UNIQUE
UNDERSTANDING GENES & CHROMOSOMES

KMT2E-related neurodevelopmental disorder (KMT2E-NDD)

(O'Donnell-Luria-Rodan syndrome (ODLURO))

rarechromo.org

This guide is designed to help families and healthcare professionals looking after people with KMT2E-NDD. It contains information about the cause, the ways in which it can affect people and suggestions about the help and management that can benefit people with this condition.

What is KMT2E-NDD?

KMT2E-related neurodevelopmental disorder (KMT2E-NDD), also referred to as O'Donnell-Luria-Rodan Syndrome (ODLURO), is a rare genetic condition associated with developmental delay, varying degrees of learning (intellectual) disability and low muscle tone (hypotonia). As is common with genetic conditions, each person can be affected differently - even among affected members within the same family. Not everyone with KMT2E-NDD will have all the possible features and each person with a certain feature won't necessarily be affected by it to the same level as other people with that feature.

KMT2E-NDD is caused by a change (variant) in the KMT2E gene or the loss (deletion) of one copy of the KMT2E gene. The loss of the gene may occur as part of a larger deletion that affects the chromosome on which the gene is located.

Unique publishes a separate guide to deletions and microdeletions

How common is KMT2E-NDD?

KMT2E-NDD is extremely rare. Currently (2025) about 73 individuals with a KMT2E gene variant have been reported in the medical literature, but more are known to have been diagnosed (O'Donnell-Luria 2019; Conforti 2021; Li 2021; Abreu 2022; Cao 2022; Velmans 2022; Sharawat 2021; Benvenuto 2024; Catana 2022; Hashim 2023; Vecchio 2025). It is expected that more people will be diagnosed with this condition as awareness increases and genetic testing becomes more routine.

What features and symptoms do people with KMT2E-NDD have?

As is common with many genetic conditions, children and adults with KMT2E-NDD can have a range of features and symptoms. As more people are diagnosed, and information is shared, the range of features, and the likelihood of a child or adult having these features, will become clearer.

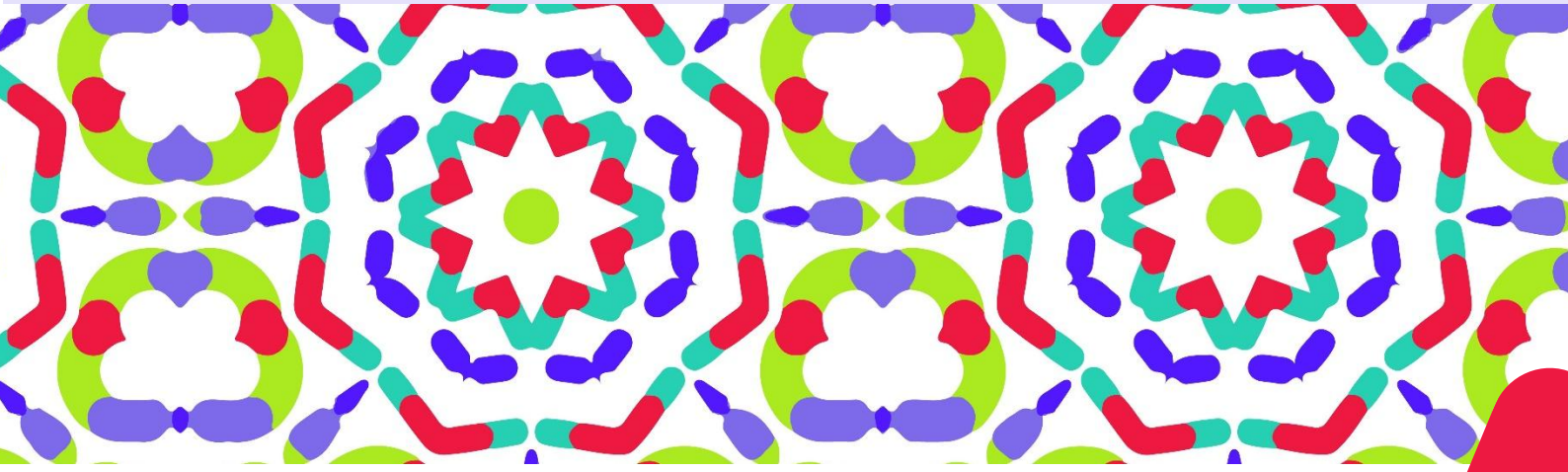
Common features

Most children with KMT2E-NDD NDDs have:

