

Diagnosis of the Marfan Syndrome

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Marfan Syndrome

Antonine B-J Marfan

(1858-1942)

Trained in Internal Medicine—1888

First Professor of Pediatrics in
France

Author of standard textbooks

Noted for development of

BCG

Subxiphoid approach to
pericardiocentesis

“Marfan’s Law” (scrofula confers
immunity to pulmonary Tbc)



Marfan Syndrome

Antonine Marfan

1896 Described Gabrielle P.
to the Parisian Society of
Internal Medicine

- Age 5
- *pattes d'araignée* (spider legs)
- Congenital contractures
- Progressive scoliosis

Termed the condition
dolichostenomelia



Marfan Syndrome

Timeline

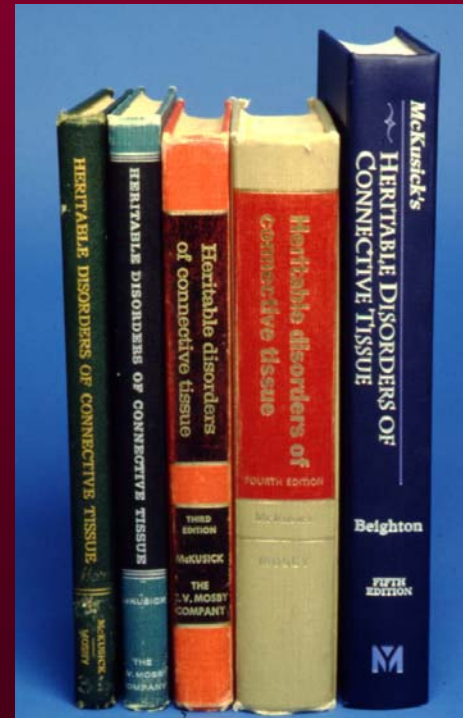
- 1896** Skeletal features
- 1902** Achard coins term "arachnodactyly"
- 1912** Mitral regurgitation
- 1914** Ectopia lentis
- 1931** Disorder of mesenchyme
- 1943** Aortic aneurysm & dissection
- 1949** Autosomal dominance, single locus



Marfan Syndrome Timeline

1955 **Extent of CV involvement defined**
**McKusick coins “Heritable
disorder of connective tissue”**

1956 McKusick publishes
First edition of *Heritable
Disorders of Connective
Tissue*



Did Marfan's Original Patient Have "His" Syndrome?

Hecht & Beals (1972) were among the first to describe a "new" heritable disorder of connective tissue, **congenital contractural arachnodactyly (CCA)**

**autosomal dominant
congenital contractures, treatable
scoliosis, progressive
"crumpled" ear helix**

They were the first to suggest that Gabrielle P. had CCA, and not what we knew as Marfan syndrome

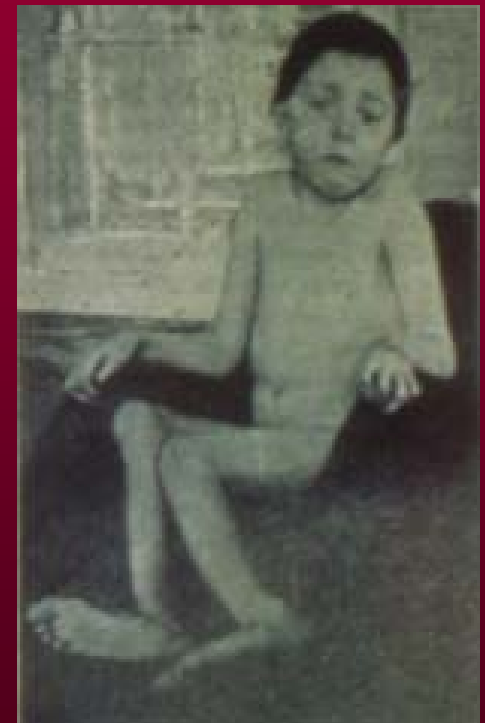


Did Marfan's Original Patient Have "His" Syndrome?

