FACTS ABOUT HEALTH CONDITIONS
CAUSED BY CHANGES IN THE *CLCN4* GENE

This fact sheet contains information about the possible impact of a change (variant) in the *CLCN4* gene on your child and family. You can talk about the information in this fact sheet with your paediatrician or GP (family doctor). The links in the fact sheet may help you move forward with family life beyond receiving this rare diagnosis.

This fact sheet relates to health conditions that are due to small variants in the genetic code of the *CLCN4* gene. These changes were identified by a genomic (DNA) test. It does not provide information about conditions caused by chromosome deletions or duplications that involve the *CLCN4* gene.

Key points

- Individuals with changes (variants) in the *CLCN4* gene may have learning and behavioural challenges, problems with their sight or hearing, and seizures (epilepsy)
- Variants in the *CLCN4* gene that cause health problems may be inherited from a parent or may be a new (*'de novo'*) change in a child. This means that future children may also have this variant. Genetic counselling before any further pregnancies is recommended.
- Supportive management is available
- You and your family are not alone in adjusting to life with the diagnosis of a change in the *CLCN4* gene. Support is available from a number of different organisations and services

Other names this condition may be referred to as

- Raynaud-Claes syndrome

When a rare condition has been diagnosed

For some families, receiving a genetic diagnosis is a relief. Others may feel overwhelmed and sad. It is very common to have a mixture of thoughts and feelings about the news, and your hopes and expectations for the future may shift and change over time.

While experiences may be shared, individuals and families can respond in different ways and have different information and support needs. Many parents describe an ongoing process of adjusting to a different focus and finding ways to celebrate their child's gains made in their own way and time. It is very important to remember that the diagnosis is only one of many things that make your child unique.

About the *CLCN4* gene

Genes contain instructions that tell our body how to grow, develop and function. *CLCN4* is a **gene** that helps regulate and control the way our brain develops and functions. Changes (**variants**) in the *CLCN4* gene mostly affect the brain and nerves.

Our genetic code, or DNA, is found in every cell in our body and is carried on chromosomes. We each have 46 chromosomes, organised into 23 pairs. One chromosome of each pair is inherited from each of our parents. The 23rd pair is known as our sex chromosomes: X and Y. Females have two X chromosomes and males have an X and a Y chromosome.

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The *CLCN4* gene is found on the X chromosome. Because males and females have a different number of X chromosomes, changes in the *CLCN4* gene can affect males and females differently.

Usually *CLCN4*-related conditions are caused by a single spelling variation in the gene. This means the message is not read or received properly. In some individuals with *CLCN4*-related conditions, the change occurred when the baby was conceived (a new or *'de novo'* variant) and is not seen in the parents. In other children, the variant was passed to the child by a parent. In most (but not all) females who are significantly affected by a *CLCN4*-related condition, the change in the gene is *de novo*.

CLCN4-related conditions are **genetic conditions**. This means that the condition was not caused by anything the mother or father did before the baby was conceived, during pregnancy or birth, or after the baby was born. *CLCN4*-related conditions are very rare, with less than 100 families identified around the world.

What could a change in the *CLCN4* gene mean for my child?

Changes in the *CLCN4* gene can affect children in different ways. Some are more severely affected than others. Even people with the exact same *CLCN4* change may have different health issues.

Common features include developmental delay/intellectual disability and behavioural challenges, problems with sight (vision) and problems with movement (motor function). Children may be slower than usual to learn to sit, stand or walk.

Around 50% (half) of children have epilepsy. Seizures generally start in early childhood, but they can also happen for the first time in teenagers. Many different **types of seizures** have been reported, including seizures that start in one part of the brain (focal seizures) and those that affect the whole of the brain (generalised seizures). Examples of generalised seizures include those where the body stiffens and jerks (generalised tonic-clonic seizure, also known as grand mal), brief loss of awareness (absence seizure, also known as petit mal), brief jerking of the arms, legs and/or body (myoclonic seizure), stiffening of the body, arms or legs (tonic seizure) or sudden loss of muscle tone and appearing to be 'floppy' (atonic seizure).

