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NDP-related retinopathies: clinical phenotype of female carriers

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ABSTRACT

Background/aims Norrin cysteine knot growth factor (*NDP*) located on the X chromosome, was previously reported to cause Norrie disease and familial exudative vitreoretinopathy (FEVR), which are blindness-causing ocular disorders, in males. In this study, we aimed to explore the clinical characteristics of female carriers with *NDP* mutations.

Methods Twelve female carriers from 11 unrelated families with pathogenic *NDP* mutations were recruited. Clinical data were collected from the *NDP* carriers. Comprehensive ocular examinations, including best corrected visual acuity, slit lamp examination, fundus photography and fundus fluorescein angiography (FFA) were evaluated. Targeted gene or whole exome sequencing was performed in the probands, and Sanger sequencing was performed to confirm *NDP* mutations in female carriers.

Results Of the 12 females, 1 (1/12, 8.3%) presented with decreased visual acuity and 11 (11/12, 91.7%) were asymptomatic. Based on the FFA, peripheral vascular changes were noted in 66.7% (16/24) of the eyes of 75.0% (9/12) of the carriers. A total of 33.3% (8/24) had typical FEVR phenotype, 33.3% (8/24) had mild vascular abnormalities and 33.3% (8/24) was unremarkable. In addition, predominant changes such as telangiectatic endings (66.7%), anomalous circumferential vessel (37.5%), supernumerary vascular branching (33.3%), fluorescein leakage (29.2%), avascular area (8.3%), retina fold (8.3%) and peripheral straightening of retinal vessels (33.3%) were noted.

Conclusion Although *NDP*-related retinopathy is an X-linked recessive disorder, most of the female carriers of *NDP* exhibited clinical features of FEVR. Thus, timely examinations and lifelong monitoring should be conducted in the *NDP* female carriers.

Key messages

What is already known on this topic?

⇒ In a small portion of diseases with X-linked recessive inheritance pattern, phenotype of the female carriers has been reported, however, phenotypes of norrin cysteine knot growth factor (*NDP*) female carriers were rarely mentioned.

What this study adds?

⇒ Although *NDP*-related retinopathy is an X-linked recessive disorder, 33.3% female carriers had typical familial exudative vitreoretinopathy phenotype, 33.3% had mild vascular abnormalities.

How this study might affect research, practice or policy?

⇒ Timely examinations and lifelong monitoring should be conducted in the *NDP* female carriers.

INTRODUCTION

Norrin cysteine knot growth factor (*NDP*)-related retinopathy is a severe congenital X-linked blindness-causing ocular disorder.[1] It is associated with a wide spectrum of clinical phenotypes, including macular ectopia, radial retinal folds, vitreous haemorrhage, peripheral retina exudation and retinal detachment.[2] *NDP*-related retinopathies include Norrie disease (ND: OMIM 310600) and familial exudative vitreoretinopathy (FEVR: OMIM 133780). Although it can be extremely challenging to distinguish ND from FEVR, the main difference is that ND is usually associated with intellectual disability or progressive sensorineural hearing loss in early childhood.[3]

Germline mutations in *NDP*, which is located on chromosome Xp11.4, have been reported to be causative of ND or XL-FEVR in a recessive inherited manner.[3] Accordingly, it is believed that ND or FEVR affects males. However, emerging evidence has shown that female carriers with other X-linked gene mutations could also present with associated disorders, such as myotubular myopathy.[4] Expanding knowledge has suggested that skewed X chromosome inactivation (XCI) may be the driving factor. XCI is a critical mechanism for gene dosage compensation of the X chromosome, in which one of the alleles gets inactivated. The determination of which X chromosome is inactive is thought to be random. When the number of cells expressing the mutant allele exceeds the number of cells expressing the wide-type allele, females may show an increased risk for multiple phenotypes ranging from mild to severe.[5 6]

Although there are sporadic case reports that describe the female carriers with *NDP* mutations could be affected, the description of the abnormalities is limited.[7 8] Moreover, female carriers may present as asymptomatic FEVR patients. Based on studies conducted by Trese *et al*,[9] patients with stage 1 or 2 FEVR usually have normal visual acuity and an unremarkable posterior pole, and the only FEVR-related anomalies observed were in the far peripheral retina, where abnormalities are not always detectable by routine indirect ophthalmoscopic

examination. In these cases, wide-field fundus fluorescein angiography (FFA) was helpful in detecting under-recognised peripheral vascular changes in the early stage and for grading the stage of FEVR.[10] Herein, we prospectively performed angiographic and biogenetic evaluations of female carriers with pathological *NDP* mutations.

