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Linking *VEGFA* and *CRP* genetic variants to serum proteins and age-related macular degeneration

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Purpose: Age-related macular degeneration (AMD) is a multifactorial retinal disease in which both angiogenesis and inflammation play pivotal roles. The current study investigated the association of vascular endothelial growth factor A (*VEGFA*) and C-reactive protein (*CRP*) gene polymorphisms along with their serum levels in North Indian patients with AMD.

Methods: A case-control study with 160 patients with AMD and 100 controls was conducted. AMD was confirmed by clinical evaluation and imaging. DNA was genotyped using polymerase chain reaction and Sanger sequencing, and serum VEGF-A and CRP levels were measured by enzyme-linked immunosorbent assay. Data were analyzed using SPSS v22.0.

Results: The rs3025039 T allele was more frequent in AMD cases. Under the dominant model (CT+TT versus CC), it was associated with increased AMD risk (adjusted odds ratio [OR] = 2.07, $p = 0.013$). A similar association was observed under the log-additive model (adjusted OR = 1.91, $p = 0.0098$), although only the latter remained significant after Bonferroni correction. The association was stronger for wet AMD, where the codominant comparison (TT versus CC) showed increased risk (adjusted OR = 5.08, $p = 0.028$), but this did not remain significant after correction. No significant associations were detected for rs699947, rs1205, or rs1130864 ($p \geq 0.05$). Adjusted VEGF-A levels were higher in AMD and increased from controls to dry to wet AMD ($p < 0.05$). Within AMD, rs3025039 TT carriers had the highest VEGF-A levels. CRP levels were also elevated in AMD and its subtypes ($p < 0.001$) but did not differ between dry and wet AMD. The rs1205 AA genotype was associated with lower CRP levels without affecting AMD risk.

Conclusions: In North Indians, VEGFA rs3025039 and higher VEGF-A strongly relate to AMD, especially wet disease, whereas common CRP variants mainly modulate CRP levels without an appreciable impact on susceptibility.

Age-related macular degeneration (AMD) is a complex, progressive ocular condition that is influenced by both genetic and environmental factors. Still, its etiology is not fully understood despite extensive research [1]. Global estimates suggest that AMD affects around 8.7% to 12.3% of individuals over midlife, with marked variation in prevalence across populations and a particularly high burden in Europeans [2,3]. Notably, the age-standardized prevalence of AMD in a multiethnic Asian cohort revealed different frequencies across Chinese (7.3%), Indian (5.7%), and Malay (7.7%) populations [4,5].

AMD is a multifactorial disorder driven by genetic susceptibility, aging, and environmental risk factors such as smoking and high body mass index [6]. Several risk variants, particularly in genes involved in inflammation, immune regulation, and angiogenesis, have been identified by genome-wide association studies so far [7–9]. Chronic low-grade inflammation and angiogenesis are critical factors in the pathophysiology of AMD. Proinflammatory cytokines, acute-phase proteins, and angiogenic growth factors also contribute to drusen formation, complement activation, and pathologic neovascularization beneath the retina [10]. Among these mediators, vascular endothelial growth factor A (VEGF-A) is central to choroidal neovascularization, the hallmark of neovascular (wet) AMD and the primary target of intravitreal anti-VEGF therapies. The *VEGFA* gene is located on chromosome 6p21.1 and contains several common polymorphisms. These variants can modulate gene expression and circulating VEGF-A levels, potentially influencing angiogenesis-related diseases [6,11–13].

Two of the most widely studied *VEGFA* variants are rs699947 (−2578C>A) in the promoter region and rs3025039 (+936C>T) in the 3′ untranslated region (3′UTR), which may influence transcriptional activity and posttranscriptional regulation, respectively [14]. These polymorphisms have been

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associated with altered VEGF-A expression or circulating levels and with susceptibility to several angiogenesis-related conditions, including cardiovascular disease, cancers, and diabetic retinopathy [14–16].

C-reactive protein (CRP) is an acute-phase reactant synthesized primarily by hepatocytes in response to interleukin-6 and is a well-recognized biomarker of systemic inflammation. In addition to its diagnostic utility, CRP has been observed to accumulate in Bruch's membrane and drusen of patients with AMD, indicating a possible pathogenic role in retinal degeneration [17,18]. The *CRP* gene, located on chromosome 1q23.2, exhibits significant interindividual variability in expression, with approximately 35% to 40% of this variability ascribed to genetic factors [19,20].

Among the most extensively investigated *CRP* variants are *rs1205* in the 3′UTR and rs1130864 in the 3′ flanking region. These variants have been associated with altered CRP levels and systemic inflammatory responses [19–21]. Elevated circulating CRP has been implicated in AMD risk and progression [18,22], as well as in the pathogenesis of several chronic inflammatory disorders, including cardiovascular disease, type 2 diabetes, rheumatoid arthritis, and autoimmune conditions [23–25].

Converging data therefore support a central role for both inflammatory and angiogenic pathways in AMD. Chronic inflammation contributes to disease progression, while angiogenesis plays a central role in neovascular complications. Inflammatory mediators such as interleukin-6 regulate hepatic CRP production [26,27], making CRP a reliable marker of systemic inflammation [22]. In contrast, VEGF-A is a key mediator of angiogenesis and is directly implicated in choroidal neovascularization [12]. Given their distinct yet biologically relevant roles, CRP and VEGF-A were selected as representative markers of inflammatory and angiogenic processes, respectively. Investigating these factors in parallel may provide broader insight into the multifactorial mechanisms underlying AMD.

Despite extensive research on angiogenic and inflammatory pathways in AMD, studies integrating *VEGFA* and *CRP* genetic variants with corresponding serum protein levels in Indian populations remain limited. Therefore, this case-control study was designed to evaluate the association of *VEGFA* (rs3025039, rs699947) and *CRP* (rs1205, rs1130864) polymorphisms with AMD risk in a North Indian cohort. It also examines the relationship between these variants and circulating VEGF-A and CRP levels. By assessing both genotype–disease and genotype–phenotype associations, this study aims to clarify the role of angiogenic and inflammatory genetic factors in AMD pathogenesis in this population.

METHODOLOGY

Participant selection and recruitment: The research protocol received ethical clearance from the Institutional Human Ethical Committee (HEC/2021/290) of Maharshi Dayanand University, Rohtak, Haryana, India. All procedures adhered to the principles outlined in the Declaration of Helsinki and conformed to the International Council for Harmonisation guidelines on Good Clinical Practice.

A total of 260 participants were enrolled in this case-control study. This included 160 patients diagnosed with AMD from the Retina Clinic at the Regional Institute of Ophthalmology, Pt. B.D. Sharma Post Graduate Institute of Medical Sciences, Rohtak, Haryana, and 100 unrelated healthy control individuals recruited from the general population during community outreach programs and health camps. All participants were aged ≥50 years at the time of recruitment and provided written informed consent before inclusion in the study. No financial or material compensation was provided to participants.

AMD cases were identified based on a confirmed clinical diagnosis established through a comprehensive ophthalmologic evaluation. Control participants were included only if no evidence of AMD or other ocular pathology was detected upon examination.

Participants were excluded if they had high refractive errors, significant media opacities, or a history of intraocular lens implantation. Additional exclusion criteria included the presence of keratitis, acute or chronic uveitis, glaucoma, optic nerve disorders, or other ocular or systemic conditions known to affect retinal health. Patients with systemic inflammatory diseases or diabetes mellitus were specifically excluded due to their potential influence on serum levels and the risk of confounding the study outcomes.

