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REVIEW ARTICLE

Effective utilization of genetic information for athletes and coaches: focus on *ACTN3* R577X polymorphism

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Naoki Kikuchi and Koichi Nakazato. Effective utilization of genetic information for athletes and coaches: focus on *ACTN3* R577X polymorphism. *JENB*., Vol. 19, No. 3, pp.157-164, 2015 **[Abstract]** Training variants (type, intensity, and duration of exercise) can be selected according to individual aims and fitness assessment. Recently, various methods of resistance and endurance training have been used for muscle hypertrophy and VO_2max improvement. Although several genetic variants are associated with elite athletic performance and muscle phenotypes, genetic background has not been used as variant for physical training. *ACTN3* R577X is a well-studied genetic polymorphism. It is the only genotype associated with elite athletic performance in multiple cohorts. This association is strongly supported by mechanistic data from an *Actn3*-knockout mouse model. In this review, possible guidelines are discussed for effective utilization of *ACTN3* R577X polymorphism for physical training. **[Key words]** Genotype, physical training, trainability, muscle phenotype, endurance performance

INTRODUCTION

Physical resistance and endurance training have beneficial effect on fitness and athletic performance for the general population and athletes [1,2]. Resistance and endurance training variants such as type, intensity, and duration of exercise can be selected according to individual aims and fitness assessment. Recently, various resistance and endurance training methods have been used for muscle hypertrophy and VO_2max improvement. However, genetic factors such as polymorphisms have not been considered for athletic- and fitness- related candidate genes.

Genetic variation may contribute to inter-individual differences in athletic performance and fitness assessments. Recent reviews have noted that variants of more than 200 genes are associated with fitness-related phenotypes [3]. There is an association between genetic polymorphism and athletic performance [4]. One of the most potent athletic performance-related genotypes is α-actinin-3 (*ACTN3*) R577X. It is associated with muscle fiber composition [5], muscle strength [6], structural factor in type II fibers [7], and elite performance [8-10]. Factors such as muscle composition and muscle tension can affect the response to resistance training with regard to muscle hypertrophy and the development of strength and power. The purpose of this review is to summarize current knowledge on training protocols for muscle hypertrophy and VO_2max improvement, genetic polymorphism (especially the *ACTN3* R577X genotype), and fitness phenotypes in athletes and the general population so that we can provide a proposal for effective utilization of genetic information to improve physical training. Effective utilization of genetic information may provide a suitable response of high and low responders to physical training (Fig. 1). Characteristics of *ACTN3* R577X are summarized in Table 1. These characteristics based on recent primary findings are discussed in details.

Training protocols for muscle hypertrophy and VO2max improvement

Current guidelines for resistance training state that loads of ≥ 65% one-repetition maximum (1RM) are necessary to elicit favorable increases in hypertrophy. Higher loads are

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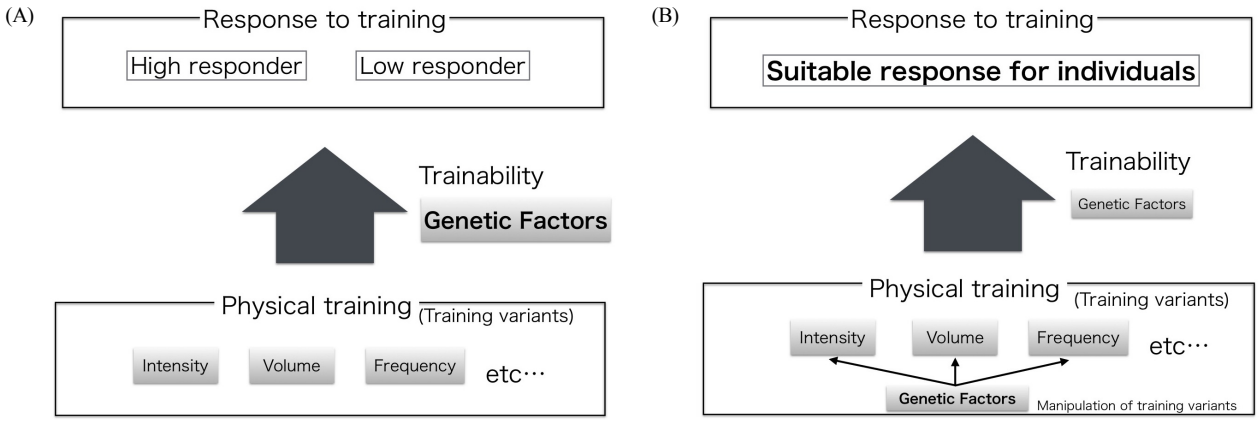

Fig. 1. Variation in physical training process and response to training (A) and a proposal for effective utilization of genetic factors such as the *ACTN3* R577X genotype for physical training (B).

