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TSPAN12-Associated Retinal Disease Presenting With a Retinitis Pigmentosa-Like Phenotype: A Case Report

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Abstract

Familial exudative vitreoretinopathy (FEVR) is an inherited vitreoretinal disorder caused by abnormal peripheral retinal vascular development, whereas retinitis pigmentosa (RP) comprises a group of inherited retinal degenerations characterized by progressive photoreceptor loss. Although phenotypic overlap has been described among inherited retinal disorders, RP-like presentations associated with pathogenic TSPAN12 variants have rarely been reported.

We report the case of a 52-year-old man with longstanding nyctalopia and high myopia who presented with findings strongly suggestive of RP. These findings included bilateral retinal vessel attenuation, optic disc pallor, sectoral perivascular bone-spicule pigmentation along the major retinal vascular arcades, and cystoid macular edema. Functional testing revealed asymmetric visual field loss-featuring dense temporal hemifield loss in the right eye and a ring-shaped scotoma with a preserved central island in the left eye-and severely reduced or non-measurable scotopic and photopic electroretinographic responses. Based on the clinical findings, an initial diagnosis of RP was made. However, genetic testing identified a heterozygous pathogenic deletion encompassing exons 3-8 of TSPAN12, a gene classically associated with autosomal dominant FEVR, prompting reinterpretation of the condition as a TSPAN12-associated retinal disease with an RP-like phenotype. To our knowledge, this specific deletion has not been previously reported, and no characteristic clinical or angiographic features of FEVR were identified within the imaged retina, distinguishing this case from prior reports of TSPAN12-associated disease.

This case broadens the recognized phenotypic spectrum associated with pathogenic TSPAN12 variants and highlights the role of molecular genetic testing in characterizing inherited retinal disorders with overlapping clinical features.

Categories: Ophthalmology
Keywords: case report, familial exudative vitreoretinopathy (fevr), retinal disease, retinitis pigmentosa, tspan12

Introduction

Familial exudative vitreoretinopathy (FEVR) is a rare inherited vitreoretinal disorder characterized by incomplete peripheral retinal vascular development resulting from disrupted retinal angiogenesis [1]. Its clinical presentation may vary considerably, ranging from asymptomatic peripheral avascularity to sight-threatening complications including retinal capillary dropout, vascular dragging, retinal folds, exudation, hemorrhage, neovascularization, vitreoretinal interface abnormalities, and retinal detachment (serous, tractional, or combined) [2]. This phenotypic heterogeneity is a hallmark of FEVR; even within the same family, disease severity can differ significantly, with some patients experiencing blindness in infancy while others retain normal vision throughout life [3]. This broad clinical spectrum may complicate diagnosis, particularly in patients with atypical presentations [3].

The marked phenotypic variability observed in FEVR is accompanied by considerable genetic heterogeneity. The disease may be inherited in autosomal dominant, autosomal recessive, or X-linked recessive patterns, with pathogenic variants of the genes FZD4, NDP, LRP5, and TSPAN12 accounting for a substantial proportion of genetically confirmed cases [3,4]. Among these, TSPAN12 underlies a small subset of autosomal dominant FEVR cases [4]. Junge et al. demonstrated that TSPAN12 encodes a membrane tetraspanin that enhances the Norrin/FZD4/LRP5-mediated β-catenin signaling pathway, which is critical for retinal vascular development [5]. Concurrently, pathogenic TSPAN12 variants were established as a cause of autosomal dominant FEVR in humans [3,6].

The diverse phenotypes observed in TSPAN12-associated FEVR can manifest as atypical clinical findings that overlap with those of other inherited retinal disorders, creating a significant diagnostic challenge [7].

Although characteristic findings such as peripheral retinal avascularity, vascular dragging, and radial retinal folds with exudation may strongly suggest FEVR [2,7], these features may be subtle or absent in milder forms of the disease, meaning that patients may remain undiagnosed until adulthood [1,7]. Due to variations in the phenotype, clinical diagnosis may be delayed or overlooked, notwithstanding the importance of early recognition for lifelong surveillance, timely intervention, and genetic counseling [8]. Furthermore, patients are frequently referred with alternative diagnoses, including nonspecific vitreoretinopathies, retinal detachment, and other inherited retinal diseases as opposed to FEVR itself [7].

