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ORPHAN DISEASES (B MANGER, SECTION EDITOR)

The Collagenopathies: Review of Clinical Phenotypes and Molecular Correlations

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Abstract Genetic defects of collagen formation (the collagenopathies) affect almost every organ system and tissue in the body. They can be grouped by clinical phenotype, which usually correlates with the tissue distribution of the affected collagen subtype. Many of these conditions present in childhood; however, milder phenotypes presenting in adulthood are increasingly recognized. Many are difficult to differentiate clinically. Precise diagnosis by means of genetic testing assists in providing prognosis information, family counseling, and individualized treatment. This review provides an overview of the current range of clinical presentations associated with collagen defects, and the molecular mechanisms important to understanding how the results of genetic testing affect medical care.

Keywords Collagen · Collagenopathies · Osteogenesis imperfecta · Stickler syndrome · Ehlers–Danlos syndrome · Alport syndrome · Porencephaly · Bethlem myopathy · Ullrich congenital muscular dystrophy · Dystrophic epidermolysis bullosa · Junctional epidermolysis bullosa non-Herlitz

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Introduction

The collagen superfamily of proteins constitutes important components of connective tissue throughout the body. Twenty-nine types of collagen have been described, each containing a domain composed of three α chains intertwined as a triple helix. The triple helix is highly dependent on Gly-X-Y repeats, which comprise the amino acid sequence of the α chains. Glycine is found at every third position of the triple helix because it is the only amino acid small enough to fit into the center of the helix. X and Y-position amino acids vary more; proline is often present at the X position and hydroxyproline at the Y position. Hydroxylation facilitates cross-linking of the α helices. The ring structure of proline and hydroxyproline residues enables the sharp turns necessary for assembly of the tight triple helix structure. Post-translational modification in the endoplasmic reticulum then generates mature collagen, which is secreted into the extracellular matrix.

Collagens are divided into groups by structure: fibrillar collagen, non-fibrillar collagen, and fibril-associated collagens with interrupted triple helices (FACIT). Fibril-forming collagens are the most abundant in the body and are comprised of a short amino telopeptide non-triple-helical domain, a long

triple-helical domain, and a short carboxyl telopeptide non-triple-helical domain [1]. Non-fibrillar collagens comprise a diverse group that neither form nor associate with fibrils: the network-forming, microfibrillar, and transmembrane collagens, and the anchoring fibrils and multiplexins. The FACIT collagen structure differs in that it has multiple triple-helical domains separated by non-collagenous domains [2].

Collagens are almost ubiquitous in the body. Consequently, mutations in the genes coding for collagen (collagenopathies) affect many organ systems. An overview of the collagens currently associated with disease, their anatomical distribution, and associated conditions is given in Table 1.

Collagenopathies Resulting in Bone Fragility

Type I collagen is the primary collagen in bone. It is the predominant component of osteoid, the extracellular tissue secreted by osteoblasts during bone formation, growth, and remodeling, and is subsequently mineralized to form bone tissue [3]. Osteogenesis imperfecta (OI) is a disorder of bone fragility and pathologically increased bone turnover, clinically characterized by fractures in the absence of commensurate trauma, and by progressive bone deformation. Patients with OI have delayed periosteal bone formation, reduced bone thickness, and thin, sparse trabeculae [4].

Approximately 90 % of OI is caused by mutations in *COL1A1* and *COL1A2* [5]. Apart from fractures, the pertinent features of OI include short stature compared with family members, progressive hearing loss, lax ligaments, abnormal teeth (dentinogenesis imperfecta), and blue sclerae. Age of onset is variable, ranging from lethal perinatal presentation to adult presentation with few fractures. The classification currently used for OI is an expansion of one originally created by Sillence et al. (1979) [6, 7]. The clinical features of the types of OI caused by collagen type I mutations are summarized in Steiner et al. (2013) [8]. Most cases of OI type I are caused by null mutations in *COL1A1*. These mutations result in abnormal mRNA that is either captured and retained in the nucleus or is subject to nonsense-mediated decay, in which truncated or abnormal mRNA is degraded before it can be fully translated [9, 10]. As a result, only half the normal amount of procollagen is synthesized. The more severe types of OI, types II, III and IV, tend instead to be the result of missense mutations which substitute an alternate amino acid for a Gly residue. The resulting abnormal procollagen chain assembles into abnormal α-helical structures, resulting in a qualitative, rather than quantitative, deficiency of type I collagen [11]. Although most OI cases are the result of mutations in *COL1A1* and *COL1A2*, at least 13 other genes have been revealed to be related to OI, and many of these are involved in post-translational modification of collagen [3]. OI types I to V are autosomal dominant disorders. All other types are inherited in an autosomal recessive manner.

In the mildest presentation (type I OI), affected individuals present with fractures, but with little or no bone deformation and reduction in adult stature. OI type II is lethal in the perinatal period, primarily because of lung hypoplasia related to rib fractures (Fig. 1). Type III, or the progressive-deforming type, causes severe fracturing early in life, progressive bone deformation, and markedly reduced stature, and independent ambulation is often never attained. Type IV is of variable severity, with bone deformity ranging from mild to moderate, and variable reduction in stature.

Treatment of OI currently focuses on ameliorating symptoms. Physiotherapy, close orthopedic follow-up, and intensive rehabilitation after fracture are important. Hearing aids, cochlear implants, and stapes surgery are used to manage hearing loss. Teeth may be capped or replaced to avoid decay and infection [12]. Adequate intake of vitamin D and calcium is encouraged to optimize bone health.

