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CLCN2-Related Leukoencephalopathy

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Summary

Clinical characteristics

CLCN2-related leukoencephalopathy is characterized by nonspecific neurologic findings, mild visual impairment from chorioretinopathy or optic atrophy, male infertility, and characteristic findings on brain MRI. Neurologic findings include mild ataxia (action tremor and gait instability following initially normal motor development; occasionally, mild spasticity), cognitive impairment in some (typically mild, rarely severe), psychiatric symptoms in some (depression and schizophrenia-like symptoms), headaches in some (usually intermittent, severe, and diffuse) and auditory symptoms in some (hearing loss, tinnitus, vertigo). Affected individuals remain ambulatory, do not require support for walking, and rarely become blind. To date *CLCN2*-related leukoencephalopathy has been reported or identified in 31 individuals from 30 families. It is not yet known if the findings occurring in a few individuals (i.e., epilepsy and paroxysmal kinesigenic dyskinesia) are part of the phenotypic spectrum or unrelated findings.

Diagnosis/testing

The diagnosis of *CLCN2*-related leukoencephalopathy is established in a proband by identification of biallelic pathogenic variants in *CLCN2* on molecular genetic testing.

Management

Treatment of manifestations: Supportive care including physical therapy and rehabilitation to improve motor function, special education as needed, treatment of headache, guidance for visual impairment.

Surveillance: Annual: neurologic examination. Every 2-3 years: ophthalmologic examination and audiologic assessment.

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Evaluation of relatives at risk: It is appropriate to clarify the genetic status of older and younger sibs of a proband in order to identify as early as possible those who would benefit from early diagnosis and routine surveillance for motor, cognitive, vision, and hearing impairment.

Genetic counseling

CLCN2-related leukoencephalopathy is inherited in an autosomal recessive manner. If both parents are known to be heterozygous for a *CLCN2* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Once the *CLCN2* pathogenic variants have been identified in an affected family member, carrier testing for at-risk family members and prenatal and preimplantation genetic testing for *CLCN2*-related leukoencephalopathy are possible.

Diagnosis

Suggestive Findings

CLCN2-related leukoencephalopathy **should be suspected** in individuals with the following findings and family history.

Clinical findings

- Mild ataxia
- Mild cognitive impairment
- Psychiatric symptoms
- Headache
- Decreased vision caused by chorioretinopathy or optic atrophy
- Auditory symptoms including hearing loss, tinnitus, and vertigo
- Male infertility caused by oligo-/azoospermia

Imaging findings on brain MRI

- Abnormally low signal on T_1-weighted images and abnormally high signal on T_2-weighted images (Figure 1) in the:
  - Posterior limbs of the internal capsules
  - Midbrain crura cerebri
  - Middle cerebellar peduncles
- Additional findings can include abnormally low signal on T_1-weighted images and abnormally high signal on T_2-weighted images in the following:
  - Pyramidal tracts in the pons
  - Central tegmental tracts in medulla, pons and midbrain
  - Superior cerebellar peduncles
  - Decussation of the superior cerebellar peduncles in the midbrain
  - Cerebellar white matter
  - Corpus callosum
  - Cerebral white matter, either with a signal behavior suggestive of hypomyelination or nonspecific, mild inhomogeneous signal abnormalities

Family history is consistent with autosomal recessive inheritance (e.g., affected sibs and/or parental consanguinity). Absence of a known family history does not preclude the diagnosis.

