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PRACTICAL USES OF GENETIC PROFILE ASSESSMENT IN ATHLETIC TRAINING – AN ILLUSTRATIVE CASE STUDY

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ABSTRACT

Recent studies suggested that several potential genes may explain athletic success. However, while genetic assessment will probably become part of future talent identification, at present, genetic testing predictive value is poor, mainly because athletic success depends on a combination of genetic, physiological, behavioral and environmental factors (including coaching, medical, nutritional, psychological, equipment, facilities and administrative aspects). However, one should consider genetic testing not only for talent identification or sport event selection, but also for possible assistance in the training process itself. In the present case study we show an example of potential practical use of genetic profile assessment for improving the athletic training process. We deliberately chose a case study of a national-level athlete to show that genetic aid should not be limited to top world-class athletes.

Keywords: *genetic profile, athletic success, training process, individualized training regimen*

INTRODUCTION

Recent studies attempted to identify genetic variants associated with elite athletic performance. These studies relied primarily on the candidate gene approach and on single nucleotide polymorphism associations with elite and

world class performance using frequently small sample size cohorts from different ethnic or geographic areas. However, while several genes have been found to potentially explain athletic success, and while genetic assessment will probably become part of future talent identification, genetic testing predictive value is poor at the present time [30].

It is now well known that athletic success depends on a combination of physiological, behavioral and environmental factors. Thus, genetic endowment is only one of several contributors for elite performance. Genetic counseling is yet a piece in the puzzle of athletic excellence together with coaching, physiological, medical, nutritional, psychological, equipment, facilities and administrative aspects. However, one should consider genetic testing not only for talent identification or sport event selection, but also for possible assistance in the training process itself (e.g. genetic explanation for specific training type difficulties).

The aim of the present case study was to give an example of potential practical use of genetic profile assessment for improving athletic training process. Since genetic profiling in the present case study was performed many years after the end of the athlete's career, findings could only give retrospective explanations for unique training process issues and limitations, and raise concerns of appropriate athletic specialty selection. We deliberately chose a case study of national-level athlete to show that genetic aid should not be limited to top world-class athletes.

Case presentation

A.E. started to train in his high school track & field team at the age of 14. Training during the first two years (9^{th} and 10^{th} grade) was performed 3 times per week. Training from September through December in each of these years was devoted to long-distance running (about 60% of the time) and different types of interval training (ranging from 150 to 400 m repetitions, about 40% of the time). During January to mid-February the school participated in a national cross country relay competition (running distances: 1000–1500 m). Therefore, training at that time included more intense interval training (50% of the time), speed training (30% of the time) and the development of general athletic skills (20% of time). From mid-February to the end of June, the school prepared for the district and for the national track & field championships. Since he also had the best school results for his age in 100 m sprint and long-jump, training at that time was more specific and focused on running and jumping technique, including improvement

of starts and run-up to the jumping board. By the end of the 10th grade he won the under 18 district championships in the 400 m run, and was second in the national under 16 championships in 400 m run (51.5 sec).
Due to the success in the 400 m run, his high-school coaches decided to focus more on this event in the 11th and 12th grade. However, the training program remained relatively similar including high-volume moderate-intensity endurance training during September to December but without participation in the cross-country competitions, increasing anaerobic endurance training as well as training intensity in January to mid-February towards the relay cross-country competitions, and more specific training until the end of school year during the preparation to the track & field championships. By the end of the 11th grade he was ranked second in the country (for under 19) in the 400 m run (50.12 sec). Although the training program skeleton in the 12th grade remained unchanged, due to the final academic examinations, the training load was reduced substantially from March (in particularly training frequency and intensity). Despite that on February he set the school record in a traditional 1080 m around school cross-country track run (2.56 min), a record still unbroken to date (35 years later). On May of that year he won the national school heptathlon competition (100 m, shot-put, high-jump, long-jump, 800 m), the national high-school 100 m title (10.7 sec, non-electronic time), and during late June and early July he won the national under 19 title in the 400 m run and broke the Israeli record (48.53 sec).

