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PPARα gene polymorphisms modulate the association between physical activity and cardiometabolic risk

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Abstract *Background and aims:* Habitual physical activity is understood to help prevent type 2 diabetes and atherosclerotic cardiovascular disease via beneficial effects on both metabolism and the vascular system. However, individuals do not have uniform cardiometabolic responses to physical activity. Here we explore the extent to which variation in the proliferator-activated receptor-alpha (*PPARα*) gene, which modulates carbohydrate and lipid metabolism, vascular function, and inflammation, predicts the overall cardiometabolic risk (CMR) profile of individuals engaging in various levels of physical activity.
Methods and results: 917 unrelated, community volunteers (52% female, of Non-Hispanic European ancestry) aged 30–54 years, participated in the cross-sectional study. Subjects were genotyped for 5 single nucleotide polymorphisms in the *PPARα* gene, from which common haplotypes were defined. A continuous measure of CMR was calculated as an aggregate of 5 traditional risk factors: waist circumference, resting blood pressure, fasting serum triglycerides, HDL-cholesterol and glucose. Regression models were used to examine the main and interactive effects of physical activity and genetic variation on CMR. One common *PPARα* haplotype (H-23) was associated with a higher CMR. This association was moderated by daily physical activity ($B = -0.11$, SE $= 0.053$, $t = -2.05$, $P = 0.04$). Increased physical activity was associated with a steeper reduction of CMR in persons carrying the otherwise detrimental H-23 haplotype.
Conclusions: Variations in the *PPARα* gene appear to magnify the cardiometabolic benefits of habitual physical activity.

Introduction

The metabolic syndrome represents a covarying cluster of risk factors that together increase the risk for type II diabetes and cardiovascular disease [1]. Obesity, aging, physical inactivity, unhealthy diet, insulin resistance and genetics are all potential causes underlying cardiometabolic disruptions, which often require multiple treatment strategies since no single medication can treat this condition [2]. Hence lifestyle related changes are recommended as the primary treatment strategy [1]. Regular aerobic physical activity has salutary effects on the individual components [3] and the syndrome [4].

Metabolic syndrome has a complex etiology determined by the interplay between genetic and non-genetic components. Heritability of the syndrome ranges between 10% and 30% [5] and several genes, mostly in energy

Abbreviations: CMR, cardiometabolic risk; IRB, Institutional Review Board; HDL, high density lipoprotein; *PPARα*, peroxisome proliferator activated receptor α; BP, blood pressure; SNP, single nucleotide polymorphism; PCR, polymerase chain reaction; FDR, false discovery rate; F_{st}, fixation index.

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metabolism pathways, have been implicated in its pathophysiology [5,6]. The peroxisome proliferator-activated receptors (PPARs) are a family of ligand-activated nuclear transcription factors which are key mediators of energy homeostasis, lipid and glucose metabolism, vascular function and inflammation [7]. The PPARα isoform is encoded by the *PPARα* gene; is robustly expressed in tissues with elevated fatty acid catabolism and regulates transcription of multiple genes involved in glucose metabolism [8] and in transport and oxidation of fatty acids (e.g., *LPL, APOA1)* [9]. Fibrates, which act as PPARα agonists, have a well-established role in lowering triglycerides and in increasing HDL levels in humans [10]. *PPARα* gene polymorphisms are associated with many cardiometabolic disturbances [8,11–14]. Consequently, *PPARα* has emerged as an important candidate gene underlying the development of the metabolic syndrome. Since physical activity and PPARα both affect lipid and glucose metabolism and vascular function understanding how they influence cardiometabolic risk (CMR) in relation to one another is important. We hypothesized that previously implicated genetic variation in *PPARα* [8,11–14] may jointly moderate the association between habitual physical activity and CMR.

Methods

Study population

Participants were from the University of Pittsburgh Adult Health and Behavior registry [9] – a compendium of behavioral and biological measurements collected on midlife community volunteers recruited via mass-mail solicitation from Southwestern Pennsylvania between 2001 and 2005. Exclusionary criteria included reported history of atherosclerotic cardiovascular disease, chronic kidney or liver disease, cancer treatment in the preceding year, major neurological disorders, schizophrenia or other psychotic illness, pregnancy and using insulin, glucocorticoid, antiarrhythmic, psychotropic, or prescription weight-loss medications. The study was approved by the University of Pittsburgh IRB and informed consent was obtained from participants prior to research. Data was collected in multiple laboratory sessions. Of the 1295 adults (30–54 years of age) who were recruited, the current investigation included 936 individuals of European ancestry who were not using antihypertensive, lipid-lowering or diabetes medications, not missing any outcome or covariate data, had valid calls for 3 of 5 SNPs genotyped and scored above 80 on normed cognitive index scores.

Risk factor assessments

Participants arrived at the laboratory between 0730 and 1030 h following an overnight fast, avoided exercise for 12 h, alcohol for 24 h and nicotine for 1 h prior to arrival. In the first visit the project nurse completed a medical history and medication use interview, obtained measurements of height, weight and waist circumference (at the umbilicus). Subjects rested in a seated position for at least 10 min, after which two blood pressure (BP) measurements were obtained by trained staff using a mercury sphygmomanometer and appropriately-sized cuff. Resting BP was measured similarly on a second occasion, providing a total of 4 readings from which an average was calculated. Following phlebotomy, a portion of the blood sample was used to collect plasma which was stored at −80 °C and used to determine fasting serum lipids and glucose levels using previously described protocol [15]. A second portion of the blood sample was collected in EDTA treated tubes and stored at −80 °C for DNA isolation. Smoking status was assessed as ever smoked vs. never smoked and used as a binary variable. Years of education was used as a surrogate measure of socioeconomic status.

Whereas the metabolic syndrome is customarily defined as present or absent based on 5 dichotomized risk factors, quantification of cardiometabolic risk from these same 5 risk factors as a continuous index has more power [4,16] and better predicts cardiovascular disease events [17]. Accordingly, we defined a composite cardiometabolic risk (CMR) index for each individual using the components of the metabolic syndrome. For these computations, mean blood pressure (BP) was estimated using the formula {(systolic BP + 2*Diastolic BP)/3}, triglycerides and glucose values were log normalized, HDL-cholesterol was multiplied by −1, waist circumference was untransformed. Each risk factor was mean standardized and a composite risk score was calculated as the mean of the 5 standardized risk factors and restandardized prior to statistical analysis.

Routine physical activity was assessed using the Paffenbarger Physical Activity Questionnaire [18]. This eight question survey measures walking, stair-climbing and leisure time sports and exercise activities from which physical activity-related energy expenditure (kcal/week) is estimated. The scale was log normalized prior to statistical analysis. Details on the validity of this scale are provided in the Supplementary Material.

Genotyping

Taqman SNP genotyping assays were used to genotype five *PPARα* SNPs: rs1800206C > G (L162V), rs135542A > G, rs135539A > C, rs4253728 G > A, rs4253778 G > C, which have previously been associated with obesity, diabetes and cardiovascular risk [8,11–14]. Genotypes were scored by allelic discrimination using the ABI 7900HT Fast Real-Time PCR system and the SDS 2.2 software (Applied Biosystems, Foster City, CA). To examine whether substantial genetic heterogeneity exists in the study population we examined a panel of 15 markers spread across the genome (rs1022106, rs1335995, rs1439564, rs1502812, rs1860300, rs548146, rs705388, rs715994, rs720517, rs722743, rs730899, rs734204, rs9059966, rs1328994, rs1485405). These markers were previously genotyped in all the participants who enrolled in the registry and have been used to control for genetic stratification in all studies from this cohort [9].