How to reach syndrome?

In 1 hour…

Manama day 16/02/2021 Damien Lederer

Syndrome

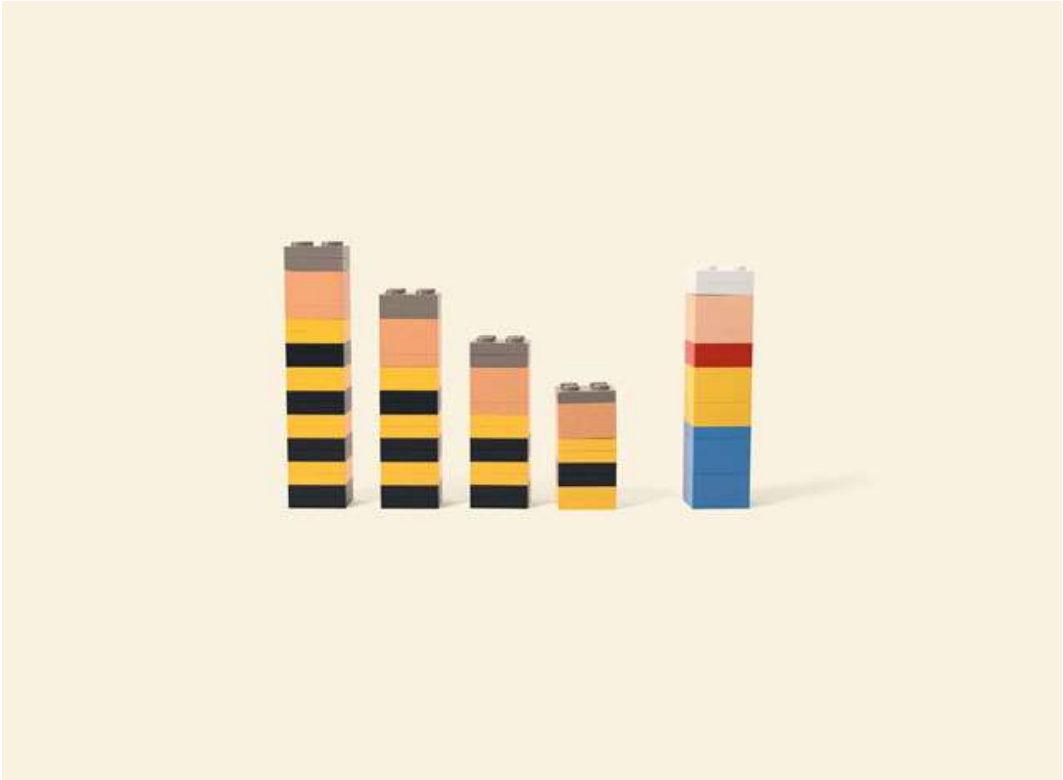
- Pattern of anomalies, at least one of wich is morphologic, known or thought to be causally related.
- Pattern of multiple anomalies thought to be pathogenetically related and not known to represent a single sequence or a polytopic field defect.
- Everybody is dysmorphic, not everybody is syndromic…

IPG

“GESTALT”

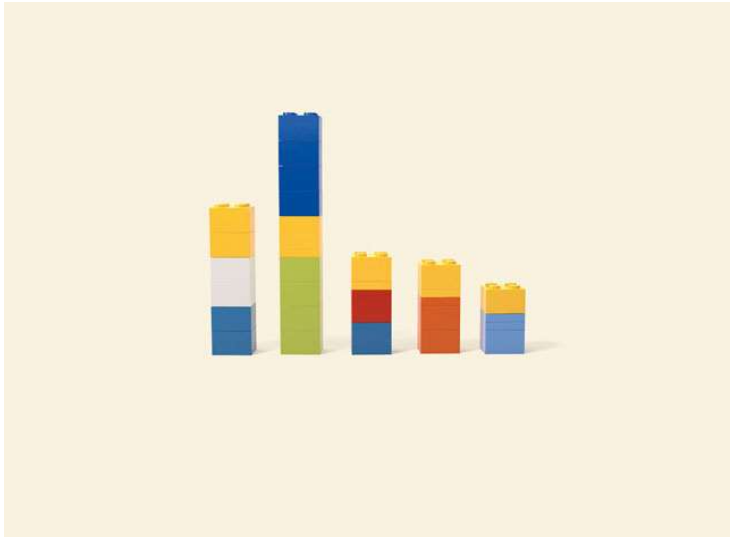
You recognize famous people on the spot…

Gestalt diagnosis …



(1) Major sign, (3) minor signs…

LEGO's minimal 'Imagine' Campaign



HPO databases

- HPO components
  - Phenotype vocabulary
  - Disease-phenotype annotations
  - Algorythm
- HPO in routine
  - Differential diagnosis in clinic
  - Phenotype driven analysis of NGS
  - Frequent updates of the database
- https://hpo.jax.org/

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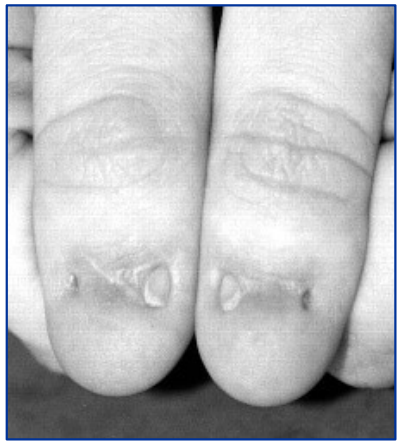
HPO database



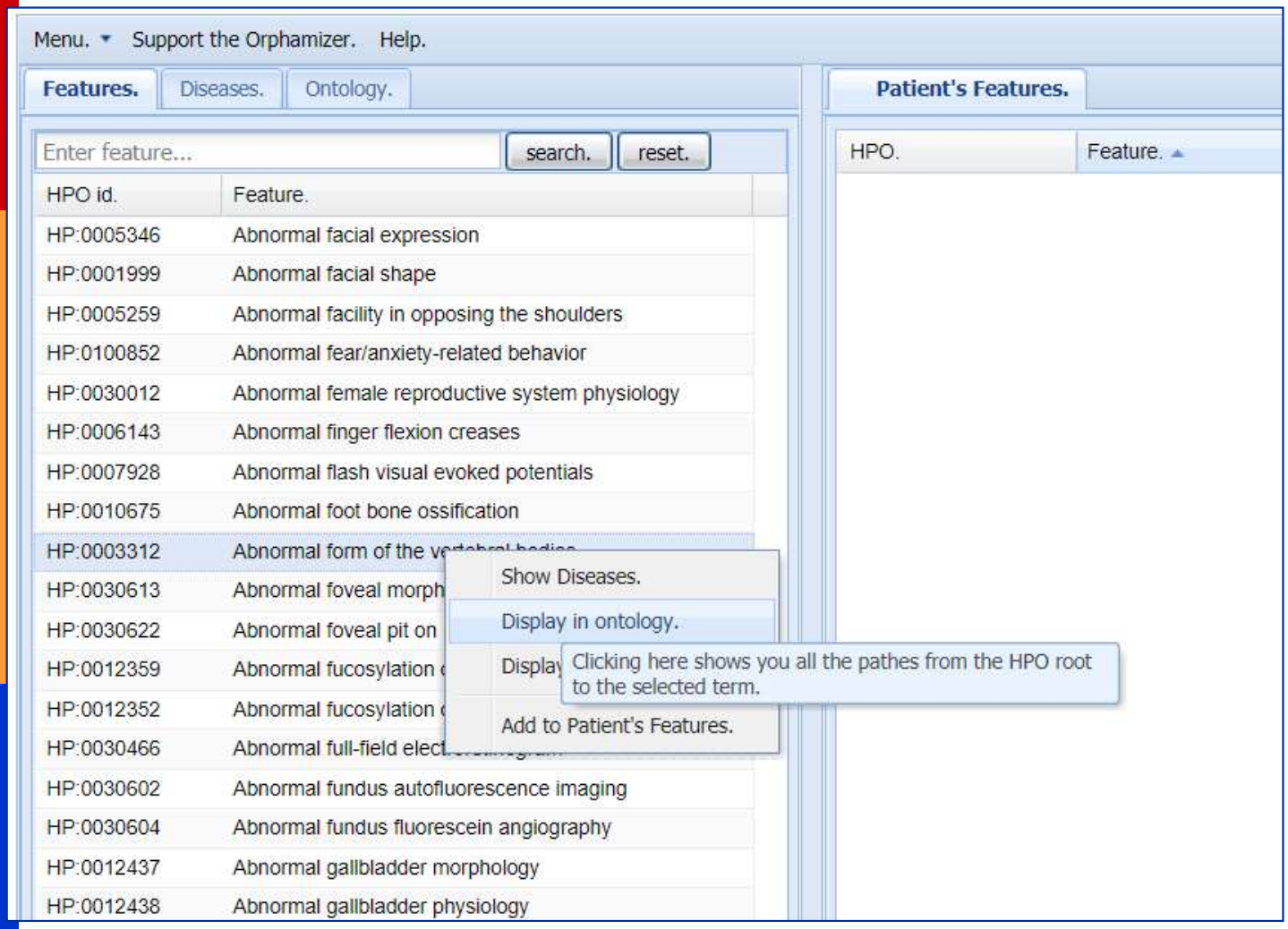
8000 diseases

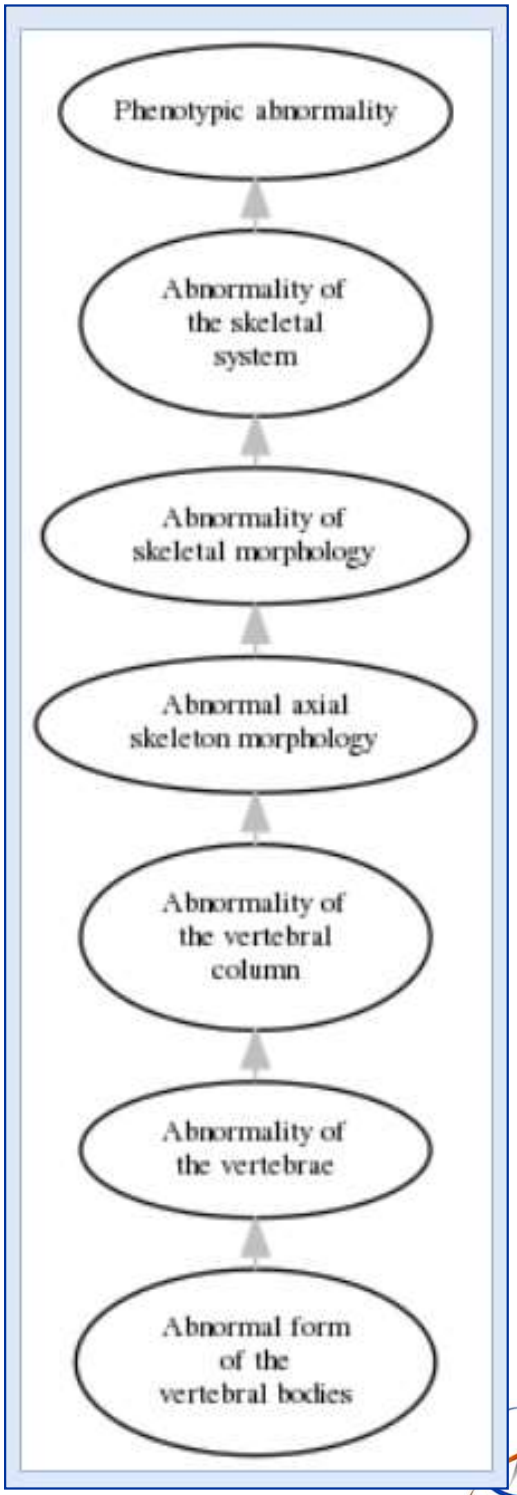
13000 terms
(phenotype)

> 110 000 annotations

Genes (OMIM, exome)

Phenomizer/Orphamizer





- http://compbio.charite.de/phenomizer/

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Phenotypic abnormality
Abnormality of the skeletal system
Abnormality of skeletal morphology
Abnormality of limbs
Abnormal appendicular skeleton morphology
Aplasia/hypoplasia involving the skeleton
Abnormality of limb bone
Abnormality of limb bone morphology
Aplasia/hypoplasia of the extremities
Abnormality of the lower limb
Aplasia/hypoplasia involving bones of the extremities
Abnormality of lower limb bone
Abnormality of the foot
Aplasia/hypoplasia involving bones of the lower limbs
Abnormality of the metatarsal bones
Aplasia/Hypoplasia involving bones of the feet
Aplasia/Hypoplasia of metatarsal bones

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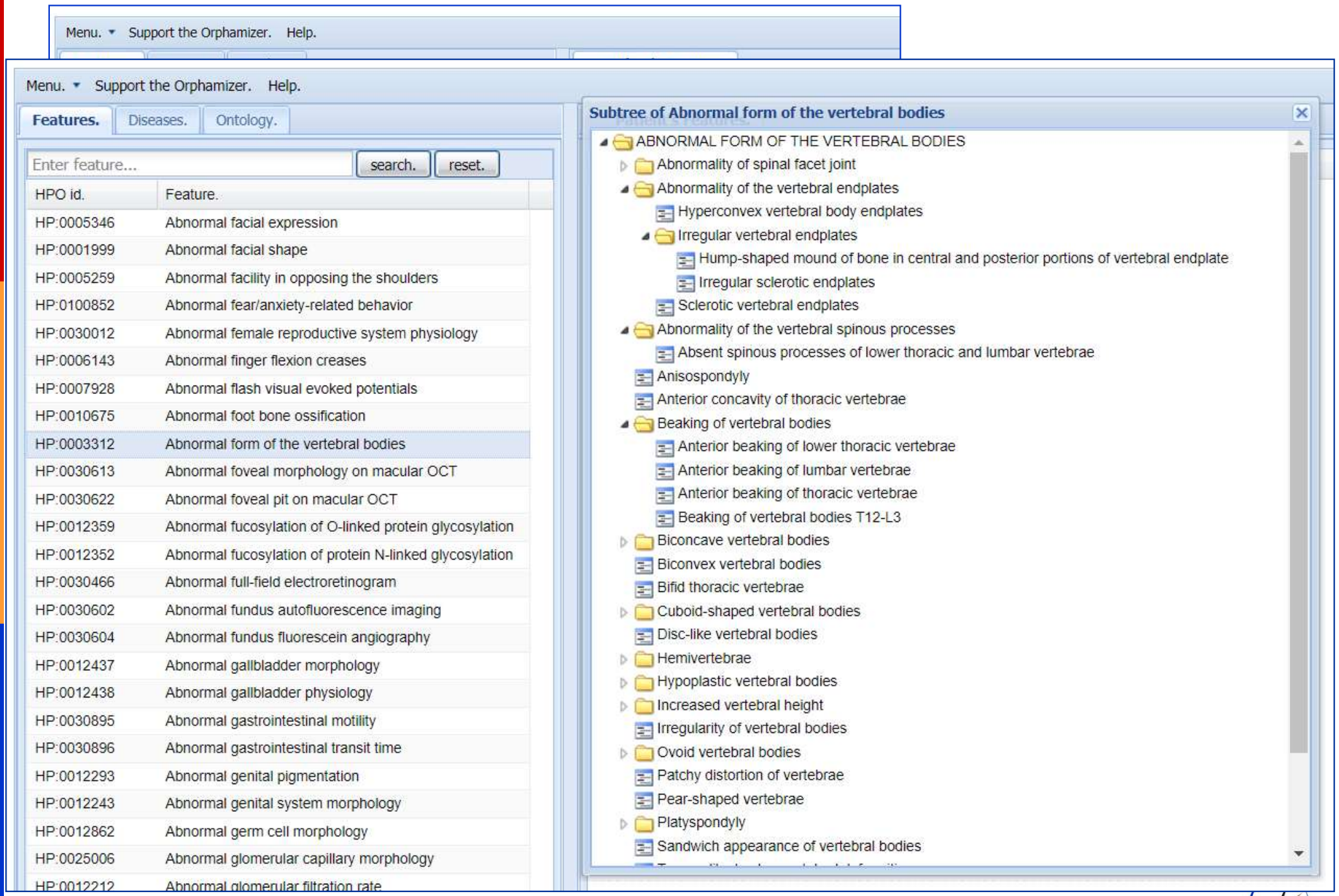
Menu. Support the Orphamizer. Help.
Menu. Support the Orphamizer. Help.
Features. Diseases. Ontology.
Enter feature...
search. reset.
HPO id. Feature.
HP:0005346 Abnormal facial expression
HP:0001999 Abnormal facial shape
HP:0005259 Abnormal facility in opposing the shoulders
HP:0100852 Abnormal fear/anxiety-related behavior
HP:0030012 Abnormal female reproductive system physiology
HP:0006143 Abnormal finger flexion creases
HP:0007928 Abnormal flash visual evoked potentials
HP:0010675 Abnormal foot bone ossification
HP:0003312 Abnormal form of the vertebral bodies
HP:0030613 Abnormal foveal morphology on macular OCT
HP:0030622 Abnormal foveal pit on macular OCT
HP:0012359 Abnormal fucosylation of O-linked protein glycosylation
HP:0012352 Abnormal fucosylation of protein N-linked glycosylation
HP:0030466 Abnormal full-field electroretinogram
HP:0030602 Abnormal fundus autofluorescence imaging
HP:0030604 Abnormal fundus fluorescein angiography
HP:0012437 Abnormal gallbladder morphology
HP:0012438 Abnormal gallbladder physiology
HP:0030895 Abnormal gastrointestinal motility
HP:0030896 Abnormal gastrointestinal transit time
HP:0012293 Abnormal genital pigmentation
HP:0012243 Abnormal genital system morphology
HP:0012862 Abnormal germ cell morphology
HP:0025006 Abnormal glomerular capillary morphology
HP:0012212 Abnormal glomerular filtration rate
Subtree of Abnormal form of the vertebral bodies
ABNORMAL FORM OF THE VERTEBRAL BODIES
Abnormality of spinal facet joint
Abnormality of the vertebral endplates
Hyperconvex vertebral body endplates
Irregular vertebral endplates
Hump-shaped mound of bone in central and posterior portions of vertebral endplate
Irregular sclerotic endplates
Sclerotic vertebral endplates
Abnormality of the vertebral spinous processes
Absent spinous processes of lower thoracic and lumbar vertebrae
Anisospondyly
Anterior concavity of thoracic vertebrae
Beaking of vertebral bodies
Anterior beaking of lower thoracic vertebrae
Anterior beaking of lumbar vertebrae
Anterior beaking of thoracic vertebrae
Beaking of vertebral bodies T12-L3
Biconcave vertebral bodies
Biconvex vertebral bodies
Bifid thoracic vertebrae
Cuboid-shaped vertebral bodies
Disc-like vertebral bodies
Hemivertebrae
Hypoplastic vertebral bodies
Increased vertebral height
Irregularity of vertebral bodies
Ovoid vertebral bodies
Patchy distortion of vertebrae
Pear-shaped vertebrae
Platyspondyly
Sandwich appearance of vertebral bodies

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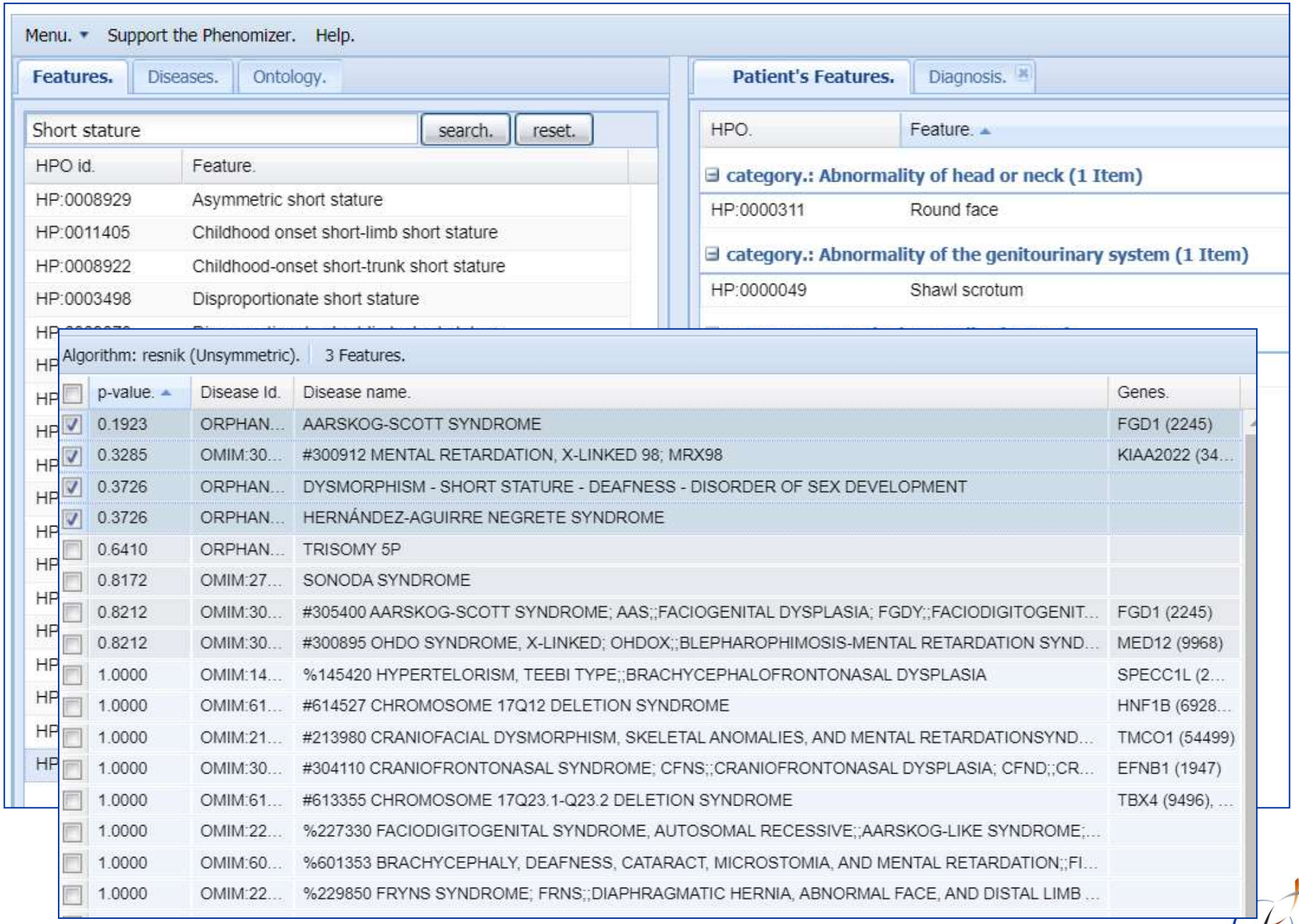
Menu.
Support the Phenomizer.
Help.
Features.
Diseases.
Ontology.
Short stature
search.
reset.
HPO id.
Feature.
HP:0008929
Asymmetric short stature
HP:0011405
Childhood onset short-limb short stature
HP:0008922
Childhood-onset short-trunk short stature
HP:0003498
Disproportionate short stature
Patient's Features.
Diagnosis.
HPO.
Feature.
category.: Abnormality of head or neck (1 Item)
HP:0000311
Round face
category.: Abnormality of the genitourinary system (1 Item)
HP:0000049
Shawl scrotum
Algorithm: resnik (Unsymmetric).
3 Features.
p-value.
Disease Id.
Disease name.
Genes.
0.1923
ORPHAN...
AARSKOG-SCOTT SYNDROME
FGD1 (2245)
0.3285
OMIM:30...
#300912 MENTAL RETARDATION, X-LINKED 98; MRX98
KIAA2022 (34...
0.3726
ORPHAN...
DYSMORPHISM - SHORT STATURE - DEAFNESS - DISORDER OF SEX DEVELOPMENT
0.3726
ORPHAN...
HERNÁNDEZ-AGUIRRE NEGRETE SYNDROME
0.6410
ORPHAN...
TRISOMY 5P
0.8172
OMIM:27...
SONODA SYNDROME
0.8212
OMIM:30...
#305400 AARSKOG-SCOTT SYNDROME; AAS;;FACIOGENITAL DYSPLASIA; FGDY;;FACIODIGITOGENIT...
FGD1 (2245)
0.8212
OMIM:30...
#300895 OHDO SYNDROME, X-LINKED; OHDOX;;BLEPHAROPHIMOSIS-MENTAL RETARDATION SYND...
MED12 (9968)
1.0000
OMIM:14...
%145420 HYPERTELORISM, TEEBI TYPE;;BRACHYCEPHALOFRONTONASAL DYSPLASIA
SPECC1L (2...
1.0000
OMIM:61...
#614527 CHROMOSOME 17Q12 DELETION SYNDROME
HNF1B (6928...
1.0000
OMIM:21...
#213980 CRANIOFACIAL DYSMORPHISM, SKELETAL ANOMALIES, AND MENTAL RETARDATIONSYND...
TMCO1 (54499)
1.0000
OMIM:30...
#304110 CRANIOFRONTONASAL SYNDROME; CFNS;;CRANIOFRONTONASAL DYSPLASIA; CFND;;CR...
EFNB1 (1947)
1.0000
OMIM:61...
#613355 CHROMOSOME 17Q23.1-Q23.2 DELETION SYNDROME
TBX4 (9496), ...
1.0000
OMIM:22...
%227330 FACIODIGITOGENITAL SYNDROME, AUTOSOMAL RECESSIVE;;AARSKOG-LIKE SYNDROME;...
1.0000
OMIM:60...
%601353 BRACHYCEPHALY, DEAFNESS, CATARACT, MICROSTOMIA, AND MENTAL RETARDATION;;FI...
1.0000
OMIM:22...
%229850 FRYNS SYNDROME; FRNS;;DIAPHRAGMATIC HERNIA, ABNORMAL FACE, AND DISTAL LIMB ...

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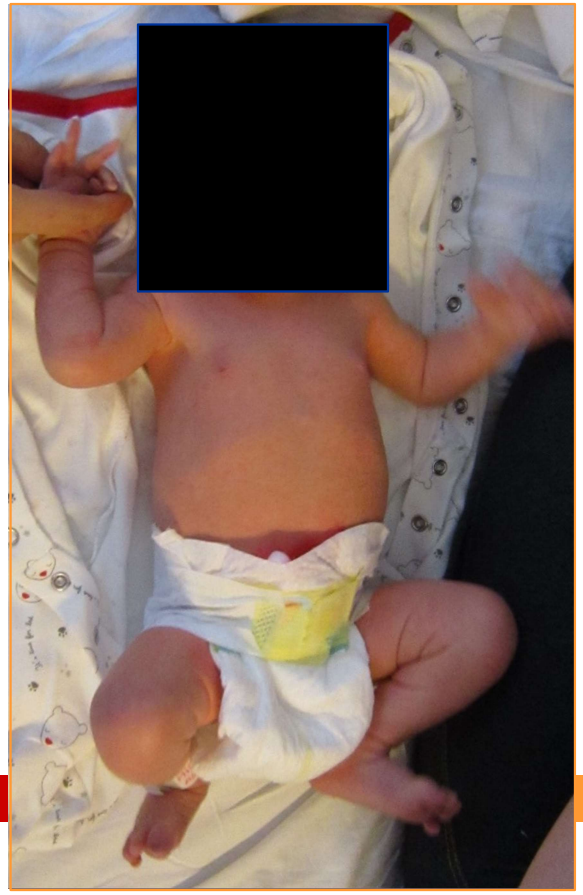
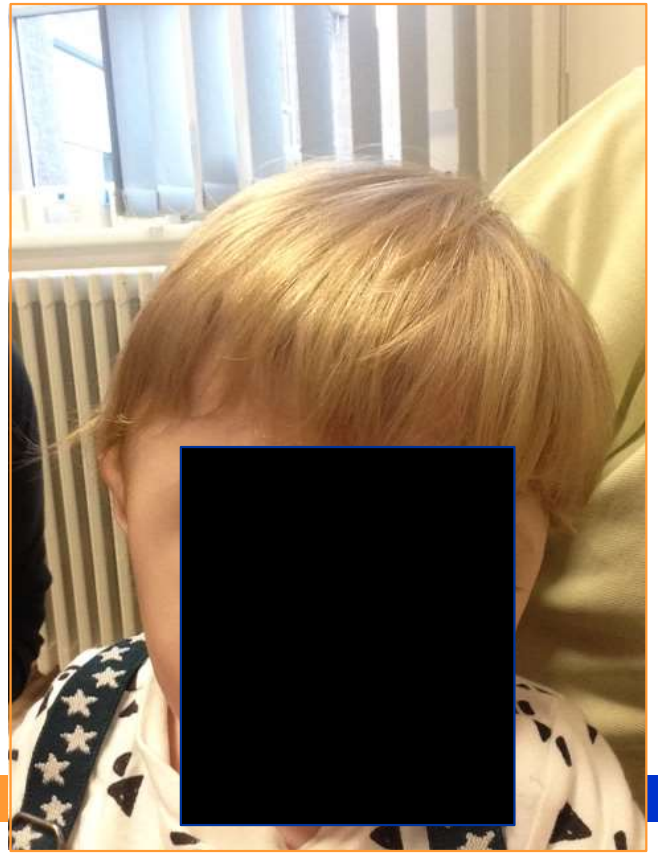
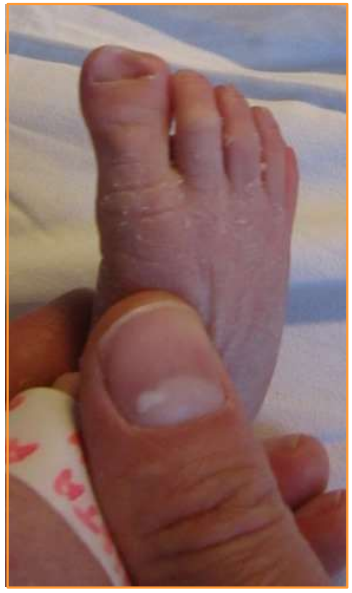
HPO annotation

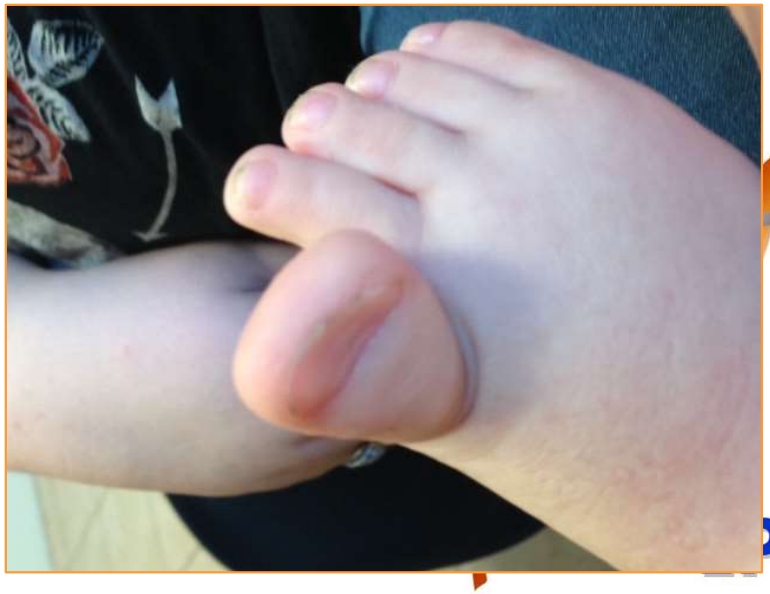
Entrez gene ID	Entrez gene name	HPO term ID	HPO term	Frequency	Frequency HPO		G-D source	Disease ID
5781	PTPN11	HP:0000689	Dental malocclusion	-		-	mim2gene	OMIM:163950
5781	PTPN11	HP:0004859	Amegakaryocytic thrombocytopenia	-		-	mim2gene	OMIM:163950
5781	PTPN11	HP:0009466	Radial deviation of finger	-		-	mim2gene	OMIM:163950
5781	PTPN11	HP:0000368	Low-set, posteriorly rotated ears	-		-	mim2gene	OMIM:163950
5781	PTPN11	HP:0000407	Sensorineural hearing impairment	-		-	mim2gene	OMIM:163950
5781	PTPN11	HP:0100769	Synovitis	-		-	mim2gene	OMIM:163950
5781	PTPN11	HP:0000006	Autosomal dominant inheritance	-		-	mim2gene	OMIM:163950
5781	PTPN11	HP:0000218	High palate	-		-	mim2gene	OMIM:163950
5781	PTPN11	HP:0000135	Hypogonadism	-	HP:0040283	-	mim2gene	OMIM:163950
5781	PTPN11	HP:0008897	Postnatal growth retardation	-		-	mim2gene	OMIM:163950
5781	PTPN11	HP:0001249	Intellectual disability	-	HP:0040284	-	mim2gene	OMIM:163950
5781	PTPN11	HP:0002967	Cubitus valgus	-		-	mim2gene	OMIM:163950
5781	PTPN11	HP:0030084	Clinodactyly	-		-	mim2gene	OMIM:163950
5781	PTPN11	HP:0000470	Short neck	-	HP:0040284	-	mim2gene	OMIM:163950

IPG









Patient's Features. | Diagnosis.

