Dural Ectasia in NF1, What do we know? What can we do?

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UMKC School of Medicine

BEST CHILDREN'S HOSPITALS U.S.News & WORLD REPORT RANKED IN 9 SPECIALTIES 2014-15

MAGNET RECOGNIZED AMERICAN NURSES CREDENTIALING CENTER

Disclosures

- None related to this talk

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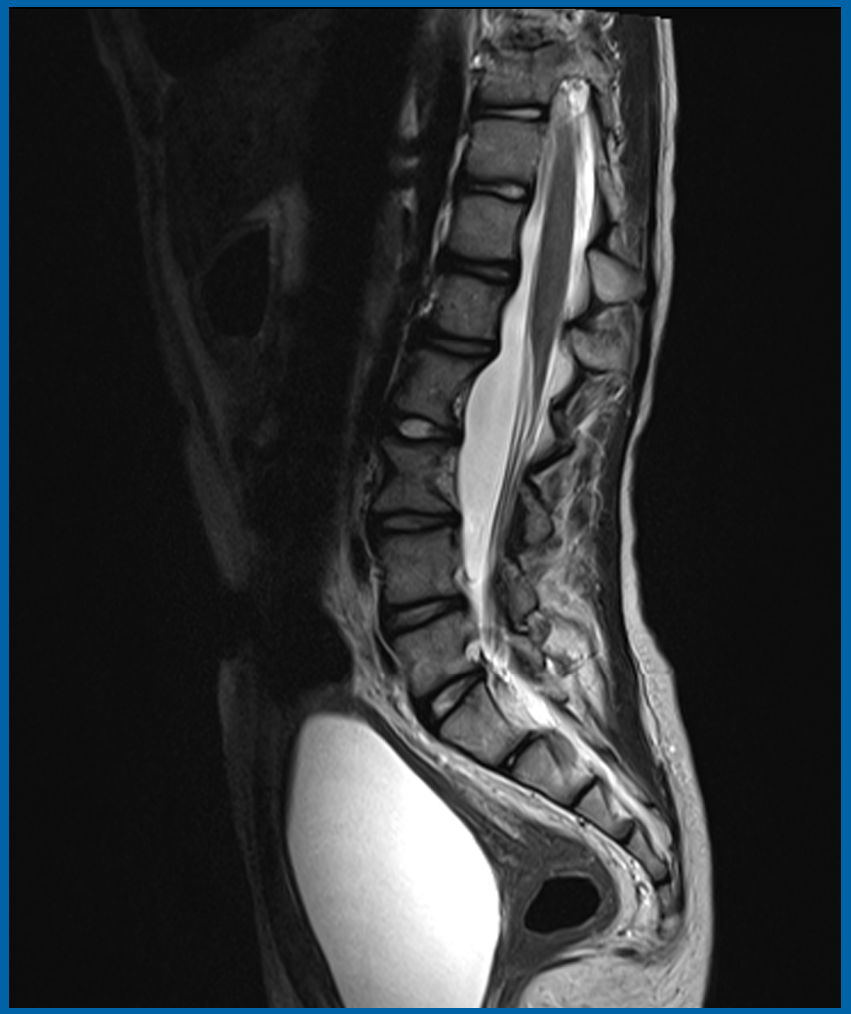
What Do We Know?

- Dural ectasia is circumferential enlargement, widening or ballooning of the dural sac, nerve root sleeves and spinal canal.
- Can affect the spinal canal in any plane.
- All spine locations, but common in lumbosacral region



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Associated Conditions

- Marfan syndrome
- Loeys Dietz syndrome
- Developmental spondylolisthesis
- NF1
- Ehlers-Danlos syndrome
- Achondroplasia
- Vertebral fractures
- Ankylosing spondylitis
- Osteogenesis imperfecta
- Post surgical
- Idiopathic

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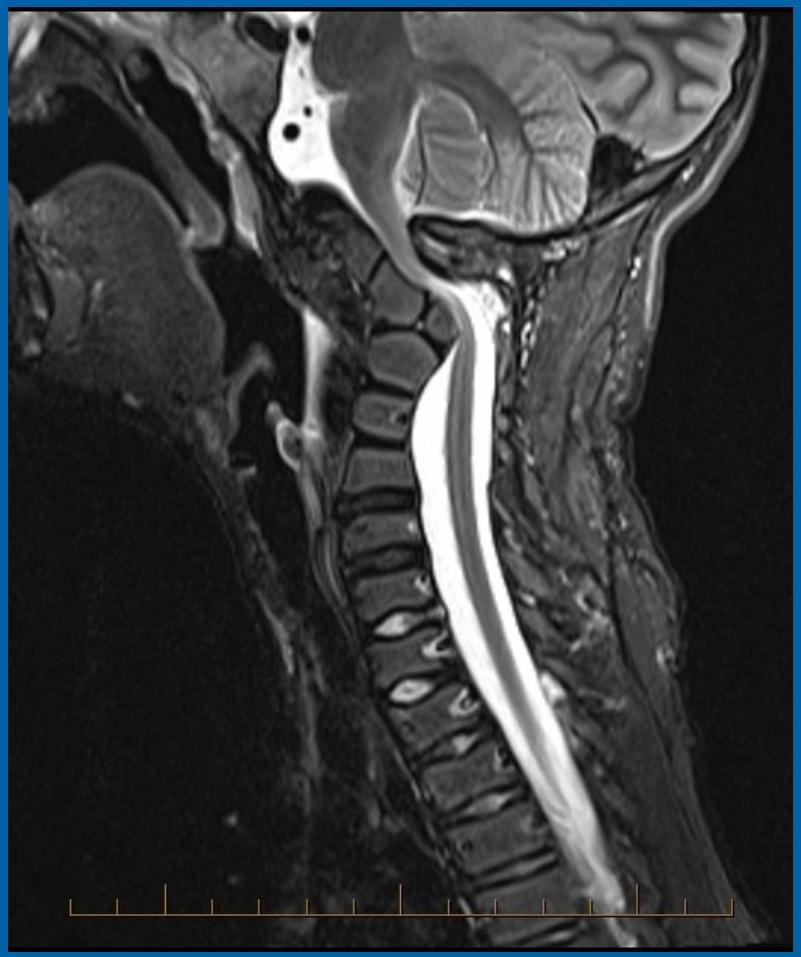

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Marfan Syndrome

- Less common than NF1 1/5000
- Deficiencies in fibrillin-1 increase the levels of B(TGF-B) leading to Marfan phenotype
    - Sponseller 2013
- Dural ectasia -one of the major (modified Ghent) diagnostic criteria.
    - Rose PS 2000
- Often in lumbosacral spine, thinning of bone, anterior meningocels, LBP.
- Over 63% prevalence of dural ectasia, peaks in adolescence
    - Mesfin 2013

