American Journal of Ophthalmology Case Reports 29 (2023) 101798

Contents lists available at ScienceDirect

American Journal of Ophthalmology Case Reports

journal homepage: www.ajocasereports.com/

Xp11.3 microdeletion causing Norrie disease and X-linked Kabuki syndrome

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ARTICLE INFO

Keywords:
Norrie disease
NDP
Norrin
KDM6A
Kabuki syndrome
Leukocoria
Retinal detachment
Vitrectomy

ABSTRACT

Purpose: To describe a novel case of Norrie disease and X-linked Kabuki syndrome caused by a microdeletion encompassing multiple genes on the X chromosome.

Observations: A 3-day-old boy born at full term had bilateral retrolental fibrovascular plaques. Surgery with lensectomy and vitrectomy revealed bilateral, closed funnel retinal detachments consistent with a clinical diagnosis of Norrie disease. In addition, the baby had congenital heart defects, hearing loss, and dysmorphic facies. His mother carried a clinical diagnosis of Kabuki syndrome. Genetic testing of the baby revealed an Xp11.3 microdeletion that included the *NDP* and *KDM6A* genes, confirming the baby had both Norrie disease and X-linked Kabuki syndrome. The mother was found via ultrawide-field fluorescein angiography to have asymptomatic peripheral retinal vascular anomalies, consistent with *NDP*-associated familial exudative vitreoretinopathy (FEVR).

Conclusions and importance: This is the first reported case of Norrie disease together with X-linked Kabuki syndrome. Contiguous gene deletions may explain some of the variable systemic involvement in Norrie disease.

1. Introduction

Norrie disease is a rare, X-linked retinopathy caused by loss-of-function mutations in the Norrie disease pseudoglioma (*NDP*) gene (OMIM: 300658). *NDP* is a 28 kb gene located on Xp11.3 that encodes the protein Norrin.[7,18] Norrin is a secreted growth factor that is vital to the regulation of retinal angiogenesis and development.[18]

A wide range of clinical phenotypes comprise the *NDP*-associated retinopathies. The most severe phenotype is Norrie disease, in which there is severe retinal disease present at birth. Often Norrie disease features fibrovascular masses ("pseudogliomas") that resemble persistent fetal vasculature (PFV) and can cause tractional retinal detachment of the posterior pole.[13] Alternatively, there can be total retinal detachment (RD) in a closed funnel configuration, with retrolental fibrovascular plaques. *NDP* mutations can also cause milder phenotypes with peripheral retinal avascularity and/or exudation, i.e., familial exudative vitreoretinopathy (FEVR).[13] Apart from vitreoretinal pathology, there may be other progressive ocular findings including cataract, iris atrophy, synechiae with secondary angle closure, corneal opacification, and ultimately phthisis bulbi.[13] Systemically, the majority of affected males also have sensorineural hearing loss, developmental delay, and intellectual impairment.

Near the *NDP* gene on chromosome Xp11.3 resides the *KDM6A* gene (OMIM: 300867). This gene encodes histone H3, which regulates cellular metabolism.[11] Loss-of-function mutations in *KDM6A* cause Kabuki syndrome type 2 (X-linked dominant Kabuki syndrome).[3,4,12] The Kabuki syndrome phenotype includes distinctive facial features, intellectual disability, hearing loss, and a spectrum of cardiovascular and musculoskeletal abnormalities.[3,5] Ocular manifestations frequently associated with Kabuki syndrome include eyelid/eyebrow abnormalities, strabismus, and amblyopia.[6]

Here we report the first case of simultaneous Norrie disease and Kabuki syndrome caused by a contiguous microdeletion encompassing the *NDP* and *KDM6A* genes.

