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UNDERSTANDING GENES & CHROMOSOMES

RAC1-related neurodevelopmental disorders

rarechromo.org

This guide is designed to help families and healthcare professionals looking after people with RAC1-related neurodevelopmental disorders. 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 are RAC1-related neurodevelopmental disorders?

RAC1-related neurodevelopmental disorders (RAC1-NDDs) are a group of rare genetic conditions that result in developmental delay, varying degrees of learning (intellectual) disability, behavioural difficulties, low muscle tone (hypotonia) and differences in head size. As is common with genetic conditions, each person can be affected differently - even among affected members within the same family. Not everyone with RAC1-NDDs 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.

How common are RAC1-NDDs?

RAC1-NDDs are an extremely rare condition. Currently (2025) about 20 individuals with a RAC1 gene variant have been reported in the medical literature, but more individuals worldwide are known to have been diagnosed with a RAC1 variant. It is expected that there will be an increasing number of people diagnosed with this condition as awareness increases and genetic testing becomes more routine.

What features and symptoms do people with RAC1-NDDs have?

As is common with many genetic conditions, children and adults with RAC1-NDDs 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.

Since the number of individuals identified with RAC1-NDDs is relatively low (2025), many symptoms are unique to individual people. This is not an exhaustive list and there are likely to be additional features that have not yet been reported.

Common features

Most children with RAC1 NDDs have:

- Some degree of developmental delay,
  ranging from mild to severe (delayed sitting, crawling, walking and speaking)
- Some degree of intellectual disability (ID) or learning difficulties (LD),
  ranging from moderate to severe
- Speech and language delay,
  some individuals are non-verbal or minimally verbal
- Behavioural difficulties,
  including autism spectrum disorder (ASD) or autistic traits, attention deficit hyperactivity disorder (ADHD), and anxiety
- Differences in head size,
  from small head size (microcephaly) to large head size (macrocephaly)
- Brain anomalies
- Low muscle tone (hypotonia)

Other possible features include:

- Sleep difficulties
- Feeding difficulties
- Constipation
- Loose (hypermobile) joints
- Frequent respiratory and ear infections
- Characteristic facial features
- Skin conditions, such as eczema
- Vision and hearing impairments, from mild to profound
- Skeletal anomaly, such as spinal curvature
- Seizures or epilepsy
- Congenital heart anomalies
- Anomalies of the kidneys and genitals (urogenital anomalies)
- Anomalies of the hands and feet
- Repetitive (stereotypic) movements
- Difficulties with co-ordination, balance and speech (ataxia)
- Gastro-oesophageal reflux (GERD/GORD)

Pregnancy and birth

While most pregnancies are unremarkable and proceed without complication, occasional concerns during pregnancy have been reported. Where a cause for concern was noted, most often parents reported slow growth in the womb (intrauterine growth restriction (IUGR)). Occasionally during pregnancy some features of RAC1-NDDs can be identified following mid-pregnancy scans, such as anomalies in development of the food pipe (oesophagus), windpipe (trachea), brain and heart.

Often pregnancies go to full term, but some babies are born prematurely. Some babies show signs of difficulty at birth, for example difficulties with feeding or a heart condition(s).

Appearance

Certain facial features are found more often in children with RAC1-NDDs than in other children. These features may mean that you see unexpected similarities between your child and others with RAC1-NDDs. Characteristic features in children with RAC1-NDDs have included:

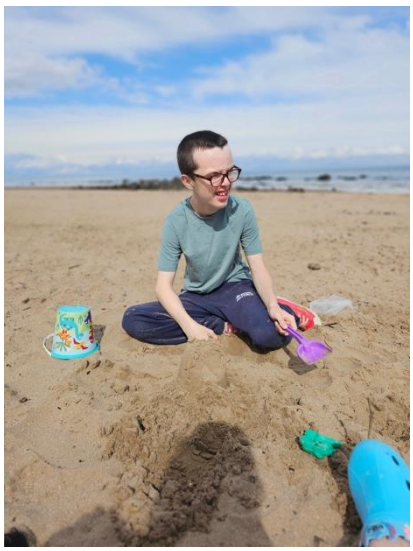
- Eye anomalies, such as wide-set or down-slanting eyes (wave-shaped palpebral fissures), skin folds at the inner corner of the eye (epicanthal folds) and different-sized pupils (anisocoria)
- Mouth and jaw anomalies, including a wide mouth, a mouth that is held open, a protruding or receding jaw (retrognathia) or an underdeveloped (micrognathia) lower jaw, cleft lip and widely-spaced teeth
- Other possible features include prominent/wide nasal bridge, a broad forehead, a high hairline, arched eyebrows, low-set or unusually-shaped ears (dysplastic ears), a longer or shorter distance between the nose and upper lip (philtrum), a short tip of the nose and overhanging nasal septum (columella)

(Reijnders 2017; Haugh 2021; Banka 2022; Priolo 2023; Nishikawa 2025; Althebaiti personal communication)

Development

Gross and fine motor skills

Developmental delay has been reported in all children with RAC1-NDDs so far (2025). The degree of delay ranges from mild to severe. Developmental 'milestones', including rolling, crawling, 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.



