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NOTCH3-Related Lateral Meningocele Syndrome

Synonym: Lehman Syndrome

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Summary

Clinical characteristics

NOTCH3-related lateral meningocele syndrome (LMS) is characterized by multiple lateral spinal meningoceles (protrusions of the arachnoid and dura through spinal foramina), distinctive facial features, joint hyperextensibility, hypotonia, and skeletal, cardiac, and urogenital anomalies. Neurologic sequelæ of the meningoceles depend on size and location and can include neurogenic bladder, paresthesia, back pain, and/or paraparesis. Other neurologic findings can include Chiari I malformation, syringomyelia, and rarely, hydrocephalus. Additional findings of LMS include developmental delay, mixed or conductive hearing loss, and cleft palate. Skeletal abnormalities may include scoliosis, vertebral fusion, scalloping of vertebrae, and wormian bones. Infants may demonstrate feeding difficulties with poor weight gain.

Diagnosis/testing

The diagnosis of *NOTCH3*-related LMS syndrome is established in a proband with consistent clinical findings and a heterozygous pathogenic variant in *NOTCH3*.

Management

Treatment of manifestations: Surgical intervention of lateral spinal meningoceles is generally avoided, but may be necessary due to neurologic manifestations secondary to meningocele size and location. Symptomatic treatment of neurologic sequelae of lateral meningoceles (neurogenic bladder, paresthesias, back pain, and/or paraparesis) provided as needed. As needed: timely supportive interventions to optimize development; management by specialists in chronic pain management or rehabilitation medicine; physiotherapy to reduce the risk for joint subluxation and dislocation. Routine management of: cleft palate, cardiovascular issues, genitourinary abnormalities, ophthalmologic issues, hearing loss, feeding difficulties.

Surveillance: Close clinical and radiographic monitoring for progressive neurologic symptoms and increase in meningocele size; an initial yearly scan to monitor for stability and subsequent spacing to every two years if

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meningoceles are small in size. Ongoing monitoring by the appropriate subspecialists for developmental, musculoskeletal, cardiovascular, genitourinary, gastrointestinal, ophthalmologic, and/or hearing issues.

Genetic counseling

All probands reported to date with *NOTCH3*-related LMS whose parents have undergone molecular genetic testing have the disorder as the result of a *de novo NOTCH3* pathogenic variant. Each child of an individual with *NOTCH3*-related LMS has a 50% chance of inheriting the pathogenic variant. Once the *NOTCH3* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for *NOTCH3*-related LMS are possible.

Diagnosis

Formal diagnostic clinical criteria for *NOTCH3*-related lateral meningocele syndrome (LMS) have not been established.

Suggestive Findings

NOTCH3-related LMS **should be suspected** in individuals with the following findings.

Multiple lateral spinal meningoceles (protrusion of the arachnoid and dura through the spinal foramina) are present in all affected individuals (Figure 1).

Characteristic craniofacial appearance [Gripp et al 2015, Ejaz et al 2016, Yamada et al 2022] includes widely spaced eyes, highly arched eyebrows, downslanted palpebral fissures, ptosis, malar flattening, long philtrum, thin vermilion of the upper lip, high and narrow palate, micrognathia, and coarse hair with a low posterior hairline (Figure 2).

Additional findings that may be present:

- **Neurologic.** Chiari I malformation, hydrocephalus, syringomyelia, and neurogenic bladder.
- **Developmental delay** or (rarely) intellectual disability
- **Musculoskeletal.** Hypotonia and joint hypermobility
- **Dermatologic.** Hyperextensibility of the skin
- **Cardiovascular malformations.** Aortic abnormalities (bicuspid aortic valve, aortic dilatation, and coarctation of the aortic arch) and ventricular septal defects
- **Genitourinary.** Cryptorchidism and (rarely) renal anomaly
- **Gastrointestinal.** Feeding difficulties, dysphagia, and gastroesophageal reflux disease

Establishing the Diagnosis

The diagnosis of *NOTCH3*-related LMS **is established** in a proband with consistent clinical findings and a heterozygous pathogenic (or likely pathogenic) variant in *NOTCH3* identified by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include likely pathogenic variants.. (2) Identification of a heterozygous *NOTCH3* variant of uncertain significance does not establish or rule out the diagnosis.

