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UNDERSTANDING GENES & CHROMOSOMES

ATP1A3-related neurologic disorders

rarechromo.org

This guide is designed to help families and healthcare professionals looking after people with ATP1A3-related neurologic disorder. 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 ATP1A3-related neurologic disorders?

ATP1A3-related neurologic disorders are a group of rare genetic conditions that have historically been grouped into the four most common syndromes.

- Alternating Hemiplegia of Childhood (AHC) (the most common)
- Rapid-onset Dystonia-Parkinsonism (RDP)
- A crossover between Relapsing Encephalopathy with Cerebellar Ataxia (RECA), and Fever-Induced Paroxysmal Weakness and Encephalopathy (FIPWE), called RECA/FIPWE
- Cerebellar ataxia, Areflexia, Pes cavus, Optic atrophy, and Sensorineural hearing loss (CAPOS)

These conditions are also referred to as ATP1A3-related disorders. In addition to these syndromes, people with ATP1A3 variants have also been identified with developmental delay, epilepsy and apnoea (when breathing temporarily stops), but their features do not fit well into these four well established syndromes.

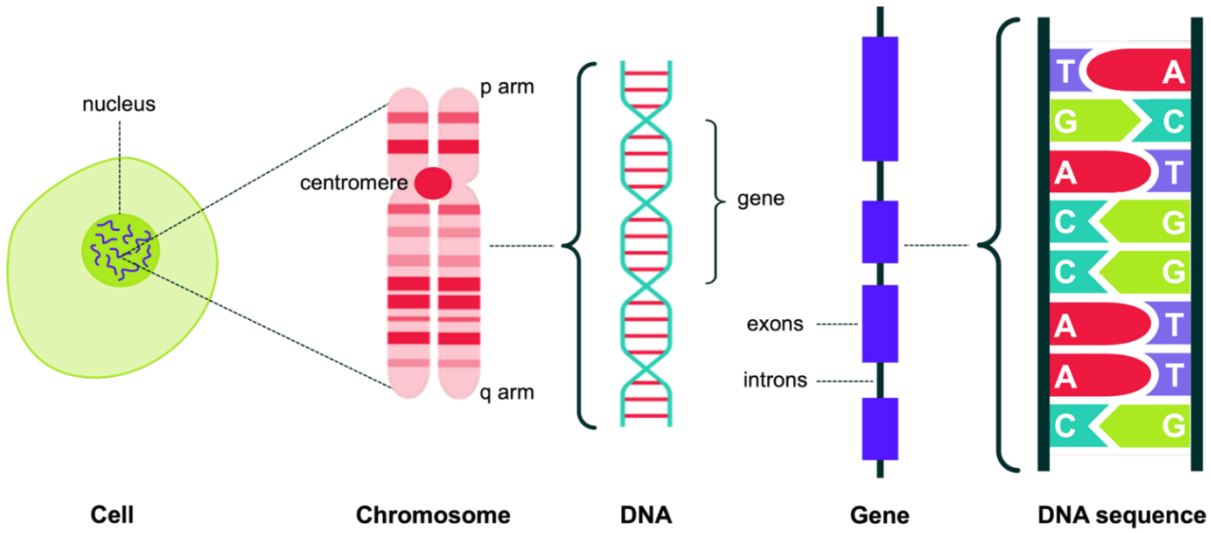
The four ATP1A3-related neurologic disorders (AHC, RDP, RECA/FIPWE and CAPOS) share common features including involuntary eye and muscle movements, seizures, and developmental, speech and language delays. These seizures can vary in severity depending on age of onset with episodes largely being triggered by fever or stress. As is common with genetic conditions, each person can be affected differently - even among affected members within the same family. Not everyone with an ATP1A3-related disorder 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.

ATP1A3-related disorders are caused by a change (variant) in the ATP1A3 gene, which alters how the gene works. Sometimes, the gene can be missing entirely due to the deletion of part of a chromosome, but this is less common.

What causes ATP1A3-related disorders?