Low muscle tone (hypotonia) and/or loose (hypermobile) joints are common and may affect mobility (Reijnders 2017; Banka 2022; Priolo 2023). Some children may have balance and co-ordination issues (known as ataxia) (Banka 2022), and this can result in frequent falls. For some, independent walking may not be achieved. 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). Some children with RAC1-NDDs show repetitive (stereotypic) movements (Reijnders 2017; Banka 2022).

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"Our son has always had low muscle tone. He has weak core strength. This was one of the first concerns raised regarding his development. The health visitor raised concerns regarding neck strength at 16 weeks old, core strength at around 9 months old (unable to sit), and strength in his legs at around 11 months old – this is when he was referred to physio. He was unable to weight bear until he was 20 months old."

"He has been described to have a 'clumsy gait'. He walks up stairs two feet per step rather than alternating. He walks with a stagger / off balance. He has slow speech. He first started walking at around 2 years 3 months."

"Professionals have described him to have a significant weakness down the left side of his body which affects him daily with walking up stairs / running / walking etc.."

"Our son sometimes experiences pains in his legs / muscles, and has had two episodes where he has had shooting pains down the left side of his body."

"He still struggles with buttons / zips etc."

Intellectual development and learning

The majority of children with RAC1-NDDs have intellectual disability (ID) or learning difficulties (Reijnders 2017; Haugh 2021; Banka 2022; Priolo 2023; Seyama 2023; Nishikawa 2025; Upadia 2025). ID ranges from mild to severe and many children have needed additional support with their learning. Early intervention can prove particularly beneficial and formal testing to assess specific individual needs is recommended.

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Speech and language

Children with RAC1-NDDs typically experience some degree of speech and language delay and some may find it difficult to co-ordinate movement of their lips, jaw and tongue to make the right sounds (apraxia of speech). The eventual range of achievement is broad, but a few may remain non-verbal (Reijnders 2017; Upadia 2025). 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. 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 no speech or very few words, 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

"Our son had around 6-10 words prior to starting school. He has a speech delay. He can talk and use full sentences but still struggles with pronunciation. He talks slowly, often loudly (and struggles to whisper)."

"Didn't speak till 5 years old. Has echolalia. Limited speech, can't have conversations."

Feeding

Feeding issues in the newborn period are common (Reijnders 2017; Banka 2022; Priolo 2023). 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. Some babies also suffer from gastro-oesophageal reflux (GERD/GORD) (in which feeds return readily up the food passage) (Banka 2022), 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). A cleft palate or lip can also cause feeding issues (see "Palate" section on page 11). 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.

Unique publishes a separate guide to Feeding

"From birth he only tolerated breastfeeding, weaning delayed due to him not being ready. At 11 months old started weaning but could only tolerate purée/liquid until 2.5 years old. Ongoing issues with food intake"

"Our son doesn't have any eating difficulties now but until he was around age 6 he used to gag / choke on food. We would always avoid foods such as bread / cake to support."

Growth and stature

Many children with RAC1-NDDs described in the medical literature so far (2025) have growth within the expected range, with some children noted as having short stature and a few with a tall stature. Children with RAC1-NNDs can also have larger (macrocephaly) or smaller (microcephaly) than expected head size, or head size can be within the expected range (Reijnders 2017; Banka 2022; Nishikawa 2025; Upadia 2025). Research has shown that variation in head size can often be linked to the location of the RAC1 gene variant, with macrocephaly linked to variants causing an amino acid change at position 51 and microcephaly linked to dominant negative variants at a range of locations in the gene (see "Genes and chromosomes" section on page 12 to learn more). Beyond infancy, height and weight can be variable.

Noticed his head growing fast due to hats no longer fitting after 2 weeks, also very floppy"

Behaviour

Children with RAC1-NDDs typically tend to have behaviour in keeping with their overall degree of developmental delay, and most have a happy disposition. Some children have sleep disturbances, an autism spectrum disorder (ASD) or attention deficit hyperactivity disorder (ADHD) diagnosis or traits (Reijnders 2017; Banka 2022). Other behaviours, including anxiety, eating disorders, hypersociability and difficulties regulating emotions have also been reported (Banka 2022; Priolo 2023; Althebaiti personal communication). Understanding this complex profile is key to providing effective support. 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

Very happy nature. Can sometimes be 'difficult' and show attention seeking behaviours."

