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NLM Citation: Giunta C, Rohrbach M, Fauth C, et al. *FKBP14* Kyphoscoliotic Ehlers-Danlos Syndrome. 2019 May 23. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

FKBP14 Kyphoscoliotic Ehlers-Danlos Syndrome

Synonym: kEDS-*FKBP14*

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Created: May 23, 2019.

Summary

Clinical characteristics

FKBP14 kyphoscoliotic Ehlers-Danlos syndrome (*FKBP14*-kEDS) is characterized by congenital muscle hypotonia and weakness (typically improving during childhood), progressive scoliosis, joint hypermobility, hyperelastic skin, gross motor developmental delay, myopathy, and hearing impairment. Most affected children achieve independent walking between ages two and four years. A decline of motor function in adulthood may be seen, but affected individuals are likely to be able to participate in activities of daily living in adulthood and maintain independent walking. Occasional features underlying systemic connective tissue involvement include aortic rupture and arterial dissection, subdural hygroma, insufficiency of cardiac valves, bluish sclerae, bladder diverticula, inguinal or umbilical herniae, and premature rupture of membranes during pregnancy. Rarer findings may include bifid uvula with submucous or frank cleft palate, speech/language delay without true cognitive impairment, and rectal prolapse.

Diagnosis/testing

Clinical diagnostic criteria rely on the finding of congenital muscular hypotonia AND congenital or early-onset kyphoscoliosis in addition to generalized joint hypermobility or further gene-specific and/or supportive clinical features. The diagnosis of *FKBP14*-kEDS is established in a proband by the identification of biallelic pathogenic variants in *FKBP14* by molecular genetic testing.

Management

Treatment of manifestations: In those with aortic dilatation or vascular dissection, use of beta-blockers may be considered; physical and occupational therapy to address age-dependent decline in muscular strength; standard treatment for severe scoliosis, clubbed foot, osteopenia/osteoporosis, refractive error, hearing impairment, and cleft palate.

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Surveillance: Blood pressure measurement at each visit; neurodevelopmental assessment at each visit until adolescence; evaluation by an orthopedic physician as clinically indicated but typically at least annually; periodic ophthalmology and hearing evaluations (e.g., every 2-3 years); DXA scan, echocardiogram with consideration of cardiac MRI, and vascular ultrasonography every 2-5 years.

Agents/circumstances to avoid: Sports that place stress on the joints; contact sports in those with an aortic aneurysm; hypertension.

Pregnancy management: An increased risk for miscarriage, premature rupture of membranes, and rupture of arteries in affected pregnant women should be considered. Delivery in a medical center with a high-risk perinatologist in attendance is recommended.

Genetic counseling

FKBP14-kEDS is inherited in an autosomal recessive manner. Each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Carrier testing for at-risk relatives and prenatal testing for a pregnancy at increased risk are possible if both *FKBP14* pathogenic variants have been identified in a family.

Diagnosis

Formal clinical diagnostic criteria for *FKBP14* kyphoscoliotic Ehlers-Danlos syndrome (*FKBP14*-kEDS) were established in the 2017 revised Ehlers-Danlos syndrome (EDS) nosology [Malfait et al 2017]; see Establishing the Diagnosis.

Suggestive Findings

FKBP14 kyphoscoliotic Ehlers-Danlos syndrome (*FKBP14*-kEDS) **should be suspected** in individuals with kyphoscoliosis, severe congenital muscle hypotonia, and joint hypermobility

Major and minor clinical features of *FKBP14*-kEDS have been outlined as follows (adapted from Malfait et al [2017] and Giunta et al [2018b]).

Major clinical features

- Congenital muscular hypotonia
- Congenital or early-onset kyphoscoliosis
- Generalized joint hypermobility

Gene-specific minor features

- Early-onset sensorineural, conductive, or mixed hearing impairment (See Clinical Description.)
- Muscle atrophy
- Follicular hyperkeratosis
- Bladder diverticula

Other suggestive findings

- Marfanoid habitus
- Pectus deformity
- Talipes equinovarus
- Skin hyperextensibility
- Easily bruisable skin
- Hernia (umbilical or inguinal)

- Rupture/aneurysm of a medium-sized artery
- Blue sclerae
- Refractive errors (myopia, hypermetropia)
- Osteopenia/osteoporosis

Supportive laboratory findings

- Normal or only slightly elevated serum creatine kinase (CK) level
- Histopathology of muscle biopsies showing nonspecific mild myopathic changes with increased variation in muscle fiber diameter to more pronounced changes with profound fiber atrophy and proliferation of fatty tissue

Note: At the time of writing, muscle biopsy is not required to make the diagnosis of *FKBP14*-kEDS.

