Marfan Syndrome

Contents

Marfan syndrome (MFS) is an inherited connective tissue disorder, noteworthy for its worldwide distribution, relatively high prevalence, clinical variability, and pleiotropic manifestations involving primarily the ocular, skeletal, and cardiovascular systems, some of which are life threatening. Its estimated frequency is 2–3 per 10,000 individuals.

Genetics/Basic Defects

1. Inheritance.
   1. Autosomal dominant.
   2. New mutation in about 25–30% of the cases.
   3. About 70–75% of individuals diagnosed with Marfan syndrome have an affected parent.
2. Caused by a wide variety of mutations in the fibrillin-1 (*FBN1*) gene located on chromosome 15q21.1 (Dietz et al. 1991a, b; Giampietro et al. 2002).
3. Molecular defects in the fibrillin gene are responsible for the impaired structural integrity of the skeletal, ocular, and cardiovascular systems (Dietz and Pyeritz 1995).
4. Almost all mutations are specific (unique) to a particular individual or family (Robinson and Godfrey 2000).
5. *FBN1* mutation is helpful diagnostically only if it has been previously found in the person who independently meets the criteria for Marfan syndrome.
6. Criteria for causal *FBN1* mutation (Loeys et al. 2010).
   1. Mutation previously shown to segregate in Marfan family
   2. De novo (with proven paternity and absence of disease in parents) mutation (one of the five following categories)
   3. Nonsense mutation
   4. In frame and out of frame deletion/insertion
   5. Splice site mutations affecting canonical splice sequence or shown to alter splicing on mRNA/cDNA level
   6. Missense affecting/creating cysteine residues
   7. Missense affecting conserved residues of the EGF consensus sequence ((D/N)X(D/N)(E/Q)Xm(D/N)Xn(Y/F) with m and n representing variable number of residues: D aspartic acid, N asparagine, E glutamic acid, Q glutamine, Y tyrosine, F phenylalanine)

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8. Linkage of haplotype for n ≥ 6 meioses to the FBN1 locus
7. A compound heterozygous Marfan patient with two defective fibrillin alleles resulting in a lethal phenotype (Kartunnen et al. 1994).
8. No obvious correlation between location of mutation and phenotypic severity (except an apparent clustering of mutations associated with the most severe form of Marfan syndrome, i.e., neonatal Marfan syndrome).
9. Pathophysiological consequence of the elastic fiber degeneration: reduced distensibility in response to the pulse pressure wave or increased stiffness (Dean 2002).
10. Intrafamilial and interfamilial variability of clinical expression.
11. Fibrillin-1 mutations also observed in related disorders of connective tissue (type I fibrillinopathies) (Aoyama et al. 1995; Pyeritz 1996; Robinson and Godfrey 2000; Dietz 2009; Loeys et al. 2010).
    1. Autosomal dominant ectopia lentis (bilateral ectopia lentis without the typical skeletal and cardiovascular manifestations of the Marfan syndrome)
    2. Shprintzen-Goldberg syndrome
        1. Unclear inheritance pattern
        2. Marfanoid habitus
        3. Craniosynostosis
        4. Mental retardation
        5. Rarely aortic root dilatation
        6. Mitral valve prolapse
        7. Majority of cases are not caused by *FBN1* mutations
    3. Autosomal dominant Weill-Marchesani syndrome
        1. Ectopia lentis
        2. Short stature
    4. Familial ectopic lentis
        1. An autosomal dominant condition
        2. Bilateral ectopia lentis
        3. Scoliosis in some cases
        4. No cardiovascular manifestations
    5. Familial aortic aneurysm
        1. Ascending aortic aneurysm and dissection
        2. No ectopia lentis
        3. No specific skeletal findings
    6. MASS phenotype
        1. An autosomal dominant condition
        2. Acronym MASS stands for:
            1. *M*itral valve prolapse
            2. *A*ortic root dilation without dissection
            3. *S*keletal abnormalities
            4. *S*kin abnormalities
    7. Mitral valve prolapse syndrome
        1. An autosomal dominant condition
        2. Mitral valve prolapse
        3. Associated with subtle skeletal features that are reminiscent of the Marfan syndrome
    8. New variant of Marfan syndrome
        1. Skeletal features of Marfan syndrome
        2. Joint contractures
        3. Knee joint effusions
        4. Ectopia lentis
        5. No cardiovascular manifestations
    9. Marfan-like (marfanoid) skeletal abnormalities
        1. Tall stature
        2. Scoliosis
        3. Pectus excavatum
        4. Arachnodactyly
12. Other disorders overlap with Marfan syndrome (Dietz 2009; Loeys et al. 2010).
    1. Loeys-Dietz syndrome: please see the chapter on "▶ Loeys-Dietz Syndrome"
        1. An autosomal dominant condition.
        2. Shares many features of Marfan syndrome but ectopia lentis is absent.
        3. Unique features.
            1. Craniofacial involvement (bifid uvula/cleft palate, hypertelorism, craniosynostosis)
            2. Skin: soft, velvety, and translucent
            3. Easy bruising
            4. Generalized arterial tortuosity and aneurysms
            5. Dissection throughout the arterial trees
        4. Other features.
            1. Clubfoot
            2. Cervical spine instability
        5. Caused by mutations in either the *TGFBR1* or *TGFBR2* gene (Loeys et al. 2005, 2006).

6. Loeys-Dietz syndrome types 1 and 2: designate those with and without severe craniofacial involvement, respectively (Loeys et al. 2006).

2. Other related disorders due to defects in components of the TGFβ pathway (Cook et al. 2015)
   1. Shprintzen-Goldberg syndrome
   2. Aneurysm-osteoarthritis syndrome
   3. Syndromic thoracic aortic aneurysms
3. Congenital contractural arachnodactyly
   1. Caused by fibrillin-2 (*FBN2*) mutations (highly homologous to BBN1, mapped to chromosome 5q23-31)
   2. Characteristic features
      1. Marfanoid habitus
      2. Arachnodactyly
      3. Camptodactyly
      4. Crumpled ears
      5. Mild contractures of the elbows, knees, and hips
      6. Mild muscle hypoplasia especially of the calf muscles
4. Ehlers-Danlos syndrome: please see the chapter on "► Ehlers-Danlos Syndrome"
5. Homocystinuria
   1. An autosomal recessive condition
   2. Caused by cystathionine β-synthase deficiency resulting from mutations in the *CBS* gene
   3. Characteristic clinical features
      1. Variable mental retardation.
      2. Ectopia lentis and/or severe myopia.
      3. Skeletal abnormalities (including excessive height and limb length).
      4. Excessive overlap with Marfan syndrome (a long and lean body habitus, pectus deformity, scoliosis, mitral valve prolapse, highly arched palate, hernia, and ectopia lentis).
      5. A tendency for intravascular thrombosis and thromboembolic events: Thromboembolic events can be life threatening. Approximately half of affected individuals are responsive to pharmacologic doses of vitamin B6, highlighting the need to consider this diagnosis.
6. Stickler syndrome: please see the chapter on "► Stickler Syndrome"
7. Fragile X syndrome: please see the chapter on "► Fragile X Syndrome"

Clinical Features

Ghent criteria: For the diagnosis of Marfan syndrome in the first (index) case in a family, major criteria must be found in at least two different organ systems and minor criteria in a third body system. If a fibrillin-1 mutation is identified, a major criterion in one system and involvement of another system are required. In a relative of an individual with confirmed Marfan syndrome, a major criterion in one body system and involvement of another system are all that are needed for the diagnosis (de Paepe et al. 1996; Pyeritz 2000).

1. Skeletal system (requires at least two majors or one major plus two minors): Affected patients are usually tall and thin with respect to the family profile. Limbs are disproportionately long compared with the trunk (dolichostenomelia). Arachnodactyly is a very common feature.
   1. Major criteria (requires at least four manifestations)
      1. Pectus carinatum.
      2. Pectus excavatum requiring surgery.
      3. Reduced upper-to-lower body segment ratio (<0.85 in Caucasians and <0.78 in African descents) or arm span-to-height ratio greater than 1.05. Arms and legs may be unusually long in proportion to the torso.
      4. Positive wrist (Walker-Murdoch) and thumb (Steinberg) signs for arachnodactyly. Two simple maneuvers may help demonstrate arachnodactyly. First, the thumb sign is positive if the thumb, when completely opposed within the clenched hand, projects beyond the ulnar border. Secondly, the

wrist sign is positive if the distal phalanges of the first and fifth digits of one hand overlap when wrapped around the opposite wrist.
5. Scoliosis $\geq$20 or spondylolisthesis. More than 60% of patients have scoliosis. Progression is more likely with curvature greater than 20° in growing patients.
6. Reduced extension of the elbows ($<$170°).
7. Medial displacement of the medial malleolus, resulting in pes planus.
8. Protrusio acetabuli (intrapelvic protrusion of the acetabulum; abnormally deep acetabulum with accelerated erosion) of any degree (ascertained by pelvic radiograph). Prevalence is about 50%.

