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NLM Citation: Boycott KM, MacDonald SK, Parboosingh JS. *VLDLR* Cerebellar Hypoplasia. 2008 Aug 26 [Updated 2020 Feb 27]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

VLDLR Cerebellar Hypoplasia

Synonym: Cerebellar Ataxia, Mental Retardation, and Dysequilibrium Syndrome 1 (CAMRQ1)

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Created: August 26, 2008; Updated: February 27, 2020.

Summary

Clinical characteristics

VLDLR cerebellar hypoplasia (*VLDLR*-CH) is characterized by non-progressive congenital ataxia that is predominantly truncal and results in delayed ambulation, moderate-to-profound intellectual disability, dysarthria, strabismus, and seizures. Children either learn to walk very late (often after age 6 years) or never achieve independent ambulation. Brain MRI findings include hypoplasia of the inferior portion of the cerebellar vermis and hemispheres, simplified gyration of the cerebral hemispheres, and small brain stem – particularly the pons.

Diagnosis/testing

The diagnosis of *VLDLR* cerebellar hypoplasia is established in a proband with suggestive clinical and brain MRI findings by identification of biallelic pathogenic variants in *VLDLR* on molecular genetic testing.

Management

Treatment of manifestations: Seizures and strabismus are treated in the standard manner. Referral to an early intervention program is recommended for access to occupational, physical, and speech therapy, as well as infant mental health services and special educators.

Surveillance: Annual neurologic and rehabilitation evaluations.

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Genetic counseling

VLDLR-CH is inherited in an autosomal recessive manner. At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Carrier testing for at-risk relatives, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible when the pathogenic variants in a family are known.

Diagnosis

VLDLR cerebellar hypoplasia (*VLDLR*-CH) is a subgroup of dysequilibrium syndrome (DES), a spectrum of genetically heterogeneous conditions that combines non-progressive cerebellar ataxia with intellectual disability inherited in an autosomal recessive manner.

Suggestive Findings

VLDLR cerebellar hypoplasia **should be suspected** in individuals with the following major diagnostic features:

- Non-progressive congenital ataxia that is predominantly truncal and results in delayed ambulation
- Moderate-to-profound intellectual disability
- Dysarthria
- MRI findings (see Figure 1) that include the following:
  - Hypoplasia of the inferior portion of the cerebellar vermis and hemispheres
  - Simplified gyration of the cerebral hemispheres with minimally thickened but uniform cortex and lack of clear anteroposterior gradient
  - Small brain stem, particularly the pons

Establishing the Diagnosis

The diagnosis of *VLDLR* cerebellar hypoplasia **is established** in a proband by identification of biallelic pathogenic variants in *VLDLR* on molecular genetic testing (see Table 1).

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing or multigene panel) and **comprehensive genomic testing** (chromosomal microarray analysis, 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. Because the phenotype of VLDLR cerebellar hypoplasia is often recognizable, individuals with the distinctive MRI findings described in Suggestive Findings can often be diagnosed using gene-targeted testing (see Option 1), whereas those in whom the diagnosis of VLDLR cerebellar hypoplasia has not been considered are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When the phenotypic and radiographic findings suggest the diagnosis of *VLDLR* cerebellar hypoplasia, molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**:

- **Single-gene testing.** Sequence analysis of *VLDLR* 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: Targeted analysis for pathogenic variants can be performed first in individuals of Hutterite ancestry. See Table 6.

