Elements of Dysmorphology I

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Common definitions (1)

- Dysmorphology: recognition and study of birth defects (congenital malformations) and syndromes [David Smith, 1960]
- Malformation: a morphological abnormality that arises because of an abnormal developmental process (e.g. clefts)
- Syndrome: a particular set of developmental anomalies occurring together in a recognizable and consistent pattern AND assumed to be of single etiology (e.g. Down syndrome)

Common definitions (2)

- Sequence: a particular set of developmental anomalies occurring together in a recognizable and consistent pattern AND consequent upon a primary defect (e.g. Pierre Robin sequence = mandibular hypoplasia → tongue displacement → cleft palate and upper airway obstruction)
- Association: a particular set of developmental anomalies not known to be a syndrome or sequence (e.g. VACTERL)
- Dysplasia: abnormal cellular organization within a tissue (e.g. bone dysplasias)

Congenital anomalies

- 2-3% singletons have a major anomaly (e.g. heart defect)
- 10% have a minor anomaly (e.g. polydactyly)
- Causes: localized errors (e.g. clefts), deformation (by physical force, e.g. oligohydramnios), disruption (by destruction, e.g. amniotic bands), teratogens (e.g. FAS), germline errors (syndromes)

What causes ‘recognized abnormalities of development’?

- Very many genes: chromosomal aneuploidies
- A number of genes: chromosomal microdeletions/microduplications
- A single gene: monogenic disorders

What does ‘dysmorphic’ mean?

- Children whose physical features are not usually found in a child of the same age or ethnic background („be aware of parental looks”)
- Some features are obvious dysmorphisms (e.g. premature cranial suture fusions) whereas others insignificant familial traits (e.g. finger syndactyly)
- Not only external variety, but also that of internal organs

What do clinical geneticists do? Reasons for referral

- To give a diagnostic opinion
- To help understand the etiology
- To discuss the genetic aspects of the condition
- To advise if there are other investigations pertinent to the diagnosis
- To advise about the prognosis and suggest various therapeutic options
- To discuss the risk of recurrence in another pregnancy
- To discuss if prenatal/preimplantation testing is available

The consultation (1)

- Intro: explanations to parents, question about their main concerns
- Observation: watching the child, incl interactions, movements, language development, the facies
- Fx: three-generation family tree, photographs (!)
- Pregnancy Hx: bleeding, fever, medications, investigations, fetal movements, amniotic fluid volume, gestation, mode of delivery
- Neonatal Hx: measurements, invasive procedures, feeding, malformations, surgery, seizures
- Developmental milestones, incl schooling
- Photographs
- Behaviour
- Vision, hearing, seizures

The consultation (2)

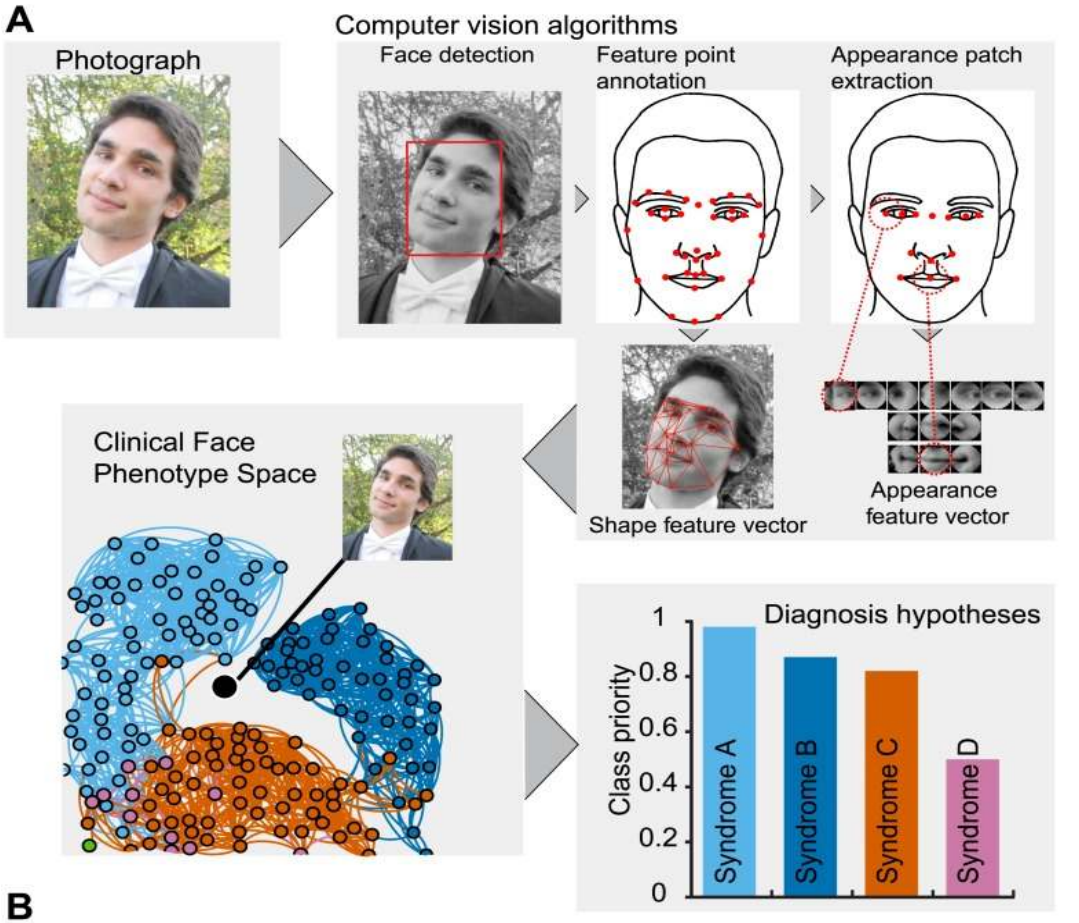
- Physical: face, profile, hands, feet, any unusual features (compare with family)
- Fishing out ‘diagnostic handles’ i.e. those that are only present in a small number of conditions
- Comparing features with info in available databases
- Making Dx (may take plenty of time and a number of consultations)

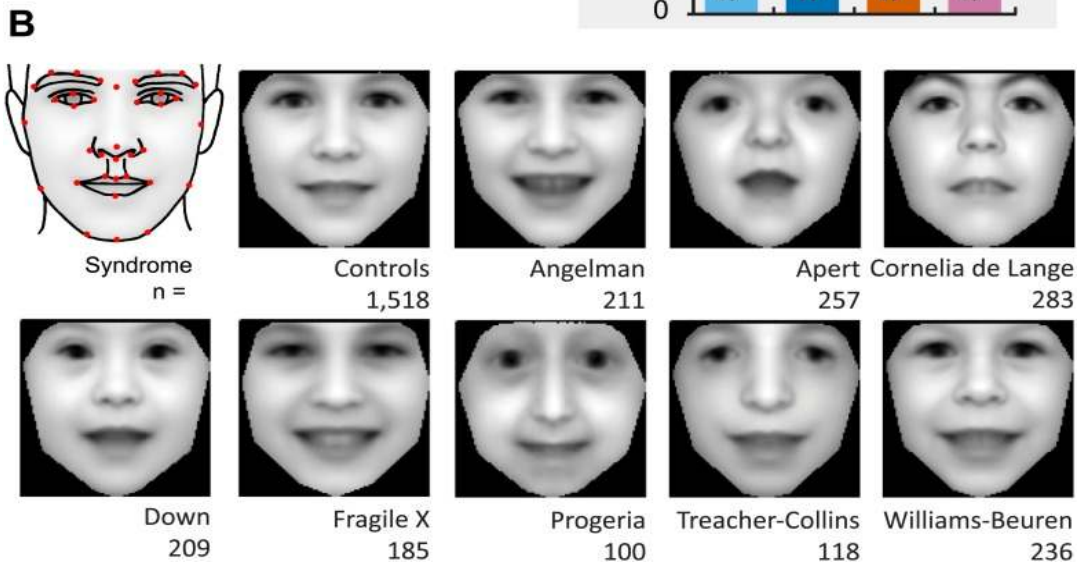
Confirmation of Dx

- Dx must be reached in an affected individual to reach conclusions for the family
- Clinical assessment: critical in neurofibromatosis (comes with age) or tuberous sclerosis
- Lab findings: from reliable source, important in e.g. Huntington disease
- Radiological investigations: e.g. skeletal dysplasias
- Death certificates
- Family photographs