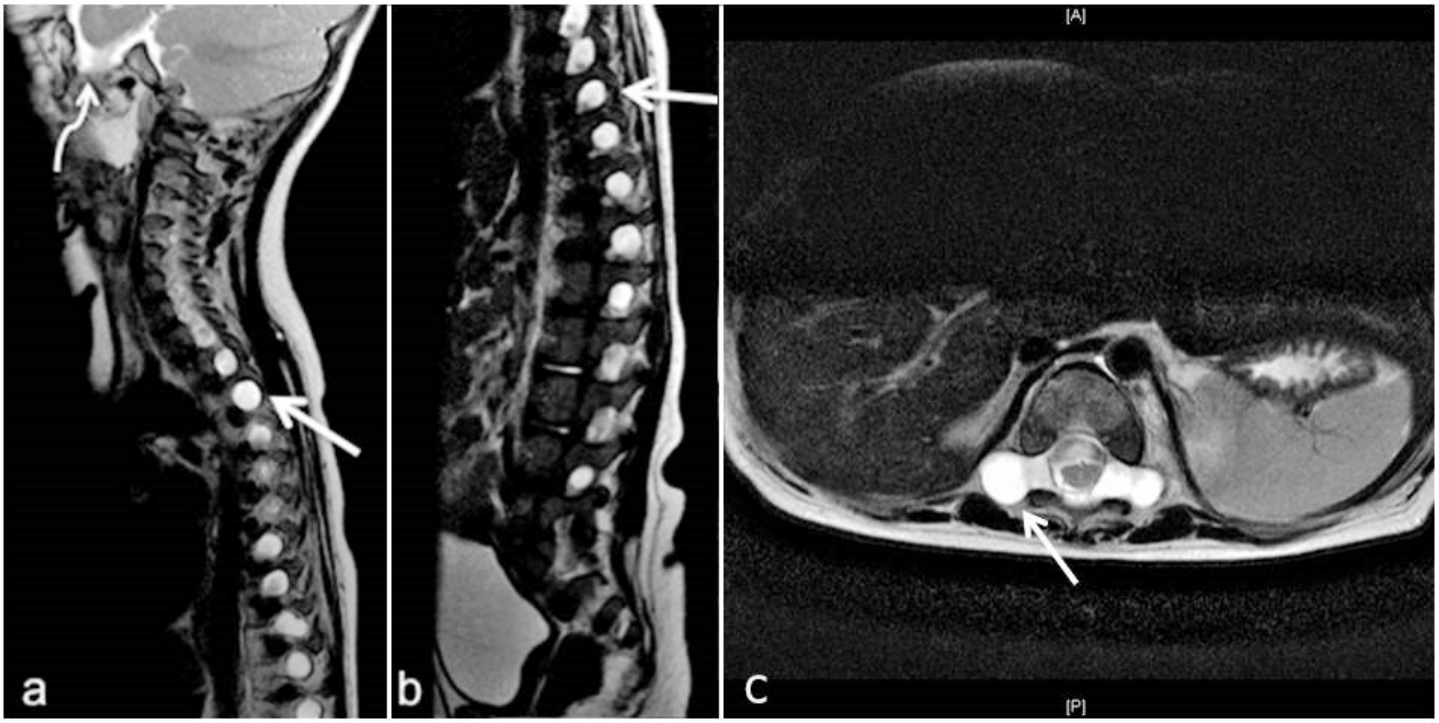

Figure 1. Numerous lateral meningoceles (see arrows) protrude through the thoracic foramina in a sagittal view (a) and through the lumbar foramina in a sagittal (b) and axial (c) view. The curved arrow in (a) shows a meningocele protruding from the middle cranial fossa.

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 LMS has not been considered are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

Single-gene testing. Sequence analysis of *NOTCH3* 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.

Typically, if 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; however, to date, such variants have not been identified as a cause of this disorder.

