**Supplementary Material**

**Literature Review Process**

To provide our perspectives on the clinical application of glaucoma personalized therapy, a comprehensive literature search on PubMed and Embase with the search terms “glaucoma,” “pharmacogenetics,” “pharmacogenomics,” “drug therapy,” and “precision medicine” for studies published from conception to May 1, 2022 was conducted independently by two authors (LSY and WLX). Associated studies in the reference list were also hand-searched and reviewed. Any clinical studies involving pharmacogenetics and pharmacogenomics findings on glaucoma medications were included. Studies were excluded if it is an animal study, a basic research study, a case report, or a review article, or if it included no parallel controls. Clinical studies with no reports of trial results were also excluded. Studies about genetic associations with glaucoma risk and progression were searched with terms such as “risk factors” and “progression” with the same inclusion and exclusion criteria. Disagreement in study selection was settled by discussion with the corresponding author (WX), who decided the final selection of included literature. The brief process of literature selection is demonstrated in Supplementary Figure 1.



**Supplementary Figure 1:** Summary of literature selection process. IOP: Intraocular pressure.

**Supplementary Table 1:** Common functional genetic polymorphisms related to drug-mediated IOP-lowering effect in candidate genes.

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| **Drugs** | **Genes** | **Function of genes** | **Genetic polymorphisms** | **Results** | **References** |
| β-Adrenergic antagonists (e.g., timolol and betaxolol) | *ADRB1* | Receptor | rs1801252 | No significant association between genotype and response to betaxolol. | [1–3] |
| rs1801253 | Patients with CC homozygotes had a greater hypotensive response to betaxolol than CG/GG heterozygotes. |
| *ADRB2* | Receptor | rs1042713 | No significant association between genotype and response to betaxolol. | [2–5] |
| rs1042714 | Patients with CC homozygotes had a greater hypotensive response to betaxolol than CG/GG heterozygotes. |
| *CYP2D6* | Enzyme | rs16947 | No significant association between genotype and response to timolol. | [6] |
| rs1135840 | No significant association between genotype and response to timolol. |
| *MLIP* | Protein | CNVs | The more copies of the MLIP variant, the weaker the capacity of timolol to reduce IOP. | [7] |
| Prostaglandin analogs (e.g., latanoprost) | *PTGFR* | Receptor | rs3753380 | Patients with CC genotype had an increased response to latanoprost than CT + TT genotypes. | [8–13] |
| rs3766355 | Patients with CC genotype had an increased response to latanoprost than AA + AC genotypes. |
| *SLCO2A1* | Transporter | rs4241366 | Patients with GG genotype had a better response to latanoprost than GC + CC genotypes. | [9, 12] |
| rs34550074 | No significant association between genotype and IOP response to prostaglandin analogs. |
| *PTGS1* | Enzyme | rs10306114 | Patients with AA homozygous had significantly higher %ΔIOP than those of AG heterozygous. | [14] |
| *ABCC4* | Transporter | rs11568658 | Patients with GG homozygous had significantly higher %ΔIOP than those of GT heterozygous. | [14] |
| *ABCB1* | Transporter | rs1045642 | Patients with TT genotype had a more remarkably reduced IOP and an improved visual acuity than CC + CT genotypes. | [15] |
| *GMDS* | Enzyme | rs9503012 | Patients with TT genotype had a better response to latanoprost than CC + CT genotypes. | [13] |
| *MLIP* | Protein | CNVs | The more copies of the MLIP variant, the greater the capacity of latanoprost to reduce IOP. | [7] |

ABCB1: ATP-binding cassette subfamily B member 1; ABCC4: ATP-binding cassette subfamily C member 4; ADRB1: Adrenoceptor beta 1; ADRB2: Adrenoceptor beta 2; CNVs: Copy number variations; CYP2D6: Cytochrome P450 family 2 subfamily D member 6; GMDS: GDP-mannose 4,6-dehydratase; IOP: Intraocular pressure; PTGFR: Prostaglandin F receptor; PTGS1: Prostaglandin-endoperoxide synthase 1; MLIP: Muscular LMNA-interacting protein; SLCO2A1: Solute carrier organic anion transporter family member 2A1.

**References**

1. Schwartz SG, Puckett BJ, Allen RC, Castillo IG, Leffler CT. Beta1-adrenergic receptor polymorphisms and clinical efficacy of betaxolol hydrochloride in normal volunteers. Ophthalmology 2005;112:2131–2136. doi: 10.1016/j.ophtha.2005.08.014.