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https://doi.org/10.1016/j.ajoc.2023.101798
Received 7 June 2022; Received in revised form 3 January 2023; Accepted 12 January 2023
Available online 19 January 2023

2. Case report

A 3-day-old Caucasian boy who was born at term was referred for bilateral leukocoria. In utero, congenital heart defects had been diagnosed, including a large ventricular septal defect, an atrial septal defect, and a hypoplastic aortic arch. At birth, he was also found to have microcephaly, ventriculomegaly, bowel dilatation, and hearing loss. External examination showed elongated palpebral fissures, wide and arched eyebrows, and low-set, posteriorly rotated ears.

On ophthalmic examination, the baby did not wince to light in both eyes. The anterior chambers were formed but shallow, and there were bilateral vascular pupillary membranes. Dilation was poor, but there appeared to be cataracts and retrolental fibrovascular plaques with no view to the retina. B-scan echography demonstrated hyperechoic lesions extending from the optic nerve to the posterior surface of the lens, concerning for bilateral funnel RD (Fig. 1).

The baby's mother carried a clinical diagnosis of Kabuki syndrome based on characteristic facies, strabismus, seizures, and learning difficulties. The mother's sister and mother also had Kabuki syndrome, but the baby's older sister did not. None of the family had undergone genetic testing. After the baby was born, focused chromosomal microarray (performed by a CLIA-certified laboratory) demonstrated a 1.9 Mb hemizygous deletion of chromosome Xp11.3 that included the *NDP* and *KDM6A* genes (Fig. 2). This microdeletion was inherited from his heterozygous mother who also underwent genetic testing that confirmed an identical microdeletion.

Although the parents understood that the prognosis was very poor, after multiple discussions they elected to proceed with bilateral, same-day vitrectomy.[17] In the first eye, after anterior chamber reformation, removal of a thick, rubbery, vascular pupillary membrane (Fig. 3A) and placement of iris hooks (Fig. 3B), the cataractous lens was removed via a limbal vitrectomy approach (Fig. 3C). The anterior hyaloid, which extended from the ciliary processes to the posterior lens capsule and retrolental fibrovascular plaque (Fig. 3D, **4A**), was incised (Fig. 4B) and released circumferentially, which allowed posterior displacement of the retrolental plaque. Although the plaque bridged the mouth of the funnel RD (Fig. 4C), the remaining retina was otherwise mobile without additional membranes (Fig. 4D). Trocars were then placed through the pars plicata, and meticulous dissection of the plaque was performed (Fig. 4C). However, the plaque was extremely adherent and the retina very atrophic, with many punctate, full-thickness atrophic retinal holes adjacent to the plaque. During dissection a frank retinal break was encountered so the surgery was concluded. There were similar intraoperative findings in the second eye.

Postoperatively, the baby was followed with serial examinations. There was no response to light bilaterally, but the eyes remain formed without evidence of phthisis four months later. MRI imaging of the brain revealed microcephaly and hydrocephalus. Electroencephalogram confirmed the presence of seizure episodes.

Since the baby's mother was heterozygous for *NDP*, she underwent ophthalmic examination and testing for possible FEVR. Her ocular examination was normal, but ultrawide-field fluorescein angiography showed mild bilateral peripheral avascularity, most prominent temporally (Fig. 5). Specifically seen in the proband's mother were faint telangiectatic endings, which are anatomic anomalies that have been reported in mild stages of FEVR.[10]

3. Discussion

The clinical presentation and systemic manifestations of *NDP*-associated retinopathies are highly variable. *NDP* deletion consistently causes severe retinal changes, whereas missense mutations can cause less severe phenotypes.[12] The most common extraocular findings are sensorineural hearing loss and cognitive impairment.[14] The baby in our study had both of these phenotypic manifestations as a result of his *NDP* deletion. Although *NDP* mutations can have intra- and inter-familial variability in retinal and auditory findings,[2,13] the presence of other systemic findings like those seen in our patient should prompt evaluation for a possible microdeletion syndrome. There are only a few prior reports of Xp deletions that include *NDP* and surrounding genes.[9,12,15] One study suggested that contiguous deletion of *MAOA* and *MAOB* may be responsible for the psychomotor impairment sometimes present in Norrie disease.[15] The family in the current study had a novel contiguous deletion of *NDP* and the nearby *KDM6A* gene, resulting in X-linked Kabuki syndrome along with Norrie disease (in the baby) and FEVR (in the mother). Since Kabuki syndrome features cognitive impairment, contiguous deletion of *KDM6A* may be an underrecognized cause of systemic involvement in Norrie disease.

