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REVIEW ARTICLE

Unraveling the role of genetics in the pathogenesis of diabetic retinopathy

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Abstract

Diabetic retinopathy (DR) is a microvascular disease of the retina and the leading cause of visual disability in diabetic patients. Genetic factors have shown to play a pivotal role in DR onset, and several candidate genes have been associated with its progression. A literature search was performed to identify the genes known to be associated with DR through linkage analysis, candidate gene association, and genome-wide association studies (GWAS). A further literature search was performed to discover their potential connection with various biological pathways. A total of 65 genes were found and several of these genes belong to major signaling pathways known to play a significant role in DR, including systemic inflammation, angiogenesis, and neurogenesis. A comprehensive analysis presented in this review will be helpful in unraveling the role of genetics in the pathogenesis of DR.

Background

Diabetic retinopathy (DR) is one of the major microvascular complications of diabetes [1]. According to its severity, DR can be classified into non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR). Hallmarks of NPDR include microaneurysms, hard exudates, cotton wool spots, intra-retinal micro-vascular abnormalities, and venous beading [2]. This condition can either remain stable or progressively develop into PDR which is characterized by neovascularization, pre-retinal hemorrhage, and vitreous hemorrhage [3]. The precise mechanisms underlying DR etiology have not been fully elucidated, and consequently, the currently available therapies are insufficient to reverse or prevent diabetic complications of the eye [1, 4–6]. Several genetic studies including linkage analysis, candidate gene association, and genome-wide association studies (GWAS) have identified a total of 65 genes associated with DR (Fig. 1). Most of the genes associated with DR have been identified through candidate gene-based association studies and GWAS (Table 1) [7–19].

To improve our understanding of the functional role of these genetic factors in DR pathogenesis, we mapped

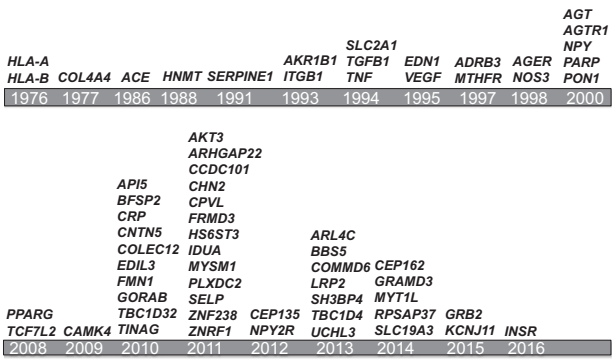

Fig. 1 Chronological list of genes associated with diabetic retinopathy. A comprehensive search of published literature was performed to generate a list of all the genes associated with diabetic retinopathy. Before 2007, most of the genes were discovered using linkage analysis or candidate gene approach. After 2007, the evolution of genome wide association studies (GWAS) led to the discovery of a large number of genes

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Table 1 List of genes associated with diabetic retinopathy

