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# *CLCN4*-Related Neurodevelopmental Disorder

Elizabeth Emma Palmer, PhD, MBBS, FRACP,[1,2] Matthew Huu Nguyen, BMedSc (Hons 1), MD,[3,4] Caitlin Forwood, MBBS (Hons), BSc (Hons), FRACGP, DCH,[2] and Vera Kalscheuer, PhD[5]

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## Summary

### Clinical characteristics

*CLCN4*-related neurodevelopmental disorder (*CLCN4*-NDD), an X-linked disorder, is characterized in the 36 males reported to date by developmental delay or intellectual disability, behavioral/mental health issues (e.g., autism spectrum disorder, anxiety, hyperactivity, and bipolar disorder), epilepsy, and gastrointestinal dysfunction. The five heterozygous females with a *de novo CLCN4* variant reported to date had findings very similar to those of affected males. Twenty-two of 25 heterozygous females identified in family studies following identification of an affected male were unaffected or had only mild specific learning difficulties and/or mental health concerns, whereas three were more severely affected.

### Diagnosis/testing

The diagnosis of *CLCN4*-NDD is established in a male proband with suggestive findings and a hemizygous pathogenic variant in *CLCN4* identified by molecular genetic testing. The diagnosis of *CLCN4*-NDD is usually established in a female proband with suggestive findings and a heterozygous pathogenic variant in *CLCN4* identified by molecular genetic testing; however, the phenotype in females with a pathogenic variant can range from asymptomatic to severe.

### Management

*Treatment of manifestations:* Treatment is supportive and often includes multidisciplinary specialists in neurology, pediatrics, mental health, physiatry, occupational and physical therapy, gastroenterology, feeding therapy, ophthalmology, audiology, and medical genetics.

**Author Affiliations:** 1 School of Women's and Children's Health, University of New South Wales, Randwick, New South Wales; Email: elizabeth.palmer@unsw.edu.au. 2 Sydney Children's Hospitals Network, Sydney, New South Wales, Australia; Email: elizabeth.palmer@unsw.edu.au; Email: caitlin.forwood@health.nsw.gov.au. 3 Department of Pathology, School of Medical Sciences, University of New South Wales, Randwick, New South Wales; Email: huu.nguyen1@health.nsw.gov.au. 4 Liverpool Hospital, Liverpool, New South Wales, Australia; Email: huu.nguyen1@health.nsw.gov.au. 5 Group Development and Disease, Max Planck Institute for Molecular Genetics, Berlin, Germany; Email: kalscheu@molgen.mpg.de.

*Surveillance:* Routine monitoring of neurologic findings (response to anti-seizure medications; emergence of new findings), development and educational progress, psychiatric/behavioral issues (response to medications; emergence of new findings), mobility and self-help skills, growth and gastrointestinal manifestations, ophthalmologic findings, hearing, and family support systems.

## Genetic counseling

*CLCN4*-NDD is inherited in an X-linked manner. The father of an affected male will not have the disorder nor will he be hemizygous for the *CLCN4* pathogenic variant. If the mother of a proband has a *CLCN4* pathogenic variant, the chance of transmitting it in each pregnancy is 50%: males who inherit the pathogenic variant will be affected; females who inherit the pathogenic variant will be heterozygotes and may be unaffected or have clinical findings ranging from mild learning difficulties and mental health concerns to severe manifestations. If the proband represents a simplex case and if the *CLCN4* pathogenic variant cannot be detected in the leukocyte DNA of the mother, the risk to sibs is presumed to be low but greater than that of the general population. Once the *CLCN4* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

# Diagnosis

No consensus clinical diagnostic criteria for *CLCN4*-related neurodevelopmental disorder have been published.

## Suggestive Findings

*CLCN4*-related neurodevelopmental disorder (*CLCN4*-NDD) **should be considered** in individuals with the following clinical and brain MRI findings and family history.

**Clinical findings**

- Developmental delay or intellectual disability
- Autism spectrum disorder
- Epilepsy
- Mental health conditions including anxiety and bipolar disorder
- Gastrointestinal dysfunction
- Unremarkable facial features. Although a subtle lengthening of the face and squaring of the chin that becomes more prominent with age has been noted in several individuals (see Figure 3 in Palmer et al [2018]; full text), these features are not likely to be distinctive enough to trigger consideration of this specific diagnosis.

