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Ocular manifestations in pediatric tumor suppressor gene mutations: a case series and literature review of RB1, NF1, NF2, VHL, and TSC

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Abstract

Background This study explores ocular manifestations in children with mutations in key tumor suppressor genes (RB1, NF1, NF2, VHL, TSC1/2), which are linked to common pediatric hereditary cancer syndromes. Mutations in these genes often lead to ocular lesions, particularly in the retina and uveal tract, including the choroid and iris. The expression of these tumor suppressor gene mutations in the eye has been a topic of interest for ophthalmologists and other healthcare professionals. We have summarized the ocular presentations of these common tumor suppressor gene mutations in pediatric patients.

Methods We reviewed 11 representative case reports, documenting in detail the ocular manifestations and progression of each case. These case studies were analyzed in conjunction with a detailed search of the relevant literature to identify specific ocular features associated with each tumor suppressor gene mutation, as well as potential underlying genetic mechanisms.

Results Our review indicates that children with mutations in RB1, NF1, NF2, VHL, and TSC1/2 exhibit a diverse range of ocular manifestations, with the specific features varying depending on the type of mutation. Early detection of ocular symptoms is crucial, as it allows for prompt intervention, significantly improving both visual and systemic outcomes. Additionally, these genetic mutations are frequently associated with systemic syndromes, emphasizing the importance of recognizing ocular symptoms and providing timely ophthalmic care and follow-up for early diagnosis and effective management. This highlights the critical role of a multidisciplinary healthcare team in managing these cases.

Conclusions This study highlights the significance of regular ophthalmic evaluations for children with hereditary cancer syndromes associated with tumor suppressor gene mutations. Early detection and timely intervention are essential for preserving vision and supporting overall development. Given the complexity of these conditions, it is

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vital for both ophthalmology and other medical specialties to closely collaborate and prioritize these patients. Future research should focus on larger cohort studies and the development of tailored strategies for managing specific gene mutations.

Keywords Tumor suppressor genes, Pediatric oncology, Ocular manifestations, Retina and uveal tumor, Early diagnosis

Introduction

Pediatric patients with mutations in tumor suppressor genes, including the retinoblastoma susceptibility gene (RB1), neurofibromatosis type 1 (NF1), NF2, Von Hippel-Lindau (VHL), and tuberous sclerosis complex (TSC), often exhibit distinct or indistinct ocular manifestations that are essential for early diagnosis. These mutations predispose children to both ocular and systemic tumors, leading to complications that can severely affect vision and quality of life. The eye space caused by the mutation of these tumor suppressor genes has accounted for the majority of space-occupying diseases in children's ophthalmology. Understanding the unique ocular manifestations in children provides critical insights for early diagnosis and potential systemic screening. Regular ophthalmic evaluations in genetically predisposed children can facilitate early detection of eye-related abnormalities, ensuring timely intervention before visual and systemic complications arise [1].

Retinoblastoma (RB) is the most common primary intraocular malignancy in children, with 1 in 15,000 to 20,000 live births, resulting in about 8,000 new cases annually [2]. The disease arises from the inactivation of both RB1 alleles, leading to a defective retinoblastoma protein (pRb) that impairs cell cycle control and triggers unchecked cell proliferation. Autosomal dominant inheritance accounts for 30–40% of cases, usually in children at a younger age and accompanied by a high risk of bilateral secondary cancer, while the rest are sporadic and unilateral [3]. The RB1 gene spans 183 kilobases and encodes a 928 amino-acid phosphoprotein, whose function depends on phosphorylation. In a hypophosphorylated state, pRB binds to E2F transcription factors, halting the cell cycle at the G1 restriction point [4]. However, in retinoblastoma, pRb becomes non-functional due to mutations or deletions, leading to genomic instability and tumor formation [4].

NF is a multisystem tumor predisposition syndrome caused by genetic mutations, with NF1 resulting from a mutation on chromosome 17 (17q11.2) and NF2 from a mutation on chromosome 22 (22q12.2) [5]. Although Riccardi originally proposed seven types of NF due to the disorder's clinical heterogeneity, more recent classifications recognize only NF1 and NF2, with the other types now considered variants [6]. NF1 also known as the von Recklinghausen disease is one of the most common hereditary diseases, with an estimated prevalence of 1/3000 ~ 3500 [7]. A wide spectrum of ophthalmological manifestations characterizes the disease. NF2 is much less common than NF1, affecting about 1 in 25,000 people worldwide regardless of sex or ethnicity [8]. Mutations in the NF2 gene are highly associated with acoustic neuroma, a benign tumor that originates from vestibular Schwann cells [9]. This tumor commonly occurs in both ears, and bilateral acoustic neuroma is the signature feature of NF2. More than 90% of patients with NF2 develop this tumor early in life, typically before the average age of 30 years [9].

VHL disease is a rare autosomal dominantly inherited multisystem neoplastic condition caused by a mutation in the VHL gene. Key clinical features include hemangioblastomas of the brain and spinal cord, renal cell carcinoma (RCC), retinal hemangiomas (RH), pheochromocytoma, and cysts in the epididymis, pancreas, and kidneys [10]. The VHL tumor suppressor gene, responsible for the disease, encodes for a major regulator of the hypoxic response by targeting the transcription factor hypoxia-inducible factor (HIF) for degradation [11]. While most cases are hereditary, up to 20% arise from new mutations. The incidence is approximately 1 in 36,000 live births, with over 90% penetrance by age 65 [12]. Despite advances in treatment, life expectancy remains 40–52 years, primarily due to metastatic RCC and central nervous system lesions [12].

TSC is an autosomal dominant disorder with near complete penetrance that results from mutations in TSCl or TSC2. TSCl is due to a heterozygous mutation of TSCl on chromosome 9q34, which encodes for the gene hamartin [13]. TSC2 is caused by a heterozygous mutation of TSC2, which encodes for the gene tuberin. Two-thirds of cases represent new events. TSC2 mutations (75–80%) are more common than TSC1 (10–30%) [13]. Tuberin and hamartin are tumor suppressor genes that inhibit the mammalian target of the rapamycin (mTOR) pathway [14]. Loss of function of the tuberin or hamartin genes results in unregulated cell growth. TSC affects cell growth in different germ layers causing hamartomas in affected organ systems [15]. In retinal hamartomas, glial astrocytes and blood vessel growth are unregulated leading to characteristic retinal astrocytic hamartomas.

