Sistema Socio Sanitario

Regione Lombardia

Fondazione IRCCS Policlinico San Matteo

ATS Pavia

GRAND ROUNDS CLINICI DEL MERCOLEDÌ

con il Policlinico San Matteo

Aula Magna "C. Golgi" & WEBINAR

08/11/2023

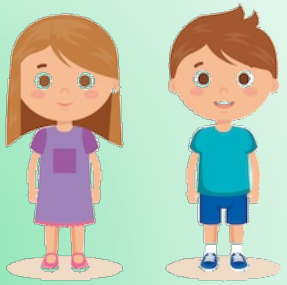
Fabio Sirchia

CASO CLINICO - Diagnosi di una "apparente" micrognazia isolata familiare, dal prenatale al post-natale

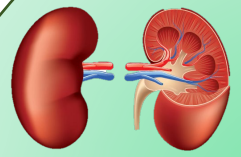
S.S.D. Genetica Medica
Dipartimento Servizi Diagnostici e per Immagini

- 1600 consulenze / anno
  - 90% ambulatoriali
  - 10% pazienti ricoverati

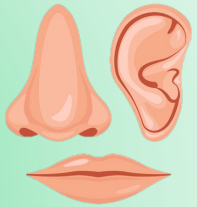
Dipartimento Donna e Materno Infantile



Cardiologia

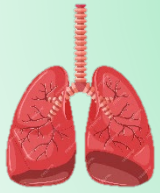


Nefrologia

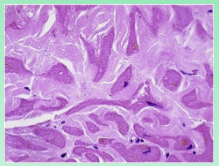


Otorinolaringoiatria

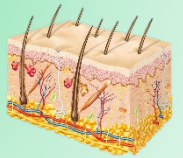
Genetica dell'adulto



Pneumologia



Centro Amiloidosi



Dermatologia

GRAND ROUNDS CLINICI DEL MERCOLEDÌ

Nel 50% delle visite viene richiesto <u>almeno</u> un test genetico

Laboratorio di Biochimica, Biotecnologie e Diagnostica Avanzata

- Sequenziamento geni amiloidosi

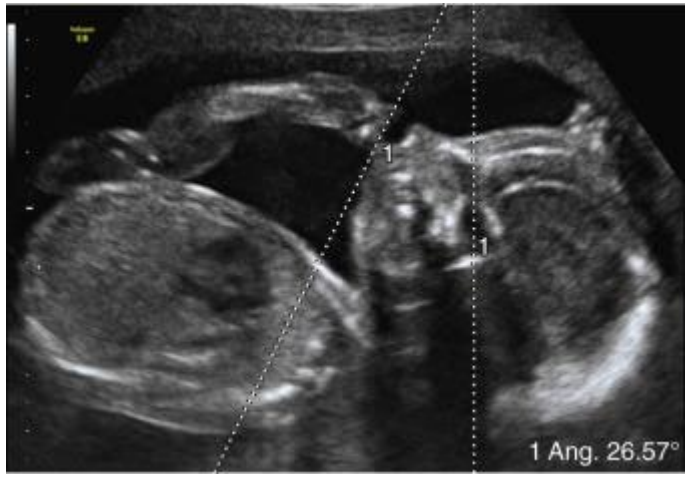
Laboratorio Genetica - Trapiantologia e Malattie Cardiovascolari

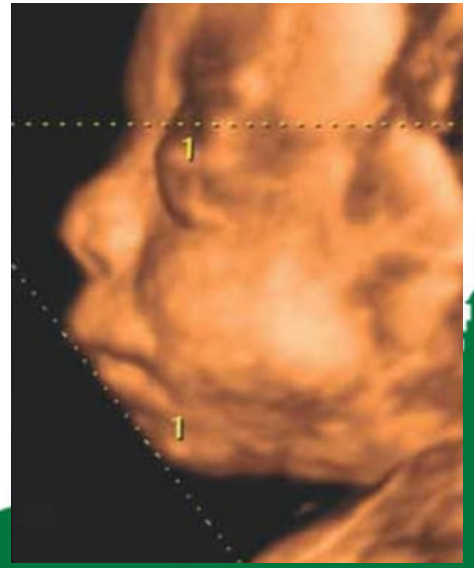
- Analisi fibrosi cistica
- Pannello NGS
  - collagenopatie
  - geni oncologici

