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Kindler Syndrome

Synonym: Congenital Bullous Poikiloderma

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Summary

Clinical characteristics

Kindler syndrome (KS), a rare subtype of inherited epidermolysis bullosa, is characterized by skin fragility and acral blister formation beginning at birth, diffuse cutaneous atrophy, photosensitivity (most prominent during childhood and usually decreasing after adolescence), poikiloderma, diffuse palmoplantar hyperkeratosis, and pseudosyndactyly. Mucosal manifestations are also common and include hemorrhagic mucositis and gingivitis, periodontal disease, premature loss of teeth, and labial leukokeratosis. Other mucosal findings can include ectropion, urethral stenosis, and severe phimosis. Severe long-term complications of KS include periodontitis, mucosal strictures, and aggressive squamous cell carcinomas. Manifestations can range from mild to severe.

Diagnosis/testing

The diagnosis of KS is established in a proband with suggestive clinical findings and biallelic pathogenic variants in *FERMT1* identified by molecular genetic testing.

Management

Treatment of manifestations: When possible, children with KS should be managed by a multidisciplinary team (dermatologist, pediatrician, ophthalmologist, dentist, gastroenterologist, urologist, nurse specialist, and dietitian) in a center experienced in caring for children with skin fragility. Skin care includes standard blister care, use of moisturizers, and protection from trauma and the sun. Mucosal involvement can require lubrication of the cornea, regular dental care to ensure optimal oral hygiene to reduce periodontal disease, and management of gastrointestinal and urethral complications.

Surveillance: Screening for premalignant keratoses and early squamous cell carcinomas starting in adolescence and repeated annually. Screening for oral ulcerations, gingivitis, and periodontitis starting in adolescence with regular dental checkups.

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Agents/circumstances to avoid: Sun exposure.

Pregnancy management: Planning for potential complications at delivery (e.g., vaginal stenosis, labial synechiae). Breast-feeding is not advised due to risk of blistering breasts.

Genetic counseling

KS is inherited in an autosomal recessive manner. If both parents are known to be heterozygous for an *FERMT1* pathogenic variant, each sib of an affected individual has at conception 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. Once the *FERMT1* pathogenic variants have been identified in an affected family member, carrier testing for at-risk relatives and prenatal and preimplantation genetic testing are possible.

Diagnosis

No consensus clinical diagnostic criteria for Kindler syndrome (KS) have been published.

Suggestive Findings

KS **should be suspected** in individuals with the following clinical findings, skin biopsy results, and family history.

Clinical findings

- **Skin fragility with trauma-induced blistering.** Blisters are present at birth and result from cutaneous trauma and/or exposure to sunlight.
- **Skin atrophy.** Thin, wrinkled (cigarette-paper) skin, developing early in life, particularly present on the dorsa of the hands and feet
- **Photosensitivity.** Erythema and burning within minutes of sun exposure; tends to improve with age.
- **Poikiloderma.** Reticular telangiectasia and mottled hypo- and hyperpigmentation of the skin appear between ages two and three years.
- **Hyperkeratosis of the palms and soles** with fissuring; a waxy appearance on the palms may be associated with the loss of the dermal ridges (i.e., fingerprints).
- **Pseudosyndactyly** (i.e., partial fusion of the third and fourth and fourth and fifth toes) is associated with repeated blistering and scarring in infancy.
- **Fragility of mucosal surfaces** including the conjunctiva, periodontal tissues, gastrointestinal tract, and/or external genitourinary structures

