Genetics of congenital heart diseases

Syndromic congenital heart diseases

Damien Bonnet

Is genetics of CHD an issue for clinical practice ?

- Incidence: 8/1000 live-births

- 28% : associated anomalies
  > 600 entries in OMIM

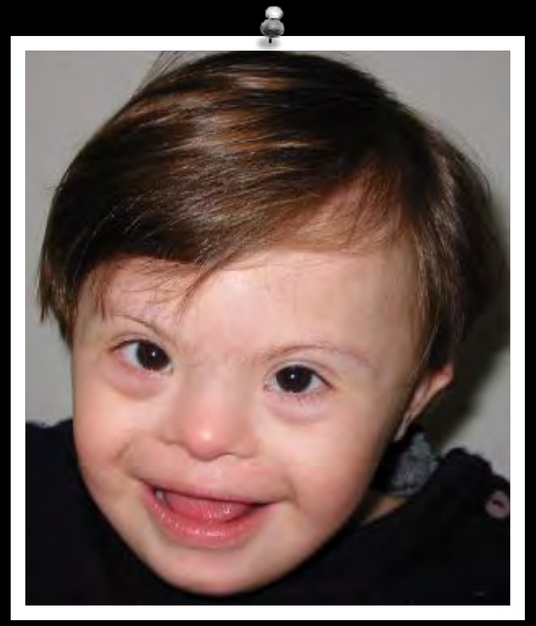
- Genetic counseling is a challenge as survival is now the rule

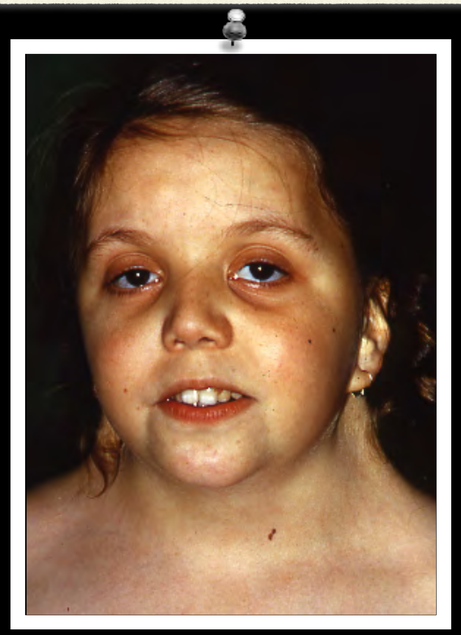
M3C

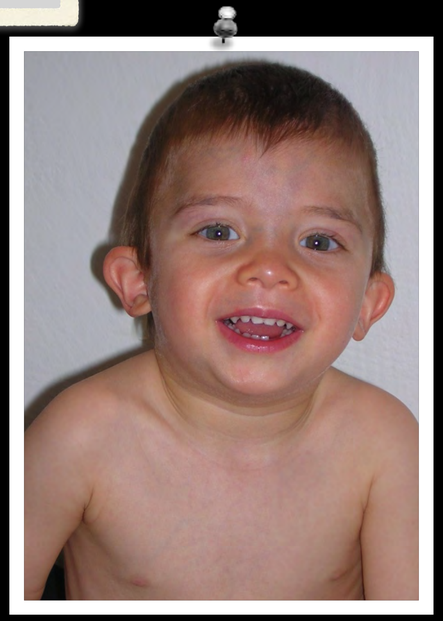
The developmental genetics of congenital heart disease

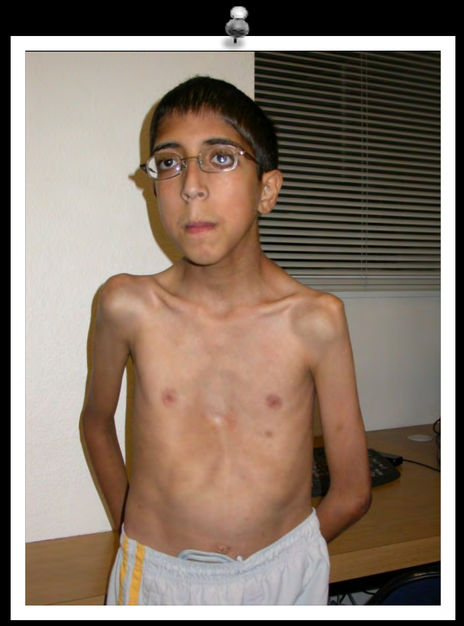
Benoit G. Bruneau[1]

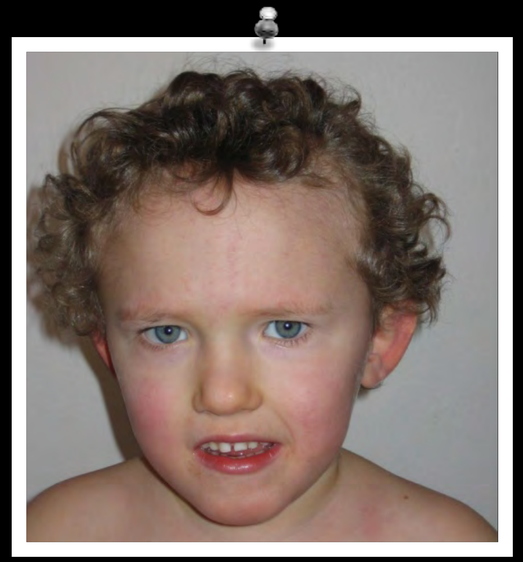
What everybody knows !

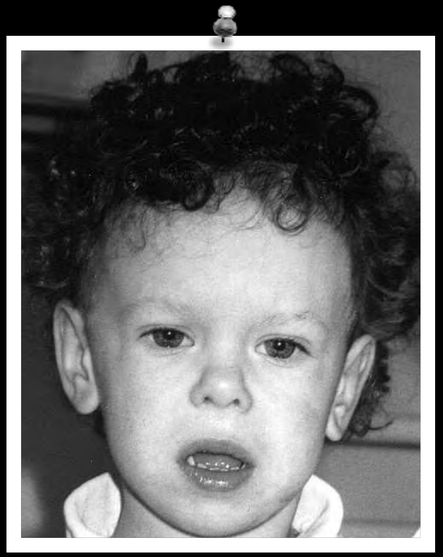


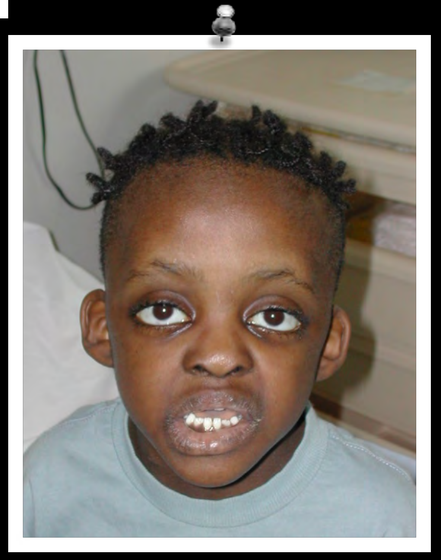




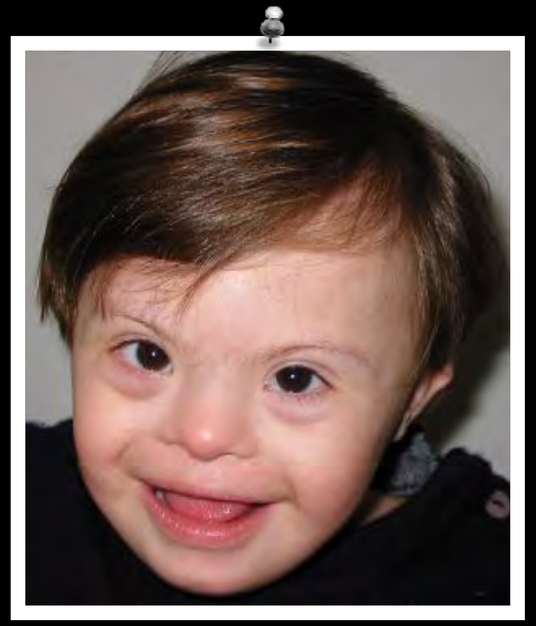
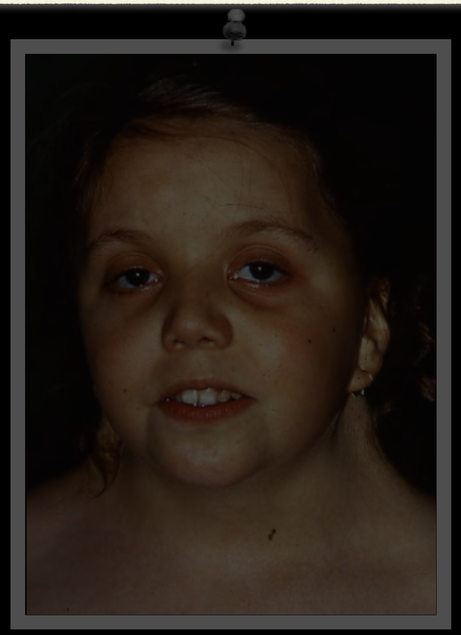
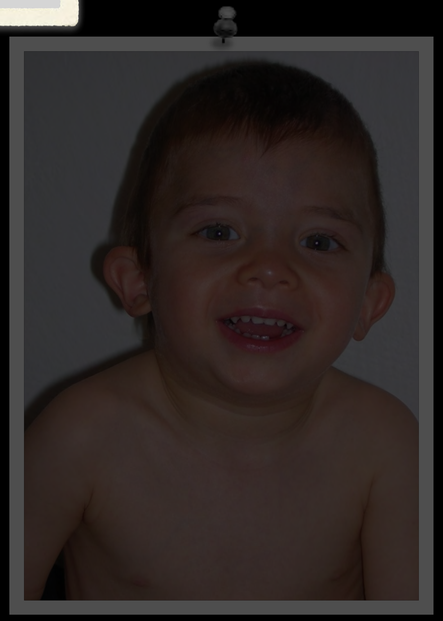
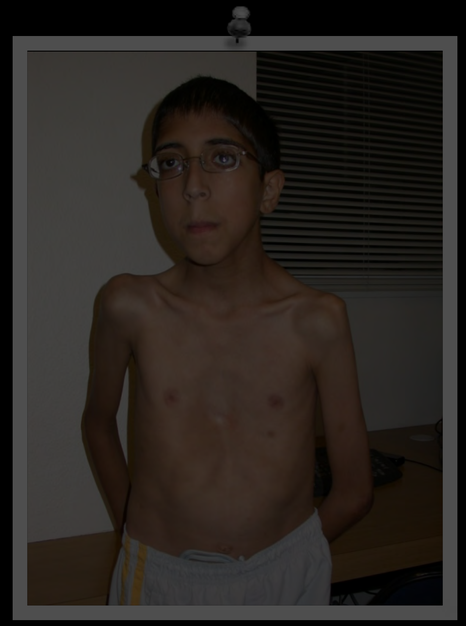
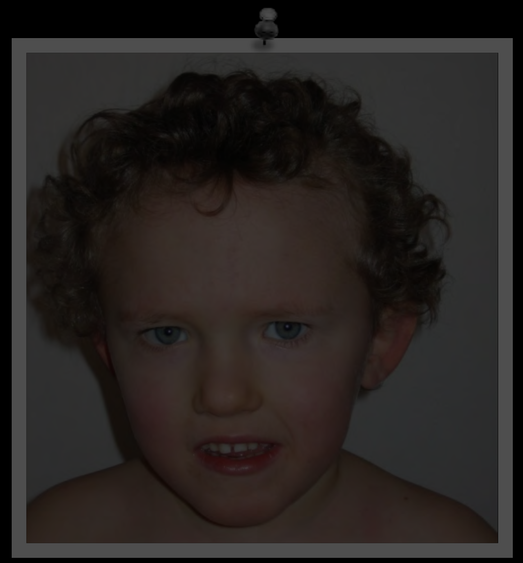
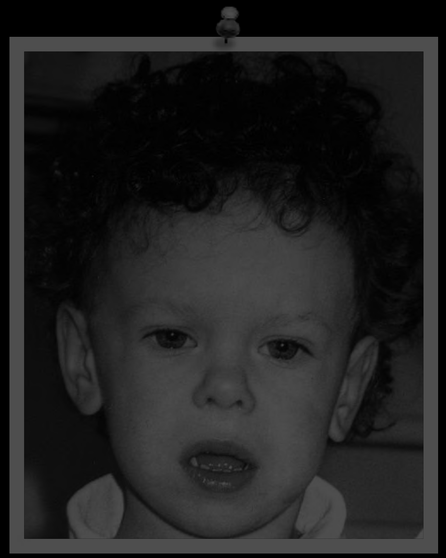
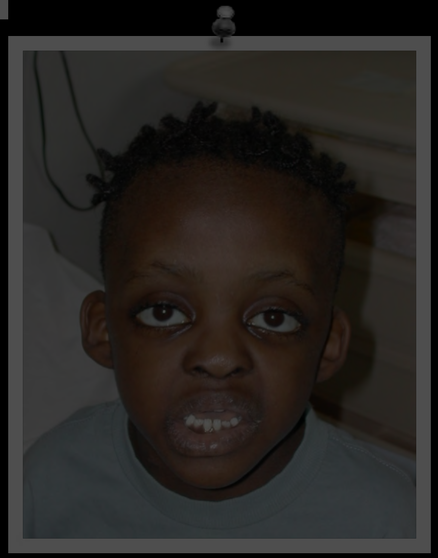


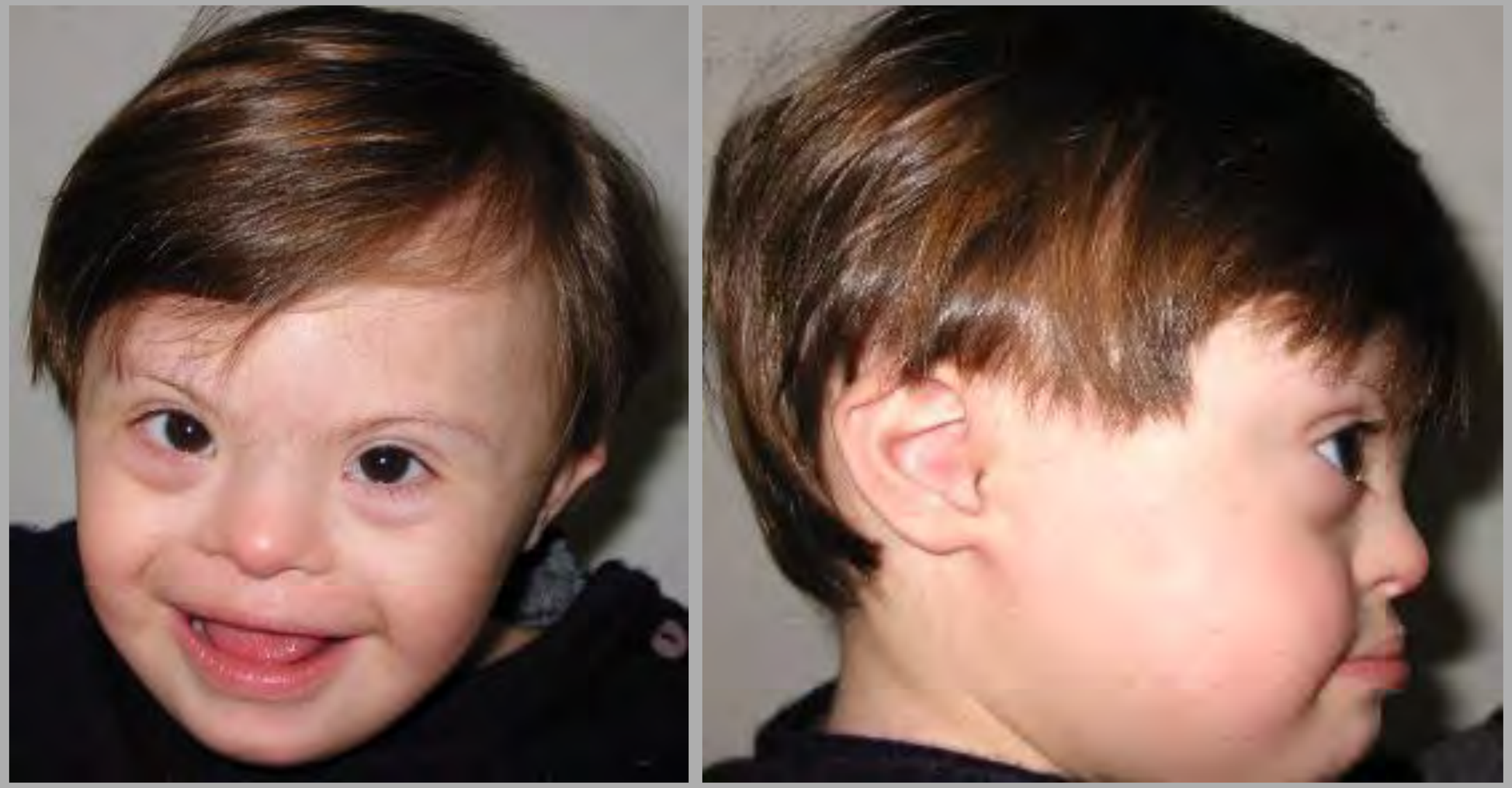






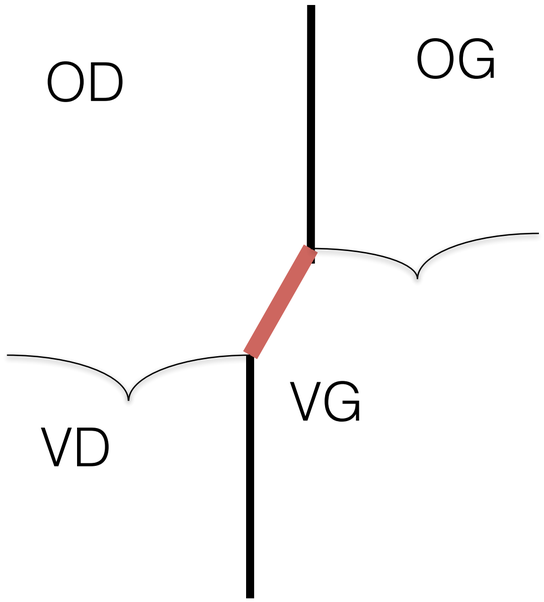
What everybody knows !

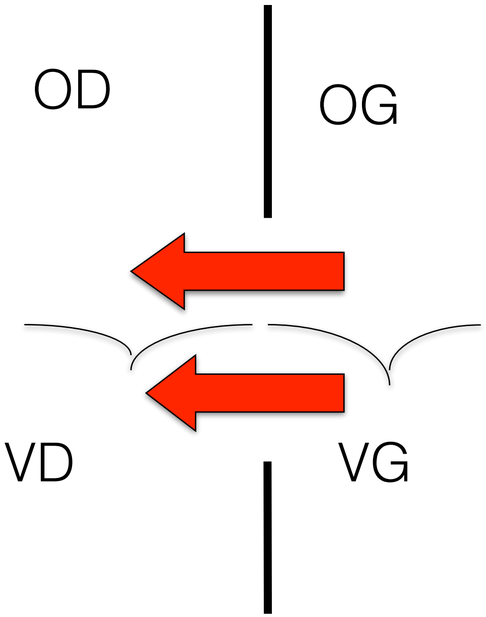



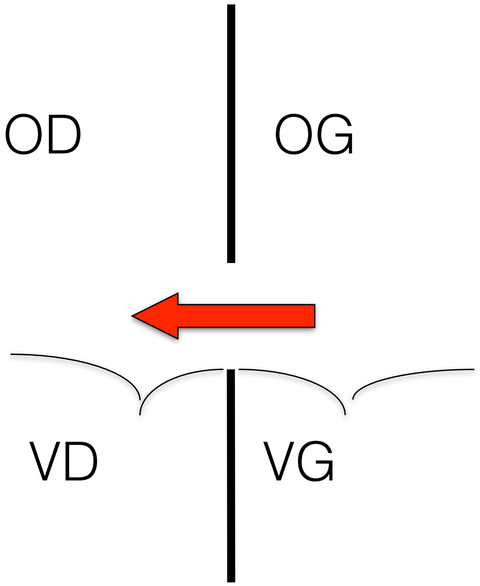
Trisomy 21 - Down syndrome

Septation atrioventriculaire

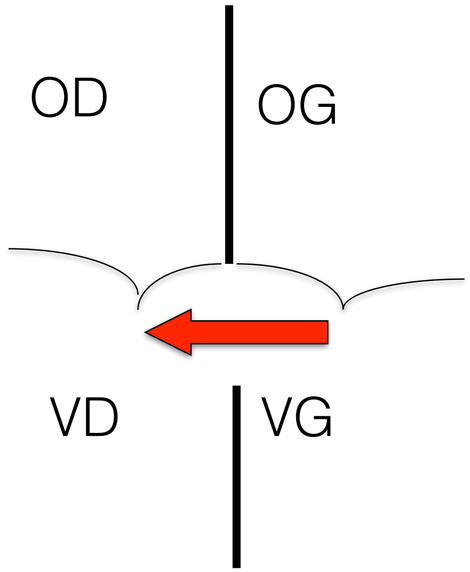


Coeur normal

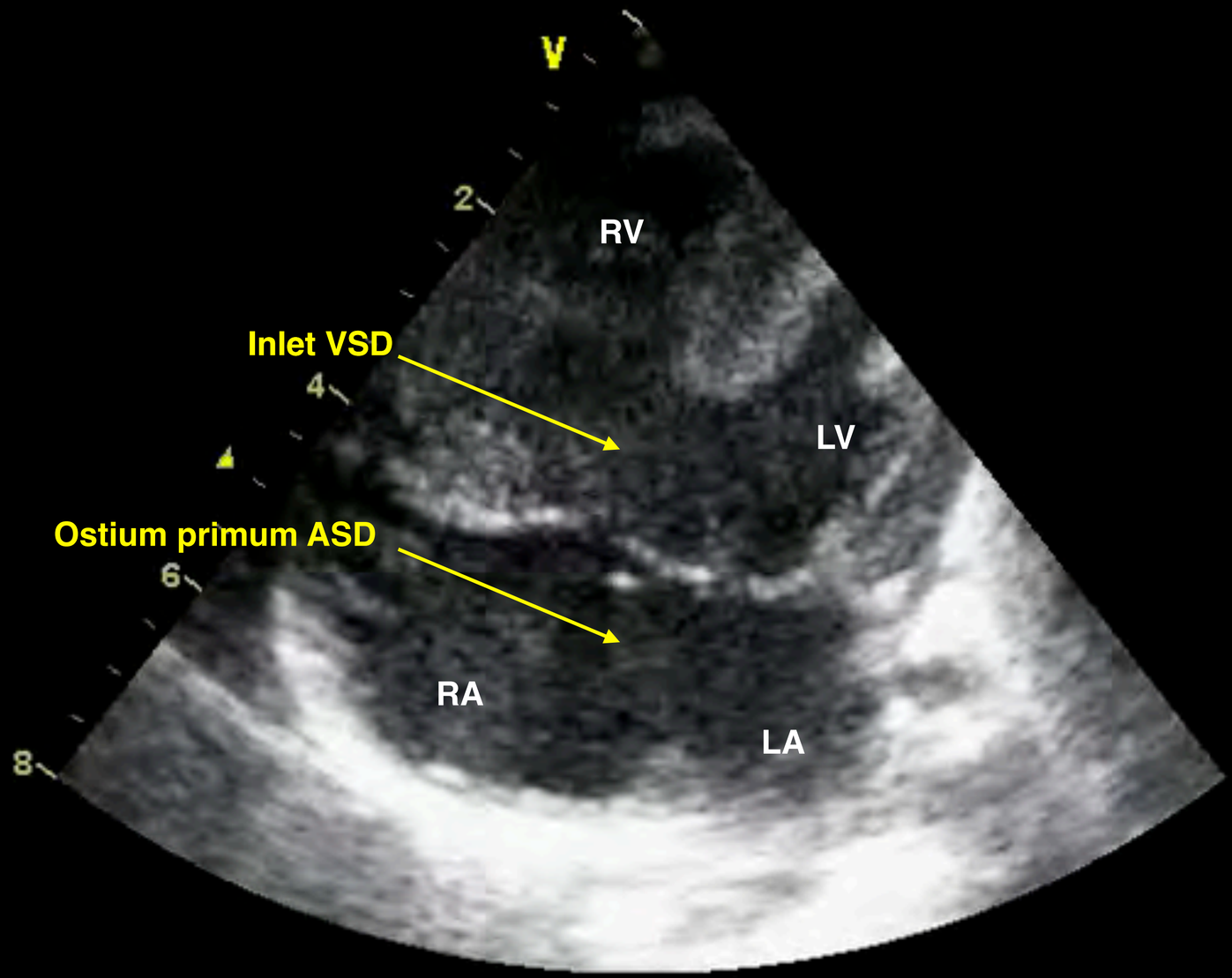




CAV



Complete AVSD



Atrioventricular Canal Defect Without Down Syndrome: A Heterogeneous Malformation

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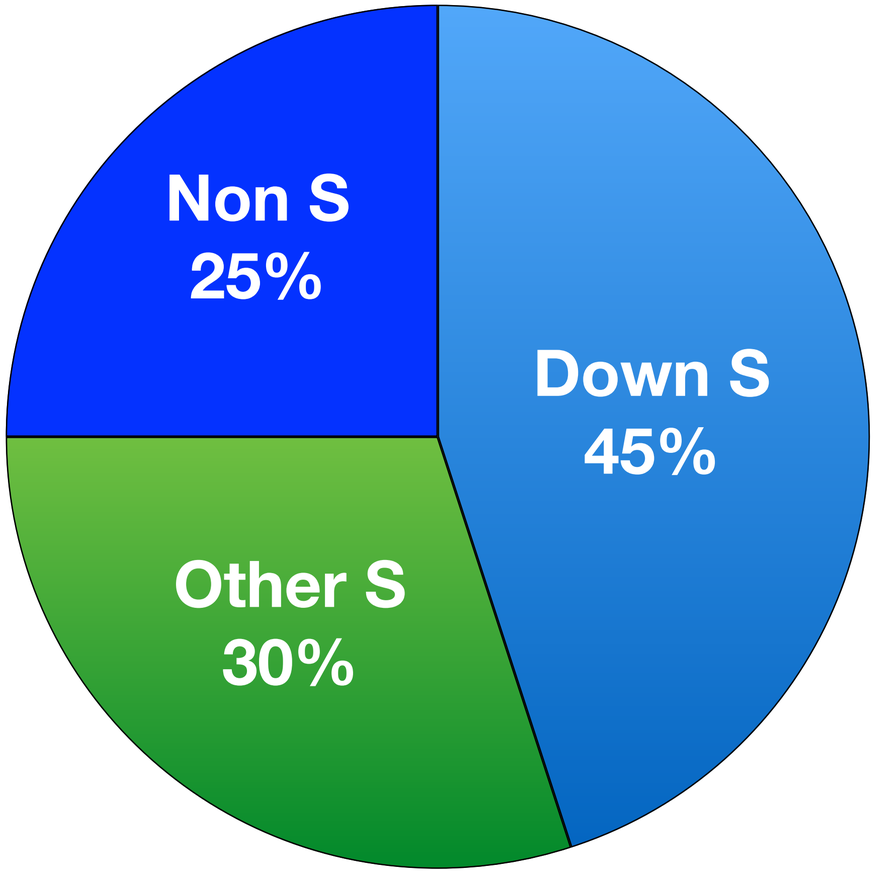
[1]Departments of Pediatric Cardiology and Medical Genetics, Bambino Gesù Hospital, Rome, Italy
[2]Chair of Medical Genetics, Tor Vergata University, and C.S.S.—Mendel Institute, Rome, Italy



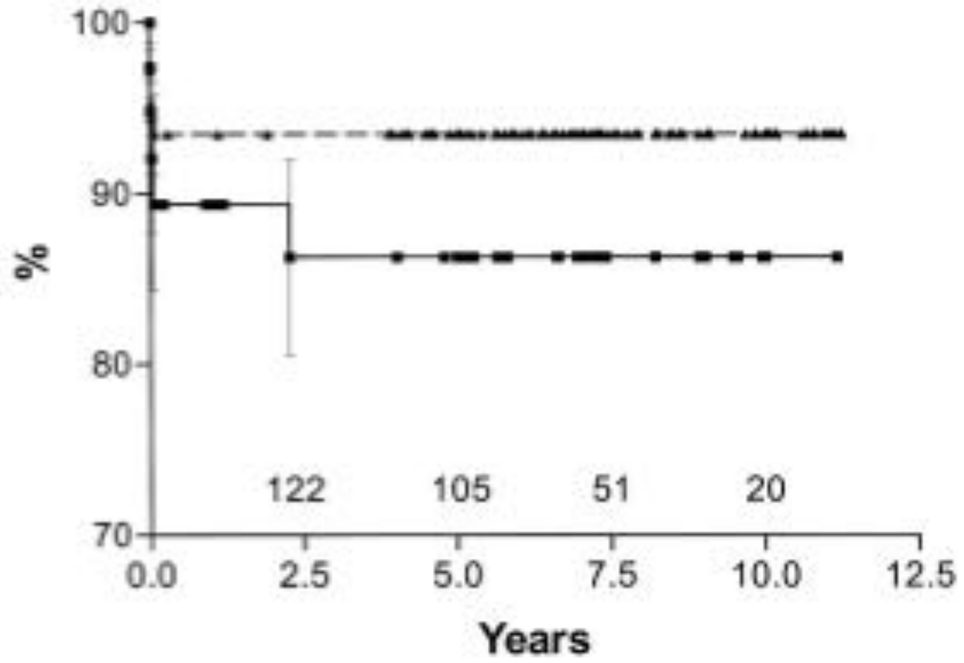
- Complete AV Canal is prevalent in patients with chromosomal imbalance
- Additional cardiac defects are prevalent in patients with:
  - chromosomal imbalance different from Trisomy 21
  - nonsyndromic AV canal

Am J Med Genet 1999;85:140

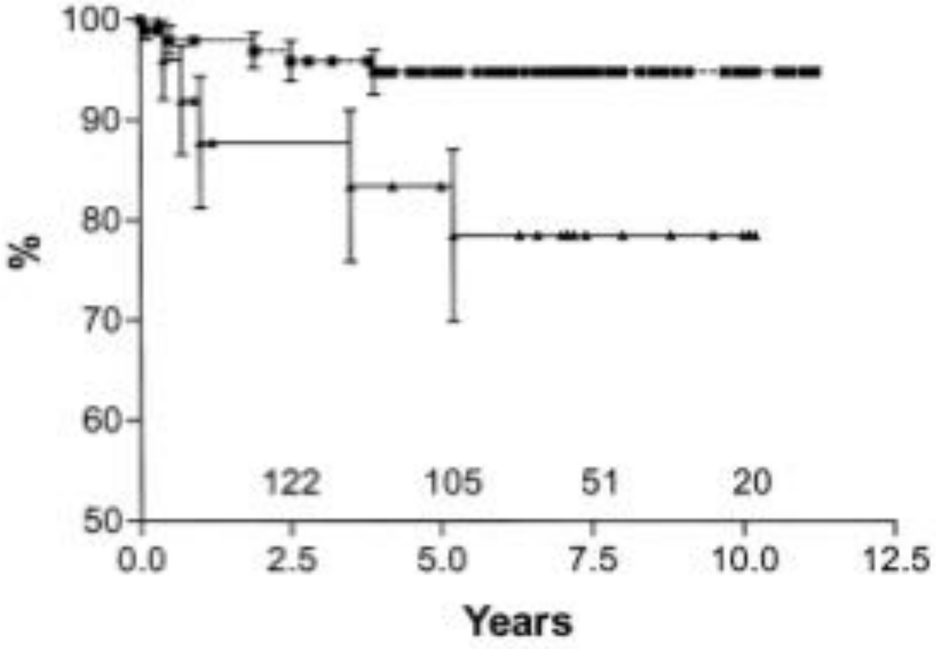
AVSD : associated cardiac defects
T21 vs non T21

Formigari R et al, Ann Thorac Surg 2004; 78:666

Survival after biventicular repair or definitive monoventricular palliation



Freedom from reoperation after biventicular repair or definitive monoventricular palliation



Major congenital heart defects by maternal age, infant sex, and maternal ethnicity

		Complete AVSD		Any AVSD		ASDII		VSD	
	N	%[a]	OR (95% CI)[b]	%[a]	0R (95% CI)[b]	%[a]	OR (95% CI)[b]	%[a]	OR (95% CI)[b]
Mother's age									
<35	735	13.7	ref	18.2	ref	19.3	ref	21.4	ref
>35	721	12.1	0.85 (0.62–1.17)	16.2	0.86 (0.66–1.16)	18.2	0.95 (0.73–1.25)	17.2	**0.76 (0.58–0.99)**
Male	787	9.5	ref	9.5	ref	16.5	ref	20.0	ref
Female	682	16.6	**1.93 (1.40–2.67)**	16.6	**2.06 (1.55–2.75)**	21.0	**1.35 (1.03–1.76)**	19.1	0.95 (0.73–1.24)
Mother's race									
White	624	15.1	ref	19.2	ref	14.9	ref	17.1	ref
Black	183	24.6	**2.06 (1.32–3.21)**	29.5	**1.98 (1.31–2.99)**	25.7	**1.63 (1.06–2.50)**	20.2	1.06 (0.68–1.65)
Hispanic	569	7.2	**0.48 (0.30–0.77)**	11.6	**0.60 (0.40–0.99)**	20.9	1.23 (0.85–1.79)	22.5	1.23 (0.87–1.76)
Asian	63	7.9	0.52 (0.20–1.36)	11.1	0.57 (0.25–1.31)	17.5	1.15 (0.57–3.02)	15.9	0.92 (0.45–1.90)

[a]Percentage of infants of specified maternal age, sex, or ethnicity with the named heart defect.
[b]Logistic regression model included maternal age and ethnicity, infant sex, and site.
Complete AVSD, complete atrioventricular septal defect; any AVSD, complete, partial, and unspecified AVSD; ASDII, secundum atrial septal defect (excludes PFO or PFO versus ASD); VSD, ventricular septal defect (excludes AVSD-type VSD and VSD that is part of TOF).

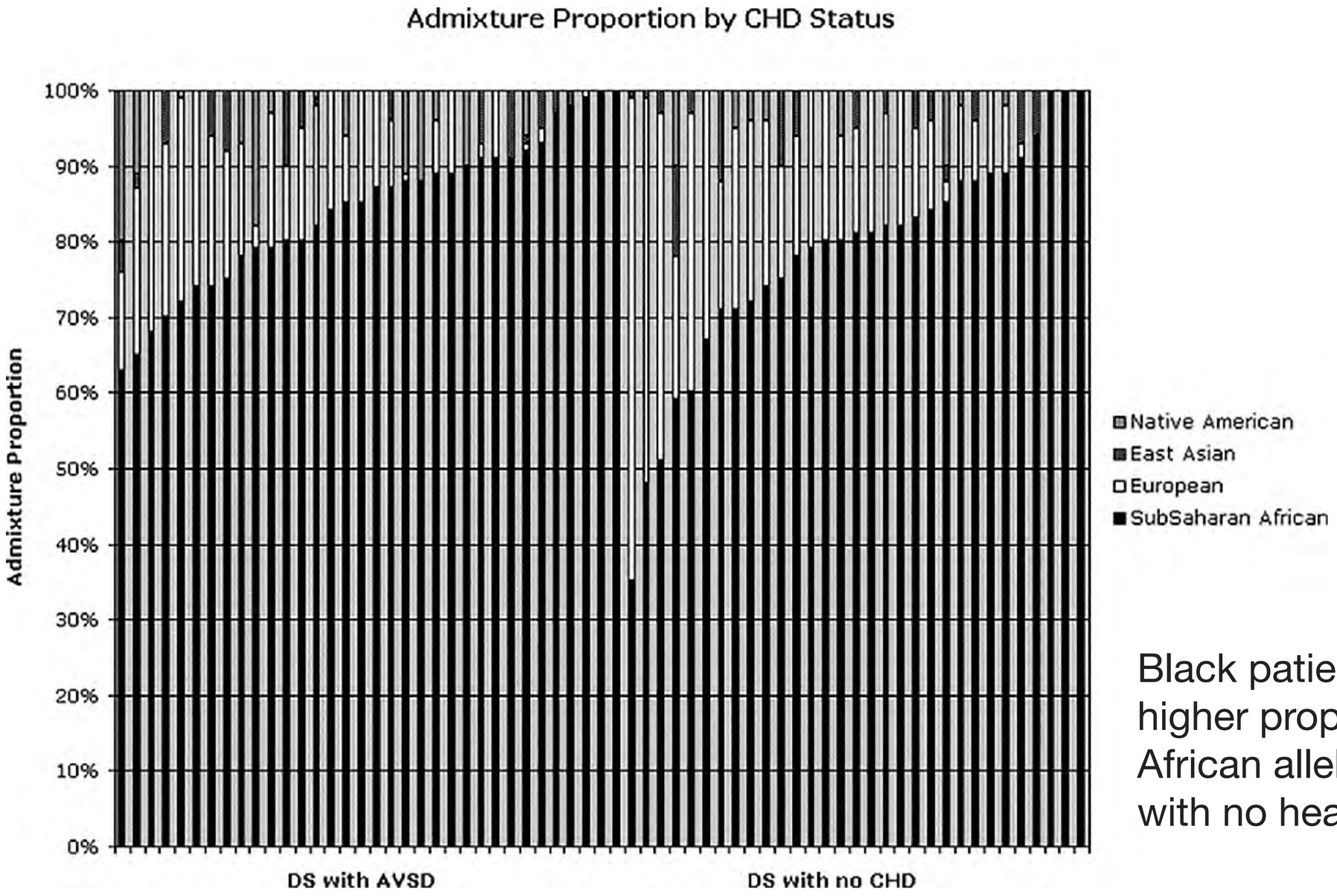
Freeman, S., Bean, L., Allen, E. et al. Ethnicity, sex, and the incidence of congenital heart defects: a report from the National Down Syndrome Project. Genet Med 10, 173–180 (2008).