Chr	Nearby genes	SNPs (top signal)	*p* value	OR	Type of diabetes	Subjects (*n*)	Type of DR	Country	Year	Reference
1p5.89	MYSM1	rs2811893	3.1×10^{-7}	1.5	T2D	174 patients, 575 controls	PDR, NPDR	Taiwan	2011	[67 GWAS]
1q23.2	CRP	rs2808629	6.0×10^{-3}	1.3	T2D	618 patients, 400 controls	PDR, NPDR	China	2015	[68]
1q24.2	SELP	rs6128	1.0×10^{-4}	0.43	T2D	6639 patients, 4047 controls	PDR	International	2011	[11]
1q24.2	GORAB	rs6427247	3.3×10^{-2}	1.37	T2D	819 patients, 1153 controls	PDR, NPDR	China	2015	[62]
			4.6×10^{-4}	2.17	T2D	103 patients, 183 controls	PDR, NPDR	USA-Mexico	2010	[36 GWAS]
1q44	AKT3, ZBTB18	rs476141	1.2×10^{-7}	1.37	T1D	973 patients, 1856 controls	PDR	USA	2011	[61 GWAS]
2p25.3	MYT1L	rs10199521	2.2×10^{-2}	1.25	T2D	309 patients, 1490 controls	PDR	China	2016	[69]
2q31.1	LRP2, BBS5	rs1399634	2.0×10^{-6}	1.50	T2D	437 patients, 570 controls	PDR, NPDR	China	2013	[25 GWAS]
2q36.3	SLC19A3	rs6713116	3.2×10^{-6}	0.41	T1D	1,566 patients, 218 controls	NPDR	Finland	2016	[70 GWAS]
2q37.2	ARL4C, SH3BP4	rs2380261	2.1×10^{-6}	1.50	T2D	437 patients, 570 controls	PDR, NPDR	China	2013	[25 GWAS]
3p25	PPARG	rs1801282	9.7×10^{-3}	0.73	T1D	518 patients, 1389 controls	PDR, NPDR	USA-Canada	2015	[19]
3q22.1	BFSP2	rs1197310	3.4×10^{-4}	2.25	T2D	103 patients, 183 controls	PDR, NPDR	USA-Mexico	2010	[36 GWAS]
4p16.3	IDUA	rs6856425	2.1×10^{-5}	2.88	T2D	969 patients, 1789 controls	PDR	International	2011	[11]
4q32.1	NPY2R	rs1902491	2.8×10^{-5}	-	T1D	208 patients, 261 controls	PDR	USA	2012	[21]
4q12	CEP135	rs4865047	2.1×10^{-5}	-	T1D	208 patients, 261 controls	PDR	USA	2012	[21]
5q9.35	KIAA0825	rs17376456	3.0×10^{-15}	3.63	T2D	174 patients, 575 controls	PDR, NPDR	Taiwan	2011	[67 GWAS]
5q14	EDIL3	rs1445754	3.4×10^{-4}	0.37	T2D	103 patients, 183 controls	PDR, NPDR	USA-Mexico	2010	[36 GWAS]
5q21	CAMK4	rs2300782	6.0×10^{-5}	2.64	T2D	103 patients, 183 controls	PDR, NPDR	USA-Mexico	2010	[36 GWAS]
5q23.3	RPSAP37,GRAMD3	rs1073203	2.7×10^{-2}	1.4	T1D, T2D	163 patients, 300 controls	PDR, NPDR	Australia	2014	[71]
6p11-12	TINAG	rs6909083	1.8×10^{-5}	-	TD2	103 patients, 183 controls	PDR, NPDR	USA-Mexico	2010	[36 GWAS]
6q14.3	CEP162	rs9362054	1.4×10^{-7}	1.36	T2D	837 patients, 1149 controls	NPDR	Japan	2014	[72 GWAS]
6q22	TBC1D32	rs17083119	2.8×10^{-5}	-	TD2	103 patients, 183 controls	PDR, NPDR	USA-Mexico	2010	[36 GWAS]
7p15.1	CPVL, CHN2	rs39059	3×10^{-4}	1.29	T2D	805 patients, 1017 controls	PDR, NPDR	China	2011	[73]
9p21.33	FRMD3	rs10868025	3.4×10^{-2}	0.83	T2D	618 patients, 280 controls	PDR, NPDR	China	2011	[73]
10p4.93	ARHGAP22	rs4838605	1.9×10^{-9}	1.65	T2D	174 patients, 575 controls	PDR, NPDR	Taiwan	2011	[67 GWAS]
10p2.06	PLXDC2	rs12219125	7.2×10^{-3}	1.40	T1D	518 patients, 1389 controls	PDR, NPDR	USA- Canada	2015	[19]
			9.3×10^{-9}	1.67	T2D	174 patients, 575 controls	PDR, NPDR	Taiwan	2011	[67 GWAS]
10q25.3	TCF7L2	rs7903146	4.0×10^{-4}	1.77	T2D	154 patients, 171 controls	PDR	Italy	2013	[43]
11p12	API5	rs899036	5.0×10^{-4}	0.34	T2D	819 patients, 1153 controls	PDR, NPDR	China	2015	[62]
		rs899036	2.5×10^{-4}	0.32	T2D	103 patients, 183 controls	PDR, NPDR	USA-Mexico	2010	[36 GWAS]
11p15.1	KCNJ11	rs5219	1.0×10^{-3}	1.61	T2D	105 patients, 475 controls	NPDR	China	2015	[23]
11q22.1	CNTN5	rs10501943	2.5×10^{-4}	3.04	T2D	103 patients, 183 controls	PDR, NPDR	USA-Mexico	2010	[36 GWAS]
13q9.57	HS6ST3	rs2038823	4.7×10^{-11}	2.33	T2D	174 patients, 575 controls	PDR, NPDR	Taiwan	2011	[67 GWAS]
13q22.2	TBC1D4	rs9565164	1.3×10^{-7}	1.70	T2D	437 patients, 570 controls	PDR, NPDR	China	2013	[25 GWAS]

