**Name of journal: World Journal of Diabetes**

**ESPS Manuscript NO: 7688**

**Columns: TOPIC HIGHLIGHT**

WJD 5th Anniversary Special Issues (2): Type 2 diabetes

Genetic polymorphisms of cytokine genes in type 2 diabetes mellitus

BanerjeeM *et al.* Cytokine genes and type 2 diabetes

Monisha Banerjee, Madhukar Saxena

**Monisha Banerjee, Madhukar Saxena,** Molecular and Human Genetics Laboratory, Department of Zoology, University of Lucknow, Lucknow226007, India

**Author contributions:** Both the authors had contributed equally in the manuscript.

**Supported by** Agencies *viz.* Department of Biotechnology (DBT), Indian Council of Medical Research (ICMR), Department of Science and Technology (DST) and Centre of Excellence (COE), UP Government, India for generous grants to our laboratory for diabetes research

**Correspondence to: Monisha Banerjee, Associate Professor,** Molecular and Human Genetics Laboratory, Department of Zoology, University of Lucknow, University Road, Lucknow226007, India. banerjee\_monisha30@rediffmail.com

**Telephone:** +91-983-9500439

**Received:**November 28, 2013 **Revised:** May 26, 2014

**Accepted:** June 14, 2014

**Published online:**

**Abstract**

**Diabetes mellitus is a combined metabolic disorder which includes hyperglycemia, dyslipidemia, stroke antd 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 has been 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 w**ill 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 in identifying **risk haplotype(s) for** disease susceptibility by developing prognostic markers **and alter treatment strategies for T2DM and related complications.** This will enable i**ndividuals 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.**

© 2014 Baishideng Publishing Group Inc. All rights reserved.

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

**Core tip:** Diabetes is third most widespread disease after heart disease and cancer. Cytokines are mediators of inflammation *viz.* interleukins (IL):1β, 1Ra, 18, 4, 6, 10, tumor nesrosis factor-α (TNF-α) and adiponectin (ADIPOQ) which cause immune responses in disease pathogenesisincluding **type 2 diabetes**. In the **present study the association of cytokine gene polymorphisms in different ethnic populations has been reviewed. Such single nucleotide polymorphism analyses and association studies in different populations will benefit individuals belonging to a particular group.**

Banerjee M, Saxena M. Genetic polymorphisms of cytokine genes in type 2 diabetes mellitus. *World J Diabetes*2014; In press

**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 bothleading to complications[1]. Diabetes mellitus has now 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 are suffering 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, hyperinsulinaemia, hyperglycemia, increased very low density lipoprotein (VLDL), increased triglycerides, decreased high density lipoproteins (HDL) cholesterol, high blood pressure, micro albuminuria, hyperuricaemia, fibrinolytic and coagulation abnormalities, *etc*[3].

Evidences have shown that T2DM is associated with chronic inflammation that can be attributed to dysregulation of innate immune systemand this represents 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 inteferons[7] secreted by white blood cells (WBCs) 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 sub group of low molecular weight cytokines called chemokines affect leukocyte behavior. Cytokines are of two types*viz.* pro-inflammatory (*e.g., IL-1*, *6*, *TNF-α*, *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 or visfatin as well as some of the classical inflammatory cytokines like TNF-α, IL-6, MCP-1 (CCL-2)*etc* help to achieve these*.* 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 due to an imbalance between pro- and anti-inflammatory cytokines lead to T2DM and its complications (Figure 1).

Mediators of inflammation such as interleukins (IL)-1β, 1Ra, 18, 4, 6, 10, tumor nesrosis factor-α (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. The adiponectin levels and its gene variantshave also been confirmed to be associated with increased risk of T2DM[10]. Till 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 same or different causal pathways[7]. It is important to understand the nature and actions of these adipocytokines in order to find out 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 different populations around the world.

**CYTOKINE GENE POLYMORPHISMS AND T2DM**

Certain chemokines/cytokines like IL-1β, 1Ra, 18, 4, 6, 10, TNF-α, *etc.,* some members of the adipocytokine family *viz.* adiponectin, leptin, and resistin are important mediators in inflammation/disease, glucose metabolism and may be involved in the pathogenesis of T2DM. They can be used as biological markers for diabetes as well as related obesity and hypertension. The SNPs present inthe regulatory regions of cytokine genes often have 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].

***Interleukin-1: α, β and Ra***

The IL-1 family consists of two pro- and one anti- inflammatory cytokines *viz.* 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 the 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 of them 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 and 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.

***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 asa 24- kDa inactive precursor, Pro-IL-18 which is cleaved byIL-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 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 haematopoietic cytokines, IL-4 regulates key events during Th2-dominated immune response and also stimulats 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 relation 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 alsoa Th2 mediated cytokine that downregulates inflammatory responses of pro-inflammatory cytokines[102]. The serum concentrations of TC, LDL, TGL, glucose (Glc) and HbA1c gradually decreases and HDL increaseswith 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 protectiveagainst T2DM and inflammationdue to itshumoral 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-folds increase in transcriptional activity[119-120]. Various groups showed association of *TNF-α* SNPs with T2DM (Table 5).

***Adiponectin***

An endocrine effect leading to the clinical expression of T2DM and cardiovascular disease (CVD) 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 level in the plasma remain constant throughout the day and is 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 (FFA) 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 (AMPK)[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 adiponectin(*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 be resulting from some genetic 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 relation to BMI, WHR, fooding habit and family history. Different correlation with lipid profile and response to anti-diabetic drugs are additional indications to a genetic predisposition. Single nucleotide polymorphisms (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, **the genotypic associations between SNPs and gene-gene interactions** willhave clinical importance as indicators of T2DM susceptibility. Association studies of cytokine genes will help in 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.**

**REFERENCES**

1 **Saxena M**, Agrawal CG, Gautam S, Bid HK, Banerjee M. Overt Diabetic Complications in Obese Type 2 Diabetes Mellitus Patients from North India. *Arch Appl Sci Res* 2009; **1**: 57-66

2 IDF "Diabetes Atlas, Fifth Edition, 2012

3 **Banerjee M,** Saxena M. An overview and molecular genetics of type 2 diabetes mellitus. Type 2 diabetes causes treatment and preventive strategies edt. Isidoros Calpis and Stefanos Frangopoulos. Nova Publishers, New York, USA 2012: 1-64

4 **Saxena M**, Agrawal CC, Bid HK, Banerjee M. An interleukin-10 gene promoter polymorphism (-592A/C) associated with type 2 diabetes: a North Indian study. *Biochem Genet* 2012; **50**: 549-559 [PMID: 22298356]

5 **Saxena M**, Banerjee M. Diabetes: History, Prevalence, Insulin Action and Associated Genes*. J Appl Biosci* 2008; **34**: 139-151

6 **Pradhan AD**, Manson JE, Rifai N, Buring JE, Ridker PM. C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. *JAMA* 2001; **286**: 327-334 [PMID: 11466099 DOI: 10.1001/jama.286.3.327]

7 **Banerjee M**, Saxena M. Interleukin-1 (IL-1) family of cytokines: role in type 2 diabetes. *Clin Chim Acta* 2012; **413**: 1163-1170 [PMID: 22521751 DOI: 10.1016/j.cca.2012.03.021]

8 **Okamoto Y**, Kihara S, Funahashi T, Matsuzawa Y, Libby P. Adiponectin: a key adipocytokine in metabolic syndrome. *Clin Sci (Lond)* 2006; **110**: 267-278 [PMID: 16464169 DOI: 10.1042/CS20050182]

9 Saxena M, Srivastava N, Banerjee M. IL-6-597 A/G (rs1800797) and -174 G/C (rs1800795) gene polymorphisms in Type 2 diabetes. Indian J Med Res 2012. (Accepted).

