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**Gene-gene, gene-environment, gene-nutrient interactions and single nucleotide polymorphisms of inflammatory cytokines**

Nadeem A *et al.* Single nucleotide polymorphisms and T2DM

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**Abstract**

Inflammation plays a significant role in the etiology of type 2 diabetes mellitus (T2DM). The rise in the pro-inflammatory cytokines is the essential step in glucotoxicity and lipotoxicity induced mitochondrial injury, oxidative stress and beta cell apoptosis in T2DM. Among the recognized markers are interleukin (IL)-6, IL-1, IL-10, IL-18, tissue necrosis factor-alpha (TNF-α), C-reactive protein, resistin, adiponectin, tissue plasminogen activator, fibrinogen and heptoglobins. Diabetes mellitus has firm genetic and very strong environmental influence; exhibiting a polygenic mode of inheritance. Many single nucleotide polymorphisms (SNPs) in various genes including those of pro and anti-inflammatory cytokines have been reported as a risk for T2DM. Not all the SNPs have been confirmed by unifying results in different studies and wide variations have been reported in various ethnic groups. The inter-ethnic variations can be explained by the fact that gene expression may be regulated by gene-gene, gene-environment and gene-nutrient interactions. This review highlights the impact of these interactions on determining the role of single nucleotide polymorphism of IL-6, TNF-α, resistin and adiponectin in pathogenesis of T2DM.

**Key words:** Cytokines; Diabetes mellitus; Single nucleotide polymorphism; Gene-gene interaction; Gene-environment interaction

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**Core tip:** Single nucleotide polymorphisms (SNPs) in inflammatory cytokines play role in insulin resistance and type 2 diabetes mellitus (T2DM). These SNPs are found to be correlated with cytokine serum levels, BMI, insulin resistance and dyslipidemia although these findings are challenged by other studies. Gene-gene, gene-environment and gene-nutrient interactions alter the impact of these SNPs in pathogenesis of T2DM. These interactions may explain the inter-ethnic variations in role of inflammatory cytokines in T2DM reported in international studies. This mini-review highlights these gene-genes, gene-environment and gene-nutrient interactions and their impact on inflammatory cytokine SNPs.

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**INTRODUCTION**

The prevalence of diabetes mellitus (DM) has increased globally over decades and is projected to continue increasing[1]. The etiology of DM is multi-factorial and inflammation plays a role in its pathogenesis. DM is considered as chronic low grade inflammatory state and markers of sub clinical inflammation increase in type 2 diabetes mellitus (T2DM) years before diagnosis of the disease[2]. They have a role in pathogenesis of the disease, obesity, insulin resistance and apoptosis of beta cells of endocrine pancreas by various mechanisms. Among the recognized markers are interleukin (IL)-6, IL-1, IL-18, tumor necrosis factor–alpha (TNF-α), C-reactive protein (CRP), tissue plasminogen activator (tPA), heptoglobulins, fibrinogen, resistin and adiponectin. These single nucleotide polymorphisms (SNPs) of pro- and anti-inflammatory cytokines have been found to influence the cytokines at translational level and modify serum levels. Inter-ethnic variations have been reported regarding association of SNPs of cytokines with T2DM and serum levels (Table 1). Pro-inflammatory cytokines induce glucotoxicity and lipotoxicity which in turns leads to mitochondrial damage, oxidative stress and beta cell apoptosis[2].

Although the relationship between single nucleotide polymorphisms of cytokines/adipokines and risk of T2DM has been robustly proven, inter-ethnic and intra-ethnic variations in this relationship cannot be explained in generalized terms. A number of factors including demographic features, sample size, gene-gene, gene-environment and gene-nutrients interaction, average age of onset, duration of disease, life style, degree of obesity and glucose tolerance and pathogenesis of disease can confound association studies.