Supportive imaging findings. MRI of the lower limbs that may demonstrate fatty degeneration of multiple muscle groups, including rectus femoris and soleus

Establishing the Diagnosis

Proposed minimal clinical diagnostic criteria for *FKBP14*-kEDS include the following [Malfait et al 2017]:

- Congenital muscular hypotonia **AND** congenital or early-onset kyphoscoliosis; **PLUS**
- Either or both of the following:
  - Generalized joint hypermobility
  - Three minor criteria (from either **Gene-specific minor features** or **Other suggestive findings**)

However, the diagnosis of *FKBP14*-kEDS **is established** in a proband by identification of biallelic pathogenic (or likely pathogenic) variants in *FKBP14* by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) Identification of biallelic *FKBP14* variants of uncertain significance (or of one known *FKBP14* pathogenic variant and one *FKBP14* variant of uncertain significance) does not establish or rule out the diagnosis.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Because the phenotype of *FKBP14*-kEDS is broad, individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those with a phenotype indistinguishable from many other inherited generalized connective tissue disorders are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When the phenotypic findings suggest the diagnosis of *FKBP14*-kEDS molecular genetic testing is indicated. Molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**:

- **Single-gene testing.** Sequence analysis of *FKBP14* detects small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected.

  Perform sequence analysis first. If only one or no pathogenic variant is found, perform gene-targeted deletion/duplication analysis to detect intragenic deletions or duplications.

  Note: A common c.362dupC variant accounts for approximately 70% of disease alleles [Baumann et al 2012, Giunta et al 2018b].

- **A connective tissue disorder multigene panel** that includes *FKBP14* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

When the phenotype is indistinguishable from many other inherited connective tissue disorders, **comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) is the best option. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

Exome array (when clinically available) may be considered if exome sequencing is non-diagnostic.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in *FKBP14* Kyphoscoliotic Ehlers-Danlos Syndrome

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
FKBP14	Sequence analysis [3]	24/24 [4, 5]
	Gene-targeted deletion/duplication analysis [6]	Unknown [7]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Baumann et al [2012], Aldeeri et al [2014], Murray et al [2014], Dordoni et al [2016], Bursztejn et al [2017], Giunta et al [2018a], Castori et al [2019]. Note: The affected individual published by Bursztejn et al [2017] was initially published by Baumann et al [2012].
5. A common pathogenic variant (c.362dupC) has been reported; see Table 6.
6. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
7. No data on detection rate of gene-targeted deletion/duplication analysis are available.

Clinical Characteristics

Clinical Description

FKBP14 kyphoscoliotic Ehlers-Danlos syndrome (*FKBP14*-kEDS) is characterized by congenital muscle hypotonia and weakness that typically improves during childhood, progressive scoliosis, joint hypermobility, hyperelastic skin, gross motor developmental delay, myopathy, and hearing impairment [Baumann et al 2012, Giunta et al 2018a]. Occasional features underlying systemic connective tissue involvement include aortic rupture and arterial dissection, subdural hygroma (potentially due to subdural bleeding or spontaneous intracranial hypotension), insufficiency of cardiac valves, bluish sclerae, bladder diverticula, inguinal or

umbilical herniae, and premature rupture of membranes during pregnancy [Murray et al 2014, Dordoni et al 2016, Giunta et al 2018a].

A range of clinical severity is observed in individuals with *FKBP14*-kEDS for each of the systems discussed in this section [Baumann et al 2012, Brady et al 2017, Giunta et al 2018a].

Prenatal. Pregnancy involving an affected fetus is often characterized by reduced fetal movements and an increased risk of premature rupture of membranes.