Table 1. Characteristics of individuals with different *ACTN3* R577X genotypes

	RR genotype	RX genotype	XX genotype	References
Athletic status				
Sprint/power status	High frequency	High frequency	Unknown	[10,24,28,29,33,45-53]
Endurance status	Unknown	Unknown	High frequency (Limited evidence)	[10,34,49,51,54-56]
Mixed events	Unknown	Unknown	Unknown	[57]
Physiological phenotype				
Strength	High	High or Moderate	Low	[6,35,58-61]
Power	High	High or Moderate	Low	[38,44,62-66]
Aerobic performance	Unknown	Unknown	High (Limited evidence in humans)	[60,67,68]
Muscle mass	High	High	Low	[36,69]
Muscle composition (Type IIx)	High	-	Low	[5,58,70]
Muscle damage (CK) after eccentric exercise	Low	Low	High	[39,71,72]
Muscle stiffness	High	Moderate	Low	[73]
Sex hormone (testosterone) after resistance training	High	High	Low	[74]
Strength training response	High (Limited evidence)	High (Limited e vidence)	Low (Limited evidence)	[43,68,75-77]

needed to maximize the strength [1,11]. It has been postulated that heavy loading is required to fully recruit higher-threshold motor units [11]. These data suggest that strength and hypertrophy can be optimized via complete motor unit activation using heavy loads. However, a recent study has suggested that low-intensity exercise such as 30-40% 1RM can induce a similar level of muscle hypertrophy as high-intensity resistance training [12-14]. Mitchell *et al*. [12] have demonstrated an effect of resistance training with low loads (30% 1RM) and high repetitions on muscle hypertrophy. They examined subjects who performed 10 weeks of unilateral knee extension resistance training. Each leg was randomly assigned in a counterbalanced fashion to one of three possible unilateral training conditions: 1) one set of knee extensions performed until voluntary failure at 80% of 1RM, 2) three sets of knee extensions performed to the point of fatigue at 80% of 1RM, and 3) three sets performed to the point of fatigue at 30% of 1RM. Similar results were observed between the 3 sets at 80% 1RM group and the 3 sets at 30% 1RM group with respect to muscle hypertrophy. However, improvement in the one set and 3 sets groups at 80% 1RM was higher than that in the 3 sets at 30% 1RM group after training. Schoenfeld *et al*. [13] have examined the effect of low-load and high-load training on muscle strength and hypertrophy in well-trained men. They divided subjects into two groups: a low-load training group (n = 9) and a high-load training group (n = 9). They found that low-load training was an effective method to increase muscle hypertrophy in the extremities of well-trained men. These results suggested that there is a different optimal load and method for obtaining muscle hypertrophy

between high-load (70-85% 1RM) and low-load (30-40% 1RM) resistance training.

VO_2max is an important factor in endurance performance. Successful athletic training involves the manipulation of training intensity, duration, and frequency to maximize the performance and related physiological characteristics. Endurance athletes normally use a high-volume low-intensity training approach incorporated with moderate volumes of high-intensity training. Recently, Gibala and Jones [15] have reported that high-intensity interval training (HIT) can enhance aerobic capacity and muscle endurance performance similar to traditional endurance training with a markedly lower total exercise volume and training-time commitment. These studies demonstrated significant improvements in peak oxygen uptake at a substantially reduced training volume. In fact, the weekly training volume for sprint interval training was ~90% lower than that in the continuous endurance training group (i.e., 225 vs. 2,250 kJ) [16]. From an athletic viewpoint, HIT is also an effective strategy to improve endurance performance when used as a supplement to high training volumes in well-trained endurance athletes [17]. The observed increase in VO_2max after HIT with low-volume training is similar to that observed in subjects who perform traditional low-intensity high-volume endurance training [15,16].

These previous studies suggest novel training protocols can vary depending on parameters such as intensity, repetition, and duration. They can differ dramatically from traditional training protocols. Previous studies considering twins and families have suggested that genetic factors can affect the trainability and training responses [18,19]. In a well-known family study, Bouchard *et al*. [19] estimated that the heritability of VO_2max training response was 47% (Health, Risk Factors, Exercise Training, and Genetics; HERITAGE). However, athletes and coaches do not consider genetic factors such as polymorphisms in athletic- and fitness- related candidate loci in the development of training programs. We will discuss one of the most extensively studied genetic polymorphisms associated with these phenotypes, *ACTN3* R577X, in the next section. Potential genotype-based training protocols are also proposed.

