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Discordance between allelic and genotype frequencies for CD36 rs3211938 between Mexican mestizo samples: sample bias, genotyping error, or microevolution?

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Discordancia entre frecuencias alélicas y genotípicas para CD36 rs3211938 entre muestras de mestizos mexicanos: ¿Sesgo de la muestra, error de genotipado o microevolución?

Sergio Flores[1], Ángel Roco-Videla[2,3], and Omar Silva-González[4]

[1]Dirección de Desarrollo y Postgrado. Universidad Autónoma de Chile. Santiago, Chile. [2]Programa de Mágister en Ciencias Químico-Biológicas. Facultad de Ciencias de Salud. Universidad Bernardo O'Higgins. Santiago, Chile. [3]Department of Civil Engineering. Facultad de Ingeniería. Universidad Católica de la Santísima Concepción. Concepción, Chile. [4]Facultad de Medicina Veterinaria y Agronomía. Universidad de las Américas. Santiago, Chile

Correspondence: Sergio Flores
e-mail: sergiovladimirflores@gmail.com

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Dear Editor-in-Chief,

The article published by Martín-Márquez et al. (1) shows evidence on the association between the GT CD36 rs3211938 genotype and high levels of glucose, ox-LDL, HDL-cholesterol, and IR, and increased BMI in Mexican mestizo T2DM (type-2 diabetes mellitus) patients from

western Mexico. The criteria used to define “mestizo” (2) allow further research to survey those statistical associations in other Latin American mestizo populations.

The cited work did not address the Hardy-Weinberg (H-W) equilibrium to contrast the concordance between allelic and genotype frequencies under the null hypothesis of absence of evolutionary factors operating on populations. The H-W test has been used to detect sampling bias (3) and genotyping errors (4). In addition, the allelic and genotype frequencies were not contrasted with data reported by other studies.

We collected information on the variation of CD36 rs3211938 from the public database 1000Genomes (1KG) (5; www.internationalgenome.org) and the allelic frequencies are different from those reported by Martín-Marquez et al. In the four Latin American population samples contained in 1KG (N = 692 individuals), including Mexico, Colombia, Peru, and Puerto Rico, only one allele G, from a Peruvian individual, was found. Thus, the frequency of the allele G is 0 % in Mexico and 0.0007 % in the pooled Latin American samples from 1KG. In Europe, East Asia, and South Asia that frequency is 0 % both in 1KG and the ALFRED database (6; https://alfred.med.yale.edu/alfred). In the article here discussed, the frequencies of G were 10.34 % and 25.44 % in the NT2DM (non-type-2 diabetes mellitus) and T2DM samples, respectively.

We analyzed genic differentiation using the exact G test implemented in Popgene (7). Significant differentiation was found between the three pairwise comparisons: NT2DM vs. TD2M, p = 0.02204; NT2DM vs. Mexico from 1KG (MXL), p = 0.00013; NT2DM vs. MXL, p = 0. Genotypic differentiation showed the same pattern: NT2DM vs. TD2M, p = 0.01100; NT2DM vs. MXL, p = 0.00010; NT2DM vs. MXL, p = 0.

Finally, the H-W equilibrium is rejected in the T2DM sample, showing heterozygote excess (Table I). In summary, our findings suggest a sample bias or genotyping error. An alternative, less plausible hypothesis is the occurrence of micro-evolutionary processes on CD36 rs3211938 in western Mexico, increasing the frequency of allele G and

heterozygosity. Further research is needed in order to understand the discordance between allelic and genotype frequencies observed in the article by Martín-Márquez et al., the differences among datasets, and their implications on the role of CD36 rs3211938 on the metabolic profile of Mexican mestizo populations.

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Table I. Hardy-Weinberg analysis for CD36 rs3211938 in Mexican mestizo populations

Sample	**Observed genotype frequencies (%)**			**Allele frequencies (%)**		**Expected genotype frequencies (%)**			**P_{chi}**	**P_{exact}**
	T/T	T/G	G/G	T	G	T/T	T/G	G/G		
NT2DM	46 (79.30)	12 (20.70)	0 (0)	104 (89.66)	12 (10.34)	46.62 (80.38)	10.76 (18.55)	0.62 (1.07)	0.680	1
T2DM	28 (49.10)	29 (50.90)	(0 (0)	85 (74.56)	29 (25.44)	31.69 (55.59)	21.62 (37.93)	3.69 (6.47)	0.036 *	0.0497 *
MXL	64 (100)	0 (0)	0 (0)	128 (100)	0 (0)	64 (100)	0 (0)	0 (0)	-	-

NT2DM: non-type-2 diabetes mellitus sample; T2DM: type-2 diabetes mellitus sample; *p value < 0.05; P_{chi} = p value for the Chi^2 test; P_{exact} = p value for the Fischer exact test implemented in Genpop.