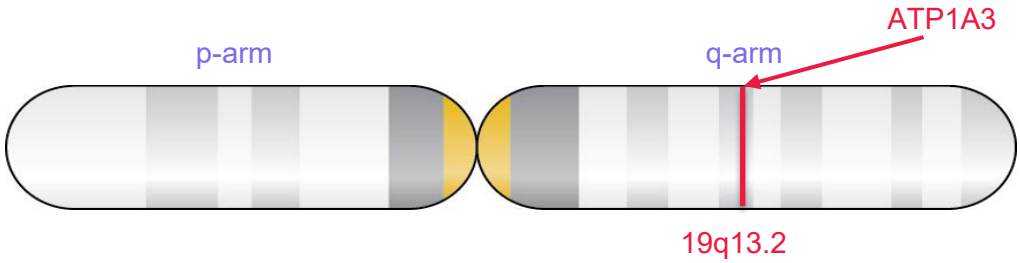
Genes are instructions that have important roles in our growth and development. They are made of DNA and are incorporated into organised structures called chromosomes. Chromosomes therefore contain our genetic information. Chromosomes are located inside our cells, the building blocks of our bodies. In people with genetic conditions, one or more of their genes don't instruct the body as we would expect, 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.



ATP1A3-related disorders are caused by specific changes (known as pathogenic variants) to the DNA sequence of a gene called ATP1A3 (ATP1A3 is an abbreviation of the gene's full name, ATPase Na+/K+ Transporting Subunit Alpha 3). ATP1A3-related disorders can also be caused by the loss of ATP1A3 due to a chromosome deletion. The ATP1A3 gene is located in the long 'q' arm of chromosome 19 in a region called 19q13.2 as shown in the image below.

Chromosome 19



We have two copies of chromosome 19 in our cells, so we also have two copies of the ATP1A3 gene. ATP1A3-related disorders occur when only one copy of the ATP1A3 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

Unique publishes a separate guide to deletions and microdeletions

The ATP1A3 gene sequence is used to make a protein called sodium/potassium-transporting ATPase subunit alpha-3 (also known as Na(+)/K(+) ATPase alpha-3 subunit). This protein is important because it is an essential subunit of a pump that transports sodium and potassium. In the brain, this pump maintains correct sodium (Na+) and potassium (K+) levels which helps nerve cells communicate properly. When this gene doesn't work as it should, nerve cells can't send signals correctly, which can increase the brain's susceptibility to damage, especially under stress, leading to a range of neurological features.

Genetic Tests

ATP1A3-related disorders 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)). 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. arrayCGH or SNParray).

Unique publishes separate guides to DNA sequencing

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 ATP1A3-related disorders might have results that look like the following examples:

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 most common variant (Salles 2021) of the *ATP1A3* gene:

p.Asp801Asn (D801N) (GAC>AAC): c.2401 G>A in exon 17 of the ATP1A3 gene (NM_152296.5)

p.Asp801Asn (D801N)	signifies the change to the protein: the amino acid aspartic acid (Asp or D) has been replaced by the amino acid Asparagine (Asn or N) at position 801 in the sequence of amino acids that make up the protein
GAC>AAC	signifies the gene sequence change; the G nucleotide has been replaced by an A nucleotide
c.2401	signifies the base pair position of the change within the gene sequence (the position where the G nucleotide has been replaced by the C nucleotide)
exon 17	signifies which part of the gene has been altered, in this case exon 17
ATP1A3 gene	signifies the gene that is affected
NM	denotes the reference sequence used

The result of a chromosome microarray (CMA) test (e.g. arrayCGH or a SNParray), that can identify deletions, is shown here for a deletion within band 19q13.2 (Kaminsky 2011):

arr[hg38] 19q13.2-13.31 (41,930,894-43,141,456)x1

arr	The analysis was by array (arr) comparative genomic hybridisation (cgh)
hg38	Human Genome build 38. 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
19q13.2q13.31	the chromosome involved is chromosome 19 and the position of the deletion is in band q13.2
41,930,894-43,141,456	the base pairs between 41,930,894 and 43,141,456 have been shown to be deleted. Take the first long number from the second and you get 1,210,562 (1.210562 Mb or 1,210.562 kb). This is the number of base pairs that are deleted
x1	means there is one copy of these base pairs, not two – one on each chromosome 2 – as you would normally expect, so this a deletion
dn	means *de novo*. The biological parents' chromosomes have been checked and no deletion or other chromosome change has been found at the same position. 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 mother
pat here would mean that it has been inherited from the father

Unique publishes a separate guide to Interpreting Genetic Test Results

What features and symptoms do people with ATP1A3-related disorders have?

