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Authors

Couser, Natario

Brooks, Brian

Drack, Arlene

et al.

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The evolving role of genetics in ophthalmology

Natario L. Couser[a,b], **Brian P. Brooks**[c], **Arlene V. Drack**[d,e], **Suma P. Shankar**[f]

[a]Departments of Ophthalmology & Human and Molecular Genetics, Virginia Commonwealth University School of Medicine, Richmond, VA, USA

[b]Department of Pediatrics, Children's Hospital of Richmond at VCU, Richmond, VA, USA

[c]Ophthalmic Genetics & Visual Function Branch, National Eye Institute, National Institutes of Health, Bethesda, MD, USA

[d]Department of Ophthalmology and Visual Sciences, University of Iowa, Iowa City, IA, USA

[e]The University of Iowa Institute for Vision Research, Iowa City, IA, USA

[f]Departments of Pediatrics & Ophthalmology, University of California Davis, Sacramento, CA, USA

Abstract

Advances in molecular genetics over the past three decades have helped identify a substantial number of genetic variants causing inherited eye diseases that can be identified rapidly by appropriate genetic tests in a clinically useful window. With this progression of knowledge, the roles of genetics and ophthalmology in patient care have become increasingly intertwined, and the necessity for subspecialists in the field of ophthalmic genetics is of paramount importance. As a result of continual medical specialization, technological progress in genetics and knowledge garnered by over a century and a half of cataloguing eye pathology, ophthalmic genetics has become an emerging subspecialty within ophthalmology. By virtue of its rapidly changing advances, genetics and genomics serves a large role within ophthalmology, and subspecialists with the same level of detailed and broad knowledge as any other ophthalmology subspecialty are now required in order to meet the growing needs of the expanding population.

Keywords

Ophthalmology subspecialist; Inherited retinal disease; gene therapy; ophthalmic genetics fellowship; ocular genetics training program

On October 1, 1990, an international consortium of researchers began the task to sequence and map all three billion base pairs of the human genome (1). Thirteen years and billions of dollars later this biomedical odyssey, the Human Genome Project, was 99% complete. Notwithstanding this astonishing collaborative feat, the clinical molecular diagnostics landscape was in an early infancy stage in 2003; genome sequencing was exceedingly costly,

CONTACT Natario L. Couser natario.couser@vcuhealth.org Departments of Ophthalmology & Human and Molecular Genetics, Virginia Commonwealth, University School of Medicine, Richmond, VA, USA.

slow and not readily available for widespread clinical applications. Advances in molecular genetics over the past three decades have helped identify a substantial number of genetic variants and conditions known to contribute to eye diseases, and now individual patient analysis can be readily performed in a clinically useful window (2). With this progression of knowledge, the roles of genetics and ophthalmology in patient care have become increasingly intertwined, and the necessity for subspecialists in the field of ophthalmic genetics is of paramount importance.

