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A prevalent caveolin-1 gene variant is associated with the metabolic syndrome in Caucasians and Hispanics

Rene Baudrand[a,b], Mark O. Goodarzi[c], Anand Vaidya[a], Patricia C. Underwood[a], Jonathan S. Williams[a], Xavier Jeunemaitre[d], Paul N. Hopkins[e], Nancy Brown[f], Benjamin A. Raby[g], Jessica Lasky-Su[g], Gail K. Adler[a], Jinrui Cui[c], Xiuqing Guo[h], Kent D. Taylor[h], Yii-Der I. Chen[h], Anny Xiang[i], Leslie J. Raffel[j], Thomas A. Buchanan[k], Jerome I. Rotter[h], Gordon H. Williams[a,1], Luminita H. Pojoga[a,*,1]

[a] Division of Endocrinology, Diabetes and Hypertension, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA 02115, USA
[b] Department of Endocrinology, School Of Medicine, Pontificia Universidad Catolica De Chile, Santiago 8330074, Chile
[c] Division of Endocrinology, Diabetes and Metabolism, Cedars-Sinai Medical Center, Los Angeles, CA 90048
[d] Centre Investigation Clinique, Assistance Publique- Georges Pompidou; Institut National de la Sante et de la Recherche Medicale, Unite Mixte de Recherche en Sante 970, Universite Paris Descartes, Paris 75014, France
[e] Cardiovascular Genetics Research Unit, University of Utah School of Medicine Salt Lake City, Utah 84112
[f] Vanderbilt University Medical Center, Nashville, TN 37232
[g] Channing Division of Network Medicine, Brigham and Women's Hospital, Boston, MA 02115
[h] Institute for Translational Genomics and Population Sciences and Department of Pediatrics, Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, Torrance, CA 90502
[i] Research and Evaluation Branch, Kaiser Permanente of Southern California, Pasadena, CA 91188
[j] Medical Genetics Research Institute, Cedars-Sinai Medical Center, Los Angeles, CA 90048
[k] Departments of Medicine and Physiology and Biophysics, University of Southern California Keck School of Medicine, CA 90033

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ABSTRACT

Context and objective. We examined whether a prevalent caveolin-1 gene (CAV1) variant, previously related to insulin resistance, is associated with metabolic syndrome (MetS).

Patients and methods. We included subjects genotyped for the CAV1 variant rs926198 from two cohorts: 735 Caucasians from the HyperPATH multicenter study, and 810 Hispanic participants from the HTN–IR cohort.

Results. Minor allele carriers from HyperPATH cohort (57% of subjects) had higher Framingham risk scores, higher odds of diabetes (10.7% vs 5.7%, $p = 0.016$), insulin resistance (44.3% vs 35.1%, $p = 0.022$), low HDL (49.3% vs 39.6%, $p = 0.018$) and MetS (33% vs 20.5%, $p < 0.001$) but similar BMI. Consistently, minor allele carriers exhibited higher odds of MetS, even when adjusted for confounders and relatedness (OR 2.83 (1.73–4.63), $p < 0.001$). The association with MetS was replicated in the Hispanic cohort HTN–IR (OR 1.61, [1.06–2.44], $p = 0.025$). Exploratory analyses suggest that MetS risk is modified by a CAV1

Abbreviations: MetS, metabolic syndrome; CAV1, caveolin-1; HOMA, homeostasis model assessment; IR, insulin resistance; eQTL, expression quantitative trait locus; KO, knockout.

* *Corresponding author at:* Division of Endocrinology, Diabetes and Hypertension, Brigham and Women's Hospital, Harvard Medical School, 221 Longwood Avenue, Boston MA 02115. Tel.: +1 617 278 0415; fax: +1 617 732 5764.
E-mail address: lpojoga@partners.org (L.H. Pojoga).

[1] Both authors contributed equally to the manuscript.

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variant–BMI status interaction, whereby the minor allele carrier status strongly predicted MetS (OR 3.86 [2.05–7.27], p < 0.001) and diabetes (OR 2.27 [1.07–4.78], p = 0.03) in non-obese, but not in obese subjects. In addition, we observed a familial aggregation for MetS diagnosis in minor allele carriers.

Conclusion. The prevalent *CAV1* gene variant rs926198 is associated with MetS in separate Caucasian and Hispanic cohorts. These findings appear to be driven by an interaction between the genetic marker and obesity status, suggesting that the *CAV1* variant may improve risk profiling in non-obese subjects. Additional studies are needed to confirm the clinical implications of our results.