In CCA, the eyes and CV system are supposedly uninvolved

We have no information about the eyes, heart or aorta of Gabrielle P. She died at 13, presumably of tuberculosis

Her family history was unrevealing
Illustrates some of the difficulties of establishing diagnoses, even today



Marfan Syndrome

Skeletal Features: *Tall Stature,*
Dolichostenomelia



Marfan Syndrome

Skeletal Features: *Joint Hypermobility*



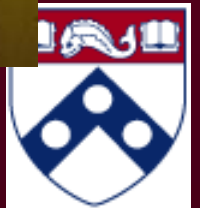
Marfan Syndrome

Skeletal Features: *Wrist and Thumb Signs*



Marfan Syndrome

Skeletal Features: *Anterior Chest Deformity*



Marfan Syndrome

Skeletal Features: *Vertebral Column Deformity*



Marfan Syndrome

Ocular Features

- Ectopia lentis (50-60%)
- Myopia (elongated globe & lenticular)
- Flattened cornea
- Cataract
- Glaucoma
- Retinal detachment



Marfan Syndrome

Ocular Features: *Ectopia Lentis*



Marfan Syndrome

Cardiovascular Features

- Mitral valve prolapse
- Aortic root dilatation
- Aortic dissection
 - Type A in 90%



Marfan Syndrome

Cardiovascular Features: *Mitral Valve Prolapse*

- ~85%
 - Age-dependent
 - More common in females
 - Dysrhythmia
- Progresses in 1/3
- TVP common but rarely clinically important



Marfan Syndrome

Cardiovascular Features: *Aortic Root Dilatation*

First recognized by
Baer, Taussig &
Oppenheimer

Bull J Hopkins Hosp
1943;72:309-331



Marfan Syndrome

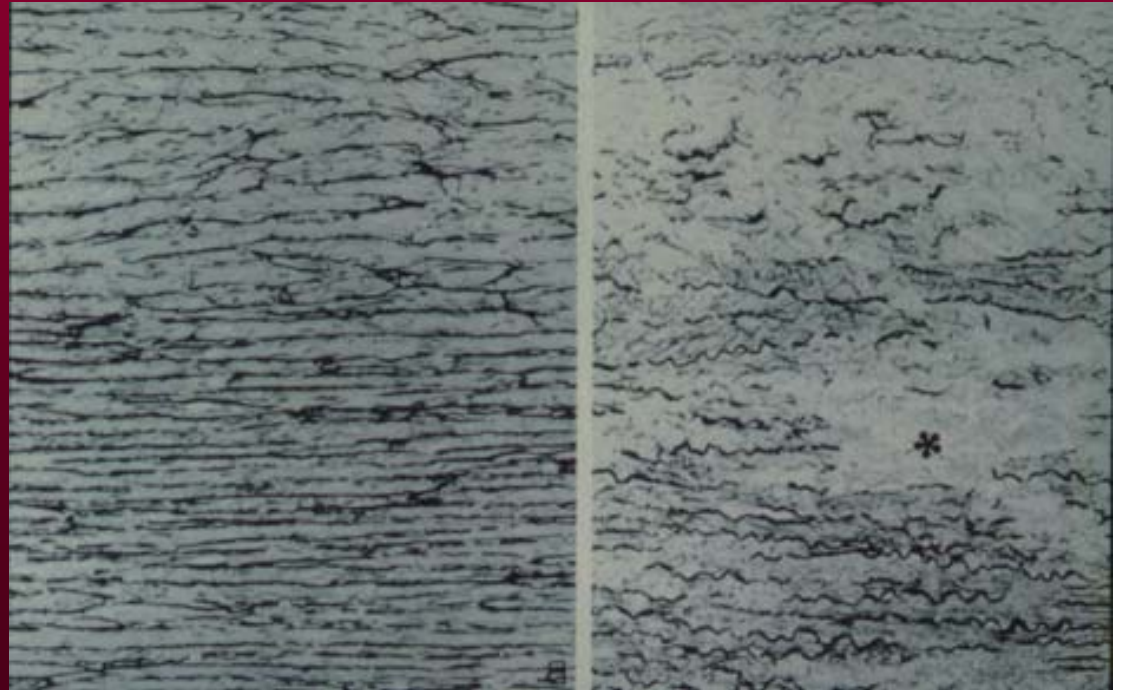
Cardiovascular Features: *Aortic Root Dilatation*



