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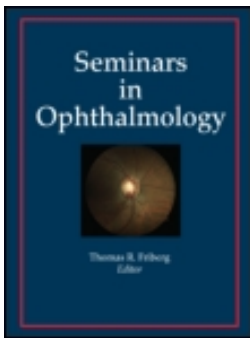
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The Interplay of Genetics and Surgery in Ophthalmic Care

Michael B. Gorin

ALTHOUGH ONLY a minor component of the surgical volume of ophthalmic care, genetic disorders are among the most challenging cases for the ophthalmic surgeon. Ophthalmic surgery may be indicated to address specific aspects of heritable disorders that involve the failure of proper development and function of ocular structures or the disruption of normal tissues by genetically determined abnormalities, such as tumors or degenerative conditions. Craniosynostoses, hereditary ptosis, congenital strabismus, corneal dystrophies, juvenile glaucoma, congenital cataracts, dislocated lenses, retinal tumors (retinoblastomas and hemangiomas), and sickle cell retinopathy are examples of ophthalmic genetic conditions that frequently require surgical management. The ophthalmologist may be called on to manage the secondary complications of genetic disorders such as exposure problems related to facial paralysis after removal of acoustic neuromas, ocular exposure from dysautonomias, or strabismus from the ocular fibrosis syndromes. In this overview of ophthalmic surgery and genetics we will consider the surgical management of ophthalmic genetic disorders, the potential impact of genetics on ophthalmic surgery, and those conditions that require special attention by the surgeon. In most instances, articles regarding the surgical management of genetic disorders are limited to case reports and small surgical series. The rarity of most conditions precludes controlled clinical studies. I have included extensive references that address surgical issues so that the reader can further explore specific disorders that are only briefly mentioned in this overview.

Limited attention has been directed to the impact of genetic conditions on routine ophthalmic surgery. Surgeons, patients, and health care payors continue to have increasing expectations for uncomplicated and successful ophthalmic procedures. It is increasingly important to identify underlying issues that may affect intraoperative safety and surgical outcomes. There are genetic factors and conditions that affect an individual's response to medications, anesthesia, pain, and wound healing that can greatly alter the outcomes of routine ophthalmic proce-

dures. Genetic conditions that affect the eye directly may also affect the surgical outcomes of routine procedures. The coexistence of Fuch's endothelial dystrophy in patients undergoing routine cataract extraction can contribute to postoperative corneal edema. Refractive surgery in individuals with unsuspected keratoconus has resulted in unsatisfactory results and progressive myopia and astigmatism.¹ Sickle cell disease and trait are risk factors for anterior segment ischemia in scleral buckling surgery and extraocular muscle surgery.² Although each of these genetic conditions is uncommon or rare, the widespread prevalence of strabismus, cataract, retinal, and refractive surgery make it highly likely that these patients will be encountered. In addition, as we come to recognize that genetics can play more subtle roles in physiological responses, there is the potential for anticipating those patients who will be at an increased risk of experiencing adverse responses to ophthalmic surgery. We will review this aspect of genetics to provide the clinician with guidelines toward avoiding surgical complications from familial disorders.

SURGICAL MANAGEMENT OF OCULAR GENETIC DISORDERS

For a number of genetic disorders, ocular surgery is well established and the treatment of choice. There is a considerable amount of literature addressing surgical methods for routine strabismus and for more difficult eye alignment problems such as Duane's syndrome. Similarly, the treatment of congenital cataracts,³⁻⁶ congenital ptosis,^{7,8} eyelid reconstruction,⁹⁻¹¹ and congenital or juvenile glaucoma¹²⁻¹⁸ has been described extensively. There are a number of rarer genetic disorders that pose additional potential challenges for the surgeon and pa-

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tient. These disorders serve as examples of why the ophthalmologist must consider the unique impact of each genetic condition on ocular and systemic anatomy and physiology.

