Etiology and Genetics In Early Onset Scoliosis

Kent A Reinker, MD
University of Texas Health Sciences Center, San Antonio
kreinker@satx.rr.com

What will be covered

- *Genetics*
- *Embryology*
  - *Anatomic*
  - *Biochemical*
- *Mechanisms of Production of Scoliosis*
- *Clinical Syndromology of Scoliosis*

Clinical Genetics

- ***Myths in Genetics***
  - ***Mutations in a single gene yield a single disease***
  - ***A single disease will result from mutation in only one gene***
  - ***Genetic diseases will always be transmitted in a Mendelian pattern***
  - ***Genetic diseases are always caused by errors in gene protein products***
  - ***A single gene produces only one protein product***
  - ***Genotype yields phenotype***

Clinical Genetics

- *Allelic mutations in a single gene can cause several different diseases*
  - *Example: Achondrogenesis, Stickler, SED, SEMD, Kneist syndrome and early onset arthritis all are associated with Collagen 2*
- *Genetic diseases can result from many separate genes*
  - *Example: Osteochondromatosis can result from EXT1, EXT2, or EXT3, all on different chromosomes*

Clinical Genetics

- *Non-Mendelian transmission is common*
  - *Imprinting*
  - *Genetic anticipation*
  - *Mosaicism*
  - *Mitochondrial transmission*
- *Genetic disease can result from intron mutation*
  - *Example: Neurofibromatosis*

Clinical Genetics

- *Post-translational alterations can yield many variants of a single gene's protein product*
  - *Alternative splicing is common*
- *Phenotypes differ despite identical genotype*
  - *Example: Identical twins are only ~80% concordant for idiopathic scoliosis*
- *More than one copy of a gene can be present in the genome*
  - *Example: Humans have 4 copies of homeobox genes*

Clinical Genetics - Implications

- Genetic tests cannot be 100% diagnostic of genetic disease
- Classifications of disease are altering as we learn more about their genetic mechanisms
  - Subclassification
  - Reclassification
- Genetic textbooks are never up-to-date

Clinical Genetics - Implications

- *Genetic diagnosis can be wrong or misleading*
- *Genetic expertise should be sought or developed*
- *Up-to-date information may be available on the internet*

Clinical Genetics - Implications

- Classes of gene products
  - Enzymes
  - Structural proteins
  - [illegible] genes / receptors
  - Oncogenes

