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L1 Syndrome

Synonym: L1 Disease

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Summary

Clinical characteristics

L1 syndrome involves a phenotypic spectrum ranging from severe to mild and includes three clinical phenotypes:

- X-linked hydrocephalus with stenosis of the aqueduct of Sylvius (HSAS)
- MASA (*m*ental retardation [intellectual disability], *a*phasia [delayed speech], *s*pastic paraplegia [shuffling gait], *a*dducted thumbs) syndrome including X-linked complicated hereditary spastic paraplegia type 1
- X-linked complicated corpus callosum agenesis

Males with HSAS are born with severe hydrocephalus, adducted thumbs, and spasticity; intellectual disability is severe. In less severely affected males, hydrocephalus may be subclinically present and documented only because of developmental delay; intellectual disability ranges from mild (IQ: 50-70) to moderate (IQ: 30-50). It is important to note that all phenotypes can be observed in affected individuals within the same family.

Diagnosis/testing

The diagnosis of L1 syndrome is established in a male proband with suggestive findings and a hemizygous pathogenic variant in *L1CAM* identified by molecular genetic testing. The diagnosis of L1 syndrome in a female is unusual but not impossible (most likely in the setting of general delay and/or hydrocephalus) and is established with the identification of a heterozygous pathogenic variant in *L1CAM* by molecular genetic testing.

Management

Treatment of manifestations: It is best to involve a multidisciplinary team with expertise in pediatrics, child neurology, neurosurgery, rehabilitation, and clinical genetics. Shunting of the cerebrospinal fluid should be performed as needed to reduce intracranial pressure. Individual educational programming is indicated for

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developmental delay and intellectual disability. Standard treatment guidelines should be followed for spasticity. A splint may help reduce the degree of thumb adduction; surgery is not generally indicated.

Surveillance: Neurologic evaluation at regular intervals to monitor hydrocephalus, developmental progress, and spastic paraplegia.

Genetic counseling

L1 syndrome is inherited in an X-linked manner. If the mother of the proband is heterozygous for an *L1CAM* pathogenic variant, the chance of transmitting it in each pregnancy is 50%. Males who inherit the *L1CAM* pathogenic variant will be affected; females who inherit the pathogenic variant will be heterozygotes and will usually not be affected but may have a range of (typically mild) clinical manifestations. Once the *L1CAM* pathogenic variant has been identified in an affected family member, heterozygote detection, prenatal testing for a pregnancy at increased risk, and preimplantation genetic testing are possible.

GeneReview Scope

L1 Syndrome: Included Phenotypes [1]
• X-linked hydrocephalus with stenosis of the aqueduct of Sylvius (HSAS) • MASA (*m*ental retardation, *a*dducted thumbs, *s*huffling gait, *a*phasia) syndrome, including SPG1 (X-linked complicated hereditary spastic paraplegia type 1) • X-linked complicated corpus callosum agenesis

1. For other genetic causes of these phenotypes see Differential Diagnosis.

Diagnosis

Suggestive Findings

L1 syndrome involves a phenotypic spectrum ranging from severe to mild. L1 syndrome **should be suspected** in individuals with any of the following clinical phenotypes or neuroimaging findings and supportive family history.

Clinical Phenotypes

X-linked hydrocephalus with stenosis of aqueduct of Sylvius (HSAS). Signs present in affected males:

- Severe hydrocephalus, often of prenatal onset. Clinical criteria for hydrocephalus:
  - Increased intraventricular fluid volume evidenced by increased occipital-frontal circumference (OFC) and imaging findings including increased ventricular size, loss of cerebral sulci, and transependymal resorption of cerebrospinal fluid
  - Increased intraventricular pressure based on: specific clinical signs and symptoms depending on age including progressive increase of OFC, headache, nausea and vomiting, and irritability; and/or ultrasound and/or brain imaging
- Adducted (clasped) thumbs caused by a developmental defect of the extensor pollicus longis and/or brevis muscles (>50% of males) [Schrander-Stumpel & Fryns 1998]
- Spasticity evidenced by brisk tendon reflexes and extensor plantar responses
- Moderate-to-severe intellectual disability