10 **Saxena M**, Srivastava N, Banerjee M. Genetic association of adiponectin gene polymorphisms (+45T/G and +10211T/G) with type 2 diabetes in North Indians. *Diabetes Metab Syndr* 2012; **6**: 65-69 [PMID: 23153972]

11 **Bid HK**, Konwar R, Aggarwal CG, Gautam S, Saxena M, Nayak VL, Banerjee M. Vitamin D receptor (FokI, BsmI and TaqI) gene polymorphisms and type 2 diabetes mellitus: a North Indian study. *Indian J Med Sci* 2009; **63**: 187-194 [PMID: 19584489]

12 **Bid HK**, Konwar R, Saxena M, Chaudhari P, Agrawal CG, Banerjee M. Association of glutathione S-transferase (GSTM1, T1 and P1) gene polymorphisms with type 2 diabetes mellitus in north Indian population. *J Postgrad Med* 2010; **56**: 176-181 [PMID: 20739761]

13 **Wilson AG**, Symons JA, McDowell TL, McDevitt HO, Duff GW. Effects of a polymorphism in the human tumor necrosis factor alpha promoter on transcriptional activation. *Proc Natl Acad Sci USA* 1997; **94**: 3195-3199 [PMID: 9096369 DOI: 10.1073/pnas.94.7.3195]

14 **Bidwell J**, Keen L, Gallagher G, Kimberly R, Huizinga T, McDermott MF, Oksenberg J, McNicholl J, Pociot F, Hardt C, D'Alfonso S. Cytokine gene polymorphism in human disease: on-line databases. *Genes Immun* 1999; **1**: 3-19 [PMID: 11197303 DOI: 10.1038/sj.gene.6363645]

15 **Fernandez-Real JM,** Vendrell J, Richart C, Gutierrez C, Ricart W. Platelet account and interleukin-6 gene polymorphism in healthy subjects. *BMC Med Genet* 2001; **2:** 6-11 [DOI: 10.1186/1471-2350-2-6]

16 **Chui MH**, Papanikolaou Y, Fontaine-Bisson B, Turcotte J, Wolever TM, El-Sohemy A, Chiasson JL, Rabasa-Lhoret R, Maheux P, Ryan E, Greenwood CE. The TNF-alpha-238G & gt; a single-nucleotide polymorphism protects against memory decline in older adults with type 2 diabetes. *Behav Neurosci* 2007; **121**: 619-624 [PMID: 17592954 DOI: 10.1037/0735-7044.121.3.619]

17 **Bid HK**, Konwar R, Agrawal CG, Banerjee M. Association of IL-4 and IL-1RN (receptor antagonist) gene variants and the risk of type 2 diabetes mellitus: a study in the north Indian population. *Indian J Med Sci* 2008; **62**: 259-266 [PMID: 18688110 DOI: 10.4103/0019-5359.42021]

18 **Ezzidi I**, Mtiraoui N, Kacem M, Mallat SG, Mohamed MB, Chaieb M, Mahjoub T, Almawi WY. Interleukin-10-592C/A, -819C/T and -1082A/G promoter variants affect the susceptibility to nephropathy in Tunisian type 2 diabetes (T2DM) patients. *Clin Endocrinol (Oxf)* 2009; **70**: 401-407 [PMID: 18616700]

19 **Koh SJ**, Jang Y, Hyun YJ, Park JY, Song YD, Shin KK, Chae JS, Kim BK, Ordovas JM, Lee JH. Interleukin-6 (IL-6) -572C--& gt; G promoter polymorphism is associated with type 2 diabetes risk in Koreans. *Clin Endocrinol (Oxf)* 2009; **70**: 238-244 [PMID: 18573122]

20 **Mtiraoui N**, Ezzidi I, Kacem M, Ben Hadj Mohamed M, Chaieb M, Haj Jilani AB, Mahjoub T, Almawi WY. Predictive value of interleukin-10 promoter genotypes and haplotypes in determining the susceptibility to nephropathy in type 2 diabetes patients. *Diabetes Metab Res Rev* 2009; **25**: 57-63 [PMID: 19031431]

21 **D'Alfonso S**, Rampi M, Bocchio D, Colombo G, Scorza-Smeraldi R, Momigliano-Richardi P. Systemic lupus erythematosus candidate genes in the Italian population: evidence for a significant association with interleukin-10. *Arthritis Rheum* 2000; **43**: 120-128 [PMID: 10643707 DOI: 10.1002/1529-0131(200001)43: 1<120: : AID-ANR15>3.0.CO; 2-3]

22 **Mantovani A**, Locati M, Vecchi A, Sozzani S, Allavena P. Decoy receptors: a strategy to regulate inflammatory cytokines and chemokines. *Trends Immunol* 2001; **22**: 328-336 [PMID: 11377293 DOI: 10.1016/S1471-4906(01)01941-X]

23 **Haukim N**, Bidwell JL, Smith AJ, Keen LJ, Gallagher G, Kimberly R, Huizinga T, McDermott MF, Oksenberg J, McNicholl J, Pociot F, Hardt C, D'Alfonso S. Cytokine gene polymorphism in human disease: on-line databases, supplement 2. *Genes Immun* 2002; **3**: 313-330 [PMID: 12209358 DOI: 10.1038/sj.gene.6363881]

24 **Welsh N**, Cnop M, Kharroubi I, Bugliani M, Lupi R, Marchetti P, Eizirik DL. Is there a role for locally produced interleukin-1 in the deleterious effects of high glucose or the type 2 diabetes milieu to human pancreatic islets? *Diabetes* 2005; **54**: 3238-3244 [PMID: 16249450 DOI: 10.2337/diabetes.54.11.3238]

25 **Steinkasserer A**, Spurr NK, Cox S, Jeggo P, Sim RB. The human IL-1 receptor antagonist gene (IL1RN) maps to chromosome 2q14-q21, in the region of the IL-1 alpha and IL-1 beta loci. *Genomics* 1992; **13**: 654-657 [PMID: 1386337 DOI: 10.1016/0888-7543(92)90137-H]

26 **López NJ**, Valenzuela CY, Jara L. Interleukin-1 gene cluster polymorphisms associated with periodontal disease in type 2 diabetes. *J Periodontol* 2009; **80**: 1590-1598 [PMID: 19792847]

27 **Bensen JT**, Langefeld CD, Li L, McCall CE, Cousart SL, Dryman BN, Freedman BI, Bowden DW. Association of an IL-1A 3'UTR polymorphism with end-stage renal disease and IL-1 alpha expression. *Kidney Int* 2003; **63**: 1211-1219 [PMID: 12631337 DOI: 10.1046/j.1523-1755.2003.00856.x]

28 **Mookherjee S**, Banerjee D, Chakraborty S, Banerjee A, Mukhopadhyay I, Sen A, Ray K. Association of IL1A and IL1B loci with primary open angle glaucoma. *BMC Med Genet* 2010; **11**: 99 [PMID: 20565898]

29 **Abrahamian H**, Endler G, Exner M, Mauler H, Raith M, Endler L, Rumpold H, Gerdov M, Mannhalter C, Prager R, Irsigler K, Wagner OF. Association of low-grade inflammation with nephropathy in type 2 diabetic patients: role of elevated CRP-levels and 2 different gene-polymorphisms of proinflammatory cytokines. *Exp Clin Endocrinol Diabetes* 2007; **115**: 38-41 [PMID: 17286233 DOI: 10.1055/s-2007-948213]

30 **Krikovsky D**, Vásárhelyi B, Treszl A, Körner A, Tordai A, Tulassay T, Madácsy L. Genetic polymorphism of interleukin-1beta is associated with risk of type 1 diabetes mellitus in children. *Eur J Pediatr* 2002; **161**: 507-508 [PMID: 12418458 DOI: 10.1007/s00431-002-1030-9]

31 **Achyut BR**, Srivastava A, Bhattacharya S, Mittal B. Genetic association of interleukin-1beta (-511C/T) and interleukin-1 receptor antagonist (86 bp repeat) polymorphisms with Type 2 diabetes mellitus in North Indians. *Clin Chim Acta* 2007; **377**: 163-169 [PMID: 17069782 DOI: 10.1016/j.cca.2006.09.012]

32 **Lee YY**, Lee NS, Cho YM, Moon MK, Jung HS, Park YJ, Park HJ, Youn BS, Lee HK, Park KS, Shin HD. Genetic association study of adiponectin polymorphisms with risk of Type 2 diabetes mellitus in Korean population. *Diabet Med* 2005; **22**: 569-575 [PMID: 15842511 DOI: 10.1111/j.1464-5491.2005.01460.x]

33 **Lee SH**, Ihm CG, Sohn SD, Lee TW, Kim MJ, Koh G, Oh SJ, Woo JT, Kim SW, Kim JW, Kim YS, Lee BC, Kim SD, Cho BS, Lee HJ, Chung JH. Polymorphisms in interleukin-1 beta and Interleukin-1 receptor antagonist genes are associated with kidney failure in Korean patients with type 2 diabetes mellitus. *Am J Nephrol* 2004; **24**: 410-414 [PMID: 15286433 DOI: 10.1159/000080044]

34 **Blakemore AI**, Cox A, Gonzalez AM, Maskil JK, Hughes ME, Wilson RM, Ward JD, Duff GW. Interleukin-1 receptor antagonist allele (IL1RN\*2) associated with nephropathy in diabetes mellitus. *Hum Genet* 1996; **97**: 369-374 [PMID: 8786086 DOI: 10.1007/BF02185776]

35 **Ruotsalainen E**, Salmenniemi U, Vauhkonen I, Pihlajamäki J, Punnonen K, Kainulainen S, Laakso M. Changes in inflammatory cytokines are related to impaired glucose tolerance in offspring of type 2 diabetic subjects. *Diabetes Care* 2006; **29**: 2714-2720 [PMID: 17130210 DOI: 10.2337/dc06-0147]