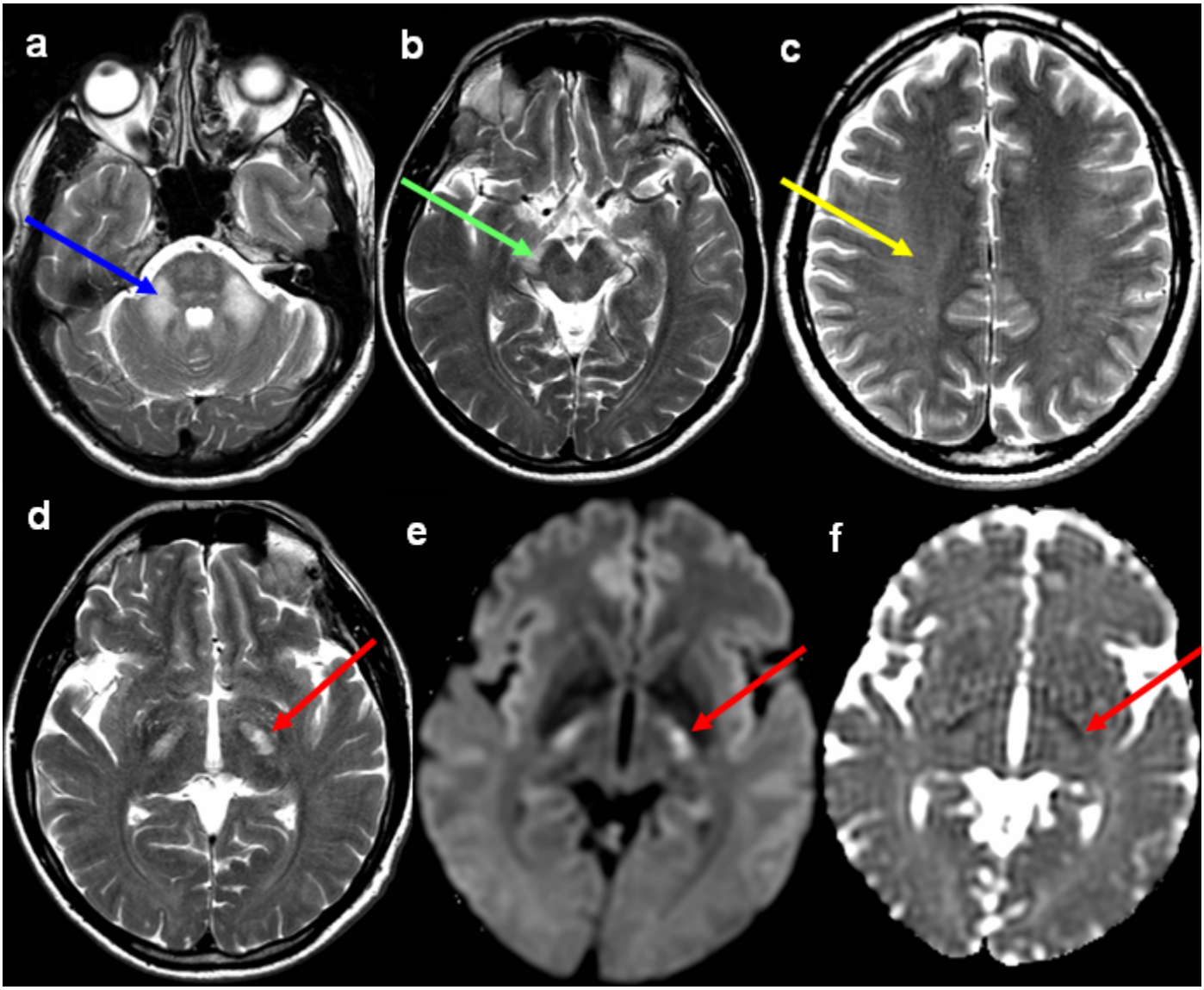

Figure 1. MRI of an individual age 50 years with *CLCN2*-related leukoencephalopathy. Note the T_2-weighted signal abnormalities (a-d) in the middle cerebellar peduncles (blue arrow in a), crura cerebri (green arrow in b), and posterior limb of the internal capsule (red arrow in d). All cerebral white matter except for the directly subcortical white matter has a slightly abnormal signal (yellow arrow in c). The diffusion-weighted image (e) and apparent diffusion coefficient map (f) show diffusion restriction in the posterior limb of the internal capsule (red arrows).

Establishing the Diagnosis

The diagnosis of *CLCN2*-related leukoencephalopathy **is established** in a proband by identification of biallelic pathogenic variants in *CLCN2* (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** (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 MRI findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those in whom the diagnosis of *CLCN2*-related

leukoencephalopathy has not been considered (individuals with absence of the typical MRI phenotype) are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

Single-gene testing. Sequence analysis of *CLCN2* is performed first to detect small intragenic deletions/insertions and missense, nonsense, and splice site variants. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If only one or no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications.