Skin biopsy results

- **Histopathologic examination** shows hyperkeratosis, nonspecific epidermal atrophy, dermal edema, incontinence of pigment with or without cytoid bodies, loss of rete ridges, and focal vacuolization of the basal layer of the epidermis and pigmentary incontinence in the upper dermis, consistent with poikiloderma [Shimizu et al 1997]. A characteristic feature is a split within the basement membrane zone at different levels. However, the most frequently encountered cleavage plane is through the lowermost portion of the basal layer of the epidermis. Extensive reduplication of the basement membrane and associated collagen deposition within the clefts are unique ultrastructural and histopathologic findings suggestive of KS.
- **Electron microscopy.** The level of cleavage of blisters can be variable; intradermal, junctional, and dermal cleavage planes have been reported in a single biopsy from one individual.
- **Transmission electron microscopy** of nonblistered skin demonstrates marked disorganization of the dermoepidermal basement membrane with reduplication of the basal lamina, focal interruptions of the

lamina densa, and cleavage at or close to the dermoepidermal junction. Desmosomes, hemidesosomes, tonofilaments, anchoring filaments, and anchoring fibrils appear normal [Shimizu et al 1997, Lanschuetzer et al 2003].

- **Immunofluorescence staining.** Antigen mapping analysis revealed that the major diagnostic criterion for KS is intense, broad, reticulate, and branching staining pattern with antibodies directed against laminin-332 and type IV and type VII collagen. Although anti-kindlin-1 immunostaining is also applied as a diagnostic test for KS, the final confirmation is made by *FERMT1* molecular genetic testing [Lanschuetzer et al 2003, Barzegar et al 2015].

Family history is consistent with autosomal recessive inheritance (e.g., affected sibs and/or parental consanguinity). Absence of a known family history does not preclude the diagnosis.

Establishing the Diagnosis

The diagnosis of KS **is established** in a proband with suggestive clinical findings and biallelic pathogenic (or likely pathogenic) variants in *FERMT1* identified 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 *FERMT1* variants of uncertain significance (or of one known *FERMT1* pathogenic variant and one *FERMT1* variant of uncertain significance) does not establish or rule out the diagnosis.

Because the phenotype of KS may be indistinguishable from many other inherited disorders with cutaneous fragility, recommended molecular genetic testing approaches include use of a **multigene panel** or **comprehensive genomic testing**:

- A **skin fragility multigene panel** that includes *FERMT1* 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.

- **Comprehensive genomic testing** does not require the clinician to determine which gene is likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

  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 Kindler Syndrome

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
FERMT1	Sequence analysis [3]	~95% [4]
	Gene-targeted deletion/duplication analysis [5]	~3% [4]

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. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]
5. 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.

Clinical Characteristics

Clinical Description

Kindler syndrome (KS), a rare subtype of epidermolysis bullosa, is characterized by skin fragility and acral blister formation beginning at birth or in early infancy, diffuse cutaneous atrophy, photosensitivity (most prominent during childhood and usually decreasing after adolescence), poikiloderma, palmoplantar hyperkeratosis, and pseudosyndactyly. Mucosal manifestations are also common and include hemorrhagic mucositis and gingivitis, periodontal disease, premature loss of teeth, and labial leukokeratosis. Other mucosal findings include ectropion, urethral stenosis, and severe phimosis. Severe long-term complications of KS include periodontitis, mucosal strictures, and aggressive squamous cell carcinomas.

To date, about 400 individuals have been identified with biallelic pathogenic variants in *FERMT1* [Guerrero-Aspizua et al 2019]. The following description of the phenotypic features associated with this condition is based on these reports.

Table 2. Kindler Syndrome: Frequency of Select Features

Feature	Frequency		
	Nearly all	Common	Infrequent
Blisters	●		
Skin atrophy	●		
Photosensitivity		●	
Poikiloderma		●	
Axillary freckling			●
Hyperkeratosis of palms & soles		●	
Pseudosyndactyly		●	
Mucosal fragility		●	
Malignancy			●

The phenotypic spectrum ranges from mild to severe based on age of onset, organs involved, and severity of manifestations. The mild end of the spectrum is characterized by minimal skin involvement (such as that

observed in adults with KS), with or without other mild manifestations. Some individuals with mild manifestations are not diagnosed until late in life; for example, two individuals were diagnosed by molecular genetic testing in their 60s and 70s after early-stage cutaneous precancerous lesions and epithelial skin cancer were identified and treated in their 50s [Has et al 2010]. In contrast, the severe end of the spectrum is characterized by such findings as severe mucosal involvement, severe esophageal stenosis, pseudoainhum, anemia, and/or malignancies.

