A Review on Role of Cytokine Gene Polymorphisms in Type 2 Diabetes Mellitus

*Ashif CM1, Balasubramanian T2, Pawan Kumar3, Dany Okais4, Fasalu Rahiman OM5

1Dept of Pharmacology, School of Pharmacy and Medical Sciences, Singhania University, Pacheri Bari, Jhunjhunu, Rajasthan, India.
2Department of Pharmacology, Al Shifa College of Pharmacy, Perintalmanna, Kerala, India.
3Department of Microbiology, Singhania University, Pacheri Bari, Jhunjhunu, Rajasthan, India.
4Department of Pharmacy, Gulf Diagnostic Center Hospital, Abu Dhabi, United Arab Emirates.
5Department of Pharmacology, MES Medical College, Perintalmanna, Kerala, India.

*Corresponding author’s E-mail: ashifcm@hotmail.co.uk

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ABSTRACT

Type 2 diabetes mellitus (T2DM) has become a pan-endemic health problem with rapid growing global incidence. According to WHO, India leads the world with largest number of Diabetic patients. T2DM is usually caused by insulin resistance and often combined with progressive defect in insulin secretion and multiple metabolic complications in patients with long disease duration. It is known that genetic and environmental factors may influence susceptibility to T2DM. Several recent studies in Asian Indian populations have replicated the association of a few genes. Abundant evidences indicate that T2DM is closely correlated with chronic inflammation, with increased levels of circulatory acute response proteins and cytokines in affected subjects. Cytokines are mediators of inflammation, namely interleukins (IL)-1β, -1Ra, -18, -4, -6, -10, tumor necrosis factor-α and adiponectin, which cause immune responses in disease pathogenesis, including type 2 diabetes. The present review was undertaken to explore the association of cytokine gene polymorphisms with T2DM in populations of different ethnicities. This will lead to the understanding of the role of cytokine genes in T2DM risk and development. Finally, the recognition of these molecules as significant pathogenic mediators in diabetic population leaves open the possibility of new potential therapeutic targets.

Keywords: Diabetes mellitus, Cytokines, Interleukins, Gene polymorphism.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is represented as a heterogeneous cluster of metabolic abnormalities with hyperglycemia due either to absolute insulin deficiency or a decrease of insulin biological function. Untreated diabetes may cause severe health complications which can be largely divided into macro vascular and micro vascular complications. The macro vascular complications include cerebrovascular disease, coronary heart disease, and peripheral vascular disease. The micro vascular complications include diabetic retinopathy, diabetic neuropathy, and diabetic nephropathy. It is one of the leading causes of death and disability. Independent on age diabetes has become a common global health problem that affects many million people worldwide.

According to the International Diabetes Federation (IDF), there were approximately 328 million people worldwide with diabetes in 2013, and this number is expected to reach more than 592 million by 2035. With in India alone having 63.0 million affected individuals with the largest number of diabetic subjects and the number is expected to rise to 101.0 million by 2030.

In recent decades, several studies have shown the role of chronic low-grade inflammation and activation of the immune system in the pathogenesis of T2D and its complications like atherosclerosis. However, the mechanisms by which chronic inflammation is involved in T2D are not completely clear. A large and diverse family of small, low molecular weight cell signaling proteins mediating complex interaction is called “cytokines”, which include interleukins and interferons secreted by white blood cells and various other cells in response to a number of stimuli. Cytokines are a group of pharmacologically active, low molecular weight polypeptides that possess autocrine, paracrine, and juxtacrine effects with characteristic features. Cytokines are produced by a wide variety of cells in the body, playing an important role in many physiological responses that have a therapeutic potential. Cytokines are key mediators which regulate immune response; and their expression by immune cells depends on several factors such as infection, inflammation, hormonal conditions and also relevant gene polymorphisms. Recent studies have shown that inflammation, and more specifically pro-inflammatory cytokines, play a determinant role in the development of micro vascular diabetic complications. Inflammation resulting from an imbalance between pro- and anti-inflammatory cytokines leads to T2DM and its complications. In 1991, Hasegawa reported that glomerular basement membranes from diabetic rats induced significantly greater amounts of TNF- and IL-1 in cultured peritoneal macrophages than when these cells were incubated with basement membranes from nondiabetic rats.

