variants are summarized and clinical manifestations are correlated with the underlying molecular defects in collagen synthesis or structure.

As might be expected, tissues rich in collagen, such as skin, ligaments, and joints, are frequently involved in most variants of EDS. Because the abnormal collagen fibers lack adequate tensile strength, *skin is hyperextensible, and the joints are hypermobile.* These features permit grotesque contortions, such as bending the thumb backward to touch the forearm and bending the knee forward to create almost a right angle. It is believed that most contortionists have one of the EDSs. A predisposition to joint dislocation, however, is one of the prices paid for this virtuosity. *The skin is extraordinarily stretchable, extremely fragile, and vulnerable to trauma.* Minor injuries produce gaping defects, and surgical repair or intervention is accomplished with great difficulty because of the lack of normal tensile strength. *The basic defect in connective tissue may lead to serious internal complications.* These include rupture of the colon and large arteries (vascular EDS), ocular fragility with rupture of cornea and retinal detachment (kyphoscoliosis EDS), and diaphragmatic hernia (classic EDS).

The biochemical and molecular bases of these abnormalities are known in several forms of EDS. These are described briefly, because they offer some insights into the perplexing clinical heterogeneity of EDS. Perhaps the best characterized is the *kyphoscoliosis type, the most common autosomal recessive form of EDS.* It results from mutations in the gene encoding lysyl hydroxylase, an enzyme necessary for hydroxylation of lysine residues during collagen synthesis. Affected patients have markedly reduced levels of this enzyme. Because hydroxylysine is essential for the cross-linking of collagen fibers, a deficiency of lysyl hydroxylase results in the synthesis of collagen that lacks normal structural stability.

The *vascular type of EDS results from abnormalities of type III collagen.* This form is genetically heterogeneous, because at least three distinct types of mutations affecting the *COL3A1* gene encoding collagen type III can give rise to this variant. Some affect the rate of synthesis of pro-α1 (III) chains, others affect the secretion of type III procollagen, and still others lead to the synthesis of structurally abnormal type III collagen. Some mutant alleles behave as dominant negatives (see discussion under "Autosomal Dominant Disorders") and thus produce severe phenotypic effects. These molecular studies provide a rational basis for the pattern of transmission and clinical features that are characteristic of this variant. First, because vascular-type EDS results from mutations involving a structural protein (rather than an enzyme protein), an autosomal dominant pattern of inheritance would be expected. Second, because blood vessels and intestines are known to be rich in collagen type III, an abnormality of this collagen is consistent with severe structural defects (e.g., vulnerability to spontaneous rupture) in these organs.

In two forms of EDS—arthrochalasia type and dermatosparaxis type—the fundamental defect is in the conversion of type I procollagen to collagen. This step in collagen synthesis involves cleavage of noncollagen peptides at the N terminus and C terminus of the procollagen molecule. This is accomplished by N-terminal–specific and C-terminal–specific peptidases. The defect in the conversion of procollagen to collagen in the arthrochalasia type has been traced to mutations that affect one of the two type I collagen genes, COL1A1 and COL1A2. As a result, structurally abnormal pro-α 1 (I) or pro-α2 (I) chains that resist cleavage of N-terminal peptides are formed. In patients with a single mutant allele, only 50% of the type I collagen chains are abnormal, but because these chains interfere with the formation of normal collagen helices, heterozygotes manifest the disease. In contrast, the related dermatosparaxis type is caused by mutations in the procollagen-N-peptidase genes, essential for the cleavage of collagens. Because in this case the disease is caused by an enzyme deficiency, it follows an autosomal recessive form of inheritance.

Finally, in *classic type of EDS,* molecular analysis suggests that genes other than those that encode collagen may also be involved. In 30% to 50% of these cases, mutations in the genes for type V collagen (*COL5A1* and *COL5A2*) have been detected. Surprisingly, in the remaining cases, no other collagen gene abnormalities have been found despite clinical features typical of EDS. It is suspected that in some cases genetic defects that affect the biosynthesis of other extracellular matrix molecules that influence collagen synthesis indirectly may be involved. One example is an EDS-like condition caused by mutation in tenascin-X, a large multimeric protein, that affects the synthesis and fibril formation of type VI and type I collagens.

To summarize, the common thread in EDS is some abnormality of collagen. These disorders, however, are extremely heterogeneous. At the molecular level, a variety of defects, varying from mutations involving structural genes for collagen to those involving enzymes that are responsible for posttranscriptional modifications of mRNA, have been detected. Such molecular heterogeneity results in the expression of EDS as a clinically variable disorder with several patterns of inheritance.

KEY CONCEPTS

Marfan Syndrome

- Marfan syndrome is caused by a mutation in the *FBN1* gene encoding fibrillin, which is required for structural integrity of connective tissues and regulation of TGF-β signaling.
- The major tissues affected are the skeleton, eyes, and cardiovascular system.
- Clinical features may include tall stature, long fingers, bilateral subluxation of lens, mitral valve prolapse, aortic aneurysm, and aortic dissection.
- Clinical trials with drugs that inhibit TGF-β signaling such as angiotensin receptor blockers are ongoing, as these have been shown to improve aortic and cardiac function in mouse models.

Ehlers-Danlos Syndromes

- There are six variants of Ehlers-Danlos syndromes, all characterized by defects in collagen synthesis or assembly. Each of the variants is caused by a distinct mutation involving one of several collagen genes or genes that encode other ECM proteins like tenascin-X.
- Clinical features may include fragile, hyperextensible skin vulnerable to trauma, hypermobile joints, and ruptures involving colon, cornea, or large arteries. Wound healing is poor.