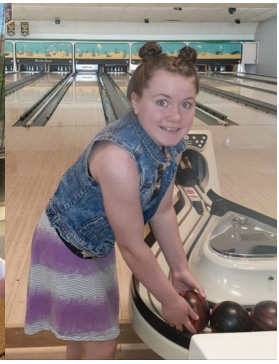
Understanding Chromosome & Gene Disorders

PCDH19 – related epilepsy



rarechromo.org

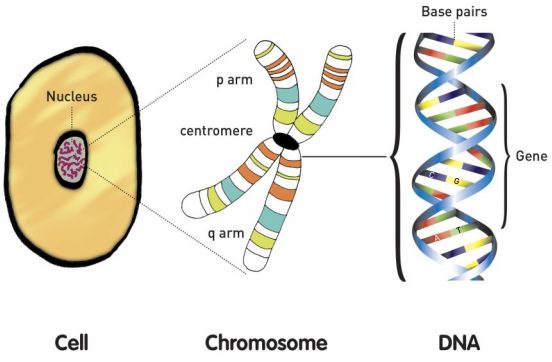
What is *PCDH19*–related epilepsy?

PCDH19-related epilepsy, otherwise known as *PCDH19* Clustering Epilepsy or Girls Clustering Epilepsy, is a rare genetic condition. Although only approximately 300 people with *PCDH19*-related epilepsy have been reported in the medical literature, it is thought to account for approximately 1% of epilepsy that presents prior to 3 years of age (Symonds 2019), and therefore affects thousands worldwide.

PCDH19-related epilepsy results from a change in, or a deletion of, a gene called *PCDH19*.

Changes to the *PCDH19* gene, known as pathogenic variants (changes to genes that can affect health), usually result in epilepsy in girls. The seizures commonly start at around 8 months, with most girls having seizure onset by 3 years of age. Typically, girls have clusters of many seizures over several days followed by longer periods where they are seizure free. Affected girls often have behavioural difficulties, learning difficulties, or intellectual disability that may not be apparent until after the seizures start.

Very rarely, boys are also affected. This occurs when a change in the *PCDH19* gene occurs after conception and during development. By mid-2020, only seventeen affected males with *PCDH19* pathogenic variants worldwide have been described in the literature.



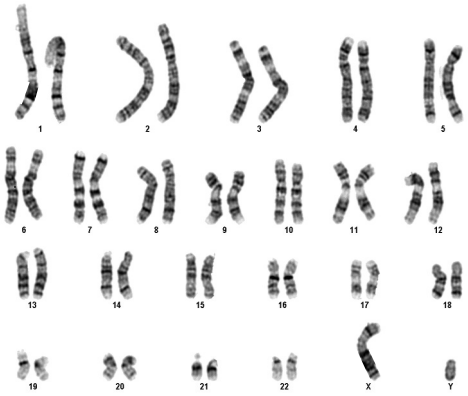
What are genes and chromosomes?

Genes are the 'instructions' that our bodies use for many functions including the control of growth and development.

Genes are made from a complex structure called DNA. You might like to think of DNA as a recipe book for making a living organism. DNA is an exceptionally long molecule that looks a bit like a twisted ladder. The rungs of the ladder are made up of pairs of letters (A-T and G-C). The order of the A, C, G, and T's in the DNA is the code that tells the cell (and organism) how to develop.

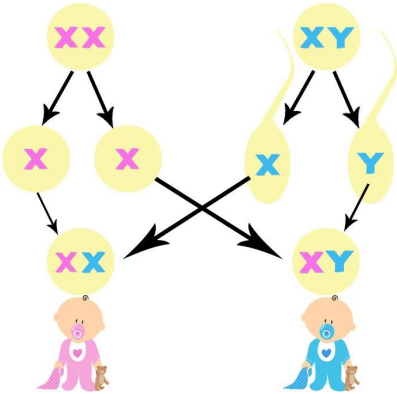
Because DNA is so long, it is coiled and folded into a chromosome, so it fits inside the microscopic cells that our bodies are made from. Most of our cells contain 46 chromosomes. Chromosome pairs are numbered 1 to 22 and the 23rd pair comprises the sex chromosomes, which determine biological sex (whether we are male or female). Females usually have two X chromosomes (XX) and males usually have an X and a Y chromosome (XY) (see the following image on page 3 for an example set of chromosomes).

We inherit 23 chromosomes from our mother and 23 from our father to make our very own unique 'recipe book' containing two copies of most genes.