In the following three years (age 18 to 21) the athlete and his coaches concentrated on the 400 m run, increasing training volume, frequency and intensity (6–8 training sessions/week, about 15% endurance, 40% anaerobic endurance, 30% speed, 15% resistance) significantly. Each of these years was characterized by a very comfortable initial part of the season (characterized by relatively more endurance training, with high-volume and moderate intensity) with running times that were close to the personal best in the first and second 400 m runs during the winter (at that time in Israel, training was planned for a single peak in the summer). Therefore, the conclusion of the preparatory part of training was accompanied by a very optimistic feeling for significant improvements by the end of the season. However, in each of these years, when training shifted to become more intense (e.g. intense anaerobic endurance type-training including interval sessions of 200–500 m at 80–90% of maximal speed), the athlete was unable to keep-up and to complete the training program in the majority of training sessions. This mandated eventually a marked reduction in training intensity up to complete rest and required a very gradual return to practice for a period that

lasted between 4 to 6 weeks. Another training feature was that although the athlete's resistance training was light to moderate at most, and consisted of only 15% of training time, he experienced confound delayed onset muscle soreness following resistance training sessions. These three training seasons presented almost a complete stagnation in his personal best result in the 400 m run (only minor improvement – from 48.53 to 48.42 sec). Due to the ability to better tolerate endurance-type training, and to the fact that his 100 m best result was not so fast, the athlete was advised several times during these years by his coaches to change training focus and to try to specialize in middle-distance runs (i.e. 800 m). However, despite the coaches' recommendations, he refused to make this change claiming that he will not be able to tolerate training for these events and to compete successfully.

After these years, at the age of 22, the athlete joined medical school, reduced his training markedly and did not compete at all for two years. During the third year of medical school he decided to start training again. Training consisted of about 20% endurance, 35% anaerobic endurance, 30% speed and 15% resistance. However, due to academic obligations, training frequency was reduced to an average of 5 sessions a week (in opposed to 6–8 sessions in previous years). In addition, at that year during the spring, training intensity was also reduced, and the number of super-intense anaerobic endurance training sessions was limited. Resistance training intensity was also reduced (not more than 70% of 1RM). Unexpectedly, given the nature of his training at that period, in his first 400 m run at that season he broke his personal best time (48.29 sec). In addition, by the end of the season he won the 400 m run national championships and broke again the Israeli national record (47.79 sec), improving his personal best time by more than half a second).

Twenty five years later we evaluated the genetic profiles of Israeli all-timers speed/power and endurance athletes [7, 14, 15]. As part of this evaluation, A.E.'s genetic profile was analyzed as well. By combining his specific genetic profile assessment with the detailed history of his athletic training and career, the present case study may demonstrate how the analysis of this profile could be used to better understand training responses and performance capabilities. Such preliminary knowledge may direct coaches in creating an appropriate *personalized* training program, one that considers the unique genetic profile of the individual.

Genetic profile

We computed the combined influence of five power-speed and five endurance polymorphisms following a model used elsewhere in order to create power and endurance genetic distance scores (PGDF5 and EGDF5, respectively). First, we scored each genotype within each polymorphism. We assumed an additive model (equaling 0, 1 or 2), based on the number of alleles associated with a higher potential for power-speed or endurance performance of the athlete for each polymorphism. Thus, we assigned a genotype score (GS) of 2, 1 and 0 to each individual genotype, theoretically associated with the highest, medium, or lowest potential for power-speed or endurance performance, respectively. PGDS5 was calculated by computing the combined influence of the 5 polymorphisms (ACE I/D, ACTN3 C/T, IL6 –174 G/C, NOS3 T/C, AGTM/T, detailed in Table 1) [32]. PGDS5 equals the Euclidean distance from the perfect endurance genetic score for each polymorphism, and was transformed into a 0–100 scale for easier interpretation. PGDS of 100 represents an "optimal" power-speed genetic profile, that is, all GSs are 2. In contrast, PGDS of 0 represents the "worst" possible profile for power-speed genetic profile, that is, all GS's are 0 (for more detailed description of the calculation see [6]. In the same way, we computed the EGDS5 based on 5 endurance genetic polymorphisms (PPARGC1A Gly482Ser, PPARA intron 7 G/C, PPARD T294C, NRF2 A/C, HIF C/T) [37]. We also computed a EGDS5/PGDS5 ratio, which represents the athlete's genetic tendency towards endurance or power events (Table 2).

The PGDS5 consists of five polymorphisms (ACTN3 C/T, ACE I/D, IL6 –174 G/C, NOS3 T/, CAGT M/T) previously described as related to power performance [32]. The ACTN3 gene encodes for the synthesis of α-actinin-3 in skeletal-muscle fibers, a sarcomeric protein necessary for producing powerful "explosive" contractions. A premature stop cod on polymorphism [Arg(R)577Ter(X)] in ACTN3 was first described by North et al. [29]. The absence of α-actinin-3 XX genotype is believed to induce top-level athletic performance in "pure" power and sprint sports [41]. In contrast, compared with the general population, the X allele is overrepresented in elite endurance athletes [22, 41]. Mechanistic explanation for the latter finding might be found in the α-actinin-3 knockout (KO) mouse. Compared with wild-type mice, the muscles of the KO mouse exhibit 33% higher endurance and a shift towards increased activity of mitochondrial oxidative metabolism [23, 24].

