Genetic Considerations in Early-Onset Scoliosis

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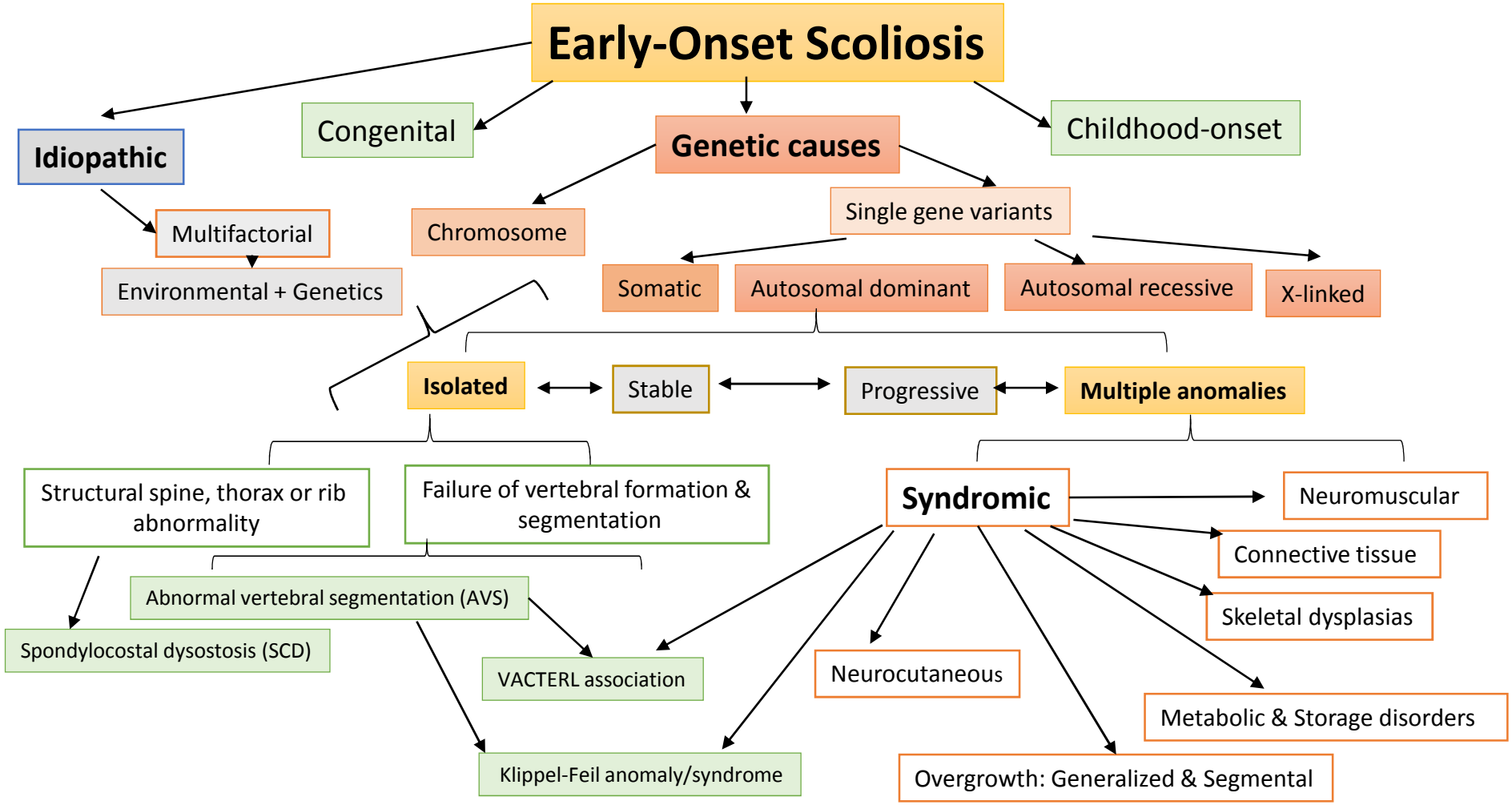
Early-Onset Scoliosis (EOS)

- Curvature of the spine in children >10 ° with onset before age 10 yrs
- Often progressive
- Often associated with thoracic constraint and impaired pulmonary development
- Associated impaired pulmonary function
- ***Multiple possible underlying causes, which may have other associated anomalies → Genetic Syndromes***
  - Treatment is complicated by these numerous factors

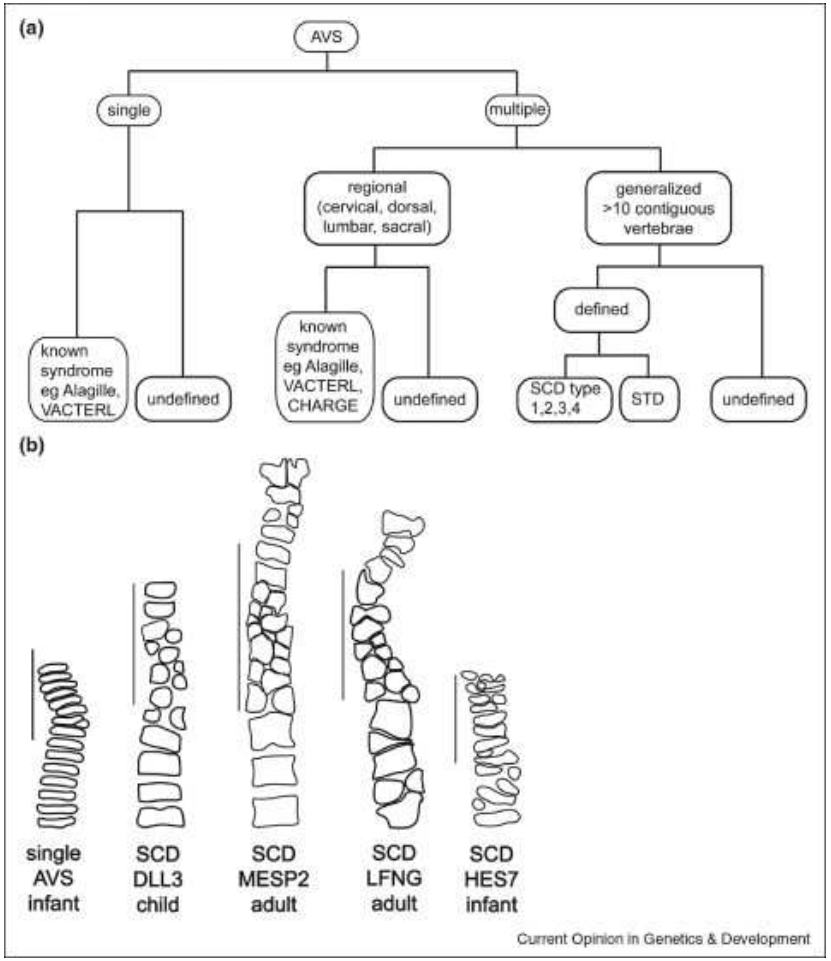
Clinical Genetics Evaluation of EOS

- Isolated VS Multiple
- **Multiple**
  - Major organ system anomalies
  - Minor anomalies – dysmorphic features
  - Patterns of multiple anomalies
  - Family history
  - Genetic & environmental causes
  - Genetic testing