Mediators of inflammation, such as IL-1β, -1Ra, -18, -4, -6, -10, TNF-α and adiponectin (ADIPOQ), have been...
proposed to be involved in causing T2DM. Elevated blood levels of certain acute phase markers such as IL-6 can characterize the immune response. IL-6 is an interleukin that acts as both a pro-inflammatory and anti-inflammatory cytokine encoded by IL-6 gene. Its location at 7p21 and -174 polymorphism is located in its promoter region. It controls transcriptional activity of IL-6 which has an important role in type 1 DM. While IL-1 regulates the basic metabolic rate, blood glucose levels, blood pressure, iron metabolism and bone remodeling. Adiponectin levels and its gene variants have also been confirmed to be associated with increased risk of T2DM. IL-10 is an anti-inflammatory and immunosuppressive sub-stance produced within the body and plays a role in the regulation of immune responses. As its expression is relatively delayed, release of IL-10 provides an efficient autocrine mechanism for regulating proinflammatory cytokine production. To date, more than 1240 gene loci are associated with diabetes in humans. The susceptibility to complex forms of T2DM is associated with frequent polymorphisms that influence the expression of genes belonging to the same or different causal pathways.

It is important to understand the nature and actions of these adipocytokines in order to find their association with diseases like T2DM, atherosclerosis, other metabolic and vascular diseases. Studies have reported that Asian Indians are a unique population for carrying out genetic studies due to their greater susceptibility to T2DM and increased insulin resistance. This alarming figure has instigated several workers worldwide to undertake genetic studies and contribute to the understanding and early detection of the disease. This review is an attempt to put together certain important cytokine gene polymorphisms and their association with T2DM in different populations around the world.

**IL-1α, -1β and -Ra**

Interlukin-1 family is consisting of 11 cytokines produced by the cells like monocytes/macrophages and keratinocytes, which regulates and initiates inflammatory responses by inducing a complex network of proinflammatory and via expression of integrins on leukocytes and endothelial cells. IL-1α and IL-1β are most important among them because of their strong proinflammatory effect. They possess a natural antagonist IL-1Ra, which regulates IL-1α and IL-1β proinflammatory activity by competing for the binding sites of the receptor. IL-1α, IL-1β and IL-1Ra are located on chromosome 2q12-21. All IL-1 genes are polymorphic and several are associated with inflammation and disease conditions.

“Autocrine apoptosis” results from prolonged exposure of human islets to high glucose which triggers IL-1β production, leading to activation of nuclear factors and upregulation of Fas signaling. IL-1β and IL-1Ra play important roles in tissue remodeling, are potent mediators of chronic inflammation and are therefore implicated in the pathogenesis of T2DM and associated complications. The IL-1 gene variants and their polymorphism studied in various regions like Caucasians and African Americans, East Indian, North Indian, Korean, Norwegian, Chineses, Europeans shows their importance in the etiology of diabetic mellitus.

**IL-4**

The interleukin 4 (IL4) is a cytokine that induces differentiation of naïve helper T cells (Th0 cells) to Th2 cells. Upon activation by IL-4, Th2 cells subsequently produce additional IL-4 in a positive feedback loop. The cell that initially produces IL-4, thus inducing Th0 differentiation, has not been identified, but recent studies suggest that basophils may be the effector cell. It has many biological roles, including the stimulation of activated B-cell and T-cell proliferation, and the differentiation of B cells into plasma cells. It is a key regulator in humoral and adaptive immunity. It also plays a crucial role in the pathophysiology of T2DM. The heterodimerization of high-affinity transmembrane receptor α-chain (IL-4Ra) is mediated by IL-4 in a sequential cascade. Several candidate genes have been identified, including the gene for IL-4Ra which is situated on chromosome 16p and is known to contain a number of polymorphisms. IL-1Ra and IL-4 are major anti-inflammatory cytokines and have been proposed to be involved in events causing T2DM. The IL-4Ra subunit forms part of the signalling complex for IL-4. In humans, the gene for IL-4 maps to chromosome 5q31.

