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**Association of genetic variants with diabetic nephropathy**

Rizvi S *et al*. Genetic variants in diabetic nephropathy

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**Abstract**

Diabetic nephropathy accounts for the most serious microvascular complication of diabetes mellitus. It is suggested that the prevalence of diabetic nephropathy will continue to increase in future posing a major challenge to the healthcare system resulting in increased morbidity and mortality. It occurs as a result of interaction between both genetic and environmental factors in individuals with both type 1 and type 2 diabetes. Genetic susceptibility has been proposed as an important factor for the development and progression of diabetic nephropathy, and various research efforts are being executed worldwide to identify the susceptibility gene for diabetic nephropathy. Numerous single nucleotide polymorphisms have been found in various genes giving rise to various gene variants which have been found to play a major role in genetic susceptibility to diabetic nephropathy. The risk of developing diabetic nephropathy is increased several times by inheriting risk alleles at susceptibility loci of various genes like *ACE, IL, TNF-α, COL4A1, eNOS, SOD2, APOE, GLUT*, *etc*. The identification of these genetic variants at a biomarker level could thus, allow the detection of those individuals at high risk for diabetic nephropathy which could thus help in the treatment, diagnosis and early prevention of the disease. The present review discusses about the various gene variants found till date to be associated with diabetic nephropathy.

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**Key words:** Diabetes mellitus; Diabetic nephropathy; Genetic polymorphism; Gene variants; Nephropathy

**Core tip:** Diabetic nephropathy is actually the most common cause of kidney failure. It is now a scientifically proven fact that there is a strong association between an individual’s genetic makeup in his predisposition to diabetic nephropathy. Multiple genes are involved in pathogenesis of diabetic nephropathy, with several allelic polymorphisms having demonstrable effects in the development and progression of the disease thus contributing to the overall risk. These gene polymorphism studies are thus conducted to identify at-risk patients and design therapeutic strategies to prevent the outcome of such complication in his later future. This review discusses about the various gene variants found till date to be associated with diabetic nephropathy.

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**INTRODUCTION**

Diabetes mellitus is a complex syndrome leading to various metabolic dysfunctions. These metabolic dysfunctions manifest characteristic long-term complications in the form of various microvascular diseases, including diabetic nephropathy, retinopathy, and neuropathy. Diabetic nephropathy is one of the major secondary complications of diabetes mellitus affecting almost 40% of the diabetic patients. Diabetic nephropathy is clinically characterized by proteinuria, declining glomerular filtration rate, hypertension eventually leading to renal failure, requiring dialysis or transplantation. Various risk factors like, hyperglycemia, increased blood pressure, and genetic alterations may predispose an individual to diabetic nephropathy in the near future[1]. It is now a scientifically proven fact that apart from the above risk factors, there is a strong association between an individual’s genetic make-up in his predisposition to diabetic nephropathy. In this context, Anderson et al. have shown that 35% of the patients with diabetes develop nephropathy, irrespective of glycemic control[2]. Identification of genetic components of diabetic nephropathy is the most important area of diabetes research because elucidation of genes (alleles) associated with diabetic nephropathy will influence all efforts toward an understanding of the disease at molecular and mechanistic levels, its related complications, cure, treatment and prevention. Association studies of candidate genes for diabetic nephropathy are being conducted all around the globe to identify the biomarkers genes which may predispose a diabetic individual to the risk of diabetic nephropathy. Among the genetic factors involved, single nucleotide polymorphisms in the genes associated with diabetic nephropathy was found to have a major impact on the disease outcome. These gene polymorphism studies are thus conducted to identify at-risk patients and design therapeutic strategies to prevent the outcome of such complication in his later future.

**GENE VARIANTS ASSOCIATED WITH DIABETIC NEPHROPATHY**

It is now a scientifically proven fact that genes are amongst the major contributors to diabetic nephropathy apart from the environmental factors involved. In this context, a wide range of genes have been assessed to see their association with diabetic nephropathy along with a number of single-nucleotide polymorphisms in diabetic nephropathy susceptibility genes[3] It is seen that different ethnic groups may have variable risk associated with a specific gene in individuals suffering from a particular disease like diabetic nephropathy. Given below is a discussion of few genes involved with diabetic nephropathy.