A leukoencephalopathy multigene panel that includes *CLCN2* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis (including high resolution gene-targeted microarray), 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 *CLCN2*-Related Leukoencephalopathy

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
CLCN2	Sequence analysis [3]	26/29 [4]
	Gene-targeted deletion/duplication analysis [5]	3/29 [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. Depienne et al [2013]; Di Bella et al [2014]; Hanagasi et al [2015]; Giorgio et al [2017]; Zeydan et al [2017]; Guo et al [2019]; Hoshi et al [2019]; Ngo et al [2020]; Ozaki et al [2020]; Parayil Sankaran et al [2020]; Authors [personal observation].
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. A large deletion in *CLCN2* has been detected using high resolution gene-targeted microarray [Authors, personal observation].

Clinical Characteristics

Clinical Description

The phenotypic spectrum of *CLCN2*-related leukoencephalopathy ranges from childhood onset with mild ataxia, learning disabilities, and headaches to adult onset with mild ataxia and decreased vision [Depienne et al 2013]. Infertility or involuntary childlessness in adulthood has been observed in four adult males [Di Bella et al 2014; Authors, personal observation]. Several individuals with psychiatric concerns (depression or psychosis) and/or auditory abnormalities including mild hearing loss, tinnitus, and vertigo have been observed. Other medical concerns occurring in a few individuals may be rare parts of the phenotype or unrelated findings. The disease course has been reported as stable to slowly progressive; considering that adults were previously normal, extremely slow progression is most likely. All individuals reported to date have remained ambulatory. The oldest known individual with *CLCN2*-related leukoencephalopathy is age 70 years. No disease-related deaths have been reported to date.

To date, 31 individuals have been identified with biallelic pathogenic variants in *CLCN2* [Depienne et al 2013; Di Bella et al 2014; Hanagasi et al 2015; Giorgio et al 2017; Zeydan et al 2017; Guo et al 2019; Hoshi et al 2019; Ngo et al 2020; Ozaki et al 2020; Parayil Sankaran et al 2020; Authors, personal observation]. The following description of the phenotypic features associated with this condition is based on these reports and personal observations.

Table 2. *CLCN2*-related Leukoencephalopathy: Frequency of Select Features

Feature	# of Persons with Feature [1]	Comment
Mild cerebellar ataxia	18/30	
Mild spasticity	2/29	
Mild cognitive impairment	14/28	
Psychiatric symptoms	7/29	Incl depression & psychosis/schizophrenia-like symptoms
Headache	12/28	
Decreased vision	8/25	Incl retinopathy & optic atrophy; blindness & double vision may occur.
Auditory abnormalities	8/29	Incl (mild) hearing loss, tinnitus, & dizziness
Male fertility problems	4/4	Not all affected males have been assessed for infertility. Involuntary childlessness in adult males was included in this category.

1. Of those assessed for the feature

Motor skills. Initial motor development is normal. At presentation, most affected individuals display signs of mild cerebellar ataxia with action tremor and gait instability; some also show mild signs of spasticity. Affected individuals remain ambulatory and do not require support for walking.

Cognitive skills. Some affected individuals have mild learning problems from early on, but most initially have normal intellect. Mild cognitive decline has been observed in some affected individuals [Guo et al 2019; Authors, personal observation]. One affected individual had severe cognitive impairment.

Psychiatric symptoms. Depression and psychosis or schizophrenia-like symptoms have been observed in several affected individuals [Depienne et al 2013; Authors, personal observation].

Headache. Some affected individuals complain of intermittent severe diffuse headaches.

Vision. Some affected individuals have a retinopathy or optic atrophy leading to mild visual impairment; blindness has been observed in one adult. Some affected individuals have visual field defects at formal testing, indicating subclinical retinopathy. Double vision has also been observed in some.

Auditory abnormality. Individuals with progressive hearing loss [Depienne et al 2013], unilateral mild hearing loss [Zeydan et al 2017], tinnitus [Guo et al 2019] and vertigo/dizziness [Parayil Sankaran et al 2020; Authors, personal observation] have been observed.

