MORPHOLOGY

Skeletal abnormalities are the most striking feature of Marfan syndrome. Typically the patient is unusually tall with exceptionally long extremities and long, tapering fingers and toes. The joint ligaments in the hands and feet are lax, suggesting that the patient is double-jointed; typically the thumb can be hyperextended back to the wrist. The head is commonly dolichocephalic (long-headed) with bossing of the frontal eminences and prominent supraorbital ridges. A variety of spinal deformities may appear, including kyphosis, scoliosis, or rotation or slipping of the dorsal or lumbar vertebrae. The chest is classically deformed, presenting either pectus excavatum (deeply depressed sternum) or a pigeon-breast deformity.

The **ocular changes** take many forms. Most characteristic is bilateral subluxation or dislocation (usually outward and upward) of the lens, referred to as ectopia lentis. This abnormality is so uncommon in persons who do not have this disease that the finding of bilateral ectopia lentis should raise the suspicion of Marfan syndrome.

Cardiovascular lesions are the most life-threatening features of this disorder. The two most common lesions are mitral valve prolapse and, of greater importance, dilation of the ascending aorta due to cystic medionecrosis. Histologically the changes in the media are virtually identical to those found in cystic medionecrosis not related to Marfan syndrome (Chapter 12). Loss of medial support results in progressive dilation of the aortic valve ring and the root of the aorta, giving rise to severe aortic incompetence. In addition, excessive TGF-β signaling in the adventitia may also contribute to aortic dilation. Weakening of the media predisposes to an intimal tear, which may initiate an intramural hematoma that cleaves the layers of the media to produce **aortic dissection.** After cleaving the aortic layers for considerable distances, sometimes back to the root of the aorta or down to the iliac arteries, the hemorrhage often ruptures through the aortic wall. Such a calamity is the cause of death in 30% to 45% of these individuals.

Clinical Features. Although mitral valve lesions are more frequent, they are clinically less important than aortic lesions. Loss of connective tissue support in the mitral valve leaflets makes them soft and billowy, creating a so-called floppy valve (Chapter 12). Valvular lesions, along with lengthening of the chordae tendineae, frequently give rise to mitral regurgitation. Similar changes may affect the tricuspid and, rarely, the aortic valves. Echocardiography greatly enhances the ability to detect the cardiovascular abnormalities and is therefore extremely valuable in the diagnosis of Marfan syndrome. The great majority of deaths are caused by rupture of aortic dissections, followed in importance by cardiac failure.

While the lesions just described typify Marfan syndrome, it must be emphasized that there is great variation in the clinical expression of this genetic disorder. Patients with prominent eye or cardiovascular changes may have few skeletal abnormalities, whereas others with striking changes in body habitus have no eye changes. Although variability in clinical expression may be seen within a family, interfamilial variability is much more common and extensive. Because of such variations, the clinical diagnosis of Marfan syndrome is currently based on the so called "revised Ghent criteria." These take into account family history, cardinal clinical signs in the absence of family history, and presence or absence of fibrillin mutation. In general, major involvement of two of the four organ systems (skeletal, cardiovascular, ocular, and skin) and minor involvement of another organ is required for diagnosis.

The variable expression of the Marfan defect is best explained on the basis of of the many different mutations that affect the fibrillin locus, which number more than 600. This genetic heterogeneity also poses formidable challenges in the diagnosis of Marfan syndrome. The evolving high throughput sequencing technologies discussed later in this chapter may overcome this problem in the future.

The mainstay of the medical treatment is administration of β blockers which likely act by reducing heart rate and aortic wall stress. In animal models inhibition of TGF-β action by use of specific antibodies has been found useful. Since lifelong use of such antibodies in humans is not feasible, other strategies to block TGF-β signaling are being tested. Blockade of angiotensin type 2 receptors accomplishes this effect in humans and several preliminary studies are very promising.

Ehlers-Danlos Syndromes (EDS)

EDSs comprise a clinically and genetically heterogeneous group of disorders that result from some defect in the synthesis or structure of fibrillar collagen. Other disorders resulting from mutations affecting collagen synthesis include osteogenesis imperfecta (Chapter 26), Alport syndrome (Chapter 20), and epidermolysis bullosa (Chapter 25).

Biosynthesis of collagen is a complex process (Chapter 1) that can be disturbed by genetic errors that may affect any one of the numerous structural collagen genes or enzymes necessary for posttranscriptional modifications of collagen. Hence, the mode of inheritance of EDS encompasses all three Mendelian patterns. On the basis of clinical and molecular characteristics, six variants of EDS have been recognized. These are listed in Table 5-5. It is beyond the scope of this book to discuss each variant individually; instead, the important clinical features common to most

Table 5-5 Classification of Ehlers-Danlos Syndromes

EDS Type*	Clinical Findings	Inheritance	Gene Defects
Classic (I/II)	Skin and joint hypermobility, atrophic scars, easy bruising	Autosomal dominant	*COL5A1, COL5A2*
Hypermobility (III)	Joint hypermobility, pain, dislocations	Autosomal dominant	Unknown
Vascular (IV)	Thin skin, arterial or uterine rupture, bruising, small joint hyperextensibility	Autosomal dominant	*COL3A1*
Kyphoscoliosis (VI)	Hypotonia, joint laxity, congenital scoliosis, ocular fragility	Autosomal recessive	Lysyl hydroxylase
Arthrochalasia (VIIa,b)	Severe joint hypermobility, skin changes (mild), scoliosis, bruising	Autosomal dominant	*COL1A1, COL1A2*
Dermatosparaxis (VIIc)	Severe skin fragility, cutis laxa, bruising	Autosomal recessive	Procollagen *N*-peptidase

*EDS types were previously classified by Roman numerals. Parentheses show previous numerical equivalents.