The ACE I/D gene variant predicts ACE enzyme activity in the blood but not the expression of ACE protein in skeletal muscle in the Gene SMART study

X. Yan,[1,2] N. Dvir,[1] L. Cavalcante,[1] M. Jacques,[1] I.D. Papadimitriou,[1] F. Munson,[1] A.P. Garnham,[1] L. O'Keefe,[1] O. Tirosh,[3] D.J. Bishop,[1] S. Voisin[1] and N. Eynon ,[1] [1]Institute of Sport, Exercise & Active Living, Victoria University, Melbourne, VIC 8001, Australia, [2]College of Health and Biomedicine, Victoria University, Melbourne, VIC 8001, Australia and [3]School of Health Sciences, Swinburne University of Technology, Hawthorn, VIC 3122, Australia.

Background: Both environmental and genetic factors are important determinants of adaptations to exercise training. One gene variant that has been associated with exercise performance across multiple cohorts is the Angiotensin Converting Enzyme (*ACE*) Insertion/Deletion (I/D). This variant has also been associated with the activity of the *ACE* enzyme. It is, however, unclear if it is associated with changes in *ACE* enzyme in response to exercise.

Aims: To investigate whether: 1) the *ACE* I/D gene variant is associated with changes in *ACE* enzyme activity in the blood and *ACE* protein content muscle, at baseline and following a session of High-Intensity Interval Exercise (HIIE); and 2) whether the *ACE* I/D variant is associated with physiological (VO_{2max}, Lactate Threshold, mitochondrial respiration) characteristics at baseline.

Methods: These analyses are part of the Gene SMART (Skeletal Muscle Adaptive Response to Training) study, investigating the influence of genetic variants on muscle metabolism and adaptation to exercise. Genotyping for the *ACE* I/D variant was performed using Taq-Man method. The *ACE* enzyme levels in the blood (serum) pre, immediately after, and 3 hours post HIIE were measured using an ELISA kit, and the *ACE* protein expression in the muscle was measured by western blots at the same time points.

Results: At baseline, DD participants had 68% higher *ACE* activity levels in the serum compared with II participants (adj. p-value = 0.0009). However, II and DD participants had similar levels of *ACE* protein content in the muscle (all adj. p-value> 0.05). Immediately post-exercise, serum *ACE* levels increased by 15.1% (adj. p-value=0.004). Three hours post-HIIE, ACE levels in blood returned to baseline levels (adj. p-value = 0.34). ACE levels in muscle were unchanged following HIIE (adj. p-values > 0.05). These changes were independent of the *ACE* I/D genotype. There were also no genotype differences in age, BMI, Lactate Threshold, VO_{2max} or mitochondrial respiration (all adj. p-values > 0.05)

Conclusion: The *ACE* I/D variant is associated with serum *ACE* content at baseline, but not with *ACE* protein expression in the muscle, and physiological characteristics at baseline. Further research is required to assess the association between other genetic variants in the Renin-Angiotensin System (RAAS) and *ACE* content in the muscle.