Inherited defects of connective tissue Ehlers–Dan

Inherited defects of connective tissue: Ehlers–Danlos syndrome, Marfan’s syndrome, and pseudoxanthoma elasticum 4670 N.P. Burrows

ESSENTIALS The inherited disorders of connective tissue are all conditions in which structural defects in collagen or other extracellular matrix pro- teins lead to its fragility, with the commonest sites of involvement being the skin, ligaments, vasculature, and hollow organs. Ehlers–Danlos syndrome Ehlers–Danlos syndromes are a heterogeneous group of disorders resulting from abnormalities in collagen synthesis and processing, or of other extracellular matrix proteins. They can be classified on the basis of descriptive clinical phenotype and/or underlying molecular cause. Most cases are autosomal dominant, but 30–50% may be sporadic. In 2017, an updated classification of the disorders replaced the Villefranche criteria and delineates 13 subtypes. Clinical features—The cardinal manifestations are cutaneous hypextensibility, soft texture (‘doughy consistency’) and fragility, liga- mentous laxity, and easy bruising. (1) Classical Ehlers–Danlos syn-

drome—commonly caused by mutations in COL5A1 or COL5A2; the cardinal features are all prominent but other notable findings include epicanthic folds, subcutaneous spheroids, and molluscoid pseudotumours. (2) Hypermobile Ehlers–Danlos syndrome previ- ously known as (type III)/benign joint hypermobility syndrome—the commonest subtype of Ehlers–Danlos syndrome; cause unknown but haploinsufficiency of tenascin-X detected in a small percentage of patients; manifest with joint hypermobility but minimal skin changes; persistent arthralgia may be difficult to treat. (3) Vascular Ehlers– Danlos syndrome—mutations in COL3A1 lead to reduction of col- lagen III in blood vessels and bowel in this life-threatening condition; about three-quarters of arterial ruptures involve medium/large thor- acic or abdominal arteries, but any site can be affected; most bowel perforations affect the sigmoid colon; significant risk of uterine rupture in pregnancy.
(4) Kyphoscoliotic Ehlers–Danlos syndrome is due to autosomal recessive mutations in PLOD1 or FKBP14. The latter pheno- type is also associated with hearing impairment. (5) Arthrochalasis a Ehlers–Danlos syndrome—due to deficient processing of collagen I; characterized by severe joint hypermobililty, congenital bilateral hip dislocations, and recurrent subluxations.
(6) Dermatosparaxis— mutations in ADAMTS2 leads to extreme skin fragility and laxity.
(7) Periodonal Ehlers–Danlos syndrome heterozygous gain of func- tion mutations in C1R or C1S in complement pathway. Typical ap- pearances overlap with vascular Ehlers–Danlos syndrome but with severe, early onset gingival recession and no propensity to internal ruptures. (8) Classical-like Ehlers-Danlos syndrome—an autosomal recessive type but with absence of scars due to truncating mutations or deletions in TNXB. (9) Spondylodysplastic type—due to mutations in either the zinc transporter gene SLC39A13 or galactosyltransferase encoding genes B4GALT7 and B3GALT6; present with Ehlers–Danlos syndrome features and short stature, hypotonia and bowing of limbs.
(10) Musculocontractural Ehlers–Danlos syndrome—mutations in CHST14 result in a phenotype of Ehlers–Danlos syndrome with dis- tinct craniofacial features and congenital contractures. (11) Myopathic Ehlers-Danlos syndrome-heterozygous or biallelic mutations in COL12A1. Typical skin features with congenital muscle hypotonia that improves with age. (12) Cardiac-valvular Ehlers-Danlos syn- drome - complete loss of the proalpha2-chain of type I collagen due to biallelic COL1A2 mutations causes severe, progressive aortic and mitral valve problems. (13) Brittle Cornea Syndrome - biallelic muta- tions in ZNF469 or PRDM5 lead to thin cornea and keratoconus with joint and skin features of Ehlers-Danlos syndrome. Marfan’s syndrome Marfan’s syndrome is caused by autosomal dominant mutations in the human fibrillin-1 (FBN1) gene, with de novo mutations occurring in about 25% of cases. Criteria for diagnosis include aortic root dilatation, aortic dissection, lens dislocation, dural ectasia, and the presence of skeletal features including pectus carinatum, pectus excavatum requiring surgery, reduced upper to lower segment ratio or arm span to height ratio greater than 1.05, wrist and thumb signs, scoliosis, or spondylolisthesis, reduced ex- tensions at the elbows, pes planus, and protrusio acetabulae. The main causes of death in Marfan’s syndrome are cardiovascular 20.2 Inherited defects of connective tissue: Ehlers–Danlos syndrome, Marfan’s syndrome, and pseudoxanthoma elasticum N.P. Burrows

 complications, in particular aortic rupture. It is currently uncer- tain whether early treatment with β blockers and/or angiotensin II receptor blockade will prevent this by slowing the progression of aortic root dilatation. Pseudoxanthoma elasticum Pseudoxanthoma elasticum is caused by molecular defects in the transporter gene (ABCC6) that lead to calcification of elastic fibres and manifests with complications including
(1) cutaneous— yellowish papules appear in flexures, leading to a ‘plucked chicken’ or ‘gooseflesh’ appearance; (2) ocular—fundoscopy reveals mot- tled peau d’orange pigmentation, progressing to

breaks in Bruch’s membrane when angioid streaks are seen; retinal haemorrhages, neovascularization, and chorioretinitis can all lead to loss of central vision; and (3) cardiovascular—calcification of arterial elastic media and intima affects predominantly peripheral arteries; intermittent claudication is the commonest symptom. Introduction The inherited disorders of connective tissue, Ehlers–Danlos syn dromes, Marfan’s syndrome, and pseudoxanthoma elasticum are a diverse group of conditions with variable manifestations from minor symptoms to life-threatening complications. All share structural defects in collagen or other extracellular matrix proteins leading to fragility of connective tissue. The commonest sites of involvement are the skin, ligaments, and vasculature, although any hollow organ can be affected, and they share some common clin ical features. Subtle inherited defects of connective tissue may exert their effects at different stages of life. Molecular interactions between structural proteins and the extracellular matrix are important early in embryogenesis, and inherited defects of protein constituents in connective tissues may thus disturb many tissues during develop ment and organogenesis. In the ageing population, increased fra gility of the skin, rupture of blood vessels, and laxity of ligaments, as well as defects of cartilage and bone, may occur. Such degen erative disorders include osteoporosis, osteoarthritis, and arterial aneurysms. With recent advances in the understanding of the mo lecular structure and genetics of connective tissue components, it seems likely that many aspects of medicine hitherto ascribed to age-related degeneration will ultimately prove to have strong genetic components. A valid, molecular understanding of these processes may well emerge. It also appears likely that the discrete clinical conditions now recognized as Ehlers–Danlos syndrome, Marfan’s syndrome, and pseudoxanthoma elasticum will prove to have diverse and genetically determined counterparts that are re sponsible for the so-called degenerative disorders in the popula tion at large. Ehlers–Danlos syndrome The first detailed description of Ehlers–Danlos syndrome (EDS) was provided by a Russian dermatologist, AN Tschernogubow, at the inaugural meeting of the Moscow Dermatological and Venereological Society in 1891. The eponymous title was proposed 30 years later following further delineation of features by Edvard Ehlers and, subsequently, Henri-Alexandre Danlos. The cardinal manifestations of the syndrome are cutaneous hypextensibility; soft texture (‘doughy consistency’) and fragility; ligamentous laxity; and easy bruising (Fig. 20.2.1 and Table 20.2.1). These fea tures vary in severity and may coexist with additional involvement of other organ systems due to abnormal collagen structures. After the original description, it was realized that some patients with EDS were susceptible to spontaneous arterial rupture with its as sociated lethal consequences. Affected women experienced fetal prematurity, and examination of their skin showed a depletion of collagen III. There are obstetric, rheumatological, orthopaedic, and abdominal complications of this vascular form of Ehlers– Danlos syndrome, known as type IV. The most recent classification (Table 20.2.2) delineates 13 subtypes. The classification provides major and minor features and is based primarily on the underlying molecular cause. The types are referred to in descriptive rather than numerical categories. Research statistics show the prevalence as 1 in 2500 to 1 in 5000 people but clinical experience suggests EDS is more common. Representative clinical features of EDS sub types are illustrated in Figs. 20.2.1 and 20.2.2. Clinical genetics Collagen synthesis and assembly is complex. Collagen type III is an example of a homotrimer with three identical α chains whereas many of the other collagen molecules are heterotrimers, composed of two or more α chains. Mutations in a single glycine located in the collagen helices disrupt up to 88% of the assembled homotrimers and 75% of collagen heterotrimers, depending on the particular stoi chiometry. For these reasons, collagen defects of this type behave as autosomal dominant traits, while the enzymatic deficiencies of col lagen formation segregate as autosomal recessive traits with little or

