Understanding Chromosome & Gene Disorders

NAA10-related disorder Arg83Cys

rarechromo.org

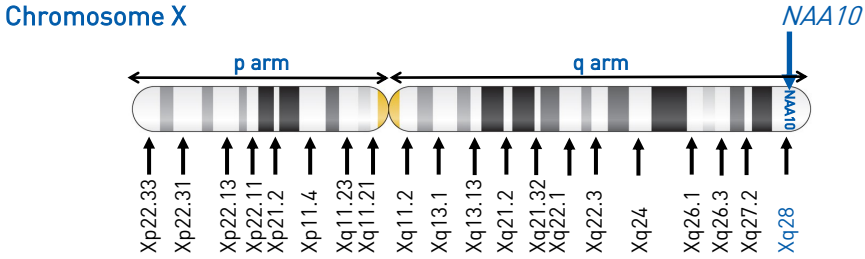
The information in this leaflet is based on information published in the medical literature, the clinical experience of Dr Eleanor Hay and personal insights from families affected by Arg83Cys NAA10-related disorder. Since so few individuals with the Arg83Cys *NAA10* gene change have been reported in the medical literature to date (2021), the information we have is limited and may change in the future when more people are identified and more research has been done.

What is Arg83Cys NAA10-related disorder?

NAA10-related disorders are a group of disorders caused by different changes to the same gene – *NAA10*. How each child or adult is affected depends on their specific genetic change but they usually have a spectrum of health and developmental concerns. This leaflet specifically relates to individuals with the *NAA10* gene change called Arg83Cys.

NAA10 encodes the active part of an enzyme (N-acetyltransferase A) that has an essential and widespread role in modifying the building blocks (proteins) in the body. Alterations in this gene can have a significant impact on many developmental processes including in the brain, heart and eye.

The *NAA10* gene is located on the X chromosome. In the cells of our bodies, females have two copies of the X chromosome and males have one X and one Y chromosome. Males who have the *NAA10* Arg83Cys change on their only copy of the X chromosome tend to be very severely affected and sadly do not live past infancy/early childhood. Females who have the *NAA10* Arg83Cys change on one of the copies of their X chromosomes have a more variable picture. This is because in each of their cells only one of the X chromosomes is active, the other is 'switched off' (this is known as X-inactivation). This process is thought to be random and therefore the proportion of Arg83Cys to unaffected *NAA10* can differ between tissues and organs.



Unique publishes a short guide explaining 'X-inactivation' in more detail as well as a short guide to 'X chromosome deletions, duplications and single gene disorders' and a general 'single gene disorders' guide. All guides are freely available at www.rarechromo.org/disorder-guides.

Frequent features:

Many of the common features in children with Arg83Cys *NAA10*-related disorder are also found in many other genetic conditions that cause developmental delay and learning difficulties, so children may not be easily recognized without genetic investigations. The first three features are found in almost all children with Arg83Cys. The other features may or may not be present.

Commonly seen:

- Moderate to severe global developmental delay and intellectual disability
- Absent speech or significant delay in speech development
- Challenging behavior, ritualistic movements and hyperactivity
- Feeding and swallowing difficulties
- Cortical visual impairment (CVI)
- Variable eye anomalies

More variable but important to recognise:

- Seizures
- Heart condition or rhythm disturbances

Other possible features:

- Sensory processing disorder
- Bone changes
- Poor growth and/or small head size
- Subtle facial differences
- Excess facial and/or body hair
- Mottled skin
- Sociable and happy demeanor

Medical concerns (in girls)

The following medical concerns have been found in some individuals with Arg83Cys *NAA10* gene changes, but may not be seen in all affected children and adults.

Changes in muscle tone

Most reported children have low tone in the core muscles and appear floppier than average as babies. This is known as hypotonia. Some have increased tone (stiffness) in the arms and legs. This is known as hypertonia.

Heart

Around half of reported children have had a heart condition, either a structural abnormality present from birth or, more commonly, a conduction defect (called long QT syndrome) that can lead to heart rhythm disturbances.

Seizures

A few reported individuals have developed seizures of varying kinds. Of those that have required medication, most have responded well to the treatment.