The polymorphisms in IL-4 gene and their relationship with T2DM have been studied by various groups.

A study conducted in North Indian population on 120 T2DM patients and 150 normal healthy by the isolation of the Genomic DNA, and the variable number of tandem repeat (VNTR) polymorphisms of IL-1RN and IL-4 genes was identified and revealed that distribution of both IL-4 and IL-1RN (VNTR) gene polymorphisms were significantly associated with T2DM subjects.

A study by Mohammad to examine polymorphisms in the -590 region of the IL-4 gene showed a significant difference between the C/C, T/C, and T/T genotypes and the C and T alleles of the -590 region of IL-4 in nephropathic patients in comparison with the healthy controls.

Results of this study suggest that the functional gene polymorphisms of IL-4 play an important role in the pathogenesis of diabetic nephropathy in patients with type 2 diabetes mellitus.

A study on Taiwanese T2DM patients shows a significant association between IL-4 C-589T alleles and T2DM, as well as C-34T alleles and T2DM.

In addition, a statistically significant association between homologous IL-4 –589 C/C genotype and lower circulatory high-density lipoprotein cholesterol levels was observed. Results suggested that IL-4 promoter polymorphisms are
associated with T2DM. A significant association between IL-4 –589 C/C genotype and lower circulatory high-density lipoprotein cholesterol level was observed as well. The above results suggested that IL-4 may participate in lipid metabolism and diabetic susceptibility.

A study to investigate the association of IL-4-590 and IL-13-1112 genetic polymorphisms with type 2 diabetes mellitus in Egyptian patients showed that a lower frequency of the IL-4-590 CC homozygous genotype compared to controls with a higher CT heterozygous genotype. Similarly, cases showed a lower frequency of the IL-13-1112 CC genotype with a higher frequency of the heterozygous IL-13-1112 CT genotype. Both polymorphisms showed significantly positive associations with T2DMin the dominant, codominant, and overdominant models of inheritance. On the other hand, comparing genotypes of subgroups related to gender, positive family history, and positive consanguinity showed a nonsignificant difference. Hence Heterozygous genotypes (IL-4-590 CT and IL-13-1112 CT) could be considered as risk factors, while the homozygous wild types (-590 CC and -1112 CC) might be considered protective to T2DM.

IL-6

Interleukin 6 (IL-6) is an interleukin that acts as both a pro-inflammatory cytokine and an anti-inflammatory myokine. In humans, it is encoded by the IL6 gene. IL-6 is secreted by T cells and macrophages to stimulate immune response, e.g. during infection and after trauma, especially burns or other tissue damage leading to inflammation. IL-6 also plays a role in fighting infection, as IL-6 has been shown in mice to be required for resistance against bacterium Streptococcus pneumoniae. In addition, osteoblasts secrete IL-6 to stimulate osteoclast formation. Smooth muscle cells in the tunica media of many blood vessels also produce IL-6 as a pro-inflammatory cytokine. IL-6’s role as an anti-inflammatory cytokine is mediated through its inhibitory effects on TNF-α and IL-1, and activation of IL-1ra and IL-10. IL-6 is secreted by immune cells, adipose tissue and muscles and is able to accelerate or inhibit the inflammatory processes. The direct affect of IL-6 may be on glucose homeostasis and metabolism or it might act indirectly by action on adipocytes, pancreatic β-cells. In humans, the gene for IL-6 maps to chromosome 7p15-p21. IL-6 mRNA expression and insulin resistance were found to have a significant correlation and increased plasma IL-6 levels with higher risk of T2DM, making it an appealing candidate gene. One of the common polymorphisms in the IL-6 gene promoter (C-174G) was found to regulate transcription in response to inflammatory stimuli, such as lipopolysaccharides or IL-1. IL-6 promoter SNPs were considered as risk factors for T2DM development, as reported by other groups.

