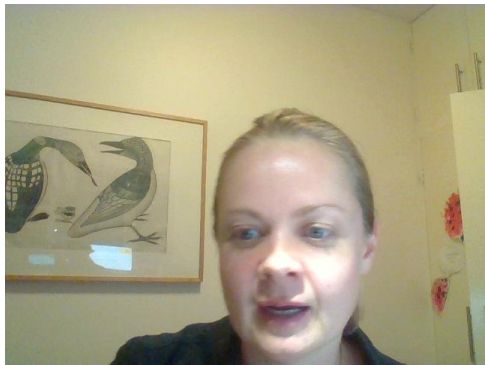
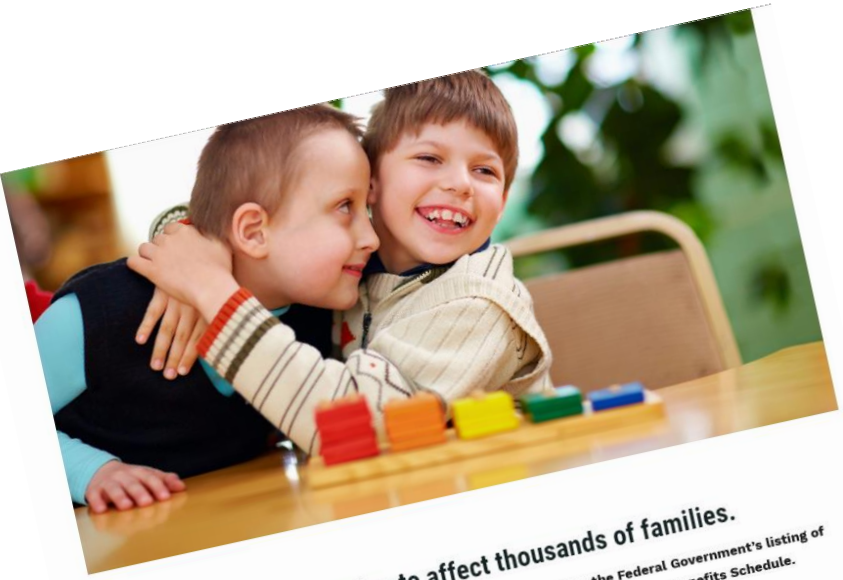
An approach to dysmorphology for the fellowship paediatric examination (Australia)

Elizabeth.palmer@health.nsw.gov.au



Why bother – don't we all just do an exome now?



NEWS

Funding for genetic testing to affect thousands of families.

Around 3000 Australian families are expected to benefit each year from the Federal Government's listing of genetic testing for childhood syndromes and intellectual disability on the Medicare Benefits Schedule.

From May 1 the newly-announced MBS item numbers will reimburse:

- Whole exome or genome sequencing to identify the genetic cause of syndromic and non-syndromic intellectual disability
- The re-analysis of data in certain circumstances
- Cascade testing for certain purposes, such as diagnosis of a biological sibling or to inform reproductive decision making

The new items also support trio testing of affected individuals, with an upper limit of $2,900 for this fee item.

The listing, which makes genetic tests more affordable, comes after Australian Genomics applied to the Medical Services Advisory Committee (MSAC) for whole exome analysis for childhood syndromes – the first in a 'pipeline' of MSAC applications established by Australian Genomics and partners.

Results 1 to 6 of 6 matches

1

Category 6 - PATHOLOGY SERV

73358

Group P7 - Genetics

Characterisation, via whole exome or genome sequencing and analysis, of germline variants known to cause monogenic disorders, if:

(a) the characterisation is:

(i) requested by a consultant physician practising as a clinical geneticist; or

(ii) requested by a consultant physician practising as a specialist paediatrician, following consultation with a clinical geneticist; and

(b) the patient is aged 10 years or younger and is strongly suspected of having a monogenic condition, based on the presence of:

(i) dysmorphic facial appearance and one or more major structural congenital anomalies; or

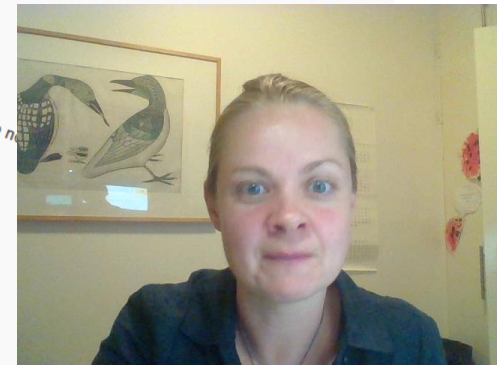
(ii) intellectual disability or global developmental delay of at least moderate severity, as determined by a specialist paediatrician; and

(c) the characterisation is performed following the performance for the patient of a service to which item 73292 applies for which the results were n

(d) the characterisation is not performed in conjunction with a service to which item 73359 applies

Applicable only once per lifetime

Fee: $2,100.00 **Benefit:** 75% = $1,575.00 85% = $2,015.30



Detailed phenotyping improves the diagnostic yield of genomic testing

- Why does exome sequencing not get an answer

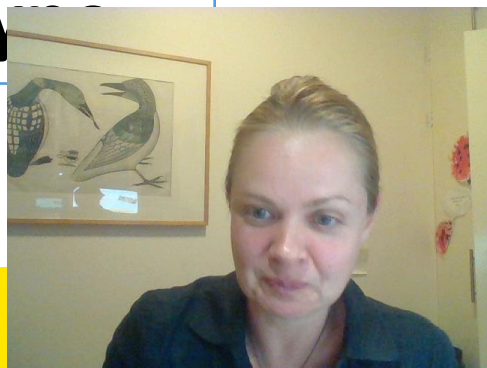
Technological limitations
(noncoding or expansion mutations, incomplete coverage, uniparental disomy, large indels, chromosomal rearrangements, and copy-number variants)

Unknown gene-disease associations

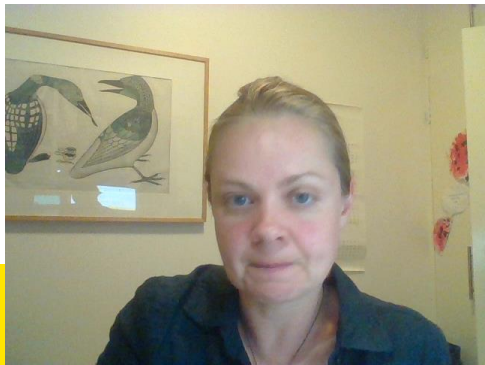
More complex genetics (polygenic, epigenetic, multi-factorial,…. Non-genetic – yes it happens!!!!)

Incomplete recognition of the patient's phenoty

Reanalysis of exome data win collaboration with referring physician can boost diagnosis by ~12% (Salmon et al. 2018)



And it might just help you describe new genetic conditions for your patients!



UNSW SYDNEY | Australia's Global University

REPORT

De Novo Variants Disrupting the HX Repeat Motif of ATN1 Cause a Recognizable Non-Progressive Neurocognitive Syndrome

Elizabeth E. Palmer,[1,2,3,4,25] Seungbeom Hong,[5,25] Fatema Al Zahrani,[6] Mais O. Hashem,[6] Fajr A. Aleisa,[5] Heba M. Jalal Ahmed,[5] Tejaswi Kandula,[1,2] Rebecca Macintosh,[1] Andre E. Minoche,[3] Clare Puttick,[3] Velimir Gayevskiy,[3] Alexander P. Drew,[3] Mark J. Cowley,[3,7] Marcel Dinger,[3,7] Jill A. Rosenfeld,[8] Rui Xiao,[8,9] Megan T. Cho,[10] Suliat F. Yakubu,[5] Lindsay B. Henderson,[10] Maria J. Guillen Sacoto,[10] Amber Begtrup,[10] Muddathir Hamad,[11] Marwan Shinawi,[12] Marisa V. Andrews,[12] Marilyn C. Jones,[13] Kristin Lindstrom,[14] Ruth E. Bristol,[15] Saima Kayani,[16] Molly Snyder,[17] María Mercedes Villanueva,[18] Angeles Schteinschnaider,[18] Laurence Faivre,[19,20] Christel Thauvin,[19] Antonio Vitobello,[19] Tony Roscioli,[1,21,22] Edwin P. Kirk,[1,2,21] Ann Bye,[1,2] Jasmeen Merzaban,[23] Łukas Jaremko,[5] Mariusz Jaremko,[23] Rani K. Sachdev,[1,2] Fowzan S. Alkuraya,[6,24,25,*] and Stefan T. Arold[5,25,*]

e 1. Clinical Images of Affected Individuals with CHEDDA

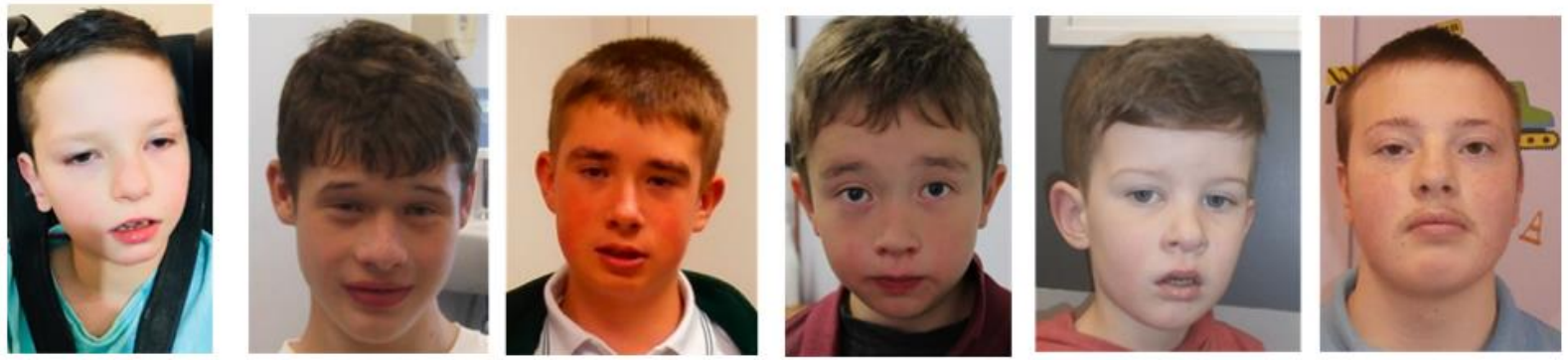
UNSW SYDNEY | Australia's Global University