Orbital Surgery for Craniodyostosis

Recently found to be caused by mutations in the FGFR2 and FGFR1 genes, Crouzon's syndrome and Pfeiffer Syndrome are part of a group of autosomal dominant disorders collectively known as the craniosynostoses. These conditions are characterized by the premature fusion of the cranial sutures creating marked deformities of the head including hypertelorism and laterally displaced orbits. Rarely, premature fusion of the metopic suture (less than 10% of craniosynostosis cases) results in close-set eyes.^{19,20} Oculoplastic surgeons, as well as maxillofacial, plastic, and neurosurgeons, have successfully tackled the surgical challenges of this genetic condition.²¹ Three-dimensional computed tomography imaging and multidisciplinary surgical teams have enhanced the surgical outcomes.²²⁻²⁴ Optic nerve compression from bony malformations and papilledema from increased intracranial pressure have been reported. Strabismus is not uncommon in these patients, and extraocular muscle surgery may be required. The surgeon may encounter abnormal muscle insertions during traditional recession or resection procedures that may alter the surgical response. Neurofibromatosis type I can also cause significant orbital deformities with bony erosion and unilateral proptosis. The surgical issues regarding this disorder are addressed in the following section on lid surgery.

Lid Surgery

The principal goals of lid surgery are to protect the eye, prevent occlusion or induced anisometropic amblyopia, ensure normal visual function, and re-establish a normal facial appearance. Serious malformations of eyelid development may be isolated or part of more complex genetic syndromes. Repair of these abnormalities is essential,^{9-11,25-29} but the ophthalmologist must also be aware of other associated abnormalities for each individual and condition. Among the most common genetic deformities are hemangiomas of the eyelids and neurofibromas from neurofibromatosis type I. For heman-

giomas, treatment is indicated when visual development and function are threatened. The natural history of these lesions frequently includes spontaneous involution, although a number of interventions including corticosteroid and interferon injections have been used.³⁰⁻³³ The majority of hemangiomas are sporadic, although familial forms have been reported. The ophthalmic surgeon, in addition to establishing the anatomic extent of the lesion or lesions that affect the lid and orbit, should take the appropriate steps to ensure that other systemic and central nervous system (CNS) manifestations are not overlooked. If an individual is found to have multiple hemangiomas (orbital, intraocular, visceral, or in the CNS), then other family members should be contacted and evaluated.

In the case of neurofibromas, surgical excision is difficult because of the plexiform nature of the lesion with the potential for damage to normal tissues. Lesions often extend beyond the orbit and can encroach on the brain. Intracranial approaches may be required and partial resections have had generally disappointing results because of recurrence and enlargement of the neurofibromas.³⁴⁻³⁹

A great deal has been written regarding the repair of congenital ptosis syndromes.^{7,8} Duke-Elder has cited eight major categories of congenital ptosis,⁴⁰ seven of which represent familial forms. The identification of unilateral or bilateral congenital ptosis in a patient should prompt an effort to identify other potential family members. The key aspects to surgical repair are the residual amount of levator function, the extent to which the eye has a normal Bell's phenomenon, the progressive or stationary nature of the underlying disorder, and the potential of associated abnormalities that may compromise the integrity of the eye.^{7,8,41,42} Some ptosis may be protective for eyes that lack an adequate Bell's phenomenon. Poor tear production (congenital Horner's, ectodermal dysplasia) or corneal hypesthesia can seriously compromise the outcome of even minor lid procedures.⁴³⁻⁴⁶ This can even be true if the surgical candidate appears to be minimally affected by the disorder under normal circumstances. A striking example of this situation was a woman whose child had ectodermal dysplasia.

The mother had been found to be mildly affected with the disorder only after her child had been diagnosed. Her mild dental anomalies had been surgically corrected, thus obscuring any obvious manifestations of the disorder, and she worked successfully as a professional model. Unfortunately, after undergoing cosmetic blepharoplasties by a plastic surgeon, she was plagued by continuous problems of eye pain and exposure difficulties, even though the surgical correction had been modest and the cosmetic result had been a success.