**Brain MRI.** Minor structural brain malformations include periventricular leukomalacia, cortical atrophy/ventriculomegaly, and hypoplasia or dysplasia of the corpus callosum [Veeramah et al 2013, Palmer et al 2018, Zhou et al 2018, He et al 2021].

**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 *CLCN4*-NDD **is established** in a male proband with suggestive findings and a hemizygous pathogenic (or likely pathogenic) variant in *CLCN4* identified by molecular genetic testing (see Table 1).

**Female proband.** The diagnosis of *CLCN4*-NDD is usually established in a female proband with suggestive findings and a heterozygous *de novo* pathogenic (or likely pathogenic) variant in *CLCN4* identified by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) Identification of a hemizygous or heterozygous *CLCN4* variant of uncertain significance does not establish or rule out a diagnosis.

**Molecular genetic testing** in a child with developmental delay or an older individual with intellectual disability may begin with chromosomal microarray analysis (CMA). Other options include use of a multigene panel or exome sequencing. Note: Single-gene testing (sequence analysis of *CLCN4*, followed by gene-targeted deletion/duplication analysis) is rarely useful and typically NOT recommended.

- **Chromosomal microarray analysis (CMA)** uses oligonucleotide or SNP arrays to detect genome-wide large deletions/duplications (including *CLCN4*) that cannot be detected by sequence analysis.
- **An intellectual disability and/or epilepsy and/or autism spectrum disorder multigene panel** that includes *CLCN4* 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, 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.
- **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 *CLCN4*-Related Neurodevelopmental Disorder

| Gene [1] | Method | Proportion of Probands with a Pathogenic Variant [2, 3] Detectable by Method |
|---|---|---|
| *CLCN4* | Sequence analysis [4] | 92% [5] |
| | Gene-targeted deletion/duplication analysis [6] | 4% [7] |
| | CMA [8] | 4% [7] |

*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.* One additional individual with a contiguous gene deletion (not included in these calculations) has been reported (see Genetically Related Disorders).
*4.* 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.
*5.* Veeramah et al [2013], Hu et al [2016], Palmer et al [2018], Zhou et al [2018], Guo et al [2021], He et al [2021], Xu et al [2021]
*6.* Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and gene-targeted array CGH (a gene-targeted microarray designed to detect single-exon deletions or duplications).
*7.* Palmer et al [2018]
*8.* Chromosomal microarray analysis (CMA) uses oligonucleotide or SNP arrays to detect genome-wide large deletions/duplications (including *CLCN4*) that cannot be detected by sequence analysis. The ability to determine the size of the deletion/duplication depends on the type of microarray used and the density of probes in the Xp22.2 region. CMA designs in current clinical use target this region.

# Clinical Characteristics

## Clinical Description

*CLCN4*-related neurodevelopmental disorder (*CLCN4*-NDD), an X-linked disorder, is characterized in the 36 males reported to date by developmental delay or intellectual disability, behavioral/mental health issues (e.g., autism spectrum disorder, anxiety, hyperactivity, and bipolar disorder), epilepsy, and gastrointestinal dysfunction. The five heterozygous females with a *de novo CLCN4* variant reported to date had findings very similar to those of affected males. Twenty-two of 25 heterozygous females identified in family studies following identification of an affected male were unaffected or had only mild specific learning difficulties and/or mental health concerns; three were more severely affected.

The findings of affected individuals reported to date are summarized in Table 2.

