Case Reports in Ophthalmology

Case Rep Ophthalmol 2022;13:1015–1023
DOI: 10.1159/000527260
Received: May 30, 2022
Accepted: September 17, 2022
Published online: December 16, 2022

Case Report

MFRP-Associated Retinopathy and Nanophthalmos in Two Irish Probands: A Case Report

Ann O'Connell[a] Julia Zhu[a] Kirk A.J. Stephenson[a] Laura Whelan[b] Adrian Dockery[c] Jacqueline Turner[a] James J. O'Byrne[a] G. Jane Farrar[b] David Keegan[a]

[a]Mater Clinical Ophthalmic Genetics Unit, The Mater Misericordiae University Hospital, Dublin, Ireland; [b]The School of Genetics and Microbiology, Trinity College Dublin, Dublin, Ireland; [c]Next Generation Sequencing Laboratory, Pathology Department, The Mater Misericordiae University Hospital, Dublin, Ireland

Keywords

Retinitis pigmentosa · Nanophthalmos · *MFRP* gene · Inherited retinal degeneration · Ocular biometry

Abstract

The conjunction of nanophthalmos (NO) and retinitis pigmentosa (RP) provides challenges to effective clinical management while narrowing the genetic spectrum for targeted molecular diagnostics. This case study describes two not knowingly related adult cases of *MFRP*-associated retinopathy and nanophthalmos (MARN). Structural features including short axial lengths (mean 16.4 mm), steep keratometry (mean 49.98 D), adult-onset signs, and symptoms of retinal dystrophy and acquired disease (i.e., cataract, angle-closure glaucoma) were evident in both cases. Pathogenic variants in the *MFRP* gene impair both prenatal eye growth and childhood emmetropization while also leading to RPE/outer retinal degeneration in 75% of cases. We discuss the "small-eye" phenotype spectrum and associated defining characteristics, molecular mechanisms with particular focus on MFRP-associated NO with RP features (MARN), the spectrum of visual morbidities (e.g., extreme refractive error, amblyopia, cystoid macular lesions, early cataract) and the challenges of their treatment/surgical management.

Correspondence to:
Ann O'Connell, AnnOConnell@rcsi.ie

Case Rep Ophthalmol 2022;13:1015–1023
DOI: 10.1159/000527260

Introduction

Inherited retinal degenerations (IRDs) are a clinically and genetically heterogeneous group of variably progressive, visually debilitating disorders representing the primary cause of visual loss in the working-age population [1]. Panel-based next-generation sequencing resolves approximately 70% of cases, and clinical validation of detected genetic variants often requires deep phenotyping to rationalize [2]. IRDs may be associated with complex systemic and ocular phenotypes (e.g., sensorineural hearing loss, nephropathy, refractive error, cataract). Retinitis pigmentosa (RP) is an umbrella term encompassing >80 genetically distinct IRDs with common features of rod-cone dystrophy, characterized by nyctalopia, gradual visual field constriction, and eventual central visual loss [3]. Molecular diagnosis is a cornerstone of IRD clinics internationally, affording improved phenotypic understanding and access to clinical trials and research where available [3]. The *MFRP* genetic locus (11q23.3) has been implicated in NO associated with RP features in adulthood [4, 5]. NO is a rare condition that shares the "small-eye" phenotype with microphthalmos (MO); however, in NO, functionality and organization of ocular structures are preserved [4, 5]. Management of complex IRD focuses on clinical and molecular diagnosis, which opens access to supports (e.g., low vision aids, counselling) while visual potential can be optimized by addressing modifiable features (e.g., cataract, refractive error, cystoid macular lesions [CMLs]). Herein, we report two cases of MFRP-associated retinopathy and nanophthalmos (MARN) with a description of diagnostic and therapeutic challenges in this complex ocular phenotype.