36 **Perrier S**, Darakhshan F, Hajduch E. IL-1 receptor antagonist in metabolic diseases: Dr Jekyll or Mr Hyde? *FEBS Lett* 2006; **580**: 6289-6294 [PMID: 17097645 DOI: 10.1016/j.febslet.2006.10.061]

37 **Zemunik T**, Skrabic V, Boraska V, Diklic D, Terzic IM, Capkun V, Peruzovic M, Terzic J. FokI polymorphism, vitamin D receptor, and interleukin-1 receptor haplotypes are associated with type 1 diabetes in the Dalmatian population. *J Mol Diagn* 2005; **7**: 600-604 [PMID: 16258158 DOI: 10.1016/S1525-1578(10)60593-4]

38 **Opstad TB**, Pettersen AÅ, Arnesen H, Seljeflot I. Circulating levels of IL-18 are significantly influenced by the IL-18 +183 A/G polymorphism in coronary artery disease patients with diabetes type 2 and the metabolic syndrome: an observational study. *Cardiovasc Diabetol* 2011; **10**: 110 [PMID: 22141572 DOI: 10.1186/1475-2840-10-110]

39 **Huang Y**, Xu M, Hong J, Gu W, Bi Y, Li X. -607 C/A polymorphism in the promoter of IL-18 gene is associated with 2 h post-loading plasma glucose level in Chinese. *Endocrine* 2010; **37**: 507-512 [PMID: 20960175 DOI: 10.1007/s12020-010-9338-0]

40 **He M**, Cornelis MC, Kraft P, van Dam RM, Sun Q, Laurie CC, Mirel DB, Chasman DI, Ridker PM, Hunter DJ, Hu FB, Qi L. Genome-wide association study identifies variants at the IL18-BCO2 locus associated with interleukin-18 levels. *Arterioscler Thromb Vasc Biol* 2010; **30**: 885-890 [PMID: 20150558 DOI: 10.1161/ATVBAHA.109.199422]

41 **Rafiq S**, Melzer D, Weedon MN, Lango H, Saxena R, Scott LJ, Palmer CN, Morris AD, McCarthy MI, Ferrucci L, Hattersley AT, Zeggini E, Frayling TM. Gene variants influencing measures of inflammation or predisposing to autoimmune and inflammatory diseases are not associated with the risk of type 2 diabetes. *Diabetologia* 2008; **51**: 2205-2213 [PMID: 18853133 DOI: 10.1007/s00125-008-1160-3]

42 **Thompson SR**, Sanders J, Stephens JW, Miller GJ, Humphries SE. A common interleukin 18 haplotype is associated with higher body mass index in subjects with diabetes and coronary heart disease. *Metabolism* 2007; **56**: 662-669 [PMID: 17445542 DOI: 10.1016/j.metabol.2006.12.015]

43 **Conti B**, Jahng JW, Tinti C, Son JH, Joh TH. Induction of interferon-gamma inducing factor in the adrenal cortex. *J Biol Chem* 1997; **272**: 2035-2037 [PMID: 8999896 DOI: 10.1074/jbc.272.4.2035]

44 **Matsui K**, Yoshimoto T, Tsutsui H, Hyodo Y, Hayashi N, Hiroishi K, Kawada N, Okamura H, Nakanishi K, Higashino K. Propionibacterium acnes treatment diminishes CD4+ NK1.1+ T cells but induces type I T cells in the liver by induction of IL-12 and IL-18 production from Kupffer cells. *J Immunol* 1997; **159**: 97-106 [PMID: 9200444]

45 **Stoll S**, Müller G, Kurimoto M, Saloga J, Tanimoto T, Yamauchi H, Okamura H, Knop J, Enk AH. Production of IL-18 (IFN-gamma-inducing factor) messenger RNA and functional protein by murine keratinocytes. *J Immunol* 1997; **159**: 298-302 [PMID: 9200466]

46 **Udagawa N**, Horwood NJ, Elliott J, Mackay A, Owens J, Okamura H, Kurimoto M, Chambers TJ, Martin TJ, Gillespie MT. Interleukin-18 (interferon-gamma-inducing factor) is produced by osteoblasts and acts via granulocyte/macrophage colony-stimulating factor and not via interferon-gamma to inhibit osteoclast formation. *J Exp Med* 1997; **185**: 1005-1012 [PMID: 9091574 DOI: 10.1084/jem.185.6.1005]

47 **Stoll S**, Jonuleit H, Schmitt E, Müller G, Yamauchi H, Kurimoto M, Knop J, Enk AH. Production of functional IL-18 by different subtypes of murine and human dendritic cells (DC): DC-derived IL-18 enhances IL-12-dependent Th1 development. *Eur J Immunol* 1998; **28**: 3231-3239 [PMID: 9808192 DOI: 10.1002/(SICI)1521-4141(199810)28: 10<3231: : AID-IMMU3231>3.0.CO; 2-Q]

48 **Gracie JA**, Forsey RJ, Chan WL, Gilmour A, Leung BP, Greer MR, Kennedy K, Carter R, Wei XQ, Xu D, Field M, Foulis A, Liew FY, McInnes IB. A proinflammatory role for IL-18 in rheumatoid arthritis. *J Clin Invest* 1999; **104**: 1393-1401 [PMID: 10562301 DOI: 10.1172/JCI7317]

49 **Pizarro TT**, Michie MH, Bentz M, Woraratanadharm J, Smith MF, Foley E, Moskaluk CA, Bickston SJ, Cominelli F. IL-18, a novel immunoregulatory cytokine, is up-regulated in Crohn's disease: expression and localization in intestinal mucosal cells. *J Immunol* 1999; **162**: 6829-6835 [PMID: 10352304]

50 **Prinz M**, Hanisch UK. Murine microglial cells produce and respond to interleukin-18. *J Neurochem* 1999; **72**: 2215-2218 [PMID: 10217305 DOI: 10.1046/j.1471-4159.1999.0722215.x]

51 **Gu Y**, Kuida K, Tsutsui H, Ku G, Hsiao K, Fleming MA, Hayashi N, Higashino K, Okamura H, Nakanishi K, Kurimoto M, Tanimoto T, Flavell RA, Sato V, Harding MW, Livingston DJ, Su MS. Activation of interferon-gamma inducing factor mediated by interleukin-1beta converting enzyme. *Science* 1997; **275**: 206-209 [PMID: 8999548 DOI: 10.1126/science.275.5297.206]

52 **Parnet P**, Garka KE, Bonnert TP, Dower SK, Sims JE. IL-1Rrp is a novel receptor-like molecule similar to the type I interleukin-1 receptor and its homologues T1/ST2 and IL-1R AcP. *J Biol Chem* 1996; **271**: 3967-3970 [PMID: 8626725 DOI: 10.1074/jbc.271.8.3967]

53 **Torigoe K**, Ushio S, Okura T, Kobayashi S, Taniai M, Kunikata T, Murakami T, Sanou O, Kojima H, Fujii M, Ohta T, Ikeda M, Ikegami H, Kurimoto M. Purification and characterization of the human interleukin-18 receptor. *J Biol Chem* 1997; **272**: 25737-25742 [PMID: 9325300 DOI: 10.1074/jbc.272.41.25737]

54 **Novick D**, Kim SH, Fantuzzi G, Reznikov LL, Dinarello CA, Rubinstein M. Interleukin-18 binding protein: a novel modulator of the Th1 cytokine response. *Immunity* 1999; **10**: 127-136 [PMID: 10023777 DOI: 10.1016/S1074-7613(00)80013-8]

55 **Frigerio S**, Holländer GA, Zumsteg U. Functional IL-18 Is produced by primary pancreatic mouse islets and NIT-1 beta cells and participates in the progression towards destructive insulitis. *Horm Res* 2002; **57**: 94-104 [PMID: 12006705 DOI: 10.1159/000057959]

56 **Mallat Z**, Corbaz A, Scoazec A, Besnard S, Lesèche G, Chvatchko Y, Tedgui A. Expression of interleukin-18 in human atherosclerotic plaques and relation to plaque instability. *Circulation* 2001; **104**: 1598-1603 [PMID: 11581135]

57 **Aso Y**, Okumura K, Takebayashi K, Wakabayashi S, Inukai T. Relationships of plasma interleukin-18 concentrations to hyperhomocysteinemia and carotid intimal-media wall thickness in patients with type 2 diabetes. *Diabetes Care* 2003; **26**: 2622-2627 [PMID: 12941729 DOI: 10.2337/diacare.26.9.2622]

58 **Esposito K**, Nappo F, Giugliano F, Di Palo C, Ciotola M, Barbieri M, Paolisso G, Giugliano D. Cytokine milieu tends toward inflammation in type 2 diabetes. *Diabetes Care* 2003; **26**: 1647 [PMID: 12716849 DOI: 10.2337/diacare.26.5.1647]

59 Blazhev A, Nicolff G, Petrova Ch, Jordanova-Laleva P. Serum levels of interleukin 12 and interleukin 18 in diabetic children. Diabetologia Croatica 2006; 35: 1-6.