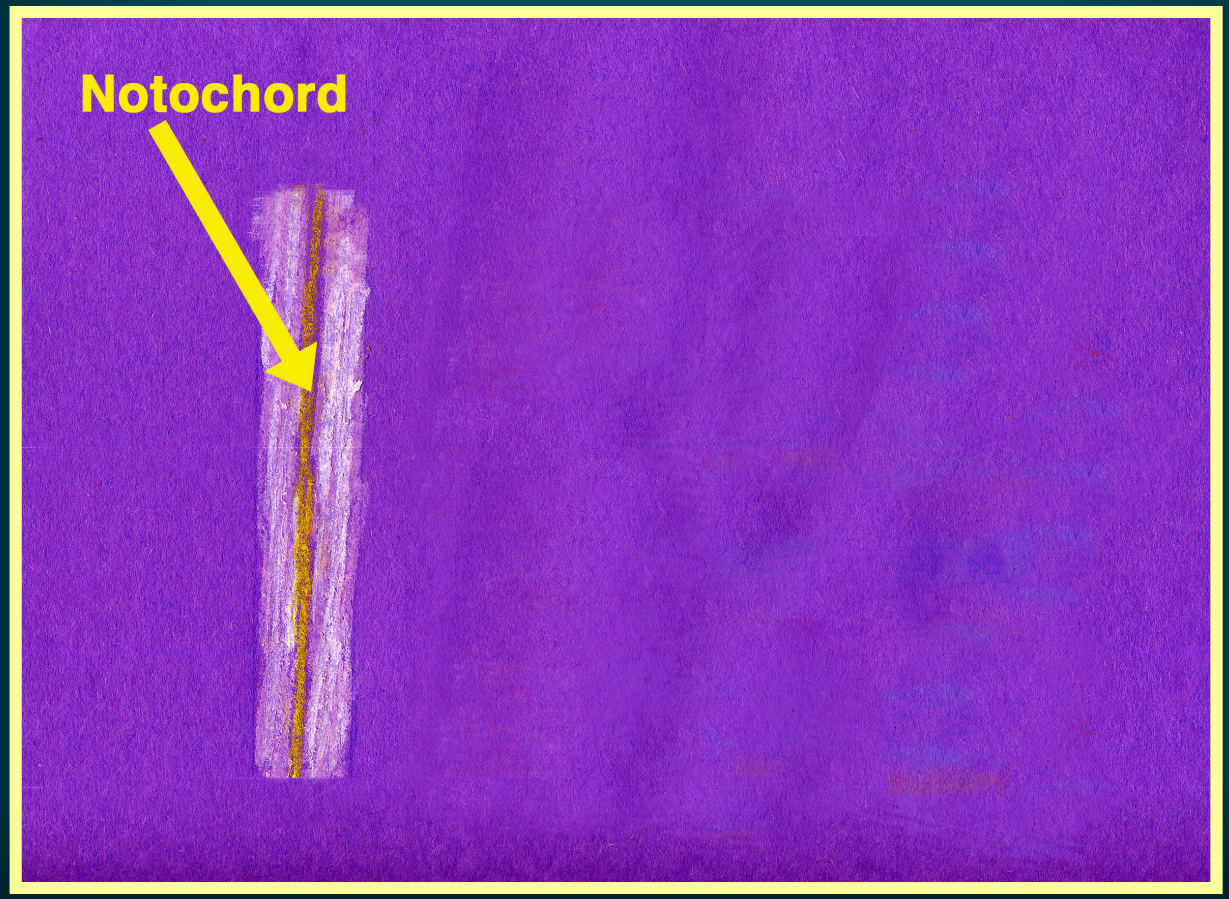
Rules change with the type of protein

Embryology- Anatomic

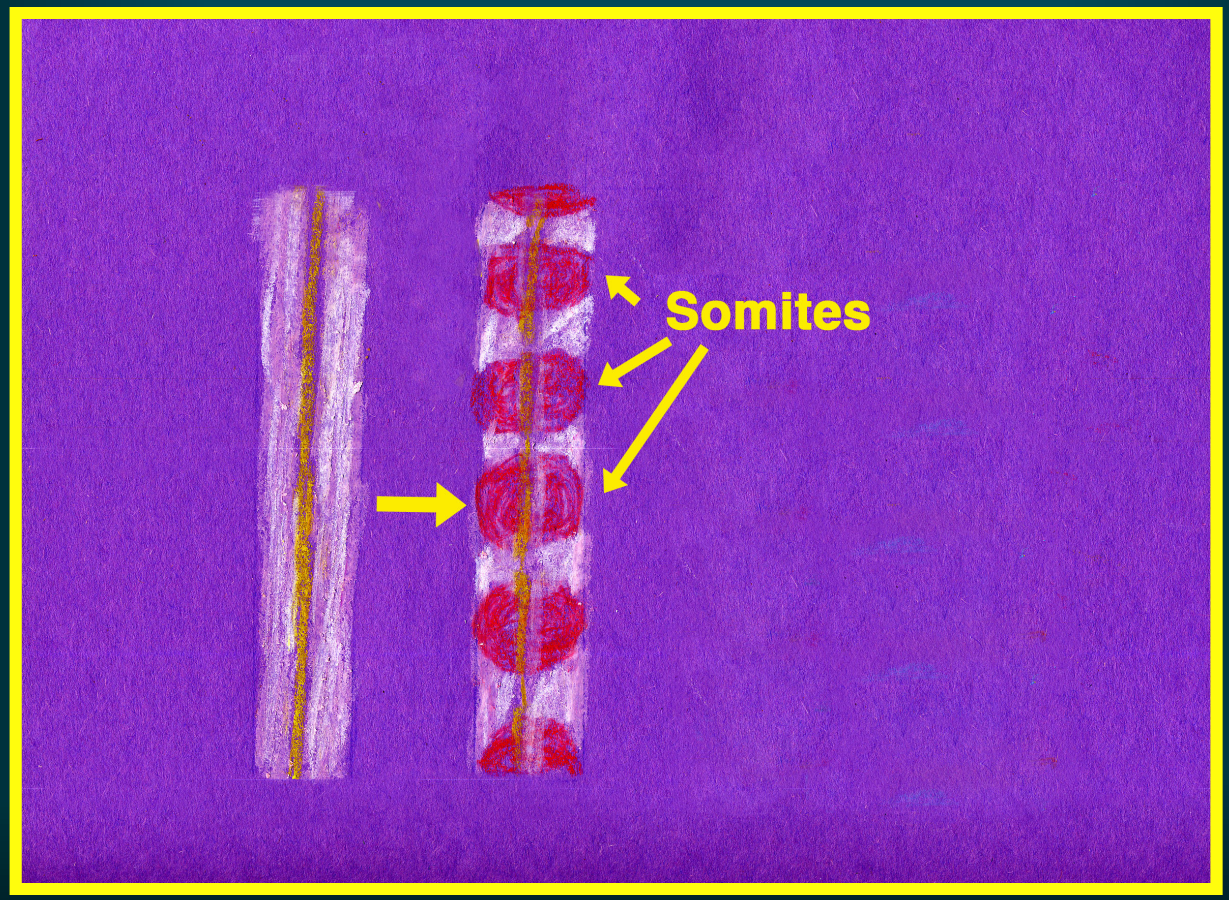
- Notochord formation - day 18
- Neurulation - 18- 29 days
- Somitization - 20-24 days
- Segmentation - 24 -33 days
- Ossification - 20 days - adulthood