Muscular features. Individuals with *FKBP14*-kEDS typically present at birth with congenital hypotonia and weakness. They often show feeding problems, and some will need airway management or respiratory support. Most affected infants have poor head control. With rare exceptions, motor developmental delay and reduced motor strength are common features in childhood, although muscle weakness typically improves during childhood [Giunta et al 2018a]. Most children achieve independent walking between ages two and four years. A decline of motor function in adulthood appears to represent an age-dependent feature in the natural course of this condition, but affected individuals are likely to be able to participate in activities of daily living in adulthood and maintain independent walking.

Wider phenotypic variability of the muscular features may exist, as suggested by the presence of early-onset muscle disease with severe involvement of the lower-limb muscles in one recently described affected individual [Castori et al 2019].

Skeletal/joint features

- Kyphoscoliosis is a hallmark of *FKBP14*-kEDS and is usually severe and progressive. Two thirds of affected individuals manifest kyphoscoliosis before age one year (range: birth to 7 years in 15 affected individuals described by Giunta et al [2018a]). Progressive kyphoscoliosis may respond to bracing, but often surgery is needed. Severe kyphoscoliosis may lead to restrictive lung disease without need for assisted ventilation.
- Pronounced joint hypermobility (mean value of Beighton score 8/9) is seen in 23/23 affected individuals [Giunta et al 2018a] for the small joints and 21/23 for the large joints. Joint hypermobility usually decreases with age.
    - Hypermobility may result in recurrent joint dislocations/sprains or chronic pain (5/23 affected individuals reported).
    - Foot deformities that include congenital or postural talipes and pes planus / planovalgus have been found in 23/23 of affected individuals.
- Despite significant joint hypermobility, congenital contractures are present in up to one third of affected individuals and may impact the fingers, wrist, elbows, or knees (7/23). Congenital hip dislocation is present in 4/17 of affected individuals.
- Fractures probably due to osteopenia/osteoporosis from immobility occurred in 3/23.
- Atlantoaxial subluxation/instability has been reported in three individuals [Dordoni et al 2016, Giunta et al 2018a, Castori et al 2019].

Eyes. Refractive errors, myopia, and hypermetropia are moderately frequent, present in about two thirds of affected individuals. Blue sclerae are present in about one third of affected individuals.

Ears. Hearing impairment can manifest at birth, in early infancy, or even later in life [Giunta et al 2018a]. Sensorineural hearing impairment is the most frequent, present in about half of affected individuals; conductive hearing loss is present in up to one quarter. Hearing impairment (either conductive or sensorineural) may manifest later in life or remain subclinical, thus necessitating periodic investigations (see Management).

Cardiovascular. Vascular complications in adulthood and their possible occurrence in childhood suggests that cardiovascular investigations in the routine assessment and follow up of affected individuals is indicated (see

Management). Cardiovascular complications can be congenital (septal defects in a minority) or acquired (usually mild mitral or pulmonary valve insufficiency or dilatation of the ascending aorta).

Additionally, artery dissections occurred in two adult individuals (internal carotid artery and celiac artery) [Murray et al 2014, Giunta et al 2018a] and a pseudoaneurysm rupture occurred in one child (hypogastric artery) [Dordoni et al 2016].

Skin and integument. All individuals described to date have had a subjective finding of soft skin texture. Hyperextensibility was found in 17/23. Atrophic and hypertrophic scarring are seen in fewer than half of affected individuals, as is easy bruising. Additional findings may include follicular hyperkeratosis and crisscross palms/soles.

Other findings

- Inguinal and/or umbilical hernia in about half of affected individuals (11/23), sometimes with redundant umbilical skin.
- Bifid uvula with submucous cleft palate or frank cleft palate (7/23)
- Speech or language delay (7/20); true intellectual disability is rare and may be unrelated in children of consanguineous relationships.
- Visceral complications, including large bladder diverticula (3/19) and (rarely) rectal prolapse.

Prognosis. It is unknown if life span in individuals with *FKBP14*-kEDS is reduced. One reported individual is alive at age 53 years [Giunta et al 2018a], demonstrating that survival into adulthood is possible. Since many adults with disabilities have not undergone advanced genetic testing, it is likely that adults with this condition are underrecognized and underreported.