MASA (*m*ental retardation [intellectual disability], *a*phasia [delayed speech], *s*pastic paraplegia [shuffling gait], *a*dducted thumbs) **syndrome** including **X-linked complicated hereditary spastic paraplegia type 1 (SPG1).** Findings in affected males:

- Mild-to-moderate intellectual disability
- Delayed onset of speech
- Hypotonia progressing to spastic paraplegia
- Possible adducted (clasped) thumbs caused by a developmental defect of the extensor pollicis longis and/or brevis muscles
- Variable abnormalities on brain MRI

X-linked complicated corpus callosum agenesis [Yamasaki et al 1995]. Findings in affected males:

- Variable spastic paraplegia
- Mild-to-moderate intellectual disability
- Corpus callosum dysplasia, hypoplasia, or aplasia

Neuroimaging Findings

Hydrocephalus with or without stenosis of the aqueduct of Sylvius is found in combination with corpus callosum agenesis/hypogenesis and/or cerebellar hypoplasia, small brain stem, and agenesis of the pyramids (corticospinal tracts) [Yamasaki et al 1995].

Bilateral absence of the pyramids detected by MRI or autopsy is an almost pathognomonic finding [Chow et al 1985].

Aqueductal stenosis is not a constant feature of L1 syndrome [Yamasaki et al 1995].

Family History

Family history is consistent with X-linked inheritance (e.g., no male-to-male transmission). Absence of a known family history does not preclude the diagnosis.

Establishing the Diagnosis

Male proband. The diagnosis of L1 syndrome **is established** in a male proband with suggestive findings and a hemizygous pathogenic variant in *L1CAM* identified by molecular genetic testing (see Table 1).

Female proband. The diagnosis of L1 syndrome in a female is unusual but not impossible (most likely in the setting of general delay and/or hydrocephalus) and **is established** with the identification of a heterozygous pathogenic variant in *L1CAM* by molecular genetic testing (see Table 1).

Note: Identification of a hemizygous or heterozygous *L1CAM* variant of uncertain significance does not establish or rule out a 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, exome array, 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 with a phenotype indistinguishable from many other inherited disorders with hydrocephalus, spastic paraplegia, and/or intellectual disability are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

Single-gene testing. Sequence analysis of *L1CAM* 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 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.

Note: Lack of amplification by PCR prior to sequence analysis can suggest a putative (multi)exon or whole-gene deletion on the X chromosome in affected males; confirmation requires additional testing by gene-targeted deletion/duplication analysis.

A multigene panel that includes *L1CAM* 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, and deletion/duplication analysis.

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

Option 2

Comprehensivegenomic 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 L1 Syndrome

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
L1CAM	Sequence analysis [3, 4]	99% [5]
	Gene-targeted deletion/duplication analysis [6]	1% [7]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Lack of amplification by PCR prior to sequence analysis can suggest a putative (multi)exon or whole-gene deletion on the X chromosome in affected males; confirmation requires additional testing by gene-targeted deletion/duplication analysis.
5. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2017]
6. 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.
7. Large deletions or duplications (including one deletion of the entire gene) have been described [Vos & Hofstra 2010, Adle-Biassette et al 2013, Alby et al 2016].

Clinical Characteristics

Clinical Description

L1 syndrome is seen almost exclusively in males.

Affected Males

L1 syndrome comprises three clinical phenotypes ranging from severe to mild; its major features are hydrocephalus, intellectual disability, spasticity of the legs, and adducted thumbs.

To date, more than 280 individuals have been identified with a pathogenic variant in *L1CAM* [Vos et al 2010, Vos & Hofstra 2010]. Table 2 compares the features among the various phenotypes associated with L1 syndrome. It is important to note that all phenotypes can be observed within the same family.