Blisters are present at birth; those observed in childhood are mainly localized to extremities.

- Blisters result from trauma and/or exposure to sunlight.
- The number of blisters decreases by age ten to 12 years [Siegel et al 2003, Penagos et al 2004].
- Pyogenic skin infections can be a complication of blistering.

Skin atrophy, characterized by thin, wrinkled (cigarette-paper) skin is initially primarily localized to hands and feet; atrophy becomes generalized by adolescence and is often present on the abdomen, thighs, knees, and elbows (Figure 1a, 1f, 1g) [Jobard et al 2003].

Photosensitivity, characterized by erythema and burning after sun exposure, tends to improve with age; however, some degree of photosensitivity usually persists (e.g., facial erythema after minimal sun exposure) [Ashton et al 2004]. Note: Affected individuals can develop redness within minutes of sun exposure.

Poikiloderma, which is not present at birth, appears first on sun-exposed areas, progressing with age to non-sun-exposed areas (Figure 1b). This is characterized by reticular telangiectasia and mottled hypo- and hyperpigmentation of the skin, frequently appearing between ages two and three years. Generalized poikiloderma (in both sun-exposed and non-sun-exposed areas) eventually develops and persists throughout adult life in most affected individuals.

Axillary freckling may be observed in some (Figure 1a) [Jobard et al 2003, Siegel et al 2003, Rayinda et al 2021].

Hyperkeratosis of the palms and soles has been reported as fissured or punctate [Penagos et al 2004] and is observed in about 65% of affected individuals. Palmar hyperkeratosis often has a waxy appearance, occasionally leading to the loss of the dermal ridges (i.e., fingerprints). Dermatoglyphics can be flattened or lost. Some individuals may have ridged, ribbed hyperkeratosis of the lateral and anterior ankles reminiscent of epidermolytic hyperkeratosis.

Pseudosyndactyly. Typically, interdigital webbing develops (Figure 1f), but without the scarring or milia noted in other forms of epidermolysis bullosa (EB) [Jobard et al 2003, Siegel et al 2003].

Constricting bands of the pseudoainhum type have also been reported (Figure 1e, 1g) [Penagos et al 2004].

Mucosal involvement can include the following [Jobard et al 2003, Penagos et al 2004]:

- **Eyes.** Conjunctivitis, conjunctival scarring, corneal erosion, and ectropion of the lower eyelids [Lelli 2010, Martinez & Siegel 2011, Signes-Soler et al 2013]
- **Mouth and periodontium.** Severe periodontal disease (e.g., hemorrhagic mucositis, gingivitis, periodontitis, premature loss of teeth, and labial leukokeratosis), usually beginning in early adolescence [Lai-Cheong & McGrath 2010]
- **Gastrointestinal tract.** Esophageal stenosis, severe colitis, bloody diarrhea, constipation, and rectal mucosal fissures and stenosis. Affected children born with an imperforate anus that required surgical repair have also been reported [Lai-Cheong & McGrath 2010].
- **Genitourinary tract**
  - Vaginal stenosis and labial synechiae
  - Urethral meatal stenosis and urethral strictures, phimosis

Malignancy. About half of individuals with KS will develop squamous cell carcinoma in their lifetime. An increased risk for malignancies has been reported:

- Squamous cell carcinomas in acral skin and the mouth (lip and hard palate) [Lotem et al 2001, Emanuel et al 2006, Guerrero-Aspizua et al 2019]
- Transitional cell carcinomas of the bladder [Alper et al 1978]

Other findings that may be present:

- Xerosis, eczema, and dermatitis
- Variable hypermobility of the thumb, fingers, knees, and elbows without skin hyperextensibility [Penagos et al 2004]
- Nail dystrophy (Figure 1e)

Morbidity and mortality mostly result from mucosal strictures and associated complications, secondary infections or cutaneous bullae, and cancer.

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been identified.