**GENE-GENE INTERACTION**

Variable results regarding association of cytokines SNPs with T2DM in different ethnic groups have been reported in international studies[1-7]. Even different studies in the same ethnic group have also reported varying results[8,9]. This variation is also found in association of cytokines SNPs with serum levels of respective cytokines, insulin resistance, serum insulin, lipid profile and BMI. Gene-gene interaction is an established fact and a few studies have reported this factor as a contributing one in inter-ethnic variations in various parameters. There might be another unidentified functional gene polymorphism in close linkage disequilibrium with cytokine SNPs.

It has been found that presence or absence of a minor allele of inflammatory cytokine genotype may influence the binding of transcription factors to promoter region altering the promoter activity from almost non-existent to augmented by many folds[4]. Similarly gene-gene interactions may also influence either the binding of transcription factors or translational activity. Polymorphism of a stress protein gene; P2/P2 genotype of heat shock protein 70-2 is found to be close to and in linkage disequilibrium with *TNF-α* promoter area and is statistically associated with obesity in Tunisian subjects and may influence the impact of *TNF-α* polymorphism[3].

*IL-6 -174 G/C* SNP is in the promoter region (*-173 to -145*) that contains multiple response elements. These functional sites respond to many factors including IL-1, TNF-alpha, NF-KB and glucocorticoids[6]. Presence or absence of a minor allele may influence the binding of transcription factors to DNA response elements. Moreover, *IL-6* gene promoter function is also effected by a variable run of *A* and *T* bases (*-257 to -276*)[4]. *IL-6* promoter variants; *G* and *C* are also affected by the *IL-6* haplotype, age and sex of the individual and presence of sex steroids[5]. Estrogen regulates protein synthesis at transcriptional levels, particularly those proteins which are involved in glucose and lipid metabolism.

In overweight IGT Finnish subjects, simultaneous polymorphism *C-174G* in *IL6* and the *G-308A* polymorphism in *TNF-α* showed a 2.2 fold increased risk of T2DM than any other SNP[6] neither of SNP, although risk was not higher in simultaneous SNP’s as compared tothe *G-308A* SNP alone showing a gene-gene interaction[6].

Individually, *IL-6-597 G/A, TNF-α -308G/A* and *IL-10 -592C/A* do not show any association between SNP and risk of T2DM in Indian population but combined genotypes of *IL-6 -597 GA* and *TNF-α -308 GG* increased the risk of T2DM up to 21 times, while triple combination of *IL-6 -597 AA, TNF-α -308 GG* and *IL-10 -592 CA* increased the risk to 314 times. Presence of minor allele *A* in all 3 genes increased the risk up to 1.41 times in Indian population, showing strong gene-gene interaction[7].

Impact of SNPs in the resistin promoter region is also found to be influenced by gene-gene interaction. Presence of Pro/Pro genotype of PPAR gamma acts synergistically with *RETN* -*420 G* allele in augmenting serum resistin levels in Japanese population[8]. SNPs in regions outside the coding region may influence transcription or mRNA stability and thus affect the expression of the gene. Nuclear proteins are specifically recognized with a single base difference at SNP*-358* in *RETN* gene but not at SNP *RETN -638*. Therefore, *A* at *RETN -358* is required for *G* at *RETN -420* to confer the highest plasma resistin in the general Japanese population[9]. In Caucasians, the association between SNP *RETN C -420G* and plasma resistin is not strong, and A at *RETN* *-358* may not exist, suggesting that SNP *RETN -358* could explain this ethnic difference[9].

Similarly, in Filipino population, common SNPs in *ADIPOQ* gene were found to be in linkage disequilibrium with a rare coding variant in *R221S* at *ADIPOQ* locus. This variant was unique to Filipino population and was not found in 12514 European individuals[10].

