

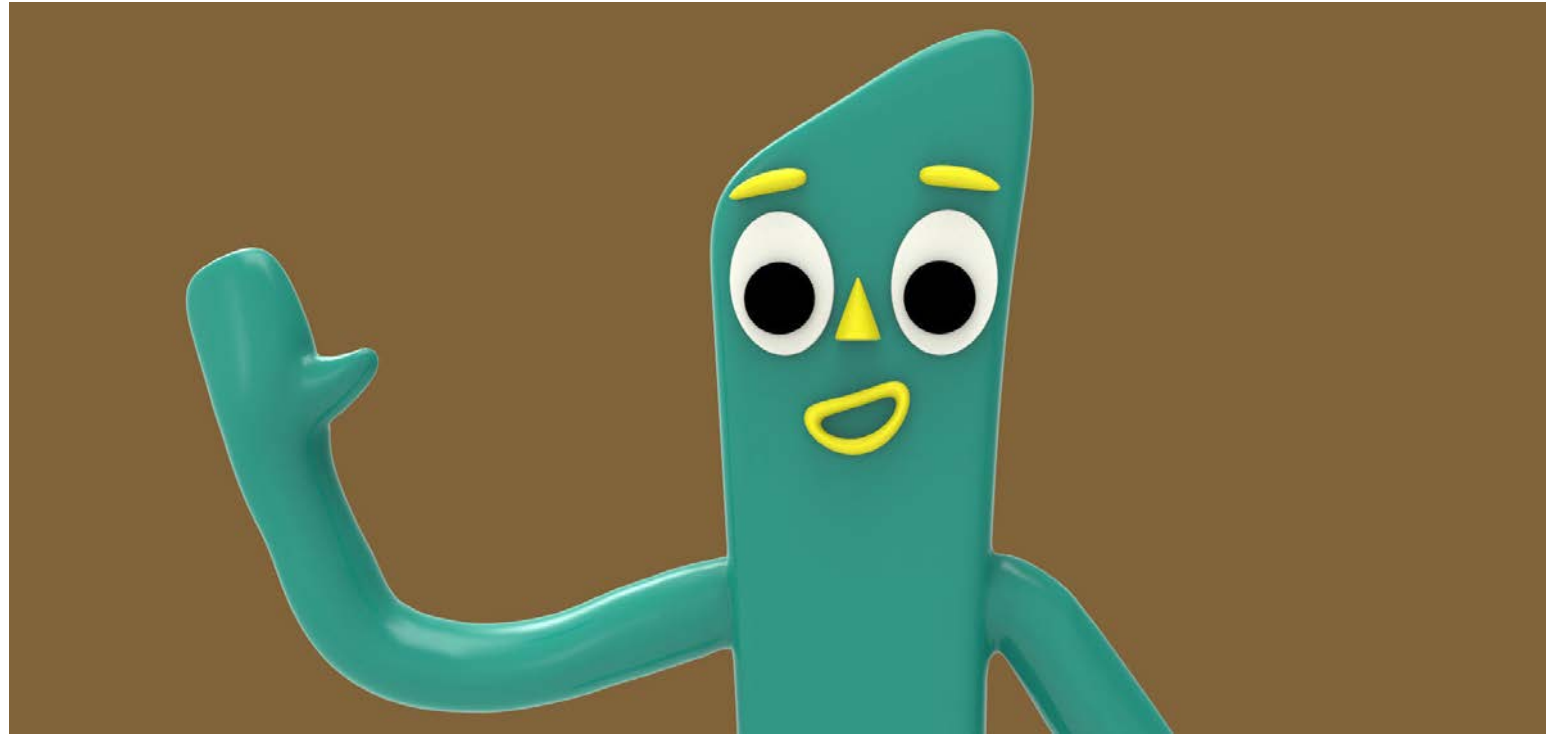
Inheritable Connective Tissue Diseases: Or It's Probably Not Marfan's

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4/23/2018



This pretty
much sums it
up.



Inheritable Connective tissues diseases

- A homogenous collection of varied syndromes with a similar phenotype; HYPERMOBILITY
- Typically caused by a defect in the genes required for structural proteins i.e. elastin or collagen
- I suspect that they are wildly under diagnosed at large.



List of stuff

- Ehlers-Danlos Syndrome
 - Hypermobility type, vascular, classic and mixed
- Loeys-Dietz Syndrome
- Peyrionie's Disease (giggle)
- Stickler Syndrome
- Congenital Contractural Arachnodactyly (Beel's)
- Bicuspid aortic valve (?)
- Benign Familial Hypermobility
- Marfan's Syndrome

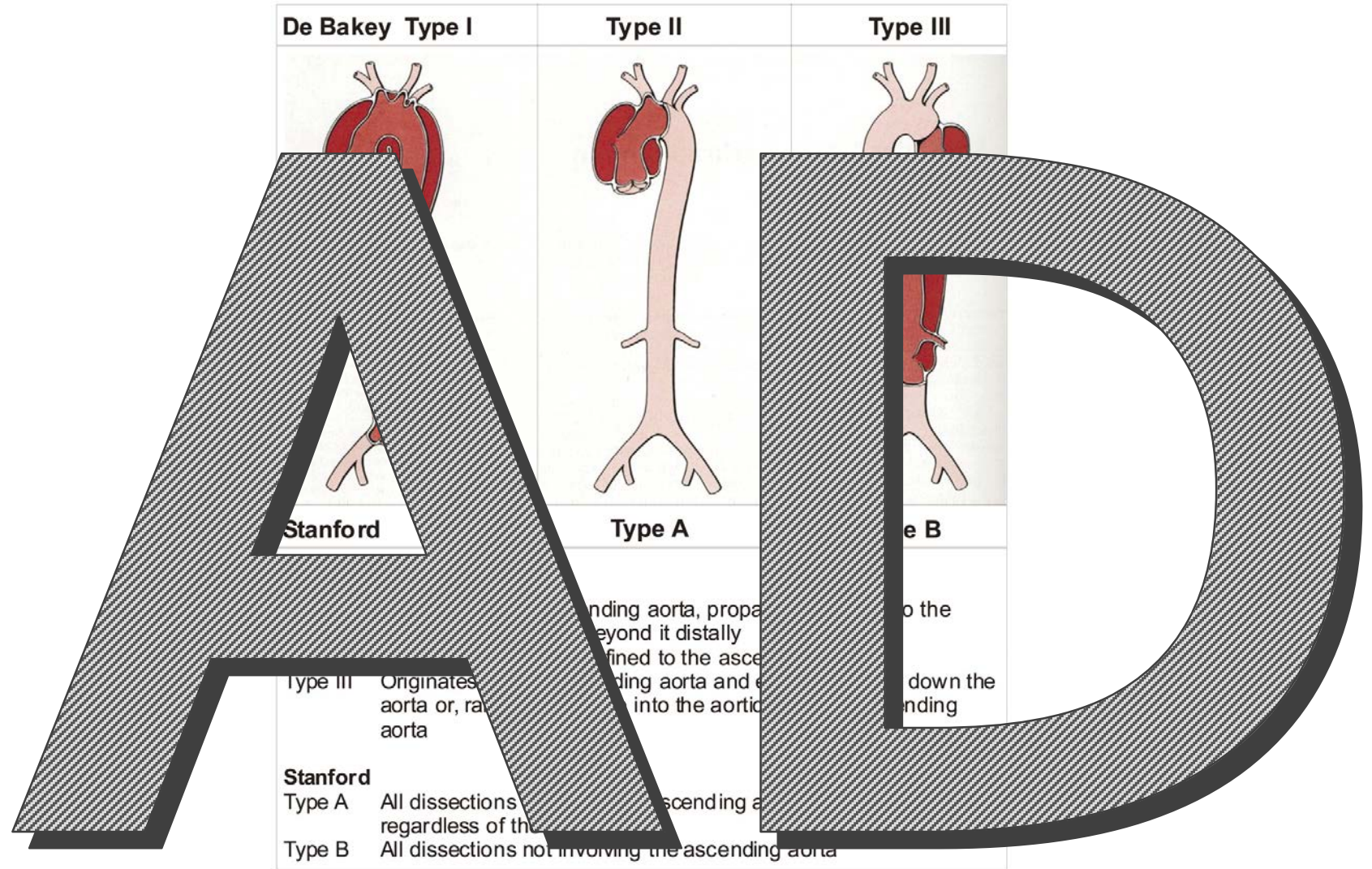
Why do cardiologists care about connective tissue diseases

