Heritable Disorders of Connective Tissue with Skin Changes

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Inherited disorders of connective tissue comprise a clinically and genetically diverse group of conditions affecting primarily the skin, joints, and, often, the cardiovascular system. The severity of the skin phenotype depends on the type of mutation and the role of the affected protein on dermal structure and function (see Chap. 61). Although genetic testing for most patients is not available commercially at this time, a listing of research laboratories that conduct testing can be found at http://www.genetests.com. Some inherited connective tissue disorders are characterized by hyperextensible skin, whereas others show cutaneous laxity. Yet other disorders have specific cutaneous changes that reflect the alternations in the dermis, such as the striae in Marfan syndrome and the cutaneous papules of pseudoxanthoma elasticum.

Miliary osteoma cutis of the face most commonly occurs as multiple small, firm nodules on the faces of young women with a history of acne vulgaris. There are, however, reports of multiple miliary osteoma cutis in older patients without acne vulgaris or other underlying skin disease.89

KEY REFERENCES

The full reference list for all chapters is available at www.digm7.com.


EHLERS-DANLOS SYNDROMES

AT A GLANCE

- Combined incidence of almost 1 in 5000 persons.
- Seven sub-types.
- Most commonly autosomal dominant (classical and hypermobile types).
- The gene encoding collagen V is most often affected.
- Cutaneous features include soft, velvety skin that bruises easily and wounds that heal as thin, atrophic, gaping scars.
- Extracutaneous manifestations include hypermobile joints with frequent dislocations, problems with pregnancy and delivery, and, less commonly, cardiovascular manifestations, particularly aortic root dilatation.

perfecta). Whereas COL5A1 is located on the long arm of chromosome 2q31, the COL5A2 gene resides on the long arm of chromosome 9q34.2-34.3. Although collagen V is not abundant in skin, tendons, or ligaments, the clinical phenotype attests to its important structural role.

Ultrasound findings show thickened collagen fibrils in skin, with an approximately 25 percent increase in diameter, underscoring the function of collagen V in limiting fibril diameter, as shown in vitro. This effect is thought to be due to the negative charge of the amino terminus of α1(V), conferred by abundant tyrosine residues, which inhibits fibril growth. Another hallmark of classical EDS is the presence of rare composite fibrils also known as “collagen cauliflowers.” These abnormalities are present in less than 5 percent of fibrils, suggesting that other factors may be responsible for the severe clinical phenotype, such as the arrangement of collagen fibrils in tissue. This disorganized arrangement of collagen fibrils and their interaction with other extracellular matrix (ECM) proteins is thought to cause the altered biomechanical properties of EDS skin.

CLINICAL FINDINGS

Classical EDS is characterized by joint laxity, hyperextensibility of skin, and poor wound healing. The skin manifestations can vary in severity from mild to severe; milder forms were previously termed the “mitis” type, or type II, EDS. The skin is soft, velvety, and can be stretched easily (Fig. 139-1). It is not lax, except in late stages. Skin hyperextensibility should be determined at the volar surface of the forearm or some other site that is not subjected to mechanical forces or scarring. Approximately 50 percent of patients with Ehlers-Danlos of the classic and hypermobile types can touch the tip of their nose with their tongue (Gorlin’s sign), in contrast to 10 percent of individuals who do not have EDS (Fig. 139-2).

The dermis is fragile and easily bruised. The shins show persistent discoloration, often beginning in early childhood (Fig. 139-3). When the skin splits from trauma, it is relatively painless and does not bleed excessively, but the wounds tend to gape. The wound margins tend to retract, heal slowly, and often become infected. Dehiscence is common, and complete wound breakdown

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**TABLE 139-1**

The Ehlers-Danlos Syndromes: Clinical Sub-Types and Associated Defects

<table>
<thead>
<tr>
<th>VILLEFRANCHE TYPE/(OMIM)</th>
<th>CLINICAL FEATURES</th>
<th>INHERITANCE</th>
<th>PROTEIN/GENE DEFECT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classical/(130000 and 130010)</td>
<td>Hypertensible skin; easy bruising; wide, atrophic scars; hypermobile joints</td>
<td>AD</td>
<td>Collagen type V(COL5A1, COL5A2)</td>
</tr>
<tr>
<td>Hypermobility/(130020)</td>
<td>Smooth, velvety skin; joint hypermobility</td>
<td>AD/AR</td>
<td>Unclear for most; collagen type III; tenascin XB(COL3A1; TNXB)*</td>
</tr>
<tr>
<td>Vascular/(130050)</td>
<td>Thin, translucent skin with easy bruising; arterial and visceral rupture; typical facies</td>
<td>AD</td>
<td>Collagen type III(COL3A1)</td>
</tr>
<tr>
<td>Kyphoscoliosis/(225400 and 229200)</td>
<td>Atrophic scars, easy bruising; neonatal hypotonia; scoliosis; ocular rupture; marfanoid habitus</td>
<td>AR</td>
<td>Lysyl hydroxylase(PLD1)</td>
</tr>
<tr>
<td>Arthrochalasia/(130060)</td>
<td>Hypertensible and fragile skin; severe joint hypermobility; congenital hip dislocation</td>
<td>AD</td>
<td>Collagen type I(COL1A1; COL1A2)</td>
</tr>
<tr>
<td>Dermatosparaxis/(225410)</td>
<td>Severely fragile, sagging, redundant skin; hernias and premature rupture of fetal membranes</td>
<td>AR</td>
<td>Procollagen I N-peptidase(ADAMTS2)</td>
</tr>
<tr>
<td>Other types*</td>
<td>Wrinkled, loose facial skin, curly fine hair, scanty eyebrows and eyelashes</td>
<td>AR</td>
<td>Due to mutations in galactosyltransferase</td>
</tr>
</tbody>
</table>

AD = autosomal dominant; AR = autosomal recessive; OMIM = Online Mendelian Inheritance in Man.

*Few reported cases.

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**TABLE 139-2**

Beighton Criteria for Joint Hypermobility

1. Passive dorsiflexion of the fifth finger > 90 degrees
2. Passive apposition of the thumbs to the flexor aspect of the forearm (Beighton sign)
3. Hyperextension of the elbow > 10 degrees
4. Hyperextension of the knees > 10 degrees
5. Ability of the palms to completely touch the floor during forward flexion of the trunk

Numbers 1–4 are scored for each side, so that a maximal score of two is possible if both left and right sides show criteria; number 5 is scored as 1. A score of ≥5/9 is hypermobile.
may require repeated suturing or healing by secondary intention (Fig. 139-4). Alternatively, the skin may appear to hold the stitches well initially, but the wound may fall apart after sutures are removed. Scars after trauma or surgical procedures are thin, papyraceous (having the consistency of paper), and may stretch considerably after healing (see Figs. 139-3 and 139-4). The more severely affected individuals have scars with a characteristic “fish mouth” or “cigarette paper” appearance. Thin, atrophic, darkly pigmented scars form as a consequence of intradermal or subdermal hematomas, and occur mainly at pressure points. Molluscoid pseudotumors, fleshy lesions associated with scars, are present at the extensor surfaces of joints, in the foot, and on the shins. Spheroids are well-defined, mobile, subcutaneous indurated nodules that occur at sites of recurrent trauma and can be confused with subcutaneous granuloma annulare. Affected persons may have pressure-induced herniation of subcutaneous fat on the wrists or on the medial or lateral aspect of the heels, evident when the patient is standing (piezogenic pedal papules). Hiatal hernia, postoperative hernias, and anal prolapse have been noted as manifestations of the tissue hyperextensibility and fragility.\(^{27}\)

Musculoskeletal features seen in classical EDS include joint hyperextensibility in all patients and a fairly high frequency of scoliosis and pes planus.\(^{26}\) Patients tend to have “double-jointed” fingers and frequent sprains or subluxation of larger joints (Fig. 139-5), either spontaneously or after slight trauma. Affected individuals complain of chronic joint and limb pain despite normal skeletal radiographs.\(^{27}\) The joint hypermobility can lead to the onset of osteoarthritis in the third or fourth decade. Muscle hypotonia and delayed gross motor development have been described.

