Published in final edited form as:

Expert Rev Ophthalmol. 2009 April ; 4(2): 145–161. doi:10.1586/eop.09.6.

Progress toward personalized medicine for glaucoma

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Abstract

How will you respond when a patient asks, “Doctor, what can I do to prevent myself from going blind from glaucoma like mom?”. There is optimism that genetic profiling will help target patients to individualized treatments based on validated disease risk alleles, validated pharmacogenetic markers and behavioral modification. Personalized medicine will become a reality through identification of disease and pharmacogenetic markers, followed by careful study of how to employ this information in order to improve treatment outcomes. With advances in genomic technologies, research has shifted from the simple monogenic disease model to a complex multigenic and environmental disease model to answer these questions. Our challenges lie in developing risk models that incorporate gene–gene interactions, gene copy-number variations, environmental interactions, treatment effects and clinical covariates.

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Disclosure: Sayoko E Moroi, MD, PhD, has disclosed that she has received funding for clinical research from Merck & Co., Inc. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed. No writing assistance was utilized in the production of this review manuscript.

Financial & competing interests disclosure

Elisa Manzotti, Editorial Director, Future Science Group, London, UK.

Disclosure: Elisa Manzotti has disclosed no relevant financial relationships.

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Disclosure: Désirée Lie, MD, MEd, has disclosed no relevant financial relationships.

Keywords

aqueous humor dynamics; genetics; glaucoma; intraocular pressure; personalized medicine; pharmacogenetics; pharmacogenomics

A 68-year-old woman presents at your clinic for advice about her glaucoma diagnosis and its impact on her children. She brings along her personal smart card containing her medical history, past visual fields, optic disc imaging and her genomic sequence. Initially, she was diagnosed with glaucoma based on the appearance of the neuroretinal rim of her optic disc, which showed a violation of the 'ISNT' rule (acronym for neuroretinal disc rim in order of thickest to thinnest is inferior > superior > nasal > temporal) (Figure 1) [1]. At the time of diagnosis, her intraocular pressure (IOP) measured 33 mmHg in both eyes and her central corneal measurements by ultrasonic pachymetry were 584 μ m in her right eye and 566 μ m in her left eye. Otherwise, she was asymptomatic.

Over an 18-year period of treatment, her IOP fluctuated between 7 and 13 mmHg with medical and surgical treatments. Despite this management, she developed progressive cupping of the optic disc and visual field loss over time (center and right optic discs, and visual fields in Figure 1) [2]. She asks: "Doctor, will this happen to my children?". Our current knowledge can only begin to answer her question. As our understanding grows about applying genomic results to this potentially blinding disease, clinicians will be expected to be informed on treatments that are personalized for their patients. These treatments will be based on a patient's genetic profile and be informative of disease risk, disease progression and likelihood of individual drug safety and efficacy.

Applied genomics & the advent of personalized medicine for glaucoma

The complete sequencing of the human nuclear genome was a major accomplishment in genetics [3,4]. We now know that there are approximately 20,500 genes encoded in the 6 billion chemical base pairs that make up human DNA, distributed on 46 chromosomes (i.e., 22 pairs of autosomes and one pair sex chromosomes) [5]. Additionally, there are 37 'mitochondrial' genes encoded in the circular mitochondrial DNA, which is inherited maternally. An off-shoot of the Human Genome Project [108] was the International HapMap project [109]. The goals of HapMap were the identification and cataloguing of genetic sequence variants among individuals across diverse populations, known as single nucleotide polymorphisms (SNPs), in order to identify chromosomal regions where genetic variants are shared [6]. With this genomic knowledge base, we are seeing the advent of 'personalized medicine' with the discovery of potential SNPs associated with disease onset, disease severity and treatment response (Box 1).

As of today, over 1300 disease-causing genes have been discovered using genetic linkage-based studies in families with clearly recognized Mendelian inheritance patterns (e.g., autosomal dominant, autosomal recessive and X-linked diseases), following the 'single gene, single disease' hypothesis [7]. However, the use of traditional Mendelian study designs has failed to identify the genetic variations (i.e., risk alleles) that have only moderate influence on an individual's likelihood of developing a common disease, the rate of disease progression and a patient's response to treatment.

Using newer genomic technologies and the tremendous information provided by the Human Genome and HapMap projects, progress in identifying risk alleles for common diseases has been made with genome-wide association (GWA) studies [8]. There has been a shift from the simple monogenic disease model to a complex multigenic and environmental disease model to answer the patient's question posed in the introduction. Using GWA studies has

raised considerable excitement to discover genetic determinants that provide insight into disease pathogenesis.

There are three fundamental components of GWA studies [8]. First, the genetic blue print of complex diseases is based on the common disease–common variant model. In other words, there is a limited number of common alleles, with each allele contributing a small risk to the common disease in an individual. Second, since those risk alleles arose thousands of years ago, few recombination events occurred within the short region of DNA that flanks the gene. Hence, approximately 80% of the human genome occurs in ‘conserved’ 10 kb regions or haplotype blocks. Thus, nearby genetic variation can serve as a proxy measurement for the risk variant. Finally, as world populations are closely related, common risk variants are likely to occur in all major ethnic groups.

