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Lipoid Proteinosis

Synonyms: Hyalinosis Cutis et Mucosae, Urbach-Wiethe Disease

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Summary

Clinical characteristics

Lipoid proteinosis (LP) is characterized by deposition of hyaline-like material in various tissues resulting in a hoarse voice from early infancy, vesicles and hemorrhagic crusts in the mouth and on the face and extremities, verrucous and keratotic cutaneous lesions on extensor surfaces (especially the elbows), and moniliform blepharosis (multiple beaded papules along the eyelid margins and inner canthus). Extracutaneous manifestations may include epilepsy, neuropsychiatric disorders, spontaneous CNS hemorrhage, and asymptomatic multiple yellowish nodules throughout the gastrointestinal tract. Generally, the disease course is chronic and fluctuating. Males and females are affected equally. Affected individuals have a normal life span unless they experience laryngeal obstruction.

Diagnosis/testing

The diagnosis of lipoid proteinosis is established in a proband with characteristic clinical findings and either biallelic *ECM1* pathogenic variants identified on molecular genetic testing or characteristic histologic and/or immunolabeling findings on skin biopsy.

Management

Treatment of manifestations: There is no curative therapy for LP. Microlaryngoscopic excision of laryngeal deposits can improve airway access and voice quality. Significant airway obstruction may require tracheostomy to ensure a safe airway. Oral dimethylsulfoxide, D-penicillamine, and oral retinoid may be used for skin softening and amelioration of mucosal lesions and hoarseness. Seizures should be assessed and managed by a neurologist with anti-seizure medications.

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Surveillance: Assessment of the airway and vocal cords by an otolaryngologist and dermatologic examinations every six months; yearly neurologic and neuropsychiatric evaluations for seizures and emotional and cognitive development.

Genetic counseling

LP is inherited in an autosomal recessive manner. If both parents are known to be heterozygous for an *ECM1* pathogenic variant, each sib of an affected individual has at conception a 25% chance of inheriting biallelic pathogenic variants and being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Once the *ECM1* 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

Lipoid proteinosis (LP), which is characterized by deposition of hyaline-like material in the larynx, oral cavity, skin, and internal organs, **should be suspected** in individuals with the following clinical manifestations, neuroimaging findings and family history.

Clinical manifestations (in order of their importance for diagnosis):

- **Hoarse voice.** The first manifestation in almost all individuals is a weak cry or hoarse voice (due to infiltration and deposition of hyaline-like material in the vocal cords) appearing during the first year of life, and often in early infancy. Hoarseness usually persists lifelong [Savage et al 1988].
- **Moniliform blepharosis** (the presence of multiple beaded papules along the eyelid margins and inner canthus; see Figure 1d, 1e), is a pathognomic sign [Belliveau et al 2015]. The papular infiltration can be quite subtle in some individuals.
- **Cutaneous findings** (appearing in two overlapping stages):
  - First, vesicles and hemorrhagic crusts, often caused by minor trauma or friction, appear in the mouth and on the face and extremities (Figure 1a). Vesicles can be one of the earliest clinical manifestations in up to 50% of affected neonates.
  - Later, with increasing hyaline deposition in the dermis, the skin becomes diffusely thickened and appears waxy with a yellowish discoloration; papules, nodules, and plaques appear on the face and lips (Figure 1d). Verrucous and keratotic cutaneous lesions may develop on extensor surfaces, especially the elbows (Figure 1f) [Hamada 2002].
- **Central nervous system and neuropsychiatric manifestations** commonly include epilepsy (predominantly temporal lobe variant) and behavioral manifestations (memory impairment, paranoia, aggressive behavior, hallucinations, and absence of fear) [Siebert et al 2003, Thornton et al 2008] in association with calcification of the temporal lobes or hippocampi (Figure 1h).
- **Ear-nose-throat.** Infiltration of the mucosae of the pharynx, tongue, soft palate, tonsils, and lips may lead to upper respiratory tract infections as well as recurrent episodes of parotitis (caused by stenosis of the parotid duct), submandibular gland inflammation, and poor dental health. The tongue may be short; thickening of the sublingual frenulum may result in difficulty protruding the tongue (Figure1c) [Chan et al 2007].
- **Hair and nails.** Patchy alopecia of the scalp, beard, eyelashes, and eyebrows as well as nail dystrophy may be present [Hamada 2002].