no expression in heterozygotes. It is now recognized that some EDS phenotypes are associ ated with molecular defects beyond the three dermal fibrillar collagens, types I, III, and V, and their processing enzymes. In particular, important roles have emerged for extrafibrillar ma trix/ground substance (glycoproteins, proteoglycans, and gly cosaminoglycans) in the pathogenesis of EDS. For example, an autosomal recessive classical-like EDS is caused by deficiency of the glycoprotein tenascin-X. Tenascin-X, encoded by the gene TNXB, plays a crucial role in the organization of extracellular matrices, and deficient states lead to reduced dermal collagen with abnormal elastic fibres. This illustrates the importance of collagen interactions with other extracellular matrix proteins. Haploinsufficiency of tenascin-X may account for up to about 5% or 10% of hypermobile EDS, but this has only been found in women. Deficiency of one of the side chains (dermatan sul phate) of decorin due to mutations in CHST14, which encodes one of the regulatory enzymes in glycosaminoglycan biosynthesis (D4ST1), results in a musculocontractural EDS with a distinct facies, characteristic cutaneous features and congenital contrac tures. The same gene is responsible for adducted thumb-clubfoot syndrome and there is considerable clinical overlap. Mutations in SLC39A13, which encodes ZIP13, a membrane bound zinc transporter is one of the causative genes for spondylodysplastic for EDS with limited skeletal dysplasia. The resulting increase

4672 Fig. 20.2.1 Ehlers–Danlos syndrome (EDS). (a) Cutaneous hyperextensibilty of the skin (classical EDS);
(b) atrophic and pigmented papyraceous scars over knees and shins (classical EDS); (c) joint hypermobility at the wrist, knees and elbow (hypermobile EDS); (d) severe pes planus (type VI, kyphoscoliosis EDS); (e) dentinogenesis imperfecta (arthrochalasia EDS), this patient had a deletion of exons 3–6 of the COL1A1 gene; (f) extremely loose and fragile skin (dermatosparaxis EDS);
(g) gingival recession due to severe periodontitis (dental plate upper teeth) (periodontal EDS); and (h) typical pretibial plaque (periodontal EDS).

20.2 Inherited defects of connective tissue 4673 in zinc in the endoplasmic reticulum may deleteriously com pete with iron, a cofactor required for hydroxylation of lysyl and prolyl residues. Defective glyscosaminoglycans synthesis due to autosomal recessive mutations in B4GALT7 and B3GALT6 lead an overlapping phenotype. Homozygous or compound heterozy gous mutations in FKBP14 are causal for a variant of EDS with progressive kyphoscoliosis, myopathy, and hearing loss due to detrimental effects on endoplasmic reticulum protein folding of extracellular matrix proteins. Several other candidate proteins, such as decorin itself, lumican, and fibromodulin, have been implicated in EDS from studies in transgenic mice but, to date, no human example has been reported. Autosomal dominant types The most common subtypes are autosomal dominant, but it is estimated that from 30% to 50% of cases may be sporadic. Mutations in COLA1 and COLA2 genes encoding pro-α-1 and pro-α-2 chains of collagen type I, respectively, lead to a failure to remove the N-terminal procollagen extensions of collagen and the features of arthrochalasia EDS. Mutations in COL3A1 lead to reduction of collagen type III in blood vessels and bowel and a vascular EDS phenotype. COL5A1 mutations cause abnormalities of the quantitatively minor collagen type V and lead to classical EDS. Haploinsufficiency of tenascin-X due to heterozygous TNXB Table 20.2.1 Beighton Hypermobility Score Movement Score Total Dorsiflex left and right 5th finger >90º 1 for each side 2 Apposition left and right thumb to forearm 1 for each side 2 Hyperextend left and right elbow >10º 1 for each side 2 Hyperextend left and right knee >10º 1 for each side 2 Palms to floor 1 1 OVERALL TOTAL 9 A score of 4 or more in an adult (either concurrently or historically) indicates

hypermobility. Table 20.2.2 Diagnostic criteria of Ehlers–Danlos syndrome Subtype Inheritance Molecular defect (OMIM number) Clinicopathological features Classical AD COL5A1 and COL5A2 mutations result in abnormal fibrillogenesis. AD (130000) Rare COL1A1 Soft, velvety, doughy, and hyperextensible skin; atrophic scars, especially over bony protuberances; easy bruising, especially on the legs; and hypermobile joints, dislocations, and pain. Cauliflower-like collagen fibrils on TEM Hypermobile AD Cause unknown. Haploinsufficiency of TNXB in a small percentage of female patients may cause aberrant collagen deposition (130020) Marked joint hypermobility, minor skin extensibility and scarring. Overlaps with other hypermobility spectrum disorders. Vascular AD COL3A1 mutations result in reduced collagen type III (130050) Thin skin with prominent venous patterns visible, pretibial haemosiderosis, variable hypermobility often of only small joints, colonic perforation, and acrogeric facies and extremities, with variable fibril diameters on TEM Kyphoscoliotic AR AR Lysyl hydroxylase deficiency due to PLOD1 mutations leads to underhydroxylated collagen (225400) Mutations in FKPB14 encoding FKBP22, a member of the F506-binding family of peptidyl-prolyl cistrans isomerases results in abnormal procollagen protein folding (614557) Severe cardinal features, and muscle hypotonia at birth, kyphodcoliosis, ocular fragility and risk of arterial rupture Additional feature of congenital hearing impairment Enlarged endoplasmic reticulum cisterns in dermal fibroblasts on TEM Arthrochalasia AD Specific loss of exon 6 mutations in COL1A1 and COL1A2 results in inability to cleave N-terminal of procollagen 1 (130060) Severe cardinal features, short stature, congenital bilateral hip dislocation, dentinogenesis imperfecta, and angulated collagen fibres on TEM Dermatosparaxis AR ADAMTS2 deficiency results in inability to cleave N-terminal of procollagens (225410) Very severe skin fragility, with redundant sagging skin, short stature, bruising, joint laxity, hernia, and blue sclera. Irregular ‘heiroglyphic’ collagen fibres on TEM Periodontal AD C1R and C1S gain of function mutations result in intracellular retention of C1r and C1s serine proteases in the classical pathway of complement. The exact pathomechanism remains to be clarified (130080) Variable cardinal features with some overlap between the classical and vascular subtypes, aggressive periodontitis, and early tooth loss. Pretibial hyperpigmented plaques Classical-like AR Deficiency of tenascin-X due to truncating mutations or deletions in TNXB is associated with abnormal deposition of collagen and abnormal elastic fibres (606408) Hypermobile joints, easy bruising, and hypermobile skin but without atrophic scars. Muscle weakness. Variable cardiac and gastrointestinal features. (continued)

SECTION 20 Disorders of the skeleton 4674 mutations manifests as hypermobile EDS in a small percentage of women. It is not known why this does not appear to lead to the same phenotype in men. Autosomal recessive types Kyphoscoliosit EDS is caused by recessively inherited muta tions in PLOD1 leading to deficiency of lysyl hydroxylase and under-hydroxylation of collagen molecules. Laboratory con firmation through quantification of deoxypyridinoline and pyridinoline cross-links in urine by high-performance liquid chromatography is a highly sensitive and specific. Less com monly FKBP14 mutations lead to kyphoscoliosis with a myop athy and congenital hearing impairment. The rare autosomal recessive subtype dermatosparaxis, is caused by deficiency of the enzyme ADAMTS2, which leads to the inability to cleave off the N-terminal of procollagen types I, II, and III and leads to loose, sagging skin (Fig.20.2.1f) with extreme fragility and joint laxity. Spondylo dysplastic EDS presents with variable EDS fea tures and due to reduction in glycosaminoglycans synthesis due to biallelic mutations in B4GALT7 or B3GALT6. A similar pheno type is seen with mutations in the zinc transporter gene SLC39A13. Musculocontractural EDS overlaps with adducted thumb-clubfoot syndrome and most likely represents a single entity with variable presentation.