Marfan Syndrome

Cardiovascular Features: *Aortic Root Dilatation*

Associated with medial degeneration (incorrectly termed "cystic medial necrosis")



Marfan Syndrome

Aortic Root Dilatation: *Complications*

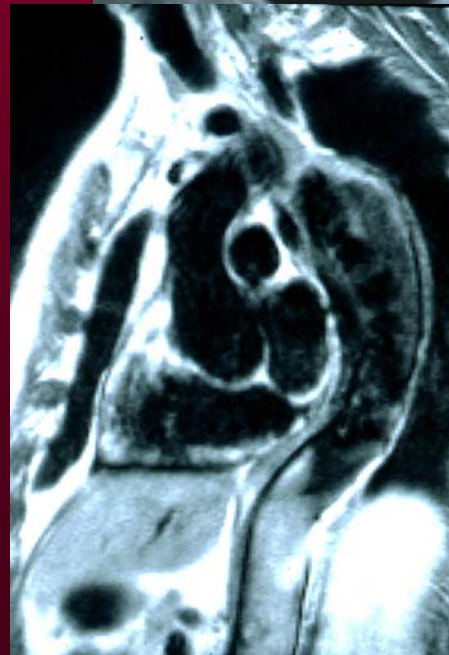
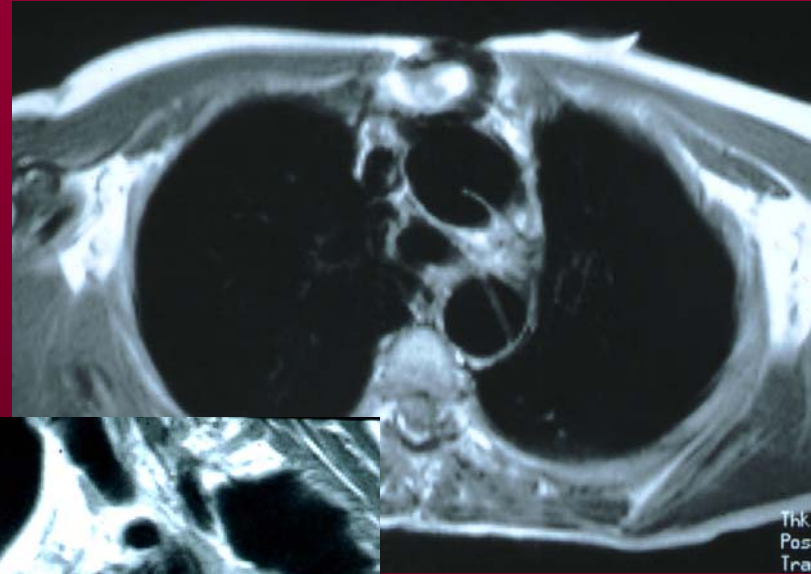
- **Aortic regurgitation**
 - CHF
 - Sudden death
- **Aortic dissection**
 - Sudden death
 - MI
 - Organ ischemia
 - Stroke
 - Late rupture



Marfan Syndrome

Cardiovascular Features: *Aortic Dissection*

- **Type A**
 - Positive association with root diameter
 - Typically involves entire aorta
- **Type B**
 - Typically postductal