In some instances, metabolic disturbances associated with some cases of congenital ptosis can substantially increase the risk of undergoing general anesthesia.^{47,48}

Strabismus Surgery

Congenital strabismus has long been recognized to have a significant genetic component.⁴⁹ Patching for amblyopia and surgical management have remained the mainstay of treatment. Botulinum toxin has become a more recent addition to the therapy of extraocular muscle imbalances. The ocular fibrosis syndrome poses a special challenge to the surgeon.^{50,51} Both the muscles and extraocular tissues are markedly fibrosed and abnormal, the conjunctiva is often friable, and the normal guidelines for recession and resection are often ineffective. In cases of Mobius syndrome the severe esotropia secondary to cranial IV nerve palsy can greatly limit the range of aligned visual field.⁵²⁻⁵⁶ Traboulsi and Maumenee⁵⁵ reported bilateral medial and lateral recti aplasia in at least one case of Mobius syndrome. A range in the integrity of the extraocular musculature occurs in this disorder and the ophthalmic surgeon must be prepared to adapt the surgical corrections accordingly.

Strabismus is a frequent finding in a spectrum of genetic disorders. Strabismus in the presence of dysmorphic facial features warrants a genetic diagnosis before surgery. Like congenital ptosis, strabismus is frequently observed in patients with progressive myopathies and ophthalmoplegias. The progressive nature of these disorders clearly affects the benefits of ocular realignment and may suggest the presence of other underlying metabolic disorders.⁴⁸ The clinician must be especially vigilant in evaluating atraumatic, non-

comitant squints, with or without the presence of ptosis, to ensure that underlying genetic causes are established. The ophthalmologist should consult with the pediatrician and geneticist about hematologic disorders, factors that may affect anesthesia or wound healing, and other neurological findings that may affect visual function.

Isaacs and Barlow⁵⁷ described a family with malignant hyperthermia and dysmorphic features that included scoliosis, ptosis, strabismus, dislocation of the shoulders and patellas, pes cavus, pectus deformity, below average IQ, and increased creatine kinase. These features were transmitted in an autosomal dominant pattern. Strabismus can be observed in association with several congenital myopathies, and in all cases there is probably an increased risk of malignant hyperthermia.⁵⁸ Given the potentially fatal outcomes of anesthesia-induced malignant hyperthermia, every effort should be made to recognize the patient who is at increased risk before administering general anesthesia for strabismus surgery.

Strabismus is frequently seen in oculocutaneous albinism. Rare forms of oculocutaneous albinism are associated with bleeding disorders (Hermansky-Pudlak syndrome) or immunodeficiency (Chediak Higashi syndrome). The Hermansky-Pudlak syndrome is particularly common in the Puerto Rican population. Any underlying form of oculocutaneous albinism, even when the hypopigmentation is minimal, can have a bearing on the long-term success of binocular alignment caused by the CNS developmental abnormalities associated with these conditions.

Corneal Surgery

There are many autosomal dominant and recessive dystrophies affecting every layer of the cornea. Although some of these conditions are relatively benign, others are major causes of visual impairment and ocular discomfort. Corneal clouding can result from systemic disorders, such as the mucopolysaccharidoses, and from cornea-specific dystrophies. Corneal dystrophies represent an important indication for penetrating keratoplasties and will comprise an increasing percentage of cases as the number of pseudophakic bullous keratopathy cases de-

creases.⁵⁹⁻⁶² Although penetrating keratoplasties have a high success rate of graft survival, recurrent disease is frequent.⁶³⁻⁷² Lamellar keratoplasties have been used for several corneal dystrophies,⁷³⁻⁷⁶ and recent work has indicated that excimer laser photokeratectomy may be a viable alternative to penetrating keratoplasty or superficial keratectomy for some of the superficial corneal dystrophies.⁷⁷⁻⁸² Current surgical experience is insufficient to determine the rate and severity of disease recurrence using photokeratectomy procedures. Table 1 summarizes the reported procedures for the treatment of different corneal dystrophies.

