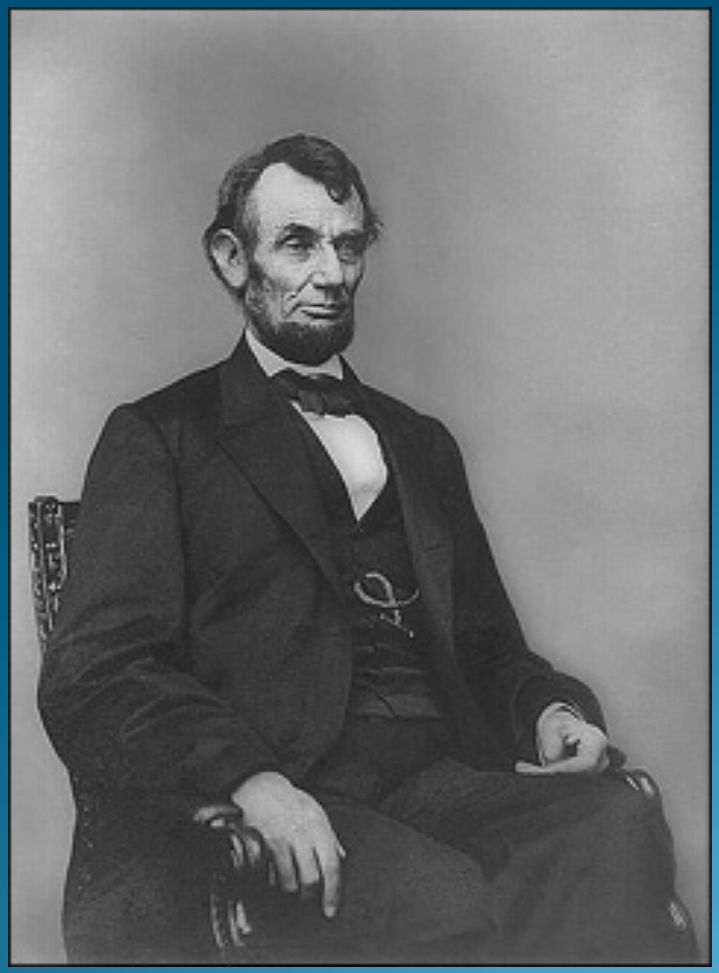
Marfan Syndrome
馬凡氏症

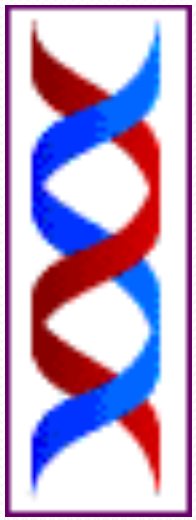
報告者 : NP 李秋慧



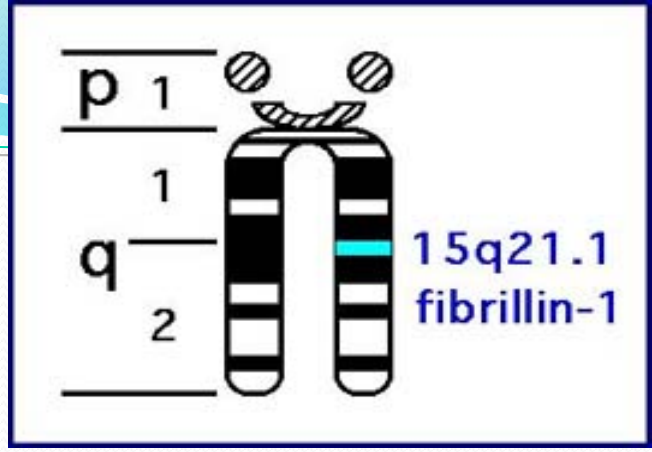

漢昭烈帝
劉備

MFS

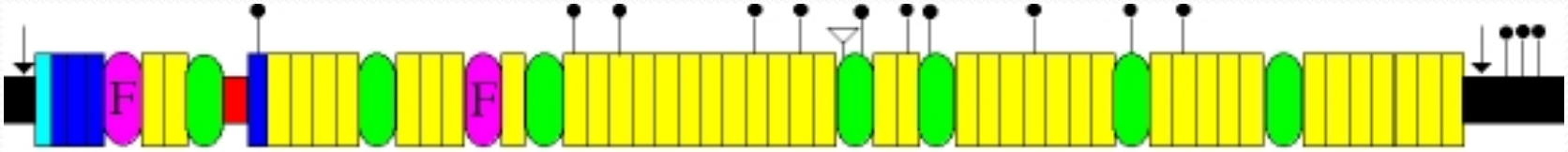
- 一種系統性的結締組織病變
- 1896年由法國小兒科醫師 **Marfan** 提出臨床報告
- 約**70%~93%**馬凡氏患者是因為位於第15對染色體上的fibrillin-1 (FBN1) 基因發生突變
- 3/4 MFS 是經由遺傳，1/4 是基因突變