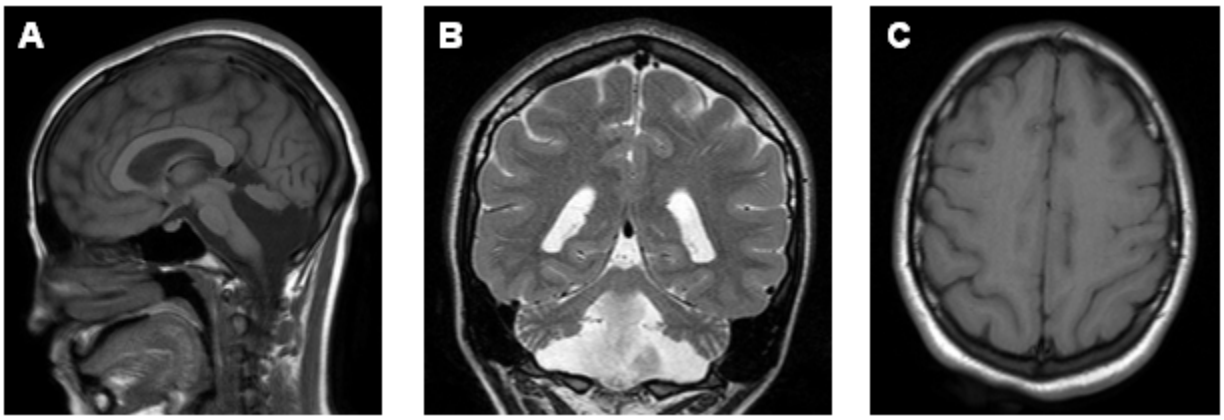

Figure 1. MRI of the brain demonstrating typical neuroimaging findings of VLDLR-CH

A. Sagittal T_1-weighted

B. Coronal T_2-weighted images demonstrating hypoplasia of the inferior vermis and cerebellar hemispheres

C. Axial T_1-weighted image demonstrating simplification of cortical gyri, a mildly thickened cerebral cortex and lack of clear anteroposterior gradient

- **A multigene panel** that includes *VLDLR* 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 this disorder a multigene panel that also includes deletion/duplication analysis can be considered if only one or no pathogenic variant is found on sequencing.

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

Option 2

When the diagnosis of *VLDLR* cerebellar hypoplasia is not considered because of its rarity and/or because an individual has atypical phenotypic features, **comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) is the best option. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

If exome sequencing is not diagnostic, exome array (when clinically available) may be considered to detect (multi)exon deletions or duplications that cannot be detected by sequence analysis.

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 *VLDLR* Cerebellar Hypoplasia

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
VLDLR	Sequence analysis [3]	85% [4]
	Gene-targeted deletion/duplication analysis [5]	15% [4]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic 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.

Clinical Characteristics

Clinical Description

VLDLR cerebellar hypoplasia is a congenital non-progressive disorder characterized by cerebellar ataxia and intellectual disability.

To date, more than 50 individuals have been identified with a pathogenic variant in *VLDLR* [Boycott et al 2005, Glass et al 2005, Moheb et al 2008, Ozcelik et al 2008, Türkmen et al 2008, Boycott et al 2009, Kolb et al 2010, Ali et al 2012, Azmanov et al 2013, Kruer et al 2013, Schlotawa et al 2013, Sonmez et al 2013, Giorgio et al 2016, Micalizzi et al 2016, Valence et al 2016, Wilker et al 2019]. The following description of the phenotypic features associated with this condition is based on these reports.

Table 2. Features of *VLDLR* Cerebellar Hypoplasia

Feature	Number (%) of Persons w/Feature	Comment
Cerebellar hypoplasia	44/44 (100%)	
Pontine hypoplasia	36/44 (81.8%)	
Simplified cortical gyration	43/44 (97.7%)	
Cerebellar ataxia	53/53 (100%)	Predominantly truncal; peripheral ataxia reported in some
Hypotonia	28/37 (75.7%)	
Dysarthria	34/42 (81.0%)	
Nystagmus	11/47 (23.4%)	
Strabismus	40/51 (78.4%)	
Cognitive impairment	53/53 (100%)	Moderate to profound
Developmental delay	53/53 (100%)	
Delayed ambulation	53/53 (100%)	Independent ambulation (if achieved) often in mid-childhood.
Epilepsy	7/53 (13.2%)	
Brisk reflexes	31/40 (77.5%)	
Microcephaly	8/38 (21.1%)	Head circumference -2SD to -4SD

Table 2. continued from previous page.

Feature	Number (%) of Persons w/Feature	Comment
Dysmorphism	1/53 (1.89%)	May not be related to *VLDLR*-CH
Short stature	19/42 (45.2%)	

Brain MRI. All affected individuals demonstrate hypoplasia of the inferior portion of the cerebellar vermis and hemispheres. In addition, the majority of patients show a simplified gyration of the cerebral hemispheres with minimally thickened but uniform cortex, lack of clear anteroposterior gradient, and small brain stem (particularly the pons). Some individuals are described as demonstrating neuroimaging features of pontocerebellar hypoplasia.