Case Report

Proband 1, a 58-year-old female, was referred to the Adult Ophthalmic Genetics Clinic with a clinical diagnosis of RP. There was no family history of RP or consanguinity. She had a history of night blindness, reduced visual acuity (VA), peripheral visual field constriction, and dyschromatopsia. VA was LogMAR 0.78 and 1.0 in right and left eyes, respectively. Her intraocular pressure measurements were 14 mm Hg in each eye. There were bilateral, visually significant nuclear sclerotic cataracts. She had typical features of RP, including bilateral symmetrical bone spicule-like intraretinal pigment migration, arteriolar attenuation, as well as left optic disc drusen (Fig. 1a, b). Refraction demonstrated high hyperopia: +15.50/−0.25 × 45 and +16.75/−0.50 × 23 in right and left eyes, respectively. Atrophy of the retinal pigment epithelium (RPE) was marked peripherally with relative sparing of the macular RPE confirmed on autofluorescence imaging (Fig. 1c, d, Optos "California," Optos plc, Dunfermline, UK). There was evidence of CMLs (Fig. 1e, f) on spectral-domain optical coherence tomography (OCT, Cirrus 5,000, Carl Zeiss MediTec, Dublin, CA, USA). The subfoveal thickness measurements were 395 μm on the right and 407 μm on the left. At presentation, full-field Ganzfeld electroretinogram (Metrovision, Perenchies, France) was unrecordable, suggestive of advanced rod-cone dystrophy. There was limited/no response in LogMAR VA or CML to topical dorzolamide tid, and the patient was scheduled for routine bilateral cataract surgery. Proband 2 was referred to the same service with a clinical diagnosis of choroideraemia (OMIM#303100). This 76-year-old male was not knowingly related to proband 1 and was of non-consanguineous parentage. Family history was positive for a maternal uncle with RP without genetic diagnosis, now deceased. Spectacle correction was prescribed in the 1st decade for high hyperopia. Night blindness and peripheral field constriction were first noticed in the 4th decade, with reduced VA noted in the 7th decade. He reported a previous episode of right acute angle closure with resultant glaucoma. VA was LogMAR 2.4 and 0.48 in right and left eyes, respectively. His intraocular pressure measurements were 14 mm Hg in each eye. He was

