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Review

The role of gene polymorphisms in diabetic retinopathy

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Summary

Diabetic retinopathy (DR) is the most frequent microvascular complication of diabetes mellitus (DM) and remains a leading cause of preventable blindness in the working-age population. Its course is notoriously variable: some patients with long-standing, poorly controlled diabetes never develop sight-threatening disease, whereas others progress rapidly despite reasonable metabolic control. This clinical heterogeneity, which the traditional risk factors cannot fully explain, has directed attention towards the inherited component of susceptibility. This review summarizes current understanding of the genetic architecture of DR, with particular emphasis on three extensively studied candidate genes: the vascular endothelial growth factor A gene (*VEGFA*), the angiotensin-converting enzyme gene (*ACE*) and the apolipoprotein E gene (*APOE*), specifically their most investigated polymorphisms: *VEGFA* rs699947, rs2010963 and rs3025039; *ACE* rs1799752 I/D; and *APOE* rs429358 and rs7412 (ε2/ε3/ε4). The evidence linking individual polymorphisms to disease is examined alongside the picture emerging from genome-wide association studies (GWAS), and the persistent inconsistency among studies is discussed in the context of ethnic differences, phenotype definition and limited statistical power. Finally, the review considers how genetic insight is beginning to inform therapy, from the established anti-VEGF paradigm to gene-based approaches now in clinical trials, and outlines the main obstacles that still separate genetic findings from routine clinical use.

Key words: genetic susceptibility, renin-angiotensin system, apolipoproteins E, VEGFA protein, microvascular complications

Introduction

Diabetes mellitus (DM) has become one of the defining public health problems of the present century, and its complications now account for a substantial share of the global burden of disability. Among these complications, diabetic retinopathy (DR) occupies a particular place, because

it threatens a faculty — sight —loss of whichis irreversible and profoundly disabling. DR is a chronic microvascular, neuroinflammatory and neurodegenerative disorder of the retina developing on the background of sustained hyperglycaemia, and it remains the principal cause of legal blindness in adults of working age throughout much of the world [1].

Recent estimates underline the scale of the problem. A systematic review and meta-analysis of 59 population-based studies placed the global prevalence of any retinopathy among people with diabetes at roughly 22%, with vision-threatening disease affecting about 6% [1]. Translated into absolute numbers, more than a hundred million adults were estimated to be living with retinopathy in 2020, and projections that track the rising tide of diabetes itself foresee that figure climbing towards 160 million by 2045 [1]. The burden is shifting, too — increasingly concentrated in low- and middle-income regions where access to screening and to modern intravitreal therapy is least secure [2].

For decades, clinical and epidemiological researches have sought to map the determinants of who develops retinopathy and who escapes it. The duration of diabetes, the quality of glycaemic control, blood pressure, dyslipidaemia, renal impairment and pregnancy allhave been firmly implicated [3]. Yet anyone who has followed a cohort of diabetic patients over time will recognize a stubborn residual: a proportion of individuals with long-standing, badly controlled disease never develops appreciable retinopathy, while others deteriorate quickly despite metabolic parameters that look almost reassuring. This discordance is not merely anecdotal. It points to a component of susceptibility that the conventional risk factors do not capture, and the most plausible candidate for that missing component is the patient's genetic constitution.

The heritable contribution to DR is supported by several lines of evidence. Familial aggregation studies have repeatedly shown that a person whose relative has retinopathy carries a higher risk than expected from shared environment alone, and concordance for retinopathy is markedly greater in monozygotic than in dizygotic twins, in both type 1 and T2D [4]. On the basis of such observations, the heritability of DR has been estimated at between a quarter and a half of the total phenotypic variance, depending on the population and the definition of disease used. These figures are high enough to justify the considerable effort that has been invested in identifying the specific genes and variants responsible.

This review aims to summarize the current state of knowledge on the genetic basis of DR, to examine in detail three of the most intensively studied candidate genes — VEGFA, ACE and APOE — together with the broader picture supplied by genome-wide approaches, and to consider how this genetic understanding is beginning to shape both therapy and the obstacles that still stand in the way of clinical application.