- Because the heart and vessels are made of connective tissues too!
- There can be significant cardiac manifestations
 - Valve dysfunction
 - Cardiac Dysfunction
 - Arrhythmia
 - ...And of course aortic dissection



What is aortic

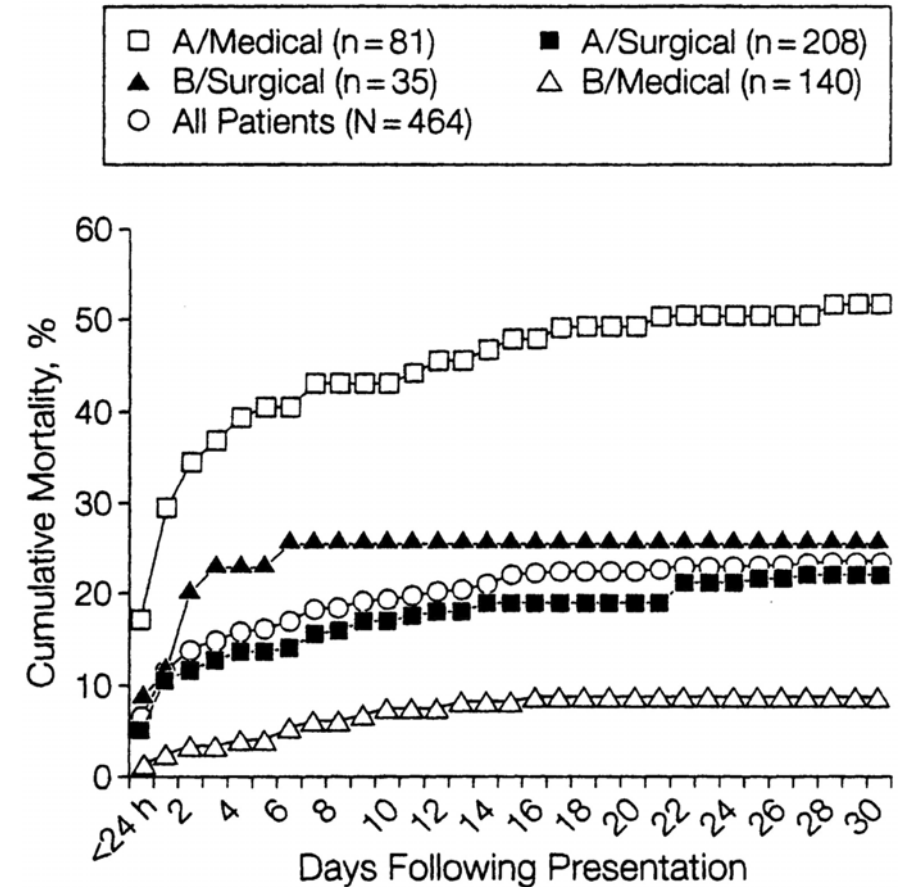
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Okay sure, but
how bad is it?

Really it's pretty bad

Guess which type of aortic
dissection our connective tissue
disease patients are at risk for?