THE UNIVERSITY of ADELAIDE

The Sydney children's Hospitals Network
care, advocacy, research, education

HNEkidshealth

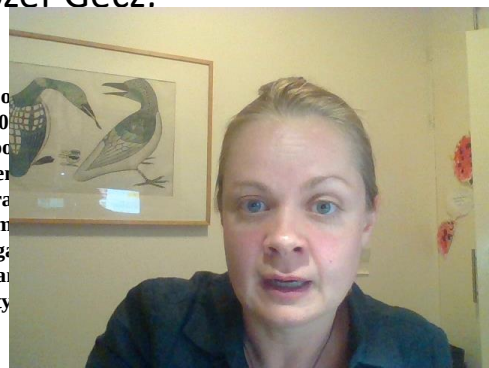
• *RLIM* is a candidate dosage sensitive gene for individuals with varying duplications of Xq13, intellectual disability and recognizable facial features



Elizabeth E. Palmer,[1,2,3,4,20]* Renee Carroll,[5,20] Marie Shaw,[5] Raman Kumar,[5] Andre E. Minoche,[4] Melanie Leffler,[1] Lucinda Murray,[1] Rebecca Macintosh,[3] Dale Wright,[7,8] Chris Troedsen,[9] Fiona McKenzie,[10,11] Sharron Townshend,[11] Michelle Ward,[11] Urwah Nawaz,[5] Anja Ravine,[12] Cassandra K. Runke,[13] Erik C. Thorland,[13] Marybeth Hummel,[14] Nicola Foulds,[15] Olivier Pichon,[16] Bertrand Isidor,[16] Cédric Le Caignec,[17] Ann Bye,[2,3] Rani Sachdev,[2,3] Edwin P. Kirk,[2,3] Mark J. Cowley,[18] Mike Field,[1] and Jozef Gecz.[5,19]**

1 Genetics of Learning Disability Service, Waratah, NSW 2298, Australia. 2 School of Women's and Children's Health, UNSW Medicine, University o
Sydney Children's Hospital, Randwick, NSW 2031, Australia 4 Kinghorn Centre for Clinical Genomics, Garvan Institute, Darlinghurst, Sydney, NSW 20
5 Adelaide Medical School and the Robinson Research Institute, University of Adelaide, Adelaide, SA5000, Australia6 St Vincent's Clinical Schoo
Australia7 Discipline of Genomic Medicine and Discipline of Child & Adolescent Health, University of Sydney, Sydney, Australia8 Department of Cytoge
Westmead, Australia 9 Children's Hospital at Westmead, Sydney, Australia 10 School of Paediatrics and Child Health, University of Western Austra
Genetic Services of Western Australia, Perth, Western Australia, Australia12 Pathwest Laboratory Medicine WA, Perth, WA, Australia.13 Genom
Medicine and Pathology, Mayo Clinic, USA 14 West Virginia University School of Medicine, Department of Pediatrics, Section of Medical Genetics Morga
Services, Southampton, UK16 Service de génétique médicale - Unité de Génétique Clinique, CHU de Nantes - Hôtel Dieu, 44093 Nantes CEDEX 1, Fra
fédératif de Biologie, CHU Hopital Purpan, 31059 Toulouse CEDEX 9, France 18 Children's Cancer Institute, Lowy Cancer Research Centre, University

Wales, Australia 199 Healthy Mothers, Babies and Children, South Australian Health and Medical Research 1 Institute, Adelaide, SA 5000, Australia•



Dys (disordered) morph (shape, form)

- Try and study and attempt to interpret patterns of human growth and structural defects

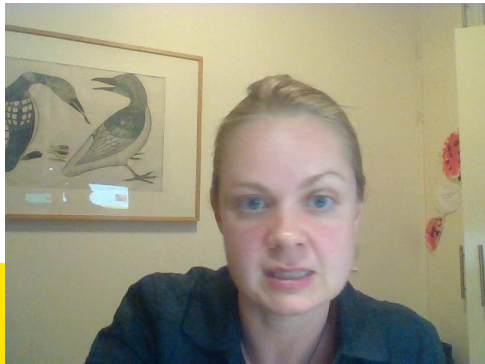
- **Malformation** (an intrinsic developmental anomaly, e.g., spina bifida),
- **Disruption** (an event disrupting intrinsically normal development, e.g., amniotic bands),
- **Deformation** (an external force altering the shape of development, e.g., face shape due to severe oligohydramnios) and
- **Dysplasia** (abnormal growth and maturation of cells, e.g., achondroplasia).
- **Syndrome** ”a recognizable pattern of dysmorphic signs that have a common cause”

Dysmorphology is just part of the puzzle

- 3 generation pedigree
- Look at the parents and sibs – ideally parent baby/child photos
- What is the pattern of functional/ congenital anomalies
- First line tests … [now will be CMA and exome]

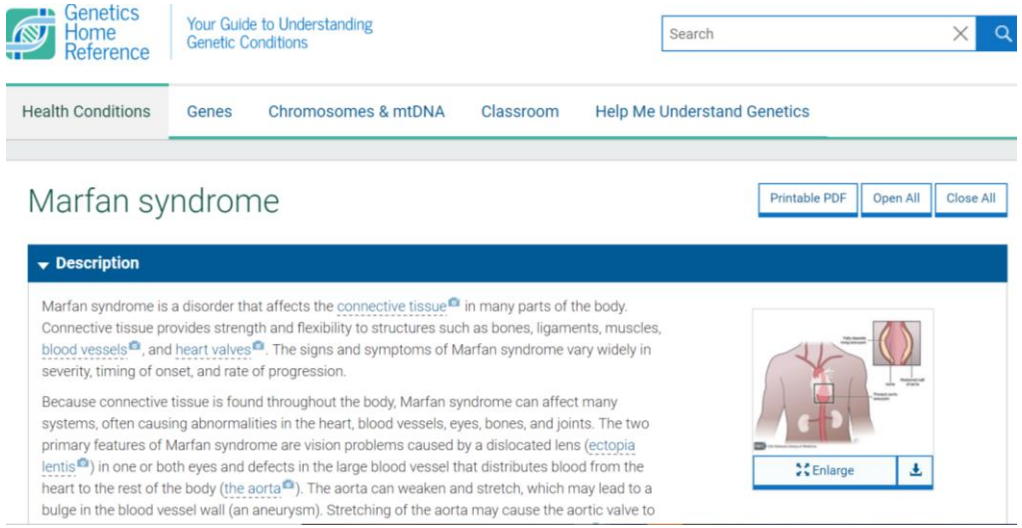
Terminology is important

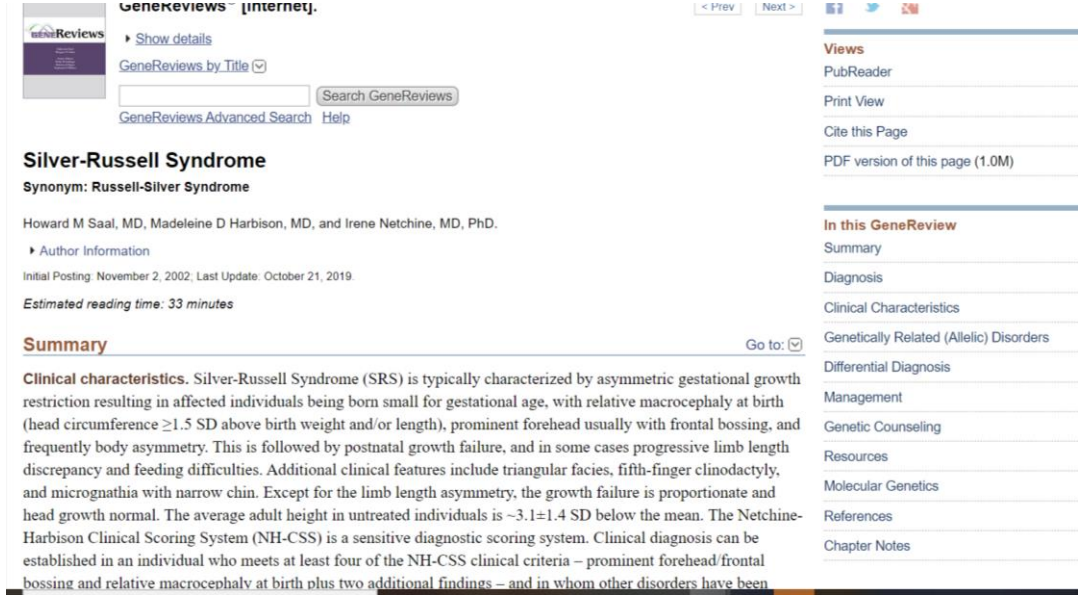
- We are all dysmorphic to some extent
- Be gentle
- ‘distinctive’ …
- ‘ features that are unique to them/ not similar to the rest of the family’