Gene selection for this review. As a narrative review, this work does not follow the systematic review methodology. The three genes discussed in detail — VEGFA, ACE and APOE — were selected based on the following criteria: (i) biological plausibility of the gene product in DR pathogenesis; (ii) volume of published literature (at least 10 case-control studies or multiple meta-analyses); (iii) evidence of functional relevance for the polymorphism; and (iv) availability of recent meta-analyses or large cohort studies. Other genes are mentioned briefly where they provide context, but detailed discussion is limited to these three.

DR: clinical and pathophysiological background

Clinically, DR is divided into a non-proliferative stage and a proliferative stage, with diabetic macular oedema able to arise at any point and constituting the commonest cause of central vision loss. Non-proliferative disease is

characterized by microaneurysms, intraretinal haemorrhages, cotton-wool spots and venous abnormalities, and is graded from mild to severe according to the extent of these changes. The transition to the proliferative stage is defined by retinal neovascularization — the growth of fragile new vessels that bleed readily and may lead to tractional retinal detachment and severe visual loss [2].

Underlying these visible changes is a complex and only partly understood pathophysiology. Chronic hyperglycaemia drives a cluster of interlinked biochemical disturbances: increased flux through the polyol pathway, accumulation of advanced glycation end-products, activation of protein kinase C and overactivity of the hexosamine pathway. These converge on a common downstream state of oxidative stress and low-grade inflammation that damages the cellular constituents of the retina — the endothelial cells and pericytes of the microvasculature, but also neurons and glia [5]. The result is a breakdown of the blood–retinal barrier, capillary non-perfusion and retinal ischaemia. Ischaemic retina, in turn, upregulates vascular endothelial growth factor (VEGF), the principal molecular driver of both the increased vascular permeability responsible for macular oedema and the neovascularization that defines proliferative disease [6–9].

It is precisely because so many of these pathways are governed by gene products — enzymes, growth factors, receptors, transporters — that inherited variation in the corresponding genes can plausibly modulate the speed and severity with which retinopathy develops. A polymorphism that alters the expression or activity of an enzyme in the polyol pathway, or that shifts the set-point of VEGF production, need not cause disease on its own; it can act as a tuning element, nudging an individual towards or away from the threshold at which retinal damage becomes manifest. This is the conceptual framework within which the genetics of DR is best understood, and it is summarized schematically in Figure 1.

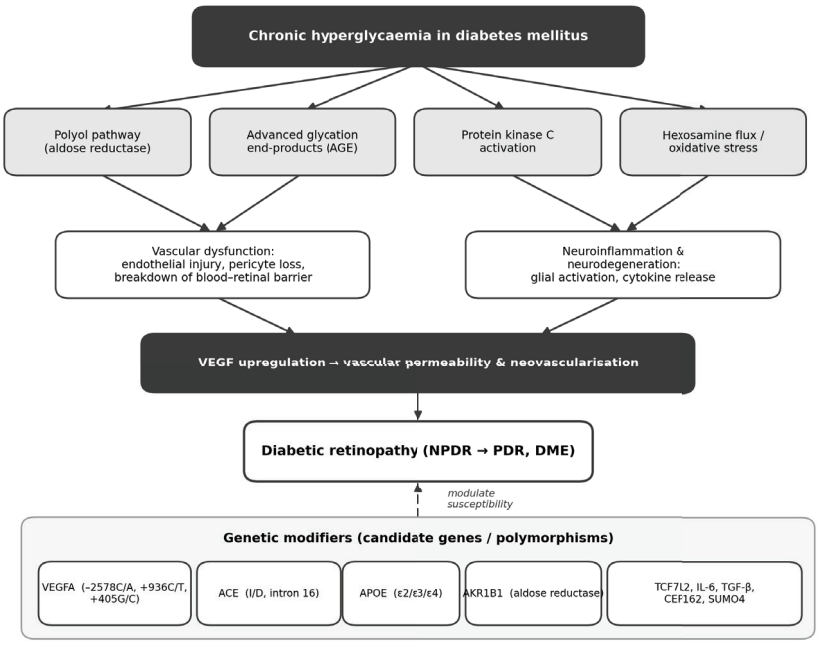

Figure 1. Schematic overview of the pathways through which chronic hyperglycaemia leads to diabetic retinopathy, and the candidate genes which polymorphisms are thought to modulate individual susceptibility. NPDR - non-proliferative diabetic retinopathy; PDR - proliferative diabetic retinopathy; DME - diabetic macular oedema; VEGF - vascular endothelial growth factor. Candidate genes discussed in this review are positioned according to the pathways they influence.