Table 2. L1 Syndrome: Comparison of Phenotypes in Male Probands by Select Features

Feature	L1 Phenotype		
	HSAS	MASA syndrome, incl SPG1	X-linked complicated CC agenesis
Hydrocephalus w/or w/o stenosis of aqueduct of Sylvius	100%	Variable dilation of the 3rd ventricle	–
CC agenesis/hypogenesis	+ (accompanies hydrocephalus)	+ in some	100%
Intellectual disability	Severe	Mild to moderate	Mild to moderate
Delayed speech	+	+	+
Spasticity of legs	+	+	Variable
Adducted thumbs	50%	<50%	<50%

CC = corpus callosum; HSAS = X-linked hydrocephalus with stenosis of aqueduct of Sylvius; MASA = *m*ental retardation [intellectual disability], *a*phasia [delayed speech], *s*pastic paraplegia [shuffling gait], *a*dducted thumbs; SPG1 = X-linked complicated hereditary spastic paraplegia type 1

Hydrocephalus may be present prenatally and result in stillbirth or death in early infancy.

- Males with hydrocephalus with stenosis of the aqueduct of Sylvius (HSAS) are born with severe hydrocephalus and adducted thumbs.

  Seizures may occur.

- In less severely affected males, hydrocephalus may be subclinically present and documented only because of developmental delay.

  Mild-to-moderate ventricular enlargement is compatible with long survival.

Other brain malformations can include corpus callosum agenesis/hypogenesis and/or cerebellar hypoplasia, small brain stem, and agenesis of the pyramids.

Intellectual disability

- The degree of intellectual impairment does not necessarily correlate with head size or severity of hydrocephalus; males with severe intellectual disability and a normal head circumference have been reported.
- In HSAS, intellectual disability is usually severe and is independent of shunting procedures in individuals with severe hydrocephalus.
- In MASA (*m*ental retardation [intellectual disability], *a*phasia [delayed speech], *s*pastic paraplegia [shuffling gait], *a*dducted thumbs) syndrome, intellectual disability ranges from mild (IQ: 50-70) to moderate (IQ: 30-50).

Behavioralconcerns. In general, there are no specific behavior problems in males with the condition. However, childhood-onset psychosis has been reported in two unrelated boys [Sato et al 2020]. Familial factors and interaction with other rare genetic variants may have modulated the presentation.

Spasticity

- Boys initially exhibit hypotonia of the legs, which evolves into spasticity during the first years of life.
- In adult males, the spasticity tends to be somewhat progressive, although this finding has not been documented in a large group.
- Spasticity usually results in atrophy of the muscles of the legs and contractures that together cause the shuffling gait.

Adducted thumbs. Absence of the musculus abductor pollicis longus causes the typical adduction position of the thumb. Surgery with tendon replacement has been used and can be successful in some individuals. Splint therapy may improve the thumb position.

Other findings

- **Hirschsprung disease (HSCR).** At least 16 individuals with an *L1CAM* pathogenic variant and a combination of L1 syndrome and HSCR have been reported [Parisi et al 2002, Basel-Vanagaite et al 2006, Tegay et al 2007, Griseri et al 2009, Takenouchi et al 2012, Yang et al 2019]. HSCR is characterized by the absence of ganglion cells and the presence of hypertrophic nerve trunks in the distal bowel. It has been suggested that failure of migration of the neural crest cells underlies aganglionosis. Parisi et al [2002] and Griseri et al [2009] hypothesized that *L1CAM* may modify the effects of a HSCR-associated gene to cause aganglionosis. An *L1CAM* pathogenic variant alone does not result in HSCR [Griseri et al 2009].
- **Congenital idiopathic intestinal pseudo-obstruction.** An association between hydrocephalus and a specific form of congenital idiopathic intestinal pseudo-obstruction was reported in an infant [Bott et al 2004] in whom an *L1CAM* pathogenic variant had been detected.