Number (%) of infants with AVSD by birth country of mother for whites, blacks, and Hispanics

Mother			Complete AVSD		
Ethnicity	Birth country	*N* (%)[a]	*N*	%	*P*
White	US	485	72	14.9[b]	NS
	Other	27 (5.3)	3	11.1	
Black	US	91	18	19.8	0.036
	Other	25 (21.6)	10	40.0	
Hispanic	US	73	10	13.7	0.022
	Other	335 (82)	20	6.0	

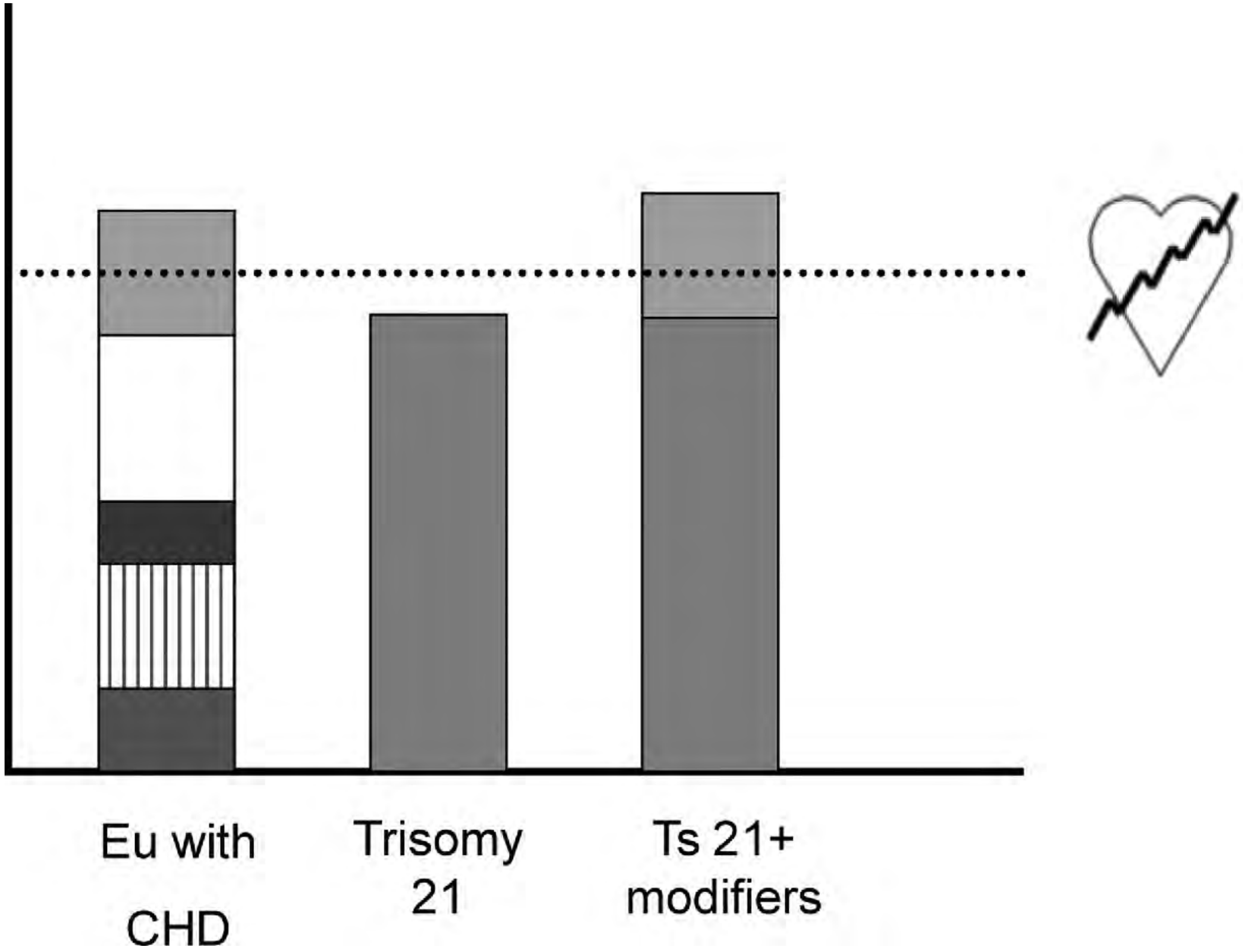
[a]Enrolled families only.
[b]Interpretation: of white infants whose mothers were born in the US, 14.9% had an AVSD.
US, United States.

Freeman, S., Bean, L., Allen, E. et al. Ethnicity, sex, and the incidence of congenital heart defects: a report from the National Down Syndrome Project. Genet Med 10, 173–180 (2008).



Black patients with AVSD had a higher proportion of ancestral African alleles compared with those with no heart defect

Freeman, S., Bean, L., Allen, E. et al. Ethnicity, sex, and the incidence of congenital heart defects: a report from the National Down Syndrome Project. Genet Med 10, 173–180 (2008).

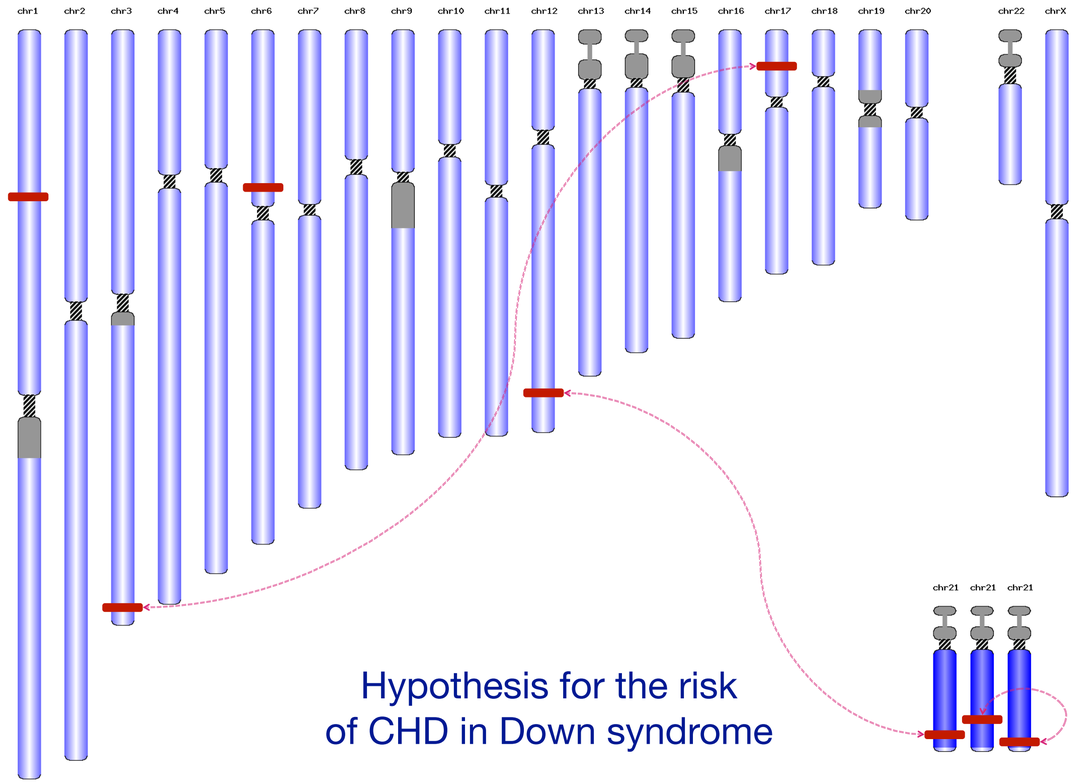


A threshold model for CHD. We hypothesize that the human population includes allelic variants in multiple genes that contribute to the risk of congenital heart disease, many of which have subtle or no effects by themselves. Additive effects of individual modifier genes can reach a threshold whereby heart septal development is disrupted (Euploidy with congenital heart disease [CHD]), but the likelihood of inheriting many predisposing modifiers is small. Trisomy 21 is a significant risk factor for CHD, but alone is not sufficient to produce heart defects; however, those people with an extra copy of Hsa21 may require fewer disomic or trisomic modifiers to reach the threshold (Ts21+modifier). The relative contribution of the modifier in the sensitized Down syndrome population is therefore more readily detectable. Li H et al Circulation: Cardiovascular Genetics. 2012;5:301–308

Various conditions associated with Down syndrome with its causative genes.

Asim, A., Kumar, A., Muthuswamy, S. et al. “Down syndrome: an insight of the disease”. J Biomed Sci 22, 41 (2015).

A multigenic model for the development of CHD in trisomy 21 with effects of several genetic variants



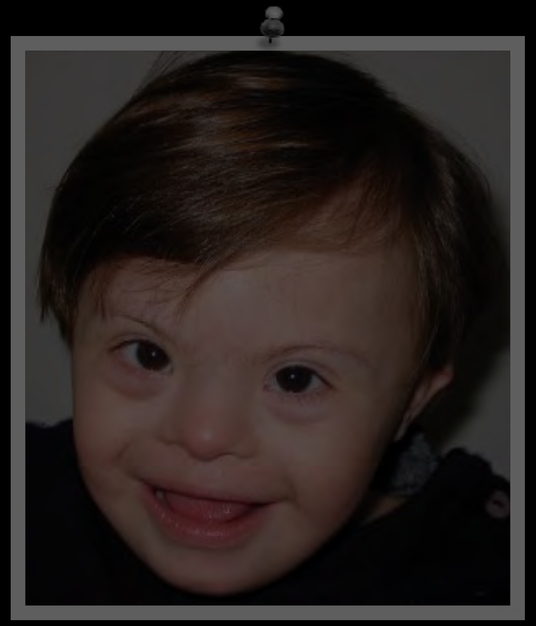
Genomic variability of chr21 (trisomic regions) may contribute to the CHD in Down syndrome.

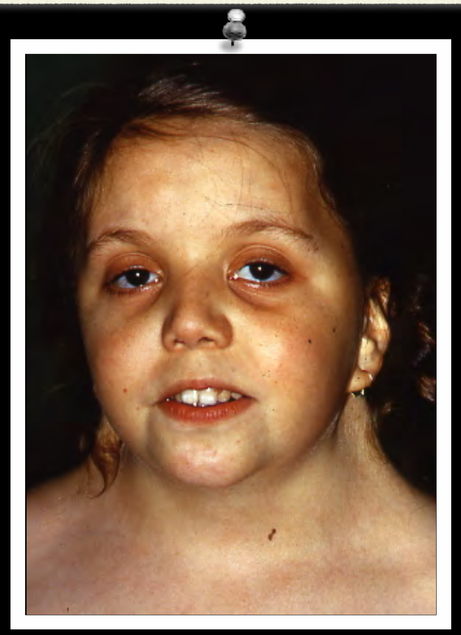
The CHD risk of Down syndrome is determined not only by trisomy 21 but also the genome-wide interaction of specific alleles.

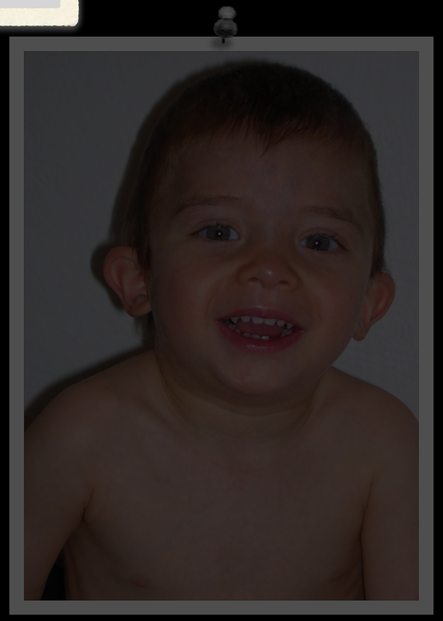
M3C

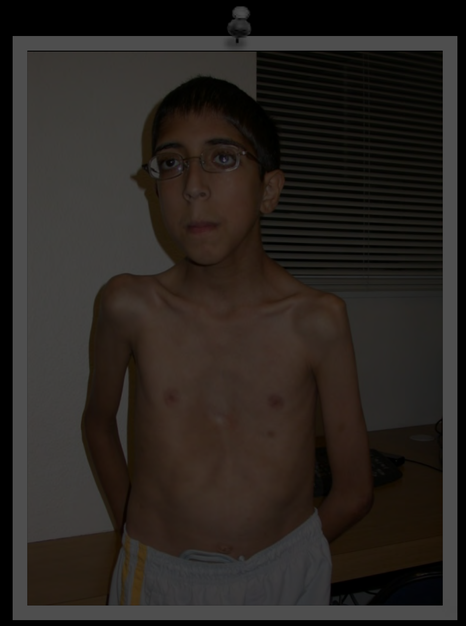
Sallani MR et al. Genome Res. 2013 Sep;23(9):1410-21

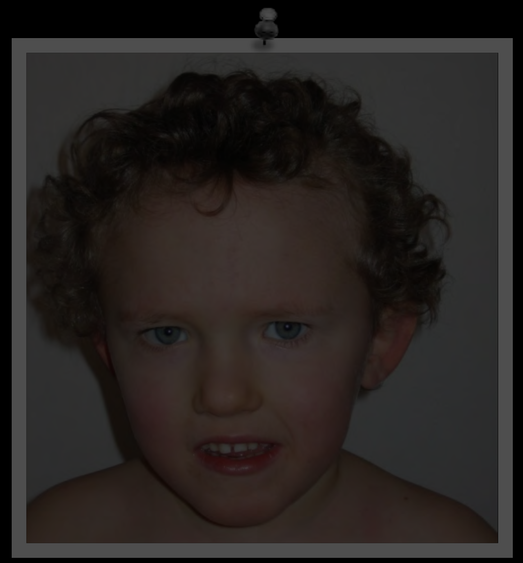
What everybody knows !

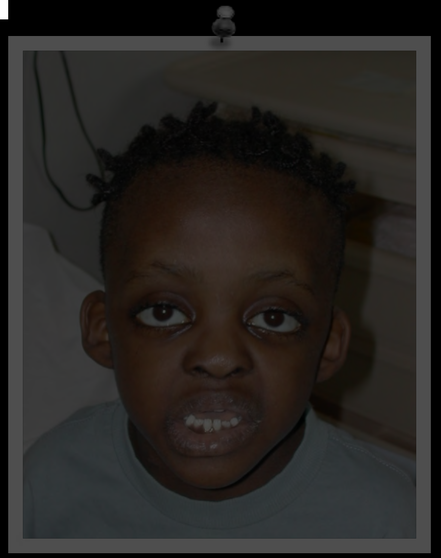


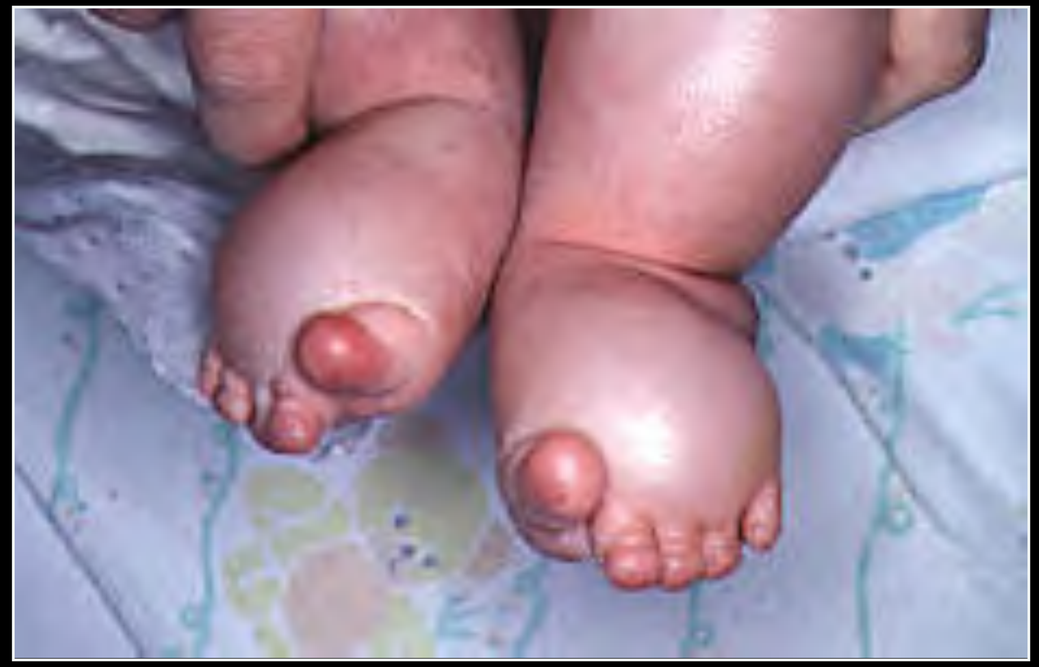


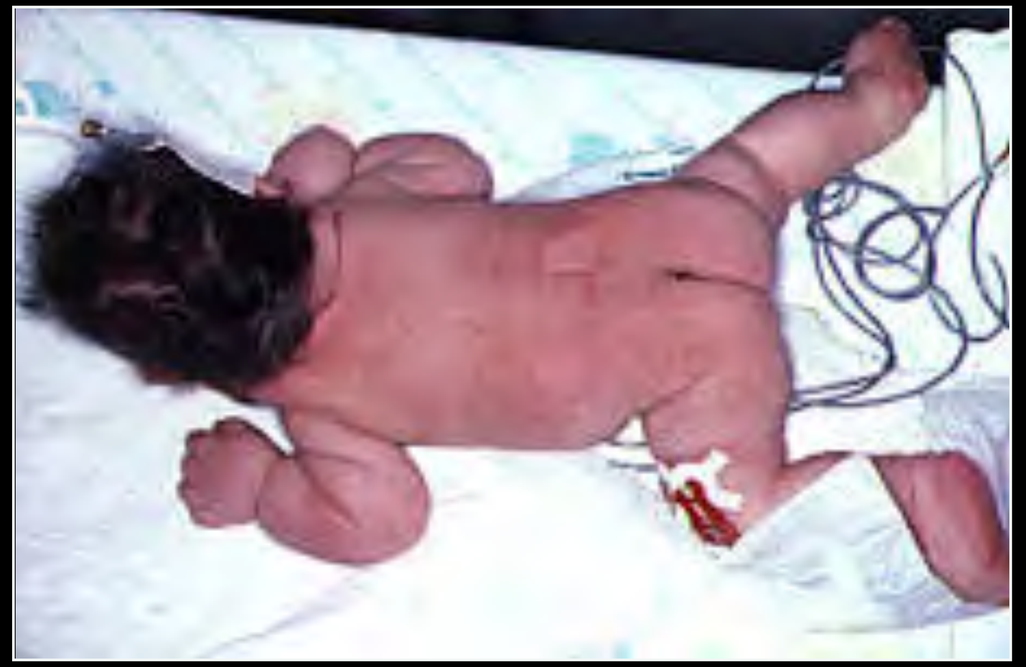






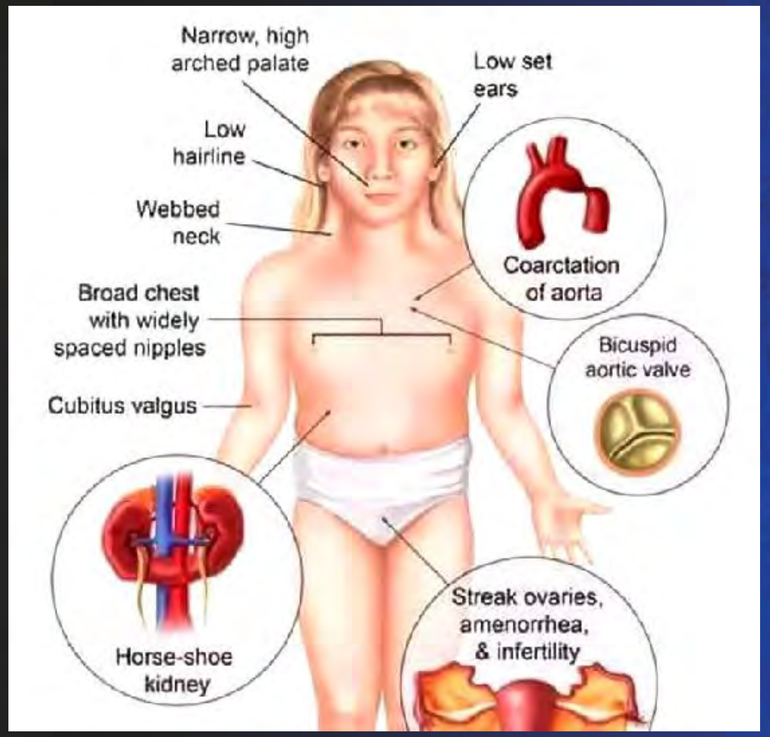


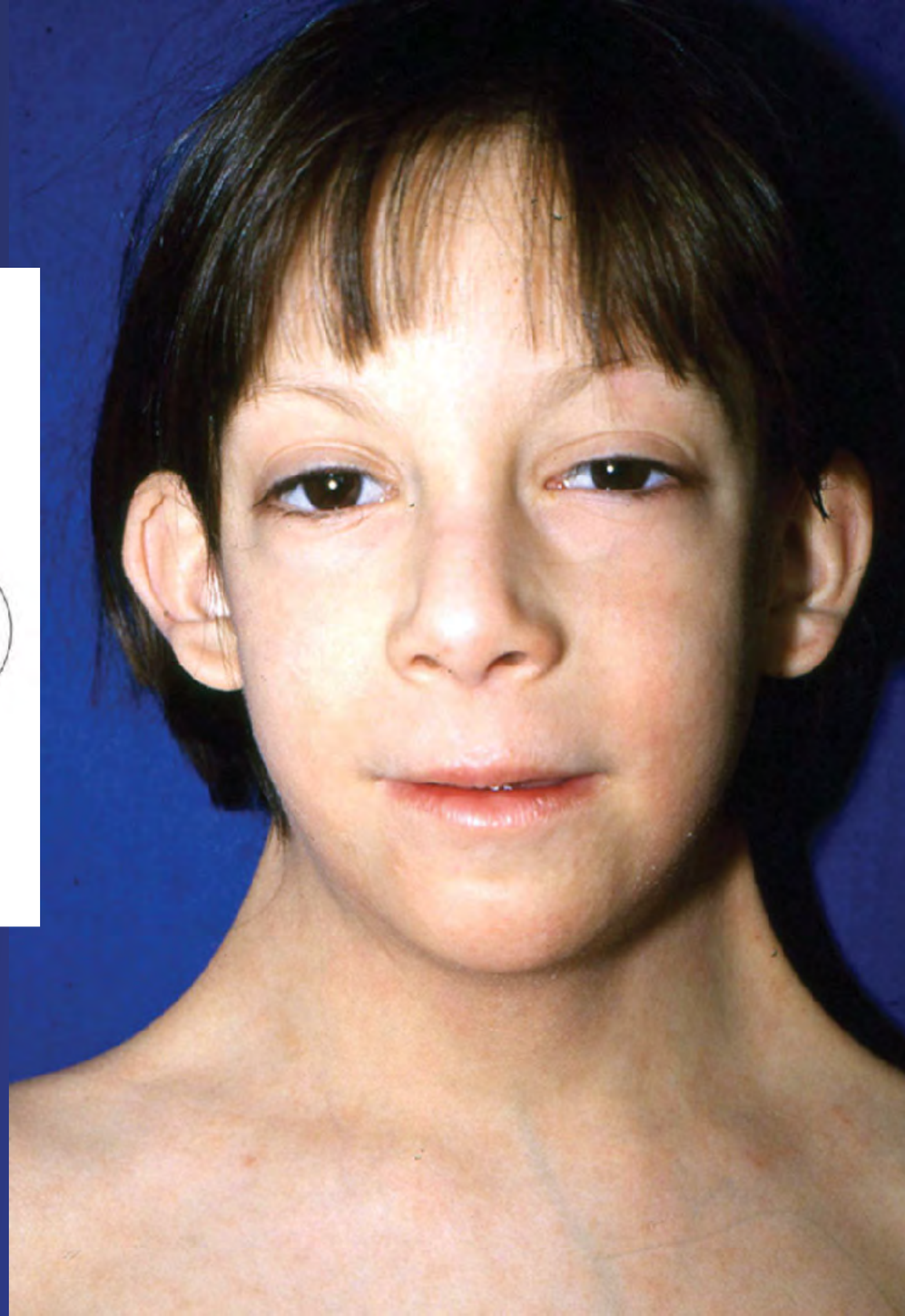


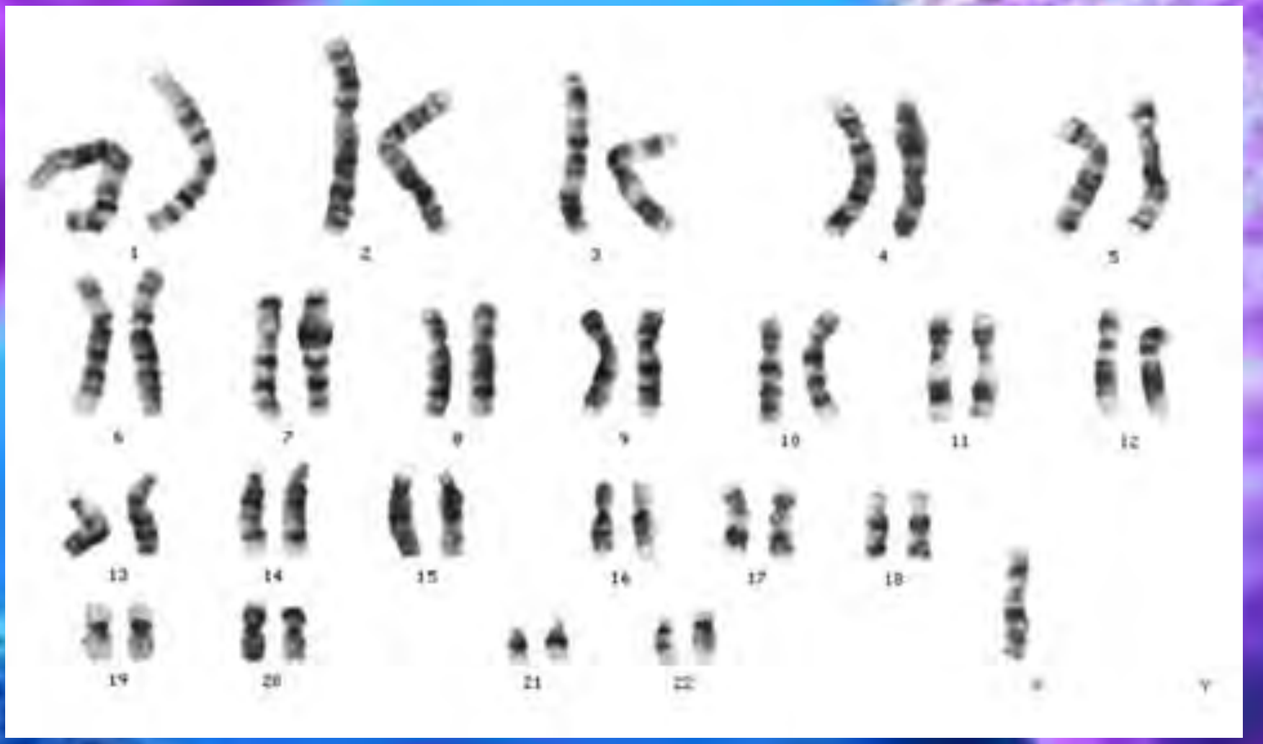


Bonnevie Ulrich syndrome

Turner syndrome



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X
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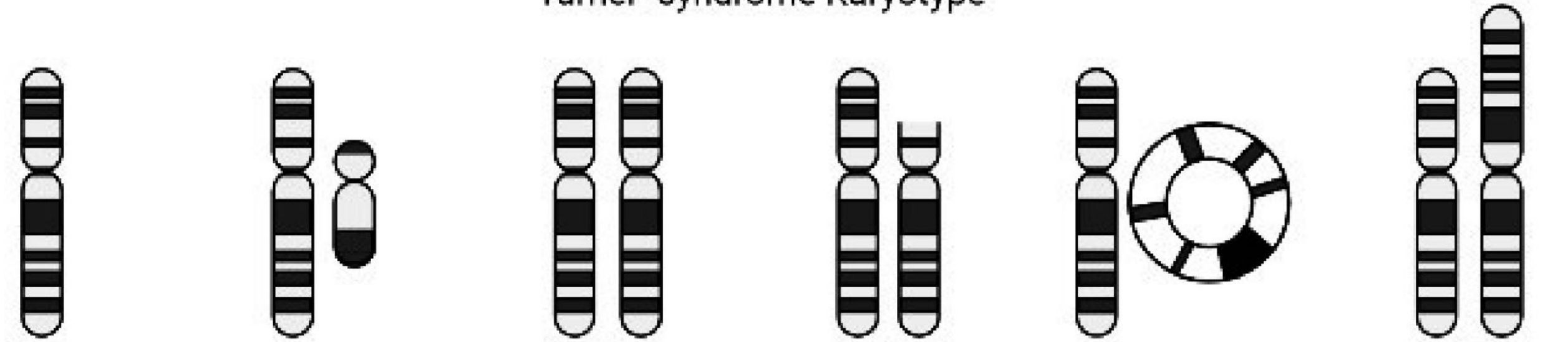
Turner syndrome Karyotype



45,X

46,XY

46,XX

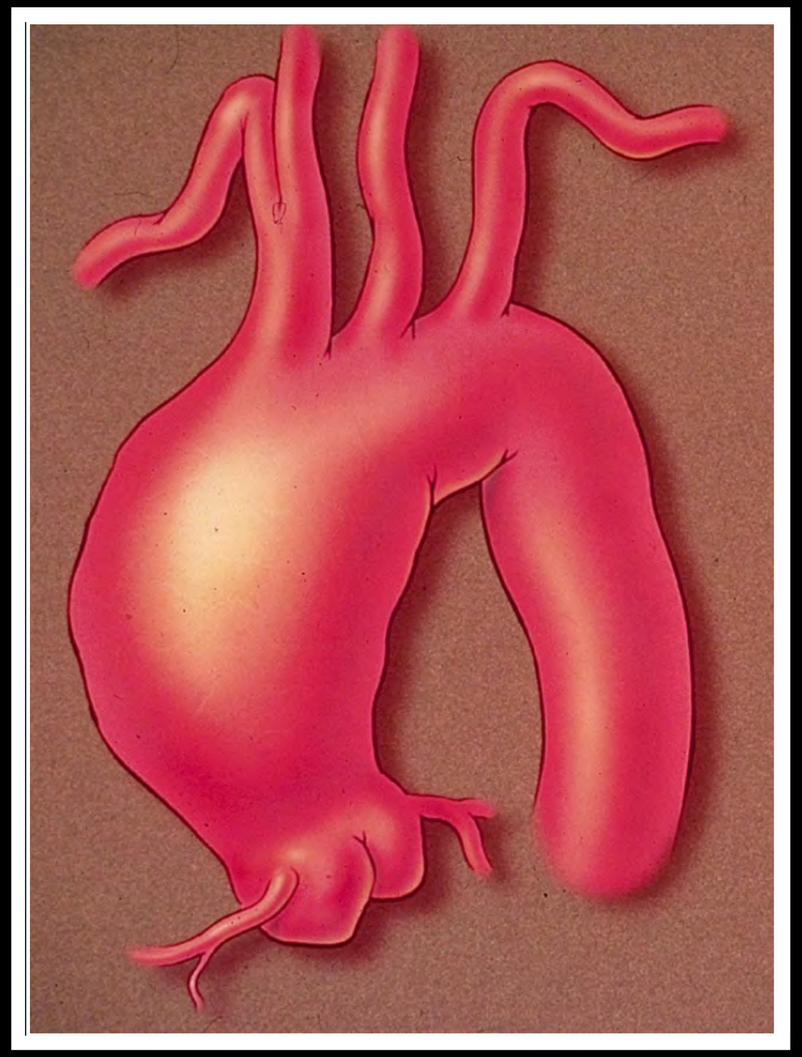
46,X,del(X)
(p11.4)

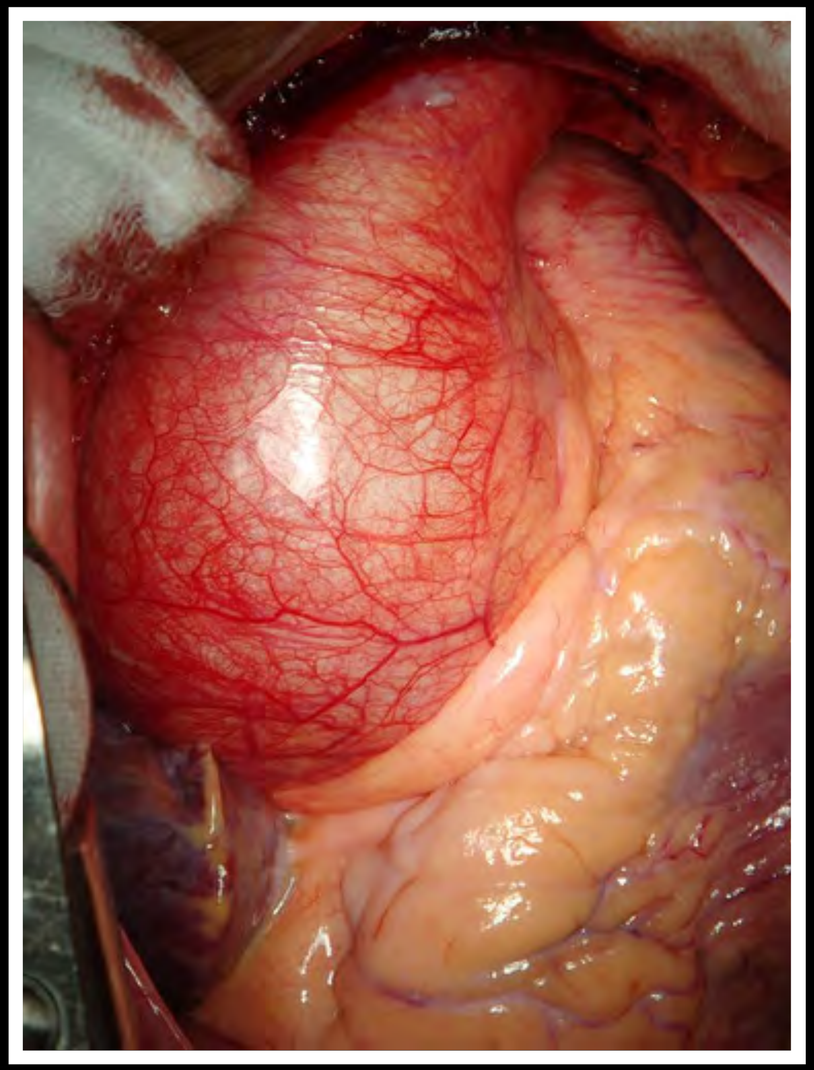
46,X,r(X)

46,X,i(Xq)

