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Original Article

Evaluation of swimmers by coaches in relation to IL-6 G/C rs56588968 Polymorphism: an Exploratory Study

BEN-ZAKEN, SIGAL[1], MECKEL, YOAV[2], NEMET, DAN[3], KAUFMAN, LEONID[4], KASSEM, EIAS[5] ELIAKIM, ALON[6]
[1,2,4,] Genetics and Molecular Biology Laboratory, The Academic College at the Wingate, Wingate Institute, Netanya, ISRAEL;
[3,6] Child Health and Sports Center, Pediatric Department, Meir Medical Center, Kfar Saba, Israel;
[3,6]Sackler School of Medicine, Tel-Aviv University, ISRAEL;
[5]Pediatric Department, Hillel-Yaffe Medical Center, Hadera, ISRAEL;

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Abstract
Interleukin-6 (IL-6) is a multi-functional cytokine which plays a pivotal role in muscle hypertrophy and repair following exercise-related muscle damage. IL-6 -174G/C (rs1800795) single nucleotide polymorphism (SNP) affects IL-6 promoter activity, and C allele associated with eccentric exercise-induced muscle damage. C-allele is highly prevalent among long-distance swimmers, whilst exercise-associated rhabdomyolysis is rare, probably due to water-related protective mechanisms. The aim of the current study is to explore whether elite swimming coaches can identify C allele carriers by evaluation of swimmer's performance dimensions. Ninety-five (95) long and short distance swimmers (70 males, 25 females, aged 14-29) and six coaches participated in the current study. All swimmers were ranked among the top Israeli results in their event/age group. All coaches graduated from the same College, and were experienced senior-level coaches with experience working in an elite competitive setting Swimmer were rated by his/her coach on 3 performance dimensions: training recovery, performance, and physiological abilities. Genomic DNA was extracted from peripheral blood following a standard protocol. IL-6 -174G/C Genotyping was performed using polymerase chain reaction (PCR). Both in-water and land training recovery were categorized by the coaches as significantly better in non C-allele carriers compared to C-allele carriers. Swimmers' aerobic performance evaluation by the coaches was significantly higher among C-allele non-carriers. The results suggest that experienced coaches can adequately classify swimmers according to their genetically determined recovery capabilities. Thus, knowing the swimmer's genetic background may possibly encourage coaches to perform individualized training adaptations in an effort to optimize their swimmers' performance.
Keywords: Performance, Aerobic, Recovery, Training, Genetics

Highlights

- The high prevalence of IL-6 C-allele, associated with exercise-related muscle damage raise the possibility that swimming selection in gifted endurance athletes who are C-allele carriers represents genetically-dependent sports. Swimming enable athletes to execute their endurance abilities in a protective environment, that decrease the incidence of muscle damage
- Training recovery was categorized by elite swimming coaches as significantly better in C-allele non-carriers, which correspond to their genetic predisposition to tolerate training load.
- knowing the swimmer's genetic background may serve as an additional tool for personalized tailor-made training that will enable athletes to fulfill their potential, and perhaps also for building effective training programs for young athletes is currently in its initial stages
- Further studies are needed before this practice becomes an integral part of conventional training.

Introduction

Athletic performance is multifactorial phenomena influenced by several interacting and interrelating intrinsic and extrinsic factors. Whilst it is well established that genetics have a large influence on phenotypes such as strength, muscle size, fiber-type composition, etc. (e.g., Bouchard, Dionne, Simoneau, and Boulay, 1992; Ruiz et al., 2009) less is known about the role of genetic in training recovery. Yet, recovery ability is of critical importance for elite swimmers and their performance(Collette *et al.*, 2018; Pollock *et al.*, 2019) Therefore coaches are in constant pursuit after those swimmers showing greater recovery potential on top of physiological, technical and anatomical traits. While traditional coaching views the coach as an informed resource and the

Corresponding Author: BEN-ZAKEN SIGAL, E-mail: sigalbz@wincol.ac.il

athlete as a reflection of expert knowledge, recent approaches have acknowledged the changing role of the coach. Therefore, equipping and enriching coaches' tool box might contribute to enhancing athletic performance.
Athletic performance related traits vary substantially among individuals. Many twins and family studies have reported that genetic factors are responsible for heterogeneity in fitness-related traits. For example, the heritability estimate of muscular strength is 52% and that of the endurance-related phenotype is 59%(Zempo *et al.*, 2019), meaning that more than 50% of the variability seen in those traits are attributed to genetic variability. Indeed, it has been suggested in recent years that several genetic polymorphisms and profiles promote athletic excellence in endurance(Williams and Folland, 2008; Ruiz *et al.*, 2009; Ben-Zaken *et al.*, 2013) and power sports.(Jonatan R Ruiz *et al.*, 2010; Ben-Zaken *et al.*, 2013). However, attempts to recognize relevant genes for athletic excellence are difficult, because each gene makes only a small contribution to overall heritability, and due to the complex nature of athletic performance related traits. The current effort to identify genetic polymorphisms that affect the athlete's ability to effectively tolerate training loads is even more complicated.
Interleukin-6 (IL-6) is a multi-functional myokine, released into the blood during exercise(Ellingsgaard, Hojman and Pedersen, 2019), with a wide range of immunologic and metabolic effects (Hirano, 1998). Depending on the situation, IL-6 can promote a pro- or anti-inflammatory state(Wolf, Rose-John and Garbers, 2014; Minciullo *et al.*, 2016)