A multigene panel that includes *NOTCH3* 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

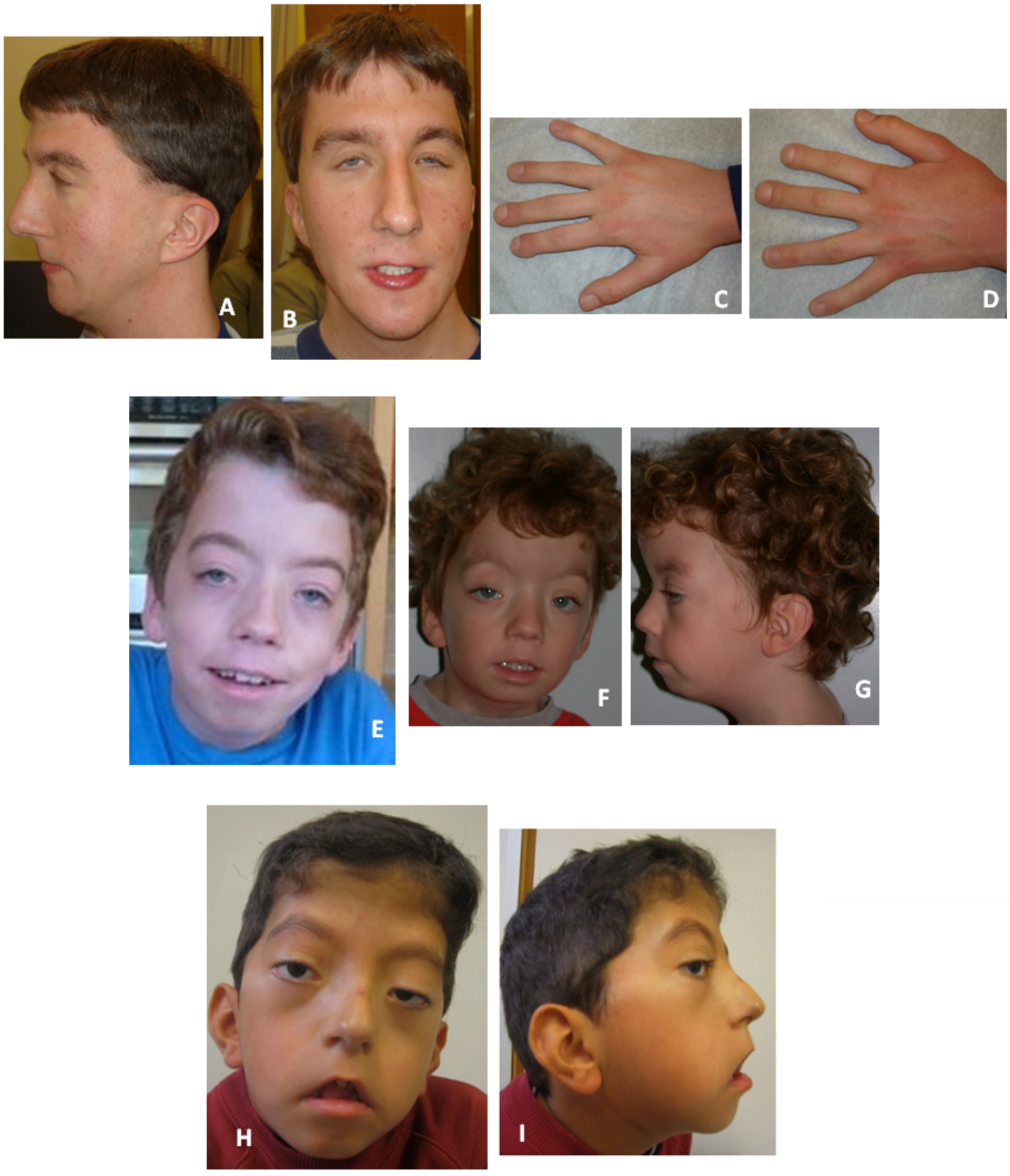

Figure 2. Photographs of individuals with *NOTCH3*-related lateral meningocele syndrome

A-D. Patient 1 at age 24 years:

Facial features with arched eyebrows, ptosis, flat midface, thin upper lip, low-set and posteriorly angulated ears, and low posterior hairline

Hands with short and wide distal second and third fingers (pseudo-clubbing)

E-G. Patient 20 at ages 13 years (E) and four years (F,G):

Facial features at age 13 years similar to those at age four years with coarse and curly hair, tall forehead, high arched brows, ptosis, midfacial hypoplasia, long flat philtrum and thin upper lip, micrognathia, and low-set ears