Table 1 (continued)

Chr	Nearby genes	SNPs (top signal)	*p* value	OR	Type of diabetes	Subjects (*n*)	Type of DR	Country	Year	Reference
15q13	FMN1	rs11635920	7.2×10^{-5}	-	T2D	103 patients, 183 controls	PDR, NPDR	USA-Mexico	2010	[36 GWAS]
16p28.5	CCDC101	rs10521145	3.4×10^{-6}	0.58	T1D	281 patients, 1715 controls	PDR	USA	2011	[61 GWAS]
16q22.3	ZNRF1	rs17684886	3.9×10^{-3}	0.81	T2D	819 patients, 1153 controls	PDR, NPDR	China	2015	[62]
17q25.1	GRB2	rs9896052	4.2×10^{-8}	-	T1D, T2D	1175 patients, 1319 controls	PDR, NPDR	Australia-India	2015	[74]
18p11.2	COLEC12	rs599019	4.1×10^{-4}	0.15	T2D	103 patients, 183 controls	PDR, NPDR	USA-Mexico	2010	[36 GWAS]
		rs599019	1.2×10^{-2}	0.84	T2D	819 patients, 1153 controls	PDR, NPDR	China	2015	[62]
19p13.2	INSR	rs2115386	1.1×10^{-4}	1.44	T2D	309 patients, 1490 controls	PDR	China	2016	[69]
		rs2115386	9.1×10^{-4}	1.28	T2D	567 patients, 1490 controls	NPDR	China	2016	[69]

these genes to biological processes and pathways. Our analyses revealed that majority of these genes belong to various biological pathways known to have a significant contribution to the DR pathology including insulin signaling, angiogenesis (HIF-1 signaling, regulation of blood vessel size, VEGF signaling), inflammation (IL-6 signaling, leukocyte adhesion, TGF-β and TNF signaling), lipid metabolic process, neurogenesis (neural cells differentiation, neurotrophin signaling), protein kinase signaling (Jak-STAT, PI3K-Akt, MAPK, Ras and mTOR signaling) and regulation of endothelial cell / leukocytes interaction (cell adhesion molecules, cell migration) (Table 2).