Bisphosphonate therapy has greatly altered clinical progression of affected individuals. Glorieux et al. (1998) [13] observed reduced bone resorption, reduced fracture incidence, increased vertebral body size, and increased bone density, without altered fracture healing, in children aged 3–16 years after cyclic treatment with pamidronate. Many further studies, mostly not controlled, have observed the same beneficial effect of bisphosphonate treatment [4].

Genetic counseling is essential for families and patients affected with OI. An individual with autosomal dominant OI has a 50 % risk of having an affected child. Because of the variability of the condition, it is important to assess parents and/or children of affected individuals. It is not uncommon for an affected parent to be identified after their child has been diagnosed with OI. Lethal or severe OI in children born to healthy parents tends to be caused by de-novo mutations in *COL1A1* and *COL1A2*, or by mutations in one of the autosomal recessive genes. The risk of recurrence in cases (both mild and severe) of apparently de-novo mutation is approximately 3 % because of the possibility of gonadal mosaicism (multiple eggs or sperm carrying a mutation in unaffected parents) [8].

Prenatal diagnosis, via ultrasound, of OI type I is unreliable. Increased nuchal translucency may be observed from 11–14 weeks of gestation, but this is nonspecific [14]. Bony deformities and fractures associated with the more severe OI types can be detected by use of ultrasound [15]. Ultrasound diagnosis can be confirmed using samples from either chorionic villus sampling (CVS) or amniocentesis, in line with approved guidelines [16•]. Caesarean delivery does not reduce intrapartum fracture for infants with non-lethal forms (types I, III and IV), nor does it prolong survival for infants with lethal forms (type II) [17].

Fertility of patients with OI is usually preserved. For women with OI, pregnancy and delivery are associated with

Table 1 The collagens currently associated with disease. Collagen types are organized by major characteristics of clinical presentation as presented in the text

Collagen gene	Collagen type	Anatomic areas of expression	Associated disease
COL1A1	Type I collagen	Most connective tissue, skin, tendon, bone, ligament	Osteogenesis imperfecta types I, II, III, IV Caffey disease Ehlers–Danlos types I, VII
COL1A2			Osteogenesis imperfecta types II, III, IV Ehlers–Danlos cardiac valvular form and type VIIB
COL2A1	Type II collagen, Type XI collagen	Cartilage, nucleus pulposus, vitreous, cornea, inner ear	Achondrogenesis II/hypochondrogenesis Platyspondylic lethal skeletal dysplasia, Torrence type Sponyloepiphyseal dysplasia congenita Spondyloepimetaphyseal dysplasia, Strudwick type Kneist dysplasia Stickler syndrome type 1, non-syndromic ocular type Osteoarthritis with mild chondrodysplasia
COL11A1	Type XI collagen	Cartilage, nucleus pulposus, vitreous, cornea, inner ear	Stickler syndrome, type II, autosomal dominant Fibrochondrogenesis Marshal syndrome
COL11A2		Cartilage, nucleus pulposus, inner ear	Stickler syndrome, type III, autosomal dominant Fibrochondrogenesis Deafness, autosomal dominant and autosomal recessive Weissenbacker–Zweymuller syndrome
COL9A1	Type IX collagen	Cartilage, vitreous, retina, inner ear	Multiple epiphyseal dysplasia type VI Stickler syndrome type IV, autosomal recessive
COL9A2			Multiple epiphyseal dysplasia type II Stickler syndrome type V, autosomal recessive
COL9A3			Multiple epiphyseal dysplasia type III Multiple epiphyseal dysplasia with myopathy
COL10A1	Type X collagen	Hypertrophic chondrocytes in calcifying cartilage	Metaphyseal chondrodysplasia, Schmid type
COL3A1	Type III collagen	Most connective tissue, especially vessels, skin and tendons	Ehlers–Danlos type III Ehlers–Danlos type IV
COL5A1	Type V collagen	Most connective tissue, especially skin, bone, tendon, cornea, placenta and fetal membranes	Ehlers–Danlos type I Ehlers–Danlos type II
COL4A1	Type IV collagen	Basement membranes	Porencephaly I Brain small vessel disease with Axenfeld–Reiger anomaly Brain small vessel disease with hemorrhage Hereditary angiopathy with nephropathy, aneurysm and muscle cramps
COL4A2			Porencephaly 2
COL4A3 COL4A4			Alport syndrome, autosomal dominant and recessive types Benign familial hematuria
COL4A5			Alport syndrome, X-linked
COL4A6			Diffuse leiomyomatosis with Alport syndrome
COL18A1	Type XVIII Collagen	Basement membranes	Knobloch syndrome
COL6A1 COL6A1 COL6A1	Type VI collagen	Most connective tissue, tendons, contributes to cell matrix adhesion in skeletal muscle	Bethlem myopathy Ullrich congenital muscular dystrophy
COL7A1	Type VII collagen	Anchoring fibrils in dermo-epidermal junctions	Epidermolysis bullosa dystrophica, autosomal recessive and dominant types, bart type, inversa type, pruriginosa type, pretibial type
COL17A1	Type XVII collagen	Component of hemidesmosomes	Junctional epidermolysis bullosa, non-Herlitz type

increased risk and, although the antenatal course is usually uneventful, should be managed by a multi-disciplinary team in high-risk perinatal centers [18]. Rare but serious intrapartum complications include: uterine rupture secondary