Protein-truncating variants of *KDM6A* have a more severe phenotype than protein-altering variants.[8] A complete deletion of the gene, as in this family, likely causes the most severe Kabuki phenotype. Manifestations of Kabuki syndrome that carry the highest morbidity are cardiovascular (*i.e.*, coarctation of the aorta, atrial septal defect, ventricular septal defect), endocrine (*i.e.*, neonatal hypoglycemia, premature thelarche), and central nervous system (CNS) anomalies (*i.e.*, microcephaly, seizures). The baby in our study had all three of these phenotypic manifestations of Kabuki syndrome as a result of complete *KDM6A* deletion, whereas his mother had a less severe phenotype. Males with X-linked Kabuki syndrome typically have a more severe phenotype than females, likely because in females *KDM6A* can partially avoid X-inactivation, allowing some expression of the normal *KDM6A* gene.[18] While Norrie disease and Kabuki syndrome overlap with cognitive impairment, there are no previously reported cases of Norrie disease causing cardiovascular, endocrine, or severe neurologic deficits. Therefore, if a child with suspected Norrie disease has any of these manifestations, a secondary syndromic cause such as Kabuki syndrome should be investigated.

Microdeletion syndromes can be diagnosed using fluorescence in situ

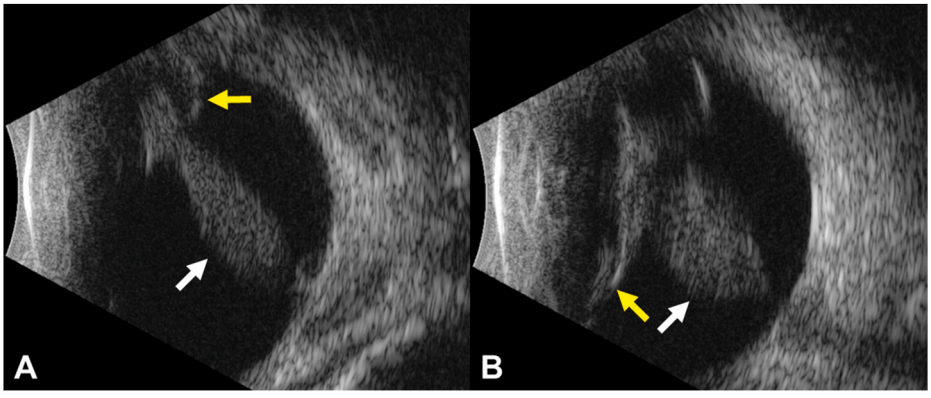

Fig. 1. B-scan echograms at presentation. In the right eye (*A*) there was a narrow, funnel-shaped membrane (*white arrow*) inserting at the optic nerve and extending into the anterior vitreous cavity, with a thinner membrane extending laterally to the pars plicata (*yellow arrow*). In the left eye (*B*) there was a similar but wider, funnel-shaped hyperechoic membrane (*white arrow*) with thinner hyperechoic membranes extending farther laterally (*yellow arrow*). Intraoperatively, both eyes were found to have closed funnel RDs, but the plaque was smaller in the left eye which had resulted in a less constricted anterior os of the funnel. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