Ocular manifestations are often among the earliest signs of these genetic syndromes, making ophthalmic examination crucial for early diagnosis. This study focuses on analyzing the ocular features of pediatric

patients with RB1, NF1, NF2, VHL, and TSC mutations treated at our institution. By combining our findings with previous reports, we emphasize overlooked clinical features to improve early detection and management strategies.

Patients and methods

This retrospective case series, combined with a systematic literature review, aimed to characterize the ocular manifestations of pediatric patients with confirmed mutations in tumor suppressor genes (RB1, NF1, NF2, VHL, TSC1/2). Between July 2022 and December 2024, 11 pediatric patients (< 18 years) were recruited from the Ophthalmology Department of the Affiliated Children's Hospital of Xiangya School of Medicine (Hunan Children's Hospital). The inclusion criteria were: (1) genetically confirmed pathogenic variants in RB1, NF1, NF2, VHL, or TSC1/2 via clinical genetic testing; (2) comprehensive ophthalmic records available for analysis.

Peripheral venous blood samples were collected from all participants, and genomic DNA was extracted using the QIAamp DNA Blood Mini Kit (Qiagen, Hilden, Germany) according to the manufacturer's protocol. Whole-exome sequencing (WES) was performed on the Illumina NovaSeq 6000 platform (Illumina, San Diego, CA, USA). Variants were analyzed using the ANNOVAR pipeline and classified per ACMG/AMP guidelines, with Sanger sequencing confirming pathogenic/likely pathogenic variants.

The study included 11 typical pediatric patients with confirmed genetic mutations, all diagnosed through WES and clinical genetic testing (Table 1). Each patient underwent detailed and comprehensive ophthalmologic evaluations. Depending on their cooperation and clinical necessity, they received slit-lamp examination, fundus examination, B-scan ultrasonography, spectral-domain optical coherence tomography (SD-OCT; Heidelberg Engineering, Heidelberg, Germany), fundus photography (TRC-50DX; Topcon, Tokyo, Japan) or ultra-widefield fundus photographs (Optos PLC; Dunfermline, Scotland, United Kingdom), orbital magnetic resonance imaging (MRI; 3.0T scanner, T1-weighted, T2-weighted, and contrast-enhanced imaging sequences Signa Premier, GE Healthcare, Chicago, IL, USA), best corrected visual acuity (BCVA) and other examinations to identify the ocular presentation.

This study was approved by the Institutional Review Board of Hunan Children's Hospital (No. HCHLL-2022-76) and conducted following the principles of the Declaration of Helsinki. Before the procedure, informed consent was obtained in writing from all participants' parents or legal guardians.

In addition to the clinical cases, a systematic literature review was performed. We searched PubMed, Scopus, and Web of Science for articles published in the last 10 years focusing on the ocular manifestations of RB1, NF1, NF2, VHL, and TSC1/TSC2. Keywords included: "ocular manifestations," "RB1," "VHL," "NF1," "NF2," "TSC/TSC1/TSC2," "retinoblastoma," and "angiogenesis." Relevant articles were selected if they focused on pediatric patients with gene mutations associated with these syndromes.

Results

Ocular manifestations of RB1 mutation in retinoblastoma

RB, resulting from RB1 gene inactivation, disrupts the normal regulation of retinal cell growth, leading to distinct ocular symptoms, particularly in children [16]. In our study, we introduced a patient, a girl with leukocoria born in December 2023 and diagnosed with Rb with autosomal dominant inheritance at 3 months, who had undergone multiple multidisciplinary treatments including intravenous chemotherapy (IVC) at a local hospital

Table 1 Characteristics of children with gene mutations in tumor suppressor genes

Gene Mutation	Sex	Age	Variant Description	Typical Ocular Manifestations
RB1	Female	Born in December 2023	c.1578delC (p.Arg527Glufs*66)	Leukocoria, retinal tumor
NF1	Female	2 years 11 months	c.3113 + 1G > T (p.?)	Lisch nodules, patchy pigmentation abnormalities, blurred optic disc, enlarged eyeball
	Female	4 years 8 months	c.3381_3382del (p.Gly1128Trpfs*66)	
	Female	5 years 7 months	c.3525_3526del (p.Arg1176Serfs*18)	
	Male	6 years 3 months	c.5546G > A (p.Arg1849Gln)	
	Male	5 years 3 months	c.702_703del (p.Tyr235Profs*6)	
	Male	1 year 9 months	c.1882dupT (p.Tyr628Leufs*6)	
NF2	Female	11 years 8 months	c.784 C > T (p.Arg262Ter)	Cataract, epiretinal membrane, macular edema
VHL	Female	14 years 2 months	c.497 C > T (p.Arg167Trp)	retinal hemangioblastoma
TSC1	Female	13 years 8 months	c.733 C > T (p.Arg245*)	Thickening orbital nerves, pupil dilation, pale optic discs, and blurred disc margins, reitnal hamartoma
TSC2	Male	5 years 10 months	c.3696dupT (p.Asn1233*)	Retinal hamartomas

by April 2024. Upon her referral to our institution, her bilateral lesions were found to be relatively stable, and she received laser photocoagulation therapy for consolidation (Fig. 1A, B). However, during a follow-up visit in August, new tumor (NT) development was noted in her right eye (Fig. 1C, D), indicating the necessity for long-term regular follow-up and timely intervention.

Leukocoria (abnormal white reflex) is the most common early symptom of RB, while delayed detection often worsens prognosis. Strabismus is frequently associated with macular tumors, and advanced cases may present with buphthalmos, neovascular glaucoma, or orbital inflammation. Tumor growth patterns include endophytic (into the vitreous), exophytic (with retinal detachment), and diffuse infiltrating (flat growth without a clear mass). Atypical variants, such as cavitary RB and retinocytoma, may also occur [17, 18]. RB can manifest bilaterally, with trilateral forms involving intracranial tumors and rare quadrilateral forms including suprasellar tumors. Metastasis, though uncommon, may involve the optic nerve, choroid, or ciliary body [3, 18].