Critical period 3-6th week

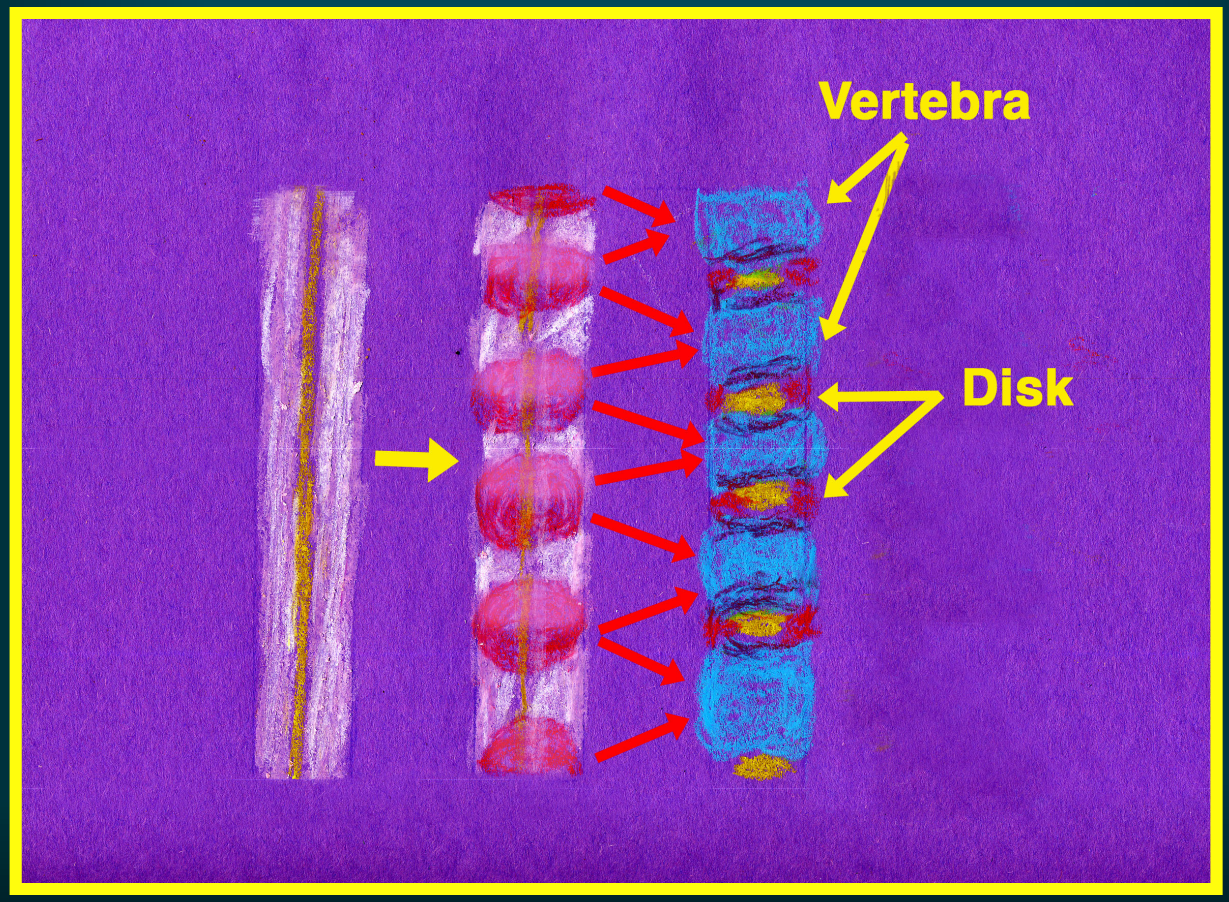
Somitization-Segmentation



Somitization-Segmentation

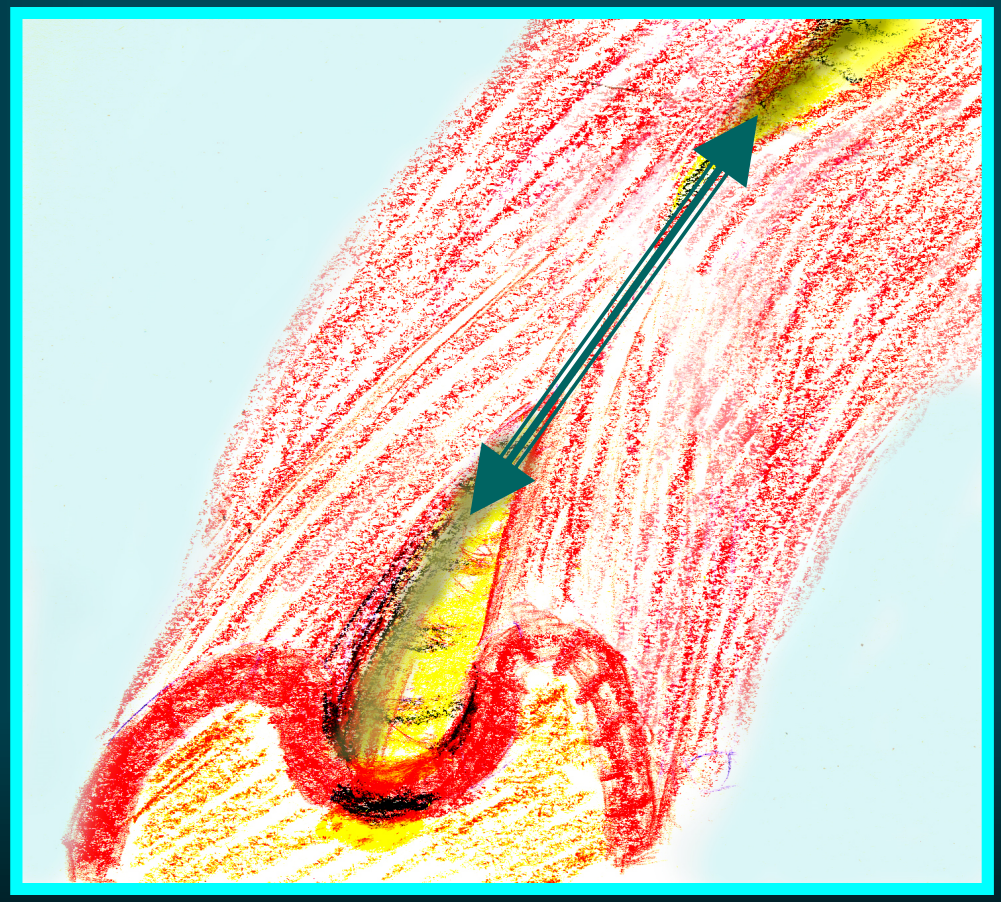


Somitization-Segmentation

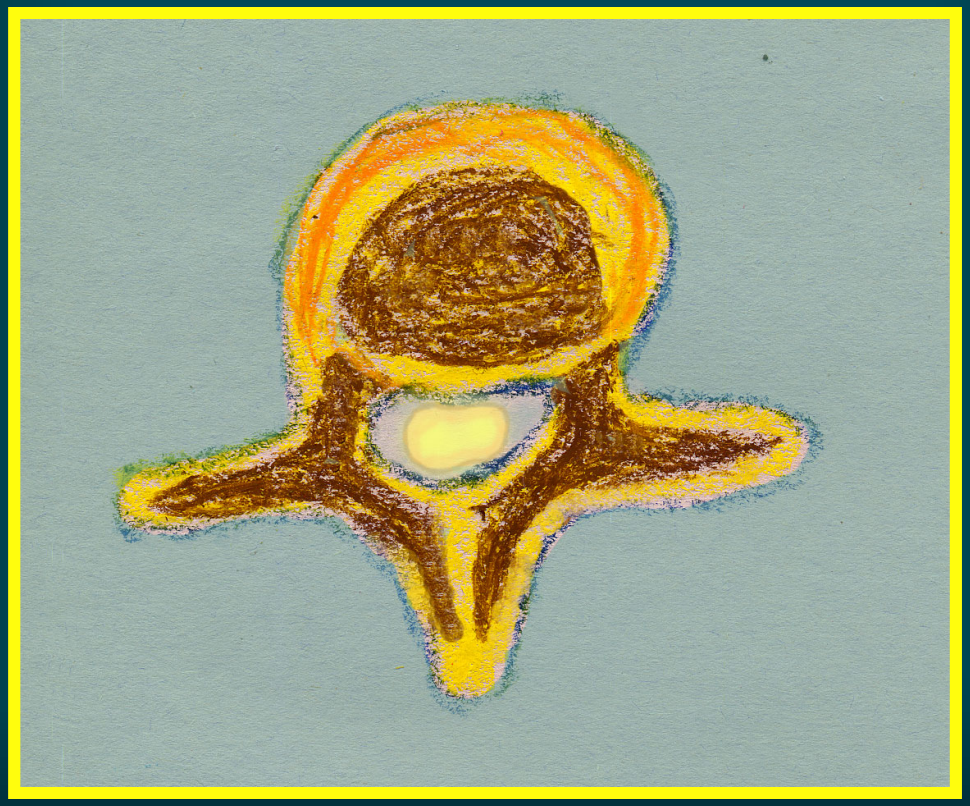


Somitization-Segmentation

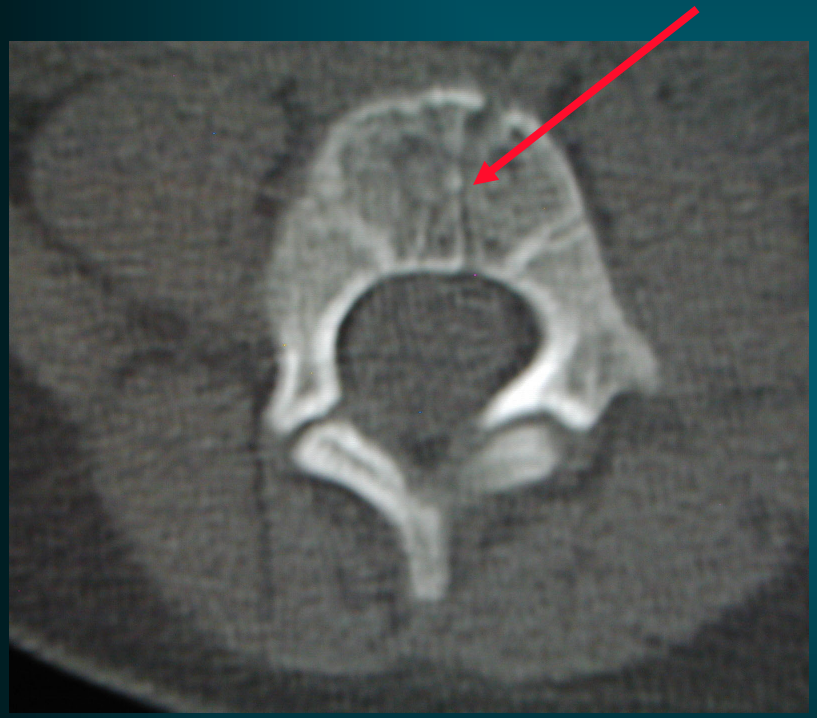