Table 1. Studied polymorphisms and genetic scores.

Symbol	Gene	Polymorphism	Genotype (2='optimal' genotype)
Endurance related genes			
ACE	Angiotensin converting enzyme	I/D (rs1799752)	0=DD, 1=ID, 2=II
ACTN3	Alpha-actinin-3	R/X (rs1815739)	0=RR, 1=RX, 2=XX
NRF2	Nuclear respiratory factor 2	A/C (rs12594956)	0=CC, 1=AC, 2=AA
PPARD	Peroxisome prolifilator-activated receptor delta	T294C (rs2016520)	0=TT, 1=CT, 2=CC
HIF	Hypoxia Inducible Factor	C/T (rs11549465)	0=CC, 1=CT, 2=TT
Power related genes			
ACE	Angiotensin converting enzyme	I/D (rs1799752)	0=II, 1=ID, 2=DD
ACTN3	Alpha-actinin-3	R/X (rs1815739)	0=XX, 1=RX, 2=RR
IL6	Interleukin-6	–174 G/C rs(1800795)	0=CC, 1=GC, 2=GG
NOS3	Endothelial nitric oxide synthase 3	–786 T>C rs(2070744)	0=CC, 1=TC, 2=TT
AGT	Angiotensinogen	Met235Thr (rs699)	0 = TT, 1= TC, 2= CC
Other genes			
ACSL A/G	Long-chain-fatty-acid–CoA ligase 1		0 = AA, 1= AG, 2= GG
MCT1	monocarboxylatelactate transporter 1	A1470T(rs1049434)	0 = TT, 1= AT, 2= AA
MnSOD	Mannose superoxide dismutase	Val19Ala (rs1799725)	0 = VV, 1= AV, 2= AA
IGF-I	Insulin-like growth factor-I	-C1245T (rs35767)	0 = CC, 1= CT, 2= TT

The ACE I/D polymorphism has been extensively studied with regard to exercise-related phenotypes. It is related to cardiovascular and skeletal muscle function. An excess of the I allele has been associated with some aspects of endurance performance [34], probably by improvement in substrate delivery [39], skeletal muscle efficiency [38] and subsequent conservation of energy stores [26]. Conversely, an excess of the D allele has been reported among elite power-oriented athletes [27] in a mechanism that is most likely mediated by differences in skeletal muscle strength gain [17]. The IL6-174 G/C polymorphism is associated with power sports performance, with the G allele exerting a favorable effect without an effect on endurance performance [33]. This could be due to the G allele-associated improved muscle repair response after eccentric damage [40]. The NOS3 gene encodes NO synthase. The T786C polymorphism is associated with elite power sports performance, where the mutant C allele exerts favorable effect on power

performance through NO-mediated vasodilatation and muscle hypertrophy. Finally, the Met235Thr polymorphism of the AGT gene is associated with elite power sports performance, with the C allele exerting a favorable effect probably due to higher ANG II levels [18]. Overall, both ACE and AGT genes play a crucial role in the renin-angiotensin-aldosterone system, which modulates important cardiac and muscle phenotypes during exertion in humans.

Table 2. The athlete's genetic polymorphisms and genetic scores.

Symbol	Gene	Polymorphism	Genotype Score (2='optimal' genotype)
Endurance related genes			
ACE	Angiotensin converting enzyme	ID	1
ACTN3	Alpha-actinin-3	RX	1
NRF2	Nuclear respiratory factor 2	AC	1
PPARD	Peroxisome prolifilator-activated receptor delta	TC	1
HIF	Hypoxia Inducible Factor	CC	0
EGDS5			**40.8**
Power related genes			
ACE	Angiotensin converting enzyme	ID	1
ACTN3	Alpha-actinin-3	RX	1
IL6	Interleukin-6	CC	0
NOS3	Endothelial nitric oxide synthase 3	CC	0
AGT	Angiotensinogen	TC1	
PGDS5			**33.8**
Other genes			
ACSL A/G	Long-chain-fatty-acid–CoA ligase 1	AG	1
MCT1	monocarboxylatelactate transporter 1	AT	1
MnSOD	Mannose superoxide dismutase	AA	2
IGF-I	Insulin-like growth factor-I	CC	0

The EGDS5 consists of five polymorphisms (PPARGC1A Gly482Ser, PPARA intron 7 G/C, PPARD T294C, NRF2 A/C, HIF C/T), previously described as strongly related to endurance performance [37]. Of the five polymorphisms composing the EGDS5, four are related to mitochondrial biogenesis