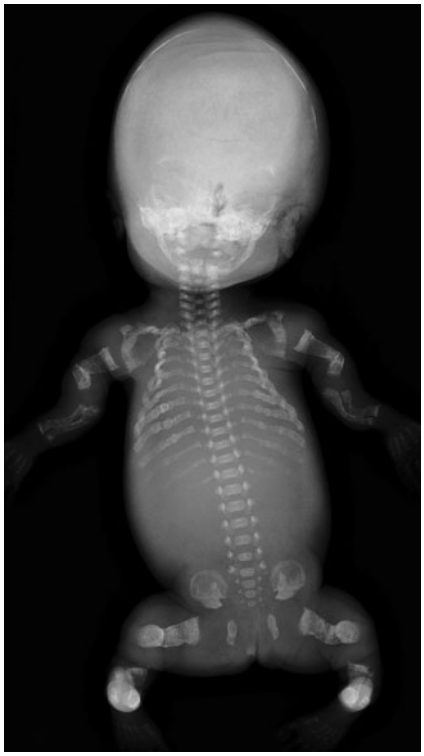

Fig. 1 OI type II in a fetus. There are fractures in all the long bones. Multiple fractures are present in the ribs, leading to shortened ribs with a characteristically "beaded" appearance. Also note the poor ossification of the skull

to reduced collagen in the myometrium [19]; pelvic fracture resulting from relatively minor obstetrical trauma; and massive intra and post-partum hemorrhage secondary to increased vascular fragility, reduced clotting factor VIII and abnormal platelet function [20]. Less serious complications include weaker surgical scars [21] and a tendency to post-operative hernia [19]. Because of spinal deformity, short necks, potential for fracture of the mandible and cervical spine, malignant hyperthermia, bleeding tendency, and possible fractured ribs caused by fasciculations from succinylcholine, these women are also at increased risk from use of anesthetic [22, 23].

Collagenopathies Associated with Short Stature, Eye Anomalies, Hearing Loss, and Joint Degeneration Causing Osteoarthritis

Type II, IX and XI collagen have an important function in formation and maintenance of cartilage, and are therefore important to long bone development and joint health. Because these three collagens have associated functions in cartilage, mutation in any one of their three corresponding genes results in chondrodysplasias, with some phenotype overlap. Extra-skeletal features, for example high myopia or retinal detachment, a small jaw, cleft palate, and a flat mid-face region, are commonly observed [24•].

Lethal Presentations

The most severe forms of type II collagenopathy are typically identified in utero, and are not compatible with life. Achondrogenesis type 2 and hypochondrogenesis are identifiable on fetal ultrasound, presenting with extreme micromelia, minimal or absent ossification of the sacrum, pubic bones and vertebrae, and short trunk and ribs. Hypochondrogenesis is a less severe presentation (with more skeletal mineralization), but is nevertheless lethal in the prenatal period. Death is usually related to lung hypoplasia resulting from a small, abnormally formed chest cavity [25]. Both phenotypes are usually caused by glycine substitutions in the COL2A1 triple helix, causing abnormal α chains and inappropriate type II-collagen retention in the rough endoplasmic reticulum. Thus, there is minimal type II-collagen deposition in the cartilage extracellular matrix [26]. Achondrogenesis type 2 and hypochondrogenesis result from de-novo dominant mutations (associated with low recurrence risk in subsequent pregnancy), although very rare reports of germline or somatic mosaicism in parents have been published [27]. Platyspondyly, Torrance type, is another lethal presentation of *COL2A1* mutations, characterized by wafer-thin vertebral bodies [24•, 28]. Mutations in *COL11A1* and *COL11A2* lead to fibrochondrogenesis type 1 and type 2, also lethal in the neonatal period as a result of a small chest and of respiratory problems.

Childhood Presentations

Usually, type II, IX and XI collagenopathies cause Stickler syndrome. Unless the phenotype is recognized at birth because of a U-shaped cleft palate and extreme micrognathia (Pierre-Robin sequence), affected individuals go undiagnosed. The ocular findings associated with Stickler syndrome (high myopia, congenital or early-onset cataracts, and retinal detachment) are important for diagnosis, because adult height is usually comparable to the height of unaffected family members. Mild joint hypermobility and, in the third or fourth decade of life, osteoarthritis affecting weight-bearing joints are also not uncommon [29]. Stickler syndrome is sub-typed on the basis of vitreous anomaly, inheritance pattern, or causative gene (Table 2). *COL11A2* gene mutations have been described as causing Stickler syndrome without ocular manifestations [30]. An autosomal recessive form of Stickler syndrome caused by mutations in two of the three genes contributing to type IX collagen, *COL9A1* and *COL9A2*, has also been described.

Table 2 Clinical and molecular classification of Stickler syndrome

Type	Inheritance	Gene	Eye features	Hearing	Facial features	Skeletal features	Other features
Type 1	Autosomal dominant	COL2A1	Myopia, retinal detachment, vitreoretinal degeneration glaucoma, cataracts, membranous vitreous anomaly	Sensorineural hearing loss, conductive hearing loss	Flat midface, Pierre–Robin sequence, cleft palate	Mild spondyloepiphyseal dysplasia, platyspondyly, kyphosis, scoliosis, premature osteoarthritis	Mitral valve prolapse
Type 2	Autosomal dominant	COL11A1	Myopia, retinal detachment, vitreoretinal degeneration glaucoma, cataracts, beaded vitreous anomaly	Sensorineural hearing loss	Flat midface, Pierre–Robin sequence, cleft palate	Mild spondyloepiphyseal dysplasia, slender extremities, premature osteoarthritis	Joint hypermobility
Type 3	Autosomal dominant	COL11A2	None	Sensorineural hearing loss	Flat midface, Pierre–Robin sequence, cleft palate	Epiphyseal dysplasia, platyspondyly, premature osteoarthritis	
Type 4	Autosomal recessive	COL9A1	Myopia, astigmatism, retinal detachment and degeneration, cataracts, vitreous anomaly with degenerated appearance	Sensorineural hearing loss	None reported	Epiphyseal dysplasia, platyspondyly, irregular vertebral endplates, genu valga	
Type 5	Autosomal recessive	COL9A2	Myopia, retinal detachment, vitroretinal degeneration, cataracts, vitreous anomaly	Sensorineural hearing loss	Flat midface, small jaw	Unknown	