HPO.	Feature.	Modifier.	Num diseases.
category.: Abnormality of head or neck (1 Item)			
HP:0011318	Bicoronal synostosis	observed.	1 of 7994
category.: Abnormality of limbs (1 Item)			
HP:0010066	Duplication of phalanx of hallux	observed.	11 of 7994
category.: Abnormality of the skeletal system (2 Items)			
HP:0011318	Bicoronal synostosis	observed.	1 of 7994
HP:0010066	Duplication of phalanx of hallux	observed.	11 of 7994

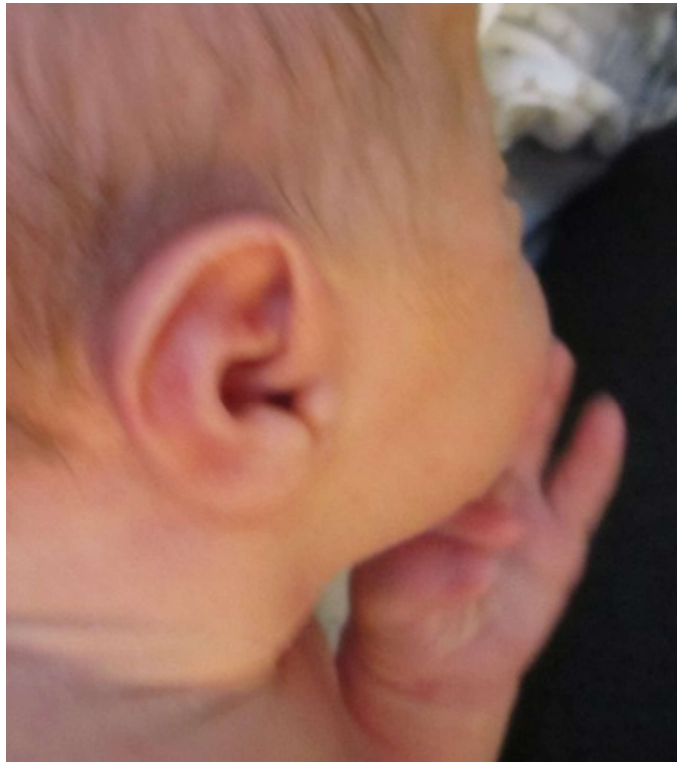
Patient's Features. | **Diagnosis.**

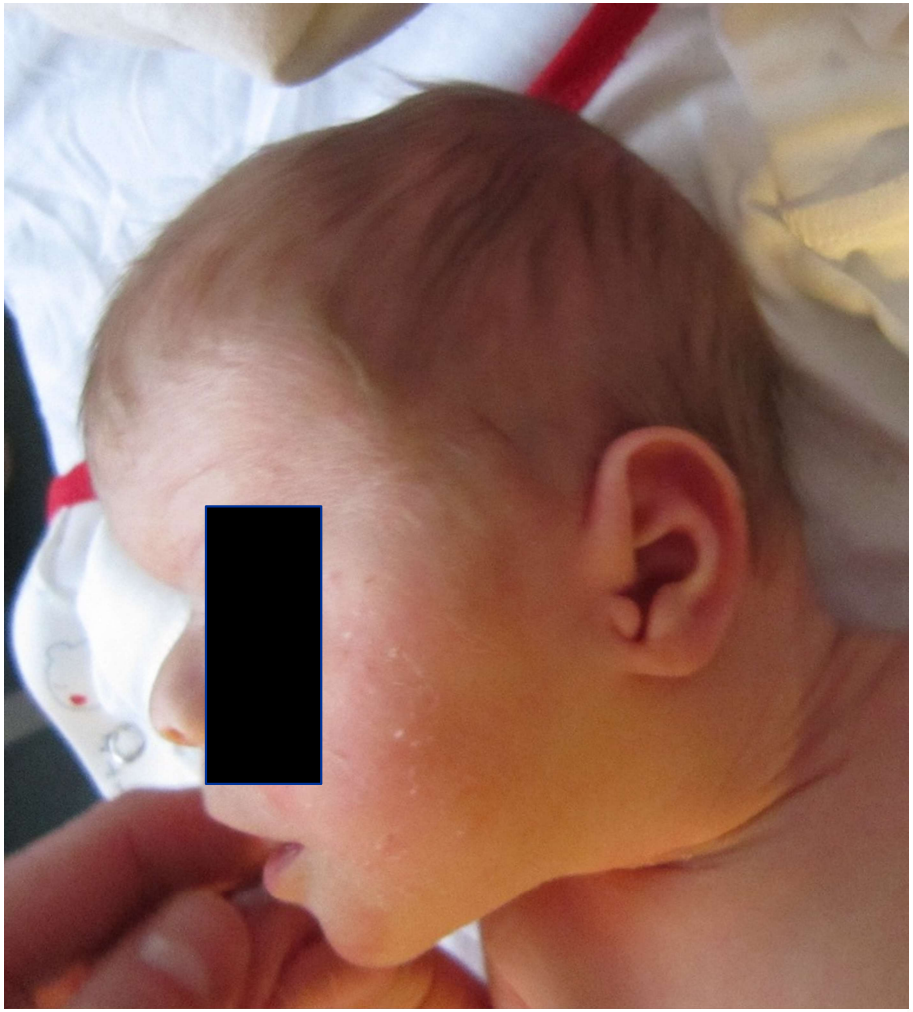
Algorithm: resnik (Unsymmetric). | 2 Features.

p-value.	Disease Id.	Disease name.	Genes.
0.5021	OMIM:614...	#614188 CRANIOSYNOSTOSIS AND DENTAL ANOMALIES; CRSDA;;KREIBORG-PAKISTANI SYNDROME	IL11RA (3590)
0.5021	OMIM:614...	#614078 CHONDRODYSPLASIA WITH JOINT DISLOCATIONS, GPAPP TYPE;;GPAPP DEFICIENCY	IMPAD1 (54928)
0.5021	OMIM:615...	#615314 CRANIOSYNOSTOSIS 3; CRS3	FGFR3 (2261)...
0.5689	OMIM:233...	%233500 GORLIN-CHAUDHRY-MOSS SYNDROME; GCMS;;CRANIOFACIAL DYSOSTOSIS, HYPERTRICHOSIS, ...	
0.6034	OMIM:218...	BALLER-GEROLD SYNDROME	RECQL4 (9401)
0.6034	OMIM:101...	#101600 PFEIFFER SYNDROME;;ACROCEPHALOSYNDACTYLY, TYPE V; ACS5;;ACS V;;NOACK SYNDROMEC...	FGFR1 (2260)...
0.6034	OMIM:175...	#175700 GREIG CEPHALOPOLYSYNDACTYLY SYNDROME; GCPS;;POLYSYNDACTYLY WITH PECULIAR SKU...	GLI3 (2737)
0.6034	OMIM:101...	#101200 APERT SYNDROME;;ACROCEPHALOSYNDACTYLY, TYPE I; ACS1;;ACS IAPERT-CROUZON DISEASE...	FGFR2 (2263)
0.6034	OMIM:304...	#304110 CRANIOFRONTONASAL SYNDROME; CFNS;;CRANIOFRONTONASAL DYSPLASIA; CFND;;CRANIOFR...	EFNB1 (1947)
0.6034	OMIM:180...	ROBINOW-SORAUF SYNDROME	TWIST1 (7291)

IPG

- FGFR1-2-3 normal





Patient's Features. | Diagnosis.

HPO.	Feature.	Modifier.	Num diseases.
category.: Abnormality of head or neck (1 Item)			
HP:0011318	Bicoronal synostosis	observed.	1 of 7994
category.: Abnormality of limbs (1 Item)			
HP:0010066	Duplication of phalanx of hallux	observed.	11 of 7994
category.: Abnormality of the ear (1 Item)			
HP:0009899	Prominent crus of helix	observed.	1 of 7994
category.: Abnormality of the skeletal system (3 Items)			
HP:0011318	Bicoronal synostosis	observed.	1 of 7994
HP:0010066	Duplication of phalanx of hallux	observed.	11 of 7994
HP:0009899	Prominent crus of helix	observed.	1 of 7994

Patient's Features. | **Diagnosis.**

Algorithm: resnik (Unsymmetric). | 3 Features.

p-value.	Disease Id.	Disease name.	Genes.
0.3612	OMIM:101...	#101400 SAETHRE-CHOTZEN SYNDROME; SCS;;ACROCEPHALOSYNDACTYLY, TYPE III; ACS3;;ACS III;;CHOT...	FGFR3 (2261)...
0.3612	OMIM:243...	#243310 BARAITSER-WINTER SYNDROME 1; BRWS1;;IRIS COLOBOMA WITH PTOSIS, HYPERTELORISM, AND...	ACTG1 (71), ...
0.3612	OMIM:233...	%233500 GORLIN-CHAUDHRY-MOSS SYNDROME; GCMS;;CRANIOFACIAL DYSOSTOSIS, HYPERTRICHOSIS, ...	
0.3612	OMIM:239...	239710 ACROFRONTOFACIONASAL DYSOSTOSIS 2;;AFFN DYSOSTOSIS 2; AFFND2;;ACROFRONTOFACION...	
0.3612	OMIM:608...	#608156 NABLUS MASK-LIKE FACIAL SYNDROME; NMLFS;;CHROMOSOME 8Q22.1 DELETION SYNDROME	
0.3612	OMIM:101...	ACROCEPHALOPOLYSYNDACTYLY TYPE III	
0.3612	OMIM:614...	#614188 CRANIOSYNOSTOSIS AND DENTAL ANOMALIES; CRSDA;;KREIBORG-PAKISTANI SYNDROME	IL11RA (3590)
0.3612	OMIM:218...	CRANIOSYNOSTOSIS WITH FIBULAR APLASIA	
0.3612	OMIM:616...	#616300 SHORT-RIB THORACIC DYSPLASIA 13 WITH OR WITHOUT POLYDACTYLY; SRTD13	TTC21B (7980...
0.3612	OMIM:614...	#614078 CHONDRODYSPLASIA WITH JOINT DISLOCATIONS, GPAPP TYPE;;GPAPP DEFICIENCY	IMPAD1 (54928)
0.3612	ORPHANE...	20P12.3 MICRODELETION SYNDROME	BMP2 (650)
0.3612	OMIM:614...	#614592 BENT BONE DYSPLASIA SYNDROME; BBDS	FGFR2 (2263)
0.3612	OMIM:615...	#615314 CRANIOSYNOSTOSIS 3; CRS3	FGFR3 (2261)...
0.3612	OMIM:241...	HYPOSPADIAS-MENTAL RETARDATION SYNDROME	
0.3612	OMIM:613...	#613610 CRANIOECTODERMAL DYSPLASIA 2; CED2	WDR19 (5772...

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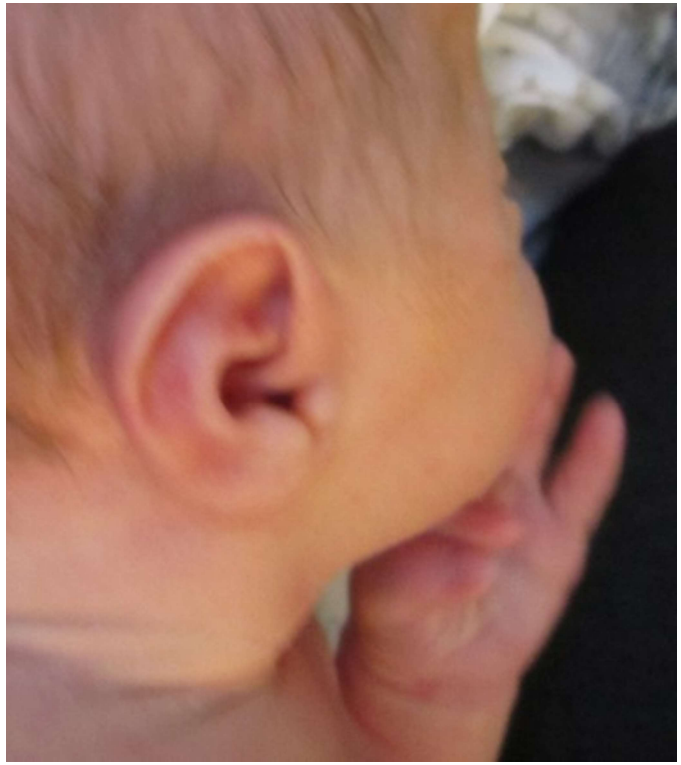
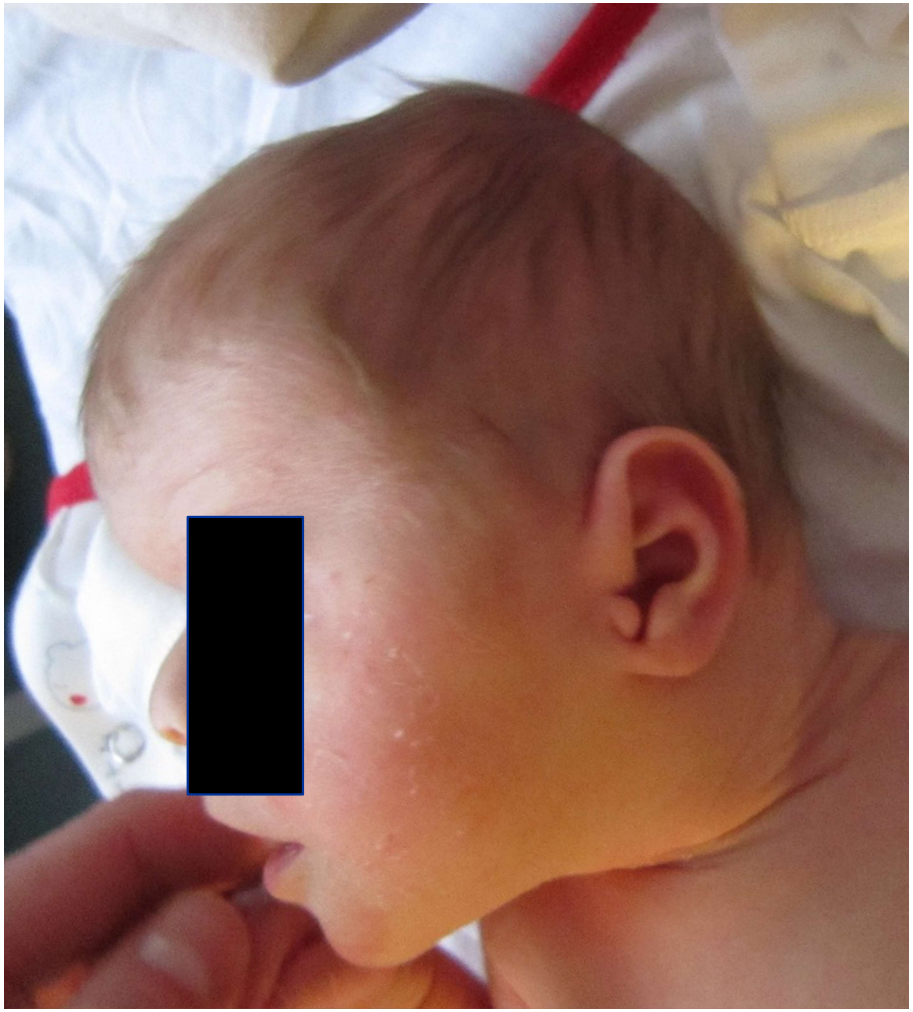
- FGFR1-2-3 normal
- TWIST1 mutation





HPO missed annotation

Limbs [7 annotations]

Term Identifier	Term Name	Onset	Frequency	Source(s)
HP:0001199	Triphalangeal thumb	-	Occasional	ORPHA
HP:0006101	Finger syndactyly	-	Very frequent	ORPHA
HP:0004209	Clinodactyly of the 5th finger	-	Very frequent	ORPHA
HP:0011304	Broad thumb	-	Occasional	ORPHA
HP:0005037	Proximal radio-ulnar synostosis	-	Occasional	ORPHA
HP:0001822	Hallux valgus	-	Occasional	ORPHA

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OMIM – Orphanet

- Orphanet
  - Database of rare disease and their description
  - Link to diagnostic lab, disease association, genereview…
  - Orphamizer (link to HPO)

- OMIM
  - Database of genes, diseases and phenotype used in HPO

IPG

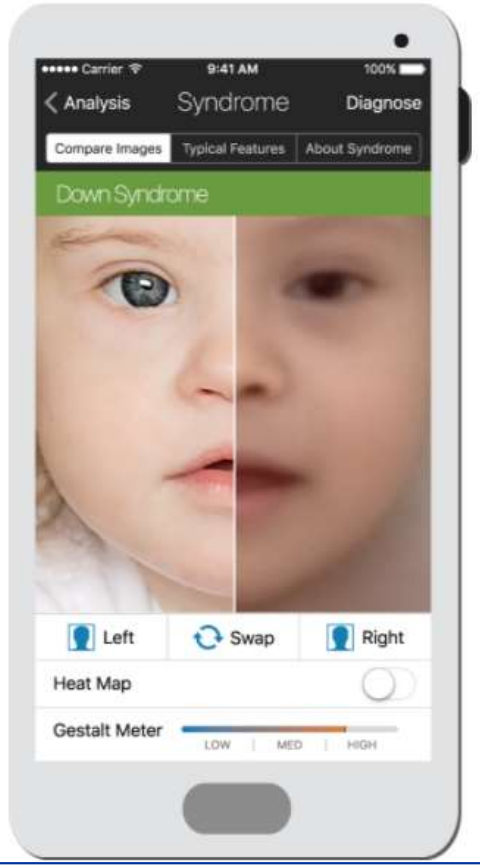
Face2gene

FACE2GENE

Smart Phenotyping. Better Genetics.

READ THE BLOG | CONTACT US | SIGN IN | REGISTER

FDNA TELEHEALTH | CLINIC | LABS | RESEARCH | PUBLICATIONS | HOW IT WORKS | ABOU



Detect Phenotypes & Reveal Relevant Facial and Non-facial Features

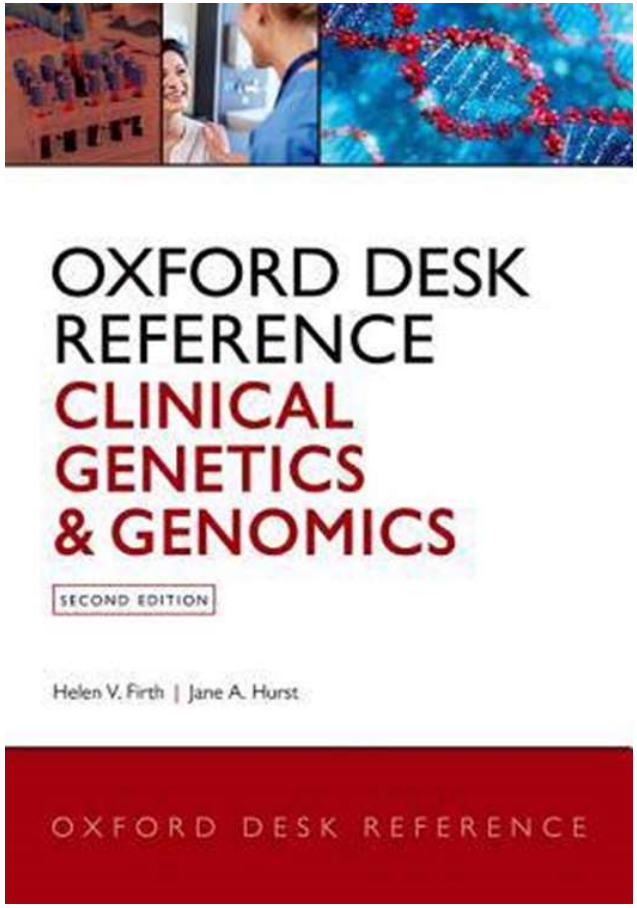
- Detection of phenotypes from facial photos
- Automatic calculation of anthropometric growth charts
- Suggestion of likely phenotypic traits to assist in feature annotation

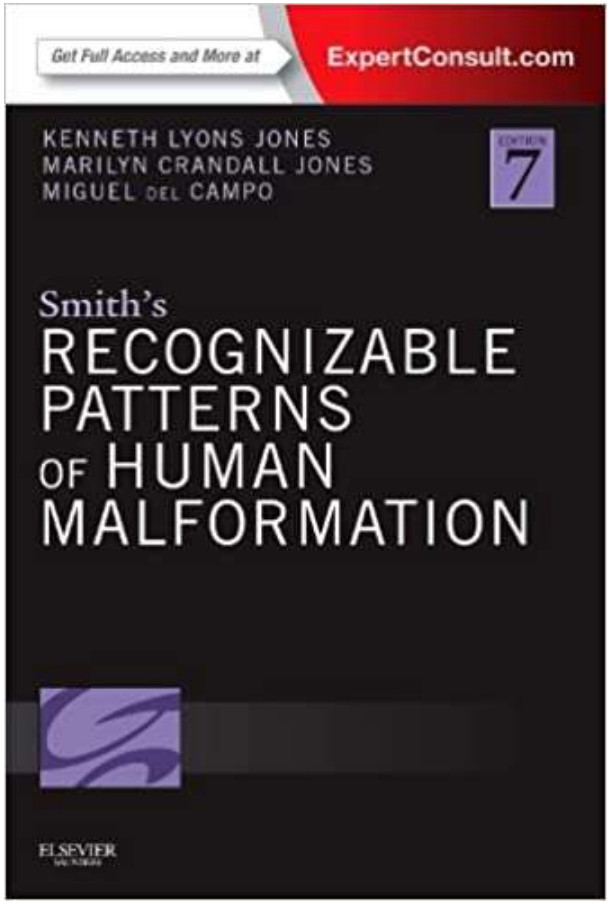
An objective computer-aided dimension to the art of dysmorphology

Dr. Michael Hayden, Clinical Genetics

IPG

Books


OXFORD DESK
REFERENCE
CLINICAL
GENETICS
& GENOMICS
SECOND EDITION
Helen V. Firth | Jane A. Hurst
OXFORD DESK REFERENCE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MALFORMATION
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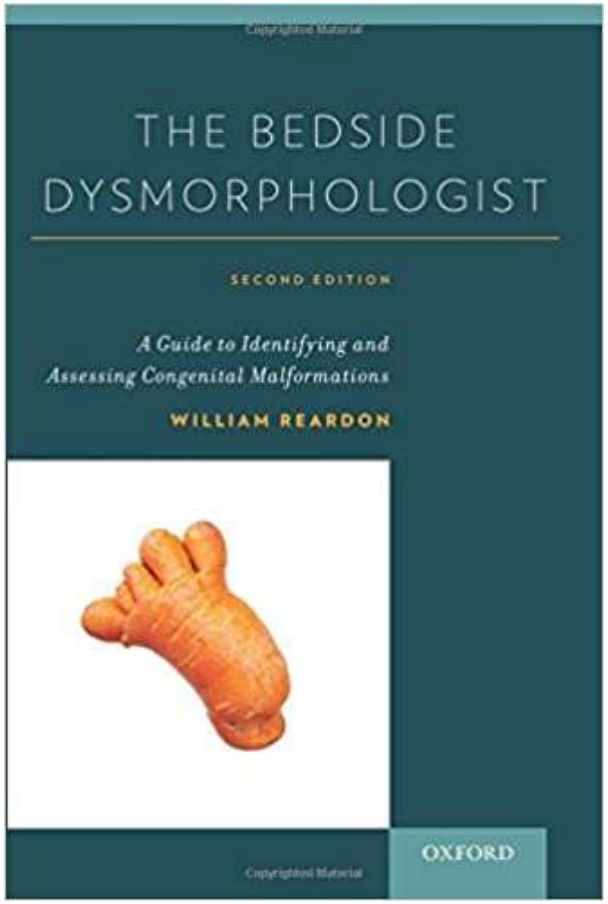
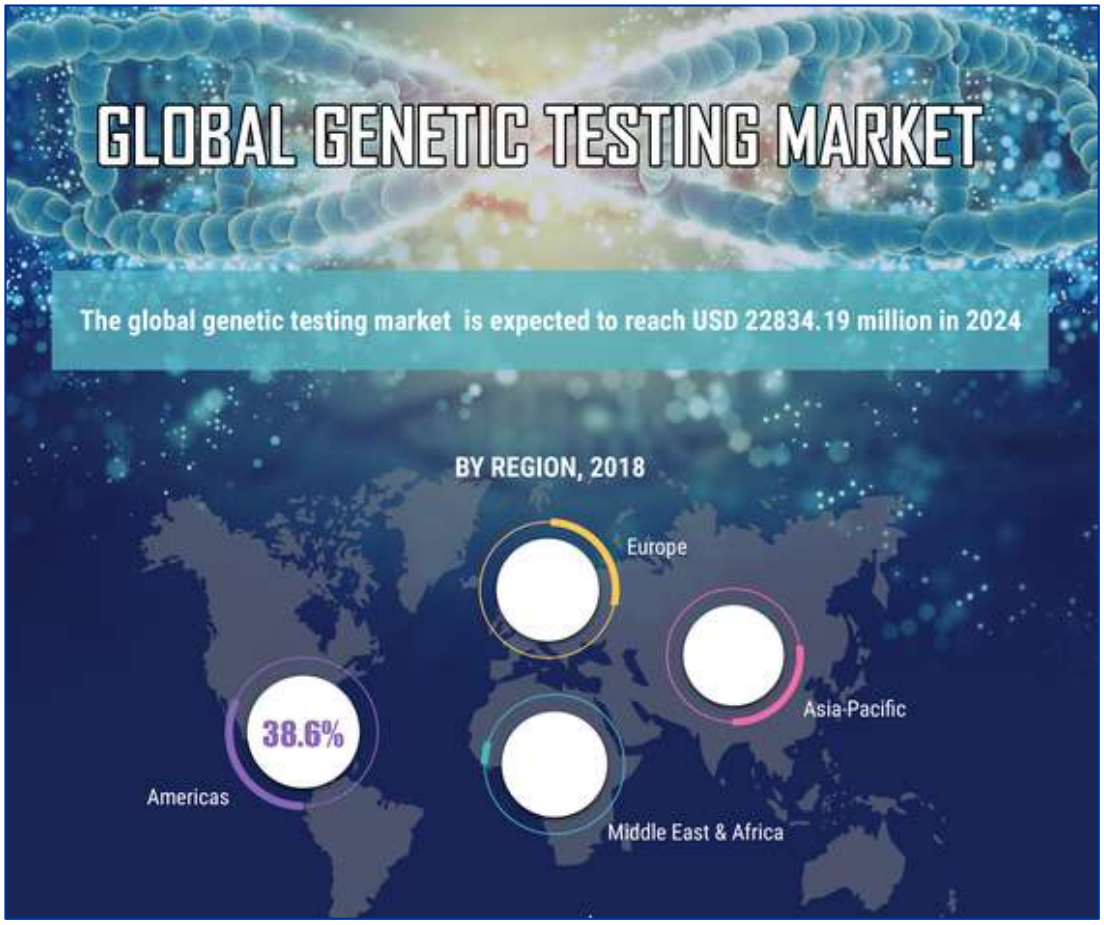
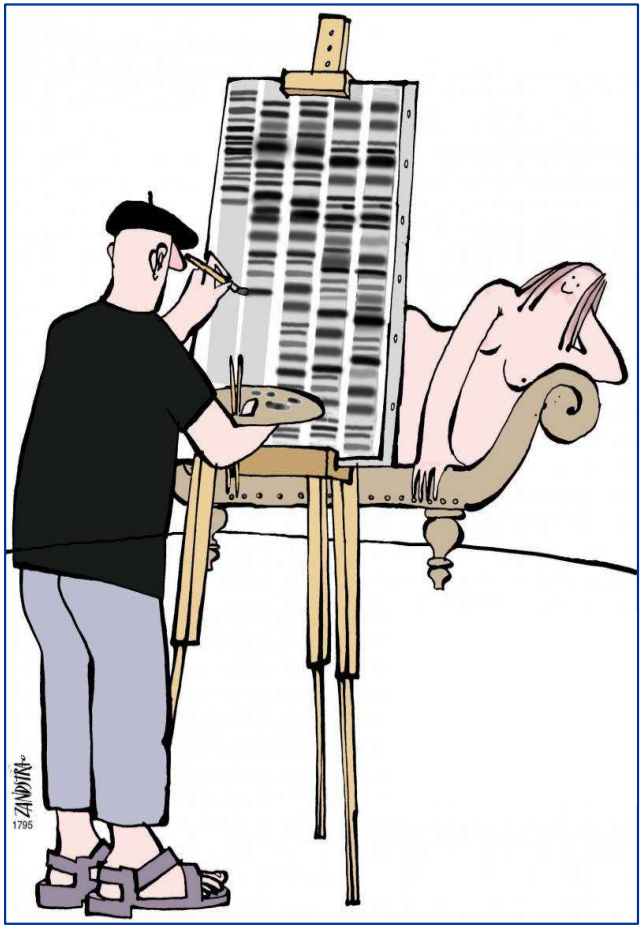
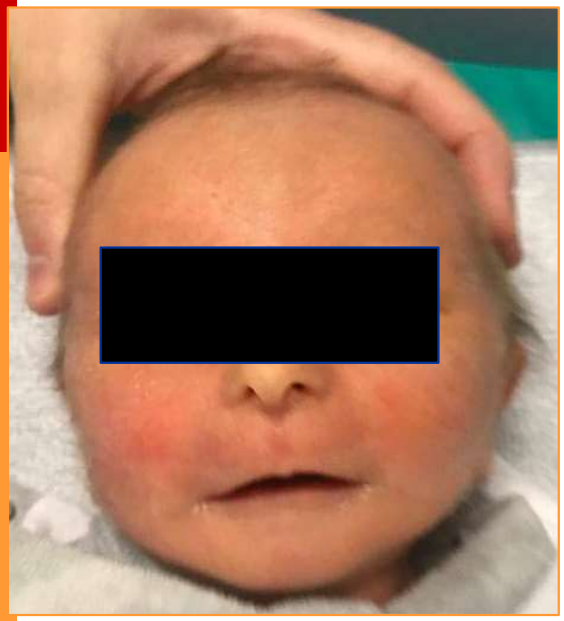

THE BEDSIDE
DYSMORPHOLOGIST
SECOND EDITION
A Guide to Identifying and
Assessing Congenital Malformations
WILLIAM REARDON
OXFORD

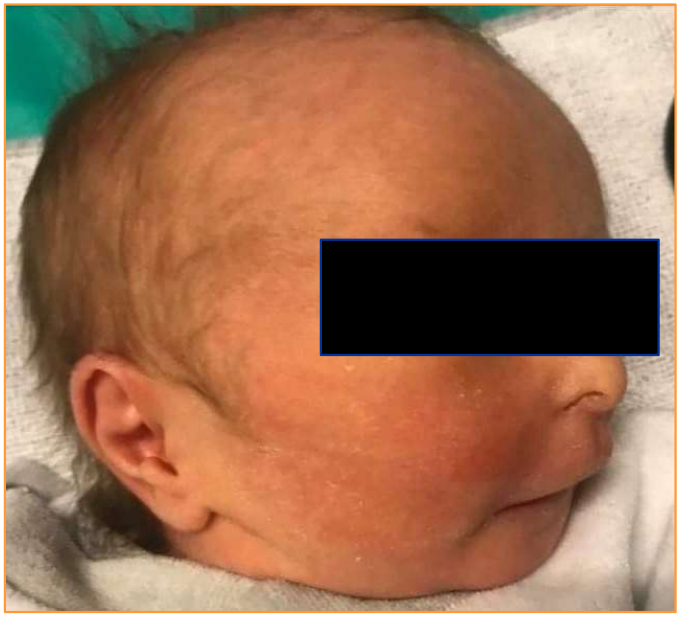
Why to phenotype?

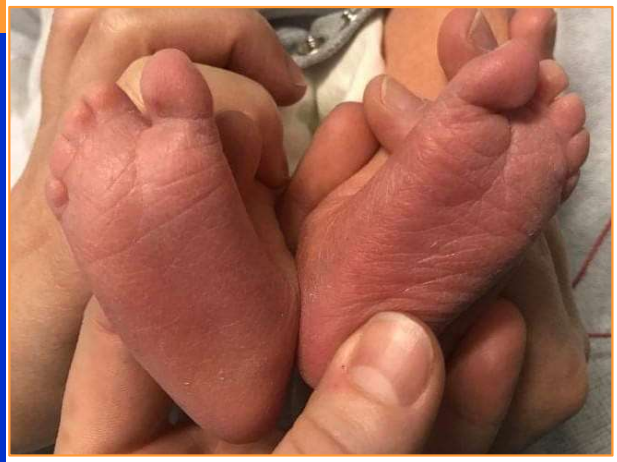


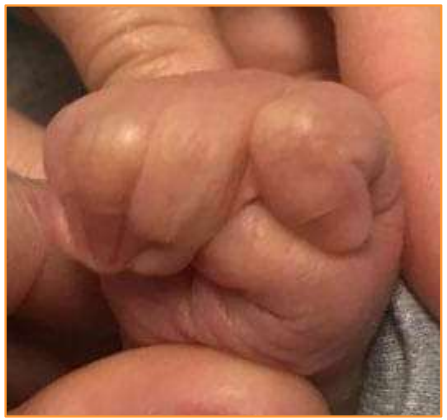


Blick diagnosis









- **1/12**: clinic
- Short palpebral fissure
- ? Microphtalmia
- Nasal alae hypoplasia
- Retrognathia
- Finger syndactyly
  - 3-4-5 full
  - 2-3 partial
- Toe syndactyly
  - 2-3-4
- No other malformation
- **16/12** molecular diagnosis (**Sanger**)

Oculo
Dento
Digitale
Dysplasia
GJA1
mutation

IPG

- Condition of examination
  - Say hello to the child
  - Make him talk (nasal speech…)
  - During anamnesis
    - Relaxed
    - Interaction
    - Hyperactivity, absences…
  - On mother knees
  - Examination table
  - Mouth, last to examine (or when crying)

Blick diagnosis

Epicanthic folds

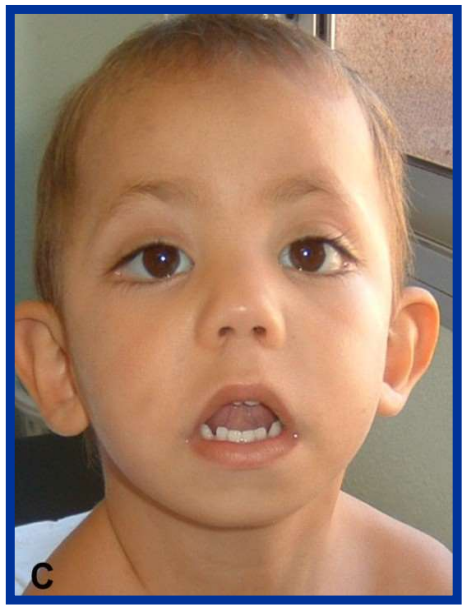
Down

Thin hair
Tongue protrusion
Upsplant of
Palpebral fissures
Brushfield spots

Velocardiofacial

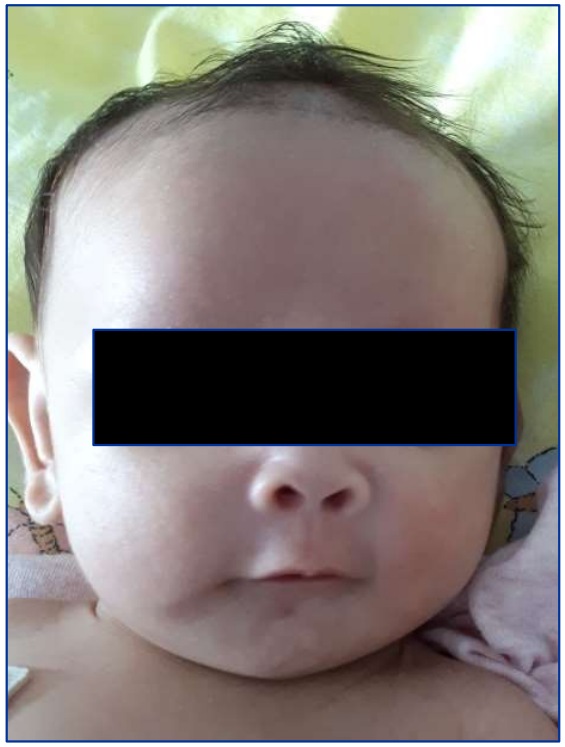
Tubular nose
Ears
Palate
Nasal speech

Kabuki

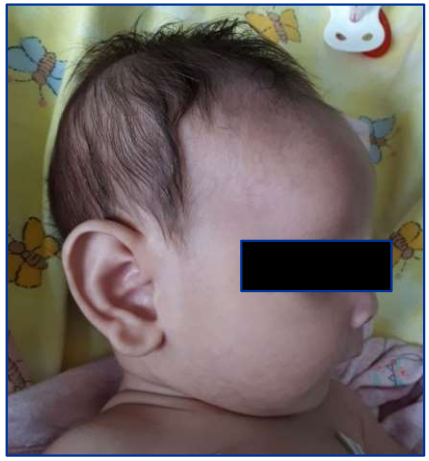


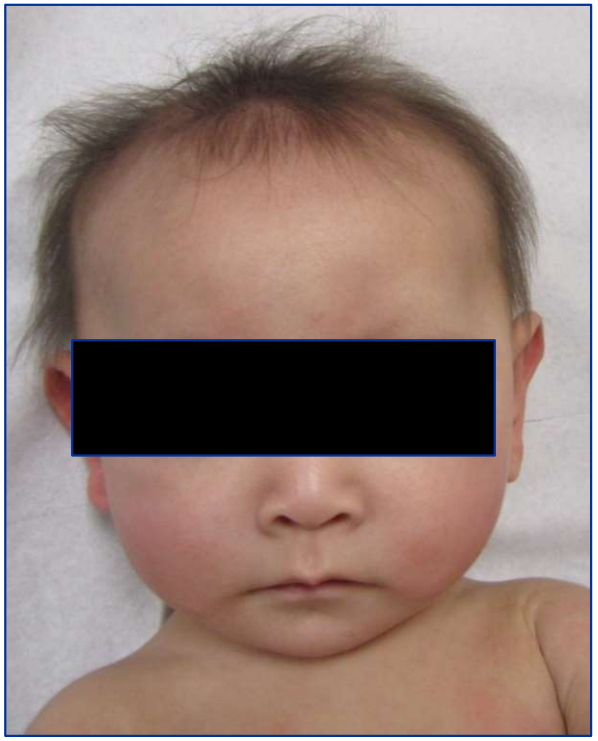
- Protruding ears
- Ectropion
- Sparse lateral eyebrows
- Hypotonia
- Cleft uvula
- Feeding difficulties
- Premature thelarche