Neuroimaging findings

- **Brain CT** readily detects mineral deposits (i.e., intracranial calcifications); in some it reveals circumscribed, horn-shaped bilateral symmetric calcifications (Figure 1h).
- **Brain MRI** can provide better anatomic details than CT but is less sensitive in detecting calcification [Siebert et al 2003, Chan et al 2004, Thornton et al 2008, Gonçalves et al 2010, Agredano et al 2020, Vahidnezhad et al 2020].

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 lipoid proteinosis **is established** in a proband with suggestive clinical findings and EITHER of the following:

- Biallelic pathogenic variants in *ECM1* identified on molecular genetic testing (see Table 1)
- Characteristic histologic findings and/or immunolabeling on skin biopsy (See Skin Biopsy.)

Note: Identification of biallelic *ECM1* variants of uncertain significance (or identification of one known *ECM1* pathogenic variant and one *ECM1* variant of uncertain significance) does not establish or rule out the diagnosis of this disorder.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those in whom the diagnosis of lipoid proteinosis has not been considered are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

Single-gene testing. Sequence analysis of *ECM1* is performed first to detect small intragenic deletions/insertions and missense, nonsense, and splice site variants. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If only one or no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications.

A multigene panel that includes *ECM1* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition at the most reasonable cost 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.

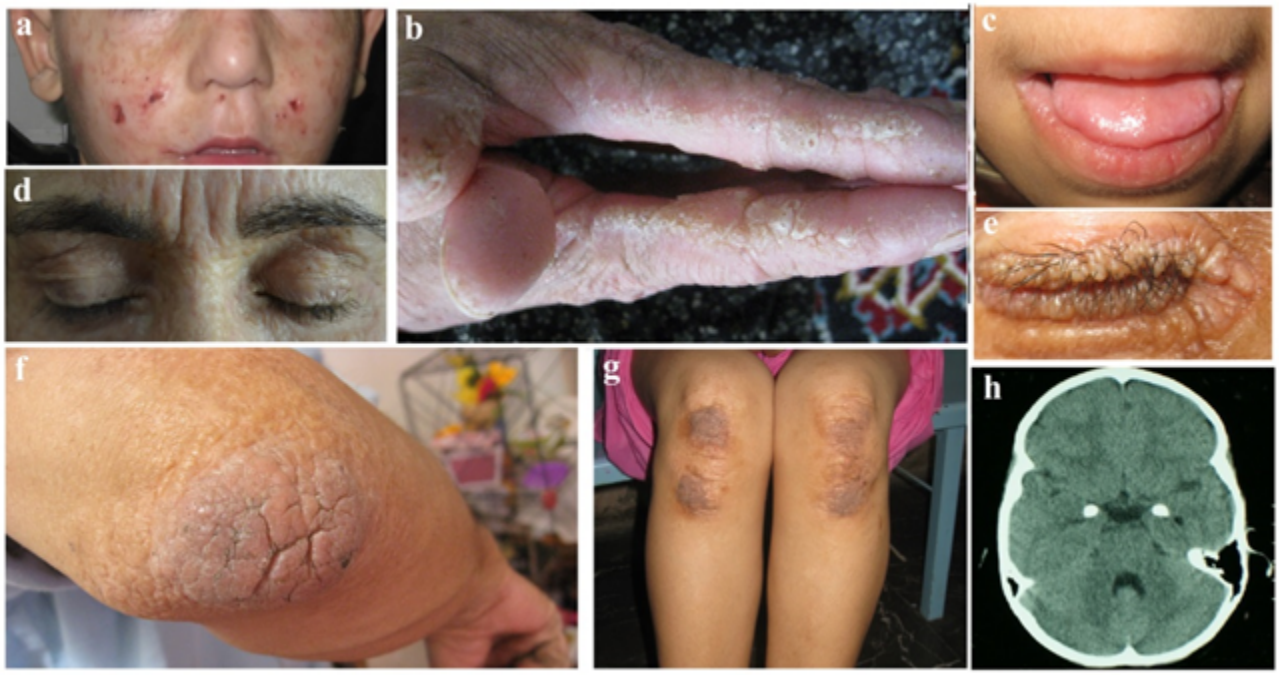

Figure 1. Clinical manifestations of lipoid proteinosis

a. Vesicles and hemorrhagic crusts and scars on the face

b. Hyperkeratotic wart-like or nodular lesions on the fingers

c. Reduced tongue movement due to thickening of the sub-lingual frenulum

d, e. Papular thickening of the upper and lower eyelids, and moniliform blepharosis (beaded papules on the eyelid margins)