[16]. Mitochondrial function is associated with aerobic performance. The peroxisome proliferator activated receptor (PPAR)-delta (gene PPARD) and PPAR-gamma co-activator 1 alpha (gene PPARGC1A) are determinants of mitochondrial function in animals and *in vitro*. PPAR-delta, in particular, regulates expression of genes involved in lipid and carbohydrate metabolism, and affects insulin sensitivity and glucose uptake by skeletal muscles. A functional 294T/C polymorphism in this gene is associated with predisposition for endurance performance [1]. The nuclear respiratory factors NRF1 and NRF2 coordinate the expression of nuclear and mitochondrial genes relevant to mitochondrial biogenesis and respiration. Carriers of a polymorphism in the sequence of translation initiator ATG in the NRF2 gene have a higher training response and improved running economy than non-carriers, thus potentially explaining some of the inter-individual variance in endurance capacity [21]. In addition to the mitochondrial biogenesis related genes, hypoxia-induced factor (HIF) also contributes to athletic endurance performance. HIF-1 alpha is involved in acclimation to hypoxic stress, by up-regulating glycolysis and the angiogenesis response to low levels of tissue oxygenation. Some of the genes that are controlled by HIFs encode proteins that stimulate red cell production (mainly erythropoietin) [25].

In addition to the PGDS5 and EGDS5 other genetic polymorphisms were assessed. The Long-chain-fatty-acid–CoA ligase 1 (ACSL A/G) is an enzyme that in humans is encoded by the ACSL1 gene [35, 36]. Studies have shown that the AA polymorphism had lower VO_2max responses to training than GG and A/G. This polymorphism explains 6.1% of the training-associated VO_2max response [10].

We also determined the SLC A1470T (MCT1) lactate proton-linked transporter polymorphism which mediates lactate transport across the sarcoplasma. Both lactate influx into or efflux out of the muscle is increased when MCT1 is increased [9]. The AA genotype carriers have higher blood lactate levels compared to the TT and TA genotypes during different exercise protocols [12].

We also assessed the MnSOD Val19Ala polymorphism. MnSOD is a mitochondrial enzyme catalyzing the conversion of superoxide radicals (O2•-) to hydrogen peroxide (H_2O_2) [2, 4]. The valine to alanine substitution affect the transport of MnSOD to the mitochondria. We recently demonstrated [5] that the Ala allele was more frequent in both endurance and power-sprint athletes than in controls suggesting that the positive association between the Ala allele and athletic performance may be related to ROS-

related angiogenesis, mitochondria biosynthesis, and muscle hypertrophy, and not to MnSOD aerobic properties.

Finally, we determined the IGF-I -C1245T polymorphism. IGF-I plays a key role in exercise-associated muscle growth and development [3, 11, 13, 19, 20, 28, 31]. Recently, we found that the presence of the rare TT genotype contributes to endurance performance, and in particular to power-speed athletic excellence in Israeli athletes [7].

DISCUSSION

The description of the training program of this athlete raises several unique and substantial issues. First, the athlete could not tolerate a transition from high-volume low-intensity training, that characterize the preparatory period of the training season, to the supra-intense training that characterize specific training required for a 400 m sprinter. Second, the athlete was able to achieve good results, and even personal records, following high-volume low-intensity training or when the total amount of training or the amount of high-intensity training was reduced. Third, despite very light resistance training, the athlete experienced confound delayed onset muscle soreness following these training sessions. Finally, the athlete refused to repeated recommendations of his coaches to change training focus and to specialize in middle distances like the 800 m run. In the following discussion we will present how genetic profiling could be used to address these points and to improve the overall training process.

The coaches' suggestion to make a transition to middle distance runs was based on their professional judgment of the athlete's ability to better tolerate endurance-type training, and on the fact that his 100 m best result was not fast enough in order to achieve top 400 m performance. Despite the professional recommendation, the athlete refused to make the change, claiming inability to tolerate training and compete successfully in middle distances. We recently described the genetic scores of Israeli power/sprint athletes using a similar scoring model [8]. It was shown that the PGDS5 score of the power/speed athletes was significantly higher than their EGDS5. Moreover, we calculated a threshold of PGDS5 and EGDS5, above which the probability of success in power/speed or endurance sport, increases substantially, respectively. The case study athlete was the *only* power/speed athlete in the Israeli cohort with a higher EGDS5 than PGDS5 (Figure 1). Moreover, his EGDS5 was higher than the threshold for endurance success (40.8 versus 34.8). A more careful look on his PGDS profile shows that in none of the five genes that consist the PGDS, he carried a power/speed promoting

polymorphism (a score of 2). Thus, although speculative, it is possible that knowledge of this genetic information at the time of training, in addition to the coaches' professional impression and recommendation, could have combined to change the athlete's decision, and a transition to middle distance runs would have been made.

