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TOPIC HIGHLIGHT

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Genetic polymorphisms of cytokine genes in type 2 diabetes mellitus

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Abstract

Diabetes mellitus is a combined metabolic disorder which includes hyperglycemia, dyslipidemia, stroke and several other complications. Various groups all over the world are relentlessly working out the possible role of a vast number of genes associated with type 2 diabetes (T2DM). Inflammation is an important outcome of any kind of imbalance in the body and is therefore an indicator of several diseases, including T2DM. Various ethnic populations around the world show different levels of variations in single nucleotide polymorphisms (SNPs). 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. Association studies of genotypes of SNPs present in cytokine genes will help to identify risk haplotype(s) for disease susceptibility by developing prognostic markers and alter treatment strategies for T2DM and related complications. This will enable individuals at risk to take prior precautionary measures and avoid or delay the onset of the disease. Future challenges will be to understand the genotypic interactions between SNPs in one cytokine gene or several genes at different loci and study their association with T2DM.

Key words: Type 2 diabetes; Cytokines; Single nucleotide polymorphisms; Disease susceptibility; Association studies

Core tip: Diabetes is the third most widespread disease after heart disease and cancer. 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. In the present study, the association of cytokine gene polymorphisms in different ethnic populations is reviewed. Such single nucleotide polymorphism analyses and association studies in different populations will benefit individuals belonging to a particular group.

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INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a group of metabolic disorders characterized by high blood sugar levels, which results from defects in insulin secretion or action or both, leading to complications[1]. Diabetes mellitus has now

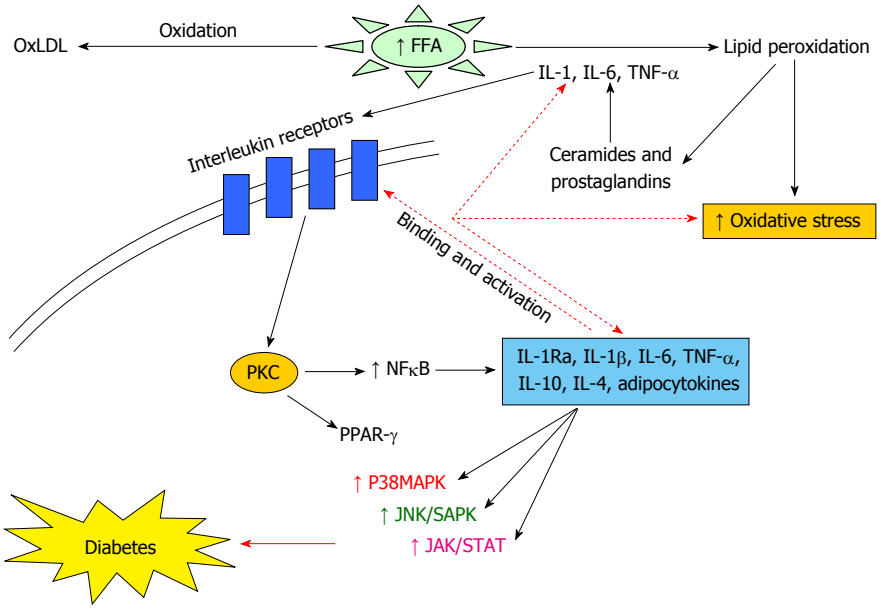

Figure 1 A schematic diagram showing the involvement of various cytokines in diabetes[3]. IL: Interleukin; TNF: Tumor necrosis factor.

been associated with the development of a long term organ disease. T2DM has changed from a mild disorder of old age to a serious cause of morbidity and mortality in young and middle-aged people. The Diabetes Atlas estimates have shown that 371 million people suffer from diabetes worldwide, with India alone having 63.0 million affected individuals and the number is expected to rise to 101.0 million by 2030[2-4]. This alarming figure has instigated several workers worldwide to undertake genetic studies and contribute to the understanding and early detection of the disease.

A predisposition to T2DM or "Adult Onset Diabetes" is probably inherited as an autosomal recessive trait[5]. T2DM is treated initially by diet control, either alone or in combination with orally administered anti-diabetic drugs. It is described as a syndrome on the basis of clustering of many abnormalities, like resistance to insulin-stimulated glucose uptake, hyperinsulinemia, hyperglycemia, increased very low density lipoprotein (VLDL), increased triglycerides, decreased high density lipoproteins (HDL) cholesterol, high blood pressure, micro albuminuria, hyperuricemia, fibrinolytic and coagulation abnormalities, *etc*[3].