Cerebellar ataxia. All affected individuals demonstrate significant truncal ataxia. Children either learn to walk very late (often after age 6 years) or never achieve independent ambulation. For those able to ambulate independently, gait is wide based; affected individuals are not able to perform a tandem gait. Affected individuals from Turkey demonstrate quadrupedal locomotion in which the palms of the hands touch the ground and the elbows, back, and knees are straight [Ozcelik et al 2008, Türkmen et al 2009], an interesting behavioral adaptation which likely depends on the presence of special environmental influences during child development [Herz et al 2008, Türkmen et al 2009]. Limb ataxia is present in most individuals but is not severe.

Intellectual disability. All reported affected individuals have intellectual disability, ranging from moderate to profound. Most individuals can follow simple commands. Some can communicate verbally using short phrases or sentences. Adults are unable to live independently.

Dysarthria. Those who are able to communicate verbally demonstrate dysarthria.

Strabismus. The majority of individuals have strabismus.

Other

- Nystagmus is reported in some individuals and is described as gaze evoked.
- Epileptic seizures were reported in 40% of the affected individuals from the Hutterite population [Glass et al 2005], and appear to be less frequent in non-Hutterite individuals. The seizures tend to be generalized.
- Deep tendon reflexes in the lower extremities tend to be brisk.
- Microcephaly (2-4 SD below the mean) has been reported in a few affected individuals.
- Short stature (height just below the 2nd centile) is a feature in a few affected individuals.

Life span. There has been no formal study of life span in this disorder, but experience from the Hutterite population suggests that life span is not significantly reduced.

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been identified.

Nomenclature

VLDLR-CH is a clinically and molecularly well-defined subgroup of dysequilibrium syndrome (DES).

Prevalence

The actual frequency of *VLDLR*-CH is unknown.

More than 25 individuals with *VLDLR*-CH from the Hutterite population in Canada and the US have been followed for many years. This condition is present in all three Hutterite *leuts* (branches) (i.e., *Schmiedeleut*, *Lehrerleut*, and *Dariusleut*).

The estimated carrier frequency in the Hutterite population is one in 15 [Glass et al 2005].

Genetically Related (Allelic) Disorders

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

Differential Diagnosis

The differential diagnosis of *VLDLR* cerebellar hypoplasia (*VLDLR*-CH) includes autosomal recessive conditions characterized by congenital or very early-onset cerebellar ataxia associated with cerebellar hypoplasia. Because cerebellar hypoplasia can be difficult to distinguish from cerebellar atrophy on early imaging, conditions characterized by the latter should also be considered (see Table 3).

Note: Diverse phenotypes associated with childhood- and adult-onset ataxia are to be excluded (see Hereditary Ataxia Overview, Table 3. Autosomal Recessive Cerebellar Ataxias: Single-Gene Disorders).

Table 3. Genes and Disorders of Interest in the Differential Diagnosis of *VLDLR* Cerebellar Hypoplasia

Gene(s)	Disorder	Brain Imaging	Neurologic Findings
AHI1 *CPLANE1* *CC2D2A* *CEP290* (~34 genes) [1]	Joubert syndrome & related disorders [2]	"Molar tooth sign" (hypoplasia of cerebellar vermis & assoc brain stem abnormalities resembling a tooth)	• DD & severe cognitive impairment (in some individuals) • Episodic hyperpnea or apnea &/or atypical eye movements • Truncal ataxia
ALG1 *ALG6* *PMM2* (~42 genes) [3]	Congenital disorders of glycosylation	Cerebellar atrophy	• DD/ID • Hypotonia & ataxia • Strabismus
ATCAY	Cayman-type cerebellar ataxia (OMIM 601238) [4]	CH	• Cerebellar ataxia w/wide-based gait • Dysarthria • Intention tremor • DD/ID
ATM	Ataxia-telangiectasia [5]	Cerebellar atrophy (may not be obvious in very young individuals)	• Choreoathetosis • Oculomotor apraxia • Progressive cerebellar ataxia beginning at ages 1-4 yrs
ATP8A2	CAMRQ4 (OMIM 615268)	Cerebellar atrophy	• Congenital cerebellar ataxia • ID
CA8	CAMRQ3 (OMIM 613227)		• Congenital cerebellar ataxia • ID

Table 3. continued from previous page.

