Retinal Hemangiomas: Understanding Clinical Features, Imaging, and Therapies

Several different vascular tumors can occur in the retina, each with its own features and findings.

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Several types of benign and malignant tumors can arise in the retina, originating from neural (retinoblastoma), vascular (hemangioma/hemangioblastoma), and glial (astrocytic hamartoma and acquired astrocytoma) elements. The various retinal vascular tumors are benign, and each has distinct funduscopic and imaging features. Related systemic findings and tumor management depend on the specific type of hemangioma. Some of these retinal vascular tumors can be associated with the oculoneurocutaneous syndromes (phakomatoses). This article reviews four such tumors and describes their clinical findings and imaging features on fluorescein angiography (FA), ultrasonography, optical coherence tomography (OCT), and other studies.

RETINAL HEMANGIOBLASTOMA

The retinal hemangioblastoma, previously termed *retinal capillary hemangioma*, is a vascular hamartoma that generally has clinical onset in the first 2 decades of life. Bilateral or multiple retinal hemangioblastomas are associated with von Hippel-Lindau (VHL) syndrome, and patients should be evaluated for this condition using brain and renal imaging as well as genetic testing (Table 1). Solitary retinal hemangioblastomas may also be associated with VHL syndrome.

Clinical Features

Retinal hemangioblastoma appears ophthalmoscopically as a reddish-orange mass, and it can be located in the peripheral retina or near the macular region or optic disc.[1-5] This tumor displays dilated retinal vessels feeding and draining the tumor. Early on, the tumor may not be clinically visible and may be seen only on FA (Figure 1). As it enlarges, the vessels become more dilated and tortuous (Figure 1). This tumor can produce subretinal fluid, subretinal and intraretinal exudation, and vitreoretinal fibrosis. The exudation has a tendency to accumulate selectively in the macular area as a macular star. In some instances, the tumors remain pinpoint and are detected only by observation of dilated vessels, confirmed later by hyperfluorescence on FA. When retinal hemangioblastoma is located at the optic disc, the mass can masquerade

At a Glance

- There are numerous types of retinal vascular tumors, and each has distinct clinical features, imaging findings, genetic alterations, and management strategies.
- Retinal hemangioblastoma appears as a reddish-orange mass and can be located in the peripheral retina or near the macular region or optic disc.
- Cavernous hemangioma does not have a feeding artery like retinal hemangioblastoma and is usually located along the course of a retinal vein.
- Acquired vasoproliferative tumor can produce findings of intraretinal and subretinal exudation, subretinal fluid, remote epiretinal membrane, cystoid macular edema, retinal hemorrhage, and vitreous hemorrhage.

TABLE 1. CRITERIA FOR THE DIAGNOSIS OF VON HIPPEL-LINDAU SYNDROME

If family history is:	Feature
Positive	for any one of the following: • retinal hemangioblastoma • brain hemangioblastoma • visceral lesion[a]
Negative	for any one of the following: • two or more retinal hemangioblastomas • two or more brain hemangioblastomas • single retinal or brain hemangioblastoma with a visceral lesion[a]

[a]Visceral lesions include renal cysts, renal carcinoma, pheochromocytoma, pancreatic cysts, islet cell tumors, epididymal cystadenoma, and endolymphatic sac tumor.

as papillitis, and the feeder vessels are often not visible. Regardless of tumor location, accumulation of subretinal fluid with exudation can lead to profound visual loss.

Genetics and Pathogenesis

In VHL syndrome, the stromal cells have a mutation on chromosome 3p25-26, which leads to dysfunctional VHL protein.[6,7] These cells cannot degrade hypoxia-inducible factor 1a (HIF-1a), so this factor accumulates and causes production of VEGF, platelet-derived growth factor (PDGF), erythropoietin, and transforming growth factor-alpha, all of which lead to proliferation and vascularization of the tumor.[7]

There are three types of mutation in the VHL gene: type 1, with deletion or nonsense mutation and manifesting mainly hemangioblastomas only; type 2, with missense mutation at risk for hemangioblastomas and pheochromocytomas (type 2A), additional renal cell carcinoma (type 2B), or only pheochromocytoma (type 2C); and type 3, with risk for polycythemia.[8]

Diagnosis

The best test for the detection and confirmation of retinal hemangioblastoma is FA because it shows rapid filling of the feeding artery, then the tumor, followed by rapid exit through the draining vein. Subclinical pinpoint tumors can be detected on angiography before they become symptomatic (Figure 1). Small to large tumors can display fluorescein dye leakage from the mass into the adjacent retina and vitreous cavity, a feature that can lead to remote macular edema and epiretinal membrane (ERM).