Neurulation

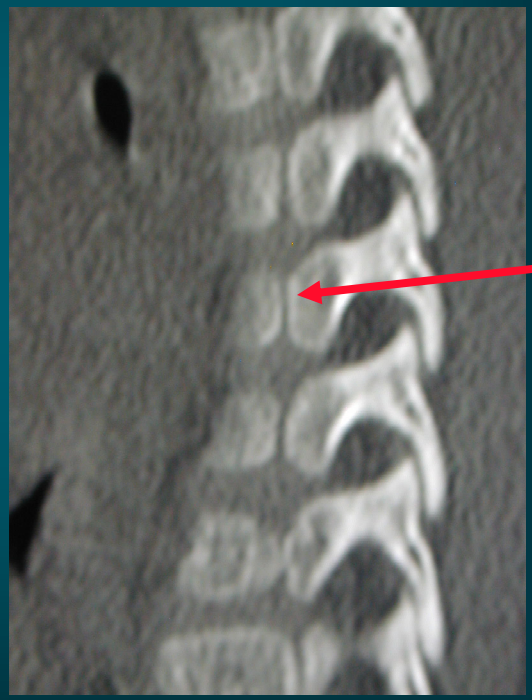


Ossification

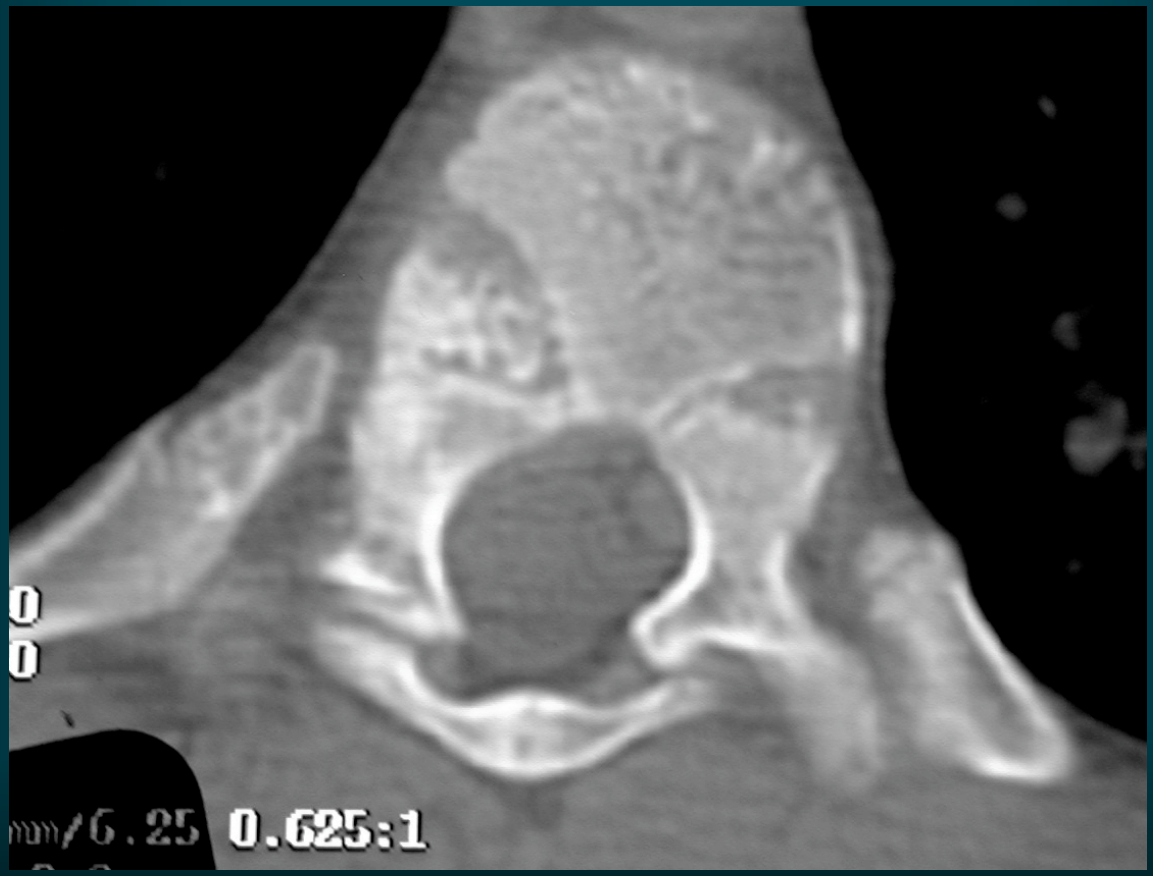


Ossification





Ossification in Cleidocranial Dysplasia (RUNX2, CBFA1)



Embryology-Biochemistry

- Homeobox genes
  - Highly conserved phylogenetically
  - Humans have 4 copies on 4 separate chromosomes
    - Redundancy yields safety
  - Organized temporally on the chromosome
    - Cranial / caudal patterning
  - Dominant posterior patterning

Molecular oscillators (clock genes)

- ***Notch Signaling Pathway***
  - ***DLL3, MESP2, LNF1 associated with three forms of spondylocostal dysostosis***

