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High prevalence of the *IGF2* rs680 GG polymorphism among top-level sprinters and jumpers

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ABSTRACT

Previous studies have shown that the *IGF1* polymorphism is associated with greater muscle mass and improved power athletic ability, but very little is known about the IGF2 polymorphism and athletic performance.

Purpose: The aim of the present study was to assess the frequency distribution of the *IGF2* rs680 polymorphism among Israeli athletes.

Methods: 185 short- (n = 72) and long-distance (n = 113) runners, 94 short- (n = 44) and long-distance (n = 50) swimmers, 54 weight lifters and 111 controls participated in the study. Genomic DNA was extracted from peripheral EDTA treated anti-coagulated blood using a standard protocol. Genotyping of the IGF2 A/G polymorphism (rs680) was performed using allelic discrimination assay.

Results: The frequency of *IGF2* (rs680) G allele carriers was significantly greater among top compared to national-level track and field sprinters and jumpers ($p < 0.05$). The IGF2 (rs680) GG genotype frequency was significantly greater among track and field sprinters and jumpers compared to weight lifters $p < 0.02$), and among top-level sprinters and jumpers compared to top-level weight lifters $p < 0.01$).

There were no statistically significant differences in the *IGF2* (rs680) GG genotype frequency among endurance athletes and between the swimmers and the other sports disciplines and the controls.

Conclusions: While a single polymorphism cannot determine athletic success or failure, the findings of the present study suggest a potential importance of the *IGF2* polymorphism, mainly regarding speed sport performance.

1. Introduction

The potential use of genetic polymorphisms, and in particular the single nucleotide polymorphism (SNP) of hormone genes, as a tool to assist in predicting future athletic performance is currently an extremely challenging topic, mainly because each possible gene makes only a small contribution to the overall heritability. Recent studies have demonstrated that the single nucleotide polymorphism of *IGF1* [1], *myostatin* (*MSTN*) [2] and the combination of *IGF1-MSTN* [3] may influence skeletal muscle phenotypes and athletic performance. However, the potential role of other growth factor polymorphisms (e.g. *IGF2*) in athletic excellence is much less studied.

IGF2 is a single-chain polypeptide, one of three protein hormones that share structural similarity to insulin, secreted by the liver and circulates in the blood. It has growth-regulating, insulin-like and mitogenic activities [4]. The *IGF2* gene is located on chromosome 11p15.5 [5] and is exclusively paternally expressed and maternally imprinted, and has a key role in fetal growth and development [6]. Variation within this gene is known to influence developing muscles and to affect muscle mass and muscle function [7].

IGFs play pivotal roles in skeletal muscle differentiation and growth. IGF2 levels increase dramatically during myogenesis [8,9]. Mice deficient in the IGF-II or IGF-I receptor exhibit muscle hypoplasia and die shortly after birth due to insufficient muscle mass to inflate their lungs [10,11]. Consistent with the in vivo studies, IGF2 antisense oligonucleotides abolish differentiation in cultured muscle cells [9], and IGF2 over-expression or exogenously added accelerates myoblast differentiation [12–14].

Several SNPs of *IGF2* gene (rs3213221, rs680, rs7924316) were associated with loss of muscle strength directly after exertional muscle damage, in particular in men [7]. Baumert et al. suggested that IGF SNPs may negatively influence the stability of the extracellular matrix. Therefore, a subsequent loss in the lateral transmission of force between adjacent muscle fibers might occur, which could lead to the decreased maximal strength observed immediately after strenuous exercise [7]. Although, no direct effect of IGF2 concentration on human extracellular

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matrix protein synthesis is known, Keller et al. [7] have shown that local IGF2 expression increases after injury in murine muscle. It is therefore possible that IGF2 is linked with exercise-induced muscle damage in human muscle, and possibly with extracellular matrix integrity. A direct or indirect influence of IGF2 level on extracellular matrix integrity would, at least in part, explain the significant strength loss after muscle damaging exercise and the association of the IGF2 13790 (C > G, rs3213221) SNP with the degree of injury in soccer players [7].

A SNP in the three untranslated regions of the *IGF2* gene (rs680) was linked to IGF2 gene transcription and expression. The rs680 G allele was associated with significantly higher levels of *IGF2* mRNA compared with the A allele, suggesting a role for this polymorphism in the IGF2 transcription [15]. However, circulating *IGF2* concentrations were higher in middle-aged men [5] homozygous for the A allele compared with those homozygous for the G allele. Several studies showed that the *IGF2* rs680 polymorphism was related to body mass index (BMI) and muscle mass [5,16], although others [17] were unable to replicate these results. Previous studies have demonstrated that hand grip [18], as well as arm and leg strength [19] were significantly higher in adult individuals with the GG and GA genotypes compared to carriers of the AA genotype. Interestingly, very few studies examined the prevalence of the *IGF2* (rs680) single nucleotide polymorphism among professional athletes.

Therefore, the aim of the present study was to assess the frequency of *IGF2* (rs680) polymorphisms among Israeli track and field athletes and swimmers. These athletes were previously tested for *IGF1* and *MSTN* polymorphisms [3,20]. We hypothesized that since carrying the *IGF2* (rs680) GG polymorphism is related to increased muscle mass and strength, its frequency will be higher among the athletes and in particular the sprinters.