Ultrasonography depicts the intraocular mass as acoustically solid with surrounding subretinal fluid. OCT can show the intraretinal, optically dense tumor occupying full-thickness retina with related subretinal fluid, intraretinal/subretinal dense exudation, intraretinal edema, and ERM.[9] OCT is also important in judging treatment response.[2,9]

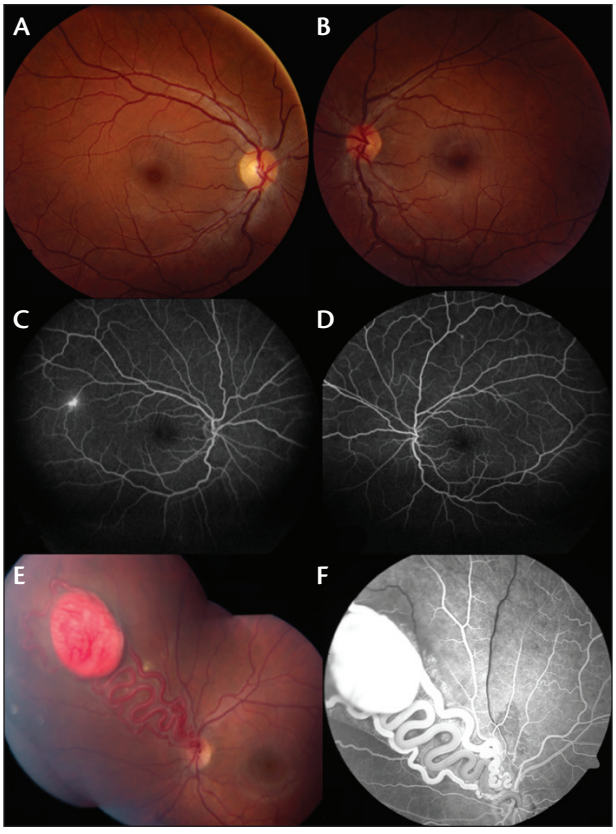

Figure 1. Young child with family history of von Hippel-Lindau syndrome, at risk for retinal hemangioblastomas. No tumors were visible in the right (A) or left (B) eyes, but retinal hemangioblastomas were clearly seen on FA in the right eye (C) temporal to the macula and in the left eye (D) as pinpoint dots superior to the macula (two sites). A large retinal hemangioblastoma (E) with prominent dilated, tortuous feeder vessels (F) that required plaque radiotherapy can be seen.

Magnetic resonance imaging (MRI) and computed tomography (CT) can expose an enhancing retinal mass in eyes with extensive retinal detachment. These scans are also essential for detecting associated central nervous system and abdominal neoplasms in VHL syndrome (Table 2). Several protocols are used for the evaluation of VHL systemic features, with variations depending on whether the genetically positive patient or at-risk relative is being examined (Table 3). Keep in mind that retinal hemangioblastoma could be the first finding of VHL syndrome, and it generally presents between the ages 12 and 25 years (Table 2). Other VHL-related tumors,

TABLE 2. TUMORS IN VON HIPPEL-LINDAU SYNDROME[a]

Tumor	Most Common Age at Diagnosis	Frequency of Tumor
Head and Neck		
Retinal Hemangioblastoma	12-25 years	25-60%
Cerebellar Hemangioblastoma	18-25 years	44-72%
Brainstem Hemangioblastoma	24-35 years	10-25%
Spinal cord Hemangioblastoma	24-35 years	13-50%
Endolymphatic Sac Tumor	16-28 years	11-16%
Trunk		
Renal Cell Carcinoma/Cyst	25-50 years	25-60%
Pheochromocytoma	12-25 years	10-20%
Pancreatic Tumor/Cyst	24-35 years	35-70%
Epididymal Cystadenoma	14-40 years	25-60% males
Broad Ligament Cystadenoma	16-46 years	10% females

[a]Data compiled from a survey of literature from 1976-2004, including data from the VHL Family Alliance and adapted from the VHL Family Alliance Handbook.
VHL Family Alliance: www.vhl.org/