Stickler syndrome management requires multidisciplinary care. Ophthalmological follow-up is mandatory, and patients should be educated about retinal detachment symptoms and encouraged to avoid high-impact sports. Early intervention may restore vision after a detachment, but delayed diagnosis results in blindness. Audiological follow-up is also recommended [31•]. Because individuals with Stickler syndrome are at increased risk of early joint degeneration, weight should be optimized and low-impact exercise encouraged.

COL2A1 mutations causing short stature from infancy include spondyloepiphyseal dysplasia congenita (SEDC), spondyloepimetaphyseal dysplasia Strudwick type (SEMD), and Kniest dysplasia (Fig. 2a, b). These conditions share many phenotype features: neonatal respiratory distress, infantile hypotonia, flat facial profile, high myopia, risk of retinal detachment, abnormal oval-shaped vertebral bodies at birth and later platyspondyly (flattened vertebral bodies), cleft palate, high risk of severe degenerative joint disease, and odontoid hypoplasia leading to risk of atalantoaxial instability and paralysis [24•, 32]. Because the metaphyseal component distinguishing SEDC from SEMD is not always seen at birth, radiographs should be repeated at approximately one year of age [24•]. Kniest dysplasia is characterized by shortened, "dumbbell-shaped" long bones, with splaying of the epiphyses and metaphyses [33]. Collagen mutations causing SEDC and SEMD are usually heterozygous missense mutations affecting the triple helix domain, whereas Kneist dysplasia is typically the result of exon-skipping mutations [34].

COL9A1, *COL9A2* and *COL9A3* mutations cause multiple epiphyseal dysplasia, a condition presenting in childhood as knee or hip pain and a limp. Radiographically, the femoral epiphyses of an affected individual are small or dysplastic. MED may sometimes be confused with Legg–Calve–Perthes disease or with childhood arthritis.

Type X collagen is found in the hypertrophic zones of the growth plate, regions important to long bone growth [35]. *COL10A1* mutations are associated with metaphyseal chondrodysplasia, Schmid type. Affected individuals present with short stature and varus or valgus deformity of the knee. Radiographically there is progressive coxa vara, flared, irregular, thickened metaphyses, mild platyspondyly, short and broad middle phalanges, hypoplastic distal phalanges, and short, irregular, wide femoral neck, visible during the first year of life [36].

Adult Presentations

As previously mentioned, many individuals affected by Stickler syndrome go undiagnosed in childhood. Some are only identified after the birth of an affected child, identification of ocular complications, or diagnosis of early osteoarthritis. *COL2A1* mutations also cause familial premature osteoarthritis

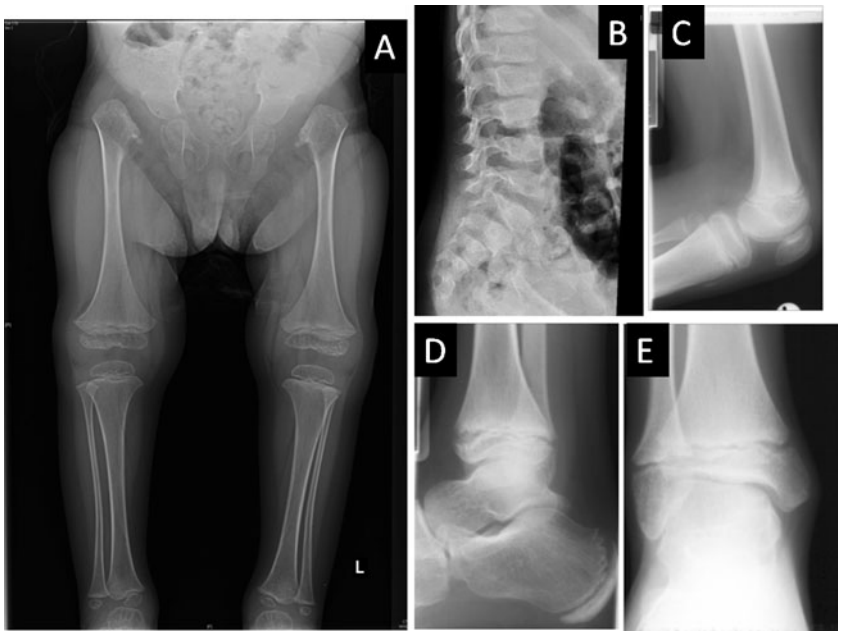

Fig. 2 Examples of skeletal changes observable in type II collagenopathies. **a** In a two-year-old patient with SEMD, note the shallow, hypoplasic acetabuli, the irregular proximal femoral metaphyses and absent proximal femoral epiphyses, irregular distal femoral epiphyses, and flared distal femoral metaphyses. **b** In the same patient, note the platyspondyly. **c**, **d**, **e** In a 23-year-old patient with familial early osteoarthritis caused by a COL2A1 mutation, note the diffuse joint-space-narrowing

and avascular necrosis of the femoral head (ANFH), but individuals with these phenotypes do not develop ocular complications, short stature or facial dysmorphisms. Glycine-to-serine mutations in *COL2A1* have been found to be associated with ANFH [37, 38]. Mutations in *COL2A1* have also been reported for families with osteoarthritis of both large and small joints, with onset by the third or fourth decade of life (Fig. 2c–e) [39].