Marfan Syndrome

Prevalence

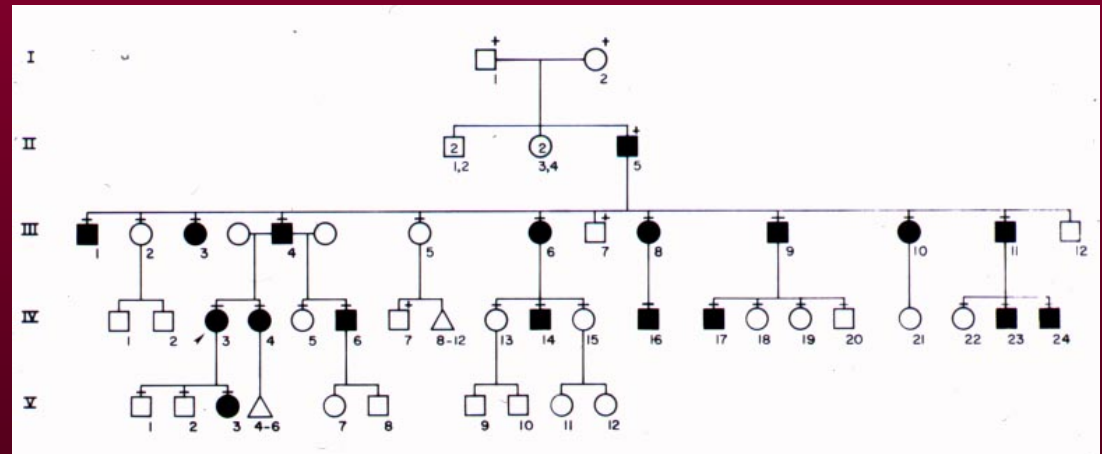
- ~1/3-5,000
- No ethnic predisposition



Marfan Syndrome

Inheritance: *Autosomal Dominant*

- Marked intra- and interfamilial variability
- ~30% cases are sporadic
 - Paternal age effect



Marfan Syndrome vs. Homocystinuria

Homocystinuria due to CBS deficiency was not recognized until 1965 and previously had been diagnosed as MFS

Distinguished by inheritance, features, urine test, plasma amino acids



Marfan Syndrome

25 Years of Research

- **Improved diagnosis**
- **Understanding of natural history**
- **Medical therapy**
- **Surgical therapy**
- **Understanding cause and pathogenesis**