- Some degree of developmental delay,
  ranging from mild to profound (delayed sitting, crawling and walking)
- Some degree of learning (intellectual) disability (LD/ID), usually ranging from mild to moderate, or learning difficulties
- Speech and language delay
- Low muscle tone (hypotonia)
- Characteristic facial features
- Brain anomalies
- Differences in head size,
  typically a large head size (macrocephaly) but a small head size (microcephaly) has been seen with some missense variants

Other possible features include:

- Behavioural difficulties, including autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD)
- Sleep difficulties
- Seizures or epilepsy
- Constipation
- Vomiting
- Gastro-oesophageal reflux (GERD/GORD)
- Anomalies of the hands and feet



Pregnancy and birth

While most pregnancies are unremarkable and proceed without complication, occasional concerns during pregnancy have been reported. Often pregnancies go to full term, but some babies are born prematurely. A few babies have shown signs of difficulty at birth, for example difficulties with feeding, neonatal jaundice and low blood sugar (hypoglycaemia) (O'Donnell-Luria 2019).

Appearance

Certain facial features are found more often in children with KMT2E-NDD than in other children. These features may mean that you see unexpected similarities between your child and others with KMT2E-NDD. Often these features are variable and can be subtle, not every child will have them. Characteristic features in children with KMT2E-NDD are not present in every child but have included:

- An elongated head (dolichocephaly)
- Large and/or protruding forehead (frontal bossing)
- Full cheeks
- Prominent folds from the corners of the mouth to the sides of the nose (nasolabial folds)
- Swelling or puffiness around the eyes (periorbital fullness)
- Deep-set eyes
- Up- or down-slanting eyes
- Skin folds at the inner corner of the eyes (epicanthal folds)
- One or both eyes turned inward (esotropia, sometimes referred to as 'cross-eyed')
- An upturned nose (anteverted nares)
- Depressed or wide nasal bridge
- Broad or square nasal tip
- A short space between the nose and upper lip (short philtrum)
- Thin upper lip
- Outward-turned (everted) lips
- Large tongue
- Small ears

(Pais 2024; Velmans 2022; Li 2021; Abreu 2022; Benvenuto 2024; Catana 2022; Hashim 2023; Vecchio 2025).

Development

Gross and fine motor skills

Developmental delay has been reported in nearly all children with KMT2E-NDD so far (2025). 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, with some children acquiring mobility and other skills around the same age as 'typical' children and others showing more obvious delay. Children with KMT2E-NDD usually achieve independent walking, with the average age for independent walking typically between 12 to 48 months (O'Donnell-Luria 2019; Velmans 2022). Low muscle tone (hypotonia) is also common in children with KMT2E-NDD and can affect mobility (O'Donnell-Luria 2019; Velmans 2022; Li 2021; Abreu 2022; Cao 2022; Vecchio 2025). Developmental delay appears to be more severe in individuals with missense gene variants (see "Genes and chromosomes" section on page 8 to learn more) (O'Donnell-Luria 2019). Many children benefit from early intervention with treatments or therapies such as orthotics e.g. insoles, braces, splints and callipers; occupational therapy (OT); and physiotherapy (PT).

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Intellectual development and learning

Most children with KMT2E-NDD have learning (intellectual) disability or learning difficulties, usually ranging from mild to moderate, and some children have needed additional support with their learning. Early intervention can prove particularly beneficial and formal testing to assess specific, individual needs is recommended to help each child reach their full potential.

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Speech and language

It appears that all children with KMT2E-NDD experience some degree of speech and language delay, often due to difficulties in language production (Vecchio 2025). The eventual range of achievement is broad, although the majority of children with KMT2E-NDD are verbal. A few individuals with missense variants are non-verbal (O'Donnell-Luria 2019). Those who do develop speech may achieve single words, short phrases or basic sentences and some go on to develop conversational skills and a broad vocabulary. Some children with KMT2E-NDD have shown speech regression, where previously learnt vocabulary is lost (Velmans 2022; Vecchio 2025; O'Donnell-Luria 2019). Many parents say that their child can understand a lot more than they can express.

An assessment by a speech therapist should be able to identify your child's specific difficulties, allowing regular therapy sessions tailored to your child's specific areas of need. Where individuals have limited or no speech, Augmentative and Alternative Communication (AAC) methods, including pointing, pictograms, gestures, facial expression and simplified sign language and high-tech communication systems (aided communication) have enabled some to communicate their thoughts and needs well.