Chromosomes pairs 1-22, X and Y (male)

Since chromosomes come in pairs, so do the genes contained within them. We therefore have two copies of each gene in chromosomes 1 to 22, and females (XX), have two copies of each gene on chromosome X. Males have one copy of chromosome X and although chromosome Y does contain some genes that also exist on chromosome X, the majority are not present, so males have a large number of genes on their X chromosome that are only present as a single copy. *PCDH19* is located on the X chromosome and is present as a single copy in males (XY).



X-chromosome-linked inheritance

Males (XY) inherit an X chromosome from their mother and a Y chromosome from their father.

Females (XX) have two X chromosomes: one inherited from their mother and one from their father.

Each X chromosome has a *PCDH19* gene. While females have two X chromosomes in each of their cells, only one of them is fully active. This is due to a natural process called X chromosome inactivation, which prevents more than one X chromosomes from being fully active in the same cell.

Most of the X-chromosome-linked syndromes identified to date affect males who only have one X chromosomes and therefore one copy of the relevant gene. Females are usually protected from being affected because they have a second, unaffected X-chromosome.

For *PCDH19*-related epilepsy, the 'opposite' happens, **females** who have a *PCDH19* pathogenic variant in one of their *PCDH19* genes are generally **affected**. Females are referred to as being heterozygous because they have an unaltered copy and an altered copy of the *PCDH19* gene (hetero means different/other, zygous refers to the cell formed when an egg and sperm join).

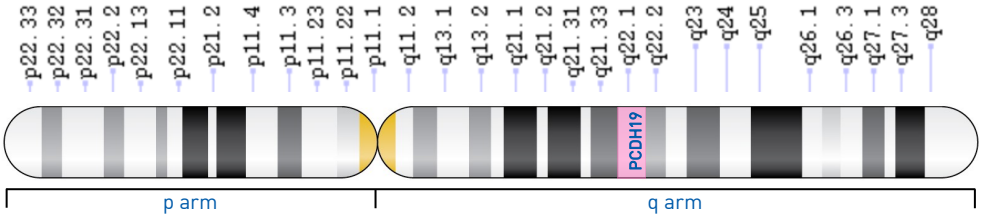
Males who inherit an X chromosome with a *PCDH19* pathogenic variant are thought to be **unaffected**. They are known as hemizygous (they only have one copy of this gene, hemi means half) transmitting carriers or transmitting males

(this means they can 'transmit' or pass on the altered gene to their children who may be affected, but since the men do not have epilepsy themselves they are known as 'carriers'). If a male does not inherit a *PCDH19* pathogenic variant, but instead the change in the *PCDH19* gene occurs after conception and during early development, they are expected to be affected.

Chromosome X and PCDH19

The *PCDH19* gene is located on chromosome X, on the long q arm, in a region called band 22.1 (shaded in pink in the image below).

Chromosome X



The *PCDH19* gene codes for the PCDH19 protein. Genes can be described as carrying instructions for our cells and proteins carry out specific tasks. The PCDH19 protein is important because it is involved in how brain cells (neurons) communicate with other cells and how they migrate when forming the developing brain. [*PCDH19* is an abbreviation of the genes full name protocadherin-19, which is a description of the protein's function ('calcium-dependent adhesion')].

What does PCDH19 do?

The functions of PCDH19 are largely unknown although it is speculated that it may have important roles during the early stages of brain development. These roles may affect the interaction of cells and attachment to neighbouring cells (PCDH19 proteins act like Velcro, keeping like cells together). PCDH19 protein may also be involved in how neurons move and where they move to (regulating neuronal migration), the activity between neurons or between a neuron and other types of cells (establishment of neural connections and plasticity), and the shape of neurons (neuronal morphology).

What genetic changes cause *PCDH19*–related epilepsy?

There are many different DNA variations that can occur in the *PCDH19* gene sequence. So far, over 140 different pathogenic variants have been reported in *PCDH19*. Some will result in the production of small amounts of a shorter (truncated) protein, these are named 'loss of function truncating variants'. Others may result in the production of a protein that has an altered function.

Some may result in no protein being produced from the altered gene sequence. The effect on the protein depends on the exact variation to the gene sequence

and how the coding regions are affected. Coding regions are the parts of the gene that are translated into amino acid sequences (amino acids are the building blocks of proteins). The gene alterations can be described as:

'Missense variants' - this is like a misprint in a recipe, for example, 'add some rice' could be changed to 'add some nice'. The genetic code is changed so it no longer codes for the correct amino acid and the function of the resulting protein may be affected.