In 1991, Sekizuka reported that serum levels of IL-6 were significantly higher in patients with type 2 diabetic nephropathy than the levels observed in diabetic patients without nephropathy, which suggests that this cytokine may play a role in the pathogenesis of diabetic nephropathy. Early after that report, Suzuki analyzed kidney biopsies in patients with diabetic nephropathy by high-resolution in situ hybridization. Furthermore, they found a relationship between the severity of diabetic glomerulopathy (mesangial expansion) and expression of IL-6mRNA in glomerular cells (mesangial cells and podocytes), which indicated that IL-6 may affect the dynamics of extracellular matrix surrounding those cells. More recent studies in type 2 diabetic patients demonstrate a significant association between IL-6 and glomerular basement membrane thickening, a crucial lesion of diabetic nephropathy and a strong predictor of renal progression.

IL-10

Interleukin 10 (IL-10), also known as human cytokine synthesis inhibitory factor (CSIF), is an anti-inflammatory cytokine. In humans, interleukin 10 is encoded by the IL10 gene. IL-10 signals through a receptor complex consisting of two IL-10 receptor-1 and two IL-10 receptor 2 proteins. The association of IL-10 in immunological disorders such as multiple sclerosis, nephrotic syndrome and type-1 diabetes is well established. The key role of IL-10 is to work as the main inhibitory cytokine against the action of inflammatory cytokines such as IL-12. Based on evidence suggesting that immune responses may be important in inducing type 2 diabetes, IL-10 promotes the proliferation and differentiation of B-lymphocytes by stimulating antibody production. The IL-10 gene is located on chromosome 1q31-q32 and several variants have been identified in its promoter region. The presence of IL-10 is protective against T2DM and inflammation due to its humoral immunity responses and prevention of pancreatic beta cell destruction. In a study conducted in Iran, aimed to find polymorphisms of this region that may be associated to type 2 diabetic patients with and without nephropathy suggest that the functional gene polymorphism of IL-10 reported here may play an important role in the pathogenesis of diabetes, but it seems that these polymorphisms do not have an effect on the nephropathic complications of the disease.

A study on Taiwanese subjects by investigated their IL-10 and tumor necrosis factor-α (TNF-α) genotyping and association of blood chemistry, plasma IL-10, TNF-α, and monocyte chemoattract protein-1 (MCP-1), and urinary MCP-1 showed that the IL-10(-592) genotype exhibited significant association with cytokine expressions in DN: significantly higher TNF-α and lower plasma IL-10 levels were observed in IL-10(-592)AA, whereas a higher urine MCP-1 level was found in Taiwanese patients with the IL-10(-592)CC genotype. Hence it was concluded as IL-10(-592) promoter polymorphisms may influence IL-10 and MCP-1 production, which may be an indicator of nephropathy risk in Taiwanese T2DM patients.

A study to test for the association of IL-10–1082 and IL-6–174 genetic polymorphisms with type 2 diabetes
mellitus in Egyptian patients showed a highly significant increase in the frequency of IL-10–1082 GG genotype, higher frequency of IL-10–1082 G allele with a significantly lower frequency of IL-10–1082 GA genotype. On the other hand, the IL-6–174 CC genotype frequency was significantly higher in the diabetic group in contrast to the IL-6–174 GC genotype that showed significantly lower frequency with a non significant differences in either G or C allelic frequencies between diabetic and control groups. Polymorphisms related to IL-10–1082 GG and IL-6–174 CC genotypes may be considered as a risk factor for type 2 diabetes mellitus among Egyptian subjects with a potential impact on family counseling and management.