Early-Onset Scoliosis
Idiopathic
Congenital
Genetic causes
Childhood-onset
Multifactorial
Environmental + Genetics
Chromosome
Single gene variants
Somatic
Autosomal dominant
Autosomal recessive
X-linked
Isolated
Stable
Progressive
Multiple anomalies
Structural spine, thorax or rib abnormality
Failure of vertebral formation & segmentation
Syndromic
Neuromuscular
Connective tissue
Skeletal dysplasias
Abnormal vertebral segmentation (AVS)
Spondylocostal dysostosis (SCD)
VACTERL association
Neurocutaneous
Metabolic & Storage disorders
Klippel-Feil anomaly/syndrome
Overgrowth: Generalized & Segmental

Abnormal Vertebral Segmentation (AVS)

- AVS in humans is a common congenital abnormality (2/1000 births) that results in uneven or fused vertebrae



Dunwoodie, Curr Opin Genetics & Dev 2009, 19:329-337

Somitogenesis

- Early patterning of the axial skeleton is controlled by genes that regulate the segmentation of paraxial mesoderm into somites and differentiation into sclerotomes
- Occurs bilaterally, in a timed rostro-caudal sequence
  - Molecular segmentation “clock”: periodic activation of genes in the *Notch* gene and related gene signaling pathways
- Somites give rise to the vertebrae, dorsolateral portion of the ribs, dermis of the dorsal skin, and skeletal muscle of the body wall and limbs

Syndromes & Disorders with AVS & EOS

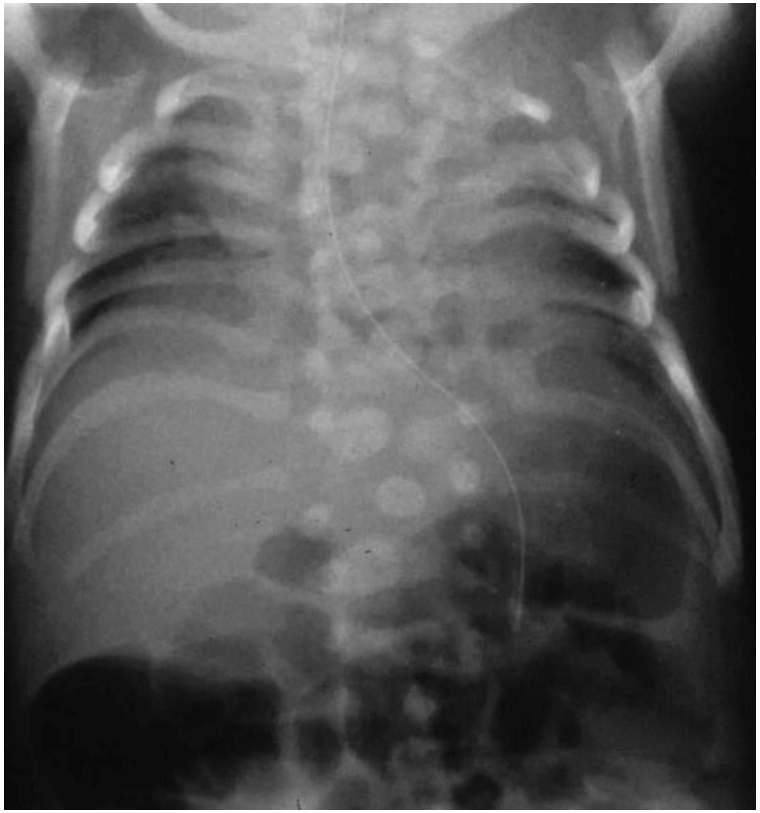
TABLE 1. Some Syndromes and Disorders That Include Abnormal Vertebral Segmentation[a]

Syndromes / disorders	OMIM reference	Gene(s)
Acrofacial dysostosis[b]	263750	
Alagille	118450	JAGGED1, NOTCH2
Anhalt[b]	601344	
Atelosteogenesis III	108721	FLNB
Campomelic dysplasia	211970	SOX9
Casamassima-Morton-Nance[b]	271520	
Caudal regression[b]	182940	
Cerebro-facio-thoracic dysplasia[b]	213980	
CHARGE	214800	CHD7
"Chromosomal"		
Currarino	176450	HLXB9
De La Chapelle[b]	256050	
DiGeorge / Sedláčková	188400	Chromosomal
Dysspondylochondromatosis[b]		
Femoral hypoplasia-unusual facies[b]	134780	
Fibrodysplasia ossificans progressiva	135100	ACVR1
Fryns-Moerman[b]		
Goldenhar[b]	164210	
Holmes-Schimke[b]		
Incontinentia pigmenti	308310	NEMO
Kabuki[b]	147920	
Kaufman-McKusick	236700	MKKS
KBG syndrome[a]	148050	
Klippel-Feil[b]	148900	?PAX1
Larsen	150250	FLNB
Lower mesodermal agenesis[b]		
Maternal diabetes[b]		
MURCS association[b]	601076	
Multiple pterygium syndrome	265000	CHRNG
OEIS syndrome[b]	258040	
Phaver[b]	261575	
Rapadilino	266280	RECQL4
Robinow	180700	ROR2
Rolland-Desbuquois[b]	224400	
Rokitansky sequence[b]	277000	? WNT4
Silverman	224410	HSPG2
Simpson-Golabi-Behmel	312870	GPC3
Sirenomelia[b]	182940	
Spondylocarpotarsal synostosis	269550	FLNB
Spondylocostal dysostosis	277300	DLL3, MESP2, LNFG
Spondylothoracic dysostosis[b]	277300	
Thakker-Donnai[b]	227255	
Toriello[b]		
Urioste[b]		
VATER / VACTERL[b]	192350	
Verloove-Vanhorick[b]	215850	
Wildervanck[b]	314600	
Zimmer[b]	301090	

[a]VATER, vertebral defects, anal atresia, tracheoesophageal fistula, radial defects, and renal anomalies; VACTERL, vertebral defects, anal atresia, cardiac defects, tracheoesophageal fistula, radial defects and renal anomalies, and nonradial limb defects.
[b]Underlying cause not known.