Dyspareunia and sexual dysfunction have been reported,\(^{28}\) and the signs of classical EDS may be aggravated by pregnancy. Forty percent of affected individuals and 21 percent of babies of affected mothers are born prematurely, typically between 32 and 37 weeks, owing to premature rupture of fetal membranes or infection of the chorioamnionic membrane.\(^{29,30}\) Fetuses with classical EDS may exhibit retarded growth, hernias, and joint dislocations. A significant number of individuals with EDS have abnormal cardiac echocardiographic parameters, showing aberrant vessels and incompetent valves.\(^{31}\) Aortic root dilatation has been described in 29 percent of patients with the classical and hypermobile forms of EDS,\(^{27,32}\) especially in the former, and may lead to rupture. The most commonly affected site is the sinus of Valsalva. Initial screening of all EDS patients by echocardiography is recommended.\(^{32}\) Aortic valve incompetence, aortic rupture, and dissection occur far less commonly than in Marfan syndrome. \(\beta\) Blocker therapy with agents such as atenolol has been attempted in individual cases, but too few data exist to determine whether therapy is indicated or effective. Mitral valve prolapse (MVP) occurs no more frequently than in the general population.\(^{31}\)

**FIGURE 139-1** Classical Ehlers-Danlos syndrome. Dermal elasticity is demonstrated. Unlike cutis laxa, the skin returns to original shape after stretching.

**FIGURE 139-2** Classical Ehlers-Danlos syndrome (EDS). Gorlin’s sign is the ability to touch the tip of the nose with the tongue and is described in approximately 50 percent of patients with Ehlers-Danlos, in contrast to 10 percent of individuals who do not have EDS.

**FIGURE 139-3** Classical Ehlers-Danlos syndrome. Chronic discolored scars on the shin and ankle after repeated trauma. This is often associated with firm subcutaneous nodules that can be confused with subcutaneous granuloma annulare. Note the widened scar at the knee area.

**FIGURE 139-4** Classical Ehlers-Danlos syndrome. After suturing for a laceration, the wound dehisced with secondary infection and marked widening. Note the evidence of former sutures at the lower border, now 3 weeks after the injury and treatment with antibiotics. Scars tend to stretch further in the 6 months after closure.

**FIGURE 139-5** Classical Ehlers-Danlos syndrome. Hyperextensibility of digits is demonstrated.
The diagnosis is confirmed by clinical examination, family history, and the identification of mutations in COL5A1 or COL5A2, a test not currently commercially available.

**Hypermobile Type**

**EPIDEMIOLOGY** Hypermobile EDS, as the classical type, is a relatively common type of EDS, affecting 1 in 10,000 to 1 in 15,000 individuals.9

**ETIOLOGY AND PATHOGENESIS** The underlying molecular abnormality for this form of EDS has not been clearly defined. However, mutations in two genes have been found in a few cases: COL3A1 (responsible for type III collagen)35 and tenasin-XB (which encodes tenascin-X [TNX])34 (see Chap. 61). TNX is a glycoprotein with a structure comprised of a cysteine-rich N-terminal domain and epidermal growth factor (EGF)–like repeats, followed by a number of fibronectin type III–like domains and a carboxy-terminal fibronogen–like domain. Most cases are AD, although patients with tenasin-XB mutations show autosomal recessive inheritance.35 EDS of the hypermobile type has been associated with congenital adrenal hyperplasia, owing to recombinational events in the gene encoding TNX. This aberration leads to deletions in CYP21, which results in congenital adrenal hyperplasia and decreased TNX messenger RNA (mRNA) and protein in fibroblasts and skin of affected individuals, causing EDS.7

**CLINICAL FINDINGS** The diagnosis of hypermobile EDS is made on the basis of clinical criteria and family history. Predominant features include generalized joint hypermobility, with recurrent dislocations and arthralgias. Hyperextensibility of both large and small joints is present, although predominantly the shoulders, hips, patellae, temporomandibular joints, and digits are affected.3 As in the classical form of EDS, scoliosis and pes planus are common. Musculoskeletal pain is a prominent, debilitating feature in many patients; temporomandibular joint disorder is seen with increased prevalence.35 and complex regional pain syndrome has been described, likely due to stretch injury to nerves traversing hypermobile joints and increased fragility of nerve connective tissue.36 Chronic pain is frequently compounded by secondary depression.37 Individuals with hypermobile EDS have mildly hyperextensible or soft, velvety skin, but near-normal scarring and no molluscoid pseudotumors. Patients with TNX deficiency tend to be intermediate in severity between the classical and more common hypermobile forms. Electron microscopic evaluation of skin biopsies show increased degeneration of elastic fibers when compared with controls.38 A significant number of individuals with both the classical form and the hypermobile form have dilatation or rupture of the ascending aorta, or both.31

**Vascular Type**

**EPIDEMIOLOGY** Vascular type EDS is the most clinically significant due to arterial or major organ rupture. It affects approximately 1 in 100,000 to 200,000 individuals.9

**ETIOLOGY AND PATHOGENESIS** The vascular type of EDS is an AD disorder59 caused by dominant-negative mutations in the gene for COL3A1,40 which is located on chromosome 2q24.3-q31.41 More than 320 mutations of this gene have been identified, most of which are either exon-skipping or nonsense, and disrupt the triple-helical structure.35 Genotype-phenotype correlations have not been demonstrated.35 Collagen III is a homotrimer, so the mutant pro α1(III) chain will be incorporated into almost all fibrils, leading to abnormalities of secretion and intracellular accumulation.42 Collagen III is an important component of vascular walls and the upper dermis. Decreased collagen III leads to dermal atrophy and weakening of vessels.43 Testing for this form of EDS can be reliably accomplished by analysis of type III procollagen and collagen chains harvested from cultured dermal fibroblasts or genetic testing.

**CLINICAL FINDINGS** The four major hallmarkst of vascular-type EDS are distinctive facial features; thin, translucent skin; bruising/hematomas; and rupture of vessels or viscera, or both.25,35 Patients with this condition often have short stature and a characteristic thin nose; thin upper lip; small earlobes; and a sunken, pigmented appearance around the eyes. The skin is thin and easily bruised; unlike in the classical or hypermobile types, hyperextensibility is minimal to absent. Individuals are prone to forming large and frequent hematomas with minimal to no trauma, including after inflation of a blood pressure cuff. Papyraceous scars are present over bony prominences. In fair-skinned individuals, subcutaneous vasculature is easily visible beneath the skin (Fig. 139-6).

Affected individuals are at high risk for life-threatening rupture of the medium-sized arteries, particularly of the mesenchymal arteries in the abdomen, the splenic and renal arteries, and the descending aorta.43 The aortic disease in this form is more prevalent than that found in the other forms of EDS and is different in its location. Rupture or dissection of the aorta, or both, when it occurs, is usually at or distal to the mid-aortic arch and extends distally. Arterial rupture generally occurs in the third, fourth, and fifth decades, and is the major cause of reduced life span in patients with this disorder. Dissection and rupture of aorta or arteries is usually not preceded by dilatation, in contrast to the rupture in Marfan syndrome and other forms of EDS.32 Patients are also at increased risk for stroke. Pregnancies are high risk, as arterial or uterine rupture in the peripartum period may lead to maternal death in 12 percent to 25 percent of cases.43,44 Vaginal or perineal tears can occur, and wounds after cesarean section frequently dehisce.9

**Kyphoscoliotic Type**

**EPIDEMIOLOGY** Characteristics of the kyphoscoliotic type of EDS have been described in fewer than 60 reported cases worldwide and are evident at birth.9

**ETIOLOGY AND PATHOGENESIS** The kyphoscoliotic type is the only type of EDS that is always inherited in an autosomal recessive fashion. It is caused by a deficiency of pro-collagen-lysine, 2-oxoglutarate 5-dioxygenase (PLOD1 or lysyl hydroxylase),45 an enzyme that adds hydroxyl groups to lysines in collagen in an X-lys-gly se-
quency. The gene coding for this enzyme is located on chromosome 1p86.3-36.2. All patients with the kyphoscoliosis form of EDS have decreased hydroxylsine content in dermal tissues. Many of the cross-links that normally occur between adjacent collagen monomers within a fibril begin as chemical modifications of hydroxy lysyl residues. Therefore, although hydroxylsine-deficient collagen is efficiently secreted from cells, it is not capable of normal cross-linking. The deficiency is highly tissue- and collagen type-specific, apparently affecting only type I and III collagens. Hautala and co-workers reported homozygosity for an intragenic duplication of exons 9 to 15 in two patients, which appears to be the only common mutant allele, with an allele frequency of 19.1 percent in families with kyphoscoliotic EDS. There appears to be a rare subtype that is clinically indistinguishable but has normal lysyl hydroxylase activity and normal hydroxy lysyl content in skin.

