Genetic aspects of craniofacial disorders

Craniofacial disorders

- may be accompanied by considerable discomfort and stress on the side of the patient,because it may be associated with a noticeable cosmetic problem,which is individually perceived
- The role of genetic counseling is necessary in the diagnostic process with respect to possible recurrence

Disorders of teeth, jaws and periodontium

Teeth

- Numerous defects of the teeth

  - Hypodontia/oligodontia
  - Hyperodontia

Hypodontia

- is the condition at which the patient has missing teeth as a result of their failure to develop.
- Most common anomaly of human dentition in a population

- Hypodontia: 1-6 missing teeth
- Oligodontia: more then 6 missing teeth
- anodontia : missing all teeth- rare

Hypodontia- prevalence

- In caucasians, the most common missing teeth are the wisdom teeth (25-35%), the upper lateral incisors (20%) ,the lower or the upper second premolars (30%), with a 4:1 female to male ratio.
- The prevalence of missing primary teeth is found at 0,1-0,9%, with a 1:1 male to female ratio. Excluding the third molars, missing permanent dentition accounts for 3-6%.
- 30-50% of people with missing primary teeth will have missing permanent teeth, as well.

Hypodontia-etiology

- Among the possible causes are genetic, hormonal, environmental and infectious factors during dental development.
- missing teeth have been reported in association with increased maternal age, low birth weight, infection during embryonic life
- Hypodontia can be associated with genetic disorders such as ectodermal dysplasia or Down syndrome and can also been seen in people with cleft lip and palate.
- Etiology due to hormonal defects: idiopathic hypoparathyroidism and pseudohypoparathyroidism.
- Environmental causes involving exposure to PCBs (ex.dioxin), radiation,anticancer chemotherapeutic agents, allergy and toxic epidermal necrolysis after drugs.

Genetic causes of hypodontia

- isolated

Several genes are known in assotiation

PAX9(14q12),MSX1(4p16), WNT10A(2q35),

AXIN2(17q24.1) (ovarian and CRC cancer susceptibility)

Inheritance: autosomal dominant or recesive(rare)

IRF6(1q32.3),TGFA(2p13),FGFR1(8p11.23),

EDA(Xq13.1),EDARADD(1q42),LTBP3(11q13.1),

- syndromic

Ectodermal dysplasia

Orofaciodigital syndrome,etc.

Ectodermal dysplasia

- there are abnormalities of two or more ectodermal structures such as the hair, teeth, nails, sweat glands, cranial-facial structure, digits and other parts of the body.
- more than 150 different syndromes have been identified
- Ectodermal dysplasia,anhidrotic

  hypotrichosis, fine-brittle-scanty hair, absent or scanty eyelashes,eyebrows, hypodontia /anodontia, hypoplastic or absent mucous glands

  danger of overheating
- Genetic heterogenity XR, AR,AD
- Heterozygous females show variable expressivity (mild

  manifestations) including hypodontia, conical teeth, reduction in scalp/body hair

Genes: EDA, EDAR, EDARADD

Hyperodontia

- **Hyperdontia** is the condition of having **supernumerary teeth**, or teeth which appear in addition to the regular number of teeth.

Supernumerary teeth can be classified by shape and by position.

- The atypical shapes include:supplemental tuberculate , conical , compound odontoma (multiple small tooth-like forms),complex odontoma (a disorganized mass of dental tissue)
- By position a supernumerary tooth may be referred to as a mesiodens, a paramolar, or a distomolar.

The most common supernumerary tooth is a **mesiodens**, which is a mal-formed, peg-like tooth that occurs between the maxillary central incisors.

Fourth and fifth molars that form behind the third molars are another kind of supernumerary teeth.

