Genetic Considerations in Early-Onset Scoliosis

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Early-Onset Scoliosis (EOS)

- Curvature of the spine in children $>10^\circ$ 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

Genetic causes:
- Single gene variants
- Chromosome
  - Somatic
  - Autosomal dominant
  - Autosomal recessive
  - X-linked

Structural spine, thorax or rib abnormality:
- Abnormal vertebral segmentation (AVS)
- Spondylocostal dysostosis (SCD)

Failure of vertebral formation & segmentation:
- VACTERL association

Idiopathic:
- Multifactorial
- Environmental + Genetics

Congenital:
- Chromosome
  - Somatic

Childhood-onset:
- Progressive
- Multiple anomalies
  - Neuromuscular
    - Connective tissue
    - Skeletal dysplasias
  - Neurocutaneous
  - Metabolic & Storage disorders
  - Overgrowth: Generalized & Segmental

Isolated:
- Stable
Abnormal Vertebral Segmentation (AVS)

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

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
**TABLE 1. Some Syndromes and Disorders That Include Abnormal Vertebral Segmentation**

<table>
<thead>
<tr>
<th>Syndromes / disorders</th>
<th>OMIM reference</th>
<th>Gene(s)</th>
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<tr>
<td>Acrofacial dysostosis</td>
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<td>Simpson-Golabi-Behmel</td>
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**Syndromes & Disorders with AVS & EOS**

<table>
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<tr>
<th>Syndrome</th>
<th>OMIM Reference</th>
<th>Gene(s)</th>
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<td>Urioste b</td>
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*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

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