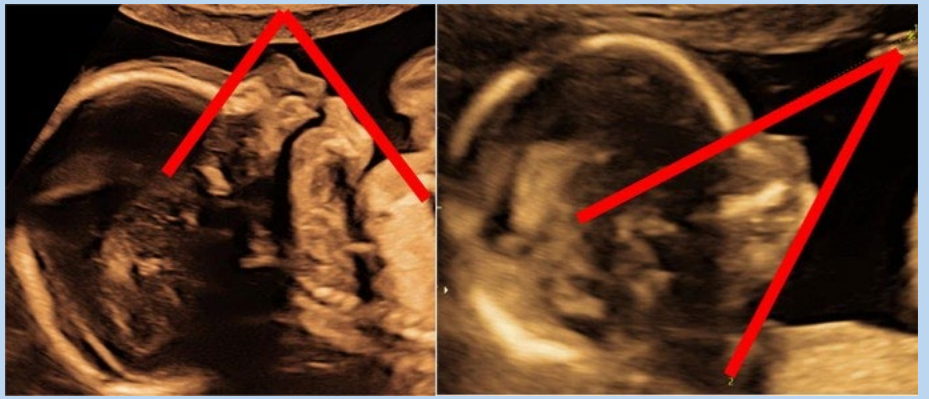
Laboratorio di Citogenetica e Genetica Molecolare IRCCS Mondino

- Cariotipo
- FISH
- Array CGH / SNP array
- Espansioni di triplette (X- fragile, M. di Huntington, SCA)
- Test di Metilazione
- **Analisi dell'Esoma (WES)**

Clinical Case





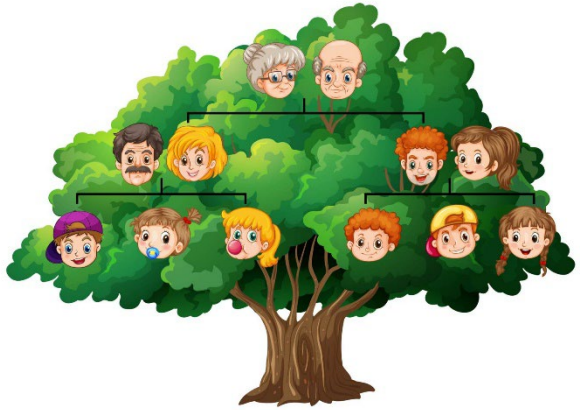


Inferior facial angle. This angle is formed by the crossing of a line orthogonal to the vertical part of the forehead drawn at the level of synostosis of nasal bones and a line through the tip of the mentum and the more protrusive lip. Normal mean value is 65 ± 16. Thus, an angle less than 49 gives the diagnosis of retrognathia.

At 20° week of gestation:
Fetal microretrognathia

«Should I be worried?»