Some of the genetic conditions associated with corneal opacities that require corneal transplants include sclerocornea,¹¹² Peter's anomaly (either genetic or in association with fetal alcohol syndrome),¹¹³⁻¹¹⁹ aniridia,¹²⁰ and lysosomal storage diseases.^{98,99,104} The major determinant in the success of these grafts is the presence of other ocular abnormalities, most notably glaucoma.¹²¹

Alternative approaches to the treatment of corneal opacities from ongoing metabolic and genetic conditions have been attempted. Conjunctival grafts to treat mucopolysaccharidosis

IV were initially reported to have some success¹²² and partial corneal clearing has been reported in response to bone marrow and tissue transplants,^{100,102,103} and there is evidence that cysteamine drops are capable of slowing and potentially reversing the early stages of accumulation of corneal crystals in nephropathic cystinosis.^{105-107,111} The combination of medications and/or gene therapy in conjunction with corneal surgery may be invaluable for maintaining the long-term clarity of grafts for progressive metabolic and corneal disorders.

Keratoconus is a special case of the corneal dystrophies because its initial manifestations may be subtle with mild to moderate astigmatism and myopic refractive error. Keratoconus can be transmitted in an autosomal dominant fashion in the absence of other abnormalities, or it can occur sporadically. It may be associated with other genetic conditions such as Down's syndrome, Ehlers-Danlos Syndrome IV, and Leber's congenital amaurosis. Keratoconus is one of the indications for penetrating keratoplasty with the highest graft survival rate.^{60,69,97} There have been several case reports in which early keratoconus was overlooked and these patients underwent refractive surgical proce-

Table 1. Major Corneal Dystrophies Treated With Surgical Intervention Procedures

	1	2	3	4	R
Basement membrane dystrophies (unspecified)	X				X
Reis Bucklers		X		X	X
Meesmann's		X			
Map-dot-fingerprint		X			
Granular		X	X	X	X
Gelatinous				X	X
Crystalline dystrophy (Schnyder)		X			
Lattice (type I and type II)				X	X
Macular		X	X		X
Avellino			X		
Fuchs Endothelial				X	
Posterior polymorphous			X		X
Corneal edema of Maumenee				X	
Keratoconus				X	
Lysosomal storage diseases				X	X
Cystinosis				X	X

Procedures: 1—Superficial excisional keratectomy/basement membranectomy, 2—Photoablative keratectomy (excimer), 3—Lamellar keratoplasty, 3—Lamellar keratoplasty, 4—Penetrating keratoplasty, R—Recurrences reported.

dures.^{1,123,124} The complications of refractive surgery in these patients included rapid progression of corneal astigmatism and acceleration of corneal decompensation. The poorer prognosis of refractive surgery for keratoconus should strongly motivate the clinician to perform a careful evaluation before initiating the procedure. The use of corneal topography imaging has shown considerable promise in distinguishing regular astigmatism from the corneal changes associated with early or mild keratoconus.¹²⁵⁻¹²⁸

Glaucoma

Glaucoma, whether congenital, juvenile, or late-onset, has a strong genetic basis. In addition to the primary glaucoma, there are a number of genetic conditions that are strongly predisposed to the development of glaucoma. In most instances, the management of glaucoma associated with genetic disorders is essentially unchanged from that of classical primary open-angle glaucoma. As noted above, the control of glaucoma is essential for the successful outcome of other ocular surgical procedures such as corneal transplants and vitreoretinal surgery. The major potential impact of genetics on the management of glaucoma is in the early recognition of the disease in at-risk individuals and in the family members. The awareness that glaucoma is a major feature of disorders such as Down's syndrome,¹²⁹⁻¹³¹ Weill-Marchesani syndrome,¹³² and aniridia¹³³ can guide the clinician to more effective screening among a high-risk population. Despite the coexistence of corneal opacities and glaucoma in Peters anomaly and Reigers syndrome, there are reports of successful surgery when the intraocular pressures are controlled.^{113,114,116,118,119}

Iris

Primary repair of iris anomalies is rarely undertaken. Most genetic disorders affecting the iris also cause abnormalities in the rest of the anterior segment, leading to glaucoma, cataracts, and corneal opacities. These are the primary complications addressed by the ophthalmic surgeon. For patients with aniridia and ocular albinism, contact lenses with artificial diaphragms are available that can provide refractive correction, cosmetic improvement, and some relief from photophobia.¹³⁴ However, in many

cases, particularly patients with aniridia, corneal problems, such as band keratopathy often limit the use of these lenses. For traumatic and hereditary aniridia there have been efforts to use an artificial diaphragm as part of an intraocular lens implant.¹³⁵⁻¹³⁷ Unfortunately, postoperative inflammation and difficulty in the control of glaucoma that often precedes the surgery remain the major obstacles to the use of these lenses. Posterior chamber intraocular lenses have been successfully implanted in patients with oculocutaneous albinism,¹³⁸ but there have been no reports of using the intraocular lens with the artificial diaphragm for these patients. Future work may provide surgical strategies that will effectively address the symptomatic and cosmetic problems associated with iris maldevelopment.