2. Inagaki Y, Mashima Y, Fuse N, Funayama T, Ohtake Y, Yasuda N, *et al*. Polymorphism of beta-adrenergic receptors and susceptibility to open-angle glaucoma. Mol Vis 2006;12:673–680.

3. Messina Baas O, Pacheco Cuellar G, Toral-López J, Lara Huerta SF, Gonzalez-Huerta LM, Urueta-Cuellar H, *et al*. ADRB1 and ADBR2 gene polymorphisms and the ocular hypotensive response to topical betaxolol in healthy Mexican subjects. Curr Eye Res 2014;39:1076–1080. doi: 10.3109/02713683.2014.900807.

4. McCarty CA, Burmester JK, Mukesh BN, Patchett RB, Wilke RA. Intraocular pressure response to topical beta-blockers associated with an ADRB2 single-nucleotide polymorphism. Arch Ophthalmol 2008;126:959–963. doi: 10.1001/archopht.126.7.959.

5. McCarty CA, Mukesh BN, Kitchner TE, Hubbard WC, Wilke RA, Burmester JK, *et al*. Intraocular pressure response to medication in a clinical setting: The Marshfield Clinic Personalized Medicine Research Project. J Glaucoma 2008;17:372–377. doi: 10.1097/IJG.0b013e31815c5f3f.

6. Nieminen T, Uusitalo H, Mäenpää J, Turjanmaa V, Rane A, Lundgren S, *et al*. Polymorphisms of genes CYP2D6, ADRB1 and GNAS1 in pharmacokinetics and systemic effects of ophthalmic timolol. A pilot study. Eur J Clin Pharmacol 2005;61:811–819. doi: 10.1007/s00228-005-0052-4.

7. Canut MI, Villa O, Kudsieh B, Mattlin H, Banchs I, González JR, *et al*. MLIP genotype as a predictor of pharmacological response in primary open-angle glaucoma and ocular hypertension. Sci Rep 2021;11:1583. doi: 10.1038/s41598-020-80954-2.

8. Sakurai M, Higashide T, Takahashi M, Sugiyama K. Association between genetic polymorphisms of the prostaglandin F2alpha receptor gene and response to latanoprost. Ophthalmology 2007;114:1039–1045. doi: 10.1016/j.ophtha.2007.03.025.

9. McCarty CA, Berg R, Patchett R, Wilke RA, Burmester JK. Lack of association between polymorphisms in the prostaglandin F2α receptor and solute carrier organic anion transporter family 2A1 genes and intraocular pressure response to prostaglandin analogs. Ophthalmic Genet 2012;33:74–76. doi: 10.3109/13816810.2011.628357.

10. Sakurai M, Higashide T, Ohkubo S, Takeda H, Sugiyama K. Association between genetic polymorphisms of the prostaglandin F2α receptor gene, and response to latanoprost in patients with glaucoma and ocular hypertension. Br J Ophthalmol 2014;98:469–473. doi: 10.1136/bjophthalmol-2013-304267.

11. Ussa F, Fernandez I, Brion M, Carracedo A, Blazquez F, Garcia MT, *et al*. Association between SNPs of metalloproteinases and prostaglandin F2α receptor genes and latanoprost response in open-angle glaucoma. Ophthalmology 2015;122:1040–1048.e4. doi: 10.1016/j.ophtha.2014.12.038.

12. Zhang P, Jiang B, Xie L, Huang W. PTGFR and SLCO2A1 gene polymorphisms determine intraocular pressure response to latanoprost in Han Chinese patients with glaucoma. Curr Eye Res 2016;41:1561–1565. doi: 10.3109/02713683.2016.1143013.

13. Cui XJ, Zhao AG, Wang XL. Correlations of AFAP1, GMDS and PTGFR gene polymorphisms with intra-ocular pressure response to latanoprost in patients with primary open-angle glaucoma. J Clin Pharm Ther 2017;42:87–92. doi: 10.1111/jcpt.12468.

14. Gao LC, Wang D, Liu FQ, Huang ZY, Huang HG, Wang GH, *et al*. Influence of PTGS1, PTGFR, and MRP4 genetic variants on intraocular pressure response to latanoprost in Chinese primary open-angle glaucoma patients. Eur J Clin Pharmacol 2015;71:43–50. doi: 10.1007/s00228-014-1769-8.

15. Liu H, Yang ZK, Li Y, Zhang WJ, Wang YT, Duan XC. ABCB1 variants confer susceptibility to primary open-angle glaucoma and predict individual differences to latanoprost treatment. Biomed Pharmacother 2016;80:115–120. doi: 10.1016/j.biopha.2016.02.028.