

Diabetic Macular Oedema: underrepresented in the genetic analysis of diabetic retinopathy

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Abstract

Diabetic retinopathy, a complication of both type 1 and type 2 diabetes, is a complex disease and is one of the leading causes of blindness in adults worldwide. It can be divided into distinct subclasses, one of which is diabetic macular oedema. Diabetic macular oedema can occur at any time in diabetic retinopathy and is the most common cause of vision loss in type 2 diabetic patients. The purpose of this review is to summarise the large number of genetic association studies that have been performed in type 2 diabetic patient cohorts and published in English language journals up to February 2017. Many of these studies have produced positive associations with gene polymorphisms and diabetic retinopathy. However this review highlights that within this large body of work, studies specifically addressing a genetic association with diabetic macular oedema, although present are vastly under-represented. We also highlight that many of the studies have small patient numbers and that meta-analyses often inappropriately combine patient datasets. We conclude that there will continue to be conflicting results and no meaningful findings will be achieved if the historical approach of combining all diabetic retinopathy disease states within patient cohorts continues in future studies. This review also identifies several genes that would be interesting to analyse in large, well defined diabetic macular oedema patient cohorts in future candidate gene association studies.

Key words

Diabetic macular oedema, diabetic retinopathy, single nucleotide polymorphism, genetic association studies

Introduction

It is well documented that diabetes is becoming more prevalent across the world, with the biggest increase being in Type 2 diabetes (T2D). A combination of increasing longevity, increasing obesity and earlier detection of disease may underlie this. In 2011 the International Diabetes Federation (IDF) estimated that 366 million people globally had diabetes and if no action is taken this number is predicted to increase to 552 million by 2030 (Guariguata et al. 2011; Ruta et al. 2013). The rise in the incidence of diabetes is a major public health concern because it is likely to be followed by a rise in its associated macrovascular complications including cardiovascular and peripheral vascular disease and microvascular complications including neuropathy, nephropathy and retinopathy. These complications result from vascular damage due to chronic elevation of blood glucose levels (hyperglycaemia) (reviewed (Forbes & Cooper 2013)).

Diabetic retinopathy (DR), a microvascular complication, is one of the leading causes of blindness in adults worldwide (Klein 2007) and has a marked effect on public health resources. It is well established that the pathogenic changes in diabetic retinopathy are brought about by changes in various pathways including metabolic processes, enzymes and growth factors and are associated with genetic polymorphisms that the patient carries in their DNA (Brownlee 2001). Diabetic retinopathy is seen in almost all patients with type 1 diabetes mellitus (T1D) and in approximately 60% of patients with type 2 diabetes (T2DM) (Scanlon 2008).

Diabetic retinopathy is a complex disease which can be subdivided into non-proliferative (NPDR) and proliferative (PDR). PDR is a more advanced state of the disease where usually the retinal circulation fails and the tissue becomes oxygen deprived resulting in fragile, leaky neovascularisation. NPDR is the early stage of the disease with no or very mild symptoms. In this state, there is neuronal loss, local inflammation and pericyte loss leading to the formation of microaneurysms which can leak fluid into the retina. When the fluid leaks into the macular region, diabetic macular oedema (DMO) occurs. Diabetic macular oedema can happen at any stage of diabetic retinopathy (Klein et al. 1994; Caldwell et al. 2003). In patients with T2DM, DMO is the most common cause of loss of vision (Romero-Aroca 2011).

It has been reported that DMO affects approximately 75,000 new patients in the United States every year (Bresnick 1986). A literature review of the burden of illness reveals that patients with DMO consume significantly more healthcare resources and incur higher costs compared to diabetic patients without retinal complications (Chen et al. 2010). DMO is not a uniform condition it can be divided into several different subtypes of disease. However a universal grading system is still lacking for this condition. As such, DMO raises many questions including why current treatments are not effective for all patients and why patient lifestyle does not always correlate with disease progression. In order to answer these questions we need to more fully understand the complex and multifactorial pathophysiological mechanisms involved in these disease processes.

DMO is thought to occur as a result of disruption of the blood-retinal barrier (BRB), which leads to swelling or thickening in the macular area as a result of the accumulation of sub- and intra-retinal fluid in the inner- and outer-plexiform layers (Murakami et al. 2011; Zhang et al. 2014). Several risk factors for the development of diabetic eye disease have been identified and well documented. These include poor blood sugar control, high blood pressure and elevated lipid levels (for reviews see (Cheung et al. 2010; Ehrlich et al. 2010)). Hyperglycaemia from poor blood sugar control leads to

a chain of damaging tissue responses in the retina resulting in the formation of free radicals (oxidative damage), microthrombi formation (microscopic clumps of fibrin, platelets and red blood cells), cell adhesion molecule activation and leukocyte and cytokine activation which results in ischaemia-mediated over-expression of growth factors and cytokines (the various mechanisms of diabetic complications are summarised schematically in **Figure 1**) (for a comprehensive review of diabetic complications see (Forbes & Cooper 2013)). However it is the breakdown of the BRB, caused by an alteration in the permeability characteristics of the retinal endothelial cells due to the elevated levels of various growth factors and cytokines, that results in the subsequent vascular dysfunction (reviewed in (Klaassen et al. 2013)). It is likely that inflammation plays a key role in some subtypes of DMO pathogenesis and the observation that the phenotype closely resembles that of cystoid macular oedema (CMO) seen in uveitis and Irvine-Gass syndrome (Freeman et al. 2001; Conway et al. 2003) supports this.

In addition to the many risk factors that have been proposed due to the complex metabolic environment of the retina (Klein et al. 1994), single nucleotide polymorphisms (SNPs) in an array of genes involved in these pathways have been shown to have an effect on the development and progression of diabetic retinopathy in different populations. The groups of genes studied are predominantly those with known metabolic or functional roles in diabetes.

To date most of the published studies have had small patient sample sizes, or have been large meta-analyses that have not fully taken into account variations in ethnicity, type of diabetes or specific type, or even subtype, of diabetic retinopathy. Therefore conclusions are difficult to draw, and this is shown by conflicting reports of significance between studies.

This review will focus on seven processes involved in the development of diabetic retinopathy that result from chronic hyperglycaemia (these are oxidative stress, microthrombi formation, cell adhesion molecule activation and leukocyte and cytokine activation resulting in ischaemia-mediated over-expression of growth factors and cytokines). It will also focus on the genes involved at each stage. It should be noted that some genes may be linked to more than one step in the disease process as some components lead to a self-perpetuating, vicious cycle of damage which can feedback to earlier stages and enhance the damage of previous stages making this a very complex disease system. In the following sections, each of these stages and the key molecules involved will be described. The full functions of many of the genes are still not completely understood.

There have been many studies using diabetic patient cohorts to find genes associated with retinopathy. We have summarised the studies that have analysed patients with type 2 diabetes and have been published in English (**Table 1**). The table lists the cohort size and ethnicity as well as the statistical finding from each study. It should be noted that associations from candidate gene studies stated in **Table 1** are based on the claims of the original paper and may not be truly significant as many of the studies did not correct for multiple hypothesis testing. There have also been Genome Wide Association Studies (GWAS) performed using type 2 diabetic retinopathy patient cohorts. Many of these studies claim to have found gene associations however, in general, results from GWAS studies should only be deemed significant when $p < 5 \times 10^{-8}$. The results of these studies and their significance have been summarised in **Table 2** and are discussed in section 1.8. Given the burden of DMO, this review demonstrates the striking under representation of DMO patients as a separate disease group in previous genetic studies (**Table 3**). Greater progress in understanding the

genetic risk factors of DMO may only be made if future studies considered DMO as a separate disease entity and treat the analysis as such.

1. Chronic hyperglycaemia

In a healthy individual, normoglycaemia is maintained by negative feedback loops controlled by the hormones glucagon and insulin. Low blood glucose triggers the release of glucagon, which instructs liver cells to convert glycogen stores to glucose, via the process of glycolysis. The glucose is then released into the bloodstream, raising blood sugar levels. When blood sugar levels are raised, insulin is released and instructs the liver to convert more glucose to glycogen and forces cells to take up glucose from the bloodstream to reduce the level. Glycolysis is abnormal in diabetic patients (Brownlee 2001). One of the cell types that is prone to diabetic complications are the endothelial cells, which line the interior surface of blood and lymphatic vessels. Endothelial cells are not able to control glucose transport rates to prevent excessive build-up of intracellular glucose under chronic hyperglycaemic conditions (Heilig et al. 1995). This results in uncontrolled energy production within these cells which can lead to the switching to other inappropriate fuel sources and the dysregulation of proteins in turn triggering damaging effects (reviewed by Forbes and Cooper 2013) (Forbes & Cooper 2013).

Hyperglycaemia is defined as having a blood glucose level of 7 mmol/l or higher when fasting or 11 mmol/l or higher 2 hours after meals (<http://www.diabetes.co.uk/Diabetes-and-Hyperglycaemia.html>), and is associated with high intracellular levels of glucose. Chronic hyperglycaemia activates the polyol pathway, transcription factors and various cellular receptors. This activation leads to the formation of free radicals (oxidative stress), and the subsequent downstream activation of protein kinase C (PKC), advanced glycation end products (AGEs) and vascular endothelial growth factor (VEGF) (Witmer et al. 2003). It is thought that these interrelated, activated pathways are the cause of the microvascular damage in patients.

1.1 Polyol pathway including aldose reductase and sorbitol dehydrogenase

The polyol pathway metabolises excess glucose via two enzymatic steps: aldose reductase which reduces glucose to sorbitol, then sorbitol dehydrogenase oxidises sorbitol to fructose. This pathway metabolises the excess glucose into toxic metabolites which can cause damage to cells (Brownlee 2001).

1.1.1 Aldo-keto reductase family 1 member B (AKR1B1) and sorbitol dehydrogenase (SORD)

Aldo-keto reductase family 1, member B1 (AKR1B1) also known as aldose reductase (ALR2) is the first and rate limiting step in the polyol pathway. This pathway becomes active when intracellular glucose levels become elevated (Gabbay 1973; Oates 2002). AKR1B1 reduces glucose to sorbitol using nicotinamide adenine dinucleotide phosphate (NADPH) as a co-factor.

Sorbitol is then metabolised to fructose by sorbitol dehydrogenase (SORD, previously known as SDH) that uses nicotinamide adenine dinucleotide (NAD⁺) as a cofactor. There are several damaging downstream effects resulting from dysfunction of this process. Sorbitol is an alcohol and does not readily diffuse through cell membranes so therefore accumulates intracellularly which in turn has

osmotic consequences. The fructose produced by the polyol pathway can become phosphorylated to fructose-3-phosphate which can be broken down to 3-deoxyglucosone; both these compounds are powerful glycosylating agents that are involved in the formation of advanced glycation end products (AGEs) (Gonzalez et al. 1988; Szwergold et al. 1990). The usage of NADPH by ALR2 may result in less co-factor being available for glutathione reductase, which is critical for the maintenance of the intracellular pool of reduced glutathione (GSH). This in turn would lessen the capability of the cell to respond to oxidative stress (Barnett et al. 1986). The usage of NAD by sorbitol dehydrogenase leads to an increased ratio of NADH/NAD⁺, which has been termed pseudohypoxia and is linked to a number of metabolic and signalling changes known to alter cell function (Williamson et al. 1993), which in turn can result in cellular damage via osmotic and oxidative stress (Lorenzi 2007). Tilton et al. used an inhibitor of SORD in diabetic rats to show attenuated vascular dysfunction even though elevated levels of sorbitol were present in the eye. Hence they postulated that it is the increased oxidation of sorbitol to fructose that causes more of the vascular damage observed and that the osmotic imbalances associated with the reduction of glucose to sorbitol by aldose reductase (Tilton et al. 1995; Amano et al. 2003). Amano et al. suggested that a haplotype of C-G in two polymorphisms (rs2055858 and rs3759890) in the promoter of the *SORD* gene could be correlated with its expression level in the retina of diabetic patients (Amano et al. 2003).

The association of various polymorphisms in the *AKR1B1* gene with diabetic retinopathy has been widely reported. These include the z-2 allele of the (CA)_n microsatellite at the 5' end of the gene and the promoter SNP rs75983. As shown in table 1 several studies have examined rs75983 and include cohorts from different ethnic backgrounds as well as meta-analysis studies. Four studies found an association in patients with diabetic retinopathy (Olmos et al. 2006; Katakami et al. 2011; Rezaee et al. 2015; Kaur & Vanita 2016) while two meta-studies and analysis in a Chinese cohort did not find association (Olmos et al. 2006; Abhary et al. 2009; Katakami et al. 2011; Deng et al. 2014; Rezaee et al. 2015; Zhou et al. 2015; Kaur & Vanita 2016). Four further SNPs (rs2259458, rs3896278, rs1790998 and rs5053) have been examined by Simoes et al. in their Portuguese cohort but none of the SNPs showed association (Simoes et al. 2014). Abhary et al. conducted a meta-analysis in 2009 and failed to show association with any SNP (Abhary et al. 2009). However the following year they analysed 14 *AKR1B1* polymorphisms in their own Caucasian cohort and found association between rs9640883 and DR (Abhary et al. 2010). Szaflik et al. (Szaflik et al. 2008) reported that a SNP upstream of *SORD* (rs3759890) may be associated with the onset of DR but not the progression and this effect is potentially strengthened with the interaction with a second promoter SNP (rs2055858). Ferreira et al. also investigated SNP rs3759890 and found no association with diabetic retinopathy (Ferreira et al. 2013).

1.1.2 Cannabinoid type 1 receptor (CNR1)

The cannabinoid type 1 receptor (CNR1) gene is located on chromosome 6q14-q15 and encodes a G-protein coupled cannabinoid receptor, CB1. CNR1 gene expression is found mainly in tissues of the central nervous system but is also found in liver, muscle and adipose tissues. CB1 along with another G-protein coupled receptor, CB2, form the endocannabinoid system (ECS) (Howlett et al. 2010; Miller & Devi 2011; Buraczynska et al. 2014). The ECS is found in the eye with CB1 receptors expressed in the retina. Matias et al. showed that EC levels are elevated in the eyes of DR patients (Matias et al. 2006). Lim et al. demonstrated that hyperglycaemia caused the upregulation of CB1 receptor expression and induced apoptosis in the retina (Lim et al. 2012). El-Remessy et al. showed that treatment with a CB1 receptor antagonist or the deletion of the CB1 receptor in a murine model

of diabetes prevented retinal cell death (El-Remessy et al. 2011). There is also evidence to suggest that the ECS may have a role in reactive oxygen species (ROS) production, inflammation and subsequent tissue injury (Janiak et al. 2007), all of which are key processes in diabetic retinopathy. Buraczynska et al. examined a polymorphism (rs1049353) in their Caucasian cohort that had previously been shown to be associated with conditions such as metabolic syndrome (Hu & Feng 2010; De Luis et al. 2011), coronary artery disease (Liu & Zhang 2011; Wang et al. 2012) and Crohn's disease (Storr et al. 2010). Their study demonstrated that this SNP was associated with the development of diabetic retinopathy (Buraczynska et al. 2014).

1.1.3 Peroxisome proliferator-activated receptor gamma (PPAR γ)

The gene that encodes peroxisome proliferator-activated receptor gamma (PPAR γ) is located on chromosome 3p25. PPAR γ is a member of the nuclear hormone receptor superfamily. Nuclear hormone receptors are intracellular transcription factors that can directly regulate gene expression in response to endogenous and exogenous lipophilic molecules. This superfamily has a variety of functions including fatty acid metabolism, reproductive development and the detoxification of foreign substrates. PPAR receptors have diverse roles in fat and carbohydrate metabolism (Olefsky 2001). PPAR γ regulates the transcription of several genes involved in glucose metabolism, adipocyte differentiation, lipid oxidation, metabolic syndrome, angiogenesis and inflammation (Francis et al. 2003; Zhang et al. 2015). The SNP rs1805192 has been associated with increased insulin sensitivity, lower BMI and diabetes (Poulsen et al. 2003; Huguenin & Rosa 2010). Due to PPAR γ regulatory function of genes involved in many of the processes associated with DR such as altered lipid oxidation, increased glucose uptake or increased effects on angiogenesis via upregulation of VEGF gene expression and reduced expression of VEGF receptor 2 (Bamba et al. 2000; Sassa et al. 2004), variation in *PPAR γ* itself may confer susceptibility to DR. Six *PPAR γ* polymorphisms (rs4684847, rs12497191, rs1801282, rs1805192, rs709158 and rs3856806) have been analysed in T2DM DR cohorts (Petrovic et al. 2005; Malecki et al. 2008; Costa et al. 2009; Ma et al. 2012; Tariq et al. 2013; Wang et al. 2013; Zhang et al. 2015; Kaur & Vanita 2016). Variant rs1801282 has been shown to be associated with DR in one cohort of Caucasian patients and also in Pakistani T2DM patients (Malecki et al. 2008; Tariq et al. 2013). However, two other studies with Caucasian patient cohorts did not find an association (Petrovic et al. 2005; Costa et al. 2009). A meta-analysis of rs1801282 found an association with DR (Ma et al. 2012). No association was found with any of the other SNPs analysed (Petrovic et al. 2005; Costa et al. 2009; Wang et al. 2013; Zhang et al. 2015; Kaur & Vanita 2016). However, the role of *PPAR γ* variants in the development of DR is still not fully understood (Ringel et al. 1999; Zietz et al. 2002; Petrovic et al. 2005; Malecki et al. 2008; Costa et al. 2009; Zhang et al. 2015). This gene is also involved in the ischaemia mediated overexpression of cytokines (see section 1.7) (Qi et al. 2011).

1.1.4 Peroxisome proliferator-activated receptor-gamma coactivator-1 alpha (PPARGC1A)

Peroxisome proliferator-activated receptor-gamma co-activator-1 (*PPARGC1A*) acts as a cofactor for several nuclear hormone receptors in many tissues and organs implicated in blood pressure regulation. The gene is located on chromosome 4p15. It is expressed in vascular endothelial and smooth muscle cells and in the brain, heart and kidney (Esterbauer et al. 1999; Oberkofler et al. 2003) and may play a role in the regulation of blood pressure by interacting with mineralocorticoid and oestrogen receptors. Petrovic et al. have shown that the AA genotype of the Gly482Ser

polymorphism (rs8192678) is associated with the development of DR (Petrovic et al. 2005). Simoes et al. showed that *PPARGC1A* SNPs (rs16874271 and rs10213440) are associated with disease progression from mild to advanced DR (Simoes et al. 2014).

1.1.5 Retinoid-X-receptor (RxR)

The retinoid-X-receptor (*RXR*) is a member of the nuclear hormone receptor superfamily and is encoded by a gene located on chromosome 1q22-q23. It can form heterodimers with several nuclear receptors, including peroxisome proliferative-activated receptor (*PPAR*), it has been shown to mediate the biological effects of several hormones and drugs (Mangelsdorf & Evans 1995; Hsieh et al. 2011). Through this mediation of lipid and glucose metabolism *RXR* can have an impact on the development of diabetic complications. A recent study revealed that *RXR* possesses antioxidant properties and was shown to be associated with the development of DR (Chai et al. 2008; Roy et al. 2009). Hsieh et al. found that rs1128977 was associated with the development of diabetic retinopathy in the Taiwanese population (Hsieh et al. 2011). This gene is also involved in ischaemia mediated overexpression of cytokines (see section 1.7).

1.1.6 Transcription factor 7-like 2 (TCF7L2)

The gene encoding transcription factor 7-like 2 (*TCF7L2*) is located on chromosome 10q25. *TCF7L2* is a transcription factor influencing the transcription of several genes by binding to distinct regulatory regions, thereby exerting a large variety of functions within the cell including insulin resistance, blood glucose homeostasis, beta cell function acting through the beta-catenin, cadherin and *Wnt* signalling pathways (Wang et al. 2016). The *Wnt* signalling pathway mediates pathological vascular growth in proliferative retinopathy (Jin & Liu 2008; Tong et al. 2009; Sudchada & Scarpace 2014; Zhang et al. 2015). Polymorphisms in *TCF7L2* have been associated with T2DM (Tong et al. 2009; Ciccacci et al. 2013; Sudchada & Scarpace 2014). SNP rs1196205 in *TCF7L2* is significantly associated with risk of T2DM risk in different populations (Damcott et al. 2006; Grant et al. 2006; Hayashi et al. 2007; Ng et al. 2007). Ciccacci et al. showed that 3 SNPs (rs7903146, rs7901695, rs12255372) were associated not only with diabetes but also associated with complications such as cardiovascular disease, coronary heart disease and retinopathy (Ciccacci et al. 2013). However, this study was relatively small with 154 Italian T2DM and 171 healthy controls. Two further studies concurred with the findings of Ciccacci et al., Luo et al. (Luo et al. 2013) and a meta-analysis (Ding et al. 2015) showed that this SNP was associated with DR but only in Caucasian populations. Fu et al. did not find an association with rs7903146 and Zhang et al. did not find an association with rs1196205 in their Chinese patient cohorts (Fu et al. 2012; Zhang et al. 2015).

1.2 Oxidative Stress

Oxidative stress occurs when there is an imbalance between the production of reactive oxygen species (ROS) such as free radicals and the ability of the tissue to remove them, using antioxidants, or to prevent their damaging effects. Oxidative stress can lead to cell death within the affected tissue.

1.2.1 Adiponectin (*ADIPOQ*)

The gene encoding adiponectin (*ADIPOQ*) (full name adiponectin, C1Q and collagen domain containing) is located on chromosome 3q27. *ADIPOQ* is a secretory protein that modulates the function of endothelial cells (Okamoto et al. 2000; Ouchi et al. 2000). *ADIPOQ* is thought to modulate several processes known to be involved in the development of DR. It has been postulated

that the binding of adiponectin to receptors in the endothelial cell membrane influences the production of nitric oxide and ROS resulting in angiogenesis (Goldstein & Scalia 2004). Li et al. analysed four polymorphisms (rs266729, rs822394, rs2241766 and rs1501299) in *ADIPOQ* in a Chinese cohort. They did not find evidence of any association with the development of DR (Li et al. 2015). However, Sikka et al. found an association with the TT genotype of rs2241766 in their cohort of Punjabi patients with DR (Sikka et al. 2014).

1.2.2 Advanced glycosylation end products (AGE) and advanced glycosylation end-product specific receptors (AGER)

Advanced glycosylation end products (AGEs) are formed by non-enzymatic glycation reactions between reducing sugars and free amino acid groups (Li et al. 1996). Amadori-glycated albumin (AGA), one of the major forms of AGEs generated under hyperglycaemic conditions, is considered to be a key inducer of the pro-inflammatory response (Ge et al. 2005; Basta 2008; Ibrahim et al. 2011; Ma et al. 2014). AGE formation has been linked to the disequilibrium between pro- and antioxidants in biological systems (Taniguchi et al. 1996; Loske et al. 1998). It results in oxidative stress (see section 1.2) which is a key factor in retinopathy (Zheng & Kern 2009; Mokini et al. 2010).

Advanced glycosylation end product specific receptor (AGER), more commonly known as RAGE, is a member of the immunoglobulin superfamily that binds to various ligands including AGEs (Basta et al. 2002). AGER is involved in the surveillance of intrinsic and extrinsic stress signals and directly modulates the host inflammatory response (Yan et al. 2010). AGEs upregulate RAGE expression in various cell types and promote RAGE-induced oxidative stress generation, which further increases the formation and accumulation of AGEs and subsequent RAGE over expression (Yamagishi et al. 2012). Many pro-inflammatory vascular diabetic complications are mediated by the activation of RAGE (Schmidt & Stern 2000). RAGE is largely localized to the inner retina and its expression is increased in diabetic conditions (Soulis et al. 1997; Barile et al. 2005).

