Materials Today: Proceedings xxx (xxxx) xxx

Contents lists available at ScienceDirect

Materials Today: Proceedings

journal homepage: www.elsevier.com/locate/matpr

Diabetic retinopathy its genetics and single nucleotide polymorphism associated with multi-ethnic cohort – A review

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ARTICLE INFO

Article history:
Received 28 June 2020
Accepted 8 July 2020
Available online xxxx

Keywords:
Diabetic retinopathy
Genetics
SNPs
UPS system
Diabetes mellitus

ABSTRACT

Diabetic Retinopathy is a microvascular impairment which leads to blindness in the developed and developing countries. The DR progress from non - proliferative diabetic retinopathy to proliferative diabetic retinopathy were new blood vessels are formed which is called as microaneurysms. The onset of diabetic retinopathy depends on the period of the diabetes mellitus. The uncontrolled blood glycaemic level results in diabetic retinopathy. The single nucleotide polymorphism or genetic variants may be responsible for the genesis of diabetic retinopathy. This review paper mainly focuses on the diabetic retinopathy, its pathophysiology and its genetics which includes VEGF, AGEs, ALR, Epo and eNOS. The ubiquitin proteasome pathway also plays a major role in DR as the expression of Proteins of the UPS system are high in retina and any variation in the gene causes the DR. The SNPs that are associated with diabetic retinopathy in different cohort is also discussed in this review.

Selection and peer-review under responsibility of the scientific committee of the International Conference on Newer Trends and Innovation in Mechanical Engineering: Materials Science.

1. Introduction

Sight is our most precious sense. Preventing sight loss is more important than to treat sight-threatening diseases when they occur. One of the causes of blindness in working age population is diabetic retinopathy which is a microvascular damage in people with prolonged diabetes mellitus. The Eye is a visual organ that is a part of sensory nervous system that process visual detail. The eye gives the vision by processing the light and converting it to the electrical impulse in neurons. The eye detects the photon through the photoreceptors in the retina that is rods and cones. The eye is characterised into three layers, they are outer layer, middle layer and the inner layer. These three layers are covered by the lens, vitreous and the aqueous. The outer layer includes cornea which transmits the light to the lens. The sclera is responsible in maintaining the shape of the eye from internal and external pressures and is surrounded by a membrane called conjunctiva. The middle layer has three parts that is the iris, the choroid and ciliary body. The lens shape is maintained by the ciliary body and the choroid provides oxygen to the outer retinal layers. The inner layer retina of the eye is made up of neurons which are responsible for processing the light and converting it to a signal to neurons [1] (Fig. 1).

The retina is present in the inner layer of the eye. It receives the light and converts it into electrical impulse. The retina consists of six neurons; they are the photoreceptor cells, the bipolar cells, the amacrine and ganglion cells, the Müllerian glia, the retinal pigment epithelium cell and the interneurons [3]. The retinal pigment epithelium are made up of pigmented cells which forms the retinal barrier, it play an important role in light absorption and supply nutrients to the photoreceptors [4]. The ganglion cells are neurons that receive the visual information from the photoreceptors which consist of rods and cones and deliver the signal to the brain cells. The neural retina consists of parallel layers to which the Mullerian glia acts as a backbone. The outer layer of the retina are made up of photoreceptor cells where the nuclei of the cells are close to RPE. The inner nuclear layer of the retina consists of Mullerian glia, the amacrine, the horizontal cells and the bipolar cells [5,6] (Fig. 2).

2. Diabetic retinopathy

Diabetes mellitus is a chronic metabolic dysfunction characterised by high blood glucose level where there is a lack of insulin or the cell doesn't react to the insulin produced. Type I diabetes

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https://doi.org/10.1016/j.matpr.2020.07.178
2214-7853/
Selection and peer-review under responsibility of the scientific committee of the International Conference on Newer Trends and Innovation in Mechanical Engineering: Materials Science.

