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REVIEW ARTICLE

Genes for Elite Power and Sprint Performance: *ACTN3* Leads the Way

Nir Eynon · Erik D. Hanson · Alejandro Lucia · Peter J. Houweling · Fleur Garton · Kathryn N. North · David J. Bishop

Abstract The ability of skeletal muscles to produce force at a high velocity, which is crucial for success in power and sprint performance, is strongly influenced by genetics and without the appropriate genetic make-up, an individual reduces his/her chances of becoming an exceptional power or sprinter athlete. Several genetic variants (i.e. polymorphisms) have been associated with elite power and sprint performance in the last few years and the current paradigm is that elite performance is a polygenic trait, with minor contributions of each variant to the unique athletic phenotype. The purpose of this review is to summarize the specific knowledge in the field of genetics and elite power performance, and to provide some future directions for research in this field. Of the polymorphisms associated with elite power and sprint performance, the α-actinin-3 R577X polymorphism provides the most consistent results. *ACTN3* is the only gene that shows a genotype and performance association across multiple cohorts of elite power athletes, and this association is strongly supported by mechanistic data from an *Actn3* knockout mouse model. The angiotensin-1 converting enzyme insertion/deletion polymorphism (*ACE* I/D, registered single nucleotide polymorphism [rs]4646994), angiotensinogen (*AGT* Met235Thr rs699), skeletal adenosine monophosphate deaminase (*AMPD1*) Gln(Q)12Ter(X) [also termed C34T, rs17602729], interleukin-6 (*IL-6* −174 G/C, rs1800795), endothelial nitric oxide synthase 3 (*NOS3* −786 T/C, rs2070744; and Glu298Asp, rs1799983), peroxisome proliferator-activated receptor-α (*PPARA* Intron 7 G/C, rs4253778), and mitochondrial uncoupling protein 2 (*UCP2* Ala55Val, rs660339) polymorphisms have also been associated with elite power performance, but the findings are less consistent. In general, research into the genetics of athletic performance is limited by a small sample size in individual studies and the heterogeneity of study samples, often including athletes from multiple-difference sporting disciplines. In the future, large, homogeneous, strictly defined elite power athlete cohorts need to be established though multinational collaboration, so that meaningful genome-wide association studies can be performed. Such an approach would provide unbiased identification of potential genes that influence elite athletic performance.

N. Eynon (✉) · E. D. Hanson · D. J. Bishop
Institute of Sport, Exercise and Active Living (ISEAL), Victoria University, PO Box 14428, Melbourne, VIC 8001, Australia
e-mail: Nir.Eynon@vu.edu.au

E. D. Hanson
College of Health and Biomedicine, Victoria University, Melbourne, VIC, Australia

A. Lucia
School of Doctorate Studies and Research, Universidad Europea de Madrid and Instituto de Investigación i+12, Madrid, Spain

P. J. Houweling · F. Garton · K. N. North
Institute for Neuroscience and Muscle Research, Children's Hospital at Westmead, Sydney, NSW, Australia

P. J. Houweling · F. Garton · K. N. North
Discipline of Paediatrics and Child Health, Faculty of Medicine, University of Sydney, Sydney, NSW, Australia

K. N. North
Murdoch Childrens Research Institute, The Royal Children's Hospital, Melbourne, VIC, Australia

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1 Introduction

Elite athletes are usually defined as athletes with exceptional performance achievements in their chosen sporting

discipline who represent their country at international-level competition, such as the Olympic Games or World Championships [1]. However, large interathlete variability exists in the performance outcomes of elite athletes. For example, the best result in the men's marathon event in the London, 2012 Olympic Games (2:08:01 h) was 8 min faster than the individual who came 25th in the same event (2:16:25) [122]; yet, both are considered as elite athletes in their own country. Recently, Druzhevskaya and colleagues [2] have developed a helpful set of definitions for describing athletic status. 'Highly elite athletes' are defined as winners of the Olympic Games, or World Championships, 'elite athletes' are defined as winners of either bronze or silver medals in the Olympic Games, or World Championships, whereas 'subelite athletes' are defined as participants at international-level competitions without winning medals. Unfortunately, these definitions have not been used consistently in the majority of studies, which makes it very difficult to compare the results in the published literature. Nonetheless, what makes an elite athlete dominant at a world-class sporting event and distinguished from other athletes, is therefore a fascinating question with implications for talent identification in sports.

Genetic variants (i.e. polymorphisms) present throughout the human genome are vital to understand the potential influence of genes on elite athletic performance; identification of these variants has been of interest for the last three decades [3]. Along with environmental factors such as training and diet, it is assumed that elite athletes possess a 'blueprint' of genetic variants that enable them to succeed at the highest levels of competition. However, the genetic variants involved and their contribution to specific aspects of elite athletic performance remains to be elucidated.

1.1 Heritability of Performance-Related Traits

Family and twin studies have demonstrated that genetics play a significant role in athletic performance and participation in exercise even when adjusting for environmental effects. A large-scale twin study composed of 37,051 twin pairs from seven European countries suggested that the heritability of participating in leisure-time exercise was between 48 % and 71 % [4]. The first genome-wide linkage scan for athletic status reported a heritability of roughly 66 % for athletic status in 700 British female dizygotic twin pairs [5]. More recent data from the HERITAGE family study suggested that the heritability of changes in maximal oxygen uptake ($\dot{V}O_{2max}$) with exercise training is ~47 % in sedentary subjects [6].

Muscle strength and mass have been reported to be influenced by genetic factors. The estimated heritability for muscle strength and muscle mass, assessed by twin and family studies, varies from 31 % to 78 %, with large differences between muscle groups, contraction velocities and muscle lengths [7]. Of particular interest are studies that have focused on the heritability of explosive strength, which is an important predictor of sprint performance. For example, Calvo et al. [8] used the 'Wingate anaerobic test' to study the heritability of muscle power in 32 Caucasian male twins, who had similar environmental backgrounds. They reported 74 % and 84 % heritability for maximal power (5-s interval) and total power (30-s interval), respectively. Therefore, the question is not whether performance-related traits are heritable, but 'which' genetic variants contribute substantially to elite athletic performance, and are we able to use these variants to identify future elite athletes.