Ophthalmologic evaluation: All enrolled participants underwent a detailed ophthalmologic evaluation. Corneal and lenticular clarity were assessed using slit-lamp biomicroscopy. Pupillary dilation was achieved using 1% tropicamide to facilitate fundus examination by direct monocular ophthalmoscopy and slit-lamp biomicroscopy with a +78 diopter double aspheric lens. Participants with clinical features suggestive of AMD were further evaluated using optical coherence tomography to assess drusen characteristics, retinal pigment epithelium alterations, and the presence of intra- or subretinal fluid. For accurate classification of AMD subtypes, individuals with suspected neovascular disease additionally underwent fundus fluorescein angiography and indocyanine green angiography. Neovascular AMD was diagnosed based on angiographic evidence of choroidal neovascularization and

associated leakage, whereas dry AMD was defined by the presence of drusen and retinal pigment epithelium changes in the absence of angiographic leakage.

Selection of single-nucleotide polymorphisms: The single-nucleotide polymorphisms (SNPs) analyzed in this study were selected based on prior reports across diverse ethnic populations demonstrating their association with inflammatory and angiogenesis-related disorders [26,27]. *VEGFA* (rs699947, rs3025039) and *CRP* (rs1205, rs1130864) polymorphisms were selected due to their previously reported relevance to circulating protein levels and disease susceptibility [13,14,28–33].

Sample collection: Approximately 5 ml of venous blood was obtained from each participant and distributed into two sterile vacutainers. EDTA vacutainers were used for the sample taken for DNA extraction, while the plain vacutainers (lacking anticoagulants) were used for serum preparation.

DNA extraction and genotyping: Genomic DNA was extracted using the phenol–chloroform–isoamyl alcohol technique [34]. For genotyping of the selected *CRP* and *VEGFA* SNPs, DNA samples were used to perform polymerase chain reaction (PCR) in a thermal cycler (S1000; BioRad, Hercules, CA). PCR was conducted for *VEGFA* SNPs using previously established primers [35,36] and for CRP SNPs employing previously reported primers [37] in all instances, including controls. Purified PCR products were outsourced for DNA sequencing to Barcode Biosciences Pvt. Ltd. (Bangalore, India), and all samples were successfully genotyped, with high call rates and negligible missing data. Quality control was further ensured by randomly selecting 5% of the samples for re-genotyping, which showed 100% concordance with the initial results.

Serum separation and measurement of serum protein levels: Blood samples were processed within 1 to 2 h of collection, and serum was separated by centrifugation and stored at −80 °C until analysis. Concentration of serum VEGF-A and CRP was quantified in serum samples using the Human VEGF-A ELISA Kit (cat. *ELH-VEGFA*; RayBio, Norcross, GA) and the Human CRP ELISA Kit (cat. *ELH-CRP*; RayBio), respectively, in accordance with the manufacturer's instructions. Absorbance readings were taken at 450 nm using the SPECTRAmax 384plus enzyme-linked immunosorbent assay microplate reader (Molecular Devices, San Jose, CA).

Samples were thawed only once to avoid degradation. All enzyme-linked immunosorbent assay measurements were performed in a blinded manner by laboratory personnel unaware of participant group (control or AMD) and SNP genotype to ensure unbiased assessment of serum levels; assays were conducted in duplicate according to the manufacturer's instructions, with samples randomized across plates to minimize batch effects. Serum VEGF-A and CRP levels were measured in pg/ml as per the assay kit guidelines, and values are reported accordingly.

Statistical analysis: Data analysis was performed using IBM SPSS Statistics version 22.0 (SPSS, Inc., Chicago, IL). Genotype distributions for each polymorphism were tested for conformity with Hardy–Weinberg equilibrium (HWE) in both control and AMD groups using the chi-square (χ^2) goodness-of-fit test, with $p > 0.05$ considered indicative of equilibrium. Differences in genotype and allele frequencies between patients with AMD and controls were evaluated using the χ^2 test. Fisher's exact test was additionally applied where expected cell counts were small.

The association between *VEGFA* and *CRP* polymorphisms and AMD risk was primarily assessed using binary logistic regression under the log-additive model. Additional inheritance models (codominant, dominant, recessive, and overdominant) were evaluated as secondary analyses. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated in both crude analyses and multivariate models adjusted for age, smoking status, and sex as potential confounders.

To account for multiple testing across the four SNPs analyzed, Bonferroni correction was applied with a corrected significance threshold of $p < 0.0125$ (0.05/4), as four independent SNPs were evaluated [38]. The p values reported for genetic models correspond to overall model-level significance unless otherwise specified, while ORs and CIs represent coefficient-level estimates for individual genotype comparisons.

To address potential bias due to small sample sizes and rare genotype frequencies, Firth logistic regression analysis was also performed using R software (version 4.3.2; R Project for Statistical Computing, Vienna, Austria), and the results are presented as Appendix 1.

A post hoc power analysis for the *VEGFA* rs3025039 polymorphism was conducted using OpenEpi (Power for Unmatched Case-Control Studies), based on observed allele frequencies and effect size, to determine the adequacy of statistical power to detect the identified association [39].

Serum VEGF-A and CRP concentrations were expressed as mean ± standard deviation. Groupwise comparisons were initially performed using unadjusted analyses, followed by analysis of covariance (ANCOVA) to adjust for potential confounders. Bonferroni correction was applied for multiple comparisons in serum analyses. All statistical tests were two-tailed, and $p < 0.05$ was considered statistically significant.

Table 1. Baseline demographic and clinical characteristics of study participants.

Variable	AMD Patients (n=160)	Controls (n=100)	Odds ratio (95% CI); p value
		Age (years)	
50–59	9	45	1.00
60–69	71	22	**16.13 (6.82 - 38.16); <0.0001**
70–79	62	19	**16.31 (6.76 - 39.38); <0.0001**
≥80	18	14	**6.43 (2.36 - 17.47); 0.0003**
		Gender	
Men	106	64	1.00
Women	54	36	0.91 (0.54 - 1.53); 0.71
		Smoking status	
Non-smoker	87	71	1.00
Smoker	73	29	**2.05 (1.21 - 3.49); 0.008**
		Alcohol consumption	
Non-drinkers	103	67	1.00
Drinkers	57	33	1.12 (0.66 - 1.9); 0.66

RESULTS

This study included two groups: a patient cohort of 160 individuals, comprising 106 males (66.25%) and 54 females (33.75%), with a median age of 69.5 years, and a control group of 100 participants, comprising 64 males and 36 females, with a median age of 60 years. Among patients with AMD, 110 had wet AMD and 50 had dry AMD. Baseline characteristics are summarized in Table 1. Patients with AMD were significantly older than controls, with higher odds observed in the 60 to 69, 70 to 79, and ≥80 years age groups ($p < 0.001$). Smoking was also significantly associated with AMD (OR = 2.05; 95% CI, 1.21–3.49; $p = 0.008$). No significant associations were observed for sex or alcohol consumption.

Hardy–Weinberg equilibrium analysis: All the investigated polymorphisms were tested for conformity with HWE in both control and patient groups (Appendix 2). The distribution of genotypes for *VEGFA* (rs3025039, rs699947) and *CRP* (rs1205, rs1130864) did not show significant deviation from HWE ($p > 0.05$) in either group.