When a change in *CLCN4* occurs, it is not possible right now to repair or reverse the change. It is also not possible to exactly predict the level of care your child will require through to adulthood. Your child's individual needs and strengths will become more obvious over time, which will help with planning for the future.

Your child's development may be helped through early use of therapy services such as physiotherapy and treating symptoms if/when they arise. It is likely that many different health professionals will be involved in caring for your child. Your paediatrician or GP will arrange referrals to other health professionals as needed and help with applications for service funding through the **National Disability Insurance Scheme (NDIS)**.

Good communication with the health professionals caring for your child is important to establish common goals, trust and shared responsibility. We encourage you to ask questions and express your concerns as the primary carer for your child.

Management recommendations

As many health or developmental problems are not immediately obvious, your child will need to be checked by their paediatrician at diagnosis and then seen at least every year or more often if needed. The list on the next page includes many of the common problems, but others may arise. If you have any concerns about your child's health, please speak with your family doctor (GP) or paediatrician.

Possible health problems (% of children affected)	Management
Developmental delay/intellectual disability (>90% of males, variable in females), including low muscle tone (hypotonia) and speech delay	• Early intervention, including speech therapy to help with language development, occupational therapy and physiotherapy
Challenging behaviours (50%)	• Diagnosis and management by paediatrician as appropriate
Autism spectrum disorder (20–40%)	• Diagnosis and management by paediatrician as appropriate
Gastrointestinal reflux (40–60%)	• Review and management by paediatrician
Constipation (40–60%)	• Close monitoring and discussion with paediatrician; low threshold for considering laxatives
Slow growth (rare except in association with specific genetic variants e.g. the p. [Ala555Val] variant – unknown cause)	• At least yearly review by GP/paediatrician • Referral to endocrinologist if appropriate for consideration of growth hormone
Minor structural brain malformations/ white matter changes (e.g. partial or complete absence of the corpus callosum and hypomyelination affecting the brain and nerves) (50–60%)	• Brain MRI if clinically indicated • Most problems with the brain structure do not progress over time and do not need any specific investigation
Seizures (epilepsy) (50%) **Severity and type varies and includes absence, generalisd tonic-clonic, myoclonic, infantile spasms, tonic and atonic**	• Standard investigations and treatments, including EEG and anti-epileptic medications. Consultation with a paediatric neurologist if seizures are difficult to control
Uncoordinated movements (ataxia) (10%)	• Management by paediatrician as appropriate. Consultation with a paediatric neurologist if required
Problems with falling asleep and staying asleep (~50%)	• Review by paediatrician. Consultation with sleep physician if warranted
Anxiety and/or depression (including bipolar disorder) (20%)	• Regular conversations between the affected individual, families and healthcare professionals. • A number of **resources** are available on mental health in individuals with intellectual disability
Visual (eyesight) problems (20%)	• Initial review by ophthalmologist for assessment of vision and squint (strabismus) • A squint (strabismus) may require patching or glasses • Long- or near-sightedness (refractive error) may require glasses

Resources, support and connecting with others

You may find it helpful to connect with other people who have personal experience of day-to-day life with a child who has a *CLCN4*-related condition. You can make these connections through:

- Social media (e.g. closed Facebook groups such as **CLCN4 Families**)
- Umbrella groups (e.g. **Genetic Alliance Australia** and **Rare Voices Australia**)
- Condition-specific groups (e.g. **CureCLCN4** Foundation)
- Groups for individuals with common symptoms that may have many different causes (e.g. intellectual disability, hearing loss, autism).

Many organisations (e.g. **Carers NSW** and **Reframing Disability**) can also offer general advice and support in caring for a family member with long-term needs.

It is important to know that you are not alone on this journey

More information about *CLCN4*-related conditions

You can find further information about *CLCN4*-related conditions by following the links below.