The genetic architecture of DR

Two broad strategies have been used to dissect the genetic basis of DR, and they rest on different assumptions. The candidate-gene approach starts from biological reasoning: a gene is selected because its product is known to participate in a pathway relevant to the disease, and variants within or around that gene are tested for association. The GWAS, by contrast, makes no prior assumption about which genes matter; it scans hundreds of thousands or millions of variants across the genome and lets the data identify the regions associated with disease [7].

The candidate-gene literature on DR is now very large, and a comprehensive narrative review has catalogued the chromosomes and individual genes implicated, organizing them around the metabolic pathways through which they are thought to act [5, 10–12]. Genes encoding components of the renin–angiotensin system, mediators of angiogenesis, enzymes of glucose metabolism, inflammatory cytokines and regulators of the extracellular matrix all appear in this catalogue. The difficulty is that, for almost every candidate, the published associations are inconsistent: a variant reported as a risk factor in one population fails to replicate in another or even shows an association in the opposite direction [13–15].

An umbrella review that pooled 32 meta-analyses covering 52 candidate SNP offers a useful corrective to over-interpretation of any single study [8]. When the evidence was graded by strength, only the transcription factor 7-like 2 (TCF7L2) C/T variant rs7903146 was supported by what the authors classed as convincing evidence, whereas the much-studied associations involving interleukin-6 and VEGF polymorphisms rested on weak evidence [8]. This sobering result illustrates a general truth about the field: many reported associations are real but small, and many others are artefacts of small samples, population stratification or selective reporting.

So far, genome-wide studies have been less transformative for DR than for many other complex traits. Nevertheless, cross-disease genome-wide meta-analysis in large biobank populations has begun to reveal that retinopathy shares genetic architecture with other ocular disorders, and that several implicated loci lie in genes governing neuronal differentiation and eye development — reinforcing the modern view of retinopathy as a neurovascular rather than a purely vascular disease, and signaling that the methodological groundwork for larger, better-powered studies is now being laid [7, 16–20].

Beyond classical candidate-gene studies, the field is gradually moving towards genome-wide and polygenic models. Genome-wide association studies offer the advantage of avoiding prior biological assumptions and can identify loci that would not have been selected through conventional pathway-based reasoning. However, compared with other complex diseases, GWAS of DR have been constrained by modest sample sizes, heterogeneous phenotyping and the difficulty of separating genetic susceptibility to diabetes itself from susceptibility to its retinal complications. Consequently, few loci have shown consistent replication across populations, and the effect sizes of individual variants remain small [21, 22].

An important implication is that DR is unlikely to be explained by single high-impact polymorphisms. Rather, susceptibility appears polygenic, with multiple common variants each contributing to a small increment of risk. Polygenic risk scores may therefore become more informative than isolated candidate variants, particularly if combined with established clinical predictors such as diabetes duration, HbA1c, blood pressure, renal function and lipid status [23, 24]. At present, such scores remain investigational and require validation in large, ethnically diverse cohorts before clinical application.

The next research frontier lies in integrating genomics with other omics layers. Transcriptomic studies may clarify which retinal or circulating genes are differentially expressed during early neurovascular injury, while proteomic and metabolomic profiling may identify molecular signatures preceding clinically visible retinopathy. Epigenomic data — including DNA methylation and microRNA expression — are particularly relevant because they may explain how long-term hyperglycaemia leaves a persistent molecular imprint, sometimes termed metabolic memory. Finally, integrating retinal imaging, OCT-derived biomarkers, artificial intelligence and molecular data may enable more precise classification of DR than clinical grading alone.

Key candidate genes

VEGFA - the angiogenic switch

If any single gene deserves to be considered first, it is VEGFA, the gene encoding vascular endothelial growth factor A. The reasoning is straightforward: VEGF is the central effector of the two processes that cause vision loss in DR — vascular hyperpermeability and neovascularization — and anti-VEGF therapy is now the mainstay of treatment for both diabetic macular oedema and proliferative disease [6]. The gene which product is so directly responsible for the disease phenotype is an obvious place to look for inherited variation influencing risk.