Genotype and allele distributions: The genotype and allele frequencies of *VEGFA* and *CRP* polymorphisms were compared between controls and patients with AMD (Table 2 and Appendix 2). A significant difference in genotype distribution was observed for *VEGFA* rs3025039 between the two groups ($\chi^2 = 8.09$, $p = 0.02$). At the allele level, the minor T allele was significantly more frequent in patients with AMD compared with controls (0.23 versus 0.13; $\chi^2 = 9.01$, $p = 0.002$), suggesting an association with increased AMD susceptibility. No significant differences were observed for *VEGFA* rs699947. Similarly, *CRP* polymorphisms rs1205 and rs1130864 did not show significant differences in genotype or allele distributions between patients with AMD and controls.

Logistic regression analysis: To further evaluate the association of *VEGFA* and *CRP* polymorphisms with AMD risk, logistic regression analysis was performed under multiple inheritance models, both crude and adjusted for age and smoking (Table 3).

For the *VEGFA* rs3025039 (C>T) polymorphism, genotype distributions differed between patients with AMD and controls. In the crude codominant model, individuals with the CT genotype showed increased odds of AMD compared to the CC genotype (OR = 1.87; 95% CI, 1.04–3.38), while TT homozygotes exhibited a higher but imprecise risk estimate (OR = 4.71; 95% CI, 1.02–21.69; overall $p = 0.013$). Under the dominant model, carriers of the T allele (CT+TT) had an approximately twofold increased risk of AMD (OR = 2.12; 95% CI, 1.21–3.72; $p = 0.0076$). The recessive model suggested increased risk (OR = 3.97; 95% CI, 0.87–18.14; $p = 0.041$), although this did not reach statistical significance, likely due to the small number of TT individuals. The overdominant model showed a nonsignificant trend (OR = 1.71; 95% CI, 0.95–3.07; $p = 0.068$).

In the primary log-additive model, each additional T allele was associated with increased AMD risk (OR = 1.98; 95% CI, 1.22–3.20; $p = 0.0034$).

After adjustment for age and smoking, the association remained consistent. In the adjusted codominant model, the CT showed elevated risk compared to CC (adjusted OR = 1.89; 95% CI, 1.02–3.54; $p = 0.03$). Under the dominant model, T allele carriers continued to show increased risk (adjusted OR

Table 2. Genotype and allele distributions of *VEGFA* and *CRP* polymorphisms in controls and AMD patients.

SNP	Genotype	Control (n=100)		AMD patients (n=160)		chi-square statistic	p-value
		Count	Proportion	Count	Proportion		
				VEGFA			
	CC	77	0.77	98	0.61		
	CT	21	0.21	50	0.31	8.09	**0.02**
rs3025039	TT	2	0.02	12	0.08		
	C	175	0.87	246	0.77	9.01	**0.002**
	T	25	0.13	74	0.23		
	CC	45	0.45	60	0.38		
	CA	43	0.43	77	0.48	1.47	0.48
rs699947	AA	12	0.12	23	0.14		
	C	133	0.67	197	0.62	1.29	0.26
	A	67	0.33	123	0.38		
				CRP			
	GG	47	0.47	68	0.43		
	GA	40	0.4	79	0.49	2.93	0.23
rs1205	AA	13	0.13	13	0.08		
	G	134	0.67	215	0.67	0.002	0.96
	A	66	0.33	105	0.33		
	CC	53	0.52	93	0.59		
	CT	35	0.35	53	0.33	1.001	0.61
rs1130864	TT	12	0.13	14	0.08		
	C	141	0.7	239	0.74	1.09	0.29
	T	59	0.3	81	0.26		

AMD: Age-related macular degeneration; SNP: Single nucleotide polymorphism; Significant values (p<0.05) are shown in bold. Fisher's exact test for *VEGFA rs3025039* showed a significant association p=0.0098.

= 2.07; 95% CI, 1.14–3.78; p = 0.013). The adjusted recessive and overdominant models were not statistically significant (recessive: OR = 3.23; 95% CI, 0.67–15.52; p = 0.10; overdominant: OR = 1.75; 95% CI, 0.94–3.28; p = 0.074). However, these associations did not remain significant after Bonferroni correction.

In the adjusted log-additive model, defined as the primary analysis, each additional T allele was associated with increased risk of AMD (adjusted OR = 1.91; 95% CI, 1.14–3.20; p = 0.0098), and this association remained significant after Bonferroni correction ($p < 0.0125$), indicating a robust association.

In contrast, *VEGFA* rs699947 did not reach statistical significance under any inheritance model in either crude or adjusted analyses. For *CRP* variants (rs1205 and rs1130864), regression analyses revealed no significant association with AMD across any genetic model.

Power analysis for rs3025039 (T allele): Based on the observed allele frequencies and an estimated OR of ~2.0, the post hoc power was 82.8% (79.5% with continuity correction) at the 95% confidence level, confirming adequate statistical power to detect the observed association.

Association with dry AMD: Subgroup analysis restricted to patients with dry AMD revealed no statistically significant associations for *VEGFA* or *CRP* polymorphisms under any genetic inheritance model in either crude or adjusted analyses (Table 4). These findings indicate that *VEGFA* genetic variation does not significantly influence susceptibility to the dry form of AMD in this cohort.

Association with wet AMD: In contrast to dry AMD, subgroup analysis of patients with wet AMD demonstrated a strong and

Table 3. Logistic regression analysis of *VEGFA* and *CRP* SNPs in control and AMD patient group. Crude analysis Multivariate analysis adjusted for age, smoking and gender.

				Crude analysis				Multivariate analysis adjusted for age, smoking and gender			
Model	**Genotype**	**Control**	**AMD patients**	**OR (95% CI)**	**p-value**	**AIC**	**BIC**	**OR (95% CI)**	**p-value**	**AIC**	**BIC**
				VEGFA (rs3025039)							
Codominant	CC CT TT	77 (77%) 21 (21%) 2 (2%)	98 (61.2%) 50 (31.2%) 12 (7.5%)	1.00 1.87 (1.04-3.38) 4.71 (1.02-21.69)	**0.013**	343.8	354.5	1.00 1.89 (1.02-3.54) 3.83 (0.79-18.56)	**0.03**	316.7	334.5
Dominant	CC CT-TT	77 (77%) 23 (23%)	98 (61.2%) 62 (38.8%)	1.00 2.12 (1.21-3.72)	**0.0076**	343.3	350.5	1.00 2.07 (1.14-3.78)	**0.013**	315.5	329.4
Recessive	CC-CT TT	98 (98%) 2 (2%)	148 (92.5%) 12 (7.5%)	1.00 3.97 (0.87-18.14)	0.041	346.3	353.4	1.00 3.23 (0.67-15.52)	0.1	318.7	332.9
Overdominant	CC-TT CT	79 (79%) 21 (21%)	110 (68.8%) 50 (31.2%)	1.00 1.71 (0.95-3.07)	0.068	347.1	354.3	1.00 1.75 (0.94-3.28)	0.074	318.2	332.2
Log-additive	---	---	---	1.98 (1.22-3.20)	**0.0034**	341.9	349	1.91 (1.14-3.20)	**0.0098**	314.7	328.7
				VEGFA (rs699947)							
Codominant	CC CA AA	45 (45%) 43 (43%) 12 (12%)	60 (37.5%) 77 (48.1%) 23 (14.4%)	1.00 1.34 (0.78-2.30) 1.44 (0.65-3.19)	0.48	351	361.7	1.00 1.72 (0.95-3.09) 1.56 (0.66-3.67)	0.18	321.9	343.2
Dominant	CC CA-AA	45 (45%) 55 (55%)	60 (37.5%) 100 (62.5%)	1.00 1.36 (0.82-2.27)	0.23	349	356.2	1.00 1.68 (0.96-2.92)	0.065	319.9	337.7
Recessive	CC-CA AA	88 (88%) 12 (12%)	137 (85.6%) 23 (14.4%)	1.00 1.23 (0.58-2.60)	0.58	350.2	357.3	1.00 1.17 (0.53-2.61)	0.69	323.2	341
Overdominant	CC-AA CA	57 (57%) 43 (43%)	83 (51.9%) 77 (48.1%)	1.00 1.23 (0.74-2.03)	0.42	349.8	356.9	1.00 1.54 (0.89-2.66)	0.12	320.9	338.7
Log-additive	---	---	---	1.24 (0.86-1.79)	0.25	349.2	356.3	1.37 (0.91-2.05)	0.13	321	338.8
				CRP (rs1205)							
Codominant	GG GA AA	47 (47%) 40 (40%) 13 (13%)	68 (42.5%) 79 (49.4%) 13 (8.1%)	1.00 1.37 (0.80-2.32) 0.69 (0.29-1.62)	0.23	349.6	360.2	1.00 1.23 (0.69-2.17) 0.68 (0.27-1.69)	0.42	323.6	345
Dominant	GG GA-AA	47 (47%) 53 (53%)	68 (42.5%) 92 (57.5%)	1.00 1.20 (0.73-1.98)	0.48	350	357.1	1.00 1.10 (0.64-1.88)	0.74	323.2	341
Recessive	GG-GA AA	87 (87%) 13 (13%)	147 (91.9%) 13 (8.1%)	1.00 0.59 (0.26-1.33)	0.21	348.9	356	1.00 0.61 (0.26-1.46)	0.27	322.1	339.9
Overdominant	GG-AA GA	60 (60%) 40 (40%)	81 (50.6%) 79 (49.4%)	1.00 1.46 (0.88-2.43)	0.14	348.3	355.4	1.00 1.32 (0.77-2.27)	0.31	322.3	340.1
Log-additive	---	---	---	0.99 (0.68-1.45)	0.96	350.5	357.6	0.95 (0.63-1.42)	0.79	323.2	341
				CRP (rs1130864)							

