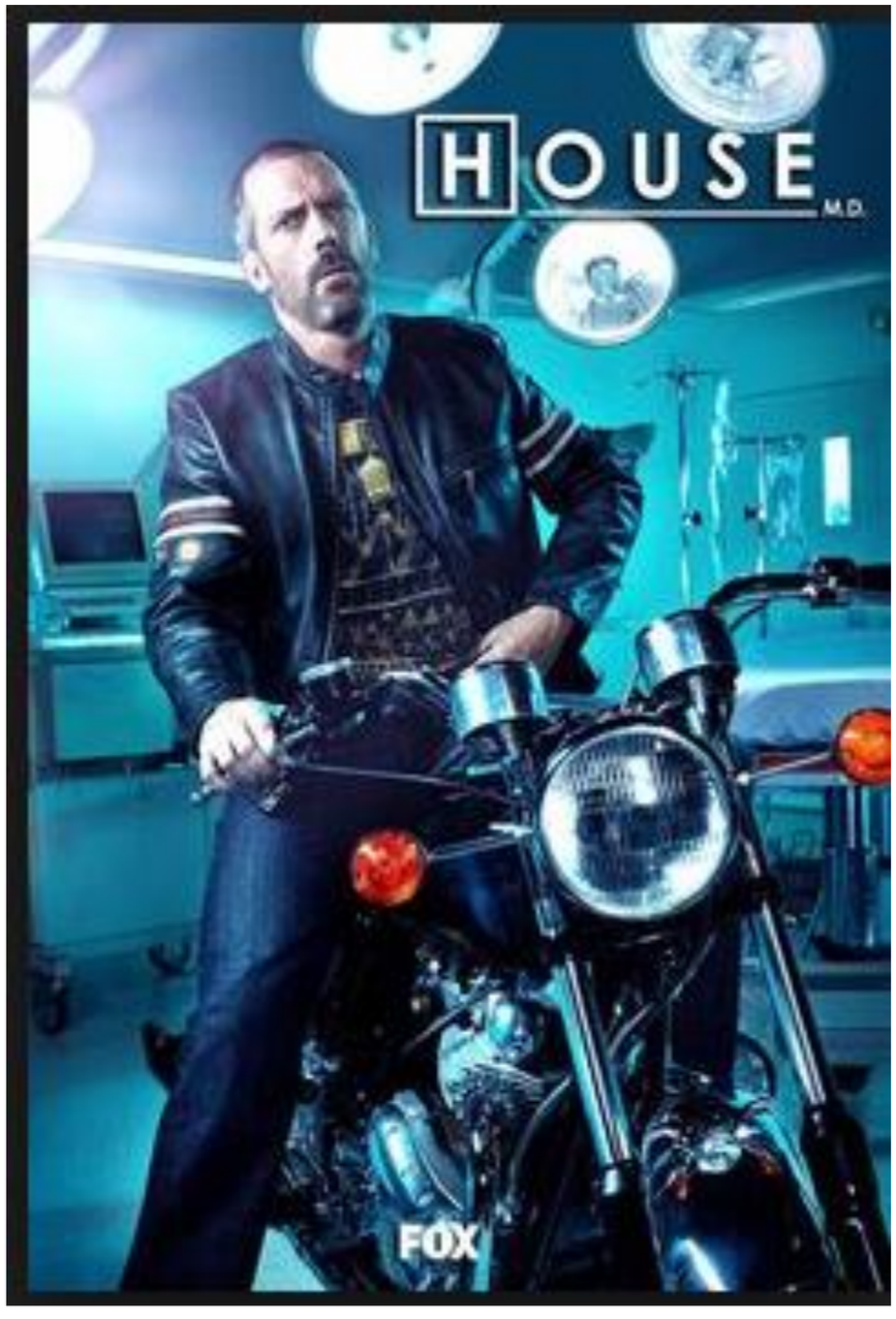
Clinical Aspects of Dysmorphology

Saskia BULK, MD MSc PhD


HOUSE M.D.
FOX

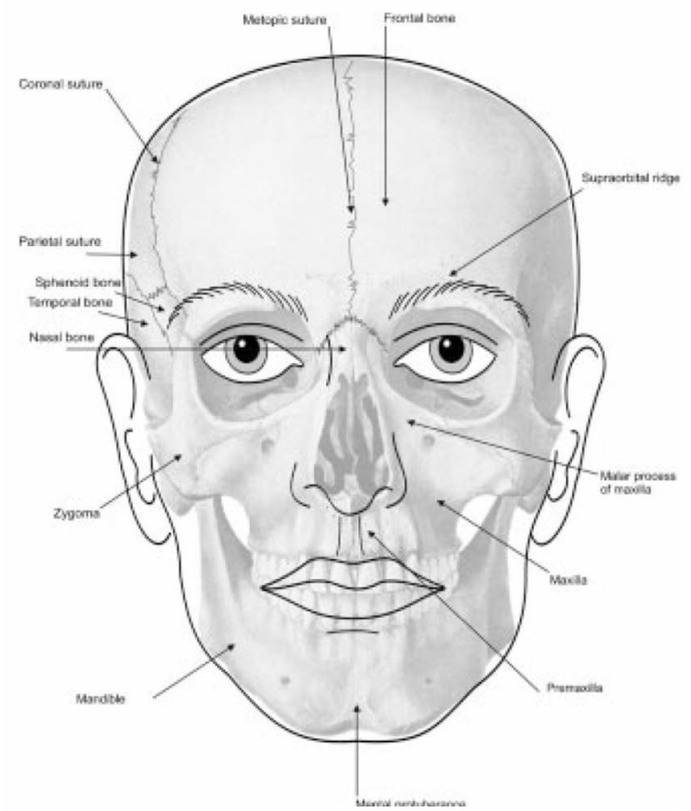
On voit quand même de drôles de trucs en pédiatrie...

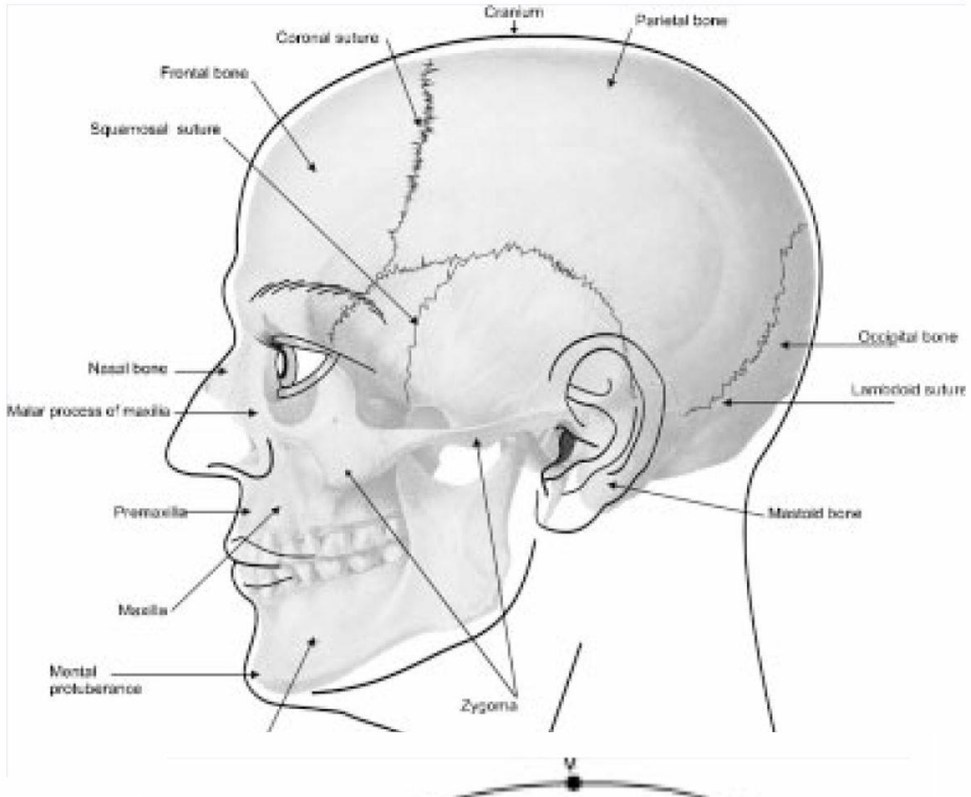
Je crois que l'enfant de la chambre 2 a une dysmorphie faciale...

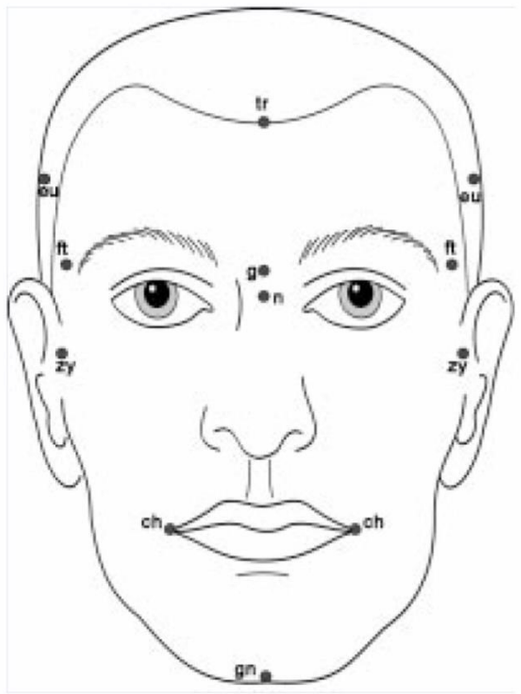
On pensait aussi mais on vient de vérifier : il est juste moche...

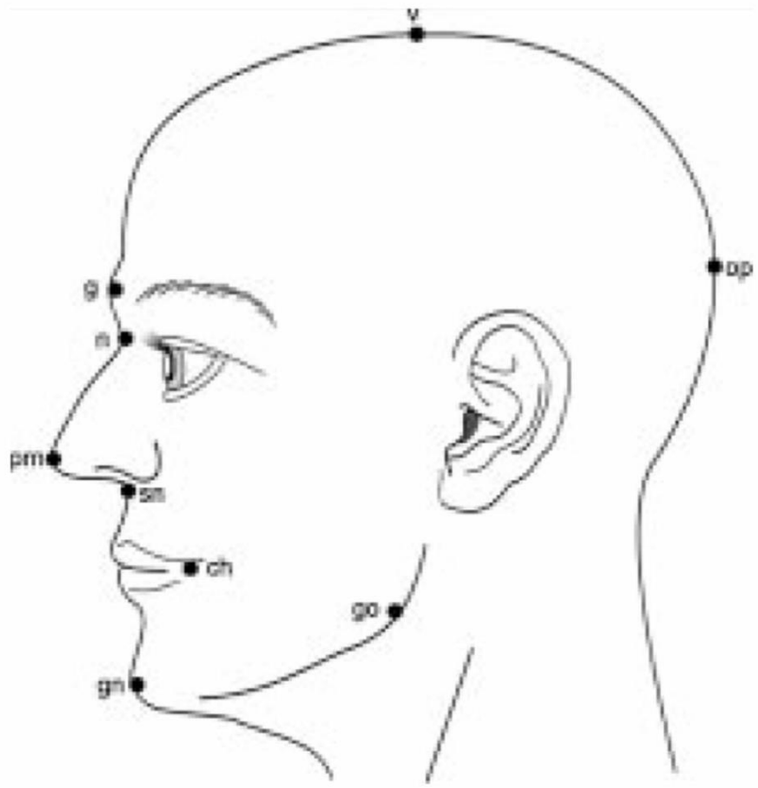
par VieDeCarabin

Elements of morphology









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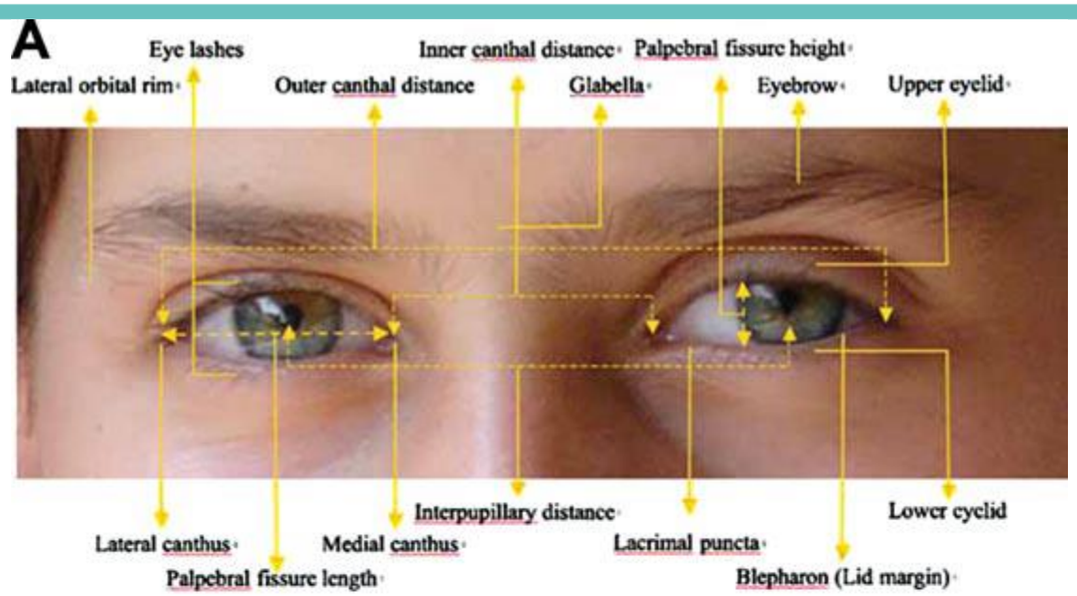

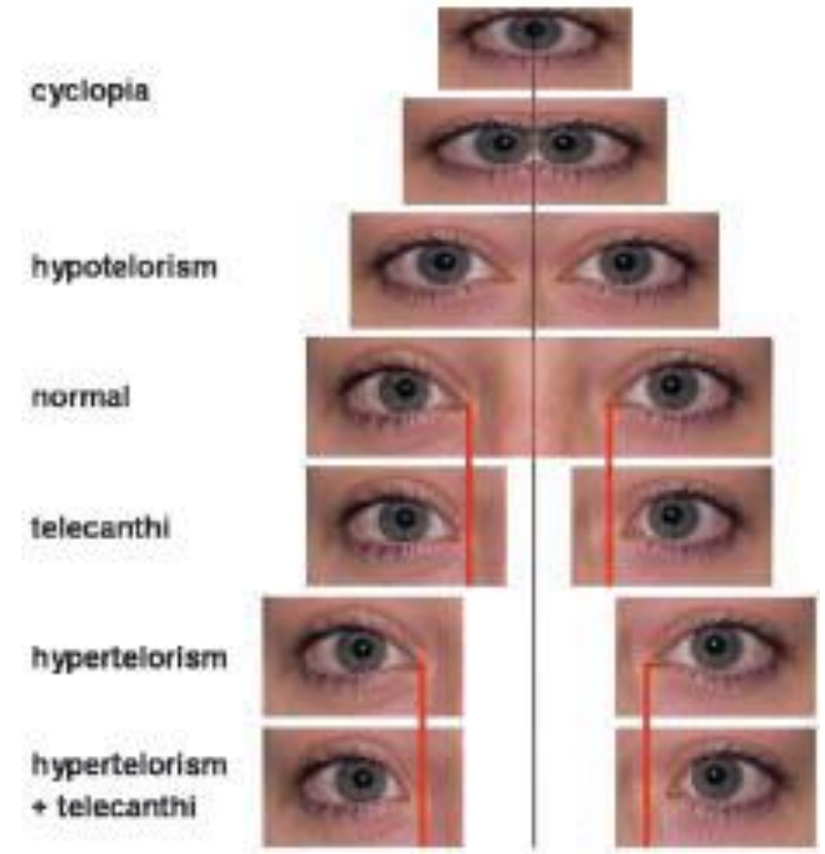

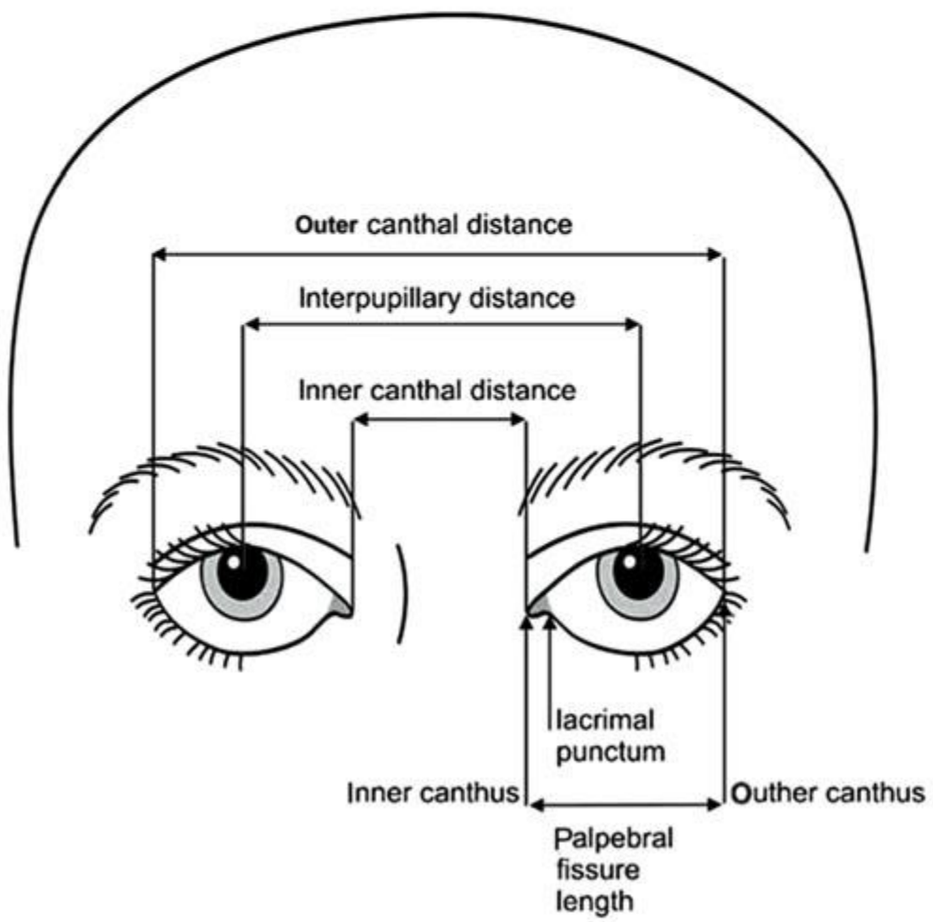

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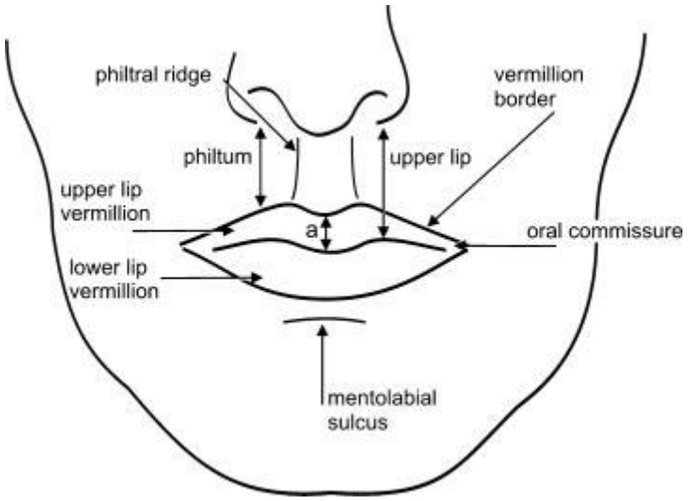

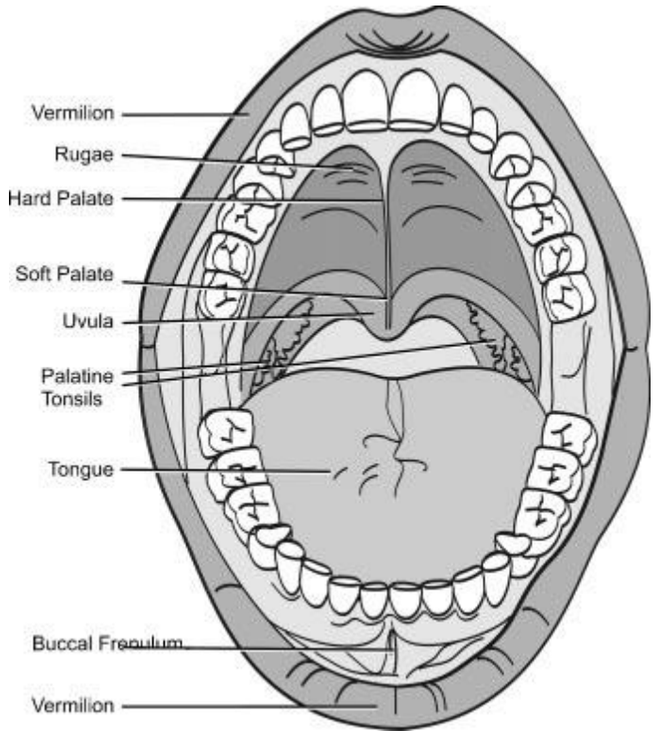

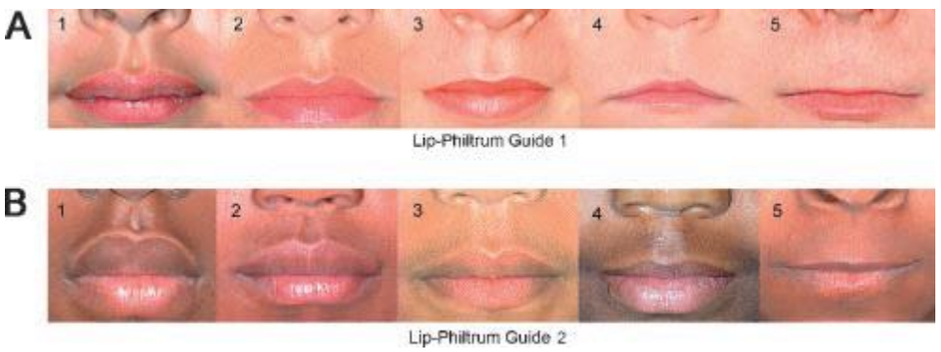

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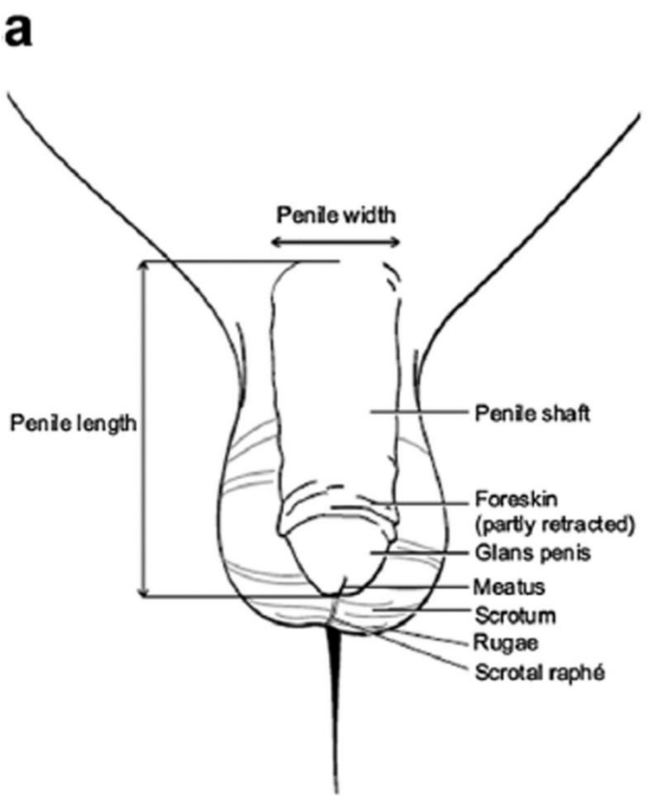