Genotype-Phenotype Correlations

Genotype-phenotype correlations that predict risk for specific complications or clinical severity have not been reported to date.

Pathophysiology

The pathomechanism of *FKBP14*-kEDS is only partially understood [Baumann et al 2012]. Pathology findings include the following:

- Normal collagen biosynthesis and secretion of collagen types I, III, and V
- Disarray of the main components of the extracellular matrix (i.e., collagen type I, III, and VI; fibronectin; tenascins; thrombospondin) by indirect immunofluorescence on skin fibroblast from affected individuals

  Type V collagen is organized in an extracellular network that is similar to control fibroblasts.
- Loss of the main receptors of collagens and fibronectin, α2β1 and α5β1 integrins.
- Marked enlargement of the ER cisterns with accumulation of flocculent material in skin cells of affected individuals by transmission electron microscopy

See also Molecular Pathogenesis.

Nomenclature

FKBP14-kEDS was initially referred to as a variant of Ehlers-Danlos syndrome with progressive kyphoscoliosis, myopathy, and hearing loss. Since the development of the 2017 EDS Nosology [Malfait et al 2017], it is known as kEDS-*FKBP14, FKBP14*-kEDS, and *FKBP14*-related kEDS.

Prevalence

FKBP14-kEDS is rare; the exact prevalence is unknown. From its first description in 2012, 30 individuals are known to the authors at the time of review (2019). A disease incidence of approximately 1:100,000 live births is a reasonable estimate. Prevalence does not vary by race or ethnicity.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *FKBP14*.

Differential Diagnosis

Table 2. Disorders to Consider in the Differential Diagnosis of *FKBP14* Kyphoscoliotic Ehlers-Danlos Syndrome

Differential Diagnosis Disorder	Gene(s)	MOI	Clinical Features of Differential Diagnosis Disorder	
			Overlapping w/*FKBP14*-kEDS	Distinguishing from *FKBP14*-kEDS
PLOD1 kyphoscoliotic EDS	*PLOD1*	AR	• Congenital muscular hypotonia • Congenital/early-onset kyphoscoliosis • Generalized joint hypermobility	• Absence of hearing impairment • ↑ ratio of urinary pyridinolines
Musculocontractural EDS (OMIM 601776, 615539)	*CHST14* *DSE*	AR	Joint hypermobility	• Characteristic craniofacial features • Peculiar fingers (tapering, slender, cylindric)
Collagen type VI-related disorders	*COL6A1* *COL6A2* *COL6A3*	AD AR	• Congenital muscular hypotonia • Progressive kyphoscoliosis • Joint hypermobility • Follicular hyperkeratosis	• Myopathy on muscle biopsy [1] • Respiratory muscle failure • Absence of skin hyperelasticity & easy bruising • Absence of hearing impairment & cardiovascular problems
Spondylodysplastic EDS (spEDS) (OMIM 130070, 612350, 615349)	*B4GALT7* *B3GALT6* *SLC39A13*	AR	• Congenital muscular hypotonia • Kyphoscoliosis (*B3GALT6*-spEDS) • Joint hypermobility • Pectus deformities	• Progressive short stature • Primary skeletal involvement • Dysplastic teeth

Table 2. continued from previous page.

Differential Diagnosis Disorder	Gene(s)	MOI	Clinical Features of Differential Diagnosis Disorder	
			Overlapping w/*FKBP14*-kEDS	Distinguishing from *FKBP14*-kEDS
Myopathic EDS (OMIM 616471)	*COL12A1*	AD AR	• Congenital muscular hypotonia • Motor developmental delay • Soft, doughy skin • Muscular atrophy	• Myopathy on muscle biopsy [1] • Severe progressive scoliosis

AD = autosomal dominant; AR = autosomal recessive; EDS = Ehlers-Danlos syndrome; MOI = mode of inheritance

1. In Bethlem myopathy, muscle biopsies reveal myopathic or dystrophic changes. Collagen VI immunolabeling is often normal or shows only subtle alterations. Conversely, in Ulrich congenital muscular dystrophy muscle biopsies more commonly show dystrophic features with degeneration and regeneration and replacement of muscle with fat and fibrous connective tissue. Collagen VI immunolabeling from the endomysium and basal lamina ranges from absent to moderately or markedly reduced, but may be normal around the capillaries (see Collagen Type VI-Related Disorders).