**Table 2.** Features in Affected Males and Heterozygous Females with *CLCN4* Variants

| Feature | | Hemizygous Males (n=36) | Heterozygous Females | |
|---|---|---|---|---|
| | | | *De novo* variant (n=5) | Inherited variant (n=25) |
| **Cognitive function** | Borderline ID | 1/36 | 1/5 | 0/25 |
| | Mild ID | 9/36 | 0/5 | 1/25 |
| | Moderate ID | 9/36 | 2/5 | 0/25 |
| | Severe/profound ID | 17/36 | 2/5 | 2/25 |
| | Normal cognitive function | 0 | 0 | 22/25 |

*Table 2. continued from previous page.*

| Feature | | Hemizygous Males (n=36) | Heterozygous Females | |
|---|---|---|---|---|
| | | | *De novo* variant (n=5) | Inherited variant (n=25) |
| **Epilepsy & response to medication** | Epilepsy | 22/36 | 2/5 | 1/25 |
| | Well controlled | 8/22 | 1/2 | 0 |
| | Drug resistant | 12/22 | 1/2 | 1/1 |
| | Data re seizure control NA | 2/22 | | |
| **Other** | Behavioral issues / Mental health disorders | 23/36 | 3/5 | 4/25 |
| | Infantile hypotonia | 11/36 | 3/5 | 1/25 |
| | Progressive neurologic manifestations | 8/36 | 1/5 | 2/25 |
| | Abnormal MRI findings | 14/18 tested | 2/4 tested | 2/2 tested |
| | Significant GI involvement | 3/36 | 2/5 | 0/25 |
| | Scoliosis | 3/36 | 1/5 | 0/25 |

Based on Palmer et al [2018], Zhou et al [2018], Guo et al [2021], He et al [2021], Xu et al [2021]
GI = gastrointestinal; ID = intellectual disability; NA = not available

## Affected Males

Males with *CLCN4*-NDD typically come to medical attention in early childhood due to concerns with developmental delay, intellectual disability, and/or epilepsy. It is possible that prenatal molecular genetic testing to evaluate abnormalities of the corpus callosum would identify a fetus with *CLCN4*-NDD.

**Developmental delay / intellectual disability** ranges from borderline to severe/profound. Of note, the severity of cognitive disability can vary widely even between affected males in the same family.

Although not a common feature, developmental regression has been reported in two families by He et al [2021] and two other families by Palmer et al [2018].

**Behavioral problems** include anxiety, hyperactivity, and features on the autism spectrum. Challenging behaviors may be associated with difficulties in communication related to the degree of intellectual disability [Kevan 2003]. The most prominent features of autism spectrum disorder are social anxiety and repetitive behaviors. Nonetheless, affected males often seek and enjoy social interaction [Palmer et al 2018].

Difficulties in sleep initiation and maintenance have been reported [Palmer et al 2018].

A proportion of older males have mental health conditions including diagnoses of depression (1/27), obsessive compulsive features (1/27), bipolar disorder (2/27), or anxiety (4/27), with improvements noted with appropriate treatment (see Management) [Palmer et al 2018].

**Epilepsy.** The range of seizure semiologies is broad and includes absence, generalized tonic-clonic, infantile spasms, myoclonic, atonic, and complex partial seizures [He et al 2021]. When reported, onset of epilepsy was before age 15 years, and most often within the first year of life or early childhood.

The severity of seizures and response to treatment vary; 12 of 22 males (55%) who had epilepsy had seizures resistant to multiple anti-seizure medications and features consistent with a developmental and epileptic encephalopathy (DEE).

Although epilepsy was reported in 61% of individuals and was reported as drug resistant in 55%, this incidence of epilepsy may reflect ascertainment bias, as several studies were based on cohorts with severe epilepsy [Veeramah et al 2013, Zhou et al 2018, He et al 2021].

He et al [2021] reported one male with a *de novo* missense variant who had a seizure-related death at age two years nine months; Palmer et al [2018] reported one family with three affected males who had seizure-related deaths in their teenage years. Sudden unexpected death in epilepsy (SUDEP) is a recognized complication of DEE in general. A larger cohort of affected individuals will be required to clarify if individuals with *CLCN4*-related DEE are at a higher risk for SUDEP.

**Other neurologic manifestations** included infantile hypotonia (12/36), later-onset spasticity (which can be progressive) (5/36), ataxic gait (5/26), and movement disorder (2/36). However, progression of neurologic features is not the rule, as several older individuals have had no deterioration in either cognition or neuromotor functioning.

**Significant gastrointestinal involvement**, present in 8%, included persistent feeding difficulties, gastroesophageal reflux disease, and constipation [Palmer et al 2018].