"He still has disturbed nights. He wakes regularly throughout the night."

"Sleep disorder, parasomnia, seizures in sleep"

"Only since he started puberty he will push, hit when he doesn't want something or is moved somewhere else."

Puberty

There is limited information available about puberty in children with RAC1-NDDs. Some families of children with chromosome disorders and behavioural or 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

Adulthood

Experiences of adulthood are likely to vary considerably and will depend on many factors. These include the level of any LD/ID, possible on-going medical concerns and improvements in early intervention and therapies/treatments.

Nearly all individuals with RAC1-NDDs described in the medical literature so far (2025) are children at or below 15 years, so it is difficult to know how children with RAC1-NDD will progress into adulthood. One woman was reported to have less pronounced facial features as a 27-year-old than as a 15-year-old (Priolo 2023).

Unique publishes a separate guide to Transition

Medical concerns

The following medical concerns have been found in children with RAC1-NDDs. They are not found in all children so not all children with RAC1-NDDs will be affected.

Brain

Most 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)
- A build-up of fluid within the brain (hydrocephaly)
- Enlarged fluid-filled cavities (ventricles) in the brain (ventriculomegaly)
- Reduction in brain volume (atrophy) or hypoplasia of the frontal cortex
- Chiari I malformation (where the lower part of the brain pushes down into the spinal canal)
- Dandy-Walker malformation (where an area at the back of the brain (cerebellum) that controls movement and balance does not develop properly)
- Excessive small folds in the brain (polymicrogyria)
- Fluid-filled sacs in the brain (cysts)
- Delayed myelination (myelin surrounds brain cells (neurones) to allow for speeded up signalling through the brain)
- White matter anomalies

(Reijnders 2017; Haugh 2021; Banka 2022; Priolo 2023; Nishikawa 2025; Althebaiti personal communication).

Seizures

Several children with RAC1-NDDs experience some form of seizure (a sudden and unexpected change in the electrical activity in the brain). 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. After assessment, three out of sixteen individuals with RAC1-NDDs were reported to have epilepsy (Reijnders 2017; Banka 2022; Priolo 2023; Haugh 2021; Upadia 2025). 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 many cases they self-resolve or can be reduced 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.

*To date (2025), seizure types reported in people with RAC1-NDDs include:

Absence seizures: 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.

Myotonic seizures: Seizure involving stiffening of the muscles.

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.

Generalised tonic-clonic seizures: 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 of the body.

Heart

A heart condition(s) has been found in many people reported so far with RAC1-NDDs, which can be present at birth (congenital) or develop later in life. 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. These can include:

- A hole between the top two chambers of the heart (atrial septal defect (ASD)) or a hole between the bottom two chambers of the heart (ventricular septal defect (VSD))
- Narrowing of the vessel carrying blood from the heart to the lungs (pulmonary stenosis)
- Failure of closure of the tube that carries blood between the aorta and the pulmonary artery during the foetal period (persistent ductus arteriosus (PDA))
- Failure of a small opening in the heart to close after birth (patent foramen ovale (PFO))
- A change in or insufficiency of one or more of the heart valves, for example a bicuspid aortic valve where there are only two 'flaps' rather than three
- Non-synchronous contractions
- Other structural changes that may impact blood flow and heart function (cardiac malformations)

(Reijnders 2017; Banka 2022; Priolo 2023; Seyama 2023; Nishikawa 2025).

Some of these conditions are relatively minor and resolve naturally in time. Medical treatment may be necessary for others, and some may require surgery.

Our son was diagnosed with an enlarged ascending aorta. He has started taking Losartan Potassium once daily and is under review with the Cardiologist."

Hearing or vision impairments

A few children have a hearing impairment, but hearing is unaffected in most children and hearing tests at birth often give a clear response. 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 hearing loss (Reijnders 2017; Banka 2022; Priolo 2023). Hearing impairments in children with RAC1-NDDs can range from mild to profound and can affect one (unilateral) or both (bilateral) ears. Hearing aids can be used for management of hearing loss. As children are at risk of speech delay, parental concerns should be acted on early and home- or school-based therapy provided.

A few children experience ‘glue ear’ (recurrent middle ear effusions), where fluid builds up behind the eardrum, which may be made worse by unusually narrow external ear canals and excess wax in the ear canal (Banka 2022). Glue ear is a type of conductive hearing loss and is typically treated by inserting aeration tubes (grommets, also known as pressure equalisation or myringotomy tubes) into the eardrum. This surgical operation may need to be repeated. A few children have recurrent ear infections (for example, chronic otitis media), which can also often be treated with aeration tubes (Reijnders 2017; Banka 2022; Upadia 2025). 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.