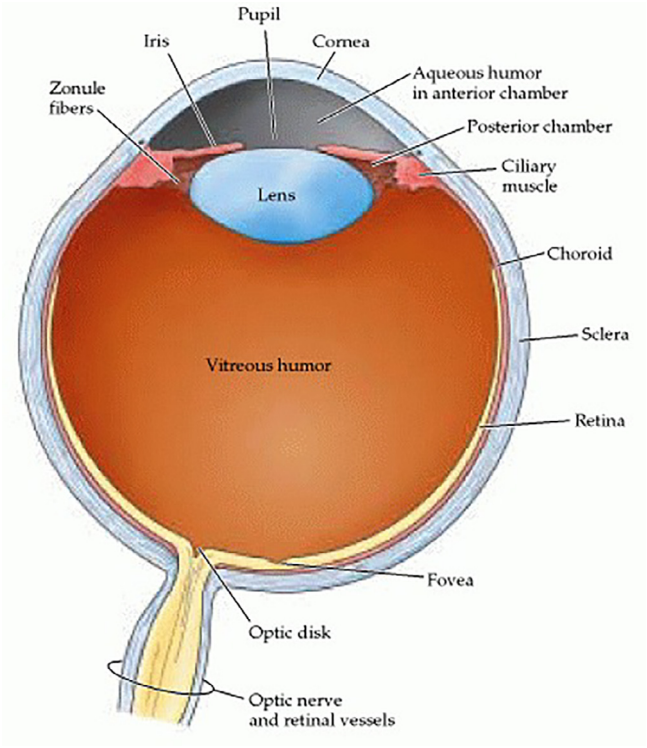

Fig. 1. Anatomy of human eye [2].

results from the lack of insulin production where the beta cells present in the pancreas fail to produce insulin this is called "insulin dependent diabetes mellitus". Type II diabetes occurs when the cells in tissues like liver, skeletal muscle and adipocytes are resistant to insulin or there is an increase in glucose level. It is associated with excessive glucose production by liver and imbalance in glucose utilisation by peripheral tissues and muscle [8].

While poor glycaemic control and long duration of illness leads to complications which can be characterised into two. They are microvascular and macrovascular complications (Table 1).

Diabetic retinopathy is one of the major causes of blindness in which damage occurs in the retina in individuals with prolonged diabetes mellitus. The onset of DR solely depends on the duration and severity of hyperglycaemia. In 2015, approximately 415 million people in worldwide population was affected with diabetes mellitus. With the statistics from above the rate of the affected

Table 1
Micro and Macro complication of Diabetes mellitus [9].

Macrovascular complication	Microvascular complication
Coronary Artery disease	Diabetic retinopathy
Peripheral arterial disease	Diabetic nephropathy
Stroke	Diabetic neuropathy

people is expected to rise in the year 2040 by 642 million. Since the cases of diabetes mellitus increasing in number and people affected with diabetes mellitus living longer, the diabetic retinopathy which is a complication of diabetes mellitus is predicted to increase worldwide [10] (Fig. 3).

Diabetic retinopathy is one of the leading causes of blindness that occurs due to damage in the retina in individuals with prolonged diabetes mellitus. The onset of DR solely depends on the duration and severity of hyperglycaemia. The DR begins with mild non-proliferative, progress to moderate and then to severe non-proliferative DR. If left untreated the NPDR further progresses to proliferative diabetic retinopathy. The development of diabetic retinopathy is expected in 60% of type II diabetes mellitus patients at the first decade of its occurrence. Genetic factors play an important role in DR. A study of identical twins found a concordance for DR in 68% of type 1 and 95% of type 2 diabetes cases [12].

2.1. Stages of diabetic retinopathy

The severity of diabetic retinopathy solely depends on the duration of diabetes, hyperglycaemia and hypertension. The stages of diabetic retinopathy are characterised into two they are non-proliferative diabetic retinopathy and proliferative diabetic retinopathy. These are further classified as follows [13] (Table 2).

3. Pathogenesis of diabetic retinopathy

3.1. Hyperglycaemia

3.1.1. Polyol pathway

The polyol pathway in an individual converts glucose to sorbitol in the presence of aldose reductase with a reduction of NADPH to $NADP^+$. In hyperglycaemic conditions, the glucose has a higher affinity on aldose reductase and the glucose is then converted to sorbitol. The sorbitol is accumulated in the retina and the polyol pathway consumes more NADPH which makes the latter unavailable for other metabolic pathways [15,16].