**Scoliosis,** hyperextensible joints, and pes planus were reported in four of 36 individuals. None required surgery.

**Growth.** Although most individuals with *CLCN4*-NDD have normal growth parameters, some have had disorders of growth including microcephaly (head circumference <3rd centile) and poor weight gain and/or linear growth below the 3rd centile. Microcephaly was reported in 20%, with two affected males having all growth parameters below the 3$^{rd}$ centile [Palmer et al 2018, He et al 2021].

Other less common findings included the following [Palmer et al 2018]:

- Strabismus
- Cortical visual impairment
- Sensorineural hearing loss
- Inguinal hernia

## Heterozygous Females

The phenotypes of 30 females heterozygous for a *CLCN4* pathogenic variant have been reported [Hu et al 2016, Palmer et al 2018, He et al 2021, Xu et al 2021]. Five of 30 had a *de novo CLCN4* variant and 25 of 30 had a *CLCN4* variant identified when testing female relatives of an affected proband.

**Females with a *de novo CLCN4* variant.** The phenotype in these five females was very similar to that reported in affected males. Intellectual disability ranged from borderline to severe. Epilepsy, which was present in two, was resistant to drug therapy in one [Palmer et al 2018].

**Females with an inherited *CLCN4* variant.** Most females (22/25), identified as being heterozygous for a *CLCN4* variant after identification of a more severely affected proband, had normal cognitive function or only mild specific learning difficulties. However, three of 25 heterozygous females had intellectual disability (1 mild and 2 severe). One of these females also had treatment-resistant epilepsy consistent with a developmental and epileptic encephalopathy [Palmer et al 2018, Xu et al 2021]. Four of the 25 had mental health diagnoses: obsessive compulsive disorder, anxiety, depression, and bipolar affective disorder [Palmer et al 2018].

Thus, although a *de novo* pathogenic variant was associated with a greater likelihood of clinical manifestations, it is nonetheless possible for a female with a variant inherited from an asymptomatic or very mildly affected mother to have a severe neurodevelopmental phenotype [Palmer et al 2018, Xu et al 2021].

To date, X-chromosome inactivation studies have not been helpful in distinguishing between female heterozygotes who are asymptomatic and those who are symptomatic [Palmer et al 2018].

### Genotype-Phenotype Correlations

No genotype-phenotype correlations have been identified to date.

Significant phenotypic variability has been observed both between individuals from different families with a recurrent variant and among individuals from a single family who have the same variant [Palmer et al 2018, He et al 2021].

The phenotypes of males with haploinsufficiency (due to exon deletions or frameshift or nonsense variants) were noted to be relatively milder than the phenotypes of individuals with missense variants [Palmer et al 2018, He et al 2021].

### Nomenclature

*CLCN4*-related neurodevelopmental disorder may also be referred to as Raynaud-Claes syndrome, based on two of the families reported by Hu et al [2016], who had been reported as families MRX15 [Raynaud et al 1996] and MRX49 [Claes et al 1997] before identification of the causative gene.

### Prevalence

*CLCN4*-NDD is rare, and (likely) pathogenic variants have, to date, only been reported in 66 individuals, 22 of whom are asymptomatic or only very mildly affected heterozygous females [Veeramah et al 2013, Hu et al 2016, Palmer et al 2018, Zhou et al 2018, Guo et al 2021, He et al 2021, Xu et al 2021].

*CLCN4*-NDD is not known to be more prevalent in any specific populations, and no founder variants are known.

## Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *CLCN4*.

## Differential Diagnosis

Because the phenotypic features associated with *CLCN4*-related neurodevelopmental disorder are not sufficient to diagnose this condition, all disorders with intellectual disability, autism spectrum disorder, and epilepsy without other distinctive findings should be considered in the differential diagnosis. See OMIM Phenotypic Series:

- Autosomal Dominant Intellectual Developmental Disorder
- Autosomal Recessive Intellectual Developmental Disorder
- Nonsyndromic X-Linked Intellectual Developmental Disorder
- Syndromic X-Linked Intellectual Developmental Disorder
- Developmental and Epileptic Encephalopathy
- Idiopathic Generalized Epilepsy
- Susceptibility to Autism

# Management

No consensus clinical practice guidelines for *CLCN4*-related neurodevelopmental disorder have been published; the following management recommendations are based on review of the literature [Veeramah et al 2013, Hu et al 2016, Palmer et al 2018, Zhou et al 2018, Guo et al 2021, He et al 2021, Xu et al 2021] and the authors' personal observations.

## Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *CLCN4*-related neurodevelopmental disorder (*CLCN4*-NDD), the evaluations summarized in Table 3 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

**Table 3.** Recommended Evaluations Following Initial Diagnosis in Individuals with *CLCN4*-Related Neurodevelopmental Disorder

| System/Concern | Evaluation | Comment |
|---|---|---|
| **Constitutional** | Measure height, weight, head circumference. | |
| **Development** | Developmental assessment | • To incl motor, adaptive, cognitive, & speech/language eval<br>• Eval for early intervention / educational support |
| **Neurologic** | Neurologic eval | • Eval for epilepsy, hypotonia, spasticity, abnormal mvmts / ataxia<br>• Consider EEG if seizures are a concern.<br>• Consider brain MRI as part of investigation for neurologic manifestations (e.g., therapy-resistant epilepsy). |
| **Psychiatric/ Behavioral** | Neuropsychiatric eval | For persons age >12 mos: screen for behavior concerns incl sleep disturbances, ADHD, anxiety, bipolar disorder, &/or traits suggestive of ASD. |
| **Musculoskeletal/ ADL** | Orthopedics / physical medicine & rehab / PT/OT eval | To incl assessment of:<br>• Gross motor & fine motor skills<br>• Mobility, ADL, & need for adaptive devices<br>• Need for PT (to improve gross motor skills) &/or OT (to improve fine motor skills)<br>Evaluate for joint hyperextensibility, *pes planus*, scoliosis, & hypotonia. |
| **Gastrointestinal/ Feeding** | Gastroenterology/ nutrition/feeding eval | • To incl eval of gastroesophageal reflux.<br>• Consider need for nasogastric feeding or percutaneous gastrostomy depending on nutritional status.<br>• Assess for constipation. |
| **Eyes** | Ophthalmologic eval | Assessment of vision & strabismus |
| **Hearing** | Audiologic eval | Assess for hearing loss. |
| **Genetic counseling** | By genetics professionals [1] | To inform affected persons & their families re nature, MOI, & implications of *CLCN4*-NDD in order to facilitate medical & personal decision making |
| **Family support & resources** | | Assess need for:<br>• Community or online resources such as Parent to Parent;<br>• Social work involvement for parental support. |

ADHD = attention-deficit/hyperactivity disorder; ADL = activities of daily living; ASD = autism spectrum disorder; MOI= mode of inheritance; OT = occupational therapy; PT = physical therapy

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

## Treatment of Manifestations

Treatment is supportive and often includes multidisciplinary specialists in neurology, pediatrics, mental health, physiatry, occupational and physical therapy, gastroenterology, feeding therapy, ophthalmology, audiology, and medical genetics.

