PERSPECTIVE

AJO Centennial: AJO Contributions to Ophthalmic Genetics

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• PURPOSE: To review the contributions to ophthalmic genetics through the *American Journal of Ophthalmology* (AJO).
• DESIGN: Perspective.
• METHODS: A literature search to retrieve original articles, letters, editorials, and published lectures from 1966 to 2017, providing a 50-year review. Titles were excluded that gave no reference to genetics or that presented findings related to a nongenetic ocular condition.
• RESULTS: From a search of the Scopus database, 719 articles were ascertained. Of these, 115 were excluded because the title did not reference a genetic condition or have a focus on genetic factors; 4 were excluded because they described animal phenotypes (1966-1967); and 4 were excluded owing to having received no citations up to and including 2015. The highest number of citations was 283 times for a single article on familial aggregation in age-related macular degeneration. The Web of Science database yielded 771 articles; of these, 118 were excluded owing to not reporting human genetic studies; 55 received no citations. The highest number of citations was 307 for a single article, a 1991 paper on Leber hereditary optic neuropathy.
• CONCLUSIONS: The *Journal*'s contributions to our understanding of the heritability of human ocular traits have been broad and deep, with international reach. The development of new techniques fostered new concepts and new approaches to rapidly expand the number of known single gene disorders with a defined molecular genetic cause. Reports on Mendelian and complex traits in the AJO abound, along with 6 Edward Jackson Memorial Lectures on retinal dystrophies, Leber congenital amaurosis, age-related macular degeneration, and glaucoma. (Am J Ophthalmol 2018;■:■–■. © 2018 Elsevier Inc. All rights reserved.)

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THE *AMERICAN JOURNAL OF OPHTHALMOLOGY* (AJO) played an early role in publishing ophthalmic genetics, including such articles as those in 1945 on the heritability of "squint,"[1] "a family of semi-albinos,"[2] 3 cases of familial corneal dystrophy,[3] and hereditary anterior megalophthalmos.[4] AJO continues to play an important role in the dissemination of research results and in increasing our understanding of the role of genetic traits that cause ocular morbidity and influence the outcome of our interventions. In this anniversary Perspective, we review the salient contributions of a host of clinicians and scientists who have individually and collectively made these discoveries, including such important historical figures and senior colleagues in ophthalmology as Berson, Bird, Blodi, Carr, Deutman, Falls, Francois, Henkind, Hoyt, Krill, Maumenee, Merin, Miller, Newell, Scheie, Schepens, Spivey, and Yanoff, to name just a few. In preparing this Perspective, we have relied on 2 bibliographic databases, Scopus and Web of Science, to collect information and ranked the articles by their number of citations. We acknowledge that authors may cite their own work in subsequent articles. We also recognize that citations do not necessarily reflect the number of times that an article was read, downloaded, used in teaching, or used in a discussion on patient management.

APPLICATIONS OF GENETIC KNOWLEDGE TO PATIENT CARE

WHILE THE 1960S AND 1970S WITNESSED MANY SINGLE-author or 2-author papers from single centers, manuscripts are now more often multiauthor, multicenter, and international in scope. Early papers were consistently helpful to the practicing comprehensive ophthalmologist, providing key tips on patient care. For example, Criswick and Schepens (1969)[5] first described a condition that they termed "familial exudative vitreoretinopathy," having identified a condition that mimicked retinopathy of prematurity (then termed "retrolental fibroplasia") but appeared to have a genetic origin, as it was present in multiple members of 2 families. Cross and Jensen (1973)[6] contrasted the ocular

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TABLE 1. History of Advances in Ocular Genetics and the *American Journal of Ophthalmology*

Date	Event	AJO Contributions
1975	Fred Sanger reported a mechanism for sequencing DNA.[8] Sanger shared the Nobel Prize for Chemistry in 1980 with Paul Berg and Walter Gilbert (www.nobelprize.org).	-
1986	Retinoblastoma gene (*RB1*) was identified.[9,10]	1977: Retinoblastoma maps to 13q
1986	Red and green opsin genes were found as an array on the X chromosome.[11]	-
1987	Applied Biosystems introduced the first automated DNA sequencer.	-
1988	The US Department of Energy and the National Institutes of Health established the Human Genome Project.	-
1988	A mitochondrial DNA mutation was associated with LHON.	1991: Newman and associates expand the LHON phenotype[12]

AJO = *American Journal of Ophthalmology*; LHON = Leber hereditary optic neuropathy.

phenotype of Marfan syndrome and homocysteinuria: lens luxation occurring earlier in homocysteinuria and displaced inferiorly vs occurring later in Marfan syndrome and displaced superiorly.

In 1984, Bunker and associates[7] reported the relative frequency of retinitis pigmentosa in Maine and provided useful population-based data suggesting an overall majority of cases being autosomal recessive or simplex (65%), followed by dominant (19%) and X-linked (8%).