Unique publishes a separate guide to Communication

Feeding

Occasionally, feeding issues in the newborn period have been reported (Vecchio 2025; O'Donnell-Luria 2019). Low muscle tone (hypotonia) may contribute to difficulties with swallowing, and some babies will suck weakly and may need high energy milks to encourage weight gain. A few babies have also had 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 percutaneous endoscopic gastrostomy tube (PEG/G-tube) (Abreu 2022; Catana 2022; Vecchio 2025).

Unique publishes a separate guide to Feeding

Growth and stature

Around half of individuals with KMT2E-NDD have a larger than expected head size (macrocephaly) (O'Donnell-Luria 2019; Velmans 2022; Conforti 2021; Abreu 2022; Benvenuto 2024; Catana 2022; Hashim 2023; Vecchio 2025). Notably, the majority of individuals with missense variants have a smaller than expected head size (microcephaly) (O'Donnell 2019; Li 2021). Nearly all children with KMT2E-NDD described in the medical literature so far (2025) have height and weight within the expected range, both during infancy and beyond.

Behaviour

Children with KMT2E-NDD typically tend to have behaviour in keeping with their overall degree of developmental delay, and most have a happy disposition. Parents have often described children as warm, friendly and with a great sense of humour.

In addition, children with KMT2E-NDD can have neurobehavioral challenges. Challenging behaviours are not a reflection of a child's character but often stem from underlying difficulties with attention, anxiety or sensory processing. Around one third of children with KMT2E-NDD have an autism spectrum disorder (ASD) diagnosis or traits (O'Donnell-Luria 2019; Velmans 2022; Vecchio 2025). Other behaviours that have been reported include attention deficit hyperactivity disorder (ADHD), repetitive movements (stereotypies), self-injurious behaviour, aggressive behaviour, difficulties regulating emotions, sensory processing difficulties, anxiety and depressive symptoms (Pais 2024; O'Donnell-Luria 2019; Velmans 2022; Vecchio 2025; Conforti 2021; Benvenuto 2024; Cai 2025; Catana 2022). Some also have sleep disturbances (Velmans 2022).

Management strategies should focus on addressing the root causes of challenging behaviours - such as providing sensory supports, using strategies to manage anxiety, and creating structured environments to help with attention - while nurturing the child's inherently friendly and sociable personality. Efforts to take into account and introduce strategies to tackle communication and other difficulties can also be beneficial.

Unique publishes separate guides to Challenging Behaviour and Sleep

Puberty

There is limited information available about puberty in children with KMT2E-NDD. Some families of children with chromosome disorders and behavioural difficulties or learning (intellectual) disability 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

Adulthood

Experiences of adulthood are likely to vary considerably and will depend on many factors. These include the level of any learning (intellectual) disability, possible on-going medical concerns and improvements in early intervention and therapies/treatments. There is little known about adults with KMT2E-NDD. We know of one family where the father, at the time in his fifties, had two children, both with KMT2E-NDD, who were 24 and 19 years of age (Conforti 2021). Many adults with learning disability have not received in-depth genetics testing, so it is likely that there are more adults with KMT2E-NDD that have not yet been recognised.

Medical concerns

The following medical concerns have been found in children with KMT2E-NDD. They are not found in all children so not all children with KMT2E-NDD will be affected.

Brain

Some children with KMT2E-NDD 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 have included:

- Underdevelopment (hypoplasia) or partial/complete absence (agenesis) of the white matter connecting the two halves of the brain (corpus callosum)
- Enlarged fluid-filled cavities (ventricles) in the brain (ventriculomegaly)
- Reduction in size (atrophy) or hypoplasia of the cerebellum (an area at the back of the brain that controls movement and balance)
- Fluid-filled sacs in the brain (cysts)
- Delayed myelination (myelin surrounds brain cells (neurones) to allow speeded up signalling through the brain) or other changes to the brain's white matter
- Incomplete inversion of/underrotated hippocampus (an area of the brain involved in memory formation)
- Changes to the folding pattern of the brain (dysgyria)

(Pais 2024; Velmans 2022; Vecchio 2025; Conforti 2021; Li 2021; Abreu 2022; Cao 2022; Benvenuto 2024; Cai 2025; O'Donnell-Luria 2019).