Collagenopathies Associated with Joint Hypermobility and Tissue Fragility

Specific Ehler–Danlos syndrome (EDS) subtypes are caused by collagenopathies (fibrillar collagens I, III and V) resulting in joint hypermobility and in skin, vessel, and internal organ fragility. The current EDS classification is an expansion of the 1997 Villefranche nomenclature, which originally recognized six subtypes [40]. Ninety percent of classical-type (type I) EDS is caused by mutations in *COL5A1* or *COL5A2*. Type V collagen is a heterotrimer made up of three α chains encoded by *COL5A1*, *COL5A2* and *COL5A3*, and is present in diverse tissues (see Table 1). Mutations causing classical-type EDS typically result in haploinsufficiency, via nonsense-mediated decay or the inability of the mutant chain to incorporate into the heterotrimer [41•]. Mutations in type 1 collagen (*COL1A1I*) have been reported for classical-type EDS [42] and for the arthrochalasia type of EDS (type VII) [43]. Mutations in type III collagen (a homotrimer) cause vascular-type EDS (type IV) in over 95 % of cases. As with the more severe types of OI, the most common mutation is substitution of a bulkier amino acid for glycine in the Gly-X-Y domain [44]. Again similarly to OI, null mutations may result in an attenuated form of the condition [45]. The etiology of joint-hypermobility-type EDS (type III) is largely unknown, although in some cases it is caused by mutations in type III collagen [46].

Classical-type EDS is clinically defined by both major and minor diagnostic criteria. Major criteria include hyperextensible skin, which stretches easily but is not loose, wide atrophic scars with a "cigarette paper"-like appearance (Fig. 3.), and joint hyperextensibility as measured by the Beighton score. Minor criteria include diverse manifestations of tissue hyperextensibility and weakness, for example velvety skin, easy bruising without coagulopathy (Fig. 3a), recurrent joint subluxations and dislocations, hernia, cervical insufficiency, and rectal prolapse [40]. Electron microscopy of the skin reveals a disorganized pattern of collagen fibrils, with abnormal "cauliflower-shaped" bundles of collagen, although this finding is not specific [47].

The arthrochalasia type has the major characteristics of the classical type, as well as short stature, osteopenia, and increased risk of fracture. Cardiac–valvular-type EDS is caused by homozygous or compound heterozygous mutations in *COL1A2* that result in an absence of α2(I) collagen propeptides, and is characterized by joint hypermobility, skin hyperextensibility, easy bruising, muscle and tendon tears, and cardiac valve insufficiency and regurgitation [48].

Vascular-type EDS is a severe and often life-limiting condition, associated with tissue fragility and increased risk of spontaneous rupture of large vessels and hollow organs. Major diagnostic criteria include arterial, bowel and uterine rupture

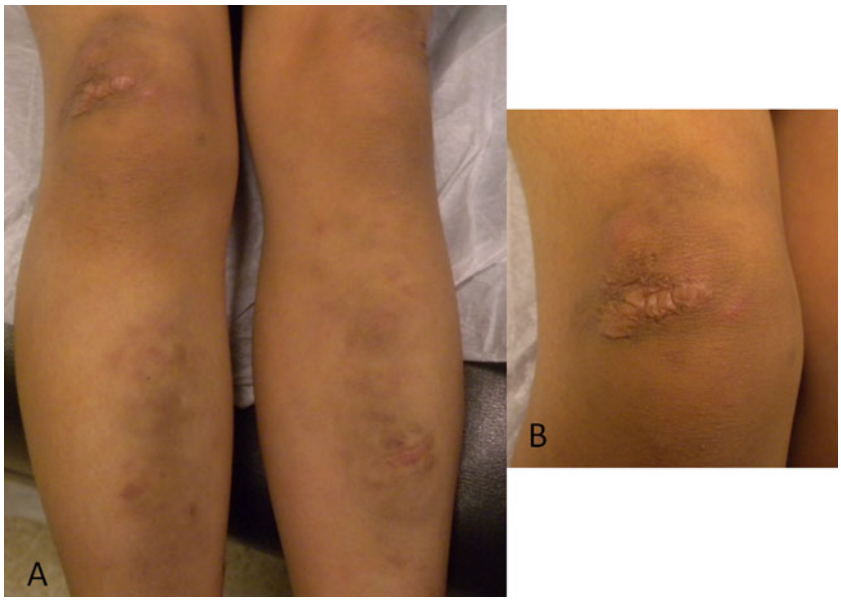

Fig. 3 **a** Scarring and bruising of a patient with classical-type EDS. **b** The typical "cigarette paper" scar

during pregnancy, and family history. Some of the many minor criteria include thin, translucent skin, thin lips and nose, a small chin, large eyes, an aged appearance of the hands (acrogeria), small-joint hypermobility, muscle and tendon rupture, easy bruising, and recurrent joint dislocation [40]. Arterial rupture most often occurs in medium-sized vessels, for example the renal, iliac, femoral, mesenteric, or hepatic arteries. It is important to be aware that these ruptures may occur without prior dilatation of the vessel [49]. Median survival was 48 years for one large cohort [44].