Marfan Syndrome

25 Years of Research

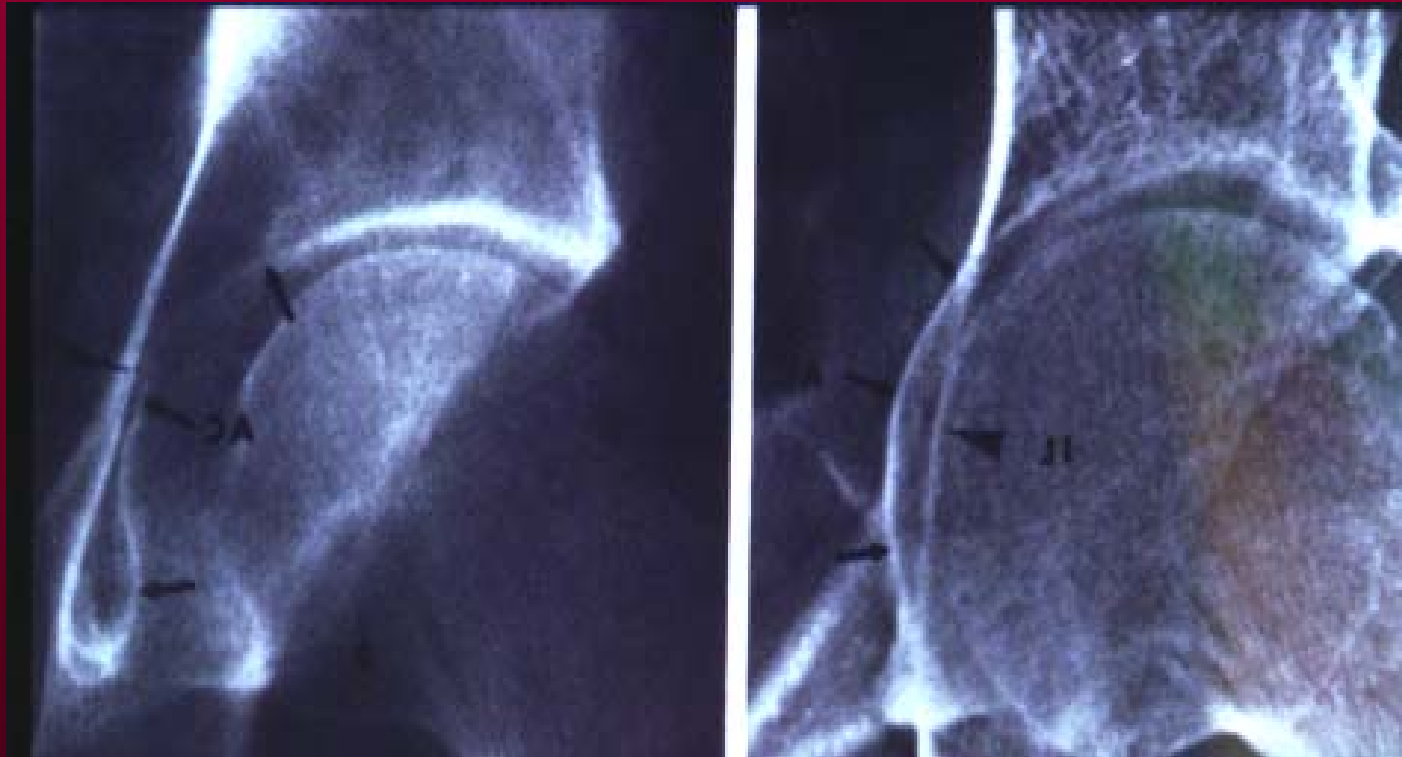
Improved diagnosis

- **Enhanced detection of features**
- **Identification of novel features**
- **Revised diagnostic criteria**