Using SNP-based GWA platforms, tremendous progress occurred in identifying potential SNPs as risk alleles for common diseases, as recently reviewed by Kingsmore *et al.* [8]. Such an approach was successful in discovering the complement factor H risk allele for age-related macular degeneration [9,10] and the *LOXLI* risk allele for pseudoexfoliation glaucoma [11]. Follow-up studies on the cell biology of these genes and their variants will provide insight into disease pathogenesis and prognosis. In pharmacogenetics, similar approaches are applied to identify SNPs that may be associated with variations in treatment response to glaucoma medication [12].

It is important to understand the differences between the earlier established linkage-based approach and the newer SNP-based GWA approach. Both approaches are useful tools to identify genetic markers of interest and the power of these methods depends upon the frequency and penetrance of the genetic variation. Table 1 summarizes these important concepts. For instance, if the frequency of the disease allele is rare but the mutation is highly penetrable, then linkage is the most cost-effective approach and has already been used successfully to identify genes underlying many uncommon diseases [7]. If the frequency of the disease allele is common but has a low penetrance, GWA can be effective at discovering potential disease risk alleles, as has been seen for age-related macular degeneration [9,10] and diabetes mellitus [8]. If the disease mutation is frequent in the general population and the phenotype is highly penetrant, then both linkage and GWA approaches can be used. If the disease mutation is rare and has low penetrance, then current methods have little power to find the disease risk alleles.

Before we are able to determine the potential for realistic clinical application of the growing genomic knowledge on ocular disease and the anticipated identification of markers for treatment outcomes, we must take the following steps:

- Continue the discovery approaches to identify the risk alleles for the common forms of glaucoma. Several groups are actively pursuing this research using GWA methods. Subsequent clinical and basic science studies will inform us about the effects of these genes on the risk for developing glaucoma, genetic modifiers that may affect age of onset or disease progression, and pathogenetic mechanisms of the disease;
- Embark on the discovery approaches to identify alleles associated with variations in treatment response to glaucoma medications [12];
- Follow-up the results with studies specifically designed to understand the population attributable risk of these identified disease risk alleles and treatment response alleles [13]. Such studies would allow us to understand the potential impact on the utility of these risk alleles for disease and treatment response in stratified populations. Thus, we may be in a position to improve upon our clinical

understanding of the greater risk for glaucoma in individuals who are of black African [14] and Hispanic [15] ancestries;

- Follow-up with studies designed to demonstrate the predictive value, clinical utility and cost-effectiveness of these alleles associated with glaucoma disease risk and treatment response;
- Educate appropriate health professionals on the interpretation of genetic tests.

As we make progress in these steps, clinicians will become empowered to prescribe personalized treatments for their patients with the promise of improved drug safety and efficacy for that specific patient and improve upon our current ‘trial and error’ dosing of medications. Although such genetic testing is not yet ready for most diseases, the emergence of self-pay genotyping services in private sectors forces us to communicate that appropriate studies need to be designed, conducted, analyzed and replicated before direct-to-consumer genetic sequencing services are meaningful to the general public.

At least 16 such companies offer DNA testing services (‘gene profiles’ [101] or ‘personal genome services’ [102]), ranging in price from less than US\$100 to a few thousand dollars. These rely on microarrays that can assess 300,000 or more SNPs in each DNA sample. The data are generated using a microarray or a similar high-throughput genotyping platform to examine interpersonal differences in inherited genetic variability, and to compare the prevalence of gene variants among patients who have a given disease with that among appropriately matched and stratified controls [16]. Typically, consumers receive a kit requiring them to swab the inside of their cheek to obtain mucosal epithelial cells as a DNA sample, which they mail back to the company. Many of these companies promise to educate their clients on issues extending from cardiovascular disease risk to their ancestry [103].

A recent study that evaluated 24 companies offering online direct-to-consumer marketing of these genetic tests showed that access to controversial risk assessment tests, such as *ApoE* for early onset Alzheimer’s disease-susceptibility testing, generally did not require physician involvement and the extent, scope, duration and nature of counseling were left to the discretion of the company [17]. This study points to a disturbing trend, in which tests with uncertain clinical utility are provided with little professional supervision and counseling. This may lead consumers to over- or underestimate their risks of developing health conditions with complex etiologies. It is imperative that further research is conducted before the services offered by these private sectors are of value to the general public [18].

Current status of glaucoma genetic markers

At the present time, 70 genes or loci have been identified that either cause glaucoma or are associated with syndromes that include glaucoma (Figure 4 & Table 2). Glaucoma forms associated with these genes include infantile- and juvenile-onset syndromic glaucoma and a very small proportion of the high- and normal-pressure glaucomas [19]. The majority represent monogenic forms of glaucoma. These monogenic forms of glaucoma account for less than 10% of all glaucoma cases and many of them represent complex multisystem diseases, within which glaucoma is only one component of the overall phenotype [20].