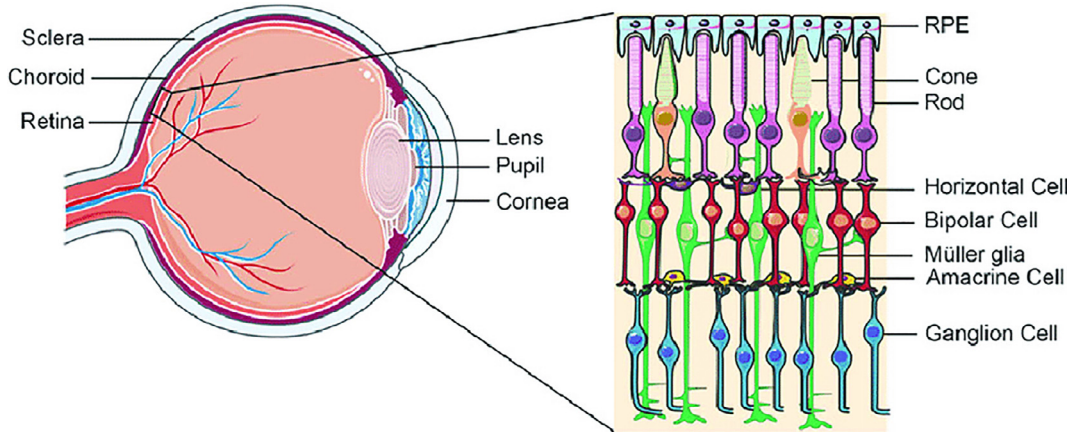

Fig. 2. Neurons of retina [7].

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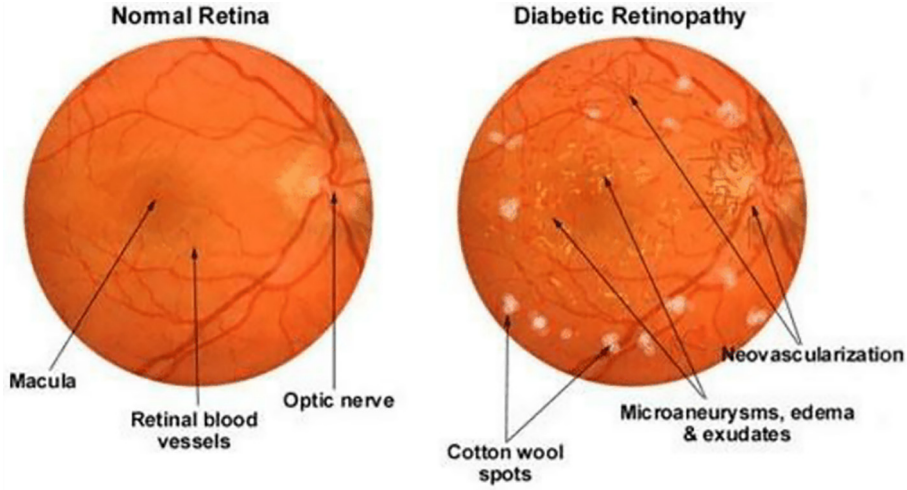

Fig. 3. Retina of normal (left) and diabetic retinopathy (right) [11].

Table 2
Pathogenic events and stages of diabetic retinopathy [10,14].

S. No.	Stages and lesions of diabetic retinopathy	
1.	Diabetic Retinopathy	
	DR	Less than one haemorrhage is present but microaneurysms absent
2.	NPDR	
	Non-proliferative DR involves changes in vascular like basement membrane thickening, VEGF produced by RPE macrophages, and glial cells. Disruption of tight junctions and loss of pericyte occurs due to endothelial injury.	
	Minimal NPDR	Microaneurysms only
	Mild NPDR	Cotton wool spots or mild haemorrhages in the retina, or both.
	Moderate NPDR	Moderate to severe haemorrhages are found. Presence of mild intraretinal microvascular abnormalities (IRMA) in one to three fields.
	Moderately severe NPDR	Presence of severe haemorrhages in one or two fields. IRMA is visible in four fields, or both.
	Severe NPDR	Atleast two field will have venous beading, Severe haemorrhages in 2–4 fields; moderate to severe IRMA in one field.
3.	PDR	
	During pre- proliferation stage the endothelial is damaged, due to which the vasoconstrictors and hypoxia are released. The vasoconstrictors includes thromboxane A2 and endothelial 1. These occurrence are aggravated due to capillary occlusion.	
	Mild PDR	Formation of new blood veins everywhere, 0·5 disk area in at least one field.
	Moderate PDR	Formation of new blood vessels everywhere, haemorrhage in vitreous, 0·5 disk area in at least one.
	Severe PDR	Vitreous haemorrhage or preretinal haemorrhage, or both equal to or exceeding one disk area; New vessels everywhere vitreous haemorrhage equal to or exceeding half disk area with vitreous haemorrhage or preretinal haemorrhage, or both.
	Advanced PDR	Advanced PDR Macula obscured by vitreous haemorrhage or preretinal haemorrhage; or retina detached at the centre of the macula, or all of these

