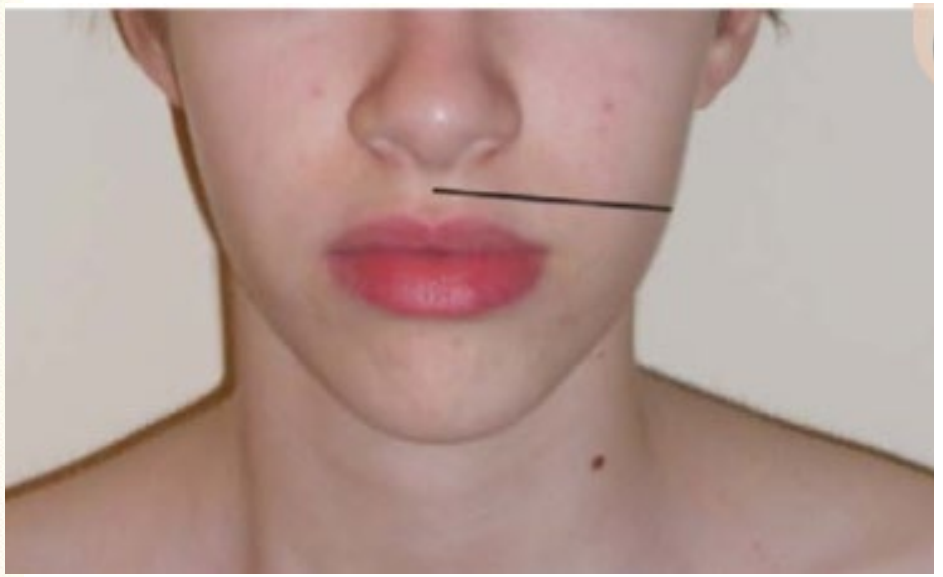

Coffin-Siris Sy

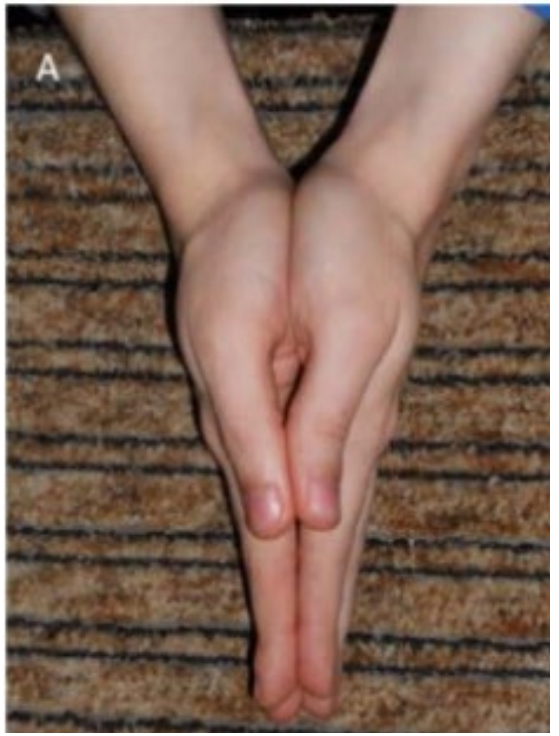





Genitopatellar Sy



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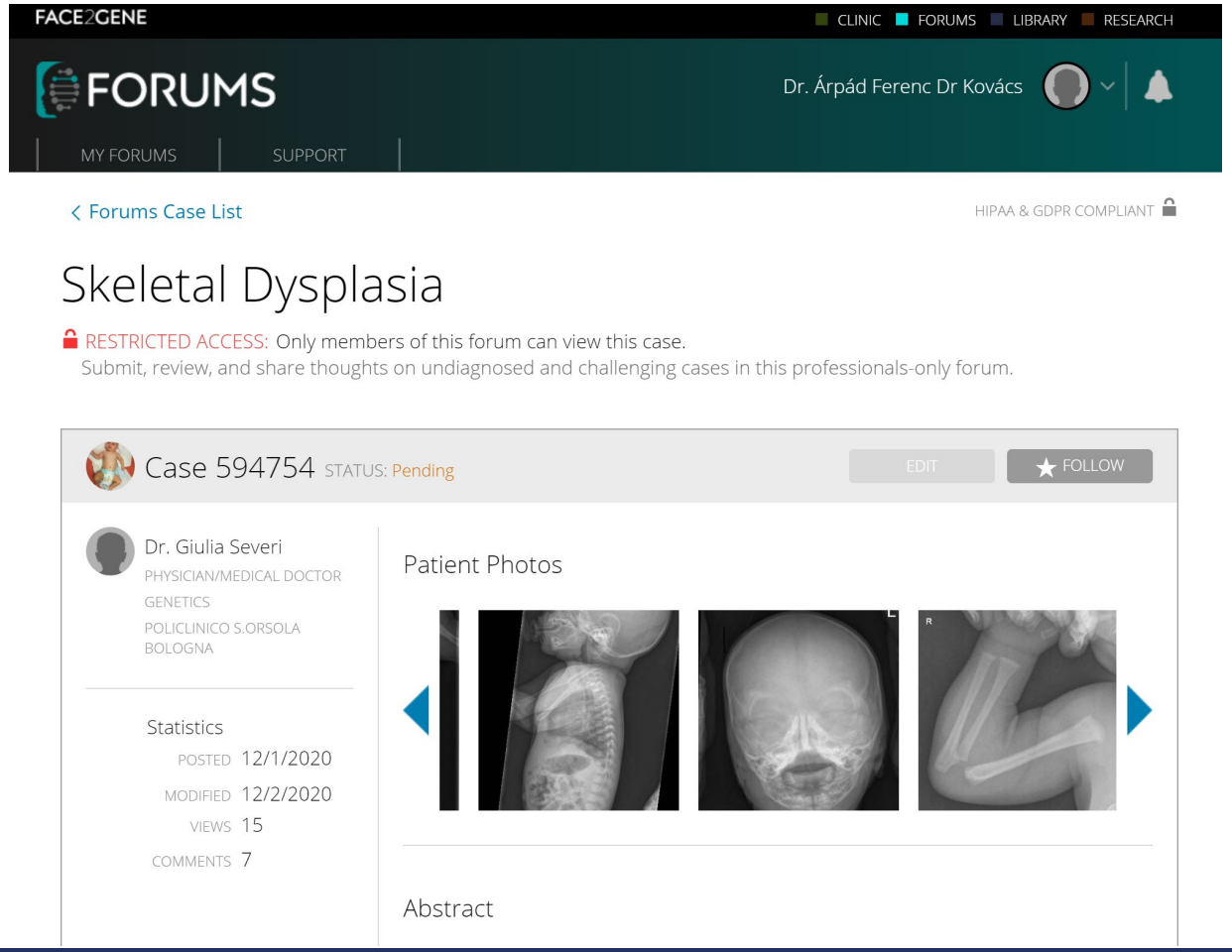
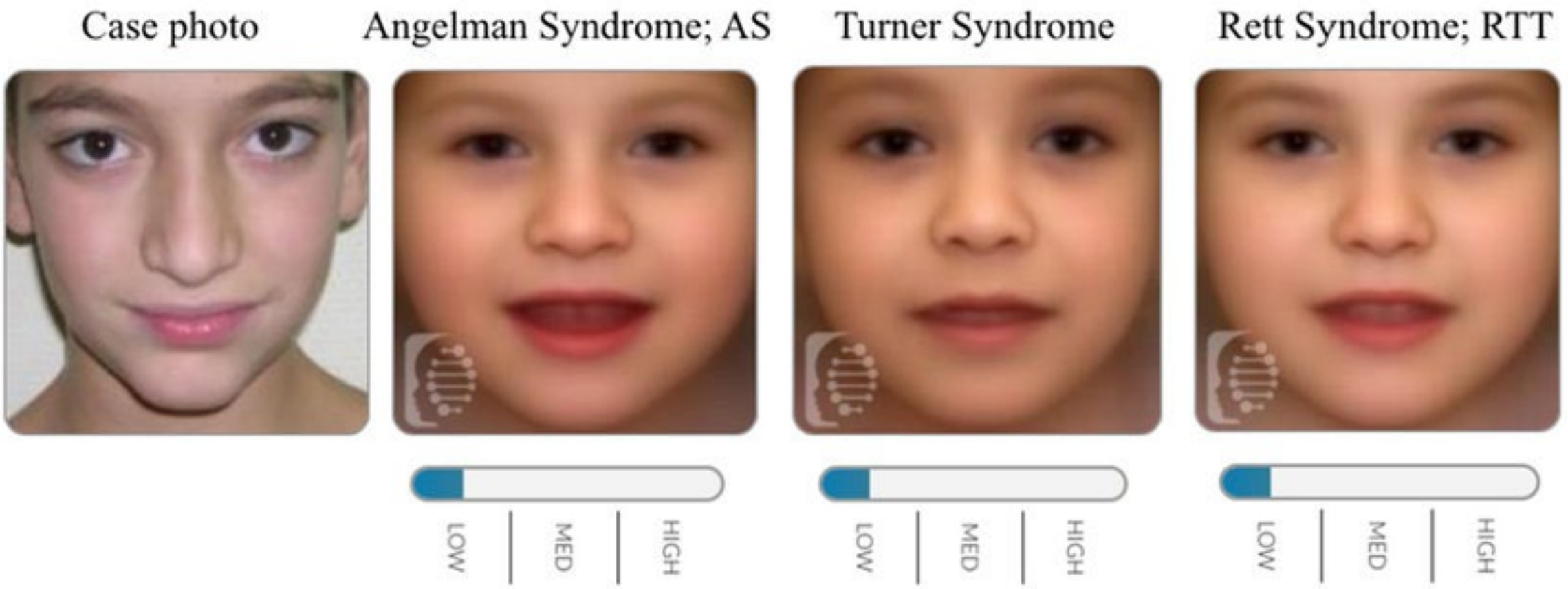
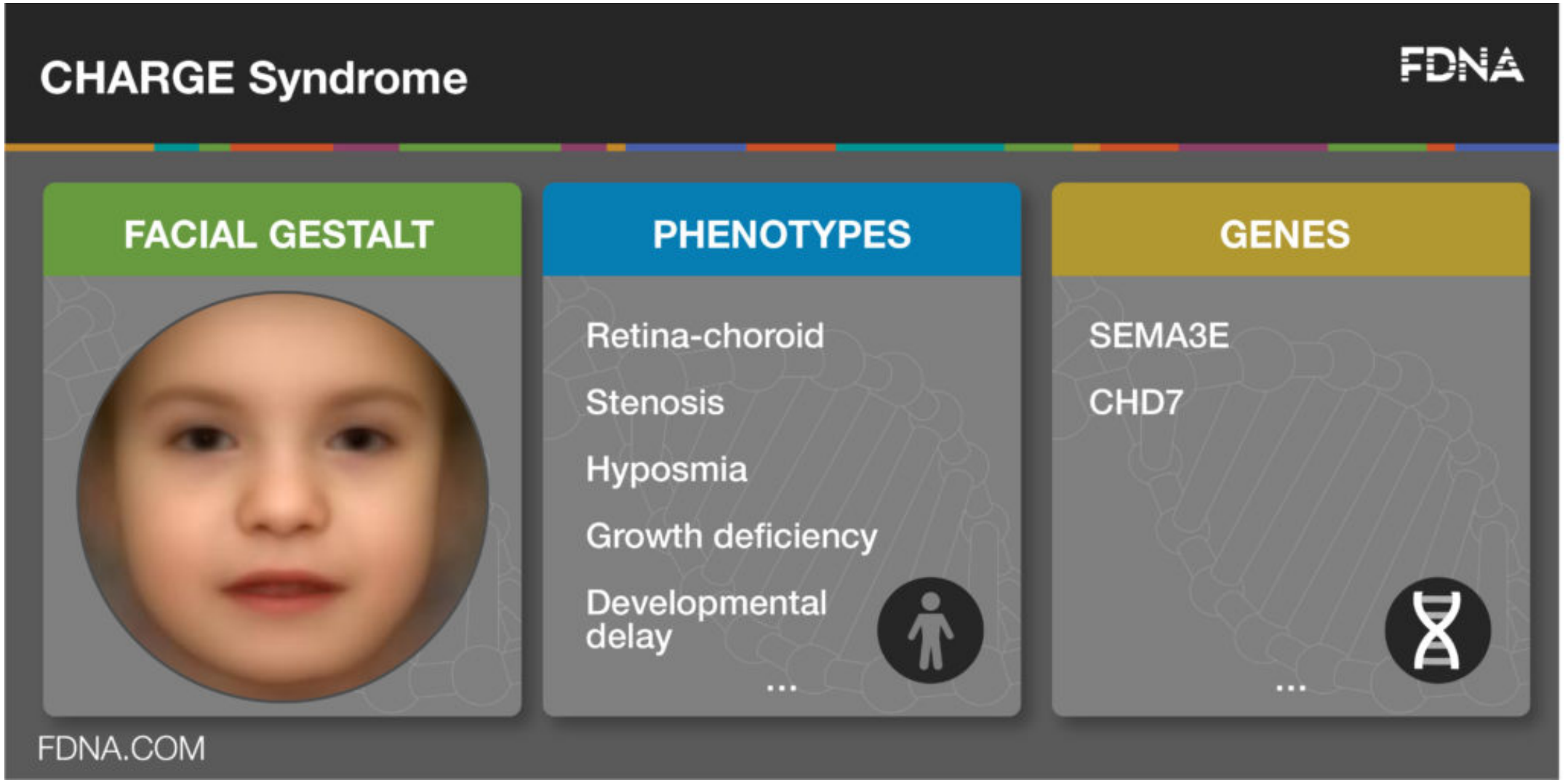
ARTIFICIAL INTELLIGENCE-ASSISTED PHENOTYPING



