Understanding Chromosome & Gene Disorders

CDK13-related disorder

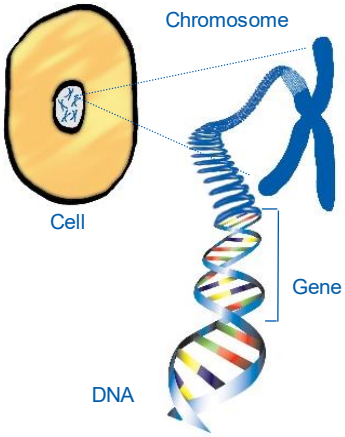
What is *CDK13*-related disorder?

CDK13-related disorder is a rare genetic condition associated with developmental delay, intellectual disability, heart conditions, and speech and language disorders. This condition may also be referred to as congenital heart defects, facial dysmorphism and intellectual developmental disorder (CHDFIDD).

CDK13-related disorder is caused by a change (variant) in the *CDK13* gene. As is common with genetic conditions, each person is affected differently (Bostwick, 2019; Sifrim 2016).

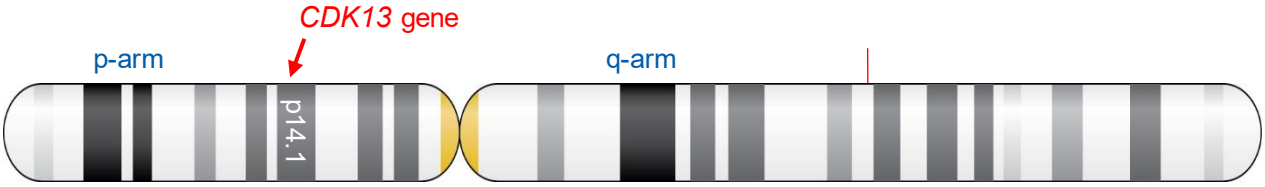
What causes *CDK13*-related disorder?

Genes are instructions which have important roles in our growth and development. They are made of DNA and are incorporated into organised structures called chromosomes. Chromosomes therefore contain our genetic information. Chromosomes are located inside our cells, the building blocks of our bodies.



CDK13-related disorder is caused by specific changes (known as pathogenic variants) to the DNA sequence of a gene called *CDK13* (*CDK13* is an abbreviation of the gene's full name, Cyclin-Dependent Kinase 13). The *CDK13* gene is located on the short 'p' arm of chromosome 7 in a region called p14.1 as shown in the image below.

Chromosome 7



We have two copies of chromosome 7 in our cells, so we also have two copies of the *CDK13* gene. *CDK13* occurs when only one copy of the *CDK13* 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.

Unique publishes a separate guide to single gene disorders – autosomal dominant inheritance.

The *CDK13* gene sequence is used to make the CDK13 protein. This protein is important because it plays multiple different roles within our cells.

"We received our diagnosis when our son was 6. We were able to find our CDK13 family online and finally felt a place where we fit in. They'll be our family for life."

"The CDK13 diagnosis came as a massive shock, like a bereavement. It also gave us the realisation that he 'isn't going to catch up'. The hardest part was knowing he has dysmorphic features, and seeing the similarities in him and the other children. It gave us answers/explanation but was devastating, especially as it's such a newly found genetic alteration, so many questions and fears for the future."

Genetic Report

An example result of a DNA sequencing test (e.g. whole exome sequencing (WES) or whole genome sequencing (WGS)), that can identify gene variants, is shown here for the *CDK13* gene:

p.Asn842Ser (N842S) (AAC>GAC): c.2525A>G in exon 6 of the *CDK13* gene (NM_003718)

p.Asn842Ser (N842S)	signifies the change to the protein; the amino acid aspartic acid (Asn) has been replaced by the amino acid histidine (Ser) at position 842 in the sequence of amino acids that make up the protein
AAC>GAC	signifies the gene sequence change; the A nucleotide has been replaced by a G nucleotide
c.2525A>G	signifies the base pair position of the change within the gene sequence (the position where the A nucleotide has been replaced by the G nucleotide)
exon 6	signifies which part of the gene has been altered, in this case exon 6
CDK13 gene	signifies the gene that is affected
NM	denotes the reference sequence used

Unique publishes a separate guide to Interpreting Genetic Test Results.

