

Support and Information



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

Understanding Chromosome & Gene Disorders

Join UniqDe for family links, information and support.

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

DDX3X Support UK is a UK based information and support group for patients and families affected by the DDX3X gene mutation <https://ddx3xsupportuk.co.uk>

DDX3X Foundation and registry (US based)

<http://ddx3x.org>

DDX3X Facebook page

www.facebook.com/groups/geneddx3x

DDX3X UK Facebook page

<https://www.facebook.com/groups/DDX3X>



This guide was made possible by contributions from:
Fonds NutsOhra, Erfocentrum, VGnetwerken and VKGN in the Netherlands.

UniqDe lists external message boards and websites in order to be helpful to families looking for information and support. 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. DDX3X is an emerging syndrome, so what we know about its effects will increase a lot in the next few years and UniqDe will do its best to regularly update this guide.

The text was written by Dr Lot Snijders Blok, MSc, MD, Department of Human Genetics, and Dr Tjitske Kleefstra, Clinical Geneticist, Nijmegen Medical Center, Netherlands, and the leaflet was compiled by UniqDe with the participation of Dr Laura van Dussen, MD (Erfocentrum), Marloes Brouns-van Engelen (Erfocentrum), Professor Conny van Ravenswaaij-Arts (UMC Groningen) and Mieke van Leeuwen (VGnetwerken). With special thanks to Annet van Betuw (VanBetuwAdvies), Marja de Kinderen (PROK Project management and training), Joyce Schaper (Chromosome Foundation) and Sarah Wynn, BSc(Hons) PhD DIC (UniqDe). This guide was updated in 2021 by Dr Anna Kolesnik-Taylor, Dr Kate Baker and Elise Ng-Cordell (MRC Cognition and Brain Sciences Unit, University of Cambridge) together with UniqDe (AP). 2016 Version 1 (PM); v1.1 (CA); v1.2 (CA); v2 (AP)

Copyright © UniqDe 2022

Rare Chromosome Disorder Support Group
Registered in England and Wales

Charity Number 1110661
Company Number 5460413



Understanding Chromosome & Gene Disorders

DDX3X syndrome



rarechromo.org

What is DDX3X syndrome and how is it caused?

DDX3X syndrome is a genetic condition that occurs in females, and very rarely in males with developmental delay and/or intellectual disability. The first individuals with this condition were reported in 2015.

DDX3X syndrome occurs when one of the two copies of the [DDX3X gene](#) has lost its expected function. This is caused by a change to the gene sequence, known as a [variant](#).

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. The [DDX3X gene](#) is located on the X chromosome. Chromosomes are located in our cells, the building blocks of our bodies.

Although DDX3X syndrome occurs primarily in females, currently (2021) a few families are known in which males have a variant in the [DDX3X gene](#) and have intellectual disability. This condition presents differently to the DDX3X syndrome in females. The inheritance pattern can also be different. In this guide we focus on DDX3X syndrome as it has been found in females but have added a section for the most recent observations made in boys with a [DDX3X variant](#) on page 3.

DDX3X is an emerging syndrome, so what we know about its effects will increase a lot in the next few years.

Most girls with DDX3X syndrome have:

- Developmental delay (DD) or intellectual disability (ID)
- Behaviour difficulties, including autism spectrum disorder (ASD) and ADHD (attention deficit hyperactivity disorder)
- Low muscle tone (hypotonia)
- Feeding difficulties
- Joint laxity and/or scoliosis

Girls and women with DDX3X syndrome have different medical problems and varying degrees of developmental delay. It is currently not fully understood what causes these differences in severity and the associated difficulties or symptoms.



“Having had contact with lots of other DDX3X parents through the Facebook page, I’ve come to realise that it seems impossible to predict the developmental path of these children as they are all so different. Although there are common traits, some of the children are much more severely affected than others.”

How many people have this condition?

Almost 150 females with DDX3X syndrome have been described in the medical literature, and 10 males (2021). However, more people are known to have DDX3X syndrome but have not been reported in the medical literature. It is thought that 1-3% of

intellectual disability in females is caused by DDX3X variants. With the increasing use of the latest gene sequencing technology, it is expected that many more children and adults will be diagnosed with this condition in the next few years.

callosum (the band of nerve fibres between the two sides of the brain), enlarged ventricles (the ventricles are the fluid-filled parts of the brain) and disorders affecting the formation of the grey matter in the brain’s outer layer (cortex).

Seizures

Some girls with DDX3X syndrome do not develop seizures but others do.

Hearing & vision

Some, but not all girls with DDX3X syndrome have hearing or vision difficulties. Hearing problems may be conductive (concerning the outer and mid-ear), sensorineural (concerning the cochlea or the neural pathway leading to the auditory cortex) or both. At present little is known about age of onset or progression of hearing loss in children with a DDX3X variant.