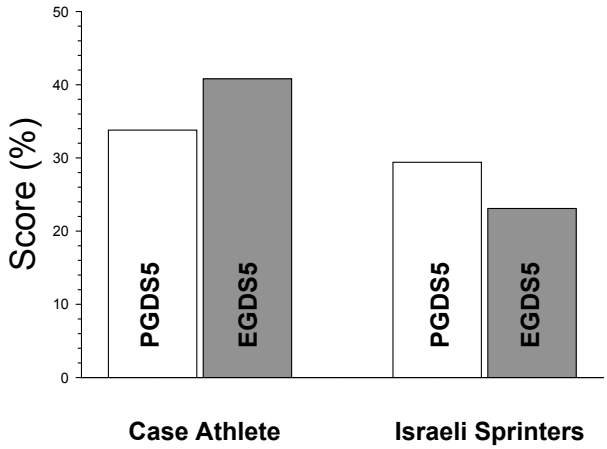

Figure 1. Power and endurance genetic distance scores (PGDF5 and EGDF5, respectively) of the case athlete compared to previously described Israeli sprinter cohort.

The only favoring genetic polymorphism that the athlete carried was the Mannose superoxide dismutase (MnSOD) Ala-Ala polymorphism. We recently reported that despite the important role of SOD in mitochondrial aerobic activity, the Ala-Ala polymorphism was found in *both* endurance and power/speed athletes [5]. Interestingly, the Ala-Ala polymorphism is associated with reduced mitochondrial processing efficiency and reduced transport of MnSOD into the mitochondria, and as a result, with decreased MnSOD efficiency against oxidative stress [2]. However, it was suggested that the positive association between the Ala allele and both endurance and power athletic performance may be related to Reactive Oxygen Species (ROS) related angiogenesis, mitochondrial biosynthesis, and muscle hypertrophy [5].

Another striking genetic finding was that the athlete was among the very few carriers of the IL-6 CC polymorphism. Recently, it was reported that the IL-6 G-174 C genotype is associated with CPK activity in a dose-dependent fashion [40]. Individuals with one or more of the C allele had reduced exercise-associated IL-6 production, reduced post-exercise anti-inflammatory response, and as a result, higher post-exercise CPK peak, compared with

individuals homozygous for the G allele. The IL6 CC genotype was associated with a greater than threefold increased risk of a massive CPK response and a greater risk for exercise-induced rabdomyolysis [40]. The rare and unique existence of this polymorphism, in particularly combined with the MnSOD Ala-Ala polymorphism that promotes accumulation of oxygen radicals, may impose a significant limitation for athletic success. Moreover, it certainly may explain the athlete's consistent difficulty to make a transition from high-volume to high-intensity training, the inadequate delayed onset muscle sourness response to light resistance training and the rather surprising ability to achieve good results and even personal records in times of reduced training intensity. The knowledge of this important genetic information, at the time of training, could be used to a faster understanding of the distinct training limitations, and to a construction of a better *individualized* training regimen.

This illustrative case study shows both sides of genetic sports counseling. It should be noted that while a favorable or non-favorable genetic predisposition is important, many other environmental and psychological factors, like coaching, training facilities, personal equipment, nutrition, familial support, motivation, and socioeconomic factors, are crucial for athletic success or failure. Furthermore, the potential use of genetic predisposition in very young athletes (e.g. at around age of 14 when selection of one sport activity is typically made), may raise some ethical issues. For example, how young athletes who lack aproper genetic profile, but are highly motivated to succeed would be treated? Should and how young athletes be told that they lack the "required" genetic profile to reach the top in their sport? The current case study demonstrates that genetic discouragement is inappropriate, since despite a non-favorable PGDS, the athlete was able to march along the challenging, demanding and rewarding pathway of athletic training and to reach the peak in his sport by winning national championships and setting a national record. On the other hand, this illustrative case gives an example for the optional use of genetic assistance not only for sport selection, but also as an important piece in the complete puzzle picture of improving and optimizing training.

Finally, this case study was chosen for several reasons. First, it gave us an exclusive opportunity to explore very specific training details and precise accompanying feelings during different training phases throughout an athlete's career. Moreover, we deliberately chose a national-level athlete, to show that genetic counseling should not be limited to top world-class athletes.

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