What features and symptoms do people with *CDK13*-related disorder have?

As is common with many genetic conditions, children and adults with *CDK13*-related disorder can have a range of symptoms. As more children are diagnosed, and information is shared, the range of symptoms and features, abilities and difficulties and the likelihood of a child or adult having these features will become more clear.

Features of *CDK13*-related disorder include:

- Some degree of developmental delay ranging from mild to moderate
- Some degree of intellectual disability (ID) or learning difficulties (LD) ranging from mild to moderate, although some individuals have been reported with average cognition
- Delayed speech and language milestones
- Cardiac malformations
- Feeding difficulties which usually resolve after early childhood
- Gastro-oesophageal reflux (GERD/GORD)
- Musculoskeletal problems, including spinal abnormalities
- Characteristic facial features including e.g. widely spaced eyes (hypertelorism), eyes that slant upwards slightly at the outer corners (up-slanting palpebral fissures), skin folds at the inner corner of the eye (epicanthal folds), highly arched eyebrows, wide nasal bridge, small mouth with thin lips, wide spaced teeth and curly hair
- Vision impairment
- Low muscle tone (hypotonia)
- Frequent ear infections
- Neurodevelopmental diagnoses such as, autism spectrum disorder (ASD), sensory processing disorder (SPD), attention deficit hyperactive disorder (ADHD), developmental coordination disorder (DCD)
- Small head size (microcephaly), particularly in older individuals
- Short stature
- Brain anomaly
- Seizures
- Sleep issues

Appearance

Certain facial features are found more often in children with *CDK13*-related disorder than in other children. These features may mean that unexpected similarities are seen between unrelated children with *CDK13*-related disorder. The most common characteristic features include curly hair, wide-set and up-slanting eyes, skin folds at the inner corner of the eye, high arched eyebrows, broad nose, small mouth with thin lips, teeth spaced wide apart, and unusual shaped ears (Bostwick 2017; Hamilton 2018; Sifrim 2016; Uehara 2018).

Development

Gross and fine motor skills

Developmental delay has been reported in most children with *CDK13*-related disorder so far (2024). The degree of delay ranges from mild to moderate (Bostwick 2019; Hamilton 2018; Morison 2023). Developmental "milestones", including rolling, sitting, walking, playing with toys, using cutlery, using zips and buttons, and toilet training, are often delayed, although there is a wide range of eventual ability. Some children acquire mobility and other skills around the same age as "typical" children and others show more obvious delay. Low muscle tone (hypotonia) and developmental coordination disorder are common and may affect mobility (Morison 2023). Many children benefit from early intervention with therapies such as occupational therapy (OT) and physiotherapy (PT).

Unique publishes separate guides to Therapies and Toilet training and continence.

"As an infant, he had delayed milestones, sat at 11 months, camo crawled at around 18 months and walked at 22 months. As a young teenager, although greatly improved, his fine and gross motor skills are not as refined as his peers. He struggles to write legibly, he can form letters but they are large and disorganised on the line. He still needs support with personal hygiene due to gross and fine motor skills. He is able to ride a bike, scooter and drive his electric quad (he's cautious on all)."

Intellectual development and learning

Many children with *CDK13*-related disorder have intellectual disability (ID) or learning difficulties. ID ranges from mild to moderate but is usually in the moderate range and most children have needed additional support with their learning (Morison 2023). Some children attend specialist schools, whilst other children attend mainstream schools. Early intervention can prove particularly beneficial and formal testing to assess specific, individual needs is recommended.

Unique publishes separate guides to Education and Further education, training and work.

"He is excelling in a small, specialized school setting. He can read, tell time, and count money. He will always require support, but makes progress all of the time."

"Aged 13 now, he is academically at aged 4-5 years old and attends a special needs school. He is highly socially and emotionally in tune with others, he can read facial expressions and situations well.