Insulin signaling

A total of 9 genes (*AKT3, GRB2, SLC2A1, KCNJ11, TBC1D4, CEP135, UCHL3*, *INSR*, and *HNMT*) were mapped to insulin signaling pathway. Insulin activates the insulin receptor (INSR) tyrosine kinase which phosphorylates numerous signaling partners. In the retina, disrupted INSR signaling has been shown to produce cellular dysfunction [20]. Among the INSR phosphorylated signaling partners, the activation of the AKT3/PKB and the PKCζ cascade regulates diverse biochemical responses including glycogen synthesis, protein synthesis, and autophagy. One such biochemical response is mediated by GRB2 activation, which forms a stable complex with phosphorylated insulin receptor substrate (IRS-1) and the SH2 domain-containing oncogenic protein, SHC. *CEP135* (Centrosomal protein 135kDa), expressed in the retina, encodes a centrosomal protein required for centriole-centriole cohesion during the interphase of the cell cycle [21]. *CEP135* interacts with SMAD9, a critical component in the TGF-β signaling pathway which is also upregulated in diabetes and diabetic retinopathy [21]. *KCNJ11* (Potassium voltage-gated channel subfamily J member 11) encodes for a potassium channel controlled by G-proteins and was found to be associated with the sulfonylurea receptor. The common variant of *KCNJ11* (rs5219) has a strong association with DR [22, 23]. *SLC2A1* (Solute carrier family 2, member 1 also known as *GLUT1*) is expressed in endothelial and epithelial barriers including the retinal capillary endothelium, retinal pigment epithelium, and the basal cells of the corneal epithelium in the eye [24]. SLC2A1 is an important target for DR as it is the only glucose transporter between the blood and retina [24]. The knockdown by intraocular injections of a pool of siRNAs directed against *SLC2A1* mRNA significantly reduced retinal glucose levels in diabetic mice. *TBC1D4* (TBC1 domain family, member 4) is known to play a role in insulin signaling in the retina and DR pathogenesis [25]. UCHL3 (Ubiquitin carboxyl-

Table 2 Candidate genes and important signaling pathways associated with diabetic retinopathy

Signaling pathways	Candidate genes
Insulin signaling	*AKT3,GRB2,SLC2A1,KCNJ11, TBC1D4,CEP135,UCHL3, HNMT, INSR*
Angiogenesis	*EDIL3,NOS3,SERPINE1,PLXDC2*
Blood vessel development	*ACE,AGT,EDN1,NOS3,SELP, TCF7L2*
HIF-1 signaling	*AKT3,EDN1, SLC2A1,NOS3, SERPINE1,VEGFA*
Patterning of blood vessels	*EDN1,VEGFA, GRAMD3*
Regulation of blood vessel size	*ADRB3,AGT,AGTR1,EDN1,NOS3*
Response to hypoxia	*ACE,EDN1, MTHFR,NOS3,TGFB1*
VEGF signaling	*AKT3,GRB2,NOS3,VEGFA*
Inflammation:	
IL-6 signaling	*AKT3,GRB2,ICAM1, CRP*
Leukocyte adhesion	*ICAM1,ITGB1,SELP,TNF*,
NF-kappa B activation	*AGT,ICAM1,PARP1,TGFB1,TNF*
NF-kappa B inhibition	*COMMD6*
TGF-beta signaling	*TGFB1,TNF*
TNF signaling	*AKT3,EDN1,ICAM1,PARP1,TNF*
Lipid metabolic process	*LRP2,PON1,ARL4C,COLEC12*
Neurogenesis:	
Apoptotic process	*API5,GORAB*
Neural cells differentiation	*ZBTB18,ZNRF1*
Neuroactive ligand-receptor interaction	*ADRB3,AGTR,NPY,NPY2R*
Neurotrophin signaling	*AKT3,CAMK4,GRB2*
Jak-STAT signaling	*AKT3, GRB2*
PI3K-Akt signaling	*AKT3,COL4A4, GRB2,ITGB1,NOS3, VEGFA*
Protein kinase cascade	*ADRB3,AGT,EDN1, TGFB1,TNF*
MAPK signaling	*AKT3,GRB2,TGFB1,TNF*
Ras signaling	*AKT3,GRB2,VEGFA*
mTOR signaling	*AKT3,TNF,VEGFA*
Regulation of endothelial cell / leukocytes interaction	
Cell adhesion molecules (CAMs)	*FMN1,ICAM1,ITGB1, SELP, COL4A4,ITGB1*
ECM-receptor interaction	*ACE,AGT,NOS3,TGFB1*
Regulation of endothelial cell migration	*AGT,EDN1,TGFB1*
Regulation of cellular localization	*AGT,EDN1,KCNJ11,TCF7L2, TGFB1,TNF*
Regulation of cell migration	*ACE,AGT,EDN1,ICAM1,ITGB1, NOS3,SELP,TGFB1*

terminal esterase L3) is a deubiquitinating enzyme playing a role in the maintenance of ubiquitin levels within the cell through processing of ubiquitin precursors and ubiquitinated proteins. Several studies have shown the role of UCHL3 in insulin signaling and retinal maintenance in stress conditions [26, 27].