Most *FERMT1* variants associated with Kindler syndrome are null variants. It has been proposed that *FERMT1* pathogenic missense variants and in-frame deletions are associated with milder disease manifestations and later onset of complications [Maier et al 2016].

Nomenclature

KS was first described by Theresa Kindler [Kindler 1954].

In May 2007, 18 leading authorities on epidermolysis bullosa (EB) revised the EB classification to include KS based on its biologic and clinical findings [Fine et al 2008, Fine et al 2014].

Prevalence

Since the first description of KS in 1954 [Kindler 1954], about 400 affected individuals have been reported worldwide.

Persons of any geographic origin can be affected and there is no sex predilection [Siegel et al 2003, Has et al 2011]. A cluster of 26 Panamanian affected individuals and 24 Iranian affected individuals with the syndrome have been identified [Penagos et al 2004, Youssefian et al 2015].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *FERMT1*.

Differential Diagnosis

Before the onset of the photosensitivity and poikiloderma in the first few years of life, Kindler syndrome (KS) is frequently confused with other variants of epidermolysis bullosa (e.g., dystrophic, junctional, and simplex epidermolysis bullosa); however, acral skin atrophy is indicative of KS. Furthermore, in contrast to blistering in other types of epidermolysis bullosa, the blistering in KS significantly improves with age.

Disorders of known genetic cause that can exhibit features of poikiloderma but are distinguishable by other clinical features are summarized Table 3.

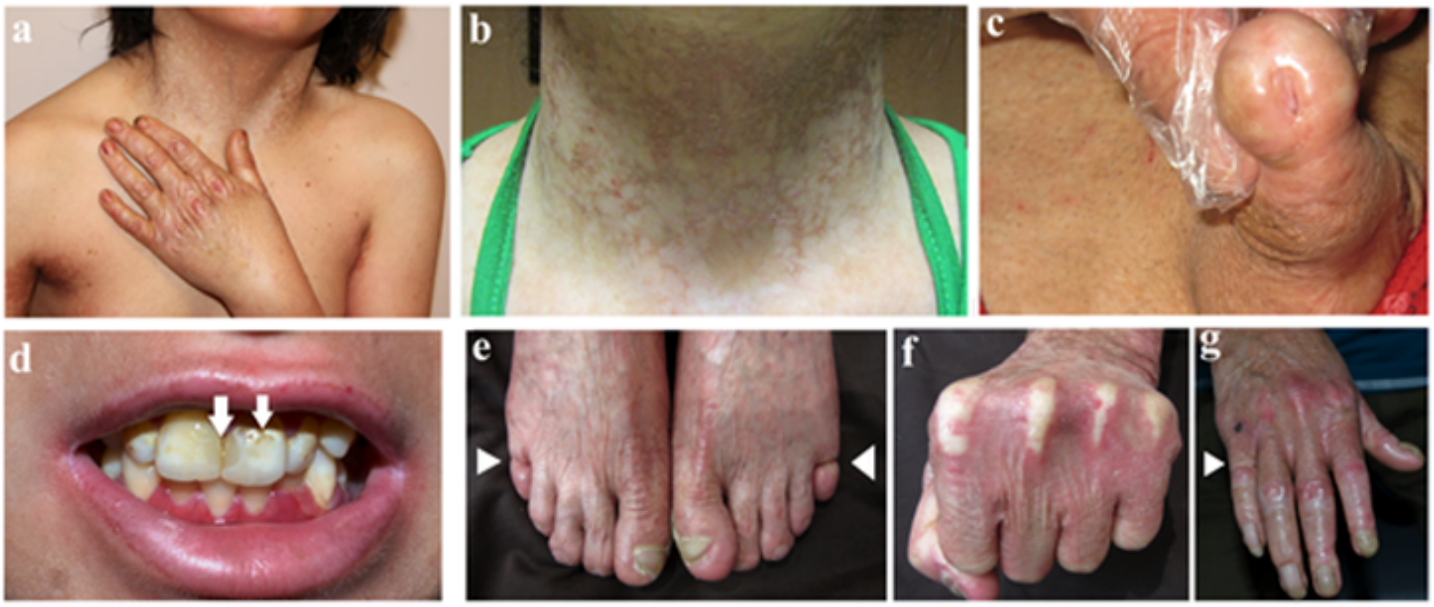

Figure 1. Characteristic clinical features of Kindler syndrome

a. Child age nine years: atrophy of skin on the dorsum of the hands and poikiloderma on the neck and axillary area