H-I. Patient 26 at age six years:

Facial features showing a high forehead, shallow supraorbital ridges with arched eyebrows, ptosis, flat midface, thin and tented upper lip, low-set and posteriorly angulated ears, low posterior hairline, and a submandibular scar with keloid formation

Reproduced with permission from Gripp et al [2015]

used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

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

Option 2

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 *NOTCH3*-Related Lateral Meningocele Syndrome (LMS)

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
NOTCH3	Sequence analysis [3]	11/11 [4]
	Gene-targeted deletion/duplication analysis [5]	Unknown [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. Han et al [2022], Yamada et al [2022]
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.
6. No data on detection rate of gene-targeted deletion/duplication analysis are available.

Clinical Characteristics

Clinical Description

NOTCH3-related lateral meningocele syndrome (LMS) is characterized by multiple lateral spinal meningoceles, distinctive facial features, joint hyperextensibility, hypotonia, and skeletal, cardiac, and urogenital anomalies.

To date, 11 individuals have been identified with a pathogenic variant in *NOTCH3* [Gripp et al 2015, Ejaz et al 2016, Brown et al 2017, Cappuccio et al 2020, Han et al 2022, Yamada et al 2022]. The following description of the phenotypic features associated with this condition is based on these reports.

Table 2. *NOTCH3*-Related Lateral Meningocele Syndrome: Frequency of Select Features

Feature	# of Persons with Feature
Multiple lateral spinal meningoceles	11/11
Characteristic facial appearance	11/11
Developmental delay	10/11
Musculoskeletal findings suggestive of a connective tissue disorder	11/11
Cardiovascular concerns	10/11
Genitourinary issues	4/8 (males w/cryptorchidism)
Gastrointestinal concerns	10/11
Eye abnormality	7/11
Hearing loss	4/11
Cleft palate	4/11

Multiple lateral spinal meningoceles (protrusions of the arachnoid and dura through the spinal foramina) are found in all affected individuals. Neurologic sequelæ of the meningoceles can include neurogenic bladder, paresthesia, back pain, and/or paraparesis depending on size and location. Other neurologic findings can include Chiari I malformation, syringomyelia, and rarely, hydrocephalus [Gripp et al 2015, Ejaz et al 2016, Cuoco et al 2020].

Craniofacial features include widely spaced eyes with downslanted palpebral fissures, highly arched eyebrows, ptosis, malar flattening, long philtrum, thin vermilion of the upper lip, high and narrow palate, micrognathia, and angulated ears (Figure 2). Cleft palate, dental crowding, epicanthal folds, dolichocephaly, and coarse hair with a low posterior hairline can also be seen.

A high nasal voice is noted in many individuals [Gripp et al 2015].

Developmental delay, particularly gross motor delay, is frequently seen in individuals with *NOTCH3*-related LMS, but cognition is typically preserved. Of ten individuals with *NOTCH3*-related LMS, all had developmental delay; only one also had intellectual disability [Gripp et al 2015, Ejaz et al 2016, Yamada et al 2022].

Musculoskeletal. Overlap with features of connective tissue disorders include neonatal hypotonia, abdominal hernias, ligamentous laxity, keloid scars, and back pain in later life.

Many individuals have skeletal changes including scoliosis, kyphosis, vertebral fusion, scalloping of vertebrae, and wormian bones [Gripp et al 2015, Cappuccio et al 2020].

Cardiovascular concerns have included atrial septal defect, ventricular septal defect, bicuspid aortic valve, dilatation of the aorta, and coarctation of the aortic arch [Gripp et al 2015, Ejaz et al 2016, Cappuccio et al 2020].

Genitourinary. Cryptorchidism is frequently seen. Prenatal hydronephrosis with postnatal left renal hypoplasia and bilateral renal cysts was reported in one individual [Cappuccio et al 2020].

Gastrointestinal. Infants with *NOTCH3*-related LMS may demonstrate feeding difficulties with poor weight gain. Feeding difficulties were severe enough to warrant gastrostomy tube feeding in two individuals [Ejaz et al 2016, Brown et al 2017].

Eye abnormalities can include proptosis and oculomotor restriction.

