

This leaflet is dedicated to Professor Maria Bitner-Glindzicz, Professor of clinical and molecular genetics at Great Ormond Street who died on the 20th September 2018. Maria was the driving force behind the creation of the Norrie Disease Foundation (NDF) and the biggest friend and advocate for the Norrie community from the very beginning. She was passionate about combatting the isolation and loneliness in ND by endeavouring to find a treatment for the hearing loss. She instigated research into Norrie-related hearing loss at the UCL Great Ormond Street Institute for Child Health and was also the chair of the Norrie Medical Advisory Board.

Further information can be obtained from the Norrie Disease Foundation (NDF)

The Norrie Disease Foundation, PO Box 12476, Colchester, CO1 9RB, UK
www.norriedisease.org.uk
Facebook.com/NorrieDiseaseUK
Twitter: @NorrieDiseaseUK



Produced in collaboration with *Unique* - Rare Chromosome Disorder Support Group
The Stables, Station Road West, Oxted, Surrey RH8 9EE, United Kingdom
Tel: +44(0)1883 723356info@rarechromo.org |
www.rarechromo.org



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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 compiled by Dr Amina Al-Yassin, the NDF & Unique (CA) in 2018.

Please contact the NDF for further support and information.

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Understanding Chromosome & Gene Disorders

Norrie Disease



norriedisease.org.uk

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“ He is such a happy child and his smile strikes you when you meet him. Having Norrie disease doesn't stop him from living life to the full. He never lets anything get him down, he is amazing.”

What is Norrie disease (ND)?

Norrie disease (ND) is a rare genetic condition that occurs when one of a person's two copies of the *NDP* gene carries a misprint ([mutation](#)). It is thought to affect approximately 40 people in the UK and 500 people globally, although this may be an underestimate. ND was named after Dr Gordan Norrie who first described the condition in 1927. Children with ND are born blind or severely sight impaired, and most will go on to develop hearing loss in the teenage years. Developmental delay is common in some young. Other medical concerns associated with ND include vascular problems and delayed puberty.

What are genes and chromosomes?

Our bodies are made up of trillions of [cells](#). Most of these cells contain an 'instruction manual' made up of ~20,000 [genes](#), which tells the body how to develop, grow and function. Genes are arranged on complex structures called [chromosomes](#).

There are 23 pairs of chromosomes and we inherit one half of each pair from each parent, making a total of 46 chromosomes. Of the 46 chromosomes, two are a pair of sex chromosomes: two Xs for a girl and an X and a Y for a boy.



Chromosome pairs 1-22,
X and Y (male)

Genes are composed of a complex chemical called [DNA](#), which is made up of a four-letter "alphabet" based on G, A, T and C nucleotides. This genetic code carries the instructions to make [protein](#) molecules.

Families say...

“ We didn't want families to feel as alone as we did after our son's diagnosis. Sharing information and resources is vital for families who have a child with a rare disease and new research gives us hope for the future. ” - T & K, parents to A aged 2, with Norrie disease



“ It is great to be in touch with other families. As it is such a rare condition you can feel very isolated. ” - J's son M, four, has Norrie disease and is blind



“ The NDF is important to me because it means I can connect with other people like me. I am also worried that one day I might start to lose my hearing, the NDF gives me hope for the future. ” - E is 13-years-old, with Norrie disease and severely sight impaired. Attends a mainstream school and is an avid musician.



T, aged 6, is blind with Norrie disease and loves skiing

The information in this booklet is drawn from published medical literature and information from the Norrie community. The first-named author and publication date from articles in the medical literature are given to allow you to look for the abstracts or original articles on the internet in PubMed. If you wish, you can obtain most articles from *NDF*.