Zhang et al. (Zhang et al. 2009), Balasubbu et al. (Balasubbu et al. 2010), Yang et al. (Yang et al. 2013) and Vanita (Vanita 2014) showed that SNP rs2070600 has is associated with DR in T2DM patients. However all reported that the A allele showed the association, apart from Balasubbu et al. who reported that it was the G allele that was associated with the disease. Four other studies, including 2 meta-analyses did not find this SNP to be associated with DR at all (Uthra et al. 2010; Kang et al. 2012; Ng et al. 2012; Niu et al. 2012). Zhang et al. showed that a haplotype drawn from rs2070600 and rs184003 may be a marker for DR in Chinese T2DM patients (Zhang et al. 2009). Two meta-analyses by Niu et al. (Niu et al. 2012) and Yuan et al. (Yuan et al. 2012) reported that rs184003 was associated with DR, however a further meta-study by Kang et al. (Kang et al. 2012) and a small Malaysian study by Ng et al. (Ng et al. 2012) reported no association. Li et al. investigated the SNP rs3134940 in their Chinese cohort, but did not find an association with DR (Li et al. 2016).

1.2.3 Calpains

Calpains are a family of 14 calcium-regulated cysteine proteases, which limit specific proteolysis to modulate cellular functions (Huang & Wang 2001). Calpains are ubiquitously expressed in the cytoplasm of mammalian cells and play a role in various cell processes, including cell proliferation, signal transduction and apoptosis (Perrin & Huttenlocher 2002). Calpains are activated by locally increased intracellular calcium levels through calcium channels and intracellular stores (Camins et al. 2006). Levels of calpain are regulated by the endogenous specific inhibitor, calpastatin. In high

calcium environments it binds and inhibits calpain but when calcium levels fall it uncouples and releases calpain (Hanna et al. 2007). Oxidative stress increases free calcium ion levels and activates calcium dependent enzymes (Ray et al. 2000). The gene encoding Calpain 10 (*CAPN10*) is located on chromosome 2q37.3. Buraczynska et al. examined the polymorphism rs3792267 in relation to complications for T2DM (Buraczynska et al. 2013). Buraczynska et al. showed that rs3792267 was associated with cardiovascular disease but not microvascular disease in their cohort. This finding was in agreement with an earlier study of rs3792267 conducted by Malecki et al. who also did not find an association with diabetic retinopathy within their cohort (Malecki et al. 2008).

1.2.4 Erythropoietin (*EPO*)

The gene encoding erythropoietin (*EPO*) is located on chromosome 7q22. *EPO* regulates erythropoiesis by inhibiting apoptosis and promoting the proliferation and differentiation of erythroid precursor cells (Fisher 2003). *EPO* also has extra-erythropoietic actions with both *EPO* and its specific receptor (*EPO-R*) expressed in other tissues including the nervous system. Studies have shown that *EPO* exerts a neuroprotective effect and can prevent neuronal injury following hypoxia (Bartessaghi et al. 2005; Fisher 2010). In the nervous system *EPO* is expressed in neuronal and glial cells (Morishita et al. 1997) and *EPO-R* is expressed in endothelial cells. *EPO* can stimulate signalling in endothelial cells and also has a protective effect on vascular stability (Ribatti et al. 1999; Chen et al. 2008). Regulation of *EPO* relies on a feedback mechanism of oxygen saturation through the activation of hypoxia-inducible factors (HIFs) (Jelkmann 2007). *EPO* and *EPO-R* expression has been found in the retina (Garcia-Ramirez et al. 2008; Hernandez & Simo 2012) with highest expression in the RPE. *EPO* has been shown to exert an anti-inflammatory effect on the brain and may also do so in the retina (Villa et al. 2003). *EPO* is a potent stimulus for the mobilisation of endothelial progenitor cells, and it could play a role in directing circulating endothelial progenitor cells towards injured retinal sites (Heeschen et al. 2003).

The retina is the most metabolically active tissue in the human body and therefore is highly sensitive to reductions in oxygen tension. Hypoxia is a major stimulus for both systemic and intraocular *EPO* production. *EPO* overexpression has been found in both the RPE and the neural retina of diabetic eyes (Garcia-Ramirez et al. 2008). Intravitreal levels of *EPO* have been found at a similar range in both PDR and DMO. *EPO* was able to improve diabetic macular oedema when it was administered for treatment of anaemia in diabetic patients with renal failure (Friedman et al. 2003) and intraperitoneal administration of a peptide based on the *EPO* helix B domain (streptozotocin) inhibits diabetes-related retinal oedema in rats (Brines et al. 2008). In addition to its anti-permeability, anti-inflammatory and neuroprotective roles, *EPO* protects against hyperglycaemic apoptosis and the damaging effects of free radicals (Sekiguchi et al. 2005; Liu et al. 2006).

To date, three *EPO* polymorphisms (rs1617640, rs507392 and rs551238) have been analysed in DR cohorts. Tong et al. and Abhary et al. showed that SNP rs1617640 was significantly associated with DR in Caucasian cohorts (Tong et al. 2008; Abhary et al. 2010). Fan et al. also found rs1617640 to be associated with DR in their Han Chinese cohort (Fan et al. 2016). However, Song et al. (Song et al. 2015) did not find any association in their Chinese cohort and neither did Narne et al. in their Indian cohort (Narne et al. 2016). Abhary et al. (Abhary et al. 2010) analysing their Caucasian cohort also showed association with the two other SNPs (rs507392 and rs551238) however their cohort was a mixed T1DM/T2DM cohort. Fan et al. and Song et al. also found an association in their Chinese cohorts with both rs507392 and rs551238 however Song et al. reported that the CC of rs507392

genotype was protective which was opposite to the finding reported Abhary et al. which showed the CC genotype was associated with the disease (Song et al. 2015; Fan et al. 2016).

1.2.5 Glutathione S-transferases (*GSTT1*, *GSTM1* and *GSTP1*)

Glutathione S-transferases (GST) are endogenous antioxidants within the body (Blanchette et al. 2007; Datta et al. 2010) and are known to neutralise reactive oxygen species along with other key toxins (Bolt & Thier 2006). There are eight highly polymorphic loci that encode GST enzymes, but previous studies have focused on glutathione S-transferase theta 1 (*GSTT1*) encoded by a gene located on chromosome 22q11.23, glutathione S-transferase mu 1 (*GSTM1*) encoded by a gene located on chromosome 1p13.3 and glutathione S-transferase pi 1 (*GSTP1*) encoded by a gene located on chromosome 11q13.2. Deletions in *GSTT1* and *GSTM1* result in non-functional enzyme activity (Pemble et al. 1994; Mo et al. 2009), whereas a polymorphism causing an amino acid substitution in the *GSTP1* enzyme results in an increased cellular sensitization to free radicals (Doney et al. 2005; Cilensek et al. 2012). Hence polymorphisms that alter the function of these molecules may contribute to the effects of oxidative stress in the diabetic retina. A study by Cilensek et al. found that polymorphisms in *GSTM1* and *GSTT1* but not *GSTP1* were associated with diabetic retinopathy in their Caucasian cohort (Cilensek et al. 2012).

1.2.6 Glyoxalase 1 (*GLO1*)

The gene encoding glyoxalase 1 (*GLO1*) is located on chromosome 6p21.3-p21.1. *GLO1* catalyses glycation reactions, a decrease in *GLO1* activity is caused by ageing and oxidative stress which can lead to increased glycation and tissue damage (Song & Schmidt 2012). A study by Miyata et al. investigating the plasma levels of AGEs, their precursor compounds and products from the glyoxalase detoxification pathway (including *GLO1*) in haemodialysis patients found that a deficiency in *GLO1* was associated with unusually high levels of AGEs (Miyata et al. 2001). Also, the knockdown model of *GLO1* mimics diabetic nephropathy in non-diabetic mice (Giacco et al. 2014; Skrha et al. 2014). Wu et al. (Wu et al. 2011) investigated two SNPs in the *GLO1* gene (rs1049346 and rs4746) they found that rs1049346 alters promoter activity and confers susceptibility to nephropathy and retinopathy in Chinese T2DM patients. They did not find association with rs4746 (Groener et al. 2013). Groener et al. did not find an association with rs4746 with diabetic retinopathy in Caucasian patients (Groener et al. 2013).

1.2.7 Methylenetetrahydrofolate reductase (*MTHFR*)

The gene encoding methylenetetrahydrofolate reductase (*MTHFR*) is located on chromosome 1p36.3. *MTHFR* is the enzyme that catalyses the transformation of homocysteine, a non-protein α -amino acid, to methionine via the re-methylation pathway (Toffoli et al. 2003). Deficiency of *MTHFR* may be associated with an increase in plasma homocysteine, which in turn is associated with an increased risk of vascular diseases among diabetic patients (Fodinger et al. 2000; Parvanova et al. 2002; Mtiraoui et al. 2007). *In vitro* studies have shown that hyperhomocysteinemia affects the nervous system by direct cytotoxic effects or by oxidative damage to endothelial cells (Schlüssel et al. 1995; Weir & Scott 1995). Changes in the activity level of *MTHFR* may account for the microvascular changes seen in diabetic retinopathy. Two polymorphisms, (rs1801133 and rs180131) have been shown to affect the enzymatic activity of *MTHFR* (Toffoli & De Mattia 2008). The polymorphism rs1801133 has been shown to reduce activity by 50% (Hankey & Eikelboom 1999). Sun et al. (Sun et al. 2003), Maeda et al. (Maeda et al. 2008) and Yigit et al. (Yigit et al. 2013) as well as a meta-analysis by Niu et al. (Niu & Qi 2012) reported that there was a moderate association with

DR and rs1801133. However a meta-analysis and a study of Japanese patients reported that there was no association with DR (Yoshioka et al. 2003; Zintzaras et al. 2005). Furthermore, Simoes et al. showed association with rs1801133 and disease progression in their Portuguese cohort (Simoes et al. 2014). A study by Lin et al. analysed two *MTHFR* SNPs (rs1537516 and rs375382), they reported that significant differences in serum triglycerides were observed among the three genotypes of rs1537516. However, neither SNP was found to be associated with the development of DR in their Chinese cohort (Lin et al. 2016).

1.2.8 Mitochondrial ribosomal protein L14 (*MRPL14*) and transmembrane protein 217 (*TMEM217*)

Mitochondrial ribosomal protein L14 (*MRPL14*) and transmembrane protein 217 (*TMEM217*) are encoded by genes located on chromosome 6p21.3 and 6p21.2 respectively. This region of chromosome 6 has been shown to be closely associated with diabetes (Stern et al. 1996; Docherty et al. 2010; Lin et al. 2013). *MRPL14* and *TMEM217* are both glutocorticotransmembrane proteins. Glutocorticotransmembrane proteins influence vascular responses and generate nitric oxide (Walker et al. 1992), hence dysfunction in the retina in hyperglycaemic conditions are likely to contribute to the disease state in DR. Lin et al. found that two SNPs in *TMEM217* (rs1224329 and rs1150790) and one SNP in *MRPL14* (rs713050) were significantly associated with the development of DR in Taiwanese T2DM patients (Lin et al. 2013).

1.2.9 Nitric oxide synthase (*NO*)

Nitric oxide (*NO*) is produced by three different isoforms of *NO* synthase (*NOS*), neuronal *NOS* (*nNOS/NOS1*), inducible *NOS* (*iNOS/NOS2*) and endothelial *NOS* (*eNOS/NOS3*). The genes encoding these isoforms are found on chromosomes 12q24.22, 17q11.2 and 7q36 respectively. In large amounts *NO*, when produced by *NOS2*, is toxic and damaging however, low concentrations produced by *NOS3* are required to maintain healthy endothelial cell function. Physiological concentrations of *NO*, maintained by *NOS3*, have a protective effect on the vascular endothelium (Gross & Wolin 1995; Albrecht et al. 2003). *NOS3* is localised to the Muller cells of the retina (Haverkamp et al. 1999), which are known to be important in the maintenance of the blood-retina-barrier (*BRB*) (Antcliff & Marshall 1999) and impaired *NOS3* function in the retina could lead to the breakdown of the *BRB* and result in the development of complications such as macular oedema (Albrecht et al. 2003). Simoes et al. did not find evidence that the *NOS1* SNP (rs155228) had any association with the progression of DR (Simoes et al. 2014). Porojan et al. did not find association with the *NOS2* SNP (rs2297518) in their Caucasian cohort (Porojan et al. 2015). The most studied of the *NO* genes is *NOS3*. Association studies of three polymorphisms (rs2070744, rs1799983 and rs3918227) have been reported (Awata et al. 2004; Ezzidi et al. 2008; Santos et al. 2012; Lin et al. 2013; Momeni et al. 2016; Narne et al. 2016). Haplotypes generated from two SNPs (rs2070744 and rs1799983) and a 27bp repeat in intron 4 in *NOS3* were shown to be a marker for diabetic retinopathy by Ezzidi et al. but did not individually show any association (Ezzidi et al. 2008). Awata et al. (Awata et al. 2004) showed that rs2070744 and the 27bp repeat in intron 4 were associated with macular oedema with the 'A' allele increasing the risk. However Narne et al. did not find either rs2070744 or rs1799983 to be associated with DR (Narne et al. 2016). A study by Santos et al. did not find an association with rs2070744 (Santos et al. 2012) and Momeni et al. did not find an association with rs1799983 (Momeni et al. 2016). Lin et al. examined rs179983 and rs3918227 in their Chinese cohort but failed to find an association with DR (Lin et al. 2016).

1.2.10 Nuclear factor, erythroid 2 like2 (*NFE2L2*)

The protein nuclear factor erythroid 1 like 2 (*NFE2L2*, previously called *NRF2*) is encoded by a gene located on chromosome 2q31.2. *NFE2L2* is a transcription factor that regulates redox balance in the cytoprotective response. *NFE2L2* protects the cell from ROS by binding to and regulating the anti-oxidant responsive element (ARE). The ARE controls antioxidant enzymes such as nicotinamide adenine dinucleotide phosphate oxidase (NADPH) and Glutathione S-transferases (GST) (see section 1.2.5) (Lee & Johnson 2004). Under normal conditions *NFE2L2* is stored in the cytoplasm and is inactive when it is bound to the repressor protein KEAP1 (Kelch-like erythroid cell derived protein with CNC homology associated protein 1). Exposure to oxidants disrupts the *NFE2L2*-KEAP1 complex and *NFE2L2* is shuttled to the nucleus. Once in the nucleus, *NFE2L2* forms a heterodimer with small Maf nuclear protein, this results in the transcription of ARE driven genes. The activation of the ARE driven genes protect the cells from oxidative damage triggered by injury and inflammation (Srisook et al. 2005). Several studies have suggested that *NFE2L2* has a preventative role in the development of T1 and T2DM (Yu et al. 2012) as well their microvascular complications (He et al. 2009; Uno et al. 2010; Negi et al. 2011; Li et al. 2012; Xu et al. 2016). Xu et al. (Xu et al. 2016) investigated six *NFE2L2* polymorphisms (rs2364723, rs13001694, rs10497511, rs1806649, rs1962142 and rs6726395). They found that rs2364723, rs10497511, rs1962142 and rs6726395 were associated with DR in their Chinese cohort, however they were examining *NFE2L2* in a mixed diabetic complication cohort and of the 214 diabetic patients with complications only 33 had DR. This study needs to be repeated in a larger cohort of DR patients to examine if association really is present.

1.2.11 Paraoxonase (*PON1*, *PON2* and *PON3*)

There are three members of the paraoxonase family (*PON1*, 2 and 3) encoded by three genes all located on chromosome 7 in the region 7q21.3-22.1 (Primo-Parmo et al. 1996; Kowalska et al. 2015). *PON1* and *PON3* are plasma enzymes while *PON2* is an intracellular enzyme which is bound to the plasma membrane. All three PONs prevent oxidative stress and fight inflammation (Precourt et al. 2011). *PON1* is a glycoprotein which binds high density lipoproteins and protects low density lipoproteins from oxidation by hydrolysing lipid peroxides (Kao et al. 1998; Durrington et al. 2001). There is evidence that the development of microvascular disease may occur through lipid oxidation (Lyons et al. 1994). It has been reported that diabetic patients show a reduced level of *PON1* activity (Mackness et al. 1991; Abbott et al. 1995; Ikeda et al. 1998; Mackness et al. 2000; Boemi et al. 2001). The exact mechanisms of *PON2* and *PON3* are not fully understood. However, *PON2* is known to reduce free radical lipids in macrophages and inhibit low density lipoprotein oxidation (Rosenblat et al. 2003). Levels of *PON2* increase in macrophages during oxidative stress (Aviram 2004; Kowalska et al. 2015). *PON3* is a calcium dependent glycoprotein that exhibits antioxidant activity (Kowalska et al. 2015). Several polymorphisms in *PON1* have been identified and at least two (rs3917594 and rs854560) have been shown to influence *PON1* activity. To date only two SNPs (rs662 and rs854560) have been examined in cohorts of type 2 diabetic retinopathy patients. Ergun et al. showed association with both rs662 and rs854560 in their Turkish cohort (Ergun et al. 2011). Murata et al. showed an association between rs662 and their Japanese T2DM patients developing DR (Murata et al. 2004). A meta-analysis study indicated association with rs854560 but not rs662, however the meta-analysis assessed data from studies containing both type 1 and type 2 diabetic participants considering both *PON1* and *PON2* for association with nephropathy and retinopathy (Wang et al. 2013). Only one study examined a *PON2* polymorphism (rs7493) in T2DM DR (Mackness et al. 2005).

and they did not find an association with DR in their Caucasian cohort. To date there have been no studies examining *PON3* polymorphism for association with T2DM.

1.2.12 Poly (ADP-Ribose) polymerase 1 (PARP1)

Poly (ADP-Ribose) polymerase 1 (*PARP1*) gene is located on chromosome 1q41-q41 and encodes the chromatin-associated enzyme, poly (ADP-ribyl) transferase, which modifies various nuclear proteins. The role of modification is important in cellular processes including differentiation, proliferation and the regulation of recovery from DNA damage. PARP1 over-activation is key in hyperglycaemia induced reversible NADPH deficiency. *In vitro* studies have demonstrated that the polymorphism rs1136410 is associated with reduced activity of PARP1 (Wang et al. 2007; Narne et al. 2016), and hence may have a role in the development of DR. Narne et al. found that there was association with rs1136410 and the development of DR (Narne et al. 2016).

1.2.13 Potassium voltage gated channel, subfamily J, member 11 (KCNJ11)

The gene encoding potassium voltage gated channel, subfamily J, member 11 (*KCNJ11*) is located on chromosome 11p15.1. The protein encoded by this gene is an integral membrane protein and inward rectifier type potassium channel. This protein is controlled by G-proteins and has a greater tendency to allow potassium to flow into the cell than out (Clement et al. 1997; Pearson et al. 2006). Variations in this gene are known to contribute to the development of several complications of diabetes, possibly due to causing a decreased sensitivity of the ion channel to ATP, leading to greater ATP consumption which in turn leads to insulin release impairment (Liu et al. 2015). The polymorphism rs5219 has been associated with T2DM susceptibility (Gloyn et al. 2003). A study by Liu et al. found that the polymorphism rs5219 was associated with the development of DR in their Chinese cohort (Liu et al. 2015).

1.2.14 Protein kinase C (PKC)

Protein kinase C (*PKC*) is an important intracellular signalling molecule that regulates many vascular functions, including permeability, vasodilation, endothelial activation and growth factor signalling. The PKC family consists of 15 isozymes (Mellor & Parker 1998). Over activation of PKC in blood vessels of the retina, kidney and nerves can produce damage by increased vascular permeability (Nagpala et al. 1996), leukocyte adhesion (Nonaka et al. 2000) and alterations in blood flow (Shiba et al. 1993). Activation of PKC has also been suggested to be involved in the induction of expression of the growth factors VEGF and TGF- β (Sheetz & King 2002). Polymorphisms in *PKC* have been shown to be associated with T2DM patients with renal complications (Ikeda et al. 2004; Araki et al. 2006; Ma et al. 2010) but not in retinopathy patients to date.

1.2.15 Reactive oxygen species modulator 1 (ROMO1)

The gene encoding reactive oxygen species modulator 1 (*ROMO1*) is located on chromosome 20q11.2. The ROMO1 protein localises to the mitochondria and increases the level of ROS in cells (Chung et al. 2006; Na et al. 2008). In addition, ROMO1 is required for cell proliferation via redox signalling (Chung et al. 2009). An increase in ROMO1 protein may contribute to the oxidative stress in the diabetic retina when variants occur that alter normal function. Petrovic et al. analysed the *ROMO1* SNP rs6060566 in a cohort of Caucasian T2DM patients and found association with DR (Petrovic et al. 2015).

1.2.16 Solute carrier family 30 member 8 (*SLC30A8*)

The solute carrier family 30 member 8 (*SLC30A8*) gene is located on chromosome 8q24.11 and encodes the zinc transporter protein ZnT8. Zinc is a co-factor involved in homeostasis, immune responses, oxidative stress, apoptosis and aging. Zinc homeostasis is controlled by the coordination of several proteins including zinc transporter families (Miao et al. 2013). ZnT8 is involved in transporting zinc into the insulin secretory granules in the pancreatic β cells and zinc is known to play a role in the synthesis and action of insulin, both physiologically and in the pathogenic state in diabetes (Chimienti et al. 2004). A downregulation of ZnT8 results in aberrant zinc homeostasis leading to ischaemic retinopathy (Deniro & Al-Mohanna 2012). ZnT8 has been shown to be expressed in the RPE and choroid (Leung et al. 2008) and a meta-analysis study has shown that the SNP rs11558471 had a stronger inverse association between total zinc intake and fasting glucose in individuals carrying the A allele (Kanoni et al. 2011). Fu et al. found association with the AA genotype of SNP rs11558471 and diabetic retinopathy in their T2DM Chinese patients (Fu et al. 2012). This indicates that the polymorphism may confer some susceptibility to diabetic retinopathy via an imbalance in zinc homeostasis and altering zinc levels in these individuals could be used as a possible treatment.

1.2.17 Superoxide dismutase 2 (*SOD2*)

Mitochondrial manganese superoxide dismutase (MnSOD) is encoded by the gene superoxide dismutase 2 gene (*SOD2*) located on chromosome 6q25.3. During development of diabetic retinopathy, superoxide levels are elevated in the retina due to oxidative stress, the antioxidant defence system is compromised, MnSOD is inhibited, and mitochondria are swollen and dysfunctional (Kowluru & Abbas 2003; Kowluru et al. 2006; Madsen-Bouterse et al. 2010; Zhong & Kowluru 2011). Zhong and Kowluru have shown that retinal mitochondrial dysfunction has a crucial role in the apoptosis of capillary cells (Zhong & Kowluru 2013), a process that precedes the development of diabetic retinopathy (Kern et al. 2000; Kowluru & Abbas 2003; Kowluru et al. 2006). High glucose levels decreased the *SOD2* transcripts by over 50% in retinal endothelial cells *in vitro* (Zhong & Kowluru 2013). Over expression of MnSOD protects against diabetes-induced mitochondrial damage and the development of retinopathy while normalizing mitochondrial superoxide production can block other pathways of hyperglycaemic damage (Nishikawa et al. 2000; Brownlee 2001). Petrovic et al. (Petrovic et al. 2008), Kangas-Kontio et al. (Kangas-Kontio et al. 2009) and Vanita (Vanita 2014) reported that rs4880 is associated with retinopathy T2DM patients. Lee and Choi did not find this polymorphism to be related to the development of diabetes and the progression of DR, but was associated with DMO in Korean T2DM patients (Lee & Choi 2006).