2. Minor criteria
1. Pectus excavatum of moderate severity
2. Joint hypermobility
3. High arched palate with dental crowding
4. Typical face
1. Dolichocephaly
2. Malar hypoplasia
3. Enophthamos
4. Retrognathia
5. Down-slanting palpebral fissures

2. Ocular system (requires one major or at least two minors).
1. Major criterion: ectopia lentis (usually superior temporal dislocation, almost always bilateral, occurs in up to 80% of affected individuals). This may present at birth or develop during childhood or adolescence.
2. Minor criteria
1. Abnormally flat cornea (measured by keratometry)
2. Increased axial length of the globe (measured by ultrasound)
3. Hypoplastic iris or hypoplastic ciliary muscle causing decreased miosis

3. Cardiovascular system (requires one major or one minor): the most serious problems associated with Marfan syndrome.
1. Major criteria
1. Dilatation of the ascending aorta with or without aortic regurgitation and involving at least the sinuses of Valsalva. The prevalence of aortic dilatation in Marfan syndrome is 70–80%. It presents at an early age and tends to be more common in men than women.
2. Dissection involving the ascending aorta.

2. Minor criteria
1. Mitral valve prolapse with or without mitral valve regurgitation. The prevalence of mitral valve prolapse is 55–69%.
2. Dilatation of main proximal pulmonary artery in the absence of valvular or peripheral pulmonic stenosis or any other obvious cause, below the age of 40 years.
3. Calcification of mitral annulus in patients less than 40 years of age.
4. Dilatation or dissection of abdominal or descending thoracic aorta in patients less than 50 years of age.

4. Pulmonary system (requires one minor).
1. Major criterion: none
2. Minor criteria
1. Spontaneous pneumothorax: occurs in about 5% of patients
2. Apical blebs (on chest radiography)

5. Skin and integument (requires one minor).
1. Major criterion: none
2. Minor criteria
1. Striae atrophicae (stretch marks) not associated with marked weight changes, pregnancy, or repetitive stress. Stretch marks are usually found on the shoulder, mid back, and thighs.
2. Recurrent or incisional hernia

6. Dura (requires the major criterion).
1. Major criterion: lumbosacral ectasia (ballooning or widening of the dural sac) by CT or MRI. Fewer than 20% of patients experience serious dural

ectasia. Dural ectasia is thought to be caused by CSF pulsations against weakened dura.
2. Minor criteria: none.

7. Family history (requires one major).
   1. Major criteria
      1. Having a parent, child, or sibling who meets the diagnostic criteria independently
      2. Presence of a mutation in *FBN1* known to cause the MFS
      3. Presence of a haplotype around *FBN1*, inherited by descent, known to be associated with unequivocally diagnosed MFS in the family
   2. Minor criterion: none
8. Other features not in the Ghent criteria.
   1. Ocular features
      1. Myopia (most common ocular feature)
      2. At increased risk for retinal detachment, glaucoma, and early cataract formation
   2. Skeletal system
      1. Bone overgrowth
      2. Disproportionately long extremities for the size of the trunk (dolichostenomelia)
      3. Overgrowth of the ribs pushing the sternum in (pectus excavatum) or out (pectus carinatum)
      4. Mild, severe, or progressive scoliosis
9. Natural history: age-related nature of some clinical manifestations and variable phenotypic expression.
   1. At birth, early in life, and childhood
      1. Dolichostenomelia
      2. Arachnodactyly
      3. Manifestations of other organ systems usually not present at birth, making the diagnosis during neonatal period difficult in the absence of family history
      4. Asthenic habitus
      5. Lens dislocation or lens subluxations (a hallmark feature) commonly diagnosed during the first year of life (not present at birth)
   2. Childhood and puberty
      1. Skeletal manifestations apparent during childhood
      2. Pectus deformities and scoliosis worsen during puberty
      3. Upper normal or larger than normal aortic root size in early childhood
      4. Rapidly increasing magnitude of dilatation during puberty
   3. Adulthood
      1. Lumbosacral dural ectasia manifesting as progressive dilatation of the dura with consequent erosion of vertebral bone during adulthood
      2. Aortic disease as the major cause of cardiovascular morbidity and reduced life expectancy (initial life expectancy: 32 ± 16 years)
      3. Increased life expectancy attributes to successive elective and emergent aortic surgery and to the use of β-adrenergic receptor antagonists for the prevention of the progression of aortic root dilatation (current life expectancy: 41 ± 18 years)
10. Revised Ghent nosology for the Marfan syndrome (Loeys et al. 2010).
    1. Established by an international expert panel.
    2. Puts more weight on the cardiovascular manifestations in which aortic root aneurysm and ectopia lentis are the cardinal clinical features.
       1. In the absence of any family history, the presence of aortic root aneurysm and ectopic lentis is sufficient for the unequivocal diagnosis of MFS.
       2. In the absence of either of aortic aneurysm or ectopic lentis, the presence of a bona fide *FBN1* mutation or a combination of systemic manifestations is required. The following new scoring system has been designed for systemic features: The score of ≥ 7 indicates systemic involvement (maximum total of 20 points).
          1. Wrist and thumb sign: 3 (wrist or thumb sign: 1)

2. Pectus carinatum deformity: 2 (pectus excavatum or chest asymmetry: 1)
3. Hindfoot deformity: 2 (plain pes planus: 1)
4. Pneumothorax: 2
5. Dural ectasia: 2
6. Protrusio acetabuli: 2
7. Reduced US/LS and increased arm/height and no severe scoliosis: 1
8. Scoliosis or thoracolumbar kyphosis: 1
9. Reduced elbow extension: 1
10. Facial features (3/5): 1 (dolichocephaly, enophthalmos, downslanting palpebral fissures, malar hypoplasia, retrognathia)
11. Skin striae: 1
12. Myopia >3 diopters: 1
13. Mitral valve prolapse (all types): 1

3. In this revised nosology, *FBN1* testing, although not mandatory, has greater weight in the diagnostic assessment.
4. Special considerations are given to the diagnosis of MFS in children and alternative diagnoses in adults.
5. These new guidelines may delay a definitive diagnosis of MFS but will decrease the risk of premature or misdiagnosis and facilitate worldwide discussion of risk and follow-up/management guidelines.

11. Neonatal Marfan syndrome.
    1. Diagnosed early in life because of striking and severe clinical manifestations (Gross et al. 1989)
        1. Two symptoms that are uncommon in severe Marfan syndrome presenting at birth but very common in neonatal Marfan syndrome (Hannekam 2005)
            1. Congenital pulmonary emphysema
            2. Mitral or tricuspid insufficiency (multivalvular involvement)
        2. Congestive heart failure
        3. Joint contractures
        4. Death usually within the first year of life
    2. Characteristic aged facial appearance
        1. Deep-set eyes
        2. Down-slanted palpebral fissures
        3. Crumpled ears
        4. High arched palate
    3. Striking arachnodactyly of the fingers and toes
    4. Pectus deformities
    5. Scoliosis
    6. Flexion contractures
    7. Pes planus
    8. Aortic root dilatation
    9. Ectopia lentis
    10. A cluster of mutations in exons 24–27 as well as in exons 31–32

Diagnostic Investigations

1. Annual physical examination including blood pressure measurement
2. Slit-lamp examination for lens dislocation
3. Electrocardiogram for symptomatic palpitations, syncope or near-syncope, and conduction disturbance
4. Echocardiography (Geva et al. 1987) and targeted imaging studies to carefully monitor the cardiovascular status
    1. Cross-sectional echocardiography for detecting aortic root dilatation
    2. Standard echocardiography for assessing mitral valve prolapse, left ventricular size and function, left atrial size, and tricuspid valve function
    3. Transesophageal echocardiography for visualizing the distal ascending and descending aorta and assessing prosthetic valves
    4. Doppler echocardiography for detecting and assessing the severity of aortic and mitral regurgitation
5. Radiography
    1. Chest X-ray for apical blebs, enlargement of cardiac silhouette, and detecting dissecting aneurysm of aorta
    2. Pelvic X-ray for additional diagnostic criteria of protrusio acetabuli
    3. Feet X-ray for medial displacement of the medial malleolus, responsible for pes planus

6. Computed tomography (CT) and magnetic resonance imaging (MRI)
    1. MRI: best choice for assessing chronic dissection of any region of the aorta
    2. CT or MRI of the lumbosacral spine for detecting dural ectasia
7. Cardiovscular MR (CMR) imaging (or CT) of the entire aorta (Dommand and Mohiaddin 2013)
    1. CMR: free from ionizing radiation; well visualization of aneurysm formation, dissection, and previous surgery; unsurpassed at characterizing vascular and myocardial tissue
    2. Advise every 5 years if normal aortic dimensions beyond root
    3. Advise at least annually if aneurysm formation beyond root
8. Avoid coronary angiography due to increased dissection risk (Dommand and Mohiaddin 2013)
9. Aortograph: still considered by many to be the gold standard for diagnosing acute aortic dissection although sensitivity is not 100% and there are associated risks
10. Molecular analysis of *FBN1* mutations by sequence analysis, mutation scanning, deletion analysis, or linkage analysis (may be used to determine if an individual has inherited an FBN1 allele that is associated with Marfan syndrome in family members)
    1. *FBN1* mutation screening not only confirms the diagnosis but also facilitates determination of prognosis and timely management (Loeys et al. 2001; Halliday et al. 2002; Chen 2014)
    2. Mutations detected nearly always specific to each family
    3. *FBN1* mutations observed in 20–80% of patients depending upon the clinical selection of patients and the mutation detection method used
        1. Mutation scanning
        2. Targeted mutation analysis
        3. Sequencing of entire coding region
    4. Genotype-phenotype correlations (Pyeritz 2000; Loeys et al. 2001)
        1. Little correlation observed in several hundred mutations reported to date
        2. Severe MFS detected in infancy (inappropriately termed neonatal MFS) usually caused by point mutations or small deletions in frame in the epidermal growth factor (ECF)-like motifs in the middle third of the fibrillin-1 protein
        3. Less severe phenotype, verging on the MASS phenotype, usually caused by chain-terminating mutations resulting in essence in null mutants
        4. Marked variability among individuals with the same mutation
    5. *FBN1* mutations of various types reported
        1. Classic Marfan syndrome
        2. Nonclassical Marfan related phenotypes
    6. Molecular diagnosis practical in the following two situations (Pyeritz 2000)
        1. Information about a known *FBN1* mutation in a person with MFS applied to relatives
        2. Linkage analysis using sufficient intragenic and tightly linked polymorphisms to MFS families with several available and willing relatives
11. Histology of the aorta
    1. Elastic fiber fragmentation and disarray
    2. Paucity of smooth muscle cells
    3. Deposition of collagen and the mucopolysaccharide between the cells of the media