3.1.2. Hexosamine pathway

The glucose when enters the glycolysis pathway it initially gets metabolized to form glucose 6 phosphate and then to fructose 6 phosphate [17]. The fructose 6 phosphate under normal condition converts to fructose 1, 6 bisphosphate but under hyperglycaemic condition, the fructose 6 phosphate is converted to glucosamine 6 phosphate in presence of the GFAT (glutamine fructose 6 phosphate amidotransferase), which is further metabolized to UDP (uridine diphosphate) N acetyl glucosamine, the latter is then attached to the serine and threonine residues in the transcript which alters the expression of the gene [18].

3.1.3. Protein kinase C (PKC) activation

The proteins involved in signal transduction are phosphorylated. This phosphorylation is catalysed by the protein kinase C. During the hyperglycaemic condition, the diacylglycerol (DAG) concentration is increased. The isoforms of PKC are upregulated by the DAG. The isoforms of PKC are expressed and activated in various tissues, especially in retina [19]. The PKC activation in the retina result in the changes in blood flow in the retina, expression of growth factors that are derived from endothelial and leukostasis. The PKC activation leads to alteration in the basement membrane resulting in pericyte loss. An increase in the activation of PKC is associated with VEGF resulting in angiogenesis and vascular permeability [20,21].

3.1.4. Accumulation of AGEs

AGEs are advanced glycation end products that play an important role in the onset of diabetic retinopathy. During the hyperglycaemic condition, AGEs are accumulated. AGEs are lipids or proteins that are oxidized when exposed to aldose sugars. The Carboxyethyl lysine and carboxymethyl lysine play a key role in the accumulation of AGEs in hyperglycaemia. The AGEs cross-link the receptors of advanced glycation end (*RAGE*) products and molecules in the extracellular matrix resulting in microvascular and macrovascular complications. The AGEs localize in the retinal blood vessel and increase the degree of diabetic retinopathy [22,23].

3.2. Oxidative stress

Every cell uses oxygen for metabolic activity, the cellular homeostasis balance the elimination and formation of reactive oxygen species that are cellular metabolism's by-products. When excessive ROS are accumulated they result in oxidative stress. The antioxidant removes the ROS and maintains the level of ROS in the cell. In the retina, the polyunsaturated fatty acids are higher in concentration resulting in oxygen uptake and oxidation of glucose. Accumulation of ROS in the retina results in oxidative stress and increases the susceptibility to Diabetic retinopathy [24,25]. The diabetic rat model was used the study the ROS activity in the retina. Superoxide levels and hydrogen peroxide levels were

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elevated in retinal cells in the rat model when incubated in high glucose media [26,27] (Fig. 4).

4. Genetics of diabetic retinopathy

4.1. Vascular endothelial growth factor gene

VEGF initiates intraocular neovascularisation and it increases the permeability of the retinal blood vessels. Expression is induced by hypoxia. The VEGF concentration was higher in PDR when compared with individuals having no diabetes and individuals having NPDR. A study was conducted which included 20 patients with both PDR and NPDR [29,30]. This study resulted in increased VEGF concentration in ocular fluids collected from proliferative diabetic retinopathy when compared with ocular fluids of non-proliferative diabetic retinopathy patients. This concludes that the expression of this gene in higher concentrations leads to proliferative diabetic retinopathy. The SNPs present in VEGF that are associated with DR are rs699947, rs833070, rs2146323, rs3025007, rs3025010, rs3025020, rs3025021, and rs3025028. Other SNPs that are associated with Diabetic retinopathy in other population that are present in VEGF gene are rs2010963, rs25648, rs1570360, rs3095039, rs35569394, rs699947, rs13207351, rs735286, rs2146323, rs833061, rs302502, rs10434 and rs833068 [31–34].