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				Crude analysis				Multivariate analysis adjusted for age, smoking and gender			
Model	**Genotype**	**Control**	**AMD patients**	**OR (95% CI)**	**p-value**	**AIC**	**BIC**	**OR (95% CI)**	**p-value**	**AIC**	**BIC**
Codominant	CC	53 (53%)	93 (58.1%)	1.00				1.00			
	CT	35 (35%)	53 (33.1%)	0.86 (0.50-1.49)	0.61	351.5	362.2	0.69 (0.38-1.24)	0.39	323.4	344.8
	TT	12 (12%)	14 (8.8%)	0.66 (0.29-1.54)				0.68 (0.27-1.67)			
Dominant	CC	53 (53%)	93 (58.1%)	1.00	0.42	349.8	356.9	1.00	0.17	321.4	339.2
	CT-TT	47 (47%)	67 (41.9%)	0.81 (0.49-1.34)				0.68 (0.40-1.18)			
Recessive	CC-CT	88 (88%)	146 (91.2%)	1.00	0.4	349.8	356.9	1.00	0.57	323	340.8
	TT	12 (12%)	14 (8.8%)	0.70 (0.31-1.59)				0.78 (0.32-1.86)			
Overdominant	CC-TT	65 (65%)	107 (66.9%)	1.00	0.76	350.4	357.5	1.00	0.28	322.1	340
	CT	35 (35%)	53 (33.1%)	0.92 (0.54-1.56)				0.73 (0.41-1.29)			
Log-additive	---	---	---	0.83 (0.57-1.20)	0.33	349.5	356.6	0.78 (0.52-1.15)	0.21	321.7	339.5

AIC: Akaike information criterion; AMD: Age-related macular degeneration; BIC: Bayesian information criterion; CI: Confidence interval; OR: Odds ratio; SNP: Single nucleotide polymorphism; Significant values ($p<0.05$) are shown in bold; p values indicate overall model significance.

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Table 4. Logistic regression analysis of *VEGFA* and *CRP* SNPs in control and Dry AMD patient group.

Model	Genotype	Control	Dry AMD patients	Crude analysis				Multivariate analysis adjusted for age, smoking and gender			
				OR (95% CI)	p-value	AIC	BIC	OR (95% CI)	p-value	AIC	BIC
				VEGFA (rs3025039)							
Codominant	CC	77 (77%)	32 (64%)	1.00				1.00			
	CT	21 (21%)	16 (32%)	1.83 (0.85-3.96)	0.24	194.1	203.2	2.00 (0.88-4.56)	0.2	183.6	201.7
	TT	2 (2%)	2 (4%)	2.41 (0.32-17.83)				2.52 (0.29-21.58)			
Dominant	CC	77 (77%)	32 (64%)	1.00	0.096	192.2	198.2	1.00	0.076	181.7	196.7
	CT-TT	23 (23%)	18 (36%)	1.88 (0.90-3.95)				2.05 (0.93-4.53)			
Recessive	CC-CT	98 (98%)	48 (96%)	1.00	0.49	194.5	200.5	1.00	0.5	184.4	199.4
	TT	2 (2%)	2 (4%)	2.04 (0.28-14.94)				2.08 (0.25-17.49)			
Overdominant	CC-TT	79 (79%)	34 (68%)	1.00	0.15	192.8	198.9	1.00	0.11	182.3	197.4
	CT	21 (21%)	16 (32%)	1.77 (0.82-3.80)				1.93 (0.85-4.37)			
Log-additive	---	---	---	1.73 (0.91-3.29)	0.097	192.2	198.2	1.85 (0.93-3.67)	0.08	181.8	196.8
				VEGFA (rs699947)							
Codominant	CC	45 (45%)	21 (42%)	1.00				1.00			
	CA	43 (43%)	25 (50%)	1.25 (0.61-2.55)	0.62	196	205	1.58 (0.73-3.42)	0.4	185	203.1
	AA	12 (12%)	4 (8%)	0.71 (0.21-2.48)				0.83 (0.22-3.14)			
Dominant	CC	45 (45%)	21 (42%)	1.00	0.73	194.8	200.9	1.00	0.36	184	199
	CA-AA	55 (55%)	29 (58%)	1.13 (0.57-2.24)				1.41 (0.67-2.96)			
Recessive	CC-CA	88 (88%)	46 (92%)	1.00	0.44	194.4	200.4	1.00	0.5	184.3	199.4
	AA	12 (12%)	4 (8%)	0.64 (0.19-2.09)				0.65 (0.18-2.31)			
Overdominant	CC-AA	57 (57%)	25 (50%)	1.00	0.42	194.3	200.3	1.00	0.19	183.1	198.1
	CA	43 (43%)	25 (50%)	1.33 (0.67-2.62)				1.63 (0.78-3.41)			
Log-additive	---	---	---	0.98 (0.58-1.64)	0.93	194.9	201	1.11 (0.64-1.93)	0.7	184.7	199.7
				CRP (rs1205)							
Codominant	GG	47 (47%)	23 (46%)	1.00				1.00			
	GA	40 (40%)	23 (46%)	1.17 (0.57-2.40)	0.59	195.9	204.9	1.07 (0.50-2.29)	0.78	186.3	204.4
	AA	13 (13%)	4 (8%)	0.63 (0.18-2.14)				0.68 (0.18-2.49)			
Dominant	GG	47 (47%)	23 (46%)	1.00	0.91	194.9	201	1.00	0.95	184.8	199.9
	GA-AA	53 (53%)	27 (54%)	1.04 (0.53-2.06)				0.98 (0.47-2.03)			
Recessive	GG-GA	87 (87%)	46 (92%)	1.00	0.35	194.1	200.1	1.00	0.5	184.3	199.4
	AA	13 (13%)	4 (8%)	0.58 (0.18-1.89)				0.65 (0.19-2.28)			
Overdominant	GG-AA	60 (60%)	27 (54%)	1.00	0.48	194.5	200.5	1.00	0.72	184.7	199.7
	GA	40 (40%)	23 (46%)	1.28 (0.64-2.54)				1. 14 (0.55-2.38)			
Log-additive	---	---	---	0.92 (0.55-1.52)	0.73	194.8	200.9	0.91 (0.52-1.57)	0.72	184.7	199.7
				CRP (rs1130864)							

