

Content available at: <https://www.ipinnovative.com/open-access-journals>

Indian Journal of Clinical and Experimental Ophthalmology

Journal homepage: www.ijceo.org

Editorial

Genetics and epigenetics of age related macular degeneration

Rajendra P Maurya^{1*}, Surbhi Jaiswal¹, Shalini Ranjan¹

¹Regional Institute of Ophthalmology, Institute of Medical Sciences, Banaras Hindu University, Varanasi, Uttar Pradesh, India



ARTICLE INFO

Article history:

Received 15-03-2024

Accepted 22-03-2024

Available online 30-03-2024

This is an Open Access (OA) journal, and articles are distributed under the terms of the [Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License](https://creativecommons.org/licenses/by-nc-sa/4.0/), which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: reprint@ipinnovative.com

Age related macular degeneration (AMD) is a multifactorial degenerative condition that causes progressive, irreversible loss of central vision among older individuals (50 years and above). Ageing, family history, epigenetic alteration, Caucasian race, obesity, hypertension, atherosclerosis/ hyperlipidemia and tobacco smoking are common risk factors linked to AMD.¹

AMD is basically of two types (1) Non-neovascular (dry or non-exudative) AMD and (2) Neovascular (wet or exudative) AMD. Non-neovascular type AMD is characterized by presence of drusens (yellowish deposits located at the level of retinal pigment epithelium) in early stage and as geographic atrophy in the advanced stage whereas neovascular AMD is characterized by choroidal neovascularization (CNV).² Choroidal neovascularization results into disruption of blood-eye barrier leading to hemorrhage, edema and retinal detachment. The underlying pathogenesis of AMD remains unclear. It may be due to age related structural changes in Bruch's membrane, defective lipid metabolism or oxidative stress and immune mediated inflammation.

Both men and women can develop AMD, although certain studies suggest women are at a 1.3 times higher risk.³ Age and positive family history of AMD are the most significant risk factors. Twin study suggest higher concordance for AMD in monozygotic twins as compared to dizygotic twins.⁴ AMD stands out as one

of the most genetically defined complex disorders. With over 50 percent of AMD's heritability attributed to two major loci containing coding and non-coding variations on chromosome 1q25-31 (ARMD1) and 10q26 (ARMS2).⁵

The several candidate genes implicated in ARMD has been reported such as CFH (complement factor H), HTRA1 (HtrA serine peptidase-1), C2-CFB (complement component 2 and complement factor B), C3 (complement 3) and Apo-E (apolipoproteinase E) etc. These genes are involved in pathways related to immunity, inflammation, lipid metabolism, angiogenesis, DNA repair and cellular repair.⁶

Normally central lamina of elastic fibers of Bruch's membrane may acts as a barrier to vessel growth and neovascularization. This layer become thickened (due to deposition of ECM) and porous with age. Single-nucleotide polymorphisms (SNPs) in elastin gene may associated with pathogenesis of AMD. Fibulin-5 is an ECM protein responsible for maturation of elastin fibrils. It has been reported that decreased fibulin-5 production or altered interaction with proteins in Bruch's membrane may lead to AMD. Alteration in sequence of fibulin-5 gene have been detected in patients with AMD.⁷ Degradation of ECM usually occur by enzyme matrix-metalloproteinases (MMPs). Enhanced level of MMP9 have been found with aging.⁸ Guo L et. al found MMP9 polymorphism associated three-fold increased risk of having AMD.⁹

Age related macular degeneration might be result from oxidative damage of Bruch's membrane and RPE by

* Corresponding author.

E-mail address: mauryarp_bhu@yahoo.com (R. P. Maurya).

free radicals. Lipofuscin accumulated after breakdown of outer segment of photoreceptor acts as photosensitizer for oxidative free radical generation which lead to RPE damage. Superoxide dismutase (SOD) enzyme which catalyzes the oxidative reaction and generate hydrogen peroxide requires copper, zinc or manganese. Kimura K et al found strong association between polymorphism in the manganese SOD2 gene and AMD.¹⁰