'Nonsense variants' - this is like a full stop being introduced into the middle of a sentence making up a recipe, for example 'add some rice' could be change to 'add some.' The gene sequence now has a stop signal where it shouldn't be and amino acids are not added to the protein after that point. This means the resulting protein will be shorter than expected and it's function will be affected.

'Frameshift variants' - these changes mean the recipe cannot be read properly since the letters have moved and the sentences no longer make sense. For example, 'add some rice' could be changed to 'ad dso mer ice'. The genetic code is now out of sync and the wrong amino acids are selected to make the protein. This means the resulting protein will not function or may function differently.

There are other, less common, *PCDH19* pathogenic variants including deletions, insertions, and duplications.

Most *PCDH19* pathogenic variants identified so far (2020) are missense or nonsense variants located at the beginning of the gene. There are also genetic changes that have been identified in the *PCDH19* gene that are thought to be 'benign', meaning the change in the code does not cause a change in the protein and so it does not affect health and development.

Will all girls with a *PCDH19* pathogenic variant be affected?

Not all females with a genetic change in *PCDH19* are affected. The extent to which the condition is present in people with a pathogenic variant is referred to as penetrance. The penetrance of *PCDH19* pathogenic variants is estimated to be 90% (Dibbens 2008; Kolc 2020), this means that 10% of girls with a *PCDH19* pathogenic variant are expected to be unaffected (unaffected females are referred to as 'non-penetrant' by medical professionals). The exact reasons why some females are unaffected by *PCDH19* pathogenic variants are not fully understood, but the unique genetic background of each individual may be involved and possibly the unique pattern of X-chromosome inactivation, particularly in the developing brain.

There is also evidence that later seizure onset is associated with milder intellectual disability and behavioural difficulties. More frequent seizures have also been associated with more severe clinical outcomes (Kolc 2020).

While *PCDH19*-related epilepsy is typically associated with normal early development, delayed development prior to seizure onset occurs in approximately 20% of children (Kolc 2020).

Boys with a *PCDH19* pathogenic variant

Males who inherit an X chromosome with a *PCDH19* pathogenic variant are not affected by *PCDH19*-related epilepsy. However, if the change in the *PCDH19* gene occurs after conception and during early development of a boy, this results in a similar outcome to girls with a *PCDH19* pathogenic variant. This is because the boy will have some cells with the unaffected *PCDH19* gene and some with the affected *PCDH19* gene. This is known as somatic mosaicism since the genetic change occurred in a somatic cell (the cells that make our body) as opposed to a germline cell (an egg or sperm) and tissues are mosaic, meaning some cells will have the variant and others will not.

A comparison of 8 males with a mosaic *PCDH19* variant and 90 females with a heterozygous *PCDH19* variant revealed they had similar clinical symptoms and difficulties (Kolc 2020).

Test results:

Many changes in the genetic code of the *PCDH19* gene have been found to cause *PCDH19*-related epilepsy. A molecular diagnostic laboratory is responsible for sequencing your or your child's DNA. If a *PCDH19* pathogenic or likely pathogenic variant is identified, the variation is recorded on the report from the testing laboratory. Sometimes it is not known if a variant causes disruption to the normal function of the PCDH19 gene/protein (these genetic changes are referred to as variants of unknown significance or VOUS).

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You may have been given a genetic test result that looks something like the following example:

p.Asp558His (D558H) (GAC→CAC): c.1672 G→C in exon 1 of the PCDH19 gene (NM_001184880.1)

p.	denotes a change to a protein
Asp558His	the amino acid Aspartic acid at position 558 of the protein has been changed to the amino acid Histidine
(D558H)	this is a repetition of the previous point written in a different way. D is the symbol used for aspartic acid H is the symbol used for histidine.
(GAC→CAC)	these letters refer to the change to the genetic code. the nucleotide sequence GAC has been changed to CAC
c.	denotes a change to the complementary DNA sequence
1672	the sequence has been changed at nucleotide position 1672
G→C	the Guanine nucleotide has been changed to Cytosine
exon 1	the sequence change occurred in exon 1 of the gene
PCDH19	the name of the affected gene

(NM_001184880.1) the code for the reference sequence used.
NM denotes a protein coding RNA, 001184880 denotes the accession number and .1 denotes the version of the sequence.

Why did this happen?