TABLE 3. THE CAMBRIDGE PROTOCOL FOR SCREENING PATIENTS WITH VON HIPPEL-LINDAU SYNDROME OR AT-RISK RELATIVES

Test	Frequency
Affected Asymptomatic Patient[a]	
Physical examination	Annually
Retinal examination[b]	Annually
FA	Annually
Renal ultrasound	Annually
Brain MRI/CT	Every 3 years until age 50 years, then every 5 years
Abdomen MRI/CT	Every 3 years
24 hour urine for VMA	Annually
At-Risk Relatives: Same Protocol as Above but With Age Limits	
Retinal examination[b]	Annually, beginning at age 5 years
FA	Annually, from age 10-60 years
Brain MRI/CT	Every 3 years from age 15-40 years, then every 5 years until age 60 years
Abdomen MRI/CT	Every 3 years from age 20-65 years

[a]Symptomatic patients should be investigated urgently and managed according to their findings.
[b]We believe that retinal examination should be performed at least twice yearly in asymptomatic patients and at-risk relatives.
Abbreviations: FA, fluorescein angiography; MRI, magnetic resonance imaging; CT, computed tomography; VMA, vanillylmandelic acid

such as pheochromocytoma, epididymal cystadenoma, and endolymphatic sac tumor, tend to occur at a similar young age. Others, such as brain hemangioblastoma and renal cell carcinoma, occur later (Table 2).

Management and Course

Management of retinal hemangioblastoma should include both systemic and ocular evaluation.

The systemic evaluation should be performed by a qualified team of specialists including clinicians and radiology experts looking for related VHL tumors such as cerebellar hemangioblastoma, pheochromocytoma, renal cell carcinoma, and other associated neoplasms and cysts (Table 2). Brain and abdominal MRI or CT should be performed periodically in affected patients.

The eye evaluation should include complete dilated funduscopic examination and FA, as per the Cambridge protocol (Table 3). This is important for the detection of subclinical retinal tumors that might be seen only on FA (Figure 1). We perform FA under anesthesia annually in VHL-documented patients 5 years of age and younger, earlier than suggested by the Cambridge protocol, to detect pinpoint tumors and allow prompt treatment.

The treatment of retinal hemangioblastoma varies with the clinical situation.[4,10-13] Tumors associated with VHL syndrome tend to be more aggressive; therefore, nearly all retinal hemangioblastomas must be considered for treatment. If lesions are small (<3 mm) in size, laser photocoagulation or photodynamic therapy (PDT) can be used; if medium (3-6 mm), PDT or cryotherapy can be used; and if large (>6 mm), PDT, plaque radiotherapy, or internal resection by pars plana vitrectomy route can be employed.

Tumors not associated with VHL syndrome that are small and have asymptomatic lesions without

subretinal fluid can be cautiously observed, particularly if they are in the macular, perimacular, or juxtapapillary region, where treatment could be detrimental to vision. Treatment is warranted if leakage ensues. Criteria for treatment are similar to those listed above. Laser photocoagulation and PDT are useful for small- to medium-sized tumors located posterior to the equator and cryotherapy for those anterior to the equator. Plaque radiotherapy is reserved for larger tumors, and surgical repair of secondary ERM or traction retinal detachment is occasionally necessary. In the case of an aggressive juxtapapillary tumor that does not respond to conventional treatment, external beam radiotherapy or plaque radiotherapy can be considered.

Some anecdotal cases have reportedly responded to oral propranolol, oral acetazolamide, and oral prednisone, but large studies have not been conducted. Oral and intravitreal anti-VEGF agents have not been successful in effecting tumor regression, but intravitreal anti-VEGF can be useful for reducing macular edema and occasionally subretinal fluid. Wong and Chew reviewed the role of anti-VEGF agents and emerging therapies for retinal hemangioblastoma.[4]

Histopathology

Histopathologically, a retinal hemangioblastoma consists of a proliferation of retinal capillaries that usually replaces the full thickness of the neurosensory retina. On light microscopy, there is a benign proliferation of endothelial cells, pericytes, and stromal cells. In the end stage, total retinal detachment with massive retinal gliosis, cataract, and phthisis bulbi can occur.

RETINAL CAVERNOUS HEMANGIOMA

Retinal cavernous hemangioma is often associated with similar skin and central nervous system lesions and therefore should be classified with the oculoneurocutaneous syndromes, or phakomatoses.