THE ERA OF GENE DISCOVERY AND MOLECULAR GENETICS

THE ADVENT OF MOLECULAR GENETIC TECHNIQUES such as Sanger sequencing in 1975[8] (Table 1) revolutionized the mapping of human ocular traits, which until then had depended largely on cytogenetic findings or blood groups for mapping traits to individual chromosomes. Cross and associates (1977) reported retinoblastoma in a patient with a translocation (13qXp), allowing the recognition that an important gene was present on the long arm of chromosome 13 and was likely disrupted by the translocation.[9] Clinicians and researchers were mainly focused on mapping Mendelian disorders. Many genes underlying human ocular conditions were initially mapped with DNA markers using restriction fragment length polymorphism and then cloned. Not until 1986 was the *RB1* gene, which underlies retinoblastoma, found.[10] There followed rapidly the red and green opsins (1986),[11] *CHM*/choroideremia (1990)[13] and *RHO*/rhodopsin (1990)[14], *PAX6* (1991),[15] and others. New methods not only allowed new approaches and ideas but also sped the process. Sanger sequencing depended first on radioisotope-labeled nucleotides (^{32}P), requiring X-ray film with multiple steps, and was laborious in nature. The introduction of fluorescently labeled nucleotides and capillary electrophoresis greatly reduced the amount of effort while coincidentally fostering the development of bioinformatic tools and concepts that would later support the interpretation of data from genome-wide association studies (GWAS).

COMPLEX TRAITS AND GENOME-WIDE ASSOCIATION STUDIES

EMPIRICALLY AND FROM PRACTICE-BASED EVIDENCE, PHYSICIANS were aware that certain ocular conditions had a familial tendency but did not fit the strict Mendelian model. Seddon and associates (1997, cited by 283)[16] showed that a subject with age-related macular degeneration (AMD) was twice as likely to have a first-degree relative with AMD as someone without AMD, suggesting shared genetic background or shared environmental factors (eg, smoking). Progress in our understanding of what specific genes might contribute to the genetic background came from GWAS. Having identified genetic modifiers, many authors chose AJO to write about these factors and their added risk for AMD (Table 2). In a similar fashion, molecular techniques have proven to be informative in sorting empiric and familial risks of glaucoma where a family history has been revealed during history taking or a first-degree relative is affected, and linking genetic modifiers to the onset of disease in specific populations (Table 3).

Finally, we would like to pay tribute to the many accomplished ophthalmologists who have been invited by AJO and the American Academy of Ophthalmology (AAO) to deliver the Edward Jackson Memorial Lecture at the Annual Meeting of the AAO over the last 50 years. We have highlighted those lecturers whose subject

TABLE 2. Genetic Risk Factors in Age-related Macular Degeneration

Year	Factor	Methodology	Population	Risk of AMD
1998[17]	Apolipoprotein E gene	Case-control (SNPs)	European	ε4 allele protects against
2000[18]	Manganese superoxide dismutase	Case-control (SNPs)	Japanese (exudative AMD)	Ala/- and ala/ala increased risk
2001[19]	Paraoxonase Plasma oxidized LDL	Case-control SNPs	Japanese AMD	LL genotype increased risk; plasma oxidized LDL
2001[20]	1q31, 2q14.3, 10q26 and 17q25 loci	GWAS, families with 2 affected by AMD	Mixed	Loci increase risk; smoking increases risk from gene in 10q26
2006[21]	*CFH* Hemicentin-1	Case-control, SNPs	Japanese: dry AMD	No association with dry AMD
2007[22]	*CFH* (Y402H)	Retrospective case-control	White	Increased risk of AMD
2007[23]	LOC387715 locus and *HTRA1* gene	Cross-sectional study (SNPs)	Japanese: PCV and AMD	Allelic risk variants stronger association to AMD than PCV
2008[24]	*VEGF* gene (+936C/T) CFH Y402H	Case-control (SNPs)	Taiwan: late AMD (wet and dry)	Both risks for exudative AMD
2009[25]	AMRS2 (LOC387715)	Case vs control	Japanese: PCV and AMD	Del1443ins54 polymorphism strongly associated with PCV and AMD
2009[26]	*CFH* ARMS2/HRTA1	Retrospective cohort study	Wet AMD with dry AMD in fellow eye	SNPs in ARMS2/HRTA1 but not CFH correlated with phenotype
2011[27]	ARMS2 LOXL1	Case-control Exudative AMD and polypoidal choroidal vasculopathy	Japanese	Both risks for exudative AMD
2011[28]	AMRS2/HTRA1 CFH, C2/CFB, C3, CFI, LIPC, TIMP3	Genetic association study	European and North American multicenter: USA, France	ARMS2 and HTRA1 risk for CNV vs geographic atrophy

AMD = age-related macular degeneration; CFH = complement factor H; CNV = choroidal neovascularization; GWAS = genome-wide association study; LDL = low-density lipoprotein; PCV = polypoidal choroidal vasculopathy; SNP = single nucleotide polymorphism.