Pathophysiology



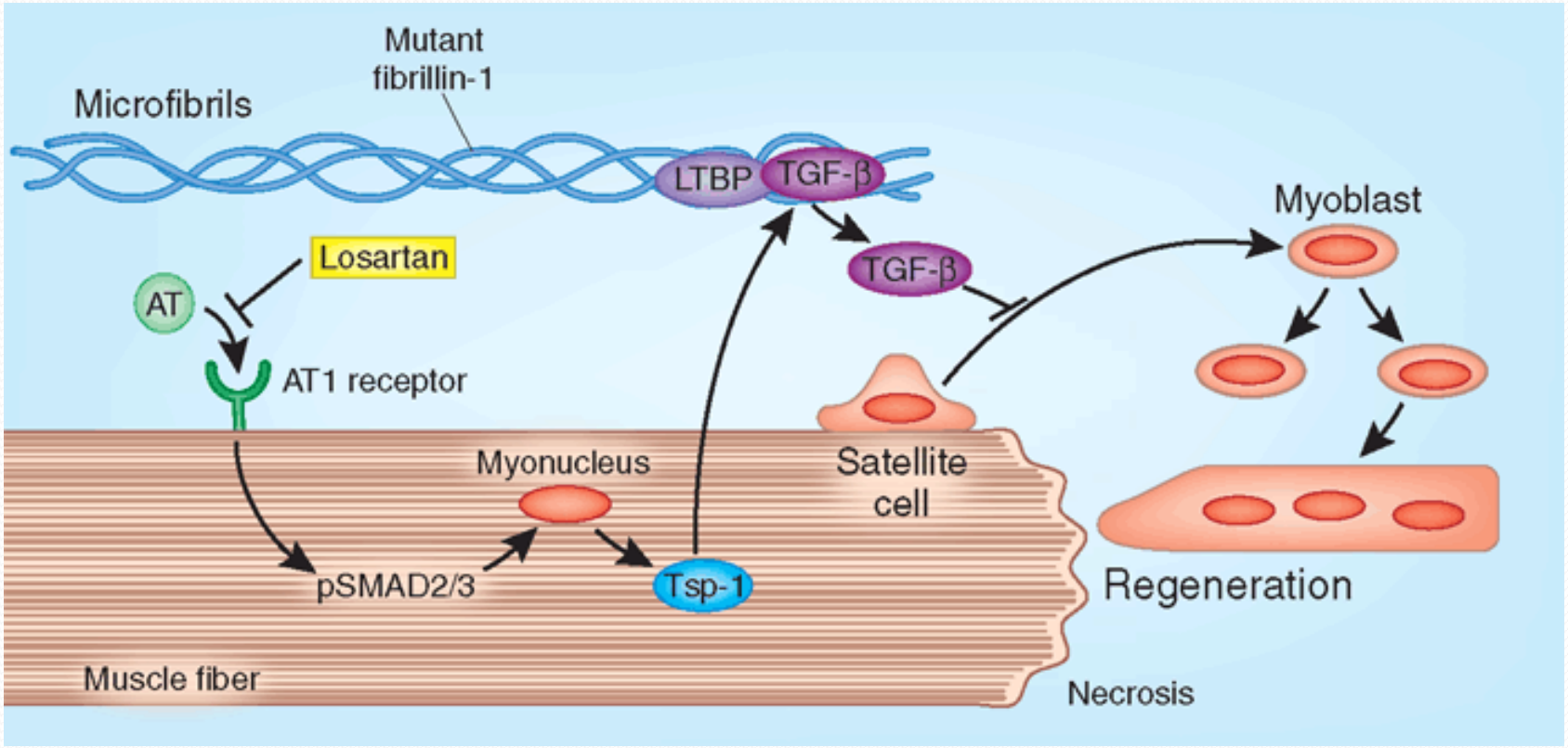
- The fibrillin-1 gene encodes the glycoprotein fibrillin, a major building block of microfibrils, which constitute the structural components of the suspensory ligament of the lens and which serve as substrates for elastin in the aorta and other connective tissues. Abnormalities involving microfibrils weaken the aortic wall
- Likewise, deficient fibrillin deposition leads to reduced structural integrity of the lens zonules, ligaments, lung airways, and spinal dura.



- Production of abnormal fibrillin-1 monomers from the mutated gene disrupts the multimerization of fibrillin-1 and prevents microfibril formation

- Fibrillin-1 mutation causes several Marfanlike disorders such as the mitral valve prolapse, aortic dilation, skin, and skeletal (MASS) phenotype or isolated ectopia lentis

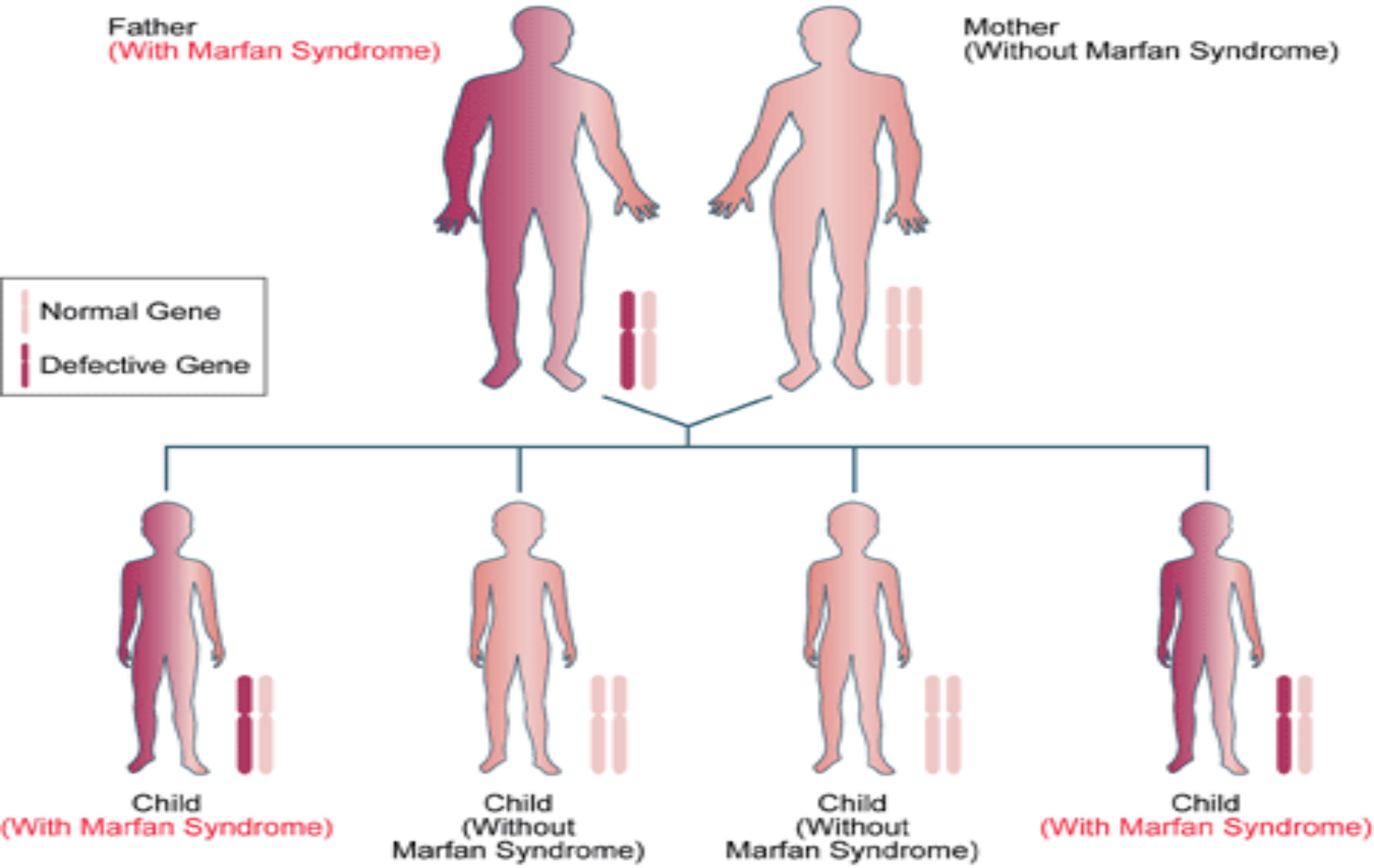
- Recent studies have suggested that abnormalities in the *TGFβ*-signaling pathway may represent a final common pathway for the development of the Marfan phenotype
- a lifelong disorder with no known cure



MFS

- U.S: Marfan syndrome affects about 1 in 10,000 individuals and perhaps as many as 1 in 3000-5000. Estimates suggest that at least 200,000 people in the United States have Marfan syndrome or a related connective-tissue disorder.
- 不具有人種或性別差異性
- 雙親中有一人患有此症，其子代不分性別，每胎皆有50%的機會患有此症

Inheritance of Marfan Syndrome



MFS

- 在1970年之前, MFS病人很少活超過 40–50歲.