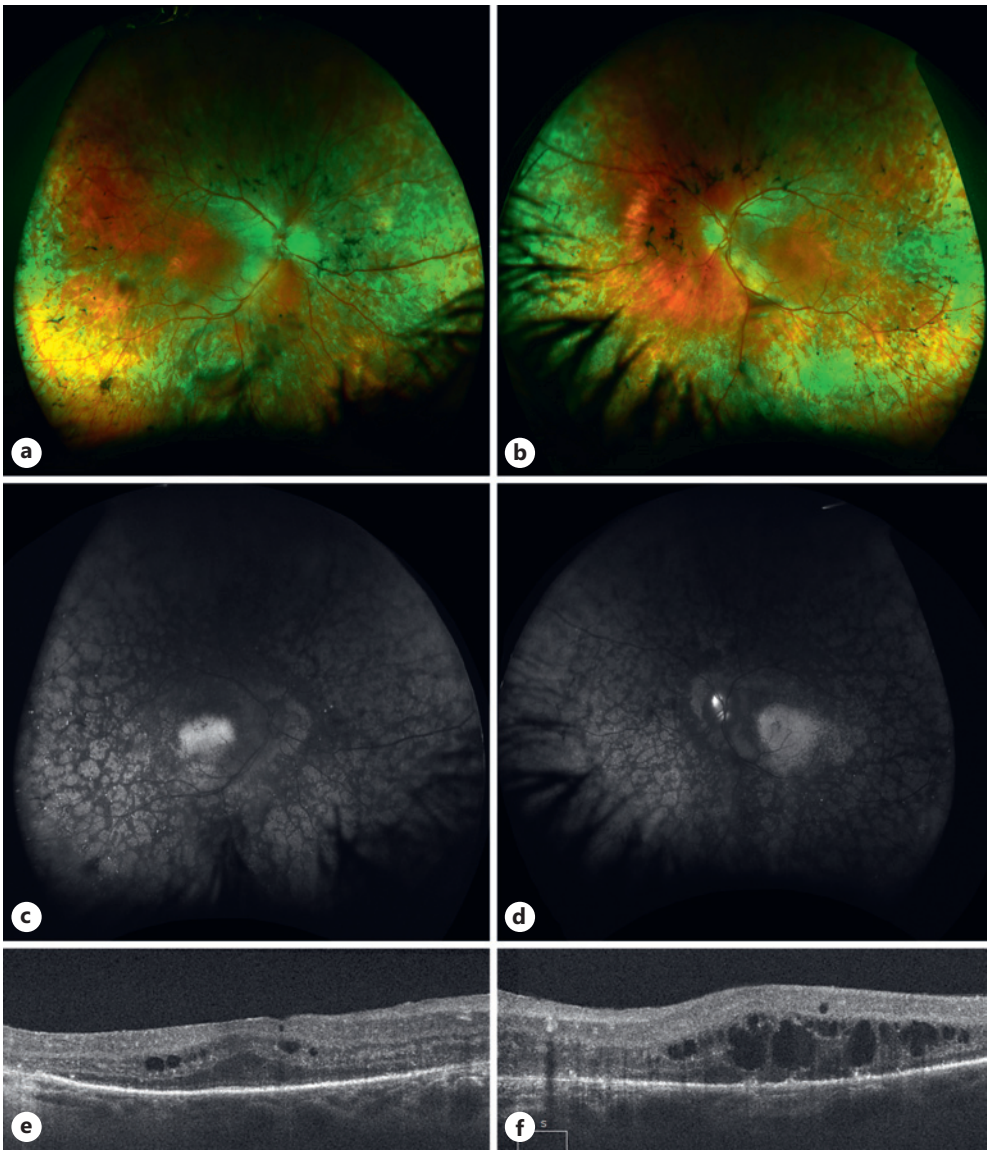

Fig. 1. Multimodal retinal imaging of proband 1, a 58-year-old female. **a**, **b** ultra-widefield (UWF) pseudocolour fundus photographs (Optos T2×00, Optos plc, Dunfermline, UK) of the right (**a**) and left (**b**) eyes showing a diffuse mottled retinal pigment epithelium (RPE). **c**, **d** Marked RPE atrophy and left optic disc drusen are demonstrated on UWF autofluorescence. e, f Spectral-domain optical coherence tomography confirms atrophy of the photoreceptor outer segments, thinning of the outer nuclear layer and CMLs (worse in the left (**f**) than right (**e**) eyes). NB: This CML may mask underlying foveal hypoplasia.

bilaterally pseudophakic with peripheral iridectomies. There were minimal signs of glaucomatous optic neuropathy. His degree of chorioretinal degeneration was more advanced than proband 1, with marked atrophy of outer retinal structures and no CML (subfoveal thickness was 278 μm right and 280 μm left) (Fig. 2). Panel-based next-generation sequencing detected biallelic canonical splice site variants in the *MFRP* gene (OMIM*606,227) on chromosome 11q23.3 (Table 1) in both patients. These variants, c.1124 + 1G>T and c.642–2A>G, have been classified as pathogenic (using the American College of Medical Genetics [ACMG] variant interpretation guidelines) [6], based on criteria such as global