Immune-mediated inflammation of retina is new concepts linked to AMD. CFH (complement factor H) inhibits multiple steps of inflammatory pathway. It bind with C-reactive protein and inhibit the CRP- mediated response to tissue damage. Edwards et al. found strong genetic link between CFH and AMD.¹¹ Several studies reported that the Y402H mutation in CFH gene and CRP-binding domain may lead to complement dysregulation in AMD.^{12,13} The initial confirmed rare variant linked to AMD was CFHR1210C (rs121913059), identified as highly penetrant variant with a higher frequency in AMD cases. This variant is also associated with an early onset of AMD, faster progression to advanced stages and a characteristic fundus phenotype, including a high burden of drusen in both macular and extra macular regions in both eyes.^{14,15} Age related maculopathy targeted sequencing (ARTS) identified new coding variants associated with advanced AMD including rare variants linked to increased AMD risk in C3(K155Q), C9(P167S), and a burden of rare coding variants in CFI.¹⁶ Following burden testing, only rare variants within the previously associated AMD genes CFH, CFI, and TIMP3 reached genome wide significance. Nevertheless, this underscored the significance of TIMP3 and CFI in AMD pathophysiology. In a recent GWAS experiment genes were found to operate not only in known AMD pathways but also underscored the significance of additional pathways, such as complement activation, collagen synthesis, lipid metabolism/cholesterol transport, receptor mediated endocytosis, endodermal cell differentiation and extra cellular matrix organization. Notably, ten variants within seven extracellular matrix genes (COL15A1, COL8A1, MMP9, PCOLCE, MMP19, CTRB1-CTRB2 and ITGA7) were associated solely with advanced AMD rather than intermediate AMD indicating activation of extracellular remodelling pathways in the progression to advanced AMD.¹⁷ In a recent study by Burgess and Davey Smith revealed an association between variants in CETP gene and AMD risk, suggesting that inhibiting CETP to elevate HDL cholesterol level might increase risk of AMD.¹⁸

STAT4 protein is a transcription factor exhibit regulatory role in pro-inflammatory signaling and promotes large vessels formation. STAT4 protein involved in pathogenesis of several inflammatory and autoimmune diseases like rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) and systemic sclerosis etc. Blekeris T et al.

investigated the association between STAT4 gene polymorphisms (rs10181656, rs7574865, rs7601754 and rs10168266) and AMD. Although they found no significant association but lower overall serum STAT4 levels were seen in exudative AMD patients as compared to the control.¹⁹

For neovascular ARMD intra vitreal Anti VEGF is an effective form of treatment. Other treatment options include Photodynamic therapy and focal laser photocoagulation.²⁰

E10030 (Fovista) is an anti-PDGF aptamer. It works by binding to platelet derived growth factor, leading to loss of pericytes from endothelial basement membranes. This makes the neovascular membrane more susceptible to anti-VEGF treatment. Genetic factors influence the response of anti VEGF in AMD. Actually SNPs in genes encoding VEGF pathway members contribute to response of chemotherapy. New AMD treatments under development focus on innovative drug delivery methods and novel molecules to reduce treatment frequency and burden.²¹ Recently successful trial of gene therapy in age related macular degeneration has been done.²²

References

1. Wong WL, Su X, Li X, Cheung CMG, Klein R, Cheng CY, et al. Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040: a systematic review and meta-analysis. *Lancet Glob Health*. 2014;2(2):106–16.
2. Ferris FL, Fine SL, Hyman L. Age-related macular degeneration and blindness due to neovascular maculopathy. *Arch Ophthalmol*. 1984;102(11):1640–2.
3. Rudnicka AR, Kapetanakis VV, Jarrar Z, Wathern AK, Wormald R, and AEF. Incidence of Late-Stage Age-Related Macular Degeneration in American Whites: Systematic Review and Meta-analysis. *Am J Ophthalmol*. 2015;160(1):85–93.
4. Hammond CJ, Webster AR, Snieder H, Bird AC, Gilbert CE, Spector TD, et al. Genetic influence on early age-related maculopathy: a twin study. *Ophthalmology*. 2002;109(4):730–6.
5. Fritsche LG, Igl W, Bailey JNC, Grassmann F, Sengupta S, Bragg-Gresham JL, et al. A large genome-wide association study of age-related macular degeneration highlights contributions of rare and common variants. *Nat Genet*. 2016;48(2):134–43.
6. Yu Y, Wagner EK, Souied EH, Seitsonen S, Immonen IJ, Häppölä P, et al. Protective coding variants in CFH and PELI3 and a variant near CTRB1 are associated with age-related macular degeneration. *Hum Mol Genet*. 2016;25(23):5276–85.
7. Stone EM, Braun TA, Russell SR, Kuehn MH, Lotery AJ, Moore PA, et al. Missense variations in the fibulin-5 gene and age related macular degeneration. *N Engl J Med*. 2004;351(4):346–53.
8. Guo L, Hussain AA, Limb GA, Marshall J. Age-dependent variation in metalloproteinases activity of isolated human Bruch's membrane and choroid. *Invest Ophthalmol Vis Sci*. 1999;40(11):2676–82.
9. Fiotti N, Pedio M, Battaglia PM, Parodi MB, Altamura N, Uxa L, et al. MMP-9 microsatellite polymorphism and susceptibility to exudative form of age-related macular degeneration. *Genet Med*. 2005;7(4):272–7.
10. Kimura K, Isashiki Y, Sonoda S, Kakiuchi-Matsumoto T, Ohba N. Genetic association of manganese superoxide dismutase with exudative age related macular degeneration. *Am J Ophthalmol*. 2000;130(6):769–73.
11. Edwards AO, Ritter R, Abel KJ, Manning A, Panhuysen C, Farrer LA. Complement factor H polymorphism and age-related macular degeneration. *Science*. 2005;308(5720):421–4.