More recent studies have identified loci implicating an individual’s potential susceptibility to glaucoma or influence the severity of disease (i.e., glaucoma risk alleles) [21–23]. Genetic modifications have been demonstrated to affect the age-of-onset for certain types of glaucoma. For instance, patients with infantile glaucoma have been found to carry two mutated copies of *CYP11B1*, an autosomal recessive gene associated with a form of glaucoma that causes elevated IOP in infants. A person who has one defective copy of

CYP11B1 may be more likely to develop juvenile- and adult-onset open-angle glaucoma at an earlier age than someone with a 'normal' or wild-type gene [24].

Other approaches that compliment the search for monogenic disease genes and risk alleles for glaucoma include the identification of genes or loci that have a major effect on IOP – the main treatable risk factor [25–31]. This approach of using a risk factor, which represents an endophenotype, for genetic association studies is an alternative to using the disease as a phenotype [32].

Progress toward understanding mechanisms for variance in IOP has been made with quantitative methods [32]. IOP may be studied as a quantitative trait because it is a risk factor [25–31], a continuous measure [33–35] and readily studied in both healthy subjects and patients [36,37]. Early family [38,39] and twin [40,41] studies supported genetic determinants of elevated IOP. Newer methods showed the contribution of heredity to elevated IOP. In population-based studies, heritability of IOP ranged from 0.29 in the Salisbury Eye Evaluation (n = 284 sibships for this analysis) [42], 0.35 in The Netherlands (n = 2434 subjects in 22 families for this analysis) [43] to 0.36 in the Beaver Dam Eye Study (n = 1136 sibling pairs, 514 parent–child pairs and 1807 cousin pairs for this analysis) [44]. In a comparative monozygotic (n = 94) and dizygotic (n = 96) twin study, additive genetic effects explained 64% of IOP variance [45].

Linkage and GWA approaches led to the identification of novel risk loci for elevated IOP. In the Beaver Dam Eye Study, using 486 pedigrees for this analysis, potential linkage was reported on chromosomes 2, 5, 6, 7, 12, 15 and 19 with logarithm (base 10) of odds (LOD) scores greater than or equal to 2.0 [46]. Among these loci, chromosomes 2 and 19 are of particular interest, because of known loci for elevated blood pressure (see Duggal discussion for details [46]). In a West African population of 244 sibling pairs who were initially studied for Type 2 diabetes mellitus, potential linkage was reported on 5q22 (LOD score: 2.50) and 14q22 (LOD score: 2.95) [47]. The Beaver Dam Eye Study chromosome 5 locus and the West African 5q22 locus are not identical; however, the 5q22 locus is of interest because of the identification of *WDR36* within a previously mapped open-angle glaucoma locus, called the *GLC1G* locus [48]. In one single, large family, known to segregate the myocilin *Q368X* mutation with juvenile open-angle glaucoma (formerly the *GLC1A* locus), significant linkage of maximum recorded IOP was reported for 10q22 with a LOD score of 3.3 [49]. Including the myocilin *Q368X* as a genetic covariate indicates a potential interaction with an IOP locus. Given these reported loci, the next steps will involve replication of these results in other populations and searching for candidate genes in these loci.

Part of the challenge persists because IOP is a complex physiological trait, determined by aqueous flow, uveoscleral outflow, trabecular outflow and episcleral venous pressure (Figure 5) [50]. Each factor has been studied in both healthy subjects and patients. These studies established our understanding of aqueous humor dynamics and glaucoma pharmacology [51–54]. It is logical to apply quantitative methods to study aqueous humor dynamic factors, which would allow for a simpler dissection of the complex trait of IOP.

We expect to learn more from genetic studies with designs to identify risk alleles for disease, genetic modifiers of age-of-onset and disease progression, and genetic markers of treatment-response to glaucoma medications. Once this knowledge is gained, the next step will be to develop models to assess the validity of using these genetic markers of glaucoma risk, disease progression and treatment outcome in appropriately stratified populations.

Current glaucoma therapeutics & variation in treatment outcomes

All of the major clinical trials have shown that lowering IOP slows disease progression in glaucoma [25–31]. Five main classes of medical treatments are currently used to lower IOP: topical β -adrenergic receptor antagonists, α 2-adrenergic receptor agonists, prostaglandin-related agonists, carbonic anhydrase inhibitors and miotic agents. The mechanism of action of these drugs is directed either to increase the outflow of aqueous humor through the trabecular meshwork or the uveoscleral pathway, or to decrease the production of aqueous humor by the ciliary body (Figure 2).

These medications are prescribed by ‘trial-and-error’, based on comorbidities, efficacy, side effects, cost and compliance. Among these, prostaglandins have minimal IOP fluctuation and once-daily dosing but are expensive [55]. β -blockers are inexpensive and well-tolerated but show more IOP fluctuation [56]. The α 2-adrenergic agonists [57,58] and carbonic anhydrase inhibitors [59] require frequent dosing and cost more than β -blockers. Muscarinic agents are rarely used due to frequent dosing and side effects. Since effective IOP lowering slows disease progression, the need for combination therapy is inescapable over the long-term for most patients [30]. Based on cost–effectiveness studies, the β -blockers are the most favorable [60,61]. The availability of three combination medications with β -blockers indicate that β -blockers will be used as first-line or adjunctive therapy in most patients.