A study\(^{41}\) to investigate the relationship between the interleukin 10 (IL10) gene single nucleotide polymorphisms (SNP) _1082 G/A (rs1800896), _819 T/C (rs1800871) and _592 A/C (rs1800872) and risk of type 2 diabetes mellitus in a Chinese population shows that the patients carrying the _1082 GG genotype had a significantly increased risk of type 2 diabetes mellitus, as did those patients carrying the _592 AA genotype. Subjects carrying both the _1082 GAPGG and _592 ACPAA genotypes had a significantly increased risk of type 2 diabetes mellitus. The SNPs _1082G/A and _592 A/C increased the risk for type 2 diabetes mellitus, and could be potential targets for screening for the early detection of the risk of type 2 diabetes mellitus.

**IL-18**

Interleukin-18 (interferon-gamma inducing factor) is a protein which in humans is encoded by the IL18 gene.\(^{42}\) The protein encoded by this gene is a proinflammatory cytokine. IL-18 is a cytokine that belongs to the IL-1 super family and is produced by macrophages and other cells. IL-18 works by binding to the interleukin-18 receptor, and together with IL-12 it induces cell-mediated immunity following infection with microbial products like lipopolysaccharide (LPS). Apart from its physiological role, IL-18 is also able to induce severe inflammatory reactions, which suggests its role in certain inflammatory disorders. Insulin-producing islet β-cells secrete IL-18 and induce IFNγ in T cells.\(^{43}\) IL-18 is highly expressed in atherosclerotic plaques with a role in plaque destabilization.\(^{44}\) Elevated levels of plasma IL-18 were reported in T2DM patients and children. However, obesity and insulin resistance showed no correlation with IL-18 plasma level. The IL-18 gene in humans is located on chromosome 11q22.2-22.3, where a diabetes susceptibility locus, lld2, resides.\(^{45}\)

Studies are reporting the correlation between IL-18 gene polymorphisms and DM. A study\(^{46}\) to determine the role of IL-18 polymorphisms with Type 1 diabetes in Iranians showed that Allele and genotype frequencies of the IL-18 gene polymorphisms were similar in the whole group of Type 1 diabetic patients and controls. However, categorizing patients according to age at onset of diabetes revealed a significant difference in distribution of the genotypes at position -137 between patients with older age at onset and control subjects. Frequency of the C allele at position -137 was significantly higher in these patients than in controls. Moreover, there was an association between -607AA/-137CC genotype combination and susceptibility to Type 1 diabetes in this subgroup of patients.

A study\(^{47}\) were analyzed three promoter single nucleotide polymorphisms (SNPs), at -656 (rs1946519), -607 (rs1946518) and -137 (rs187238) position, in 181 children and adolescents with T1D and 122 healthy individuals, both from metropolitan area of Recife, Northeast of Brazil. T1D patients were stratified according to the presence autoimmune thyroiditis and celiac disease. Allele and genotype frequencies of IL18 SNPs were Hardy-Weinberg equilibrium in patients and controls. The allele -137G and the haplotype -656G/-607C/-137G were more frequent in T1D patients then in healthy controls. Hence the findings suggest an association between IL18 promoter SNPs and susceptibility to T1D in Brazilian patients.

**Adiponectin**

Adiponectin is a protein which in humans is encoded by the ADIPOQ gene.\(^{48}\) It is involved in regulating glucose levels as well as fatty acid breakdown. The main insulin-sensitizing action of adiponectin results from decrease in hepatic gluconeogenesis and increase in muscle glucose transport and, secondly from enhancement of energy consumption and fatty acid oxidation in peripheral tissues with the aim of increasing ATP production. Besides these effects, the potential role of adiponectin on insulin secretion, as well as on energy expenditure, through central action, has also been investigated. Accumulating evidence from clinical, experimental animal and genetic studies support a close association between hypoadiponectinemia and insulin resistance/ type 2 diabetes. Since the role of classical cytokines and adipocytokines in metabolic syndrome and associated disease conditions came to light, several workers have shown the role of activated innate immunity in the pathogenesis of T2DM.\(^{49}\) It is involved in the homeostatic control of circulating glucose and lipid levels.\(^{50}\) Reduced adiponectin levels are documented in obese, insulin resistant and T2DM patients. Adiponectin regulates glucose/lipid homeostasis via phosphorylation and activation of adenosine monophosphate activated protein kinase.\(^{51}\) Therefore, high adiponectin levels are associated with reduced risk of T2DM. A meta-analysis\(^{52}\) of the data published to date supports this hypothesis.

