

Support and Information



Rare Chromosome Disorder Support Group.

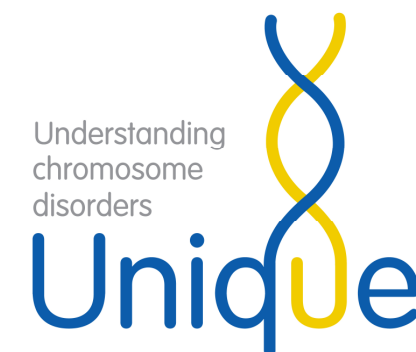
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MED12 related disorders

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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 Laura van Dussen, MD, Erfocentrum, Netherlands and the guide was compiled by UniquE with the participation of 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).

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What are the MED12 related disorders?

MED12 related disorders are a group of disorders that primarily affect boys. Most boys with MED12 related disorders have intellectual disability/developmental delay, behavioural problems and low muscle tone. MED12 related disorders occur when the MED12 gene has lost its normal function. 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 in our cells, the building blocks of our bodies.

The MED12 gene is located on the X chromosome. The X chromosome is one of the sex chromosomes that determine a person's gender. Men have one X chromosome and one Y chromosome, while women have two X chromosomes. Because the MED12 gene is located on the X chromosome, men have only one copy of the gene, while women have two copies. A change in the MED12 gene can cause symptoms in men. Women with a change in the MED12 gene usually have no symptoms. They carry a second copy of the gene that does function normally. Women may show mild features such as learning difficulties.

The MED12 related disorders are [FG syndrome](#), [Lujan syndrome](#) and the [X-linked recessive form of Ohdo syndrome](#). Although these syndromes differ, they also have the overlapping features listed on page 2. The way that these conditions are inherited is called 'X-linked' or 'X-linked' recessive.

In 2007 it was discovered that changes in the MED12 gene were responsible for the symptoms and features in several boys with FG syndrome. In the same year, it was discovered that different changes in the MED12 gene were responsible for several cases of Lujan syndrome. In 2013 it was shown that changes in the MED12 gene could also lead to the X-linked recessive form of Ohdo syndrome.

Sources and references

The information in this leaflet is drawn from what is known about children with MED12 related disorders from the medical literature. Articles consulted are: Opitz 1974; Keller 1976; Riccardi 1977; Briault 1997; Graham 1998; Graham 1999; Ozonoff 2000; Risheg 2007; Schwartz 2007; Graham 2008; Lyons 2008; Opitz 2008; Clark 2009; Graham 2010; Rump 2010; Callier 2013; Lesca 2013; Vulto-van Silfhout 2013; Isidor 2015; Langley 2015; Tzschach 2015; GeneReview MED12 related disorders, updated 6-6-2013.

The first-named author and publication date are given to allow you to look for the abstracts or original articles on the internet in PubMed (www.ncbi.nlm.nih.gov/pubmed). When this guide was written the full text of the articles was used as far as possible, but sometimes only the abstracts were available. Also included in this guide are quotations from some Dutch parents with a child with a change in the MED12 gene who filled out a questionnaire.

Can MED12 disorders 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.

Management recommendations

Children with MED12 related disorders should be followed up by a general paediatrician 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 behavioural therapy.

Once a diagnosis has been established it is important to perform an ultrasound of the heart. Annual eye checks are also recommended. The hearing of boys with the X-linked recessive form of Ohdo syndrome should be monitored. Individualised educational support is important.

Why did this happen?

In almost all boys with a MED12 related disorder, the mother was found on investigation to be a carrier of the change in the MED12 gene. Women who carry a mutation in the MED12 gene usually have no signs or symptoms themselves (see page 2). Most mothers did not know that they were a carrier of a mutation in the MED12 gene until they had a son with a MED12 related disorder. A change in the MED12 gene cannot be prevented. No environmental, dietary or lifestyle factors are known to cause a spontaneous change in the MED12 gene. No one is to blame when they occur and nobody is at fault.