Evidence has shown that T2DM is associated with chronic inflammation that can be attributed to dysregulation of the innate immune system and this is a potential link between metabolic syndrome, diabetes and atherosclerosis[6]. A large and diverse family of small, low molecular weight cell signaling proteins mediating complex interaction are called "cytokines", which include interleukins and interferons[7] secreted by white blood cells and various other cells in response to a number of stimuli. The cytokines and their receptors exhibit a very high affinity for each other. Another subgroup of low molecular weight cytokines called chemokines affect leukocyte behavior. Cytokines are of two types, namely pro-inflammatory [*e.g.*, interleukins (IL)-1, -6, tumor necrosis factor (TNF)-α, transforming growth factor (TGF)-β] and anti-inflammatory (*e.g.*, IL-1Ra, -4, -10, -13), which function opposite to each other. The release of adipocytokines by adipocytes, such as leptin, resistin, adiponectin and visfatin, as well as some of the classical inflammatory cytokines like TNF-α, IL-6, MCP-1 (CCL-2) *etc*., help to achieve this. Studies have shown that it is the fat tissue that exerts the endocrine and immune functions. Macrophages and T cells are found in abundance in adipose tissue which develops into an organized immune organ[8]. Inflammation resulting from an imbalance between pro- and anti-inflammatory cytokines leads to T2DM and its complications (Figure 1).

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[9], 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[10]. To date, more than 1240 gene loci are associated with diabetes in humans[3]. 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[7]. 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 (Figure 2). 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[11,12]. This review is an attempt to put together certain important cytokine gene polymorphisms and their association with T2DM in

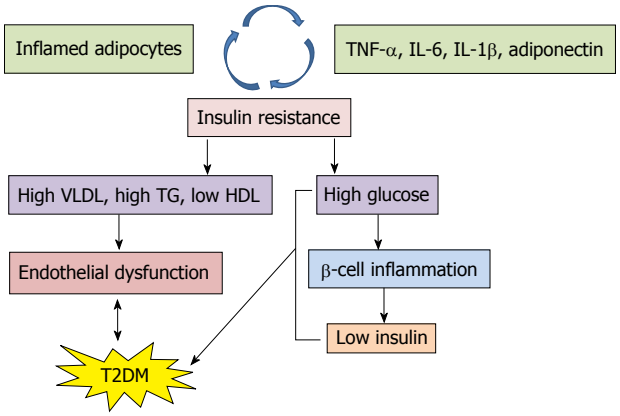

Figure 2 A schematic diagram showing the metabolic defects and biochemical effects of cytokines leading to type 2 diabetes. T2DM: Type 2 diabetes; IL: Interleukin; TNF: Tumor necrosis factor.

different populations around the world.

CYTOKINE GENE POLYMORPHISMS AND T2DM

Certain chemokines/cytokines, like IL-1β, -1Ra, -18, -4, -6, -10, TNF-α, *etc.*, and some members of the adipocytokine family, namely adiponectin, leptin and resistin, are important mediators in inflammation/disease and glucose metabolism and may be involved in the pathogenesis of T2DM. They can be used as biological markers for diabetes and are related to obesity and hypertension. The single nucleotide polymorphisms (SNPs) present in the regulatory regions of cytokine genes often have an impact on their expression levels and can be disease modifiers. The degree of inflammation is controlled, thereby leading to the progression of various immunological diseases, including T2DM[13-20]. The polymorphisms in cytokine genes lead to interindividual differences in their production, leading to variations in immune responses[21].

IL-1α, -1β and -Ra

The IL-1 family consists of two pro- and one anti-inflammatory cytokines, namely 1α, 1β and the IL-1 receptor antagonist (IL-1Ra), respectively. While IL-1α and -1β enhance inflammation and host defense, IL-Ra counteracts their function. A variety of cell types like monocytes/macrophages and keratinocytes are known to produce these cytokines. All three secreted glycoproteins bind to IL-1 receptors[22].

The *IL-1* genes (*IL-1α*, *-β* and -Ra) are located on chromosome 2q12-21. All *IL-1* genes are polymorphic and several are associated with inflammation and disease conditions[7,23]. "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[24]. IL-1β and IL-1Ra play important roles in tissue remodeling, are potent mediators of chronic inflammation[25] and are therefore implicated in the pathogenesis of T2DM and associated complications[7]. The *IL-1* gene variants studied in various groups are shown in Table 1.

