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EFEMP2-Related Cutis Laxa

Synonym: Autosomal Recessive Cutis Laxa Type 1B (ARCL1B)

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Summary

Clinical characteristics

EFEMP2-related cutis laxa, or autosomal recessive cutis laxa type 1B (ARCL1B), is characterized by cutis laxa and systemic involvement, most commonly arterial tortuosity, aneurysms, and stenosis; retrognathia; joint laxity; and arachnodactyly. Severity ranges from perinatal lethality as a result of cardiopulmonary failure to manifestations limited to the vascular and craniofacial systems.

Diagnosis/testing

The diagnosis of *EFEMP2*-related cutis laxa is established in a proband with suggestive findings and biallelic pathogenic variants in *EFEMP2* identified by molecular genetic testing.

Management

Treatment of manifestations: Treatment of aortic root dilatation with beta-blockers or angiotensin receptor inhibitors can be considered. Aortic aneurysm replacement has been performed successfully. Symptomatic treatment of pulmonary emphysema; muscle-reinforcing physical therapy for joint hypermobility; routine repair of hernias. Tracheostomy may be necessary when retrognathia leads to upper-airway obstruction.

Surveillance: Follow-up evaluations with a cardiologist and pulmonologist at least annually starting from the time of diagnosis. Annual MR angiography from head to pelvis.

Agents/circumstances to avoid: Sun tanning to avoid damaging the skin; cigarette smoking to avoid worsening of emphysema.

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Genetic counseling

EFEMP2-related cutis laxa is inherited in an autosomal recessive manner. If both parents are known to be heterozygous for an *EFEMP2* 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 *EFEMP2* pathogenic variants have been identified in an affected family member, carrier testing for at-risk relatives, prenatal testing for a pregnancy at increased risk, and preimplantation genetic testing are possible.

Diagnosis

Suggestive Findings

The diagnosis of *EFEMP2*-related cutis laxa **should be considered** in individuals with the following clinical characteristics:

- **Vascular involvement**
  - Arterial and aortic tortuosity
  - Aortic and arterial aneurysms. The ascending aorta and aortic arch are typically most dilated.
  - Aortic stenosis. The isthmus aorta in particular is often stenotic.
  - Stenosis and dilatation of pulmonary arteries
  - Pulmonary hypertension
  - Hemorrhagic stroke
- **Cutis laxa.** Furrowing of the skin of the whole body that can be displaced more than normal skin and shows abnormal recoil; the skin has a "doughy" consistency. It does not display redundancy as in the Ehlers-Danlos syndromes.
- **Respiratory involvement.** Diaphragmatic hernia or hypoplasia
- **Craniofacial involvement**
  - Retrognathia
  - Widely spaced eyes
  - High palate
  - Long philtrum
  - Sagging cheeks
  - Dysplastic ears
- Other evidence of a **generalized connective disorder**
  - Joint laxity or contractures
  - Arachnodactyly
  - Pectus excavatum
  - Inguinal hernias
  - Hypotonia
  - Bone fragility

Establishing the Diagnosis

The diagnosis of *EFEMP2*-related cutis laxa **is established** in a proband with suggestive findings and biallelic pathogenic (or likely pathogenic) variants in *EFEMP2* 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 *EFEMP2* variants of

uncertain significance (or identification of one known *EFEMP2* pathogenic variant and one *EFEMP2* variant of uncertain significance) does not establish or rule out the diagnosis.

Because the phenotype of *EFEMP2*-related cutis laxa is indistinguishable from many other inherited disorders with cutis laxa and/or arterial abnormalities (tortuosity, aneurysm, and/or stenosis), recommended molecular genetic testing approaches include use of a **multigene panel** or **comprehensive genomic testing**.

Note: Single-gene testing (sequence analysis of *EFEMP2*, followed by gene-targeted deletion/duplication analysis) is rarely useful and typically NOT recommended.

- **A cutis laxa or arteriopathy multigene panel** that includes *EFEMP2* 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.

  If exome sequencing is not diagnostic, **exome array** (when clinically available) may be considered to detect (multi)exon deletions or duplications that cannot be detected by sequence analysis. Note: To date such variants have not been identified as a cause of this disorder.

  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 *EFEMP2*-Related Cutis Laxa

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
EFEMP2	Sequence analysis [3]	~100% [4]
	Gene-targeted deletion/duplication analysis [5]	None reported [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

EFEMP2-related cutis laxa (autosomal recessive cutis laxa type 1B, ARCL1B) is a highly variable disorder ranging from perinatal lethality caused by cardiopulmonary failure [Hoyer et al 2009, Letard et al 2018] to manifestations limited to the vascular and craniofacial systems [Renard et al 2010]. The most common shared features besides cutis laxa include arterial tortuosity, aneurysms, and stenosis; retrognathia; joint laxity; and arachnodactyly.