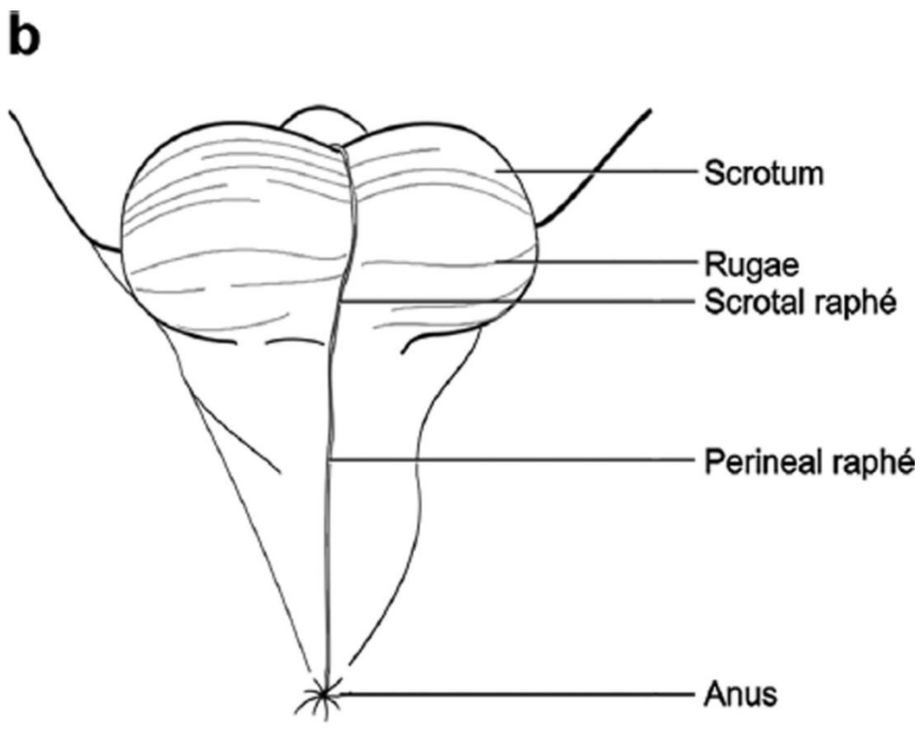

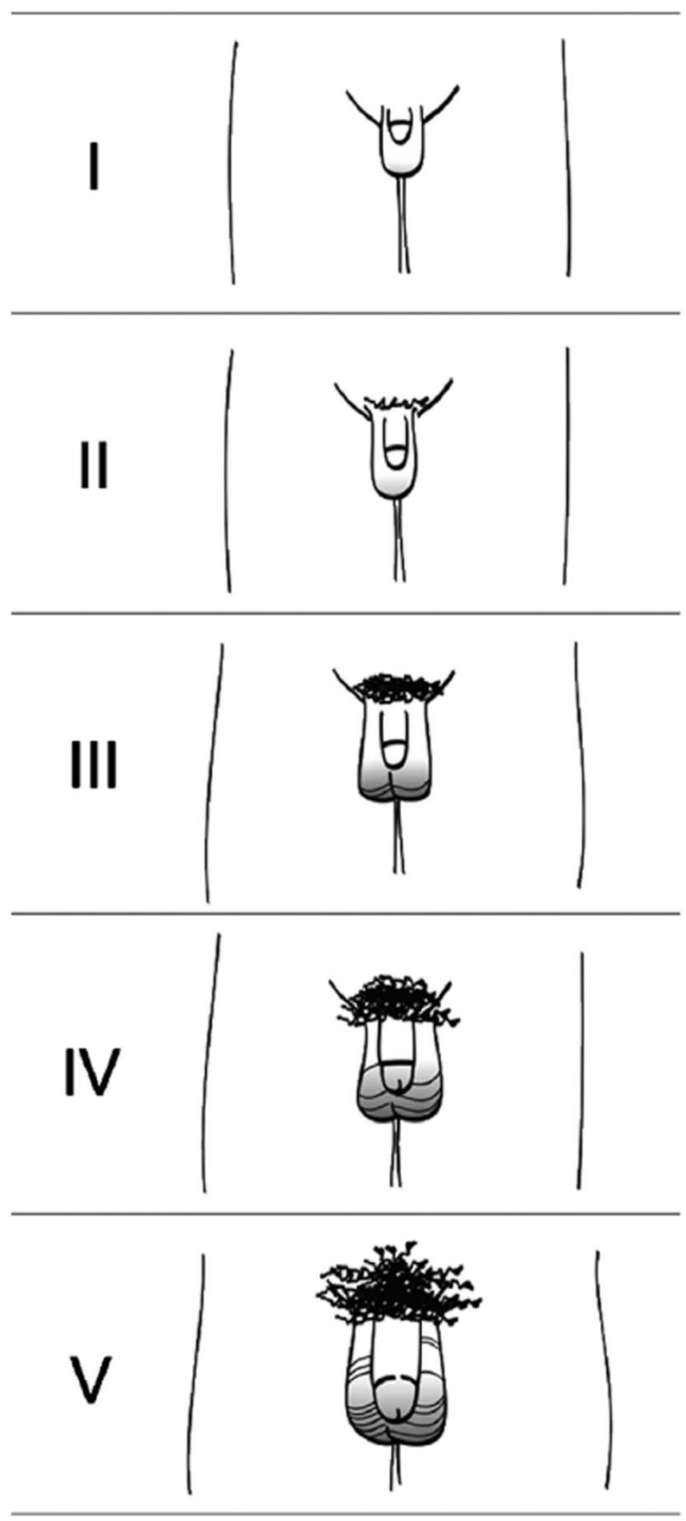

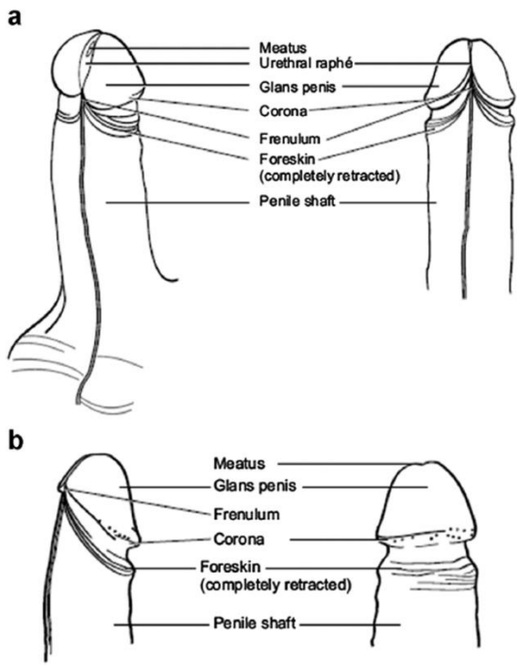

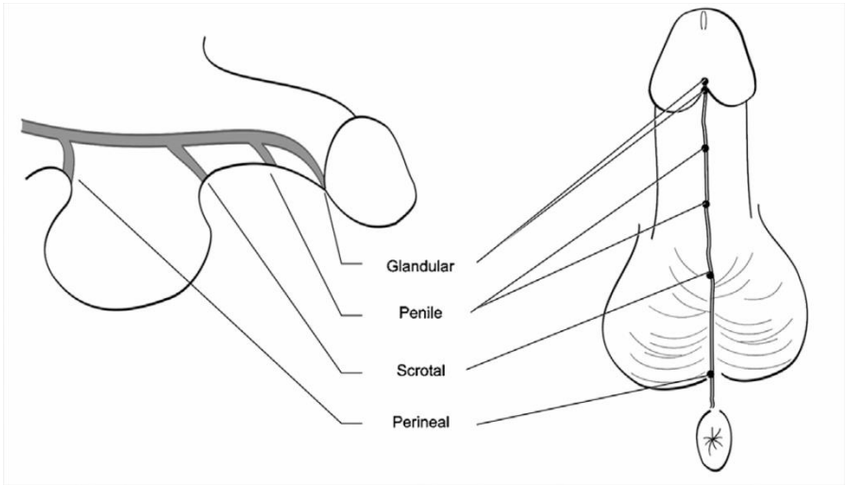

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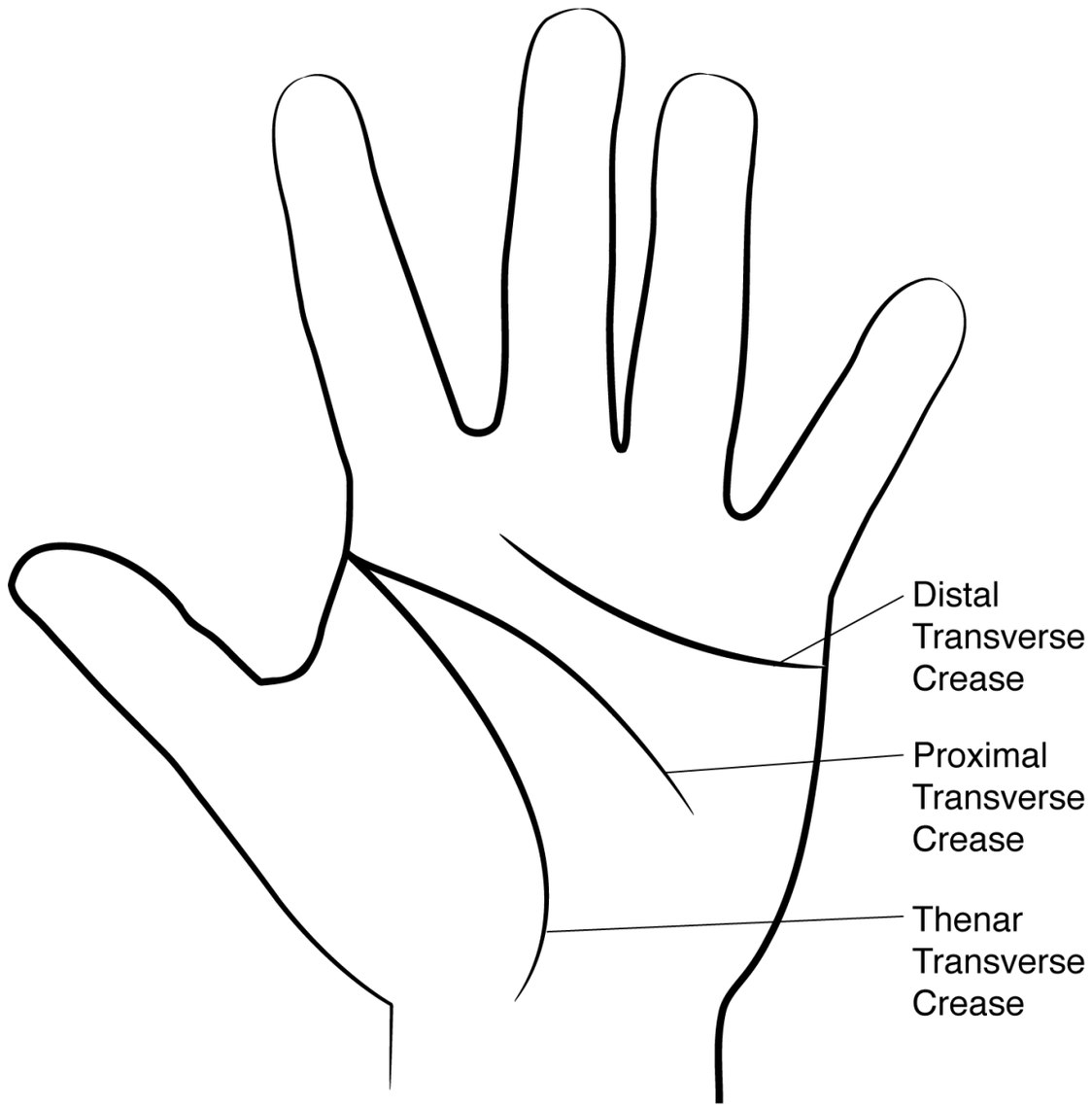

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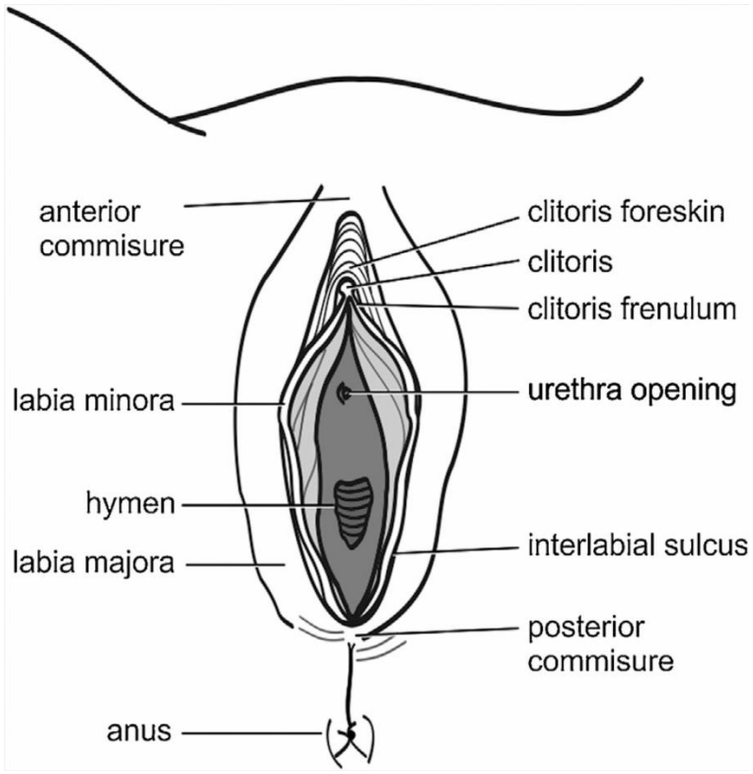
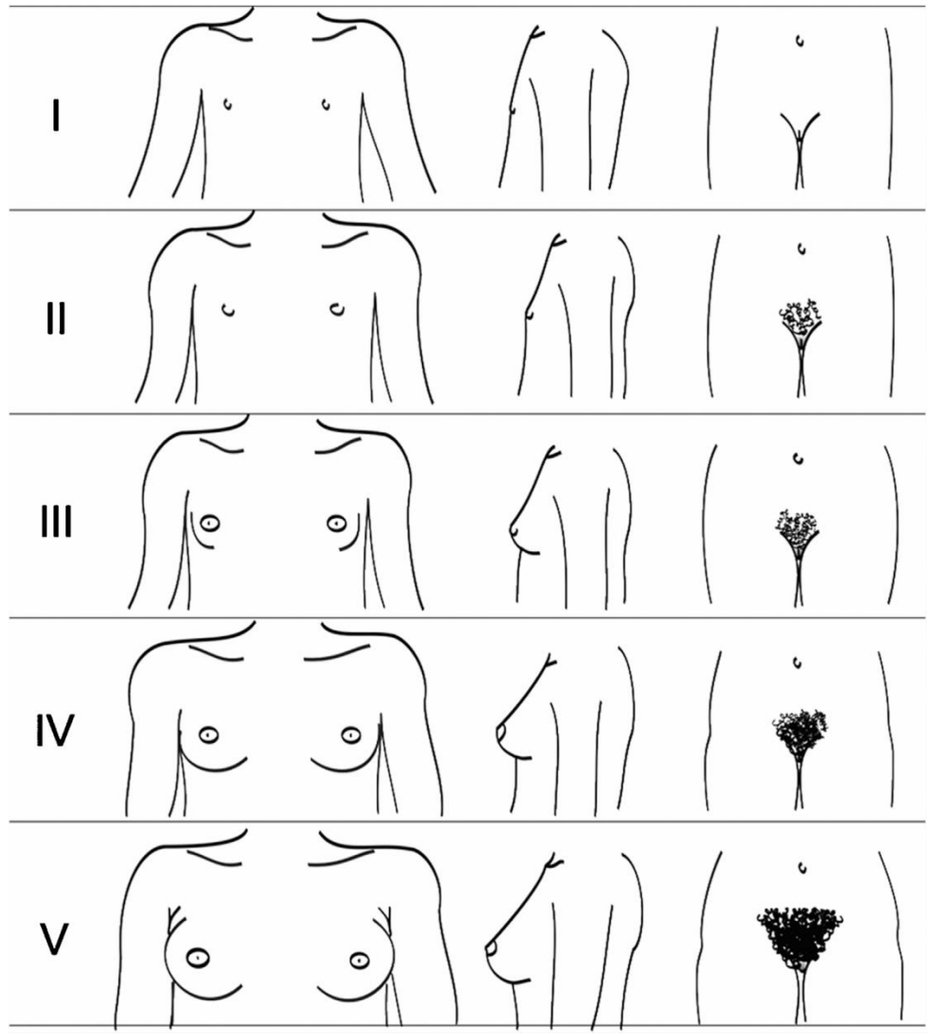




Essential syndromes

De klinisch geneticus kent de belangrijkste klinische en genetische kenmerken van de volgende syndromen (n=100)

- Aarskog syndroom (*)
- Achondroplasie
- Aicardie syndroom(*)
- Alagille syndroom (20p12.1)
- Albright hereditaire osteodystrofie (*)
- Alpha thalassemie mentale retardatie syndroom (ATRX)
- Amnionstreng syndroom
- Angelman syndroom (15q11-13)
- Apert syndroom
- Bardet-Biedl syndroom
- Beckwith-Wiedemann syndroom
- Bloom syndroom
- Branchio-oto-renaal syndroom (Melnick-Fraser)
- Cardiofaciocutaneous (CFC) syndroom (*)
- Cat eye syndroom (*)
- Cerebrocostomandibulair syndroom (*)
- CHARGE associatie
- Cockayne syndroom
- Coffin-Lowry syndroom
- Coffin-Siris syndroom (*)
- Cri du chat (5p-) syndroom
- Cohen syndroom (*)
- Cornelia de Lange syndroom
- Costello syndroom (*)
- Crouzon syndroom
- Down (trisomie 21) syndroom
- EEC-syndroom
- Fanconi syndroom
- Floating Harbor syndroom (*)
- Foetaal alcohol syndroom
- Fragile X syndroom
- Fryns syndroom
- Gorlin syndroom
- Greig cephalopolysyndactylie syndroom
- Holt-Oram syndroom
- Homocystinurie
- Hunter syndroom
- Hurler syndroom
- Hydrolethalus syndroom
- Hypochondroplasie
- Incontinentia pigmenti
- Jarcho-Levin syndroom
- Kabuki syndroom
- Kartagener syndroom
- Killian/Teschler-Nicola syndroom (tetrasomie 12p) (*)
- Klinefelter syndroom
- Klippel-Feil sequentie
- Langer-Gideon syndroom (8q24)
- Meckel-Gruber syndroom
- Miller-Dieker syndroom (17p13)
- Moebius sequentie
- Morquio syndroom
- MURCS associatie
- Nail-patella syndroom
- Noonan syndroom
- Oculoauriculovertebraal spectrum (Goldenhar)
- Oligohydramnion sequentie (*)
- Opitz syndroom
- Oral-facial-digital syndroom
- Otopalatodigital syndromen
- Pallister-Hall syndroom (*)
- Peutz-Jeghers syndroom
- Pfeiffer syndroom
- Pierre Robin sequentie
- Poland sequentie
- Prader-Willi syndroom (15q11-13)
- Proteus syndroom
- Rieger syndroom
- Roberts phocomelie
- Robinow syndroom (*)
- Rothmund-Thompson syndroom(*)
- Rubinstein-Taybi syndroom (16p13.3)
- San Filippo syndroom
- Scheie syndroom
- Seathre-Chotzen syndroom
- Seckel syndroom (*)
- Silver-Russell syndroom (*)
- Simpson-Golabi-Behmel syndroom (*)
- Smith-Lemli-Opitz syndroom
- Smith-Magenis syndroom (17p11.2)
- Sotos syndroom (*)
- Stickler syndroom
- Sturge-Weber syndroom
- Treacher-Collins syndroom
- Tricho-rhino-phalangeaal syndroom (*)
- Trisomie 18 (Edwards) syndroom
- Trisomie 13 (Patau) syndroom
- Turner syndroom
- Twee-en-twintig q11 syndroom (22q11)
- VATER associatie
- Waardenburg syndroom
- Walker-Warburg syndroom
- Weaver syndroom (*)
- Werner syndroom
- Williams syndroom (7q11.23)
- Wilms tumor-aniridie syndroom (11p13)
- Wolf-Hirschhorn (4p-) syndroom
- van der Woude syndroom
- Zellweger syndroom
- Marfan syndroom
- Ehlers-Danlos syndroom
- osteogenesis imperfecta
- cutis laxa
- pseudoxantoma elasticum
- hypermobiliteit syndroom
- congenitale contracturele arachnodactylie.

« Essential » syndromes

- Angelman syndrome
- Craniostenosis syndromes
- CHARGE syndrome
- Fetal alcohol syndrome
- Fragile X syndrome
- Goldenhar syndrome (OAVS)
- Kabuki syndrome
- Marfan syndrome
- Neurofibromatosis type I
- Noonan syndrome
- Prader-Willi syndrome
- Sotos syndrome
- Silver-Russell syndrome
- VATER/VACTERL-H sequence
- Williams syndrome
- 22q11 syndrome

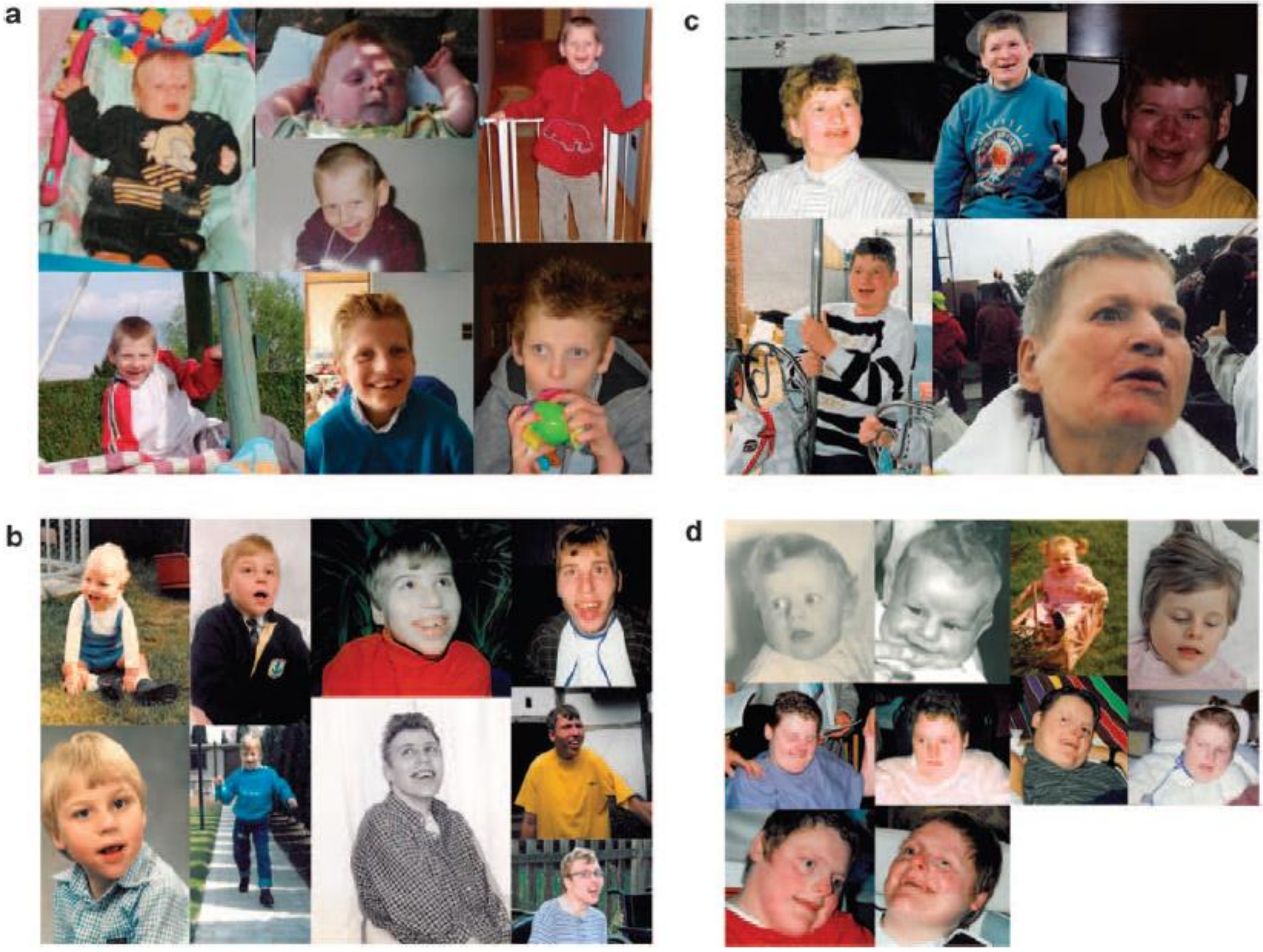


Figure 1 (a–d) Four AS patients at different ages presenting the typical facial dysmorphic features: round face, microcephaly and happy personality.