1.2 Genetic Association with Elite Power and Endurance Performance

Over 200 polymorphisms influencing exercise-performance traits, and over 20 polymorphisms influencing elite athletic status, have been reported in the literature and are summarized on a yearly basis in *Advances in Exercise, Fitness, and Performance Genomics* [9–11]. The notion shared by researchers in the field is that elite performance is a polygenic trait by nature (e.g. a phenotypic trait produced by multiple genes working together), with a minor contribution of each variant to the unique athletic phenotype. However, the contribution of each variant to the unique athletic phenotype is not necessarily similar. As such, the probability of becoming an elite athlete increases based upon having a currently unknown high number of athletic-related alleles [12, 13].

The so-called 'genetic profile' for success in elite-level endurance performance is different from that of the elite power/sprint athlete [3]. From a physiological and biochemical point of view, pure endurance (e.g. marathons, triathlons, etc.) and pure sprint and power (100–200 m sprints, etc.) performance represent distinct endpoints of the sporting continuum. Importantly, the metabolic phenotypes required to perform either endurance or power/sprint events are polar opposites of each other. Elite endurance performance requires sustained muscular contraction over a long period of time. To achieve this, athletes have a high $\dot{V}O_{2max}$ lactate threshold and other traditional endurance phenotypes achieved by increases in several components of the mitochondrial respiratory chain [14]. Short-distance sprint and power performance, on the other hand, requires high-speed and forceful muscle contraction, is dependent on the anaerobic pathways and utilizes intramuscular stores of creatine phosphate (CP), adenosine triphosphate (ATP) and glucose [15].

There may be evolutionary 'trade-offs' in performance traits for endurance versus sprint and power activities, that is an individual may be inherently predisposed toward better performance in either power/sprint or endurance events [16]. This theory was supported by Van Damme and colleagues [17] who demonstrated that world-class decathletes who specialized in explosive-power events, such as the 100-m sprint or long jump, had performances that were negatively correlated with their performance in an endurance-oriented event such as the 1,500-m race. These trade-offs have imposed important constraints on the evolution of physical performance in humans and may explain why it is unusual to identify an athlete who excels in power/sprint as well as endurance events.

Unlike the vast number of investigations into the genetics of endurance performance, the genetic influence on elite power/sprint performance has received limited attention, and only a few studies have characterized the associations between genetic variants and elite power/sprint performance. Most studies to date are hampered by insufficient sample size and, apart from the *ACTN3* R577X and the angiotensin-1 converting enzyme insertion/deletion (*ACE* I/D) polymorphisms (that will be discussed in detail in Sects. 2, 3.1), all other variants have been tested in less than three elite athlete cohorts. Furthermore, most studies provide genetic associations rather than demonstrating cause and effect or providing any proposed cellular or molecular mechanisms to explain the phenomena. Consequently, the genetic profile of elite power and endurance athletes remains poorly characterized.

Despite all the current drawbacks, a commonly shared hypothesis is that genetics markedly influence elite power/sprint performance. In fact, several studies have reported that muscle power and muscle strength, which are important for power/sprint performance, are strongly genetically influenced [8, 18–20] and that absence of an appropriate genetic make-up will dramatically reduce ones chances of becoming an exceptional power athlete and/or sprinter. Therefore, the purpose of this review is to summarize the specific knowledge in the field of genetics and elite power/sprint performance and to provide future perspectives and directions for research in this field.

We searched for all published genotype–phenotype associations for elite athletic performance in the relevant databases (e.g. PubMed, Scopus, MEDLINE, Google Scholar) in the period from January 1998 to May 2012. Suitable key words such as: 'elite athletes', 'polymorphism', 'genes', 'athletic performance', 'exercise genomic' and 'single nucleotide polymorphism' were used. Search results were then narrowed using the following terms: 'elite athletes', 'power', 'sprint' and 'strength'. To enhance the accuracy of searching, we also visually scanned the reference lists of relevant publications. In this review, we have summarized a subset of the variants described to date that are believed to be associated with elite power/sprint athletic performance.

In addition to the *ACTN3* R577X polymorphism (Arg577stop rs1815739), which has been significantly associated with power/sprint performance in multiple independent cohorts, there are several other polymorphisms that have been associated with elite power and sprint performance including *ACE* I/D, registered single nucleotide polymorphism (rs)4646994, angiotensinogen (*AGT* Met235Thr, rs699), skeletal adenosine monophosphate deaminase (AMPD1) Gln(Q)12Ter(X) [also termed C34T, rs17602729], interleukin-6 (IL-6 −174 G/C, rs1800795), endothelial nitric oxide synthase 3 (*NOS3* −786 T/C, rs2070744; and Glu298Asp, rs1799983), peroxisome proliferator-activated receptor-α (*PPARA* Intron 7 G/C, rs4253778), and mitochondrial uncoupling protein 2 (*UCP2* Ala55Val, rs660339). The primary findings for these polymorphisms, including *ACTN3*, are further discussed in this review and are summarized in Table 1.

2 α-Actinin-3 (*ACTN3*) R577X Polymorphism Influence Elite Power/Sprint Athletic Performance

The α-actinins comprise a family of actin-binding proteins. The two skeletal muscle isoforms, (α-actinin-2 and α-actinin-3) are major components of the Z-line, where they bind and anchor actin filaments. α-Actinin-2 is expressed in all muscle fibres (slow and fast), whereas α-actinin-3 (encoded by the *ACTN3* gene) is more specialized and is expressed only in the fast, glycolytic, myosin heavy chain isoform (MyHC) type 2X muscle fibres that produce 'explosive', powerful contractions [21, 22]. North et al. [23], discovered a common polymorphism (C→T, rs1815739) in exon 16 of the *ACTN3* gene, resulting in the replacement of an arginine (R) with a premature stop codon (X) at amino-acid 577. The frequency of the 577X null allele differs across ethnic groups, with a frequency of ∼10 % or less in some African populations and approaching 50 % in groups of Eurasian descent [22]. The *ACTN3* 577XX genotype, associated with complete deficiency of α-actinin-3, occurs in an estimated 1.5 billion humans worldwide. α-Actinin-3 deficiency is not associated with any disease phenotype—likely due to compensatory upregulation of the closely related isoform, α-actinin-2. At the amino acid level, human α-actinin-2 and α-actinin-3 are 80 % identical and 90 % similar [22]. However, the specialized expression pattern and strong sequence conservation of α-actinin-3 over 300 million years suggests that it has a specific role in fast muscle fibres [21, 22].

