How common is *SETD2* –neurodevelopmental disorder (*SETD2*-NDD)

SETD2-neurodevelopmental disorder (*SETD2*-NDD) is extremely rare. Currently (2023) about 35 individuals with a *SETD2* gene variant have been reported in the medical literature. It is expected that more people will be diagnosed with this condition as awareness increases and genetic testing becomes more routine.

Why did this happen?

When children are conceived, their parents' genetic material is copied in the egg and sperm that make a new child. The biological copying method is not perfect, and random rare changes occur in the genetic code of children that are not present in the DNA of their parents. These types of change happen naturally and are not due to lifestyle factors or anything a parent did prior to, during or after pregnancy. No one is to blame and nobody is at fault. Such changes happen to everyone but it's only when a change affects an important gene that health and/or development are affected.
In most cases, the change in the *SETD2* gene occurred by chance for the first time in the child with the variant (this is known as *de novo*) and the genetic change was not found in either parent. In a few cases children have inherited their genetic change from a (mildly) affected parent.

Can it happen again?

The chance of having another child affected by a rare gene disorder depends on the genetic code of the parents. If a parent is found to carry the genetic variant, the chance of having another child with *SETD2*-NDD is 50% (1 in 2) for each pregnancy. If the change in the *SETD2* gene has been shown to be *de novo*, meaning neither parent was found to carry it, the chance of having another child with *SETD2*-NDD is very low. There is still a very small chance that another child could be affected if a parent has mosaicism (*Unique* publishes a separate guide to mosaicism). If a child with an altered or deleted *SETD2* gene has a child of their own, there is a 50% chance of them passing on their genetic change. A clinical geneticist or genetic counsellor can give you specific advice for your family.

Can it be cured?

At present, there is no cure for *SETD2*-NDD since the effects of the genetic change took place during a baby's formation and development. However, knowing the diagnosis means appropriate monitoring and treatment can be put in place.

Management recommendations

Children with *SETD2*-NDD should be under the care of a multidisciplinary team. This team should include a geneticist and paediatrician, who can oversee care so that development and behaviour can be monitored, and the best help given in the form of physiotherapy, occupational therapy, speech therapy and, if needed, behavioural therapy. Individuals may have initial evaluations with neurology, endocrinology, cardiology, ophthalmology and audiology. Evaluations with gastroenterology, urology or nephrology may also be recommended.

Inform Network Support

Rare Chromosome Disorder Support Group

The Stables, Station Road West,
Oxted, Surrey, RH8, 9EE, UK,
Tel: +44(0)1883 723356
info@rarechromo.org | www.rarechromo.org

Websites, Facebook groups and other links:

www.facebook.com/Luscanlumishsyndrome - private support group for Luscan-Lumish Syndrome and *SETD2*-related conditions

Simons Searchlight Community – www.facebook.com/groups/384794018852000/

This guide was written by Rachel Rabin (MS, CGC), Clinical Genetic Services, Department of Pediatrics, NYU Grossman School of Medicine, New York, USA, and Unique (CA). The guide was reviewed by Dr John Pappas, Pediatrics-Human Genetics Division, NYU Grossman School of Medicine, New York, USA.

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Understanding Chromosome & Gene Disorders

SETD2-neurodevelopmental disorders (*SETD2*-NDD)

rarechromo.org

What is *SETD2*-neurodevelopmental disorder?

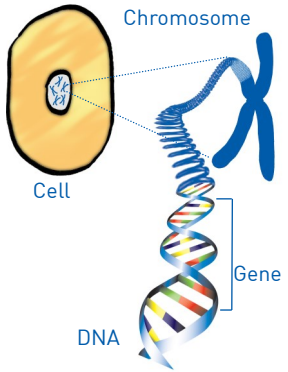
SETD2-NDD is a rare genetic condition associated with varying degrees of learning (intellectual) disability and behavioural differences. There are two types of the condition:

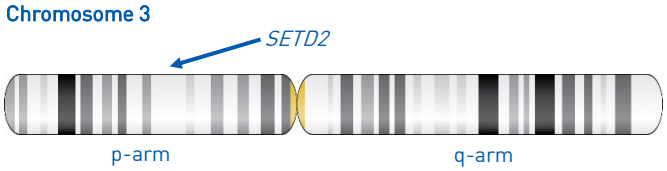
- *SETD2*-NDD with or without macrocephaly/overgrowth, also called Luscan Lumish syndrome (LLS)
- *SETD2*-NDD with multiple health conditions that are present from birth (SETD2-NDD with MCA), also called Rabin-Pappas syndrome (RAPAS).