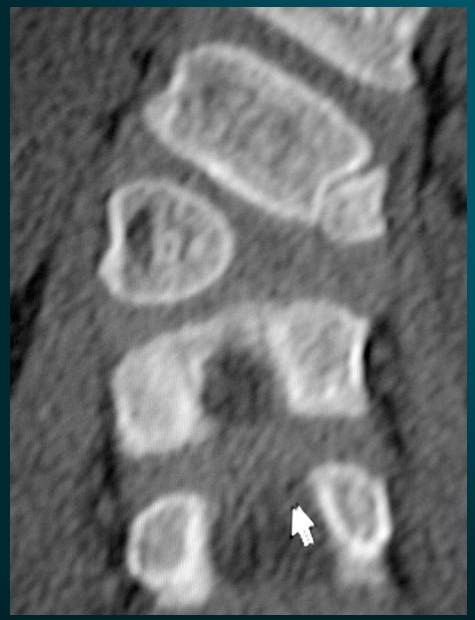
Wnt Signaling Pathway

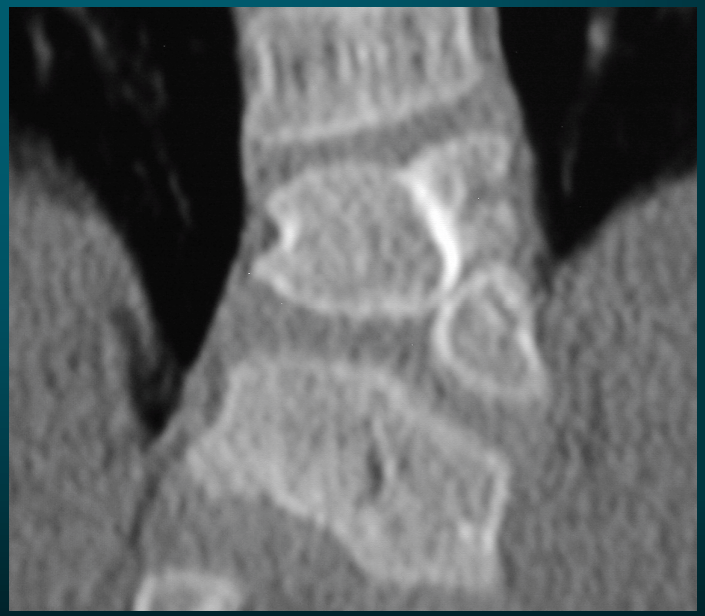
Folate and neural tube defects

- *Myelomeningocoele rates significantly decreased by folate administration*
  - *Lipomeningocoele rates are not affected*
- *Retinoic acid can induce myelomeningocoeles in rats*
- *Are there associated mutations in folate metabolism genes?*
  - *MTHFR (Methylene tetrahydrofolate reductatase) in Italy*
  - *BHMT (Betaine homocysteine methyltranferase) in USA*

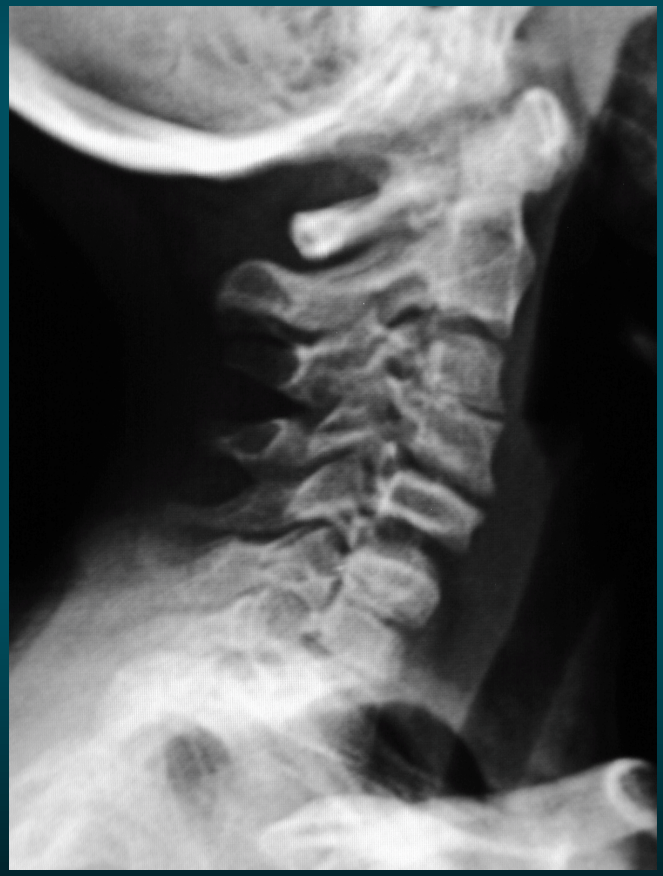
Congenital Scoliosis

- *Which hemivertebra is more likely to progress?*





Congenital Scoliosis



Congenital Scoliosis

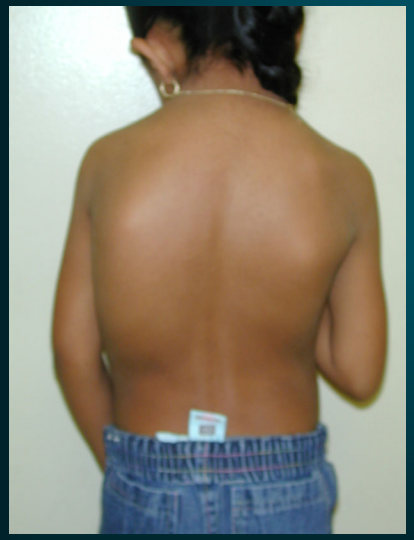
- ***What causes the deformity?***
  - ***Asymmetric growth potential***
  - ***Neurologic dysfunction from spinal cord anomaly***
  - ***Mechanical growth disruption from large curves***
  - ***Associated rib anomalies***