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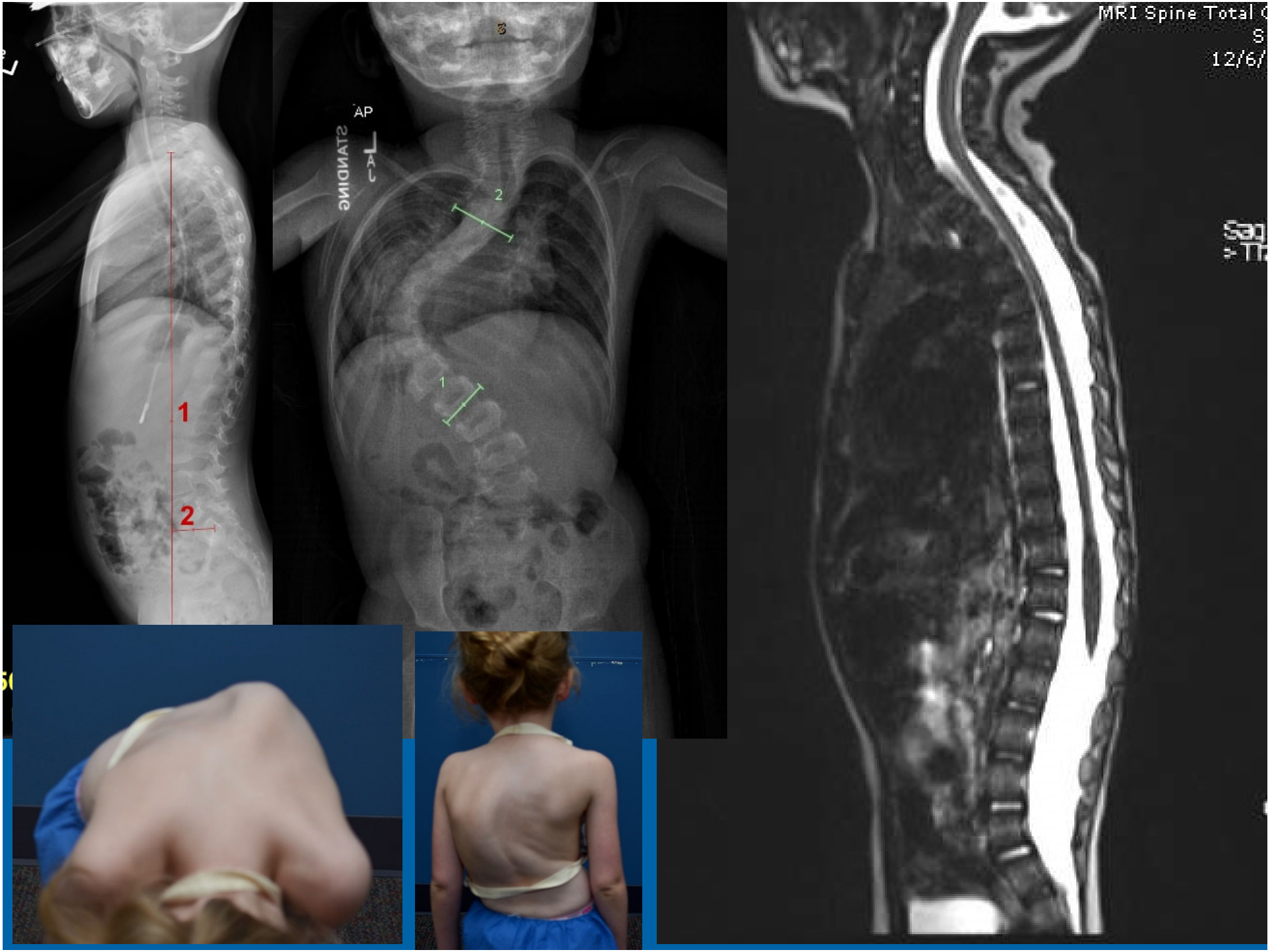
35°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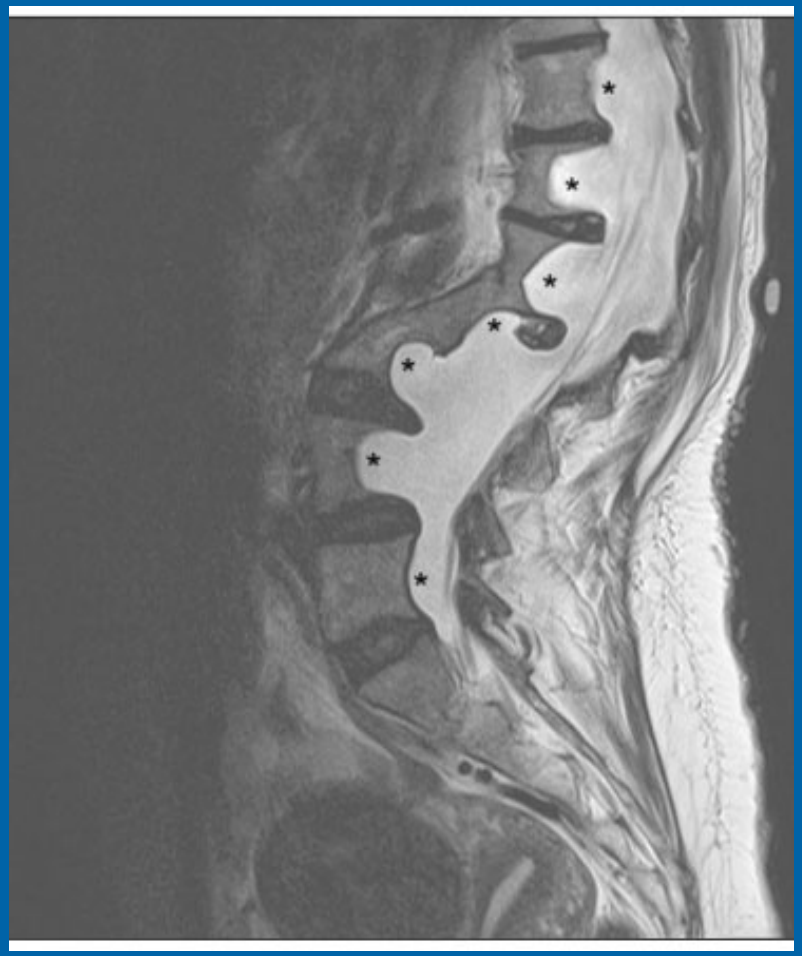
Dural Ectasia. Radiographic Critera



- Plain radiographs
- Scalloping (92% specific but only 57% sensitive
  - Ahn 2001
- Major: Width dural sac below L5 > width above L4, anterior sacral meningocel. Minor: L5 nerve root sleave diameter >6.5 mm. S1 scalloping >3.5 mm
  - Ahn 2000

