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ADIPONECTIN (ADIPOQ) GENE POLYMORPHISM AND TYPE 2 DIABETES: A META- ANALYSIS OF 2210 SUBJECTS

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KEYWORDS :

Introduction

The increasing prevalence of Type 2 Diabetes has become a major public health challenge throughout the world, with 366 million prevalent diabetes cases in 2011 and a projected 552 million cases expected by the year 2030[1]

Both lifestyle factors, including diet and physical activity, and genetic factors contribute to the accelerating diabetes epidemic. Knowledge of lifestyle risk factors affecting Type 2 Diabetes incidence and the complications of Type 2. In addition, Type 2 Diabetes aetiology is known to have a considerable genetic component.

With the rapid development of modern genotyping techniques, numerous Type 2 Diabetes loci have been identified and replicated by genome-wide association studies (GWAS) among the world's major ethnic populations. Early identification of individuals at high Type 2 Diabetes risk enables delay or prevention of Type 2 Diabetes onset through effective lifestyle and/or pharmacological interventions, and has been shown to reduce costs of care.[1-3]

From a genetic perspective, the conditions broadly defined as "diabetes mellitus" can be classified as either monogenic, including neonatal diabetes mellitus (NDM) and maturity-onset diabetes of the young (MODY), or polygenetic, including Type 1 Diabetes and Type 2 Diabetes.[4]

Several studies have indicated that different genetic variants (single nucleotide polymorphisms [SNPs]) are associated with Type 2 Diabetes. The main aim of the study is to derive a relation between pro-inflammatory and anti-inflammatory gene polymorphism and associated biochemical changes in Type 2 Diabetes

Type 2 Diabetes is associated with a complicated interaction between genetic mutants and environmental factors. Adipose tissue, as an energy storage depot, is an active endocrine organ that secretes various proteins involved in the regulation of glucose, lipid metabolism, and energy homeostasis

Adiponectin is a specific protein secreted by adipocytes; it participates in the regulation of glucose and lipid metabolism, amelioration of insulin resistance (IR), improvement of the insulin sensitivity, and has anti-inflammation and anti-atherosclerosis effects [5]

Adiponectin is the exclusive adipokine of which the plasma concentration is reduced when the adipose tissue volume is increased [6] Hypoadiponectinemia has been detected in Type 2 Diabetes or obesity patients [7].

Adiponectin is encoded by one of the most abundant adipose gene transcripts (ADIPOQ), also referred to as the 30 kDa Adipocyte complement-related protein (ACRP30) and 28 kDa Gelatin binding protein (GBP28). Adiponectin comprises 244 amino acids. The adiponectin gene, located in 3q27, spans 16 kb and contains 3 Exons And 2 Introns. The adiponectin rs266729 locus point, -11377C-⟶G mutation in the proximal promoter is cytosine (C), which is substituted by guanine (G).

The adiponectin rs2241766 locus point, +45T------⟶G silent mutation in exon 2

In the current study, a meta-analysis of 11 individual studies with a total of 2210 subjects (1165 with Type 2 Diabetes) was conducted to determine whether there was a relationship between adiponectin gene polymorphism and Type 2 Diabetes.

Materials and Methods

The words as "adiponectin," "rs2241766" "Type 2 Diabetes, " and "polymorphism" were used to search electronic databases. The research studies with publication years ranging from 2007 to 2017 were selected.

The selected studies had to be in accordance with the following major criteria.

a) The adiponectin rs2241766 gene polymorphism and Type 2 Diabetes must be evaluated.
b) The Type 2 Diabetes diagnosis criteria were derived from the American Diabetes Association fasting plasma criteria (2005).

Criteria for Diabetes Diagnosis: 4 options
FPG ≥126 mg/dL (7.0 mmol/L)* Fasting is defined as no caloric intake for ≥8 hours
2-hr PG ≥200 mg/dL (11.1 mmol/L) during OGTT (75-g)* Using a glucose load containing the equivalent of 75g anhydrous glucose dissolved in water
A1C ≥6.5% (48 mmol/mol)* *Performed in a lab using NGSP-certified method and standardized to DCCT assay*
Random PG ≥200 mg/dL (11.1 mmol/L) In individuals with symptoms of hyperglycemia or hyperglycemic crisis

c) The individual studies should be case-control or cohort studies published in the official journals or peer-reviewed postgraduate dissertations.
d) The study should be in agreement with the Hardy- Weinberg equilibrium (HWE).