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Model	Genotype	Control	Dry AMD patients	Crude analysis				Multivariate analysis adjusted for age, smoking and gender			
				OR (95% CI)	p-value	AIC	BIC	OR (95% CI)	p-value	AIC	BIC
Codominant	CC	53 (53%)	30 (60%)	1.00				1.00			
	CT	35 (35%)	15 (30%)	0.76 (0.36-1.61)	0.72	196.3	205.3	0.71 (0.32-1.59)	0.69	186.1	204.1
	TT	12 (12%)	5 (10%)	0.74 (0.24-2.29)				0.78 (0.23-2.59)			
Dominant	CC	53 (53%)	30 (60%)	1.00	0.42	194.3	200.3	1.00	0.39	184.1	199.1
	CT-TT	47 (47%)	20 (40%)	0.75 (0.38-1.50)				0.73 (0.35-1.52)			
Recessive	CC-CT	88 (88%)	45 (90%)	1.00	0.71	194.8	200.8	1.00	0.84	184.8	199.8
	TT	12 (12%)	5 (10%)	0.81 (0.27-2.46)				0.88 (0.28-2.83)			
Overdominant	CC-TT	65 (65%)	35 (70%)	1.00	0.54	194.6	200.6	1.00	0.45	184.2	199.3
	CT	35 (35%)	15 (30%)	0.80 (0.38-1.65)				0.74 (0.34-1.62)			
Log-additive	---	---	---	0.82 (0.50-1.36)	0.45	194.4	200.4	0.82 (0.48-1.41)	0.47	184.3	199.4

AIC: Akaike information criterion; AMD: Age-related macular degeneration; BIC: Bayesian information criterion; CI: Confidence interval; OR: Odds ratio; SNP: Single nucleotide polymorphism; Significant values ($p<0.05$) are shown in bold; p values indicate overall model significance.

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consistent association with *VEGFA* rs3025039, suggesting a subtype-specific genetic effect (Table 5). In the codominant model, TT homozygotes showed a significantly increased risk of wet AMD compared with CC carriers in both crude (OR = 5.83; 95% CI, 1.23–27.58; p = 0.0096) and adjusted analyses (OR = 5.08; 95% CI, 1.02–25.35; p = 0.028). The dominant model also revealed a significant association in crude (OR = 2.23; 95% CI, 1.22–4.07; p = 0.0079) and adjusted analyses (OR = 2.15; 95% CI, 1.13–4.10; p = 0.018). However, the associations observed under the codominant and dominant models did not retain statistical significance after Bonferroni correction. Additionally, the recessive model indicated an elevated risk in crude analysis (OR = 4.90; 95% CI, 1.05–22.94; p = 0.02), although significance was attenuated after adjustment. The log-additive model further confirmed an increased risk per T allele in both crude (OR = 2.09; 95% CI, 1.27–3.46; p = 0.0027) and adjusted analyses (OR = 2.01; 95% CI, 1.17–3.44; p = 0.0082), and this association remained statistically significant after Bonferroni correction (p < 0.0125). No significant associations were detected for *VEGFA* rs699947 or *CRP* polymorphisms rs1205 and rs1130864 in the wet AMD subgroup.

Overall, these findings highlight distinct genetic patterns across AMD subtypes, with *VEGFA rs3025039* showing a significant association predominantly in wet AMD but not in dry AMD.

Estimation of serum VEGF-A levels: Serum VEGF-A levels were compared between controls, patients with AMD, and AMD subtypes using crude analysis and ANCOVA adjusted for age and smoking status, with Bonferroni correction applied for multiple comparisons (Table 6). In the unadjusted analysis, VEGF-A levels were significantly higher in patients with AMD (46.25 ± 28.37 pg/ml) than in controls (19.89 ± 13.25 pg/ml; p < 0.0001). This difference remained significant after adjustment, with adjusted mean VEGF-A levels of 45.86 pg/ml in patients with AMD and 20.52 pg/ml in controls (p < 0.001).

Subtype-based analysis showed that VEGF-A concentrations were significantly elevated in both dry AMD (38.89 ± 25.16 pg/ml) and wet AMD (49.49 ± 29.18 pg/ml) compared with controls in the crude analysis (p < 0.0001). These differences persisted after adjustment, with adjusted mean VEGF-A levels of 38.64 pg/ml for dry AMD and 49.18 pg/ml for wet AMD (both p < 0.001 versus controls). Direct comparison between dry and wet AMD demonstrated higher VEGF-A levels in wet AMD in both the unadjusted (p = 0.049) and adjusted analyses (p = 0.027).

Genotype-stratified analyses revealed a significant effect of rs3025039 on VEGF-A protein levels. In patients with AMD, TT carriers had the highest VEGF-A concentrations (66.74 ± 33.75 pg/ml), significantly greater than those observed in CC carriers (43.97 ± 26.29 pg/ml; p = 0.023). A similar trend was observed when the total cohort (patients + controls) was considered, with TT carriers showing significantly higher VEGF-A levels than CC carriers (p = 0.009). Conversely, rs699947 genotypes did not demonstrate significant differences in VEGF-A serum concentrations (Appendix 3).

Estimation of serum CRP levels: Serum CRP levels were compared between controls, patients with AMD, and AMD subtypes using crude analysis and ANCOVA adjusted for age and smoking status, with Bonferroni correction applied for multiple comparisons (Table 6). In the unadjusted analysis, CRP levels were significantly higher in patients with AMD (2,500.85 ± 977.19 pg/ml) than in controls (2,008.52 ± 1,010.25 pg/ml; p < 0.001). This difference remained significant after adjustment, with adjusted mean CRP levels of 2,494.60 pg/ml in patients with AMD and 2,018.54 pg/ml in controls (p < 0.001).

Subtype-based analysis showed that CRP concentrations were significantly elevated in both dry AMD (2,591.59 ± 1,073.40 pg/ml; p < 0.01) and wet AMD (2,459.60 ± 932.46 pg/ml; p < 0.01) compared with controls in the crude analysis. These differences persisted after adjustment, with adjusted mean CRP levels of 2,586.99 pg/ml for dry AMD (p = 0.005) and 2,452.10 pg/ml for wet AMD (p = 0.010) relative to controls. Direct comparison between dry and wet AMD revealed no significant difference in CRP levels in either the crude analysis (p = 0.21) or the adjusted analysis (p = 1.00).

Analysis of the *CRP* rs1205 polymorphism revealed a genotype-dependent effect in the AMD patient group, with carriers of the AA genotype showing significantly lower serum CRP levels compared with GG (p = 0.036) and AG (p = 0.048) genotypes. No significant genotype-dependent differences were detected for rs1205 in controls or for rs1130864 in either patients or controls (Appendix 3). A schematic representation summarizing the key genetic associations and serum biomarker findings in AMD is provided in Figure 1.

