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Pharmacogenetics and pharmacogenomics in glaucoma therapeutics: the way to personalized therapy

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Glaucoma is a leading cause of irreversible optic nerve damage, with a significant proportion of patients (approximately 10%) suffering from blindness or severe visual field damage during their lifetime.[1] The number of patients suffering from glaucoma worldwide is estimated to be 76 million in 2020 and is expected to rise to 111.8 million by 2040.[2] The estimated global prevalence of primary open-angle glaucoma (POAG) is 3.05% and primary angle-closure glaucoma is 0.50% in those aged 40 to 80 years, and the prevalence increases with age,[2] which imposes a significant economic burden. Elevated intraocular pressure (IOP) is a well-recognized risk factor for glaucoma progression; although some natural products such as citicoline and coenzyme q10 have been shown to possess neuroprotective properties for delaying the progression of glaucoma,[3,4] IOP-lowering medications are currently the mainstay in its medical management.

Prostaglandin analogs, β-adrenergic antagonists, α2-adrenergic agonists, carbonic anhydrase inhibitors, cholinergic agonists, and rho-associated protein kinase inhibitors are the six basic classes of drugs now utilized to decrease IOP.[5] Unfortunately, patients respond differently to IOP-lowering medications. In a clinical trial, 20% and 31% of patients with glaucoma and ocular hypertension (OH) receiving either latanoprost once daily or timolol twice daily, respectively, were found to be non-responders at two weeks, which remained as high as 18% and 28% at three months.[6] Switching to a new monotherapy or combination therapy for poor responders is challenging, as there is also a relatively high rate of inadequate IOP control (approximately 20%).[7] The poor control rate, in turn, can result in permanent vision impairment. Patients with normal-tension glaucoma (NTG) were estimated to have a cumulative risk of newly developed visual impairment in at least one eye with 2.8% at 10 years and 8.7% at 15 years.[8]

Pharmacogenetics and pharmacogenomics (PGx) studies focus on genetic variants with a clinically significant effect on drug reactions. As an emerging idea in glaucoma management, personalized selection of IOP-lowering medications based on PGx information may have potential benefits and has been advocated by some experts in the field.[9] In recent decades, a plethora of gene–drug interactions of glaucoma medications have been explored by PGx studies with the help of technological advancements in genome-wide association studies (GWASs), next-generation sequencing, and deep machine learning. In addition to genetic factors, environmental factors can also contribute to glaucoma risk and progression, but the findings are contradictory because their effects are likely to be mediated by genetic susceptibility.[10] Epigenetic variations caused by environmental factors have an important role in regulating gene expression in biological processes, such as cell proliferation, apoptosis, migration, the inflammatory response, and autophagy. Epigenetic factors, such as DNA methylation and RNA-associated gene regulation (lncRNA and microRNA), have been actively investigated and have been found to contribute to glaucoma risk and progression.[11-13] Glaucoma PGx research focuses on five basic aspects: genes related to drug targets, drug metabolism and transportation, downstream pathways, disease risk factors, and drug-related adverse events [Figure 1]. The chief findings are summarized in Supplementary Material, http://links.lww.com/CM9/B228. As the cornerstone in personalized glaucoma therapy, PGx provides the potential to take advantage of the genetic information of patients to prevent glaucoma progression and guide clinical decisions. However, currently, no actionable drug labels or guidelines for IOP-lowering medications have been released by international groups due to controversial findings and a lack of convincing evidence.

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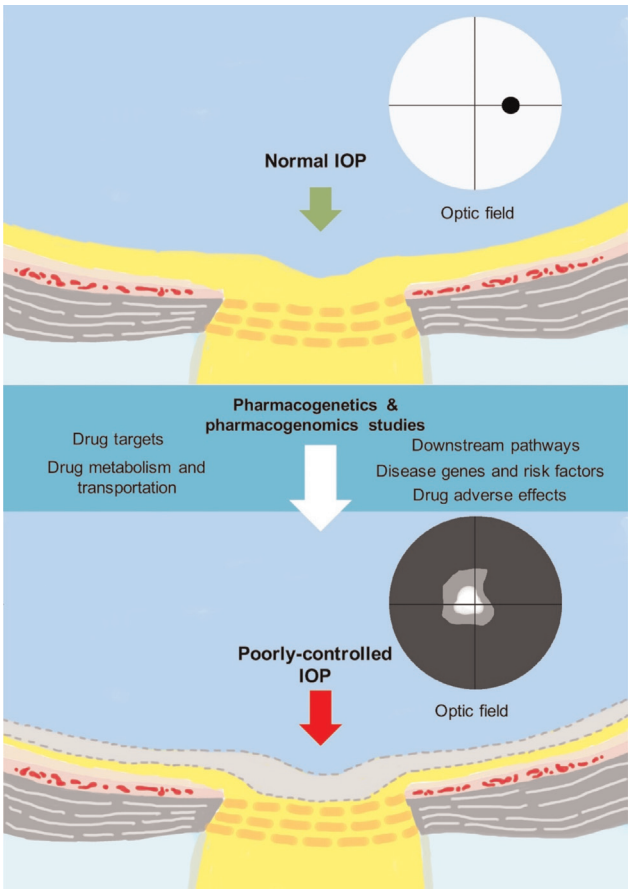