Hyperodontia-causes

- there is evidence of hereditary factors along with some evidence of environmental factors leading to this condition-multifactorial inheritance
- Many supernumerary teeth never erupt, but they may delay eruption of nearby teeth or cause other dental or orthodontic problems. Dental X-rays are often used to diagnose hyperdontia.
- Supernumerary teeth in deciduous (baby) teeth are less common than in permanent teeth.
- Hyperdontia is seen in a number of genetic disorders, including Cleidocranial dysostosis or Gardner´s syndrome

Cleidocranial dysplasia

- persistently open skull sutures with bulging calvaria, hypoplasia or aplasia of the clavicles permitting abnormal facility in opposing the shoulders, wide pubic symphysis, short middle phalanx of the fifth fingers, dental anomalies, and often vertebral malformation
- Occurence 1:100 000
- Inheritence AD,variable expressivity
- Location 6p21, gene CBFA1(RUNX2)
- One third of patients represent new mutations

Cleidocranial dysplasia- unfavorable effects

- 18% scoliosis
- 28% coxa vara, coxa valga
- 57% pedes plani
- 34% inflammation of the paranasal sinuses frequently
- 70% oral disorders
- 19% difficulty breathing
- 39% deafness

Cleidocranial dysplasia- oral symptoms

- Cleft palate(submucous)
  Narrow, high-arched palate

- Delayed eruption of deciduous teeth
  Delayed eruption of permanent teeth
  Supernumerary teeth
  Retention cysts
  Enamel hypoplasia

- Delayed closure mandibular symphysis, prognathia relative-normal mandibular growth and limited growth of praemaxila

Teeth- disorders of enamel

- amelogenesis imperfecta -presents with abnormal formation of the enamel or external layer of teeth.

  inheritance: AD, AR, X-linked
- Syndromic association (trichodentoosseous syndrome – TDO-AD, Kohlschutter syndrome – AR -epilepsy,mental retardation,amelogenesis imp.)
- Non-genetic forms abnormal enamel (fluorosis, the use of tetracycline antibiotics,etc)

Teeth- dentin disorders

- Dentinogenesis imperfecta
- Non-syndromic AD inheritence
- syndromic assotiation-diffrent forms of osteogenesis imperfecta- brittle bone disease, defective connective tissues(AD,AR, defects of collagen I)- COL1A1,COL1A2 genes
- Disorders of dentin in number of systemic diseases associated with impaired metabolism of calcium and phosphate

  (eg. Hypophosphatemic rickets ,hypoparathyroidism etc)

Teeth

- Caries- multifactorial, interaction between environmental and genetic factors -

  susceptibility of tooth tissue, composition of oral microflora, eating habits, oral hygiene

Periodontal diseases

- Frequent cause of tooth loss
- Multifactorial
- Syndromic assotiation

Papillon-Lefévre syndrome

- Inheritence autosomal recessive
- occurence 1-4/1 000 000
- Keratosis palmoplantaris
- periodontopathia

Anomalies of jaws

- Prognathia(excessive growth of maxilla) affects about 14% population, multifactorial probably, with high correlation between siblings.

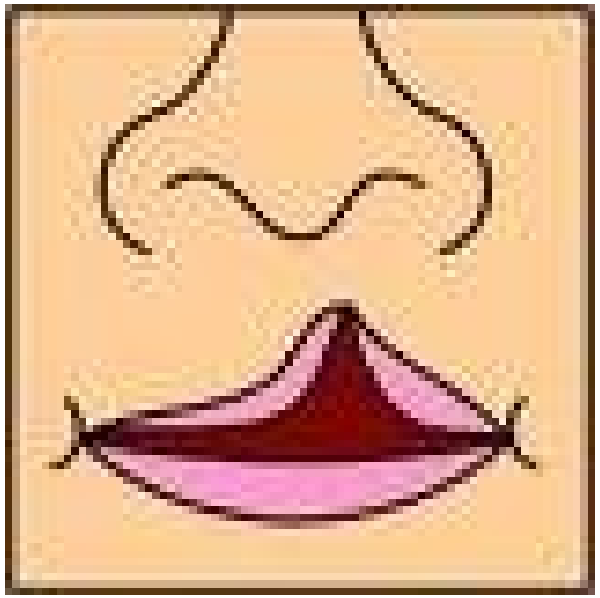
- Progenia(excessive growth of mandibula, often in all three dimensions)

  affects 3-9% population

  polygenic (multifaktorial)

  familial cases with AD inherritence have been reported(the best known is the case of the Habsburgs)

Facial cleft defects



Cleft lip and palate-CLP

- CL- incidence : 1/500-1/1000
- CP- incidence: 1/2500

Cleft defects-clasification

- clefts typical
  lip (cheiloschisis)
  lip + palate (cheilognathoschisis)
  palate-isolated(palatoschisis)
  total (cheilognathopalatoschisis).