Heterozygous Females

Females heterozygous for an *L1CAM* pathogenic variant may manifest minor features such as adducted thumbs and/or mild intellectual disability. Rarely do females manifest the complete L1 syndrome phenotype. Severe hydrocephalus has been reported in a heterozygous female [Kaepernick et al 1994, Vos et al 2010]. A pathogenic variant was detected in a girl with aqueduct stenosis, adducted thumbs, and mild intellectual disability, and without a positive family history [Author, personal observation]. Skewed X inactivation was demonstrated. Otter et al [2017] reported epilepsy in the daughter of a man with very mild L1 syndrome; although the daughter is presumed to be heterozygous for an *L1CAM* pathogenic variant, this has not been confirmed.

Genotype-Phenotype Correlations

In their review, Weller & Gärtner [2001] noted that pathogenic missense variants in extracellular domains or pathogenic variants in cytoplasmic regions cause milder phenotypes than those resulting from truncation in extracellular domains or from nondetectable L1 protein.

Pathogenic missense variants that affect "key amino acid residues" are most likely to result in a severe phenotype. Key amino acid residues are those crucial for the structure of the immunoglobulin or fibronectin type III-like domains of the L1 protein [Bateman et al 1996].

A statistical analysis was performed on 33 individuals with L1 syndrome in whom a pathogenic variant was identified to detect any possible genotype-phenotype correlation. Children harboring a pathogenic truncating variant were more likely to die before age three years (52%) than children with a pathogenic missense variant

(8%), indicating a relationship between the seriousness of the disease and the type of pathogenic variant. These results are statistically significant (Fisher exact p=0.02) [Vos et al 2010].

The above generalizations about genotype-phenotype correlations notwithstanding, clinical findings in L1 syndrome can range from mild to severe even within a family, indicating that other factors must influence the clinical presentation [Finckh et al 2000].

Prevalence

HSAS is the most common genetic form of congenital hydrocephalus, with an estimated prevalence of 1:30,000. It accounts for approximately 5%-10% of males with nonsyndromic congenital hydrocephalus [Finckh et al 2000].

In males with complicated spastic paraplegia, the prevalence of L1 syndrome is unknown.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *L1CAM*.

Differential Diagnosis

The differential diagnosis of males with developmental delay or intellectual disability (ID) and early hypotonia evolving into spastic paraplegia during childhood, with or without adducted thumbs, includes many conditions. See OMIM Phenotypic Series: autosomal dominant ID, autosomal recessive ID, and X-linked nonsyndromic ID.

Nonsyndromic congenital hydrocephalus. Individuals with L1 syndrome and hydrocephalus do not have major additional physical anomalies. Other single-gene causes of nonsyndromic congenital hydrocephalus include biallelic pathogenic variants in *CCDC88C*, *MPDZ*, and *WDR8* (see OMIM PS236600).

Nonsyndromic congenital hydrocephalus may also occur as part of (or secondary to) the following:

- Neural tube defect
- Congenital aqueductal stenosis (isolated hydrocephalus)
- CNS malformation
  - Arnold-Chiari malformation
  - Dandy-Walker malformation
  - Hydranencephaly
  - Vein of Galen malformation
  - Midline hyperplasia with malformation of the fornical system
  - Congenital cyst
  - Other midline abnormalities
- Congenital communicating hydrocephalus secondary to hemorrhage

Spastic paraplegia. To date, approximately 50 genetic types of complicated hereditary spastic paraplegia have been defined (see Hereditary Spastic Paraplegia Overview).

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with L1 syndrome, 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 L1 Syndrome

System/Concern	Evaluation	Comment
Hydrocephalus / Brain malformation	Brain imaging study	MRI is preferred.
Intellectual disability	Developmental eval	
Spasticity	Complete neurologic eval	
Adducted thumbs	Clinical observation	
Hirschsprung disease association	Eval for Hirschsprung disease if there is history of constipation	
Genetic counseling	By genetics professionals [1]	To inform patients & families re nature, MOI, & implications of L1 syndrome to facilitate medical & personal decision making
Family support/ resources	Assess: • Use of community or online resources, e.g., 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, or certified advanced genetic nurse

Treatment of Manifestations

Optimal management involves a multidisciplinary team with expertise in pediatrics, child neurology, neurosurgery, rehabilitation, and clinical genetics.

