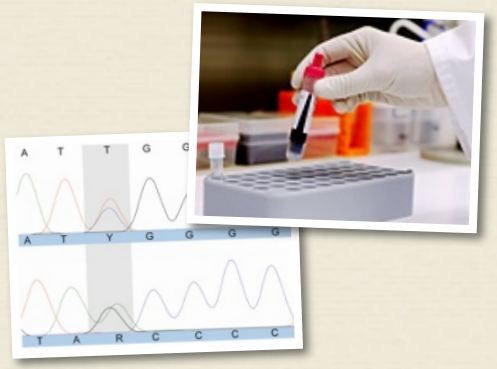


Blood sample for DNA extraction and final DNA sequence profile

Genetic Testing

Clinical genetic testing can confirm the diagnosis, and is available to assess genetic risk in family members for prenatal counseling. The Norrie gene, *NDP*, consists of three exons and codes for a protein of 133 amino acids. Disease-causing mutations in *NDP* can be detected in the majority of male cases by direct sequencing. In cases where clinical suspicion of Norrie disease could not be confirmed through DNA analysis, other genes that have been associated with similar clinical conditions should be investigated (*FZD4*, *LRP5*, *TSPAN12*).

Treatment

By the time the disease is first noticed, irreversible total retinal detachment usually already occured. However, patients who have not completely lost their vision may be treated with surgery or laser therapy very early in life. Hearing loss can be treated with hearing aids and cochlear implants. Counseling, behavorial or pharmacologic management and care by special education professionals can assist with improvement of behavioral abnormalities and cognitive difficulties. Men with Norrie disease may need varying degrees of assistance from family, friends and caretakers, but can live a full and rewarding life. For further information, please feel free to contact the Norrie Disease Association (NDA) or any of the associated professionals indicated on the back of this brochure.

MASSACHUSETTS GENERAL HOSPITAL & HARVARD MEDICAL SCHOOL
Katherine B. Sims, MD
Center for Human Genetic Research
Simches Research Building, 5-238
185 Cambridge St.
Boston, MA 02114, USA
Phone: +1 (617) 726-5718
email: ksims@partners.org
Diagnostic lab: www.dnalab.org

UNIVERSITY OF ZURICH
Wolfgang Berger, PhD
Medical Molecular Genetics & Gene Diagnostics
Schorenstrasse 16
8603 Schwerzenbach, Switzerland
Phone: +41 (44) 655-7031
email: berger@medgen.uzh.ch
www.medmolgen.uzh.ch

BOSTON EYE GROUP & HARVARD MEDICAL SCHOOL
Tatsuo Hirose, MD
1101 Beacon Street, 6W
Brookline, MA 02446, USA
Phone: +1 (617) 566-0062
email: tatsuohirose@mac.com

MASSACHUSETTS EYE & EAR INFIRMARY
Chris Halpin, PhD
Department of Audiology
243 Charles St.
Boston, MA 02114, USA
Phone: +1 (617) 573-3266
email: chris_halpin@meei.harvard.edu

NORRIE DISEASE

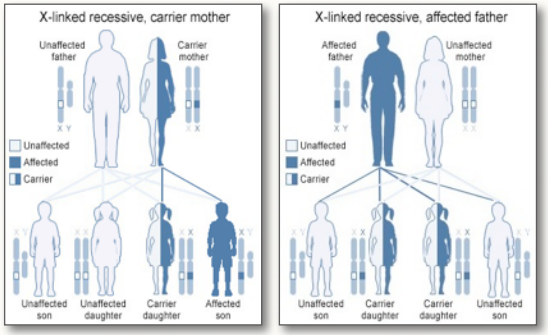
"A rare form of congenital or early onset blindness affecting both eyes that is accompanied by later onset hearing impairment. Some of the usually male patients may also have cognitive difficulties or behavioral abnormalities."

NORRIE DISEASE ASSOCIATION
email: joinnda@norriedisease.org
www.norriedisease.org

X-LINKED RECESSIVE INHERITANCE

Norrie disease (ND) is a familial disorder caused by mutations in the Norrie Disease Pseudoglioma (*NDP*) gene. It is inherited in an X-linked recessive mode and usually affects only males.