MATERIALS AND METHODS

Study samples

Twenty-four eyes of 12 females with hemizygous pathological *NDP* mutations were recruited for this study from November 2016 to August 2019.

Ocular examination

All carriers underwent a complete ophthalmic investigation, including best corrected visual acuity (BCVA) measured by the Snellen chart, intraocular pressure measurement and slit lamp examination of the anterior segment (cornea, iris and lens). FFA and fundus autofluorescence (FAF) were performed using Spectralis HRA (Heidelberg Engineering, Heidelberg, Germany), and wide-field FFA was performed using Optomap (OptosAdvance, Massachusetts, USA) after full mydriasis, and the peripheral retina was carefully evaluated. Optical coherence tomography (OCT) and OCT angiography (OCTA) were performed using Cirrus 5000 AngioPlex (Zeiss, Oberkochen, Germany). Any peripheral retinal vascular abnormalities were documented by two experienced ophthalmologists (SL and HL). The diagnosis of FEVR was according to the following reported criteria: (1) a lack of peripheral retinal vascular development; (2) full-term birth and (3) variable degrees of non-perfusion, vitreoretinal traction, subretinal exudation or retinal neovascularisation occurring at any age.[9]

Genetic analysis

DNA was extracted from peripheral blood samples of the female carriers, as well as from their available family members (affected children, parents and siblings). Targeted gene sequencing (TGS) (from 1 January 2015 to 31 December 2017) or whole exome sequencing (WES) (from 1 January 2018) was performed on the probands of the family, followed by bioinformatics analysis of the TGS or WES data. Sanger sequencing was further used to verify the *NDP* mutations in the female carriers and to perform a segregation analysis of their available family members. Copy number variant (CNV) was detected by SeqCNV and verified by semiquantitative multiplex PCR. A panel consisting of SIFT, Polyphen2, HDIV, LRT, GER and P++_RS was used to confirm whether the variants were pathogenic.[11]

RESULTS

Genetic confirmation of pathological *NDP* mutation in female carriers

Overall, 12 female carriers from 11 unrelated families were recruited in this study. Ten different pathogenic variants in *NDP* were identified through TGS or WES and validated by Sanger sequencing. Among the 10 mutations, 8 mutations—c.109C>T (p.Arg37*), c.281A>T (p.His94Leu), c.338G>A (p.Gly113Asp), c.362G>A (p.Arg121Gln), c.391T>G (p.Cys131Gly), c.334del (p.Gly113Alafs) and 2 CNVs, 1 whole gene deletion and 1 exon2 deletion—have been reported in previous studies.[12–15] Two novel mutations, c.181C>G (p.Leu61Val) and c.401G>C (p.*134Ser), were predicted to be pathogenic based on bioinformatic analysis (table 1). N4 and N6 had the same mutation c.391T>G (p.Cys131Gly), N9 and N10 had the same mutation c.109C>T (p.Arg37*).

Demographic and novel clinical characteristics of *NDP* mutation carriers

The mean age of the *NDP* carriers was 29.8 years, ranging from 22 to 41 years. No systemic features of Norries were detected in these female carriers. Only one patient (1/12, 8.3%) was symptomatic, complaining of bilateral visual loss in the past 2 years, with BCVA 20/500 and 20/125 in right and left eyes, respectively. She received laser photocoagulation in the left eye. The remaining 11 *NDP* carriers were asymptomatic, with BCVA 20/25 and more. The anterior segment was unremarkable in all eyes. Table 1 summarises the demographics of these *NDP* mutation carriers.

Fluorescein angiography characteristics of *NDP* mutation female carriers

Among the 12 female carriers, standard FFA was performed in 9, while wide-field FFA in 3. Peripheral sweeps with manual steering of the camera were undergone in all patients with standard FFA. Special care was taken to observe the temporal

Table 1 Clinical and genetic features of female carriers with norrin cysteine knot growth factor mutations