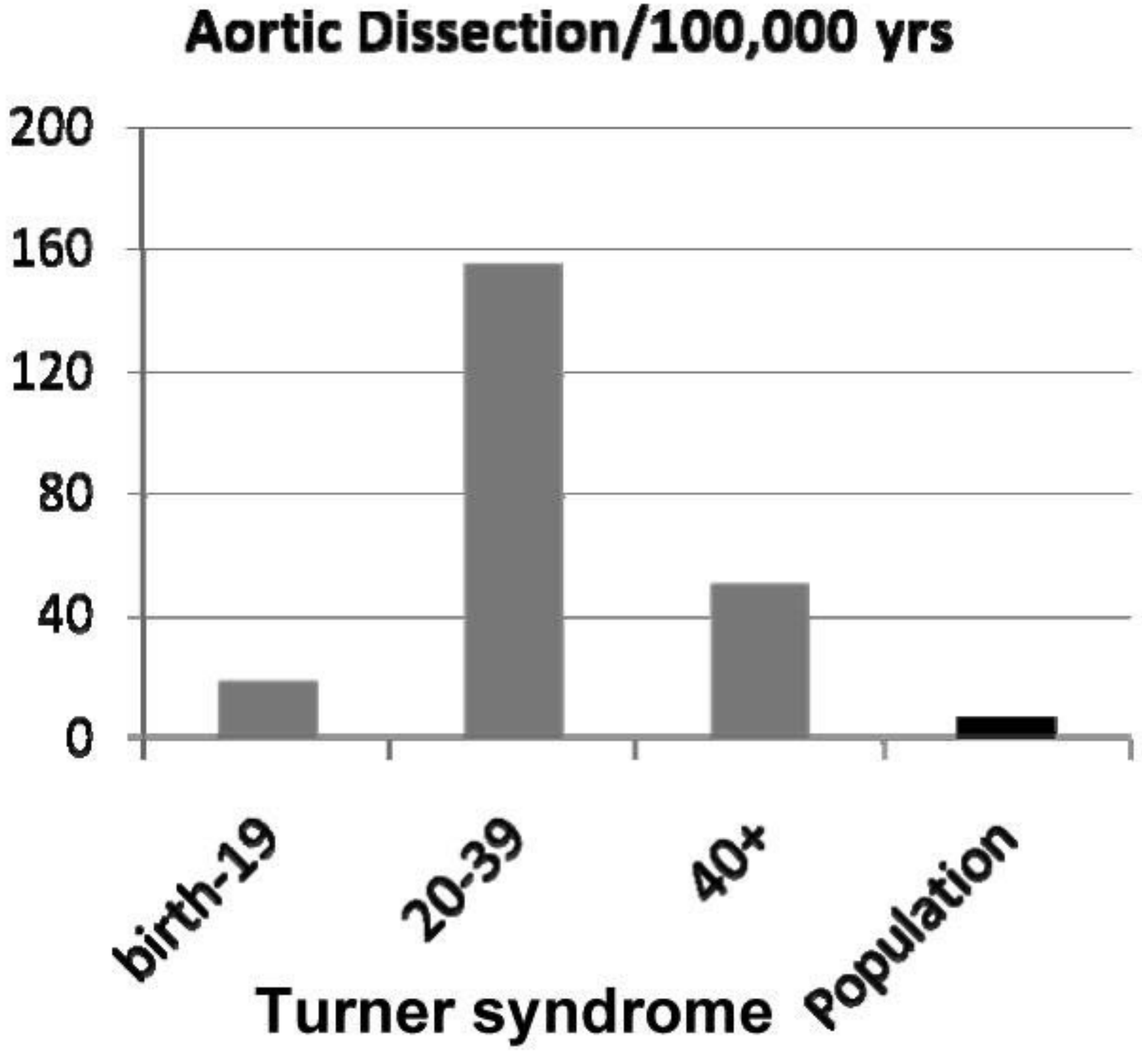
45,X/46,XY
mosaicism

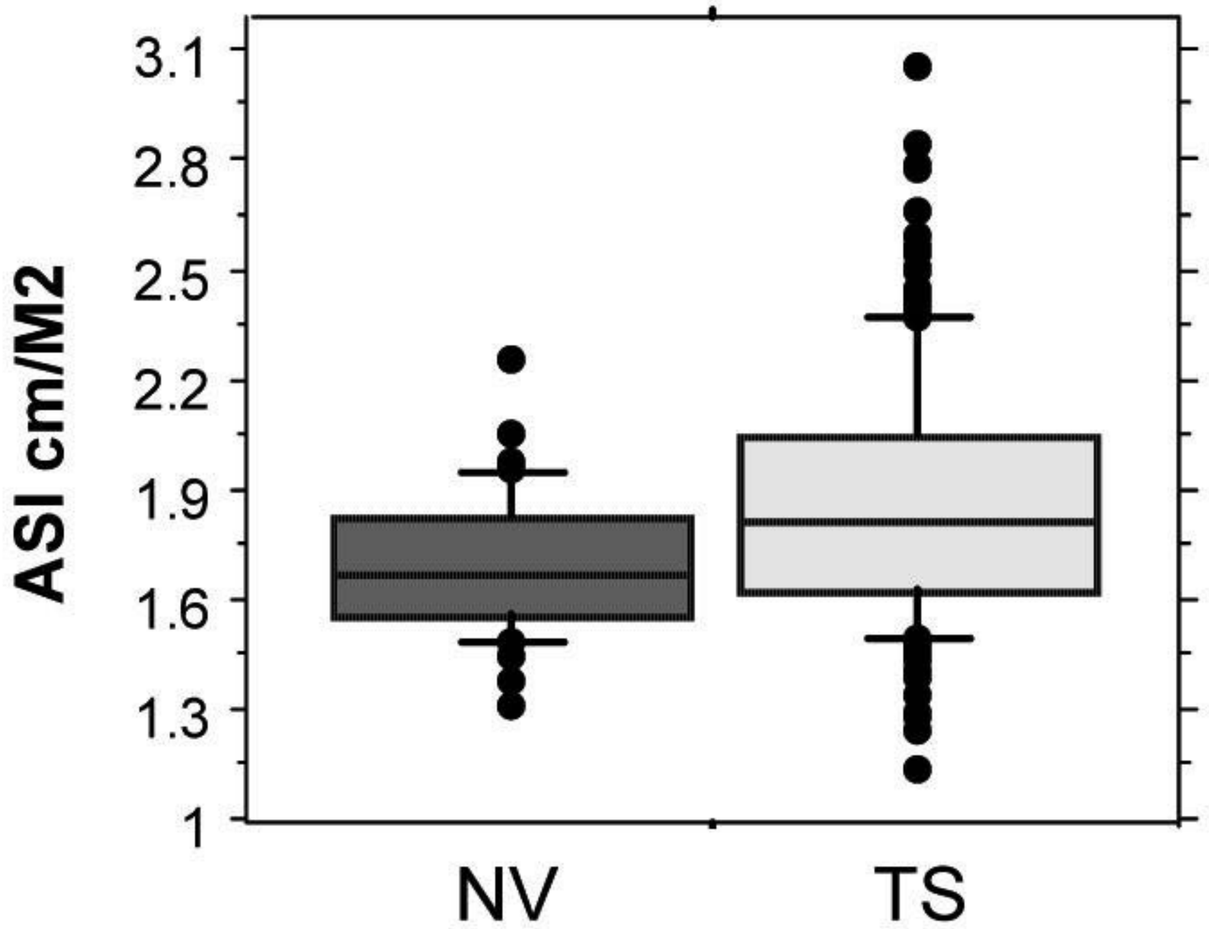
45,X/46,XX
mosaicism





Aortic dissection (both type A and type B) occurs in approximately 40 per 100 000 person-years compared with 6 per 100 000 person-years in the general population





2.5 cm^2/m^2

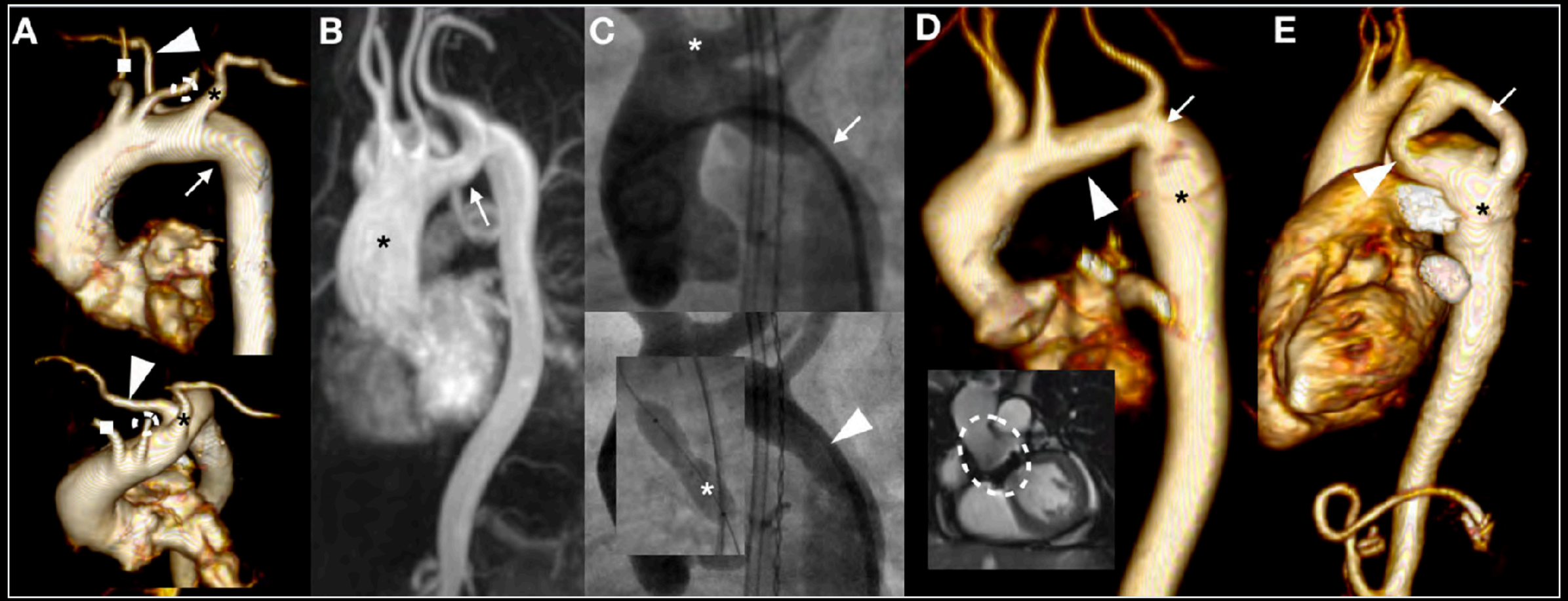
Bondy CA. Aortic dissection in Turner syndrome. Curr Opin Cardiol. 2008 Nov;23(6):519-26.

Recommendations	Class[a]	Level[b]
Turner syndrome		
Elective surgery for aneurysms of the aortic root and/or ascending aorta should be considered for women with Turner syndrome who are >16 years of age, have an ascending aortic size index >25 mm/m^2, and have associated risk factors for aortic dissection.[f]	IIa	C
Elective surgery for aneurysms of the aortic root and/or ascending aorta may be considered for women with Turner syndrome who are >16 years of age, have an ascending aortic size index >25 mm/m^2, and do not have associated risk factors for aortic dissection.[f]	IIb	C

Associated risk factors for dissection
Bicuspid aortic valve
Coarctation
Systemic hypertension
Elongated transverse arch

ESC Guidelines 2020

Phenotypes of the aortic arch in Turner syndrome



Elongated transverse aortic arch (kink at aortic isthmus (A, arrow)) with an incidental and benign aberrant right subclavian artery

Elongated transverse aortic arch (kink at aortic isthmus (A, arrow)) with an incidental and benign aberrant right subclavian artery

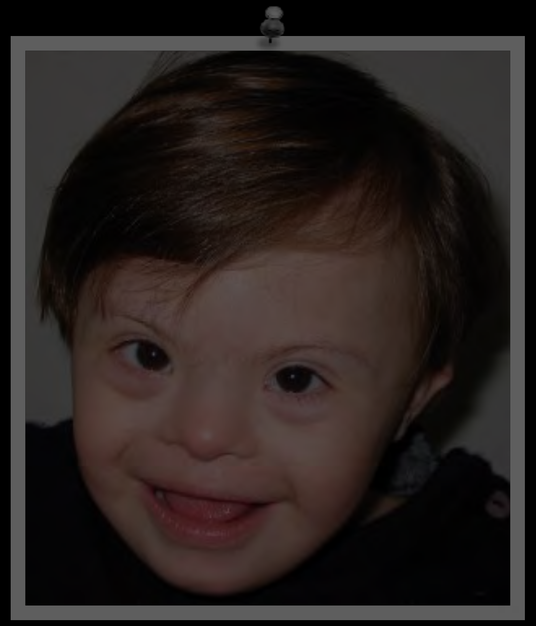
Coarctation of the aorta

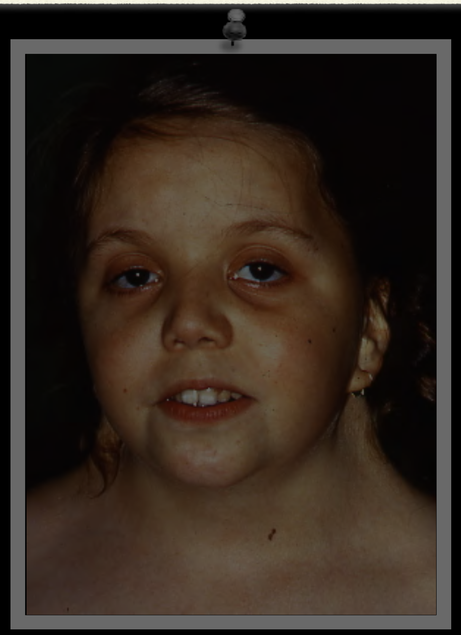
Mild transverse arch hypoplasia (arrowhead) and mild dilation of the descending aorta

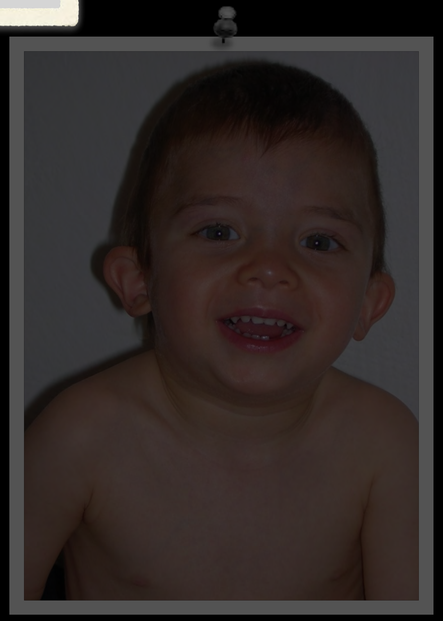
Extra-anatomical jump graft (arrow) inserted for bypass of severe native coarctation (arrowhead) with a dilated descending aorta (asterisk)

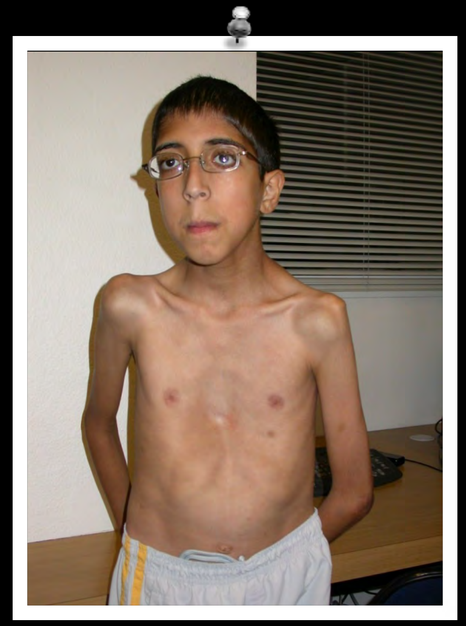
Mortensen KH, et al. Heart 2018;0:1–9.

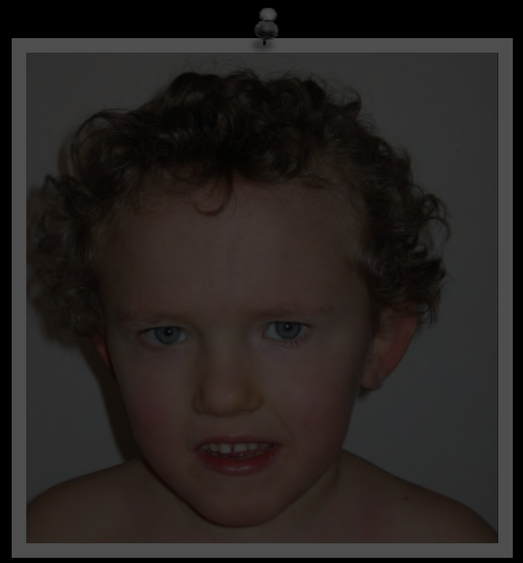
What everybody knows !