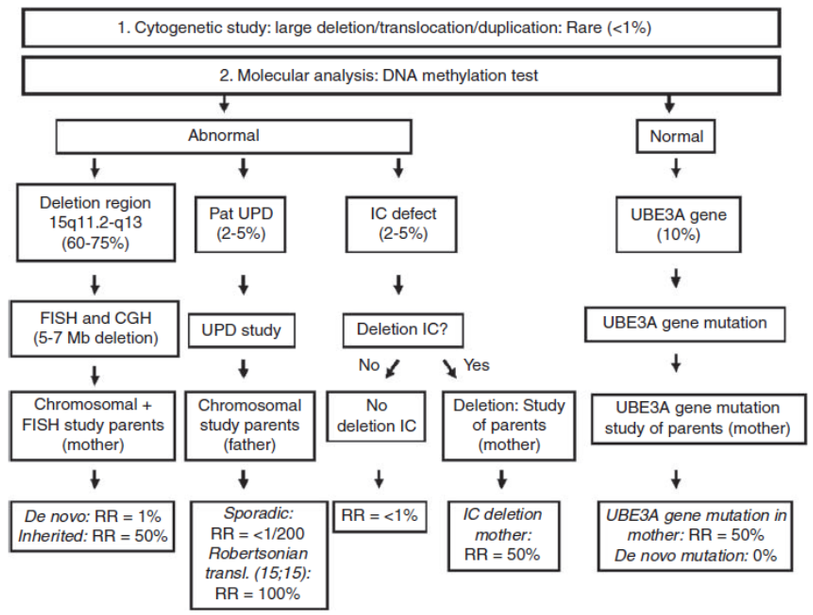
Symptoms

- Severe mental retardation with absent speech
- Dysmorphic facial features (macrostomia, maxillary hypoplasia, prognathia, relative hypopigmentation)
- Microcephaly
- Epileptic seizures and EEG abnormalities
- Ataxia
- Hyperactivity, sleeping problems, happy personality and periods of inappropriate laughter

Genetic mechanisms

Recurrence varies between 0 and 50%, depending on the underlying genetic mechanism

- deletion of 15q11.2-q13 critical region (60–75%)
- paternal uniparental disomy (2–5%),
- imprinting defect (2–5%)
- mutation in the *UBE3A* gene (10%).



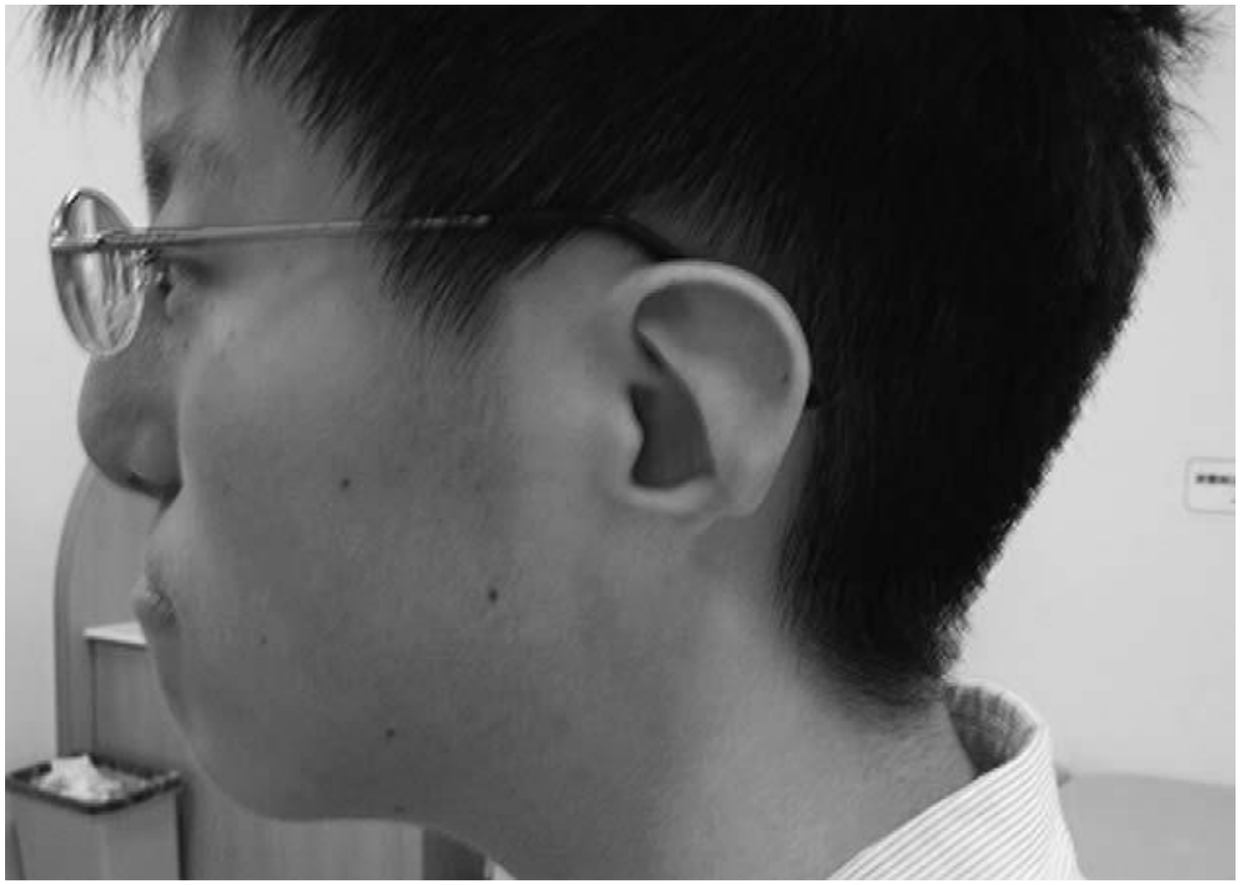
Differential diagnosis

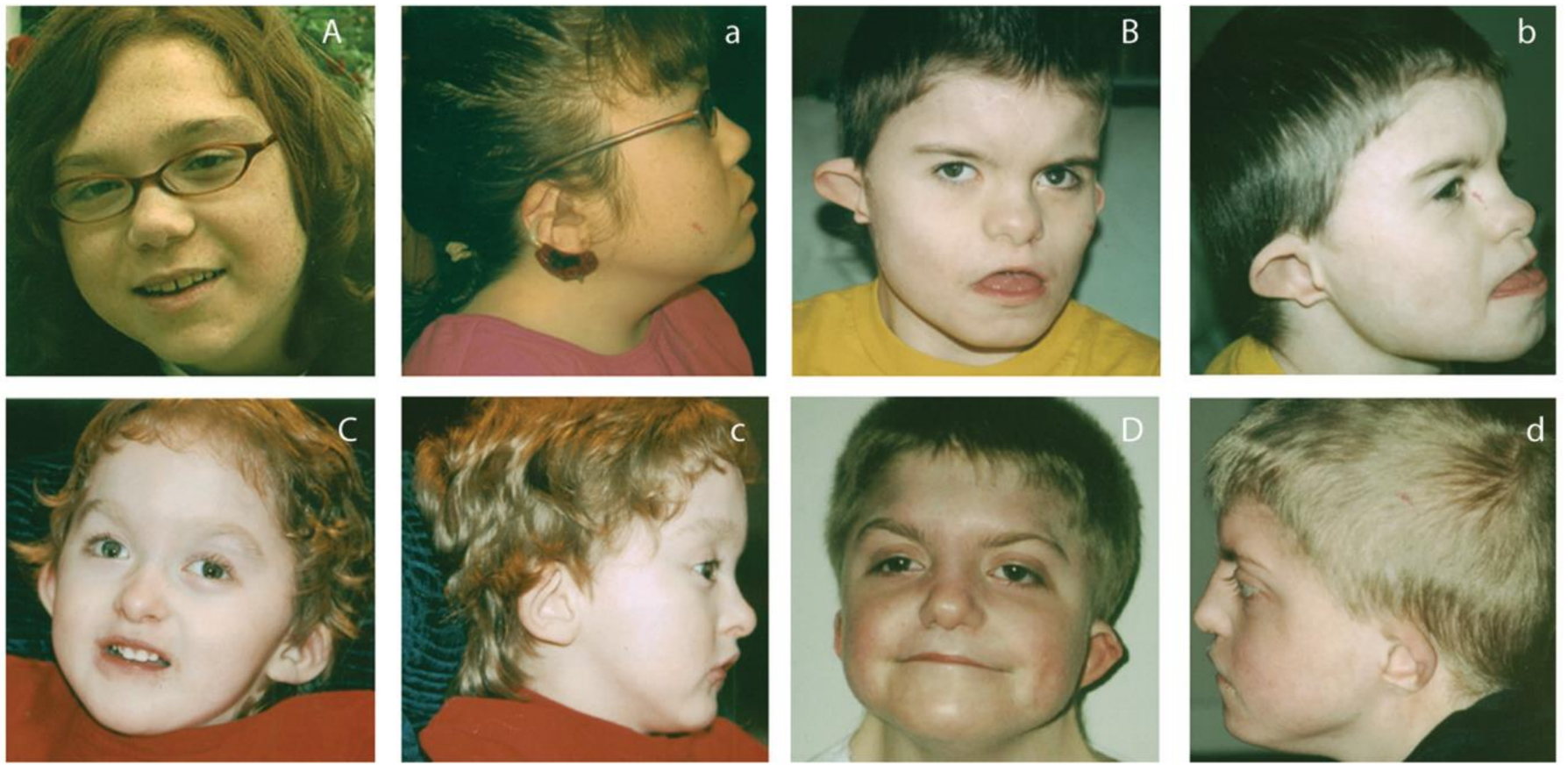
- Pitt–Hopkins syndrome (*TCF4*)
- Christianson syndrome (*SLC9A6*)
- Mowat–Wilson syndrome (*ZEB2*)
- Typical Rett syndrome (*MECP2*)

Less likely (but still possible)

- Prader–Willi syndrome (at <2 years of age)
- 22q13.3 deletion/Phelan–McDermid syndrome
- 2q23.1 deletion/*MBD5* haploinsufficiency syndrome
- 17q21.31 deletion/ *KANSL1* haploinsufficiency (Koolen–de Vries) syndrome
- Kleefstra syndrome (9q34.3 deletion, *EHMT1* haploinsufficiency)
- *HERC2* deficiency syndrome
- Adenylosuccinase deficiency
- *FOXG1* haploinsufficiency syndrome
- *STXBP1* haploinsufficiency syndrome
- *MECP2* duplication
- *MEF2C* haploinsufficiency syndrome
- Alpha-thalassemia/intellectual disability syndrome (ATRX)

« Essential » syndromes




A
a
B
b
C
c
D
d

Symptoms

- **C**oloboma (80%-90% of individuals)
- **H**eart malformation (75%-85%)
- choanal **A**tresia (50%-60%)
- **R**etardation of growth and/or development
- **G**enital anomalies (Cryptorchidism and hypogonadotropic hypogonadism)
- **E**ar anomalies (Abnormal outer ears, ossicular malformations, Mondini defect of the cochlea and absent or hypoplastic semicircular canals (>90%))

Also: cranial nerve dysfunction, orofacial clefts (15%-20%) and tracheoesophageal fistula (15%-20%)

Genetic mechanisms

Recurrence risk is usually low (1-2 %)

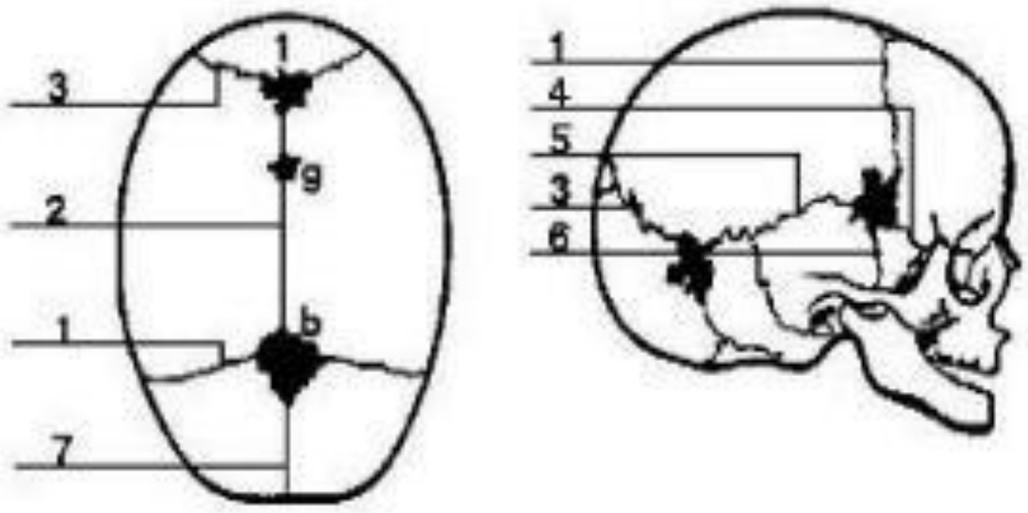
- Mutations in *CHD7* (>90%)
- Deletions/duplications of *CHD7*

Differential diagnosis

- 22q11 deletion syndrome
- VACTERL association
- Guion-Almeida syndrome (*EFTUD2*)
- Kabuki syndrome (*MLL2*)
- Renal coloboma syndrome
- Cat-eye syndrome
- Joubert syndrome
- Branchiootorenal (BOR) syndrome
- Choanal atresia
- Retinoic embryopathy secondary to prenatal Roaccutane exposure

« Essential » syndromes


300 × 300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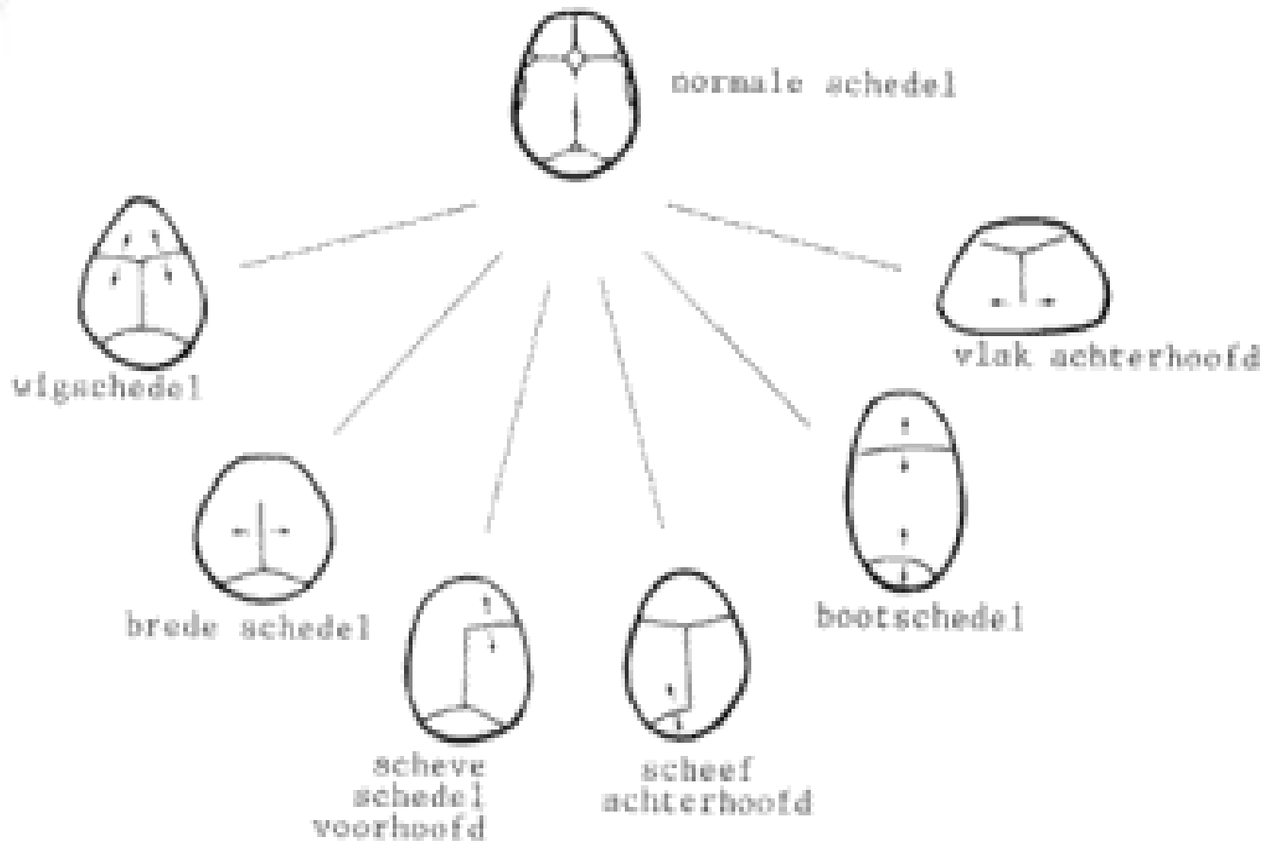

normale schedel
vlgschedel
vlak achterhoofd
brede schedel
bootschedel
scheve schedel voorhoofd
scheef achterhoofd

Craniostenosis syndrome

Symptoms

- Uni- or bicoronal craniosynostosis or cloverleaf skull
- Distinctive facial features
- Variable hand and foot findings.

Pfeiffer syndrome (*FGFR1*, rarely *FGFR2*)
Apert syndrome (*FGFR2*)
Crouzon syndrome (*FGFR2*)
FGFR2-related isolated coronal synostosis,
Muenke syndrome (p.Pro250Arg in *FGFR3)*
Saethre-Chotzen syndrome (*TWIST1*)

Genetic mechanisms

Usually de novo mutations, sometimes inherited from affected parent

Differential diagnosis

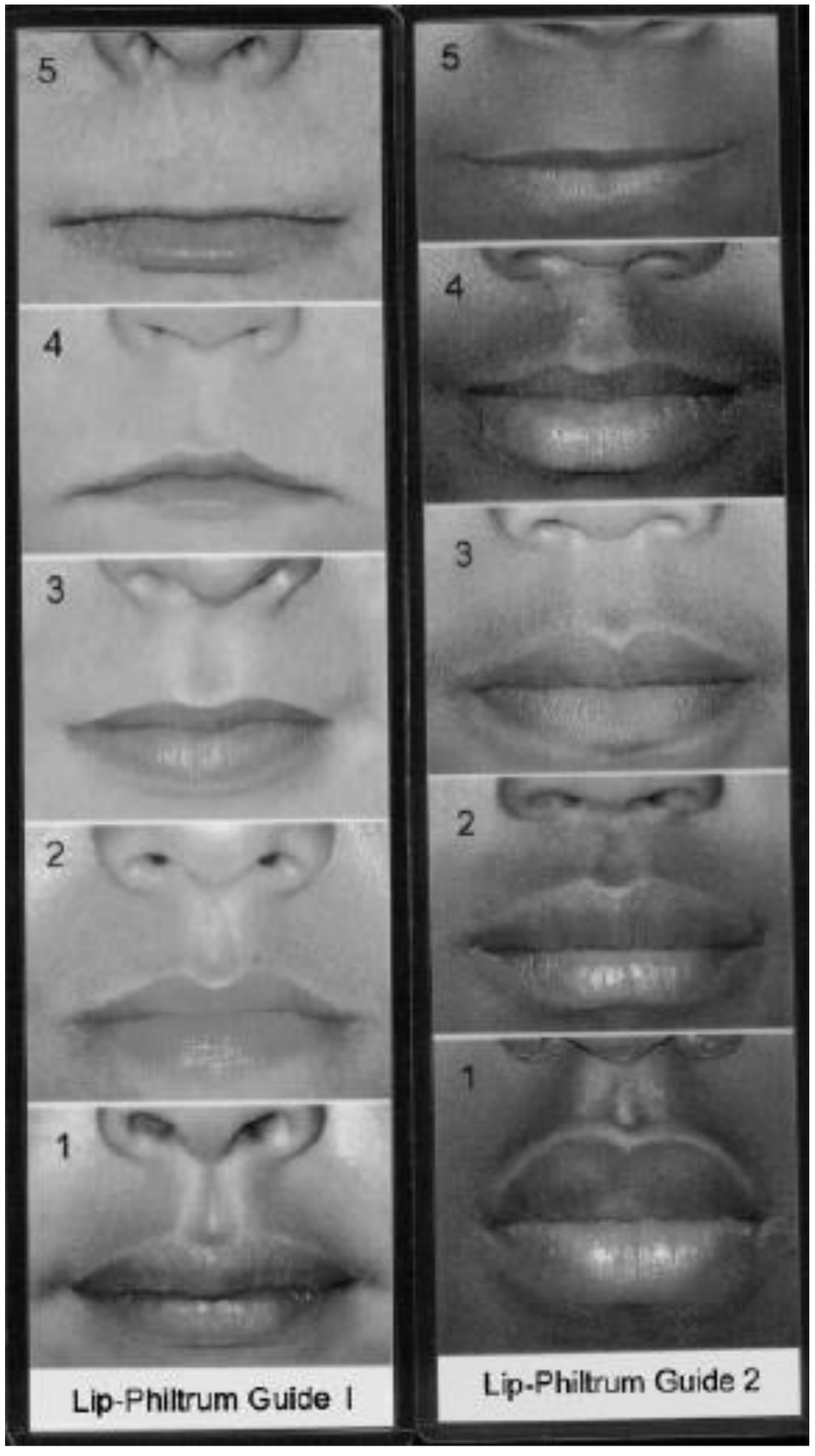
- Primary Craniosynostosis
- Isolated Craniosynostosis
- Syndromic Craniosynostosis
    - Boston-type craniosynostosis (*MSX2*)
    - Antley-Bixler syndrome (POR)
    - Baller-Gerold syndrome (*RECQL4)*
    - Carpenter syndrome syndrome (*RAB23)*
    - Craniofrontonasal syndrome syndrome (*EFNB1*)
    - Greig cephalopolysyndactyly (*GLI3)*
    - Opitz trigonencephaly C syndrome.
    - Philadelphia-type craniosynostosis (duplications within and around *IHH*)
    - Shprintzen-Goldberg syndrome (*SKI*)
    - Loeys-Dietz syndrome (*TGFBR1* and *TGFBR2*)

« Essential » syndromes

TABLE II. Dysmorphology Scoring System [Hoyme et al., 2005]*

Feature	Points
Height <10%	1
Weight <10%	2
Occipitofrontal circumference <10%	3
Inner canthal distance <10%	0
Palpebral fissure length <10%	3
Attention deficit/hyperactivity	1
Fine motor dysfunction	1
Midfacial hypoplasia	2
"Railroad Track" ears	1
Strabismus	0
Ptosis	2
Epicanthal folds (non-racial)	1
Flat nasal bridge	1
Anteverted nares	2
Long philtrum	2
Smooth philtrum	3
Thin vermilion border of upper lip	3
Prognathism	0
Cardiac murmur	1
Cardiac malformation (confirmed)	1
Hypoplastic nails	0
Decreased pronation/supination of elbow	2
Clinodactyly of fifth fingers	1
Camptodactyly	1
"Hockey Stick" palmar creases	1
Hirsutism	1
Total possible dysmorphology score	36

*The dysmorphology score is a weighted calculation based on assigning points to clinical findings characteristic of FASD (the highest point values are assigned to the cardinal findings of FAS, that is, growth deficiency, microcephaly, short palpebral fissures, smooth philtrum, and a thin upper lip). The score is an objective method of quantifying dysmorphology, but is *not* used in assigning clinical diagnoses in the FASD continuum.