Table 1 Elite power and sprint performance polymorphisms

Primary findings	Ethnicity; sex; country	Power athletes (n)	Controls (n)	Reference
***ACTN3* (R577X, rs1815739)**				
↑ RR genotype and R allele frequency in POW versus CON. No F elite or Olympian had XX genotype	Caucasian; M and F; Australia	107, Olympic (32), elite (75), Sp, Sw, Sk, judo, Cy	194, END; 436, CON	[24]
↓ XX genotype in POW versus END. Inverse correlation between frequency of XX genotype and sprinting success. No elite sprinter had XX genotype	Caucasian; M and F; Finland	89, elite (23), national (66), Sp	52, END; 120, CON	[26]
No genotype or allele frequency differences in POW versus END versus CON	African, M and F; Nigeria	62, elite (20), national (42), Sp, Ju	60, END	[31]
POW and sprinters had ↓ XX genotype and X allele frequency versus CON. No Olympic sprinter had XX genotype	Caucasian; M and F; Greece	73, Sp, Ju, Th	28, END; 181, CON	[33]
↓ XX genotype and X allele frequency in POW versus CON. Decreasing linear trend for XX genotype and increasing level of athletic performance. Only one XX genotype present in highly elite group	Caucasian; M and F; Russia	486, Highly elite (29), elite (71), sub-elite (206), average (180), Sp, Th, Ju, Sk, Wt, Vb, Sw, ski, soccer, hockey, wrestling	1197, CON	[2]
↓ XX genotype in POW versus CON. ↓ XX genotype in Caucasian POW versus CON, whereas there was only a trend for African American POW versus CON. No African American POW had XX genotype	Caucasian and African American; M and F (US)	75, Wt	876, CON	[35]
↑ RR and RX genotypes in POW versus END and CON. Tendency for ↑ R allele frequency in POW versus END and CON	Caucasian; M (96.7 %); F (3.3 %); Spain (91.7 %), non-Spanish European (8.3 %)	60, soccer	102, END; 123, CON	[121]
↑ RR genotype and R allele frequency in POW versus END and CON. ↑ RR and R allele frequency in elite POW versus national POW	Caucasian; M and F; Israel	81, elite (26), national (55), Sp	72, END; 240, CON	[39]
No genotype or allele frequency differences in POW vs. CON	African American and Jamaican; M and F; USA and Jamaica	114 (USA), 116 (Jamaica), Sp	191, CON (USA); 311, CON (Jamaica)	[30]
No genotype or allele frequency differences in POW versus CON	Caucasian; M and F; Spain	66, Vb	334, CON	[32]
No genotype or allele frequency differences in POW versus CON. ↑ R allele frequency in elite female POW versus national and CON	Asian; M and F; Taiwan	168, elite (81), national (87), Sw	603, CON	[37]
No genotype or allele frequency differences in POW versus CON	Caucasian; M; Italy	29, Sp, Sw, Vb	45, CON	[54]
***ACE* (I/D, rs4646994)**				
Genotype and allele frequency differences were observed between athletes and CON, with ↑ DD genotype and D allele in POW and II genotype and I allele frequency in END. ↑ I allele frequency with increasing of distance run	Mixed population; M and F, UK	20, Sp	37, Mixed; 34, END; 1096, CON	[48]

Table 1 continued

Primary findings	Ethnicity; sex; country	Power athletes (n)	Controls (n)	Reference
Across event duration, there was excess D allele frequency in elite POW and excess I allele frequency in elite END. ↑ DD genotype and D allele frequency in elite Sp and ↑ D allele frequency in elite Sw	Caucasian; M and F; Russia	65, elite (30), average (35), Sp, Sw,	91, END; 449, CON	[51]
D allele frequency ↑ in elite POW versus 4 different CON groups. No differences in non-Elite Sw	Caucasian; M and F; multinational	103, elite (56), non-Elite (47), Sw	615–1,906, CON (range of sample sizes for multiple CON groups used)	[52]
DD genotype and D allele frequency ↓ in elite POW versus END	Caucasian; M and F; Israel	42, Sp	79, END; 247 CON	[55]
↑ ID and ↓ II genotype in POW versus END. No differences between POW versus CON	Caucasian; M (92.5 % and 7.5 % F), multinational	54, soccer	52 END; 123 CON	[50]
↑ DD genotype and D allele frequency in elite POW versus CON. ↑ D allele frequency in elite POW versus average POW and versus elite END	Caucasian; M and F; Portugal	71, elite (39), average (32), Sw,	23, END, elite (14), average (9); 100, CON	[49]
No genotype or allele frequency differences in POW versus CON. Tendency for ↑ DD genotype in POW versus CON	Caucasian; M and F; Greece	73, Sp, Ju, Th	28, END; 181, CON	[53]
↓ DD genotype and D allele frequency in POW (elite + non-elite) versus CON. Frequency of D allele ↓ with advancing level of performance such that ↓ D allele frequency and DD genotype in elite POW versus CON	Asian; M and F; Korea	155, elite (55), non-Elite (100), Sp, Ju, Th, Wt	693, CON	[56]
No genotype or allele frequency differences in POW versus CON in either cohort. DD genotype ↑ in US POW M versus CON	African American and Jamaican; M and F; USA and Jamaica	114 (USA), 116 (Jamaica), Sp	191, CON (USA); 311, CON (Jamaica)	[30]
No genotype or allele frequency differences in POW versus CON	Caucasian; M; Italy	29, Sp, Sw, Vb	61, CON	[54]
***AGT* (T/C Met235Thr, rs699)**				
CC genotype and C allele frequency ↑ in POW versus END and CON	Caucasian, M, Spanish	63, not specified	100 END; 119 CON	[71]
***AMPD1* (C34T, rs17602729)**				
No genotype or allele frequency differences in POW versus CON. CT genotype ↑ in POW and CON versus END	Caucasian; M (92.5 %); multinational	54, soccer	52 END; 123 CON	[50]
CC genotype and T allele frequency ↑ and ↓, respectively, in POW versus END	Caucasian; M; Poland	158, Sp, Sw, Wt	160 CON	[79]
***IL6* (-174 G/C, rs1800795)**				
GG genotype and G allele frequency ↑ in POW versus END and CON	Caucasian; M; Spain	53 Sp, Ju, Th	100 END; 100 CON	[85]
No genotype or allele frequency differences in POW versus CON versus END for (1) Israeli athletes; (2) elite Israeli athletes; and (3) when pooled with Spanish athletes	Caucasian; M and F; Israel and Caucasian; M; Spain	81, elite (26), national (55), Sp	72, END; 205 CON	[38]
***NOS3* (*−786 T/C, rs2070744; #T/G Glu298Asp, rs1799983)**				
*TT genotype and T allele frequency ↑ in POW versus both END and CON	Caucasian; M; Spain	53, Sp, Ju, Th	100 END; 100 CON	[97]