Approximately half of the children with *PCDH19*-related epilepsy identified so far (2020) have a family history of epilepsy and the *PCDH19* pathogenic variant has been passed on by either a mother or father. The other half have a pathogenic variant that has occurred as a new event in the child (the variant is *de novo*).

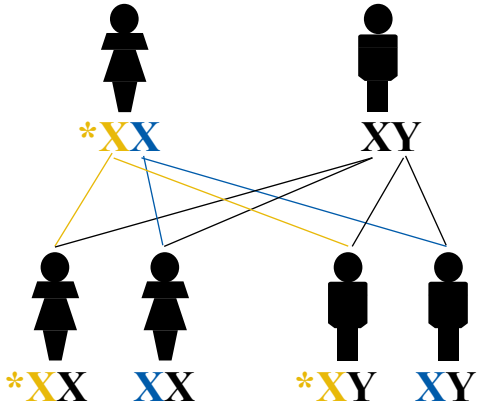
We all carry variants in our DNA, they occur when our chromosomes are copied, and new cells are formed. We all have new variants that we did not inherit from our parents, but most of these variants are benign (they do not affect health and development). A genetic condition is diagnosed when a variant changes an important sequence in our DNA that affects health and development. These variants are known as pathogenic, and so far, most have been identified in genes that code for important proteins.

It is important to know that as a parent there is nothing you could have done to prevent the genetic change from occurring. *PCDH19* variants are not caused by environmental, dietary or lifestyle factors and there is nothing that either parent did before or during pregnancy that caused the change.

Can it happen again?

The chance of having another child affected by a rare gene disorder depends on whether the genetic change is in one of the parents. It is important to establish if the *PCDH19* pathogenic variant is present in the mother, or the father, or if it occurred as a new genetic change in the child.

Mothers with a *PCDH19* pathogenic variant

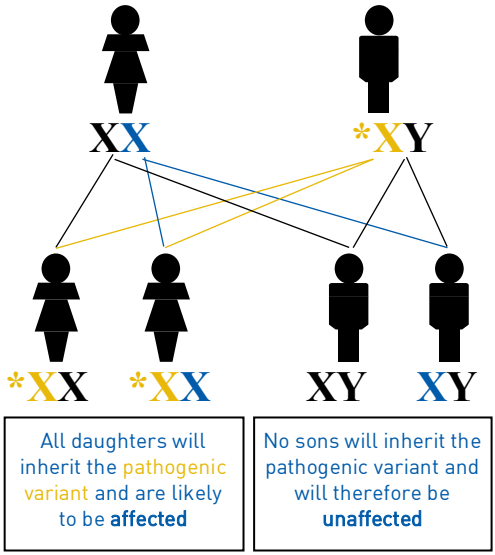


Women with a *PCDH19* pathogenic variant have a 50% chance of passing on the X chromosome with the unaffected *PCDH19* gene and a 50% chance of passing on the X chromosome with the *PCDH19* pathogenic variant to any future daughter or son.

*X chromosome with the *PCDH19* pathogenic variant

X chromosome with the unaffected *PCDH19* gene

Fathers with a *PCDH19* pathogenic variant



Men pass on an X chromosome to all their daughters and a Y chromosome to all their sons. A man who has a *PCDH19* pathogenic variant will pass that variant on to **all** of his daughters. This means there is a high chance that daughters will develop *PCDH19*-related epilepsy. Since a man with a *PCDH19* pathogenic variant passes on a Y chromosome to his sons (and not an X chromosome), his sons will **not** have their father's *PCDH19* pathogenic variant.

*X chromosome with the *PCDH19* pathogenic variant

X chromosome with the unaffected *PCDH19* gene

About half of females with *PCDH19*-related epilepsy have no family history of the disorder. The majority of these have a new (*de novo*) *PCDH19* pathogenic variant that occurred in them. However, it is possible for a parent to pass on the genetic change without knowing they have it since sometimes it can be found only in their sperm or egg cells (referred to as germline or sex cells) but not in the rest of the cells in their body (referred to as somatic cells). This is known as germline mosaicism (or gonadal mosaicism). Since the pathogenic variant is not present in the mother or father's somatic cells, such as those in the brain, they do not have seizures or other symptoms of *PCDH19*-related epilepsy. Since the variant is not present in the cells found in blood, a genetic blood test result will come back negative. In this situation parents can have another child with the variant even though a genetic test, taken from a blood sample, states they do not carry the variant. Germline mosaicism is **very rare** (usually estimated at <1%), however, the risk of having another affected child for individuals with germline mosaicism can vary greatly depending on the number of germline cells that carry the *PCDH19* pathogenic variant. If the variant occurred earlier on in the development of the germline cells, then the recurrence rate would be higher because a greater number of cells would carry the *PCDH19* pathogenic variant.

