Marfan Syndrome and Congenital Contractural Arachnodactyly
Marfan Syndrome

- Autosomal dominant connective tissue disorder
- Incidence: 1-3,000-5,000
- Potentially lethal
  - If untreated, life expectancy reduced (32 yrs)
  - If treated, normal life span possible (early 70th)
- Classical manifestations:
  - Cardiovascular
  - Ocular
  - Skeletal
Genetics of Marfan Syndrome

- NOT ONE MUTATION
- Series of mutations
  - FBN-1
    - Large gene
    - Chromosome 15q-21.1
  - 90% of MFS patients
- TFGβ receptor II gene
  - < 10% cases of MFS
  - AD inheritance with variable penetration
  - Phenotype may overlap with Loeys-Dietz syndrome
- 25% of MFS patient are sporadic mutations
Fibrillins

- Cysteine rich glycoproteins
  - Important structural component of microfibrils
    - Elastic fibers of the medial layer of the ascending aorta

- Fibrillin-1
  - Discovered: 1986 by Sakai et al.
    - MFS pathogenesis

- Fibrillin-2
  - Discovered: 1991 by Lee et al.
    - CCA
How to Diagnose MFS?

- Clinical criteria
  - Diagnosis is made based on clinical criteria
- Echocardiogram/EKG
- Slit light eye exam
- CT or MRI of the lumbosacral spine
- Genetic Testing
### Diagnostic Clinical Criteria

#### Family/genetic history

<table>
<thead>
<tr>
<th>Major manifestations - need one of the following:</th>
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<tbody>
<tr>
<td>A parent, child or sib who meets these criteria independently</td>
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<tr>
<td>Presence of a mutation in FBN1 known to cause the Marfan syndrome</td>
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<tr>
<td>Presence of a haplotype around FBN1 inherited by descent known to be associated with unequivocally diagnosed Marfan syndrome in the family</td>
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- **Ghent nosology (1996)**
  - A set of stringent criteria
  - 4 out 8 skeletal manifestations
  - Ectopia lentis
  - Aortic root dilation or dissection
  - Lumbrosacral dural ectasia

- **2010 Revised Ghent nosology:**
  - Cardinal features
    - Aortic root dilation
    - Ectopia lentis
    - In the absence of family history
**Skeletal findings**

**Major manifestations - need four of the following:**

- Reduced upper to lower segment ratio (0.85 versus 0.93 in normals)
- Arm span exceeding height (ratio >1.05)
- Arachnodactyly of fingers and toes with positive wrist and thumb signs* 
- Scoliosis >20° or spondylolisthesis
- Pectus carinatum
- Pectus excavatum requiring surgery
- Reduced extension of elbows (<170°)
- Medial displacement of medial malleolus causing pes planus
- Protrusio acetabuli of any degree

**Minor manifestations**

- Pectus excavatum of moderate severity
- Joint hypermobility
- High arched palate with crowding of teeth

**Facial features**

- Dolichocephaly
- Malar hypoplasia
- Enophthalmos
- Retrognathia
- Down-sloping palpebral fissures
# Cardiovascular findings

## Major manifestations - need one of the following:

- Dilatation of the ascending aorta involving the sinuses of Valsalva, with or without aortic regurgitation
- Dissecting of the ascending aorta

## Minor manifestations

- Mitral valve prolapse
- Mitral regurgitation
- Dilatation of the pulmonary artery, in the absence of valvular or peripheral pulmonic stenosis, below age 40
- Calcification of mitral annulus below age 40
- Dilatation or dissection of descending thoracic or abdominal aorta below age 50
### Ocular findings

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<td>Ectopia lentis</td>
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<table>
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<tr>
<th>Minor manifestations</th>
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<tr>
<td>Flat cornea (measured by keratometry)</td>
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<tr>
<td>Increased axial globe length (measured by ultrasound)</td>
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<tr>
<td>Hypoplastic iris or hypoplastic ciliary muscle causing decreased miosis</td>
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<tr>
<td>Myopia</td>
</tr>
<tr>
<td>Retinal detachment</td>
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### Other findings

<table>
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<th>Major manifestations</th>
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<tr>
<td>Dural ectasia affecting the lumbosacral spinal canal</td>
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</table>

<table>
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<tr>
<th>Minor manifestations</th>
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</thead>
<tbody>
<tr>
<td>Spontaneous pneumothorax</td>
</tr>
<tr>
<td>Apical blebs</td>
</tr>
<tr>
<td>Cutaneous striae distensae</td>
</tr>
<tr>
<td>Recurrent or incisional hernias</td>
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</table>
Aortic Disease

- Nearly all patients will show evidence of aortic disease
  - Aortic dilation is present:
    - Children 50%
    - Adults 60-80%

- Main cause of M&M:
  - Dilation
  - Regurgitation
  - Dissection

- 2010 ACC/AHA/AATS guidelines for TAD:
  - Echo: baseline and at 6 mo.
  - Beta-blockers: HR < 110 beats/min
  - Ace inhibitors: losartan
    - Reduced aortic stiffness and aortic root dilation

- Surgery:
  - AoD > 5.0 cm
  - Growth > .45 cm/yr
  - Family history of dissection/rupture < 5 cm
Ectopia Lentis

- Upward displacement of the lens
- Up to 80% pts
- Treatment options:
  - Correction of myopic astigmatism
  - Aphakia correction
  - Lensectomy/vitrectomy
  - Intraocular lens implantation

Slit-lamp photomicrography shows ectopia lentis with microspherophakia; the lens is completely luxated into the anterior chamber, predisposing to pupillary block glaucoma. Reproduced with permission from: Gold DH, MD, and Weingeist TA, MD, PhD. Color Atlas of the Eye in Systemic Disease. Baltimore: Lippincott Williams & Wilkins, 2001. Copyright © 2001 Lippincott Williams & Wilkins.
Orthopedic Problems