Speech and language

Children with *CDK13*-related disorder typically experience delayed speech and language milestones and speech and language disorders (Morison 2023). Many individuals may find it difficult to co-ordinate movement of their lips, jaw and tongue to make the right sounds, this

is known as childhood apraxia of speech or CAS. The eventual range of achievement is broad, but some individuals may remain non- or minimally-verbal (Morison 2023). Those who do develop speech may achieve single words, short phrases or basic sentences and many go on to develop conversational skills and a broad vocabulary. As CAS is common in *CDK13*-related disorder many children would benefit from tailored CAS speech therapy (Morgan 2018).

"He didn't babble until about 2.5years and on commencing school, at 4years 3 months, his vocabulary was very limited and speech was very unclear. As a young teenager, his speech is better than we ever imagined, his speech diagnosis is a lengthy one, but is fundamentally verbal apraxia."

An assessment by a speech therapist/pathologist should be able to identify each child's specific difficulties, allowing regular therapy sessions tailored to each child's specific areas of need. Where individuals cannot use speech for all their daily communication needs, they may benefit from Augmentative and Alternative Communication (AAC) methods, including pointing, pictograms, gestures, facial expression and simplified sign language and high-tech communication systems (aided communication). Most individuals with *CDK13*-related disorder have used AAC at some point in their lives (Morison 2023). Early access to AAC supports language and learning development, particularly in the presence of speech disorders such as childhood apraxia of speech.

Individuals may also benefit from targeted literacy intervention, as many individuals with *CDK13*-related disorder experience difficulties with reading and writing (Morison 2023).

Unique publishes a separate guide to Communication.

Feeding

Feeding issues in infancy are common (Bostwick 2019; Morison 2023; Van den Akker 2018). Low muscle tone may contribute to difficulties with swallowing and some babies will suck weakly and may need high energy milks to encourage weight gain. Many babies also suffer from gastro-oesophageal reflux (GERD/GORD) (in which feeds return readily up the food passage), which may require treatment, including careful positioning for feeds, medication, nutritional supplements or, in some cases, insertion of a nasogastric tube (NGT) or gastrostomy tube (G-tube). Some children have benefited from attending a feeding clinic where an assessment can be made, and advice to help treat any eating and drinking difficulties provided.

"As a baby, he was very difficult to feed, he had poor oral muscle tone, he didn't 'realise' he had to open his mouth to feed."

Unique publishes a separate guide to Feeding.

Constipation

Constipation is common among children with *CDK13*-related disorder (Hamilton 2018; Morison 2023; Rouxel 2022). It is important that possible causes are discussed with the child's health visitor or doctor, who may recommend diet adaptation or give stool softeners or laxatives.

Growth and stature

Some children with *CDK13*-related disorder described in the medical literature so far (2024) are noted as having short stature (Bostwick 2019; Bostwick 2017; Morison 2023). Some of these children also have smaller than expected head size (microcephaly). Weight and length in childhood should be closely monitored, particularly in the first few months of life when feeding difficulties are present.

Behaviour

Children with *CDK13*-related disorder typically tend to have behaviour in keeping with their overall degree of developmental delay, and most have a happy disposition. Social motivation is a relative strength for most people with *CDK13*-related disorder. Many children have an autism spectrum disorder (ASD) diagnosis or traits. Other behaviours or diagnoses include attention deficit hyperactivity disorder (ADHD), anxiety, and challenging behaviours when feeling angry have also been reported (Hamilton 2019; Morison 2023; Van den Akker 2018). Many children also have sleep problems, including frequent waking, early waking and difficulty falling asleep (Morison 2023). Children usually benefit from consistent routines, boundaries, rewards and other behaviour management techniques. Support from a sleep specialist could also assist. Communication therapy and supports (such as AAC) may support a child's behaviour, for example reducing feelings of frustration.

Unique publishes separate guides to Challenging Behaviour and Sleep.

"Ou son is a joy. He makes us laugh every day. Where ever we go, people know him and are delighted to see him."

"He has fixed interests and likes, he's never played with toys/had imaginary play. He is very sensory and mouths objects a lot. He enjoys tearing tissue/paper into perfect strips! Playdoh and kinetic sand. He is very anxious, he's a worrier, shy and wary."

Puberty

There is limited information available about puberty in children with *CDK13*-related disorder. Some families of children with learning difficulties can be particularly concerned at their daughter's ability to cope with menstruation, and for some, discussing menstrual regulation options with a paediatrician may be beneficial.