- clefts atypical
  Cross
  upper middle (nose, upper lip, upper lip defect with defect of praemaxilla)
  lower middle (lower lip, lower lip + jaw)
  oblique (lip + face, + faces of the lower lid, with cleft palate typical + atypical).

Facial clefts -pathogenesis

- Cleft lip and palate: failure of fusion of the maxillary and medial nasal processes (formation of the primary palate).

- Cleft palate: failure of fusion of the lateral palatine processes, the nasal septum, and/or the median palatine processes

(formation of the secondary palate)

Cleft lip and palate- cause

- Multifactorial with significant inheritance component

Enviromental factors: viruses , toxoplasmosis, CMV,hypervitaminosis A + D, ATB(tetracyclines, erythromycine), AEDs, corticoids, X-ray, drugs, organic solvents ,other teratogens

- Congenital chromosomal aberration
- Syndromes asociated with CL/CP/CLP

Cleft lip and palate-ethnic differences

- most common in Caucasians and Japanese
- least frequently in Negroid race

Cleft lip and palate- empiric risks(Harper)

Relationship to index case	CLP	CP
Sibs (overall risk)	4%	1,8%
Sib (no other affected)	2.2%	
Sib(2 affected sibs)	10%	8%
Sib and parent affected	10%	
Children	4,3%	3%
Second-degree relatives	0,6%	

Empirical risk according to severity of defect

Defect	risk for sibs
Bilateral CLP	5,7 %
Unilateral CLP	4,2 %
Unilateral CL	2,5 %

Chromosomal aberration associated with CLP/CP

- trisomy 13
- trisomy 18
- Structural aberrations autosomes
- velocardiofacial syndrome 22q11microdeletion syndrome

Patau syndrome

- 47,XX(XY), +13
- 1 in 5000-10 000 newborns,
- 1 in 90 SA

- CLP bilateral, congenital defects of the brain, eyes, postaxial hexadaktyly…)

Edwards syndrome

- 47,XX(XY),+18
- 1in 5000 newborns
- IUGR
- microcephaly
- dolichocephaly
- CP
- rethrognathia

