Hereditary disorders of connective tissue: A guide to the emerging differential diagnosis

Maureen Murphy-Ryan, BS[1], Apostolos Psychogios, MD[2], and Noralane M. Lindor, MD[2]

Purpose: To create a practical desk reference for clinicians focused on the differential diagnosis of individuals presenting with features that suggest an inherited disorder of connective tissue. **Methods:** We searched the medical literature for distinct clinical entities that shared clinical features with Marfan syndrome and other classical inherited disorders of connective tissue. **Results:** Thirty-six distinct heritable disorders of connective tissue were identified that have overlapping features. These disorders were organized into two matrices according to clinical characteristics and according to causative genes. **Conclusions:** A broad differential diagnosis is emerging for individuals presenting with features suggestive of altered connective tissue. Recent advances in molecular genetics have aided in the delineation of these disorders. ***Genet Med*** **2010:12(6):344–354.**

Key Words: *connective tissue, aneurysm, dissection, aorta, vascular disease*

Many clinicians have a basic knowledge of Marfan syndrome, a relatively common genetic disorder of connective tissue with clinical manifestations involving the musculoskeletal, cardiovascular, respiratory, ophthalmologic, and cutaneous systems.[1] However, it is less well known that there is an emerging and complex differential diagnosis to be considered for patients evaluated for a possible heritable disorder of connective tissue. Molecular genetic discoveries have greatly advanced the ability to correctly classify these disorders, and recent reviews have compared clinical features of subsets of the inherited connective tissue disorders.[2–5] The aim of this article was to consolidate new clinical and genetic information in an accessible, comprehensive format to aide in the diagnostic evaluation of individuals who have features that may initially raise the possibility of a connective tissue disorder. The accompanying tables will provide the majority of necessary information to develop a thorough differential diagnosis. Limited text is included to add relevant syndrome-specific information that could not be adequately captured in table format.

Background

The constitution of the normal connective tissue varies from one tissue to another, both in the specific elements—collagen, elastin, fibrillin, fibulin,[6] and others—and in the proportion of each element. Proteins that modify these component elements—such as the metalloproteinases[7] and lysyl hydroxylase 3, which act on the structure of collagen fibers, and homocysteine, which can affect the integrity of fibrillin in elastic tissues—have also been implicated in disorders of connective tissue. In addition, mutations in genes that affect protein glycosylation are also implicated in the differential diagnosis of connective tissue disorders. Because each of these elements contribute to connective tissue structure in a number of different body locations, genetic defects in a single connective tissue component may manifest in more than one organ in the body (pleiotropy). This results in clinically overlapping multisystemic findings that may make diagnosis of a specific entity especially challenging.

Recent advances in molecular diagnostics have greatly increased our appreciation of the complexity of disorders of connective tissue. The fibrillinopathies illustrate this complexity. Marfan syndrome is but one clinical entity caused by *FBN1* mutations. Depending on the nature or location of the mutation within the *FBN1* gene, different clinical entities may result including familial ectopia lentis; ascending aortic aneurysm; mitral valve, aorta, skeleton, and skin (MASS) syndrome; and Marfan syndrome. These allelic disorders have been grouped together as "fibrillinopathies" and are distinguished by their clinical presentations.[8] As the prognosis and management is quite different between the various fibrillinopathies, precision in diagnosis is important. In light of the recent rapid accumulation of knowledge in the realm of genetics of connective tissue disorders, we sought to organize the clinical and molecular features in a way that help health care professionals who regularly encounter such disorders to establish a reasonable differential diagnosis to guide clinical evaluation and genetic testing.

MATERIALS AND METHODS

We developed a graphical format to consolidate the key clinical and genetic features of heritable disorders of connective tissue. Marfan syndrome was used as a platform for comparison. Each of the clinical features of Marfan syndrome, as specified by the revised Ghent Criteria, were subjected to PubMed and OMIM literature searches to identify other Mendelian syndromes or clinical entities that shared that feature. Thirty-six different clinical entities that might share one or more of the presenting features in Marfan syndrome were identified and included in the matrices, involving more than 40 different genes or gene loci. As some of these clinical entities are very new or very rare, only limited data may be available. Boxes are marked with an "x" when that sign was fairly well established in the medical literature as a nonrandom association with that disorder. In Table 1, we present a list of clinical signs that were shared between at least two of the identified syndromes organized by organ system (available as Supplemental Digital Content 1, http://links.lww.com/GIM/A111). Table 2 shows the causative genes for these clinical entities (available as Supplemental Digital Content 2, http://links.lww.com/GIM/A112). This format best illustrates that there is no one-to-one correspondence between genes and disorders.

From [1]Mayo Medical School, Rochester, Minnesota; and [2]Department of Medical Genetics, Mayo Clinic, Rochester, Minnesota.

Noralane M. Lindor, MD, E7B Mayo Clinic, Rochester, MN 55902; E-mail: nlindor@mayo.edu.

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Table 1 Clinical features of disorders of connective tissue (also available at: http://links.lww.com/GIM/A111)

Clinical Entities	Cardiovascular							Craniofacial								
	abdominal aortic aneurysm	aneurysms of medium-sized arteries	aortic dilatation, ascending	arterial stenosis	arterial tortuosity	mitral valve prolapse	thrombosis	anterior fontanel, large or wide	cranial abnormality	ear dysmorphism	facies, characteristic	hypertelorism	midfacial hypoplasia	oral clefting (bifid uvula, cleft palate)	palate, highly arched	retrognathia/micrognathia
Aneurysms, Aortic Abdominal	x															
Arterial Tortuosity Syndrome	x	x	x	x	x						x				x	x
Bicuspid Aortic Valve with Thoracic Aortic Aneurysm			x													
Camurati-Engelmann Disease																
CATSHL Syndrome																
Congenital Contractural Arachnodactyly			x			x			x	x					x	x
Cutis Laxa, AD			x													
Cutis Laxa, AR Type I		x	x		x											
Cutis Laxa, AR Type II								x	x		x					
Cutis Laxa, X-linked					x			x			x					
Ectopia Lentis, Familial																
Ehlers-Danlos, Arthrochalasia																
Ehlers-Danlos, Cardiac Valvular						x										
Ehlers-Danlos, Classical			x			x										
Ehlers-Danlos, Dermatosporaxis								x			x					x
Ehlers-Danlos, Kyphoscoliotic			x													
Ehlers-Danlos, Progeroid											x					
Ehlers-Danlos, Spondylocheiro Dysplastic											x					
Ehlers-Danlos, Vascular	x	x									x					
Ehlers-Danlos-like Syndrome, Tenascin X						x										
Familial Thoracic Aortic Aneurysm and/or Dissection	x	x	x		x											
Fragile-X Syndrome			x			x				x	x				x	
Homocystinuria							x									
LH3 Deficiency Syndrome		x								x	x					
Loeys-Dietz Syndrome, Type I	x	x	x		x				x			x		x		
Loeys-Dietz Syndrome, Type II	x	x	x		x											
Lujan Syndrome									x		x					x
MACS Syndrome			x						x		x					x
Marfan Syndrome	x	x	x			x			x		x				x	x
MASS Phenotype			x			x			x		x				x	x
Mitral Valve Prolapse Syndrome						x										
Persistent Patent Ductus with Familial Thoracic Aneurysm			x													
Shprintzen-Goldberg Syndrome						x		x	x	x		x			x	x
Snyder-Robinson Syndrome											x			x	x	
Stickler Syndrome						x							x	x		x
Weill-Marchesani Syndrome																