Marfan Syndrome

Skeletal Features: *Protrusio Acetabulae*



Marfan Syndrome

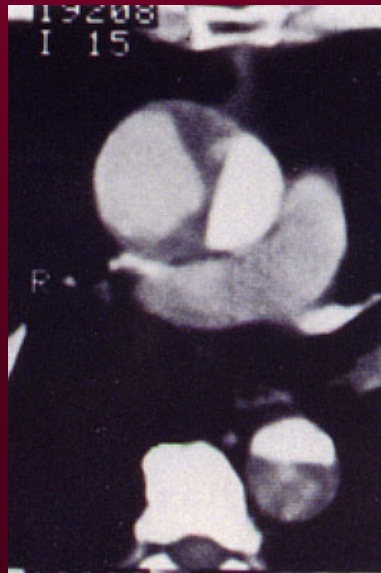
Enhanced Detection of Features

MRI

**Noninvasive ability to
detect and follow
entire aorta**



CT



Marfan Syndrome

Extensive Pleiotropy

- **Skin & Integument**
- **Pulmonary**
- **CNS**



Marfan Syndrome

Novel Features: *Skin and Integument*

Striae atrophicae

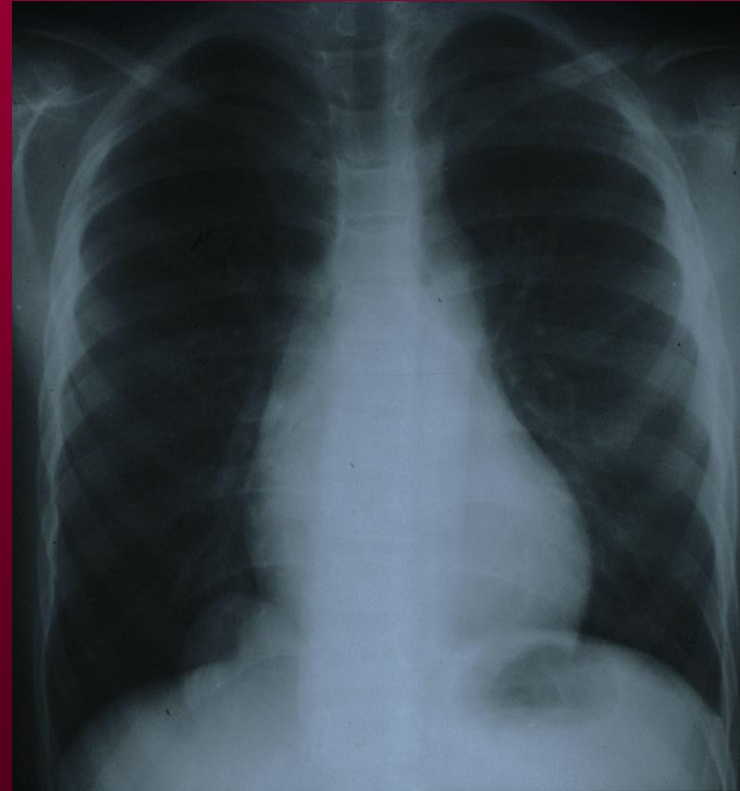


Marfan Syndrome

Novel Features: *Skin and Integument*

Herniae

Wound healing



Marfan Syndrome

Novel Features: *Pulmonary*

Pneumothorax

Restrictive disease

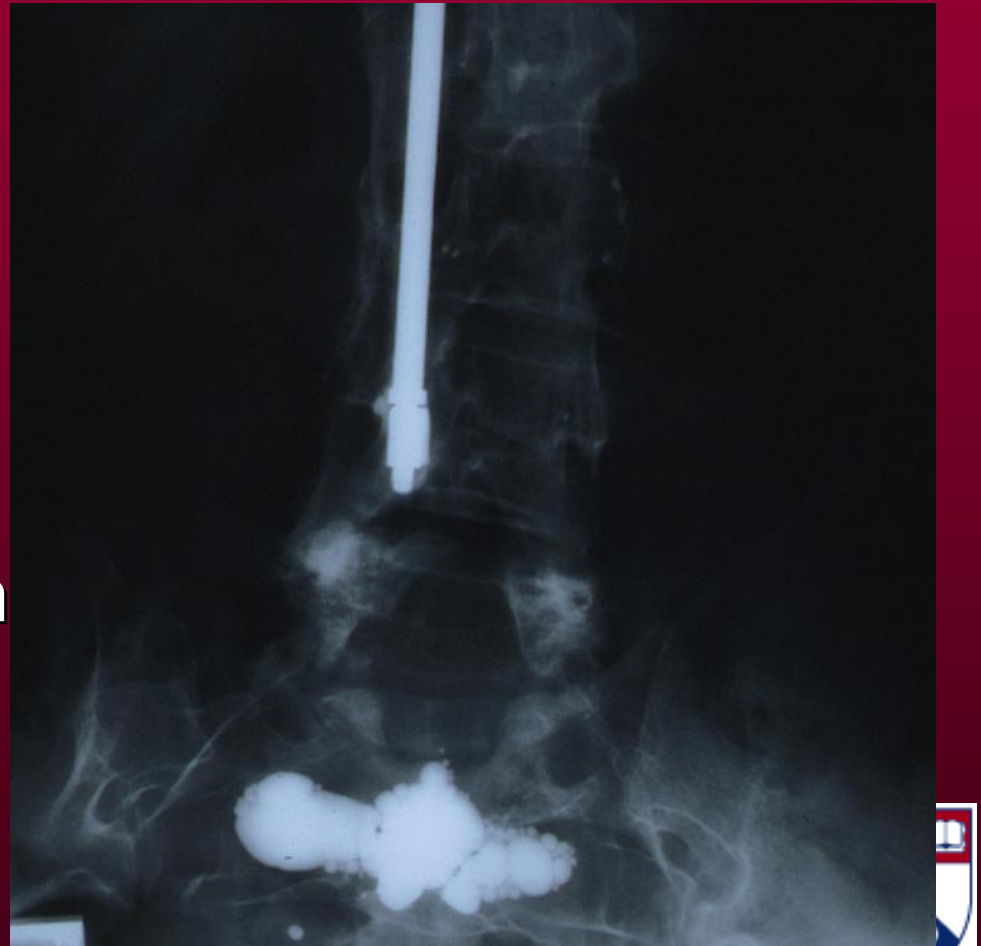


Marfan Syndrome

Novel Features: *CNS*

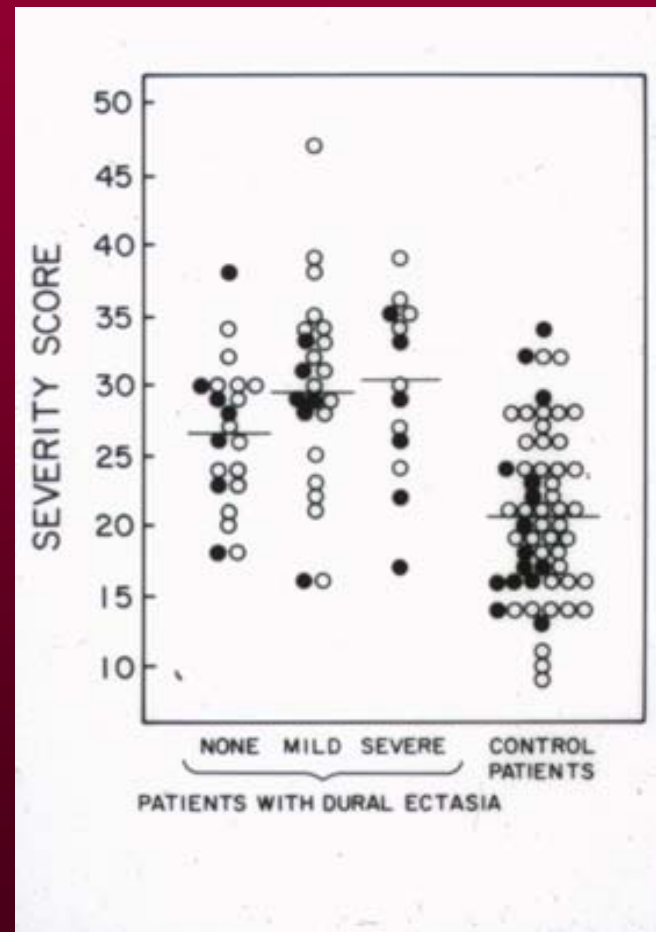
**ADHD & verbal-
performance
discrepancies**

Dural ectasia



Marfan Syndrome

Novel Features: *Dural Ectasia*



Marfan Syndrome

Revised Diagnostic Criteria

- **Berlin, 1988**

- **Ghent, 1996**

**DePaepe, Devereux, Dietz, Hennekam, Pyeritz.
Am J Med Genet 1996;62:417-26.**



Marfan Syndrome

Revised Diagnostic Criteria: *Ghent*

- Recognize extended phenotype
- Incorporate molecular approaches
- More restrictive
 - Some people no longer require careful follow-up
 - Identification of separate syndromes
 - Familial aortic aneurysm/dissection
 - MASS phenotype
 - Familial ectopia lentis



Marfan Syndrome

