AN UPDATE ON THE GENETICS OF DIABETIC RETINOPATHY

Many studies have found statistically significant associations between genetic polymorphisms and DR, but other studies have found no associations.

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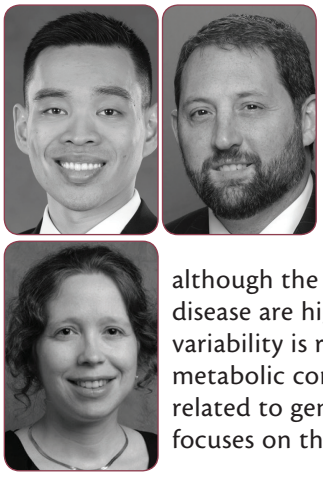


Diabetic retinopathy (DR) is a leading cause of vision loss worldwide.[1,2] Nearly all patients with type 1 diabetes and more than 60% of patients with type 2 diabetes will eventually develop retinopathy,[3] although the age of onset and severity of disease are highly variable. Some of this variability is related to the intensity of metabolic control,[4,5] and some may be related to genetic factors.[6] This article focuses on the latter.

WHAT WE KNOW ABOUT GENETICS AND DR

Genetic variability may explain why the incidence and progression of DR varies substantially, even among patients with similar metabolic factors.[7] Reports from different nations suggest that African and Afro-Caribbean, South Asian, Latin American, and indigenous tribal populations have significantly higher reported rates of DR than European-derived populations.[8,9] These findings support a genetic influence on the development and progression of DR. Although there are no proven genetic associations with DR, this is an important area of research.[10,11]

It is hypothesized that DR is an example of a complex genetic disease, as opposed to a monogenic (single gene or Mendelian) disease.[12] In general, monogenic diseases (eg, retinitis pigmentosa, Leber congenital amaurosis) are relatively uncommon and are caused by a mutation in a single gene that produces the observed phenotype. In contrast, complex genetic diseases, or polygenic diseases (eg, age-related macular degeneration and DR), may be common and are associated with (rather than caused by) multiple genetic and environmental factors. These genetic factors are typically called *variants* or *polymorphisms* rather than *mutations*. Variants may be associated with either increased or decreased risk of disease, whereas a polymorphism is typically defined as a gene variant present in 1% or more of the general population. Gene variants may interact with environmental factors in unknown ways.

Genetic association studies may be difficult to interpret because a statistically significant genotype-phenotype correlation observed in a study population may not be true outside that specific study population. Furthermore, because the likelihood of obtaining a spurious correlation increases as the number of individual comparisons increases, it is important to replicate any reported associations with other studies in different study populations. Differences in baseline population characteristics and in clinical endpoints, inadvertent selection bias, and other factors may be responsible for a genotype-phenotype association that is highly statistically significant in one population but not in another.

GENES LINKED TO THE PATHOGENESIS OF DR

Most published findings regarding the genetics of DR have implicated four genes in the pathogenesis of DR (Table).

Aldose Reductase

Aldose reductase (AR) is found in high concentration in retinal pericytes and Schwann cells, where it converts glucose into osmotically active sorbitol.[13] Variants in *AR*,

AT A GLANCE

- Because the age of onset and severity of DR are highly variable, researchers have looked for possible connections to genetic factors.
- No definitive proof has been found to support a genetic association with DR.
- Additional information distilled from future studies may help to guide clinical management decisions and to aid in the development of novel drug targets.

TABLE. CANDIDATE GENES STUDIED FOR ASSOCIATION WITH DR

Well-studied Candidate Genes	
AR	Converts glucose into osmotically active sorbitol
eNOS	Regulates retinal vascular tone
RAGE	Induces production of inflammatory cytokines and growth factors
VEGF	Induces retinal neovascularization and increases vascular permeability
Newer Candidate Genes	
INSR	Involved in retinal insulin signaling
ACE	Converts angiotensin I into angiotensin II
GRB2	Activates mitogen-activated protein kinase pathway in response to insulin
CRP	Sensitive marker of inflammation involved in endothelial dysfunction and angiogenesis
SELP	Involved in leukocyte recruitment and platelet adhesion

Abbreviations: *ACE, angiotensin-converting enzyme; AR, aldose reductase; CRP, C-reactive protein; eNOS, endothelial nitric oxide synthase; GRB2, growth factor receptor bound protein 2; INSR, insulin receptor; RAGE, receptor for advanced glycation endproducts; SELP, P-selectin; VEGF, vascular endothelial growth factor*

including the rs759853 (−106C/T) polymorphism, have been significantly associated with DR in some populations but not in others. For example, this polymorphism was highly associated with DR in a series of 206 Iranian patients with type 2 diabetes[14] but not in a series of 268 Chinese patients with type 2 diabetes.[15] A meta-analysis of 7,831 patients included in 17 studies from Asia, South America, Europe, and Australia reported a significant association between this polymorphism and DR in patients with type 1 diabetes but not in patients with type 2 diabetes.[16]