Clinical Entities	Eye						Internal Organs				
	keratoconus	lens dislocation	myopia	retinal detachment	strabismus/blue sclera	vitreous abnormalities	abdominal/inguinal/diaphragmatic hernia	gastrointestinal/ genitourinary diverticula	lung manifestations	prolapse of viscera	rupture of hollow organs
Aneurysms, Aortic Abdominal											
Arterial Tortuosity Syndrome	x						x				
Bicuspid Aortic Valve with Thoracic Aortic Aneurysm											
Camurati-Engelmann Disease											
CATSHL Syndrome											
Congenital Contractural Arachnodactyly	x		x								
Cutis Laxa, AD							x	x	x	x	
Cutis Laxa, AR Type I							x	x	x		
Cutis Laxa, AR Type II											
Cutis Laxa, X-linked							x	x			
Ectopia Lentis, Familial		x	x								
Ehlers-Danlos, Arthrochalasia							x				
Ehlers-Danlos, Cardiac Valvular							x				
Ehlers-Danlos, Classical											
Ehlers-Danlos, Dermatosporaxis							x				x
Ehlers-Danlos, Kyphoscoliotic											
Ehlers-Danlos, Progeroid											
Ehlers-Danlos, Spondylocheiro Dysplastic											
Ehlers-Danlos, Vascular									x		x
Ehlers-Danlos-like Syndrome, Tenascin X								x	x		
Familial Thoracic Aortic Aneurysm and/or Dissection							x				
Fragile-X Syndrome					x						
Homocystinuria		x	x								
LH3 Deficiency Syndrome			x								
Loeys-Dietz Syndrome, Type I			x	x	x		x		x		x
Loeys-Dietz Syndrome, Type II			x	x	x		x		x		x
Lujan Syndrome											
MACS Syndrome											
Marfan Syndrome		x	x	x			x		x		
MASS Phenotype			x	x			x				
Mitral Valve Prolapse Syndrome											
Persistent Patent Ductus with Familial Thoracic Aneurysm											
Shprintzen-Goldberg Syndrome											
Snyder-Robinson Syndrome											
Stickler Syndrome			x	x		x					
Weill-Marchesani Syndrome		x	x	x		x					

Clinical Entities	Musculoskeletal														
	arachnodactyly	brachydactyly	hyperostosis	joint laxity/subluxations	joint contractures	limb/bone pain	Marfanoid habitus	motor developmental delay	muscular hypoplasia	muscular hypotonia	osteopenia, osteoporosis/ fractures	pectus deformities, scoliosis	precocious osteoarthritis	protrusio acetabuli	short stature
Aneurysms, Aortic Abdominal															
Arterial Tortuosity Syndrome				x	x					x					
Bicuspid Aortic Valve with Thoracic Aortic Aneurysm															
Camurati-Engelmann Disease			x		x	x	x					x			
CATSHL Syndrome	x				x		x					x			
Congenital Contractural Arachnodactyly	x				x		x	x	x		x	x		x	
Cutis Laxa, AD															
Cutis Laxa, AR Type I				x							x				
Cutis Laxa, AR Type II				x				x		x	x				
Cutis Laxa, X-linked					x			x		x	x	x			
Ectopia Lentis, Familial															
Ehlers-Danlos, Arthrochalasia				x							x	x			x
Ehlers-Danlos, Cardiac Valvular				x											
Ehlers-Danlos, Classical				x								x			
Ehlers-Danlos, Dermatosporaxis				x											x
Ehlers-Danlos, Kyphoscoliotic				x				x		x		x			
Ehlers-Danlos, Progeroid				x						x	x				x
Ehlers-Danlos, Spondylocheiro Dysplastic				x		x				x	x				x
Ehlers-Danlos, Vascular				x	x										
Ehlers-Danlos-like Syndrome, Tenascin X				x											
Familial Thoracic Aortic Aneurysm and/or Dissection												x			
Fragile-X Syndrome				x			x	x				x			
Homocystinuria	x			x			x				x	x			
LH3 Deficiency Syndrome	x				x			x			x	x			x
Loeys-Dietz Syndrome, Type I	x			x			x					x			
Loeys-Dietz Syndrome, Type II	x			x			x					x			
Lujan Syndrome	x			x			x			x					
MACS Syndrome				x							x	x			x
Marfan Syndrome	x			x	x		x		x			x		x	
MASS Phenotype	x			x	x		x					x		x	
Mitral Valve Prolapse Syndrome				x											
Persistent Patent Ductus with Familial Thoracic Aneurysm															
Shprintzen-Goldberg Syndrome	x			x	x		x	x			x	x			
Snyder-Robinson Syndrome	x						x			x	x				
Stickler Syndrome				x								x	x	x	
Weill-Marchesani Syndrome		x			x										x

Clinical Entities	Neurological					Skin				
	brain structural anomalies	dural ectesia	mental retardation/developmental delay	psychiatric disorders	sensorineural hearing loss	atrophic scars/delayed wound healing	easy bruising	hyperelastic skin	loose, redundant, inelastic skin	striae
Aneurysms, Aortic Abdominal										
Arterial Tortuosity Syndrome								x		
Bicuspid Aortic Valve with Thoracic Aortic Aneurysm										
Camurati-Engelmann Disease										
CATSHL Syndrome			x		x					
Congenital Contractural Arachnodactyly										x
Cutis Laxa, AD									x	
Cutis Laxa, AR Type I									x	
Cutis Laxa, AR Type II			x						x	
Cutis Laxa, X-linked			x						x	
Ectopia Lentis, Familial										
Ehlers-Danlos, Arthrochalasia								x		
Ehlers-Danlos, Cardiac Valvular						x	x	x		
Ehlers-Danlos, Classical						x	x	x		
Ehlers-Danlos, Dermatosporaxis						x	x	x		
Ehlers-Danlos, Kyphoscoliotic								x		
Ehlers-Danlos, Progeroid			x			x	x	x		
Ehlers-Danlos, Spondylocheiro Dysplastic						x	x	x		
Ehlers-Danlos, Vascular						x	x			
Ehlers-Danlos-like Syndrome, Tenascin X							x	x		
Familial Thoracic Aortic Aneurysm and/or Dissection										
Fragile-X Syndrome			x	x						
Homocystinuria			x	x						x
LH3 Deficiency Syndrome			x		x		x			
Loeys-Dietz Syndrome, Type I		x				x	x			
Loeys-Dietz Syndrome, Type II		x				x	x			
Lujan Syndrome	x		x	x						
MACS Syndrome									x	
Marfan Syndrome		x					x			x
MASS Phenotype							x			x
Mitral Valve Prolapse Syndrome										
Persistent Patent Ductus with Familial Thoracic Aneurysm										
Shprintzen-Goldberg Syndrome	x		x							
Snyder-Robinson Syndrome			x							
Stickler Syndrome					x					
Weill-Marchesani Syndrome										