- Today, because of early diagnosis and better medical and surgical treatments, people with Marfan syndrome can live longer and healthier lives, with fewer and less severe complications

外觀

- A tall, slender body build.
- Long arms, legs, fingers, and toes. A person's arm span (the distance from the fingertips of one hand to the fingertips of the other with the arms stretched out from the sides) may be greater than his or her height.
- A long and narrow face.
- A highly arched roof of the mouth with crowded te
- A receding lower jaw, causing an overbite.
- A protruding or sunken chest.
- A curved spine.
- Flat feet that are rotated inward

臨床症狀及診斷

- Marfan syndrome is currently diagnosed using criteria based on an evaluation of the family history, molecular data, and 6 organ systems

:

- . The diagnosis cannot be based on molecular analysis alone because molecular diagnosis is not generally available, mutation detection is imperfect, and not all fibrillin-1 mutations are associated with Marfan syndrome

Berlin criteria

- Marfan syndrome was diagnosed on the basis of involvement of the skeletal system and 2 other systems, with the requirement of at least one major manifestation (ectopia lentis, aortic dilatation or dissection, or dural ectasia)

Ghent criteria

- Revised in 1995
- based on clinical observation of various organ systems and on the family history.
- intended to serve as an international standard for clinical and molecular studies and for investigations of genetic heterogeneity and genotype-phenotype correlations

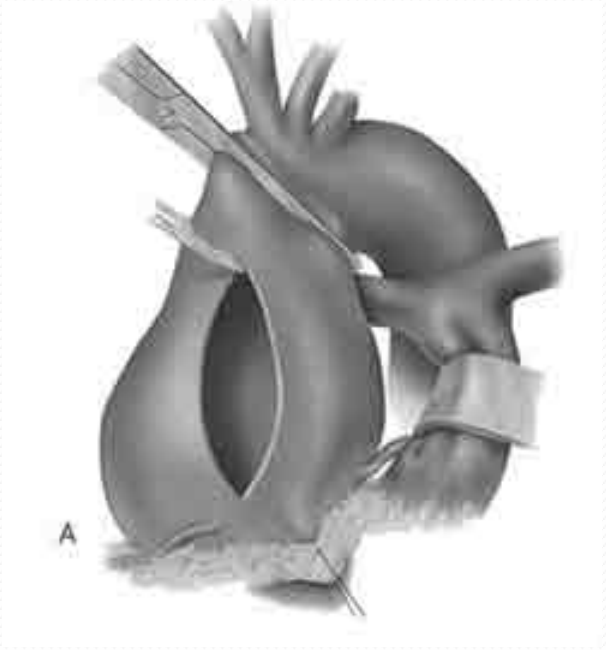
Family history

- A first-degree relative (parent, child, or sibling) who independently meets the diagnostic criteria
- Presence of an *FBN1* mutation
- Inheritance of an *FBN1* haplotype known to be associated with unequivocally diagnosed Marfan syndrome in the family
- In family members, major involvement in 1 organ system and involvement in a second organ system

- If the family and genetic histories are not contributory, major criteria in 2 different organ systems and involvement of a third organ system are required to make the diagnosis