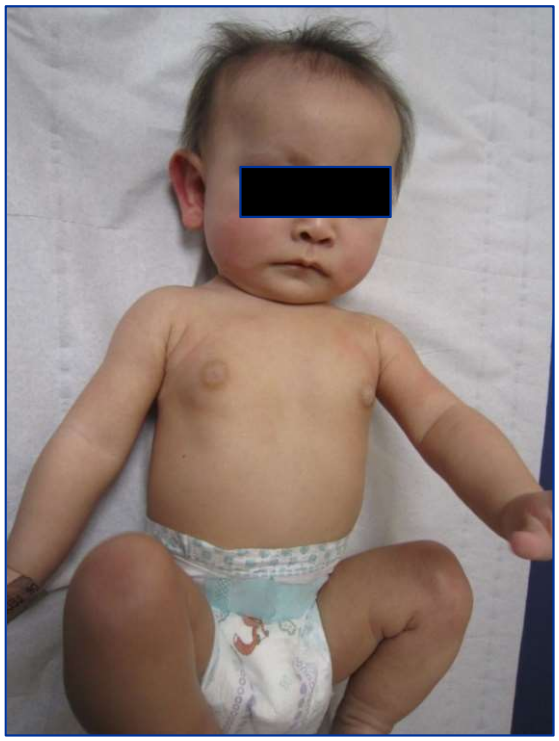
Facial gestalt? Patience…



2 months







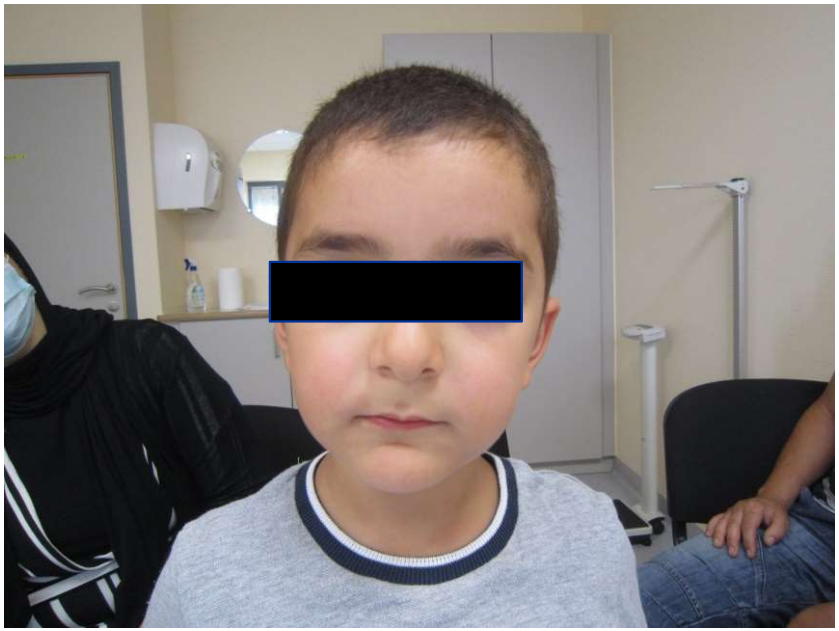
6 months

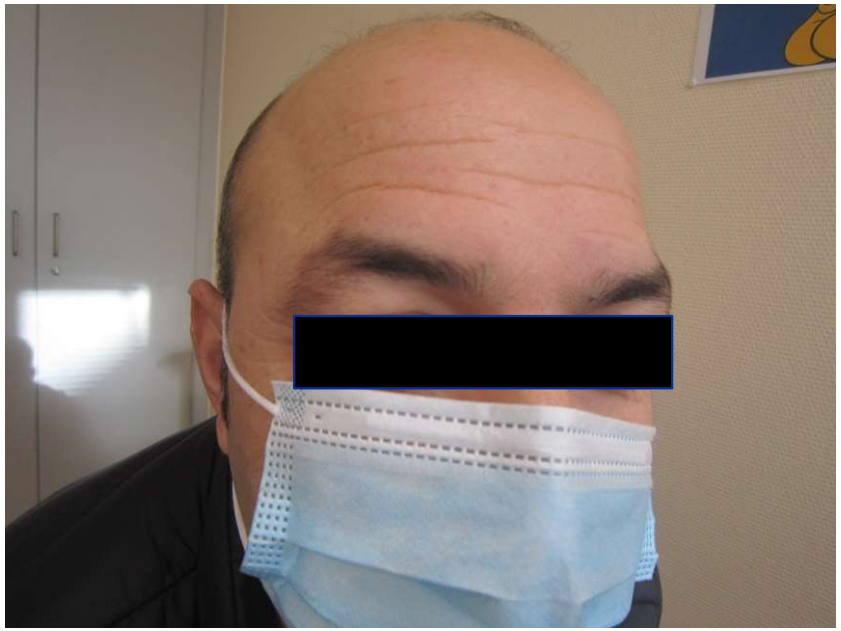
Kabuki in neonate

- Hypotonia
- Feeding difficulties
- Neonatal teeth

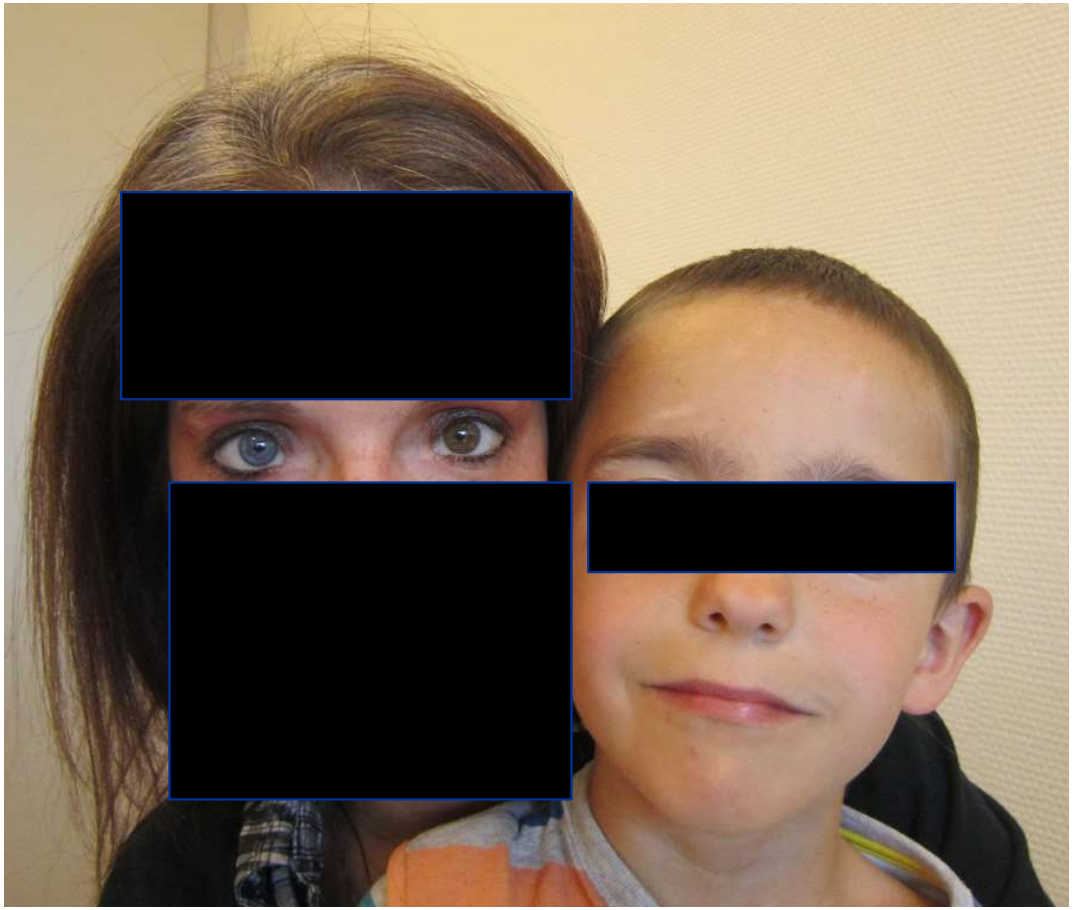
IPG

Facial gestalt?





Blick diagnosis

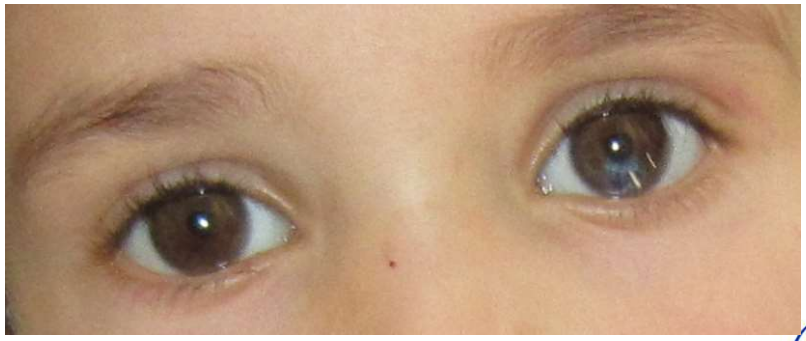


Waardenburg syndrome

PAX3 deletion

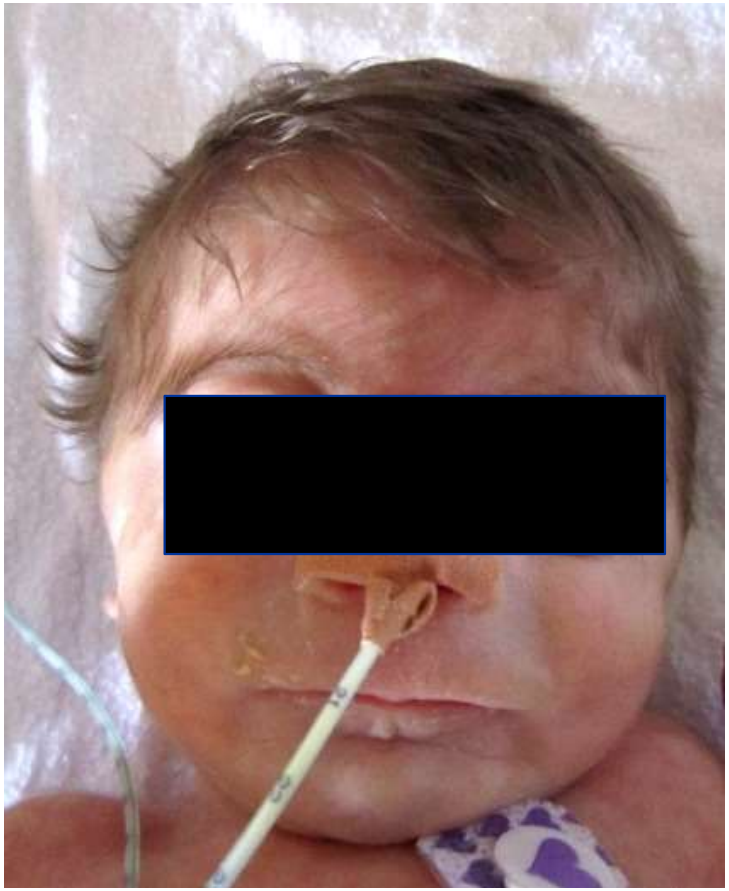
Shah-Waardenburg syndrome SOX10 c.425G>T; p.(Trp142*)

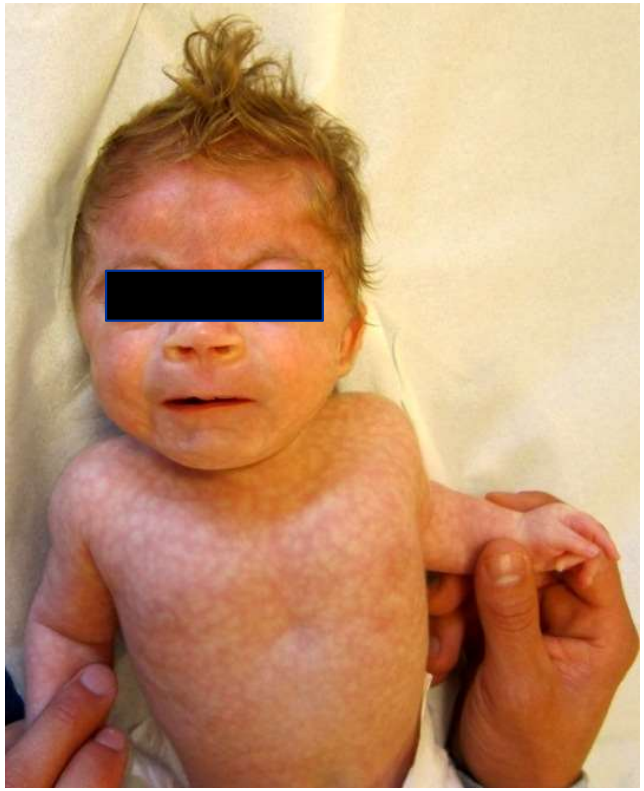
- Neurosensorial deafness
- Pigmentary anomalies
  - Iris
  - Hair
  - Skin
- Dystopia canthorum
- No epilepsy or developmental delay

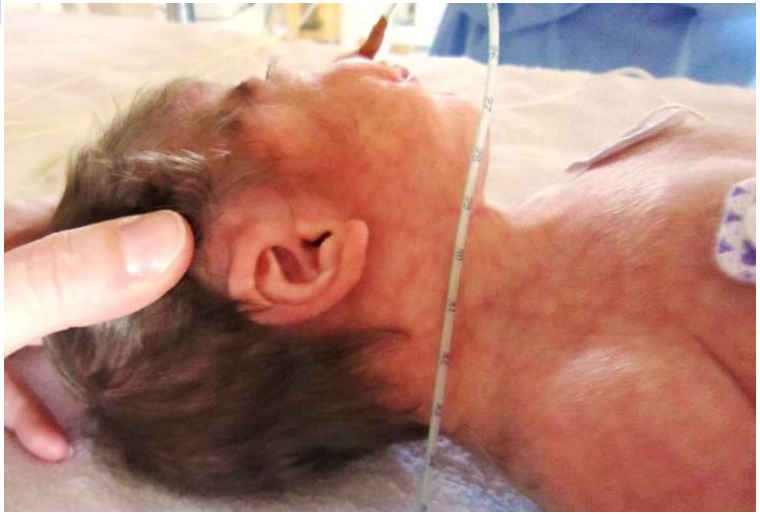


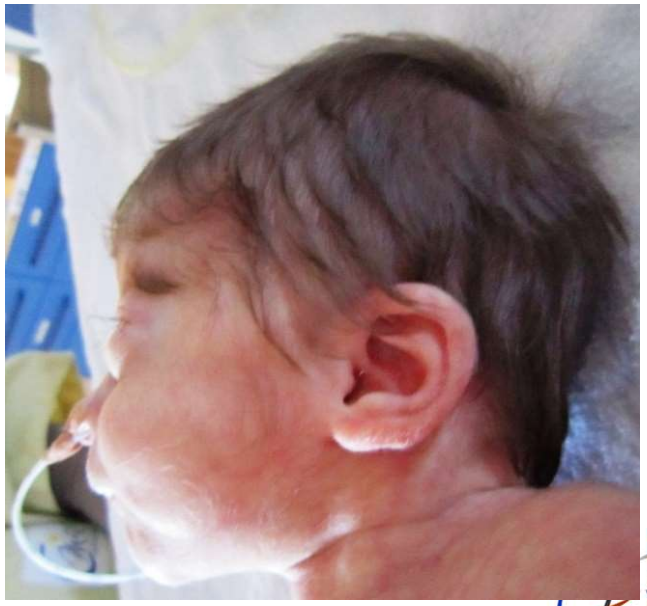
Blick

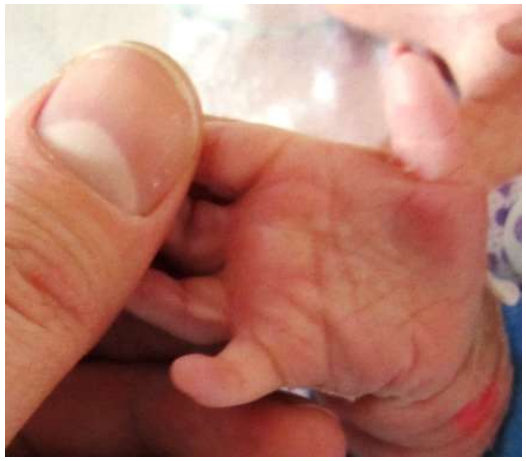
- IUGR
- Short stature
- Microcephaly
- GE reflux
- Psychomotor retardation

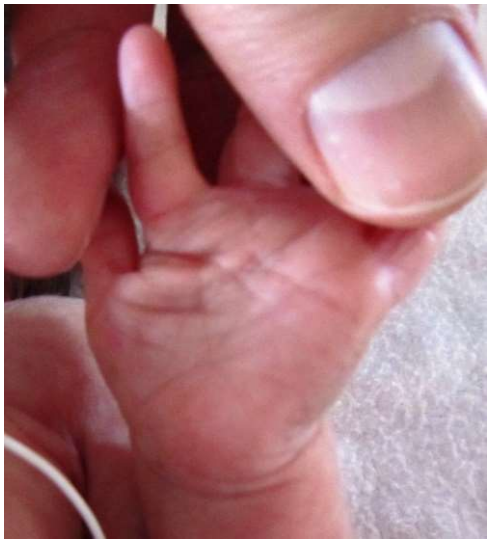


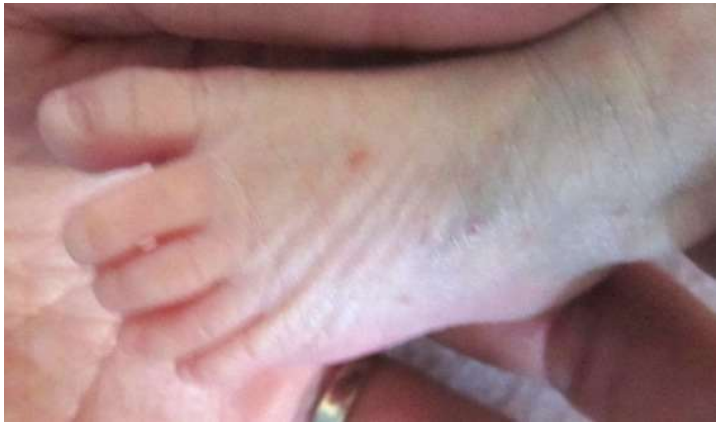


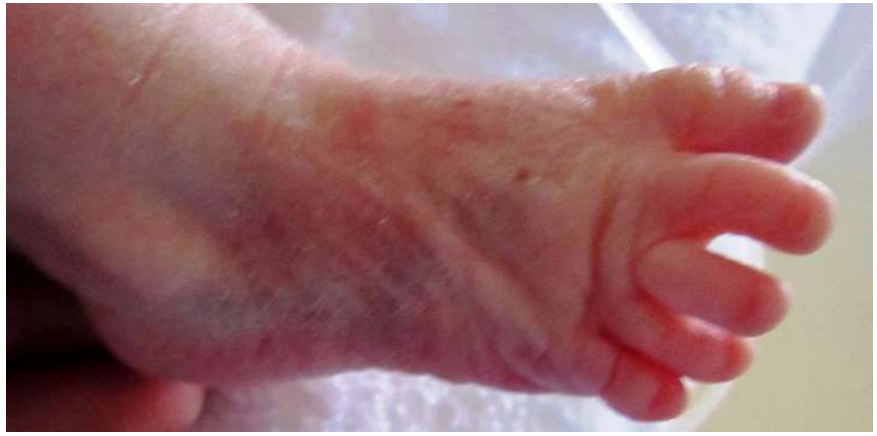


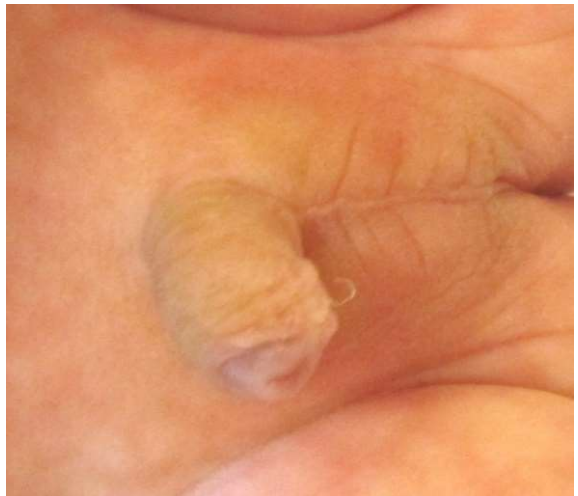


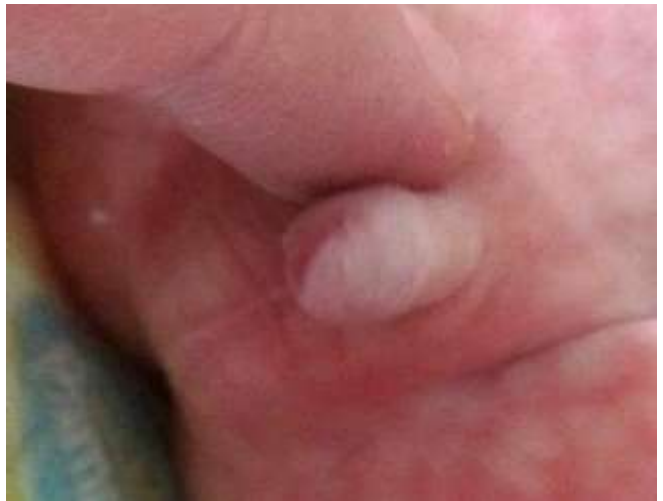








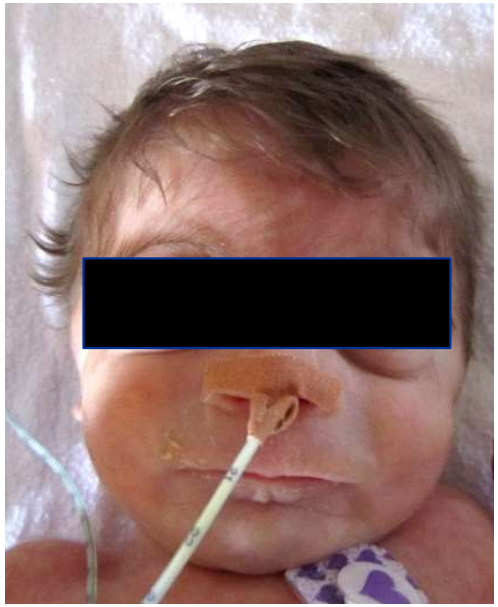


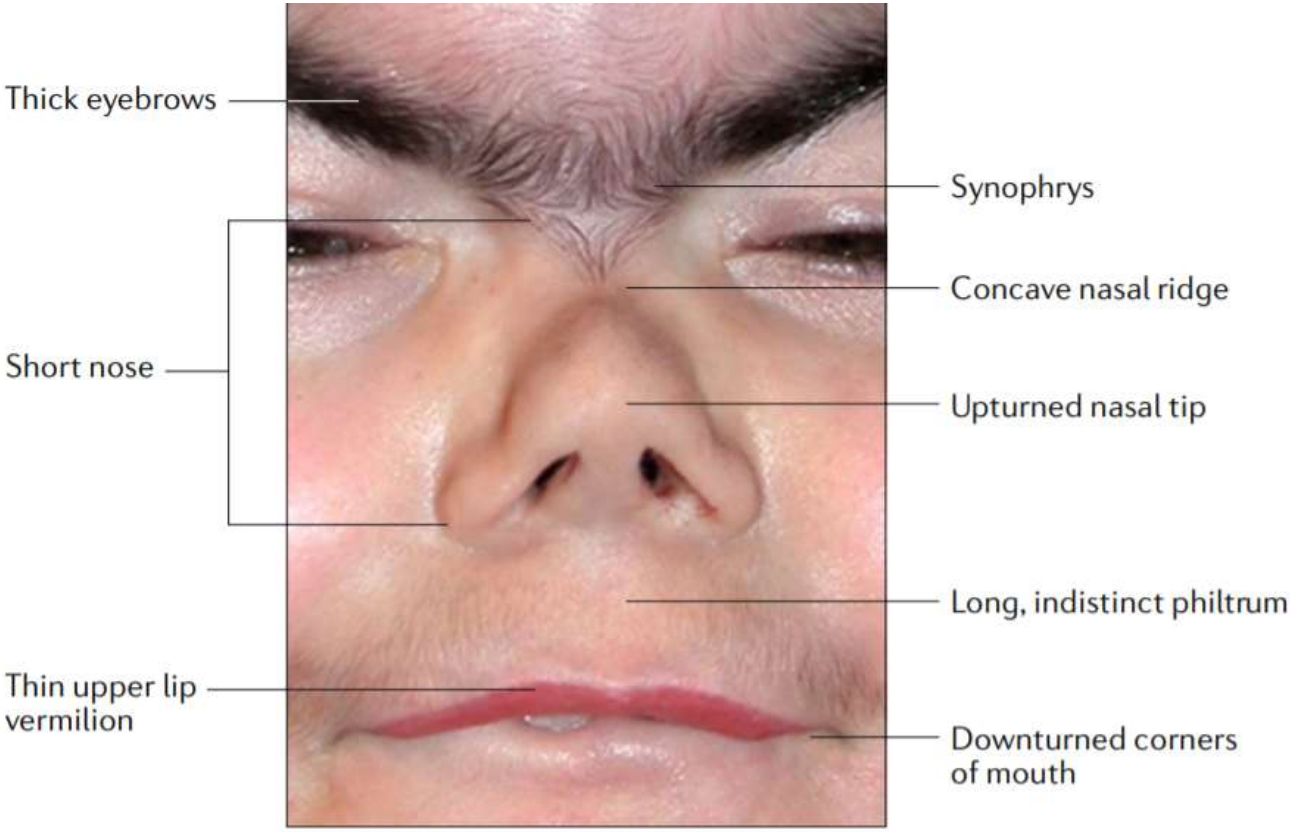


IPG

Cornelia de Lange

- c.6655_6657del in NIPBL gene
- http://**www.cdlsusa.org**/cdls-for-professionals.htm
  - Clinical checklist
  - Specific growth curve
  - Specific developmental skills chart
  - Treatment guideline

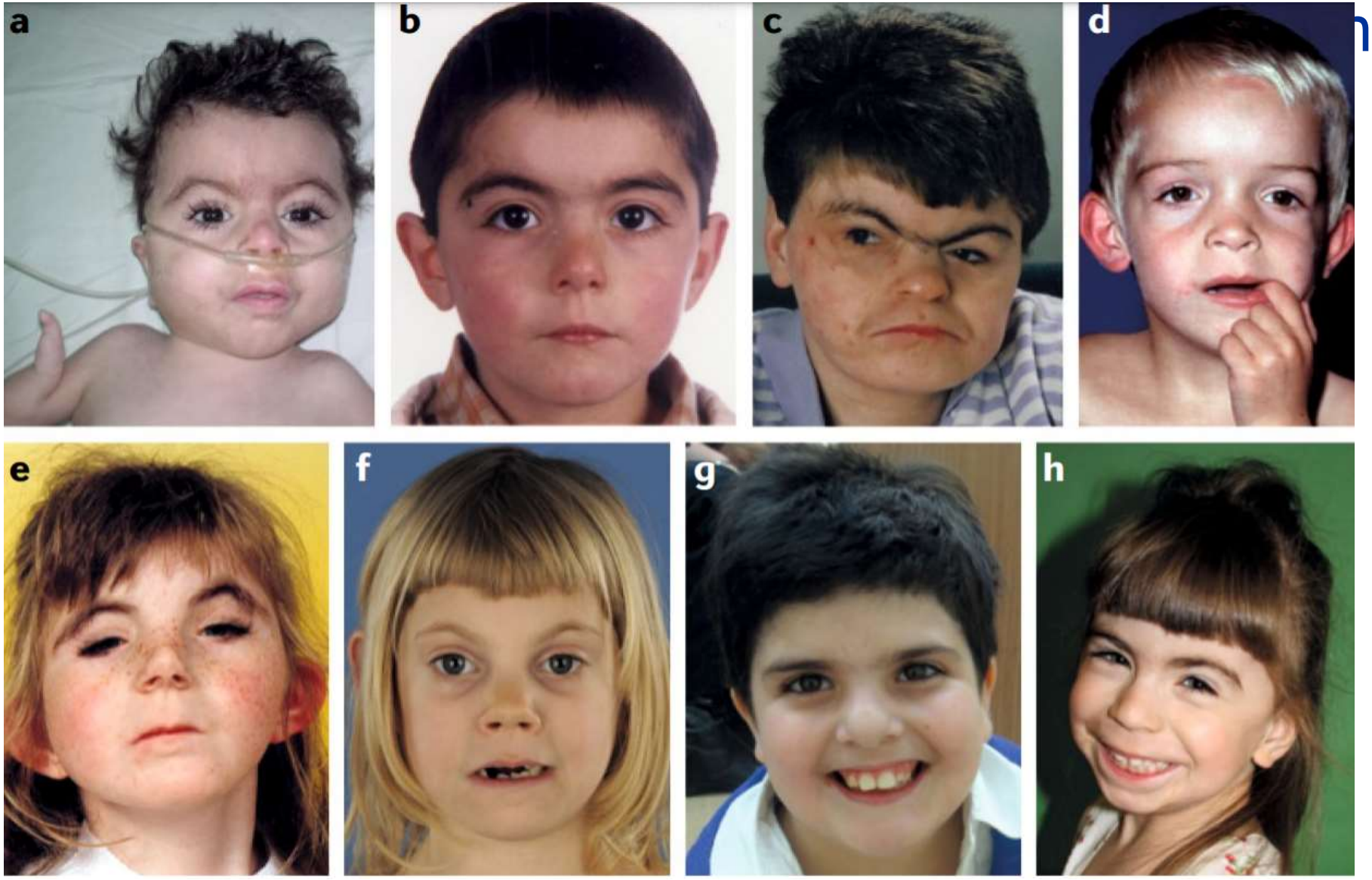




Kline et al. Nat Rev Genet

Many genes, one diagnosis?