**Table 4.** Treatment of Manifestations in Individuals with *CLCN4*-Related Neurodevelopmental Disorder

| Manifestation/ Concern | Treatment | Considerations/Other |
|---|---|---|
| **DD/ID** | See Developmental Delay / Intellectual Disability Management Issues. | |
| **Epilepsy** | Standardized treatment w/ASM by experienced neurologist | • While 5/25 persons w/epilepsy had some response to lamotrigine, more dedicated natural history studies are needed to clarify which ASMs are more (or less) effective. [1]<br>• Education of parents/caregivers [2] |
| **Psychiatric/ Behavioral** | • Review by pediatrician or adult disability specialist<br>• Regular conversations between affected person, family, & health care professionals | • Refer to developmental pediatrician or psychiatrist if concerns re ASD.<br>• Refer to psychiatrist w/expertise in mgmt of persons w/learning disabilities if concerns re mental health complications.<br>• Consultation w/sleep physician if warranted<br>• Consider appropriate pharmacotherapy in consultation w/pediatrician or psychiatrist as indicated. |
| **Musculoskeletal** | Orthopedics / physical medicine & rehab / PT/OT | Monitor for joint hyperextensibility, *pes planus*, scoliosis, & hypotonia. |
| **GI or growth concerns** | • Consider treatment for symptoms of gastroesophageal reflux &/or constipation.<br>• Feeding therapy; nasogastric or gastrostomy tube placement may be required for persistent feeding issues. | Low threshold for clinical feeding eval, as oral feeding may be difficult to establish |
| **Movement disorder / Ataxia** | • Mgmt by pediatrician, developmental pediatrician, or physiatrist as appropriate<br>• Consultation w/neurologist if required | A newly emerging manifestation that may occur in up to 10% |
| **Abnormal vision &/or strabismus** | Standard treatment(s) as recommended by ophthalmologist | Community vision services through early intervention or school district for those w/delayed visual maturation [3] |
| **Hearing** | Hearing aids may be helpful; per audiologist/ otolaryngologist evals. | Community hearing services through early intervention or hearing program |
| **Family/ Community** | • Ensure appropriate social work involvement to connect families w/local resources, respite, & support.<br>• Coordinate care to manage multiple subspecialty appointments, equipment, medications, & supplies. | Consider involvement in adaptive sports or Special Olympics. |

ASD = autism spectrum disorder; ASM = anti-seizure medication; DD/ID = developmental delay / intellectual disability; GI = gastrointestinal; OT = occupational therapy; PT = physical therapy

*1.* He et al [2021]

*2.* Education of parents/caregivers regarding common seizure presentations is appropriate. For information on non-medical interventions and coping strategies for children diagnosed with epilepsy, see Epilepsy Foundation Toolbox.

*3.* Author, unpublished observations

## 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.
  - Special education law requires that children participating in an IEP be in the least restrictive environment feasible at school and included in general education as much as possible, when and where 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.

**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, but rather support optimal speech and language development.

### 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 5.** Recommended Surveillance for Individuals with *CLCN4*-Related Neurodevelopmental Disorder

| System/Concern | Evaluation | Frequency |
|---|---|---|
| **Neurologic** | Monitor those w/seizures as clinically indicated. | At each visit |
| | Assess for new manifestations incl seizures, changes in tone, mvmt disorders. | |
| **Development** | Monitor developmental progress & educational needs. | |
| **Psychiatric/ Behavioral** | Behavioral assessment for autistic features, anxiety, ADD, & aggressive or self-injurious behavior &/or mood disorders | |
| **Musculoskeletal** | • Physical medicine, OT/PT assessment of mobility, self-help skills<br>• Monitor for joint hyperextensibility, *pes planus*, scoliosis, & hypotonia. | |
| **Gastrointestinal** | Assess for symptoms of gastroesophageal reflux & constipation. | |
| **Endocrine/ Growth** | Monitor growth incl stature, head circumference, & weight. | |
| **Eyes** | Per treating ophthalmologist | Per treating ophthalmologist or concerns raised by patient/caregiver |
| **Sensorineural hearing loss** | Per treating audiologist | Per treating audiologist or concerns raised by patient/caregiver. |
| **Family/ Community** | Assess family need for social work support (e.g., respite care, home nursing, other local resources) & care coordination. | At each visit |

ADD = attention deficit disorder; OT = occupational therapy; PT = physical therapy

## 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

*CLCN4*-related neurodevelopmental disorder (*CLCN4*-NDD) 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 *CLCN4* 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 *CLCN4* 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 a *de novoCLCN4* pathogenic variant (in which case the mother is not a heterozygote), or the mother may have somatic/germline mosaicism.

  About 16% of affected males have the disorder as the result of a *de novo* pathogenic variant [Veeramah et al 2013, Palmer et al 2018, Zhou et al 2018, He et al 2021].
- Molecular genetic testing of the mother is recommended to confirm her genetic status and to allow reliable recurrence risk assessment.