We report the case of a 52-year-old man who had bilateral sectoral perivascular bone-spicule pigmentation along the major retinal vascular arcades, initially raising clinical suspicion for retinitis pigmentosa (RP). RP is a rare hereditary retinal dystrophy characterized by bone spicule pigmentation, attenuation of retinal vessels, and waxy pallor of the optic nerve head, leading to nyctalopia followed by progressive peripheral vision loss with no definitive cure and complex inheritance patterns requiring genetic testing [9]. Genetic testing identified a heterozygous pathogenic deletion of exons 3-8 of TSPAN12, a gene classically associated with autosomal dominant FEVR, prompting reinterpretation of the phenotype as TSPAN12-associated retinal disease. This case suggests that, even in the absence of clinically recognizable FEVR vascular features, TSPAN12-associated retinal disease may present with an RP-like phenotype, thereby adding to the current literature on this presentation, which has only one reported case [10].

Case Presentation

A 52-year-old man presented for evaluation of longstanding nyctalopia and retinal pigmentary changes noted on examination. He reported that nyctalopia had been present since early adulthood and had not subjectively progressed. His ocular history was also notable for high myopia. His medical history was significant for hypertension. He reported occasional alcohol use and denied a family history of retinal disease.

At presentation, his best-corrected visual acuity was 20/40 in both eyes. Intraocular pressure was 14 mmHg in the right eye and 18 mmHg in the left eye. On slit-lamp examination, the patient had mild (1+) bilateral nuclear sclerotic cataracts.

On dilated fundus examination and ultra-widefield color fundus photography (Figures *1A*-*1B*), both eyes showed sectoral optic nerve pallor (involving the superonasal optic disc in the right eye and the superotemporal optic disc in the left eye), bilateral retinal vessel attenuation, and moderate bilateral sectoral perivascular bone-spicule pigmentation along the major retinal vascular arcades. In addition, irregular areas of retinal pigment epithelial (RPE) depigmentation and chorioretinal atrophy were present in the peripapillary region, extending along the major vascular arcades into the midperiphery. The affected regions showed increased visibility of the underlying choroidal vessels and scattered pigment clumping, which corresponded spatially to the branching areas of hypoautofluorescence on fundus autofluorescence imaging (Figures *1C*-*1D*), with the central macular region appearing relatively spared. Cystoid macular edema was present in the left eye.