Table 1 continued

Primary findings	Ethnicity; sex; country	Power athletes (n)	Controls (n)	Reference
*T allele frequency ↑ in POW versus CON	Caucasian; M; Italy	29, Sp, Sw, Vb	38, CON	[54]
G allele frequency ↑ in POW versus CON	Caucasian; M; Italy	29, Sp, Sw, Vb	41, CON	[54]
***PPARA* (Intron 7 G/C, rs4253778)**				
CC and GC genotype and C allele frequency ↑ in POW versus CON. Linear trend for ↑ frequency of C allele from END to mixed to POW	Caucasian; M and F; Russia	180, Sp, Wt Sk, Sw	491 END; 115 Mixed; 1,242 CON	[103]
No genotype or allele frequency difference in POW versus CON. Trend for ↑ GG genotype (10 %) in END versus POW (1 %)	Caucasian; M and F; Israeli	81, elite (26), national (55), Sp	72, END; 240 CON	[104]
***UCP2* (Ala55Val, rs660339)**				
C allele frequency ↑ in POW versus CON	Caucasian; M; Italy	29, Sp, Sw, Vb	47, CON	[54]
Polygenic profile				
Total genotype score was ↑ in POW versus END and CON. 5 POW (9.4 % of group) had perfect genotype score yet none were among the best sprinters	Caucasian; M; Spain	53 Sp, Ju, Th	100, END; 100 CON	[40]
Of 36 selected polymorphisms, IL-6 (−174G/C), NAT2 (K268R), and NOS3 (−786 T/C) significantly predicted sports performance and explained 21.4 % of variance	Caucasian; M; l Spain	53 Sp, Ju, Th	100, END	[110]

ACE I/D angiotensin converting enzyme insertion/deletion, *ACTN3* α-actinin 3, *AGT* angiotensinogen, *AMPD* adenosine monophosphate deaminase, *CON* control population, *END* endurance athletes, *Cy* track cyclists, *F* females, *IL-6* interleukin-6, *Ju* jumpers, *M* males, *Mixed* athletes with event duration between POW and END, *POW* power athletes, *NAT2N*-acetyltransferase 2, *NOS3* nitric oxide synthase 3, *PPARα* peroxisome proliferator-activated receptor α, *rs* registered single nucleotide polymorphism, *Sk* speed skaters, *Sp* sprinters, *Sw* swimmers, *Th* throwers, *UCP2* uncoupling protein 2, *Vb* volleyball players, *Wt* weightlifters, ↑ indicates higher; ↓ indicates lower

2.1 Human Association Studies

Almost a decade ago, the *ACTN3* R577X polymorphism was first shown to be associated with elite human athletic performance in a cohort of Australian athletes of White European descent. α-Actinin-3 deficiency (*ACTN3* 577XX genotype) was significantly underrepresented in elite power/sprint athletes and significantly overrepresented in elite endurance athletes compared with healthy controls [24]. Replication studies with independent cohorts of elite endurance athletes have shown that the X allele or the *ACTN3* 577XX genotype is associated with elite endurance performance in some [24–26] but not all [27–32] cohorts.

In contrast, the influence of *ACTN3* R577X on elite power performance is much more consistent. The initial results provided by Yang et al. [24], have been subsequently replicated in many other independent cohorts of elite power athletes. The frequency distribution of *ACTN3* 577XX genotype is significantly lower in elite power track and field athletes (i.e. sprinters, jumpers and throwers), and elite weight lifters compared with either controls and/or elite endurance athletes (summarized in Fig. 1) [24–26, 28, 33–35]. Additional support for the influence of *ACTN3* R577X polymorphism on elite power/sprint performance arises from our recent study of a large group of elite male

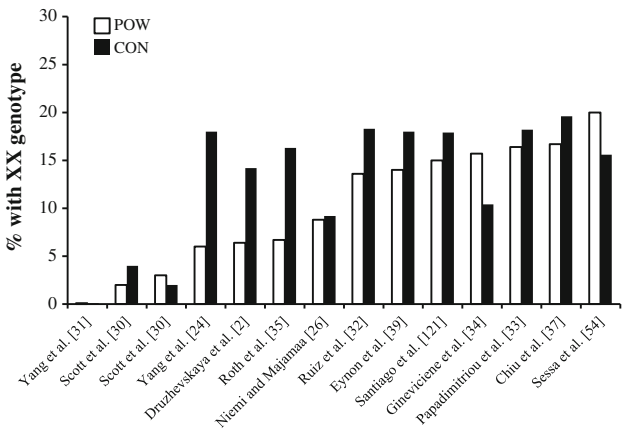

Fig. 1 Distribution of the *ACTN3* 577XX genotype frequency in elite power/sprint athletes (i.e., sprinters, jumpers, throwers and weight lifters) compared with either controls and/or elite endurance athletes [31]. *POW* power athletes, *CON* control populations or endurance athletes

European athletes ($n = 633$), in which we found that elite power athletes were ~50 % less likely to harbour the *ACTN3* 577XX genotype compared with sedentary controls ($p = 0.006$) [36].

The *ACTN3* 577XX genotype is also associated with the level of athletic competition achieved. Among Olympic (i.e. elite-level) sprint athletes, there were no cases of *ACTN3* 577XX genotype in both Australian and Israeli athletes [24, 25], and elite Taiwanese short-distance swimmers have significantly lower *ACTN3* 577XX genotype frequency compared with their non-elite (i.e. national-level) counterparts [37]. In addition, *ACTN3* R577X polymorphism may combine with other variants to create a 'favourable haplotype' or 'preferred polygenic profile' (to be discussed in section.4) for elite power performance [38–40]. Overall, these studies suggest that the *ACTN3* 577XX genotype is detrimental to power/sprint performance, particularly at the elite-level.