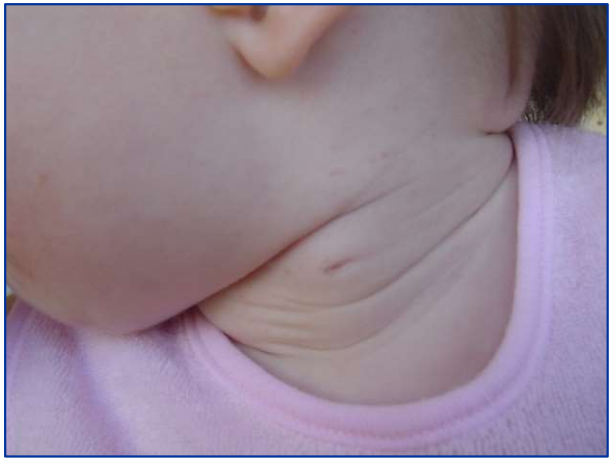
NIPBL NIPBL NIPBL SMC1A

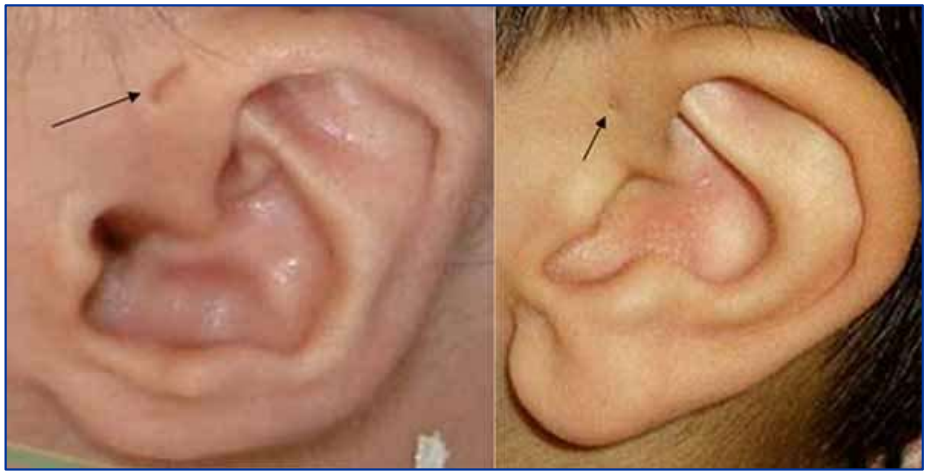


NIPBL RAD21 HDAC8 ANKRD11

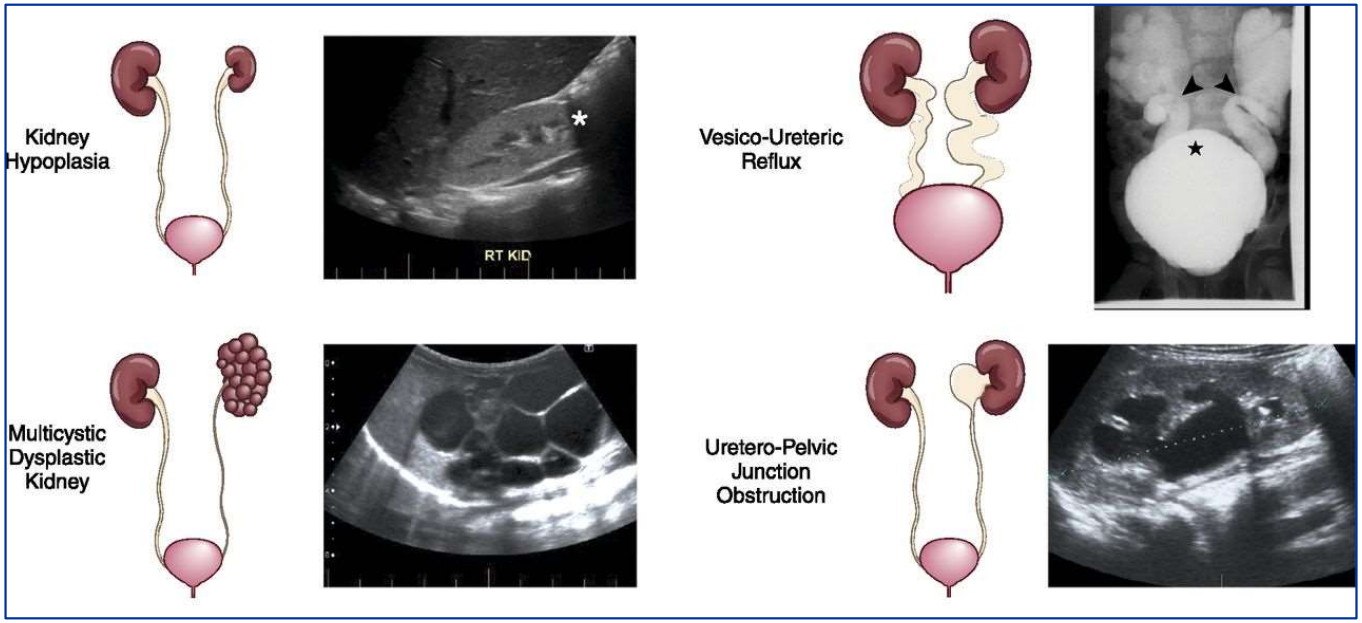
IPG

Unique association

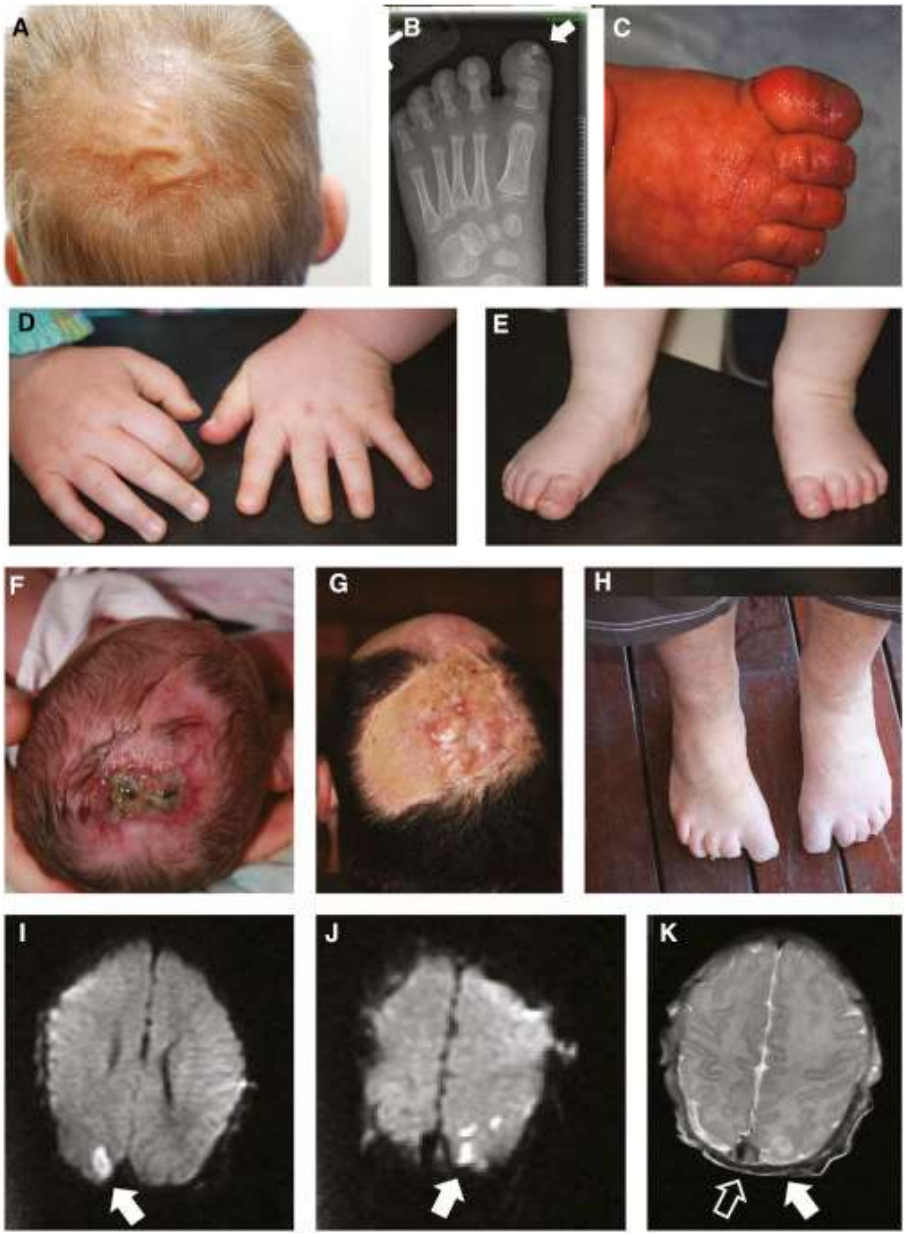


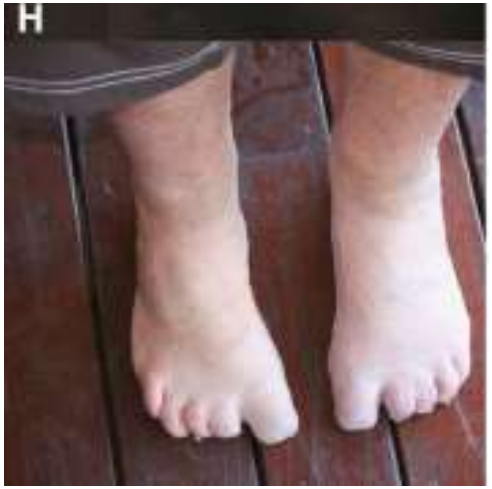


Branchio
Oto
Renal
EYA1



Unique association

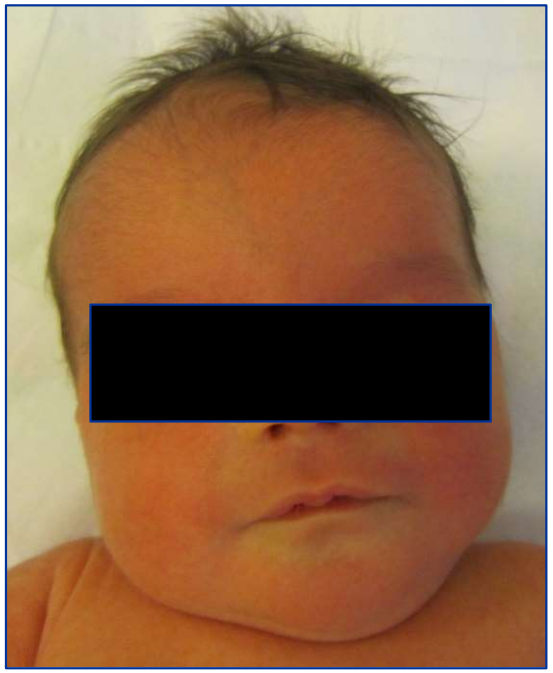




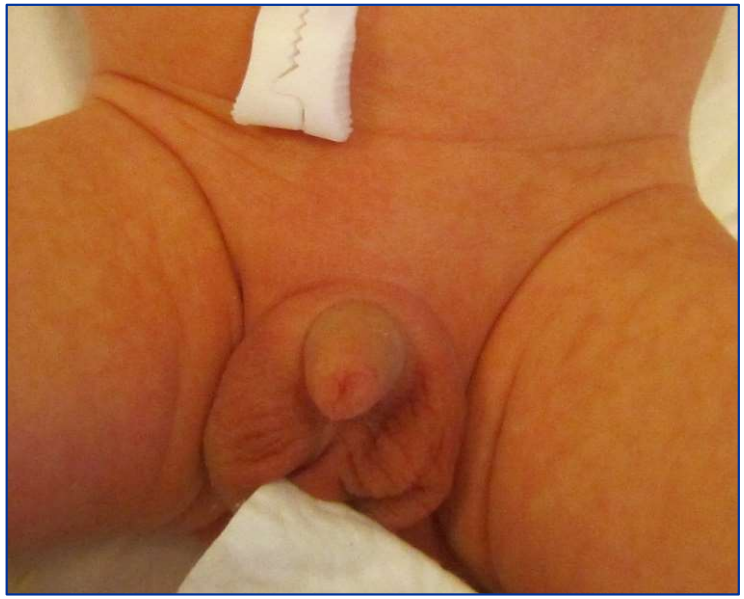
- Adams Oliver syndrome
  - Transverse limb defect
  - Aplasia cutis congenita (scalp)
  - Cutis marmorata (inconstant)

IPG

Unique association

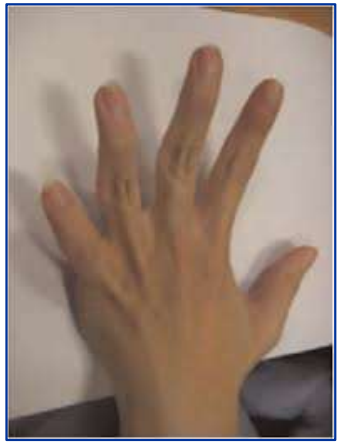


Round face



Shawl scrotum

Short limbs

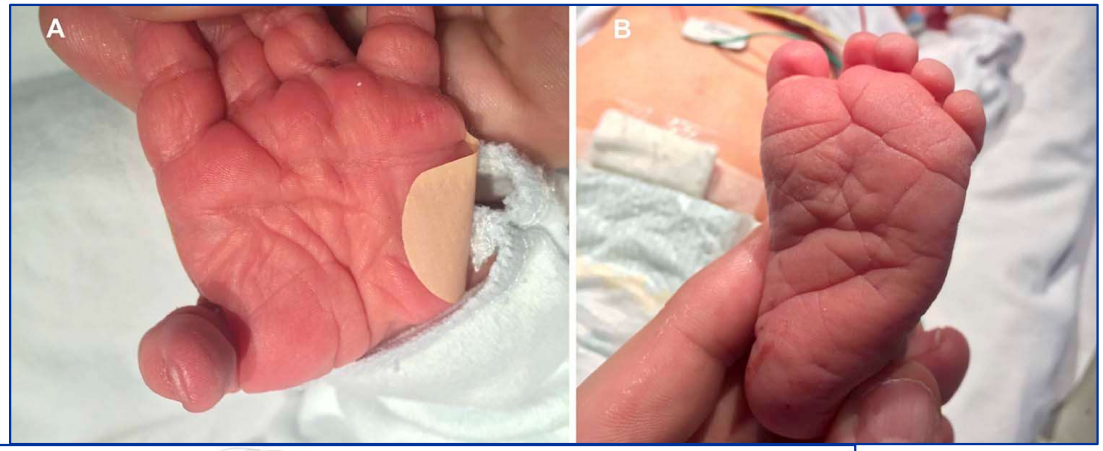


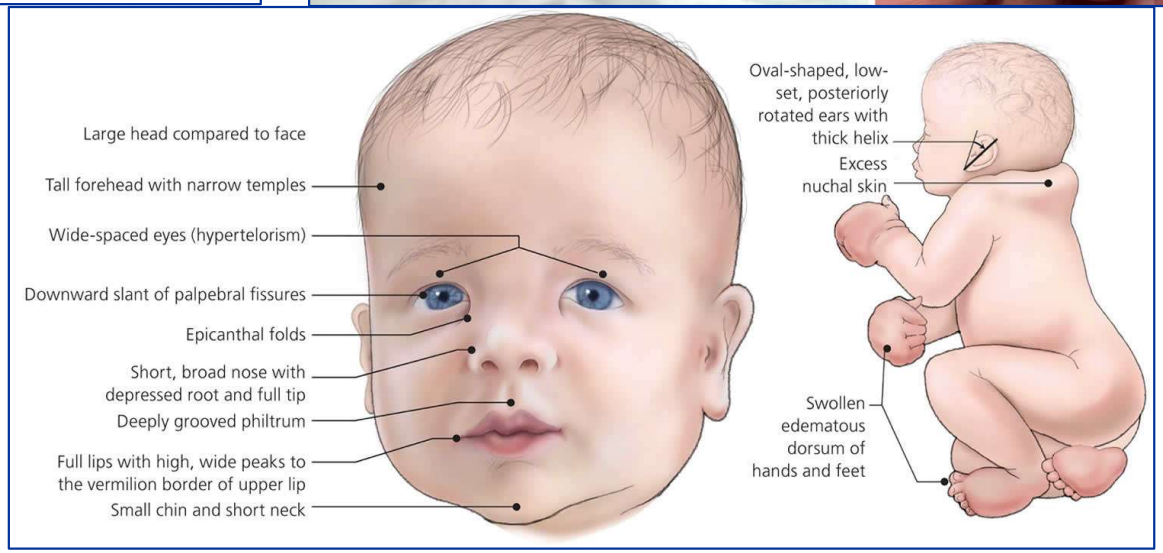
Aarskog Scott syndrome
FGD1
X-linked
Maternal grand father, uncle?

IPG

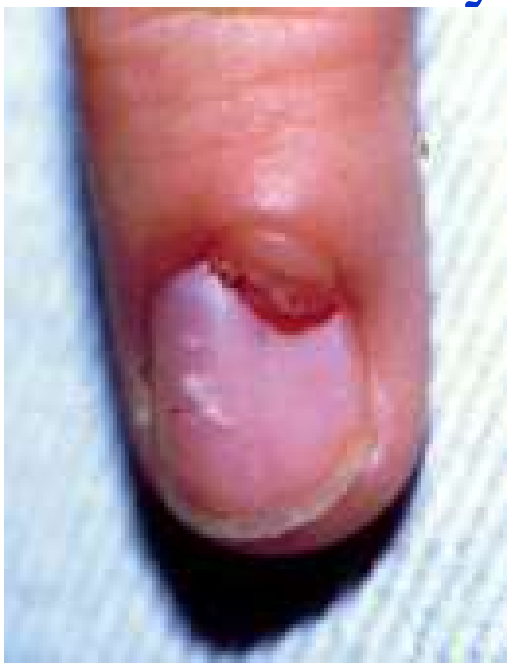
One sign, one metabolic pathway

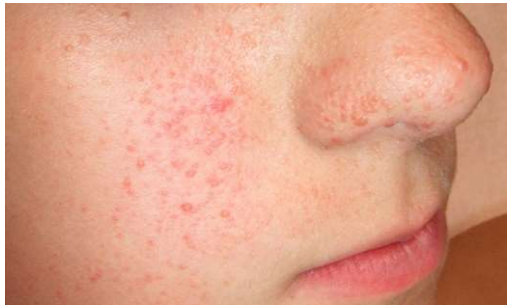
- Rasopathy hands



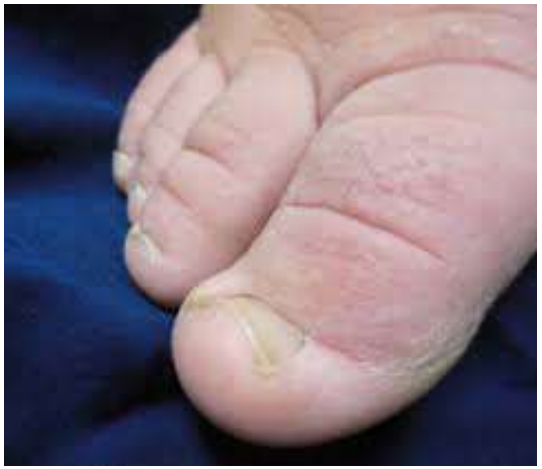


Nail and syndromes

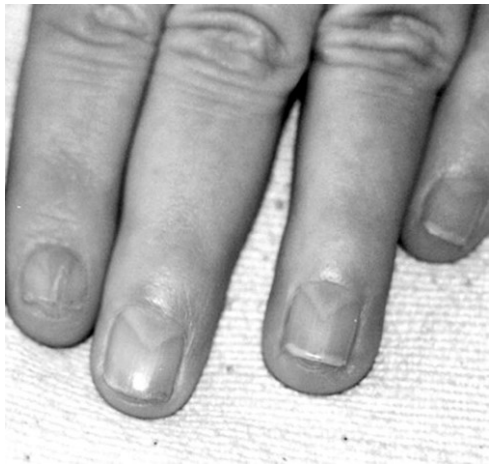


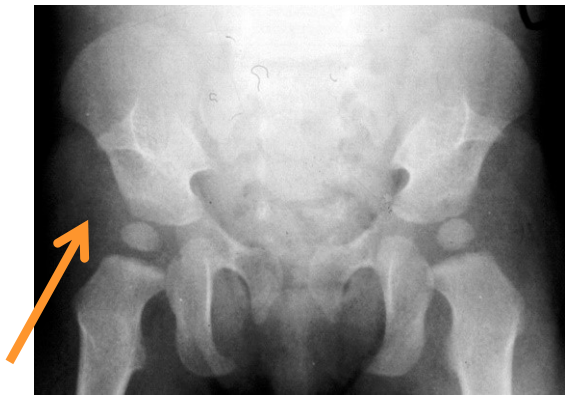


Periungueal fibroma
Tuberous sclerosis
TSC1-2



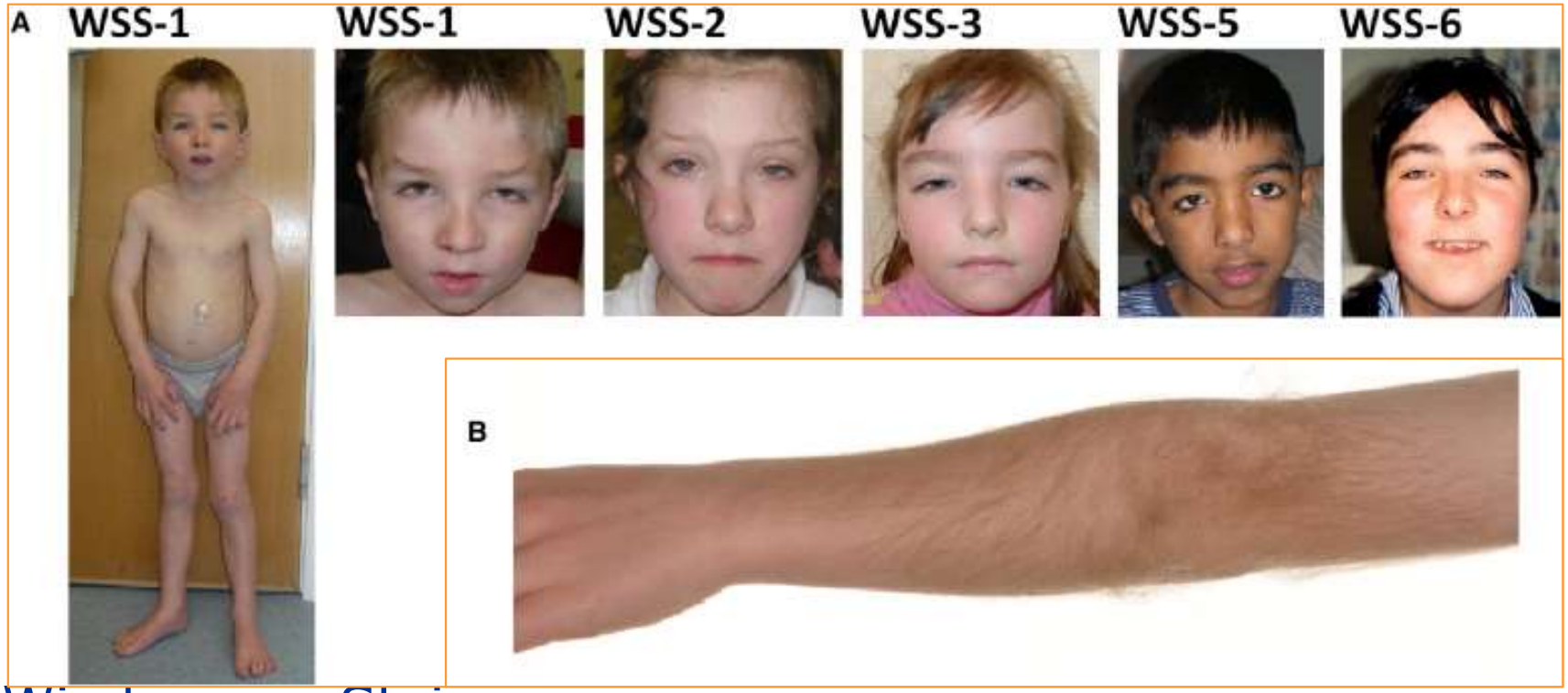
Ski jump nail
Congenital lymphoedema
Distichiasis
FOXC2





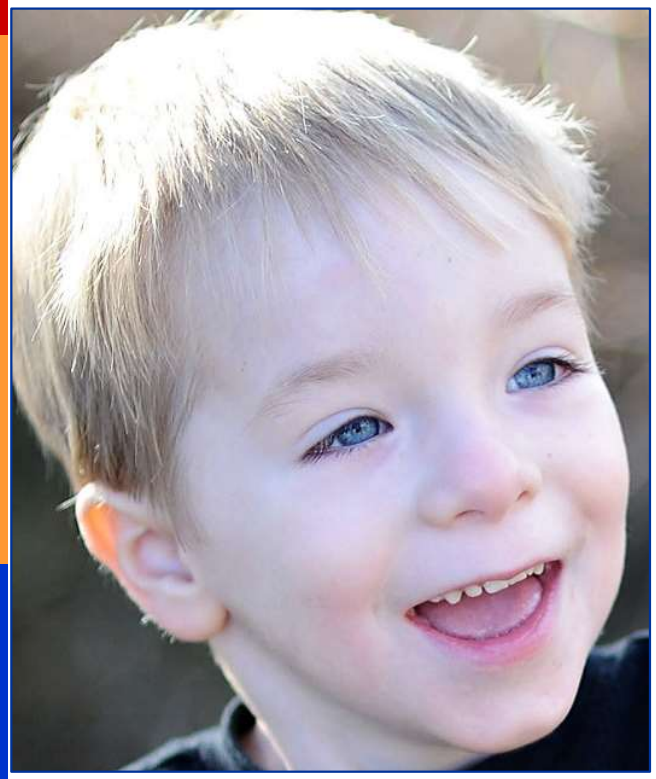
Nail dystrophy
Triangular lunules
Iliac horn
Absent patella
Nail-patella
LXMB1

Major sign



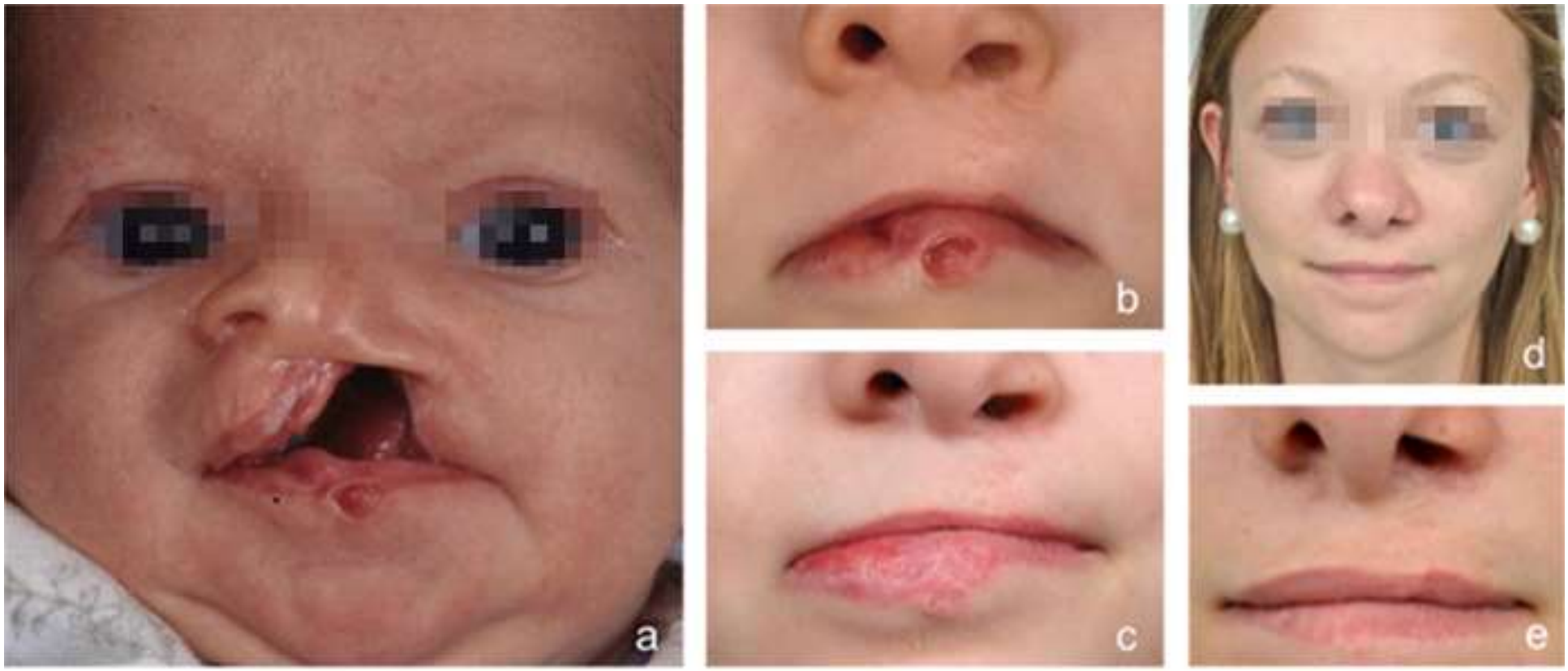
- Wiedemann Steiner
  - Intellectual disability
  - Short stature
  - Medial flare of eyebrows
  - Hypertelorism
  - Short hands - feet

What to look at next?



- Something in the eyes

Unique association

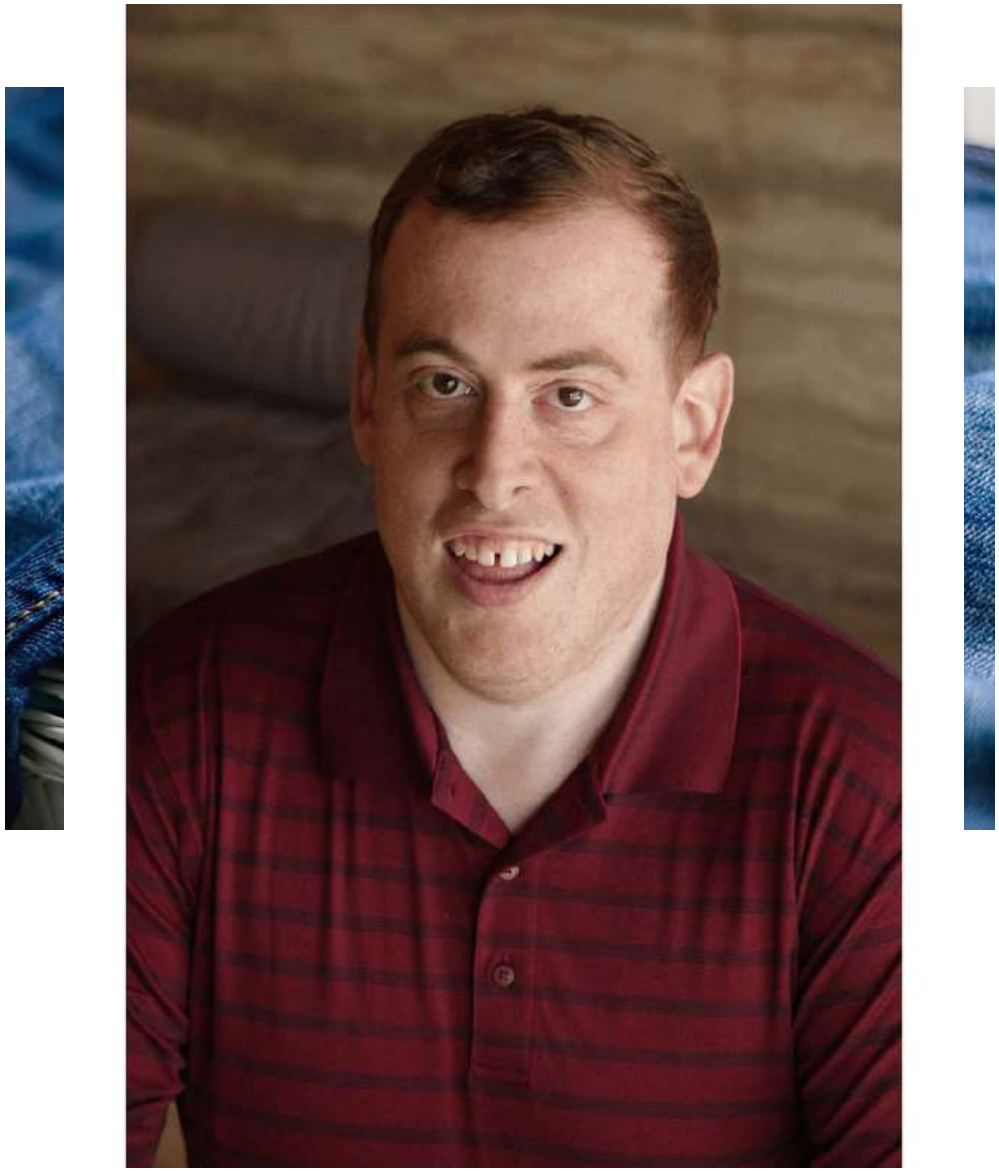


!!!aesthetic surgery!!!

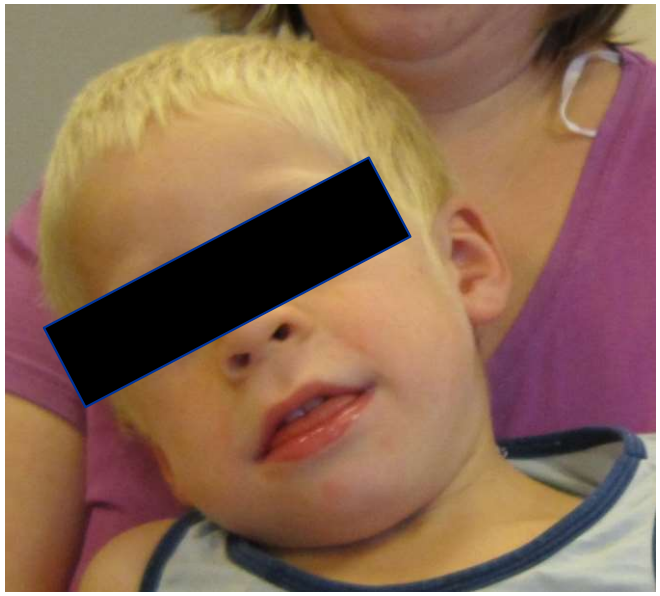
- **Van Der Woude syndrome**
- IRF6 72%
- GRHL3 17%
- Autosomal dominant, incomplete penetrance (! Parents examination!)

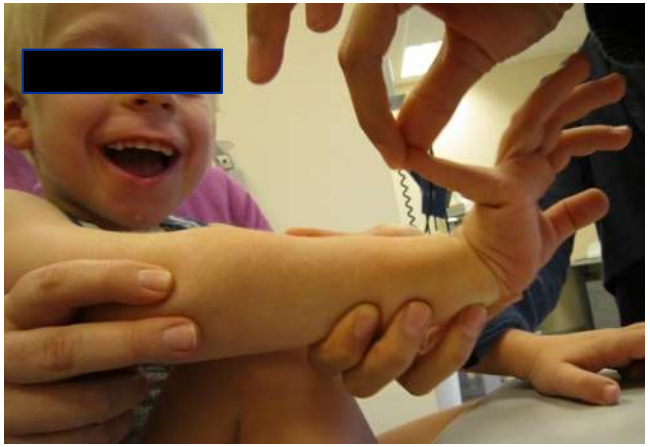
A syndrome not to miss!!!