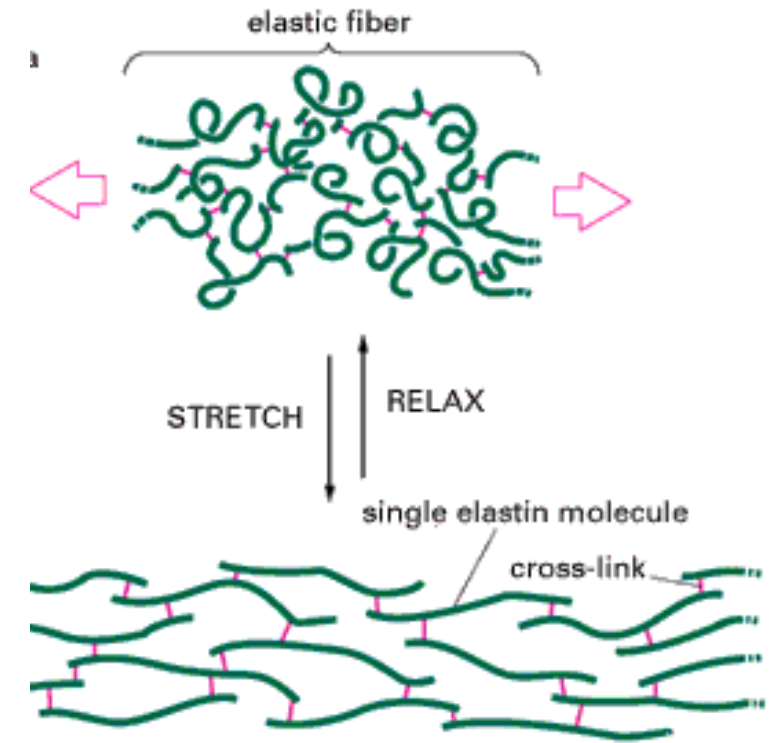
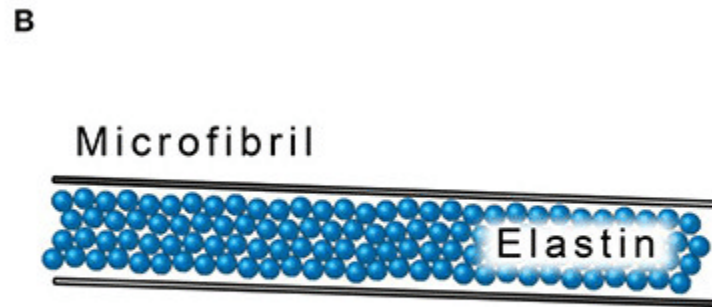
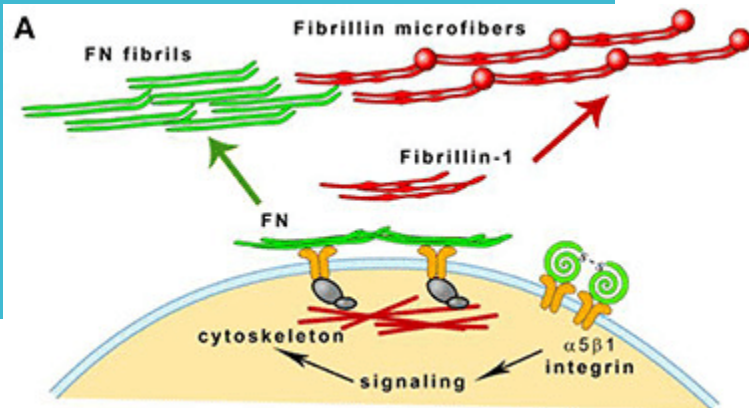


At baseline...

- Aortic dissections occur at roughly 5-30 million people a year.
- Untreated Marfan's patients carry a risk of roughly 0.8%/year of acute dissection.
- When we replace the roots ahead of time we can expect < 2% mortality on the 30 day prospectus.
- We really want to catch these patients before they have problems.

Fibrillin-1

- Extracellular matrix protein
- The core building block of microfibrils that are used with elastin fibers
- Elastin is the stringy aspect of our tissues.



Kinsey et al 2008

This is the offending gene in Marfans

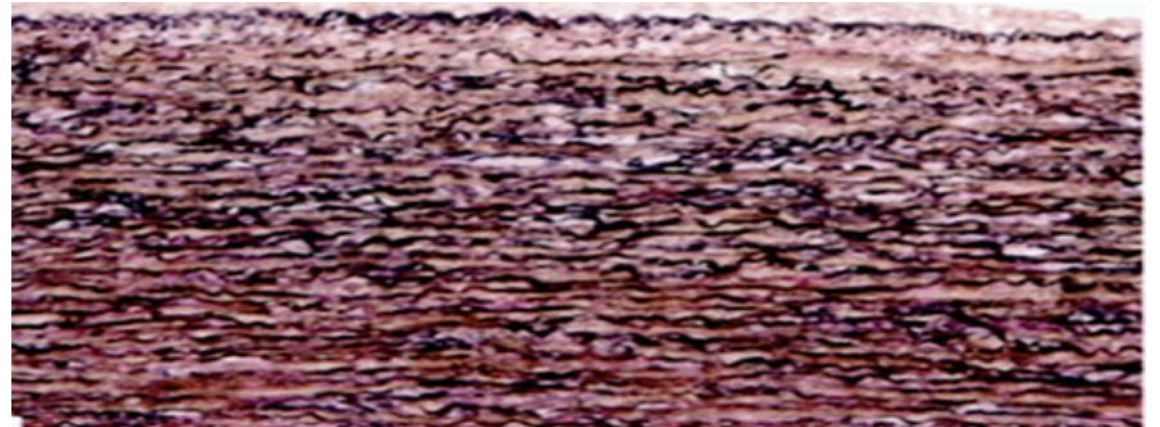
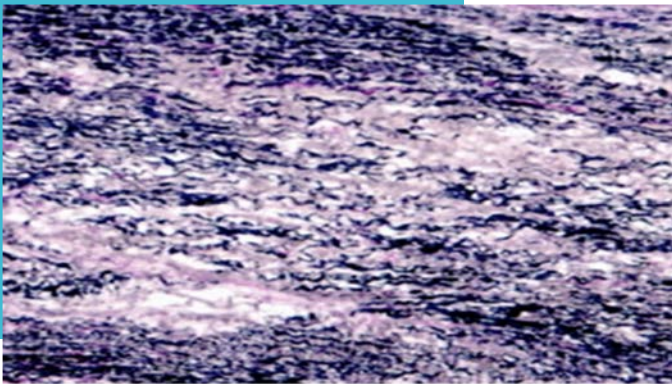
- Our understanding of this gene accounts for the
 - Hypermobility
 - Marfan Phenotype
- Doesn't really explain
 - Muscle abnormalities
 - Long bone overgrowth
 - Abnormal subcutaneous fat

TGF- β

- Normally important
 - Regulates cell cycle
 - Regulates apoptosis
 - Causes cell differentiation
 - Plays a critical role in extracellular structure

Some cool physiology

- Fibrillin grabs TNF-B
- Defective fibrillin doesn't
- Mice who received TGF-B blocking antibodies didn't develop the stigmata of mitral valve disease or aortic root dilation.



Which brings
us to...