Table 2 Genes causing disorders of connective tissue (also available at: http://links.lww.com/GIM/A112)

Clinical Entities	OMIM #	ACTA2	ADAMTS2	ADAMTS10	ADAMTSL4	ATP6V0A2	ATP7A	B4GALT7	CBS	COL1A1	COL1A2	COL2A1	COL2A2	COL3A1	COL9A1	COL5A1, COL5A2	COL11A1	COL11A2	ELN	FAA1 locus 11q23-q24	FBLN4	FBLN5	FBN1	FBN2	FGFR3	FMR1	LTBP-2	MED12	MYH11	NOTCH1, KCNJ2, other	P5CS	PLOD1	PLOD3	PYCR1	RIN2	SLC2A10	SLC39A13	SMS	TAAD1 locus 5q13-q14	TGFB1	TGFBR1	TGFBR2	TNXB	UPF3B	unknown
Aneurysms, Aortic Abdominal*	#100070												AD,M																																
Arterial Tortuosity Syndrome	#208050																																	AR											
Bicuspid Aortic Valve with Thoracic Aortic Aneurysm	#109730																											AD?																
Camurati-Engelmann Disease	#131300																																					AD					?		
CATSHL Syndrome	#610474																						AD																					
Congenital Contractural Arachnodactyly	+121050																					AD																					?		
Cutis Laxa, Autosomal Dominant	#123700																AD				AD																						?		
Cutis Laxa Type I, Autosomal Recessive	#219100																			AR	AR																						?		
Cutis Laxa Type II, Autosomal Recessive	#219200					AR																							AR			AR												
Cutis Laxa, X-linked	#304150						X																																						
Ectopia Lentis, Familial	#129600				AR																	AD				AR															AD			AR		
Ehlers-Danlos, Arthrochalasia	#130060								AD	AD																																		
Ehlers-Danlos, Cardiac Valvular	#225320									AR																																			
Ehlers-Danlos, Classical	#130010														AD																														
Ehlers-Danlos, Dermatosporaxis	#225410		AD																																									
Ehlers-Danlos, Kyphoscoliotic	#225400																														AR													
Ehlers-Danlos, Progeroid	#130070							AR																																				
Ehlers-Danlos, Spondylocheiro Dysplastic	#612350																																		AR									
Ehlers-Danlos, Vascular	#130050												AD, AR																																
Ehlers-Danlos-like Syndrome, Tenascin-X	#606408																																									AR			
Familial Thoracic Aortic Aneurysm and/or Dissection	(multiple)	AD																	AD			AD					AD									AD		AD	AD					
Fragile-X Syndrome	#300624																							X																				
Homocystinuria	+236200								AR																																			
LH3 Deficiency Syndrome	#612394																														AR													
Loeys-Dietz Syndrome Type I	#609192 TGFBR1 #610168 TGFBR2																																							AD	AD				
Loeys-Dietz Syndrome Type II	#608967 TGFBR1 #610380 TGFBR2																																							AD	AD				
Lujan Syndrome	#309520																										X															X		
MACS Syndrome	*610222																																	AR										
MASS Phenotype	#604308																					AD																						
Marfan Syndrome	#154700																					AD																						
Mitral Valve Prolapse Syndrome	#157700*																					AD?																					?		
Persistent Patent Ductus Arteriosus with Familial Thoracic Aneurysm	#132900																										AD																	
Shprintzen-Goldberg Syndrome	#182212																					AR, *dn*																					AR, *dn*		
Snyder-Robinson Syndrome	#309583																																		X										
Stickler Syndrome	#108300 (COL2A1)										AD	AD		AR		AD	AD																									?		
Weill-Marchesani Syndrome	#608328 AD #277600 AR			AR																		AD																						

RESULTS

Listed alphabetically below are additional facts to supplement the main body of information in the tables.

Aneurysms, aortic abdominal

Aneurysms, aortic abdominal (AAA) may be present in isolation or as part of a syndrome such as vascular Ehlers-Danlos syndrome (EDS), Loeys-Dietz syndrome, or Marfan syndrome. Three loci for isolated AAA have been identified: 19q13, 4q31, and 9p21. However, most AAAs are of multifactorial etiology.[9]

Arterial tortuosity syndrome

Arterial tortuosity syndrome is distinguished from forms of EDS by the generalized tortuosity of the arterial bed. Arterial tortuosity syndrome may include occasional manifestations such as inguinal and diaphragmatic hernias, intestinal elongation, keratoconus, macrocephaly, arachnodactyly, joint contractures, and hypotonia in addition to the more common features listed in Table 1 (Supplemental Digital Content 1, http://links.lww.com/GIM/A111). Characteristic facial features can include a distinctive elongated facies, micrognathia, small mouth, high arched palate, low set ears, long philtrum, beaked nose, down-slanting palpebral fissures, long ears, and sagging cheeks.[10,11]

Bicuspid aortic valve with thoracic aortic aneurysm

Bicuspid aortic valve (BAV) with thoracic aortic aneurysm (TAA) is often associated with aortic calcification,[12] and research in mice and humans suggests that these conditions have a common etiology through genes such as *NOTCH1*.[13–15] Individuals with normal tricuspid aortic valves in families with BAV/TAA can also be at risk for aortic valve calcification or TAA, especially if they carry a known familial mutation in *NOTCH1*.[16] Clinical management suggestions for BAV/TAA may include pharmacologic therapy with beta-blockers and angiotensin converting enzyme inhibitors or angiotensin receptor blockers, aggressive hypertension control, annual imaging of ascending aortas with diameters >4.0 cm, and elective surgical repair of dilated aortas >5.0 cm in diameter or >4.5 cm with additional risk factors.[16]

Camurati-Engelmann disease

Camurati-Engelmann disease (CED) is a rare bone dysplasia, also known as progressive diaphyseal dysplasia, within the group of craniotubular hyperostosis disorders resulting from activating mutations in transforming growth factor β1 (TGF-β1), a bone growth promoter. Skeletal scintigraphy can be used detect CED even at early stages. In addition to pain in the extremities (the most common symptom), other diagnostic clinical features include a waddling gate, easy fatigability, and muscle weakness. Reduced subcutaneous fat and cranial nerve defects including hearing loss are reported in a subset of CED patients.[17] CED and Ribbing disease (OMIM no. 601477) are phenotypic variations of the same genetic disorder.