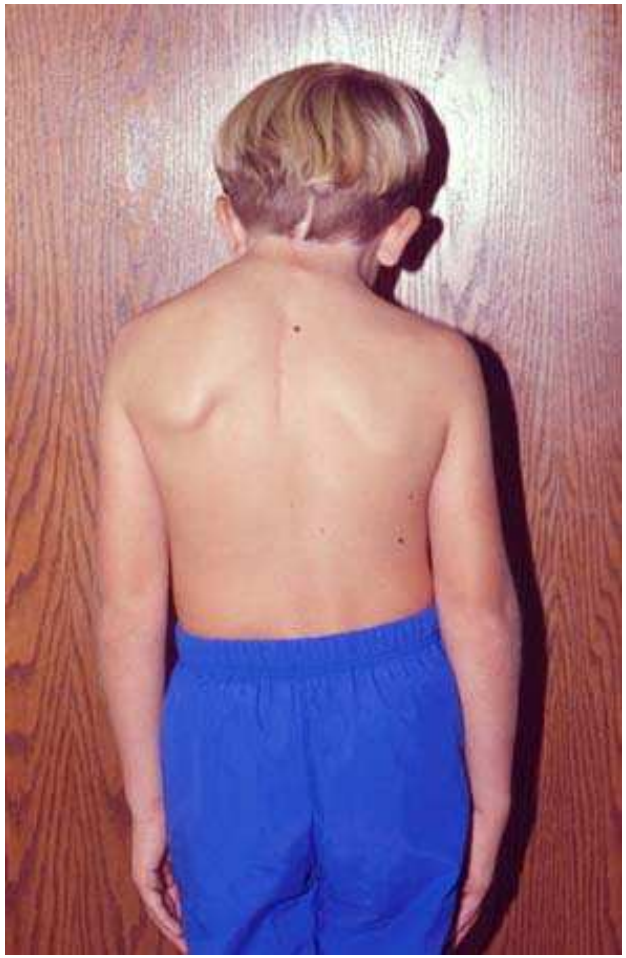
Spondylocostal Dysostosis (SCD)

- Characterized by rib fusions, rib deletions, hemivertebrae and loss of vertebrae, causing truncal shortening
- Vertebral segmentation anomalies in SCD involve primarily cervical vertebrae similar to Klippel-Feil Syndrome
  - Mutation in 4 genes involved in the Notch signaling pathway (DLL3, MESP2, LFNG and HES7) account for ~30% of SCD cases
  - DLL3 most common cause

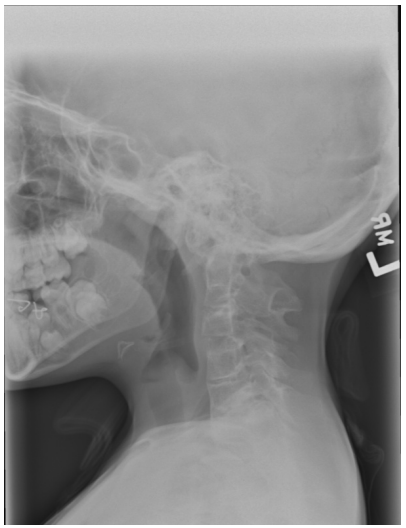


Klippel-Feil Anomaly/ Syndrome (KFS)

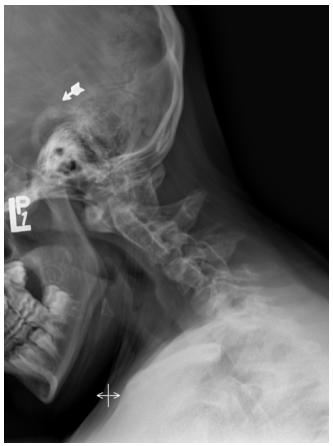
- Characterized by variable segmentation defects in the cervical vertebrae (Types I-III)
- Accompanied by other organ malformations, including the skeletal, cardiac, hearing, ophthalmologic and renal systems
- Genetically heterogenous
  - Etiology for most cases unknown



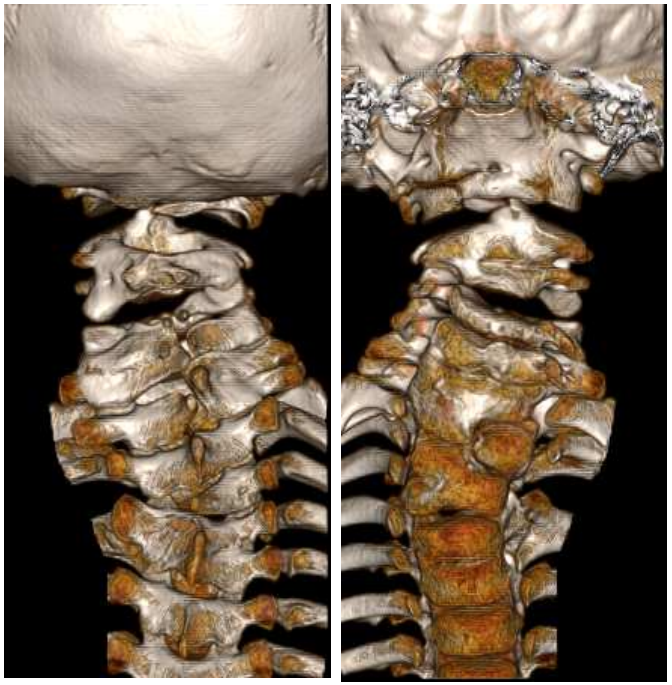
Radiological findings ~ Vertebral anomalies