Familial anamnesis

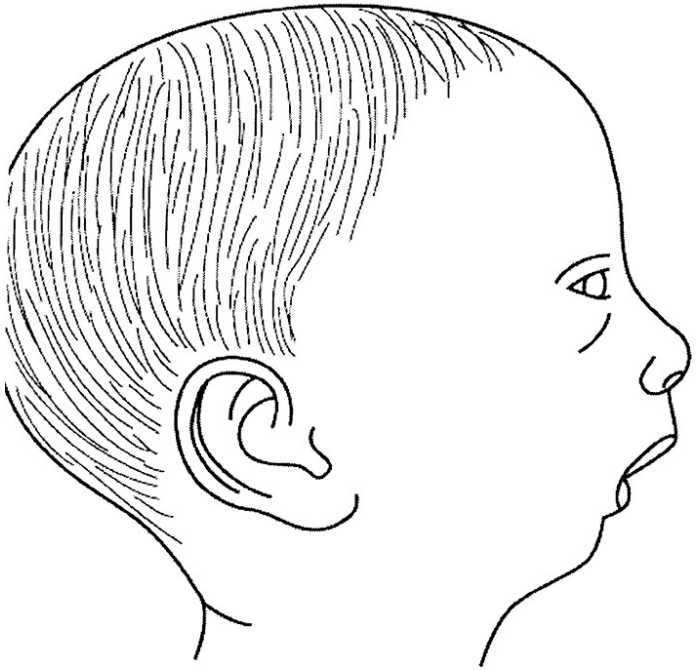


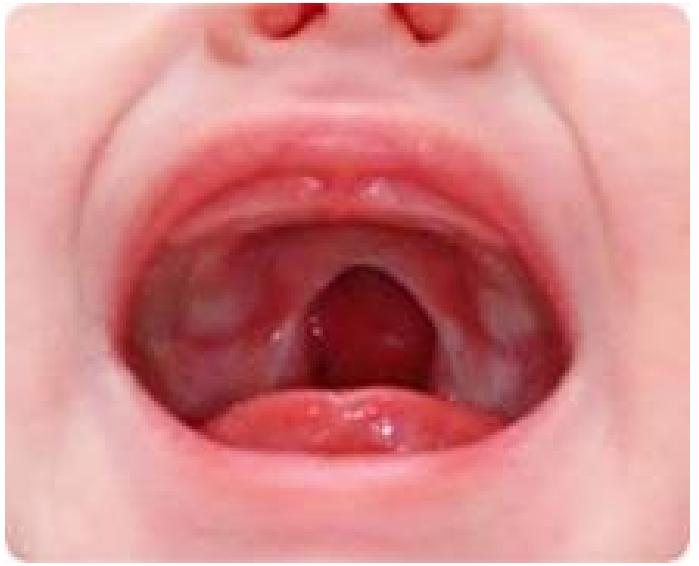
- Mother: good health, micro-retrognathia, multiple intervention for crowded teeth;
- Father: referred good health;
- No consanguinity, negative family history;

Amniocentesis

- Karyotype: 46,XY
- Array-CGH: normal

At birth…

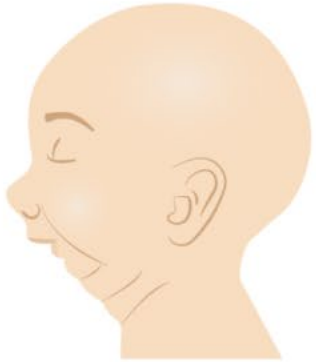




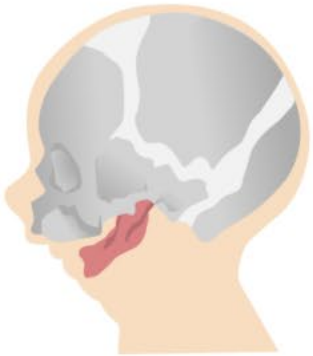
- Micro-retrognathia;
- Cleft palate

Pierre Robin sequence?

Pierre Robin sequence?

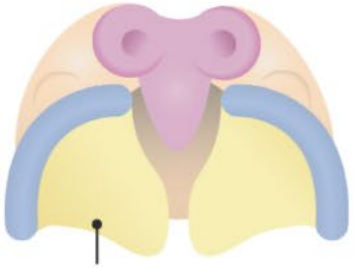


Typical Robin facies with micrognathia

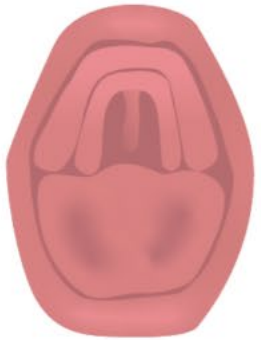


Hypoplastic mandible (primary anomaly)

Glossoptosis (secondary anomaly)



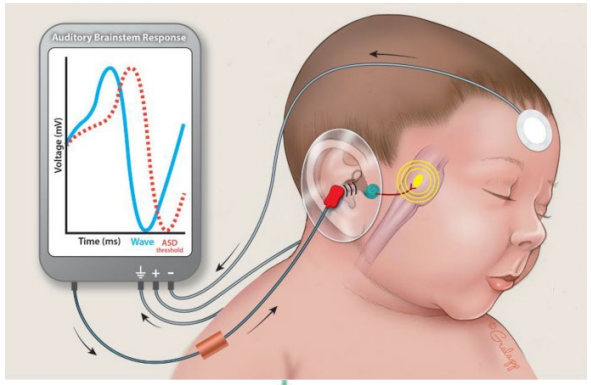
Tongue obstructs palatal fusion (secondary anomaly)

