Int Ophthalmol (2025) 45:282
https://doi.org/10.1007/s10792-025-03657-5

ORIGINAL PAPER

von Willebrand factor A domain containing 8 (*VWA8*)-associated retinitis pigmentosa: description of a novel case and expansion of the phenotype

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Received: 21 February 2025 / Accepted: 28 June 2025

Abstract

Purpose Retinitis pigmentosa, the most common type of inherited retinal dystrophy, is known to have great genetic heterogeneity, as pathogenic variants in approximately 100 genes have been recognized as causative. In the last decade, wide application of next-generation DNA sequencing has allowed identification of pathogenic variants in novel retinal dystrophies genes. Recently, a pathogenic variant in von Willebrand factor A domain containing protein 8 (*VWA8*) gene, was demonstrated to segregate in a large Chinese family with autosomal dominant (AD) retinitis pigmentosa. The current study describes the clinical and molecular characteristics of a novel retinitis pigmentosa patient carrying a pathogenic variant in the *VWA8* gene.

Methods Ophthalmic examination, fundus photography, autofluorescence, spectral-domain optical coherence tomography, Goldmann perimetry, Full Field Stimulus Threshold (FST), full-field electroretinogram, and chromatic perimetry testing were carried out. Peripheral blood DNA was isolated, and whole exome sequencing was performed in the index case. Bioinformatic analysis was performed for the identification of the pathogenic causal variant. Analysis of the candidate variant in first-degree relatives by Sanger DNA sequencing was also performed.

Results A Mexican patient suffering from retinitis pigmentosa and her first-degree relatives were included. Classical features of retinal dystrophy were identified, including nyctalopia, peripheral visual field loss, as well as vascular attenuation, and bone spicules on fundus examination. Genetic analysis identified a novel pathogenic c.3069C > G (p.Tyr1023Ter) heterozygous *VWA8* variant. Additionally, optic nerve drusen were identified, a feature not described in the family previously reported in literature.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10792-025-03657-5.

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Published online: 10 July 2025

Conclusion Our results confirm *VWA8* as a retinitis pigmentosa-associated gene and contributes to the phenotypic expansion of the disorder.

Keywords Retinitis pigmentosa · Rod-cone dystrophy · *VWA8* gene · Hereditary eye disease · Exome sequencing · Optic disc drusen

Introduction

The term retinitis pigmentosa (RP) (rod-cone retinal dystrophy) encompasses a group of inherited and progressive diseases characterized by primary death of rod photoreceptors and subsequent loss of cone photoreceptors. RP has a prevalence of 1:4,000 in the general population and is the leading cause of inherited blindness worldwide [1]. Typical symptoms include nyctalopia, progressive peripheral visual field loss, and ultimately severe constriction of central visual field leading to tunnel vision. Fundus abnormalities include intraretinal hyperpigmentation, optic disc pallor, and retinal vessel attenuation [2]. RP exhibits extreme genetic heterogeneity as mutations in approximately 100 genes have been demonstrated to be disease-causing, which can be familiarly transmitted as an autosomal recessive, an autosomal dominant or an X-linked trait. Approximately, a quarter of RP genes are associated with AD forms of the disease [3]. The growing incorporation of massive sequencing in clinical practice has allowed the recognition of novel RP-causing genes [4, 5]. Recently, a heterozygous truncating variant in the *von Willebrand Factor A domain containing 8* (*VWA8*) gene was identified by means of exome sequencing as a novel cause of AD RP in a large Chinese family [7]. Since then, no additional cases of *VWA8*-linked RP have been reported precluding a more comprehensive understanding of a potential genotype–phenotype correlation. Here, we describe the clinical and molecular features of a Mexican RP patient carrying a novel pathogenic *VWA8* variant. To our knowledge, this is the second report of a *VWA8* pathogenic variant in the literature and our results support the gene as a cause of AD RP and expands the phenotypic and mutational spectrum of the disorder.

