Genetic variants in the *SLC16A11* gene are associated with increased BMI and insulin levels in nondiabetic Chilean population

Lorena Mardones[1]
https://orcid.org/0000-0001-8037-4296

Fanny Petermann-Rocha[2,3]
https://orcid.org/0000-0002-4384-4962

Maria Adela Martinez-Sanguinetti[4]
https://orcid.org/0000-0002-7609-7705

Ana Maria Leiva[5]
https://orcid.org/0000-0001-8390-6366

Claudia Troncoso-Pantoja[6]
https://orcid.org/0000-0002-8433-5750

Miquel Martorell[7]
https://orcid.org/0000-0003-3183-7623

Nicole Lasserre[8]
https://orcid.org/0000-0002-7217-5198

Natalia Ulloa[9]
https://orcid.org/0000-0002-0437-5016

Francisco Perez-Bravo[10]
https://orcid.org/0000-0002-5660-5717

Carlos Celis-Morales[2,11]
https://orcid.org/0000-0003-2612-3917

Marcelo Villagran[1]
https://orcid.org/0000-0003-3645-5659

on behalf of the ELHOC group (Epidemiology of Lifestyle and Health Outcomes in Chile)

[1] Departamento de Ciencias Básicas, Universidad Católica de la Santísima Concepción, Concepción, Chile
[2] BHF Glasgow Cardiovascular Research Centre, Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, United Kingdom
[3] Institute of Health and Wellbeing, University of Glasgow, Glasgow, United Kingdom
[4] Instituto de Farmacia, Universidad Austral de Chile, Valdivia, Chile
[5] Instituto de Anatomía, Histología y Patología, Universidad Austral de Chile, Valdivia, Chile
[6] Centro de Investigación en Educación y Desarrollo, Departamento de Salud Pública, Universidad Católica de la Santísima Concepción, Concepción, Chile
[7] Departamento de Nutrición y Dietética, Facultad de Farmacia, Universidad de Concepción, Concepción, Chile
[8] Escuela de Nutrición y Dietética, Universidad Santo Tomas, Sede los Ángeles, Chile
[9] Centro de Vida Saludable, Departamento de Bioquímica Clínica e Inmunología, Facultad de Farmacia, Universidad de Concepción, Concepción, Chile
[10] Instituto de Nutrición y Tecnología de Alimentos (INTA), Universidad de Chile, Santiago, Chile
[11] Human Performance Lab, Education, Physical Activity and Health Research Unit, University Católica del Maule, Talca, Chile

Correspondence to:
Marcelo Villagran
Universidad Católica de la Santísima Concepción
Alonso de Ribera, 2850,
Concepción, Chile
marcelo.villagran@ucsc.cl

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ABSTRACT

Objective: To study the association of *SLC16A11* gene variants with obesity and metabolic markers in nondiabetic Chilean adults. **Materials and methods:** This cross-sectional study included 263 nondiabetic adults. The genotype of the rs75493593 polymorphism of SLC16A11 gene was performed by real-time PCR. It's association with adiposity markers (body weight, BMI, waist circumference and fat mass percentage), metabolic markers (glucose, insulin, $HOMA_{IR}$, leptin, total cholesterol, LDLc, HDLc, triglycerides, ALT, GGT and hsCRP) and blood pressure was analyzed by linear regression. **Results:** The minor allele (T) of the *SLC16A11* gene (rs75493593) has a frequency of 29.7% among Chileans. Risk genotypes (GT and TT) were associated with a significant 1.49 mU/l increase in plasmatic insulin for each copy of the minor allele (95% CI: 0.12, 2.87, $p < 0.05$). This association remained significant after adjusting for socio-demographic variables, physical activity and smoking (1.36 mU/l, 95% CI: 0.16, 2.58 $p < 0.05$), but was lost when BMI was included as a confounding factor. Higher BMI was also significantly associated with polymorphic genotypes in *SLC16A11*, independent of socio-demographic variables. **Conclusion:** The minor allele of the *SLC16A11* gene (T) is highly prevalent among Chileans and is associated with increased insulin and BMI in nondiabetic individuals. These findings suggest that the genetic variant in *SLC16A11* is not only associated with type 2 diabetes as previously shown in Mexicans, but is also related to early metabolic alterations in healthy subjects that may lead to type 2 diabetes. Arch Endocrinol Metab. 2021;65(3):305-14