The tissue fragility associated with vascular EDS results in increased morbidity and mortality after invasive procedures [50]. Expert consultation is advised before performing such procedures. There are no standard surveillance procedures for vascular aneurysm or dissection, because data necessary to establish these are lacking. General advice includes avoiding strenuous exercise or contact sport, and where possible selecting alternatives to such elective procedures as routine colonoscopy [51•]. One randomized, open-label trial suggested that the beta-blocker celiprolol may help prevent vascular events [52].

The joint hypermobility form of EDS is characterized by hyperextensibility of large and small joints, recurrent joint dislocation, mitral valve prolapse, early-onset osteoarthritis, and skin hyperextensibility. Affected individuals complain of chronic joint pain, muscle pain, headaches, and fatigue, which in combination with the recurrent dislocations leads to significant morbidity, chronic disability, and a reduced quality of life [53]. Unfortunately management is difficult, and many affected individuals are frustrated by the lack of symptom relief.

An increased risk of preterm premature rupture of membranes and preterm birth is associated with all types of EDS [54, 55]. For patients with classical and hyperextensible EDS, pregnancy is usually well tolerated and outcomes are favorable [56]. Among patients with vascular EDS maternal mortality can be as high as 12 %, mainly as a result of uterine or vascular rupture in the peripartum period [57].

The optimum mode of delivery is still debatable, and the increased risk of uterine and vascular rupture has contributed to the general recommendation of early caesarean delivery for patients with vascular EDS [54, 55, 58]. No uterine or vascular ruptures have been reported with other types of EDS. There is increased risk of wound dehiscence, deep-vein thrombosis, and coccyx dislocation [56, 59]. There may be an increased risk of urinary incontinence and pelvic organ prolapse [56]. Post-partum hemorrhage is common, probably as a result of vascular fragility.

As a predominantly autosomal dominant disorder, there is a 50 % risk of the fetus being affected. If there is prior knowledge that the affected parent has the disease-causing mutation, prenatal diagnosis is possible via analysis of fetal DNA obtained by means CVS or amniocentesis.

Collagenopathies Associated with Cerebral Small Vessel Anomalies and Fragility

COL4A1 and *COL4A2* mutations cause thickened and damaged vascular basement membranes, resulting in vessel fragility [60•]. Type IV collagen is a non-fibrillar collagen, comprising three heterotrimers formed from α-chain polypeptides which are the products of six different genes [61]. Unlike fibrillar collagen, type IV collagen molecules connect to form a latticework held together with S-hydroxylysyl methionine bonds, lysyl-derived crosslinks and hydroxylysine-linked

disaccharides [62, 63]. This lattice is a major structural component of basement membranes underlying epithelia throughout the body, including the glomeruli, mesangial matrix, and vascular basement membranes [60•].

Thus far, all *COL4A1* and *COL4A2*-related disorders seem to be inherited in an autosomal dominant fashion. Identified mutations are predominantly glycine substitutions for a bulkier amino acid in the Gly-X-Y domain [60•].

Porencephaly type 1 and type 2 are characterized by cystic cerebral cavities that often communicate with the ventricles. Affected individuals suffer hemorrhage pre or perinatally, and continue to be at risk of intracerebral hemorrhage throughout life [64, 65]. In the neonatal period presentation may resemble hypoxic ischemic encephalopathy, and presentation may resemble cerebral palsy in later infancy. There is also risk of diffuse or periventricular leukoencephalopathy, cerebral calcifications and microbleeds, and intracranial aneurysms [60•, 66]. Cerebral microbleeds, leukoencephalopathy, and intracranial hemorrhage in conjunction with tortuous retinal arteries and anterior chamber abnormalities are described in autosomal dominant "brain small vessel disease with hemorrhage" or "brain small vessel disease with Axenfeld–Reiger anomaly" [67]. *COL4A1* mutations may also affect kidneys, heart, muscle, and peripheral and central vasculature. In HANAC syndrome (hereditary angiopathy with nephropathy, aneurysms, and muscle cramps), affected individuals present with hematuria, renal cysts, intracranial aneurysms, muscle cramps with elevated creatine kinase, and retinal artery tortuosity with retinal hemorrhage [68]. Magnetic resonance imaging of patients as young as 24 years reveals signs of chronic cerebral vascular disease, but comparatively low incidence of intracerebral hemorrhage compared with that associated with other *COL4A1*-related disorders [69].

Collagenopathies Associated with Kidney Disease and Deafness

Type IV collagen ($\alpha3\alpha4\alpha5$) is a vital component of the glomerular basement membrane (GBM) and of basement membrane tissues in the cochlea and eyes [70, 71]. Mutations or deletions in *COL4A3*, *COL4A4* and *COL4A5*, which encode the $\alpha3$, $\alpha4$ and $\alpha5$ chains, cause Alport syndrome. Approximately 80 % of cases are caused by mutations or deletions in *COL4A5* (X-linked inheritance), and 20 % are related to *COL4A4* or *COL4A3* (autosomal recessive inheritance). Of clinical significance is the realization that heterozygous mutation carriers may be affected [72]. Non-progressive benign familial hematuria is also caused by heterozygous mutations in *COL4A3* or *COL4A4*.