Materials and methods

Clinical and multimodal imaging studies

The protocol was approved by Institutional Review Board of the Institute of Ophthalmology "Conde de Valenciana" in Mexico City. All procedures followed the tenets of the Helsinki Declaration and patients gave written permission for their inclusion in the study. A family of Mexican mestizo ethnic origin (individuals II-10, III-1, III-2, and III-3, Fig. 1) was ascertained. The index case (individual III-2), underwent a complete eye examination including biomicroscopy, funduscopy, Best corrected visual acuity (BCVA) determination, Goldmann visual field perimetry, chromatic perimetry (Metrovision/Mon CV One, Perenchies, France), Full Field Stimulus Threshold (FST; Metrovision/Mon CV One), fundus autofluorescence imaging (FAF; OPTOS/California), SD-OCT Heidelberg Spectralis (Heidelberg Engineering, Heidelberg, Germany). Full-field electroretinogram (ffERG; Metrovision/Mon Pack One) was also performed following the recommendations of the International Society for Clinical Electrophysiology of Vision (ISCEV). The unaffected mother (II-10) and two healthy sibs (III-1 and III-3) underwent complete ophthalmological evaluation including biomicroscopy, funduscopy, and BCVA determination.

Genetic analysis

Exome sequencing analysis was performed in the index case (III-2). Briefly, genomic DNA (gDNA) was extracted from peripheral blood leukocytes using the QIAaMP DNA Blood kit (Qiagen), according to the manufacturer's recommendations. Exon regions of all human genes (~22,000) were captured by means of the xGen Exome Research Panel v2 (Integrated DNA Technologies, Coralville, Iowa, USA). The captured genomic regions were sequenced employing a Novaseq X instrument (Illumina, San Diego, CA, USA). The raw genome sequencing data analyses, including alignment to the GRCh38 human reference genome, variant calling, and annotation were conducted with open-source bioinformatics tools as well as in-house software. The average > 20 × coverage was 99.5%. Variant prioritization was performed with the automatic variant interpretation software EVIDENCE [8] based on ACMG guidelines [9].

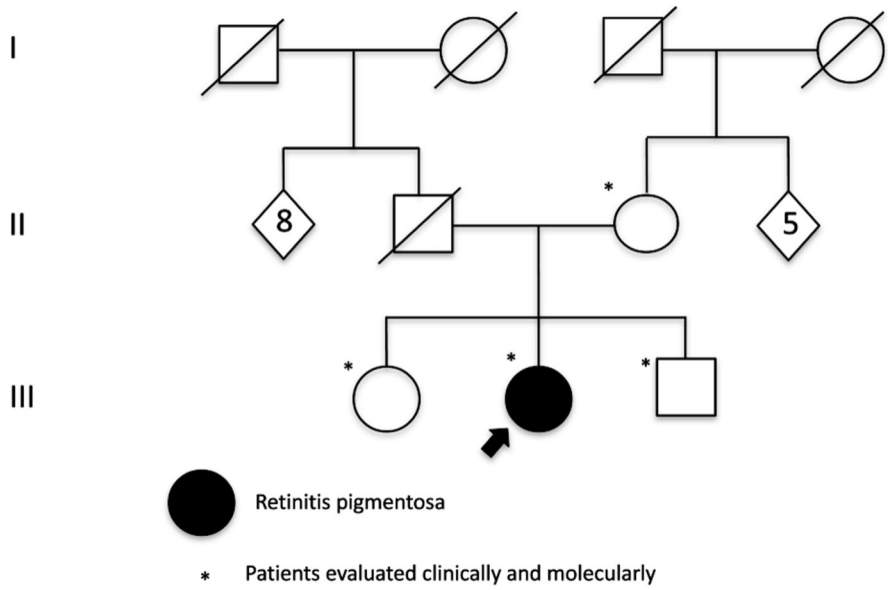

Fig. 1 Pedigree of Mexican patient with retinitis pigmentosa. The affected proband is designed with a solid black symbol

Family segregation of candidate causal variants was done by direct Sanger sequencing on genomic DNA from available relatives (II-10, III-1, and III-3, Fig. 1) using specific oligonucleotide primers designed using the Primer-BLAST tool based on the *VWA8* (gene reference sequence NM_015058.2; http://www.ensembl.org). Primer sequences and PCR conditions are available on request. PCR products were purified and sequenced using the BigDye Terminator Cycle sequencing kit (Thermo Fisher, Waltham, MA, USA).