1.2.18 Thioredoxin 2/thioredoxin interacting protein (TXN2/TXNIP) and thioredoxin reductase 2 (TXNRD2)

Reactive oxygen species (ROS) (see section 1.2) are produced by cells in many ways, but 90% of ROS are mitochondrial in origin (Adam-Vizi 2005). The thioredoxin system (TRX) is one of the antioxidant defences in a cell. Mammalian cells have two TRX systems, the cytosolic TRX1 and the mitochondrial TRX2 system (Lu & Holmgren 2014). The TRX system consists of thioredoxin (TRX), the selenoprotein thioredoxin reductase (TRXR), the thioredoxin interacting protein (TXNIP) and the electron donor NADPH. This system plays a role in maintaining a reduced cellular environment (Lu & Holmgren 2014). The TRX system is highly induced in the diabetic retina and plays a critical role in the pathogenesis of DR (Perrone et al. 2009; Perrone et al. 2010; Devi et al. 2012; Devi et al. 2013). Under normal conditions TXNIP is located in the nucleus however when the cell is under oxidative

stress TXNIP can be relocated to the cytosol or mitochondria. When it is in the mitochondria, TXNIP binds to oxidised TRX2 leading to mitochondrial dysfunction (Saxena et al. 2010). The TRX/TXNIP redox-related protein complex, called the 'redoxisome', is a critical regulator of intra- and extracellular redox signalling and is highly induced in the diabetic retina (Perrone et al. 2009; Perrone et al. 2010; Devi et al. 2012; Yoshihara et al. 2014). Ramus et al. investigated seven polymorphisms in the TRX system in their Caucasian cohort (see **Table 1** for details). Only the polymorphism rs4485648 in *TXNRD2* showed association with DR (Ramus et al. 2016).

1.2.19 Uncoupling Proteins (UCPs)

Uncoupling proteins (UCPs) are transporters located in the inner membranes of mitochondria and belong to the family of anion mitochondrial carriers. UCPs act as proton carriers, they are activated by metabolites and create a shunt between complexes of the respiratory chain and ATP synthesis. A relationship between UCPs and ROS was demonstrated by Negre-Salvayre et al. They showed that by inhibiting UCP1 there was an increased production of ROS (Negre-Salvayre et al. 1997). A study by Echtay et al. suggested that the interaction between superoxide and UCPs may be a mechanism for decreasing ROS (Echtay et al. 2002). Five different UCPs have been identified UCP1-4 and UCP5, also called brain mitochondrial carrier protein 1 (BCMP1). These proteins are expressed in different tissues and play different roles in cellular metabolism. UCP1-3 are involved in the limitation of free radical levels in cells. Immunocytochemistry and RT-PCR have shown that UCP1 and UCP2 are expressed in endothelial cells and pericytes of retinal capillaries. However, further studies have shown that it is UCP1 that plays a role in the protection against oxidative stress in retinal capillary cells of diabetic patients (Kowluru & Abbas 2003; Cannon et al. 2006). It is well known that ROS can damage the structure and function of cells directly (see section 1.2) and that mitochondrial ROS in endothelial cells are increased at high glucose levels. ROS overproduction could activate other pathways involved in diabetic microvascular complications.

The SNP rs1800592 in the promoter of *UCP1* has been shown to be associated with glucose homeostasis, adiposity and obesity, as well as changes in BMI and body weight, resulting from metabolic disorders (Skulachev 1998; Oh et al. 2004; Kotani et al. 2008). Zhang et al. found association with UCP1 SNP rs1800592 in their Chinese diabetic retinopathy patients (Zhang et al. 2015). Crispim et al. reported that a *UCP2* haplotype consisting of two SNPs (rs659366 and rs660339) and a 45bp Ins/Del is a risk factor for PDR in both T1DM and T2DM patients (Crispim et al. 2010). Shen et al. also found association with the two *UCP2* SNPs and diabetic retinopathy in their Chinese cohort (Shen et al. 2014).

1.2.20 X-ray repair cross complementing protein 1 (XRCC1)

The gene encoding X-ray repair cross complementing protein 1 (*XRCC1*) is located on chromosome 19q13.2 and is involved in DNA repair. XRCC1 protein forms complexes with PARP1, polymerase beta and DNA ligase III to participate in the base excision repair pathway (Caldecott et al. 1996). The polymorphism rs25487 in the *XRCC1* gene has been shown to reduce the complexing ability of the protein and hence reduce the repair potential in a diabetic milieu which may result in increased oxidative damage (Caldecott et al. 1996; Narne et al. 2016). Narne et al. analysed this polymorphism in their T2DM DR cohort and found that there was an association with the polymorphism and the development of DR (Narne et al. 2016).

1.3 Microthrombin Formation

Under normal conditions walls of arteries are composed of three coats, the innermost consists of the endothelium (see below) separated by a thin layer of connective tissue from the internal elastic lamina, which is kept taut *in vivo* by blood pressure. The middle coat, the media, is formed by a tight spiral of smooth muscle cells which lie in a meshwork of elastic and collagen fibres. The external elastic lamina separates the media from the final coat, the adventitia. The adventitia, is a thin layer of loosely arranged collagen and elastic fibres rich in lymphatics and transversed by nerves that supply the medial smooth muscle (Bridges et al. 1965; Shaw et al. 1967; Yamashiro et al. 2003). Small arteries and arterioles are supplied with oxygen and nutrients via diffusion from the lumen. These are referred to as resistance vessels and regulate the overall arterial pressure and blood flow to individual organs and tissues. They have a higher ratio of smooth muscle cells in their media compared to larger arteries. The smooth muscle cells are autonomically innervated and are exposed to vasoactive hormones produced by the endothelial cells.

In addition to being contractile, smooth muscle cells also synthesise the matrix proteins of the artery, collagen, elastin and proteoglycans. In disease states, such as response to injury, the smooth muscle cells undergo hypertrophy and synthesise increased amounts of matrix. They also migrate into the innermost coat of the artery where they may multiply and synthesise extracellular matrix proteins.

Endothelial cells are heterogeneous and synthesise and secrete numerous regulatory molecules. The endothelium directly regulates vascular tone by secreting vasodilating factor and vasoconstricting factors such as endothelin. Interactions between endothelial cells and soluble factors in the circulation are crucial to many metabolic processes. The most important role of the endothelial cell is in regulating haemostasis. In healthy non-damaged blood vessels blood clots (thrombi) do not usually form. This is because the endothelial cell surface is antithrombotic and the cell also secretes antithrombotic molecules. In addition endothelial cells form a barrier which prevents the blood interacting with the prothrombotic vascular basement membrane. The endothelial cells can exhibit prothrombotic activity by synthesising von Willebrand factor, platelet activating factor and fibronectin which mediate platelet adhesion and coagulation factors. These opposing functions of the endothelial cells control thrombo-haemorrhagic balance.

Injury to the endothelium results in platelet and leukocyte adherence. Activation of these cells results in the release of growth factors and cytokines which affect the proliferative activities of the smooth muscle cells.

Platelet microthrombi formation in the diabetic retina is due to the apoptosis of the endothelial cells in the vasculature as a result of oxidative stress of the diabetic retina. These are likely to form since the haemostatic properties of the platelets are altered in diabetes resulting in an increased adhesiveness and increased sensitivity to aggregating agents or their receptors (Bridges et al. 1965; Shaw et al. 1967; Yamashiro et al. 2003). Several genes are involved in this process and these are summarised below with the evidence for their involvement in the development of DR.

1.3.1 Glutamate receptor, ionotropic, kainite 2 (*GRIK2*)

Glutamate receptor, ionotropic, kainite 2 (*GRIK2*), like *MRPL14* and *TMEM217* (see section 1.2.9) is located on chromosome 6 (6p16.3) in a region known to contain several loci associated with

diabetes (Lin et al. 2013). GRIK2 is a transmembrane glutamate receptor which plays a role in platelet function and hence has an impact on vascular disease (Sun et al. 2009). Mouse models of oxygen-induced retinopathy have found that GRIK2 is involved in retinal neovascularisation (Recchia et al. 2010). Lin et al. showed that the *GRIK2* SNP rs487083 is significantly associated with DR in their Chinese T2DM cohort (Lin et al. 2013).

1.3.2 Integrin Alpha 2 (*ITGA2*)

Integrins are cell surface receptors that interact with extracellular matrix and mediate signalling both inside and outside of cells (Hynes 2002; Hynes 2002). Four of the 24 integrins that have been identified to date bind collagens. These four share a common $\beta 1$ subunit that forms a heterodimer with either an $\alpha 1$, $\alpha 2$, $\alpha 10$ or $\alpha 11$ subunit (McCall-Culbreath & Zutter 2008; Kang et al. 2011). Integrin $\alpha 2\beta 1$ is profibrotic and activation leads to increased ROS production (Honore et al. 2003) and collagen expression (Langholz et al. 1995), it is also anti-angiogenic (Zhang et al. 2008). The platelet membrane glycoprotein Ia/IIa, ($\alpha 2\beta 1$ integrin) is a platelet receptor for collagen (Moroi & Jung 1997). Polymorphisms in the α -subunit (including rs2910964) have been shown to have an effect on the density of receptors on the platelet surface (Kritzik et al. 1998). Alterations in platelet receptor density can result in pathological changes and platelet dysfunction. Platelets from diabetic patients are hyper-reactive to aggregating agents, such as collagen, thrombin and adenosine diphosphate (Winocour et al. 1992; Petrovic et al. 2003). Platelet dysfunction has been demonstrated to play a role in diabetic retinopathy (Stratmann & Tschöepe 2005).

Several studies have examined the polymorphism rs2910964 in the alpha subunit of $\alpha 2\beta 1$. Matsubara et al. (Matsubara et al. 2000), Petrovic et al. (Petrovic et al. 2003), Azmy et al. (Azmy et al. 2012) and two meta-analyses by Abhary et al. (Abhary et al. 2009) and Gong et al. (Gong et al. 2015) showed association with the development of DR. However, studies by Arsene et al. (Arsene et al. 2011), Cepeda-Nieto et al. (Cepeda-Nieto et al. 2015) and Li et al. (Li et al. 2008) did not find association in their cohorts. Cepeda-Nieto et al. investigated a second SNP (rs3212515) in their Mexican cohort but did not show association with DR (Cepeda-Nieto et al. 2015).

1.3.3 Integrin subunit beta 3 (*ITGB3*)

The gene encoding integrin subunit beta 3 (*ITGB3*) also known as glycoprotein IIIa (GPIIIa) is located on chromosome 17q21.32. The *ITGB3* protein is a cell surface protein that participates in cell adhesion and cell surface mediated cell signalling and forms a calcium dependent fibrinogen receptor by building a glycoprotein complex with integrin subunit alpha 2b (*ITGA2B*, also known as GPIIb) (see section 1.3.2) on the membrane of platelets (Kozieradzka et al. 2007). In the resting state the complex is in a low affinity conformation with the ligand binding site concealed. When platelets are activated by antagonists such as adenosine diphosphate, thrombin or collagen, inside out signalling occurs exposing the ligand binding site (Shattil & Newman 2004; Collier & Shattil 2008; Nikolajevic-Starcevic et al. 2011). Fibrinogen binding to the active complex leads to platelet aggregation and thrombus formation (Calvete 1995). Several polymorphisms in both *ITGA2B* and *ITGB3* have been shown to alter fibrinogen binding affinities. However, the most frequently studied polymorphism (rs5918) is the platelet-specific antigen (PIA1/A2) polymorphism in *ITGB3*. This polymorphism can alter both platelet activation and aggregation (Nurden 1995; Zotz et al. 1997; Feng et al. 1999). A study by Nikolajevic-Starcevic et al. found that the A2/A2 genotype was associated with the development of DR in their Caucasian cohort (Nikolajevic-Starcevic et al. 2011).

1.3.4 Serpin family E, member 1 (*SERPINE1*)

Serpin family E, member 1 (*SERPINE1*) is also known as plasminogen activator inhibitor 1 (*PAI1*) and is located on chromosome 7q22.1. The gene encodes a member of the serine proteinase inhibitor (serpin) superfamily. *SERPINE1* is the principle inhibitor of tissue plasminogen activator and urokinase and acts as an inhibitor of fibrinolysis. The 4G/5G polymorphism (rs1799768) in the promoter of *SERPINE1* has been linked to circulating levels of *SERPINE1* and to hypofibrinolysis (Margaglione et al. 1998). Several studies have investigated this polymorphism in T2DM DR patient cohorts. Nagi et al. (Nagi et al. 1997) reported an association in Pima Indians however, with the exception of Ezzidi et al. (Ezzidi et al. 2009) who found association with the 4G/4G genotype and the risk of developing retinopathy, no other independent study found any association in other ethnic groups (Broch et al. 1998; Globocnik-Petrovic et al. 2003; Santos et al. 2003; Murata et al. 2004; Ezzidi et al. 2009; Saleem et al. 2015). To add to the conflicting evidence regarding this polymorphism, a meta-analysis by Zhang et al. (Zhang et al. 2013) found there was an association with the development of DR, however a larger meta-analysis did not find any association (Xu et al. 2013). Ezzidi et al. also found association with a second polymorphism (rs1799889) and DR in their cohort (Ezzidi et al. 2009).

1.4 Cell adhesion molecule activation

The first step in the immune response to the diabetic environment is the sensitisation of endothelial cells (see section 1.3) to the effects of molecules such as TNF which in turn upregulates molecules such as ICAM that promote leukostasis. This sensitisation may be due to a change in the sub-endothelial basement membrane of cells in response to the altered environment possibly creating further vascular malformations (Ghosh et al. 2008; Yang et al. 2016).

1.4.1 Chimerin 2 (*CHN2*)

The chimerin 2 (*CHN2*) gene is located on chromosome 7p15.3 and encodes a GTP-metabolising protein which plays a role in the proliferation and migration of vascular smooth muscle cells (Caloca et al. 2008). In addition, the *CHN2* gene has been identified as a key element of proximal insulin signalling (Suliman et al. 2009). Chen et al. examined four *CHN2* polymorphisms (rs39059, rs2023908, rs1002630 and rs1362363) in their Taiwanese cohort (Chen et al. 2014). They only found association with rs1002630 and DR. A study by Hu et al. (Hu et al. 2011) only examined rs39059 which they found to be associated with DR in their Chinese cohort.

1.4.2 Tumour necrosis factors (*TNFs*)

Tumour necrosis factors (*TNFs*) are a family of 19 cytokines that along with their receptors are expressed in a wide variety of cells but predominantly are expressed in the cells of the immune system. TNF binding initiates many signalling pathways and promotes cell survival, apoptosis, differentiation or inflammation in TNF-Receptor expressing cells (reviewed (Sun & Fink 2007)). Sesti et al. showed association of the *TNFα* polymorphism rs1800629 with PDR in T2DM Brazilian patients (Sesti et al. 2015) however a second Brazilian study failed to find an association (Rodrigues et al. 2015). A previous study had shown association of this SNP to DR but in conjunction with another gene polymorphism found in the *ADIPOQ* gene (rs2241766) (Sikka et al. 2014). Yoshioka et al. did not find association with their Japanese cohort (Yoshioka et al. 2006), neither did Simoes et al. or Kaidonis et al. in their respective Portuguese and Caucasian cohorts (Simoes et al. 2014; Kaidonis et

al. 2016). A meta-analysis performed by Meng et al. also did not show association between rs1800629 and DR (Meng et al. 2014). Sesti et al. examined two further polymorphisms (rs1799724 and rs361525) and failed to find an association with DR (Sesti et al. 2015). Two other studies analysed rs361525, Paine et al. showed an association with DR in their Indian cohort (Paine et al. 2012), but Kaidonis et al. did not find an association in their Caucasian patients (Kaidonis et al. 2016). Simoes et al. examined a fourth SNP (rs11574936) but failed to find an association with DR in their cohort (Simoes et al. 2014). A promoter microsatellite repeat was analysed by three laboratories and all found association with a GT repeat in Indian T2DM patients with DR (Hawrami et al. 1996; Kumaramanickavel et al. 2001; Uthra et al. 2010).

1.4.3 Urotensin-II (*UTS2*)

Urotensin-II (*UTS2*) is a potent vasoconstrictor that acts through a G-protein coupled receptor and is encoded by the gene *UTS2* (Ames et al. 1999). *UTS2* is closely linked with endothelial cell dysfunction, PKC activation, ROS generation, altered gene expression of growth factors and cytokines, and macrophage activation all of which are involved in diabetic vascular complications. *UTS2* can modulate endothelial cell permeability and proliferation to induce angiogenesis (Gendron et al. 2004; Spinazzi et al. 2006). *UTS2* levels are up-regulated by lipopolysaccharide and inflammatory cytokines, such as IL-6 and IL-1b, IFN- γ and TNF- α (Birker-Robaczewska et al. 2003; Segain et al. 2007) and the expression of *UTS2* in vascular walls is also increased by hypoxia (Hongfang et al. 2006).

Suguro et al. have shown that there is a relationship between plasma levels of *UTS2* and progression of retinopathy as well as an association between rs2890565 and diabetic retinopathy in a T2DM Japanese population (Suguro et al. 2008). Okumus et al. reported association between rs2890565 and rs228648 and DR in a Caucasian cohort (Okumus et al. 2012).

1.5 Retinal Leukostasis

Retinal leukostasis is caused by an increased adhesion to the capillary endothelium. This leads to increased leukocyte/monocyte adhesion which results in intravascular clumping of the white blood cells (Miyamoto et al. 1999; Abiko et al. 2003). An increase in retinal leukostasis in DR occurs secondary to activation of leukocytes or endothelial cells by increased expression of intracellular adhesion molecules. The intravascular cell clumping due to leukocyte adhesion leads to a decrease in retinal blood flow, a breakdown of the blood-retina-barrier, internalisation of the leukocytes leading to local inflammation and an increase in activation of cytokines such as VEGF (see section 1.6).

1.5.1 C-C motif chemokine receptor 5 (*CCR5*)

C-C motif chemokine receptor 5 (*CCR5*) is a member of the beta chemokine receptor family and is a G-protein coupled receptor found on the surface of white blood cells. Chemokines and their receptors play a central role in leukocyte trafficking in during the process of inflammation (Charo & Ransohoff 2006). The key ligands that bind to *CCR5* are C-C motif chemokine ligand 5 (CCL5) and macrophage inflammatory proteins (MIPs) (Raport et al. 1996). Inflammatory molecules, including cytokines, chemokines and their receptors, have been proposed as crucial factors in the development of microvascular diabetic complications (Rivero et al. 2009).

Genetic variation in the genes encoding these cytokines might confer susceptibility to diabetic complications, to date Prasad et al. and Buraczynska et al. have shown association between the *CCR5* polymorphism rs1799987 and diabetic nephropathy (Prasad et al. 2007; Buraczynska et al. 2012). However, no studies have looked at DR.

1.5.2 C-reactive protein (*CRP*)

The gene encoding C-reactive protein (*CRP*) is located on chromosome 1q21-23. CRP binds to lysophosphatidylcholine expressed on the surface of dead or dying cells in order to activate an immune response via the complement system. Hence an increase in CRP levels is a marker of inflammation and has been shown to be involved in angiogenesis and endothelial cell dysfunction. CRP may inhibit endothelium-dependent nitric oxide mediated dilation arterioles required to maintain healthy blood flow, thus facilitating the development of vascular disease (Nagaoka et al. 2008). The decrease in nitric oxide and stimulation of endothelial-leukocyte interactions may further enhance endothelial cell dysfunction (Kalka et al. 2000; Venugopal et al. 2002; Devaraj et al. 2006). For these reasons CRP may be an important molecule in the development of diabetic complications (Verma et al. 2002; Verma et al. 2002; Peng et al. 2015).

Peng et al. analysed four polymorphisms (rs2808629, rs3093077, rs1130864 and rs2808634) in their Chinese T2DM diabetic cohort. They found only rs2808629 to be associated with the development of diabetic retinopathy in their patient cohort (Peng et al. 2015).

1.5.3 Htra serine peptidase 1 (*HTRA1*)

The gene encoding htra serine peptidase 1 (*HTRA1*) is located on chromosome 10q26.3. The protein product of *HTRA1* is ubiquitously expressed but is enriched in fibroblasts and mature epithelium and moderately expressed in vascular endothelial cells. In the eye, *HTRA1* expression is highest in the epithelial layers of the lens and cornea (De Luca et al. 2003; De Luca et al. 2004) with moderate expression in the RPE and photoreceptor layers (De Luca et al. 2003; De Luca et al. 2004; Oka et al. 2004).

HTRA1 protein has several domains including a MAC25 domain similar to that found in the insulin-like growth factor-1 (IGF-1) binding protein (IGFBP) superfamily which is encoded by the first exon. The expression patterns of *HTRA1* and IGF1 overlap and *HTRA1* is capable of associating with IGF-1 (Oka et al. 2004; Tsuchiya et al. 2005; Hara et al. 2009; Mendioroz et al. 2010; Nishimoto et al. 2011) however two polymorphisms (rs1049331 and rs2293870) in exon 1 have been shown to compromise its ability to do so. Studies have shown two SNPs (rs2293870 and rs11200638) in *HTRA1* to be associated with the development of neovascular age-related macular degeneration (nAMD) (DeAngelis et al. 2008; Jacobo et al. 2013). The findings of Jacobo et al. support the idea that *HTRA1* keeps IGF-1 levels in check and therefore regulates angiogenic homeostasis (Jiang et al. 2012; Jacobo et al. 2013). *HTRA1* overexpression in the RPE may serve as an IGF-1 sink and therefore may compromise photoreceptor and choriocapillary survival. *HTRA1* expression increases with age (Ly et al. 2000) and may have a function in protecting against age-related diseases (Grau et al. 2005). Balasubbu et al. have shown a marginal association between rs11200638 and DR in Indian T2DM patients (Balasubbu et al. 2010).

1.5.4 Intercellular adhesion molecule 1 (*ICAM-1*)

The gene encoding intercellular adhesion molecule 1 (*ICAM-1*) is located on chromosome 19p13.2. *ICAM-1* is a cell surface glycoprotein and a member of the immunoglobulin superfamily of adhesion

molecules. It mediates the adhesion of circulating leukocytes to the blood vessel wall and their migration through the endothelial cell into the vascular system (Hayflick et al. 1998). It is thought that increased retinal expression of ICAM-1 plays a key role in leukostasis-mediated blood-retinal barrier breakdown, capillary occlusion and endothelial cell damage in diabetic retinopathy (Jousen et al. 2004). Polymorphisms in the *ICAM-1* gene may have a functional role in DR by altering the expression and activity of ICAM-1 (Jain et al. 2013). To date three *ICAM1* polymorphisms have been analysed. Polymorphism rs5498 has been examined in six case control studies (Kamiuchi et al. 2002; Liu et al. 2006; Petrovic et al. 2008; Balasubbu et al. 2010; Vinita et al. 2012; Lv et al. 2016) and in three meta-analyses (Su et al. 2013; Sun et al. 2014; Fan & Liu 2015). Association with DR was found by four groups (Kamiuchi et al. 2002; Liu et al. 2006; Petrovic et al. 2008; Vinita et al. 2012), the studies by Balasubbu et al. and Lv et al. however did not find an association in their Indian or Chinese cohorts (Balasubbu et al. 2010; Lv et al. 2016). Interestingly the study by Vinita et al. that did find rs5498 to be associated with DR was also analysing the SNP in an Indian cohort (Vinita et al. 2012), and the study by Liu et al. (Liu et al. 2006) found an association in their Chinese cohort so the differences in findings may not be due to ethnicity. Three meta-analyses have been performed for SNP rs5498, none found an association with DR (Su et al. 2013; Sun et al. 2014; Fan & Liu 2015). Two further *ICAM1* SNPs (rs5030400 and rs1801714) were analysed by Simoes et al. in their Portuguese cohort. They reported an association with DR and rs1801714 but not rs5030400 (Simoes et al. 2014).

