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Case report

Case report: A case of Norrie disease due to deletion of the entire coding region of *NDP* geneYujia Zhou, MD^a, Michael J. Shapiro, MD^b, Barbara K. Burton, MD^{c,d}, Marilyn B. Mets, MD^{a,e}, Sudhi P. Kurup, MD^{a,e,*}^a Division of Ophthalmology, Ann & Robert H. Lurie Children's Hospital of Chicago, 225 E Chicago Ave, Chicago, IL, 60611, USA^b Retina Consultants, Ltd., 2454 E Dempster St Ste 400, Des Plaines, IL, 60016, USA^c Division of Genetics, Birth Defects & Metabolism, Ann & Robert H. Lurie Children's Hospital of Chicago, 225 E Chicago Ave, Chicago, IL, 60611, USA^d Department of Pediatrics, Northwestern University Feinberg School of Medicine, 420 E Superior St, Chicago, IL, 60611, USA^e Department of Ophthalmology, Northwestern University Feinberg School of Medicine, 645 N Michigan Ave, Suite 440, Chicago, IL, 60611, USA

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ABSTRACT

Purpose: Norrie disease is a rare X-linked recessive vitreoretinopathy. Variants of the *NDP* gene are associated with this condition. This case reports aims to demonstrate the variations of clinical presentations and exam findings of this disease.**Observations:** A retrospective chart review of the patient's ocular and systemic findings and imaging results was performed. The patient had received genetic testing, including mutational analysis of targeted genes associated with retrolental masses. The patient had a comprehensive eye exam for bilateral leukocoria, demonstrating large retrolental masses, anterior polar cataracts, stretched ciliary processes, and roving eye movements. B-scan ultrasonography and magnetic resonance imaging indicated total, funnel-shaped retinal detachments, which is a unique retinal configuration in Norrie disease. Genetic testing confirmed deletion of the coding region of all three exons in the *NDP* gene, which confirmed Norrie disease. He has not shown any extraocular involvement to date.**Conclusions and Importance:** This is a case demonstrating the association between deletion of the coding region *NDP* gene and Norrie disease. The phenotypical variation of this disease warrants further studies of genotype-phenotype correlations and mutations of the *NDP* gene.

1. Introduction

Norrie disease is a rare X-linked recessive disorder that is characterized by a varying degree of fibrovascular changes within the eyes.¹ Encoded by the "Norrie disease (pseudoglioma)" (*NDP*) gene (MIM: 300658; cytogenetic location: Xp11.3), Norrin is a protein that is thought to be important in retinal neuroprotection and retinal angiogenesis.^{2,3} Pathogenic variants of *NDP* are associated with Norrie disease and related vitreoretinopathies of milder phenotypes. To date, more than 100 mutations of *NDP* have been identified — which include missense, null, splice, and deletions — leading to an abnormal gene product.⁴ Patients with Norrie disease may have congenital blindness associated with abnormal findings such as leukocoria, iris atrophy, corneal opacity, cataract, and retinal dysgenesis⁵ with an associated fibrovascular mass (a.k.a. pseudoglioma).^{1,4} Secondary tractional

retinal detachment is very common at birth,⁶ and thus, there is a high risk of developing phthisis bulbi with age.⁷ In addition, there may be extraocular manifestations such as sensorineural hearing loss and mental cognitive and behavioral impairments.⁴ Herein, we present a case of Norrie disease due to a deletion of the coding region of *NDP* gene and the associated clinical findings, including some unique retinal configurations.