Angiogenesis

The crucial role of angiogenesis in DR has been recognized since 1985 when Rand et al. reported how changes in retinal venular caliber could predict vision loss [28]. VEGF is a heparin-binding homodimeric glycoprotein that acts via endothelial-specific receptor tyrosine kinases, among which VEGFR2 is the main VEGF receptor regulating angiogenesis. VEGF is one of the targets of the HIF (Hypoxia-Inducible Factor), a basic helix-loop-helix transcription factor that regulates the response to hypoxia. HIF induces expression of proteins controlling glucose metabolism, cell proliferation, vascularization, and blood vessel development such as SELP (P-selectin), EDN1 (Endothelin 1), LDHA (Lactate dehydrogenase-A), TGFβ1, and b-FGF (basic fibroblast growth factor) [29]. VEGF was amongst the first factors known to regulate retinal neovascularization and blood-retinal barrier (BRB) breakdown in DR [30]. The absence of the SLC2A1 carrier in neovascular tissue of PDR is a sign of the loss of glucose selective permeability [31] and GRB2 participates in the MAPK pathway via Ras in response to vascular endothelial growth factor signaling [32].

ACE, AGT and AGTR belong to the renin-angiotensin system, a crucial pathway which regulates blood pressure. The production of Ang II within the retina leads to a series of hemodynamic and growth promoting effects that trigger DR development [33]. Ang-II induces capillary growth, vascular permeability, and an increase in oxidative stress via stimulation of growth factors such as TGF-β, VEGF, and PDGF [34]. Furthermore, the increase of Ang-II has been shown in diabetic patients, particularly with microangiopathy and microvascular damage [35]. *EDIL3* (EGF-like repeats and discoidin domains 3) encodes for an integrin ligand which plays an important role in mediating angiogenesis and vessel wall remodeling. It also influences retinal endothelial cell behavior [36]. The *EDN1* (Endothelin 1) gene encodes a protein that is primarily produced in vascular endothelium, vascular smooth muscle cells, macrophages, leukocytes, cardiomyocytes, and fibroblasts [37]. Endothelin 1 plays a pivotal role in endothelial dysfunction, one of the significant elements in the pathogenesis of DR [38]. Studies have shown high EDN1 expression in vascular and extravascular sites in the retina and its contribution to abnormal retinal hemodynamics in DR [39].

Endothelial nitric oxide synthase (eNOS) plays an essential role in maintaining vascular homeostasis. Deficiency in eNOS expression coupled with concomitant activation of inducible nitric oxide synthase (iNOS) triggers

highly reactive nitrogen species (RNS) formation, thus, leading to oxidative stress and accelerated retinopathy [40]. PLXDC2 (Plexin domain-containing protein 2), also known as TEM7R (tumor endothelial marker seven-related protein), has been implicated in neurogenesis and angiogenesis [19, 41]. PDR results in part from the formation of fibrovascular membranes (FVMs) in the posterior fundus. Tumor endothelial marker 7 (TEM7) is a protein that is highly expressed in the endothelial cells of tumors. TEM7 has been shown to play a significant role in the proliferation and maintenance of neovascular endothelial cells in the FVMs [42]. TCF7L2 (Transcription factor 7-like 2) participates in the WNT signaling pathway and regulates MYC expression by binding to its promoter in a sequence-specific manner [43]. *ARHGAP22* encodes a Rho family GTPase protein, which is a component in the regulation of endothelial cell capillary tube development during angiogenesis [44]. Similar to PLXDC2, ARHGAP22 has been implicated in PDR and is involved in endothelial cell angiogenesis.