Gene(s)	Disorder	Brain Imaging	Neurologic Findings
EXOSC3 *RARS2* *SEPSECS* *TSEN2* *TSEN34* *TSEN54* *VRK1* [6]	PCH types 1 & 2 (see *EXOSC3*-PCH & *TSEN54*-PCH)	Cerebellar vermis hypoplasia & hypoplasia of the pons (more severe than small pons seen in *VLDLR*-CH)	• Progressive motor degeneration (similar to spinal muscular atrophy) in PCH1 • Dyskinesia in PCH2
RELN	*RELN* lissencephaly w/ CH [7] (OMIM 257320)	Cerebellar signs of *RELN*-LCH that differ from *VLDLR*-CH: • More significant lissencephaly w/anterior>posterior gradient • A malformed hippocampus • Profound CH w/complete absence of detectable folia	• Congenital cerebellar ataxia • Hypotonia • ID • Epilepsy • Strabismus
SACS	ARSACS (*a*utosomal *r*ecessive *s*pastic *a*taxia of *C*harlevoix-*S*aguenay)	Atrophy of superior vermis	• Distal muscle wasting • Distal sensorimotor neuropathy (predominant in legs) • Dysarthria • Early-onset ataxia • Extensor plantar reflexes • Horizontal gaze-evoked nystagmus • Spasticity
SIL1	Marinesco-Sjögren syndrome [8]	Cerebellar atrophy	• Cerebellar ataxia • Mild-to-severe cognitive impairment • Hypotonia & muscle weakness
TWNK	Infantile-onset spinocerebellar ataxia [9]	Atrophy of cerebellum, brain stem, & spinal cord	• Normal development until age 1 yr, followed by onset of ataxia, muscle hypotonia, loss of deep-tendon reflexes, athetosis, ophthalmoplegia, & sensorineural deafness in childhood [10] • Epilepsy can → serious & often fatal encephalopathy.

Table 3. continued from previous page.

Gene(s)	Disorder	Brain Imaging	Neurologic Findings
WDR81	CAMRQ2 (OMIM 610185)	CH	• Congenital cerebellar ataxia • ID

CAMRQ = cerebellar ataxia, mental retardation, and dysequilibrium syndrome; CDG = congenital disorder of glycosylation; CH = cerebellar hypoplasia; DD = developmental delay; ID = intellectual disability; LCH = lissencephaly with cerebellar hypoplasia; PCH = pontocerebellar hypoplasia

1. To date, pathogenic variants in 34 genes are known to cause Joubert syndrome. *AHI1*, *CPLANE1*, *CC2D2A*, and *CEP290* are some of the most commonly involved genes.

2. Variable features include: retinal dystrophy, renal disease, ocular colobomas, occipital encephalocele, hepatic fibrosis, polydactyly, oral hamartomas, and endocrine abnormalities.

3. *PMM2*-CDG (CDG-Ia), *ALG6*-CDG (CDG-Ic), and *ALG1*-CDG (CDG-Ik) represent some of the more frequently identified CDG types. Forty-two different enzymes in the N-linked oligosaccharide synthetic pathway or interactive pathways are currently recognized to be deficient in each of the types of CDG-N-linked or among the multiple-pathway disorders (see Congenital Disorders of N-Linked Glycosylation and Multiple Pathway Overview).

4. Affected individuals are from a Grand Cayman Island isolate.

5. Also characterized by immunodeficiency, frequent infections, telangiectasias of the conjunctivae, and increased risk for malignancy (particularly leukemia and lymphoma)

6. About 50% of individuals with pontocerebellar hypoplasia type 1 (PCH1) have pathogenic variants in *EXOSC3*. See Pontocerebellar hypoplasia: OMIM Phenotypic Series for other genes associated with PCH in OMIM.

7. The presentation of lissencephalies with cerebellar hypoplasia (LCH) ranges from the classic pattern of pachygyria/agyria to less severe phenotypes. The cerebellar manifestations range from relatively preserved hemispheres to marked hypoplasia with foliation defects. The malformations seen in VLDLR-CH fall within the LCH spectrum. Forms of LCH other than *RELN*-LCH are easily distinguished from VLDLR-CH based on the severity of the cortical phenotype or additional features.