DISCUSSION

This North Indian case-control study shows that the *VEGFA* rs3025039 polymorphism and elevated serum VEGF-A levels are associated with AMD, particularly the neovascular (wet) subtype. In contrast, *CRP* variants rs1205 and rs1130864 were not associated with AMD, despite higher circulating CRP levels in patients. These findings indicate that angiogenesis-related genetic variation contributes more directly to AMD susceptibility in this population than regulatory variation in *CRP*.

Table 5. Logistic regression analysis of *VEGFA* and *CRP* SNPs in control and Wet AMD patient group.

Model	Genotype	Control	Wet AMD patients	Crude analysis				Multivariate analysis adjusted for age, smoking and gender			
				OR (95% CI)	p-value	AIC	BIC	OR (95% CI)	p-value	AIC	BIC
				VEGFA (rs3025039)							
Codominant	CC	77 (77%)	66 (60%)	1.00				1.00			
	CT	21 (21%)	34 (30.9%)	1.89 (1.00-3.57)	**0.0096**	287.4	297.4	1.84 (0.93-3.66)	**0.028**	265.3	282
	TT	2 (2%)	10 (9.1%)	5.83 (1.23-27.58)				5.08 (1.02-25.35)			
Dominant	CC	77 (77%)	66 (60%)	1.00				1.00			
	CT-TT	23 (23%)	44 (40%)	2.23 (1.22-4.07)	**0.0079**	287.6	294.3	2.15 (1.13-4.10)	**0.018**	264.9	278.3
Recessive	CC-CT	98 (98%)	100 (90.9%)	1.00				1.00			
	TT	2 (2%)	10 (9.1%)	4.90 (1.05-22.94)	**0.02**	289.3	296	4.32 (0.87-21.32)	0.045	266.4	279.8
Overdominant	CC-TT	79 (79%)	76 (69.1%)	1.00				1.00			
	CT	21 (21%)	34 (30.9%)	1.68 (0.90-3.16)	0.1	292	298.7	1.66 (0.84-3.27)	0.14	268.3	281.6
Log-additive	---	---	---	2.09 (1.27-3.46)	**0.0027**	285.6	292.3	2.01 (1.17-3.44)	**0.0082**	263.4	276.8
				VEGFA (rs699947)							
Codominant	CC	45 (45%)	39 (35.5%)	1.00				1.00			
	CA	43 (43%)	52 (47.3%)	1.40 (0.77-2.52)	0.3	294.2	304.3	1.73 (0.91-3.28)	0.19	271.2	291.2
	AA	12 (12%)	19 (17.3%)	1.83 (0.79-4.23)				1.76 (0.71-4.37)			
Dominant	CC	45 (45%)	39 (35.5%)	1.00				1.00			
	CA-AA	55 (55%)	71 (64.5%)	1.49 (0.86-2.59)	0.16	292.7	299.3	1.74 (0.95-3.17)	0.07	269.2	285.9
Recessive	CC-CA	88 (88%)	91 (82.7%)	1.00				1.00			
	AA	12 (12%)	19 (17.3%)	1.53 (0.70-3.34)	0.28	293.5	300.2	1.33 (0.57-3.07)	0.51	272	288.7
Overdominant	CC-AA	57 (57%)	58 (52.7%)	1.00				1.00			
	CA	43 (43%)	52 (47.3%)	1.19 (0.69-2.05)	0.53	294.3	301	1.49 (0.82-2.70)	0.19	270.7	287.4
Log-additive	---	---	---	1.36 (0.92-2.02)	0.12	292.3	299	1.42 (0.92-2.18)	0.11	269.8	286.6
				CRP (rs1205)							
Codominant	GG	47 (47%)	45(40.9%)	1.00				1.00			
	GA	40 (40%)	56 (50.9%)	1.46 (0.82-2.60)	0.23	293.7	303.7	1.34 (0.73-2.49)	0.38	272.5	292.6
	AA	13 (13%)	9 (8.2%)	0.72 (0.28-1.86)				0.70 (0.26-1.93)			
Dominant	GG	47 (47%)	45 (40.9%)	1.00				1.00			
	GA-AA	53 (53%)	65 (59.1%)	1.28 (0.74-2.21)	0.37	293.9	300.6	1.19 (0.66-2.14)	0.56	272.1	288.8
Recessive	GG-GA	87 (87%)	101 (91.8%)	1.00				1.00			
	AA	13 (13%)	9 (8.2%)	0.60 (0.24-1.46)	0.25	293.3	300	0.61 (0.23-1.58)	0.3	271.4	288.1
Overdominant	GG-AA	60 (60%)	54 (49.1%)	1.00				1.00			
	GA	40 (40%)	56 (50.9%)	1.56 (0.90-2.69)	0.11	292.1	298.8	1.44 (0.80-2.58)	0.22	271	287.7
Log-additive	---	---	---	1.03 (0.68-1.56)	0.89	294.6	301.3	0.99 (0.64-1.54)	0.97	272.4	289.2
				CRP (rs1130864)							

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				Crude analysis				Multivariate analysis adjusted for age, smoking and gender			
Model	**Genotype**	**Control**	**Wet AMD patients**	**OR (95% CI)**	**p-value**	**AIC**	**BIC**	**OR (95% CI)**	**p-value**	**AIC**	**BIC**
Codominant	CC	53 (53%)	63 (57.3%)	1.00				1.00			
	CT	35 (35%)	38 (34.5%)	0.91 (0.51-1.64)	0.62	295.7	305.7	0.68 (0.36-1.29)	0.4	272.6	292.7
	TT	12 (12%)	9 (8.2%)	0.63 (0.25-1.61)				0.63 (0.23-1.73)			
Dominant	CC	53 (53%)	63 (57.3%)	1.00	0.53	294.3	301	1.00	0.18	270.6	287.3
	CT-TT	47 (47%)	47 (42.7%)	0.84 (0.49-1.45)				0.67 (0.37-1.21)			
Recessive	CC-CT	88 (88%)	101 (91.8%)	1.00	0.36	293.8	300.5	1.00	0.52	272	288.8
	TT	12 (12%)	9 (8.2%)	0.65 (0.26-1.62)				0.73 (0.27-1.93)			
Overdominant	CC-TT	65 (65%)	72 (65.5%)	1.00	0.94	294.6	301.3	1.00	0.31	271.4	288.2
	CT	35 (35%)	38 (34.5%)	0.98 (0.56-1.73)				0.73 (0.39-1.36)			
Log-additive	---	---	---	0.83 (0.56-1.25)	0.38	293.9	300.6	0.75 (0.48-1.17)	0.2	270.8	287.5

AIC: Akaike information criterion; AMD: Age-related macular degeneration; BIC: Bayesian information criterion; CI: Confidence interval; OR: Odds ratio; SNP: Single nucleotide polymorphism; Significant values ($p<0.05$) are shown in bold; p values indicate overall model significance.

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Table 6. Serum VEGF-A and CRP Levels in control, AMD patients and AMD subtypes.