PPAR-γ agonists are identified transcription factor for *ADIPOQ* expression. In differentiated 3T3L1 mice adipocytes cell line, the haplotype *AC* or *AG* both at *-11426* and *-11377* position results in 2-3 fold increase in rosiglitazone induced promoter activity whereas *GG* haplotype result in almost non-existent promoter activity. The result indicates that inducibility of *ADIPOQ* promoter activity by rosiglitazone (PPAR-γ agonist) depend on SNP variant combination rather than a particular allele[11].

Genome-wide association studies GWAS on large sample size and various ethnic groups are required to reach a definitive conclusion about gene-gene interaction.

**GENE-ENVIRONMENT INTERACTION**

T2DM is a disease in which environmental factors play a very significant role. Physical activity, BMI, physical and mental stress, dietary habits, smoking and life-style not only influence the pathogenesis of the disease but also the age of onset of disease, response to treatment, and onset of complications of the disease. These environmental factors are not functioning alone and there is strong gene-environmental interaction.

Adipose tissue is the source of 30% of IL-6. Some studies suggested the role of adiposity in modulating the association between IL-6 genetic variability and T2DM risk[12,13]. Association of *IL-6* SNP with S. IL-6 levels has also been found highly variable in different ethnic groups. *IL-6* SNP is suggested to enhance IL-6 expression, IL-6 mRNA levels and thus serum levels but these effects are cell-type specific[12]. Various IL-6 producing cell types may respond differently to various risk factors like inflammation, obesity, insulin resistance or yet unidentified parameters and thus altering the impact of SNP. This hypothesis is supported by the finding that *IL-6 -174C* allele was associated with significant elevation of IL-6 expression after but when catering for genotypes, *A* allele association with insulin resistance in presence of obesity but not in absence of it, has been reported in diabetic Canadians[14]. Interestingly not many studies were found in literature indicating positive association of *A* allele presence with higher insulin resistance even in absence of obesity. In one study, insulin resistance was found greater in both obese and lean Romans[15] in either allele carriers. It may indicate the possibility that insulin resistance may be secondary to raised BMI, in all obese irrespective of genotype; a fact supported by studies on obese Australian[16], obese Americans[17], overweight IGT Finnish subjects[6] and obese female Polish Caucasians[18], where insulin resistance was present in obese subjects carrying either allele. TNF-α polymorphism may act as a genetic factor enhancing the insulin resistance in presence of obesity, irrespective of serum TNF-α levels as found in many studies. Why in some studies, this association between polymorphism and insulin resistance is not found even in presence of obesity is not known.

Smoking is a known factor inducing oxidative stress and increased levels of inflammatory cytokines are found in smokers. Genotype-smoking interaction has been found statistically significant in Korean healthy subjects. The presence of coronary artery bypass surgery, although IL-6 levels were same in both genotypes before surgery. It indicates that probably stress led to an altered impact of the SNP on IL-6 expression[19]. Similarly, *C* allele was found to be associated with reduced levels of IL-6 after long term exercise although no difference was reported between genotypes before exercise training program[4,20]. Although, the low level of physical activity may increase the risk of T2DM in the absence of the risk allele, presence of the risk allele may not always assure the protection from the disease with exercise.

Association of *TNF-α -308 G/A* polymorphism with T2DM is explained by increased insulin resistance caused by raised serum levels of TNF-α. Despite quite a large number of studies on association of T2DM with this SNP, insulin resistance and BMI; very few studies correlated the TNF-α SNPs with serum levels of TNF, insulin resistance, BMI, or risk of T2DM. Association of *A* allele with higher serum levels of TNF has been reported in various ethnic groups such as in overweight Finnish subjects[6], in Danish Caucasians[21] and in Chinese[22]. Negative association has been reported in healthy controls, impaired glucose tolerant and diabetic Czech Caucasians[23] and in healthy Chinese[24].

It is well documented that insulin resistance is associated with BMI homozygous *IL6 -572GG* genotype results in higher serum IL-6 in smokers as compared to *GC* and *CC* genotype (*P* value = 0.04)[25]. Evidences indicate that environmental factors not only alone through metabolic derangement but also through gene-environmental interaction influence the impact of cytokine SNPs on pathogenesis of T2DM.