Two independent effects, corresponding to the two linkage disequilibrium blocks that can be identified at the adiponectin locus, appear to be present. In the 5’ block, the g.−11391G→A variant has a modest but significant effect on adiponectinemia, with a mean difference between genotypes of 1.64 ng/ml. In the 3’ block, the g.+276G→T variant is a strong determinant of insulin resistance and CAD, with minor allele homozygotes
having a lower homeostasis model assessment of insulin resistance (HOMAIR) index and a lower cardiovascular risk than carriers of other polymorphisms. Polymorphisms in the genes coding for the adiponectin receptors may also influence the risk of insulin resistance and CAD, but data on these genes are still too sparse to draw firm conclusions. In summary, the studies published to date indicate that polymorphisms at the adiponectin locus are indeed predictors of circulating adiponectin levels, insulin sensitivity, and atherosclerosis, highlighting the pivotal role of this adipokine in the modulation of metabolism and atherogenesis.

A comprehensive association analysis of 24 single-nucleotide polymorphisms (SNPs) in the adiponectin gene was performed for type 2 diabetes and diabetic nephropathy in African Americans shows an Association tests between age at onset of type 2 diabetes and the rs182052 genotypes also revealed significant association between the presence of the minor allele (A/A or A/G) and earlier onset of type 2 diabetes. The SNP rs182052 in intron 1 of the adiponectin gene is associated with type 2 diabetes in African Americans. Another study in South Indian population aimed to investigate the association among SNP 45 T > G of adiponectin gene and type 2 diabetes shows a positive association between SNP45 T > G and type 2 diabetes in the study population.

A meta-analysis consisting of 12 individual studies investigated the association of adiponectin −11377CG gene polymorphism with T2DM shows a significant relationship under allelic, recessive, dominant, additive, and homozygous genetic models. No significant association was found between them under the heterozygous genetic model. Adiponectin −11377CG gene polymorphism was significantly associated with T2DM risk susceptibility.

A study on six common adiponectin single nucleotide polymorphisms in Singaporean Chinese adults with follow-up functional genetic experiments shows a distributions of genotypes for all SNPs among controls were consistent with Hardy-Weinberg Equilibrium. Single locus, genotypes-based analysis suggested borderline significant association between an exon-2 coding-synonymous +45T/G (rs2241766) and T2DM. Another study to investigate the possibility of relation between single nucleotide polymorphisms of adiponectin gene (+45 T/G and −11391 G/A) and waist circumferences (WC) in patients with type 2 diabetes from Rafsanjan city in south – east of Iran shows a significant association between −11391 G/A adiponectin gene polymorphism with WC in diabetic group.

A study to asses the association between early-onset type 2 diabetes mellitus and variability within these two genes in the Han Chinese population of Taiwan. Polymorphisms at the position rs10937273 in ADIPOQ and at the positions rs1892534 and rs2211651 in LEPR were statistically associated with early-onset T2DM. C-reactive protein levels were significantly different among the early-onset T2DM patients with different genotypes at the SNPs rs1892534 and rs2211651 in LEPR. In addition, fasting glucose levels were also significantly different among different genotypes at the SNP rs1892534 in LEPR and conclude that the polymorphisms in the adipokine genes ADIPOQ and LEPR are significantly associated with the age at diagnosis of T2DM.

**TNF-α**

Tumor necrosis factor alpha (TNF-α) is an adipocytokine involved in systemic inflammation and stimulates the acute phase reaction.1 TNF-α is primarily secreted by macrophages, and also by a broad variety of other cells including adipocytes. TNF-α inhibits insulin transduction, and has an effect on glucose metabolism. Disturbances in the TNF-α metabolism have been implicated in metabolic disorders, such as obesity and insulin resistance, indicating that perturbations of TNF-α metabolism may affect the onset of type 2 diabetes mellitus and the progression of the disease. It is reported that TNF-α is a possible mediator of insulin resistance and diabetes since it decreases the tyrosine kinase activity.