Unique publishes a separate guide to Puberty.

Medical concerns

The following medical concerns have been found in children with *CDK13*-related disorder. They are not found in all children, so not all children with *CDK13*-related disorder will be affected.

Heart conditions

A heart condition(s) has been found in many people reported so far with *CDK13*-related disorder, most of which are present at birth (congenital) (Bostwick 2017; Hamilton 2018; Morison 2023; Uehara 2018). In children for whom heart problems are suspected, these can be diagnosed using tests like an electrocardiogram (ECG) (recording the electrical activity of the heart), echocardiogram (ultrasound scan of the heart), or chest X-ray. The type of heart condition(s) is variable but includes anomalies affecting the size and structure of the heart muscle and valves. Common heart conditions include a whole between the top two chambers of the heart (atrial septal defect) and a hole between the bottom two chambers of the heart (ventricular septal defect). Some of these conditions are relatively minor and resolve naturally with time. Medical treatment may be necessary for others, and some may require surgery.

"His heart is technically structurally fine but, at age 13, he's had tachycardia for the last 6 months, we are awaiting a beta blocker."

■ Eyes and eyesight

Problems with eyes and vision are common in children with CDK13-related disorder (Bostwick 2019; Morison 2023). A wide range of conditions have been reported and an individual may have more than one vision or eye-related concern. Known concerns include short-sightedness (myopia), which can usually be corrected by glasses; a squint (strabismus), where one eye or both turns inward, outward, up or down, which may be treated with patching, glasses, exercises or surgical correction.

■ Brain anomalies

Many children have a structural brain anomaly, which can be detected by MRI (magnetic resonance imaging) or a CT (computerised tomography) scan of their brain. The changes seen vary but include underdevelopment (hypoplasia) or partial/complete absence (agenesis) of the white matter connecting the two halves of the brain (corpus callosum) and the lower part of the brain pushing down into the spinal canal (Chiari I malformation) (Bostwick 2019; Morison 2023; Rouxel 2022; Timberlake 2023).

■ Seizures

Some children with *CDK13*-related disorder experience some form of seizure (a sudden and unexpected change in the electrical activity in the brain) (Hamilton 2018; Morison 2023; Rouxel 2022). Depending on the part(s) of the brain affected, symptoms vary, but include temporary confusion, uncontrollable jerking movements and loss of consciousness or awareness. Electroencephalograph (EEG) and video telemetry (video EEG) are medical tests that can be used to measure and record the electrical activity of the brain and are tools that, when used alongside other tests, can help diagnose the type of seizure experienced. Seizures can cause a lot of worry for families and can be frightening to observe, but in the majority of cases they resolve with medical treatment. If your child has a seizure for the first time, it is important to remove nearby hazards so they can't hurt themselves, and contact a medical professional.

Seizure types include:

Absence seizure: A change in behaviour as if the child 'switches off', sometimes with staring, eyelid flickering or lip smacking. Absences are very brief often lasting less than half a minute.

Generalised tonic clonic: At the onset of a seizure, the abnormal electrical activity involves both sides of the brain. The seizure involves a phase of stiffening of the body followed by jerking.

Myoclonic generalised seizure: Involving jerky or shock-like contraction of different muscles anywhere in the body but usually the arms or legs. Each myoclonic seizure lasts for a fraction of a second or a second at most.

■ Hearing

A few children with *CDK13*-related disorder have a hearing impairment, but hearing is unaffected in most children and hearing tests at birth often give a clear response (Morison 2023). A hearing loss may be conductive, where sound is unable to travel effectively to the inner ear; sensorineural, where there are problems with the inner ear, sometimes with the cochlea or auditory nerve (the nerve that sends signals to the brain about sound); or a combination of both conductive and sensorineural.

Many types of hearing loss can be managed by using hearing aids. As ear infections, which can cause hearing loss, are common in *CDK13*-related disorder, hearing should be checked regularly (Morison 2023). As children are at risk of speech and language disorders, parental concerns should be acted on early and home- or school-based therapy provided.