Data extraction

The data were abstracted according to a standard protocol. Studies that did not follow the Inclusion criteria, those considered double publications, or those that provided inadequate data were excluded. If the same data appeared in different studies, the data were used only once. The below mentioned information and data were carefully extracted and checked:

a) First and corresponding authors
b) Country in which the study was performed
c) Year of publication
d) Genotype distribution
e) Hardy Weinberg principle

f) Genotyping methods
g) Control population

Inclusion criteria:
The study types were restricted to case control or cohort study. The frequency of genotype was extracted from the studies published in English. The diabetes criteria should be matched with American diabetes association.

Genetic Analysis
Although there are 683 SNPs for the human *ADIPOQ* gene listed in the National Center for Biotechnology Information SNP database (http://www.ncbi.nlm.nih.gov/SNP), we only selected single SNPs i.e. rs2241766 in the present study

Statistical Analysis
Statistical heterogeneity among studies was evaluated by chi square test. The association b/w adiponectin gene polymorphism and Type 2 Diabetes demonstrated by odds ratio (OR) and 95% confidence level.

Table 1
According to study of Biswas et al distribution of polymorphism in percentage among controls and cases

Wild type	93.3	78.7
heterozygote	6.7	21.3

Chi square test of above table data is 7.68 and p value is 0.005 which is statistically significant.

Table 2
According to study of Biswas et al distribution of adiponectin genotypes and allele frequencies

Genotypes	TT	TG	GG
Control	70	4	1
cases	59	16	0

Chi square test of above table data is 9.14 and p value is 0.01 which is statistically significant.

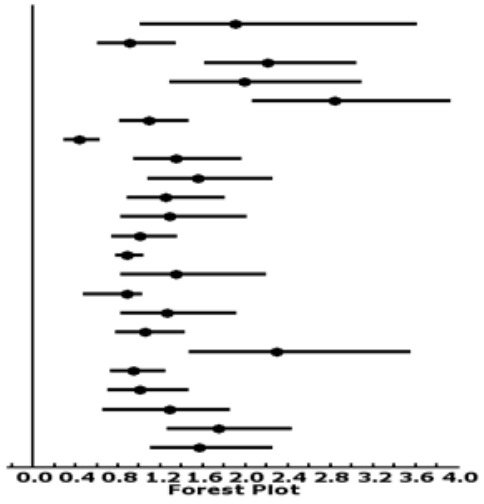
Table 3
A study compared association of gene polymorphism and adiponectin level

TT	73.21	6.80
TG	24.14	8.01
GC	2.65	10.75

Chi square test of above table data is 27.57 and p value is < 0.001 which is statistically significant

Pooled analysis:
In whole population a significant association was found between ADPIOQ gene +45T>G polymorphism and T2DM.

Study	Odds Ratio	95% CL	
		LOW	HIGH
LI LL 2007	1.91	1.01	3.61
ZHANG J 2007	0.91	0.61	1.34
WANG Y 2007	2.21	1.61	3.03
WEI YL 2007	1.99	1.29	3.08
CHENG W 2007	2.84	2.06	3.92
SHI XH 2007	1.09	0.81	1.45
WANG SF 2007	0.43	0.29	0.62
WU WJ 2008	1.35	0.94	1.95
SUN H 2008	1.55	1.08	2.25
KANG Z 2008	1.25	0.88	1.8
CHEN QY 2008	1.29	0.82	2
WANG Y 2008	1.01	0.74	1.35
WANG YB 2009	0.89	0.78	1.03
HAO JM 2009	1.35	0.83	2.18
ZHOU Q2009	0.89	0.47	1.02
YE H 2009	1.26	0.83	1.91
WENDRAMINI MF 2010	1.05	0.77	1.42
WANG YC 2010	2.29	1.47	3.55
WANG B 2011	0.95	0.73	1.24
HE HJ 2012	1.01	0.7	1.45
KANG XL 2012	1.29	0.66	1.85
NV Y 2012	1.75	1.26	2.43
KANG Z 2013	1.57	1.1	2.25



Results
By searching above databases 06 case control studies with 1165 cases and 1045 controls were included in meta-analysis. Very few studies were published in India and other was foreign articles. The genotyping method was PCR-RFLP. Most of the articles were hospital based case control studies.

