

Letter to the Editor

Are the CYP2D6*G and MDR1, 3435T Alleles Associated with the Risk of Ulcerative Colitis in Iranian Population?

Sergio Alberto Ramirez Garcia, MD, PhD^{1,2}; Luis Javier Flores Alvarado, MD, PhD³; Luz Margarita Baltazar Rodríguez, MD, PhD⁴; Diana García Cruz, MD, PhD^{2*}

¹University of the Sierra Southern, SUNE0, Miahuatlán de Porfirio Díaz, Oaxaca, México

²Faculty of Medicine of the University of Colima, Colima, Mexico

³Laboratory of Biochemistry, Department of Molecular and Genomic Biology, University Center of Health Sciences, University of Guadalajara, Jalisco, Mexico

⁴Institute of Human Genetics Enrique Corona Rivera, Department of Molecular and Genomic Biology, University Center of Health Sciences, University of Guadalajara, Jalisco, Mexico

Dear Editor,

The paper published by Lotfi et al¹ concerning the public health of the Iranian population explores three polymorphisms of genes that code for proteins that contribute to drug-related treatment of ulcerative colitis (UC): CYP2D6, NAT2 and MDR1. We analyzed the data shown in Tables 2 and 3 of both cases and control subjects, using the Epi InfoOpen program of the CDC. We found that the allele CYP2D6*4 G variant is associated as a protective factor with the development of UC with $\chi^2=3.812$, $df=1$, $P=0.05088$, odds ratio (OR) = 0.8163 (95% CI= 0.6776–0.9834) (see Table 1), while the A allele was associated as a risk factor; $\chi^2=3.812$, $df=1$, $P=0.05088$, OR = 1.2251 (95% CI = 1.017–1.476). While Lotfi et al have only reported the allele A as a risk factor (OR = 1.56, $P=0.0471$), both results are important. Evaluating the effect of variation in a gene on a disease like UC can be achieved under five inheritance genetic models; dominant, recessive, co-dominant, overdominant, and paradominant, which Lotfi et al¹ do not present completely in the text.²⁻⁵ Table 2 only shows data for a co-dominant (AG vs. GG or AA vs. GG) and a recessive (AA+AG vs. GG) model. Therefore, we analyzed the distribution of genotypes by these five models for the polymorphisms CYP2D6 *A/G and N-acetyltransferase-2 (NAT2*7), A/G, but we only found a trend which shows that lack of two copies of G modifies the risk, $P=0.099552$ through the recessive model. Consistent with the results presented by Lotfi et al, no other epidemiological model was found with a trend or significant values.

Finally, in Table 5, Lotfi et al present six haplogroups; since result from the allelic construction of the loci or chromosomes.²⁻⁵ In addition to the work by Lotfi et al, we distributed the study groups in carriers of haplogroups with G allele in CYP4502D6, with G allele in NAT2*7

and T allele in MDR1, finding a trend as a protective factor haplogroups with G allele in NAT2*7, $P=0.08267$, ORR = 0.8151. These results suggest that the sample should be further expanded to analyze the epidemiological effect of NAT2 on the risk of UC. The lack of association with the polymorphism NAT2*7, A/G may be related to the loss of the Hardy-Weinberg equilibrium.^{2,3} This represents a bias in many association studies, since it is selected by traits, and is not analyzed first in a general population a small limitation of the study by Lotfi et al the polymorphism MDR1 3435T/C could not be analyzed, because the authors did not present the results of their genotypes. In general, the statistical analysis that we carried out on data reported by Lotfi et al concludes that the G allele of the CYP2D6*4 polymorphism is associated as a protective factor with the development of UC in the Iranian population, while allele A is associated as a risk factor, and MDR1 3435 T allele increases the risk. Nevertheless, it is suggested to further expand the sample of UC cases in other studies, to analyze the effect of NAT2*7.

Authors' Contributions

SARG conceived, designed the study, analyzed data and wrote the manuscript, LJFA analyzed data, LMBR analyzed data, DGC conceived, wrote the manuscript and designed the study. All authors read and approved the version final.