Can it happen again?

If a woman is found to carry the change in the MED12 gene there is a 50% (1 in 2) chance that any future child will inherit the same change. A girl who inherits the change from her mother will, like her mother, become a carrier but is unlikely to show any signs or symptoms. A boy who inherits the change will have a MED12 related disorder.

Each family situation is different and a clinical geneticist can give you specific advice on the chances of recurrence in your family and, if applicable, options for testing regarding future pregnancies.



Outlook

The symptoms and features of FG syndrome can be severe. Sadly, early death can often occur in the first year of life usually because of heart problems, but sometimes also because of problems with the lungs or the gastrointestinal tract. If a boy survives beyond this period, life expectancy is probably normal. A history of miscarriages is more common in families with FG syndrome, but it is not known if the miscarriages were caused by the syndrome.

Development and behaviour

■ Growth

Feeding difficulties are common in boys with FG syndrome and the X-linked recessive form of Ohdo syndrome. Height is usually normal, but some boys are short. Feeding problems also occur in Lujan syndrome. Lujan syndrome is characterised by a tall and slender stature.

■ Sitting, moving and walking

Boys with MED12 related disorders usually show delay in reaching their developmental milestones such as sitting and walking. This may partly be caused by their low muscle tone.

■ Speech

Speech delay is common in MED12 related disorders. A number of boys do not speak or only say single words. Some boys can speak a lot, but they are not always able to convey what they want.

■ Learning

Boys with MED12 related disorders show some degree of intellectual disability. The degree can be from mild to moderate and boys may profit from special education. In general, boys with MED12 related disorders will not be able to live independently as adults, although exceptions have been reported of men who lived independently with some support.

■ Behaviour

Most boys with FG syndrome are friendly and easy going. Nevertheless, behaviour problems are common. Hyperactivity, problems concentrating, aggressive behaviour, anxiety, temper tantrums and self-injurious behaviour have been reported. Some boys with Lujan syndrome are friendly and sociable and they may have no behaviour problems. Some boys can be hyperactive, shy or have Asperger syndrome. Boys with the X-linked recessive form of Ohdo syndrome are generally friendly. Temper tantrums, hyperactivity and autistic features have been described.

Families say ...

“ Bas is very active and seeks out activity. He does not play with others, but enjoys watching them and likes to play outside. He does need to be accompanied. He is sweet and headstrong. The diagnosis was made when he was 16 years old. Until then life was a journey of exploration! ”
– 19 years

In the medical literature one family with a MED12 related disorder has been reported in which both men and women are affected. The change in the MED12 gene in this family was different from the change reported in other families. This might be the reason that women in this family are clearly affected.

How many people have these disorders?

More than 50 boys with a MED12 related disorder have been described in the medical literature. In approximately half of these boys, the diagnosis was made because doctors suspected that they had FG syndrome. More children have been diagnosed in the past and reported in the medical literature with FG syndrome, Lujan syndrome or the X-linked recessive form of Ohdo syndrome. It is unknown if the syndromes were caused by a change in the MED12 gene in all of these children, because the relationship between changes in the MED12 gene and these syndromes has only recently been discovered.

With the increasing use of the latest ‘gene sequencing’ technology, it is expected that many more people will be diagnosed with MED12 related disorders over the next few years.



6½ years old

Most boys with MED12 related disorders have:

- Developmental delay and/or intellectual disability
- Behaviour problems
- Low muscle tone (hypotonia)
- Strabismus (a squint) occurs in some boys

More information on these and other features is given on pages 4-6.

Appearance



A number of facial features have been observed in boys with a MED12 related disorder, although naturally they also look like other members of their family.

Boys with FG syndrome often have a high and prominent forehead with an upswept frontal hair pattern. Their eyes may be widely spaced (hypertelorism) and are often downslanting. Their palate may be high and narrow. Their upper jaw (maxilla) can be underdeveloped and

their lower jaw small and receding (microretrognathia). This may lead to overcrowding of their teeth. Their ears are often remarkably small.