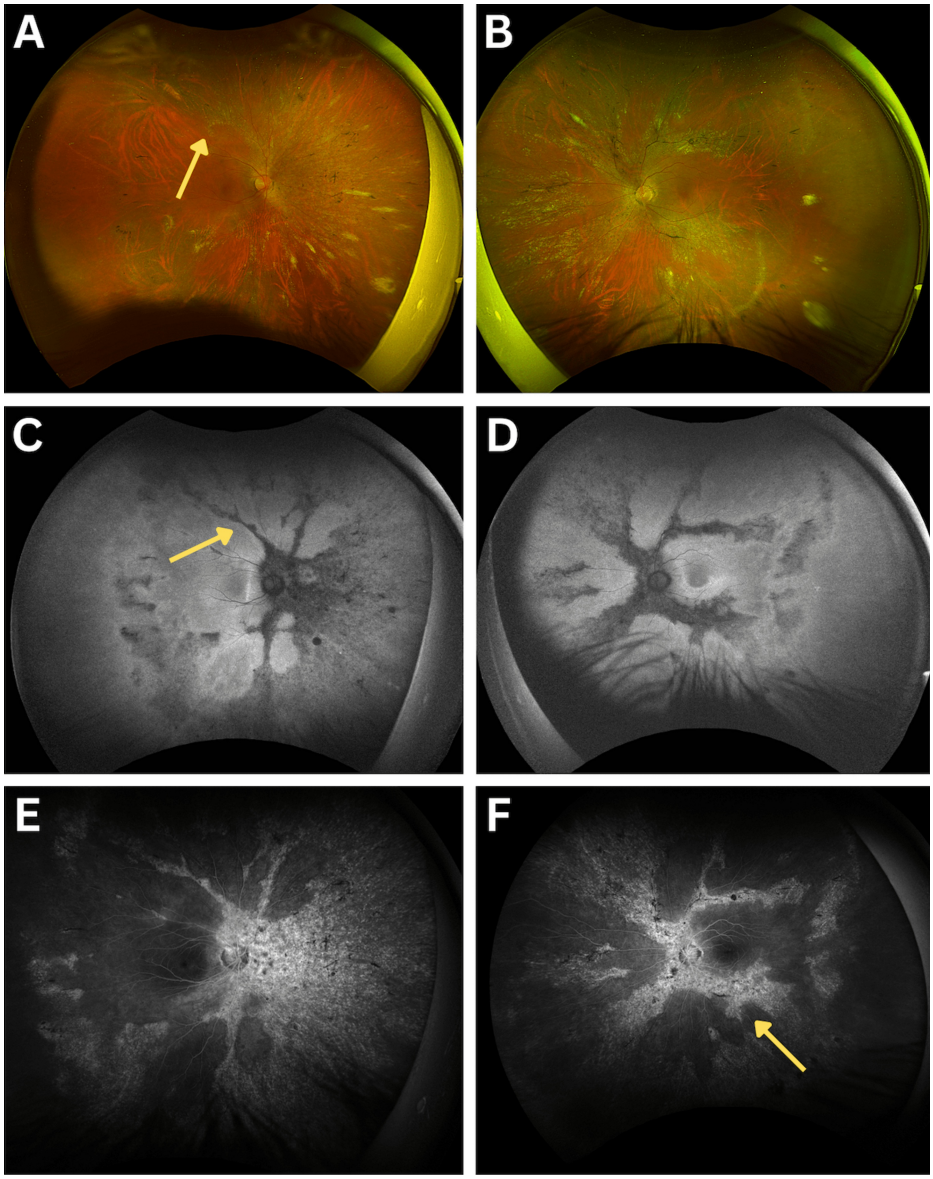


FIGURE 1: Multimodal imaging of both eyes.

Ultra-widefield color fundus photographs of the right eye (A) and left eye (B) show bilateral retinal vessel attenuation, diffuse retinal pigment epithelium (RPE) alterations, and sectoral perivascular bone-spicule pigmentation (yellow arrow) along the major retinal vascular arcades. Fundus autofluorescence of the right eye (C) and left eye (D) shows symmetric sectoral hypoautofluorescence corresponding to perivascular RPE atrophy along the superior and inferior retinal arcades (yellow arrow) with relative preservation of the central macula. Ultra-widefield fluorescein angiography of the right eye (E) and left eye (F) demonstrates well-demarcated sectoral hyperfluorescence secondary to window defects from RPE atrophy (yellow arrow). Within the imaged peripheral retina, there is no identifiable temporal retinal avascularity, peripheral capillary nonperfusion, vascular straightening or dragging, neovascularization, vascular leakage, optic disc leakage, or other characteristic angiographic features of familial exudative vitreoretinopathy.

Ultra-widefield fundus autofluorescence (Figures *1C*-*1D*) revealed bilateral irregular, confluent areas of hypoautofluorescence extending radially from the peripapillary region along the major vascular arcades into the midperiphery. These areas exhibited branching, predominantly perivascular distribution, with surrounding heterogeneous autofluorescence and localized hyperautofluorescent borders. Additional patchy hypoautofluorescent foci were visible throughout the midperiphery. The central macular region remained relatively spared from the confluent areas of hypoautofluorescence.

Ultra-widefield fluorescein angiography (Figures *1E*-*1F*) demonstrated bilateral well-demarcated sectoral hyperfluorescence secondary to window defects from RPE atrophy. Within the imaged peripheral retina, there was no identifiable temporal retinal avascularity, peripheral capillary nonperfusion, vascular straightening or dragging, neovascularization, vascular leakage, optic disc leakage, or other characteristic angiographic features of FEVR.

Spectral-domain optical coherence tomography demonstrated complete parafoveal ellipsoid zone loss with relative preservation of the foveal ellipsoid zone in both eyes. The right eye showed relative preservation of the central foveal architecture, while the left eye had multiple intraretinal cystoid spaces consistent with cystoid macular edema.

Humphrey 30-2 automated perimetry demonstrated marked bilateral visual field loss with an asymmetric pattern (Figure *2*). The right eye showed dense loss of the temporal hemifield with relative preservation of the nasal hemifield, whereas the left eye showed a ring-shaped scotoma with a preserved central island of vision. The mean deviation was -12.98 dB in the right eye and -18.55 dB in the left eye, and the visual field indices were 76% and 57%, respectively. Reliability indices were acceptable in both eyes (right eye: fixation losses 0/15, false positives 4%, false negatives 0%; left eye: fixation losses 3/19, false positives 1%, false negatives 0%).