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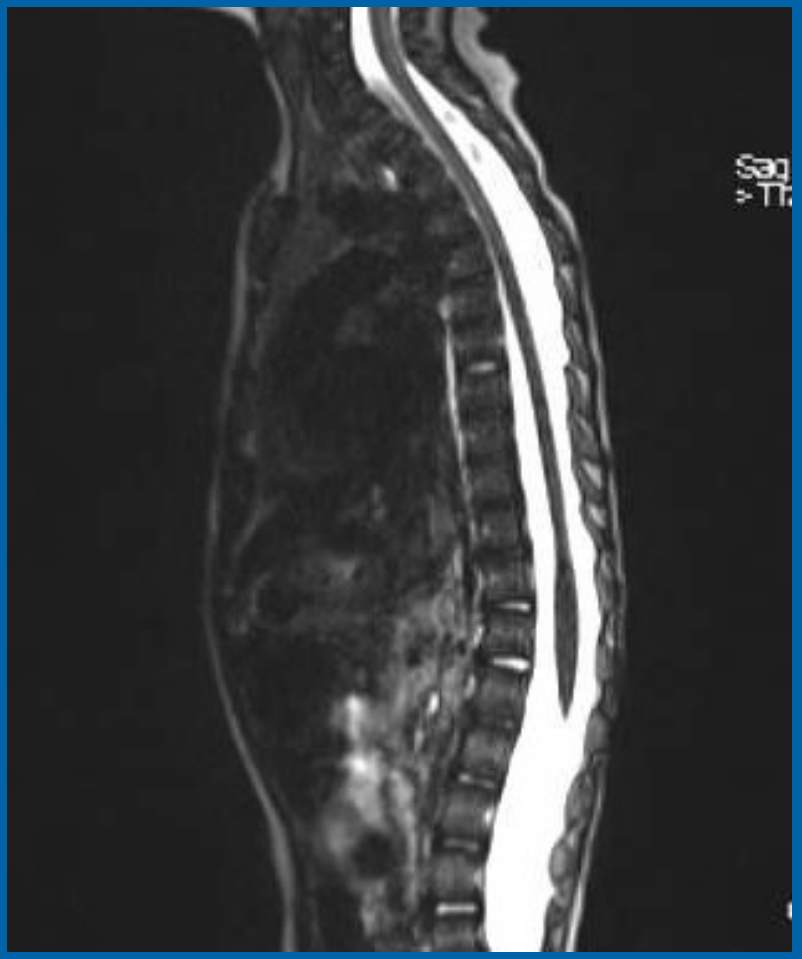
MRI for Dural Ectasia Children

- Only dural sac ratio at L5 and S1 and sagittal dural sac width at S1 greater than L4 significant for dural ectasia
    - Habermann CR 2005



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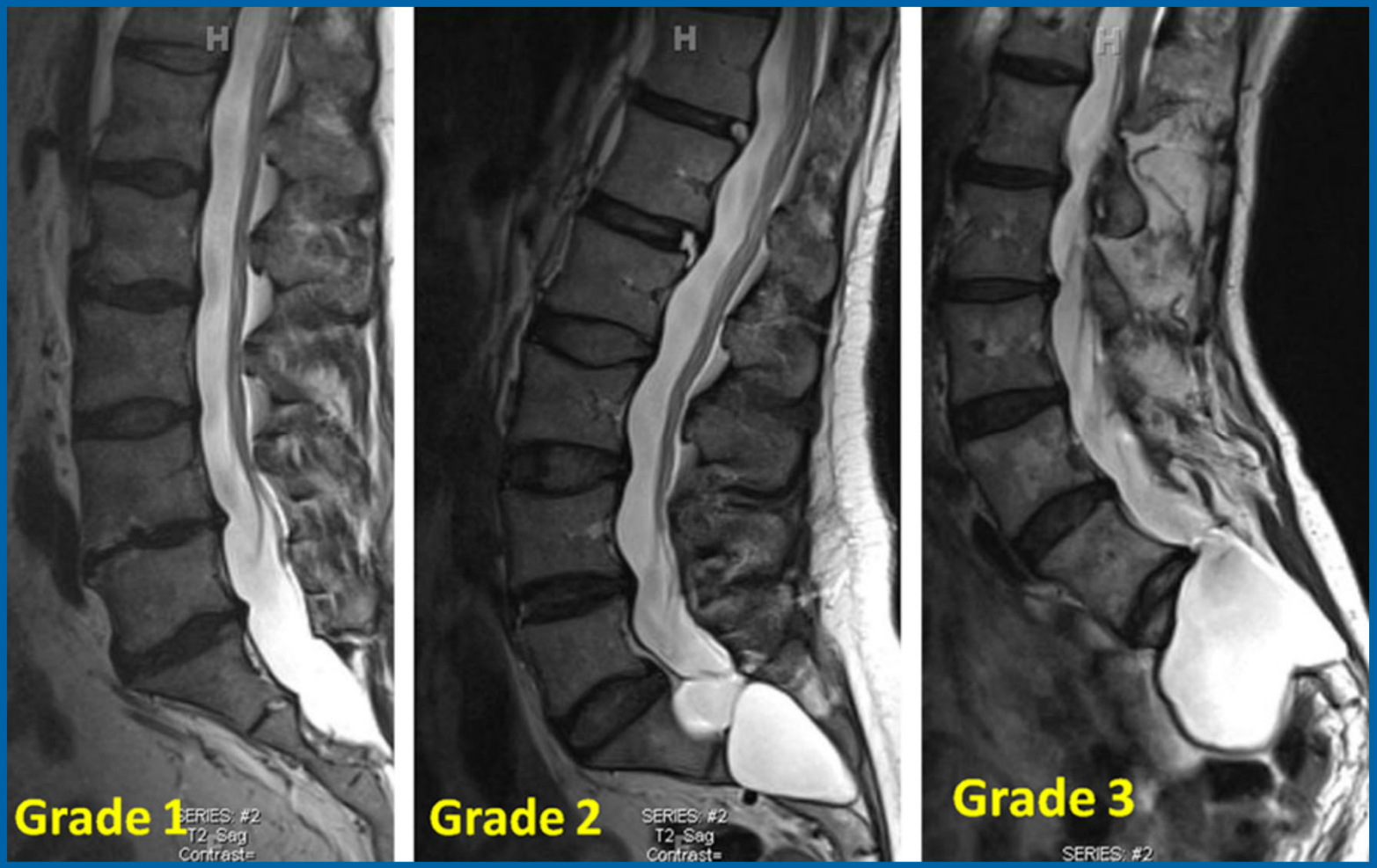

- Grading system of Fattori for Marfan Lancet 1999

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Neurofibromatosis

- Autosomal dominant
- Deletion of the *NF*1 gene on chromosome 17q11.2
- 1/3000-4000 globally
- 50% de novo mutations
- Varied presentation and penetrance.
- Diagnosis based on clinical findings >=2/7 NIH diagnostic criteria