Eyesight

Across the spectrum of *NAA10*-related disorders, eye abnormalities are present in over half of individuals. In those with Arg83Cys, reported issues include a refractory error [near sightedness (myopia) or farsightedness (hyperopia)], squint, curvature of part of the eye that results in blurred vision (astigmatism) and altered function of the part of the brain that controls vision (cortical vision impairment).

Bones/Spine

Some children have been reported to have a dip or protrusion of the chest wall (known as pectus excavatum or pectus carinatum), others have minor rib or spine abnormalities and/or a discrepancy in leg length.

MRI brain imaging

Of those reported who have had a brain scan, non-specific changes have been identified including a loss of white matter, changes to the corpus callosum (the nerve bundle that connects the left and right hemispheres of the brain) and an increase in ventricle size (cavities within the brain that contain cerebral spinal fluid).

Other less common medical conditions:

Early puberty

A smaller number of girls have entered puberty earlier than usual (<8 years).

Development (in girls)

Growth

Most babies are born at term and are of average or low-average weight. Many experience feeding difficulties and consequently a degree of restricted growth in early life. Many have low average or small head size (known as microcephaly).

Feeding

Parents are likely to need support as feeding difficulties can be considerable at first. Typically, babies suck weakly and some need high energy milks to encourage weight gain. Many babies readily bring feeds back up the food-pipe (gastro oesophageal reflux) and need careful positioning for feeding and while sleeping. Some babies are helped by medicines for reflux. Occasionally surgery is helpful to improve the effectiveness of the valve between the stomach and the food pipe (a fundoplication). Some babies need to be fed temporarily through a tube through the nose (nasogastric feeding) or direct into the stomach (gastrostomy). Older children typically have chewing difficulties and may have an oral aversion secondary to a sensory processing disorder. Older children have been reported to have difficulties with gut motility, food allergies and constipation.

Differences in appearance

Whilst the facial characteristics vary, many individuals are noted to have prominent eyebrows that sometimes meet in the midline and long eye lashes. Children may be noted to have more body hair than is typical for their family.

Physical Development

Most affected children have low muscle tone and show delayed motor milestones. With the help of physiotherapy, standing and walking aids, some children gain independent walking abilities, though those who do often tire easily. For others this is not possible, though they may be able to sit independently.

Speech and language

Children typically experience a significant delay in communicating and learning to use words. The eventual range of achievement is broad, though most have a very limited vocabulary or use a combination of picture exchange and gestures to communicate. Many children remain non-verbal or use noises to express their needs.

Learning

All reported girls to date have had moderate to severe learning difficulties. A limited number have learned to read, though many more are able to use picture exchange communication. Most children need considerable support with their learning and may need to attend a special school where the right support can be given and non-academic and daily living skills focused on. Supervision may be needed even for adults.

Behaviour

As a group, children with Arg83Cys NAA10-related disorder appear to have a happy disposition and are very sociable. Some families have noticed autistic tendencies in young children and hyperactivity/inattentiveness at school age. This can be controlled with medication in some, but others may continue to have quite challenging behaviour requiring specialist advice and support. Specific repetitive behaviours described include continuous mouthing of objects, self-hugging, outburst of an aggressive nature and unmotivated laughter.

Development and Medical concerns in boys

Only one boy has been reported in the medical literature with the *NAA10* Arg83Cys gene change (2021). He was much more significantly affected with profound hypotonia, heart, brain, digit and kidney anomalies and an inability to breathe without support. He sadly died shortly after birth.

How common is Arg83Cys NAA10-related disorder?

NAA10-related disorders are very rare and even though the Arg83Cys is a recurrent gene change, this has still only been reported in the medical literature in around 20 individuals. There are, however, many more unreported individuals. From working with the founder of the NAA10 Facebook community, we are aware that almost 100 children have been identified worldwide with a NAA10 variant, about 40 of whom have the Arg83Cys change.

What causes Arg83Cys NAA10-related disorder and why did it happen?

When children are conceived their parents' genetic material is copied in the egg and sperm that makes a new child. The biological copying method is not perfect and occasionally random, rare changes occur in the genetic code of children that are not seen in the DNA of their parents. Arg83Cys *NAA10*-related disorder occurs when one of these random, rare changes affects the *NAA10* gene on the X chromosome and changes the amino acid building block at position 83 from Arginine to Cytosine.