VEGFA lies on the short arm of chromosome 6, and it is markedly polymorphic, particularly in its promoter and untranslated regions where variants can plausibly affect the level of gene expression. The most extensively studied variants include the promoter polymorphism −2578C/A (rs699947), −634G/C (rs2010963, also designated +405G/C in some nomenclatures) and the 3′ untranslated region variant +936C/T (rs3025039). A systematic review and meta-analysis of 26 studies covering 10VEGFA polymorphisms found that the associations were both variant-specific and population-specific: rs2010963 was associated with retinopathy risk in Caucasian and overall populations, rs3025039 in Asians, and several other variants showed associations confined to particular ethnic groups or particular disease subtypes [10]. The authors concluded, reasonably, that VEGF polymorphisms contributed to susceptibility but that the effect of any individual variant was modest and context-dependent. Beyond individual SNP, specific VEGFA haplotypes combining these variants have been associated with altered promoter activity in functional studies, though their clinical utility remains unproven.

Subsequent meta-analyses focused on single variants have refined this picture. For the +936C/T polymorphism, pooled analysis of eight studies including over 1,500 patients with DR and type 2 DM found that the C allele and C-containing genotypes were associated with a reduced risk of retinopathy, an effect seen across allelic, dominant and recessive models [11]. For the −2578C/A promoter variant, a separate meta-analysis of 10 studies reported the opposite directionality, with the A allele associated with an increased risk of DR in type 2 DM under allelic and dominant models, though not under the recessive or homozygous models [12]. The contrast between these two variants is instructive: it shows that polymorphisms within the same gene can pull risk in opposite directions, presumably because they affect VEGF biology in different ways.

The umbrella review cited above, however, tempers enthusiasm by classing the VEGF associations as weak when judged against the most rigorous methodological standards [8]. The most honest summary is therefore that VEGFA variation genuinely modulates the risk of DR, but that the effect sizes are small, the directionality is variant-dependent, and replication across ethnic groups is imperfect. None of this diminishes the biological centrality of VEGF; it simply reflects the gap be-

tween a gene mattering mechanistically and a particular common variant being a reliable predictor of disease.

ACE - the renin–angiotensin system in the retina

The angiotensin-converting enzyme gene, ACE, situated on the long arm of chromosome 17, has attracted sustained interest because the renin–angiotensin system is active locally within the retina and contributes to the ischaemia and endothelial injury that characterize retinopathy [5]. The gene contains a well-known insertion/deletion (I/D) polymorphism, defined by the presence or absence of a 287-base-pair Alu repeat sequence within intron 16 (rs1799752). This variant is functionally relevant because the deletion allele is associated with higher circulating and tissue ACE activity, and thus, in principle, with greater generation of angiotensin II.

On biological grounds one might expect the D allele to predispose to retinopathy, and a number of individual studies have reported exactly that. The literature as a whole, however, has proved inconsistent, and the most recent and methodologically careful synthesis does not support a simple association. An updated meta-analysis of 16 studies found no significant relationship between the ACE I/D polymorphism and the risk of DR in T2D, whether the data were analyzed by genotype under a dominant model or by allele frequency [13]. The forest plots suggested that the discrepancies between earlier studies arose largely from differences in sample size, with smaller studies more prone to spuriously positive results [13]. Stratification by diabetes type in some studies has suggested a possible association between the D allele and retinopathy in type 1 but not T2D, indicating that the effect — if present — may be disease-subtype specific.

A subtler possibility is that polymorphism influences not the occurrence of retinopathy, but its severity once established. A cross-sectional case–control study in middle-aged Indian patients with T2D illustrates this nuance: the I/D genotype was not associated with the presence of retinopathy, yet the severity of retinopathy did vary with genotype under a recessive model and with allele contrast [14]. Such a dissociation between susceptibility and progression is biologically plausible and may partly explain why studies that lump all grades of retinopathy together reach divergent conclusions. The practical lesson is that phenotype definition matters: an effect on progression can be masked when cases are defined simply as the presence or absence of any retinopathy.