Seizures

Around one third of people with KMT2E-NDD experience some form of seizure (a sudden and unexpected change in the electrical activity in the brain). All reported children with missense variants have epilepsy (Pais 2024; O'Donnell-Luria 2019; Li 2021). Epilepsy appears to be more common in females compared to males with KMT2E-NDD. Depending on the part(s) of the brain affected, symptoms vary, but include temporary confusion, uncontrollable jerking movements and loss of consciousness or awareness. Age of onset can vary considerably, while seizures may be isolated to a single incident or occur more regularly. More than one type of seizure may be present in the same individual*. 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 some cases they self-resolve or resolve with medical treatment. Some individuals have shown improvements following use of anti-epileptic drugs (Conforti 2021). Anti-epileptics that have been used include valproic acid, levetiracetam, clonazepam, oxcarbazepine and topiramate. These anti-epileptic drugs do not always stop seizures, but they may reduce their frequency (Li 2021). Several individuals with KMT2E-NDD have developed treatment-resistant epilepsy (Conforti 2021; Li 2021). 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 reported in people with KMT2E-NDD include:

Focal seizures This type of seizure begins in one side of the brain and was previously called partial seizures. Focal onset seizures are the most common type of seizures experienced by people with epilepsy.

Febrile seizure Episodes only occur when the child has a high temperature.

Infantile spasm Type of seizure usually occurring in clusters in babies between 3-10 months. Seen most often when a baby wakes and may be obvious or subtle.

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 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.

Myotonic Seizure involving stiffening of the muscles.

Myoclonic-atonic Seizure involving jerky or shock-like contraction of muscles, followed by a loss of tone so someone standing up falls to the ground.

Convulsive status epilepticus This is when generalised tonic-clonic (convulsive) seizures last more than 5 minutes or when seizures occur very close together and the person doesn't recover consciousness between them.

Gastrointestinal System

Gastrointestinal issues are relatively common in individuals with KMT2E-NDD, and constipation is the most commonly reported (Pais 2024; O'Donnell-Luria 2019; Velmans 2022; Vecchio 2025). Constipation can be related to low muscle tone, low activity/exercise, a low-bulk diet and small fluid intake, among other reasons that are not fully understood. It is important that possible causes are discussed with a health visitor or doctor, who may recommend adapting diet or giving stool softeners or laxatives. Some children have benefitted from enemas when symptoms were particularly severe. Other gastrointestinal symptoms have included gastro-oesophageal reflux and chronic vomiting.

ERIC is a children's bladder and bowel charity providing trusted resources and support

Hands and feet

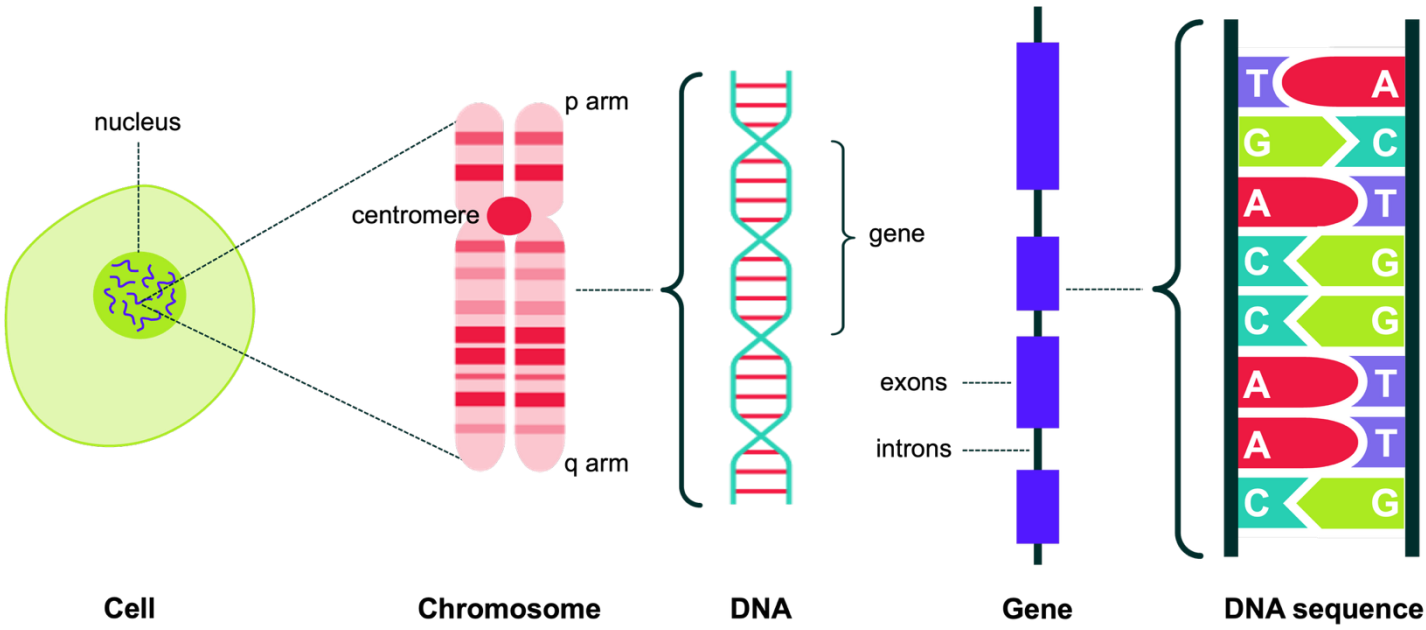
Children with KMT2E-NDD rarely have anomalies of the hands and feet. The only features reported so far (2025) being fingers or toes that curve inwards (clinodactyly) and club foot (talipes). Some children are only mildly affected, and any condition will not require treatment. Others may benefit from massages, orthotics and physiotherapy.