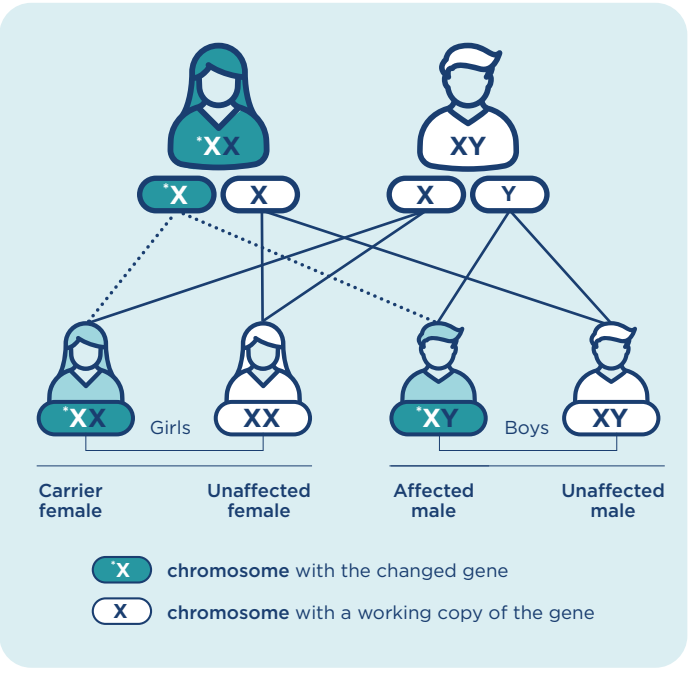
- Human Disease Genes: **CLCN4**
- CureCLCN4 Foundation **Website**

For more information about genetic conditions and to find your local Clinical Genetics services, visit the **NSW Centre for Genetics Education**.

Family planning

Genetic conditions can be passed from a parent to their child or they can be *de novo* genetic conditions, as explained earlier. Since the *CLCN4* gene is on the X chromosome, *CLCN4*-related conditions are known as **X-linked** conditions, and can be inherited in an X-linked manner. Females who are genetic carriers of the condition will have one X chromosome with a *CLCN4* variant, and the other X chromosome has a 'backup' working copy of the gene. Female carriers may not show any signs or symptoms of the condition. Males have one X chromosome (with the variant), and no second working copy of the *CLCN4* gene to act as a backup. So the effect of the variant is usually more obvious in boys than girls.

Female members of the same family (e.g. aunties, nieces or female cousins on the mother's side) may show few or no symptoms even though they may carry a *CLCN4* variant in their DNA. The diagram below shows what can happen when a female who is carrying a *CLCN4* variant has children. The genetic 'carrier' may pass the variant on to her children, who could then have a *CLCN4*-related condition.



If you are thinking about having more children, it is recommended that you talk with your local **Clinical Genetics service**. Some people may choose to have **genetic testing** before or during a pregnancy. Specialised health professionals such as **genetic counsellors** can advise you on your options. Even if the same variant was not found in the mother, it is still possible to have another child with the same condition. The chance of this happening is ~4%.

Genetic carrier testing can tell us who is a carrier of a *CLCN4* variant. Women who are found to be carriers are encouraged to see their local genetics service to:

- Discuss concerns about the possibility of having a child with a *CLCN4*-related condition
- Discuss options available for genetic testing around a future pregnancy
- Find out what this may mean for other family members, who may then consider genetic counselling and/or genetic testing.

You can also speak with your GP about options for **reproductive genetic carrier screening**, a genetic test that looks for changes in many different genes.

Research, registries and clinical trials

Some people with rare conditions are able to participate in **research**, which may be of benefit to your child. This may investigate how a particular variant causes health problems or it may be a clinical trial testing new treatments. Sharing information about your child's signs and symptoms through registries such as the **CureCLCN4 Foundation patient registry**, **FaceMatch** and **IAMRARE** can help build further knowledge about this condition.

Information about current clinical trials can be found by searching the international databases **ClinicalTrials.gov** or **EudraCT** and through the **CureCLCN4 foundation** website.

To print more copies of this fact sheet and access links to the underlined topics, go to **www.genetics.edu.au** and search for 'CLCN4'.

This fact sheet should not replace a consultation with a specialist healthcare professional.