The ophthalmic genetics assessment involves a complex and time-consuming process

Similar to cancer, cardiomyopathies and hearing loss, inherited eye diseases often have considerable genetic heterogeneity (3). Thousands of human disorders are known to be determined by single gene defects or chromosomal abnormalities, many of which encompass the bulbus oculi, eyelids, external ocular adnexa, or visual pathway from the retina to the brain (4). Although hereditary eye diseases are rare, genetic factors are a significant underlying cause of childhood blindness and cause significant visual impairment in adults globally (5). Some ophthalmic genetic conditions are known for significant visual limitation while others may have no associated visual compromise, but have physical characteristics that represent a marker for an underlying systemic disease (6). The journey to reach a diagnosis in a patient with a rare genetic disease may take weeks to several years. This process often involves numerous doctor visits and diagnostic tests, which may lead to a significant emotional and financial burden on the patient and family. During an ophthalmic encounter, a suspicion for a genetic etiology may arise in a patient with congenital anomalies, dysmorphic features, developmental delays, intellectual disability, multisystem abnormalities, nyctalopia, nystagmus, unexplained visual deterioration, or a family history of a known genetic syndrome. The purpose of an ophthalmic genetic assessment should be aimed to establish or confirm diagnosis, provide recurrence risk counseling and determine who else in the family may be at risk, and to inform the patient and family regarding management decisions and treatment and/or clinical trial eligibility (Figure 1). An ophthalmic genetic assessment is performed by an ophthalmologist experienced with managing ophthalmic genetic disorders in collaboration with a team that may include a genetic counselor, orthoptist, ophthalmic technician and possibly other specialists who may be additionally involved at multidisciplinary clinics. The relationship with the referred patient often begins several weeks before the office appointment to provide expectations of the visit and retrieve relevant medical records including any past genetic testing results. The actual patient visit may last several hours. Clinical evaluation during the visit may include detailed history-taking and documentation of the family pedigree, and a directed physical examination including a comprehensive anterior and posterior ocular assessment. In some cases, systemic examination, for example cardiac or renal echography, and other specialized testing is needed to arrive at a clinical diagnosis. In addition, genetic and financial counseling, ophthalmic imaging, visual field and electrophysiology testing, discussion of resources for additional services and further specialty referrals, addressing low-vision needs and psychosocial adjustments, and education pertaining to relevant research and clinical trials may be provided. Genetic testing, when warranted, should be aimed at pursuing the

most specific test based on the individual's clinical presentation and should be performed in laboratories meeting appropriate relevant regulatory standards, for example CLIA and CAP certified in the United States (7). Subsequent follow-up visits are common for ongoing management and return of genetic testing results discussions. The interpretation and delivery of molecular genetic testing results is every bit as important as the ordering of the test itself.

Challenges of establishing a correct diagnosis

It is not uncommon for the initial referral *clinical* diagnosis to be found incorrect or incomplete upon pursuing additional specialized testing and/or genetic testing to obtain the *molecular genetic* diagnosis; see examples of this in Figure 2. Establishing an accurate diagnosis allows for optimal medical management and often life-changing care, for example, initiating medical therapy following accurate diagnosis of homocystinuria in individuals presenting with ectopia lentis (8). Previous reports have found that consultations to an ocular genetics service revealed 30%−50% of patients were carrying an incorrect or incomplete diagnosis or had been given inaccurate information regarding their eye disease (9,10). A recent survey of practice patterns among American Association for Pediatric Ophthalmology and Strabismus (AAPOS) members revealed that over 90% of respondents reported caring for at least one patient per week with a suspected genetic disorder affecting the eye. However, there were significant knowledge gaps in areas such as genetic testing – 11.7–34.1% reporting baseline understanding depending on testing modality with 48% reporting no understanding in any modality. Additionally, only 42% reported that they can identify and refer genetic patients for clinical trials (11). Furthermore, most respondents expressed a desire for further education within this area (11). It is likely this assessment reflects concerns by ophthalmologists in similar ways across most traditional subspecialties, thus, reinforcing the need for experts in this area.

The emergence of ophthalmic genetics as a subspecialty within ophthalmology

As a result of continual medical specialization, technological advances in genetics and knowledge garnered by over a century and a half of cataloguing eye pathology, ophthalmic genetics has become an emerging subspecialty. Post-residency clinical fellowship opportunities exist that offer training within this area; national committees and international societies focused on genetic diseases of the eye are well established; and a small number of ophthalmologists worldwide now devote a significant portion, if not all, of their practice toward the care and management of patients with ophthalmic genetic conditions. A recent analysis of ophthalmic genetic contributions in the literature from a single journal showed 719 articles were published from 1966 to 2017 (12). Over this 50-year period, published reports have largely reflected evolving genomic advancements and medical applications of genetic technologies, and have evolved from many single author, single center reports in the 1960s to now multiauthor, multicentered with national and international collaborative approaches (12). This evolution has included next-generation sequencing and chromosomal microarray technology as recently added tools in the armamentarium, and the first gene therapy for an inherited retinal disease caused by biallelic *RPE65* variants has been approved