4.2. Aldose reductase (ALR) gene

The aldose reductase monitor and control the polyol pathway. The polyol pathway is responsible for the conversion of glucose to sorbitol under normal condition but during hyperglycaemic condition, the sorbitol will accumulate resulting in the osmotic stress. ALR produces inactive alcohols by reducing the toxic aldehydes which are generated by reactive oxygen species [35]. Reduction in the availability of the cofactor NADPH could induce intracellular oxidative stress. Chronic hyperglycaemia and oxidative stress can result in permanent irreversible damage to pancreatic β-cells [36,37]. The genetic variation in AKR1B1 (member of aldose reductase) alters the ALR activity resulting in induction of oxidative stress. A research study was conducted which included 54 patients from Australia with diabetic retinopathy where the SNPs rs17773344, rs9640883, rs12666669, rs782054, rs1708414, rs1791001, rs2259458, rs3896278 were found in this gene. Out of all the SNPs mentioned above, the SNP rs9640883 is the most the significantly associated with diabetic retinopathy [38].

4.3. Advanced glycation end products (AGEs) gene

The Advanced glycation end products gene express protein and accumulates in tissue if it is exposed to glucose for a longer duration. The AGEs then stimulate endothelial proliferation. It has been proposed that intracellular AGE formation occurs in retinal pericytes which affect the DNA function and damage the capillary in the retina [39]. These advanced glycated products modulate the signalling pathways by binding with Receptors of Advanced Glycated End products (RAGE), this modulation is reported in the development of diabetic retinopathy [40]. This plays an important role in vascular complications where the RAGEs are expressed on the endothelial cells, vascular smooth muscle cells. A polymorphism in AGE-R1 is associated with the severity of retinopathy [36]. The SNPs rs1800624, rs2070600, rs1800625 are reported to be associated with diabetic retinopathy in these research paper [41,42].

4.4. Endothelial nitric oxide synthase (eNOS)

The gene encoding eNOS protein catalyses the production of nitric oxide (NO). NO increase the oxidative stress in the cell which plays an important role in microvascular complication. The production of NO increases when there is a high concentration of glucose. NO plays a major role in retinal circulation and vascular remodelling [43]. The VEGF activity is enhanced by the NO production. Hence eNOS gene is associated with diabetic retinopathy [44].

4.5. Erythropoietin (Epo)

The erythropoietin gene plays a crucial role in the progress of NPDR to PDR. PDR is the growth of new blood vessels. The erythropoietin is induced by ischemia which shows retinal angiogenic properties. The erythropoietin level in vitreous collected from PDR patients was higher when compared to non-diabetic patients. This paper also states that the Epo is more strongly associated with PDR than that of VEGF and a potent retinal angiogenic factor [45]. The paper [46] stated that the Single nucleotide polymorphism rs1617640 (T allele) in the promoter region of the Epo gene was

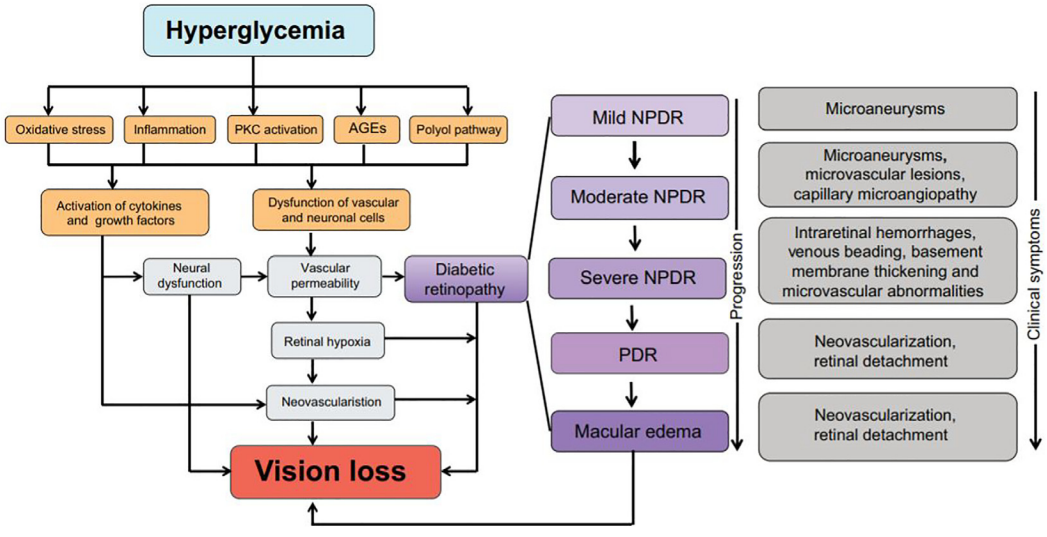

Fig. 4. Pathogenesis of diabetic retinopathy [28].