CATSHL syndrome

CATSHL syndrome stands for "camptodactyly, tall stature, and hearing loss." This rare syndrome was identified in a family with a missense mutation in the tyrosine kinase domain of *FGFR3*, predicted to result in a partial loss of function.[18] Generally, strong genotype-phenotype correlations characterize *FGFR*-related disorders. Mutations in *FGFR3* predominantly affect bones that develop by endochondral ossification, whereas mutations in closely related genes, *FGFR1* and *FGFR2*, exert their primary effects on bones developing by intramembranous ossification. *FGFR3* mutations may promote (as in the case of CATSHL) or inhibit (as in the achondroplasias) endochondral bone growth.

Congenital contractural arachnodactyly

Congenital contractural arachnodactyly (CCA) is also known as Beals-Hecht syndrome. The classic ear dysmorphism involves a "crumpled" appearance with a folded upper helix, although this feature is not always present. Medial degeneration of the proximal aorta leading to aortic aneurysm and possibly dissection is occasionally seen in CCA and should be closely monitored. Contractures of the knees and ankles may be present at birth and often improve with age. Flexion contractures in the small joints of the digits also occur, and hip contractures, thumb adduction, and clubfoot are less common. Paradoxical patellar laxity, keratoconus, and pyeloureteral junction stenosis have also been reported. A rare severe/lethal form of CCA has also been identified, which includes severe cardiovascular and gastrointestinal symptoms.[19] Significant clinical differences have not been observed between FBN2-mutation-positive and FBN2-negative patients, suggesting locus heterogeneity.[20] Of FBN2-positive patients, frequency of joint dislocation is significantly higher with FBN2 missense mutations compared to splice-site mutations.[21] The proportion of de novo cases is unknown, but many patients diagnosed with CCA have an affected parent.[22]

Cutis laxa, autosomal dominant

Cutis laxa, autosomal dominant (ADCL) was originally thought to involve minor systemic manifestations; however, thoracic aortic aneurysmal disease, inguinal hernias, and emphysema are now recognized as serious potential clinical manifestations.[23–25]

Cutis laxa, autosomal recessive type I

Cutis laxa, autosomal recessive AR type I (ARCLI) has the poorest prognosis of the cutis laxas and is thought to be less common that ARCLII. The lung manifestations in ARCLI involve severe cardiopulmonary lesions, including infantile emphysema and/or supravalvular aortic stenosis. Clinical differences exist between ARCLI caused by *FBLN4* and *FBLN5*; for example, only *FBLN4* has been linked to collagen-related abnormalities such as bone fragility and aneurysms of medium-sized arteries.[26,27] The genetic basis for the majority of ARCLI cases remains unknown. Recently, Morava et al.[28] published a comprehensive comparison of the autosomal recessive cutis laxa syndromes.

Cutis laxa autosomal recessive Type II

Cutis laxa autosomal recessive Type II (ARCLII) often includes a characteristic facies with down-slanting palpebral fissures, a short nose, and a small mouth. Central nervous system and systemic involvement is variable, and microcephaly is often present. The skin phenotype tends to attenuate with age, whereas neurological symptoms may emerge or worsen later in life. The large anterior fontanel exhibits late closure. Many patients with ARCLII have a congenital defect of glycosylation (CDG type II, ATP6V0A2 mutation), whereas others have defects in proline biosynthesis associated with wrinkly skin, osteopenia, and progeroid appearance (PYCR1, P5CS mutations).[29,30] Analysis of apolipoprotein C-III isoelectric focusing, demonstrating a disturbance of *O*-glycosylation, is diagnostic, and isoelectric focusing of transferrin may also be disturbed. Evaluation of protein glycosylation status is recommended for all children presenting with congenital wrinkled skin/cutis laxa, late fontanel closure, developmental delay, and variable CNS

involvement. Wrinkly skin syndrome (OMIM no. 278250) and ARCLII are part of a spectrum of phenotypic variation caused by defects in a single gene.[31] The phenotype may also overlap with gerodermia osteodysplasia (OMIM no. 231070) and de Barsy syndrome (OMIM no. 219150).

Cutis laxa, X-linked

Cutis laxa, X-linked (XLCL) is also known as occipital horn syndrome, due to the presence of diagnostic bilateral, symmetric wedge-shaped bony outgrowths beside the foramen magnum at the site of trapezius and sternocleidomastoid muscle attachment. There may be hyperextensibility of wrist and interphalangeal joints but contractures of elbow and knee. Facial features may include a hooked nose and long philtrum, which are characteristic of cutis laxa in general. Failure to thrive may be due to chronic diarrhea, malabsorption, congenital hydronephrosis, or urethral and bladder diverticulae.[27] Mental retardation may or may not be present. XLCL is a copper transport disease allelic with Menkes Disease (OMIM no. 309400), often sharing the feature of brittle hair. Serum ceruloplasmin may be low or normal, and lysyl oxidase activity may also be decreased.

Ectopia lentis, familial

Ectopia lentis, familial is caused by mutations in *FBN1* that are predicted to disrupt normal disulfide bond formation and native protein structure.[30] Glaucoma can be present secondary to lens subluxation. Although mutations in *FBN1* result in autosomal dominant isolated ectopia lentis, autosomal recessive variations have also been described, some of which are due to mutations in *LTBP-2*[32] and *ADAMTSL4*[33]. Three families with autosomal recessive ectopia lentis due to mutations in *LTBP-2* exhibited mild-to-moderate osteopenia in carriers and affected individuals as well as a high arched palate, although no other features overlapping with Marfan syndrome were present, whereas all cases with *LTBP-2*-null mutations in a fourth family had Marfanoid skeletal and joint features without osteopenia.[32] Ectopia lentis may also occur in combination with mild skeletal symptoms, mitral valve prolapse, or nonprogressive aortic root dilatation, especially when due to mutations in *FBN1*. Some patients diagnosed with familial ectopia lentis may develop aortic aneurysm later in life and could be considered to have late forms of Marfan syndrome. Ectopia lentis has also been identified in a subset of patients with TGFBR2 mutations and minimal skeletal findings.[34]

Ehlers-Danlos syndrome, arthrochalasia type (EDS type VIIA, VIIB)

Ehlers-Danlos syndrome, arthrochalasia type (EDS type VIIA, VIIB) is distinguished from other types of EDS by a high frequency of early-onset congenital hip dislocation, extreme joint laxity with recurrent joint subluxations (large and small, particularly of the hips), and minimal skin involvement. Hyperelasticity of skin is usually mild when present. Individuals with arthrochalasia type of EDS may exhibit a history of frequent fractures, a phenotypic overlap with osteogenesis imperfecta, and short stature may also be associated.[35] The pathologic basis of this disorder is an inability of α-1 or α-2 chains of type I procollagen to be converted to collagen due to mutations altering the procollagen cleavage site.