APOE - lipid transport and a protective allele

The apolipoprotein E gene, APOE, on chromosome 19, occupies an unusual position in this discussion because the most credible association points towards protection rather than harm. Apolipoprotein E is central to plasma lipid metabolism and to lipid homeostasis within the central nervous system, and it is synthesized locally in the retina by Müller cells, from where it is thought to participate in intraretinal lipid transport. The gene is polymorphic, with three common alleles — ε2, ε3 and ε4, defined by the variants rs429358 and rs7412 — that give rise to isoforms differing in their handling of lipids.

A case–control study in a Czech population that genotyped more than 1,200 patients with T2D found that carriers of at least one ε4 allele were protected against retinopathy, with the protective effect driven mainly by women and remaining significant after adjustment for diabetes duration and body mass index [15]. This finding is intriguing precisely because the ε4 allele is, in other contexts, a recognized risk factor — most famously for Alzheimer's disease and for cardiovascular events in diabetic

patients [16]. The apparent reversal of its effect in the retina is a reminder that the consequences of a genetic variant are tissue- and disease-specific, and that a single allele can be harmful in one organ and protective in another. The mechanism remains uncertain, but isoform-dependent differences in retinal lipid handling and in the local inflammatory response are plausible contributors. The ε2 allele has shown no consistent association with retinopathy risk in most studies, although isolated reports of modestly increased risk in ε2/ε2 homozygotes warrant further investigation.

Beyond these three genes, the candidate list extends considerably. Variants in the aldose reductase gene (AKR1B1), the rate-limiting enzyme of the polyol pathway, have been associated both with DR and with other microvascular complications, although the findings are not uniform across populations [17, 18]. More recent case–control work in Chinese populations has implicated variants in genes not previously prominent in the retinopathy literature — osteoprotegerin, and loci such as CEP162 and SUMO4 — broadening the catalogue of plausible contributors and underscoring how much of the genetic architecture remains to be charted [19, 20]. The principal genes discussed here, together with the directionality of their reported associations, are summarized in Figure 2 and Table 1.

Epigenetic modulation

Beyond fixed DNA sequence variation, epigenetic mechanisms — particularly DNA methylation and microRNAs — add another layer of regulation. In DR, hyperglycaemia-induced DNA methylation changes have been documented at the VEGFA promoter and at the SOD2 gene. Circulating microRNAs (e.g., miR-146a, miR-21, miR-155) are also dysregulated in patients with retinopathy. While a detailed discussion is beyond the scope of this review, these epigenetic factors likely interact with genetic polymorphisms to influence individual susceptibility.

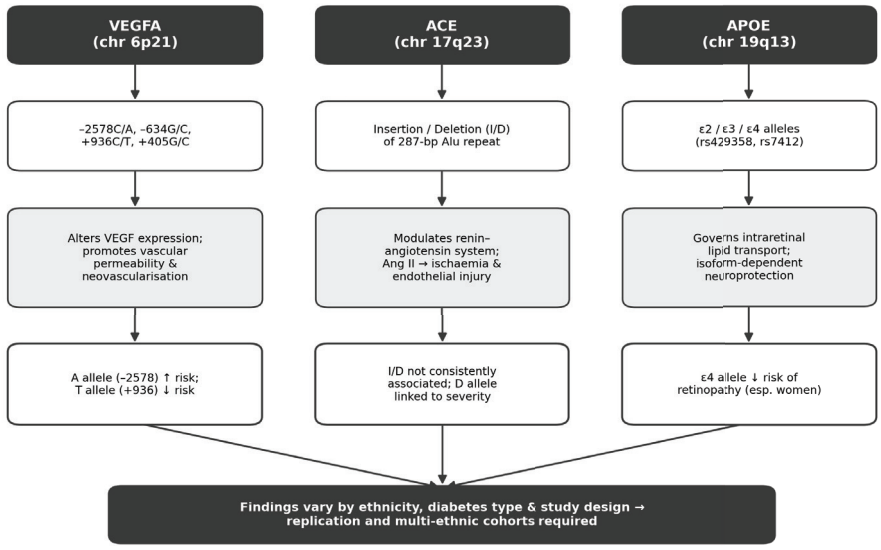

Figure 2. The three principal candidate genes discussed in this review, their key polymorphisms, putative mechanisms in the retina and the reported direction of association with diabetic retinopathy. The convergence at the foot of the figure indicates that, for all three genes, findings vary by ethnicity, diabetes type and study design.