Deficiency of tenascin-X causes an autosomal recessive classical- like type of EDS. Affected patients have hypermobility, marked bruising, and hyperextensible fragile skin but without scarring. The relative risk of systemic complications is uncertain. Brittle Cornea Syndrome is now included in the EDS classification due to many overlapping skin and joint features. Investigations Skin biopsy for haematoxylin and eosin staining or immunohisto chemistry will not detect abnormalities of collagen, although may demonstrate thinning of the dermis in vascular EDS (type IV). Ultrastructural analysis (transmission electron microscopy of dermal collagens) is necessary to delineate the variable patterns of collagen fibril pathology. Although not specific, ‘cauliflower’ fibrils are seen in classical EDS and represent abnormal fibrillogenesis due to defects in collagen type V, which regulates fibril formation (Figs. 20.2.3a, b). The result is abnormally large and loosely bound fibrils giving the end appearance of ‘frayed rope’. Vascular EDS reveals more subtle changes with bimodal distribution of large and small fibrils (Fig. 20.2.3c). More specific features are seen Subtype Inheritance Molecular defect (OMIM number) Clinicopathological features Spondylodysplastic AR AR AR Galactosyl transferase I activity is reduced due to mutations in B4GALT7 gene. Leads to defect in synthesis of glycosaminoglycans (130070) Mutations in B3GALT6, which encodes a key enzyme in the early stage of glycosaminoglycans synthesis (615349) Mutations in SLC39A13, which encodes ZIP13, a membrane bound zinc-transporter leads to reduced hydroxylation of lysyl and prolyl residues (612350) EDS features and significant clinical overlap in each type. The hallmarks of B4GALT7 type include short stature, muscle hypotonia, radio-ulnar synostosis, and intellectual impairment The hallmarks of B3GALT6 type include characteristic craniofacial features, kyphoscoliosis, peripheral joint hypermobility, joint contractures, short stature, muscle hypotonia, osteoporosis with multiple fractures, radiographic skeletal abnormalities compatible with SEMD, and intellectual disability. The hallmarks of SCL39A13 type include, Moderate short stature,thin skin, bruising, slender, tapering fingers, wrinkled palms, and thenar (and hypothenar) atrophy, distal joint hypermobility and later onset contractures, characteristic radiographic abnormalities Musculocontractural AR AR Mutations in CHST14, which encodes one of the regulatory enzymes in glycosaminoglycan biosynthesis (D4ST1), leads to deficiency of dermatan sulphate and impaired collagen fibril assembly (601776) Loss of dermatan sulphate epimerase (DSE) function resulting in impaired dermatan sulphate production (615539) Typical EDS features with additional distinctive craniofacial appearance, congenital multiple contractures, including adducted thumbs and talipes equinovarus, large subcutaneous hematomas and possible congenital defects in cardiovascular, gastrointestinal, renal, ocular and CNS Milder phenotypic features Myopathic AD or AR COL12A1 mutations lead to impaired interaction between collagen1 and extracellular matrix proteins in skin, joints and muscle. Also referred to as Bethlem-myopathy type 2. Muscle weakness in infancy or childhood, proximal large joint contractures and distal joint hypermobility. Recessive form has more severe phenotype Cardiac-valvular AR COL1A2 mutations result in nonsense- mediated RNA decay and loss-of-function Mild classical or hypermobile EDS features with cardiac valvular (mitral or aortic) disease Brittle Cornea Syndrome AR AR ZNF469 encodes, a zinc finger protein of unknown function, but mutations may impair collagen transcription and fibrillogenesis Mutations in PRDM5 result in altered regulation of collagen transcription and fibrillogenesis EDS features with thin, fragile cornea resulting in increased risk of corneal rupture. No clear genotype-phenotype correlation noted TEM, transmission electron microscopy; AD, autosomal dominant; AR, autosomal recessive; CND, central nervous system; RNA, ribonucleic acid. Table 20.2.2 Continued

20.2 Inherited defects of connective tissue 4675 in arthrochalasia with the presence of angulated fibrils and in dermatosparaxis with hieroglyphic fibrils (Fig. 20.2.3d). Reduced collagen density and irregular elastic fibres are seen in tenascin-X deficiency. Spondylodysplastic and FKBP14-related EDS both dem onstrate normal collagen fibrils but enlarged endoplasmic reticulum cisterns within dermal fibroblasts are identified in the latter. Molecular analysis of candidate genes is confirmatory test of choice however, further analysis of collagen synthesis and secretion can be performed on cultured, usually dermal, fibroblasts (Fig. 20.2.4). The collagen proteins are visualized by incorporating radiolabelled pro line and separated on a polyacrylamide gel. Radioimmunoassay can also be used. Protein chemistry analysis can be helpful particularly for those subtypes in which consistent molecular defects lead to ab normal synthesis or processing of collagens as occurs in vascular EDS kyphoscoliosit EDS and arthrochalasia EDS. It is less likely to detect aberrations in collagen for classical EDS despite the molecular evidence that up to 90% are due to collagen type V mutations. Serum tenascin-X levels or direct sequencing of the gene can be undertaken for Classical-like EDS. No consistent molecular or protein chemistry finding is present for hypermobile EDS. Classical Ehlers–Danlos syndrome This form is the most common after the hypermobile type. Classical EDS is associated with the cardinal features outlined in Table 20.2.2. The skin is hyperextensible but retains its normal elastic recoil. Skin fragility manifests once the child is mobile, at trauma-prone sites such as knees, elbows, forehead, and chin. The scars are ‘fish-mouth’ or gaping and their atrophic nature produces ‘cigarette paper-like’ scars. Fibrous nodules (molluscoid pseudotumours) may arise at sites of repetitive trauma. As an incidental finding calcification is seen on radiographs in some cases along the shins or forearms due to subcutaneous, firm, small, cyst-like nodules (spheroids), They probably represent subcutaneous fat lobules that have fibrosed due to the loss of blood supply and subsequent calcification. Other notable features of the condition include epicanthic folds and blue sclerae. Mitral valve prolapse is probably more common but does Fig. 20.2.2 Vascular EDS. (a) Acrogeria, a specific clinical feature of vascular EDS, note the large eyes, thin, short nose (Madonna face), lobeless ears, scar over the chin, and diffuse hair thinning. (b) obvious visible network of veins on upper chest due to cutaneous atrophy in seven-year-old boy; (c) premature atrophy and wrinkling on the dorsum of the hands (acrogeria) affecting the same child; (d) similar features present on the dorsum of feet; and (e) pretibial bruising and haemosiderosis.

 not usually result in dilatational rupture of the valve. Some degree of proximal aortic root dilatation may be found although the clin ical significance is unclear and further longitudinal studies are re quired. Venous varicosities, premature bilateral hallux valgus, and distortion of the cornea leading to astigmatism, as well as prema ture osteoarthritis, are common. Bladder diverticulae are more common in men. Approximately 90% of the families with classical EDS have mutations in COL5A1 or, less commonly, COL5A2 genes; glycine substitutions and exon-skipping events are most common. Most mutations generate null alleles leading to deficiency of col lagen type V. Defects in the interactive properties of the N-terminal of collagen type V, which normally protrudes from the surface compound fibres comprising collagen types I, II, and V, impair normal interactions with other matrix components. Misdirection of the collagen fibrils leads to the generation of the so-called ‘cauli flower’ fibrils of classical EDS (Figs. 20.2.3a, b). The clinical con sequences are fragile skin, ligaments, tendons, and corneas, as well as defective articular surfaces. Inter- and intrafamilial phenotype variability is observed, but no genotype–phenotype correlation can be made. Rarely patients with a classical EDS have a propensity to arterial rupture at an early age due to a nonglycine substitution in the