Table 6. Treatment of Manifestations in Individuals with L1 Syndrome

Manifestation/ Concern	Treatment	Considerations/Other
Hydrocephalus	Surgical treatment should be performed as needed.	• Shunting of CSF is indicated to ↓ intracranial pressure. • Prenatal shunting offers no advantage [Pinckert & Golbus 1988].
DD/ID	See DD/ID Management Issues.	Developmental outcome is variable & individualized educational program is important.
Spastic paraplegia	Standard treatment guidelines for spasticity should be followed.	Neurologic features should be monitored.
Adducted thumbs	A splint may help ↓ degree of adduction.	• Surgical intervention is not generally indicated. • In some milder cases, tendon transfer may improve thumb function.

CSF = cerebrospinal fluid; DD = developmental delay; ID = intellectual disability

Developmental Delay / Intellectual Disability Management Issues

The following information represents typical management recommendations for individuals with developmental delay / intellectual disability in the United States; standard recommendations may vary from country to country.

Ages 0-3 years. Referral to an early intervention program is recommended for access to occupational, physical, speech, and feeding therapy as well as infant mental health services, special educators, and sensory impairment

specialists. In the US, early intervention is a federally funded program available in all states that provides in-home services to target individual therapy needs.

Ages 3-5 years. In the US, developmental preschool through the local public school district is recommended. Before placement, an evaluation is made to determine needed services and therapies and an individualized education plan (IEP) is developed for those who qualify based on established motor, language, social, or cognitive delay. The early intervention program typically assists with this transition. Developmental preschool is center based; for children too medically unstable to attend, home-based services are provided.

All ages. Consultation with a developmental pediatrician is recommended to ensure the involvement of appropriate community, state, and educational agencies (US) and to support parents in maximizing quality of life. Some issues to consider:

- IEP services:
  - An IEP provides specially designed instruction and related services to children who qualify.
  - IEP services will be reviewed annually to determine whether any changes are needed.
  - As required by special education law, children should be in the least restrictive environment feasible at school and included in general education as much as possible and when appropriate.
  - PT, OT, and speech services will be provided in the IEP to the extent that the need affects the child's access to academic material. Beyond that, private supportive therapies based on the affected individual's needs may be considered. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.
  - As a child enters the teen years, a transition plan should be discussed and incorporated in the IEP. For those receiving IEP services, the public school district is required to provide services until age 21.
- A 504 plan (Section 504: a US federal statute that prohibits discrimination based on disability) can be considered for those who require accommodations or modifications such as front-of-class seating, assistive technology devices, classroom scribes, extra time between classes, modified assignments, and enlarged text.
- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a US public agency that provides services and support to qualified individuals. Eligibility differs by state but is typically determined by diagnosis and/or associated cognitive/adaptive disabilities.
- Families with limited income and resources may also qualify for supplemental security income (SSI) for their child with a disability.

Motor Dysfunction

Gross motor dysfunction

- Physical therapy is recommended to maximize mobility and to reduce the risk for later-onset orthopedic complications (e.g., contractures, scoliosis, hip dislocation).
- Consider use of durable medical equipment and positioning devices as needed (e.g., wheelchairs, walkers, bath chairs, orthotics, adaptive strollers).
- For muscle tone abnormalities including hypertonia or dystonia, consider involving appropriate specialists to aid in management of baclofen, tizanidine, Botox®, anti-parkinsonian medications, or orthopedic procedures.

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

Oral motor dysfunction should be assessed at each visit and clinical feeding evaluations and/or radiographic swallowing studies should be obtained for choking/gagging during feeds, poor weight gain, frequent respiratory

illnesses, or feeding refusal that is not otherwise explained. Assuming that the child is safe to eat by mouth, feeding therapy (typically from an occupational or speech therapist) is recommended to help improve coordination or sensory-related feeding issues. Feeds can be thickened or chilled for safety. When feeding dysfunction is severe, an NG-tube or G-tube may be necessary.