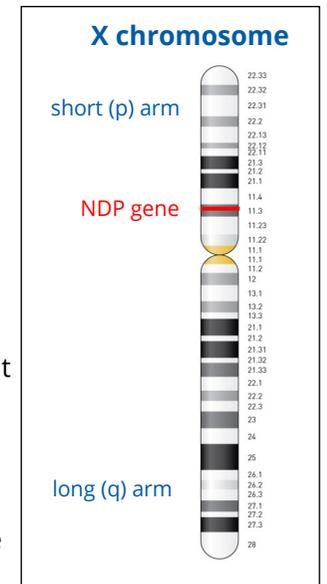
Which genetic changes cause ND?

ND is caused by a mutation in the **ND pseudoglioma (NDP)** gene. This is a gene located on the short (p) arm of the **X chromosome** at position 11.3.

Different mutations in the *NDP* gene can cause ND and most people with ND have a mutation that is unique to their family. Little is known about the effect of individual mutations on the condition and in most cases it is not possible to predict the severity of the condition by looking at the mutation alone.

Approximately 20% of people with ND have a **contiguous deletion** - this means that as well as missing the whole *NDP* gene other genes that lie nearby on the X chromosome are also missing.

These genes include the *MAOA*, *MAOB* and *EFHC2* genes, which are important for brain development and function, so a contiguous deletion may lead to additional deficits in development and intellectual ability.



What does the NDP gene/protein do?

The *NDP* gene codes for a protein called **Norrin**. Norrin is involved in processes that are believed to be critical for the development of cells in the **retina** (the thin layer at the back of the eye that senses light and color) and the establishment of a blood supply to the retina and the inner ear.

We do not yet know all the functions of the NDP gene/protein. Our knowledge of *NDP* and its functions and our knowledge about other genetic causes of ND will improve over the years with further research.

Why did this happen and could it happen again?

ND is passed on in families in an '**X-linked recessive**' pattern of inheritance.

Females (XX) have two copies of the *NDP* gene, one on each of their two X chromosomes. Males (XY) have only one copy on their single X chromosome. ND occurs in males when there is a misprint in this single copy of the *NDP* gene. Otherwise healthy females can carry an altered *NDP* gene with the working copy on their other X chromosome usually being enough to compensate for this, preventing them from developing the condition. However, some females are affected with Norrie, although much less frequently than males, due to a process called [X-inactivation](#).

Women who are [carriers](#) of ND have a 1 in 2 (50%) chance of passing the condition on to each son they have. Each of their daughters has a 1 in 2 (50%) chance of being a carrier of the condition. When a man with ND has children he will pass on his X chromosome to all his daughters and so all (100%) his daughters will be carriers of ND. None of the sons of a father with ND will inherit the condition from him as they will inherit his Y chromosome and their single X chromosome from their mother.

The vast majority of mothers of a boy with ND are carriers of the condition. Very occasionally ND can occur due to a new spontaneous (*de novo*) mutation, without the mother actually being a carrier of the condition. If the mother has had carrier testing for ND and has not been found to be a carrier then the chance of her having another child with a Norrie gene alteration is low but still slightly higher than that of the general population. This is because of the very small possibility of there being a few egg cells in her ovaries that have a Norrie gene alteration (a situation known as [germline mosaicism](#)).

For these reasons genetic counselling is recommended for families wanting to have further children. Whatever the inheritance, it is important to emphasize that this is nobody's fault.

Can ND be cured?

There is no cure as the effects of the genetic change took place during an individual's development in the womb. However, knowing the diagnosis means that appropriate monitoring and therapies can be put in place.

Research is currently underway at University College of London, Great

- Vascular-varicose veins and ulcers should be assessed by the GP. TEDS socks may be recommended.
- Erectile dysfunction should be discussed with the GP and appropriate referral should be offered if there is no benefit from first line medications.
- Maintain a healthy weight, diet and body mass index to reduce cardiovascular risks as a universal measure.
- Access to genetic counsellors to discuss reproductive decisions if interested.