**GENE-NUTRIENT INTERACTION**

Single nucleotide polymorphisms in cytokines also interact with dietary factors influencing the cytokine expression induced by diet. *IL 6 -174G* allele has been found to be associated with higher energy expenditure as compared to *C* allele which could be one of the possible causes of lower BMI in *G* allele carriers in this cohort[26]. A recent study indicate the higher BMI in *IL 6 -174 CC* genotype in Koreans but greater reduction in weight in *CC* genotype as compared to *GG* genotype by low fat diet/virgin olive oil diet for 3 years. The effect of gene variant on obesity indices was reversed by low fat diet[27].

*TNF-α -238 A* allele alter the post-prandial suppression of FFA and levels remain high in obese, but not in non-obese A carriers. High TNF-expression in obese due to presence of *A* allele but also due to larger adipocytes may explain the absence of this effect in non-obese despite having *A* allele in Canadians[14].

A recent study highlighted the strong gene-nutrient interaction affecting the serum levels of adiponectin. Marine fish oil contains unsaturated fatty acids which are ligands for transcription factor; PPARγ which enhances the adiponectin expression thus increasing its serum level. The presence of SNPs in *ADIPOQ* fosters the effect of dietary marine fish oil on adiponectin expression[28].

Another example of gene-nutrient interaction is dependence of insulin sensitivity on plasma saturated fatty acid (SFA) levels in the presence of homozygous minor alleles *ADIPOQ -11377 GG.* Insulin resistance was higher in *GG* carriers with high SFA levels. In the presence of homozygous major alleles; *ADIPOQ -11377 CC* and heterozygous *CG* genotypes, the insulin sensitivity was not altered by plasma concentrations of SFA[29]. *ADIPOQ -11377* SNP also influences the extent to which energy is derived from dietary fat in obese women[30]. *ADIPOQ CC* homozygotes men have less insulin resistance after consumption of a monounsaturated fatty acid and carbohydrate diet as compared to saturated fatty acid diet; an effect not seen in females[31]. On the other hand, serum adiponectin was reduced after α-linolenic acid supplementation in obese individuals irrespective of *C* or *G* allele at *-11377 ADIPOQ*[29].

Heterogeneity in serum levels of cytokines in response to lipid lowering drugs in various patients may be due, in part to genotypes of inflammatory cytokines. *IL6 -572 GG* is associated with higher S.IL-6 levels as compared to *GC* and *CC* genotypes in those who are not taking lipid-lowering drugs while levels are comparable in *GG, GC* and *CC* genotypes who were taking those drugs. It is possible that statins might reduce the augmented effect of *GG* genotype on inflammation[32].

**CONCLUSION**

Pathogenesis of T2DM is multi-factorial. Genetic background has a profound effect especially in T2DM. The genetic makeup itself is governed by many factors; some of which are still unidentified. Contribution of T2DM susceptibility genes in insulin resistance and beta cell failure and their interaction with cytokine genes, environment and nutrients need to be explored. There could be additional, still unidentified risk factors which obscure the impact of SNP with specific genetic/environmental/nutrient background in various ethnic groups in population. Single nucleotide polymorphism may be considered as a susceptibility factor in certain population segments based on other risk factors; both genetic and environmental. Genome-wide association studies (GWAS) with large number of sample size**s** may indeed be required to statistically manifest SNP-related risk factors. Most of the studies are done in relatively small population groups in a particular ethnic group. Sampling might include patient selection inherent biases and do not reflect the general risk of population for the disease.