2. Case report

2.1. Clinical findings

A 7-week-old, African-American male was referred to our institution for bilateral leukocoria. His mother and primary care provider noted normal red reflexes until 5 weeks of age. His family history was

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significant for a paternal great uncle who had unilateral blindness causing strabismus at 3 years old and his paternal grandfather who had high myopia. On exam, the patient had roving eye movements and did not blink or wince to light in either eye. The anterior chamber of both eyes appeared quiet but shallow. The anterior segment was otherwise notable for an anterior polar cataract with fine persistent pupillary membrane and peripheral maldevelopment of the anterior leaflet of the iris. A large, white retroental mass could be seen in each eye, which had an irregular surface but no prominent vascular dilatation or tortuosity. The mass appeared to be stretching the ciliary processes, particularly in the right eye (Fig. 1A and B). B-scan of each eye demonstrated a funnel shaped retinal detachment but no hyperechoic spots within the intraocular mass that would be consistent with calcifications (Fig. 1C and D). Magnetic resonance imaging (MRI) of the brain and orbits (Fig. 2A) showed heterogeneous masses in each globe and retinal detachment with mild microphthalmia. The optic nerves were hypoplastic with markedly diminutive prechiasmatic size and a barely discernible optic chiasm. In addition, bilateral enhancement of the intraorbital optic nerves, oculomotor nerves, and trigeminal nerves was noted — albeit partially visualized in the case of cranial nerves III (Fig. 2B) and V (Fig. 2C). The patient was followed with serial exams and B-scans to ensure there was no calcification formation, and a normal *RB1* analysis helped rule out retinoblastoma. Cranial nerve enhancement raised the possibility of an infectious or inflammatory condition. TORCH titers, including for lymphocytic choriomeningitis virus (LCMV), were unremarkable. Lumbar puncture, complete blood count, and complete metabolic panel were also unremarkable. At the age of 3 months, his right eye had a funnel-shaped retinal detachment; his left eye showed central hyperechoic area with globe disorganization, posterior synechiae, retinal detachment in the periphery, and probable funnel detachment. Subsequently, he had vitrectomy of both eyes after which he was able to track light with both eyes. At surgery, the retinal detachment was directly viewed, confirming the funnel shape (Fig. 3). Genetic analysis ultimately revealed complete deletion of the *NDP* gene, confirming the diagnosis of Norrie disease. He underwent additional vitrectomy, membranectomy, and retinal repair of the right eye. The structural outcome resulted in an open funnel-shaped retinal detachment. His most recent visit at the age of 3.5 years old indicated no measurable vision in either eye, and his left eye was phthisical.

2.2. Genetic testing

Initial whole-genome microarray analysis at the Cytogenetics Laboratory of Lurie Children's Hospital was normal. Given the early onset of bilateral leukocoria with retroental masses and the inability of the microarray to detect small or single gene deletions, targeted gene analysis was performed at GeneDx to evaluate for retinoblastoma (*RB1*), Norrie disease (*NDP*), familial exudative vitreoretinopathy (FEVR) (*FZD4*, *TSPAN12*), and osteoporosis-pseudoglioma syndrome (*LRP5*). *NDP* analysis indicated complete deletion of the gene, confirming the diagnosis of Norrie disease. Exons 1–3 of *NDP* and their flanking splice sites were analyzed using PCR-amplification of genomic DNA extracted from the patient's peripheral blood. The test was designed to amplify and sequence the coding region of the gene, using cDNA as the reference. Table 1 shows the primer sequences that were used for PCR amplification of the *NDP* gene, and Fig. 4 shows the coordinates of the primers in relation to the exons. There was no amplification of the entire coding region of *NDP* (entire exons 1–2 and coding region of exon 3) and attempted amplification with a new preparation of DNA failed with repeat PCR. A control gene (*PTEN*) was able to be successfully amplified from the provided sample. Alternate primers were not found to be needed as allele drop-out was not a concern. The patient continued to have outside follow-up, so specific information on familial testing was unfortunately unclear. There was reported family history of “blindness” in the patient's sibling and uncle, but specific testing results were not available to confirm this.

