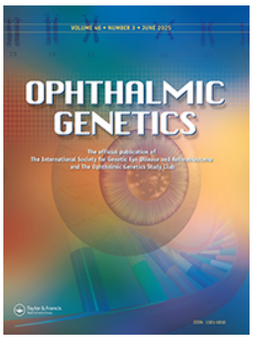

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CASE REPORT

WDR19-associated retinopathy presenting with adult-onset Stargardt-like phenotype

Annamaria Nunziata[a,b], Alessio Antropoli[a,b], Lorenzo Bianco[a,b], Sebastiano Del Fabbro[a,b], Alessandro Arrigo[a,b], Gabriella Doddato[c], Paola Carrera[c,d], Francesco Bandello[a,b], and Maurizio Battaglia Parodi[a,b]

[a]Ophthalmology Department, IRCCS San Raffaele Scientific Institute, Milan, Italy; [b]Vita-Salute San Raffaele University, Milan, Italy; [c]Laboratory of Clinical Molecular Genetics, IRCCS San Raffaele Scientific Institute, Milan, Italy; [d]Unit of Genomics for Human Disease Diagnosis, IRCCS San Raffaele Scientific Institute, Milan, Italy

ABSTRACT

Background: Pathogenic variants in the *WDR19* gene are linked to a spectrum of ciliopathies, which can present with ophthalmic symptoms. In this study, we describe the multimodal imaging findings of a patient with an adult-onset Stargardt-like phenotype associated with biallelic *WDR19* variants.

Methods: The patient underwent a comprehensive ophthalmologic evaluation, including slit-lamp examination, optical coherence tomography (OCT), fundus autofluorescence (FAF), and OCT-angiography (OCTA). Genetic testing was conducted using next-generation sequencing (NGS).

Results: The patient carried the *WDR19* p.(Arg477Leu) missense variant (class 3) in trans with the c.1777 + 1delG splice variant (class 4), never described before in association with a clinical phenotype. Multimodal imaging revealed bilateral areas of definitely decreased autofluorescence (DDAF), which progressively expanded over time. Additionally, bilateral thickening of the ellipsoid zone and intraretinal cysts in the left eye were observed.

Conclusions: Biallelic variants in the *WDR19* gene can cause an autosomal recessive, adult-onset Stargardt-like phenotype. Ophthalmologists should consider this as possible molecular differential diagnosis when encountering atypical features on multimodal imaging in cases with negative genetic testing for *ABCA4*.

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KEYWORDS
WDR19; *ABCA4*; Stargardt disease; Inherited retinal diseases

1. Introduction

WDR19 (also known as *IFT144*) is a gene encoding IFT144, a core component of intraflagellar transport complex A (IFT-A). This protein is essential for an efficient transport of opsins and the distal elongation of photoreceptors' outer segments. Pathogenic variants in *WDR19* are implicated in various ciliopathies, including Sensenbrenner syndrome (Cranioectodermal dysplasia 4, MIM #614378), Jeune syndrome (Short-rib thoracic dysplasia 5 with/without polydactyly, MIM #614376), Senior-Loken syndrome 8 (MIM #616307), and nephronophthisis (NHPH13, MIM #614377) (1). *WDR19* is also associated with autosomal recessive retinal diseases, including isolated retinitis pigmentosa (RP) or the above mentioned Senior-Loken syndromic RP (2), and more recently, Stargardt-like disease (3, 4). Herein, we report the case of a 45-year-old male patient with *WDR19*-related adult-onset Stargardt-like phenotype with a six-year follow-up.

2. Case report

A 39-year-old man with a negative past medical history was referred to the Inherited Retinal Diseases Unit (IRCCS San Raffaele Hospital, Milan, Italy) in September 2018 for suspected Stargardt disease. He complained of visual impairment with night blindness. Full-field electroretinogram turned out to be slightly abnormal, whereas fluorescein angiography revealed dark choroid. Upon his initial examination, his visual acuity was 20/20 Snellen in both eyes, with a minor correction for astigmatism. The anterior segment and intraocular pressure were within normal limits. On fundus examination, diffuse fleck-like lesions were scattered both inside and outside the arcades, while sharply demarcated areas of macular atrophy with foveal sparing, more pronounced in the left eye, were visible.