These types of changes happen naturally and are not due to your lifestyle or anything parents did or did not do. In most families the DNA change in *NAA10* starts for the first time in the child (*de novo*) and is not inherited.

Can it happen again?

The possibility of having another child affected by a rare gene disorder depends on the genetic code of the parents. As the DNA change causing Arg83Cys almost always starts for the first time in the child (*de novo*), the chances of having another child are only a little higher than for anyone else in the population. There is a small risk, however, that one parent is mosaic for this gene change (has a mixture of both the unaffected *NAA10* gene in some cells and the Arg83Cys variant in a small number of others).

One family has been reported where a mosaic parent has passed on the change to more than one child. Parents should therefore be tested and if the results are normal the overall risk of having another affected child are less than 1%. Each family situation is different and a clinical geneticist or genetic counsellor can give you specific advice for your family.

Management recommendations

There is no cure for this disorder as the effects of the genetic change took place during your baby's development. However, early intervention is key and being aware of this diagnosis means that appropriate monitoring and treatment can be put in place for your child. Community paediatricians should oversee care so that development and behaviour can be monitored and the best help, in the form of physiotherapy, occupational, speech and behavioural therapies (including medications), can be given early if needed.

Dietician

As many babies and young children experience feeding difficulties, the input of a dietician can be hugely beneficial in optimizing nutrition.

Cardiac review

All newly diagnosed individuals should have a full cardiac assessment including an echo to look for structural anomalies and an ECG to look for a prolonged QT interval.

Seizure review

Children or adults who develop unusual movements/ behaviours or periods of apparent daydreaming should be formally assessed for a seizure disorder.

Eye review

Review by an ophthalmologist is recommended as many children develop eye issues over time.

ASD assessment

Autistic spectrum disorders and sensory processing disorders (SPD) are more common in children with this diagnosis and recognition can aid communication and development

NAA10 Families

Families say ...

“ My daughter is severely disabled with complex health needs, she needs a lot of care across many areas and can be a challenging little pickle but she does make progress. She is very determined, happy, sociable and loveable and has a smile that melts everyone's hearts. Having such a rare condition has its challenges but the Facebook community is a huge source of support full of welcoming families. ”

“ Their smiles are contagious, their love is unconditional by definition, the work we put in is unwavering and under-recognized, but those giant wet kisses are God's Gift! ”

“ Our daughter's needs can be extremely challenging but her love for life, people and happy personality has given us patience and resilience we didn't know we had. ”

“ Our children can be hard work and challenging but with love and therapeutic input they do make progress with their development and they all have such happy personalities. ”

Inform Network Support

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Understanding Chromosome & Gene Disorders

Join Unique for family links, information and support

Unique is a charity without government funding, existing entirely on donations and grants. If you can, please make a donation via our website at http://www.rarechromo.org/donate Please help us to help you!

Websites, Facebook groups and other links:

We are NAA10 Families Together

We are the global patient support organisation for families affected by mutations to the NAA10 gene also known as Odgen syndrome.
Our website: https://www.naa10gene.com/

Our community: https://www.facebook.com/groups/NAA10/
Join our welcoming private Facebook support community run by the global patient organisation solely for parents & guardians of children affected by mutations to the NAA10 gene. (You will need to provide your child's exact variant)

Public Facebook site: https://m.facebook.com/NAA10FamiliesTogether/
Twitter: https://twitter.com/naa10gene
Instagram: http://instagram.com/naa10familiestogether

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

This information guide is not a substitute for personal medical advice. Families should consult a medically qualified clinician in all matters relating to genetic diagnosis, management and health. Information on genetic changes is a very fast-moving field and while the information in this guide is believed to be the best available at the time of publication, some facts may later change. *Unique* does its best to keep abreast of changing information and to review its published guides as needed. This booklet was written by Dr Eleanor Hay, Specialist Registrar in Clinical Genetics, North East Thames Regional Genetics Service, Great Ormond Street Hospital, London, UK and compiled by Unique (AP).

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