by the US Food and Drug Administration, European Commission and UK's National Institute for Health and Care Excellence (13–15). Numerous gene and stem cell therapy clinical trials for additional retinal disorders are underway, while clinical applications for nanotechnology and gene editing using CRISPR technology are on the horizon. As the function of the eye is intertwined with the central and peripheral nervous system, ocular features may be a presenting manifestation of a wider systemic disorder or a syndrome, therefore the care of these patients necessitates a multifaceted approach. Understanding the genetic mechanisms may assist in directing clinical management decisions for the provider, and afford the affected patient a sense of relief and empowerment over uncertainty, as well as unlock access to resources, support networks, clinical trial eligibility and personalized treatment.

A growing need for experts in ophthalmic genetics

At the present writing, the Online Mendelian Inheritance of Man (OMIM) reports there are 6,665 phenotypes of genetic disorders for which the molecular basis is known; a search for 'eye' within the database provides descriptions on 2,494 separate entries (16). The World Health Organization reports a global prevalence of all single-gene disorders of 10/1000 (17). The world population is expected to double in the next 80 years (18); as such, the number of individuals with an ophthalmic genetic diagnosis will substantially increase. The process to become a clinical medical geneticist involves acquiring a broad understanding of inherited conditions, inheritance patterns and molecular genetic testing techniques, however, gaining an experience in the diagnosis, management and treatment of eye disease is not a component of medical genetic training programs. Similarly, ophthalmologists are experienced with all aspects of eye examination and care with sophisticated imaging, psychophysical and electrophysiologic diagnostic techniques, however, may be less familiar with underlying genetic mechanisms and lack training in the latest genetic testing modalities and counseling aspects required upon return of results. Some ophthalmologists and/or physician-scientists may develop an expertise of genetic disorders in a specific area and collaborate with a medical geneticist and/or genetic counselor to incorporate genetic testing and counseling aspects. However, there is a significant demand for ophthalmologists who can manage genetic diseases in all ophthalmic subspecialty areas. Genetics and genomics has become more nuanced and complicated and interpreting molecular results is often difficult, requiring expertise. Because detailed examination of the eyes requires special training and equipment, medical geneticists are unable to make the clinical diagnosis and cannot discuss prognosis and treatment options in depth. These diagnoses are so specialized that the majority of ophthalmologists also do not have the clinical expertise or the time allotted in their busy schedules to clinically diagnose and counsel these patients. For these reasons, options for additional training in genetics/genomics need to be considered. At present, an internship and 3 years of ophthalmology residency training are required to sit for the American Board of Ophthalmology (ABO) examination. Ophthalmic genetic fellowships are listed in the fellowship matching program and may be completed as a primary subspecialty training or in addition to training for pediatric, retina, or another subspecialty. The American Board of Medical Genetics and Genomics (ABMGG) allows for individuals with a minimum of 12 months of training in an ACGME-accredited residency with direct patient care

to be eligible to pursue a medical genetics residency program for 2 years, and upon completion be eligible for board certification in genetics. Ophthalmologists with an interest in genetics could consider training for an additional 2 years to be exposed to a wide range of genetic disorders in both children and adults, by including rotating through Clinical Cytogenetics and Molecular Diagnostics laboratories, Prenatal/maternal-fetal medicine, and Cancer Genetics, while working closely with geneticists and a genetic counseling service during their training. Medical Geneticists with an interest in inherited eye diseases may similarly choose to complete an ophthalmology residency after their genetics training to gain understanding of the presentation and course of ophthalmic genetic disorders. Impediments to dual training for the subspecialty include adding more years to an already long course of study, compounded by the decreased income that accompanies longer exams necessitating fewer patient visits per day, with extensive follow up needs. Increased training requirements could make the specialty out of reach for many physicians in training, although individualized pathways for dual training of interested persons could be requested by the ABO and ABMGG. Outside of the US, similar organizations overseeing certification may allow for a model that accounts for the varying length of training and dual accreditation options within each individual country.