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *FKBP14* kyphoscoliotic Ehlers-Danlos syndrome (*FKBP14*-kEDS), the evaluations summarized in Table 3 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 3. Recommended Evaluations Following Initial Diagnosis in Individuals with *FKBP14*-kEDS

System/Concern	Evaluation	Comment
Musculoskeletal	• Clinical & radiologic documentation of kyphoscoliosis & measurement of curvature • Eval for joint contractures & other skeletal features [1]	Referral to orthopedist
	PT eval	To develop a specific program to be followed by patient
	DXA scan	In those w/frequent fractures or ↓ ambulation
Eyes	Ophthalmologic eval	To evaluate for refractive errors
Ears	Audiology eval	A repeat hearing eval is recommended even if patient had normal newborn hearing screen.
Cardiovascular	Echocardiography	• To incl measurement of aortic root size & assessment of heart valves • Cardiac & abdominal ultrasound/MRI may also be considered to monitor for aortic dilatation.
	Measurement of blood pressure	Maintenance of blood pressure in normal range for age recommended to ↓ risk of arterial rupture
Craniofacial	Assessment of palate for submucous or frank cleft	Referral to craniofacial clinic if palatal anomalies are suspected

Table 3. continued from previous page.

System/Concern	Evaluation	Comment
Miscellaneous/ Other	Developmental assessment	To incl motor, speech-language eval, general cognitive, & vocational skills
	Consultation w/clinical geneticist &/or genetic counselor	

DXA = dual-energy x-ray absorptiometry; PT = physical therapy
1. Care providers should be made aware of the possibility of atlantoaxial instability; however, proactive assessment for this finding is not typically done.

Treatment of Manifestations

Table 4. Treatment of Manifestations in Individuals with *FKBP14*-kEDS

Manifestation/ Concern	Treatment	Considerations/Other
Severe scoliosis	Standard treatment, ideally in multidisciplinary setting	• Surgery may be indicated for severe scoliosis. • At surgery caution should be taken due to risk for vascular complications, atlantoaxial instability, & primary muscle disease.
Clubbed foot/ Foot deformity	Standard treatment, ideally in multidisciplinary setting	Orthopedic shoe insoles may be beneficial for those w/foot deformity & joint instability
Osteopenia/ Osteoporosis	Standard treatment	
Age-dependent muscle decline	PT program	• Orthopedists, rehab medicine, & PTs/OTs can assist in recommending appropriate devices to improve joint stability. • Walker or wheelchair may be necessary for mobility.
Ocular refraction abnormality	Standard treatment(s) as recommended by ophthalmologist	
Hearing impairment	Standard treatment; may incl use of hearing aid	See Hereditary Hearing Loss and Deafness Overview.
Aortic dilatation / Vascular dissection	Eventually, use of beta-blockers in patients w/aortic dilatation to prevent further expansion	• Use of beta-blockers (e.g., celiprolol) may be considered based on their efficiency in vascular EDS. [1] • Vascular surgery is extremely risky because of vascular fragility in EDS.
Cleft palate	Standard treatment	

OT = occupational therapist; PT = physical therapist/therapy
1. Ong et al [2010]

Motor Dysfunction

Gross motor dysfunction

- Physical therapy is recommended to maximize mobility.
- Consider use of durable medical equipment as needed (e.g., wheelchairs, walkers, bath chairs, orthotics, adaptive strollers).

Fine motor dysfunction. Occupational therapy is recommended for difficulty with fine motor skills that affect adaptive function such as feeding, grooming, dressing, and writing.

Oral motor dysfunction. Assuming that the individual is safe to eat by mouth, feeding therapy (typically from an occupational or speech therapist) is recommended for individuals who have difficulty feeding due to poor oral motor control.

Surveillance

Standardized medical surveillance guidelines for individuals with *FKBP14*-kEDS have not been published.

