**Influence of ACTN3 gene on muscle health and physical fitness to inform future interventions in spaceflight missions**

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**INTRODUCTION:** Exposure to reduced gravity environments leads to diminished muscle size, strength, and endurance. Preservation of physical fitness is critical for mission essential tasks such as extravehicular activities or adaptation to changes in gravity loads. Current countermeasures to maintain ISS astronauts’ muscle mass and fitness include dedicated time for a combination of cardiovascular exercise and resistance training. Countermeasure effectiveness is monitored through VO2 max and isometric mid-thigh pulls. It is important to understand both environmental and genetic contributors to astronaut physical fitness. Multiple genes, including ACTN3, are known to correlate with exercise phenotypes and have the potential to help personalize countermeasures based on an astronaut’s genotypic makeup.

**TOPIC**: The ACTN3 gene encodes a protein expressed only in fast-twitch muscles and correlates with sprint and power phenotypes. A common polymorphism in ACTN3 gene is R577X (rs1815739), produced by a C−to−T base substitution resulting in a nonsense mutation from arginine (R) to a premature stop codon (X) present in approximately 18% of the population. This polymorphism causes an absence of α−actinin−3 in type II muscle fibers but does not lead to a disease phenotype. The RR genotype is associated with elite athletes, especially in sprint and power sports. The XX genotype is believed to be more common in endurance athletes. The ACTN3 gene also has potential associations with training adaptation, post-exercise recovery, and exercise-associated injuries.

**APPLICATION**: Understanding how ACTN3 and other genetic determinates of fitness phenotypes affect astronaut physical performance can inform personalized exercise and recovery prescriptions. For example, individuals with the RR or RX genotype may respond better to high-load and low repetition exercise, while XX may benefit from high repetition with low weight exercise. Since the wild-type protein may confer more resistance to muscle damage, those individuals with the RR or RX genotype may benefit from high intensity interval training for improved VO2 max, whereas those with an XX genotype may benefit from low intensity, high volume endurance activity. Additionally, omics data related to health and performance could be used as biomarkers to monitor astronaut fitness and the effectiveness of training regimens during a mission.

Learning objectives:

* Learn about the phenotypic effects on muscle function and fitness secondary to R577X mutation in the ACTN3 gene
* Learn how mutations in the ACTN3 gene may inform future countermeasures for future spaceflight missions