f. Warty skin thickening and infiltration on the elbow

g. Warty nodules over infiltrated plaques on knees

h. Axial CT showing bilateral symmetric amygdalae calcifications

Option 2

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 Lipoid Proteinosis

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
ECM1	Sequence analysis [3]	>99% [4]
	Gene-targeted deletion/duplication analysis [5]	Rare [4, 6]

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 2017]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. Gross deletions and duplications have been reported in several individuals [Hamada et al 2002, Hameed et al 2009, Nasir et al 2009, Lee et al 2015a].

Skin Biopsy

Hematoxylin and eosin (H&E) staining shows hyperkeratosis and accumulation of hyaline-like material in the dermis.

Periodic acid-Schiff (PAS)-diastase staining shows PAS-positive, diastase-resistant basement membrane thickening and reduplication at the dermal-epidermal junction around blood vessels [An et al 2019].

Immunolabeling using polyclonal anti-ECM1 antibody shows reduced levels of ECM1 protein, providing a means of rapid diagnosis especially in the early stages of the disease [Chan et al 2004].

Clinical Characteristics

Clinical Description

Lipoid proteinosis (LP) is characterized by deposition of hyaline-like material that results in a hoarse voice from early infancy and characteristic skin lesions.

To date, more than 400 individuals have been identified with biallelic pathogenic variants in *ECM1* [LeWitt et al 2021]. The following description of the phenotypic features associated with this condition is based on these reports.

Table 2. Lipoid Proteinosis: Frequency of Select Features

Feature	Frequency		
	In nearly all	Common	Infrequent
Hoarse voice	●		
Severe dysphonia &/or complete aphonia		●	
Breathing difficulties		●	
Recurrent parotitis			●
Poor dental health		●	
Thickened sublingual frenulum	●		

Table 2. continued from previous page.

Feature	Frequency		
	In nearly all	Common	Infrequent
Vesicles & hemorrhagic crusts	●		
Moniliform blepharosis	●		
Hyperkeratotic & verrucous lesions		●	
Patchy & diffuse alopecia			●
Epilepsy			●
Neuropsychiatric disorders		●	
Spontaneous CNS hemorrhage			●
Gastrointestinal bleeding			●

Oral and upper-airway manifestations. A hoarse voice, often evident at birth or in early infancy as a weak cry, is present in essentially all individuals with LP, usually persists lifelong, and can progress to severe dysphonia and/or complete aphonia [Savage et al 1988]. In addition, involvement of the mucosae of the pharynx, soft palate, tonsils, and lips may lead to pulmonary manifestations, especially upper-respiratory tract infection. In some individuals, infiltration of the laryngeal mucosa may lead to breathing difficulties.

Recurrent episodes of parotitis caused by stenosis of the parotid duct and submandibular gland inflammation are reported. Infiltration of the tongue may destroy the dorsal papillae, causing the tongue to have a smooth surface.

Dental health is often poor [Chan et al 2007, Ravi Prakash et al 2013].

Skin lesions consist of vesicles and hemorrhagic crusts in the mouth and on the face and extremities induced by minor trauma, verrucous and keratotic cutaneous lesions on extensor surfaces (especially the elbows), and moniliform blepharosis (multiple beaded papules along the eyelid margins and inner canthus). Skin lesions usually progress during the first few years of life in two overlapping stages:

- During childhood the skin may be easily damaged by minor trauma or friction, resulting in blisters and scar formation. Pock-like or acneiform scars, vesicles, and hemorrhagic crust are particularly evident on the face and extremities (Figure1a).
- At later stages with increasing hyaline-like deposition within the dermis, skin becomes diffusely thickened and appears waxy with yellowish discoloration; papules, nodules, and plaques appear on the face and the lips (Figure1d).