Unique publishes a separate guide to Hearing

Hearing tests have been difficult. They vary from borderline hearing to moderate loss. Several grommet operations to help hearing but still unsure of his actual hearing loss."

Some children have visual impairments, such as short- (myopia) or long- (hypermetropia/hyperopia) sightedness, or irregular curves (astigmatisms) in their lens or front surface of the eye (cornea) and require glasses to see (Priolo 2023; Upadia 2025). A few babies have clouded lenses at or soon after birth (congenital cataracts) which should be treated early to prevent potential vision loss (Banka 2022; Haugh 2021).

Clear crystalline lens, astigmatism, visual processing disorder and pupil anisocoria."

Hands and feet

Children with RAC1-NDDs occasionally have anomalies of the hands and feet. Among these are:

- Small hands and feet
- Additional creases in the hands (simian crease)
- Fingers or toes that curve inwards (clinodactyly), are unusually short (brachydactyly) or fused (syndactyly)
- Additional fingers or toes (polydactyly)
- Broad fingertips (foetal finger pads)
- Long, slender fingers (spider fingers/arachnodactyly)
- Underdeveloped (hypoplastic) bones/nails
- Flat feet (pes planus)

Some children are only mildly affected, and any condition will not require treatment. Others may benefit from massages, orthotics and physiotherapy. Treatment is tailored to the individual child, and in some cases surgical correction will best enhance eventual mobility.

Curled under toes. Over the last few years, I have been concerned about the movement inability in our son's toes. If we ask him to wiggle his toes or move them, he tries but nothing happens. He is able to move his foot up and down. We involved physiotherapy but the physio said that they think it's neurological. He doesn't experience pain in his toes or feet, just the lack of movement in his toes. The neurologist hasn't said what they think this could be."

Skeletal

Occasionally babies are born with or develop a spinal curvature, either a sideways curve of the spine (scoliosis), a rounding of the upper back (kyphosis), a combination of kyphosis and scoliosis (kyphoscoliosis) or excessive rounding of the lower spine (lumbar hyperlordosis) (Banka 2022; Seyama 2023; Priolo 2023). The curvature can be treated with physiotherapy and exercises, or a support brace or surgery may be needed. A sunken breastbone (pectus excavatum) has been observed in children with RAC1-NDDs. Klippel-Feil syndrome, where two or more vertebrae in the spine have fused together, often resulting in a short neck with limited movement, has also been seen in children with a RAC1-NDD (Banka 2022).

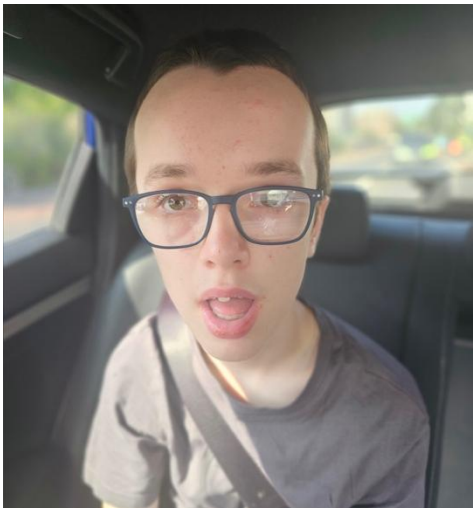
Joints

Joint anomalies can occur in children with RAC1-NDDs. These include extremely loose (hyper-mobile) joints (elbows, wrists, knees, hips), which mean babies and children can move their limbs into positions others find impossible. While this may cause no problems, hyper-mobility is sometimes associated with pain and stiffness in the joints and muscles, joints that dislocate (come out of position) easily, and injuries including sprains. Children with very loose joints may need physiotherapy, massage or additional braces (supports, splints) before they are able to walk. Some children have a degree of hip dysplasia, in which the hip joints are easily dislocated (Unique member). This may be apparent at birth or develop later. In either case it is treated with splinting and, if necessary, immobilisation in plaster and possibly surgery.

Skin

Several children with RAC1-NDDs have a skin condition(s), such as eczema, where the skin becomes red, itchy and inflamed. Your doctor should be able to recommend self-care techniques, emollients and other treatments that may help to relieve symptoms. Other skin conditions that have been reported include small areas of skin loss from the scalp (cutis aplasia); skin folds; nodules on the heels; small rough bumps on the skin (keratosis pilaris); and other skin rashes, such as heat rash or prickly heat (miliaria) and recurrent allergic skin reactions (papular urticaria).

He had eczema / very dry skin but this seems to be getting better with age."