3. Discussion

Norrie disease is caused by pathogenic variants of the *NDP* gene. *NDP* is comprised of three exons located on chromosome Xp11.3, which spans 28kb.^{8,9} Exons 2 and 3 are coding regions of *NDP*, while exon 1 is untranslated and may act as the promoter for gene transcription.^{4,10} As the protein product of *NDP*, Norrin is involved in regulating retinal development and regression of hyaloid vessels in the eye.^{3,11} It contains a cysteine knot motif, which is a highly conserved region in many growth factors and is important for the stable structure and proper folding of the Norrin protein.⁷ Mutations in the initiation and stop codons of *NDP* that cause Norrie disease have been identified.^{7,12,13} Non-cysteine mutations may also be associated with familial exudative vitreoretinopathy, Coats disease, and retinopathy of prematurity.¹⁴

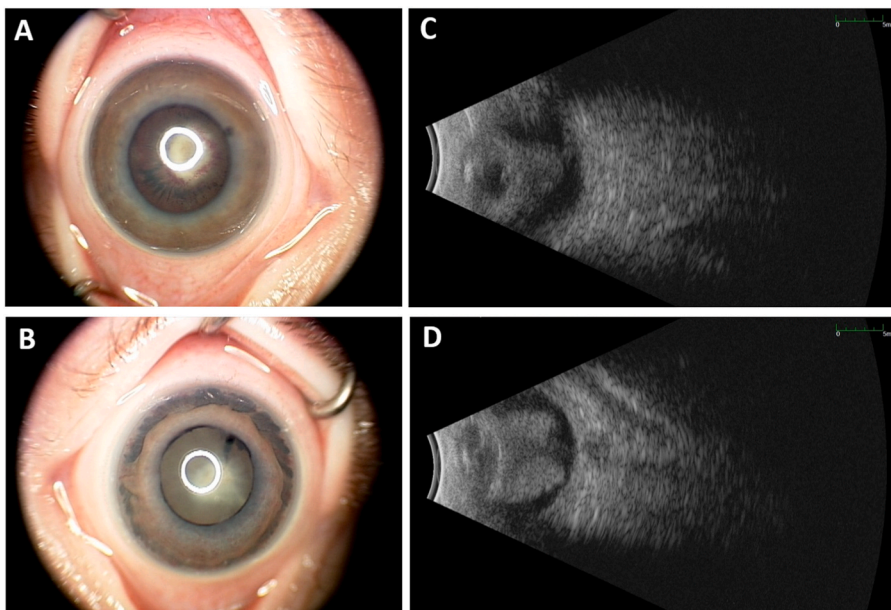


Fig. 1. External color photographs and B-scans. A–B: External color photographs of the right (A) and left (B) eyes highlight the large, white retroental mass in each eye with stretched ciliary processes (right > left eye) and anterior iris atrophy (left > right eye). C–D: B-scan ultrasonography of right (C) and left (D) eyes show a retroental mass taking up the majority of the posterior segment and absent of discrete hyperechoic spots that would indicate calcifications. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

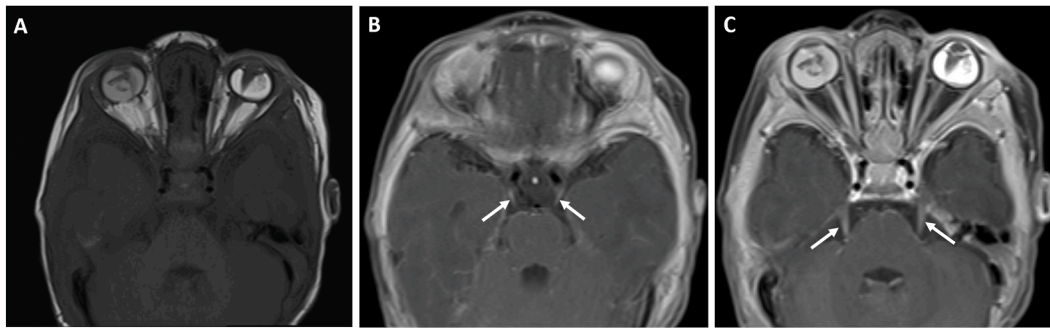


Fig. 2. Magnetic resonance imaging of the brain and orbits

A: Axial T1-weighted image showing heterogeneous masses in both eyes, funnel-shaped retinal detachment in the left eye, and mild microphthalmia of both eyes B–C: Axial fat saturated, T2-weighted image highlighting bilateral enhancement of cranial nerves III (arrows in B) and V (arrows in C).