IL-6 plays a pivotal role in the processes of muscle hypertrophy and repair following exercise-related muscle damage (Jeunemaitre *et al.*, 1992). IL-6 mRNA and subsequent circulatory IL6 typically elevated during exercise (Petersen and Pedersen, 2005; Pedersen and Febbraio, 2008) This elevation is associated with exercise intensity and duration, the mass of recruited muscles, and endurance capacity.(Petersen and Pedersen, 2005). Studies have shown that muscular glycogen depletion trigger IL-6 release from the working muscles(Pedersen, 2019).

IL-6 is encoded by the *IL6* gene located on chromosome 7. The *IL-6* -174G/C (rs1800795) is a common functional single nucleotide polymorphism (SNP) located on the promotor region of the *IL6* gene. This SNP results in substitute of the cytosine nucleotide (C) with Guanin (G) affecting the level of circulatory IL6, with the C allele produces less IL6 than the G allele (Fishman *et al.*, 1998; Terry, Loukaci and Green, 2000; Bennermo *et al.*, 2004) Moreover, the GG genotype and G allele were found to be over-represented in Spanish(Jonatan R. Ruiz *et al.*, 2010), but not Israeli(Eynon *et al.*, 2011), elite power athletes. In contrast, the C allele was found to be associated with eccentric exercise-induced skeletal muscle damage and rhabdomyolysis.(Yamin *et al.*, 2008; Funghetto *et al.*, 2013) We previously demonstrated(Ben-Zaken *et al.*, 2017) a higher frequency of the C-allele and CC genotype among long-distance swimmers, suggesting first, that the rarity of exercise-associated rhabdomyolysis among swimmers(Galvez, Stacy and Howley, 2008; Stella and Shariff, 2012) is probably related to other sports-specific or water-related protective mechanisms; and second, a possibility that swimming selection in talented endurance athletes who are C-allele carriers represents an example of genetically-dependent sports selection based on the athlete's ability to tolerate training.

The aim of the present study was to examine whether elite swimming coaches can identify C allele carriers by assessment of their swimmers' ability to recover from training, or by their performance, physiological, and personality characteristics.

Methods

Participants

Swimmers. Ninety-five (95) swimmers (70 males and 25 females, ages 14-29) from six swimming clubs participated in the currents study. All the swimmers were ranked among the top Israeli results in their event/age group, and had competed in national- and/or international-level meets on a regular basis (e.g. the average 100 m swim time in freestyle was 50.90± 1.53 s for males and 57.5 ± 1.9 s for females, the average female 800m swim time was 9:20.30 ± 00:20.15 min, and the average male 1500 m swim time was 15:50.20 ± 00:07.20 min). Although the swimmers trained under different coaches, the coaches all used similar training principles. Training experience of the participants consisted of an average of 10 swimming sessions per week, covering distances of about 40 to 50 km/week. Out of that, about 50% was devoted to long-distance aerobic-type training, 25% to interval training, and 15% to sprint training. In addition, the swimmers practiced special water technical drills (about 10% of the total distance). Characteristics of the swimmers are presented in Table 1.

Coaches. Six coaches participated in the study. All had graduated from the same College, and were experienced senior-level coaches with experience working in an elite competitive setting. The study was approved by Hillel-Yaffe Medical Center ethics committee. Participants and their parents or guardians (in participants under 18 years old) provided written informed consent prior to participation in the study.