Hearing loss. Mixed or conductive hearing loss has been noted. Brain MRI of one individual showed an apical turn of the cochlea and modiolus, and dysmorphic vestibule [Cappuccio et al 2020]

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been identified.

Penetrance

Penetrance appears to be complete but data are limited.

Nomenclature

Lehman et al [1977] first described a woman with dysmorphic facial features, skeletal sclerosis, and multiple meningoceles, and her mother with similar craniofacial dysmorphisms. Philip et al [1995], who published a second report, named the syndrome after Lehman. The authors prefer the term "lateral meningocele syndrome" as it emphasizes the hallmark feature of the condition.

The title of this *GeneReview*, *NOTCH3*-related lateral meningocele syndrome, is based on the dyadic naming approach proposed by Biesecker et al [2021] to delineate mendelian genetic disorders.

Prevalence

NOTCH3-related lateral meningocele syndrome is very rare, with 11 reported individuals. There does not appear to be increased prevalence in specific populations.

Genetically Related (Allelic) Disorders

See Table 3 for other phenotypes associated with germline pathogenic variants in *NOTCH3*.

Table 3. *NOTCH3* Allelic Disorders

Disorder	MOI	Comment
CADASIL	AD	*NOTCH3* pathogenic variants are detected in exons 2-24 in persons w/CADASIL. The majority of sequence alterations are missense variants, characteristically leading to loss or gain of a cysteine residue in 1 of the 34 epidermal growth factor-like repeat domains of NOTCH3.
Infantile myofibromatosis 2 (OMIM 615293)	AD	A heterozygous *NOTCH3* pathogenic variant was predicted to cause infantile myofibromatosis in 1 family w/9 affected persons.

AD = autosomal dominant; CADASIL = *c*erebral *a*utosomal *d*ominant *a*rteriopathy w/subcortical *i*nfarcts & *l*eukoencephalopathy; MOI = mode of inheritance

Differential Diagnosis

The differential diagnosis for *NOTCH3*-related lateral meningocele syndrome (LMS) is summarized in Table 4.

Table 4. Genes and Disorders of Interest in the Differential Diagnosis of *NOTCH3*-Related Lateral Meningocele Syndrome (LMS)

Gene(s)	Disorder	MOI	Key Features /Comment
BRAF, *KRAS*, *LZTR1*, *MAP2K1*, *MRAS*, *NRAS*, *PTPN11*, *RAF1*, *RASA2*, *RIT1*, *RRAS2*, *SOS1*, *SOS2*	Noonan syndrome (NS)	AD (AR) [1]	*NOTCH3*-related LMS & NS share similarities in their characteristic facial features (incl widely spaced eyes, ptosis, epicanthus, & low-set ears w/↑ posterior angulation) & a low posterior hairline. Prenatal signs of NS (e.g., nuchal edema & congenital cardiac defect) were also seen in 2 persons w/ *NOTCH3*-related LMS. [2]
FBN1	Marfan syndrome (MFS)	AD	*NOTCH3*-related LMS has significant overlap w/other connective tissue disorders. Spinal meningeal anomalies, specifically dural ectasias, are frequently seen in MFS. Persons w/MFS may also have joint laxity, scoliosis, cardiovascular anomalies, & some shared facial features (e.g., malar flattening & retrognathia).
NF1	Neurofibromatosis type 1 (NF1)	AD	Lateral meningoceles & dural ectasia have been described in some persons w/NF1. [3] The distinctive facial features of *NOTCH3*-related LMS are not seen in persons w/NF1; other distinctive characteristics of NF1 incl café au lait spots, neurofibromas, & Lisch nodules. NF1 & *NOTCH3*-related LMS may also have similar skeletal & neurologic changes incl scoliosis, hydrocephalus, & developmental delays.
NOTCH2	Hadju-Cheney syndrome (OMIM 102500)	AD	Skeletal disorder characterized by dysmorphic facial features (e.g., malar flattening, thick eyebrows, micrognathia), osteoporosis w/ acro-osteolysis, wormian bones, premature loss of dentition, & joint laxity. 1 person w/*NOTCH3*-related LMS was initially misdiagnosed w/Hadju-Cheney syndrome due to presence of acro-osteolysis. [4]
FKBP14, *PLOD1*	*FKBP14*- & *PLOD1*-related kyphoscoliotic Ehlers-Danlos syndrome (kEDS)	AR	Lateral meningocele has been described in 1 person w/kEDS, & dural ectasia in at least 2 persons. [5] Persons w/kEDS also present w/joint hypermobility, congenital hypotonia, progressive scoliosis & kyphosis, motor delays, & hyperextensibility of the skin.
SMAD2, *SMAD3*, *TGFB2*, *TGFB3*, *TGFBR1*, *TGFBR2*	Loeys-Dietz syndrome (LDS)	AD	Overlapping features in LDS & *NOTCH3*-related LMS incl spinal pathology (dural ectasia in LDS), some facial features (e.g. downslanted palpebral fissures, proptosis, high arched palate), congenital heart defects, joint hypermobility, & spine deformities.