Revised Diagnostic Criteria: *Ghent*

- For the patient with a negative family history:
 - Must have a major criterion in two systems and a third involved
 - eg., aortic root dilatation, ectopia lentis, pectus excavatum, joint hypermobility and disproportionate tall stature



Marfan Syndrome

Revised Diagnostic Criteria: *Ghent*

- For the patient with a positive family history (a 1st –degree relative who is definitely affected):
 - Must have a major criterion in one system and a 2nd involved
 - eg., aortic root dilatation, pectus excavatum, joint hypermobility and disproportionate tall stature with an affected father



10 Related (Overlap) Connective Tissue Disorders

- **Congenital contractural arachnodactyly**
- **Homocystinuria**
- **Familial aortic aneurysm/dissection**
Autosomal dominant mapping to multiple loci
- **Familial ectopia lentis**
- **Familial defects of TGF β receptors**
 - **Loeys-Dietz syndrome with hypertelorism, bifid uvula & arterial tortuosity**
 - **Vascular EDS-like condition**



10 Related (Overlap) Connective Tissue Disorders (cont.)

- **MASS phenotype**
MVP, top-normal aorta, myopia, skeletal (mild), striae
- **Arterial tortuosity syndrome**
- **Bicuspid aortic valve/ascending aortic aneurysm/ aortic coarctation syndrome**
- **Ehlers-Danlos syndromes**
- **Stickler syndrome**