ARTIFICIAL INTELLIGENCE-ASSISTED PHENOTYPING



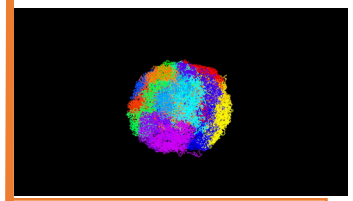
ARTIFICIAL INTELLIGENCE-ASSISTED PHENOTYPING



PHENOTYPE-GENOTYPE PATHWAY

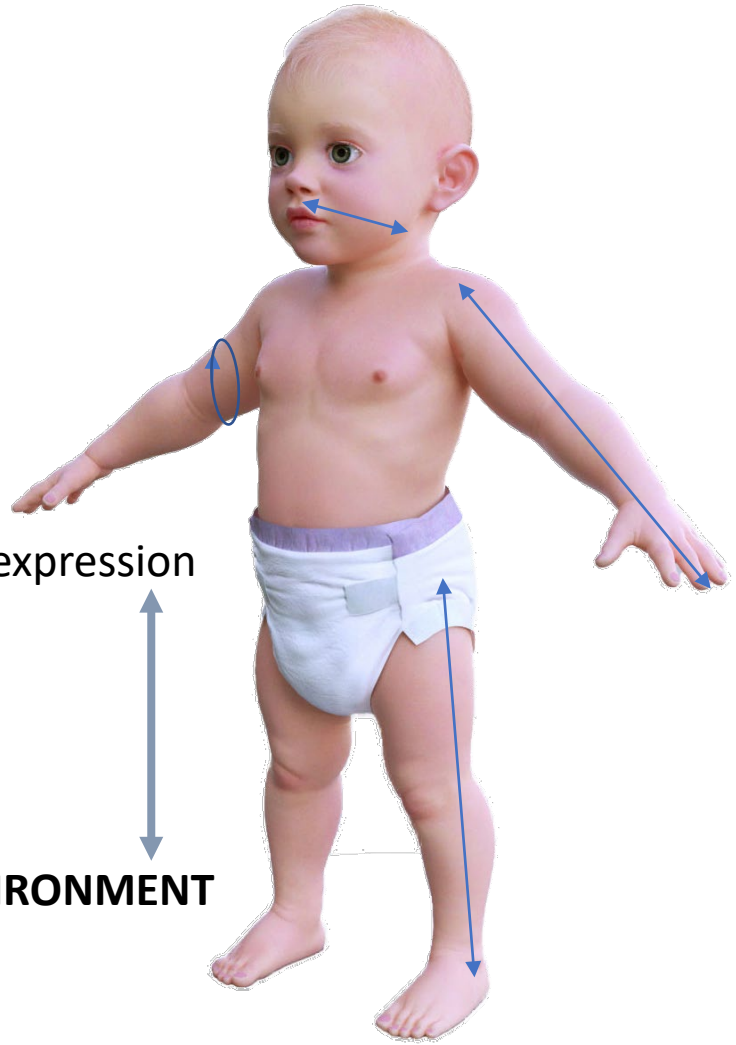
GENOTYPE

(pathogen) SEQUENCE VARIANT



epiGENOTYPE

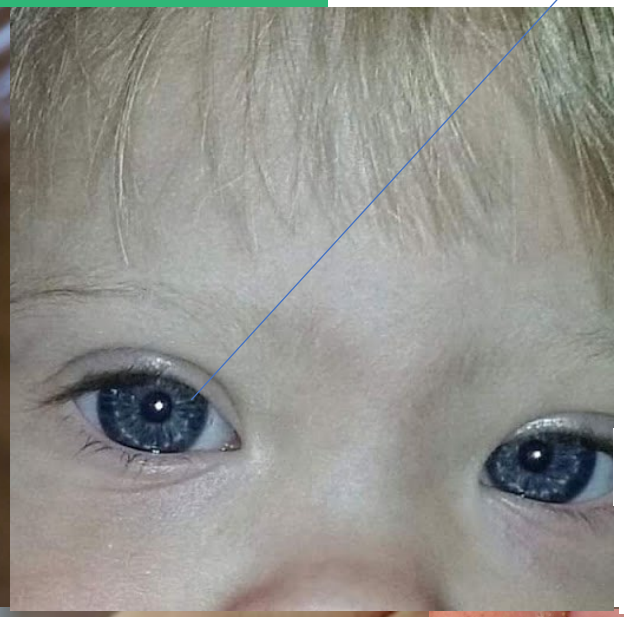
PHENOTYPE

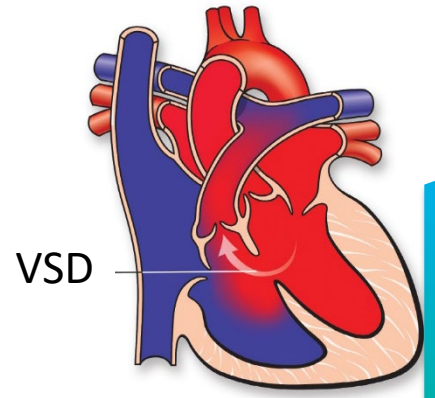


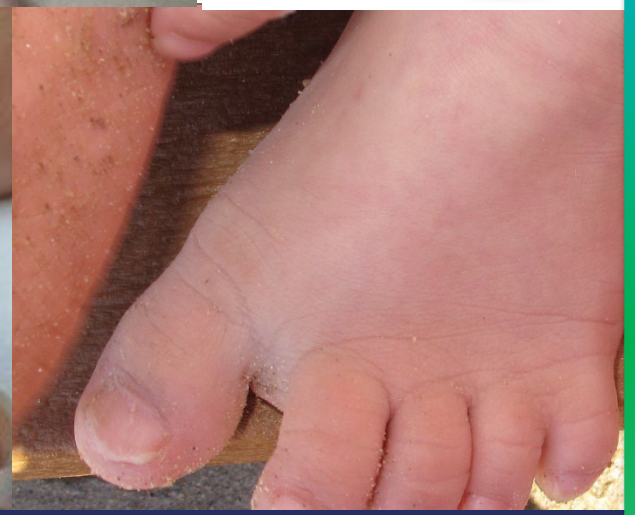
Time and tissue-specific fluctuation of gene expression

ENVIRONMENT

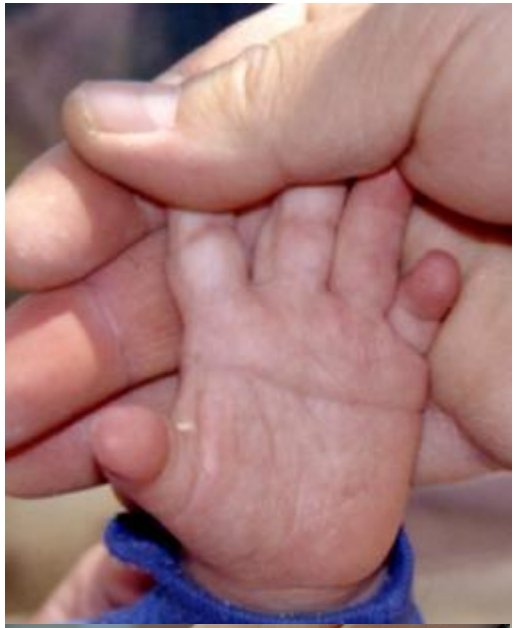
Down-syndrome (1)

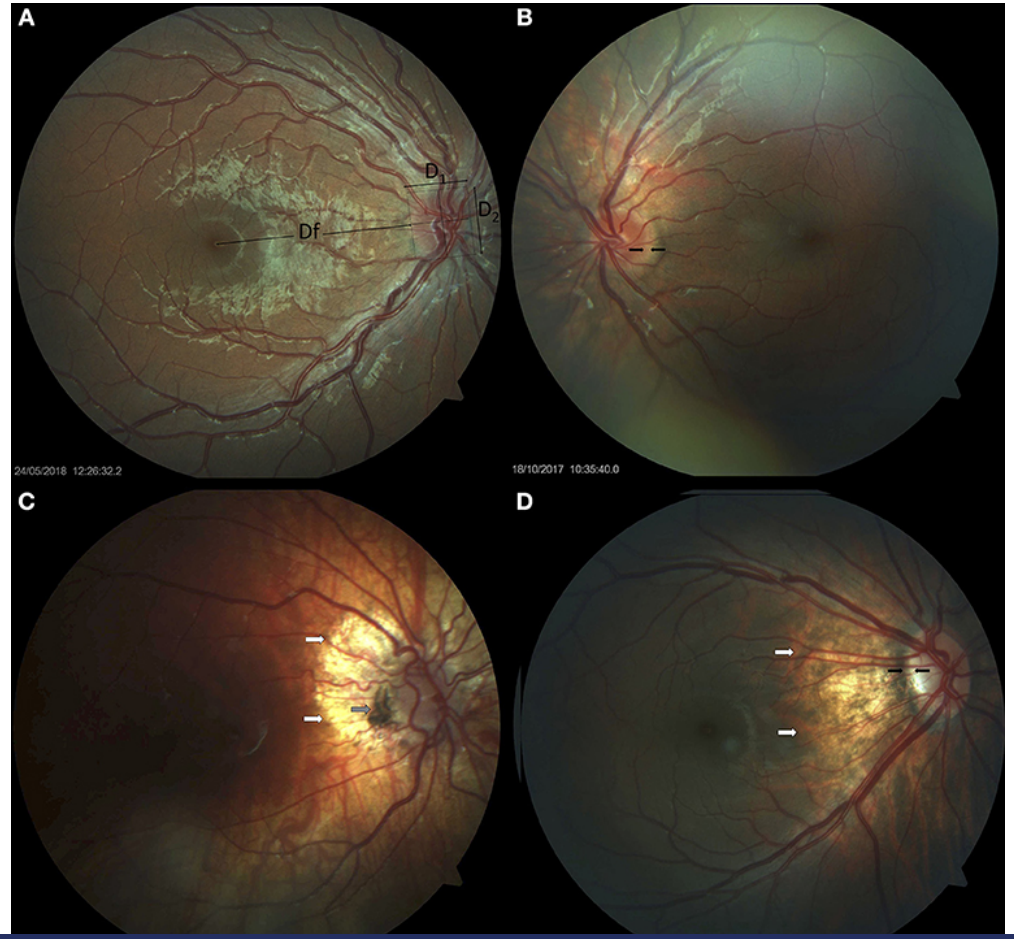






Down-syndrome (2)





Down syndrome

Epidemiology
Incidence: ~ 1:700 live births

Etiology
Three complete copies of chromosome 21; due to meiotic nondisjunction in 95% of cases

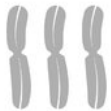
Karyotype
♀ : 47,XX,+21
♂ : 47,XY,+21

Complications
Due to organ malformations and immunodeficiency.
Increased risk of AML/ALL.
Early onset Alzheimer's disease