Genotyping

Genomic DNA was extracted from peripheral EDTA treated anti-coagulated blood using a standard protocol, described elsewhere.(Miller, Dykes and Polesky, 1988) Briefly, Lyses buffer (5 mL) containing 100 mM of tris HCl, pH = 8.5 + 0.5 M of EDTA + 10% SDS + 5 M of NaCl 40 mL added D.D.W. to 1000 mL was added to the white cell solution. Proteinase K (200 µg) was added to the solution. The tubes were incubated overnight at 50°C in a shaker incubator for digestion. After digestion, one volume of ethanol (-20°C) was added to the lysate and the samples were swirled until precipitation was completed (20-30 min, until it became completely transparent). The DNA was recovered by lifting the aggregated precipitate from the solution, using a disposable tip. Excess liquid was dabbed off and the DNA was dispersed in a pre-labeled Eppendorf tube. The DNA was washed in TE solution. Genotypes were determined using the TaqMan allelic discrimination assay. The Assay-by-Design service (http://www.thermofisher.com) was used to set up a TaqMan allelic discrimination assay for the IL-6 –174G/C (rs1800795). Primer sequences were forward: GACGACCTAAGCTGCACTTTTC, reverse: GGGCTGATTGGAAACCTTATTAAGATTG. Probe sequences were for –174G/C forward: VICCTTTAGCATGGCAAGAC, reverse: FAMCTTTAGCATCGCAAGAC. The PCR reaction mixture included 5 ng genomic DNA, 0.125 μl TaqMan assay (40*, ABI), 2.5 μl Master mix (ABI) and 2.375 μl water. PCR was performed in 96 well PCR plates in an ABI 7300 PCR system (Applied Biosystems Inc., Foster City, CA, USA) and consisted of initial denaturation for 5 min at 95 °C, and 40 cycles with denaturation of 15 s at 95 °C and annealing and extension for 60 s at 63 °C. Results were analyzed by the ABI TaqMan 7900HT using the sequence detection system 2.22 software (Applied Biosystems Inc.).

Swimmers' Evaluation by the Coach

Each swimmer was rated by his/her coach on 3 performance-relevant dimensions: training recovery (the ability to return to optimal performance after training or intensive competition) in water and on land; performance (optimal performance without signs of fatigue) at different effort's intensity – aerobic, mixed, anaerobic-lactic, anaerobic a-lactic); and physiological abilities: aerobic abilities (endurance, velocity perseverance over time) and anaerobic abilities (speed, explosive power). Ratings were made on an average Likert scale ranging from 1 (insufficient) to 5 (excellent). Reliabilities of these averaged ratings ranged from 0.60 to 0.71.(Rosenthal and Rosnow, 1984) Coaches were blinded to the IL-6 -174G/C (rs1800795) single nucleotide polymorphism of the swimmers.

Statistical Analysis

The SPSS statistical package, version 20.0, was used to perform all statistical analyses (SPSS, Chicago, IL, USA). A one-way ANOVA used to compare means of coaches' evaluation between IL-6 rs56588968 C allele carriers and non- carriers.

Results

The swimmers anthropometric and swimming characteristics are shown in Table 1.

Table 1

Swimmers' data

Gender, N [%]	Males	70 [74]
	Females	25 [26]
Main event, N [%]	50-100m	27 [28]
	100-200m	36 [38]
	200-400m	26 [27]
	800-1500m	6 [7]
Swimming level, N [%]	National	50 [53]
	Top-level	45 [47]
Age (Range, AVG+SD)	14-29, 18.1±3.6	
BMI (Range, AVG+SD)	15-25, 20.2±2.4	
Practice years (Range, AVG+SD)	2-12, 7.0±2.9	

Swimmers' evaluations by the coaches according to IL-6 G/C rs56588968 polymorphism are shown in Table 2.

Table 2

Swimmers' evaluation by coach, according to IL-6 G/C rs56588968 polymorphism.

	Non-Carriers	**C-allele Carriers**	p
n	43	52	
Training recovery			
In water	3.42	3.02	0.033
In land	3.21	2.62	0.005
Performance			
Aerobic	3.42	2.96	0.048
Mixed	3.40	3.08	ns
Anaerobic lactic	3.23	2.96	ns
Anaerobic a-lactic	3.16	3.02	ns
Physiological characterization			
Aerobic	3.40	3.50	ns
Anaerobic	3.00	3.00	ns

Both in-water training recovery, and particularly land training recovery, were categorized by the coaches as significantly better in non C-allele carriers compared to C-allele carriers. Swimmers' aerobic performance evaluation by the coaches was significantly higher among non C-allele carriers. No significant differences between carriers and non C-allele carriers were found in the coaches' evaluation of mixed aerobic-anaerobic, anaerobic lactic and anaerobic a-lactic performance. No significant differences between carriers and non C-allele carriers were found in the coaches' evaluation of physiological characteristics.

Discussion

The present study examined the ability of elite swimming coaches to identify C-allele carriers – a polymorphism associated with a greater tendency to develop eccentric exercise-induced skeletal muscle damage – among their swimmers. The main finding of the study was that both in-water training recovery, and in particular land training recovery, were categorized by the coaches as significantly better in non-C-allele carriers compared to C-allele carriers. In addition, the swimmers' aerobic performance evaluation by the coaches was significantly, although mildly, higher among the non C-allele carriers. The results suggest that experienced elite swimming coaches can adequately classify swimmers according to their genetically determined recovery capabilities.