b. Poikiloderma of the neck

c. Urethral stenosis

d. Gingival fragility and enamel hypoplasia (arrows)

e. Individual age 35 years: atrophy of the skin on the dorsum of the feet, nail dystrophy, and bilateral pseudoainhum (acquired constricting ring around a digit) of fifth toes (arrow heads)

f. Cutaneous atrophy with calcinosis cutis of the dorsum of the hands and pseudosyndactyly

g. Pseudoainhum in the fifth finger (arrow head)

Table 3. Disorders with Features of Poikiloderma in the Differential Diagnosis of Kindler Syndrome

Gene(s)	Disorder	MOI	Clinical Characteristics	
			Ectodermal Findings	Other Findings
ACD *CTC1* *DKC1* *NHP2* *NOP10* *PARN* *RTEL1* *TERC* *TERT* *TINF2* *WRAP53*	Dyskeratosis congenita	XL AD AR	Dysplastic nails, lacy reticular pigmentation of upper chest &/or neck. Poikiloderma & nail dystrophy occur in late childhood.	Oral leukoplakia. ↑ risk for progressive bone marrow failure, myelodysplastic syndrome or acute myelogenous leukemia, solid tumors, & pulmonary fibrosis.
ANAPC1 *RECQL4*	Rothmund-Thomson syndrome	AR	Rash that typically develops ages 3-6 mos (occasionally as late as age 2 yrs) as erythema, swelling, & blistering on face, then spreading to buttocks & extremities. Over mos to yrs, rash evolves into poikiloderma. Sparse hair, eyelashes, &/or eyebrows.	Small size; skeletal & dental abnormalities; juvenile cataracts; ↑ risk for cancer, esp osteosarcoma

Table 3. continued from previous page.

Gene(s)	Disorder	MOI	Clinical Characteristics	
			Ectodermal Findings	Other Findings
BLM	Bloom syndrome	AR	Skin at birth & during early infancy appears normal. During 1st or 2nd yr of life, typically following sun exposure, red, sun-sensitive rash appears on nose & cheeks (sometimes also on dorsa of hands & forearms). Rash varies in severity & extent & is usually characterized by telangiectasia but in others is described as poikiloderma.	Severe pre- & postnatal growth deficiency, highly characteristic sparseness of subcutaneous fat tissue throughout infancy & early childhood, & short stature throughout postnatal life. Gastroesophageal reflux is common.
CD151	KS-like epidermolysis bullosa [1]	AR	Facial freckling, poikiloderma, atrophy of skin, & acrogeria of backs of hands on sun-exposed areas. Unlike KS, which presents w/blistering during childhood, 1 person described [1] presented widespread blistering & erosions primarily in pretibial area in adulthood. Dystrophic nails in all fingers & toes & early-onset alopecia were also observed.	The person described [1] had history of nephropathy manifesting w/ proteinuria.
DDB2 *ERCC1* *ERCC2* *ERCC3* *ERCC4* *ERCC5* *POLH* *XPA* *XPC*	Xeroderma pigmentosum (XP)	AR	Sun sensitivity w/marked freckle-like pigmentation of face before age 2 yrs. Sunlight-induced ocular involvement. Greatly ↑ risk of sunlight-induced cutaneous neoplasms. XP typically does not have acral bullae whereas in KS acral bullae are observed in childhood.	~25% of affected persons have neurologic manifestations.
FAM111B	Hereditary fibrosing poikiloderma w/ tendon contractures, myopathy, & pulmonary fibrosis	AD	Poikiloderma (typically beginning in 1st 6 mos & mainly localized to face), hypohidrosis w/heat intolerance, mild lymphedema of extremities, chronic erythematous & scaly skin lesions on extremities, sclerosis of digits, & mild palmoplantar keratoderma. Typically scalp hair, eyelashes, &/or eyebrows are sparse; nail dysplasia may be assoc.	Muscle contractures usually seen in childhood; progressive weakness of proximal & distal muscles of all 4 limbs
USB1	Poikiloderma w/ neutropenia (Clericuzio-type poikiloderma w/ neutropenia) [2]	AR	Inflammatory eczematous rash (ages 6-12 mos) followed by post-inflammatory poikiloderma (age >2 yrs); nail dystrophy & palmar/plantar hyperkeratosis	Chronic noncyclic neutropenia typically assoc w/recurrent sinopulmonary infections in 1st 2 yrs of life & (often) bronchiectasis. ↑ risk for myelodysplastic syndrome. Reactive airway disease.