**Clinical Findings**

Patients show joint laxity, kyphoscoliosis, and hypotonia. Ocular fragility with microcornea, which was observed in the original reports, is found in only a minority of patients. Skin fragility, easy bruising, large fontanels, blue sclerae, puffy eyelids, micrognathia, umbilical hernia, and short fingers. Orofacial features include micrognathia, malocclusion, and hyperkeratotic gingival hyperplasia. The deciduous teeth show abnormal molars and severe enamel attrition. Treatment and Prevention

The most productive avenue of therapy for EDS involves a triad of anticipatory guidance, pain management, and physical therapy. Regular evaluation by a physician familiar with EDS is strongly recommended. Early intervention is key, along with appropriate education.

Avoidance of injury is critical, including making homes safe to prevent falls and avoiding contact sports. Gentle skin care should be encouraged, using mild soaps and non-adherent bandages. Sun protection is critical to prevent the skin thinning and loss of dermis associated with ultraviolet radiation–induced damage. When injuries occur that disrupt skin integrity, sutures should be placed. In addition to supplemental absorbable sutures within the wound, retention sutures tied at a distance from the incision may help. Adhesive strips may be used to support the skin during scar formation, but must be
retained for long periods. Given the problems with skin infection, prophylactic anti-staphylococcal antibiotics should be considered. Scar revision is often requested at the knees and elbows but may require grafting. Early adolescence is often the optimal time for this surgery, because subsequent traumatic events are less likely. Pseudotumors are more easily removed from the elbows and knees than those over the heels.

With the exception of congenital dislocation of the hip, joint dislocations in EDS either spontaneously resolve or can usually be corrected by closed reduction. Orthopedic procedures designed to reduce ligamentous laxity and therefore prevent recurrent dislocations include bracing or fusion of joints.

Avoidance of standing or working on hardened floors for long periods and the wearing of supportive, cushioned shoes reduces foot, knee, hip, and back pain. Nonsteroidal anti-inflammatory drugs (NSAIDs) may bring temporary relief; none are demonstrably superior. The relevant issue is the best-tolerated drug at the least cost. Other medications that may be used include fixed combination products (NSAID/opioid) or single-entity opioids and tricyclic antidepressants. There is some evidence that a subset of patients with the kyphoscoliotic type of EDS may respond to hydralazine and ascorbic acid. Hydrotherapy and behavioral or cognitive coping strategies, or both, may also be tried to improve pain. Physical therapy, particularly directed at strengthening the shoulder girdle, has lowered the frequency of shoulder dislocations in individuals with chronic or recurrent dislocation. A regular exercise program may be helpful for strengthening muscles, helping to stabilize the joints, and relieve stress. Swimming and lifting weights are noncontact sports that have been tolerated well by many patients. Some patients use orthopedic devices such as orthotics and braces.

Pregnant women with EDS should be referred to high-risk obstetric practices when possible because of increased pregnancy risks. The extremely friable arteries of vascular-type EDS are very difficult to repair.

Marfan syndrome is a generalized connective tissue disease affecting approximately 1 in 5000 to 10,000 individuals, with no racial, gender, or geographic predilection. Whereas most affected individuals will have a family history of the disease, approximately 25 percent will not, suggesting de novo mutations.

Etiology and Pathogenesis
Routine histopathologic examination of biopsies do not show significant changes. However, ultrastructurally the dermis of Marfan patients demonstrates abnormal collagen fibrils with varied thickness, whirled and wave-formed disarray, and twisted fibrils with flower-like shapes with zigzagged margins, similar to EDS. In addition, the ratio of collagen I–collagen III content is decreased.

Marfan syndrome is typically an AD disorder caused by heterozygous mutations in the gene for fibrillin 1 (FBN1), localized to 15q21.1. More than 500 mutations in the FBN1 gene have been reported that span the entire coding region of the gene (65 exons). Some, but not all, mutations result in the classical features of Marfan syndrome, and a few genotype-phenotype correlations are possible. Most missense mutations in the EGF domains result in the classic form of the disease. Patients with dramatic structural rearrangements, such as exon skipping (approximately 10 percent of the total), have comparatively severe forms of the disease. Patients with mutations that lead to premature stop codons and reduced mRNA transcripts from the mutant allele have a surprisingly wide range of clinical severity, which is unlike the clear differences seen between Ol patients with dominant-negative mutations and loss-of-function mutations (null alleles). The only established genotype-phenotype correlation is that of severe neonatal onset with mutations clustered in the middle of the FBN1 gene.

FBN1 is a major constitutive element of ECM microfibrils throughout the body. It is abundant in tissues affected in Marfan syndrome—the ascending aorta, suspensory ligament of the lens, periosteum, and the skin. Fibrillin plays a major role in the normal functioning of microfibrils, which are critical structural components of many tissues. The fibrillin molecule is spanned by cysteine-rich repeats interspersed with latent transforming growth factor-β (TGF-β)–binding protein-like and EGF-like motifs.

Genetic alterations in FBN1 produce a spectrum of clinical abnormalities well beyond the classic Marfan phenotype, the so-called fibrillopathies. The spectrum includes the severe neonatal Marfan phenotype at one end, extending to isolated aortic root dilatation or marfanoid skeletal features lacking cardiovascular involvement or ectopia lentis at the other. Other phenotypes that can result from mutations in FBN1 include: the mitral, aortic, skin, and skeletal manifestations (MASS) phenotype; bicommissural aortic valve with ascending aortic aneurysm; Shprintzen-Goldberg syndrome; MVP syndrome; familial ectopia lentis; isolated marfanoid habitus, and Weill-Marchesani syndrome.

Mutations in the FBN2 gene on chromosome 5q23 can result in an AD disorder that resembles neonatal Marfan syndrome, especially in its skeletal manifestations—congenital contractual arachnodactyly (Beals syndrome). It is characterized by multiple flexion contractures (especially elbow, knee, and finger joints), arachnodactyly, severe kyphoscoliosis, crumpled pinnae, and muscular hypoplasia. Aortic root dilatation and the ocular manifestations of Marfan syndrome do not tend to be associated.

Heterozygous mutations in the TGF-β receptor 2 on chromosome 3p24.2-25 have also been described in a subset of patients with prominent aortic dilatation but without ocular abnormalities.
Clinical Findings

Marfan syndrome is a generalized disorder of connective tissue that has primary manifestations in the skeletal, ocular, and cardiovascular systems. Patients with Marfan syndrome may have major abnormalities primarily in three organ systems: in the eye—most characteristically dislocation of the lenses; in the skeletal system—excessive length of extremities, loose-jointedness, kyphoscoliosis, and anterior chest deformity; and in the cardiovascular system—most characteristically aortic aneurysm and mitral valve redundancy. Skin manifestations consist of striae distensae, a common finding, and elastosis perforans serpiginosa (see Chap. 67), a rare finding.

Virtually all patients with Marfan syndrome have myopia as the result of an abnormally long anterior-posterior axis of the orbit and relatively flat corneas. In addition, approximately 70 percent of affected patients have ectopia lentis, with the lens usually displaced upward. In an examination after the dilation of the pupil, the margin of the lens is usually visible in the lower part of the pupil. Dislocation of the lens into the anterior chamber or trapping of the lens in the pupil sometimes occurs, and acute glaucoma may result. Detection of mild ectopia lentis requires full dilation of the pupils and slit-lamp examination for redundancy of the suspensory ligament of the lens. Therefore, clinical exclusion of ectopia lentis in an individual suspected of having Marfan syndrome must include a slit-lamp examination after dilation of the pupils. Strabismus and cataracts may also develop.