- **Skeletal manifestations**
  - Arachnodactyly
  - Dolichostenomelia
  - Kyphoscoliosis
  - Dolichocephaly
  - Sternal deformities
    - Pectum excavatum
    - Pectum Carinatum

- **Connective tissue abnormalities such as**
  - Joint laxity
  - Dural ectasia

- ⅓ Require surgical intervention
Dural Ectasia

- Enlargement of the spinal canal with progressive ectasia of the dura and neural foramina

- 90% of MFS patients
  - Unclear clinical significance

- Treatment:
  - Pain management
  - VP shunts
Scoliosis

- ½ Develop scoliosis
- Early screening before 5\textsuperscript{th} grade
- Braces often not helpful
- > 40 degrees require surgery
  - 1/3 require surgery
Men: > 3 mm between acetabular line and ilioischial line

Women: > 6 mm

Early arthritic changes
  - Hip replacement: 40-50th
Arachnodactyly

- Not unique to Marfan
- Overgrowth of the long bones
- Metacarpal Index
  - A measure of the relative slenderness of the MCs
  - An average of the ratios of the length to the width of the 2\textsuperscript{nd}-5\textsuperscript{th} MC bones at the mid-shaft
  - Normal: < 7.9
  - Arachnodactyly: > 8.4
Arachnodactyly

• THUMB SIGN:
  - Distal phalanx protrudes beyond clenched fist

• WRIST SIGN:
  - 1\textsuperscript{st} and 5\textsuperscript{th} digits overlap when encircling the wrist
Joint and Ligament Laxity

- Most common site → the wrist

- Manifestations:
  - Recurrent dislocations
    - Shoulder
    - Patella
  - Pes planus
  - Hallux valgus

- Treatment:
  - Splinting
  - Muscle strength training
  - Surgery → rarely needed
    - Bone stabilization procedures
    - Soft tissue reconstruction procedures
Carpal Ligamentous Laxity with Bilateral Perilunate Dislocation in Marfan Syndrome

D.R. Pennes, M.D., E.M. Braunstein, M.D., and K.K. Shirazi, M.D.
Department of Radiology, University of Michigan Hospitals, Ann Arbor, Michigan, USA

- 14 yo girls with MFS
  - Marfanoid habitus
  - Arachnodactyly
  - 1st CMC joint subluxation
  - Scoliosis: spinal fusion

- Wrist Hypermobility
  - Bil. Perilunate dislocation
  - Splinted x 5 yrs → persistent

- Retrospective review of 8 wrist films from MFS patients:
  - Normal
<table>
<thead>
<tr>
<th>Condition</th>
<th>Symptom Overlap with Marfan Syndrome</th>
<th>Mutation in Fibrillin-1 Gene?</th>
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<tbody>
<tr>
<td>Loeys-Dietz Syndrome</td>
<td>Aortic enlargement and dissection. Variable skeletal findings</td>
<td>No (TGFBR 1/2 mutation)</td>
</tr>
<tr>
<td>Familial Aortic Aneurysm</td>
<td>Aortic enlargement and dissection. Variable skeletal findings</td>
<td>Generally not</td>
</tr>
<tr>
<td>Bicuspid Aortic Valve with Aortic Dilation</td>
<td>Aortic enlargement and/or dissection</td>
<td>Unknown</td>
</tr>
<tr>
<td>Familial Ectopia Lents (Dislocated Lens)</td>
<td>Eye lens dislocation. Common skeletal findings</td>
<td>Yes</td>
</tr>
<tr>
<td>MASS phenotype, Mitral Valve Prolapse, Myopia</td>
<td>Borderline aortic enlargement. Skin and skeletal findings</td>
<td>At least sometimes</td>
</tr>
<tr>
<td>Marfanoid Habitus (Marfan Body Type)</td>
<td>Skeletal findings</td>
<td>At least sometimes</td>
</tr>
<tr>
<td>Mitral Valve Prolapse Syndrome</td>
<td>Mitral valve prolapse. Variable skeletal findings</td>
<td>At least sometimes</td>
</tr>
<tr>
<td>Congenital Contractural Arachnodactyly (CCA or Beals syndrome)</td>
<td>Mitral valve prolapse. Variable skeletal findings</td>
<td>No (FBN-2 mutation)</td>
</tr>
<tr>
<td>Stickler Syndrome</td>
<td>Myopia. Retinal detachment. Joint hypermobility or contracture. Scoliosis. Mitral Valve Prolapse</td>
<td>No (Collagen genes mutation)</td>
</tr>
<tr>
<td>Shprintzen-Goldberg Syndrome</td>
<td>Aortic enlargement. Skin and skeletal findings</td>
<td>Rare</td>
</tr>
<tr>
<td>Ehlers-Danlos Syndrome</td>
<td>Skin and skeletal findings. Aortic enlargement / dissection in selected types only</td>
<td>No (Collagen gene mutation)</td>
</tr>
<tr>
<td>Homocystinuria</td>
<td>Mitral Valve Prolapse. Eye lens dislocation. Skin and skeletal findings</td>
<td>No (metabolic disorder)</td>
</tr>
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The Role of the Hand Surgeon

- Limited
- Important:
  - Identify individuals with MFS
    - Referral to a geneticist
    - Cardiac evaluation for Thoracic Aortic disease
  - Educate on the importance of low impact activity
- Hand problems rarely an issue
  - Often treated with PT and splinting
  - Surgery choose bone stability vs ligament reconstruction