- Marfans
 - Arachnodactyly
 - Tall and thin
 - Scoliosis
 - Pectus excavatum/carianatum
 - Hypermobility
 - Pes Planus
 - Poor tooth alignment
 - Stretch marks



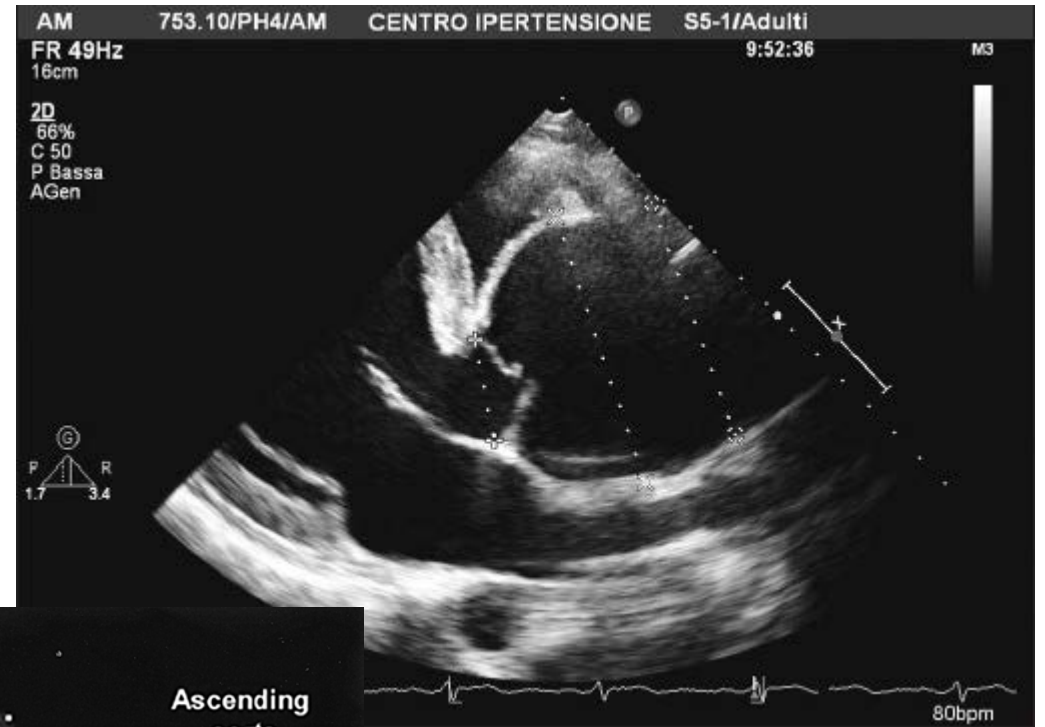
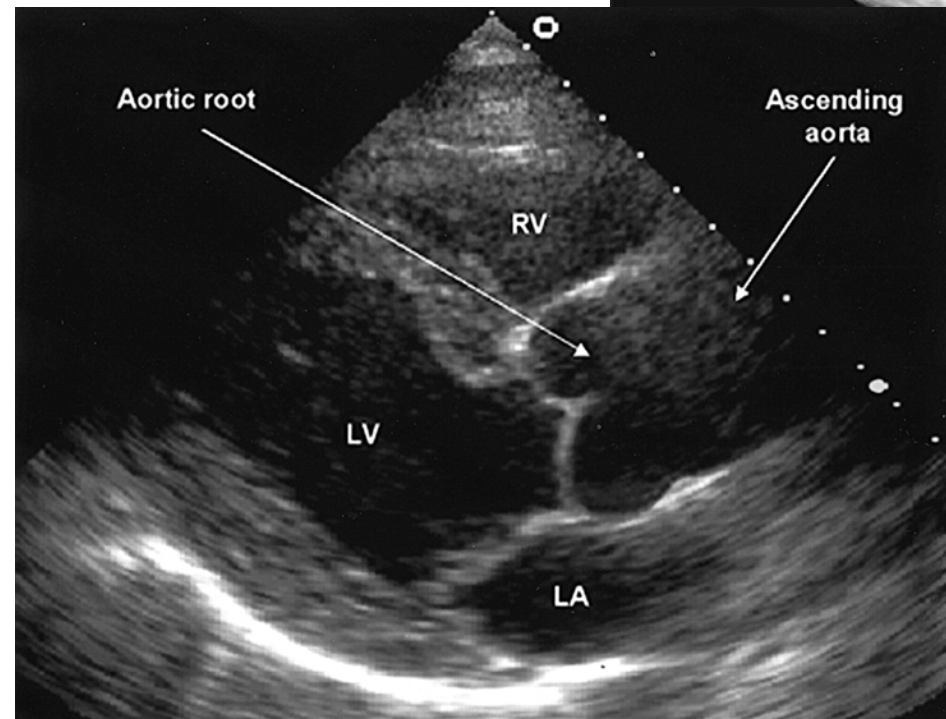
Are just the
things
diagnostic?

NO

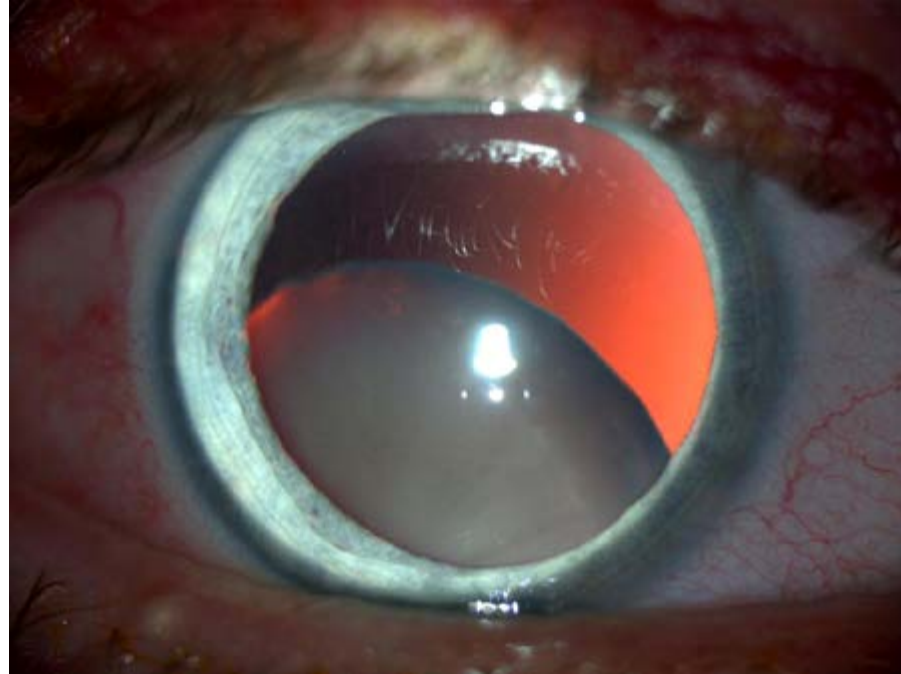
More specific findings

- Aortic dilation
- Ectopia Lentis
- FBN1 Deletions
- Wrist and thumb sign
- Hindfoot deformity
- Plain flat foot
- Spontaneous Pneumothorax
- Dural Ectasia
- Protutio Acetabulae
- Scoliosis
- Reduced elbow extension
- Skin Striae
- Severe Myopia
- Mitral valve prolapse
- Increase wingspan/reduced upper segment ratio