COL1A1 gene. Hypermobile Ehlers–Danlos syndrome This is the most common subtype of Ehlers–Danlos syndrome with recent estimates of between 1:1000 to 1:5000. The hallmark is joint hypermobility but with minimal skin changes and for this reason the diagnosis is frequently overlooked. Hypermobile EDS and other forms of hypermobility (hypermobility spectrum disorders) overlap phenotypically. New diagnostic criteria have been proposed to segregate hypermobile EDS from other patterns of hypermobility. Varying degrees of hypermobility are also a common feature of many other disorders of connective tissues including, osteogenesis imperfecta, Marfan's syndrome, and pseudoxanthoma elasticum. Persistent arthralgia without evidence of inflammatory joint disease is not uncommon and is difficult to treat. It is unknown whether hypermobile EDS patients have defective pain receptors. A subset of these also report the failure of local anaesthetic agents. Many pa tients complain of easy fatigue, gastrointestinal symptoms, ortho static intolerance, and other features of autonomic dysfunction. It is likely that the underlying cause for this subtype is heterogeneous. Haploinsufficiency of tenascin-X has been identified in some auto somal dominant hypermobile patients and linkage to chromosome 8p22–8p21.1 in one family. As yet uncharacterized, defects in extra cellular matrix proteins and connective tissue-modifying enzymes may be responsible for the hypermobility of joints and other mani festations in this EDS type (Fig. 20.2.1c). Patients with Marfan's syn drome may show features of extensible skin and osteoporosis that overlap with hypermobile kyphoscoliosis and arthrochalasis types of EDS. Treatment of joint symptoms includes physiotherapy, rest, and graded exercise combined with conventional pain relief. Later, joint-stabilizing exercises or supports combined with propriocep tive enhancement, and cognitive therapy may be beneficial. Vascular Ehlers–Danlos syndrome This autosomal dominant form of EDS is life-threatening due to severe arterial and gastrointestinal fragility. Approximately 70% of Fig. 20.2.3 Ultrastructural abnormalities of collagen in EDS. (a) Misassembled 'cauliflower' fibrils of skin and ligaments in classical EDS, resembling transversely sectioned cauliflower heads, the left panel showing transversely fused fibres, which appear to splay distally in longitudinal sections; (b) diagrammatic representation (A) of compound collagen types I and III fibres, composed of quarter- staggered individual triple helices, and dark collagen type V molecules (B), which regulate fibril diameter, and their protruding N-termini (C), which can interact with other matrix components; (c) dual distribution of large and small collagen fibres in vascular EDS; and (d) 'hieroglyphic' collagen fibres in EDS type VII, indicating very severe disruption of fibril packing in comparison with the healthy collagen shown on the right of the figure. (a) Reproduced from J Med Genet, Nicholls AC et al., 33, 940–6, 1996 with permission from BMJ Publishing Group Ltd.

 arterial ruptures involve medium or large thoracic or abdominal arteries, although any site can be affected. The diagnosis should be considered in any young adult presenting with an unexplained cerebral vascular event. Most bowel perforations affect the sigmoid colon. A useful clue to the diagnosis is the history or presence of easy bruising typically accompanied by pretibial ecchymoses over the knees and shins as well as acrogeria (Fig. 20.2.2). Acrogeria refers to prematurely aged appearance of the extremities with thinning of the skin on the dorsum of the hands, feet, and shins. These features are combined with the so-called 'Madonna' facial appearance of large eyes, nasal thinning with lengthened philtrum, and small earlobes. Some patients may have a marfanoid appearance. Rarely there is acro-osteolysis, unexplained alopecia in women, congenital talipes, hip dislocations, and tendon contractures. Displacement of the metacarpophalangeal joints in the hands may superficially resemble the changes of rheumatoid arthritis. Fragility of pleuroperitoneal membranes leading to pneumothoraces may complicate this

and other types of EDS, including the classical and hypermobile types. Arterial ruptures are not always preceded by aneurysmal dila tation and the clinical course of arterial disease in vEDS is unpre dictable. Angiographic studies may reveal a dilatated and tortuous arterial tree, including the carotid bifurcation, and major aortic or iliac disease. The use of noninvasive imaging techniques such as computed tomography (CT) angiography, MR angiography, and Doppler ultrasound are preferable. Conventional angiography should be avoided, if possible, because of the high risk of dissection. Pepin and colleagues have recently reported the largest review of the medical and surgical complications in vascular EDS patients involving 630 index patients and 601 of their affected relatives. Most deaths resulted from arterial rupture, but there were also 181 bowel perforations in this cohort. Eighteen percent of deaths in males, all due to vascular dissection or rupture, occurred before 20 years old compared with 7% for females. The mean age of aortic events (dis section, aneurysm, or rupture), spontaneous coronary artery dissec tions or cervical vascular complications was between 30.8 years to 35.7 years, with younger involvement in men. Overall, the median lifespan of the whole group was reduced to 51 years. Treatment with celiprolol (a β-blocker) may improve outcome. Pregnancy-related deaths have been reported in 30 out of 565 deliveries (5.3%) but there is no difference in the overall survival between parous and nulliparous women with vascular EDS. Loeys–Dietz syndrome (LDS) was described in 2005. The major features of this autosomal dominant disorder, namely, aortic an eurysms, arachnodactyly, and dural ectasia overlap clinically with Marfan's syndrome. LDS is heterogeneic with approximately 75% classified as type I due to TGFBR1 mutations typically presenting with craniofacial involvement consisting of cleft palate, bifid uvula, craniosynostosis, or hypertelorism. LDS type II patients may also have a bifid uvula, but no other craniofacial abnormalities and fea tures overlapping with the vascular EDS phenotype. Mutations in LDS type II are typically found in TGFBR2. Phenotypic overlap oc curs with the other LDS types arising due to SMAD3, TFGB2, or TGFB3 mutations. The median overall survival of Loeys–Dietz pa tients in a series of 52 families was 37 years. There is also a high incidence of pregnancy-related complications. The reduced life ex pectancy is mainly due to early onset aortic dissections and brain haemorrhages. With earlier detection and treatment outcome rates improve. The survival during or immediately after vascular surgery is significantly higher compared to vascular EDS patients. This il lustrates one of the important reasons for genotyping such patients. Molecular pathology Histological examination of the skin reveals dermal thinning with depletion of dermal collagen and an overproliferation of elastic Fig. 20.2.4 Molecular analysis of collagen in EDS. (a) Typical collagen type III electrophoretic profile in fibroblasts after biosynthetic labelling in culture. There is virtually complete deficiency (tracks 5–8) or haploinsufficiency (tracks 1–4) compared with the normal pattern (9–10); and (b) electrophoresis of radiolabelled collagen proteins in fibroblasts obtained from a patient with severe pes planus due to kyphoscoliosit type EDS, showing accelerated migration (tracks 3–4) of underhydroxylated, compared with normal, collagen molecules (tracks 1–2; 5–6). C, collagen recovered from cells; M, collagen in culture medium.

SECTION 20 Disorders of the skeleton 4678 fibres. Examination of the skin by electron microscopy usually re veals marked variability in collagen fibril diameter (Fig. 20.2.3c). Collagen type III is an important collagen in skin, blood vessels, tendons, ligaments, gastrointestinal tract, and pleuroperitoneal cavity linings, which thus explains the diverse multisystem phenotype of vascular EDS. Disturbed assembly, as well as haploinsufficiency of collagen type III, explains the wide-ranging severity of vascular EDS, although some affected patients have a mild clinical phenotype resembling hypermobile EDS. Numerous mutations in the collagen type III gene have been found; most are private, although several mutations are associated with hot spots in the complex collagen