Genetic Counseling

1. Recurrence risk
    1. Patient's sib
        1. Recurrence risk: small if neither parent is affected
        2. Gonadal mosaicism reported as the cause of multiple affected offspring being born to unaffected parents
        3. Fifty percent if one parent is affected
    2. Patient's offspring
        1. Fifty percent if the spouse is normal

2. "Homozygous" MFS reported in case of an affected spouse
3. "Compound heterozygosity" at the *FBN1* locus confirmed at the molecular level; the affected child had a severe phenotype leading to early death

2. Prenatal diagnosis
   1. Ultrasonography insensitive in the first two trimesters for detecting a fetus with MFS
   2. Presumptive prenatal diagnosis of fetal Marfan syndrome by fetal echocardiography at 34 weeks of gestation (Lopes et al. 1995)
      1. Cardiomegaly
      2. Pericardial effusion
      3. Prolapse of the tricuspid and mitral valves with mitral and tricuspid regurgitation
      4. Dilatation of Valsalva with typical "clover-lead" appearance
      5. Aortic and pulmonary regurgitation
   3. Main clinical cardiovascular features for the prenatal diagnosis of Marfan syndrome (Lopes et al. 2006)
      1. Cardiomegaly
      2. Dilated great vessels
      3. Dysplastic atrioventricular valves with tricuspid regurgitation and aneurysms of the pulmonary artery and/or sinus of Valsalva
   4. Prenatal diagnosis of Marfan syndrome can be confirmed in affected families by gene identification using chorionic villus sampling (Godfrey et al. 1993; Rantamaki et al. 1995).
      1. Only if the family's mutation is known in an affected parent
      2. Neonatal Marfan syndrome, mostly sporadic, appears to be more severe than those in familiar forms (Gross et al. 1989). Inability to predict exons 24–32 mutation to be associated with "classic, atypically severe or neonatal" Marfan syndrome (Tieck et al. 2001)
      3. Presence of sufficient affected family members available for genetic linkage analysis if linkage with markers in and around the *FBN1* locus can be established
   5. Preimplantation diagnosis accomplished but complicated by the potential for selective PCR amplification of the normal allele as with all autosomal dominant conditions (Eldadah et al. 1995; Kilpatrick et al. 1996; Blaszczyk et al. 1998; Sermon et al. 1999)
3. Management (Pyeritz and McKusick 1979; Nienaber and Von Kodolitsch 1999; Castellano et al. 2014)
   1. Address patients' perceptions of Marfan syndrome and its associated pain, fatigue, and depressive symptoms to enhance patient adaptation.
   2. Stress benefits of medication use (β-blockers or calcium-channel blockers to retard aortic root dilatation and dissection) and restriction of physical activities (to delay the onset of a severe cardiovascular event and prevent other syndrome-related problems such as lens dislocation).
      1. β-Blockers
         1. Should be considered in all Marfan patients, particularly in the younger age group
         2. Not suitable for patients with asthma, cardiac failure, or bradyarrhythmias
      2. Other treatments aimed at reducing the ejection impulse
         1. Calcium antagonists
         2. Angiotensin converting enzyme (ACE) inhibitors
   3. Lifestyle changes
      1. Avoid competitive and collision/contact sports which are potentially dangerous due to underlying aortic weakness and dilatation, valvular insufficiency, ocular abnormalities, and skeletal problems (Braverman 1998)
      2. Avoid blows to the head such as boxing and high diving.
      3. Protect against blows to the globe (racquet sports) with cushioned spectacles.

4. Avoid activities involving isometric work to prevent excessive elevations of systolic blood pressure and sudden death.
    1. Weight lifting
    2. Climbing steep inclines
    3. Gymnastics
    4. Water skiing
    5. Pull-ups
5. Avoid rapid decompression associated with quick ascents in elevators, scuba diving, and flying in unpressurized aircraft to protect against pneumothorax.
6. Favor noncompetitive, isokinetic activity performed at a nonstrenous aerobic pace.
    1. Golfing
    2. Walking
    3. Fishing

4. Surgical intervention recommended for affected individuals with significantly dilated or dissected aortic roots or aortic aneurysm (Baumgartner et al. 1999)
5. Management of scoliosis (Sponseller et al. 1997)
    1. Bracing
    2. Physical therapy
    3. Surgery for severe scoliosis
6. Pectus repair
    1. Repair of pectus excavatum to improve respiratory mechanics: should be delayed until midadolescence to lessen the chance of recurrence
    2. Repair of pectus carinatum performed mainly for cosmetic purpose
7. Pneumothorax
    1. Chest tube: an appropriate initial therapy
    2. Bleb resection and pleurodesis recommended after one recurrence
8. Ocular management (Koenig and Mieler 1996)
    1. Removal of dislocated lens (pars plana lensectomy and vitrectomy), only in the following few instances, due to an increased risk of retinal detachment related to lens extraction
        1. Dislocation of a lens in the anterior chamber, especially when it touches the corneal endothelium
        2. Significant lens opacity
        3. Evidence of lens-induced uveitis and glaucoma
        4. Inadequate visual acuity that is not correctable by refraction and iris manipulation
        5. Imminent complete luxation of the lens
    2. Lasers to restore a detached retina
9. Pregnancy in women with MFS (Curry et al. 2014)
    1. Preconceptional counseling of maternal risks during pregnancy and risk of transmitting the condition to offspring.
    2. A significantly increased risk of cardiovascular complications during pregnancy.
        1. Particularly risk of dissecting aortic aneurysm
        2. Increase in aortic root diameter
        3. Worsening mitral or aortic regurgitation, as seen in echocardiography
        4. Myocardial infarction
        5. Pulmonary edema
        6. Arrhythmia
        7. Endocarditis
        8. Cardiac death
        9. Aortic surgery within 6 months of delivery
    3. Obstetric complications.
        1. Antepartum hemorrhage
        2. Pregnancy-induced hypertension
        3. Pre-eclampsia
        4. Eclampsia
        5. Gestational diabetes
        6. Preterm labor/rupture of membranes
        7. Postpartum hemorrhage
        8. Thromboembolism
    4. Fetal/neonatal complications.
        1. Preterm birth
        2. Respiratory distress syndrome
        3. Intraventricular hemorrhage
        4. Fetal demise

5. Perinatal/neonatal mortality
5. Need for close surveillance during pregnancy.
6. Avoid pregnancy if echocardiography suggests a high risk of life-threatening cardiovascular compromise. Pregnancy bears a 1% risk of fatal complication; the risk rises with increasing aortic root diameter.
7. β-Blockers recommended in pregnant women to prevent aortic dilatation.
8. Cesarean section should be offered at 38 weeks gestation if aortic root diameter is greater than 4.5 cm (Child 1997).
9. Favorable outcomes in a tertiary referral center (Allyn et al. 2013).
    1. Pre- or early pregnancy evaluation
    2. Early β-blocker therapy
    3. Serial echocardiographic assessments
    4. Multidisciplinary planning of mode of delivery
    5. Avoidance of hemodynamic stress on the aortic root with appropriate analgesia/anesthesia technique
10. More extensive screening for Marfan syndrome and a search for additional risk factors are desirable because of high fatality rate in Marfan syndrome aortic root dissection (Groenink et al. 1999).
11. Genetic counseling that addresses patients' perception of Marfan syndrome and its associated pain, fatigue, and depressive symptoms may enhance patient adaptation to the condition (Peters et al. 2001a).
12. Genetic counseling should address beliefs about medication use and physical activity restrictions, as perception of these health behaviors may have a significant impact on how adults with Marfan syndrome adhere to these recommendations and cope with their condition (Peters et al. 2001b).
13. Dramatic increase in life expectancy (Silverman et al. 1995).
    1. Median (50%) cumulative probability of survival in 1993 was 72 years compared with 48 years in 1972.
    2. Overall improvement in population life expectancy.
    3. Benefits arising from cardiovascular surgery.
    4. Greater proportion of milder cases due to increased frequency of diagnosis.
    5. Medical therapy including β-blockers.