Some children experience “glue ear”, where fluid builds up behind the ear drum, which may be made worse by unusually narrow external ear canals and excess wax in the ear canal. Glue ear is a type of conductive hearing loss and is typically treated by inserting aeration tubes (grommets) into the eardrum. This surgical operation may need to be repeated. Improved hearing may not be achieved with aeration of the space behind the eardrum (middle ear) and hearing aids may help as a temporary or longer-lasting measure, although this appears to be uncommon.

Unique publishes a separate guide to Hearing.

■ Spine

Some babies are born with or develop a spinal curvature, either a sideways curve of the spine (scoliosis), a rounding of the upper back (kyphosis) or a combination of both (kyphoscoliosis) (Bostwick 2019; Bostwick 2017; Morison 2023). The curvature can be treated with physiotherapy and exercises, or a support brace or surgery may be needed.

A sacral dimple (dimple or hole in the skin just above the crease between the buttocks) is also sometimes seen. The dimple may be shallow so you can see the base, but stools can collect there before your child is toilet-trained, so keeping it clean and protected is important. A sacral dimple may be deep and even connect to the spinal canal or the colon. If there is any concern about this, a baby’s spine will be imaged, usually with ultrasound or an MRI scan.

■ Joint anomalies

Joint anomalies are a known feature of *CDK13*-related disorder. These include limited range of motion (joint contractures, particularly in the neck and the spine), which mean children can have a hyperextended posture (Bostwick 2019; Van den Akker 2018).

■ Skin conditions

Many children with *CDK13*-related disorder have a skin condition, notably eczema, where the skin becomes red, itchy and inflamed (Morison 2023). Your doctor should be able to recommend self-care techniques, emollients and other treatments that may help to relieve symptoms.

■ Teeth

Dental concerns are very common in children with chromosome disorders. A number of issues have been described by parents including complex dental problems and wide-spaced or peg-shaped teeth (Morison 2023). Children and adults may also benefit from specialist hospital dental services and may require treatment under general anaesthetic.

Unique publishes separate guides to Looking after your child’s teeth and Teeth: common concerns.

■ Hernias

Some babies are born with a hernia, where an organ or fatty tissue pushes through a weak spot in a surrounding muscle or tissue (Morison 2023). The most common hernia location in individuals with *CDK13*-related disorder is in the inner groin area (inguinal). In most cases surgical repair was required.

■ Palate

Many individuals with *CDK13*-related disorder have a high/arched palate (roof of the mouth). Anomalies of the palate may cause difficulties in feeding, hearing, teething and speech production.

■ Kidneys and bladders

Some babies are born with anomalies of the kidneys. Reported anomalies include an enlarged kidney(s) (hydronephrosis) due to a build-up of urine inside, being born with only one kidney, a horse-shoe kidney (where the bottom points of the two usually separate

kidneys are joined, creating a U (horseshoe) shape) and bladder cysts (Bostwick 2017; Hamilton 2018; Morison 2023; Van den Akker 2018).

■ Anomalies of the genitals

Minor anomalies of the genitals have been reported frequently in boys with *CDK13*-related disorder. Most common among these are the relocation of the hole normally at the end of the penis to the underside (hypospadias) and undescended testes (cryptorchidism) (Morison 2023). Many of these anomalies can also be seen in children without *CDK13*-related disorder and are not of major concern. If necessary, most can be corrected with surgery. Girls are much less likely to be affected. Conditions that have been reported rarely include changes to the labia.

How common is *CDK13*-related disorder?

CDK13-related disorder is extremely rare. Currently (2024) less than 100 individuals with a *CDK13* gene variant have been reported in the medical literature, although many more are known to have this diagnosis. It is also 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 (DNA) is copied in the egg and sperm that makes a new child. The biological copying method is not perfect, and random changes occur in the genetic code of all children, that are not seen in the DNA of their parents. This happens naturally and is not due to the parents' diet, environment or lifestyle. Most of these DNA changes have no obvious effect. But in rare instances these random DNA changes can lead to health issues or affect development. When such a random change disrupts the function of the *CDK13* gene then a child will have *CDK13*-related disorder. In almost all people identified so far (2024) with *CDK13*-related disorder, the genetic change was a random (or "*de novo*") change, meaning the change occurred for the first time in that family in the affected individual. Very rarely, one parent may have the same change (or variant) in some of their egg or sperm cells and pass it on to their child (this is known as germline mosaicism). However, it is important to recognize that no one should be blamed for variants in their DNA and no parent is at fault when a new DNA change occurs in their child.