AD = autosomal dominant; AR = autosomal recessive; KS = Kindler syndrome; MOI = mode of inheritance; XL = X-linked
1. Vahidnezhad et al [2018]
2. Vahidnezhad et al [2021]

Disorders of unknown genetic cause with features of poikiloderma

- The designation **Weary-Kindler syndrome (WKS)** has been used for a disorder with features that overlap with KS including vesicopustules, eczema, poikiloderma, and acral keratotic papules in infancy. In WKS the bullae are not congenital and photosensitivity and mucosal involvement are not observed [Weary et al 1971, Larrègue et al 1981, Lai-Cheong et al 2009]. It has been suggested that Weary and Kindler syndromes are aspects of the same disorder [Lee et al 2012].

- **Mendes da Costa syndrome**, also referred to as hereditary bullous dystrophy, macular type (OMIM 302000), is characterized by microcephaly, short stature, mild intellectual disability, cone-shaped fingers, and poikiloderma. The disorder has been described in Dutch and Italian families [Sybert 2010].
- **Hereditary sclerosing poikiloderma** (OMIM 173700) is characterized by progressive poikiloderma in flexural areas (manifest as hyper- and hypopigmentation without telangiectasia or atrophy), sclerotic bands, poor dentition, and occasionally calcinosis cutis [Weary et al 1969]. A later-onset complication is stenosis of cardiac valves. Absence of bullae and photosensitivity distinguish hereditary sclerosing poikiloderma from KS.

Management

No clinical practice guidelines for Kindler syndrome (KS) have been published.

Evaluation Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with KS, the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 4. Recommended Evaluations Following Initial Diagnosis in Individuals with Kindler Syndrome

System/Concern	Evaluation	Comment
Skin issues	Comprehensive dermatologic eval for skin fragility, blistering, photosensitivity, & risk for squamous cell carcinoma	
Eyes	Ophthalmologic consult for conjunctival involvement	
Mouth	Dental consult for periodontal involvement	
GI tract	• Gastroenterology eval for strictures affecting GI tract • Incl eval of nutritional status, diet, & oral intake	
Genitourinary tract	• Males: urology consult for urethra or foreskin stricture/stenosis • Females: gynecology eval for vaginal or labial stricture/stenosis	
Genetic counseling	By genetics professionals [1]	To inform affected persons & families re nature, MOI, & implications of KS to facilitate medical & personal decision making
Family support & resources	Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental support; • Home nursing referral.	

GI = gastrointestinal; KS = Kindler syndrome; MOI = mode of inheritance

1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

No established treatment for KS exists. The goals of care are to treat manifestations and prevent complications.

When possible, children with KS should be managed in a center experienced in caring for children with skin fragility by a multidisciplinary team that includes a dermatologist, pediatrician, ophthalmologist, dentist, gastroenterologist, urologist, nurse specialist, and dietitian.