gene structure, which are located in exons 7, 16, and 24. The risk of complications of vascular EDS have recently been correlated to mutation type. Individuals with ‘null’ mutations that result in either mRNA instability or proα1(III) chain instability have the longest survival compared to other types of COL3A1 mutations. For those with missense mutations the nature of the substituting amino acid also has an effect on survival. Prenatal diagnosis is technically feas ible but obtaining tissue is hazardous due to inherent tissue fragility. If vascular EDS is still suspected despite normal collagen type III or COL3A1 analyses, then subsequent screening of TGFBR genes should be undertaken. Other forms See Table 20.2.2. Marfan’s syndrome Marfan’s syndrome affects both sexes with a prevalence of about 1 in 5000. It has a high penetrance with marked inter- and intrafamilial variability and is characterized by defects of connective tissue causing skeletal, cardiovascular, and ocular disease. Patients with Marfan’s syndrome are disproportionately tall and thin with ab normally long extremities and, often, a cadaverous physique (Fig. 20.2.5). Abraham Lincoln was possibly affected. Marfan’s syn drome overlaps with other inherited connective tissue disorders including hypermobile EDS, pseudoxanthoma elasticum, osteo genesis imperfecta, homocystinuria, and Loeys–Dietz syndrome. Marfan’s syndrome is caused by autosomal dominant mutations in the human fibrillin 1 gene (FBN1) with de novo mutations occurring in about 25% of cases. Abnormal fibrillin 1 exerts its detrimental ef fect by disrupting binding to transforming growth factor-β (TGFβ) resulting in increased expression of TGFβ. This appears to account for some of the more diverse features of Marfan’s syndrome, which should now be considered part of a group of developmental dis orders with defects in morphogenesis, homeostasis, and organ function. Diagnostic criteria The Ghent nosology for the diagnosis of Marfan’s syndrome was revised in 2010. More weight has been put on the cardiovascular features, with aortic root aneurysm as a cardinal feature alongside ectopia lentis. These two, in the absence of features suggesting an alternative diagnosis, are sufficient for the diagnosis of Marfan’s syndrome. The range of additional features with their weighted systemic score in Marfan’s syndrome are listed in (Table 20.2.3). Due to lack of specificity, the following criteria have been removed from the current nosology: joint hypermobility, highly arched palate, and herniae. The revised criteria for Marfan’s syndrome therefore allows for a diagnosis in the absence of a family history, with the presence of (1) aortic root dissection or dilatation (diam eter Z-score of 2 or more), and (2) either ectopia lentis, a patho genic FBN1 mutation, or seven or more points in the systemic score. In the presence of a family history, any one of the following three features are sufficient for a diagnosis: ectopia lentis; seven or Fig. 20.2.5 Inheritance of Marfan’s syndrome. Early illustration of a family with skeletal and ophthalmic features transmitted in an autosomal dominant pattern from the affected father to his daughter and two sons. Table 20.2.3 Diagnostic criteria for Marfan’s syndrome Systemic feature Score Wrist and thumb sign 3 Wrist OR thumb sign 1 Pectus carinatum deformity 2 Pectus excavatum or chest asymmetry 1 Hindfoot derformity/Pes planus 2/1 Pneumothorax 2 Dural ectasia 2 Protusio acetabuli 2 Reduced US/LS AND increased arm/height AND no severe scoliosis 1 Scoliosis or thoracolumbar kyphosis 1 Reduced elbow extension 1 Facial features (3/5): dolichocephaly, enophthalmos, downslanting papebral fissures, malar hypoplasia, retrognathia 1 Skin striae 1 Myopia (>3 diopters) 1 Mitral valve prolapse 1 US/LS, upper segment/lower segment ratio. Maximum score; 20; score >/= 7 indicates systemic involvement. Reproduced from Loeys BL, et al. (2010), J Med Genet, 47, 476–85, with permission from BMJ Publishing Group Ltd.

 more points in the systemic score; aortic root dissection or dilata tion (diameter Z-score of 2 or more at age >20 years, or of three or more at

age <20 years). Marfan’s syndrome shares features with other type I fibrillinopathies: mitral valve prolapse syndrome; aortic aneurysms; dominant ectopia lentis; Shprintzen–Goldberg syndrome (craniosynostosis and retarded neurodevelopment, with marfanoid features); Weill– Marchesani syndrome (short stature, brachycephaly, and other facial abnormalities); as well as Beals’ syndrome (congenital contractural arachnodactyly) due to fibrillin 2 mutations. Clinical features Classical Marfan’s syndrome arises from mutations in fibrillin 1. Typically, there are long fingers and toes (arachnodactyly), long slender limbs (dolichostenomelia), scoliosis, pectus excavatum, or pectus carinum (Fig. 20.2.6). Up to 80% have lens dislocation (ectopia lentis) (Fig. 20.2.7), usually bilateral and upwards due to rupture of the ciliary zonules, often in early childhood. Ectopia lentis is not unique to Marfan’s syndrome: homocystinuria, Weill– Marchesani syndrome, and familial ectopia lentis need to be ex cluded. Mitral valve prolapse and aortic dilatation (Fig. 20.2.8) with dissection is the commonest cause of premature death. Rarely, dissection and rupture of the pulmonary artery occurs in Marfan’s syndrome. Since homocystinuria and Marfan’s syndrome are distinct disorders—and because many patients with homocystinuria re spond to specific therapies (e.g. pyridoxine supplements)—clear distinction is necessary. Confusion between these two conditions is particularly likely in tall young patients with ectopia lentis. Except in unequivocal cases, patients with suspected Marfan’s syndrome should always undergo appropriate analysis (in patients not receiving vitamin B6 supplements) for homocystinuria due to cystathionine β-synthase deficiency or other causes. Genetics Marfan’s syndrome is typically inherited as an autosomal dominant trait (Fig. 20.2.5) and belongs to that group of genetic diseases in which a strong paternal-age effect occurs. The mean age of fathers of individuals who appear to harbour ‘new’ mutations is from 5 to 10 years greater than average. Approximately 25% of all patients with Marfan’s syndrome are sporadic cases. The role of fibrillin 1 Mutations in FBN1 (chromosome 15) encoding fibrillin 1, an elastin- associated microfibril, are responsible for Marfan’s syndrome A sep arate gene FBN2 (chromosome 5) is responsible for Beals’ syndrome (congenital contractural arachnodactyly that is not associated with defects in the ciliary zonules). The fibrillins are elastin-associated microfibrils, which assemble autonomously to form beaded microfilaments with ordered quasi crystalline structures that can be studied by electron microscopy and other methods. The fibrillin 1 gene has a complex multiexon or ganization and encodes calcium-binding epidermal growth factor- like and noncalcium binding epidermal growth factor regions. The gene encodes 65 exons encoding several conserved cysteines, and in 1991 common mutations were identified as responsible for Marfan’s syndrome. Of the mutations between exons 59 and 65, 40% are re sponsible for mild Marfan’s syndrome without aortic dilatation. Patients with neonatal and atypically severe Marfan’s syndrome have mutations clustered between exons 24 and 32. Despite this, muta tions associated with classic Marfan’s syndrome also occur in the same region and it is currently not possible to predict the phenotype for a given FBN1 mutation. Truncating mutations in the penulti mate exon 64 cause a specific marfanoid phenotype with congenital lipodystrophy and a neonatal progeroid appearance. Most mutations in fibrillin 1 are private, and the large and com plex genetic structure greatly impedes the molecular analysis of the fibrillin gene in patients with suspected Marfan’s syndrome. The role of TGFβ Until recently, the various structural defects observed in Marfan’s syndrome were understood to occur by the dominant-negative ef fect of mutant fibrillin 1 on normal tissues. However, the lack of (a) (b) Fig. 20.2.6 Chest deformity in Marfan’s syndrome. (a) Frontal and (b) lateral views showing pectus deformity and mild kyphosis. The abnormal sternum and ribs are laterally compressed. Fig. 20.2.7 Ectopia lentis in Marfan’s syndrome. The lens is displaced upwards and medially. Typically, strong concave spectacle (aphakic) lenses are required to correct the extreme myopia.

 genotype–phenotype correlation and clinical features that would suggest abnormal morphogenesis, such as bone overgrowth, has been difficult to adequately explain. It is now clear that changes in growth factor signalling are critical in Marfan's syndrome. The fibrillins share similar modular domain structures with the latent TGFβ binding protein (LTBP) family of glycoproteins. These pro teins have a structural role as well as the ability to bind to TGFβ, controlling its secretion and activity. Fibrillin binds to TGFβ and LTBPs and increased levels of active TGFβ are found in the pres ence of abnormal fibrillin (Fig. 20.2.9). Furthermore, mutations in the genes for the TGFβ receptors (TGFBR1 and TGFBR2) have been identified in several disorders with phenotypic overlap with classical Marfan's syndrome. Examples are the newly described arterial tortuosity syndrome, with aortic aneurysm, bifid uvula, or cleft palate, and hypertelorism as well as craniofacial and skel etal abnormalities (Loeys–Dietz syndrome), which is caused by heterozygous mutations in TGFBR1 and TGFBR2 (as well as TGFβ2, TGFβ3, and SMAD3). Interestingly, some of these patients have cutaneous features indistinguishable from vas cular EDS. TGFBR2 mutations have also been identified in some (a) (b) Fig. 20.2.8 Aortic disease in Marfan's syndrome. (a) Excised dilatated aortic root; and (b) histological section of the aorta showing elastic degeneration of the aortic media. Excess TGFβ signalling Excess TGFβ activation Emphysema Mitral valve prolapse Aortic aneurysm Myopathy Others? p p p p p p TF LAP LAP LAP LAP R-Smad R-Smad Smad4 Smad4 TGFβ TGFβ Marfan's syndrome Cytoplasm Normal Microfibrils Latent complex Nucleus Phenotypic consequences 3 2 1 L T B P TGFβ L T B P R-Smad Fig. 20.2.9 The role of TGFβ in Marfan's syndrome. (1) Normal regulation of TGFβ; (2) microfibril (fibrillin 1) deficiency in Marfan's syndrome; and (3) excess TGFβ signalling, which gives rise to variable phenotypic consequences. Reprinted from Ramirez F, Dietz HC. (2007). Marfan's syndrome: from molecular pathogenesis to clinical treatment. Current Opinion in Genetics & Development, 17, 252–8, Copyright © 2007, with permission from Elsevier.