Ehlers-Danlos syndrome, cardiac valvular type

Ehlers-Danlos syndrome, cardiac valvular type can have the typical skin and joint involvement of classical EDS (although not always) as well as an increased risk for cardiac valvular involvement. This is a very rare variant of EDS, with only a handful of patients having been described to date. The molecular basis is a complete absence of proα2(I) collagen chains, resulting from homozygosity or heterozygosity for *COL1A2* null mutations.[36] Cardiac-valvular EDS is a relatively mild variant on the spectrum of clinical phenotypes resulting from *COL1A2* mutations, which also includes osteogenesis imperfecta. Unlike for osteogenesis imperfecta, no skeletal abnormalities are observed in cardiac valvular EDS. The cardiac valvular type of EDS may overlap with mild form of hypermobility type EDS during childhood, with cardiac valvular complications emerging during adulthood.[37]

Ehlers-Danlos syndrome, classical type (EDS type I, II)

Ehlers-Danlos syndrome, classical type (EDS type I, II) features skin that is often characterized as smooth and velvety. Atrophic scarring is a key dermatological finding. Typical facial features may include epicanthic folds, excess eyelid skin, and a prematurely aged appearance. It is distinct from the hypermobility type, which has much more subtle skin manifestations. Bruising may be the presenting symptom in pediatric patients.[38] Type V collagen defects (COL5A1 and COL5A2) are identified in ~50% of classical EDS cases. For the major and minor diagnostic features of the six commonly recognized types of EDS, see the revised nosology created by the Ehlers-Danlos National Foundation (USA) and Ehlers-Danlos Support Group (UK).[39]

Ehlers-Danlos syndrome, dermatosparaxis type (EDS type VIIC)

Ehlers-Danlos syndrome, dermatosparaxis type (EDS type VIIC) is characterized by extreme skin fragility. Patients with dermatosparaxis type EDS may exhibit a delayed onset of a typical phenotype, and at-risk infants may thus require follow-up during the first 2 years. Facial dysmorphism may include eyelid fullness, epicanthal folds, and down-slanting palpebral fissures. Blue sclera may be observed. The deciduous and permanent dentition may exhibit a variety of abnormalities.[40] Similar to the arthrochalasia type of EDS, the dermatosparaxis type is caused by deficiencies in the processing of procollagen into collagen. Although the arthrochalasia type of EDS is caused by mutations in COL1A1 or COL1A2, the dermatosparaxis type involves mutations in the gene for the protease ADAMTS-2.[41]

Ehlers-Danlos syndrome, kyphoscoliotic type (EDS type VI)

Ehlers-Danlos syndrome, kyphoscoliotic type (EDS type VI) is distinguished from other types of EDS by gross motor developmental delay resulting from muscular hypotonia combined with joint laxity. Because of these clinical features, the differential diagnosis of infants with kyphoscoliotic EDS may initially include congenital muscular dystrophies, congenital myopathies, and lower motor neuron diseases. Adolescents with this form of EDS may present with generalized muscle weakness in addition to the reduced muscle tone in rest of hypotonia.[42] Kyphoscoliotic EDS should be considered if results of neuromuscular tests come back normal, contractures are absent, and Marfanoid habitus is present. Diagnosis of kyphoscoliotic EDS can be biochemically confirmed by a significantly increased ratio of total urinary lysyl pyridinoline to hydroxylysyl pyridinoline.[43,44]

Ehlers-Danlos syndrome, progeroid type

Ehlers-Danlos syndrome, progeroid type is a congenital disorder of glycosylation, such as type II AR cutis laxa.[45] As its name suggests, this type of EDS may be characterized by a distinctive progeroid facies as well as facial skin wrinkling, fine curly hair, scanty eyebrows and eyelashes, and downslanting palpebral fissures. Developmental delay and skeletal abnormalities are also typical. Skin may be loose but still elastic. A spectrum of severity is seen in the skin phenotype and may be as mild as slight facial wrinkling and no remarkable skin laxity.[46]

Ehlers-Danlos syndrome, spondylocheirodysplastic type

Ehlers-Danlos syndrome, spondylocheirodysplastic type (SCD-EDS) features skin that is described as smooth, velvety, thin, fragile, and translucent with atrophic (cigarette-paper) scarring, as in classical EDS. Over the hands and feet, the skin can appear wrinkled and prematurely aged, and the fingers are described as slender and tapering. Small joint contractures and substantial atrophy of the thenar and hypothenar muscles may limit fine motor skills and gives the hands a similar appearance to that seen in LH3 deficiency syndrome. Growth retardation occurs postnatally. Protruding eyes with down-slanting palpebral fissures and bluish sclera are characteristic of this disorder. Flat feet (pes planus), a common feature of connective tissue disorders, is also characteristic of SCD-EDS. Persons with SCD-EDS may exhibit a distinctive waddling gait and experience pain in the knees and hips when walking.[47]

Ehlers-Danlos syndrome, vascular type (EDS type IV)

Ehlers-Danlos syndrome, vascular type (EDS type IV) stems from a reduction or absence of normal type III collagen within the tunica media of large elastic arteries. This predisposes persons to abnormalities in major blood vessels and resultant aneurysms, spontaneous vascular rupture, dissections, and arteriovenous fistulas. Individuals with vascular EDS exhibit extreme bruisability. Commonly ruptured hollow organs include the intestines, particularly the colon, and the uterus, making pregnancy highly risky for women with vascular EDS. Lung manifestations, although less common, have recently been reported and may include recurrent hemoptysis, spontaneous pneumothorax, or bulla and bleb formation. Distinctive facial features inconsistently may include acrogeria, characterized as a slender facies with prominent bones; sunken cheeks; thin, pinched nose; bulging eyes; and thin lips.[48,49] Skin hyperelasticity and joint hypermobility are limited in vascular EDS. The majority of familial vascular EDS cases are inherited in an autosomal dominant fashion, although a case of recessively inherited vascular EDS has been identified.[50] There is significant phenotypic overlap between vascular EDS and familial arterial aneurysms. It is important to distinguish between Loeys-Dietz Syndrome and vascular EDS because of the significantly higher rate of intraoperative mortality associated with the latter.[51]