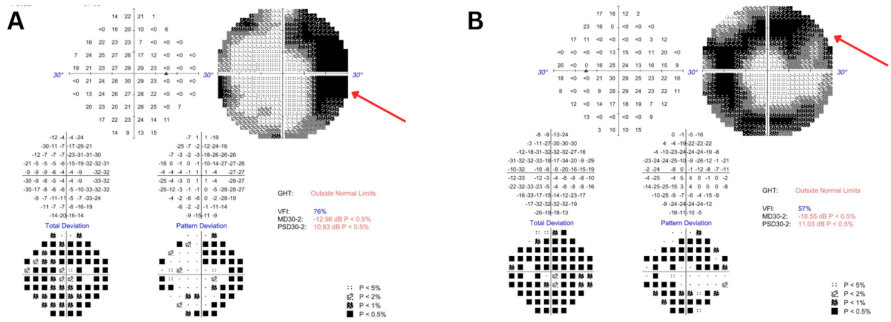


FIGURE 2: Humphrey 30-2 visual fields.

Humphrey 30-2 visual fields of the right eye (A) and left eye (B) demonstrate marked, asymmetric visual field loss within the tested central 30°. The right eye (A) shows dense loss of the temporal hemifield (red arrow) with relative preservation of the nasal hemifield, whereas the left eye (B) has a ring-shaped scotoma with preservation of a central island of vision (red arrow), a pattern compatible with advanced pigmentary retinal degeneration. The mean deviation is -12.98 dB in the right eye and -18.55 dB in the left eye, and the visual field indices are 76% and 57%, respectively. Reliability indices: right eye, fixation losses 0/15, false positives 4%, false negatives 0%; left eye, fixation losses 3/19, false positives 1%, false negatives 0%.

Full-field electroretinography (RETeval, KC Technologies, Inc., Germantown, Maryland, USA, device preset labeled “ISCEV 5 Step Dark First”; Figure *3*) demonstrated severely attenuated and inconsistently measurable responses in both eyes. Under dark-adapted 0.01 cd·s/m² testing, a b-wave was measurable in only one recording per eye (device-reported amplitude and peak time: 6.7 µV at 78.6 ms in the right eye and 2.8 µV at 98.3 ms in the left eye). Under dark-adapted 3.0 cd·s/m² testing, small a-waves were recorded bilaterally (mean amplitudes: -4.4 µV in the right eye and -6.4 µV in the left eye); the b-wave was measurable in only one right-eye recording (4.3 µV at 34.6 ms) and was non-measurable in the left eye. Under light-adapted 3.0 cd·s/m² testing, the right-eye response was markedly attenuated (mean a-wave: -0.84 µV at 16.5 ms; mean b-wave: 2.1 µV at 32.8 ms), whereas both components were non-measurable in the left eye. Flicker responses at 28.3 Hz had device-reported amplitudes of 2.2 µV and 2.7 µV in the right and left eyes, respectively, with non-measurable peak times. These findings are consistent with severe generalized dysfunction of both rod- and cone-mediated retinal pathways.

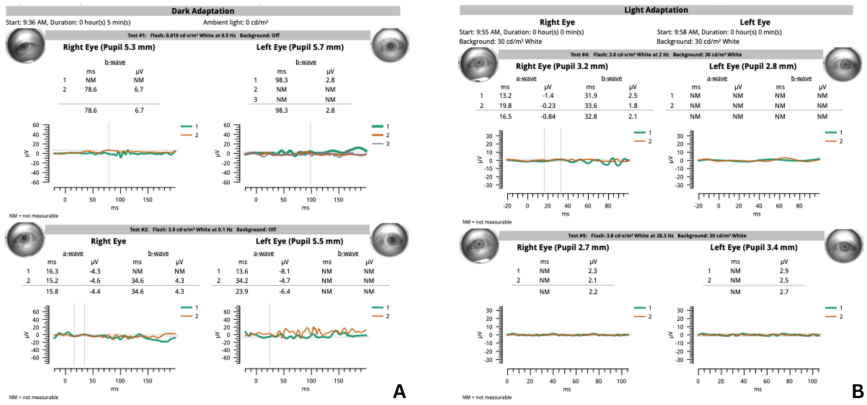


FIGURE 3: RETeval electroretinography using the device preset labeled "ISCEV 5 Step Dark First."