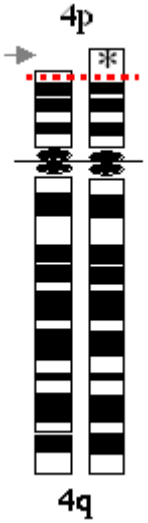
Wolf-Hirschhorn syndrome, 4p-

1:50 000

8% de novo deletion

13% due to familial translocation

F:M 2:1



symptoms

-dwarfism

-microcefaly, craniofacial stigmatisation

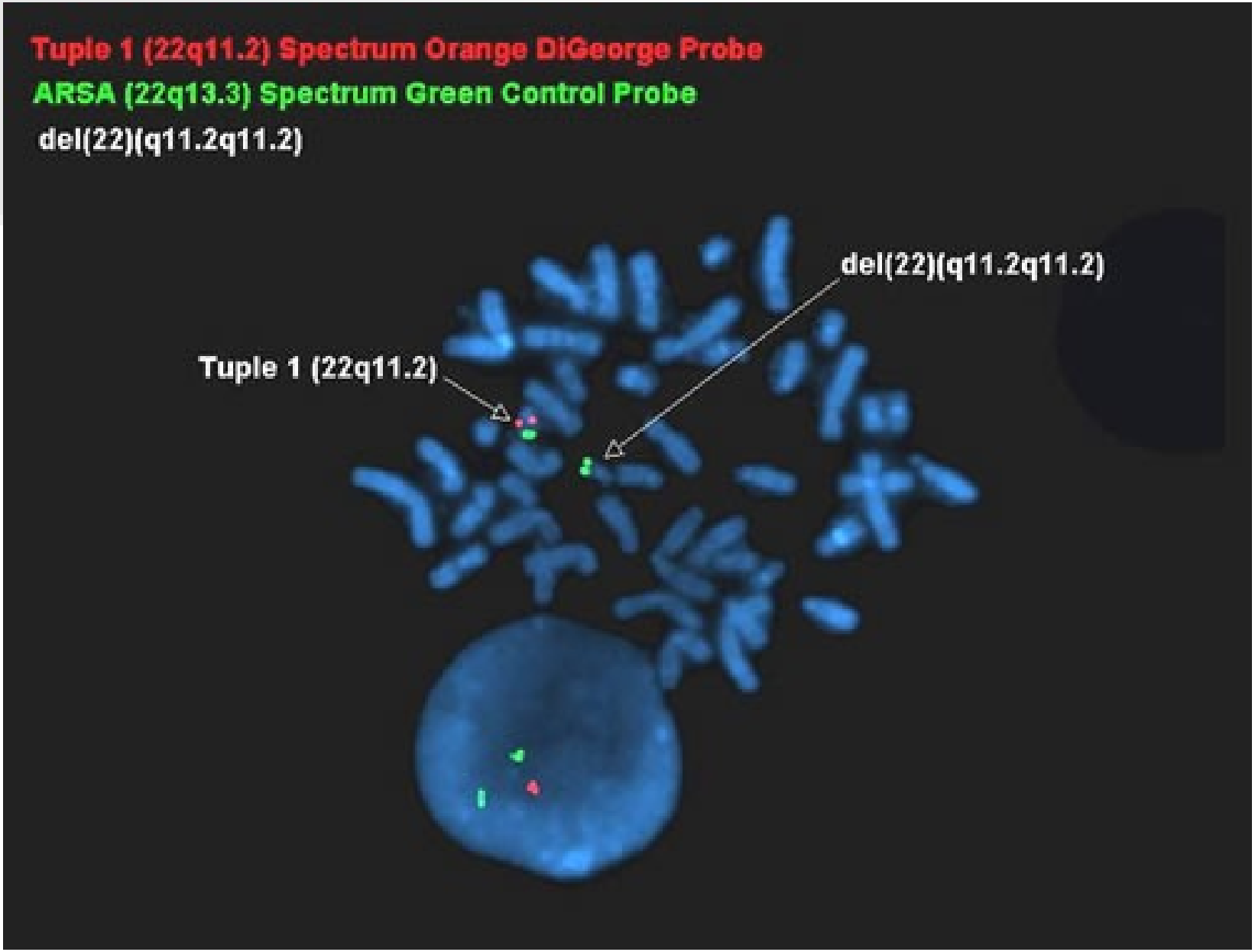
- CL,CP,CLP

-heart defects

Di George syndrome – velocardiofacial

- Microdeletion 22q11

- Symptoms:
  - heart defects
  - facial stigmatisation
  - CP(submucous too)
  - hypoplasia of thymus and parathyroids)
    (immunodefects, hypocalcemia)


Tuple 1 (22q11.2) Spectrum Orange DiGeorge Probe
ARSA (22q13.3) Spectrum Green Control Probe
del(22)(q11.2q11.2)
del(22)(q11.2q11.2)
Tuple 1 (22q11.2)

Syndromes without Mendelian inheritance

- Pierre-Robin sequence
  - Mandibular hypoplasia
  - Glossoptosis
  - Cleft of palate

May be part of a variety of skeletal or muscular syndromes, some mendelian (e.g. Stickler sy, Congenital myotonic dystrophy)

AD hereditary syndromes with CLP

- van der Woude syndrome
- EEC syndrome
- Stickler syndrome
- Larsen syndrome

van der Woude syndrome

-Autosomal dominant, incomplet penetrance
variable expressivity !!!

