

## Lack of Correlation Between IL-10R1 S138G Loss-of-function Allele and IBD in the Lebanese Population

### To the Editor:

The polygenetic basis of inflammatory bowel disease (IBD) has been recognized with the identification of an increasing number of susceptibility genes.<sup>1,2</sup> For example, mutations in the *NOD2/CARD15* gene and variations in *SLC22A4* and *SLC22A5* genes are associated with Crohn's disease (CD),<sup>3,4,5</sup> while the *MEP1A* gene was proposed to be an ulcerative colitis (UC) susceptibility gene.<sup>6</sup> More recently, new genetic mutations affecting the interleukin-10 (IL-10) receptor have been identified by Glocker et al.<sup>7</sup> IL10R1 and IL10R2 proteins constitute the different subunits that form the IL10 receptor. These proteins are encoded by the *IL10RA* and *IL10RB* genes, respectively. Three different homozygous mutations that perturb STAT3 (signal transducer and activator of transcription 3) phosphorylation via abrogated IL-10-induced immunomodulatory signaling were found to be associated with early-onset severe enterocolitis.<sup>7</sup> These mutations are: mutation W159X in *IL10RB* and mutations G141R and T84I in *IL10RA*.

In an earlier study on IL-10 signaling pathway genetic variations and their association with IBD, Grundtner et al<sup>8</sup> identified two single-nucleotide polymorphisms (SNPs) on the *IL-10R1* gene. These variants of *IL-10R1* were called SNP3 (*S138G*) and SNP4 (*G330R*). *IL-10R1* SNP3 showed decreased IL-10-induced signal trans-

duction via reduced STAT3 and trace or absent STAT1 phosphorylation. While SNP4 was found to have insignificant effects on STAT activation, SNP3 was found to be a loss-of-function variant for STAT3 and STAT1 activation. Grundtner et al tried to study the association between *IL-10R1* and susceptibility to UC. The data they collected showed that SNP3 might have a UC-protective effect and that *IL-10R1* wildtype allele may correlate with UC susceptibility. This UC-protective effect of SNP3 was suggested in a medium-sized Hungarian study but was later unconfirmed in a large Belgian IBD cohort. DNA samples from 52 different populations were studied for *IL10-R1* variants distribution, showing considerable dissimilarity in allele distribution between the same population and major geographical regions. The highest frequency of occurrence of SNP3 and SNP4 alleles was among Caucasians and Semites, while neither allele was evident in American and East Asian populations. On the other hand, the frequency of SNP3 was diminished in the Sub-Saharan African population in whom SNP4 allele was evident. We studied the association between *IL-10R1* variants and IBD subtypes in Lebanon.

### METHODOLOGY

Refer to the original article "The IL-10R1 S138G loss-of-function allele and ulcerative colitis."<sup>8</sup>

### RESULTS

DNA samples from 230 individuals were analyzed, of which there were 115 controls, 48 CD, 62 UC, and 5 with indeterminate colitis (Table 1). One control sample and 1 UC sample were not analyzable for the *SNP3* genotype, while 1 CD sample and 3 UC samples were not analyzable for the *SNP4* genotype. In agreement with the

findings in the Belgian cohort, our data showed that both SNP3 and SNP4 were not significantly different between the IBD subgroups and the control groups. This suggests that, in the Lebanese population, the loss-of-function allele *IL-10R1-S138G* (SNP3) is unlikely to provide a protective effect against UC and that both *IL-10R1* variants do not correlate with IBD.

Ola A. Ghaith, MD\*  
Mustapha M. El Halabi, MD\*  
Heitham Abdul-Baki, MD\*  
Christoph Gasche, MD†  
Manuela Nemeth†  
Ala I. Sharara, MD\*

\*American University of Beirut Medical Center, Division of Gastroenterology and Hepatology, Beirut, Lebanon

†Medical University of Vienna, Medicine 3 Gastroenterology, Christian Doppler Laboratory for Molecular Cancer Chemoprevention, Vienna, Austria