(A) Dark-adapted 0.01 cd·s/m² b-waves were inconsistently measurable and severely attenuated (6.7 µV in the right eye and 2.8 µV in the left eye in only one recording per eye). Dark-adapted 3.0 cd·s/m² testing showed small a-waves bilaterally; the b-wave was measurable in only one right-eye recording (4.3 µV) and was non-measurable in the left eye. (B) Under light-adapted 3.0 cd·s/m² testing, the mean right-eye b-wave amplitude was 2.1 µV, while the left-eye response was non-measurable. The 28.3-Hz flicker amplitudes were 2.2 µV and 2.7 µV in the right and left eyes, respectively, with non-measurable peak times. Overall, the findings are consistent with severe generalized rod-and-cone retinal dysfunction.

The horizontal axis represents time in milliseconds (ms), and the vertical axis represents electrical response amplitude in microvolts (µV). Green, orange, and purple traces correspond to the first, second, and third recordings, respectively, when available. NM indicates non-measurable responses.

Based on the patient's clinical presentation and multimodal imaging, an initial clinical diagnosis of RP was made. Dorzolamide 2% ophthalmic solution was initiated for management of the associated cystoid macular edema in the left eye with significant improvement. The patient was also referred for genetic counseling and genetic testing to confirm the underlying molecular diagnosis.

Genetic testing was performed using the Invitae Inherited Retinal Disorders Panel, comprising sequence analysis and deletion/duplication analysis of 330 genes. The testing identified a heterozygous pathogenic deletion encompassing exons 3-8 of TSPAN12, a gene associated with autosomal dominant FEVR. Variants were classified according to the laboratory's Sherloc framework, a refinement of the American College of Medical Genetics and Genomics/Association for Molecular Pathology (ACMG/AMP) criteria [11]. According to the report, the pathogenic classification was based on the deletion of a clinically significant protein region, in which the variant p.Gly205Asp has been established as pathogenic [12], and the absence of the deletion in affected individuals in the literature. The reference transcript was NM_012338.3. Following identification of this pathogenic variant, the patient's clinical findings were re-evaluated in the context of FEVR. Given the absence of characteristic clinical or angiographic vascular manifestations of FEVR, the condition was reinterpreted as TSPAN12-associated retinal disease with an RP-like phenotype rather than clinically typical FEVR. Genetic testing also identified two heterozygous variants of uncertain significance: GNB3 c.847C>T (p.Arg283Cys) and ZNF513 c.1504C>T (p.Pro502Ser). Neither variant was considered diagnostic. No additional pathogenic or likely pathogenic variants associated with inherited retinal degeneration were identified.

Over 12 months of follow-up, visual acuity, fundus appearance, and the pigmentary changes remained stable, with no subjective or clinically evident progression.

Discussion

Criswick and Schepens first described FEVR as a hereditary vitreoretinal disorder characterized by incomplete peripheral retinal vascularization [13]. Subsequent studies have shown that its phenotype ranges from asymptomatic peripheral avascularity to retinal folds, neovascularization, and retinal detachment [14]. However, our patient lacked the hallmark vascular manifestations of FEVR. Targeted re-evaluation of the ultra-widefield fluorescein angiogram after identification of the pathogenic TSPAN12 variant did not reveal temporal avascularity, peripheral capillary nonperfusion, vascular straightening or dragging, neovascularization, or other characteristic vascular abnormalities of FEVR within the imaged peripheral

retina. Instead, multimodal imaging demonstrated bilateral retinal vessel attenuation, optic disc pallor, diffuse RPE alterations, sectoral perivascular bone-spicule pigmentation along the major retinal vascular arcades, and cystoid macular edema. Fundus autofluorescence demonstrated a bilateral symmetric sectoral and perivascular pattern of hypoautofluorescence corresponding to RPE atrophy, with relative preservation of the central macula, compatible with an RP-like pigmentary retinal degeneration. Functional testing further supported an RP-like phenotype. Humphrey 30-2 automated perimetry demonstrated marked, asymmetric visual field loss, with dense temporal hemifield loss in the right eye and a ring-shaped scotoma with a preserved central island in the left eye. These patterns are compatible with advanced pigmentary retinal degeneration. In addition, RETeval electroretinography demonstrated severely reduced or non-measurable responses under both dark- and light-adapted conditions, consistent with severe generalized rod and cone retinal dysfunction. The patient's history of longstanding nyctalopia, along with the results of multimodal imaging and functional testing, strongly supported an initial clinical diagnosis of RP as opposed to FEVR.