60 **Hung J**, McQuillan BM, Chapman CM, Thompson PL, Beilby JP. Elevated interleukin-18 levels are associated with the metabolic syndrome independent of obesity and insulin resistance. *Arterioscler Thromb Vasc Biol* 2005; **25**: 1268-1273 [PMID: 15790931 DOI: 10.1161/01.ATV.0000163843.70369.12]

61 **Sarvetnick N**. IFN-gamma, IGIF, and IDDM. *J Clin Invest* 1997; **99**: 371-372 [PMID: 9022066 DOI: 10.1172/JCI119167]

62 **Hülsmeyer M**, Scheufler C, Dreyer MK. Structure of interleukin 4 mutant E9A suggests polar steering in receptor-complex formation. *Acta Crystallogr D Biol Crystallogr* 2001; **57**: 1334-1336 [PMID: 11526337]

63 **Dinarello CA**. Biologic basis for interleukin-1 in disease. *Blood* 1996; **87**: 2095-2147 [PMID: 8630372]

64 **Kazemi Arababadi M**. Interleukin-4 gene polymorphisms in type 2 diabetic patients with nephropathy. *Iran J Kidney Dis* 2010; **4**: 302-306 [PMID: 20852371]

65 **Ho KT**, Shiau MY, Chang YH, Chen CM, Yang SC, Huang CN. Association of interleukin-4 promoter polymorphisms in Taiwanese patients with type 2 diabetes mellitus. *Metabolism* 2010; **59**: 1717-1722 [PMID: 20580039 DOI: 10.1016/j.metabol.2010.04.010]

66 **Mohamed-Ali V**, Goodrick S, Rawesh A, Katz DR, Miles JM, Yudkin JS, Klein S, Coppack SW. Subcutaneous adipose tissue releases interleukin-6, but not tumor necrosis factor-alpha, in vivo. *J Clin Endocrinol Metab* 1997; **82**: 4196-4200 [PMID: 9398739]

67 **Fried SK**, Ricci MR, Russell CD, Laferrère B. Regulation of leptin production in humans. *J Nutri* 1998; **130:** 3127S-3131S

68 **Kristiansen OP**, Mandrup-Poulsen T. Interleukin-6 and diabetes: the good, the bad, or the indifferent? *Diabetes* 2005; **54** Suppl 2: S114-S124 [PMID: 16306329 DOI: 10.2337/diabetes.54.suppl\_2.S114]

69 **Cardellini M**, Perego L, D'Adamo M, Marini MA, Procopio C, Hribal ML, Andreozzi F, Frontoni S, Giacomelli M, Paganelli M, Pontiroli AE, Lauro R, Folli F, Sesti G. C-174G polymorphism in the promoter of the interleukin-6 gene is associated with insulin resistance. *Diabetes Care* 2005; **28**: 2007-2012 [PMID: 16043746 DOI: 10.2337/diacare.28.8.2007]

70 **Spranger J**, Kroke A, Möhlig M, Bergmann MM, Ristow M, Boeing H, Pfeiffer AF. Adiponectin and protection against type 2 diabetes mellitus. *Lancet* 2003; **361**: 226-228 [PMID: 12547549 DOI: 10.1016/S0140-6736(03)12255-6]

71 **Qi L**, van Dam RM, Meigs JB, Manson JE, Hunter D, Hu FB. Genetic variation in IL6 gene and type 2 diabetes: tagging-SNP haplotype analysis in large-scale case-control study and meta-analysis. *Hum Mol Genet* 2006; **15**: 1914-1920 [PMID: 16644865 DOI: 10.1093/hmg/ddl113]

72 **Fishman D**, Faulds G, Jeffery R, Mohamed-Ali V, Yudkin JS, Humphries S, Woo P. The effect of novel polymorphisms in the interleukin-6 (IL-6) gene on IL-6 transcription and plasma IL-6 levels, and an association with systemic-onset juvenile chronic arthritis. *J Clin Invest* 1998; **102**: 1369-1376 [PMID: 9769329 DOI: 10.1172/JCI2629]

73 **Terry CF**, Loukaci V, Green FR. Cooperative influence of genetic polymorphisms on interleukin 6 transcriptional regulation. *J Biol Chem* 2000; **275**: 18138-18144 [PMID: 10747905 DOI: 10.1074/jbc.M000379200]

74 **Kubaszek A**, Pihlajamäki J, Komarovski V, Lindi V, Lindström J, Eriksson J, Valle TT, Hämäläinen H, Ilanne-Parikka P, Keinänen-Kiukaanniemi S, Tuomilehto J, Uusitupa M, Laakso M. Promoter polymorphisms of the TNF-alpha (G-308A) and IL-6 (C-174G) genes predict the conversion from impaired glucose tolerance to type 2 diabetes: the Finnish Diabetes Prevention Study. *Diabetes* 2003; **52**: 1872-1876 [PMID: 12829659 DOI: 10.2337/diabetes.52.7.1872]

75 **Vozarova B**, Fernández-Real JM, Knowler WC, Gallart L, Hanson RL, Gruber JD, Ricart W, Vendrell J, Richart C, Tataranni PA, Wolford JK. The interleukin-6 (-174) G/C promoter polymorphism is associated with type-2 diabetes mellitus in Native Americans and Caucasians. *Hum Genet* 2003; **112**: 409-413 [PMID: 12589429]

76 **Illig T**, Bongardt F, Schöpfer A, Müller-Scholze S, Rathmann W, Koenig W, Thorand B, Vollmert C, Holle R, Kolb H, Herder C. Significant association of the interleukin-6 gene polymorphisms C-174G and A-598G with type 2 diabetes. *J Clin Endocrinol Metab* 2004; **89**: 5053-5058 [PMID: 15472205 DOI: 10.1210/jc.2004-0355]

77 **Himelfarb ST**, Silva FA, Arazi SS, Farjado CM, Garofalo A, Bertolami MC, Bertolami A, Faludi A, Sampaio MF, Rezende AA, Hirata RD, Hirata MH. Tumor necrosis factor-α and interleukin-6 expression in leukocytes and their association with polymorphisms and bone markers in diabetic individuals treated with pioglitazone. *Drug Metabol Drug Interact* 2011; **26**: 37-40 [PMID: 21480818 DOI: 10.1515/dmdi.2011.100]

78 **Underwood PC**, Chamarthi B, Williams JS, Sun B, Vaidya A, Raby BA, Lasky-Su J, Hopkins PN, Adler GK, Williams GH. Replication and meta-analysis of the gene-environment interaction between body mass index and the interleukin-6 promoter polymorphism with higher insulin resistance. *Metabolism* 2012; **61**: 667-671 [PMID: 22075267 DOI: 10.1016/j.metabol.2011.09.018]

79 **Popko K**, Gorska E, Demkow U. Influence of interleukin-6 and G174C polymorphism in IL-6 gene on obesity and energy balance. *Eur J Med Res* 2010; **15** Suppl 2: 123-127 [PMID: 21147639]

80 **Mendoza-Carrera F**, Ramírez-López G, Ayala-Martínez NA, García-Zapién AG, Flores-Martínez SE, Sánchez-Corona J. Influence of CRP, IL6, and TNFA gene polymorphisms on circulating levels of C-reactive protein in Mexican adolescents. *Arch Med Res* 2010; **41**: 472-477 [PMID: 21044752 DOI: 10.1016/j.arcmed.2010.08.015]

81 **Mukhopadhyaya PN**, Acharya A, Chavan Y, Purohit SS, Mutha A. Metagenomic study of single-nucleotide polymorphism within candidate genes associated with type 2 diabetes in an Indian population. *Genet Mol Res* 2010; **9**: 2060-2068 [PMID: 20967696 DOI: 10.4238/vol9-4gmr883]

82 **Kilpeläinen TO**, Laaksonen DE, Lakka TA, Herder C, Koenig W, Lindström J, Eriksson JG, Uusitupa M, Kolb H, Laakso M, Tuomilehto J. The rs1800629 polymorphism in the TNF gene interacts with physical activity on the changes in C-reactive protein levels in the Finnish Diabetes Prevention Study. *Exp Clin Endocrinol Diabetes* 2010; **118**: 757-759 [PMID: 20361391 DOI: 10.1055/s-0030-1249686]

83 **Bouhaha R**, Baroudi T, Ennafaa H, Vaillant E, Abid H, Sassi R, Vatin V, Froguel P, Gaaied AB, Meyre D, Vaxillaire M. Study of TNFalpha -308G/A and IL6 -174G/C polymorphisms in type 2 diabetes and obesity risk in the Tunisian population. *Clin Biochem* 2010; **43**: 549-552 [PMID: 20132806 DOI: 10.1016/j.clinbiochem.2010.01.008]