Table 1 Variants of interleukin-1 gene cluster (interleukin-1α, interleukin-1β, interleukin-1Ra, interleukin-18) and their association with type 2 diabetes in different populations

Gene	Variants (SNPs)	Population-Ethnic group	Association	Ref.
IL-1α	-889		NS	[26]
IL-1β	3954			
IL-1β	-511			
IL-1Ra	VNTR			
IL-1α	3'UTR	Caucasians and African Americans	S	[27]
IL-1	C-889T	East Indian	S	[28]
IL-1β	C-511T			
IL-1β	C3953T			
IL-1α			S	[29]
IL-Ra	VNTR			
IL-1β	C3954T		S	[30]
IL-1β	-511	North Indian	S	[31]
IL-1Ra	VNTR			
IL-1β	C-511T		S	[32]
IL-1Ra	VNTR			
IL-1β	C-511T	Korean	S	[33]
IL-1Ra	VNTR			
IL-1Ra	VNTR		NS	[29]
IL-1Ra	VNTR		S	[34]
IL-1Ra	VNTR	North Indian	S	[17]
IL-1Ra	VNTR	Caucasians	NS	[35]
IL-1Ra	VNTR		S	[36]
IL-1RI	PstI, HinfI, AluI (promoter region) PstI (exon 1B region)	Dalmatian population of South Croatia	S	[37]
IL-18	+183 A/G	Norwegian	S	[38]
	-137 G/C		NS	
	-607 C/A		NS	
	-607 C/A	Chinese	S	[39]
	BCO2	European	S	[40]
	rs2250417	European	NS	[41]
	5 SNPs	European	S	[42]

UTR: Untranslated region; VNTR: Variable number of tandem repeats; S: Significant; NS: Nonsignificant; IL-1: Interleukin-1; SNPs: Single nucleotide polymorphisms.

IL-18

IL-18, a unique IL-1 family cytokine is expressed in macrophages, keratinocytes, osteoblasts, synovial fibroblasts, dendritic, Kupffer, adrenal cortex, intestinal epithelial and microglial cells[43-50]. IL-18 shares structural homology with IL-1β. It is produced as a 24-kDa inactive precursor, Pro-IL-18, which is cleaved by IL-1β-converting enzyme (ICE; caspase-1) to a mature 18-kDa molecule[51]. The extracellular binding of IL-18 is mediated by IL-18R, a heterodimer complex containing α chain (IL-1Rrp) and β chain (AcPL)[52-54].

Insulin-producing islet β-cells secrete IL-18 and induce IFNγ in T cells[55]. IL-18 is highly expressed in atherosclerotic plaques with a role in plaque destabilization[56]. Elevated levels of plasma IL-18 were reported in T2DM patients and children[57-59]. However, obesity and insulin resistance showed no correlation with IL-18

Table 2 Variants of interleukin-4 gene and their association with type 2 diabetes in different populations

Gene variants (SNPs)	Disease	Population-Ethnic groups	Association	Ref.
-590 C/T	T2DM	Iranian	S	[64]
-589 C/T	T2DM	Chinese	S	[65]
-34 C/T	T2DM			
VNTR	T2DM	North Indian	S	[17]

VNTR: Variable number of tandem repeats; S: Significant; T2DM: Type 2 diabetes; SNPs: Single nucleotide polymorphisms.

plasma level[60]. The *IL-18* gene in humans is located on chromosome 11q22.2-22.3, where a diabetes susceptibility locus, Idd2, resides[61]. Studies reporting *IL-18* gene polymorphisms are shown in Table 1.

IL-4

One of the hematopoietic cytokines, IL-4 regulates key events during Th2-dominated immune response and also stimulates T cells, leading to the production of other cytokines. It causes β-cell isotype switching from IgM to IgE and stimulates IgE production in allergic sensitization. IgE stimulation during allergic reactions and infections is the natural defense mechanism. It also plays a crucial role in the pathophysiology of T2DM[62]. The heterodimerization of high-affinity transmembrane receptor α-chain (IL-4Rα) 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[63] 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 (Table 2).

IL-6

IL-6 is secreted by immune cells, adipose tissue and muscles and is able to accelerate or inhibit the inflammatory processes[66,67]. 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, *etc*[68]. 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[69] and increased plasma IL-6 levels with higher risk of T2DM[6,70,71], 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[72-74]. IL-6 promoter SNPs were considered as risk factors for T2DM development, as reported by other groups[75,76] (Table 3).