AD = autosomal dominant; AR = autosomal recessive; MOI = mode of inheritance

1. NS is most often inherited in an autosomal dominant manner. NS caused by pathogenic variants in *LZTR1* can be inherited in either an autosomal dominant or an autosomal recessive manner.

2. Ejaz et al [2016], Brown et al [2017]

3. Ueda et al [2015]

4. Avela et al [2011], Gripp [2011]

5. Brown et al [2017]

Management

No clinical practice guidelines for *NOTCH3*-related lateral meningocele syndrome have been published.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *NOTCH3*-related lateral meningocele syndrome (LMS), the evaluations summarized in Table 5 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 5. Recommended Evaluations Following Initial Diagnosis in Individuals with *NOTCH3*-Related Lateral Meningocele Syndrome (LMS)

System/Concern	Evaluation	Comment
Lateral spinal meningoceles	• Spine MRI to assess for meningoceles • Neurosurgical assessment to evaluate effect of lateral spinal meningocele size & location on neurologic function	
Associated neurologic issues	Neurologic eval	Assess for neuropathy, pain, neurogenic bladder &/or paraparesis.
	Brain MRI	Assess for Chiari I malformation or hydrocephalus.
Developmental delay	Developmental assessment	• To incl motor, adaptive, cognitive, & speech-language eval • Eval for early intervention / special education
Musculoskeletal	Assessment for abdominal hernia, ligamentous laxity / joint concerns, scoliosis	
Cardiovascular	Eval w/cardiologist to incl echocardiogram	
Genitourinary	Assessment for cryptorchidism	
Gastrointestinal	Infant feeding eval	Assess for GERD & any palate abnormalities.
Eyes	Ophthalmologic eval	Assess for ↓ vision, abnormal ocular mvmt, & structural eye abnormality.
Hearing	Audiologic eval	Assess for hearing loss.
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of *NOTCH3*-related LMS in order 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.	

GERD = gastroesophageal reflux disease; MOI = mode of inheritance
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

The following medical issues are managed in a routine manner: cleft palate, cardiovascular issues, genitourinary abnormalities, ophthalmologic issues, hearing loss, feeding difficulties.

Table 6. Treatment of Manifestations in Individuals with *NOTCH3*-Related Lateral Meningocele Syndrome (LMS)

Manifestation/ Concern	Treatment	Considerations/Other
Lateral spinal meningoceles	• There is no standard operative mgmt of lateral spinal meningoceles [Cuoco et al 2020]. • Symptomatic treatment of neurologic sequelæ (e.g., neurogenic bladder, paresthesias, back pain, &/or paraparesis) as needed	• Surgical intervention is generally avoided but may be necessary due to neurologic manifestations secondary to meningocele size & location [Cuoco et al 2020]. • 1 person benefited from CSF diversion w/a VP shunt for symptomatic relief of thoracolumbar meningocele [Brown et al 2017]. • When required, surgical approach is individualized & can incl laminectomy for smaller meningoceles, costotransversectomy for larger meningoceles.
Developmental delay	Timely supportive interventions as needed to optimize development through OT & education resources	
Musculoskeletal issues	• PT to ↓ risk for joint subluxation & dislocation • Mgmt by specialists in chronic pain mgmt or rehab medicine as needed	

OT = occupational therapy; PT = physical therapy

Surveillance

There are no established surveillance guidelines for lateral spinal meningoceles. Close clinical and radiographic monitoring is recommended for progressive neurologic symptoms and meningocele size enlargement [Cuoco et al 2020]. MRI of the spine can be considered at a one- to two-year interval; an initial yearly scan to monitor for stability and subsequent spacing to every two years if meningoceles are small in size has been suggested. Larger lesions may require closer follow up [JA Cuoco 2022, personal communication].