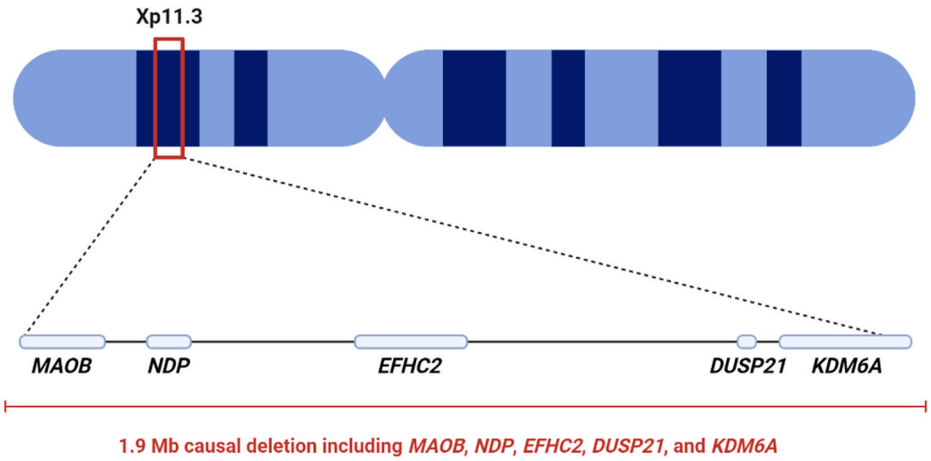

Fig. 2. Xp11.3 microdeletion containing *NDP* and *KDM6A* genes associated with Norrie disease and X-linked Kabuki syndrome.

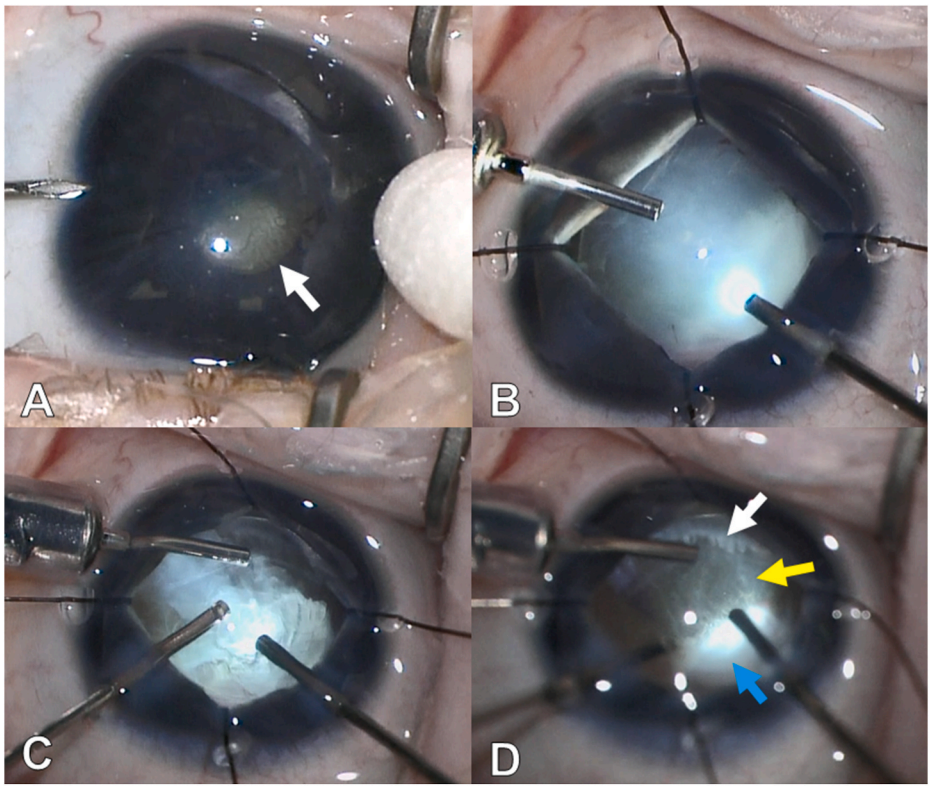

Fig. 3. Intraoperative still images of the right eye. (*A*) Thick pupillary membrane extending onto the iris with vascularization (*white arrow*), (*B*) cataractous lens, (*C*) limbal lensectomy, and (*D*) elongated ciliary processes (*white arrow*) with extension of the anterior hyaloid (*yellow arrow*) from the fibrovascular retrolental plaque (*blue arrow*) to the ciliary processes. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

hybridization, chromosomal microarray analysis, or whole exome sequencing.[1] Understanding the genetic mutation and associated abnormalities allows for early involvement of a multi-disciplinary team to address all relevant comorbidities. Genetic diagnosis is particularly important in planning future pregnancies, as pre-implantation genetic diagnosis or planned preterm delivery with early treatment can be offered.[19,20]