 nonsyndromic individuals with familial thoracic aortic aneur ysms and dissections. Treatment The main causes of death in patients with Marfan's syndrome re sult from cardiovascular disease and complications elsewhere in the vascular system. Vigorous and regular surveillance is recommended with careful monitoring of aortic root width and of the function of aortic and mitral valves by transthoracic echocardiography and periodic electrocardiography. Halpern and colleagues, in 1971, first proposed the use of adren ergic β-blockers in patients with Marfan's syndrome to reduce the mean arterial pressure and pulse rate. After an open-label, random ized trial comparing propranolol with no treatment was published in 1994 β-blockers were widely used. While many studies have shown reduction in the development of aortic complications by β-blockers, two recent meta-analyses found no improvement in the endpoints measured of aortic dissection, rupture, cardiovascular surgery, or death for patients taking β-blockers. Reflecting this uncertainty, the 2010 guidelines of the American College of Cardiology Foundation and the American Heart Association recommend the use of β- blockers, whereas the 2014 guidelines of the European Society of Cardiology do not. The two most important determinants of risk of dissection of the aorta are the maximal dimension and family history of dissection. In adults, surgery is recommended when the aorta reaches 50 mm. For pa tients with evidence of progressive aortic disease, including dilatation of the ascending aorta and valve ring, a Dacron graft, with or without an artificial or reconstituted aortic valve (the Bentall procedure), may be considered. After excision of a terminally dilatated aorta, insertion of a Dacron graft to the aortic valvular ring requires reimplantation of the coronary arteries; in the best hands, the mortality rate

of this pro cedure is less than 5%, with more than three-quarters of patients sur viving five years. Gott and colleagues from Johns Hopkins Hospital, in the United States of America described the highly successful results of aortic root replacement in 271 patients with Marfan's syndrome over the period from 1976 to 2000. Most (>85%) patients underwent the Bentall procedure involving composite graft replacement of the aortic root. Mid-term results from valve-sparing, modified Dacron grafts, which allow annular stability and recreating sinuses that minimize leaflet stress, also look promising. In managing the cardiovascular complications of young pa tients with Marfan's syndrome, there is a need to balance advice regarding restrictive lifestyle, drug therapy, the benefit of long- term monitoring, and the maturation and development of an often asymptomatic child. Recent advances in the molecular pathology of Marfan's syn drome have opened up the possibility of alternative treatment strategies. Different fibrillin deficient mice have been shown to lead to variable impairment of distal alveolar septation, myxoma tous changes in the mitral valve and myopathy through increased TGFβ signalling. These pathological changes were prevented by perinatal, systemic administration of TGFβ neutralizing antibody. This is clearly not practical in humans. Mice heterozygous for a common Marfan's syndrome mutation (cysteine substitution in the epidermal growth factor-like domain of FBN1) develop pro gressive aortic root dilatation. Dietz and colleagues have elegantly shown, in mice, that postnatal administration of losartan, an angiotensin II type 1 receptor antagonist, which antagonizes TGFβ signalling, can reverse these aneurismal changes as well as partially reversing the noncardiovascular complications. It is worth noting that muscle regeneration was also seen in a dystrophin deficient mouse treated with losartan. A retrospective study of 18 paedi atric Marfan's syndrome patients (aged 1–16 years) treated with angiotensin II receptor blockers (17 patients received losartan and 1 received irbesartan) showed that the blockers significantly slowed the rate of progression of aortic root dilatation. All pa tients had received β-blockers, but the treatment was either inef fective or poorly tolerated. The first prospective, multicentre trial in adult patients has shown that the addition of losartan reduces aortic root dilatation and after aortic root replacement it reduces the dilatation rate of the aortic arch. However, this data has not been replicated in all studies with the largest, most recent study demonstrating no difference in aortic root dilatation between chil dren and young adults receiving either atenolol or losartan over a three-year period. Uncertainty now surrounds the best pharma cological approach and discrepancies may have occurred due to differing study designs and the clinical and genetic heterogeneity of Marfan's syndrome. Pending further data, from ongoing ran domized trials, it is currently advocated that losartan can be safely given in addition to, or as an alternative, to β-blockade in Marfan's syndrome. Other potential, future medical treatments that have shown benefit in Marfan's syndrome mice include antibiotics; tetracycline (doxycyline) and macrolide (roxithromycin) therapy and statins (pravastatin). These novel treatments need further validation in appropriate mouse models before translation to patients. Despite some earlier small studies indicating that angiotensin converting enzyme inhibitors may also play a beneficial role a more recent retrospective review showed no effect on aortic growth velocity. Further studies are required before this treatment modality is considered. Lens dislocation can be generally managed conservatively. Surgical removal is indicated if cataract, secondary glaucoma, or diminished visual acuity that cannot be corrected with spectacles occurs. This can be followed by artificial lens implantation. Other complications of Marfan's syndrome, including unstable joints, dislocation of the patella, progressive kyphoscoliosis, and recurrent pneumothoraces, with frequently complicating emphy sema, require surgical intervention. Clearly, many patients with Marfan's syndrome will require support with the psychological aspect and in the light of their diminished life expectancy. Women with Marfan's

syndrome require counselling, not only about the genetic risk to their offspring but, also because of the intrinsic risks of carrying a pregnancy to term. In addition to cardiovascular com plications, pregnancy is associated with a high rate of premature deliveries, premature rupture of membranes, and increased mor tality in the offspring. Prognosis Historically, patients with Marfan's syndrome have a reduced life expectancy, principally as a result of the cardiovascular compli cations. Indeed, about 80% of all deaths are due to aortic dilata tion and its complications; the mean age of death in a series of 257 patients published in 1972 was 32 years. However, possibly with the introduction of β-blocking agents, better monitoring and

SECTION 20 Disorders of the skeleton 4682 improvements in vascular and cardiac surgery, the prognosis has improved greatly, and the early cohort studies were almost certainly subject to bias, since outcome was better in patients ascertained on the basis of family studies compared with those with sporadic dis ease. With careful management, the life expectancy of an individual with Marfan's syndrome approximates that of the general popula tion. Patients with Marfan's syndrome are at risk if they participate in competitive athletics. Pseudoxanthoma elasticum (Grönblad–Strandberg syndrome) Pseudoxanthoma elasticum (PXE) has an estimated prevalence of from 1 in 25 000 to 1 in 100 000 with a predominance in women, although the latter may reflect presentation bias. It is an inherited disorder, caused by mutations in the ABC transporter gene (ABCC6) gene that leads to fragmentation and ultimately calcification of elastic fibres in the skin, eyes, and cardiovascular system. Clinical problems arise as a result of fragmentation and ultimately calcifica tion of elastic fibres. Premature arterial stiffening and calcification leads most commonly to lower leg claudication, hypertension, and, rarely, cerebral haemorrhage. Gastrointestinal bleeding and retinal disease causing visual loss are among the most frequent complica tions of PXE. Clinical genetics PXE is inherited as autosomal recessive (OMIM 264 800) and het erozygotes for an ABCC6 mutation are probably relatively common (0.8% prevalence for R1141X mutation in a Dutch population). Instances in which the disease occurs in two generations can be at tributed to pseudodominance due to matings between an affected (homozygote or double heterozygote) and randomly distributed heterozygotes. Carriers of a heterozygous mutation in ABCC6 are usually asymptomatic but may have mild ocular and cutaneous findings. Clinical features The full syndrome consists of the distinctive skin lesions, retinal changes (particularly angioid streaks), and vascular involvement. The diagnosis can be delayed by at least 20 years after the onset of skin lesions, which appear first, because many patients do not seek medical advice until ophthalmic complications occur. Cutaneous The average age of onset of the characteristic skin lesions is 13 years. Yellowish papules appear at flexural sites with predilection for par ticularly the neck and also the axillae antecubital fossae, inguinal folds as well as the umbilicus. The papules (1–3 mm) develop in a linear or reticular pattern and subsequently in confluent plaques re sembling goose flesh or the skin of a plucked chicken (Fig. 20.2.10). Examination of the palate and mucous membranes may show similar changes. Endoscopy of the stomach may reveal nodular submucosal lesions comparable to those present in peripheral skin. Sometimes the skin changes are very subtle but in severe cases the skin may become inelastic, leading to increased folds and a hound-dog ap pearance to the face, neck, and groins, due to secondary cutis laxa. These changes may be aggravated by sun exposure and smoking. Less commonly reticulate pigmentation on the abdomen may occur and acneiform lesions have been reported. The presence of an exag gerated mental crease may also be a useful sign of PXE, particularly in affected individuals under the age of 30 years. Ophthalmic Ophthalmoscopy is necessary to detect the typical ocular features. (Fig. 20.2.11). The first retinal change seen in most patients is a mottled peau d'orange pigmentation