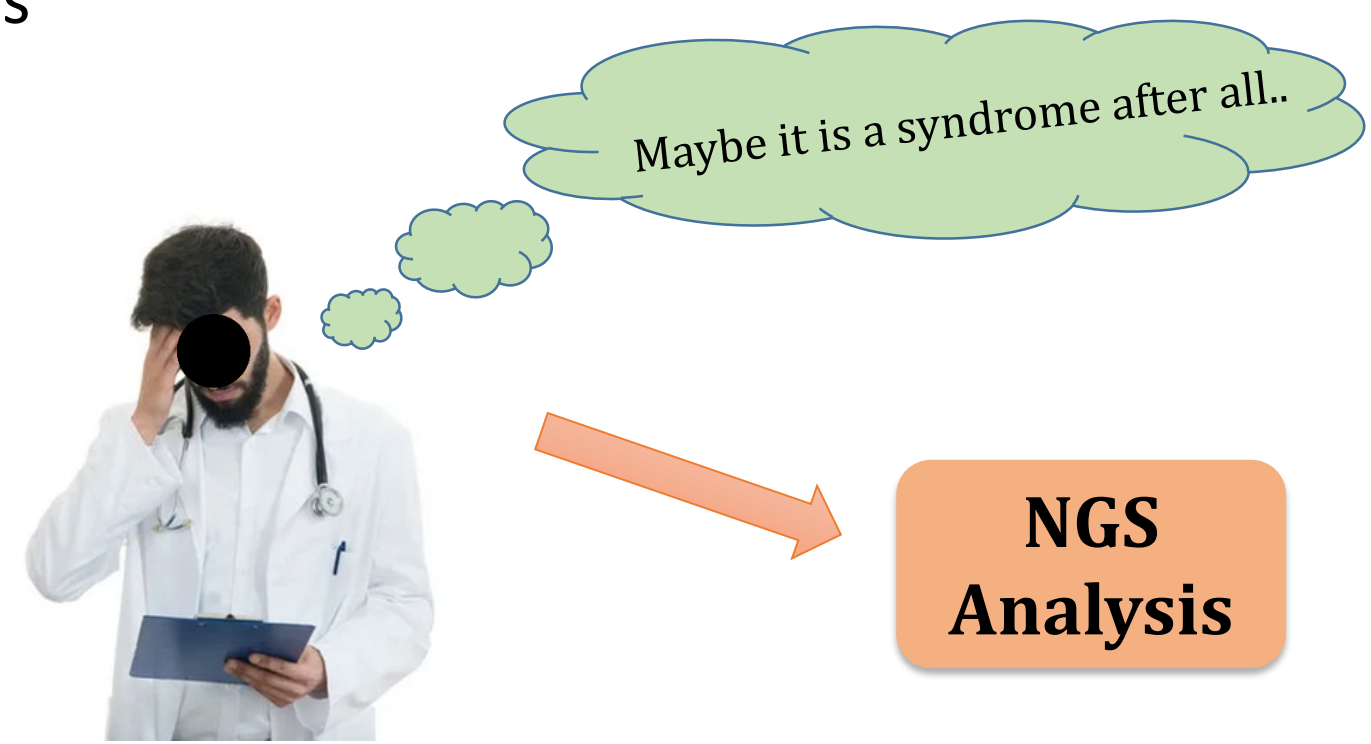


U-shaped palate (secondary anomaly)

Rigth after birth…

- Neonatal otoacustic emission: refer (bilateral)
- Brainstem Auditory Evoked Potentials (BAEP): moderate-severe right deafnees, moderate left deafness





NGS Result

Gene	*Trascritto*	*OMIM*	*Ered*	*Variante/i*	*Genot*	*GnomAD (%)*	*Class*
COL2A1	*NM_001844.5*	120140	AD	c.871-3_878del	Eter	-	LP

Likely pathogenic

OMIM

STICKLER SYNDROME, TYPE I; STL1

Alternative titles; symbols

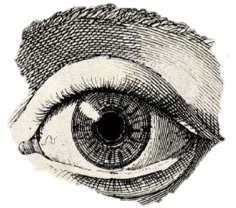
STICKLER SYNDROME, VITREOUS TYPE 1
STICKLER SYNDROME, MEMBRANOUS VITREOUS TYPE
ARTHROOPHTHALMOPATHY, HEREDITARY PROGRESSIVE; AOM