Male infertility. One male with azoospermia (but no neurologic dysfunction) was found to have *CLCN2*-related leukoencephalopathy during a workup for infertility [Di Bella et al 2014]. Three adult males diagnosed with *CLCN2*-related leukoencephalopathy have had a history of involuntary childlessness [Authors, personal observation]. To date, no affected males with offspring have been observed.

Other. A single individual with paroxysmal kinesigenic dyskinesia [Hanagasi et al 2015] has been reported.

An infant who presented with frequent generalized tonic-clonic seizures at age three months has been reported. Seizures were effectively controlled by anti-seizure medication (phenobarbital and valproate). A boy age 13 years with the exact same homozygous pathogenic variant as the infant did not have epilepsy [Ozaki et al 2020].

Two additional individuals with biallelic pathogenic variants in *CLCN2* and epilepsy were identified [Authors, personal observation]. Since epilepsy has a fairly high incidence in the general population and any brain disease in itself enhances the risk of epilepsy, it is not possible to say whether this is related to *CLCN2*-related leukoencephalopathy. Animal studies are also inconclusive; one study reports interictal epileptic brain activity and a lowered seizure threshold in *Clcn2*-null mice [Cortez et al 2010], while two other studies report no alteration of seizure threshold in *Clcn2*-null mice [Bösl et al 2001, Blanz et al 2007]. Therefore, the link between partial or complete loss of chloride channel-2 function and epilepsy remains unresolved.

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been identified.

Prevalence

The prevalence of *CLCN2*-related leukoencephalopathy is unknown. The small number of known affected individuals suggests that the disease is exceedingly rare. Numerous individuals with *CLCN2*-related leukoencephalopathy, however, may also be undiagnosed because they remain asymptomatic at an advanced age, lack a specific clinical phenotype, or have findings (e.g., headaches or infertility due to azoospermia or oligozoospermia) that do not prompt evaluation by brain MRI.

Genetically Related (Allelic) Disorders

Heterozygous *CLCN2* pathogenic variants have been reported as a cause of idiopathic generalized epilepsies, including childhood absence epilepsy, juvenile myoclonic epilepsy, and epilepsy with grand mal seizures on awakening [Haug et al 2003, D'Agostino et al 2004, Stogmann et al 2006, Everett et al 2007, Combi et al 2009, Kleefuss-Lie at al 2009, Saint-Martin et al 2009, Klassen et al 2011]; however, these findings remain controversial. The original paper supporting these results was retracted [Haug et al 2009]. While the authors still believed that *CLCN2* pathogenic variants may contribute to epilepsy in some cases [Haug et al 2009, Kleefuss-Lie at al 2009], functional studies of the *CLCN2* variants identified in individuals with epilepsy did not confirm their pathogenicity. Furthermore, similar variants were observed in individuals who did not have epilepsy [Planells-Cases & Jentsch 2009, Niemeyer at al 2010].

Heterozygous gain-of-function pathogenic variants in *CLCN2* can cause early-onset primary aldosteronism [Fernandes-Rosa et al 2018, Scholl et al 2018]. These specific variants affect chloride channel-2 gating, leading to

increased channel opening in zona glomerulosa cells of the adrenal glands. This, in turn, increases aldosterone biosynthesis. Therefore, gain-of-function pathogenic variants in *CLCN2* lead to a fundamentally different pathology from loss-of-function variants.

Differential Diagnosis

The differential diagnosis of the MRI findings of bilateral symmetric signal abnormalities of the middle cerebellar peduncles and variable signal abnormalities in the brain stem and cerebellar and cerebral white matter includes the disorders summarized in Table 3. All disorders in Table 3 can be differentiated from *CLCN2*-related leukoencephalopathy by the MRI findings mentioned and the diagnosis can be confirmed by appropriate biochemical and/or genetic testing.