Women carrying the mutated gene are typically healthy, but statistically have a 50% risk to pass the disease to their children (Figure 1A). Sons of a carrier mother are at 50% risk of being affected and 50% of daughters will be carriers like their mothers. Norrie males will only have healthy sons, but all of their daughters will be mutation carriers (Figure 1B).



A B

Figure 1: X-linked recessive inheritance. **(A)** Carrier mother. (**B)** Affected father. Modified images from the U.S. National Library of Medicine (http://ghr.nlm.nih.gov/handbook/illustrations).

Some carrier women may express mild clinical signs. One explanation for this small risk may arise from skewed X-inactivation and clinical mosiacism. Usually one X-chromosome in each cell is randomly silenced in women (they have two X chromosomes, while men have one X and one Y chromosome) and it is possible that the disease could manifest in cells/organs if the healthy gene copy is preferentially inactivated.

NORRIE DISEASE

CLINICAL FEATURES

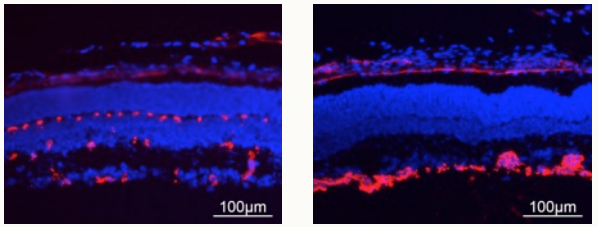
The first visible symptom typically is a white pupillary reflex (*leukocoria; pseudoglioma*). The disease is highly variable (even within a family), and additional ocular signs can include an *avascular retinal periphery*, *vitreoretinal haemorrhages*, *retinal folding*, *exudative* and/or *tractional retinal detachment*, and *persistent fetal vasculature*. Later, shrinkage of the eye bulb (*phthisis bulbi*) can be observed, and the *lens* becomes *cataractous*. The cornea, iris, ciliary body and/or retinal pigment epithelium may be affected by the disease. In addition to the ocular signs, most Norrie males experience the onset of progressive hearing loss during late childhood or early adolescence, initially affecting high frequencies. Further, up to half of the patients exhibit cognitive impairments or behavioral abnormalities that can include autism-like features. A few patients can have epileptic seizures. There may be increased risk of peripheral vascular abnormalities (e.g. *venous insufficiency*).

DIFFERENTIAL DIAGNOSIS

Several other human diseases can be easily confused with Norrie disease, including: *retinoblastoma, primary retinal dysplasia, persistent hyperplastic primary vitreous, retinopathy of prematurity, retinal dysplasia of Reese, Coats' disease, X-linked juvenile retinoschisis, osteoporosis pseudoglioma syndrome*, and especially *familial exudative vitreoretinopathy* (*FEVR*). This latter disease has been associated with mutations in four different genes (*NDP, FZD4, LRP5, TSPAN12*) to date. Thus, clinical genetic testing is essential for the proper diagnosis.

RESEARCH

Research continues to reveal more about how these genetic mutations cause the clinical features of Norrie disease and to explain the biological factors that lead to blindness, hearing loss, and characteristic features in cognition and behavior. With increased understanding of these issues, we hope to learn how to improve prevention or treatment of the clinical symptoms and to better support the patients and families affected by Norrie disease.



Sections through retinas of a healthy (left) and a Norrie mouse (right), showing the differences in the blood vessel system (labeled in red).

The high similarity between ND and FEVR has lead to the discovery that the gene products of the associated genes (*NDP, FZD4, LRP5, TSPAN12*) interact with each other in the so-called *canonical Wnt-pathway*. Mutations in one of these genes cause blood vessel defects, which appear to be the common mechanism underlying the different clinical symptoms.

NORRIE DISEASE ASSOCIATION

The Norrie Disease Association (NDA) is a diverse organization eager to serve individuals with ND, as well as their families, social circles, educators, employers, and medical professionals. We are working to expand our collective knowledge of ND by facilitating collaboration among these groups. Our vision is to become the primary resource and advocate for the international ND community. The NDA depends entirely on volunteers and member donations to operate, and its list of services will expand as the organization grows. *Learn more on:* www.norriedisease.org