Results

Case report

A 32-year-old female complaining of nyctalopia and peripheral visual field reduction since the age of 12 years was evaluated. She reported photophobia, photopsia, dyschromatopsia, and visual acuity reduction since the age of 26 years with a history of phacoemulsification with intraocular lens implantation in both eyes at that age. At examination, BCVA was 0.6 logMAR in the right eye and hand movements in the left eye. On fundus inspection, pink-orange tilted optic discs with normal cupping, and white/yellow refractile bodies on the inferior surface of the optic nerve head (drusen) were observed, bilaterally; in addition, vascular narrowing, bone spicule pigmentation and punctate hypopigmentation were also evident (Fig. 2A, B). Ultra-widefield FAF showed central macular hyperautofluorescent dot, focal peripapillary hyperautofluorescent clusters, and peripheral mottled hypoautofluorescence (Fig. 2C, D). Kinetic Goldmann perimetry was performed only in the right eye, due to poor visual acuity in the left eye; functional cone retinal evaluation using V4e stimulus disclosed a central vision island, while a central dot response was exclusively noticed under 14e stimulus (Supplementary Fig. 1). High resolution SD-OCT in both eyes demonstrated thinning of the outer nuclear layer, with foveal ellipsoid zone preservation, hyperreflective foci in external and internal layers and subtle hyperreflective linear structure on the inner retinal surface (Fig. 2E, F). Peripapillary masses with poor signal core and partial hyperreflective margins were also seen (Fig. 2G, H). ERG showed abolished scotopic and photopic responses (Supplementary Fig. 2). FST showed a deficit in scotopic and photopic retinal function in all visual fields (Supplementary Fig. 3). Chromatic fields were evaluated only in the right eye, showing abolished functional evaluation of retinal rods and cones on scotopic and photopic response, respectively (Supplementary Fig. 4). General physical examination was normal and systemic diseases were denied. No biomicroscopic or funduscopic anomalies were identified in her healthy mother and her two