Subsequent studies by Poulter et al. and Nikopoulos et al. established TSPAN12 as a cause of autosomal dominant FEVR in humans [3,6]. Genotype-phenotype correlations are varied, with TSPAN12 variants generally associated with milder disease [15], although severe phenotypes have also been reported [16]. A substantial proportion of affected individuals are initially diagnosed with disorders other than FEVR [17]. The presentation observed in this patient reflects the reported clinical variability and raises the possibility that the recognized phenotypic spectrum may extend to a predominantly degenerative RP-like phenotype without clinically identifiable hallmark vascular features of FEVR. Because this observation derives from a single patient, it should be regarded as a possible association rather than a demonstrated causal relationship.

Pigmentary retinal degeneration has rarely been described in association with TSPAN12. Poulter et al. characterized heterozygous carriers of recessive TSPAN12 variants as only mildly affected [18], although neither the original nor subsequent reports described bone-spicule or RP-like pigmentary changes [3,18]. A directly relevant precedent is provided by Surl et al., who described a patient initially diagnosed with RP carrying a heterozygous TSPAN12 variant (c.194C>T, p.Pro65Leu); the clinical reevaluation prompted by the genetic finding revealed temporal retinal vessel dragging, a hallmark of FEVR, and the diagnosis was revised accordingly [19]. Similarly, Schatz and Khan described retinal pigmentary alterations in a patient harboring variants in both FZD4 and TSPAN12, but classic FEVR findings, including macular dragging and atrophy, were also present [20]. More recently, Abraham et al. reported a patient whose retinal pigmentary changes, arteriolar narrowing, and waxy disc pallor were consistent with RP and who carried a novel heterozygous likely-pathogenic nonsense variant in TSPAN12; in that patient, however, fluorescein angiography demonstrated peripheral nonperfusion. Furthermore, full-field electroretinography and electro-oculography were within normal limits [10]. In contrast, our patient had bone-spicule pigmentation in the setting of a pathogenic TSPAN12 deletion and exhibited an RP-like phenotype with severely reduced to non-recordable electroretinographic responses and without any identifiable clinical or angiographic hallmark of FEVR, even after targeted reevaluation prompted by the molecular diagnosis. Large deletions of TSPAN12 have been reported previously: Seo et al. identified two whole-gene deletions and a deletion of exon 4 in three Korean FEVR families and observed that patients with large deletions had relatively milder phenotypes than a patient with a point mutation [21], and Jiang and Wang described a heterozygous deletion of exon 7 in a three-generation family in which the proband, initially managed as high myopia with retinopathy, showed typical angiographic features of FEVR together with full-field electroretinographic abnormalities [22]. To our knowledge, a heterozygous deletion encompassing exons 3-8 of TSPAN12 has not been previously reported; as a heterozygous loss-of-function deletion, however, it is mechanistically comparable to the previously reported whole-gene deletions. This case suggests that TSPAN12-associated retinal disease may closely mimic RP clinically and that molecular testing may be necessary to clarify the underlying diagnosis in atypical inherited retinal degeneration phenotypes.

The biological basis for this clinical mimicry remains uncertain. Bone-spicule pigmentation is not specific to RP but reflects migration of RPE cells following photoreceptor degeneration [23], providing a plausible explanation for why a TSPAN12 variant could produce an RP-like fundus manifestation. Tetraspanins contain four transmembrane domains connected by two extracellular loops [24]. The large second extracellular loop (EC2), which contains the conserved Cys-Cys-Gly motif characteristic of tetraspanins [25], contributes to incorporation of TSPAN12 into the Norrin/FZD4 receptor complex and enhancement of Norrin-selective β-catenin signaling [26,27]. Our patient had a heterozygous pathogenic deletion encompassing exons 3-8 that includes the termination codon and is predicted to disrupt EC2 and downstream coding sequence. According to the clinical genetic testing report, the deletion extends beyond the assayed region and may encompass additional genes. It is not anticipated to lead to nonsense-mediated decay but is expected to alter mRNA translation or result in a truncated protein product. Because the complete genomic boundaries were not defined, the precise transcript and protein consequences could not be determined; no functional RNA or protein studies were performed. Loss of TSPAN12 function is an established disease mechanism through impaired Norrin/FZD4 signaling; however, how this molecular defect relates to the predominantly degenerative phenotype observed in this patient remains uncertain. The laboratory classified the deletion as pathogenic on the basis of its disruption of a clinically significant protein region in which another variant, p.Gly205Asp, has been reported as pathogenic [12], together with its absence from prior reports in affected individuals. We note that absence from prior reports does not by

itself establish pathogenicity, and the classification therefore rests primarily on the predicted structural consequence of the deletion. Accordingly, the relationship between this deletion and the observed phenotype should be regarded as an association rather than a demonstrated causal mechanism.