2.2 Potential Biological Mechanisms

To gain a greater understanding of the effects of the *ACTN3* R577X polymorphism on physiological and metabolic function at baseline and in response to exercise training, an *Actn3* knock-out mouse model has been developed [41]. Compared with wild-type, *Actn3* knockout mice (i.e. *ACTN3* 577XX genotype) have (1) reduced muscle mass due to decreased diameter of fast muscle fibres (where α-actinin-3 is primarily expressed); (2) a significant decrease in grip strength; and (3) increased endurance capacity, with knockout mice running 33 % further than their wild-type littermates at baseline. The absence of α-actinin-3 results in a shift in muscle properties towards those of a slow muscle fibre. Fast muscles from knockout mice have significantly decreased anaerobic enzyme activity and increased oxidative/mitochondrial enzyme activity, without a shift in fibre-type distribution [42]. Isolated knockout muscles have longer twitch half-relaxation times and enhanced recovery from fatigue compared to wild-type [42, 43]. Thus, the phenotypes of the *Actn3* knockout mouse mimic the gene association studies performed in humans and provide a plausible explanation for the reduced sprint capacity, and possible improved endurance performance in humans with the *ACTN3* XX genotype (Fig. 2) [44].

To date there have not been adequate studies of human muscle to determine if results from the *Actn3* knockout mouse are relevant and reproducible in humans. Vincent et al. [45], have studied human muscle biopsies of different *ACTN3* genotypes and have shown that the cross-sectional area and number of human Type IIB/X muscle fibres are significantly greater in untrained individuals who have the *ACTN3* 577RR genotype compared with those who have the

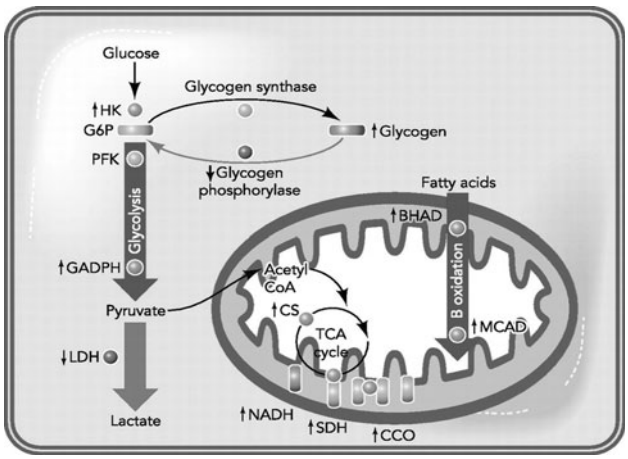

Fig. 2 Endurance versus power/sprint: metabolic pathway of *Actn3* knockout mouse muscle metabolism. Knockout mice display a shift toward a more oxidative pathway of muscle metabolism. Enzyme analyses show increased expression in the glycolysis pathway hexokinase activity, and glyceraldehyde 3-phosphate dehydrogenase, which is thought to provide greater muscle endurance performance, to the detriment of muscle power/sprint. The anaerobic conversion of pyruvate to lactate by lactate dehydrogenase is reduced, whereas the activity of enzymes involved in mitochondrial oxidative metabolism (citrate synthase, succinate dehydrogenase, cytochrome c oxidase) and fatty acid oxidation (3-hydroxyacyl-CoA dehydrogenase, and medium chain acyl-CoA dehydrogenase) are increased in *Actn3* knockout mice. Glycogen content is increased in *Actn3* knockout mice, due to reduced glycogen phosphorylase activity. Reproduced from Berman and North [44] *BHAD* 3-hydroxyacyl-CoA dehydrogenase, *CS* citrate synthase, *CCO* cytochrome c oxidase, *CoA* coenzyme A, *G6P* glucose 6 phosphate, *GAPDH* glyceraldehyde 3-phosphate dehydrogenase, *LDH* lactate dehydrogenase, *MCAD* medium chain acyl-CoA dehydrogenase, *NADH* nicotinamide adenine dinucleotide, *PFK* phosphofructokinase, *SDH* succinate dehydrogenase, *TCA* tricarboxylic cycle. ↑, increased; ↓, reduced

ACTN3 577XX genotype. The authors suggest that the detrimental effect of α-actinin-3 deficiency on muscle power in humans may be related to the fibre-type proportions through a decrease in size of the fast-twitch fibres of the muscle.

The *Actn3* knockout mouse, together with the above-mentioned preliminary results in humans [45], have outlined potential mechanisms behind the influence of α-actinin-3 deficiency on human athletic performance. However, more research is needed to determine whether the insights provided by the *Actn3* knockout mouse apply to the human α-actinin-3 deficient state, and the major gap in the field is a direct demonstration of the effects of the *ACTN3* genotype on the characteristics of human muscle pre- and post-endurance and sprint training. This will have implications for our understanding of the genetic factors that influence elite power/sprint performance. It is important to keep in mind that *ACTN3* R577X alone is the only one of what seems like a set of genetic variants that may contribute to elite power/sprint performance. The number of polymorphisms that make up this set of genetic variants

and contribute to the power/sprint performance phenotype is currently unknown.

3 Additional Variants Linked with Elite Power/Sprint Performance

3.1 Angiotensin-Converting Enzyme Insertion/Deletion (*ACE I/D*)

The *ACE* I/D is the second most commonly studied polymorphism (after *ACTN3* R577X) with respect to power performance. The presence of a 287 base pair fragment (I allele), rather than the absence (D allele), is associated with lower ACE activity in serum [46] and in the heart [47]. There is evidence of both alleles being associated with performance; the I allele is associated with endurance phenotypes and the D allele with sprint and power phenotypes. Because this review is focused on the latter, we will review only the associations with elite power performance.

3.1.1 Human Association Studies

There are conflicting results regarding the association between *ACE* I/D and elite power performance with an excess of DD genotypes and D allele frequencies [48–52], no genotype distribution differences [30, 53, 54] or an excess of II genotype and I allele frequencies [55, 56] shown in elite power athletes compared with sedentary controls and/or elite endurance athletes. Some studies have subdivided their athlete cohorts into elite and national level, but the majority did not observe an association with the level of performance [49, 51, 52]. In contrast, other studies have shown linear trends as such that the DD genotype and D allele and II genotype and I allele frequencies are overrepresented in elite power and elite endurance athletes, respectively [47, 50]. Along this same line, not all studies have shown a relationship between the D allele and power performance. No association was identified in Greek and American cohorts [30, 53], with the opposite finding (D allele associated with endurance performance) in Israeli and Korean cohorts [55, 56]. In fact, the studies by Scott et al. [30], and Kim et al. [56], were performed in non-Caucasian populations, suggesting that the association between the ACE D allele and power performance may be restricted to elite Caucasians. Similarly, Amir et al. was criticized for failing to account for the multi-ethnic nature of Israeli Caucasians, which may explain this finding [57]. Between-study differences in the competition level of athletes, gender and a small sample size further complicate this issue and provide a reasonable explanation for the conflicting findings.

