# Diagnosing Marfan syndrome and Loeys-Dietz syndrome

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# Genetics of aortopathies

- Aortopathy may be caused by genetic or nongenetic (environmental) factors
- 20% of TAD cases are attributed to genetic causes
- Up to 20% of individuals with a TAD have a positive family history of aortopathy
- >30 genes have been associated with TAD so far

# TAD syndromes and conditions attributed to genetic causes

**Syndromic TAD**

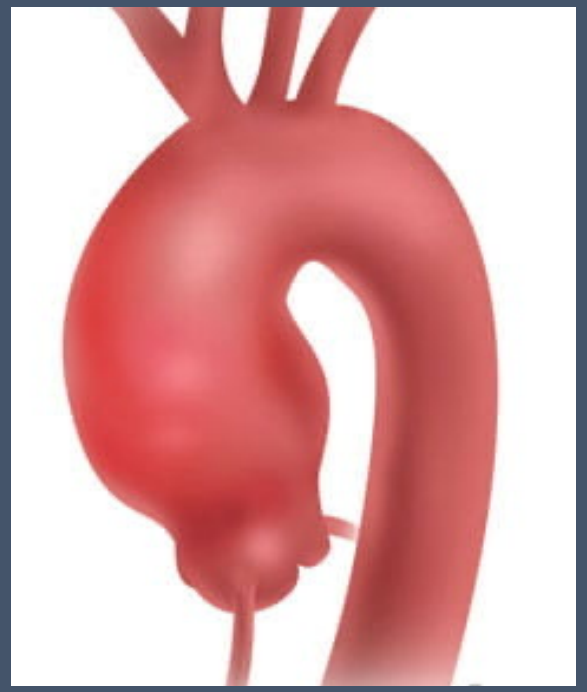
- Marfan syndrome
- Loeys Dietz syndrome
- Vascular EDS
- other

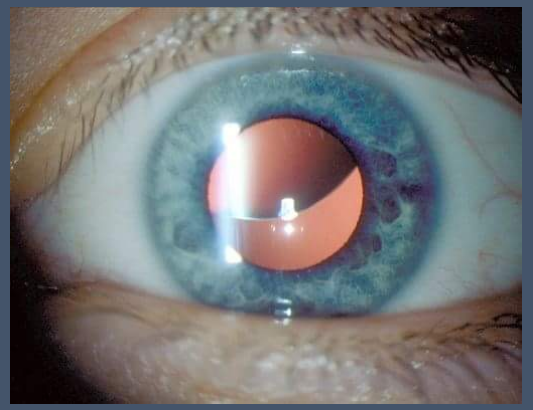
**Nonsyndromic TAD**

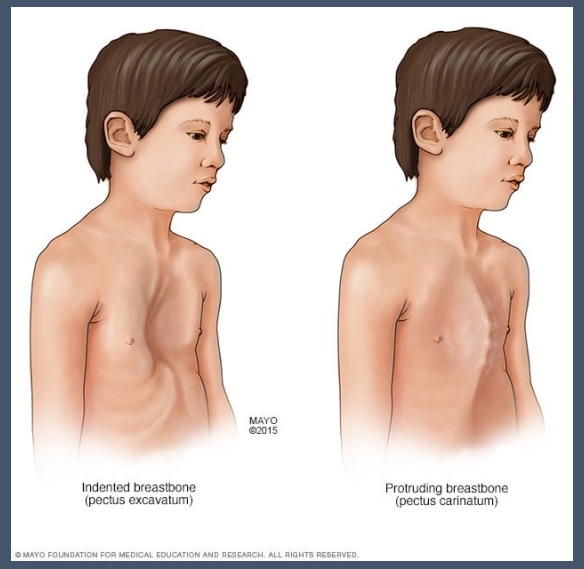
- ACTA2
- MYH11
- other

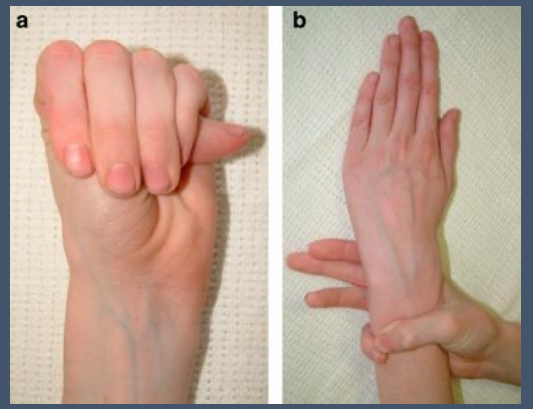
# Marfan syndrome

- Systemic disorder of connective tissue: CVS, eyes, skeletal system and skin
- FBN1 gene found in 95% MFS patients
- FBN1 mutations lead to weakened connective tissue, abnormal elastic fiber formation, and dysregulated TGF-β signaling—leading to features such as aortic aneurysms, lens dislocation, and skeletal overgrowth
- High degree of clinical variability








# Marfan syndrome: symptoms

**CVS**

- Aortic root dilation (80%)
- Aortic rapture (25%)
- MVP (50%)