Fundus autofluorescence (FAF) disclosed patchy atrophy areas of definitely decreased autofluorescence (DDAF) within a broader area of questionably decreased autofluorescence (QDAF) around the vascular arcades and optic disc. Notably, ultra-widefield (UWF)-FAF allowed a better visualization of a peripheral area of hypopigmentation nasally. This region had a granular hypoautofluorescent aspect with a hyperautofluroescent border (Figure 1, top rows). Optical coherence tomography (OCT) revealed outer retinal atrophy sparing the macular center, with increased hyperreflectivity and thickness of the ellipsoid zone at the fovea. Intraretinal cysts were observed only in the left eye (Figure 1, bottom rows), although with no evidence of choroidal or type 3

CONTACT Alessio Antropoli antropoli.alessio@hsr.it IRCCS San Raffaele Scientific Institute, Department of Ophthalmology, Via Olgettina, 60, Milan, Lombardy 20132, Italy

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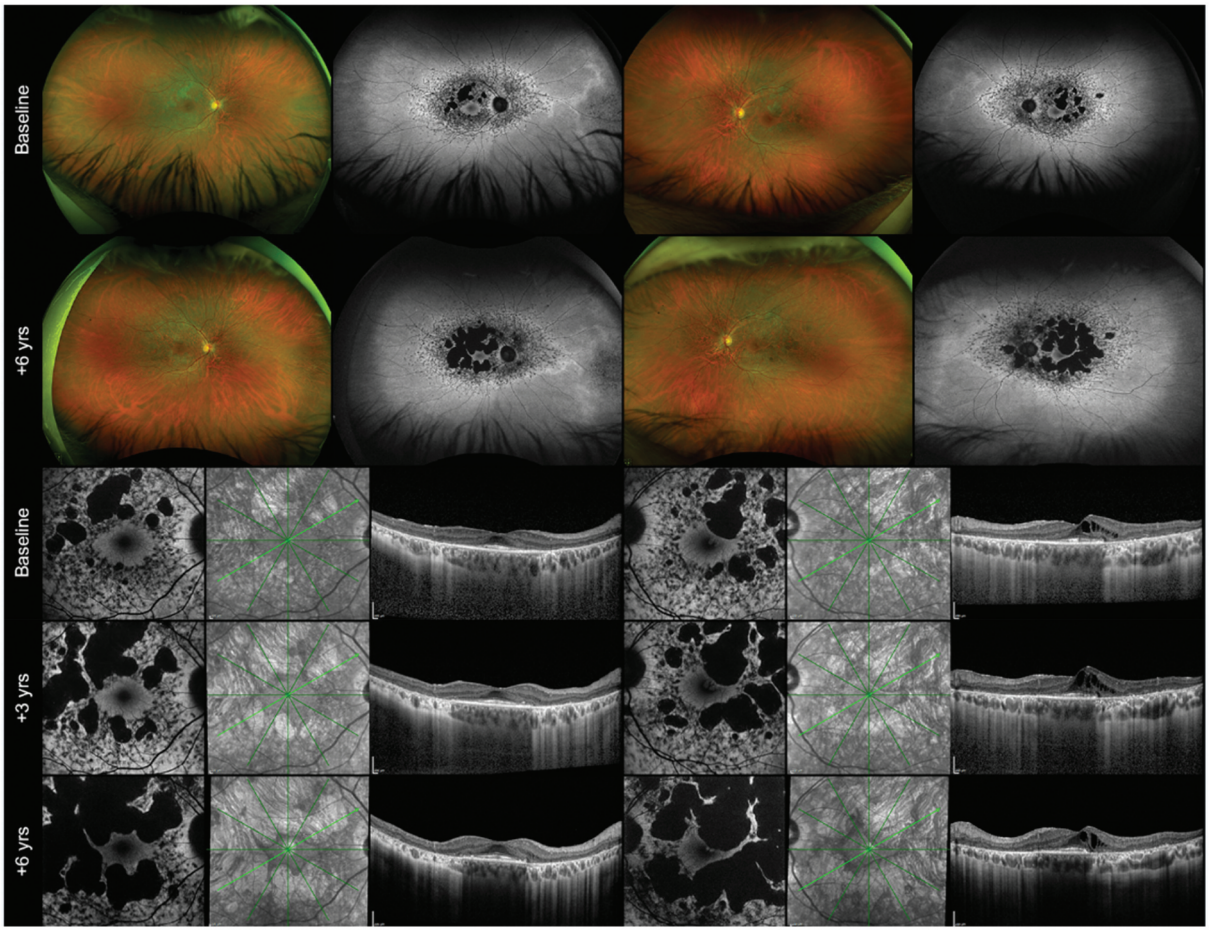