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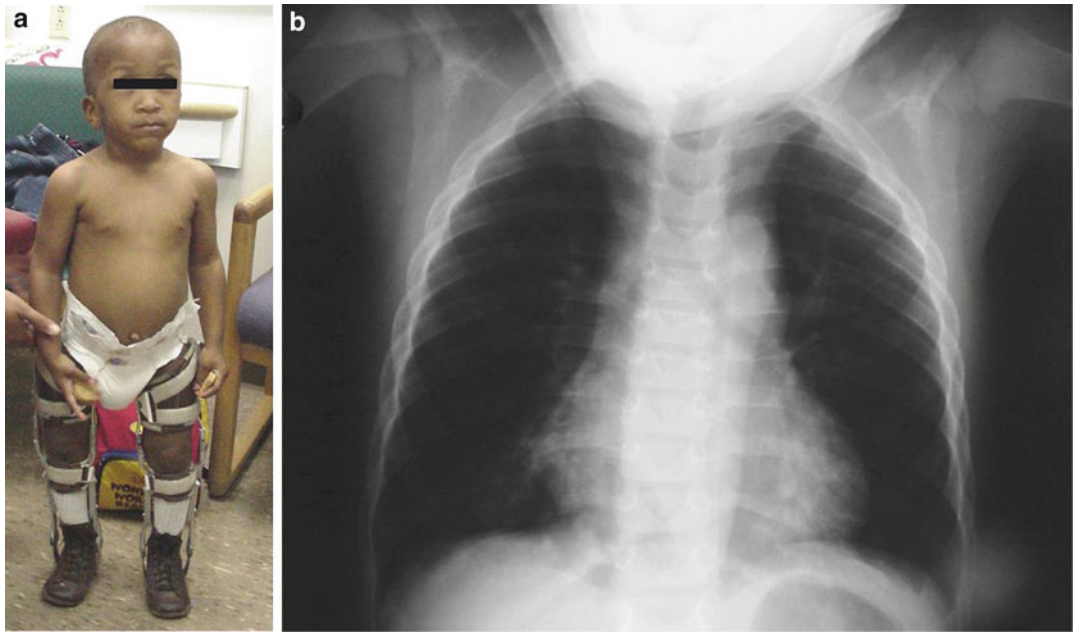


Fig. 1 (**a**, **b**) A boy with severe Marfan syndrome showing arachnodactyly, joint contractures, and aortic root dilatation, illustrated by the chest radiography

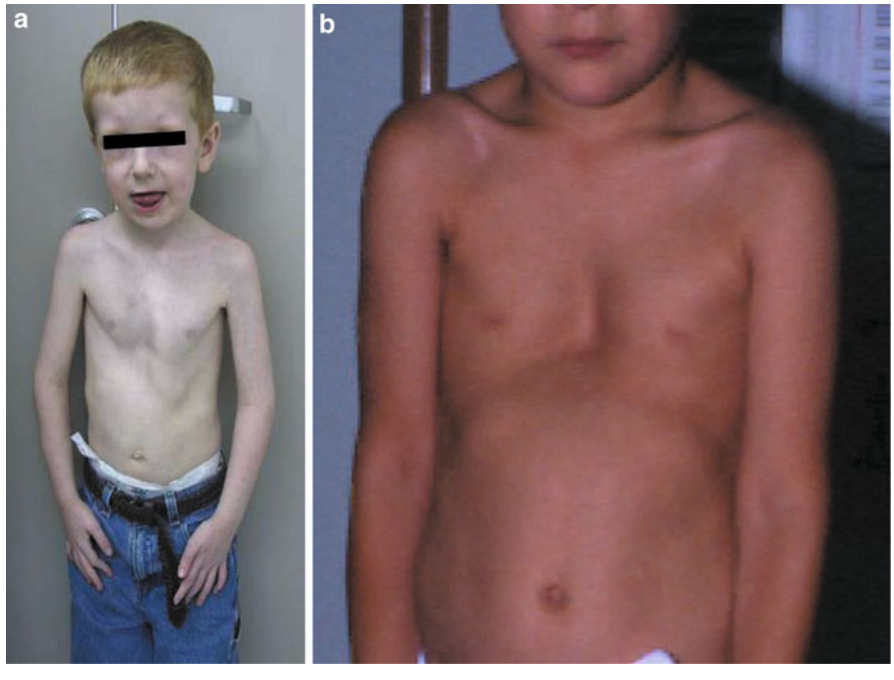


Fig. 2 (**a**, **b**) Two children with Marfan syndrome showing pectus and arachnodactyly. The first patient had dural ectasia detected by MRI. The second patient had aortic root dilatation and mitral valve prolapse

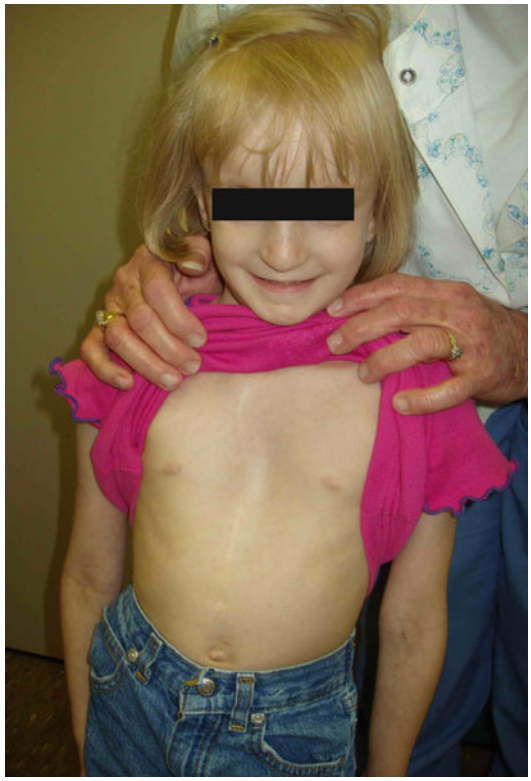


Fig. 3 A 4-year-old girl with Marfan syndrome showing pectus excavatum and the operation scar from surgical correction of marked aortic dilatation. She also has hyperextensible joints and scoliosis

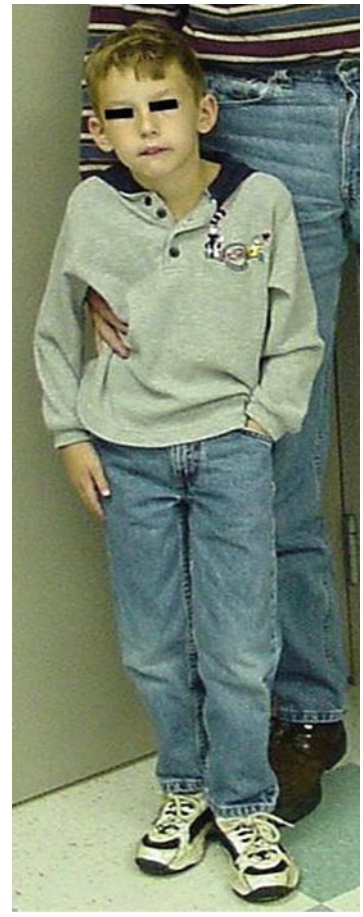


Fig. 4 A 5-year-old boy with Marfan syndrome showing tall and slender body habitus. He was noted to have mitral valve prolapse and aortic root dilatation at age 2. In addition, he has bilateral lens dislocations and scoliosis

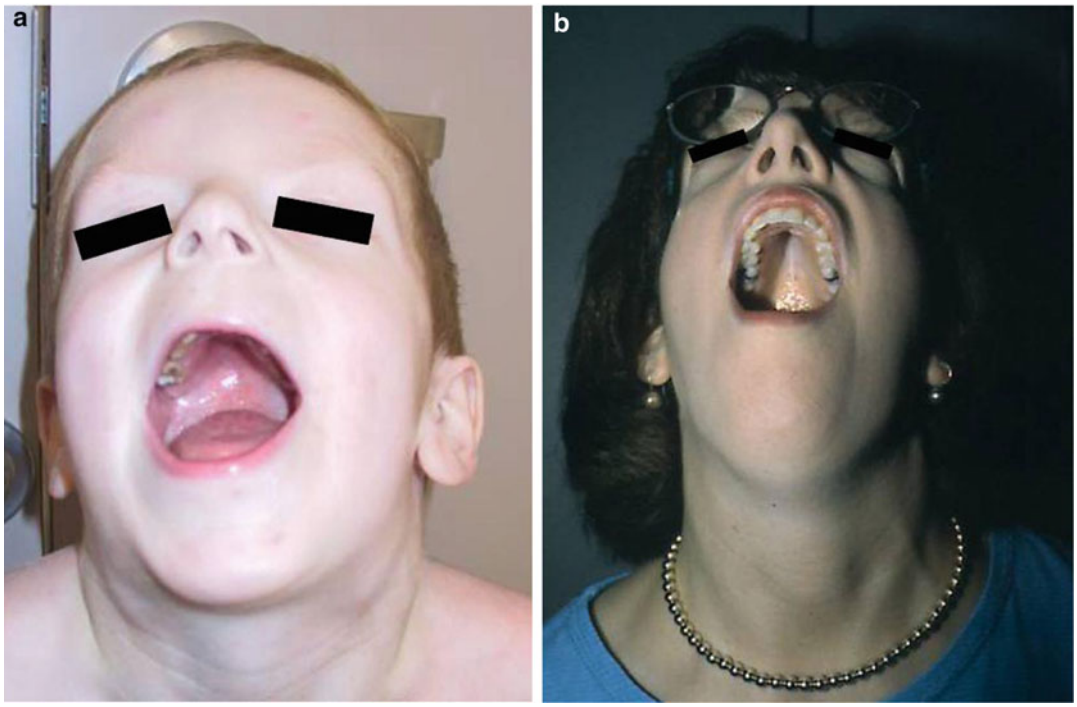


Fig. 5 (**a**, **b**) A child and an adult with Marfan syndrome showing high arched palate