TABLE 3. Genetic Associations With Glaucoma

Year	Factor	Methodology	Population	Glaucoma Risk
1998[29]	GLC1D locus	Linkage analysis	North American family	Familial
2003[30]	Optineurin	Prospective case-control (SNPs)	Mostly white, remainder Japanese	*OPTN* variants not significantly associated (except familial case)
2006[31]	*WDR36* D658G mutation	Case-control	Tasmania, Australia	No added risk
2007[32]	*OPA1*	Prospective case-control	Japanese, NTG, high-tension glaucoma	Twofold risk of NTG with *OPA1* IVS 8 + 32 C allele
2008[33]	*LOXL1* gene	Case-control (SNPs)	Nordic and Japanese	Differing haplotype risks in each population

NTG = normal-tension glaucoma; SNP = single nucleotide polymorphism.

matter has been predominantly genetic in nature (Table 4). The lectures have summarized the burden of genetic eye disease and how genetic research has improved our understanding of the pathophysiology of both specific retinal disorders and the 2 major multifactorial conditions, glaucoma and AMD, that have significant underlying genetic associations. The lectures have highlighted how recent advances in molecular genetic testing have provided a specific diagnosis for patients and families. Providing a more specific genetic link is allowing the modern application of "precision medicine" to our management of eye disease.

TABLE 4. The Edward Jackson Lectures and Eye Genetics

Lecture	Author	Topic
1991[34]	Irene Maumenee	Hereditary blindness: a worldwide scourge
1994[35]	Paul Lichter	Genetic clues to glaucoma's secrets
1995[36]	Alan Bird	Retinal photoreceptor dystrophies
2000[37]	Ted Dryja	Molecular genetics of Oguchi disease, fundus albipunctatus, and other forms of stationary night blindness
2007[38]	Ed Stone	Leber congenital amaurosis—a model for efficient genetic testing of heterogeneous disorders
2013[39]	Joan Miller	Age-related macular degeneration revisited—piecing the puzzle

APPLICATIONS OF GENETIC TECHNOLOGIES

WITH THE ADVENT OF HUMAN OCULAR GENE THERAPY FOR Leber congenital amaurosis (LCA), a number of similar trials of subretinal injection or intravitreal injection of vectors carrying a replacement gene are either being currently reported or in progress. The foundation of these experiments is based in the lengthy process of gene discovery (with collaborations of clinicians, geneticists, and vision scientists), preclinical studies with animal or cell models, cloning of genes into suitable vectors, fundraising with multiple stakeholders, and final approvals from regulatory bodies. Valid and reproducible outcome measures for these interventions need to be carefully selected based on whatever natural history data may be available for the disease in question. Jacobson and associates recently discussed this aspect in relation to LCA owing to mutations in the guanylate cyclase gene, GUCY2D.[40] A functional measure such as the final scotopic threshold and anatomic measures from optical coherence tomography could, in their opinion, provide evidence of efficacy.

BIBLIOMETRIC ANALYSIS

BIBLIOMETRICS USES THE METADATA SURROUNDING CITAtions to tease out information about trends in publications; the Web of Science database provides useful analytics. Publications varied per year, from a low of 3 in 1975 to a high of 43 in 2001. Eight of the most productive years have been in the current century, averaging 34 papers each of those years. Papers in 2017 averaged 9 authors; in the 1960s, the average paper had fewer than 2 authors. A total of 184 papers studied here acknowledged National Institutes of Health funding, of which 106 were funded by the National Eye Institute; some of the others did not specify beyond "NIH," but, remarkably, others mentioned the National Cancer Institute, the National Heart Lung and Blood Institute, the National Center for Research Resources, or 10 other institutes. Research to Prevent Blindness was acknowledged on 27 papers; the Foundation Fighting Blindness funded 10. Alcon, Genentech, Pfizer, and Santen were the most often acknowledged commercial funders. One paper published in 2017 listed 32 funding agencies. Researchers from 47 countries authored these papers.

DISCUSSION

OUR BIBLIOGRAPHIC SYSTEMS HAVE SINCE BECOME FAR more comprehensive in allowing individual authors a comprehensive understanding of the impact of their work. Some journals are beginning to allow authors to know not only how many times an article was cited, but also how often it was downloaded. These data signal a real change in how research is shared and how scientists communicate and collaborate across many fields. Commentary on articles in the past might occur in Letters to the Editor, with an instructive banter back and forth, extending the process of peer review beyond the review of a manuscript for publication. Now commentary can be more direct and timely, engaging the author and reader in a private or, in some cases, public exchange of opinion. The published AJO articles will continue to be a source of fact and expert opinion to guide the reader in both research endeavors and improved patient care. AJO looks forward to the future contributions from clinicians and scientists whose subjects expand our knowledge of genetic eye disease.

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