1.5.5 Selectin P (*SELP*)

Selectin P (*SELP*) is a molecule involved in the inflammatory response and is encoded by a gene located on chromosome 1q24.2. *SELP* functions in early phases of leukocyte recruitment by promoting rolling behaviour in the cell which is characterised by rapid formation and breaking of bonds formed by selectin before the cell finally adheres to the endothelium (Ley et al. 1995). This process can be initiated by many factors including oxidative injury (Harlan et al. 1985; Mullins et al. 2011) and complement attack (Bless et al. 1998). *SELP* is expressed in the veins of the choroid in a healthy eye, this expression is elevated, and is also seen in the arteries, of diabetics (McLeod et al. 1995). In addition, an increased number of circulating polymorphonuclear neutrophils (PMN) are activated in diabetics indicative of an altered immune state (Wierusz-Wysocka et al. 1987). PMNs contribute to the capillary obstruction and vascular injury thereby enhancing the degree of retinal and choroidal injury in the diabetic eye. Three SNPs have been analysed (rs6128, rs6133 and rs3917779). Polymorphism rs1628 was assessed in a small Iranian T2 cohort (Kolahdouz et al. 2015), a T2DM African American cohort (Penman et al. 2015) and also a large mixed ethnicity consortium study (Sobrin et al. 2011). Association with rs1628 and retinopathy was found in the study by Penman (Penman et al. 2015) and in the consortium study but interestingly only in Caucasian participants (Sobrin et al. 2011). No association was found in the Iranian study (Kolahdouz et al. 2015). The remaining two SNPs (rs6133 and rs3917779) were only assessed by the Iranian group and the consortium. Sobrin et al. found association with both SNPs, but again only in their Caucasian participants (Sobrin et al. 2011). Kolahdouz et al. found association with rs3917779 but not rs6133 in their Iranian cohort (Kolahdouz et al. 2015).

1.6 Cytokine activation

Cytokines are small cell signalling proteins released by immune response cells such as macrophages, lymphocytes and mast cells as well as endothelial cells and fibroblasts. The role of cytokines is to

modulate the behaviour of other cells. Cytokines include chemokine, interferon and interleukin proteins. These molecules play key roles in the immune and inflammatory response in health and disease. In response to an immune injury neovascularisation can occur. This is where the endothelial cells (see section 1.3) within small pre-existing blood vessels form solid buds which subsequently develop a central lumen. The new vessels made under these conditions are thin-walled, fragile and can be leaky. Inflammatory response cytokines can be induced by oxidative stress, which can trigger the release of other cytokines leading to further oxidative stress (Vlahopoulos et al. 1999; Carpenter et al. 2002; Tian et al. 2005; Chokkalingam et al. 2013).

1.6.1 Activating transcription factor 4 (ATF4)

Activating transcription factor 4 (ATF4) is an ER stress inducible transcription factor and the gene encoding ATF4 is located on chromosome 22q13.1. ATF4 is a regulator of the immune response and of chemokine (C-C motif) ligand 2 (CCL2) expression (see section 1.6.4) and is produced in the brain and retinal microvascular endothelial cells using the nuclear factor kappa B subunit 1 (NFκB) and mitogen-activated protein kinase (MAPK) pathways. *ATF4* is a major stress response gene activated in cells under conditions of both ER and oxidative stress (Chen et al. 2012; Zhong et al. 2012). Activation of ATF4 has been shown to promote the secretion of interleukin 6 (IL6) and interleukin 8 (IL8) (see section 1.6.5) and chemokine (C-C motif) ligand 5 (CCL5) through interaction with c-Jun of the toll-like receptor 4 – myeloid differentiation primary response 88 (TLR4-MyD88) pathway (Zhang et al. 2013). In diabetic retinopathy, increased CCL2 production is a major factor responsible for leukocyte migration and interaction with the endothelium resulting in microvascular injury of the retina (Jiang et al. 2007; Lange et al. 2008; Bouman et al. 2011; Chen et al. 2012; Suragani et al. 2012; Zhong et al. 2012; Huang et al. 2015). No studies to date have examined polymorphisms in this gene for association with DR.

1.6.2 Angiotensin I converting enzyme (ACE)

The renin-angiotensin system (RAS) plays an important role in the regulation of blood pressure and electrolyte homeostasis. The enzyme renin cleaves angiotensinogen to form angiotensin I, angiotensin I converting enzyme (ACE) then converts angiotensin I to angiotensin II. Angiotensin II is a potent controller of blood flow (Dzau et al. 1986; Paul et al. 1993; Wagner et al. 1996). Components of RAS are found both in circulating blood and in many tissues including the eye. Angiotensin II receptors have been shown to be expressed in retinal blood vessels (Ferrari-Dileo et al. 1987), and may play a role as a regulator of ocular circulation (Rockwood et al. 1987; Wagner et al. 1996). High levels of the inactive precursor of renin, prorenin, have been found in the plasma and vitreous of diabetic patients with retinopathy suggesting that the RAS pathway is activated in the ocular tissues of retinopathy patients and suggestive of a breakdown in the blood retina barrier and the enhancement of angiogenesis within the retina (Fernandez et al. 1985; Ariza et al. 1988; Danser et al. 1989). Several studies have looked at an insertion/deletion polymorphism (rs1799752) in the *ACE* gene (Fujisawa et al. 1995; Nagi et al. 1995; Doi et al. 1996; Gutierrez et al. 1997; Fujisawa et al. 1998; Matsumoto et al. 2000; Araz et al. 2001; Kankova et al. 2001; Globocnik-Petrovic et al. 2003; Thomas et al. 2003; Degirmenci et al. 2005; Nikzamir et al. 2010; Lu et al. 2012; Luo et al. 2016; Narne et al. 2016), five of which, including two meta-analysis studies found association with diabetic retinopathy (Matsumoto et al. 2000; Degirmenci et al. 2005; Nikzamir et al. 2010; Lu et al. 2012; Luo et al. 2016). Two other polymorphisms (rs4343 and rs4461142) have been analysed (Liang et al. 2013; Simoes et al. 2014). No association was found with rs4461142 when examined in a Portuguese

cohort (Simoes et al. 2014). Liang et al. found association between rs4343 and DR in their small Chinese cohort (Liang et al. 2013). This gene may be only involved in the development of DR in certain ethnic populations and further studies are needed.

1.6.3 Apelin receptor (APLNR)

The gene encoding the endogenous peptide apelin (APLN) is located on chromosome Xq26.1. The receptor for APLN (APLNR), encoded by a gene located on chromosome 11q12.1, is expressed on the cell surface of endothelium cells (Tatemoto et al. 2001) including vascular endothelial cells. The APLNR participates in the control of blood pressure (Lee et al. 2000). Activation causes the release of the potent vasodilator, nitric oxide, which relaxes the smooth muscle cells in the artery wall (Tatemoto et al. 2001). Activation of the receptor by APLN can cause endothelial cell migration and neovascularisation to occur (Saint-Geniez et al. 2002). The mouse model deficient in *Apln* shows developmental delay of the retinal vasculature (Kasai et al. 2004). Soualmia et al. (Soualmia et al. 2017) performed a study on a small cohort of Tunisian patients analysing one SNP in *APLNR* (rs376527330) they did not find any association between the *APLNR* polymorphism and DR.

1.6.4 Chemokine (C-C motif) ligand 2 (CCL2)

Chemokine (C-C motif) ligand 2 (CCL2) is also referred to as monocyte chemotactic protein 1 (MCP1). The gene encoding CCL2 is located on chromosome 17q12. CCL2 is a small cytokine that recruits monocytes, memory T cells and dendritic cells to sites of inflammation. It binds to chemokine receptors CCR2 and CCR4 (Matsushima et al. 1989; Rollins et al. 1991).

Chemokine (C-C motif) ligand 2 (CCL2) has been shown to exert many effects including superoxide production, cytokine expression and induction of adhesion molecules (reviewed in (Kolattukudy & Niu 2012)). CCL2 expression in the retina and RPE is very low in healthy young individuals (Chen et al. 2008) but increases in acute inflammation (de Vos et al. 1994; Nakazawa et al. 2007; Yamada et al. 2007) with aging (Chen et al. 2008) and under oxidative stress (Higgins et al. 2003; Raoul et al. 2010). The pathogenesis of DMO involves all three of these processes (reviewed in (Ehrlich et al. 2010)). Interestingly levels of CCL2 have also been shown to be increased in both the vitreous and aqueous of patients with diabetic retinopathy. These data indicate that increased expression of CCL2 appears to play an important role in the pathogenesis of diabetic retinopathy. Studies have shown that changes in the hypomethylation of CpG sites in the CCL2 promoter may be affected by blood glucose and triglycerides, which then increase the serum level of CCL2 and may play a role in the vascular complications of type 2 diabetes (Liu et al. 2012).

To date only a small number of genetic association studies of *CCL2* and diabetic retinopathy and/or DMO have been reported, often with conflicting findings (Jeon et al. 2013; Dong et al. 2014; Jiang et al. 2015; Ninomiya et al. 2015; Jiang et al. 2016). Recently a polymorphism in the promoter of *CCL2* (rs1024611) has been shown to have an association with the development of proliferative diabetic retinopathy (PDR) in Korean T2DM patients (Jeon et al. 2013). In this study Jeon et al. reported that the prevalence of PDR was significantly higher with the A/A genotype of rs1024611 compared to either A/G or G/G (Jeon et al. 2013). However, a study by Katakami et al. showed that the G/G allele of rs1024611 is the susceptibility allele for diabetic retinopathy in their Japanese population (Katakami et al. 2010). Most recently Jiang et al. has also found association with the G/G genotype and increased risk of PDR in a Chinese Han cohort (Jiang et al. 2015). Intriguingly a study on the effect of this polymorphism on the expression of CCL2 in peripheral mononuclear cells treated with

interleukin-1 beta (IL1 β) showed that individuals who had the genotype G/G or G/A produced more CCL2 than those with genotype A/A (Rovin et al. 1999).

1.6.5 C-X-C motif chemokine ligands (CXCL) and interleukins

C-X-C motif chemokine ligands play important roles in the regulation of immune mechanisms, four such examples are interleukin 6 (IL6) encoded by a gene located on chromosome 7p15.3, C-X-C motif chemokine ligand 8 (CXCL8, previously IL8) encoded by a gene located on chromosome 4q13-21, interleukin 10 (IL10) encoded by a gene on chromosome 1q32 and C-X-C motif chemokine ligand 10 (CXCL10, previously interferon-inducible protein 10 (IP10)) encoded by a gene located on chromosome 4q21. IL6 is a pro-inflammatory cytokine (Ferguson-Smith et al. 1988) whereas IL10 is an anti-inflammatory cytokine (Eskdale et al. 1998). CXCL8 is secreted by any cells expressing toll-like receptors (see section 1.6.17) as part of the innate immune response. CXCL8 is a neutrophil chemotactic factor which induces chemotaxis in target cells making them migrate to sites of infection and once in place CXCL8 will induce phagocytosis. CXCL8 is also a potent angiogenic promoter (Mukaida et al. 1998). CXCL10 is secreted by monocytes, fibroblasts and endothelial cells in response to Interferon gamma (INF γ) (see section 1.6.10). Under normal conditions CXCL10 is an inhibitor of angiogenesis (Angiolillo et al. 1995; Dufour et al. 2002). As previously mentioned, neovascularisation is the common final pathway in PDR. This mechanism occurs at the vascular, metabolic, endocrine, haematologic and immunological level by dysregulating the expression of many inflammatory cytokines and angiogenic factors such as IL6, IL8 and IL10 (Katakami et al. 2010; Jiang et al. 2016). Paine et al. reported that the *IL10* SNP rs1800896 but not *IL6* (rs1800795) was associated with PDR (Paine et al. 2012). In a study by Rudofsky et al. they also did not find association with the *IL6* promoter SNP (Rudofsky et al. 2009). Rodrigues et al. did not find an association with either *IL6* or *IL10* SNPs and DR in their Brazilian cohort (Rodrigues et al. 2015). Dong et al. found the *CXCL8* SNP, rs4073, was associated with susceptibility and progression of PDR and that the *CXCL10* polymorphism rs147164925 was associated with DR, however, neither of the polymorphisms in the study were found to be associated with DMO in their Chinese cohort.

1.6.6 Complement Factors H, B (CFH/CHB) and C5

The complement system is a part of the innate immune system that enhances (compliments) the abilities of phagocytic cells to clear bacteria and damaged cells. The complement system can be subdivided into three pathways; classic, lectin and alternative. The complement system modulates the inflammatory and immune response (Walport 2001; Walport 2001). This system is tightly regulated and any imbalance can result in the development of inflammatory or autoimmune diseases including AMD and diabetic retinopathy (Chen et al. 2007; Chen et al. 2008; Muramatsu et al. 2013). Increased levels of complement factors CFH, CFB, component 3 (C3) and component 5 (C5) have been detected in the vitreous of diabetic retinopathy patients (Muramatsu et al. 2013; Xu et al. 2016; Yang et al. 2016). CFB is a competitor of CFH and both regulate the activation of the complement alternative pathway (Wang et al. 2013). The gene encoding CFH is located on chromosome 1q32 and is a soluble inhibitor of alternative pathway activation (Liszewski & Atkinson 1996). The polymorphism, rs800292, which causes an amino acid substitution and may cause structural changes that alters the binding site has been shown to be associated with inflammatory and neovascular diseases for example AMD, due to an increased activation of the pathway (Pechtl et al. 2011). The gene encoding *CFB* is located on 6p21 in the MHCIII region. Wang et al. investigated the polymorphism rs800292 in the *CFH* gene and four *CFB* polymorphisms (rs1048709, rs53160, rs4151657 and rs2072633) in a cohort of Chinese T2DM DR patients (Wang et al. 2013). They found

that the *CFH* SNP and one of the *CFB* polymorphisms (rs1048709) were associated with diabetic retinopathy. Yang et al. (Yang et al. 2016) analysed six polymorphisms (rs12237774, rs2269066, rs17611, rs1548782, rs10985126 and rs1017119) in the gene encoding *C5* in their Chinese cohort. They found that two of the SNPs were associated with DR (rs17611 and rs1548782). A second study by Xu et al. (Xu et al. 2016) analysed three *C5* polymorphisms (rs2269067, rs7040033 and rs7027797) in their Chinese cohort and found association between rs2269067 and PDR.

1.6.7 Endothelin1 (*EDN1*)

Endothelin1 (*EDN1*) is a potent vasoconstrictor and is crucial for autoregulation of retinal blood flow, causes constriction of blood vessels, and enhances endothelial cell production of such vasodilators as nitric oxide and prostacyclins (Zhu & Shi 2007). The gene encoding *EDN1* is located on chromosome 6p24.1. Li et al. reported that the SNP rs5370 was associated with DR and also the time of onset of T2DM (Li et al. 2008).

1.6.8 High-mobility group AT-hook 1 (*HMGA1*)

High mobility group (HMG) proteins are a group of proteins that are involved in transcription, replication, recombination and DNA repair mechanisms (Rajeswari 2002). HMGs can be divided into 3 superfamilies HMGA (AT-hook domain containing), HMGB (HMG-box domain containing) and HMGN (nucleosomal binding domain containing). HMGA proteins contain the AT-hook (a DNA binding motif) and modulate transcription by altering the chromatin architecture (Mayr et al. 2007). The gene encoding *HMGA1* is located on chromosome 6p21.31. *Hmga1* has been shown to be highly expressed in the murine retina (Chau et al. 2000). *Hmga1* deficient mice are diabetic and express low levels of the insulin receptor (Semple 2009). HMGA1 is a hypoxia inducible factor that modulates the expression of several angiogenic proteins including NFkB and VEGF (see section 1.6.19) (Ji et al. 1998), as well as cytokines and adhesion molecules, which leads to inflammation and endothelial cell dysfunction which may play a role in DR (Chiefari et al. 2016). There have been two studies analysing the *HMGA1* gene polymorphism rs139876191. Chiefari et al. found association between the SNP and a reduced risk of developing PDR in their Caucasian cohort (Chiefari et al. 2016). However, Lv et al. did not find any association in their Chinese cohort (Lv et al. 2016).

1.6.9 Hypoxia-inducible factor (*HIFs*)

Hypoxia-inducible factors (HIFs) are a family of 6 transcription factors that are stabilised and constitutively expressed and regulated in an oxygen dependent manner (Lisy & Peet 2008). However, they can also be activated in different cell populations in the ischemic retina (Mowat et al. 2010). Upon stabilisation the HIFs are transported into the nucleus of the cell and become transcription factors for a variety of downstream oxidative stress related genes including *VEGF*, *SOD1* and *EPO* that are required for cell survival under hypoxic conditions (Wright et al. 2012; Kurihara et al. 2014).

The gene that encodes HIF1 α (*HIF1A*) is located on chromosome 14q23.2. Yamada et al. analysed 35 polymorphisms in the *HIF1A* gene. They found that the polymorphism rs11549465 was associated with T2DM in Japanese patients but did not find any association with the development of DR in their patients (Yamada et al. 2005).

1.6.10 Interferon gamma (*IFN γ*)

Interferon gamma (*IFN γ*) is a pro-inflammatory cytokine that participates in the pathogenesis of DM by upregulating the expression of MHC I/MHC II antigens and adhesion molecules, activating NOS2,

promoting adhesion and binding for leukocyte migration (Campbell et al. 1985; Sarvetnick et al. 1988; Rodrigues et al. 2015). IFN γ is expressed at high levels in ocular tissues in PDR patients and is thought to be an indirect inducer of angiogenesis via activation of VEGF (Nagineeni et al. 2003). The gene encoding IFN γ is located on chromosome 12q14. A study by Pravica et al. demonstrated that the T variant of the polymorphism rs2430561, which is situated in the binding site for NF κ B, resulted in a higher production of IFN γ (Pravica et al. 2000). Two groups have investigated this polymorphism in relation to the development of DR. The results were contrasting with Rodrigues et al. (Rodrigues et al. 2015) not finding association with the polymorphism in their Brazilian cohort, however Paine et al. (Paine et al. 2012) did find that the polymorphism was associated with the development of diabetic retinopathy in their Indian cohort.

1.6.11 Lipase G, endothelial type (*LIPG*)

Lipase G, endothelial type (*LIPG*) is a member of the triacylglycerol lipase family and acts primarily as a phospholipase (Azumi et al. 2003; Shiu et al. 2008). The gene encoding *LIPG* is located on chromosome 18q21.1. Shiu et al. were the first to show that serum *LIPG* concentration is increased in patients with type 2 diabetes treated with oral anti-diabetic agents but not in those on insulin therapy and was associated with the degree of subclinical inflammation (Shiu et al. 2008). It has been reported that *LIPG* is expressed in endothelial cells, macrophages and smooth muscle cells in atherosclerotic lesions of human coronary arteries (Azumi et al. 2003). Two laboratories have shown that the gene polymorphism rs2000813 in *LIPG* is associated with diabetic retinopathy in Caucasian cohorts (Durlach et al. 2011; Arndt et al. 2014).

1.6.12 MicroRNA 126 (miR 126)

MicroRNA 126 (miR 126) is an 85bp mature circulating microRNA that has been shown to regulate the response of endothelial cells to Vascular Endothelial Growth Factor (VEGF) (see section 1.6.19) (Fish et al. 2008). miR 126 is thought to be involved in neovascular disease processes by promoting VEGF as well as reducing the inflammatory response by inhibiting Vascular Cell Adhesion Molecule 1 (VCAM1) (Harris et al. 2008). miR 126 is located within the seventh intron of the epidermal growth factor-like protein 7 (*EGFL-7*) gene. *EGFL-7* is located on chromosome 9q34.3. McAuley et al. (McAuley et al. 2015) investigated the effect of the intronic *EGFL-7* SNP (rs4636297) in their Caucasian cohort, they found that there was a significant association with the development of DR. This variant is thought to allow mature miR-126 to circulate but does not regulate circulating VEGF, this is thought to increase VEGF production and hence increase the risk of DR.

1.6.13 MicroRNA 146a (miR 146a)

MicroRNA 146a (miR 146a) is involved in the innate immune system. The gene encoding *miR 146a* is located on chromosome 5q33.3. miR 146a is cleaved by the cytoplasmic dicer ribonuclease to generate 22 nucleotide mature miRNA. The mature miRNA is incorporated in to the RNA-induced splicing complex (RISC) and results in translational inhibition or destabilisation of target mRNA (Gregory et al. 2005). miR 146a is a mediator of inflammation and the expression of miR 146a is upregulated by IL1 and TNF α (see sections 1.4.2) (Sheedy & O'Neill 2008). The targets of miR 146a are involved in the toll-like receptor pathways (see section 1.6.17) that cause a cytokine response (Sheedy et al. 2008; Sonkoly et al. 2008). miR146a operates in a feedback system to finely regulate the immune response (Ma et al. 2011; Quinn & O'Neill 2011). Kadonis et al. (Kaidonis et al. 2016) analysed polymorphism rs2910164 in miR 146a in a cohort of Caucasian T2 DMO patients. They found association between rs2910164 and DMO (Kaidonis et al. 2016).

1.6.14 Serpin family F, member 1 (*SERPINF1*)

Serpin family F, member 1 (*SERPINF1*) is also known as pigment epithelium derived factor (PEDF) (Iizuka et al. 2007), the gene encoding *SERPINF1* is located on chromosome 17p13.3. *SERPINF1* is a neuroprotective and angiogenic factor that may play an important role in the pathogenesis of diabetic retinopathy. It is thought that under normal circumstances the *SERPINF1* protein is released in the retina and inhibits neovascularisation, this process is inhibited in diabetic patients. The exact pathway that *SERPINF1* uses to exert its function is still not fully understood (Frank 2004). *SERPINF1* and vascular endothelial growth factor (VEGF) (see section 1.6.19) appear to have a reciprocal relationship in the eye. In proliferative diabetic retinopathy, levels of VEGF increase while those of *SERPINF1* decrease (Guo et al. 1995). *SERPINF1* has also been shown to reduce VEGF-induced vascular leakage probably through an anti-inflammatory effect, hence it may contribute to the development of DMO (Zhang et al. 2006). It is likely that the polymorphisms in *VEGF* and *SERPINF1* lead to an imbalance of VEGF and *SERPINF1* expression and jointly contribute to the development of DR. Four SNPs have been investigated in relation to diabetic retinopathy; rs12150053, rs12948385, rs9913583 and rs1136287. In the study by Iizuka et al., only rs12150053 and rs12948385 SNPs showed an association with diabetic retinopathy within the Japanese cohort examined (Iizuka et al. 2007). Uthra et al. only analysed one SNP (rs1136287) in their South Indian patient cohort and found an association with DR (Uthra et al. 2010).