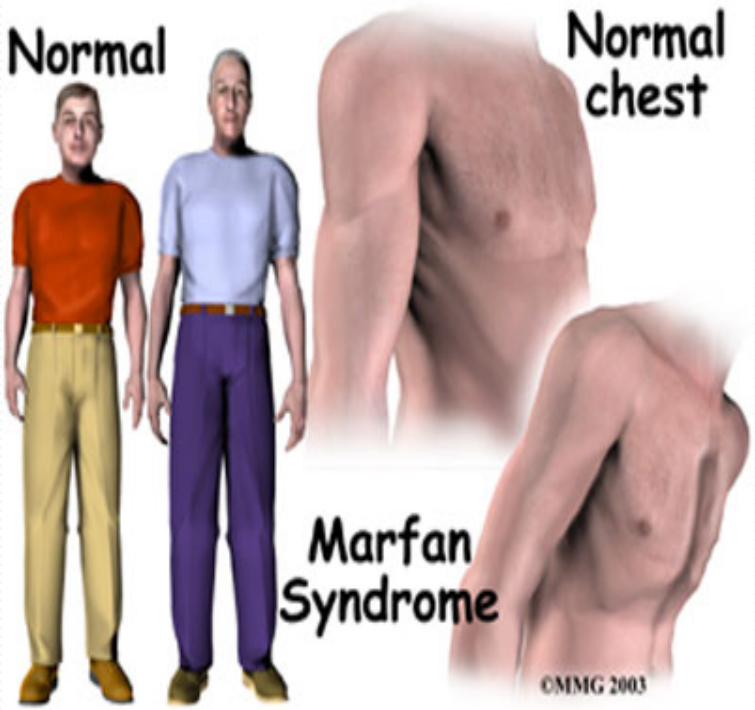
1996 年 DePaepe 等人所提出的主要及次要特徵作為診斷的參考：

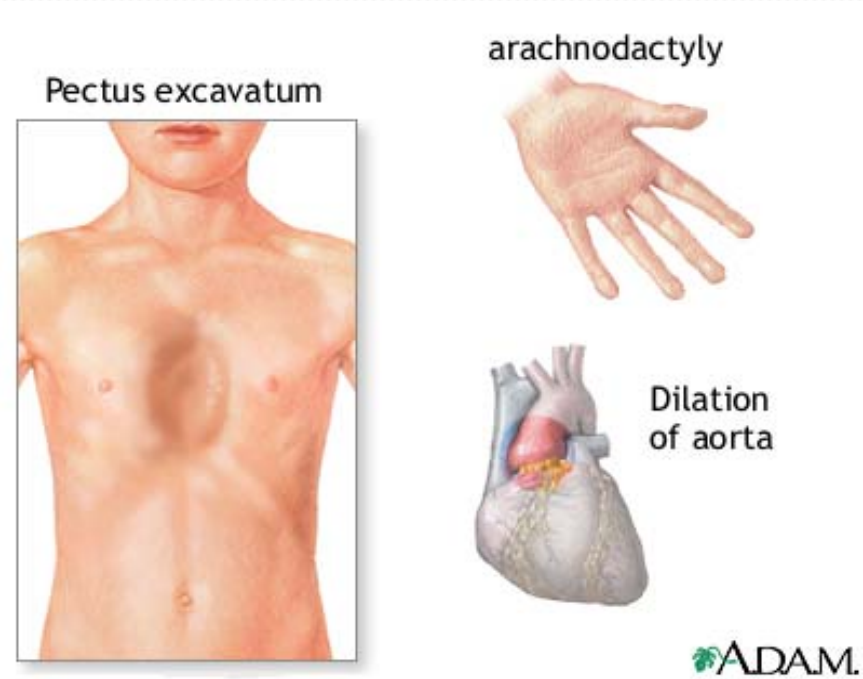
- 一、 骨骼系統
- 二、 眼睛系統
- 三、 心血管系統
- 四、 其他



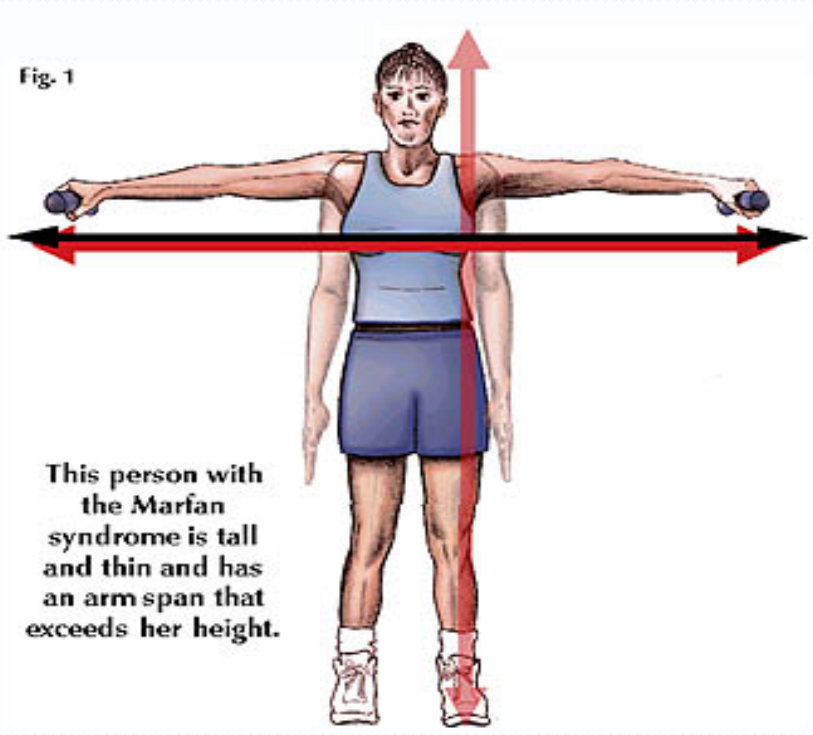
一、骨骼系統

- 胸腔骨骼異常：胸骨突出或凹陷（雞胸或漏斗胸）Pectus excavatum that requires surgery or pectus carinatum

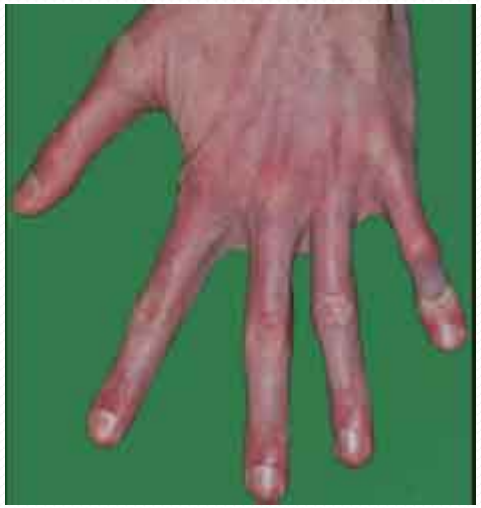


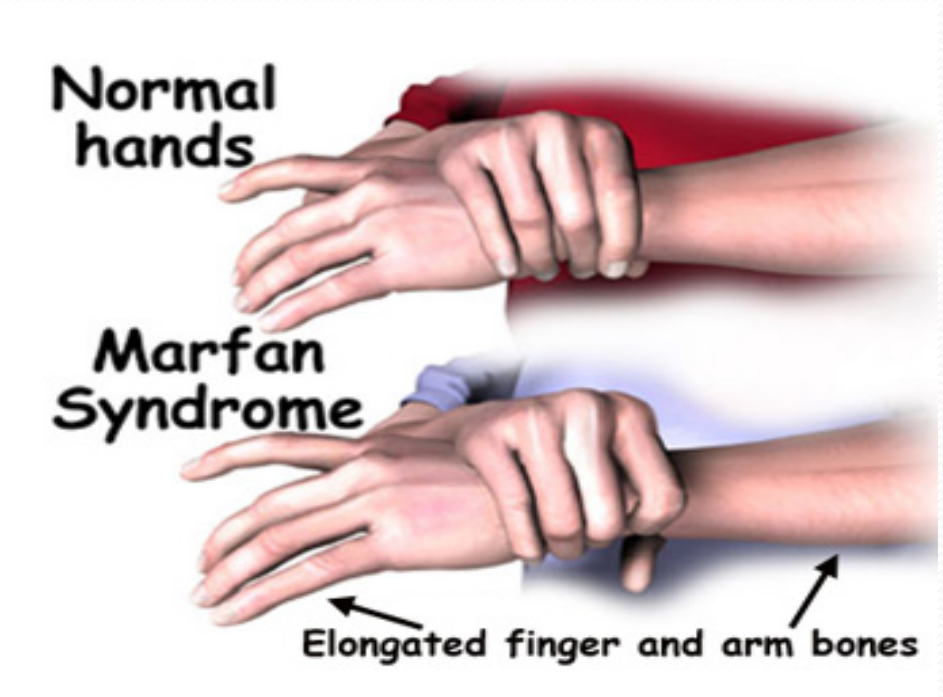


- 上下半身比例縮減（ < 0.85／成年及年長之兒童）、展臂長與身高之比值過高（ > 1.05）
)

