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The PPAR γ (P12A) Locus-Associated Diabetes Risk is Modulated by Central Obesity in Punjabi Sikhs

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Abstract

Background: Several studies have reported a common proline-to-alanine substitution (P12A) in the peroxisome proliferator-activated receptor gamma (PPARγ) gene to be invariably associated with obesity, insulin resistance, type 2 diabetes mellitus (T2DM) and dyslipidemia. The purpose of this study was to determine whether the PPARγ gene (P12A) polymorphism contributes to susceptibility to T2DM and central obesity in Khatri Sikh community from India.

Methods: We studied 1711 subjects comprising 1186 individuals from 324 families and 525 unrelated non-diabetic controls. We tested the association between T2D and P12A polymorphism using logistic regression before and after adjusting for age, gender, and other covariates. We also examined the impact of these variants on obesity, glucose homeostasis and lipid traits using multiple linear regression analysis.

Results: Our findings could not confirm the association of PPARγ polymorphism with T2DM in this family-based sample. However, the comparison of unrelated controls with affected relatives (n=537) revealed a marginally significant association with this locus with T2DM (odds ratio (OR) 1.48, *P*=0.016). However, in the data stratified by traits related to abdominal obesity, there was a significant increase in T2DM risk in the individuals with waist circumference (>37 inches, OR 3.51, *P*=0.005) and waist to hip ratio (>0.95, OR 3.02, *P*= 0.003) in younger relatives.

Conclusions: PPARγ (P12A) locus appears to have profound influence in promoting insulin sensitivity through its interaction with central obesity particularly at younger age.

Introduction

India has the highest number of diabetics in the world and type 2 diabetes mellitus (T2DM) has become a major public health problem in urban and sub-urban areas [1]. Despite the absence of conventional risk factors such as high smoking, obese body mass index (BMI), and diet rich in meats, people from India, as well as from the entire Indian subcontinent have high prevalence of a characteristic metabolic syndrome. This includes elevated plasma triglycerides and small low-density lipoprotein (LDL) particle, reduced high-density lipoprotein cholesterol (HDL-C), early onset of insulin resistance, central obesity, and premature atherosclerosis [2-9]. Insulin resistance is predominantly associated with obesity, especially when obesity is centrally distributed and becomes a major risk factor for developing T2DM and cardiovascular disease (CVD) [10,11].

Obesity and its metabolic consequences such as T2DM and CVD have increased to epidemic proportions during the past two decades. This phenomenon could be attributed to the adoption of sedentary and western lifestyles, and enhanced intake of high-density caloric diets with little physical activity. The modern day lifestyles have increased the genetic susceptibility to generalized metabolic conditions when central obesity is observed [12-15]. In particular the interplay between genes and central obesity and the pathophysiology of T2DM and CVD is complex and thus, it is likely that a common set of genes with pleiotropic effects might influence obesity, T2DM and CVD.

A candidate gene with pleiotropic effects is the peroxisome proliferator-activated receptor gamma (PPARγ). It is a nuclear hormone receptor and is an important regulator of adepocyte differentiation [16,17]. The critical role of PPARγ in the development of adipose tissue in mammals was confirmed by the absence of adipose tissue in the PPARγ knockout murine embryos [18]. The human PPARγ gene maps to chromosome 3p24, and a common missense mutation in PPARγ (proline12 to alanine12 or P12A) has been implicated in increasing T2DM risk in several independent datasets including recent genome-wide association studies (GWAS) and is widely studied for its role in insulin resistance, central obesity and T2DM, and other related phenotypes [17,19-24]. Differential splicing of human messenger RNA generates two different isoforms: PPARγ-1 and PPARγ-2 that differ at their 5' ends [25,26]. PPARγ-1 is expressed in diverse tissues including adipose, skeletal muscle, heart, liver, and large intestine, while PPARγ-2 is exclusively expressed in adipose tissues [27,28]. In addition, PPARγ-2 is involved in insulin signaling, inflammation, obesity, and the development of T2DM [29]. The 'Ala12' allele with lower transcriptional activity has been associated with reduced risk of T2DM [29]. However, the common 'Pro12' protein (with greater *in vitro* activity than 'Ala12') has been associated with decreased insulin sensitivity, obesity and T2DM in many but not all studies [19,30,31]. We have previously reported significant association of the P12A (rs1801282) with T2DM in this population [32]. To further define the role of the PPARG locus in T2DM pathophysiology and to discover functional variant in this gene, we performed a comprehensive screening using 14 tagging single nucleotide polymorphisms (tagSNPs) from the PPARG locus in our case-control cohort of Khatri Sikhs [23]. With the exception of a strong association of P12A with T2DM

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