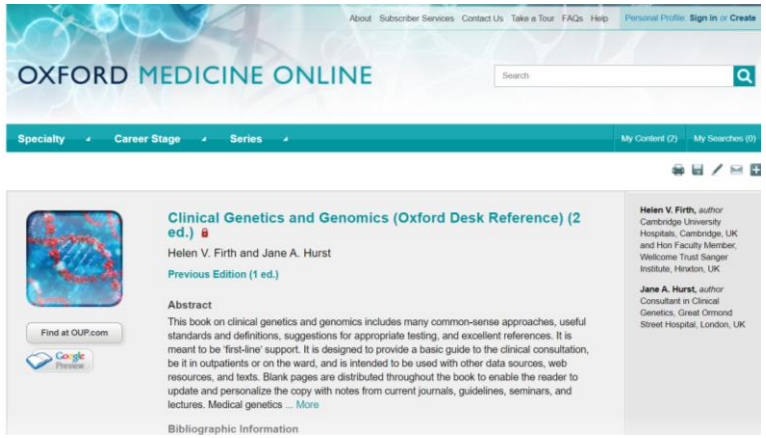


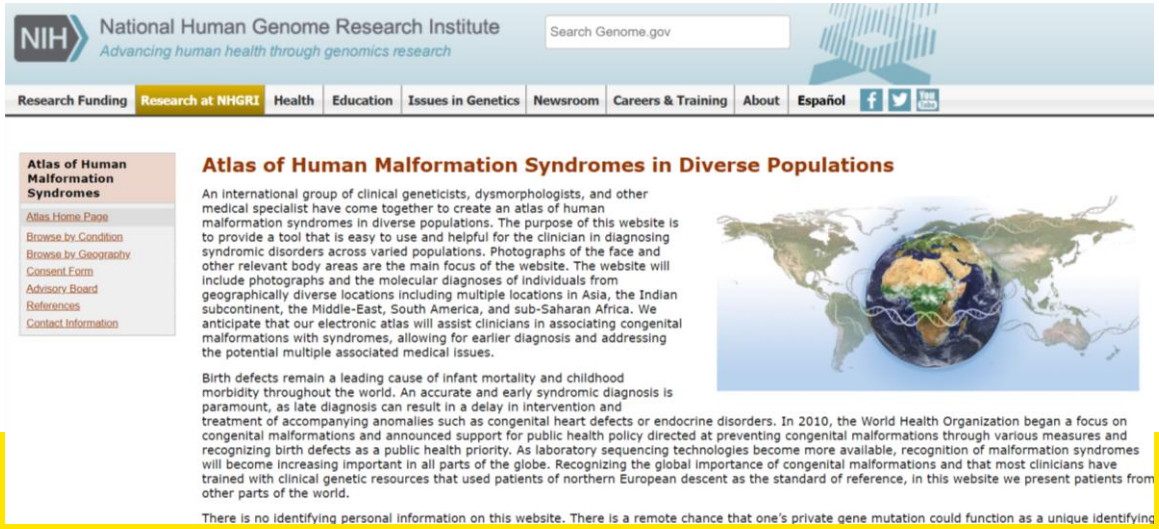
Some good resources

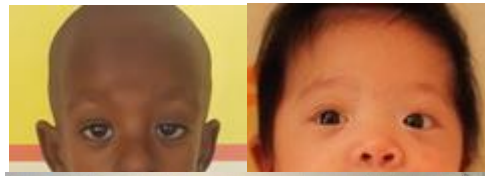
Elements of Morphology: Standard Terminology for the ….
(ACMG series: Allanson et al….2009)

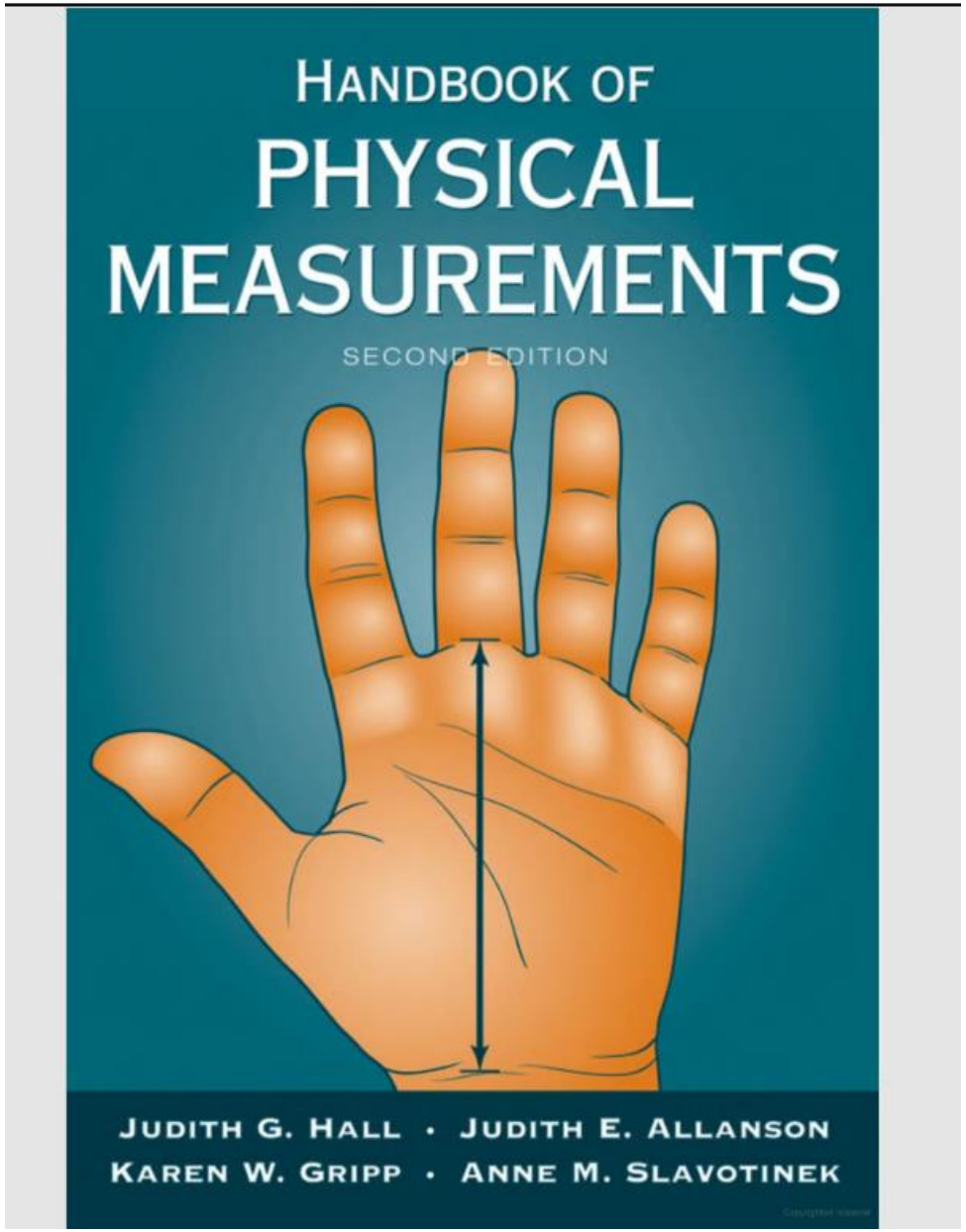












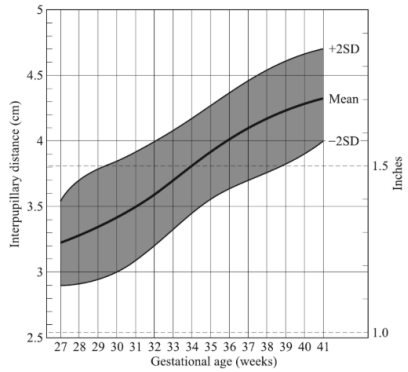
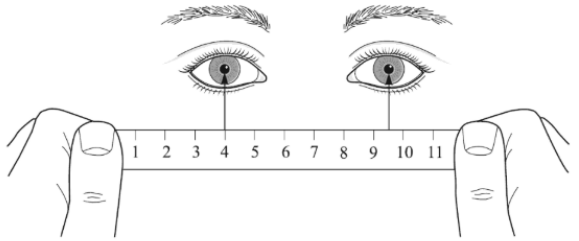


Figure 7.40 Interpupillary distance, both sexes, at birth. From Merlob et al. (1984), by permission.