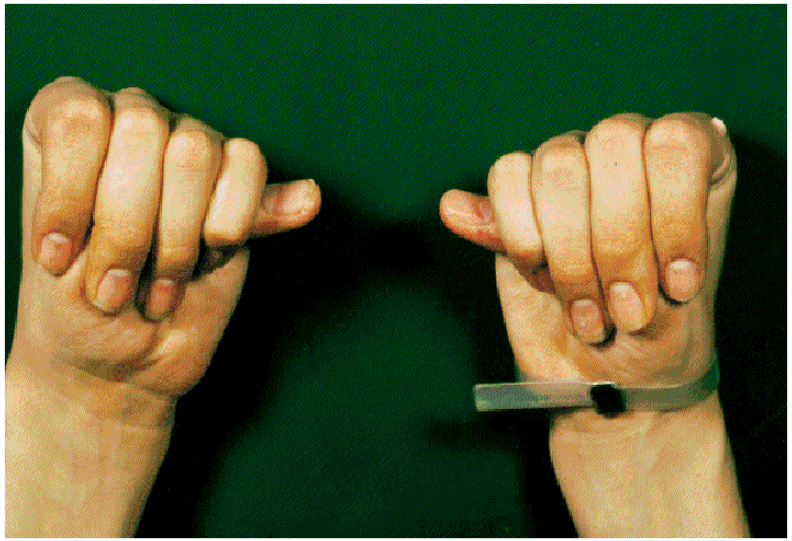


因為四肢骨骼過度生長，因此具有蜘蛛狀手指，使得手腕有Walker-Murdoch之特徵（當一邊手掌握住對側的手腕時，其姆指與小指能夠重疊在一起）





姆指有 Steinberg特徵（指在沒外力的協助下，當手姆指可以向尺骨側彎曲時，可以超出掌面）



脊柱側彎（scoliosis）、脊柱後凸（kyphosis）或脊柱脫位（spondylolithesis）

- Scoliosis greater than 20°
- More than 60% of patients have scoliosis. Progression is most likely with curvature of more than 20° in growing patients.

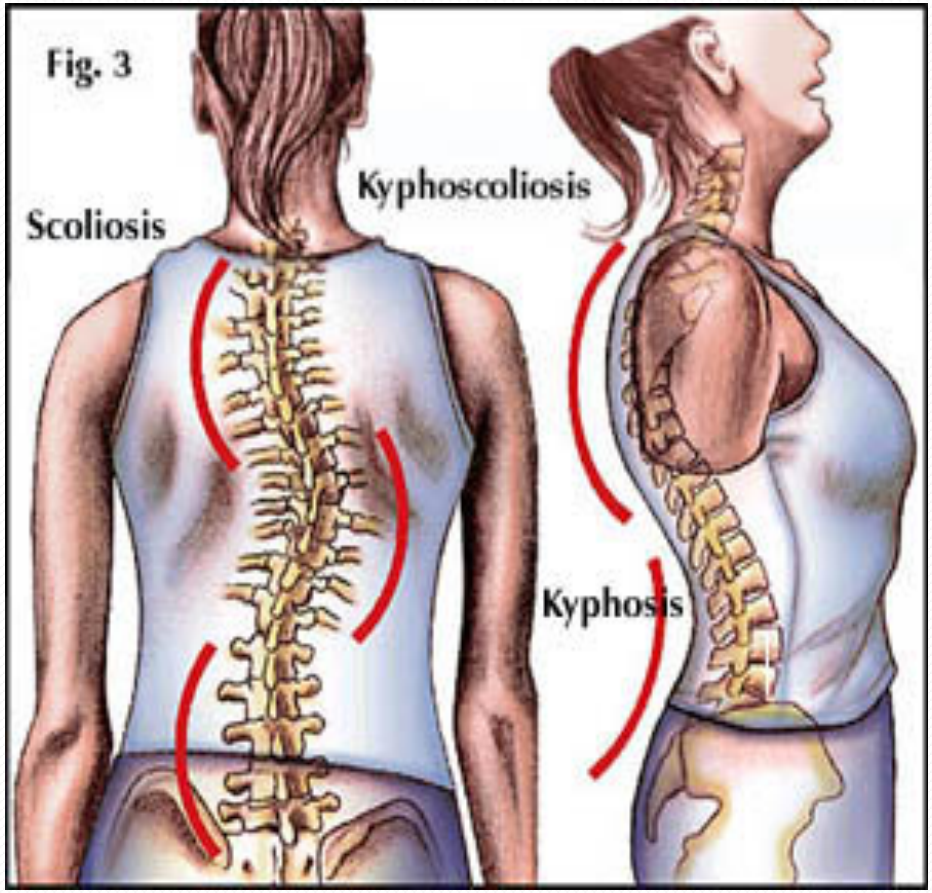
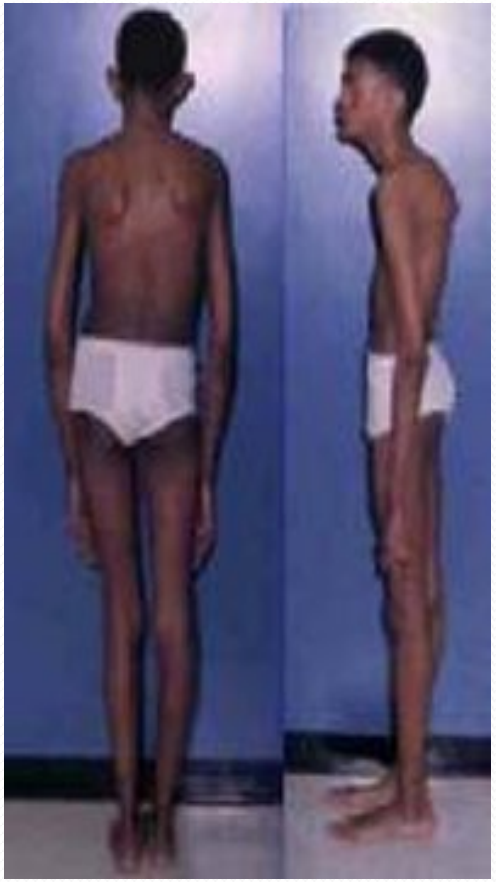
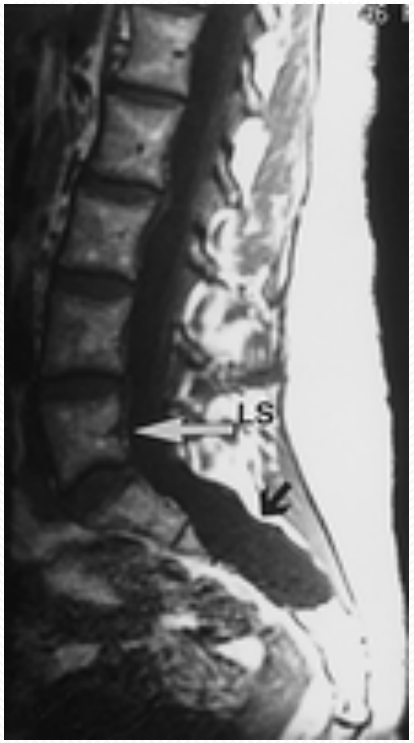


Fig. 3
Scoliosis
Kyphoscoliosis
Kyphosis



Dural ectasia

- a hallmark of Marfan syndrome that is very rare in the general population. (65-92%)