IL-10

IL-10 is also a Th2 mediated cytokine that downregulates inflammatory responses of pro-inflammatory cytokines[102]. The serum concentrations of TC, LDL, TGL, glucose and HbA1c gradually decreases and HDL increases with an increase in IL-10 production. These observations implied that low IL-10 production was associated with hyperglycemia and T2DM[68,103]. IL-10 promotes the proliferation and differentiation of B-lymphocytes by stimulating antibody production[104]. The *IL-10* gene is located on chromosome 1q31-q32 and several variants have been identified in its promoter region[105-106]. The presence of IL-10 is protective against T2DM and

Table 3 Variants of Interleukin-6 gene and their association with type 2 diabetes and related complications in different populations

Gene variants (SNPs)	Diseases	Population-Ethnic groups	Association	Ref.
-174 G/C	T2DM and OGTT	Brazilian	S	[77]
	T2DM and IR	American	S	[78]
	T2DM and obesity	Polish	S	[79]
	T2DM and obesity	Mexican	NS	[80]
	T2DM	Indian	S	[81]
	T2DM	Finnish	NS	[82]
	T2DM and Obesity	Tunisian	S	[83]
	T2DM	Caucasian	S	[84]
	T2DM	German	S	[85]
	DM, micro-, macrovascular complications	Australian	NS	[29]
	-do-	German	NS	[86]
	T2DM and IR	Italian	S	[87]
	T2DM	KORA Survey	S	[88]
	T2DM	Framingham Heart Study	S	[89]
	T2DM	KORA Survey	S	[90]
	T2DM	Taiwanese	S	[91]
	T2DM	Nutrition-Potsdam cohort	S	[92]
	T2DM	Finnish	S	[93]
	T2DM	Native Americans, Spanish, Caucasians	S	[75]
	T2DM and IR	Spanish	S	[94]
	T2DM and PAD	Italian	S	[95]
	T2DM	KORA Survey	S	[76]
	DM and Periodontitis	Chinese	S	[96]
	T2DM and Endothelial Dysfunction	Chinese	S	[97]
	T2DM	21 studies	S	[71]
-174 G/C -597 A/G	T2DM	Boston	NS	[98]
GWS (18 SNPs)	T2DM	Canadian	S with Fasting	[99]
PREDIAN study	DN	Spanish	S	[100]
Five tagging SNPs	T2DM and Impaired Renal Function	Singaporean	S	[101]

S: Significant; NS: Non-significant; T2DM: Type 2 diabetes; PAD: Peripheral arterial disease; SNPs: Single nucleotide polymorphisms; OGTT: Oral glucose tolerance test; DM: Diabetes mellitus; IR: Insulin resistance; DN: Diabetic nephropathy.

Table 4 Variants of interleukin-10 gene and their association with type 2 diabetes and related complications in different populations

Gene variants (SNPs)	Diseases	Population-Ethnic groups	Association	Ref.
-592 A/C	T2DM	Iranian	NS	[108]
	T2DM	Chinese	NS	[109]
	T2DM	North Indian	S	[4]
-1082 G/A	proliferative diabetic retinopathy	Indian	S	[110]
	T2DM	South Indian	S	[111]
-1082 G/A -819 C/T -592 C/A	T2DM	Caucasian Italian	S	[112]
-1082 G/A	T2DM	Turkish	NS	[113]
-1082 G/A -819 C/T -592 C/A	T2DM	Greek	NS	[106]
-592 A/C -819 C/T	T2DM	Taiwanese	NS	[107]
-592 A/C	T2DM	Taiwanese	S	[114]
-1087 G/A -824 C/T -597 C/A	T2DM	Italian	S	[115]
-592 A/C	T2DM	Tunisian	S	[18]

S: Significant; NS: Non-significant; T2DM: Type 2 diabetes; SNPs: Single nucleotide polymorphisms.

Table 5 Variants of tumor necrosis factor-α gene and their association with type 2 diabetes and related complications in different populations

Gene variation (SNPs)	Diseases	Population-Ethnic groups	Association	Ref.
G-308A	T2DM	Tarragona	S	[120]
	T2DM	Taiwanese	S	[121]
	T2DM	Croatian Caucasians	S	[122]
	T2DM and peridontitis	Chinese	S	[123]
	T2DM, MS and Obesity	Indian	S	[124]
	T2DM	Mexican	S	[125]
	Glucose metabolism	Brazilian	S	[126]
	T2DM	Japanese	NS	[127]
	T2DM	Mexican	NS	[128]
	T2DM	Chinese	NS	[129]
	T2DM	Greek	NS	[130]
	atherosclerotic diabetic	Hungarian	S	[131]
	T2DM	Indian	S	[81]
	T2DM	United Kingdom/ Irish	NS	[132]
	T2DM	Finnish	S	[82]
sTNFR1 and sTNFR2	Glucose metabolism	Hungarian	NS	[133]
C-857T	IR and T2DM	Japanese	S	[134]

S: Significant; NS: Non-significant; T2DM: Type 2 diabetes; SNPs: Single nucleotide polymorphisms; MS: Metabolic syndrome; TNFR1: Tumor necrosis factor receptor 1.

inflammation due to its humoral immunity responses and prevention of pancreatic beta cell destruction[4,107]. The association of *IL-10* gene polymorphisms is shown in Table 4.