Patients presenting to genetic eye disease clinics desire to learn about what can be done to improve or save their vision, what the expected clinical course is, and how to make compensations to continue with their daily activities. The ideal way to serve these patients with genetic eye disorders is therefore to work in collaborative teams of subspecialty trained inherited eye disorder ophthalmic specialists and genetic counselors or medical geneticists, along with low vision specialists.

By virtue of its rapidly changing advances, genetics and genomics serves a large role within ophthalmology, and, subspecialists with the same level of detailed and broad knowledge as any other ophthalmology subspecialty are now required in order to meet the growing needs of the expanding population. These genetic eye disorder subspecialists may choose to be subspecialty trained in ophthalmic genetics, and collaborate extensively with medical geneticists, genetic counselors, and low vision specialists. The training for all of these providers will need to include models for this collaboration. Ophthalmology residency programs should be teaching trainees that ophthalmologists without specialty training in ophthalmic genetics must consider referral of patients to ophthalmic genetics specialty clinics when a genetic eye disorder is suspected.

Declaration of interest

Natario L. Couser MD, MS disclosures: Retrophin Inc, Elsevier, National Cancer Institute/Children’s Oncology Group. Brian P. Brooks, MD, PhD reports no conflicts of interest. Arlene V. Drack, MD disclosures: Spark Therapeutics, ProQr, Retrophin Inc. Suma P. Shankar MD, PhD disclosures: Holds Children’s Miracle Network endowed chair in Pediatric Genetics & receives salary support from CMN. The authors alone are responsible for the content and writing of this article.

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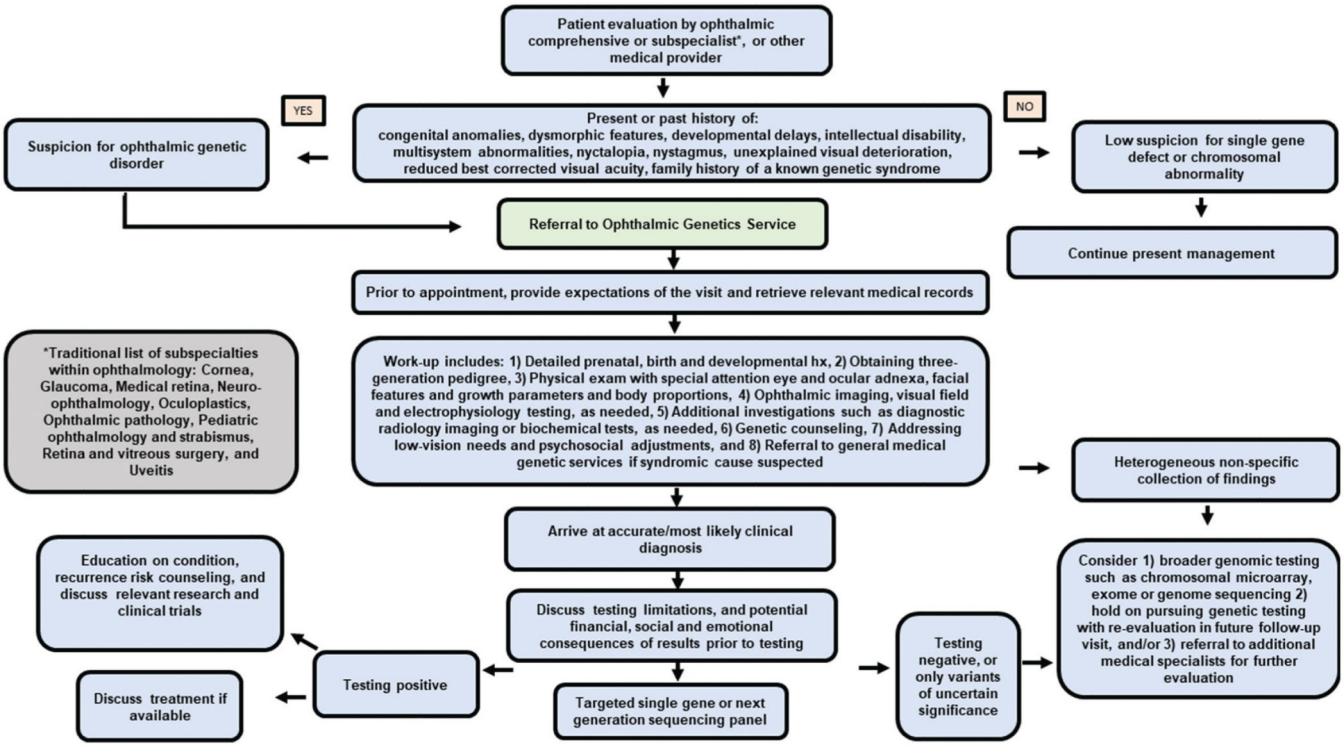

