

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

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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; Gene-environment interaction; Diabetes mellitus; Single nucleotide polymorphism; Gene-gene 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, body mass index, 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. The 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, 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 body mass index (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- α , NF- κ B 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 *IL-6* 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 to the *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].

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

S no	Ethnic group	n	IL6 -174G/C genotype frequency			Ref.
			GG (%)	GC (%)	CC (%)	
1	Diabetic Turkish	96		83.9	16.1	Karadeniz <i>et al</i> ^[5]
2	Diabetic Indians	40	57	28	15	Mukhopadhyaya <i>et al</i> ^[33]
	Healthy Indians	40	30	33	37	
3	Diabetic Finnish	737		61	39	Razquin <i>et al</i> ^[27]
4	Diabetic Mexicans	90	76.7	20	3.3	Guzmán-Guzmán <i>et al</i> ^[34]
			IL6 -572 G/C allele frequency			
			GG (%)	GC (%)	CC (%)	
5	Healthy Chinese	581	3.74	39.8	56.4	Zhou <i>et al</i> ^[35]
6	Diabetic Mexicans	90	61.1	30	8.9	Guzmán-Guzmán <i>et al</i> ^[34]
7	Healthy Caucasians	677	6.2	39	54.8	Paik <i>et al</i> ^[36]
			TNF α -308G/A allele frequency			
			GG (%)	GA (%)	AA (%)	
8	Diabetic Mexicans	278		76	24	Pérez-Martínez <i>et al</i> ^[31]
9	Diabetic Caucasians	350		87	13	Chan <i>et al</i> ^[37]
10	Diabetic Indians	40	87.5	5	7.5	Mukhopadhyaya <i>et al</i> ^[33]
	Healthy Indians	40	92.5	0	7.5	
			TNF α -238 G/A allele frequency			
			GG (%)	GA (%)	AA (%)	
11	Healthy Iranians	202	79.3	19.2	1.5	Hedayati <i>et al</i> ^[38]
12	Diabetic Canadians	123	85.4	14.6		Fontaine-Bisson <i>et al</i> ^[14]
13	Diabetic Chileans	230	90	10	0	Santos <i>et al</i> ^[30]
			RETN -420 G/C allele frequency			
			CC %	GC%	GG%	
14	Diabetic Japanese	161	47.2	46	6.8	Hishida <i>et al</i> ^[39]
	Healthy Japanese	2491	42.6	43.7	13.7	
15	Diabetic Han Chinese	318	60	40		Chi <i>et al</i> ^[40]
	Healthy Han Chinese	370	61.5	38.5		
16	Diabetic Finnish	258	65	35		Kunnari <i>et al</i> ^[41]
	Healthy Finnish	494	73	27		
			ADIPOQ -11377 G/C allele frequency			
			GG (%)	GC (%)	CC (%)	
17	Diabetics White	503	79	21		Chiodini <i>et al</i> ^[42]
18	Diabetic Han Chinese	212	68.6	31.4		Yang <i>et al</i> ^[43]
19	Diabetic Germans	365	71	29		Schwarz <i>et al</i> ^[44]

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* C-174G 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 TNF- α -308A allele was associated with significant elevation of TNF- α expression 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. IL-6 -174C allele was associated with significant elevation of IL-6 expression after coronary artery bypass surgery, although IL-6 levels were same in either C or G allele carriers before surgery. It indicates that probably stress led to an altered impact of the IL-6 G-174C 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. Association of A allele with higher serum levels of TNF has been reported various ethnic groups such as in overweight Finnish subjects^[6], 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].

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; PPAR γ 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. IL-6 -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. GWAS with large number of sample sizes 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 interactions 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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