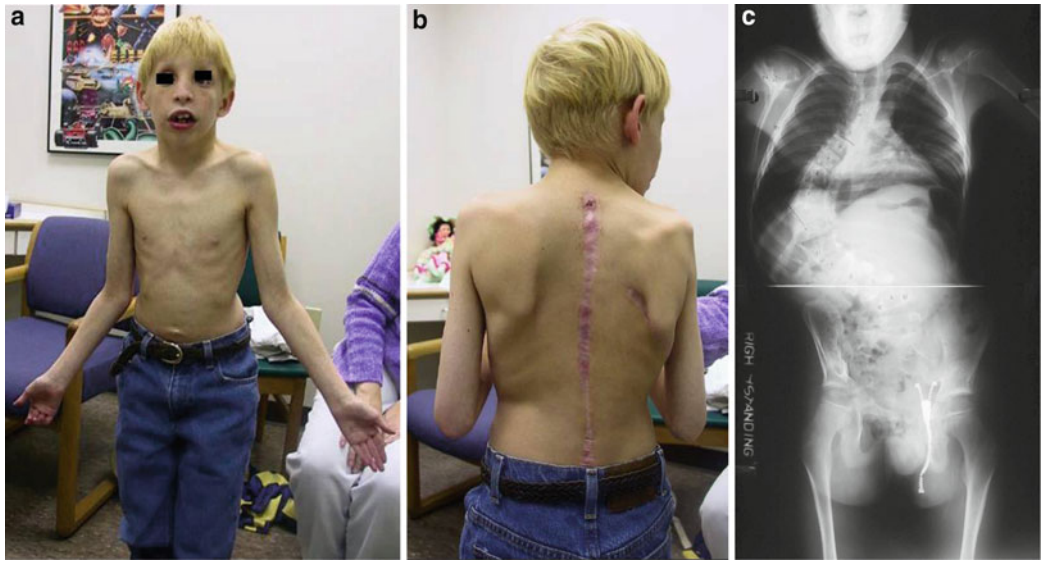


Fig. 6 (**a**–**c**) A child with Marfan syndrome showing cubitus valgus, arachnodactyly, and postsurgical spinal fusion for severe scoliosis (Illustrated by radiograph)

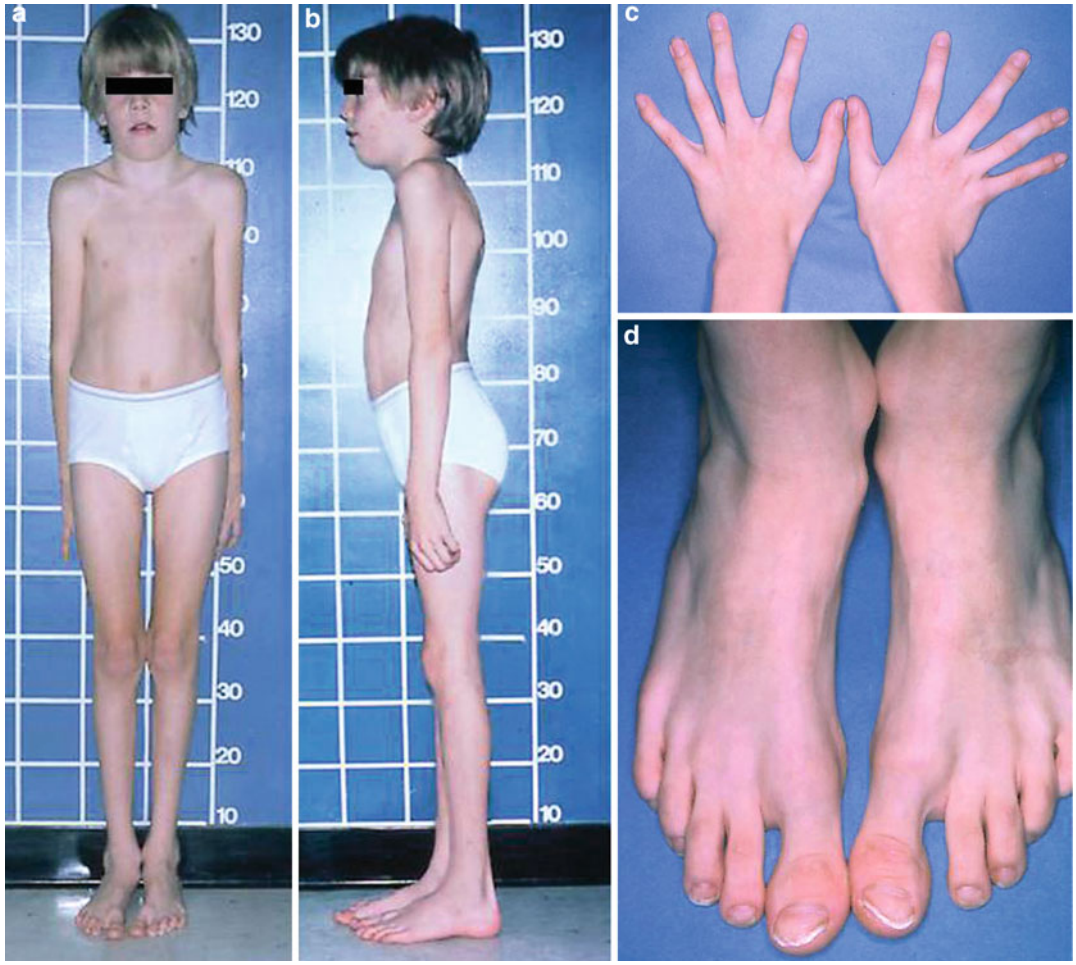


Fig. 7 (**a**–**d**) A boy with Marfan syndrome showing a slender/tall habitus and arachnodactyly

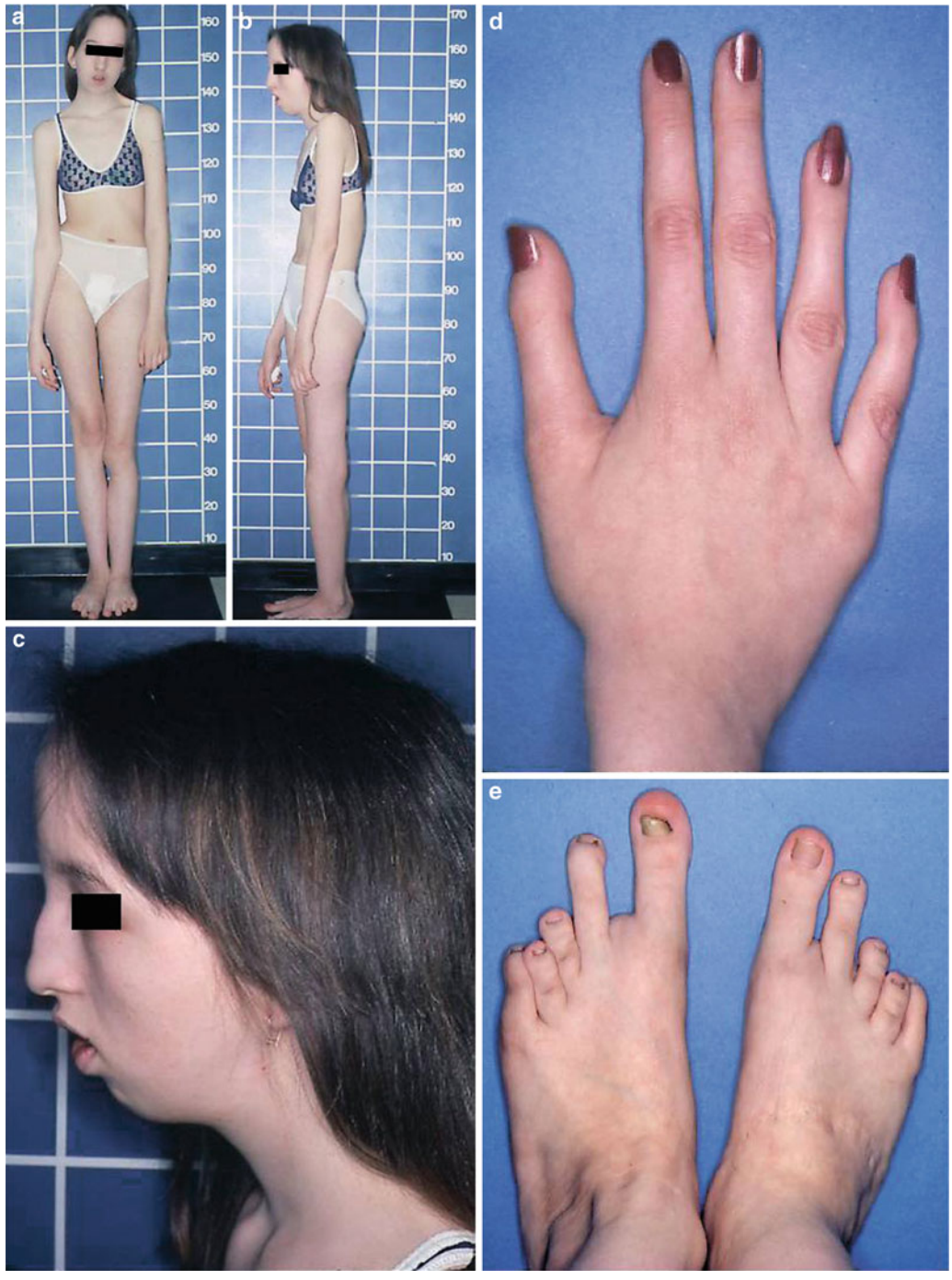


Fig. 8 (**a**–**e**) A girl with Marfan syndrome showing a slender/tall habitus, typical facies, arachnodactyly, and toe anomalies