Vision

Unique’s experience is that vision problems can occur. Those reported include: immature visual perception; squint (strabismus); long or short sight; astigmatism, causing some distortion or blurring of vision; nystagmus (uncontrolled eye movement); palsy of the optic nerve with difficulty coordinating the movement of both eyes and the possibility of intermittent interruptions in vision; and CVI (cortical visual impairment) causing difficulties with tracking. Vision problems were reported in one in 3 girls or women in a large study of DDX3X syndrome.

Feeding

Families have met a variety of feeding issues. They include:

- Weak, ineffective sucking and slow feeding as a baby.
- Chewing and swallowing difficulties.
- Severe reflux and eosinophilic oesophagitis, an inflammation of the oesophagus (food passage).
- Difficulties using a knife and fork together due to problems integrating actions on both sides of the body.
- Slow gut transit time.
- Overeating and difficulty sensing when full.
- Constipation, responding to medication.

Toilet training

“When she was younger she had a lot of UTIs, put down to her toilet training difficulties and being wet a lot.”

“She toilet trained in the day at 8 years. We are still working on being dry at night, and are to try Desmopressin (a medicine that reduces the amount of urine).” 11 years

Sleep

Families commonly face sleep problems, particularly in the first two years.

“Under a year she never slept longer than 3 hours at a time, day or night. As she grew, she could not self settle and needed constant reassurance. She has woken every night since birth with differing success in getting her back to sleep or into her own bed. She can now self settle at bedtime, but still wakes occasionally.” 11 years

Short concentration span and hyperactivity

“Sensory processing difficulties (sensory seeking but also sensory sensitive to aural and visual stimulation) affect her attention and focusing.” 9 years

“When younger she was hyperactive with a short attention span. Now she is much calmer and still has a short but better attention span.” 16 years

spectrum of these behaviours, with some children experiencing a few difficulties in social functioning versus severe difficulties in others.

Some girls with DDX3X syndrome may experience increased anxiety, triggered by uncertainty about future events, specific objects or situations, and/or sensory sensitivity. Anxiety in DDX3X syndrome may be more common than in other genetic disorders. Sometimes, responses to distress can include self-injurious behaviours such as self-hitting, biting, head-banging, or skin-picking and scratching.

“ She very much enjoys sport and dog training. P is also very keen on indoor climbing on climbing walls. A real outdoor girl. ” 16 years



Medical concerns

Low muscle tone, joints and movement disorders

Most babies with DDX3X syndrome have low muscle tone (hypotonia) at birth. This means that the baby is floppy. Low muscle tone may persist throughout childhood. Some girls and boys develop increased muscle tone (spasticity) in the legs. An unusual gait is seen in some children and adults, mainly a stiff-legged and/or wide based gait, where they walk with their feet wide apart.

Joint bendiness (hyperlaxity) is a feature that is commonly seen in girls with DDX3X syndrome. In addition, most girls with DDX3X syndrome experience difficulties with balance and coordination.

Unique's experience is that babies learned to sit unsupported at 11-18 months and to walk at 23 months-5 years. This may not be possible for all. Low muscle tone generally improves, but may not disappear altogether. Families attribute persisting movement difficulties to a variety of causes: proprioception (not knowing where they are in space) and crossing the midline (bilateral integration); motor control; motor planning; and musculoskeletal issues (in-turned hips).

“ She has always 'flapped' and bounced up and down when excited. She currently licks her chin intermittently. ” 9 years

“ Quite recently a big increase in involuntary movements, jerks and tics as well as intermittent difficulties with motor control. She is unable at times to complete a task, such as picking up a cup or making the next step. This can even affect chewing co-ordination. ” 16 years

Brain

In about half of the girls with DDX3X syndrome some abnormalities are seen on a brain MRI scan. Brain anomalies have also been found in MRI scans of boys with a *DDX3X* variant. These can be diverse, but include underdevelopment of the corpus

Boys with DDX3X

So far (2021), ten males from different families have been identified as having a *DDX3X*-related neurodevelopmental disorder. Although there is a lot less information available than for females, the following observations have been made:

- All reported individuals have intellectual disability or developmental delay, ranging from mild to severe
- Many, but not all boys have a small head circumference (microcephaly)
- Similarly to girls, the following features have been observed in boys: behavioral difficulties, spasticity, tremor, hypotonia, vision problems, congenital heart disease, and delayed puberty

Brain scans have shown abnormalities in the bundle of nerve fibres (corpus callosum) that connects the two halves of the brain, which may lead to loss of communication between the two brain parts. Enlarged ventricles (ventriculomegaly) and white matter abnormalities associated with slower speech processing, have also been identified.

Why did this happen?

When children are conceived, genetic material is copied, with one half coming from the egg and one half from the sperm. 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, this is known as *de novo*. These types of change happen naturally and are not due to anything anybody did. A spontaneous change in the *DDX3X* gene cannot be predicted or prevented. No environmental, dietary or lifestyle factors are known to cause a spontaneous change in this gene. No one is to blame when they occur and nobody is at fault.