***Inflammatory cytokines gene variants***

Inflammatory cytokines are involved in pathogenesis of diabetic nephropathy and the genetic variability in the genes encoding these cytokines may predispose a person to diabetic nephropathy. Some of the cytokine gene variants found to be associated with diabetic nephropathy are:

**Interleukins (IL):** There is a significant association between carriage of Interleukins (IL) -1β allele 2 (-511 C/T polymorphism) and IL-1RN (IL-1 receptor Antagonist gene) allele 2 (2 copies of the repeat sequence) with diabetic nephropathy. In case of *IL-6* gene, C/G polymorphism at position 634 in the promoter region of the *IL-6* gene is a susceptibility factor for the progression of diabetic nephropathy where G/G homozygote showed a significant positive association with macroalbuminuria in type 2 diabetic patients from Japan[4]. In another study, wang et al. identified a new amino acid change (V385I) that is associated with type 2 diabetic nephropathy[5]. In case of IL-10, polymorphism (-592) in promoter region influence IL-10 and MCP-1 production, which may be an indicator of type 2 diabetic nephropathy risk in Taiwanese patients[6].

**Tumour necrosis factor:** Gene for tumour necrosis factor (TNF)-α is highly polymorphic and is located on chromosome 6p. *TNF-* α -308G/A polymorphism has been implicated in susceptibility to diabetic nephropathy but the results have been contradictory. Studies have shown that polymorphism of the TNF- α gene at the -308 position is significantly related to an increased risk of kidney failure in patients with type 2 diabetes (T2DM)[7,8]. In contrast to this, Lindholm *et al*[9], demonstrated that the allele frequencies of *TNF* -308 G→A and *LTA* T60N polymorphisms were similar in type 1 diabetic patients with and without diabetic nephropathy and no differences were observed between type 2 diabetic patients with and without diabetic nephropathy in allele or haplotype frequencies of the studied polymorphisms. In a recent meta analysis it was demonstrated that A allele of *TNF*- α -308G/A polymorphism might be protective against diabetic nephropathy but with ethnic selectivity[10].

***Genetic variants of extracellular matrix components***

**Collagen, type IV, alpha 1:** The Collagen, type IV, alpha 1 gene *(COL4A1)* provides instructions for making one component of type IV collagen, which is a flexible protein important in the structure of many tissues throughout the body. Two single nucleotide polymorphism’s in intron 1 (rs614282 and rs679062) showed significant association with diabetic nephropathy[3]. Other studies on genetic variants of *COL4A1* gene have shown contradictory results where Krolewski *et al*[11] showed that a polymorphic *Hin*dIII restriction site was associated with increased risk for progression to diabetic nephropathy and contradictory to it, Chen *et al*[12] found no association in larger sample size.

**Laminins:** Laminins (LAM) are extracellular matrix glycoproteins which are the major noncollagenous constituent of basement membranes. They are involved in various biological processes like cell adhesion, differentiation, migration, signaling, neurite outgrowth and metastasis. Ewans *et al*[3] found a gene variant (rs3734287) located in *LAMA4* gene’s intronic region and Asn837Asn variant (rs20557) in *LAMC1* gene, to be significantly associated with diabetic nephropathy.

**Matrix metalloproteinase 9:** Two studies conducted by Maeda *et al*[13] and Hirakawa *et al*[14] had found evidence for association between diabetic nephropathy and Short Tandem-Repeat Polymorphism in the promoter microsatellite locus (D20S838) of matrix metalloproteinase 9 (*MMP9*) in Japanese and Caucasian type 2 diabetic patients, respectively. In contrast, Ewens *et al*[3], found no evidence of association between any D20S838 allele with diabetic nephropathy. However, significant association was seen between diabetic nephropathy and rs11697325, an SNP located 8.2 kb 5′ of *MMP9*[13,14].

***Gene variants of renal function components***

**Angiotensin I-converting enzyme:** Angiotensin-converting enzyme is a potent vaso-constrictor and increases blood pressure. Polymorphisms in this gene are clearly associated with circulating angiotensin I-converting enzyme (ACE)levels and studies have shown positive association between the *ACE* DD allele and type 1 diabetic nephropathy[15-17]. This study is in confirmation to a meta analysis where subjects with the II genotype had a 22% lower risk of diabetic nephropathy than carriers of the D allele suggesting a genetic association of the *ACE* I/D polymorphism with diabetic nephropathy in type I[18] and type II patients[19]. Although a large meta-analysis failed to confirm the diabetic nephropathy association in white individuals[20] but another report from the European Rational Approach for the Genetics of Diabetic Complications (EURAGEDIC) Study Group detected evidence for association of several *ACE* polymorphisms (including the “D” deletion allele) in a large case-control study, with somewhat consistent findings in a family-based transmission disequilibrium testing analysis[15]. However, another meta analysis failed to confirm the association of gene polymorphism in *ACE* gene with diabetic nephropathy[21]. A study on Iranian population also showed similar results where neither the DD genotype nor the D allele was associated with diabetic nephropathy[22].