S. No	STUDY	Year	GENOTYPING	CASES	CONTROLS
1.	Devadrita Biswas et al	2011	PCR-RFLP	75	75
2.	Jai prakash et al	2015	PCR-RFLP	303	333
3.	Mohd. Mustafa Khan et al	2017	PCR-RFLP	150	150
4.	Wan Ching Toy et al	2011	PCR-RFLP	300	288
5.	Morteza Kordafshari et al	2016	PCR-RFLP	168	80
6.	Arikogolu et al	2014	PCR-RFLP	169	119

As the data from case control study was not sufficient for meta-analysis, three meta-analysis research articles were also included.

Discussion
The current meta-analysis showed a significant relationship between adiponectin rs2241766 gene polymorphism and Type 2 Diabetes. Based on the current study indicating that adiponectin gene polymorphism may increase Type 2 Diabetes risk. It can be concluded that the SNP allele might confer Type 2 Diabetes susceptibility. Adipocytes have various endocrine, paracrine, and autocrine functions. Adiponectin is a cytokine specifically secreted by adipose tissue. Meijer et al. found extremely low adiponectin expression of pre-adipocytes compared with adipocytes. Thus, the adiponectin is considered as a marker for adipocytes differentiation [8]

Adiponectin has a number of key physiological functions, and most of them are mediated by the activation of AMP-activated protein [9]

Adiponectin can improve the glycolipid metabolism and IR; it can also restrain the adhesion molecule expression in the human aorta endothelial cells and exert the anti-atherosclerosis effects. Adiponectin can regulate the inflammatory response by inhibiting the pre-macrophage growth and mature macrophage function. Chen et al. investigated the relationships between the levels of

inflammation, adiponectin, and oxidative stress in subjects with metabolic syndrome (MS), and found that a higher level of hs-CRP (>1.00 mg/L) or IL-6 (>1.50 pg/mL) or a lower level of adiponectin (<7.90 mg/mL) were associated with a significantly greater risk of MS. They concluded that a higher inflammation status was significantly correlated with a decrease in the adiponectin level and an increase in the risk of MS[10]

Although the exact mechanism of the association of adiponectin rs266729 and rs2241766 gene polymorphism and Type 2 Diabetes has not been clarified, decreased or deficient serum adiponectin levels presumably contributed to the Type 2 Diabetes risk. Adiponectin is a significant adipokine, which is only expressed and secreted by the adipose tissue [11]

Adiponectin has anti-inflammatory and anti-atherosclerotic properties, and as such, it can increase insulin sensitivity. In most cases, the adiponectin levels are significantly decreased in patients with obesity, IR, Type 2 Diabetes, and cardiovascular diseases [12]

The -11377CG gene locus, rs266729, is in the upstream of the transcription start point, and the -11377CG CG variant alters some transcription regulation elements as well as influences the adiponectin secretion. Vasseur et al. reported that a nucleotide sequence [TCCTGC] was next to the 211377 position, which was similar to an enhanced element of the epidermal growth factor receptor (EGFR). They speculated that this nucleotide sequence might indirectly influence the adiponectin gene expression and lead to Type 2 Diabetes [13]

Zhang et al. found that -11377 CG loci was in the SP1 binding site, and when the C allele was substituted by the G allele, the SP1 binding site disappeared, thus contributing to the decreased plasma adiponectin level[14]

Sun et al. found that the – 113776 G allele was distinctly associated with low plasma adiponectin level and IR, thus resulting in Type 2 Diabetes risk [15]

Han et al. also conducted a meta-analysis of the relationship between adiponectin -11377CG gene polymorphism and T2DM, and concluded that the adiponectin -11377 G allele was a risk factor for T2DM.

There are certain limitations in the current meta-analysis. Large-scale studies on the association of Type 2 Diabetes with adiponectin -11377CG gene polymorphism remain insufficient. The adiponectin expression level was influenced not only by the adiponectin gene polymorphism, but also by other hereditary and environmental factors. Given that Type 2 Diabetes is a multigenic hereditary disease, adiponectin gene polymorphism can be associated with the gene linkage disequilibrium which can influence Type 2 Diabetes development [17]

Conclusion

In conclusion, adiponectin gene polymorphism was obviously associated with Type 2 Diabetes susceptibility. This conclusion contributes to the formulation of more effective individual Type 2 Diabetes therapy strategies.

In consideration of the aforementioned limitations, more large-scale studies as per Indian scenario are necessary to validate the significance of our findings.

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