-Mouth lower lip pits
-Cleft lip
-Cleft palate
-Cleft uvula
-Hypodontia

- Molecular Basis - caused by mutations in the interferon regulatory factor 6 gene (IRF6)
-

EEC syndrome

-Ectrodaktyly-deformities of hands and feet

-Ectodermal dysplasia-skin ,hair,nails

-Cleft lip/palate

-other defects-kidneys,eyes,teeth

Genetic heterogenity

Two loci described – EEC1(7q11)

and EEC3 (3q28)

Majority of EEC cases appear to be

to TP63 mutations

Stickler syndrome

Incidence 1 in 10 000

Mutation in COL11A1,COL11A2,COL2A1 genes

Symptoms

-Pierre-Robin sequence

-eye:glaucoma,cataracts, retinal detachment

-sensorineural hearing loss

-artropathy, scoliosis,mitral valve prolaps

Larsen syndrome

Incidence 1 in 100 000

Caused by mutation in the

filamin B gene (FLNB)-3p14.3

Multiple joint dislocation

Deformities of feet

Facial stigmatisation

Others: dwarfism, skeletal defects , heart defects, CP, deafness, mental retardation

Rare AR inheritance

AR hereditary syndromes with CLP

- Fryns syndrome
- Roberts syndrome(pseudothalidomid)
- Diastrophic dysplasia
- Smith-Lemli-Opitz syndrome
- Orofaciodigital syndrome II
- Meckel-Gruber syndrome

Fryns syndrome

- Diaphragmatic hernia
- Abnormal face, and distal limb anomalies
- Cleft lip/palate

Roberts syndrome

- Pseudothalidomid syndrome
- Pre-/postnatal growth deficiency
- Cleft lip/ palate(bilat.)
- cataracta
- Oligodactyly
- Phocomelia
- Radial hypoplasia
- Mental retardation
- Caused by mutations in ESCO2 gene (8p21)

Diastrophic dysplasia

- dwarfism, adult high 100-120 cm
-short limbs
-short, thick tubular bone, with
  broad metaphyses and flattened,
  irregular epiphyses
-cleft palate
-ear abnormalities
-joint deformities
-hip contractures
-hands deformities(„ hitchhiker thumb“)
-vertebral deformities
SLC26A2 gene (5q32)

Smith-Lemli-Opitz syndrome

- pre- and postnatal growth deficiency
- Microcephaly
- Facial stigmatisation
- Cleft palate
- Mental retardation
- Hypospadias,ambiguous genitalia,micropenis
- Syndaktyly of second and third toes of feet
- Mutation in DHCR gene, locus 11q12-q13
- low cholesterol,elevated 7-dehydrocholesterol

Orofaciodigital syndrome, type II

- Mohr syndrome
- Medial cleft of upper lip
- micrognathia
- Cleft and lobation of tongue,
- hypertelorism
- Bilateral postaxial hexadactyly of hands, bilateral polysyndaktyly of hallux

Meckel-Gruber syndrome

- microcephaly, encephalocele
- Microphtalmia
- Cleft lip and/or palate
- Congenital defect of heart
- Postaxial polydactyly
- Polycystic kidneys

A lethal disorder, with death occuring in the perinatal period

Heterogenity:loc.17q21-24,11q13 and 8q24

X-linked hereditary syndromes with CLP

- Orofaciodigital syndrome, type I
- Otopalatodigital syndrome
- Isolated X-linked cleft of palate with ankyloglossia

Orofaciodigial syndrome,type I

- Papillon-Léage-Psaume syndrome

- Hyperplasia of fraenulum
- Multiply lobulated tongue
- Hypoplasia of lateral nasal cartilages
- Medial pseudocleft of upper lip
- Asymetrical cleft of palate
- Variable malformation of digits
- Moderate mental retardation

Otopalatodigital syndrome

- Type I

- A characteristik face(prominent supraorbital arches, joined eyebrows,antimongoloid position of eye slits, hypertelorism, a broad and flat root of the nose)
- Cleft palate
- Conductive hearing loss
- Mental retardation
- Somatic retardation