Hyperkeratotic and verrucous lesions may appear in regions exposed to mechanical trauma, such as the hands, elbows, knees, buttocks, and axillae (Figure 1b, 1f, 1g) [Hamada 2002].

Patchy and diffuse alopecia of the scalp, beard, eyelashes, and eyebrows may be present; however, alopecia is not a significant finding in most. Nail dystrophy has been reported [Hamada 2002].

Extracutaneous manifestations may include the following:

- **Epilepsy.** Seizure onset may be in childhood or adulthood. Temporal lobe epilepsy is the most common type, with both partial and (less frequently) secondarily generalized seizures observed. Seizures may be resistant to therapy [Claeys et al 2007].
- **Neuropsychiatric disorders** can include impairment of day-to-day memory (but not distant memory), paranoia, aggressive behavior and rage, hallucinations, absence of fear, and lack of normal sense of distrust

or danger. Neuropsychiatric disorders can appear in childhood and are progressive. Individuals with lipoid proteinosis perform poorly on facial recognition of positive and negative emotions. These neuropsychiatric manifestations sometimes occur in association with calcification in the temporal lobes in the region of the amygdalae (Figure1h) [Siebert et al 2003, Thornton et al 2008].

- **Spontaneous CNS hemorrhage** (including small deep brain hemorrhages and large brain hematomata) has been reported and can lead to hemiparesis and hemiplegia [Siebert et al 2003, Messina et al 2012, Teive et al 2013].
- **Gastrointestinal manifestations.** Multiple yellowish nodules can be found throughout the esophagus, stomach, duodenum, and colon, and are usually asymptomatic [Custódio Lima et al 2014]; however, small intestinal bleeding has been observed in one individual [Caccamo et al 1994].

Clinical variability. A wide range of clinical manifestations and disease progression, including presence of neurologic abnormalities in the absence of skin manifestations, occurs in individuals with the same *ECM1* pathogenic variants even within the same family or population isolate [Youssefian et al 2015].

Course and prognosis. Generally, LP follows a chronic and fluctuating course. Males and females are affected equally. Affected individuals have a normal life span unless they experience laryngeal obstruction.

Genotype-Phenotype Correlations

No *ECM1* genotype-phenotype correlations have been identified [Hamada et al 2003].

Prevalence

More than 400 individuals with lipoid proteinosis (LP) have been reported worldwide [LeWitt et al 2021].

LP tends to be more common in countries with extensive consanguinity and/or in areas (e.g., South Africa) in which a founder variant has been postulated [Van Hougenhouck-Tulleken et al 2004, Chan et al 2007].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *ECM1*.

Differential Diagnosis

Table 3. Genes and Disorders of Interest in the Differential Diagnosis of Lipoid Proteinosis

Gene	Disorder	MOI	Overlapping Features	Distinguishing Features
ABCC6	Pseudoxanthoma elasticum (PXE)	AR	Some skin changes in LP (e.g., yellowish papules seen on the neck) are reminiscent of those in PXE.	Ocular manifestations are different: • LP is characterized by moniliform blepharosis. • PXE is characterized by subretinal neovascularization w/hemorrhage that can cause significant visual impairment.
FECH	Autosomal recessive erythropoietic protoporphyria (EPP)	AR	The early vesicular lesions in LP can resemble those in EPP.	• Hepatic dysfunction is rare in LP but may occur in 20%-30% of those w/EPP. • Hoarseness & moniliform blepharosis (features characteristic of LP) are not found in those w/ EPP.

AR = autosomal recessive; LP = lipoid proteinosis; MOI = mode of inheritance

Management

No clinical practice guidelines for lipoid proteinosis (LP) have been published.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with LP, 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 Lipoid Proteinosis (LP)

System/Concern	Evaluation	Comment
Skin lesions	Dermatologist	Assess for hemorrhagic or crusting lesions.
Upper airway	Otolaryngologist	Assess for airway obstruction assoc w/vocal cord infiltration.
Epilepsy	Neurologist	If clinical findings suggest seizures
Neuropsychiatric disorders	Neurobehavioral testing	Assess for memory impairment, hallucinations, paranoia, & aggressive behavior.
	Brain MRI	Assess for calcification in temporal lobes in the region of the amygdalae.
Genetic counseling	By genetics professionals [1]	To inform patients & families re nature, MOI, & implications of LP in order to facilitate medical & personal decision making
Family support & resources	Assess: • Use of community or online resources such as Parent to Parent; • Need for social work involvement for parental support; • Need for home nursing referral.	