Clinically, Alport syndrome progresses from microscopic hematuria to microalbuminuria, frank proteinuria, impaired kidney function, hypertension, and, eventually, end-stage kidney disease. Men with X-linked Alport syndrome have a 90 % chance of developing end-stage kidney disease by age 40; however, patients with large deletions or nonsense mutations have significantly earlier disease onset than those with missense mutations [73]. The vast majority (95.5 %) of women who carry *COL4A5* mutations develop microscopic hematuria. In one large cohort, 12 % progressed to end-stage kidney disease before age 40 and 40 % before age 80 [74]. Autosomal recessive Alport syndrome presents as gross proteinuria in childhood, and progression to end-stage kidney disease often, but not universally, before the fourth decade [75]. In cases where patients are carriers of a single mutation, kidney disease usually progresses slowly, and end-stage disease occurs in the 4th–6th decades or not at all [75]. In addition to renal disease, a childhood-onset progressive sensorineural hearing loss is present in most affected individuals. Ocular anomalies are frequent in Alport syndrome. Anterior lenticonus, in which the central portion of the lens bulges into the anterior chamber, is virtually pathognomonic. There are multiple potential eye complications, including lens rupture, cataracts, and corneal erosions [71]. Importantly, eye findings can precede proteinuria in 40 % of patients, so that a suggestive eye exam should prompt further investigation.

Individuals at risk should be monitored for proteinuria, hypertension and IgA nephropathy annually after diagnosis. Cohort studies have suggested that renin–angiotensin–aldosterone inhibition may slow disease progression [76, 77••]. Transplantation is the only curative option for kidney disease. A rare but important complication of transplantation for these patients is post-transplantation anti-GBM disease, which can endanger the graft [78].

Pregnancy of patients with Alport syndrome is very challenging and often complicated by deterioration of renal function, preeclampsia, severe placental dysfunction, and, sometimes, acute renal failure [79•]. Pre-pregnancy renal function seems to significantly affect pregnancy outcome [80], and therefore pregnancy should only be undertaken once renal function and blood pressure are optimized. Preterm delivery, either spontaneous or iatrogenic, seems to be characteristic, with only one uncomplicated pregnancy delivering at term having been reported to date [79•].

Collagenopathies Associated with Muscle Weakness, Joint Contractures and Joint Laxity

Type VI collagen, a microfibrillar collagen, is a heterotrimer with α chains encoded by *COL6A1*, *COL6A2* and *COL6A3*. The collagen VI α-chain structure consists of a short chain of Gly-X-Y repeats with N and C telopeptide domains. Intracellularly, the α chains form a monomer (heterotrimer), and two monomers align in an antiparallel manner to form a dimer that subsequently aligns into staggered parallel tetramers, all

stabilized by disulfide bridging of cysteine residues. After secretion into the extracellular matrix the tetramers associate end-to-end, forming the characteristic beaded microfillamentous network [81, 82].

The type VI collagenopathies vary in severity, from severe Ullrich congenital muscular dystrophy (UCMD), to Bethlem myopathy characterized by a combination of progressive muscle weakness, joint hypermobility, and contractures. Infants with UCMD are hypotonic and have extremely hyperextensible distal joints. Motor milestones are delayed because of hypotonia, and independent ambulation may not be achieved. Contractures in the knees, elbows, and spine often present in infancy and progressively worsen. Throughout childhood and adolescence, muscle strength and motor milestones are progressively lost and missed. Respiratory insufficiency eventually develops; the first manifestation is usually hypoxemia during sleep. Muscle pathology takes the form of type 1 fiber-atrophy early in the course of disease, and progresses to overtly dystrophic features including prominent interstitial fibrosis [83]. Individuals with Bethlem myopathy often have mild symptoms in infancy, including subtle muscle weakness and distal hyperextensibility. Weakness and contractures progress slowly, with two-thirds of patients requiring assistance with ambulation by the sixth decade [84]. Collagen VI mutations have also been described in two other phenotypes: autosomal dominant limb-girdle muscular dystrophy, and autosomal recessive myosclerosis myopathy [85, 86].

Historically, Bethlem myopathy and UCMD were believed to be inherited in an autosomal dominant and autosomal recessive manner, respectively; however, UCMD also results from autosomal dominant inheritance [87]. Several studies have reported genotype–phenotype correlations for a large cohort of patients [88, 89]. Usually, homozygous or compound heterozygous mutations that result in a total loss of type VI collagen in the ECM lead to a more severe UCMD phenotype, whereas mutations that only affect specific splicing variants may lead to attenuated progression [90, 91].

Collagenopathies Associated with Epidermolysis Bullosa

Type VII collagen is a homotrimer, comprising an α-helical domain interrupted in several places by insertions or deletions in the Gly-X-Y pattern. Type VII collagen is found in several epithelia, especially skin, where it is synthesized by dermal fibroblasts and epidermal keratinocytes [92]. It is a major component of the anchoring fibrils that stabilize the dermal–epidermal junction [93]. Collagen XVII, a homotrimer encoded by the *COL17A1*, is a transmembrane collagen, and a component of hemidesmosomes that mediate the attachment of epithelial cells to underlying connective tissue [94]. Mutations in *COL7A1* cause dystrophic epidermolysis bullosa (DEB), and mutations in *COL17A1* cause two types of junctional epidermolysis bullosa (JEB): JEB non-Herlitz (JEB-nH) generalized and JEB-nH localized.

In the most recent classification of epidermolysis bullosa (EB), DEB is subdivided into dominant DEB (DDEB) and recessive DEB (RDEB) types; each subtype is further divided into different variants, many of them very rare [95]. Histology of the generalized type of DDEB reveals the anchoring fibrils can be normal or reduced. In contrast, in RDEB severe generalized type the anchoring fibrils are absent or rudimentary, leading to more severe phenotypes.