Although the pharmacology of these medications has been studied extensively, we still do not fully understand the mechanisms responsible for variations in treatment response among patients. The reasons for variations in treatment response are complex but approachable if we consider the basic factors involved in pharmacology, access to healthcare and active participation of the patient in disease management, based on adherence to treatment and follow-up appointments. While these latter, nonpharmacological factors are very important considerations to interpret efficacy of treatment [62,63], these topics are beyond the scope of this review. Variations in drug response are phenotypes that represent pharmaco-kinetic and -dynamic processes, affected by tissue-specific biology, environment, pathophysiology and genetics (Figure 3) [12].

With respect to pharmaco-kinetic and -dynamic processes, we have a solid understanding of the pharmacology of glaucoma medications. Pharmacokinetics involves absorption, distribution, metabolism and excretion (Figure 3), all of which contribute to how the body affects drug levels. Pharmacodynamic processes have been more extensively studied in ocular pharmacology, and involve the drug target, mechanism of action and network pathways that are unique to the tissue target (Figure 3), all of which contribute to how the drug affects the body. We relate to both processes as clinical efficacy (i.e., amount of IOP lowering), adverse reactions and toxicity.

Given the long-term experience and widespread use of topical β -blockers, we can examine both the pharmaco-kinetic and -dynamic details of this class of medication. In considering the pharmacokinetic processes, the ocular tissues are not a major barrier to absorption of β -blockers [64]. The 1–2 h peak effect of timolol was reported to be less in brown eyes compared with blue eyes [65]. In a more recent study, timolol has been shown to be less effective in black patients compared with nonblack patients [66]. It is attractive to consider that a possible explanation for this difference is due to increased, nonspecific drug binding to melanin [67], which implies that drug distribution was altered because the higher melanin content of darkly pigmented eyes decreased the bioavailability of the drug for the target receptors. However, the more recent Ocular Hypertension Treatment Study reported no difference in IOP response to topical β -blocker therapy between African–Americans and whites, when using a multivariate analysis that involved central corneal thickness

measurement [68]. From these clinical studies both drug binding to melanin in ocular tissues and thinner central corneas should be considered as covariates in variations of IOP response to topical β -blockers.

Another potentially important pharmacokinetic consideration for the variations in IOP response to the β -blockers is drug metabolism. This drug class is metabolized by the cytochrome P450 enzyme, CYP2D6, which has been extensively studied for sequence variants of the gene having functional consequences on drug metabolism [69]. A small, prospective clinical trial showed that excessive β -blockade of heart rate and higher plasma timolol concentration occurred in subjects who were genotyped as CYP2D6-poor metabolizers compared with those who were CYP2D6-extensive metabolizers [70].

With respect to pharmacodynamic processes, the mechanism of action of β -blockers is antagonism of the β -adrenergic receptors (ARs), of which there are three subtypes: β_1 -AR or ADRB1, β_2 -AR or ADRB2 and β_3 -AR or ADRB3. The β -blockers lower IOP by decreasing aqueous humor formation [71,72] (aqueous humor inflow, Figure 2) through β -ARs in the ciliary body, as shown by radioligand binding [73] and adenylate cyclase assays [74]. These studies were performed before the discovery of the β_3 -AR. Although we know the ciliary epithelial drug targets of β -blockers, we do not fully understand the downstream network pathways uniquely expressed in ciliary body that mediate aqueous humor secretion.

Since the genes encoding these ARs are polymorphic [75], *ADRB1* and *ADRB2* are highly likely candidates for contributing to the genetic variance of drug response variations to β -blockers. In another study, the homozygous allele genotype for *ADRB2* was found to be associated with a 20% or greater decrease in IOP in response to topical β -blockers [76]; however, given the central role of these ARs in the ciliary body, these genes have also been considered possible elevated IOP risk genes and glaucoma susceptibility loci. In a Japanese case-control study, the *ADRB1* Arg389Gly allele frequency was significantly different in patients with normal tension glaucoma compared with controls [77]. In this same study, patients with primary open-angle glaucoma (POAG) carrying the *ADRB2* Gly16 allele were younger at diagnosis and those with the *ADRB2* Glu27 allele had higher IOP. In our appropriately powered case-control study, we determined that the *ADRB2* gene was not a POAG disease risk locus in Caucasians or in black African ancestral populations since there were no differences in haplotypes between controls and patients with POAG [78]. The results from other studies [79–82] are unclear due to small sample size or study design. From these results, we can conclude that these AR genes have a complex role in ciliary body physiology and pharmacology.

Future studies need to be conducted to understand how genetic variability and population history influence physiological responses to drugs, encompassing the study of absorption and metabolism, pharmacologic action, and therapeutic effect. We are well aware that the efficacy of a certain drug in a particular patient may not always match published efficacy and safety statistics. Since there are five glaucoma drug classes available, the clinician must account for the patient's systemic diseases and medications, economic status, compliance and impact on quality of life when prescribing a therapeutic agent. Perhaps in the future, clinicians will be able to use the patient's genetic profile to guide the optimal medical therapy for a patient with glaucoma.