Fetal alcohol syndrome

Symptoms

- Confirmed maternal alcohol consumption during pregnancy
- Pre- and postnatal growth retardation (L/W/HC<P10)
- Facial dysmorphisms (short palpebral fissures, flat/wide philtrum, thin upper lip)
- Microcephaly
- Executive malfunctioning

Genetic mechanisms

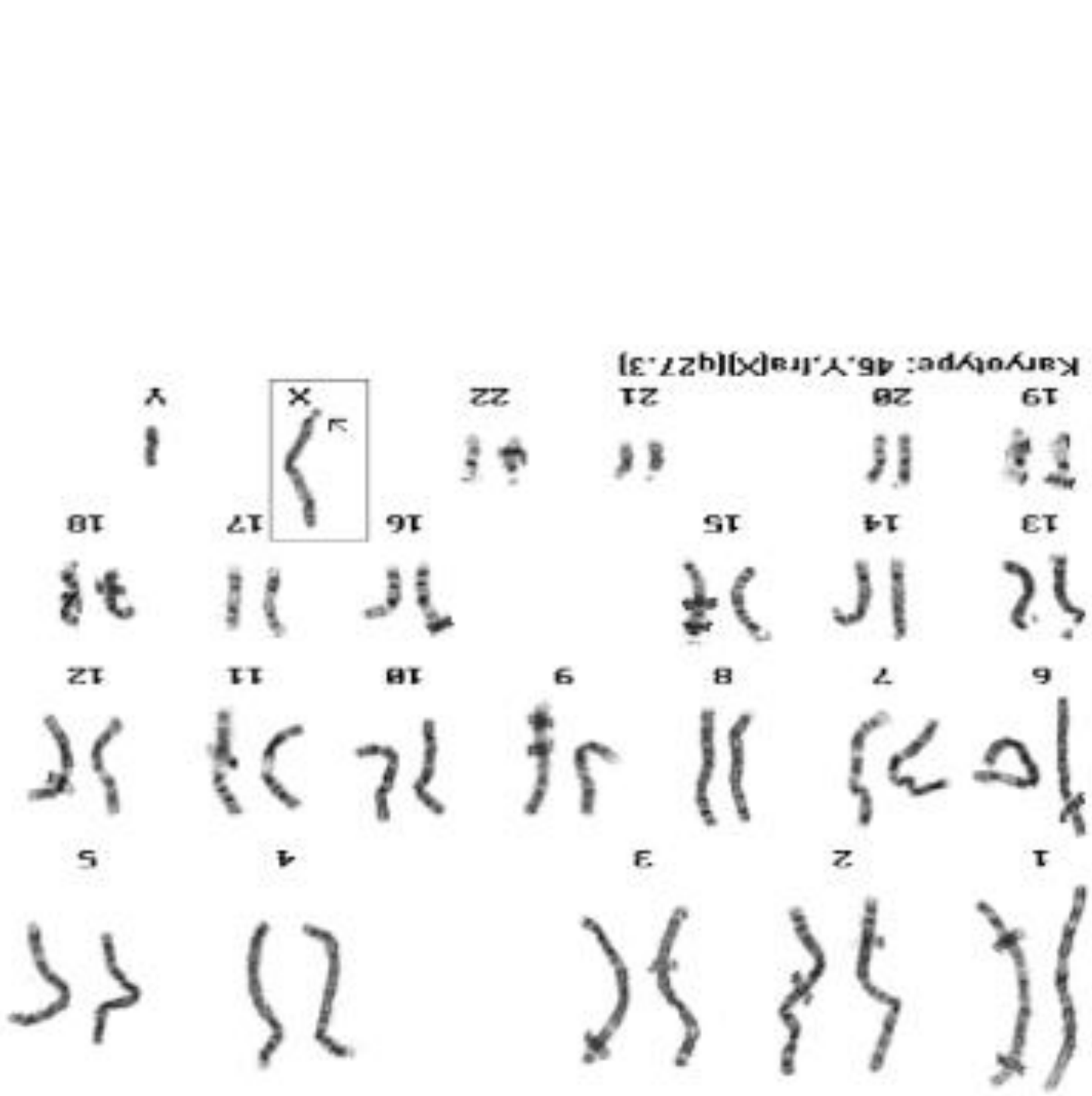
Fetal exposition to teratogenic effects of alcohol

Low recurrence risk when abstaining…

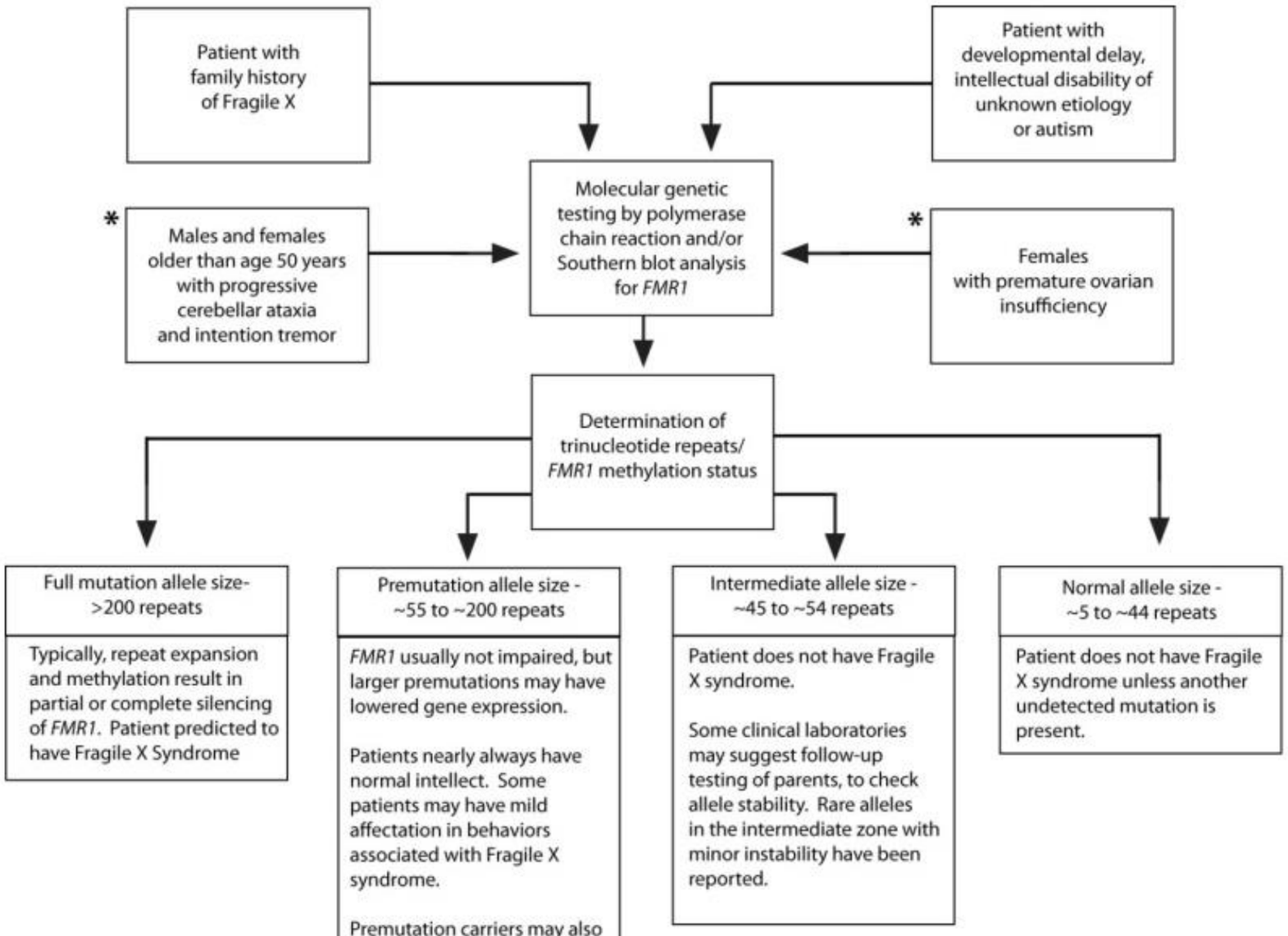
Differential diagnosis

- Aarskog syndrome
- BPES Syndrome
- Cornelia De Lange syndrome
- Dubowitz syndrome
- Fetal anticonvulsant syndrome
- Maternal PKU effects
- Noonan syndrome
- Toluene embryopathy
- Williams syndrome
- Chromosomal disorders

« Essential » syndromes



Karyotype: 46,Y,inv(X)(q27.3)



Tabel 2: risico op expansie van het aantal maternale CGG repeats tot boven de 200 (Uit Nolin et al, 2003 [116])

Maternale repeats	% nageslacht met expansie naar volle mutatie (indien aangedane allel overgeërfd)
55 – 59	4
60 – 69	5
70 – 79	31
80 – 89	58
90 – 99	80
100 – 200	ongeveer 100

Disorders

Fragile X syndrome,
Fragile X-associated tremor/ataxia syndrome (FXTAS)
FMR1-related primary ovarian insufficiency (POI)

Symptoms Fragile X syndrome

- Moderate intellectual disability (males)
- Mild intellectual disability (affected females).
- Characteristic appearance (large head, long face, prominent forehead and chin, protruding ears)
- Connective tissue findings (joint laxity)
- Large testes after puberty
- Behavioral abnormalities, including autism spectrum disorder

Genetic mechanism

- Repeat expansion disorder
- Recurrence risk can be high depending on allele size and sex

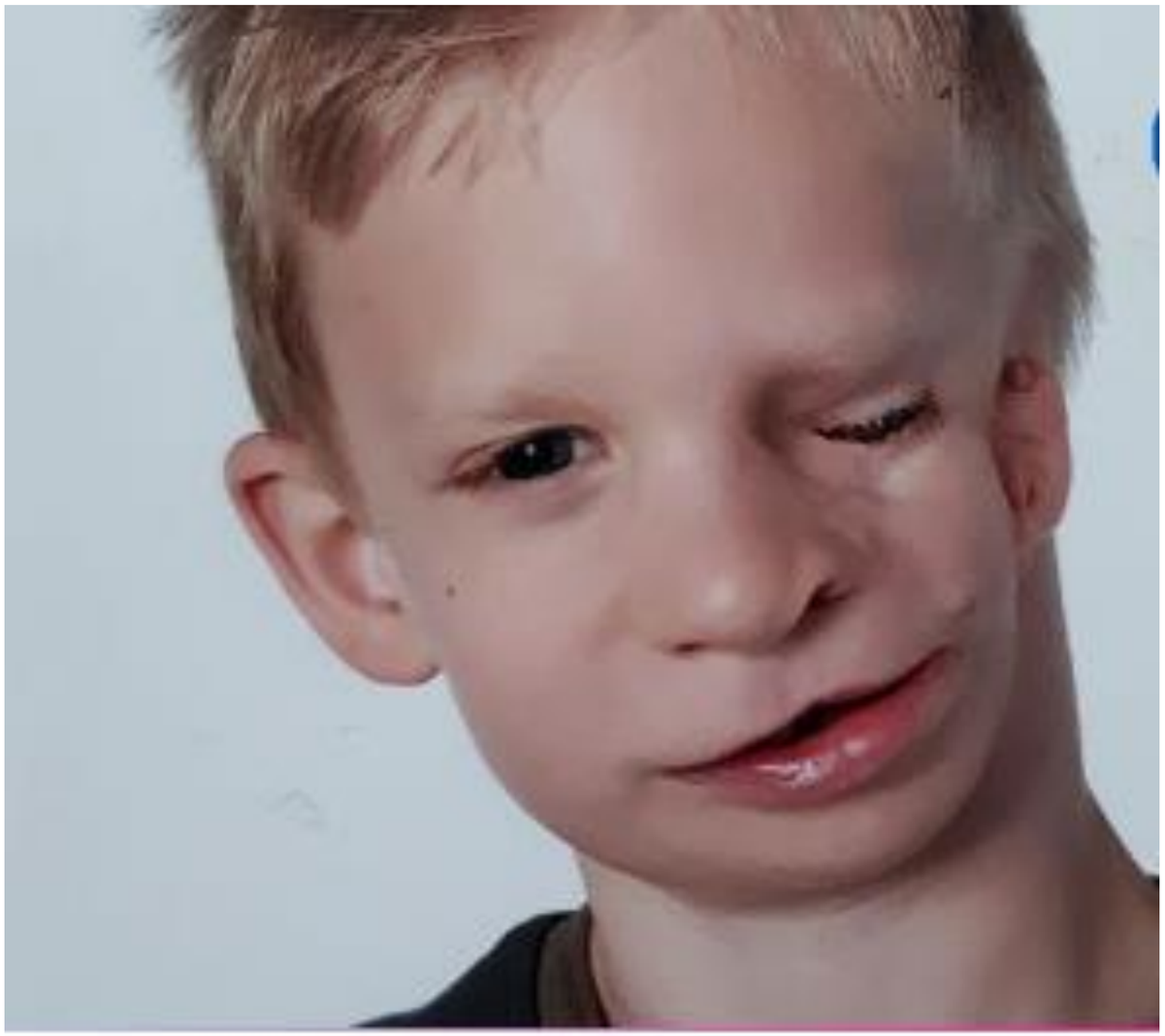
Differential diagnosis

- Sotos syndrome (*NSD1)*
- Prader-Willi syndrome (15q11q13)
- Fragile XE syndrome (*FMR2)*
- Non-syndromic mental retardation

Other FMR1-related disorders:

FXTAS: late-onset, progressive cerebellar ataxia and intention tremor.
FMR1-related POI occurs in approximately 20% of females who have an *FMR1* premutation.

« Essential » syndromes



Oculo-auriculo-vertebral syndrome
Goldenhar syndrome/Craniofacial microsomia

Symptoms

- Spectrum of malformations involving structures derived from first and second branchial arches
    - Facial asymmetry resulting from maxillary a/o mandibular hypoplasia
    - Preauricular or facial tags
    - Ear malformations (microtia, anotia, or aural atresia and hearing loss)
    - Cleft lip, cleft mouth and/or palate
    - Epibulbar dermoid
- Non-craniofacial malformations (vertebral, renal, cardiac, and limb).
- Normal development

Genetic mechanisms

Sporadic condition, vascular disruption?

Recurrence risk usually low

Differential diagnosis

- VATER association
- CHARGE syndrome
- MURCS
- OEIS
- Auriculocondylar syndrome (*PLCB4* or *GNAI3)*
- Bixler syndrome
- Branchiootorenal (BOR) syndrome (*EYA1, SIX5* or *SIX1*)
- Hemifacial myohyperplasia sequence
- Guion-Almeida syndrome (*EFTUD2)*
- Miller syndrome (*DHODH)*
- Nager syndrome (*SF3B4*)
- Oculoauriculofrontonasal syndrome.
- Parry Romberg syndrome
- Townes-Brocks syndrome (*SALL1)*
- Treacher-Collins syndrome (*TCOF1*, *POLR1C* and *POLR1D*)

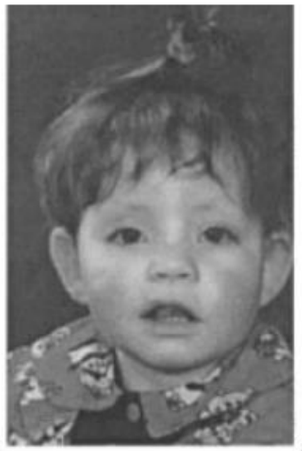
« Essential » syndromes


1


2


3


4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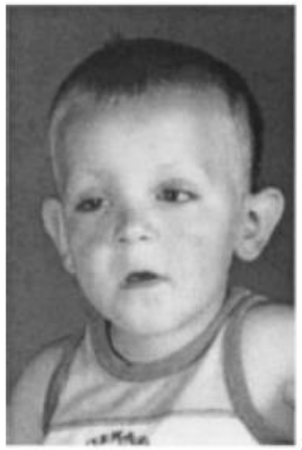
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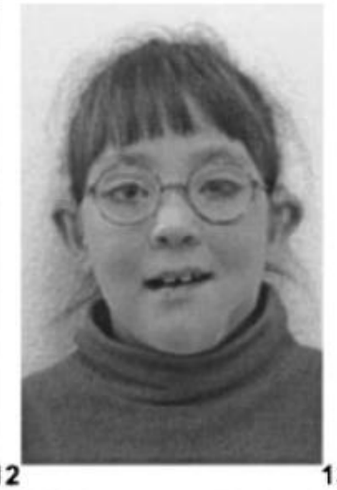
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Symptoms

- Typical facial features
  - elongated palpebral fissures with eversion of lateral third of lower eyelid
  - arched, notched and broad eyebrows
  - short columella with depressed nasal tip
  - large, prominent, or cupped ears
- Persistence of fetal fingertip pads,
- Mild to moderate intellectual disability
- Postnatal growth deficiency.
- Congenital malformations (heart defects, cleft lip and/or palate, etc)

Genetic mechanisms

Recurrence risk is usually low (1-2 %)

- Mutations in *KMT2D* (formerly *MLL2*) or *KDM6A*

Differential diagnosis

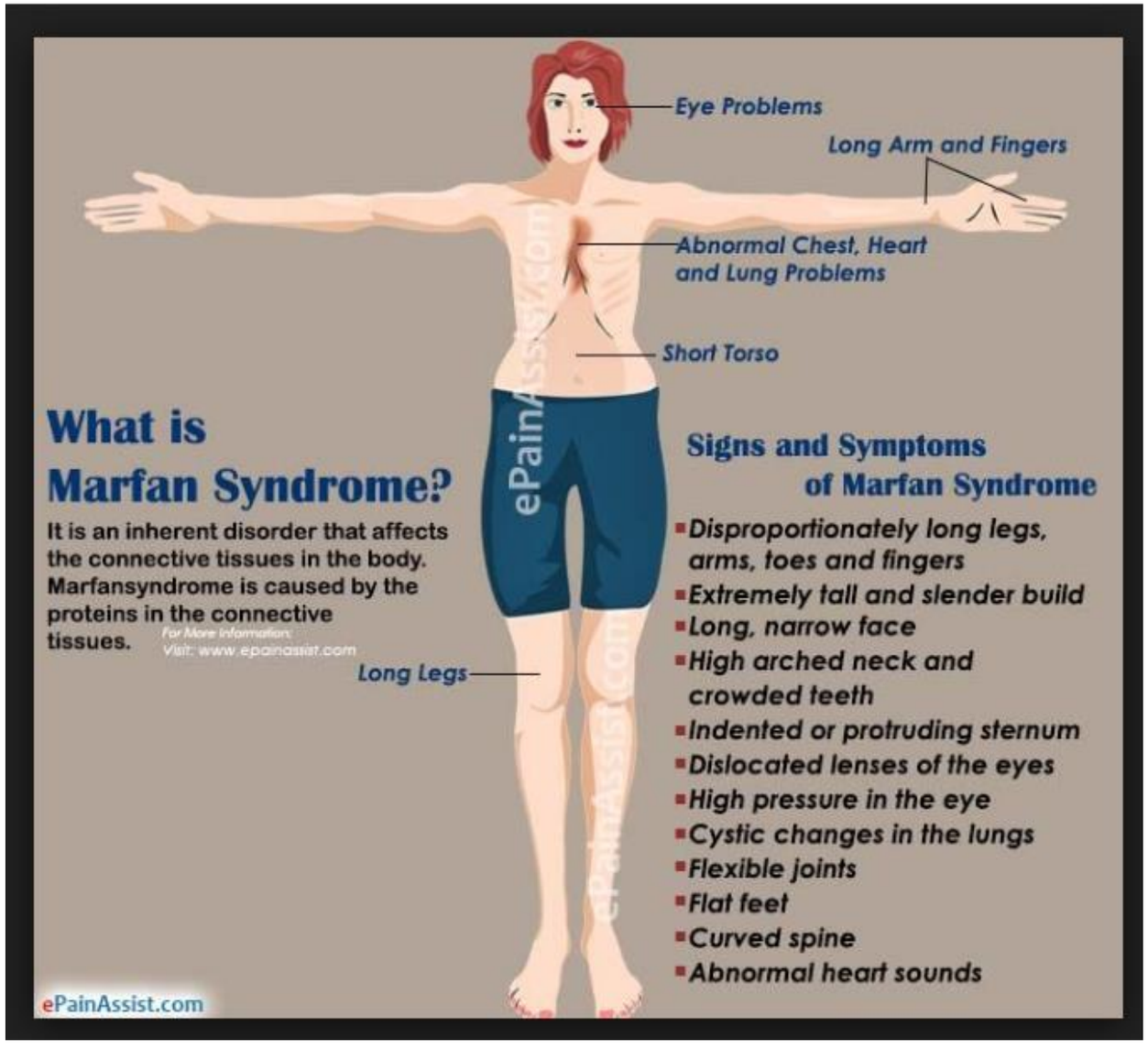
CHARGE syndrome (*CHD7)*

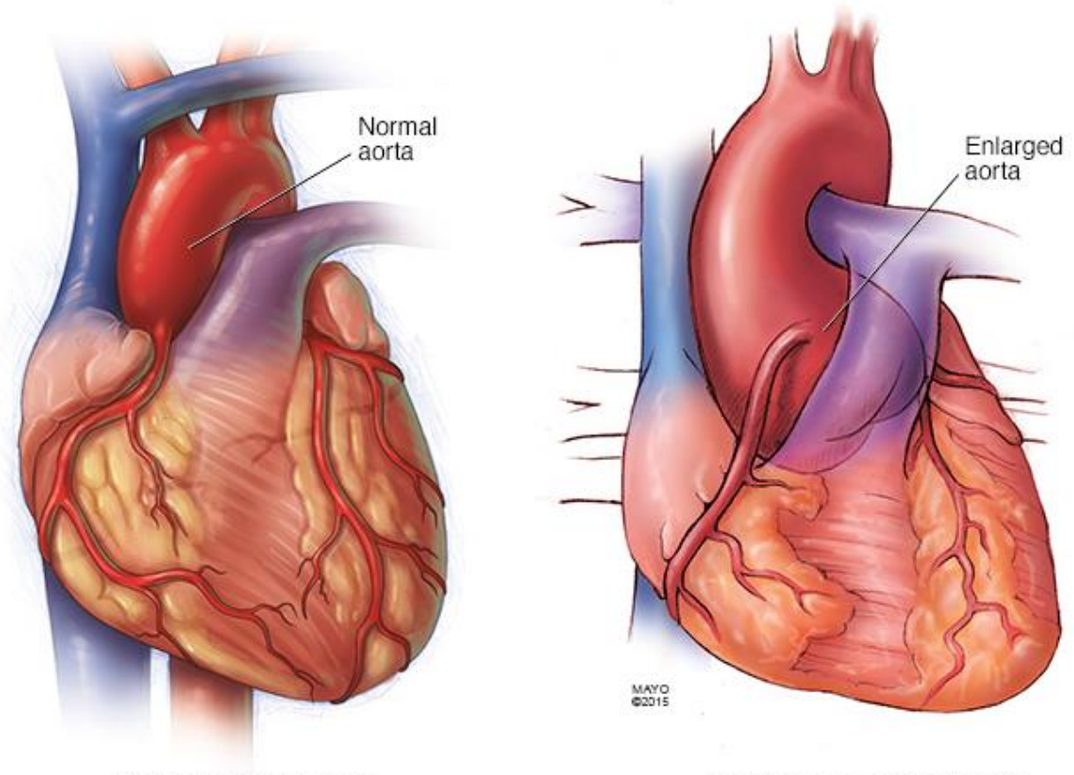
22q11 deletion syndrome

Van der Woude syndrome (*IRF6)*

Branchiootorenal (BOR) syndrome

« Essential » syndromes





Normal heart and aorta

Heart with an enlarged aorta

THE MARFAN FOUNDATION

CALCULATION OF SYSTEMIC SCORE Ghent criteria!

Clinical manifestations of MFS in other organ systems were critically evaluated for their specificity and diagnostic utility based on expert opinion and the available literature. Several of the "minor" criteria from the old Ghent nosology were eliminated, but the most selective systemic features were included in the "systemic score".

Feature		Value	Click to include
Wrist AND thumb sign	+	3	☐
Wrist OR thumb sign	+	1	☐
Pectus Carinatum Deformity	+	2	☐
Pectus Excavatum or Chest Asymmetry	+	1	☐
Hindfoot Deformity	+	2	☐
Plain Flat Foot	+	1	☐
Spontaneous Pneumothorax	+	2	☐
Dural Ectasia	+	2	☐
Protucio Acetabulae	+	2	☐
Scoliosis or Thoracolumbar Kyphosis	+	1	☐
Reduced Elbow Extension	+	1	☐
3 of 5 Facial Features	+	1	☐
Skin Striae	+	1	☐
Severe Myopia	+	1	☐
Mitral Valve Prolapse	+	1	☐
Reduced Upper Segment / Lower Segment & Increased Arm span / Height	+	0	Open to calculate

Z-SCORE CALCULATION

Different methods are used for aortic root dilatation in different publications (eg.diastolic versus systolic measurement, inner to inner or leading edge to leading edge diameters). One should take into account these differences when choosing a formula to calculate Z-scores. Aortic root refers to the measurement at the sinuses of Valsalva.

