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The PPAR-γ Pro12Ala allele polymorphism of the Peroxisome Proliferator-Activated Receptor (γ) Gene (PPARG2) is a risk factor with a self-identified obese Dutch population

Research Article

Kenneth Blum[1,3,4,5,#,*], Thomas JH Chen[2], Brian Meshkin[3,#], Seth H. Blum[4], Julie F. Mengucci[4], Alison Notaro[5], Vanessa Arcuri[5], Roger L. Waite[6], Eric R. Braverman[5]

[1]Wake Forest University School of Medicine, NC. USA
[2]Chang Jung Christian University, Tainan, Taiwan, Republic of China
[3]Salugen, Inc. San Diego, CA, USA
[4]Synapatamine, Inc. San Antonio, TX, USA
[5]Path Medical Research Foundation, NY, USA
[6]GenWellness Inc. San Diego, California

***Correspondence**: Kenneth Blum, Ph.D. Department Physiology & Pharmacology, Wake Forest University School of Medicine, Medical Center Boulevard, Winston–Salem, North Carolina, 27157-1083, USA; Tel. 210-823-1504; Fax. 210-462-1516; email: drd2gene@aol.com

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Abbreviations: body mass index (BMI); coronary heart disease (CHD); insulin resistance syndrome (IRS); myocardial infarction (MI); peroxisome proliferators-activated receptor (PPAR)

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Summary

Obesity has been identified as a global epidemic and presents a significant increased risk factor for a variety of co-morbidities. Positive energy balance and resultant weight gain is largely attributed to a chronic mismatch between energy intake and energy expenditure. The PPAR gene (PPAR-γ Polymorphism - Pro12Ala Allele) influences many biological factors including serving as the master regulator of fat-cell formation and influencing insulin resistance. Based on the literature and proposed associations of the PPAR gene and the Pro12Ala allele polymorphism as a fat regulator gene, we decided to determine its allelic presence in a self-identified (via a cross sectional survey questionnaire) obese Dutch population. In this preliminary observational study, a total of 1,058 subjects were genotyped for the PPARG2 polymorphism. The PPAR gene Ala allele polymorphic frequency was 25.05% of the study subjects (n=1,058) versus 14% of the literature controls (n=2,245). This difference was significant (Z=17.398, p= 0.001). Our results suggest that in a highly motivated (wanting to loose weight) group of self-identified obese subjects (n= 1,058) from the Netherlands, the Pro 12A1a polymorphism of the PPARG2 gene significantly associates with these individuals compared to non-obese controls (n=2,245) and may be considered a risk factor.

I. Introduction

Obesity has been identified as a global epidemic and presents significant increased risk factors for a variety of co-morbidities. Positive energy balance and resultant weight gain is largely attributed to a chronic mismatch between energy intake and energy expenditure (Cecil et al, 2006).

The Pro12Ala polymorphism peroxisome proliferators-activated receptor *(*PPAR)-γ, caused by a missense mutation in exon B of the adipocyte –specific γ 2 isoform, was identified in 1997 and is believed to confer transcriptional activity (Yen et al, 1997). Several more genetic variants in PPAR γ are known but are much less frequent (Valve et al, 1999). Since PPAR γ 2 is exclusively expressed in adipose tissue, the prevalent PRO12Ala polymorphism was originally studied for an association with obesity. In recent years evidence pointed to an association of the Ala variant with increased insulin sensitivity in nondiabetic Caucasians.

Most recently, Tonjes et al performed a meta analysis of 57 studies on nondiabetic individuals with pre-diabetic phenotypes and concluded that across all studies, the PRO12Ala polymorphism had no significant effect on diabetic-related traits. Only in selected subgroups, such as Caucasians and obese subjects, did Tonjes's group see an association of the Ala allele with greater body mass index (BMI) and greater insulin sensitivity. Meta analysis of Ala homozygotes more clearly demonstrated the association with greater insulin sensitivity of carriers of the Ala allele (Tonjes et al, 2006).

A. Recent research supporting an anti-obesity role for the PPAR gene

The PPAR gene (PPAR-γ Polymorphism-Pro12Ala Allele) influences many biological factors including serving as the master regulator of fat-cell formation and influence over insulin resistance (Jo-SH et al, 2006). PPARs exert a measure of transcriptional control regulating glucose transport and insulin sensitivity, lipid metabolism, oxidative stress, and inflammation (Lehrke and Lazar, 2005).

In a study of 311 subjects who participated in a population-based study, weight at birth, 7 years, 20 years, and 41 years, as well as ponderal index at birth, BMI and waist circumference at 41 years were recorded. The PPAR gene was associated with high ponderal index at birth (baby birth weight (p=0.007) and weight at 7 years (p=0.045). The PPAR gene tended to be associated with high birth weight (p = 0.094). Subjects with this gene gained less weight between 7 and 20 years (p = 0.043), more weight between 20 and 41 years (p = 0.001) and ended up having higher waist circumference (p = 0.040) in adulthood than did subjects with the normal genotype. The study authors concluded that the PPAR gene regulates weight and body composition from utero to adulthood (Verreth et al, 2004).