Aortic Root dilation



Ectopia Lentis



Wrist and thumb sign



Hindfoot deformity

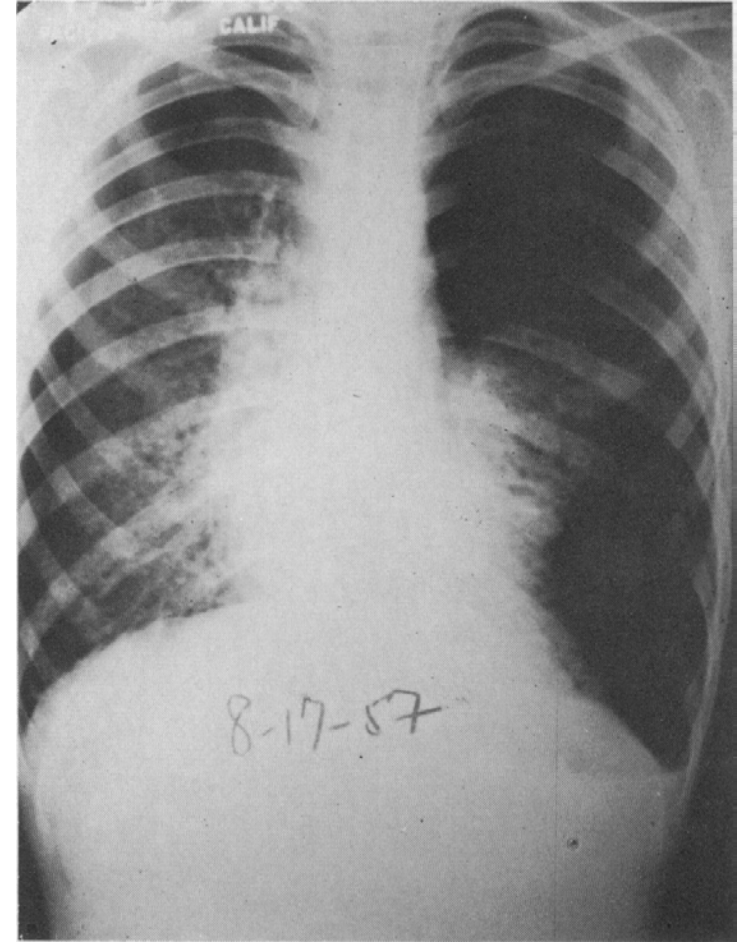
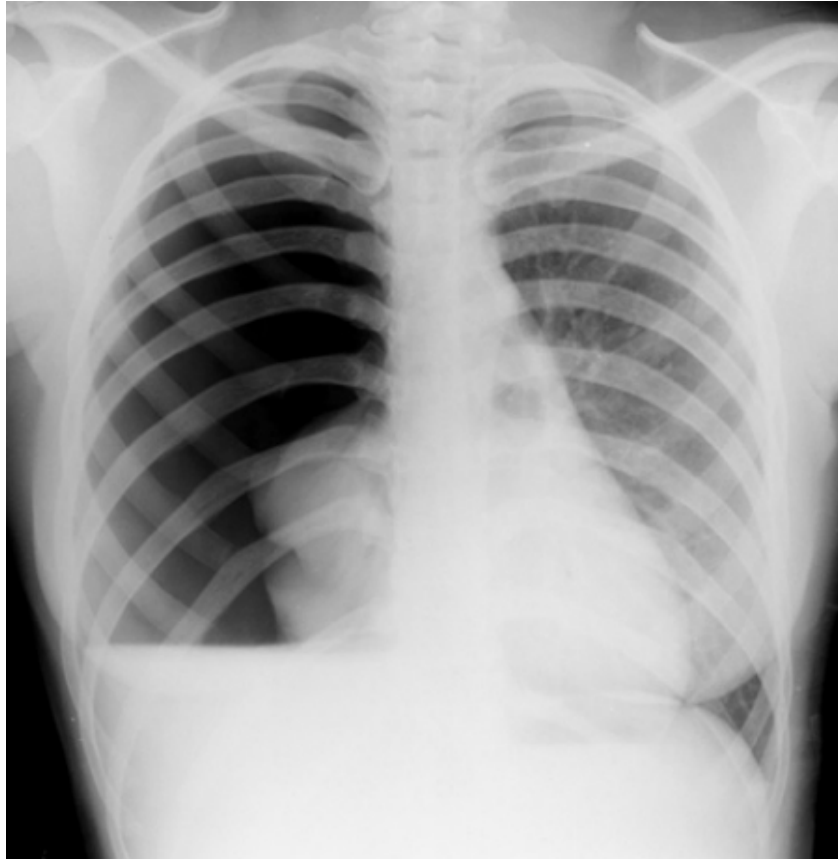


PES PLANUS

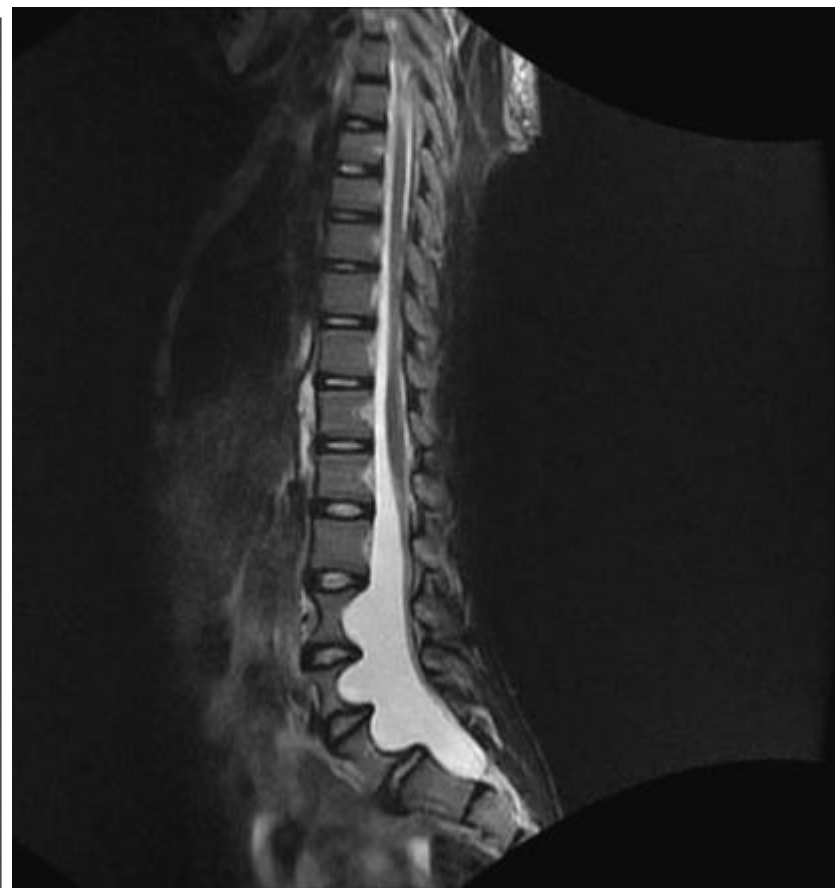
(RHA / American College of Rheumatology)