ID	Age range at examination (years)	Exon	cDNA change	Protein change	Mutation type	Reference	BCVA		FFA	
							OD	OS	OD	OS
N1	30s	3	c.362G>A	p.Arg121Gln	Missense	Reported	20/20	20/20	B	B
N2	20s	3	c.281A>T	p.His94Leu	Missense	Reported	20/20	20/20	C	C
N3	30s	3	c.334del	p.Gly113Alafs	Frameshift	Reported	20/20	20/25	A	A
N4	20s	3	c.391T>G	p.Cys131Gly	Missense	Reported	20/20	20/20	B	B
N5	40s	3	c.338G>A	p.Gly113Asp	Missense	Reported	20/20	20/20	B	B
N6	20s	3	c.391T>G	p.Cys131Gly	Missense	Reported	20/25	20/25	A	C
N7	20s	3	c.401G>C	p.*134Ser	Stoploss	Novel	20/500	20/125	A	A
N8	30s	2	whole gene deletion	–	CNV	Reported	20/20	20/20	C	C
N9	20s	2	c.109C>T	p.Arg37*	Non-sense	Reported	20/20	20/20	B	B
N10	20s	2	c.109C>T	p.Arg37*	Non-sense	Reported	20/20	20/20	A	A
N11	30s	2	exon2 deletion	–	CNV	Reported	20/20	20/20	C	A
N12	20s	3	c.181C>G	p.Leu61Val	Missense	Novel	20/25	20/25	C	C

A, typical FEVR phenotype; B, milder vascular abnormalities previously reported in familial exudative vitreoretinopathy patients; BCVA, best corrected visual acuity; C, normal vasculature; CNV, copy number variant; OD, right eye; OS, left eye.

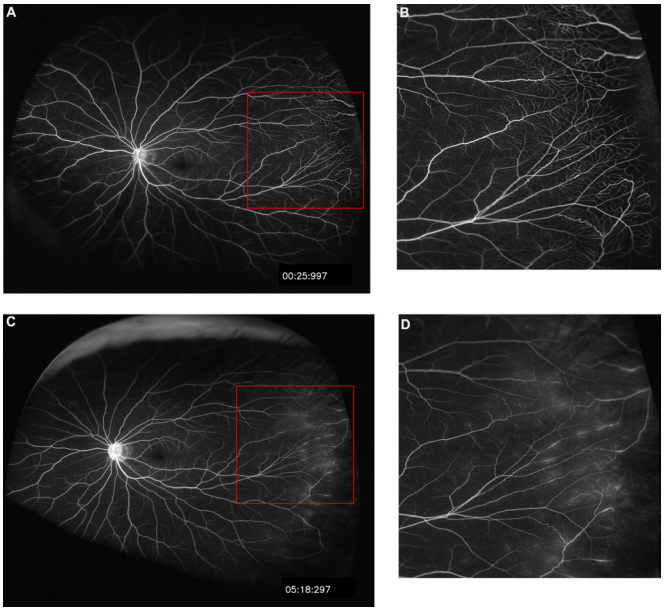

Figure 1 Fundus fluorescein angiography of N10 with norrin cysteine knot growth factor c.109C>T (p.Arg37*) mutation. (A) Early-phase wide-field angiogram shows supernumerary vascular branching and peripheral straightening of retinal vessels. (B) High-magnification image of the area in the red box in (A) reveals supernumerary vascular branching. (C) Late-phase wide-field angiogram shows mild leakage. (D) High-magnification image of the area in the red box in (C).

peripheral retina. Based on the FFA or wide-field FFA presentations, peripheral vascular changes were noted in 75% (18/24) of the eyes of 83.3% (10/12) of the carriers.

To further characterise the vascular abnormalities, these fundus features were classified into three grades: grade A, defined as typical FEVR phenotype, including avascular area, supernumerary vascular branching, peripheral straightening of retinal vessels and retinal folds; grade B, defined as milder vascular abnormalities which were previously reported in FEVR patients,[10] including telangiectatic endings, vascular dilation and anomalous circumferential vessel; and group C, referred to as normal vasculature.[2 9 10]

Overall, group A abnormalities were identified in 8 (33.3%, 8/24) eyes of five carriers. Three females (N3, N7 and N10) had bilateral FEVR (figure 1). Retinal folds were noted only in one female (N7) (figure 2), a patient in her 20s who visited the clinic with complaints of bilateral vision reduction. She had been treated previously with a laser for leakage in the peripheral retina of her left eye. Two females (N6 and N11) presented with unilateral FEVR; one eye was normal, and the other eye had an avascular area and supernumerary vascular branching and telangiectatic endings (online supplemental figure 1). A total of eight (33.3%, 8/24) eyes of four (33.3%, 4/12) carriers with peripheral abnormalities were identified with grade B changes (figure 3). The peripheral abnormalities of group B occasionally coexisted with the abnormalities of group A. The predominant changes noted were avascular area (8.3%), supernumerary vascular branching (33.3%), telangiectatic endings (66.7%), anomalous circumferential vessel (37.5%), fluorescein leakage (29.2%), retinal fold (8.3%) and peripheral straightening of retinal vessels (33.3%) (tables 1 and 2). Moreover, 25.0% (6/24) of the eyes from four carriers were identified with grade C with normal fundus (table 2).

