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Introduction to the special issue on *Ophthalmic Genetics: Vision in 2020*

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ABSTRACT

In this special issue of the American Journal of Medical Genetics, Part C, we explore the ever-expanding field of Ophthalmic Genetics. The eye is unique among organs for its accessibility to physical examination, permitting exploration of every tissue by slit lamp microscopy, ophthalmoscopy, and imaging including color and autofluorescent photography, ultrasound, optical coherence tomography (OCT), electrophysiology, and adaptive optics confocal and scanning laser ophthalmoscopy. This accessibility permits a variety of surgical and nonsurgical treatments, including the first FDA-approved gene therapy, voretigene neparvovec-rzyl for *RPE65*-associated Leber Congenital Amaurosis. In this issue, we sought to provide a survey highlighting how heritable ophthalmic disorders are recognizable and accessible to clinical geneticists as well as ophthalmologists.

INTRODUCTION

In this special issue of the American Journal of Medical Genetics, Part C, we explore the ever-expanding field of Ophthalmic Genetics. The eye is unique among organs for its accessibility to physical examination, permitting exploration of every tissue by slit lamp microscopy, ophthalmoscopy, and imaging including color and autofluorescent photography, ultrasound, optical coherence tomography (OCT), electrophysiology, and adaptive optics. This accessibility permits a variety of surgical and nonsurgical treatments, including the first FDA-approved gene therapy, voretigene neparvovec-rzyl for *RPE65*-associated Leber Congenital Amaurosis.

The eye comprises tissues originating from all three germ layers and neural crest, and is susceptible to a variety of neurodegenerative, inflammatory, connective tissue, vascular, infectious, and other disease processes. As nearly one-third of afferent neuronal inputs to the brain originate from the eye, this organ is critical among the human senses and the patient is acutely aware of physiologic changes. Patient symptoms correlate to and often precede physical signs, particularly in the retina. The retina detects and translates light into neurotransmissions to the brain. The cone-rich central retina facilitates high acuity color vision, and foveal and macular disorders result in color vision impairment, visual acuity deficits, photophobia, and nystagmus. The rod-rich peripheral retina is highly sensitive and functions in dim light vision, and peripheral retinopathies manifest as peripheral vision constriction and nyctalopia.

Heritable genetic disorders have been described since antiquity, with the invention of the ophthalmoscope opened a window for clinicians and scientists to describe posterior eye disorders such as retinal degenerations and optic atrophies. Hundreds of recognizable, heritable disorders of anterior segment dysgenesis, glaucoma, congenital cataract, aniridia, retinopathies, and optic neuropathies have been described, and nearly 30% of the Mendelian Inheritance in Man database include ocular

phenotypes (Freund, Horsford, & McInnes, 1996). Together, they represent all facets of clinical genetics, including all known and even unique hereditary forms (Chou et al., 2015), noncoding etiologies (Silva et al., 2019), locus heterogeneity, variable expressivity, and incomplete penetrance. Modern imaging and electrophysiologic modalities permit tissue- and even cellular-level descriptions in vivo, which correlate with histopathological investigations of disease.

Since the discovery of the first genes associated with retinitis pigmentosa in the late 1980s, a vast locus heterogeneity has emerged, with over 90 genes and loci now associated with this disorder. Further, hundreds of described syndromes, including ciliopathies, peroxisomal disorders, and mitochondrial diseases are associated with RP-like retinal degeneration. Thus, a common cellular mechanism of cell death among these has been pursued, facilitating research into common treatments, including vitamin A and N-acetylcysteine. Recognition of this group of disorders with emerging treatments is tantamount in the era of genomic medicine.

In this issue, we sought to provide a survey highlighting how heritable ophthalmic disorders are recognizable and accessible to clinical geneticists as well as ophthalmologists. We arranged these in three parts.