Over the last three decades, IVC has played a major role in the conservative treatment of RB. The eventual globe salvage rate has usually been >70% in several previous reports employing IVC and focal treatments [19]. However, long-term tumor control and the development of recurrence and NTs are still major concerns after IVC. High-risk factors for recurrence include age < 12 months at diagnosis, shorter tumor distance to the optic disc, higher International RB Classification, and subretinal seeds, while NT development is strongly associated with age < 6 months, familial RB, bilateral disease, and subretinal seeds [19–22]. Recurrence and NTs are treated with IVC, transpupillary thermotherapy, cryotherapy, plaque radiotherapy, external beam radiotherapy, and intra-arterial chemotherapy, either alone or in combination [17, 23]. Advances in RB treatment have significantly reduced poor outcomes, such as vision loss and enucleation. Emerging strategies, including biomarker-based staging, targeted therapies, and extracellular vesicle analysis, offer promising prospects for early detection and improved outcomes, paving the way for precision medicine in RB care [24].

Ocular manifestations in NF1 and gene basis

NF1 is caused by mutations in the NF1 tumor suppressor gene, which encodes neurofibromin, a protein that inhibits the RAS-MAPK pathway [7]. Disruption of this pathway promotes excessive cell growth and survival, leading to ocular neoplasms and other systemic manifestations.

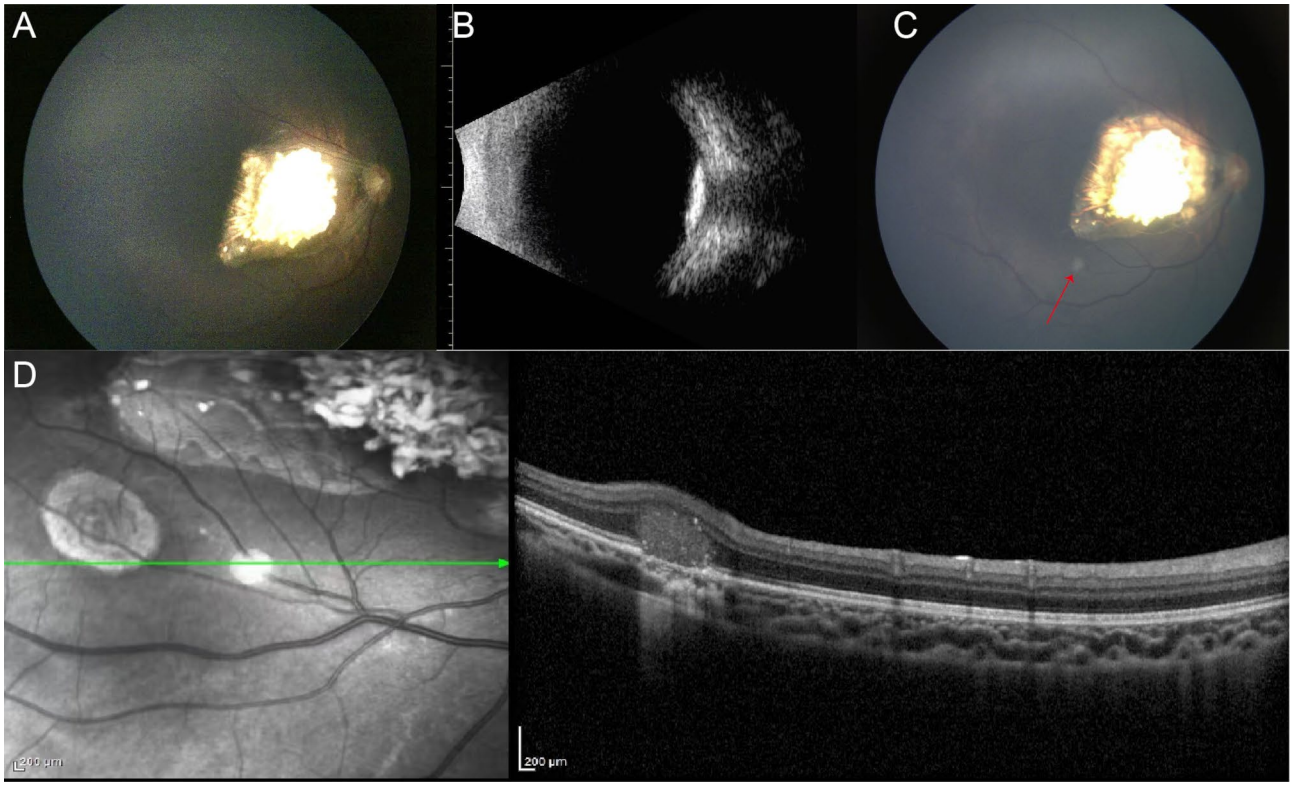

Fig. 1 Ocular manifestations caused by RB1 gene mutation. (**A**) Initial diagnosis of a stable tumor in a child with RB. (**B**) B-scan ultrasonography shows a high-density shadow adjacent to the posterior wall of the eyeball. (**C**) Four months later, a new tumor pattern appeared in the infratemporal portion of the primary lesion (red arrow). (**D**) OCT shows the retinal interlayer status corresponding to C's new tumor mass, with unclear boundaries and medium-low reflectivity

In this study, we analyzed six pediatric NF1 patients: three females aged 2 years 11 months, 4 years 8 months, and 5 years 7 months, and three males aged 6 years 3 months, 5 years 3 months, and 1 year 9 months. Many of these patients exhibited Lisch nodules, a hallmark of NF1, which appear on the surface of the iris (Fig. 2A). However, one child did not present with Lisch nodules, but rather with focal, flattened patches of pigment on the iris (Fig. 2B). Although these symptoms concerning the iris did not show clear ocular complaints, these benign iris hamartomas are a key diagnostic feature, easily detectable via slit-lamp examination [25]. In cases with orbital-facial involvement, associated ocular globe enlargement is often observed. Orbital MRI may demonstrate features such as enlarged eyeballs, abnormally thickened extraocular muscles, as shown in Fig. 2D, bilateral optic nerve enlargement, thickening of the optic chiasm, and abnormal signal intensities in the brainstem and basal ganglia. These findings are highly suggestive of NF1 and align with observations reported in the existing literature [26]. OCT images revealed choroidal hyperreflectivity and blurred optic disc margins can be detected in some patients (Fig. 2C, E). Systemically, nearly all presented with café-au-lait spots in the axillary, facial, or groin regions, further supporting the diagnosis of NF1 [27].