Inflammation

Eleven genes associated with DR (*CRP*, *AKT3, GRB2, ICAM1, ITGB1, SELP, TNF, AGT, PARP1, COMMD6*, and *EDN1*) were mapped to pathways involved in inflammation. Several studies have shown that patients exhibit higher blood levels of inflammatory markers such as C-reactive protein (CRP), interleukin-6 (IL-6), transforming growth factor (TGF-β), tumor necrosis factor-alpha (TNF-α) [27], cyclooxygenase-2 (COX-2), and interleukin-1 (IL-1) [45, 46]. Moreover, soluble TNF-receptor levels have been associated with an increased risk of severe DR [25]. IL-6 is a cytokine that provokes a broad range of cellular and physiological responses including the immune response, inflammation, hematopoiesis, and oncogenesis by regulating cell growth, gene activation, proliferation, survival, and differentiation. AKT3, CRP, ICAM1 and GRB2 are known to be involved in the IL-6 signaling. AKT3, a member of the AKT (or PKB) serine/threonine-protein kinase family, regulates many processes including metabolism, proliferation, cell survival, growth and angiogenesis. In particular, AKT3 has been shown to be stimulated by platelet-derived growth factor (PDGF), insulin, and insulin-like growth factor 1 (IGF1), both implicated in proliferative retinopathy [21, 47]. The *GRB2* gene codes for an adapter protein that is involved in the Ras-mediated pathway which leads to the activation of transcription factors such as *EIK1* and *NF-IL-6* (C/EBP-Beta). Burton et al. [32]. recently described *GRB2* as a promising candidate for DR susceptibility because increase of this protein in mouse retina was correlated to retinal stress leading to DR. Also, GRB2 protein is expressed in all layers of the human retina. The *COMMD6* (COMM domain containing 6) gene belongs to a family of NF-kB inhibiting proteins characterized by the presence of a COMM domain and down-regulates TNF-induced NF-kB activation [48]. PARP1 (poly(ADP-ribose) polymerase), a DNA repair enzyme activated by oxidative damage, mediates the hyperglycemia-induced activation of NF-kB, pro-inflammatory molecules, cytokines, and iNOS. Its overexpression leading to a depletion of ATP, NAD+ and NADH [49]. The loss of these cofactors cause an impairment in glycolysis and mitochondrial respiration that affect cellular viability. The *TNF* gene encodes for a pro-inflammatory cytokine which is member of the tumor necrosis factor superfamily. Studies have described the involvement of TNF-α in diabetic retinal microvascular damage and drugs that target TNF-α have been shown to reduce leukostasis, retinal vascular leakage, and retinal cell death in animal models [50] . TGF-β, a cytokine implicated in multiple cellular functions including proliferation, differentiation, adhesion, and migration, has been shown to be involved in the basement membrane thickening and matrix accumulation in the blood vessels [51]. The gene expression profile of retinal vessels isolated from streptozotocin- treated rats revealed an increased expression in 20 genes of the TGF-β signaling pathways [52]. *ICAM1, ITGB1* and *SELP* are particularly important in leukocyte adhesion, one of the earliest signs of retinal complications. ICAM1 (Intercellular adhesion molecule 1 or CD18) is a member of the ICAM proteins that act as ligands for the leukocyte adhesion protein, LFA-1. This gene encodes for a cell surface glycoprotein, typically on endothelial cells, whose expression is induced by increased levels of VEGF. Specific inhibition of ICAM1 in diabetic animals leads to reduction of leukostasis and BRB breakdown [53]. The *ITGB1* (Integrin, beta 1) belongs to the integrins family and plays a pivotal role in PDR and proliferative vitreo-retinopathy due to its contribution to the terminal event of tractional retinal detachment [54].

Neurogenesis

Several DR associated genes (*API5, GORAB, ZBTB18, ZNRF1, ADRB3, AGTR, NPY, NPY2R, AKT3, CAMK4*, and *GRB2*) belong to the neurological processes. Despite the retina's peripheral localization, it is actually part of the central nervous system. DR is a multifactorial disease involving not only the vasculature, but also the neurons and glia and studies have suggested that neuronal changes in the retina may occur before vascular alterations [55, 56]. There is sufficient evidence of neurodegenerative changes in DR including increased apoptosis of ganglion cells, glial cell reactivity, microglial activation, and altered glutamate metabolism [57].