84 **Huth C**, Illig T, Herder C, Gieger C, Grallert H, Vollmert C, Rathmann W, Hamid YH, Pedersen O, Hansen T, Thorand B, Meisinger C, Doring A, Klopp N, Gohlke H, Lieb W, Hengstenberg C, Lyssenko V, Groop L, Ireland H, Stephens JW, Wernstedt Asterholm I, Jansson JO, Boeing H, Mohlig M, Stringham HM, Boehnke M, Tuomilehto J, Fernandez-Real JM, Lopez-Bermejo A, Gallart L, Vendrell J, Humphries SE, Kronenberg F, Wichmann HE, Heid IM. Joint analysis of individual participants' data from 17 studies on the association of the IL6 variant -174G& gt; C with circulating glucose levels, interleukin-6 levels, and body mass index. *Ann Med* 2009; **41**: 128-138 [PMID: 18752089 DOI: 10.1080/07853890802337037]

85 **Oberbach A**, Lehmann S, Kirsch K, Krist J, Sonnabend M, Linke A, Tönjes A, Stumvoll M, Blüher M, Kovacs P. Long-term exercise training decreases interleukin-6 (IL-6) serum levels in subjects with impaired glucose tolerance: effect of the -174G/C variant in IL-6 gene. *Eur J Endocrinol* 2008; **159**: 129-136 [PMID: 18469018 DOI: 10.1530/EJE-08-0220]

86 **Rudofsky G**, Schlotterer A, Reismann P, Engel J, Grafe IA, Tafel J, Morcos M, Humpert PM, Nawroth P, Bierhaus A, Hamann A. The -174G& gt; C IL-6 gene promoter polymorphism and diabetic microvascular complications. *Horm Metab Res* 2009; **41**: 308-313 [PMID: 19140096 DOI: 10.1055/s-0028-1119373]

87 **Testa R**, Olivieri F, Bonfigli AR, Sirolla C, Boemi M, Marchegiani F, Marra M, Cenerelli S, Antonicelli R, Dolci A, Paolisso G, Franceschi C. Interleukin-6-174 G & gt; C polymorphism affects the association between IL-6 plasma levels and insulin resistance in type 2 diabetic patients. *Diabetes Res Clin Pract* 2006; **71**: 299-305 [PMID: 16140413 DOI: 10.1016/j.diabres.2005.07.007]

88 **Illig T**, Bongardt F, Schöpfer-Wendels A, Huth C, Heid I, Rathmann W, Martin S, Vollmert C, Holle R, Thorand B, Wichmann HE, Koenig W, Kolb H, Herder C. Genetics of type 2 diabetes: impact of interleukin-6 gene variants. *Gesundheitswesen* 2005; **67** Suppl 1: S122-S126 [PMID: 16032529 DOI: 10.1055/s-2005-858396]

89 **Herbert A**, Liu C, Karamohamed S, Schiller J, Liu J, Yang Q, Wilson PW, Cupples LA, Meigs JB. The -174 IL-6 GG genotype is associated with a reduced risk of type 2 diabetes mellitus in a family sample from the National Heart, Lung and Blood Institute's Framingham Heart Study. *Diabetologia* 2005; **48**: 1492-1495 [PMID: 15965659]

90 **Mostafazadeh A**, Herder C, Haastert B, Hanifi-Moghaddam P, Schloot N, Koenig W, Illig T, Thorand B, Holle R, Eslami MB, Kolb H. Association of humoral immunity to human Hsp60 with the IL-6 gene polymorphism C-174G in patients with type 2 diabetes and controls. *Horm Metab Res* 2005; **37**: 257-263 [PMID: 15952088 DOI: 10.1055/s-2005-861209]

91 **Chang YH**, Huang CN, Shiau MY. The C-174G promoter polymorphism of the interleukin-6 (IL-6) gene that affects insulin sensitivity in Caucasians is not involved in the pathogenesis of Taiwanese type 2 diabetes mellitus. *Eur Cytokine Netw* 2004; **15**: 117-119 [PMID: 15319170]

92 **Möhlig M**, Boeing H, Spranger J, Osterhoff M, Kroke A, Fisher E, Bergmann MM, Ristow M, Hoffmann K, Pfeiffer AF. Body mass index and C-174G interleukin-6 promoter polymorphism interact in predicting type 2 diabetes. *J Clin Endocrinol Metab* 2004; **89**: 1885-1890 [PMID: 15070960 DOI: 10.1210/jc.2003-031101]

93 **Kubaszek A**, Pihlajamäki J, Punnonen K, Karhapää P, Vauhkonen I, Laakso M. The C-174G promoter polymorphism of the IL-6 gene affects energy expenditure and insulin sensitivity. *Diabetes* 2003; **52**: 558-561 [PMID: 12540635 DOI: 10.2337/diabetes.52.2.558]

94 **Fernandez-Real JM**, Broch M, Vendrell J, Gutiérrez C, Casamitjana R, Pugeat M, Richart C, Ricart W. Interleukin-6 gene polymorphism and insulin sensitivity. *Diabetes* 2000; **49**: 517-520. doi: 10.2337/diabetes.49.3.517

95 **Libra M**, Signorelli SS, Bevelacqua Y, Navolanic PM, Bevelacqua V, Polesel J, Talamini R, Stivala F, Mazzarino MC, Malaponte G. Analysis of G(-174)C IL-6 polymorphism and plasma concentrations of inflammatory markers in patients with type 2 diabetes and peripheral arterial disease. *J Clin Pathol* 2006; **59**: 211-215 [PMID: 16443741 DOI: 10.1136/jcp.2004.025452]

96 **Xiao LM**, Yan YX, Xie CJ, Fan WH, Xuan DY, Wang CX, Chen L, Sun SY, Xie BY, Zhang JC. Association among interleukin-6 gene polymorphism, diabetes and periodontitis in a Chinese population. *Oral Dis* 2009; **15**: 547-553 [PMID: 19549135 DOI: 10.1111/j.1601-0825.2009.01584.x]

97 **Zhang X**, Ma L, Peng F, Wu Y, Chen Y, Yu L, Lei Z, Zhang C. The endothelial dysfunction in patients with type 2 diabetes mellitus is associated with IL-6 gene promoter polymorphism in Chinese population. *Endocrine* 2011; **40**: 124-129 [PMID: 21424184 DOI: 10.1007/s12020-011-9442-9]

98 **Huth C**, Heid IM, Vollmert C, Gieger C, Grallert H, Wolford JK, Langer B, Thorand B, Klopp N, Hamid YH, Pedersen O, Hansen T, Lyssenko V, Groop L, Meisinger C, Döring A, Löwel H, Lieb W, Hengstenberg C, Rathmann W, Martin S, Stephens JW, Ireland H, Mather H, Miller GJ, Stringham HM, Boehnke M, Tuomilehto J, Boeing H, Möhlig M, Spranger J, Pfeiffer A, Wernstedt I, Niklason A, López-Bermejo A, Fernández-Real JM, Hanson RL, Gallart L, Vendrell J, Tsiavou A, Hatziagelaki E, Humphries SE, Wichmann HE, Herder C, Illig T. IL6 gene promoter polymorphisms and type 2 diabetes: joint analysis of individual participants' data from 21 studies. *Diabetes* 2006; **55**: 2915-2921 [PMID: 17003362 DOI: 10.2337/db06-0600]

99 **Arora P**, Garcia-Bailo B, Dastani Z, Brenner D, Villegas A, Malik S, Spector TD, Richards B, El-Sohemy A, Karmali M, Badawi A. Genetic polymorphisms of innate immunity-related inflammatory pathways and their association with factors related to type 2 diabetes. *BMC Med Genet* 2011; **12**: 95 [PMID: 21756351 DOI: 10.1186/1471-2350-12-95]

100 **Navarro-González JF**, Muros M, Mora-Fernández C, Herrera H, Meneses B, García J. Pentoxifylline for renoprotection in diabetic nephropathy: the PREDIAN study. Rationale and basal results. *J Diabetes Complications* 2010; **25**: 314-319 [PMID: 21144773 DOI: 10.1016/j.jdiacomp.2010.09.003]

101 **Ng DP**, Nurbaya S, Ye SH, Krolewski AS. An IL-6 haplotype on human chromosome 7p21 confers risk for impaired renal function in type 2 diabetic patients. *Kidney Int* 2008; **74**: 521-527 [PMID: 18496509 DOI: 10.1038/ki.2008.202]

102 **Pakala SV**, Kurrer MO, Katz JD. T helper 2 (Th2) T cells induce acute pancreatitis and diabetes in immune-compromised nonobese diabetic (NOD) mice. *J Exp Med* 1997; **186**: 299-306 [PMID: 9221759 DOI: 10.1084/jem.186.2.299]