8. Also characterized by early-onset cataracts

9. Infantile-onset spinocerebellar ataxia is well recognized in Finland.

10. By adolescence affected individuals are profoundly deaf and no longer ambulatory; sensory axonal neuropathy, optic atrophy, autonomic nervous system dysfunction, and hypergonadotropic hypogonadism in females become evident.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *VLDLR* cerebellar hypoplasia (*VLDLR*-CH), 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 *VLDLR* Cerebellar Hypoplasia

System/Concern	Evaluation	Comment
Neurologic	Neurologic eval	• Brain MRI • Consider EEG if seizures are a concern.
Developmental	Developmental assessment	Adaptive, cognitive, & speech/language eval
Musculoskeletal	Orthopedics / physical medicine & rehab / PT/OT evaluation	To incl assessment of: • Mobility, activities of daily living, & need for adaptive devices; • Need for PT (to improve gross motor skills) &/or OT (to improve fine motor skills);
Eyes	Ophthalmologic eval	To assess for strabismus

Table 4. continued from previous page.

System/Concern	Evaluation	Comment
Miscellaneous/ Other	Consultation w/clinical geneticist &/or genetic counselor	To incl genetic counseling & reproductive options
	Family support/resources	• School support • Community support

OT = occupational therapy; PT = physical therapy

Treatment of Manifestations

Treatment of seizures and strabismus is done in the standard manner.

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. 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:

- Individualized education plan (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.
  - Vision and hearing consultants should be a part of the child's IEP team to support access to academic material.
  - 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 promote ambulation.
- Consider use of durable medical equipment and positioning devices as needed (e.g., wheelchairs, walkers, bath chairs, orthotics, adaptive strollers).

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

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.

Surveillance

Table 5. Recommended Surveillance for Individuals with *VLDLR* Cerebellar Hypoplasia

System/Concern	Evaluation	Frequency
Seizures	Neurologic evaluation	Annually
Cerebellar ataxia	Rehabilitation evaluation	

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

VLDLR cerebellar hypoplasia (*VLDLR*-CH) is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected child are obligate heterozygotes (i.e., carriers of one *VLDLR* pathogenic variant).
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. To date, individuals with *VLDLR*-CH are not known to reproduce.

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

Carrier Detection

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

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are carriers or are at risk of being carriers.

Population screening. In the Hutterite population, the high carrier frequency (~1:15) could warrant population screening for reproductive purposes [Glass et al 2005]. Carrier testing for the Hutterite population involves targeted analysis for the founder deletion [Boycott et al 2005].

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

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

- **National Institute of Neurological Disorders and Stroke (NINDS)**

PO Box 5801
Bethesda MD 20824
Phone: 800-352-9424 (toll-free); 301-496-5751; 301-468-5981 (TTY)
Cerebellar Hypoplasia Information Page

- **American Association on Intellectual and Developmental Disabilities (AAIDD)**
  Phone: 202-387-1968
  Fax: 202-387-2193
  www.aaidd.org
- **CDC - Developmental Disabilities**
  Phone: 800-CDC-INFO
  Email: cdcinfo@cdc.gov
  Intellectual Disability
- **National Ataxia Foundation**
  Phone: 763-553-0020
  Fax: 763-553-0167
  Email: naf@ataxia.org
  www.ataxia.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. VLDLR Cerebellar Hypoplasia: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
VLDLR	9p24.2	Very low-density lipoprotein receptor	VLDLR database	VLDLR	VLDLR

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 VLDLR Cerebellar Hypoplasia (View All in OMIM)

192977	VERY LOW DENSITY LIPOPROTEIN RECEPTOR; VLDLR
224050	CEREBELLAR ATAXIA, IMPAIRED INTELLECTUAL DEVELOPMENT, AND DYSEQUILIBRIUM SYNDROME 1; CAMRQ1

Molecular Pathogenesis

VLDLR encodes a protein of 873 amino acids and is expressed abundantly in the heart, skeletal muscle, kidney, and brain. VLDLR protein is part of the reelin signaling pathway, which guides neuroblast migration in the developing cerebral cortex and cerebellum [Tissir & Goffinet 2003]. In an evolutionarily conserved pathway, reelin engages two lipoprotein receptors, VLDLR and apolipoprotein E receptor-2 (Apoer2), resulting in phosphorylation of disabled-1 (Dab1) and activation of an intracellular signaling cascade that allows neuroblasts to complete migration.