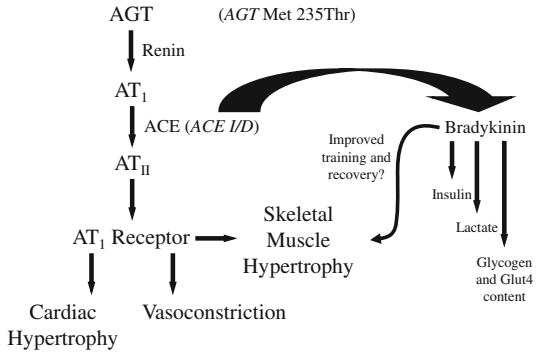

Fig. 3 Possible mechanisms by which the angiotensin converting enzyme insertion/deletion and angiotensinogen Met 235 Thr polymorphisms influences skeletal muscle mass and elite power performance. These polymorphisms may have direct effects on skeletal muscle via the angiotensin 1 receptor or by modulating bradykinin levels and metabolic substrates, which may influence the training sessions and the subsequent adaptations during recovery from exercise. *ACE I/D* angiotensin converting enzyme insertion/deletion, *AGT* angiotensinogen, AT_I angiotensin 1, AT_{II} angiotensin 2, *Glut4* glucose transporter type 4

3.1.2 Biological Mechanisms

A possible mechanism for the genotype association that may be present in elite power athletes is related to the renin-angiotensin system. ACE is responsible for cleaving the inactive peptide angiotensin I into angiotensin II and has been strongly implicated in left ventricular hypertrophy [58–60], smooth muscle hypertrophy [61, 62] and, also, skeletal muscle hypertrophy (Fig. 3). Angiotensin II appears critical to overload-induced hypertrophy in skeletal muscle, as animal studies that inhibit ACE have shown attenuated overload-induced hypertrophy [63, 64]. D allele carriers with higher ACE activity may have higher angiotensin II levels, which appear to translate into higher muscle strength in non-elite individuals [65, 66]. The *ACE* genotype may also influence fibre type [67], as untrained volunteers with the DD genotype have a higher proportion of Type II/X and lower proportion of Type I fibres than Type II. An increased muscle mass and a higher percentage of fast-twitch fibres would favour power and sprint performance. However, these findings are not supported in the ACE partial-knockout mouse [68], as fibre-type proportions were similar in the soleus muscle. The conflicting findings cast doubt on the mechanism by which ACE may contribute to elite power performance.

3.2 Angiotensinogen

AGT is a circulating protein produced by the liver that is cleaved by renin to yield a 10-amino acid peptide, angiotensin I, that is further cleaved to an 8-amino acid peptide, angiotensin II, by ACE [69]. A T→C polymorphism in the

angiotensinogen (*AGT*) gene (also known as *AGT* Met235Thr) has also been associated with performance phenotypes. The resulting protein is associated with left ventricular hypertrophy in endurance athletes [70]. Given that the D allele of the *ACE* I/D polymorphism (that is located in the same gene pathway) is associated with power performance, it was hypothesized that the C (Thr) allele would be overrepresented in elite power athletes. The CC genotype frequency was higher in elite Spanish power athletes than in either controls or endurance athletes. [71] This is supported by studies examining higher *ACE* DD genotype frequencies in power/sprint athletes [48–52], as higher levels of angiotensin II are produced, which can be a skeletal muscle growth factor and therefore beneficial to high-velocity, power performance [63–66]. However, given the modest sample size ($n = 63$) in a single study [71], definitive conclusions regarding the role of *AGT* Met235Thr polymorphism in power athletic performance cannot be drawn at this juncture.

3.3 Adenosine Monophosphate Deaminase 1

The breakdown of ATP results in an equimolar formation of inosine monophosphate (IMP), which is produced by deamination of adenosine monophosphate (AMP) in a reaction catalyzed by AMP deaminase (AMPD). The skeletal muscle isoform of AMPD is activated during short-term, high-intensity exercise, when the rate of ATP utilization exceeds the cell's potential to resynthesize ATP [72]. AMPD, encoded by the *AMPD1* gene, appears to be an important regulator of skeletal muscle energy metabolism during exercise [73]. Similar to the *ACTN3* R577X variant, a polymorphism in the *AMPD1* gene results in a premature stop codon (*AMPD1* C34T), and complete deficiency of the AMPD protein, causing impaired AMP metabolism that produces muscle fatigue, weakness and cramping [74]. However, unlike *ACTN3*, homozygosity for the null allele (TT genotype) is rare ($\sim$2 % of population) [75]. Heterozygotes have intermediate levels of AMPD activity [76], which has been shown to be associated with power/sprint exercise capacity [77], with the CT genotype present at a higher frequency in power compared with endurance athletes [50].

While power performance requires the capability to perform rapid, repeated muscle contractions, the practical relevance of the *AMPD* C34T association needs to be clarified. To this effect, reduced anaerobic performance during a Wingate anaerobic test was shown in physically active men and women with the TT genotype [78], but specific phenotype testing has yet to be assessed in elite athletes. In contrast, a recent study found that the CC genotype and C allele were higher in power athletes versus controls [79]. These associations were consistently observed across several different types of power athletes (e.g. short-distance runners and swimmers, and weightlifters) and no power athlete had the TT genotype. Thus, it would appear that the C allele is beneficial for power performance, but, given the low frequency of the TT genotype, the implications of this polymorphism remain to be determined.