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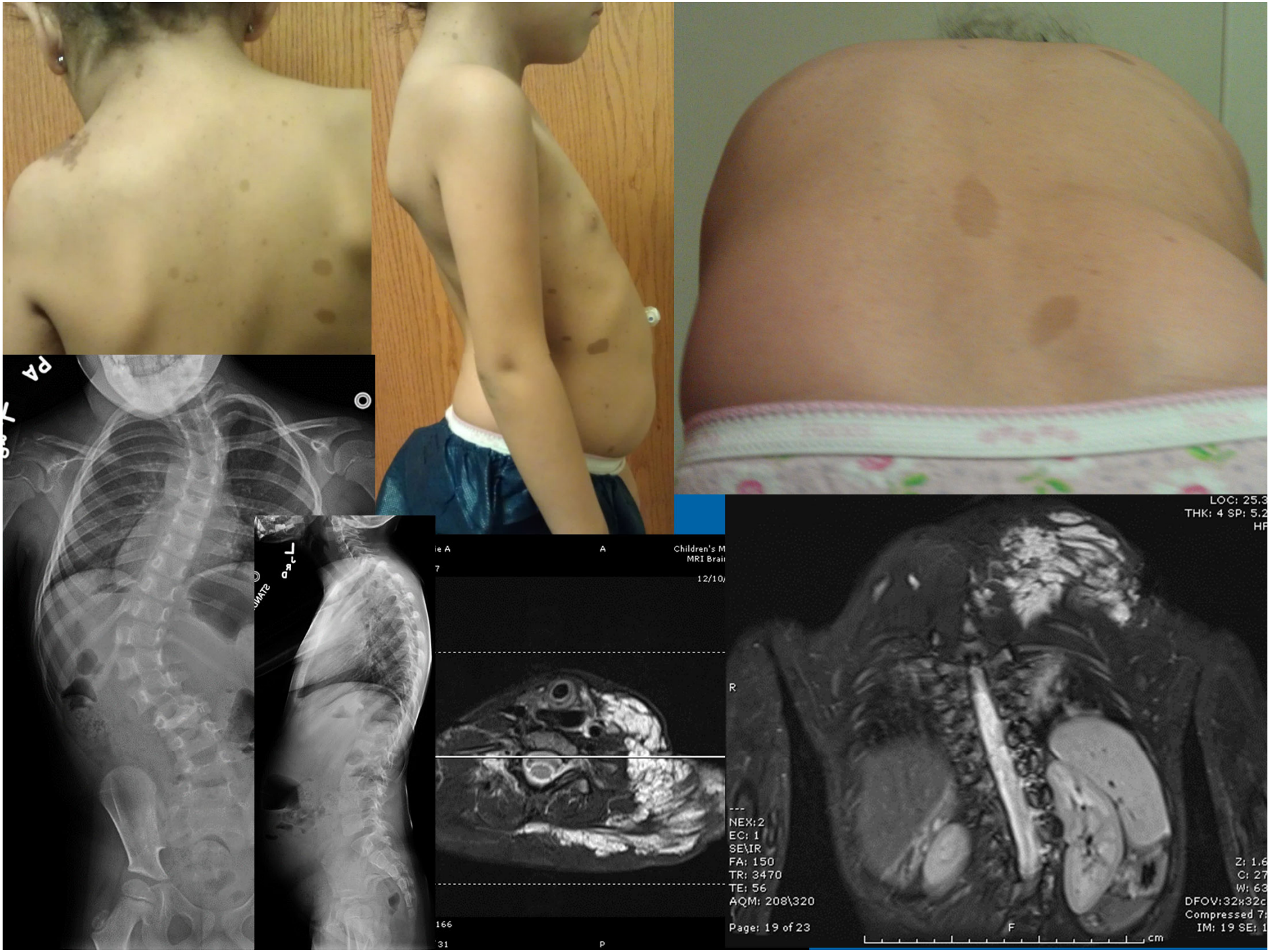
57°
15°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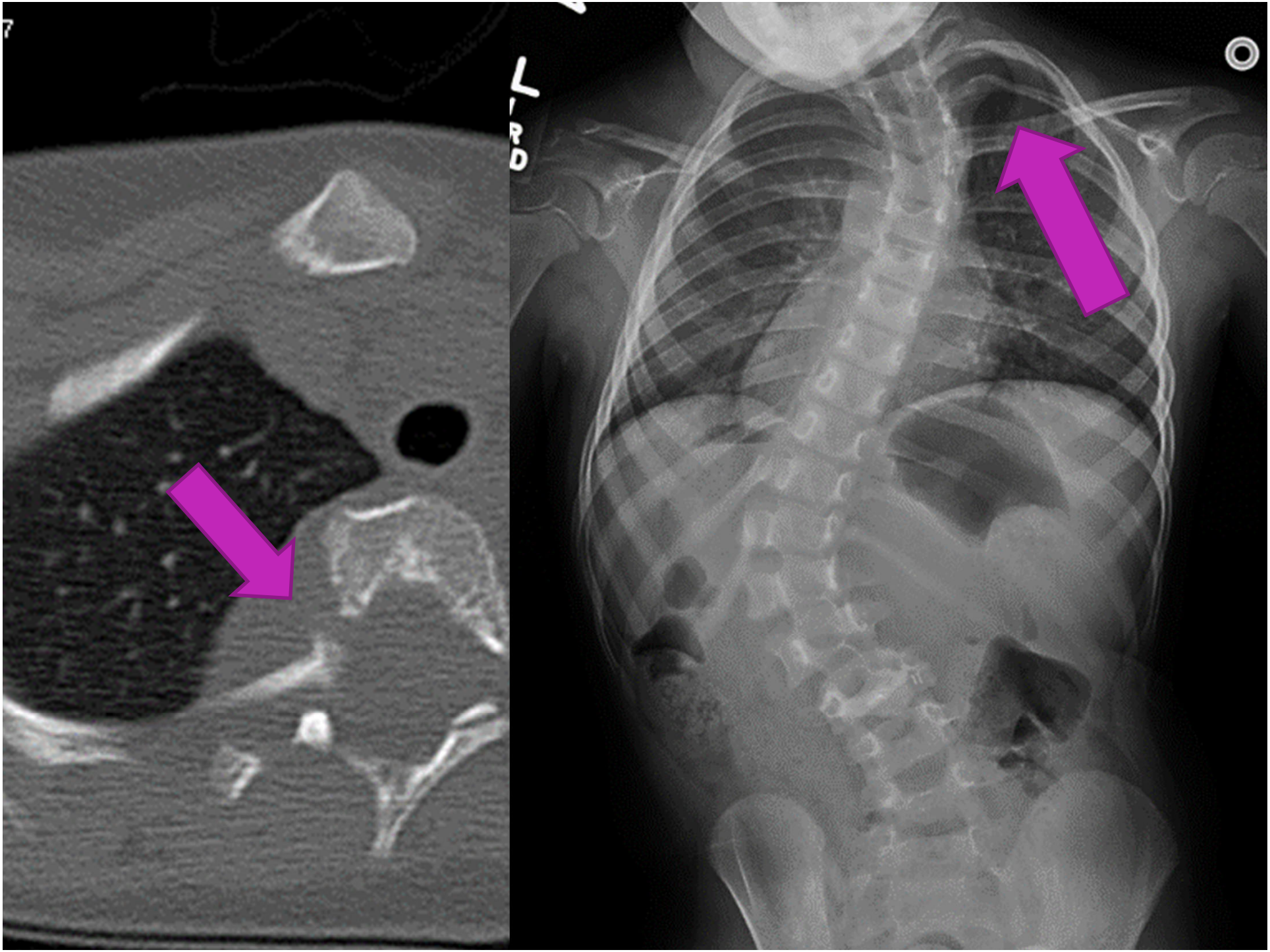