Communication issues. Consider evaluation for alternative means of communication (e.g., Augmentative and Alternative Communication [AAC]) for individuals who have expressive language difficulties. An AAC evaluation can be completed by a speech-language pathologist who has expertise in the area. The evaluation will consider cognitive abilities and sensory impairments to determine the most appropriate form of communication. AAC devices can range from low-tech, such as picture exchange communication, to high-tech, such as voice-generating devices. Contrary to popular belief, AAC devices do not hinder verbal development of speech, and in many cases can improve it.

Social/Behavioral Concerns

Children may qualify for and benefit from interventions used in treatment of autism spectrum disorder, including applied behavior analysis (ABA). ABA therapy is targeted to the individual child's behavioral, social, and adaptive strengths and weaknesses and typically performed one on one with a board-certified behavior analyst.

Consultation with a developmental pediatrician may be helpful in guiding parents through appropriate behavior management strategies or providing prescription medications, such as medication used to treat attention-deficit/hyperactivity disorder, when necessary.

Concerns about serious aggressive or destructive behavior can be addressed by a pediatric psychiatrist.

Surveillance

Table 7. Recommended Surveillance for Individuals with L1 Syndrome

System/Concern	Evaluation	Frequency
Hydrocephalus	Neurologic eval	At regular intervals as indicated individually
DD/ID		
Spastic paraplegia		

DD = developmental delay; ID = intellectual disability

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

L1 syndrome is inherited in an X-linked manner.

Risk to Family Members

Parents of a male proband

- The father of an affected male will not have the disorder nor will he be hemizygous for the *L1CAM* pathogenic variant; therefore, he does not require further evaluation/testing.
- In a family with more than one affected individual, the mother of an affected male is an obligate heterozygote. Note: If a woman has more than one affected child and no other affected relatives and if the *L1CAM* pathogenic variant cannot be detected in her leukocyte DNA, she most likely has germline mosaicism.
- If a male is the only affected family member (i.e., a simplex case), the mother may be a heterozygote, the affected male may have *de novoL1CAM* pathogenic variant (in which case the mother is not a heterozygote), or the mother may have somatic/germline mosaicism. About 40% of affected males represent simplex cases [Vos et al 2010].
- Molecular genetic testing of the mother is recommended to confirm her genetic status and to allow reliable recurrence risk assessment.

Note: Paternal somatic and germline mosaicism for an *L1CAM* pathogenic variant was described in the unaffected father of two heterozygous daughters [Du et al 1998].

Sibs of a male proband. The risk to sibs depends on the genetic status of the mother:

- If the mother of the proband is heterozygous for an *L1CAM* pathogenic variant, the chance of transmitting it in each pregnancy is 50%.
  - Males who inherit the pathogenic variant will be affected. Note: All phenotypes within the L1 syndrome spectrum can be observed in affected individuals within the same family.
  - Females who inherit the pathogenic variant will be heterozygotes and will usually not be affected. However, they may manifest minor features such as adducted thumbs and/or mild intellectual disability. Females rarely manifest the complete L1 syndrome phenotype. Severe hydrocephalus has been reported in a heterozygous female [Kaepernick et al 1994, Vos et al 2010] (see Clinical Description, Heterozygous Females).
- If the proband represents a simplex case (i.e., a single occurrence in a family) and if the *L1CAM* pathogenic variant cannot be detected in the leukocyte DNA of the mother, the risk to sibs is greater than that of the general population because of the possibility of maternal germline mosaicism. Maternal germline mosaicism has been reported in at least one family [Vos et al 2010] in which a second male fetus was found to have the pathogenic *L1CAM* variation.

Offspring of a proband

- Affected males transmit the *L1CAM* pathogenic variant to all of their daughters and none of their sons; however, males with a hemizygous *L1CAM* pathogenic variant typically do not reproduce.
- In one family, a male with a very mild phenotype transmitted an *L1CAM* pathogenic variant to his daughter [Otter et al 2017].