Case Rep Ophthalmol 2022;13:1015–1023
DOI: 10.1159/000527260

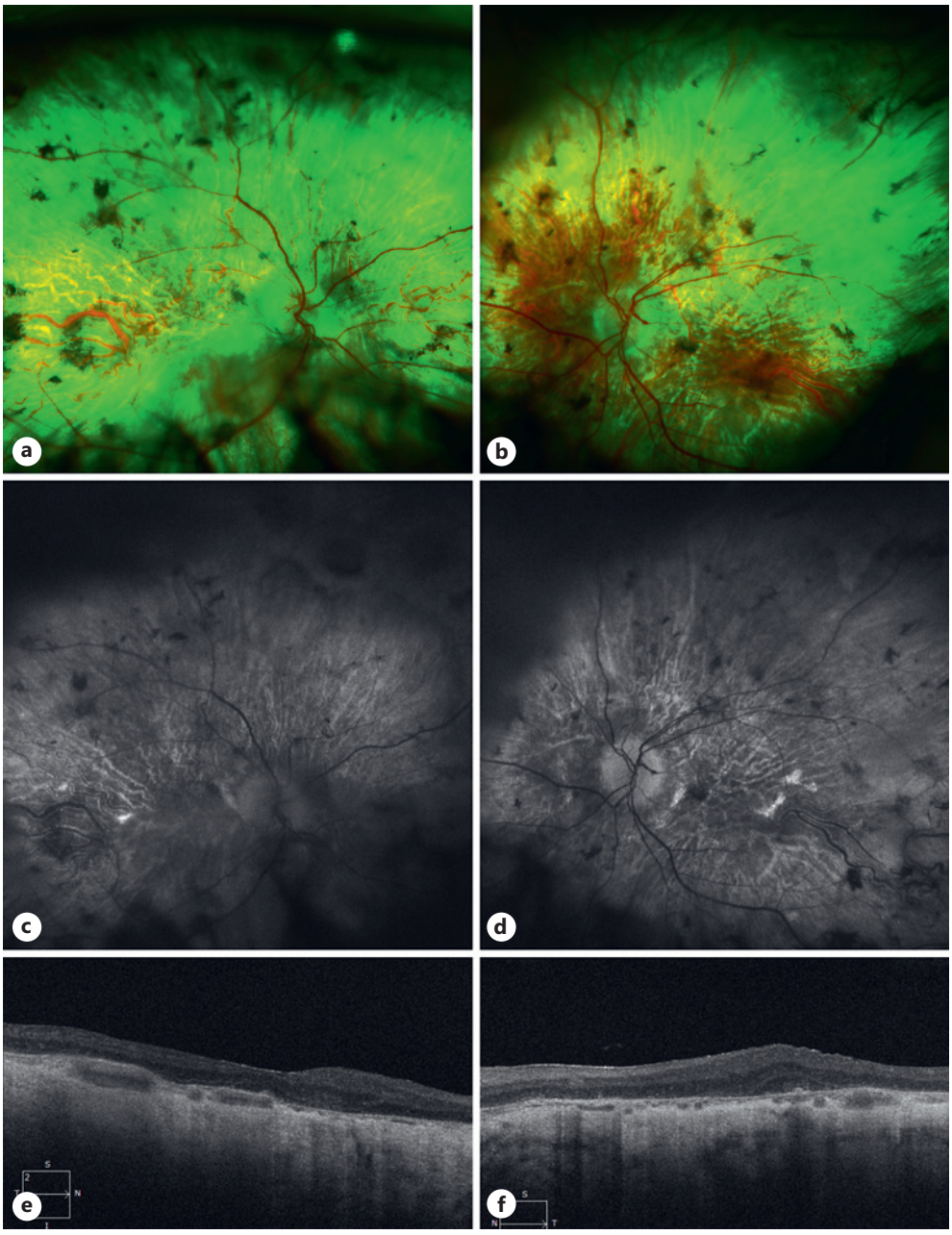

Fig. 2. Multimodal retinal imaging of proband 2, a 76-year-old male. **a**, **b** UWF pseudocolour fundus photographs (Optos T2×00) showing advanced chorioretinal degeneration with progression of bone spicule-like intraretinal pigment migration within the macula. **c**, **d** Largely extinguished autofluorescence (Optos T2×00) with a small residual macular island in the right and two small islands in the left. **e**, **f** OCT (Cirrus 5,000) showing near complete outer retinal atrophy at the fovea with choroidal thinning. NB Foveal hypoplasia may be masked by advanced chorioretinal degeneration.

population frequency (ACMG evidence: PM2_Supporting), in silico prediction of their effect on the splicing process location in the canonical splice site region (ACMG evidence: PVS1) and previous reports in the literature or in open-source genetic databases such as ClinVar (ACMG evidence: PS4_Moderate). Further deep phenotyping via optical biometry (IOLMaster 500, Carl Zeiss MediTec, Dublin, CA, USA) confirmed incredibly short axial length (AL, mean 16.40 mm)

with steep keratometry readings (mean 49.98 D, Table 2), meeting the criteria for nanophthalmos (NO), and thus, phenotype and genotype were in agreement. No other IRD-associated gene variants were detected.