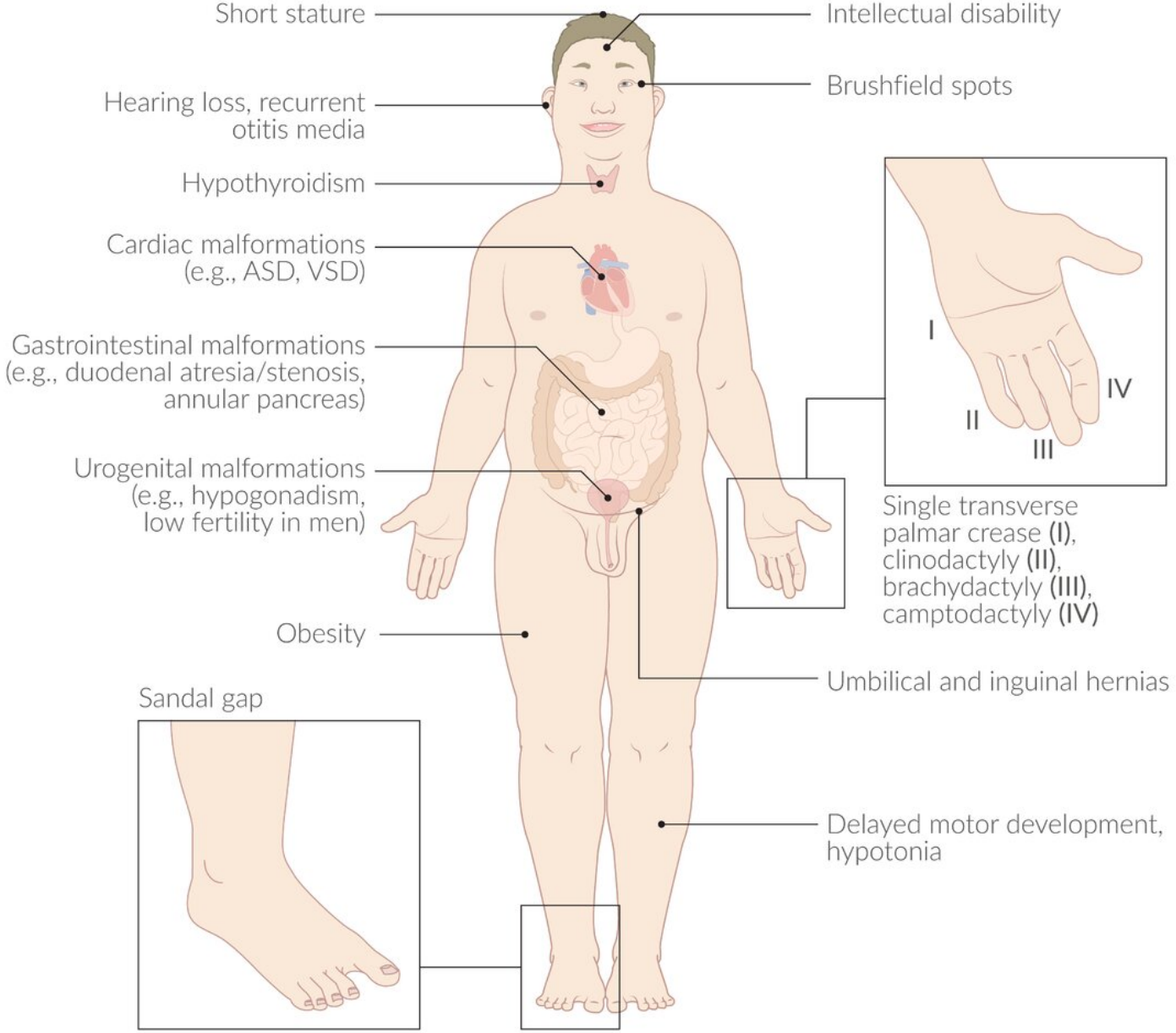
Important
Risk increases with maternal age

Life expectancy
~50 years

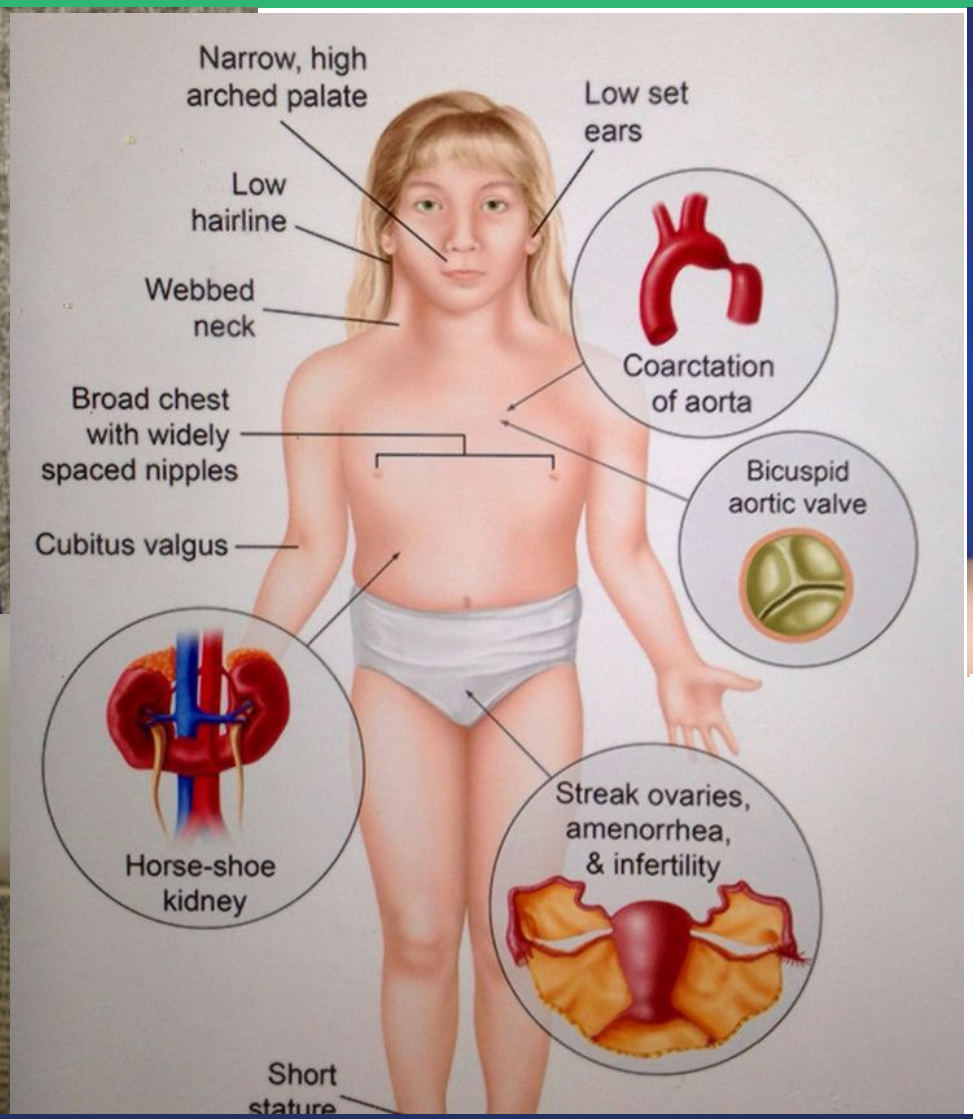
Karyotype

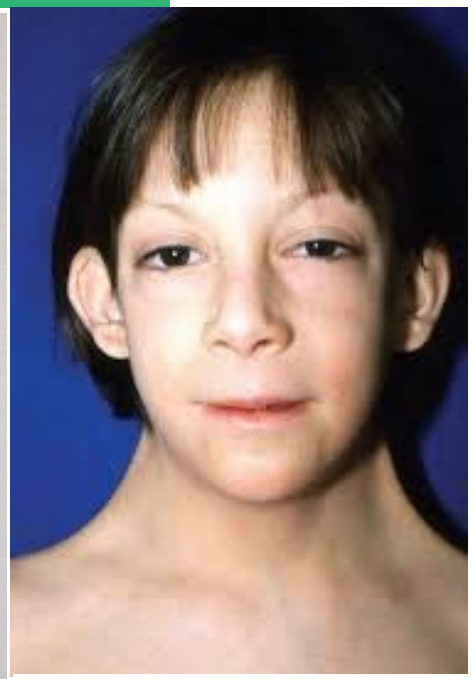


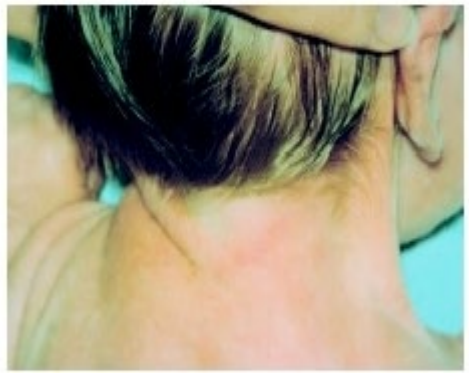
+21

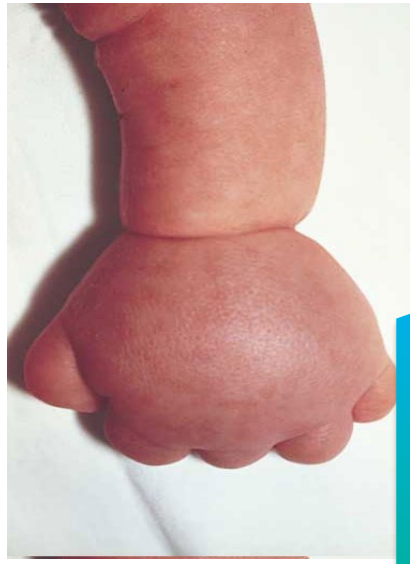


TURNER syndrome

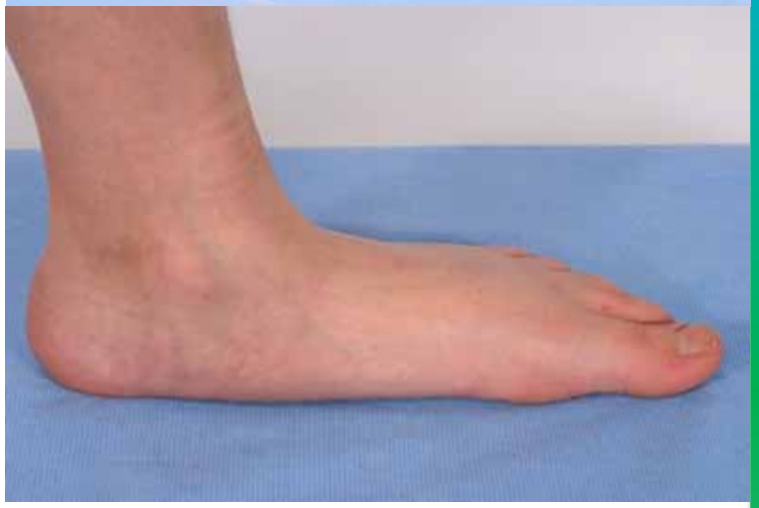








KLINEFELTER syndrome



Klinefelter syndrome

Epidemiology
Incidence approx. 1:650 in the US

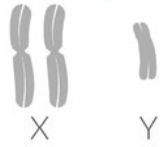
Etiology
Usually due to nondisjunction of sex chromosomes during meiosis.
Associated with an advanced maternal age