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

- If the mother of the proband has a *CLCN4* pathogenic variant, the chance of the mother transmitting it in each pregnancy is 50%.
  - Males who inherit the pathogenic variant will be affected.
  - Females who inherit the pathogenic variant will be heterozygotes and may be unaffected or have clinical findings ranging from mild learning difficulties and mental health concerns to severe manifestations (see Clinical Description, Heterozygous Females). X-chromosome inactivation status has not been found to be helpful in assessing degree of severity of features in female heterozygotes [Palmer et al 2018].
- If the proband represents a simplex case and if the *CLCN4* pathogenic variant cannot be detected in the leukocyte DNA of the mother, the risk to sibs is presumed to be low but greater than that of the general population because of the possibility of maternal germline mosaicism. To date, sib recurrence due to parental germline mosaicism has not been reported; however, somatic mosaicism has been reported in one female proband and one severely affected male [Palmer et al 2018].

**Parents of a female proband**

- A female proband may have inherited the *CLCN4* pathogenic variant from either her mother or her father, or the pathogenic variant may be *de novo*. Five of the eight females reported to date with manifestations of

*CLCN4*-NDD have the disorder as the result of a *de novo* pathogenic variant (see Clinical Description) [Palmer et al 2018].

- Detailed evaluation of the parents and review of the extended family history may help distinguish probands with a *de novo* pathogenic variant from those with an inherited pathogenic variant. Molecular genetic testing of the mother (and possibly the father, or subsequently the father) can help to determine if the pathogenic variant was inherited.

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

- If the mother of the proband has a *CLCN4* pathogenic variant, the chance of the mother transmitting it in each pregnancy is 50%.
  - Males who inherit the pathogenic variant will be affected.
  - Females who inherit the pathogenic variant will be heterozygotes and may be unaffected or have clinical findings ranging from mild learning difficulties and mental health concerns to severe manifestations (see Clinical Description, Heterozygous Females).
  - The manifestations of *CLCN4*-NDD in a female sib with a maternally-inherited pathogenic variant cannot be predicted on the basis of the phenotype in the heterozygous mother. It is possible for a female who inherits a *CLCN4* pathogenic variant from an asymptomatic or very mildly affected mother to have a severe neurodevelopmental phenotype [Palmer et al 2018, Xu et al 2021].
  - X-chromosome inactivation status has not been found to be helpful in assessing degree of severity of features in female heterozygotes [Palmer et al 2018].
- If the father of the proband has a *CLCN4* pathogenic variant, he will transmit it to all his daughters and none of his sons.
- If the proband represents a simplex case and if the *CLCN4* pathogenic variant cannot be detected in the leukocyte DNA of either parent, the risk to sibs is greater than that of the general population because of the possibility of parental germline mosaicism.

**Offspring of a male proband.** Affected males transmit the *CLCN4* pathogenic variant to all their daughters and none of their sons.

**Offspring of a female proband.** Women with a *CLCN4* pathogenic variant have a 50% chance of transmitting the pathogenic variant to each child.

**Other family members.** The risk to other family members depends on the status of the proband's parents: if a parent has the *CLCN4* pathogenic variant, the parent's family members may be at risk.

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 members of the extended family.

## Heterozygote Detection

Identification of female heterozygotes requires prior identification of the familial *CLCN4* pathogenic variant.

Note: Females who inherit the pathogenic variant will be heterozygotes and may be unaffected or have clinical findings ranging from mild learning difficulties and mental health concerns to severe manifestations (see Clinical Description, Heterozygous Females). X-chromosome inactivation status has not been found to be helpful in assessing degree of severity of features in female heterozygotes [Palmer et al 2018].

## Related Genetic Counseling Issues

**Family planning**

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

### Prenatal Testing and Preimplantation Genetic Testing

Once the *CLCN4* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing 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.*

- **Cure CLCN4**

  www.cureclcn4.org

- **Simons Searchlight**

  CLCN4

- **Human Disease Gene Website Series - Registry**

  *This website was created to share and collect information about clinic, management and research projects to gather more knowledge and provide better treatment of patients with mutations in the CLCN4 gene.*

  CLCN4

## 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.** CLCN4-Related Neurodevelopmental Disorder: Genes and Databases

| Gene | Chromosome Locus | Protein | Locus-Specific Databases | HGMD | ClinVar |
|---|---|---|---|---|---|
| *CLCN4* | Xp22.2 | H(+)/Cl(-) exchange transporter 4 | CLCN4 @ LOVD | CLCN4 | CLCN4 |