3.4 Interleukin-6

Skeletal muscle produces IL-6 as a means of increasing substrate delivery and possibly helping to reduce inflammation following exercise [80]. A functional C→G polymorphism at position -174 was described in the 5′ promotor region of the *IL-6* gene [81], with the mutant G allele, rather than the wild-type C allele, being associated with increased transcriptional response in in vitro [81, 82] and in in vivo conditions [83]. In terms of human performance, the C allele and the CC genotype have been associated with a higher creatine kinase activity following eccentric exercise [84]. The authors concluded that the G allele may protect skeletal muscle during powerful contractions and may aid in repair, thus promoting beneficial adaptations during power training. Consequently, Ruiz et al. [85] have found that the GG genotype and G allele frequencies are higher in power versus endurance athletes and controls. To confirm these findings, and to address sample size limitations that plague gene association studies, we have examined the role of *IL-6* polymorphism on sprint performance in a separate cohort [86] and then pooled our data with that of Ruiz et al. [85]. We did not observe an association with genotype in any groups, nor were any differences detected when the athletes were stratified into elite versus national competitors. Finally, when the Spanish and Israeli cohorts were pooled, the previously observed genotype association in power athletes was no longer present. Considering that the association was not confirmed using separate and combined cohorts and no other studies are available, the *IL-6* genotype does not appear to be a prominent factor in elite power performance. However, given the possible influence of *IL-6* -174G/C on muscle repair and the inflammation process, it can be hypothesized that it is related to muscle recovery following exercise performance. These contradictory findings highlight the need to replicate studies in large cohorts and to account for different ethnic backgrounds.

3.5 Nitric Oxide Synthase 3

The *NOS3* gene, located on human chromosome 7q35–36, encodes endothelial NOS (eNOS), which converts L-arginine to L-citrulline and NO. NO has effects on vascular tone [87, 88], muscle blood supply [89, 90] and may

influence skeletal muscle glucose update during exercise [91], which is the preferred substrate during high-intensity, anaerobic sprint activities.

There are two *NOS3* polymorphisms that have been associated with power performance. The *NOS3* -786 T/C polymorphism results in decreased gene promoter activity and NO synthesis [92]. In addition, there is a missense glutamine/aspartame (*NOS3* Glu298Asp) that is associated with reduced endothelial activity, NO production [93, 94] and improved response to exercise training in non-athletes [95, 96]. Both polymorphisms were hypothesized to improve endurance performance. Instead, the opposite was observed, as the TT genotype frequency of the *NOS3* −786 T/C polymorphism was higher in elite Spanish power athletes versus endurance athletes and sedentary controls [97], while the T allele frequency was higher in both Spanish and Italian power athletes compared with controls [54, 97]. Looking at a second polymorphism within *NOS3* (Glu298Asp), the Glu298 allele frequency was higher in Italian power athletes compared with controls [54]. Greater NO abundance, which may influence muscle hypertrophy [98, 99], has been suggested as a potential link between these *NOS3* genotypes and power performance. Beyond this, the authors do not elaborate on the interpretations of their findings. However, unlike previous polymorphisms and elite power performance, the findings for the *NOS3* genotypes are consistent both within and across studies, so this may be a true association that warrants further study.

3.6 Peroxisome Proliferator-Activated Receptor Alpha

Peroxisome proliferator-activated receptor alpha PPARα, encoded by the *PPARA* gene, is a transcription factor related to metabolism and energy homeostasis, and is present at high levels in tissues such as liver, skeletal muscle and myocardium where catabolism of fatty acids occur [100]. The C allele in the intron (non-coding region) 7 G/C polymorphism of the *PPARA* gene is thought to be associated with cardiac growth [101], and increased risk of coronary artery disease [102]. The CC genotype and the C allele frequency were higher in elite Russian power athletes versus controls [103]. Moreover, an increasing linear tendency for presence of the C allele was observed with increasingly anaerobic sports. These results, however, were not confirmed in a subsequent study. We found no significant genotype association for *PPARA* in a cohort of Israeli athletes, with only a tendency for higher GG genotype in elite endurance athletes (10 %) versus power athletes (1 %, $p = 0.051$) [104]. The disagreement between these two studies reinforces the need for replication studies, as the finding by our group is likely limited by sample size.

3.7 Mitochondrial Uncoupling Protein 2

The uncoupling protein 2 (*UCP2* is a member of the uncoupling protein family that functions in the mitochondria to dissipate the proton gradient before it can be used to produce energy via oxidative phosphorylation. There is only one study investigating the *UCP2* polymorphism in elite power athletes. This paper reported that, with respect to the *UCP2* C/T polymorphism, there is a greater C allele frequency in elite Italian power athletes compared with controls [54]. It has been suggested that this polymorphism influences resting leptin levels [105] and obesity [106, 107], in which the T allele is the risk allele and could decrease the likelihood of achieving athletic success. However, whether it plays a role in elite power performance remains to be seen and further replication is required.

4 Polygenic Profiles

A common theme amongst all of the studies reviewed is the low percentage of variation explained by each individual polymorphism. For example, the *ACTN3* R577X polymorphism has been estimated to account for only 2.5 % of the variance in athletic performance [108]. Recently, studies have begun to examine the interactions between two or more genes on performance. Williams and Folland [109] determined the probability for the existence of an individual with a theoretically 'optimal' polygenic profile for endurance sports. They quantified this 'optimal' profile using a so-called 'total genotype score' (TGS, ranging from 0–100, with '0' and '100' being the worst and best genotype combinations, respectively), a simple algorithm resulting from the combination of 23 candidate polymorphisms explaining individual variations in endurance performance. They estimated that there was a 0.0005 % chance of a single individual in the world having the 'preferable' form of all 23 endurance-related polymorphisms.

Two recent studies have examined the role of a polygenic profile on elite power performance. In the first study, TGS was determined using six polymorphisms that have been previously associated with power-related phenotypes, including *ACE, ACTN3, AGT, NOS3, IL-6,* and the myostatin gene (*MSTN*) [40]. Elite power athletes had a significantly higher total genotype score than either endurance athletes or controls, who had similar scores. Interestingly, five (9.4 %) of the power athletes had perfect scores, yet none of these athletes were amongst the best sprinters. In a similar approach, the same group then tried to predict sports performance in elite athletes based on genotype. Microarray analysis of 20 genes (36 polymorphisms within

the selected genes) were examined and it was revealed that *IL-6, NOS3*, and *N*-acetyltransferase (*NAT2*) significantly predicted sports performance (both endurance and/or power) and explained 21.4 % of the variation [110]. It is to be noted that the probability of a Spanish individual possessing an optimal polygenic profile (i.e. TGS = 100) for up to the six studied power-related polymorphisms [40] is small, i.e. ~0.2 %. Assuming that other polymorphisms influencing sprint performance are yet to be identified further decreases the probability of a single person possessing the 'optimal' polygenic trait.