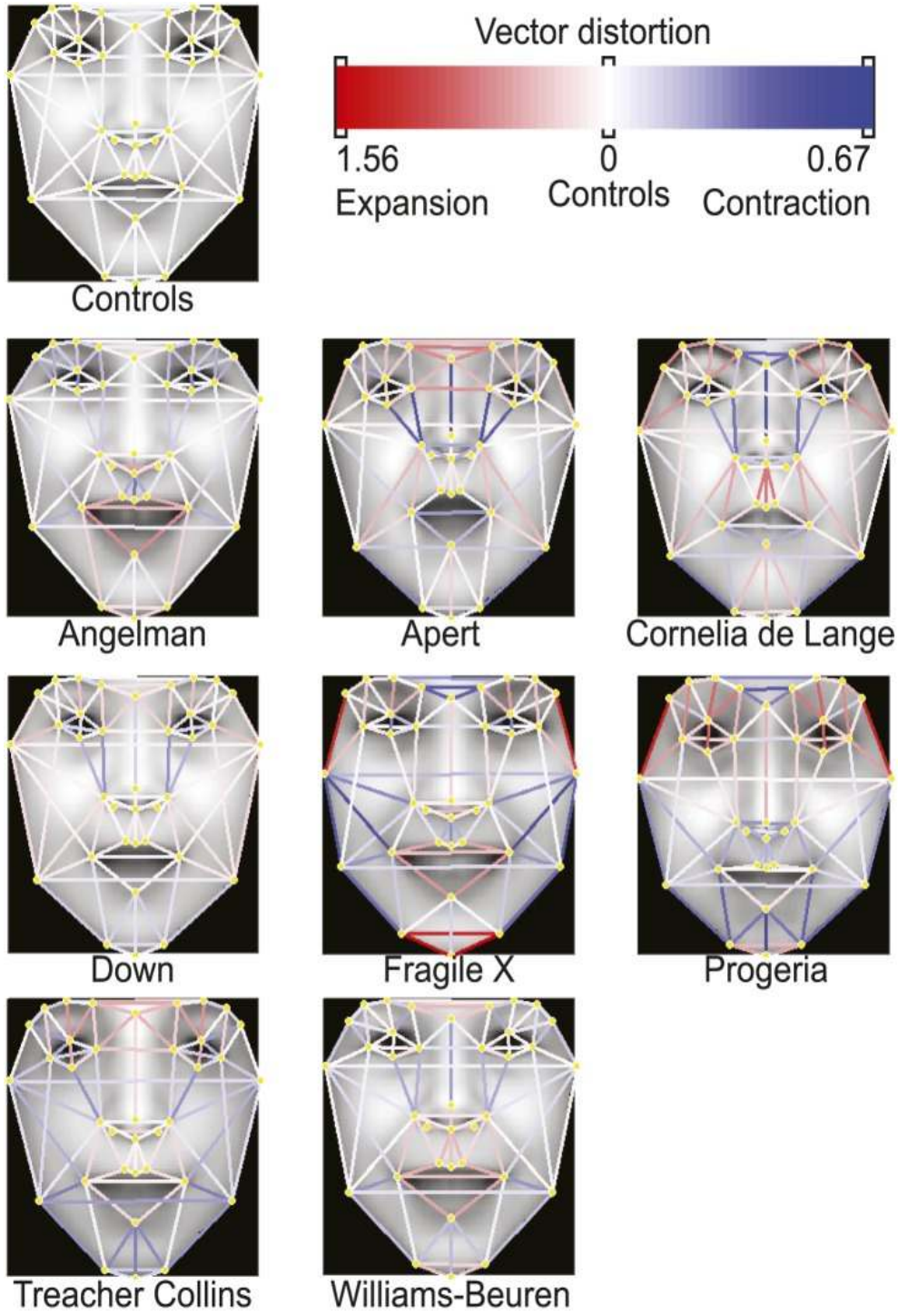
Facial *Gestalt* on photos – attempt at digitalization (eLife; 3: e02020)

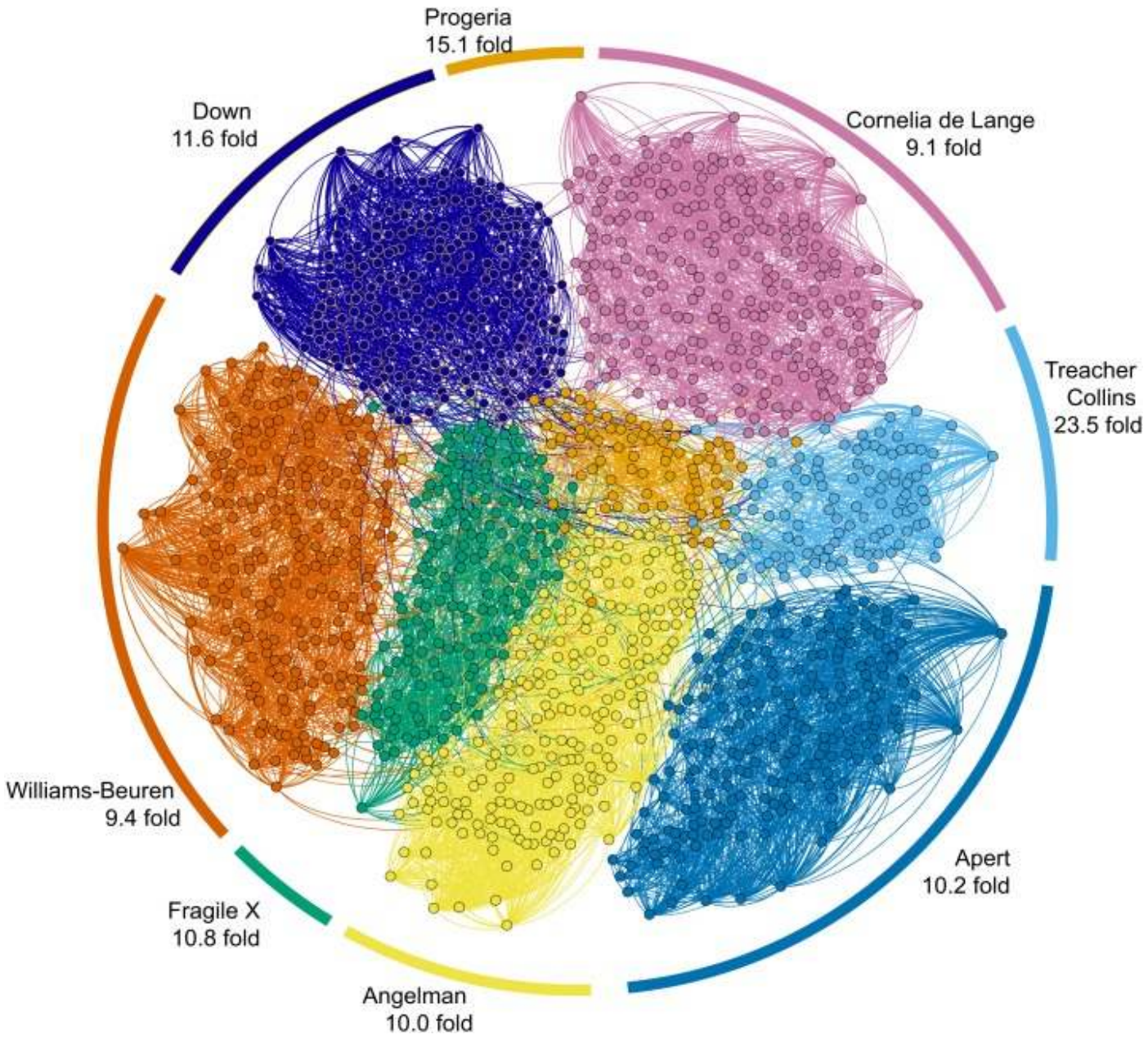
- Facial dysmorphism – 30-40% genetic syndromes
- Computer model matching *gestalt* with pictures of typical faces seen in 91 syndromes; 36 facial points (7 for mandible, 6 for oral region, 7 for nose, 8 for eyes, 8 for brows)
- Proteomic implications (networks of protein interactions)
- Other papers: mostly Hammond, Arch Dis Child 2007, AJHG 2005, Hum Mutat 2012


A
Computer vision algorithms
Photograph
Face detection
Feature point annotation
Appearance patch extraction
Shape feature vector
Appearance feature vector
Clinical Face Phenotype Space
Diagnosis hypotheses
Class priority
1
0.8
0.6
0.4
0.2
0
Syndrome A
Syndrome B
Syndrome C
Syndrome D