Children | Adults

Aortic Root Z-Scores for Children

For patients up to 25 years of age: utilizing systole, inner to inner edge measurement of the sinuses of valsalva according to Colan SD et al. J Am Coll Cardiol 2006;47:1858–65)

Height (cm) : 0.00

Weight (kg) : 0.00

BSA : 0.00

Ao Root at sinuses of Valsalva (in cm) : 0.00

Calculate | Print Result | Clear Entries

Z-Score: 0

Patient Identifier

E-mail results to *

SUBMIT

Symptoms

- Cardiovascular system
  - dilatation of the aorta (at the sinuses of Valsalva)
  - mitral valve prolapse
  - tricuspid valve prolapse
  - enlargement of the proximal pulmonary artery.
- Skeletal system
  - bone overgrowth and joint laxity
  - disproportionately long extremities (dolichostenomelia)
  - pectus excavatum or pectus carinatum
  - scoliosis
- Ocular findings
  - myopia
  - ectopia lentis
  - increased risk for retinal detachment, glaucoma, and early cataracts

Genetic mechanisms

Autosomal dominant; 25% de novo

- Haploinsufficieny of *FBN1* (95% mutations)

Differential diagnosis

Loeys-Dietz syndrome

TAAD

Ehlers-Danlos syndrome (vascular type; kyphoscoliotic type)

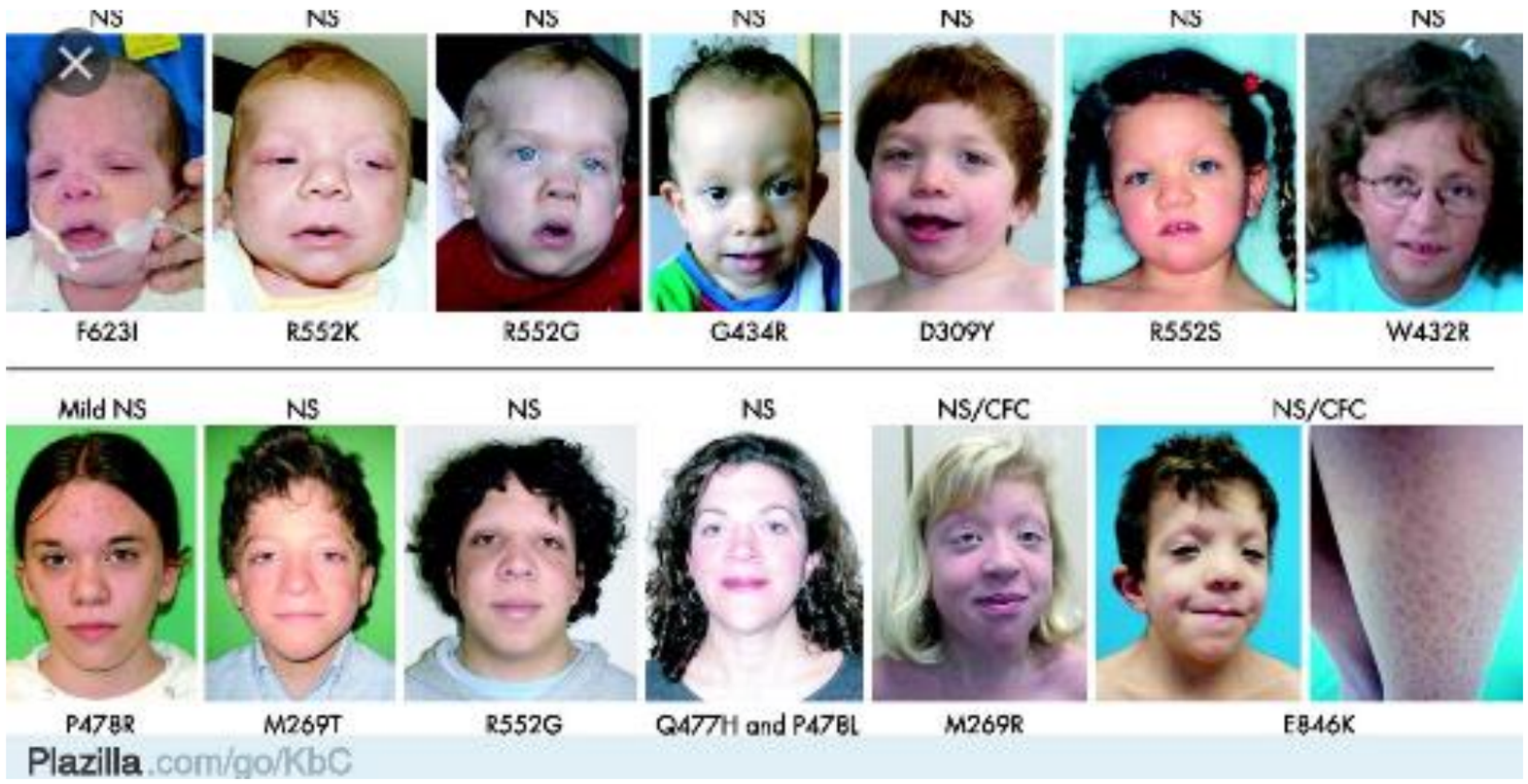
Congenital contractural arachnodactyly

Stickler syndrome

Homocystinuria

Fragile X syndrome

« Essential » syndromes


NS
NS
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NS
F623I
R552K
R552G
G434R
D309Y
R552S
W432R
Mild NS
NS
NS
NS
NS/CFC
NS/CFC
P47BR
M269T
R552G
Q477H and P47BL
M269R
E846K
Plazilla.com/go/KbC

Noonan syndrome

Symptoms

- Short stature
- Typical facial dysmorphology
    - hypertelorism with down-slanting palpebral fissures
    - ptosis
    - low-set posteriorly rotated ears with a thickened helix
- Congenital heart defects
    - pulmonary stenosis
    - hypertrophic cardiomyopathy.

Frequency

Incidence estimated to be between 1:1000 and 1:2500 (not a rare disease!)
De novo or inherited from affected parent; recurrence risk 1-5
RAS-MAPK pathway, including *PTPN11, SOS1, RAF1, RIT1, KRAS, NRAS, BRAF, MAP2K1, MAPK2* etc

Differential diagnosis

- Turner syndrome (45,X0)
- Cardiofaciocutaneous (CFC) syndrome (*BRAF*, *MAP2K1*, *MAP2K2* or *KRAS*)
- Costello syndrome (*HRAS*)
- Noonan syndrome-like disorder with loose anagen hair (*SHOC2*)
- Noonan syndrome-like disorder with or without JMML (*CBL)*.
- Williams syndrome
- Aarskog syndrome
- Fetal alcohol syndrome
- Neurofibromatosis type I (*NF1)*

Table 1: Scoring system for Noonan syndrome (NS) #

Feature	A = Major	B = Minor
1 Facial	Typical face dysmorphology	Suggestive face dysmorphology
2 Cardiac	Pulmonary valve stenosis, HOCM and/or ECG typical of NS	Other defect
3 Height	<P3*	<P10*
4 Chest wall	Pectus carinatum/excavatum	Broad thorax
5 Family history	First degree relative with definite NS	First degree relative with suggestive NS
6 Other	Mental retardation, cryptorchidism and lymphatic dysplasia	One of mental retardation, cryptorchidism, lymphatic dysplasia

HOCM: hypertrophic obstructive cardiomyopathy;
*P3 and P10 refer to percentile lines for height according to age, with the normal range of variation defined as P3-P97 inclusive
Definitive NS: 1 "A" plus one other major sign or two minor signs; 1 "B" plus two major signs or three minor signs
adapted from [2]

« Essential » syndromes

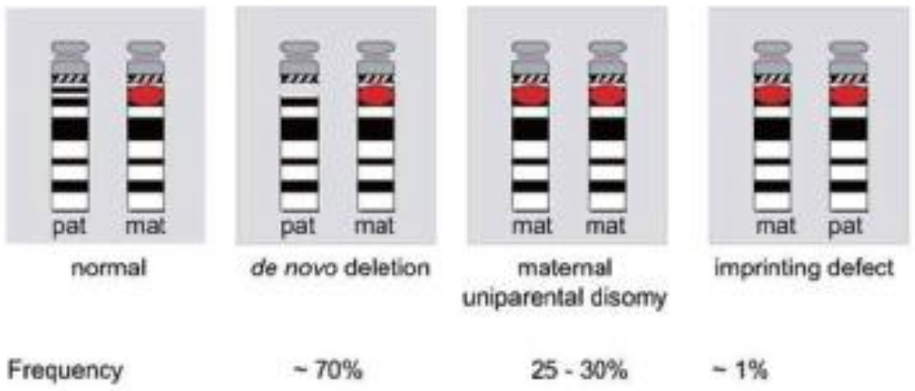
Symptoms

- Severe hypotonia and feeding difficulties in early infancy
- In later infancy or early childhood by excessive eating and gradual development of morbid obesity
- Developmental delay with distinctive behavioral phenotype (temper tantrums, manipulative behavior, and obsessive-compulsive characteristics)
- Hypogonadism
- Short stature
- Characteristic facial features (narrow bifrontal diameter, almond-shaped palpebral fissures, narrow nasal bridge, thin vermilion of the upper lip with down-turned corners of the mouth)
- Hypopigmentation

Genetic mechanisms

Recurrence risk mostly low

- Deletion paternal allele 15q11q13 (~75%)
- Maternal disomy 15q11q13 (~24%)
- Imprinting disorder (~1%)



Differential diagnosis

- Neonatal hypotonia
  - Congenital myotonic dystrophy type I (*DMPK)*
  - Spinal muscular atrophy (*SMN1*).

Neonatal hypotonia: always exclude MD type I, SMA and AS/PWS!!!

- Developmental delay and obesity
  - Angelman syndrome (15q11q13)
  - Maternal uniparental disomy 14
  - Albright hereditary osteodystrophy (*GNAS*)
  - Bardet-Biedl syndrome
  - Cohen syndrome (*VPS13B)*
  - Borjeson-Forssman-Lehmann syndrome (*PHF6)*
  - Alstrom syndrome (*ALMS1)*
  - 1p36 deletion

Treatment

- Growth hormone supplementation
  - ↓Hyperpaghia
  - ↓Obesity

Wout
20 jaar

Tamira
7 jaar

Martin
15 jaar

Lou
4 jaar

Evi
35 jaar

« Essential » syndromes

FIG. 1. A photographic natural history of Sotos syndrome shows the patient as a child (specific age unknown), at about 11–12 years, and currently, at 63 years. She has features characteristic of Sotos syndrome including tall stature, typical facial appearance with high forehead and small chin, and those which can be associated with Sotos syndrome and aging, including diffuse contractures and wrinkled skin.

FIG. 2. Serial photographs of a Spanish male with Sotos syndrome. Note that the chin becomes less prominent, while the high forehead with a receded hairline and the malar hypoplasia persist.

Sotos syndrome

Symptoms

- Distinctive facial appearance (broad and prominent forehead, sparse frontotemporal hair, downslanting palpebral fissures, malar flushing, long and narrow face, long chin)
- Learning disability (early developmental delay, mild to severe intellectual impairment)
- Overgrowth (height and/or head circumference ≥2 SD above the mean)

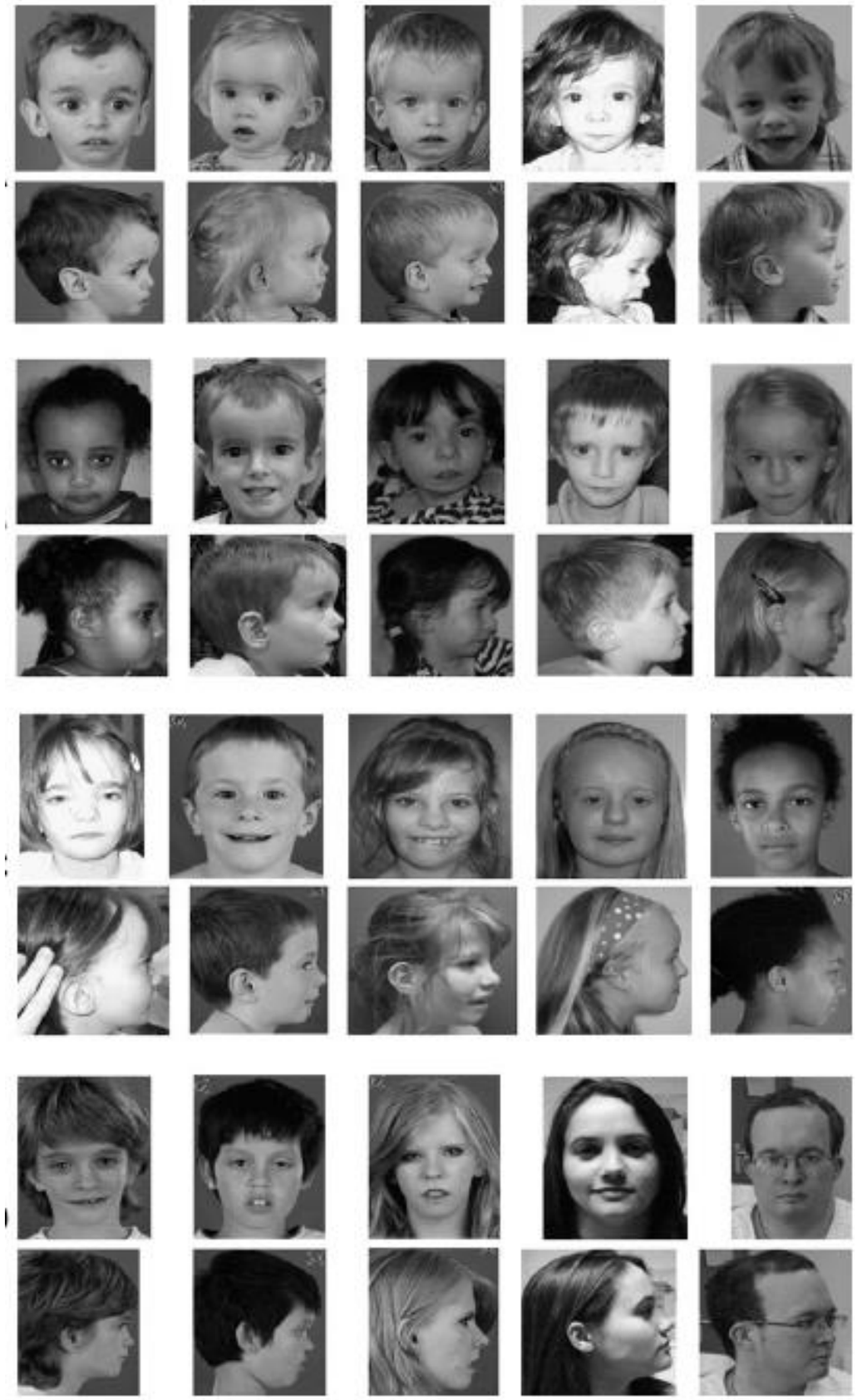
Genetic mechanisms

Recurrence risk mostly low

- Mutation *NSD1* gene
- Deletion including the *NSD1* gene

Differential diagnosis

- Weaver syndrome (*EZH2*)
- Malan syndrome (*NFIX*)
- Beckwith-Wiedemann syndrome (11p15 or *CDKN1C)*
- Simpson-Golabi-Behmel syndrome (*GPC3)*
- *PTEN*-hamartoma tumor syndrome
- Benign familial macrocephaly
- Fragile X syndrome (*FMR1*)
- Gorlin Syndrome (*PTCH*)



Silver-Russell syndrome

Major criteria

- Intrauterine growth retardation/small for gestational age (<10th percentile)
- Postnatal growth with height/length <3rd percentile
- Normal head circumference (3rd-97th percentile)
-Limb, body, and/or facial asymmetry

Minor criteria

- Short (arm) span with normal upper- to lower-segment ratio
- Fifth finger clinodactyly
- Triangular facies
- Frontal bossing/prominent forehead

Supportive criteria

- Café au lait spots or skin pigmentary changes
- Genitourinary anomalies (cryptorchidism, hypospadias)
- Motor, speech, and/or cognitive delays
- Feeding disorder
- Hypoglycemia

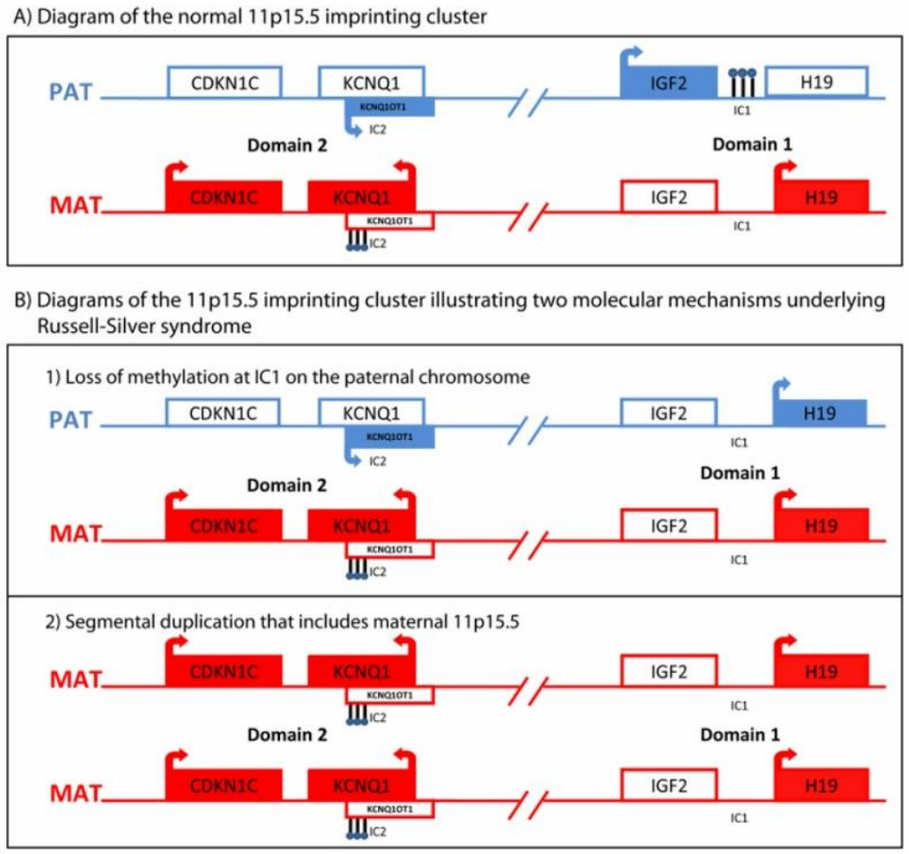
Genetic mechanisms

Recurrence risk mostly low

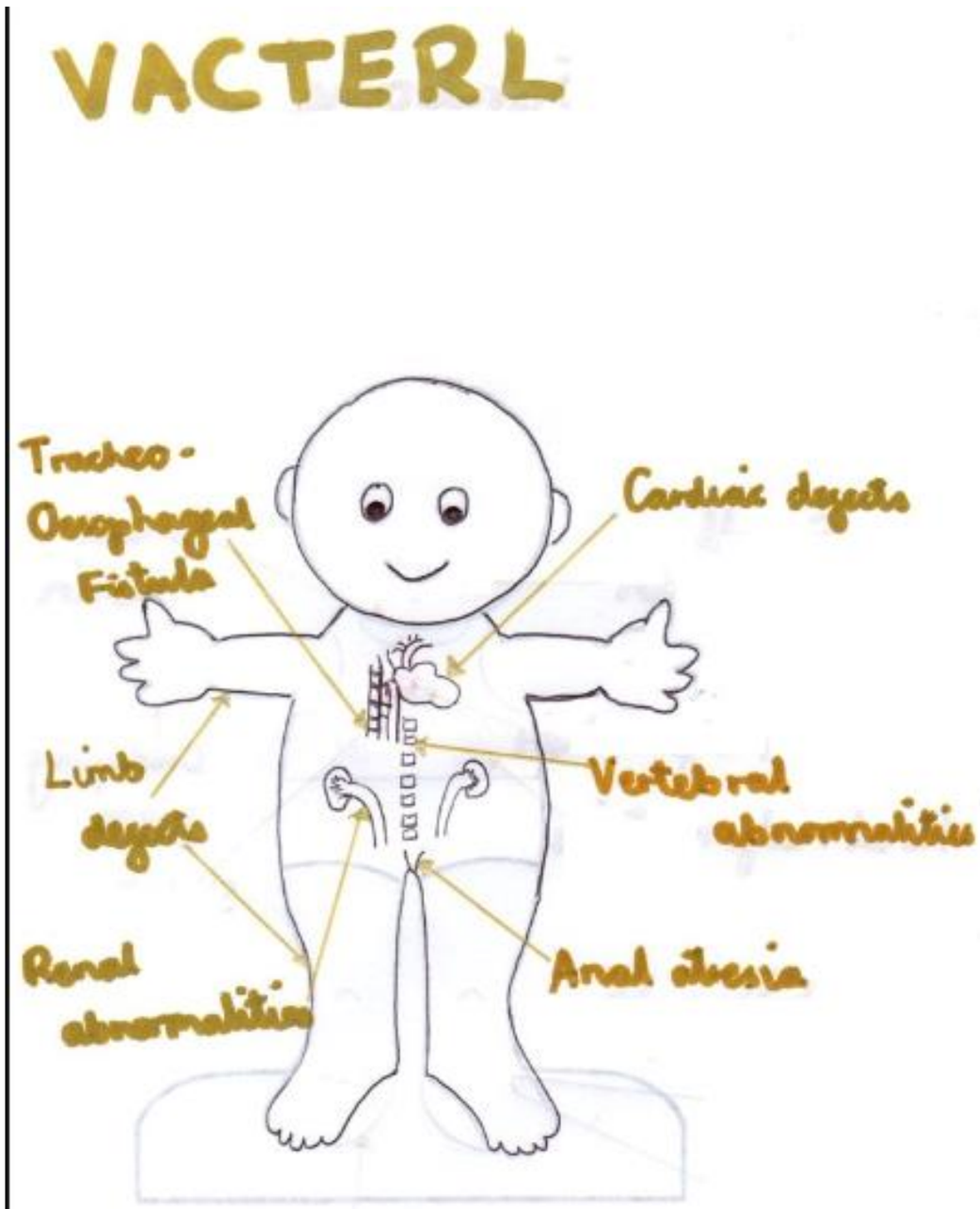
- Chromosome 11p15 related SRS
- Chromosome 7 related SRS (UPD mat)

Differential diagnosis

- Any condition associated with IUGR/SS
- Chromosomal anomalies
- Disorders of DNA repair (Fanconi, Nijmegen, etc)
- 3M syndrome
- FAS
- IMAGe (maternally inherited *CDKN1C*)
- Any skeletal dysplasia



VATER/VACTERL-H sequence



Symptoms VATER/VACTERL

V = **V**ertebral defects

A = **A**nal atresia

C = **C**ardiac malformations

TE = **T**racheo**E**sophageal fistula + esophageal atresia

R = **R**adial (preaxial)/ **R**enal dysplasia

L = **L**imb anomalies

Certain diagnosis: 3 or more criteria

Possible diagnosis: 2 criteria

Genetic mechanisms

Mechanism unknown

Recurrence risk mostly low (2-3% for parents of an affected child)

Differential diagnosis
- Chromosomal anomaly
- Townes Brocks syndrome
- MURCS
- Fanconi anemia
- OAVS