VLDLR belongs to a subset of cell surface receptors called the LDL receptor protein family. Family members share a number of domains arranged in a similar pattern: ligand-binding repeat domain, EGF repeat, YWTD

domain, O-linked sugar domain, transmembrane domain, and a cytoplasmic domain containing a NPXY motif. VLDLR was initially identified to function in the receptor-mediated endocytosis of apoE-containing lipoproteins.

Mechanism of disease causation. All of the reported pathogenic variants to date are predicted to result in loss of function of the VLDLR protein. In the absence of this receptor, neuroblasts are unable to complete migration and adopt their ultimate position in the developing central nervous system.

Table 6. Notable *VLDLR* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NC_000009	g.2479657_2678818del	Entire gene deletion	Hutterite founder variant [Boycott et al 2005]
NM_003383 NP_003374.3	c.1256G>A	p.Cys419Tyr	Patient reported w/a less severe phenotype, predicted due to pathogenic variant in a less essential domain (EGF-B) [Micalizzi et al 2016]

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.

References

Literature Cited

Ali BR, Silhavy JL, Gleeson MJ, Gleeson JG, Al-Gazali L. A missense founder mutation in VLDLR is associated with dysequilibrium syndrome without quadrupedal locomotion. BMC Med Genet. 2012;13:80. PubMed PMID: 22973972.

Azmanov DN, Chamova T, Tankard R, Gelev V, Bynevelt M, Florez L, Tzoneva D, Zlatareva D, Guergueltcheva V, Bahlo M, Tournev I, Kalaydjieva L. Challenges of diagnostic exome sequencing in an inbred founder population. Mol Genet Genomic Med. 2013;1:71–6. PubMed PMID: 24498604.

Boycott KM, Bonnemann C, Herz J, Neuert S, Beaulieu C, Scott JN, Venkatasubramanian A, Parboosingh JS. Mutations in VLDLR as a cause for autosomal recessive cerebellar ataxia with mental retardation (dysequilibrium syndrome). J Child Neurol. 2009;24:1310–5. PubMed PMID: 19332571.

Boycott KM, Flavelle S, Bureau A, Glass HC, Fujiwara TM, Wirrell E, Davey K, Chudley AE, Scott JN, McLeod DR, Parboosingh JS. Homozygous deletion of the very low density lipoprotein receptor gene causes autosomal recessive cerebellar hypoplasia with cerebral gyral simplification. Am J Hum Genet. 2005;77:477–83. PubMed PMID: 16080122.

Giorgio E, Ciolfi A, Biamino E, Caputo V, Di Gregorio E, Belligni EF, Calcia A, Gaidolfi E, Bruselles A, Mancini C, Cavalieri S, Molinatto C, Cirillo Silengo M, Ferrero GB, Tartaglia M, Brusco A. Whole exome sequencing is necessary to clarify ID/DD cases with de novo copy number variants of uncertain significance: Two proof-of-concept examples. Am J Med Genet A. 2016;170:1772–9. PubMed PMID: 27108886.

Glass HC, Boycott K, Adams C, Barlow K, Scott JN, Chudley AE, Fujiwara T, Morgan K, Wirrell E, McLeod D. Autosomal recessive cerebellar hypoplasia in the Hutterite population: a syndrome of nonprogressive cerebellar ataxia with mental retardation. Dev Med Child Neurol. 2005;47:691–5. PubMed PMID: 16174313.

Herz J, Boycott KM, Parboosingh JS. "Devolution" of bipedality. Proc Natl Acad Sci U S A. 2008;105:E25. PubMed PMID: 18487453.

Kolb LE, Arlier Z, Yalcinkaya C, Ozturk AK, Moliterno JA, Erturk O, Bayrakli F, Korkmaz B, DiLuna ML, Yasuno K, Bilguvar K, Ozcelik T, Tuysuz B, State MW, Gunel M. Novel VLDLR microdeletion identified in

two Turkish siblings with pachygyria and pontocerebellar atrophy. Neurogenetics. 2010;11:319–25. PubMed PMID: 20082205.