Endothelial Nitric Oxide Synthase

Endothelial nitric oxide synthase (eNOS) is an important regulator of retinal vascular tone.[17] A meta-analysis of 3,145 patients across nine studies from multiple nations reported a significant negative association between the rs3138808 (4b/a) polymorphism of *eNOS* and DR in patients with type 1 and type 2 diabetes.[18] Another meta-analysis of 6,664 patients across 16 studies from multiple nations also reported a significant negative association between the rs3138808 (4b/a) polymorphism and DR, but only in African populations with type 2 diabetes.[19] Several other studies have reported no significant associations between the rs3138808 (4b/a) polymorphism and DR in patients with type 2 diabetes.[20-22]

Receptor for Advanced Glycation Endproducts

Advanced glycation endproducts (AGEs) are metabolic byproducts of a hyperglycemic state.[23] Upon binding to AGE receptors (RAGEs) on retinal pericytes and endothelial cells, AGEs induce the production of inflammatory cytokines and growth factors, including VEGF.[23,24] A meta-analysis of 3,339 Asian, African, and white patients across seven studies reported a significant negative association between the AA genotype of the rs1800624 (−374T/A) polymorphism of *RAGE* and DR in patients with type 2 diabetes.[25] However, in a series of 577 Malaysian patients, no significant association was reported between the rs1800624 (−374T/A) polymorphism of *RAGE* and DR in patients with type 2 diabetes.[26] A significant positive association between the homozygous Ser82 genotype of the Gly82Ser polymorphism of *RAGE* and DR was reported in a series of 758 North Indian patients with type 2 diabetes.[27] By contrast, a series of 283 Malaysian patients[28] and a meta-analysis of more than 1,000 patients across 29 studies from the United States, Europe, and Asia[29] found no significant association between the Gly82Ser polymorphism of *RAGE* and DR in patients with type 2 diabetes.

Vascular Endothelial Growth Factor

The best studied gene in the context of DR is *vascular endothelial growth factor (VEGF)*. VEGF induces retinal neovascularization and increases vascular permeability.[30] Anti-VEGF drugs are commonly used in the management of patients with diabetic macular edema.[31] Four polymorphisms of *VEGF* have been well studied.

rs833061 (-460C/T)

The rs833061 (−460C/T) polymorphism has shown the most promise. In a meta-analysis of 746 Asian patients across three studies[32] and another meta-analysis of 1,654 Asian and white patients across six studies,[33] a significant positive association between the rs833061 (-460C/T) polymorphism and DR in patients with type 2 diabetes was reported. However, in a series of 500 Chinese patients, no significant association between this polymorphism and DR in patients with type 2 diabetes was reported.[34]

rs699947 (−2578C/A)

In a meta-analysis of 2,402 Asian and European patients across eight studies[35] and a study of 500 Chinese patients,[34] the authors reported a significant association between the rs699947 (−2578C/A) polymorphism and DR in patients with type 2 diabetes. In another meta-analysis of 1,702 Asian and

white patients across six studies, the rs699947 (−2578C/A) polymorphism was significantly associated with DR in Asian but not white patients with type 2 diabetes.[36] However, in a meta-analysis of 2,208 Asian and white patients across six studies,[33] a meta-analysis of 1,868 Asian and white patients across six studies,[32] a study of 128 Egyptian patients,[37] and a series of 1,040 Chinese patients,[38] there was no significant association between the rs699947 (−2578C/A) polymorphism and DR in patients with type 2 diabetes.

rs2010963 (-634G/C)

In a meta-analysis of 2,947 patients across nine studies, a significant association between the rs2010963 (-634G/C) polymorphism and DR in patients with type 2 diabetes was reported.[39] However, in a meta-analysis of 2,104 Asian and white patients across seven studies, the authors reported no significant association between the rs2010963 (-634G/C) polymorphism and DR in patients with type 2 diabetes.[32]

rs3025039 (+936C/T)

In a meta-analysis of 1,147 Asian patients across four studies, a significant association between the rs3025039 (+936C/T) polymorphism and DR was found in patients with type 2 diabetes.[32] However, no significant association between the rs3025039 (+936C/T) polymorphism and DR was found in a study of 1,040 Chinese patients with type 2 diabetes.[38]