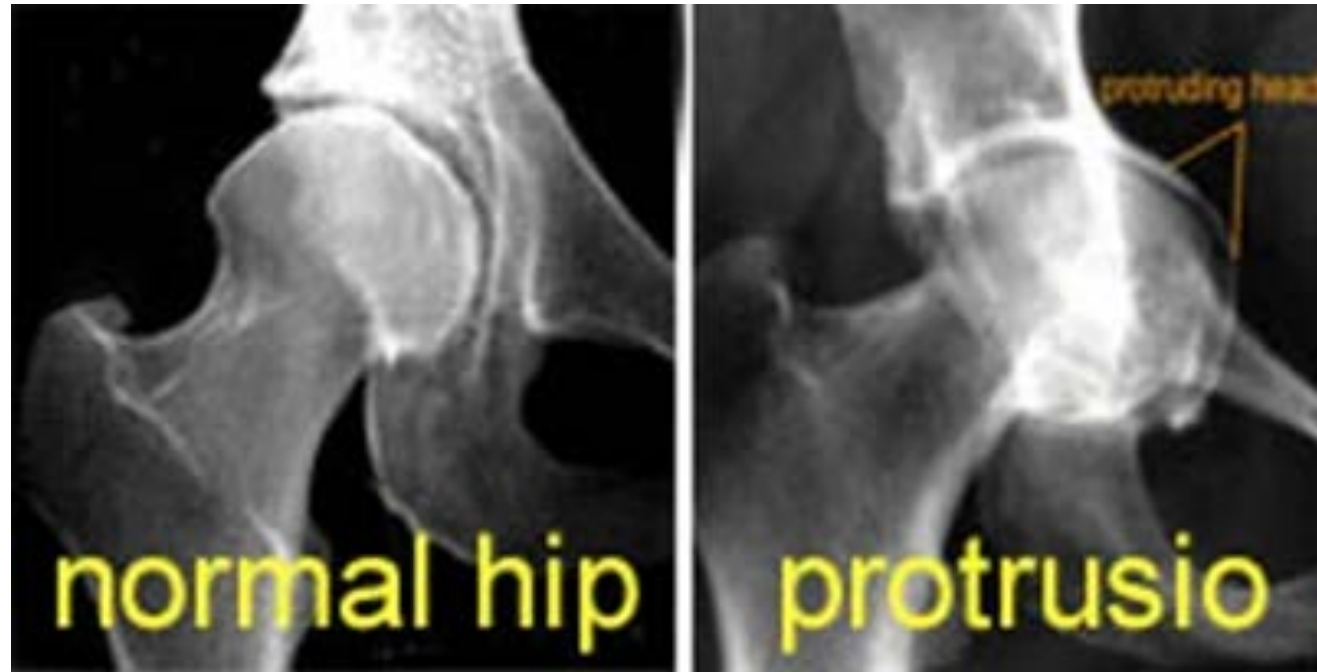
Spontaneous Pneumothorax



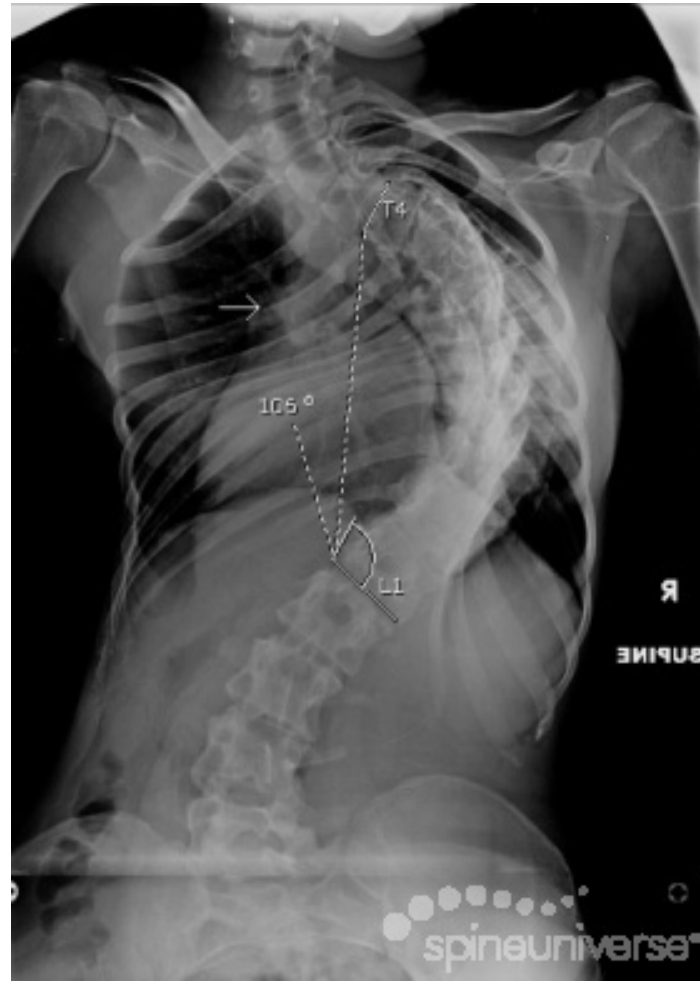
Dural Ectasia



Protrusio Acetabuli



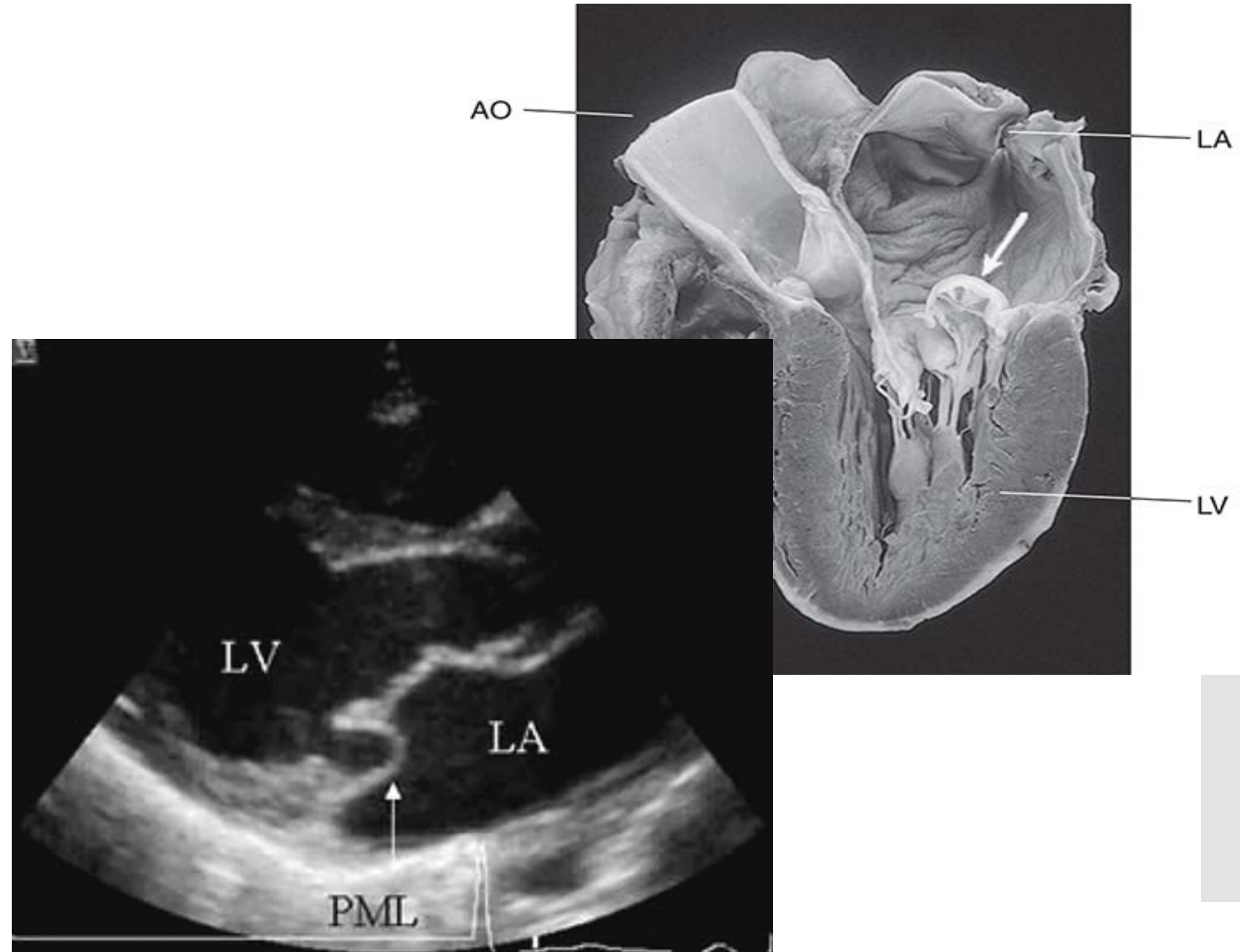
Scoliosis



Stretch marks



Mitral Valve prolapse



Wingspan



Ghent criteria

- In the absence of family history
 - 1. Aortic root dilation AND Ectopia Lentis
 - 2. Aortic root dilation AND an FBN1
 - 3. Aortic root dilation AND 7 pts on the the stigmata scale
 - 4. Ectopia Lentis AND an FBN1 mutation

THAT'S

With a family
history

- Ectopia Lentis
- 7 points on the scale
- Aortic root dilation (degree depends on age)

IT

So what about
people who
don't meet
criteria

- They probably have a different disease

Loeys-Dietz

- Positive for aortic root enlargement
- Skeletal stuff
- Dural Ectasia



What's different

- Craniosynostosis