Due to the unusual nature of *PCDH19*-related epilepsy inheritance, it is important that families are offered comprehensive genetics counselling, especially if they are planning another pregnancy. Their children should also be offered counselling when they grow up. Since the sons of a mother with a *PCDH19* pathogenic variant have a 50% chance of inheriting the pathogenic variant, they have a high risk of having daughters with *PCDH19*-related epilepsy even though they do not have it themselves.

How common is *PCDH19*-related epilepsy?

PCDH19-related epilepsy was first clinically described in 1971 (Juberg & Hellman 1971) as a hereditary early onset seizure disorder triggered by fever, and only found in females. The causative gene was identified almost 50 years later during a study of the same family described in 1971 and six additional families with similar symptoms and pattern of inheritance (Dibbens 2008). A few males have since been identified who are mosaic for the *PCDH19* gene and have similar symptoms to those of affected females.

PCDH19 is considered one of the most clinically relevant genes in epilepsy, affecting between 15,000 and 30,000 people in the United States and 1000 in Australia (Homan 2017).

Genetic testing was once a complicated, costly, and time-consuming process. Recently, there have been major advances in technology and cost efficiency that have enabled a more prolific use of genetic testing, so it is likely that increasingly more people will be diagnosed with *PCDH19* pathogenic variants.

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A recent population-based study identified *PCDH19* as one of the most common single-gene epilepsies in young children with an incidence of 1 per 20 600 live female births (Symonds 2019).

Can *PCDH19*–related epilepsy be cured?

Currently, there is no known cure for *PCDH19*-related epilepsy. Epilepsy should be managed by a paediatric neurologist or a paediatrician with expertise in epilepsy. Early developmental and behavioural diagnosis and intervention with education programs can help children reach their full cognitive and social potential.

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Parents are encouraged to promptly discuss concerns about possible seizures, learning difficulties, or behavioural difficulties with their child's paediatrician or paediatric neurologist so that these symptoms can be appropriately diagnosed and managed.

The seizures in *PCDH19*-related epilepsy can be hard to control in some individuals. There are no published placebo-controlled trials, however, a recent retrospective study suggested that levetiracetam has a positive impact in this disorder (Sadleir 2020).

Girls with *PCDH19* pathogenic variants have previously been shown to be deficient in a naturally occurring steroid called allopregnanolone (Tan 2015). Marinus Pharmaceuticals are currently running a clinical trial of a drug called ganaxolone, which is a compound (synthetic analogue) similar to allopregnanolone. Further information about this study can be found on the clinical trial page as follows:

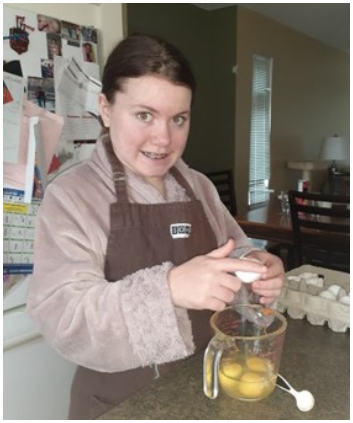
https://www.clinicaltrials.gov/ct2/show/NCT03865732?term=ganaxolone&draw=2&rank=3

Research into the potential mechanisms and therapeutic targets for *PCDH19*-related epilepsy is ongoing. Families are encouraged to visit the PCDH19 page as part of the Human Disease Genes Website Series for up to date information about current research projects and initiatives:

https://humandiseasegenes.nl/pcdh19/research-collaboration/.

Families say:

" She absolutely loves ballet and performing. She fell in love with ballet after watching an impromptu show at our local mall during the holidays and has been in love with the dance and the beautiful costumes ever since. "

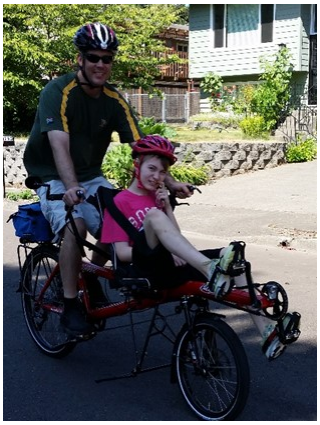


" She loves to be helpful. She is very compassionate and caring. "

A young boy, aged 16 months

“ She is an incredibly resilient, strong-willed, goofy and affectionate girl. Once she sets her mind to do or learn something, she keeps at it, and will not let seizures or medications keep her from it. After all the seizures, hospitalizations, IVs, and blood draws she has endured, she still has hugs for the doctors and nurses, and is generally a happy girl. ”

“ She loves swimming, biking, and the beach. ”



“ She loves to help her mom cook, loves nature, loves to paint, and has a passion for flowers! “

What symptoms do individuals with *PCDH19*-related epilepsy have?