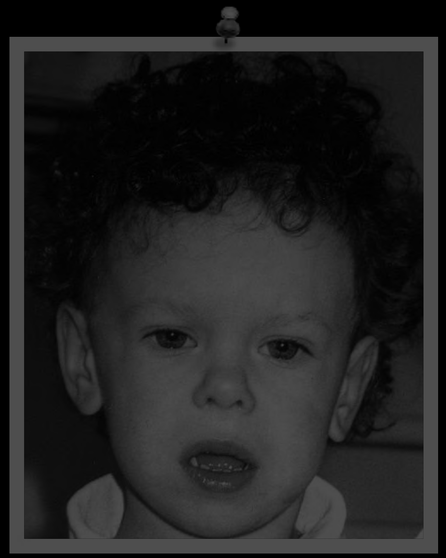


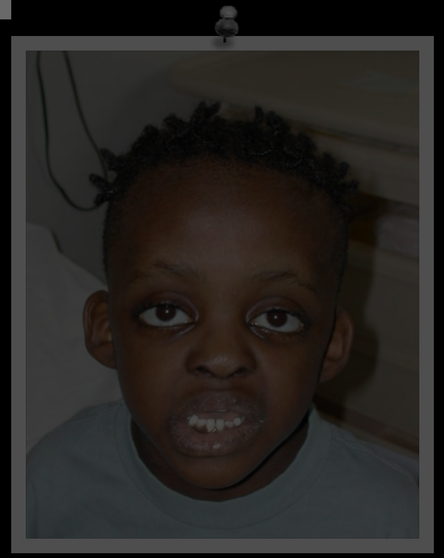




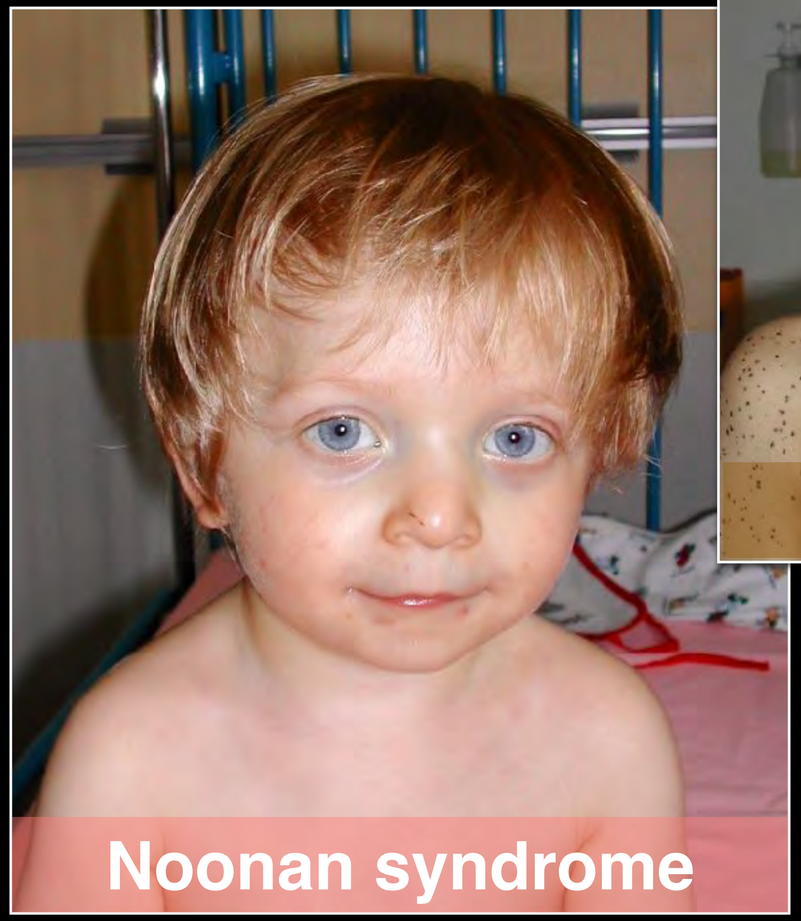


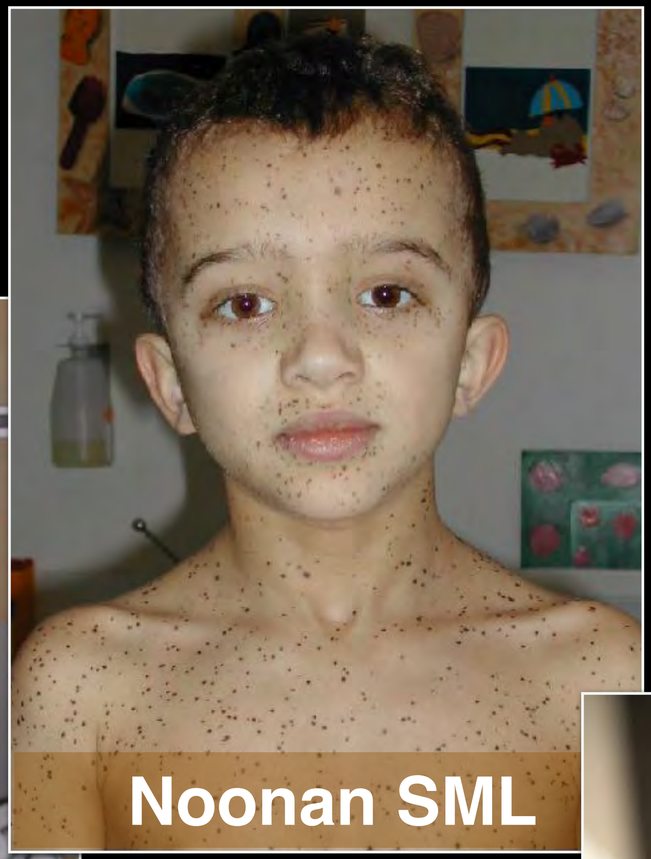




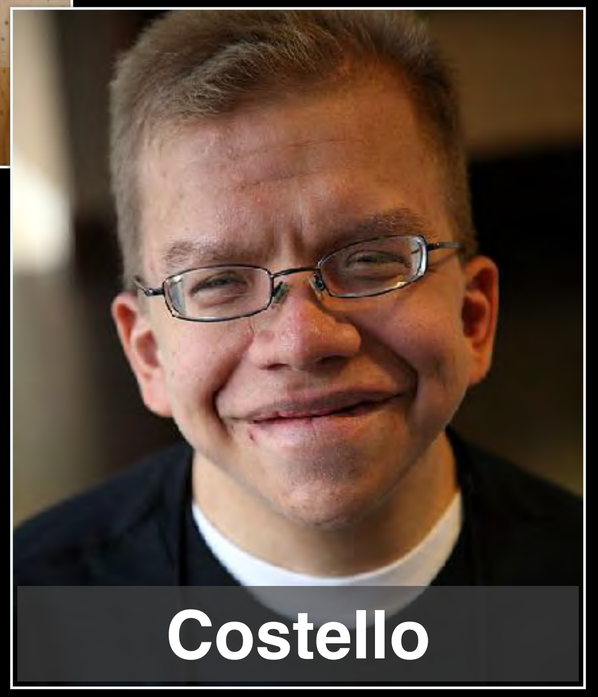


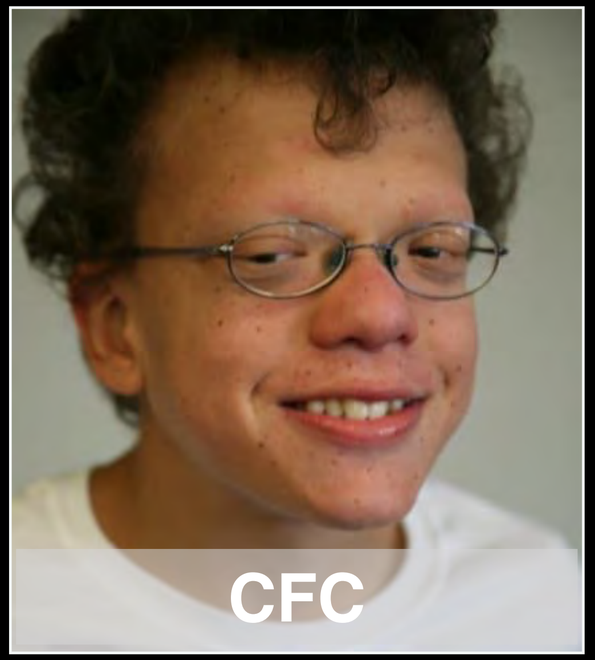

A
B

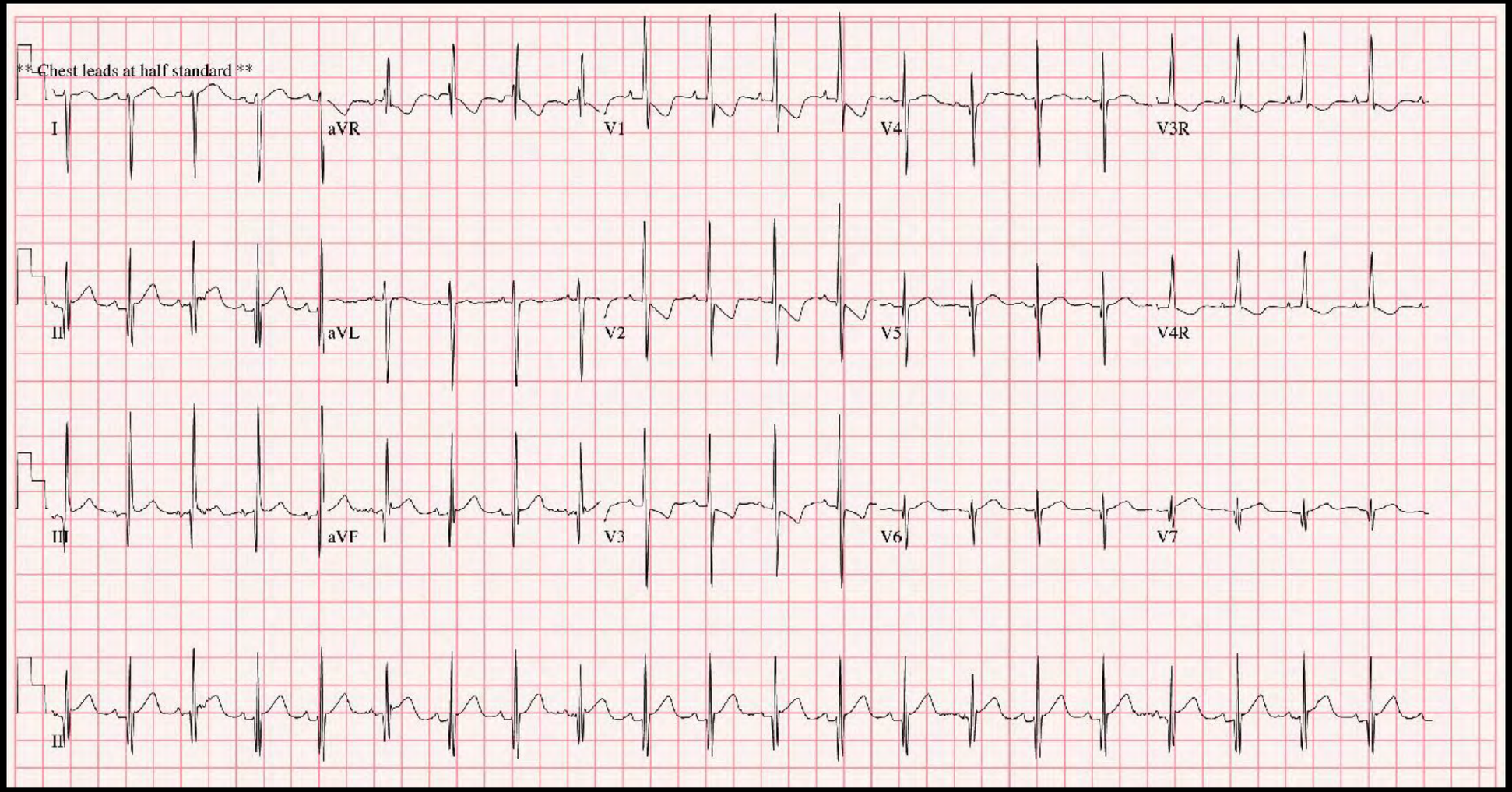

Noonan syndrome


Noonan SML

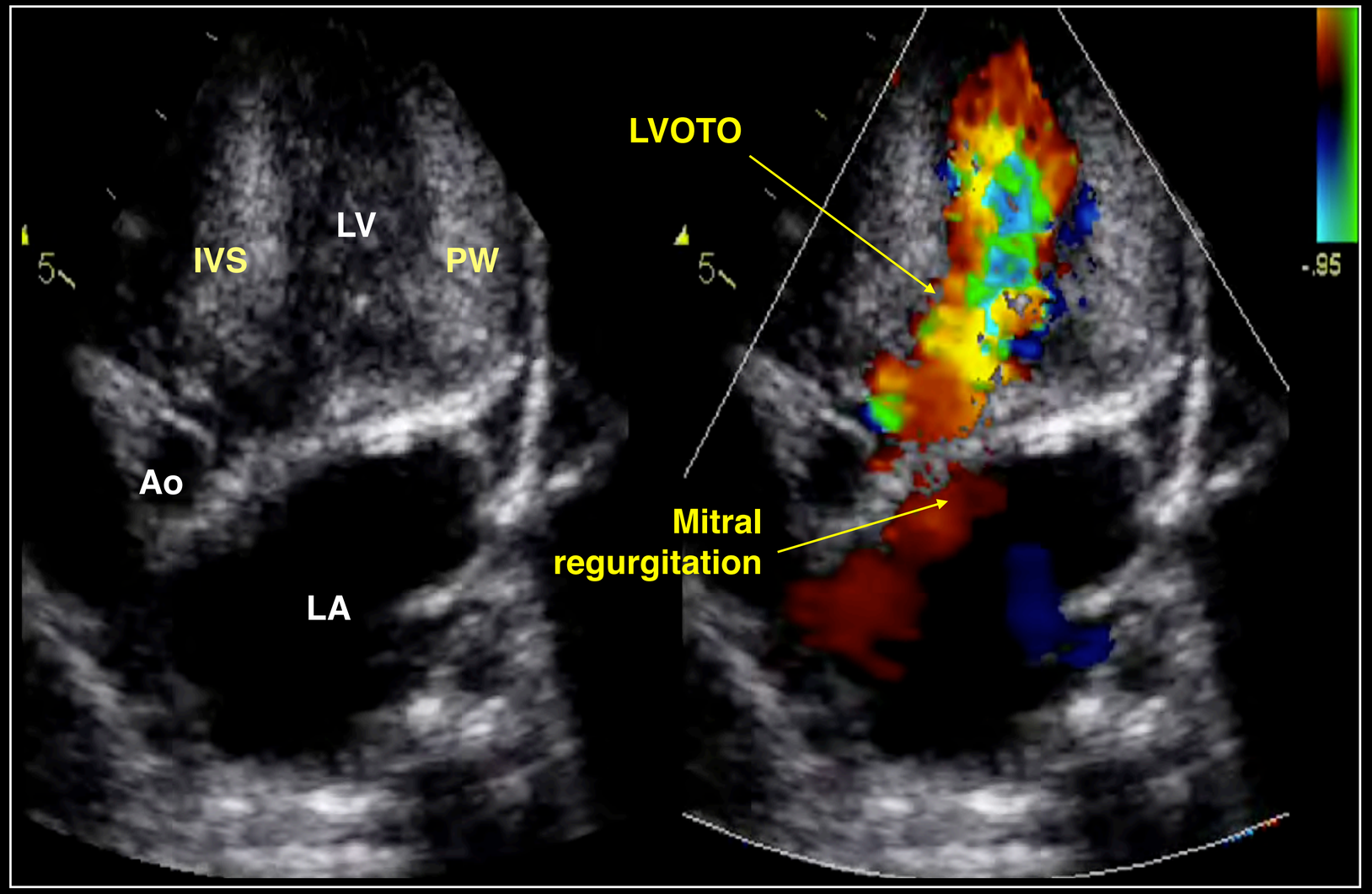

Legius syndrome


Costello


CFC

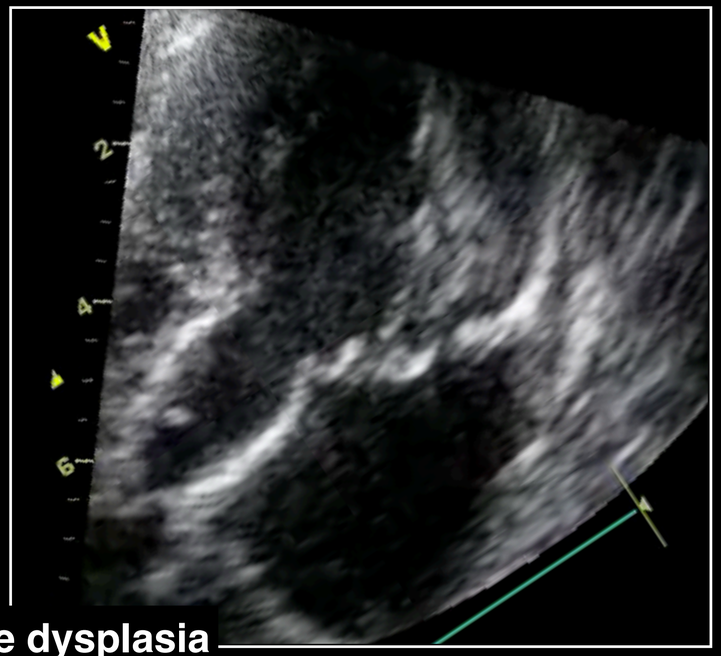


ECG Noonan syndrome

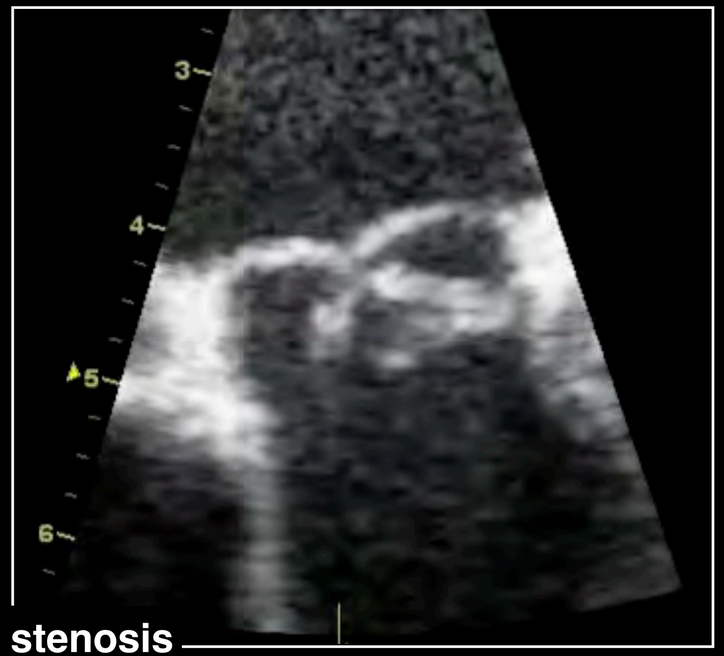


Hypertrophic obstructive cardiomyopathy in Noonan syndrome

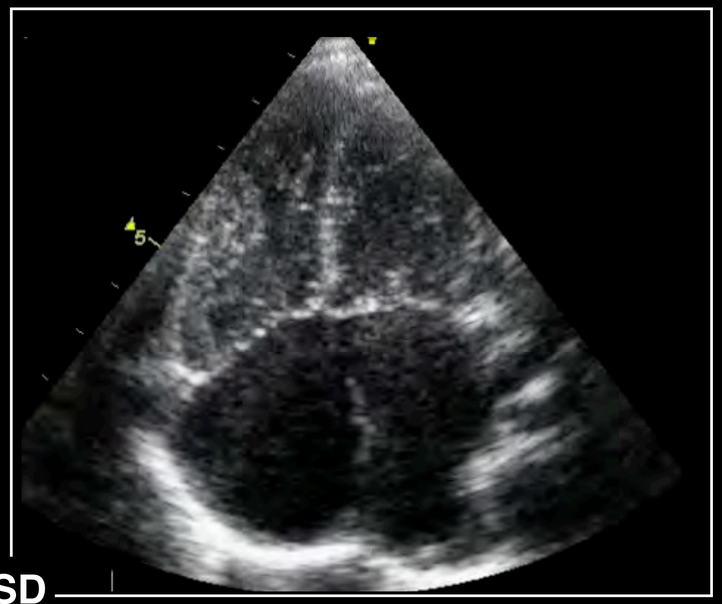
CHD in Noonan syndrome



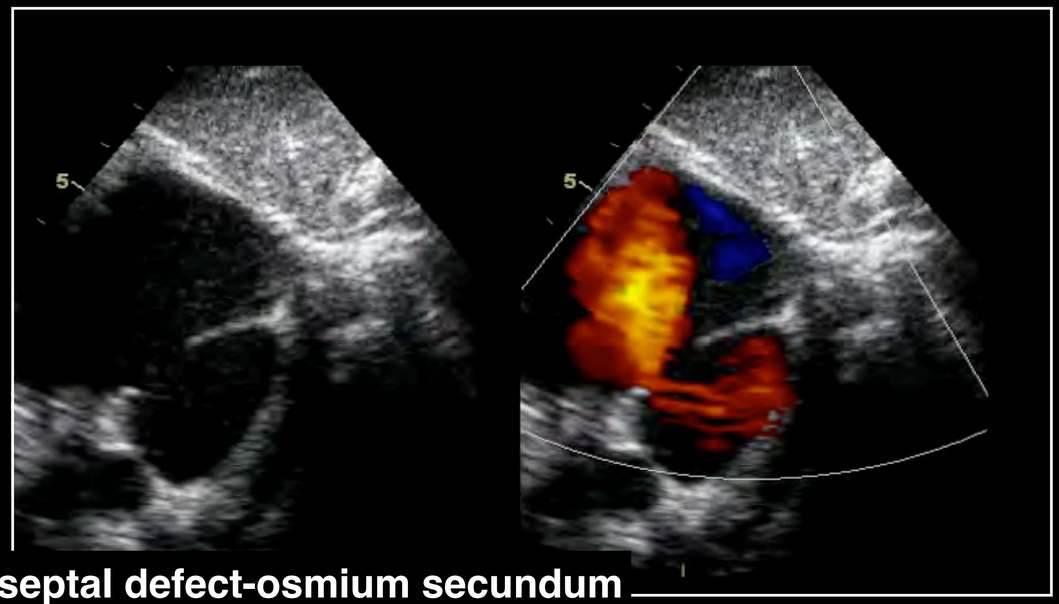
Mitral valve dysplasia



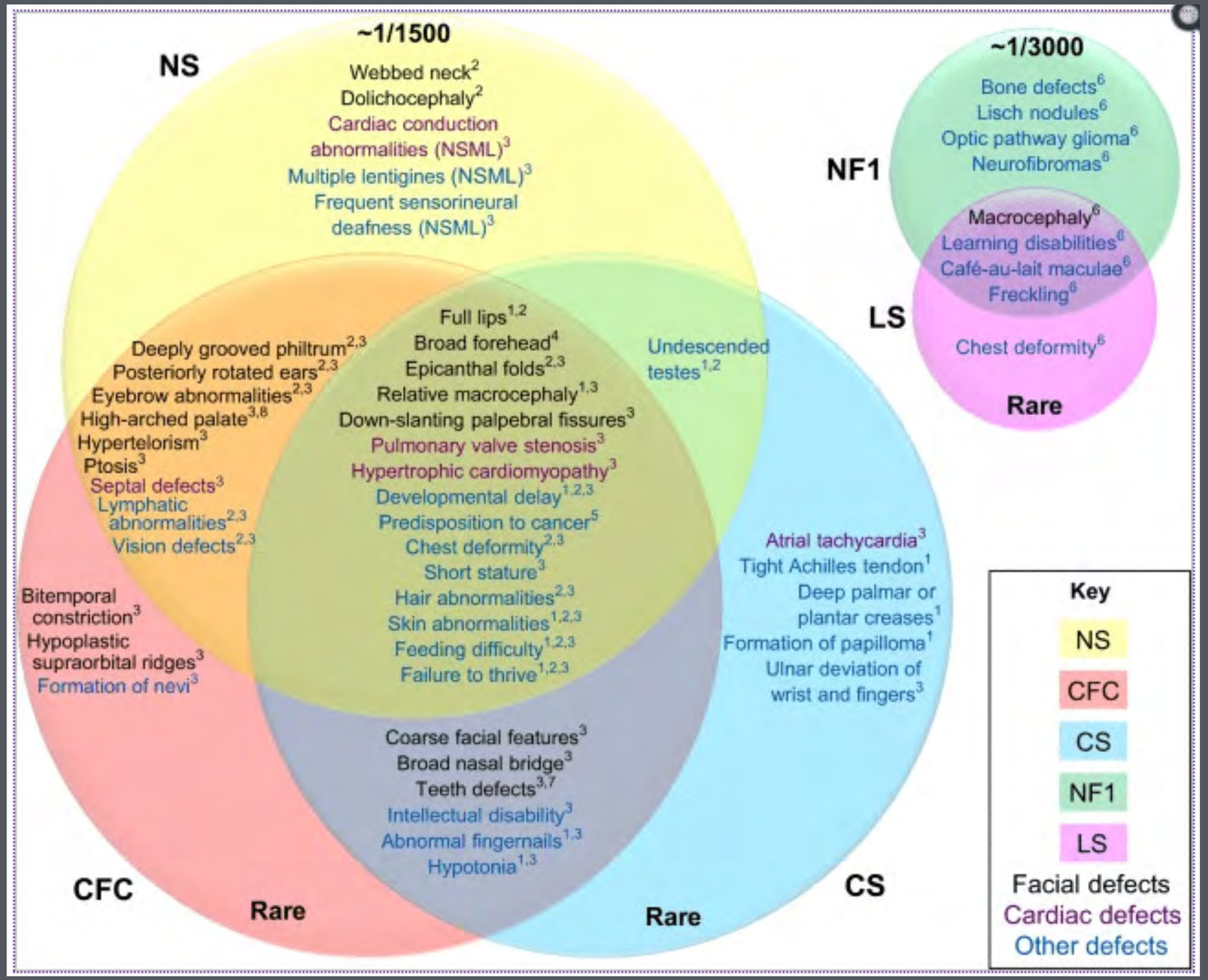
Pulmonary stenosis



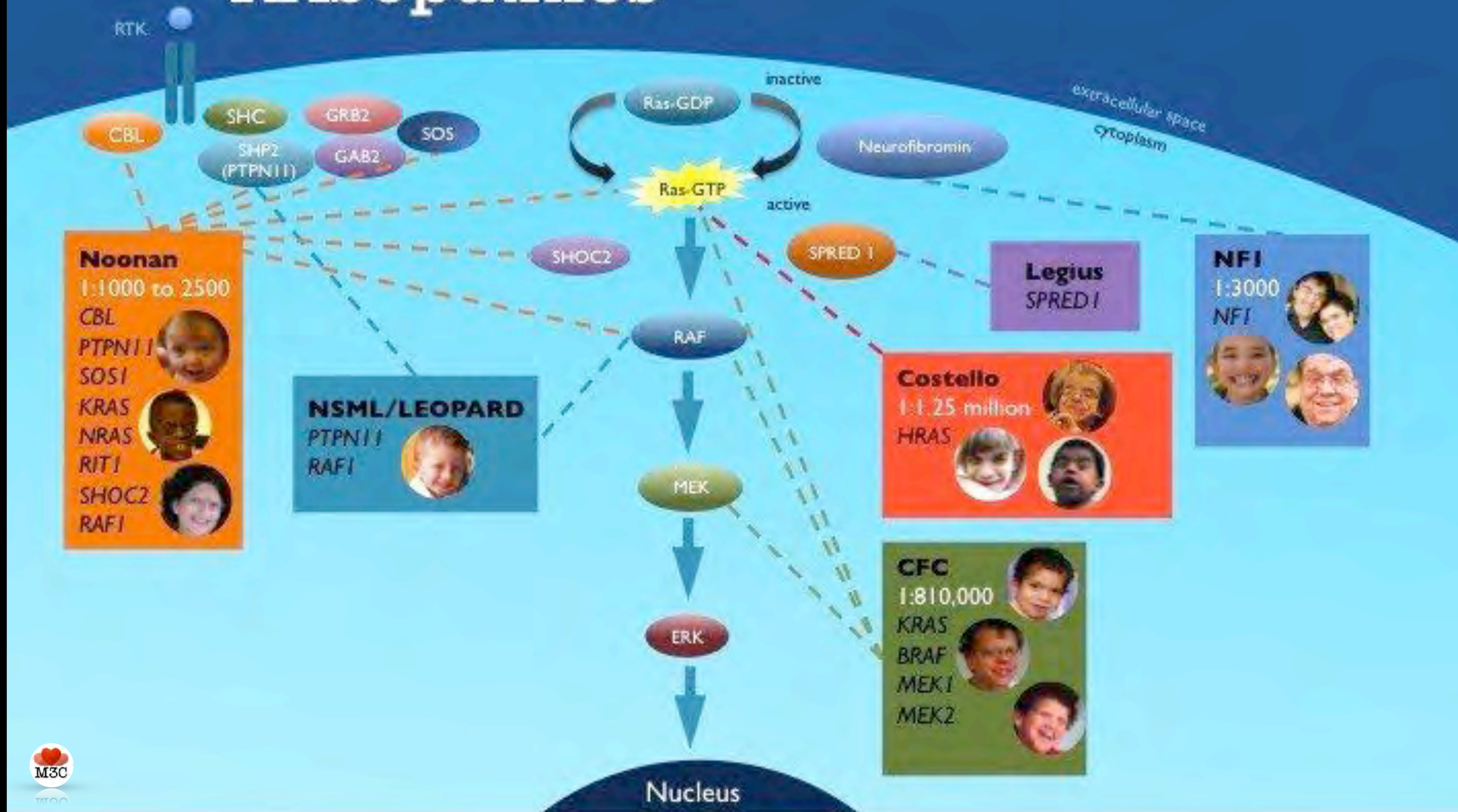
AVSD

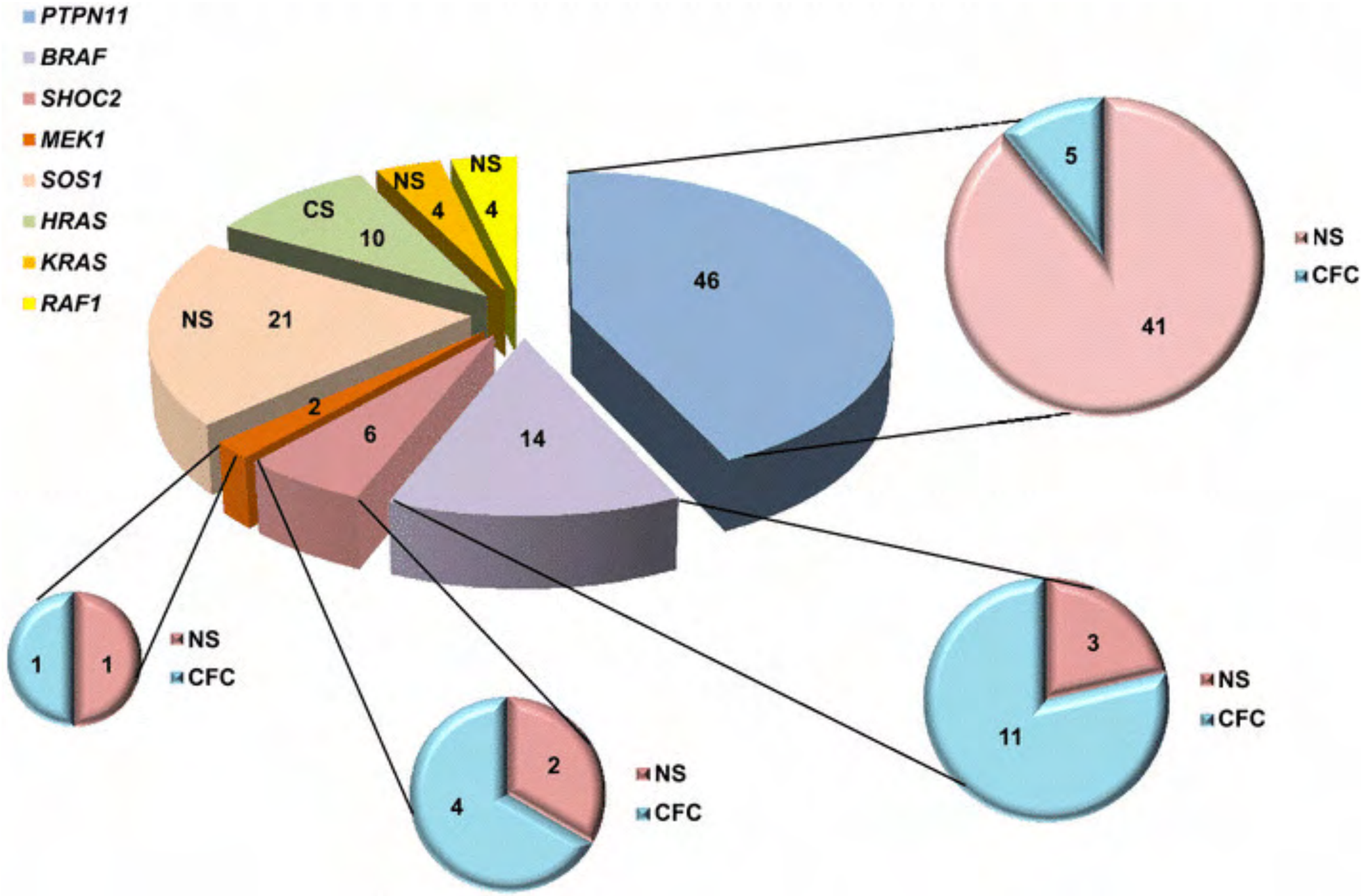


Atrial septal defect-osmium secundum

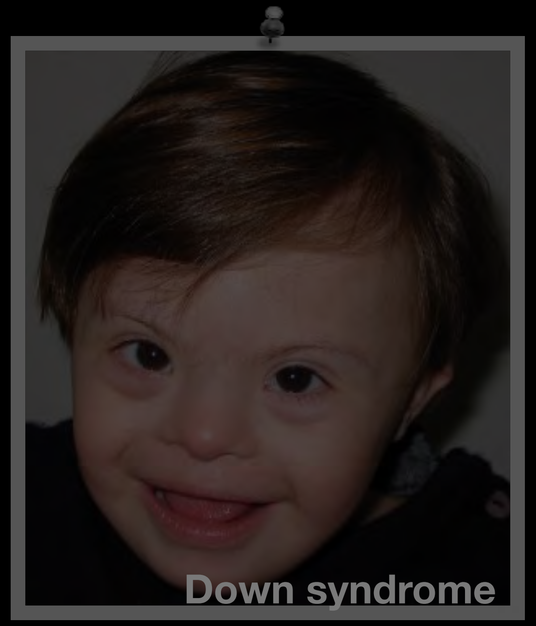

~1/1500
NS
Webbed neck[2]
Dolichocephaly[2]
Cardiac conduction abnormalities (NSML)[3]
Multiple lentigines (NSML)[3]
Frequent sensorineural deafness (NSML)[3]
~1/3000
NF1
Bone defects[6]
Lisch nodules[6]
Optic pathway glioma[6]
Neurofibromas[6]
Macrocephaly[6]
Learning disabilities[6]
Café-au-lait maculae[6]
Freckling[6]
LS
Chest deformity[6]
Rare
Deeply grooved philtrum[2,3]
Posteriorly rotated ears[2,3]
Eyebrow abnormalities[2,3]
High-arched palate[3,8]
Hypertelorism[3]
Ptosis[3]
Septal defects[3]
Lymphatic abnormalities[2,3]
Vision defects[2,3]
Full lips[1,2]
Broad forehead[4]
Epicanthal folds[2,3]
Relative macrocephaly[1,3]
Down-slanting palpebral fissures[3]
Pulmonary valve stenosis[3]
Hypertrophic cardiomyopathy[3]
Developmental delay[1,2,3]
Predisposition to cancer[5]
Chest deformity[2,3]
Short stature[3]
Hair abnormalities[2,3]
Skin abnormalities[1,2,3]
Feeding difficulty[1,2,3]
Failure to thrive[1,2,3]
Undescended testes[1,2]
Bitemporal constriction[3]
Hypoplastic supraorbital ridges[3]
Formation of nevi[3]
Atrial tachycardia[3]
Tight Achilles tendon[1]
Deep palmar or plantar creases[1]
Formation of papilloma[1]
Ulnar deviation of wrist and fingers[3]
Coarse facial features[3]
Broad nasal bridge[3]
Teeth defects[3,7]
Intellectual disability[3]
Abnormal fingernails[1,3]
Hypotonia[1,3]
CFC
Rare
Rare
CS
Key
NS
CFC
CS
NF1
LS
Facial defects
Cardiac defects
Other defects

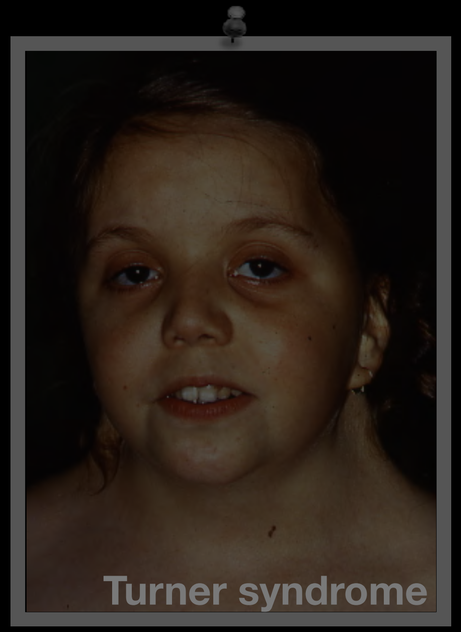
RASopathies

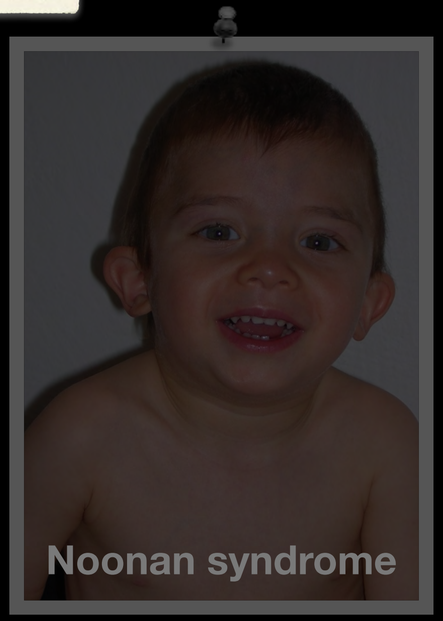


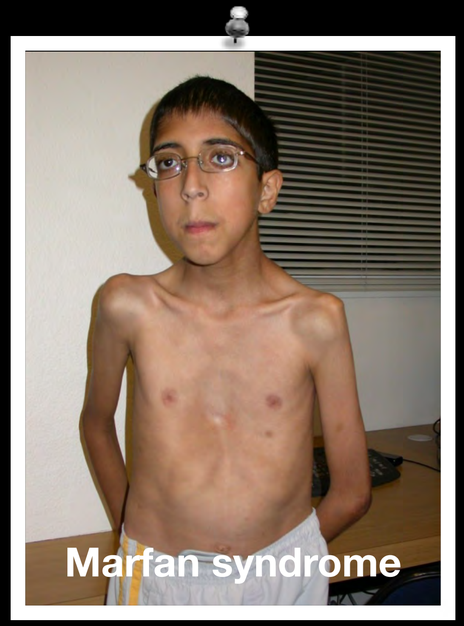

PTPN11
BRAF
SHOC2
MEK1
SOS1
HRAS
KRAS
RAF1
NS 21
CS 10
NS 4
NS 4
2
6
14
46
5
41
NS
CFC
1
1
NS
CFC
4
2
NS
CFC
11
3
NS
CFC

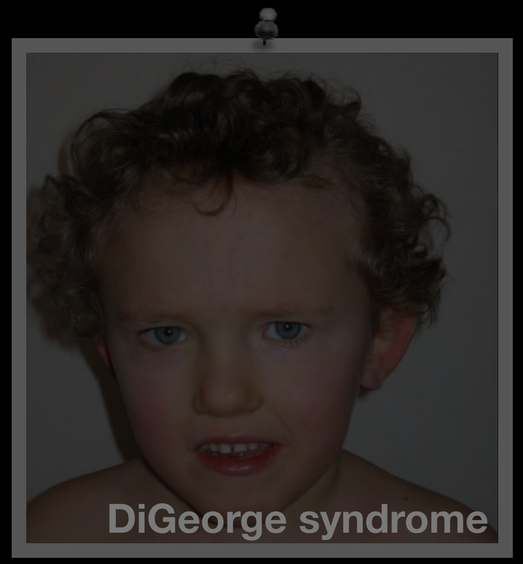
Old textbooks and clinical genetics

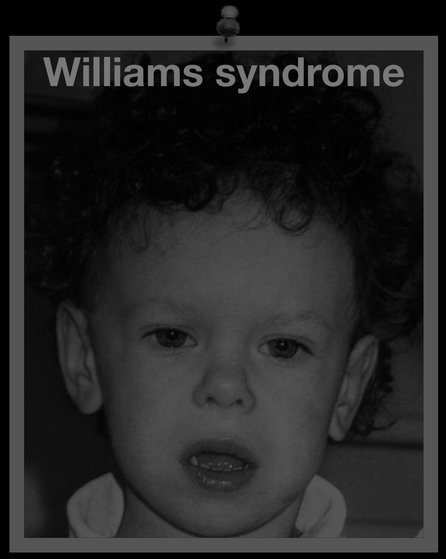


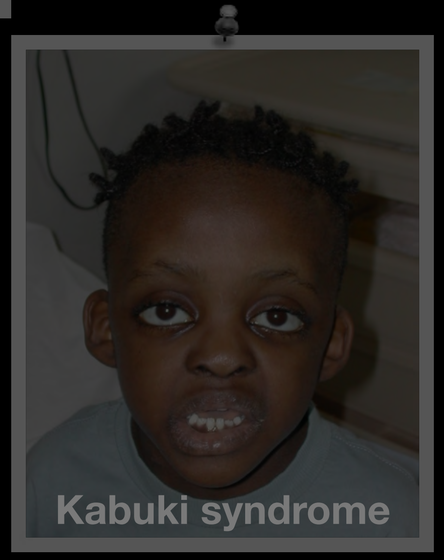


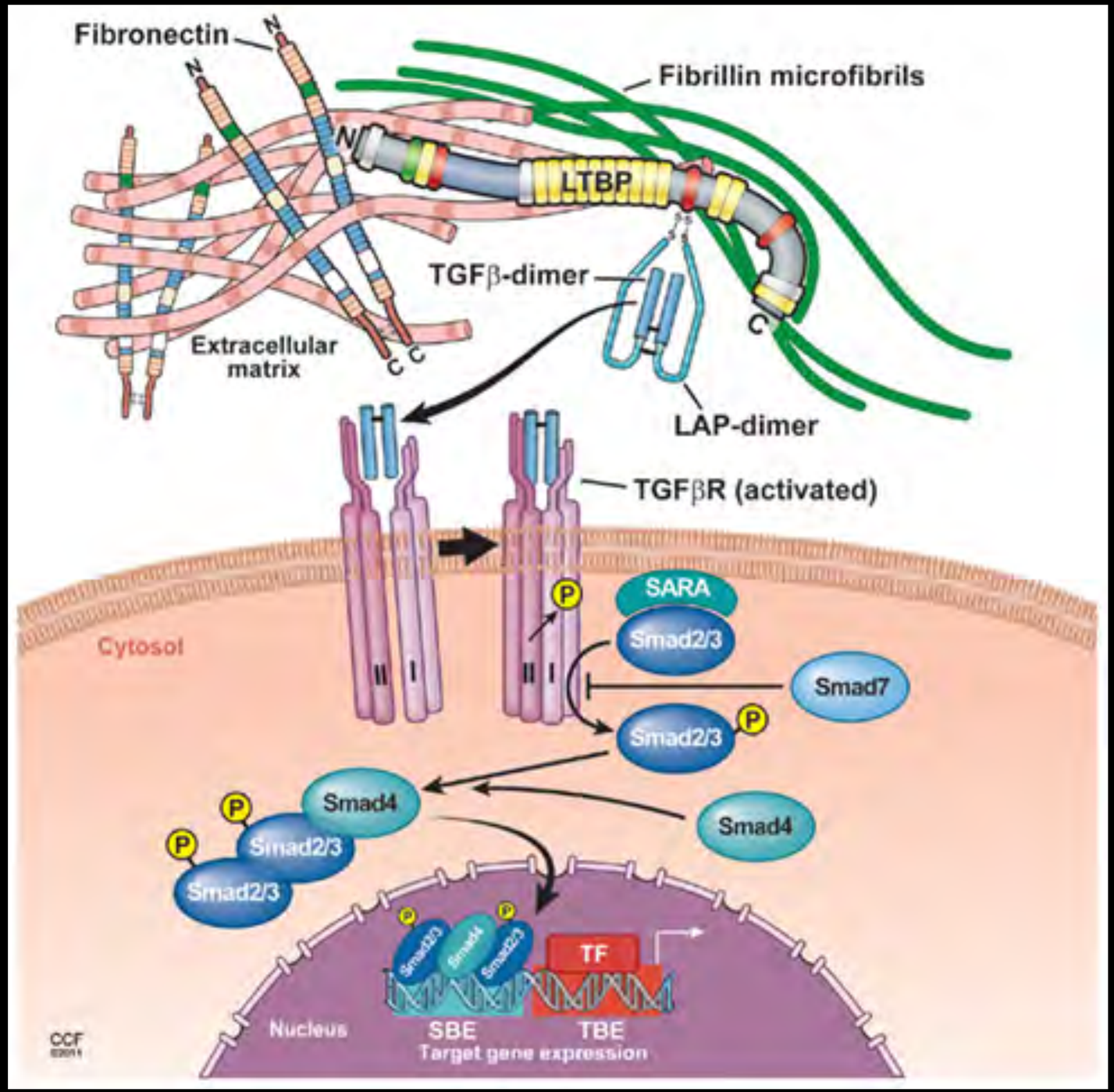


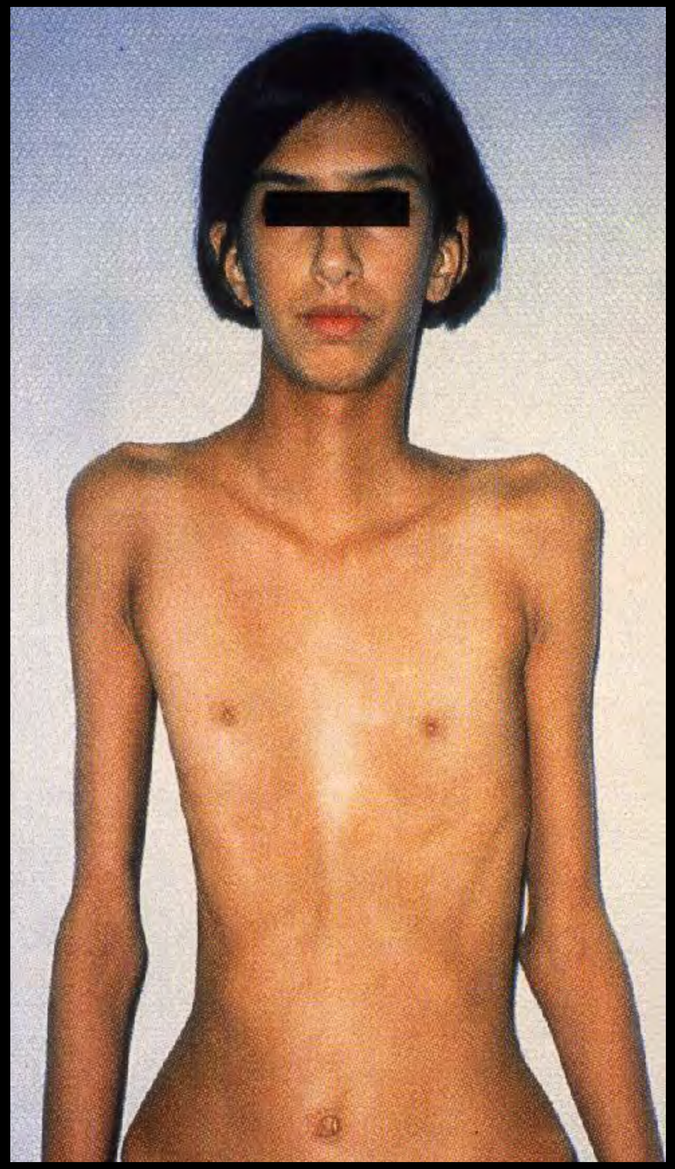


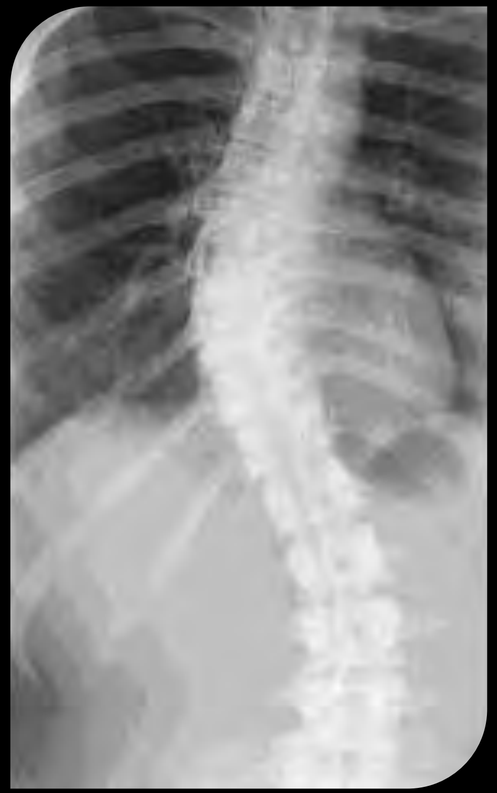


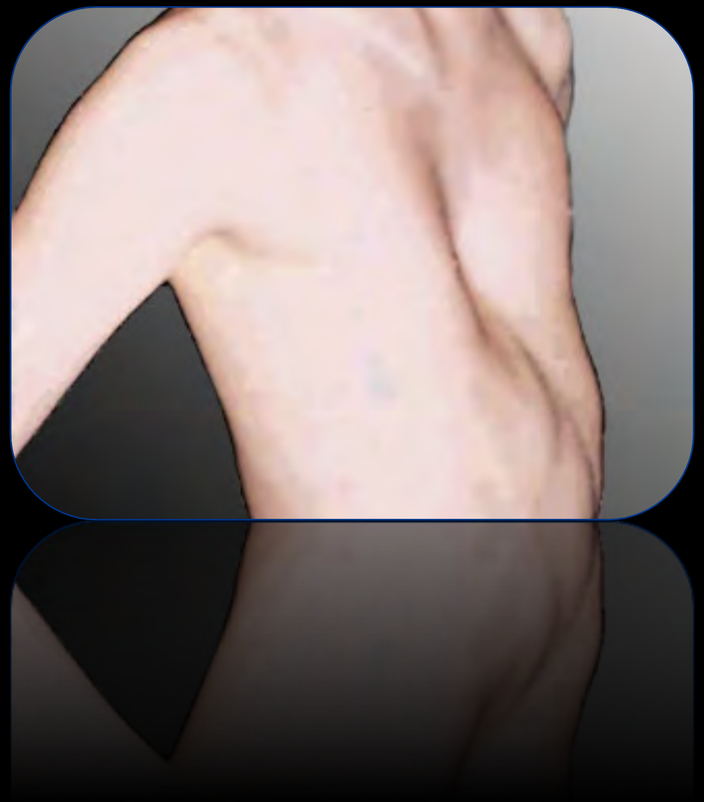





Fibronectin
Fibrillin microfibrils
N
LTBP
TGFβ-dimer
C
Extracellular matrix
C
C
LAP-dimer
TGFβR (activated)
P
SARA
Smad2/3
Cytosol
Smad7
Smad2/3
P
Smad4
P
Smad2/3
P
Smad2/3
Smad4
P
P
Smad2/3
Smad4
Smad2/3
TF
Nucleus
SBE
TBE
Target gene expression
CCF



