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Research paper

Association of Native American ancestry and common variants in *ACE*, *ADIPOR2*, *MTNR1B*, *GCK*, *TCF7L2* and *FTO* genes with glycemic traits in Colombian population

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ABSTRACT

Insulin resistance and defects in other related glycemic traits are common findings in the context of Metabolic Syndrome. Although genetic factors are clearly implied in susceptibility, and some gene variants have been identified mainly in populations of European ancestry, little is known about this aspect in admixed populations. The association of insulin resistance, β-cell function, fasting insulin and glucose levels with 48 gene variants, previously related to metabolic syndrome components, and with the ancestral genetic composition, estimated on 50 ancestry informative markers, was evaluated in 417 individuals from the Colombian admixed population. The Native American genetic ancestry was associated with a low β-cell function (odds ratio (OR) of 1.73 and 95% confidence interval (95% CI) of 1.07–2.81, $p = 0.026$). Significant genotypic associations were obtained (q-*value* < 0.05) for gene variants in *ACE* (rs4340; OR (95% CI): 2.79 (1.58–4.91), insulin resistance; mean difference (95% CI): 0.273 (0.141; 0.406), fasting insulin), *ADIPOR2* (rs11061971; OR (95% CI): 0.14 (0.04–0.48), low β-cell function), *MTNR1B* (rs10830963; mean difference (95% CI): 0.032 (0.013; 0.051), fasting glucose) and *GCK* (rs4607517; mean difference (95% CI): 0.038 (0.020;0.056) and rs1799884; mean difference (95% CI): 0.027 (0.013–0.041), fasting glucose). Also the well-known gene variants rs7903146 in *TCF7L2,* and rs17817449 in *FTO*, were nominally associated with hyperglycemia (rs7903146), as well as with higher fasting insulin levels (rs17817449). Our findings indicate that gene variants in *ACE*, *ADIPOR2*, *MTNR1B*, *GCK*, *TCF7L2* and *FTO*, are associated with glycemic traits in the admixed Colombian population, while a higher Native American genetic component is related to lower β-cell function.

Abbreviations: ACE, angiotensin converting enzyme; *MTNR1B*, melatonin receptor 1B; *GCK*, glucokinase; *TCF7L2*, transcription factor 7 Like 2; *FTO*, alpha-ketoglutarate dependent dioxygenase; OR, odds ratio; IR, insulin resistance; T2D, type 2 diabetes; MS, metabolic syndrome; GWAS, genome wide association study; BMI, body mass index; HOMA-IR, Homeostatic Model Assessment for insulin resistance; HOMA-%B, Homeostatic Model Assessment for β-cell function; HOMA, Homeostatic Model Assessment; PCR, polymerase chain reaction; PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism; AIMs, ancestry informative markers; INDEL, insertion/deletion; HWE, Hardy-Weinberg Equilibrium; SES, socio-economical status; IQR, interquartile range; FDR, false discovery rate; CI, confidence interval; SE, standard error; *LEPR*, leptin receptor; *ADIPOR1*, adiponectin receptor 1; *CLOCK*, clock circadian regulator; *ADIPOQ*, adiponectin; *ADIPOR2*, adiponectin receptor 2; *KLF14*, Kruppel Like Factor 14; PI3K, phosphatidylinositol-3-kinase; AMPK, AMP-activated protein kinase; MAPK, mitogen-activated protein kinase; ERK1/2, extracellular signal-regulated kinases 1/2; RAAS, renin-angiotensin-aldosterone system; PCOS, polycystic ovary syndrome; LD, linkage disequilibrium; GLP-1, glucagon-like peptide 1; GIP, gastric inhibitory peptide; *IRX3*, Iroquois homeobox 3; FOXO, Forkhead Box O; *GCKR*, glucokinase regulator; *IRS1*, insulin receptor substrate 1

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1. Introduction

Insulin resistance (IR) and β-cell function defects are hallmarks of type 2 diabetes (T2D) development (American Diabetes Association, 2012) and common findings in other metabolic syndrome (MS) components such as obesity, hypertension and dyslipidemia (Wallace and Matthews, 2002). Due to this tight relationship some researchers consider IR as the convergence point which underlies MS (Alberti et al., 2005; Reaven, 1988), a diagnostic category grouping, in some countries, about 30% of population (Rochlani et al., 2015). This high prevalence has aroused great interest in the identification of risk factors, including those of genetic origin, that favor IR development, as well as other glucose homeostasis defects (Dupuis et al., 2010a).

In recent years, many genome wide association studies (GWAS) for T2D, and other phenotypes related to glucose homeostasis, have been performed, mainly in populations of European ancestry. These studies have allowed the identification of some genes involved in those phenotypes, and although they have been less successful in the identification of IR related genes, these have contributed to reveal the essential role of β-cell functioning in hyperglycemia and T2D physiopathology (Dupuis et al., 2010a; Scott et al., 2012). Despite their relevance, these findings, cannot be extrapolated to other populations due to dissimilarities in culture, demographic and evolutionary processes, as well as to differential influence of IR and β-cell dysfunction on the expression of MS associated disturbances (Trikudanathan et al., 2013).