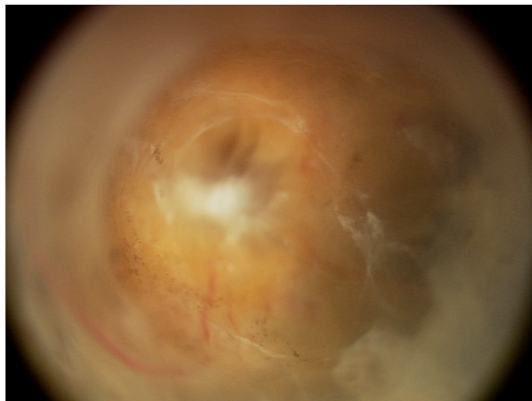


Fig. 3. Post-vitrectomy color fundus photograph demonstrating funnel-shaped configuration of retinal detachment. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Table 1

Primer sequences used for PCR amplification of the *NDP* gene.

| Exon | Forward Primer Sequence | Reverse Primer Sequence |
|-------|-------------------------|-------------------------|
| 1 (A) | CTGAGTCCCGATAACGA | GACTTCAAAGACCCGTTTCAT |
| 1 (B) | CCCTGTGTGCTTAAACAAC | GACTTCAAAGACCCGTTTCAT |
| 2 (A) | CTATTCTGGCCCTAGGAACAT | GCATAGAAAAGGATGCAGCTAG |
| 2 (B) | CTGGATCCTAGGAGGTGAAGC | AAAAGCCTCATTCTCCACAA |
| 3 | GCATTGAGCCACTGGTCTAAT | CTGCAAAGAAGTCCAGAGT |

Norrin is expressed on endothelial cells of the developing retina to provide protection for ocular capillaries and retinal neurons; in turn, the retinal neurons are involved in normal expression and processing of Norrin.^{15,16} Norrin binds to frizzled-4 (Fzd4) receptors as a dimer with a co-receptor, LRP5, which activates the Wnt/ β -catenin signaling pathway, acting on the developing endothelial cells to regulate retinal vasculature development.^{17,18} Disruption of this pathway may lead to dysgenesis of the retina, as well as abnormal angiogenesis in the eye, ear, or brain.^{17,18} Evidence has suggested that the neuroprotective effects of Norrin are also mediated by the Wnt/ β -catenin pathway, leading to an increased production of neuroprotective factors that is considered an independent process from Norrin’s role in vascular development and protection.¹⁶ Persistent fetal vasculature (PFV) syndrome also has been reported in previous studies in patients with Norrie disease. It is a result of abnormal regression of the hyaloid vasculature and may share a common molecular mechanism with Norrie disease.^{5,18}

Existing literature indicates that *NDP* deletions are associated with more severe disease manifestations than other types of mutations.^{5,11}

Our patient had many of the ocular features of Norrie disease: bilateral fibrovascular retrolental masses, cataract, PFV stigmata, and retinal detachment — causing severe vision impairment. However, his retinal detachment was similar to stage 5 retinopathy of prematurity (i.e., anterior and posterior, narrow-funnel retinal detachment) rather than the retinal dysgenesis hypothesized to be associated with more severe Norrie disease deletions.⁷

Larger deletions that extend beyond *NDP* may lead to more neurological abnormalities and other complications.^{10,19} Since our patient had deletion of the entire coding sequences of *NDP*, it is expected that he did not have any Norrin protein product and would have more profound impairments. Interestingly, our patient has not shown any signs of hearing loss or mental retardation, which are two common non-ocular features of Norrie disease. Although there was enhancement of the cranial nerves on the MRI, he did not have any corresponding neurological deficits. Hearing loss can be gradual and manifest later in life.¹² In mouse models of Norrie disease, Rehm et al. found that the hearing impairment purportedly has complete penetrance, but it may have variable phenotypic expression.²⁰ Previous reports have presented patients who had deletions of the coding regions of *NDP* (exons 2 and 3) who only had ocular manifestations. Epigenetic factors are thought to play a role in genotype-phenotype correlations, which is probably why even the same mutation in the *NDP* gene can result in different phenotypes.^{10,12,21} It has also been suggested that the severity of Norrie disease is more correlated with the age of the patient than the type of *NDP* mutation.²¹