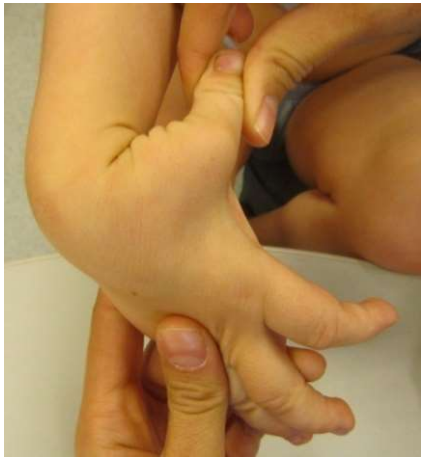
- Macroorchidy and ID
  - Fragile X
  - Triplet expansion repeat
  - Not seen in panel/exome



- Fragile X in childhood
  - **ID**
  - Macrocephaly
  - Behaviour trouble
  - Hyperlaxity
  - « fleshy hands »

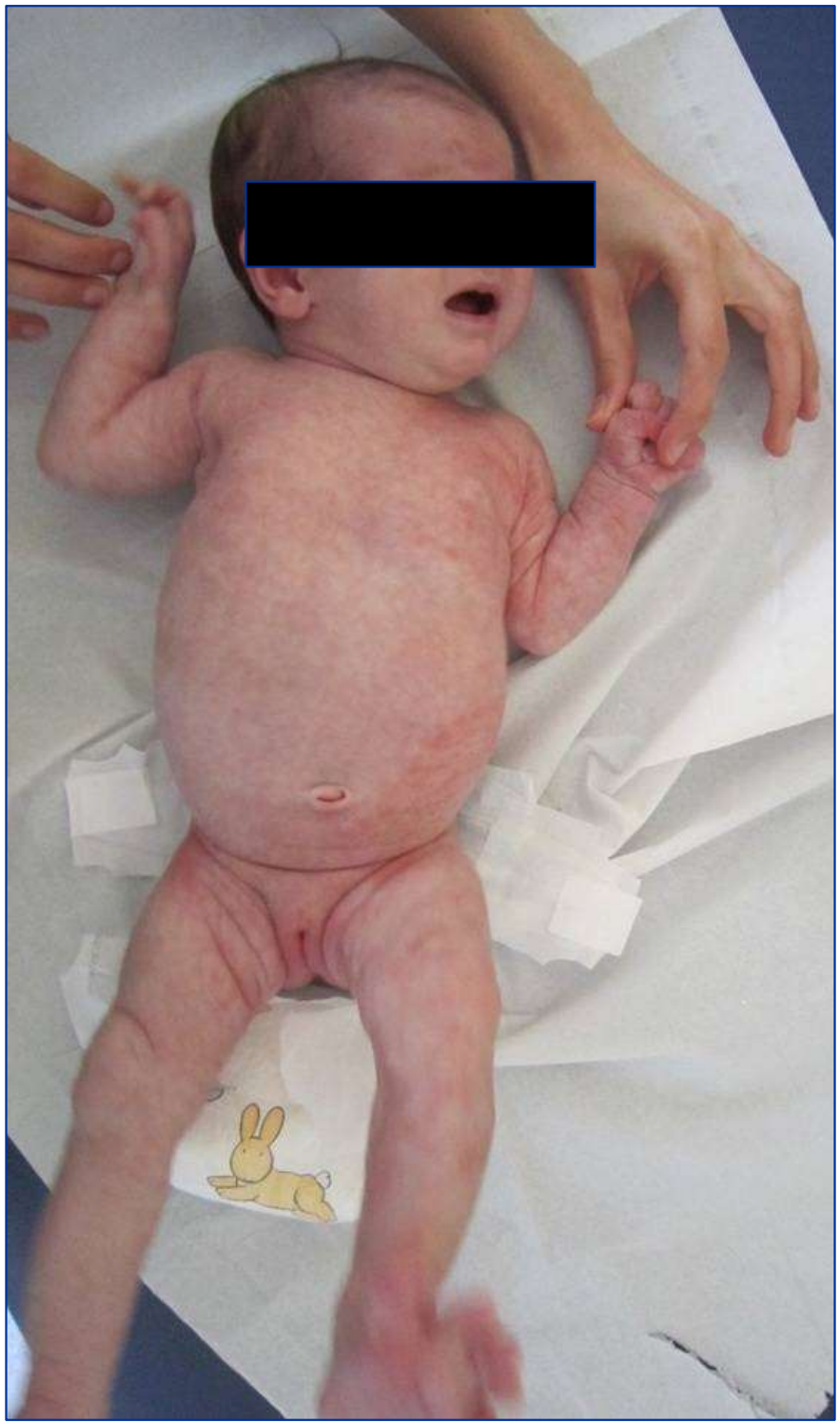


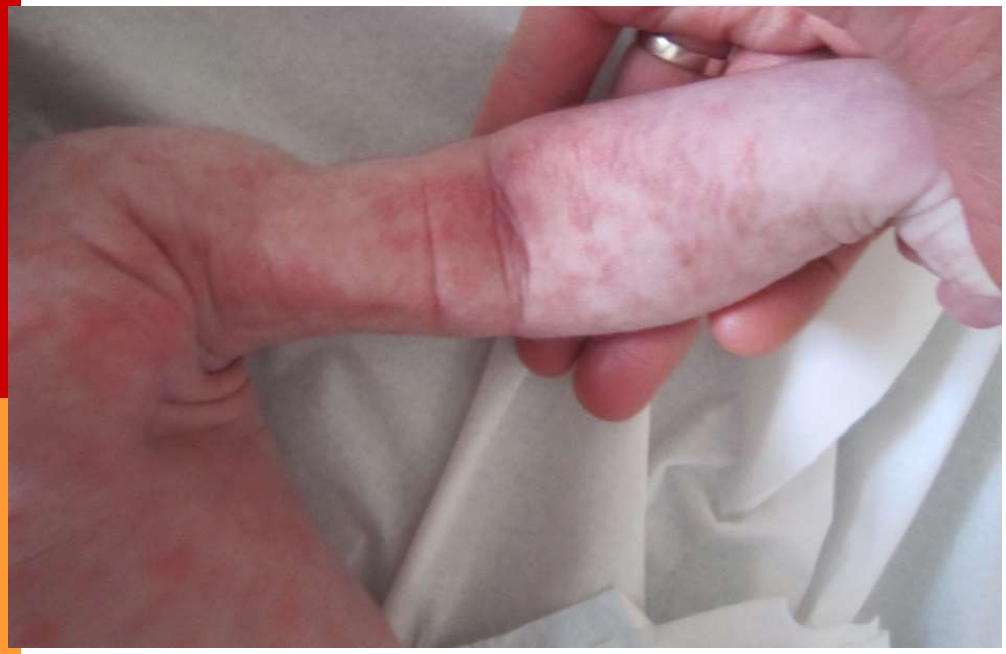


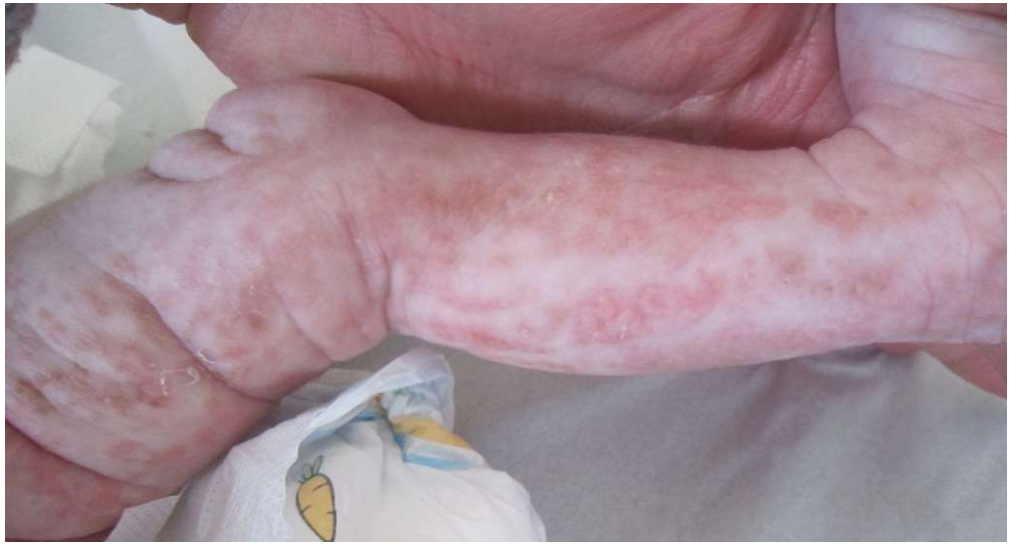


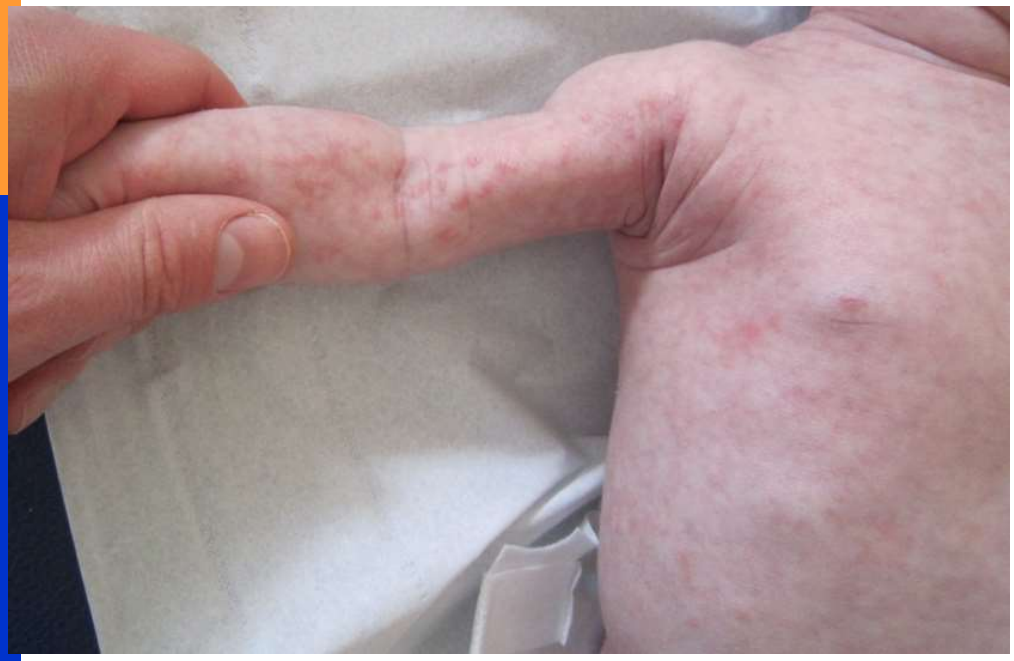
Skin diagnosis

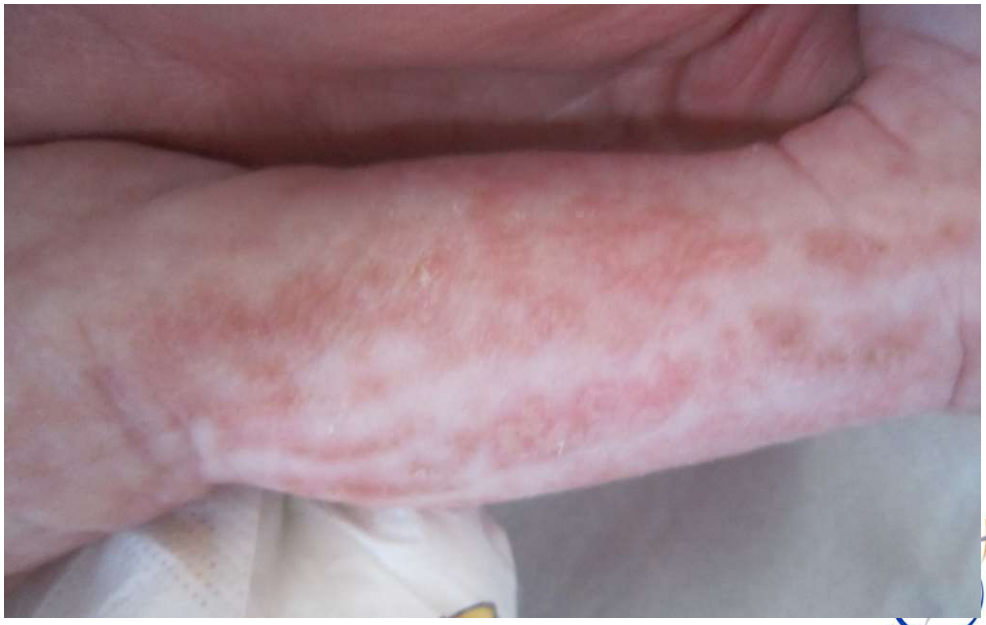
- Normal pregnancy
- Normal birth parameters
- 10 days: erythema and blisters, linear distribution
- !!!**Timing of lesions**!!!





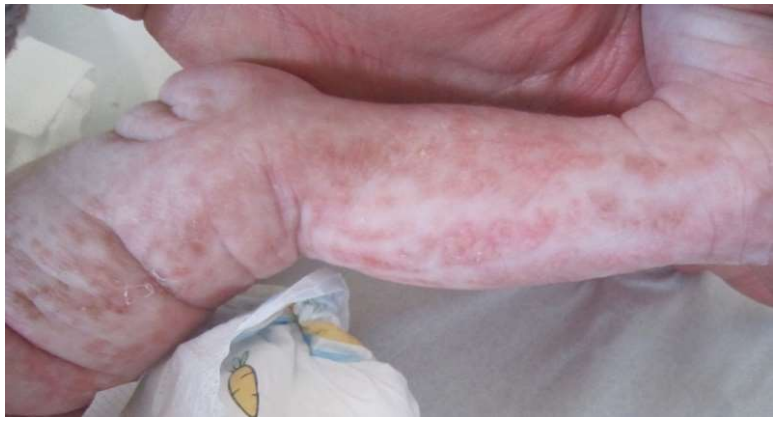


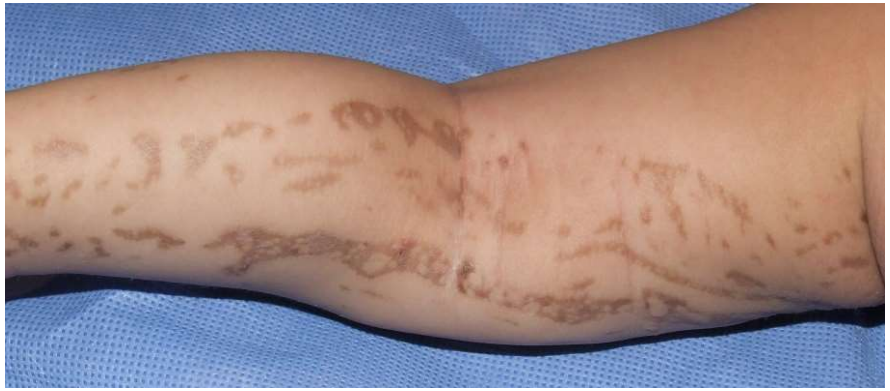


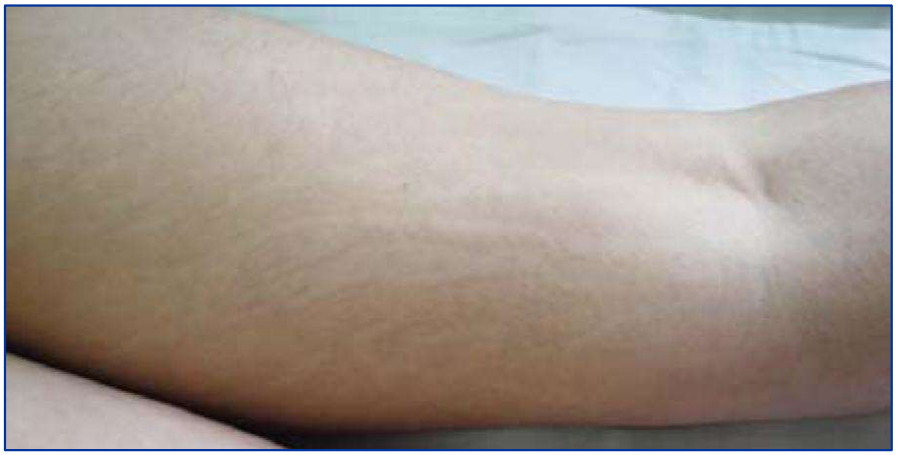


Incontinentia Pigmenti

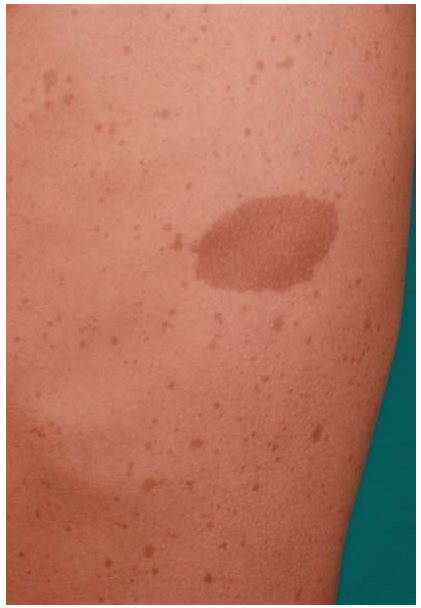
- *IKBKG* mutation c.305_314del, p.Lys102Argfs*10 (exon 3)



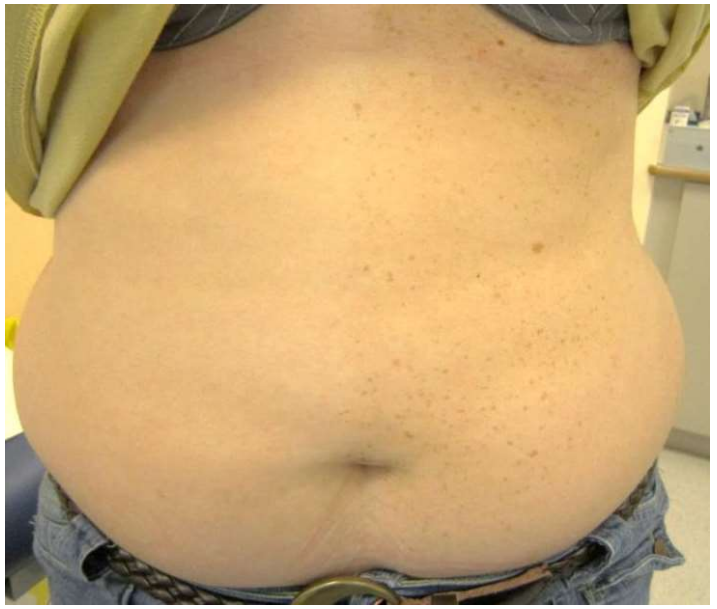




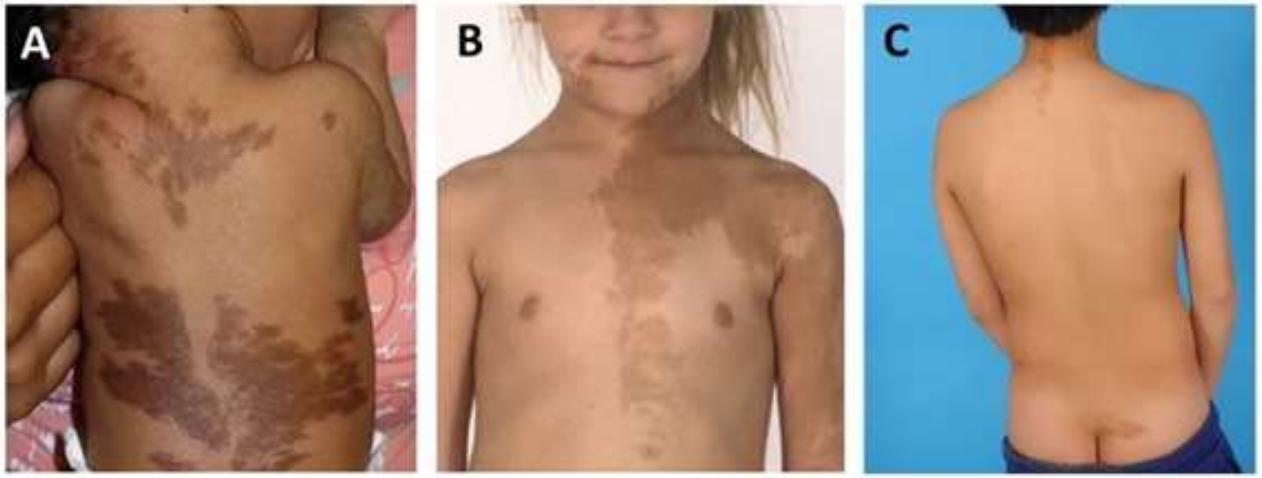
Skin diagnosis



NF1

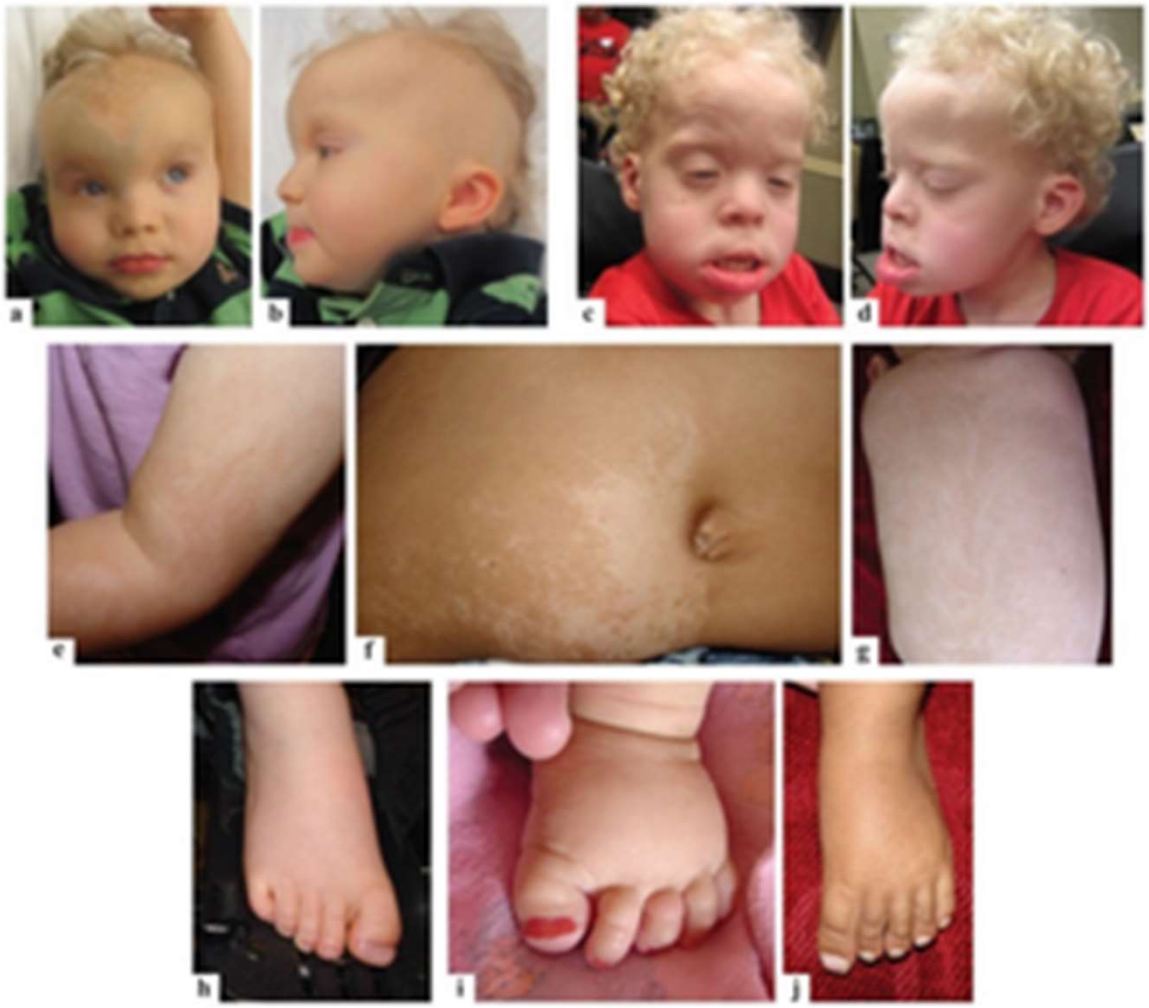


Segmental NF1 (skin biopsy)



GNAS mutation
Mosaic in blood
Skin biopsy

Skin diagnosis



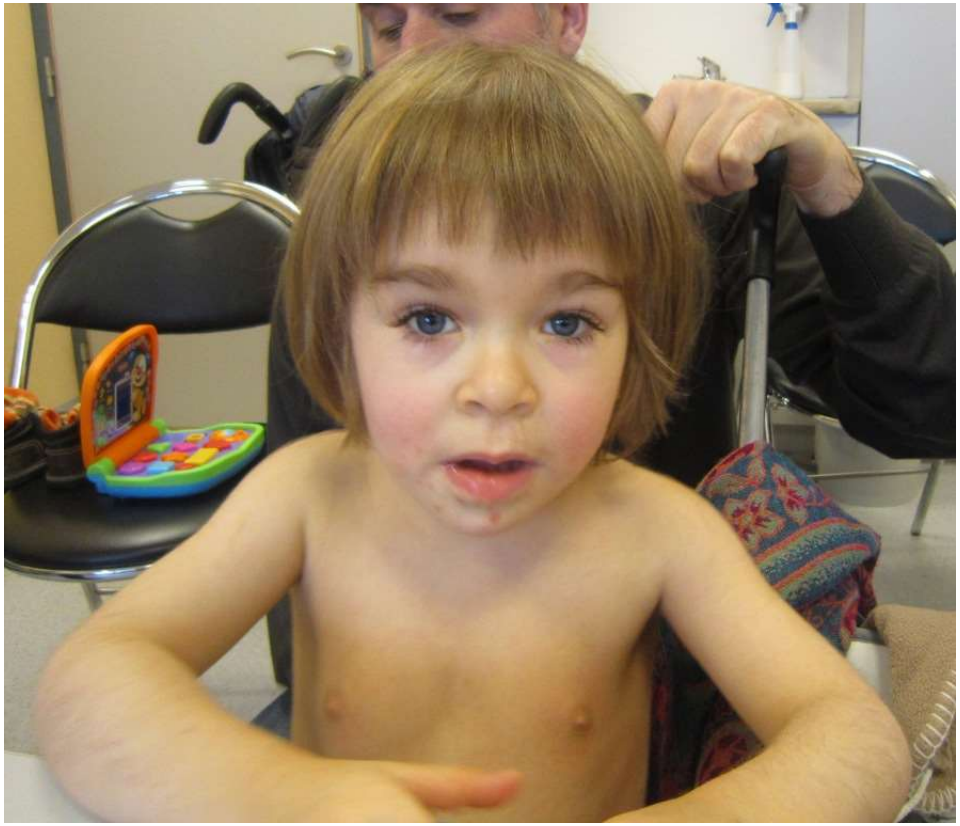
- Mosaic tetrasomy 12p
- **Skin biopsy** required

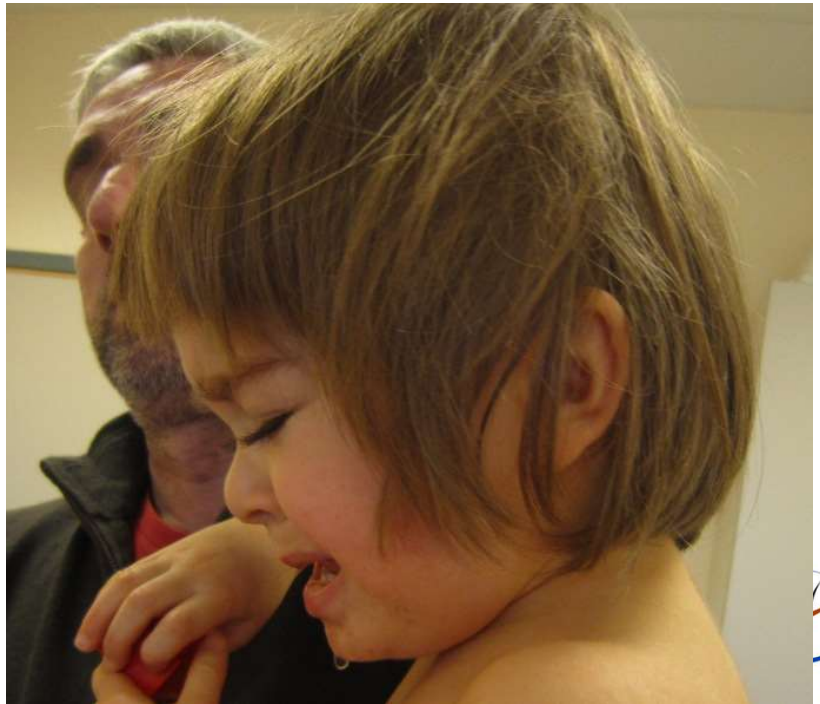
A little sign…

- Uneventful pregnancy
- Normal birth parameters
- Neonate
  - Apnea
  - Laryngomalacia
- Sit: 7 m
- Walk: 23m
- Develomental delay
- Speech delay
- Atopic dermatitis
- Behaviour trouble, ASD

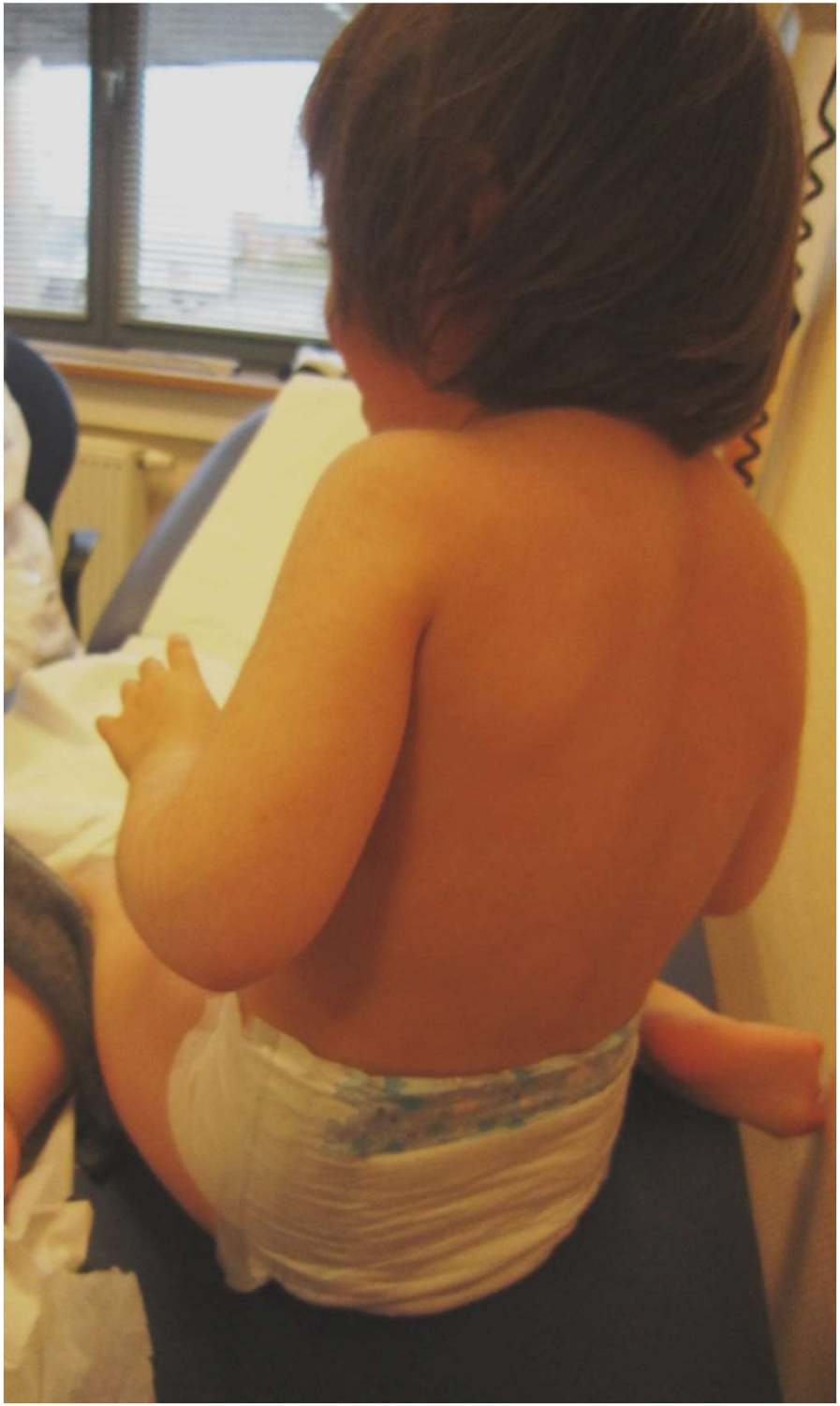
- Brain MRI: partial CCA

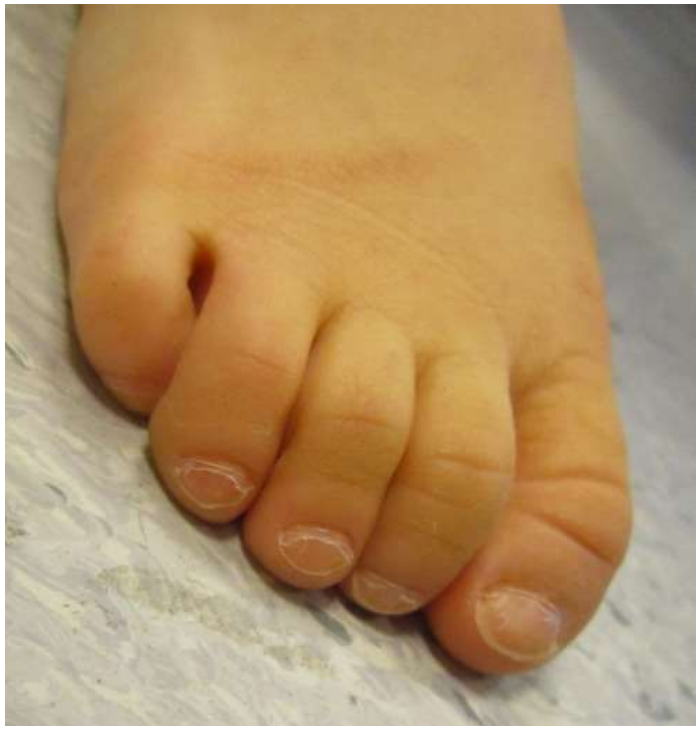
- Normal CGH

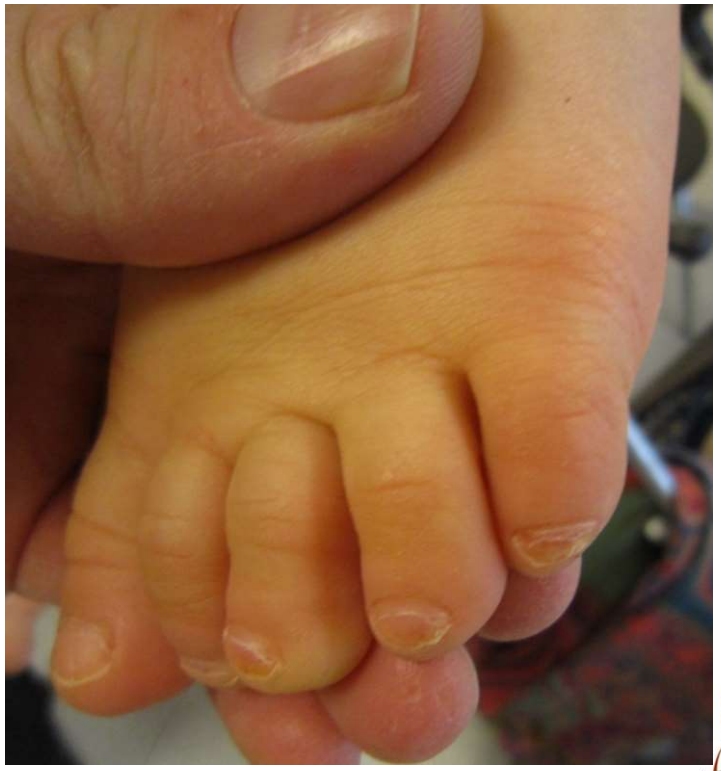




IPG

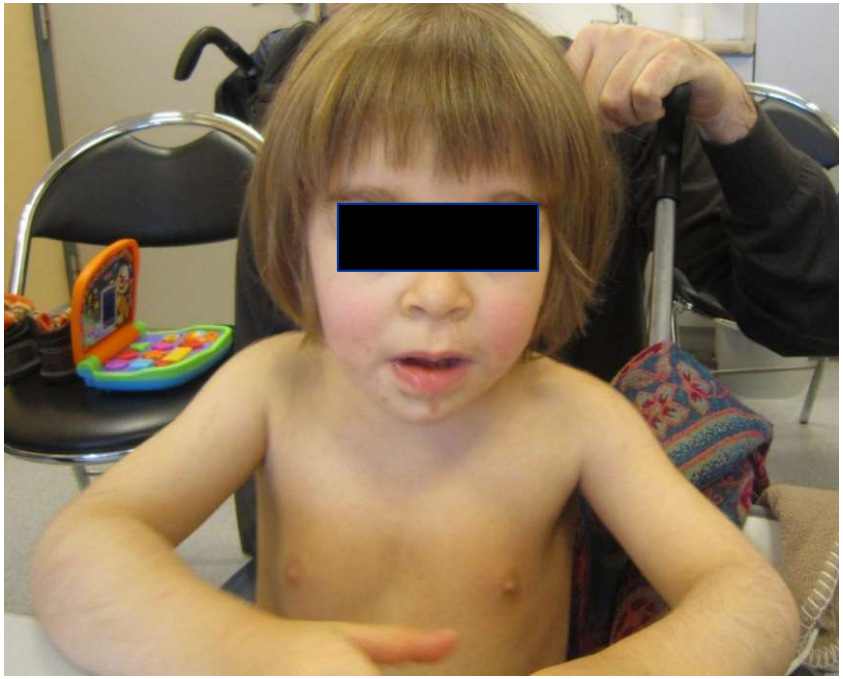


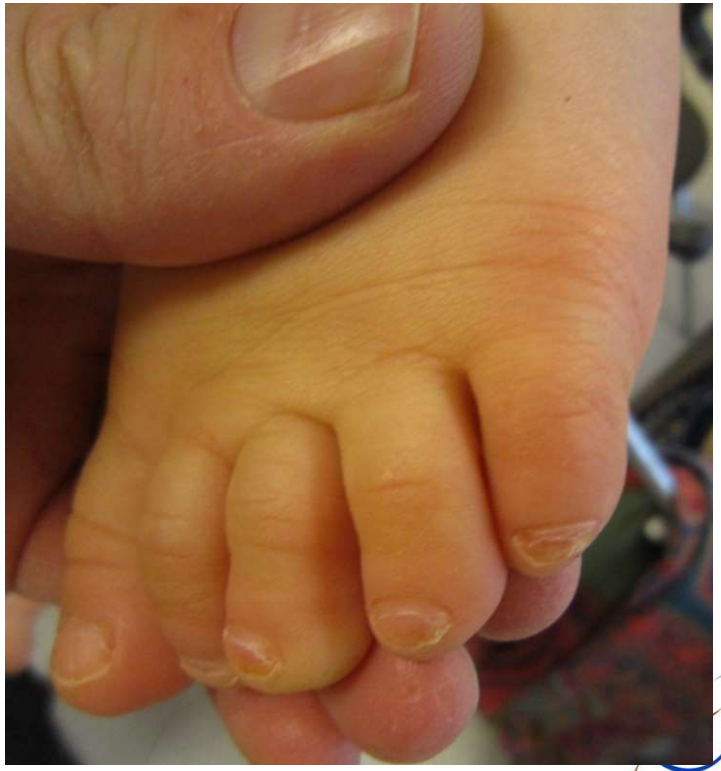




Coffin Siris

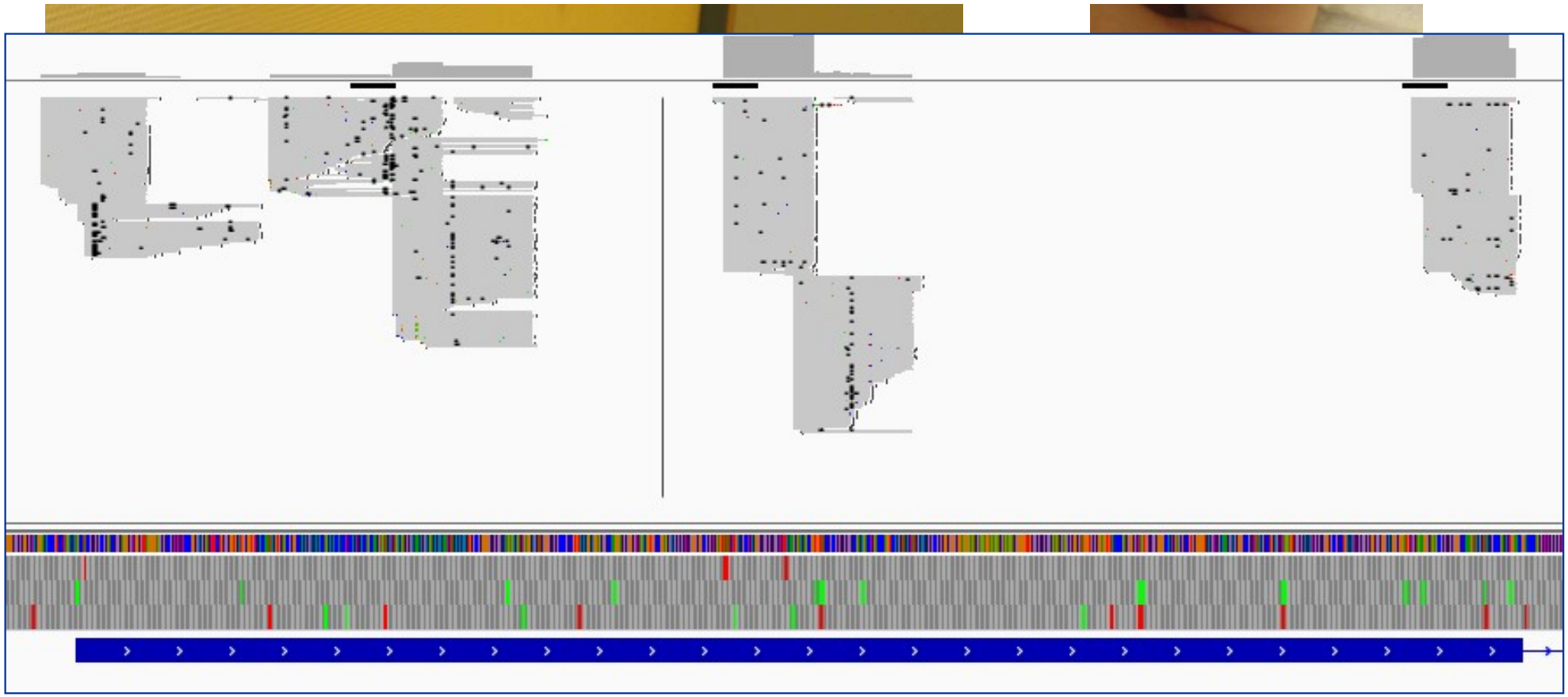
- ARID1B (Sanger)
  - c.4110G>A
  - p.Arg1338Argfs*76 (Splice, Hoyer 2012)