**Angiotensinogen and angiotensin II receptor type 1 and 2 (AGT and AGTR1, AT2R):** A meta-analysis conducted by Mooyart *et al*[23], found no association between gene variants in the renin–angiotensin system, such as the rs699 variant of *AGT* and the rs5186 polymorphism of *AGTR1*, with diabetic nephropathy. In contrast, a recent study on angiotensin type 2 receptor (*AT2R*) found an association between the AT2R -1332 G:A polymorphism and the risk of diabetic nephropathy in females[76].

***Gene variants of endothelial function and oxidative stress***

**NOS 3:**It is considered as a potential candidate gene for diabetic nephropathy susceptibility[24,25]. Three polymorphisms in this gene G894T missense mutation (rs1799983), a 27-bp repeat in intron 4, and the T786C single nucleotide polymorphism (SNP) in the promoter (rs2070744) have been found to be associated with diabetic nephropathy susceptibility[26-30].

The G894T variant was found to increase the risk of macroalbuminuria and progression from microalbuminuria to macroalbuminuria, with declining glomerular filtration rate as serum creatinine value rises progressively, culminating in nephropathy[31,32] However, these results have been contradictory and not all studies support this association[33-35] Recent studies on different gene variants observed that there was an association between *eNOS-*4b/a polymorphism and the risk of type 2 diabetic nephropathy[36,37] while others suggested that there was no significant association[38,39].Recently, a report from Arab population also failed to find an association between *eNOS* gene G894T polymorphism with the risk of type 2 diabetic nephropathy.

**Catalase:** This enzyme protects the cell from [oxidative damage](http://en.wikipedia.org/wiki/Oxidative_stress) by [reactive oxygen species](http://en.wikipedia.org/wiki/Reactive_oxygen_species) (ROS) by breaking down [hydrogen peroxide](http://en.wikipedia.org/wiki/Hydrogen_peroxide) to [water](http://en.wikipedia.org/wiki/Water) and [oxygen](http://en.wikipedia.org/wiki/Oxygen). Two variants of catalase (CAT) gene one located in the 5′-untranslated region (rs1049982) and other located in intron 1 (rs560807) were found to be involved with the risk of type 1 diabetic nephropathy[3].

**Superoxide dismutase 2 (MnSOD/SOD2):** Manganese superoxide dismutase (MnSOD) protects the cells from oxidative damage by scavenging free radicals. The study on valine/alanine polymorphism in *MnSOD* gene(V16A, rs4880) revealed that, the subjects with Val allele were associated with increased risk of type 1 diabetic nephropathy[40]. The result of this study is in agreement with results by other studies[41,42], who found lower frequency of the Ala allele in Japanese and Korean type 2 diabetic patients with diabetic nephropathy as compared to controls. This Val allele was more common in the Japanese and Korean populations (85%–90%) than the northern Caucasian population (50%) and is strongly associated with diabetic nephropathy. A recent study showed that *SOD2* Val16Ala polymorphism was significantly associated with macroalbuminuria in a sample of Mexican type 2 diabetes patients where the frequency of the TT genotype was 6.7% higher in participants with macroalbuminuria than in the normoalbuminuria group[43].

***Gene variants of glucose and lipid metabolism***

**Adiponectin (ADIPO):** It is a adipocytokine encoded by adiponectin gene with substantial anti-inflammatory properties and is a major modulator of insulin resistance and dyslipidemia. The minor allele (A) in intron 1 (rs182052) of adiponectin gene was found to be associated with diabetic nephropathy in an African American population[44]. Another study showed the strongest association between a polymorphism in the promoter region of adiponectin gene, rs17300539 (*ADIPOQ*\_prom2/rs17300539 G>A) and diabetic nephropathy where the A-allele was found to increase the risk for nephropathy while the G-allele was found to be protective against the same. This association was found to be significant in Denmark and marginal in France but was not significant in Finland[45]. However, in a study conducted by Mooyaart *et al*[23], found no link between rs17300539 of adiponectin gene with diabetic nephropathy.