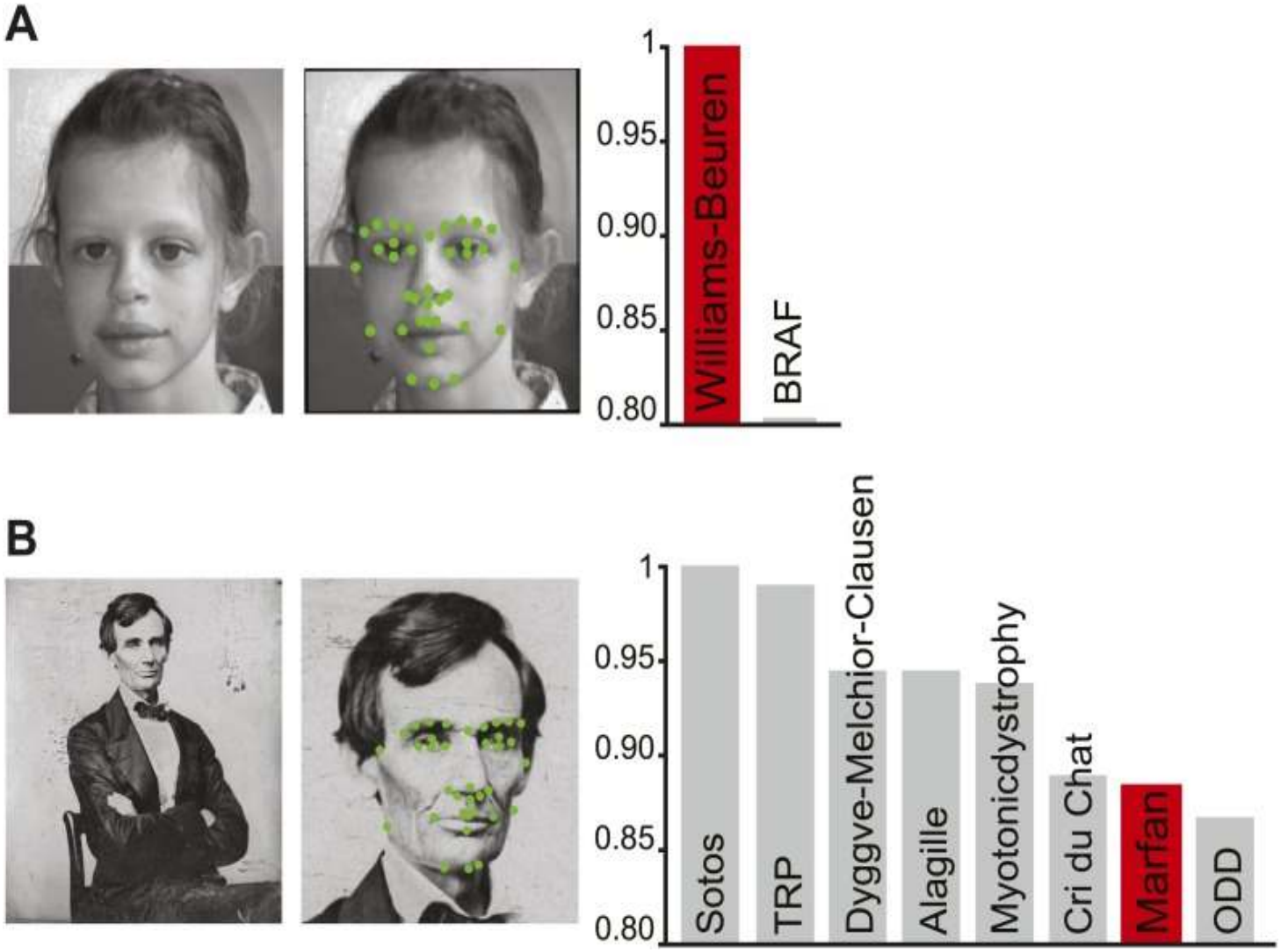

B
Syndrome
n =
Controls
1,518
Angelman
211
Apert
257
Cornelia de Lange
283
Down
209
Fragile X
185
Progeria
100
Treacher-Collins
118
Williams-Beuren
236

Facial *Gestalt* modelling (eLife; 3: e02020)