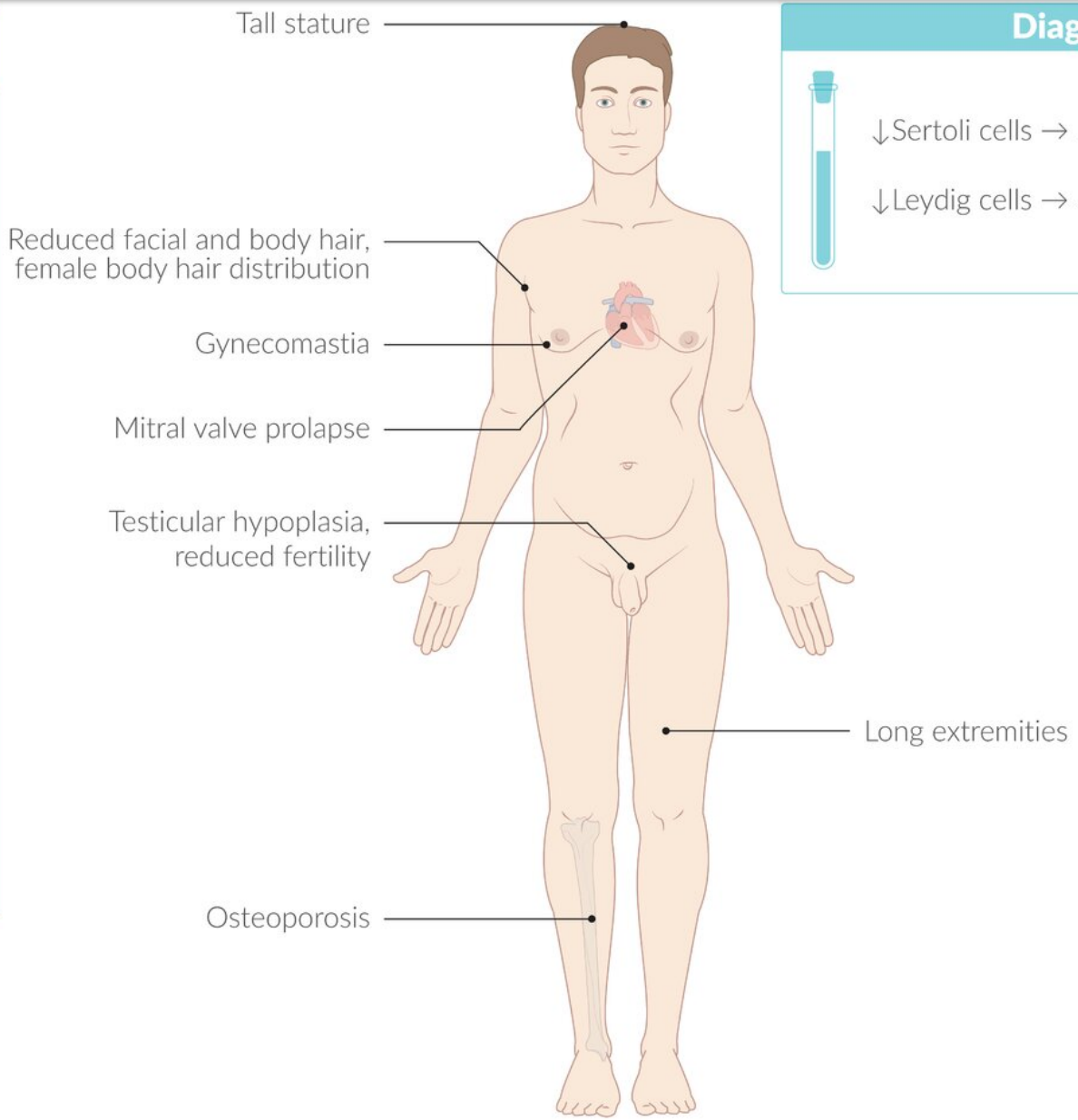
Karyotype
47,XXY
Rarely 48,XXXY or 48,XXYY
Barr body is present

Phenotype
Male

Important
Possible developmental delay;
onset of symptoms usually at the start of puberty;
one of the most common causes of male hypogonadism

Karyotype



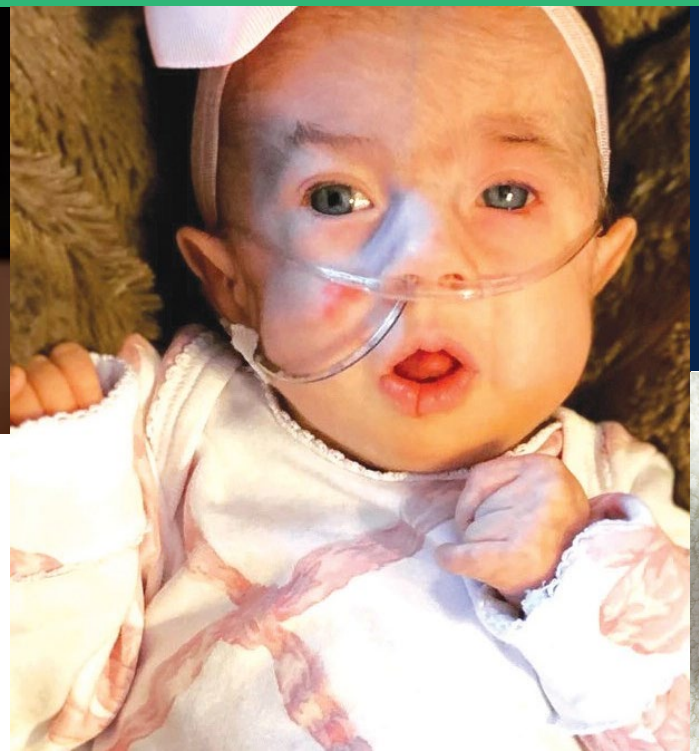


Diagnosis

↓Sertoli cells → ↓inhibin B → ↑FSH

↓Leydig cells → ↓testosterone → ↑LH

EDWARDS syndrome



Clenched hands

„rocker-bottom” feet

Edwards syndrome

Epidemiology
Incidence: ~ 1:6.000
♀>♂

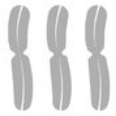
Etiology
presence of an extra chromosome 18

Karyotype
♀ : 47,XX+18
♂ : 47,XY+18

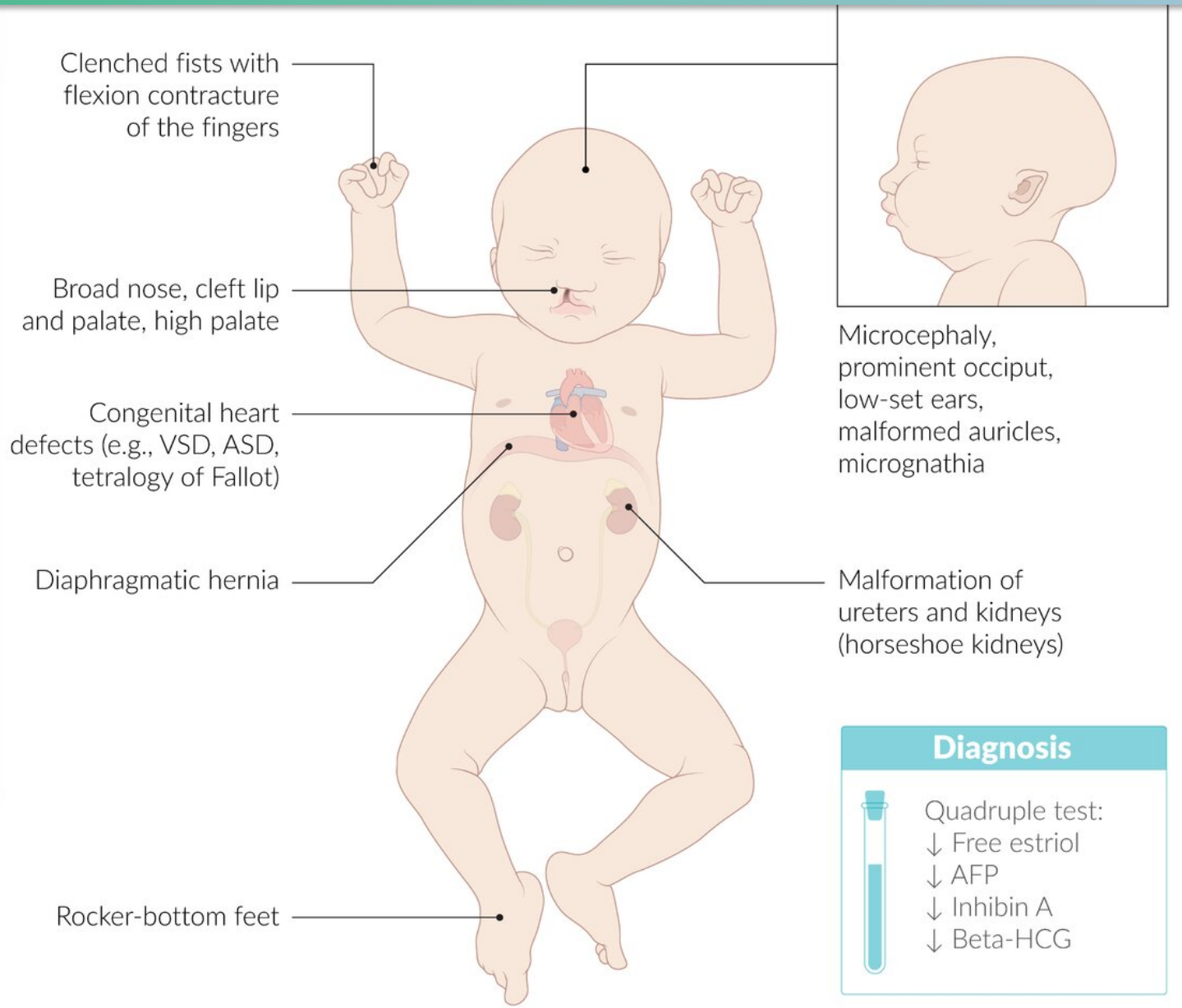
Important
Second most common trisomy after Down syndrome (trisomy 21); risk increases with maternal age

Life expectancy
Only 5–10% survive past 12 months of age

Karyotype



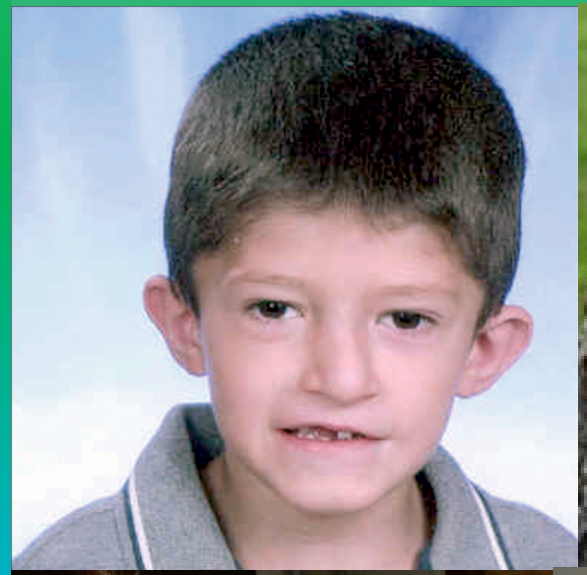
+18

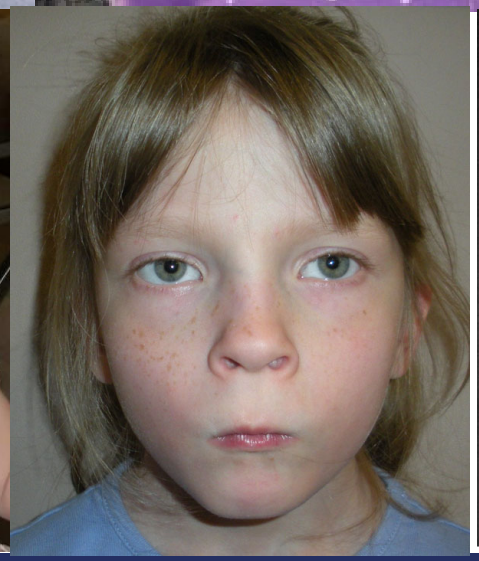


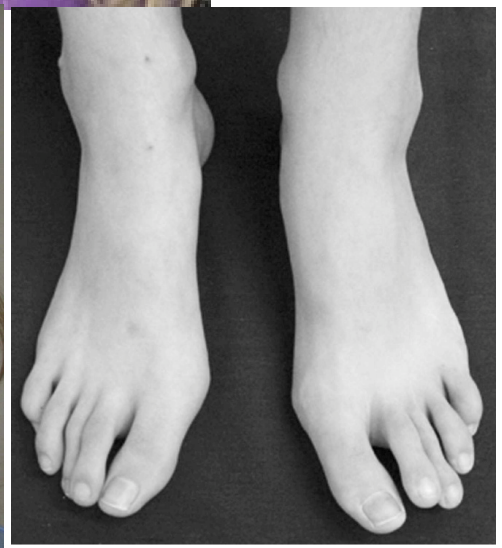
Diagnosis

Quadruple test:
↓ Free estriol
↓ AFP
↓ Inhibin A
↓ Beta-HCG

DiGeorge syndrome







22q11.2 Deletion syndrome (DiGeorge syndrome)

Epidemiology
Incidence ~1 in 2,000 - 7,000 live births

Etiology
Microdeletion on chromosome 22 (22q11.2)
(>90% spontaneous mutations)