Table 3. Differential Diagnosis of MRI Findings Seen in *CLCN2*-Related Leukoencephalopathy

Gene	DiffDx Disorder	MOI	Clinical Features	Key Brain MRI Findings
ABCD1	Adrenomyeloneuropathy (See X-Linked Adrenoleukodystrophy.)	XL	Most commonly manifests in late 20s w/progressive paraparesis, sphincter disturbances, sexual dysfunction, & often impaired adrenocortical function. All features progress over decades.	Primary MRI finding: spinal cord atrophy [1]
ATP7B	Wilson disease	AR	May present w/hepatic, neurologic, or psychiatric disturbances (or a combination of these) in persons age 3 yrs to >50 yrs. Kayser-Fleischer rings resulting from copper deposition in Descemet's membrane of the cornea are frequently present.	Abnormalities are highly variable, mostly involve basal ganglia & may involve brain stem, but w/ configuration different from that of CLCN2L
CYP27A1	Cerebrotendinous xanthomatosis	AR	Infantile-onset diarrhea, childhood-onset cataract, adolescent- to young adult-onset tendon xanthomas, & adult-onset progressive neurologic dysfunction w/dementia, psychiatric disturbances, pyramidal &/or cerebellar signs, dystonia, atypical parkinsonism, peripheral neuropathy, & seizures.	Most important & earliest MRI abnormalities: signal abnormalities in the dentate nucleus & cerebellar hemispheric white matter [2]
DARS2	Leukoencephalopathy w/brain stem & spinal cord abnormalities & lactate elevation	AR	Slowly progressive cerebellar ataxia & spasticity w/dorsal column dysfunction. Deterioration of motor skills usually starts in childhood or adolescence, but occasionally in adulthood.	MRI invariably shows spinal cord signal abnormalities over its entire length. [3]
FMR1	Fragile X-associated tremor/ataxia syndrome (See *FMR1* Disorders.)	XL	Late-onset, progressive cerebellar ataxia & intention tremor followed by cognitive impairment. Typical onset: age 60-65 yrs.	On brain MRI: as in CLCN2L, typical middle cerebellar peduncle signal abnormalities; unlike CLCN2L, no signal abnormalities in the crura cerebri & posterior limbs of the internal capsules & no diffusion restriction

Table 3. continued from previous page.

Gene	DiffDx Disorder	MOI	Clinical Features	Key Brain MRI Findings
GBE1	*GBE1* adult polyglucosan body disease	AR	Progressive neurogenic bladder; gait difficulties from mixed upper & lower motor neuron involvement; sensory loss predominantly in distal legs; autonomic dysfunction; mild cognitive difficulties	Cerebral white matter abnormalities w/periventricular preponderance; long tract abnormalities in brain stem
GFAP	Alexander disease, adult form	AD	Mainly affects lower brain stem; typically characterized by bulbar or pseudobulbar findings, motor/gait abnormalities w/pyramidal tract signs, or cerebellar abnormalities	Hallmark brain MRI abnormality: atrophy of the medulla oblongata [4]
GJB1	*GJB1* disorders: Charcot-Marie-Tooth neuropathy and central nervous system phenotypes	XL	Neuropathy, stroke-like episodes of CNS dysfunction w/transient ataxia, dysarthria & weakness; persistent CNS abnormalities in some persons (ataxia, spasticity, & dysarthria)	During acute episodes, MRI shows mild signal abnormalities w/ profound diffusion restriction in specific white matter regions which disappear after the episode. In some w/persistent CNS involvement, MRI is indistinguishable from MRI findings in CLCN2L, w/mild signal abnormality & mildly restricted diffusion of all brain white matter structures. [5]
LMNB1	Autosomal dominant leukodystrophy w/autonomic disease	AD	Executive dysfunction, memory decline, personality changes, motor impairments, & seizures; affected persons are eventually bedridden w/ spasticity & rigidity. Mean age of onset: 4th decade.	Cerebral white matter abnormalities w/frontal preponderance

AD = autosomal dominant; AR = autosomal recessive; CLCN2L = *CLCN2*-related leukoencephalopathy; DiffDx = differential diagnosis; MOI = mode of inheritance; XL = X-linked

1. Corticopontine & corticospinal projection fibers are frequently involved.

2. Signal abnormalities are often present in the corticospinal tracts & medial lemniscus in the brain stem, & slight signal changes are often seen in the periventricular cerebral white matter.