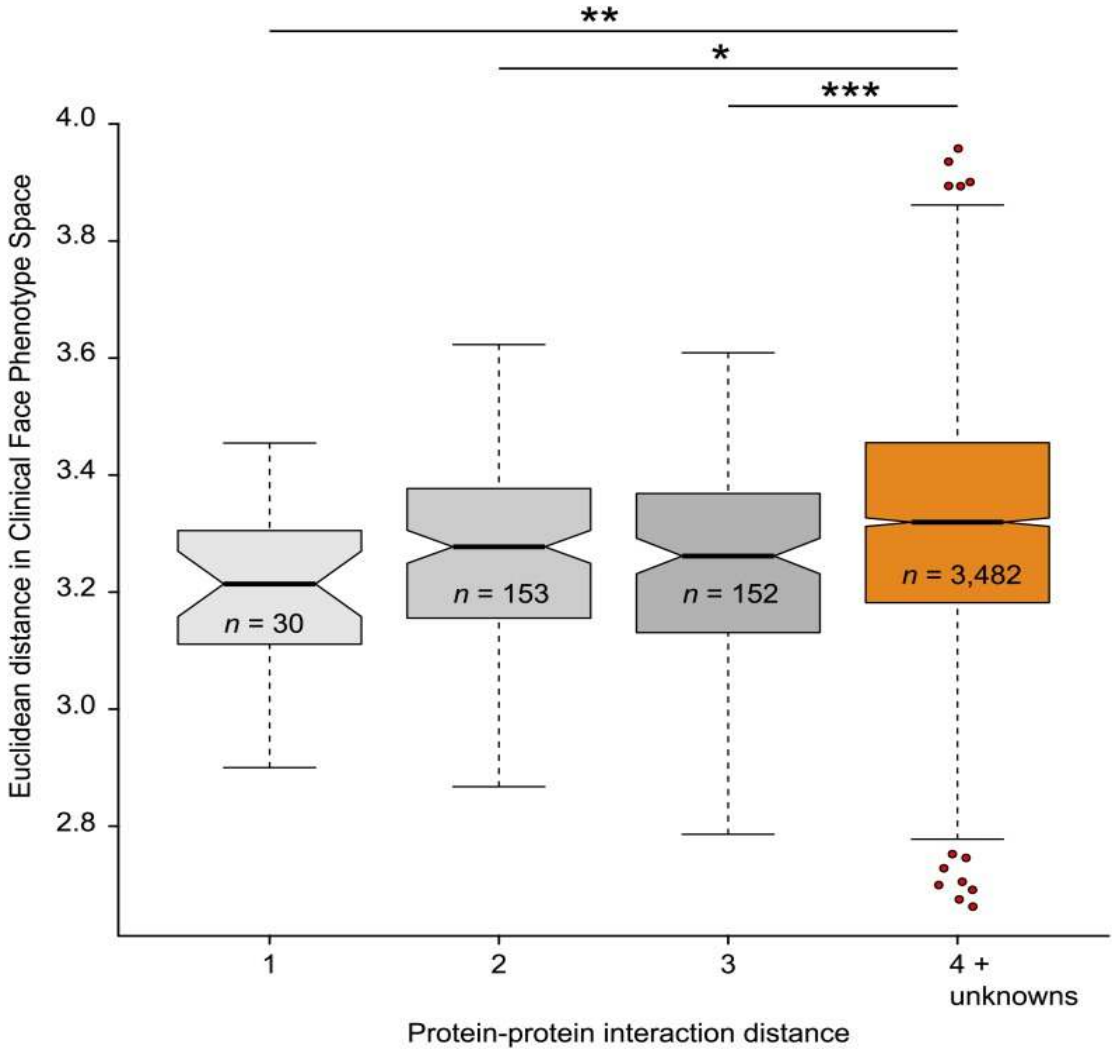


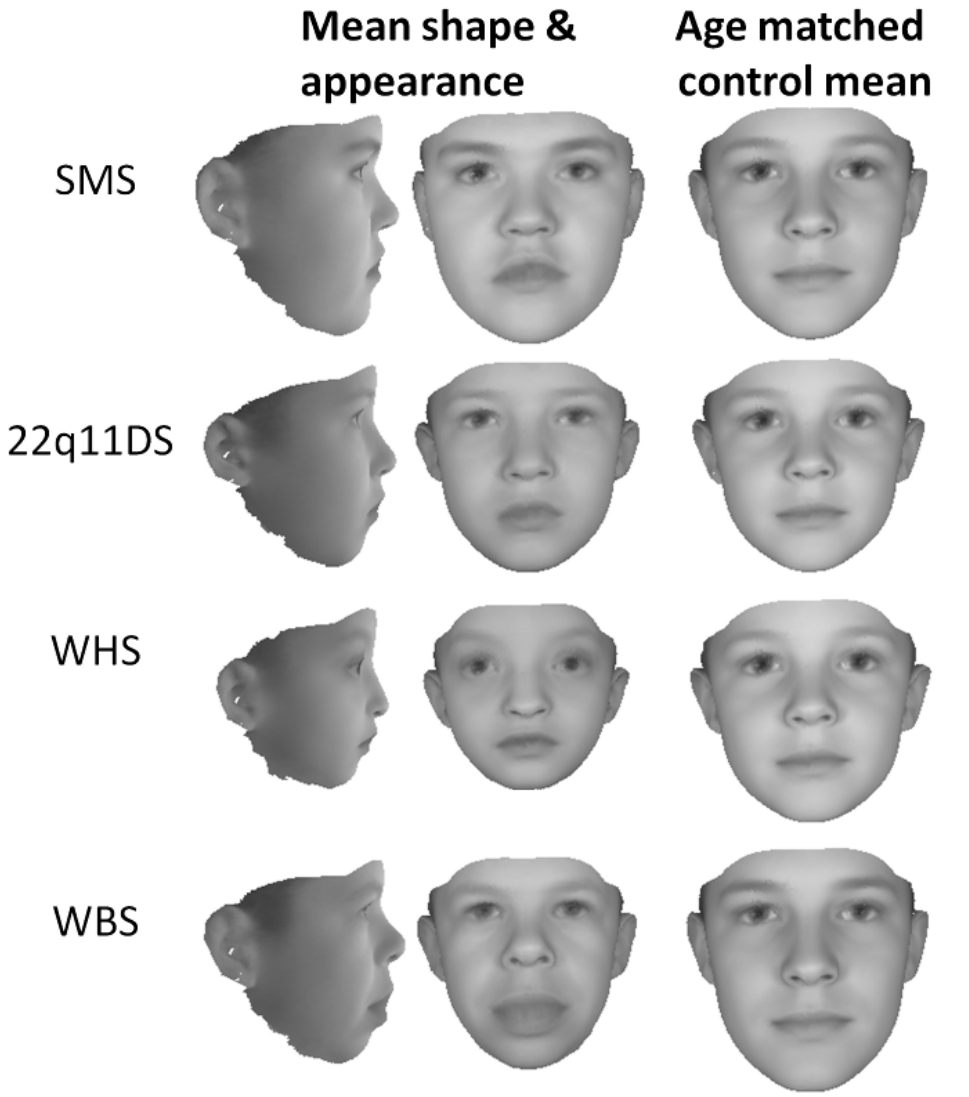

Progeria
15.1 fold
Down
11.6 fold
Cornelia de Lange
9.1 fold
Treacher
Collins
23.5 fold
Williams-Beuren
9.4 fold
Apert
10.2 fold
Fragile X
10.8 fold
Angelman
10.0 fold

Facial *Gestalt* (eLife; 3: e02020)

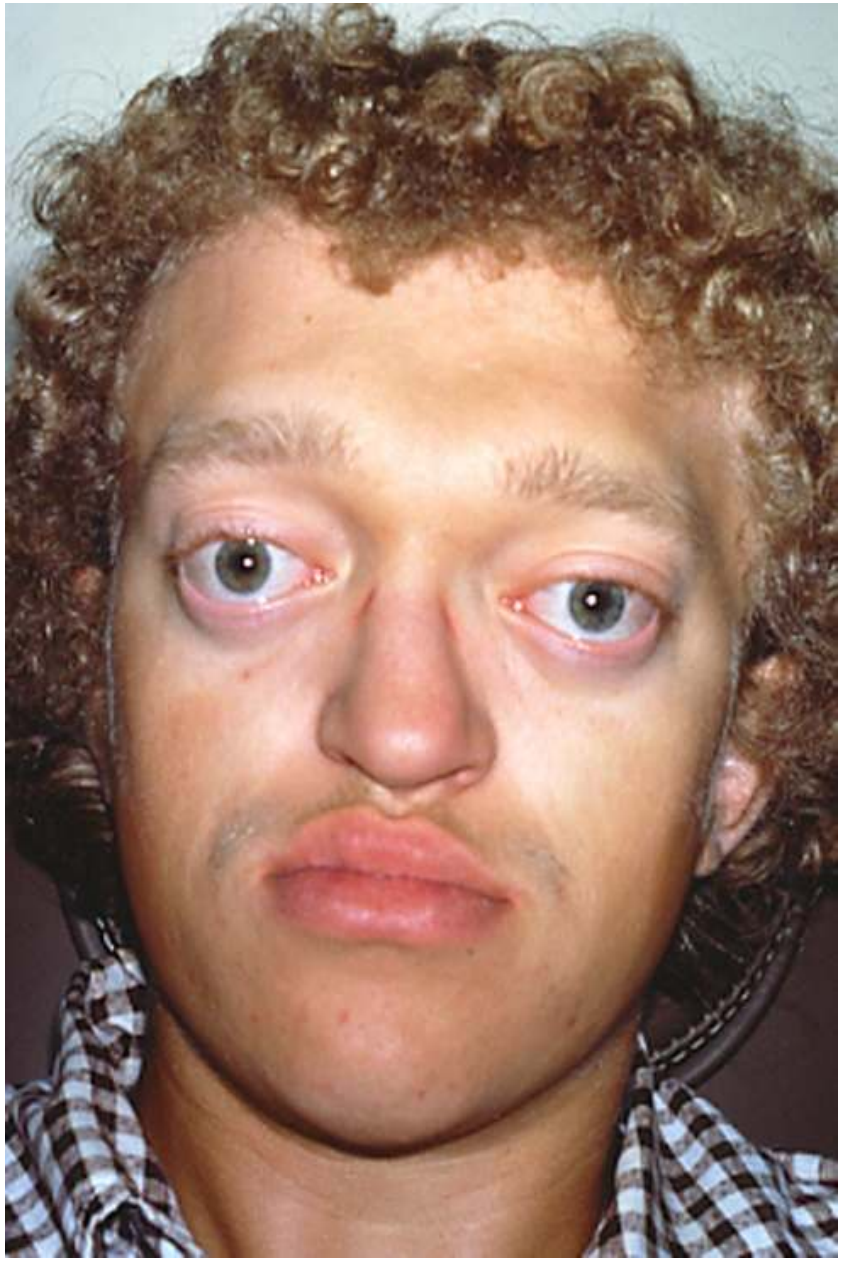


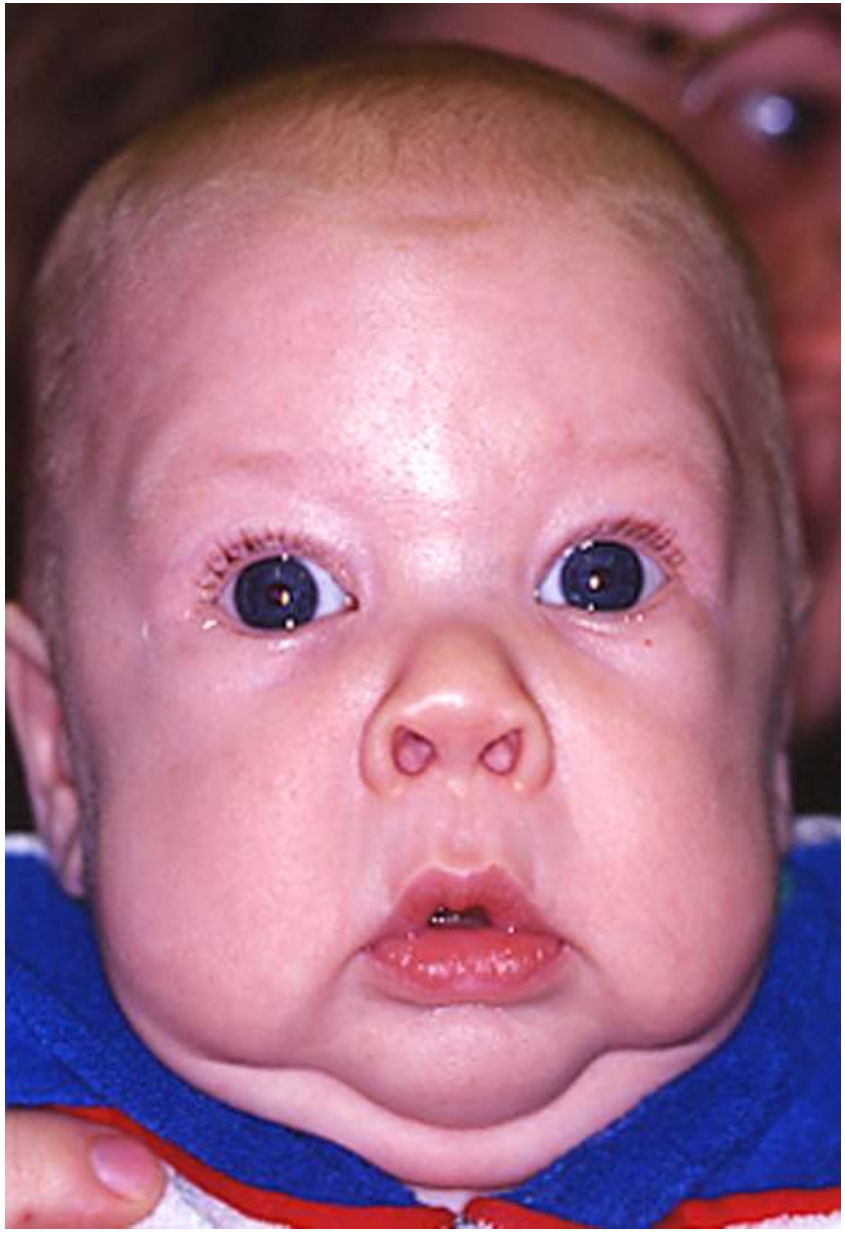
Facial *Gestalt* (eLife; 3: e02020)