103 **van Exel E**, Gussekloo J, de Craen AJ, Bootsma-van der Wiel A, Frölich M, Westendorp RG. Inflammation and stroke: the Leiden 85-Plus Study . *Stroke* 2002; **33**: 1135-1138 [PMID: 11935072 DOI: 10.1161/01.STR.0000014206.05597.9E]

104 **Sankaran D**, Asderakis A, Ashraf S, Roberts IS, Short CD, Dyer PA, Sinnott PJ, Hutchinson IV. Cytokine gene polymorphisms predict acute graft rejection following renal transplantation. *Kidney Int* 1999; **56**: 281-288 [PMID: 10411704 DOI: 10.1046/j.1523-1755.1999.00536.x]

105 **Turner DM**, Williams DM, Sankaran D, Lazarus M, Sinnott PJ, Hutchinson IV. An investigation of polymorphism in the interleukin-10 gene promoter. *Eur J Immunogenet* 1997; **24**: 1-8 [PMID: 9043871 DOI: 10.1111/j.1365-2370.1997.tb00001.x]

106 **Tsiavou A**, Hatziagelaki E, Chaidaroglou A, Manginas A, Koniavitou K, Degiannis D, Raptis SA. TNF-alpha, TGF-beta1, IL-10, IL-6, gene polymorphisms in latent autoimmune diabetes of adults (LADA) and type 2 diabetes mellitus. *J Clin Immunol* 2004; **24**: 591-599 [PMID: 15622443 DOI: 10.1007/s10875-004-6239-0]

107 **Chang YH**, Huang CN, Wu CY, Shiau MY. Association of interleukin-10 A-592C and T-819C polymorphisms with type 2 diabetes mellitus. *Hum Immunol* 2005; **66**: 1258-1263 [PMID: 16690414 DOI: 10.1016/j.humimm.2005.05.001]

108 **Arababadi MK**, Reza Mirzaei M, Ali Sajadi SM, Hassanshahi G, Ahmadabadi BN, Salehabadi VA, Derakhshan R, Kennedy D. Interleukin (IL)-10 gene polymorphisms are associated with type 2 diabetes with and without nephropathy: a study of patients from the southeast region of Iran. *Inflammation* 2012; **35**: 797-802 [PMID: 21909800 DOI: 10.1007/s10753-011-9376-7]

109 **Yin YW**, Sun QQ, Zhang BB, Hu AM, Liu HL, Wang Q, Zeng YH, Xu RJ, Ma JB, Shi LB. Association between interleukin-10 gene -592 C/A polymorphism and the risk of type 2 diabetes mellitus: a meta-analysis of 5320 subjects. *Hum Immunol* 2012; **73**: 960-965 [PMID: 22732092 DOI: 10.1016/j.humimm.2012.06.006]

110 **Paine SK**, Sen A, Choudhuri S, Mondal LK, Chowdhury IH, Basu A, Mukherjee A, Bhattacharya B. Association of tumor necrosis factor α, interleukin 6, and interleukin 10 promoter polymorphism with proliferative diabetic retinopathy in type 2 diabetic subjects. *Retina* 2012; **32**: 1197-1203 [PMID: 22105495 DOI: 10.1097/IAE.0b013e31822f55f3]

111 **Kolla VK**, Madhavi G, Pulla Reddy B, Srikanth Babu BM, Yashovanthi J, Valluri VL, Ramesh J, Akka J. Association of tumor necrosis factor alpha, interferon gamma and interleukin 10 gene polymorphisms with peripheral neuropathy in South Indian patients with type 2 diabetes. *Cytokine* 2009; **47**: 173-177 [PMID: 19608431 DOI: 10.1016/j.cyto.2009.06.007]

112 **Scarpelli D**, Cardellini M, Andreozzi F, Laratta E, Hribal ML, Marini MA, Tassi V, Lauro R, Perticone F, Sesti G. Variants of the interleukin-10 promoter gene are associated with obesity and insulin resistance but not type 2 diabetes in caucasian italian subjects. *Diabetes* 2006; **55**: 1529-1533 [PMID: 16644716 DOI: 10.2337/db06-0047]

113 **Erdogan M**, Cetinkalp S, Ozgen AG, Saygili F, Berdeli A, Yilmaz C. Interleukin-10 (-1082G/A) gene polymorphism in patients with type 2 diabetes with and without nephropathy. *Genet Test Mol Biomarkers* 2012; **16**: 91-94 [PMID: 21861711 DOI: 10.1089/gtmb.2011.0075]

114 **Kung WJ**, Lin CC, Liu SH, Chaung HC. Association of interleukin-10 polymorphisms with cytokines in type 2 diabetic nephropathy. *Diabetes Technol Ther* 2010; **12**: 809-813 [PMID: 20809684 DOI: 10.1089/dia.2010.0085]

115 **Forte GI**, Pilato G, Vaccarino L, Sanacore M, Candore G, Romano GC, Testa R, Franceschi C, Capri M, Marra M, Bonfigli AR, Caruso C, Scola L, Lio D. Risk profiles in type 2 diabetes (metabolic syndrome): integration of IL-10 polymorphisms and laboratory parameters to identify vascular damages related complications. *Curr Pharm Des* 2010; **16**: 898-903 [PMID: 20388104 DOI: 10.2174/138161210790883642]

116 **Hotta K**, Funahashi T, Arita Y, Takahashi M, Matsuda M, Okamoto Y, Iwahashi H, Kuriyama H, Ouchi N, Maeda K, Nishida M, Kihara S, Sakai N, Nakajima T, Hasegawa K, Muraguchi M, Ohmoto Y, Nakamura T, Yamashita S, Hanafusa T, Matsuzawa Y. Plasma concentrations of a novel, adipose-specific protein, adiponectin, in type 2 diabetic patients. *Arterioscler Thromb Vasc Biol* 2000; **20**: 1595-1599 [PMID: 10845877 DOI: 10.1161/01.ATV.20.6.1595]

117 **Hotamisligil GS**, Spiegelman BM. Tumor necrosis factor alpha: a key component of the obesity-diabetes link. *Diabetes* 1994; **43**: 1271-1278 [PMID: 7926300 DOI: 10.2337/diab.43.11.1271]

118 **Tsiotra PC**, Tsigos C, Raptis SA. TNFalpha and leptin inhibit basal and glucose-stimulated insulin secretion and gene transcription in the HIT-T15 pancreatic cells. *Int J Obes Relat Metab Disord* 2001; **25**: 1018-1026 [PMID: 11443501 DOI: 10.1038/sj.ijo.0801657]

119 **Kroeger KM**, Carville KS, Abraham LJ. The -308 tumor necrosis factor-alpha promoter polymorphism effects transcription. *Mol Immunol* 1997; **34**: 391-399 [PMID: 9293772 DOI: 10.1016/S0161-5890(97)00052-7]

120 **Guzmán-Flores JM**, Muñoz-Valle JF, Sánchez-Corona J, Cobián JG, Medina-Carrillo L, García-Zapién AG, Cruz-Quevedo EG, Flores-Martínez SE. Tumor necrosis factor-alpha gene promoter -308G/A and -238G/A polymorphisms in Mexican patients with type 2 diabetes mellitus. *Dis Markers* 2011; **30**: 19-24 [PMID: 21508505 DOI: 10.1155/2011/360312]

121 **Vendrell J**, Fernandez-Real JM, Gutierrez C, Zamora A, Simon I, Bardaji A, Ricart W, Richart C. A polymorphism in the promoter of the tumor necrosis factor-alpha gene (-308) is associated with coronary heart disease in type 2 diabetic patients. *Atherosclerosis* 2003; **167**: 257-264 [PMID: 12818408 DOI: 10.1016/S0021-9150(02)00429-X]

122 **Shiau MY**, Wu CY, Huang CN, Hu SW, Lin SJ, Chang YH. TNF-alpha polymorphisms and type 2 diabetes mellitus in Taiwanese patients. *Tissue Antigens* 2003; **61**: 393-397 [PMID: 12753658 DOI: 10.1034/j.1399-0039.2003.00059.x]

123 **Mustapic M**, Popovic Hadzija M, Pavlovic M, Pavkovic P, Presecki P, Mrazovac D, Mimica N, Korolija M, Pivac N, Muck-Seler D. Alzheimer's disease and type 2 diabetes: the association study of polymorphisms in tumor necrosis factor-alpha and apolipoprotein E genes. *Metab Brain Dis* 2012; **27**: 507-512 [PMID: 22580620 DOI: 10.1007/s11011-012-9310-1]

124 **Liu B**, Yu N, Tan LS, Liu JB, Guo Y, Pan YP. [A study of frequency of TNF alpha gene with type 2 diabetes mellitus with chronic periodontitis]. *Shanghai Kou Qiang Yi Xue* 2011; **20**: 169-173 [PMID: 21566867]