- Arterial Tortuosity
- Cleft palate
- Club foot
- Cervical Spine instability
- No ectopia lentis
- Hypertelorism
- Easy bruising
- Translucent skin

Aortic Root
Size doesn't
matter for
these kids!

- They dissect at pretty much any size root



Familial Thoracic Aortic Aneurysm and Dissection

- Like Marfans without the stretchy stuff
- Unique findings:
 - Iris Flocculi
 - No ectopia lentis
 - No dural ectasia



Shprintzen-Goldberg

- Has
 - Mitral Valve prolapse
 - Systemic Findings
 - Myopia
- Unique
 - Craniosynostosis
 - Hypertelorism
 - Significant cognitive delay
 - Aortic root involvement rare
 - C1-C2 malformations

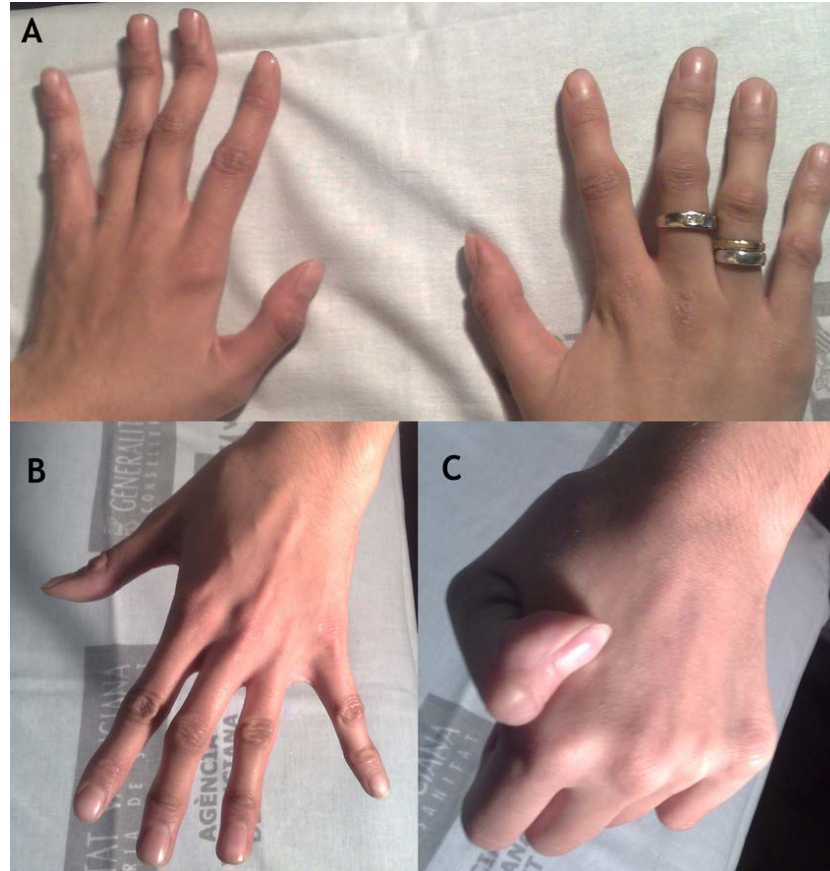


Homocysteinuria

- In common with Marfans
 - Ectopia Lentis!
 - Mitral Valve prolapse
 - Skeletal findings
- Unique
 - Developmental delay
 - Seizures
 - Thrombosis