Figure 1.
Ophthalmic genetics clinical algorithm.

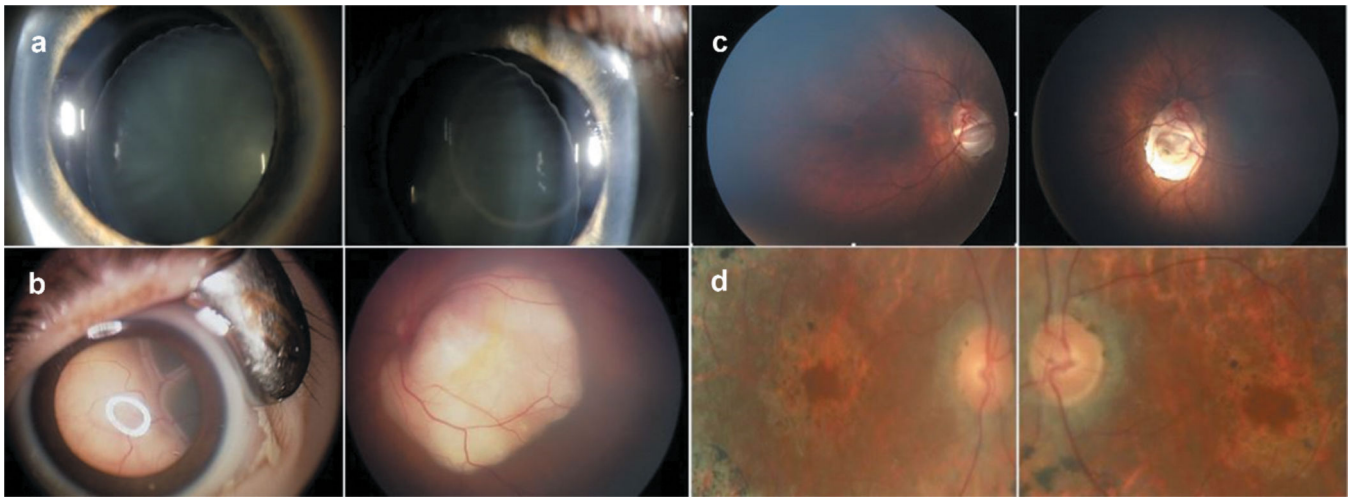

Figure 2.

Comparison of suspected initial *clinical* diagnosis upon referral to the final *molecular genetic* diagnosis obtained after an ophthalmic genetics comprehensive evaluation. (a) Referral clinical diagnosis-Marfan syndrome; final molecular diagnosis-Homocystinuria. (b) Referral clinical diagnosis-Retinoblastoma; final molecular diagnosis-Retinoblastoma with dysmorphic features and intellectual disability due to large deletion involving *RB1* gene. (c) Referral clinical diagnosis-Bilateral optic nerve colobomas; final molecular diagnosis-CHARGE syndrome. (d) Referral clinical diagnosis-Age-related macular degeneration; final molecular diagnosis-Retinitis Pigmentosa.