Among our cases, a 1-year-9-month-old child presented with a white cornea resulting from increased intraocular pressure. Initially diagnosed with glaucoma at a local hospital, further investigation revealed a family history of glaucoma in both the mother and grandfather. Upon referral to our hospital, further diagnostic evaluation, including ocular B-scan ultrasonography, revealed an enlarged eyeball with an abnormally elongated axial length, thickened optic nerve, and a band-like high echo within the vitreous cavity (Fig. 2F, G). Subsequent genetic testing confirmed the diagnosis of NF1. This case underscores diverse ocular clinical manifestations and initial symptoms of NF1 and highlights the critical importance of thorough clinical evaluation and genetic testing. Clinicians should adopt a meticulous approach, carefully investigating beyond initial findings to uncover deeper systemic or genetic abnormalities that may underlie the ocular symptoms.

Additionally, multiple patients developed optic pathway gliomas, which are observed in approximately 15% of NF1 patients [26]. These gliomas sometimes led to strabismus and proptosis, necessitating neuroimaging and visual field testing for regular monitoring. Early intervention in symptomatic cases remains crucial to prevent visual loss [27].

Literature also suggests further ocular findings, including choroidal nodules and retinal vascular abnormalities, detectable using near-infrared reflectance imaging. OCT has provided detailed insights into retinal changes and assisted in managing optic gliomas, becoming essential for tracking ocular complications in pediatric NF1 patients [28, 29].

Beyond ocular involvement, some patients in our cohort exhibited behavioral and cognitive deficits, common in NF1 [7]. These systemic manifestations underscore multidisciplinary care's importance in effectively addressing ocular and non-ocular complications. Early diagnosis and comprehensive management are vital for optimizing outcomes in these patients.

Ocular manifestations in NF2 and gene basis

NF2 is caused by mutations in the NF2 gene on chromosome 22, which encodes Merlin, a protein that regulates cell proliferation and contact inhibition [30]. The disruption of this regulatory mechanism promotes uncontrolled cell growth and increases the likelihood of tumor formation. NF2 occurs in approximately 1 in 25,000 individuals worldwide, with about 50% of cases inherited through an autosomal dominant pattern, while the remaining cases arise from de novo mutations [31]. Although systemic manifestations such as bilateral vestibular schwannomas typically present in young adulthood, ocular symptoms often appear much earlier, particularly in pediatric patients, underscoring the importance of early screening [31].

Our cohort included an 11-year 8-month-old female patient who had experienced bilateral visual decline for over three years before hearing loss in both ears. Her family history revealed that her brother had been previously diagnosed with NF2 and had passed away three years after brain tumor surgery. The patient presented with multiple café-au-lait spots on her body and, during ophthalmologic evaluation, was found to have exotropia in the left eye, and mild cataracts in both eyes. And the epiretinal membrane (ERM) and macular edema as confirmed by OCT (Fig. 3A). Her BCVA was 20/50 in both eyes, and no abnormalities were observed in the iris and other structures.

These findings are consistent with prior studies, which report that ocular manifestations of NF2, can appear in childhood and precede the onset of more severe systemic symptoms [32]. Cataracts, observed in up to 80% of NF2 patients, may require surgical intervention to restore vision, especially as they progress. Retinal hamartomas and ERM, as identified in this patient, though less common, can significantly impair visual acuity and warrant continuous monitoring with OCT. The exotropia observed is aligned with previous reports of cranial nerve involvement in NF2, which may also lead to optic nerve sheath meningiomas or vestibular schwannomas affecting ocular motility [8, 31].