- 肘關節伸展程度減小（ < 170 度）
  丨
- 扁平足
  丨
- 髖骨突出（protrusio acetabuli）: 50%

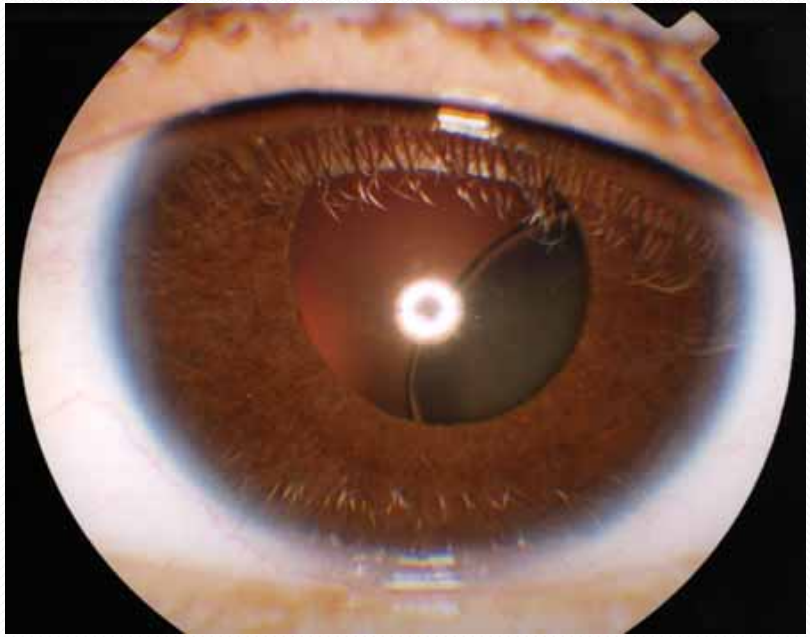
次要特徵

at least 2 major criteria or 1 major criterion plus 2 minor criteria must be present.

- 漏斗胸嚴重程度中度
  ⌉
- 關節過動（hypermobility）
  ⌉
- 高而呈拱形的上顎及發育不全的下顎、牙齒排列擁擠
  ⌉
- 臉部特徵：頭骨細長（dolichocephaly）、Malar hypoplasia、眼球內陷（enophthalmos）、下顎後縮（retrognathia）、眼瞼下垂、眼裂。

二、眼睛系統

1. 主要特徵



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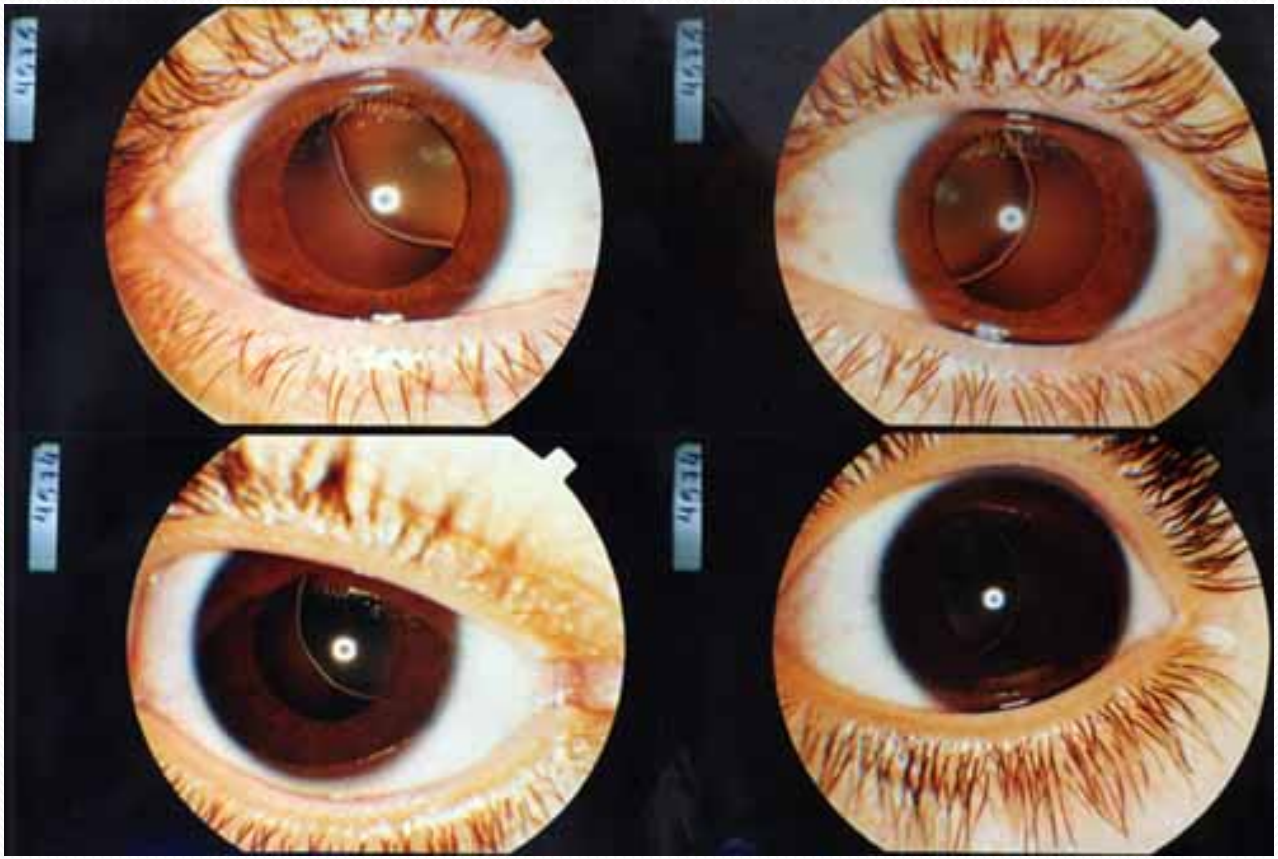
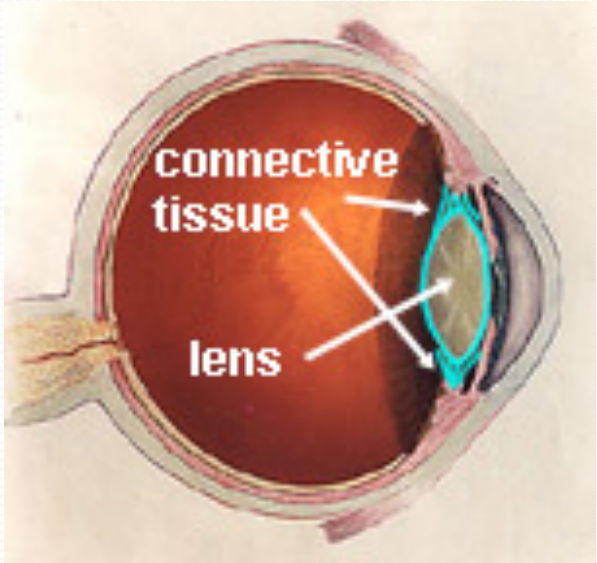
- 水晶體異位（ectopia lentis）: 50%