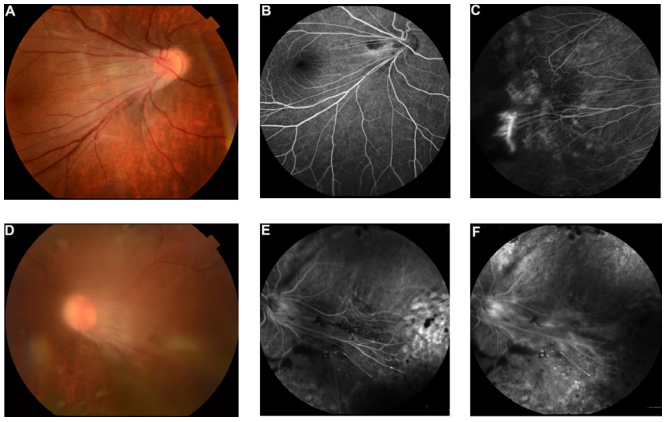

Figure 2 Fundus photographs and fundus fluorescein angiography (FFA) of N7 with norrin cysteine knot growth factor c.401G>C (p.*134Ser). (A) Fundus photograph of the right eye show prominent macular dragging. FFA shows supernumerary vascular branching, macular dragging and peripheral straightening of retinal vessels (B) and avascular peripheral retina with leakage (C). (D) Fundus photographs of the left eye show prominent macular dragging with vitreous opacity. FFA shows macular dragging and retinal fold (E), and avascular peripheral retina with leakage (F).

FAF, OCT and OCTA of *NDP* female carriers

FAF was available in three subjects (N2, N4 and N7), which was unremarkable (online supplemental figure 2). OCT was available in two subjects (N4 and N7). N4 has normal OCT presentations as well as unremarkable OCTA (online supplemental figure 3). N7 has macular ectopia and retinoschisis (online supplemental figure 4).

DISCUSSION

The *NDP* gene is located on the X chromosome and plays an important role in retinal vascular development, which is critical for the differentiation and maintenance of the retina.[16] Mutations in the *NDP* gene are associated with ND and FEVR.[3] The phenotype in males with *NDP* mutations has been well documented in previous reports,[8 17] whereas, female carriers of X-linked FEVR or ND have not been fully studied. To the best of our knowledge, this is the first report describing angiography characteristics in female *NDP* carriers.

One of the interesting findings of this study is that female carriers of the *NDP* mutation exhibited mild to severe peripheral vascular anomalies, which were previously reported in FEVR patients.[10] Although rare, in sporadic cases with *NDP* mutations, some female carriers have been noted exhibiting fundus abnormalities.[7 8 18] One female carrier with c.268del mutation was reported to have straightened retinal vessels and temporally dragged maculae bilaterally,[7] and the other female with heterozygous c.47T>C (p. L16P) mutation exhibited phthisis bulbi in her right eye, while her left eye was normal.[8] However, clinical manifestations, especially angiography features, have not been presented in detail. In this cohort, 66.7% of the female carriers were identified with mild to severe vascular abnormalities with the benefit of FFA and wide-field FFA. In particular, five patients in this cohort had typical FEVR-associated fundus features, including the avascular area, supernumerary vascular branching and retinal folds. Our results indicated that peripheral retinal telangiectasias were the most notable and common finding in female carriers with *NDP* mutations, followed by anomalous circumferential vessels, and supernumerary vascular branching.