2. Participants and methods

2.1. Participants

Three hundred and thirty-three athletes (222 men and 111 women, age: 29.8 ± 12.8 yrs) participated in the study. Athletes who had participated in national/international level competitions were included in the study. The athletes were divided into five groups: 1) long-distance runners (LDR; 113 athletes, main sport events ranged from 1500 m run to half-Ironman); 2) short-distance runners (SDR; 72 athletes, main sport events were the 100- to 200-m runs and the long jump); 3) weight lifters (WL; 54 athletes); 4) long-distance swimmers (LDS; 50 athletes, main sport events 400 m–1500 m swim); and 5) short-distance swimmers (SDS; 44 athletes, main sport events 50 m–100 m swim). Within each group, athletes were further divided into two subgroups according to their individual best performance: elite athletes (representing the country in a world championship or in the Olympic Games) and national-level athletes. Control group participants were 111 nonathletic healthy individuals (74 men and 37 women, age: 26 ± 3 yrs) who were not engaged in a regular basis physical activity. All participants were Israeli Caucasians. Characteristics of the athletes and controls are presented in Table 1.

The study was approved by the Institutional Review Board of the Hillel Yaffe Medical Center, Hadera, Israel. A written informed consent was obtained from each participant.

2.2. Genotyping

Genomic DNA was extracted from samples of peripheral venous blood according to the salting-out procedure [22]. Genotypes were determined using the Taqman allelic discrimination assay. The Assay-by-Design service (www.appliedbio-systems.com) was used to set up a Taqman allelic discrimination assay for the *IGF2* G/A SNP (rs3680). Primer sequences were: forward: TGAGTCCCTGAACCAGCAAAG, reverse: GACGTGCCCACCTGTGAT. Probe sequences were for *IGF2* G/A, forward: VIC-AGAAAAGAAGGACCCCAGAA, reverse: FAM-AAAAGAAGGGCCCCAGAA. 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 384 well PCR plates in an ABI 9700 PCR system (Applied Biosystems Inc., Foster City, CA, USA), and consisted of initial denaturation for 10 min at 95 °C and 40 cycles with denaturation of 15 s at 92 °C, and annealing and extension for 60 s at 60 °C. Results were analyzed by the ABI Taqman 7900HT using the sequence detection system 2.22 software (Applied Biosystems Inc.).

2.3. Data analysis

The SPSS statistical package, version 20.0, was used to perform all statistical evaluations (SPSS, Chicago, IL, USA). A $\chi 2$-test was used to confirm that the observed genotype frequencies were within the Hardy-Weinberg equilibrium and to compare alleles and genotype frequencies between athletes and controls, and between athletes from different sports and different competitive levels. Fisher's exact test to compare alleles and genotype frequencies was used if observed or expected values included a cell with a value of 5. Statistical significance was adjusted for multiple testing.

3. Results

The complete data on allele and genotype frequencies are presented in Table 2. No gender differences were found in genotypes and allele frequencies. The frequency of G allele carriers was greater among top-level track and field sprinters and jumpers compared to the controls, although this difference only approached statistical significance ($\chi 2(1) = 3.648$, $p = 0.056$). The frequency of *IGF2* (rs680) G allele carriers was significantly greater among top compared to national-level track and field sprinters and jumpers ($\chi 2(2) = 3.921$, $p = 0.047$) (Fig. 1).

The *IGF2* (rs680) GG genotype frequency was significantly greater among track and field sprinters and jumpers compared to weight lifters ($\chi 2(2) = 8.74$, $p = 0.012$), and among top levels sprinters and jumpers compared to top-level weight lifters ($\chi 2(2) = 11.696$, $p = 0.0029$) (Fig. 1).

There were no statistically significant differences in the *IGF2* (rs680) GG genotype frequency among endurance athletes and between the swimmers and the other sports disciplines and the controls.

4. Discussion

We examined the prevalence of the *IGF2* (rs680) GG polymorphism among Israeli long- and short-distance runners and swimmers and among weight lifters. The main findings of the study were that the GG genotype frequency was significantly greater among sprinters compared to weight lifters, suggesting that carrying this polymorphism is beneficial mainly for speed rather than strength sport events. Moreover, the frequency of the *IGF2* (rs680) G allele carriers was significantly greater among top compared to national-level track and field sprinters, suggesting that this polymorphism is associated with sprint excellence. There were no significant differences in GG carriers between the long-distance runners, swimmers (short- and long-distance), weight-lifters and controls.

The majority of previous reports of hormonal gene polymorphism and athletic performance among professional athletes studied variations in the *IGF1* polymorphism. The polymorphism of *IGF1* promoter frequency was significantly greater in athletes (9.2%) compared to controls (2.4%) and in particularly among strength (11%) compared to athletes participating in team-sport (7.8%) [23]. We previously demonstrated [1] a higher frequency of the *IGF1* C1245T T/T polymorphism among Israeli athletes (4.8%), compared to controls (non-existence). Interestingly, while T/T polymorphism carriers were both endurance and power athletes, endurance athletes were of a national