A 34 year old man (superior images) and his 10 year old son presenting nasal superior lens subluxation in MFS

次要特徵 (至少兩個)

- 高度近視
- 視網膜剥離
- 青光眼
- 白內障
- 異常平坦角膜]
- 眼球軸長過長]
- 虹膜或睫狀肌發育不全

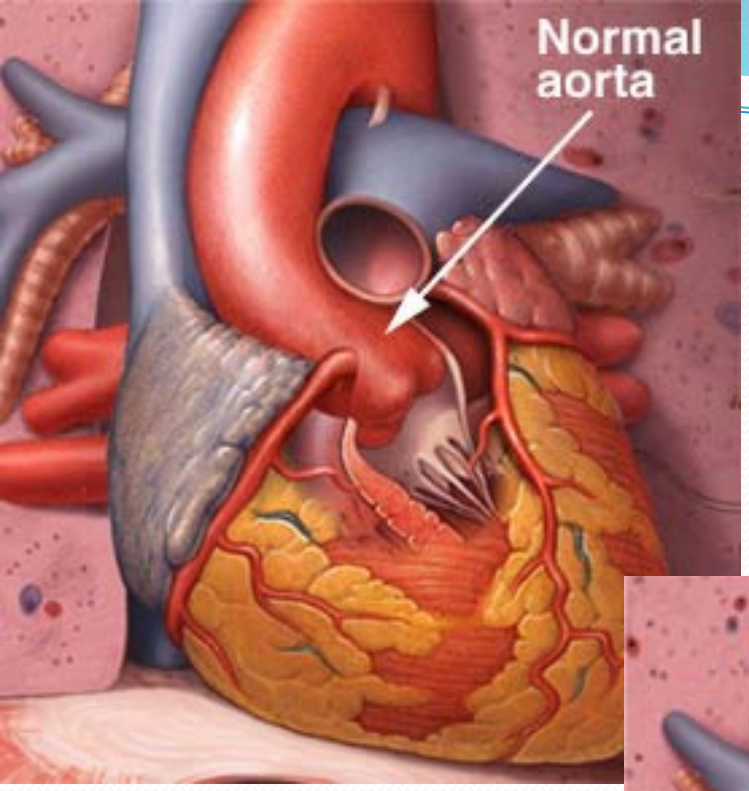


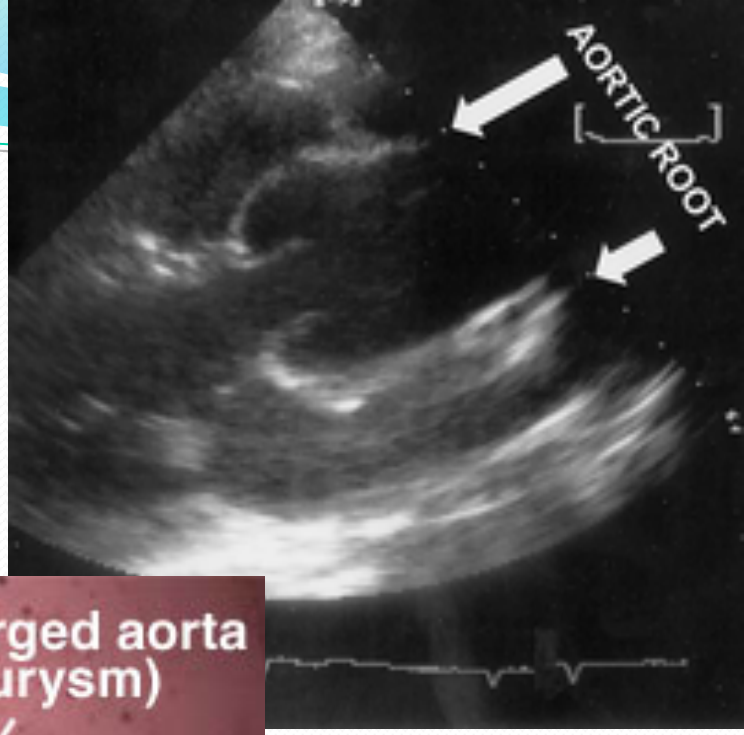
三、心血管系統

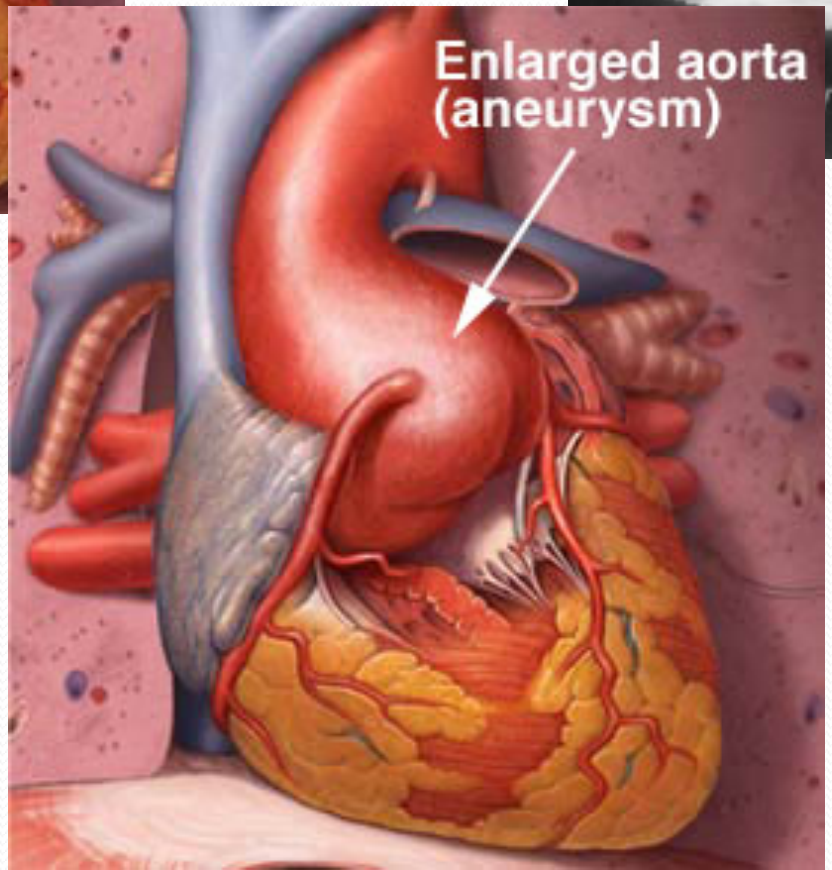
1. 主要特徵
   the major cause of morbidity and mortality

- Aortic root dilatation involving the sinuses of Valsalva : The prevalence is 70-80%.