Conflict of Interest Disclosures

None.

Ethical Statement

This research was realized according to Helsinki Declaration.

Acknowledgment

CONACYT for the National Postdoctoral Sabbath Fellowship to Dr. Sergio A. Ramirez from the Universidad de la Sierra Sur.

References

1. Lotfi F, Bahrehmand F, Vaisi A, Khodarahmi R, Tanhapour

Table 1. Supplementary Analysis by CYP450, 2D6, NAT2*7, A and MDR1, 3435

Genetic Model 1	n = UC patients	n = Control subjects	Statistical Test
Allele G	367	388	$\chi^2 = 3.812$, OR = 0.8163, $P = 0.05088$, 95% CI = 0.63–0.984, df = 1
Allele A	53	36	—
Genetic Model 2	n = UC patients	n = Control subjects	Statistical Test
Allele A	53	36	$\chi^2 = 3.812$, OR = 1.225, $P = 0.05088$, 95% CI = 1.017–1.476, df = 1
Allele G	367	388	—
Gene CYP450, 2D6*A/G	n = UC patients	n = Control subjects	P Value
Dominant	7	3	0.2382
AA vs. (AG+GG)	208	199	—
Paradominant	39	30	0.2282
AG vs No AG	171	181	—
Overdominant	171	182	0.22
(AA+GG) vs AG	39	30	—
Recessive	46	33	0.09552
(AA+AG) vs GG	164	179	—
Co-dominant			—
AA	39	30	0.187
AG	164	179	0.41
GG	7	3	0.16
NAT2*7, A/G	n = UC patients	n = Control subjects	P Value
Dominant	187	192	0.6062
GG vs. (AG+AA)	23	20	—
Paradominant	23	20	0.6062
AG vs No AG	187	192	—
Overdominant	187	192	0.6062
(AA+GG) vs AG	23	20	—
Recessive	23	20	0.6062
(AA+AG) vs GG	187	192	—
Co-dominant			—
AA	0	0	Data NE
AG	123	20	0.6062
GG	187	192	—
Haplogrups	n = UC patients	n = Control subjects	P Value
Haplogroups with allele G in NAT2*7 vs rest	162	175	0.0826
	46	32	—
Haplogroups with allele T in MDR1 vs rest	171	158	0.1394
	37	49	—
Haplogroups with allele G in CYP2D6. vs. rest	162	175	0.0826
	46	32	—

df, degree of the freedom; IC, confidence interval; OR, odds ratio; n, probands; UC, ulcerative colitis.

- M, Kiani A, et al. Cytochrome P450 (CYP450, 2D6*A), N-Acetyltransferase-2 (NAT2*7, A) and multidrug resistance 1 (MDR1 3435, T) alleles collectively increase risk of ulcerative colitis. Arch Iran Med. 2018;21(11):530-5.
- Flores E, Burguete AI, Salazar E. Diseños de investigación en epidemiología genética. Rev Panam Salud Publica. 2012;31:88–94.
- Wyszynski DF. La epidemiología genética: disciplina científica en expansión. Rev Panam Salud Publica. 1998;3:26-34.
- Ramirez SA, Charles NC, Mazariegos M, Topete L, Flores LJ, Santiago J, et al. Association of the ELMO1 gene (snp rs1345365) with development of type 2 diabetes mellitus in the Mexican mestizo population. Invest Clin. 2015;56(4):341-55.
- García EG, Leal E, Peralta V, Durán J, Meza JP. Genetic epidemiology of type 2 diabetes in Mexican Mestizos. Biomed Res Int. 2017;2017:3937893. doi: 10.1155/2017/3937893.

Received: April 19, 2019, Accepted: August 4, 2019, ePublished: November 1, 2019

Cite this article as: Ramirez Garcia SA, Flores Alvarado LJ, Baltazar Rodríguez LM, García Cruz D. Are the CYP2D6*G and MDR1, 3435T alleles associated with the risk of ulcerative colitis in Iranian population? Arch Iran Med. 2019;22(11):680-681.

© 2019 The Author(s). This is an open-access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0/>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.