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significantly associated with the progression of PDR. The research paper [47] states that the variants rs507392, rs1617640, rs551238 in the erythropoietin gene are significantly associated with DR.

5. Role of ubiquitin – proteasome pathway in diabetic retinopathy

The Ubiquitin-Proteasome Pathway degrade the misfolded protein or protein that are present in higher concentration by proteolysis process. The ubiquitin–proteasome consists of three different enzymes that degrade proteins by linking the polypeptide chains and mark them for degradation by tagging five molecules of ubiquitin to the protein which is a cofactor. The three different enzymes are E1 ubiquitin-activating enzyme, E2 ubiquitin-conjugating enzyme, and E3 ligases. This whole degradation process in ATP dependent. The ubiquitinated protein is recognised by the 26S proteasome which degrades the protein to small peptides [48]. The function of the UPP is as follows

1. Removal of protein
2. Regulation of gene transcription
3. Mechanism of Quality control
4. Provide a source of amino acids

Removal of protein:

The protein degradation by UPP is irreversible. The protein destruction leads to rapid, complete and sustained termination of the process involving a change in the cell composition. This rapid degradation of specific protein permits adaptation to new physiologic conditions.

Regulation of Gene transcription:

The transcription is affected by the ubiquitin conjugation by various mechanisms. The transcriptional factors at times are ubiquitinated and degraded by the proteasome. The signals for ubiquitin conjugation and activation domains of transcription factors overlap each other. The transcriptional activity is stimulated by the activators that are undergoing proteolysis by UPP48. During inflammatory response, the proinflammatory transcriptional activator NF-κB remains outside the nucleus by interacting with IκB. The IκB is ubiquitinated and degraded when it is phosphorylated and recognised by E3 beta transducing containing protein. The NF-κB released and is then translocated to the nucleus. This plays an important role in the inflammatory response [49].

Mechanism of Quality Control:

The UPP controls the quality of the protein by degrading the abnormal or damaged proteins that are translated from missense or nonsense mutated strand or from the DNA strand that are damaged by reactive oxygen species.

Provide a source of Amino Acids:

The amino acids that are released during the degradation by UPP are provided to gluconeogenesis to synthesis new protein and energy production. This process is activated during fasting (Fig. 5).

5.1. Ubiquitin proteolytic pathway in eye

The cell processes are regulated by degrading the regulators by the ubiquitin pathway (UP). The UP regulates cell cycle, transcriptional regulation, organogenesis, proliferation, differentiation, development and signal transduction in the lens and retina. On exposure to stress and aging, the damaged proteins which are cytotoxic are accumulated in the lens and retina. These damaged proteins require UP for their removal. The pivotal role of UP in the retina is signal transduction, development, and differentiation. Ubiquitin is present throughout the retina in specific in ganglion cells and retinal pigment epithelium [51].

5.2. Ubiquitin proteasome system in diabetic retinopathy

Diabetic retinopathy upregulates angiotensin II which increases the retinal blood pressure. The angiotensin II downregulates the UPS mediated expression of synaptophysin which is protein in synaptic vesicles in the retina. Angiotensin activates ERK which belongs to the MAPK family of protein kinase by binding to Angiotensin II Type 1 Receptor (AT1R). The ERK increases the ubiquitin conjugate SYP by involving the action of siah E3 ubiquitin ligase. The ROS level is higher in the retina in diabetic retinopathy mice,