- Aortic dissections involving the ascending aorta


Normal
aorta


AORTIC ROOT

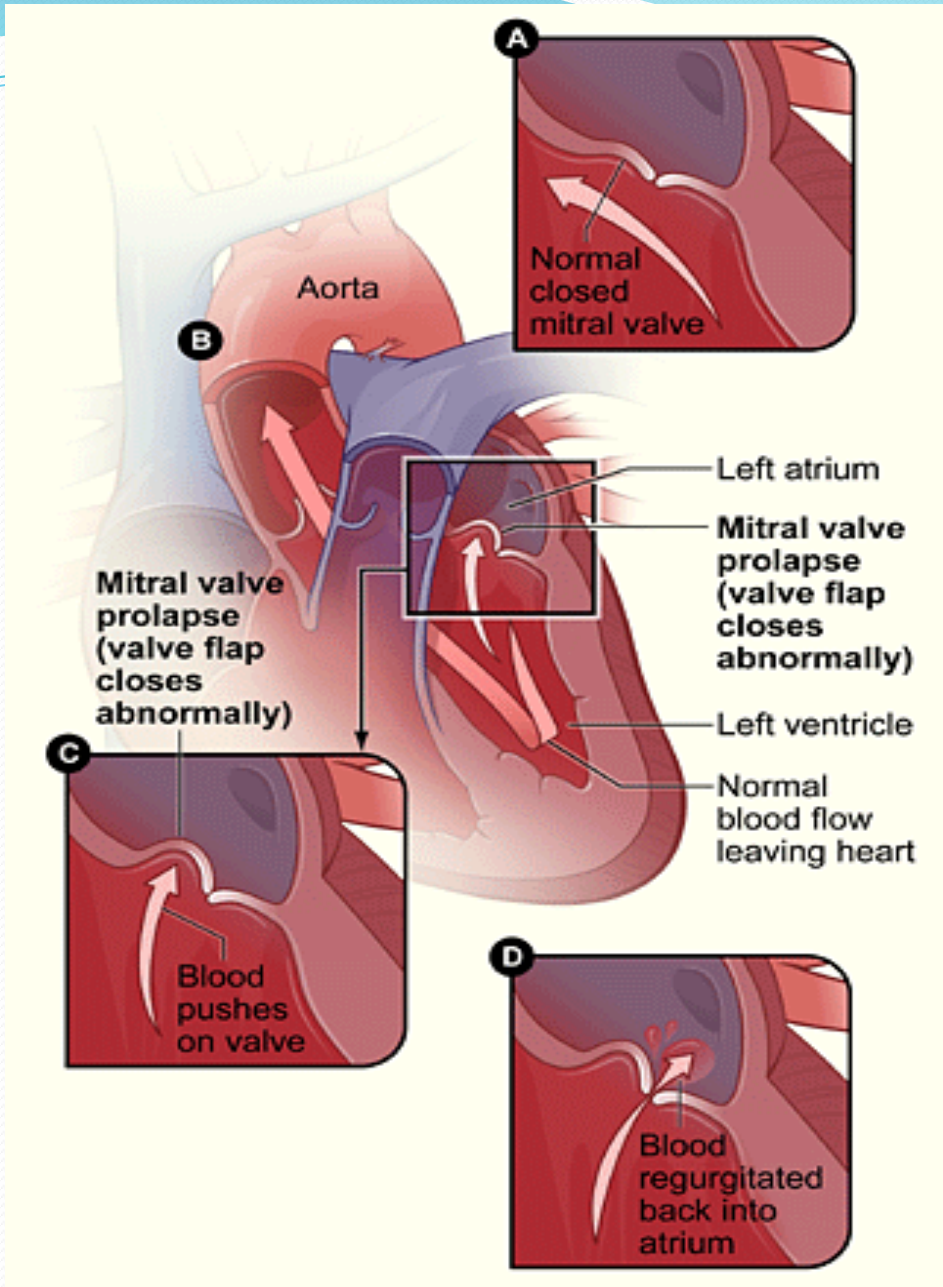

Enlarged aorta
(aneurysm)

三、心血管系統

2. 次要特徵

- **Mitral Valve Prolapse** (75%)

- 肺動脈擴張（40歲以前且無其他影響因素）
- 二尖瓣鈣化（40歲以前）
- 其他動脈擴張或破裂（50歲以前）


A
Normal closed mitral valve
Aorta
B
Left atrium
Mitral valve prolapse (valve flap closes abnormally)
Mitral valve prolapse (valve flap closes abnormally)
Left ventricle
Normal blood flow leaving heart
C
Blood pushes on valve
D
Blood regurgitated back into atrium

四、其他

Pulmonary findings

- Spontaneous pneumothorax (about 5% of patients)
- Apical blebs on chest radiography
- Sleep apnea : a problem that is often associated in the general population with being overweight or obese. But thin people with Marfan syndrome can also suffer from it. This may be due to looseness of the connective tissue in the airways.

Skin

- Striae atrophicae :
- Stretch marks (2/3 in MFS) : occur without excessive weight gain or loss; usually on the lower back, buttocks, shoulders, breasts, thighs, and abdomen.

TREATMENT

1. Beta-blockers :

- potential agents for delaying aortic expansion and for delaying the progression to rupture or dissection.
- rate of surgical interventions has substantially declined
- retards aortic growth in children and adolescents with Marfan syndrome
- 使用的時機有爭議

2. Intravenous antibiotic therapy is required during cardiac and noncardiac procedures to prevent bacterial endocarditis.

3. Progesterone and estrogen therapy have been used to induce puberty and reduce the patient's ultimate height if hormonal treatment is begun before puberty

4. Myopia is treatable with refraction

Future therapeutic strategy

- TGFβ antagonism :

  rescue aortic aneurysm in C1039G/+ mice

Surgical Care

- Cardiovascular surgery
  - MVR, AVR
  - Bentall procedure: when the aorta exceeds 55-60 mm in diameter
  - An aortic valve–sparing procedure (long term result?)

- Scoliosis surgery :

  Results of spinal fusion are better in children older than 5 years , Indications for surgery in adults include pain, neurologic signs, and thoracic curves greater than 45°, which can cause restrictive lung disease

Tex Heart Inst J 2005;32:424-6

Pectus repair

The shape of the front of the thorax becomes stable and established by mid adolescence. Therefore, repair of pectus excavatum to improve respiratory mechanics should be delayed until then to lessen the risk of recurrence.

- Pectus carinatum repair is mainly performed for cosmetic reasons

謝謝聆聽!!