Can it happen again?

The possibility of having another child affected by a rare gene disorder depends on the genetic code of the parents. In almost everyone reported with *CDK13*-related disorder so far (2024) the genetic alteration has been found to be *de novo* (dn), which means neither parent was found to have the same *CDK13* gene change as their child. Therefore, the chance of having another child with *CDK13*-related disorder is usually less than 1%.

One reason why there is some residual chance of recurrence is due to the rare phenomenon called germline mosaicism that was mentioned above. This is when a parent carries a genetic change, but it is limited to some of their egg or sperm cells. The genetic change would not, therefore, be detected in the parents' blood tests.

Unique publishes a short general guide to mosaicism that covers this phenomenon. A clinical geneticist or genetic counsellor can provide specific advice for each family about the chance of having further children with *CDK13*-related disorder.

Unique publishes separate guides to Planning your next child, Prenatal genetic testing and diagnosis, A clinical genetics appointment and Supporting siblings of children with a rare genetic condition.

Can *CDK13*-related disorder be cured?

There is no cure for *CDK13*-related disorder since the effects of the genetic change took place during a baby's formation and development. However, knowing the diagnosis means that appropriate monitoring and interventions can be put in place.

Management recommendations

Children with *CDK13*-related disorder should be under the care of a multidisciplinary team. The 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 speech therapy, physiotherapy, occupational therapy, and, if needed, behavioural therapy. Individuals may have evaluations with neurology, endocrinology, cardiology, ophthalmology, audiology, gastroenterology, urology and nephrology (Bostwick 2019; Morison 2023).

Ongoing research/Is there any research into new treatments for *CDK13*-related disorder.

The genetic change causing *CDK13*-related disorder affects development of the brain and other parts of the body before birth. Therefore, a complete cure is unlikely, even in the future, since the brain has already formed by the time a diagnosis is made. However, research into improved treatments and management for various features of *CDK13*-related disorder, like autism, is ongoing.

Families say …

"We discovered our daughter was not using her left arm at all when she was around 6 months old, after numerous referrals and appointments we discovered she had hemiplegic cerebral palsy. Her MRI at 1 years old then showed she had fronto-temporal pachygyria which was the reason for her hemiplegia. We were aware that this was a genetic disorder but didn't know which gene until she was 2. It was a relief to know it didn't come from either of us, but it was also a shock, especially hearing about some of the traits of CDK13-related disorder. Our daughter is doing amazing, she is using her left arm so much more as she has got older, she is very close to walking, we are just working on her balance and confidence at the moment. She can talk and fully understand everything and we are so proud of her and every little thing that she does."

"No one could tell us if our son would be able to walk, talk, etc. when he was a baby. The unknown was the most difficult part. With the help of early intervention (occupational therapy, physical therapy, speech language pathology) he has exceeded our expectations. He continues to meet his therapy goals and surprises us all of the time. He develops and meets milestones on his timeline and that's ok."

"I wish as a new mother I had trusted my instincts more, all the little things I noticed, didn't seem right. I felt fobbed off a lot by professionals, friends and family. Being told 'he was prem', 'he'll catch up' etc. I knew it was more, but felt like I was a neurotic mother."

"We have always given our son the opportunities that his peers and younger brother has. He has gained confidence over the years and will attempt most things, he's very aware of his own limitations and is always very cautious. He is very sociable and loves spending time with family and friends. He's very loving and tell us often he loves us, still holds our hands. He's so strong and resilient and makes us proud every single day."

Sources

The information in this booklet is drawn from the published medical literature and information from Unique members. In 2024, Unique had 14 members with *CDK13*-related disorder.

The first-named author and publication date for articles in the medical literature are given to allow you to look for the abstracts or original articles on the internet in PubMed (https://pubmed.ncbi.nlm.nih.gov/). You can obtain most articles from Unique.

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Note: an asterisk indicates articles which are “open access” and available to everyone at https://pubmed.ncbi.nlm.nih.gov

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

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Facebook group:
CDK13 – Genetic Disorder https://www.facebook.com/groups/121545531684772

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.

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