MOI = mode of inheritance

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

Treatment of Manifestations

There is no curative therapy for LP.

Table 5. Treatment of Manifestations in Individuals with Lipoid Proteinosis (LP)

Manifestation/Concern	Treatment	Considerations/Other
Airway obstruction	Microlaryngoscopic excision of laryngeal deposits	Improves airway access & voice quality
	Tracheostomy	For significant airway obstruction
Cutaneous papules & plaques	Oral dimethylsulfoxide, D-penicillamine, & oral retinoid (e.g., acitretin)	For skin softening & concomitant amelioration of mucosal lesions & hoarseness
Seizures	ASM as determined by neurologist	• Some persons are resistant to ASMs. • Successful treatment w/ASMs incl Tegretol® & Keppra® has been reported [Omrani et al 2012].

ASM = anti-seizure medication

Surveillance

Table 6. Recommended Surveillance for Individuals with Lipoid Proteinosis (LP)

System/Concern	Evaluation	Frequency
Airway obstruction	Otolaryngologist assessment of airway & vocal cords	Every 6 mos
Cutaneous papules & plaques	Dermatologic exams	
Seizures	Neurologic eval	Annually
Neuropsychiatric disorders	Monitor for emotional & cognitive development.	

Evaluation of Relatives at Risk

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

Lipoid proteinosis (LP) 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 *ECM1* pathogenic variant based on family history).
- If a molecular diagnosis has been established in the proband, molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for an *ECM1* 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 are typically asymptomatic but may have variable findings. Youssefian et al [2015] reported voice hoarseness in cold seasons and thickening of the frenulum and a firm tongue in heterozygous family members.

Sibs of a proband

- If both parents are known to be heterozygous for an *ECM1* pathogenic variant, each sib of an affected individual has at conception a 25% chance of inheriting biallelic pathogenic variants and being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- A wide range of clinical manifestations and disease progression may be observed in sibs with the same *ECM1* pathogenic variants [Youssefian et al 2015].
- Heterozygotes are typically asymptomatic but may have variable findings. Youssefian et al [2015] reported voice hoarseness in cold seasons and thickening of the frenulum and a firm tongue in family members heterozygous for the c.507delT pathogenic variant in *ECM1*.

Offspring of a proband. Unless an individual with LP has children with an affected individual or a carrier, his/her offspring will be obligate heterozygotes (carriers) for a pathogenic variant in *ECM1*.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of an *ECM1* pathogenic variant.

Carrier (Heterozygote) Detection

Carrier testing for at-risk relatives requires prior identification of the *ECM1* 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.

DNA banking. Because it is likely that testing methodology and our understanding of genes, allelic variants, 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 genetic alteration/s are unknown).

Prenatal Testing and Preimplantation Genetic Testing

Once the *ECM1* pathogenic variants have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for LP 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.

- **Genetic and Rare Diseases Information Center (GARD)**
  Lipoid proteinosis of Urbach and Wiethe
- **MedlinePlus**
  Lipoid proteinosis

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. Lipoid Proteinosis: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
ECM1	1q21.2	Extracellular matrix protein 1	ECM1 database	ECM1	ECM1

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 Lipoid Proteinosis (View All in OMIM)

247100	LIPOID PROTEINOSIS OF URBACH AND WIETHE
602201	EXTRACELLULAR MATRIX PROTEIN 1; ECM1

Molecular Pathogenesis

Lipoid proteinosis (LP) is characterized by deposition of hyaline-like material in the larynx, oral cavity, skin, and internal organs and caused by pathogenic variants in *ECM1*, which codes for extracellular matrix protein 1 (ECM1).