1. Introduction

The metabolic syndrome (MetS) is a composite of central obesity, hyperglycemia/insulin resistance (IR), dyslipidemia and hypertension that is highly prevalent worldwide [1]. MetS is also associated with all-cause mortality, myocardial infarction, and stroke in subjects with and without diabetes [2]. Interestingly, current evidence shows that metabolically unhealthy normal-weight individuals have similar mortality and cardiovascular disease risk compared with metabolically unhealthy overweight or obese persons [3,4]. These prospective observations suggest that individual cardiometabolic risk should involve more in-depth considerations than body-mass index (BMI) alone.

Our group has previously described that variations in the CAV1 gene were associated with IR in hypertensive humans, consistent with our bench studies that demonstrated that CAV1 deficiency in mice leads to abnormal glucose metabolism and hyperinsulinemia [5–7]. CAV1, the main component of plasma membrane caveolae, has been widely studied in cardiovascular and kidney tissues for its critical role in signal transduction and trafficking, and also for its interplay with steroid receptors and ion channel activation [5]. In adipose tissue, caveolae are typically abundant, occupying up to 30% of the surface area, and have been shown to regulate adipocyte differentiation, transport and lipid droplet formation [8]. Of note, CAV1 knockout mice display abnormal glucose tolerance, hypertension and dyslipidemia despite a lean body habitus. Also, humans with undetectable CAV1 expression due to severe CAV1 gene (*CAV1*) mutations display a lipodystrophic phenotype associated with insulin resistance, acanthosis nigricans, diabetes mellitus, and hypertriglyceridemia, suggesting that *CAV1*-related metabolic disorders may be secondary to adipocyte dysfunction rather than to increased fat mass [8–10].

In the present study, we tested the hypothesis that a prevalent *CAV1* variant is associated with MetS. We investigated this hypothesis in a large Caucasian cohort with subsequent replication in a Hispanic cohort; in contrast to our previous report [5], the current analysis included not only hypertensives, but also normotensives and diabetics. We further performed exploratory analyses to investigate the role of this *CAV1* variant in (1) predicting MetS in non-obese individuals and (2) in familial aggregation for MetS diagnosis.

2. Methods

2.1. *HyperPATH Protocol (Caucasian Cohort)*

Participants were selected from the HyperPATH Cohort, a protocol that controls for factors that influence the renin–angiotensin–aldosterone system (RAAS). A total of 735 Caucasian adults with available genotype were included in the analysis. All participants were studied under a common protocol in Clinical Research Centers located at Brigham and Women's Hospital (Boston, MA), University of Utah Medical Center (Salt Lake City, UT), Vanderbilt University Medical Center (Nashville, TN), Hospital Broussais (Paris, France), and San Salvatore Hospital (Rome, Italy).

HTN was defined as described previously [11]. Type 2 diabetes mellitus and prediabetes were defined as per American Diabetes Association criteria [12]. IR estimation was calculated by HOMA-IR and IR as a categorical variable considering the upper quartile of HOMA-IR in the HyperPATH Cohort (HOMA-IR ≥2.8). As previously published by our group and following World Health Organization suggestions, to be diagnosed with MetS a participant needed to have diabetes, prediabetes or IR plus ≥2 of the following characteristics: 1) HTN, 2) dyslipidemia (triglyceride measurement ≥150 mg/dL or high-density lipoprotein <35 mg/dL in men and <39 mg/dL in women), or 3) BMI ≥30 kg/m^2 and/or waist: hip ratio >0.9 in men, >0.85 in women [11,13]. Sensitivity analysis using the harmonized MetS criteria was also performed [14]. Participants were also classified as "metabolically unhealthy normal-weight" if they presented MetS with a BMI in the 20–27 kg/m^2 range as proposed in non-Asian subjects [15,16].

Framingham risk score and laboratory analyses were performed using standardized and validated methods, as previously described [11].

2.2. *The HTN–IR Cohort and Study Protocol (Hispanic Cohort)*

Hispanic subjects with available genotype (810 participants) were analyzed from the Mexican–American Hypertension–Insulin Resistance (HTN–IR) cohort and recruited through the Hypertension Clinic at Los Angeles County, University of Southern California Medical Center or the Clinical Research Center at the University of California [17]. The criteria for MetS diagnosis were the same as outlined above for Caucasian