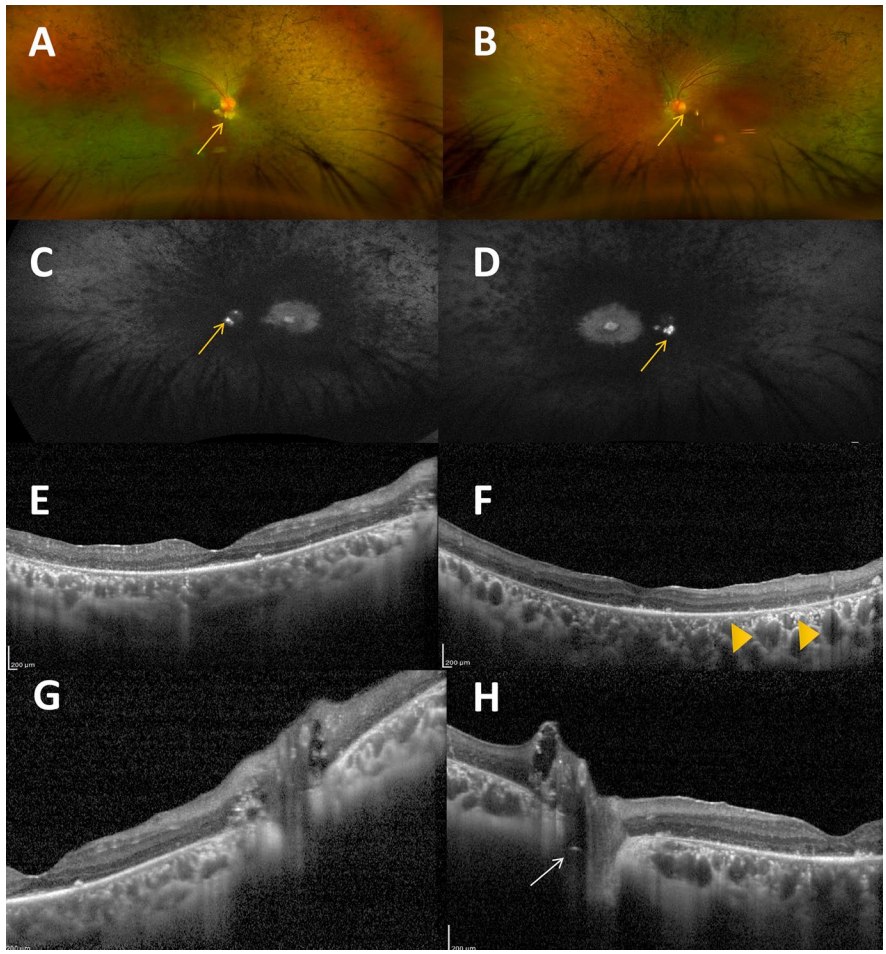

Fig. 2 Ultra-widefield pseudocolor image of right (**A**) and left (**B**) eye. Optic disc drusen (yellow arrows), punctate hypopigmentation, vascular narrowing and bone spicule pigmentation are observed. Ultra-widefield fundus autofluorescence image of right (**C**) and left (**D**) eye: Optic disc drusen observed as hyperautofluorescent peripapilary clusters (yellow arrows), hyperautofluorescent central macular dot, and peripheral hypoautofluorescent equatorial confluent dotting can be observed. Macular SD-OCT of right (**E**) and left (**F**): Foveal ellipsoid zone preservation, reduced Haller and Sattler layers, and choroidal caverns in the left eye (yellow arrowheads) are observed. Optic nerve SD-OCT of right (**G**) and left (**H**) eye: Peripapillary hyperreflective structure anterior to lamina cribosa corresponding to optic disc drusen seen as peripapillary masses are present. An hyperreflective horizontal line could be noticed on left eye in relation with the presence of drusen (white arrow)

unaffected siblings. The father, who was deceased at the age of 49 years, was referred with no visual complaints.

Molecular analysis

Exome sequencing in DNA from the index case identified a novel heterozygous c.3069C > G transversion in exon 26 of the *VWA8* gene (transcript ID NM_015058.2), which predicts a truncating p.Tyr1023Ter variant at the protein level (Fig. 3). This variant is not included in population databases (gnomAD, ExAC, ESP6500, 1000 Genomes) and is also absent in a set of 1600 Mexican *VWA8* alleles from in-house exomes. According to the standards and guidelines of the ACMG, this variant is classified as pathogenic based on PVS1, PM2, PP1, and PP4 criteria [9]. No other pathogenic or likely pathogenic variants in genes related to retinal dystrophies were identified in the exome sequencing data from the proband. Sanger sequencing demonstrated the absence of the *VWA8* variant in three unaffected first-degree family

