FACTS ABOUT HEALTH CONDITIONS

CAUSED BY CHANGES IN THE *NALCN* GENE

This fact sheet contains information about the possible impact of a change (variant) in the *NALCN* 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 *NALCN* 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 *NALCN* gene.

Key points

- A change in the *NALCN* gene will usually cause developmental delay/intellectual disability, together with altered muscle tone and movements, difficulties with feeding, constipation, or seizures
- Irregular breathing is common and it is very important that this is assessed when the child is a baby
- Certain changes in the *NALCN* gene can cause tightening of the arms and/or legs and face
- Changes (variants) in the *NALCN* gene that cause health problems may be inherited from both parents, 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
- Treatment may be available for some medical problems such as breathing difficulties, epilepsy, altered movements, sleep disturbance, and constipation
- You and your family are not alone in adjusting to life with the diagnosis of a change in the *NALCN* gene. Support is available from a number of different organisations and services.

Other names this condition may be referred to as:

- Congenital contractures of the limbs and face, hypotonia and developmental delay (CLIFAHDD)
- Overlaps with Freeman Sheldon syndrome
- Hypotonia, infantile, with psychomotor retardation and characteristic facies 1 (IHPRF1 or IHPRF)

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.

Content updated November 2021
NOV21/V1 NS12693
SHPN: (HETI) 240986

About the *NALCN* gene

Genes contain instructions that tell our body how to grow, develop and function. *NALCN* is a **gene** that provides instructions for a special sodium channel, also known as *NALCN*, which stands for Na+ (sodium)-leak channel, non selective. This channel affects the 'excitability' of nerve cells, and is important for the communication of signals between nerve cells within the brain and other organ systems. In particular, it regulates rhythmic behaviours within the body, such as breathing, movement of the gut (intestines) and the sleep-wake (circadian) cycle.

Changes (**variants**) in the *NALCN* gene can affect health and development. Most of these health problems are due to differences in brain development and function.

The *NALCN* gene is found on chromosome 13. Usually *NALCN*-related conditions are caused by a spelling variation in the gene, which means the message is not read or received properly. This spelling error can be on one or both copies of the *NALCN* gene. In some individuals with *NALCN*-related conditions, the change in one copy of the gene occurred when the baby was conceived (a new or *'de novo'* variant), and is not seen in the parents. Other individuals may have inherited two variants, one from each of their parents.

NALCN-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. *NALCN*-related conditions are very rare, affecting less than one in one million (<1:1,000,000) individuals.

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

A change in the *NALCN* gene can affect children in different ways. Some are more severely affected than others. There may be a range of signs and symptoms even in children with the same genetic variant.

There are two main groups of health problems in children with *NALCN* genetic changes, depending on the type of change and whether the child has a change in one or both copies of the *NALCN* gene. However, there are many health problems that both groups of individuals have in common.

IHPRF1 (changes in both copies of the *NALCN* gene)

IHPRF1 stands for Infantile Hypotonia, Psychomotor Retardation, and characteristic Facies 1 (IHPRF1 or IHPRF). Children with IHPRF have changes in both copies of the *NALCN* gene. These children usually have very low muscle tone. They may have problems with feeding and gaining weight. Muscle bulk may be reduced. Constipation can be a significant problem.

Some children may display altered movements (called dyskinesia/ataxia), and/or seizures (epilepsy). They can be slow to reach their developmental milestones, including walking and speaking. Some children may not develop these abilities. Intellectual disability can range from mild to very severe.

Children may have problems with their skeleton such as a curved spine (scoliosis), or an abnormal chest shape (pectus carinatum). Some children have hernias in the groin (inguinal hernias), and undescended testes (cryptorchidism), requiring surgery. Eye problems, including non-aligned eyes (strabismus), and minimal eye contact, are common. Many children with IHPRF have similar facial features.

Children may have abnormal breathing patterns from birth, and can require close monitoring and breathing support, in consultation with doctors who specialise in respiratory conditions. This may affect the child's normal cycles of sleeping and waking.

Children with *NALCN* variants may have life-threatening events related to their breathing, and these can occur quite suddenly. Parents/carers should be trained to perform cardiopulmonary resuscitation (CPR). Breathing needs to be monitored closely in these children, in consultation with doctors who specialise in respiratory conditions. Special monitoring and care is required with general anaesthetics.