Figure 1. Top rows: at baseline, ultra-widefield fundus autofluorescence and color fundus photograph show irregular, hypoautofluorescent fleck-like lesions and RPE atrophy with definitely decreased autofluorescence at the posterior pole sparing the fovea. Additionally, peripheral pigmented lesions are visible in the nasal quadrant, bilaterally. Six years later, the atrophy areas enlarged centrifugally without involving the fovea. **Bottom rows**: Optical coherence tomography (OCT) and fundus autofluorescence (FAF) imaging over the follow-up. OCT reveals progressive perifoveal retinal thinning with relative foveal sparing and notable ellipsoid zone thickening. Furthermore, intraretinal hyporeflective cystoid spaces are present in the left eye. FAF displays a gradual confluence of the macular atrophy areas over time.

neovascularization on swept-source OCT-angiography (Topcon Medical Systems, Tokyo, Japan).

The patient was recommended to undergo genetic analysis through Next-Generation Sequencing (NGS). Three years later (February 2021), the patient underwent NGS using the TruSight One Clinical Exome sequencing panel on an Illumina NexSeq500 platform, enriching for 4800 genes including *ABCA4*, *CNGB3*, *ELOVL4*, *PROM1*, and *PRPH2*, which resulted negative for variants in all IRD-associated genes. Clinically, his condition remained mostly unchanged, except for a slight reduction in visual acuity in the left eye, now reaching 20/25 Snellen. Fundus examination, FAF, and OCT demonstrated an enlargement of the chorioretinal atrophy at the posterior pole, which occurred predominantly within the QDAF area of outer retinal atrophy, rather than toward the fovea (Figure 1, bottom rows). Given the inconclusive NGS results, the patient was advised to perform a larger genetic analysis through sequencing of a clinical exome panel (TruSight One Expanded Illumina). All the NGS called variants have been prioritized taking into account patient's phenotype as well as genes already described in association with inherited retinal disorders. This time, molecular testing unveiled two *WDR19* variants: the novel deletion at c.1777 + 1 within the donor splicing site (class 4) and the rare c.1430 G>T variant causing the amino-acid substitution p.(Arg477Leu) (class 3) in the putative protein. Additionally, a heterozygous c.1793A>G (class 3) variant in the *CDH23* gene was found, though it was deemed as not contributive to the patient's clinical phenotype. All reported variants were confirmed through Sanger sequencing.

The patient's clinical picture was stable, with persistent foveal sparing despite the slow but detectable atrophy progression on multimodal imaging. At this time, the patient also underwent fundus controlled microperimetry with the macular integrity assessment (MAIA) microperimeter and ffERG with a Retimax device (CSO, Florence, Italy). Retinal sensitivity was absent in areas of retinal pigment epithelium (RPE) and outer retinal atrophy, although a significant sensitivity reduction was detected within the area of foveal sparing as well (Figure 2). ffERG displayed moderate rod-cone dysfunction with reduced but discernible responses under both scotopic and photopic conditions (Supplemental Material).