To date, 49 individuals have been identified with a pathogenic variant in *EFEMP2* [Hucthagowder et al 2006, Dasouki et al 2007, Hoyer et al 2009, Renard et al 2010, Al-Hassnan et al 2012, Erickson et al 2012, Iascone et al 2012, Kappanayil et al 2012, Sawyer et al 2013, Hebson et al 2014, Hibino et al 2018, Letard et al 2018, Mauger et al 2019, Yetman et al 2019]. The following description of the phenotypic features associated with this condition is based on these reports.

Table 2. *EFEMP2*-Related Cutis Laxa: Frequency of Select Features

Feature	% of Persons w/Feature [1]	Comment
Arterial/aortic aneurysms	>90%	Most typically occurring in ascending aorta & aortic arch
Arterial tortuosity	>90%	
Arterial stenosis	25%-90%	Typically occurs in aortic isthmus
Early mortality	25%-90%	
Emphysema	<25%	
Diaphragmatic abnormalities	25%-90%	Diaphragmatic herniation, rupture
Cutis laxa	25%-90%	
Thin translucent skin	<25%	
Velvety skin	<25%	
Hernia	25%-90%	Inguinal, umbilical hernia
Micro-/retrognathia	25%-90%	
Long philtrum	25%-90%	
Widely spaced eyes	25%-90%	
Keratoglobus	<25%	
High palate	25%-90%	
Dysplastic ears	<25%	
Joint laxity or contractures	25%-90%	
Hypotonia	25%-90%	
Arachnodactyly	25%-90%	
Pectus deformity	<25%	Pectus excavatum or carinatum
Bone fragility	<25%	Bone fractures, rib/long bone defects, ↓ bone mineral density

1. Based on Hebson et al [2014] and subsequent individual case reports

Cardiovascular. The most typical cardiovascular findings are marked aortic dilatation, aortic and arterial tortuosity, isthmic aortic narrowing, and dilatation/stenosis of the pulmonary arteries. Aberrant branching of the right pulmonary artery is also a frequent finding. Additional cardiovascular findings that have been

described occasionally include cardiac hypertrophy, bradycardia [Dasouki et al 2007, Hoyer et al 2009], pulmonary hypertension, and tricuspid insufficiency [Dasouki et al 2007]. In a cohort of 16 affected individuals from India, almost all died from cardiopulmonary failure in the neonatal period [Nampoothiri et al 2010]. Other individuals underwent successful aortic surgery and survived [Sawyer et al 2013, Hebson et al 2014, Hibino et al 2018, Yetman et al 2019].

Lung. Most common lung problems are related to diaphragmatic hypoplasia or hernia. Developmental emphysema has been described in one individual [Hoyer et al 2009], but emphysema is more typical for *FBLN5*-associated cutis laxa.

Skin. Although *EFEMP2*-related cutis laxa is classified within the cutis laxa group, skin findings can be minor or even normal. If present, pertinent skin findings include cutis laxa and thin translucent or velvety skin.

Craniofacial. The most recurrent characteristics are mirognathia or retrognathia, long philtrum, widely spaced eyes, high palate, and dysplastic ears. Additional features include thin vermilion of the upper lip and prominent eyes. A single individual has been reported with keratoglobus [Mauger et al 2019].

Musculoskeletal. Individuals with *EFEMP2*-related cutis laxa usually present with muscle hypotonia. Other common findings are joint laxity or contractures, arachnodactyly, and pectus deformities (carinatum or excavatum). Fractures also appear to be common [Hoyer et al 2009]. Additional skeletal observations include soft cranial bones, bowing and elongation of the long bones, and flaring of the metaphyses.

Other. Inguinal/umbilical hernias may be present.

Genotype-Phenotype Correlations

Survival analysis comparing four individuals with at least one truncating *EFEMP2* pathogenic variant with 22 individuals with biallelic missense *EFEMP2* pathogenic variants showed a shorter median survival in the first group (9.45 months vs 36 months) [Letard et al 2018].

Prevalence

Very few reliable estimates of the prevalence of cutis laxa exist. The prevalence at birth for all types of cutis laxa is 1:4,000,000 according to the Rhone-Alps Eurocat Registry [E Robert, personal observation].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *EFEMP2*.

Differential Diagnosis

Table 3. Genes of Interest in the Differential Diagnosis of *EFEMP2*-Related Cutis Laxa (ARCL1B)

Gene(s)	Disorder	MOI	Clinical Findings					Comment
			CL	Emphysema	ID	GI & GU malformation	Cardiovascular	
ALDH18A1	ARCL3A (OMIM 219150)	AR	+	–	+++	–	–	ARCL3A is not assoc w/ cardiovascular & pulmonary involvement.