1.6.15 Serpin family G member 1 (*SERPING1*)

The gene encoding serpin family G member 1 is located on chromosome 11q12.1. *SERPING1* controls the complement cascade (see section 1.6.4) by inhibiting Complement component 1 (C1). Polymorphisms in the *SERPING1* gene have been associated with age-related macular degeneration (Ennis et al. 2008). Yang et al. analysed two *SERPING1* polymorphisms (rs1005511 and rs3824988) but did not find any association in their Chinese cohort (Yang et al. 2014).

1.6.16 TNF receptor super-family member 11b (*TNFRSF11B*)

The glycoprotein TNF receptor superfamily member 11b (*TNFRSF11B*), previously called osteoprotegerin (OPG), is a member of the tumour necrosis factor receptor superfamily and is an important molecule in the maintenance of the vascular system (Knudsen et al. 2003; Jorgensen et al. 2009; Mankoc Ramus et al. 2013). *TNFRSF11B* is expressed in the endothelial and smooth muscle cells and is modulated by cytokines and hormones such as insulin and TNF α (Rasmussen et al. 2006; Lieb et al. 2010). The gene encoding *TNFRSF11B* is located on chromosome 8q24. Mankoc Ramus et al. (Mankoc Ramus et al. 2013) investigated the effect of two SNPs (rs2073618 and rs3134069) in their cohort of Slovenian DR patients. They showed that the minor allele of rs2073618 was associated with the development of DR. The second SNP (rs3134069) did not confer increased susceptibility on its own. However, the combination of both SNPs together conferred the strongest risk for the development of DR in T2DM patients (Mankoc Ramus et al. 2013).

1.6.17 Toll-like receptor 4 (*TLR4*)

Toll-like receptors (TLRs) are proteins that play a role in the innate immune system and are expressed in macrophages and dendritic cells. They belong to the pattern recognition receptor (PRR) family of transmembrane receptors, involved in regulating immune activation by pathogen recognition (Akira et al. 2006). Genetic variations within genes encoding PRRs have been shown to be involved in several inflammatory diseases (Armant & Fenton 2002).

One of the most documented of the TLRs is toll-like receptor 4 (*TLR4*), which is expressed in various cell types including cardiomyocytes, macrophages, respiratory epithelium, endothelium and smooth muscle cells (Zarembek & Godowski 2002; Elner et al. 2005; Lee et al. 2012). The gene encoding *TLR4* is located on chromosome 9q33.1. Several studies have implicated *TLR4* in the regulation of a variety of inflammatory or immune-related disorders (Tang et al. 2010; Ben et al. 2012; Millien et al. 2013). After a ligand binds to *TLR4*, activation of a pro-inflammatory response occurs via the NF κ B pathway (Singh et al. 2014). SNPs in the extracellular domain of *TLR4* can alter ligand binding efficiency and disturb the balance of pro- and anti-inflammatory cytokines. SNPs, rs4986790 and rs4986791 have been shown to modulate *TLR4* effector function (Prohinar et al. 2010). Recent studies have reported that *TLR4* polymorphisms are associated with the inflammatory state during DM and resulting complications (Kawamoto et al. 2014; Liu et al. 2014). To date five *TLR4* SNPs have been examined in T2DM cohorts for associations with DR with conflicting results. Singh et al. and Xu et al. examined SNPs rs1075993, rs1927914 and rs1927911 (Singh et al. 2014; Xu et al. 2015). Singh et al. found an association with rs1075993 and rs1927914 but not rs1927911. Xu et al. only found an association with rs1927914. Singh et al. analysed two additional SNPs (rs4986790 and rs4986791) but failed to find an association with either (Singh et al. 2014). The finding for rs4986790 by Singh et al. contradicts that of Buraczynska et al. who have shown an association with DR firstly in a small cohort and a much stronger association in an expanded cohort (Buraczynska et al. 2009; Buraczynska et al. 2016).

1.6.18 Transforming growth factor beta (*TGF β*)

Transforming growth factor beta (*TGF β*) has an important role in angiogenesis, endothelial cell proliferation, adhesion and the deposition of extracellular matrix (Battegay et al. 1995; Nunes et al. 1998). In the retina, constitutive *TGF β* signalling is important for maintaining the structure and function of retinal capillaries, inhibition of *TGF β* signalling results in apoptosis of vascular cells, the formation of leaky capillaries, and the impairment of retinal perfusion (Walshe et al. 2009).

A study by Braunger et al. showed that impairment of *TGF β* signalling in the retinal microenvironment led to structural changes in the retina that mimic the phenotype of non-proliferative and proliferative diabetic retinopathy (Braunger et al. 2015). The authors conclude that the interaction of pericytes, vascular endothelial cells, and microglia is required for maintenance of retinal capillaries and that *TGF β* signalling plays an essential role in this process. The *TGF β 1*, gene located on chromosome 19q13.1 is highly polymorphic (Liu et al. 2014). Buraczynska et al. (Buraczynska et al. 2007), and Rodrigues et al. (Rodrigues et al. 2015) showed association between the SNP rs1800470 and DR, this was confirmed by Liu et al. through a meta-analysis study (Liu et al. 2014). Simoes et al. analysed a second *TGF β 1* SNP (rs104894719) but failed to find association with DR in their Portuguese cohort (Simoes et al. 2014).

1.6.19 Vascular endothelial growth factor (*VEGF*)

Vascular endothelial growth factor (*VEGF*) is a potent multifunctional cytokine that acts on the endothelium (Dvorak et al. 1995; Ferrara & Davis-Smyth 1997). Retinal neovascularisation is one of the events in the pathogenesis of diabetic retinopathy and this state is brought about by the complex interplay of various stimuli including growth factors such as *VEGF* (Uthra et al. 2008). *VEGF* has four main alternatively spliced isoforms VEGFA-D (Tischer et al. 1991; Paques et al. 1997; Nagy et al. 2008) and is unusually polymorphic in the promoter and 5'UTR (Brogan et al. 1999; Churchill et al. 2008). The main isoform is VEGFA₁₆₅. This isoform acts directly and selectively through the

tyrosine kinase receptors VEGFR1 and VEGFR2 expressed on the membrane of vascular endothelium (Dvorak et al. 1995; Vailati et al. 2012). The binding activates a signalling cascade that in turn, activates the transcription of several genes involved in cell growth and differentiation, which leads to new vessel formation (Xia et al. 1996; Larrivee & Karsan 2000; Gao et al. 2001; Gliko et al. 2002; Yadav et al. 2012). VEGF causes increased vascular permeability, promotes angiogenesis and stimulates endothelial cell proliferation and migration in a variety of physiological and pathological processes (Nagy et al. 2008). VEGF promotes the growth of vascular endothelial cells from arteries, veins and lymphatic vessels and prevents apoptosis induced by nutrient deprivation (Ferrara & Davis-Smyth 1997; Gerber et al. 1999). Although the VEGFA isoform is a major mediator of ischaemic ocular neovascularisation it is expressed in the normal retina and has a role in retinal preservation (Kim et al. 1999; Saint-Geniez et al. 2008). Many retinal cells produce VEGFA including RPE, capillary pericytes (Adamis et al. 1993), endothelial (Aiello et al. 1995), Muller (Pierce et al. 1995), ganglion (Donahue et al. 1996) and glial cells (Amin et al. 1997; Al-Kateb et al. 2007). A significant increase in vitreous levels of VEGF have been seen in diabetic retinopathy patients especially those with the proliferative form (Aiello et al. 1994). Diabetic microvascular changes in the retina lead to hypoxia which further stimulates the expression of VEGF and increases the accumulation of AGEs (see section 1.2.2). AGEs then further increase VEGF in a dose dependent manner (Lu et al. 1998; Poulaki et al. 2004). VEGF is believed to play a role in DR by inducing hyperpermeability of retinal vessels, the breakdown of the blood retinal barrier and neovascularisation (Schlingemann & van Hinsbergh 1997; Ferrara 2001; Ribatti 2005). Complications can arise as a result of abnormal barrier function of new vessels, leading to intraretinal haemorrhage and exudation. New vessels are more fragile and sudden loss of vision can occur due to vitreous haemorrhage (Abhary et al. 2009). Twenty one *VEGF* polymorphisms have been studied to establish if they are associated with DR, many have been extensively studied, with rs2010963 the most studied (See **Table 1**). Within this large body of work there have been mixed results as to whether individual SNPs have shown association with DR or not (**Table 1**).

1.7 Ischaemia-mediated overexpression of growth factors and cytokines

The processes that have resulted in the ischaemic state of a diabetic retina caused by hypoglycaemia have been outlined in the previous sections. Ischaemia is the restriction of blood flow to a tissue which causes a shortfall in the oxygen levels needed to keep the tissue alive. The ischaemic environment of the retina modulates the following molecules causing further tissue damage (Grant et al. 2004).

1.7.1 Fibroblast growth factor 2 (*FGF2*)

The fibroblast growth factor family consists of 22 members (FGF1-14, 16-23 there is no human FGF15). Fibroblast growth factor 2 (FGF2) is key member of this family it plays an essential role in mediating cell proliferation, development and migration (Bikfalvi 2007). The gene encoding FGF2 is located on chromosome 4q26. FGF2 is a potent stimulator of endothelial cell proliferation and of the physical organisation of endothelial cells to promote angiogenesis. Dysregulation of FGF2 can result in pathological processes such as neovascularisation (Teshima-Kondo et al. 2004) by stimulating angiogenesis and preventing apoptosis (Yang et al. 2001; Iwai-Kanai et al. 2002).

FGF2 mRNA levels were reported to be increased several fold in the eye, heart and brain of diabetic rats (Karpen et al. 1992) and *FGF2* expression is upregulated in diabetes-induced vascular complications, such as proliferative diabetic retinopathy (Teshima-Kondo et al. 2004). Plasma *FGF2* activity was reported to be significantly associated with glycaemic levels, and independently associated with both micro-albuminuria and retinopathy (Zimering & Eng 1996).

Studies have suggested that polymorphisms within the promoter region of the *FGF2* gene could interfere with existing transcription factor binding sites or produce new binding sites and thus influence *FGF2* expression (Beranek et al. 2003). To date there have been two studies examining a total of 6 polymorphisms in *FGF2*, both studies examined PDR in Caucasian cohorts (Beranek et al. 2008; Petrovic et al. 2008) and a meta-analysis using the data from these studies (Abhary et al. 2009). Petrovic et al. examined 3 SNPs (rs308398, rs41456044 and rs308395) and reported an association between rs308398 and PDR (Petrovic et al. 2008). Beranek et al. examined the same three SNPs as well as an addition three polymorphisms (rs1449683, rs373341357 and rs111250029). They did not find an association with rs308398 but did identify an association with SNP rs373341357 (Beranek et al. 2008). Abhary et al. meta-analysis did not find association with any of the *FGF2* SNPs (Abhary et al. 2009).

1.7.2 Haptoglobin (HP)

The glycoprotein haptoglobin (HP) is encoded by the *HP* gene located on chromosome 16q22.2. Under normal conditions red blood cells constantly leak low levels of haemoglobin (trivial haemolysis) which the body tolerates. However, both intravascular and extravascular haemolysis can induce inflammation and result in tissue damage. The damage is caused by haem (iron-protoporphyrin IX) released from methaemoglobin (metHb) (Bunn & Jandl 1968). The redox-active haem-iron participates in oxygen radical reactions unless haem is bound to haptoglobin (HP) and iron is bound to transferrin (see section 1.7.5) (reviewed in (Smith & McCulloh 2015)). Binding of free haemoglobin (Hb) by HP inhibits oxidative reactions. The HP-Hb complex is removed by the reticuloendothelial system in the spleen. HP is an acute phase protein and inflammatory responses can result in increased levels of HP in the plasma. Hepatic synthesis of HP is induced by IL-6, IL-1 and TNF- α (see sections 1.4.2). HP is highly expressed in arteries after chronic changes in flow induced by stress and NO (Asleh et al. 2005) and is believed to play a role in arterial restructuring (Smeets et al. 2002). *Hp* knockout mice were shown to be more prone to oxidative tissue damage (Lim et al. 1998). There are 2 major alleles for *HP*, 1 and 2, they are inherited in a codominant manner and may combine to result in three genotypes, *HP1-1*, *HP2-2* and *HP2-1*. Allele 1 is encoded by 5 exons and allele 2 is encoded by 7 exons. Allele 2 arose from an intrageneic duplication of exons 3 and 4 (Maeda et al. 1984). The different *HP* genotypes seem to have different antioxidant, scavenging and immunoregulatory properties. A study by Philippidis et al. demonstrated that the *HP1-1* genotype formed Hb complexes that resulted in a greater production of IL-10 compared to the complexes formed by the *HP2-2* genotypes (Philippidis et al. 2004). Asleh et al. (Asleh et al. 2005) have reported that the *HP1-1* genotype confers significant protection against diabetic vascular complications, compared to *HP2-2* (Nakhoul et al. 2001). Amiri et al. investigated the *HP1/2* genotypes in a cohort of T2DM Iranian patients, but did not find association between genotype and DR on their patients (Amiri et al. 2013).

1.7.3 Haemochromatosis (*HFE*)

Iron is essential for many metabolic pathways but needs to be tightly controlled as imbalances can lead to toxicity. Transferrin is one molecule that is involved in iron balance and is normally in excess so can accommodate large influxes of iron into the circulation. The iron binds to transferrin for its redistribution to sites of requirement. The binding of iron to transferrin avoids the generation of ROS. The transferrin receptor is a homodimer that can bind one transferrin molecule at each subunit. Upon binding at the cell surface the iron loaded transferrin and the receptor are internalised through clathrin-mediated endocytosis (Mayle et al. 2012; Recalcati et al. 2017). The haemochromatosis gene (*HFE*) is thought to control circulating serum iron levels by regulating the interaction between the transferrin receptor and transferrin. The gene encoding *HFE* is located on chromosome 6p21.3. Autosomal recessive hereditary haemochromatosis is caused by mutations (C282Y or H63D) in the *HFE* gene. These mutations ultimately lead to increased serum iron levels resulting in the excess iron being deposited in a variety of organs leading to their failure (Feder et al. 1996). An association between diabetic retinopathy and idiopathic haemochromatosis was reported in 1978 (Walsh & Malins 1978) and iron metabolism has recently been associated with angiogenesis, extracellular matrix remodelling and fibrosis (Parkes et al. 2000; Simonart et al. 2001; Gardi et al. 2002). Moreover emerging evidence has discovered bidirectional influences between iron metabolism and T2DM (Fernandez-Real et al. 2002). Peterlin et al. reported that SNP rs1800562 could be associated with an increased risk of PDR progression via increased iron concentrations in a Caucasian cohort (Peterlin et al. 2003), however Balasubbu et al. did not find association with rs1800562 in their Indian cohort (Balasubbu et al. 2010).

1.7.4 Kinase domain insert receptor (*KDR*)

Kinase domain insert receptor (*KDR*) is also known as VEGF receptor 2 (*VEGFR-2*) is located on chromosome 4q12. *KDR* plays an essential role in the regulation of angiogenesis, vascular development and vascular permeability as well as promoting endothelial cell proliferation, survival, migration and differentiation. A study by Gilbert et al. showed that there was increased expression of *KDR* in the retinae of diabetic rats (Gilbert et al. 1998) and Witmer et al. showed that microvascular expression of *KDR* was associated with leaky vessels in retinae from diabetic donor eyes (Witmer et al. 2002). The *KDR* gene has been found to be associated with other vascular conditions including AMD (Huang et al. 2011), cancer (Forsti et al. 2007) and coronary heart disease (Kariyazono et al. 2004; Wang et al. 2007). To date there has only been one published study analysing a polymorphism in the *KDR* gene and diabetic retinopathy. Yang et al. analysed the SNP rs2071559 in their Chinese cohort and found that there was an association with the development of DR (Yang et al. 2014).

1.7.5 Sarcolemma associated protein (*SLMAP*)

The gene encoding sarcolemma associated protein (*SLMAP*) is located on chromosome 3p14.3. Expression levels of *SLMAP* have been linked with vascular dysfunction in diabetes. *SLMAP* expression may be modulated by PPAR γ (see section 1.1.3) (Ding et al. 2005). However, the mechanism for this is not fully understood. A study by Upadhyay et al. analysed three polymorphisms in a Qatari cohort of patients. They observed an association with rs17058639 in their cohort, while the remaining two polymorphisms (rs1043045, rs1057719) only showed association when analysed as a haplotype (Upadhyay et al. 2015). This is the only study on *SLMAP* to date.

1.7.6 Vitamin D receptor (VDR)

The gene encoding the vitamin D receptor (VDR) is localised to chromosome 12q12-q14. The vitamin D receptor is a nuclear hormone receptor that is principally involved in mineral metabolism but also regulates other pathways including those involved in immune responses. Vitamin D can have anti-proliferative and anti-angiogenic effects (Lin & White 2004). VDR is expressed in most retinal cells including the vascular endothelial cells (Johnson et al. 1995). When VDR is activated it forms a heterodimer with the retinoid-X-receptor (RXR) (see section 1.1.5). Glucocorticoids decrease expression of VDR (Pike & Meyer 2010). To date four polymorphisms (rs7975232, rs1544410, rs2228570 and rs731236) in the VDR have been analysed for an association with DR. The SNP rs731236 was not found to be associated with DR by a meta-analysis study (Zhang et al. 2016). The other three polymorphisms were also considered in the meta-analysis by Zhang et al. and they found an association with rs2228570 however, they combined data from both T1DM and T2DM and included articles from non-English language reports not included here. Cyganek et al. did not find an association with any of the polymorphisms in their Caucasian patient cohort (Cyganek et al. 2006). This contradicts the findings of Zhong et al. who showed an association with rs2228570 and also with rs7975232 and rs1544410 when they are considered as a haplotype in their Chinese cohort (Zhong et al. 2015). Hong et al. analysed rs1544410 in their Korean patient cohort and found an association with DR, however the classification of retinopathy was not clear in their report (Hong et al. 2015).

1.8 Analysing Genome Wide Association Studies (GWAS) results

Analysing the significance of data generated from genome wide association studies (GWAS) is challenging. The international HapMap consortium suggested a threshold p value of 5×10^{-8} for association (Pe'er et al. 2008). This was based on the number of common independent variants (minor allele frequency (MAF) $\geq 5\%$) in a European population (Pe'er et al. 2008; Welter et al. 2014; Fadista et al. 2016). Fadista et al. have recently revisited this figure to:

“provide guidelines for GWAS and exome wide association P -value thresholds needed to correct for multiple testing, explaining the impact of linkage disequilibrium thresholds for distinguishing independent variants, MAF and ancestry characteristics” (Fadista et al. 2016).

Their study confirms the original threshold figure for GWAS for common MAFs in European populations however an even more stringent threshold should be applied when analysing SNPs with rarer MAFs in a European cohort (3×10^{-8} for MAF $\geq 1\%$, 2×10^{-8} for MAF $\geq 0.5\%$ and 1×10^{-8} for MAF $\geq 0.1\%$) and studies with other ancestries in their cohorts should consider the degree of genetic variation when deciding on the threshold. **Table 2** lists some of the SNPs the authors of GWAS studies thought might be of interest in regards to diabetic retinopathy. As can be seen very few reach close to the P -value threshold accepted as significant. One SNP (rs4838605) in the gene *ARHGAP22* has been found to reach significance both in a GWAS study (Huang et al 2011) and in a candidate gene study (McAuley et al 2013). However, the reasoning behind the selection of SNPs that the authors of several GWAS studies claim to be significant (even though they do not reach the threshold) is based on their function and how they may contribute to the disease state. Therefore they are compelling candidates for further investigation in well-defined cohorts where significance may be achieved. Examples of this can be found in a study by Sheu et al. (Sheu et al 2013). The authors identify several SNPs that they claim to be associated with DR (**Table 2**). These genes include; ADP-ribosylation factor-like 4C which is involved in cholesterol transport (Engel et al. 2004);

SH3-Domain Binding Protein 4 which plays a role in iron-mediated free-radical toxicity (Tosoni & Cestra 2009); Copper metabolism domain containing 6 which down-regulation of TNF-induced NF- κ B activation, an important reaction in inflammation (de Bie et al. 2006); low density lipoprotein receptor-related protein 2 which encodes megalin and is critical for the uptake of several ligands including lipoproteins, retinol and vitamin D (Marzolo & Farfan 2011); TBC (tre-2, BUB2, CDC16) domain family member 4 which acts as a regulatory switch, both inhibiting and facilitating the insulin-induced glucose transporter solute carrier family 2 member 4 (SLC2A4, previously known as GLUT4) translocation to the plasma membrane (Baus et al. 2008; Tan et al. 2012) and Ubiquitin C-terminal hydrolase L3 which may have a role in preventing mitochondrial oxidative stress-related apoptosis in the retina (Sano et al. 2006). It will be interesting to see if any of these genes show association in future candidate gene studies.

Discussion

Genetic variations in DR patients have been extensively studied and are summarised in **Table 1**. This illustrates the conflicting evidence between studies exacerbated by many of the studies combining patients with different disease phenotypes, such as PDR, NPDR and DMO, some studies even combine T1DM and T2DM patients in their analyses. This is a common issue found in both meta-analyses and GWAS studies, and may have contributed to conflicting reports of association. Limitations of such studies have been discussed at length elsewhere (Li & Keating 2014), but may be in part due to the lack of discrimination not only between disease types but also having mixed ethnic groups. Combining patients into a single cohort may have unintentionally concealed any genuine association of polymorphism to disease state. Also candidate gene studies have not been entirely successful in identifying true associations in complex diseases such as DR. GWAS on the other hand has enabled genes and regulatory regions with previously unknown functions to be identified. However as discussed above the *p*-value for significance needs to be monitored. Ultimately collecting large, well characterised DMO cohorts will aid the identification of true associations.

As previously discussed, DMO has a completely different disease phenotype. Of the many studies identified in **Table 1**, only 34 studies specifically state that their cohort contains patients with DMO. However, of these 34 only 12 distinguish the data from the DMO subjects when performing association analysis and of the 12, 8 have shown an association with DMO. The studies that have considered DMO as a separate entity are listed in **Table 3**, with the criteria used to diagnose DMO (if stated) and the *p* value indicated for the DMO patients if known. Although these studies have separated DMO patients as a distinct patient group, it should be noted that within each of the studies the actual numbers of DMO patients are low compared to the other DR categories. The studies have as few as 37 to a maximum of 93 DMO patients (Lee & Choi 2006; Abhary et al. 2009). Larger cohorts of patients with well characterised DMO need to be collected alongside matched controls to validate the results of these studies.

If DMO is considered to be a consequence of the breakdown of the blood-retinal-barrier, or a result of an episode of inflammation, then the analysis of genes directly associated with these events should be prioritised in well characterised DMO cohorts. There are 33 genes that would fall in to this category that have previously been studied within diabetic retinopathy cohorts (**Table 4**). Of these, 11 genes have been analysed in 23 studies which stated that their cohorts contained DMO subjects. However these have been studies containing small DMO patient numbers and 13 of the 23 studies

analysed their results without taking DMO patients as separate phenotypes so potentially any association may have been obscured.