The skeletal features, particularly the long, narrow extremities, figured prominently in Marfan’s initial description in 1896 of the syndrome that now bears his name. Patients with Marfan syndrome are usually taller than their same-sex siblings. There is skeletal disproportion, with the most consistent and reliable measure being an abnormally low ratio of the upper segment (height minus lower segment) to the lower segment (measured from the pubic symphysis to the floor) (Fig. 139-7). The arm span (fingertip to fingertip when expanded) is usually longer than the height by several centimeters. These discrepancies may be magnified by associated kyphoscoliosis. The ribs appear to undergo the same excessive longitudinal growth, as do the bones of the extremities. Depressions of the sternum (pectus excavatum) or projection (pectus carinatum) or an asymmetric deformity of the anterior chest results.

Joint hyperextensibility is present in some, but not all, patients with Marfan syndrome. Flat-footedness, hyperextensibility at the knees (genu recurvatum) and elbows, and occasional dislocation of joints are manifestations of the loose-jointedness. Because of joint hyperextensibility and long, narrow extremities, the patient is often able to touch his or her umbilicus with the right hand passed around the back and approaching the umbilicus from the left. A relatively narrow palm of the hand with a long thumb and hyperextensibility is the basis of Steinberg’s sign, in which the thumb propped across the palm extends well beyond the ulnar margin of the hand.

The cardiovascular manifestations of Marfan syndrome are by far the most clinically significant and account for the overwhelming majority of morbidity and mortality associated with this disorder. The two major cardiovascular manifestations are MVP and aortic root dilatation. MVP is a consequence of the redundancy of the valve leaflets, the stretching of the chordae tendineae, and dilatation of the valve annulus. The prevalence of MVP in Marfan syndrome increases with age and is present in approximately 75 percent of individuals. MVP can occasionally be associated with abnormal electrocardiograms, regurgitation, and cardiac arrhythmias that can lead to sudden death.

Dilatation of the proximal aorta is progressive and, in some cases, may even occur in utero. Dilatation is often first seen in the sinuses of Valsalva, but is often discontinuous and unpredictable. Patients with Marfan syndrome should be monitored on a yearly basis, as aortic complications of Marfan syndrome do not occur in aortas that are normal for age or in adults in aortas less than 40 mm in diameter. The aortic pathology of Marfan syndrome is almost always in the proximal (ascending) aorta; distal pathology is usually a result of forward progression of a dissecting lesion. Premature death in Marfan syndrome is a result of its cardiovascular complications: proximal aortic dilatation associated with aortic valve incompetence, aortic rupture, or aortic dissection. Other manifestations of this syndrome include a high-arched palate and crowding of the anterior teeth, emphysema, spontaneous pneumothorax, and dural ectasia.

Cutaneous lesions develop in approximately two-thirds of patients with Marfan syndrome and represent minor diagnostic signs in the revised 1996 Ghent criteria. These include striae distensae (more prominent during adolescence and on the buttocks, thighs, breasts, abdomen, and thighs) and inguinal or incisional hernias. Histology reveals abnormal elastic fibers with a moth-eaten appearance and collapsed, distorted adipocytes.

The large size of the gene, along with the absence of mutational hot spots and the heterogeneity of these mutations preclude sensitive testing for FBN1 mutations. Clinical assessment remains the current diagnostic method, but in individuals with a familial phenotype, mutational or linkage analysis may yield positive results.

Treatment

Management of patients with Marfan disease should be multi-disciplinary, targeting each affected organ system.

Prevention

Patients with aortic dilatation are encouraged to avoid caffeine, stressful circumstances, and vigorous exercise. Contact sports or heavy lifting should be avoided. Early use of either a valve-
saving aortic repair or composite graft placement is now prudent because of significant improvements in the success of these procedures and the well-known difficulties in managing an acute aortic dissection in Marfan patients. To prevent pneumothorax, patients should avoid smoking and activities that involve rapid changes in pressure such as flying or scuba diving.95

HOMOCYSTINURIA

Epidemiology

The incidence of homocystinuria varies from 1 in 344,000 worldwide101 to a much greater incidence of 1 in 65,000 in Ireland.102 It is the second most common treatable aminoaciduria after phenylketonuria.

Etiology and Pathogenesis

Patients with homocystinuria have primary hepatic deficiency of cystathionine β-synthase (CBS), a pyridoxine-dependent enzyme in the methionine transsulfuration pathway,103,104 resulting in high plasma levels of the toxic amino acid L-homocysteine.105 A minority of patients have an acquired (dietary) deficiency of cobalamin or heritable disorders that prevent conversion of dietary cobalamin to its biologically active forms; rarely, some have defects that cause decreased availability of 5-methyltetrahydrofolate, which is also required in the metabolism of methionine.

By definition, homocystinuria is a biochemical abnormality, not a specific disease entity. By far the most common cause of this condition is a deficiency of the enzyme CBS because of recessive mutations in its gene. The CBS gene is located at chromosome 21q22.3.106 More than 92 disease-causing mutations have been described.107 Molecular analysis of the CBS locus has identified several mutant alleles in patients with homocystinuria. Substitution of serine for threonine in the T191M point mutation is found frequently in northern European populations, and (G370S) is the most common mutation (OMIM #277400). Features often manifest during infancy, significantly reduces the risk of thrombosis, grand mal seizures, and mental retardation. Increases in responsiveness are likely caused by increased production of pyridoxal-5'-phosphate, the active form of vitamin B₆, that is the co-factor for CBS. Sensitivity to pyridoxine may be predicted by the specific CBS mutation,108 is constant in affected siblings, and only occurs in the presence of residual CBS activity. Betaine is a methyl donor agent that lowers homocysteine through remethylation of methionine.118 Increase in methionine levels is a potential risk of betaine therapy and led to cerebral progressive cerebral edema in a child with CBS deficiency.119 Betaine should be used as an adjunct to other therapies, particularly to dietary restriction of methionine.

Clinical Findings

The major clinical manifestations of CBS deficiency include ocular, skeletal, vascular, and central nervous system abnormalities.114 These include ectopia lentis, osteoporosis, mental retardation, and thromboembolism. By the age of 10 years, 82 percent of patients develop ectopia lentis, and by 15 years, 50 percent have radiographic signs of osteoporosis.115

The cutaneous manifestations include malar flush, thin hair and skin, and cutis reticulata. A prominent malar flush has been reported in many patients, which is most easily seen after vigorous exercise or after cold exposure. This malar flush was also found to be more frequent in pyridoxine responders, although the difference was not significant, likely due to the small sample of patients.114 The dermis is usually fair and thin, and livedo reticularis is commonly seen on the extremities. In patients with deep venous thromboses, collateral venous channels are visible through the skin. Hair is often thinned and fair. Treatment may cause hair to darken.

HOMOCYSTINURIA

AT A GLANCE

- Incidence: 1 in 65,000 to 344,000 (Online Mendelian Inheritance in Man #236200).
- Autosomal recessive inheritance, mutations in cystathionine β-synthase, chromosome 21q22.3.
- Cutaneous features include malar flush, fair and thin skin and hair, and livedo reticularis.
- Extracutaneous manifestations include downward lens displacement, osteoporosis, mental retardation, thromboembolism, and severe hyperhomocysteinemia.


PSEUDOXANTHOMA ELASTICUM

Epidemiology

The disease prevalence is estimated at 1 in 25,000 to 100,000 persons and occurs

HOMOCYSTINURIA

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The incidence of homocystinuria varies from 1 in 344,000 worldwide101 to a much greater incidence of 1 in 65,000 in Ireland.102 It is the second most common treatable aminoaciduria after phenylketonuria.

Etiology and Pathogenesis

Patients with homocystinuria have primary hepatic deficiency of cystathionine β-synthase (CBS), a pyridoxine-dependent enzyme in the methionine transsulfuration pathway,103,104 resulting in high plasma levels of the toxic amino acid L-homocysteine.105 A minority of patients have an acquired (dietary) deficiency of cobalamin or heritable disorders that prevent conversion of dietary cobalamin to its biologically active forms; rarely, some have defects that cause decreased availability of 5-methyltetrahydrofolate, which is also required in the metabolism of methionine.