		Crude analysis			Analysis adjusted for age and smoking		
Group	**Count**	**Mean (pg/ml)**	**SD (pg/ml)**	**p-value**	**Mean (pg/ml)**	**SEM (pg/ml)**	**p-value**
				VEGFA levels			
Control	100	19.89	13.25		20.52	2.47	
AMD patients	160	46.25	28.37	**<0.0001**	45.86	1.92	**<0.001**
Control	100	19.89	13.247		20.52	2.47	
Dry AMD patients	50	38.89	25.16	**<0.0001**	38.64	3.33	**<0.001**
Control	100	19.89	13.25		20.48	2.44	
Wet AMD patients	110	49.49	29.18	**<0.0001**	49.18	2.28	**<0.001**
Dry AMD	50	38.89	25.1575		38.64	3.33	
Wet AMD patients	110	49.49	29.19	**0.049**	49.18	2.28	**0.027**
				CRP levels			
Control	100	2008.52	1010.25		2018.54	103.46	
AMD Patient	160	2500.85	977.19	**<0.001**	2494.60	80.58	**<0.001**
Control	100	2008.52	1010.25		2018.54	103.46	
Dry AMD	50	2591.59	1073.40	**<0.01**	2586.99	141.41	**0.005**
Control	100	2008.52	1010.25		2018.54	103.46	
Wet AMD	110	2459.60	932.46	**<0.01**	2452.10	96.73	**0.010**

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		Crude analysis			Analysis adjusted for age and smoking		
Group	**Count**	**Mean (pg/ml)**	**SD (pg/ml)**	**p-value**	**Mean (pg/ml)**	**SEM (pg/ml)**	**p-value**
Dry AMD	50	2591.59	1073.40		2586.99	141.41	
				0.21			1.00
Wet AMD	110	2459.60	932.46		2452.10	96.73	

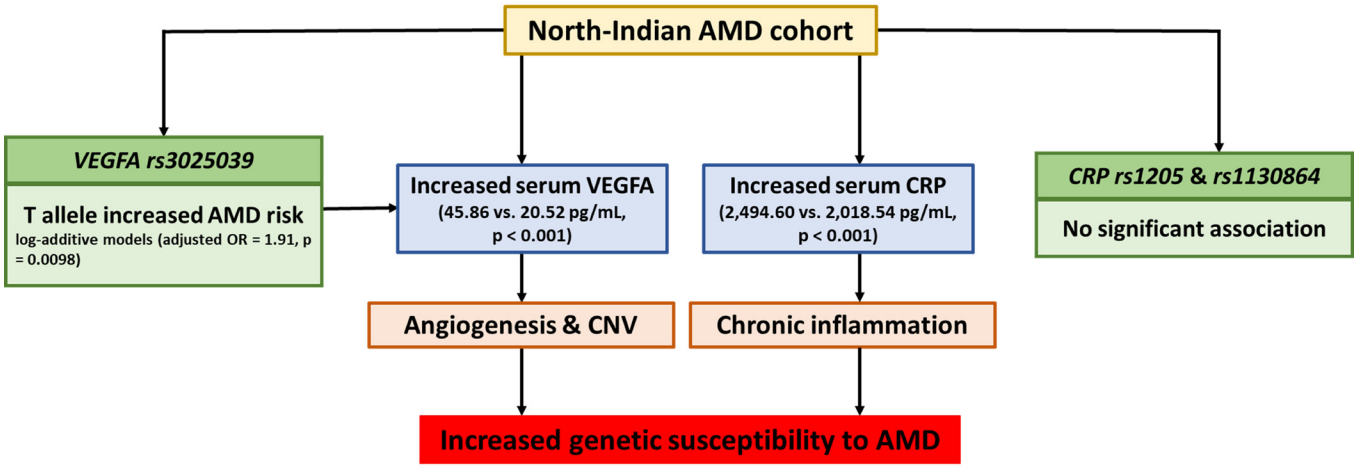


Figure 1. A schematic diagram outlines the major findings of this study. The vascular endothelial growth factor A (*VEGFA*) rs3025039 T allele was associated with increased age-related macular degeneration (AMD) risk. Patients with AMD showed elevated serum VEGF-A and C-reactive protein (CRP) levels, indicating enhanced angiogenesis and inflammation. No significant associations were observed for *CRP* polymorphisms, suggesting a combined role of genetic and inflammatory factors in AMD susceptibility.

In the studied cohort, the rs3025039 T allele was more frequent in patients with AMD than in controls. It was associated with increased risk under codominant, dominant, and log-additive models. The effect sizes were larger in wet AMD than in dry AMD. This pattern is consistent with prior reports describing population-specific or suggestive associations between *VEGFA* rs3025039 and AMD susceptibility [11]. A landmark Taiwanese case-control study found that the rs3025039 T allele was significantly enriched in wet AMD, with an OR of 2.61 for T-allele carriers compared with CC homozygotes, supporting a role for this variant in neovascular AMD susceptibility [6].

Meta-analyses pooling multiple case-control studies have identified rs3025039 as a *VEGFA* variant of interest, although effect sizes vary considerably across populations and AMD subtypes. Barchitta and colleagues [40] reported heterogeneous associations for rs3025039, emphasizing ethnic diversity and clinical stratification as key contributors to inconsistent replication. The present findings extend support to rs3025039 as a relevant risk marker for neovascular AMD in North Indians. Importantly, subtype-stratified analyses revealed that this association was confined to wet AMD, with no significant effect observed in dry AMD. This subtype-specific pattern suggests that rs3025039 may primarily influence angiogenesis-driven mechanisms rather than early degenerative changes characteristic of dry AMD [41]. These findings highlight distinct genetic architectures underlying AMD subtypes and reinforce the role of *VEGFA* variation in modulating susceptibility to neovascular progression.

The low frequency of the TT homozygous genotype resulted in wide confidence intervals, potentially affecting the precision of effect estimates. Therefore, findings from genotype-specific analyses should be interpreted cautiously.

In contrast, *VEGFA* rs699947 showed no significant association with AMD or serum VEGF-A levels under any genetic model in this cohort. This finding is consistent with several studies reporting no clear association between rs699947 and AMD susceptibility, despite its functional relevance in other vascular conditions [42,43]. Although some European studies have suggested modest effects of rs699947 on AMD risk or response to anti-VEGF therapy, these associations have been inconsistent and often attenuated after correction for multiple

testing [44,45]. The lack of rs699947 effect, despite a strong rs3025039 association, suggests that ethnic differences in genetic architecture and gene–environment interplay shape AMD risk in this population.

Consistent with the genetic findings, serum VEGF-A levels were markedly higher in patients with AMD than in controls and showed a clear gradient from controls to dry AMD to wet AMD. This aligns with the established role of VEGF-A as a central mediator of choroidal neovascularization and vascular leakage in wet AMD and with clinical evidence that intraocular VEGF-A levels are elevated in active exudative disease [46–48]. Importantly, we also observed genotype–phenotype correlation for rs3025039, with TT carriers exhibiting significantly higher VEGF-A levels than CC carriers. This is consistent with prior studies linking the T allele to increased VEGF-A expression [14,49] and provides a plausible mechanism for its role in AMD pathogenesis. Notably, the significant elevation of VEGF-A levels in dry AMD, despite the absence of overt neovascularization, suggests that angiogenic signaling may be initiated early in the disease process. This may reflect subclinical vascular or inflammatory activity, as VEGF expression is increased in both dry and wet AMD and can be induced by hypoxia and retinal stress [50,51]. Evidence further indicates that VEGF-A expression can occur in early-stage disease before clinically detectable neovascularization. The progressive increase in VEGF-A levels from dry to wet AMD supports a continuum model of disease progression, with VEGF upregulation intensifying with severity and contributing to the transition toward neovascular AMD [50,52].