As is common with many genetic conditions, children and adults with ATP1A3-related disorders 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 ATP1A3-related disorders have:

- Repetitive muscle movements (dystonia)
- Speech and language delay
- Feeding, swallowing and breathing difficulties (due to paralysis of the muscles in the face, throat, or tongue)
- Low muscle tone (hypotonia)
- Coordination or balance difficulties (ataxia)
- Unusual eye movement (nystagmus)
- Sudden paralysis affecting one or both sides of the body (alternating hemiplegia) or all four limbs (quadriplegia)
- Some degree of intellectual disability (ID) or learning difficulties (LD) ranging from mild to moderate
- Seizures or seizure-like episodes
- Some degree of developmental delay ranging from mild to severe

Other possible features include:

- High arched feet (pes cavus) (CAPOS specific)
- Hearing impairment (CAPOS specific)
- Vision impairments caused by deterioration or damage of the optic nerve (CAPOS specific)
- anxiety or depression
- Behavioural differences including autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD), anxiety or mood disorders (more frequent in RDP specifically)
- Altered heart rhythm (arrhythmia)
- Gastrointestinal manifestations (gastroesophageal reflux (GERD), constipation, nausea, anorexia)
- Episodes of confusion or loss of consciousness (rare)

Pregnancy and birth

While most pregnancies are unremarkable and proceed without complication, occasional concerns during pregnancy have been reported, sometimes following mid-pregnancy anomaly scans. If a cause for concern was noted, parents reported slow growth in the womb (intrauterine growth restriction, IUGR) or more rarely, reduced foetal movements. However, reports are not common and onset of symptoms is typically postnatal, ranging from infancy to adulthood depending on specific disorder.

The majority of pregnancies go to term but a few babies are born prematurely where some babies show some signs of difficulty at birth, related to difficulties with feeding. Birth weights are usually average and babies are otherwise healthy at birth. In very rare cases, some features have been reported following birth such as seizures that don't respond to medication (intractable epilepsy), stopping breathing for short periods (apnoea), very floppy muscles (hypotonia), or smaller than normal head/brain (microcephaly). It should be noted that women with ATP1A3-related neurologic disorders should be monitored for development of symptoms which can be triggered by pregnancy or childbirth.

Appearance

Most children with an ATP1A3-related disorder do not have unusual facial features or a distinctive appearance. However, some children with an ATP1A3-related disorder may have specific facial features including wide-set eyes, long and wide eyes, a mouth with down-turned corners, and thin and well-defined eyebrows.

Development

Gross and fine motor skills

Developmental delay has been reported in most children with ATP1A3-related disorders, and more frequently in those with RECA/FIPWE or RDP so far (2025). The degree of delay ranges from mild to severe. In general, 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 typically developing children and others showing more obvious delay.

In children with RECA/FIPWE, episodes of movement difficulty, such as poor coordination or balance (ataxia) or muscle weakness or low muscle tone (hypotonia), can be triggered by fevers. Low muscle tone (hypotonia) is common and may affect mobility. Some children may have an unusual gait when walking because of these balance issues (ataxia). These episodes may worsen over time but they can also decrease in frequency and severity and balance and weakness episodes usually stop after the trigger (fever) is resolved.

Most children with RDP will have involuntary muscle movements or contractions (dystonia). This can begin with cramping of hands or arms usually starting abruptly. These involuntary movements can progress into seizure-like movements or can improve over time for some people.

For some, independent walking may not be achieved. Many children benefit from early intervention with treatments or therapies such as physiotherapy (PT) and occupational therapy (OT). Sometimes the use of special equipment (orthotics) such as insoles, braces, or splints can help with movement.

Unique publishes separate guides to Therapies and Toilet training and continence

Intellectual development and learning

Most children with ATP1A3-related disorders have intellectual disability (ID) or learning difficulties. ID ranges from mild to profound but is usually moderate and most 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 ATP1A3-related disorders typically experience some degree of speech and language delay and many 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 some may remain non-verbal. 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 believe 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 many to communicate their thoughts and needs well.

Unique publishes a separate guide to Communication

Feeding

Feeding issues in the new-born period are common. 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), 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). Other issues that have been reported include aspiration (where fluid, food or saliva enters the airway or lungs). 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

Growth and stature

Growth patterns in children with ATP1A3-related disorders described in the medical literature so far (2025) are noted as being variable. Some children grow at the expected rate, while others may be smaller or larger than average. Some children with an ATP1A3-related disorder also have a smaller than expected head size (microcephaly). Beyond infancy, height and weight is variable.