Figure 7.39 Measuring interpupillary distance.



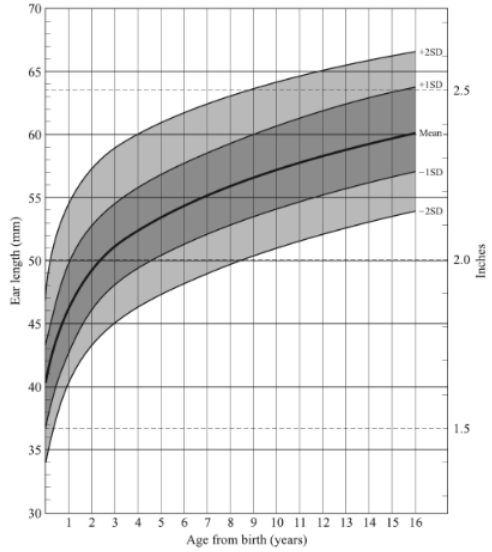
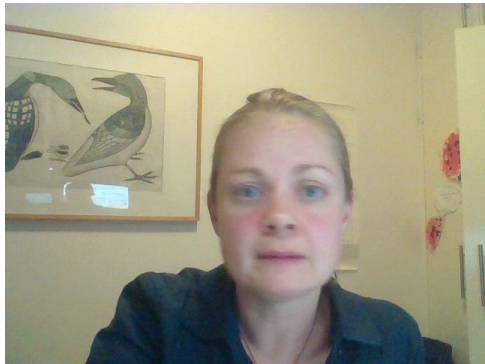


Figure 7.57 Ear length, both sexes, birth to 16 years. From Farkas (1981) and Feingold and Bossert (1974), by permission.



An approach … with thanks to Noe

A) General inspection

A1) Growth

- HC
- Length/ Height
- Weight
- BMI

- Centiles
- Mid parental height

Short and tall stature

- Q? Proportionate or not proportionate. Compare to siblings. Pre or post natal onset
- Short stature: non proportionate
  - Consider skeletal dysplasia

MANY chromosomal and single gene neurodevelopmental genetic disorders affect growth

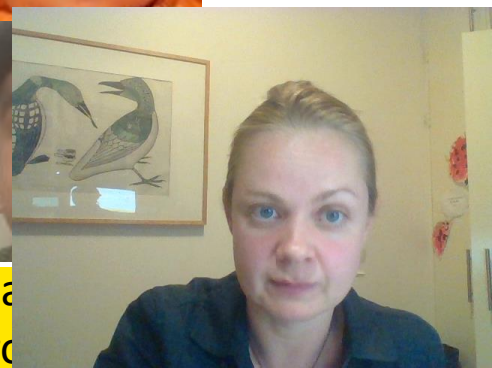
Silver Russell syndrome

IUGR (<<-2.SD_ poor growth after birth, a relatively large head size, a triangular facial appearance, a prominent forehead (looking from the side of the face), body asymmetry and significant feeding difficulties. Majority have normal intelligence.
60% : detectable abnomality in imprinting regions chr 7 and 11

Turner syndrome

1:2000 female births
Complete or partial deletion of X chromosome.
Fertility impact

Noona syndro



Tall: Marfan, Homocystinuria, Klinefelters, Sotos

MARFAN & RELATED CONDITIONS | WHAT TO EXPECT | RESOURCES & ANSWERS | WALK FOR VICTORY | GET INVOLVED | ABOUT US | DONATE

E3 SUMMIT

DX HOME
CRITERIA
SYSTEMIC CALCULATOR
Z-SCORE
TESTING INFO
DIFFERENTIAL DIAGNOSIS
RELATED DISORDERS
RESOURCES

CALCULATION OF SYSTEMIC SCORE

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".

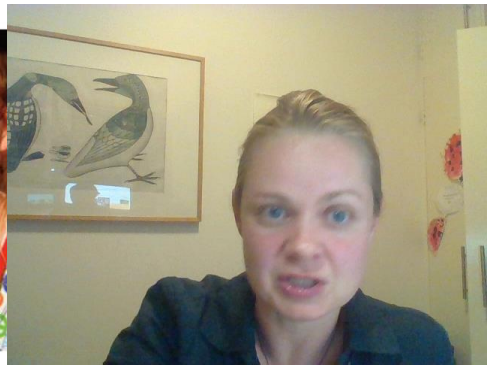
Feature		Value	Click to include
Wrist AND thumb sign	+	3	☐
Wrist OR thumb sign	+	1	☐
Pectus Carinatum Deformity	+	2	☐
Pectus Excavatum or Chest Asymmetry	+	1	☐
Hindfoot Deformity	+	2	☐
Plain Flat Foot	+	1	☐
Spontaneous Pneumothorax	+	2	☐
Dural Ectasia	+	2	☐
Protucio Acetabulae	+	2	☐
Scoliosis or Thoracolumbar 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

*A score of ≥ 7 is considered a positive systemic score.

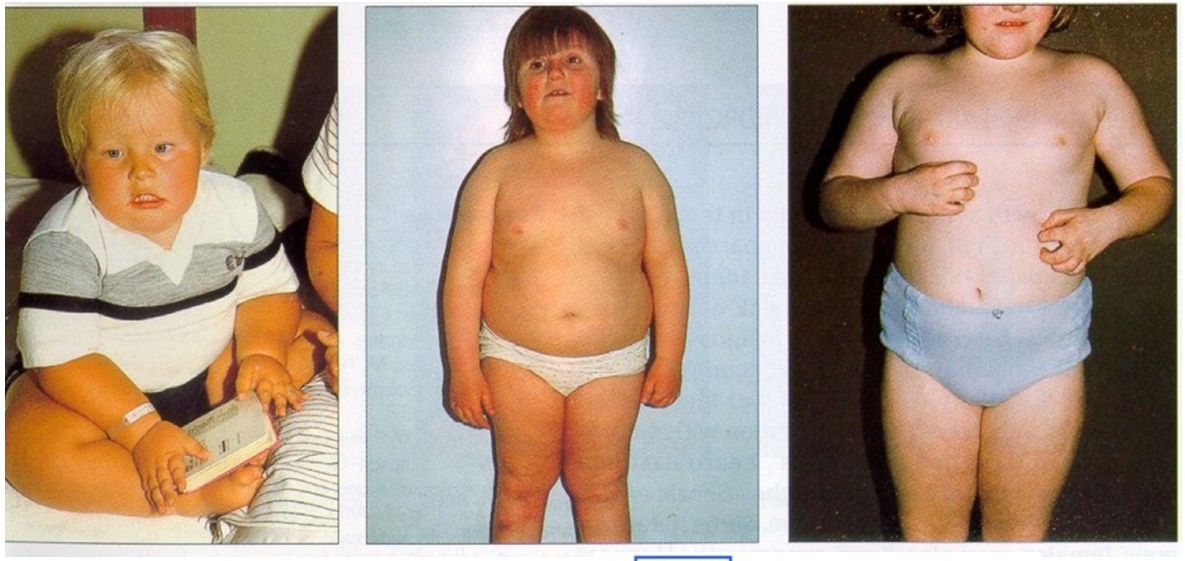
- https://info.marfan.org/
- Diagnostic criteria
- An *FBN1* pathogenic variant known to be associated with Marfan syndrome AND one of the following:
  - Aortic root enlargement (Z-score ≥2.0)
  - Ectopia lentis
- Demonstration of aortic root enlargement (Z-score ≥2.0) and ectopia lentis OR a defined combination of features throughout the body yielding a systemic score ≥7

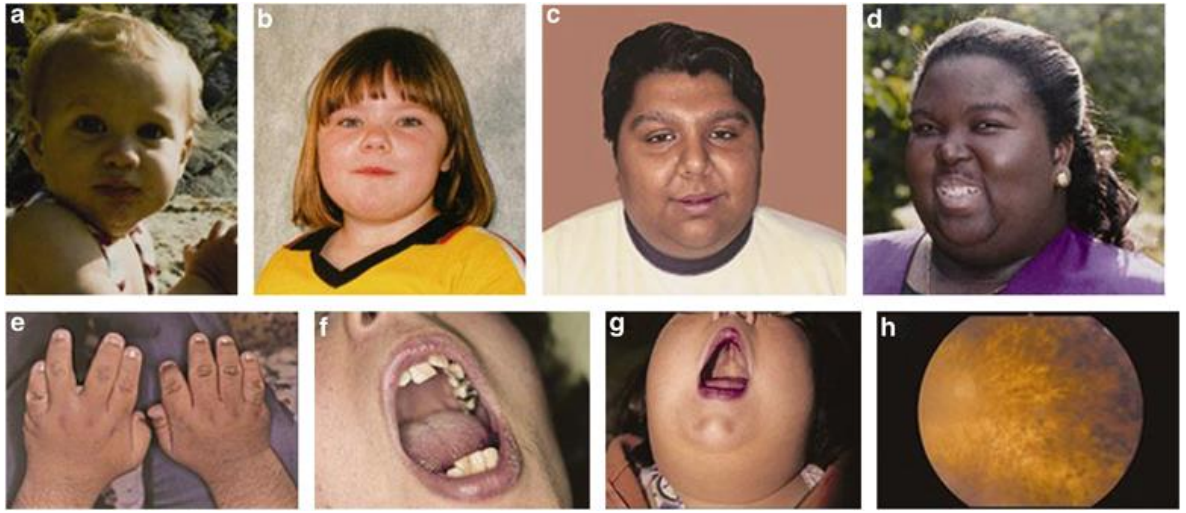
Marfan syndrome is a serious condition, and some complications are potentially life-threatening. Advances in medical care have made it possible for people with Marfan syndrome to live a normal lifespan if they are diagnosed and treated properly.