4. Conclusions

In conclusion, we have reported a patient with deletion of the entire coding region of *NDP* gene that resulted in Norrie disease of a non-dysplastic ocular phenotype with neuroimaging findings but no clinically neurologic or other systemic issues thus far. There is no clear mechanism to explain the phenotypic variation of this disease, and it is difficult to discern genotype-phenotype correlations. Broader investigation of the role of the *NDP* gene and Norrin are required to understand their roles in Norrie disease and other vitreoretinopathies.

Patient consent

Written consent was obtained from the patient’s mother for the personal and/or clinical details along with the relevant images to be published in this study.

Institutional review board approval

The study was approved by Institutional Review Board of Ann & Robert H. Lurie Children’s Hospital of Chicago.

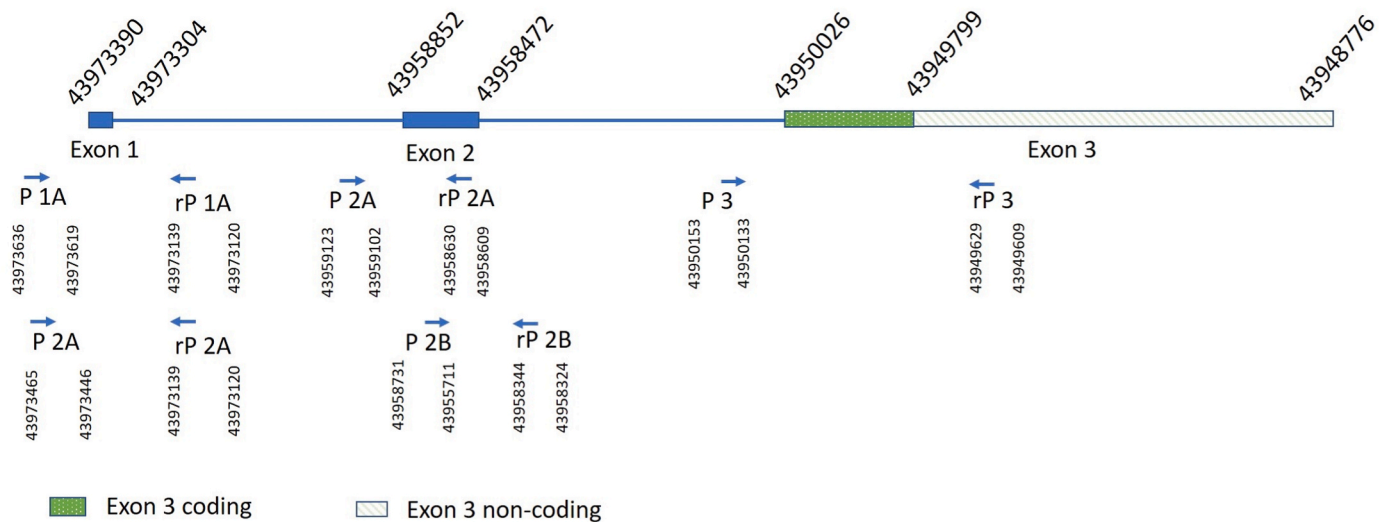


Fig. 4. Coordinates of primers used in PCR amplification and exons of *NDP* gene

P1A: Forward Primer 1A. rP 1A: Reverse Primer 1A. P1B: Forward Primer 1B. rP 1B: Reverse Primer 1B. P2A: Forward Primer 2A. rP 2A: Reverse Primer 2A. P2B: Forward Primer 2B. rP 2B: Reverse Primer 2B. P3: Forward Primer 3. rP 3: Reverse Primer 3.

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Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

Declaration of competing interest

The following authors have no financial disclosures: YZ, MJS, BKB, SK, MBM.

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