Behaviour

Children with ATP1A3-related disorders typically tend to have behaviour in keeping with their overall degree of developmental delay, and most have a happy disposition and are very sociable. Some children have an autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD) diagnosis or traits. Other behaviours including anxiety or aggressive behaviours have also been reported. Some children also have sleep problems. Children with AHC specifically see seizures relieving during sleep, but this can be a cause of sleep disruptions. Children usually benefit from consistent routines, boundaries, rewards and other behaviour management techniques. Efforts to take into account and introduce strategies to tackle communication and other difficulties can also be beneficial.

> *He has autism and struggles to understand emotion and attends a specialist school setting as he has a severe learning difficulty."*

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Puberty

There is limited information available about puberty in children with an ATP1A3-related disorder. We do know that most boys and girls appeared to go through puberty as expected. During puberty, significant neurological and hormonal changes occur in all children. In children with ATP1A3-related disorders, these changes can potentially manifest these symptoms, trigger or intensify them. 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. Physical or psychological stress, common during puberty, can trigger or worsen symptoms in ATP1A3 disorders (Oblak 2014), but typically these can be managed very well.

It is typical that AHC manifests during early childhood while RDP often manifests in adolescence or early adulthood. CAPOS syndrome usually appears between six months and four years of age, but some symptoms can persist or worsen into adolescence (De Vrieze 2021).

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 or intellectual disability, possible on-going medical concerns and improvements in early intervention and therapies/treatments.

RDP is the predominant form of ATP1A3-related disorders which manifests during adulthood. Adults with ATP1A3-related disorders have varying levels of independence. ATP1A3 -related disorders can impact quality of adulthood life, with varying levels of neurological, cognitive, and emotional challenges. However, management of symptoms and avoidance of triggers significantly improves quality where most people with an ATP1A3-related disorder have gone on to have families of their own and manage to run their own households and work. Some continue to live with their parents or in supported settings such as a group/residential care home, with caregivers who can provide support. Some may live independently but require some support from family or friends with certain tasks. Levels of employment and the nature of employment varies but many people with an ATP1A3-related disorder do undertake some form of paid or unpaid employment.

Unique publishes a separate guide to Transition

Medical concerns

The following medical concerns have been found in children with ATP1A3-related disorders. They are not found in all children so not all children with ATP1A3-related disorders will be affected.

Paralysis

Children, with AHC specifically, are likely to see episodes of sudden paralysis before the age of 18 months. This can affect one or both sides of the body (alternating hemiplegia) or all four limbs (quadriplegia). These episodes can last from minutes to days but temporarily pause during sleep.

Seizures

Children with ATP1A3-related disorders can experience some form of seizure (a sudden and unexpected change in the electrical activity in the brain). This is seen most frequently in children with AHC, with 50% of children having seizures by early childhood, and least frequently in children with CAPOS syndrome. 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. Children with AHC experience seizures frequently with early onset (infancy to early childhood) and often in the early stages of the condition. Individuals with CAPOS syndrome, RECA/FIPWE and RDP rarely have seizures but they can occur.

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 self-resolve or resolve with medical treatment. Levetiracetam, phenobarbital, valproic acid, and topiramate are reported as the best medications for seizure control. 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.

More than one type of seizure may be present in the same individual. Seizure types reported in individuals with an ATP1A3-related disorder include:

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.

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.

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.

Focal seizure: Starting in one part of the brain, can involve frontal, temporal, or posterior regions.

Tonic seizure: Sudden stiffening of the body or limbs.

Eyes and sight

Problems with eyes and vision are common in children with ATP1A3-related disorders, especially those with CAPOS syndrome. A wide range of conditions have been reported and an individual may have more than one vision or eye-related concern. Known concerns include a squint (strabismus); uncontrolled eye movements (nystagmus); damage to the nerve between the eye and brain (optic atrophy); short or long-sightedness (myopia and hypermetropia), which can usually be corrected by glasses. Children with CAPOS syndrome specifically are most commonly affected by vision loss caused by optic nerve atrophy.

> *He is known to have strabismus and intermittent bilateral extropia (his squint switches eyes) and this is triggered by tiredness.*

Hearing

In CAPOS syndrome specifically, most children have a hearing impairment, but hearing is unaffected in children with other ATP1A3-related disorders (such as AHC and RDP) and hearing tests at birth often give a clear response. This hearing loss is sensorineural and related to the inner ear, sometimes to the cochlea (the main sensory organ for hearing) or auditory nerve (the nerve that sends signals to the brain about sound). Hearing loss in children with CAPOS syndrome is usually progressive and largely variable but can be the first or only symptom they have.