Skin symptoms associated with all types of DEB are present from birth. Skin fragility leads to blistering and bullae formation at sites of minor friction or trauma (Fig. 4a). Blisters and bullae can appear anywhere in the body and heal with atrophic scarring; it is also common for these patients to

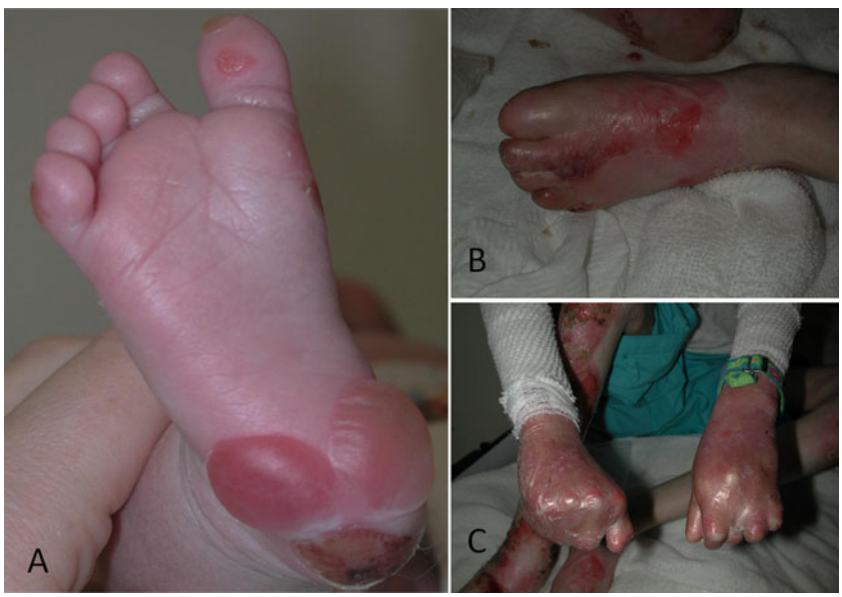

Fig. 4 Skin findings in type VII-collagen-related DEB. **a** Blisters and bullae in an affected newborn. **b**, **c** Pseudosyndactyly in a severely affected patient

develop milia (small keratin-filled cysts located under the epidermis). Dystrophic or absent nails are often observed. In RDEB, severe generalized type, patients present with different degrees of mucosal involvement. In the oral mucosa, blistering can interfere with eating and maintaining adequate oral hygiene. It can also lead to esophageal strictures, requiring dilatation in order for patients to swallow. In the eye blistering can affect conjunctiva, leading to scarring and visual impairment. Pseudosyndactyly (loss of web spaces between digits as a result of fibrous scarring) is also a common symptom of these patients (Fig. 4b, c). Other symptoms, including anemia, nutritional deficiencies, delayed puberty, dilated cardiomyopathy, osteoporosis, renal amyloidosis, and IgA nephropathy, are also reported [96, 97]. Skin surveillance is mandatory because of an increased risk of squamous cell carcinoma [98].

Patients with DDEB have a less severe phenotype. Their skin fragility is not as severe as that of patients with RDEB, and they do not typically develop pseudosyndactyly. They have lower incidences of anemia, caries, dilated cardiomyopathy, and ocular complications [96, 97]. The degree of gastrointestinal involvement is variable, and the risk of squamous cell carcinoma is lower than that associated with RDEB [98].

There are multiple rare variants of *COL7A1*-associated DEB, with characteristic clinical findings and less extracutaneous involvement; these are summarized in Fine et al. 2008 [95]. An acquired type of bullous disorder, EB acquisita (EBA), also involves collagen VII. EBA is a rare, chronic subepidermal immunobullous disorder that is more commonly seen in adults, but also reported in children. Autoantibodies to type VII collagen structures lead to the same skin fragility associated with inherited forms of DEB [99].

In JEB-nH generalized and JEB-nH localized variants, because of mutations in *COL17A1*, hemidesmosomes may be normal or reduced in size and number. Immunofluorescence mapping reveals absence of type XVII collagen in generalized JEB-nH and reduced expression in localized JEB-nH. For patients with JEB-nH generalized, skin fragility, atrophic scarring, and milia are more severe than for patients with the localized type. Patients with generalized JEB-nH can also present with focal keratoderma on palms and soles. Both variants are associated with nail changes, excessive caries, and enamel hypoplasia. Extracutaneous manifestations, including anemia, nutritional deficiencies, GI involvement, genitourinary involvement, ocular findings, and respiratory tract involvement, are more common for generalized JEB-nH [97, 98]. Squamous cell carcinomas are uncommon for these variants, but have been reported [98].

Conclusions

Because collagen is present throughout the body, collagen disorders can affect all organ systems, and overlap of clinical features is frequent. DNA diagnosis often enables the different disorders to be distinguished. DNA diagnosis is important in several clinical situations: informing parental decision-making regarding an affected pregnancy, enabling accurate prenatal counseling, avoidance of invasive diagnostic procedures (for example muscle biopsy in a type VI collagen myopathy), enabling early diagnosis and initiation of appropriate screening, and informing treatment including bone marrow transplant, which is becoming available for specific forms of epidermolysis bullosa. Knowledge of the relationship between mutation and disease is increasingly important to patient care.

Compliance with Ethics Guidelines

Conflict of Interest Rebekah Jobling, Rohan D'Souza, Naomi Baker, Irene Lara-Corrales, Roberto Mendoza-Londono, Lucie Dupuis, Ravi Savarirayan, L. Ala-Kokko, and Peter Kannu declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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