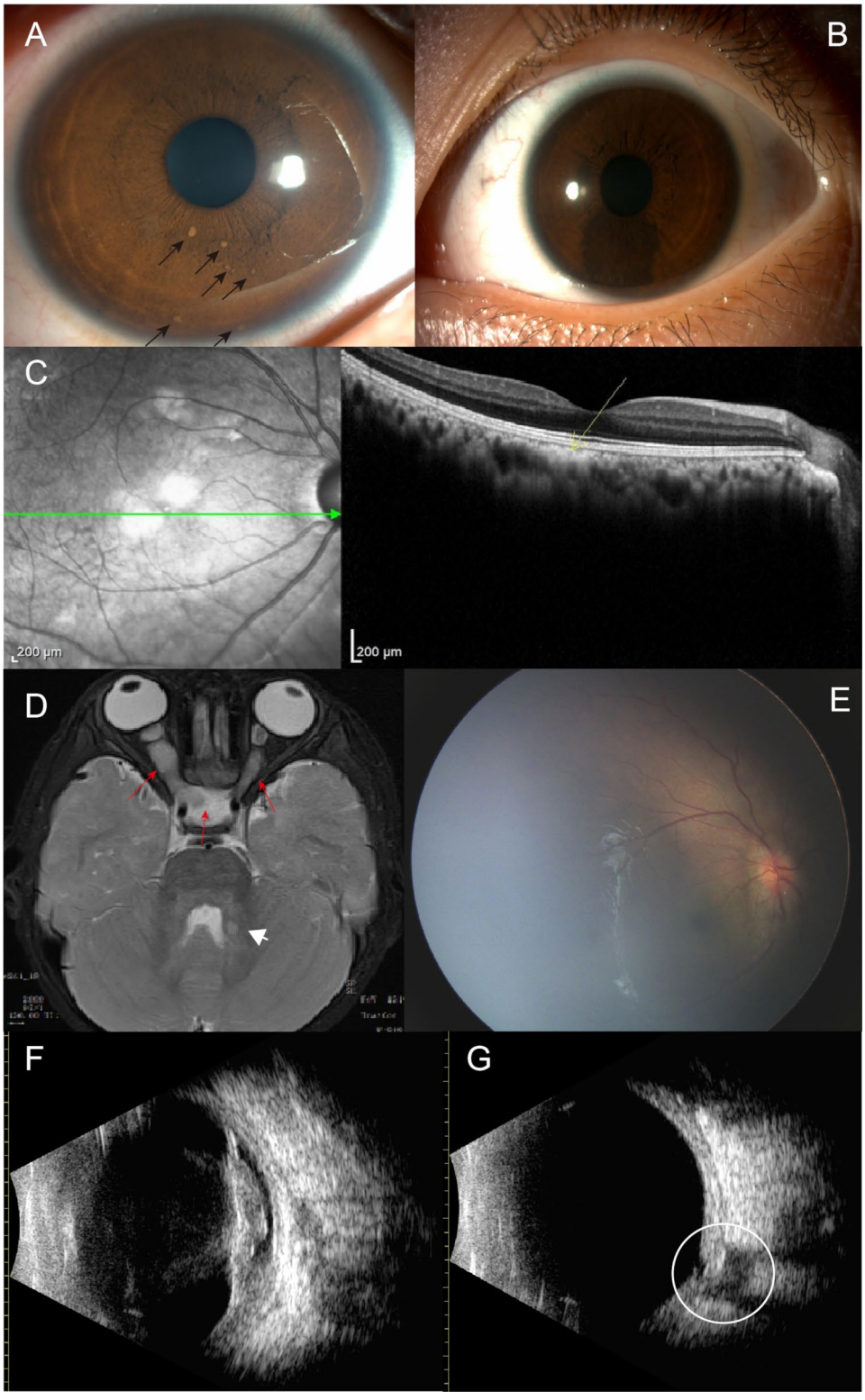

Fig. 2 Ocular clinical manifestations caused by NF1 gene mutation. (**A**) The characteristic clinical manifestations of NF1 include Lisch nodules, appearing as protrusions on the iris surface with a scattered distribution (black arrows). (**B**) Patchy pigmentation abnormalities in the lower iris represent another iris-related feature associated with NF1. (**C**) OCT imaging demonstrates hyperreflective dots in the choroid (yellow arrow). (**D**) Orbital MRI in the T2 phase shows different degrees of abnormal thickening of the bilateral optic nerves and optic chiasma, with the right side heavier than the left side (red arrow) and abnormal signals near the brainstem (white arrow). (**E**) Fundus examination in this child with NF1 reveals a blurred optic disc. (**F, G**) Ocular B-scan ultrasonography identifies vitreous opacities, band-like echoes in the vitreous cavity, and optic nerve thickening (white circle)

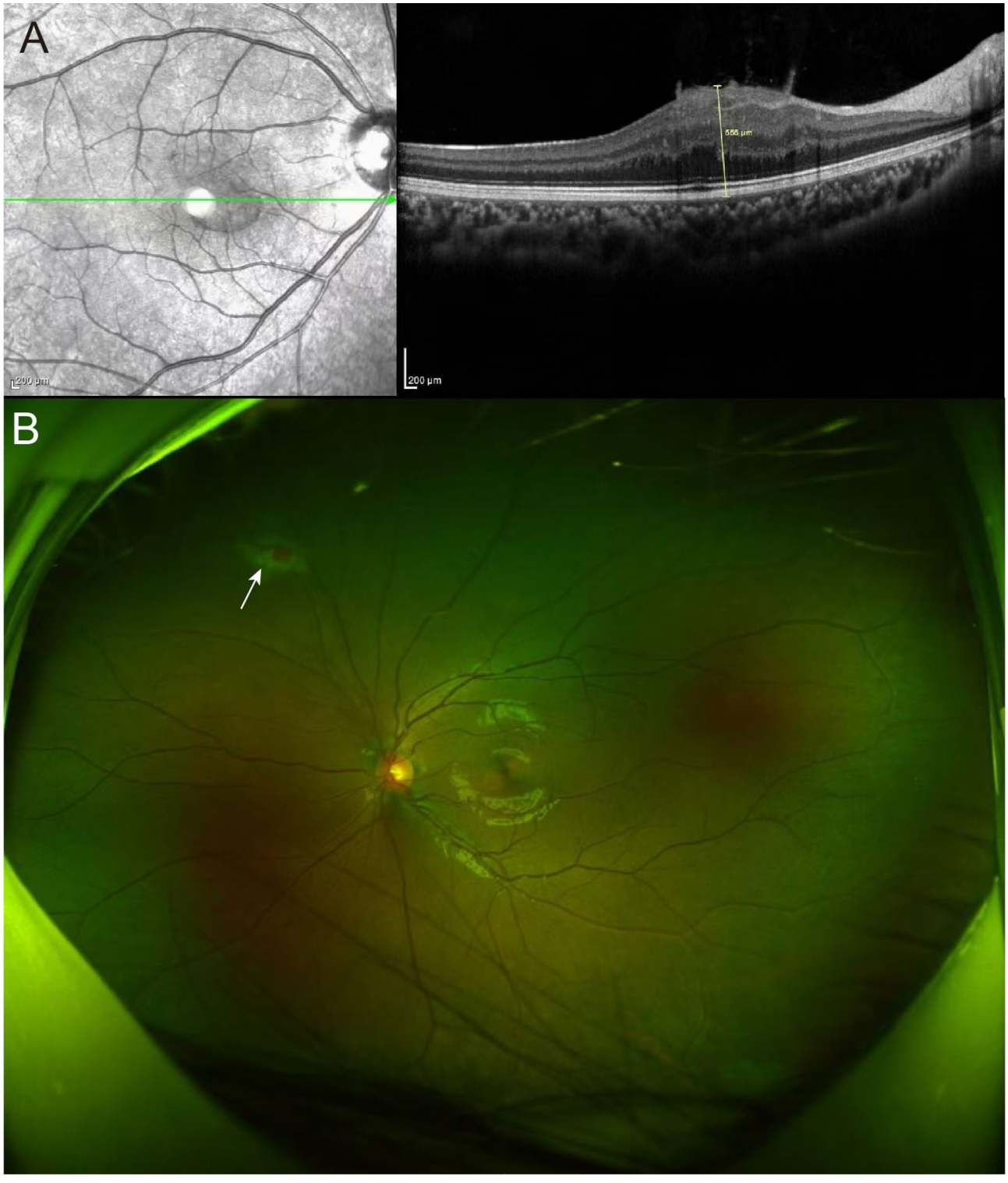

Fig. 3 Ocular clinical manifestations caused by NF2 and VHL gene mutation. (**A**) A child with an NF2 gene mutation presenting with macular epiretinal membrane. OCT demonstrates disruption of the macular foveal contour and macular edema with a central retinal thickness of 550 µm. (**B**) Fundus photograph of a child with a VHL gene mutation showing a retinal hemangioma located superior to the nasal aspect of the optic disc

Although ocular manifestations occur as the first sign in only 12% of NF2 cases, they often develop much earlier than systemic tumors, with some reports indicating onset as early as 5.6 years [5, 32]. Therefore, regular ophthalmologic follow-ups are crucial in identifying these early changes, especially in children with a family history of NF2. Timely detection and intervention can help manage vision loss and provide better outcomes for these patients.