In a published study of 2,141 subjects, the study authors found that PPAR gene impacted responses to dietary fat intake. Among individuals without the mutation, those in the highest quintile of total fat intake had significantly higher mean BMI compared with those in the lowest quintile (27.3 versus 25.4 kg/m^2, respectively; P-trend<0.0001) whereas among PPAR gene variant allele-carriers, there was no significant trend observed between dietary fat intake and BMI (P-trend=0.99; P-interaction=0.003). In contrast, intake of monounsaturated fat was not associated with BMI among women without the gene, but was inversely associated with BMI among PPAR gene variant allele-carriers (mean in lowest quintile=27.6 versus mean in highest quintile=25.5 kg/m^2; P-trend=0.006; P-interaction=0.003). The relationship between dietary fat intake and plasma lipid concentrations also differed according to the PPAR γ genotype (Pihlajamaki et al, 2004). These data suggest that PPAR-γ genotype is an important factor in physiological responses to dietary fat in humans (Memisoglu et al, 2003).

In a case-control study of the Pro12Ala PPAR-γ 2 polymorphism, obese subjects with Ala12 were more insulin sensitive than those without. The frequency of Ala12 was significantly lower in the diabetic group, suggesting that this polymorphism protects against Type 2 diabetes. These results revealed that PPAR-γ is a thrifty gene mediating Type 2 diabetes. In one study, the authors confirmed a contribution of the PPAR-γ 2 Pro12 allele in the genetic risk for type-2 diabetes, especially in obese subjects, where this allele worsens insulin resistance and increases fasting insulin levels (Kadowaki et al, 2002).

Concerning body weight, subjects with a mutation in PPAR- γ (Pro12Ala) had significantly higher body weight than those with a normal genotype (Pro12Pro) (Moon et al, 2005). In another study relating the PPAR gene and weight, the study authors found significantly increased risk for heart disease (nonfatal myocardial infarction (MI) or fatal coronary heart disease (CHD) associated with the A12 allele among individuals with a body mass index > or =25 kg/m^2 (women: RR, 1.88; 95% CI, 1.01 to 3.50; men: RR, 1.55; 95% CI, 0.92 to 2.60; pooled: RR, 1.68; 95% CI, 1.13 to 2.50) but not among those <25 kg/m^2 (pooled RR, 0.86; 95% CI, 0.37 to 1.97; P heterogeneity overweight versus non overweight 0.16) (Pischon et al, 2005). This has been supported by others (Ghoussaini, 2005; Rhee et al, 2006).

For children and obesity, a study found that the Pro12Ala variant is significantly associated with greater insulin sensitivity in childhood. Because obesity is one of the most important risk factors for cardiovascular diseases and type 2 diabetes, obese children, who are presumably at a higher risk, may be protected from these diseases by the phenotypic effect of the Ala 12 allele on insulin resistance (Buzzetti et al, 2006).

Based on the literature and proposed associations of the PPAR gene and the Pro12Ala allele polymorphism as a fat regulator gene, we decided to determine its allelic presence in a self-identified obese Dutch population.

B. The PPAR Gene polymorphisms in screened controls

In an attempt to evaluate the potential association of the Pro12Ala polymorphsm in peroxisome prolifeator-

activated receptor γ with our self-identified Dutch population, we decided to utilize literature controls as a comparative baseline frequency of the Ala allele. In our search, we could not find a study that screened for non-obese and related co-morbidities such as diabetes in a Dutch population. Thus we turned to a study involving a large population of Danish people.

The Pro12Ala polymorphism of PPAR-γ 2 has been shown to influence insulin sensitivity and the risk of type 2 diabetes in various ethnic populations. Frederiksen and colleagues examined in 2003 whether the polymorphism was related to the insulin resistance syndrome (IRS) among nondiabetic Danish subjects. The Pro12Ala variant was examined using PCR-restriction fragment length polymorphism in a phenotypically well characterized population-based sample of 2.245 nondiabetic subjects. The study participants were characterized by a number of anthropometric and biochemical measurements and the European Group for the Study of Insulin Resistance criteria enabling a classification of the study population in an IRS group and a non-IRS group. The allelic frequency of the Pro12Ala polymorphism in the total study sample was 14% (95% confidence interval, 13-15%). Two hundred ninety-four subjects fulfilled the European Group for the Study of Insulin Resistance criteria defining the IRS. The frequency of the Ala allele was 12.6% in the IRS group and 14.2% among subjects classified as not having the IRS (P = 0.15). However, the frequency of the variant in the homozygous form was significantly lower in the IRS group [0.7% (0-1.6%)] compared with the frequency in the non-IRS group [2.8% (2.1-3.5%); P = 0.02; odds ratio, 0.24 (0.06-0.99)]. Moreover, in the total study population, homozygous carriers of the variant had lower levels of fasting serum triglyceride [1.1 +/- 0.4 mmol/liter (means +/- SD) vs. 1.4 +/- 0.9 mmol/liter; P = 0.04] and a lower diastolic blood pressure (79 +/- 8 mm Hg vs. 82 +/- 11 mm Hg; P = 0.01) compared with wild-type carriers. The same tendency was observed with regard to the homeostasis model assessment estimate of insulin resistance (P = 0.16).