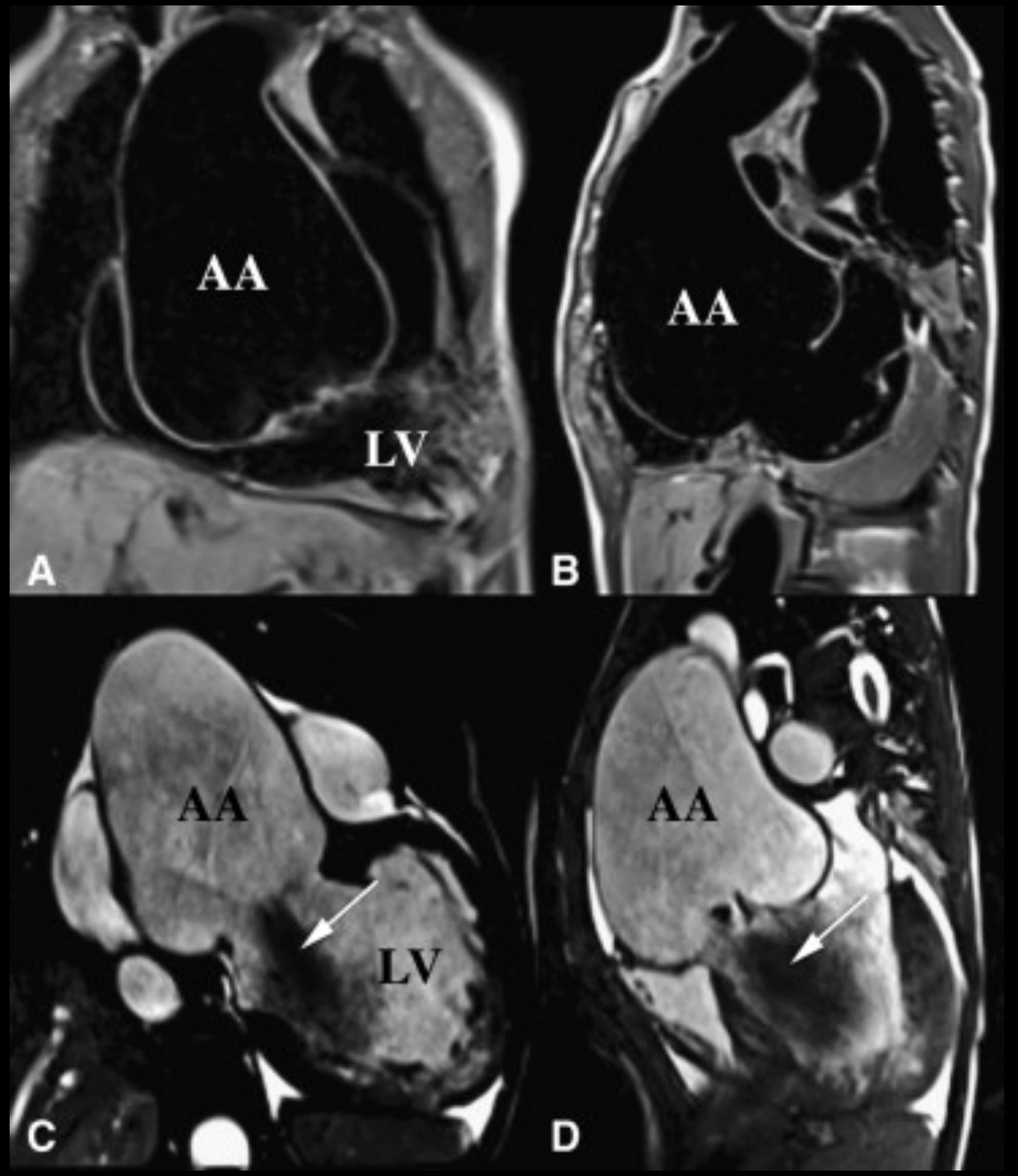


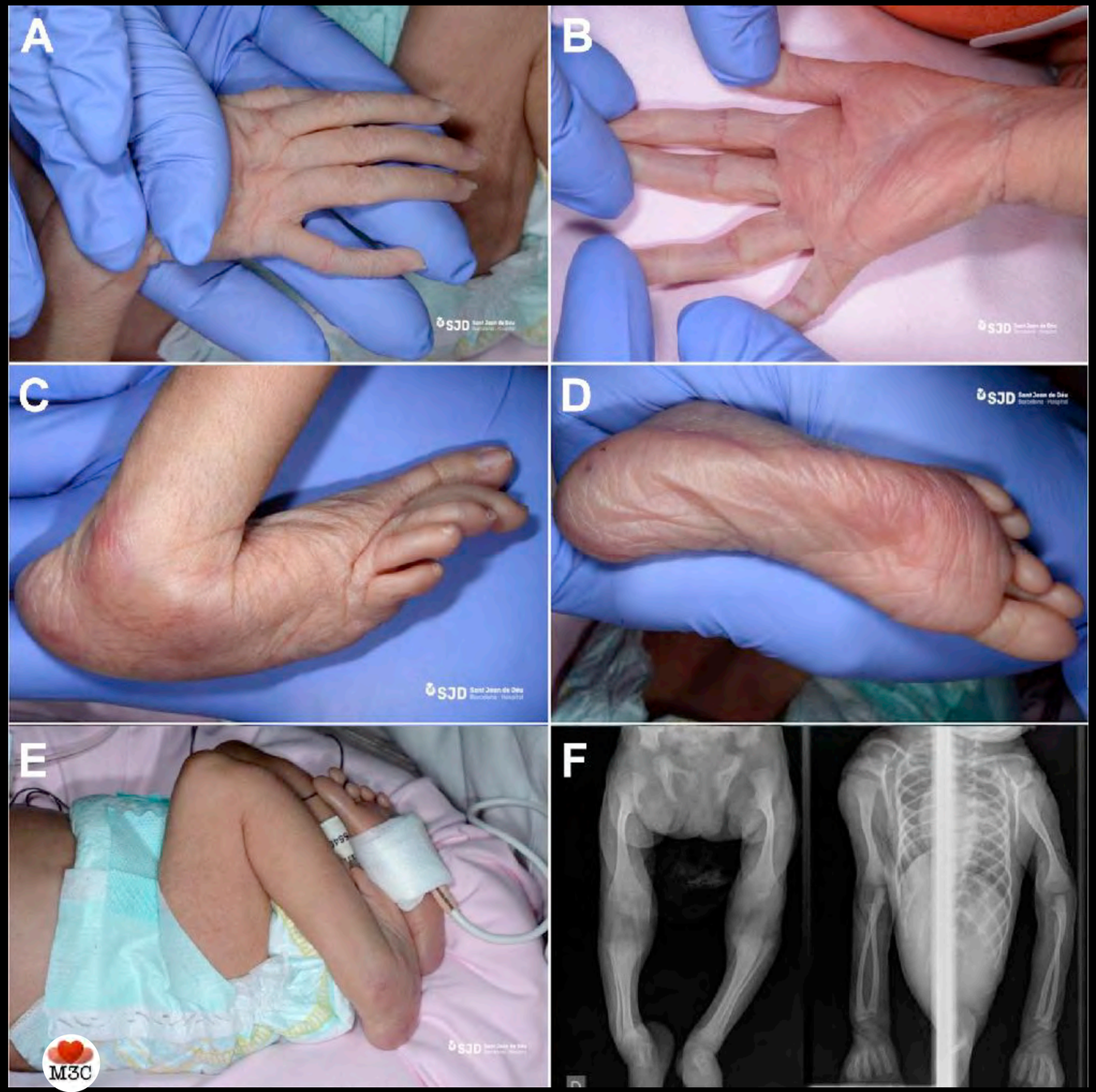


Skeletal anomalies in Marfan syndrome

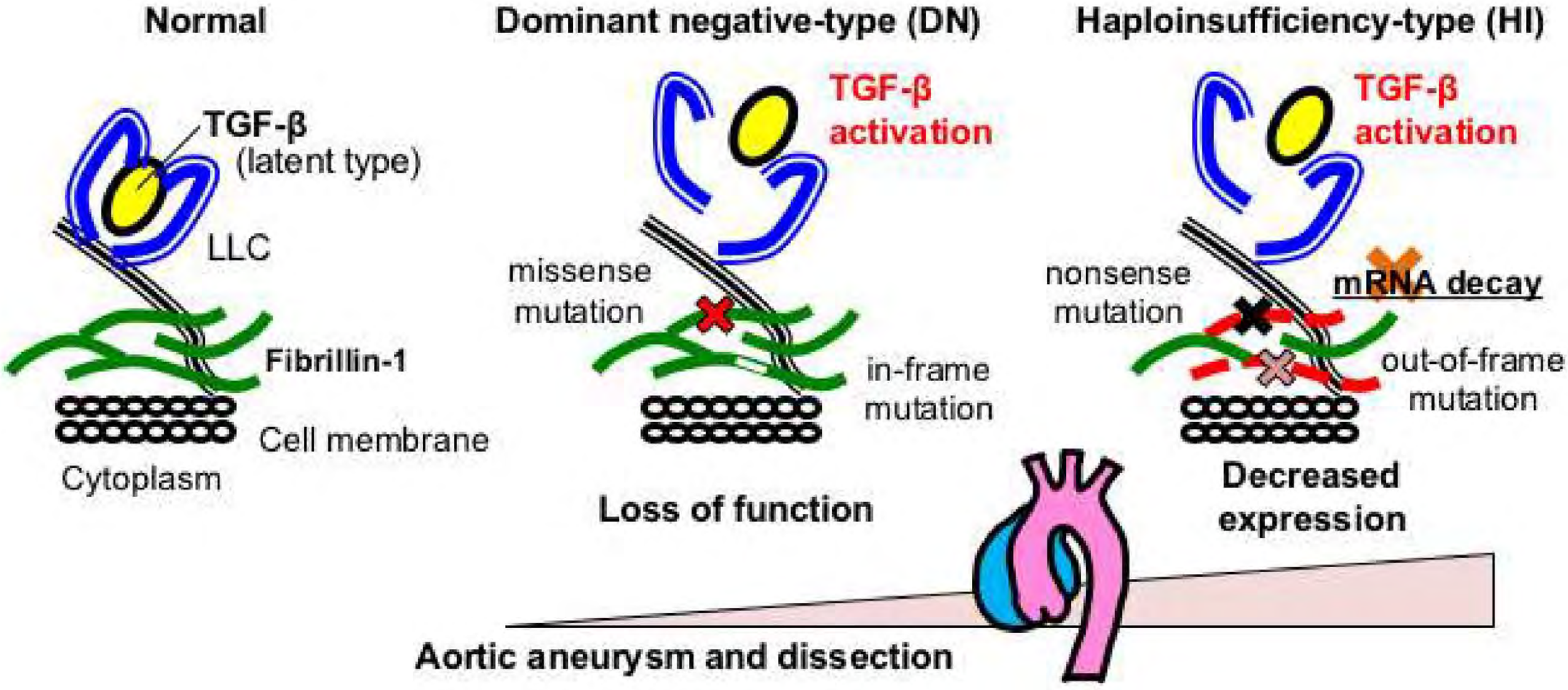
Hands-Marfan syndrome

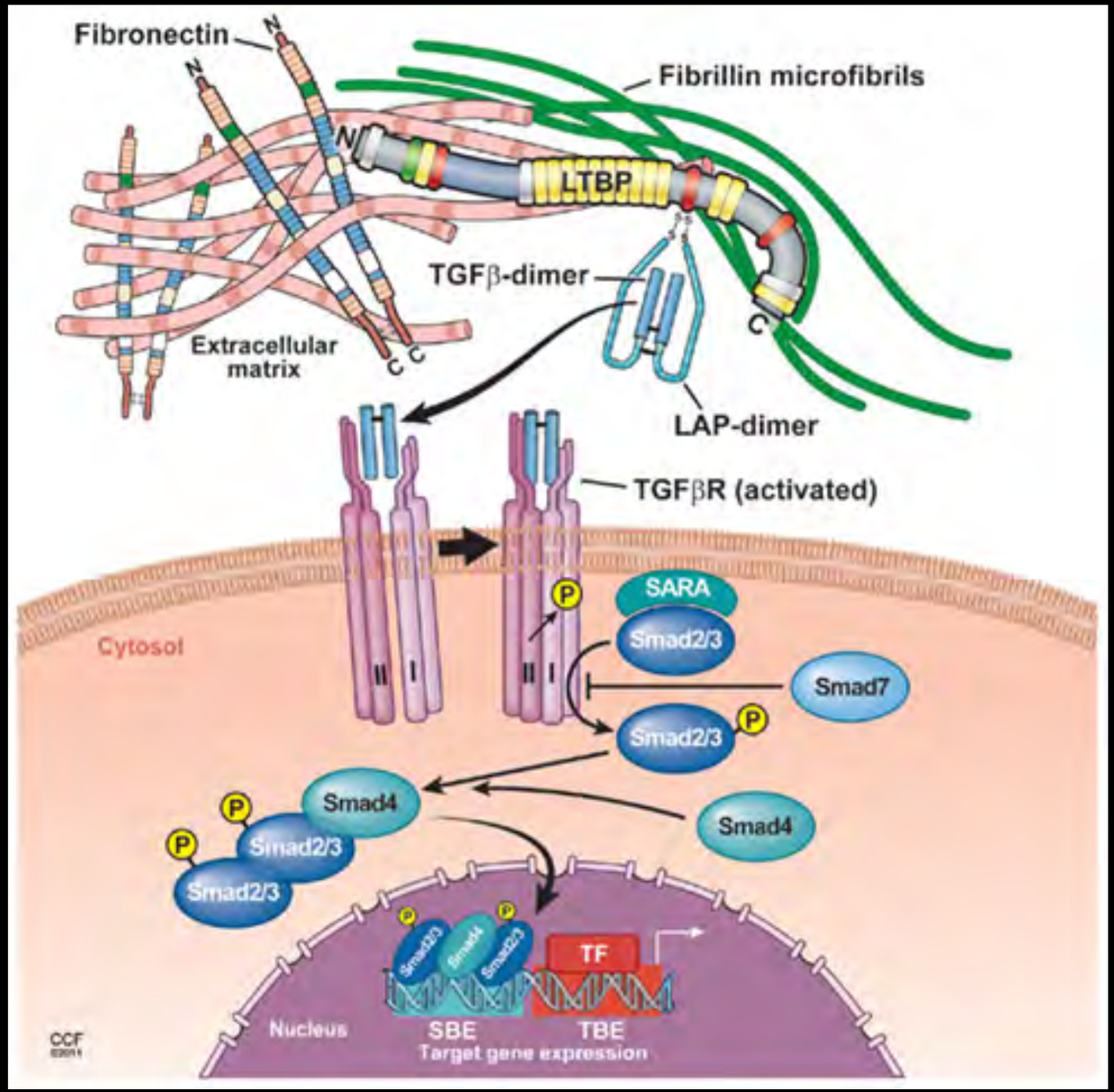

Cristallin

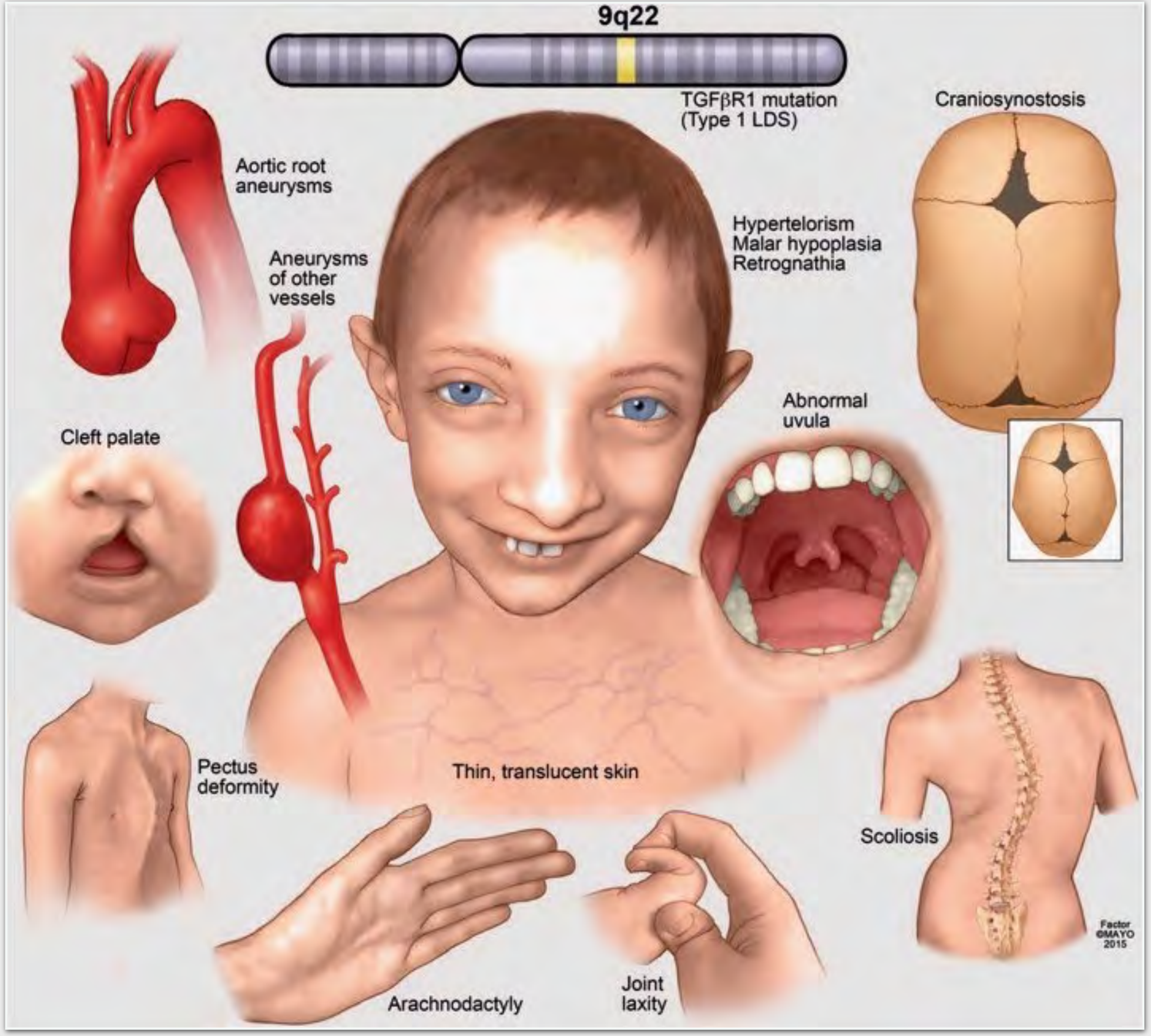

AA
LV
A
AA
B
AA
LV
C
AA
D

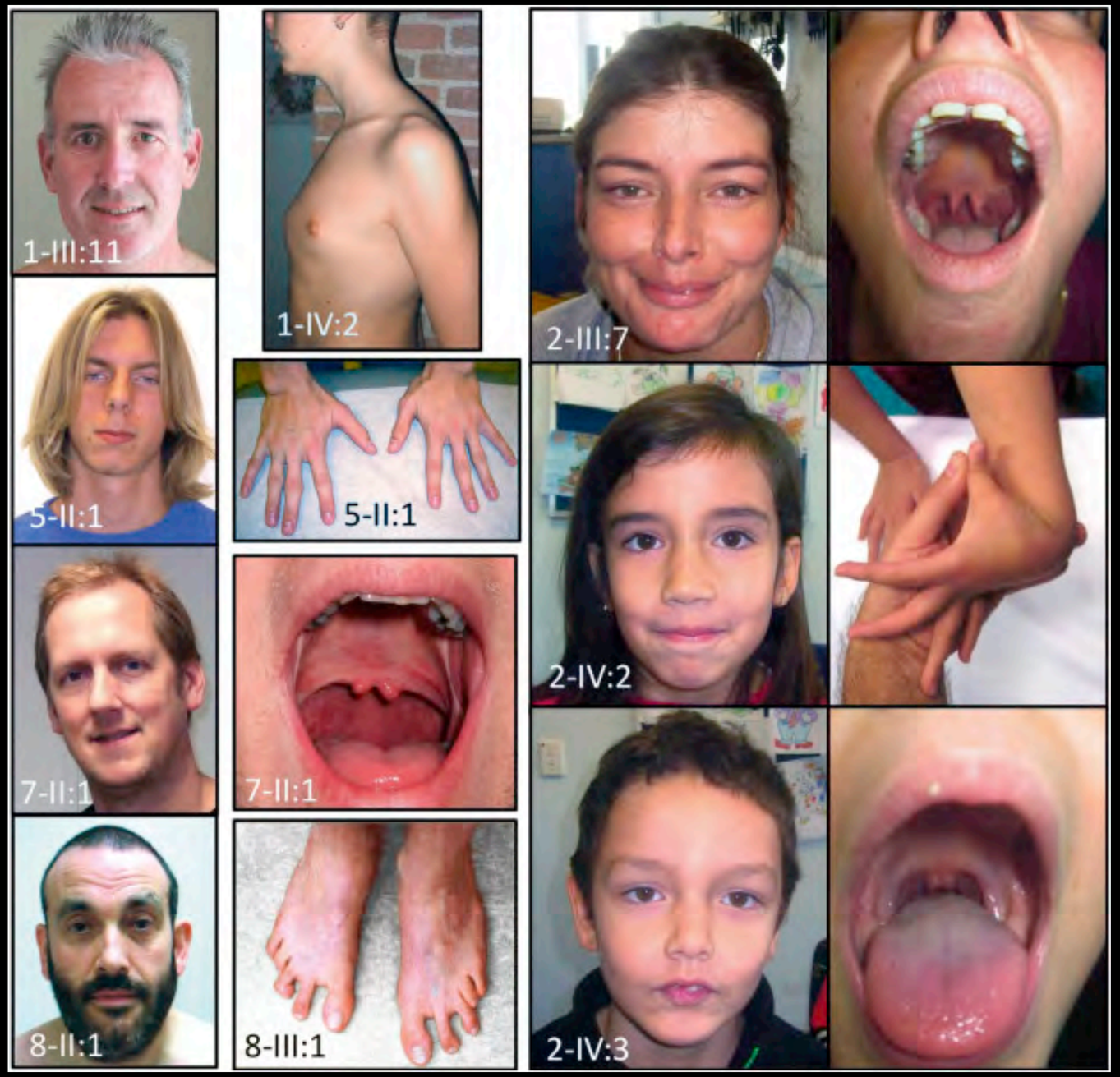


Neonatal Marfan syndrome


Normal
TGF-β
(latent type)
LLC
Fibrillin-1
Cell membrane
Cytoplasm
Dominant negative-type (DN)
TGF-β
activation
missense
mutation
in-frame
mutation
Loss of function
Haploinsufficiency-type (HI)
TGF-β
activation
nonsense
mutation
mRNA decay
out-of-frame
mutation
Decreased
expression
Aortic aneurysm and dissection


Fibronectin
Fibrillin microfibrils
N
LTBP
TGFβ-dimer
C
Extracellular matrix
C
C
LAP-dimer
TGFβR (activated)
P
SARA
Smad2/3
Cytosol
Smad7
Smad2/3
P
Smad4
P
Smad2/3
P
Smad2/3
Smad4
P
P
Smad2/3
Smad4
Smad2/3
TF
Nucleus
SBE
TBE
Target gene expression
CCF

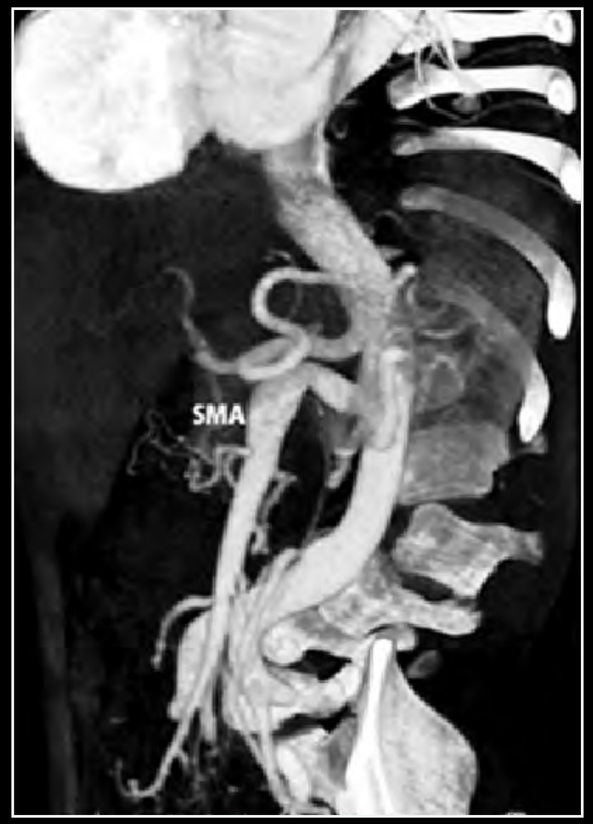

9q22
TGFβR1 mutation
(Type 1 LDS)
Craniosynostosis
Aortic root
aneurysms
Aneurysms
of other
vessels
Hypertelorism
Malar hypoplasia
Retrognathia
Abnormal
uvula
Cleft palate
Pectus
deformity
Thin, translucent skin
Scoliosis
Arachnodactyly
Joint
laxity
Factor
©MAYO
2015



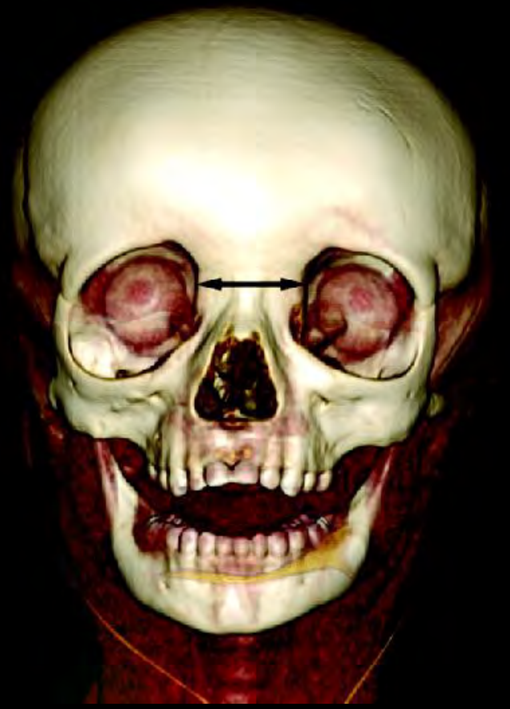
Loeys-Dietz syndrome

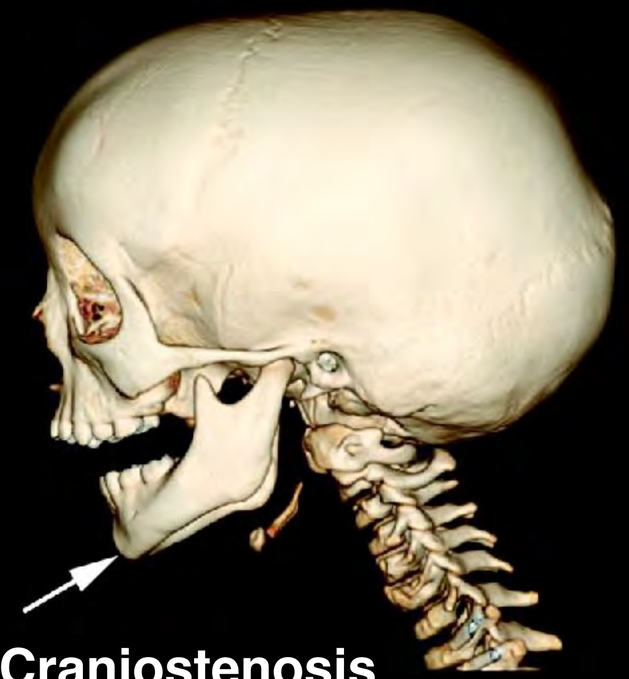
Loeys-Dietz syndrome - Phenotype

Bot pie

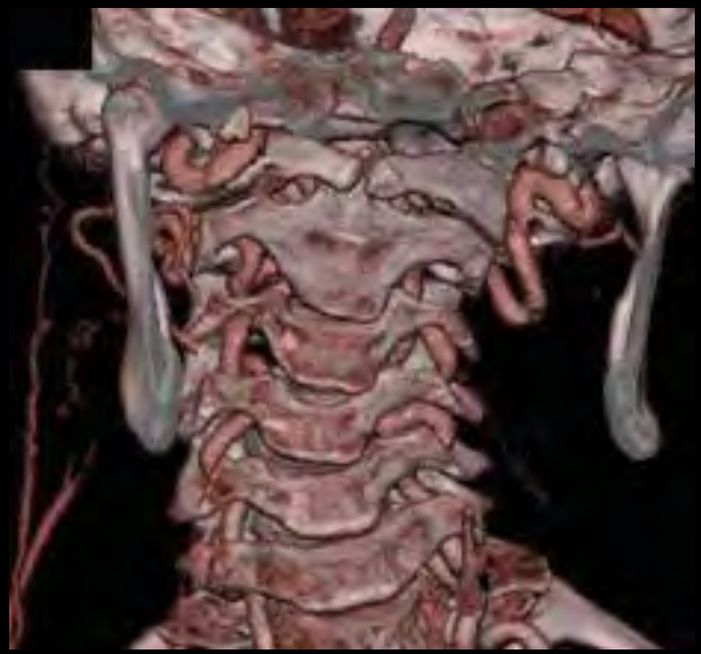


Vertebral anomalies

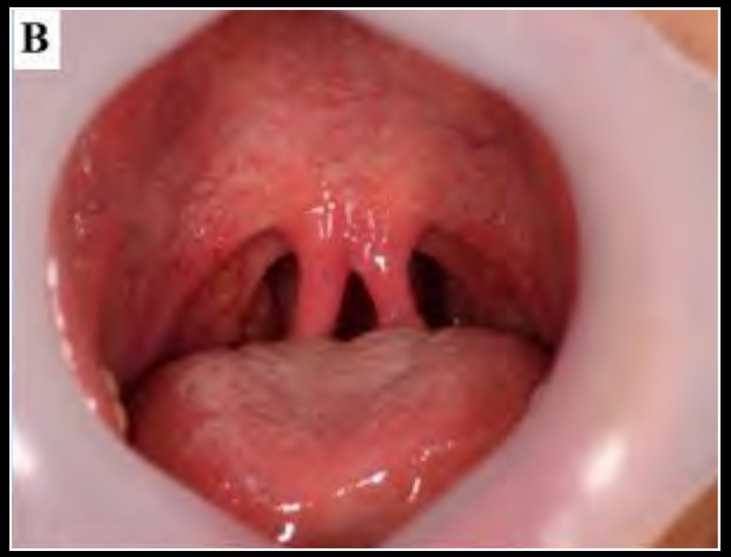




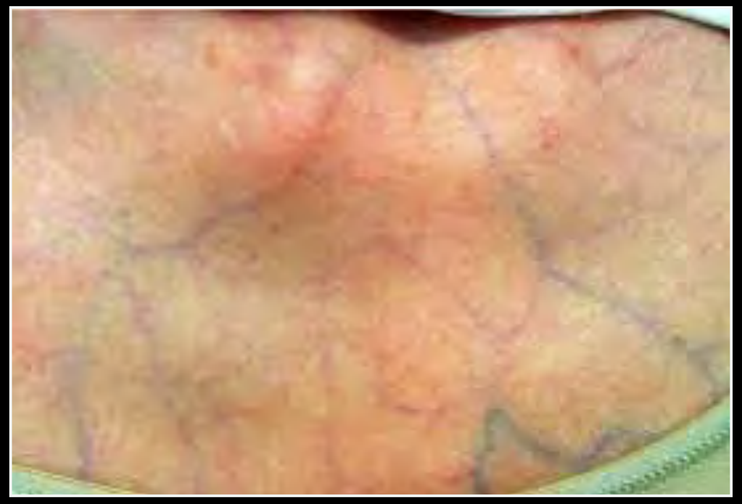
Craniostenosis



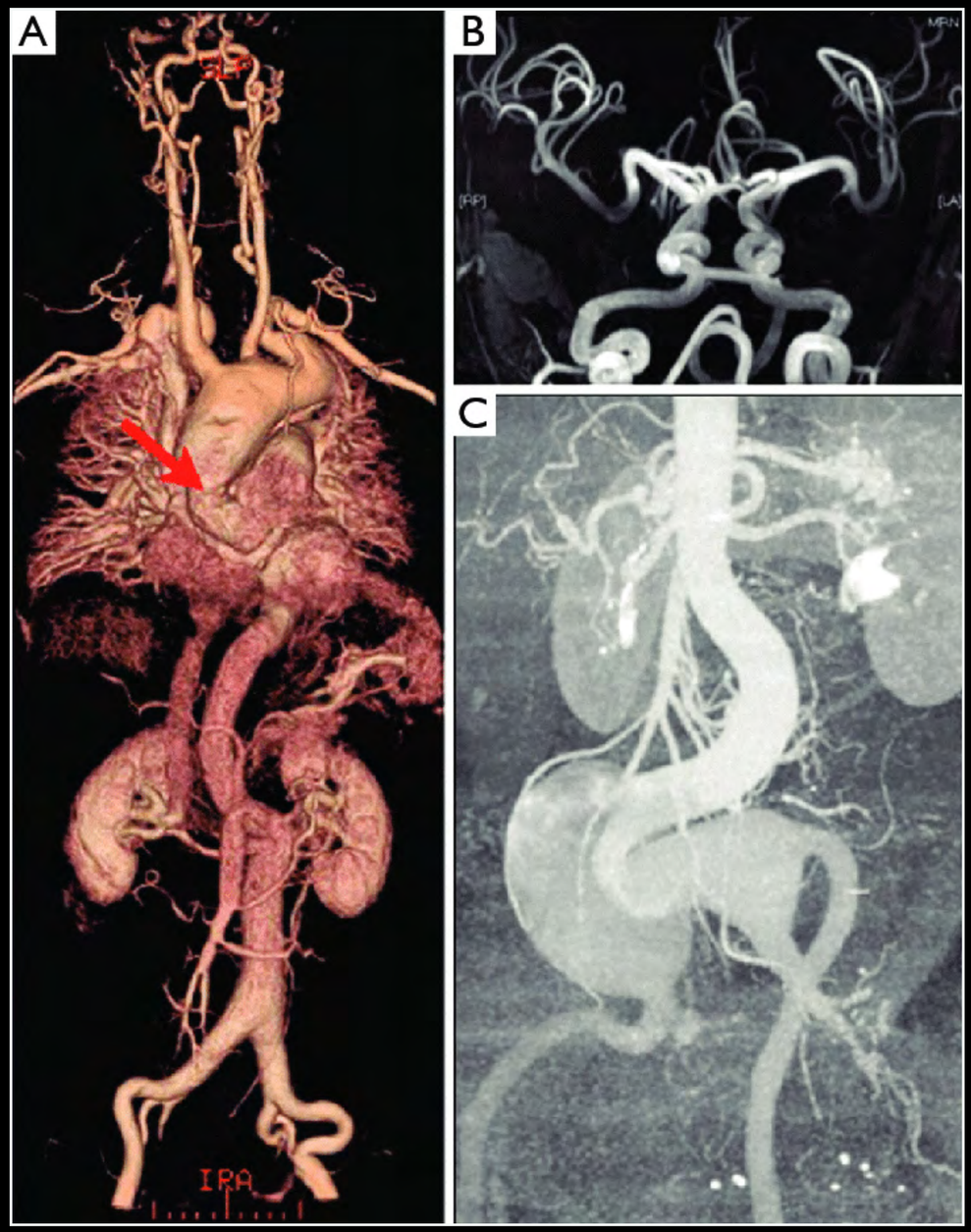
Loeys-Dietz syndrome - Phenotype



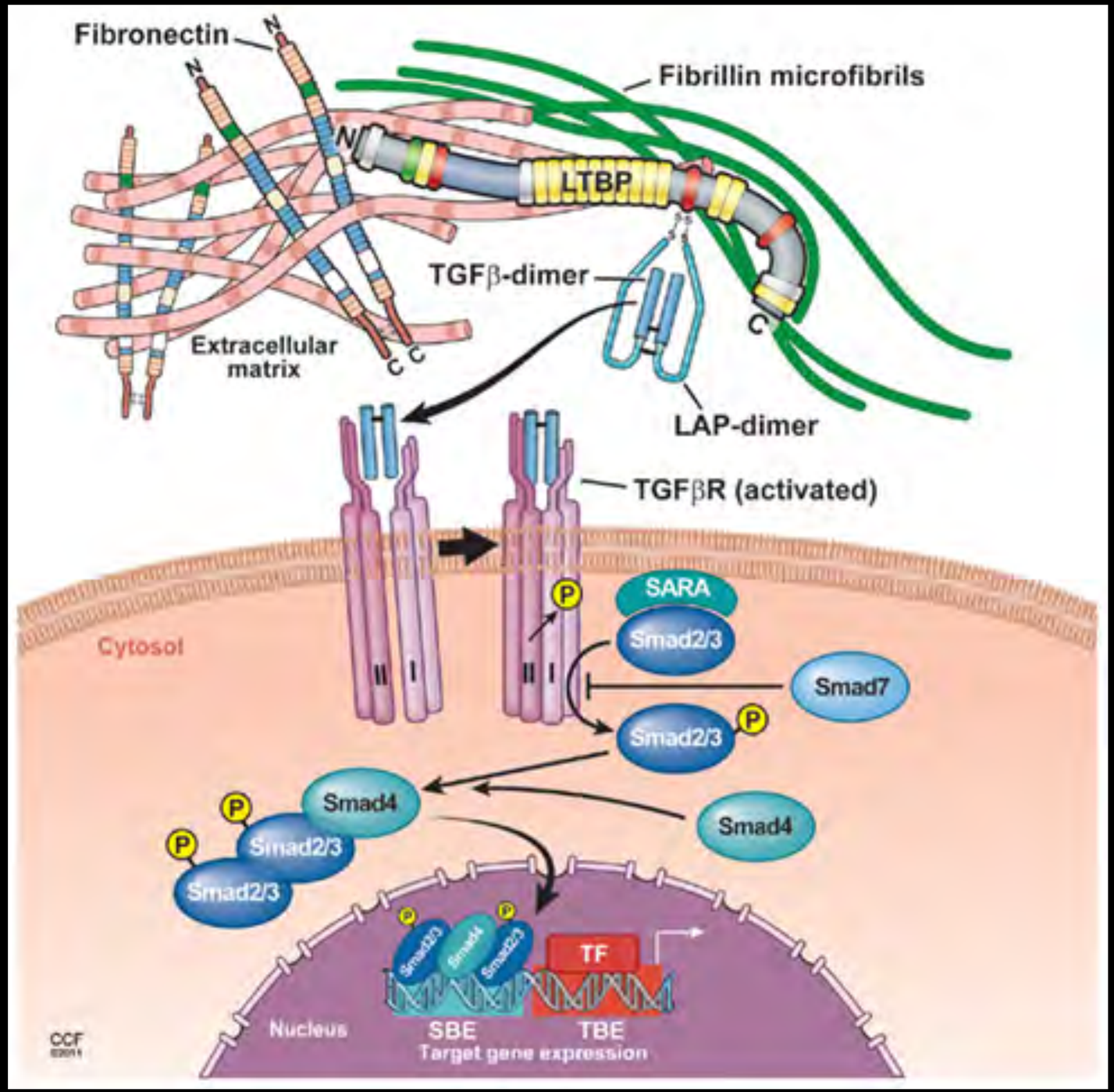
Bifid uvula



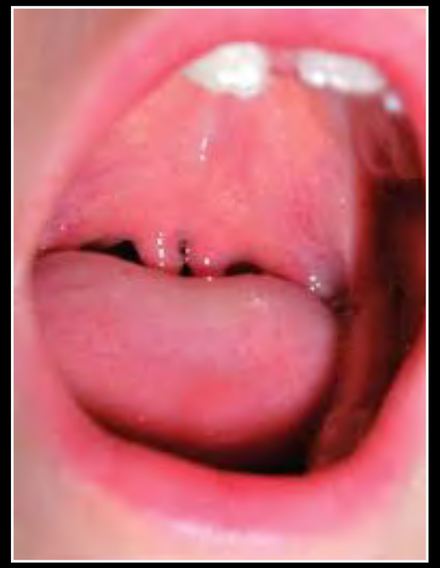
Translucent skin



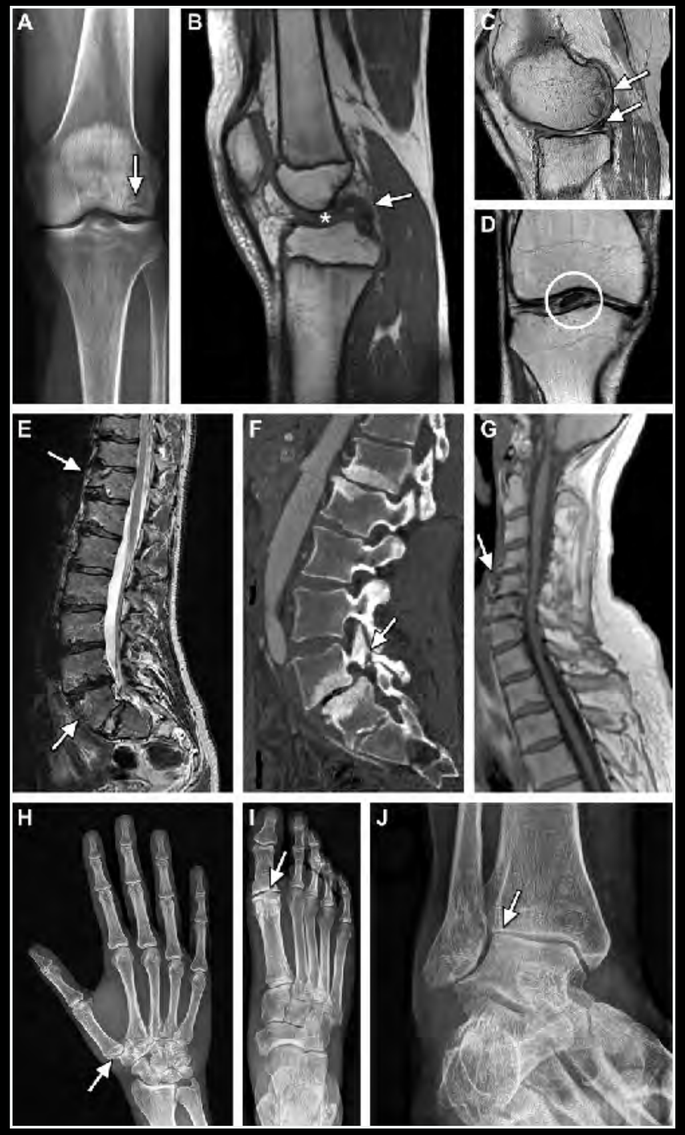
Tortuous vessels -Aneurysms


Fibronectin
Fibrillin microfibrils
N
LTBP
TGFβ-dimer
C
Extracellular matrix
C
C
LAP-dimer
TGFβR (activated)
P
SARA
Smad2/3
Cytosol
Smad7
Smad2/3
P
Smad4
P
Smad2/3
P
Smad2/3
Smad4
P
P
Smad2/3
Smad4
Smad2/3
TF
Nucleus
SBE
TBE
Target gene expression
CCF

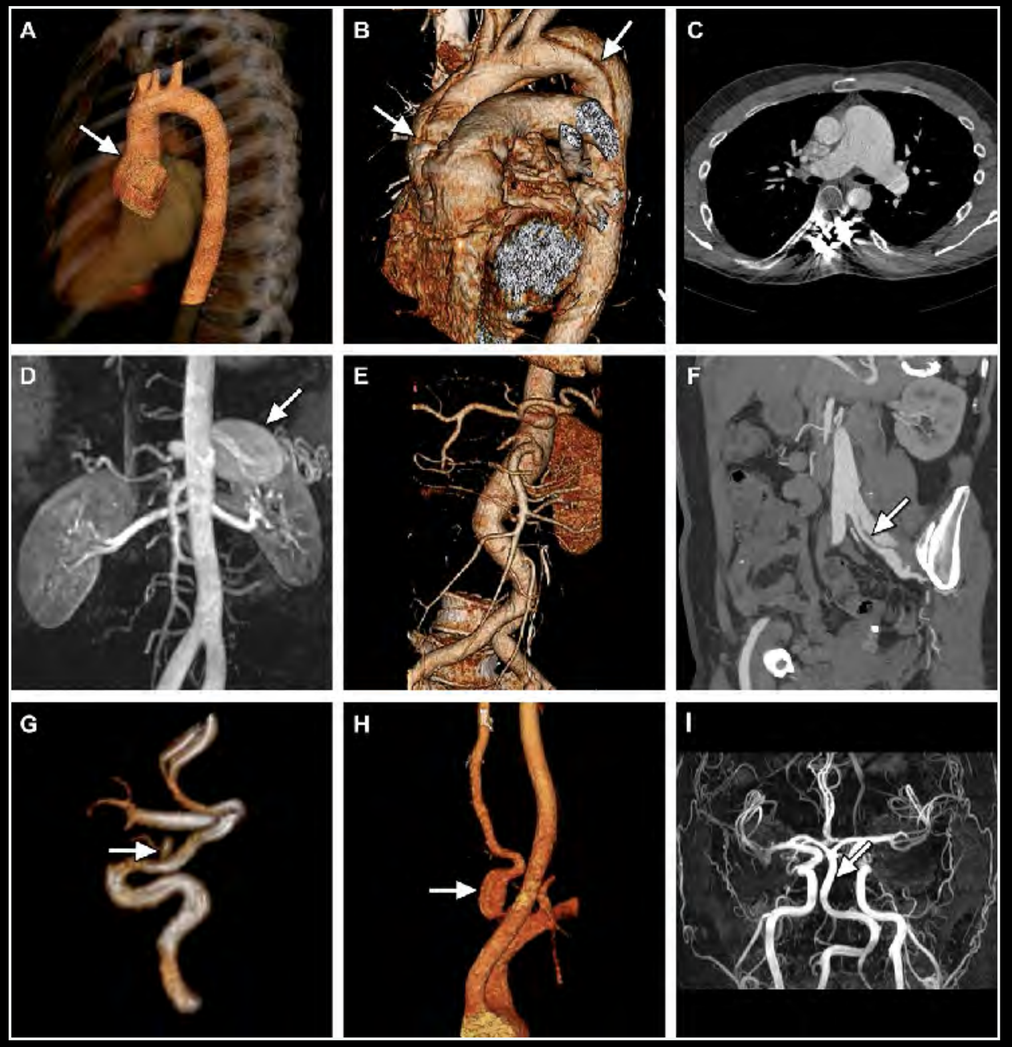
Aneurysms Osteoarthritis syndrome - Phenotype *SMAD3* mutations