Ocular manifestations in VHL and gene basis

VHL disease is a rare, autosomal dominant hereditary syndrome caused by mutations in the VHL tumor suppressor gene, which encodes a protein regulating cellular responses to hypoxia and angiogenesis by targeting the transcription factor HIF for degradation [11]. Mutations in the VHL gene result in abnormal angiogenesis and the development of various tumors, with retinal hemangioblastomas being the most common ocular manifestations associated with the condition with a prevalence ranging from 30–58% [12, 33].

In our study, we included a 14-year-old and 2-month-old female patient who had previously undergone adenoma resection for a hemangioblastoma at our institution. Following her surgery, she was advised to visit the ophthalmology department. Upon examination, a clear retinal lesion consistent with a retinal hemangioblastoma was identified in the superior nasal quadrant of her right eye (Fig. 3B). Fortunately, her visual acuity remained stable, and there were no signs of inflammation, choroidal detachment, or other complications. Our department promptly performed laser photocoagulation treatment on her right eye, and she has shown stability in her condition during regular follow-up visits.

In addition to retinal hemangioblastomas, patients with VHL may present with other ocular manifestations, such as retinal cysts and choroidal hemangiomas [10]. Retinal hemangioblastomas are often the earliest manifestation of VHL, potentially leading to vision loss through exudation, hemorrhage, or retinal detachment. Therefore, early detection via fundoscopy and subsequent treatment, including laser or cryotherapy, is crucial for preserving visual function and preventing complications.

Given the potential ocular involvement in VHL, it is essential for patients diagnosed with this condition by other specialties to undergo routine ophthalmic evaluations.

Ocular manifestations in TSC and gene basis

TSC is a genetic disorder characterized by multi-system hamartomas resulting from mutations in the TSC1 and TSC2 genes, leading to the overactivation of the mTOR signaling pathway and dysregulation of cell proliferation [14, 34]. Typically diagnosed in early childhood or adolescence, TSC is a chronic, multisystemic disorder with age-dependent manifestations that pose challenges for lifelong surveillance. In some studies, epilepsy remains one of the main neurological challenges, with over 90% of cases manifesting in childhood [13]. The abnormal performance of the eye requires vigilance in monitoring, paralleling the broader systemic challenges.

Retinal hamartomas are the most common ocular feature in TSC, appearing as yellowish or calcified lesions. While typically asymptomatic, they may affect vision in rare cases, especially when lesions are located near the macula or optic disc.

In our study, we included a 13-year-8-month-old female patient with a confirmed TSC1 mutation. She initially presented to the neurosurgery department with nausea and headache and was subsequently diagnosed with a subependymal giant cell astrocytoma with thickening bilateral orbital nerves, requiring neurosurgical intervention (Fig. 4A, B). Since the onset of systemic symptoms, her vision has been severely impaired, and limited to light perception. Preoperative evaluation in our department revealed bilateral pupil dilation, pale optic discs, and blurred disc margins (Fig. 4C-E). Postoperative examination showed no improvement in BCVA. While optic nerve edema had subsided, the optic discs remained pale (Fig. 4F). OCT revealed the disorganization of outer photoreceptor segments in both eyes, with a suspected hamartoma in the right eye (Fig. 4G-H). This case highlights the significant ocular complications associated with TSC1 mutations, particularly in the context of systemic manifestations and neurosurgical interventions.

Additionally, we included a TSC2 patient, a 5-year and 10-month-old male, who presented with vision decline. Whole-exome sequencing confirmed a TSC2 mutation, and upon examination, bilateral retinal hamartomas were identified (Fig. 5A-C). He underwent bilateral retinal laser photocoagulation, resulting in stable vision, with corrected visual acuity of 30/50 in the right eye and 20/50 in the left. Some TSC patients also exhibit choroidal depigmentation or other abnormalities, which can be observed during comprehensive ophthalmic exams [35, 36]. The clinical significance of these findings remains under investigation.

Cross-mechanisms in tumor suppressor genes affecting ocular manifestations

Dysregulation of key signaling pathways, including E2F, Ras, mTOR, HIF-1α, and Hippo, was related to mutations in RB1, NF1, NF2, VHL, TSC1, and TSC2, contributing to abnormal cell growth, impaired apoptosis, disordered angiogenesis, and microenvironmental imbalances. Mutations in RB1, NF1, NF2, VHL, TSC1, and TSC2 play a significant role in these processes, and overlapping ocular manifestations may occur. The RB1 gene is involved