- Type II

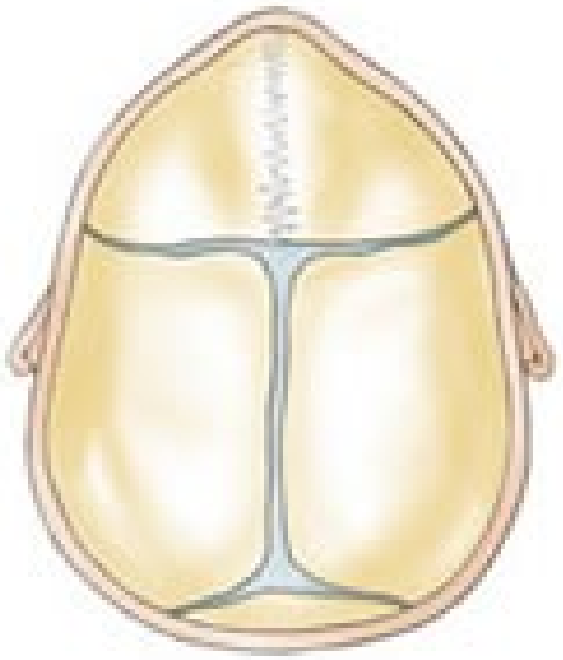
- + other multiple skeletal anomalies

Cleft palate and ankyloglossia

X-linked inheritance

- Cleft of uvula- heterozygot female
- Incomplet cleft of palate
- Incompetention of palate
- ankyloglossia

Craniosynostoses



Craniosynostoses

- Premature closing of cranial sutures
- This early fusion affects the shape of the head and face.
- different patterns of growth of the skull include:

trigonocephaly (fusion of the metopic suture),

brachycephaly (fusion of the coronal suture)

dolichocephaly (fusion of the sagittal suture)

plagiocephaly (unilateral premature closure of lambdoid and coronal sutures)

turicephaly(fusion of coronal and lambdoidal sutures)

Craniosynostoses

- Heterogenous group etiologically and pathogenetically
- Isolated or part of syndrome units

- Syndromic- AD inheritance in most case

Apert syndrome

- AD inheritance
- turribrachycephaly
- Hypoplasia of the central part of the face,
- Mental defect- varying degree(also normal intelligence)
- Glove-like asymetrical fusion of fingers and toes
- Mutation in FGFR2 gene

Crouzon syndrome

- AD inheritance
- Craniosynostosis of coronal,sagital and lambdoid sutures
- parrot-like nose
- hypoplastic maxilla
- exoftalmus, shallow orbits
- impressiones gyrorum
- Mutations in FGFR2 and FGFR3 gene

Pfeiffer syndrome

- AD inheritance
- Brachycephaly,plagiocephaly
- Hypoplasia of medial part of face
- Exophtalmus
- skin syndactyly of fingers
- Medial deviation of thumbs
- Mutation in FGFR1 gene