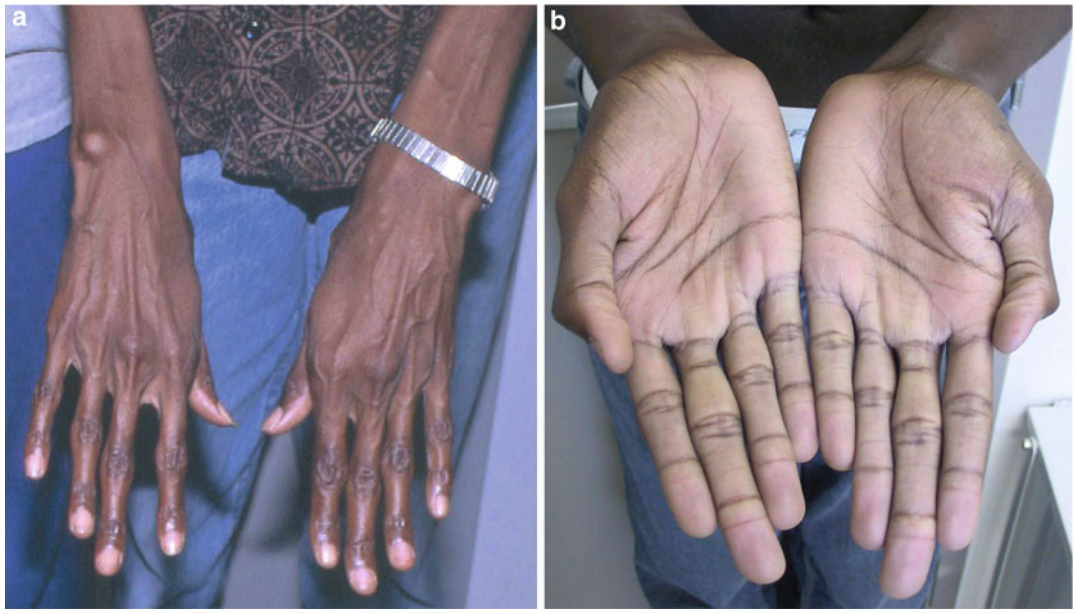


Fig. 9 (**a**, **b**) Arachnodactyly in two adult patients with Marfan syndrome

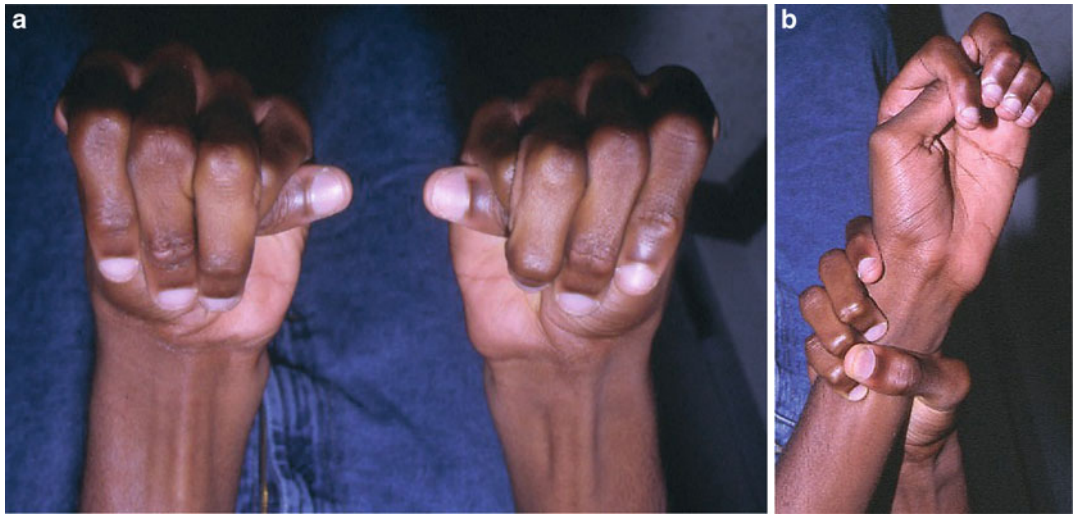


Fig. 10 (**a**, **b**) Thumb and wrist signs

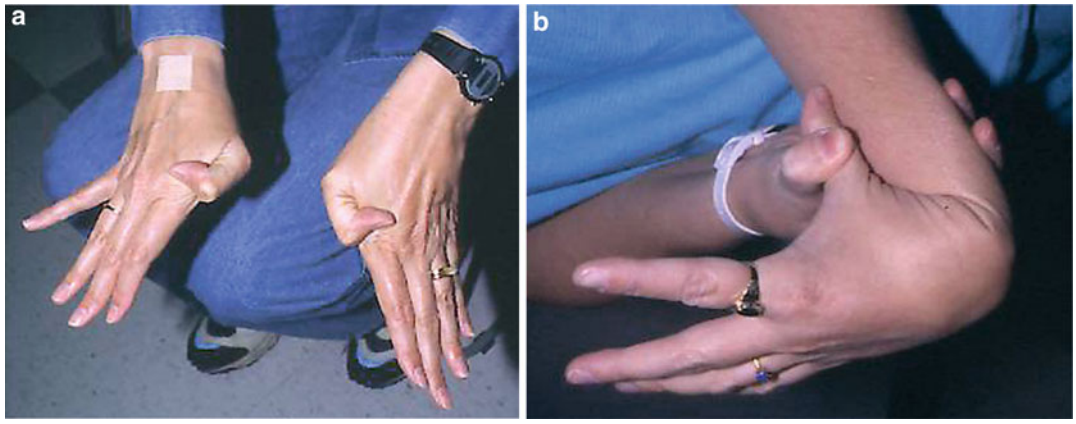
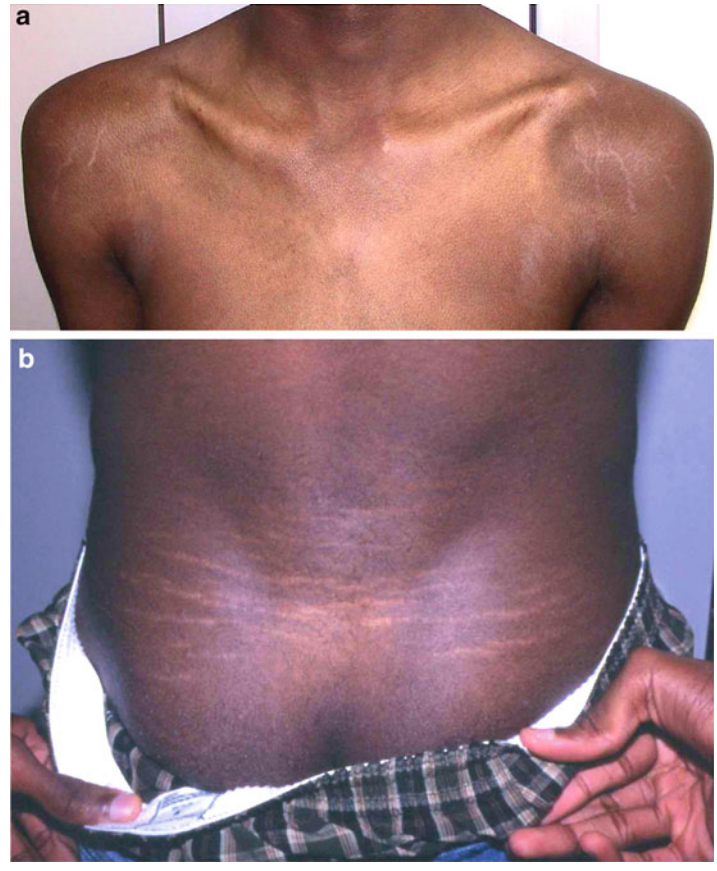


Fig. 11 (**a**, **b**) Hypermobile joints in two patients with Marfan syndrome

Fig. 12 (**a**, **b**) Stretch marks in the shoulders in one patient and in the buttock region in other patient with Marfan syndrome