Cataract Surgery

Congenital cataracts. Like strabismus surgery, the indications and surgical approaches for congenital cataracts are beyond the scope of this review. Although it is generally preferable to recognize congenital cataracts as early as possible to avoid amblyopia, there is evidence that even surgery later in childhood can be associated with good visual outcomes.³ Glaucoma is a relatively frequent complication of congenital cataract surgery, affecting up to 24% of operated eyes¹³⁹ for more than a decade after the time of surgery.¹⁴⁰ Certain types of congenital cataracts and those associated with other intraocular malformations, such as persistent hyperplastic primary vitreous, are particularly challenging for the ophthalmic surgeon. Anterior lenticonus is frequently associated with Alport's syndrome¹⁴¹ but is readily recognizable. In contrast, the ectasia associated with the posterior capsule in posterior lenticonus can create significant surgical problems if this type of cataract is not detected or suspected before surgery. Posterior lenticonus has been observed sporadically, in familial forms,¹⁴²⁻¹⁴⁴ and in association with X-linked Alport's syndrome.¹⁴² The examination of family members may be helpful in recognizing this condition in a child with a congenital cataract. Ultrasonography should be seriously considered if the lens is too opaque for a complete examination of the posterior aspect of the lens, the vitreous, and the retina.

Ectopic lenses. The major causes of atraumatic ectopia lentis are Marfan's syndrome, homocystinuria, and Weill-Marchesani syndrome. Each of these conditions has significant systemic consequences and ocular problems. Given that many of these patients first come to the attention of the ophthalmologist, it is essential that the underlying diagnosis is established. The ophthalmologist is responsible for addressing visual rehabilitation and safeguarding the eye from glaucoma and retinal detachment. Achieving an unobstructed visual axis can be accomplished by either YAG zonulysis¹⁴⁵ and/or lens removal.¹⁴⁶⁻¹⁴⁹ The long-term safety of promoting lens dislocation by zonulysis has not been established. Other aspects of these disorders must not be overlooked. Marfan's syndrome is associated with significant cardiac abnormalities. Cardiovascular assessment should be undertaken before surgery to avoid situations in which local anesthesia might be proarrhythmic. Homocystinuria carries a serious risk of thromboembolic events and adequate precautions must be taken.^{150,151} Finally, Weil Marchesani patients have major ocular abnormalities in addition to ectopia lentis, and nearly 100% of these patients will develop glaucoma.¹³² The high incidence of narrow-angle glaucoma in these individuals has led some to recommend that prophylactic treatment be considered for narrow angles before cataract surgery.

Retina Surgery and Laser

Retinal detachment remains a major cause of visual loss for a large set of vitreoretinal genetic disorders. Pathological myopia and lattice degeneration are relatively common disorders for which autosomal dominant inheritance has been reported. Stickler's syndrome and Wagner syndrome are associated with vitreous abnormalities and a high incidence of retinal detachments. The surgical management of serious retinal detachments from optic pits and optic nerve colobomas¹⁵² and retinal detachments in conjunction with choroidal colobomas¹⁵³ have been discussed. Progressive peripheral retinoschisis and outer-layer retinal detachments have been a source of concern for patients with x-linked retinoschisis.¹⁵⁴ Despite the fact that most patients with x-linked retinoschisis remain stable, at least one investigator has advocated

prophylactic peripheral photocoagulation to prevent progressive changes.¹⁵⁵

Familial exudative retinopathy, whether of the x-linked or autosomal dominant type, bears striking similarities to retinopathy of prematurity. The management of these eyes parallels that of retinopathy of prematurity.¹⁵⁶⁻¹⁵⁹