Clinical Features

Ophthalmoscopically, retinal cavernous hemangioma usually appears as a cluster of dark intraretinal venous aneurysms, sometimes described as a bunch of concord grapes (Figure 2).[1,2,14-20] This tumor is usually without symptoms but can be associated with visual impairment from vitreous hemorrhage, secondary retinal traction, or macular scarring. Unlike a retinal hemangioblastoma, the cavernous hemangioma does not have a feeding artery and is typically located along the course of a retinal vein. Occasionally, this lesion is on the optic disc. Rarely is there exudation, but commonly there is overlying, white, fibroglial tissue on the tumor surface, suggesting previous vitreous or preretinal hemorrhage. Retinal cavernous hemangiomas are usually nonprogressive but can show minimal enlargement over time. Vitreous hemorrhage is the most commonly reported complication.

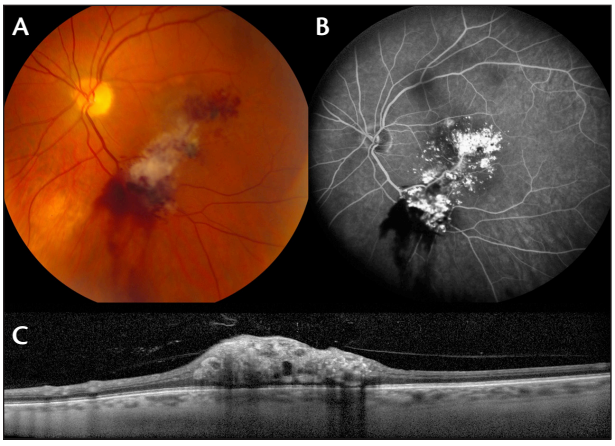

Figure 2. Macular retinal cavernous hemangioma (A) with late onset partial fluorescence (B) and an OCT scan showing multiloculated cavernous spaces (C) within the retina.

Genetics

Retinal cavernous hemangioma can occur with cerebral cavernous malformation (CCM) as a sporadic or familial autosomal dominant disorder with incomplete penetrance. Three genes cause CCM: CCM1/KRIT1, CCM2/MGC4607, and CCM3/PDCD10.[18] CCM3 is related to a higher risk for cerebral hemorrhage in childhood.

Diagnosis

In most instances, retinal cavernous hemangioma has a typical ophthalmoscopic appearance. FA is the most helpful diagnostic ancillary test because it produces nearly pathognomonic findings of arterial phase hypofluorescence with slow fluorescein appearance within the venous aneurysms. Within the aneurysmal space, the red blood cells deposit in the inferior portion and plasma deposits in the superior region, without leakage of dye. This is called the fluorescein-erythrocyte interface, a characteristic feature of cavernous hemangioma.

Vitreous hemorrhage can occur with large retinal cavernous hemangiomas, obscuring the tumor and causing it to be detectable only by ultrasonography. On A-scan ultrasonography, there is a high initial spike and high internal reflectivity; on b-scan, the lesion shows an irregular but well-defined surface, acoustic solidity, and no choroidal excavation. OCT demonstrates a markedly irregular retinal surface, with numerous cavernous spaces within the retina. In general, the retinal anatomy is disorganized from tumor compression.

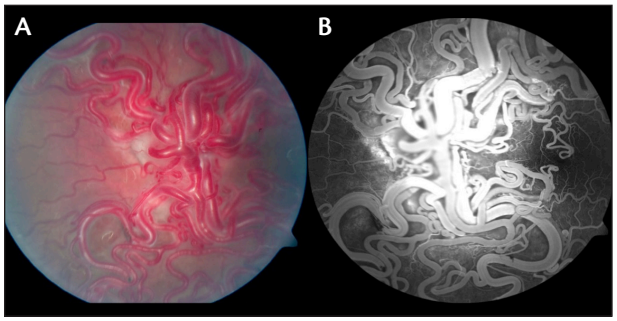

Figure 3. Advanced racemose hemangioma (A) in the peripapillary region showing prominence on FA (B).