Breathing

Babies and children with rare chromosome and gene disorders tend to have a higher rate of respiratory concerns, which may become less frequent with age and maturity, although they can persist throughout childhood. Children may also be prone to recurrent respiratory infections. Other issues may include softening/collapse of the main airways, trachea and bronchi when breathing (tracheobronchomalacia), leading to noisy breathing (stridor); unusual connections between the respiratory airways and the digestive tract (oesophagobronchial fistula); and scarring at the back of the throat (velopharyngeal synechiae) (Reijnders 2017; Banka 2022; Seyama 2023). One individual has been reported with chronic lung disease (Banka 2022).

Teeth

Dental concerns are very common in children with chromosome disorders. A number of issues have been described by parents of children with a RAC1-NDD including an unusual size of the jaw; thin, weak enamel (enamel hypoplasia); dental caries leading to tooth removal; and tooth grinding (bruxism), which can prematurely wear down the enamel. Teeth may emerge late, and milk teeth may be late to fall out. A high standard of dental care is important to minimise damage by decay and erosion. 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

Palate

Anomalies of the roof of the mouth (palate), ranging from those that may be invisible to the casual onlooker such as a high or arched palate to more obvious conditions such as a cleft palate or lip, have been reported in children with a RAC1-NDD. Anomalies of the palate, particularly clefting, can cause difficulties in feeding, hearing, teething and speech production. As well as helping aesthetically, surgical repair eases these problems and may even eliminate them altogether.

Hernias

A few babies with RAC1-NDDs are born with a hernia, where an organ or fatty tissue pushes through a weak spot in a surrounding muscle or tissue. These have included umbilical (at or near the belly button) and inguinal (inner groin) hernias (Reijnders 2017). In many individuals with genetic conditions hernias have healed naturally without the need for treatment, but sometimes surgical repair is required.

Kidney and urinary tract

Some babies are born with minor anomalies of the kidneys and/or urinary tract. Reported anomalies include an enlarged kidney(s) (hydronephrosis) due to a build-up of urine inside (Haugh 2021; Priolo 2023), which may sometimes be diagnosed during mid-pregnancy anomaly scans. In mild cases this requires monitoring but no treatment. More serious cases can cause urinary tract infections (UTIs), which can be treated with antibiotics or, very occasionally, a catheter may need to be inserted to remove the build-up of urine and prevent damage to the kidney. Kidney stones (renal lithiasis) have also been reported (Priolo 2023). A few children with a RAC1-NDD have difficulty controlling urination during the day or at night (incontinence or nocturnal enuresis) (Banka 2022).

Constipation

Constipation can occur in children with RAC1-NDDs and can be related to low muscle tone, little exercise, a low-bulk diet and small fluid intake, among other reasons that are not fully understood. One individual with a RAC1-NDD was found to have digestive duplication (Althebaiti personal communication), where part of the digestive system forms an additional separate structure, which can cause symptoms such as abdominal pain or bowel obstruction. 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. A small anal opening in an additional location has also been observed in one child (Nishikawa 2025).

