Reviewer's report

Title: Functional polymorphism of the NFKB1 gene promoter is related to the risk of dilated cardiomyopathy

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Reviewer: Gisela Orozco

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In this manuscript, the role of the -94 ins/del ATTG polymorphism of the NFKB1 gene in susceptibility to dilated cardiomyopathy was analyzed.

NF-κB is a key mediator of inflammatory processes, and has been shown to be implicated in a large number of autoimmune/inflammatory diseases. The analysis of this polymorphism, which seems to alter the promoter activity of the gene, with regard to DCM susceptibility is therefore of interest.

However, this variant has been studied in the past by many groups in a broad range of diseases, obtaining conflicting results (Sun, X.F. & Zhang, H. NFKB and NFKBI polymorphisms in relation to susceptibility of tumour and other diseases. Histol. Histopathol. 22, 1387-1398 (2007)). Then, in order to test whether this variant is associated with a disease, a well powered study should be carried out, including a sufficiently large cohort.

MAJOR COMMENTS

1. The introduction is perhaps too long. It could be shortened:
Page 4, line 8: the list of the diseases in which NF-κB is involved should be replaced by “…for initiation and progression of pathogenesis of many autoimmune and inflammatory diseases”

Delete the entire paragraph from line 11 to line 22 of page 4, in which NF-κB function is explained. The authors could simply cite a review article on that matter.

2. Is the number of patients and controls included in the study large enough to achieve at least 80% statistical power? The authors should comment their statistical power. I have used the Quanto software (http://hydra.usc.edu/GxE/), and I am afraid that this study is underpowered to detect an association with an effect size similar to the one found in Karban et al.

3. In the results section (page 7 line 17) it is stated that both patients and controls had no deviation from Hardy-Weinberg equilibrium. However, according to my calculations, the patient’s genotype distribution is slightly out of the HW equilibrium (P = 0.04). When allele frequencies are compared, no statistically significant differences were found. On the other hand, the authors found a significant decrease of the ATTG1/ATTG1 in patients compared with controls. Interestingly, the frequency of this genotype in patients is lower than that
expected (from HW equilibrium calculations; maybe an excess of heterozygous due to genotype errors?). Could this have influenced the results obtained?

4. In order to clarify whether the NFKB1 variant is associated with DCM, an additional, well powered cohort could be analyzed. The results presented here are not robust enough, due to a lack of power and deviation from HWE.

5. The decrease of the ATTG1/ATTG1 genotype found in DCM patients compared with controls is in contrast to the work of Karban el al, where an increase in this genotype was found for ulcerative colitis patients. The authors could comment this in the discussion, and provide a possible explanation for this phenomenon.

6. The paragraph about NF-#B and NFKB1 structure could be removed from the Discussion (page 8 line 20-page 9 line 6) in order to shorten this section.

7. Discussion, page 9 line 15: The authors could cite a meta-analysis of the association of NFKB1 and UC, where no statistically significant differences were found (Latiano A, Palmieri O, Valvano MR, Bossa F, Latiano T, Corritore G, et al. Evaluating the role of the genetic variations of PTPN22, NFKB1, and FcGRIIIA genes in inflammatory bowel disease: a meta-analysis. Inflamm Bowel Dis 2007;13:1212-9), and remove reference number 16, since it is from a study regarding celiac disease, not UC.

Minor comments
1. Abstract, conclusion section: line 17-18 should be moved to the Results section of the Abstract.
2. Introduction, line 7. Should be “…severe symptoms, including heart failure AND sudden death, and asymptomatic individuals.”
3. Introduction, page 3, line 18: remove from this sentence the associated polymorphisms and keep only the names of the genes, as in the sentences it is stated: “Some susceptibility genes…, including...”

Level of interest: An article of importance in its field

Quality of written English: Needs some language corrections before being published

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interests