The POWERGENE consortium: Identifying the genetics of sprint/power performance in elite athletes

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What makes an elite athlete dominate at a world-class level is a fascinating question. In combination with environment (*e.g.* training and diet), genetics plays a key role in elite athlete performance. For over 40 years researchers have analysed individual candidate genes in an attempt to understand the role genetics plays. Characterizing the athlete genome will be vital in understanding the role genetics plays in these individuals as well as highlighting novel genes and pathways which may influence health, aging and disease.

Critical aspects of professional athleticism (including discipline and mental training) are shared between athletes, however the physiological and genetic contributions in elite sprint/power and endurance competitors are different. Endurance athletes utilize high cardiovascular, metabolic and respiratory system performance to maintain a high relative oxygen uptake (VO_2) to sustain muscle contractions. While sprint/power athletes require powerful muscle contractions for acceleration and speed, utilizing intramuscular creatine, ATP and glucose for energy (Eynon *et al.*, 2013; Bishop *et al.*, 2014). The majority of genetic studies have focused on profiling these characteristics in elite endurance athlete either *via* candidate gene or more recently, genome wide analyses (*i.e.* GENATHLETE). These studies have begun to highlight the polygenic nature of athletic performance and the importance of a large, well-controlled, population based research approach.

Of the genes which influence sprint/power performance, the α-actinin-3 R577X polymorphism has provided the most consistent findings. In Australian sprint/power athletes we have shown that the absence of α-actinin-3 (577XX) is significantly underrepresented in elite athletes (n = 107) compared to healthy controls (n = 436) (Yang *et al.*, 2003). This association has since been replicated in over 14 sprint/power athlete cohorts around the worldwide. In addition, we developed an α-actinin-3 knockout (Actn3 KO) mouse to study the functional changes associated with the R577X polymorphism *in vivo* (MacArthur *et al.*, 2007). The Actn3 KO mouse has been vital in determining the mechanistic changes in skeletal muscle - highlighting key changes in muscle metabolism (MacArthur *et al.*, 2008; Quinlan *et al.*, 2010) and the calcineurin pathway (Seto *et al.*, 2013) that support the association in humans.

Over 200 polymorphisms have now been predicted to influence exercise-performance (with more than 20 associated with elite athletic status) (Eynon *et al.*, 2013). It is therefore important to consider that no single variant accounts for athletic performance. Given the large number of candidates and variation in current association studies, the use of unbiased whole genome analyses are thought to provide a robust assessment of the athlete genome.

To further study the genetic contribution to athletic performance we have established an international consortium (POWERGENE) of sprint/power athletes and matched controls to perform a case-control study. To date, DNA from a total of 445 sprint/power athletes and 1200 population controls from nine countries (Australia, Belgium, Greece, Italy, Lithuania, Poland, Spain, the United Kingdom, and the United States of America) have been obtained for a discovery phase analysis. Using a combination of candidate genes and genome wide approach we will begin to delve into the genetic influences of elite sprint/power athlete performance. This ongoing project will highlight novel genes involved in human performance, providing candidates for replication in additional cohorts and functional *in vivo* studies using animal models to determine the mechanistic changes associated with these novel variants.

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