Missed mutation

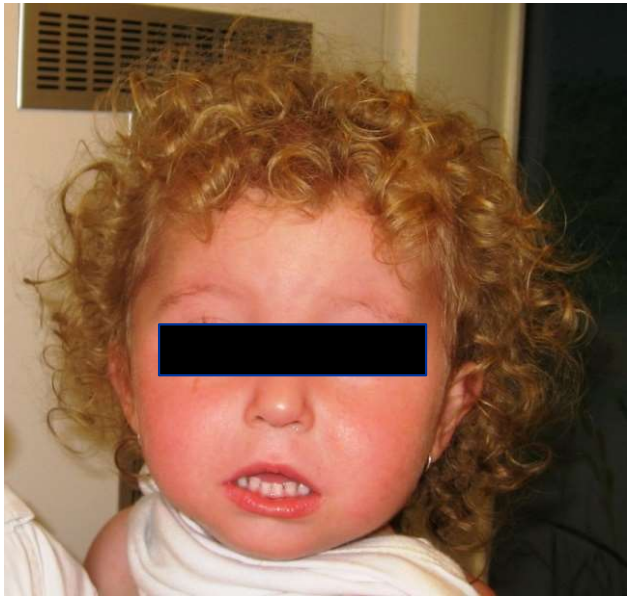
- ARID1B c.662_669del (p.Gly221Alafs*)

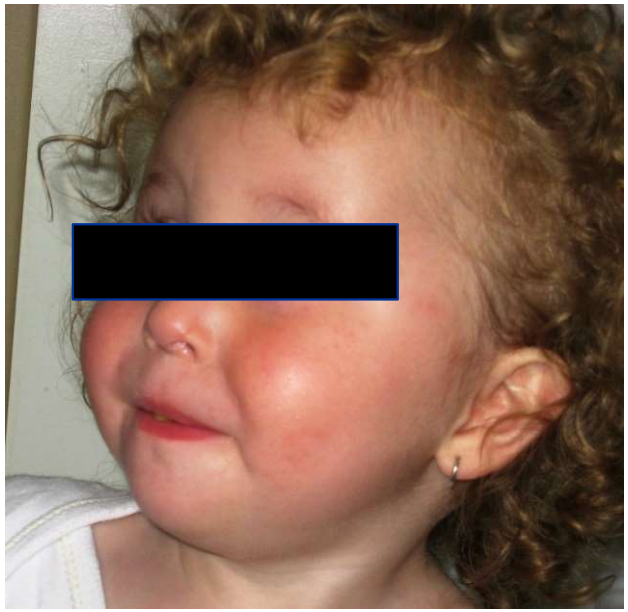


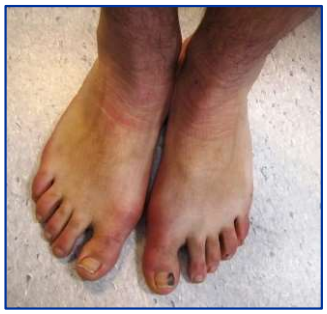
Phenotype without genotype

- 2y ½
- Birth parameters: P25
- Height P25
- HC P75
- Developmental delay
- Severe speech delay
- Mild behaviour trouble
- Eye-audition: nl
- Caryotype/CGH: nl

- Pregnancy:
  - Valproate 500 mg 2x (first 7 weeks)



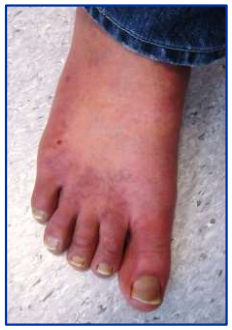




500 mg

1000 mg

1500 mg



Valproate syndrome

1000 mg

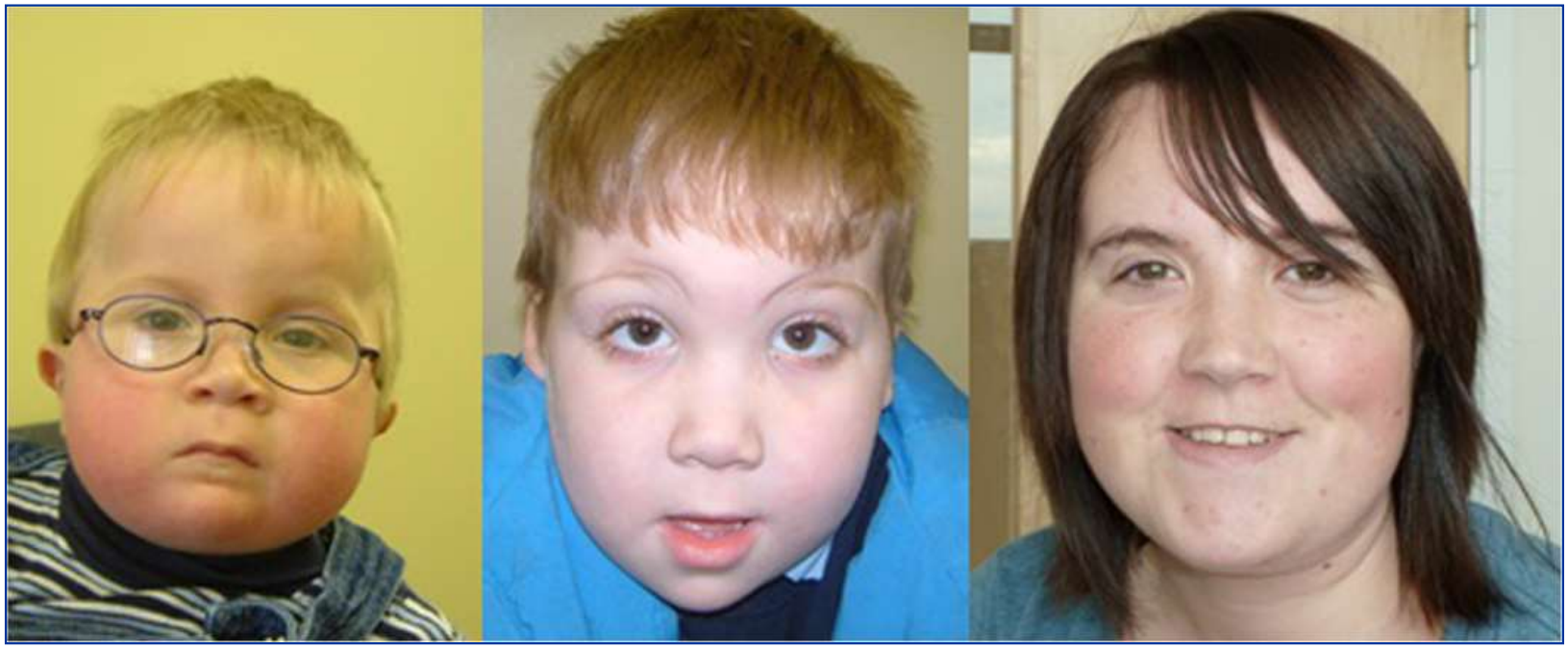
1500 mg

Criteria based diagnosis

Grade	Criterion	Comments
Essential	Confirmed exposure to VPA during pregnancy	Any dose or duration
Essential	Has no other recognisable diagnosis which would explain the phenotype	As evidenced on assessment by a clinical geneticist or other professional with relevant expertise
Essential	Normal microarray-CGH and Fragile X studies	Part of diagnostic work-up
Essential	Other teratogenic disorders with clinical overlap excluded	In particular fetal alcohol syndrome / spectrum disorder
Suggestive	Facial dysmorphism consistent with VPA exposure (flat philtrum, thin upper lip, full, everted lower lip, short anteverted nose, small mouth, epicanthic folds, neat arched eyebrows, broad nasal root) see Fig. 3	Include review of photographs at a younger age and take into account variability of phenotype with age (see Fig. 3)
Suggestive	Cognitive profile consistent with current knowledge of that associated with valproate exposure	a) discordant from parents b) in infancy: motor and speech delay, c) school aged: IQ, verbal reasoning, communication and executive functioning deficits
Suggestive	Presence of social communication difficulties/autism spectrum disorder	Occurs in 6–15%
Suggestive	Spina bifida	20 fold risk
Supportive	Congenital cardiac defect	Confirmed on echo
Suggestive	Cleft palate	

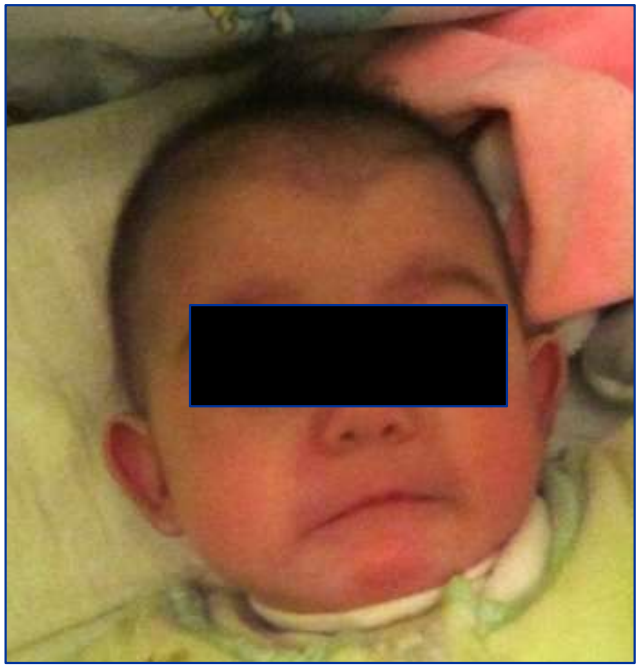
Clayton Smith et al. 2019

IPG



Phenoytpe without gene

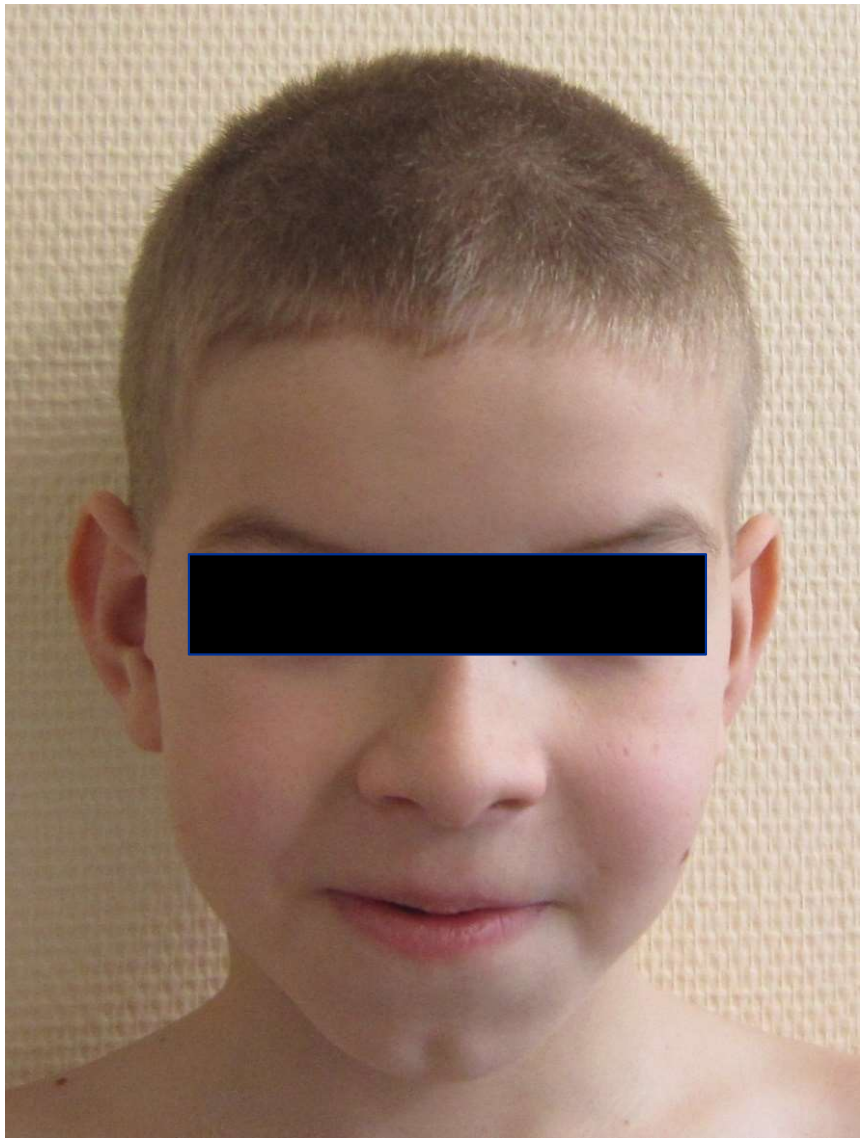
- Short stature
- Microcephaly
- Developmental delay
- Foster care child

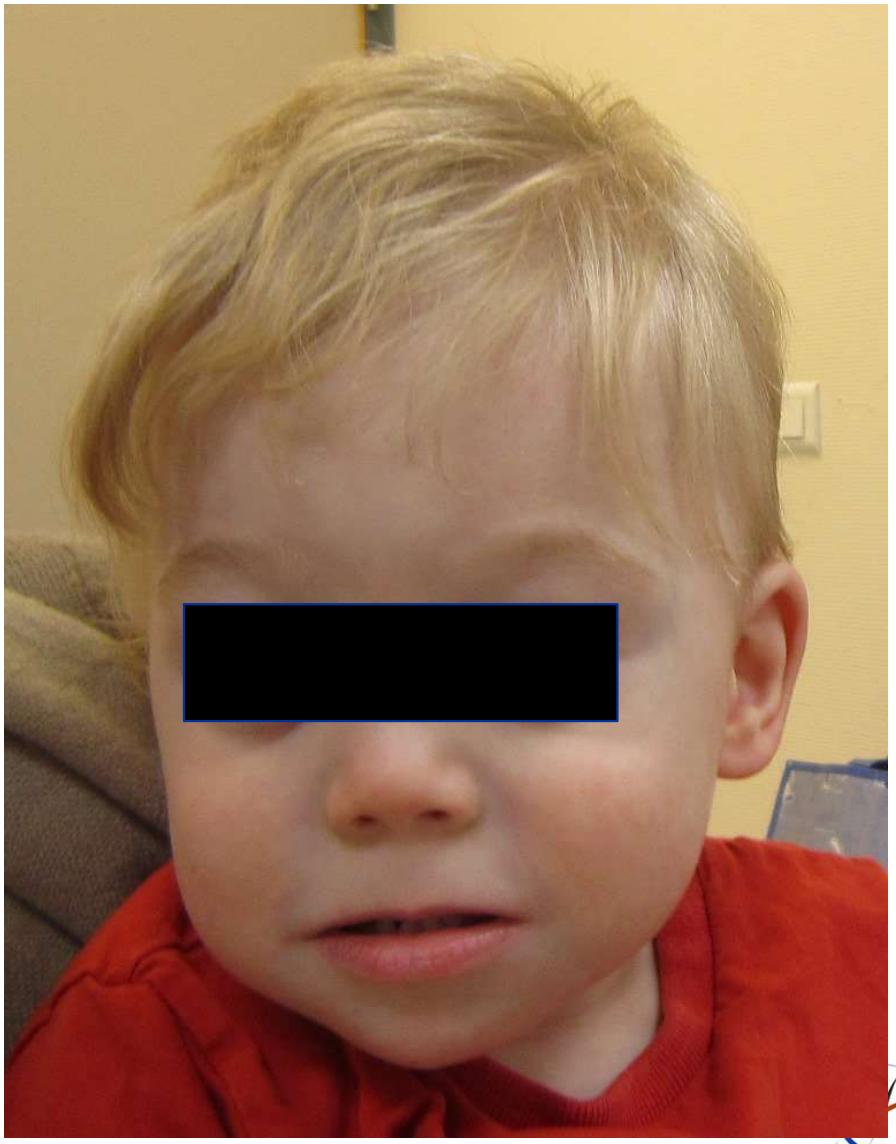


Fœtal
Alcohol
Syndrome

IPG

FAS suspicion





Criteria based diagnosis

I. **FAS**

(With or without documented prenatal alcohol exposure)

A diagnosis of FAS requires all features, A–D:

A. A characteristic pattern of minor facial anomalies, including ≥2 of the following:

1. **Short palpebral fissures** (≤10th centile)
2. **Thin vermilion border of the upper lip** (rank 4 or 5 on a racially normed lip/philtrum guide, if available)
3. **Smooth philtrum** (rank 4 or 5 on a racially normed lip/philtrum guide, if available)

B. Prenatal and/or postnatal growth deficiency

1. **Height and/or weight ≤10th centile** (plotted on a racially or ethnically appropriate growth curve, if available)

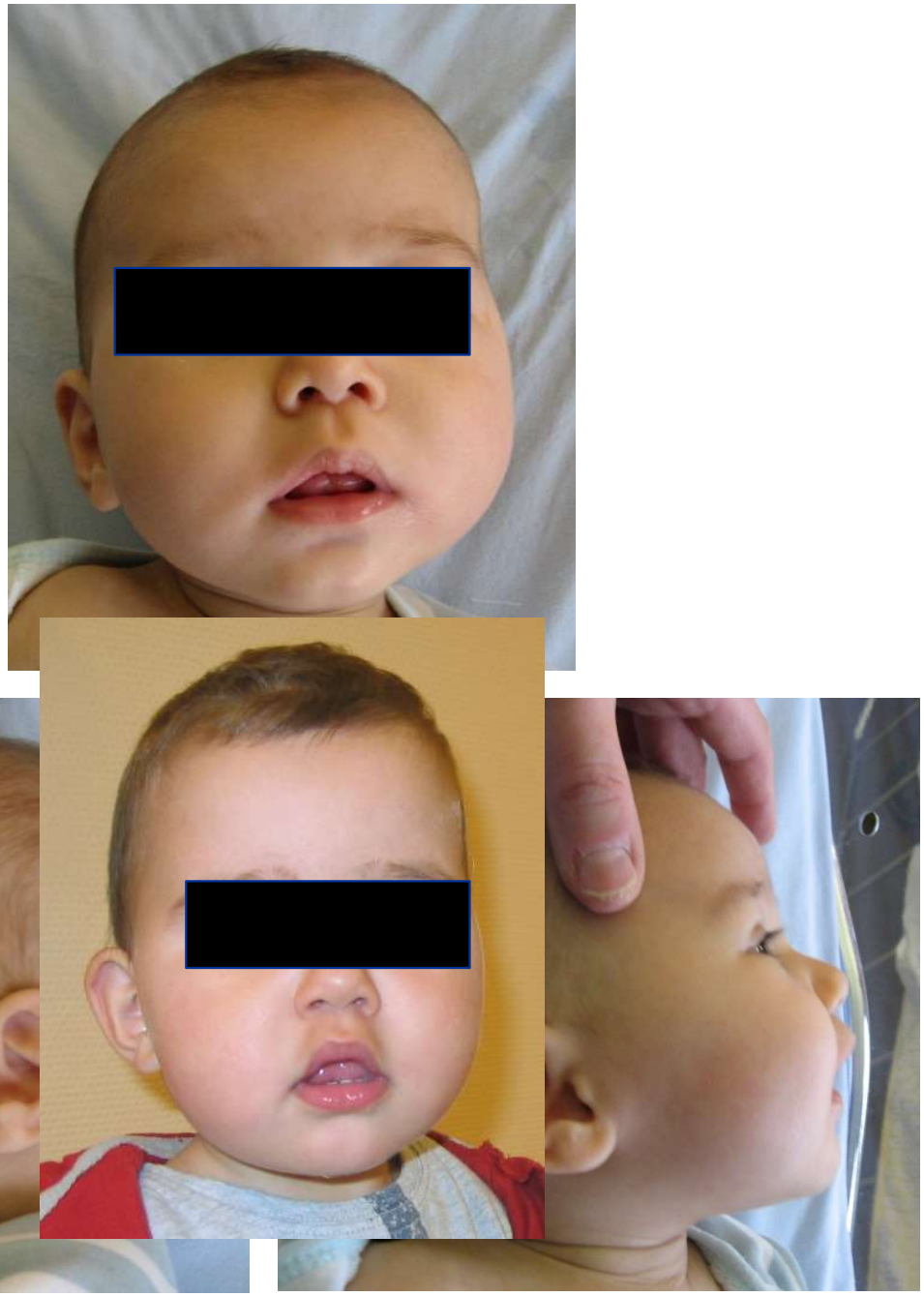
C. Deficient brain growth, abnormal morphogenesis, or abnormal neurophysiology, including ≥1 of the following:

1. **Head circumference ≤10th percentile**
2. **Structural brain anomalies**
3. **Recurrent nonfebrile seizures** (other causes of seizures having been ruled out)

D. **Neurobehavioral impairment**[a]

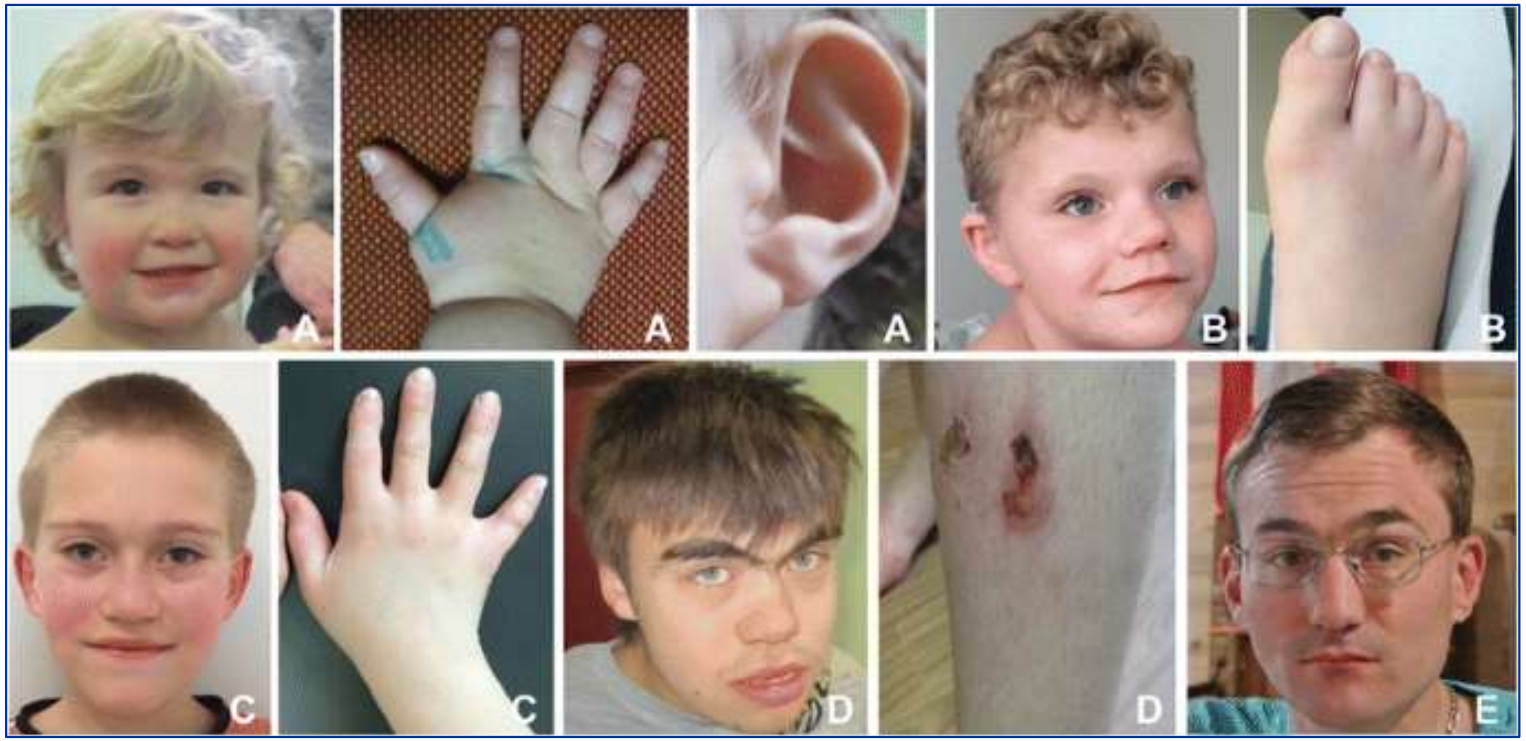
Pediatrics 2016

- 5 months
- Pregnancy/birth: nl
- Growth parameter:nl
- Neonatal:
  - Cyanosis and bradycardia
  - Investigation nl (metabolic, cardiac, EEG)
- 5 months:
  - Cyanosis and clonic movement
  - EEG: epilepsy
  - Mild DD
- Diagnostic with MLPA

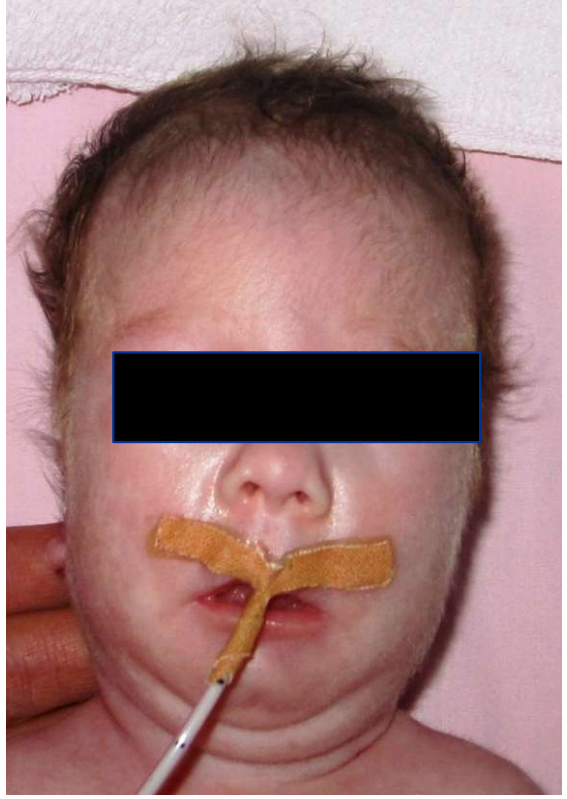


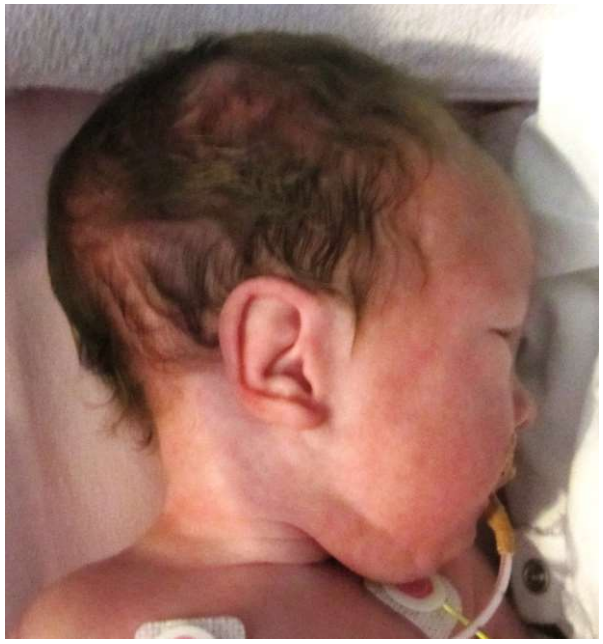
Diagnostic based on sleep/behaviour

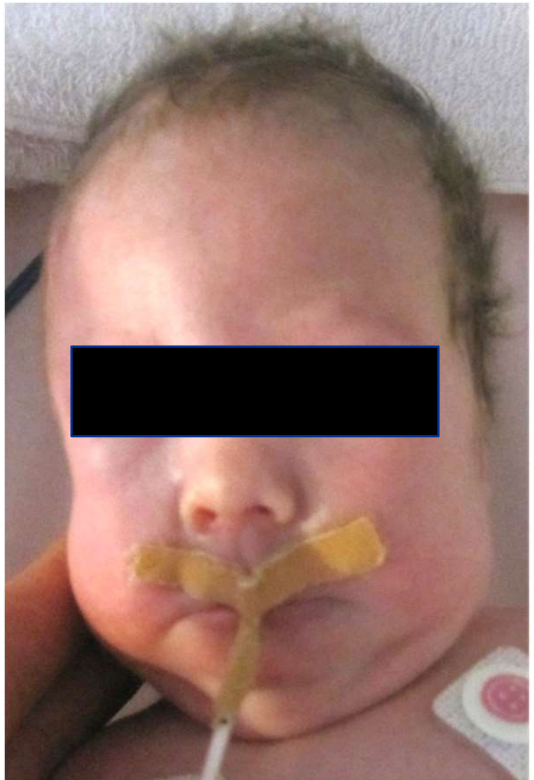
- 17p11.2 microdeletion/RAI1 mutation (Smith Magenis)
- Abnormal sleep pattern
- Behaviour trouble
- Intellectual disability/developmental delay
- Short stature, brachydactyly

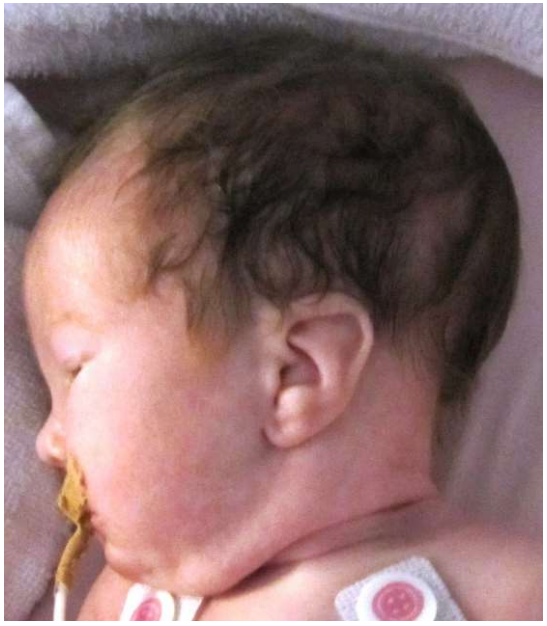


- Pregnancy:
  - 2 beers/day, stop at 15 wks (mother's words)
  - 10 cig a day
  - IUGR
  - Poor foetal movements
- Birth: 33 wks 2/7
  - Weight <P10
  - Lenght <P10
  - HC <P3
- Severe hypotonia
- Camptodactyly
- Labia majora hypoplasia
- Feeding difficulties (gastrostomy)