Ongoing monitoring by the appropriate subspecialists for developmental, musculoskeletal, cardiovascular, genitourinary, gastrointestinal, ophthalmologic, and/or hearing issues is indicated.

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

NOTCH3-related lateral meningocele syndrome (LMS) is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- All probands reported to date with *NOTCH3*-related LMS whose parents have undergone molecular genetic testing have the disorder as the result of a *de novo NOTCH3* pathogenic variant.
- Molecular genetic testing is recommended for the parents of the proband to confirm their genetic status and to allow reliable recurrence risk counseling.
- If the *NOTCH3* pathogenic variant identified in the proband is not identified in either parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
  - The proband has a *de novo* pathogenic variant.
  - The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ cells only.

Sibs of a proband. The risk to the sibs of the proband depends on the genetic status of the proband's parents:

- If a parent of the proband has the *NOTCH3* pathogenic variant identified in the proband, the risk to the sibs of inheriting the pathogenic variant is 50%.
- If the *NOTCH3* pathogenic variant identified in the proband cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 1% because of the theoretic possibility of parental germline mosaicism [Rahbari et al 2016].
- If the parents are clinically unaffected but their genetic status is unknown, the risk to the sibs of a proband is presumed to be low but slightly greater than that of the general population because of the theoretic possibility of parental germline mosaicism.

Offspring of a proband. Each child of an individual with *NOTCH3*-related LMS has a 50% chance of inheriting the *NOTCH3* pathogenic variant.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has the *NOTCH3* pathogenic variant, members of the parent's family may be at risk.

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 the parents of affected individuals and young adults who are affected.

Prenatal Testing and Preimplantation Genetic Testing

Once the *NOTCH3* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing for *NOTCH3*-related LMS 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.

- **MedlinePlus**
  Lateral meningocele syndrome

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. NOTCH3-Related Lateral Meningocele Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
NOTCH3	19p13.12	Neurogenic locus notch homolog protein 3	Notch homolog 3 (NOTCH3) @ LOVD	NOTCH3	NOTCH3

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 NOTCH3-Related Lateral Meningocele Syndrome (View All in OMIM)

130720	LATERAL MENINGOCELE SYNDROME; LMNS
600276	NOTCH RECEPTOR 3; NOTCH3

Molecular Pathogenesis

NOTCH3 encodes the neurogenic locus notch homolog protein 3 (NOTCH3), a transmembrane receptor involved in cell signaling and activation of target genes. It appears to be universally expressed and is a part of a highly conserved signaling pathway that is responsible for cell differentiation, proliferation, and apoptosis, through regulating transcription of target genes.

In *Notch3* variant mouse models, an osteopenic phenotype was thought to result from induction of RANKL by cells of osteoblast lineages with subsequent increased osteoclastogenesis [Canalis 2021].

In all individuals with *NOTCH3*-related LMS to date, the causative pathogenic variants (nonsense and frameshift) have been in exon 33, the last exon of *NOTCH3* [Gripp et al 2015, Ejaz et al 2016, Han et al 2022, Yamada et al 2022]. It is predicted that the transcripts of such variants in this location escape nonsense-mediated decay and express a truncated NOTCH3 protein, which has been documented in the cells of one individual [Gripp et al 2015]. Through negative regulation of protein stability these truncated NOTCH3 proteins would lack the C-terminal PEST domain, which is responsible for degradation of the intracellular signaling portion of activated NOTCH3. The truncated protein is more likely to escape degradation, thereby prolonging its cellular half-life [Wang et al 2015, Canalis 2021].

Mechanism of disease causation. *NOTCH3*-related LMS is thought to be caused by a gain-of-function mechanism [Gripp et al 2015, Wang et al 2015]. The precise mechanism by which excess NOTCH3 results in *NOTCH3*-related LMS is not understood.

Chapter Notes

Author Notes

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- 19 February 2016 (re) Original submission

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