Effect of ACTN3 R577X polymorphism on athletic performance and muscle phenotypes

ACTNs (actin binding proteins) are major structural components of Z-line in skeletal muscles [20]. Two ACTN isoforms (ACTN2 and ACTN3) encoded by *ACTN2* and *ACTN3* are expressed in human skeletal muscles [21,22]. ACTN3 is expressed only in fast-twitch skeletal muscle fibers [22]. It is important for anchoring actin. It also plays a regulatory role in the coordination of muscle fiber contraction [23]. ACTN3 is absent in approximately 18% of the European population and 25-29% of the Japanese population. These individuals are homozygous for an allele encoding a premature stop codon at R577X (rs1815739, C-to-T transition at nucleotide position 1729 in the *ACTN3* open reading frame) [22,24]. The *ACTN3* 577XX genotype associated with a complete deficiency of α-actinin-3 occurs in approximately 1.5 billion people worldwide. The *ACTN3* XX genotype (complete α-actinin-3 deficiency) is not associated with any disease phenotype possibly due to compensatory upregulation of its closely related isoform α-actinin-2. At amino acid level, human α-actinin-2 and α-actinin-3 are 80% and 90% similar to *ACTN3*, respectively [21]. The specialized expression pattern and strong sequence conservation of α-actinin-3 over 300 million years suggests that it plays a specific role in fast-twitch skeletal muscle fibers [21,25].

In the first study on *ACTN3* R577X genotype, Yang *et al*. [10] have suggested that RR and RX genotypes are associated with sprint/power performance while the XX genotype is associated with endurance performance in Australian athletes. Interestingly, the XX genotype was not observed in elite sprint/power athletes who participated in the Olympic Games [10]. The *ACTN3* R allele and RR genotype are associated with top-level power-oriented athletic performance in a broad variety of ethnic groups [26-30]. In a meta-analysis, Alfred *et al*. [31] have reported that the *ACTN3* RR genotype is more common among European sprint/power athletes than in non-athletes. Another meta-analysis [32] also revealed a positive association between *ACTN3* RR and RX genotypes and sprint/power athletic status in Europeans but not in Asians or Africans. Recently, a few studies have evaluated the association between the *ACTN3* R577X genotype and athletic status in Asian athletes such as wrestlers, track athletes, and field athletes [24,33]. In our recent study [30], the frequency of RR and RX genotypes was positively associated with the level of athletic status (i.e., regional < national < international) for sprint/power track and field athletes and wrestlers. However, we did not detect carriers of the XX genotype in a sample of Olympic wrestlers [30], similar to the results of Yang *et al*. [10]. In replication studies considering independent cohorts of elite endurance athletes, the X allele and the *ACTN3* XX genotype were associated with elite endurance performance in some studies, but not all studies [34]. Although it has been reported that the *ACTN3* RR genotype is associated with endurance performance [34], the role of *ACTN3* R577X genotype in endurance performance remains unclear.

The relationship between the *ACTN3* R577X genotype and muscular phenotypes in the general population and in athletes belonging to several ethnic groups has been examined extensively [35-38]. Previous studies have suggested that the XX genotype is associated with smaller thigh-muscle cross-sectional area and lower muscle function than the RR or RX genotype in adult Japanese population [35,36]. In addition, individuals with the *ACTN3* XX genotype (complete ACTN3 deficiency) have higher creatine kinase activities after eccentric training than individuals with the *ACTN3* RR genotype [5]. Soccer players with the XX genotype also exhibited higher creatine kinase activities and higher levels of α-actin and cortisol than those with the RR genotype [39]. The possible mechanisms underlying the association between ACTN3 and structural advantage in type II fibers have been discussed in details [7]. The proportional surface area and number of type IIx fibers are greater in subjects with the RR and RX genotypes than in those with the XX genotype [5]. In addition, muscles of *Actn3*-knockout mice have reduced force generation associated with response to muscle disuse [6,40,41]. Therefore, *ACTN3* R577X genotype affects structural factors of type II fibers.

Previously, we have found that athletes with the *ACTN3* RR or RX genotype have higher peak power in the 30-s Wingate anaerobic performance test (WAnT) than those with the XX genotype [44]. We also found that 4.6% of variability in the relative peak power in WAnT among male Japanese athletes was due to the *ACTN3* R577X genotype [44]. Massidda *et al*. [42] have reported that the *ACTN3* R577X genotype accounts for 8.0% of the variation in squat-jump performance of elite soccer players. In the general population, the *ACTN3* R577X polymorphism is responsible for 1-2% of the variation in muscle strength [37,43]. These results suggest that the *ACTN3* R577X genotype has an apparent contributing role in competitive athletes, particularly elite athletes compared to that in the general population.

