

Understanding
chromosome
disorders

Unique



DDX3X syndrome



rarechromo.org

What is DDX3X syndrome and how is it caused?

DDX3X syndrome is a recently discovered disorder in females with developmental delay and/or intellectual disability. The first girls and women with this disorder were reported in 2015.

DDX3X syndrome occurs when one of the two copies of the *DDX3X* gene has lost its normal function. This is caused by a spelling mistake in the gene. Genes are instructions, which have important roles in our growth and development. They are made of DNA and are incorporated along with many other genes into organised structures called chromosomes. Chromosomes therefore contain our genetic information. Chromosomes are located in our cells, the building blocks of our bodies. The *DDX3X* gene is located on the X chromosome.

Although DDX3X syndrome only occurs in females, at the moment a few families are known in which males have spelling mistakes in the *DDX3X* gene and have intellectual disability. This is a different disorder to the DDX3X syndrome in females. The inheritance pattern can also be different. In this guide we only focus on DDX3X syndrome in females.

DDX3X is an emerging syndrome, so what we know about its effects will increase a lot in the next few years and Unique will do its best to regularly update this guide.

Most girls with DDX3X syndrome have:

- Developmental delay or intellectual disability
- Behaviour problems, including autism and ADHD (attention deficit hyperactivity disorder)
- Low muscle tone (hypotonia)

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



“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 girls have this condition?

Around 40 girls with DDX3X syndrome have been described in the medical literature. However, more girls are known with DDX3X syndrome who have not been reported in the medical literature. With the increasing use of the latest ‘gene sequencing’ technology, it is expected that many more people will be diagnosed with this condition in the next few years.

Why did this happen?

In all females with DDX3X syndrome known so far the DNA change in the *DDX3X* gene occurred out of the blue (de novo). No parents were found to be carriers of the same change in the *DDX3X* gene.

When children are conceived your 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. These types of change happen naturally and are not due to your lifestyle or anything you did. A spontaneous change in the *DDX3X* gene cannot be 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.



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 parents do not carry the same DDX3X change as their child, the chances of having another child with DDX3X syndrome are very low (less than 1%). Nonetheless, there is a very small chance that part of the egg cells of the mother or part 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 DDX3X syndrome. This has not been reported in DDX3X syndrome in the medical literature so far.

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 syndrome be cured?

There is no cure as the effects of the genetic change took place during your baby's formation and development. However, knowing the diagnosis means that appropriate monitoring and treatment can be put in place for your child.

Managing DDX3X syndrome

Children with DDX3X syndrome should be followed up by a paediatrician to monitor growth, development, speech and behaviour. Depending on the medical problems that are present in each girl, the paediatrician can provide parents with the best help in the form of for example physiotherapy, 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 problems 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.

“ Marie 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

“ Alix 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

Learning

All girls with DDX3X syndrome who we currently know about have some degree of developmental delay or intellectual disability. The range of disability is very broad, varying from mild to severe. So far, the girls we know about have needed special education. Some have a mild intellectual disability, and are able to communicate and to learn several skills. Others have a severe intellectual disability, have major difficulties with communicating and need a lot of supervision and support.

“ When Alex 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

“ Pip's school report shows a fairly spiky profile of development.” 16 years

Behaviour

Many have behaviour problems, which can include autistic behaviour, hyperactive behaviour and sometimes aggressive behaviour.

Families say that behaviour problems are easily provoked by fear and anxiety or by being in the wrong environment. Many families also say their daughter has sensory processing problems, 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

“Diagnosed as autistic, but happy and smiley.”

16 years

“A happy girl with a passion for music and trying to dance. Alix 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

“Marie 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

Medical concerns

Low muscle tone, joints and movement disorders

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

Joint hyperlaxity (bendiness) is a feature that is commonly seen in girls with DDX3X syndrome.

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



9 years

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 she is in space) and crossing the midline (bilateral integration); motor control; motor planning; and musculoskeletal issues (inturned 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 effect chewing co-ordination. ” 16 years

Brain

In about half of the girls with DDX3X syndrome some abnormalities are seen on a brain MRI scan. These can be diverse, but include underdevelopment of the corpus 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

Hearing and vision are usually unaffected but a minority of girls with DDX3X syndrome have hearing or vision problems.

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 the largest study of DDX3X syndrome to date.

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.
- 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

Support and Information



Rare Chromosome Disorder Support Group,
G1, The Stables, Station Road West, Oxted, Surrey RH8 9EE,
United Kingdom
Tel/Fax: +44(0)1883 723356
info@rarechromo.org | www.rarechromo.org

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 www.rarechromo.org. Please help us to help you!

DDX3X Foundation and registry

<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.

Unique 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. Unique does its best to keep abreast of changing information and to review its published guides as needed. The text was written by Dr Lot Snijders Blok, MSc, MD, Department of Human Genetics, Radboud University Medical Center, Nijmegen, the Netherlands and the leaflet was compiled by Unique 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 (Unique).

2016 Version 1 (PM)

Copyright © Unique 2016