Health, behavior & genes

Most direct-to-consumer genetic testing companies do not take lifestyle issues, such as smoking or family history, into account, despite the fact that such factors may impact the odds of disease onset and severity. Interventions, such as weight loss, smoking cessation and increased physical activity, are likely to be beneficial, regardless of the individual's genetic

susceptibility to a specific disease [16]. For instance, exercise has been shown to decrease IOP in certain populations [83]. The potential environmental and behavioral effects of smoking on IOP and glaucoma surgery outcome has been suggested [84]. In the Nurses' Health Survey and the Health Professional Follow-up Study, antioxidant consumption [85] and smoking [86] were not associated with risk for developing POAG. In these same two cohorts, a high ratio of n-3 to n-6 polyunsaturated fat appears to increase the risk for glaucoma [87]. Incorporating an individual's health behavior into the final 'risk assessment' of a disease and drug response is essential, since lifestyle choices may have a bigger effect than any genetic variant on disease risk [88]. At the present time, there is no strong evidence for actionable behavioral recommendations for glaucoma.

Genetic testing privacy & legislation

The fear of genetic discrimination has presented an impediment to the widespread application of personalized medicine, which has been creating difficulties in conducting genetic research studies [18]. However, policy discussions over more than a decade have resulted in the conclusion that federal legislative protection is essential. In May 2008, the Genetic Information Nondiscrimination Act (GINA) was signed into law, which offers protection against discrimination based on genetic information regarding health insurance and employment [104]. This has been a long awaited measure that will pave the way for people to take full advantage of the promise of personalized medicine, without fear of discrimination. GINA is expected to limit an insurers' ability to use genetic information and to extend protections to individual health insurance plans; it, therefore, sets a nationwide level of protection [89]. In addition, the American College of Medical Genetics has recently published a statement on direct-to-consumer genetic testing, outlining a specific protocol as a minimum requirement for any genetic testing [103]. These steps are likely to lead to a surge in demand for personal genetic testing.

As a recent example, the US FDA approved a warfarin label that encourages specific genotyping without specific guidance toward personalized medicine [105]. Healthcare professionals may now incorporate genetic information on *CYP2C9* and *VKORC1*, along with other clinical considerations, when estimating the initial warfarin dose for patients [90,91]. *CYP2C9* is a cytochrome P450 enzyme that metabolizes warfarin. *VKORC1* is a vitamin K epoxide reductase complex that recycles reduced vitamin K, which is essential for the post-translational γ -carboxylation of vitamin K-dependent clotting factors II, VII, IX and X.

There are currently over 110 National Institutes of Health studies that investigate pharmacogenetics in various clinical settings [106]. The May 2008 FDA issue of new guidelines regarding the definitions for genomic biomarkers, pharmacogenomics and pharmacogenetics is an additional step to harmonize pharmacogenomic definitions and additional information related to aspects applicable to proteomics and metabolomics [107].

Future approaches in glaucoma therapeutics

The challenge of genomics is to determine, whether we can predict disease risk, disease progression and treatment outcome, despite the intricate biological and physiological interactions among expression of drug target genes, drug metabolizing enzymes and disease-causing genes. Identification of genetic markers of 'poor IOP response has the potential to target those patients with disease to more appropriate treatment, such as surgery, to lower IOP more effectively, thus, minimizing progressive optic nerve damage and visual field loss. Another application for genetic markers in glaucoma treatment involves the variation in response to the anti-fibrotic agents of 5-fluorouracil and mitomycin C and, consequently, the outcomes of glaucoma surgery [92], which is beyond the scope of this review. We imagine

that a 'genetic panel' will be developed with robust markers for common diseases, such as diabetes, hypertension, some cancers, age-related macular degeneration, glaucoma and the response to commonly prescribed medications. Such genetic markers will need to be tested in stratified patient populations for predictive value and then validated in separate cohorts. A cost-benefit analysis with economic modeling will also need to demonstrate the health benefits and long-term cost savings to improve treatment outcomes and, thereby, decrease disease morbidity. The coverage of genetic testing will be determined through the process of technology assessment by national insurance and private payers [93,94]. The future application of such a genetic profile could lead to fewer return office visits for follow-up in order to change medical therapy, thus improving treatment outcomes.

Expert commentary

Personalized ocular healthcare will be a major research focus in this post-genomic era, with the application of the newer genomic approaches and the knowledge gained from the Human Genome Project [108] and HapMap Project [109]. The promises of personalized medicine are new abilities in clinical decision-making regarding individualized treatment regimens based on the patient's genetic profile and health behaviors, after appropriately designed studies are conducted. Lifestyle factors, such as diet, exercise, smoking and alcohol, are all included in the individual health behaviors. The genetic profile would enable the assessment of risk for disease, protective genetic factors, disease progression and variations in treatment responses of both efficacy and toxicity.