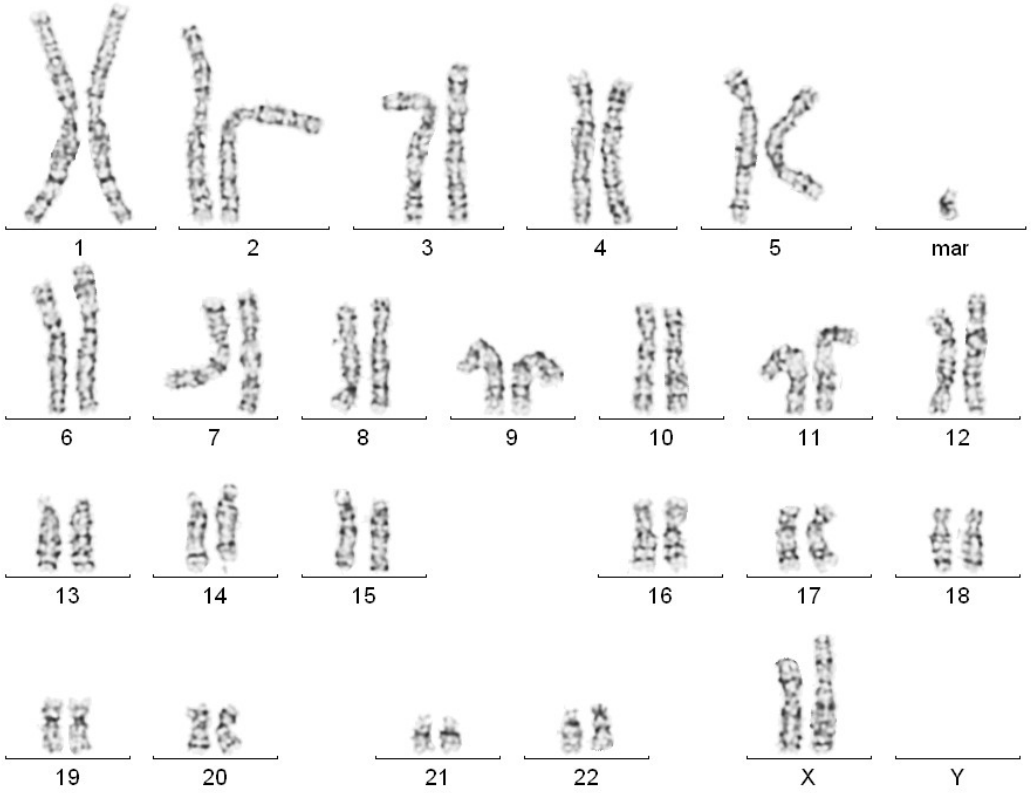




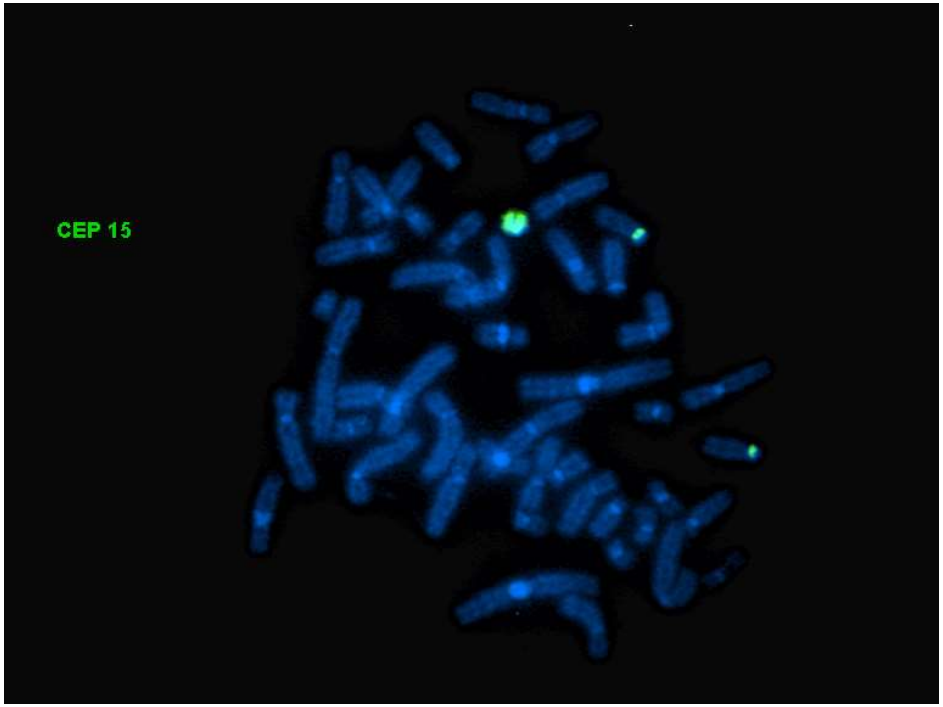


IPG

Karyotype



FISH



CGH: normal

UPD15 by microsatellites

PW by maternal UPD15

- **Prader-Willi**
  - Mat UPD 15 with marker chromosome 15
    - 6 cases reported (2005)

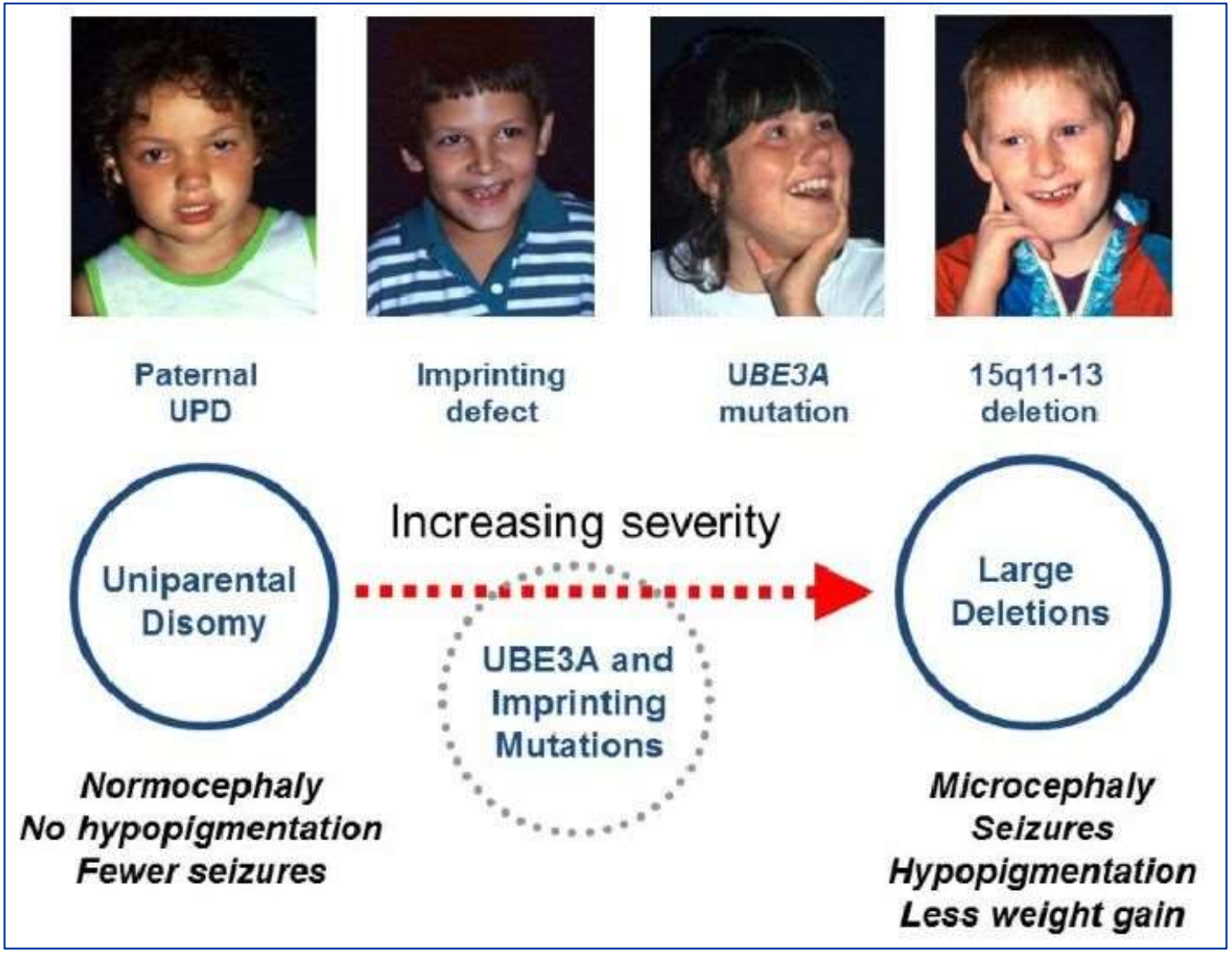
- **Fœtal-alcohol syndrome**
  - 4-5 liters of beer a day during pregnancy (re-asking the mother)
  - 2g/kg/d of alcohol during pregnancy (high doses)
  - Dysmorphology score (Hoyme et al, 2005)
    - 23/36
  - Meets the Revised IOM criteria for FAS

IPG

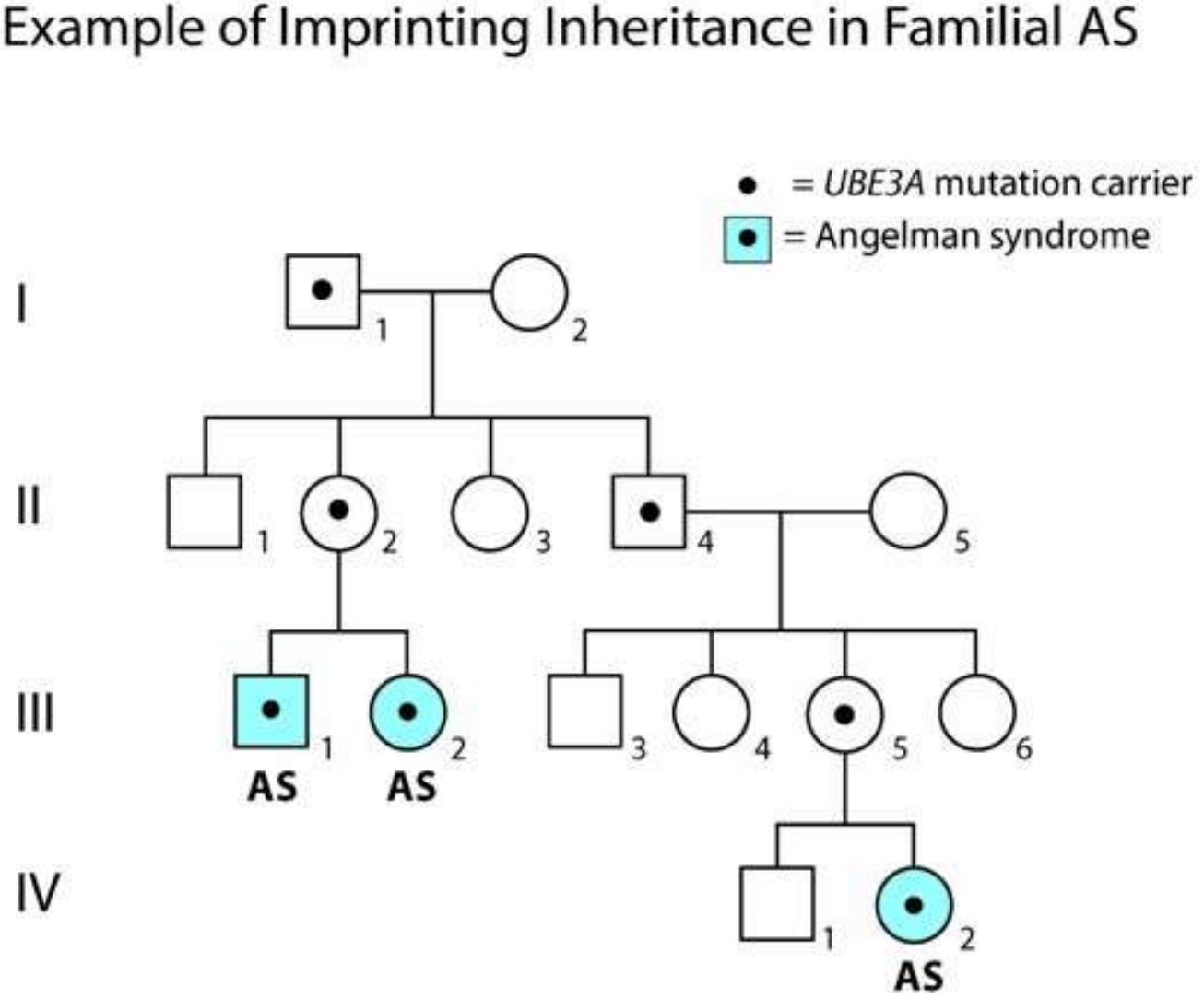
No exome diagnosis

- Severe developmental delay or intellectual disability,
- Severe speech impairment,
- Gait ataxia and/or tremulousness of the limbs
- Unique behavior
  - inappropriate happy demeanor
  - frequent laughing,
  - Smiling
  - excitability.
- Microcephaly
- Seizures
- Hypopigmented skin, light haire, blue eyes

Angelman syndrome

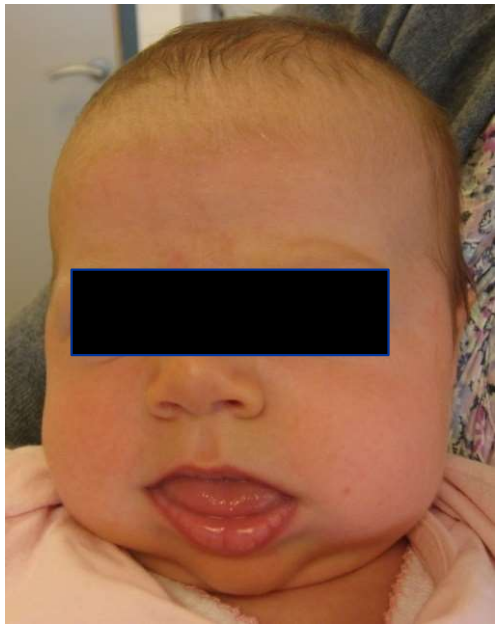


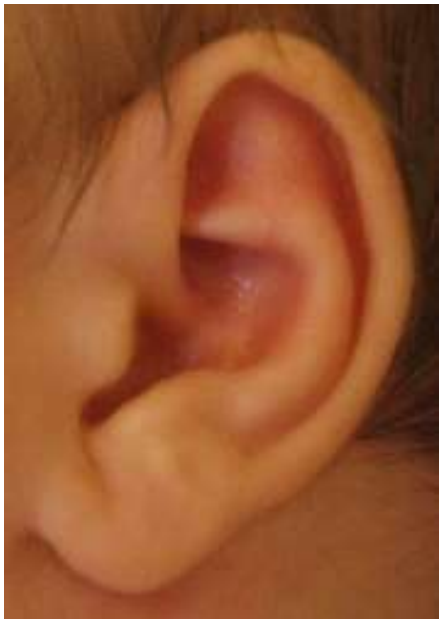
Angelman syndrome

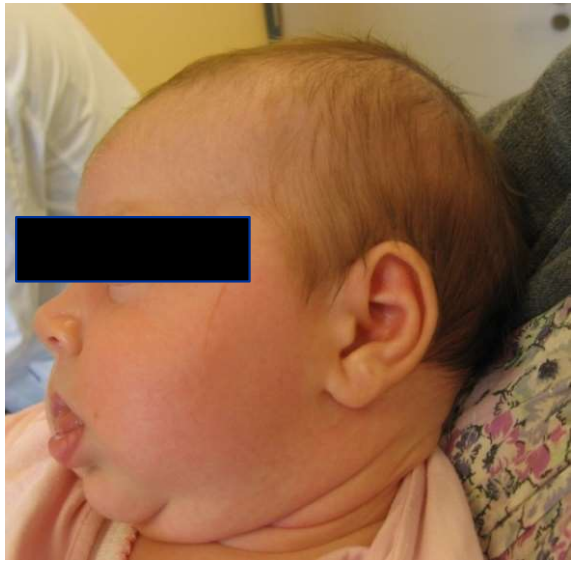


No exome diagnosis

- 5 months
- Birth
  - Weight P90
  - Height P90
  - HC P75-90
- Hemihyperplasia
- Macroglossia
- Hypotonia
- No hypoglycemia







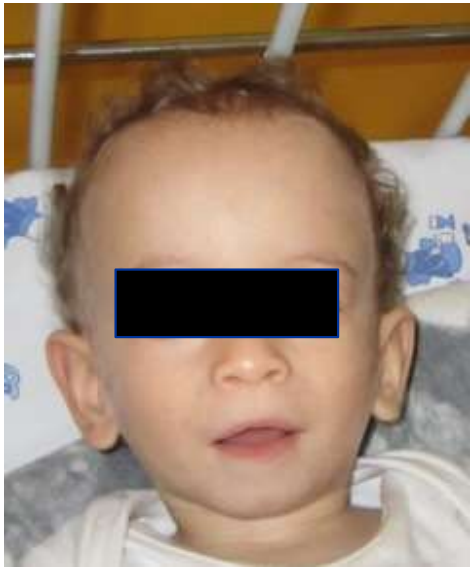
Beckwith-Wiedemann syndrome

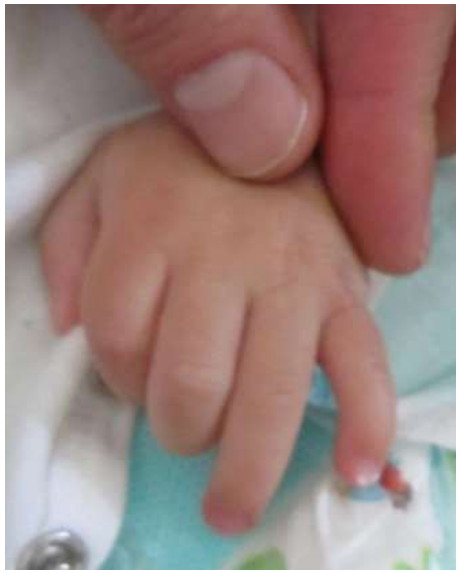
- Abnormal methylation profile of LIT1 (KvDMR) and H19 on 11p15

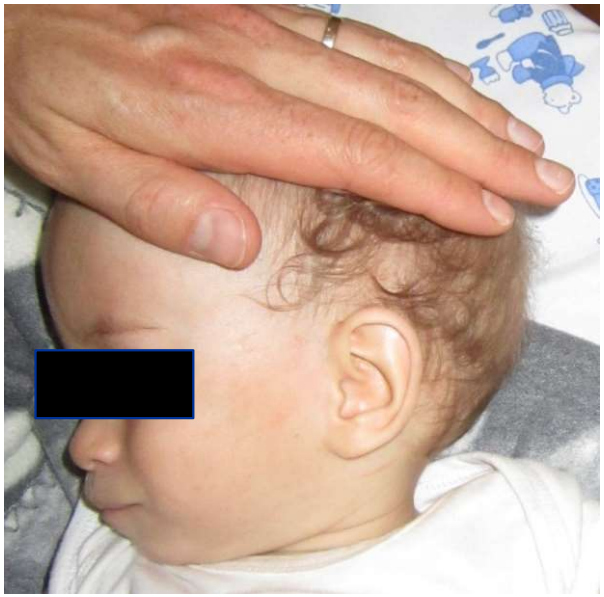
No exome diagnosis

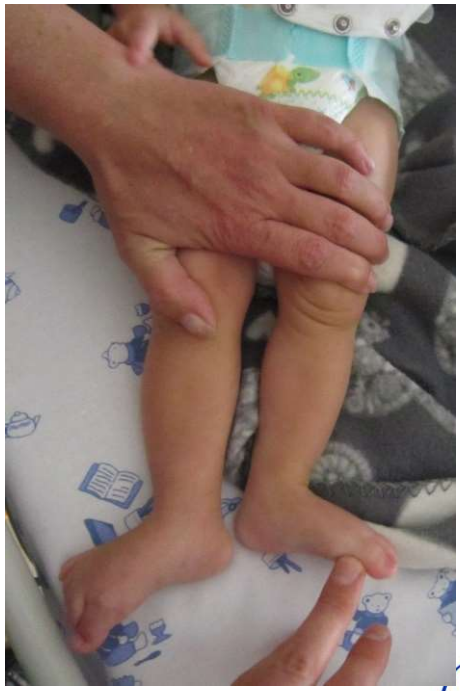
- 8 months
- Pregnancy
  - IUGR
  - Alcohol
  - Cocain (substitute)
- Birth 36 2/7
  - 1,36 kg
  - Atrophia
  - Gingival hypertrophy
  - Large ant. fontanelle
  - Pelvic kidney
- Feeding difficulties
- Growth retardation
- Hypotonia

- Cryptorchidia
- Relative macrocephaly









IPG

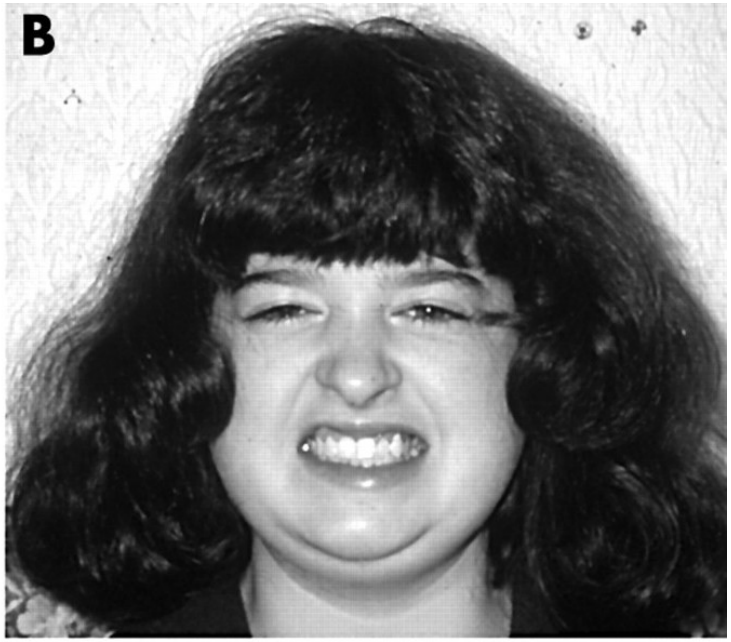
Silver Russel Syndrome

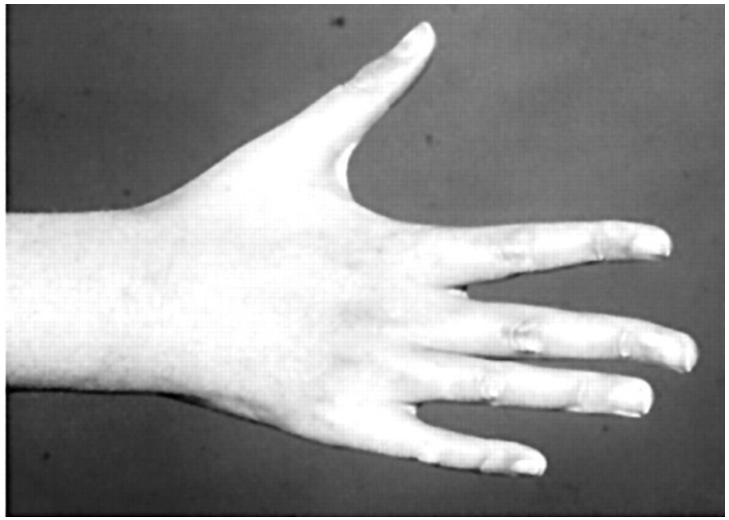
H19 hypomethylation

Chr11p15 methylation status
UPD7
UPD20

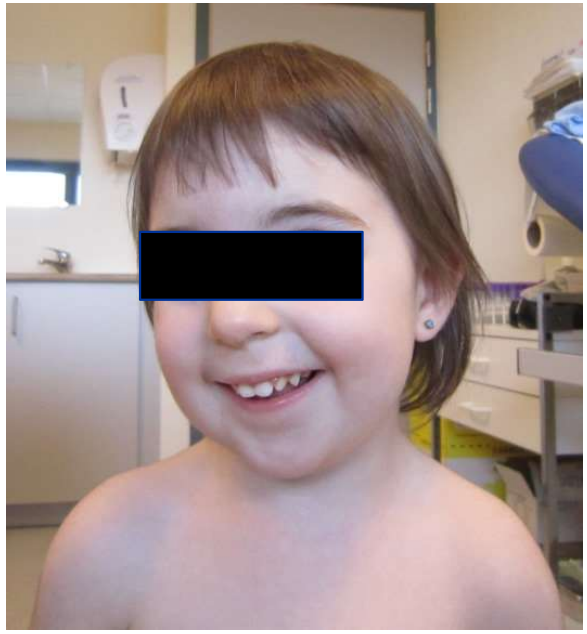
IPG

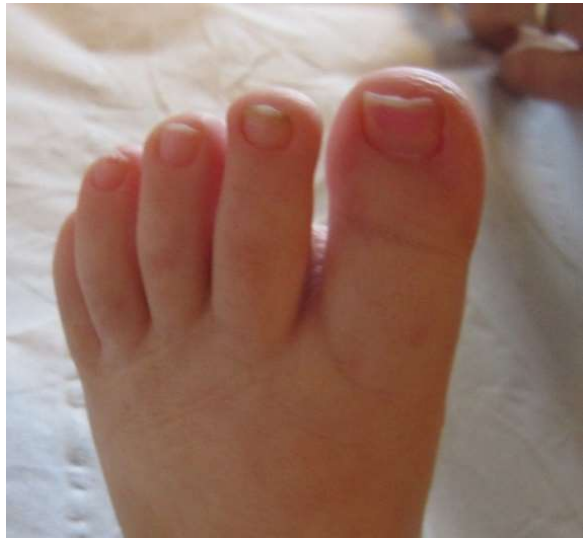
Smiling diagnosis





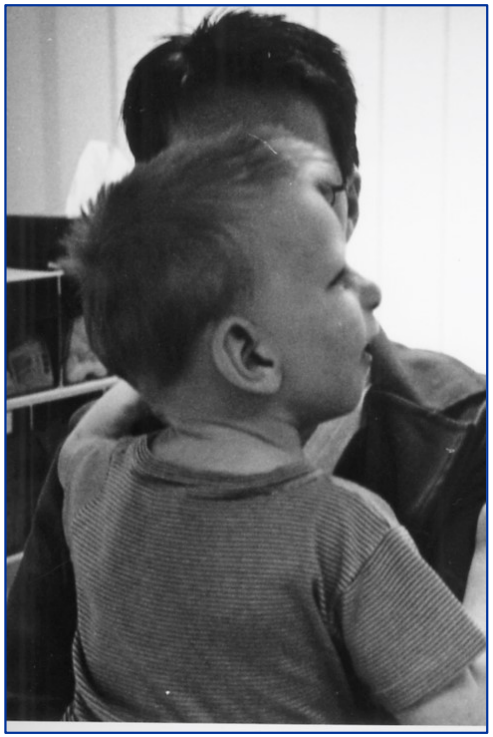
Cohen

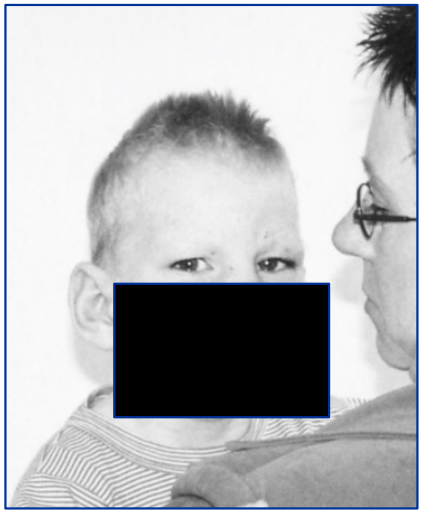




Rubinstein Taybi

Face expression diagnosis





- Adult
  - Marfanoid habitus
  - Pectus excavatum
  - Microcephaly

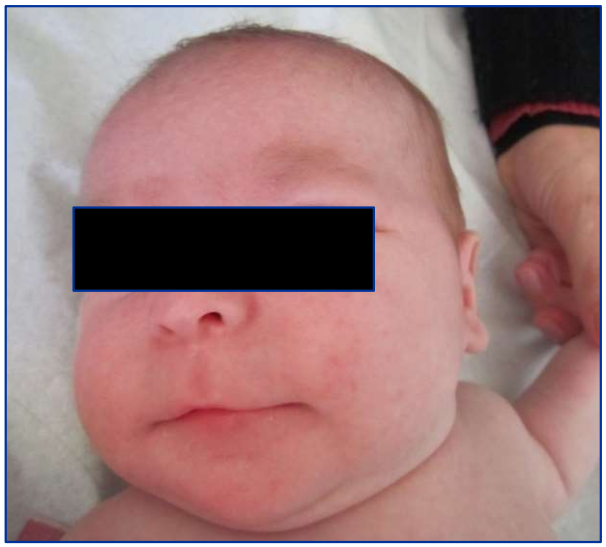
IPG

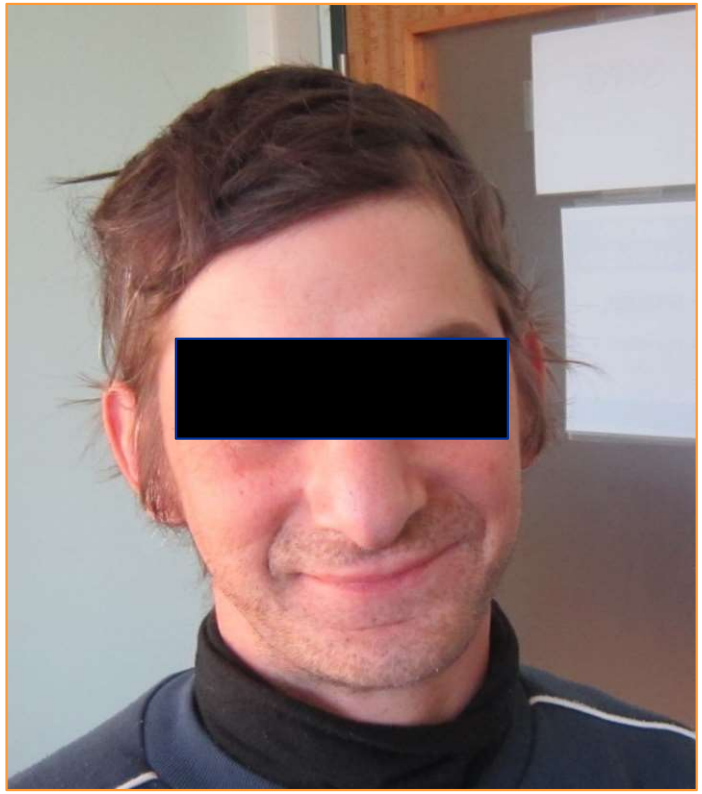
- **DYRK1A : c.1031del ; p.(Met344Serfs*24).**

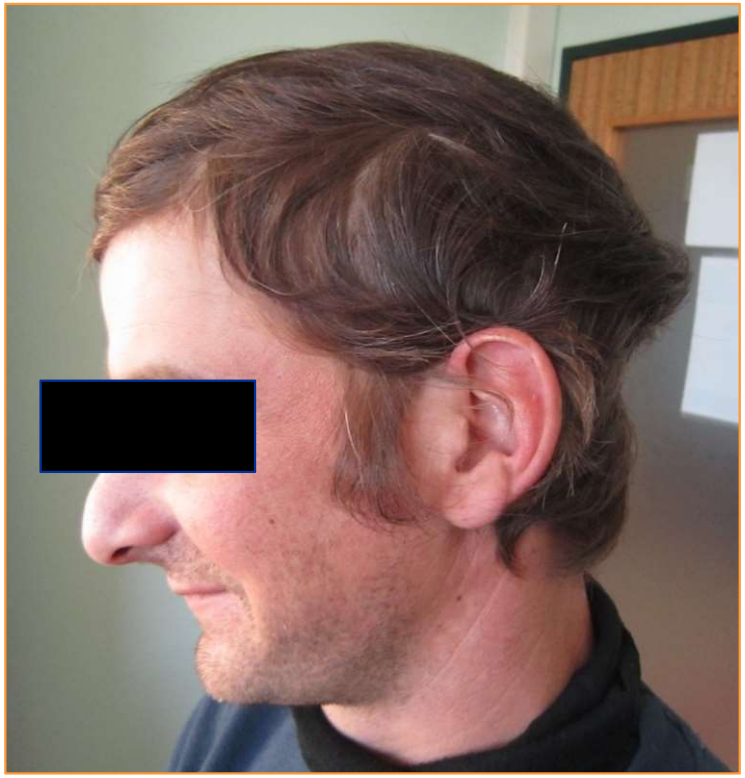
- Intellectual disability
- ASD
- Microcephaly
  - Mostly nonsense, frameshift
  - Less frequent in missense
- Epilepsy
- Scoliosis/kyphosis
- Pectus excavatum
- Short stature
- Angry/anxious face