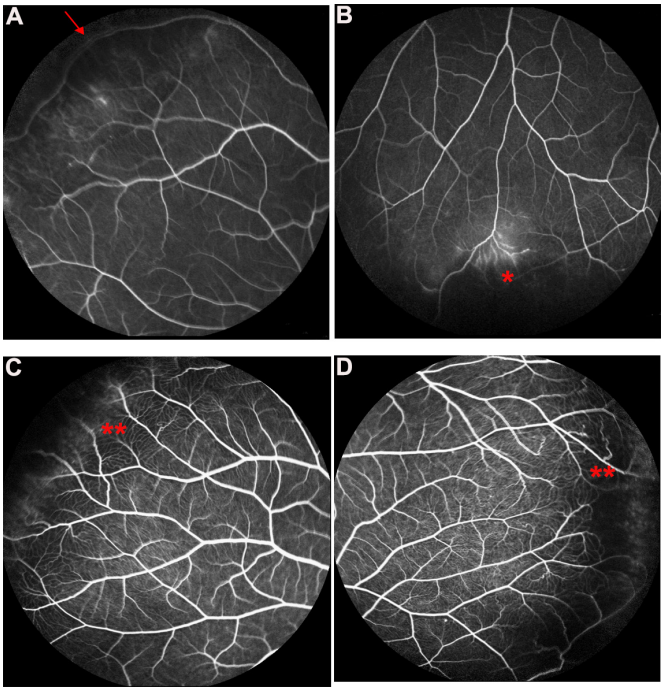

Figure 3 Other fundus changes detected by fundus fluorescein angiography (FFA). (A) and (B) FFA of N9 with c.109C>T (p.Arg37*) mutation. (A) Anomalous circumferential vessel (arrow), (B) Telangiectatic endings with leakage (asterisks). (C) and (D) FFA of N4 with c.391T>G (p.Cys131Gly) with telangiectatic endings and vascular tortuosity (asterisks).

Similarly, aberrant circumferential peripheral vessels, peripheral vascular telangiectasias, supernumerary vascular branching and peripheral avascular areas were observed in the other large wide-field angiographic survey of FEVR patients; however, the frequency is unclear.[10] Although little is known about the pathological mechanism, given the result that telangiectasias was common in female patients with *NDP* mutations, we hypothesise that the *NDP* gene may play an important role in capillary development. As the discourse of these subtle changes remains unknown, a long-term routine follow-up visit is recommended for 'healthy' female carriers of *NDP* mutations.

The reason for such a broad spectrum of phenotypes observed in *NDP* mutation carriers could be attributed to XCI. The *NDP* gene is located on chromosome Xp11.4. Recessive inheritance patterns led to a common agreement that female carriers were expected to be healthy. However, increasing evidence supports the fact that female carriers with X-linked genes could have full clinical manifestations and that XCI is the main reason.[19] XCI refers to a phenomenon in which one of two X chromosomes in females is randomly silenced to achieve dosage compensation between two sexes.[20] Therefore, the positive selection of cells with a mutated allele in heterozygous females may lead to a more severe stage of the disease.[21] The number of selected cells may determine the degree of the disease.

NDP was one of the genes that led to X-linked retinopathies. Indeed, several other genes have also been reported to cause retinopathies-*RPGR* causing retinitis pigmentosa and cone/cone-rod dystrophy, *RP2* causing retinitis pigmentosa, *CHM* causing choroideraemia, *RS1* causing X-linked retinoschisis, *NYX* causing complete congenital stationary night blindness, *CACNA1F* causing incomplete congenital stationary night blindness, *OPN1LW/OPN1MW* causing blue cone monochromacy, *GPR143* causing ocular albinism and *COL4A5* causing Alport syndrome.[22] A disease phenotype of variable severity was reported in female carriers with *RPGR, RP2*,[23] CMH,[24] CACNA1F[25] and GPR143.[26] No clinical disease phenotype was reported in female carriers with *RS1* and *NYX* mutations.

This study has several limitations. First, although FFA was performed in all the *NDP* female carriers, ultra-widefield imaging was performed in only three of the cases. Therefore, some peripheral retinal vascular findings may have been missed. Second, it would be more ideal to obtain multimodal images such as spectral domain OCT, OCTA and FAF in the *NDP* female carriers.

Table 2 Angiographic features of female carriers with norrin cysteine knot growth factor mutations

FFA findings	Eyes (n, %)
Avascular area	2 (8.3)
Supernumerary vascular branching	8 (33.3)
Telangiectatic endings	16 (66.7)
Anomalous circumferential vessel	9 (37.5)
Fluorescein leakage	7 (29.2)
Retinal fold	2 (8.3)
Peripheral straightening of retinal vessels	8 (33.3)

FFA, fundus fluorescein angiography.

CONCLUSION

Our study illustrates the under-recognised ocular findings in female *NDP* mutation carriers. The results indicated that most of the female carriers had vascular abnormalities or, in some cases, a full manifestation of FEVR. The clinical variability is suspected to be caused by variable XCI patterns, which can affect the disease severity. Thus, timely examinations and lifelong monitoring should be conducted in the female carriers with *NDP* mutations.

Contributors Study concept and design and drafting of the manuscript: XD, LH and LS. Data collection: LH, LS, XL, SL and TZ. Analysis and interpretation of the data: LH, LS, XL, SL and ZZ. Revision of the manuscript: XD and LH. Making the decision to submit the paper for publication: LH, SL, XL, SL, TZ, ZZ and XD. XD, responsible for the overall content as the guarantor.

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Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by Zhongshan Ophthalmic Center, Sun Yat-sen University (2014MEKY048) and the protocol adhered to the tenets of the Declaration of Helsinki. Informed consent was obtained from all participants or their guardians to obtain their clinical data and gene information.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

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