Diabetes is a complex disease and defining the disease status of participants is difficult to do with certainty due to the chronic nature of the disease. DMO can develop at any stage of the DR spectrum and is responsible for most of the vision loss suffered by diabetic patients making it important that it should be recognised as a stand-alone group within the umbrella of diabetic retinopathy.

As can be clearly underlined from this review, only a very small number of papers specifically address results in DMO patients. Addressing the specific disease states within a cohort of patients is key for future studies to produce meaningful data.

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Figure legends

Figure 1. Overview of the complex interacting pathways known to be altered in diabetes. ROS, reactive oxygen species; AGE, advanced glycation end products; RAAS, renin-angiotensin-aldosterone system; ER, endoplasmic reticulum; FFA, free fatty acids. Adapted from (Forbes & Cooper 2013).

Table 1. Genetic polymorphism studies of diabetic retinopathy in Type 2 diabetics.

Gene	SNP	Position	Population	Type	Disease	Sample size	Association	p-value	Reference
ACE	rs1799752	NC_000017.10:g. 61565890_61565891insG	Caucasian	T1DM/T2DM	DR vs NDR	271/85	no		(Nagi et al. 1995)
			Japanese	T2DM	DR vs NDR	267	no		(Fujisawa et al. 1995)
			Japanese	T2DM	Diabetic vs Healthy	362/105	no		(Doi et al. 1996)
			Caucasian	T2DM	DR vs NDR	68/92	no		(Gutierrez et al. 1997)
			Meta-analysis	T1DM/T2DM	DR vs NDR	1008/1002	no		(Fujisawa et al. 1998)
			Japanese	T2DM	DR vs NDR	120/	yes ³	p=0.012	(Matsumoto et al. 2000)
			Caucasian	T2DM	PDR vs NDR	74/	no		(Kankova et al. 2001)
			Turkish	T2DM	Diabetic vs Healthy	239/138	no		(Araz et al. 2001)
			Caucasian	T2DM	DR vs NDR	124/80	no		(Globocnik-Petrovic et al. 2003)
			Chinese	T2DM	DR vs NDR	326/501	no		(Thomas et al. 2003)
			Turkish	T2DM	DR vs NDR	57/	yes		(Degirmenci et al. 2005)
			Iranian	T2DM	DR vs NDR	178/206	yes	p=0.008	(Nikzamir et al. 2010)
			Chinese Meta-analysis	T2DM	DR vs NDR	1039/1185	yes	p=0.005	(Lu et al. 2012)
			Indian	T2DM	DR vs NDR	149/162	no		(Narne et al. 2016)
			Meta-analysis	T1DM/T2DM	DR vs NDR	4252/5916	Yes	p<0.05	(Luo et al. 2016)
	rs4646994	NC_000017.10:g. 61565900_61565901 ins	Pakistani	T2DM	DR vs NDR vs healthy	160/193/198	yes ^{NPDR}	p=0.009	(Saleem et al. 2015)
	rs4343	NC_000017.10:g. 61566031G>A	Han Chinese	T2DM	DR vs NDR	82/63	yes	p=0.0328	(Liang et al. 2013)
	rs4461142	NC_000017.10:g. 61578048T>C	Portuguese	T2DM	progression of DR	307	no		(Simoes et al. 2014)
ADIPOQ	rs266729	NC_000003.11:g. 186559474C>G	Chinese	T2DM	DR vs NDR	372/145	no		(Li et al. 2015)
	rs822394	NC_000003.11:g. 186566728A>C	Chinese	T2DM	DR vs NDR	372/145	no		(Li et al. 2015)
	rs2241766	NC_000003.11:g. 186570892T>G	Punjab	T2DM	DR vs NDR	672	yes	p=0.001	(Sikka et al. 2014)
			Chinese	T2DM	DR vs NDR	372/145	no		(Li et al. 2015)
	rs1501299	NC_000003.11:g. 186571123G>T	Chinese	T2DM	DR vs NDR	372/145	no		(Li et al. 2015)
AGER	rs3134940	NC_000006.11:g. 32149816T>C	Han Chinese	T2DM	DR vs NDR	285/658	no		(Li et al. 2016)
	rs184003	NC_000006.11:g. 32150296C>A	Meta-analysis	T2DM	DR vs NDR	923/1782	no		(Kang et al. 2012)
			Malaysian	T2DM	DR vs 'healthy'	98/185	no	p=>0.05	(Ng et al. 2012)
			Meta-analysis	T2DM	DR vs NDR	2843/3302	yes	p<0.05 ⁺	(Niu et al. 2012)
			Meta-analysis	T2DM	DR vs NDR	880/1103	yes	p=0.002++	(Yuan et al. 2012)
	rs2070600	NC_000006.11:g. 32151443C>T	Chinese	T2DM	DR vs NDR	166/340	yes	p=0.01	(Zhang et al. 2009)
			South Indian	T2DM	DR vs NDR	345/356	yes	p=0.012	(Balasubbu et al. 2010)
			Indian	T2DM	DR vs NDR	118/115	no	P=0.22	(Uthra et al. 2010)
			Meta-analysis	T2DM	DR vs NDR	1388/2620	no		(Kang et al. 2012)
			Malaysian	T2DM	DR vs 'healthy'	98/185	no	p=>0.05	(Ng et al. 2012)
			Meta-analysis	T2DM	DR vs NDR	7029/5266	no	p=>0.05	(Niu et al. 2012)
			Chinese	T2DM	DR vs NDR	372/668	yes	p=0.01	(Yang et al. 2013)

			North Indian	T2DM	DR vs NDR	446/312	yes	$p>0.05$	(Vanita 2014)
			Egyptian	T2DM	PRD vs NPDR vs NDR	12/15/34	no		(Kamal et al. 2016)
	rs3131300	NC_000006.11:g. 32151934A>G	Portuguese	T2DM	progression of DR	307	no		(Simoes et al. 2014)
AKR1B1	rs17773344	NC_000007.13:g. 134115551G>C	Australian	T2DM	DR vs NDR	447/191**	no		(Abhary et al. 2010)
	rs9640883	NC_000007.13:g. 134116633G>A	Australian	T2DM	DR vs NDR	447/191**	yes	$p=0.002$	(Abhary et al. 2010)
	rs12666691	NC_000007.13:g. 134116954C>G	Australian	T2DM	DR vs NDR	447/191**	no		(Abhary et al. 2010)
	rs782054	NC_000007.13:g. 134119228G>A	Australian	T2DM	DR vs NDR	447/191**	no		(Abhary et al. 2010)
	rs1708414	NC_000007.13:g. 134124005C>T	Australian	T2DM	DR vs NDR	447/191**	no		(Abhary et al. 2010)
	rs1791001	NC_000007.13:g. 134125056G>C	Australian	T2DM	DR vs NDR	447/191**	no		(Abhary et al. 2010)
	rs2259458	NC_000007.13:g. 134131955T>G	Portuguese	T2DM	progression of DR	307	no		(Simoes et al. 2014)
			Australian	T2DM	DR vs NDR	447/191**	no		(Abhary et al. 2010)
	rs3896278	NC_000007.13:g. 134137705C>T	Portuguese	T2DM	progression of DR	307	no		(Simoes et al. 2014)
			Australian	T2DM	DR vs NDR	447/191**	no		(Abhary et al. 2010)
	rs1790998	NC_000007.13:g. 134138380C>A	Portuguese	T2DM	progression of DR	307	no		(Simoes et al. 2014)
	rs17188118	NC_000007.13:g. 134142068A>C	Australian	T2DM	DR vs NDR	447/191**	no		(Abhary et al. 2010)
	rs1424426	NC_000007.13:g. 134143690T>C	Australian	T2DM	DR vs NDR	447/191**	no		(Abhary et al. 2010)
	rs5053	NC_000007.13:g. 134143863G>C	Portuguese	T2DM	progression of DR	307	no		(Simoes et al. 2014)
	rs759853	NC_000007.13:g. 134143958G>A	Chilean	T2DM	DR vs NDR	53/96	yes	$p=0.0072$	(Olmos et al. 2006)
			Meta-analysis	T2DM	DR vs NDR	1494/1769	no		(Abhary et al. 2009)
			Japanese	T2DM	DR vs NDR	1505/2092	yes	$p=0.0015$	(Katakami et al. 2011)
			Australian	T2DM	DR vs NDR	447/191**	no		(Abhary et al. 2010)
			Chinese	T2DM	DR vs NDR	129/139	no		(Deng et al. 2014)
			Iranian	T2DM	DR vs NDR/healthy	109/97/114	Yes	$p=0.03$	(Rezaee et al. 2015)
			Meta-analysis	T2DM	DR vs NDR	3512/4319	no		(Zhou et al. 2015)
			North Indian	T2DM	DR vs NDR	487/439	yes	$p<0.01$	(Kaur & Vanita 2016)
			Meta-analysis of Chinese	T2DM	DR vs NDR vs healthy	1386/1549/472	no		(Song et al. 2016)
	rs1708403	NC_000007.13:g. 134152364G>A	Australian	T2DM	DR vs NDR	447/191**	no		(Abhary et al. 2010)
	rs1553976	NC_000007.13:g. 134155533C>T	Australian	T2DM	DR vs NDR	447/191**	no		(Abhary et al. 2010)
	rs4728326	NC_000007.13:g. 134159995G>A	Australian	T2DM	DR vs NDR	447/191**	no		(Abhary et al. 2010)
APLNR	rs376527330	NC_000011.10:g. 57236790G>T	Tunisian	T2DM	DR vs Healthy	100/105	no		(Soualmia et al. 2017)
ARHGAP22	rs4838605	NC_000010.10:g. 49699957C>T	Caucasian	T1DM/T2DM*	DR vs NDR	163/300	yes	$p>0.05$	(McAuley et al. 2014)
C5	rs12237774	NC_000009.12: g. 120963693C>T	Han Chinese	T2DM	DR vs NDR	295/275	no		(Yang et al. 2016)
	rs2269066	NC_000009.12: g. 120974740C>T	Han Chinese	T2DM	DR vs NDR	295/275	no		(Yang et al. 2016)
	rs2269067	NC_000009.12: g. 120974762G>C	Han Chinese	T2DM	PDR vs NPDR	400/600	yes	$p=0.003$	(Xu et al. 2016)
	rs7040033	NC_000009.12: g. 120996766G>A	Han Chinese	T2DM	PDR vs NPDR	400/600	no		(Xu et al. 2016)
	rs17611	NC_000009.12: g. 121006922C>T	Han Chinese	T2DM	DR vs NDR	295/275	yes	$p=0.009$	(Yang et al. 2016)
	rs1548782	NC_000009.12: g. 121007564T>A	Han Chinese	T2DM	DR vs NDR	295/275	yes	$p=0.023$	(Yang et al. 2016)
	rs7027797	NC_000009.12: g. 121009521T>C	Han Chinese	T2DM	PDR vs NPDR	400/600	no		(Xu et al. 2016)

	rs10985126	NC_000009.12: g. 121021656T>C	Han Chinese	T2DM	DR vs NDR	295/275	no		(Yang et al. 2016)
	rs1017119	NC_000009.12: g. 121045260T>C	Han Chinese	T2DM	DR vs NDR	295/275	no		(Yang et al. 2016)
CAPN10	rs3792267	NC_000002.11: g. 241531174G>A	Caucasian	T2DM	DR vs NDR	121/238	no		(Malecki et al. 2008)
			Caucasian	T2DM	DR vs 'healthy'	399/506	Marginal	$p=0.057$	(Buraczynska et al. 2013)
CCL2	rs1024611	NC_000017.10: g. 32579788A>G	Japanese	T2DM	DR vs NDR	1588/2214	yes	$p=0.0012$	(Katakami et al. 2010)
			Korean	T2DM	PDR vs NDR	142/448	yes	$p=0.009$	(Jeon et al. 2013)
			Chinese	T2DM	DR vs NDR**	528/515	yes ²	$p=0.046$	(Dong et al. 2014)
			Chinese	T2DM	DR vs NDR	391/198	yes	$p=0.02$	(Jiang et al. 2015)
			Japanese	T2DM	DR vs NDR	377/379	yes	$p=0.03$	(Ninomiya et al. 2015)
			Chinese	T2DM	DR vs NDR	528/515	yes ²	$p=0.046$	(Dong et al. 2014)
			Meta-Analysis	T2DM	DR vs NDR	3468/3415	yes	$p=0.03$	(Wang et al. 2016)
CCRS5	rs1799987	NC_000003.11: g. 46411935A>G	Caucasian	T2DM	DC vs DUC/Healthy	637/237+596	marginal		(Buraczynska et al. 2012)
CDKAL1	rs7756992	NC_000006.11: g. 20679709A>G	Tunisian	T2DM	DR vs NDR	84/97	no		(Lasram et al. 2015)
	rs10946398	NC_000006.11: g. 20661034A>C	Han Chinese	T2DM	DR vs NDR	105/474	yes	$p<0.05$	(Liu et al. 2016)
CFB	rs1048709	NC_000006.11: g. 31914935A>G	Chinese	T2DM	DR vs NDR	277/275	yes	$p=0.02$	(Wang et al. 2013)
	rs537160	NC_000006.11: g. 31916400A>G	Chinese	T2DM	DR vs NDR	277/275	no		(Wang et al. 2013)
	rs4151657	NC_000006.11: g. 31917540T>C	Chinese	T2DM	DR vs NDR	277/275	no		(Wang et al. 2013)
	rs2072633	NC_000006.11: g. 31919578A>G	Chinese	T2DM	DR vs NDR	277/275	no		(Wang et al. 2013)
CFH	rs800292	NC_000001.10: g. 196642233G>A	Chinese	T2DM	DR vs NDR	277/275	yes	$p=0.015$	(Wang et al. 2013)
CHN2	rs39059	NC_000007.13: g. 29255470A>G	Chinese	T2DM	Dr vs NDR	374/280	yes	$p=0.0022$	(Hu et al. 2011)
			Taiwanese	T2DM	DR vs NDR	171/548	no		(Chen et al. 2014)
	rs2023908	NC_000007.13: g. 29327526C>A	Taiwanese	T2DM	DR vs NDR	171/548	no		(Chen et al. 2014)
	rs1002630	NC_000007.13: g. 29428070G>A	Taiwanese	T2DM	DR vs NDR	171/548	yes ¹	$p=<0.05$	(Chen et al. 2014)
	rs1362363	NC_000007.13: g. 29511689T>C	Taiwanese	T2DM	DR vs NDR	171/548	no		(Chen et al. 2014)
CNR1	rs1049353	NC_000006.11: g. 88853635C>T	Caucasian	T2DM	DR vs healthy	205/450	yes	$p=0.0005$	(Buraczynska et al. 2014)
CRP	rs2808629	NC_000001.10: g. 159676796G>A	Chinese	T2DM	DR vs NDR	618/400	yes	$p=<0.006$	(Peng et al. 2015)
	rs3093077	NC_000001.10: g. 159679636A>C	Chinese	T2DM	DR vs NDR	618/400	no		(Peng et al. 2015)
	rs1130864	NC_000001.10: g. 159683091G>A	Chinese	T2DM	DR vs NDR	618/400	no		(Peng et al. 2015)
	rs2808634	NC_000001.10: g. 159692573T>C	Chinese	T2DM	DR vs NDR	618/400	no		(Peng et al. 2015)
CXCL8	rs4073	NC_000004.11: g. 74606024A>T	Chinese	T2DM	DR vs NDR	528/515	yes ²	$p=0.001$	(Dong et al. 2016)
CXCL10	rs147164925	NC_000023.10: g. 70839763C>T	Chinese	T2DM	DR vs NDR	528/515	yes ²	$p<0.001$	(Dong et al. 2016)
EDN1	rs5370	NC_000006.11: g. 12296255G>T	Chinese	T2DM	DR vs NDR	216/127	yes	$p=0.002$	(Li et al. 2008)
EPO	rs1617640	NC_000007.13: g. 100317298C>A	European-American	T2DM	PDR vs NDR	374/239	yes	$p=0.0019$	(Tong et al. 2008)
			Caucasian	T1DM/T2DM	DR** vs NDR	285**/233	yes	$p=0.008$	(Abhary et al. 2010)
			Chinese	T2DM	DR vs nDR	448/344	no		(Song et al. 2015)
			Han Chinese	T2DM	DR vs NDR	397/796	yes	$p=0.001$	(Fan et al. 2016)
	rs507392	NC_000007.13: g. 100319936G>A	Caucasian	T1DM/T2DM	DR** vs NDR	285**/233	yes	$p=0.008$	(Abhary et al. 2010)
			Chinese	T2DM	DR vs nDR	448/344	yes ¹	$p=<0.003$	(Song et al. 2015)
			Han Chinese	T2DM	DR vs NDR	397/796	yes	$p=0.001$	(Fan et al. 2016)
	rs551238	NC_000007.13: g. 100321528G>T	Caucasian	T1DM/T2DM	DR** vs NDR	285**/233	yes	$p=0.008$	(Abhary et al. 2010)
			Chinese	T2DM	DR vs nDR	448/344	yes ¹	$p=<0.003$	(Song et al. 2015)
			Han Chinese	T2DM	DR vs NDR	397/796	yes	$p=0.001$	(Fan et al. 2016)
FGF2	rs308395	NC_000004.11: g. 123746942C>G	Caucasian	T2DM	DR vs NDR	206/107	no		(Petrovic et al. 2008)
			Caucasian	T2DM	PDR vs NPDR vs	129/175/184	no		(Beranek et al. 2008)

NDM									
		Meta-analysis	T2DM	DR vs NDR		no			(Abhary et al. 2009)
rs41456044	NC_000004.11: g. 123747029T>A	Caucasian	T2DM	DR vs NDR	206/107	no			(Petrovic et al. 2008)
		Caucasian	T2DM	PDR vs NPDR vs NDM	129/175/184	no			(Beranek et al. 2008)
		Meta-analysis	T2DM	DR vs NDR		no			(Abhary et al. 2009)
rs308398	NC_000004.11: g. 123747310A>T	Caucasian	T2DM	DR vs NDR	206/107	yes	$p=0.03$		(Petrovic et al. 2008)
		Caucasian	T2DM	PDR vs NPDR vs NDM	129/175/184	no			(Beranek et al. 2008)
rs1449683	NC_000004.11: g. 123748086C>T	Caucasian	T2DM	PDR vs NPDR vs NDM	129/175/184	no			(Beranek et al. 2008)
rs373341357	NC_000004.11: g. 123748564C>G	Caucasian	T2DM	PDR vs NPDR vs NDM	129/175/184	yes	$p=0.05$		(Beranek et al. 2008)
rs111250029	NC_000004.11: g. 123813558T>C	Caucasian	T2DM	PDR vs NPDR vs NDM	129/175/184	no			(Beranek et al. 2008)
FND5	rs1570569	NC_000001.11:g. 32871355G>T	Chinese	T2DM	DR vs NDR	617/352	yes ^{PDR}	$p=0.029$	(Tang et al. 2016)
	rs16835198	NC_000001.11:g. 32861080G>T	Chinese	T2DM	DR vs NDR	617/352	no		(Tang et al. 2016)
	rs3480	NC_000001.11:g. 32862564G>A	Chinese	T2DM	DR vs NDR	617/352	no		(Tang et al. 2016)
GLO1	rs4746	NC_000006.11:g. 38650628T>G	Chinese	T2DM	DR vs NDR/Healthy	126/122/301	No		(Wu et al. 2011)
		Caucasian	T2DM	DR vs NDR	524	no			(Groener et al. 2013)
	rs1049346	NC_000006.11:g. 38670837G>A	Chinese	T2DM	DR vs NDR/Healthy	126/122/301	yes	$p=0.04$	(Wu et al. 2011)
GRIK2	rs487083	NC_000006.11:g. 102026932T>G	Chinese	T2DM	Dr vs NDR	174/575	yes	$p=0.000001$	(Lin et al. 2013)
GSTM1	+/-	Caucasian	T2DM	DR vs NDR	284/320	yes ¹	$p<0.001$		(Cilensek et al. 2012)
		Meta-analysis	T2DM		3563	yes			(Sun et al. 2015)
GSTP1	rs1695	NC_000001.10:g.67585218A>G	Caucasian	T2DM	DR vs NDR	284/320	no		(Cilensek et al. 2012)
GSTT1	+/-	Caucasian	T2DM	DR vs NDR	284/320	yes	$p<0.001$		(Cilensek et al. 2012)
		Meta-analysis			3563	yes			(Sun et al. 2015)
HFE	rs1800562	NC_000006.11:g. 26093141G>A	Caucasian	T2DM	PDR vs NDR	90/133	yes	$p=0.02$	(Peterlin et al. 2003)
		South Indian	T2DM	DR vs NDR	345/356	no			(Balasubbu et al. 2010)
HIF1A	rs11549465	NC_000001.4.8:g.62207557C>T	Japanese	T2DM	DR vs NDR	180/260	yes	$p=0.0028$	(Yamada et al. 2005)
HMGA1	rs139876191	NC_000006.12:g. 34242693_3424269insC	Caucasian	T2DM	NDR vs NPDR/PDR ¹	936/587/436	yes	$p=0.013$	(Chiefari et al. 2016)
		Chinese	T2DM	NDR vs DR	344/448	no			(Lv et al. 2016)
HP	dup	Iranian	T2DM	DR vs healthy	109/114	no			(Amiri et al. 2013)
HTRA1	rs11200638	NC_000010.10: g. 124220544G>A	South Indian	T2DM	DR vs NDR	345/354	Marginal	$p=0.055$	(Balasubbu et al. 2010)
ICAM1	rs5498	NC_000019.10: g. 10285007A>G	Japanese	T2DM	DR vs NDR	81/50	yes	$p=0.035$	(Kamiuchi et al. 2002)
		Chinese	T2DM	DR vs NDR/healthy	132/32	yes	$p<0.05$		(Liu et al. 2006)
		Caucasian	T2DM	DR vs NDR	195/143	yes	$p=0.013$		(Petrovic et al. 2008)
		Indian	T2DM	DR vs NDR	345/356	no			(Balasubbu et al. 2010)
		Indian	T2DM	DR vs NDR	157/199	yes	$p=0.012$		(Vinita et al. 2012)
		Meta-analysis	T2DM	DR vs NDR	952/741	no			(Su et al. 2013)
		Meta- analysis	T2DM	DR vs NDR	1094/909	no			(Sun et al. 2014)