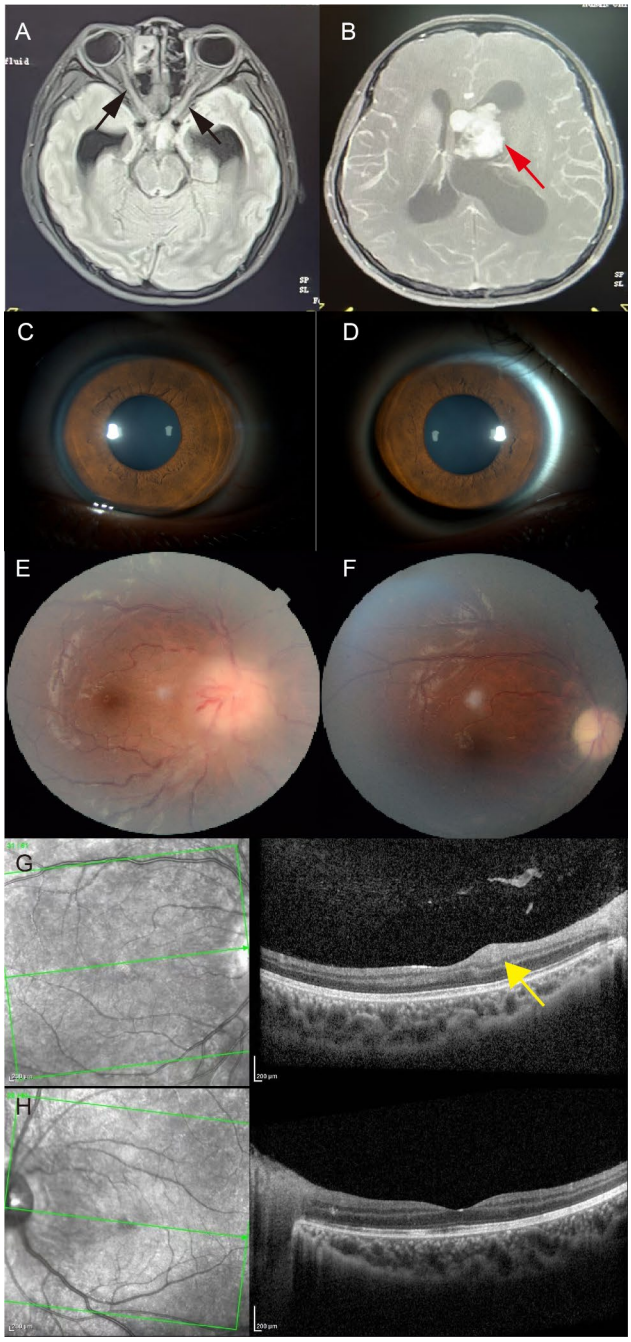

Fig. 4 Ocular clinical manifestations caused by TSC1 gene mutation. (**A, B**) The MRI scan during the T2 phase showed thickening bilateral optic nerves (black arrows) and high signal intensity in the ependyma (red arrow). (**C, D**) The pupil of the child with TSC1 gene mutation was dilated and fixed without light reflection. (**E**) Fundus photography revealed pale optic discs with blurred edges in the right eye before the neurosurgery operation. (**F**) Postoperative fundus images showed that the patient's optic disc edema improved, but the color of the optic disc was still pale. (**G, H**) OCT showed structural disorganization in the outer photoreceptor segment in both eyes. In G, foveal deformation and suspected hamartoma can be detected (yellow arrow)

in regulating the cell cycle, genomic stability, apoptosis, metabolism, and angiogenesis. Mutations in RB1 can activate the E2F pathway, driving the development of retinoblastoma, while its role in apoptosis is linked to the mTOR pathway [37, 38]. Similarly, TSC1/TSC2 mutations upregulate mTOR signaling, causing hamartomas and disrupting cellular metabolism [34].

NF1 and NF2 mutations impact the Ras and Hippo pathways, respectively, leading to schwannomas and optic gliomas [5]. Notably, NF2 mutations also affect cell adhesion and cytoskeletal stability, thereby maintaining tissue integrity [9, 30]. VHL gene mutations impair the regulation of HIF-1α, promoting abnormal angiogenesis and contributing to the formation of RH [11]. Furthermore, the mTOR and HIF-1α pathways intersect under hypoxic conditions, exacerbating oxidative stress and driving further pathological changes [39]. Both VHL and TSC1/TSC2 are crucial regulators of vascular homeostasis and metabolic responses, playing a central role in the tumor microenvironment [33, 34].

The Ras-PI3K-AKT-mTOR and interaction between mTOR and HIF are particularly important in regulating cell growth and tissue metabolism, while pathways such as Ras, mTOR, HIF-1α, and Hippo also modulate the tumor microvascular environment [40, 41].

Dysregulation of these interconnected signaling pathways not only underpins the development of systemic and ocular tumors but also contributes to progressive ocular damage and retinal pathologies. These processes highlight the complex interplay between tumor suppressor genes, their downstream pathways, and their roles in ocular disease manifestation.

Discussion

The ocular manifestations of tumor suppressor gene mutations in pediatric patients, particularly those associated with RB1, NF1, NF2, VHL, and TSC, are critical for early diagnosis and management of systemic diseases. These findings often precede other clinical symptoms, underscoring the importance of comprehensive pediatric ophthalmologic examinations.

In this study, we presented a case of bilateral retinoblastoma diagnosed at three months of age, which recurred in one eye following treatment. This case, along with previous literature, highlights several important points: (1) Children with retinoblastoma in both eyes are at a higher risk of relapse; (2) Smaller infants with retinoblastoma are more likely to experience recurrence; (3) Long-term follow-up is crucial for all retinoblastoma patients [3, 16].

Interestingly, most cases in this study were not initially seen in the ophthalmology department; patients came to us for eye examinations after surgical or neurosurgical treatment. NF1 patients often exhibit distinctive ocular findings, such as Lisch nodules, which are