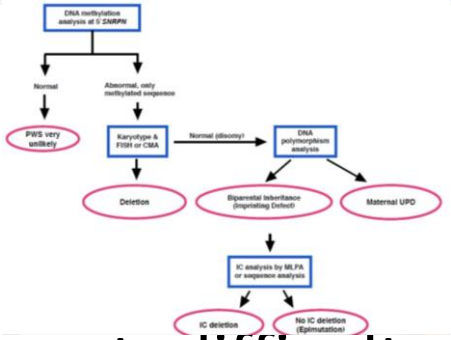
Marfan syndrome most often affects the heart, blood vessels, bones, joints, and eyes.



Obesity: Prader-Willi, Bardet-Biedl







- Hypotonia
- Hypogonadism
- Hyperphagia
- Cognitive impairment; difficult behaviours

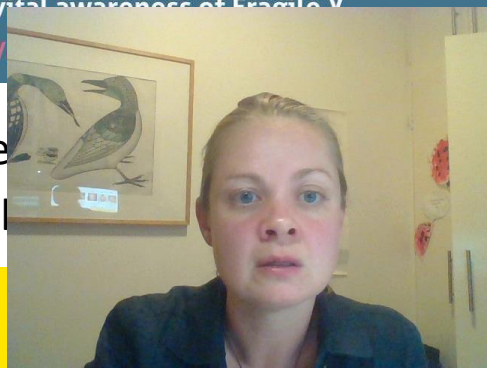
Typical facial features; these are often subtle and are not always present. Features include deeply set eyes, widely spaced eyes, downslanted palpebral fissures, a depressed nasa
bridge, small mouth, malar flattening,
e. Brachydactyly and scars from excisi
f. Dental crowding
g. High palate
h. Fundoscopy demonstrating **rod-cor**

Development, characteristic behaviours/autistic features

- Rett syndrome – Clinical findings

- Most distinguishing finding: A period of regression (range: ages 1-4 years) followed by recovery or stabilization (range: ages 2-10 years; mean: age 5 years)
- Main findings
  - **Partial or complete loss of acquired purposeful hand skills**
  - **Partial or complete loss of acquired spoken language or language skill (e.g., babble)**
  - Gait abnormalities: impaired (dyspraxic) or absence of ability
  - **Stereotypic hand movements including hand wringing/squeezing, clapping/tapping, mouthing, and washing/rubbing automatisms**
- Supportive findings
  - Breathing disturbances when awake
  - **Bruxism when awake**
  - Impaired sleep pattern
  - Abnormal muscle tone
  - Peripheral vasomotor disturbances
  - Scoliosis/kyphosis
  - Growth retardation
  - Small, cold hands and feet
  - **Inappropriate laughing/screaming spells**
  - **Diminished response to pain**
  - **Intense eye communication - "eye pointing"**

Fragile X syndrome: autistic fe
avoidance very common, flap
hyperactivity,

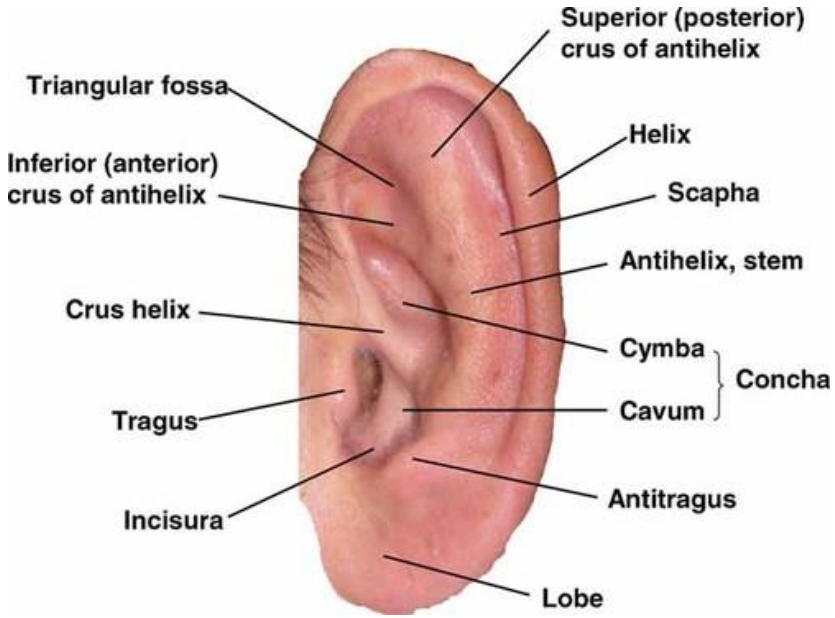


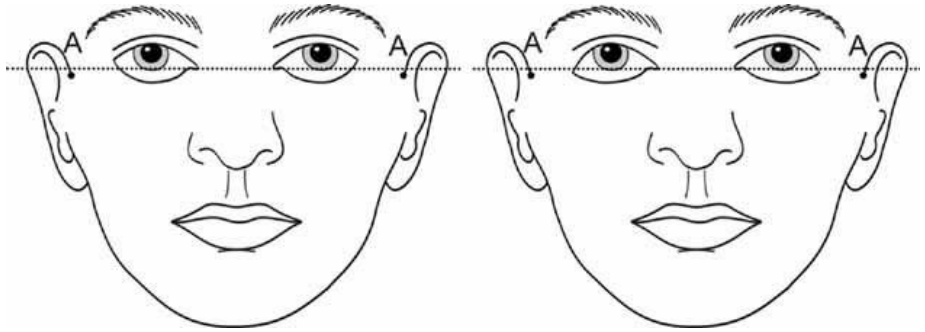
Head

- Head circumference
- Shape
- Craniosynostosis - 0.5-3.4%
  - Sagittal 50% (dolicocephlay)
  - Coronal 22% (brachycephaly)
  - Metopic 6% (trigonencephaly)
  - Look at hands
- Fontanelles –
  - Size and time of closure
- Radiology-
  - sutures
  - Thick/thin/hyperostosis

Head: size, shape, fontanelles, sutures, hair (quality, quantity), position of hairline	**Craniosynostosis syndromes**
Face: shape, symmetry, forehead	Alagille's

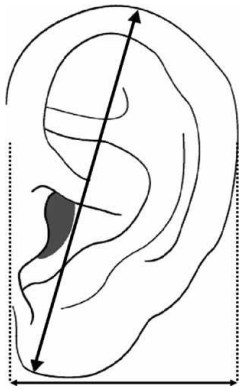
Ears

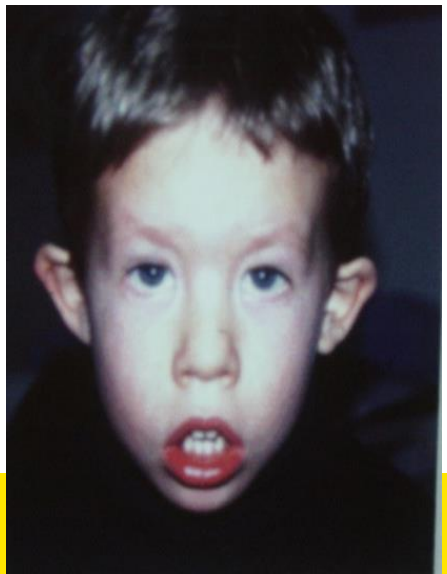


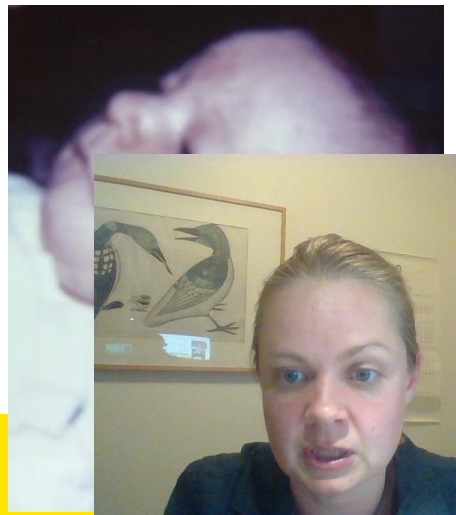


- Microtia/Anotia Macrotia
- Shape
- Position
- Configuration
- Auricular tag
- Pits
- Creases
- Hearing!

