Commentary: The genetics of pseudoexfoliation syndrome/glaucoma

Genetics forms the basis of all life and evolution. The study of genetics primarily deals with trait inheritance and gene expression. Medical genetics has revolutionized the understanding of health and disease and opened several new prospects in prevention, diagnostics, and therapy. Genetic determinants of several ocular diseases are now well elucidated, with work in progress in many others.

Ocular pseudoexfoliation (PXF) results from the accumulation of abnormal fibrillar aggregates in the anterior segment of the eye, blocking the trabecular meshwork and leading to glaucoma. These fibrils consist of elastic fiber components of elastin, fibrillin-1, fibulins, latent TGF-ß binding proteins, and the crosslinking enzyme lysyl oxidase-like 1 (*LOXL1*), produced by the epithelial cells in the anterior segment (lens epithelial cells, ciliary epithelial cells, and trabecular meshwork cells).[1] The *LOXL1* locus on chromosome 15q24.1 has shown the most significant genetic association in PXF glaucoma, similar to the current study's findings.[2,3] *LOXL1* encodes a member of the lysyl oxidase (LOX) family of enzymes (LOX and LOXL1-4) required for lysine-derived covalent crosslinking in collagen and elastin, contributing to the tensile strength and elasticity of connective tissues. The LOXL1 isoform catalyzes the crosslinking of soluble tropoelastin into insoluble elastin in elastic fibers. Two common nonsynonymous protein-coding variants in exon 1 of the *LOXL1* gene, rs1048661 (p.R141L) and rs3825942 (p.G153D), have consistently been associated with PXF in numerous population-based and well-powered

genome-wide association studies (GWASs).[3] However, the phenomenon of allele reversal of these two variants in different ethnic populations reflects our ignorance of the exact biological mechanism underlying PXF and the need for further work in elucidating it.[4] Studies in transgenic mice models showed an inverse relationship between *LOXL1* expression and intraocular pressure (IOP), with increased IOP in Loxl1$^{-/-}$ mice from elevated episcleral venous pressure.[5] *LOXL1* animal models have been unsuccessful in duplicating the PXF phenomenon seen in humans, indicating additional unknown mechanisms.

A deep resequencing approach has identified a single common variant (minor allele G of the intergenic sequence variant rs7173049: A>G) downstream of *LOXL1* that downregulates two genes affecting vitamin A metabolism in ocular tissues in PXF patients. This allele did not show any reversal in different populations and suggested potential therapeutic targets.[6] The GWAS method identified another polymorphism outside of LOXL1, at 19p13, rs4926244, in the intronic region of *CACNA1A*, affecting calcium metabolism.[7] Another locus at 13q12 (proteasome maturation protein, *POMP*) showed increased strength of genetic association with increasing distance from the equator, consistent with the observed prevalence of ocular PXF, indicative of gene-environment interaction.[4] It is interesting to note that several other single nucleotide polymorphisms (SNPs) associated with PXF glaucoma have been identified in different ethnic groups. Multiple genetic loci identified in PXF open the prospect of developing polygenic risk scores (PRS) for PXF in the future.

The prospect of gene–environment interactions has spawned several epigenetic investigations with exciting results. These include DNA hypermethylation in the promoter of the LOXL1 gene, downregulation of HSP70 (heat shock protein 70), long non-coding RNAs such as LOXL1 antisense RNA 1 (evidence for regulatory function in immortalized lens epithelial cells), and microRNAs, particularly miR-122-5p (shown to regulate the TGF-β/Smad signaling pathway and lipoprotein metabolism).[3] MicroRNAs are involved in the epigenetic regulation of gene expression and are potential biomarkers of disease identifiable in blood and aqueous humor. Mass spectrometric proteomic analyses of various biological samples have also revealed cellular stress/inflammation, lipid metabolism, coagulation, and dietary factors (altered vitamin D and retinol-binding proteins) contributing to PEX development. Specific metabolomic profiles in plasma and aqueous humor have been identified and validated using machine-learning prediction models.[3] These analyses implicate oxidative stress in the pathophysiology of PXF. However, there is a significant knowledge gap in the exact pathomechanism of the PXF syndrome that requires well-designed and extensive functional investigations.

The vast proportion of work done in genetics in PXF comes from the developed world. Studies from India are extremely few, underlining the need to cover a lot of ground, particularly as genetics and epigenetics vary with ethnicity and region. Studies similar to this one and more extensive/multicentric investigations from different parts of India will go a long way in unraveling the specifics of PXF pathobiology among South Asians.[2] The primary challenge in conducting genetic research is the relative scarcity of geneticists/trained researchers in the developing world and funding requirements. Stalwarts in the field have called for equity in genomics.[8] The onus of responsibility lies on clinician-scientists to convince policy-makers and funding agencies for more significant funding in core research in this field.

Geeta Behera, Subashini Kaliaperumal

Department of Ophthalmology, Jawaharlal Institute of Post-Graduate Medical Education and Research (JIPMER), Puducherry, India

Correspondence to: Dr. Geeta Behera, Assistant Professor of Ophthalmology, Jawaharlal Institute of Post-Graduate Medical Education and Research (JIPMER), Puducherry - 605 006, India.
E-mail: geeta.anandaraja@gmail.com

References

1. Zenkel M, Schlötzer-Schrehardt U. The composition of exfoliation material and the cells involved in its production. J Glaucoma 2014;23(Suppl 1):S12–14
2. Vallabh NA, Sambare C, Muszynska-Lyons D, Patiyal S, Kelkar A, Killedar M, *et al*. Prevalence of risk alleles in the lysyl oxidase-like 1 gene in pseudoexfoliation glaucoma patients in India. Indian J Ophthalmol 2022;70:2024-8.
3. Schlötzer-Schrehardt U, Khor CC. Pseudoexfoliation syndrome and glaucoma: From genes to disease mechanisms. Curr Opin Ophthalmol 2021;32:118-28.
4. Aung T, Ozaki M, Lee MC, Schlötzer-Schrehardt U, Thorleifsson G, Mizoguchi T, *et al*. Genetic association study of exfoliation syndrome identifies a protective rare variant at LOXL1 and five new susceptibility loci. Nat Genet 2017;49:993-1004.
5. Li G, Schmitt H, Johnson WM, Lee C, Navarro I, Cui J, *et al*. Integral role for lysyl oxidase-like-1 in conventional outflow tissue function and behavior. FASEB J 2020;34:10762-77.
6. Berner D, Hoja U, Zenkel M, Ross JJ, Uebe S, Paoli D, *et al*. The protective variant rs7173049 at LOXL1 locus impacts on retinoic acid signaling pathway in pseudoexfoliation syndrome. Hum Mol Gen 2019;28:2531-48.
7. Aung T, Ozaki M, Mizoguchi T, Allingham RR, Li Z, Haripriya A, *et al*. A common variant mapping to CACNA1A is associated with susceptibility to exfoliation syndrome. Nat Genet 2015;47:387-92.
8. McGuire AL, Gabriel S, Tishkoff SA, Wonkam A, Chakravarti A, Furlong EEM, *et al*. The road ahead in genetics and genomics. Nat Rev Genet 2020;21:581-96.

Access this article online

Quick Response Code:

Website: www.ijo.in

DOI: 10.4103/ijo.IJO_30_22

Cite this article as: Behera G, Kaliaperumal S. Commentary: The genetics of pseudoexfoliation syndrome/glaucoma. Indian J Ophthalmol 2022;70:2028-9.