Table 1. Summary of the main candidate genes implicated in diabetic retinopathy

Gene	Key polymorphism(s)	Putative role in the retina	Reported direction of association
VEGFA	−2578C/A (rs699947); +936C/T (rs3025039); −634G/C (rs2010963)	Central driver of vascular permeability and neovascularization	Variant-dependent: A allele (−2578) ↑ risk; C allele (+936) ↓ risk [10–12]
ACE	Insertion/deletion (I/D) of 287-bp Alu repeat (rs1799752)	Local renin–angiotensin system; angiotensin II promotes ischaemia and endothelial injury	No consistent association with occurrence; D allele may relate to severity [13, 14]
APOE	ε2 / ε3 / ε4 alleles (rs429358, rs7412)	Intraretinal lipid transport; isoform-dependent neuroprotection	ε4 allele associated with reduced retinopathy risk [15]
AKR1B1	Promoter and intronic variants (e.g. rs759853, rs752010122)	Rate-limiting enzyme of the polyol pathway	Inconsistent; some variants linked to altered risk [17, 18]

VEGFA - vascular endothelial growth factor A gene; ACE - angiotensin-converting enzyme gene; APOE - apolipoprotein E gene; AKR1B1 - aldo-keto reductase family 1 member B1 (aldose reductase) gene; ↑ - increased; ↓ - decreased

As shown in Table 2, several additional candidate genes have been investigated in DR, with varying levels of evidence supporting their association with disease susceptibility.

The level of evidence is approximate and reflects consistency of published associations, biological plausibility and availability of meta-analytic or replicated data. Most candidate-gene findings remain population-dependent and should not be interpreted as clinically validated markers.

From gene to therapy: gene-based treatment of diabetic retinopathy

Understanding the genetic and molecular basis of DR is not the end in itself; it points towards new ways of treating the disease. The current standard of care for sight-threatening retinopathy — repeated intravitreal injection of anti-VEGF agents such as ranibizumab, aflibercept and bevacizumab — is effective but burdensome. It demands frequent visits, imposes a cumulative risk of injection-related complications, and depends on a degree of adherence that many patients, particularly in resource-limited settings, cannot sustain [6]. The logic of gene therapy is to convert the retina itself into a durable biofactory producing a therapeutic protein continuously after a single administration, thereby removing the need for repeated injections.

Most gene-therapy programs in this field exploit adeno-associated virus (AAV) vectors to deliver a transgene encoding an anti-VEGF protein. Several such candidates have progressed into clinical trials. ABBV-RGX-314 uses an AAV vector to deliver a transgene encoding a ranibizumab-like antibody fragment and has reported encouraging results in early-phase studies, with later-phase trials under way; ixoberogenesoroparvovec employs an engineered capsid to express aflibercept after intravitreal delivery; and 4D-150 combines expression of aflibercept with an RNA-interference element directed against the second angiogenic factor [21]. A broader review of gene therapy for choroidal and retinal neovascularization sets these developments in the context of the wider effort to provide a one-time, long-lasting alternative to chronic anti-VEGF injection [22].

It is important to be clear about what these therapies are and are not. They are, for the most part, not corrections of an inherited defect; the patient's VEGFA, ACE or APOE

Table 2. Other candidate genes investigated in DR and approximate strength of evidence