■ Education

- A qualified teacher for the visual impaired (QT VI), habilitation and mobilisation services should be introduced early (0-6 months). Having early input from a specialist teacher for the visually impaired is important.
- Speech and language therapy: Given the impact of dual sensory impairment, the impact on communication needs to be considered and assessed from an early age.
- An assessment of special educational needs should be carried out so that extra help can be put in place at school.
- Input may be needed from occupational therapy for fine motor skills and from physiotherapy for head and neck posture.

diagnosis. Advice on adaptations to care and play at home to help the young child learn through other senses is given. Habilitation support is also available and includes mobility training

The STS for the hearing impaired provides advice if hearing impairment is present.

Medical & Educational Guidance Summary

■ Medical

- Children should be monitored by a multidisciplinary team including specialists in the developmental vision field and audiovestibular physicians who are used to dealing with children with dual sensory impairment.
- Audiology testing should take place at birth, during early childhood, at school-entry and annually thereafter. Additional testing should be based on any parental concerns or abnormal results. Audiological follow-up should be life -long.
- Ophthalmology assessment should take place annually during childhood and on an as-required basis thereafter.
- Children in the UK are rarely offered eye surgery. Decisions about surgery are made on a case-by-case basis following a risk-benefit assessment.
- Input from the neurology/neurodevelopment teams may be required if there are seizures or developmental delay.
- Growth/Endocrine: Growth should be monitored. The child should be referred to endocrinology for an assessment by the age of 11-12 years so that puberty can be monitored carefully.
- Diet and nutritional needs should be considered with referral to a dietician if needed.
- Sleep disturbance may sometimes improve with melatonin. This can be discussed with the child's paediatrician.

Ormond Street Institute of Child Health to see whether [gene therapy](#) can offer any treatment.

What features and symptoms do people with ND have?

People with ND have many features in common with each other.

Main features

Almost all people with ND have:

- [Problems with the eyes leading to visual impairment](#)
- [Hearing loss](#)

Other possible features

Some people with ND have:

- [Developmental delay](#)
- [Autism](#)
- [Seizures](#)
- [Vascular problems and erectile dysfunction](#)
- [Growth delay](#)
- [Delayed puberty](#)
- [Behavioural concerns](#)
- [Feeding difficulties](#)
- [Sleep problems](#)

Main Features

■ [Problems with the eyes leading to visual impairment](#)

Most people with ND are born completely blind. Some of the families known to us report that their baby seemed to have some light perception for the first few months which was then lost.

The [retina](#) is the sensitive part at the back of the eye that detects light and colour. ND causes abnormal development of the blood vessels and tissues in the retina, resulting in a white appearance in the pupil when

light is shone in the eye. This white appearance is called [leukocoria](#). Abnormal retinal development can also lead to retinal detachment, and cataracts often develop. The iris and entire eyeball may shrink during the first few months of life. If the retina cannot function properly, profound visual impairment results. The families we contacted have also reported issues with [glaucoma](#), [corneal ulceration](#) (surface of the eye) and [overactive tear ducts](#). It is important therefore for children to be under regular review with an [ophthalmologist](#) who can detect any problems early.

Some surgeons operate on children with ND to attempt to restore some light perception. In the UK this is rarely done as in most cases the surgery is unsuccessful and any beneficial effects are usually short-lived. Options for treatment can be discussed on a case-by-case basis with your ophthalmologist.

■ **Hearing loss**

Over time, most people with ND develop [sensorineural hearing loss](#) (caused by damage to the hair cells or cochlea within the inner ear); this is often the greatest concern for people living with ND. The age of onset is typically between five and 48 years, with a median (average) age of 12 years. Between 85-90% of individuals with ND will experience the onset of hearing loss by their mid-20s (Smith *et al*, 2012). The hearing loss is often described as “waxing and waning” or as being sudden hearing loss episodes”. Many people also report on-going issues with [tinnitus](#) (ringing in the ears). [Hearing aids](#) and [cochlear implants](#) can be used to help with hearing.