Table 5. Recommended Surveillance for Individuals with *FKBP14*-kEDS

System/Concern	Evaluation	Frequency
Musculoskeletal	Evals by orthopedic physician & specialist in rehab medicine for mgmt of kyphoscoliosis, contractures, & foot deformities	As clinically indicated but at least annually
	DXA scan	Every 2-5 yrs, or in those w/↓ ambulation
Eyes	Routine ophthalmologic eval	Every 2-3 yrs
Ears	Formal hearing eval	
Cardiovascular	Blood pressure measurement [1]	At each visit
	• Echocardiography w/consideration of cardiac MRI • Vascular ultrasonography to evaluate abdominal & peripheral arteries & veins	Every 2-5 yrs starting in early childhood
Neurodevelopment	Assessment of developmental progress	At each visit until adolescence

DXA = dual-energy x-ray absorptiometry

1. Maintenance of blood pressure in the normal range for age is recommended to reduce the risk of arterial rupture.

Agents/Circumstances to Avoid

Avoid the following:

- For children with severe joint hypermobility, sports that place stress on the joints
- High blood pressure
- For individuals with aortic aneurysm, contact sports

Evaluation of Relatives at Risk

It is appropriate to clarify the genetic status of apparently asymptomatic older and younger at-risk relatives of an affected individual in order to identify as early as possible those who would benefit from prompt initiation of treatment and surveillance measures. Molecular genetic testing can be used if the pathogenic variants in the family are known.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

No pregnancies in women with *FKBP14*-kEDS have been reported to date. An increased risk for miscarriage, premature rupture of membranes, and rupture of arteries in affected pregnant women should be considered. Delivery in a medical center with a high-risk perinatologist in attendance is recommended.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

FKBP14 kyphoscoliotic Ehlers-Danlos syndrome (*FKBP14*-kEDS) is inherited in an autosomal recessive manner.

Parents of a proband

- The parents of an affected child are obligate heterozygotes (i.e., carriers of one *FKBP14* pathogenic variant).
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. The offspring of an individual with *FKBP14*-kEDS are obligate heterozygotes (carriers) for a pathogenic variant in *FKBP14*.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of a *FKBP14* pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *FKBP14* pathogenic variants in the family.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Family planning

- The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at risk of being carriers.

Prenatal Testing and Preimplantation Genetic Testing

Once the *FKBP14* pathogenic variants have been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **Ehlers-Danlos Society - Europe**
  United Kingdom
  Phone: +44 203 887 6132
- **Ehlers-Danlos Support UK**
  United Kingdom
  Phone: 0208 736 5604; 0800 9078518
  www.ehlers-danlos.org
- **MedlinePlus**
  Ehlers-Danlos Syndrome
- **The Ehlers-Danlos Society**
  Phone: 410-670-7577
  www.ehlers-danlos.com
- **DICE EDS and HSD Global Registry**
  www.ehlers-danlos.com/eds-global-registry

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. FKBP14 Kyphoscoliotic Ehlers-Danlos Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
FKBP14	7p14.3	Peptidyl-prolyl cis-trans isomerase FKBP14	FKBP14 homepage - FKBP14 @ LOVD	FKBP14	FKBP14

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for FKBP14 Kyphoscoliotic Ehlers-Danlos Syndrome (View All in OMIM)

614505	FK506-BINDING PROTEIN 14; FKBP14
614557	EHLERS-DANLOS SYNDROME, KYPHOSCOLIOTIC TYPE, 2; EDSKSCL2

Molecular Pathogenesis

FKBP14 (transcript variant 1) encodes a 211-amino acid FKBP22 (alias FKBP14) protein, which contains a signal peptide of 18 residues and forms a dimer of identical subunits [Boudko et al 2014]. The protein consists of three domains:

- The PPIase catalytic domain (aa 45-135)
- The first EF-hand1 domain (aa 135-170)
- The second EF-hand2 domain (aa 179-211)