3. Brain stem signal abnormalities are more variable & rarely involve the middle cerebellar peduncles & crura cerebri.

4. Brain stem signal abnormalities with a predilection for the medulla may also be present.

5. Depienne et al [2013]

Management

No clinical practice guidelines for *CLCN2*-related leukoencephalopathy have been published.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *CLCN2*-related leukoencephalopathy, 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 *CLCN2*-Related Leukoencephalopathy

System/Concern	Evaluation	Comment
Motor skill issues (cerebellar ataxia & gait instability)	Neurologic exam; brain MRI; PT/OT assessment	
Mild learning problems w/potential for cognitive decline	Baseline cognitive skill assessment	
Vision concerns	Ophthalmologic exam	Attn to visual acuity & visual fields
Hearing loss	Audiologic exam	
Male infertility	Eval of testicular function (in adult males)	
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of CLCN2L to facilitate medical & personal decision making

CLCN2L = *CLCN2*-related leukoencephalopathy; MOI = mode of inheritance; OT = occupational therapy; PT = physical therapy
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Table 5. Treatment of Manifestations in Individuals with *CLCN2*-Related Leukoencephalopathy

Manifestation/Concern	Treatment
Motor skill dysfunction	PT, OT, & assistive devices as needed for motor function
Mild learning problems	Special educational services & support as needed
Psychiatric symptoms	Individualized treatment by psychiatrist
Headache	Standard treatment
Visual impairment	Guidance from low vision specialist
Male infertility	Treatment from male infertility specialist

OT = occupational therapy; PT = physical therapy

Surveillance

Table 6. Recommended Surveillance for Individuals with *CLCN2*-Related Leukoencephalopathy

System/Concern	Evaluation	Frequency
Motor skill dysfunction & learning disability	Neurologic exam	Annual
	Brain MRI	Every 2-3 yrs or as neurologic changes occur
Visual impairment	Ophthalmologic exam	Every 2-3 years
Hearing loss	Audiologic assessment	Every 2-3 years

Evaluation of Relatives at Risk

It is appropriate to clarify the genetic status of older and younger sibs of a proband in order to identify as early as possible those who would benefit from early diagnosis and routine surveillance for motor, cognitive, vision, and hearing impairment.

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

CLCN2-related leukoencephalopathy is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected individual are obligate heterozygotes (i.e., presumed to be carriers of one *CLCN2* pathogenic variant based on family history).
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for a *CLCN2* pathogenic variant and to allow reliable recurrence risk assessment. If a pathogenic variant is detected in only one parent, the following possibilities should be considered:
  - One of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent [Jónsson et al 2017].
  - Uniparental isodisomy for the parental chromosome with the pathogenic variant resulted in homozygosity for the pathogenic variant in the proband.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- If both parents are known to be heterozygous for a *CLCN2* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. The offspring of an individual with *CLCN2*-related leukoencephalopathy are obligate heterozygotes (carriers) for a pathogenic variant in *CLCN2*.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of a *CLCN2* pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *CLCN2* pathogenic variants in the family.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Family planning

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

Prenatal Testing and Preimplantation Genetic Testing

Once the *CLCN2* pathogenic variants have been identified in an affected family member, prenatal and preimplantation genetic testing for *CLCN2*-related leukoencephalopathy 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.

- **European Leukodystrophy Association (ELA)**
  Phone: 03 83 30 93 34
  www.ela-asso.com
- **United Leukodystrophy Foundation**
  Phone: 800-SAV-LIVE; 815-748-3211
  Email: office@ulf.org
  ulf.org
- **Myelin Disorders Bioregistry Project**
  Phone: 215-590-1719
  Email: sherbinio@chop.edu
  Myelin Disorders Bioregistry Project

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. CLCN2-Related Leukoencephalopathy: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
CLCN2	3q27.1	Chloride channel protein 2	CLCN2 database	CLCN2	CLCN2

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 CLCN2-Related Leukoencephalopathy (View All in OMIM)

600570	CHLORIDE CHANNEL 2; CLCN2

Table B. continued from previous page.

615651	LEUKOENCEPHALOPATHY WITH ATAXIA; LKPAT

Molecular Pathogenesis

CLCN2 codes for the chloride channel-2 (ClC-2), which is expressed in the plasma membrane of almost all mammalian cells. All pathogenic variants leading to *CLCN2*-related leukoencephalopathy identified to date have been shown or suggested to result in either complete or partial loss of function of ClC-2 by different mechanisms [Depienne at al 2013, Gaitán-Peñas et al 2017]. Despite its ubiquitous expression, loss of ClC-2 function leads to specific pathology of the brain, eyes, and testes.