125 **Sobti RC**, Kler R, Sharma YP, Talwar KK, Singh N. Risk of obesity and type 2 diabetes with tumor necrosis factor-α 308G/A gene polymorphism in metabolic syndrome and coronary artery disease subjects. *Mol Cell Biochem* 2012; **360**: 1-7 [PMID: 22081334 DOI: 10.1007/s11010-011-0917-z]

126 **Perez-Luque E**, Malacara JM, Garay-Sevilla ME, Fajardo ME. Association of the TNF-α -308G/A polymorphism with family history of type 2 diabetes mellitus in a Mexican population. *Clin Biochem* 2012; **45**: 12-15 [PMID: 22015686 DOI: 10.1016/j.clinbiochem.2011.09.018]

127 **Ferreira AP**, Ferreira CB, Souza VC, Furioso AC, Toledo JO, Moraes CF, Córdova C, Nóbrega OT. Risk of glycemic disorder in elderly women adjusted by anthropometric parameters and cytokine genotypes. *Rev Assoc Med Bras* 2011; **57**: 565-569 [PMID: 22012292 DOI: 10.1590/S0104-42302011000500016]

128 **Yamashina M**, Kaneko Y, Maesawa C, Kajiwara T, Ishii M, Fujiwara F, Taneichi H, Takebe N, Ishida W, Takahashi K, Masuda T, Satoh J. Association of TNF-alpha gene promoter C-857T polymorphism with higher serum LDL cholesterol levels and carotid plaque formation in Japanese patients with type 2 diabetes. *Tohoku J Exp Med* 2007; **211**: 251-258 [PMID: 17347550 DOI: 10.1620/tjem.211.251]

129 **Feng RN**, Zhao C, Sun CH, Li Y. Meta-analysis of TNF 308 G/A polymorphism and type 2 diabetes mellitus. *PLoS One* 2011; **6**: e18480 [PMID: 21494616 DOI: 10.1371/journal.pone.0018480]

130 **Vourvouhaki E**, Carvalho CS. A Bayesian approach to the probability of coronary heart disease subject to the -308 tumor necrosis factor-α SNP. *Biosystems* 2011; **105**: 181-189 [PMID: 21477635 DOI: 10.1016/j.biosystems.2011.03.010]

131 **Szabó GV**, Acsády G. Tumornecrosis-factor-α 308 GA polymorphism in atherosclerotic patients. *Pathol Oncol Res* 2011; **17**: 853-857 [PMID: 21455632 DOI: 10.1007/s12253-011-9393-8]

132 **Boraska V**, Rayner NW, Groves CJ, Frayling TM, Diakite M, Rockett KA, Kwiatkowski DP, Day-Williams AG, McCarthy MI, Zeggini E. Large-scale association analysis of TNF/LTA gene region polymorphisms in type 2 diabetes. *BMC Med Genet* 2010; **11**: 69 [PMID: 20459604 DOI: 10.1186/1471-2350-11-69]

133 **Jermendy A**, Körner A, Kovács M, Madácsy L, Cseh K. PPAR-gamma2 pro12Ala polymorphism is associated with post-challenge abnormalities of glucose homeostasis in children and adolescents with obesity. *J Pediatr Endocrinol Metab* 2011; **24**: 55-59 [PMID: 21528816 DOI: 10.1515/jpem.2011.111]

134 **Ohara M**, Maesawa C, Takebe N, Takahashi T, Yamashina M, Ono M, Matsui M, Sasai T, Honma H, Nagasawa K, Fujiwara F, Kajiwara T, Taneichi H, Takahashi K, Satoh J. Different susceptibility to insulin resistance and fatty liver depending on the combination of TNF-α C-857T and adiponectin G+276T gene polymorphisms in Japanese subjects with type 2 diabetes. *Tohoku J Exp Med* 2012; **226**: 161-169 [PMID: 22327199 DOI: 10.1620/tjem.226.161]

135 **Yudkin JS**, Kumari M, Humphries SE, Mohamed-Ali V. Inflammation, obesity, stress and coronary heart disease: is interleukin-6 the link? *Atherosclerosis* 2000; **148**: 209-214 [PMID: 10657556 DOI: 10.1016/S0021-9150(99)00463-3]

136 **Hu FB**, Meigs JB, Li TY, Rifai N, Manson JE. Inflammatory markers and risk of developing type 2 diabetes in women. *Diabetes* 2004; **53**: 693-700 [PMID: 14988254 DOI: 10.2337/diabetes.53.3.693]

137 **Pickup JC**. Inflammation and activated innate immunity in the pathogenesis of type 2 diabetes. *Diabetes Care* 2004; **27**: 813-823 [PMID: 14988310 DOI: 10.2337/diacare.27.3.813]

138 **Gimeno RE**, Klaman LD. Adipose tissue as an active endocrine organ: recent advances. *Curr Opin Pharmacol* 2005; **5**: 122-128 [PMID: 15780819 DOI: 10.1016/j.coph.2005.01.006]

139 **Lazar MA**. How obesity causes diabetes: not a tall tale. *Science* 2005; **307**: 373-375 [PMID: 15662001 DOI: 10.1126/science.1104342]

140 **Wellen KE,** Hotamisligil GS. Inflammation, stress, and diabetes. *J Clin Invest* 2005; **115:** 1111-1119. doi: 10.1172/JCI200525102

141 **Scherer PE**, Williams S, Fogliano M, Baldini G, Lodish HF. A novel serum protein similar to C1q, produced exclusively in adipocytes. *J Biol Chem* 1995; **270**: 26746-26749 [PMID: 7592907 DOI: 10.1074/jbc.270.45.26746]

142 **Kadowaki T**, Yamauchi T. Adiponectin and adiponectin receptors. *Endocr Rev* 2005; **26**: 439-451 [PMID: 15897298 DOI: 10.1210/er.2005-0005]

143 **Kadowaki T**, Yamauchi T, Kubota N, Hara K, Ueki K, Tobe K. Adiponectin and adiponectin receptors in insulin resistance, diabetes, and the metabolic syndrome. *J Clin Invest* 2006; **116**: 1784-1792 [PMID: 16823476 DOI: 10.1172/JCI29126]

144 **Ouchi N**, Kihara S, Arita Y, Maeda K, Kuriyama H, Okamoto Y, Hotta K, Nishida M, Takahashi M, Nakamura T, Yamashita S, Funahashi T, Matsuzawa Y. Novel modulator for endothelial adhesion molecules: adipocyte-derived plasma protein adiponectin. *Circulation* 1999; **100**: 2473-2476 [PMID: 10604883 DOI: 10.1161/01.CIR.100.25.2473]

145 **Kim JY**, van de Wall E, Laplante M, Azzara A, Trujillo ME, Hofmann SM, Schraw T, Durand JL, Li H, Li G, Jelicks LA, Mehler MF, Hui DY, Deshaies Y, Shulman GI, Schwartz GJ, Scherer PE. Obesity-associated improvements in metabolic profile through expansion of adipose tissue. *J Clin Invest* 2007; **117**: 2621-2637 [PMID: 17717599 DOI: 10.1172/JCI31021]

146 **Mohammadzadeh G**, Zarghami N. Associations between single-nucleotide polymorphisms of the adiponectin gene, serum adiponectin levels and increased risk of type 2 diabetes mellitus in Iranian obese individuals. *Scand J Clin Lab Invest* 2009; **69**: 764-771 [PMID: 19929719 DOI: 10.3109/00365510903137237]

147 **Low CF**, Mohd Tohit ER, Chong PP, Idris F. Adiponectin SNP45TG is associated with gestational diabetes mellitus. *Arch Gynecol Obstet* 2011; **283**: 1255-1260 [PMID: 20552210 DOI: 10.1007/s00404-010-1548-4]

148 **Melistas L**, Mantzoros CS, Kontogianni M, Antonopoulou S, Ordovas JM, Yiannakouris N. Association of the +45T& gt; G and +276G& gt; T polymorphisms in the adiponectin gene with insulin resistance in nondiabetic Greek women. *Eur J Endocrinol* 2009; **161**: 845-852 [PMID: 19755407 DOI: 10.1530/EJE-09-0492]

149 **Wang ZL**, Xia B, Shrestha U, Jiang L, Ma CW, Chen Q, Chen H, Hu ZG. Correlation between adiponectin polymorphisms and non-alcoholic fatty liver disease with or without metabolic syndrome in Chinese population. *J Endocrinol Invest* 2008; **31**: 1086-1091 [PMID: 19246975 DOI: 10.1007/BF03345657]

150 **Hara K**, Boutin P, Mori Y, Tobe K, Dina C, Yasuda K, Yamauchi T, Otabe S, Okada T, Eto K, Kadowaki H, Hagura R, Akanuma Y, Yazaki Y, Nagai R, Taniyama M, Matsubara K, Yoda M, Nakano Y, Tomita M, Kimura S, Ito C, Froguel P, Kadowaki T. Genetic variation in the gene encoding adiponectin is associated with an increased risk of type 2 diabetes in the Japanese population. *Diabetes* 2002; **51**: 536-540 [PMID: 11812766 DOI: 10.2337/diabetes.51.2.536]