due to irregularity of elastic fibres in the pretinal Bruch’s membrane. Progession leads to ‘salmon spots’, or drusen, reflecting hyaline degeneration, and when breaks occur in the Bruch’s membrane, angioid streaks are seen. These retinal streaks vary in colour from dark red or maroon to black. Angioid streaks occur in at least 85% patients above the age of 50 years but only in about one-third of patients under 10 years. Retinal haemorrhage, neovascularization, and chorioretinitis can all lead to loss of central vision and around half of patients will have some visual impairment. Myopia is more common in PXE patients. Cardiovascular Pseudoxanthoma elasticum is associated with disease of both large and small arteries, as shown in the retina. Calcification of arterial elastic media and intima affects predominantly peripheral arteries. Intermittent claudication is the most common cardiovascular symptom and reduced pulses of both arms and legs helps differen tiate from ordinary atherosclerosis. Occasionally, ischaemic features develop in the hands that are associated with resorption of digital tufts. Symptoms of intermittent claudication of the lower limbs occur in 30% of patients by the age of 30 years. Renovascular hypertension is not uncommon in patients with PXE and increases the risk of bleeding, which may also be associated with premature arterial calcification in peripheral arteries as well as coronary vessels. Ischaemic heart disease has been reported in a child as young as nine years. Other cardiac abnormalities identified in PXE include endocardial calcification, mitral valve prolapse and stenosis, re strictive cardiomyopathy, atrial septal aneurysm, and abnormal left ventricular diastolic function. Additional features include episodic and often severe gastrointes tinal haemorrhage usually from the stomach with, or without, a co incidental hiatal hernia or peptic ulcer. Bleeding may occur at other points including the renal, retinal, uterine, bladder, or subarachnoid spaces. Hyperechogenic dots representing calcified vessels can be detected by ultrasonography in the kidneys as well as the spleen and pancreas. Diagnosis Over the years, several clinical criteria for the diagnosis of PXE have been defined. In 2010, mutations in ABCC6 were incorporated in to the clinical classification. A more recent proposed update was put forward in 2014 (Table 20.2.4). The gold standard for diagnosis is homozygosity or compound heterozygosity for known disease- causing mutations in the ABCC6 gene. Characteristic changes on biopsy of affective skin are also very informative. In a study of 18 pa tients with angioid streaks, a skin biopsy of normal-looking skin did

20.2 Inherited defects of connective tissue 4683 not yield any additional diagnostic information. The main clinical features of PXE are listed in Table 20.2.5. Differential diagnosis Angioid streaks occur without any systemic associations in about 50% of cases. However, they may be seen in Paget’s disease, haemoglobinopathies, particularly sickle cell anaemia, acro megaly, and Ehlers–Danlos syndrome. They are rarely as florid as those occurring in pedigrees affected by PXE. Rarely, diabetic retinopathy may be associated with angioid streaks. Angioid streaks have also been reported in patients with neurofibroma tosis and tuberous sclerosis. Cutaneous manifestations of PXE may resemble those of extreme solar injury to skin associated with ageing. Late-onset PXE-like phenotypes have been ob served in patients with β-thalassaemia and sickle cell disease, with no evidence of mutations in ABCC6. Characteristically, long-term penicillamine therapy leads to a syndrome that is a close phenocopy of pseudoxanthoma elasticum (pseudo-pseudoxanthoma elasticum). Elastosis serpiginosa perforans may also be present. Saltpeter, calcium salts, l-tryptophan, and chronic renal failure (periumbilical) can all induce pseudoxanthomatous skin changes. Recently phenotypic and geneotypic overlap has been observed between generalized arterial calcification of infancy (GACI) and PXE. GACI is caused by mutations in ENPP1. Absence of ENPP1 leads to reduction of inorganic pyrophosphate (PPi), an inhibitor of tissue mineralization. Affected patients present in infancy with severe vascular

calcification and many die by the age of six months. Older children show cutaneous features resembling PXE. Furthermore, some patients with cutaneous findings indistinguish able from patients with ABCC6 mutations in fact harbour muta tions in ENPP1. Fig. 20.2.10 Skin lesions in pseudoxanthoma elasticum (PXE). (a) Typical flexural skin lesions of PXE of the lateral neck; (b) more widespread changes on anterior neck with secondary cutis laxa; (c) mucosal infiltration of the lower lip in PXE; and (d) an elastic ponceau S stain of skin biopsy (magnification ×10) showing mid-dermal elastic fibre fragmentation and degeneration.

SECTION 20 Disorders of the skeleton 4684 Another disorder with PXE-like cutaneous findings is associated with vitamin K dependent coagulation deficiencies due to GGCX gene mutations, which encodes γ glutamyl carboxylation of matrix Gla protein (MGP). MGP is another inhibitor of tissue mineralization. In these patients, skin changes are associated with a bleeding tendency. Pathology Pseudoxanthoma elasticum is diagnosed principally because of the occurrence of the constellation of clinical features, the family history, and a skin biopsy that reveals a characteristic fragmenta tion and disruption as well as calcification of the elastic fibres of the middle and deep zones of the dermis. The use of von Kossa's stain, which identifies carbonate and phosphate complexes of cal cium, together with van Gieson's stain for elastic fibres is diag nostic; electron microscopy, which is not required for diagnosis, usually reveals electron-dense deposits throughout elastin fibres in the skin with a central core of minerals as well as altered col lagen fibres. Fig. 20.2.11 Retinal changes in pseudoxanthoma elasticum (PXE). (a) Angioid streaks caused by fracture of the retroretinal Bruch's membrane, an early feature; (b) macular haemorrhage with consequential choroideretinitis; (c) specked peau d'orange mottling; and (d) salmon spotting (drusen).
Table 20.2.4 Diagnostic criteria for pseudoxanthoma elasticum (PXE) Definitive PXE 1) Two pathogenic mutations in the ABCC6 gene Or 2) Ocular findings – angioid streaks >1 disc diameter or peau d'orange in an individual under 20 years of age Together with 1) Pseudoxanthomatous papules and plaques on the neck or flexural creases, And 2) Calcified elastic fibres in the mid and lower dermis, confirmed by positive calcium stain in lesional skin If definitive findings are present only in the skin or eyes, the presence of two pathogenic ABCC6 mutations revealed by subsequent genetic testing would confirm the diagnosis of PXE even in the absence of a complete phenotype Source data from Uitto J, et al. (2014) Pseudoxanthoma elasticum: diagnostic features, classification, and treatment options. Expert Opin Orphan Drugs, 2(6), 567–77.