Tissue Defects in NF1

- *NF1* - potent tumor suppressor gene.
- *NF1* gene encodes for protein neurofibromin, expressed in many cells/tissues
- Genetically modified mouse models and NF1 patient cells
- Deficiency in osteoblast differentiation/commitment
- Increase in osteoclast differentiation/survival
- NF1 haploinsuficiency or double inactivation of NF1 gene in range of cells: osteoblasts, chondrocytes, fibroblasts, vascular endothelia –defective bone healing
  - Schindeler A, Little DG 2008
    -

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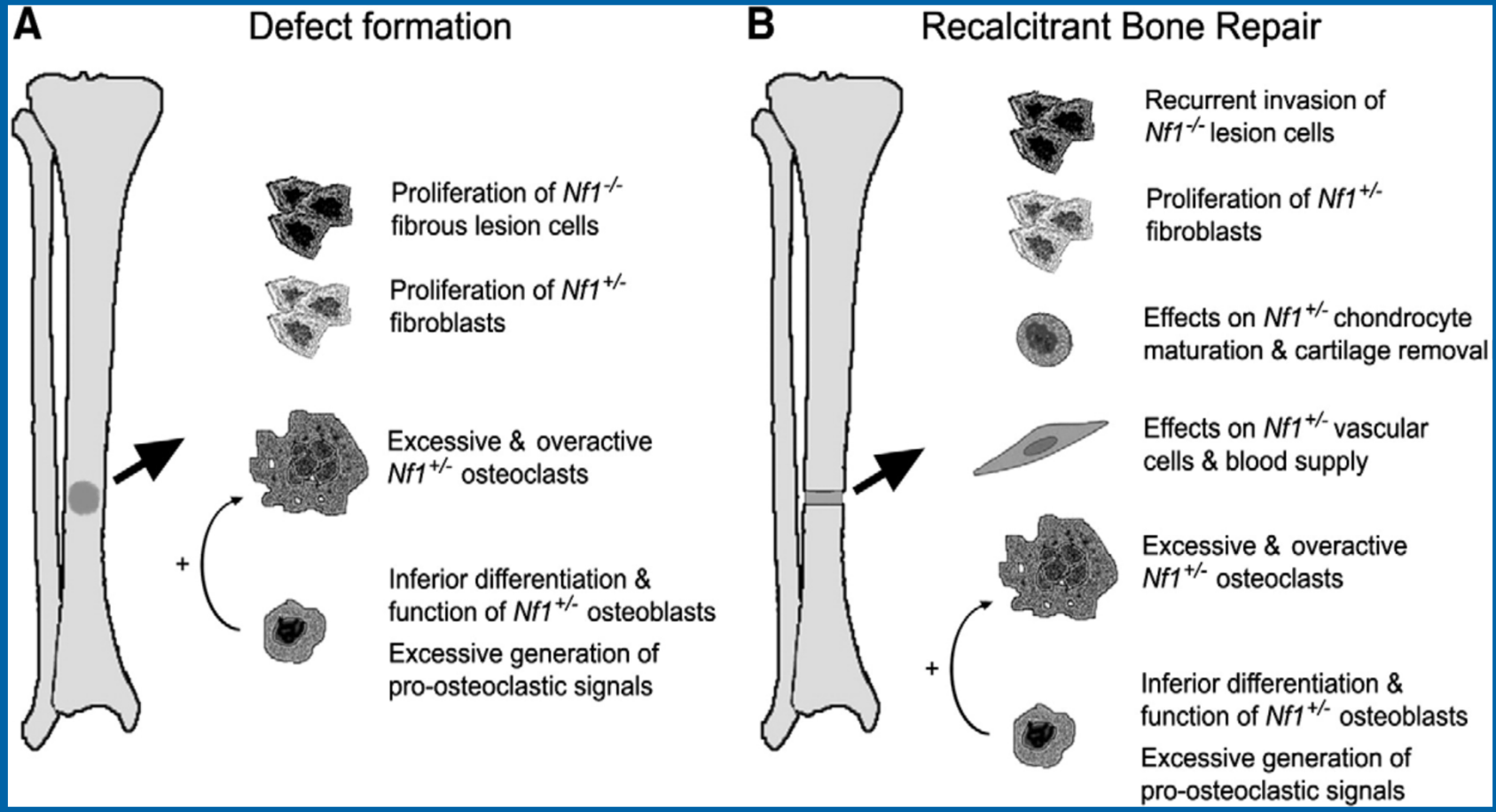
Cellular basis for osseous defect formation and recalcitrant repair

Schindeler A and Little DG, 2008



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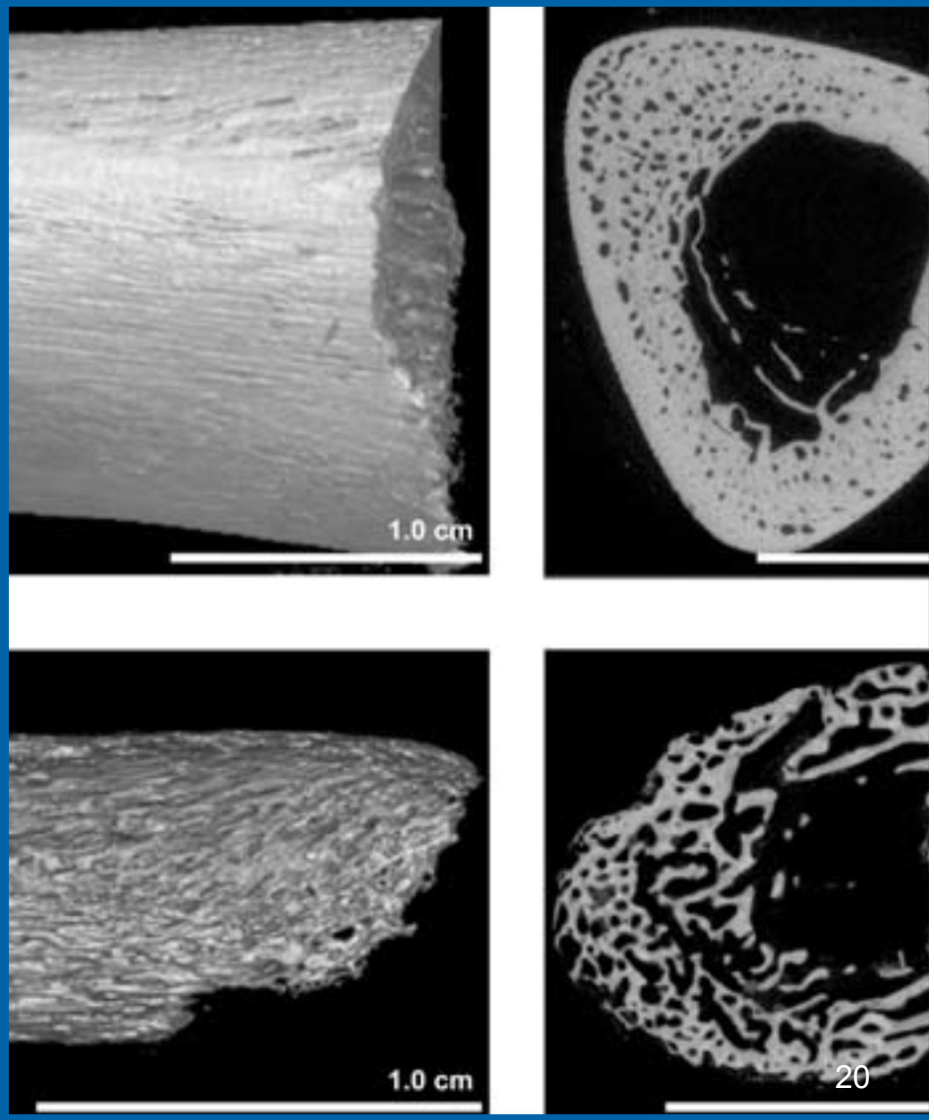
What does *NF1* Do?