PCDH19 pathogenic variants cause distinctive symptoms. Typically, children with normal development present with clusters of frequent seizures in the first year of life, often triggered or exacerbated by fever. In approximately 95% of children with *PCDH19*-related epilepsy, seizure onset is associated with fever (Kolc 2019).

Seizures are usually focal (which means they start in one part of the brain). What happens to the child varies depending on which part of the brain is affected. Children can appear frightened and have altered awareness followed by stiffness or jerking of their arm or leg on one side of their body. The seizure can spread so that both sides of the brain are involved. This results in bilateral (affecting both sides) stiffening and jerking of the body and limbs (this is known as a tonic-clonic seizure). It may be difficult to stop clusters from occurring, and the epilepsy is often resistant to medication. The epilepsy can improve after the first 10 years (average 18 years), with many children becoming seizure free (with medication) in adolescence (Kolc 2020).

Developmental course is varied. Although most children have typical development at the onset of their seizures, approximately 20% may have had developmental concerns raised before their seizures started. With the onset of seizures, development may slow and in some cases children loose developmental skills during the cluster of seizures. Approximately 70% of individuals with *PCDH19*-related epilepsy ultimately end up with a degree of intellectual disability ranging from mild to profound. Other neurodevelopmental disorders are common, most frequently autism spectrum disorder (ASD) and behavioural difficulties; later onset psychosis (when understanding of reality is altered so that people can see, hear and/or believe things as real when they are not) occurs in approximately 20% of females (Vlaskamp 2019). These cognitive and behavioural conditions can have a significant impact on the quality of life for people with *PCDH19*-related epilepsy and their families.

Common features:

- Epilepsy
- Developmental delay
- Developmental regression
- Speech and language delays and difficulties (in severe cases, absent speech)
- Learning difficulties
- Intellectual disability (ID)
- Autism spectrum disorder or ASD-like behaviour

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Other possible features include:

- Executive dysfunction
- Hyperactivity or attention-deficit hyperactivity disorder (ADHD)
- Obsessions and compulsions or obsessive-compulsive disorder
- Aggressive behavior
- Late-onset psychosis

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Pregnancy and birth

There do not appear to be any difficulties with pregnancy or birth for mothers and babies with *PCDH19* pathogenic variants.

Feeding and growth

There have been no reports in the literature of feeding difficulties in children with *PCDH19*-related epilepsy, although children may have trouble following established routines for eating. Through correspondence with parents, we have learned that children may refuse to try new foods or that food is one of the most important things for their child.

" Our daughter doesn't seem to have interests in important things like school, her health, purpose in life. Food, friends, video games and her iPad are most important. "

Children with *PCDH19*-related epilepsy are expected to have normal growth.

Development

All children with *PCDH19*-related epilepsy develop differently and intellectual abilities vary. Developmental regression (losing skills once learnt) is common. Regression often occurs with seizure clusters. Initially, development subsequently improves with a return to normal between clusters. Over time, with subsequent clusters, return to previous levels of function may not occur.

Motor skills and self-care

Some children with *PCDH19*-related epilepsy have been described by their parents as being delayed in reaching motor milestones like sitting and walking. Most children can sit and stand at, or shortly after, the expected age.

" She had weak muscles; she had delay in ability to roll from back to belly, delay in sitting. "

Most children for whom we have information have adequate gross motor skills, but this can vary, especially for more severely affected children.

Children may benefit from physiotherapy (also known as physical therapy) and occupational therapy to help them achieve their full potential. Once a child has

shown their individual pattern of development, it will become easier to predict their longer-term potential.

Most children for whom we have information do not require assistance in areas of daily living. In severe cases, assistance is required.

Intellectual abilities and schooling

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Intellectual disability (ID) is a term used to describe significant limitations in intellectual functioning (measured by IQ scores) and adaptive behaviour (types of behaviour used to adjust to other behaviours or situations). Approximately 70% of children reported in the medical literature with *PCDH19*-related epilepsy also have ID, ranging from mild to profound for girls and mild to severe for boys.