Furthermore, TNF-α inhibits insulin signaling and impairs its secretion. TNF-α interacts with IL-6, regulating its expression and downregulating itself. In humans, the gene for TNF-α maps to chromosome 6p21. One of the SNPs in TNF-α gene showed a two-fold increase in transcriptional activity.

A study to evaluate the association of TNF-α promoter−308 G/A polymorphism with T2DM in Iranian Kurdish Ethnic Group shows that the allelic frequency of the A allele was significantly different between case and control participants. Genotypes GA and AA were found to be significantly associated with 2.24- and 3.18-fold increased risk for T2DM, respectively. Similarly, the dominant model of -308 G/A polymorphism was found to have a higher risk for T2DM. Individuals with T2DM carrying the GA + AA genotypes of -308 G/A variation had significantly lower fasting plasma insulin than those carrying GG genotype. Hence the findings revealed that there is an association between the TNF-α promoter -308 G/A polymorphism and T2DM in this population.

A study to investigate the role of promoter polymorphisms of the tumor necrosis factor-α (TNF-α; G-308A) and interleukin 6 (IL-6; C-174G) genes predict the conversion from impaired glucose tolerance (IGT) to type 2 diabetes in the Finnish Diabetes Prevention Study. The −308A allele of the TNF-α gene was associated with an approximate twofold higher risk for type 2 diabetes compared with the G-308G genotype. Subjects with both the A allele of the TNF-α gene and the C-174G genotype of the IL-6 gene had a 2.2-fold higher risk of developing type 2 diabetes than subjects without the risk genotypes.

Hence 308A allele of the promoter polymorphism (G-308A) of the TNF-α gene is a predictor for the conversion from IGT to type 2 diabetes. Furthermore, this
polymorphism seems to have a gene-gene interaction with the C-174C genotype of the IL-6 gene. The tumor necrosis factor (TNF)-alpha -308G/A polymorphism has long been suspected of being a gene variant that is associated with type 2 diabetes, but studies have reported conflicting outcomes. An updated meta-analysis was performed to investigate whether the TNF-alpha -308A variant is associated with an increased risk of type 2 diabetes. A total of 38 case-control studies in 38 articles were included. Statistical analyses of the results suggested that the TNF-alpha -308G/A polymorphism was associated with an increased risk of type 2 diabetes mellitus in a dominant model, particularly for Asian carriers of the A mutation (GA+AA), who were shown to have a 39% increased risk of type 2 diabetes compared with wild-type subjects.\(^\text{52}\)

CONCLUSION

The prevalence of diabetes worldwide is increasing rapidly and its complications are a major fear. Complications of diabetes affect many tissues and organs, causing retinopathy, nephropathy, neuropathy, cardiovascular diseases, peripheral vascular diseases, stroke, and periodontal pathologies.

The greater tendency to diabetes in Indians may result from some genetic factors in addition to environmental and dietary factors. Although the initiation and etiology of T2DM still await to be identified, accumulating evidences have proved the hypothesis that T2DM is a state of chronic inflammation, with increased acute phase proteins and various cytokines. SNPs in specific genes which show considerable levels of variation amongst ethnic groups around the world have been implicated in the pathogenesis of diabetes. Therefore, identification of polymorphic variants of cytokine genes in different populations and the genotypic associations between SNPs and gene-gene interactions will have clinical importance as indicators of T2DM susceptibility. Genetic studies regarding the exploration of susceptible or resistant genes for T2DM could provide clues for understanding the mystery of diabetic pathogenesis and for future designing of diabetic treatment especially needs for the development of personalized medicine based on the contribution of distinct genetic heterogeneity to diabetic development and complications.

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