- Required for proper endochondral ossification
- Intervertebral disc formation
- Proper axial skeleton formation
- Bone remodeling and skeletal properties
  - Wang W 2001



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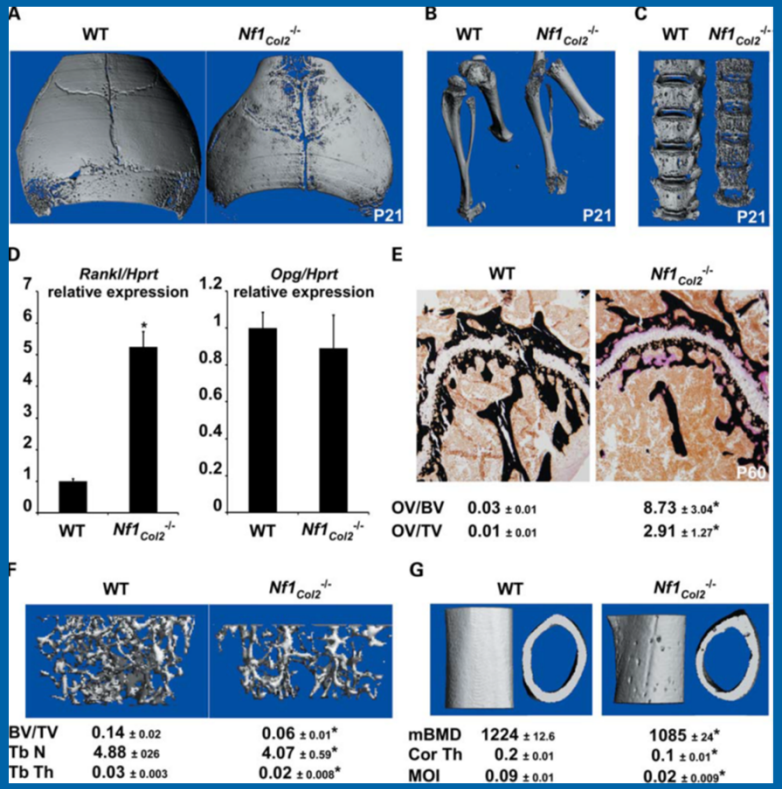
NF1 and Osteoprogenitor

- Lack of *Nf1*$_{Col2}^{-/-}$ in osteochondroprogenitor cells in mice show progressive spine deformity
- Low bone mass phenotype
  - Wang W, 2011