**Ocular**

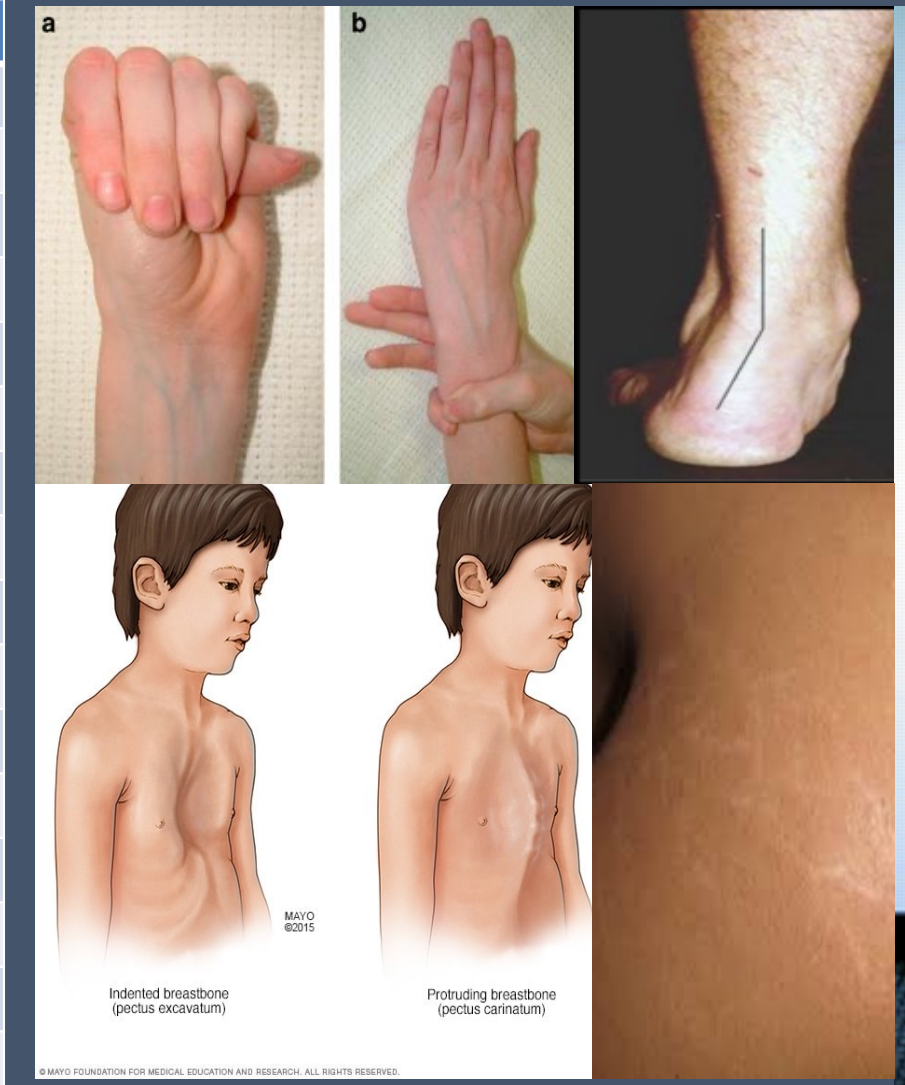
- Ectopia lentis (60%)
- Myopia (50%)
- other