Kruer MC, Jepperson TN, Weimer JM, Mroch A, Davis-Keppen L, Crotwell P, Parboosingh J. Mutations in VLDLR associated with ataxia with secondary vitamin E deficiency. Mov Disord. 2013;28:1904–5. PubMed PMID: 23813796.

Micalizzi A, Moroni I, Ginevrino M, Biagini T, Mazza T, Romani M, Valente EM. Very mild features of dysequilibrium syndrome associated with a novel VLDLR missense mutation. Neurogenetics. 2016;17:191–5. PubMed PMID: 27251579.

Moheb LA, Tzschach A, Garshasbi M, Kahrizi K, Darvish H, Heshmati Y, Kordi A, Najmabadi H, Ropers HH, Kuss AW. Identification of a nonsense mutation in the very low-density lipoprotein receptor gene (VLDLR) in an Iranian family with dysequilibrium syndrome. Eur J Hum Genet. 2008;16:270–3. PubMed PMID: 18043714.

Ozcelik T, Akarsu N, Uz E, Caglayan S, Gulsuner S, Onat OE, Tan M, Tan U. Mutations in the very low-density lipoprotein receptor VLDLR cause cerebellar hypoplasia and quadrupedal locomotion in humans. Proc Natl Acad Sci USA. 2008;105:4232–6. PubMed PMID: 18326629.

Schlotawa L, Hotz A, Zeschnigk C, Hartmann B, Gärtner J, Morris-Rosendahl D. Cerebellar ataxia, mental retardation and dysequilibrium syndrome 1 (CAMRQ1) caused by an unusual constellation of VLDLR mutation. J Neurol. 2013;260:1678–80. PubMed PMID: 23670308.

Sonmez FM, Gleeson JG, Celep F, Kul S. The very low density lipoprotein receptor-associated pontocerebellar hypoplasia and dysmorphic features in three Turkish patients. J Child Neurol. 2013;28:379–83. PubMed PMID: 22532556.

Stenson PD, Mort M, Ball EV, Evans K, Hayden M, Heywood S, Hussain M, Phillips AD, Cooper DN. The Human Gene Mutation Database: towards a comprehensive repository of inherited mutation data for medical research, genetic diagnosis and next-generation sequencing studies. Hum Genet. 2017;136:665–77. PubMed PMID: 28349240.

Tissir F, Goffinet AM. Reelin and brain development. Nat Rev Neurosci. 2003;4:496–505. PubMed PMID: 12778121.

Türkmen S, Guo G, Garshasbi M, Hoffmann K, Alshalah AJ, Mischung C, Kuss A, Humphrey N, Mundlos S, Robinson PN. CA8 mutations cause a novel syndrome characterized by ataxia and mild mental retardation with predisposition to quadrupedal gait. PLoS Genet. 2009;5:e1000487. PubMed PMID: 19461874.

Türkmen S, Hoffmann K, Demirhan O, Aruoba D, Humphrey N, Mundlos S. Cerebellar hypoplasia, with quadrupedal locomotion, caused by mutations in the very low-density lipoprotein receptor gene. Eur J Hum Genet. 2008;16:1070–4. PubMed PMID: 18364738.

Valence S, Garel C, Barth M, Toutain A, Paris C, Amsallem D, Barthez MA, Mayer M, Rodriguez D, Burglen L. RELN and VLDLR mutations underlie two distinguishable clinico-radiological phenotypes. Clin Genet. 2016;90:545–9. PubMed PMID: 27000652.

Wilker M, Hans-Jürgen C, Schuster S, Abicht A, Boltshauser E. VLDLR-associated pontocerebellar hypoplasia with nonprogressive congenital ataxia and a diagnostic neuroimaging pattern. Neuropediatrics. 2019;50:404–5. PubMed PMID: 31261436.

Chapter Notes

Revision History

- 27 February 2020 (ha) Comprehensive update posted live
- 8 August 2013 (me) Comprehensive update posted live

- 26 August 2008 (cg) Review posted live
- 7 July 2008 (kmb) Original submission

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