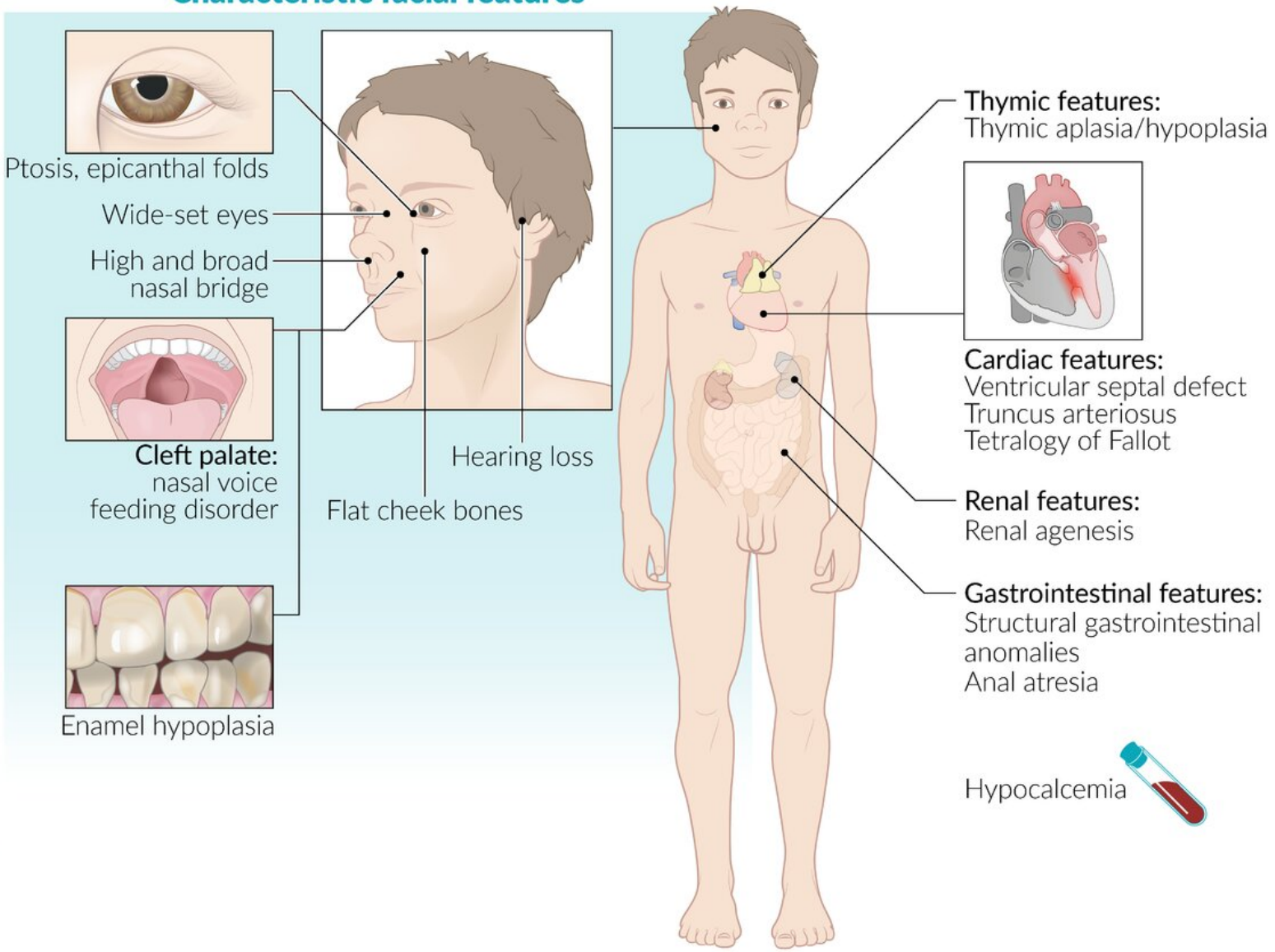
Prognosis
Highly variable, depending on severity of symptoms
Degree of cardiac involvement is the most important prognostic factor

Life expectancy
Mostly normal life expectancy

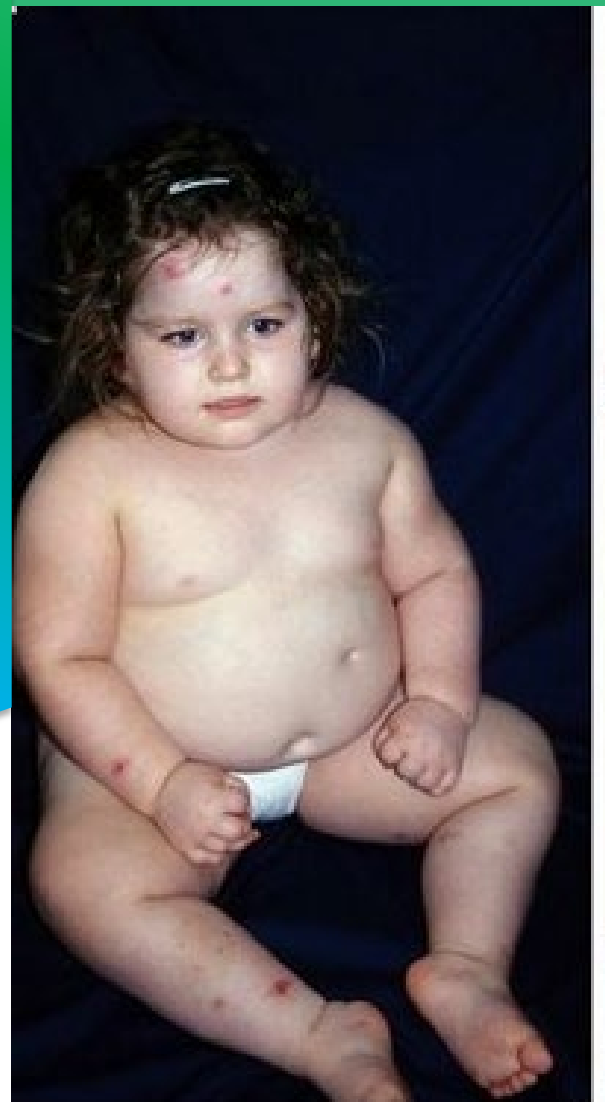
Psychiatric features

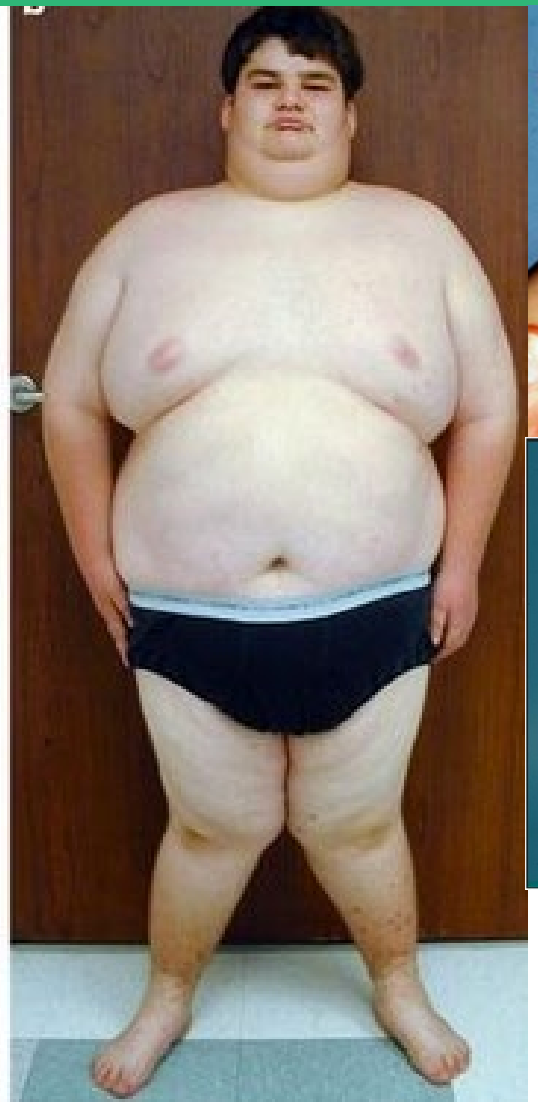
Learning difficulties and psychiatric disorders (e.g., ADHD, schizophrenia)

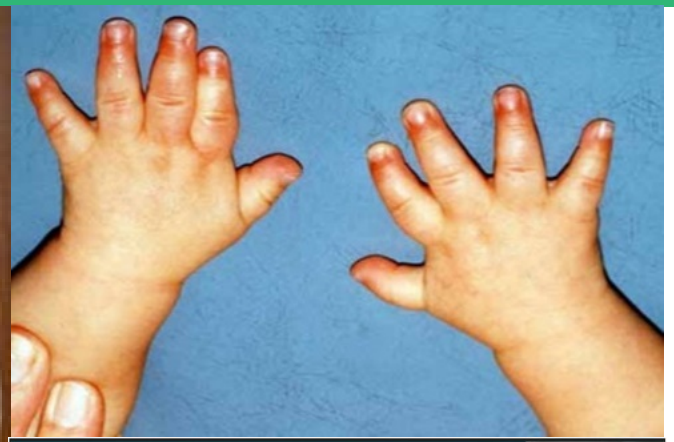
Characteristic facial features

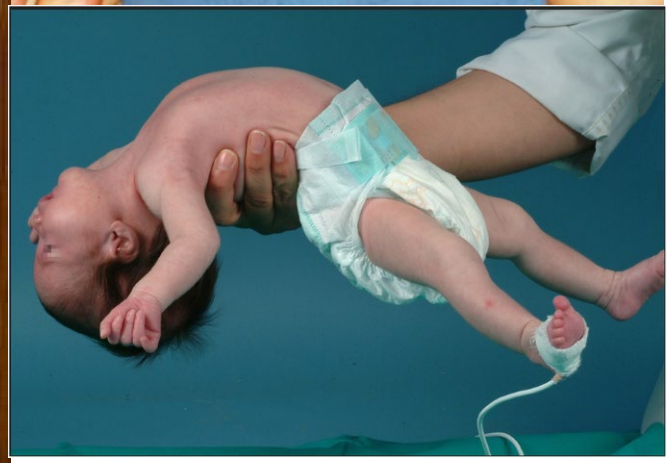


Prader–Willi syndrome









Prader-Willi syndrome

Epidemiology
Prevalence ~ 1 in 16000 - 25000
♂ = ♀

Etiology
Paternal deletion 15q11q13 (> 70%)
Maternal uniparental disomy
Low risk of inheritance (mostly spontaneous mutation)
Etiology similar to that of Angelman syndrome

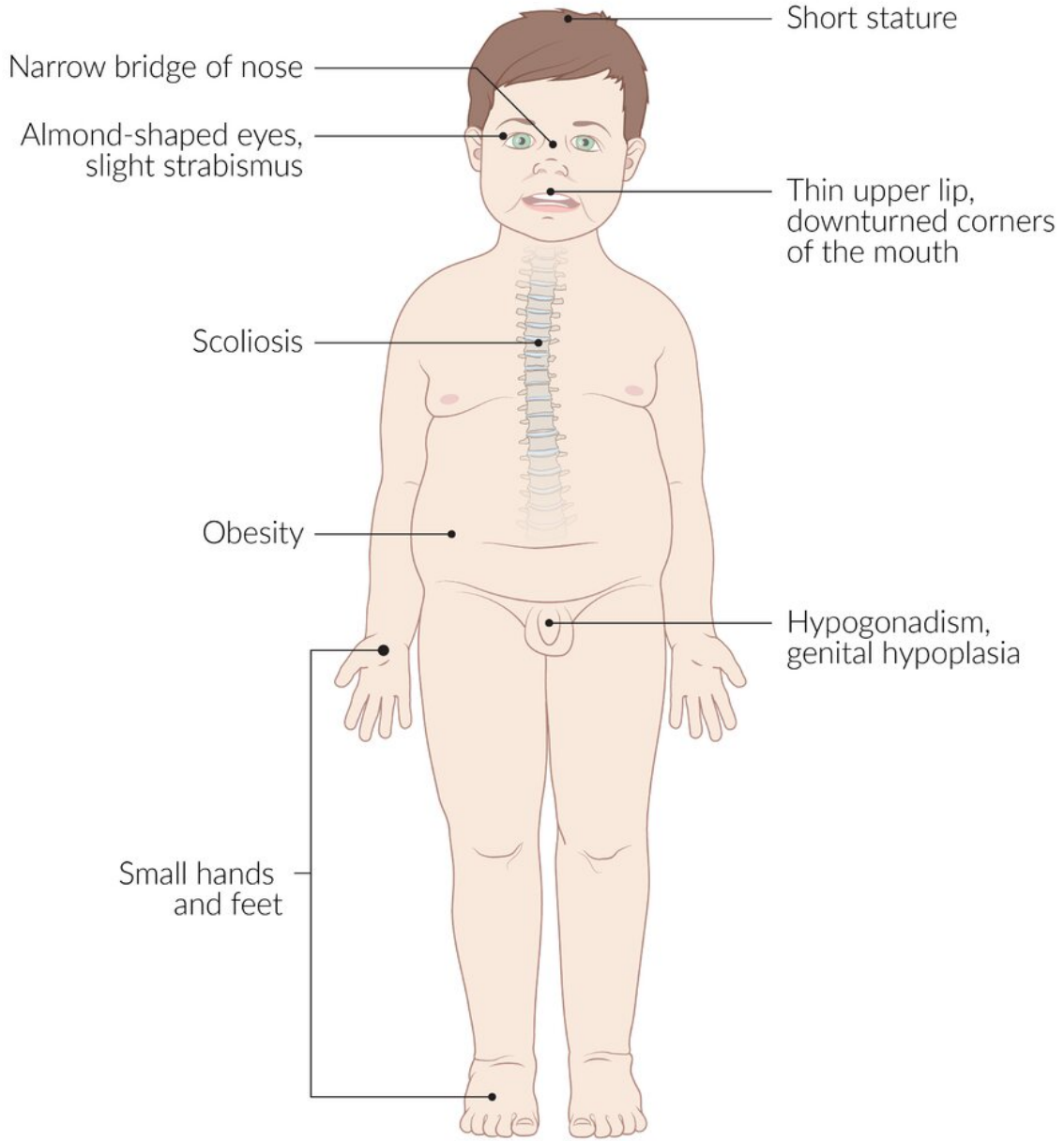
Complications
Obesity and sequelae, e.g., diabetes mellitus and respiratory disorders