Gene-gene, gene-environment and gene-nutrient interaction**s** strongly influence the impact of cytokine polymorphisms on not only serum levels of cytokines but also on the insulin sensitivity, susceptibility to disease, response to weight reduction and lipid lowering drugs, energy expenditure and energy derivation from dietary fats. Such multi-dimensional regulatory factors can explain the wide variations in the role of single nucleotide polymorphisms in cytokines in pathogenesis of T2DM and MS reported in various ethnic groups.

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**Table 1 Frequencies of single nucleotide polymorphisms of cytokines in various ethnic groups**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Sno | **Ethnic Group** | ***N*** | **IL6 -174G/C allele frequency** | **Ref.** |
| **GG (%)** | **GC (%)** | **CC (%)** |
| 1 | Diabetic Turkish | 96 | 83.9 | 16.1 | Karadeniz *et al*[5] 2014  |
| 2 | Diabetic Indians | 40 | 57 | 28 | 15 | Mukhopadhyaya *et al*[33] 2010 |
| Healthy Indians | 40 | 30 | 33 | 37 |
| 3 | Diabetic Finnish | 737 | 61 | 39 | Razquin *et al*[27] 2010  |
| 4 | Diabetic Mexicans | 90 | 76.7 | 20 | 3.3 | Guzman *et al*[34] 2010  |
|  |  |  | **IL6 -572 G/C allele frequency** |  |
| **GG (%)** | **GC (%)** | **CC (%)** |
| 5 | Healthy Chinese | 581 | 3.74 | 39.8 | 65.4 | Zhou *et al*[35] 2010  |
| 6 | Diabetic Mexicans | 90 | 61.1 | 30 | 8.9 | Guzman *et al*[34] 2010  |
| 7 | Healthy Caucasians | 677 | 6.2 | 39 | 54.8 | Paik *et al*[36] 2007  |
|  |  |  | **TNFα -308G/A allele frequency** |  |
| **GG (%)** | **GA (%)** | **AA (%)** |  |
| 8 | Diabetic Mexicans | 278 | 76 | 24 | Perez-Lugue *et al*[31] 2012  |
| 9 | Diabetic Caucasians | 350 | 87 | 13 | Chan *et al*[37] 2011 |
| 10 | Diabetic Indians | 40 | 87.5 | 5 | 7.5 | Mukhopadhyaya *et al*[33] 2010  |
| Healthy Indians | 40 | 92.5 | 0 | 7.5 |
|  |  |  | **TNFα -238 G/A allele frequency** |  |
| **GG (%)** | **GA (%)** | **AA (%)** |
| 11 | Healthy Iranians | 202 | 79.3 | 19.2  | 1.5 | Hedayati *et al*[38] 2012  |
| 12 | Diabetic Canadian**s** | 123 | 85.4 | 14.6 | Fontaine-Bisson *et al*[14] 2007  |
| 13 | Diabetic Chileans | 230 | 90 | 10  | 0 | Santos *et al*[30] 2006  |
|  |   |  | **RETN -420 G/C allele frequency** |  |
| **CC %** | **GC%** | **GG%** |
| 14 | Diabetic Japanese | 161 | 47.2 | 46 | 6.8 | Hishida *et al*[39] 2013  |
| Healthy Japanese | 2491 | 42.6 | 43.7 | 13.7 |
| 15 | Diabetic Han Chinese | 318 | 60 | 40 | Chi *et al*[40] 2009 |
| Healthy Han Chinese | 370 | 61.5 | 38.5 |
| 16 | Diabetic Finnish | 258 | 65 | 35 | Kunnari *et al*[41] 2005  |
| Healthy Finnish | 494 | 73 | 27 |  |
|  |  |  | **ADIPOQ -11377 G/C allele frequency** |  |
| 17 | Diabetics White | 503 | 79 | 21 | Chiodini *et al*[42] 2010  |
| 18 | Diabetic Han Chinese  | 212 | 68.6 | 31.4 | Yang *et al*[43] 2009  |
| 19 | Diabetic Germ**a**ns | 365 | 71 | 29 | Schwarz *et al*[44] 2006  |