TNF-α

TNF-α is released by monocytes/macrophages and has an initial role in β-cell damage of the islets. It is reported that TNF-α is a possible mediator of insulin resistance and diabetes since it decreases the tyrosine kinase activity[116]. Furthermore, TNF-α inhibits insulin signaling[117] and impairs its secretion[118]. TNF-α interacts with IL-6, regulating its expression and downregulating itself[73]. In humans, the gene for *TNF-α* maps to chromosome 6p21. 3. One of the SNPs in *TNF-α* gene showed a two-fold increase in transcriptional activity[119,120]. Various groups showed an association of *TNF-α* SNPs with T2DM (Table 5).

Adiponectin

An endocrine effect leading to the clinical expression of T2DM and cardiovascular disease was attributed to the cytokines secreted by adipocytes[135,136]. 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[70,137]. Adiponectin levels in the plasma remain constant throughout the day and are not affected by food intake, unlike insulin and leptin.

Adipocytes secrete a plethora of cytokines, including adiponectin, resistin, leptin, IL-6, TNF-α, visfatin, RBP4, as well as free fatty acids, which alter insulin action and hepatic glucose production[138-140]. Adiponectin is a serum protein produced and secreted exclusively by adipose tissues, also known as adipocytes complement-related protein of 30 KDa (147 amino acids) (Acrp30). It is involved in the homeostatic control of circulating glucose and lipid levels[141]. Reduced adiponectin levels are documented in obese, insulin resistant and T2DM patients[116]. Adiponectin regulates glucose/lipid homeostasis *via* phosphorylation and activation of adenosine monophosphate activated protein kinase[142,143]. Another important function of adiponectin is to prevent the atherosclerotic vascular damage by suppressing interaction of monocytes/endothelial cells and adhesion molecules[144,145]. Therefore, high adiponectin levels are associated with reduced risk of T2DM[70]. In humans, the gene for *ADIPOQ* maps to chromosome 3q27. The SNPs in ADIPOQ studied by other researchers are shown in Table 6.

CONCLUSION

The greater tendency to diabetes in Indians may result from some genetic factors in addition to environmental and dietary factors. It is reported that the severity of diabetes (T2DM) in patients, from chronic to newly diagnosed, is related to certain biochemical and pathological examinations. The risk factors include lipid metabolism abnormalities (VLDL, HDL, LDL, TGA *etc.*) and re-

Table 6 Variants of adiponectin gene and their association with type 2 diabetes and related complications in different populations

Gene variants (SNPs)	Diseases	Population-Ethnic groups	Association	Ref.
+45 G/T	Obesity	Iranians	NS	[146]
	T2DM	Malaysian	S	[147]
	T2DM	Greek	NS	[148]
	MS	Chinese	S	[149]
	T2DM	Japanese	NS	[150]
	T2DM	Chinese	S	[151]
	Non-T2DM	Caucasian Canadians	NS	[152]
	T2DM	Hispanic Americans	NS	[153]
	T2DM	French Caucasian	NS	[154]
	T2DM	Korean	NS	[155]
	T2DM	Caucasians	S	[154]
	T2DM	Spanish	NS	[156]
	IGT	European/ Canadian	NS	[157]
	Non-T2DM	Japanese	NS	[158]
	Obesity	Swedish	NS	[159]
	T2DM	Caucasian Italians	NS	[160]
	T2DM	Caucasian Italians	NS	[161]
	T2DM	Pima Indians	NS	[162]
	T2DM	European Caucasians	NS	[163]
	T2DM	French Caucasians	S	[164]
+10211 T/G	T2DM	Asian Indians	S	[165]

S: Significant; NS: Non-significant; T2DM: Type 2 diabetes; SNPs: Single nucleotide polymorphisms; MS: Metabolic syndrome; IGT: Impaired glucose tolerance.

lationship to body mass index, WHR, food habits and family history. Different correlation with lipid profile and response to anti-diabetic drugs are additional indications of a genetic predisposition. 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. Association studies of cytokine genes will help in the development of prognostic markers to identify individuals at risk. The prognostic regimens arising from such genetic studies will alter and ease out treatment strategies for T2DM and related complications. Individuals at risk will be able to take prior precautionary measures and avoid or delay the onset of the disease.

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