Phenotypic overlap between FEVR and RP has also been described at other loci. Pathogenic variants in ZNF408 lead to both phenotypes, indicating that the pathways involved in retinal vascular development and photoreceptor survival are not mutually exclusive [28]. Our findings raise the possibility that a similar phenotypic overlap may occur in TSPAN12-associated retinal disease, although the mechanism by which loss of TSPAN12 function produces a degenerative as opposed to exudative phenotype remains unknown and warrants further investigation.

This report has several limitations. First, as it describes a single case, it cannot establish the frequency or mechanism of this phenotype among TSPAN12 carriers. Second, the deletion was identified by a clinical multigene panel incorporating deletion/duplication analysis, an approach that detects copy-number loss at the exon level but does not resolve the exact genomic breakpoints. Because the deletion extends beyond the assayed region, its full genomic boundaries and the potential involvement of neighboring genes could not be determined. Whole-genome sequencing or a targeted structural variant analysis (e.g., long-read sequencing or breakpoint-spanning polymerase chain reaction (PCR)) would be required to map the breakpoints precisely, but these were not available for this patient. Therefore, although TSPAN12 loss is consistent with the molecular diagnosis, an additional effect from other genomic elements within the deleted interval cannot be excluded. Third, no RNA studies (e.g., transcript analysis) or protein expression studies were performed; therefore, the proposed molecular mechanism remains a hypothesis rather than a demonstrated consequence of the deletion. Finally, segregation analysis was not performed because family members were not available for genetic testing or ophthalmic phenotyping. Consequently, whether the deletion was inherited or arose de novo could not be established, and the presence of subtle or subclinical phenotypes in relatives, as has been described in TSPAN12-associated FEVR, could not be assessed. Genetic testing also identified heterozygous variants of uncertain significance in GNB3 and ZNF513. The ZNF513 variant represents an additional source of uncertainty; however, because it remains classified as a variant of uncertain significance, it cannot currently be considered diagnostic or used to establish an alternative molecular etiology for the patient's ocular phenotype. The GNB3 variant likewise remains of uncertain significance and was not considered diagnostic.

Conclusions

This case describes an association between a heterozygous pathogenic deletion encompassing exons 3-8 of TSPAN12 and an RP-like phenotype in the absence of clinically recognizable vascular manifestations of FEVR and suggests that the phenotypic spectrum of TSPAN12-associated retinal disease may extend beyond the classic vascular manifestations of FEVR. This proposed expansion of the phenotypic spectrum should be regarded as tentative: a single case cannot establish causality, particularly because the genomic boundaries of the deletion are undefined, neighboring genes may be involved, and functional validation was not performed. Confirmation will require additional cases, segregation analysis, and functional studies. Nevertheless, in the absence of characteristic FEVR features, clinical examination, multimodal imaging, and electrophysiologic testing alone could not establish the molecular diagnosis; comprehensive genetic testing enabled molecular characterization of the disease and informed genetic counseling and the consideration of familial screening.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Maria Garcia, Arlene Perez Zierenberg, Andres Emanuelli, Natalio Izquierdo, Alanis Ponce Cotto, Jose Garcia Gonzalez

Acquisition, analysis, or interpretation of data: Maria Garcia, Arlene Perez Zierenberg, Andres Emanuelli, Natalio Izquierdo, Jose Garcia Gonzalez

Drafting of the manuscript: Maria Garcia, Arlene Perez Zierenberg, Andres Emanuelli, Natalio Izquierdo, Alanis Ponce Cotto

Critical review of the manuscript for important intellectual content: Maria Garcia, Arlene Perez Zierenberg, Andres Emanuelli, Natalio Izquierdo, Jose Garcia Gonzalez

Supervision: Andres Emanuelli, Natalio Izquierdo

Disclosures

Human subjects: Informed consent for treatment and open access publication was obtained or waived by all participants in this study. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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