Figure 1: PGx in glaucoma management. IOP: Intraocular pressure; PGx: Pharmacogenomics.

Undoubtedly, patients will benefit from an individualized regimen if genetic polymorphisms are truly associated with drug effects or its adverse reactions. For regulatory agencies, the decision to incorporate PGx testing into glaucoma management should be based on solid benefits and a cost-effectiveness analysis, which lacks in glaucoma. Challenges in basic methodologies, research design and implementation, and clinical interpretation and translation are major hurdles in the clinical translation of glaucoma PGx findings. The first unmet challenge in the glaucoma PGx study is to find more putative loci and confirm their clinical significance. These putative loci are generally found in two major ways, through GWASs or the direct pathway of drug reaction.[14] Genes located directly in the drug action pathway are rationally suspected of potential gene–drug interactions, such as drug-receptor genes, drug-metabolizing enzyme genes, and downstream pathway genes. However, the effects of rare polymorphisms can be easily offset in individuals carrying other polymorphisms and tested as non-significant if the study lacks sufficient power and quality. Knowledge of disease and drug pathways is also needed to search for putative susceptible genes. GWAS is a powerful and affordable tool to detect a great number of susceptible genes of glaucoma independent of the primary hypothesis but faces technological and statistical challenges in elucidating true significant associations. Different from cancers and cardiac diseases, most subtypes of glaucoma have an obscure and chronic disease course. The real benefits of PGx guidance on the selection of IOP-lowering medications may not be obvious in the short term. In addition, most short-term studies use the degree or absolute value of IOP reduction as the only indicator to evaluate the genetic effect on drug response, which is subject to large fluctuations between different measurements in an individual.[15] It should be noted that many different factors, including the study design (prospective, retrospective, or randomized controlled trials), participants (age, ethnicity, number of cases, and normal volunteers or patients with NTG, POAG, or OH), interventions (drug types and dosages), genotyping methods, and methods of IOP evaluation (measurement methods, measurement parameters, and follow-up time), may have an impact on the study results and should be well controlled to balance these confounding factors. Close cooperation between regional and international groups is needed to confirm genetic effects in a larger population with a more diverse genetic background.

Currently, PGx testing on glaucoma medication is prescribed on the empirical basis of some clinicians. Some researchers have proposed a panel of genetic loci to generate a risk score for glaucoma onset and progression,[16-18] which have even been commercialized by private health providers. However, the clinical benefits of applying screening of risk factor genes for glaucoma progression and for guiding decision-making are questionable due to the lack of long-term observation data and the reliable interpretation of genetic effects, and the European Glaucoma Society recommends against routine genotyping in such cases.[5] Instead of private practices, large glaucoma centers should be qualified to interpret genetic findings and play a major role in future research and clinical translation. Furthermore, because most PGx studies on glaucoma focus on POAG, it would be worthwhile to give priority to examining whether a POAG-specific genetic test might be developed utilizing the data already available to acquire initial experience. Nevertheless, awareness of the general knowledge of PGx is surprisingly low among health-care workers, although the concept of PGx and personalized therapy has been established for decades in many fields of disease management.[19-21] The top obstacles in the implementation of pharmacogenetics in clinical practice by clinicians are cost-related concerns, insufficient knowledge, controversial opinions, and lack of evidence on test benefits.[22] Thus, education of clinicians should be considered to boost broader cooperation of basic and clinical research and implement the clinical translation of PGx labels into personalized glaucoma medicine in the future.

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Conflicts of interest

None.

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