Phenotype-Gene Relationships

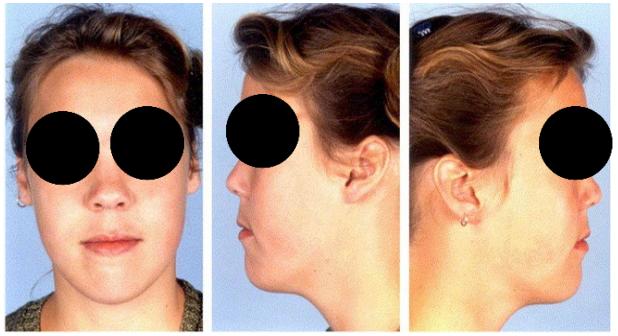
Location	Phenotype	Phenotype MIM number	Inheritance	Phenotype mapping key	Gene/Locus	Gene/Locus MIM number
12q13.11	Stickler syndrome, type I	108300	AD	3	COL2A1	120140

STICKLER SYNDROME

prevalence: 1/7500



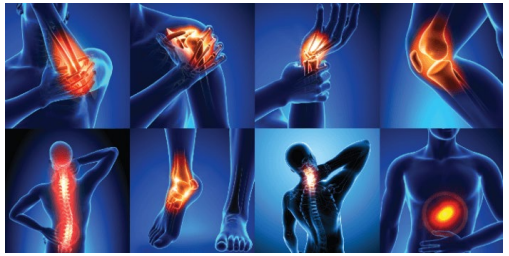
- **OCULAR SIGNS** (Vitreo-retinopathy): juvenile cataract, myopia, strabismus, vitreoretinal or chorio-retinal degeneration, retinal detachment and chronic uveitis



https://doi.org/10.1016/j.ijporl.2004.07.015

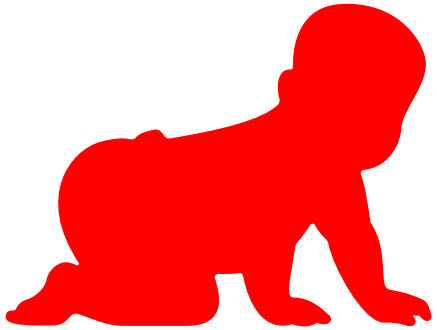
- **FACIAL DYSMORPHISM**: Pierre Robin sequence, Midline clefts in ¼ of patients; ogival palate, midface hypoplasia with flattened profile, depressed nasal root, antiverse nostrils and micrognathia

- **SKELETAL ALTERATIONS**: Juvenile joint laxity is followed by early signs of osteoarthritis. Fingers elongated and thin. Scoliosis



- **NEUROSENSORY DEAFNESS** (50% of cases), there is also a transmissive component

STICKLER SYNDROME (OMIM phenotype)



INHERITANCE
- Autosomal dominant

GROWTH

Height
- Normal height

Other
- Marfanoid habitus

HEAD & NECK

Face
- Flat midface

Ears
- Sensorineural hearing loss
- Occasional conductive hearing loss

Eyes
- Myopia
- Retinal detachment
- Blindness
- Occasional cataracts
- Glaucoma
- Membranous (type I) vitreous phenotype

Nose
- Anteverted nares
- Depressed nasal bridge

Mouth
- Cleft palate
- Pierre-Robin sequence

CARDIOVASCULAR

Heart
- Mitral valve prolapse

CHEST

Ribs Sternum Clavicles & Scapulae
- Pectus excavatum

SKELETAL
- Mild spondyloepiphyseal dysplasia

Spine
- Platyspondyly with anterior wedging
- Scoliosis
- Kyphosis

Limbs
- Flat, irregular femoral epiphyses
- Arachnodactyly
- Arthropathy

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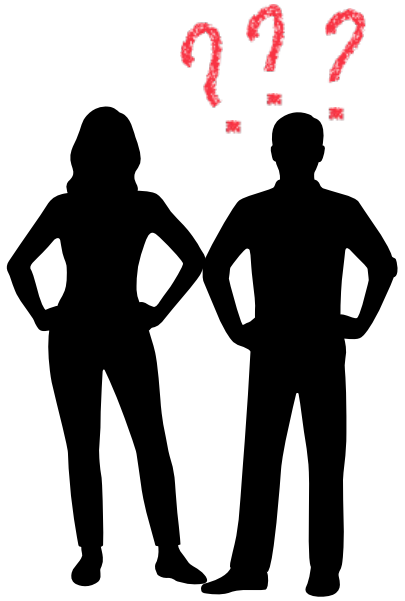
Gene	*Trascritto*	*OMIM*	*Ered*	*Variante/i*	*Genot*	*GnomAD (%)*	*Class*	*Segr*
COL2A1	*NM_001844.5*	120140	AD	c.871-3_878del	Eter	-	LP	pat