Genitals

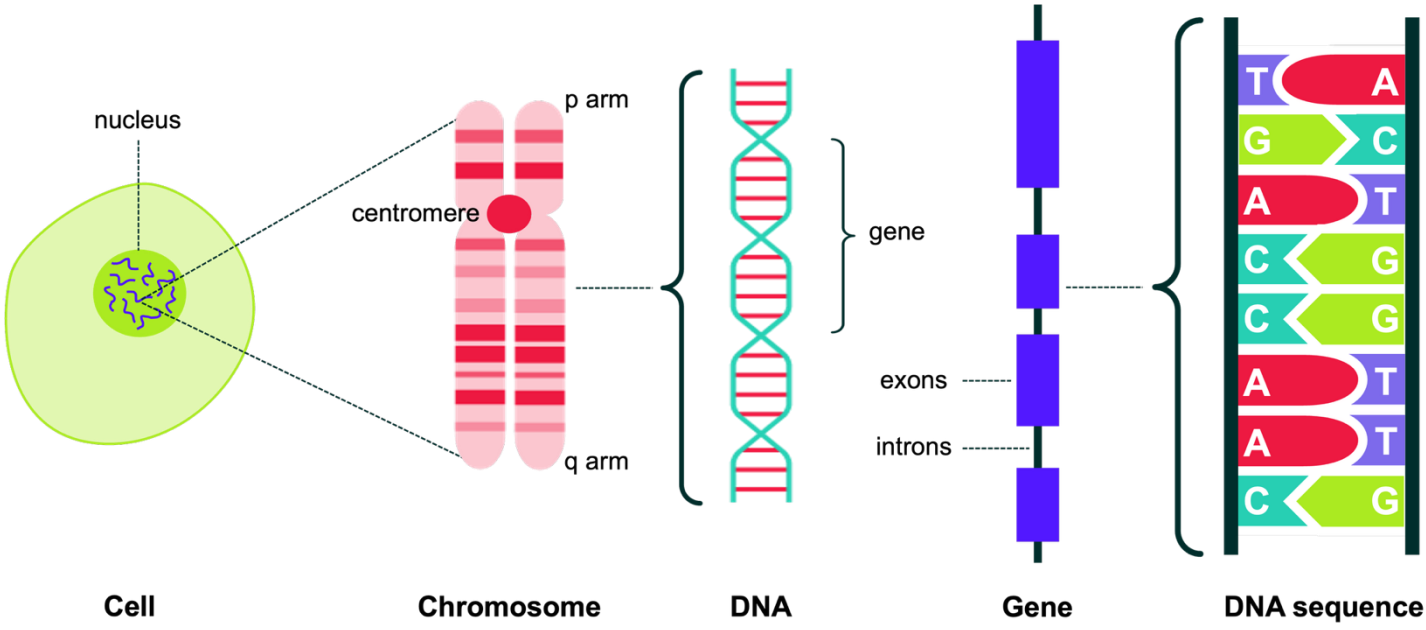
Minor anomalies of the genitals in boys have been reported occasionally. Among these are undescended testes (cryptorchidism), which may affect one (unilateral) or both (bilateral) testes, and the relocation of the hole normally at the end of the penis to the underside (hypospadias) (Reijnders 2017; Banka 2022). Many of these anomalies can also be seen in children without RAC1-NDDs and are not of major concern. If necessary, most can be corrected with surgery. Girls are much less likely to be affected.

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 RAC1-related NDDs?

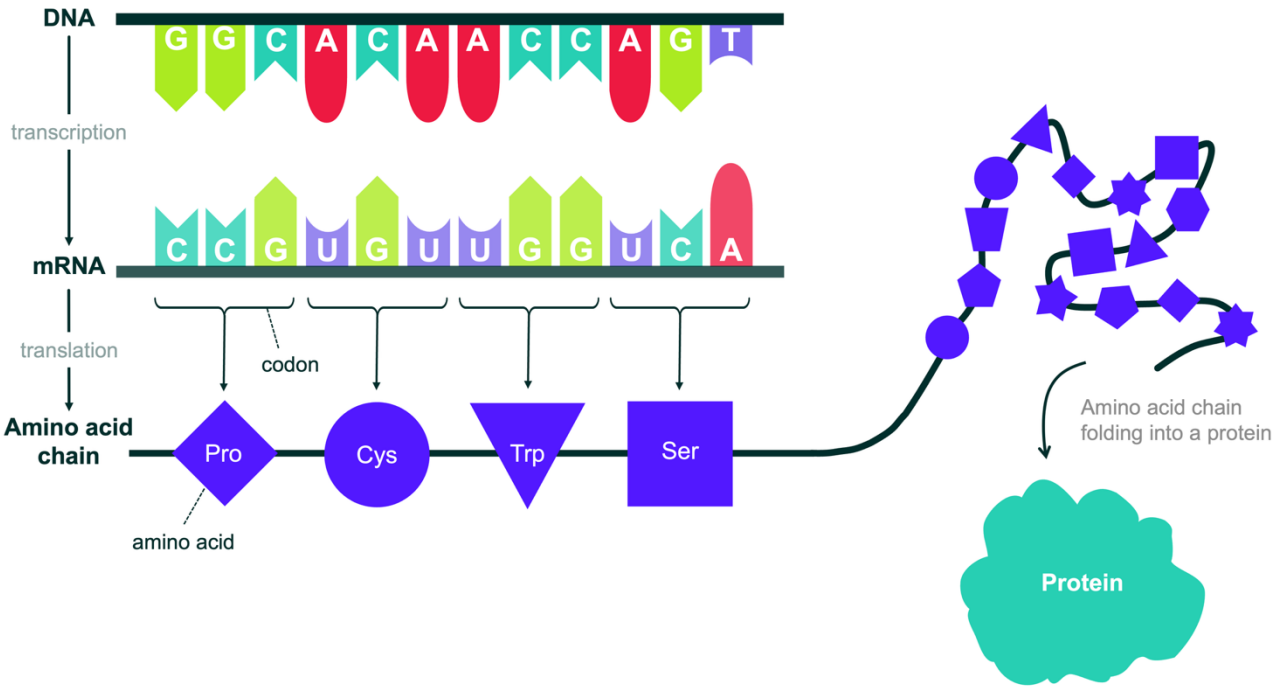
RAC1-NDDs are caused by specific changes (known as pathogenic variants) to the DNA sequence of a gene called RAC1 (RAC1 is an abbreviation of the gene's full name, Ras-related C3 botulinum toxin substrate 1). The RAC1 gene is located in the short 'p' arm of chromosome 7 in a region called p22.1 as shown in the image below.