Many types of hearing loss can be managed by using hearing aids. As children are at risk of speech delay, parental concerns should be acted on early and home- or school-based therapy provided.

Unique publishes a separate guide to Hearing

Brain

Most children with an ATP1A3-related disorder will have unaffected brain structures. A few children may have a structural brain anomaly but this is not always the case. MRI (magnetic resonance imaging) or a CT (computerised tomography) scan of their brain can detect differences including areas where the brain tissue has started to reduce (focal atrophy), or reduced size of certain areas such as the cerebellum which helps with balance and movement. These findings can help you and your doctor plan the best care for your child. The changes seen vary and are less common but can include reduction in localised areas of the brain (focal atrophy) or reduction in brain volume (cerebellar atrophy).

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 with AHC specifically may experience difficulty breathing or shortness of breath (respiratory distress) during seizure episodes but otherwise breathing related features are not commonly reported in children with an ATP1A3-related disorder.

> *He uses a ventilator at night as he has apnoea although our picture is slightly complicated by how prematurely he was born (26 weeks) so it's hard to unpick what is due to his genetic change and what could be his prematurity."*

Feet

Children with ATP1A3-related disorders occasionally have anomalies of the feet. Most common among these are high arched feet (pes cavus). Some children are only mildly affected, and any condition will not require treatment. Others may benefit from massage, orthotics and physiotherapy. Treatment is tailored to the individual child, and in some cases surgical correction will best enhance eventual mobility.

Spine

Rarely babies are born with or develop a sideways spinal curvature (scoliosis). The curvature can be treated with physiotherapy and exercises, or a support brace or surgery may be needed. If there is any concern about this, your baby's spine will be imaged, usually with ultrasound or an MRI scan.

Heart

Heart conditions are uncommon in people reported with ATP1A3-related disorders. Most children do not have heart defects, but 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. Possible heart conditions, such as irregular heartbeat (arrhythmia), are relatively minor but may need treatment, although some resolve naturally with time. If a more severe heart condition is diagnosed, medical treatment or surgery may be needed.

Dental and Feeding

Dental concerns are very common in children with chromosome disorders but are not specific to ATP1A3-related disorders. However, dental concerns may occur especially if feeding or swallowing is affected, as such, issues described by parents include feeding difficulties and delayed eating and chewing activity. A high standard of dental care is important to minimise damage by decay and erosion (by teeth grinding). Children and adults may also benefit from specialist hospital dental services and may require treatment under general anaesthetic.

Children with ATP1A3-related disorders, more so for those with AHC, may need feeding assistance due to swallowing difficulties and muscle weakness. The need for this would be determined by assessment from a gastroenterologist who may recommend feeding assistance such as gastronomy tube (feeding tube) placement, or by a nutritionist who may recommend dietary changes or recommended supplements to ensure necessary caloric and nutritional intake is met.

Unique publishes separate guides to Looking after your child's teeth, Teeth: common concerns and Feeding

How common are ATP1A3-related disorders?

ATP1A3-Related disorders are extremely rare. Currently (2025) about 1,100 individuals with an ATP1A3 gene variant have been reported in the medical literature, but more are known to have been diagnosed. It is expected that more people will be diagnosed with this condition as awareness increases and genetic testing becomes more routine.

Why did this happen?

When children are conceived, their parents' genetic material (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 ATP1A3 gene then a child will have an ATP1A3-related disorder. In almost all people identified so far (2025) with an ATP1A3-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. All individuals with AHC and 50% of people with CAPOS syndrome or RDP have a *de novo* variant. Very rarely, one parent may have a chromosomal rearrangement that led to an ATP1A3-related disorder in their child, or 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 an ATP1A3-related disorder so far (2025) the genetic change has been found to be *de novo* (dn), which means neither parent was found to have the same ATP1A3 gene change as their child, and neither parent was found to have a chromosomal rearrangement that might have resulted in an ATP1A3 deletion in their child. Therefore, the chance of having another child with an ATP1A3-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. Parental mosaicism for a ATP1A3 variant has been reported only a handful of times in the medical literature.