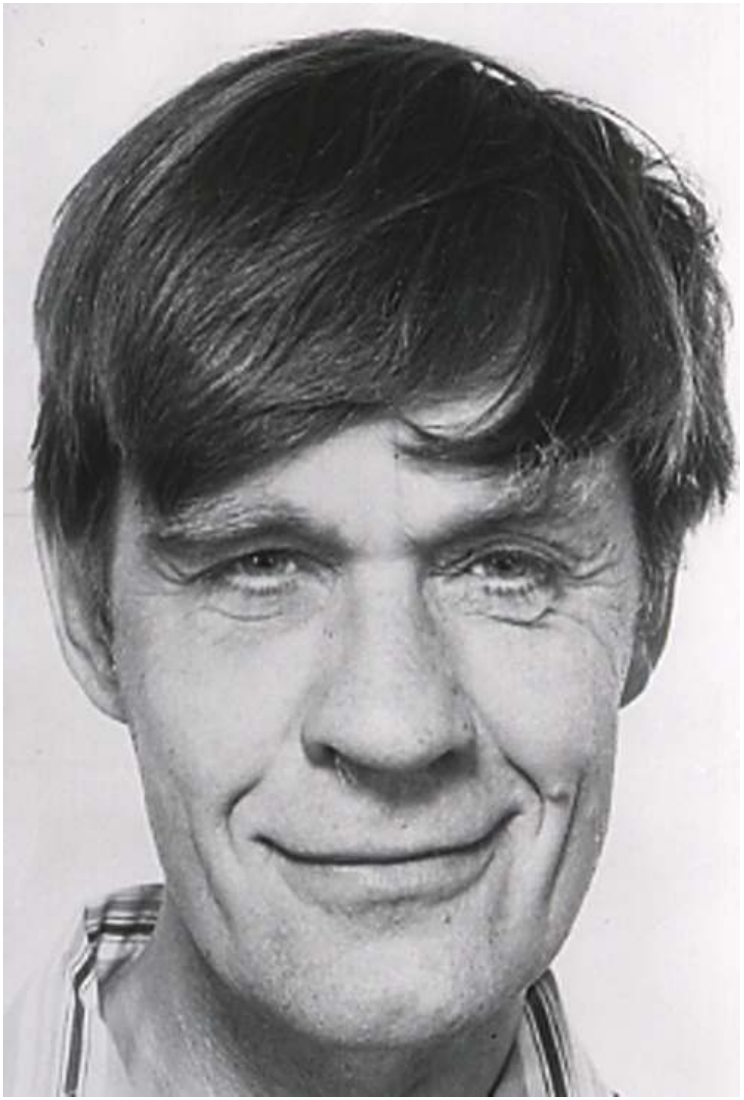


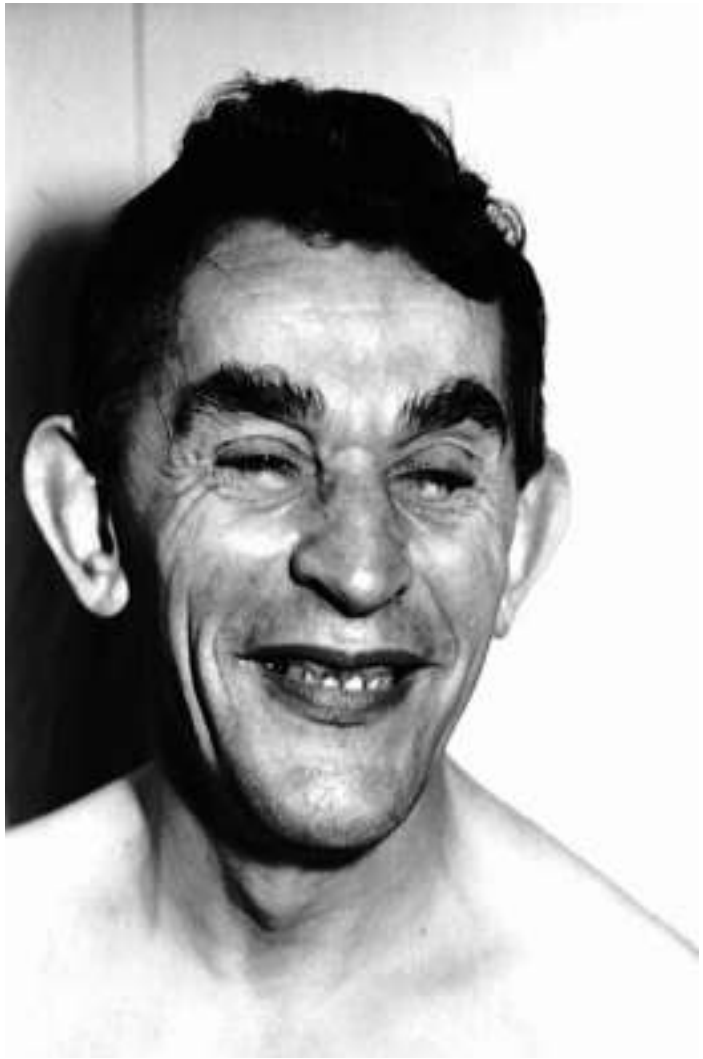


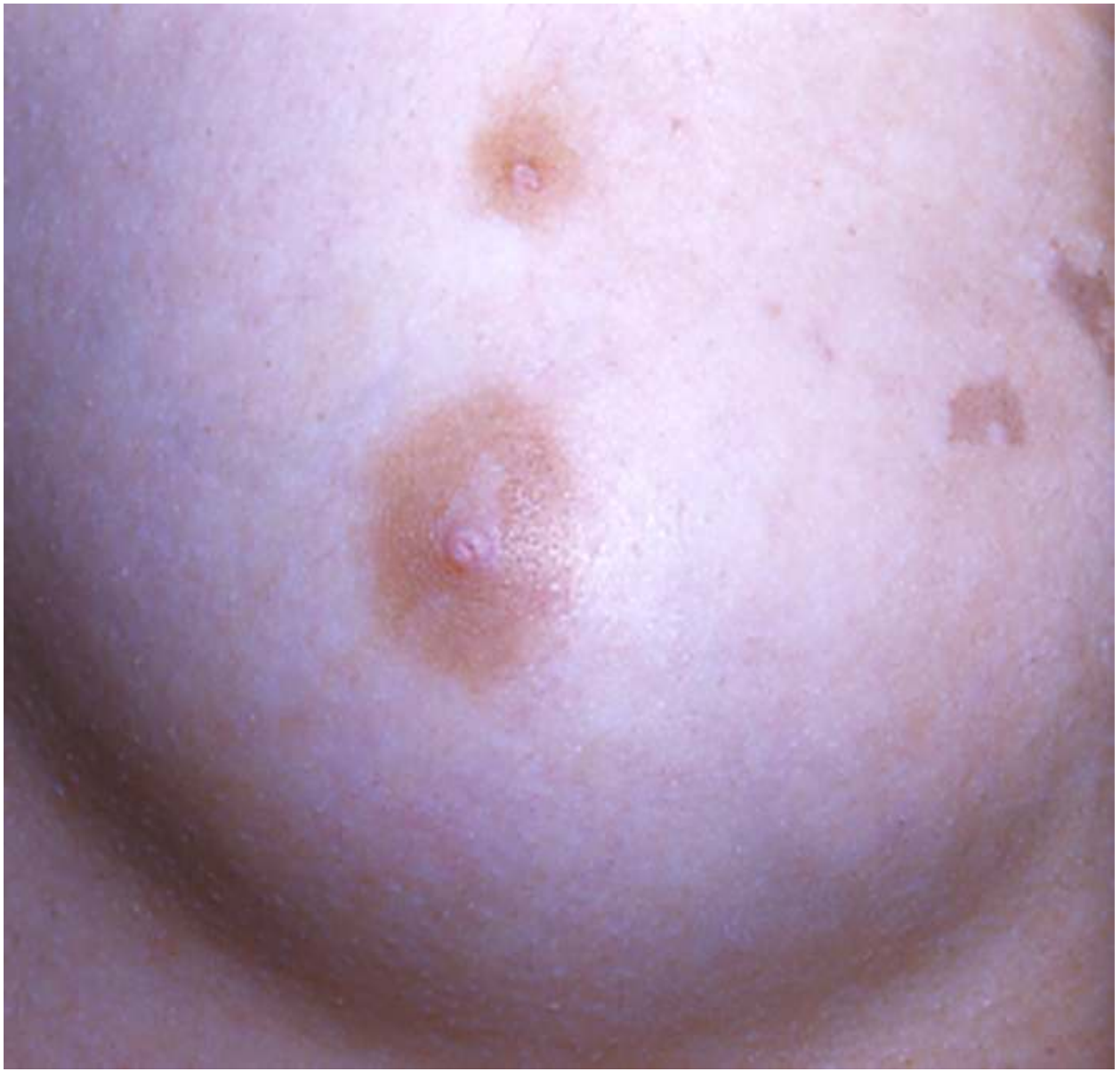
SMS = Smith-Magenis syndrome
22q11DS = 22q11 deletion syndrome
WHS = Wolf-Hirschhorn syndrome
WBS = Williams-Beuren syndrome