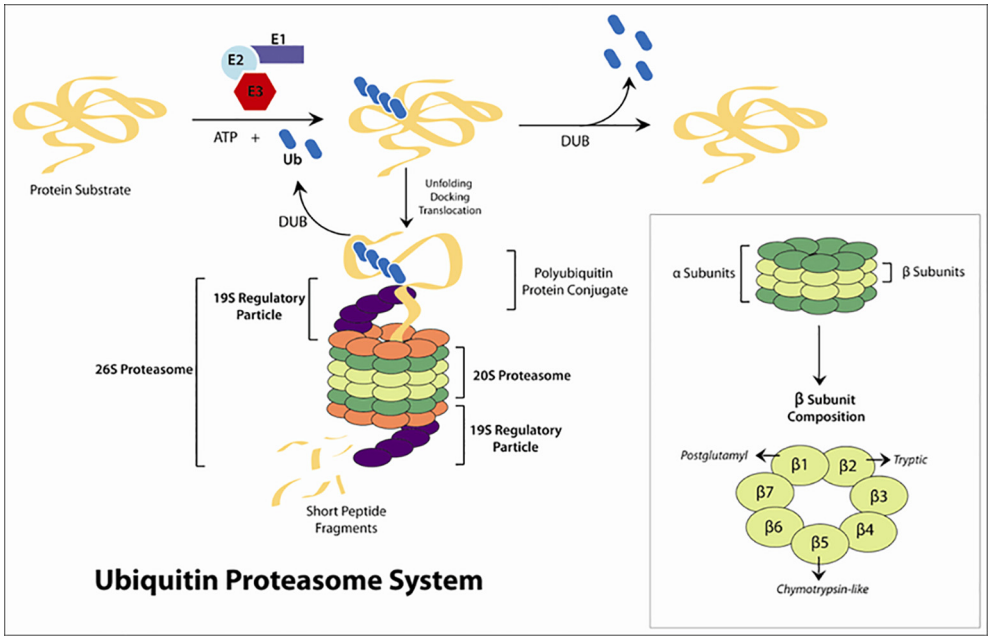

Fig. 5. Ubiquitin proteasome pathway [50].

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Table 3
Tabulation of SNPs population wise that are associated to DR [55–62].

S. No.	Candidate Gene	Function of The Gene	SNPs	Type of DM (I And II)	Population
1	Aldose reductase gene	Polyol pathway – glucose is converted to sorbitol	rs35839483	I and II	Chinese, Japanese, Indian, Chileans, Brazilians
			rs759853	II	Euro-Brazilian, Mainland Chinese, Han Chinese, Japanese
			rs9640883	II	Australian
2	Sorbitol dehydrogenase	Polyol pathway – sorbitol is converted to fructose	rs2055858	II	Poles (Poland)
			rs3759890	II	Japanese, Poles (Poland), Caucasian-Brazilians
3	Vascular endothelial growth factor	Stimulation of angiogenesis and vasculogenesis	rs2010963	II	Japanese, Indian, Caucasian
			C-460T	I and II	Caucasian
			rs25648	II	Multi – ethnic
			rs1570360	II	Multi - ethnic
			rs3095039	II	Multi - ethnic
			rs35569394	II	Multi - ethnic
			rs699947	II	Multi - ethnic
			rs13207354	I and II	Caucasian
			rs735286	I and II	Caucasian
			rs2416323	I and II	Caucasian
			rs833061	II	Chinese
			rs3025021	II	Chinese
			rs10434	I and II	Caucasian
			rs833068	I and II	Caucasian
			rs833070	I	Japanese
			rs3025039	II	Caucasian
4	Fibroblast growth factor 2	Stimulation of angiogenesis, tissue regeneration and replacement	rs41456044	II	Multi - ethnic
			rs308395	II	Multi - ethnic
			C-754G	II	Slovak
			T-553A	II	Caucasian
			T-834A	II	Caucasian
5	Insulin – like growth factor 1	Stimulates cell growth and proliferation, inhibits apoptosis	(CA)n repeats	II	Southern Indian
6	Erythropoietin	Stimulates proliferation, migration of angiogenesis and controls erythropoiesis	rs1617640, rs507392, rs551238	I and II	Multi – ethnic, European, American, Australian
7	Advanced glycosylation end product	Activate pro - inflammatory genes	rs1800624	II	Indian, Chinese, African – Brazilian
			rs1800625	II	Caucasian, Indian, Danish
			rs2070600	II	Caucasian, Indian, Chinese, Malaysian
8	Angiotensin – I converting enzyme	Activates angiotensin II	rs4646994 (insertion/ deletion at intron 16)	I and II	Chinese, Japanese, Iranian
9	Mitochondrial manganese superoxide dismutase	Peroxide is converted to oxide which results in reduction of ROS	rs4880	I and II	Finnish, Indian
10	Endothelial nitric oxide synthases	Synthesis of nitric oxide	rs3138808	II	Indian, Caucasian – Brazilian, West African
			rs1799983	II	Caucasian – Brazilian, Danish
11	Retinoid X receptor alpha	Nuclear receptor – gene activation mediated by retinoic acid	rs3132300	I	African American
12	Retinoid X receptor gamma	Nuclear receptor – gene activation by retinoic acid	rs3818569	–	Taiwanese
13	Uncoupling protein – 1	Mitochondrial anion carrier protein	rs1800592	I and II	Brazilian, Chinese, Danish
14	Uncoupling protein – 2	Controls ROS production	rs660339	I and II	Brazilian
15	Toll – like receptor 4	Innate immunity activation by pathogen recognition	rs10759931, rs1927914	II	Indian, Chinese
16	Complement factor H	Complement system activation	rs800292	II	Chinese
17	Complement factor B	Complement system activation	rs1048709	II	Chinese
18	Vitamin D receptor	Nuclear hormone receptor for vitamin D3, associated with insulin secretion and sensitivity	rs2228570	II	Han Chinese
19	Tumor necrosis factor - alpha	Responsible for cell proliferation, differentiation, lipid metabolism and coagulation	rs361525	II	Indian
			rs1800629	II	Caucasian – Brazilian
20	26S proteasome non – ATPase regulatory subunit 9	Present in catalytic protein complex- proteasome	rs74421874, rs14259, rs3825172	II	Italian
21	Integrin β5	Interactions between cells and cell – extracellular matrix	rs9865359	I	African American
22	Insulin receptor	Activate insulin signalling pathway	rs10500204	I	African American
23	Interleukin – 10	Cytokine that takes part in immunoregulation and inflammation	A – 1082G	II	Indian
24	Serotonin receptor 1B (HTR1B)	Regulate serotonin dopamine, retinal blood flow	rs1228814	I	African American
25	Major histocompatibility complex class I, B (HLA - B)	Regulate immune system by presenting peptides on cell surface	rs2523608	I	African American