5 Summary: *ACTN3* Leads the Way

This review has examined the current evidence for a genetic blueprint in elite power/sprint athletes. Promising findings exist in just a handful of genes with varying depths of supporting evidence. Even though DNA biobanks of athlete cohorts have rapidly increased the number of athletic performance genetic association studies, replication of 'significant' results and the provision of mechanistic evidence is still to be established for the majority of the reviewed genes. The presence of specific variants across the genome that influence our ability to generate power/speed, as well as the occurrence of polygenic traits and the role of the environment, requires further investigation and more robust research. Presently, the *ACTN3* R577X polymorphism has provided the most consistent results, being the only muscle gene to show an elite power performance association across multiple athlete cohorts. We believe three key reasons underlie the robust nature of this polymorphism that currently sets it apart from the other reviewed genes (1) the *ACTN3* R577X allele is a loss of function (LoF) variant in a gene with a high degree of evolutionary conservation. Homozygosity results in complete loss of α-actinin-3 expression in fast (MyHC type 2X) skeletal muscle fibres, which are depended on for exceptional athletic performance. This is not necessarily typical of other Single Nucleotide Polymorphisms and gives tangible evidence to support this association; (2) the original study performed by Yang et al. [24] was well powered, with large numbers relative to the minor allele frequency—providing sufficient statistical power to detect a genetic difference; again this is not typical of all association studies with most involving smaller cohorts and a lower minor allele frequency; and (3) the follow up research utilizing an *Actn3* knockout mouse model to mimic the human 577XX genotype, continues to provide mechanistic insight to explain this LoF variant. The original strong study design and substantial follow-up experiments has kept *ACTN3* firmly on the radar of other investigators for almost 10 years resulting in many replicating studies. Understanding the *ACTN3* R577X polymorphism has been strengthened by international contributions from multiple populations and ethnic groups. These studies have replicated the result and contributed to our further understanding of α-actinin-3 deficiency in training [108, 111, 112], aging [113–116], muscle function and damage [112, 117, 118] studies. As a result, there is now a rich literature on α-actinin-3 function and a substantial body of evidence to support its role in muscle performance. We note that the other tested variants have much less depth, provide less consistent results (i.e. *ACE* I/D) or require additional testing in multiple cohorts (e.g. *IL-6, AMPD1, NOS3, PPAR, UCP2*), making it difficult to form firm conclusions as to the accuracy of these associations.

6 Moving Forward: *Citius, Altius, Fortius* (Faster, Higher, Stronger)

Despite advances in our understanding of the genetic basis of power and sprint performance, there are limitations that have hampered the progression of genetic-based athletic research that need to be addressed. Given the low percentage of variation explained by each individual polymorphism, undiscovered novel SNPs are likely to exist. Using *ACTN3* as an example of a successful model, a focus on LoF variants would appear to be a likely place to focus current efforts in identifying novel performance variants. Data from the 1,000 Genomes Project have reported that on average each individual genome carries over 100 LoF variants, with up to ~20 % present in a homozygous state. Homozygous inactivation of a gene can have a range of effects: from the development of severe recessive disease, to inactivation without obvious clinical implication; the latter are referred to as LoF-tolerant genes [119]. These LoF-tolerant genes may constitute specific variations between populations and could account for novel performance traits. The evolutionary selection of these LoF variants can also be estimated in order to determine the presence of positive selection that would suggest functional changes as a result of the polymorphism. Similarly, significant improvements in sequencing technologies have enabled large amounts of genomic data to be generated from different human populations, providing an excellent source of allele frequency estimates and novel variants for further analysis.

Improving cohort numbers in current biobanks would pave the way for genome-wide testing. To date, the analysis of single variant candidate genes (often poorly justified) using low-throughput techniques has yielded conflicting findings and inconsistent results. Current genome-wide association study technology means that up to one-million polymorphisms are analysed per individual. A

genome-wide approach, designed with sufficient power could narrow down specific regions or polymorphisms that contribute to athletic performance. To utilize this technology large (in excess of 1,200 individuals [120]), good quality cohorts of sprint and endurance athletes (performance tradeoff) and appropriately matched controls could be used to identify novel single variants and complex polygenic profiles related to elite athlete performance.

Lack of replication in the literature is typically due to between-study differences in the type and quality of recruited athletes. This reflects the absence of a universally accepted definition of what is considered an 'elite-level' athlete. Race qualifying standards to compete at a national or international (Olympic Games) level are not always equal between countries and an athlete's result in major competitions (national vs. regional vs. world championships) may be better indicators of performance. In the future, using standardized criteria, such as that outlined by Druzhevskaya and colleagues [2], and rigid definitions of athletic status, based on an athlete's achievements (as detailed above) will enable greater comparisons between studies. Likewise, the addition of quantitative traits (such as 100–200 m sprint time, marathon run time or $\dot{V}O_{2max}$) in athlete cohort analyses could significantly improve comparisons between studies and reduce the total number of athletes required for statistically relevant analyses.

A primary limiting factor in athlete studies is the recruitment of large groups of elite and 'highly elite' individuals (i.e. medal winners in Olympic Games and/or World Championships) due to the rarity of athletic champions worldwide for a given ethnicity and sporting event. The sample size for detecting genetic associations is known to be highly affected by factors such as the allele frequency, degree of linkage disequilibrium (i.e. a measure of association between alleles at different loci), inheritance models (e.g. additive vs. dominant) and effect size (e.g. odds ratio) of the variants. Recently, it was estimated that, testing a single polymorphism using a case (athletes) control (non-athletes) design would require $\sim$250 cases to obtain a statistical power of 80 % [120]. It is difficult to recruit a homogenous cohort of 250 elite power/sprint athletes from the same country. To address this, large multisite collaborations and data sharing between researchers will be necessary to ensure sufficient statistical power is obtained.

7 Conclusions

Our review highlights promising evidence in the field and future potential for building and improving knowledge of athletic performance, particularly with established athlete biobanks. We note that identification of novel genotypes associated with performance is only the tip of the iceberg, and the implications of training and environment must always be considered. Replication studies and establishing the functional significance of these variants is critical to understand their role in performance. Similar to an athlete's pursuit of Olympic achievement, there is much knowledge to be gained in the field. Determining the significance of these variants will enhance our understanding of the role our genes play in the power athlete's pursuit of the Olympic motto, *Citius, Altius, Fortius*.

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