In all females with *DDX3X* syndrome reported in the medical literature so far (2021) the DNA change in the *DDX3X* gene occurred *de novo*. For boys, some have been found to have a *de novo* variant, and others have inherited a *DDX3X* variant from an unaffected mother.

Can it happen again?

The risk of having another child affected by a rare gene disorder depends on the genetic code of the parents. For *DDX3X* syndrome, where a parent does not carry the same *DDX3X* change as their child, the chances of having another child with *DDX3X* syndrome are very low (estimated at less than 1%). Nonetheless, there is a very small chance that some of the egg cells of the mother or some of the sperm cells of the father could carry the change in the *DDX3X* gene. This is called **germline mosaicism**. It means that parents who are not found to be carriers of the same *DDX3X* change as their child on a blood test still have a very small chance of having another child with a *DDX3X* variant. In an individual with a diagnosis of a *DDX3X*-related disorder, there is a 1 in 2 chance of passing the genetic variant on to their children.

The risk for healthy brothers and sisters of having a child with *DDX3X* syndrome is not increased and is the same as for anyone else in the population. However, each family situation is different and a clinical geneticist can give you specific advice for your family and, if applicable, discuss options for testing regarding future pregnancies.

Can DDX3X related conditions be cured?

There are no cures since the effects of the genetic change take place during a baby's formation and development. However, knowing the diagnosis means that appropriate monitoring and treatment can be put in place for each child.

Managing a DDX3X related condition

Children with a DDX3X related condition should be followed up by a paediatrician to monitor growth, development, speech and behaviour. Depending on the medical problems that are present in each individual, the paediatrician can provide parents with the best help in the form of physio-, occupational, behaviour and speech therapies.

Development

Growth

Most babies are a normal weight and length at birth. Around one third of babies have a small head circumference (microcephaly). Girls' height and weight often remain normal as they are growing up. However, being underweight is more common in girls with DDX3X syndrome compared with other girls of the same age.

Speech

Most girls and women with DDX3X syndrome have speech difficulties and/or a delayed development of speech and language.

Unique's experience is that girls said their first words at 2-5 years. However, speech is not possible for some, and all girls rely to a greater or lesser extent on other means of communicating. These can include gesture, sound approximations, pictures, signing, and electronic communication devices.

"M can repeat words or phrases but it's extremely difficult for her to use language to express herself. But she loves to communicate one to one." 16 years

"A is working hard at using a communication aid to speak, and is doing well with 2-3 word sentences. It is lovely to hear her enthuse about her favourite things - music, trains, sharks, her dog." 16 years

"When A began mainstream school she was about a year to 18 months behind the other kids, but this increases year on year and she's now more like 3 years behind. Though several years below the other children, she has coped in a mainstream primary school with full time 1:1 support, although she will certainly need to attend a special school at secondary level. She has memory problems: working memory, short term memory and general recall." 9 years

"P's school report shows a fairly spiky profile of development." 16 years

Learning

All girls with DDX3X syndrome who we currently know about have some degree of developmental delay or intellectual disability. The range of difficulties are very

broad, varying from mild to severe. So far, most of the girls we know about have needed special education. Some girls go to mainstream primary schools, but most switch to specialised schooling in the secondary school years. Some have a mild intellectual disability, and are able to communicate, learn many skills and have independence. Others have a severe intellectual disability, have major difficulties with communicating and need a lot of supervision and support.

Families say that any behaviour difficulties are easily provoked by fear and anxiety or by being in the wrong environment. Many families also say their daughter has sensory processing difficulties, meaning that their nervous system fails to receive and/or respond appropriately to incoming messages. They point to their daughters' happy and affectionate nature, empathy and love of music.

"Behaviour problems is an unfortunate term used to umbrella a lot of traits."



"A happy, perky nature is a common trait."

"A charming child.

Naturally cheerful and stoic, which is amazing when you consider the challenges she faces every day. She's now also cheeky, funny, understands humour and is humorous herself." 9 years

"Always happy, smiles a lot, and has a great sense of fun and slapstick humour." 11 years

"A happy girl with a passion for music and trying to dance. She loves her cocker spaniel." 16 years

"When she was little we had terrible problems with her pulling hair. Sometimes she was aggressive and quick to anger, mostly due to frustration, feeling thwarted or problems with transition. Fear or worry can also lead her to instinctively lash out." 9 years

"There are only very brief moments of aggression when she is really struggling in an overwhelming situation. But she is very aware and sorry once the moment has passed. This is her reacting to the environment not being right for her as opposed to a problem with her." 16 years

"M requires a one to one supportive loving care with a lot of reassurance and stability, the ability and freedom to regulate herself regularly and the option to be at the edge as opposed to being in the middle of a group." 16 years

"Diagnosed as autistic, but happy and smiley." 16 years

Sensory difficulties and anxiety

Families often point to their daughter's happy, friendly and caring nature. If any difficulties do occur, they can include autistic features, some level of hyperactivity, difficulty regulating emotions, and sometimes aggression. There is a large