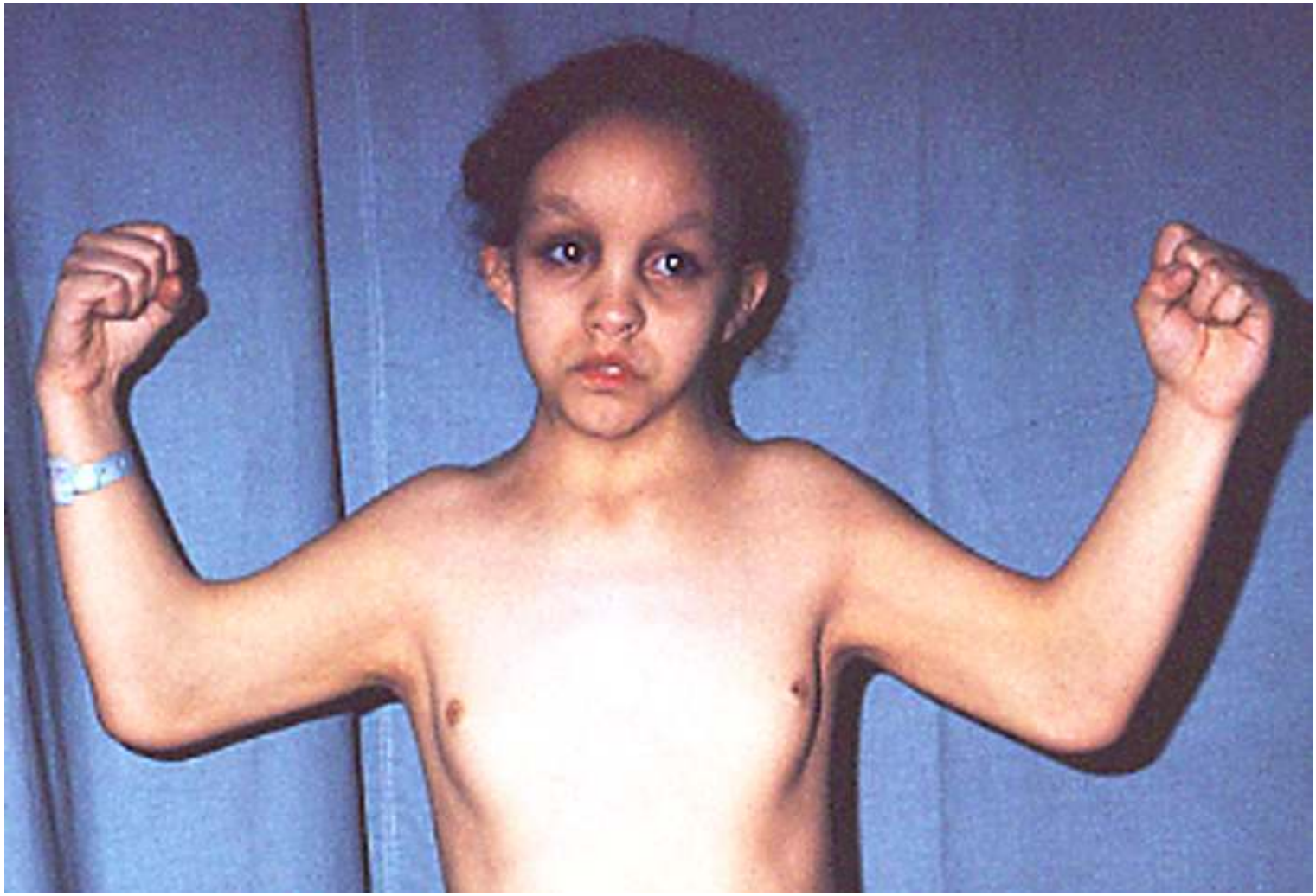


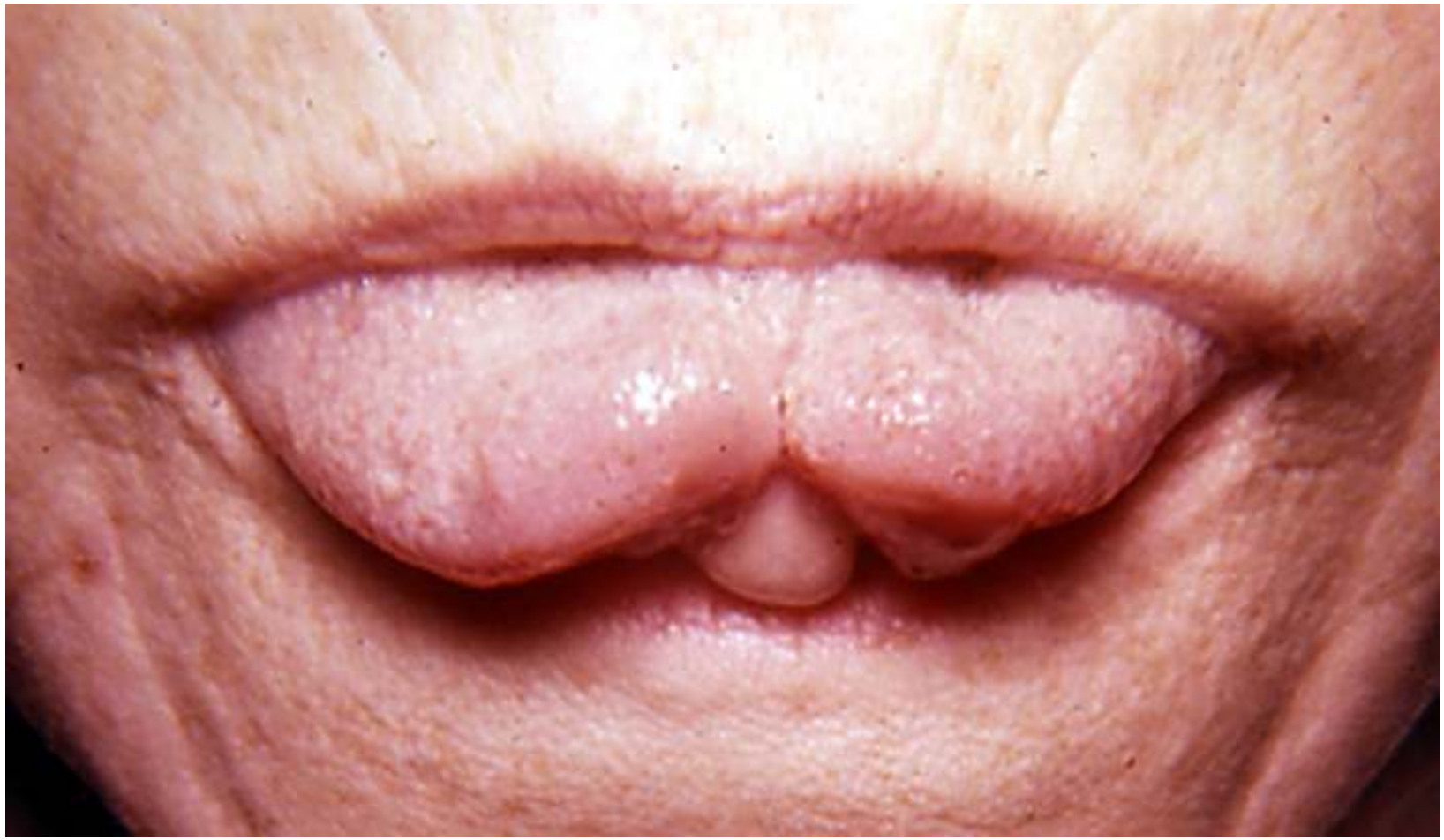


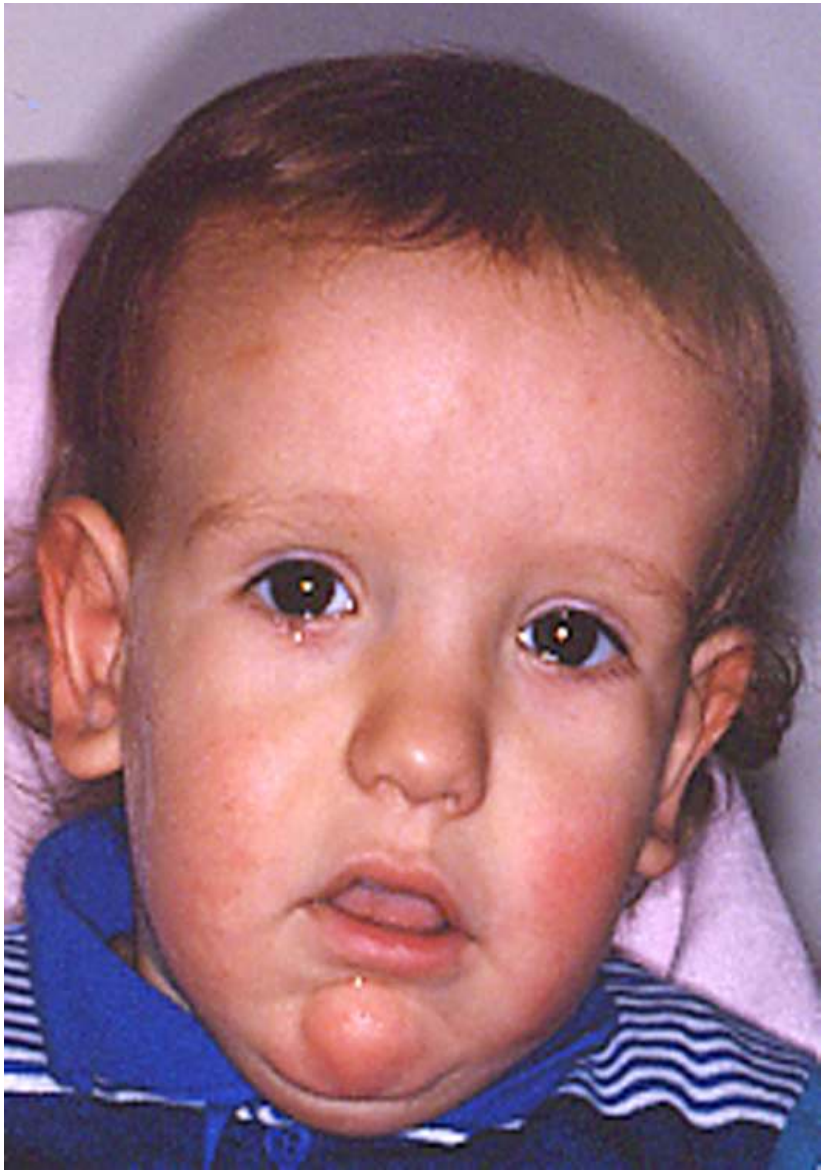


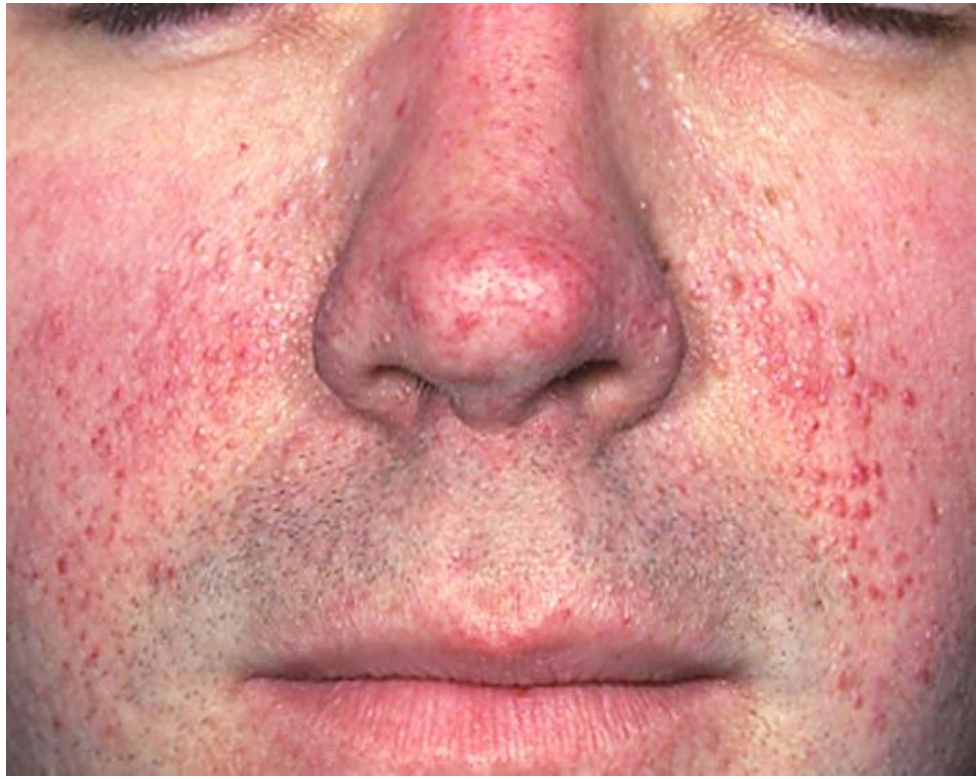


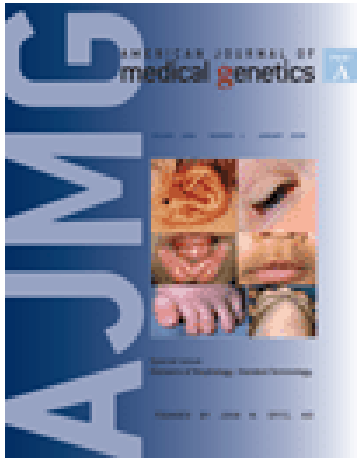












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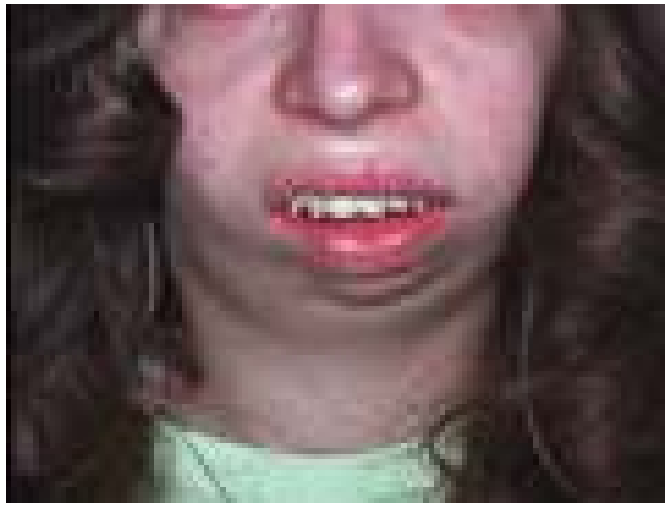
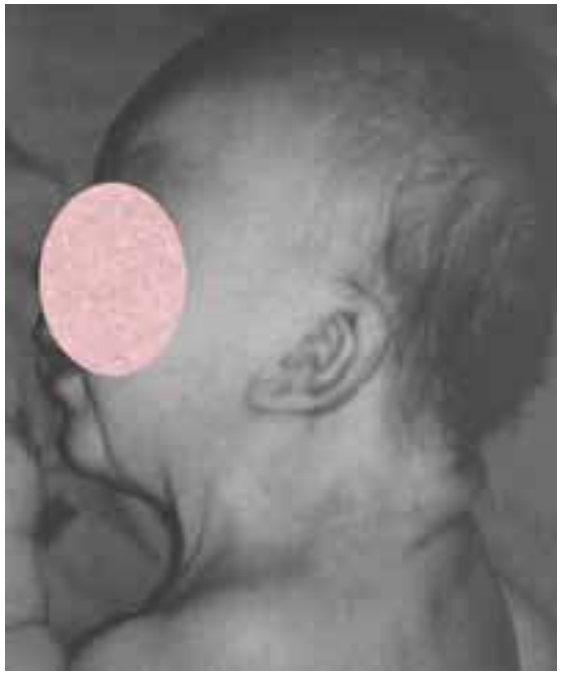


Micrognathia