Beals Syndrome



- Commonalities:
 - Mitral Valve prolapse
 - Aortic involvement
 - General skeletal stuff
- Differences:
 - Finger contractures
 - Crumpled ear
 - Motor delay
 - No dissection really

Stickler Syndrome

- Stickler Syndrome
 - Myopia, retinal detachment
 - Joint hypermobility
 - Scoliosis
 - Mitral Valve prolapse
- Differences:
 - Hearing involvement
 - Chorioretinal and vitreous degeneration
 - Orofacial involvement
 - Osteoarthritis as a prominent features



MASS Phenotype

- Mitral valve disease
 - Aortic Root Involvement
 - Skin findings
 - Skeletal Findings
 - Myopia
- Minimal risk of dissection
 - No ectopia lentis
 - No smoking gun genetically

Ehler's Danlos Syndrome

- Four “main” categories
 - Vascular type
 - Hypermobility type
 - Kyphoscoliotic Type
 - Classic Type
- Genetic causes
 - Collagen defects
 - Or PLOD₁

Vascular EDS

- Arterial, intestinal, uterine fragility
- Facial phenotype
- Translucent skins
- Easy bruising
- Dystrophic scars



Hindawi et al 2011

Kyphoscoliotic EDS

- Presents at birth to first of life
- Scleral Fragility
- Severe hypotonia
- Friable hyperextensible
- Generalized joint laxity



Classic Type

- Skin fragility
- Atrophic Scars
- Joint laxity
- Aortic root dilation
- Dermatographia



Hypermobility type...or is it benign familial hypermobility syndrome?

Name of EDS Subtype	IP*	Genetic Basis	Protein Involved
Classical EDS (cEDS)	AD	Major: <i>COL5A1</i> , <i>COL5A2</i>	Type V collagen
		Rare: <i>COL1A1</i> c.934C>T, p.(Arg312Cys)	Type I collagen
Classical-like EDS (clEDS)	AR	<i>TNXB</i>	Tenascin XB
Cardiac-valvular EDS (cvEDS)	AR	<i>COL1A2</i> (biallelic mutations that lead to <i>COL1A2</i> NMD and absence of pro $\alpha 2(I)$ collagen chains)	Type I collagen
Vascular EDS (vEDS)	AD	Major: <i>COL3A1</i>	Type III collagen
		Rare: <i>COL1A1</i> c.934C>T, p.(Arg312Cys) c.1720C>T, p.(Arg574Cys) c.3227C>T, p.(Arg1093Cys)	Type I collagen
Hypermobile EDS (hEDS)	AD	Unknown	Unknown
Arthrochalasia EDS (aEDS)	AD	<i>COL1A1</i> , <i>COL1A2</i>	Type I collagen
Dermatosparaxis EDS (dEDS)	AR	<i>ADAMTS2</i>	ADAMTS-2
Kyphoscoliotic EDS (kEDS)	AR	<i>PLOD1</i>	LH1
		<i>FKBP14</i>	FKBP22
Brittle cornea syndrome (BCS)	AR	<i>ZNF469</i>	ZNF469
		<i>PRDM5</i>	PRDM5
Spondylodysplastic EDS (spEDS)	AR	<i>B4GALT7</i>	$\beta 4$ GalT7
		<i>B3GALT6</i>	$\beta 3$ GalT6
		<i>SLC39A13</i>	ZIP13
Musculocontractural EDS (mcEDS)	AR	<i>CHST14</i>	D4ST1
		<i>DSE</i>	DSE
Myopathic EDS (mEDS)	AD or AR	<i>COL12A1</i>	Type XII collagen
Periodontal EDS (pEDS)	AD	<i>C1R</i>	C1r

- So EDS is a big ol' mess of diagnoses of similar phenotypes (marfanoid + skin stuff) that covers a huge breadth of diseases with widely variable pathology

Where to start

- Beighton
 - It's a screening tool
 - It's not diagnostic



Pull little finger back
beyond 90°
(one point for each side)



Pull thumb back to
touch forearm
(one point for each side)



Bend elbow backwards
beyond 10°
(one point for each side)



Bend knee backwards
beyond 10°
(one point for each side)



Lie hands flat on floor
while keeping knees
straight and bending
forward at waist

Even this test
is kind of a
mess

- >4 is suggestive of Benign Joint Hypermobility syndrome
- >5 in adults or 6 in kids is concerning for EDS...
- I have no idea why 1 point on this test carries so much weight.
- Generally I look to systemic involvement to lean more towards connective tissue disease vs benign phenomena

Next step

- In the presence of skin fragility I think that the genetic testing is appropriate
- If the aortic root is appreciably enlarged then I also recommend genetic testing
- Otherwise I bump them into a “screening pool” with the diagnosis of hypermobility type with annual or every other year screening.

Chasing a meaningful diagnosis.

- Diagnostic criteria:
- Must have a positive Beighton
- Two of the following
 - Systemic manifestations of generalized connective tissue disease
 - Family history of a relative who meets criteria
 - Musculoskeletal complications
- Can't have any of the other diseases that we've discussed
- Big rule outs:
 - Skin fragility
 - On going autoimmune disease

Systemic manifestations

- Soft velvety skin
 - Skin hyperextensibility
 - Striae
 - Piezogenic papules of the heel
 - Recurrent hernias
 - Atrophic Scarring, but not as bad as classic EDS
 - Rectal prolapse
 - Dental crowding
 - Arachnodactyly
 - Wingspan >1.05
 - Aortic Root $z > 2$
 - Mitral Valve prolapse
- Have to have 5 of these

Musculoskeletal Complications

- Pain in two or more limbs of 3 months
- Chronic wide spread pain for 3 months
- Recurrent joint dislocation
- Have to have one.

Hypermobility type

These kids have all the complaints

The internet has kind of ruined this diagnosis, which is why stringent application of the diagnostic criteria is so important.



So this is it

- We care about connective tissue disease because there is real risk of morbidity if it goes undetected
- We also care because it can account for a lot of non-specific complaints
- When to refer?
 - A positive beighton
 - Multiple stigma present, but failing to meet diagnostic criteria

Thanks!