Discussion

NO shares the "small-eye" phenotype with MO; however, in NO, functionality and organization of ocular structures are preserved [4, 5]. NO is a rare condition with a prevalence of 0.0009–0.017% in Western countries [7]. An acknowledged wide variety of diagnostic criteria (e.g., AL cutoffs) across the literature may cause variance in national ophthalmic anomaly registers [4, 8]. For example, MO and NO can be differentiated by AL criteria of 18.5–20.5 mm and 16.0–18.49 mm, respectively [5, 7]. However, these are somewhat arbitrary cutoffs as genotype-driven clinical studies (e.g., *MFRP*-associated NO) suggest that autosomal recessive (AR) NO likely represents the extreme end of hyperopia while heterozygous carriers and those with milder biallelic mutations may manifest less severe axial hyperopia [5]. Furthermore, AL is not routinely assessed, particularly in children where cooperation may be limited, unless it will impact clinical management (e.g., pre-operatively for cataract surgery). Some sources consider NO a special subtype of MO, distinguished by the histopathological finding of abnormal collagen fibrils in all three scleral layers [4]; abnormal scleral thickening and inelasticity [4, 5, 7] are thought to impair normal postnatal eye growth and trans-scleral vortex vein drainage/flow, likely underpinning the acquired pathologies of nanophthalmic eyes (e.g., secondary angle closure, uveal effusion syndrome, and retinal detachment) [4]. Furthermore, eyes with NO demonstrate increased incidence of crystalline lens abnormalities compared to MO [4]. The lens in NO is unusually thick (>150% average for age-matched individuals) in anteroposterior dimension which is attributed to lack of horizontal/radial tension of a non-expanding ciliary ring [5]. Terminology used includes "simple MO," where ocular contents are axially compressed without other structural abnormalities or "complex MO," when short AL is associated with congenital ocular malformations (e.g., colobomata, anterior segment dysgenesis, persistent foetal vasculature) [7].

NO, anophthalmos, MO, and coloboma (NAMC) can be grouped for practical clinical purposes as a spectrum of embryologic congenital "small-eye" abnormalities, estimated to account for up to 20% of blindness and severe visual impairment in children worldwide [8]. NAMC has a combined incidence of 0.0119% and is bilateral in 55% of affected

Table 1. *MFRP* Genotypes and American college of medical genetics classification

	Transcript ID	Variant 1	Chromosomal location (GRCh37)	AF (NFE)	V1 classification	Variant 2	Chromosomal location (GRCh37)	AF (NFE)	V2 classification
Proband 1	NM_031433.3	c.1124+1G>T, *p.*(?)	11:119,214,525	0.0002352	Pathogenic	c.1124+1G>T, *p.*(?)	11:119,214,525	0.0002352	Pathogenic
Proband 2	NM_031433.3	c.1124+1G>T, *p.*(?)	11:119,214,525	0.0002352	Pathogenic	c.642–2A>G, *p.*(?)	11:119,215,716	0.0001029	Likely pathogenic

V1 – variant 1. V2 – variant 2. AF (NFE) = allele frequency in non-Finnish Europeans (gnomAD v3.1.2).
Variant classification is based on Blueprint Genetics variant classification scheme (https://blueprintgenetics.com/variant-classification/).

Table 2. Refraction and optical biometry (IOLMaster 500; Carl Zeiss MediTec, Dublin, CA, USA) characteristics of both probands

	Phakic refraction	AL (R/L)	Ks	ACD	WTW (R/L)
Proband 1	R: +15.50/−0.25 × 45 L: +16.75/−0.50 × 23	R: 16.33 mm L: 16.40 mm	R: 47.00/47.85 D L: 46.87/48.01 D	R: 2.62 L: 2.69	R: 12.1 L: 12.0
Proband 2	R: +10.25/−2.00 × 92 L: +8.50/−0.25 × 169	R: 16.41 mm L: 16.45 mm	R: 52.16/52.98 D L: 52.49/52.49 D	R: 2.73 mm L: 2.03 mm	R: – L: –
Normal ranges	−1.00 to +1.50 D	22–24 mm	42–44 D	2.5–3.5 mm	11.5–12 mm

AL, axial length; D, dioptres; K, keratometry; L, left; R, right; WTW, white to white; NB Values indicated by "-" were unavailable.

children [8]. In a prospective epidemiological study in the UK, Shah et al. [8] did not differentiate NO from MO; inclusion was based on AL, where available, and physician discretion on clinical exam in the remainder. Similarly, Ragge et al. [9] grouped "small-eye" conditions together in terms of practical clinical management strategies. This again acknowledges that standardized classification within this spectrum of related conditions is lacking [8].