FKBP22 is an ER resident protein that belongs to the FK506-binding protein (FKBP) class of immunophilins, which have been implicated in catalyzing cis-trans-isomerization of peptidyl-prolyl peptide bonds and are supposed to accelerate protein folding. FKBP22 catalyzes the folding of type III collagen and interacts with type III collagen, type VI collagen, and type X collagen, but not with type I collagen, type II collagen, or type V collagen [Ishikawa & Bächinger 2014]. Remarkably, pathogenic variants in type III and type VI collagens cause the vascular type of EDS (vEDS) and *COL6*-related muscular dystrophies, respectively. Therefore, the clinical features of vascular abnormalities and myopathy documented in the affected individuals clearly correlates with the interaction of FKBP14 with type III and VI collagens [Giunta et al 2018a] (see also Pathophysiology).

Mechanism of disease causation. The majority of *FKBP14* pathogenic variants are loss-of-function variants [Baumann et al 2012, Giunta et al 2018a]. The common c.362dupC frameshift, which is found with a frequency of approximately 70%, is the most common pathogenic variant [Baumann et al 2012, Giunta et al 2018a] and has been linked to the same haplotype in all individuals tested [Murray et al 2014].

A missense variant, p.Met48Lys [Giunta et al 2018a], and an in-frame deletion, p.Glu191del [Dordoni et al 2016], have also been reported. Mapping of the missense variant p.Met48Lys onto the protein crystal structure near the potential PPIase active site of FKBP22 supports complete or partial loss of function of *FKBP14* as a further disease mechanism in addition to loss of protein [Giunta et al 2018a].

Western blot analysis using a FKBP14 mouse polyclonal antibody showed deficiency of FKBP14 in two individuals with *FKBP14*-kEDS [Baumann et al 2012].

***FKBP14*-specific laboratory technical considerations.** *FKBP14* consists of three small exons, a rather large fourth exon, which includes the 3' UTR, and three rather large introns. Transcript variants 2 and 3 are noncoding.

Table 6. Notable *FKBP14* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_017946.3 NP_060416.1	c.573_575del	p.Glu191del	Only in-frame variant reported [Dordoni et al 2016]
	c.362dupC	p.Glu122ArgfsTer7	Common pathogenic variant [Baumann et al 2012, Dordoni et al 2016, Giunta et al 2018a, Castori et al 2019]
	c.143T>A	p.Met48Lys	Missense change reported near PPIase active site [Giunta et al 2018a]

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

References

Literature Cited

Aldeeri AA, Alazami AM, Hijazi H, Alzahrani F, Alkuraya FS. Excessively redundant umbilical skin as a potential early clinical feature of Morquio syndrome and FKBP14-related Ehlers-Danlos syndrome. Clin Genet. 2014;86:469–72. PubMed PMID: 24773188.

Baumann M, Giunta C, Krabichler B, Rüschendorf F, Zoppi N, Colombi M, Bittner RE, Quijano-Roy S, Muntoni F, Cirak S, Schreiber G, Zou Y, Hu Y, Romero NB, Carlier RY, Amberger A, Deutschmann A, Straub V, Rohrbach M, Steinmann B, Rostásy K, Karall D, Bönnemann CG, Zschocke J, Fauth C. Mutations in FKBP14 cause a variant of Ehlers-Danlos syndrome with progressive kyphoscoliosis, myopathy and hearing loss. Am J Hum Genet. 2012;90:201–16. PubMed PMID: 22265013.

Boudko SP, Ishikawa Y, Nix J, Chapman MS, Bachinger HP. Structure of human peptidyl-prolyl cis-trans isomerase FKBP22 containing two EF-hand motifs. Protein Sci. 2014;23:67–75. PubMed PMID: 24272907.

Brady AF, Demirdas S, Fournel-Gigleux S, Ghali N, Giunta C, Kapferer-Seebacher I, Kosho T, Mendoza-Londono R, Pope MF, Rohrbach M, Van Damme T, Vandersteen A, van Mourik C, Voermans N, Zschocke J, Malfait F. The Ehlers-Danlos syndromes, rare types. Am J Med Genet Part C Semin Med Genet. 2017;175:70–115. PubMed PMID: 28306225.

Bursztejn AC, Baumann M, Lipsker D. Ehlers–Danlos syndrome related to FKBP14 mutations: detailed cutaneous phenotype. Clin Exp. Dermatol. 2017;42:64–7. PubMed PMID: 27905128.