Management and Course

Most cases of retinal cavernous hemangioma require no treatment because these tumors rarely progress or produce visual symptoms. Vitreous hemorrhage can occur and can be managed with observation or vitrectomy. For repetitive hemorrhage, the tumor can be sclerosed with plaque radiotherapy, PDT, or cryotherapy. It is important to perform brain MRI to evaluate for related cerebral cavernomas, and genetic testing for the CCM genes is advised, especially if there is a family history of cavernomas or the patient shows multiple cavernomas.

Histopathology

Histopathologically, retinal cavernous hemangioma appears as a mass of large-caliber vascular spaces in the inner retina and all layers of the retina. This tumor is lined by endothelium interconnected by narrow channels.[20] There can be extensive cystic and fibrous degeneration of the retina.

RETINAL RACEMOSE HEMANGIOMA

Retinal racemose hemangioma is not a true neoplasm but rather a simple or complex arteriovenous communication. It can occur as a solitary unilateral lesion, or it can be part of Wyburn-Mason syndrome (WMS; also called Bonnet-Dechaume-Blanc syndrome), which is anatomically termed retinoencephalofacial angiomatosis. This arteriovenous malformation can affect the retina, visual pathways, midbrain, and facial bones, including the mandible and maxilla. There is no hereditary tendency.

Clinical Features

Clinically, the retinal racemose hemangioma manifests as a large, dilated, tortuous retinal artery that passes from the optic disc for some distance into the fundus, communicating directly with a dilated retinal vein and then back to the optic disc (Figure 3). In some cases, the vascular anomaly displays a complex array of blood vessels. This retinal malformation does not usually produce exudation or hemorrhage. Archer classification is used to categorize the affected eye according to size and location of the vascular malformation (Table 4).[21-26]

TABLE 4. ARCHER CLASSIFICATION FOR WYBURN-MASON SYNDROME[a]

Group	Feature	Comments
I	Abnormal capillary plexus between the major vessels of the arteriovenous malformations.	Such lesions tend to be small, patients asymptomatic, and intracranial involvement uncommon.
II	Arteriovenous malformations lack any intervening capillary bed between the artery and vein.	Risk of retinal decompensation resulting in retinal edema, hemorrhage, and vision loss. Low risk for intracranial arteriovenous malformations.
III	Extensive arteriovenous malformations with dilated and tortuous vessels and no distinction between artery and vein.	High risk for visual loss due to retinal decompensation or retinal compression of nerve fiber layer, optic nerve, or other vessels. High risk for intracranial arteriovenous malformations.

[a]Adapted from Archer DM, Deutman A, Ernest JT, Krill AE. Arteriovenous communications of the retina. *Am J Ophthalmol*. 1973;75(2):224-241.

Genetics

There is evidence that genetic or developmental factors that occur early in gestation lead to dysgenesis of the embryologic vascular plexus.[26] The time of insult determines the location and extent of manifestations.

Diagnosis

The tumor is established with ophthalmoscopy and confirmed with FA, which shows rapid filling of the affected dilated artery and vein, usually with no intervening capillary channels and typically without leakage into surrounding tissues.

Management and Course

The management of a patient with this vascular tumor consists of systemic and ophthalmic monitoring. Furthermore, the patient should be evaluated for WMS with imaging studies for similar vascular abnormalities in the brain and facial bones. The retinal lesion usually remains stable, and treatment is rarely needed.

TABLE 5. OCULAR CONDITIONS ASSOCIATED WITH SECONDARY VASOPROLIFERATIVE TUMOR[a]

Associated Ocular Condition	Secondary VPT n = 56 patients n (%)
Retinitis pigmentosa	10 (18)
Pars planitis	11 (20)
Coats disease	11 (20)
Previous retinal detachment repair	8 (14)
Idiopathic peripheral retinal vasculitis	3 (5)
Familial exudative vitreoretinopathy	3 (5)
Toxoplasmosis	3 (5)
Aniridia	1 (2)
Congenital hypertrophy of retinal pigment epithelium	2 (4)
Idiopathic choroiditis	1 (2)
Retinopathy of prematurity	2 (4)
Histoplasmosis	1 (2)
Total	56

[a]Data adapted from Shields CL, Kaliki S, Al-Daamash S, et al. Retinal vasoproliferative tumors. Comparative clinical features of primary versus secondary tumors in 334 cases. *JAMA Ophthalmol*. 2013;131(3):328-334.
Abbreviations: VPT, vasoproliferative retinal tumor

Histopathology

Little histopathologic information has been published on retinal racemose hemangioma. The large, dilated retinal vessels appear to have an acellular adventitial covering, and the retina is thin and can show extensive degeneration.

