Reviewer 1:

Commentaries	Answers
They claim that this is the first study evaluating the allelic contribution of PADI4 SNPs on mRNA expression of the PADI4 gene. However, the same group already published earlier the relationship of PADI4 polymorphisms with anti-CCP and PADI4 mRNA expression. They described in this paper that the polymorphisms and functional haplotype (GTG) in PADI4 are associated with RA susceptibility as well as anti-CCP antibodies in a Mexican population (DOI: 10.1016/j.imlet.2014.10.029). Several other groups also published similar results in the last 10-12 years that the authors correctly cite in their manuscript. Still, there are some controversies regarding the relation between PADI4 polymorphism and the autoantibody level.	We greatly appreciate the comments. As mentioned by the reviewer, we have previously published studies on the relationship of *PADI4* polymorphisms with *PADI4* mRNA expression and its association with clinical variables of RA patients. In this new study, in addition to evaluating the relationship of the polymorphisms with the mRNA expression by q-PCR, we also evaluated the allelic contribution of the *PADI4* SNPs in the mRNA expression of the gene evaluated by the ATSQ method. The novelty of the present study is then the technique used, which does not evaluate the contribution of the genotypes on the expression of the mRNA, but instead evaluates the contribution of each allele to the expression of PADI4. Even though several other groups have published similar results in the last 10-12 years, our study also evaluates PAD4 activity in leukocyte samples from CS and RA patients carrying ACC and GTG haplotypes. Therefore, we provide a pooled analysis of the association between haplotype with RA susceptibility, the genotypic and allelic contribution of PADI4 polymorphism to mRNA expression, and the PAD4 enzyme activity To avoid confusion, we specified the above in lines 375-377; and lines 426-429 (changes were highlighted in green).
In an earlier study, the authors described: The GTG haplotype was significantly associated with RA but did not show an association with levels of anti-CCP antibodies and clinical parameters (DOI: 10.1016/j.humimm.2017.05.005). Others also could not confirm the association between susceptibility haplotype presence and ACPA positivity (Clin Dev Immunol. doi: 10.1155/2013/383681). How can the authors explain these apparently controversial conclusions?	The lack of association observed in previous studies between PADI4 haplotypes with Anti-CCP levels may be because the levels of these autoantibodies can be altered by various factors, including disease activity, disease progression time, the methodology used to measure the antibodies, or by the active exposure to environmental factors associated with protein citrullination such as smoking. Furthermore, the effect of haplotypes on Anti-CCP levels is only indirect. Our study demonstrated the relationship of PADI4 alleles, genotypes, and haplotypes with PAD4 enzymatic activity and the PADI4 mRNA expression, which could be explained more directly since these variants could explain this functional effect.

Reviewer 2:

Commentaries	Answers
Interesting study conducted with rigorous methodology. It can be considered the starting point for organizing a multicenter study-Indeed one of the limitations of your's study is the sample size; therefore, it is essential to develop future studies with a larger sample size that allows us to confirm this association between the presence of the GTG haplotype with increased mRNA expression and PADI4 activity. One of the limitations of this study is the sample size; it is essential to develop 420 future studies with a larger sample size that allows us to confirm this association between the presence of the GTG haplotype with increased mRNA expression and PADI4 activity.	Thank you for the comment. We are aware that the main limitation of this study was the sample size and declare it in lines 423 to 425. We recognize that future studies with a larger sample size are essential. Therefore, in the future, we intend to carry out a study increasing the sample size to confirm these associations of the *PADI4* polymorphisms and haplotypes with the expression of the mRNA and the activity of PAD4. Some typographical and grammatical errors were corrected to improve the manuscript.