Definition: Apparently reduced length and width of the mandible when viewed from the front but not from the side

Comments: This is a bundled term comprising shortening and narrowing of the mandible and chin. It is defined here as it is a term in common usage.

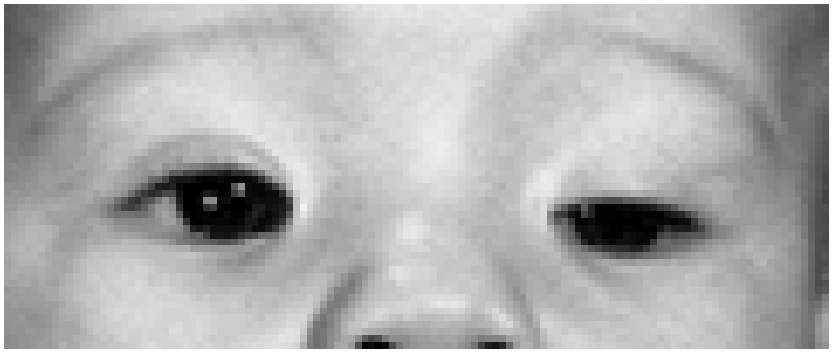
Synonyms: Micrognathism; Jaw, small



Definition: Excess skin around the neck, often lying in horizontal folds.