Bifid uvula

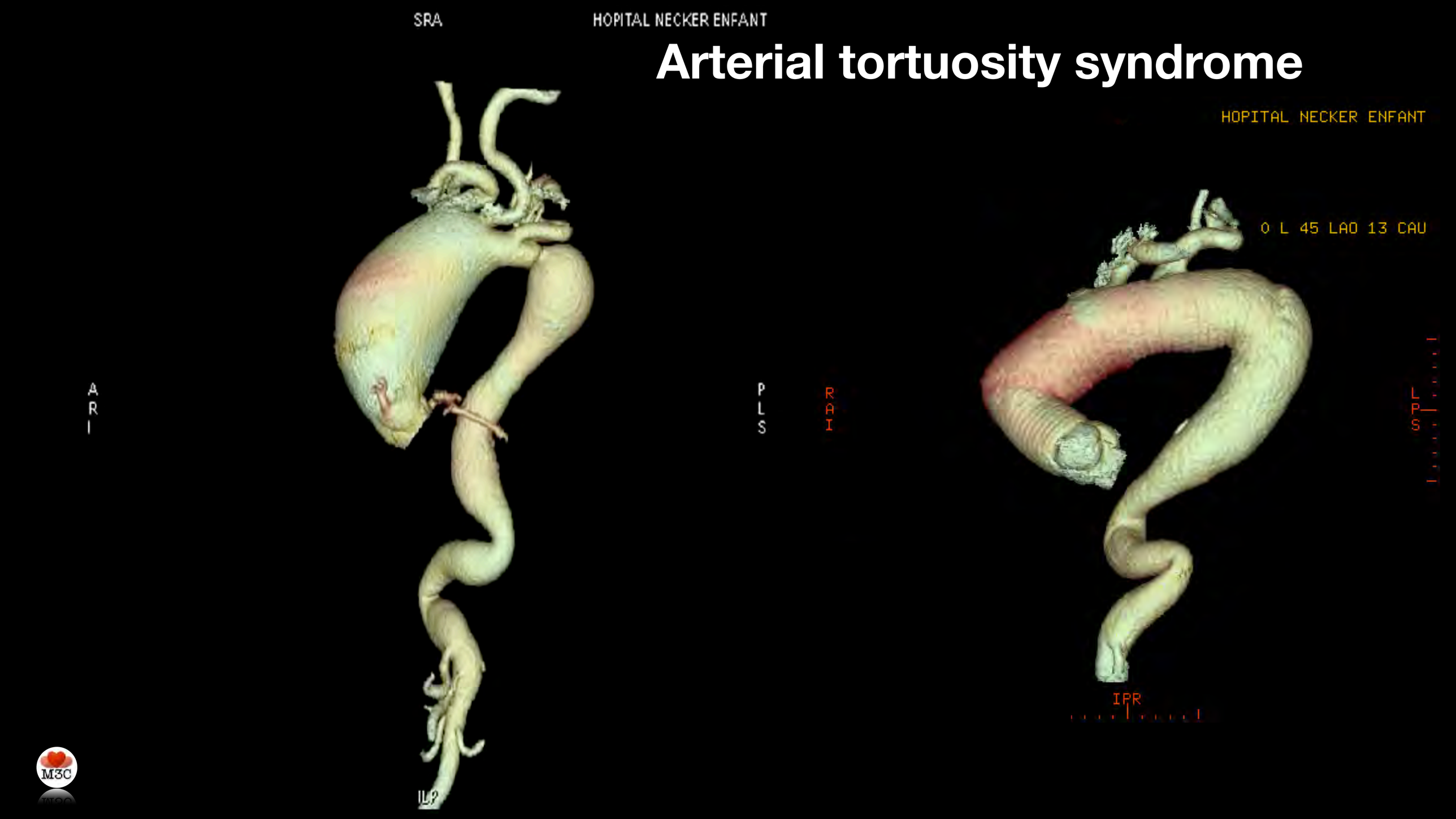


Arthritis

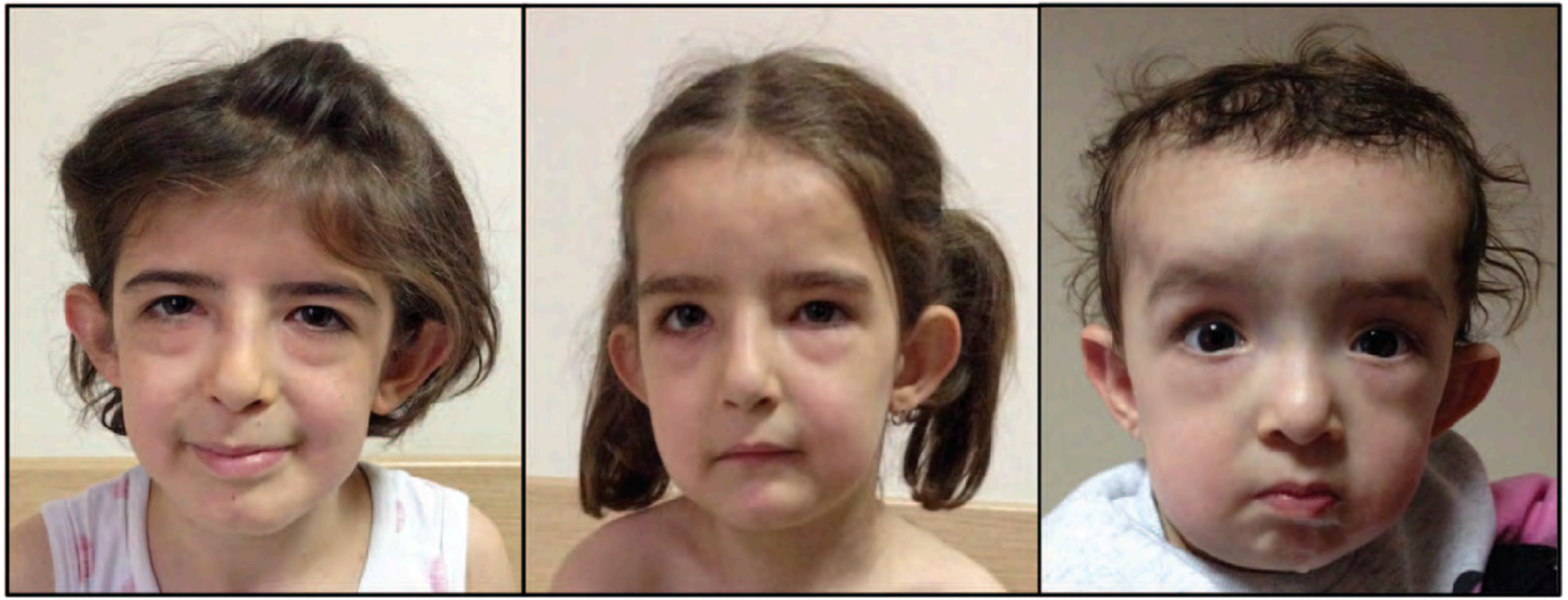


Tortuous vessels -Aneurysms

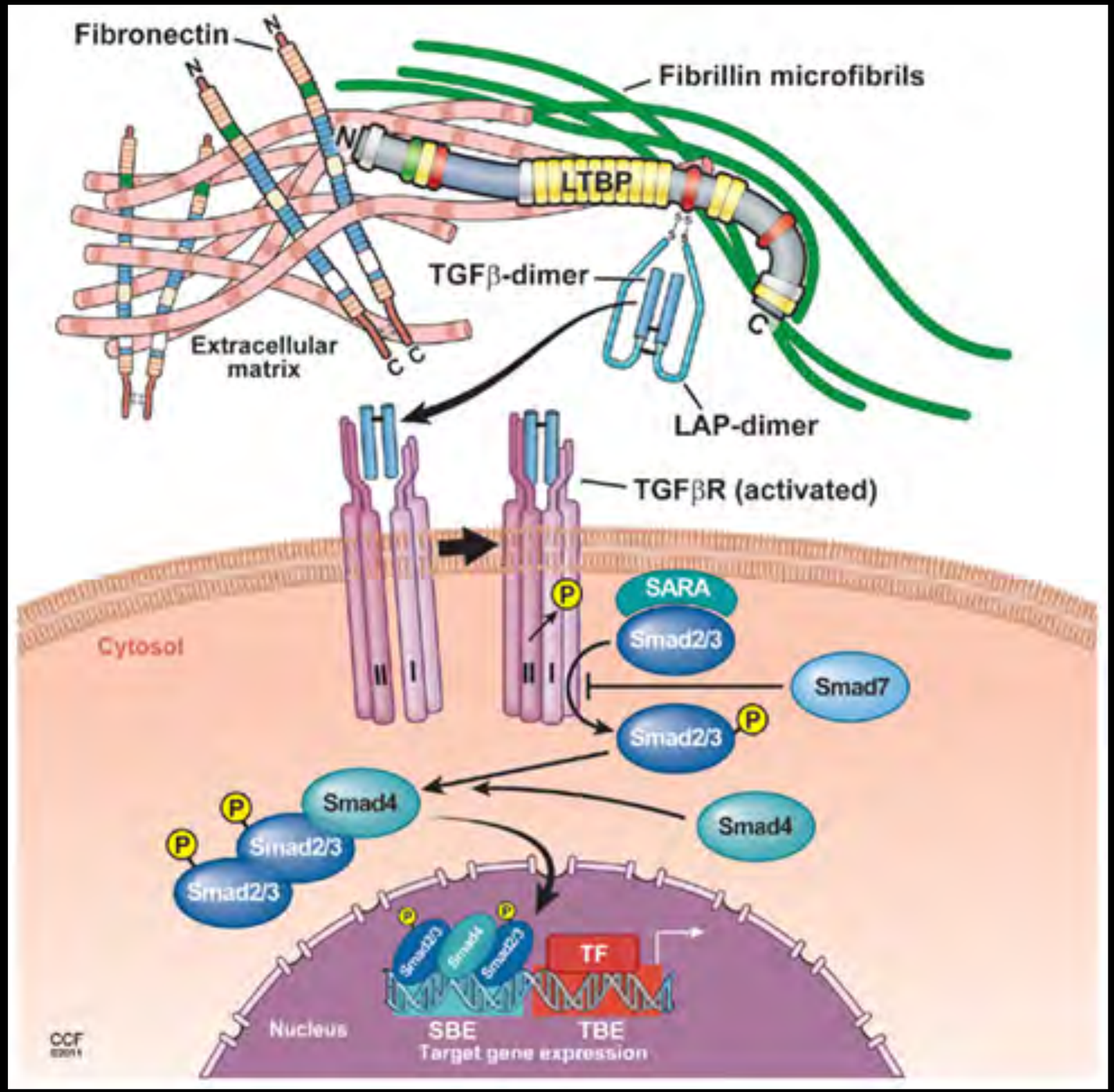
Arterial tortuosity syndrome



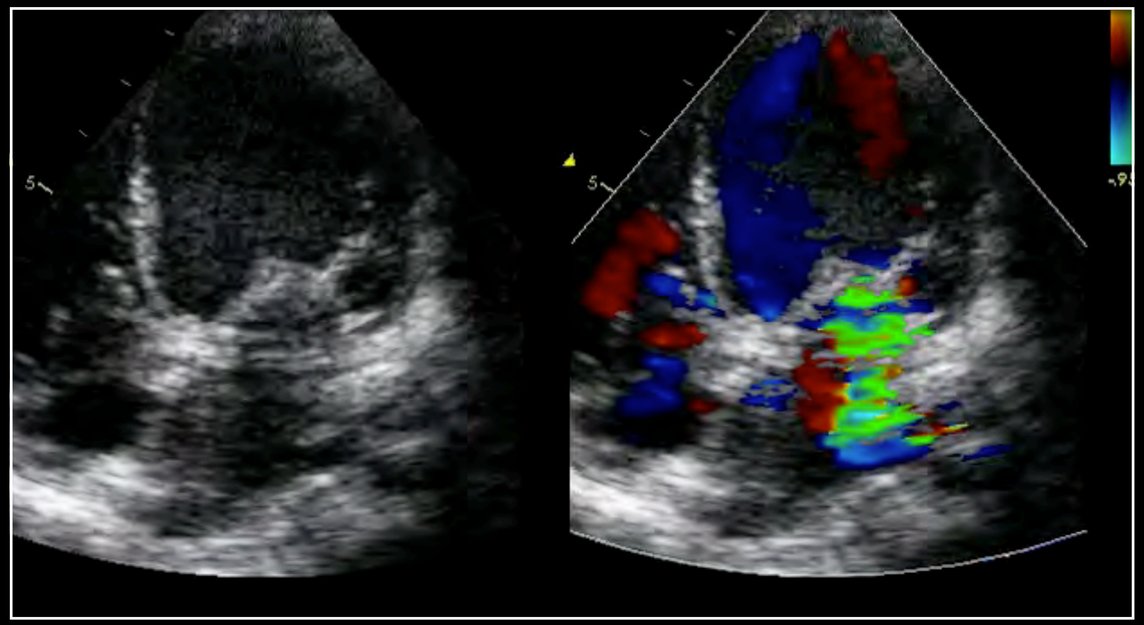
Arterial tortuosity syndrome (ATS) is a rare connective tissue disorder characterized by tortuosity of the large and medium sized arteries, caused by mutations in SLC2A10. Inherited as a recessive trait.

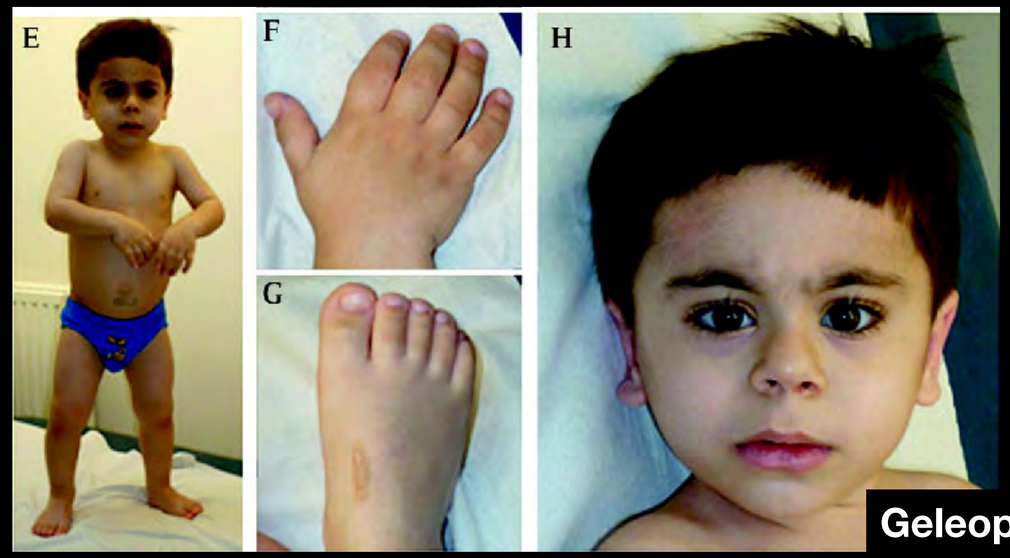


Beyens A et al. Genetics in Medicine


Fibronectin
Fibrillin microfibrils
N
LTBP
TGFβ-dimer
C
Extracellular matrix
C
C
LAP-dimer
TGFβR (activated)
P
SARA
Smad2/3
Cytosol
Smad7
Smad2/3
P
Smad4
P
Smad2/3
P
Smad2/3
Smad4
P
P
Smad2/3
Smad4
Smad2/3
TF
Nucleus
SBE
TBE
Target gene expression
CCF