Since *NDP*-associated ocular phenotypes encompass a wide spectrum of disease, asymptomatic family members may need screening. Some obligate female carriers never manifest clinical disease in X-linked retinopathies because of variable X-inactivation. This is exemplified by the proband's mother, who was heterozygous for *NDP* deletion and was found to have asymptomatic FEVR. Asymptomatic patients with FEVR can develop visually significant complications such as exudation or neovascularization later in life, so they should be identified and monitored.

Surgical management of Norrie disease is difficult. Pre-operatively, B-scan may not definitively differentiate between a PFV-like, pseudoglioma phenotype and a closed funnel RD configuration, though in our case the B-scans suggested RD. The PFV-like phenotype is more amenable to surgical repair, although outcomes are poor.[21] The closed funnel RD configuration is usually inoperable. To our knowledge, there is only one PubMed-listed case of successful retinal reattachment of closed funnel RD in Norrie disease.[22] The surgery is technically challenging because the large, thick fibrovascular plaque bridging the mouth of the funnel RD is tightly adherent to a severely atrophic retina, making

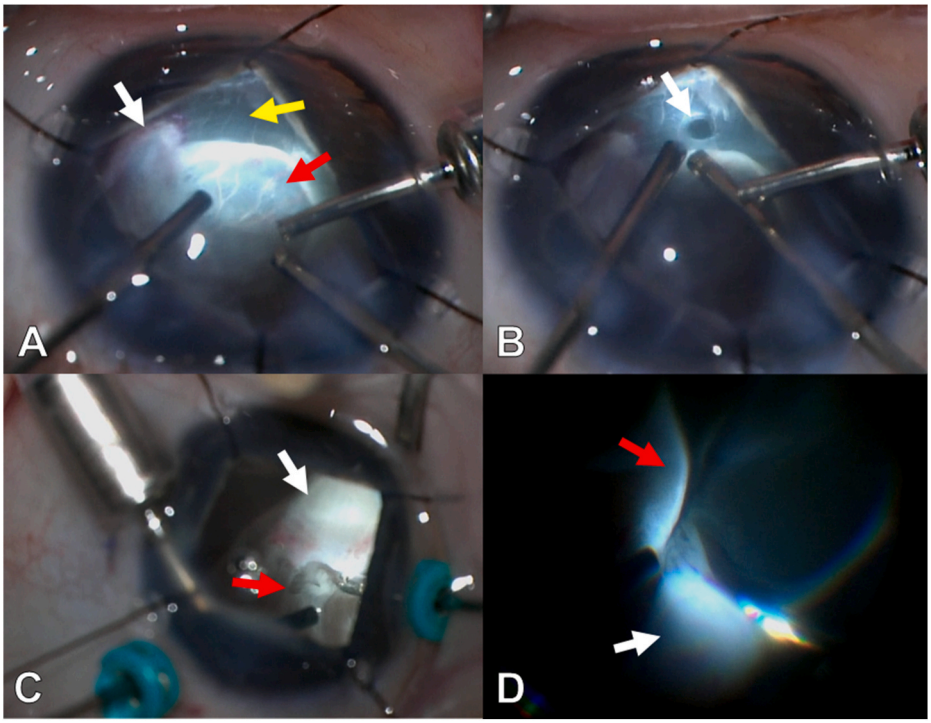

Fig. 4. Intraoperative still images of the left eye. (A) Fibrovascular retrolental plaque (*white arrow*) with total retinal detachment (*red arrow*) lateral to the mouth of the funnel, which is obscured by the plaque. The anterior hyaloid is denoted by the yellow arrow. (B) Incision (*white arrow*) in the anterior hyaloid. (C) Fibrovascular plaque (*white arrow*) with underlying atrophic retina (*red arrow*). (D) Fibrovascular plaque (*white arrow*) bridging the mouth of closed funnel retinal detachment; adjacent detached retina is denoted by the red arrow. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