The rs3025039 polymorphism is located in the 3′UTR of the *VEGFA* gene, a region known to influence posttranscriptional regulation. This variant may affect messenger RNA stability, polyadenylation, and microRNA binding, potentially leading to altered VEGF-A expression levels. Elevated VEGF-A can promote angiogenesis, vascular permeability, and inflammation, contributing to the pathogenesis of AMD [53]. Furthermore, gene–gene interactions may modulate the impact of rs3025039 on AMD risk. For instance, a study by Chen et al. [54] found that the effect of *LOXL1* rs1048661 on AMD risk was influenced by *VEGFA* rs3025039 genotypes, with the T allele potentially altering the expression of both genes and thereby modulating disease susceptibility. Serum CRP concentrations were significantly higher in patients with AMD compared to controls, consistent across both dry and wet subtypes, suggesting the presence of systemic inflammation in AMD.

These findings align with earlier reports demonstrating increased CRP levels in AMD [22,55–59], including a pooled analysis by Mitta et al. [58], indicating that elevated CRP is associated with an increased risk of overall and neovascular AMD. Although some studies, including Mendelian randomization analyses, have suggested a potential link between CRP and AMD, our findings did not demonstrate any association between CRP genetic variants and disease risk, indicating that elevated CRP levels in our cohort are more likely to reflect systemic inflammation rather than a direct causal role [59].

Despite their known influence on CRP levels, neither rs1205 nor rs1130864 showed significant association with AMD under any genetic model, in agreement with previous studies in other populations [27,60]. However, rs1205 displayed a genotype-dependent effect on CRP expression, with the AA genotype associated with lower serum CRP concentrations, consistent with prior reports [60,61]. Furthermore, evidence from other conditions, such as depression, has similarly shown that the A allele corresponds to ~30% lower CRP levels and altered disease risk, underscoring the regulatory role of rs1205 on CRP expression [62]. However, this modulation did not translate into AMD susceptibility in our cohort, suggesting that common CRP polymorphisms contribute only modestly to interindividual variability in CRP levels and have a limited impact on AMD risk [63].

Potential therapeutic implications of VEGF-A and CRP as targets for AMD management: The observed association of *VEGF* rs3025039 with AMD risk, along with elevated serum VEGF-A levels, particularly in the neovascular subtype, highlights the clinical relevance of angiogenesis-driven mechanisms. Similarly, increased CRP levels in patients with AMD support the contribution of systemic inflammation. Together, these findings provide a rationale for therapeutic strategies targeting both VEGF-A–mediated angiogenesis and inflammation.

1. Targeting VEGF-A—suppress pathologic angiogenesis: VEGF-A plays a central role in choroidal neovascularization, the defining feature of wet AMD, and underpins current anti-VEGF therapies. Intravitreal anti-VEGF agents such as ranibizumab and bevacizumab remain the standard of care; however, the need for repeated injections has driven the development of more durable approaches [64–66]. Gene therapy strategies using adeno-associated virus (AAV) vectors aim to achieve sustained intraocular expression of anti-VEGF agents (e.g., aflibercept), with clinical platforms such as ADVM-022 and RGX-314 demonstrating prolonged VEGF-A suppression and reduced treatment burden [67–69]. Emerging approaches, including CRISPR/Cas-mediated genome editing and RNA-targeting strategies (small interfering RNA, antisense, CRISPR-Cas13), have shown efficacy in reducing VEGF-A

expression and choroidal neovascularization in preclinical models, although safety and long-term effects require further evaluation [70,71].

2. Targeting CRP—reduce inflammation/complement activation: Although CRP polymorphisms were not associated with AMD risk in this study, elevated CRP levels indicate an underlying inflammatory component. CRP is a constituent of drusen and contributes to complement activation and retinal inflammation [58]. In particular, monomeric CRP has been identified as a proinflammatory mediator in AMD [72,73]. Therapeutic strategies under investigation include stabilization of pentameric CRP to prevent dissociation into its pathogenic form, inhibition of phospholipase A2–mediated conversion, enhancement of complement factor H binding, and direct CRP neutralization using monoclonal antibodies or aptamers [18,72,74]. Modulation of the CRP–complement axis and systemic CRP-lowering strategies, such as statins or anti-inflammatory interventions, may further contribute to the development of adjunctive therapeutic approaches aimed at reducing chronic retinal inflammation and limiting disease progression in AMD.

3. Combined/multimodal strategies:

Anti-VEGF + anti-CRP/anti-inflammatory combination—This approach can replace injections with a combined regimen: (a) anti-VEGF to halt active choroidal neovascularization (CNV) and (b) a local CRP blocker or complement modulator to reduce recurrent inflammation and slow progression to advanced disease. Such combination strategies may complement existing anti-VEGF therapy by addressing both angiogenic activity and inflammatory mechanisms that contribute to disease progression and recurrence [68].

Limitations of the study: This study has several limitations. It was conducted in a North Indian cohort with a moderate sample size, which may limit generalizability. A significant age difference existed between patients with AMD and controls; although multivariate analyses adjusted for age, smoking, and gender, residual confounding cannot be excluded given the strong age dependence of AMD and the absence of age-matched subgroup analysis. Other potential confounders, including clinical and lifestyle factors such as body mass index, were not included due to incomplete data. The lack of longitudinal follow-up prevents causal inferences regarding genetic variants, serum biomarkers, and disease progression. Finally, the low frequency of certain genotypes, particularly TT homozygotes, resulted in wide confidence intervals and may have reduced the precision of effect estimates. Future studies with larger sample sizes and age-matched designs may further validate these findings.

Conclusion: This study highlights the involvement of angiogenic and inflammatory pathways in AMD. *VEGFA* rs3025039 showed a significant association with AMD, with carriers of the risk genotype exhibiting higher serum VEGF-A levels, suggesting a potential role of VEGF-A–mediated angiogenesis. *CRP* polymorphisms were not associated with AMD, although elevated serum CRP levels in patients likely reflect underlying systemic inflammation rather than a direct causal role. Overall, these findings suggest that *VEGFA* variants may serve as potential markers of AMD susceptibility, while increased CRP levels represent secondary inflammatory responses.

Future perspective: Future research should validate these findings in larger, multicentric cohorts across diverse populations to define population-specific risk profiles. Functional genomics and transcriptomic studies are needed to clarify how *VEGFA* polymorphisms regulate gene expression in AMD. Longitudinal studies integrating clinical follow-up, imaging, and systemic risk factors will help establish the temporal links between inflammation, angiogenesis, and disease progression. Such efforts could advance precision medicine by enabling early risk prediction, individualized monitoring, and targeted therapies in AMD.

APPENDIX 1. SUPPLEMENTARY TABLE 1.

To access the data, click or select the words "Appendix 1." Association of VEGFA rs3025039 genotypes with AMD subtypes using Firth logistic regression analysis was applied to account for small sample sizes and rare genotypes

APPENDIX 2. SUPPLEMENTARY TABLE 2.

To access the data, click or select the words "Appendix 2." Hardy–Weinberg equilibrium analysis of *VEGFA* and *CRP* polymorphisms in controls and AMD patients.

APPENDIX 3. SUPPLEMENTARY TABLE 3.

To access the data, click or select the words "Appendix 3." A: Serum VEGF-A levels (pg/ml) in AMD patients and controls stratified by *VEGFA (rs3025039)* genotypes in AMD patients, controls, and the total cohort. **b:** Serum VEGF-A levels (pg/ml) in AMD patients and controls stratified by *VEGFA (rs699947)* genotypes in AMD patients, controls, and the total cohort. **c:** Serum CRP levels (pg/ml) in AMD patients and controls stratified by *CRP (rs1205)* genotypes in AMD patients, controls, and the total cohort. **d:** Serum CRP levels (pg/ml) in AMD patients and controls stratified by *CRP (rs1130864)* genotypes in AMD patients, controls, and the total cohort.

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