By definition, homocystinuria is a biochemical abnormality, not a specific disease entity. By far the most common cause of this condition is a deficiency of the enzyme CBS because of recessive mutations in its gene. The CBS gene is located at chromosome 21q22.3.106 More than 92 disease-causing mutations have been described.107 Molecular analysis of the CBS locus has identified several mutant alleles in patients with homocystinuria. Substitution of serine for threonine in the T191M point mutation is found frequently in northern European populations, and (G370S) is the most common mutation (OMIM #277400). Features often manifest during infancy, significantly reduces the risk of thrombosis, grand mal seizures, and mental retardation. Increases in responsiveness are likely caused by increased production of pyridoxal-5'-phosphate, the active form of vitamin B₆, that is the co-factor for CBS. Sensitivity to pyridoxine may be predicted by the specific CBS mutation,108 is constant in affected siblings, and only occurs in the presence of residual CBS activity. Betaine is a methyl donor agent that lowers homocysteine through remethylation of methionine.118 Increase in methionine levels is a potential risk of betaine therapy and led to cerebral progressive cerebral edema in a child with CBS deficiency.119 Betaine should be used as an adjunct to other therapies, particularly to dietary restriction of methionine.

Clinical Findings

The major clinical manifestations of CBS deficiency include ocular, skeletal, vascular, and central nervous system abnormalities.114 These include ectopia lentis, osteoporosis, mental retardation, and thromboembolism. By the age of 10 years, 82 percent of patients develop ectopia lentis, and by 15 years, 50 percent have radiographic signs of osteoporosis.115

The cutaneous manifestations include malar flush, thin hair and skin, and cutis reticulata. A prominent malar flush has been reported in many patients, which is most easily seen after vigorous exercise or after cold exposure. This malar flush was also found to be more frequent in pyridoxine responders, although the difference was not significant, likely due to the small sample of patients.114 The dermis is usually fair and thin, and livedo reticularis is commonly seen on the extremities. In patients with deep venous thromboses, collateral venous channels are visible through the skin. Hair is often thinned and fair. Treatment may cause hair to darken.

HOMOCYSTINURIA

AT A GLANCE

- Incidence: 1 in 65,000 to 344,000 (Online Mendelian Inheritance in Man #236200).
- Autosomal recessive inheritance, mutations in cystathionine β-synthase, chromosome 21q22.3.
- Cutaneous features include malar flush, fair and thin skin and hair, and livedo reticularis.
- Extracutaneous manifestations include downward lens displacement, osteoporosis, mental retardation, thromboembolism, and severe hyperhomocysteinemia.


PSEUDOXANTHOMA ELASTICUM

Epidemiology

The disease prevalence is estimated at 1 in 25,000 to 100,000 persons and occurs
PSEUDO-XANTHOMA ELASTICUM

AT A GLANCE

- Incidence: 1 in 25,000 to 100,000 (Online Mendelian Inheritance in Man #177850 and #264800).
- Autosomal recessive inheritance, occasional pseudo-dominant.
- Mutations in multidrug resistance associated protein (MRP6), encoded by \( ABCC6 \) on chromosome 16q13.1.
- Cutaneous features include yellow, flat papules in the neck, flexures, and periumbilical areas. Less frequent skin lesions include acneliform lesions, elastosis perforans serpiginosa, reticulate pigmentation, and granulomatous nodules.
- Extracutaneous manifestations include angiod streaks, visual impairment, \textit{peau d'orange} retinal hyperpigmentation, cardiovascular disease, and bleeding.
- Histopathology shows swollen, clumped, fragmented elastic fibers and calcium deposits in the mid and deep reticular dermis. Alterations easily visualized with calcium (\textit{von Kossa's}) or elastic (Verhoeff-van Gieson) stains. As evidenced with electron microscopy, calcification occurs in a centripetal fashion within the fiber.\(^{121}\) Affected skin also reveals deposits of other ECM components associated with elastic fibers such as fibronectin, vitronectin, and proteoglycans.\(^{122}\) Some patients also show increased levels of urinary and skin glycosaminoglycans.\(^{123}\)

\subsection*{Etiology and Pathogenesis}

PXE, also known as Grönblad-Strandberg syndrome, is characterized by progressive calcification and fragmentation of elastic fibers in various tissues, including skin (particularly flexural sites), eye (angioid streaks and retinal defects), and cardiovascular system (hypertension, gastrointestinal bleeding, and vascular disease).

At the histologic level, PXE is known to be caused by progressive calcification and fragmentation of elastic fibers. Elastic fibers in the deep and reticular dermis show a swollen, clumped, and fragmented appearance with calcium deposits (Fig. 139-8). Interspersed are more normal-appearing elastic fibers, which may also stain blue because of their high calcium content. These changes are also present in fibers of other organs, including blood vessels, Bruch's membrane of the eye, and the heart. Dermatopathologic findings are more easily seen with the use of calcium (\textit{von Kossa's}) or elastic (Verhoeff-van Gieson) stains. As evidenced with electron microscopy, calcification occurs in a centripetal fashion within the fiber.\(^{121}\) Affected skin also reveals deposits of other ECM components associated with elastic fibers such as fibronectin, vitronectin, and proteoglycans.\(^{122}\) Some patients also show increased levels of urinary and skin glycosaminoglycans.\(^{123}\)

The gene responsible for PXE has been localized to chromosome 16p13.1, and it encodes an adenosine triphosphate–binding cassette (ABC) subfamily C member 6 (\( ABCC6 \)) transporter.\(^{124-127}\) The \( ABCC6 \) gene is a member of a family of 48 genes, some of which have also been associated with other dermatologic conditions (for example, \( ABCA12 \) with lamellar ichthyosis and harlequin ichthyosis)\(^{128}\) (see Chap. 47). The gene consists of 51 exons spanning 75 kb and encodes the 165-kd transmembrane multidrug resistance–associated protein 6 (MRP6), which is a transporter protein. MRP6 expression in liver and kidneys is low in PXE, suggesting a metabolic origin with secondary tissue involvement in this disease.\(^{129}\)

More than 60 mutations have been detected in \( ABCC6 \), of which more than 90 percent result in recessive inheritance and less than 10 percent in dominant fashion (likely pseudo-dominant forms of PXE with milder manifestations).\(^{126,129-131}\) Most of which are inactivating mutations. Although most mutations appear to be unique variants, two disease-causing alleles occur frequently in apparently unrelated individuals. \( R1441X \) has been found predominantly in Europe at a frequency of 28.4 percent (overall, 18.8 percent). \( ABCC6del23–29 \) occurs at an overall frequency of 12.9 percent and is most prevalent in patients from the United States (28.4 percent). These results suggest that \( R1441X \) and \( ABCC6del23–29 \) might be derived regionally from founder alleles.\(^{125}\) Molecular studies can be performed to confirm the clinical diagnosis and to help recognize asymptomatic patients with a positive family history.

The precise function of the \( ABCC6 \) transporter is unknown, and the genotype-phenotype relationship between \( ABCC6 \) mutation and pathologic changes in PXE tissues remains to be elucidated. Abnormalities in the attachment and proliferation of cultured fibroblasts from the dermis of affected patients suggest a functional role for \( ABCC6 \).\(^{132}\) However, recent studies support the concept that a circulating factor in the serum of affected individuals interferes with the normal assembly

\begin{figure}
\centering
\includegraphics[width=\textwidth]{image}
\caption{Pseudoxanthoma elasticum, elastic tissue stain. The elastic fibers show marked degeneration: They are swollen, tortuous, and irregularly clumped.}
\end{figure}
Clinical Findings

PXE usually involves the skin, Bruch’s membrane of the eye, and vascular tissues. Cases with involvement of other systems have occasionally been reported, including urinary tract and pulmonary tissues. The mortality and morbidity of PXE is dependent on the extent of extracutaneous involvement, especially the extent of vascular disease.

Typically, yellowish papules giving a “plucked chicken” or “cobblestone” appearance in flexural skin begin in childhood. These 1- to 5-mm symmetric papules may form a reticulated pattern but often coalesce to form plaques that have also been compared with “Moroccan leather.” However, their presence is usually not noted until adolescence or even later adulthood because of their asymptomatic nature. These papules are generally first seen on the lateral areas of the neck. Additional commonly involved areas include the antecebital, popliteal, inguinal, neck, axillary, and periumbilical regions, as well as oral, vaginal, and rectal mucosae. Involvement may be progressive, and the disease may ultimately involve the entire skin, although severe involvement is rare. In time, the skin may become soft, lax, wrinkled, and hang in folds, particularly in the neck, axillae, and groin. Prominent horizontal and oblique mental creases (separating the lower lip from the chin) before 30 years of age are highly specific. Patients usually present to their physicians with these lesions because of cosmetic concern. Careful complete physical examination is warranted, and a skin biopsy of scars or flexural skin should be performed, as abnormal histologic findings may be present in the absence of visible cutaneous lesions. The differential diagnosis of the skin lesions of PXE is listed in Box 139-1.