The NAMC spectrum of conditions has complex aetiology, with contributions from chromosomal, monogenic, and environmental factors [10]. Genotype-driven deep phenotyping shows that this clinical grouping may represent multiple different embryonic eye growth pathways under one heading (e.g., colobomata are not seen in *MFRP*-associated NO as *MFRP* expression begins in the 2nd trimester), though there may be interaction between several regulatory mechanisms [5]. Such anomalies may occur in isolation or a part of a syndrome (up to 50%) such as "coloboma, heart defects, atresia of nasal choanae, growth retardation, genital, and ear abnormalities (CHARGE) syndrome" [9]. Shah et al. [8] report higher prevalence of NAMC amongst children of Pakistani and Bangladeshi ethnicity (X3.7 times higher risk) and suggest increased incidence is seen in the context of socioeconomic deprivation. Within this spectrum of "small-eye" conditions, NO is thought to have a strong genetic basis, with both familial and sporadic cases reported [4, 11]. Up to 70% receive a genetic diagnosis while a degree of the remainder may be attributed to developmental noise, environmental factors in utero, or both; however, complex genetic-environmental interplay may have a role [10]. AR forms express a more severe phenotype than autosomal dominant (AD) cases [11]. Several genetic loci have been implicated in familial NO, most notably the *MFRP* (AR, 20% of NO, 11q23.3), *PRSS56* (AR, 2q37.1), *CRB1* (AR, 1q31.3), *BEST1* (AD, 11q12.3), and *TMEM98* (AD, 17q11.2) genes and 2 additional loci at chromosomes 2q11-q14 and 11p12-q13 [4, 5]. The *MFRP* gene (OMIM*606,227) encodes a type-II transmembrane protein which contains a cysteine-rich domain essential for Wnt binding and signalling [12]. It is expressed in the RPE, pigmented and non-pigmented ciliary epithelium, and in very low levels in the brain [4, 13]. The most commonly reported pathogenic *MFRP* variant is the c.1124 + 1G>T canonical splice site variant (intron 9) [13], in either homozygous or compound heterozygous conformations [12]. Implicated genes are expressed in retina (*CRB1*), RPE (*MFRP, TMEM98, BEST1*), ciliary body (*MFRP, TMEM98, BEST1*), and sclera (*TMEM98, PRSS56*) and are all transmembrane proteins, with the exception of *PRSS56* (intracytoplasmic) [4, 5].

Normal eye growth is affected by factors such as complex interplay between retina, RPE, and sclera, with feedback via focus/defocus on photoreceptors. *MRFP* is first detected embryologically at 14 weeks, thus, does not participate in ocular growth until after optic cup formation, providing an explanation why there are no associated early globe defects (e.g., colobomata) in MARN [5]. Embryonic function of the *MFRP* gene is necessary for the eye to

achieve normal dimensions by the third trimester [5], with dysfunction of the NO-implicated genes appearing to interrupt this process.

MFRP also substantially contributes to postnatal ocular growth regulation (childhood) and RPE maintenance (adulthood); thus, it has secondary implications for ongoing photoreceptor function (i.e., may be associated with a progressive retinal dystrophy, termed MARN herein and demonstrated in both clinical case report subjects) [4]. Foveal hypoplasia with corrected LogMAR VA of 0.3 has been reported in isolated *MFRP*-associated NO (i.e., without RP) which likely represents the impaired foetal axial eye growth and congested anatomy of the posterior segment, rather than a primary photoreceptor dysfunction [5, 14].

The phenotype of subjects with biallelic *MFRP* null variants has been reported as high hyperopia with a globe volume 25% of that expected for age, with a shorter AL than the typical neonatal eye [5]. Sundin et al. [5] postulate that, in *MFRP*-NO, all postnatal eye growth is exclusively axial expansion of the anterior segment with no change in posterior segment dimensions. Lack of ciliary ring expansion causes a round/thick crystalline lens and maintains steep corneal curvatures, predisposing to angle closure, which occurs in approximately 12.5%, as seen in 1 eye of our probands [5]. Overall, disruption of growth pathways (pre- and postnatal) in this group of ocular disorders leads to mismatch of AL and lens/corneal refractive power causing large hyperopic refractive errors and subsequent visual impairment [4]. Despite compensatory increase in corneal power (mean 50D), only one-third of hyperopia is corrected by this mechanism [5]. Children with a "small-eye" phenotype, deprived of the normal emmetropization process, demonstrate extreme refractive error through combined axial and refractive hyperopia, inciting a risk of amblyopia and visual morbidity in adulthood.