Prognosis
Partial autonomy is possible

Life expectancy
Slightly below normal if obesity can be controlled

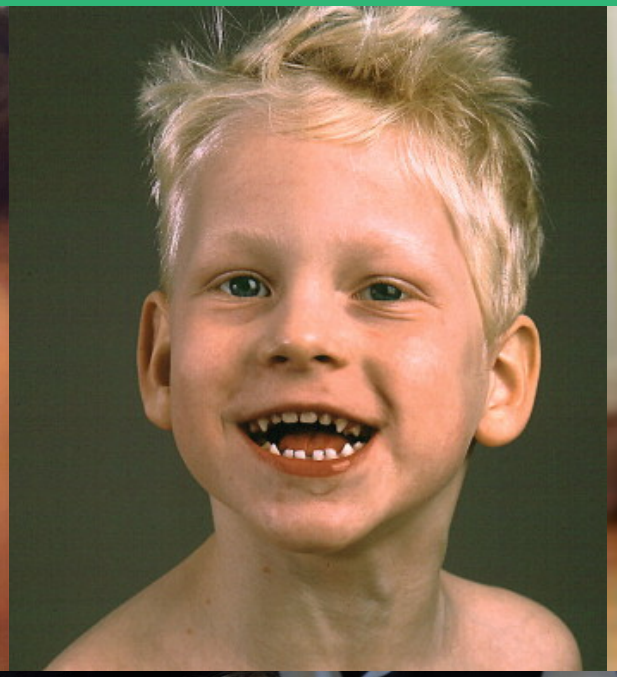
Psychiatric and neurological features

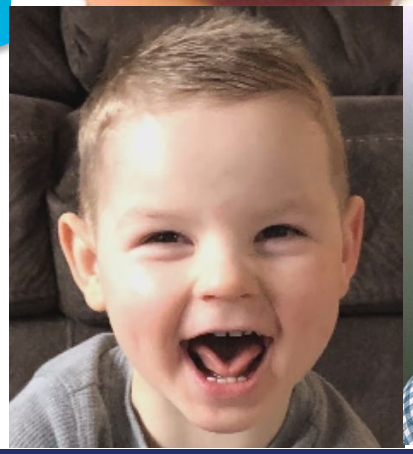
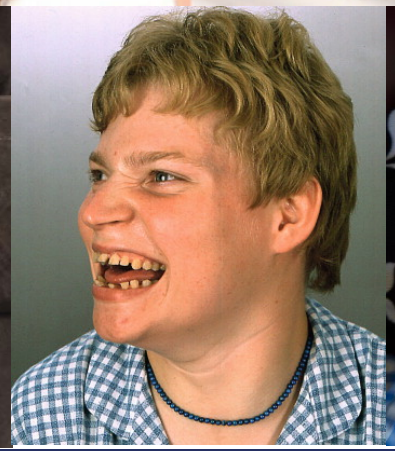
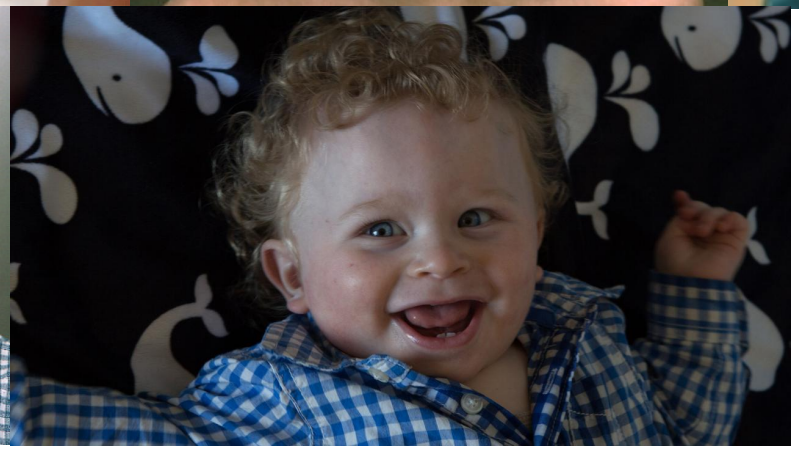
Uncontrolled appetite with hyperphagia, learning difficulties, cognitive deficits, low impulse control, defiant behavior, psychosis



ANGELMAN syndrome






Angelman syndrome

Epidemiology
Worldwide prevalence: 4–8/100,000
♂ = ♀

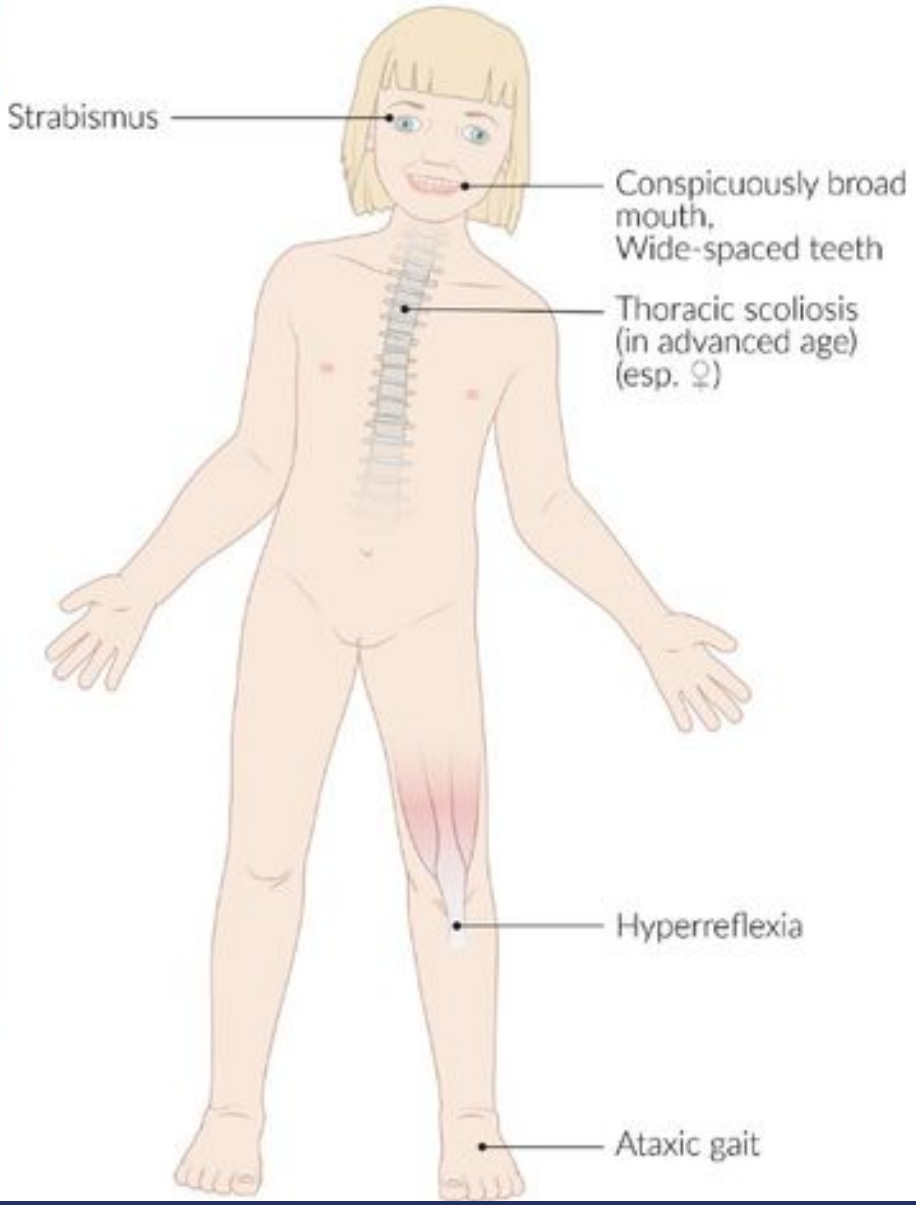
Etiology
Maternal deletion 15q11q13 (> 70%)
Rarely paternal uniparental disomy
Low risk of inheritance (mostly spontaneous mutation)
Etiology similar to Prader-Willi syndrome