Neurotrophins (NTs) are a family of growth factors that mediate the growth, differentiation, and survival of developing neurons. A significant increase was observed in the expression of NT-3 and NT-4 in vitreous samples from PDR patients compared to non-diabetic controls [58]. Interestingly, AKT3 and GRB2 have been shown to participate in NT signaling. API5 (Apoptosis inhibitor 5) is an anti-apoptotic factor which acts as a suppressor of the transcription factor E2F1 which induces apoptosis and also interacts with, and negatively regulates, Acinus, a nuclear factor involved in apoptotic DNA fragmentation. CAMK4 (Calcium/calmodulin-dependent protein kinase IV) acts in the calcium-triggered CaMKK-CaMK4 signaling cascade. This kinase is expressed in the brain, spleen, thymus, and regulates the activity of several transcription factors implicated in the immune response, inflammation, and memory consolidation [59]. Neuropeptide Y (NPY) and its receptor (NPY2R) play a pivotal role in the central nervous system regulating many physiological processes. The Leu7Pro (codon 7) polymorphism in NPY was identified as a risk factor for DR development in a well-characterized cohort of patients with Type 2 diabetes [16]. *ZBTB18* (Zinc finger and BTB domain containing 18) encodes a C2H2-type zinc finger protein which acts as a transcriptional repressor of key pro-neurogenic genes such as Neurogenin2 and NeuroD1[60]. *ZBTB18* is also involved in various developmental processes such as myogenesis and other aspects of brain development [61]. ZNRF1 (Zinc and ring finger 1, E3 ubiquitin protein ligase) is an E3 ubiquitin-protein ligase that mediates the ubiquitination of AKT1 and glutamate-ammonia ligase (GLUL), playing a role in neuronal cell differentiation. ZNRF1 regulates neurodegeneration, maintenance of neuronal transmission, plasticity, and Schwann cell differentiation in DR [62].

Regulation of endothelial cell / leukocytes interaction

An important cause of damage in the vascular endothelium in DR is leukocyte activation and migration that is mediated by the specific adhesion molecules expressed on the cell surface of leukocytes and the endothelium. A significant correlation between the number of leukocytes accumulated within the vessel and capillary damage in the retina has been identified in post-mortem DR patients [63]. Moreover, pre-clinical animal studies of early DR have also highlighted the disruption of the retinal endothelium caused by adhering leukocytes and the subsequent increase of the vascular permeability [64]. Thirteen genes (*ACE, AGT, COL4A4, EDN1, FMN1, ICAM1, ITGB1, KCNJ11, NOS3, SELP, TCF7L2, TGFB1, TNF)* were mapped to this pathway. ICAM1, EDN1, and SELP are important markers of endothelial dysfunction that have been linked with the development of DR [65]. ICAM-1 level increases in the diabetic retina, even in the early stages of DR. Endothelial complications in DR are dramatically reduced in animals treated with anti-ICAM-1 antibodies [64]. EDN-1 is known to be a potent vasoconstrictor molecule, implicated in the disruption of retinal hemodynamics and DR progression [39]. *COL4A4* (Collagen, type IV, alpha 4) encodes one of the six subunits of type IV collagen, the major structural component of basement membranes and modification of collagen metabolism in the basement membrane is associated with DR [66]. FMN1 (Formin 1) is involved in cell adhesion and morphogenesis [36].

Conclusions

In this review, we compiled a comprehensive list of genetic factors associated with DR. Further analyses revealed the biological functions of these genes in DR pathogenesis. The identification of genetic factors and their contribution to DR etiology will allow for tailored pharmacogenomics approaches for the treatment of DR.

Summary

- Diabetic retinopathy (DR) is a microvascular disease of the retina and the leading cause of visual disability in diabetic patients.
- Genetic factors have shown to play a pivotal role in DR onset, and several candidate genes have been associated with its progression.
- This review presents an insight into genes associated with DR and their role in various biological functions and signaling pathways.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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