Focusing on NO with associated RP features*, MFRP, CRB1,* and *BEST1* gene variants have been associated with adult-onset RP features on a background of NO [4, 5]. The discriminating characteristic being that RP features are not grossly present at birth in NO while anterior and posterior segment anomalies in "complex MO" are congenital [10, 11]. Out of 13 biallelic *MFRP* variants with detailed phenotyping reported on ClinVar, 75% manifested RP features in addition to NO [13]. There are no known reported extraocular syndromic manifestations [5]. Notably, in our national study of >1,000 Irish IRD patients, only 4 unrelated patients (~0.4%) had an *MFRP* genotype, though the authors note that this study investigated IRD pedigrees and not specifically individuals with NO/NAMC spectrum [2].

MARN patients develop early cataracts, a known association of the coexistent IRD/RP phenotype [3] and affecting both of our case report subjects. Cataract surgery is challenging in eyes with short AL due to deep set globe anatomy, shallow anterior chambers (endothelial injury, iris prolapse), and a risk of uveal effusions (intraoperative or post-operative). There is an increased risk of complications such as posterior capsule rupture, severe post-operative uveitis, aqueous misdirection, CML, vitreous haemorrhage, and retinal detachment [4, 7]. RPE-pump dysfunction exacerbated by surgical inflammation and a higher complication rate (e.g., posterior capsule rupture) may lead to CML, refractory to standard management strategies (e.g., topical non-steroidal anti-inflammatory agents, topical CAIs). Management of post-operative choroidal effusions is also challenging, due to both anatomical and histopathological features (i.e., thickened yet weakened sclera with impaired venous drainage via vortex veins; intraoperative scleral windows may be considered) [7]. Post-operative target refraction prediction is statistically less accurate in short eyes, requiring the judicious use of intraocular lens formulae best suited to shorter AL (e.g., Kane, Hoffer Q, Holladay 2, and Haigis formulae) [7]. Up to 67% of NO eyes achieve a post-operative refraction within 1.00 D of target refraction [7]. There is a paucity of published data on post-op refractive outcomes for the subgroups with NO and coexistent IRD/MARN. Patients should be counselled regarding the guarded prognosis/outcomes of cataract surgery in MARN due to underlying retinal

dysfunction. While 75% of isolated NO patients (i.e., without RP) attain up to 3 Snellen lines of improvement, these figures may not be attained for MARN eyes [7].

In summary, the extreme short AL, high-keratometry readings, and scleral abnormalities associated with MARN predispose MARN patients to a number of blinding acquired pathologies including (1) amblyopia due to anisometropic hypermetropia, (2) angle-closure glaucoma (as evident unilaterally in proband 2, HM vision), (3) retinal detachment, (4) premature cataract, and (5) uveal effusion syndrome [4] and CML, as demonstrated in proband 1. For such patients where NO coexists with features of progressive outer retinal degeneration, the surgical management of early, visually significant cataract poses particular challenges. The primary take-away message is that, for the ophthalmologist, often the primary carer, early clinical and genetic diagnosis of both the NAMC spectrum of congenital eye anomalies and associated IRD benefit the patient and family. This reflects the focus of international ophthalmic genetics services internationally on prompt molecular characterization.

The first approved gene therapy is available for biallelic *RPE65*-associated retinopathy (Luxturna™), and examples of ongoing clinical trials include for retinopathy associated with the *RPGR, USH2A, ABCA4, CEP290, CHM* genes [3]. Even without immediate, gene-therapy implications, optimizing visual potential (e.g., correction of refractive error, glaucoma screening), and treating symptomatic complications (e.g., cataract, CML), with molecular characterization as the cornerstone [3, 15] leads to better outcomes. The ophthalmologist often coordinates multidisciplinary team input (i.e., ophthalmic physician/surgeon, molecular and clinical geneticists, genetic counsellors, other medical specialties as appropriate), efficient and equitable access to treatment, visual rehabilitation strategies, and genetic counselling for parents/families [8, 9, 15].

Acknowledgments

The authors would like to thank Ophthalmic Photography Department Mater Misericordiae and Mater Private Hospitals, Dublin, Ireland.

Statement of Ethics

This study abided by the tenets of the Declaration of Helsinki. All patients provided written informed consent for participation and publication of data and images. All data in this manuscript have been anonymized to protect patient confidentiality. This study protocol was reviewed and approved by the Institutional Review Board of the Mater Misericordiae University Hospital, Dublin, Ireland, approval number (1/378/1,358).