Prognosis
Autonomy is never achieved

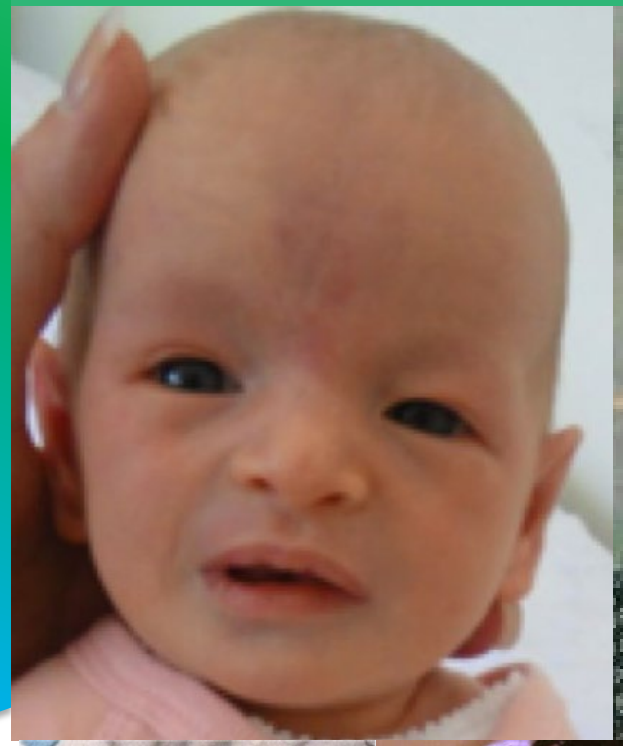
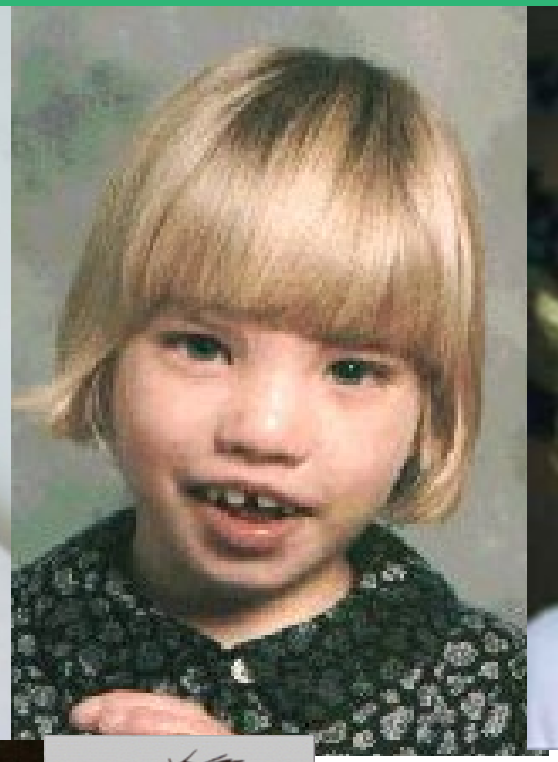
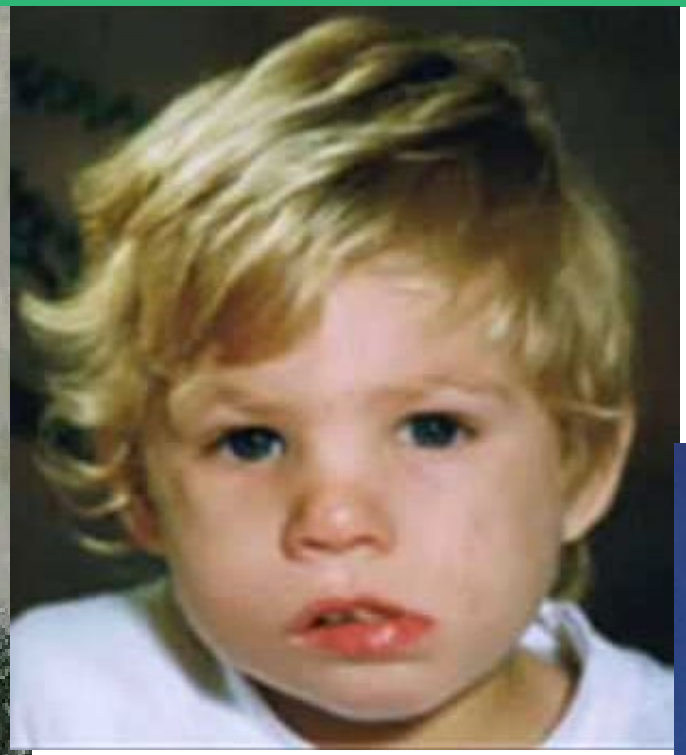
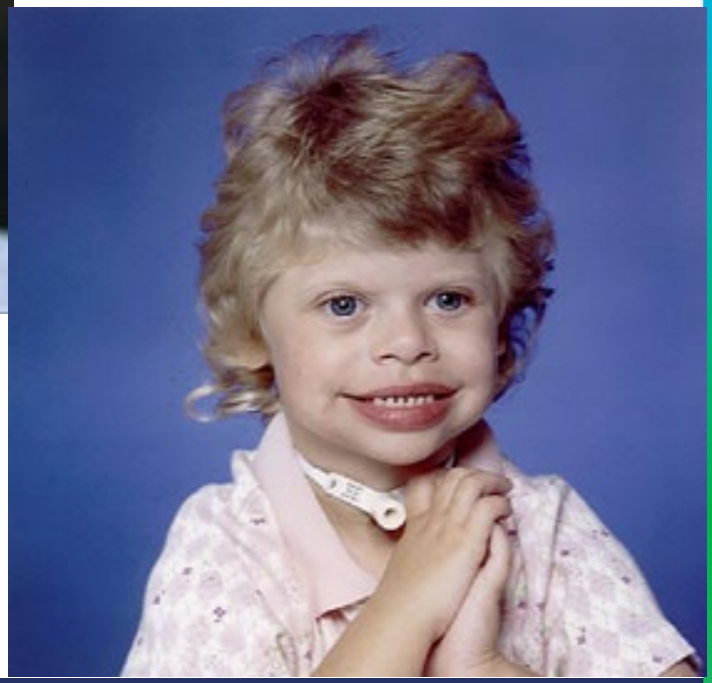
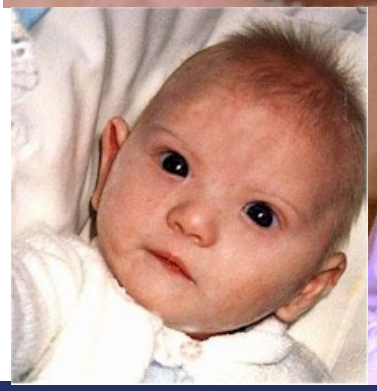
Life expectancy
Normal

Psychiatric and neurological features

Severe intellectual deficiency
Severe speech development disorders
Cheerful demeanor with frequent smiling
Hyperactivity associated with hand-flapping movements
Seizures



CRI-DU-CHAT syndrome

Cri-du-chat syndrome

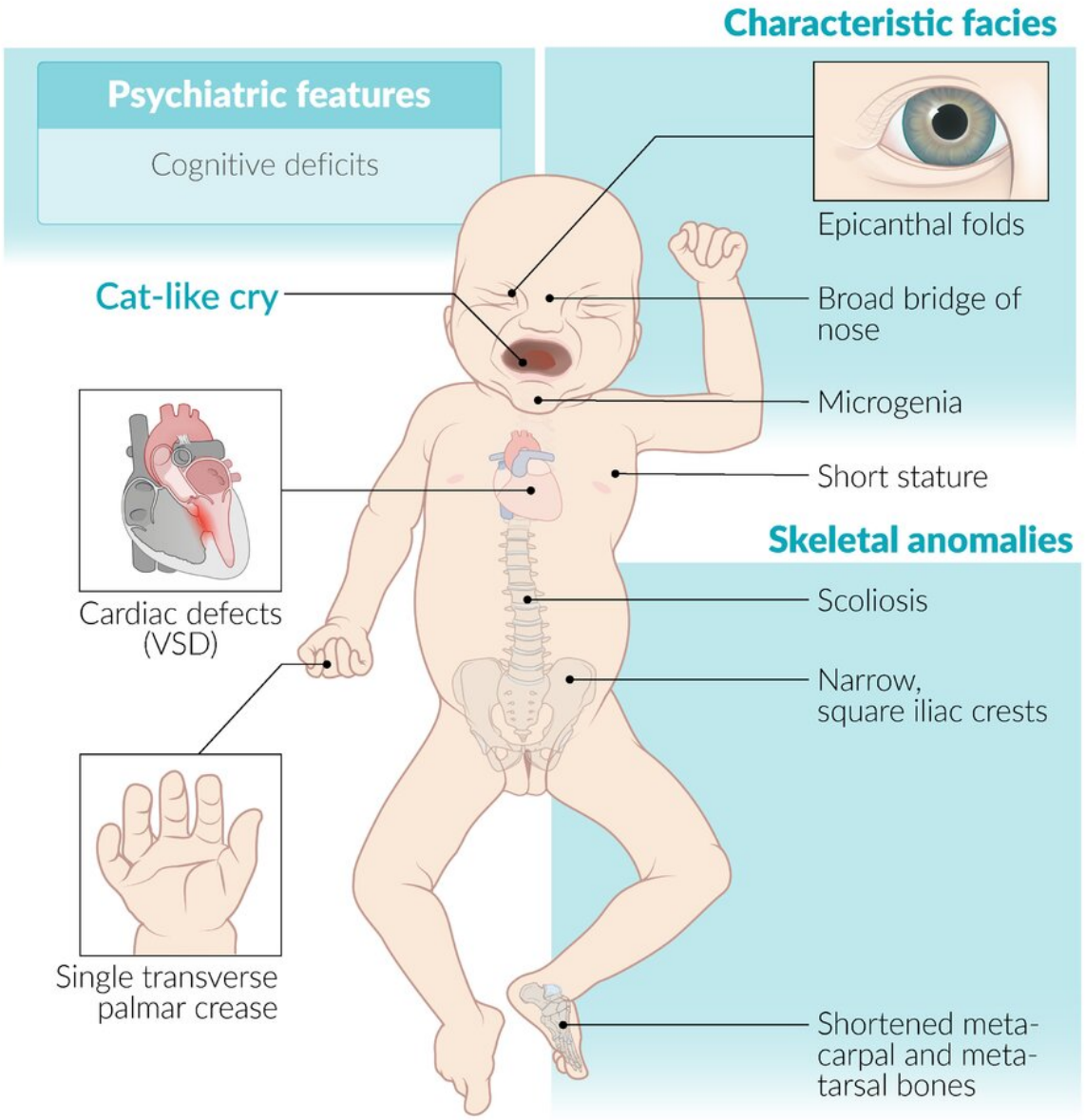
Epidemiology
Approximately 1:45,000 liveborn infants
Sex: ♀ > ♂ (2:1)

Etiology
Structural aberration of the short arm of chromosome 5

Karyotype
♀: 46,XX -5p
♂: 46,XY -5p

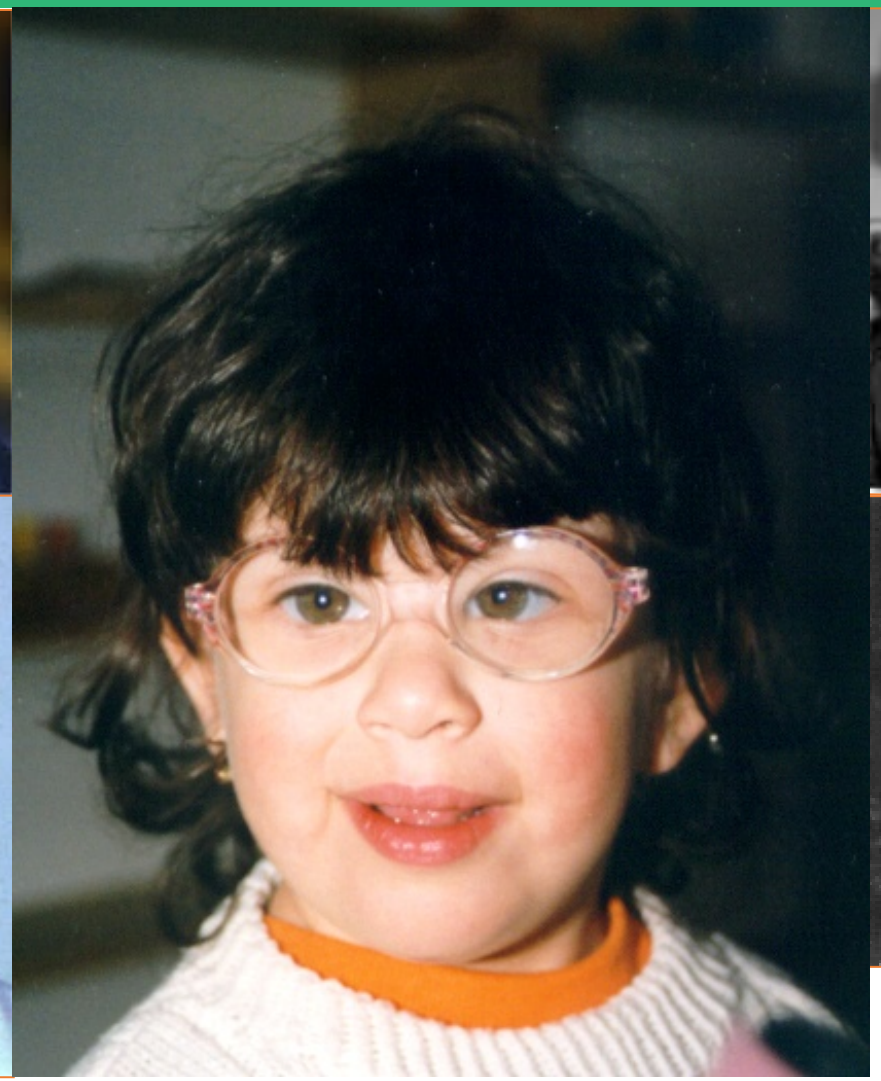
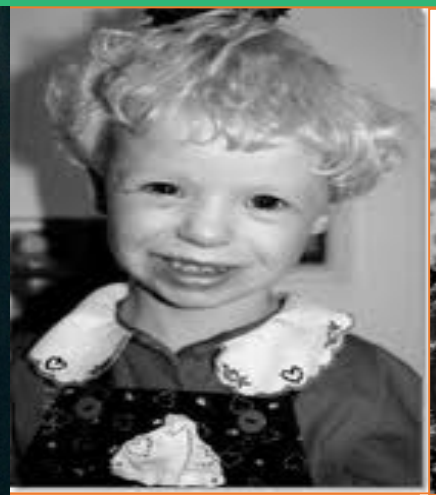
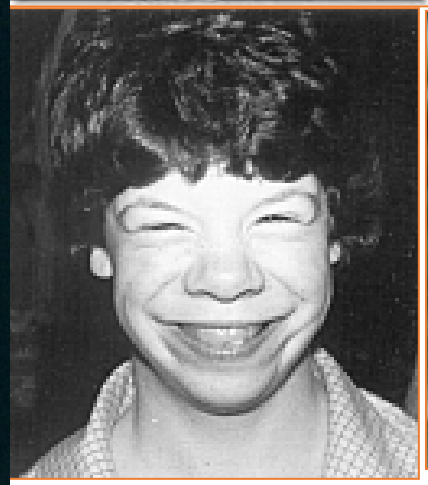
Note
Cardinal symptom is a cat-like cry during infancy