C2-3 & T1-T5 segmentation anomalies;
C6-7 hemivertebrae

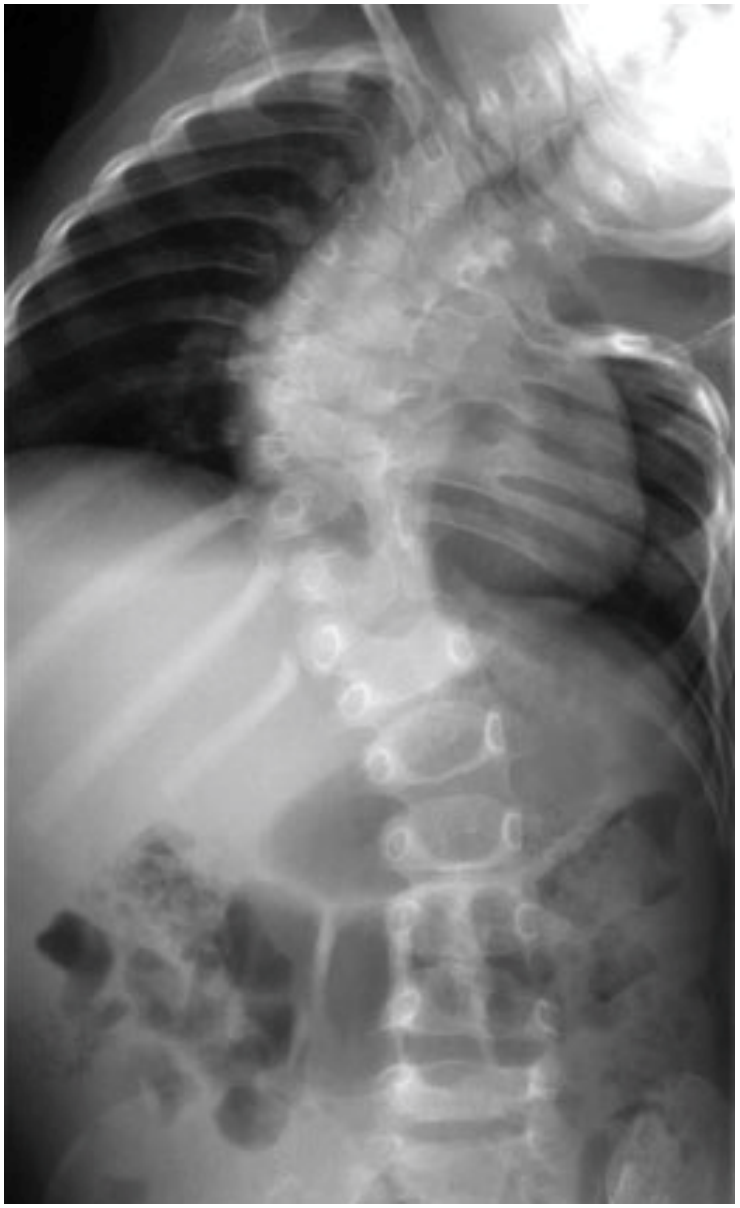


C2-C3 and C4-C5 segmentation anomalies



Dorsal **Ventral**

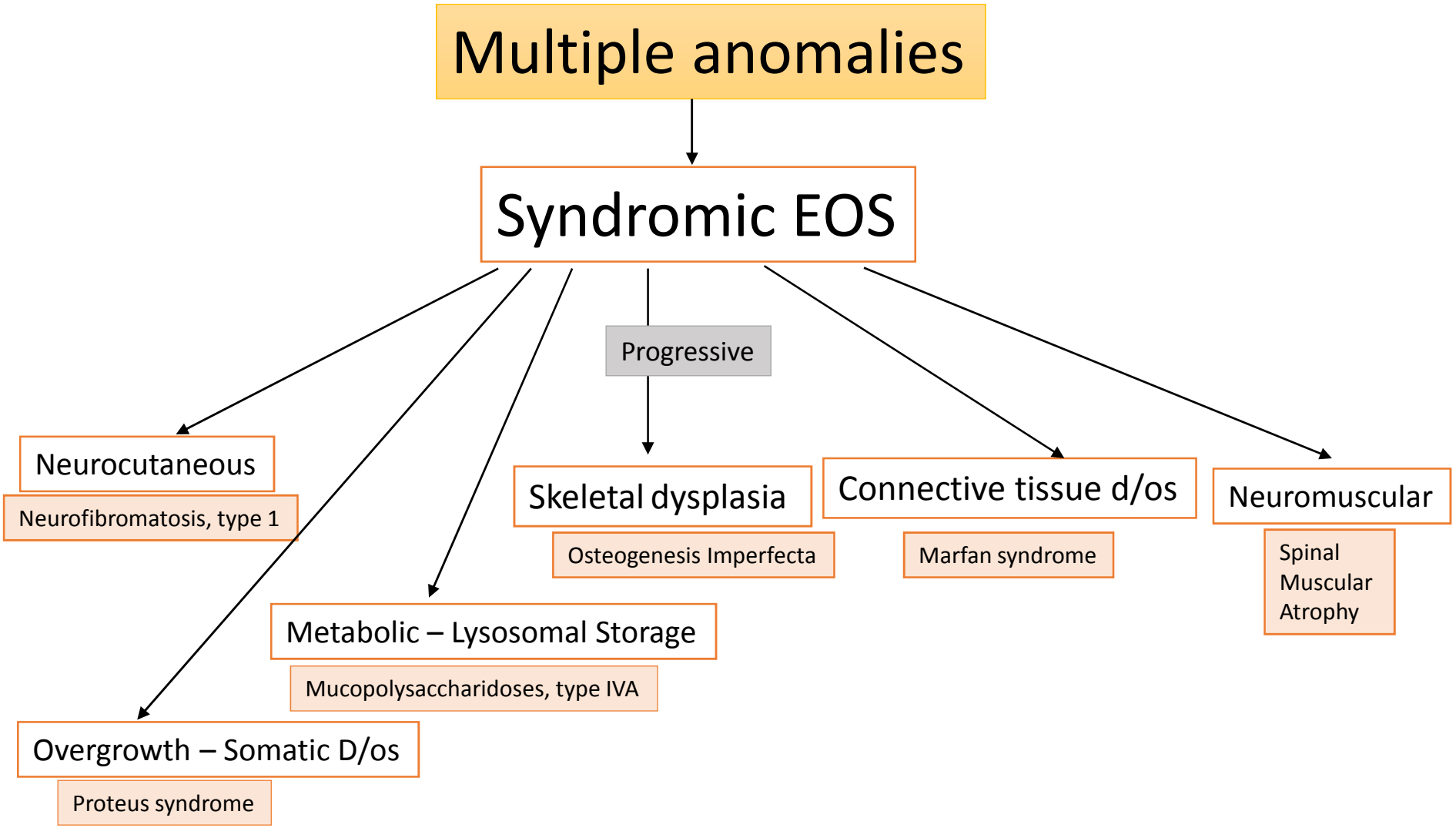
C2-3, C4-6 segmentation failure;
T4 hemivertebrae



VACTERL Association

Vertebral- Anal- Cardiac-Tracheo-Esophageal-
Renal-Radial-Limb Defects

- **V** vertebrae
- **A** imperforate anus or anal atresia
- **C** cardiac anomalies.
- **TE** tracheoesophageal fistula
- **R** renal or kidney anomalies.
- **L** limb anomalies (radial agenesis).


Multiple anomalies
Syndromic EOS
Progressive
Neurocutaneous
Neurofibromatosis, type 1
Skeletal dysplasia
Osteogenesis Imperfecta
Connective tissue d/os
Marfan syndrome
Neuromuscular
Spinal Muscular Atrophy
Metabolic – Lysosomal Storage
Mucopolysaccharidoses, type IVA
Overgrowth – Somatic D/os
Proteus syndrome