Low set ears
Definition : Upper insertion of the ear to the scalp below an imaginary horizontal passing through the inner canthi and extend that line posteriorly to the ear



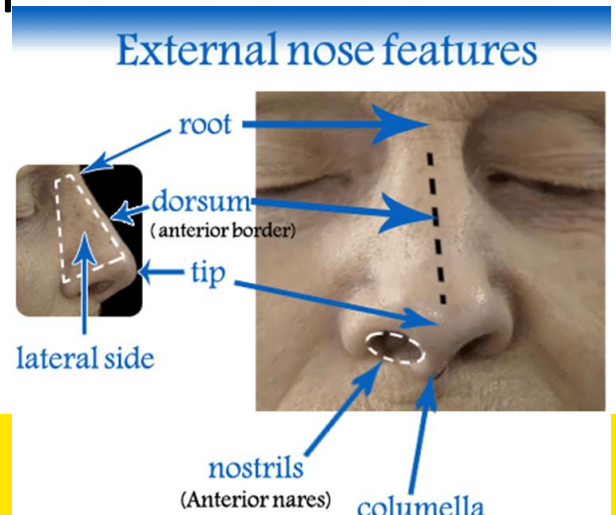




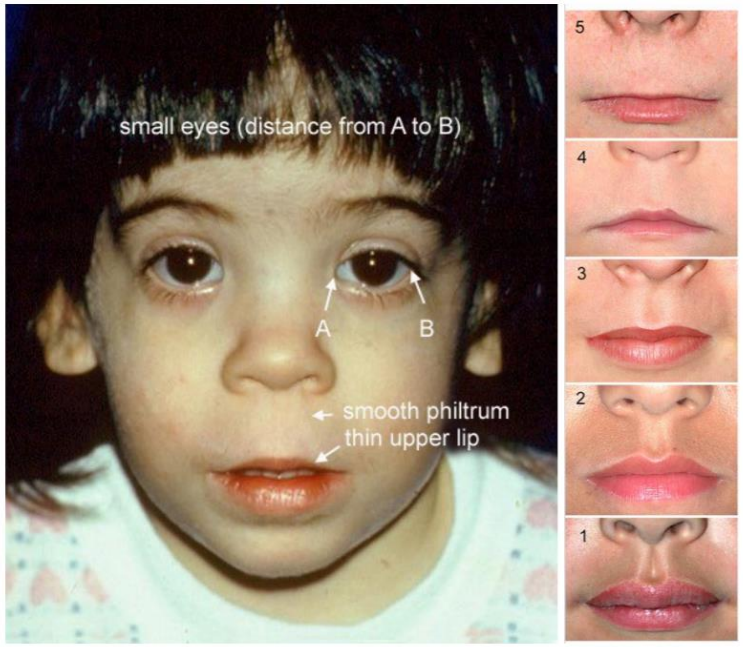
Deafness: Goldenhar, CHARGE, Waardenburg, Treacher Collins, Alport, NF-2, BOR, GJB2 (connexin 26), Jervell and Lange Nielsen, Alport

Nose

- size,
- shape,
- nasal bridge,
- tip,
- nostrils,
- philtrum



Fetal exposure to alcohol during the first trimester affects development of facial features.
A range of facial anomalies can occur as result of prenatal alcohol exposure. There are three features which commonly occur across age, gender and ethnic groups:

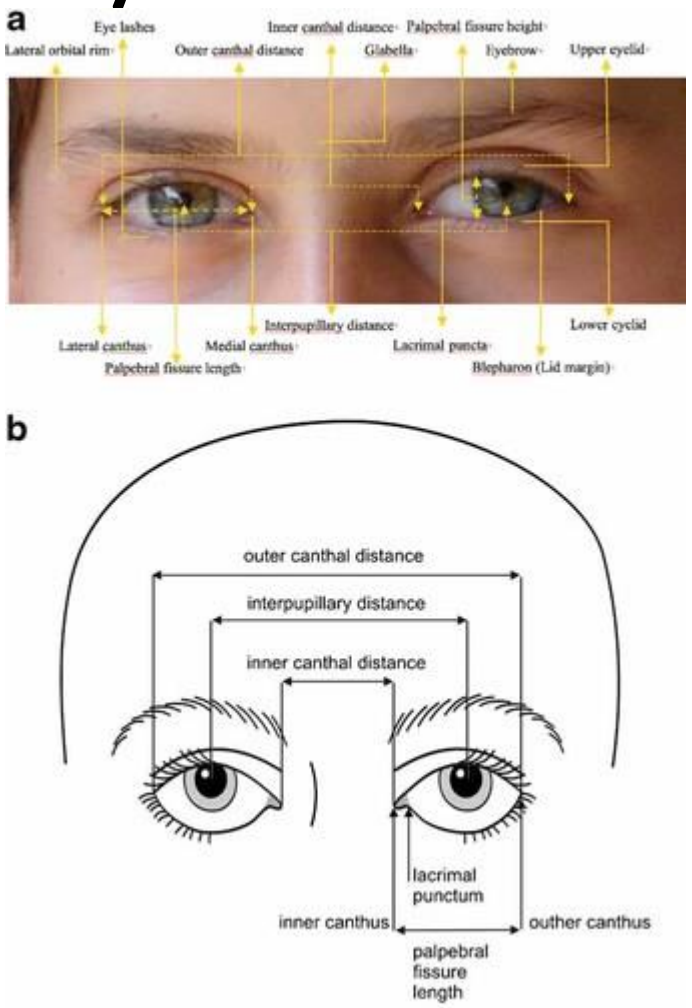


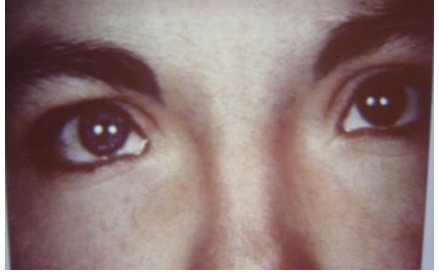
(Photo reproduced with permission from Susan Astley, University of Washington)

- Small palpebral fissures: short horizontal length of the eye opening, defined as the distance from the endocanthion to the exocanthion (points A and B on photo below)
- Smooth philtrum: diminished or absent ridges between the upper lip and nose
- Thin uppe
volume

https://www.fasdhub.org.au/siteassets/pdfs/australi
diagnosis-of-fasd_all-appendices.pdf

Eyes

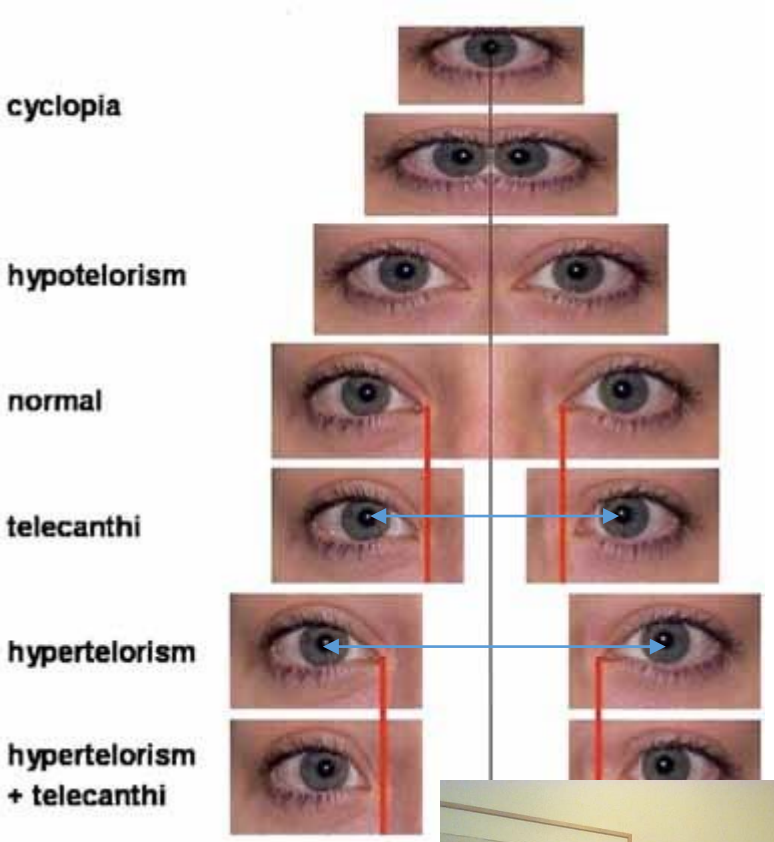


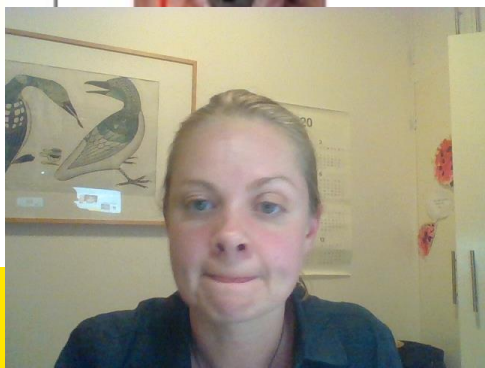


Telecanthus – increased distance between inner canthus- varies with ethnicity

Critically – is the intra-pupillary distance increased or not

Hypertelorism- widely spaced eyes- increased intra-pupillary distance





Mouth

- mouth,
- jaw,
- lips,
- teeth,
- palate,
- tongue,
- uvula,
- midline defects

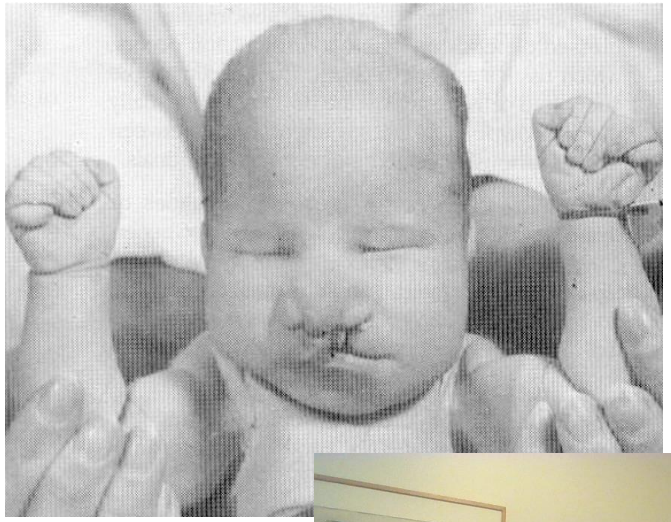
Cleft lip/palate: 22q11 deletion, Stickler