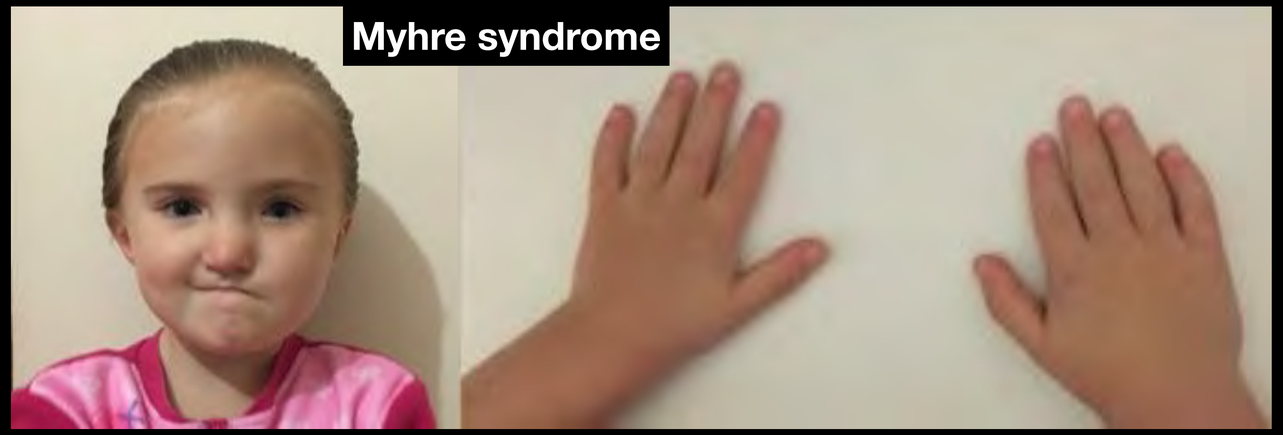
Acromelic dysplasias



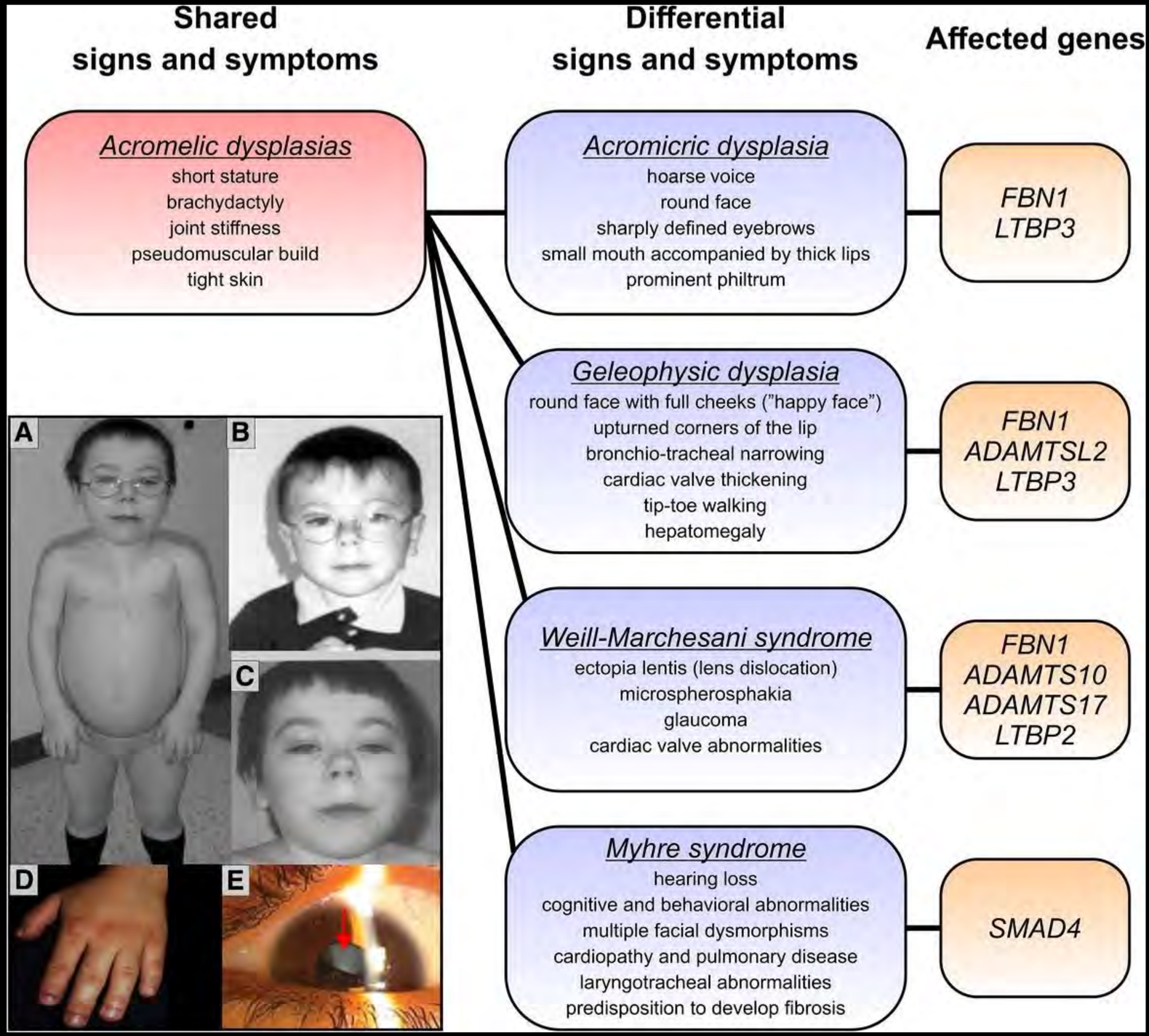


Geleophysic

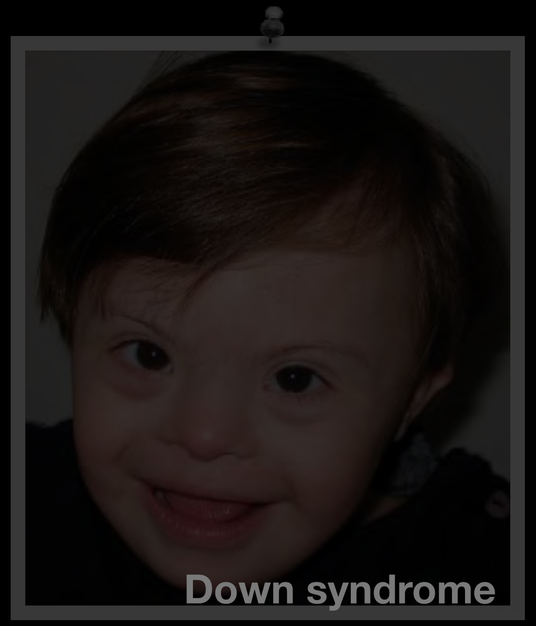
Myhre syndrome

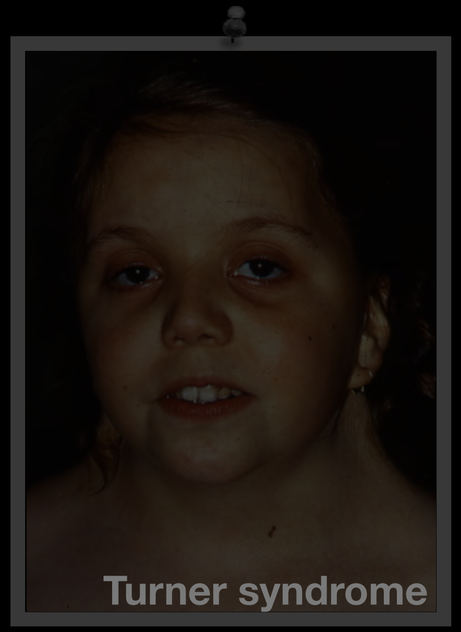


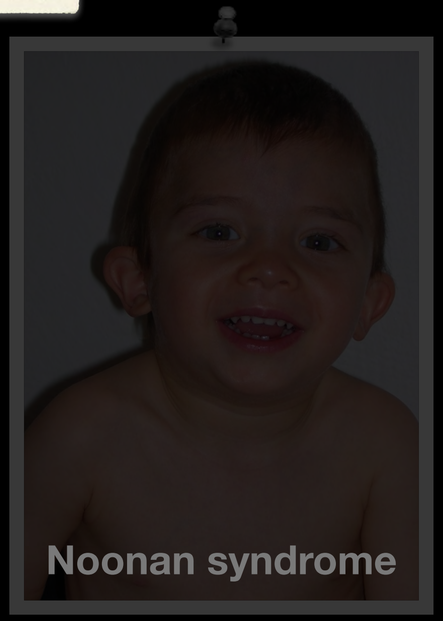
Acromelic dysplasias

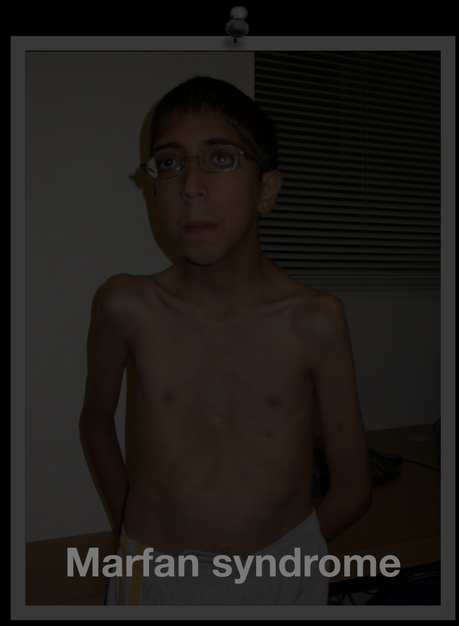


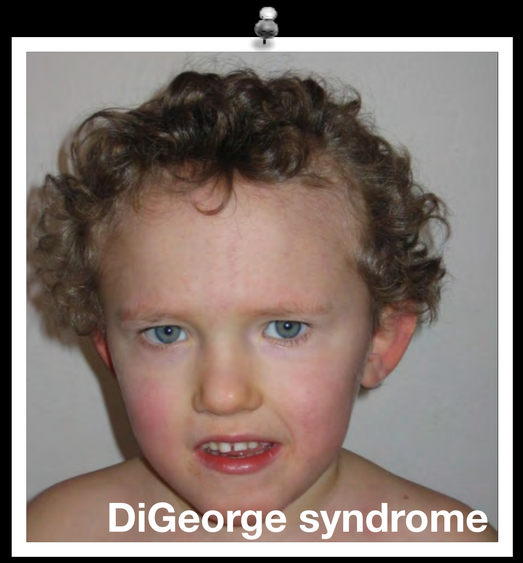
Old textbooks and clinical genetics

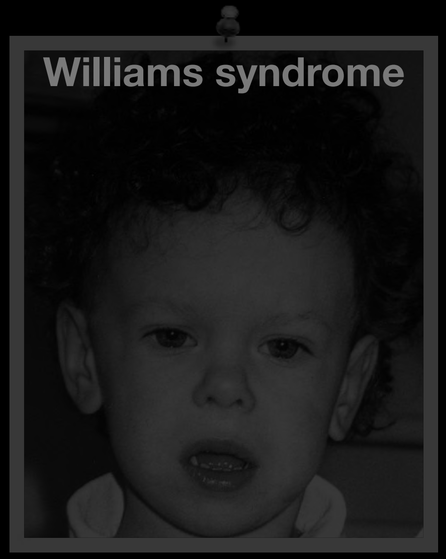


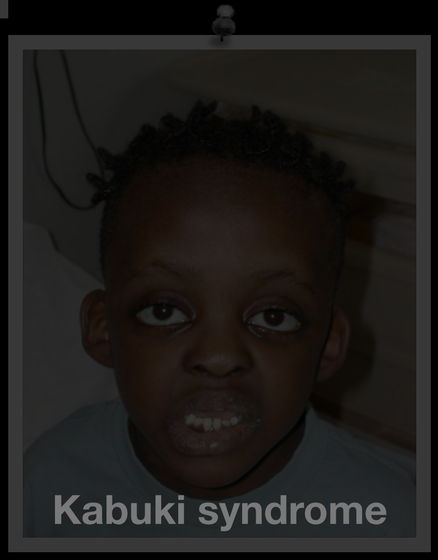


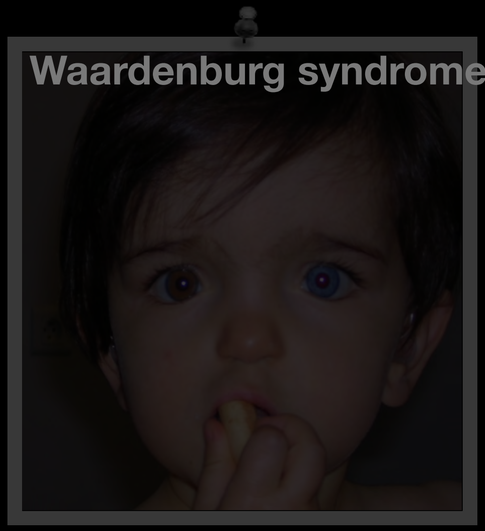


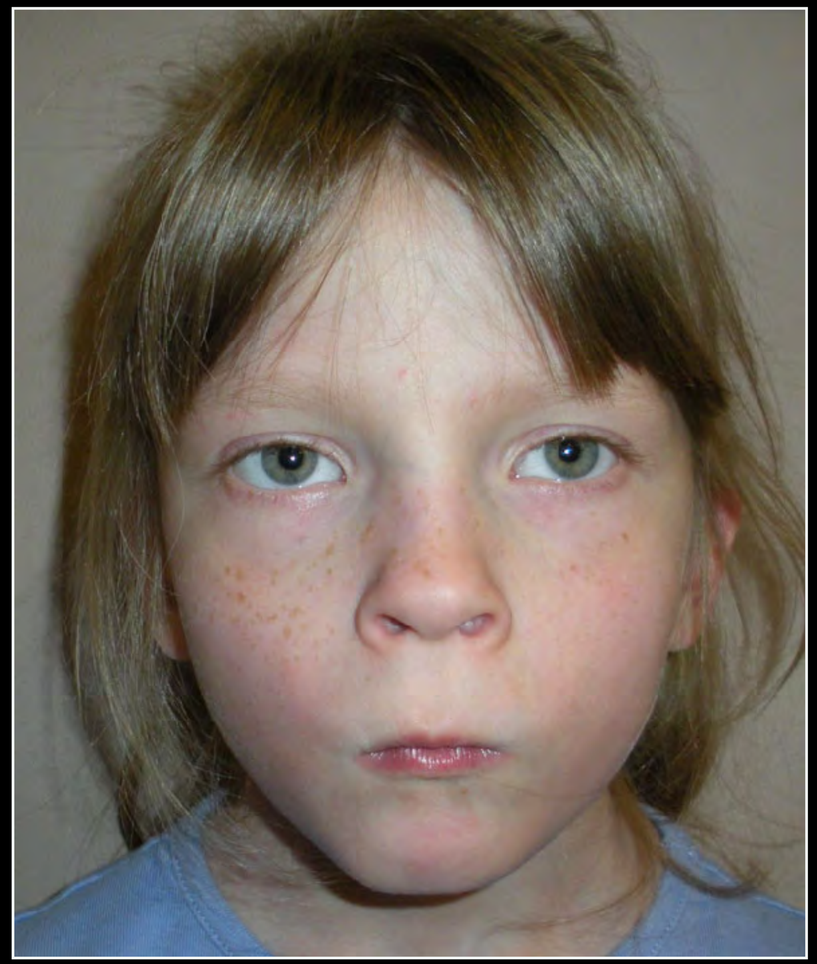


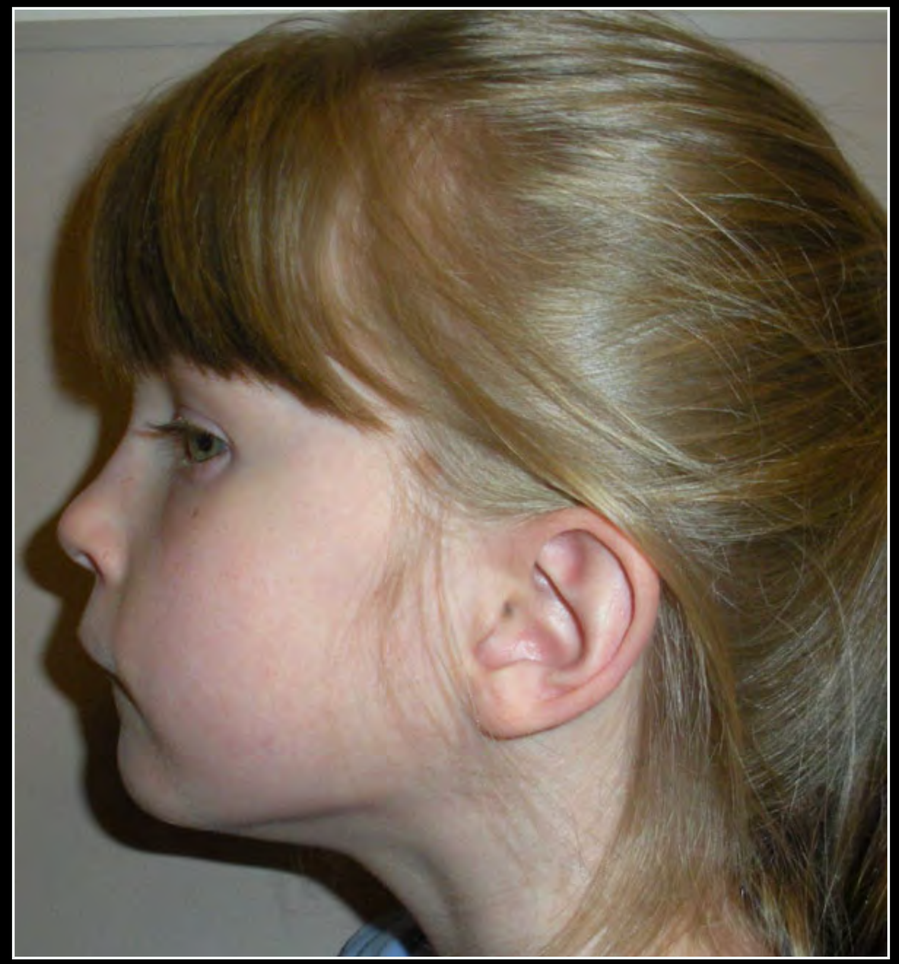




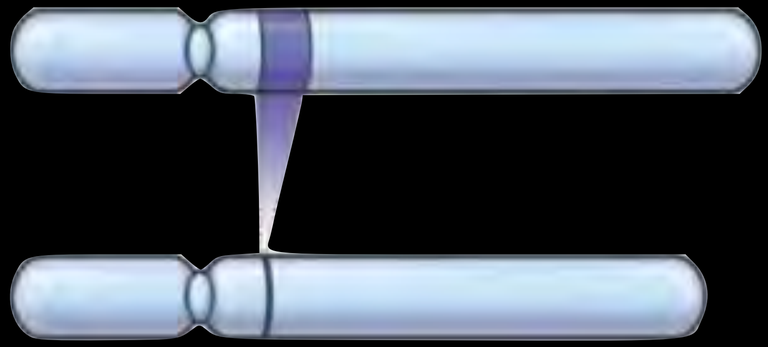




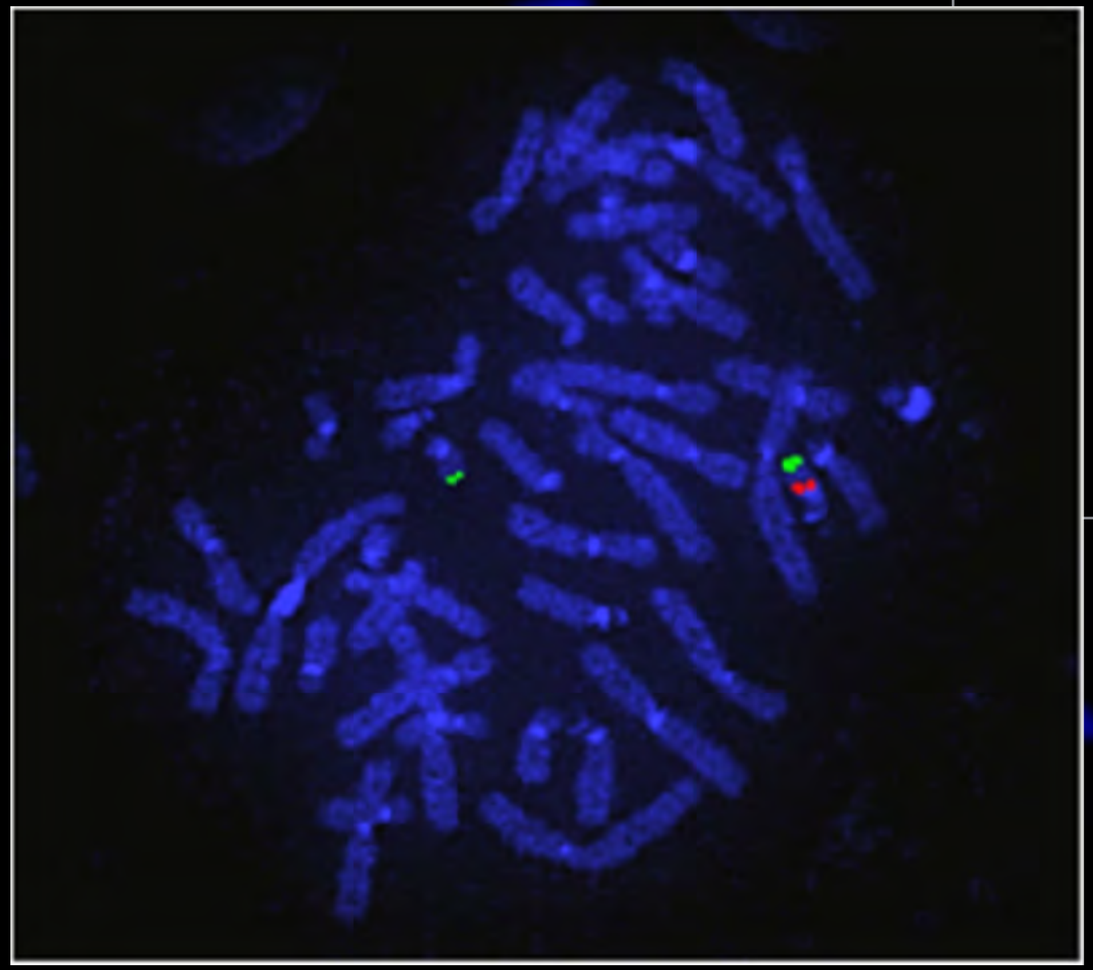


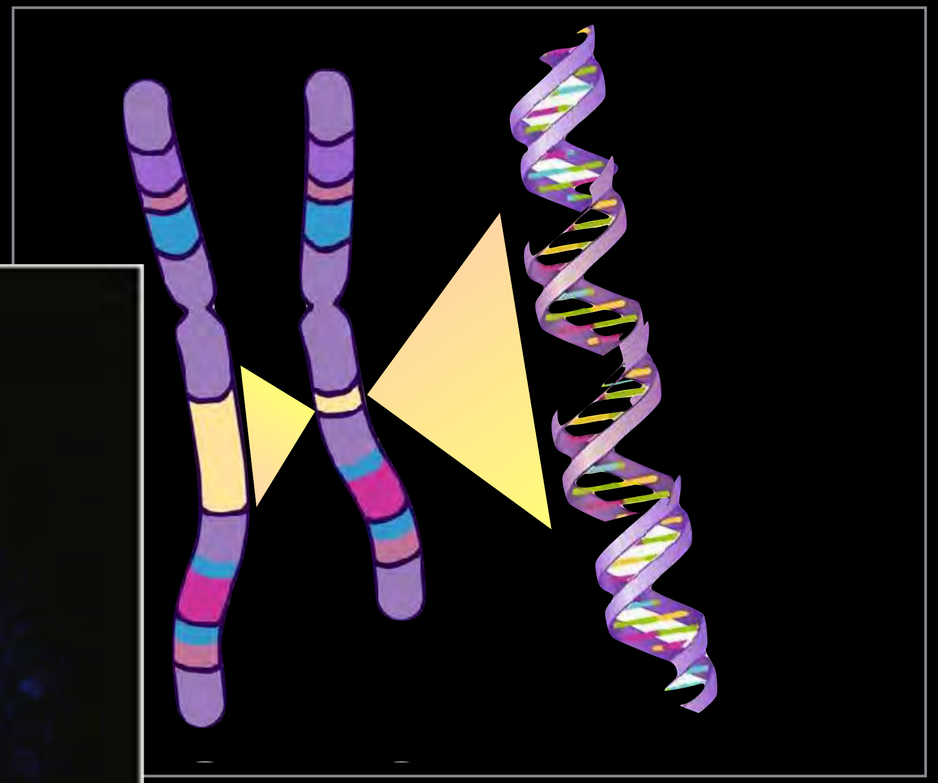


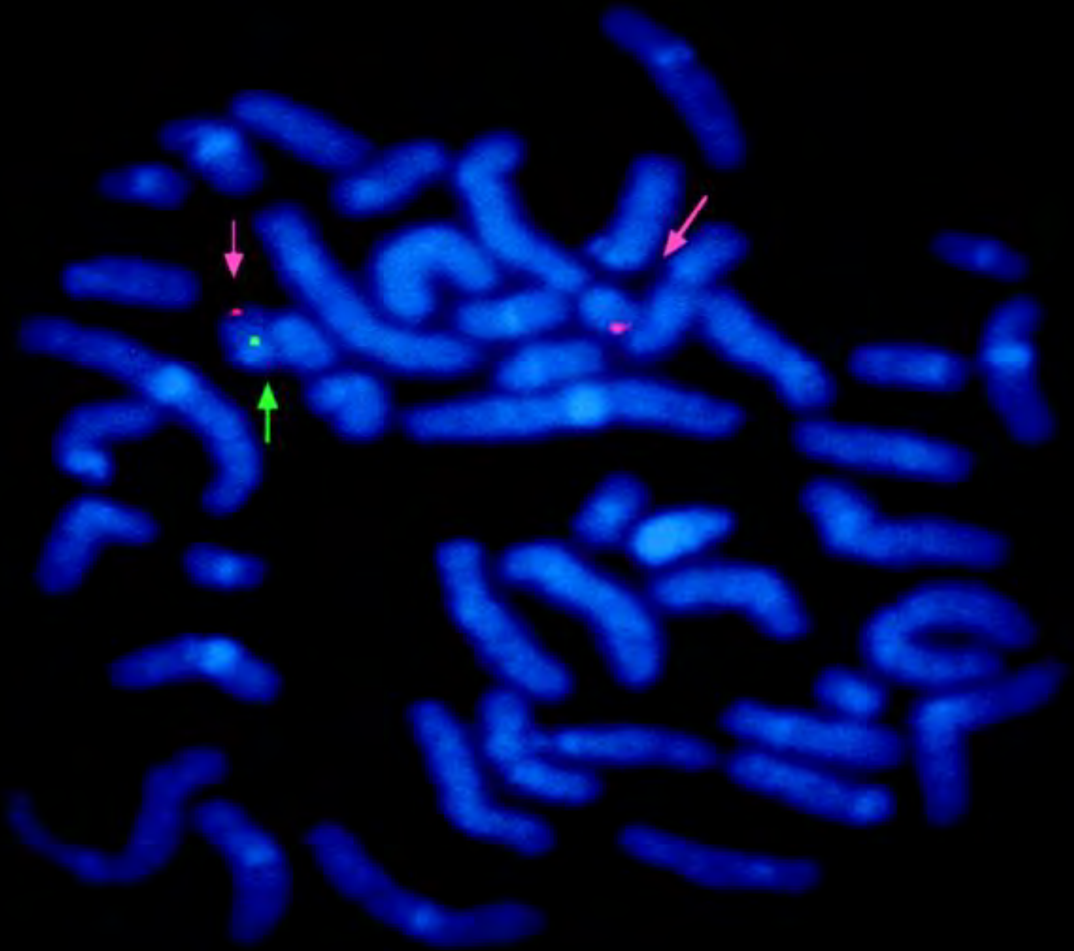
Normal chromosome 22



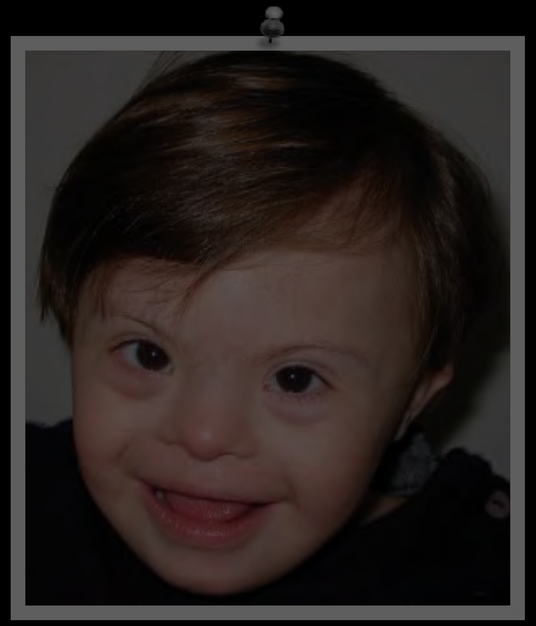
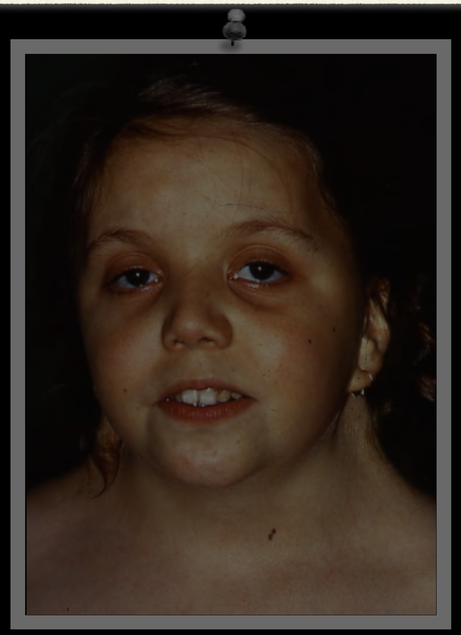
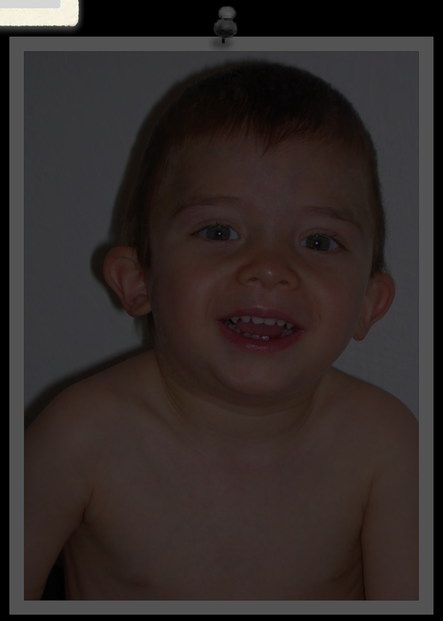
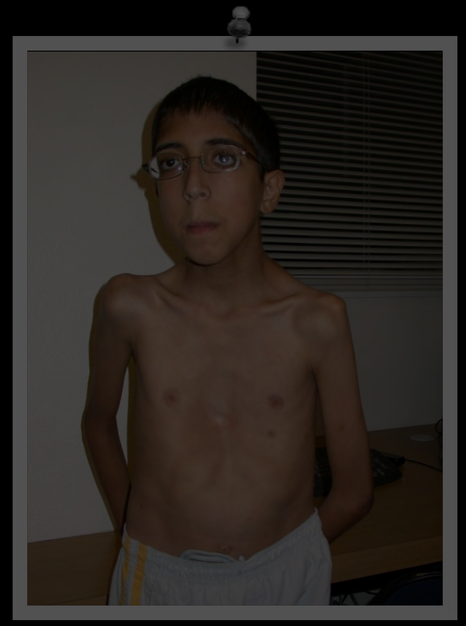
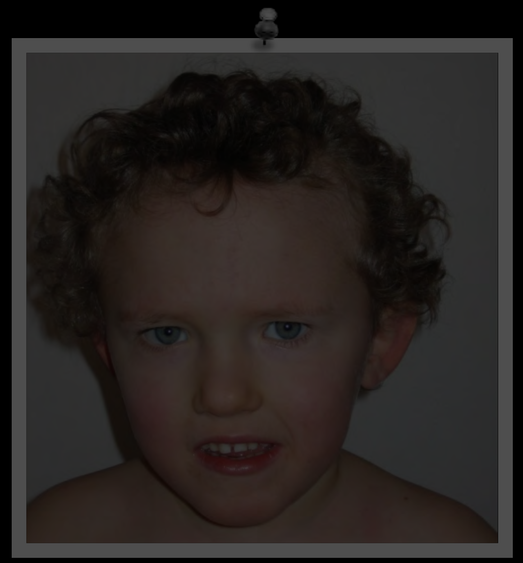
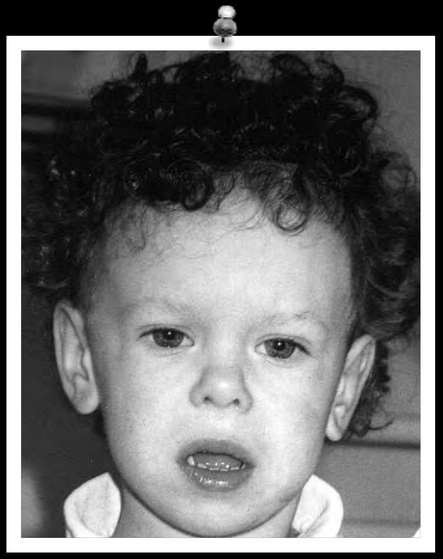
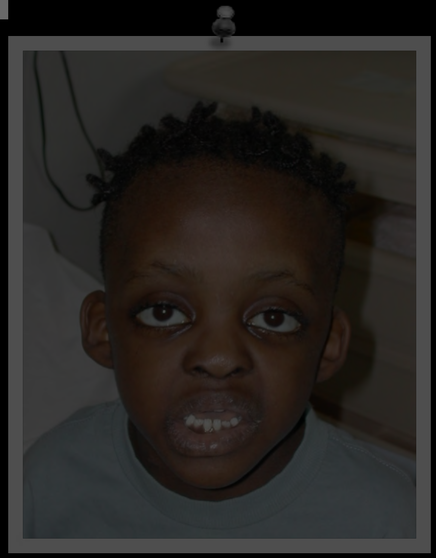
Chromosome 22q11 deletion

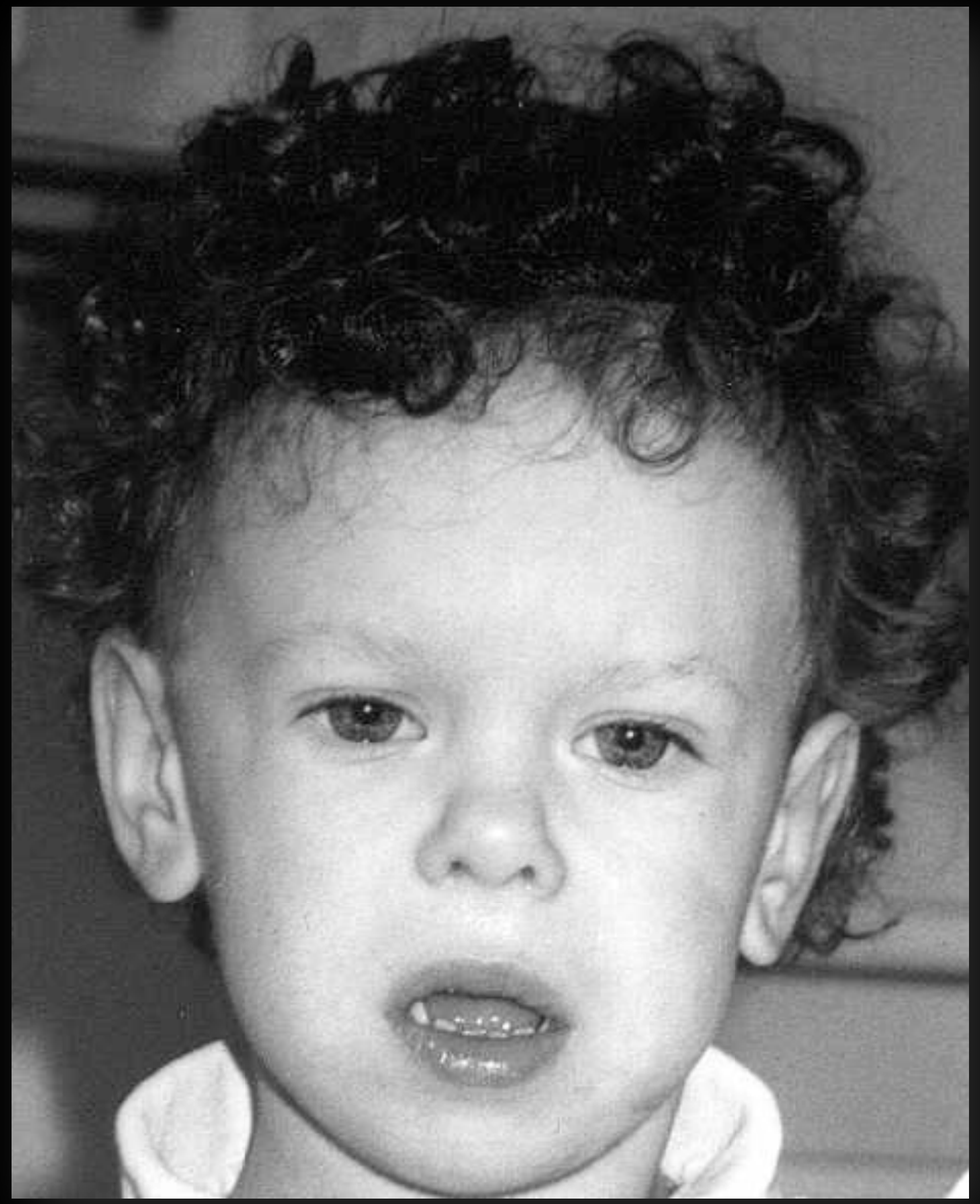


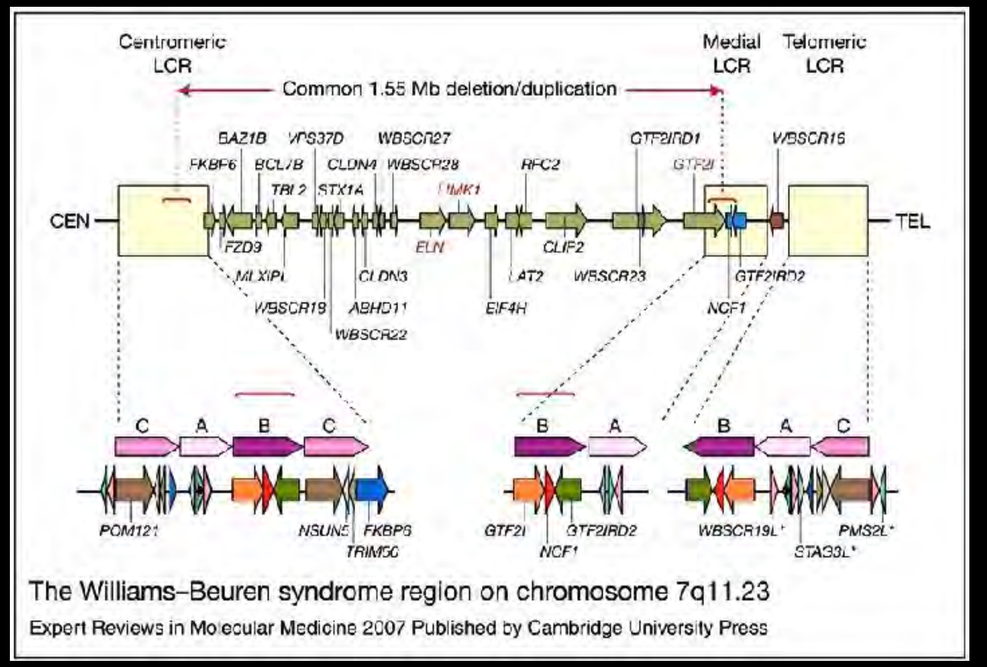




What everybody knows !

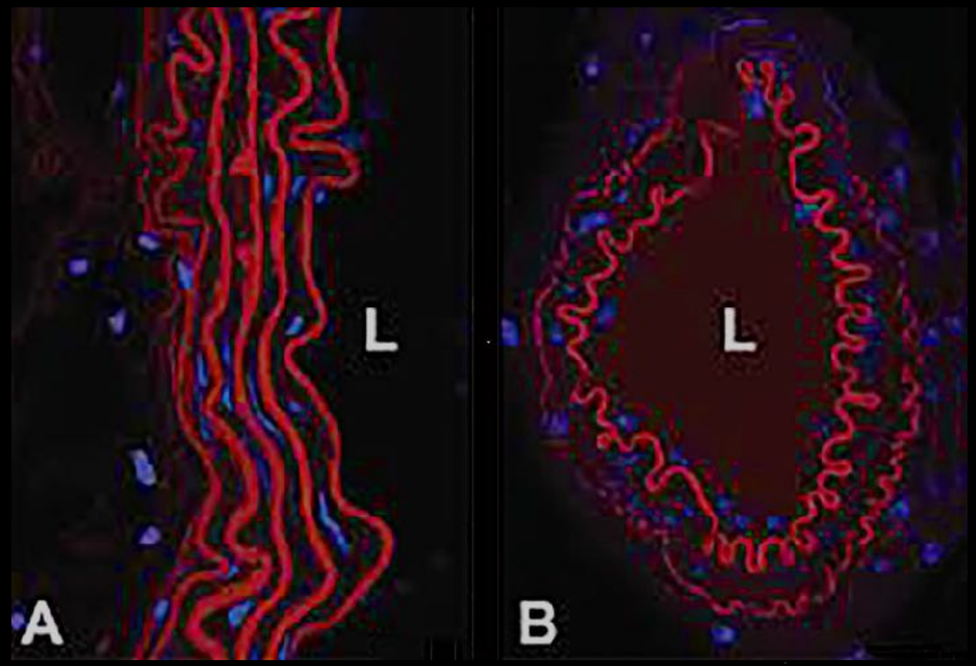








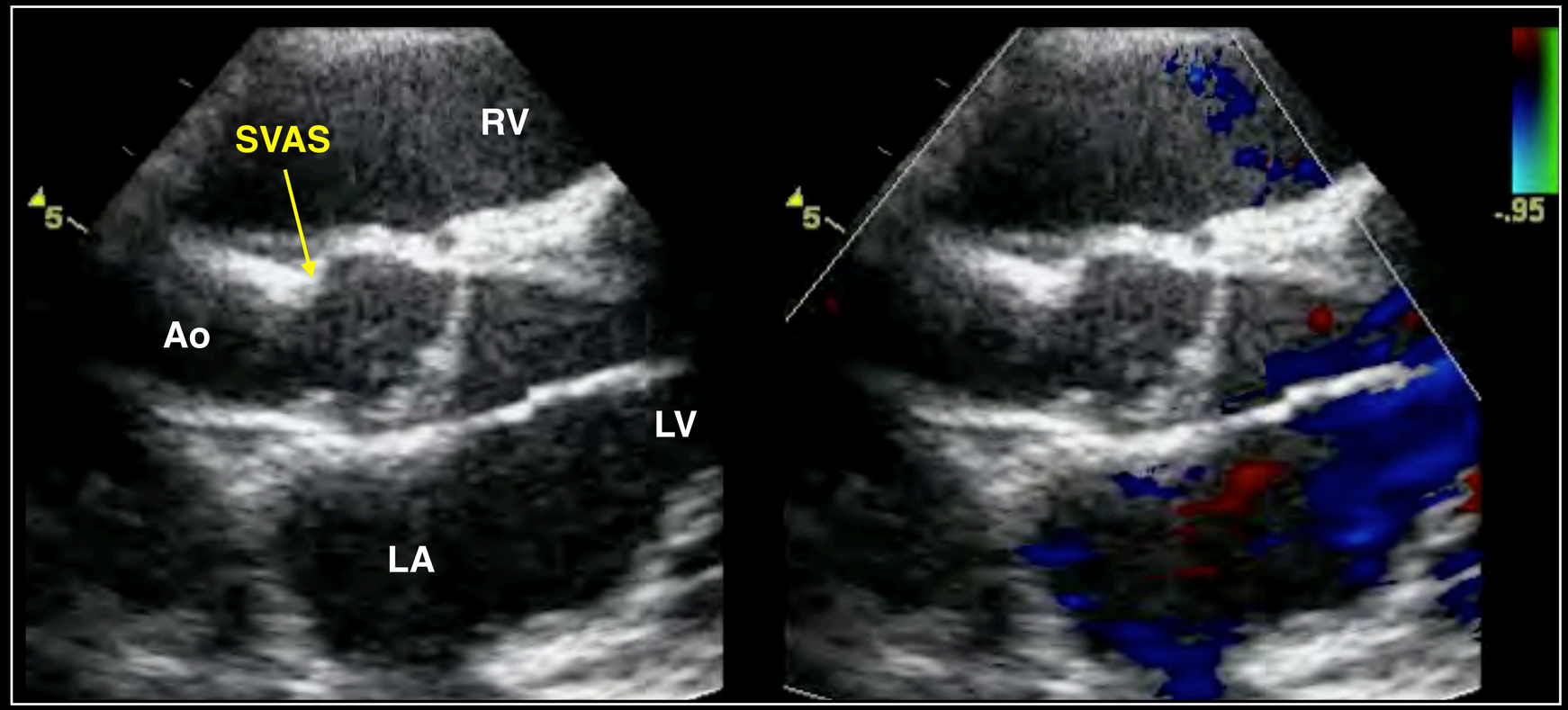


The Williams–Beuren syndrome region on chromosome 7q11.23

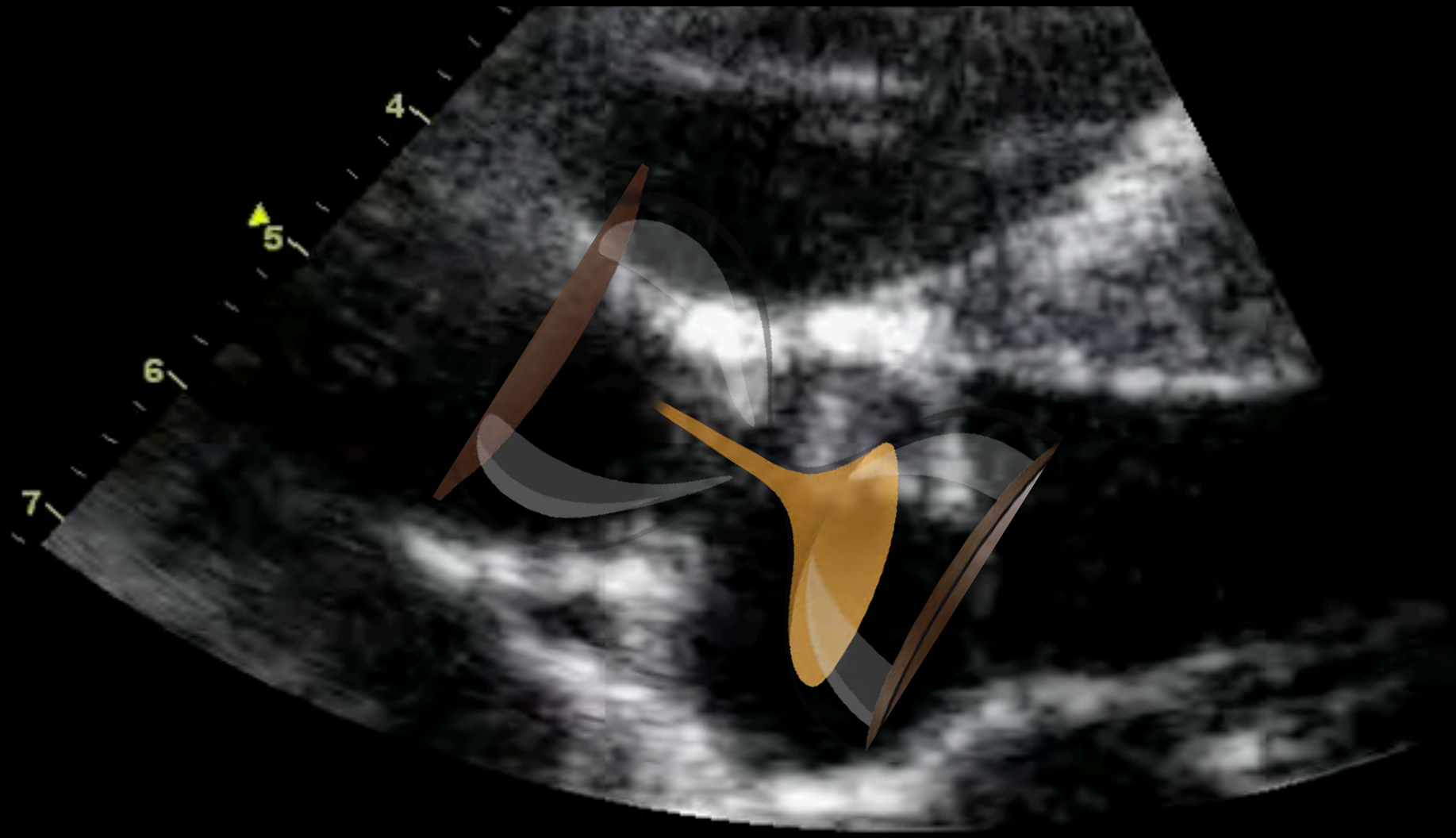
Expert Reviews in Molecular Medicine 2007 Published by Cambridge University Press



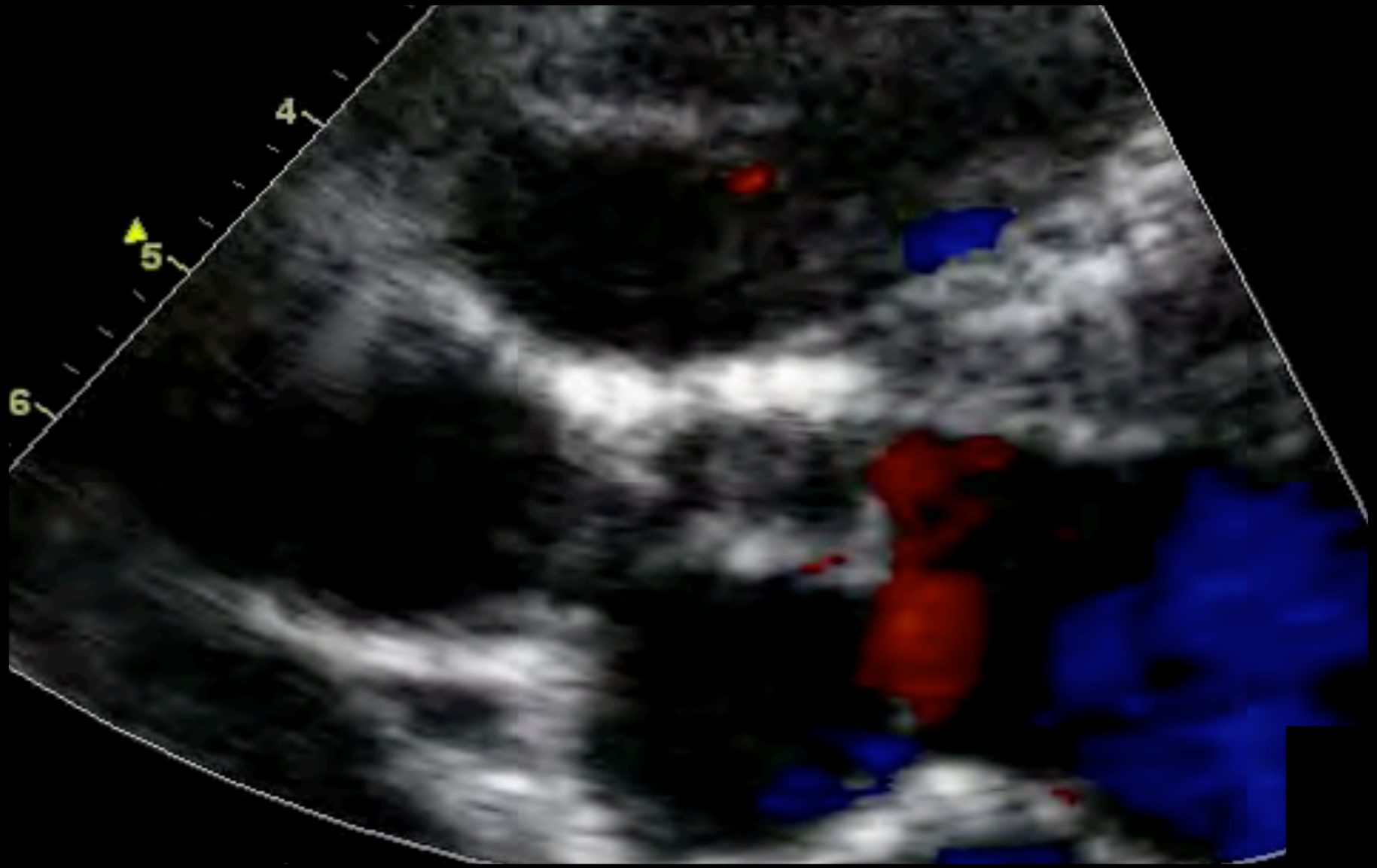
Williams-Beuren syndrome


SVAS
RV
Ao
LV
LA
5
5
-.95

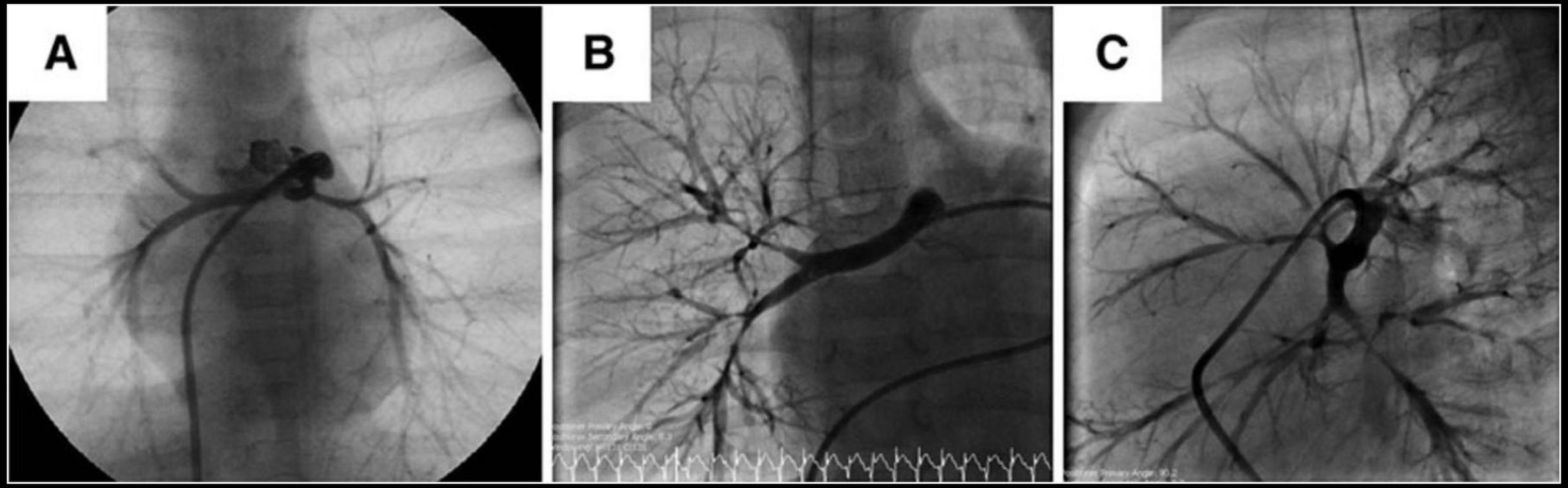
Supravalvar aortic stenosis



Supravalvar aortic stenosis

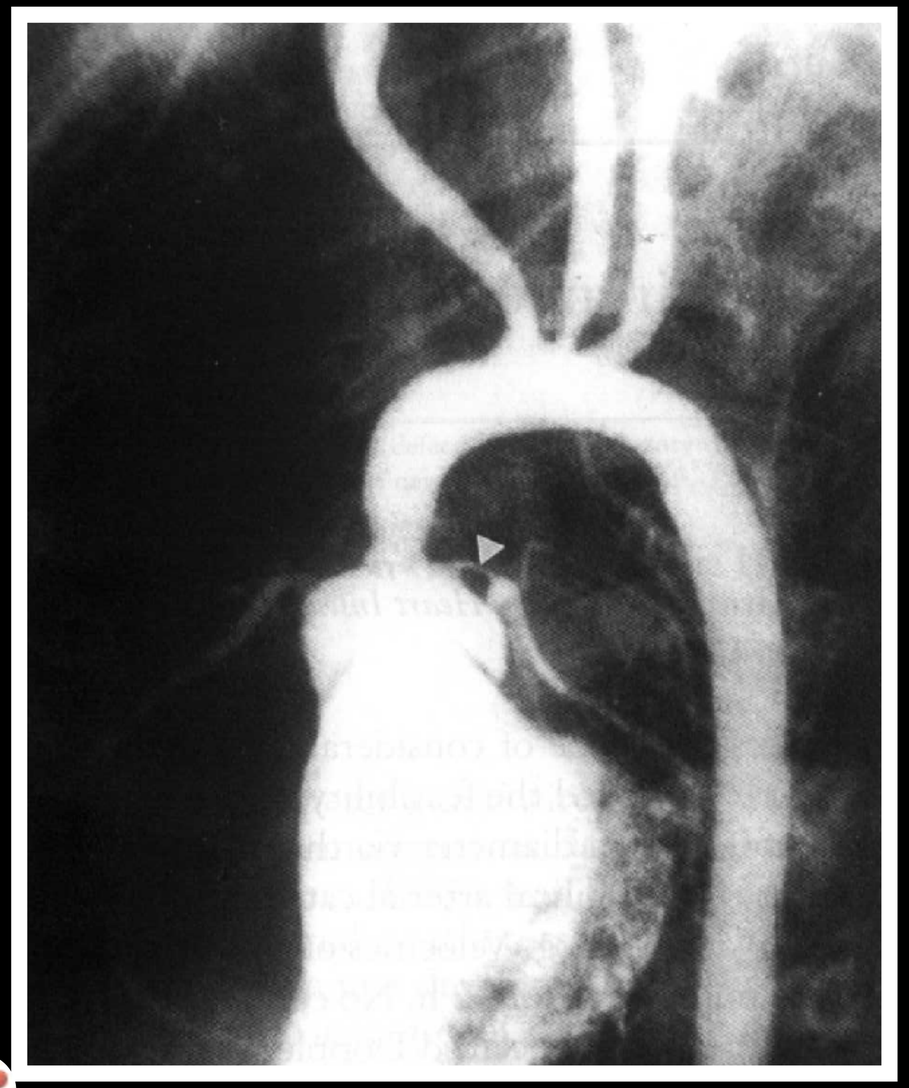


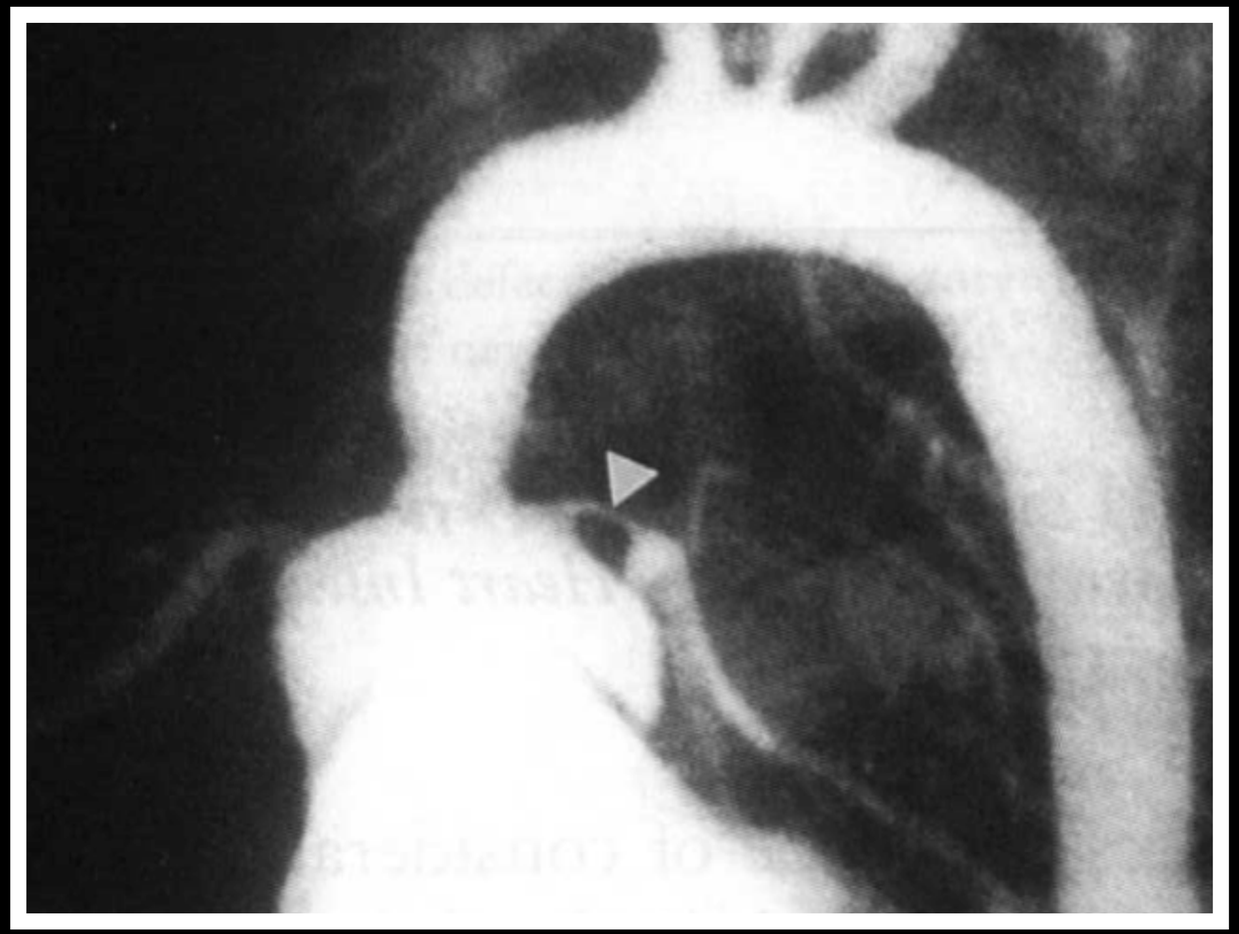
Peripheral pulmonary arterial stenosis in Williams syndrome