Chromosome 7

We have two copies of chromosome 7 in our cells, so we also have two copies of the RAC1 gene. RAC1-NDDs occur when only one copy of the RAC1 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. RAC1 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.



In RAC1-NDDs the affected copy of the RAC1 gene contains a random '*de novo*' change, meaning the change occurred for the first time in that family in the affected individual. This single letter change to the sequence of DNA bases (known as a 'missense') results in a different amino acid being used at this position in the chain of amino acids that make up the RAC1 protein, which alters how the protein functions.

The RAC1 protein plays many roles in the body and is particularly important for shaping and organising our cells. Its role in determining how cells grow, move and communicate is essential for the development of the complex structures and systems that make up the body. Therefore, changes in the protein can disrupt development of the brain and other systems. The RAC1 protein acts like a switch that is controlled by other proteins, which can either 'switch on' RAC1, which increases its activity, or 'switch off' its activity and stop it carrying out these roles. This on/off switch is tightly controlled as it is important to have the right balance of RAC1 activity, too much or too little activity can affect the body.

Different types of variant effects

Pathogenic RAC1 variants can have different types of effects on the RAC1 protein, depending on where they occur in the RAC1 gene.

- **Activating variants:** Some variants result in increased levels of its 'switched on' state.
- **Dominant negative variants:** Some variants can disrupt the activity of RAC1 protein.
- **Unknown effect variants:** The impact of some variants on RAC1 protein function is not known.

These changes in RAC1 protein activity affect the shape and behaviour of cells, including the cells in the brain (neurones) that usually form long branches to communicate with each other (Banka 2022).

Groups of RAC1-NDDs

Due to these different types of effect, RAC1 variants can cause different disorders in individuals. To date (2025), RAC1-NDDs can be divided into three groups based on the additional features they lead to on top of the developmental delay, intellectual disability, facial features, and brain anomalies seen in the majority of individuals with RAC1-NDDs:

Q61-R68 RAC1-NDD:

- The change to the gene sequence results in a different amino acid at or between positions 61 and 68 in the amino acid sequence
- These are activating variants resulting in the RAC1 protein being more active
- People with these variants typically have a head size within the expected range, but head size can vary from mildly smaller than expected for the child's age (microcephaly) to mildly larger than expected (macrocephaly)

V51 RAC1-NDD:

- The genetic variant causes an amino acid change at position 51 in the amino acid sequence – two variants have been reported at this location, V51M and V51L
- The effect on RAC1 protein function is unknown
- All individuals reported with a variant at this location have a large head size (macrocephaly)

All other RAC1-NDDs:

- These variants are thought to have dominant negative effects on the RAC1 protein
- Individuals with these variants tend to have a small head size (microcephaly)
- Additionally, some individuals may have other features which are specific to individual variants

(Reijnders 2017; Banka 2022)

Genetic Tests

RAC1-NDDs caused by gene sequence variants, can be identified by a type of genetic test called sequencing (e.g. whole exome sequencing (WES) or whole genome sequencing (WGS)).

Genetic Test Results

The results of genetic (genomic) testing are likely to be provided by a geneticist, a genetic counsellor or the clinician who ordered the test. Depending on the test that was carried out, an example result of a DNA sequencing test (e.g. WES or WGS) that identifies gene variants, is shown here for the RAC1 gene:

Unique publishes a separate guide to DNA sequencing

p.Asn39Ser (N39S) (AAC>AGC): c.116 A>G in exon 3 of the RAC1 gene (NM_006908.5)

p.Asn39Ser (N39S)	signifies the change to the protein: the amino acid asparagine (Asn) has been replaced by the amino acid serine (Ser) at position 39 in the sequence of amino acids that make up the protein
A>G	signifies the gene sequence change: the A nucleotide has been replaced by a G nucleotide
c.116	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 3	signifies which part of the gene has been altered, in this case exon 3
RAC1 gene	signifies the gene that is affected
NM_006908.5	this is the specific 'reference sequence' or blueprint of the gene that scientists use to identify the location of the variant

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.