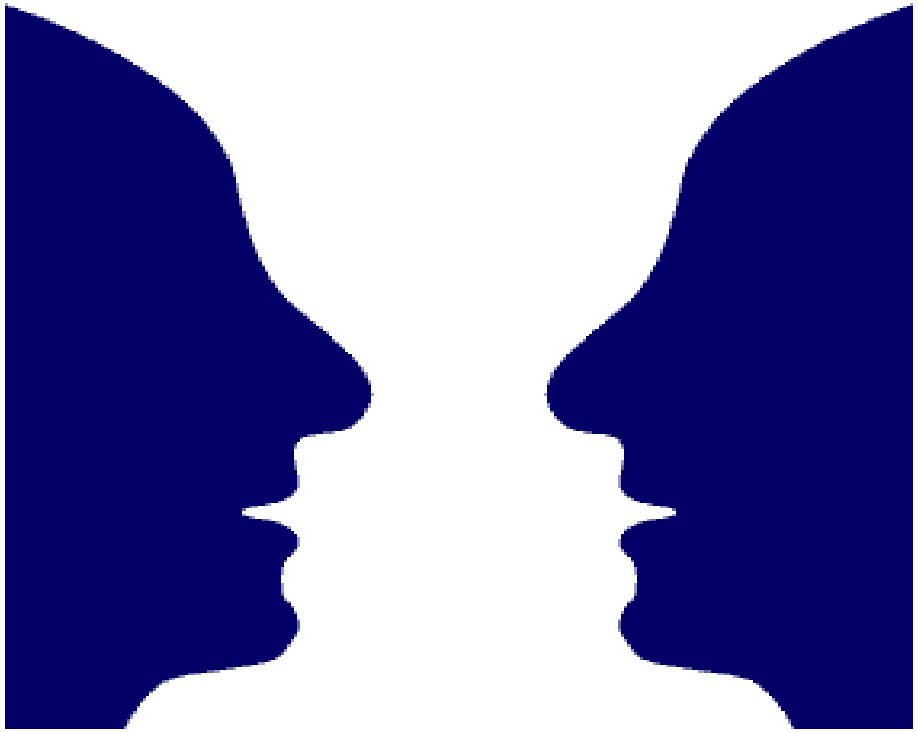
Seathre-Chotzen syndrome

- AD inheritance
- Brachycephaly
- Hypoplastic maxilla
- Facial asymetry
- Syndactyly, hallux valgus, brachydactyly
- Mutation in TWIST gene

Carpenter syndrome

- AR inheritance
- Brachycephaly
- Midface hypopalsia
- hypertelorism, flat nasal bridge
- Obesity
- Mental retardation
- Brachydactyly, postaxial polydactyly, clinodaltyly, syndaktyly, camptodactyly
- Locus 6p11

Craniofacial syndromes



Goldenhar syndrome

- Hypoplastic face(often unilateral)
- Colobomas of upper eyelids
- Epibulbar dermoids
- Rudimentary auricles
- Accesory auricular apendages
- macrostomia
- Vertebral anomalies
- Inheritance : polygenic, AD, AR

Treacher Collins syndrome

- Antimongoloid slant of palpebral fissures
- colobomas of the lower eyelids,
- Partial absence of lower eyelashes
- macrostomia, microgenia,
- rudimentary auricles,conductive hearing loss
- inheritance AD, with variable expressivity
- TCOF1 gene(5q32)

Hallermann-Streiff syndrome

Oculomandibulodyscrania

- Dyscrania with hypotrichosis
- Anomalies of the face , especially of the eye(microftalmia, colobomas, strabism catharacta)
- Dental anomalies- congenital teeth, supernumerary teeth, maloclusion etc.
- Somatic retardation
- AD,AR,heterogenia, sporadic in most case

Orofaciodigital syndrome

- Dysmorphic face
- Oral symptoms(CLP, hyperplastic fraenulum,multiply lobulated tongue)
- Digital anomalies(brachydacktyly,syndactyly,polydactyly, clinodactyly)
- Heterogenia, 8 types

Type I : XD

Type II-VI: AR

Typ VIII: XR

Typ VII: AD/XD

Oculodentodigital syndrome

- narrow nose with hypoplastic wings and thin nostrils,
- microcornea with iridial anomalies,
- syndactyly and/or camptodaktyly of postaxial digits, hypoplastic/aplastic middle phalanx of the fith toe
- Hypoplasia of enamel
- Inheritance AD, with as much 50%of the cases on the basis of new mutations

Frontonasal dysplasia

- Median cleft face syndrome
- Hypertelorism
- brachycephaly, prominent forehead wit a broad ridge of nose
- Sagitally lined up to cleft nose(often frontal cranium bifidum occultum and/or medial cleft of the face)
- Widely opened fontanelle,sutura metopica ,synostosis of coronal sutures
- Facial asymetry, high palate, diastematous teeth.
- Sporadic mostly, both AD or AR inheritance has been reported
- Prevalence of female 6:1.