Unique publishes a short general guide to Mosaicism

In families where the ATP1A3 variant has been inherited from a parent, the possibility of having another child - either a girl or a boy - with the same ATP1A3-related disorder 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 an ATP1A3 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 an ATP1A3-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 ATP1A3-related disorders be cured?

There is no cure for an ATP1A3-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

No clinical practice guidelines for ATP1A3-related disorders have been published (2025). The following suggestions have been provided by clinicians, who have personal experience of managing/treating individuals with ATP1A3-related disorders, to improve quality of life and reduce complications.

Children and adults with ATP1A3-Related disorders should 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. Individuals may have evaluations with neurology, ophthalmology, or audiology.

Immediately following diagnosis

When not carried out as part of the diagnostic process, an evaluation of the features of ATP1A3-related disorders that are present in the child or adult who has been diagnosed with this genetic condition should be carried out. This can determine which of the features of ATP1A3-related disorders are present and how severe they are.

Supportive care

Children with ATP1A3-related disorders who have a range of features are likely to be under the care of a multidisciplinary team. The team should include a community or hospital paediatrician who can oversee care; monitor growth, development and behaviour; and link in with affiliated services.

How a person with an ATP1A3-related disorder is supported will depend on which and how many features they have and may require co-ordinated care by a team of specialists, which may include a/an:

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.

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 an ATP1A3-related disorder but may include:

Physiotherapy for dystonia and movement issues, which usually includes stretching and mobility exercises to help prevent contractures and reduce falls.

Occupational therapy for daily activity and dystonia related challenges, which can include positioning and mobility devices to improve motor skills and maintain independence.

Speech therapy for dysarthria (slurred speech), which can include improving articulation, fluency, and language comprehension to help improve communication and may include alternative communication devices (AAC).

Behavioural therapy for behavioural or psychiatric symptoms such as autism, ADHD, behavioural challenges, which can include Applied Behaviour Analysis (ABA), Cognitive-Behavioural Therapy (CBT), social skills training, parent/caregiver support, routine development, or alternative communication methods to improve coping, social and communication skills and daily functioning.

Audiology and hearing support for sensorineural hearing loss, which can include hearing aids or cochlear implants to improve hearing sensitivity.

Ophthalmologist vision support for vision concerns such as a squint (strabismus), which can include corrective eyeglasses, eye patches, or surgery to improve eyesight.

Medications may be prescribed such as Flunarizine for AHC to decrease frequency and severity of one-sided paralysis episodes, this medication works by calming overactive brain signals. For RDP, anticholinergics may be prescribed to reduce muscle stiffness and cramping by calming overactive muscle signals. To reduce the likelihood of severe seizures, anti-seizure medications (ASMs) such as Topiramate, Valproate, Levetiracetam may be prescribed which work by reducing excessive nerve signalling.

Avoidance of triggers for preventing and relieving episodes. Triggers usually include fever, heat, stress and excessive physical exertion.

Surveillance

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

- Neurological evaluations to monitor seizures, ataxia, dystonia changes or development or new neurologic signs
- Speech and swallowing evaluations
- Consider an annual cardiac review
- Hearing and vision checks
- Consider a neurologic review (including MRI and EEG, if indicated by seizures)
- Developmental and cognitive progress checks
- Psychiatric and behavioural assessments