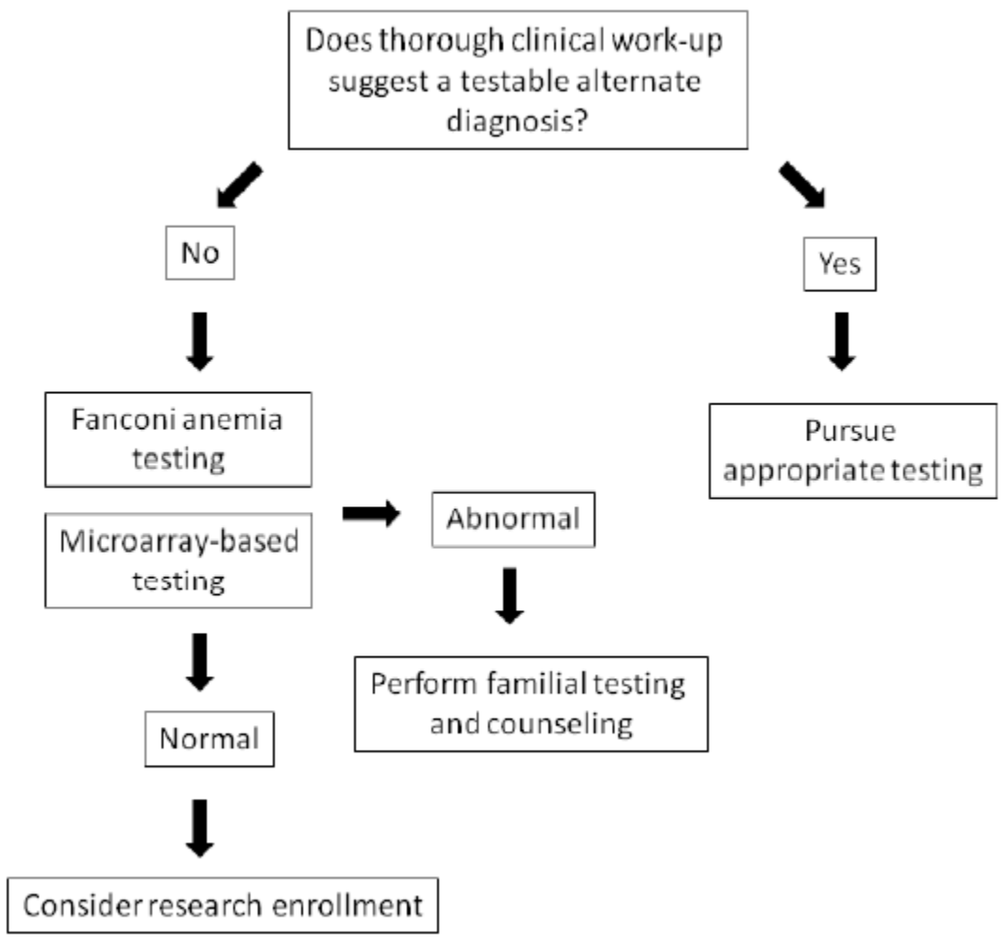
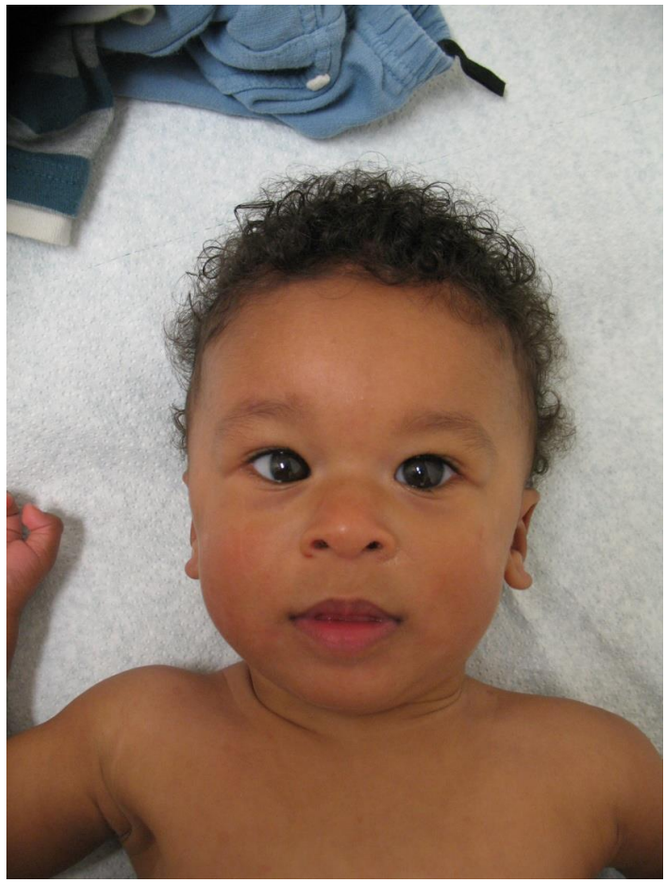
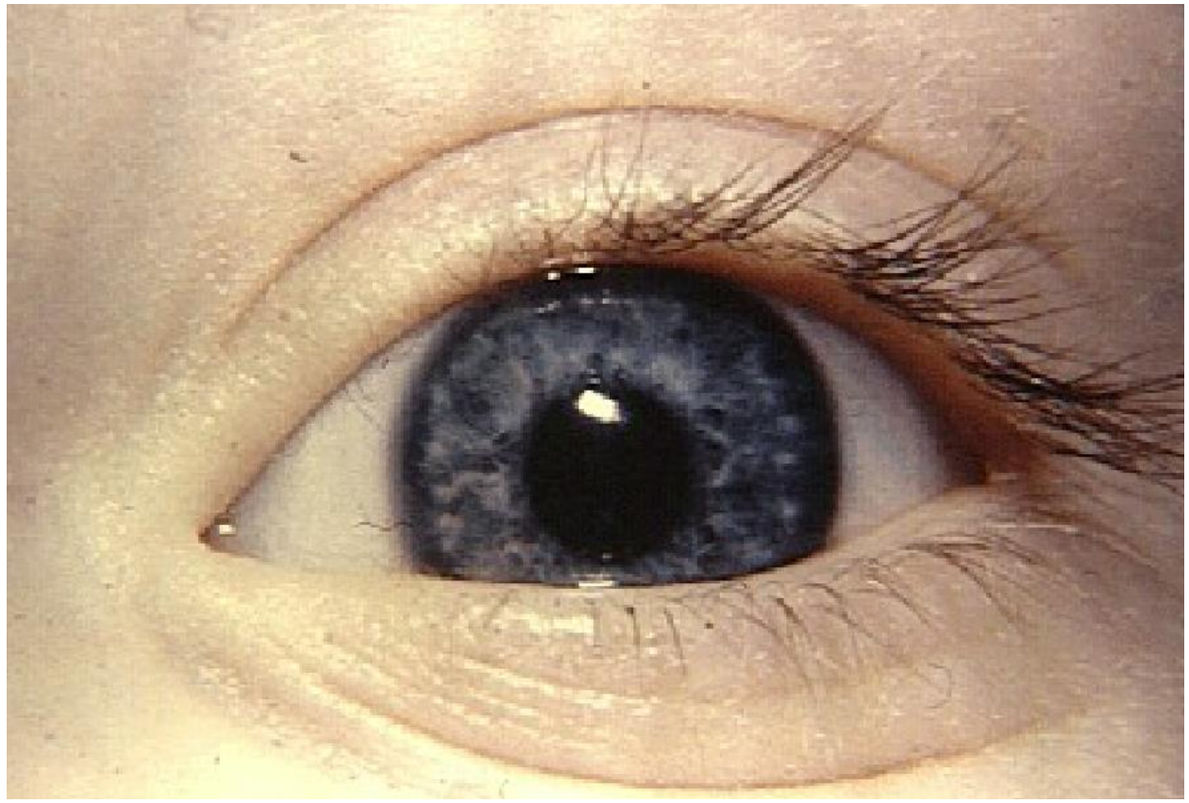


Table 1 Differential diagnosis: conditions with multiple features in common with VACTERL association

Condition	Features in common with VACTERL association	Features distinct from VACTERL association	Cause(s)
Alagille syndrome	Vertebral anomalies, cardiac anomalies; may have renal anomalies	Bile duct paucity and cholestasis, ophthalmologic anomalies (especially posterior embryotoxon), neurological anomalies, characteristic facial appearance	Heterozygous mutations in *JAG1, NOTCH2*
Baller-Gerold syndrome	Radial anomalies, may also include anal anomalies	Craniosynostosis, skin anomalies	Heterozygous mutations in *RECQL4*
CHARGE syndrome	Cardiac malformations, genitourinary anomalies; may also include TEF	Colobomata, choanal atresia, neurocognitive and growth impairment, ear anomalies, cranial nerve dysfunction, characteristic facial features	Heterozygous mutations in *CHD7*
Currarino syndrome	Sacral malformations, ARM	Presacral mass	Heterozygous mutations/ deletions of *HLXB9*
22q11.2 deletion syndrome (also known by other names, such as DiGeorge syndrome or velocardio-facial syndrome)	Cardiac malformations, renal anomalies, other VACTERL-type anomalies also reported	Hypocalcemia, palatal anomalies, learning difficulties, immune dysfunction, neuropsychiatric disturbances, characteristic facial features,	Deletion of one copy of chromosome 22q11.2
Fanconia anemia	Virtually all features of VACTERL association may occur; radial anomalies are considered an especially key feature	Hematologic anomalies, pigmentation anomalies	Recessive or X-linked mutations in multiple genes; typically detected by chromosomal breakage studies
Feingold syndrome	GI atresia, cardiac defects, renal anomalies	Brachymesophalangy, toe syndactyly, microcephaly, cognitive impairment, characteristic facial appearance,	Heterozygous mutations in *MYCN*
Fryns syndrome	GI malformations, cardiac defects, GU anomalies	Diaphragmatic defects, neurocognitive impairment, characteristic facial appearance,	No well-characterized unifying causes
Holt-Oram syndrome	Cardiac malformations, limb malformations	Cardiac conduction disease (also reported in VACTERL association)	Heterozygous mutations in *TBX5*
Müllerian duct aplasia, renal aplasia, and cervico-thoracic somite dysplasia (MURCS assoc-iation); also known as Mayer-Rokitansky- Küster-Hauser syndrome type II	Vertebral anomalies, renal anomalies, GU anomalies and anorectal malformations; may also have cardiac and limb anomalies	Syndactyly and hearing loss have been described	Unknown; likely heterogeneous
Oculo-auriculo-vertebral syndrome	Vertebral anomalies, cardiac abnormalities, limb abnormalities, urogenital anomalies	Ear anomalies (microtia), hemifacial microsomia, neurocognitive impairment, facial clefts (also described in patients with VACTERL association)	Unknown; likely heterogeneous
Opitz G/BBB syndrome	Anal anomalies, heart defects, TEF, hypospadias	Hypertelorism, syndactyly	X-linked form: heterozygous/ hemizygous mutations in *MID1*; autosomal dominant form: some cases due to deletion 22q11.2
Pallister-Hall syndrome	Imperforate anus, renal anomalies, limb anomalies (postaxial polydactyly should serve as a clue for the Pallister-Hall syndrome)	Hypothalamic hamartoma, bifid epiglottis (ranging to more severe types of clefts), nail hypoplasia	Heterozygous mutations in *GLI3*
Townes-Brocks syndrome	Imperforate anus, thumb anomalies, renal anomalies, cardiac anomalies	Dysplastic ears, hearing loss	Heterozygous mutations in *SALL1*






SCHOOL DAYS
1932

Symptoms

- Cardiovascular disease (elastin arteriopathy, peripheral pulmonary stenosis, supravalvar aortic stenosis)
- Distinctive facies (Williams elfin face)
- Connective tissue abnormalities
- Intellectual disability (specific cognitive profile and unique personality)
- Growth abnormalities
- Endocrine abnormalities (hypercalcemia, hypercalciuria, hypothyroidism, and early puberty).
-Hypotonia and hyperextensible joints

Genetic mechanisms

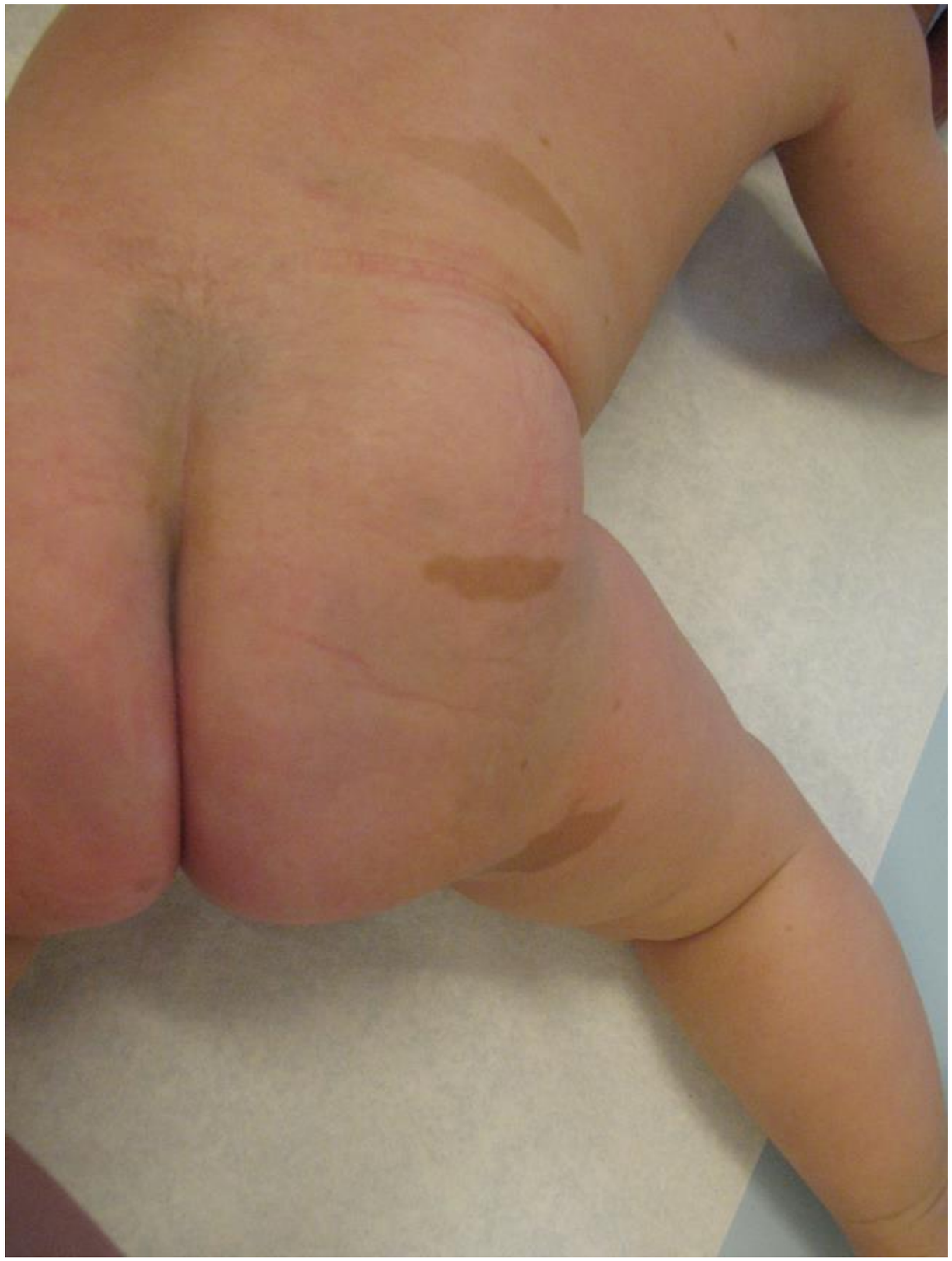
Recurrence risk mostly low

– Deletion of the 7q11.23 region including the *ELN* gene

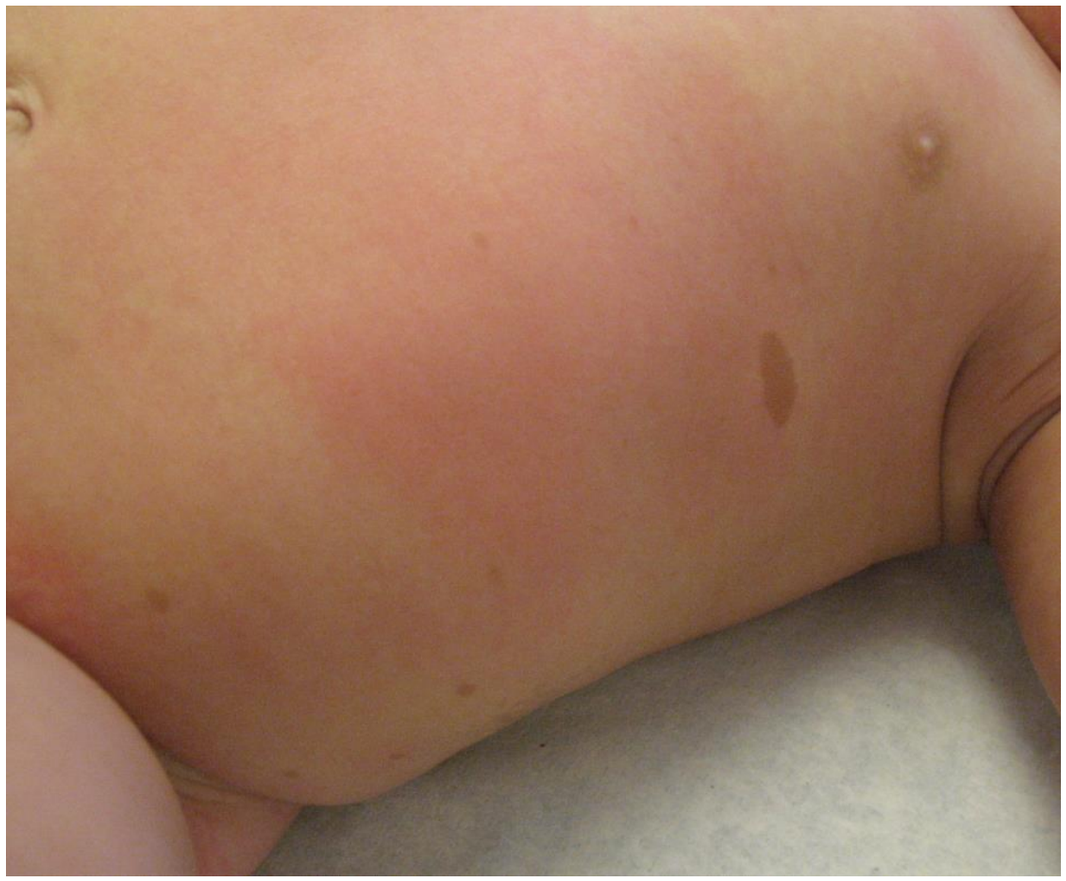
Differential diagnosis

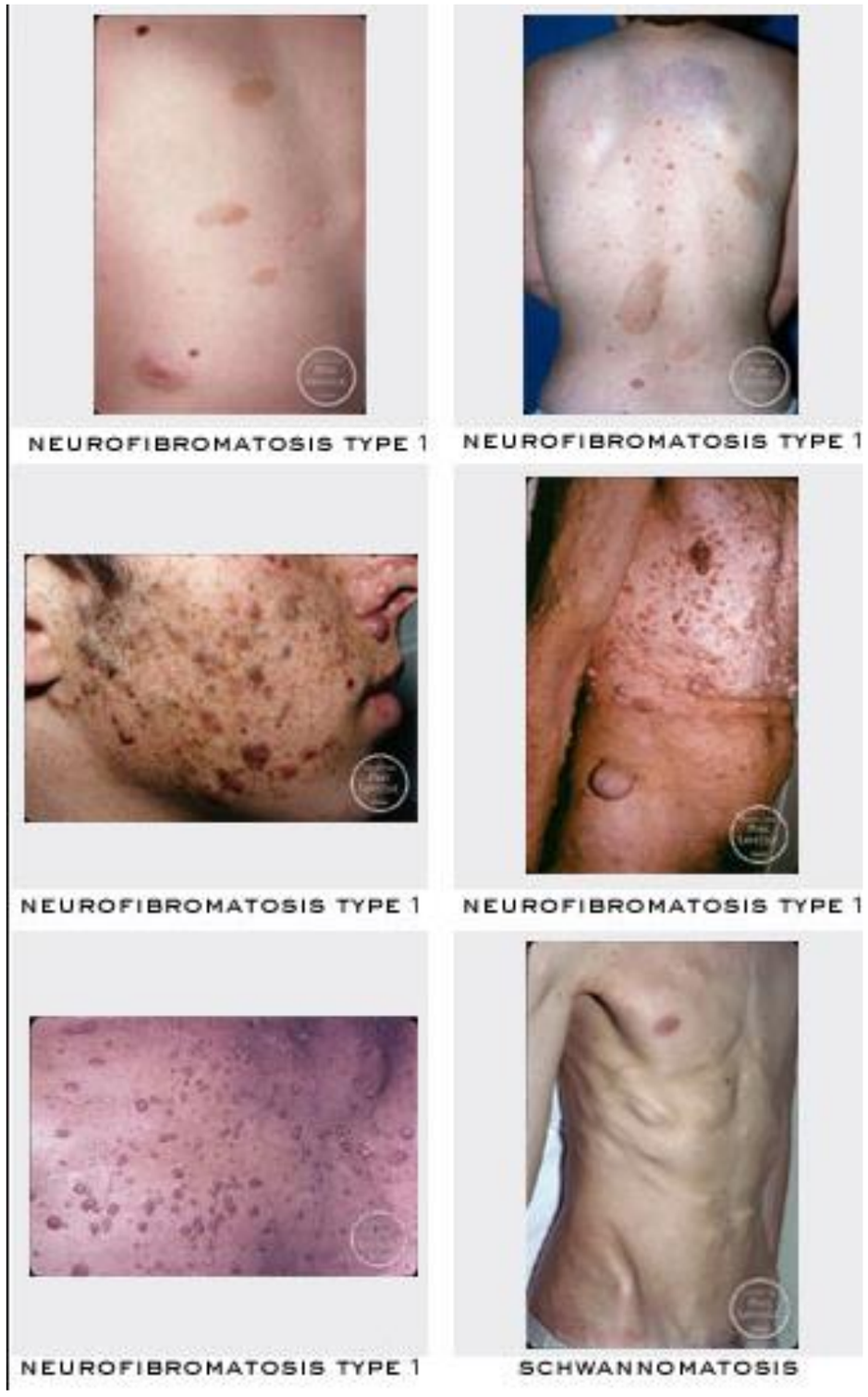
- Noonan syndrome
- 22q11 deletion (DiGeorge syndrome)
- Smith-Magenis syndrome
- Kabuki syndrome
- fetal alcohol syndrome.