Finally, one must consider localized abnormalities of the retina and/or choroid that contribute to retinal detachment or vision loss. Retinal angiomas secondary to von Hippel Lindau disease are frequently the earliest manifestations of this multisystem disorder that includes CNS hemangiomas, renal cell carcinoma, and pheochromocytoma. Laser and cryosurgery have been used for the ablation of these lesions and vitreoretinal surgery has been used when chronic exudative or rhegmatogenous retinal detachments occur. The treatment of peripapillary angiomas has been generally disappointing. Some investigators report that the natural history of the condition is better than the results of laser photocoagulation. Peripheral lesions can be successfully treated, especially when the angiomas are small. Careful, regular surveillance and treatment of small lesions can greatly reduce the morbidity of this disease.¹⁶⁰

Other genetic conditions that also contribute to retinal detachment or damage include sickle-cell retinopathy^{2,161-164} and the Coat's response observed in some patients with retinitis pigmentosa.^{165,166} Early recognition of these disorders in at-risk individuals can have a significant impact on the efficacy of treatment and avoidance of severe complications.

Subretinal neovascular membranes can arise from angioid streaks such as those associated with pseudoxanthoma elasticum or from other genetic disorders,^{167,168} macular dystrophies, lacquer cracks associated with pathological myopia, and age-related macular degeneration. It is unclear if treatment of choroidal neovascular membranes arising from different underlying genetic disorders has success rates that are comparable to the treatment of lesions associated with presumed ocular histoplasmosis syndrome (POHS) or classic age-related maculopathy. With the recent interest in the use of laser photocoagulation to promote resorption of drusen¹⁶⁹ and the possibility that such treatment may reduce the incidence of subretinal neovas-

cular membranes, there may be a major indication for the early recognition and management of age-related maculopathy before the onset of visual loss. By appreciating the familial nature of age-related maculopathy, the clinician can extend the recognition of an affected individual to other at-risk members within a family.

GENETIC ASPECTS OF OCULAR SURGERY

Anesthesia

The transition of ophthalmic surgery from general to local or regional anesthesia and topical anesthesia has had an enormous impact on the safety of ophthalmic surgery. However, the majority of pediatric ophthalmic surgery continues to require general anesthesia and there are still indications for adults to have general anesthesia while undergoing ocular surgery. Because of the potential fatal complications of malignant hyperthermia, most surgeons and anesthesiologists are aware of this condition. Unfortunately, family histories are often incomplete and patients at risk for this condition may have previously undergone general anesthesia without difficulty.¹⁷⁰⁻¹⁷² As noted previously, some myotonias are associated with an increased risk of malignant hyperthermia and can serve to alert the clinician. A number of cases of anesthetic management of hyperkalemic periodic paralysis have been described.¹⁷²⁻¹⁷⁶ More importantly, the clinician whose patient has developed malignant hyperthermia should properly inform the patient and arrange for the family members to be evaluated and counseled.

Studies in mice and drosophila have shown genetic differences in the susceptibility to inhalation anesthetics.^{177,178} It is reasonable to expect that individuals may show wide variations in requirements and responses for different doses of anesthetics. Halothane hepatitis has been described in families¹⁷⁹ and special precautions for general anesthesia have been advised for a number of specific genetic disorders including prolonged QT syndrome,^{180,181} porphyria,^{182,183} hereditary angioneurotic edema,¹⁸⁴ homocystinuria,^{150,151,185} and thalassemia.¹⁸⁶ Other neurological conditions, such as familial dysautonomia, and related syndromes, such as Biemond's syndrome, familial analgesia and congenital sensory neuropathy with anhidrosis, can also contribute to unstable responses to

general anesthesia and may require additional precautions at the time of surgery.^{187,188} Corneal sensation is an important attribute for normal healing after ophthalmic surgery and, although rare, hereditary disorders affecting corneal innervation have been described.^{44,189-191}