Most Latin American populations, including Colombians, are the result of recent genetic admixture between Native Americans, Europeans and Africans, in proportions varying among regions and individuals in the same country (Moreno-Estrada et al., 2013). This variability in genetic composition, coupled with physiological differences among parental populations could modify, in the admixed population, the contribution of each parental population to the genetic risk, as well as the magnitude and direction of allelic and/or genetic associations previously reported in populations of diverse origins.

Here we performed a genetic association analysis using IR and β-cell function surrogate measures, and other glycemic traits (fasting glucose and insulin levels), in order to identify genetic determinants contributing to glycemic traits in the admixed Colombian population, taking into consideration the effect of the ancestral genetic composition on the expression of the analyzed phenotypes.

2. Materials and methods

2.1. Study population

471 adults from the Colombian provinces of Antioquia, Bolívar and Nariño were enrolled independently of their health status. All participants completed a questionnaire assessing information about their personal and family medical history, as well as sociodemographic and lifestyle aspects. Blood samples were collected for biochemical and genetic analysis. Insulin resistant (IR)/non insulin resistant (Non IR) and low β-cell function (Low%B)/high β-cell function (High %B) individuals were defined based on the distribution of the Insulin resistance and β-cell function indexes as described in (Caro-Gomez et al., 2017) and in Section 2.3 below. All participants agreed to join the study and signed an informed consent previously approved by the Ethics Committee of the *Universidad de Antioquia* in compliance with the Helsinki declaration guidelines.

2.2. Anthropometric and biochemical analysis

Body mass index (BMI) was calculated as kg/m^2; to this end weight and height were measured without shoes, in light clothing, keeping the body to maximum extension and with the head in an upright position. Waist circumference was measured using a metric tape at the midpoint between the coastal ridge and the iliac crest. Plasmatic levels of glucose and insulin were determined as single measurements after a 12 h fasting and no alcohol consumption the day before.

2.3. Estimation of insulin resistance and β-cell function

Insulin resistance index (HOMA-IR) and β-cell function (HOMA-%B) were estimated indirectly based on fasting insulin and glucose levels under the Homeostatic Model Assessment (HOMA) using the HOMA Calculator v2.2.2 software (http://www.dtu.ox.ac.uk/homacalculator/, University of Oxford), an updated version of the original model proposed by Matthews et al. (1985) which offers non-linear exact solutions for the model. Based on these measurements, insulin resistant individuals were identified as those with HOMA-IR values above the 75th per-centile of the distribution of this measure within a reference subgroup taken from the sample, individuals ($n = 358$) with a BMI ranging from 18.5 to 30 kg/m2, fasting glucose levels lower than 100 mg/dL, without a previous diagnostic of T2D, hypertension or thyroid disease, according to Buccini and Wolfthal (2008) (Buccini and Wolfthal, 2008). For HOMA-%B the value corresponding to 25th percentile of the respective distribution was taken as a reference, in this case HOMA-%B values below this cut-off point were taken as indicative of secretory deficit (Buccini and Wolfthal, 2008). According to these criteria, for this sample, participants with HOMA-IR > 1.3 and HOMA-%B < 88% were insulin resistant (IR) and had low β-cell function (Low %B), respectively.

2.4. Genotyping

DNA was extracted from whole blood using the phenol-chloroform standard method (Sambrook et al., 1989). Forty-eight variants in or near to thirty-two genes previously reported to be associated with metabolic syndrome components in candidate gene association studies, GWAS and/or meta-analysis (Table S1, supplementary material) were selected. Variant genotyping was performed by polymerase chain reaction (PCR), polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP), or by allelic discrimination method using KASPar technology (LGC, Middlesex, UK) (Table S1, Supplementary material).

European, Native American, and African ancestries were estimated using a panel of 50 ancestry informative markers (AIMs) (Table S2, Supplementary material). These markers were selected, based on their discrimination power among parental populations, from Latino populations panels reported by Parra et al. (1998), Shriver et al. (2003) and Molokhia et al. (2003), as well as from Marshfield Diallelic Insertion/Deletion Polymorphisms (Weber et al., 2002) and Retrotransposon Insertion Polymorphisms in humans (dbRIP) (Wang et al., 2006) databases. AIMs genotyping was performed by PCR, PCR-RFLP or PCR and capillary electrophoresis on an ABI-PRISM 310 genetic analyzer (Perkin Elmer – Applied Biosystems), according to the type of marker (single nucleotide variant or insertion/deletion (INDEL)) (Table S2, supplementary material).

Hardy-Weinberg Equilibrium (HWE) was calculated using GENEPOP 3.2a (Rousset, 2008) and Arlequin (Excoffier and Lischer, 2010). Only markers with a call rate over 80% and without significant deviations from HWE after Bonferroni correction and a minimum allele frequency > 1% were used for ancestry estimation and association analyses.

2.5. Statistical analysis

Statistical analyses were performed using the R package 2.14.1 (http://www.r-project.org/) (R Core Team, 2014) and PASW Statistics 18. Comparisons between Insulin resistant (IR)/non-insulin resistant (Non IR) and low β-cell function (Low%B)/high β-cell function (High %B) individuals for biochemical and anthropometric measurements, as well as for demographic parameters, were established using Mann-