### REFERENCES

- Cooney R, Jewell D. The genetic basis of inflammatory bowel disease. *Dig Dis.* 2009; 27:428–442.
- Cho JH, Weaver CT. The genetics of inflammatory bowel disease. *Gastroenterology.* 2007;133:1327–1339.
- Brand S, Staudinger T, Schnitzler F, et al. The role of Toll-like receptor 4 Asp299Gly and Thr399Ile polymorphisms and CARD15/NOD2 mutations in the susceptibility and phenotype of Crohn's disease. *Inflamm Bowel Dis.* 2005;11:645–652.
- Hugot JP, Chamaillard M, Zouali H, et al. Association of NOD2 leucine-rich repeat variants with susceptibility to Crohn's disease. *Nature.* 2001;411:599–603.
- Peltekova VD, Wintle RF, Rubin LA, et al. Functional variants of OCTN cation transporter genes are associated with Crohn disease. *Nat Genet.* 2004;36:471–475.
- Banerjee S, Oneda B, Yap LM, et al. MEP1A allele for meprin A metalloprotease is a susceptibility gene for inflammatory bowel disease. *Mucosal Immunol.* 2009;2:220–231.
- Glocker EO, Kotlarz D, Boztug K, et al. Inflammatory bowel disease and mutations affecting the interleukin-10 receptor. *N Engl J Med.* 2009;361:2033–2045.
- Grundtner P, Gruber S, Murray SS, et al. The IL-10R1 S138G loss-of-function allele and ulcerative colitis. *Genes Immun.* 2009;10:84–92.

Copyright © 2010 Crohn's & Colitis Foundation of America, Inc.  
DOI 10.1002/ibd.21230

Published online in Wiley InterScience (www.interscience.wiley.com).

**TABLE 1. Allele, Genotype, and Haplotype Frequencies of IL-10R1 SNP3 and IL-10R1 SNP4 in the Lebanese IBD Patients and Healthy Controls<sup>a</sup>**

Allele or genotype	Controls (n = 114)	CD (n = 48)	P-value <sup>b</sup>	UC (n = 61)	P-value	IBD <sup>c</sup> (n = 114)	P-value
<b>SNP3 genotype</b>							
1 <sup>d</sup> -1	95/83.3%	41/85.4%		50/82.0%		95/83.3%	
1-2 <sup>e</sup>	17/14.9%	7/14.6%		11/18.0%		19/16.7%	
2-2 (n/%)	2/1.8%	0	0.650	0	0.517	0	0.348
	Controls (n = 228)	CD (n = 96)	P-value	UC (n = 122)	P-value	IBD (n = 228)	P-value
<b>SNP3 allele</b>							
1	207/90.8%	89/92.7%		111/91.0%		209/91.7%	
2	21/9.2%	7/7.3%	0.575	11/9.0%	0.952	19/8.3%	0.741
	Controls (n = 115)	CD (n = 47)	P-value	UC (n = 59)	P-value	IBD (n = 111)	P-value
<b>SNP4 genotype</b>							
1-1	55/47.8%	23/48.9%		30/50.8%		55/49.5%	
1-2	48/41.7%	19/40.4%		27/45.8%		49/44.1%	
2-2	12/10.4%	5/10.6%	0.988	2/3.4%	0.269	7/6.3%	0.534
	Controls (n = 230)	CD (n = 94)	P-value	UC (n = 118)	P-value	IBD (n = 222)	P-value
<b>SNP4 allele</b>							
1	158/68.7%	65/69.1%		87/73.7%		159/71.6%	
2	72/31.3%	29/31.9%	0.936	31/26.3%	0.330	63/28.4%	0.497
	Controls (n = 228)	CD (n = 94)	P-value	UC (n = 118)	P-value	IBD (n = 222)	P-value
<b>Haplotypes</b>							
1:1 (haplotype 1)	157/68.9%	65/69.15%		87/73.7%		159/71.6%	
2:1 (haplotype 3)	0	0		0		0	
1:2 (haplotype 4)	50/21.9%	22/23.4%		21/17.8%		45/20.3%	
2:2 (haplotype 7)	21/9.2%	7/7.45%	0.859	10/8.5%	0.620	18/8.1%	0.808

<sup>a</sup>Nonanalyzable samples were not included in the analysis.<sup>b</sup>Compared to control.<sup>c</sup>IBD = UC+CD+IBD of unknown subtype.<sup>d</sup>1 = wildtype allele.<sup>e</sup>2 = mutant allele.