Table 5. Treatment of Manifestations in Individuals with Kindler Syndrome

Manifestation/Concern	Treatment
Skin blistering	• If blister is not painful, it should be kept intact. • Otherwise alleviate blister-related pain by draining fluid using a sterile needle, leaving overlying skin in place. • Apply ointment to blister & cover w/nonstick gauze bandage. • Antibiotics may be used to treat infected blister.
Skin fragility	Protection from trauma, e.g., by use of soft & protective clothing & avoiding contact sports to prevent physical trauma
Skin atrophy	Use of moisturizers for dry, pruritic skin
Photosensitivity	Sun safety education, incl use of high sun-protective factor (>30 SPF) sunscreens, use of sun-protective clothing (hats & long-sleeve shirts), & avoidance of sun exposure as much as possible
Eyes	• Lubrication of cornea by artificial tears & eye drops • Prevention of infections by use of local antibiotics • Surgical correction of corneal scarring by ophthalmologist as needed
Mouth & periodontium	Regular dental care to ensure optimal oral hygiene to reduce periodontal disease
GI tract	• Esophageal dilation may be indicated for those w/dysphagia. • Esophageal strictures & stenosis may require fluoroscopically guided balloon dilations [Sadler et al 2006]. • Temporary parenteral nutrition may be necessary when esophageal dysfunction is severe. • Anal stenosis & bleeding requires regular laxatives. • Severe colitis may require surgical bowel resection in some cases.
Genitourinary tract	• Urethral meatal stenosis may require dilation. Strictures may require stenting &/or surgical intervention. • Most males require circumcision for phimosis. • Vaginal or labial stricture/stenosis may require surgical intervention. In case of pregnancy, delivery should be considered by an elective cesarean section.

GI = gastrointestinal

Surveillance

Table 6. Recommended Surveillance for Individuals with Kindler Syndrome

System/Concern	Evaluation	Frequency
Risk for skin cancer	Screen for premalignant keratoses & early squamous cell carcinomas.	Starting in adolescence; annually thereafter
Risk for oral mucosa tumors	Screen for oral ulcerations, gingivitis, & periodontitis.	Starting in adolescence & w/regular dental checkups

Agents/Circumstances to Avoid

Avoid sun exposure by using sunscreen (SFP >30) and sun-protective clothing.

Evaluation of Relatives at Risk

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

Pregnancy Management

Although the cutaneous manifestations of KS are not exacerbated by pregnancy, vaginal stenosis and labial synechiae have been reported; thus, obstetric planning, such as consideration of delivery by elective cesarean section, warrants consideration [Mansur et al 2007]. Of note, specialized perioperative cesarean section management is needed to protect vulnerable skin and mucosa.

Breastfeeding is not advised because of the risk of blistering the breasts [Hayashi et al 2007].

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

Kindler syndrome (KS) is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected individual are obligate heterozygotes (i.e., presumed to be carriers of one *FERMT1* pathogenic variant based on family history).
- Molecular genetic testing is recommended for the parents of the proband to confirm that both parents are heterozygous for an *FERMT1* pathogenic variant and to allow reliable recurrence risk assessment. If a pathogenic variant is detected in only one parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
  - One of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent [Jónsson et al 2017].
  - Uniparental isodisomy for the parental chromosome with the pathogenic variant resulted in homozygosity for the pathogenic variant in the proband.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- If both parents are known to be heterozygous for an *FERMT1* pathogenic variant, each sib of an affected individual has at conception 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

- Unless an individual with KS has children with an affected individual or a carrier, offspring will be obligate heterozygotes (carriers) for a pathogenic variant in *FERMT1*.

- KS is reported more frequently in populations with high rates of consanguinity [Penagos et al 2004, Youssefian et al 2015]. Consanguinity increases the likelihood that an affected individual may have a reproductive partner who is heterozygous for an *FERMT1* pathogenic variant.
- The offspring of a proband and an individual heterozygous for an *FERMT1* pathogenic variant have a 50% chance of being affected and a 50% chance of being heterozygotes.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of an *FERMT1* pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *FERMT1* pathogenic variants in the family.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk 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.
- *FERMT1* molecular genetic testing for reproductive partners of known carriers is appropriate, particularly if consanguinity is likely.