Gene	Main biological pathway	Representative polymorphisms	Reported association with DR	Level of evidence
AKR1B1	Polyol pathway; sorbitol accumulation; osmotic and oxidative stress	rs759853, rs752010122 and promoter variants	Several studies report association; findings vary by population	Moderate but inconsistent
TCF7L2	Glucose metabolism; β-cell function; diabetes susceptibility	rs7903146	One of the more convincing associations among studied variants	Relatively stronger
IL6	Inflammation and endothelial activation	−174G/C and other promoter variants	Associations reported in some populations; meta-analytic support weak	Weak to moderate
TNF-α	Inflammation, endothelial dysfunction, blood–retinal barrier disruption	−308G/A	Biologically plausible; findings inconsistent	Weak
NOS3 / eNOS	Nitric oxide production; vascular tone; endothelial function	Glu298Asp, 4a/4b VNTR	Some association with vascular complications; limited replication	Weak to moderate
RAGE / AGER	Advanced glycation end-product signaling	Gly82Ser and promoter variants	Plausible link with hyperglycaemic injury; inconsistent genetic evidence	Weak
ICAM1	Leukostasis, endothelial adhesion and inflammation	K469E and other variants	Candidate pathway relevant; genetic associations not robust	Weak
HIF1A	Hypoxia signaling and VEGF regulation	Pro582Ser and related variants	May influence ischaemia-driven angiogenesis; limited direct evidence	Emerging / limited
MTHFR	Homocysteine metabolism and endothelial injury	C677T, A1298C	Some associations; not consistently replicated	Weak to moderate
OPG / TNFRSF11B	Vascular calcification, inflammation and endothelial protection	Several SNPs in Asian cohorts	Recent population-specific associations; requires replication	Emerging

genotype is not being altered. Rather, they use the tools of gene transfer to deliver a sustained pharmacological effect — a refinement of the anti-VEGF strategy rather than a treatment aimed at a specific susceptibility variant. Genuine genotype-directed therapy, in which a patient's polymorphism profile guides the choice of treatment, remains aspirational for DR. The path towards it runs through better identification of variants with reliable, clinically meaningful effects — exactly the work that the candidate-gene and genome-wide studies discussed above are intended to advance.

Challenges in clinical translation

Several obstacles continue to separate the genetics of DR from its bedside application. The first and most pervasive is the inconsistency

of association findings. As the umbrella review made plain, the great majority of reported gene–disease associations rest on weak evidence, and only a handful survive rigorous methodological scrutiny [8]. Small sample sizes, inadequate correction for multiple testing and selective publication of positive results have all contributed to literature that is larger than reliable.

The second obstacle is ethnic heterogeneity. The frequency of the given allele, and the strength of its association with disease, can differ substantially between populations, so that the variant that is informative in one ethnic group may be uninformative or even misleading in another [10]. This is not a statistical nuisance to be eliminated but a biological reality reflecting differences in genetic background and in the environmental exposures with which genes interact. It implies that genetic prediction tools will need to be developed and validated separately across populations, rather than transplanted wholesale from the cohorts in which they were derived.

The third challenge concerns phenotype. DR is not a single entity but a spectrum, and the genetic determinants of whether retinopathy develops at all may differ from those that govern its progression to a proliferative or oedematous stage. The ACE example, in which the effect on severity was detectable while the effect on occurrence was not, shows how a coarse phenotype definition can obscure a real genetic signal [14]. Future studies will need to phenotype retinopathy more finely, distinguishing carefully between the events of onset, progression and the development of macular oedema.

Finally, the inherited component of DR is polygenic and embedded in a dense web of gene–environment interaction. No single variant explains more than a small fraction of risk, and the clinically useful unit may turn out to be a polygenic score that aggregates the small effects of many variants, weighted appropriately for the patient's ancestry and combined with conventional risk factors. Building such scores, and demonstrating that they improve on existing clinical prediction, is a substantial undertaking that has only begun. Until it is accomplished, genetic testing for DR will remain a research tool rather than a part of routine care.

Future perspectives

Future research on the genetics of DR should move beyond isolated candidate-gene associations towards integrated, multi-layered models of disease risk. Large multicenter cohorts with standardized retinal phenotyping will be essential — particularly cohorts that distinguish between onset of any retinopathy, progression to proliferative disease and development of diabetic macular oedema. This distinction is important because the genetic determinants of susceptibility, severity and treatment response may not be identical.

The second priority is the development of ancestry-specific and externally validated polygenic risk scores. Such tools should not be evaluated in isolation but in combination with conventional clinical risk factors. Their clinical value will depend on whether they improve prediction sufficiently to alter screening intervals, identify patients requiring closer follow-up, or guide early preventive intervention.

Third, genetic data should be linked with high-resolution retinal imaging. OCT, OCT angiography and fundus photography analyzed by artificial intelligence may provide quantitative phenotypes that are more sensitive than traditional clinical categories. Combining these imaging biomarkers with genomic, transcriptomic, proteomic and epigenetic data could help define biologically distinct subtypes of DR.