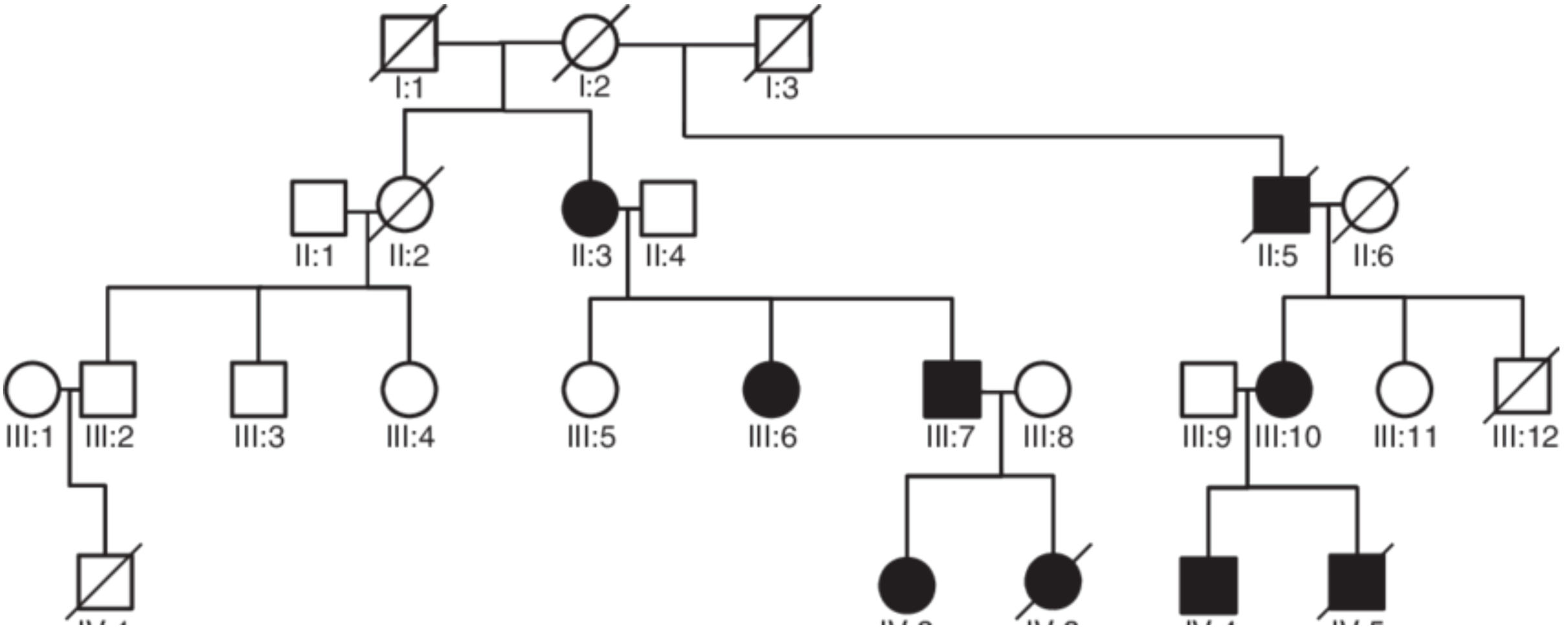


Collins R T Circulation. 2013;127:2125-2134

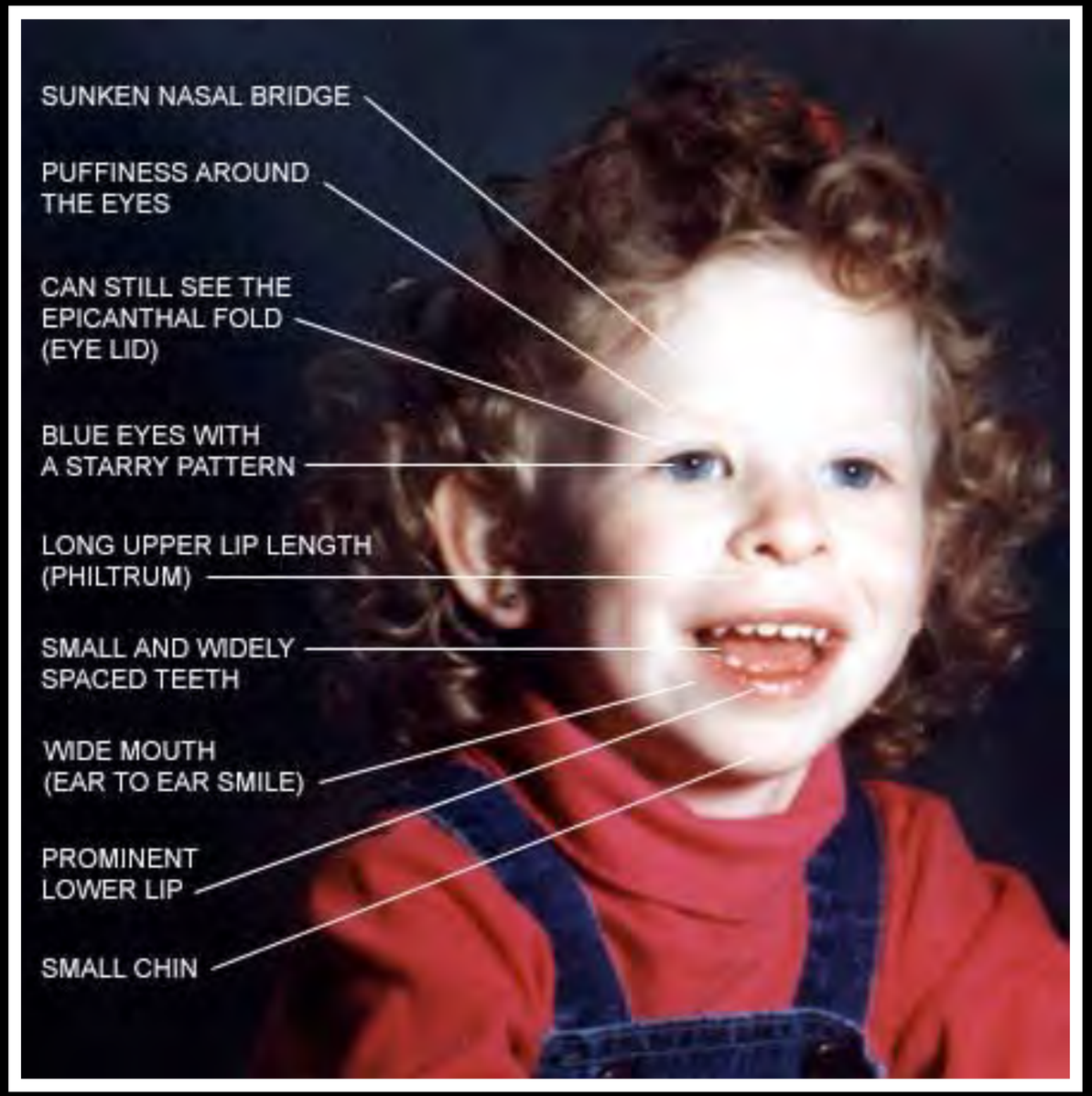
Coronary artery abnormalities in WS

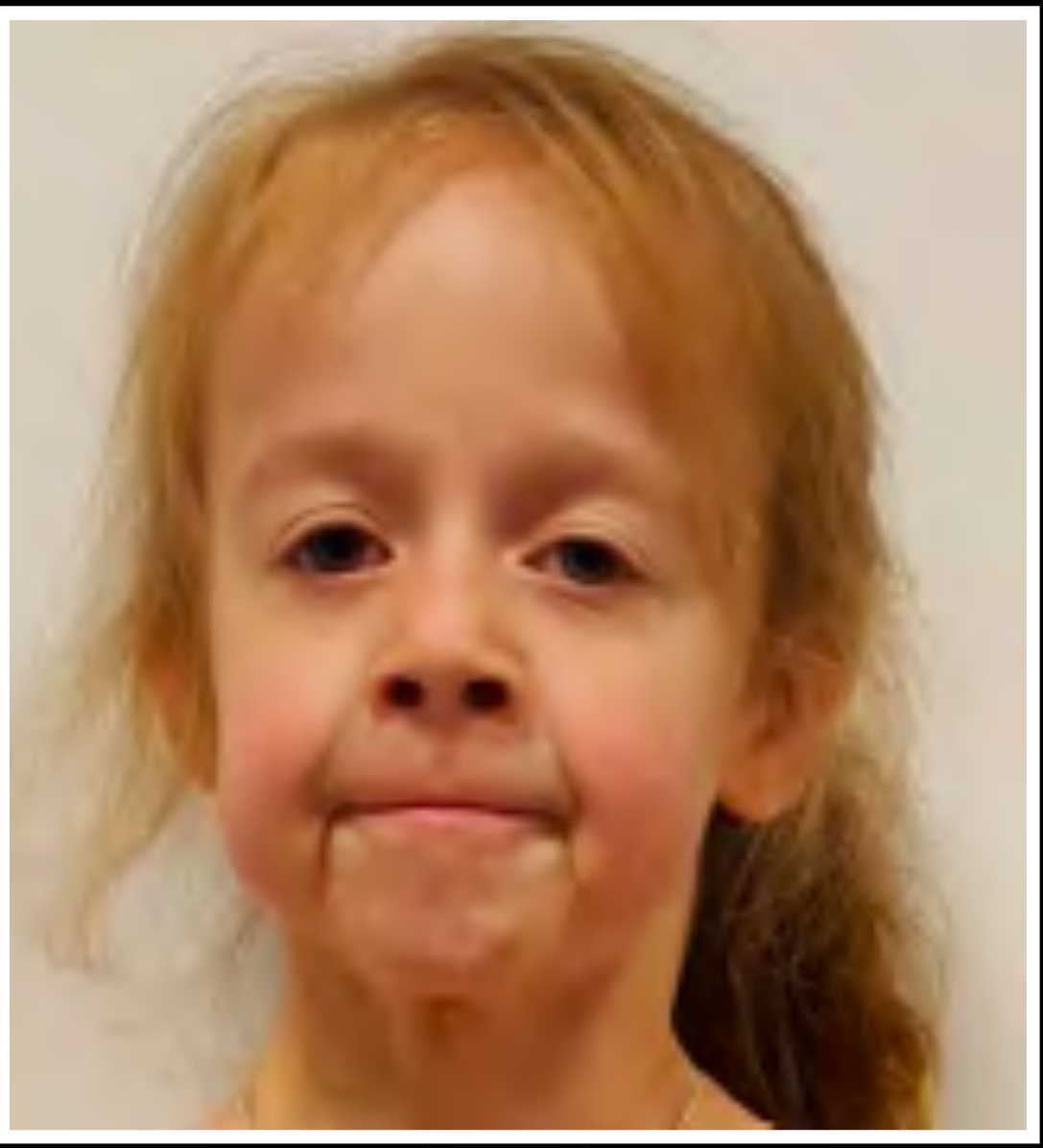




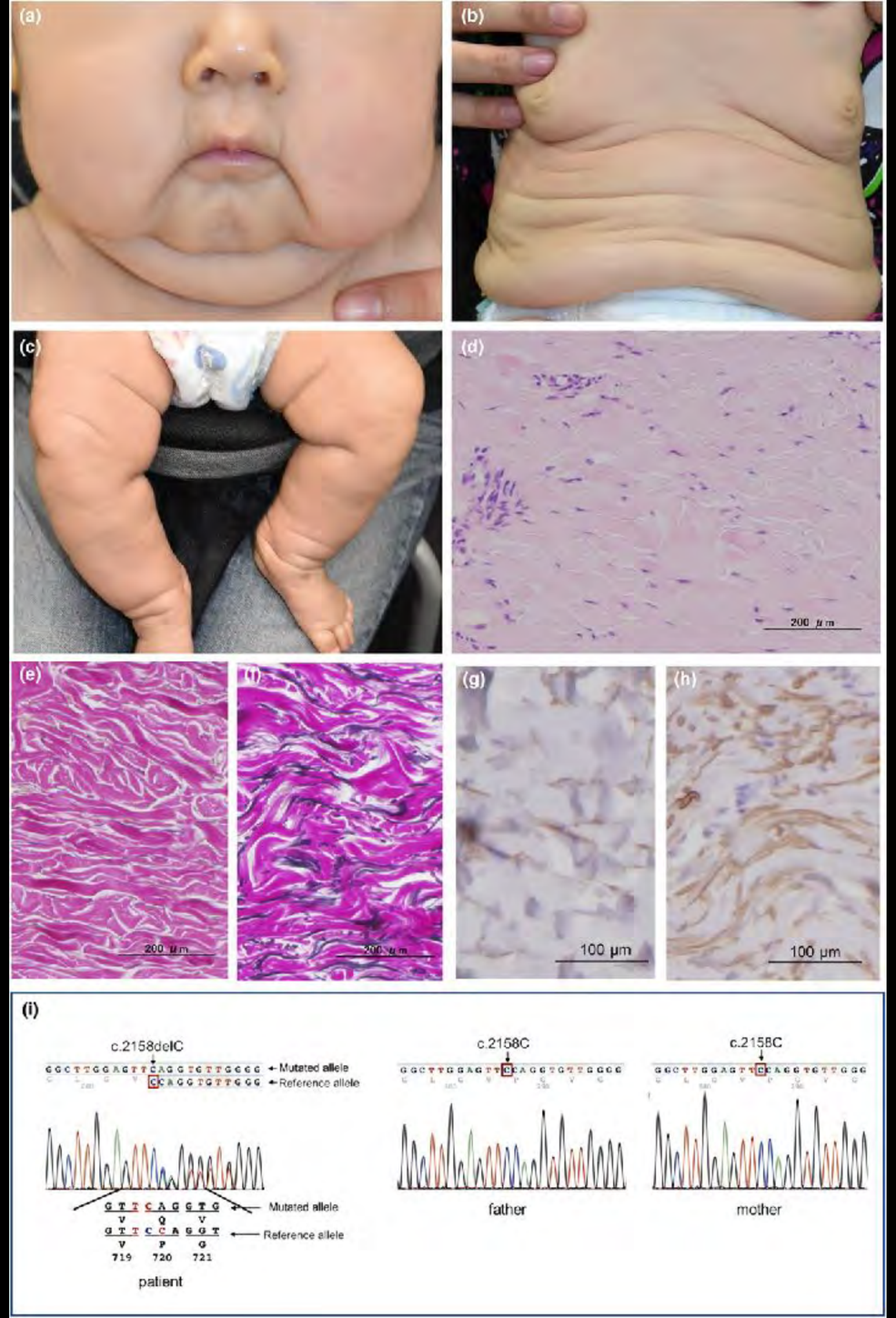


Elastin mutation pedigree

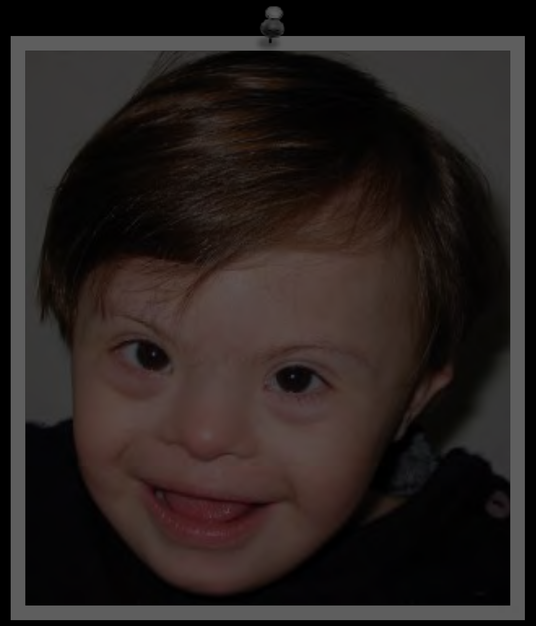
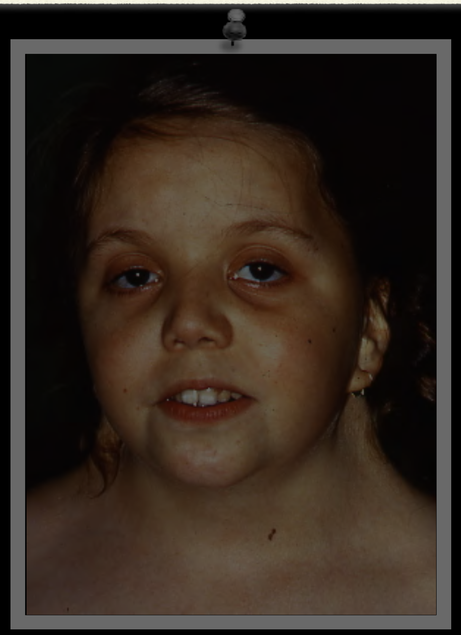
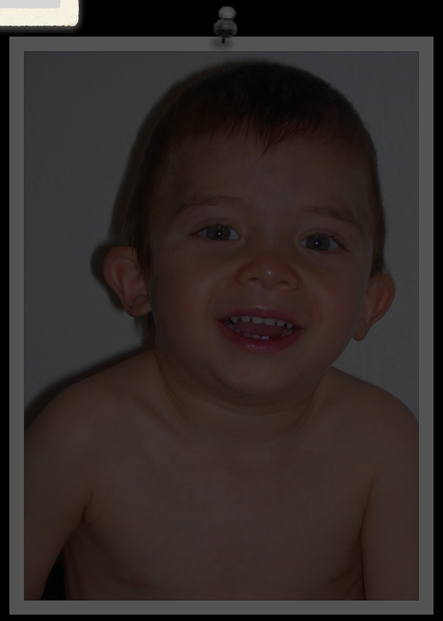
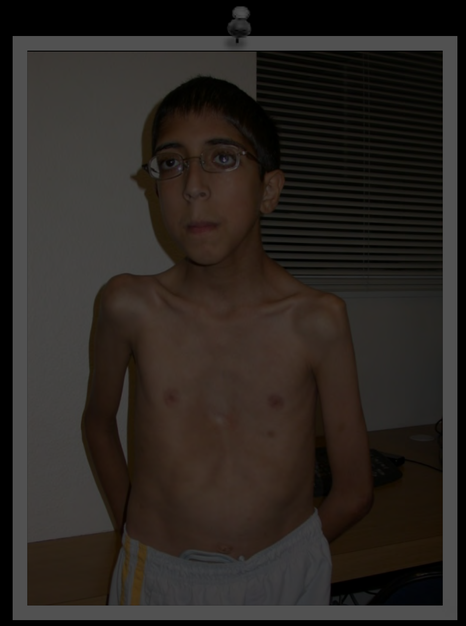
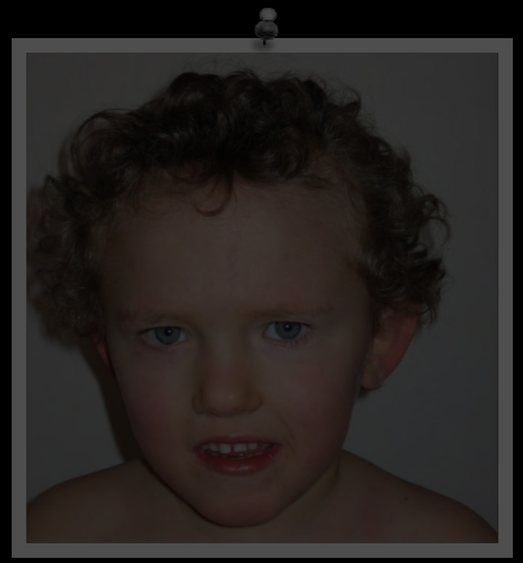
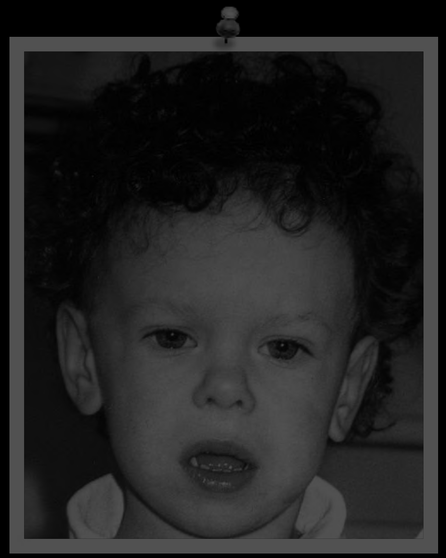
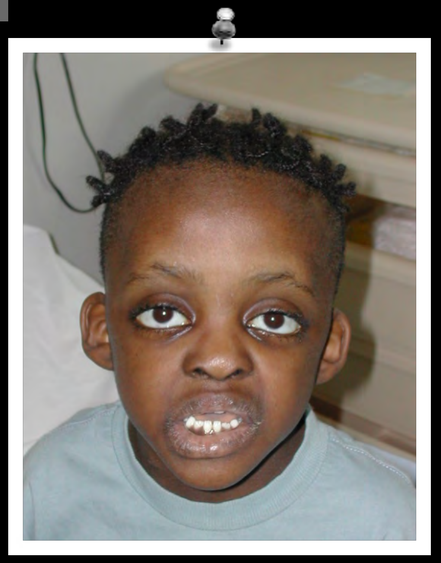

SUNKEN NASAL BRIDGE
PUFFINESS AROUND THE EYES
CAN STILL SEE THE EPICANTHAL FOLD (EYE LID)
BLUE EYES WITH A STARRY PATTERN
LONG UPPER LIP LENGTH (PHILTRUM)
SMALL AND WIDELY SPACED TEETH
WIDE MOUTH (EAR TO EAR SMILE)
PROMINENT LOWER LIP
SMALL CHIN



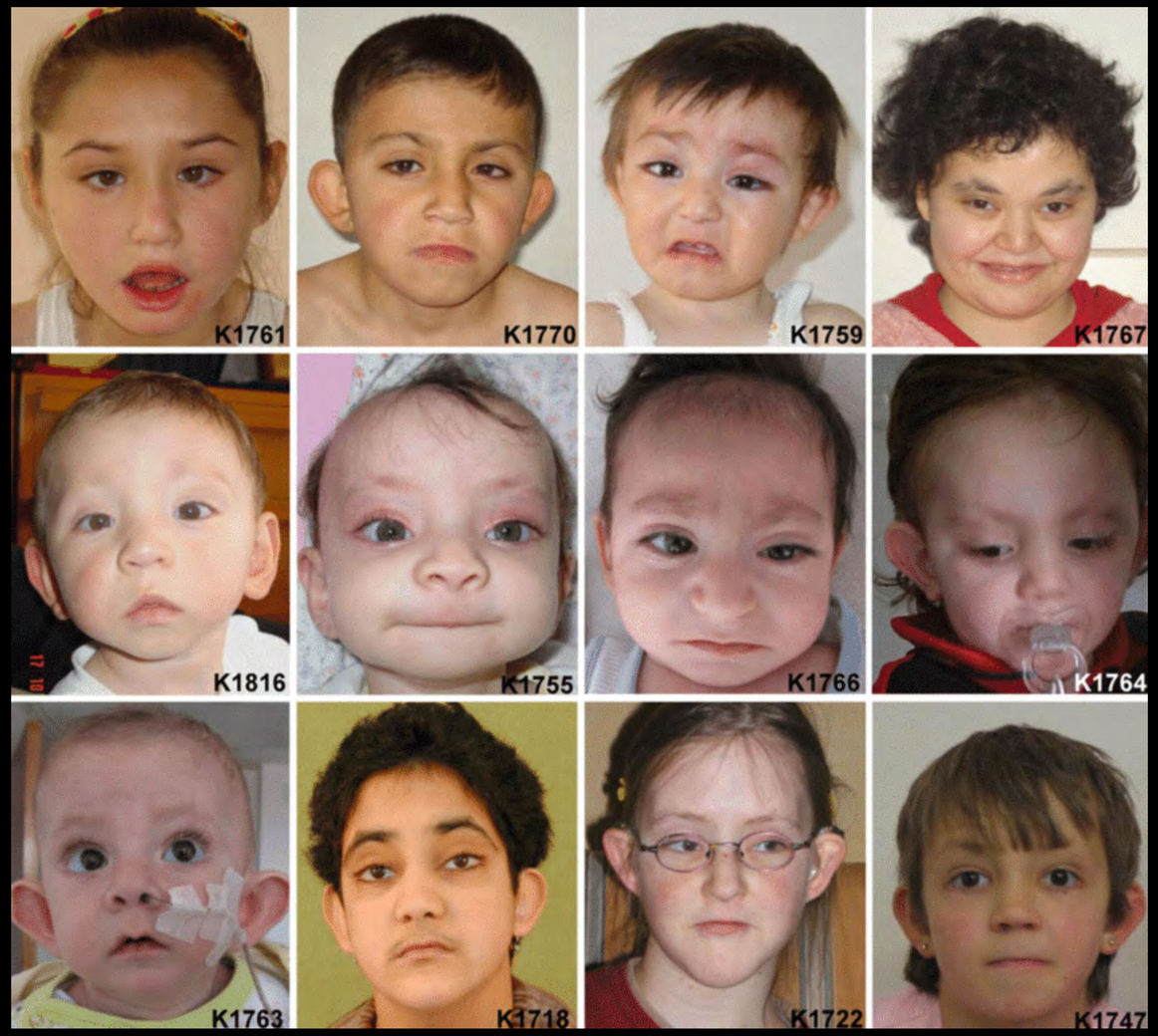
Cutis laxa - Elastin gene mutation

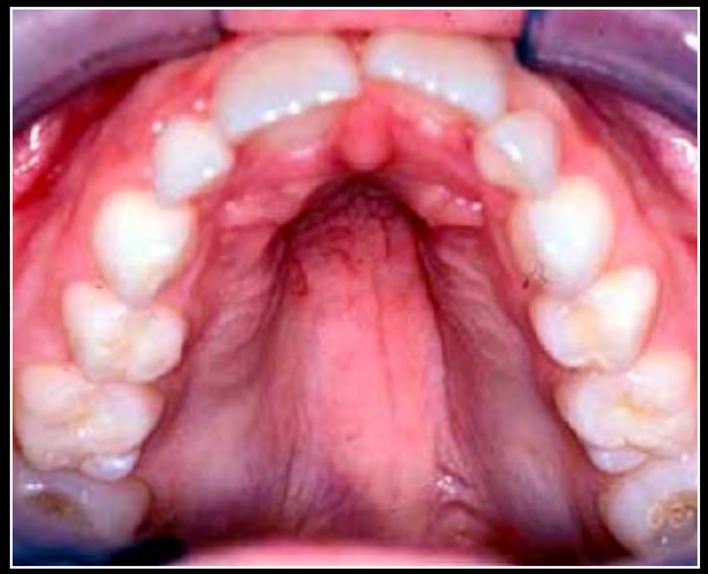


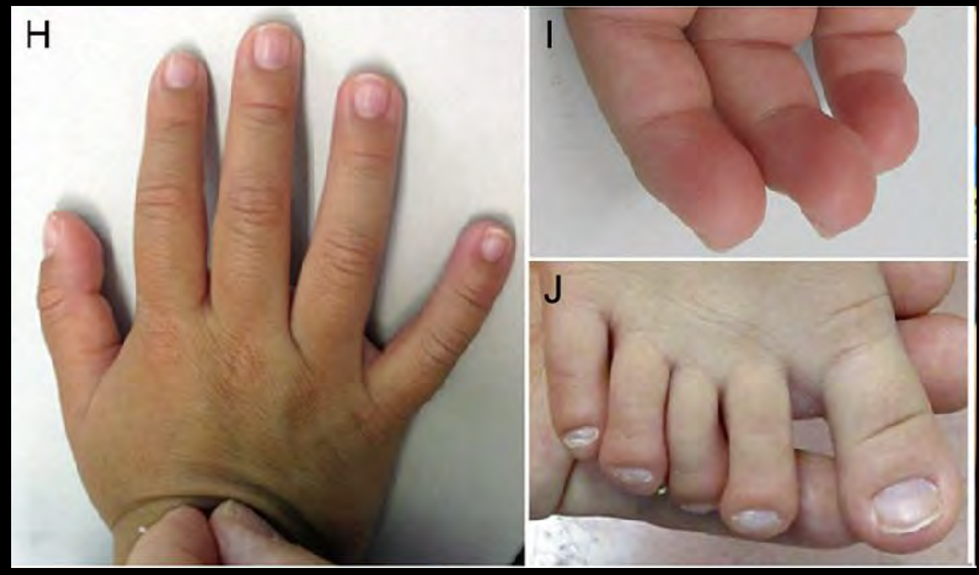
What everybody knows !


Kabuki syndrome - Phenotype







Variants in genes *KMT2D* and *KDM6A* are found in 70% of patients with KS Variants in HNRNPK in others

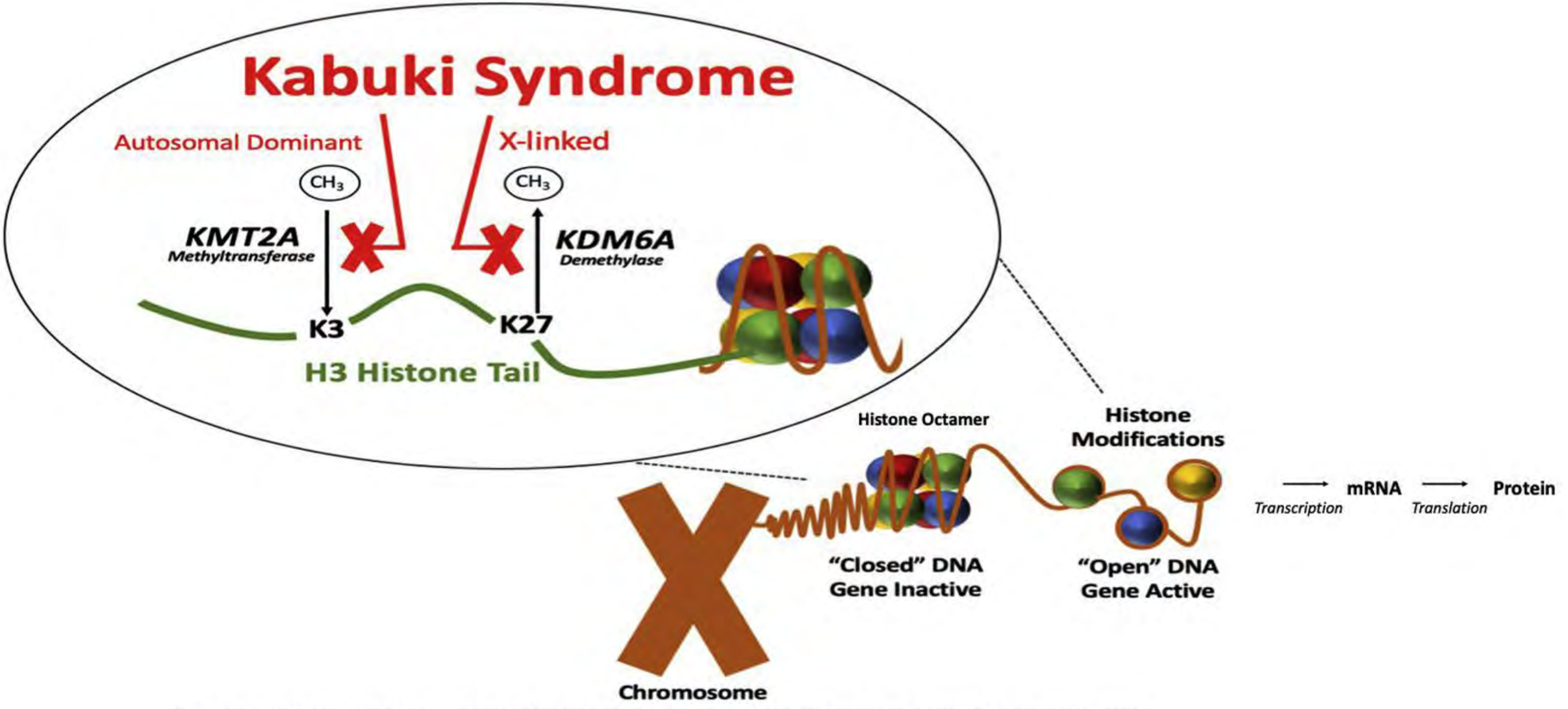
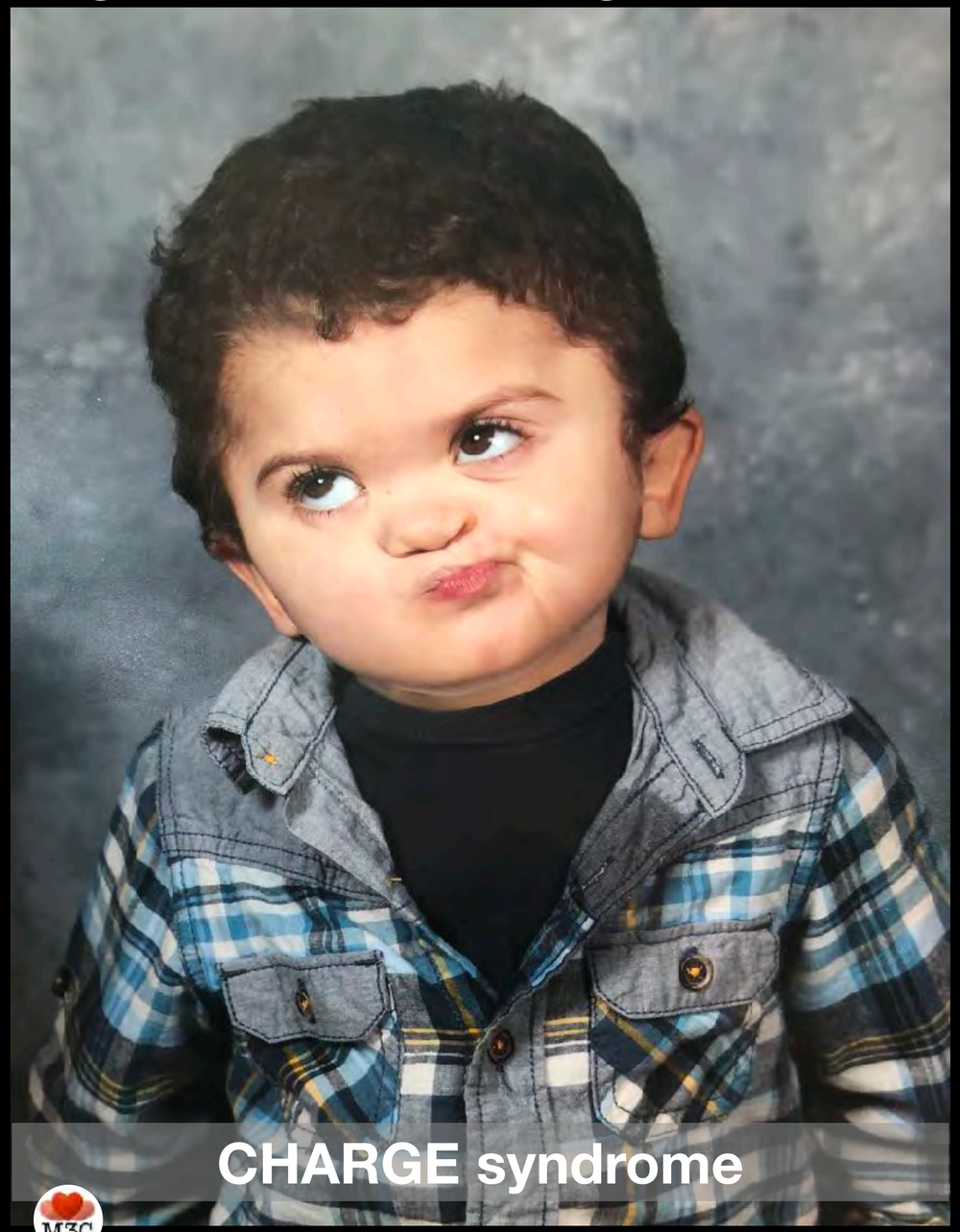


Figure 1. A general scheme of the epigenetic roles of KMT2A and KDM6A in histone modification that results in activation of gene transcription.

Epigenetics and congenital heart diseases

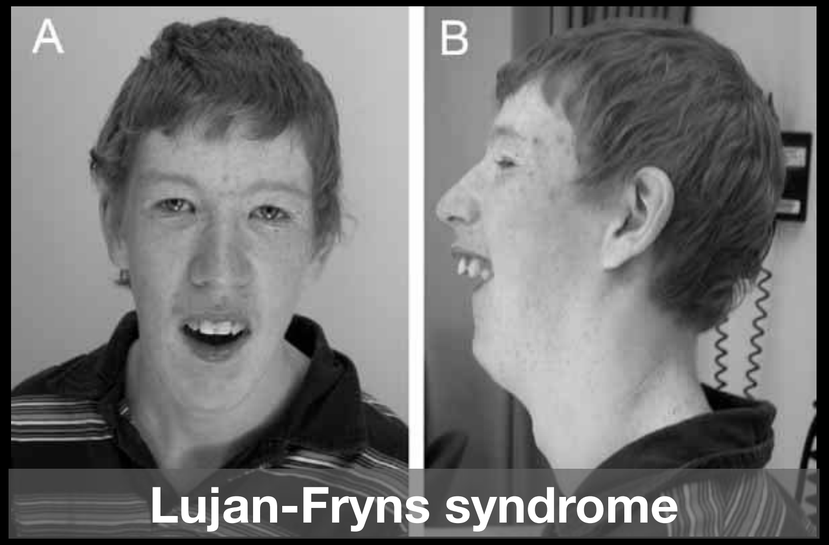
Linglart L & Bonnet D. Epigenetics in congenital heart diseases. JCDD 2022



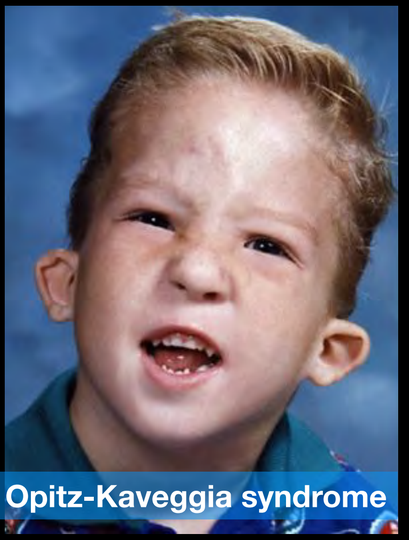
CHARGE syndrome

Cornelia de Lange syndrome

Ohdo syndrome



Lujan-Fryns syndrome



Opitz-Kaveggia syndrome

What are the lessons from this short overview of a few syndromes ?

- Trisomy 21 + modifying genes causes CHD : polygenic mechanisms
- *RASopathies : common genetic path and multiple cardiac phenotypes*
- Marfan and related syndromes : Similar cardiac phenotype - different genes in the same path and countertype phenotype in the same path.
- *22q microdeletion syndrome : Altered developmental mechanism and variety of defects with the same developmental field*
- Kabuki and other epigenetic syndromes: role of epigenetic (age, environment)

Thank you