- Approx 50% of cleft lip/palate will have other anomalies
  - isolated CP (30%)
  - isolated CL (11%)
  - CLP (9%)

Recurrence risk depends on family history and type:

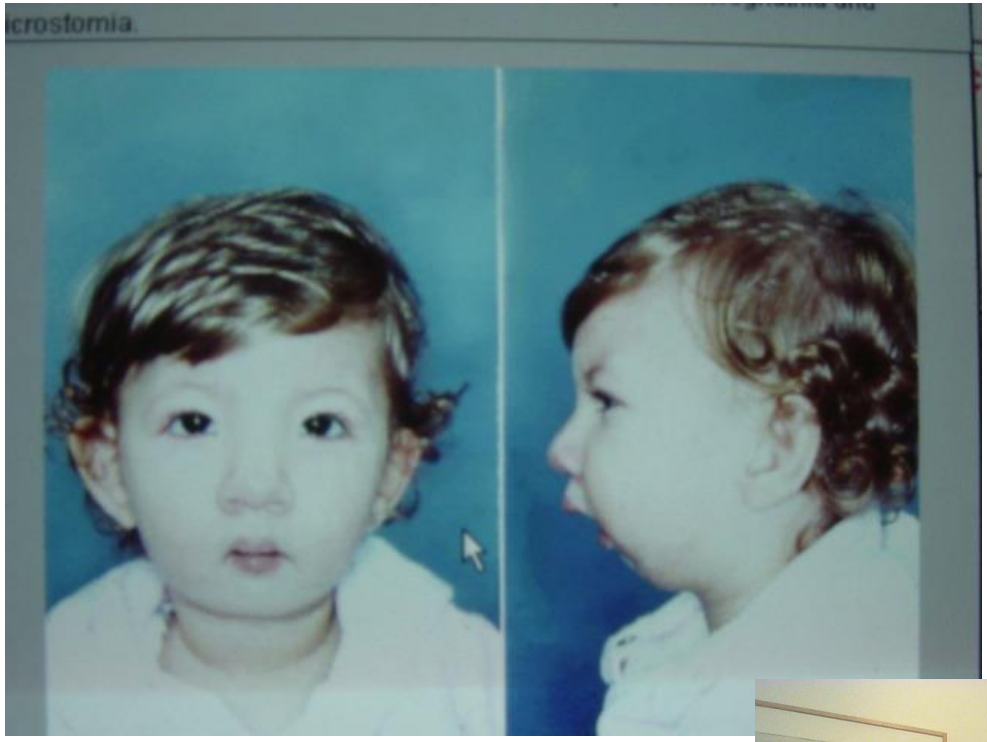
Non syndromal cleft palate (CP)
- One affected child RR 2%
- One affected parent RR 6%
- One affected parent and one affected child RR 15%

Non syndromal Cleft lip and palate
- One affected child RR 4%
- One affected parent RR 4%
- One affected parent and one affected child RR 10%



Mandible

- Agnathia
- +/- holoprosencephaly
- Micrognathia –
- associated with > 130 syndromes
- >47 chromosomal abnormalities
- Contribution to sequence .eg. Pierre Robin
- Retrognathia
- Normal size and shape -posteriorly positioned jaw



Limbs

Hands: shape, size, symmetry, nails, finger length and shape, palmar creases

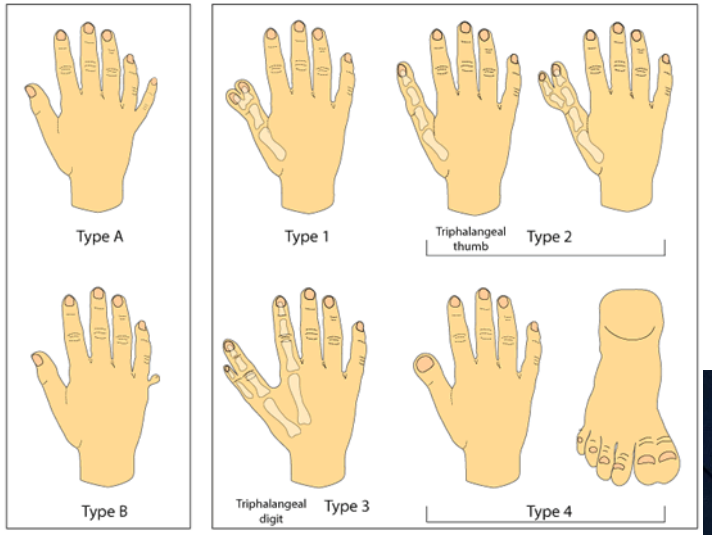
Length –brachdactyly/arachnodactyly

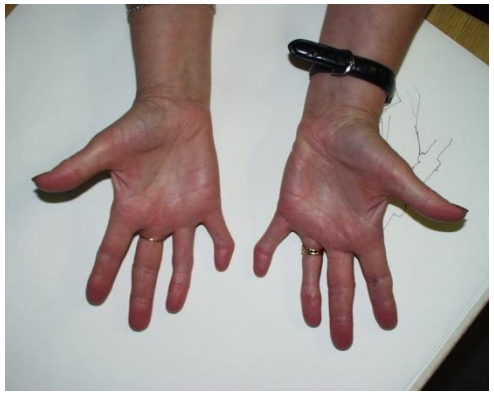
digits-

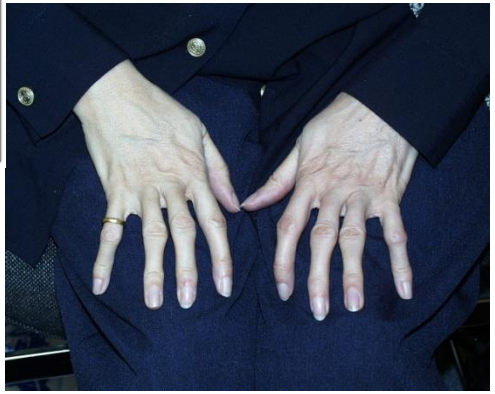
- oligodactyly
- polydactyly
- clinodactyly
- syndactyly

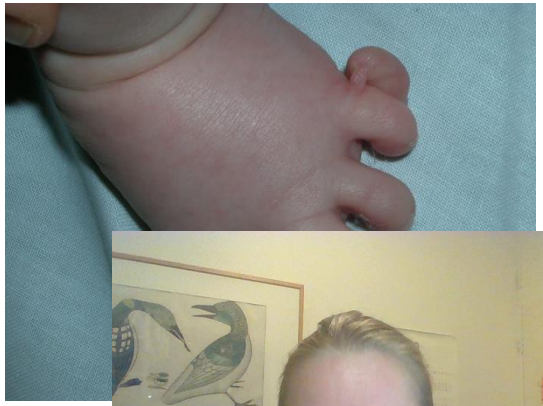
Arms: segment proportions, asymmetry, joint hypermobility

Marfan, Ehler Danlos, Beckwith-Wiedemann





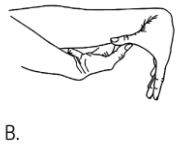




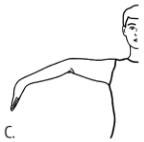
Hands: shape, size, symmetry, nails, finger length and shape, palmar creases	**Radial ray anomalies: Fanconi anaemia, VACTERL, TAR, Blackfan diamond**
Arms: segment proportions, asymmetry, joint hypermobility	Marfan, Ehler Danlos, Beckwith-Wiedemann

Joint hypermobility scale (Beighton) https://www.ehlers-danlos.com/assessing-joint-hypermobility/

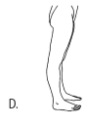
- (A) With the palm of the hand and forearm resting on a flat surface with the elbow flexed at 90°, if the metacarpal-phalangeal joint of the fifth finger can be hyperextended more than 90° with respect to the dorsum of the hand, it is considered positive, scoring 1 point.



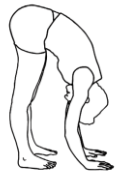
- (B) With arms outstretched forward but hand pronated, if the thumb can be passively moved to touch the ipsilateral forearm it is considered positive scoring 1 point.