Other family members. The proband's maternal aunts may be at risk of being heterozygous and the aunts' offspring, depending on their gender, may be at risk of being hemizygous (and affected) or heterozygous (and usually not affected).

Note: Molecular genetic testing may be able to identify the family member in whom a *de novo* pathogenic variant arose, information that could help determine genetic risk status of the extended family.

Heterozygote Detection

Identification of female heterozygotes requires either prior identification of the *L1CAM* pathogenic variant in the family or, if an affected male is not available for testing, molecular genetic testing first by sequence analysis, and if no pathogenic variant is identified, by gene-targeted deletion/duplication analysis.

Note: Females who are heterozygotes for this X-linked disorder will usually not be affected but may have a range of clinical manifestations (see Clinical Description, Heterozygous Females).

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk, clarification of genetic 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 heterozygous or are at risk of being heterozygous.

DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. 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 of affected individuals.

Prenatal Testing and Preimplantation Genetic Testing

Molecular genetic testing. Once the *L1CAM* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible. (Note: The prenatal finding of an *L1CAM* pathogenic variant **cannot** be used to accurately predict the phenotype in a hemizygous male fetus; all phenotypes within the L1 syndrome spectrum can be observed in affected individuals within the same family.)

Ultrasound examination. L1 syndrome cannot be reliably diagnosed on the basis of prenatal ultrasound only. A diagnosis of hydrocephalus often requires serial ultrasound examination and cannot be guaranteed before 20-24 weeks' gestation or even the third trimester of pregnancy. Furthermore, apparently normal ultrasound findings in a pregnancy with a priori increased risk are not reliable in ruling out L1 syndrome in the fetus.

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**
  L1 syndrome
- **Hydrocephalus Association**
  870 Market Street

Suite 705
San Francisco CA 94102
Phone: 888-598-3789 (toll-free); 415-732-7040
Fax: 415-732-7044
Email: info@hydoassoc.org
www.hydroassoc.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. L1 Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
L1CAM	Xq28	Neural cell adhesion molecule L1	HSP mutation database (L1CAM) L1CAM Mutation Web Page	L1CAM	L1CAM

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 L1 Syndrome (View All in OMIM)

303350	MASA SYNDROME
304100	CORPUS CALLOSUM, PARTIAL AGENESIS OF, X-LINKED
307000	HYDROCEPHALUS DUE TO CONGENITAL STENOSIS OF AQUEDUCT OF SYLVIUS; HSAS
308840	L1 CELL ADHESION MOLECULE; L1CAM

Molecular Pathogenesis

L1 is a transmembrane glycoprotein belonging to the immunoglobulin superfamily cell adhesion molecules; it contains thirteen distinct domains: six immunoglobulin- (Ig) and five fibronectin (Fn) III-like domains at the extracellular surface, one single-pass transmembrane domain, and one short cytoplasmic domain. L1 may mediate axon growth during development and axon bundling (fasciculation). It is also involved in interactions between Schwann cells and axons, neuronal cell migration, and neuronal cell survival. The activity is known to be mediated by hemophilic (L1-L1) and heterophilic (L1-non L1 protein) interactions and transduction of a variety of signaling events through associated proteins [Kenwrick et al 2000].

Mechanism of disease causation. L1 syndrome occurs via a loss-of-function mechanism, due to truncating variants, exon/gene deletions, or missense variants. Missense variants in one of the key residues as predicted by Bateman et al [1996] are often disease causing. The key residues are essential for the protein folding of the immunoglobulin and fibronectin III-like domains. Missense variants in other residues influencing the conformation of one of the protein domains could be disease causing.

Chapter Notes

Author Notes

Connie Stumpel is a professor of clinical genetics in Maastricht, the Netherlands. She wrote her thesis on the X-linked type of hydrocephalus and is especially interested in X-linked intellectual disability and Kabuki syndrome.

Web page: www.mumc.nl/specialisten/stumpel (in Dutch)

Yvonne J Vos is a clinical laboratory geneticist at the University Medical Center in Groningen, the Netherlands. She wrote her thesis on the genetics of L1 syndrome.

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