Prenatal Testing and Preimplantation Genetic Testing

Once the *FERMT1* pathogenic variants have been identified in an affected family member, prenatal and preimplantation genetic testing for KS 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.

- **DEBRA International**
  Austria
  www.debra-international.org
- **DebRA of America**
  Phone: 833-debraUS; 212-868-9296
  Email: staff@debra.org
  www.debra.org
- **DebRA UK**
  United Kingdom
  Phone: +44 01344 771961
  Fax: +44 01344 762661
  Email: debra@debra.org.uk

www.debra.org.uk

- **Epidermolysis Bullosa Medical Research Foundation**
  Phone: 310-205-5119
  Email: a.pett@bep-la.com
  EBMRF

- **EBCare Registry**
  Email: connect@invitae.com
  ebcare.patientcrossroads.org

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. Kindler Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
FERMT1	20p12.3	Fermitin family homolog 1	FERMT1 database	FERMT1	FERMT1

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 Kindler Syndrome (View All in OMIM)

173650	KINDLER SYNDROME; KNDLRS
607900	FERM DOMAIN-CONTAINING KINDLIN 1; FERMT1

Molecular Pathogenesis

FERMT1 is located on chromosome 20; it consists of 15 exons and encodes kindlin-1 protein with 677 amino acids (~77.4 kd). The gene is expressed in different tissues including skin keratinocytes and epithelial cells of colon, lung, placenta, adrenal, and prostate [Jobard et al 2003]. Kindlin-1 is a focal adhesion protein that like other cytoskeletal proteins has "the four point one ezrin radixin and moesin" (FERM) and "pleckstrin" homology (PH) domains [Larjava et al 2008]. Kindlin-1 is an adaptor protein that links filamentous actin in the cell to membrane proteins and is involved in integrin-associated signaling pathways [Has et al 2011].

To date, a total of 91 loss-of-function pathogenic variants have been reported in *FERMT1*, including: missense, nonsense, and splicing variants; indels; and Alu-mediated gene rearrangements. The absence of kindlin-1 leads to disorganized keratinocytes as a result of aberrant integrin-mediated cell adhesion and migration [Larjava et al 2008, Rognoni et al 2016].

Mechanism of disease causation. Kindler syndrome is thought to occur via a loss-of-function mechanism; pathogenic variants may lead to absent kindlin-1 protein or production of nonfunctional protein.

Table 7. Notable *FERMT1* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_017671.5 NP_060141.3	c.328C>T	p.Arg110Ter	Common pathogenic variant [Has et al 2010, Almeida et al 2013, Guerrero-Aspizua et al 2019]
	c.910G>T	p.Glu304Ter	Common pathogenic variant [Ashton et al 2004, Sadler et al 2006, Techanukul et al 2011, Youssefian et al 2015]
	c.676dupC	p.Gln226fsTer16	Common pathogenic variant [Martignago et al 2007, Kiritsi et al 2012, Almeida et al 2013, Heidari et al 2016, Guerrero-Aspizua et al 2019, Valinotto et al 2020]
	c.862C>T	p.Arg288Ter	Common pathogenic variant [Siegel et al 2003, Krishna et al 2014]
	c.676C>T	p.Gln226Ter	Common pathogenic variant [Heidari et al 2016, Guerrero-Aspizua et al 2019]
	c.456dupA	p.Asp153fs	Common pathogenic variant [Kiritsi et al 2012, Guerrero-Aspizua et al 2019]
	c.811C>T	p.Arg271Ter	Common pathogenic variant [Penagos et al 2004, Burch et al 2006]

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.

Chapter Notes

Author Notes

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Leila Youssefian, PhD and **Hassan Vahidnezhad, PhD** are researchers in medical genetics working on genodermatoses at Jefferson Institute of Molecular Medicine of Thomas Jefferson University in Philadelphia, Pennsylvania.

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Individuals with Kindler syndrome, Kindler epidermolysis bullosa, or Kindler-like syndrome interested in receiving information and free genetic testing can contact Leila Youssefian (email: leila.youssefian@jefferson.edu or phone: 610-999-9402).

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