Ehlers-Danlos-like syndrome, tenascin X deficiency

Ehlers-Danlos-like syndrome, tenascin X (TNX) deficiency is characterized by hypermobile joints, hyperelastic skin, and very easy bruising but without the atrophic scarring or poor wound healing seen in classical EDS. Other significant medical problems occurring in persons with this disorder include severe diverticular intestinal disease (e.g., pancolonic) with ruptured diverticula, gastrointestinal bleeding, rectal prolapse, mitral valve prolapse requiring valve replacement, and chronic obstructive airway disease. Abnormal nerve conduction studies indicating polyneuropathy are common and significantly more frequent in tenascin-X deficient EDS compared with other forms of EDS.[52] Although this is a recessive condition, up to 2/3 of females heterozygous for TNX deficiency may have isolated joint hypermobility. Less invasive alternatives to endoscopy should be considered for patients with TNX deficient EDS because of the theoretical risk of bowel perforation. Baseline pulmonary testing is recommended for all patients with TNX deficient EDS, and smoking patients should be strongly encouraged to stop because of the risk for COPD.[53] Contiguous gene deletions involving both tenascin X and 21-hydroxylase genes can result in congenital adrenal hyperplasia with tenascin X deficiency.[54,55]

Familial thoracic aneurysm and/or dissection

Familial thoracic aneurysm and/or dissection (FTAAD) results in heritable aortic dilatation, aneurysm, and dissection.[56] Cerebral vessels may also be affected with fusiform aneurysms or tortuosity. Multiple genes, the majority of which act in an autosomal dominant manner, cause FTAAD, and linkage to other loci indicates that additional genes await discovery. Smooth muscle cell contraction has been found to be important in maintaining the structural integrity of the thoracic/ascending aorta, and mutations in the genes coding for smooth muscle cell α-actin (*ACTA2*) and β-myosin heavy chain (*MYH11*) have been identified as causes of FTAAD.[57] Mutations in *ACTA2* are the most common cause of FTAAD and may be associated with livedo reticularis, iris flocculi, PDA, and BAV. FTAAD caused by TGBFR mutations often involves skeletal manifestations of a connective tissue disorder (such as joint hypermobility, pes planus, dolichocephaly, or a highly arched palate) that do not meet diagnostic criteria for a particular syndrome. Differences in clinical presentation between individuals with FTAAD due to TGFBR1 and TGFBR2 have been identified, including an increase in cancer incidence with TGFBR1 compared with TGFBR2 and better survival for women with vascular disease due to TGFBR1 mutation with no gender difference seen in TGFBR2.[58] An inclusive overview of the molecular basis of FTAAD was published by Milewicz et al.[59] in 2008.

Fragile-X syndrome

Fragile-X syndrome, also known as Martin-Bell syndrome, is the most common cause of X-linked mental retardation. The syndrome includes a variety of clinical features of disordered connective tissue, and skin and cardiac tissues from individuals with Fragile-X syndrome demonstrate elastin fibers that are aberrantly distributed and structured.[60,61] Pes planus is a common musculoskeletal finding in addition to those listed in Table 1 (Supplemental Digital Content 1, http://links.lww.com/GIM/A111). Facial features may be subtle; the characteristic facies is long with a high forehead, large jaw and prominent chin, and ears are characteristically large and low set. Strabismus (but not blue sclera) was present in roughly half of affected individuals in one study.[60] Affected individuals may display features of autism. Behavioral-cognitive manifestations most commonly include a combination of poor eye contact, perseverative speech, echolalia, poor attention span, hyperactivity, and unusual hand mannerisms; a patient who presents with this characteristic facies, joint laxity, macroorchidism, a family history of mental retardation, and any of the psychiatric manifestations listed above should be evaluated for Fragile-X syndrome. Female Fragile X premutation carriers are at risk for premature ovarian failure.

Premutations are also associated with a syndrome of tremor and ataxia.[62]

Homocystinuria

Homocystinuria is due to cystathionine beta-synthase deficiency (CBS). There is a high risk for morbidity and mortality due to vascular thrombosis and stroke.[63] Clinical clues to the diagnosis include generalized hypopigmentation, pancreatitis, malar flush, and livedo reticularis. Subluxation of the lens is usually downward in homocystinuria, whereas in Marfan syndrome, the lens is generally dislocated upward. Neuropsychiatric disease is common in untreated patients.

LH3 deficiency syndrome

LH3 deficiency syndrome can manifest with a characteristic facies of shallow orbits, a small nose, down-turned mouth corners, a flat facial profile, and low-set, simplified ears. Osteopenia and fractures may be present, and growth retardation is both prenatal and postnatal. In addition to the features listed in Table 2 (Supplemental Digital Content 2, http://links.lww.com/GIM/A112), nonscarring skin blistering, hypoplastic nails, spontaneous hemorrhage, and cataracts were present. Progressive scoliosis was identified but not pectus deformities. Clubfoot (talipes equinovarus), small joint contractures, and atrophy of the thenar and hypothenar muscles are similar to the spondylocheirodysplastic form of EDS. The clinical features in LH3 (lysyl hydroxylase 3) deficiency are thought to stem from the loss of the glucosyltransferase activity of LH3, which normally modifies the pyridinoline crosslinks of collagen extracellularly via hydroxylysine glycosylation. Thus, the absence of the disaccharide derivative of pyridinoline (Glc-Gal-PYD) in urine is biochemically diagnostic but not yet clinically available.[64]

Loeys-Dietz syndrome

Loeys-Dietz syndrome has a continuum of presentations that generally include both vascular and skeletal findings and is divided into two types based on the third major system involved. Craniofacial findings are seen particularly in LDS type I, which accounts for about three quarters of LDS. Cutaneous findings are seen in the quarter of LDS patients diagnosed with LDS II. These features of organ rupture and vascular events are similar to those seen in vascular EDS. As in classical EDS, the skin may be described as translucent and velvety in LDS II. Genotype-phenotype correlations do not explain the distinction between LDS I and LDS II. *TGFBR1* mutations account for 25% of LDS patients and *TGFBR2* mutations account for 75% of LDS patients with no correlation to type.[65] In both types of LDS, the vascular manifestations tend to be more severe than in Marfan syndrome and require more aggressive screening and treatment. Pneumothorax is the primary lung manifestation of Loeys-Dietz syndrome. Organs including the spleen, bowel, and uterus are at risk for rupture. Hernias are often recurrent. In addition to dural ectasia, neuroradiologic findings may include Arnold-Chiari type I manifestation, but this may be relatively rare. A minority of LDS patients will have developmental delay.