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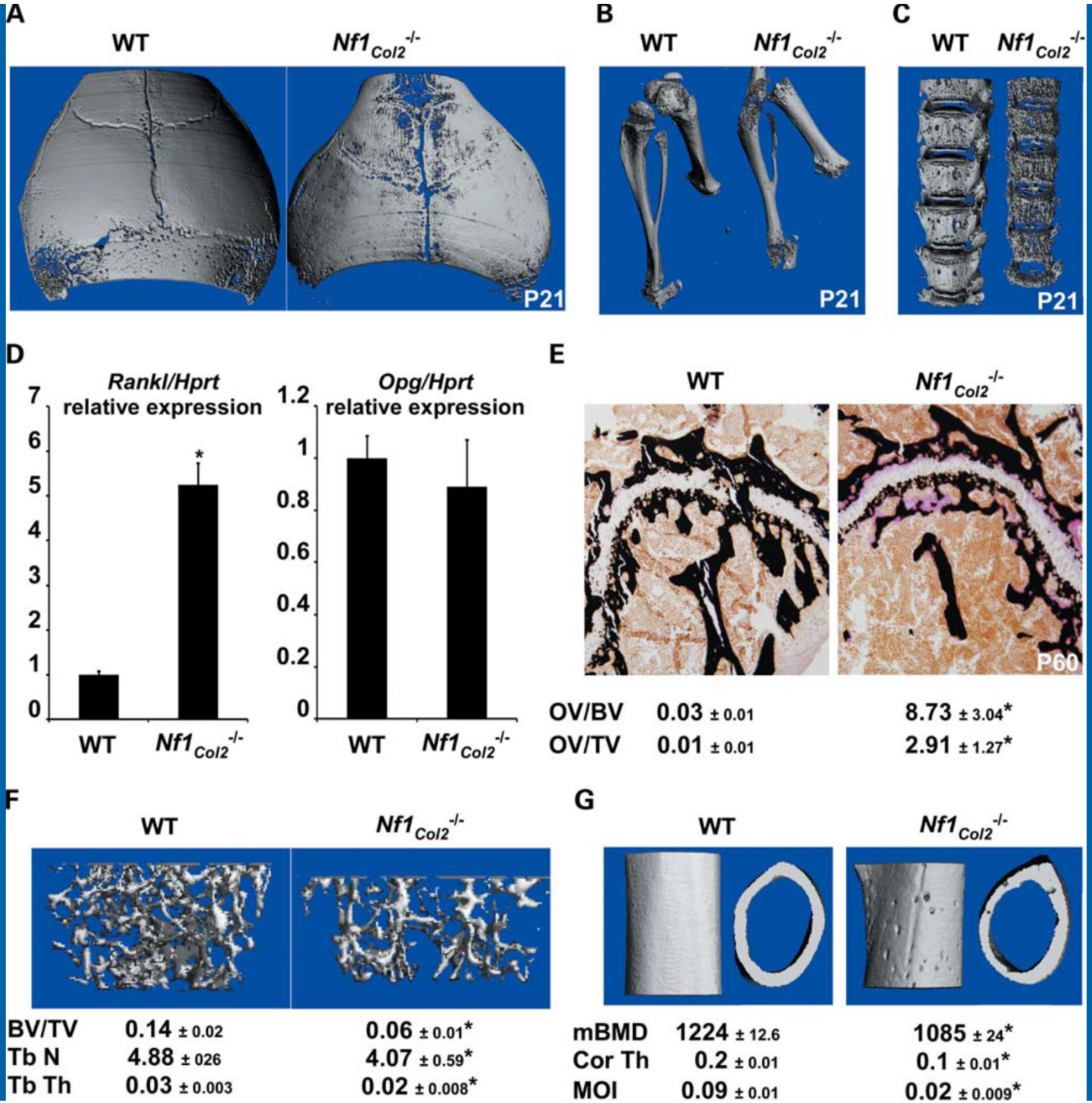
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C
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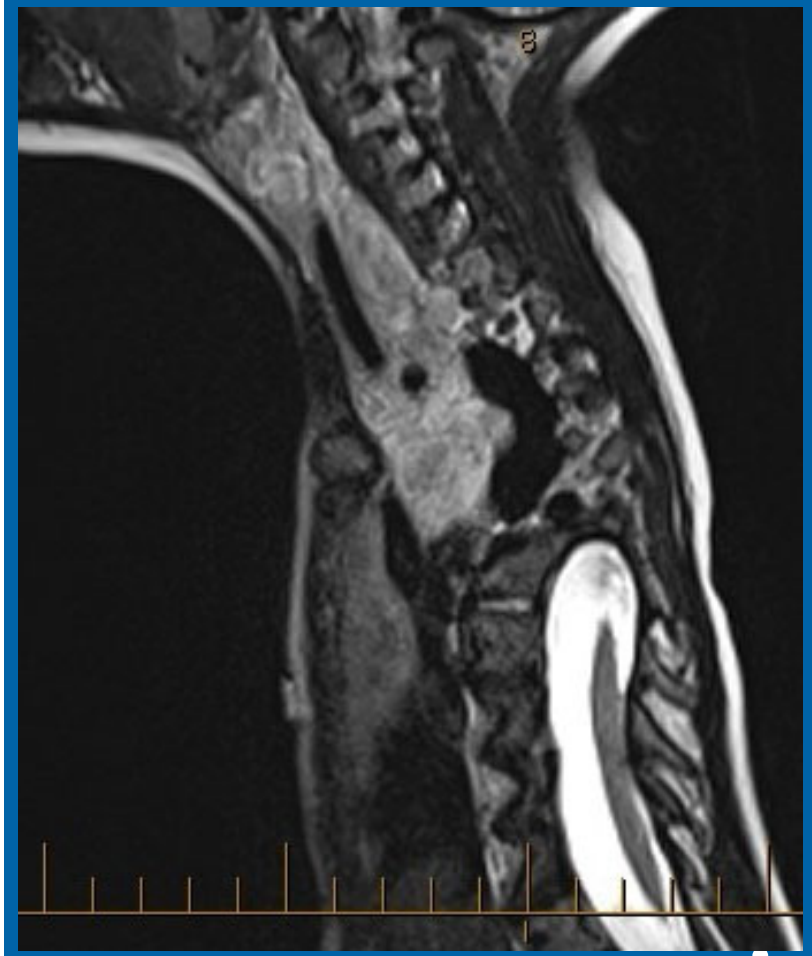
D
Rankl/Hprt
relative expression
7
6
5
4
3
2
1
0
*
WT
Nf1 Col2 -/-
Opg/Hprt
relative expression
1.2
1
0.8
0.6
0.4
0.2
0
WT
Nf1 Col2 -/-
E
WT
Nf1 Col2 -/-
P60
OV/BV 0.03 ± 0.01 8.73 ± 3.04*
OV/TV 0.01 ± 0.01 2.91 ± 1.27*
F
WT
Nf1 Col2 -/-
BV/TV 0.14 ± 0.02 0.06 ± 0.01*
Tb N 4.88 ± 026 4.07 ± 0.59*
Tb Th 0.03 ± 0.003 0.02 ± 0.008*
G
WT
Nf1 Col2 -/-
mBMD 1224 ± 12.6 1085 ± 24*
Cor Th 0.2 ± 0.01 0.1 ± 0.01*
MOI 0.09 ± 0.01 0.02 ± 0.009*

Pathophysiology of Dural Ectasia NF1



- General primary mesodermal dysplasia

Weakness in the collagen through proliferation and invasion of NF1 deficient fibroblasts

  - Atit 1999

30% have osteopenia due to haploinsufficiency

Osteomalacia, osteoporosis, vitamin D deficiency, stress fracture

- CSF pulsations

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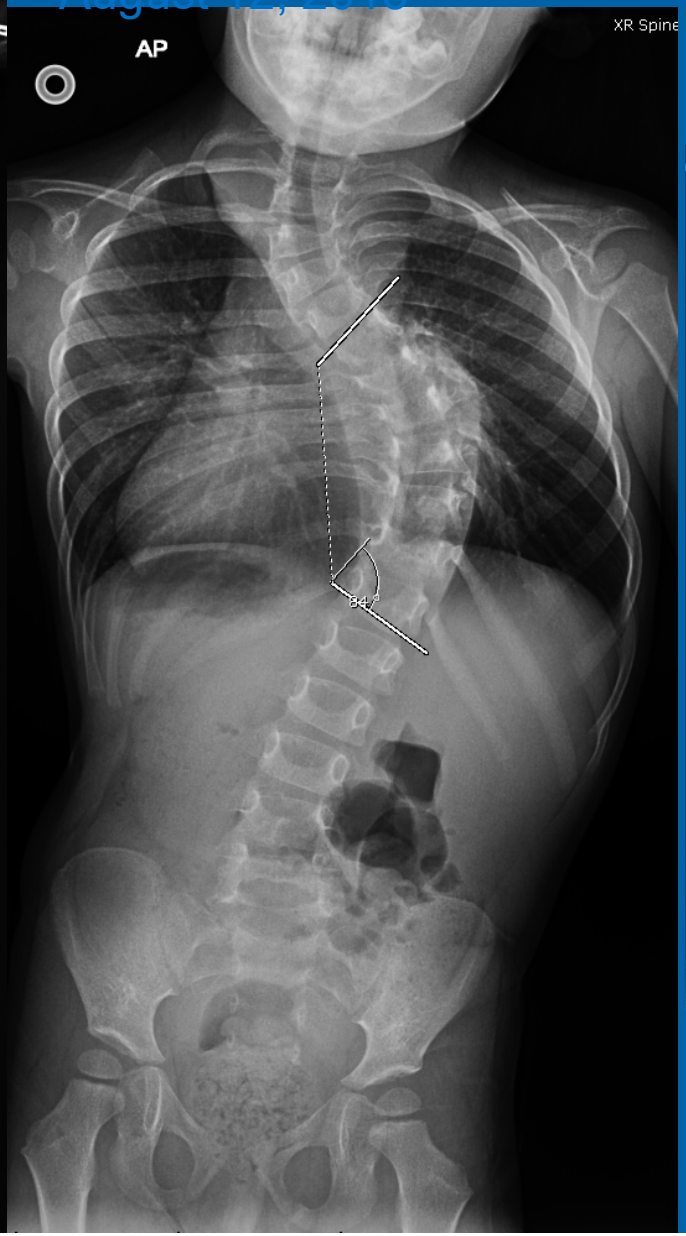
Progressive NF1 Scoliosis