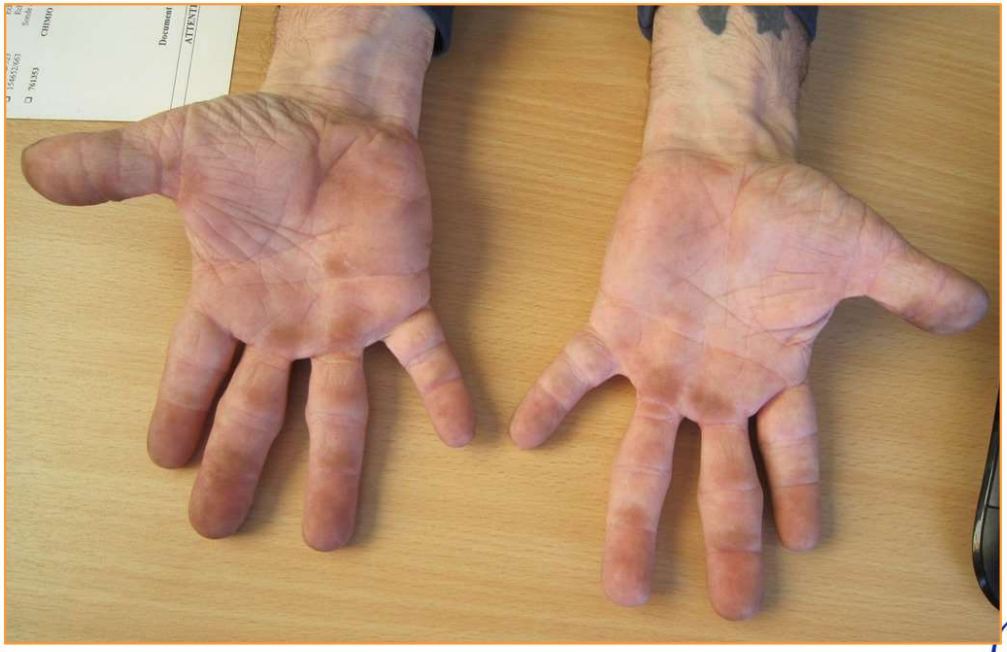
Diagnosis through parents

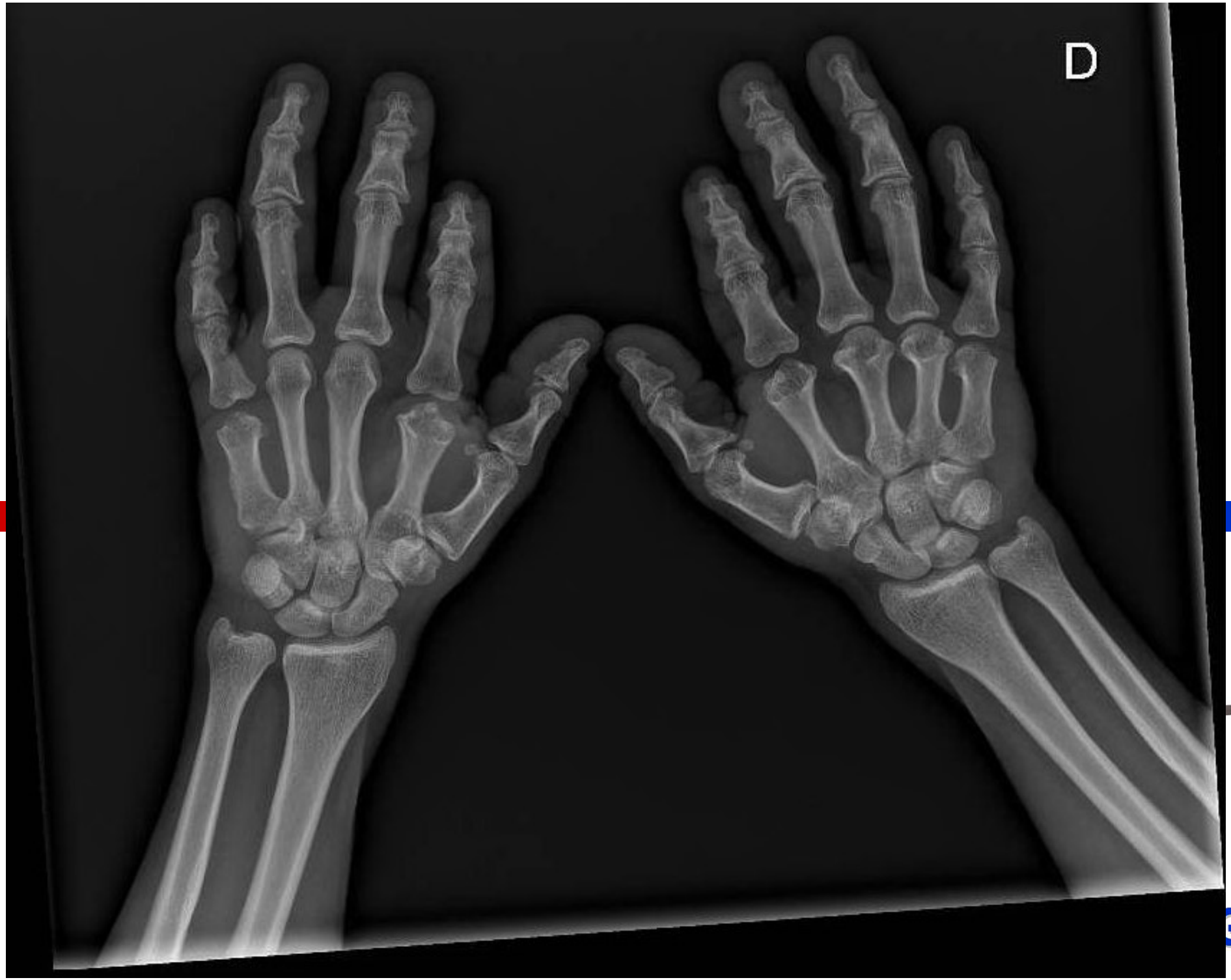
- Birth at 38 weeks
  - Weight 1,81 kg (<P3)
  - Length 44,5 cm (P3)
  - HC: 30,3 cm (<P3)
  - 10 days in neonate for feeding difficulties
  - Normal heart, kidney, EEG
- 1 year old
  - Weight 7,73 kg
  - Length 66,5 cm (<-2,5SD)
  - HC 43,8 cm (P3-10)
- Normal development







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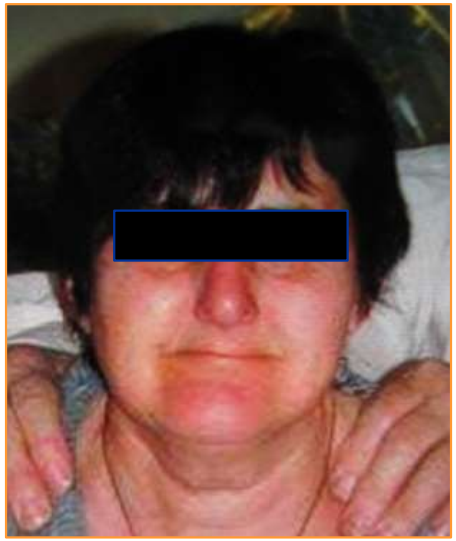


130 cm

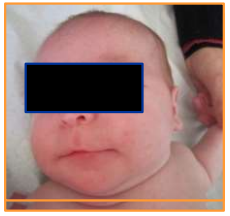
140 cm

168 cm

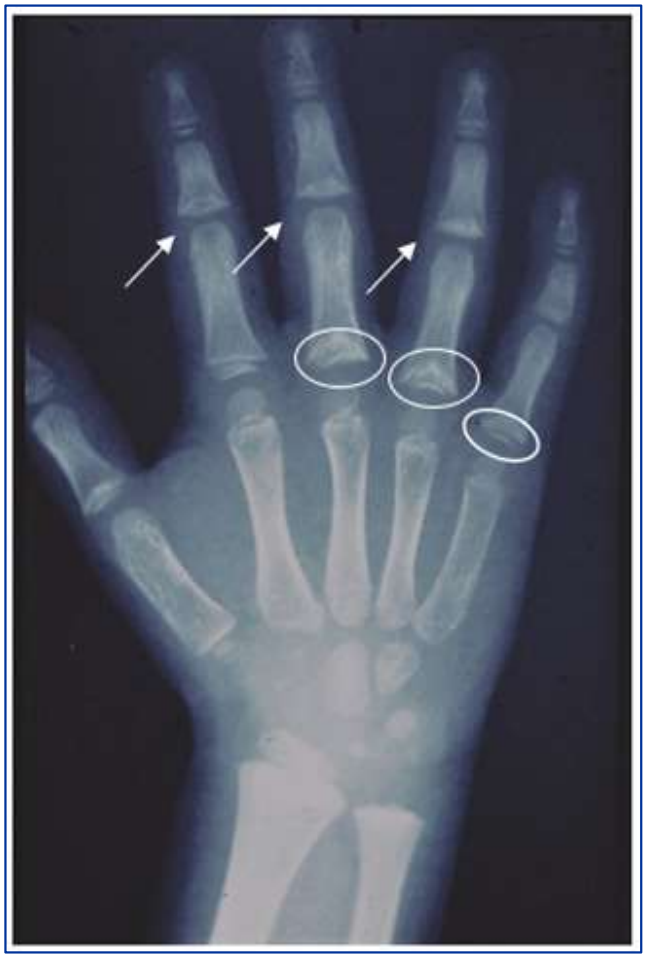
165 cm

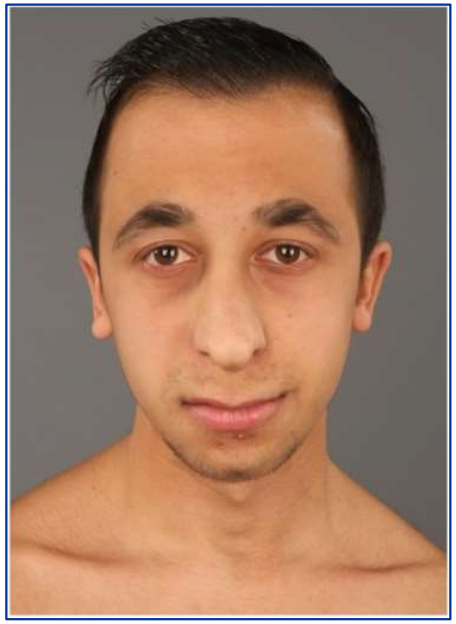
155 cm

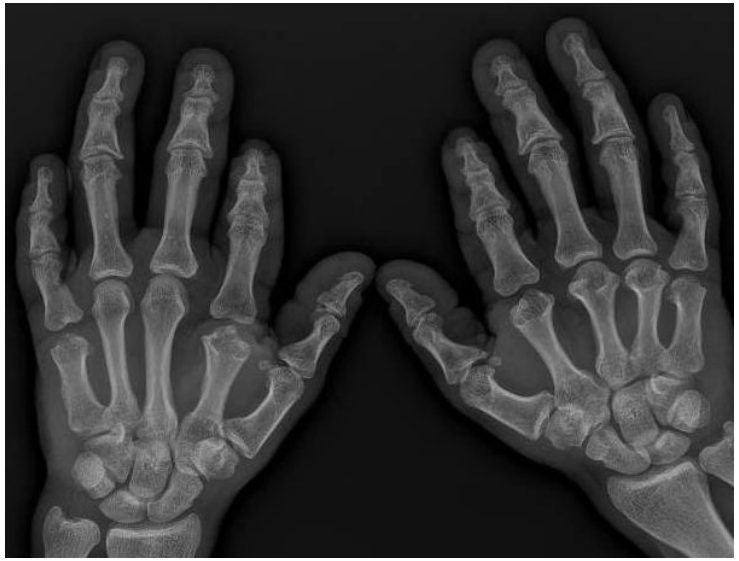
160 cm



- **TRPS1 c.2828C>T;p(Pro943Leu).**

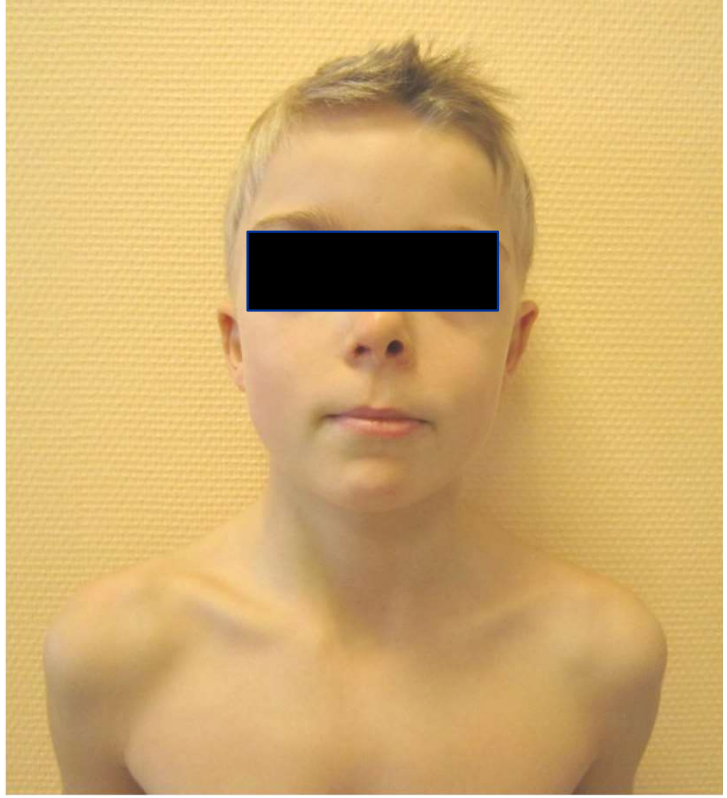


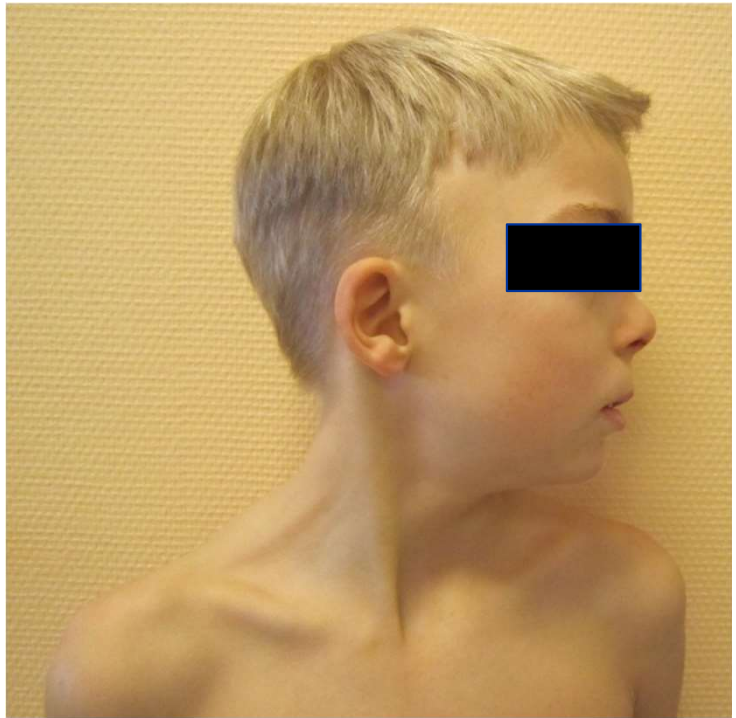


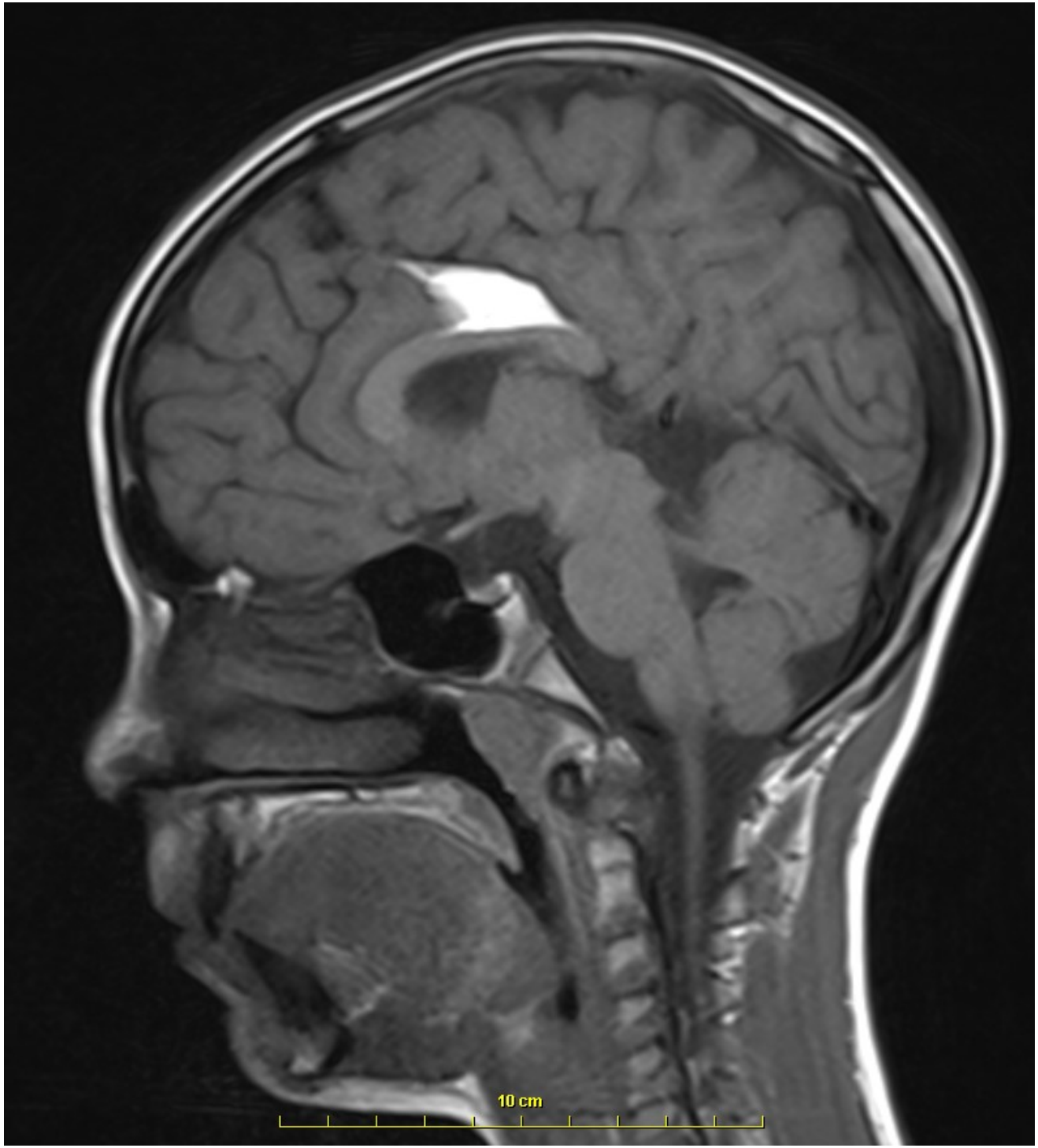


A missing piece…

- Birth 35 wks
  - W: 2,51 kg
  - L: 46 cm
  - HC: 36 cm
  - Nasal polype (hamartomatous)
  - Hypospadias
  - Sacral dimple
  - TFE, hip, renal us scan: nl
- Recurrent bronchitis/pneumonia
  - Fibroscopia:True tracheal bronchus (supernumerary)
  - Cardiac echo: nl
- Gastro-oeso reflux
- Swallowing difficulties
- Bucco-linguo-facial dyspraxia (palate hypotonia)






10 cm

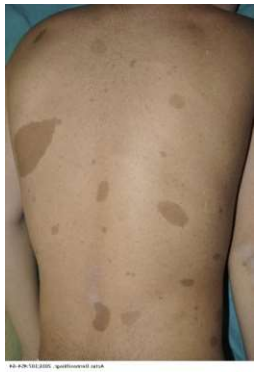
Diagnosis?

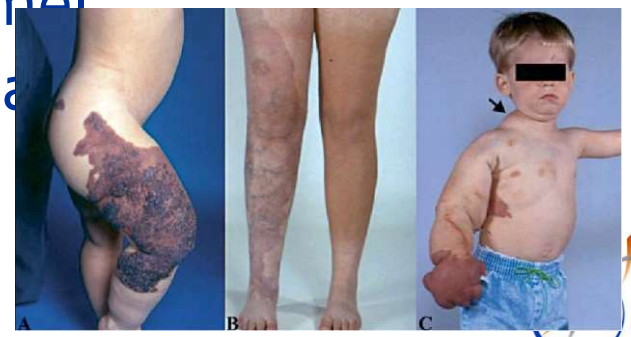
→ Pai syndrome

- Diagnostic criteria: association of very rare features
  - Congenital midline nasal polyp
  - Midline facial cleft
  - Peri-callosal lipoma
- Signs prioritisation !!!

One sign, many possibilities

- Macrocephaly:
  - **parents head circumference**
  - body proportion: hypochondroplasia, overgrowth
  - body asymmetry: klippel trenauney, Proteus
  - frontal bossing, large chin: sotos
  - polydactyly: Greig syndrome
  - facial hemangioma: macrocephaly capillary malformation
  - skin signs, penis macule: Cowden syndrome
  - café-au-lait spot: NF1
  - accesory nipples: Simpson Golabi Behmel
  - coarseness, gingival thickening...: meta
  - Autism (PTEN), deterioration





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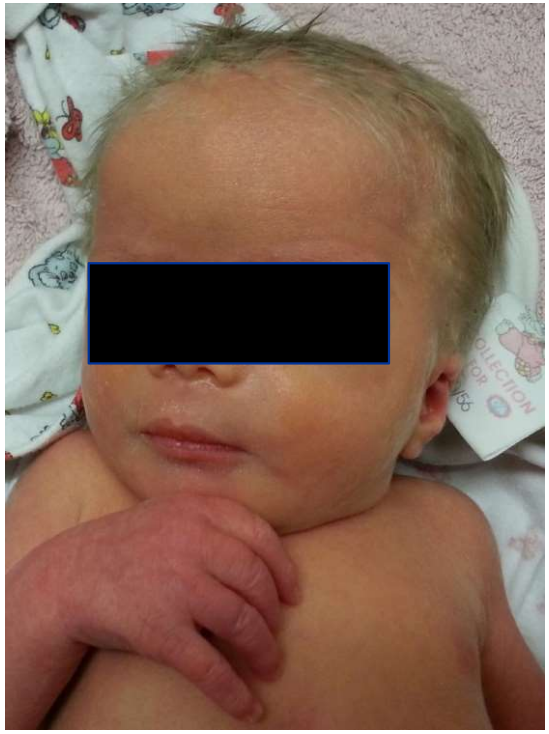
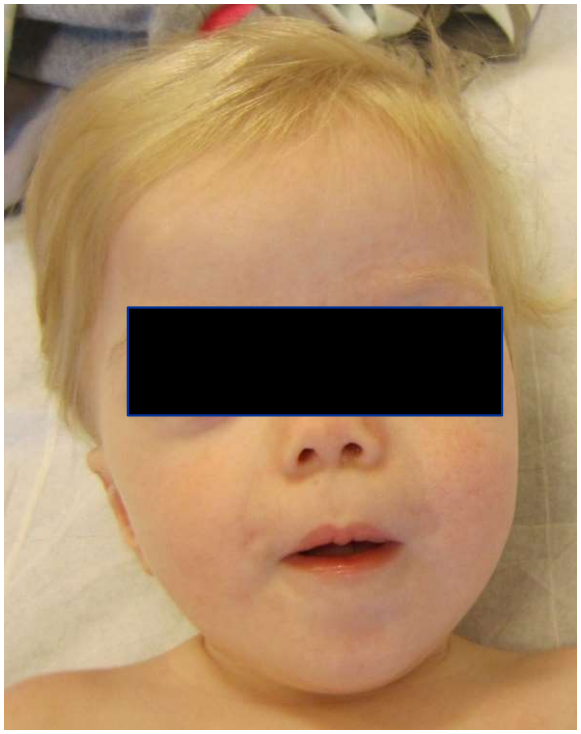
One sign many possibilities

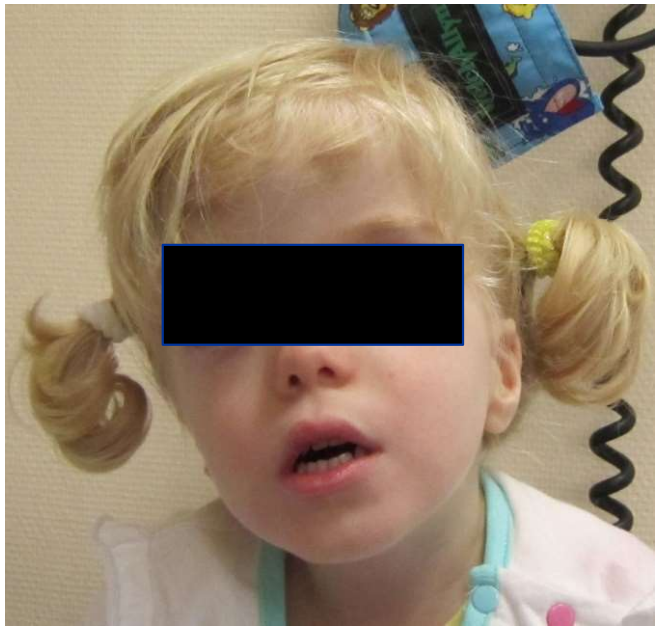
- Microcephaly
  - **parents head circumference**
  - Primary microcephaly
    - Congenital autosomal recessive
  - Antenatal exposure (alcohol, virus…)
  - Metabolic disease
  - 2-3 syndactyly, male genitalia…: SLO
  - deep set eyes, sun sensitivity, photophobia: Cockayne
  - Retinopathy: Cohen (AR), KIF11 (AD)
  - Small ears, absent patella: Meier Gorlin
  - Nipple inversion, abnormal fat distribution: CDG

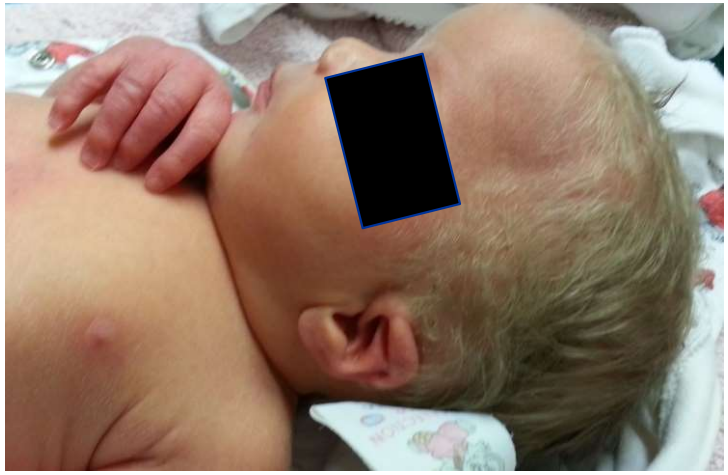
KIF11

A diagnosis? Patience…









- 2014 – 2021
- Exome
- MN1: c.3883C>T p.Arg1295*

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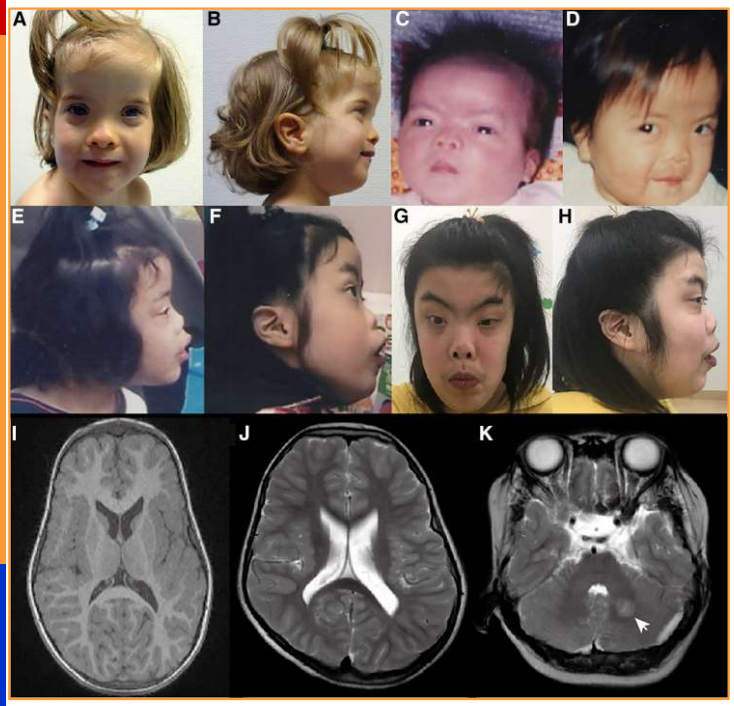
ARTICLE

Gain-of-Function *MN1* Truncation Variants Cause a Recognizable Syndrome with Craniofacial and Brain Abnormalities

Noriko Miyake,[1,*] Hidehisa Takahashi,[2] Kazuyuki Nakamura,[3] Bertrand Isidor,[4] Yoko Hiraki,[5] Eriko Koshimizu,[1] Masaaki Shiina,[6] Kazunori Sasaki,[2] Hidefumi Suzuki,[2] Ryota Abe,[2] Yayoi Kimura,[7] Tomoko Akiyama,[7] Shin-ichi Tomizawa,[8] Tomonori Hirose,[2] Kohei Hamanaka,[1] Satoko Miyatake,[1,9] Satomi Mitsuhashi,[1] Takeshi Mizuguchi,[1] Atsushi Takata,[1] Kazuyuki Obo,[8] Mitsuhiro Kato,[3,10] Kazuhiro Ogata,[6] and Naomichi Matsumoto[1,*]

AJHG 01/2020

Brain 11/2(



doi:10.1093/brain/awz379 BRAIN 2019: 0; 1–14 | 1

BRAIN
A JOURNAL OF NEUROLOGY

MN1 C-terminal truncation syndrome is a novel neurodevelopmental and craniofacial disorder with partial rhombencephalosynapsis

Christopher C.Y. Mak,[1,*] Dan Doherty,[2,3,*] Angela E. Lin,[4] Nancy Vegas,[5,6] Megan T. Cho,[7]

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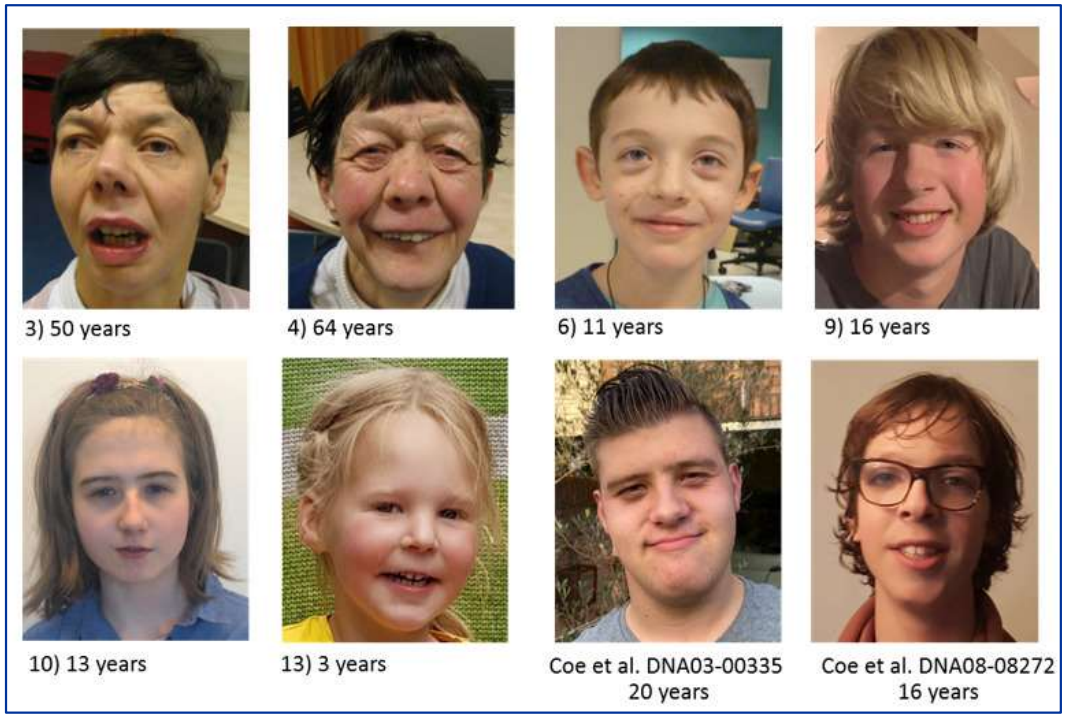
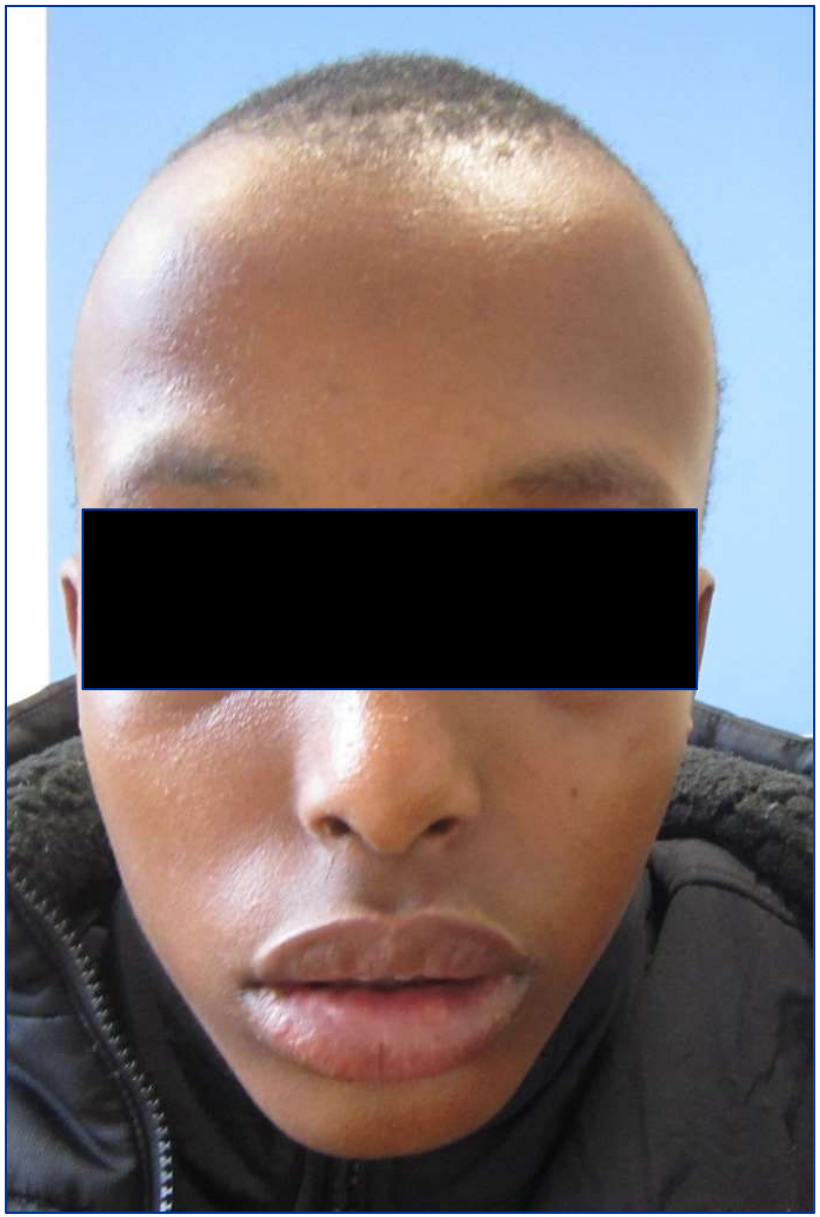
Syndrome?

- Macrocephaly
- Absent speech
- ASD
- ID





FOXP1 variant
Father not available

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Tips and tricks

- Anamnesis
  - Intellectual deficiency
  - Behaviour
  - Sleep pattern
  - History of feeding difficulties
  - Early surgical operations
  - Neonatal skin rash (Blashko line pigmentary abnormalities)
- Priotizing phenotype (coloboma vs epicanthus)
- Ethnicity (hirsutism)
- Body asymmetry, local pigmentation abnormality → skin biopsy
- Parents: height, head circumference, syndactyly, eyebrows, syndrome in adult…

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TRUMPETTES

Conclusion

- Deep anamnesis
- Full clinical examination
- Photos from parents, grand-parents
- Photos from childhood.
- Good phenotype and description of clinical signs important for exome analysis
- Some syndromes not diagnosed by exome!
  - UPD
  - Triplet expansion
  - Mosaic (pigmentary changes, body asymmetry)
- Case sharing!!!
- Be curious!