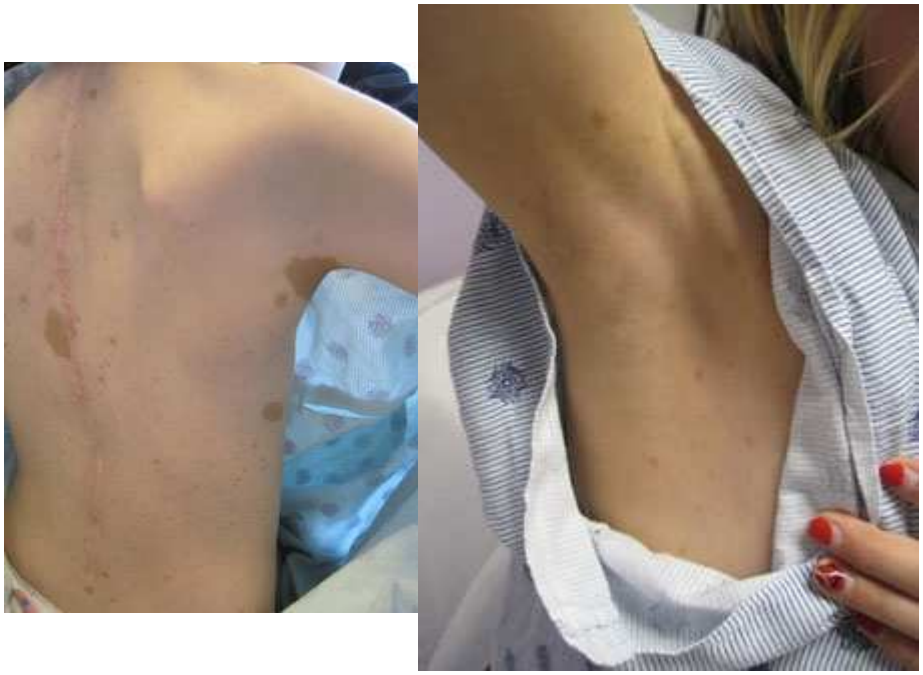
Neurocutaneous Disorders - key features

- Skin abnormalities
  - Hyperpigmentation/hypopigmentation
- CNS
  - Learning disabilities
  - Seizures/focal neurologic abnormalities
  - Macrocephaly
- Tumors
- Vasculopathies
- Skeletal - Scoliosis

Neurofibromatosis, type 1 (NF1)

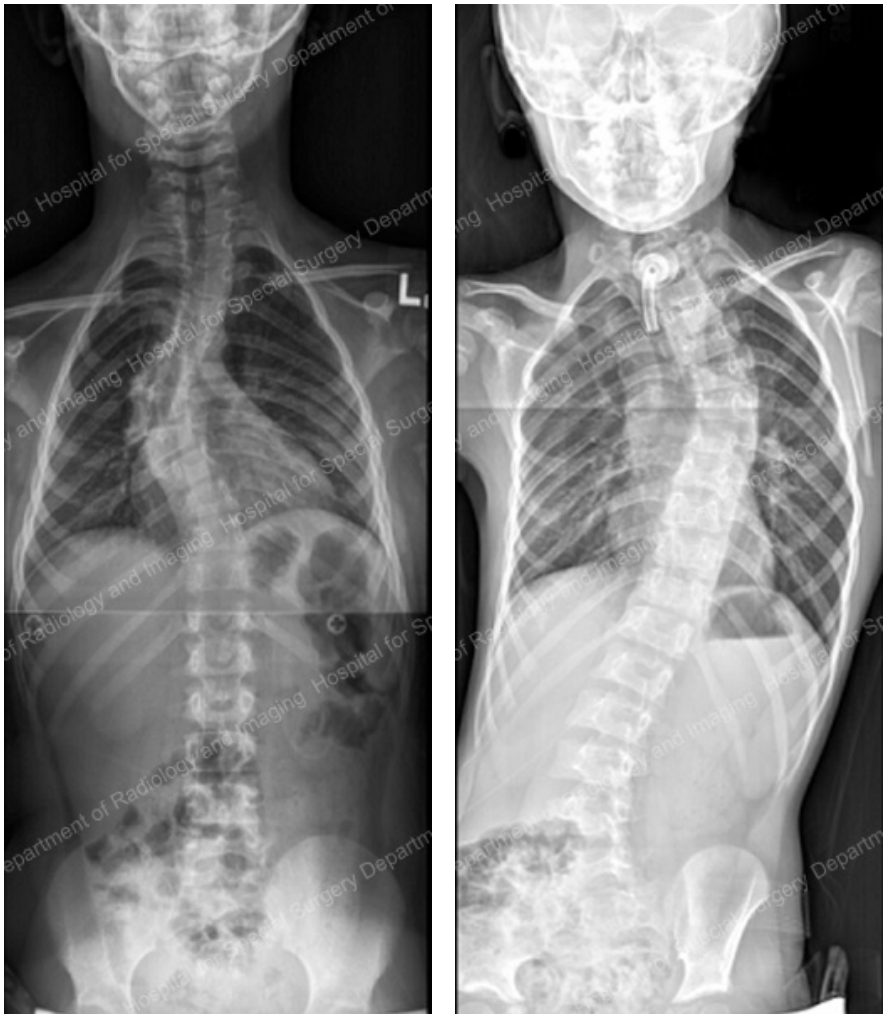
A diagnosis of NF1 is made in children with two or more of the following criteria:

- Skin lesions (neurofibromas)
- Multiple “café au lait” spots (light coffee-colored spots)
- Freckling in the groin and armpits
- Eye abnormalities, including Lisch nodules (tiny pigmented tumors in the iris)
- Certain skeletal abnormalities
- A family member with NF1.