We are cognizant that utilization of this control sample may impact future results and thus, these following results should be interpreted with caution and must await further controlled studies on non-obese and non-IRS Dutch subjects. In this regard, it is noteworthy that the X/Ala frequency varies amongst ethnic groups (Asian lean individuals show only a 5% frequency (Kahara et al, 2003) and studies on lean Caucasians moderately varied whereby one study (n=280) showed an Ala frequency of 15% (Vaccaro et al, 2000).

II. Materials and Methods

A. Subjects

In this observational study, a total of 1,058 subjects were genotyped in the nutrigenomics laboratory of Salugen, Inc. (San Diego, CA). Each Caucasian subject self-identified themselves as obese or overweight by selecting GenoTrim™, a DNA-customized nutraceutical as a potential adjunct to their weight loss efforts. The participants filled out a cross sectional questionnaire related to obesity. The subjects are part of the Dutch Investigation to Evaluate Treatments of DNA-customized nutritional solutions for weight management (D.I.E.T.) Study.

B. Genotyping

Each subject was genotyped for the allelic presence of the Peroxisome Proliferator-Activated Receptor-γ Gene Pro12Ala polymorphism (PPAR-γ Pro12Ala Allele).

DNA was isolated from buccal cells by standard techniques and the Pro-12Ala polymorphism was detected by the PCR utilizing Taq-Man, standard PCR techniques, DNA sequencing and fragmentation that entered the study. The PCR conditions and primers used were those indicated by Hara and colleagues in 2000. The recommendations of Xu and colleagues in 2002 were followed for quality of genotype identification.

C. Statistics

The prevalence of these genotypes was measured against literature controls from independent, published clinical studies involving the same genetic mutation in a similar ethnic population. Statistical significance was performed by a biostatistician at Brooklyn College (NY) and determined using the Z-test for two independent proportions (Kanji, 1997).

III. Results

In this study, we compared the alleleic frequencies of the self-identified Dutch obese subjects with a well screened non-obese and non insulin resistant Danish control derived from the literature (Frederiksen et al, 2003).

The PPAR gene Ala allele polymorphic frequency was present in 25.05% of the study subjects (n=1.058) versus 14% of the literature controls (n=2,245). This difference was statistically significant (Z=17.398, p= 0.001) (**Figure 1**).

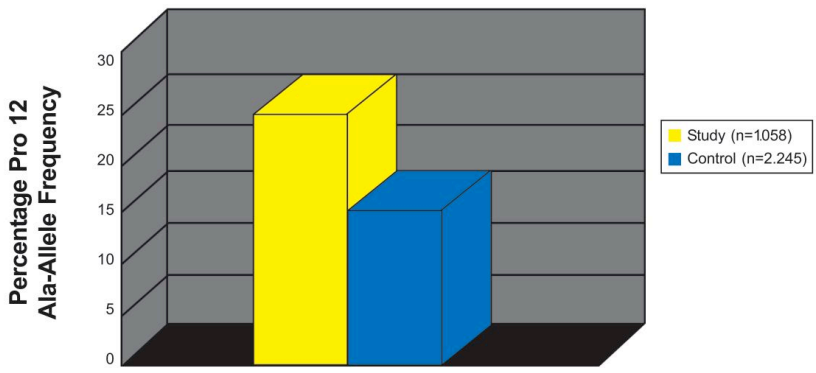

Figure 1. PPAR-γ gene frequency.

IV. Discussion

Our results suggest that in a highly motivated (wanting to loose weight) group of self-identified obese subjects (n=1.058) from the Netherlands, the Pro 12A1a polymorphism of the PPARG2 gene significantly associates with these individuals compared to non-obese controls (n=2.245) and may be considered as a risk factor.

While this is the first study to genotype highly motivated obese individuals of Dutch descent, many other studies have shown associations with the PPARG2 gene in related conditions. These include type 2 diabetes mellitus (Auboeuf et al, 1997; Rendell, 2004; Wang et al, 2004; Allen et al, 2006; Bergeron et al, 2006; Cecile et al, 2006; Hansen et al, 2006; Soriguer et al, 2006); down regulation of glucose (Roduitt et al, 2000; Xu et al, 2006); childhood obesity (Scaglioni et al, 2006); adiposity (Meng et al, 2002; Kepez et al, 2006); lymphocyte survival (Jo-SH et al, 2006); reduction of obesity-related inflammation in adipose tissue (Tsuchida et al, 2005) and adipocyte differentiation (Huang et al, 2006).

While there have been a number of earlier studies that reveal a significant association of the Ala allele in obesity and related problems, this is the first study to genotype a rather large self-identified and highly motivated Dutch population.

Information derived from this and other studies will further our knowledge related to obesity and the potential development of DNA directed personalized therapeutics to treat obesity as a disease involving neurologic, metabolic, and genetic factors (Blum et al, 2006).

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