The first section describes the current state of the clinical field and diagnostic challenges. Yang et al provide a nosology for syndromic retinopathies with intellectual disability, classifying a vast and heterogeneous set of disorders to improve clinical diagnosis and guide molecular genetic testing. Highlighting challenges with the latter, Branham et al describe their experience with molecular genetic testing at a single center, highlighting important diagnostic dilemmas and lessons learned for this group of disorders with high molecular diagnostic yield (Ellingford et al., 2016). In contrast, ocular malformations represent a group of disorders seemingly intolerant to defining monogenic etiologies. Three papers herein describe limitations in diagnostic testing for developmental eye malformations

(Jackson et al), experimental animal models for validating candidate disease genes (Yoon et al), and ocular manifestations of CHARGE syndrome in patients without coloboma (Dosunmu et al). Finally, this section concludes with a series of papers highlighting the wide spectrum of disorders arising from the same genetic locus. These include novel clinical and molecular descriptions of adult forms of peroxisomal disorders (Heimler syndrome; Daich Varela et al), inborn errors of metabolism (Nonsyndromic retinal degeneration; Schiff et al), and the wide spectrum of ocular phenotypes arising from postzygotic genetic mosaicism (Coffin-Siris syndrome; Utz et al).

The second section depicts the globalization of clinical and molecular diagnostics across continents. The Global Eye Genetics Consortium has emerged as a collaborative research effort spanning Asia, India, and South America with collaborators in Europe and the USA. Two papers from Fujinami et al describe the largest series of *PROM1*-related retinopathy and *RP2*-related X-linked RP in Japan, and Liu et al depicts the prevalence of Stargardt-associated pathogenic *ABCA4* variants in China. Ophthalmic genetics experiences in New Zealand (Hull et al), India (Bonsal et al), Brazil (Sallum et al), and Argentina, Colombia, and Chile (Daich Varela et al) outline clinical practices and molecular genetic testing algorithms in their counties. Ophthalmic genetics is further developing in the Middle East, as highlighted in a paper by Mejecase et al describing the consecutive experience of an ophthalmic genetics clinic in the United Arab Emirates, and Tuncay et al recounting their clinical practices in Turkey. Finally, Elahe et al from Iran describe the current clinical and basic research landscape of glaucoma, which represents both complex and monogenic forms of disease. These important papers also highlight common threads among global consortia: a desire to work together to improve clinical and molecular diagnostics and leveraging these critical datasets to describe population-specific disease manifestations, recurrent variants, and describe altogether new conditions. By understanding the global rather than local burden of rare eye diseases, efforts can be better focused to generate therapies to save sight in the most possible people.

The third and final section highlights translational research efforts to facilitate clinical trials for therapies directed at heritable human disorders. Two research registries in the United States, the National Ophthalmic Disease Genotyping Network (eyeGENE®; Goetz et al) and the Foundation Fighting Blindness My Retina Tracker (FFB MRT; Mansfield et al) describe their respective experiences in large scale genetic testing and association of genotype-phenotype correlations in patient-and provider-submitted clinical data. Such registries are critical for better defining variant classification as pathogenic or benign, which in turn defines patient eligibility for gene-directed therapies. Ku and Pennesi provide a comprehensive survey of the current status of the rapidly expanding therapeutic field for heritable retinal degenerations. Finally, Walter et al offer insight into the future of clinical diagnostics with respect to noncoding and structural variations.

In summary, ocular genetics is a lens for clinical genetics and the future of precision medicine, leading the way in gene therapy and large-scale clinical molecular testing. In the genomic era, patients must get genetic testing interpreted with standardized classification criteria, as is being done by the ClinGen Ocular Clinical Domain Working Group (clinicalgenome.org/working-groups/clinical-domain/ocular-cdwg/). Undoubtedly, the future of genetic diagnostics to complete unsolved cases relies on the integration of genomics with transcriptomics, epigenomics, and machine learning tools. Thank you for your interest in this issue, and we hope you enjoy reading it.

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