CLIFAHDD (a change in one copy of the *NALCN* gene)

Children who have a single copy of a new (*'de novo'*) *NALCN* variant are said to have a condition called Congenital contractures of the Limbs and Face, Hypotonia and Developmental Delay (CLIFAHDD). These children will often have many of the same health problems seen in individuals with IHPRF. Occasionally, children may have abnormally increased muscle tone rather than low tone. They often have very short and stiff joints in their hands, feet and jaw from the time they are born (congenital contractures/arthrogryposis), and distinctive facial features that can differ from children with IHPRF.

Caring for a child with an *NALCN*-related condition

At this point in time, it is not possible to reverse or repair this gene change. It is also not possible to accurately 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 every 6–12 months, 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
Abnormal breathing (breathing dysregulation), with repeated stopping and starting of breathing (central and/or obstructive apnoeas) while awake and asleep (~40%); disrupted sleep (~40%)	• Early review by respiratory and sleep paediatricians is strongly recommended. Investigations may include a sleep study and consideration of supplemental oxygen • **It is recommended that carers are trained to perform cardiopulmonary resuscitation (CPR).** Life-threatening respiratory events have been reported
Developmental delay/intellectual disability (>90%)	• Early intervention, including speech therapy, occupational therapy and physiotherapy • At least yearly checks by GP/paediatrician
Difficulty/delayed walking (>90%)	• Physiotherapy/occupational therapy to help with using medical devices such as wheelchairs, if needed
Low or high muscle tone (hypotonia or hypertonia) (~60% to >90%)	• Physiotherapy and/or occupational therapy may be helpful
Feeding difficulties (~90%)	• Children with severe feeding problems may need to be referred to a paediatric gastroenterologist and may need a feeding (nasogastric or gastrostomy) tube • Dietician support to ensure the child is receiving enough food (caloric supplementation), if required
Constipation (~40–80%)	• Will most likely require treatment with laxatives
Gastrointestinal reflux (uncertain frequency)	• Gastroesophageal reflux may respond to upright posture, thickened feeds, early introduction of solids and/or medications
Brain structural malformations/ developmental differences of brain (~30–45%)	• Brain MRI if clinically indicated • Most structural problems do not require any specific treatment
Small head size (microcephaly) (~70%)	• Regular review of height, weight and head size (circumference). • No treatment is needed
Seizures (epilepsy) (~15–40%)	• Standard investigations and treatments, including EEG and anti-epileptic medications • Consultation with paediatric neurologist if seizures are difficult to control
Curved spine (scoliosis) (~15–35%)	• Can be early onset and severe • Refer to orthopaedics and physiotherapy to discuss treatments such as bracing
Abnormal genital or kidney structure (genitourinary malformations) (uncertain frequency)	• Undescended testes (cryptorchidism) and inguinal hernias are usually treated with surgery
Visual (eyesight) problems/vision loss (~60–80%)	• Yearly eye review by ophthalmologist • A squint (strabismus) may require patching or glasses
Sensitivity to general volatile anaesthetic agents and ethanol (uncertain frequency)	• Anaesthetic review should be sought prior to any procedure requiring use of volatile general anaesthetic agents (e.g. Sevoflurane)
Mostly seen in children with CLIFAHDD	
Muscle weakness and tightness, and joint tightness (contractures) (~80%)	• Orthopaedics/physiotherapy and rehabilitation/physiotherapy/occupational therapy, including stretching to help avoid fixed tightness of the muscles (contractures) and falls
Talipes (clubfoot) (~80%)	• Physiotherapy/use of splints • May require a review by an orthopaedic specialist if severe
Excessive salivation (~35%)	• Medication such as anticholinergics • Injection of botulinum toxin (botox) into the salivary glands or other types of surgery can be considered

Further information for health professionals on the clinical presentation of patients with *NALCN* variants can be found at **MedGen**.

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 *NALCN*-related condition. You can make these connections through:

- The **Libellas Foundation**, an advocacy organisation for individuals affected by *NALCN* ion channel-related conditions
- Social media (e.g. closed Facebook groups: **IHPRF1 NALCN gene condition**, **Libellas Foundation**, **NALCN CLIFAHDD syndrome**)
- Umbrella groups (e.g. **Genetic Alliance Australia** and **Rare Voices Australia**)
- Condition-specific groups
- 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

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 are sometimes passed from a parent to their child. Even if the same variant was not found in one of the parents, it is still possible to have another child with the same condition. The chance of this happening depends on the type of *NALCN* change in your child, and can be up to 1 in 4 (25%) in children with IHPRF1, or 1–2% in children with CLIFAHDD.

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.

You can also speak with your GP about options for **reproductive genetic carrier screening**. When planning a family, it is best to explore your options before becoming pregnant.

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 **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**.

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

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