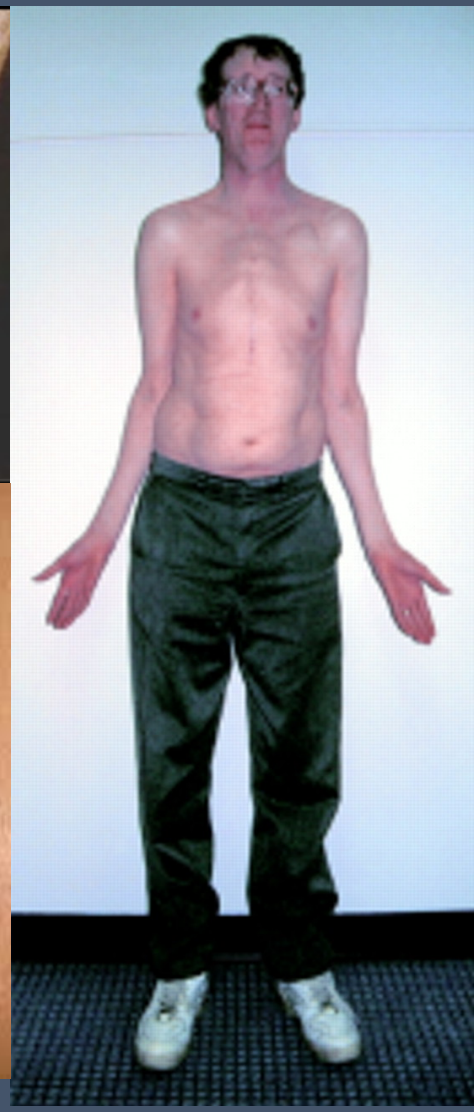
**Systemic**

- Scoliosis (50%)
- Long extremities (50%)
- Pectus deformity (60%)
- other

# MFS Systemic score

| Feature | Points |
|---|---|
| Wrist and thumb sign | 3 |
| Wrist or thumb sign | 1 |
| Pectus carinatum | 2 |
| Pectus excavatum / chest asymmetry | 1 |
| Hindfoot deformity | 2 |
| Flatfoot (pes planus) | 1 |
| Pneumothorax | 2 |
| Dural ectasia | 2 |
| Protrusio acetabuli | 2 |
| Arm span > height + low upper/lower segment ratio | 1 |
| Scoliosis / kyphosis | 1 |
| Reduced elbow extension | 1 |
| ≥3 facial features | 1 |
| Skin striae | 1 |
| Myopia >3D | 1 |
| Mitral valve prolapse | 1 |



# Diagnosing Marfan syndrome: revised Ghent criteria (2010)

- Patients with negative family history of MFS:
  - Aortic root dilation* AND FBN1 mutation
  - Aortic root dilation* AND ectopia lentis
  - Aortic root dilation* AND MFS score >7
  - Ectopia lentis and FBN1
- Patients with positive family history of MFS:
  - Aortic root dilation* AND + FHx
  - MFS score >7 AND + FHx
  - Ectopia lentis AND + FHx

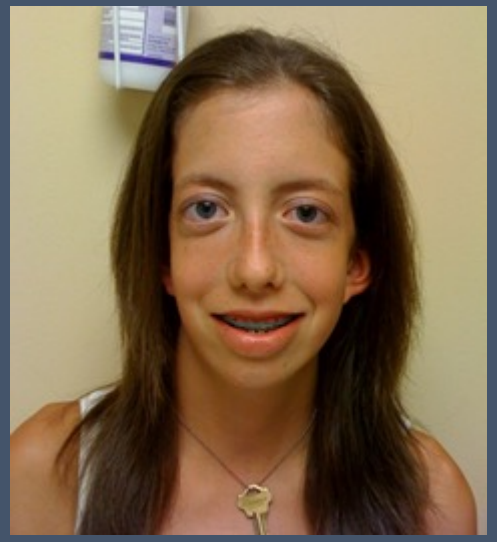
* Z score > 2

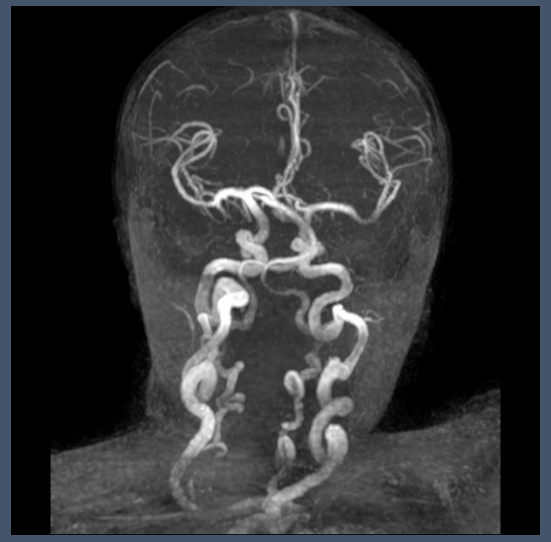
# Genetic testing

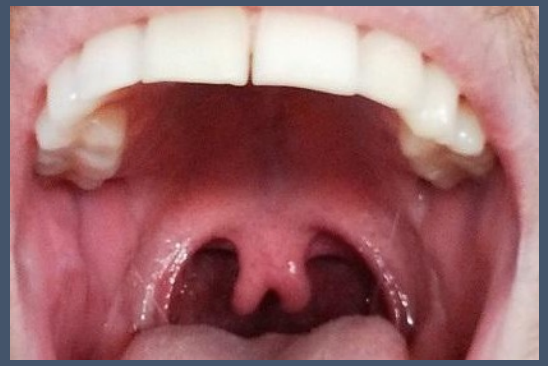
- FBN1 gene analysis
- TAAD or CTD panel
- WES/WGS

# Loeys Dietz syndrome

- Aneurysms are found through the arterial tree; aorta and branches are tortuous; dissections happen earlier
- No lens dislocation
- Distinct facial features including hypertelorism, cleft palate and bifid uvula
- Skeletal findings: arachnodactyly, pectus deformity, joint laxity
- Skin sxs: soft and velvety
- Other: increased risk of allergic diseases







# Diagnosing Loeys-Dietz syndrome

- No consensus clinical diagnostic criteria for Loeys-Dietz syndrome (LDS) have been published.
- LDS should be suspected in individuals with the vascular, skeletal, craniofacial, cutaneous, allergic/inflammatory, ocular, and family history findings

# Genetic testing for LDS

- Mutations found in *TGFBR1, TGFBR2, TGFB2, TGFB3, SMAD3* genes (75% *de novo*)
- Genes involved in TGF-β signaling pathway; crucial for connective tissue development, vascular integrity, and immune regulation
- Genetic testing: TAAD panel, exome/genome sequening