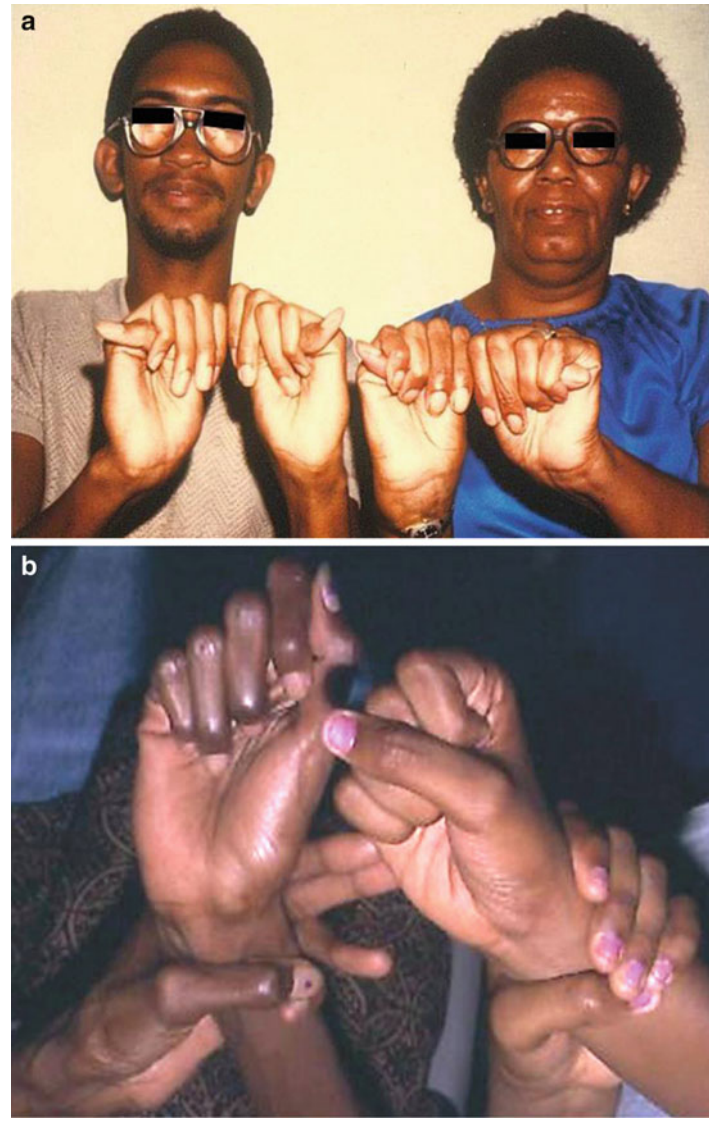


Fig. 13 (**a**, **b**) Familial Marfan syndrome in a mother and a son showing extreme myopia (lens dislocation) and thumb and wrist signs

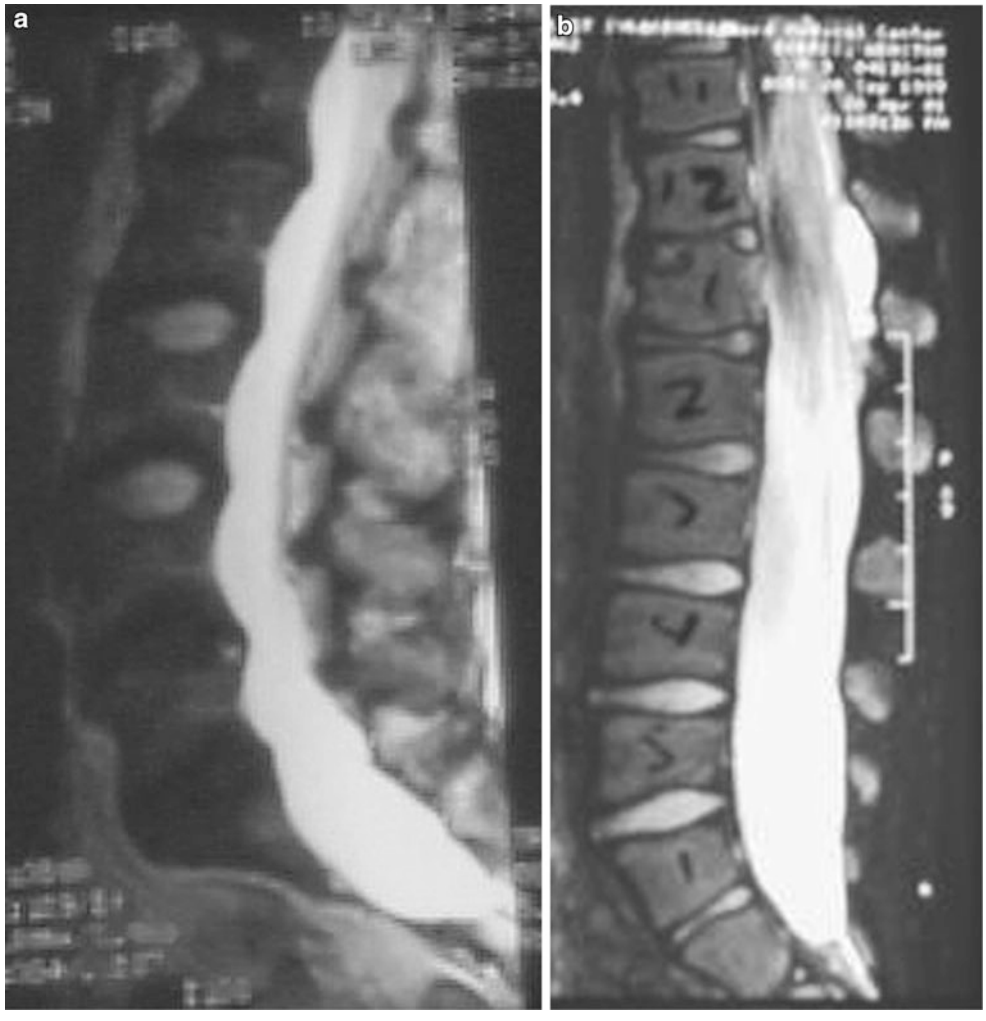


Fig. 14 (**a**, **b**) MRI of the lumbosacral spine in two patients showing dural ectasia

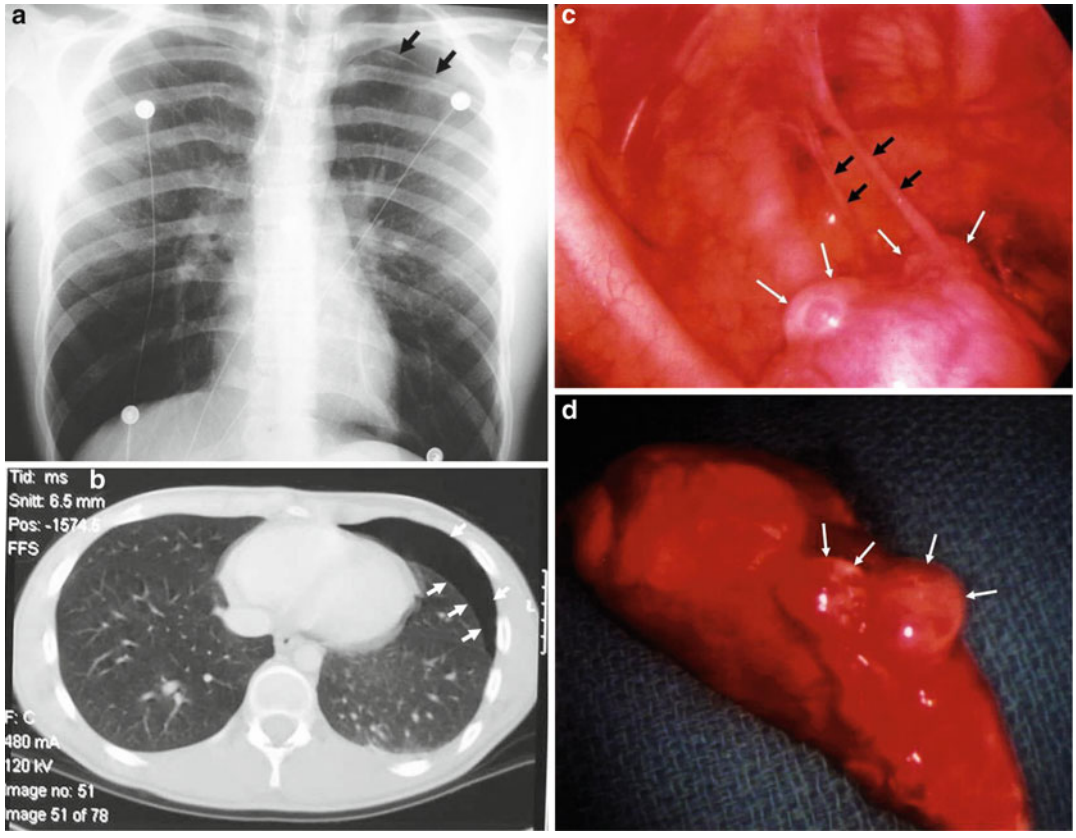


Fig. 15 (**a**–**d**) A 20-year-old male with Marfan syndrome with repeat spontaneous pneumothorax from ruptures of apical blebs. The chest X-ray shows collapsed left lung with pleural line (*arrows*). The CT of the chest shows pneumothorax on the right lung (*arrows*). Thoracoscope image from the right lung shows two bands representing the old adhesions due to previously ruptured apical blebs (*black arrows*) and two intact blebs (*white arrows*). The wedge biopsy specimen of the right apex shows two emphysematous blebs (*white arrows*) which were demonstrated in the previous figure