In the brain, ClC-2 is found in both neurons and glia. *Clcn2*-knockout mice show a leukodystrophy phenotype with extensive myelin vacuolization [Blanz et al 2007]. Vacuolization appears to depend on neuronal activity. *Clcn2*-knockout mice are typically blind due to retinal degeneration that results in reduced or absent activity in the optic nerve. Remarkably, this optic nerve is selectively spared from vacuolization [Blanz et al 2007], suggesting that myelin vacuolization in *Clcn2*-knockout mice is mainly a consequence of action potential-mediated disruption of ionic homeostasis. In neurons, ClC-2 may alter levels of excitability and modulate synaptic transmission [Földy et al 2010, Ratté & Prescott 2011]. However, using cell type-specific transgenic techniques in mice, it was recently shown that loss of ClC-2 from supportive glial cells (both astrocytes and oligodendrocytes), with intact neuronal expression, fully recapitulates the leukodystrophy phenotype [Göppner et al 2020].

In astrocytes, ClC-2 shows enhanced expression in processes around blood vessels, in the glia limitans, in the ependymal lining, and in astrocyte-astrocyte contacts [Depienne et al 2013]. Loss of ClC-2 function from glial cells is thought to lead to a disturbance in brain ion and water homeostasis. Myelin vacuolization, as seen in individuals with *CLCN2*-related leukoencephalopathy, is a common pathologic occurrence in diseases in which ion and water homeostasis is disturbed [Min & van der Knaap 2018].

ClC-2 interacts with the glial proteins GlialCAM and MLC1 [Sirisi et al 2017], which are associated with the leukodystrophy known as megalencephalic leukoencephalopathy with subcortical cysts. However, it should be noted that the leukodystrophy caused by pathogenic variants of *CLCN2* fundamentally differs from MLC in its clinical and MRI manifestations. The exact nature of the interaction between these proteins is therefore still unclear.

Retinal and testicular degeneration have been described in *Clcn2*-knockout mice [Bösl et al 2001]. Using cell-type specific loss of *Clcn2* in mouse models, it was shown that retinal pathology is specifically due to loss of ClC-2 in retinal pigment epithelial cells. Testicular degeneration and azoospermia are caused by loss of ClC-2 from Sertoli cells [Göppner et al 2020]. A common denominator for all affected organs therefore appears to be that ClC-2 function is crucial in "supportive" cell types (glia, retinal pigment epithelial cells, sertoli cells). The chloride channel is likely important for balancing ions and water in the extracellular milieu of the brain, retina, and testes [Göppner et al 2020].

Mechanism of disease causation. Loss of function

***CLCN2*-specific laboratory technical considerations.** Two large multiexon deletions identified in this gene are difficult to detect using standard sequencing. An updated list of more than 25 *CLCN2* pathogenic variants specifically linked to *CLCN2*-related leukoencephalopathy is available from the authors. See Author Notes.

Chapter Notes

Author Notes

The Amsterdam Leukodystrophy Center (ALC; Amsterdam UMC, the Netherlands) is headed by Professor Marjo van der Knaap. The purpose of the Center is to optimize diagnostics and care for patients with leukodystrophies, and to perform translational research with the aim to advance insight into disease mechanisms and develop and implement new therapies. Within the center, patient care, clinical studies, and fundamental experimental work on genetics, molecular biology, and neurophysiology are combined. Prof Van der Knaap has pioneered MRI diagnostics, and was the first to describe and genetically define many leukodystrophies. The research team of Dr Rogier Min within the ALC focuses on understanding cellular aspects of ion and water homeostasis in the brain using electrophysiologic and imaging methods.

To obtain a list of known pathogenic variants in *CLCN2* associated with *CLCN2*-related leukoencephalopathy, please contact us (ms.vanderknaap@amsterdamumc.nl).

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- 20 May 2021 (ha) Comprehensive update posted live
- 5 November 2015 (me) Review posted live
- 22 April 2015 (mvdk) Original submission

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