Lujan syndrome

Lujan syndrome is also known as Lujan-Fryns syndrome. The psychiatric manifestations may include a combination of hyperactivity, emotional lability, shyness, aggressiveness, autistic mannerisms, and psychoses.[66] The major structural defect of the brain is some degree of corpus callosum agenesis. The characteristic facies of Lujan syndrome is long and thin with a tall forehead, short philtrum and sometimes micrognathia. Other distinctive features not mentioned in Table 2 include a hypernasal voice and macrocephaly. For more information on the differential diagnosis for Lujan Syndrome, see Van Buggenhout and Fryns[67] and Staholpu et al.[68] FG syndrome type 1, also known as Opitz-Kaveggia syndrome type 1, is allelic to Lujan syndrome[69] and shares many clinical features, but none that are characteristically marfanoid. Anal anomalies or constipation are restricted to FG Syndrome, and tall stature, long hands and fingers, and hypernasal speech resulting from a high nasal root are more characteristic of LS.[70] Lujan syndrome and FG syndrome are caused by mutations in *MED12*. Mutations in *UPF3B* have also been identified in families with Lujan-Fryns phenotype and the FG phenotype.[71]

MACS syndrome (macrocephaly, alopecia, cutis laxa, and scoliosis)

MACS syndrome (macrocephaly, alopecia, cutis laxa, and scoliosis) is a newly described hereditary disorder of connective tissue based on three members of two related families.[72] The clinical presentation is expected to evolve as more individuals with *RIN2* mutations are identified. Macrocephaly and retrognathia are the predominant cranial abnormalities. Alopecia refers to the sparse scalp hair seen in this disorder. Cutis laxa is most notable in the face and mild ichthyosis may also be present. Severe scoliosis appears in the second decade of life (not at birth as in kyphoscoliotic EDS), resulting in short stature. The characteristic facies includes downslanting palpebral fissures, puffy eyelids, sagging cheeks, and everted lower lip. Ortho- and periodontal manifestations include abnormal positioning of the teeth (irregularly placed or unerupted) and gingival hyperplasia. The cutaneous phenotype becomes more pronounced with age in contrast to ARCLII, in which skin manifestations attenuate over time. Skin biopsy of affected individuals revealed fibulin-5 deficiency and a decrease in dermal microfibrils. Facial features resemble GAPO (growth retardation, pseudoanodontia, optic atrophy) syndrome (OMIM no. 230740), a rare autosomal recessive disorder that is phenotypically more severe and includes eye abnormalities, and the dermatosparaxis type of EDS, which also shares gingival hyperplasia but differs in having transparent, easy bruising skin.

Marfan syndrome

The diagnosis of Marfan syndrome is a clinical diagnosis, relying on the revised Ghent consensus criteria. The diagnosis requires major clinical signs in at least two systems and milder or less specific clinical signs in a third system.[73] Skeletal findings include tall stature relative to other family members (attributed at least in part to disproportionately long limbs), long digits (arachnodactyly), anterior chest deformity including protrusion (pectus carinatum) or sunken appearance (pectus excavatum) of the sternum and anterior ribs which is related to overgrowth of ribs, joint laxity or contractures, scoliosis, and craniofacial manifestations including highly arched palate, crowded teeth, and overbite. Dural ectasia is a major diagnostic clinical criterion involving the lumbosacral spine. Ophthalmologic findings include myopia, lens subluxation (ectopia lentis), and increased axial globe length and corneal flatness. Cardiovascular findings include mitral valve prolapse, mitral regurgitation, aortic regurgitation, and dilatation of the aortic root at the level of sinuses of Valsalva that may result in an aneurysm and/or dissection. Cutaneous features include striae and recurrent hernia formation. Respiratory involvement may manifest as pulmonary blebs, which predispose to pneumothorax. *FBN1* mutations are inherited in about two-thirds of cases and rise de novo in the remainder. Hundreds of *FBN1* mutations have been

described, with the number continuing to grow. Few genotype-phenotype correlations have been established because of the extreme allelic heterogeneity within Marfan syndrome and genetically related disorders.[74–77] Although there is no known genetic heterogeneity in Marfan Syndrome, *TGFBR2* mutations have also been recognized in patients with Marfan-like phenotypes. Clinical outcomes appear similar to those of patients with *FBN1* mutations, with prognosis in either group depending more on the clinical disease expression and treatment than the responsible gene. Patients with *FBN1* mutations were found to have more extensive skeletal involvement, whereas patients with *TGFBR2* mutations had more severe aortic phenotypes overall.[34]

MASS phenotype

MASS phenotype indicates the involvement of the MASS. The aortic enlargement is borderline and nonprogressive, and the skin and skeletal findings are nonspecific. These clinical characteristics overlap significantly with those of Marfan syndrome and provide clear evidence of a systemic extracellular matrix defect but are not sufficient for a diagnosis of Marfan syndrome. Thus, the MASS phenotype is part of the clinical continuum of *FBN1* disorders that ranges from Marfan syndrome to isolated features such as ectopia lentis.[78] Consequently, it is difficult to distinguish MASS phenotype from the early stages of Marfan syndrome when assessing individuals, particularly children, in the absence of family history. Intermittent cardiovascular monitoring is therefore indicated.

Mitral valve prolapse syndrome

Mitral valve prolapse (MVP) syndrome refers to cases of idiopathic MVP in which other cardiac and connective tissue disorders have been ruled out. MVP syndrome is associated with systemic features that may include chest pain, dyspnea, thoracic cage deformity (including narrow A-P diameter), dysrhythmia, mild joint laxity, and long limbs. Prolapse occurs when the leaflets of the mitral valve billow into the left atrium and is estimated to be present in 2.4% of the general population, exhibiting age- and sex-dependent penetrance.[79] MVP may be sporadic or familial, isolated, or as part of a syndrome.[80] To date, no specific genes for MVP have been described, although three autosomal and one X-linked loci have been identified. Prognosis in MVP syndrome is better than for MVP in Marfan syndrome, with significantly lower risk for mitral regurgitation.