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Table 3 (*continued*)

S. No.	Candidate Gene	Function of The Gene	SNPs	Type of DM (I And II)	Population
26	Ectonucleotide pyrophosphatase/ phosphodiesterase 1	Interacts with integrins and resistance to insulin	rs1409181	I	African American
27	Carboxypeptidase, vitellogenic – like (*CPVL*)	Function is unknown	rs39059 rs1002630	II II	Chinese Taiwanese

both the ROS and AT1R promote the ERK. On recognising the ubiquitin conjugate SYP, the proteasomal system degrades it resulting in malfunctions of synaptic activity, neuronal cell survival, and visual function. In diabetic retinopathy, hyperglycaemia leads to ROS production especially superoxide which is released by autooxidation of glucose. On oxidative stress, the glucose transporter 1 (GLUT1) is ubiquitinated and degraded by the UP thus reducing the GLUT1 concentration in the plasma membrane of retinal endothelial cells. In an advanced stage of DR, macular ischemia result in decreased oxygen which result in the proliferation of capillary endothelial cells. This result in formation of new blood vessels in the vitreous and retina leading to vision loss. The transcription of the angiogenic growth factors gene is activated by the hypoxia-inducible factor (HIF) mediated signalling cascade. The HIF-1α and HIF-1β subunits are protected by proteasomal degradation and associate together to form active HIF-1 transcription factor, this binds to the target genes and activates the expression of angiogenic factors like VEGF, endothelin-1 and erythropoietin [52–54].

6. SNPs of diabetic retinopathy in different cohorts

It has been proposed in various journals that the Single Nucleotide Polymorphism (SNP) influence the susceptibility to common diseases. To prove this proposal, Case-Control studies have been done to find SNPs that are significantly associated with diseases. The SNPs that are associated with diabetic retinopathy based on cohorts are discussed in this review paper [63–72] (Table 3).

7. Conclusion

Many genome wide association studies involving individuals have reported statistical analysis which results in significant association of SNP with a particular disease. This paper gives a detailed report on the most associated SNP with diabetic retinopathy with respect to the different ethnic traits. These SNPs can be used as a therapeutic target on treating diabetic retinopathy and also a biomarker.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

The authors thank Vels Institute of Science, Technology and Advanced Studies (VISTAS) management for constantly supporting in writing this review article successfully.

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Please cite this article as: R. Thiruchelvi and K. Raghunathan, Diabetic retinopathy its genetics and single nucleotide polymorphism associated with multi-ethnic cohort – A review, Materials Today: Proceedings, https://doi.org/10.1016/j.matpr.2020.07.178

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Please cite this article as: R. Thiruchelvi and K. Raghunathan, Diabetic retinopathy its genetics and single nucleotide polymorphism associated with multi-ethnic cohort – A review, Materials Today: Proceedings, https://doi.org/10.1016/j.matpr.2020.07.178