			Meta- analysis	T2DM	DR vs NDR	1120/956	no		(Fan & Liu 2015)
			Chinese	T2DM	DR vs NDR	448/344	no		(Lv et al. 2016)
	rs5030400	NC_000019.10:g. 10285120C>T	Portuguese	T2DM	progression of DR	307	no		(Simoes et al. 2014)
	rs1801714	NC_000019.10:g. 10284532C>T	Portuguese	T2DM	progression of DR	307	yes	$p=0.012$	(Simoes et al. 2014)
IDUA	rs6856425	NC_000004.11: g. 976918T>C	Mixed Ethnicities	T2DM	DR vs NDR	598/1789	yes	$p=0.000021$	(Sobrin et al. 2011)
IGSF21-KLHDC7A	rs3007729	NC_000001.10: g. 18795255T>C	Han Chinese	T2DM	DR vs NDR	175/144	yes	$p=0.013$	(Lin et al. 2016)
IGF2BP2	rs4402960	NC_0.000003.11:G. 185511687G>T	Tunisian	T2DM	DR vs NDR	84/97	no		(Lasram et al. 2015)
IL6	rs1800795	NC_000007.14: g.22727026C>G	Caucasian	T2DM	DR vs NDR	498	yes	$P=0.016$	(Rudofsky et al. 2009)
			Asian	T2DM	DR vs NDR	253/240	no		(Paine et al. 2012)
			Brazilian	T2DM	DR vs NDR/healthy	102/66/36	no		(Rodrigues et al. 2015)
IL10	rs180896	NC_000013.10: g. 42129372A>G	Asian	T2DM	DR vs NDR	253/240	yes	$p=0.0037$	(Paine et al. 2012)
			Brazilian	T2DM	DR vs NDR/healthy	102/66/36	no		(Rodrigues et al. 2015)
IFNg	rs2430561	NC_000012.11: g. 68552522T>A	Indian	T2DM	DR vs NDR	253/240	yes	$p=0.0011$	(Paine et al. 2012)
			Brazilian	T2DM	DR vs NDR/healthy	102/66/36	no		(Rodrigues et al. 2015)
ITGA2	rs3212515	NC_000005.10:g. 53054608T>C	Mexican	T2DM	DR vs NDR	121/56	no		(Cepeda-Nieto et al. 2015)
	rs2910964	NC_000005.10:g. 53054691G>A	Japanese	T2DM	DR vs NDR/healthy	119/108/169	yes	$p=0.0036$	(Matsubara et al. 2000)
			Caucasian	T2DM	DR vs NDR	163/95	yes	$p<0.05$	(Petrovic et al. 2003)
			Chinese	T2DM	DR vs NDR	216/127	no		(Li et al. 2008)
			Meta-analysis	T2DM	DR vs NDR	561/403	yes	$p=0.0002$	(Abhary et al. 2009)
			French	T2DM	DR vs NDR	103/72	no		(Arsene et al. 2011)
			Egyptian	T2DM	DR vs NDR	50/20	yes	$p<0.01$	(Azmy et al. 2012)
			Meta-analysis	T2DM	DR vs NDR	758/570	yes	$p=0.0003$	(Gong et al. 2015)
			Mexican	T2DM	DR vs NDR	121/56	no		(Cepeda-Nieto et al. 2015)
ITGB3	rs5918	NC_000017.10:g. 45360730T>C	Caucasian	T2DM	DR vs NDR	222/120	yes	$p=0.018$	(Nikolajevic-Starcevic et al. 2011)
KCNJ11	rs5219	NC_000011.10:g. 17388025T>C	Han Chinese	T2DM	DR vs NDR	105/475	yes	$p<0.05$	(Liu et al. 2015)
KDR	rs2071559	NC_000004.11:g. 55992366A>G	Chinese	T2DM	DR vs NDR	216/284	yes	$p=0.034$	(Yang et al. 2014)
LEKR1_CCNL1	rs13064954	NC_000003.11:g. 156854742G>A	Han Chinese	T2DM	DR vs NDR	175/144	yes	$p=0.032$	(Lin et al. 2016)
LIPG	rs2000813	NC_000018.10: g. 4956494C>T	Caucasian	T2DM	DR vs NDR	63/332	yes	$p=0.025$	(Durlach et al. 2011)
				T2DM			yes		(Arndt et al. 2014)
LOC101928923	rs2518344	NC_000006.11:g. 101775146A>G	Chinese	T2DM	DR vs NDR	174/575	yes		(Lin et al. 2013)
	rs10499299	NC_000006.11:g. 156133888A>G	Chinese	T2DM	DR vs NDR	174/575	yes^		(Lin et al. 2013)
	rs10499298	NC_000006.11:g. 156134070C>T	Chinese	T2DM	DR vs NDR	174/575	yes		(Lin et al. 2013)
	rs17827966	NC_000006.11:g. 156138709T>C	Chinese	T2DM	DR vs NDR	174/575	yes^		(Lin et al. 2013)
LOC105369178	rs1073203	NC_000005.10:g. 125983763C>G	Caucasian	T1DM/T2DM*	DR vs NDR	163/300	yes	$p>0.05$	(McAuley et al. 2014)
miR-126 (EGFL7)	rs4636297	NC_000009.11:g. 139565150A>G	Caucasian	T1DM/2DM	DR vs NDR (both groups contain DME)	163/368	yes	$P=0.006$	(McAuley et al. 2015)

miRNA-146a	rs2910164	NC_000005.10:g. 160485411C>G	Caucasian	T2DM	DME Vs NDR	856/895	yes	$p=0.025$	(Kaidonis et al. 2016)
MRPL14	rs713050	NC_000006.11:g. 44092129T>G	Chinese	T2DM	DR vs NDR	174/575	yes	$p<0.05$	(Lin et al. 2013)
MTHFR	rs1801133	NC_000001.11:g. 11796321G>A	Japanese	T2DM	DR vs NDR	98/268	no	$p=0.98$	(Yoshioka et al. 2003)
			Meta-analysis	T2DM	DR vs NDR	435/620	no		(Zintzaras et al. 2005)
			Japanese	T2DM	DR vs NDR	115/75	yes	$p=0.017$	(Maeda et al. 2008)
			Meta-analysis	T2DM	DR vs NDR	1599	yes	$p=0.04$	(Niu & Qi 2012)
			Turkish	T1DM/T2DM	DR vs 'healthy'	230/282	yes	$p=0.039$	(Yigit et al. 2013)
			Chinese	T2DM	DM vs Healthy	208/57	yes ⁴	$p<0.05$	(Sun et al. 2003)
			Portuguese	T2DM	progression of DR	307	yes	$p=0.024$	(Simoes et al. 2014)
			Meta-analysis	T1DM/T2DM	DR vs NDR	1747/3146	yes	$p<0.05$	(Luo et al. 2016)
	rs3753582	NC_000001.11:g. 11865542A>C	Han Chinese	T2DM	DR vs NDR	175/144	no		(Lin et al. 2016)
	rs1537516	NC_000001.11:g. 11847861G>A	Han Chinese	T2DM	DR vs NDR	175/144	no		(Lin et al. 2016)
NFE2L2	rs2364723	NC_000002.11:g. 178126546G>C	Han Chinese	T2DM	DC vs DNC vs Healthy	214/236/359 (only 33 with DR)	yes		(Xu et al. 2016)
	rs13001694	NC_000002.11:g. 178118990A>G	Han Chinese	T2DM	DC vs DNC vs Healthy	214/236/359 (only 33 with DR)	no		(Xu et al. 2016)
	rs10497511	NC_000002.11:g. 178119296G>A	Han Chinese	T2DM	DC vs DNC vs Healthy	214/236/359 (only 33 with DR)	yes		(Xu et al. 2016)
	rs1806649	NC_000002.11:g. 178118152C>T	Han Chinese	T2DM	DC vs DNC vs Healthy	214/236/359 (only 33 with DR)	no		(Xu et al. 2016)
	rs1962142	NC_000002.11:g. 178113484A>G	Han Chinese	T2DM	DC vs DNC vs Healthy	214/236/359 (only 33 with DR)	yes		(Xu et al. 2016)
	rs6726395	NC_000002.11:g. 178103229A>G	Han Chinese	T2DM	DC vs DNC vs Healthy	214/236/359 (only 33 with DR)	yes		(Xu et al. 2016)
NOS1	rs1552228	NC_000012.11:g. 117779170A>G	Portuguese	T2DM	progression of DR	307	no		(Simoes et al. 2014)
NOS2	rs2297518	NC_000017.11:g. 27769571G>A	Caucasian	T2DM	DR vs NDR	123/77	no		(Porojan et al. 2015)
NOS3	rs2070744	NC_000007.13:g. 150690079C>T	Japanese	T2DM	DR** vs NDR/ 'healthy'	116/296	yes*	$p=0.001$	(Awata et al. 2004)
			Tunisian	T2DM	DR** vs NDR	383/489	no	$p=>0.05$	(Ezzidi et al. 2008)
			Brazilian	T2DM	DR** vs NDR	434/196	no	$p=>0.05$	(Santos et al. 2012)
			South Indian	T2DM	DR vs NDR	149/162	no		(Narne et al. 2014)
	rs1799983	NC_000007.13:g. 150696111T^>G	Tunisian	T2DM	DR** vs NDR	383/489	no		(Ezzidi et al. 2008)
			South Indian	T2DM	DR vs NDR	149/162	no		(Narne et al. 2014)
			Iranian	T2DM	DR vs normal	94/94	no		(Momeni et al. 2016)
			Han Chinese	T2DM	DR vs NDR	175/144	no		(Lin et al. 2016)
	rs3918227	NC_000007.13:g. 150700946C>A	Han Chinese	T2DM	DR vs NDR	175/144	no		(Lin et al. 2016)
PON1	rs662	NC_000007.13: g. 94937446C>T	Japanese	T2DM	DR vs NDR	188/92	yes	$P=0.0046$	(Murata et al. 2004)
			Turkish	T2DM	DR vs NDR	68/103	yes	$p<0.05$	(Ergun et al. 2011)

			Meta-analysis	T1DM/T2DM	DR vs NDR	336/314	no		(Wang et al. 2013)
	rs854560	NC_000007.13: g. 94946084A>T	Turkish	T2DM	DR vs NDR	68/103	yes	$p<0.05$	(Ergun et al. 2011)
			Meta-analysis	T1DM/T2DM	DR vs NDR	392/537	yes	$p<0.05$	(Wang et al. 2013)
PON2	rs7493	NC_000007.13: g. 95034775G>C	UK	T2DM	DR vs NDR vs healthy	101/151/281	no		(Mackness et al. 2005)
			Meta-analysis	T1DM/T2DM	DR vs NDR	347/414	no		(Wang et al. 2013)
PPAR-g	rs4684847	NC_000003.11: g. 12386337C>T	Chinese	T2DM	DR vs NDR	247/253	no		(Wang et al. 2015)
	rs12497191	NC_000003.11: g. 12390135A>G	Chinese	T2DM	DR vs NDR	488/344	no		(Zhang et al. 2015)
	rs1801282	NC_000003.11: g. 12393125C>G	Caucasian	T2DM	DR vs NDR	160/101	no		(Petrovic et al. 2005)
			Caucasian	T2DM	DR vs NDR	121/238	yes	$p=0.026$	(Malecki et al. 2008)
			Caucasian	T2DM	DR vs NDR	102/254	no		(Costa et al. 2009)
			Meta-analysis	T2DM	DR vs NDR	2720/2450	yes	$p=0.01'$	(Ma et al. 2012)
			Pakistani	T2DM	DR vs NDR/'healthy'	180/193/200	yes	$p<0.05$	(Tariq et al. 2013)
			Chinese	T2DM	DR vs NDR	488/344	no		(Zhang et al. 2015)
			North Indian	T2DM	Dr vs NDR	717/608	no		(Kaur & Vanita 2016)
	rs1805192	NC_000003.11: g. 12421238C>G	Chinese	T2DM	DR vs NDR	247/253	yes	$p=0.012$	(Wang et al. 2015)
	rs709158	NC_000003.11: g. 12463176A>G	Chinese	T2DM	DR vs NDR	247/253	no		(Wang et al. 2015)
	rs3856806	NC_000003.11: g. 12475557C>T	Caucasian	T2DM	DR vs NDR	102/254	no		(Costa et al. 2009)
			Chinese	T2DM	DR vs NDR	488/344	no		(Zhang et al. 2015)
			Chinese	T2DM	DR vs NDR	247/253	no		(Wang et al. 2015)
PPARGC1A	rs8192678	NC_000004.11: g. 23815662C>T	Caucasian	T2DM	DR vs NDR	160/101	yes	$P=0.035$	(Petrovic et al. 2005)
	rs10213440	NC_000004.11: g. 23866339T>C	Portuguese	T2DM	progression of DR	307	yes (severe)	$p=0.03$	(Simoes et al. 2014)
	rs16874271	NC_000004.11: g. 23879727A>G	Portuguese	T2DM	progression of DR	307	yes (mild)	$p=0.045$	(Simoes et al. 2014)
ROMO1	rs6060566	NC_000020.10: g. 34288226T>C	Caucasian	T2DM	Dr vs NDR	278/528	yes	$p<0.024$	(Petrovic et al. 2015)
RXR-α	rs1128977	NC_000001.10: g. 165389129G>A	Taiwanese	T2DM	DR vs NDR	132/81	yes	$p=0.0057$	(Hsieh et al. 2011)
SELP	rs6128	NC_000001.11: g. 16953666C>A	Mixed Ethnicities	T2DM	DR vs NDR	598/1789	yes^^	$P=0.0001$	(Sobrin et al. 2011)
			Iranian	T2DM	PDR vs NDR	55/55	no	$p=0.2$	(Kolahdouz et al. 2015)
			African American	T1DM/T2DM	DR vs NDR	266/423	yes	$p<0.02$	(Penman et al. 2015)
	rs6133	NC_000001.11: g. 169596108C>A/G	Mixed Ethnicities	T2DM	DR vs NDR	598/1789	yes^^	$P=0.0001$	(Sobrin et al. 2011)
			Iranian	T2DM	PDR vs NDR	55/55	no	$p=0.19$	(Kolahdouz et al. 2015)
	rs3917779	NC_000001.11: g. 169601610G>A	Mixed Ethnicities	T2DM	DR vs NDR	598/1789	yes^^	$P=0.0001$	(Sobrin et al. 2011)
			Iranian	T2DM	PDR vs NDR	55/55	yes	$p = <0.0001$	(Kolahdouz et al. 2015)
SERPINE1	rs1799889	NC_000007.13: g. 100769711A>G	Tunisian	T2DM	DR** vs NDR	383/473	yes	$p<0.05$	(Ezzidi et al. 2009)
	rs1799768	NC_000007.13: g. 100769706_100769707insG	Pima Indians	T2DM	DR vs NDR	70/101	yes	$p=0.02$	(Nagi et al. 1997)
			Caucasian	T2DM	DR vs NDR	82/177	no		(Broch et al. 1998)
			Caucasian	T2DM	DR vs NDR	124/80	no		(Globocnik-Petrovic et al. 2003)

			Euro-Brazilian	T2DM	DR vs NDR	99/111	no		(Santos et al. 2003)
			Japanese	T2DM	DR vs NDR	188/92	no		(Murata et al. 2004)
			Meta-analysis	T1DM/T2DM	Diabetic complications	4330/6749	no		(Xu et al. 2013)
			Meta-analysis	T2DM	DR vs NDR	1217/1459	yes	$p<0.05$	(Zhang et al. 2013)
			Pakistani	T2DM	DR vs NDR vs healthy	160/193/198	no		(Saleem et al. 2015)
			Tunisian	T2DM	DR** vs NDR	383/473	yes	$p<0.05$	(Ezzidi et al. 2009)
SERPINF1	rs12150053	NC_000017.10: g. 1664469T>C	Japanese	T2DM	DR vs NDR	187/229	yes	$p=0.0004$	(Iizuka et al. 2007)
	rs12948385	NC_000017.10: g. 1664901G>A	Japanese	T2DM	DR vs NDR	187/229	yes	$p=0.0081$	(Iizuka et al. 2007)
	rs9913583	NC_000017.10: g. 1665330C>A	Japanese	T2DM	DR vs NDR	187/229	no		(Iizuka et al. 2007)
	rs1136287	NC_000017.10: g. 1673276C>T	Japanese	T2DM	DR vs NDR	187/229	no		(Iizuka et al. 2007)
			South Indian	T2DM	DR vs NDR	128/82	yes	$p=0.04$	(Uthra et al. 2010)
SERPING1	rs1005511	NC_000011.10: g. 57599183C>T	Han Chinese	T2DM	DR vs NDR	295/275	no		(Yang et al. 2016)
	rs3824988	NC_000011.10: g. 57610495A>G	Han Chinese	T2DM	DR vs NDR	295/275	no		(Yang et al. 2016)
SLC30A8	rs11558471	NC_000008.10: g. 118185733A>G	Chinese	T2DM	DR vs NDR	479/650	yes	$p=0.05$	(Fu et al. 2012)
SLMAP	rs17058639	NC_000003.11: g. 57882601C>T	Qatari	T2DM	DR vs NDR/healthy	78/160/104	yes	$p=<0.009$	(Upadhyay et al. 2015)
	rs1057719	NC_000003.11: g. 57913714A>G	Qatari	T2DM	DR vs NDR/healthy	78/160/104	yes^	$p=<0.05$	(Upadhyay et al. 2015)
	rs1043045	NC_000003.11: g. 57914178T>C	Qatari	T2DM	DR vs NDR/healthy	78/160/104	yes ^	$p=<0.05$	(Upadhyay et al. 2015)
SOD2	rs4880	NC_000006.11: g. 160113872A>G	Korean	T2DM	DR**vs healthy	304/192	yes*	$p=<0.05$	(Lee & Choi 2006)
			Caucasian	T2DM	DR/NDR	283/143	yes	$p=0.006$	(Petrovic et al. 2008)
			Finnish	T1DM/T2DM	DR vs NDR	131/98	yes	$p=0.03$	(Kangas-Kontio et al. 2009)
			North Indian	T2DM	DR vs NDR	446/312	yes	$p>0.05$	(Vanita 2014)
SORD	rs2055858	NC_000015.10: g. 45022070G>C	Caucasian	T2DM	DR vs NDR	154/61	marginal		(Szaflik et al. 2008)
	rs3759890	NC_000015.10: g. 45022396C>G	Caucasian	T2DM	DR vs NDR	154/61	marginal		(Szaflik et al. 2008)
			Brazilian-Caucasians	T2DM	DR vs NDR	241/205	no		(Ferreira et al. 2013)
TCF7L2	rs7903146	NC_000010.11: g. 112998590C>T	Chinese	T2DM	DR vs NDR	479/650	no	$p=>0.05$	(Fu et al. 2012)
			Caucasian	T2DM	DR vs 'healthy'	154/171	yes	$p=0.003$	(Ciccacci et al. 2013)
			Caucasian	T2DM	DR vs NDR	383/756	yes	$p=0.02$	(Luo et al. 2013)
			Meta-Analysis	T2DM	DR vs NDR	2269/4153	yes '	$p=0.001$	(Ding et al. 2015)
	rs7901695	NC_000010.11: g. 112994329T>C	Caucasian	T2DM	DR vs 'healthy'	154/171	yes	$p=0.004$	(Ciccacci et al. 2013)
	rs12255372	NC_000010.11: g. 113049143G>T	Caucasian	T2DM	DR vs 'healthy'	154/171	yes	$p=0.012$	(Ciccacci et al. 2013)
	rs11196205	NC_000010.11: g. 114807047G>C	Chinese	T2DM	DR vs NDR	448/344	no		(Zhang et al. 2015)
TGFα	rs104894719	NC_000019.10: g. 41342209A>G	Portuguese	T2DM	progression of DR	307	no		(Simoes et al. 2014)
	rs1800470	NC_000019.10: g. 41353016G>A/C	Caucasian	T2DM	DR vs NDR	195/168	yes	$p=<0.05$	(Buraczynska et al. 2007)
			Meta-Analysis	T2DM	DR vs NDR	268/340	yes	$p<0.01$	(Liu et al. 2014)
			Brazilian	T2DM	DR vs NDR/healthy	102/66/36	yes	$p=0.018$	(Rodrigues et al. 2015)
TLR4	rs10759931	NC_000009.11: g. 120464147G>A	North Indian	T2DM	DR vs NDR/'healthy'	128/250/320	yes	$p=0.05$	(Singh et al. 2014)
			Han Chinese	T2DM	DR vs	139/236/274	no		(Xu et al. 2015)

				NDR/healthy				
	rs1927914	NC_000009.11:g. 120464725G>A	North Indian	T2DM	DR vs NDR/'healthy'	128/250/320	yes	$p=0.05$ (Singh et al. 2014)
			Han Chinese	T2DM	DR vs NDR/healthy	139/236/274	yes	$p<0.05$ (Xu et al. 2015)
	rs1927911	NC_000009.11:g. 120470054A>G	North Indian	T2DM	DR vs NDR/'healthy'	128/250/320	no	(Singh et al. 2014)
			Han Chinese	T2DM	DR vs NDR/healthy	139/236/274	no	(Xu et al. 2015)
	rs4986790	NC_000009.11:g. 120475302A>G	Caucasian	T2DM	DR/NDR	352/512	yes	$p<0.001$ (Buraczynska et al. 2009)
			North Indian	T2DM	DR vs NDR/'healthy'	128/250/320	no	(Singh et al. 2014)
			Caucasian	T2DM	DR vs healthy	1090/716	yes	$p=0.0002$ (Buraczynska et al. 2016)
	rs4986791	NC_000009.11:g. 120475602C>T	North Indian	T2DM	DR vs NDR/'healthy'	128/250/320	no	(Singh et al. 2014)
TMEM217	rs1224329	NC_000006.11:g. 37180237G>A	Chinese	T2DM	DR vs NDR	174/575	yes	$p=0.000001$ (Lin et al. 2013)
	rs1150790	NC_000006.11:g. 37180523A>G	Chinese	T2DM	DR vs NDR	174/575	yes	$p=0.000001$ (Lin et al. 2013)
TNFR2	rs1799724	NC_000006.11: g. 31542482C>T	Brazilian	T2DM	DR vs NDR	414/331	no	(Sesti et al. 2015)
	rs1800629	NC_000006.11: g. 31543031G>A	Meta-analysis	T2DM	DR vs NDR	1105/1935	no	(Meng et al. 2013)
			Indian	T2DM	DR vs NDR/healthy	169/155/203	no	(Sikka et al. 2014)
			Portuguese	T2DM	progression of DR	307	no	(Simoes et al. 2014)
			Brazilian	T2DM	DR vs NDR/healthy	102/66/36	no	(Rodrigues et al. 2015)
			Brazilian	T2DM	DR vs NDR	414/313	yes	$p=0.035^{PDR}$ (Sesti et al. 2015)
			Caucasian	T1DM/T2DM	DR vs NDR	999/901	no	(Kaidonis et al. 2016)
			Japanese	T2DM	DR vs NDR	75/176	no	(Yoshioka et al. 2006)
	rs361525	NC_000006.11: g. 31543101G>A	Asian	T2DM	DR vs NDR	253/240	yes	$p=0.0001$ (Paine et al. 2012)
			Brazilian	T2DM	DR vs NDR	414/313	no	(Sesti et al. 2015)
			Caucasian	T1DM/T2DM	DR vs NDR	999/901	no	(Kaidonis et al. 2016)
	rs11574936	NC_000006.11:g. 31545193T>A	Portuguese	T2DM	progression of DR	307	no	(Simoes et al. 2014)
TNFRSF11B	rs2073618	NC_000008.10:g. 119964052G>C	Slovenian	T2DM	DR vs NDR	280/365	yes	$p=0.004$ (Mankoc Ramus et al. 2013)
	rs3134069	NC_000008.10:g. 119964988A>C	Slovenian	T2DM	DR vs NDR	280/365	yes	$p=0.01^{\wedge}$ (Mankoc Ramus et al. 2013)
TXN2	rs8140110	NC_000022.11:g. 36472588C>T	Caucasian	T2DM	DR vs NDR	277/525	no	(Ramus et al. 2016)
TXNIP	rs7211	NC_000001.11:g. 145993449G>A	Caucasian	T2DM	DR vs NDR	277/525	no	(Ramus et al. 2016)
	rs7212	NC_000001.11:g. 145992816G>C	Caucasian	T2DM	DR vs NDR	277/525	no	(Ramus et al. 2016)
	rs4755	NC_000001.11:g. 145992806T>A	Caucasian	T2DM	DR vs NDR	277/525	no	(Ramus et al. 2016)