Three transcripts of *ECM1* (ECM1a, ECM1b and ECM1c) in human have been discovered. This gene encodes an 85-kd soluble and widely expressed glycoprotein that is involved in endochondral bone formation, mineralization, angiogenesis, and epidermal differentiation. ECM1 is found within the epidermis and also as a secreted protein in the dermis. It interacts with a variety of extracellular and structural proteins, contributing to the maintenance of skin integrity and homeostasis. It has a physiologic role in the proliferation of endothelial cells and maintains skin integrity and homeostasis [Hamada et al 2003].

The ECM1 protein structure has four functional domains including a cysteine-free N-terminal segment, two tandem repeats, and a C-terminal segment. The tandem domains contain highly conserved sequence and numerous cysteine residues that are involved in protein-protein interactions and allow the ECM1 protein to function as a transport protein or to be involved in binding of growth or differentiation factors [Chan 2004]. It was shown by a yeast two-hybrid genetic system and confirmed by coimmunoprecipitations that ECM1 interacts with the C-terminal segments of fibulins 1C and 1D splice variants through its tandem repeat domain. It was proposed that alteration of this strong protein-protein interaction of ECM1/fibulin-1 is involved in LP disease pathogenesis [Fujimoto et al 2005]. Also, it has been shown that ECM1 inhibits the activity of MMP-9 through protein-protein interaction, and increased MMP-9 activity in individuals with LP may explain the hyaline changes of the dermis in these individuals [Fujimoto et al 2006].

Mechanism of disease causation. Lipoid proteinosis is caused by *ECM1* loss-of-function variants, which may lead to absence of ECM1 protein or production of nonfunctional protein [Chan et al 2007].

Table 7. Notable *ECM1* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_004425.4 NP_004416.2	c.826C>T	p.Gln276Ter	South African founder variant [Hamada 2002, Van Hougenhouck-Tulleken et al 2004]
	c.742G>T	p.Glu248Ter	In Pakistani families [Nasir et al 2014]
	c.658T>G	p.Cys220Gly	In Chinese families [Zhang et al 2014]

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.

Cancer and Benign Tumors

No correlation between increased cancer incidence and lipoid proteinosis has been reported; however, evidence linking expression of ECM1 with aspects of malignancy has emerged as ECM1 is dysregulated in some carcinomas [Wang et al 2003, Gómez-Contreras et al 2017]. ECM1 has been shown to have an important role in growth, angiogenesis, metastasis, and epithelial-stromal interactions [Lee et al 2015b, Steinhaeuser et al 2020].

Chapter Notes

Author Notes

Jouni Uitto, MD, PhD, has been Professor of Dermatology and Cutaneous Biology, and Biochemistry and Molecular Biology, and Chair of the Department of Dermatology and Cutaneous Biology at The Sidney Kimmel Medical College at Thomas Jefferson University, in Philadelphia, Pennsylvania, since 1986. He is also Director of the Jefferson Institute of Molecular Medicine at Thomas Jefferson University. He received his MD and PhD degrees from the University of Helsinki, Finland, and completed his residency training in dermatology at Washington University School of Medicine, St Louis, Missouri. Dr Uitto is internationally recognized for his research on connective tissue biology and molecular genetics in relation to cutaneous diseases. Dr Uitto's publications include 745 original articles in peer-reviewed journals, 346 textbook chapters and review articles, and 1,043 abstracts on presentations in national and international meetings. Dr Uitto has been the recipient of numerous national and international awards, including honorary doctorate degrees from the University of Kuopio, University of Oulu, and University of Turku (all in Finland) as well as the University of Buenos Aires. He also holds honorary professorships at China Medical University, Shenyang, Hebei United University, Tangshan, and The Fourth Military Medical University, Xi'an, all in China. Dr Uitto has held office in several scientific and professional societies, including as President of the Society for Investigative Dermatology and President and Chairman of the Board of Trustees of Dermatology Foundation. Dr Uitto is also Section Editor of the Journal of Investigative Dermatology and Associate Editor of the American Journal of Pathology; he is on the editorial boards of numerous peer-reviewed journals. In 2021, he was bestowed the honor of The Knight of White Rose, First Order, Republic of Finland, in recognition of his contributions to science.

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