This section includes some more complicated scientific terms and concepts - don't worry if it's a lot to take in, you can always come back to this section later if you want to.

Genes and chromosomes

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. In people with genetic conditions, one or more of their genes don't instruct the body as expected, which can lead to changes in how their body works.

DNA is made up of building blocks called 'bases' or 'nucleotides'. There are four DNA bases which can be abbreviated to the letters A, C, G, and T. These DNA bases are paired up in the DNA structure into 'base-pairs'. The full sequence of our DNA is over three billion base-pairs long. There are changes in the DNA sequence (variants) present in everyone's genes. It is variants in our genes that make each one of us unique individuals.



What causes KMT2E-NDD?

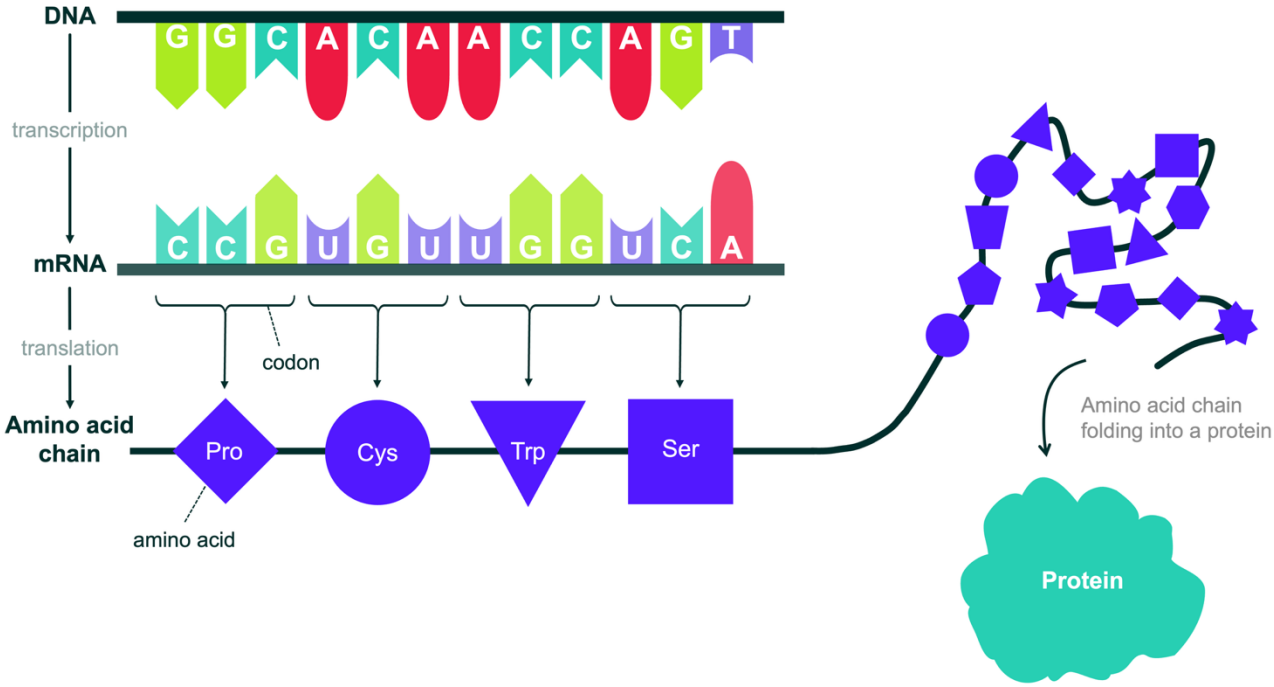
KMT2E-NDD is caused by specific changes (known as pathogenic variants) to the DNA sequence of the KMT2E gene (KMT2E is an abbreviation of the gene's full name, Lysine-specific methyltransferase 2E (also previously known as myeloid/lymphoid or mixed-lineage leukaemia 5 (MLL5)). KMT2E-NDD can also be caused by the loss of KMT2E due to a chromosome deletion. The KMT2E gene is located in the long 'q' arm of chromosome 7 in a region called 7q22.3, as shown in the image on the next page.