Many people with ND report having regular middle ear infections and [glue ear](#) (fluid in the middle ear). These may be coincidental and may cause a temporary worsening of hearing loss; fluctuations in hearing; and difficulty in assessing hearing levels, especially in young children.

It is difficult to get an accurate estimate of hearing levels in children and young people with ND due to their visual difficulty, and difficulties in development, language and communication. If standard hearing tests

■ **Clinical Geneticist**

The role of the clinical geneticist is to establish the genetic origin of the disease and to provide genetic counselling to the family.

■ **Paediatrician**

The role of the paediatrician is to assess development in early childhood and to co-ordinate medical care and educational support as required. Families should be put in contact with the local child development service (community paediatricians and therapists). Developmental paediatricians, with experience working with visually impaired children, are able to provide assessment and guidance on the developmental needs of children with severe to profound visual impairment.

■ **Audiologists & Audiovestibular Physicians**

The role of the audiologist is to carry out regular hearing tests and to advise on hearing aids or cochlear implants, if required. An audiovestibular physician supports the audiological care by advising on medical aspects of hearing loss.

■ **Endocrinologist**

Paediatric endocrinologists who work within the multidisciplinary team will ensure that any growth and pubertal issues are dealt with promptly. They will also make sure that the growth of children and young people with ND is optimised.

■ **Therapy support**

This may include a speech and language therapist, occupational therapist and physiotherapists.

Other healthcare professionals may also be needed to systematically and comprehensively plan the treatment and management of the condition on a case by case basis.

■ **Specialist Educational Support**

The Specialist Teaching Service (STS) for children with visual impairment is the key service providing home-based support from the moment of

difference in the world.

The more social interaction a person has with others in their peer group and the more those peers come to accept the person for who they are, rather than what they cannot do, the happier that person will be.” - E, an adult with Norrie

■ Other concerns

Other concerns reported by families with ND include [joint hypermobility](#) (double jointed-ness), which can lead to painful joints. Sessions with a physiotherapist may be helpful. Many families report issues with [picky eating](#) and [difficulty gaining weight](#). One child has required a PEG tube to help with eating and low blood sugar levels. A dietician should be consulted for on-going concerns.

Some children with blindness have difficulty [sleeping](#). This includes difficulty going to sleep and frequent waking. Some children take medication called melatonin to help with this. This is not helpful for all children but may be tried if children have severe difficulties sleeping.

Professionals that may be involved

■ Ophthalmologists

The role of the ophthalmologist is to examine the eyes, confirm the diagnosis and decide on any appropriate treatment. This could include removal of cataracts, treatment for glaucoma, laser treatment, shells for the eyes (for structural and cosmetic purposes) or prostheses. Those who have not completely lost their vision have been treated with surgery or laser therapy in infancy in the US. Children in the UK are rarely offered eye surgery. If surgery is offered, it would be to maintain light perception. However, there is no good data available yet as to whether surgery achieves this aim, and there are significant risks associated with surgery.

As ND is a rare condition, you may wish to make an appointment to see a paediatric ophthalmologist with a particular interest in this condition. Please discuss this with your local ophthalmologist, GP and/or paediatrician, who will be able to make the appropriate referral.

are not adequate, a hearing test under general anaesthetic may be required.

Additional Features

■ Developmental delay

The visual impairment associated with ND impacts on early development. Children with ND, like those with blindness due to other causes, may be slower to reach certain milestones e.g. sitting, crawling, walking, reading and writing, than children with full vision. Therefore, seeking advice to support all aspects of early development and learning is crucial.

When children develop at a slower rate than expected, they may be said to show ‘[developmental delay](#)’. However, it is important to recognise that a slower pace of learning is very common in children with visual impairment, and assessment using tools specifically designed for children with visual impairment is therefore recommended (Dale *et al*, 2002).

Up to one-third of children with ND may have developmental delay when compared with fully-sighted children (Smith *et al*, 2012). Parent support materials that give specific guidance for promoting development in a child with visual impairment may be particularly valuable.