A large head circumference and prominent, high forehead are also common features in Lujan syndrome. The face is often long and thin. Most boys have a downwards slant of the eyes. The nasal bridge may be high and the palate high and narrow. The upper jaw (maxilla) can be underdeveloped and the lower jaw small and receding (microretrognathia). This may lead to overcrowding of the teeth.

In boys with the X-linked recessive form of Ohdo syndrome the face is often triangular with full cheeks and a small mouth. The eyes may be widely spaced (hypertelorism) and there may be an extra skinfold at the inner corner of the eye (epicanthus). Some children have drooping eyelids (ptosis) and the eyelids may be short. Eyebrows are often thin. The nasal bridge is often wide and the tip of the nose full. Most boys have a high, narrow palate. The upper jaw can be underdeveloped and the lower jaw can be small and receding. A number of boys have dental abnormalities. The ears are often remarkably small. The facial features can coarsen over time.

Medical concerns

■ Low musculature (hypotonia)

An important number of boys with MED12 related disorders have low muscle tone. This can result in a delay in reaching certain developmental milestones such as rolling, sitting, crawling and walking. It may also contribute to the feeding and respiratory difficulties seen in some children. The low muscle tone may improve in time.

■ Gastrointestinal tract and genitals

Constipation occurs in some boys, in particular in FG syndrome. Boys with FG syndrome also more often show anal anomalies. The anal opening may be displaced to the front or back or closed off (anal atresia). Genital anomalies can also occur in FG syndrome or in the X-linked recessive form of Ohdo syndrome. The penis may be small or curved (chordee). Some boys have undescended

testicles (cryptorchidism). In some boys the opening of the urethra (the tube through which boys and men urinate) is not on the tip of the penis, but slightly below (hypospadias).

■ Head and brain

In some boys with FG syndrome or Lujan syndrome, MRI or CT scans may show abnormalities of the corpus callosum. The corpus callosum is a brain structure that connects the left side of the brain with the right side. The corpus callosum can be absent or underdeveloped. Epilepsy is more common in boys with MED12 related disorders.

■ Heart

One large study reported heart abnormalities in more than half of the boys with FG syndrome and a change in the MED12 gene. The most common heart problems are a hole between the upper or lower chambers of the heart (atrial septal defect (ASD)) or ventricular septal defect (VSD)). Other heart problems such as a patent ductus arteriosus (a persisting feature of fetal circulation) have also been reported.

Heart problems have also been reported in a number of children with Lujan syndrome or the X-linked recessive form of Ohdo syndrome.

■ Skeletal features

Boys with Lujan syndrome are often tall and slender with hypermobile finger joints. Pectus excavatum (sunken appearance of the chest) can also occur. Hypermobile fingers also occur in the X-linked recessive form of Ohdo syndrome. In FG syndrome and Lujan syndrome the thumbs are often broad.

■ Vision and hearing

Strabismus (a squint) is quite common in MED12 related disorders. In addition, boys with FG syndrome or the X-linked recessive form of Ohdo syndrome may show other eye abnormalities such as a cataract (clouding of the lens of the eye), myopia (short sight), small eyeballs and coloboma (a developmental defect of the eye). Half of the boys with the X-linked recessive form of Ohdo syndrome have hearing problems.

■ Other

A number of medical articles report an association between changes in the MED12 gene and the occurrence of fibroids (leiomyoma) of the uterus and prostate cancer. In these cases, tissue from fibroids and prostate cancer was found to contain a change in the MED12 gene while surrounding tissue did not (somatic mutations). For now, it is unclear if people with a change in the MED12 gene have any increased risk of developing these conditions.

Families say ...

“ Dylan’s development is slower than his peers. In some matters he is one to two or three years behind. In others he is a little behind or almost normal. ” – 7 years