Reviewer's report

Title: Variable number of tandem repeat polymorphisms of the interleukin-1 receptor antagonist gene IL-1RN: a novel association with the athlete status.

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Reviewer: Emidio Pistilli

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Article Review
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“Variable number of tandem repeat polymorphisms of the interleukin-1 receptor antagonist gene IL-1RN: a novel association with the athlete status” – Cauci et al.

Overall
The study by S. Cauci et al., examines the associations between two SNPs in the IL-1# gene and one VNTR in the IL-1RN gene with athletic status. The study utilized a population of 205 athletes (53 high-grade athletes and 152 medium grade athletes) and 458 non-athlete controls that were Caucasian and of Italian nationality. The data are interesting, especially given the observations of significant associations of the VNTR genotypes with athlete status. Please see specific comments below.

Major Compulsory Revisions

Comment 1
The authors state that haplotypes were examined in the study and report this in the results. However, it is not stated whether the SNPs were in linkage disequilibrium. The LD calculation and data should be presented, especially given the significant association of the haplotype (-511)C-(+3954)T-(VNTR)2 with athlete versus non-athlete status.

Minor Compulsory Revisions

Comment 2
The authors state in the Conclusion section that it is beyond the scope of the paper to address the SNP associations with aerobic versus anaerobic types of sports. Why is this the case? These analyses would be extremely interesting, especially given the facts that: 1) in general anaerobic types of activities would include more forceful types of muscle contractions that would expose the muscles to more microinjuries in fibers, and 2) this study examines SNPs in
immune related genes that, as the authors state, may be involved with the post-exercise inflammatory phase. In a study by David Nieman’s group in 2003, IL-1β mRNA was one of three genes that showed the biggest increase in muscle following a 2hr bout of resistance exercise in resistance trained men, and this study also states that the serum cytokine profile was different from that noted following aerobic treadmill exercise at 70% VO2max. Given the significant and interesting association observed in this study with athlete versus non-athlete, a sub-analysis of aerobic versus anaerobic athletes would be quite interesting. A sub-analysis could potentially be performed to address this fact, by separating the purely aerobic athletes in the study (triathletes, runners, swimmers) with purely anaerobic athletes.

Comment 3
More clarification in the Methods section is needed on how the distinction between high grade athlete status and medium grade status was performed, especially given the fact that significant associations were found when comparing professional athletes and non-professional athletes and also when comparing athletes and non-athletes.

Comment 4
The authors state that the specific SNPs examined in these studies were chosen because “these were the most frequently studied polymorphisms in the IL-1β and IL-1ra cytokines.” More clarification on the location of these SNPs within the gene structure would be helpful. The authors state that the -511 IL-1β SNP is in the promoter region, but do not state where the +3954 SNP or the VNTR on IL-1ra is. Also, are there additional SNPs in the IL-1RN gene that have been studied. Given the fact that the significant associations in the study were found in the VNTR of this gene, perhaps other SNPs in this gene would provide additional useful data.

Comment 5
The first sentence of the Discussion section states that this study “supports the notion that IL-1ra levels are critically important in physical exercise.” This statement should be revised, as IL-1ra levels were not measured in this study nor was physical exercise per se measured in this study. The study does identify SNP associations with athletes, but the study does not provide data on levels of IL-1ra following exercise. Please revise this.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

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.