151 **Li LL**, Kang XL, Ran XJ, Wang Y, Wang CH, Huang L, Ren J, Luo X, Mao XM. Associations between 45T/G polymorphism of the adiponectin gene and plasma adiponectin levels with type 2 diabetes. *Clin Exp Pharmacol Physiol* 2007; **34**: 1287-1290 [PMID: 17973869 DOI: 10.1111/j.1440-1681.2007.04713.x]

152 **Ruchat SM**, Loos RJ, Rankinen T, Vohl MC, Weisnagel SJ, Després JP, Bouchard C, Pérusse L. Associations between glucose tolerance, insulin sensitivity and insulin secretion phenotypes and polymorphisms in adiponectin and adiponectin receptor genes in the Quebec Family Study. *Diabet Med* 2008; **25**: 400-406 [PMID: 18294218 DOI: 10.1111/j.1464-5491.2008.02396.x]

153 **Sutton BS**, Weinert S, Langefeld CD, Williams AH, Campbell JK, Saad MF, Haffner SM, Norris JM, Bowden DW. Genetic analysis of adiponectin and obesity in Hispanic families: the IRAS Family Study. *Hum Genet* 2005; **117**: 107-118 [PMID: 15843989 DOI: 10.1007/s00439-005-1260-9]

154 **Mackevics V**, Heid IM, Wagner SA, Cip P, Doppelmayr H, Lejnieks A, Gohlke H, Ladurner G, Illig T, Iglseder B, Kronenberg F, Paulweber B. The adiponectin gene is associated with adiponectin levels but not with characteristics of the insulin resistance syndrome in healthy Caucasians. *Eur J Hum Genet* 2006; **14**: 349-356 [PMID: 16418740 DOI: 10.1038/sj.ejhg.5201552]

155 **Lee SH**, Lee TW, Ihm CG, Kim MJ, Woo JT, Chung JH. Genetics of diabetic nephropathy in type 2 DM: candidate gene analysis for the pathogenic role of inflammation. *Nephrology (Carlton)* 2005; **10 Suppl**: S32-S36 [PMID: 16174285 DOI: 10.1111/j.1440-1797.2005.00454.x]

156 **González-Sánchez JL**, Zabena CA, Martínez-Larrad MT, Fernández-Pérez C, Pérez-Barba M, Laakso M, Serrano-Ríos M. An SNP in the adiponectin gene is associated with decreased serum adiponectin levels and risk for impaired glucose tolerance. *Obes Res* 2005; **13**: 807-812 [PMID: 15919831 DOI: 10.1038/oby.2005.91]

157 **Zacharova J**, Chiasson JL, Laakso M. The common polymorphisms (single nucleotide polymorphism [SNP] +45 and SNP +276) of the adiponectin gene predict the conversion from impaired glucose tolerance to type 2 diabetes: the STOP-NIDDM trial. *Diabetes* 2005; **54**: 893-899 [PMID: 15734870 DOI: 10.2337/diabetes.54.3.893]

158 **Nakatani K**, Noma K, Nishioka J, Kasai Y, Morioka K, Katsuki A, Hori Y, Yano Y, Sumida Y, Wada H, Nobori T. Adiponectin gene variation associates with the increasing risk of type 2 diabetes in non-diabetic Japanese subjects. *Int J Mol Med* 2005; **15**: 173-177 [PMID: 15583845]

159 **Ukkola O**, Ravussin E, Jacobson P, Sjöström L, Bouchard C. Mutations in the adiponectin gene in lean and obese subjects from the Swedish obese subjects cohort. *Metabolism* 2003; **52**: 881-884 [PMID: 12870165 DOI: 10.1016/S0026-0495(03)00074-X]

160 **Menzaghi C**, Ercolino T, Salvemini L, Coco A, Kim SH, Fini G, Doria A, Trischitta V. Multigenic control of serum adiponectin levels: evidence for a role of the APM1 gene and a locus on 14q13. *Physiol Genomics* 2004; **19**: 170-174 [PMID: 15252189 DOI: 10.1152/physiolgenomics.00122.2004]

161 **Bacci S**, Menzaghi C, Ercolino T, Ma X, Rauseo A, Salvemini L, Vigna C, Fanelli R, Di Mario U, Doria A, Trischitta V. The +276 G/T single nucleotide polymorphism of the adiponectin gene is associated with coronary artery disease in type 2 diabetic patients. *Diabetes Care* 2004; **27**: 2015-2020 [PMID: 15277433 DOI: 10.2337/diacare.27.8.2015]

162 **Vozarova de Courten B**, Hanson RL, Funahashi T, Lindsay RS, Matsuzawa Y, Tanaka S, Thameem F, Gruber JD, Froguel P, Wolford JK. Common Polymorphisms in the Adiponectin Gene ACDC Are Not Associated With Diabetes in Pima Indians. *Diabetes* 2005; **54**: 284-289 [PMID: 15616040 DOI: 10.2337/diabetes.54.1.284]

163 **Lacquemant C**, Froguel P, Lobbens S, Izzo P, Dina C, Ruiz J. The adiponectin gene SNP+45 is associated with coronary artery disease in Type 2 (non-insulin-dependent) diabetes mellitus. *Diabet Med* 2004; **21**: 776-781 [PMID: 15209773 DOI: 10.1111/j.1464-5491.2004.01224.x]

164 **Vasseur F**, Helbecque N, Dina C, Lobbens S, Delannoy V, Gaget S, Boutin P, Vaxillaire M, Leprêtre F, Dupont S, Hara K, Clément K, Bihain B, Kadowaki T, Froguel P. Single-nucleotide polymorphism haplotypes in the both proximal promoter and exon 3 of the APM1 gene modulate adipocyte-secreted adiponectin hormone levels and contribute to the genetic risk for type 2 diabetes in French Caucasians. *Hum Mol Genet* 2002; **11**: 2607-2614 [PMID: 12354786 DOI: 10.1093/hmg/11.21.2607]

165 **Vimaleswaran KS**, Radha V, Ramya K, Babu HN, Savitha N, Roopa V, Monalisa D, Deepa R, Ghosh S, Majumder PP, Rao MR, Mohan V. A novel association of a polymorphism in the first intron of adiponectin gene with type 2 diabetes, obesity and hypoadiponectinemia in Asian Indians. *Hum Genet* 2008; **123**: 599-605 [PMID: 18465144 DOI: 10.1007/s00439-008-0506-8]

**P-Reviewers:** Barzilay JI, Balamuthusamy S, Hegardt FG, Trachtman H, Tsilibary PEC **S-Editor:** Wen LL  **L-Editor:**  **E-Editor:**

**IL-1Ra, IL-1β, IL-6, TNF-α, IL-10, IL-4, adipocytokines**

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

Inflamed Adipocytes

TNF-α, IL-6, IL-1β,

Adiponectin

Insulin Resistance

High VLDL, High TG, Low HDL High Glucose

Endothelial Dysfunction

β-cell Inflammation

Low Insulin

T2DM

**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.

**Table 1 Variants of *interleukin-1* gene cluster (*interleukin-1α, interleukin-1β, interleukin-1Ra, interleukin-18*) and their association with type 2 diabetes** i**n 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-1α* | C-889T | East Indian | S | [28] |
| *IL-1β* | C-511T |
| *IL-1β* | C3953T |
| *IL-1α* |  VNTR |   | S | [29] |
| *IL-Ra* |
| *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) | Dalmatian population of South Croatia.  | S | [37] |
| PstI (exon 1B region) |
| *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.

**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; NS: Non-significant; T2DM: **Type 2 diabetes.**

**Table 3** V**ariants 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 Peripheral arterial disease (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] |
| -174G/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 | Singaporian | S | [101] |

S: Significant; NS: Non-significant; T2DM: **Type 2 diabetes.**

**Table 4 Variants of *interleukin-10* gene and their association withtype 2 diabetesand 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 | T2DM | Caucasian Italian | S | [112] |
| -819 C/T |
| -592 C/A |
| -1082 G/A | T2DM | Turkish | NS | [113] |
| -1082 G/A | T2DM | Greek | NS | [106] |
| -819 C/T |
| -592 C/A |
| -592 A/C  | T2DM | Taiwanese | NS | [107] |
| -819 C/T |
| -592 A/C | T2DM | Taiwanese | S | [114] |
| -1087 G/A  | T2DM | Italian | S | [115] |
| -824 C/T |
| -597 C/A |
| -592 A/C  | T2DM | Tunisian | S | [18] |

S: Significant; NS: Non-significant; T2DM: **Type 2 diabetes.**

**Table 5 Variants of tumor nesrosis factor-αgene 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 | Tarragonan | 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.**

**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.**