Scoliosis in NF1

Dystrophic
vs. Non-dystrophic



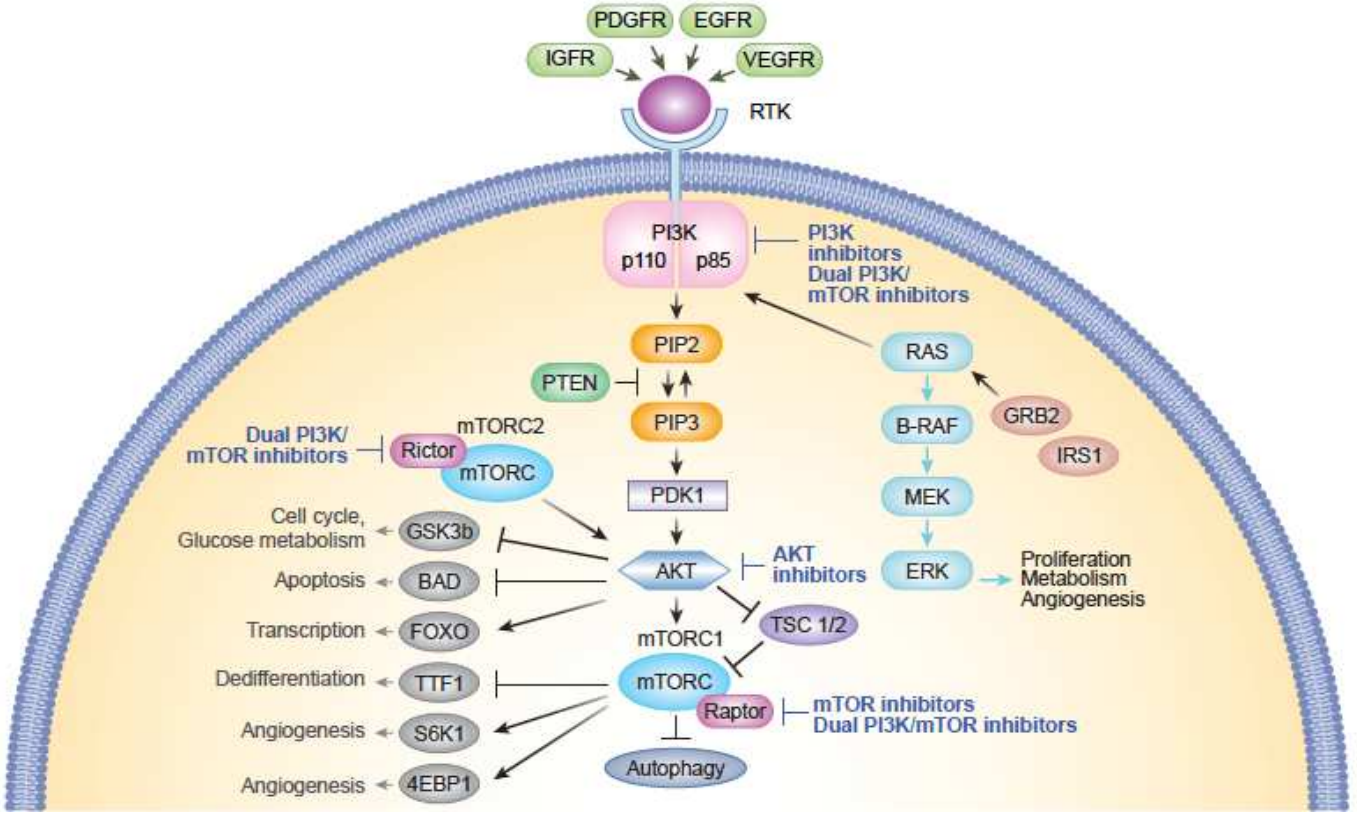
Overgrowth Syndromes – key features

- Generalized OG: Height & Head circumference >2SD above the mean (>98%)
- Advanced bone age
- Symmetric enlargements of other body parts, e.g. hands, feet
- Usually have ID and/or congenital anomalies

*** Distinguished by other minor (dysmorphic) and major anomalies

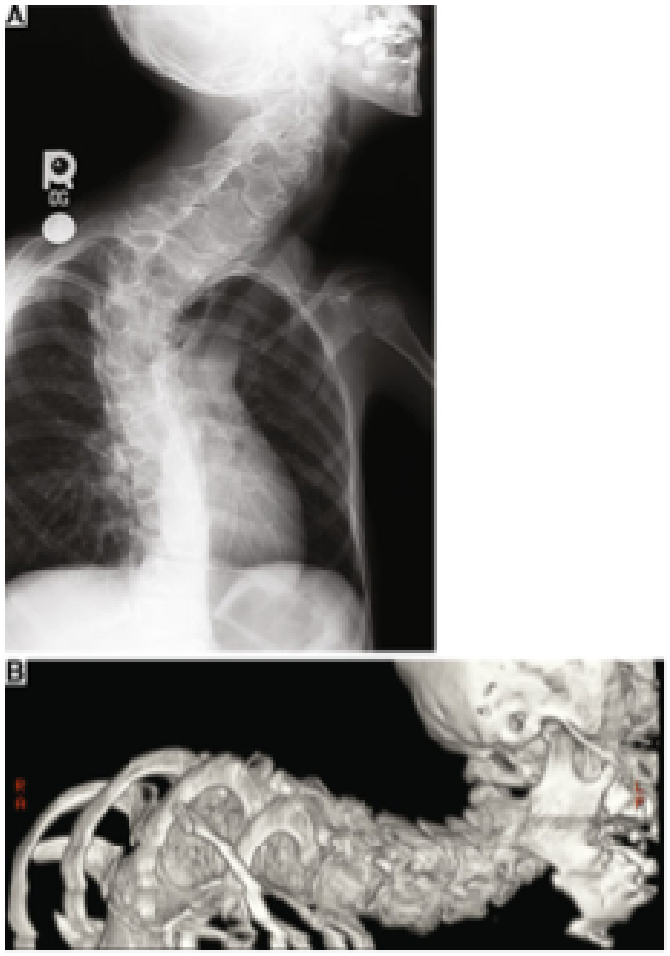
- Sotos syndrome most common, ~30% with scoliosis

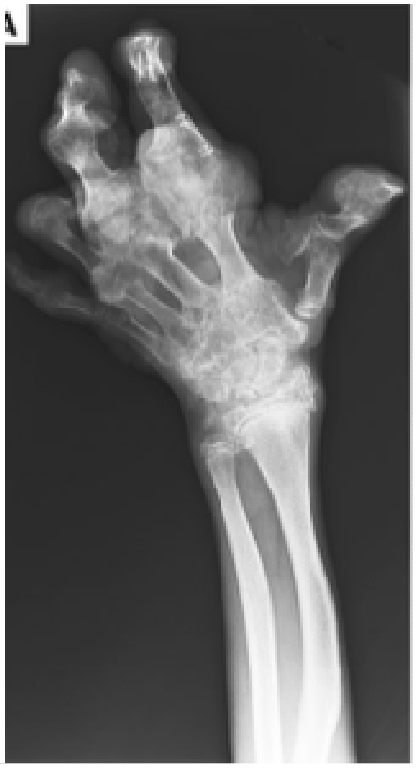
PI3K-AKT Signaling Pathway



Keppler-Noreuil, Parker, Darling, Martinez-Agosto, 2016, AJMG Semin

Segmental overgrowth disorder – Proteus syndrome





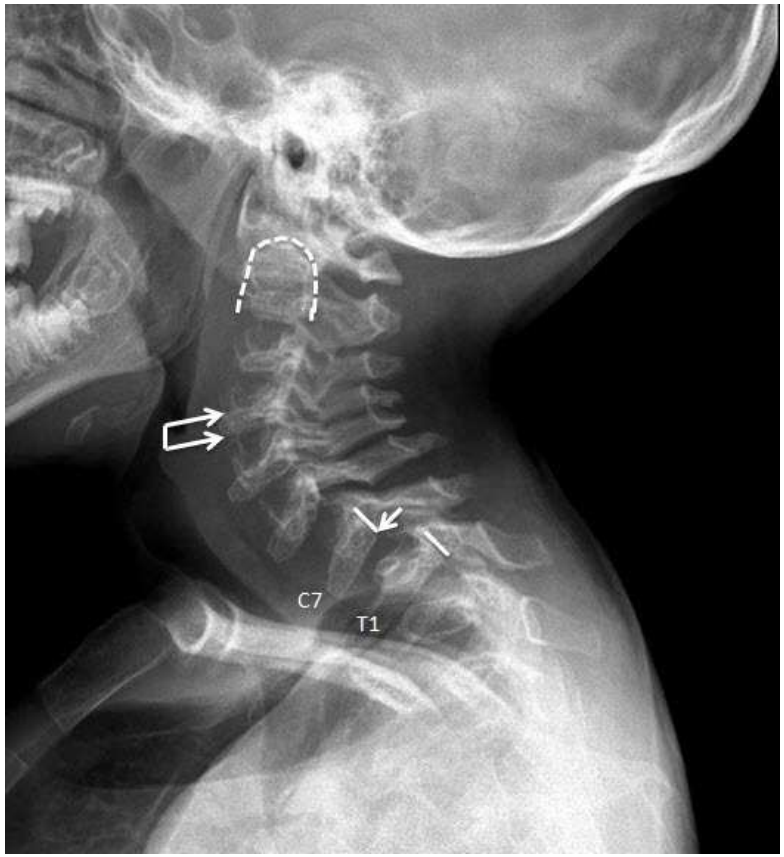
Metabolic & Storage Disorders –key features