Once they appear, the skin defects of PXE usually remain unchanged throughout life. Elastosis perforans serpiginosa

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**Box 139-1**

### Differential Diagnosis of the Skin Lesions of Pseudoxanthoma Elasticum (PXE)

<table>
<thead>
<tr>
<th>DISORDER</th>
<th>MORPHOLOGY</th>
<th>DISTRIBUTION</th>
<th>ASSOCIATIONS</th>
<th>DIFFERENTIATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dermatofibroma lenticularis</td>
<td>Asymptomatic, flat-topped yellowish papules and nodules, which, when grouped, form large plaques several centimeters in diameter</td>
<td>Often proximal extremities, truncal; symmetric; may be more widespread</td>
<td>Osteopoikilosis, fractures in Buschke-Ollendorff syndrome (due to LEMD3 (MAN1) mutations)</td>
<td>Clinical; biopsy shows increased elastic tissue</td>
</tr>
<tr>
<td>Localized acquired cutaneous PXE</td>
<td>Asymptomatic, coalescing yellow macules and papules, occasional reticulate or checkered pattern; lax, redundant areas</td>
<td>Neck, axillae, groin, flexural surfaces, areas exposed to salt peter fertilizer (calcium-ammonium-nitrate)</td>
<td>Older age, exposure to salt peter fertilizer in Norwegian farmers, uremia</td>
<td>Histology shows fragmented, thickened, mineralized elastic fibers in mid and deep reticular dermis</td>
</tr>
<tr>
<td>Perforating periumbilical PXE</td>
<td>Asymptomatic or pruritic, erythematous lesions that progress to hyperpigmented plaques, with central atrophy, a red, scaly border, and peripheral hyperkeratotic papules, sometimes expressing elastic debris</td>
<td>Periumbilical or breast area</td>
<td>Multiparity, ascites, abdominal surgery; uremia and hyperphosphatemia in chronic renal failure</td>
<td>Histopathology shows elimination of basophilic, elastic debris through channels in addition to thickened and mineralized elastic fibers in mid and deep reticular dermis</td>
</tr>
<tr>
<td>Long-term penicillamine therapy</td>
<td>Varied presentations; may resemble pseudoxanthoma elasticum, elastosis perforans serpiginosa, cutis laxa, and anetoderma</td>
<td>Similar to those seen in idiopathic forms of disease (i.e., neck and flexures for PXE, flexures in elastosis perforans serpiginosa)</td>
<td>Use of D-penicillamine</td>
<td>Histopathology shows thickened elastic bundles with prominent lateral protrusions (“bramble-bush”), granulomatous dermal inflammation, infrequent calcification, and trans-epidermal elimination of elastic fibers</td>
</tr>
<tr>
<td>Actinic damage to neck</td>
<td>Numerous small, asymptomatic, discrete, white papules</td>
<td>Neck</td>
<td>Middle aged to elderly individuals</td>
<td>Histology shows elastolysis and fibrosis in papillary and mid- reticular dermis</td>
</tr>
<tr>
<td>Papular elastorrhexis</td>
<td>Asymptomatic, firm, non-follicular 1- to 5-mm whitish papules on trunk and upper extremities</td>
<td>Chest, abdomen, shoulders, back, proximal extremities</td>
<td>Rarely familial occurrence</td>
<td>Loss of elastic tissue in reticular dermis (relative increase in fibrillar component) and fragmentation, with occasional perivascular mixed infiltrate</td>
</tr>
</tbody>
</table>
may co-exist with PXE, and perforating disease may occur, with transdermal elimination of calcium (see Chap. 67).136 Hyperpigmented, reticulated macules, telangiectasias of the lips, and acneiform and granulomatous lesions may also occur.136,137

The characteristic ocular defects of PXE are angioid streaks of the retina, characterized by reddish-brown curvilinear bands that radiate from the optic disc. Angioid streaks result from calcification of the elastic fibers in Bruch’s membrane of the retina, with cracking and fissuring in its outer portion, the lamina elastica. Approximately 85% of the patients with PXE may have those lesions identified on routine ophthalmologic examination.121,134 The angioid streak is usually present bilaterally and is often first noted between the ages of 20 and 40 years, typically many years after the onset of cutaneous lesions. The streaks may progress slowly or remain stationary for years. Angioid streaks are often mistaken for blood vessels, though they are irregular and generally wider. They are not unique to PXE and may be present in EDS, Marfan syndrome, lead poisoning, sickle cell anemia, thalassemia,138 Paget disease of bone, acromegaly and other pituitary disorders, and familial hyperphosphatemia.139 The most common retinal feature associated with angioid streaks is the presence of “peau d’orange,” a mottled fundus appearance that usually precedes the appearance of the streaks. These are small, relatively symmetric, drusen-like, flat, yellow, and, occasionally, confluent lesions in the retinal pigment epithelium. Leopard spotting of the posterior pole of the retina is another early sign. Fibrovascular ingrowth in the retina may result in retinal hemorrhages and lead to a risk of retinal detachment and vision loss that increases with each hemorrhage.139 Other retinal changes include salmon patches (typically a healing subretinal hemorrhage), black dots (pigmentation after focal hemorrhage), and “pears” (tiny white foci after subretinal or pigment epithelium hemorrhage, or a focal scar). The most visually devastating complication is disciform degeneration of the central visual area. Peripheral vision is generally spared. Cardiovascular complications occur primarily in affected adults, but occasionally occur in children.140,141 Calcification of the elastic media of blood vessels with subsequent intimal proliferation leads to a variety of physical findings and to serious complications of PXE. Intermittent claudication is the most common cardiovascular manifestation and the one that presents the earliest. In adults, peripheral pulses are often severely diminished. Angina pectoris or abdominal angina may become incapacitating. Hypertension, caused by renal artery involvement, is three times more common in patients with PXE than in the general population. Severe coronary artery disease may cause early myocardial infarction. MVP has a higher prevalence in PXE than the general population and is almost always accompanied by a murmur.142 Cerebral artery involvement has also been reported. Seizures occur more frequently than in the general population because of the cerebral involvement.143 Subarachnoid hemorrhage has been a major cause of death. Gastrointestinal hemorrhage, apparently caused by the fragility of calcified submucosal vessels, is the most significant vascular complication of PXE, and it is usually gastric in origin. Hemorrhage may occur early in the disease progression and is often the presenting sign, beginning without warning in the second to fourth decade of life. Approximately 10% to 15% of patients with PXE have a gastrointestinal hemorrhage at some point in their lives. Lung involvement has been seen, but rarely. Bleeding may occur in the urinary tract, and the patient presents with hematuria.144 Pregnancy is uncomplicated and thus not contraindicated in these patients, but there is an increased risk of miscarriage in the first trimester, and multiple pregnancies may aggravate the disease course.145

Tissue alterations in PXE patients are irreversible, so most efforts are directed toward minimizing complications. Early diagnosis of this disease allows early recognition of ocular and cardiovascular manifestations, thus reducing potential major complications. Surgical excision of the sagging skin seen late in the disease can be corrected by surgical excision if desired.146 Fillers or autologous fat injections may improve the appearance of the mental creases.

**Prevention**

Prevention or minimization of complications in patients with PXE through education is of critical importance. Providing information on support groups is extremely important (PXE International, Inc., at http://www.pxe.org and National Association for Pseudoxanthoma Elasticum, or NAPE, at http://www.napxe.org). Recommended testing for patients with PXE is reviewed in Table 139-3. A healthy diet and exercise regimen are key components to minimizing the extent of the cardiovascular disease. Diet should be low in calcium (60 to 1200 mg/day)147 and lipids, and medications to control these should be introduced if diet and exercise alone are not sufficient. Medications that decrease coagulation, such as NSAIDs and aspirin, should be avoided.