August 12, 2013



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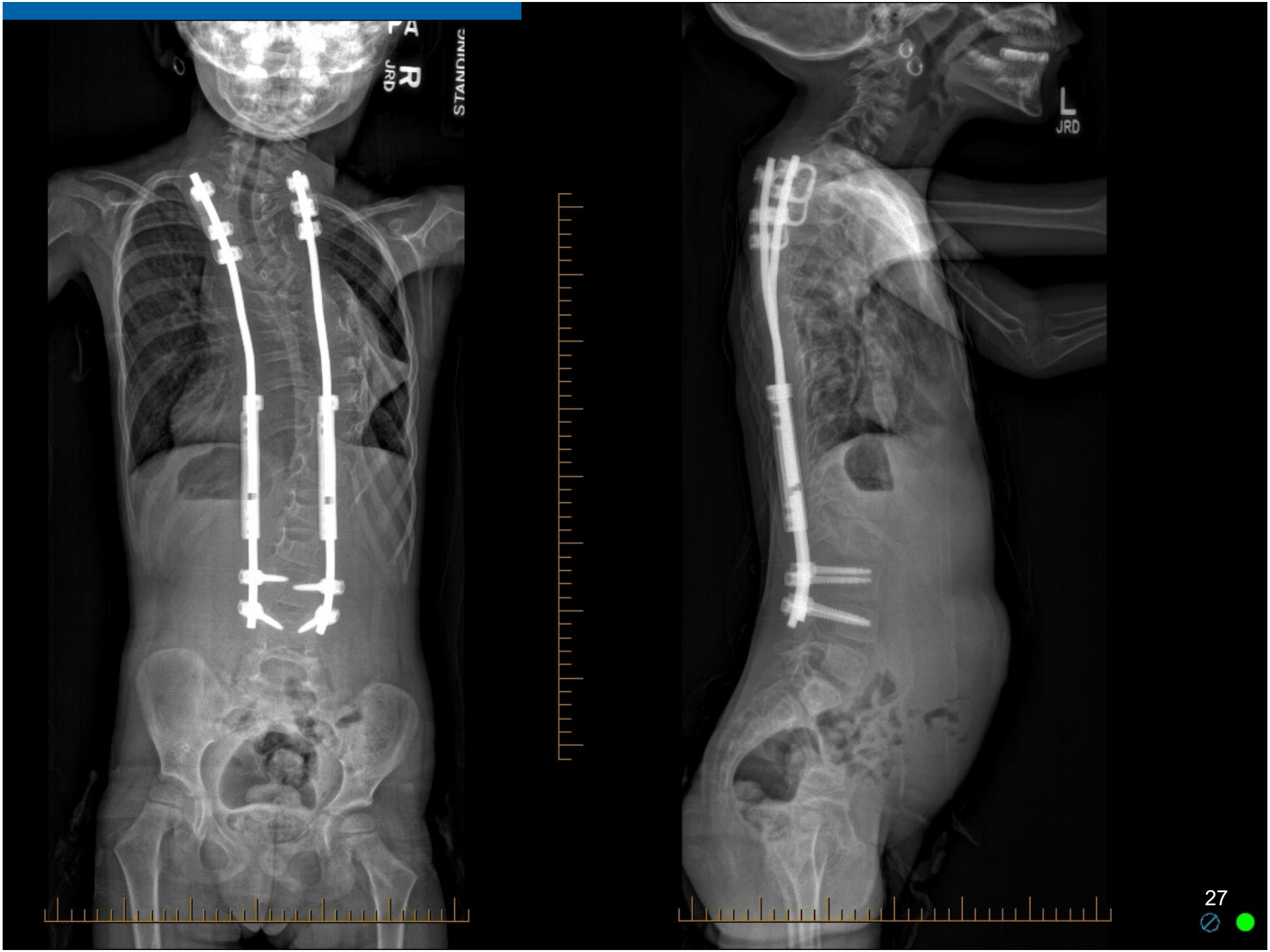
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NF1 and Dural Ectasia

Frequently thoracic

Can be relatively protective, increased SAC

Posterior scalloping commonly associated with dural ectasia

Lateral and anterior scalloping commonly result of primary mesodermal dysplasia

- Tsirikos AI 2004

Anterior dural ectasia and dislocation of the spine

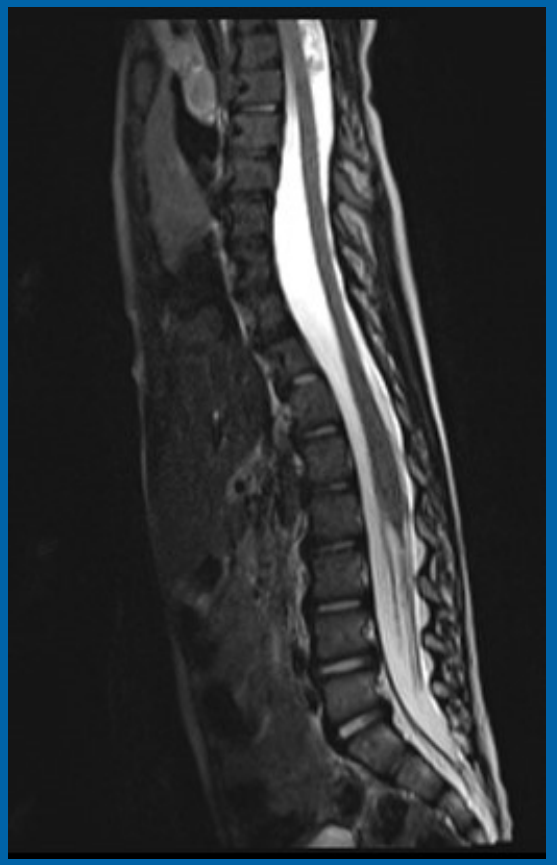
- Winter 1991

Modi HN 2009

De Kleuver M 2004

What Can We Do?

- Only case series and case reports.
- Stick to sound principles
- Preserve growth/prevent deformity
- Avoid the dural ectasia and tumors
- Anterior- posterior fusion
- Be aware of ribs in the canal
- sharp curves/relative stenosis
- Therapies
- BMP/Bisphophonates
- Mouse model – (RAS/ERK pathway activation by *Nf1* loss of function)



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