« Essential » syndromes



- 5 month old baby
- café-au-lait spots, increasing in number and size
- normal development

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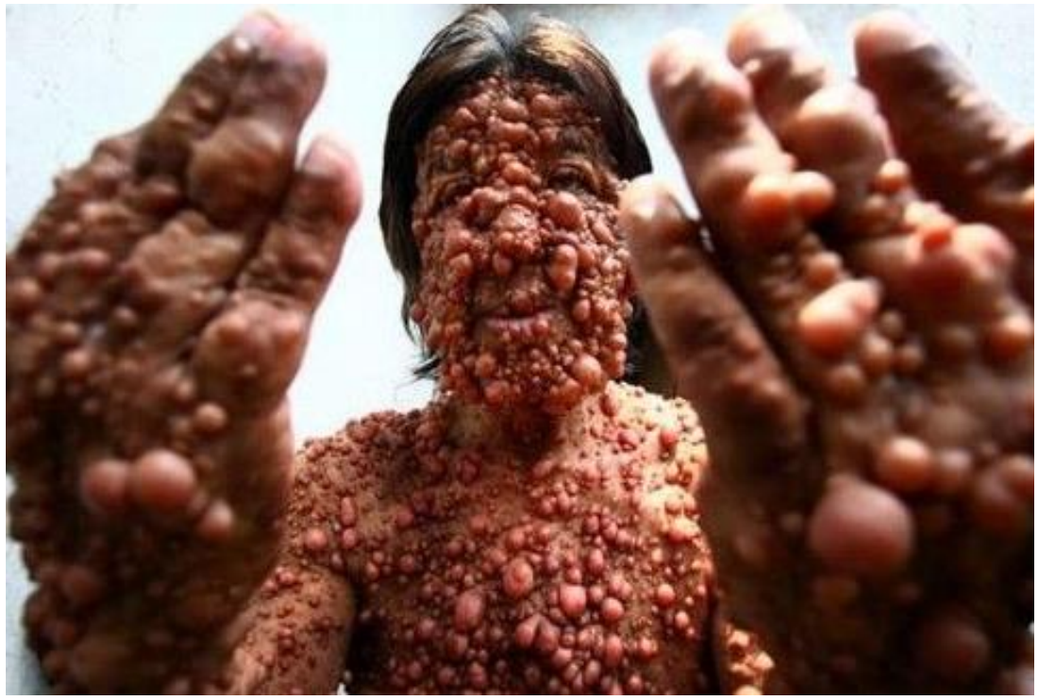
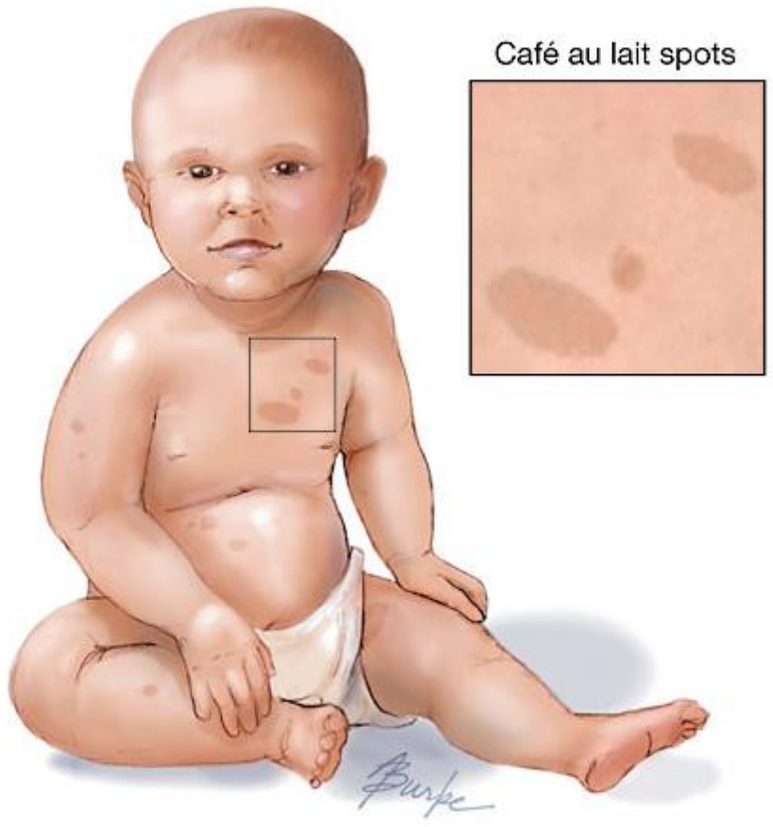
SCHWANNOMATOSIS




Café au lait spots

Neurofibromatosis type I/ Von Recklinghausen syndrome

Symptoms

- Six or more **café au lait macules** >5 mm in greatest diameter in prepubertal individuals and >15 mm in greatest diameter in postpubertal individuals
- Two or more **neurofibromas** of any type or one **plexiform neurofibroma**
- Freckling in the axillary or inguinal regions
- Optic glioma
- Two or more Lisch nodules (iris hamartomas)
- A distinctive osseous lesion such as sphenoid dysplasia or tibial pseudarthrosis

A first degree relative (parent, sib, or offspring) with **NF1** as defined by the above criteria

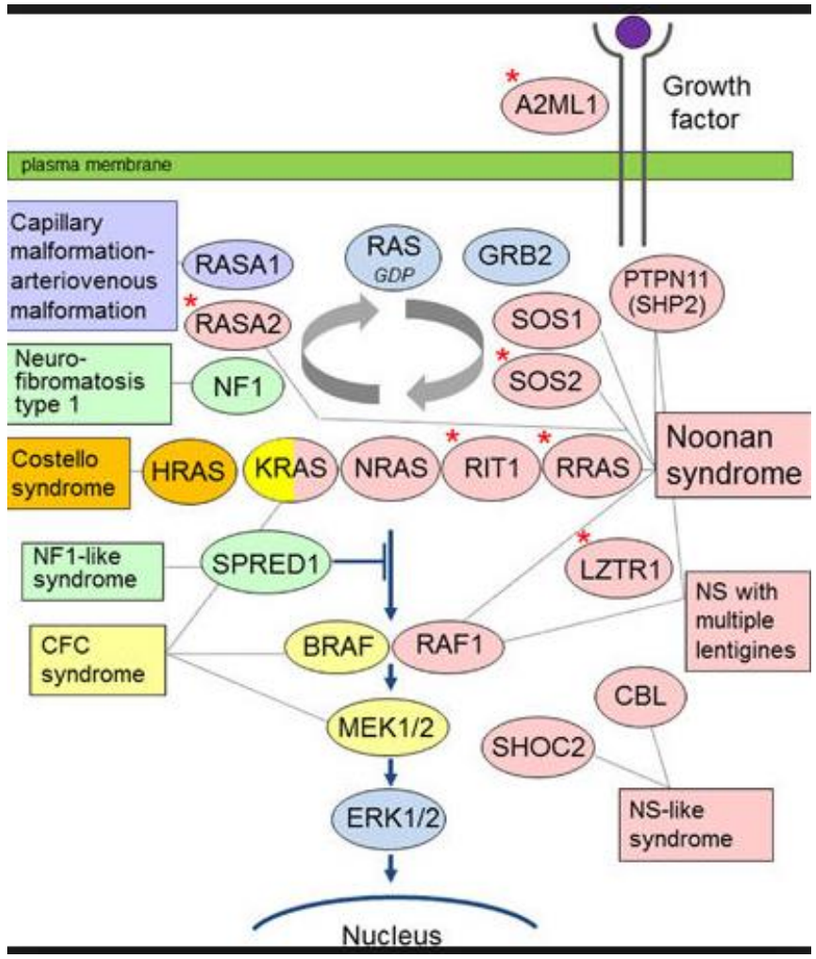
Genetic mechanisms

Autosomal dominant; 50% de novo

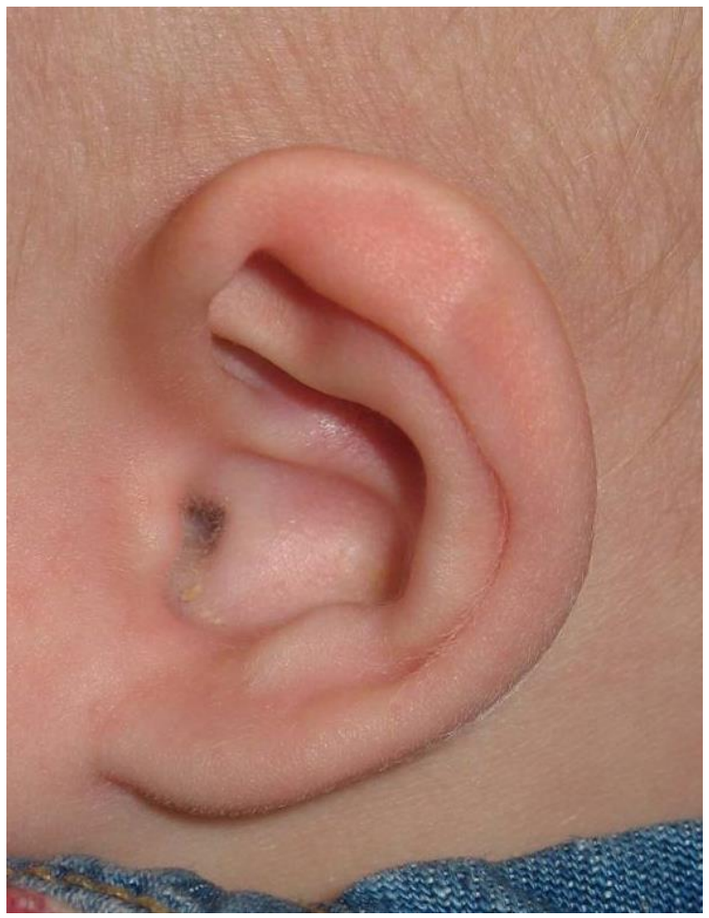
- Haploinsufficieny of *NF1* (95% mutations)

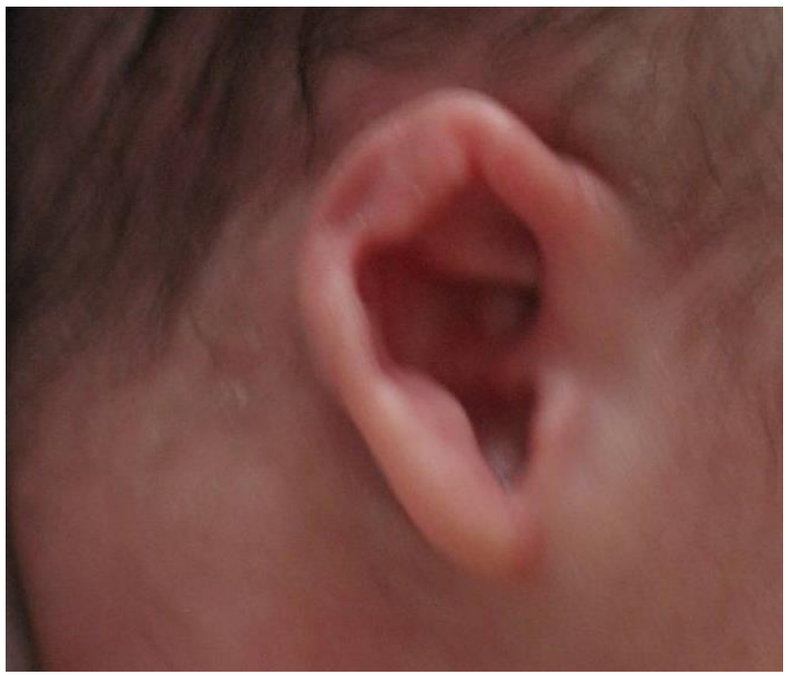
Differential diagnosis

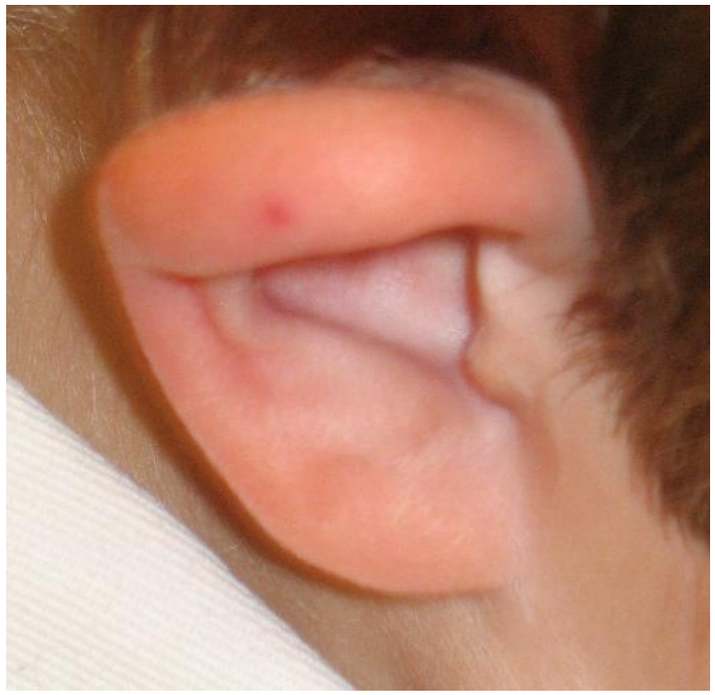
- Legius syndrome (*SPRED1*)
- Noonan syndrome (with lentigines)
- Constitutional mismatch repair deficiency (« biallelic Lynch syndrome »)
- Fibrous dysplasia/McCune-Albright syndrome (*GNAS*)
- Piebald trait
- Neurofibromatosis type 2 (*NF2*)
- Schwannomatosis
- Infantile myofibromatosis
- Proteus syndrome

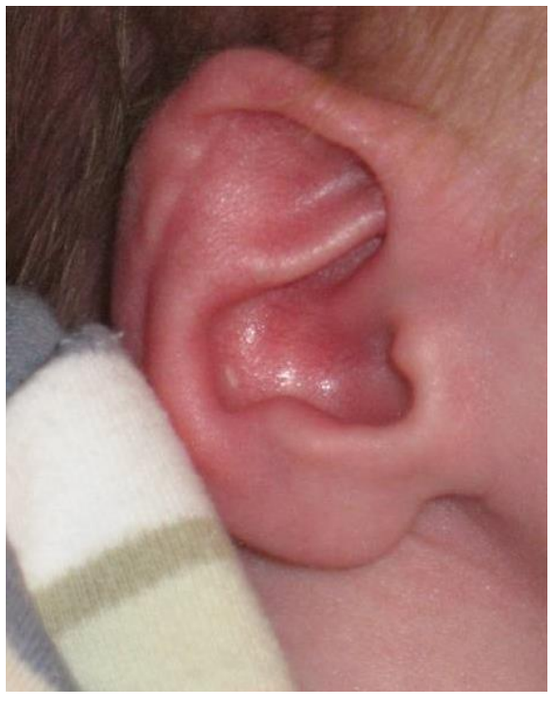


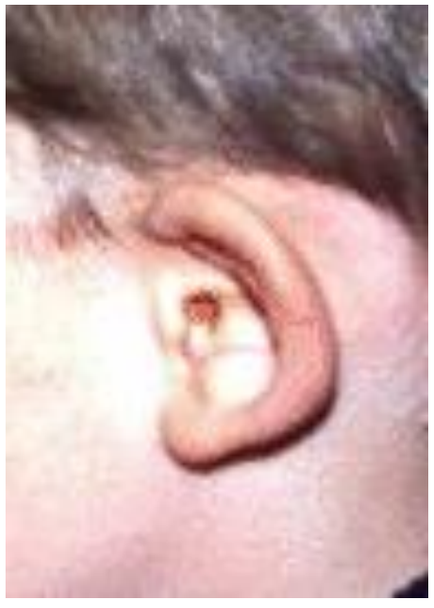
« Essential » syndromes

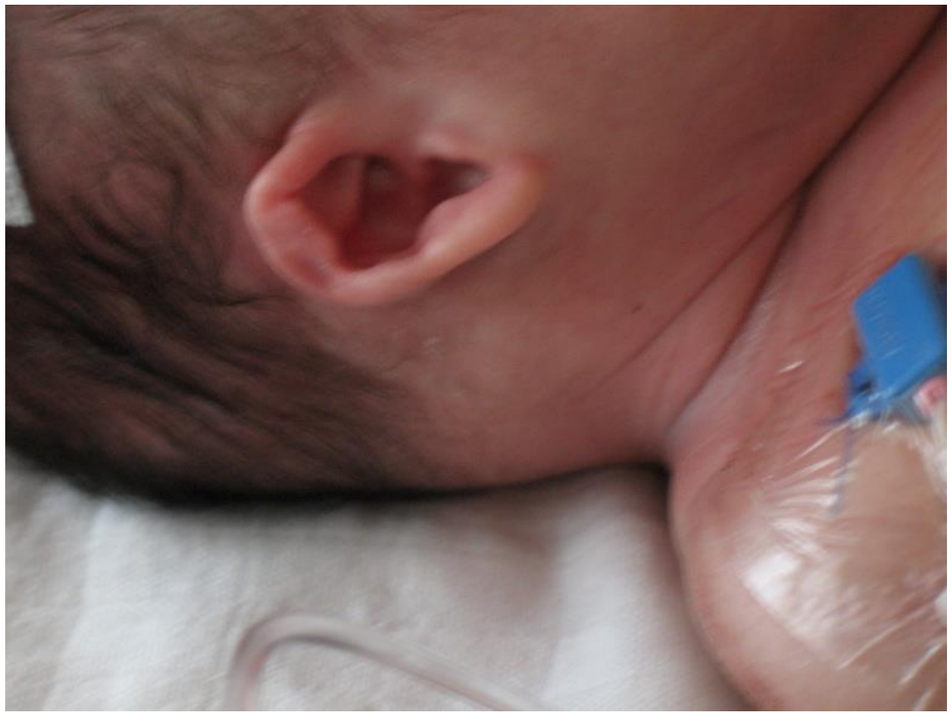


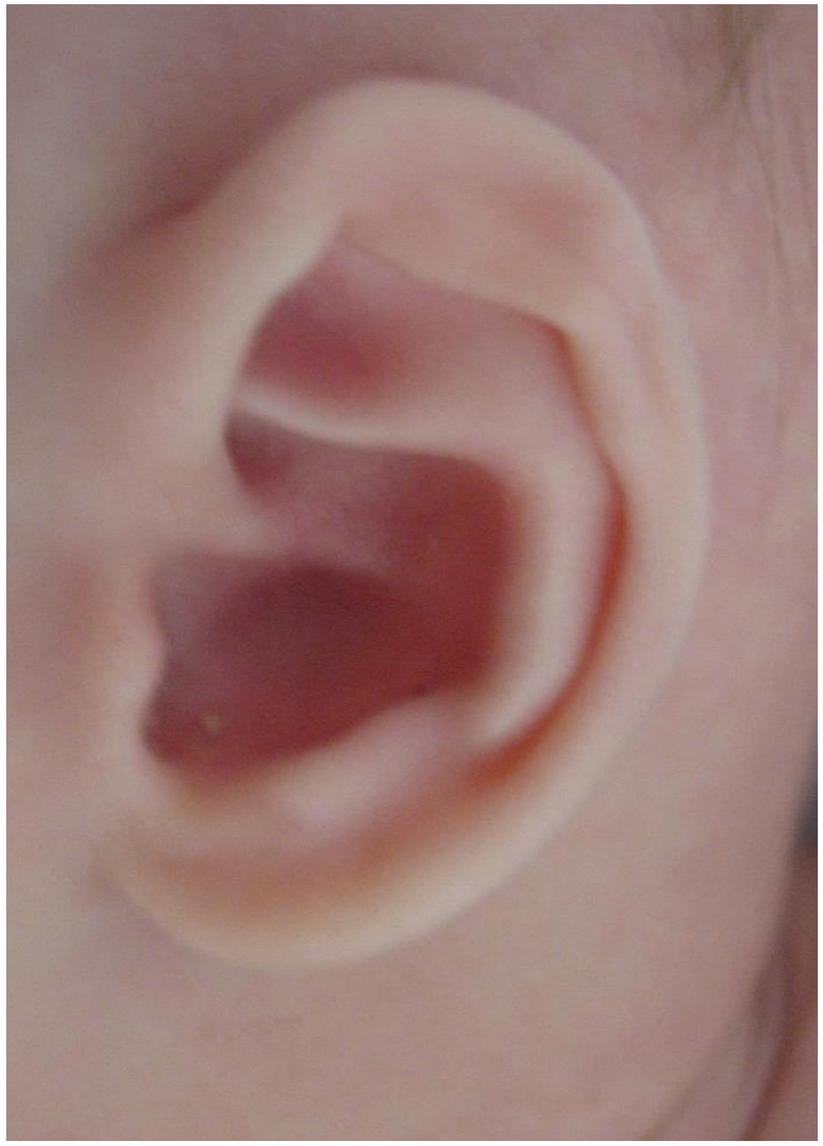


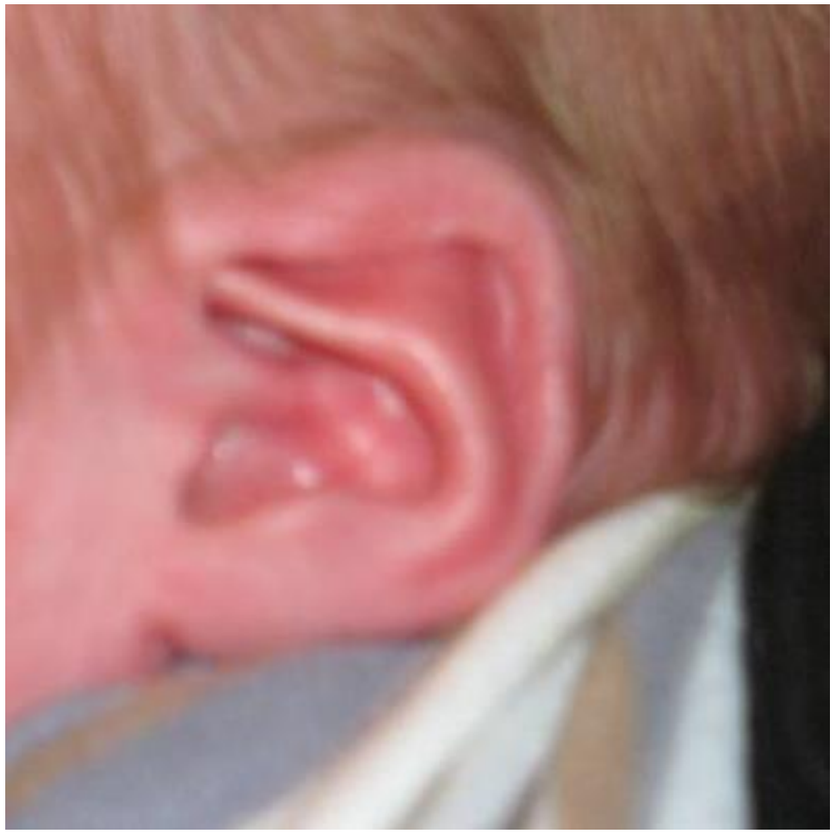












22q11 deletion syndrome
Di George syndrome/velocardiofacial syndrome

Symptoms

Congenital heart disease (conotruncal malformations; outflow tract)
Palatal abnormalities (velopharyngeal incompetence, short palate, hypotonia of velopharyngeal musculature, submucuous cleft palate, cleft palate)
Characteristic facial features (hypoplastic alae nasi)
Learning difficulties (20% normal IQ); most frequent genetic condition underlying schizofrenia
Immune deficiency (thymic hypoplasia)

Genetic mechanisms

Microdeletion syndrome; 93% de novo (7% inherited from a parent, RR 50%)

Also known as:
- Shprintzen syndroom
- DiGeorge syndroom
- Conotruncal face syndrome
- Cayler cardiofacial syndrome
- Catch22 (Cardiac defects, abnormal facies, thymic hypoplasia, cp & hypocalcemia)
- Sedlackova syndrome
-Takao syndrome

Differential diagnosis
- non-syndromic CP
- non-syndromic congenital cardiac malformation
- Goldenhar/OAVS
- CHARGE syndroom
- VATER/VACTERL-H
- Alagille syndrome
- Smith-Lemli-Opitz syndrome

Tools

How to diagnose?

Choix de l'analyse

- Analyse spécifique
- Analyse plus large

Type d'analyse

- Analyse d'expansions
- Séquençage Sanger
- MLPA (délétions/duplication/empreinte)
- Séquençage de la nouvelle génération (WES/WGS)
- Quantité d'ADN (CGH-array, SNP-array et cytogénétique)
- Distribution d'ADN (caryotype)

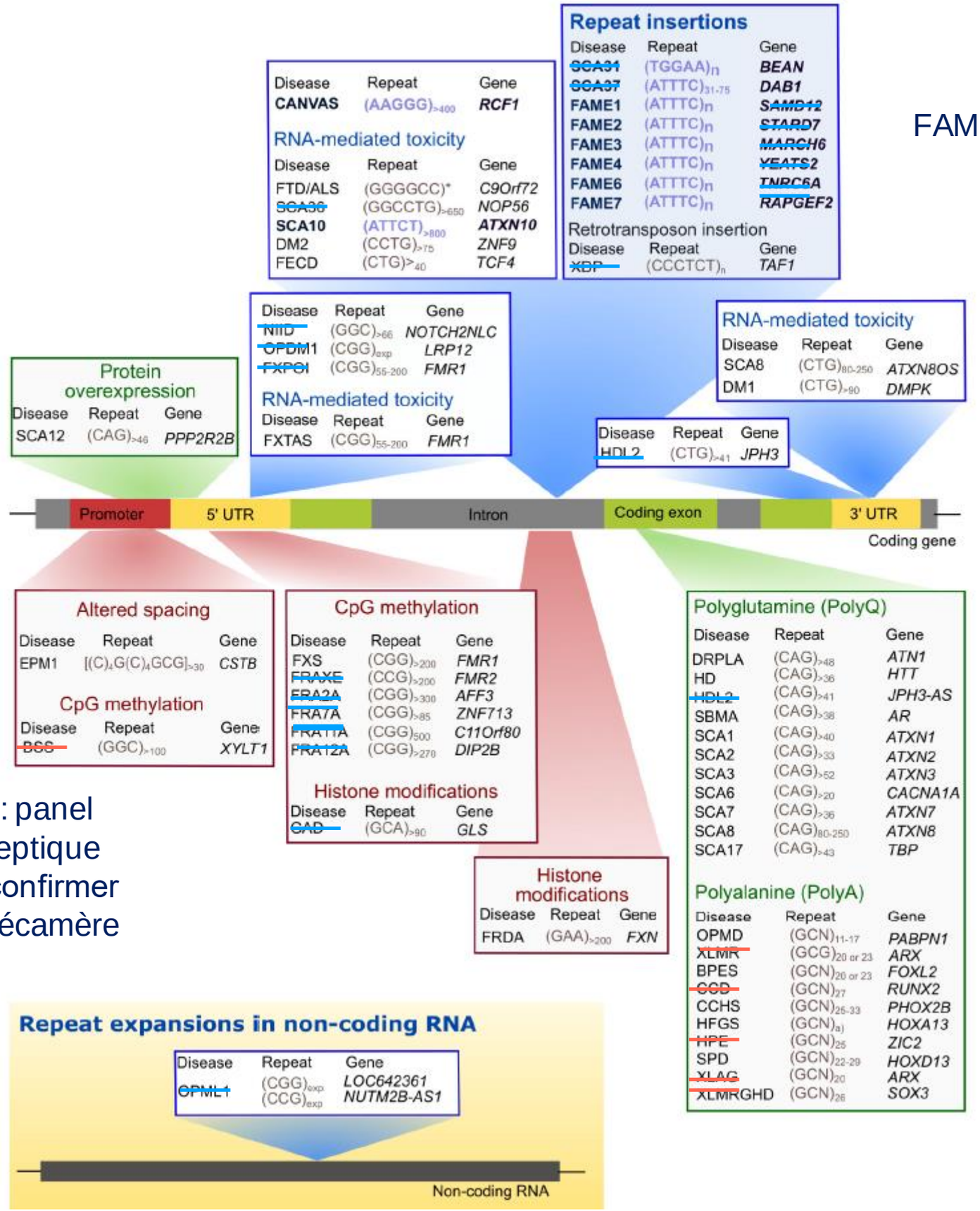
Interprétation

- En fonction des données cliniques
- Classification des variants
- Une analyse négative confirme l'absence d'une atteinte???
- La présence d'un variant confirme l'atteinte du cas???
- Type d'anomalie décrit pour l'atteinte clinique
- Une anomalie ne sera pas être confirmée si la technique n'en est pas capable

L'anomalie moléculaire ne sera pas confirmée si la technique n'en est pas capable

FAME: analyse diagnostique n'existe pas encore

Unverricht-Lundborg: panel encéphalopathie épileptique n'est pas capable de confirmer une expansion du dodécamère



Pattern recognition…

Phenomizer

http://compbio.charite.de/phenomizer/ — The Phenomizer - Clinical ...