There are conflicting results regarding the association between the *ACTN3* R577X genotype and sex differences in muscle phenotypes, e.g., muscle strength and power [35,37, 44]. Yang *et al*. [10] have reported that the *ACTN3* XX genotype is associated with endurance performance only in female athletes. We detected a positive relationship between the *ACTN3* R577X genotype and relative peak power in WAnT of Japanese male athletes but not in female athletes [44]. However, another study showed that the absence of ACTN3 negatively influenced peak isokinetic torque during knee extension in middle-aged women but not in middle-aged men [37]. We can only speculate on possible reasons responsible for the conflicting results between male and female subjects in these *ACTN3* R577X genotype studies. Sex hormones are associated with muscle volume and stiffness. For example, estrogen may affect results. In addition, absolute muscle mass and fiber type distribution may be associated with differences in muscle phenotypes between *ACTN3* genotypes. Future studies are necessary to determine the sex-dependent effect of *ACTN3* R577X genotype on muscle phenotypes.

Proposal for effective utilization of ACTN3 R577X polymorphism for physical training

Strength training

In resistance training for hypertrophy, we propose that individuals with *ACTN3* RR or RX genotypes who have relatively high strength and power should choose high-load low-repetition resistance training. In contrast, individuals with the XX genotype of *ACTN3* should prefer a low load with high repetitions. Our proposal for genotype-based training protocols is based on the observation that the *ACTN3* R577X genotype affects structural factors in type II fibers and muscle strength as well as power output [35-38]. Individuals with the RR genotype have increased muscle strength and higher tolerance for muscle damage. However, previous studies on the *ACTN3* R577X genotype used resistance training with a relatively high load (e.g., 10RM or 70-75% 1RM). Therefore, it is necessary to investigate the association between the *ACTN3* R577X genotype and training response using various training types such as low-load resistance and short intervals to obtain useful genotype-based training protocols.

Endurance training

In endurance training to improve VO_2max, we propose that individuals with the RR or RX genotypes of *ACTN3* should choose HIT. Individuals with the RR and RX genotypes of *ACTN3* R577X polymorphism are more resistant to muscle damage resulting from high-intensity training than athletes with the XX genotype [39]. In addition, there is a positive relationship between *ACTN3* RR or RX genotype and the relative peak power in the Wingate test for Japanese athletes [44]. MacArthur *et al*. [6] have reported that *Actn3*-knockout mice (animal model of α-actinin-3 deficiency) have skeletal muscle with higher oxidative capacity than the skeletal muscle of the wild-type mice. In addition, *Actn3*-knockout mice are able to run 33% farther than wild-type mice in a treadmill endurance test. Individuals with the XX genotype are completely deficient in the a-actinin-3 protein. They will exhibit inferior skeletal muscle function in terms of force generation from contraction and poor ability to recover from high-intensity intermittent exercise. Therefore, individuals

with the *ACTN3* XX genotype will have higher oxidative capacity. They should choose the traditional endurance training, i.e., low intensity and high volume. However, the role of the *ACTN3* XX genotype in endurance capability remains unclear. It is necessary to investigate the association between the *ACTN3* R577X genotype and endurance capability or training response using various training types to determine useful genotype-based training protocols.

Concluding remarks and future studies

This review examined the evidence regarding the effect of *ACTN3* R577X genotype on athletic performance and muscle phenotypes. We provided a proposal for effective utilization of *ACTN3* R577X polymorphism for physical training. Many previous studies have reported that the *ACTN3* R577X genotype is associated with athletic performance, especially with sprint/power athletic performance and muscle phenotypes in several ethnic populations. Individuals with the *ACTN3* RR or RX genotypes have higher muscle strength and power as well as stronger structural factors in type II fibers than individuals with the *ACTN3* XX genotype. Other novel or known genetic variants require additional testing in multiple cohorts, similar to studies on *ACTN3* R577X genotype.

As described above, most case-control studies of athletic performance compared the frequency of genetic polymorphisms between athletes and controls. This method using definitions of sporting performance based on Olympic or world championship appearances or various event types (e.g., sprints/power events, endurance events, mixed-type events, etc.) is utilized by researchers worldwide to identify genes associated with sporting performance. Recently, genome-wide association studies have enabled exhaustive searches for genes related to athletic phenotypes. However, these searches have not yielded a narrow list of candidate genes. It is important to carry out studies on the effect of genes and a range of environmental factors on sporting performance. This may clarify the effect of genes on sporting performance and the effectiveness of training.

The *ACTN3* R577X polymorphism is the only genetic factor that is conclusively related to sports performance and muscle phenotypes. Individuals with the *ACTN3* XX genotype are completely lack of α-actinin-3. Follow up research utilizing an *Actn3*-knockout mouse model to mimic individuals with the XX genotype may provide additional mechanistic insight into the development of phenotypes associated with the loss of α-actinin-3. These genetic factors might predict various aspects of response to training, thus providing useful information for athletes and their coaches.

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