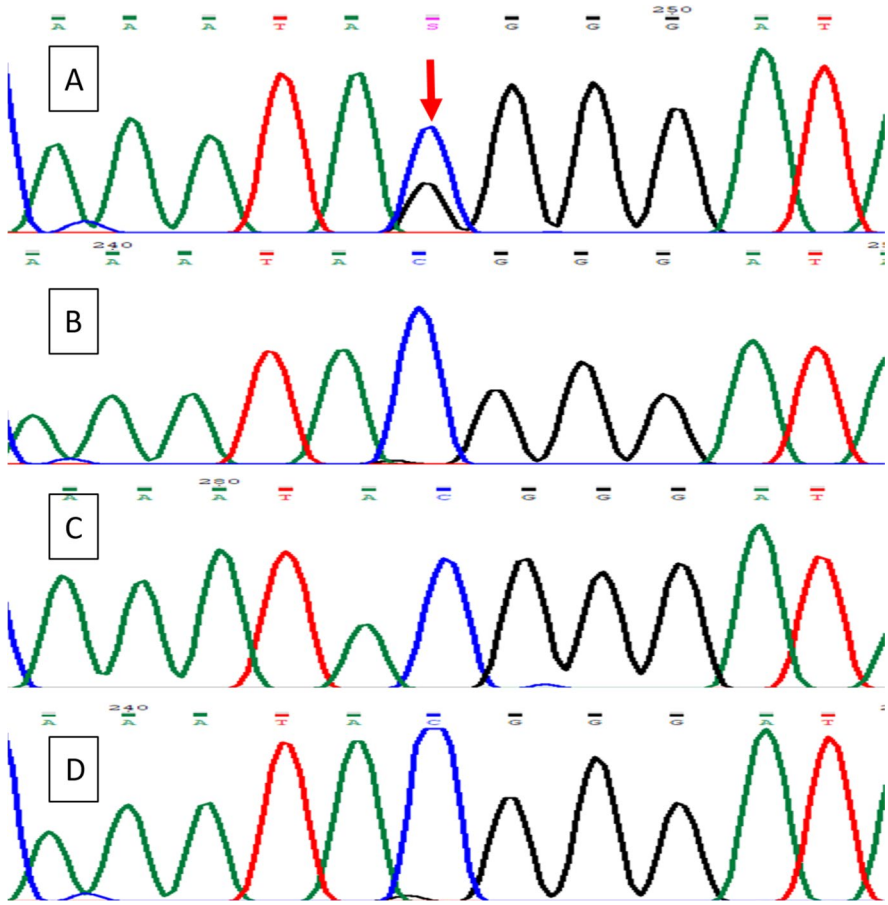

Fig. 3 Partial sequence of *VWA8*. Chromatograms of the proband (**A**) and proband's mother (**B**) and siblings (**C**, **D**) are shown. A heterozygous c.3069C > G transversion in *VWA8* exon 26, predicting a p.Tyr1023Ter variant was only identified in the index case. In **A**, Red arrow indicates the position of the involved nucleotide in the DNA sequence

members (II-10, III-1, and III-3, Fig. 3). DNA from the father, who died at the age of 49 years without any known ocular disease, was not available.

Discussion

AD RP accounts for 30–40% of all diseases cases [3] with 32 causative genes listed in Retnet (accessed in February 2025). Recently, a large Chinese AD RP family was shown to harbor a truncating c.4558C > T (p.Arg1520Ter) heterozygous *VWA8* gene pathogenic variant for which expression and functional analyses supported its causative role [7]. In addition to the nonsense variant, a c.3070G > A, (p.Gly1024Arg) was identified in the same *VWA8* allele in such family. Although it is unknown if such missense variant has a phenotypic effect, the identification here of a single p.Tyr1023Ter variant in an RP patient supports that truncating VWA8 mutations could be associated with retinal degeneration. *VWA8* encodes a mitochondrial matrix-targeted protein with three ATPase-associated domains and a von Willebrand factor type A domain associated with ATPase activity [7]. While WVA8 is highly expressed in murine heart, kidney, and liver [10], it is also expressed in fetal ocular tissues, particularly in the retina [7].

In the 4-generation-family reported by Kong et al. [7], the disease age of onset ranged from infancy to 12 years of age, mainly manifesting as nyctalopia, visual field disturbances, and later decreased visual acuity. Funduscopic changes included bone spicule-like pigment deposits in the peripheral retina, macular atrophy, and arteriolar attenuation. OCT findings included structural discontinuity of retinal layers with areas of atrophy and volume loss of the outer nuclear layer; ERG demonstrated reduced scotopic and photopic responses [7]. In the patient described here, symptoms were first noted at adolescence and were suggestive of a progressive rod-cone dystrophy

(nyctalopia, reduced peripheral visual fields, photophobia, dyschromatopsia, reduced visual acuity); at funduscopy, bone spicules, vascular attenuation, and a pink-orange optic disc were observed. Of note, drusen on the inferior surface of the optic nerve were bilaterally identified as peripapillary hyperautofluorescent clusters in an autofluorescent fundus, suggesting it as a novel feature of *VWA8*-linked RP. Optic disc drusen (ODD) are deposits of acellular calcified or proteinaceous materials [11]. ODD are predominantly bilateral and its prevalence ranges from 0.3 to 2.4% in the general population [12]. The pathogenesis of ODD is unknown although it has been suggested to be multifactorial with multiple mechanisms, including compromised blood supply to the optic nerve, disruption and abnormalities of axonal metabolism, alterations in mitochondrial calcium storage, among others [13]; nonetheless, some ODD pedigrees have suggested an AD inheritance pattern with incomplete penetrance [14, 15]. ODD is a prominent feature of some retinal dystrophies, with particular high prevalences in Usher syndrome and rod-cone dystrophies [16, 17]. Of note, the frequency of ODD in retinal dystrophy patients ranges from 3 to 7% [13, 18, 19]. In conclusion, we describe a Mexican RP patient with a novel *VWA8* mutation supporting the involvement of this gene in AD RP gene and expands the currently known retinal findings by describing the occurrence of optic disc drusen. Additional descriptions of *VWA8*-linked RP cases will allow a better characterization of the clinical-molecular spectrum of the disease.

Author contribution Conceptualization, data collection, and analysis: OFCC, JCZ. Review of manuscript and data analysis: JCZ. Examination of patients and writing of clinical description: RAG, AMA NGS by whole exome sequencing: JCZ Authors have read and agreed to the published version of the manuscript.

Data Availability No datasets were generated or analysed during the current study.

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