12. Souied EH, Leveziel N, Richard F, Dragon-Durey MA, Coscas G, Soubrane G, et al. Y402H complement factor H polymorphism associated with exudative age-related macular degeneration in the French population. *Mol Vis.* 2005;11:1135–40.
13. Zareparsa S, Branham KEH, Li M, Shah S, Klein RJ, Ott J, et al. Strong association of the Y402H variant in complement factor H at 1q32 with susceptibility to age-related macular degeneration. *Am J Hum Genet.* 2005;77(1):149–53.
14. Raychaudhuri S, Iartchouk O, Chin K, Tan PL, Tai AK, Ripke S, et al. A rare penetrant mutation in CFH confers high risk of age-related macular degeneration. *Nat Genet.* 2011;43(12):1232–6.
15. Seddon JM, Wijdjajahakim R, Rosner B. Rare and common genetic variants, smoking, and body mass index: progression and earlier age of developing advanced age-related macular degeneration. *Invest Ophthalmol Vis Sci.* 2020;61(14):3. doi:10.1167/iovs.61.14.32.
16. Seddon JM, Yu Y, Miller EC, Reynolds R, Tan PL, Gowrisankar S, et al. Rare variants in CFI, C3 and C9 are associated with high risk of advanced age-related macular degeneration. *Nat Genet.* 2013;45(11):1366–70.
17. Fritsche LG, Igl W, Bailey JNC, Grassmann F, Sengupta S, Bragg-Gresham JL, et al. A large genome-wide association study of age-related macular degeneration highlights contributions of rare and common variants. *Nat Genet.* 2016;48(2):134–13.
18. Burgess S, Smith GD. Mendelian randomization implicates high-density lipoprotein cholesterol-associated mechanisms in etiology of age-related macular degeneration. *Ophthalmology.* 2017;124(8):1165–74.
19. Blekeris T, Gedvilaite G, Kaikaryte K, Kriauciuniene L, Zaliuniene D, Liutkeviciene R, et al. Association of STAT4 Gene Polymorphisms (rs10181656, rs7574865, rs7601754, rs10168266) and Serum STAT4 Levels in Age-Related Macular Degeneration. *Biomedicine.* 2023;12(1):18.
20. Stahl A. The diagnosis and treatment of age-related macular degeneration. *Dtsch Arztebl Int.* 2020;117(29-30):513–20.
21. Yonekawa Y, Miller JW, Kim IK. Age-Related Macular Degeneration: Advances in Management and Diagnosis. *J Clin Med.* 2015;12(2):343–59.
22. Maurya RP, Gupta S. Gene therapy in age-related macular degeneration. *Indian J Clin Experi Ophthalmol.* 2023;9:1–2.

Author biography



Rajendra P Maurya, Editor in Chief IJCEO, Associate Professor & I/c Orbit, Ocular Oncology and Oculoplasty Unit Regional Institute of Ophthalmology, Institute of Medical Sciences, Banaras Hindu University, Varanasi, (UP), India
E-mail: editorijceo@gmail.com, mauryarp_bhu@yahoo.com
 <https://orcid.org/0000-0001-9343-6003>

Surbhi Jaiswal, Junior Resident

Shalini Ranjan, Junior Resident

Cite this article: Maurya RP, Jaiswal S, Ranjan S. Genetics and epigenetics of age related macular degeneration. *Indian J Clin Exp Ophthalmol* 2024;10(1):1-3.