Patients and family members should be monitored by an ophthalmologist regularly for fundoscopy, as early eye changes often precede skin changes.148 Patients should be instructed to self-test with an Amsler grid, which can find early evidence of retinal hemorrhage. Changes can be confirmed by intravenous fluorescein angiography. Patients should avoid heavy lifting, straining, and head trauma, as in weight lifting or head-contact sports, to decrease the risk

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**TABLE 139-3**

**Monitoring Studies for Patients with Pseudoxanthoma Elasticum**

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete blood cell count</td>
<td>Occult blood loss; iron-deficiency anemia</td>
</tr>
<tr>
<td>Calcium, phosphate</td>
<td>Rare reports of hypercalcemia and hyperphosphatemia</td>
</tr>
<tr>
<td>Fasting lipids</td>
<td>Hyperlipidemia aggravates risk of cardiovascular disease</td>
</tr>
<tr>
<td>Urinalysis</td>
<td>Hemorrhage from urinary tract</td>
</tr>
<tr>
<td>Fecal test for blood</td>
<td>Occult blood loss from GI hemorrhage</td>
</tr>
<tr>
<td>Eye examination</td>
<td>To detect angioid streaks, retinal hemorrhage, early retinopathy</td>
</tr>
<tr>
<td>Endoscopy</td>
<td>If evidence of GI bleeding</td>
</tr>
<tr>
<td>Echocardiography</td>
<td>If murmur, angina, or personal or family history of coronary artery disease</td>
</tr>
<tr>
<td>Doppler blood pressure</td>
<td>To investigate claudication or if decreases peripheral pulses</td>
</tr>
<tr>
<td>(ankle, brachial)</td>
<td></td>
</tr>
<tr>
<td>Computed tomography of head</td>
<td>If focal neurologic problems or evidence of cerebral hemorrhage</td>
</tr>
<tr>
<td>Radiographs</td>
<td>If seeking calcifications</td>
</tr>
</tbody>
</table>

Gl = gastrointestinal.
of retinal hemorrhage. This early detection allows for the use of laser photocoagulation to minimize vision loss. Although early attempts to treat with laser photocoagulation were disappointing, more recent studies show Verteporfin photodynamic therapy every 3 months for the choroidal neovascularization to be promising.149

Regular cardiologic monitoring is also important. Prophylactic antibiotics should be prescribed before any dental procedure or surgical procedures if mitral valve insufficiency is present to prevent bacterial endocarditis. Intermittent claudication can be treated by weight reduction and exercises that stimulate collateral blood vessel development, and tobacco use should be prohibited. Patients should be monitored carefully for gastrointestinal bleeding. Depending on its severity, hospitalization, blood transfusion, endoscopic treatment, and surgery with partial gastrectomy may be necessary to manage bleeding. Appropriate referrals for urologic, pulmonary, and neurologic consultation should be made based on concerns and physical findings.

**CONGENITAL CUTIS LAXA**

**AT A GLANCE**

- Inheritance may be autosomal dominant (Online Mendelian Inheritance in Man (OMIM) #123700), autosomal recessive (OMIM #219100 or #219200), or X-linked recessive (also known as occipital horn syndrome (OMIM #304150)).
- Mutations in elastin (ELN) or fibulin-5 (FBLN5) or fibulin-4 (FBLN4) or fibulin in autosomal recessive; a copper transport adenosine triphosphatase (ATP7A) in the X-linked type.
- Cutaneous features include pendulous, inelastic skin, with an aged facies.
- Extracutaneous manifestations may include pulmonary emphysema, aortic aneurysm, pulmonary artery and valve stenosis, hernias, gastrointestinal diverticula, joint laxity, low serum ceruloplasmin, and bilateral exostoses of the occiput (or occipital horn syndrome).
- Histopathology shows sparse and fragmented elastic fibers, better visualized with stains (i.e., Verhoeff-van Gieson or orcein).
- Information for patients and professionals at http://www.orpha.net/ Intelli execis cutsis laxa/.

**Epidemiology**

Few cases reported.

**Etiology and Pathogenesis**

Cutis laxa (CL) describes a group of disorders that share loose, redundant skin as a feature. Most cases are inherited in an AD, autosomal recessive, or X-linked manner,150-153 but acquired cases have also been described.154

Because of histologic abnormalities in elastin quantity or structure in virtually all forms of CL, investigations into the molecular pathogenesis have focused on genetic mutations that result in alterations in the structure or processing of elastin in the ECM. The genetic heterogeneity of CL reflects the fact that several genes are required for normal elastin biosynthesis and function.155 Decreased synthetic activity of skin fibroblasts and quantitative and qualitative abnormalities of elastic fibers have been reported.156,157

Elastin gene mutations that result in abnormal tropoelastin and abnormal elastic fibers result in AD CL (OMIM #123700).150,153 Elastin is one of several matrix components responsible for the properties of reversible deformability in many tissues, including the skin, lungs, and large blood vessels. The human elastin gene (ELN) is 45 kb in length and has been mapped to 7q11.2.159 Elastin initially is synthesized as individual tropoelastin molecules that are aligned on a network of elastic fibers. This alignment is stabilized by the formation of intermolecular cross-links that are mediated by the copper-dependent enzyme lysyl oxidase.

Type I autosomal recessive CL (OMIM #219100) is frequently fatal and is caused by mutations in the fibulin-5 gene (FBLN5, also known as EVEC or DANCE),160 which is critical for elastic fiber development.161 Mutations in FBLN5 can rarely lead to AD disease. The molecular basis for type II CL, (also known as CL with joint laxity and developmental delay; OMIM #219200),152 remains elusive, but lysyl oxidase deficiency is also found in these patients.158,162,163 A girl with CL in association with severe aortic dilatation and arachnodactyly has recently been described and found to have a mutation in the fibulin-4 (FBLN4) gene164 (Fig. 139-10).

Mutations in the gene encoding ATP7A, a member of the P-type adenosine triphosphatase family responsible for copper transport, have been described in the X-linked type of CL, which is allelic to Menkes syndrome.153 ATP7A mediates copper transport from the gastrointestinal tract, efflux of excess copper from cells, and delivery of intracellular stores of copper to cuproenzymes.

Acquired forms of this disease are present after skin inflammation and structural damage of elastic fibers. Increased neutrophil elastase is found in affected skin and is presumed to disrupt elastic fiber integrity.165 A recent report described heterozygous mutations in FBLN5 and ELN in an adult with “acquired” CL and aortic root aneurysm after a toxocara infection; predisposition to inflammatory damage by the mis-sense mutations is theorized.166

**Clinical Manifestations**

The clinical presentation of CL shows considerable heterogeneity.167,168 Congenital onset is generally indicative of an autosomal recessive or X-linked form of CL; later onset is consistent with either a heritable or acquired form. In both inherited and acquired forms, internal organs can be involved. As a rule, the AD form
of CL has primarily skin involvement, and is thus largely a cosmetic problem with a good prognosis.

The autosomal recessive and X-linked forms are often associated with more severe multisystem complications that include emphysema, diaphragmatic hernia, and gastrointestinal and genitourinary diverticula. Type I autosomal recessive CL is associated with severe cardiorespiratory complications and early death from cor pulmonale. Type II is a less severe recessive form, characterized by growth retardation, developmental delay, and ligamentous laxity. X-linked CL is characterized by mild joint laxity, bladder diverticula, hernias, and cranial occipital exostoses or horns. Many cases of acquired CL have developed after a febrile illness and/or inflammatory skin diseases such as lupus erythematosus, urticaria, eczema, erythema multiforme, vesicular eruption, amyloidosis, and angioedema, as well as reactions to penicillin and D-penicillamine.154 CL may also be associated with amyloidosis and plasma cell dyscrasias.

**CUTANEOUS FEATURES** In all forms of CL, the skin gives the appearance of being too large for the rest of the body (see eFig. 139-10.1 in on-line edition). CL may affect any portion of the body, but it often causes attention when it is present with loose appearance around the face, neck, shoulders, and thighs. At birth, the skin may be noticeably soft, loose, and hyperextensible. It tends to sag in the areas where the skin is normally loose, for example, around the face and eyes (see Fig. 139-10). In contrast to the skin of EDS, it returns very slowly to its normal position after being stretched; skin fragility, easy bruising, joint hypermobility, and poor wound healing are not usually associated with CL. The skin may be excessively wrinkled and appears prematurely aged. Children with severe CL may have characteristic facial features known as the “bloodhound” look—an aged appearance with sagging jowls (see Fig. 139-10).