**Apolipoprotein E (APOE):** The apolipoprotein gene has been found to be associated with increased susceptibility to diabetic nephropathy[46]. It is a triallelic gene consisting of ε2, ε3, and ε4 alleles which are defined by a single amino acid substitution at two sites[47]. Amongst these alleles, E2 and the E4 allele of APOE gene were found to be associated with diabetic nephropathy in a meta-analysis[23] where, E2 allele lead to an increased risk of diabetic nephropathy and the E4 allele was found to have a protective effect[23,48]. However, the influence of three-allelic variations in the *APOE* gene for the development of diabetic nephropathy may be weak or moderate, but not strong[49].

**Aldose reductase (AKR1B1):** This enzyme catalyzes the reduction of glucose to sorbitol in the first step in polyol pathway of glucose metabolism. Ko *et al* first identified seven alleles at the locus of the (AC)n dinucleotide repeat sequence upstream of Aldose reductase gene *(AKR1B1)*. Several studies have demonstrated a correlation between the Z-2 allele (23 AC repeats) and susceptibility to an increased risk of diabetic nephropathy in both type1 and type 2 diabetes mellitus[50,51]. Angela *et al*[52] also showed that individuals with the Z+2 allele are more than seven times less likely to develop diabetic nephropathy than those without this gene variant. A meta-analysis found a correlation between the (AC)n dinucleotide repeat polymorphism and the occurrence of diabetic nephropathy in Caucasian type 1 diabetic subjects in contrast to type 2 diabetic subject population in which neither the risk ZK2 allele nor the protective ZC2 allele in type 1 diabetic subjects appeared to have an effect on nephropathy in type 2 diabetic subjects[53]. A second polymorphism in this gene has been observed at position-106 of its promoter region. This polymorphism in aldose reductase gene was also found to be associated with nephropathy in type 1 and type 2 diabetic patients[54,55]. This polymorphism was also found to be involved in the early development of microalbuminuria in Finnish T2DM patients[73] and was proposed as a risk factor for development of nephropathy in T2DM patients with poor glycaemic control[56].

**Glucose transporter 1 (GLUT1 or SLC2A1):** Glucose transporter 1 (*GLUT1 or SLC2A1*) is the major facilitative glucose transporter in glomerular mesangial cells. Experimental evidence suggests that *GLUT1* may be associated with hypertensive glomerulopathy[57]. Ng *et al*58], showed that SNPs at the *GLUT1* (XbaI -intron 2 and HaeIII SNPs -exon 2) were associated with susceptibility to diabetic nephropathy in type 1 diabetes[. A meta-analysis on the other hand demonstrated a significant association between the another polymorphic site *SLC2A1* XbaI in *GLUT1* gene with Diabetic nephropathy[59].

A study of those with type 1 diabetes examined six *GLUT1* single nucleotide polymorphisms (SNPs) and found homozygosity for the XBAI A allele and for minor allele(C-to-T) of the enhancer-2 SNP1 (ENH2 SNP) was associated with diabetic nephropathy in type 1 diabetes[58] whereas, no statistically significant association was found between XbaI gene variants and type 2 diabetic nephropathy[60]. Among the gene variants identified in the *GLUT1* putative enhancer elements, the AA genotype of enhancer-2 SNP1 (rs841847) is a “risk genotype”[58] and that the TT genotype of the 5’ promoter region (rs710218) was associated with nephropathy[61]. Moreover, the patients with the AG haplotype (rs841847–rs841853) have an increased risk of diabetic nephropathy and the TT haplotype (rs710218– rs841853) was more frequent in nephropathic patients. These findings showed that two haplotypes (composed of rs1385129–rs841847–rs841848) are associated with a 4.4 and 2.6-fold increased risk of nephropathy in the Tunisian T2DM patients[61].

However, the results of various case-control studies on *GLUT1* gene variants and their association with diabetic nephropathy have been inconsistent showing heterogeneity between studies[58,60,62-64].