The IL-6 response to exercise depends on the type of polymorphism *(-174 G/C*) within the IL-6 promoter (G-allele or C-allele).(Pedersen *et al.*, 2003) Presence of the G allele was associated with a higher circulating level of IL-6.(Fishman *et al.*, 1998) The increase of IL-6 activity reduces muscle inflammation by stimulating the production of anti-inflammatory cytokines, including IL-1ra, IL-10(Petersen and Pedersen, 2005), and by inhibiting the production of pro-inflammatory cytokines such as TNF-α and IL-1β.(Aderka, Le and Vilcek, 1989) In addition, increased production of IL-6 by skeletal muscles following acute exercise can also improve glucose utilization and sustain muscle energy demands by enhancing adenosine monophosphate-activated protein kinase activity.(Carey *et al.*, 2006) Therefore, the protective effects of the *IL-6 -174G* genotype against exercise-induced muscle damage are mainly due to increased muscle glucose uptake and restricted inflammation by stimulation of anti-inflammatory and inhibition of inflammatory cytokines' production, all known to play an important role in post-exercise muscle damage repair. In contrast, individuals with one or more of the *IL-6 -174C* alleles had a higher post-exercise creatine kinase (CK) peak compared with individuals homozygous for the G allele.(Yamin *et al.*, 2008) The *IL-6 -174CC* genotype was associated with a greater than three-fold risk of massive CK response.

We previously reported a significantly higher CC genotype and C allele among long-distance swimmers compared to long and middle-distance runners.(Ben-Zaken *et al.*, 2017) These differences were not found between short-distance swimmers and runners. This may suggest two important possibilities. First, despite the higher frequency of the C allele and CC genotype, exercise-associated rhabdomyolysis is less common in swimmers, suggesting other swimming-related protective mechanisms such as reduced weight bearing in water sports, lower water temperature, and predominant concentric-type exercise. Second, this finding may have implications for genetically-dependent sports selection. Both long-distance runners and swimmers must have excellent endurance capabilities. Individuals carrying the *IL-6 -174C* allele are increasingly susceptible to developing eccentric exercise-induced muscle damage, in particular when performing exercises on the ground, and therefore their ability to recover from intense training might be reduced. Thus, it is possible that individuals with enhanced endurance characteristics, but with an unfavorable *IL-6 -174C* polymorphism, subconsciously choose to specialize in swimming, a sport that would be significantly less affected by their genetic disadvantage.

In most cases, as a routine, coaches rely on their experience and on a general impression of swimmers' responses when making changes in training load throughout the season. The results of the present study suggest that experienced elite swimming coaches can identify their swimmers' recovery capabilities. However, the reduced ability of a swimmer to appropriately recover following training may be interpreted by the coach as reduced fitness, with a need to increase training volume and/or intensity. The importance of the present study's findings is that knowing that the reduced recovery capability is genetically determined may lead the coach to the opposite decision, and instead of increasing the training load he or she may individualize training according to the swimmer's genetic profile. This may indicate that the number of highly intense water practices, and in particularly ground/land and weight practices, should be monitored very carefully among swimmers who are carriers of the *IL-6 -174C* allele, and predominantly among *IL-6 -174CC* homozygotes. Whether the knowledge of the swimmers' genetic background can be used by the coaching staff to optimize training programs is still speculative and need further research. In addition, for a better understanding, the present study should probably be replicated, but on less experienced and younger coaches who are working with non-elite or young groups of swimmers.

In summary, the *IL-6 -G174C* polymorphism represents a genetic polymorphism that is possibly associated with sports selection based on the athlete's ability to effectively tolerate training. We found that both in-water training recovery, and particularly land training recovery, were categorized by elite swimming coaches as significantly better in non-C-allele carriers compared to C-allele carriers. The results suggest that experienced elite swimming coaches can adequately classify swimmers according to their genetically determined recovery capabilities.

Perspective

Identifying genetic polymorphisms that affect the athlete's ability to tolerate training loads is intricating task, due to the multifactorial nature of trainability. The high prevalence of the Il-6 C-allele (which is associated with exercise induced muscle damage) on one hand and the rarity of exercise induced rhabdomyolysis on the other hand, among long distance swimmers raise the possibility that swimming selection in talented endurance athletes who are C-allele carriers represents an example of genetically-dependent sports selection based on the athlete's ability to tolerate training. The in-water environment enables swimmers to execute their endurance abilities whilst avoiding muscle damage associated with IL6 C allele carrying. We found that training recovery was categorized by elite swimming coaches as significantly better in C-allele non carriers compared to C-allele carriers, which correspond to their genetic predisposition to tolerate training load. knowing the swimmer's genetic background may serve as an additional tool for personalized tailor made training that will enable athletes to fulfill their potential.

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