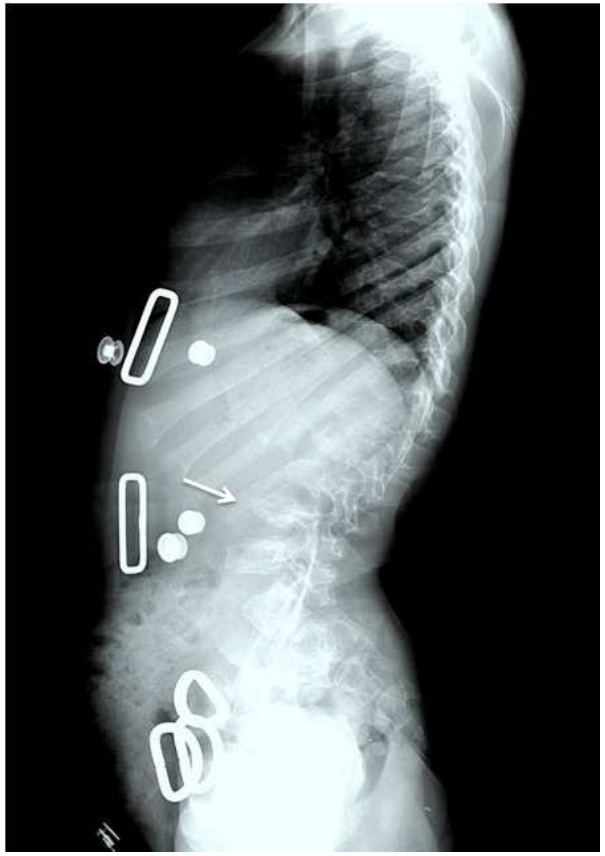
- Often **progressive**
- Many with “coarsening” of craniofacial features, macrocephaly
- Distinctive skeletal abnormalities
- Skin and connective tissue changes
  - Thickening of skin, ectodermal dysplasias
- Cataracts or corneal clouding
- Developmental and neurologic abnormalities
- Cardiomyopathy and valvular abnormalities
- Liver/spleen enlargement

Mucopolysaccharidosis Type IVA

- Lysosomal storage disorder – reduced N-acetylgalactosamine 6-sulfatase (GALNS) activity
- Characteristic findings:
  - Marked disproportionate short stature with short trunk and normal limbs (arm span exceeds height)
  - Ulnar deviation of the wrists
  - Pectus carinatum and flaring of the lower rib cage
  - **Gibbus (short-segment structural thoracolumbar kyphosis resulting in sharp angulation of the back), kyphosis, and scoliosis**
  - Genu valgum
  - Hypermobile joints
  - Waddling gait with frequent falls

Mucopolysaccharidoses Type IVA





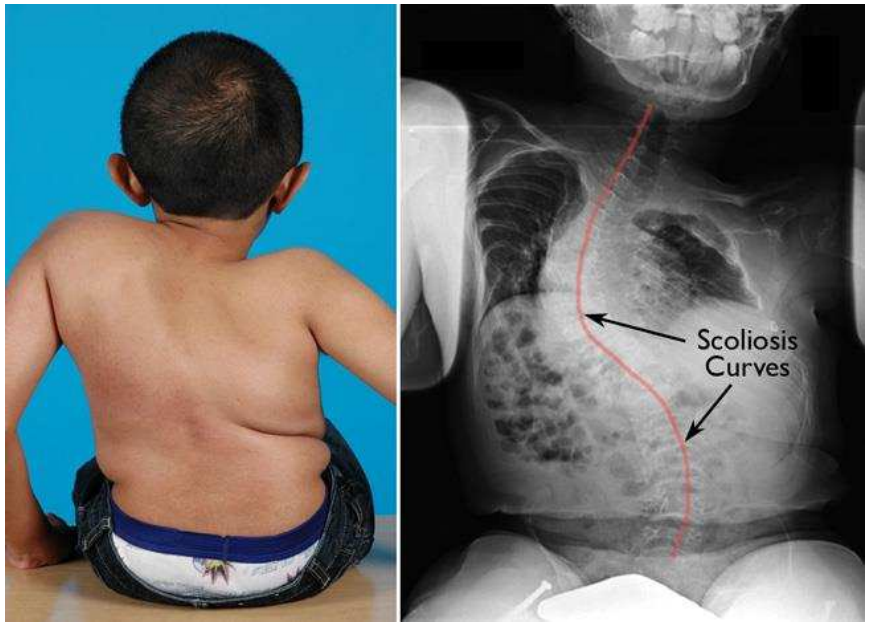
Congenital Skeletal Dysplasias – key features

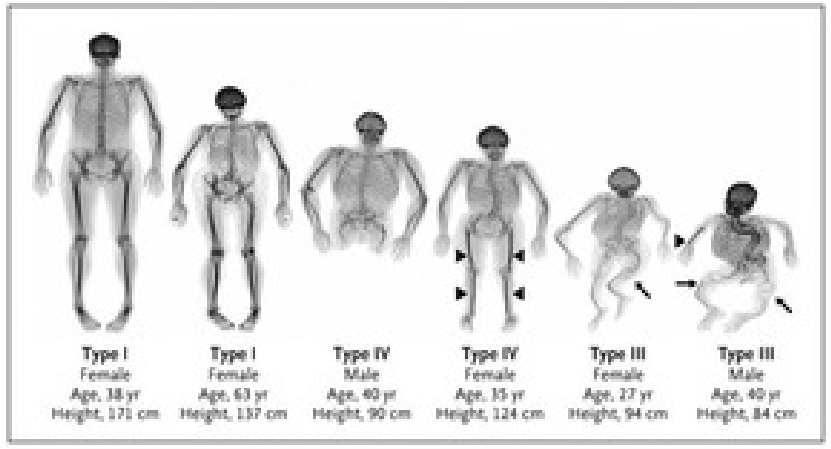
- Overall number of disorders: >450
  - Most have single gene etiology
- Suspect in **disproportionate short stature**
  - Short limbs
  - Short trunk
- Distinctive skeletal abnormalities on X-rays
  - Abnormalities of epiphysis, metaphysis, diaphysis
  - Abnormal bone density

Osteogenesis Imperfecta (OI)

- Skeletal dysplasia
- Collagen-related gene variants: 19 different types
  - Type III has higher prevalence of severe scoliosis than Types I and IV
- Presence of blue sclera, hearing loss, bone fragility, bone deformities, Wormian bones
- Scoliosis in 36-89%
  - Onset from age 2 years (some congenital onset), rapidly progresses after 5 years or curve >50 degrees
- Vertebral defects: codfish, wedge-shaped, platyspondyly

