

Genetic Polymorphism of Adiponectin, a potential biomarker in Type-II Diabetes Mellitus

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Abstract

Adiponectin (ADIPOQ) is an abundant protein hormone which belongs to a family of adipokines. It is expressed mostly by adipocytes and is an important regulator of lipid and glucose metabolism. It was shown that decreased serum adiponectin concentration indicated insulin resistance in type 2 diabetes mellitus (T2DM) with the risk of cardiovascular complications. The fact that adiponectin is an insulin-sensitizing hormone with anti-diabetic, anti-inflammatory and anti-atherogenic properties. In this short commentary we are trying to confirm the association of ADIPOQ gene polymorphisms in subjects with T2DM. Furthermore, genetic study in a larger population will address the answer.

Keywords: Type 2 Diabetes; Mellitus; Adiponectin; Polymorphism; Hypoadiponectinemia

Abbreviation: T2DM: Type 2 Diabetes Mellitus; ADIPOQ: Adiponectin; SNPs: Single Nucleotide Polymorphisms; AMPK: AMP-activated protein kinase

Type 2 diabetes mellitus (T2DM) is a complex disease characterized by elevated fasting or post-prandial systemic glucose concentrations [1]. Multiple loci pre-disposing to T2DM have been discovered, many of which have emerged from genome-wide association studies [2]. Adiponectin, an adipokine secreted by adipocytes, is believed to play an important role in various metabolic processes including glucose regulation and fatty acid catabolism. It was shown that decreased serum adiponectin concentration indicated insulin resistance in **type 2 diabetes (T2D)** with the risk of cardiovascular complications. The fact that adiponectin is an insulin-sensitizing hormone with anti-diabetic, anti-inflammatory and anti-atherogenic properties. An estimated 30–70% of the variability in plasma adiponectin levels is explained by genetic variation [3]. Adiponectin, encoded by ADIPOQ on chromosome 3q27 has been identified as a susceptibility locus for metabolic syndrome and T2DM by genome wide scans [3]. ADIPOQ gene is one of the adipocyte-expressed proteins that enhances insulin sensitivity and functions in regulating the homeostatic control of glucose, lipid and energy metabolism [4]. Single nucleotide polymorphisms (SNPs) of ADIPOQ gene associated with hypoadiponectinemia, obesity and T2DM have been genotyped in various ethnic groups [5]. The greater risk of T2DM in the obese can be explained by changes in adipose tissue function [6]. Circulating plasma adiponectin concentrations have been reported to be reduced in the obese state. In healthy lean humans, circulating adiponectin levels range from 2–30 mg/L [7]. Hypoadiponectinemia is associated with obesity and diabetes [8].

Adiponectin has also been reported to activate AMP-activated protein kinase (AMPK) via phosphorylation at threonine172 (Thr172) to yield phosphorylated AMPK (pAMPK), which is the 'metabolic master switch' controlling pathway of hepatic ketogenesis, cholesterol synthesis and triglyceride synthesis [9].

Interestingly, single nucleotide polymorphisms in the adiponectin gene have been reported in humans. I164T polymorphism is one such mutation (isoleucine is substituted by threonine at the 164th position) that is reported to be a causative factor for hypoadiponectinemia and the development of type 2 diabetes [10].

The adiponectin gene has several variants. The prevalence of these variants has been studied in several populations including European, North American, and Japanese [11]. The most commonly studied

variants are -11391 G/A, -11377 C/G, +45 T/G and +276 G/T [11]. Although these variants have shown associations with markers of metabolic syndrome, **T2DM**, and cardiovascular disease (**CVD**), studies have shown different result discrepancies. For example in one French sample, -11391G represented a risk haplotype in diabetes [12], but in another French sample, the G haplotype was the protective allele. In yet another study, Esteghamati et al. did not find an association between variants of adiponectin genes such as +45T/G and +276 G/T with T2D [13]. However, they found an association between +276 G/T and T2D, after as well to the diabetic risk factors. In a study of diabetic Pima Indians, no association could be detected between adiponectin gene polymorphisms and T2D [14]. In an earlier study by a group, they could not find an association between +45T/G and -11391G/A polymorphisms of the adiponectin gene with T2D in an Iranian population. Similar results were found in a Korean population study by Lee et al. who examined the distribution of single nucleotide polymorphism (SNP)+45 T/G and SNP +276 G/T frequencies [15]. However, in another study, it was found that some of the adiponectin gene polymorphisms were associated with diabetes, in a gender-dependent manner [16].

The epidemic of T2DM observed in recent years is a clear indication of the importance of environmental factors in diabetes onset; in particular, obesity and physical inactivity. In another study genotypic variation and adiponectin levels in T2DM patients confirmed that the 'G' allele +45T/G and +10211T/G gene polymorphisms increases the risk of T2DM. In addition, adiponectin levels may be useful for identifying persons likely to benefit most from interventions to treat "dysfunctional adipose tissue" and its metabolic complications mainly through pharmaceutical and lifestyle interventions [17].

Quantifying the prevalence of diabetes and the number of people affected by diabetes, now and in the future, is important to allow rational planning and allocation of resources. The prevalence of diabetes for all age-groups worldwide was found to be 2.8% in 2000,

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6.4% in 2010, and (estimated to be) 7.7% in 2030! The total number of people with diabetes is projected to rise from 171 million in 2000, to 285 million in 2010 to 440 million in 2030 [18]. The urban population in developing countries is projected to double between 2000 and 2030. Between 2010 and 2030, there will be a 69% increase in numbers of adults with diabetes in developing countries like India and a 20% increase in developed countries [18].

Research groups on adiponectin gene polymorphism and T2DM in different ethnic groups have shown controversial results [19]. A case-control cohort study urban Asian Sikhs showed that adiponectin variants in (5tag SNPs of ADIPOQ) were not involved in causing T2DM [20], while in Whitehall II study, adiponectin was found to be an independent predictor of diabetes and glycemic impairment [21].

Furthermore, studies are still needed to confirm the associations of ADIPOQ gene polymorphism with T2DM, especially for +45T/G (rs2241766) because T2DM is strongly related to life style, genetic distribution, gender and environmental factors also. So deep study in this direction will probably increase our insight into the impact of adiponectin in the development and/or progression of T2DM.

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