Finally, pharmacogenetic studies are needed to determine whether inherited variation influences response to anti-VEGF therapy, corticosteroids or future gene-based

treatments. At present, gene therapy for DR mainly represents sustained intraocular delivery of anti-angiogenic molecules rather than correction of inherited susceptibility. In the longer term, however, genotype-informed screening, risk stratification and therapeutic selection may become realistic components of precision ophthalmology.

Limitations

As a narrative review, this work has several inherent limitations. The selection of genes for detailed discussion, while justified, inevitably omits other candidates with plausible biological roles (e.g., IL-6, TNF-α, AKR1B1). The literature cited reflects the authors' judgement and may not be exhaustive. Furthermore, the predominance of studies from European and East Asian populations limits the generalizability of conclusions to other ancestries. These caveats should be considered when interpreting the associations discussed.

Conclusion

DR is a heritable as well as a metabolic disease, and the search for genes governing its inherited susceptibility has now occupied investigators for several decades. The three genes examined most closely here — VEGFA, ACE and APOE — illustrate both the promise and the difficulty of this enterprise. Each is biologically compelling: VEGFA sits at the heart of the angiogenic process causing blindness, ACE links DR to the renin–angiotensin system, and APOE connects it to retinal lipid biology. Yet for each, the association between a specific common polymorphism and the disease is modest, variable across populations and, in the case of ACE, perhaps confined to severity rather than occurrence.

The most realistic assessment is that no single polymorphism will ever serve as a standalone marker of risk. The future of genetic prediction in DR lies in larger and more carefully phenotyped cohorts, in genome-wide and polygenic approaches validated across diverse ancestries, and in the integration of genetic information with the established clinical risk factors. In parallel, the molecular understanding that genetic research has helped to build is already bearing fruit in therapy, as gene-transfer strategies move the anti-VEGF paradigm towards durable, single-administration treatment. Recognizing the genetic determinants of DR therefore matters on two fronts at once: it promises better identification of the patients at the greatest risk, and it deepens the mechanistic understanding from which the next generation of treatments will emerge. Future progress will depend on larger, more diverse cohorts and on integrating genetic data with clinical risk factors to determine whether genotype-informed screening or treatment stratification improves outcomes.

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Uloga genskih polimorfizama u dijabetičkoj retinopatiji

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Dijabetička retinopatija (DR) je najčešća mikrovaskularna komplikacija dijabetes melitusa (DM) i ostaje jedan od vodećih uzroka sljepila koje se može spriječiti u radno sposobnoj populaciji. Tok bolesti je izrazito promjenljiv: neki bolesnici sa dugogodišnjim, loše regulisanim dijabetesom nikada ne razviju oblik bolesti koji ugrožava vid, dok kod drugih dolazi do brze progresije uprkos zadovoljavajućoj metaboličkoj kontroli. Ova klinička heterogenost, koju tradicionalni faktori rizika ne mogu u potpunosti objasniti, usmjerila je pažnju ka nasljednoj komponenti sklonosti ka bolesti. U ovom radu sažeto je prikazano savremeno razumijevanje genske arhitekture DR, sa posebnim osvrtom na tri detaljno proučavana kandidat-gena: gen za vaskularni endotelni faktor rasta (*VEGFA*), gen za angiotenzin-konvertujući enzim (*ACE*) i gen za apolipoprotein E (*APOE*), posebno njihovi najistraženiji polimorfizmi: *VEGFA* rs699947, rs2010963 i rs3025039; *ACE* rs1799752 I/D, i *APOE* rs429358 i rs7412 (ε2/ε3/ε4). Razmatraju se dokazi koji povezuju pojedine polimorfizme sa bolešću, nalazi studija asocijacije na nivou cijelog genoma, kao i razlozi za nedosljednost rezultata između studija u pogledu etničkih razlika, definicije fenotipa i ograničene statističke snage. Na kraju se razmatra kako genetski uvidi počinju da oblikuju terapiju, od ustaljenog anti-VEGF pristupa do genskih terapija koje se ispituju u kliničkim studijama.

Ključne riječi: genska sklonost, renin-angiotenzin sistem, apolipoprotein E, VEGFA, mikrovaskularne komplikacije