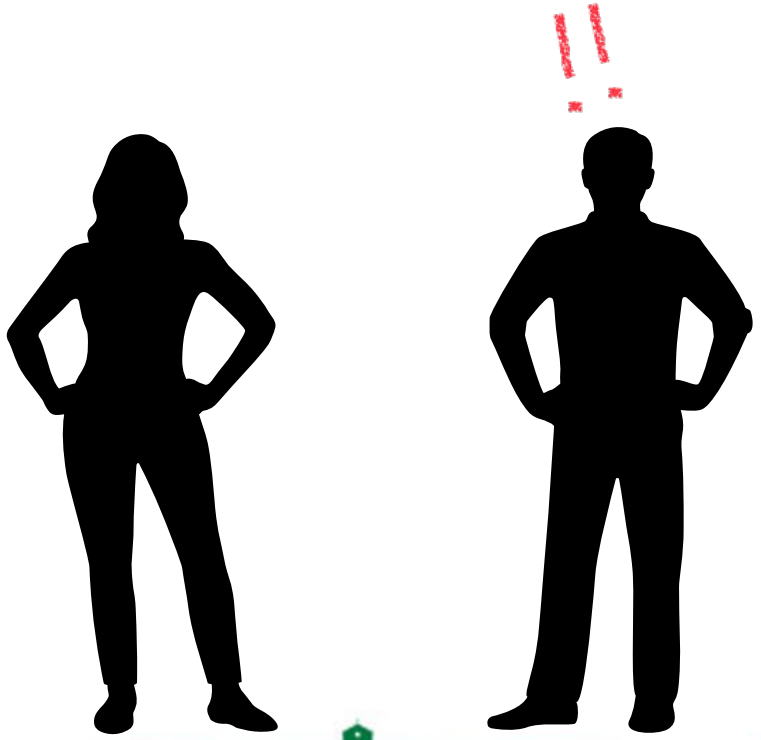
Inherited from the father

The «healthy» father

I see you wear glasses.. Any ocular sign?

"Well.. Now that you mention it…"

- Severe myopia from early childhood;
- Bilateral retinal detachment between 11 and 13 years;
- Left cataract already operated, mild cataract on the right;

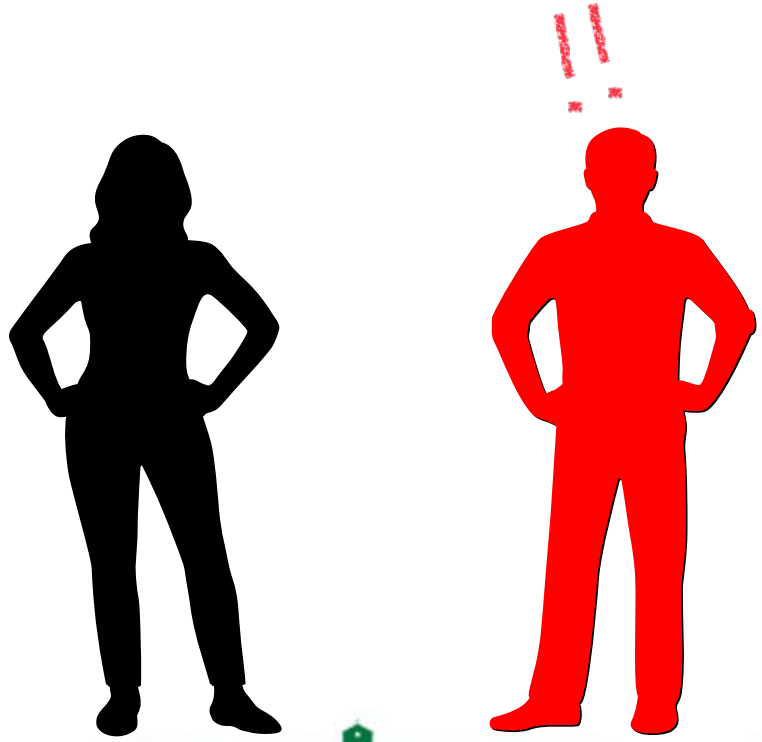


The «healthy» father

Any joint pain or skeletal sign?