Chromosome 7

We have two copies of chromosome 7 in our cells, so we also have two copies of the KMT2E gene. KMT2E-NDD occurs when only one copy of the KMT2E 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

Most genetic conditions are caused by changes to genes that provide instructions for making proteins; these are called protein-coding genes. KMT2E is one of thousands of these protein-coding genes. Proteins are molecules that are made up of long chains of chemicals called amino acids and play critical roles in the body. This is because proteins are essential for lots of processes such as breaking down food, moving our muscles, and growing the body's organs and making sure they function properly. To make these amino acids a copy of the DNA sequence is created, called messenger RNA (mRNA). mRNA uses the same A, C and G bases as DNA, but the 'T' bases are swapped to 'U' bases. Within a gene, each three-letter sequence (codon) of mRNA bases provides the instructions for one amino acid.



The majority of variants that have been identified in the KMT2E gene result in production of no protein or a small amount of a shorter (truncated) protein. These are named 'loss of function (LOF) truncating variants'. LOF variants are thought to be responsible for KMT2E-NDD. A small number of individuals with deletions involving the entire KMT2E gene have also been reported in the medical literature and have a similar presentation to those with LOF variants.

Types of LOF variants that have been seen in individuals with KMT2E-NDD:

- **Nonsense variants:** The amino acid change, caused by the DNA base change, results in a 'STOP' signal. This stops protein production too early, leading to a shorter, unfinished protein.
- **Frameshift variants:** The DNA coding sequence is shifted by the addition or deletion of an individual DNA base. This means the incorrect amino acid sequence is used to produce the protein or protein production is stopped too early.
- **Deletions:** One entire copy of the gene or a large part of the gene is missing.

Other types of variants seen in individuals with KMT2E-NDD:

- **Missense:** One amino acid is replaced by another. This alters the structure of the KMT2E protein, which may affect its function. These missense variants are thought to have a different effect on the protein, not LOF, because they result in a distinctly different group of clinical features to the LOF variants and deletions. Typically, individuals with missense variants have more severe features.

The role of the KMT2E protein?

The KMT2E gene sequence is used to make the inactive histone-lysine N-methyltransferase 2E (KMT2E) protein. The exact function of the KMT2E protein isn't fully understood but it is thought to interact with another class of proteins (called histones) that DNA wraps around so that it can fit inside the body's cells. These interactions can 'tell' the DNA to be more 'open' (be less tightly wound up around histones) or more 'closed' (be more tightly wound up around histones) in certain places along the DNA sequence. Opening and closing the DNA sequence in this way affects the expression of other genes, and therefore the production of other proteins. It is the resulting effect on these other proteins in the body that is thought to cause the features of KMT2E-NDD.

Genetic Tests

KMT2E-NDD can be identified by a type of genetic test called sequencing (e.g. whole exome sequencing (WES) or whole genome sequencing (WGS)). Gene deletions can also be identified by a sequencing test but are more commonly found using a different type of genetic test called a chromosome microarray (CMA, e.g., array CGH or SNP array).

Unique publishes separate guides to DNA sequencing, arrayCGH and SNParrays

Genetic Test Results

The results of genetic (genomic) testing are likely to be given to you by your geneticist, a genetic counsellor or the clinician who ordered the test. Depending on the test that was carried out, someone with KMT2E-NDD might have results that look like one of these examples:

An example result of a DNA sequencing test (e.g., WES or WGS), that can identify gene variants, is shown here for the KMT2E gene:

p.Glu703* (E703Ter): c.2107 G>T in exon 17 of the *KMT2E* gene (NM_182931.2)

p.Glu703* (E703Ter)	signifies the change to the protein: the amino acid glutamine (Glu (E)) has been replaced by a stop signal (* or Ter) at position 703 in the sequence of amino acids that make up the protein – this is a type of nonsense variant
G>T	signifies the gene sequence change: the G nucleotide has been replaced by a T nucleotide

c.2107	signifies the base pair position of the change within the gene sequence (the position where the G nucleotide has been replaced by the T nucleotide)
exon 17	signifies which part of the gene has been altered, in this case exon 17
KMT2E gene	signifies the gene that is affected
NM_182931.2	this is the specific 'reference transcript sequence' or blueprint of the gene that scientists use to identify the location of the variant