There is great optimism that genetic profiling will help target patients with glaucoma to individualized treatments based on validated disease risk alleles, validated pharmacogenetic markers and specific behavioral modification. It is important to remember, however, that genes merely represent the 'blueprint' to uncover genetic variants in common diseases and, without a doubt, do not provide 'the answer'. Considerable strides are still needed to fully understand factors that affect gene expression, such as DNA methylation, gene repair, copy number variation and telomerase action. In addition, proteomics is, arguably, just as crucial to genomics when looking at normal physiology and disease. For instance, post-translational modifications, such as glycosylation, ADP-ribosylation and phosphorylation that affect cell function [95–98] may also contribute to differences in an individual's disease manifestation and response to treatment. We are still a long way from the day when a patient presents an electronic card bearing the patient's health record and genetic sequence. Considerable basic and clinical research needs to be done to make strides toward personalized medicine for improving treatment outcomes for our patients with glaucoma.

Five-year view

Over the next 5 years, we will continue to see progress in the field of pharmacogenomics in relation to ocular disease. The initial steps will be towards identification of markers associated with medical treatment response. It seems hopeful that clinical trials examining the clinical efficacies of new drugs will incorporate a genomic element for prospective research in order to determine genetic factors that influence drug response. The application of genomics to glaucoma therapy will inform us whether there will be a time when we can offer our patients options customized to their genetic profile. We will be able to provide prognosis with more confidence, depend less upon our current 'trial-and-error' approach to treatment and give the chance for the best possible treatment outcome with the long-term goal of preventing glaucoma-related vision loss. Pharmacogenomics and pharmacogenetics have the potential of changing the face of glaucoma therapeutics and their advent has been considered one of the most exciting developments in the arena of personalized medicine.

Acknowledgments

The authors appreciate the graphic design assistance of David Murrel.

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Box 1**Frequently used terms in the field of genetics**

- **Alleles:** In a given gene, alleles differ in DNA sequence. For some allelic variants present on one or both copies of a gene, a difference in the phenotype may be seen. Other alleles having a different sequence may not cause a change in the phenotype.
- **Association study:** Comparison of cases to controls in order to assess the relative contribution of genetic variants or environmental effects to the trait being studied. For a continuous trait, the relative contribution of genetic variants or environmental effects may be assessed in the single, appropriately powered group.
- **Candidate gene:** A gene selected for evaluation as a possible cause or contributing factor to a disease or trait. Information suggesting that the gene might be involved can come from a combination of genetic studies, association studies or functional information about the gene product.
- **Copy number variants (CNV):** Loosely defined as regions of the genome, thousands to millions of bases in size, which are deleted or duplicated in varying numbers of copies in comparison to a reference sequence.
- **Genotype:** The set of DNA variants located at one or more loci in an individual.
- **Genome-wide association study (GWA or GWAS):** A study of genetic variation across the entire human genome aimed at identifying associations between phenotypes and genotypes at hundreds of thousands or even millions of locations spread across the human genome.
- **Haplotype:** A group of alleles on neighboring genes or markers that tend to be inherited together because they are so closely spaced that recombination events are unlikely to separate them during meiosis.
- **HapMap:** A database that organizes information on single nucleotide polymorphisms (SNPs) from throughout the genome into haplotypes. It presents information on frequencies of individual SNPs and haplotypes in different human populations and indicates regions of the genome where associations among SNPs are weak.
- **Heritability:** The proportion of phenotypic variance that is caused by variation in the genotype.
- **Linkage analysis:** A genetic mapping approach based on the cotransmission of genetic markers and phenotypes from one generation to the next in families.
- **Linkage disequilibrium:** The non-random association of alleles or “allelic association” that tend to be inherited together. Linkage disequilibrium can result from close physical proximity of two loci on the same chromosome, from natural selection or population stratification.
- **Logarithm (base 10) of odds (LOD) score:** A measure of the probability that the observed genetic data arose because the marker and trait are linked, rather than by chance. For a usual human genome linkage experiment, a LOD score of 3.0 or greater provides statistically significant evidence of linkage and a LOD score of –2.0 or lower provides statistically significant evidence that the tested marker is not linked to the trait in question.

- **Mendelian trait:** A single gene disorder that follows Mendelian patterns of heredity – the law of segregation of alleles and the law of independent assortment. Common examples of Mendelian patterns of inheritance include autosomal dominant, autosomal recessive and X-linked inheritance.
- **Non-Mendelian trait:** A genetic trait that does not follow the classical rules of Mendelian inheritance. Examples of situations that do not follow Mendel's rules include quantitative traits that result from the additive effects of many genetic and/or environmental effects, polygenic traits that happen only if there are defects present in more than one gene, traits displaying incomplete penetrance, co-dominant inheritance, in which each of the three genotypic combinations for an allele have a different phenotype, imprinting effects caused by chemical modifications to the DNA, or mitochondrial inheritance.
- **Penetrance:** The frequency with which the presence of a particular genotype in an organism results in the corresponding phenotype. The trait may be non-penetrant in individuals who never display the trait or may show age-related penetrance in individuals who do not become affected until later in life.
- **Pharmacogenetics:** The study of how an individual's genes affect the way the individual's body responds to a medication or treatment.
- **Pharmacogenomics:** The study of drug responses in the context of the entire genome.
- **Polymorphism (or polymorphic):** The presence of genetic variation at a particular point in the genome. Some disciplines use this term for variants present in more than 1% of a population, while other disciplines use this term to refer to any variant in the sequence.
- **Population stratification:** A systematic difference in allele frequencies among subpopulations. If case and control populations are not well-matched for genetic background, then stratified population structure may lead to false-positive association findings, whereby it appears that cases and controls differ not only in the prevalence of the trait in question but also in frequencies of alleles in the genetic background that are unrelated to the trait.
- **Power:** The probability of being able to arrive at a statistically significant answer to the question being asked.
- **Quantitative trait loci (QTL):** Loci that contribute to a trait that shows a continuum of values rather than a discrete yes–no trait.
- **Single-nucleotide polymorphism (SNP, pronounced 'snip'):** A DNA sequence variation that exists as a single base difference. A SNP may result in an amino acid change (a non-synonymous base variation), or no amino acid change (a synonymous base variation).