**Peroxisome proliferator-activated receptor gamma 2:**

Peroxisome proliferator-activated receptor gamma 2 (PPARG2) is a receptor expressed selectively in the adipose tissue where it modulates the expression of genes involved in adipocyte differentiation and glucose homeostasis. The Pro12Ala gene variant was associated with lower albumin excretion rates among Ala12 carriers with type 2 diabetic nephropathy. Thus it could be suggested that Pro12Ala polymorphism may be protective against the disease since microalbuminuria is considered to be a risk factor for diabetic nephropathy[65,66]. This study was confirmed by Pollex *et al*[67] who showed that the Ala12 allele carriers have 1.5-fold reduction of the albumin/creatinine ratio and thus reduced occurrence of microalbuminuria. A recent meta-analysis showed that Pro12Ala polymorphism in *PPARγ2* gene is not a risk factor for diabetic nephropathy in type 2 diabetes[74].

***Other gene variants involved***

Apart from the above mentioned genes and their variants, there are various other gene variants for various genes like genes coding for growth factor, inflammatory factors, transcription factors, cytoskeletal proteins, components of immune system etc which have also been implicated in predisposing an individual to the risk of developing diabetic nephropathy. Some of these gene variants are discussed in Table 1.

**CONCLUSION**

Diabetic nephropathy is progressively becoming a major challenge for the health care system, since it is as yet poorly understood in many aspects. It is the leading cause of premature death in young diabetic patients (between 50 and 70 years old). It is a heterogenous and a multifactorial disease with several genes, proteins and environmental factors contributing to its risk. Due to the growing burden of the disease in diabetic patients, it is important to identify diabetic nephropathy predictors, for the proper management of this disease. Genetic susceptibility has been proposed as an important factor for diabetic nephropathy. Multiple genes are involved in pathogenesis of diabetic nephropathy, with several allelic polymorphisms having demonstrable effects in the development and progression of the disease thus contributing to the overall risk. These polymorphisms in several genes distributed widely across the human genome, each with a modest effect size, may be causal or protective factors in the development and progression of diabetic nephropathy. The combining of the various gene polymorphism studies in diabetic nephropathy related genes with recent researches/developments in the fields of human genomics, proteomics and bioinformatics would help in early diagnosis, treatment and prevention by giving us a better understanding of the pathogenesis of diabetic nephropathy. Identification of genes associated with diabetic nephropathy could provide a powerful tool for identifying patients at risk of developing diabetic nephropathy in the late future. In this context research efforts have been invested worldwide to identify the susceptibility gene for diabetic nephropathy. Epidemiologic studies and candidate-gene-based association studies are the most common approaches employed to identify susceptibility genes for diabetic nephropathy. Many genes were found to be associated with the disease but the results had been inconsistent and most of the candidate genes for diabetic nephropathy remain still to be identified. The inclusion of genetic studies in design and analysis of drug trials could lead to development of genetic biomarkers that predict treatment response. Thus, collaborative efforts are needed to achieve substantial findings in the study of genetics of diabetic nephropathy which could give us a better prospective of biochemical and molecular mechanism of disease on the whole. Early identification of at risk patients will facilitate earlier intervention; ultimately delaying and reducing the impact of nephropathy remain still to be identified. Thus, collaborative efforts are needed to achieve substantial.

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**Table 1 Gene variants associated with diabetic nephropathy**

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| --- | --- | --- | --- | --- | --- |
| **Gene category** | **Gene bame** | **Gene variant symbol** | **Location** | **Phenotype** | **Ref.** |
| **Growth Factors****Matrix metallo****proteinases****and dipeptidases****Transcription factors****Other genes** | Insulin-like growth factor 1IGF-binding protein 1TGF-β receptor IITGF-β receptor IIITissue inhibitor of metalloproteinase 3Matrix metalloproteinase 9Carnosinasetranscription factor 2, hepaticNeuropilin 1Protein kinase C β 1Upstreamtranscription factor 1Engulfment and cell motility factorCytochrome b, α polypeptideGlutathione peroxidase 1B-cell leukemia/lymphoma 2 (bcl-2)Aquaporin 1 | IGF-1IGFBP1TGF β R2TGF β R3TIMP3MMP9CNDP1HNF1B1/TCF2NRPIPRKCBIUSFIELMO1p22phoxGPXIBCL2AQP1 | 12q23.27p143p24.11p22.122q12.320q13.1218q22.317q1210p11.2216p12.11q23.37p1416q24.33p21.318q21.337p14.3 | Type 1 DNType 2 DNType 1 DNType 1 DNType 1 DNType 1 DNType 2 DNType 1 DNType 1 DNType 1 DNType 1 DNType 2 DNType 1 DNType 1 DNType 1 DNType 1 DN | [3][67][3][3][3][3][68, 69][3][3][3][3][70-72][3][3][3][3] |
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