Table 3. continued from previous page.

Gene(s)	Disorder	MOI	Clinical Findings					Comment
			CL	Emphysema	ID	GI & GU malformation	Cardiovascular	
ATP6V0A2	*ATP6V0A2*-related cutis laxa (ARCL2A)	AR	++	–	++	–	–	ARCL2A is also assoc w/hip dislocation & delayed closure of fontanelle. Secondary effects of strokes (DD, structural brain defects) [1] may complicate distinction between ARCL2A & ARCL1B.
ATP6V1A	ARCL2D (OMIM 617403)	AR	+++	–	–	+	Aneurysm	Progeroid facial features
ATP6V1E1	ARCL2C (OMIM 617402)	AR	+++	–	–	+	Aneurysm	Progeroid facial features; overlapping features w/ ARCL2A
ATP7A	Occipital horn syndrome (OHS) (See *ATP7A* Copper Transport Disorders.)	XL	+	–	+	+	Vascular tortuosity (mainly of cerebral vasculature)	
ELN	*ELN*-related cutis laxa (ADCL1)	AD	+	+	–	–	Aortic root dilatation, aneurysm	Absence of arterial tortuosity, infantile aneurysms, infantile developmental emphysema, death in infancy/early childhood, arachnodactyly, & retrognathia in ADCL1 distinguish it from ARCL1B.
EMILIN1	*EMILIN1*-related cutis laxa [2]	AR	+	–	–	+	Aneurysm, arterial tortuosity	Bone fragility, congenital anomalies of kidney & urinary tract
FBLN5	*FBLN5*-related cutis laxa (ARCL1A & ADCL2)	AR AD	+++	+++	–	+	Peripheral pulmonary arterial stenosis	No aortic/arterial aneurysms
GORAB	Gerodermia osteodysplastica (GO) (OMIM 231070)	AR	++	–	–	–	–	GO is generally not assoc w/CV & pulmonary manifestations.
LTBP4	*LTBP4*-related cutis laxa (URDS, ARCL1C)	AR	++	+++	–	+++	Peripheral pulmonary artery stenosis	URDS craniofacial & pulmonary phenotype is similar to ARCL1B. Relatively mild CV involvement & severe GI & urinary complications in URDS distinguish ARCL1C from ARCL1B.

Table 3. continued from previous page.

Gene(s)	Disorder	MOI	Clinical Findings					Comment
			CL	Emphysema	ID	GI & GU malformation	Cardiovascular	
PYCR1	ARCL3B (OMIM 614438)	AR	+	–	+	–	Arterial stenoses, intracranial artery malformation	
	ARCL2B (OMIM 612940)	AR	+	–	+++	–	–	
SLC2A10	Arterial tortuosity syndrome	AR	+	+ [3]	–	–	Severe & widespread arterial tortuosity of aorta & middle-sized arteries (w/↑ risk of aneurysms & dissections); focal & widespread stenosis	
SMAD2 *SMAD3* *TGFB2* *TGFB3* *TGFBR1* *TGFBR2*	Loeys-Dietz syndrome	AD	+	–	–	–	Cerebral, thoracic, & abdominal arterial aneurysms &/or dissections; arterial tortuosity often present	

AD = autosomal dominant; ADCL = autosomal dominant cutis laxa; AR = autosomal recessive; ARCL = autosomal recessive cutis laxa; CL = cutis laxa; CV = cardiovascular; DD = developmental delay; GI = gastrointestinal; GU = genitourinary; ID = intellectual development; MOI = mode of inheritance; URDS = Urban-Rifkin-Davis syndrome

1. Hoyer et al [2009], Renard et al [2010]

2. Adamo et al [2022]

3. Single case report of emphysema in arterial tortuosity syndrome reported by Takahashi et al [2013]

Management

No clinical practice guidelines for *EFEMP2*-related cutis laxa have been published.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *EFEMP2*-related cutis laxa, 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 *EFEMP2*-Related Cutis Laxa

System/Concern	Evaluation	Comment
Arterial aneurysm, tortuosity, &/or stenosis	Echocardiography, 3D CT scan, MRA from head to pelvis	Recommend involvement of pediatric cardiologist
Emphysema / Obstructive lung disease	Lung function test & bronchoscopy	Recommend involvement of pediatric pulmonologist
Bony abnormalities	Radiographs	
Recurrent bone fractures	Bone densitometry	
Keratoglobus	Ophthalmologic eval	

Table 4. continued from previous page.