The Promise of Molecular Testing

Today, testing *FBN1* still has issues

**Mutations in the gene encoding fibrillin-1
cause Marfan syndrome & some related
disorders**

**Mutations in the gene encoding fibrillin-2
(*FBN2*) cause CCA**

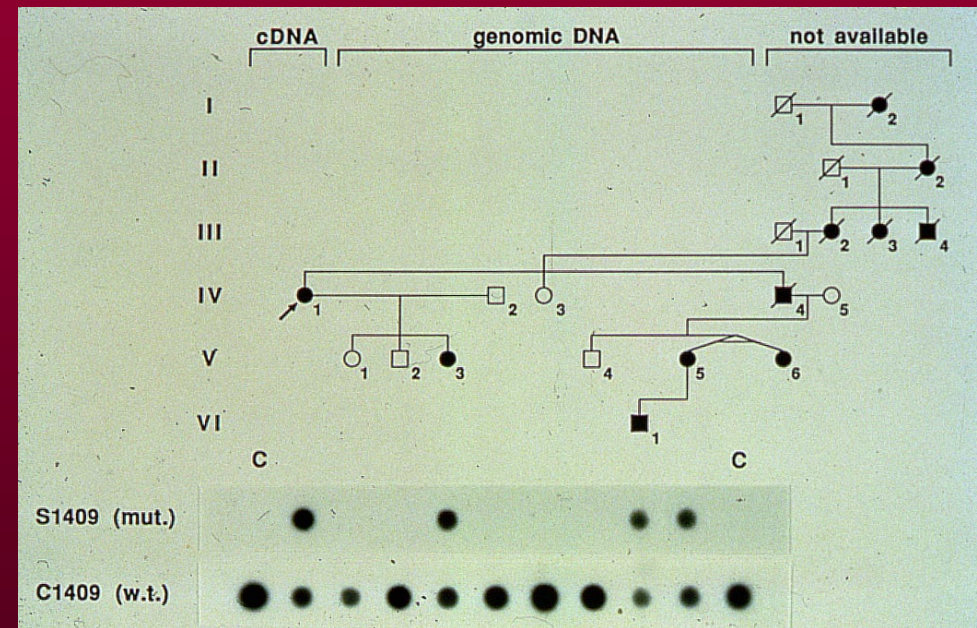
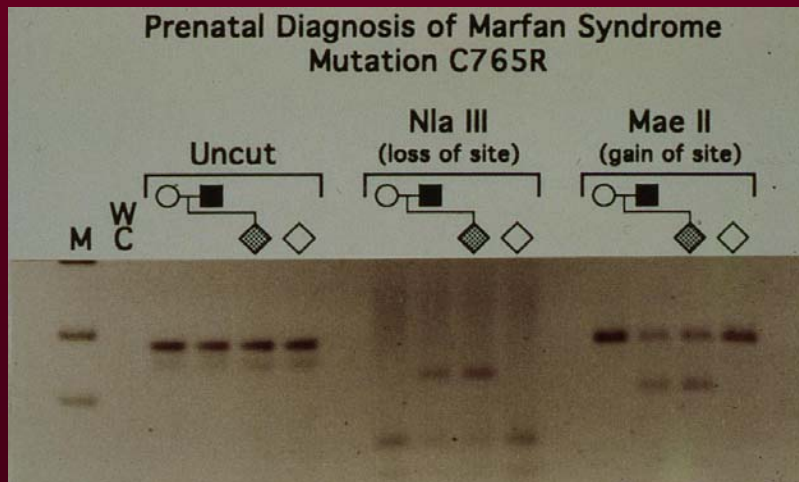
**Mutation testing is of less than ideal
sensitivity (~90%) and is costly**



Marfan Syndrome

Utility of *FBN1* Testing

- Confirmation of dx
- Presymptomatic dx
- Prenatal dx



Utility of *FBN1* Testing: *Limitations*

Mutations in *FBN1* Associated with Phenotypes Other Than MFS

<u>Mutation</u>	<u>AA change</u>	<u>Exon & type</u>	<u>Phenotype</u>
(364)C→T	R122C	4 EGF(ncb)	atypical skeletal, no CV
(3379)G→A	G1127S	27 EGF(cb)	familial aortic aneurysm
(3668)G→A	C1223Y	29 EGF(cb)	Sprintzen-Goldberg syn.
(5138)ins4	frame shift	41 TGFβBP	MASS
(7339)G→A	E2447K	59 EGF(cb)	familial ectopia lentis
(8176)C→T	R2726W	64 CT	familial tall stature
(8236)delGA	W2756X	65 CT	MSS



Utility of *FBN1* Testing: *Limitations*

Improving sensitivity for classic MFS

Inadequate sensitivity for related disorders

Low specificity for MFS

Expensive

Cost analysis of *FBN1* mutation detection (Yuan et al 1999)

SSCP/HD \$ 865.84

DS analysis 1741.02

EMC 1585.82

Commercial labs charge \$ 1200-2400



Marfan Syndrome Diagnosis

Marfan syndrome remains a clinical diagnosis



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