Castori M, Fiorillo C, Agolini E, Sacco M, Minetti C, Novelli A, Guglielmi G, Bertini E. Primary muscle involvement in a 15-year-old girl with the recurrent homozygous c.362dupC variant in FKBP14. Am J Med Genet A. 2019;179:317–21. PubMed PMID: 30561154.

Dordoni C, Ciaccio C, Venturini M, Calzavara-Pinton P, Ritelli M, Colombi M. Further delineation of FKBP14-related Ehlers-Danlos syndrome: a patient with early vascular complications and non-progressive kyphoscoliosis, and literature review. Am J Med Genet A. 2016;170:2031–8. PubMed PMID: 27149304.

Giunta C, Baumann M, Fauth C, Lindert U, Abdalla EM, Brady AF, Collins J, Dastgir J, Donkervoort S, Ghali N, Johnson DS, Kariminejad A, Koch J, Kraenzlin M, Lahiri N, Lozic B, Manzur AY, Morton JEV, Pilch J, Pollitt RC, Schreiber G, Shannon NL, Sobey G, Vandersteen A, van Dijk FS, Witsch-Baumgartner M, Zschocke J, Pope FM, Bönnemann CG, Rohrbach M. A cohort of 17 patients with kyphoscoliotic Ehlers-Danlos syndrome caused by biallelic mutations in FKBP14: expansion of the clinical and mutational spectrum and description of the natural history. Genet Med. 2018a;20:42–54. PubMed PMID: 28617417.

Giunta C, Yeowell HN, Steinmann B. Kyphoscoliotic, arthrochalasia and dermatosparaxis Ehlers-Danlos syndrome. In: Jacobs JWG, Cornelissens LJM, Veenhuizen MC, Hamel BCJ, eds. *Ehlers-Danlos Syndrome: A Multidisciplinary Approach.* Amsterdam: IOS Press; 2018b:97-125. Available online.

Ishikawa Y, Bächinger HP. A substrate preference for the rough endoplasmic reticulum resident protein FKBP22 during collagen biosynthesis. J Biol Chem. 2014;289:18189–201. PubMed PMID: 24821723.

Malfait F, Francomano C, Byers P, Belmont J, Berglund B, Black J, Bloom L, Bowen JM, Brady AF, Burrows NP, Castori M, Cohen H, Colombi M, Demirdas S, De Backer J, De Paepe A, Fournel-Gigleux S, Frank M, Ghali N, Giunta C, Grahame R, Hakim A, Jeunemaitre X, Johnson D, Juul-Kristensen B, Kapferer-Seebacher I, Kazkaz H, Kosho T, Lavallee ME, Levy H, Mendoza-Londono R, Pepin M, Pope FM, Reinstein E, Robert L, Rohrbach M, Sanders L, Sobey GJ, Van Damme T, Vandersteen A, van Mourik C, Voermans N, Wheeldon N, Zschocke J, Tinkle B. The 2017 International classification of the Ehlers-Danlos syndromes. Am J Med Genet Part C Semin Med Genet. 2017;175:8–26. PubMed PMID: 28306229.

Murray ML, Yang M, Fauth C, Byers PH. FKBP14-related Ehlers-Danlos syndrome: expansion of the phenotype to include vascular complications. Am J Med Genet A. 2014;164A:1750–5. PubMed PMID: 24677762.

Ong KT, Perdu J, De Backer J, Bozec E, Collignon P, Emmerich J, Fauret AL, Fiessinger JN, Germain DP, Georgesco G, Hulot JS, De Paepe A, Plauchu H, Jeunemaitre X, Laurent S, Boutouyrie P. Effect of celiprolol on prevention of cardiovascular events in vascular Ehlers-Danlos syndrome: a prospective randomised, open, blinded-endpoints trial. Lancet. 2010;376:1476–84. PubMed PMID: 20825986.

Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17:405–24. PubMed PMID: 25741868.

Chapter Notes

Revision History

- 23 May 2019 (ma) Review posted live
- 5 October 2018 (cg) Original submission

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