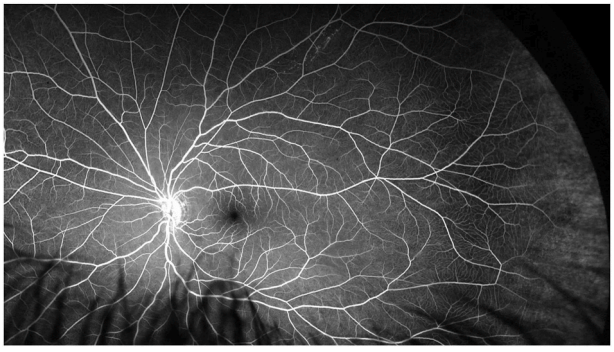

Fig. 5. Mid-phase ultrawide-field fluorescein angiography of the mother's left eye demonstrated subtle peripheral capillary dropout, most prominent temporally, with faint telangiectatic vascular endings.

a retinal break (with consequent relentless proliferative vitreoretinopathy) almost inevitable. While the primary goal is to re-attach the posterior pole, even when this is not possible the surgery may be considered useful because vitrectomy severs the abnormal connection (i.e., the plaque and the anterior hyaloid) between the anterior and posterior segments.[16] Release of the tractional stretch on the ciliary processes may decrease the risk of hypotony and future phthisis by allowing eye growth.[16]

4. Conclusions

Norrie disease can occur simultaneously with X-linked Kabuki syndrome due to contiguous Xp11.3 microdeletion. Contiguous gene deletions may explain some of the variable systemic involvement in Norrie disease.

Funding

Unrestricted research support from the Institute for Vision Research, The University of Iowa.

Authorship

All authors attest that they meet the current ICMJE criteria for Authorship. All work was completed at the University of Iowa Department of Ophthalmology and Visual Sciences.

Patient consent

Written consent was obtained from the patient's mother permitting publication of details about her and her child.

Declaration of competing interest

The following authors have no financial disclosures: MM, MRS, RGC, SAL.

JFR: Consultant, Carl Zeiss Meditec.

Acknowledgements

None.

References

1. Adam MP, Banka S, Bjornsson HT, Bodamer O, Chudley AE, et al. Kabuki syndrome: international consensus diagnostic criteria. *J Med Genet.* 2019;56:89–95.
2. Allen RC, Russell SR, Streb LM, Alsheikheh A, Stone EM. Phenotypic heterogeneity associated with a novel mutation (Gly112Glu) in the Norrie disease protein. *Eye.* 2006;20:234–241.
3. Banka S, Lederer D, Benoit V, Jenkins E, Howard E, et al. Novel KDM6A (UTX) mutations and a clinical and molecular review of the X-linked Kabuki syndrome (KS2). *Clin Genet.* 2015;87:252–258.
4. Bögershausen N, Gatinois V, Riehmer V, Kayserili H, Becker J, et al. Mutation update for kabuki syndrome genes KMT2D and KDM6A and further delineation of X-linked kabuki syndrome subtype 2. *Hum Mutat.* 2016;37:847–864.
5. Bögershausen N, Wollnik B. Unmasking kabuki syndrome. *Clin Genet.* 2013;83:201–211.
6. Cheon CK, Choi HY, Park SH, Jung JH, Kim SJ. Ocular manifestations in kabuki syndrome: a report of 10 cases and literature review. *Ophthalmic Genet.* 2021;42:101–104.
7. De Silva SR, Arno G, Robson AG, Fakin A, Pontikos N, et al. The X-linked retinopathies: physiological insights, pathogenic mechanisms, phenotypic features and novel therapies. *Prog Retin Eye Res.* 2021;82, 100898.