- (C) With the arms outstretched to the side and hand supine, if the elbow extends more than 10°, it is considered positive scoring 1 point.

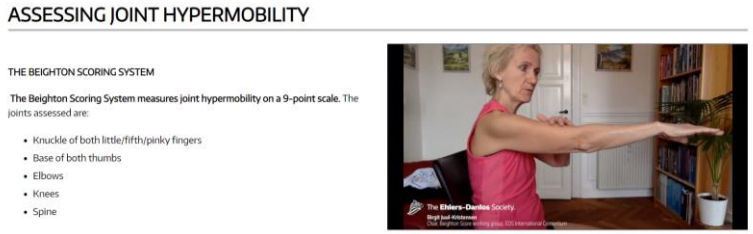


- (D) While standing, with knees locked in genu recurvatum, if the knee extends more than 10°, it is considered positive scoring 1 point.



- (E) With knees locked straight and feet together, if the patient can bend forward to place the total palm of both hands flat on the floor just in front of the feet, it is considered positive scoring 1 point.

≥6 for prepubertal children
≥5 for pubertal children and adults up to age 50
≥4 for those age >50 years



Hypermobile EDS requires three criteria to be met

- Generalized joint hypermobility (Criterion 1)
- Evidence of syndromic features, musculoskeletal complications, and/or family history (Criterion 2)*
- Exclusion of alternative diagnoses (Criterion 3)#

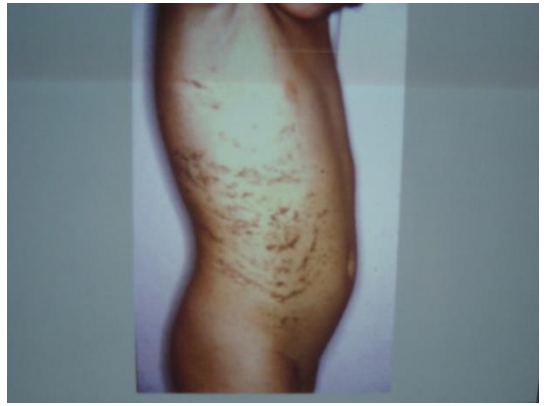
Must do an echo to look at aortic root size
Repeat 3-5 years if N to late teens

- Management: low impact exercise, physical therapy, splints/ supports/ pe
  accommodations (OT)/ GI/ y
  family therapy/ pain therapy

*musculoskeletal pain, joint dislocations,
e.g. skin fragility, atrophic scaring, vasc
Williams, aortic enlargement

Skin

Skin: scars, neurocutaneous stigmata, pigmentation	Café-au-lait macules: NF-1, Fanconi Anemia, McCune-Albright Hypo-pigmentation: Tuberous sclerosis



Neurofibromatosis 1 (NF1) should be suspected in individuals who have any of the following findings:

Six or more café au lait macules (Figure 1) >5 mm in greatest diameter in prepubertal individuals and >15 mm in greatest diameter in postpubertal individuals
Two or more neurofibromas (Figure 2) of any type or one plexiform neurofibroma (Figure 3)
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

Tuberous sclerosis diagnostic criteria

Major features
- **Angiofibromas (≥3) or fibrous cephalic plaque**
- Cardiac rhabdomyoma
- Cortical dysplasias, including tubers and cerebral white matter migration lines
- **Hypomelanotic macules (3 to >5 mm in diameter)**
- Lymphangioleiomyomatosis (LAM) Multiple retinal nodular hamartomas
- Renal angiomyolipoma (Shagreen patch
- Subependymal giant cell astrocytoma (SEGA)
- Subependymal nodules (SENs)
- **Ungual fibromas (≥2)**

Minor features
- **"Confetti" skin lesions (numerous 1- to 3-mm hypopigmented macules scattered over regions of the body such as the arms and legs)**
- Dental enamel pits (>3)
- Intraoral fibromas (≥2)
- Multiple renal cysts
- Nonrenal hamartomas
- Retinal achromic patch

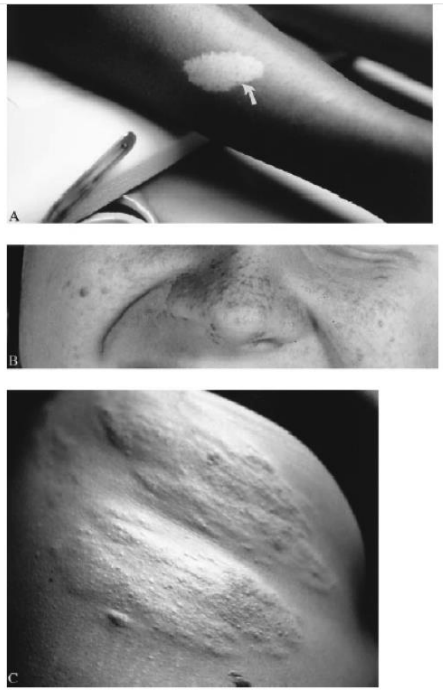
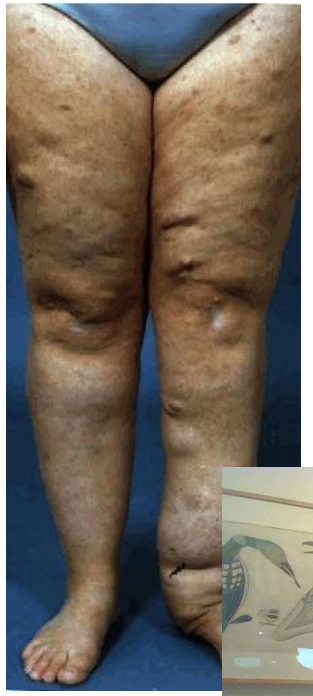


Figure 1. Classic cutaneous manifestations of tuberous sclerosis include (A) hypomelanotic macule (ash-leaf spot) (arrows), (B) facial angiofibromas. (C) Shagreen patch. Figures 1A and 1C reprinted from Roach ES, Semin Neurol 1988; 8:83–96, with permission. Figure 1B reprinted from Roach ES, Delgado MR, Derm



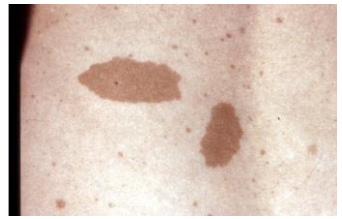
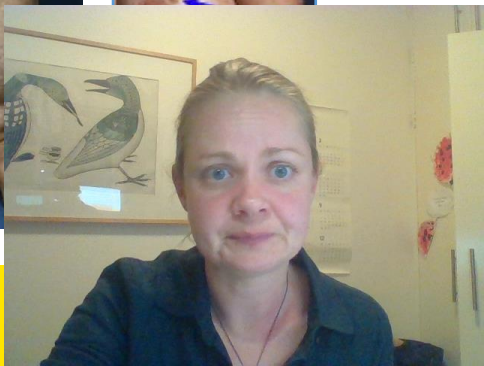


Fig 1

Fig 3



Rest of the body1!

Torso	
Neck: webbing, skin folds	Noonan
Back/chest: spine (scoliosis, surgery, stature), sternum, chest, nipples, heart sounds	Klippel Feil Congenital cardiac malformations in various syndromes (partly also covered in cardiology)
Abdomen: organomegaly, scars, hernia	
Lower limbs and feet	
Legs: segment proportions, asymmetry, hypermobility	Beckwith-Wiedemann
Feet: nails, toes, webbing, foot size and shape (flat, curved, symmetry)	Syndactyly
Genitalia	
Phallus, scrotum, testes (size and development), labia, puberty	Pubertal delay: Turner, Klinefelter
Anus: position/perforate	VACTERL

SELECTED GENETIC DISEASES WITH DYSMORPHIC FEATURES

- For the conditions listed below: features on examination/dysmorphic features; where applicable - diagnosis, treatment, prognosis for the condition.
- Alagille syndrome
- Disorders of chromosomal duplication or deletion, such as cri-du-chat syndrome
- Duchenne and Becker muscular dystrophy (DMD) – also covered in neurology
- Fragile X syndrome (FXS)
- Genetic imprinting disorders:
  - Angelman syndrome
  - Beckwith–Wiedemann syndrome
  - Prader–Willi syndrome
- Genetic disorders with neurological features (also covered in neurology)
  - Ataxia telangiectasia
  - Charcot–Marie–Tooth disease
  - Huntington disease
  - Rett syndrome
  - tuberous sclerosis
- Genetic disorders of growth and musculoskeletal development
  - achondroplasia
  - Treacher Collins syndrome
- Klinefelter syndrome
- Marfan syndrome
- Microarray abnormalities:
  - 15q11.2 deletion
  - 16p11.2 deletion or duplication
  - 22q11.2 deletion or duplication
- Myotonic dystrophy (also covered in neurology)
- Neurofibromatosis type 1 (NF1) and type 2 (NF2)
- Noonan syndrome (NS)
- Osteogenesis imperfecta (OI)
- Trisomy 13, 18, 21
- Turner syndrome
- Williams syndrome

UNSW SYDNEY | Australia's Global University

- Moving into the frontier technology age

.... Facial recognition software