Research into new treatments for ATP1A3-related disorders

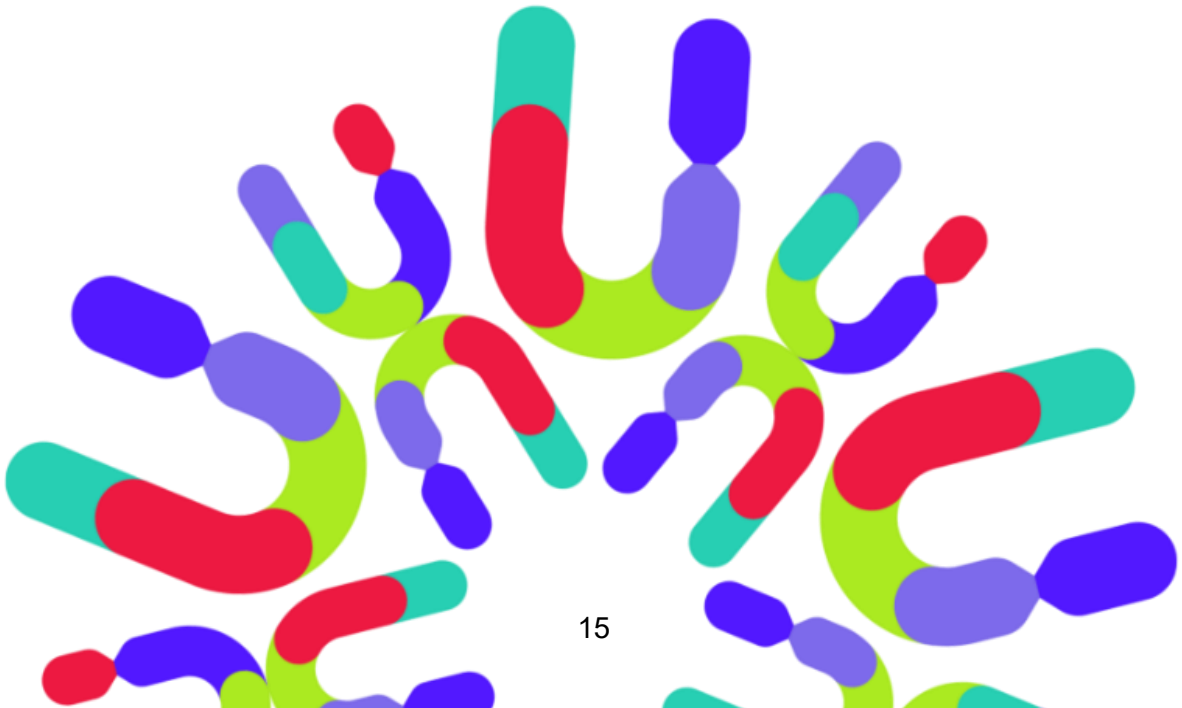
The genetic change causing ATP1A3-related disorders affects development of the brain and other parts of the body before birth. Therefore, a complete cure is unlikely, even in the future, since the brain has already formed by the time a diagnosis is made. However, research into improved treatments and management for various features of ATP1A3-related disorders is ongoing. Currently, a clinical trial studying variability of symptoms across individuals with ATP1A3-related disorders is currently underway to better understand causes and links between each symptom.

In addition, although ATP1A3-related disorders is a relatively rare, the ATP1A3 gene is the subject of a lot of research. Researchers are also exploring potential for gene therapy in animal studies, where a copy of the ATP1A3 gene with a pathogenic variant is replaced by an unaffected copy, and this has been shown to improve motor function in mice.

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

Families say ...

> Our child's ATP1A3 variant is very rare and doesn't fit any of the "traditional" syndromes, it is also complicated by the fact that he was born prematurely (26 weeks)."



Sources

The information in this booklet is drawn from the published medical literature and information from Unique members. In 2025, Unique had 11 members with an ATP1A3-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/**).

References

* Brashear (2008). [Updated 2024] ATP1A3-Related Disorder. GeneReviews ® [Internet]. PMID 20301294. **Link to article**

* Salles (2021). ATP1A3-Related disorders: An Ever-Expanding Clinical Spectrum. Frontiers in Neurology [Internet]. PMID 33868146. **Link to article**

* Kaminsky (2011). An evidence-based approach to establish the functional and clinical significance of copy number variants in intellectual and developmental disabilities. Genetics in Medicine [Internet] PMID 21844811. **Link to article**

* De Vrieze (2021). Expanding Phenotype of ATP1A3 - Related disorders: A Case Series. Child Neurology Open. [Internet] PMID. **Link to article**

* Oblak (2014). Rapid-onset dystonia-parkinsonism associated with the I758S mutation of the ATP1A3 gene: a neuropathologic and neuroanatomical study of four siblings. Acta Neuropathologica [Internet] PMID 24803225. **Link to article**

* Vezyroglou (2022). The Phenotypic Continuum of *ATP1A3*-Related disorders. Neurology. Oct 4;99(14):e1511-e1526. doi: 10.1212/WNL.0000000000200927. Epub 2022 Jul 18. PMID: 36192182; PMCID: PMC9576304. **Link to article**

* Note: an asterisk indicates articles which are “open access” and freely 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
help@rarechromo.org I rarechromo.org

Join Unique for family links, information and support:

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Please help us to help you!

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Donate via our website

AHC Specific Websites:

- Alternating Hemiplegia of Childhood UK
- AHC Europe
- Alternating Hemiplegia of Childhood Foundation (USA)
- Cure AHC (USA)
- IAHCRC International Consortium

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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