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

Funding was supplied for this study by grant awards from Fighting Blindness Ireland (FB Irl; FBCRE18, FB2020DOC, FBMMUH20, FBMMUH21). The funder was not actively involved in the preparation of data or of the manuscript.

Author Contributions

Conceptualization: Ann O'Connell, Julia Zhu, and Kirk AJ Stephenson. Manuscript creation: Ann O'Connell, Julia Zhu, Kirk AJ Stephenson, and Laura Whelan. Manuscript editing/revision: Ann O'Connell, Julia Zhu, Kirk AJ Stephenson, Laura Whelan, Adrian Dockery, Jacqueline Turner, James J. O'Byrne, G. Jane Farrar, and David Keegan. Funding acquisition: G. Jane Farrar and David Keegan.

Data Availability Statement

All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author. Anonymized source data can be shared upon reasonable request.

References

1 Liew G, Michaelides M, Bunce C. A comparison of the causes of blindness certifications in England and Wales in working age adults (16–64 years), 1999–2000 with 2009–2010. BMJ Open. 2014;4(2):e004015.
2 Whelan L, Dockery A, Wynne N, Zhu J, Stephenson K, Silvestri G, et al. Findings from a genotyping study of over 1000 people with inherited retinal disorders in Ireland. Genes (Basel). 2020;11(1):105.
3 Georgiou M, Fujinami K, Michaelides M. Inherited retinal diseases: therapeutics, clinical trials and end points-a review. Clin Exp Ophthalmol. 2021;49(3):270–88.
4 Carricondo PC, Andrade T, Prasov L, Ayres BM, Moroi SE. Nanophthalmos: a review of the clinical spectrum and genetics. J Ophthalmol. 2018;2018:2735465.
5 Sundin OH, Dharmaraj S, Bhutto IA, Hasegawa T, McLeod DS, Merges CA, et al. Developmental basis of nanophthalmos: MFRP Is required for both prenatal ocular growth and postnatal emmetropization. Ophthalmic Genet. 2008;29(1):1–9.
6 Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of medical genetics and genomics and the association for molecular pathology. Genet Med. 2015;17(5):405–24.
7 Yosar JC, Zagora SL, Grigg JR. Cataract surgery in short eyes, including nanophthalmos: visual outcomes, complications and refractive results. Clin Ophthalmol. 2021;15:4543–51.
8 Shah SP, Taylor AE, Sowden JC, Ragge NK, Russell-Eggitt I, Rahi JS, et al. Anophthalmos, microphthalmos, and typical coloboma in the United Kingdom: a prospective study of incidence and risk. Invest Ophthalmol Vis Sci. 2011;52(1):558–64.
9 Ragge NK, Subak-Sharpe ID, Collin JRO. A practical guide to the management of anophthalmia and microphthalmia. Eye. 2007;21(10):1290–300.
10 Verma AS, Fitzpatrick DR. Anophthalmia and microphthalmia. Orphanet J Rare Dis. 2007;2:47.
11 Siggs OM, Awadalla MS, Souzeau E, Staffieri SE, Kearns LS, Laurie K, et al. The genetic and clinical landscape of nanophthalmos and posterior microphthalmos in an Australian cohort. Clin Genet. 2020;97(5):764–9.
12 Katoh M. Molecular cloning and characterization of MFRP, a novel gene encoding a membrane-type Frizzled-related protein. Biochem Biophys Res Commun. 2001;282(1):116–23.
13 Godinho G, Madeira C, Grangeia A, Neves-Cardoso P, Santos-Silva R, Brandão E, et al. A novel MFRP gene variant in a family with posterior microphthalmos, retinitis pigmentosa, foveoschisis, and foveal hypoplasia. Ophthalmic Genet. 2020;41(5):474–9.
14 Walsh MK, Goldberg MF. Abnormal foveal avascular zone in nanophthalmos. Am J Ophthalmol. 2007;143(6):1067–8.
15 Stephenson KAJ, Zhu J, Wynne N, Dockery A, Cairns RM, Duignan E, et al. Target 5000: a standardized all-Ireland pathway for the diagnosis and management of inherited retinal degenerations. Orphanet J Rare Dis. 2021;16(1):200.