Persistent patent ductus arteriosis with familial thoracic aneurysm

Persistent patent ductus arteriosis with familial thoracic aneurysm (PDA with FTA) is a monogenic pathophysiologic entity within the heterogenous group of TAA disease. It is caused by mutations in a specific region of the smooth muscle cell myosin heavy chain gene *MYH11*, which are associated with marked aortic stiffness even in nonsymptomatic individuals with the disease haplotype.[81–83] Risk in patients with PDA with FTA may be assessed through noninvasive measurement of aortic compliance and distensibility using MRI. FTA without PDA is also caused by *MYH11* mutations. *MYH11* is only rarely involved in sporadic isolated PDA.[84]

Shprintzen-Goldberg syndrome

Shprintzen-Goldberg syndrome (SGS) shares many clinical manifestations with MFS and LDS, suggesting that SGS may also act through disturbance of TGF-β signaling pathways, although no unique genetic loci have yet been established. The identification of *TGFBR1*, *TGFBR2*, and *FBN1* mutations in some patients diagnosed with SGS suggests that recognition of SGS as a separate pathogenetic entity may be inappropriate, although the issue continues to be controversial.[85–87] The characteristic facies in SGS can include hypertelorism, down-slanting palpebral fissures, a highly arched palate, micrognathia, proptosis (protruding eyes), and low set, posteriorly rotated ears.[88] The presence of this characteristic facies, craniosynostosis, and mental retardation are the major features used to distinguish SGS clinically. Other features include Chiari malformation, rib anomalies, and equinovarus deformity (clubfeet). SGS is distinct from Goldberg-Shprintzen syndrome (OMIM no. 609640) and Shprintzen syndrome (OMIM no. 192430).

Snyder-Robinson syndrome

Snyder-Robinson syndrome is a rare X-linked mental retardation syndrome with marfanoid skeletal features with similarities to Lujan syndrome. Other characteristic features of this syndrome include facial asymmetry with a prominent lower lip, nasal voice, unsteady gait, nonspecific movement disorder, EEG abnormalities, seizures, and diminished muscle bulk.[89–91]

Stickler syndrome

Stickler syndrome is a relatively common connective tissue disorder. Cataracts and glaucoma may accompany the other ocular findings in Table 2 (Supplemental Digital Content 2, http://links.lww.com/GIM/A112). Mild spondyloepiphyseal dysplasia may also be present, and the hearing loss may be conductive and sensorineural. A flat facies and enlarged knees are also frequently seen. The presence of some clinical features—including retinal detachment, cataract, sensorineural hearing loss, early-onset degenerative joint disease, and certain skeletal abnormalities—is a function of age. Molecular analysis may assist in the diagnosis of the disorder but is not very useful in predicting the phenotypic expression of the disease, except in the case of ocular manifestations.[92] Two vitreoretinal phenotypes are clinically recognized.[93] Mutations in *COL2A1* are associated with a type 1 "membranous" vitreous phenotype. Because exon 2 of *COL2A1* is preferentially expressed in the eye, mutations in this exon result in an isolated type 1 vitreous defect.[94] The less common type II "beaded" vitreous phenotype is associated with mutations in *COL11A1*. Mutations in *COL11A2* produce a Stickler phenotype lacking vitreous manifestations, because *COL11A2* is not expressed in this tissue.[95]

Weill-Marchesani syndrome

Weill-Marchesani syndrome (WMS) exhibits significant clinical homogeneity despite its genetic heterogeneity. In comparing autosomal dominant (AD—due to *FBN1*) and autosomal recessive (AR—due to *ADAMTS10*) WMS, no significant difference was found for the incidence of most clinical features.[96] There was approximately a 20% difference in incidence between AR and AD WMS for microspherophakia and cardiac anomalies (more prevalent in AR WMS) as well as joint limitations and ectopia lentis (more prevalent in AD WMS),[97] although these characteristics are commonly seen in both forms of WMS. Further complicating differentiation between AR and AD WMS based on family history, some heterozygotes for AR WMS display mild clinical manifestations of the disease, including short stature, brachydactyly, and abnormal gonioscopic findings. In addition to the eye manifestations listed in Table 2 (Supplemental Digital Content 2, http://links.lww.com/GIM/A112), shallow orbits and glaucoma can be features of WMS. Congenital cardiac abnormalities reported for patients with WMS include MVP, prolonged QT interval, and pulmonary and aortic valve

stenoses. Patients with WMS and a history of palpitation, lightheadedness, dizziness or syncope should be evaluated for prolonged QTc, as it may be associated with serious arrhythmia.[98] The differential diagnosis of WMS includes Hunter-MacDonald Syndrome.[99]

DISCUSSION

The cornerstones for establishing a diagnosis are a personal medical history, a family history extended through third-degree relatives, and a comprehensive genetics physical examination, with special attention to potential dysmorphic features, cardiac murmurs, body proportions, joint mobility, and skin characteristics. This article is meant to help guide the development of an informed differential diagnosis and suggest possible targets for further clinical evaluation and genetic testing. Considerations for specific testing in heritable disorders of connective tissue may include the following:

- Evaluation by an ophthalmologist with knowledge of disorders of connective tissue to assess abnormalities of the lens, retina, vitreous, and refraction.
- Radiographic imaging, including transthoracic or esophageal echocardiography, with careful, serial measurements of the aortic root at the level of the sinuses of Valsalva to compare with normal references for age and/or body mass index and evaluation of the aortic arch.
- CT or MR angiogram of the cerebral, neck, thoracic, abdominal, and pelvic arteries. An abnormality such as dissection, dilation, tortuosity, or aneurysm in any one artery should prompt a systematic assessment of all major arteries.
- A skeletal survey that may help evaluate underlying skeletal dysplasia, acetabular abnormalities, hyperostosis, or osteopenia.
- A bone densitometry study may be useful for identifying osteopenia.
- Special spine films, to help accurately diagnose the degree of any scoliosis.
- Brain imaging that may be indicated in individuals with neurologic signs or symptoms but not usually in individuals lacking such neurological features.
- Audiologic assessment, recommended when disorders with hearing loss are included in the differential diagnosis list.
- Clinical molecular testing when available for genes included in Table 2 (Supplemental Digital Content 2, http://links.lww.com/GIM/A112) associated with the disorders under consideration in the differential diagnosis. Current information on test availability and links to the laboratories offering testing can be found at Genetests.org.

Genetic disorders of connective tissue comprise a rapidly expanding list of Mendelian syndromes that can manifest with significantly overlapping clinical findings, especially involving the musculoskeletal, cardiovascular, respiratory, ophthalmologic, and cutaneous systems. Diagnostic accuracy is most critical in serious but highly treatable disorders. Such disorders include homocystinuria and potentially, with the recent development of beta-blocker therapy or angiotensin II receptor antagonist like losartan as potential therapies to limit the risk of further vessel dilatation or dissection in Marfan syndrome and Loeys-Dietz syndrome.[100,101] An accurate diagnosis can guide the physician and patient in monitoring for the progression of known symptoms or emergence of new symptoms, identifying high-risk situations, and identifying other at-risk family members. Standard management recommendations have been published for the more common inherited connective tissue disorders such as Marfan syndrome, and the importance of diagnostic accuracy will increase as further disorder-specific evidence-based treatment regimes are developed. Diagnostic accuracy may improve the quality of life for patients, even those with disorders for which no major treatment has yet been developed. The matrices constructed from this project may be of clinical use to geneticists as well as other clinicians who encounter patients with apparent alterations affecting connective tissue.

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