Schooling can be a concern for some parents. While some children with *PCDH19*-related epilepsy will attend a mainstream school, with or without support, many will require special needs schooling. Few have extremely limited intellectual ability. Early seizure onset (less than 12 months of age) is associated with more severe ID.

The association between seizure onset and clinical outcome has been studied (Kolc 2020; Trivisano 2018). As seizure onset age increases, executive functioning improves, and autism spectrum disorder symptoms decrease.

Speech, language, and communication

Speech and language skills can be variable in children with *PCDH19*-related epilepsy, however marked speech difficulties are rare. Children are often slightly delayed in their ability to speak and ultimately some have limited language. In the most severe cases, children have no spoken language but can communicate their feelings and needs in other ways.

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Research in this area is limited, however, from a PCDH19 survey we have learned that communication is delayed for approximately 50% of children. You can access the PCDH19 survey publication by following this link:

https://www.nature.com/articles/s41398-020-0803-0.

Speech and language therapists can assess communication skills. They can help with speech development and introduce communication devices. They can also help to ensure that whatever your child's ability, they are supported in achieving their full communication potential.

Behaviour

Although behavioural difficulties have not been comprehensively described for all children reported in the medical literature, behavioural, social, and communication difficulties are common in children with *PCDH19*-related epilepsy. Vulnerability in these areas means that children should be monitored, and families offered early support.

Autism spectrum disorder (ASD) occurs in children with *PCDH19*-related epilepsy, with a little over half of children reported to have ASD-like features. These features may include disliking changes in routine or loud noises. Some children may also have stereotypic movements (non-purposeful movements) such as rocking or hand flapping.

Attention-Deficit Hyperactivity Disorder (ADHD) or ADHD-like symptoms (i.e., hyperactivity or inattention) are also common (identified in approximately 65% of children with *PCDH19*-related epilepsy (Kolc 2020) and are characterized by an inability to pay attention and control behaviour. Aggression is also a prominent feature in those with ADHD and is particularly difficult for families.

Late onset psychosis has recently been shown to occur after the age of 11 years in females (Vlaskamp 2019). Adolescents and adults with *PCDH19*-related epilepsy should be carefully monitored for later-onset mental health conditions.

Executive function deficits are also common, occurring in approximately 70% of individuals (Kolc 2020). Executive functions involve a set of cognitive processes that include:

- Attention
- Working memory
- Inhibition (ability to control actions and stop engaging in a behaviour)
- Mental flexibility (ability to move from one task to another and tolerate change)
- Problem-solving
- Planning
- Reasoning

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Deficits of this nature are also often seen in people with ASD and ADHD.

Other behaviours, such as obsessions and compulsions may also be evident. Obsessions are intrusive and repetitive thoughts, urges, or images that remain even following attempts to ignore or confront them; and compulsions are behaviours or mental acts that are performed to alleviate the discomfort associated with obsessions. Obsessions and compulsions are the hallmarks of obsessive-compulsive disorder, however, they can also occur as part of other conditions (i.e., ASD).

Recent research has shown that the impact of behavioural difficulties on family members is profound (Kolc 2020). Depending on a child's abilities, joining a social skills group may help with social difficulties, enabling children to learn and practice important skills. A parenting course may also help families to develop behavioural management tools and encourage communication and cooperative behaviour in their child to strengthen their emotional wellbeing. Medication can also help manage a child's behaviour when it becomes concerning (such as self-harming or aggression). These behaviours may be more prominent when a child is feeling anxious and has difficulties with comprehension and communication. An occupational therapist or psychologist may be able to help manage difficult behaviours by giving your child tools to deal with their sensitivities.

Sleep

Children affected by genetic disorders often have more sleep difficulties than typically developing children. Some families have reported their child with *PCDH19*-related epilepsy finds it difficult to fall asleep at night and early waking and insomnia have also been reported. The reasons for these sleeping difficulties are not yet well understood.

It can be challenging having a child who won't settle to sleep or who does not have sufficient undisrupted sleep, and it can be very difficult for parents to function well during the day if they have a continuous lack of sleep.

Illustration by Freepik Stories: https://stories.freepik.com/

There are many interventions that can be put in place to help improve a child's sleep difficulties. Some of these include having a good routine, blocking out natural light in the bedroom, or the use of the hormone melatonin (this is not helpful for all children but may be tried if children have severe sleeping difficulties). Daytime exercise may also improve a child's ability to sleep at night. Unique also publishes a freely available sleep guide as part of the practical guide series, it can be found at the following link:

https://www.rarechromo.org/practical-guides-for-families.