TXNRD2	rs1548357	NC_000022.11:g. 19890839T>C	Caucasian	T2DM	DR vs NDR	277/525	no		(Ramus et al. 2016)
	rs4485648	NC_000022.11:g. 19931882T>C	Caucasian	T2DM	DR vs NDR	277/525	yes	$p=0.03$	(Ramus et al. 2016)
	rs5748469	NC_000022.11:g. 19919576C>A	Caucasian	T2DM	DR vs NDR	277/525	no		(Ramus et al. 2016)
UCP1	rs1800592	NC_000004.11:g. 141493961T>C	Chinese	T2DM	DR vs NDR	448/344	yes	$p=0.03$	(Zhang et al. 2015)
UCP2	rs660339	NC_000011.10: g. 73978059G>A	Brazilian	T2DM	DR vs NDR	242/259	yes	$p=0.006$	(Crispim et al. 2010)
			Chinese	T2DM	DR vs NDR	215/264	no	$p=0.44$	(Shen et al. 2014)
	rs659366	NC_000011.10: g. 73983709C>T	Brazilian	T2DM	DR vs NDR	242/259	yes	$p=0.006$	(Crispim et al. 2010)
			Chinese	T2DM	DR vs NDR	215/264	yes	$p=0.016$	(Shen et al. 2014)
UTS2	rs2890565	NC_000001.10: g. 7909737C>T	Turkish	T2DM	DR vs NDR	280/113	yes^	$p=0.018$	(Okumus et al. 2012)
			Japanese	T2DM	DR vs NDR vs healthy	28/36/24	yes	$p<0.05$	(Suguro et al. 2008)
	rs228648	NC_000001.10: g. 7913430G>A	Turkish	T2DM	DR vs NDR	280/113	yes	$p=0.0092$	(Okumus et al. 2012)
VDR	rs7975232	NC_000012. 11:g. 48238837C>A	Caucasian	T2DM	DR vs NDR	85/182	no		(Cyganek et al. 2006)
			Meta	T1DM/T2DM	DR vs NDR	707/649	no		(Zhang et al. 2016)
			Chinese	T2DM	DR vs NDR	44/110	yes ^	$p<0.05$	(Zhong et al. 2015)
	rs1544410	NC_000012. 11:g. 48239835C>T	Caucasian	T2DM	DR vs NDR	85/182	no		(Cyganek et al. 2006)
			Meta	T1DM/T2DM	DR vs NDR	707/649	no		(Zhang et al. 2016)
			Korean	T2DM	DR vs NDR	537	yes	$p<0.037$	(Hong et al. 2015)
			Chinese	T2DM	DR vs NDR	44/110	yes^	$p<0.05$	(Zhong et al. 2015)
	rs2228570	NC_000012. 11:g. 48272895A>G	Caucasian	T2DM	DR vs NDR	85/182	no		(Cyganek et al. 2006)
			Chinese	T2DM	DR vs NDR	44/110	yes	$p<0.01$	(Zhong et al. 2015)
			Meta-analysis	T1DM/T2DM	DR vs NDR	707/649	yes	$p<0.01$	(Zhang et al. 2016)
	rs731236	NC_000012. 11:g. 4844974A>G	Meta-analysis	T1DM/T2DM	DR vs NDR	707/649	no		(Zhang et al. 2016)
VEGFA	rs699946	NC_000006.11: g. 43732669A>G	Caucasian	T1DM/T2DM	DR** vs NDR	319/235	no		(Abhary et al. 2009)
	rs699947	NC_000006.11: g. 43736389A>G	Caucasian	T2DM	DR vs NDR	703/936	no	$p=0.974$	(Abhary et al. 2009)
			Korean	T2DM	DR vs NDR	253/143	yes	$p=0.001$	(Chun et al. 2010)
			Chinese	T2DM	DR vs NDR	129/139	yes	$p=0.02$	(Yang et al. 2011)
			Spanish	T2DM	DR vs NDR	14/26	yes	$p=0.02$	(Bleda et al. 2012)
			Meta-analysis	T1DM/T2DM	DR vs NDR	1071/1137	no		(Gong & Sun 2013)
			Meta-analysis	T2DM	DR vs NDR	1204/1198	yes	$p=0.04$	(Lu et al. 2013)
			Meta-analysis	T2DM	DR vs NDR	887/981	no	$p=>0.05$	(Han et al. 2014)
			Chinese	T2DM	DR vs NDR	216/284	yes	$p<0.001$	(Yang et al. 2014)
			Egyptian	T1DM/T2DM	DR vs NDR	77/74	no		(Shahin et al. 2015)
			Meta-analysis	T2DM			no		(Xie et al. 2016)
			Egyptian	T2DM	DR vs NDR vs Healthy	46/4141	no		(Abdel Fattah et al. 2016)
	rs833061	NC_000006.11: g. 43737486C>T	Japanese	T2DM	DR vs NDR	150/118	no		(Awata et al. 2002)
			UK Caucasians	T1DM/T2DM	PDR vs NPDR/NDR	69/198	yes	$p=0.027$	(Ray et al. 2004)
			Indian	T2DM	PDR vs NDR	120/90	yes	$p=0.0001$	(Suganthalakshmi et al. 2006)
			European	T1DM/T2DM	PDR vs NDR	45/61	yes	$p=0.006$	(Churchill et al. 2008)

		Polish	T2DM	DR vs NDR	154/61	no		(Szaflik et al. 2008)
		Chinese	T2DM	DR vs NDR	129/139	yes	$p=0.03$	(Yang et al. 2011)
		Indian	T2DM	PDR vs NDR	253/240	yes	$p=0.0043$	(Paine et al. 2012)
		Meta-analysis	T2DM	DR vs NDR	932/722	yes	$p=0.02$	(Gong & Sun 2013)
		Meta-analysis	T2DM	DR vs NDR	399/347	yes	$p=0.002$	(Han et al. 2014)
		Chinese	T2DM	DR vs NDR	216/284	yes	$p=0.001$	(Yang et al. 2014)
		Han Chinese	T2DM	DR vs NDR	232/144	yes (NPDR)	$p<0.0.13$	(Yuan et al. 2014)
		Meta-analysis	T2DM			yes	$p=0.001$	(Xie et al. 2016)
rs13207351	NC_000006.11: g. 43737794A>G	Chinese	T2DM	DR vs NDR	129/139	Yes	$p=0.029$	(Yang et al. 2011)
		Chinese	T2DM	DR vs NDR	216/284	yes	$p<0.001$	(Yang et al. 2014)
rs1570360	NC_000006.11: g. 43737830A>G	Korean	T2DM	DR vs NDR	253/134	yes	$p=0.006^{\wedge}$	(Chun et al. 2010)
		Meta-analysis	T2DM	DR vs NDR		no		(Han et al. 2014)
		Meta-analysis	T2DM			no		(Xie et al. 2016)
rs2010963	NC_000006.11: g. 43738350C>G	Japanese	T2DM	DR vs NDR	150/118	yes	$p=0.0037$	(Awata et al. 2002)
		Japanese	T2DM	*DR vs NDR	203/175	yes	$p=0.004^*$	(Awata et al. 2005)
		Indian	T2DM	DR vs NDR	120/90	yes	$p=0.008$	(Suganthalakshmi et al. 2006)
		European	T2DM	PDR vs NDR	167/334	yes	$p=0.003$	(Errera et al. 2007)
		Slovene	T2DM	PDR vs NDR	206/143	no	$p=0.27$	(Petrovic et al. 2008)
		Polish	T2DM	DR vs NDR	154/61	yes	OR=	(Szaflik et al. 2008)
		South Indian	T2DM	DR** vs NDR	120/79	no	$p=0.42$	(Uthra et al. 2008)
		Meta-analysis	T2DM	NPDR vs NDR	457/505	yes	$p=0.0005$	(Abhary et al. 2009)
		Finnish	T1DM/T2DM	DR vs NDR	131/98	no	$p=0.5846$	(Kangas-Kontio et al. 2009)
		East Asian	T2DM	PDR vs NDR	177/292	no	$p=0.309$	(Nakamura et al. 2009)
		Korean	T2DM	DR vs NDR	253/134	yes	$p=0.006^{\wedge}$	(Chun et al. 2010)
		Meta-analysis	T2DM	DR** vs PDR	1183/1057	no	$p=>0.05$	(Zhao & Zhao 2010)
		Han Chinese	T2DM	DR vs healthy	285	yes	$p=0.0063$	(Yang et al. 2011)
		Spanish	T2DM	DR vs NDR	14/26	no	$p=>0.05$	(Bleda et al. 2012)
		Egyptian	T2DM	DR* vs NDR	212/180	yes	$p=0.019$	(El-Shazly et al. 2013)
		Meta-analysis	T2DM	DR vs NDR	1666/1782	no	$p=>0.05$	(Lu et al. 2013)
		Meta-analysis	T2DM	DR vs NDR	1525/1422	yes	$p=0.03$	(Qiu et al. 2013)
		Meta-analysis	T2DM	DR vs NDR	1085/1019	no	$p=>0.05$	(Han et al. 2014)
		Han Chinese	T2DM	DR vs NDR	232/144	no	$p>0.05$	(Yuan et al. 2014)
		Taiwanese	T2DM	DR vs NDR	53/31	yes	$p=0.00793$	(Chen et al. 2016)
		Meta-analysis	T2DM			no		(Xie et al. 2016)
		Egyptian	T2DM	PRD vs NPDR vs NDR	12/15/34	yes	$p=0.021$	(Kamal et al. 2016)
		Mexican	T2DM	NPDR vs PDR	71/71	no		(Gonzalez-Salinas et al. 2017)
rs25648	NC_000006.11: g. 43738977C>G/T	Japanese	T2DM	DR vs NDR	150/118	no		(Awata et al. 2002)
		Indian	T2DM	PDR vs NDR	120/90	yes	$p=0.002$	(Suganthalakshmi et al. 2006)
rs833068	NC_000006.11: g. 43742527G>A	Caucasian	T1DM*/T2DM	DR** vs NDR	319/235	yes	$p=0.017$	(Abhary et al. 2009)
rs833069	NC_000006.11: g. 43742579T>C	Chinese	T2DM	DR vs NDR	129/139	no	$p=0.74$	(Yang et al. 2011)
rs3024994	NC_000006.11: g. 43743507C>T	Portuguese	T2DM	progression of DR from mild to	307	no		(Simoes et al. 2014)

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rs2146323	NC_000006.11: g. 43745095C>A	Chinese	T2DM	DR vs NDR	129/139	yes	$p=0.021$	(Yang et al. 2011)
		Chinese	T2DM	DR vs NDR	216/284	yes	$p=0.006$	(Yang et al. 2014)
		Meta-analysis	T1DM/T2DM	DR vs NDR	598/709	yes	$p=0.005$	(Zeng et al. 2015)
rs3025007	NC_000006.11: g. 43747371C>T [^]	Caucasian	T1DM/T2DM*	DR** vs NDR	319/235	no		(Abhary et al. 2009)
rs3025020	NC_000006.11: g. 43749110C [^] >T	Caucasian	T1DM/T2DM*	DR** vs NDR	319/235	no		(Abhary et al. 2009)
rs3025021	NC_000006.11: g. 43749163T>C	Caucasian	T1DM/T2DM*	DR** vs NDR	319/235	yes	$p=0.002$	(Abhary et al. 2009)
		Mexican	T2DM	NPDR vs PDR	71/71	no		(Gonzalez-Salinas et al. 2017)
rs3025030	NC_000006.11: g. 43750587G>C	Caucasian	T1DM/T2DM*	DR** vs NDR	319/235	no		(Abhary et al. 2009)
rs3025035	NC_000006.11: g. 43751359C [^] >T	Caucasian	T1DM/T2DM*	DR** vs NDR	319/235	yes	$p=0.046$	(Abhary et al. 2009)
		Mexican	T2DM	NPDR vs PDR	71/71	no		(Gonzalez-Salinas et al. 2017)
rs3025039	NC_000006.11: g. 43752536C>T	Japanese	T2DM	DR vs NDR	118/150	yes	$p=0.0035$	(Awata et al. 2002)
		Chinese	T2DM	DR vs NDR	129/139	no	$p=0.93$	(Yang et al. 2011)
		Meta-analysis	T2DM	DR vs NDR	531/616	yes	$p=0.01$	(Han et al. 2014)
		Meta-analysis	T2DM			yes	$p=0.002$	(Xie et al. 2016)
		Caucasian	T2DM	DR vs NDR	123/77	no		(Porojan et al. 2015)
rs3025040	NC_000006.11: g. 43753051T>C	Han Chinese	T2DM	DR vs NDR	175/144	no		(Lin et al. 2016)
rs10434	NC_000006.11: g. 43753212A>G	Caucasian	T1DM/T2DM*	DR** vs NDR	319/235	yes	$p=0.002$	(Abhary et al. 2009)
		Egyptian	T2DM	DR vs NDR vs Healthy	46/4141	no		(Abdel Fattah et al. 2016)
VEFGC	rs17697419 NC_000004.12:g.176687012G>A	Caucasian	T1DM/T2DM*	DR vs NDR	1919/980	yes	$p=0.001$	(Kaidonis et al. 2015)
		Caucasian	T1DM/T2DM*	DR vs NDR	1919/980	yes*	$p=0.001$	(Kaidonis et al. 2015)
		Caucasian	T1DM/T2DM*	DR vs NDR	1919/980	yes	$p=0.005$	(Kaidonis et al. 2015)
XRCC1	rs25487 NC_000019. 10:g. 43551574T>C	South Indian	T2DM	DR vs NDR	149/162	yes	$p=0.02$	(Narne et al. 2014)

Abbreviations: DMO, Diabetic Macular Oedema; T1DM, Type 1 Diabetes Mellitus; T2DM, Type 2 Diabetes Mellitus; DR, Diabetic Retinopathy; NDR, no Diabetic Retinopathy; PDR, Proliferative Diabetic Retinopathy; NPDR, Non-Proliferative Diabetic Retinopathy. Annotations: **, study includes DMO;

*, study shows an association with DMO; [^], significant as part of a haplotype; ⁺, significant in East Asian populations; ++, significant in Asian populations; ^{^^}, significant in European American sub cohort; [‘], significant in Caucasians; ^{PDR}, significant in PDR; ¹, Protective; ², not associated with DMO, ³, progression of DR, ⁴, associated with DR.

Table 2. GWAS studies of diabetic retinopathy in Type 2 diabetics

Gene	SNP	Position	Population	Type	Disease	Sample size	Association	p-value	Reference
ARHGAP22	rs4838605	NC_000010.10:g. 49699957C>T	Taiwanese GWAS	T2DM	DR vs NDRvs Healthy	174/575/100	Yes	$p=1.87 \times 10^{-9}$	(Huang et al. 2011)
	rs11101355	NC_000010.10:g. 49723037C>T	Taiwanese GWAS	T2DM	DR vs NDRvs Healthy	174/575/100	no	$p=8.92 \times 10^{-7}$	(Huang et al. 2011)
	rs11101357	NC_000010.10:g. 49723300G>A	Taiwanese GWAS	T2DM	DR vs NDRvs Healthy	174/575/100	no	$p=8.92 \times 10^{-7}$	(Huang et al. 2011)
ARL4C-SH3BP4	rs2380261	NC_000002.11:g. 235641180C>A	Chinese GWAS	T2DM	DR vs NDR	437/570	no	$p=0.0000021$	(Sheu et al. 2013)
CAMK4	rs2300782	NC_000005.10:g. 111453087C>T	Mexican-American GWAS	T2DM	DR vs NDR	103/183	no	$p=6.04 \times 10^{-5}$	(Fu et al. 2010)
FMN1	rs10519765	NC_000015.10:g. 32913223G>A	Mexican-American GWAS	T2DM	DR vs NDR	103/183	no	$p=6.21 \times 10^{-5}$	(Fu et al. 2010)
LRP2-BBS5	rs1399634	NC_000002.11:g. 170244607T>A	Chinese GWAS	T2DM	DR vs NDR	437/570	no	$p=0.000002$	(Sheu et al. 2013)
	rs4668142	NC_000002.11:g. 170264277G>T	Chinese GWAS	T2DM	DR vs NDR	437/570	no	$p=<0.05$	(Sheu et al. 2013)
PLXDC2	rs1571942	NC_000010.10:g. 20542634A>G	Taiwanese GWAS	T2DM	DR vs NDRvs Healthy	174/575/100	no	$P=3.47 \times 10^{-7}$	(Huang et al. 2011)
TBC1D4-COMMD6-UCHL3	rs9565164	NC_000013.10:g. 76039376T>C	Chinese GWAS	T2DM	DR vs NDR	437/570	no	$p=0.00000013$	(Sheu et al. 2013)

Abbreviations: T2DM, Type 2 Diabetes Mellitus; DR, Diabetic Retinopathy; NDR, no Diabetic Retinopathy

Table 3. Studies that specifically state that their cohort contains patients with DMO

Gene(s)	DMO identified in study	Type of DMO	Statistics for DMO presented	Population	Type of Diabetes	Association	p-value (For DMO if known)	Reference
ACE	yes	n/s	no	Indian	T2DM	no (WS)		(Narne et al. 2014)
AGER	yes	CSMO	no	Indian	T2DM	no (WS)		(Uthra et al. 2010)
AKR1B1	yes	n/s	no	Iranian	T2DM	yes (WS)	$p=0.03$	(Rezaee et al. 2015)
AKR1B1	yes	CSMO	no	Australian	T2DM	yes (WS)	$p=0.02$	(Abhary et al. 2010)
CCL2	yes	n/s	yes	Chinese	T2DM	yes (not DMO)	$p=0.046$	(Dong et al. 2014)
CXCL8	yes	n/s	yes	Chinese	T2DM	no		(Dong et al. 2016)
CXCL10	yes	n/s	yes	Chinese	T2DM	no		(Dong et al. 2016)
EDN1	yes	n/s	no	Chinese	T2DM	yes (WS)	$p=0.002$	(Li et al. 2008)
EPO	yes	CSMO	yes	Caucasian	T2DM	yes	$p=0.008$ (0.016)	(Abhary et al. 2010)
EPO	yes	n/s	no	Chinese	T2DM	yes	$p<0.03$	(Song et al. 2015)
ICAM1	yes	CSMO	no	Indian	T2DM	yes (WS)	$p=0.012$	(Vinita et al. 2012)
ICAM1	yes	CSMO	no	Meta-Analysis	T2DM	no		(Fan & Liu 2015)
ITGA2	yes	n/s	no	Chinese	T2DM	yes (WS)	$p=0.002$	(Li et al. 2008)
KCNJ11	yes	n/s	no	Han Chinese	T2DM	yes (WS)	$p<0.05$	(Liu et al. 2015)
miR126	yes	n/s	no	Caucasian	T1DM/T2DM	yes (WS)	$p=0.006$	(McAuley et al. 2015)
NOS3	yes	n/s	no	Chinese	T2DM	yes (WS)	$p=0.002$	(Li et al. 2008)
NOS3	yes	n/s	yes	Japanese	T2DM	yes	$p=0.001$ (0.029)	(Awata et al. 2004)
PARP1	yes	n/s	no	Indian	T2DM	no (WS)		(Narne et al. 2014)
SELP	yes	CSMO	no	African American	T1DM/T2DM	yes	$p=0.02$	(Penman et al. 2015)
SERPINF1	yes	n/s	yes	Japanese	T2DM	yes	$p=0.0081$ (0.0081)	(Iizuka et al. 2007)
SERPINF1	yes	CSMO	no	South Indian	T2DM	yes (WS)	$p=0.04$	(Uthra et al. 2010)
SLMAP	yes	n/s	yes	Qatari	T2DM	yes	$p=0.009$ (0.0425)	(Upadhyay et al. 2015)
SOD2	yes	n/s	no	Finnish	T1DM/T2DM	yes (WS)	$p=0.03$	(Kangas-Kontio et al. 2009)
SOD2	yes	n/s	yes	Korean	T2DM	yes	$p=0.05$ (0.05)	(Lee & Choi 2006)
VEGF	yes	n/s	no	Finnish	T1DM/T2DM	no (WS)		(Kangas-Kontio et al. 2009)
VEGF	yes	CSMO	no	South Indian	T2DM	no		(Uthra et al. 2008)
VEGF	yes	n/s	yes	East Asian	T2DM	no		(Nakamura et al. 2009)
VEGF	yes	CSMO	no	Spanish	T2DM	yes (WS)	$p=0.02$	(Bleda et al. 2012)
VEGF	yes	n/s	no	Caucasian	T1DM/T2DM	yes (WS)	$p=0.027$	(Ray et al. 2004)
VEGF	yes	n/s	no	Korean	T2DM	yes (WS)	$p=0.006$	(Chun et al. 2010)
VEGF	yes	CSMO	yes	Caucasian	T1DM/T2DM	yes	$p=0.04$ (0.003)	(Abhary et al. 2009)
VEGF	yes	n/s	yes	Japanese	T2DM	yes	$p=0.004$ (0.047)	(Awata et al. 2005)

VEGF	yes	CSMO	yes	Egyptian	T1DM/T2DM	yes	$p=0.019$ (0.019)	(El-Shazly et al. 2013)
XRCC1	yes	n/s	no	Indian	T2DM	no (WS)		(Narne et al. 2014)

Abbreviations: CSMO: clinically significant macular oedema; n/s: not stated; WS: whole study.

Table 4. A list of genes that have a role in inflammation and the immune response that would be beneficial to study in cohorts of DMO patients.

Gene	Population	Association	Reference
ACE	Indian	no	(Narne et al. 2014)
ADIPOQ	n/a	n/a	n/a
AGE	n/a	n/a	n/a
AGER	n/a	n/a	n/a
ATF4	n/a	n/a	n/a
CCL2	Chinese	yes	(Dong et al. 2014)
CCR5	n/a	n/a	n/a
CFH/CFB	n/a	n/a	n/a
COMMD6	n/a	n/a	n/a
CRP	n/a	n/a	n/a
CXCL8	Chinese	yes (not DMO)	(Dong et al. 2016)
CXCL10	Chinese	yes (not DMO)	(Dong et al. 2016)
EPO	Caucasian and Chinese	yes	(Abhary et al. 2010; Song et al. 2015)
HIFs	n/a	n/a	n/a
HP	n/a	n/a	n/a
HTRA1	n/a	n/a	n/a
ICAM1	Indian and Meta-analysis	yes (WS) & no	(Vinita et al. 2012; Fan & Liu 2015)
IL6	n/a	n/a	n/a
IL10	n/a	n/a	n/a
IFN γ	n/a	n/a	n/a
LRP2	n/a	n/a	n/a
miR126	Caucasian	yes (WS)	(McAuley et al. 2015)
NOS3	Japanese	yes	(Awata et al. 2004)
PGF	n/a	n/a	{Nguyen, 2016 #1006}
PPAR γ	n/a	n/a	n/a
RXR γ	n/a	n/a	n/a
SELP	African-American	yes	(Penman et al. 2015)
SERPINF1	Japanese and South Indian	yes & yes (WS)	(Iizuka et al. 2007; Uthra et al. 2010)
SLC30A8	n/a	n/a	n/a
TLR4	n/a	n/a	n/a
TNFs	n/a	n/a	n/a
UTS2	n/a	n/a	n/a
VEGF	many	yes	
VDR	n/a	n/a	n/a

Abbreviations: WS: whole study; n/a: not available

Figure 1

