Reviewer’s report

Title: COL5A1 rs12722 polymorphism is not associated with passive muscle stiffness and sports-related muscle injury in Japanese athletes

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Reviewer: P. Bryant Chase

Reviewer's report:

In this well-written manuscript, Miyamoto-Mikami et al. expand on published observations by Collins and colleagues to "...test the hypothesis that the COL5A1 rs12722 [collagen] polymorphism influences joint flexibility via muscle stiffness, and is accordingly associated with the incidence of muscle injury." Specifically, they "...hypothesized that the T allele of the COL5A1 rs12722 polymorphism is associated with high muscle stiffness, and accordingly poor joint flexibility and a high incidence of muscle injury." The polymorphism is located "...in the 3'-untranslated region of the collagen type V alpha1 chain gene (COL5A1)..." The authors present two related studies correlating the rs12722 polymorphism with: joint flexibility and muscle stiffness in 363 healthy young adults; and muscle injury in 1559 Japanese athletes. These sample sizes are much larger than prior studies, as was required according to power analyses. There was no significant association of the biomechanical parameters with the polymorphism: the results "[do] not support the view that COL5A1 rs12722 polymorphism has a role as a risk factor for sports-related muscle injury, or that it is a determinant for muscle stiffness." The authors identify factors (age and ethnicity) that distinguish the populations in the current study from prior work, and could possibly provide at least a partial explanation for the differences in results.

Major

The authors apparently demonstrate that correlation is not always causality. If there were a correlation found in this study, I would want to see some information about molecular mechanism, i.e., how a genome variant in the untranslated region of a collagen gene might affect the amount of protein, protein structure and function, and/or assembly of connective tissue and its integration into muscle. Since there is no correlation in this large cohort, molecular mechanisms are not necessary.

Abstract (and elsewhere, as noted below): When the authors state in the Background section of the Abstract that "Joint flexibility is largely determined by muscle stiffness, which is influenced by intramuscular collagenous connective tissues including type V collagen" they should clarify that they are referring to the passive condition, i.e., the muscles are not activated. The stiffness
of activated muscle is, of course, much greater than that of relaxed muscle, and the stiffness of actively contracting is largely determined by actomyosin interactions (i.e., cycling crossbridges). The authors might also want to further clarify that they are referring to normal joints (i.e., joints not affected by debilitating diseases such as arthritis). This issue comes up again in the introductory Background section of the main document, starting around line 80. I note that the authors do introduce this briefly in the Discussion (starting on line 289).

Minor

Line 78: presumably "…tests is…” should be either "…test is…” or "…tests are…”

Line 242: presumably "modulus" should be "moduli"

**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.

Yes

**Does the work include the necessary controls?**
If not, please specify which controls are required in your comments to the authors.

Yes

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If not, please explain in your comments to the authors.

Yes

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I am able to assess the statistics

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