Menu. Support the Phenomizer. Help. The Phenomize

Features. Diseases. Ontology.

Enter feature... search. reset.

HPO id.	Feature.
HP:0010704	1-2 finger syndactyly
HP:0005767	1-2 toe complete cutaneous syndactyly
HP:0010711	1-2 toe syndactyly
HP:0010706	1-3 finger syndactyly
HP:0001459	1-3 toe syndactyly
HP:0010707	1-4 finger syndactyly
HP:0010712	1-4 toe syndactyly
HP:0006088	1-5 finger complete cutaneous syndactyly
HP:0010708	1-5 finger syndactyly
HP:0010713	1-5 toe syndactyly
HP:0030300	10 pairs of ribs
HP:0000878	11 pairs of ribs
HP:0030306	11 thoracic vertebrae
HP:0001233	2-3 finger syndactyly
HP:0005709	2-3 toe cutaneous syndactyly
HP:0004691	2-3 toe syndactyly
HP:0010709	2-4 finger syndactyly
HP:0005768	2-4 toe cutaneous syndactyly
HP:0010714	2-4 toe syndactyly
HP:0010692	2-5 finger syndactyly
HP:0010715	2-5 toe syndactyly
HP:0008083	2nd-5th toe middle phalangeal hypoplasia
HP:0011939	3-4 finger cutaneous syndactyly
HP:0006097	3-4 finger syndactyly
HP:0009779	3-4 toe syndactyly
HP:0010710	3-5 finger syndactyly
HP:0010716	3-5 toe syndactyly

Page 1 of 424 Features 1 - 27 of 11443

Patient's Features.

HPO.	Feature.	Modifier.	Num diseases.

News

Info

- The Phenomizer is developed and maintained by Sebastian Köhler (see group website for more info).
- The Phenomizer Orphanet uses the latest Orphanet date and a different algorithm for ranking the differential diagnoses.

Please cite the following papers when you use this tool/HPO in your publications.

Köhler et al., Clinical diagnostics in human genetics with semantic similarity searches in ontologies.
Am J Hum Genet (2009) vol. 85 (4) pp. 457-64

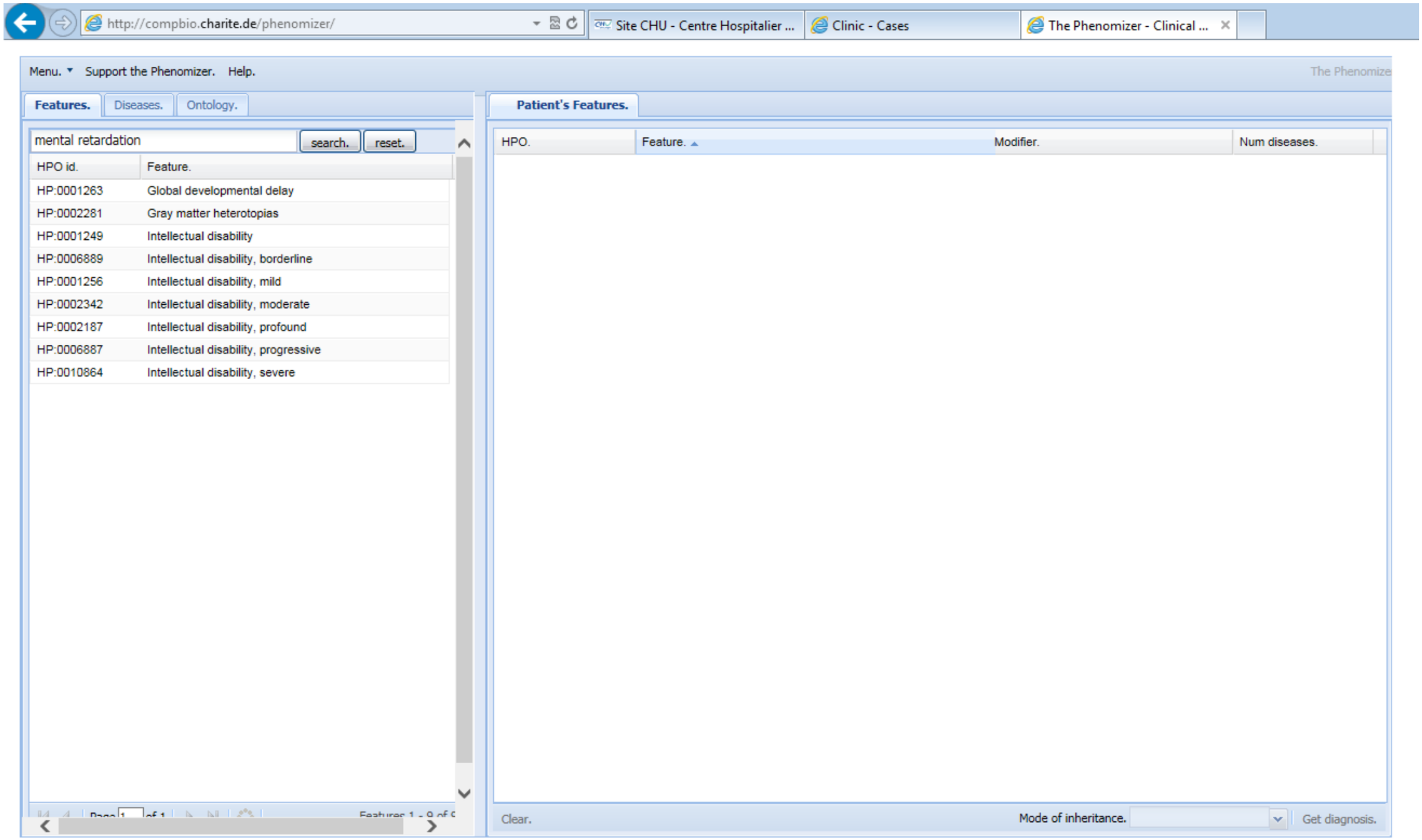
Köhler et al., The Human Phenotype Ontology in 2017.
Nucleic Acids Research (2017) doi: https://doi.org/10.1093/nar/gkw1039

Clear. Mode of inheritance. Get diagnosis.

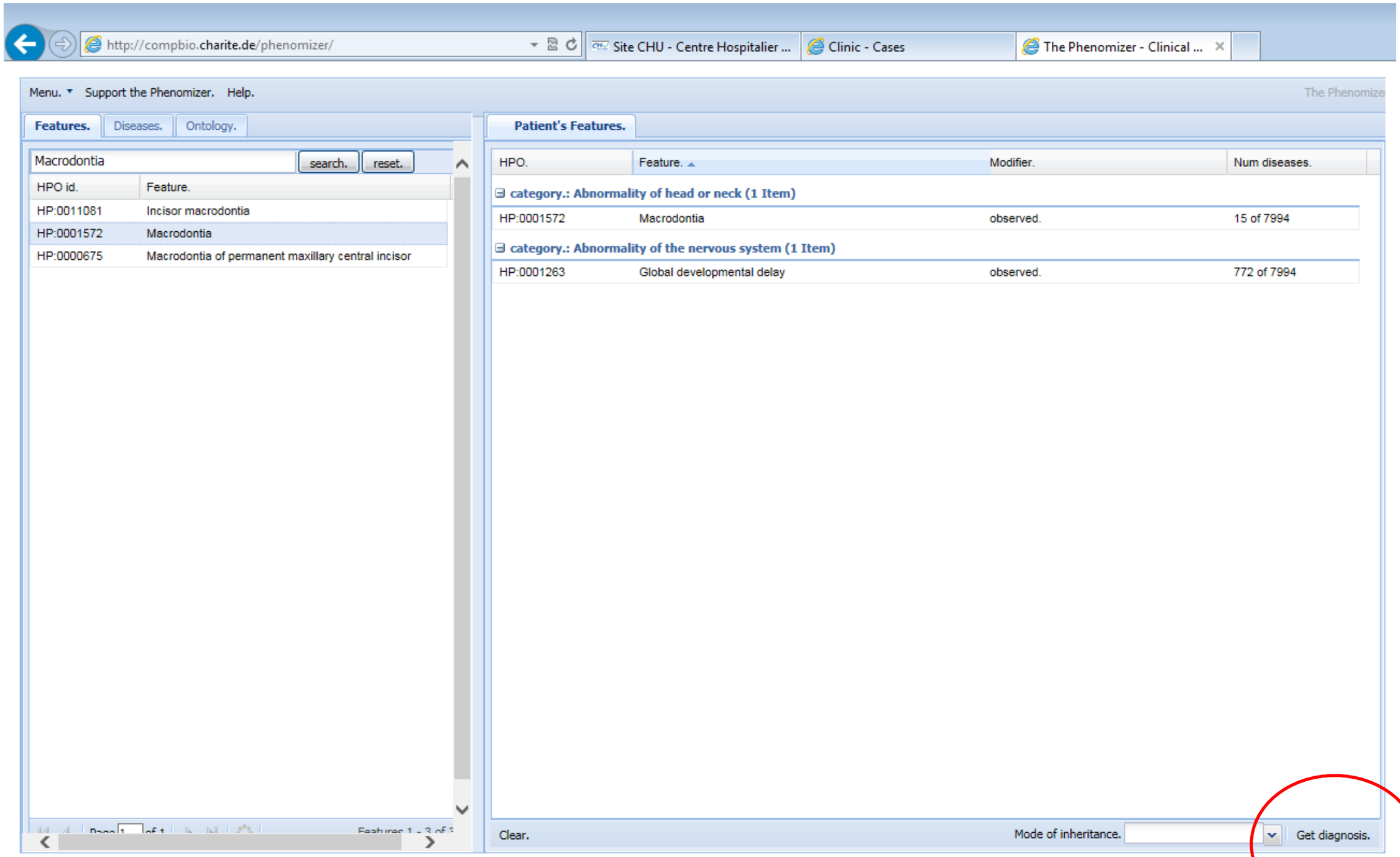
Phenomizer

- 10 year old boy
- developmental delay
- short stature
- dysmorphic features (hypertelorism, epicanthic folds, macrodontia)

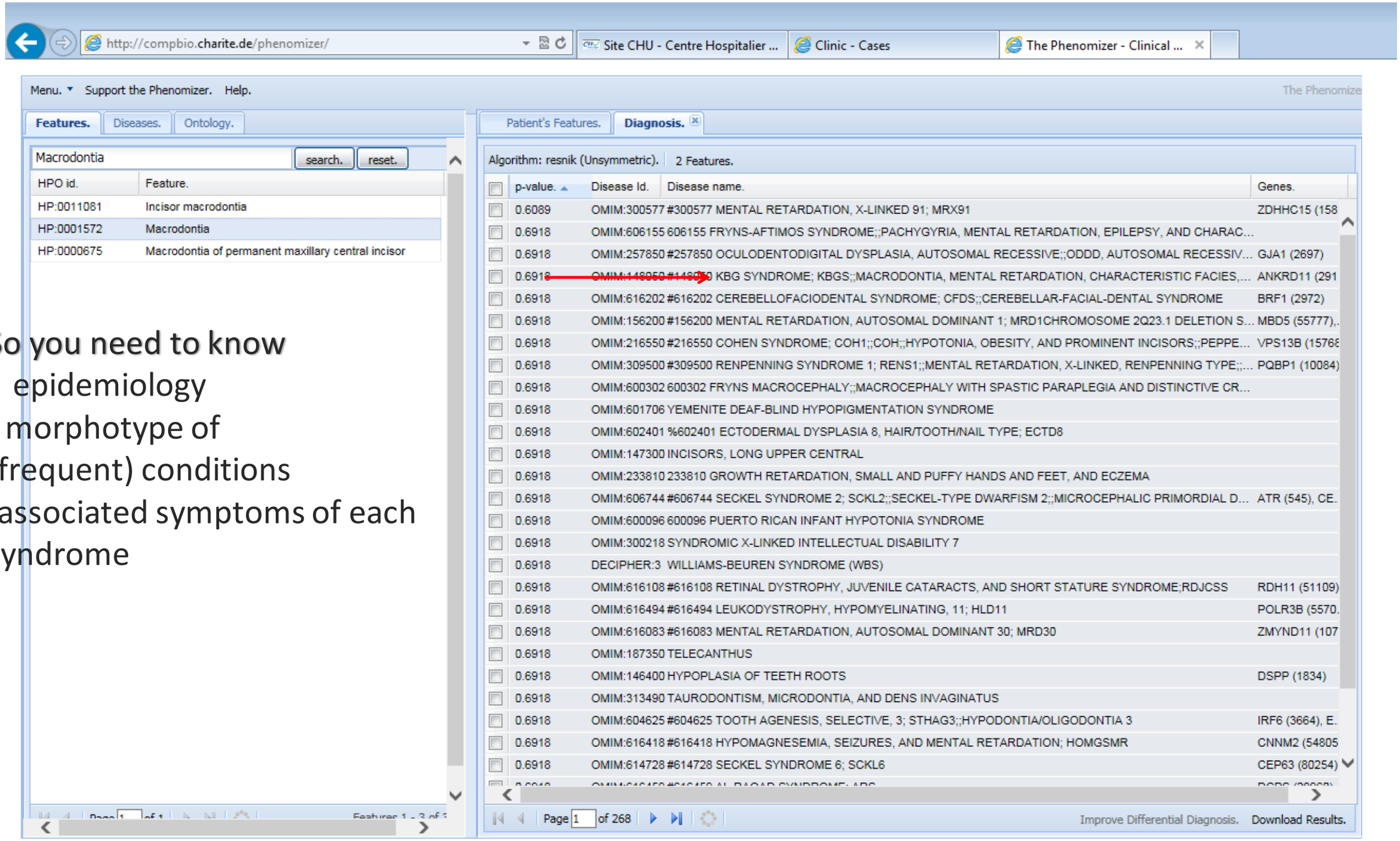
Phenomizer


http://compbio.charite.de/phenomizer/
Site CHU - Centre Hospitalier ...
Clinic - Cases
The Phenomizer - Clinical ...
Menu.
Support the Phenomizer.
Help.
Features.
Diseases.
Ontology.
mental retardation
search.
reset.
HPO id.
Feature.
HP:0001263 Global developmental delay
HP:0002281 Gray matter heterotopias
HP:0001249 Intellectual disability
HP:0006889 Intellectual disability, borderline
HP:0001256 Intellectual disability, mild
HP:0002342 Intellectual disability, moderate
HP:0002187 Intellectual disability, profound
HP:0006887 Intellectual disability, progressive
HP:0010864 Intellectual disability, severe
Patient's Features.
HPO.
Feature.
Modifier.
Num diseases.
Clear.
Mode of inheritance.
Get diagnosis.

Phenomizer


http://compbio.charite.de/phenomizer/
Site CHU - Centre Hospitalier ...
Clinic - Cases
The Phenomizer - Clinical ...
Menu.
Support the Phenomizer.
Help.
Features.
Diseases.
Ontology.
Macrodontia
search.
reset.
HPO id.
Feature.
HP:0011081
Incisor macrodontia
HP:0001572
Macrodontia
HP:0000675
Macrodontia of permanent maxillary central incisor
Patient's Features.
HPO.
Feature.
Modifier.
Num diseases.
category.: Abnormality of head or neck (1 Item)
HP:0001572
Macrodontia
observed.
15 of 7994
category.: Abnormality of the nervous system (1 Item)
HP:0001263
Global developmental delay
observed.
772 of 7994
Clear.
Mode of inheritance.
Get diagnosis.

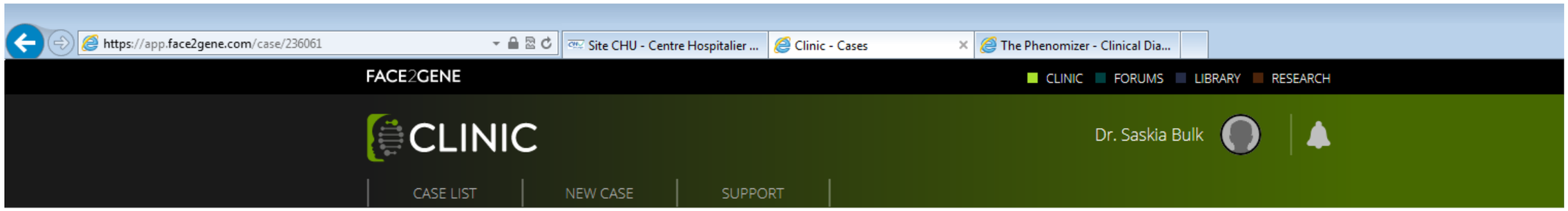
Phenomizer



So you need to know
- epidemiology
- morphotype of (frequent) conditions
-associated symptoms of each syndrome

Phenomizer

Face2Gene



Overview

Exam Visit

- 14 year old boy
- developmental delay
- dysmorphic features (hypertelorism, epicanthic folds, hooded eyelids, synophris, arched eyebrows)

- Cornelia de Lange – light?

CLINICAL GENETICS An International Journal of Genetics, Molecular and Personalized Medicine

Clin Genet 2016: 89: 74–81

CLINICAL GENETICS
doi: 10.1111/cge.12564

Short Report

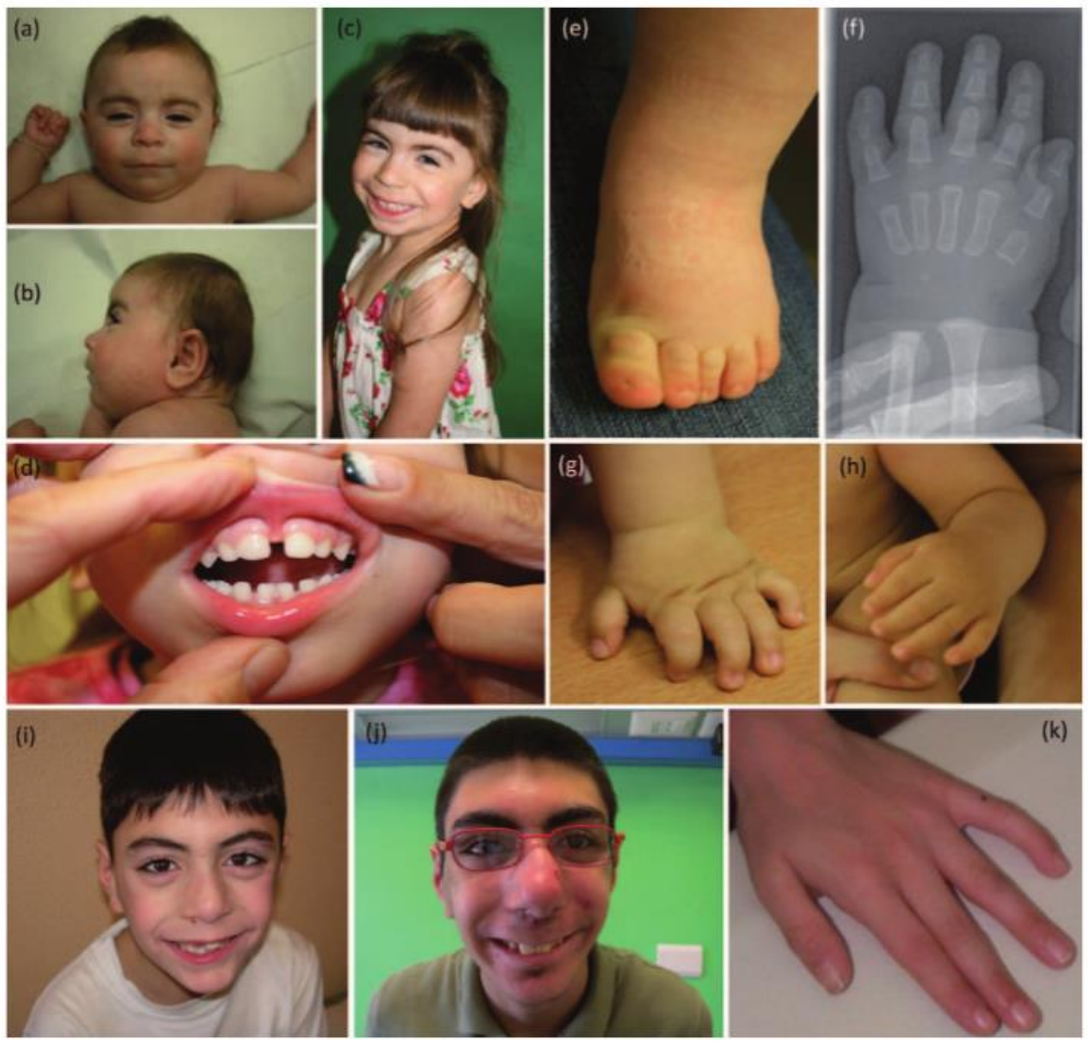
Broadening of cohesinopathies: exome sequencing identifies mutations in *ANKRD11* in two patients with Cornelia de Lange-overlapping phenotype

Parenti I., Gervasini C., Pozojevic J., Graul-Neumann L., Azzollini J., Braunholz D., Watrin E., Wendt K.S., Cereda A., Cittaro D., Gillessen-Kaesbach G., Lazarevic D., Mariani M., Russo S., Werner R., Krawitz P., Larizza L., Selicorni A., Kaiser F.J. Broadening of cohesinopathies: exome sequencing identifies mutations in *ANKRD11* in two patients with Cornelia de Lange-overlapping phenotype.
Clin Genet 2016: 89: 74–81. © John Wiley & Sons A/S. Published by John Wiley & Sons Ltd, 2015

Cornelia de Lange syndrome (CdLS) and KBG syndrome are two distinct developmental pathologies sharing common features such as intellectual disability, psychomotor delay, and some craniofacial and limb abnormalities. Mutations in one of the five genes *NIPBL*, *SMC1A*, *SMC3*, *HDAC8* or *RAD21*, were identified in at least 70% of the patients with CdLS.

I. Parenti[a,b], C. Gervas
J. Pozojevic[b],
L. Graul-Neumann[c],
J. Azzollini[a], D. Braun
E. Watrin[d], K.S. Wendt
A. Cereda[f], D. Cittaro[g]
G. Gillessen-Kaesbach
D. Lazarevic[g], M. Mari
S. Russo[i], R. Werner[j],
P. Krawitz[c,k], L. Larizz
A. Selicorni[f,†] and F.J.

[a]Medical Genetics, Departm



Clinical Aspects of Dysmorphology

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