The result of a CMA test (e.g., arrayCGH or a SNParray), that can identify deletions and duplications, is shown here for a deletion affecting the KMT2E gene:

arr[hg19] 7q22.3 (104,696,686_105,407,628)x1 dn

arr	the analysis was by array (arr) comparative genomic hybridisation (cgh)
hg19	Human Genome build 19. This is the reference DNA sequence that the base pair numbers refer to. As more information about the human genome is found, new 'builds' of the genome are made, and the base pair numbers may be adjusted. This means base pair positions change depending on the assembly used
7q22.3	the chromosome involved is chromosome 7 and the position of the deletion is in band q22.3 (said as queue two two point three)
104,696,686-105,407,628	the base pairs between 104,696,686 and 105,407,628 have been deleted. Subtract the first long number from the second and you get 710,942 (0.711Mb or 711kb). This is the number of base pairs that are deleted
x1	means there is one copy of these base pairs, not two - as you would normally expect one on each chromosome 7, so this is a deletion
dn	means *de novo*. The biological parents' chromosomes have been checked and no deletion or other chromosome change has been found at position 7q22.3. The deletion is very unlikely to be inherited and has almost certainly occurred for the first time in this family with this child mat here would mean that the deletion has been inherited from the biological mother pat here would mean that it has been inherited from the biological father

Unique publishes a separate guide to Interpreting Genetic Test Results

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. 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.

When such a random change disrupts the function of the KMT2E gene, then a child will have KMT2E-NDD. In most people identified so far (2025) with KMT2E-NDD, 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. Rarely, KMT2E variants are inherited from an affected parent (typically the parent has mild features/ID/LD) or one parent may have a chromosomal rearrangement that led to the deletion of the KMT2E gene in their child. 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).

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 KMT2E-NDD so far (2025), the genetic alteration has been found to be *de novo* (dn), which means neither parent was found to have the same KMT2E gene change as their child, and neither parent was found to have a chromosomal rearrangement that might have resulted in a KMT2E deletion in their child. Therefore, the chance of having another child with KMT2E-NDD 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

In families where the KMT2E variant has been inherited from a parent, the possibility of having another child - either a girl or a boy - with KMT2E-NDD rises to 50% (I in 2) in each pregnancy. However, the effect on the child's development, health and behaviour cannot be reliably predicted as for many conditions, individuals even within a family can have wide variability in how severely a genetic condition presents. Your genetics centre should be able to offer counselling before you have another pregnancy.

If your child with a KMT2E variant goes on to have children of their own, the chances of passing on the variant to their child are 50% in each pregnancy. Your child's ability to look after their own child is very likely to be closely related to their own learning ability and behaviour.

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 KMT2E-NDD be cured?

There is currently no cure for KMT2E-NDD since most of 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

No clinical practice guidelines for KMT2E-NDD have been published (2025). The following suggestions have been provided by clinicians, who have personal experience of managing/treating individuals with KMT2E-NDD, to improve quality of life and reduce complications.

Children and adults with KMT2E-NDD are likely to be under the care of a multidisciplinary team. The team should include a geneticist and paediatrician (for children) 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. Often other evaluations and specialists are required depending on the features observed.

Immediately following diagnosis

When not carried out as part of the diagnostic process, an evaluation of the features of KMT2E-NDD that are present in the child or adult who has been diagnosed with this genetic condition is recommended. This can determine which of the features of KMT2E-NDD are present and how severe they are.

The following assessments are recommended:

- A physical examination to look for macro- or microcephaly, and establish whether gross and fine motor skills and mobility are affected.
- A neurologic or developmental assessment to determine whether conditions such as learning (intellectual) disability are present. Brain magnetic resonance imaging (MRI), a technique that can be used to visualise the brain, should be carried out to see if there are any structural changes to the brain, and to investigate seizures, if reported. If seizures are present an electroencephalograph (EEG) should be performed.
- A neuropsychiatric assessment to investigate any behavioural concerns.
- A gastrointestinal assessment for signs of reduced bowel motility, constipation, gastro-oesophageal reflux or recurrent vomiting.
- Genetic counselling for affected individuals and their families.

Supportive care

How a person with KMT2E-NDD is supported may require co-ordinated care by a team of specialists, which may include a:

Paediatrician – a doctor who specialises in the physical, mental and social health of children from birth to young adulthood.

Neurologist – a doctor who specialises in conditions of the brain, spinal cord and nervous system.

Gastroenterologists – a doctor who deals with conditions of the stomach and intestines.