Key issues

- Pharmacogenomics is the study of the impact of genetic variation on the response to a specific drug.
- Appropriate studies need to be designed, conducted, analyzed and replicated before direct-to-consumer genetic sequencing services are meaningful to the general public.
- Given the five different main classes of drugs for glaucoma therapy, it is important to recognize that genetic variability among the pharmaco-kinetic and -dynamic pathways may influence responses to these drugs.
- Genetic variations have been found that either cause glaucoma or are associated with syndromes that include glaucoma and loci have been identified that affect an individual's potential susceptibility to glaucoma.
- There is growing evidence that there are genetic markers for the risk of developing elevated intraocular pressure.
- Incorporating an individual's health behavior into the final 'risk assessment' of a disease is essential, which many direct-to-consumer genetic testing companies currently overlook.
- The recent passage of the Genetic Information Nondiscrimination Act, a federal law that protects consumers from discrimination by health insurers and employers on the basis of genetic information, will undoubtedly result in positive effects on the fields of clinical research and healthcare.
- Future approaches to glaucoma therapeutics encompass identification of genetic markers for 'non-responders' and delayed wound healing, as well as incorporating the utility of growth factors, stem cells and other non-pressure-based mechanisms to decrease glaucoma neuropathy.

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Learning objectives

Upon completion of this activity, participants should be able to:

- Describe the utility of Mendelian study design in managing genetic diseases
- Describe the use of genome-wide association studies in disease management
- Identify the steps in using genomic knowledge to improve clinical care of ocular disease
- Describe the prevalence of monogenic forms of glaucoma
- Identify treatment approaches to glaucoma

Figure 1. Case demonstrating progression of glaucoma based on right optic disc photos (top panel) and right visual fields (bottom panel) over 18 years despite medical and surgical treatments with intraocular pressure reduction and fluctuation between 7 and 13 mmHg. Reproduced with permission from [19].

Figure 2. Schematic of anterior segment of the eye that demonstrates the mechanism of action of five different classes of glaucoma medication

Reproduced with permission from Nature Publishing Group [12].

Figure 3. Variations in intraocular pressure response to glaucoma medical therapy are determined by pharmacokinetic and -dynamic processes (arrow between glaucoma drugs and clinical outcome) and interaction with the environment, disease and pathophysiological processes The sequence variants among pharmaco-kinetic and -dynamic genes are predicted to have functional consequences that contribute to the genetic component of variance in intraocular pressure response. Modified from [110].

Figure 4. Cytogenetic location (left labels) and gene symbol (right labels) for glaucoma genes and loci located on human chromosomes

The p-arm is shown at the top of each ideogram using 550-band level (graphic files source from Current Protocols in Human Genetics 1998: A.4B.1-A.4B.21). Idiogram Album: Human, Copyright 1991 David Adler and Michael Willis. Additional details are found in Table 1.

Figure 5. Modified Goldmann equation representing four variables that determine IOP

The boxes list conditions in the categories of 'general', 'disease' and 'treatment', which influence the given variable.

AHF: Aqueous humor flow; C_{trab} : Trabecular outflow; Fu : Uveoscleral outflow; IOP: Intraocular pressure; Pe : Episcleral venous pressure.

Table 1

Application of linkage and genome-wide association approaches to identify disease genes.

Penetrance of the genetic variation	Frequency of the genetic variation	
	High frequency	Low frequency
High penetrance	Both linkage and association approaches	Linkage approach
Low penetrance	Association approach	Remains a challenge

Application of linkage and association approaches to identify disease genes depends upon the frequency of the disease mutation and the penetrance of the disease mutation. These approaches can be applied to the discovery of genes underlying treatment outcomes in the field of pharmacogenetics and pharmacogenomics.

Table 2

Summary of genes (and loci) associated with glaucoma.