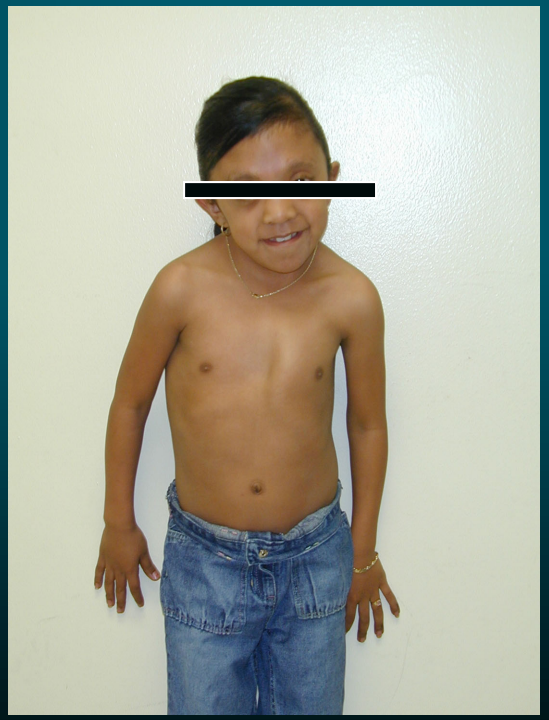
Clinical problems in dealing with syndromic scoliosis

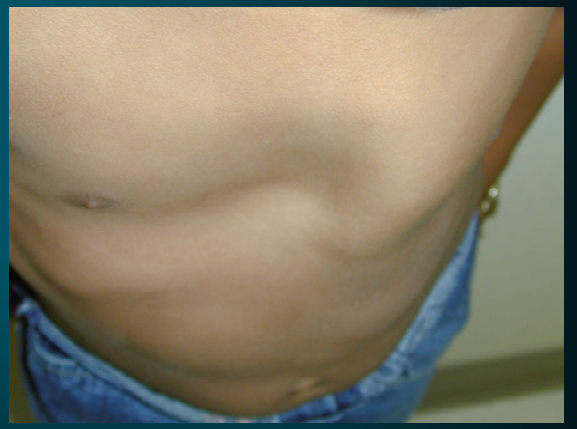
- *Diagnosis may be unclear or wrong*
- *Description of syndrome may not be accurate*
  - *Orthopaedic descriptions are almost never accurate*
  - *Surgical complications may not be defined*
- *Literature may be obsolete*

Example

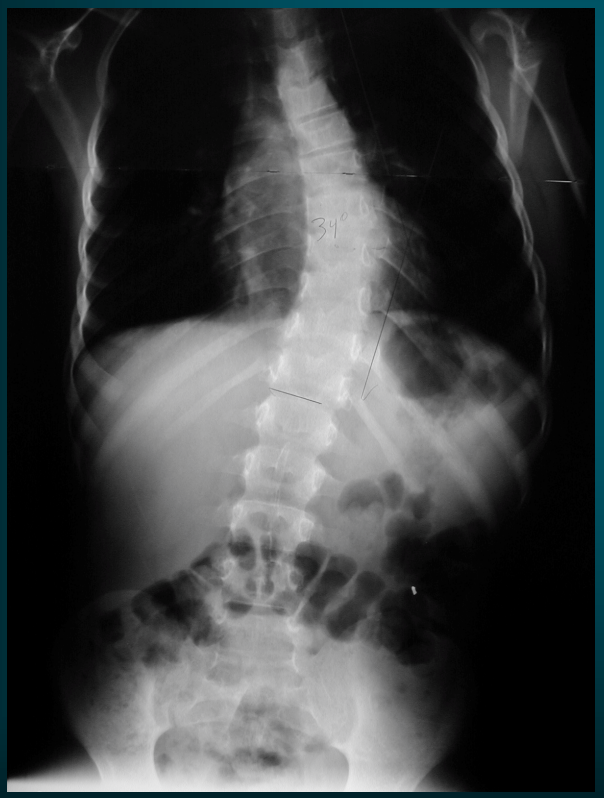
- 9 Year old male with scoliosis
- Carries diagnosis of Noonan syndrome

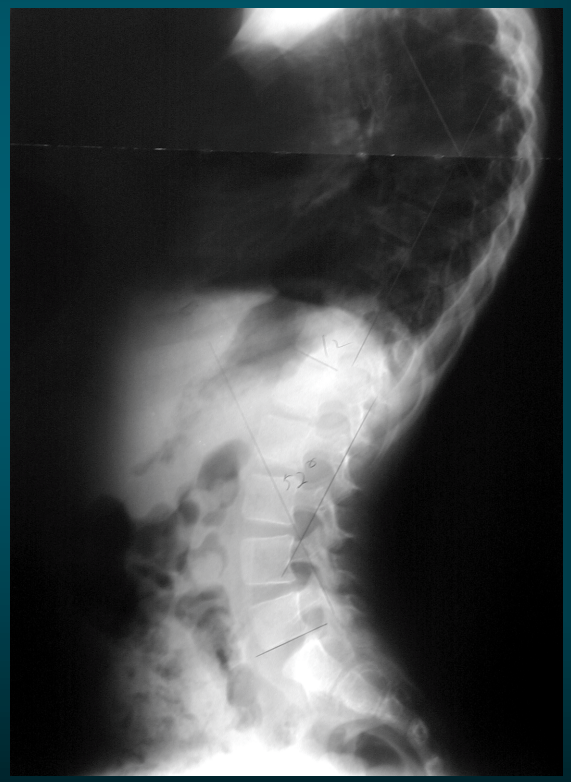






9 Year old male with scoliosis





Noonan syndrome

- Pseudo-Turner syndrome
- Neck webbing
- Characteristic facies
- Congenital heart disease
  - Usually Pulmonic stenosis
  - May have hypertrophic cardiomyopathy