Coagulopathies and Vascular Disease

Although much of ophthalmic surgery involves only minimal blood loss, bleeding disorders, whether genetic or drug-induced, constitute a major risk factor. Patients with serious bleeding disorders such as von Willebrand's disease or hemophilia are generally aware of these problems before surgery. However, some bleeding disorders are more subtle and patients need to be specifically asked if they have experienced specific episodes of bleeding in association with injuries or previous surgery. The Bernard-Soulier syndrome is associated with abnormal platelet aggregation, which may be exacerbated by halothane anesthesia.¹⁹² Dysfibrinogenemia has recently been identified as a cause of abnormal bleeding and poor wound healing.¹⁹³ Individuals harboring the sickle trait may have relatively normal bleeding times but the increased risk of glaucoma from hyphemas is significant.²

Wound Healing

Wound healing is a critical aspect of ocular surgery whether or not tissues are cut with a blade, ablated, disrupted, or burned by a laser. Much of our postoperative therapy is directed toward controlling the rate of the healing and inflammatory processes to achieve predictable surgical results. Inadequate wound healing can contribute to persistent corneal epithelial defects, wound leaks, ocular hypotony, and infection. Excessive wound healing can result in corneal scarring and haze, failure of filtering blebs from glaucoma surgery, and proliferative vitreoretinopathy. A number of genetic conditions are associated with alterations in wound healing, particularly those that involve connective tissue. Some disorders, such as osteogenesis imperfecta and several types of Ehlers Danlos, are associated with poor wound healing, whereas others, such as Rubinstein Taybi syndrome and pseudoxanthoma elasticum, are associated with hyperplastic reactions and keloid formation in

surgical scars. As much as 3% of cases of keloids appear to be familial.¹⁹⁴ Keloid scar formation in darkly-pigmented individuals appears to be more frequent than in fair-skinned ethnic groups.¹⁹⁵ An unusual example of altered tissue healing that was indirectly implicated to a genetic disorder was two cases of familial Mediterranean fever whose strabismus surgery was complicated by corneal surface breakdown secondary to the use of colchicine for the treatment of the underlying genetic condition.¹⁹⁶

Ophthalmic Genetic Disorders That May Affect Routine Ocular Surgery

In the previous discussion, I have already mentioned the impact of a number of genetic disorders on refractive surgery (ie, keratoconus) and cataract surgery (ie, syndromes associated with ectopia lentis, aniridia, and posterior lenticonus). However, one must often consider the implications of performing ocular surgery in the face of pre-existing genetic abnormalities of the eye. There is surprisingly little information regarding the outcomes for cataract surgery for patients with hereditary retinal degenerations, aniridia, Down's syndrome, and other disorders in comparison with uncomplicated surgery. Timing of cataract surgery for patients with retinitis pigmentosa can be difficult because of the combined mechanisms of visual loss and the patient's perception about when cataract surgery is indicated.¹⁹⁷ Cataract extraction with intraocular lens placement is generally successful for patients with retinitis pigmentosa.¹⁹⁸⁻²⁰⁰ Some clinicians have expressed concerns that operative light exposure be kept to a minimum and that every effort be taken to minimize the risk of cystoid macular edema, which often occurs in these individuals independently of cataract surgery. Prophylaxis for cystoid macular edema has been suggested,²⁰¹⁻²⁰⁵ but its efficacy for patients with retinal degenerations remains in doubt. One study²⁰⁶ suggested that ultraviolet (UV) protective intraocular lenses (IOLs) might be beneficial in reducing the incidence of cystoid macular edema in routine patients, whereas a later study²⁰⁷ failed to confirm a benefit. Given the equivalent safety of IOLs with UV blocking agents, most surgeons will use these lenses in patients with retinal degenerations. Patients with oculocutaneous

albinism may be at a higher risk for light-induced toxicity (based on light toxicity studies in normal and albino mice) during cataract extraction, but they appear to tolerate the procedure well.¹³⁸

Aniridia is a more extensive disorder than simply dysgenesis or incomplete agenesis of the iris. As a result, patients with aniridia can experience a range of difficulties ranging from persistent epithelial defects after combined keratoplasty and cataract surgery,^{120,208} high failure rate after standard glaucoma filtering procedures,¹³³ and problems with control of intraocular pressure after cataract surgery.¹³⁵⁻¹³⁷

Despite reports of complications after cataract extractions in patients with iris and choroidal colobomas, more recent experience with extracapsular methods has been fairly successful.^{209,210} Cataract surgery in patients with Down's syndrome and Marfan's syndrome can also be complicated by postoperative glaucoma and retinal detachment. It is important to recognize that the complications from cataract surgery may occur in Marfan's patients who have no evidence of lens dislocation. If the syndrome is suspected based on nonophthalmic features or a family history, then the ophthalmologist must be prepared to deal with zonular fragility and an increased risk of anterior vitreous prolapse at the time of surgery.