Comments: With age and increased vertical growth of the neck, excess nuchal skin may disappear and the neck may become broad or webbed. If the skin folds are vertical or paravertical, the term ***Neck webbing*** should be used.

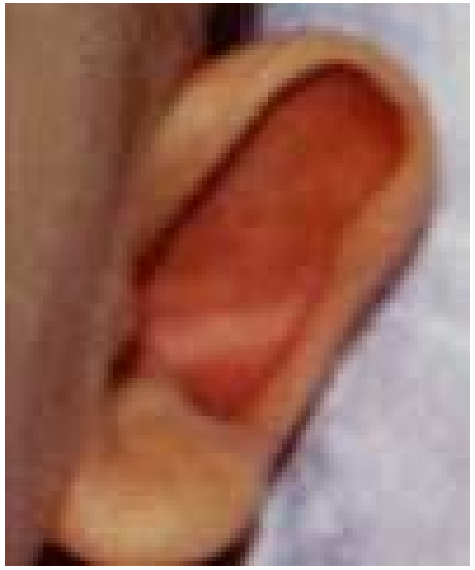
Redundant nuchal skin



Definition: A fixed reduction in the vertical distance between the upper and lower eyelids with short palpebral fissures.

Comments: This term is based on Saal et al. 1992. This is an acknowledged bundled term, though the separate coding of the components (palpebral fissure absence; presence of eyelashes) was deemed impractical. This is typically associated with a rudimentary or small globe. Frequently, a tuft of hair accompanies the aberrant skin

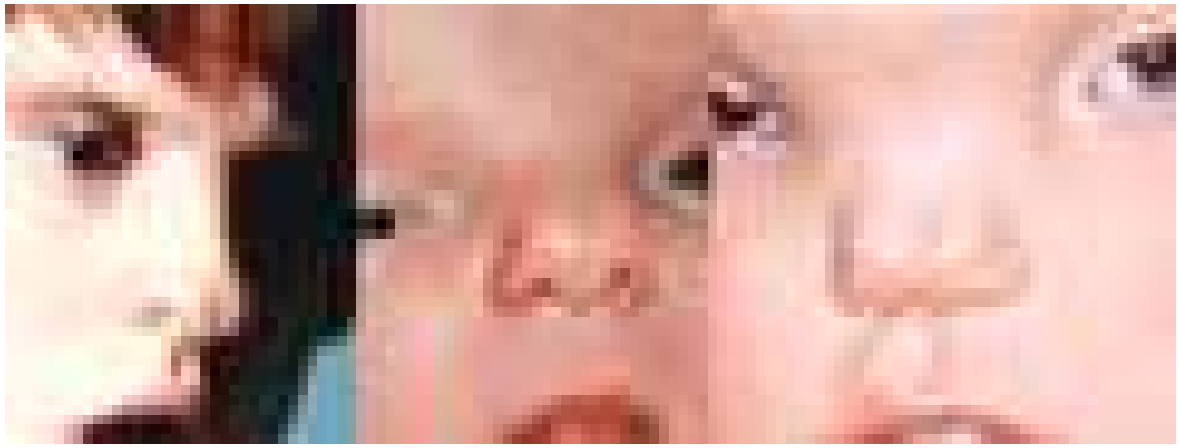
Blepharophimosis



Cupped ear

Definition: Laterally protruding ear that lacks antihelical folding (including absence of inferior and superior crura)

Definition: Visually assessable vertical indentation, cleft, or depression of the nasal tip

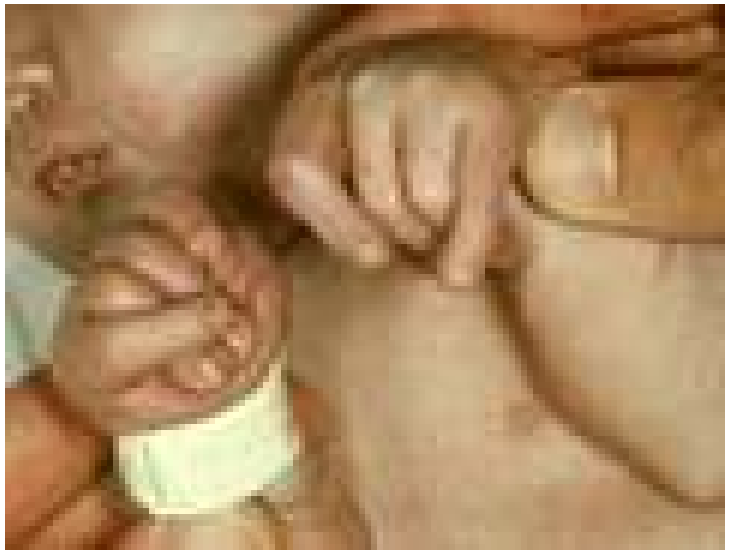


Bifid nasal tip

Short fingers

The middle finger is more than 2 SD below the mean for newborns 27–41 weeks EGA or below the 3rd centile for children from birth to 16 years of age AND the five digits retain their normal length proportions relative to each (i.e., it is not the case that the middle finger is the only shortened digit)

This is an acknowledged bundled term as the definition in most anthropometric sources assumes that the other fingers are all as relatively short as is the middle finger. As the determination of the proportionality of the other four digits is clearly subjective, the term must be regarded as subjective.



Clenched hand

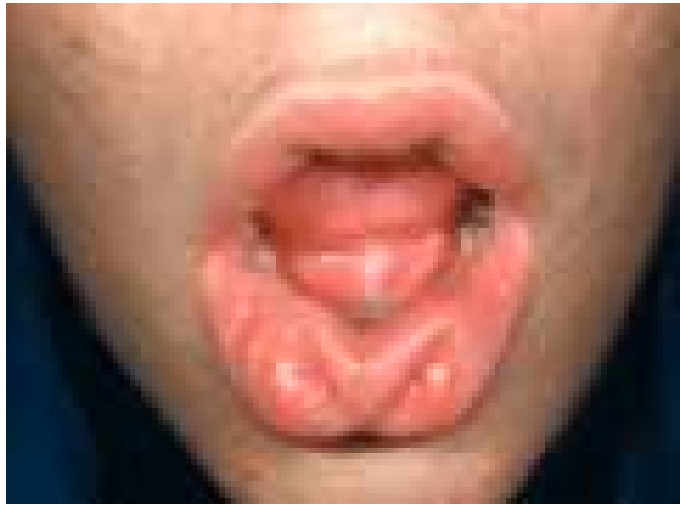
Definition: All digits held completely flexed at the metacarpophalangeal and interphalangeal joints

Comment: Is distinguished from ***Camptodactyly,*** as that term may describe fewer than five digits of a eudactylous hand and does not involve the MCPJ. The digits may overlap when they lie flexed in the palm. It is not necessary to specify the overlapping fingers finding separately.

Synophrys

Meeting of the medial eyebrows in the midline.

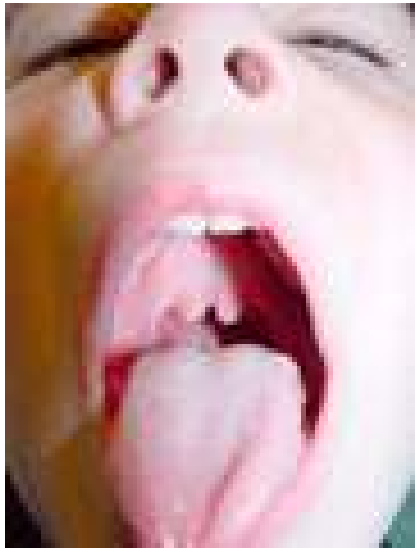
Cosmetic hair removal or shaving may obscure this feature. It is controversial whether the medial eyebrows must meet in the midline to warrant this descriptor, as opposed to eyebrows that extend markedly toward the midline but do not meet.



Depression located on the vermilion of the lower lip, usually paramedian

A lip pit may be connected by a fistula to mucous minor salivary glands in the lower lip. In addition, a lip pit may on occasion be seen with a surrounding tissue elevation (mound). Pits located at the labial commissure (cheilion) are distinct from lip pits

Lip pit



Soft palatal defect with intact overlying mucosa comprising two of the following three findings: (1) notching of the posterior border of the hard palate, (2) bifid uvula, or (3) muscular diastasis leading to a midline translucent zone or furrow in the soft palate

The notch of the posterior hard palate can sometimes be palpated. Submucous cleft palate is a bundled term but because of its common usage is included here.

Submucous Cleft Palate