Biopsy sections of clinically affected skin show a reduced number of elastic fibers in the dermis, with the remaining fibers being fragmented, shortened, clumped, or granular. Calcifications are not present. CL can also be an acquired condition and present diffusely or localized, giving individuals the characteristic “bloodhound-like” facies.170 It is more common in adults, although children may also be affected. In more than one-half of cases, the disorder is preceded by a urticarial eruption, which may respond to dapsone, but progression will be unaffected.171 Common associated findings include hiatal hernias, aortic aneurysm and rupture, intestinal and genitourinary diverticula, and emphysema. Some cases with cardiovascular or pulmonary involvement may be fatal.172 Moreover, associated systemic conditions include multiple myeloma, lymphoma, sarcoidosis, amyloidosis, and α1-antitrypsin deficiency.154 Histology shows initial inflammation with concurrent loss of elastic fibers.

**EXTRACUTANEOUS FEATURES** The X-linked form of CL is known as “cutis laxa syndrome” because of occipital exostoses. Characteristic facial features include inverted lower eyelids, a hooked nose, inverted nostrils, a short columella, and a long upper lip. The cry of an affected infant may be hoarse, and a low-pitched voice is often associated redundancy of the vocal cords. Diagnostic skeletal features of this condition can be identified radiologically and include short flat clavicles, fused carpal bones, and the occipital horns, which may not be present until a few years of age. This is the only form of CL with joint laxity.

The autosomal recessive forms of CL are often associated with severe internal complications, such as genitourinary and gastrointestinal diverticula. Chronic diarrhea is a widely reported complication, and secondary kidney damage may result from diverticula causing urinary tract obstruction. The most serious complications are diaphragmatic hernia and emphysema, which may lead to cor pulmonale and death in the first few years of life, especially in patients with FBLN5 mutations. Rare cardiovascular features include aortic dilatation with secondary cardiomegaly and congestive heart failure. Rectal prolapse, diaphragmatic atony, pneumothorax, peripheral pulmonary stenosis, and aortic dilatation have also been reported. Facial features include down-slanting palpebral fissures, broad/flat nose, and large ears.

Several multisystemic disorders have features that have been called “cutis laxa,” and must be considered in the differential diagnosis listed in Box 139-2.

**Treatment**

Surgical correction of redundant skin folds, rectal prolapse, or any hernias is temporarily beneficial and can be undertaken without major complication. Botulinum toxin has also been used to improve facial cosmesis.173 There is no known medical treatment to prevent disease progression in the inherited
The incidence of OI varies depending on type: I (1 in 20,000 to 30,000); II (1 in 60,000); III (1 in 70,000); IV (rare); V, VI, and VII (very rare).175

Etiology and Pathogenesis

Primary osteopenia and fractures are the hallmarks of OI.176 Decreased bone mass is a consequence of mutations in either \( \text{COL1A1} \) or \( \text{COL1A2} \), both of which encode the polypeptide chains forming the collagen type I molecule.177–179 Type I collagen is the most abundant protein in skin and bone. It provides tensile strength and interacts with other matrix proteins. As a result, OI osteoblasts show abnormal expression of thrombospondin, proteoglycans, hyaluronan, decorin, and fibronectin.180

The mineral phase is also affected, and bones from OI patients have higher average mineralization density than controls. Although the severe forms of OI were once assumed to be autosomal recessive, almost all cases of OI are now known to result from mutations in a single allele. Germline mosaicism has been shown to explain the lack of parental involvement in some cases of OI with affected siblings, and uniparental disomy has also been described. Glycine residues, which are normally present at every third position, are critical for triple helical conformation of type I collagen. Thus, point mutations in glycine have profound effects on molecular structure. Frameshift and null mutations lead to early termination and nonsense-mediated mRNA decay; as a result, only normal collagen is produced, but at a decreased rate, and a mild phenotype results.

Clinical Findings

The most notable finding in OI patients is the development of multiple fractures throughout life.181 Whereas type I tends to be mild, type II tends to be lethal in the perinatal period, with fractures in utero. Type III individuals survive birth but have severely deforming fractures, with a short triangular face and severe scoliosis. Types IV to VII are moderately deforming and rare.180 Individuals with OI type I (relatively milder type) have very blue sclerae (Fig. 139-12) that stays intensely blue throughout life, in contrast to the sclerae in OI type III and OI type IV, which may also be blue at birth and during infancy, but tends to fade by later childhood or adolescence. Other abnormalities include limb deformities, dentinogenesis imperfecta, short stature, triangular face, scoliosis, and hearing loss (> 50 percent of individuals).182,183 Just as in the bone, the cutaneous findings in the skin of OI patients reflect the decreased type I collagen,184,185 and cultured skin fibroblasts from affected individuals show decreased or abnormal type I procollagen molecules, a finding often used as a diagnostic tool. The skin is stiffer and less elastic than normal, as documented using the suction cup technique.186 Histologic analysis shows a relative increase of argyrophil and elastic fibers when compared to collagen.

Treatment

Therapy for OI involves a multi-disciplinary approach. Orthopedic surgeons, physical therapists, and rehabilitation personnel are the primary providers of care. Careful mobility is encouraged, and surgical repairs and support are frequently employed, giving patients a more active lifestyle.187 More recently, remarkable success has been attributed to the use of potent antiresorptive bisphosphonates. Intravenous and oral administration of these agents has been shown to decrease bone pain, increase muscle strength, enhance well-being, and increase bone mineral density. However, these preliminary results are currently being further investigated in randomized clinical trials.188 Transplantation of adult mesenchymal stem cells is currently under investigation as a means to correct bone fragility, and HLA-mismatched mesenchymal stem cells have led to
clinical improvement when transplanted into an affected fetus at 32 weeks gestational age. 159

CHAPTER 140

Hereditary Disorders of Genome Instability and DNA Repair

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Because the genome is the basic control for cellular function, maintaining genome stability is important for the continued function of cells, tissues, and organisms. DNA is the carrier of genetic information. Its structure is regularly threatened by damaging agents that include oxidative stress, ultraviolet (UV) and x-radiation, and chemical agents. Although much damage is repaired, failure to maintain genomic integrity may lead to abnormal cell function or cell death. If the cell divides, progeny may accumulate additional damage and this progressive accumulation of damage can lead to malignancy (see Chap. 109).

This chapter describes the relevant skin disorders with genome instability and the underlying defective mechanisms of DNA repair or DNA maintenance (Table 140-1). All of these exhibit prominent cutaneous abnormalities that involve dermatologists in their diagnosis and management. Most, but not all, are also characterized by an increased risk of malignancies. This demonstrates that the maintenance of genome integrity is of utmost importance for the prevention of malignant transformation. As malignant transformation requires the accumulation of several mutations in specific genes of a single cell, a mutator phenotype is often regarded a prerequisite for carcinogenesis, because without genome instability it would be exceedingly unlikely that all of those mutations occur in a single cell. 1–4 The same genes that are affected in the hereditary genome instability disorders can also confer genome instability to individual cells when impaired through acquired mutations, thereby playing an important role early in spontaneous carcinogenesis.

In addition, although these heritable diseases are rare (on the order of 10^{-5} or 10^{-6}), carriers of the affected genes may comprise several percent of the general population. These individuals are usually free of clinical symptoms, as most of these disorders are characterized by autosomal recessive inheritance. However, epidemiologic studies suggest that heterozygote carriers may have an increased risk of neoplasia as well. 

Spontaneous genome instability is present in Bloom syndrome (BS), ataxia telangiectasia, and Fanconi anemia (FA) as manifested by increased chromosome breakage in primary blood or skin cells. On the other hand, genome instability is present in cells from patients with xeroderma pigmentosum (XP) only after exposure to DNA-damaging agents such as UV radiation or other carcinogens such as benzo[a]pyrene, which is present in cigarette smoke. In XP, many of the severe disease manifestations such as cancer and corneal scarling leading to blindness are the result of the interplay between genetic risk and environmental exposure. For example, XP patients who avoid UV radiation dramatically reduce or eliminate the probability of developing skin cancer and blindness.

HEREDITARY DISORDERS OF GENOME INSTABILITY AND DNA REPAIR


In some of the disorders discussed here, genome instability is caused by an impaired ability to repair damage to DNA introduced by certain physical or chemical agents. Cells are equipped with different DNA repair pathways

KEY REFERENCES

The full reference list for all chapters is available at www.digm7.com.

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