■ Autism and behaviours

Young children with visual impairment - whatever the cause - can show some unusual behaviours, such as repetitive actions and unusual patterns of speech. The term ‘[blindisms](#)’ has been used in the past to describe these. It is therefore beneficial if development is assessed by professionals with experience in visual impairment.

A study in the UK (unpublished) and one in the US (Smith *et al*, 2012) found that ~27% of people with ND have [autism](#). Rates of autism are higher in individuals with severe and profound visual impairment so it is important that parents seek further advice from their doctors if they are worried about any aspects of their child’s behaviour. Your GP will be able to signpost you to specialist services who will be able to help you.

Approximately 75% of adults with Norrie disease are [living independently](#) (Smith *et al*, 2012). There is a very high proportion of [university graduates](#) in the ND community, and many have [stable jobs](#) and are married or in [committed relationships](#). Music is a major part of many people's lives.



“ I am a communications Trainee at the European parliament. I am working in the Media Directorate, the group that heads up all the media in the European Parliament in Brussels.

The very best parting gift any parent could give a child with Norrie is teaching them to be as independent as they can be. How to make tea, cook, clean and perhaps even (oh perish the thought) live on their own. It is not easy, there are worries and tears and hazards to be faced along the way. But

with this gift a child with Norrie will grow up feeling they are every bit as good as their peers.” - D, an adult with Norrie is blind and uses hearing aids

■ Seizures

One study undertaken in America (Smith *et al*, 2012) found that 1 in 10 (9%) of participants had a [chronic seizure disorder](#) or [epilepsy](#). This was not found in the UK population but is important to know. Discuss any concerns about seizures with your doctor.

■ Vascular problems and erectile dysfunction

Individuals with ND may experience problems with their blood vessels, including: [varicose veins](#), [non-healing foot ulcers](#) and [erectile dysfunction](#). Up to 38% of people experience varicose veins in adulthood. Those affected may benefit from TED stockings or other interventions; therefore, advice from your GP should be sought.

Erectile dysfunction (sexual dysfunction) is reported in 4 in 10 males with ND. This can be either pre-pubertal (lack of erectile function noticed by parents of young children) or post-pubertal (self-reported). The cause of this is thought to be small vessel disease ([arteriopathy](#)). Erectile dysfunction management can be complex – some patients report no

benefit from Viagra (pharmacological management) and therefore specialist referral may be needed to consider an implant, penile pump or penile prosthesis.

■ Growth and endocrine concerns

Approximately one-third of children with ND experience [delayed puberty](#) (no growth of testes in boys by the age of 14). In all cases puberty subsequently developed naturally and did not require growth hormone or medical intervention. Some babies with ND have had undescended testes ([cryptorchidism](#)), which can often resolve by itself. Since surgery may be required, boys should be checked at birth (as part of the normal new born baby screening) and monitored.

Growth should be monitored carefully by your local team, and children must be referred to a paediatric endocrinologist if there are concerns with respect to growth. All children must be referred by the age of 11-12 years so that puberty can be monitored carefully and any interventions, if needed, can be started early. Management of growth and pubertal disorders may include the use of hormones such as growth hormone and testosterone. However, each child must be carefully evaluated and the most appropriate investigations performed. Treatment must then be directed appropriately and tailored to the individual.

■ Mental health concerns

Sensory impairment can be socially isolating and can lead in some cases to anxiety or depression. Depression can be related to the onset of hearing loss. Your family doctor and patient support groups can be useful sources of information.

“ Living with a disability, but particularly blindness, can be very isolating for someone, both as a child and an adult. The lack of eye contact and perhaps the inability to hear what someone has said properly can form a barrier between the person with Norrie and their peers.

The good news is that there is hope. Ignorance of how to treat someone with a disability is often purely a lack of information ... a group of close friends, colleagues, people that deal with the person on a daily basis will make all the