Identification of Novel Therapeutic Candidates for Primary Congenital Glaucoma Targeting CYP1B1 Mutations

Mario Markho[1*], Hunter Eby[1], John Vergis[1], Jonathan Kopacz[1], Young Min Yu[1], Michael Hershey[1], Kayla Cartwright[1], Morgan Markho[2], Chase Arnold[1], Connor Knight[1], Robert McCullumsmith[3]

[1]College of Medicine and Life Sciences, 3000 Arlington Avenue, The University of Toledo, Toledo OH 43615

[2]Student, 281 West Lane Avenue, The Ohio State University, Columbus OH 43210

[3]Professor, Department Chair of Neurosciences and Psychiatry, 3000 Arlington Avenue, The University of Toledo, Toledo OH 43615

Email: mario.markho@rockets.utoledo.edu

Received: 2024-08-16

Accepted: 2024-09-16

Published: 2025-06-30

Background: Primary congenital glaucoma (PCG) presents in infancy with enlargement of the corneal and scleral diameters, potentially leading to endothelial tears, corneal clouding, and irreversible vision loss if untreated (1). The CYP1B1 gene is crucial in trabecular meshwork development, and mutations impair aqueous outflow, elevating intraocular pressure and causing optic nerve damage, making it a major genetic cause of PCG (2).

Objective: This in silico study aims to identify novel perturbagens that reverse the gene expression changes from CYP1B1 loss to mitigate PCG complications. Methods The Kaleidoscope data exploration tool identified knockdown (KD) iLINCS signatures for CYP1B1. KD signatures were processed through Sig2Lead to find drug candidates with significantly positive or negative concordance. Candidates with the most negative concordance with CYP1B1 KD signatures were further evaluated as potential therapeutic targets for PCG.

Results: Kaleidoscope identified nine CYP1B1 KD signatures. Sig2Lead revealed four top candidates with a concordance score of -0.5 or less: benperidol (-0.517), ecopipam (-0.507), aclidinium bromide (-0.506), and benfluorex (-0.504). The current standard of treatment for PCG includes surgery as first-line, but also includes maintenance therapy with drugs such as timolol (-0.384), latanoprost (-0.31), bimatoprost (-0.469), acetazolamide (-0.330), and pilocarpine (-0.331) (3).

https://dx.doi.org/10.46570/utjms-2025-1394

Conclusion: This study supports the efficacy of current PCG maintenance therapy, as each drug was significantly discordant with multiple CYP1B1 KD signatures. Dopamine antagonists benperidol (D2 antagonist) and ecopipam (D1 antagonist) were identified as the two most discordant perturbagens. While the mechanism of action between dopamine antagonism and intraocular pressure reduction is unclear, future studies may investigate this relationship. Aclidinium bromide is an anti-muscarinic typically used to treat COPD, and the relationship between this anti-cholinergic and intraocular pressure warrants further investigation. Finally, while benfluorex seems like a viable candidate, it is no longer widely available due to significant cardiovascular side effects (4).

Keywords: Glaucoma, Potential Drugs, Genetics, Bioinformatics, Intraocular Pressure, Ophthalmology

---

References

1. Leysen, L., Cassiman, C., Vermeer, S., Casteels, I., Balikova, I. *Genetics in primary congenital glaucoma: Implications in disease management and counseling*. Eur J Med Genet, 2022. **65**(1), 104378. doi:10.1016/j.ejmg.2021.104378

2. Yu, M., Bouhenni, R., Kurup, S. K., He, W. *Editorial: Genetic Mutations Associated With Ocular Diseases*. Front Cell Dev Biol, 2021. **9**:815522. doi:10.3389/fcell.2021.815522

3. Mehran, N. A., Sinha, S., Razeghinejad, R. *New glaucoma medications: latanoprostene bunod, netarsudil, and fixed combination netarsudil-latanoprost*. Eye (Lond), 2020. **34**(1), 72-88. doi:10.1038/s41433-019-0671-0

4. Menard, J. *Benfluorex: analysis of a drug-related public health crisis*. Diabetes Metab, 2011. **37**(3), 169-175. doi:10.1016/j.diabet.2011.04.001