ACQUIRED VASOPROLIFERATIVE TUMOR

Acquired vasoproliferative tumor of the ocular fundus is a vascular mass that can occur as a primary or secondary condition from predisposing intermediate uveitis, retinitis pigmentosa, Coats disease, or chronic retinal detachment (Table 5).[27-34]

Clinical Features

Ophthalmoscopically, acquired vasoproliferative tumor appears as an elevated sessile or dome-shaped mass that is typically located in the equatorial inferotemporal region (Figure 4). The mass can be circumscribed or quite ill-defined. Minimally dilated retinal feeding artery and draining vein can be found, but not as markedly dilated or tortuous as seen with retinal hemangioblastoma. The tumor can produce findings of intraretinal and subretinal exudation, subretinal fluid, remote ERM, cystoid macular edema, retinal hemorrhage, and vitreous hemorrhage. The retinal exudation generally begins at the tumor margin and gradually marches posteriorly into the macula, with ensuing visual loss.

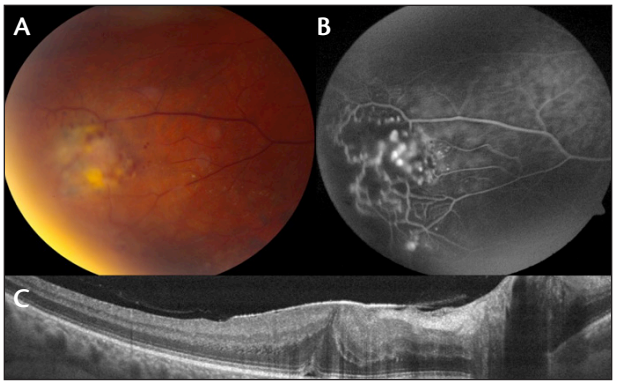

Figure 4. Subtle, ill-defined peripheral retinal vasoproliferative tumor (A) documented with telangiectasia, nonperfusion, and leakage on FA (B), and showing remote epiretinal membrane in the fovea on OCT (C).

Genetics

No genetic abnormalities have been associated with this condition, but patients with secondary tumors should be evaluated for underlying retinal conditions. Rarely, this lesion is associated with neurofibromatosis type 1.[30]

Diagnosis

FA demonstrates filling of the mass through a slightly dilated and minimally tortuous retinal artery and draining vein. There is frequently leakage from the vasoproliferative tumor into the surrounding retina and vitreous cavity. Remote macular edema or ERM can be seen on FA and confirmed on OCT; OCT can also demonstrate related remote ERM.

Management and Course

Small, peripheral tumors can be cautiously observed if there is no leakage, but it is important to realize that they can progress slowly and potentially lead to profound visual loss. This progression might be anticipated and halted with early treatment. Tumors with active leakage require therapy, which can include laser photocoagulation, thermotherapy, indocyanine green-enhanced thermoablation, PDT, cryotherapy, or plaque radiotherapy.[28-33] Cryotherapy often leads to tumor control and has been reported to induce release of the ERM in 63% of cases.[32] Intravitreal injection of an anti-VEGF agent can assist in

reducing remote macular edema, and sub–Tenon fascia injection of triamcinolone can minimize inflammatory response at treatment.

Histopathology

Histopathology of acquired vasoproliferative tumor in the early phases when the tumor is mostly vascular has not been clearly established. It is believed to represent a proliferation of blood vessels, glial tissue, and retinal pigment epithelium, often in response to a previous insult from intermediate uveitis, retinitis pigmentosa, Coats disease, or other conditions. Later, as the tumor becomes clinically fibrotic, a more reactive astrocytic appearance can be documented.[34,35]

CONCLUSION

There are a number of vascular tumors of the retina, and each has distinct clinical features, imaging findings, genetic alterations, and management strategies. It is important to remember that several of these tumors could potentially carry genetic mutations that imply systemic disease and related brain lesions, so genetic testing and MRI can be instrumental in management. We have found an informative website (www.genetests.org) for ocular genetic testing that is helpful in directing clinicians toward relevant laboratories that can provide genetic evaluation. As of April 2015, this website had logged 44 003 tests on 4176 disorders with 4747 genes from 649 laboratories. ■

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