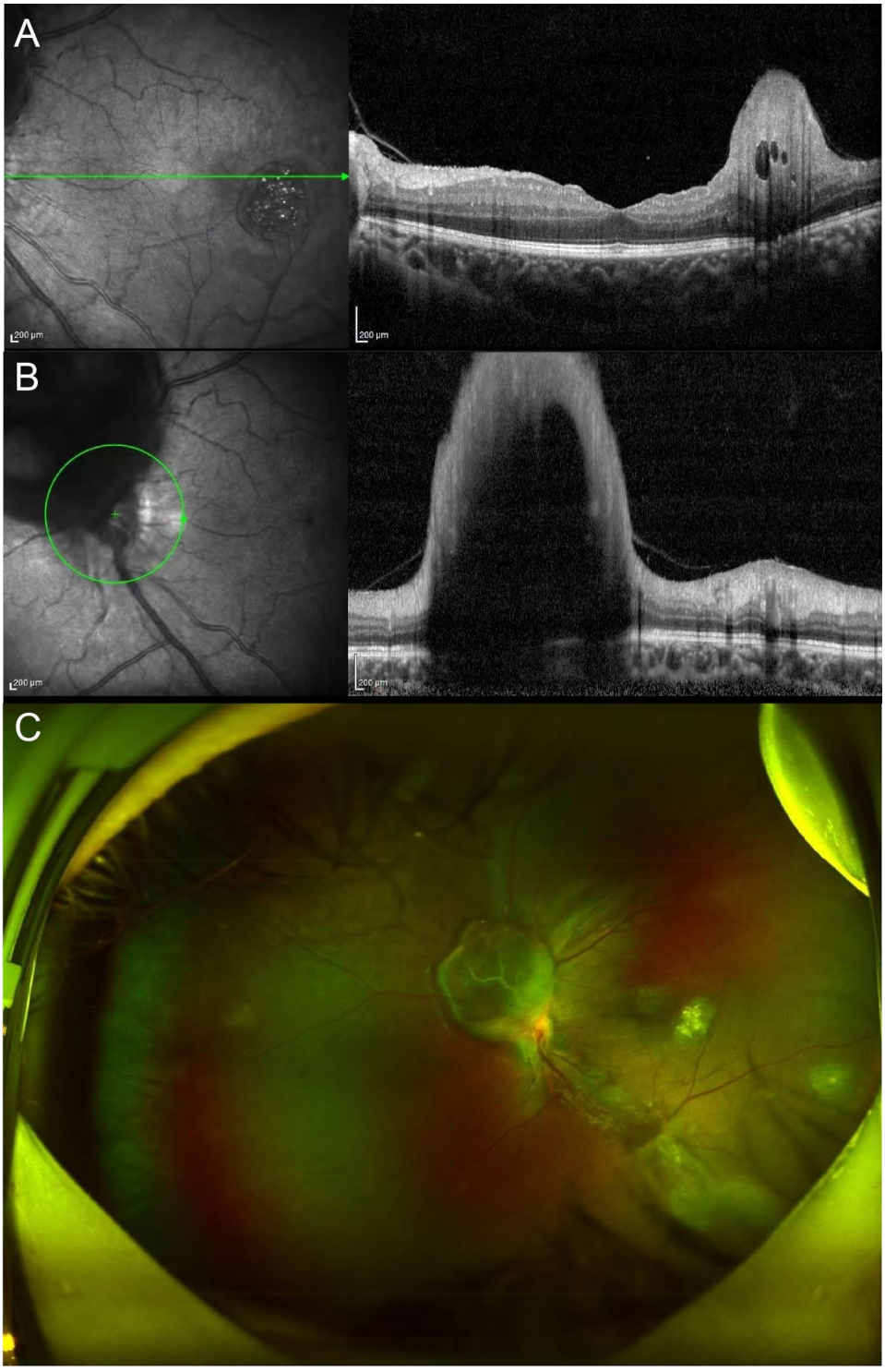

Fig. 5 Ocular clinical manifestations caused by TSC2 gene mutation. (**A, B**) Retinal hamartomas were identified in the optic disc and macular regions, with evidence of retinal structural disorganization. Retinal cavities were observed within the internal layers of the tumors, along with irregular and abnormally high spot-like reflections between retinal layers in other areas. (**C**) Fundus photography revealed multiple retinal hamartomas as circular protrusions in various locations of the retina

pathognomonic and can be easily observed. These findings, along with the risk of optic pathway gliomas, underscore the need for routine ophthalmic evaluations. Our findings also highlight the importance of ongoing ocular assessments in TSC and VHL patients. For instance, retinal hemangioblastomas in VHL are often the first detectable signs and require early intervention to prevent complications like retinal detachment. Additionally, patients diagnosed with VHL in other specialties should receive regular eye evaluations. In TSC, retinal hamartomas serve as key diagnostic markers, reinforcing the need for routine eye examinations to facilitate early intervention for potential vision-threatening issues.

This study has several limitations. First, the limited sample size ($n = 11$) may restrict the generalizability of findings, particularly for rare genotypes like NF2 and VHL. Second, incomplete long-term follow-up data preclude definitive conclusions on disease progression and treatment outcomes. Third, as a single-center study, results may not reflect regional variations in genetic epidemiology or healthcare practices. Future research should prioritize multicenter collaborations to expand sample size, and include comprehensive longitudinal outcomes.

This study emphasizes the importance of tumor suppressor gene expression in ocular manifestations. Even when initial symptoms may not present in the eye, they serve as critical warning signs for other healthcare providers. As ophthalmologists, we must remain vigilant not only to ocular findings but also to the systemic manifestations associated with these gene abnormalities. A multidisciplinary approach involving pediatric ophthalmologists, geneticists, and other specialists is essential. Regular ophthalmic follow-ups are crucial for monitoring disease progression and adjusting treatment strategies. Ultimately, early diagnosis and continuous ophthalmic monitoring, combined with advancements in genetic research and personalized medicine, are vital for preserving vision and managing systemic complications in children with mutations in tumor suppressor genes. Functional studies exploring the mTOR-HIF-1α axis in VHL/TSC-related angiogenesis may uncover new therapeutic targets. We believe the integration of targeted therapies and personalized treatment protocols based on genetic profiles holds promise for improving patient outcomes and quality of life.

Conclusion

Ocular manifestations serve as critical early indicators for hereditary cancer syndromes linked to RB1, NF1, NF2, VHL, and TSC mutations. Regular ophthalmic evaluations, and genetic testing combined with multidisciplinary care, are essential for timely diagnosis and improved outcomes. Larger sample sizes and long-term follow-up data are required to validate the generalizability of our findings and develop more comprehensive diagnostic and treatment protocols.

Abbreviations

RB1	Retinoblastoma susceptibility gene
NF1	Neurofibromatosis type 1
VHL	Von Hippel-Lindau
TSC	Tuberous sclerosis complex
RB	Retinoblastoma
pRb	Retinoblastoma protein
RCC	Renal cell carcinoma
RH	Retinal hemangiomas
HIF	Hypoxia-inducible factor
mTOR	Mammalian target of the rapamycin
WES	Whole-exome sequencing
IVC	Intravenous chemotherapy
NT	New tumor
OCT	Optical coherence tomography
ERM	Epiretinal membrane

Author contributions

CRediT authorship contribution statementAoxiang Wang: Writing– original draft, Investigation, Visualization, Formal analysis. Chanyuan Wang: Writing– review & editing, Software, Methodology. Wen Li: Data curation. Jing Qiao: Conceptualizations. Yulin Luo: Writing– review & editing, Validation. Yu Tian: Writing– review & editing, Supervision, Funding acquisition, Conceptualization.

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Data availability

The datasets used in this study are available from the corresponding author upon reasonable request. Data sharing is subject to ethical review and patient confidentiality protocols.

Declarations

Ethics approval and consent to participate

This study was conducted following the principles of the Declaration of Helsinki. Informed consent was obtained in writing from the parents or legal guardians of all participants before the procedure. The Ethics Committee of Hunan Children's Hospital granted ethical approval (No. HCHLL-2022-76).

Consent for publication

All co-authors have given their approval for the final manuscript and consented to its publication.

Clinical trial number

Not applicable.

Competing interests

The authors declare no competing interests.

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