Chromosome	HUGO symbol	Phenotype
1	<i>PLOD1</i>	Ehlers–Danlos syndrome VI
1	<i>GLC3B</i>	Infantile glaucoma, Type B
1	<i>COL8A2</i>	Posterior polymorphous corneal dystrophy 2, Fuchs endothelial corneal dystrophy
1	<i>POMGNT1</i>	Muscle–eye–brain disease
1	<i>COL11A1</i>	Marshall syndrome, Stickler syndrome 2
1	<i>MYOC</i>	Juvenile open-angle glaucoma
2	<i>CYP1B1</i>	Infantile glaucoma, Peters anomaly, primary open-angle glaucoma, juvenile-onset open-angle glaucoma
2	<i>GLC1H</i>	High-tension open-angle glaucoma
2	<i>GLC1B</i>	High-tension open-angle glaucoma
3	<i>GLC1L</i>	Open-angle glaucoma
3	<i>GLC1C</i>	High-tension open-angle glaucoma
3	<i>OPA1</i>	Optic nerve atrophy, normal-tension open-angle glaucoma
4	<i>IDUA</i>	Hurler syndrome, Hurler–Scheie syndrome, Scheie syndrome
4	<i>SLC4A4</i>	Renal tubular acidosis, mental retardation, glaucoma
4	<i>PITX2</i>	Iridogoniodysgenesis 2 or Rieger Type 1, Peters anomaly, ring dermoid of cornea
5	<i>ARSB</i>	Mucopolysaccharidosis 6, Maroteaux–Lamy syndrome
5	<i>VCAN</i>	Wagner syndrome 1
5	<i>GLC1M</i>	Open-angle glaucoma
5	<i>WDR36</i>	Open-angle glaucoma
6	<i>COL11A 2</i>	Stickler syndrome III, Weissenbacher–Zweymuller syndrome
6	<i>FOXC1</i>	Iridogoniodysgenesis 1, anterior segment mesenchymal dysgenesis, Rieger anomaly, Axenfeld anomaly, iris hypoplasia, juvenile glaucoma
6	<i>GJA1</i>	Oculodentodigital dysplasia, microphthalmia
7	<i>GLC1F</i>	High-tension open-angle glaucoma
7	<i>GPDS1</i>	Pigment dispersion 1
8	<i>KTWS</i>	Klippel–Trenaunay–Weber syndrome
8	<i>GLC1D</i>	High-tension open-angle glaucoma
9	<i>GLIS3</i>	Neonatal diabetes mellitus and hypothyroidism, infantile glaucoma
9	<i>GLC1J</i>	Juvenile-onset open-angle glaucoma
9	<i>PTCH1</i>	Basal cell nevus syndrome
9	<i>FKTN</i>	Walker–Warburg syndrome
9	<i>LMX1B</i>	Nail–Patella syndrome
9	<i>POMT1</i>	Walker–Warburg syndrome
10	<i>OPTN</i>	Normal- and high-tension open-angle glaucoma
10	<i>ZEB1</i>	Posterior polymorphous corneal dystrophy 3
10	<i>PAX2</i>	Renal–coloboma or papillorenal syndrome, ‘morning glory’ optic nerve
10	<i>PITX3</i>	Anterior segment dysgenesis

Chromosome	HUGO symbol	Phenotype
11	<i>PAX6</i>	Aniridia II, Peters anomaly, 'morning glory' optic nerve, coloboma
11	<i>SBF2</i>	Charcot–Marie–Tooth disease Type 4B2
11	<i>NN01</i>	Nanophthalmos 1
11	<i>MFRP</i>	Nanophthalmos 2
11	<i>C1QTNF5</i>	Late-onset retinal degeneration and long anterior zonules
11	<i>LRP5</i>	Osteogenesis imperfecta, ocular form
12	<i>COL2A1</i>	Stickler syndrome I
13	<i>RIEG2</i>	Rieger syndrome 2
13	<i>MCOR</i> *	Congenital microcoria
14	<i>SIX6</i>	Microphthalmia with cataract 2
14	<i>POMT2</i>	Walker-Warburg syndrome
14	<i>GLC3C</i>	Infantile glaucoma
14	<i>VSX2</i>	Microphthalmos
14	<i>MCOP</i> *	Microphthalmos
15	<i>GLC1I</i>	High-tension open-angle glaucoma
15	<i>FBN1</i>	Weill–Marchesani syndrome, ectopia lentis, Marfan syndrome
15	<i>LOXL1</i>	Risk allele for pseudoexfoliation glaucoma
15	<i>GLC1N</i>	Juvenile-onset open-angle glaucoma
16	<i>CREBBP</i>	Rubinstein-Taybi syndrome
17	<i>NF1</i>	Neurofibromatosis 1
18	<i>RAX</i>	Microphthalmos
19	<i>ADAMTS10</i>	Weill–Marchesani syndrome
19	<i>FKRP</i>	Walker–Warburg syndrome
20	<i>GLC1K</i>	Juvenile-onset open-angle glaucoma, 3
20	<i>VSX1</i>	Posterior polymorphous corneal dystrophy 1
21	<i>CBS</i>	Homocystinuria, ectopia lentis
22	<i>NF2</i>	Neurofibromatosis 2
22	<i>LARGE</i>	Walker-Warburg syndrome
X		Coats disease, uveitis, secondary glaucoma, Norrie disease
X	<i>BCOR</i>	Microphthalmia, syndromic 2
X	<i>HCCS</i>	Microphthalmia, syndromic 7
X	<i>OCRL</i>	Lowe oculocerebrorenal syndrome
X	<i>MRXSA</i> *	Armfield X-linked mental retardation syndrome

HUGO symbols are used and were cross checked with GeneCards.

* The symbol is based on EntrezGene, since there is no approved symbol in HUGO.

HUGO: Human Genome Organization.