Life expectancy
May be normal, depending on severity of symptoms and treatment



Williams – Beuren syndrome



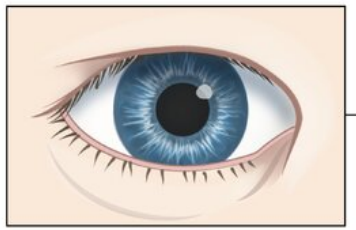
Williams syndrome

Epidemiology
1/10,000 live births

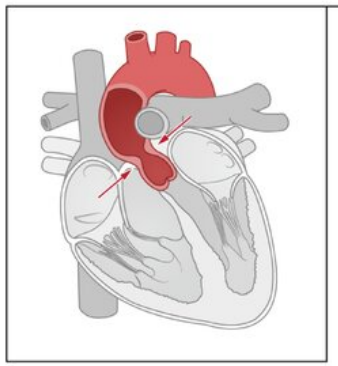
Etiology
Microdeletion on chromosome 7
(includes deletion of elastin gene)
Mostly spontaneous mutation, rarely
autosomal-dominant Inheritance

Laboratory findings
Intermittent hypercalcemia,
mainly during early childhood
(due to increased vitamin D sensitivity)

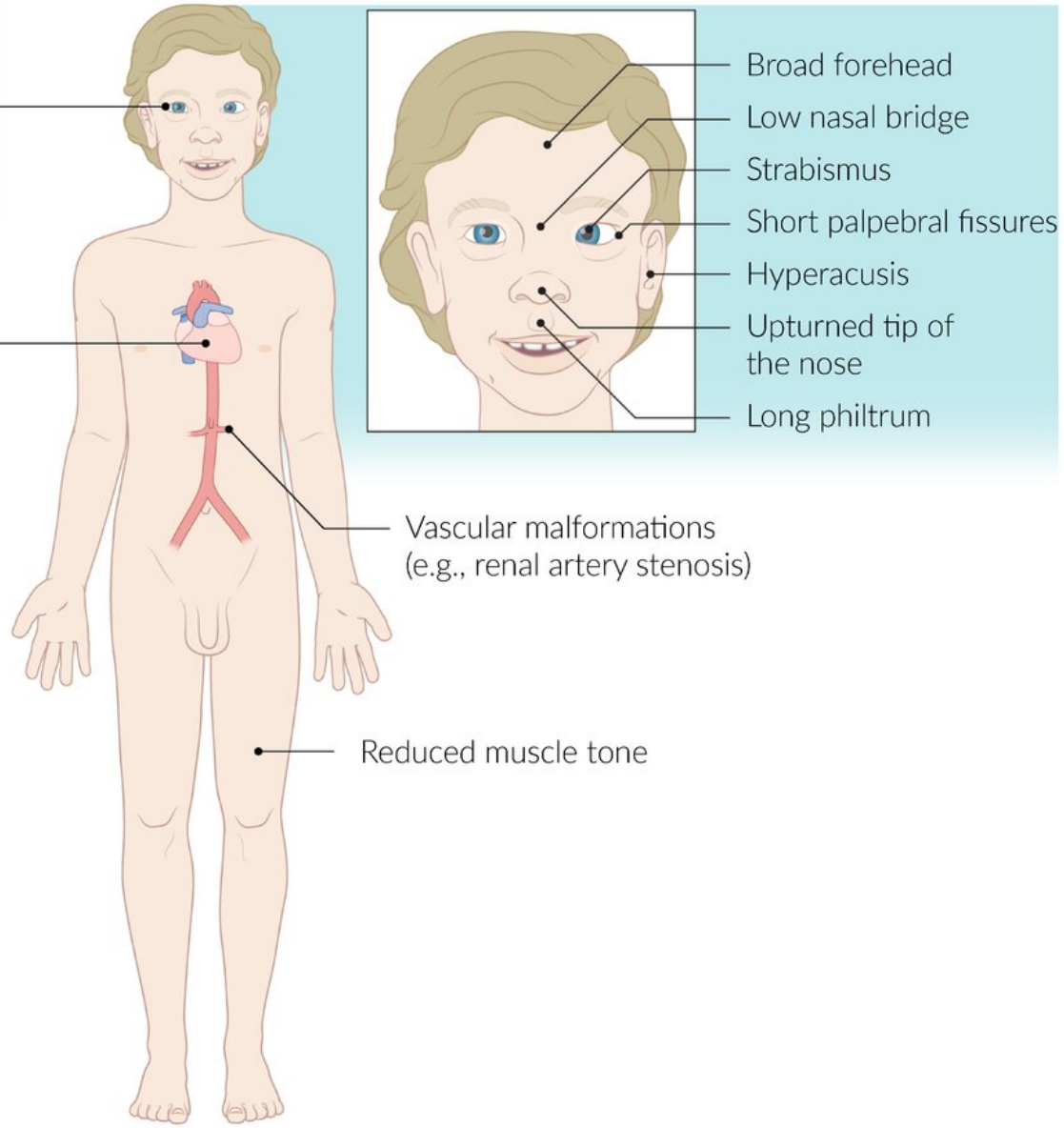
Complications
Mostly cardiovascular
Gastrointestinal symptoms, vomiting
and, subsequently,
failure to thrive



Stellate pattern in the iris



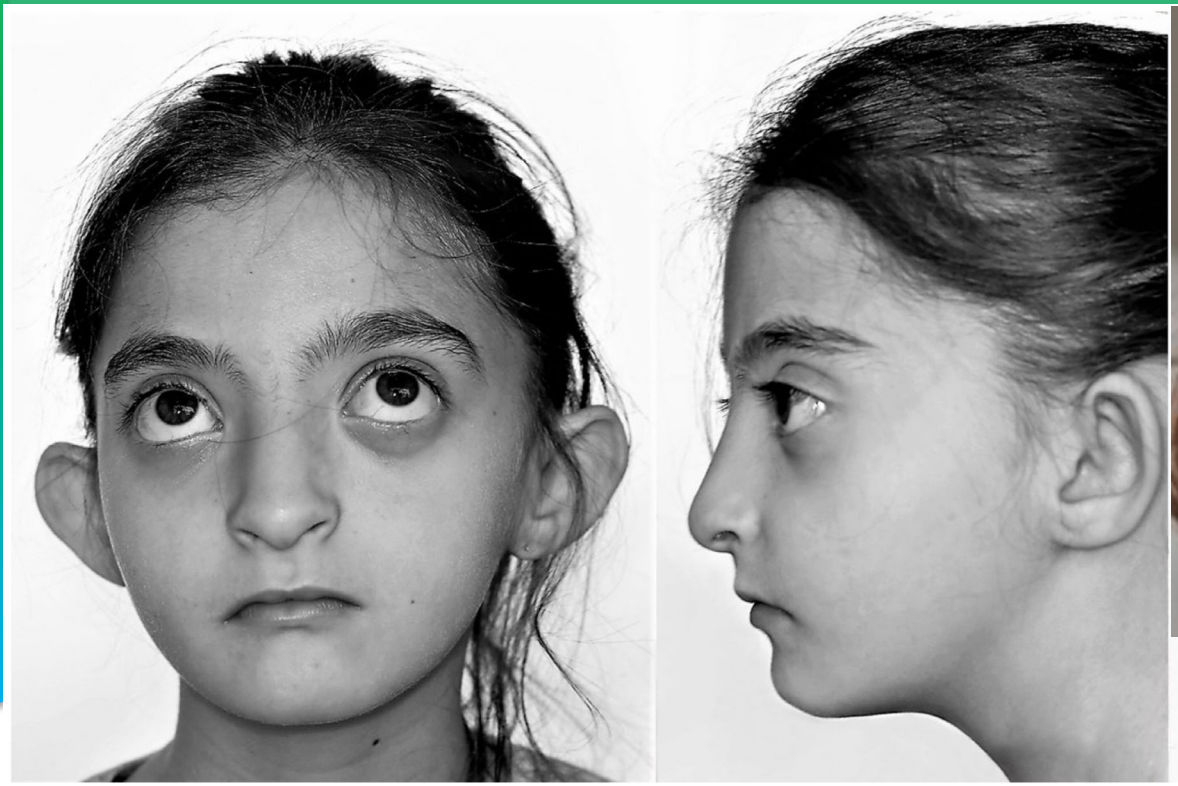
Cardiac malformations
(esp. supravalvular
aortic stenosis)



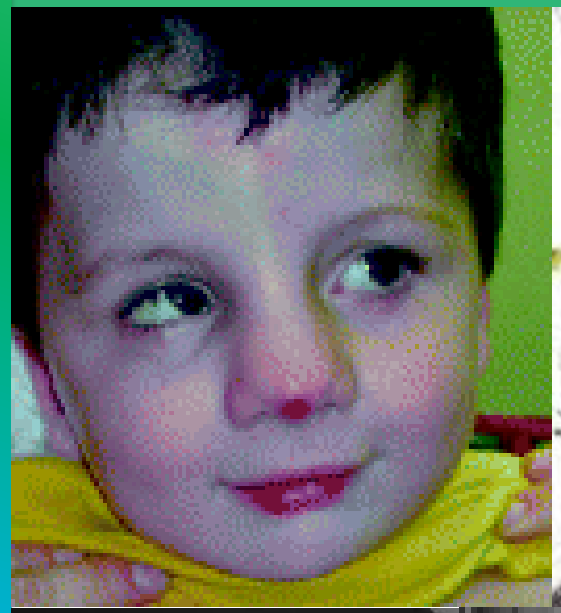
Psychiatric manifestations

Cognitive deficits
Typically sociable personality with good verbal skills
(cocktail party personality)
Anxiety disorders, phobias

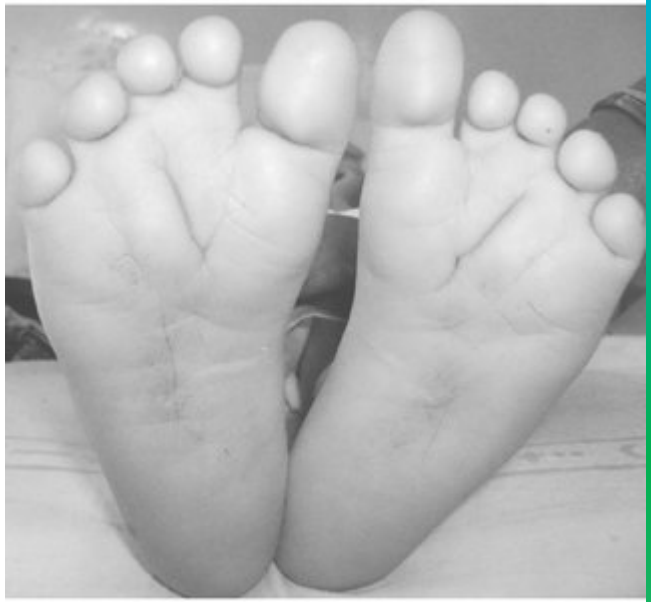
WOLF-HIRSCHHORN (del4p) syndrome



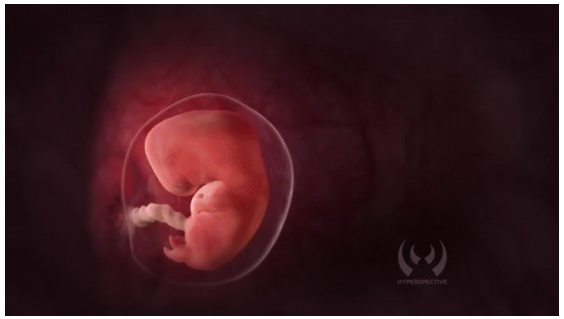
WARKANY (trisomy 8) syndrome





WHAT IS THE AIM OF GENETIC COUNSELLING?



- Precise diagnosis
- Mode of inheritance
- Follow-up strategy
- Specific rehabilitation
- Intrauterine diagnosis

THE ROLE OF GENETICIST: WAY TO DIAGNOSIS AND FOLLOW-UP STRATEGY

PHYSIO-THERAPIST

SPEECH THERAPIST

PSYCHOLOGIST

RADIOLOGIST

PEDIATRICIAN

CLINICAL GENETICIST

PATIENT

CARDIOLOGIST

ENDOCRINOLOGIST

HEART SURGEON

PEDIATRIC SURGEON

THANK YOU FOR YOUR ATTENTION!