Children with *SETD2*-NDD with MCA are more likely to have additional medical concerns. As is common with genetic conditions, each person is affected differently.

What causes *SETD2*-NDD?

SETD2-NDD is caused by specific changes (known as pathogenic variants) to the DNA sequence of a gene called *SETD2* (*SETD2* is an abbreviation of the gene's full name, SET domain-containing protein 2). The *SETD2* gene is located on the short 'p' arm of chromosome 3 in a region called 21.31 as shown in the image below.





We have two copies of chromosome 3 in our cells, so we also have two copies of the *SETD2* gene. *SETD2*-NDD occurs when only one copy of the *SETD2* gene is affected; the second copy is fully functional. This is known as autosomal dominant since all numbered chromosomes are called autosomes and genetic conditions that occur when only one copy of an autosomal gene is affected are known as dominant.

The *SETD2* gene sequence is used to make the SETD2 protein. This protein has a number of different functions in different parts of the body as it forms different complex structures with other proteins.

SETD2-NDD features

Most children with *SETD2*-NDD have:

- Developmental delay
- Intellectual disability (ID) or learning difficulties
- Low muscle tone (hypotonia)
- Brain anomaly

Other possible features associated with LLS include:

- Macrocephaly
- Overgrowth
- Behavioural differences
- Joint hypermobility

Other possible features with RAPAS include:

- Seizures *
- Heart anomaly *
- Anomalies of the kidneys and genitals *
- Endocrine anomalies *
- Skeletal anomaly *
- Eye anomaly
- Hearing loss

* - also seen rarely with LLS

Development

Development

Developmental delay has been reported in most children with *SETD2*-NDD. The degree of delay ranges from mild to profound. Speech and language are likely to be particularly affected. Low muscle tone (hypotonia) is common.

Intellectual development and learning

Many children with *SETD2*-NDD have intellectual disability (ID) or learning difficulties. ID ranges from mild to profound. Most individuals with LLS are in the moderate range while most individuals with RAPAS are in the profound range. Speech may be limited and some may be non-verbal.

Growth

Half of children with LLS described in the medical literature so far (2023) are noted as having overgrowth. Many of these children also have larger than expected head size (macrocephaly). Their bone age is also advanced compared to their chronological age. Children with RAPAS are small in infancy and have smaller than expected head size (microcephaly). Beyond infancy, height is variable.

Behavioural differences

About 75% (3 in 4) of children with LLS are described as having autism spectrum disorder (ASD). Other behaviours including ADHD and anxiety have also been reported. Children with RAPAS are not described as having behavioural differences.

Medical concerns

Heart conditions

Most children with RAPAS have a heart anomaly. The type of heart anomaly is variable. Some may require surgery, while others may not. Rarely, babies with LLS may been born with a heart condition.

Brain anomalies

Most children have a structural brain anomaly. Children with RAPAS have specific brain anomalies called hypoplasia (underdevelopment) of the corpus callosum, pons and cerebellum. Children with LLS have different brain findings, which may include Chiari I malformation, hydrocephaly, ventriculomegaly or Dandy-Walker malformation.

Seizures

Seizures are reported rarely in children with LLS. In these children, seizures are successfully controlled with medication. More than half of children with RAPAS develop seizures in infancy. The types of seizures are variable and may be more difficult to control with medication.

Endocrine anomalies

Children with LLS may have conditions that affect their hormones. These conditions include precocious (early) puberty, polycystic ovarian syndrome, hypothyroidism, growth hormone deficiency and/or advanced bone age. Children with RAPAS may develop low sodium in infancy (hyponatremia), which can be treated with sodium supplements. Rarely, additional conditions affecting hormones have been observed.

Eyes and eyesight

Problems with vision are uncommon in children LLS. Most children with RAPAS develop a specific eye anomaly called Coats disease, which is a condition that affects the blood vessels of the eye. These children may also develop additional eye conditions including optic nerve hypoplasia, glaucoma and/or cataracts.

Feeding

Children with RAPAS may have difficulty feeding and may require tube feeding. Other issues that have been reported include aspiration, where fluid, food or saliva enters the airway or lungs. Constipation and gastro-oesophageal reflux disease are sometimes associated with LSS.

Breathing

Some children with RAPAS have respiratory issues. These may include sleep apnoea (when there is an abnormal breathing pattern during sleep) and tracheomalacia (where the airway collapses during breathing).