Other VEGF *Polymorphisms*

Recently, a meta-analysis of 1,307 Asian and white patients across four studies identified a significant positive association between the rs2146323 (A/C) polymorphism and DR in patients with type 1 and type 2 diabetes.[40] Another study of 2,899 white patients found a significant association between the rs17697419 (A/G), rs17697515 (C/T), and rs2333526 (C/T) polymorphisms with DR in patients with type 1 and type 2 diabetes.[41]

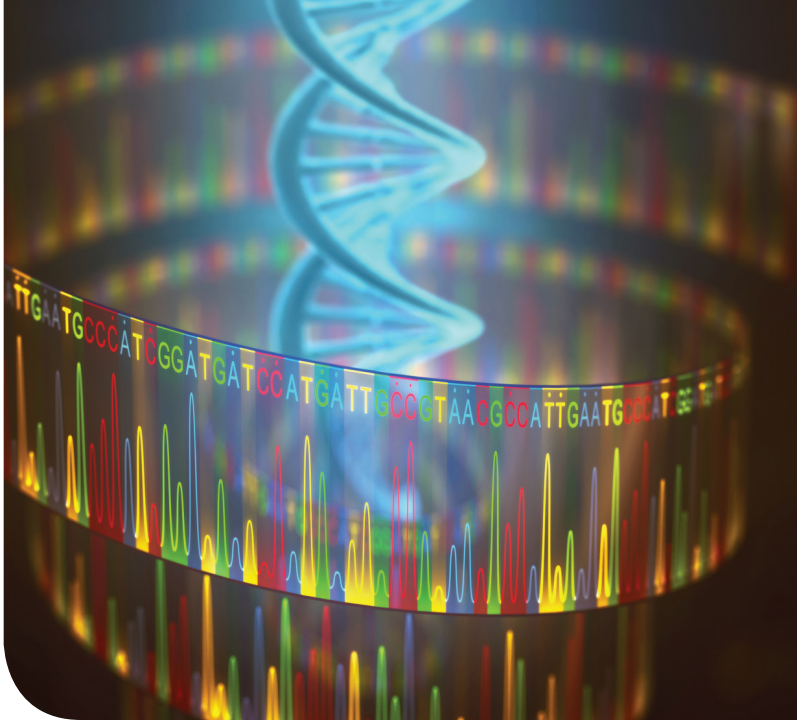
Recent research has focused on other candidate genes, including those listed below (see also Table).

Insulin Receptor

The insulin receptor (INSR) plays a key role in insulin signaling in insulin-sensitive tissues, including the retina.[42] A recent study of 2,057 Chinese patients found a significant association between the rs2115386 polymorphism of *INSR* and DR in type 2 diabetes.[43] However, two previous studies found no significant association between this polymorphism and DR.[44,45]

Angiotensin-Converting Enzyme

Angiotensin-converting enzyme (ACE) regulates the systemic and renal circulations by converting angiotensin I into angiotensin II, a potent vasoconstrictor.[46] In a study of 353 Pakistani patients, a significant association was identified between the rs4646994 polymorphism of *ACE* and DR



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in type 2 diabetes.[47] Another study of 743 Chinese patients identified a significant association between the rs2074192 and rs714205 polymorphisms of *ACE* and DR in type 2 diabetes.[48] However, a previous review of 73 studies found no significant association between the rs699, rs1799752, or rs5186 polymorphisms of *ACE* and DR in type 1 and type 2 diabetes.[49]

Growth Factor Receptor Bound Protein 2

Growth factor receptor bound protein 2 (GRB2) is an activator of the mitogen-activated protein kinase pathway in response to insulin and is involved in VEGF signaling.[50] In a recent study of 1,650 Indian and white patients, a significant positive association was identified between the rs9896052 polymorphism of *GRB2* and DR in type 1 and type 2 diabetes.[51]

C-reactive Protein

C-reactive protein (CRP) is a sensitive marker of inflammation and is involved in endothelial dysfunction and angiogenesis.[52,53] A recent study of 1,018 Chinese patients found a significant positive association between the rs2808629 polymorphism of *CRP* and DR in type 2 diabetes.[54]

P-selectin

P-selectin (SELP) is involved in leukocyte recruitment and platelet adhesion.[55] A recent study of 895 black patients identified a significant negative association between the rs6128 polymorphism of *SELP* and DR in type 2 diabetes.[56]

CONCLUSION

It is reasonable to suspect that there is a genetic component of DR, but at this time there are no validated genotype-phenotype associations. Although the authors of many individual studies and meta-analyses have reported statistically significant associations between various genetic polymorphisms and DR, other studies have identified no significant associations.

Searching for genetic associations with DR is an intriguing area of research, but genetic testing is not helpful in routine clinical management of DR today. As we continue to collect information and search for genetic associations, perhaps future discoveries will permit stratification of patients into different risk groups to guide clinical management decisions and to aid in the development of novel drug targets. ■

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