System/Concern	Evaluation	Comment
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of *EFEMP2*-related cutis laxa to facilitate medical & personal decision making

MOI = mode of inheritance; MRA = magnetic resonance angiography
1. Medical geneticist, certified genetic counselor, or certified advanced genetic nurse

Treatment of Manifestations

Table 5. Treatment of Manifestations in Individuals with *EFEMP2*-Related Cutis Laxa

Manifestation/ Concern	Treatment
Arterial dilatation/ aneurysm	• Based on experience in related disorders (e.g., Marfan syndrome), treatment w/beta-blockers or angiotensin receptor blockers can be considered when aortic root dilatation is present. • Surgical repair of large aortic aneurysms (at risk for dissection) should be considered. • Aortic aneurysm replacement has been performed successfully.
Pulmonary emphysema	Treated symptomatically
Micrognathia	Tracheostomy may be necessary when retrognathia leads to upper airway obstruction.
Joint hypermobility	Muscle-strengthening PT
Hernia	Routine surgical repair

PT = physical therapy

Surveillance

Table 6. Recommended Surveillance for Individuals with *EFEMP2*-Related Cutis Laxa

System/Concern	Evaluation	Frequency
Cardiovascular & pulmonary concerns	Follow-up evals w/cardiologist & pulmonologist	At least annually from time of diagnosis
Arterial abnormalities	MRA from head to pelvis	Annually

MRA = magnetic resonance angiography

Agents/Circumstances to Avoid

Avoid the following:

- Sun tanning, which can damage skin
- Cigarette smoking, which can worsen emphysema

Evaluation of Relatives at Risk

It is appropriate to clarify the genetic status of older and younger sibs of an affected individual in order to identify as early as possible those who should undergo regular cardiovascular and pulmonary surveillance to allow prompt initiation of treatment and preventive measures.

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

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

EFEMP2-related cutis laxa is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected child are obligate heterozygotes (i.e., presumed to be carriers of one *EFEMP2* pathogenic variant based on family history).
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for an *EFEMP2* pathogenic variant and to allow reliable recurrence risk assessment. (*De novo* variants are known to occur at a low but appreciable rate in autosomal recessive disorders [Jónsson et al 2017].)
- 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 *EFEMP2* 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.
- In general, similar clinical manifestations are observed in sibs with *EFEMP2* pathogenic variants, but exceptions exist.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. The offspring of an individual with *EFEMP2*-related cutis laxa are obligate heterozygotes (carriers) for a pathogenic variant in *EFEMP2*.

Other family members. Each sib of the proband's parents has a 50% risk of being a carrier of an *EFEMP2* pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *EFEMP2* 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.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

Once the *EFEMP2* pathogenic variants have been identified in an affected family member, prenatal testing 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.

- **DermNet NZ**
  New Zealand
  Cutis Laxa
- **MedlinePlus**
  Cutis laxa

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. EFEMP2-Related Cutis Laxa: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
EFEMP2	11q13.1	EGF-containing fibulin-like extracellular matrix protein 2	EFEMP2 database	EFEMP2	EFEMP2

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 EFEMP2-Related Cutis Laxa (View All in OMIM)

604633	EGF-CONTAINING FIBULIN-LIKE EXTRACELLULAR MATRIX PROTEIN 2; EFEMP2
614437	CUTIS LAXA, AUTOSOMAL RECESSIVE, TYPE IB; ARCL1B

Molecular Pathogenesis

Different mechanisms have been suggested for the pathogenetic consequences of *EFEMP2* mutation [Papke & Yanagisawa 2014, Papke et al 2015, Sasaki et al 2016]. Biallelic pathogenic variants in *EFEMP2* lead to diminished secretion or stability of the fibulin-4 protein into the extracellular matrix. This leads to decreased activity of lysyl oxidase (important for collagen and elastin cross-linking) and other extracellular matrix components such as collagen IV, fibrillin-1, and elastin. Finally, a role in transforming growth factor-beta (TGFß) signaling has been proposed based on interactions with LTBP1 and LTBP4 (latent transforming growth factor beta binding protein).

Mechanism of disease causation. *EFEMP2*-related cutis laxa occurs via a loss-of-function mechanism, leading to impaired collagen and elastin function [Papke et al 2015].

Table 7. Notable *EFEMP2* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_016938.5 NP_058634.4	c.376G>A	p.Glu126Lys	Recurrent variant [Renard et al 2010, Sawyer et al 2013, Hebson et al 2014]
	c.481G>A	p.Glu161Lys	Founder variant in Saudi Arabia [Al-Hassnan et al 2012]
	c.608A>C	p.Asp203Ala	Founder variant in Malabar Mappila community in southern India [Kappanayil et al 2012]

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

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Revision History

- 15 June 2023 (aa) Revision: added *EMILIN1*-related cutis laxa to Differential Diagnosis
- 22 October 2020 (ha) Comprehensive update posted live

- 23 July 2015 (me) Comprehensive update posted live
- 12 May 2011 (me) Review posted live
- 9 July 2010 (bl) Original submission

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