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 CLCN4-Related Neurodevelopmental Disorder (View All in OMIM)

| | |
|---|---|
| 300114 | RAYNAUD-CLAES SYNDROME; MRXSRC |
| 302910 | CHLORIDE CHANNEL 4; CLCN4 |

## Molecular Pathogenesis

CLCN4/ClC-4 is broadly expressed in many tissues, with highest expression in brain and skeletal muscle. ClC-4 is a strongly outwardly rectifying, electrogenic 2Cl-/H+ exchanger, predominantly expressed in membranes of the endolysosomal system. Its biological function remains largely unknown but may be related to ion homeostasis [Jentsch & Pusch 2018].

ClC-4 forms heterodimers with its close homolog ClC-3, encoded by *CLCN3* [Weinert et al 2020]. Of note, homozygous and heterozygous pathogenic variants in *CLCN3* are associated with developmental delay / intellectual disability, mood or behavioral disorders, dysmorphic features, structural brain abnormalities, and seizures [Duncan et al 2021].

It is currently unknown how genetic alterations in *CLCN4* cause *CLCN4*-NDD. This is an area of active research.

**Mechanism of disease causation.** All *CLCN4* missense variants published to date that were tested functionally in *Xenopus* oocytes by electrophysiologic studies showed impaired protein function (i.e., loss of function).

# Chapter Notes

## Author Notes

Dr Vera Kalscheuer (PhD) is a scientist at the Max Planck Institute for Molecular Genetics in Berlin, Germany. She obtained her degree and PhD in biochemistry from the Free University in Berlin, Germany and conducted postdoctoral research at the Radboud University Nijmegen Medical Centre, the Netherlands. Her work focuses on the identification of novel genes linked to neurodevelopmental disabilities, and on the molecular and functional characterization of selected genes and proteins in order to better understand the underlying molecular and pathogenic mechanisms. With her research, she has discovered and contributed to the identification of numerous genes associated with various forms of neurodevelopmental disabilities, including *CLCN4*, thereby establishing a molecular diagnosis for patients and their families. In order to better understand *CLCN4*-related neurodevelopmental disorder, she and Dr Emma Palmer together with other collaborators conducted a large study on the genetic, clinical, and functional effect of newly identified *CLCN4* variants. She and Dr Palmer are currently studying an even larger group of patients with *CLCN4* defects.
Email: kalscheu@molgen.mpg.de
Website: www.molgen.mpg.de/Vera-Kalscheuer

Dr Emma Palmer (PhD, MBBS, FRACP, BA (Hons I) Oxon) is a clinician scientist at Sydney Children's Hospital Network & University of New South Wales in Sydney, Australia. She has extensive experience at the interface of clinical and research genetics leading multidisciplinary teams and establishing international collaborations to discover new genetic conditions. She has led five international projects delineating the following novel genetic conditions:

- *ARV1*-developmental and epileptic encephalopathy, inherited in an autosomal recessive manner
- *ATN1*-congenital hypotonia, epilepsy, developmental delay, digital anomalies (CHEDDA); caused by *de novo* heterozygous variants
- *KCNT2*-developmental epileptic encephalopathy; caused by *de novo* heterozygous variants
- *RLIM* duplication; Tonne-Kalscheuer syndrome; inherited in an X-linked manner
- *ZSWIM6*-neurodevelopmental disorder with movement abnormalities, abnormal gait, and autistic features (NEDMAGA) acromelic frontonasal dysplasia

She works closely with rare genetic disease advocacy and consumer reference groups and aims to translate genomic discoveries to improved education and management for patients and families. She was the first author on a publication describing the effect of *CLCN4* changes in 52 individuals, moderates the *CLCN4* gene pages on

the Human Disease Gene Webseries along with Dr Vera Kalscheuer, and is leading the clinical aspects of an international study to better understand the genetic and clinical spectrum of *CLCN4*-related neurodevelopmental disorder.
Email: elizabeth.palmer@unsw.edu.au
Website: research.unsw.edu.au/people/dr-elizabeth-emma-palmer

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