20.2 Inherited defects of connective tissue 4685 Molecular genetics The gene for PXE, ABCC6, was identified in 2000 and maps to chromosome 16p31.1 (Fig. 20.2.12). It encodes the multidrug resistance-associated protein 6 (MRP6) and is an ATP-binding cas sette transporter gene belonging to the same family as the cystic fibrosis transmembrane regulator gene, CFTR. ABCC6 is expressed primarily in the liver and to a lesser degree in the proximal tubules of the kidneys and it is present, if at all, in very low levels in the skin. There are several lines of investigations to suggest that PXE is likely to be a primary metabolic disorder due to an imbalance of serum factors. The endogenous substrate for this transporter remains uncharacterized. Affected individuals are either homozygous or compound het erozygous for loss-of-function mutations (most commonly missense mutations) clustering in exons 24–28 corresponding to the second nucleotide-binding fold and the last intracellular domain. There is considerable inter and intrafamilial pheno typic variability and no genotype–phenotype correlation exists. Polymorphisms in the SPP1 promoter region and the xylosyl transferase genes have been identified as possibly secondary gen etic risk factors. Environmental factors such as diet are also likely to effect manifestations. Treatment and

management At present there is no specific treatment to manage the systemic complications of PXE. Patients are prone to premature ageing ap pearance of their skin and protective measures to avoid excess exposure to ultraviolet light should be advised. Patients with PXE may benefit from plastic surgery to remove redundant skin around the neck and groins, abdomen, and breasts. This is par ticularly applicable to women who can develop rapid cutaneous changes after pregnancy or the menopause. The skin is not fra gile in PXE, but keloid formation may complicate such cosmetic surgery and it is advisable that those who operate are apprised of this risk in PXE. Although the skin and vascular lesions of PXE are associated with calcification, there is no evidence that calcium restriction influences the development of the disease. Nonetheless, some au thorities recommend restricting calcium intake without evidence that this impedes the progression of the disorder. If a low calcium diet is adhered to, osteoporosis should be excluded, particularly in postmenopausal women. Because of their risk of severe sys temic arterial disease, patients with PXE are advised to undergo regular monitoring of their vascular integrity and blood pressure. The prompt use of β-blockers for hypertension where possible may delay the onset of peripheral vascular insufficiency and coronary heart disease. The rapid onset of severe systemic hypertension that is refractory to treatment may be due to unilateral renal artery stenosis—a well-described abnormality in PXE. Prompt treatment of systemic hyperlipidaemia, which may independently complicate the arteriopathy of PXE, is indicated to arrest arterial narrowing and prevent thrombosis. Antiplatelet drugs such as aspirin and nonsteroidal anti-inflammatory drugs are contraindicated because of the increased risk of visual loss due to retinal bleeding and of gastrointestinal haemorrhage. Coronary bypass surgery is as suc cessful and no riskier than for the general population; there is little evidence to judge the outcome of vascular surgical procedures that may be indicated for stenoses of carotid or other major peripheral arteries. Regular light exercise, maintaining normal body weight and avoidance of cigarette smoking are simple measures that also likely to be beneficial. Contact sports, including boxing, and arduous exercise such as cross-country running should be avoided. Regular monitoring by an ophthalmologist may be beneficial. The occurrence of new vessel formation in relation to angioid streaks traditionally has been arrested by ocular laser therapy to prevent or diminish the risk of retinal haemorrhage. However, several recent studies have dem onstrated the effectiveness of intravitreal antivascular endothelial growth factor (anti-VEGF) therapy for the treatment of choroidal neovascularizations secondary to angioid streaks. Table 20.2.5 Features of PXE in different tissues Tissue Feature Skin Classical flexural eruption of initially yellowish papules which coalesce Elastic fragmentation and calcification and/or central elastic fibre calcification (by electron microscopy) Increased cutaneous extensibility (heterozygotes) Exaggerated mental crease in younger patients Occasional striae Blood vessels Decreased elasticity, hypertension Arteriosclerosis, claudication, cerebrovascular disease Medial calcification, venous varicosities Gastrointestinal haemorrhage Eyes Peau d’orange changes Angioid streaks potentially leading to choroidal neovasculization, retinal haemorrhages, and reduced vision Optic drusen Owl’s eyes (paired hyperpigmented spots) Late-onset macular degeneration, macular central visual loss Altered corneal geometry, myopia, blue sclerae Miscellaneous Mitral valve prolapse Organ calcification Membrane spanning domain 1 Membrane spanning domain 2 Membrane spanning domain 3 Walker motif A Walker motif B Nucleotide binding folds COOH NH2 Fig. 20.2.12 Organization of the human PXE gene. ABCC6 is a member of the ABC transmembrane ion transporter family. There are three membrane-spanning domains and two nucleotide-binding folds.

SECTION 20 Disorders of the skeleton 4686 Pregnancy Despite earlier concerns of the increased risk of first trimester mis carriage this was found not to be the case in a large study where there was no excess fetal loss or adverse reproductive outcomes. Twelve percent of pregnancies were associated with worsening of skin manifestations. Although the demonstrable incidence of gastric bleeding and retinal complications is low at less than 1%, monitoring of systemic arterial blood pressure with additional eye checks are re commended in pregnant patients with this disorder and during the peripartum period. Prognosis The prognosis of PXE is determined by the severity of extracutaneous organ involvement. Patients typically have a normal lifespan, but in some premature death results from vascular disease, which may cause critical occlusion of the arterial supply to essential organs or fatal bleeding. Death from a recurrent massive gastrointestinal haemorrhage was recorded in a 13-year-old patient and severe bleeding due to PXE has been reported in younger children. FURTHER READING Beighton P, et al. (1998). International nosology of heritable disorders of connective tissue. Am J Med Genet, 29, 581–94. Beighton P, et al. (1999). Ehlers–Danlos syndrome: revised nosology, Villefrache, 1997. Am J Med Genet, 77, 31–7. Bercovitch L, et al. (2004). Pregnancy and obstetrical outcomes in pseudoxanthoma elasticum. Br J Dermatol, 151, 1011–8. Bergen AA, et al. (2000). Mutations in ABCC6 cause pseudoxanthoma elasticum. Nat Genet, 25, 288–31. Birk DE, et al. (1990). Collagen fibrillogenesis in vitro. Interaction of types I and V collagen regulates fibril diameter. J Cell Sci, 95, 649–57. Brady AF, et al. (2017). The Ehlers-Danlos syndromes, rare types. Am J Med Genet C Semin Med Genet, 175C:70–115. Brooke BS, et al. (2008). Angiotensin II blockade and aortic-root dila tion in Marfan's syndrome. N Engl J Med, 358, 2787–95. Brown SJ, et al. (2007). Pseudoxanthoma elasticum: biopsy of clinically normal skin in the investigation of patients with angioid streaks. Br J Dermatol, 157, 748–51. Buntinx IM, et al. (1991). Neonatal Marfan syndrome with congenital arachnodactyly flexion contractures and severe cardiac valve insuf ficiency. J Med Genet, 28, 267–73. Burrows NP, et al. (1996). The gene encoding collagen alpha 1 type V (COL5A1) is linked to mixed Ehlers–Danlos type I/II. J Invest Dermatol, 106, 1273–6. Byers PH, et al. (1979). Clinical and ultrastructural integrity of type IV Ehlers–Danlos syndrome. Hum Genet, 47, 141–50. Byers PH, Murray ML (2014). Ehlers–Danlos syndrome: a showcase of conditions that lead to understanding matrix biology. Matrix Biol, 33, 10–5. De Paepe A, et al. (1996). Revised diagnostic criteria for the Marfan syndrome. Am J Med Genet, 62, 417–26. Dietz HC, et al. (1991). Marfan syndrome caused by a recurrent de novo missense mutation in the fibrillin gene. Nature, 352, 337–9. Frank M, et al. (2019). Vascular Ehlers-Danlos syndrome: long-term observational study. J Am Coll Cardiol, 73, 1948–57. Franken R, Mulder BJM (2015). Losartan versus atenolol in the Marfan aorta—how to treat? Nat Rev Cardiol, 12, 447–8 Germain DP. (2017). Pseudoxanthoma elasticum. Orphanet J Rare Dis 12:85. Comprehensive review of clinical features and current under- standing of genetic and pathophysiology of PXE. Godfrey M (1993). The Marfan syndrome. In: Beighton P (ed) McKusick's heritable disorders of connective tissue, 5th edition, pp. 51–135. Mosby Year Book, St. Louis, MO. Gott VL (2002). Aortic root replacement in 271 Marfan patients: a 24-year experience. Ann Thorac Surg, 73, 438–43. Grahame R (2000). Heritable disorders of connective tissue. Baillieres Clin Rheumatol, 14, 345–61. Gray JR, et al. (1998). Life expectancy in British Marfan syndrome populations. Clin Genet, 54, 124–8. Groenink M, et al. (2013). Losartan reduces aortic dilatation in adults with Marfan syndrome: a randomized controlled trial. Eur Heart J, 34, 3491–500. Habashi JP, et al. (2006). Losaratan, an AT1 antagonist, prevents aortic aneurysm in a mouse model of Marfan syndrome. Science, 312, 117–21. Halpern BL, et al. (1971). A prospectus on the prevention of aortic rupture in the Marfan syndrome with data on survivorship without treatment. Johns Hopkins Med J, 129, 123–29. Hofmann Bowman MA, Eagle KA, Milewicz DM (2019). Update on clinical trials of losartan with and without b-blockers to block

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