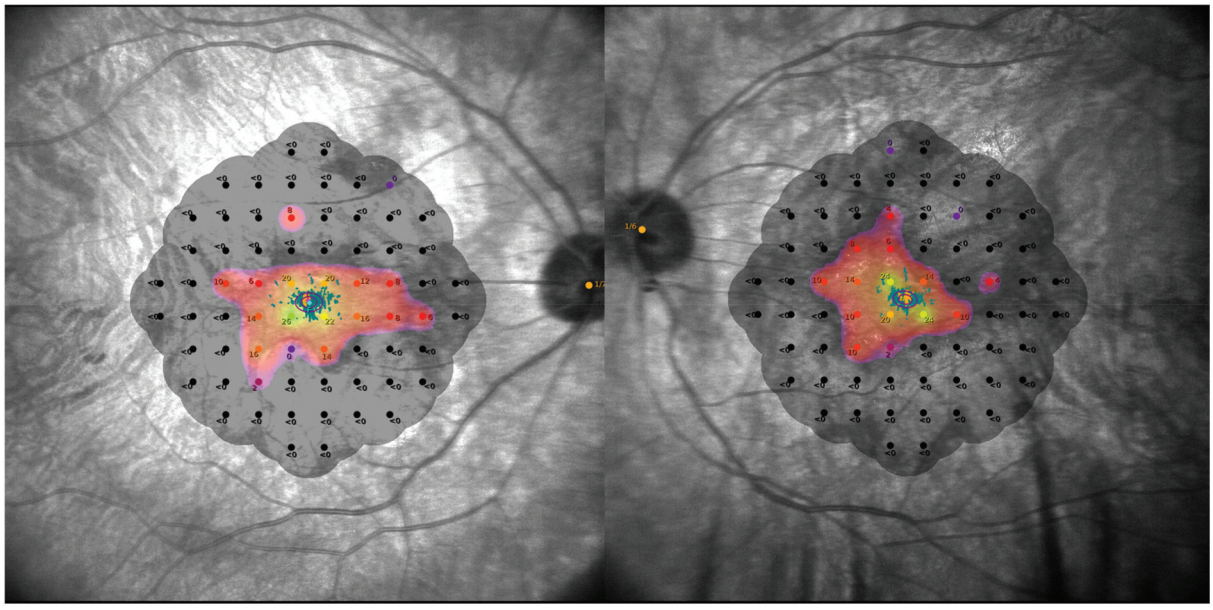

Figure 2. Fundus-controlled microperimetry reveals absolute perifoveal scotomas with reduced foveal sensitivity in the foveal sparing zone as well.

3. Discussion

The present case report describes the case of a 45-year-old male patient affected by adult onset Stargardt-like disease attributed to novel variants of *WDR19* gene, namely the missense p.(Arg477Leu) and the c.1777 + 1delG splice variant. The former leads to the substitution of arginine with leucine at position 477, with an extremely low frequency in the European population and no homozygotes found on GnomAD v.4.1.0, while the c.1777 + 1delG variant located within a canonical splice site is predicted to disrupt normal splicing, potentially leading to aberrant or null protein products. Pathogenic variants in *WDR19* have been associated with both isolated and syndromic forms of retinitis pigmentosa (RP), and more recently, with Stargardt-like diseases (3, 4).

Shamseldin et al. identified a founder mutation in *WDR19* in three unrelated patients, which supported the link between pathogenic variants in this gene and Stargardt-like retinal dystrophies (4). Nonetheless, their finding was part of a broader study on ciliopathies lacking a thorough assessment of the retinal phenotype with multimodal imaging. Interestingly, Sajovic et al. described the clinical features and disease progression in a patient with *WDR19* variants presenting a Stargardt-like phenotype, as well (3). This patient showed a mild maculopathy with fleck-like lesions and prolonged foveal sparing, and its retinal phenotype was compared by the authors to individuals with *ABCA4*-related retinopathy. Interestingly, the authors identified a characteristic hyper-reflectivity of the external limiting membrane as further similarity with *ABCA4*-related retinopathy, suggesting that *WDR19*-associated retinopathy may present with Stargardt-like features.

In the present study, we report a case of *WDR19*-related retinopathy with diffuse hypoautofluorescent fleck-like lesions at the posterior pole accompanied by macular RPE atrophy with DDAF sparing the fovea. Our patients showed a relatively mild phenotype, with slow but progressive enlargement of the atrophy areas and prolonged foveal sparing. In contrast with Sajovic et al., our patients' phenotype shared many characteristics with adult-onset Stargardt disease, which usually presents around the age of 45 with parafoveal atrophic lesions that slowly merge, leaving the fovea unaffected until later stages (5). Despite these similarities, the presence of atypical characteristics could raise the suspicion for *WDR19*-associated retinopathy, including a relatively younger onset, night blindness consistent with rod-cone dysfunction on ffERG, intraretinal cystoid spaces, and characteristic thickening of the ellipsoid zone, in contrast to the changes observed at the external limiting membrane in Stargardt disease (6). Notably, cystoid maculopathy was noted unilaterally in our patient, present only in the left eye. While we do not have a definitive explanation, unilateral cystoid macular edema is not uncommon in diseases like RP and diabetic retinopathy and may be related to interocular differences (7, 8).

In conclusion, we report two novel *WDR19* variants associated with an adult-onset Stargardt-like phenotype. Ophthalmologists may consider genetic testing in this gene in unsolved recessive cases of adult-onset Stargardt disease, especially when abnormal thickening of the ellipsoid zone is present. Our findings suggest that the phenotypic spectrum of well-known syndromic ciliary genes may extend to isolated retinal dystrophies with predominantly central involvement. Large natural history studies are needed to improve our understanding of the complex retinal phenotype associated with WDR19-retinopathy.

Disclosure statement

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ORCID

Alessio Antropoli http://orcid.org/0000-0001-9630-0830
Lorenzo Bianco http://orcid.org/0000-0002-4023-5387

Ethics statement

This work was conducted in line with the Declaration of Helsinki and was approved by the institutional review board (study ID: MIRD).

Generative artificial intelligence (AI)

ChatGPT4 was employed to improve readability and language of the manuscript. After using this tool, the authors have reviewed and edited the content as needed and take full responsibility for the content of the publication.

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