Noonan Syndrome

- Hypotonia / Myopathy?
  - King Syndrome
- Frequent association with neurofibromatosis
  - Watson syndrome
- Association with mutation in PTPN-11
- Now also associated with mutations in KRAS, SOS1, RAF1
  - Different mutations yield different phenotypes

Syndromes overlapping with Noonan Syndrome

- *Costello syndrome*
  - *HRAS*
- *Cardiofaciocutaneous (CFC) syndrome*
  - *KRAS, BRAF, Mek1,Mek2*
- *Leopard syndrome*
  - *PNP-11, RAF1*
- *King syndrome*
  - *MHS 1-4*
- *Watson syndrome*
  - *NF1*

Associated findings in Noonan syndrome

- *Clotting anomaly*
- *Upper cervical instability*
- *High incidence of cord anomalies*
- *Malignant hyperthermia*
- *Cardiomyopathy*

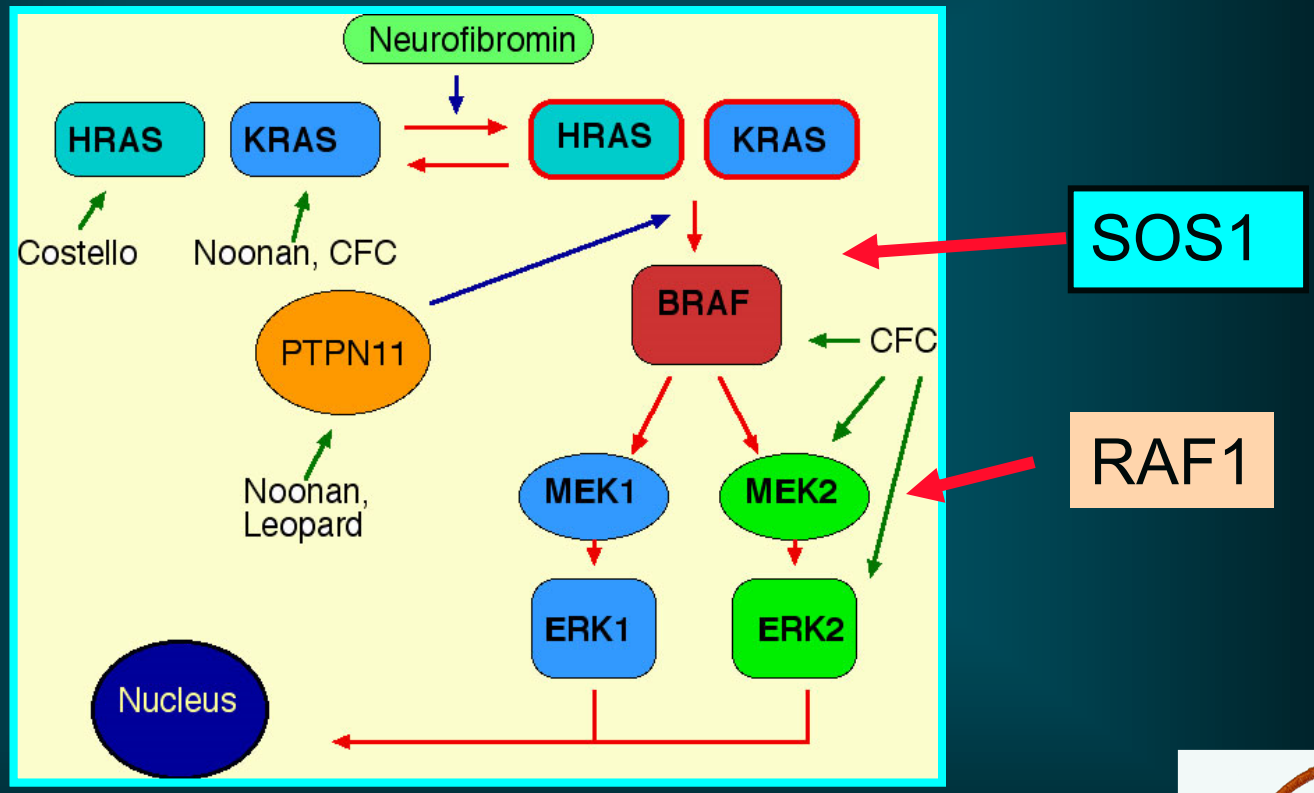
How should I treat this patient?

- *Bracing may not be effective*
- *Surgery may be very complicated*
- *Does he really have Noonan syndrome?*
- *If he doesn't, does he have the same risk factors?*

Minimal Pre-op Assessment in Noonan Syndrome

- *Clotting studies*
  - *Noonan patients have a high incidence of bleeding disorders*
- *Heart & lung evaluation*
  - *Decreased lung volume*
  - *Pulmonary stenosis, etc.*
- *Evaluation for malignant hyperthermia*
  - *Creatine Kinase blood test*
- *C-spine X-rays*
- *MRI of spine to rule out cord abnormality*

Noonan Syndrome & Its Mimics



From: Roberts, A, J Med Genet 43(11), 833, 2006

Thanks for your attention

Muchas Gracias