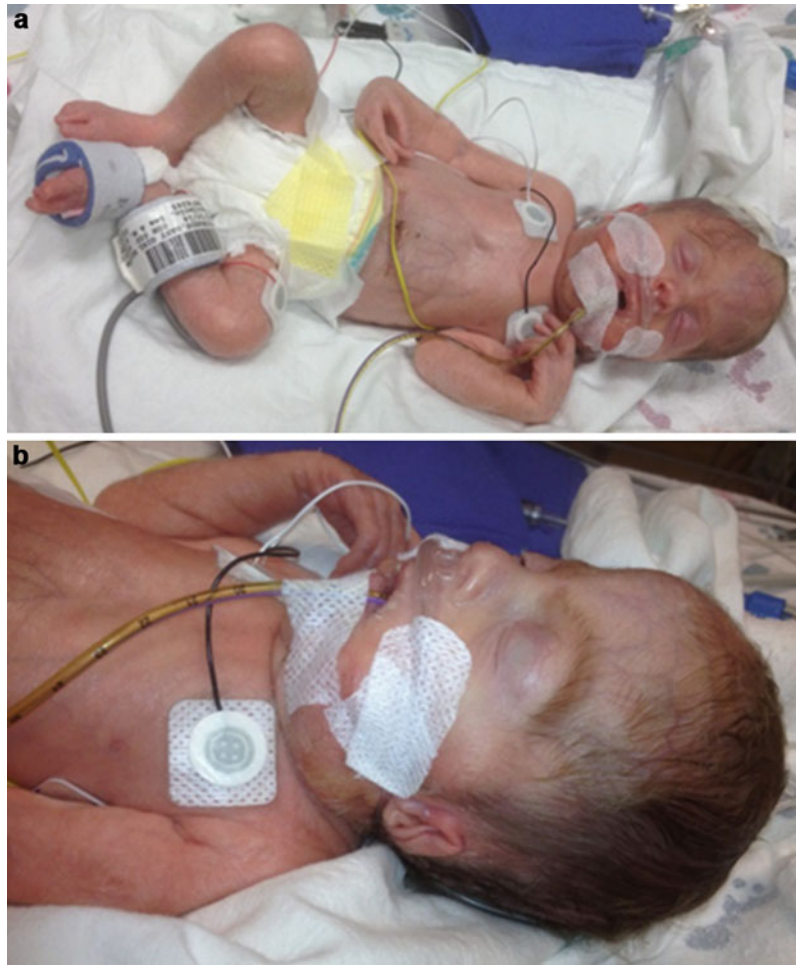


Fig. 16 (**a, b**) This premature baby girl (**a, b**) was born at 30 4/7 weeks gestation via cesarean section due to pregnancy-induced hypertension and omphalocele. Craniofacial features were characterized by trigonocephaly, anti-mongoloid slant of the palpebral fissures, cleft palate, and crumpled low-set ears. The neck was short. Fingers and toes were long. Echocardiograms showed a large patent ductus arteriosus and obstructive right ventricular muscle bundle at 70 %. Due to family history of her mother with Marfan syndrome and baby's clinical features of cardiac anomalies and long fingers and toes, *FBN1* gene test for neonatal Marfan syndrome and full gene sequence of *FBN1* were performed (Mayo Clinical Laboratories). A pathogenic variant was not detected in exons 24–32 of *FBN1*gene which has been reported in individual with neonatal Marfan syndrome to harbor mutations in exons 24–32 of the *FBN1* gene. However, one copy of the following mutations was detected in *FBN1*: exon 2, nucleotide c.240dupT, and amino acid p.Ile81Tyrfs*48.This pathogenic FBN1 variant is consistent with Marfan syndrome. In addition, chromosome microarray analysis identified a complex 9p rearrangement, resulting in a terminal deletion from 9p24.3 to 9p22.2, spanning approximately 17.5 megabases. FISH studies using a 9p subtelomere probe (Abbott Molecular) and a probe within the duplicated interval (CTD-2054C7) confirmed the deletion and are consistent with an inverted duplication. Similar complex 9p rearrangements have been reported in patients with developmental delay, intellectual disability, trigonocephaly, facial dysmorphism, hypotonia, and additional phenotypic features (Recalcati et al. 2012; Di Bartolo et al. 2012) (Courtesy of Dr. Lea Bonifacio)

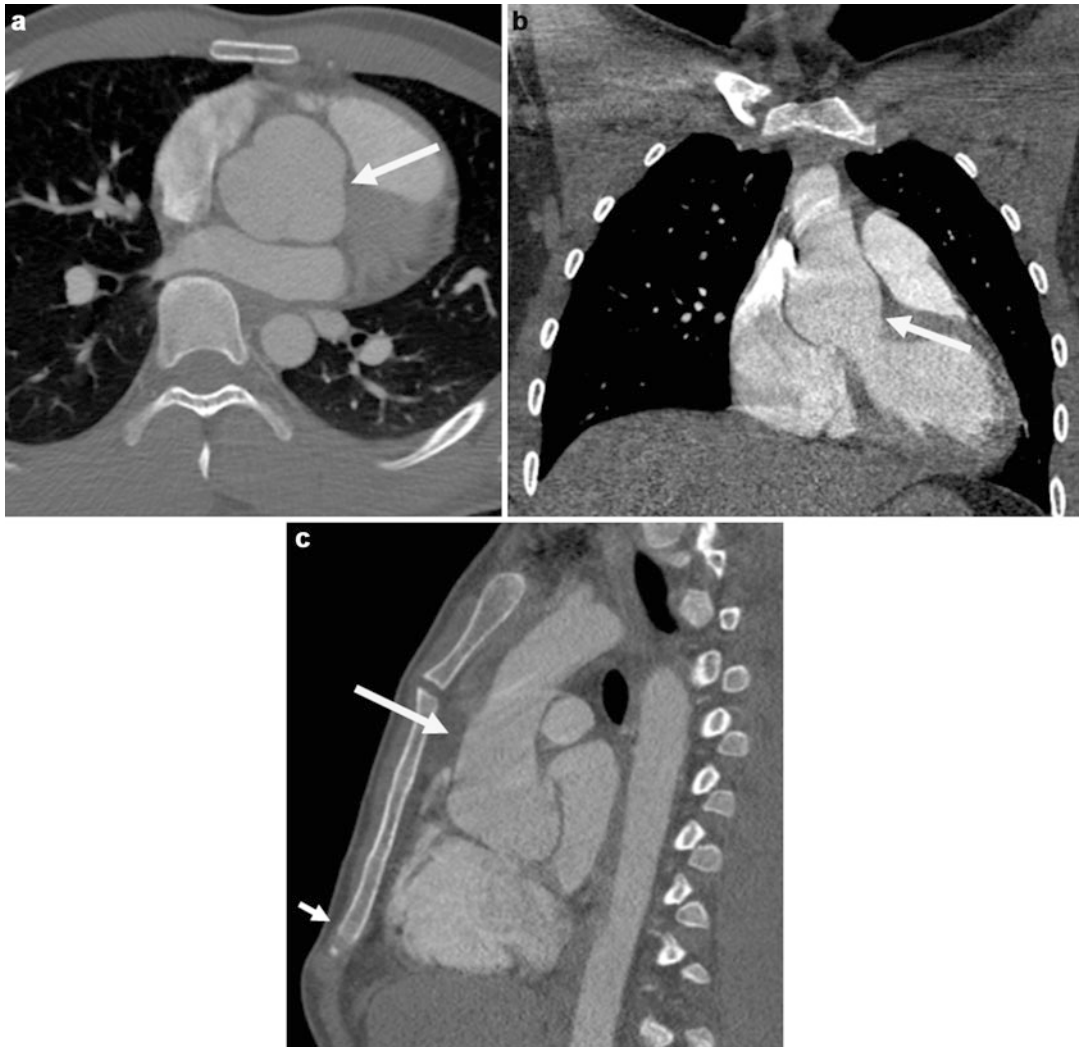


Fig. 17 (**a**–**c**) A 17-year-old male was evaluated because of a history of Marfan syndrome with complaints of headache and tearing back pain. He was noted to have pectus carinatum since birth. Since 12 years of age, he was noted to have flat feet and hyperextensible joints. He wore glasses and was told that he did not have lens dislocation (no ophthalmologic record was available). Previous echocardiogram (not shown) confirmed a markedly dilated aortic root of 3.8 cm (a Z-score of approximately +5.5). There was clover-leafing, also suggesting dilated aortic root. There was mild ascending aorta dilation and trivial mitral valve prolapse. Chest radiographs (not shown) showed a good expansion of left aortic arch and a prominent aortic knob. CT images (**a–c**) showed moderate dilation of the aortic root (*large arrows*) which measured 4.8 × 5 cm in AP and transverse dimensions. No evidence of aortic dissection or pulmonary embolism was noted. Sagittal image (**c**) showed mild pectus carinatum (*small arrow*). He was diagnosed with Marfan Syndrome at 12 years of age. His diagnosis was based on aortic root dilation, skeletal features, and FBN1 mutation (C.2695GG insertion resulting in a frameshift mutation and abnormal mRNA processing). He is now status post valve sparing aortic root replacement. (Courtesy of Dr. Grace Guo)