Surgeon – a doctor who is specially trained to perform medical operations.

Occupational therapist (OT) – a health care professional who uses activities to aid self-management of a condition and can provide equipment.

Physiotherapist (PT) – a health care professional who uses exercise, movement, manual therapy, education and advice to help with the body's strength and mobility.

Speech and language therapist (SALT) – a health care professional who helps with speech, language communication and sometimes feeding/swallowing difficulties.

Psychiatrist – a doctor who specialises in mental health.

Specialist nurses and/or other healthcare professionals may need to systematically and comprehensively plan a child or adult's treatment.

Treatments and therapies

Early intervention can prove particularly beneficial and formal testing to assess specific, individual needs is recommended. An education, health and care plan (EHCP) in the UK, individualized education plan (IEP) in the US, or equivalent document in other countries, may be issued after a child has undergone an assessment, to help ensure that the educational, health and social provisions deemed necessary to support the child's needs are delivered.

Treatment will depend on the specific features and symptoms experienced by the person with KMT2E-NDD but may include:

Physiotherapy for low muscle tone (hypotonia) and gross motor delays, which usually includes exercises to build core strength, improve balance and enhance coordination to help children achieve motor milestones like sitting, crawling, and walking, and to improve overall mobility.

Occupational therapy for fine motor skill delays and sensory sensitivities, which can include activities to improve hand strength and coordination for daily tasks (e.g., feeding and dressing) and sensory integration therapy to help individuals better process and respond to sensory information from their environment.

Speech therapy for speech and language impairments, which can include regular sessions focusing on Augmentative and Alternative Communication (AAC) methods (e.g., sign language, picture exchange systems and high-tech communication devices) to provide a functional means of communication for individuals who are non-verbal or have very limited speech.

Behavioural therapy for features of autism, ADHD, and anxiety, which can include structured therapies like Applied Behaviour Analysis (ABA) for/to help manage challenging behaviours, improve social skills, and develop coping strategies.

Medications may be prescribed for management of features such as epilepsy, sleeping difficulties and constipation.

Diet, such as a high-fibre diet or stool softeners and/or laxatives may be recommended to help relieve constipation. Some benefit from enemas when symptoms are particularly severe. In addition, a ketogenic diet has been suggested to benefit two individuals with epilepsy (Pais 2024), but more evidence is needed to support this.

Surgery such as the placement of a gastrostomy tube (G-tube) for severe, long-term feeding difficulties.

Surveillance

It is recommended that the following evaluations are carried out/considered to monitor an individual's existing symptoms, how they respond to care and treatment, and whether any new symptoms emerge over time:

- Monitor for growth and adequate nutritional intake
- Neuropsychiatric and learning assessments every few years to optimise the EHCP/IEP
- Consider a neurologic review (including MRI and EEG, if indicated by seizures)
- Consider a musculoskeletal review, such as occupational and/or physical therapy to continue to assess mobility needs
- Assessment for constipation and chronic vomiting and treatment as directed by the primary care provider or gastroenterologist
- Consider need for a sleep study
- Assessment of the need for social support, such as respite care and home nursing care, or genetic counselling and family planning advice

Research into new treatments for KMT2E-NDD

The discovery of KMT2E-NDD is still relatively recent with the first publication in 2019. The genetic changes that can cause KMT2E-NDD affect 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 KMT2E-NDD, like autism and epilepsy, is ongoing. Future research aims to link the effect of KMT2E gene variants on the KMT2E protein to the specific clinical features seen in people with KMT2E-NDD. In addition, although KMT2E-NDD is a relatively rare condition, there is ongoing research into the role of the KMT2E gene in the cell.

Details of clinical trials related to a particular condition or gene can be found at **ClinicalTrials.gov** and **EU Clinical Trials Register**.

Families say ...

"My son is kind and helpful. He doesn't have a diagnosis of ASD or ADHD, but he does have a lot of traits of both. He likes routine and has sensory issues - he finds smells very strong and is sensitive to them. He suffers from anxiety and can find his temper and emotions hard to control, and finds getting to sleep and staying asleep difficult. He has moderate learning disability, has problems with his joints and suffers pain as a result, and experiences tonic-clonic seizures. He shows care to others and has a happy, funny personality. He definitely keeps me on my toes!"

Sources

The information in this booklet is drawn from the published medical literature and information from Unique members. In 2025, Unique had 9 members with KMT2E-NDD. 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 (**pubmed.ncbi.nlm.nih.gov/**).

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

Inform Network Support

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Simons Searchlight KMT2E Gene Guide

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