Seizures

All children with *PCDH19*-related epilepsy have seizures (sudden and unexpected electrical activity in the brain). More than one type of seizure may be present in the same individual. The types of seizures are most commonly focal seizures, but tonic-clonic seizures can also occur. During a seizure, children appear fearful and may scream. They are not aware of what is going on around them. They may have stiffening or jerking of one limb, which can sometimes spread to involve the entire body. Most seizures are short, lasting less than a

few minutes, but sometimes there are so many of them in a cluster that the child does not recover between seizures. Seizures can cause a lot of worry for families and can be frightening to observe. If your child has a seizure, it is important to remove nearby hazards so they cannot hurt themselves.

Anti-epileptic medications are used to stop seizures and prevent further clusters. In some individuals, the medications do not work well, and it is difficult to prevent seizures occurring. There is some evidence to suggest that levetiracetam is effective in reducing or ameliorating seizures. For more information about this research, access the following link:

https://www.sciencedirect.com/science/article/pii/S1090379819304404.

Fortunately, the epilepsy often improves over time, with seizures becoming less severe and less frequent during adolescence. Some individuals become seizure-free around this time.

Management:

At diagnosis:

Individuals and their families with a *PCDH19* pathogenic variant should be referred to a geneticist and for genetic counselling. This is especially important given the unusual X-chromosome linked pattern of inheritance.

After diagnosis:

Epilepsy should be managed by a paediatric neurologist or a paediatrician with expertise in epilepsy.

Developmental should be monitored by a paediatrician with appropriate referral for early cognitive assessment and interventions as needed (including speech therapy, physio(physical) therapy and occupational therapy).

Ongoing support at school and on leaving school would be beneficial.

Individuals should be referred for early intervention and ongoing support by a psychologist or psychiatrist, if behavioural management is required.

For more severely affected individuals, behavioural medications may be required.

Support groups:

PCDH19 Alliance

The PCDH19 Alliance's mission is to improve the lives of children and families who are affected by *PCDH19*-related epilepsy.

The Alliance focuses on raising and directing funds to scientific research with the goal of finding better, more effective treatments and, ultimately, a cure; providing information and support to affected families; and assisting the efforts of the medical community, so that no family suffers without a diagnosis and the most appropriate medical treatment.

PCDH19info.org™

Insieme per la Ricerca PCDH19 Onlus ("Together for the research on PCDH19")

Isieme per la Ricerca PCDH19 is a non-profit organization (based in Italy) that aims to:

- Know and fight this rare genetic disease
- Support the research, making a reality of the hope of finding a cure to fight this disease
- Solicit the cooperation and exchange of information among researchers and investigators
- Improve the quality of life of affected children
- Promote the communication among the families involved
- Raise public awareness by spreading information on the disease

Support groups in other countries and languages include:

France/French : https://pcdh19france.fr/
Spain/Spanish : Asociocion eplilepsia Rosa (PCDH19) www.pcdh19.com

The cute syndrome also supports PCDH19 families :
https://www.thecutesyndrome.com/

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Inform Network Support

Rare Chromosome Disorder Support Group
The Stables, Station Road West, Oxted, Surrey RH8 9EE, United Kingdom
Tel: +44(0)1883 723356
info@rarechromo.org | www.rarechromo.org

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PCDH19 Alliance

PCDH19info.org™

INSIEME PER LA RICERCA PCDH19 ONLUS
http://www.pcdh19research.org

This guide was prepared with help from the PCDH19 Alliance and Insieme per la Ricerca PCDH19 Onlus.

Unique mentions other organisations' message boards and websites to help families looking for information. This does not imply that we endorse their content or have any responsibility for it.

This information guide is not a substitute for personal medical advice. Families should consult a medically qualified clinician in all matters relating to genetic diagnosis, management and health. Information on genetic changes is a very fast-moving field and while the information in this guide is believed to be the best available at the time of publication, some facts may later change. *Unique* does its best to keep abreast of changing information and to review its published guides as needed. This guide was compiled by Kristy Kolc, Adelaide Medical School, Faculty of Health & Medical Sciences, The University of Adelaide, Australia and Unique (AP). Dr Jozef Gécz, Senior Principal Research Fellow and Professor of Human Genetics at the Adelaide Medical School, the University of Adelaide reviewed this guide.

Version 1 2020 (AP)