Keywords
SLC16A11; diabetes mellitus type 2; obesity; monocarboxylate transporter; hyperinsulinemia

INTRODUCTION

Obesity has been identified as a major modifiable risk factor for type 2 diabetes (T2D). Pathophysiological conditions that occur with obesity, like low-grade inflammation, increased plasmatic-free fatty acids and insulin resistance, are directly related to the pathogenesis of T2D (1). As a reflection of the close interrelationship between these two conditions, it has been reported that more than 80% of people with T2D are overweight or obese (2). Furthermore, worldwide trends in the prevalence of T2D have closely mirrored those of obesity, doubling from 1980 to 2014 (3).

There are important differences in the prevalence of T2D among populations. Mexico and some Caribbean nations have over a 14.5% prevalence, which are the highest in the North American continent (4). In South America, Chile leads in T2D prevalence at 12.3%, according to the latest national health survey (5). Culturally-based lifestyle differences are a major contributor to the different prevalence of T2D among populations, including nutrition, physical activity and sedentarism. However, genetic variability related to ethnicity is also likely because the heritability of T2D and obesity has been estimated to be between 40% and 70% (6,7).

Genome-wide association studies (GWAS) for diabetes and obesity have been conducted mainly with European populations, revealing that both pathologies are highly polygenic and share some genetic determinants (6,7). For instance, the single nucleotide polymorphism (SNP) rs9939609 in the *FTO* gene has been identified as a common risk factor for obesity and T2D in several populations, including Chileans (8,9). Subsequent studies with non-European groups have discovered additional genetic variants with low prevalence among Europeans, but that are highly associated with T2D in other populations (10,11). For example, a haplotype of 5 SNPs in the *SLC16A11* gene was found in association with a 22% increase in T2D incidence in a Mexican population (12). Interestingly, this haplotype has a frequency of 50% in Mexican Native Americans but less than 1% in Europeans and Africans, therefore it was suggested that the haplotype may represent a common genetic T2D-susceptibility variant for Latin Americans (12). Although the association was later confirmed for Mexicans in the HCHS/SOL cohort, it was not replicated for other Latin American groups like Caribbeans, Central Americans or South Americans, even after the exclusion of young controls and adjustment for BMI (13). Subsequent in vitro studies have shown that the haplotype affects the aminoacidic sequence of the gene product, the monocarboxylate transporter type 11, which is most abundantly expressed in the thyroid gland and liver (14). In the latter tissue, these gene variants provoke reduced expression levels and impaired translocation of the transporter to plasma membrane, leading to intracellular accumulation of triglycerides (14).

Due to the high prevalence of obesity and T2D among Chileans and the heterogenic effect of the haplotype on T2D in different Hispanic groups, we studied the association of *SLC16A11* with adiposity and metabolic markers, using the rs75493593 SNP as a proxy for the 5 SNP haplotype in healthy Chilean adults.

MATERIALS AND METHODS

The complete sample was composed of 472 individuals from the GENADIO study, but only 263 of them had information regarding the rs75493593 genotype in the *SLC16A11* gene. The GENADIO project was approved by the ethics committees of University of Concepcion, University of Chile and University of Glasgow; and took place between 2009 and 2011. The objective was to evaluate the prevalence of risk factors for cardiovascular diseases in Chile (15). The studied population included individuals of Mapuche and European descent living in the Biobío and Los Ríos regions. The Mapuche are the most populous indigenous group in Chile, accounting for a 79.8% of the indigenous people in the country (16). Individuals were selected who had no history of metabolic or cardiovascular disease or use of prescribed drugs (15).

Allelic variant determination of *SLC16A11* gene

Allelic variants of the SNP rs75493593 in the *SLC16A11* gene were determined in genomic DNA isolated from blood leukocytes through QIAamp DNA Blood Midi Kit (QUIAGEN, Ltd, UK). Alleles were identified through real time PCR on an ABI 7900-HT thermocycler, using TaqMan pre-designed SNP genotyping assay with specific probes. All of the analyses were performed in duplicate, with a 98% of reproducibility.

Adiposity markers

The anthropometric measurements were taken by trained personnel using standardized protocols (17). Body weight and height were determined with an