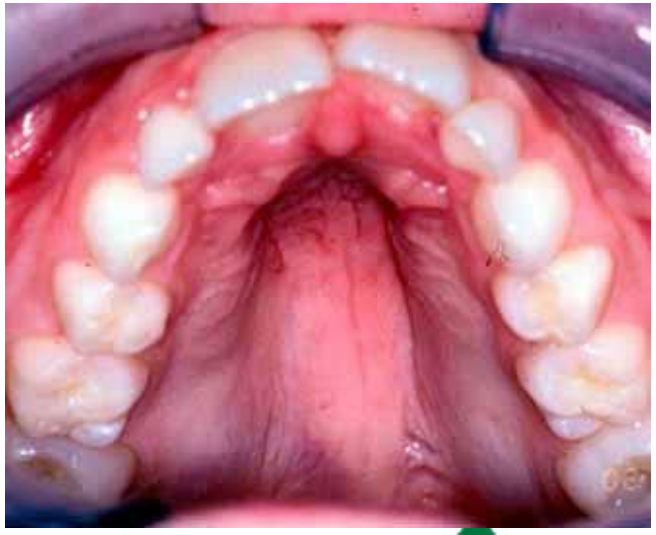
"Well.. Now that you mention it…"

- Osteoarthritis of the hips and mild scoliosis;

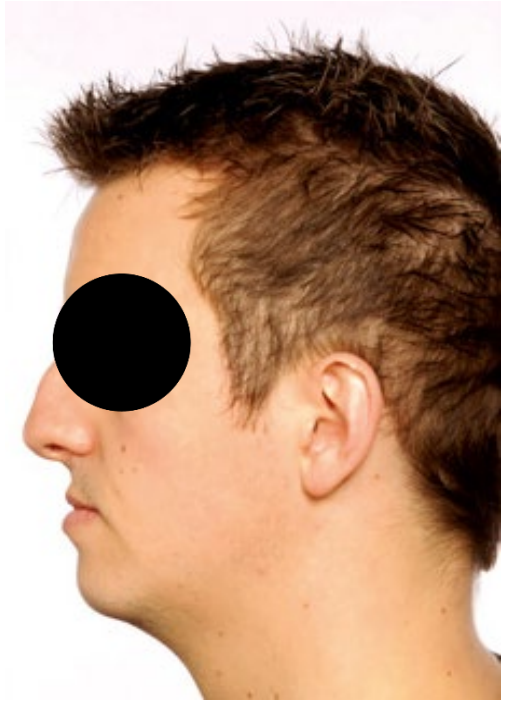


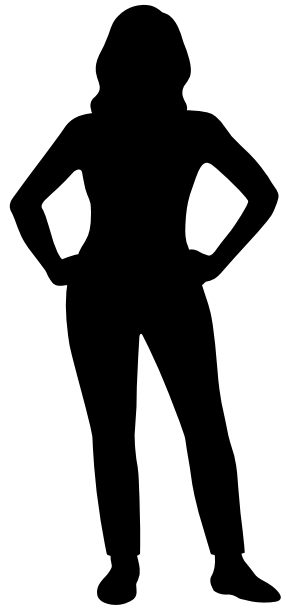
Could you please take off your mask?

- High arched palate



- Flat midface





Mid-facial augmentation with malar implants | The PMFA Journal

https://www.thepmfajournal.com/features/features/post/mid-facial-augmentation-with-malar-implants

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SKELETAL
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- Arachnodactyly
- Arthropathy

Variable expressivity

Take home messages

- Always lower the mask of both parents in case of fetal dysmorphisms
- Vision and hearing problems are often not considered as 'illnesses'.
- In case of micrognathia or Pierre-Robin sequence, always consider Stickler syndrome.
- Stickler syndrome is underdiagnosed

3 more diagnosis
From 2020 to date

«Incidental»
Diagnosis in relatives

Grazie per l'attenzione!