When such a random change disrupts the function of the RAC1 gene, a child will have a RAC1-NDD. In almost all people identified so far (2025) with RAC1-NDDs, 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 RAC1-NDDs so far (2025) the genetic alteration has been found to be *de novo* (dn), which means neither parent was found to have the same RAC1 gene change as their child. Therefore, the chance of having another child with a RAC1-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 RAC1 variant has been inherited from a parent, the possibility of having another child - either a girl or a boy - with RAC1-NDDs rises to 50% (1 in 2) in each pregnancy. However, the effect on the child's development, health and behaviour cannot be reliably predicted. Your genetics centre should be able to offer counselling before you have another pregnancy.

If your child with a RAC1 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.

A clinical geneticist or genetic counsellor can provide specific advice for each family about the chance of having further children with a RAC1-NDD.

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 RAC1-NDDs be cured?

There is no cure for a RAC1-NDD 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

No clinical practice guidelines for RAC1-NDDs have been published (2025). The following suggestions have been provided by clinicians, who have personal experience of managing/treating individuals with RAC1-NDDs, to improve quality of life and reduce complications.

Children and adults with RAC1-NDDs 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.

> ***"Our son still depends quite heavily on adult interaction and support from an adult within daily routine tasks – help and self-care."***

Immediately following diagnosis

When not carried out as part of the diagnostic process, an evaluation of the features of RAC1-NDDs 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 RAC1-NDD are present and how severe they are.

Supportive care

How a person with RAC1-NDDs 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.

Cardiologist – a doctor who specialises in heart conditions.

Endocrinologist – a doctor who specialises in hormones and their effect on the body.

Urologist – a doctor who specialises in diagnosing and treating conditions affecting the urinary system.

Nephrologist – a doctor who specialises in conditions affecting the kidneys.

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

Ophthalmologist – a doctor who specialises in conditions affecting the eyes.

Audiologist – a health care professional who diagnoses, treats and helps manage a condition that involves hearing or balance.

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 a RAC1-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 managing challenging behaviours, improving social skills and developing coping strategies.

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

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.

Surgery may be required to improve, for example, heart conditions, visual and hearing impairments, and skeletal anomalies.

Surveillance

It is recommended that the following evaluations are 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
- Regular dental check-ups
- Consider a palate review (particularly if there are feeding difficulties or speech concerns)
- Check position of testes in boys
- Consider an annual cardiac review
- Consider a neurologic review (including MRI and EEG, if indicated by seizures)
- Consider a skeletal review
- On-going (likely annual) examinations by an ophthalmologist
- Ultrasound imaging, to monitor for evidence of urinary tract dysfunction after diagnosis
- Kidney function should be monitored, particularly in the setting of ultrasound findings or recurrent urinary tract infections, as per the recommendations of a nephrologist and according to whether there is evidence of kidney disease and disease progression
- Monitor for constipation (at least once a year) and treatment as directed by the primary care provider or gastroenterologist
- Monitor for hearing impairment
- Monitor hormone (endocrine) function

Research into new treatments for RAC1-NDDs

The discovery of RAC1-NDDs is still relatively recent (2017). The genetic changes that cause RAC1-NDDs 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 RAC1-NDDs, like autism, is ongoing. In addition, although RAC1-NDDs are a relatively rare condition, the RAC1 gene is the subject of a lot of research.

Researchers are screening each pathogenic variant in the RAC1 gene to understand how the location of each variant affects protein function, with the aim of identifying groups of variants that have similar effects in people with RAC1-NDDs. Ultimately, this could improve diagnosis and potentially offer more specific treatment options. There are also efforts to understand how the changes to the RAC1 protein result in the clinical features and symptoms experienced by people with RAC1-NDDs.

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

Families say ...

"He simply brings joy to people, always smiling, his excitement over the smallest, simple things makes people appreciate the small things. He has taught us patience and love and understanding of his world."

"Our son is so happy. He is kind, caring, thoughtful and overall a complete joy. He is lovable and forms nice connections and bonds with those he cares about."

Sources

The information in this booklet is drawn from the published medical literature and information from Unique members. In 2025, Unique had 4 members with a RAC1-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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Inform Network Support

Rare Chromosome Disorder Support Group
The Stables, Station Road West, Oxted, Surrey, RH8, 9EE, UK
Tel: +44(0)1883 723356
help@rarechromo.org I rarechromo.org

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Websites, Facebook groups and other links:

- Raising kids with RAC1 Private Facebook Group

This guide was written by Ruby Allen, PhD student, Department of Developmental Biology and Medicine, University of Manchester, UK and Unique. This guide was reviewed by Prof Siddharth Banka MBBS, MRCPCH, PhD, Professor of Genomic Medicine and Rare Diseases, University of Manchester, Consultant Clinical Geneticist, Manchester University Foundation NHS Trust, and Clinical Director, Manchester Rare Conditions Centre, UK.

Version 1 (CA) 2025

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Charity Number 1110661
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