8. Faundes V, Goh S, Akilapa R, Bezuidenhout H, Bjornsson HT, et al. Clinical delineation, sex differences, and genotype-phenotype correlation in pathogenic KDM6A variants causing X-linked Kabuki syndrome type 2. *Genet Med*. 2021;23:1202–1210.
9. Jia B, Huang L, Chen Y, Liu S, Chen C, et al. A novel contiguous deletion involving NDP, MAOB and EFHC2 gene in a patient with familial Norrie disease: bilateral blindness and leucocoria without other deficits. *J Genet*. 2017;96:1015–1020.
10. Kashani AH, Brown KT, Chang E, Drenser KA, Capone A, Trese MT. Diversity of retinal vascular anomalies in patients with familial exudative vitreoretinopathy. *Ophthalmology*. 2014;121:2220–2227.
11. Lee MG, Villa R, Trojer P, Norman J, Yan KP, et al. Demethylation of H3K27 regulates polycomb recruitment and H2A ubiquitination. *Science*. 2007;318:447–450.
12. Murakami H, Tsurusaki Y, Enomoto K, Kuroda Y, Yokoi T, et al. Update of the genotype and phenotype of KMT2D and KDM6A by genetic screening of 100 patients with clinically suspected Kabuki syndrome. *Am J Med Genet*. 2020;182:2333–2344.
13. Scruggs BA, Reding MQ, Schimmenti LA. NDP-related retinopathies. GeneReviews (®). In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, et al., eds. *Seattle (WA): University of Washington, Seattle Copyright © 1993-2022*. Seattle: University of Washington; 1993 (GeneReviews is a registered trademark of the University of Washington, Seattle. All rights reserved. Number of).
14. Smith SE, Mullen TE, Graham D, Sims KB, Rehm HL. Norrie disease: extraocular clinical manifestations in 56 patients. *Am J Med Genet*. 2012;158a:1909–1917.
15. Suárez-Merino B, Bye J, McDowall J, Ross M, Craig IW. Sequence analysis and transcript identification within 1.5 MB of DNA deleted together with the NDP and MAO genes in atypical Norrie disease patients presenting with a profound phenotype. *Hum Mutat*. 2001;17:523.
16. Todorich B, Thanos A, Yonekawa Y, Capone Jr A. Repair of total tractional retinal detachment in Norrie disease: report of technique and successful surgical outcome. *Ophthalmic Surg Laser Image Retina*. 2017;48:260–262.
17. Walsh MK, Drenser KA, Capone Jr A, Trese MT. Early vitrectomy effective for Norrie disease. *Arch Ophthalmol*. 2010;128:456–460.
18. Ye X, Wang Y, Cahill H, Yu M, Badea TC, et al. Norrin, frizzled-4, and Lrp5 signaling in endothelial cells controls a genetic program for retinal vascularization. *Cell*. 2009;139:285–298.
19. Sisk RA, Hufnagel RB, Bandi S, Polzin WJ, Ahmed ZM. Planned preterm delivery and treatment of retinal neovascularization in Norrie disease. *Ophthalmology*. 2014;121:1312–1313.
20. Ebert JJ, Utz VM, Hartnett ME, Tiao G, Sisk RA. Planned preterm delivery and treatment of severe infantile FEVR with osteoporosis-pseudoglioma syndrome. *Ophthalmic Surg Laser Imag Retina*. 2022;53:228–232.
21. Walsh MK, Drenser KA, Capone Jr A, Trese MT. Early vitrectomy effective for bilateral combined anterior and posterior persistent fetal vasculature syndrome. *Retina*. 2010;30:S2–S8.
22. Todorich B, Thanos A, Yonekawa Y, Capone Jr A. Repair of total tractional retinal detachment in Norrie disease: report of technique and successful surgical outcome. *Ophthalmic Surg Laser Imag Retina*. 2017;48:260–262.