Author’s response to reviews

Title: IL17A and IL17F gene polymorphisms in patients with rheumatoid arthritis

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Author’s response to reviews:

Dr Roman Krawetz
Associate Editor
BMC Musculoskeletal Disorders

Dear Dr Krawetz,
Thank you very much for critical review of our manuscript. The authors appreciate valuable remarks of the Referee that led to improved quality of the manuscript. All the comments were taken into consideration and the manuscript has been enhanced according to the Reviewer’s suggestions.

Reviewer reports:

Reviewer #1:
The manuscript by Pawlik and collaborators is an association study that addresses the influence of different IL17a and IL17F polymorphisms in RA patients in a Polish population. The role of IL17 in RA and other autoimmune diseases is relevant and the study of the influence of genetic variation in disease predisposition is justified. However, the authors should consider several points:

1) The rationale behind the SNP selection is not stated in the introduction paragraph but in the discussion. I would recommend the authors to restructure the text. The text of the manuscript has been restructured.

2) There have been several GWAS in RA that have increased the number of RA associated-loci to more than one hundred (Okada 2014). However, IL17 was not one of these loci, authors should comment on this. This has been commented in Discussion. Our results seem to be concordant with data of a large genome-wide association study meta-analysis suggesting that IL17 is not one of RA associated loci [12].

3) Since the sample size is very modest and this is a major drawback for this study, the statistical power for each SNP and the different groups should be mentioned in the text. We performed the statistical power analysis which has been added to the Statistical analysis section: The power of the study to detect an association of the analyzed SNPs with presence of RA was estimated using the PS program ver. 3.0.43. The study sample size was sufficient to detect with 80% probability the true effect size of differences in allele frequencies between groups measured as odds ratio (OR) equal to 0.736 or 1.347 for rs2275913, 0.302 or 2.106 for rs763780, 0.435 or 1.822 for rs11465553 and 0.593 or 1.543 for rs2397084. 4) Considering the distance between some of the SNPs and the similar ORs and high D’, it is very uncommon that R2 values are so low. Can the
authors justify this? Are the values similar to the European Hapmap population? We checked the Haploview results and confirm that they are correct. The combination of high D and low r² is typical for linkage disequilibrium when one of four possible two-loci haplotypes is absent (or very rare) in population, while the other three are present. High r² values are observed only when two of four possible two-loci haplotypes are absent (or very rare), while the other two dominate in population, which was not our case. Our values are similar to those in HapMap Data Rel 27 database where e.g. for rs763780-rs2397084 in CEU population D =1 and r²=0.003.5) The IL17 receptor structure is not clearly explained. This explanation is added to Background. All IL-17 receptors contain extracellular domains composed of fibronectin type-III domains, and cytoplasmic SEF/IL-17R domains. IL-17 receptor stimulation results in activation of NF-κB and mitogen-activated protein kinases. These signaling properties of IL-17 receptors enable TH-17 cells to act as a bridge between innate and adaptive immune cells. 6) Are the 6 SNPs forming a real haplotype according to some algorithm (Haploview) or did the authors make a allele combination analysis instead? The four analyzed SNPs are in linkage disequilibrium due to short distances between loci and form a real haplotype which was analyzed by Haploview 4.2 software. This information has been added to the revised Methods section. 7) The % symbols in the tables are already included in the headings, authors can simplify by not including them also in the numbers. Tables have been corrected. With kind regards, Andrzej Pawlik.