CONCLUSION AND RECOMMENDATIONS

For the busy clinician, it is difficult to take a complete genetic history that might uncover a significant hereditary condition. Most individuals have limited awareness or accuracy of genetic disorders in family members beyond first-degree relatives. This is especially true when the conditions may be subtle or obscure. The ophthalmologist who is contemplating routine ocular surgery can consider a simplified approach based on our knowledge of ocular disease, physiology, and genetics. The physician can ask a limited set of pertinent questions that include the patient and their first-degree relatives. In some cases it may be worthwhile to have a prepared written questionnaire so that the individual can contact family members and obtain more complete histories. The clinician should be aware that family histories without clinical verification serve only as potential indicators of

Table 2. Guidelines for the Clinician

Patient examination:	
Ocular abnormalities	Corneal sensation, abnormal lid closure, high myopia, extensive lattice degeneration. For refractive surgery, one may wish to consider the evaluation of corneal topography if there is more than minimal astigmatism.
Systemic abnormalities suggestive of a genetic disorder	Body shape, joint deformities, distinctive facies, skin or teeth abnormalities, unusual scarring
Patient history	
Known genetic conditions of any type and complete ocular history	
Previous history of surgery and (if appropriate) general anesthesia	If yes: Specific complications with local or general anesthesia, surgery, wound healing after surgery or an injury, pain management
History of bleeding problems, sickle cell trait or disease, excessive joint laxity, muscle weakness, or congenital heart problems.	
Family history (at least all first-degree relatives: parents, siblings, children)	
Eye conditions that were not corrected by glasses or that required surgery, especially glaucoma, cataracts at an early age, high myopia, macular degeneration, strabismus	
Known genetic conditions of any type, cause of death	
History of bleeding problems, sickle cell trait or disease, excessive joint laxity, muscle weakness, or congenital heart problems.	
Previous history of surgery and (if appropriate) general anesthesia	If yes: Specific complications with local or general anesthesia, surgery, wound healing after surgery or an injury, pain management

genetic issues. In Table 2, a strategy for a genetically based examination and medical history is provided. This guideline incorporates the principles illustrated by the genetic conditions that have been discussed previously. They should not be viewed as a definitive or closed set of topics and the questions should be individualized by each clinician. This discussion of genetic

factors affecting ophthalmic surgery also highlights the need for the clinician to completely examine the eye and to be aware of the systemic features of genetic disorders. The clinician who can appropriately suspect Marfan's syndrome in a patient with cataracts who does not have lens dislocations, detect occult keratoconus before refractive surgery, or anticipate the development of malignant hyperthermia during general anesthesia is not only more effectively serving the interests of the patient but working toward ensuring surgical success.

Continued studies of both rare and common inherited disorders will lead to a better understanding of the causes of eye disease and offer the physician the information with which to better optimize and individualize patient care. The appreciation of the multifaceted components of genetic diseases can allow the surgeon to anticipate potential problems and perhaps use prophylactic measures that will lessen the risk of vision loss. A number of the genetic conditions that have been mentioned in this review strongly predispose individuals to corneal clouding, glaucoma, or retinal detachment. In some of these cases, prophylactic treatments (such as scleral buckling for Stickler's, peripheral photocoagulation for x-linked retinoschisis, peripheral iridotomy for Weil-Marchesani, and cysteamine drops for nephropathic cystinosis) have been proposed and tested. As more treatments are developed and tested for conditions such as glaucoma and age-related macular degeneration, we will need to increasingly call on genetics to identify those individuals who are at risk for disease. We can use our knowledge of genetics to develop appropriate screening strategies to cost-effectively detect and minimize the ocular complications, not only for our patients but for the members of their families.

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