Scoliosis in Osteogenesis Imperfecta

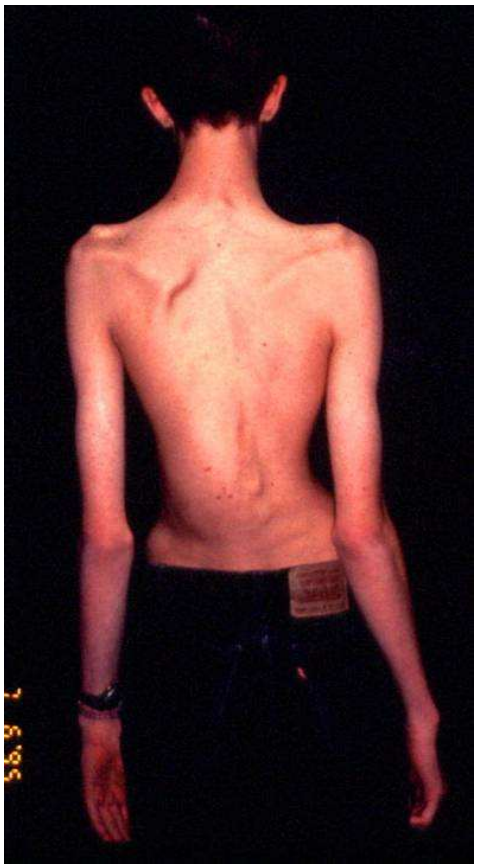


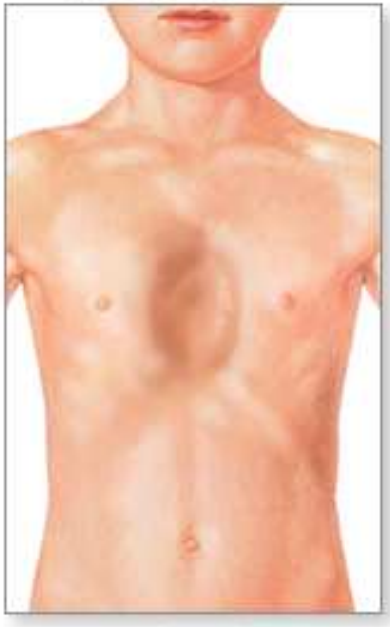


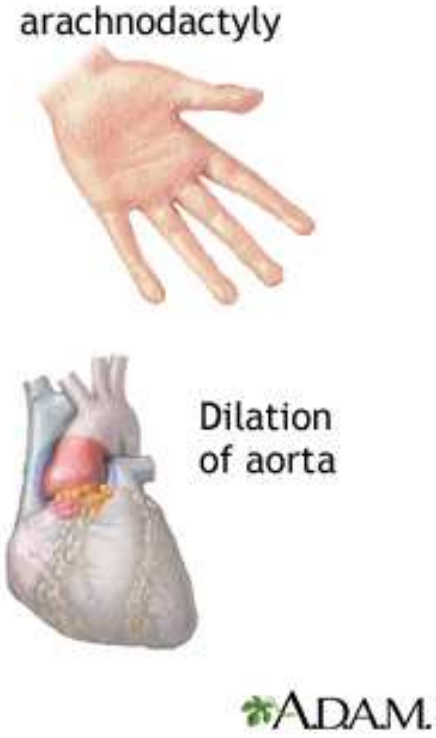
Connective Tissue Disorders – key features

- Joint
  - Hypermobile joints - sometimes contractures
  - Hernias
- Skeletal
  - Disproportionate stature
  - Chest wall abnormalities: pectus excavatum/carinatum
  - Craniofacial minor anomalies
- Cardiac and vascular: aortic and other arterial dilatations
- Ophthalmologic: lens dislocation, keratoconus, globe rupture
- Skin: hyperelasticity, bruising, bleeding

Marfan syndrome – characteristic features

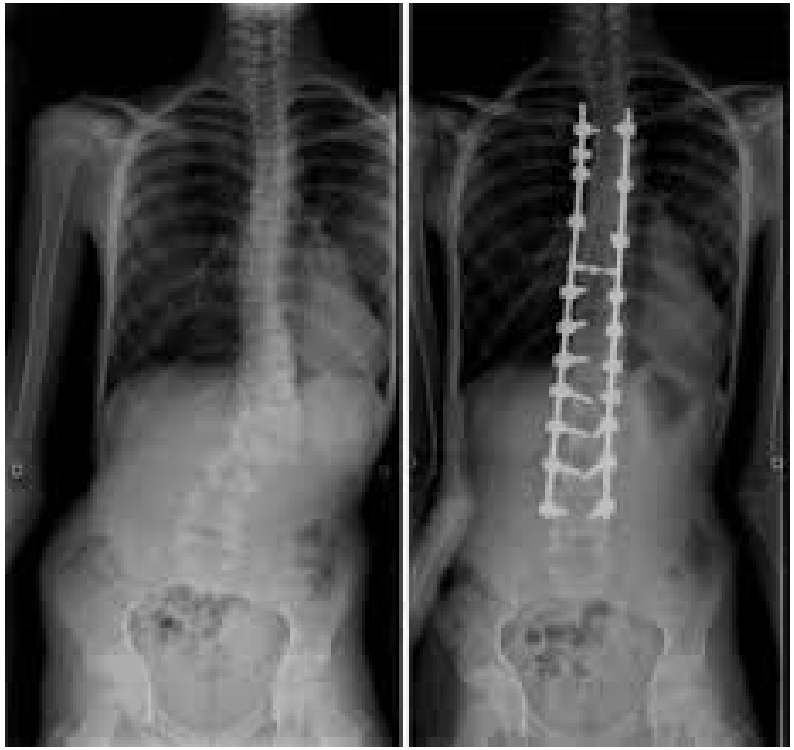






The Spine in Marfan Syndrome

- Scoliosis in 60% patients
- Few need treatment
  - Bracing
    - 15-25 degrees (<40 degrees)
    - Slow progression
  - Surgery: spine fusion
    - 35-40 degrees have more rapid progression through growth, risk for pulmonary c/os
    - Cardiac workup
    - Higher complication rates



Neuromuscular disorders e.g. Spinal muscular atrophy

- AR disorder of degenerative anterior horn cells of spinal cord
- 3 types – continuum of clinical severity
- Symmetric proximal muscle weakness and atrophy of skeletal muscles
  - Infants: Floppy, preservation of EOM, small movements of fingers
  - Child: Gower's sign
- Intelligence unaffected
- In SMA type II and type III
  - Progressive scoliosis
  - Onset after loss of ability to walk – common in children <4 years (SMA II)

Summary

- Heterogenous etiologies & pathogeneses – single gene variants, teratogens, multifactorial
- Genetic
  - Isolated – Congenital structural vertebral formation & segmentation
  - **Syndromic**
    - Connective tissue disorders
    - Skeletal dysplasias
    - Metabolic/Storage disorders
    - Neuromuscular disorders
    - Neurocutaneous disorders
    - Generalized and segmental overgrowth disorders
    - Other Multiple Congenital Anomaly syndromes

Thank you!